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Development of electrophilic amination reactions for the synthesis of nitrogen heterocycles

Development of electrophilic amination reactions for the synthesis of nitrogen heterocycles

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(107,680 words)

Author’s Declaration

I declare that the work in this dissertation was carried out in accordance with the requirements of the University's Regulations and Code of Practice for Research Degree Programmes and that it has not been submitted for any other academic award. Except where indicated by specific reference in the text, the work is the candidate's own work. Work done in collaboration with, or with the assistance of, others, is indicated as such. Any views expressed in the dissertation are those of the author.

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Abstract

A range of C-N bond forming reactions using hydroxylamine-derived N-O donors have been developed. Initial studies focused on the development of a dearomatising amination reaction of phenols and naphthols. Whilst attempts at developing C-N bond forming dearomatisation reactions of *N*-acyloxysulfonamides and *N*-acyloxycarbamates were largely unsuccessful, further studies identified an effective transition metal-free protocol for dearomatising aminations of *N*-tosyloxycarbamates. Under acidic conditions, *in situ* Boc-deprotection of *N*-tosyloxycarbamate derivatives occurs to generate an electrophilic nitrogen source that can trigger dearomatisation *via* nucleophilic attack of a pendant arene. Through the dearomative cyclisation of phenol- and naphthol-substituted *N*-tosyloxycarbamates, spirocyclic pyrrolidines were obtained in good to excellent yield. Mechanistic experiments suggest the reaction proceeds *via* an S_EAr-like mechanism. Annulative derivatisations of the dearomatised products provides access to complex natural product-like scaffolds. Preliminary studies demonstrated the feasibility of an asymmetric variant of the dearomatising amination reaction.

Additionally, a metal-free aziridination of alkenes using the previously developed N-O donors was demonstrated. The stereospecific aziridination of di-, tri- and tetrasubstituted alkenes was achieved to form azabicyclo[3.1.0]hexane and azabicyclo[4.1.0]heptane motifs. Computational studies validate a concerted mechanism akin to an aza-Prilezhaev-type pathway.

Acknowledgements

First of all, I am thankful to my supervisor Professor John Bower. His enthusiasm and encouragement have contributed massively to the quality of the results presented in this thesis. I believe my knowledge of chemistry and practical abilities have improved significantly over the course of my PhD due to John's enthusiasm and encouragement. I am also extremely grateful for his feedback and advice during the writing of this thesis.

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Thank you to everyone in the Bower group past and present that I had the great pleasure to work and socialise with over the years; Ian, Steven, Phillippa, Andrew, Olivia, Olga, Lauren, Jamie, Ben, Maddy, Tim, Wenbin, Giacomo, Craig, Jess, Rafa, Gangwei, Xiaofeng, Takayuki, Simon, James, Adam, Javi, Rajender, hopefully I haven't missed anyone.

Finally, I want to thank my parents for their constant support and encouragement.

Contents

Abbreviations

BHT	butylated hydroxytoluene
Bz	$C(O)C_6H_5$
^{F}Bz	$C(O)C_6F_5$
1,4-CHD	1,4-cyclohexadiene
COD	cyclooctadiene
d.r.	diastereomeric ratio
dba	dibenzylideneacetone
DCC	*N*,*N*'-dicyclohexylcarbodiimide
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
DMAP	*N*,*N*-dimethylpyridin-4-amine
dppbz	1,2-bis(diphenylphosphino)benzene
dtbpf	1,1′-bis(di-*tert*-butylphosphino)ferrocene
e.e.	enantiomeric excess
e.r.	enantiomeric ration
HFIP	1,1,1,3,3,3-hexafluoro-2-propanol
HTIB	[hydroxy(tosyloxy)iodo]benzene
LDA	lithium diisopropylamide
LHMDS	lithium bis(trimethylsilyl)amide
NaHMDS	sodium hexamethyldisilazide
NBS	*N*-bromosuccinimide
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TFE	2,2,2-trifluoroethanol

Chapter 1 - Introduction

1.1 The importance of nitrogen-containing compounds

Nitrogen is prevalent in many biologically active compounds and pharmaceuticals. Of the top 100 best-selling small molecule drugs in 2018 90% contain at least one nitrogen atom.[1] Many of these compounds contain aryl-substituted amines such as anilines, but chiral *N*-heterocycles including pyrrolidines and piperidines are also well represented. The frequency of nitrogen in natural products and pharmaceutical agents makes efficient and versatile carbon-nitrogen bond forming reactions highly valuable.

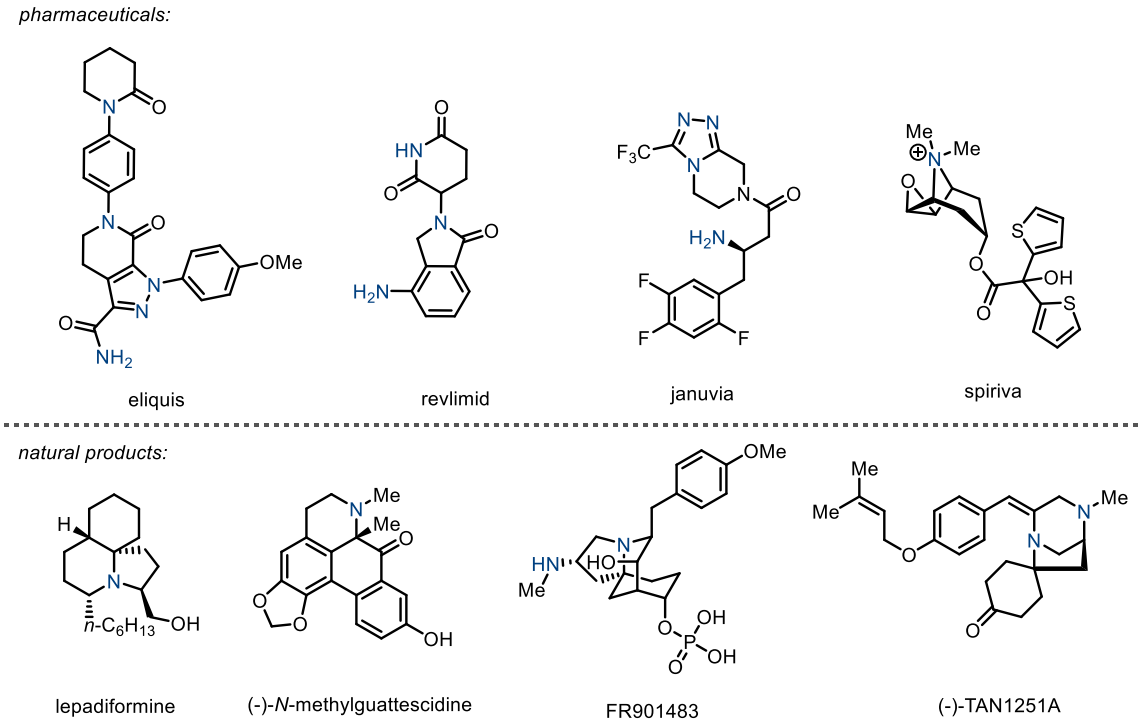


Figure 1 *Examples of pharmaceuticals[1] and natural products[2-5] containing nitrogen.*

Classically, C-N bonds are formed by either S_N2 attack of a nucleophilic amine derivative on an electrophilic carbon or by reductive amination;[6] however, these approaches are limited in their effectiveness due to possible problems of regioselectivity and the potential for over alkylation of nitrogen. More recently, metal-promoted C-N cross-coupling reactions have emerged as powerful approaches for the formation of C(sp^2)-N bonds. The palladium-catalysed cross-coupling of nucleophilic amines with aryl halides (Buchwald-Hartwig amination)[7-9] and the copper-mediated oxidative coupling of amines with arylboronic acids (Chan-Lam-type coupling)[10-12] are two of the most effective and reliable methods for the synthesis of aryl-nitrogen bonds.

An alternative, umpolung strategy for C-N bond formation is electrophilic amination[13-17] which employs an electrophilic nitrogen source (R_2N^+) and a nucleophile such as an organometallic reagent. Although in the past this approach has received little attention, over the last 10 years or so it has become an effective means for the construction of C(sp^2)-N and C(sp^3)-N bonds. A range of aminating reagents for electrophilic amination have been developed, many of which contain a nitrogen bonded to a more electron-withdrawing atom such as oxygen or a halide. Commonly used electrophilic nitrogen reagents include *O*-substituted hydroxylamines, *N*-haloamines, oxaziridines and oxime esters (Figure 2). A brief overview of some of the key advances in the field of electrophilic amination is given below. In particular, examples of C-N bond forming reactions that utilise *O*-substituted hydroxylamines and oxime esters as electrophilic nitrogen sources will be highlighted.

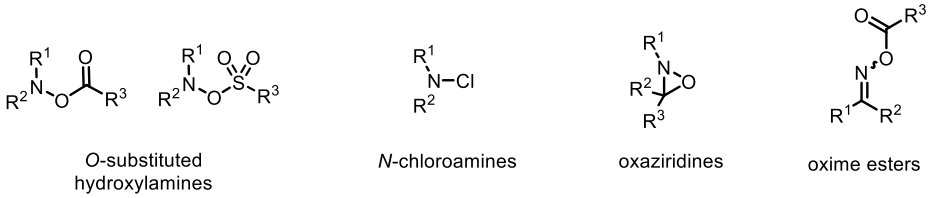


Figure 2 *Common electrophilic aminating reagents.*

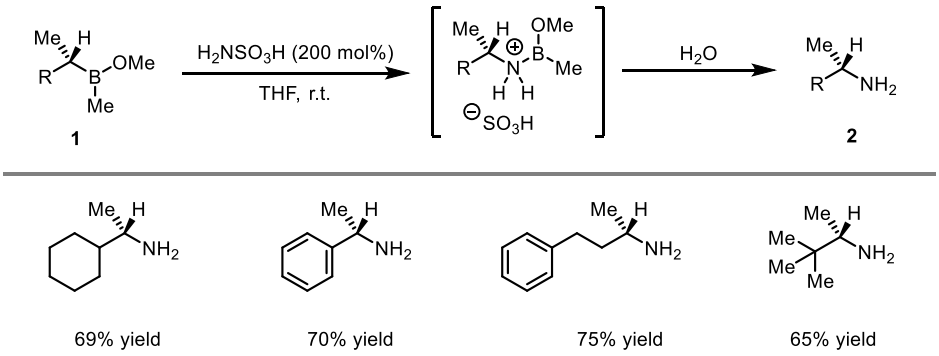
1.2 Electrophilic amination reactions of *O*-substituted hydroxylamines

Due to their versatility *O*-substituted hydroxylamine derivatives such as 2,4-dinitrophenylhydroxylamine (DPH) and hydroxylamine-*O*-sulfonic acid (HOSA) have emerged as effective reagents for the preparation of C-N bonds by electrophilic amination. Generally, these and other related reagents can be accessed using straightforward synthetic methods from cheap and available precursors. For this reason, *O*-substituted hydroxylamines have received attention in transition metal-catalysed electrophilic aminations as well as a number of metal-free electrophilic amination protocols.[I]

1.2.1 Amination of organoboron reagents

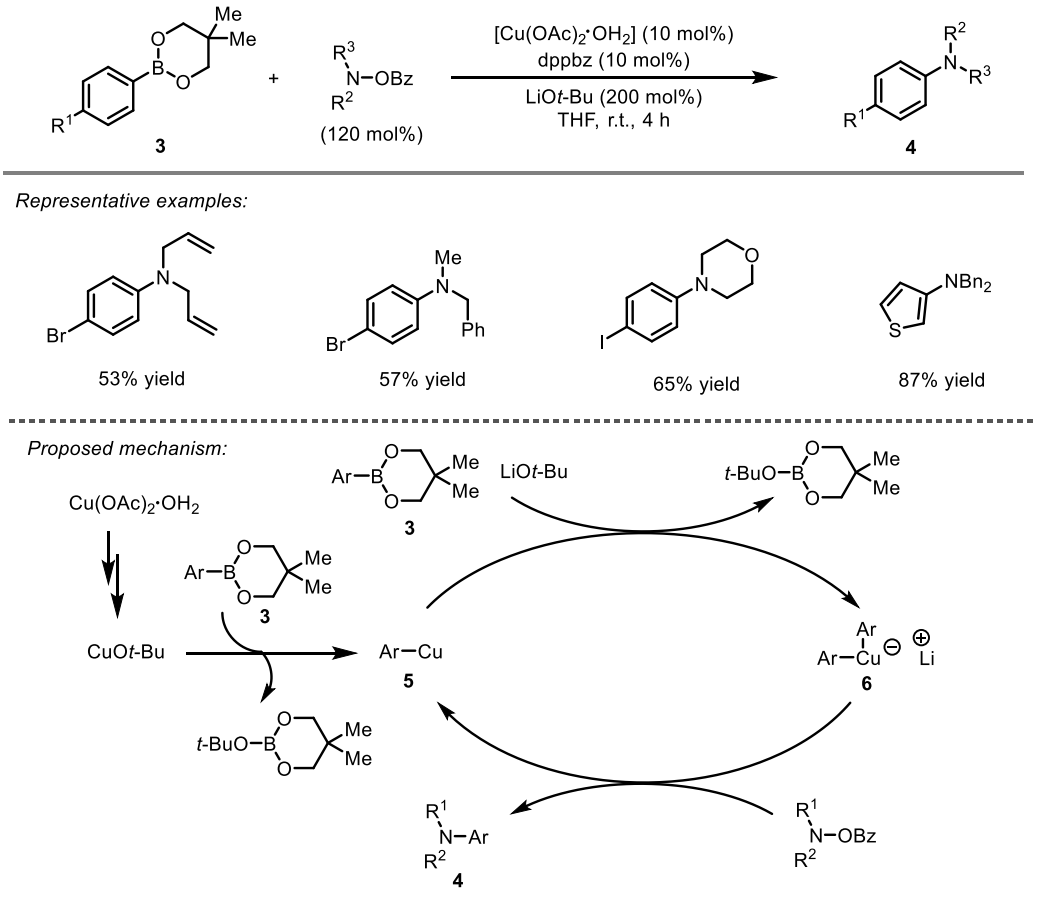
Many different organometallic species have been reported as nucleophiles in electrophilic amination reactions but, organoboron reagents are amongst the most common. The amination of organoboron reagents using hydroxylamine-*O*-sulfonic acid was first reported by Brown and co-workers for the synthesis of primary amines.[18,19] Using enantioenriched borinate esters **1** a range of chiral primary amines **2** were generated in good yields (Scheme 1).[20]

[I] An overview of relevant electrophilic amination approaches to dearomative C-N bond formations and for alkene aziridinations is given in Chapter 2 and Chapter 3 respectively.



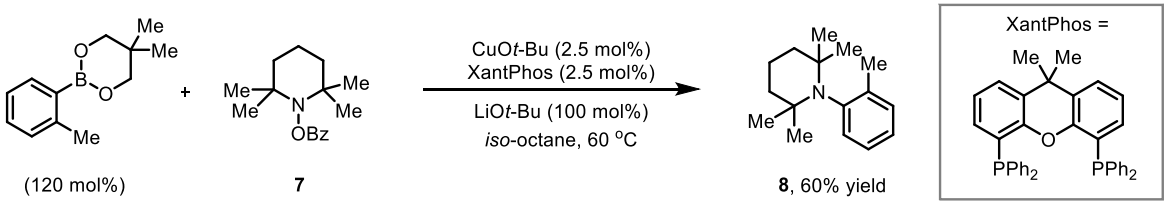
Scheme 1 *Synthesis of chiral amines from enantioenriched borinate esters.*[20]

More recently a number of transition metal-catalysed electrophilic amination reactions of organoboron derivatives have been developed; typically, these approaches involve the use of copper catalysts. In 2012, Miura and Hirano reported a mild procedure for the copper(I)-catalysed coupling of arylboronic esters **3** with *O*-benzoylhydroxylamines for the synthesis of arylamines **4** (Scheme 2).[21]



Scheme 2 *Copper-catalysed amination of organoboronic esters with O-benzoylhydroxylamines.*[21]

The reaction was proposed to proceed by the mechanism illustrated in Scheme 2. Following reduction of Cu(II) and ligand exchange with LiO*t*-Bu, the reactive CuO*t*-Bu species is generated. Transmetalation with boronate **3** forms monoarylcopper species **5** which then reacts with a second equivalent of boronate **3** to generate the more reactive diarylcuprate **6**. Reaction with *O*-benzoylhydroxylamine forms the arylamine product **4** and regenerates the monoarylcopper species **5** to complete the catalytic cycle. Using this approach, a variety of secondary amines underwent arylation in good to excellent yields. The reaction tolerates a variety of functional groups including halides, aldehydes, ketones and esters. A modified version of this transformation was later reported by Lalic and co-workers.[22] This approach utilised a combination of a wider bite-angle ligand, Xantphos and a non-coordinating solvent, *iso*-octane to achieve a more efficient amination of arylboronic esters (Scheme 3). Of particular note was the compatibility of bulky hydroxylamines **7** which enabled the synthesis of highly congested tertiary anilines **8**.

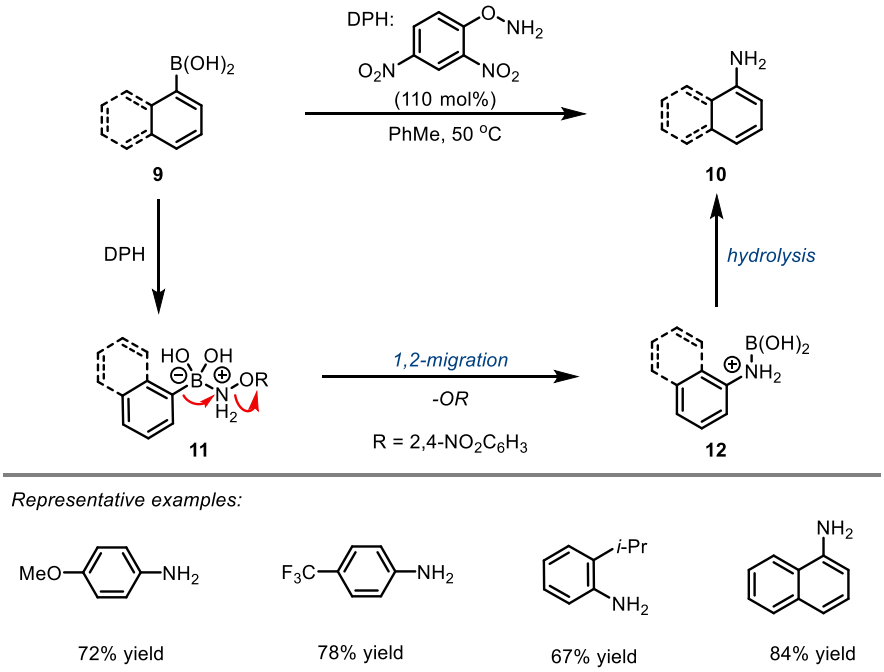


Scheme 3 *Copper-catalysed amination of organoboronic esters with O-benzoylhydroxylamines.*[22]

In 2012 Kürti and Falck reported a transition metal-free electrophilic amination of arylboronic acids for the synthesis of primary aromatic amines (Scheme 4).[23] The authors demonstrated that heating arylboronic acids **9** with *O*-2,4-dinitrophenylhydroxylamine (DPH) as a stoichiometric aminating agent afforded the desired primary anilines **10** in good to excellent yields.[II] The reaction is proposed to proceed *via* formation of intermediate **11** which subsequently undergoes facile 1,2-aryl migration to generate intermediate **12** aided by the strongly electron-withdrawing nature of the dinitrophenyl group. The desired aniline is obtained following subsequent hydrolysis of **12**. The reaction tolerates a variety of functional groups and in particular provides a means of accessing halogenated primary anilines that are otherwise difficult to prepare by transition metal-catalysed amination. Electron-rich arylboronic acids were effective substrates for this transformation whilst electron-deficient arylboronic acids were generally less reactive requiring longer reaction times. More recently,

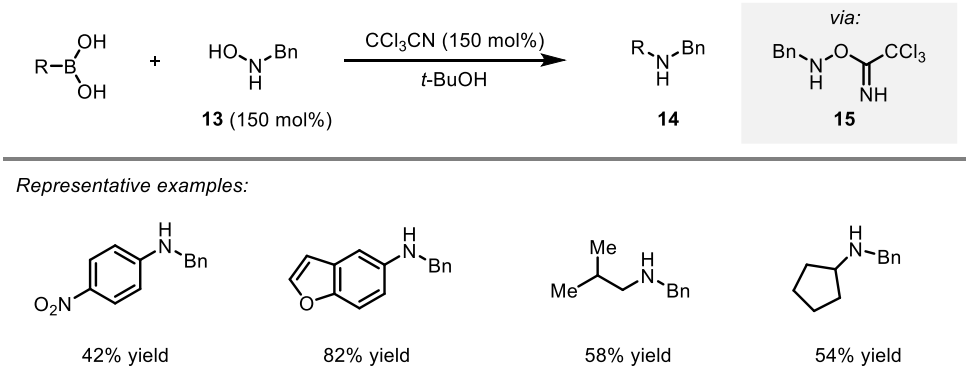
[II] Two examples of transition metal-free electrophilic amination of arylboronic acids[24] and arylboroxines had previously been reported;[25] however, these required harsh reaction conditions (>130 °C).

it has been shown that related hydroxylamine reagents such as hydroxylamine-*O*-sulfonic acid[26] can also facilitate this transformation.



Scheme 4 *Transition metal-free amination of arylboronic acids using O-2,4-dinitrophenylhydroxylamine.*[23]

A related transition metal-free approach for the amination of boronic acids with *N*-alkylhydroxylamines was recently reported by Niu and co-workers (Scheme 5).[27] Using *N*-alkylhydroxylamines **13** in the presence of trichloroacetonitrile the conversion of aryl- and alkylboronic acids to the corresponding secondary amines **14** was achieved. The authors proposed that the reaction proceeds *via* activated intermediate **15**, which acts as the aminating agent in this transformation.[III]

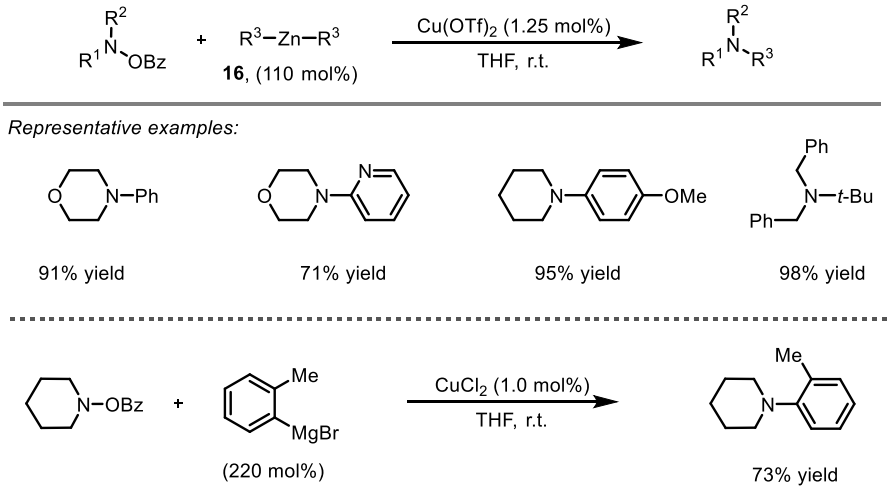


Scheme 5 *Amination of aryl- and alkylboronic acids using N-benzylhydroxylamine* ***13****.*[27]

[III] When **15** was reacted with phenylboronic acid the corresponding aniline was obtained in high yield.

1.2.2 Amination of organozinc and Grignard reagents

In addition to electrophilic amination reactions of organoboronic acids, electrophilic aminations of other organometallic reagents have also been reported. In 2004 Johnson and co-workers pioneered an approach for electrophilic amination of organozinc reagents **16** using *O*-acylhydroxylamines and $Cu(OTf)_2$ (Scheme 6).[28-30] The reaction is compatible with a variety of functional groups and both primary and secondary amines are tolerated.[IV] This methodology was later expanded to include electrophilic aminations of Grignard reagents.[32]



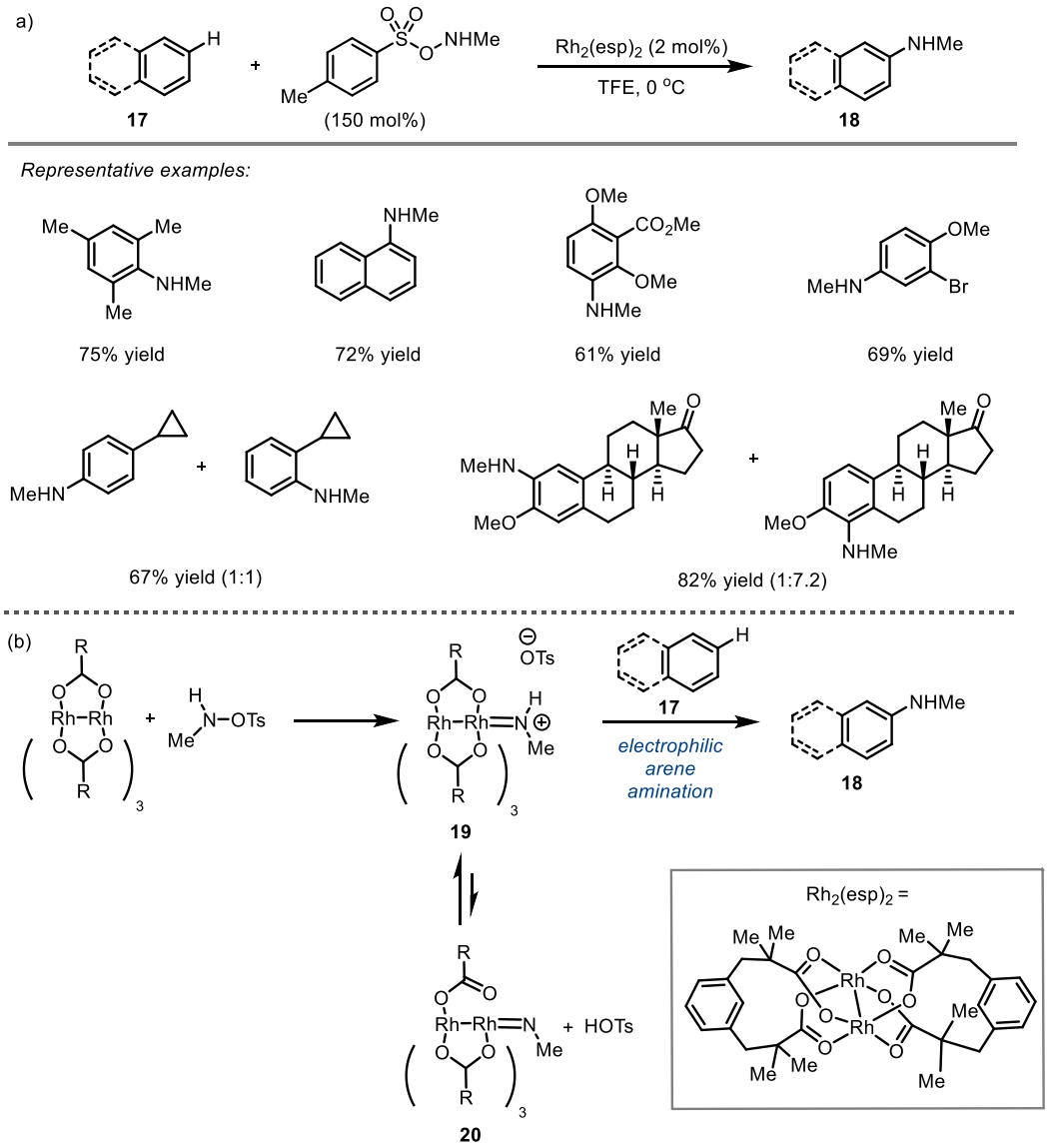
Scheme 6 *Copper-catalysed amination of organozinc and Grignard reagents with O-acylhydroxylamines.*[29,30,32]

1.2.3 Aryl C-H amination of *O*-substituted hydroxylamines

The application of hydroxylamine-derived electrophilic nitrogen sources has also been extended to the direct amination of aryl C-H bonds. Although regioselectivity can be a problem these reactions have the advantage of negating the requirement for stoichiometric organometallic reagents. In 2016 Falck and co-workers reported an efficient protocol for direct aryl C-H amination of arenes **17** using *N*-methyl-*O*-tosylhydroxylamine (TsONHMe) and $Rh_2(esp)_2$ (Scheme 7a).[33] The reaction is compatible with a wide variety of functional groups including halide, hydroxyl, ether, silyl and carbonyl groups and also tolerates potentially sensitive groups, such as benzylic, tertiary and α-keto hydrogens. Epoxides and acetals, however, are not tolerated and were cleaved under the reaction conditions. Many electron-rich arenes underwent efficient amination, but arenes with only electron withdrawing groups such as CF_3 and CN groups were unreactive. A key facet of the reaction is the release of a

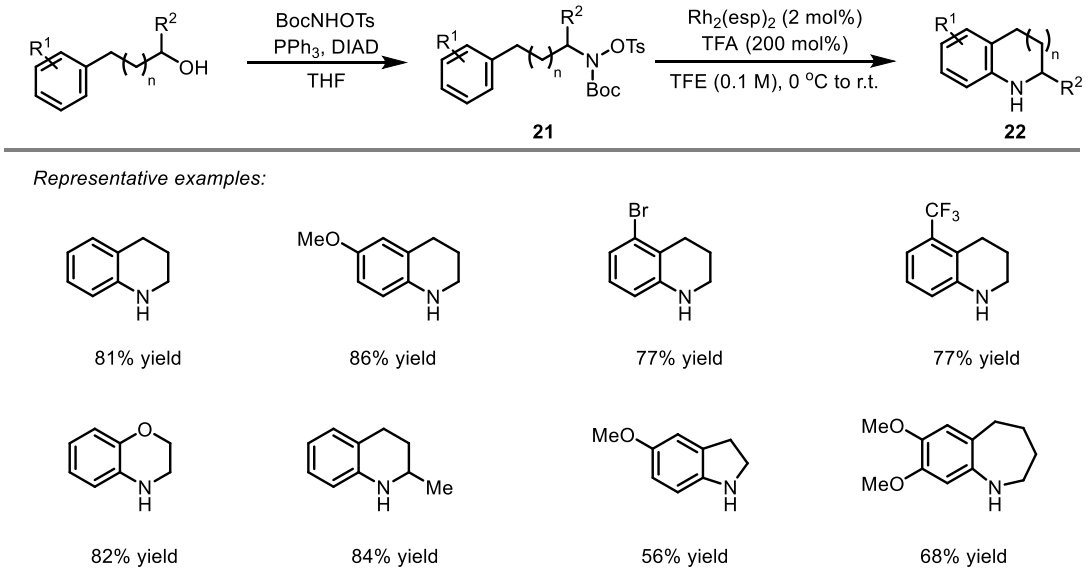
[IV] The same group later reported that $Ni(PPh_3)_2Cl_2$ was also an effective catalyst for this transformation.[31]

stoichiometric amount of tosic acid which protonates the arylamine product **18** and prevents inhibition of the rhodium catalyst. For the mechanism of this transformation the authors propose that initial reaction of the dirhodium catalyst with TsONHMe generates electrophilic intermediate **19** (Scheme 7b). This intermediate exists in an equilibrium with rhodium-nitrenoid species **20**; however, the weakly basic nature of the tosylate anion results in the equilibrium lying in favour of **19**. Intermediate **19** undergoes intermolecular aryl C-H amination with arenes to generate the corresponding arylamine **18**. An alternative mechanism involving a C-H activation pathway was disfavoured based on deuterium labelling studies.



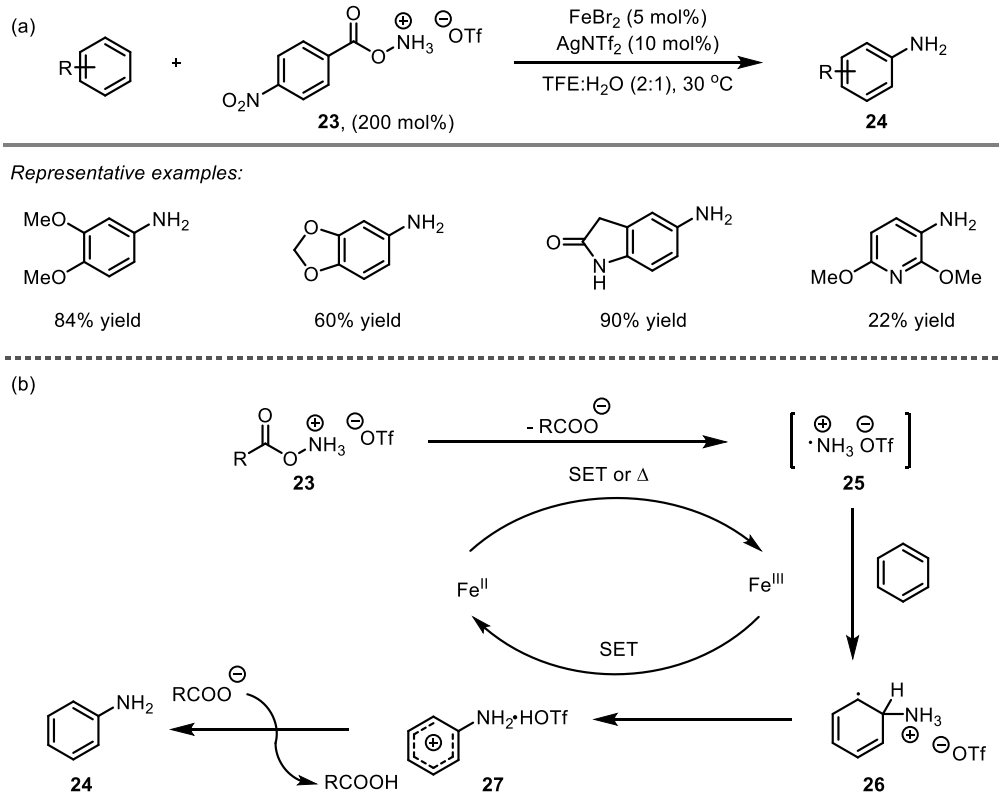
Scheme 7 (a) *Rhodium-catalysed aryl C-H amination. (b) Proposed mechanism for rhodium-catalysed aryl C-H amination.*[33]

As part of the same study the authors reported an intramolecular version of this transformation.[33] For this approach the aminating functionality was introduced in an efficient manner by Mitsunobu alkylation of BocNHOTs with the corresponding alcohol. Through the addition of TFA (200 mol%) to the reaction conditions, *in situ* cleavage of the *N*-Boc group of **21** reveals the activated aminating agent for aryl C-H amination. This protocol enabled the formation of a range of fused aza-bicycles **22** in good to excellent yields (Scheme 8). The same group later reported a copper(II)-catalysed aryl C-H amination using HOSA as the electrophilic nitrogen source.[34]



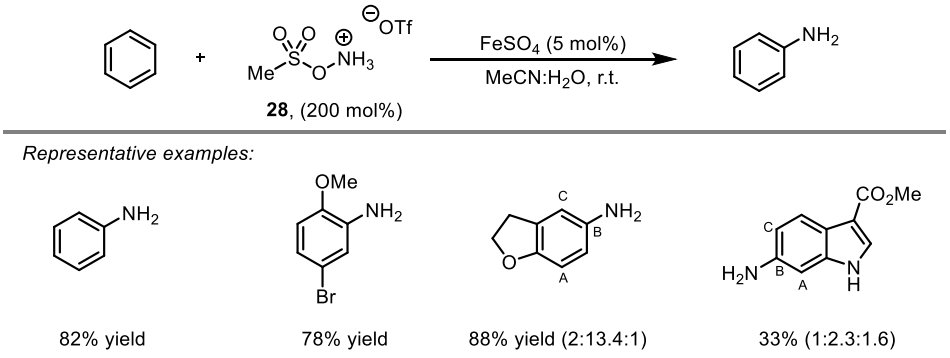
Scheme 8 *Rhodium-catalysed intramolecular aryl C-H amination.*[33]

More recently Jiao and co-workers reported a related iron-catalysed approach to unprotected aryl amines by direct aryl amination.[35] Using *O*-(*p*-nitrobenzoyl)hydroxylammonium salt **23** and $FeBr_2$ a variety of arenes were converted to the corresponding anilines **24** in good to excellent yield (Scheme 9a). The reaction tolerates a wide variety of functional groups and was effective for the late state amination of several bioactive compounds. The reaction is proposed to proceed by the mechanism shown in Scheme 9b. An outer-sphere single-electron transfer from $FeBr_2$ to **23** initiates N-O bond cleavage forming *N*-centred radical intermediate **25**. C-N bond formation occurs between **25** and the arene generating radical intermediate **26**. This intermediate is then oxidised by iron(III) in a single-electron transfer process to form cationic intermediate **27** which is subsequently deprotonated to the desired aryl amine product.



Scheme 9 *(a) Iron(II)-catalysed electrophilic aryl amination. (b) Proposed mechanism of iron(II)-catalysed aryl amination.*[35]

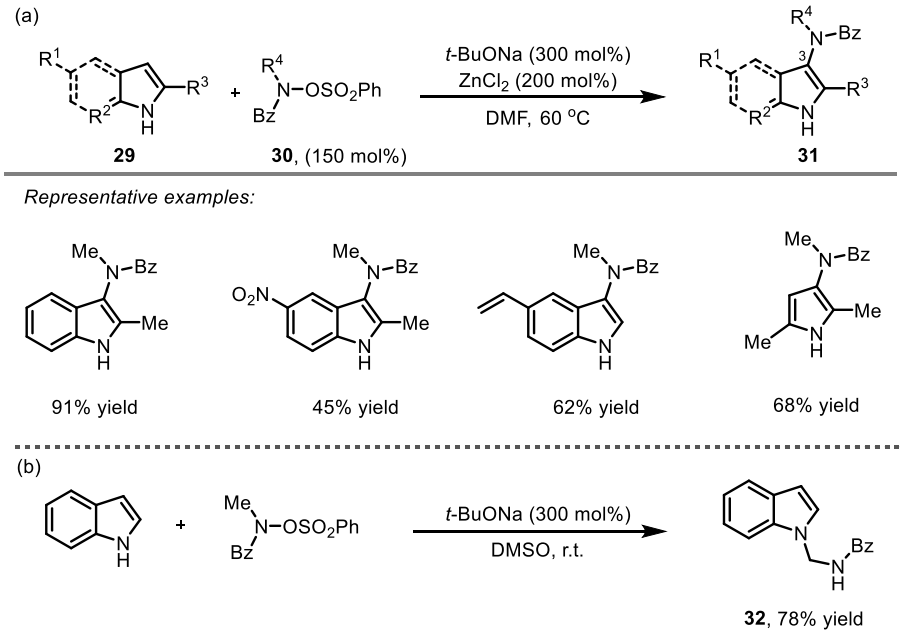
A related protocol for direct aryl C-H amination was reported by Morandi and co-workers using methanesulfonylhydroxylammonium salt **28** and $FeSO_4$ (Scheme 10).[36] This approach enabled the synthesis of primary anilines from a variety of arenes. Heteroarenes such as dihydrobenzofuran and indole also underwent efficient amination. A variety of functional groups on the arene were tolerated including hydroxy, halo and amino groups.[V]



Scheme 10 *Iron(II)-catalysed aryl amination with **28**.*[36]

[V] Recently Ritter and co-workers reported an improved procedure for direct aryl C-H amination using **28** that enabled the amination of electron-poor arenes; previously this was a limitation of this approach.[37]

A further example of direct aryl C-H amination using electrophilic nitrogen reagents was recently reported by Wang and co-workers. The authors demonstrated a direct and selective amidation of indoles **29** to 3-aminoindoles **31** using *N*-[(benzenesulfonyl)oxy]amides **30** in combination with $ZnCl_2$ (Scheme 11a).[38] The reaction was compatible with a variety of electron-rich indoles but was less efficient with electron-poor indoles. In addition to indoles this approach was also effective for the amidation of pyrroles. The use of $ZnCl_2$ was shown to be crucial for selective reaction at the C3-position. In the absence of $ZnCl_2$, the aminal product **32** was formed as the major product through alkylation of the indole nitrogen (Scheme 11b).



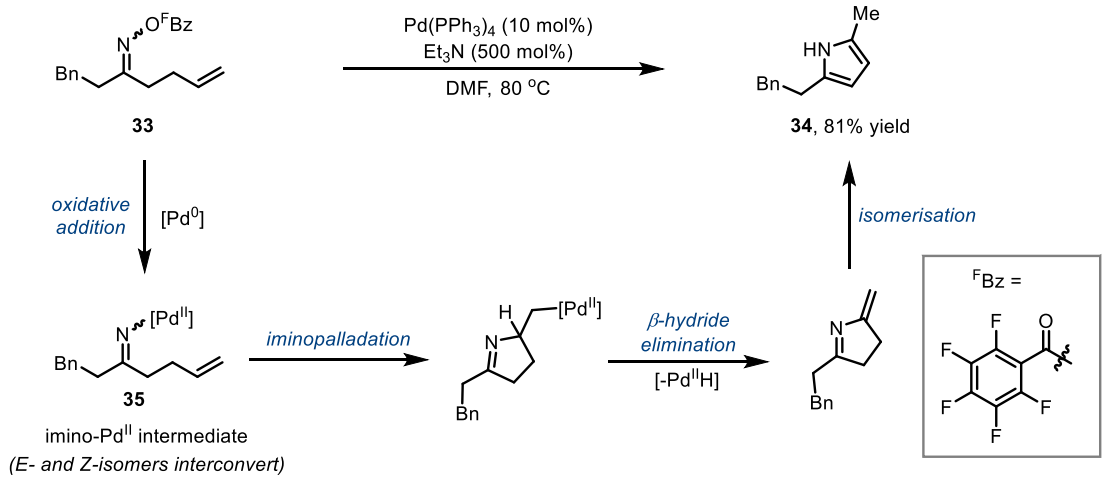
Scheme 11 *(a) Selective 3-amidation of indoles **29** using N-[(benzenesulfonyl)oxy]amides **30**. (b) Formation of aminal **32** in the absence of $ZnCl_2$.*[38]

1.3 Electrophilic amination reactions of oxime esters

1.3.1 The Narasaka-Heck reaction

In 1999 Narasaka and co-workers pioneered the use of *O*-pentafluorobenzoyl oxime esters as electrophilic nitrogen sources in palladium(0)-catalysed cyclisations to generate substituted pyrroles.[39,40] Exposure of γ,δ-unsaturated pentafluorobenzoyl oxime ester **33** to 10 mol% $Pd(PPh_3)_4$ afforded pyrrole **34** in 81% yield (Scheme 12). The reaction was proposed to proceed *via* oxidative addition of palladium(0) into the N-O bond of the oxime ester generating imino-palladium(II) intermediate **35**. From this intermediate, migratory insertion of the alkene into the Pd-N bond occurs and following β-hydride elimination and alkene isomerisation the desired pyrrole product is obtained. With many of the key steps being analogous to the

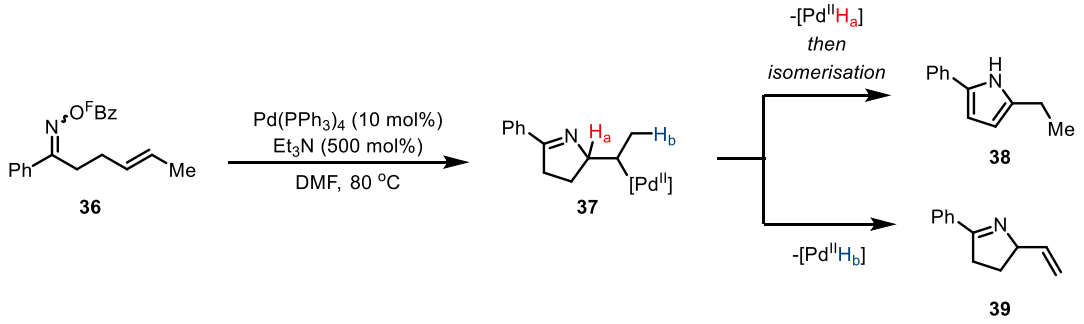
conventional Mizoroki-Heck reaction,[41] the transformation has become known as the 'Narasaka-Heck reaction'. Evidence for the mechanism was provided by the groups of Hartwig[42] and Stahl,[43] who have characterised imino-palladium(II) intermediates related to **35** using crystallography.



Scheme 12 *Palladium(0)-catalysed cyclisation of oxime esters (Narasaka-Heck reaction).*[39]

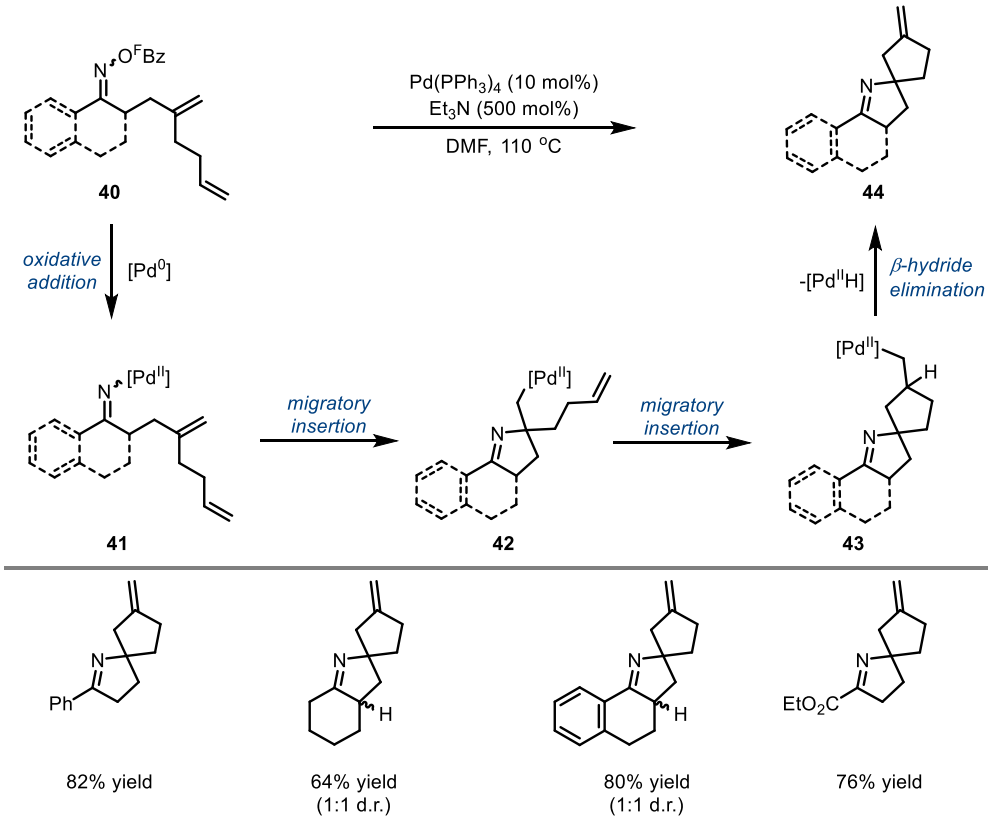
1.3.2 Synthesis of chiral heterocycles *via* aza-Heck reactions

Whilst the Narasaka-Heck reaction is an effective means of generating new C(sp^2)-N bonds, the importance of C(sp^3)-N bonds in natural products and pharmaceuticals has inspired previous work in the Bower group aimed at developing aza-Heck reactions to form C(sp^3)-N bonds, allowing access to chiral products.[44] Prior to this there were only a few examples of aza-Heck reactions in which a C(sp^3)-N bond is retained in the product. One of these examples came from the work of Narasaka who observed that cyclisation of oxime ester **36** afforded a mixture of pyrrole **38** and dihydropyrrole **39** (Scheme 13). This mixture of products arises because alkyl-palladium(II) intermediate **37** can undergo β-hydride elimination in two different directions. Elimination of H_a generates pyrrole **38** (after isomerisation), whilst elimination of H_b affords dihydropyrrole **39**.



Scheme 13 *Competitive formation of dihydropyrrole **39** in the Narasaka-Heck cyclisation of **36**.*[39]

Chiral *N*-heterocycles have also been generated through cascade Narasaka-Heck reactions of oxime esters (Scheme 14).[45, 46] In these transformations, oxime ester **40** undergoes oxidative addition with Pd(0) to form imino-palladium(II) intermediate **41**, which subsequently undergoes cyclisation to alkyl-palladium(II) intermediate **42**. The lack of any β-hydrogens prevents β-hydride elimination from this intermediate which instead undergoes 1,2-insertion with the second alkene to generate alkyl-palladium(II) intermediate **43**. At this point β-hydride occurs to generate spirocyclic imine **44**.[VI]

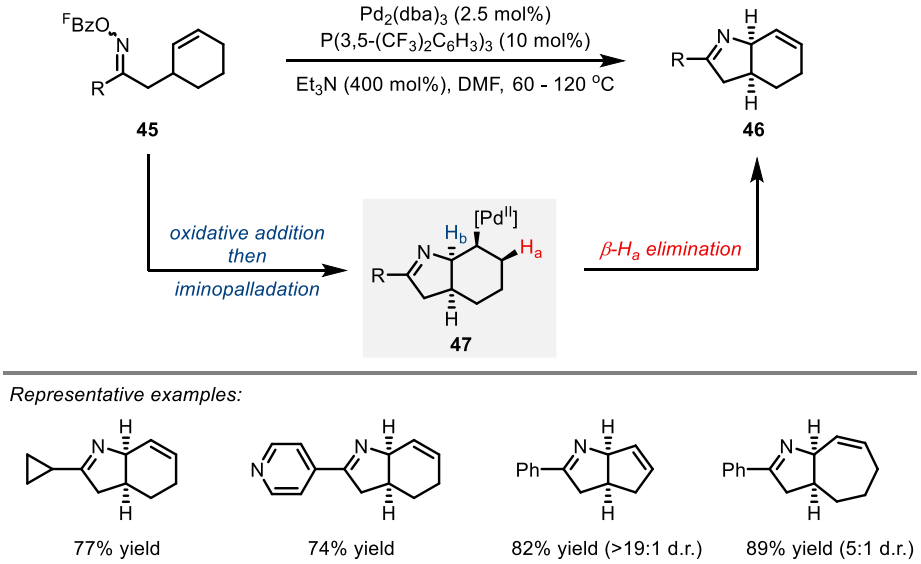


Scheme 14 *Synthesis of spirocyclic imines through a cascade Narasaka-Heck reaction.*[45]

[VI] The use of molecular sieves was required to obtain high yields.

1.3.3 Work at Bristol: aza-Heck reactions to access chiral heterocycles

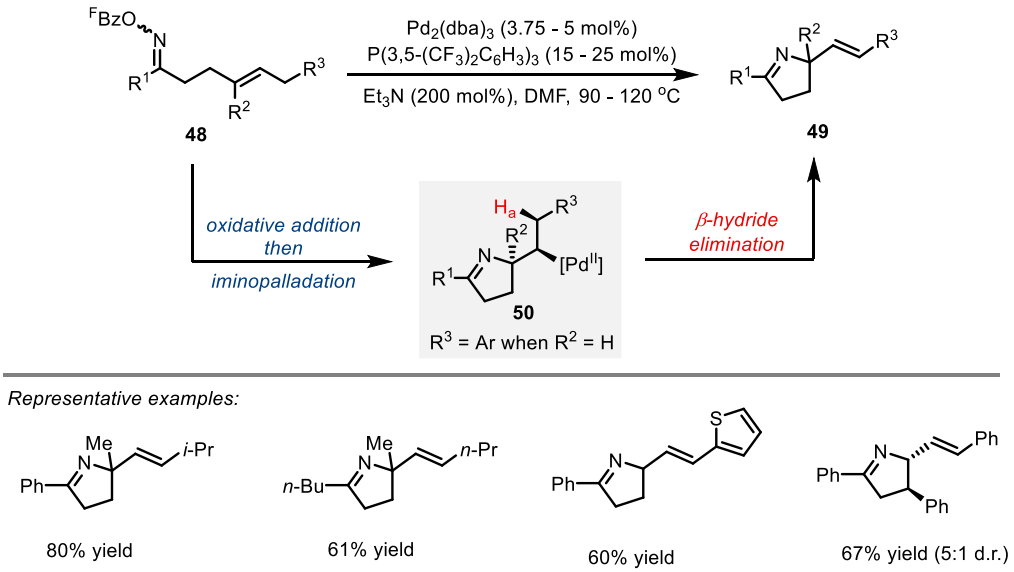
Due to the lack of a general method for the synthesis of chiral *N*-heterocycles by aza-Heck reactions, work has been carried out at Bristol aimed at developing aza-Heck reactions to form C(sp^3)-N bonds. A number of novel classes of aza-Heck reactions which access dihydropyrrole products have been developed. The first of these strategies involved the cyclisation of oxime esters onto cyclic alkenes (Scheme 15).[47] A variety of oxime esters **45** with aryl, alkyl or heteroaryl substituents underwent aza-Heck cyclisation to the corresponding *cis*-fused bicycles **46** in good to excellent yields. In addition, cyclic alkenes with a range of ring sizes from 5 to 7 were effective. Important to the success of this transformation is the use of electron-deficient phosphine ligands, with P(3,5-$(CF_3)_2C_6H_3)_3$ being particularly effective. This is consistent with a study by Hartwig which has shown that alkene migratory insertion into a Pd-N bond is facilitated by bulky and/or electron-deficient ligands.[48] The selectivity for the formation of dihydropyrrole product **46** is rationalised due to H_b in **47** not being available for *syn*-β-hydride elimination.



Scheme 15 *Aza-Heck cyclisation of oxime esters with cyclic alkenes.*[47]

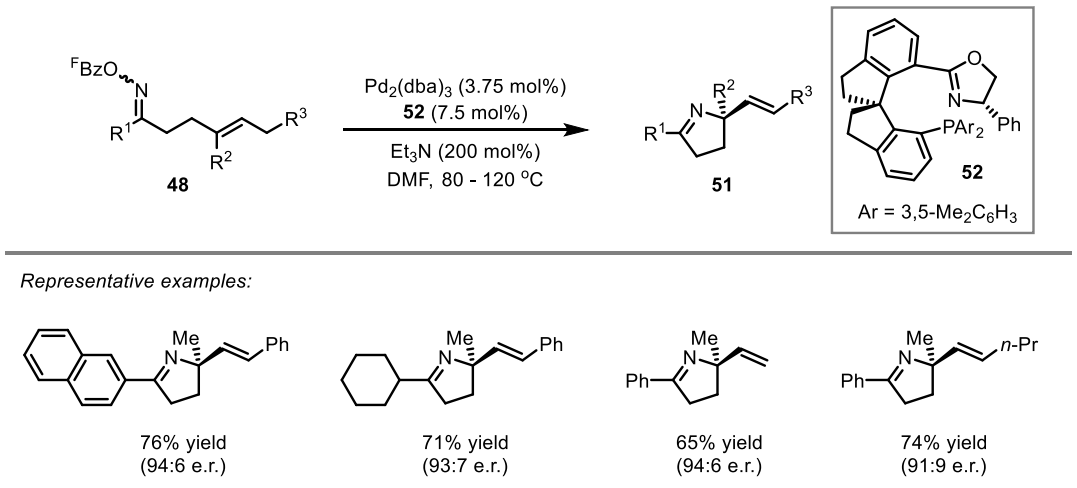
The scope of aza-Heck reactions which access chiral products was further expanded to the use of 1,1-[49] and 1,2-disubstituted[50] alkenes as substrates (Scheme 16). A range of 1,1- and 1,2-disubstituted alkenes **48** cyclised to afford dihydropyrrole products **49** in good yields. For 1,1-disubstituted alkenes ($R^2 \neq H$) only one hydrogen is available for β-hydride elimination which removes any selectivity issues. For 1,2-disubstituted alkenes (R = H) the β-hydride elimination step could lead to either the dihydropyrrole or pyrrole product; however, selectivity

for the dihydropyrrole product was achieved by activating H_a in **50** by incorporating an aryl substituent in the R^3 position.



Scheme 16 *Synthesis of dihydropyrroles by aza-Heck cyclisations of 1,1-disubstituted*[49] *and 1,2-disubstituted alkenes.*[50]

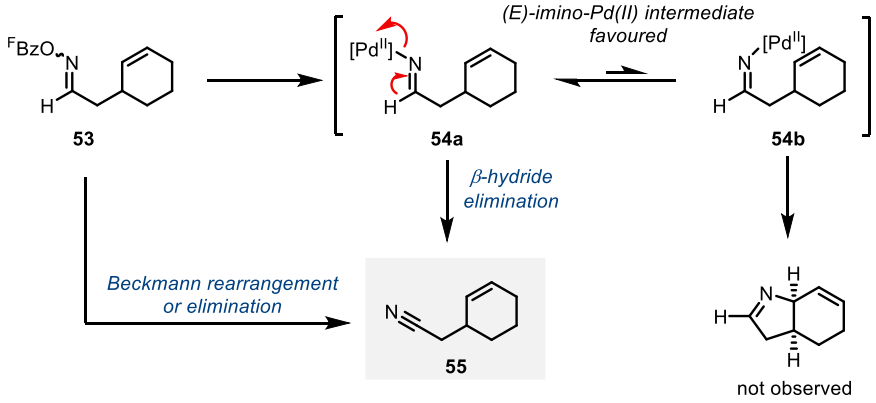
An enantioselective aza-Heck cyclisation for the preparation of enantiopure dihydropyrroles **51** was developed using SPINOL-derived ligand **52** (Scheme 17).[51] This ligand promoted highly enantioselective cyclisations of oxime esters **48**, containing 1,1-disubstituted alkenes, allowing for the efficient preparation of sterically congested tetrasubstituted C-N stereocentres.



Scheme 17 *Palladium(0)-catalysed enantioselective aza-Heck cyclisations.*[51]

One of the major limitations of the Narasaka-Heck reaction is that successful cyclisations typically require a large substituent α to nitrogen and as such aldoximes **53** are generally not suitable substrates. In the case of aldoximes the small size of hydrogen means that formation

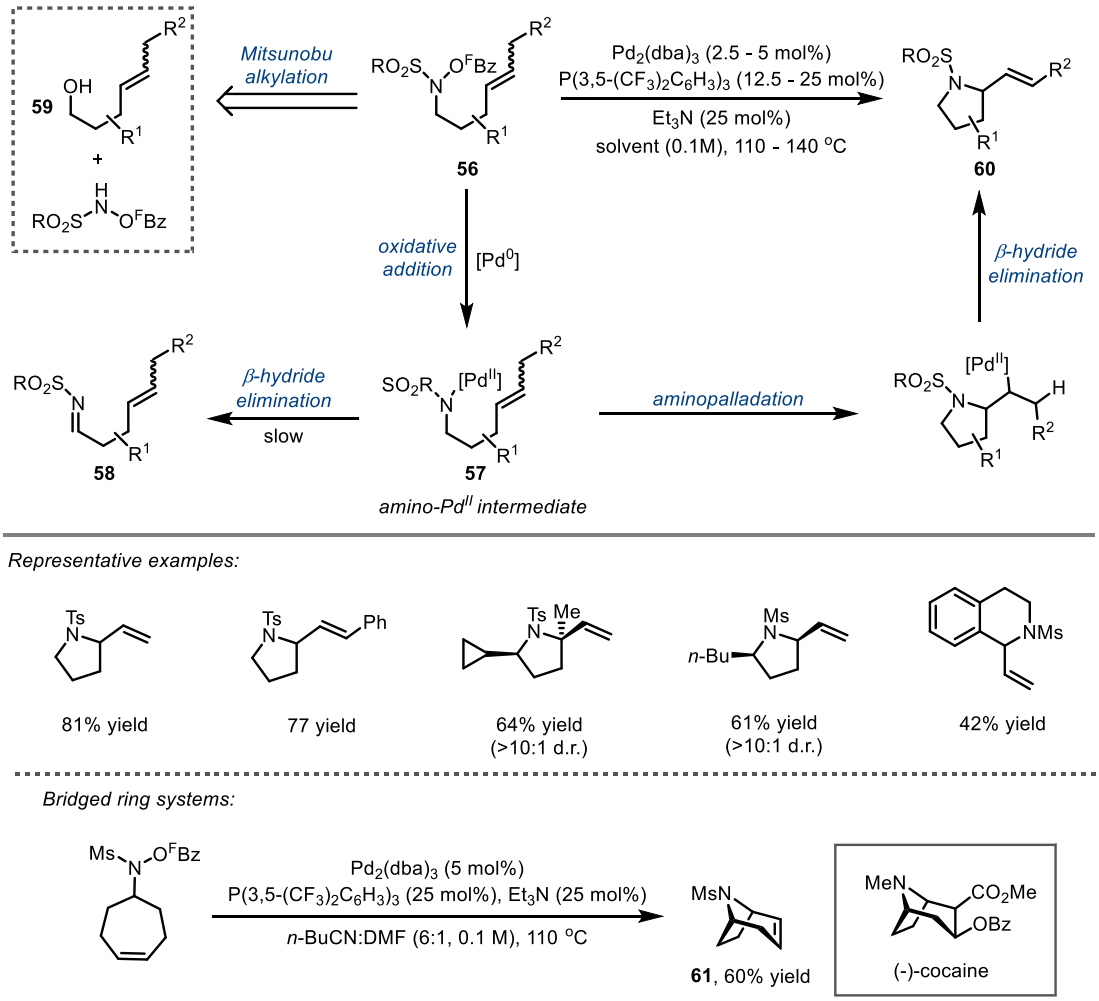
of the reactive (*Z*)-imino-palladium(II) intermediate **54b** is not enforced with the (*E*)-imino-palladium(II) intermediate **54a** being more sterically favourable (Scheme 18). As intermediate **54a** is unreactive the rate of aza-Heck cyclisation is reduced and unproductive β-hydride elimination from **54a** can occur to generate nitrile **55**.[VII]



Scheme 18 *Aldoxime esters are ineffective substrates in aza-Heck cyclisations.*[44]

To overcome this limitation a new class of N-O donors for aza-Heck reactions was sought and to this end *N*-(pentafluorobenzoyloxy)sulfonamides **56** were identified as being suitable substrates (Scheme 19).[52] This approach has a number of advantages over previous aza-Heck reactions. Firstly, substitution in the α-position is not required as β-hydride elimination from the resulting aza-palladium(II) intermediate **57** is slow due to the formation of a less thermodynamically stable imine **58** and thus the aza-Heck pathway dominates. Another benefit of this approach is that the substrates can be easily prepared by Mitsunobu reaction of the corresponding alcohol **59** with an *N*-(pentafluorobenzoyloxy)sulfonamide reagent allowing for an effective approach to transforming homoallylic alcohols to chiral pyrrolidines **60**. The synthesis of bicyclic nitrogen heterocycles such as **61** which make up the core structure of natural products like cocaine was also possible using this methodology.[VIII]

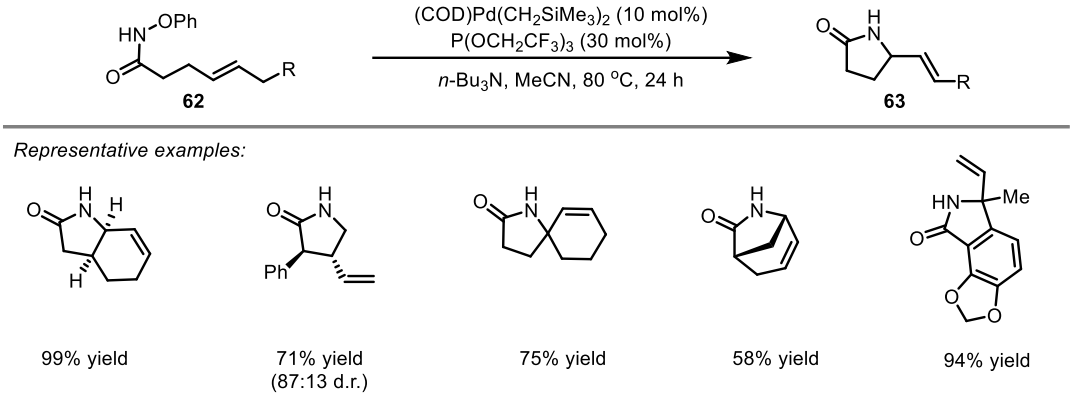
[VII] Alternatively, this could form by Beckmann rearrangement of oxime ester **53**.
[VIII] This approach has since been adapted to the cyclisation of *N*-acyloxycarbamates.[53]



Scheme 19 *Aza-Heck cyclisations of N-(pentafluorobenzoyloxy)sulfonamides.*[52]

1.3.4 Aza-Heck reactions of *O*-phenyl hydroxamates

A related aza-Heck cyclisation of *O*-phenylhydroxamates **62** was reported by Watson and co-workers to afford 5-membered lactams **63** (Scheme 20).[54] The reaction was compatible with a wide range of alkenes including tetrasubstituted alkenes which had not previously been successful in aza-Heck reactions. Although not confirmed the reaction is proposed to proceed by an aza-Heck mechanism. This methodology has also been extended to the synthesis of cyclic ureas.[55]

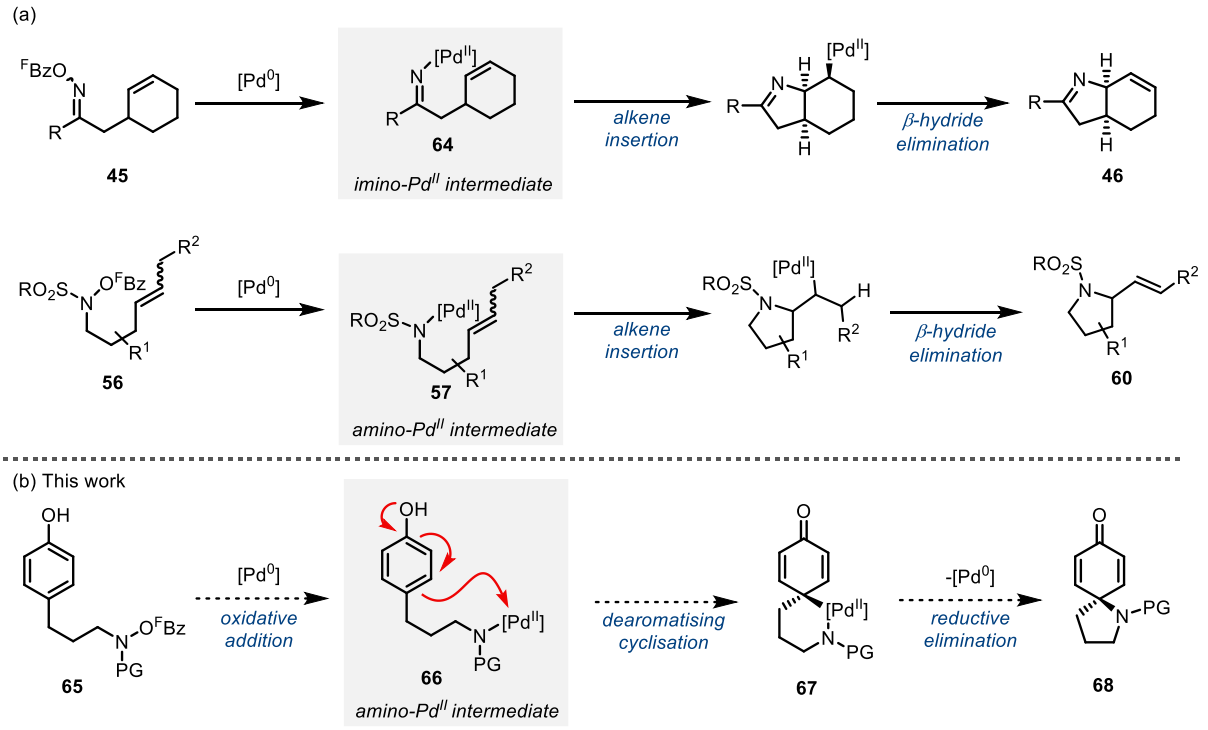


Scheme 20 *Aza-Heck cyclisations of O-phenylhydroxamates.*[54]

1.4 Project objectives

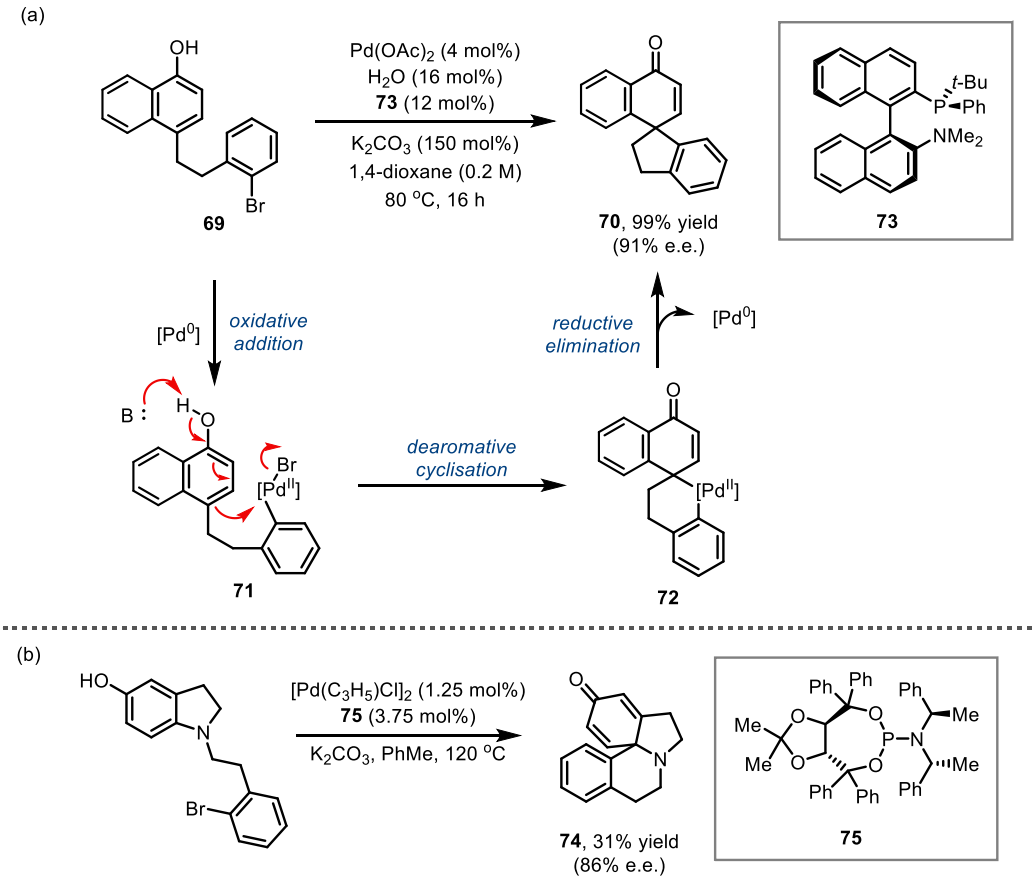
The dearomative amination of aromatic compounds has emerged as a powerful means of converting simple 'flat molecules' into highly functionalised 3-dimensional products. Over the past few decades in the field of drug development there has been an over-reliance on well-established metal-catalysed sp^2-sp^2 cross coupling reactions such as the Suzuki cross-coupling.[56] This has contributed to drug libraries consisting of 'flatter' compounds containing multiple aromatic rings.[57] However, the increasing need to produce more effective drug candidates is seeing a new focus towards the synthesis of more 3-dimensional, saturated compounds which are recognised as more likely to be successful drug candidates than 'flatter' aromatic based compounds.[58] The development of new and efficient dearomative processes to access complex scaffolds is therefore of significant value.

In previous work carried out at Bristol, aza-Heck reactions to access chiral *N*-heterocycles from pentafluorobenzoyl oxime esters[47,49-51] and *N*-acyloxysulfonamides[52] have been developed. These reactions proceed *via* formation of an electrophilic imino- or amino-palladium(II) intermediate such as **64** or **57** (Scheme 21a). It was envisaged that intermediates of this type may be exploited to trigger other C-N bond forming reactions such as dearomatisation reactions as outlined in Scheme 21b. It was proposed that amino-palladium(II) intermediate **66** generated *via* oxidative addition of palladium(0) into the N-O bond of hydroxylamine-derived **65** would induce nucleophilic attack of a pendent arene ring. Reductive elimination from the resulting palladacycle **67** would then afford the dearomatised spirocycle **68** and regenerate palladium(0) to complete the catalytic cycle.



Scheme 21 *(a) Previous work in Bristol: palladium(0)-catalysed aza-Heck reactions.*[47,52] *(b) Proposed palladium(0)-catalysed dearomatising amination reaction.*

Although there appears to be no direct precedent for the use of amino-palladium(II) intermediates like **66** in C-N bond forming dearomatisations, related palladium(0)-catalysed C-C bond forming dearomatisations have been reported. In 2011 Buchwald and co-workers developed a palladium(0)-catalysed arylative dearomatisation of phenols **69** to generate spirocyclohexadienones **70** (Scheme 22a).[59] This process involves generation of an aryl-palladium(II) intermediate **71** *via* oxidative addition of palladium(0) into the aryl-halide bond, followed by nucleophilic attack of the tethered phenol onto the palladium(II) centre. The resulting spirocyclic palladacycle **72** then undergoes reductive elimination to form the desired spirocyclic product. The use of a chiral phosphine ligand **73** enabled an asymmetric variant of this reaction to be developed with high levels of enantioselectivity. A related palladium-catalysed arylative dearomatisation approach was used by You and co-workers for the synthesis of the spirocyclic core of the *Erythrina* alkaloids. Good enantioselectivity for the synthesis of spirocycle **74** was achieved using chiral P-N ligand **75** (Scheme 22b).[60]



Scheme 22 *(a) Palladium(0)-catalysed arylative dearomatisation reaction.*[59]

(b) Palladium(0)-catalysed arylative dearomatisation for the synthesis of the erythrinane skeleton.[60]

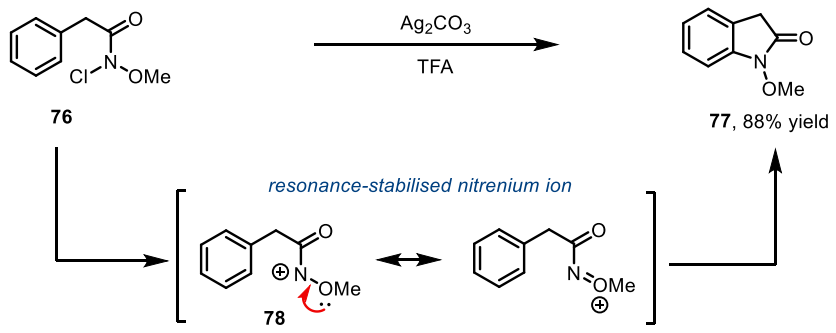
Chapter 2 - Electrophilic nitrogen-promoted dearomatising amination reactions

2.1 Introduction

Before presenting the results in this chapter on the development of an electrophilic nitrogen-enabled dearomatising amination reaction, a brief survey of relevant literature relating to C-N bond forming dearomatisation reactions will be given. In particular, methods that harness the use of electrophilic nitrogen sources will be discussed; however, a conceptually distinct, oxidative amination approach pioneered by Ciufolini, in which nucleophilic nitrogen sources are used, will also be highlighted.

2.1.1 Electrophilic nitrogen-promoted dearomatising amination reactions

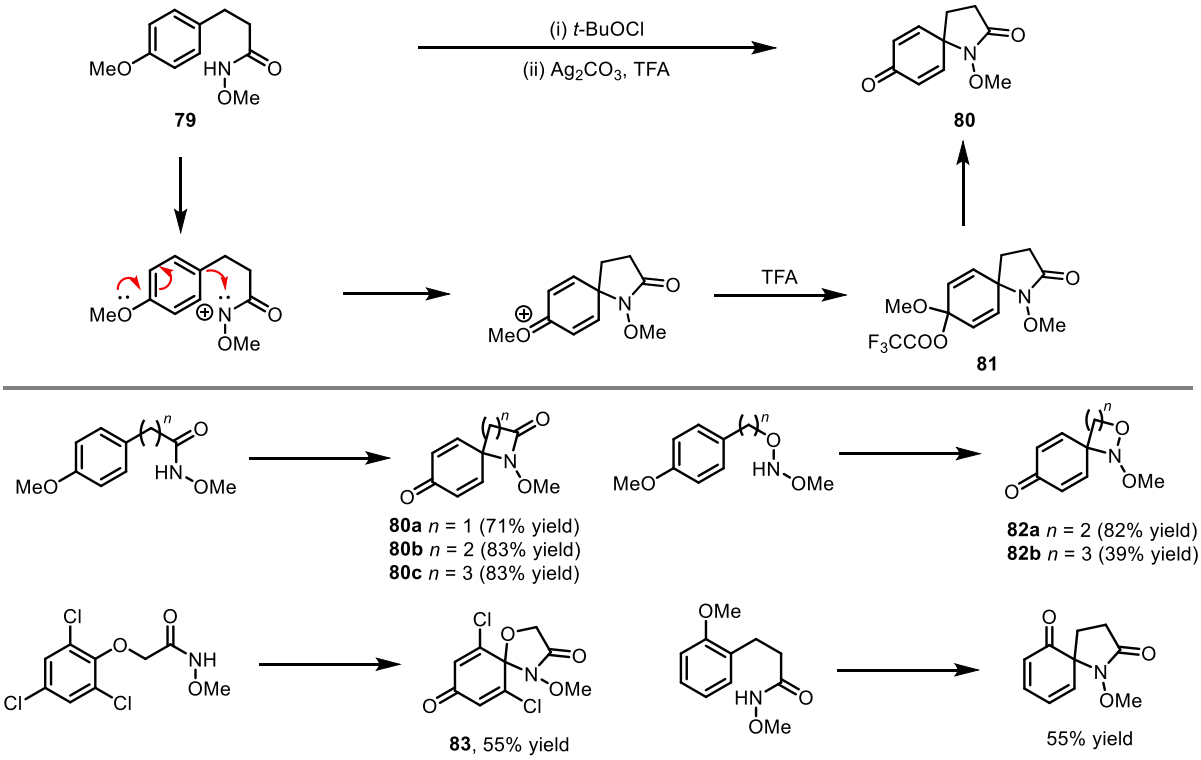
In 1984 Kikugawa[61] and Glover[62] independently reported the conversion of *N*-chloro-*N*-methoxyamides **76** into lactams **77** by electrophilic aromatic substitution (Scheme 23). These transformations invoked the intermediacy of *N*-methoxynitrenium ions **78**, which were generated by treatment of **76** with silver salts in TFA or benzene. These highly electrophilic species induced cyclisation with the pendent arene to generate lactam products. Efficient cyclisation *via* a nitrenium ion was attributed primarily to the stabilising effect of the oxygen lone pair of the *N*-alkoxy group through electron donation, which enables the nitrenium ion to be long-lived enough to undergo cyclisation.[IX] As expected, based on an electrophilic aromatic substitution mechanism, cyclisation proceeded efficiently with electron-donating or mildly electron-withdrawing substituents on the arene; however, strongly electron-withdrawing groups resulted in low yields.



Scheme 23 *Nitrenium ion-induced aryl amination of N-chloro-N-alkoxyamides.*[61]

[IX] This was supported by MNDO molecular orbital calculations.

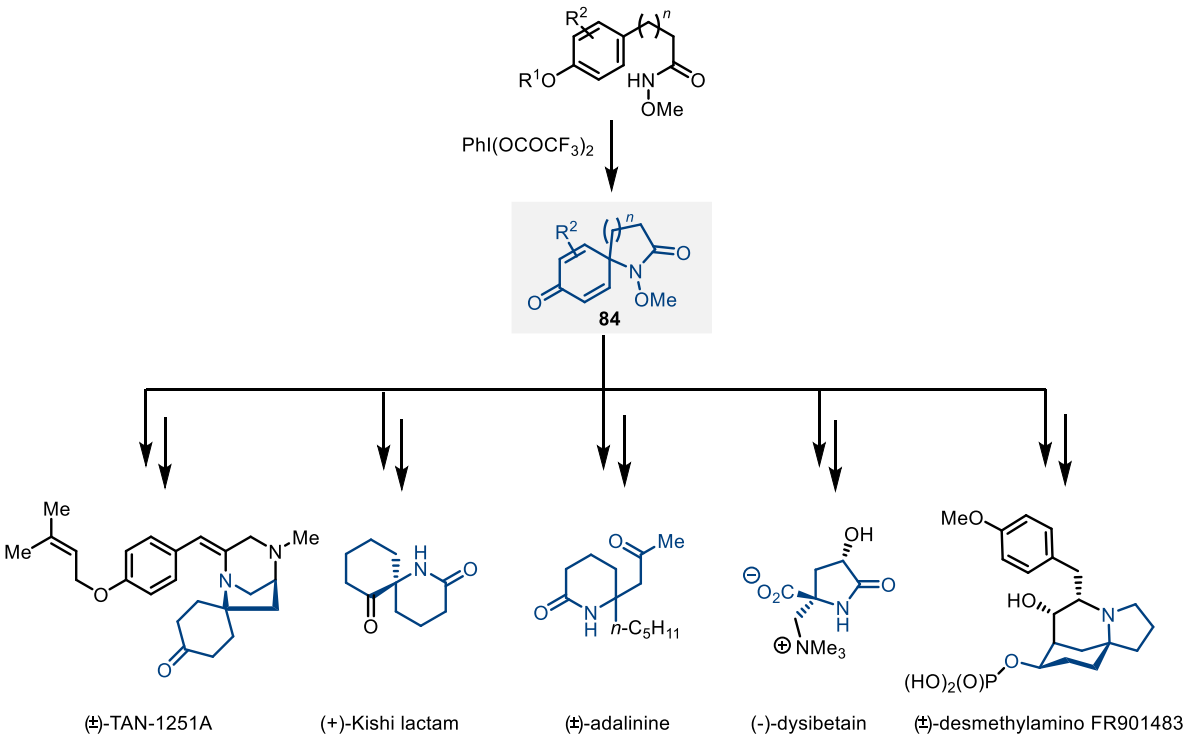
Both Kikugawa[63] and Glover[64] expanded the application of nitrenium ion-induced cyclisations to the synthesis of spirolactams through a dearomative transformation (Scheme 24). Using *N*-chloro-*N*-methoxyamides **79** with pendent *ortho*- or *para*-methoxyphenyl groups, the generation of spirolactams **80** was achieved through intramolecular *ipso*-attack of the resulting nitrenium ion intermediate. The electron-donating methoxy group increases electron density at the *ipso*-position leading to cyclisation to intermediate **81** which then undergoes hydrolysis to the spirodienone compound. By using this approach, Kikugawa demonstrated the synthesis of a variety of spirolactams, including β-, γ- and δ-lactams **80a-c**.[63] The synthesis of spirocyclic oxazetidines **82a-b** was also possible by this method, whilst spirocyclisation also occurred with a *para*-chloro substituent in place of a methoxy group to give **83** in good yield.



Scheme 24 *Synthesis of spirodienones by nitrenium ion-induced cyclisation.*[63]

These 'first generation' nitrenium ion-induced dearomative cyclisations relied on the generation of nitrenium ions from *N*-chloro-*N*-alkoxyamides. These were in turn prepared by reaction of the corresponding *N*-alkoxyamides with *t*-BuOCl. However, the use of *t*-BuOCl is not ideal due to environmental factors and so an improved route to *N*-alkoxynitrenium ions was developed by Kikugawa, which involved the direct oxidation of *N*-alkoxyamides with hypervalent iodine reagents such as [bis(trifluoroacetoxy)iodo]benzene (PIFA).[65] Using this improved protocol, Wardrop and co-workers harnessed the reactivity of nitrenium ion

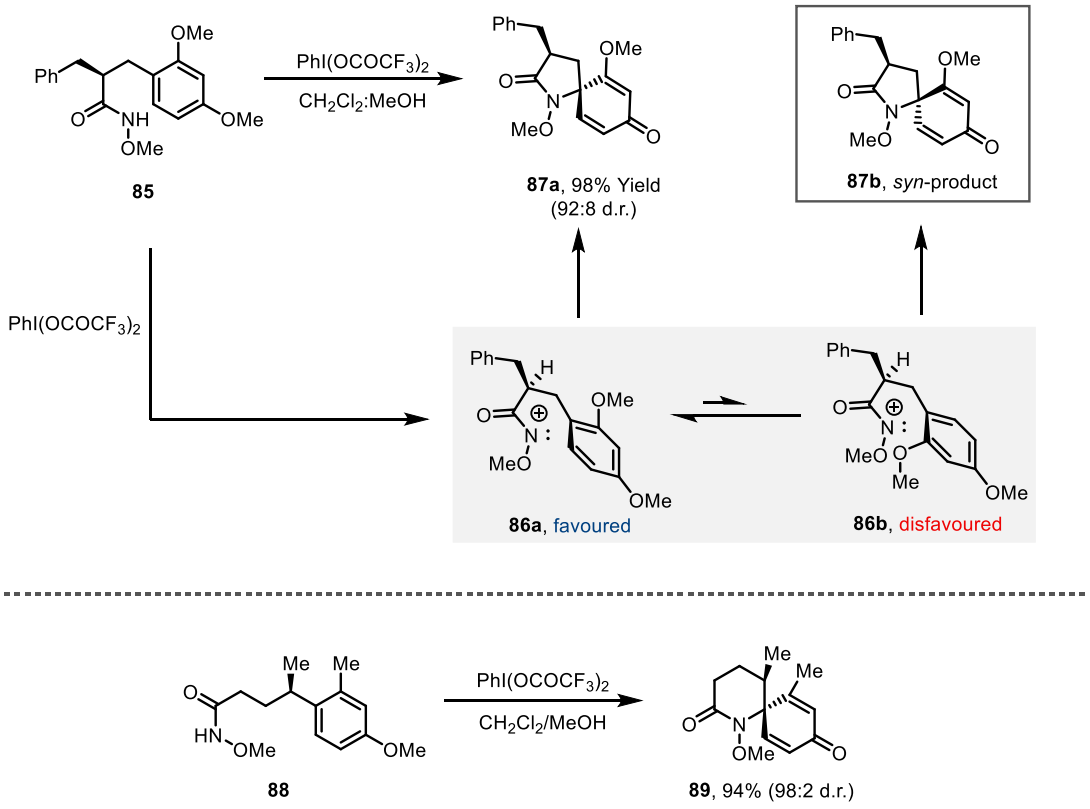
intermediates in a number of natural product syntheses. In a series of reports, nitrenium ion-induced C-N bond forming dearomatisations of phenol derivatives were used as key steps in the total syntheses of (-)-TAN1251A,[66] (±)-adalinine,[67] (+)-Kishi lactam,[68] (-)-dysibetaine[69] and (±)-desmethylamino FR901483 (Scheme 25).[70] In each case the reactive nitrenium ion **84** was generated from the corresponding *N*-methoxyamide using PIFA before undergoing dearomative cyclisation. This work highlights the scope of dearomatising amination reactions for accessing a wide range of natural products.



Scheme 25 *Application of nitrenium ion-induced spirocyclisation in natural product synthesis.*[66-70]

As part of the same group's studies into dearomative cyclisations, stereoselective spirocyclisations of α- and β-substituted 3-(methoxyphenyl) propiohydroxamates were reported.[71,72] Until this point substrates used in spirocyclic cyclisations to afford hexa-2,5-dienones typically contained an arene with a plane of symmetry and as such led to the formation of a non-stereogenic centre. However, if the arene is instead substituted in a way that breaks the symmetry, then the π-faces become enantio-/diastereotopic and a new stereogenic centre is formed upon spirocyclisation. Wardrop and co-workers harnessed this to carry out spirocyclisations with high levels of diastereoselectivity. For example, reaction of α-substituted *N*-methoxyamide **85** with PIFA afforded the spirocycle with complete stereoselectivity for the *anti*-product **87a** (Scheme 26).[71] The selective formation of the *anti*-product was rationalised by the preference of the reaction to proceed *via* transition state

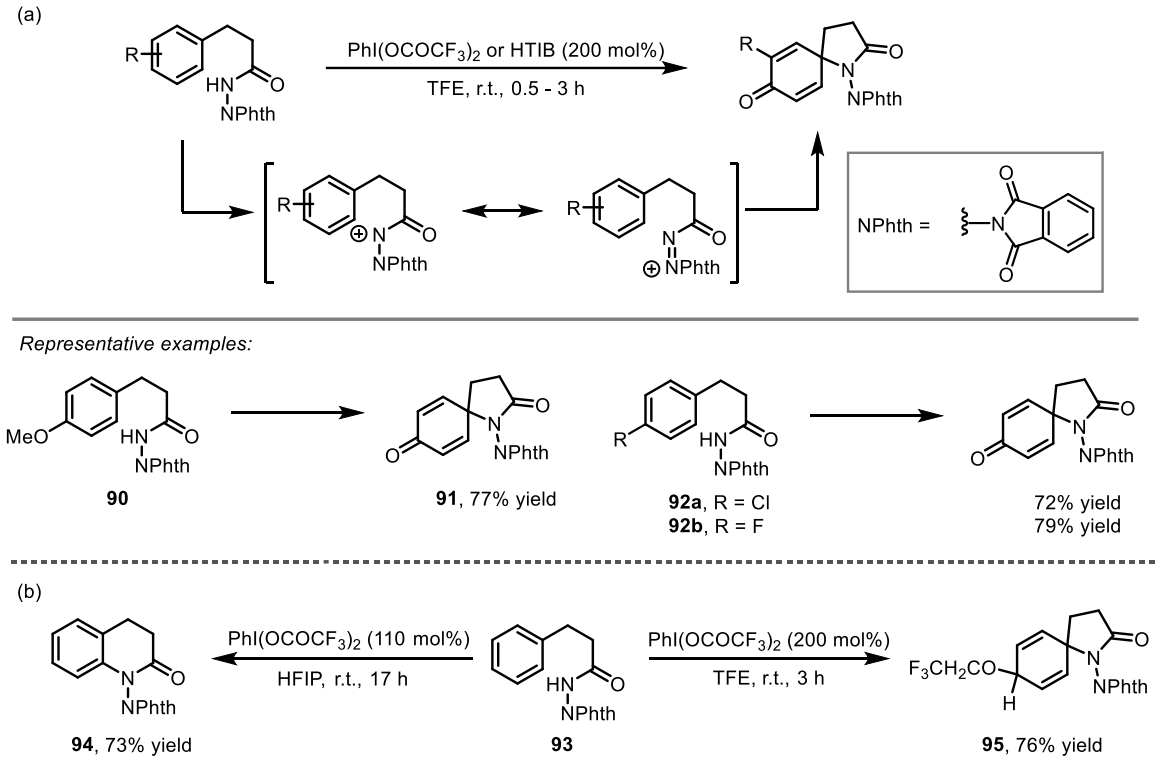
86a. Cyclisation *via* transition state **86b**, which leads to the *syn*-product **87b**, is disfavoured due to unfavourable steric interactions between the benzyl substituent on the side chain and the methoxy substituent on the aromatic ring. This transformation was also extended to 6-ring cyclisations: *N*-methoxyamide **88** was converted to δ-lactam **89** in high yield and excellent diastereoselectivity.[72]



Scheme 26 *Nitrenium ion-induced diastereoselective spirocyclisations.*[71,72]

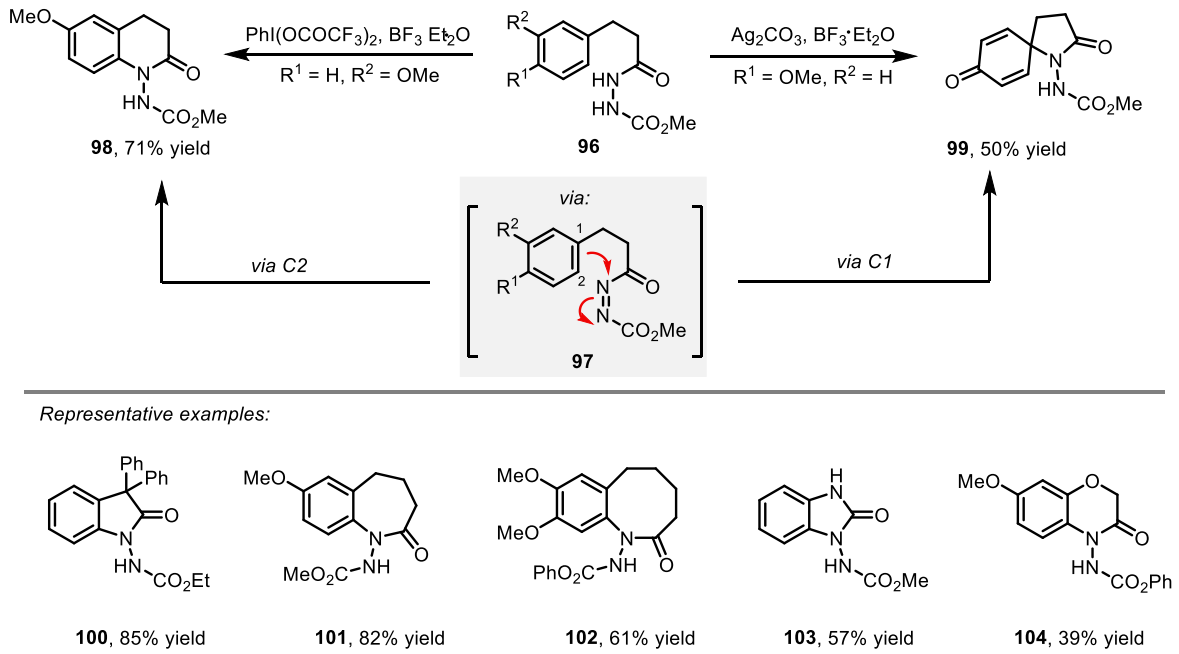
The nitrenium ion intermediates described thus far rely on electron-donating *N*-alkoxy groups for stabilisation; however, other stabilised nitrenium ion-induced cyclisations have also been explored. In 2003 Kikugawa and co-workers reported the use of *N*-phthalimido-*N*-acylnitrenium ions as a new class of electrophilic intermediates. These were used to carry out electrophilic aromatic substitutions as well as dearomative spirocyclisations.[73] Treatment of *N*-acylaminophthalimide **90**, containing a *para*-methoxy group, with PIFA in TFE afforded spirocycle **91** in 77% yield (Scheme 27a). In addition to a *para*-methoxy substituent, substrates containing halogen substituents, such as chloro- or fluoro-groups in the *para* position (**92a** and **92b**), also underwent efficient spirocyclisation. Whilst the reaction of unsubstituted phenyl substrate **93** with PIFA in HFIP led to the expected benzannulated product **94**, when TFE was used as the solvent the unexpected formation of spirocyclic product **95** was also observed (Scheme 27b). The formation of **95** can be attributed to the attack of the

nitrenium ion formed from **93** on the *ipso*-carbon followed by trapping with a molecule of solvent.



Scheme 27 (a) *Spirocyclisation of para-substituted N-acylaminophthalimides. (b) Effect of solvent on the cyclisation of unsubstituted phenyl system* ***93****.*[73]

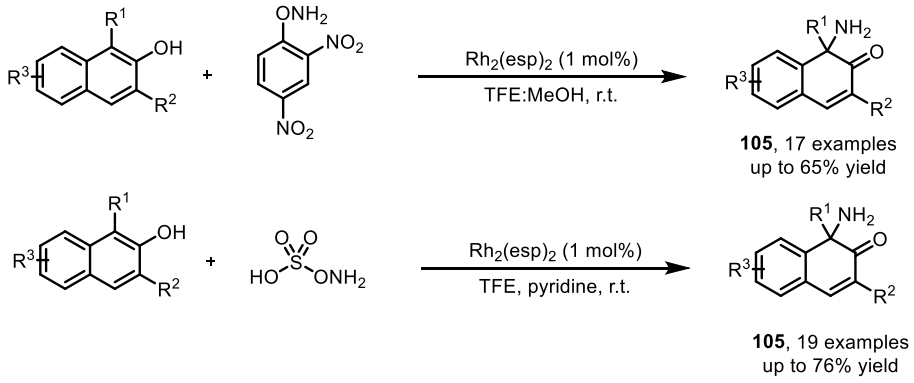
A related electrophilic amination of aromatic compounds was reported in 1994 by Prabhakar and co-workers; this approach harnessed the electrophilicity of azodicarbonyl compounds **97**.[74,75] These highly electrophilic species were generated by oxidation of the corresponding bishydrazide **96** and underwent Lewis acid-promoted cyclisation with pendent arenes to generate *N*-substituted amino dihydrocarbostyrils **98** or spiro-γ-lactams **99** depending on the nature of substitution on the aryl ring (Scheme 28). Other *N*-heterocycles were also accessed by this method, including oxindoles **100**, benzazepinones **101**, benzazocinones **102**, benzimidazolones **103** and benoxazinones **104**. However, a limitation of this reaction is that it is restricted to the cyclisation of highly electron rich arenes.



Scheme 28 *Intramolecular electrophilic amination of azodicarbonyls.*[74,75]

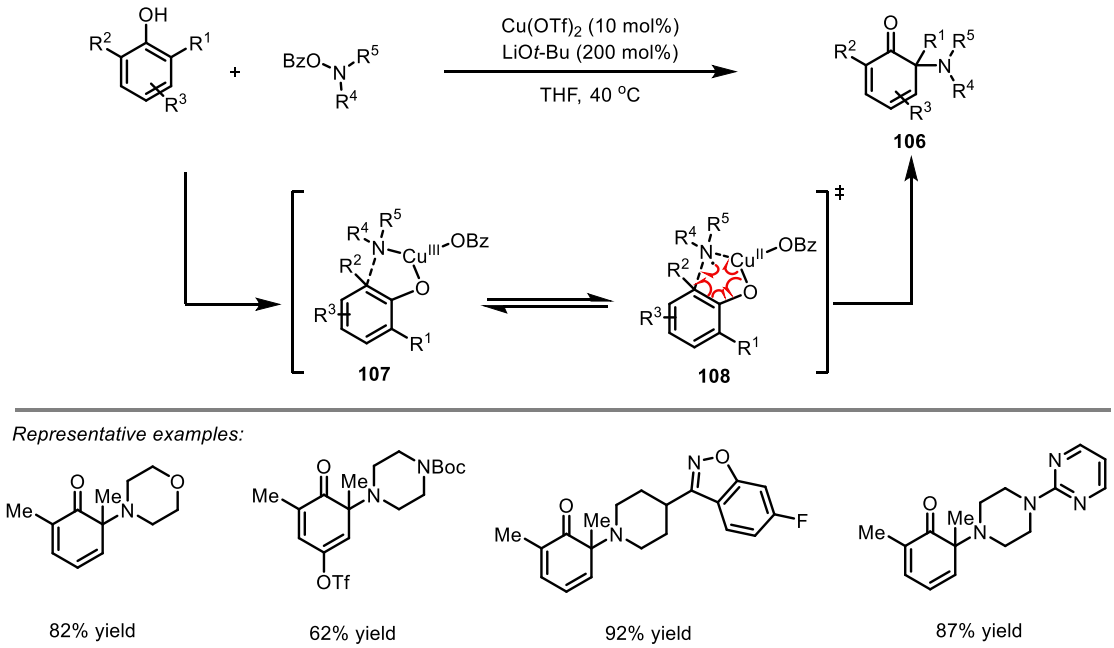
It is also pertinent to highlight several recent reports of transition metal-catalysed dearomatising amination reactions using electrophilic nitrogen sources, these were published after the studies presented in this chapter were completed. These examples rely on the generation of metal-nitrenoids which act as the reactive electrophile.

You and co-workers developed an efficient rhodium-catalysed intermolecular aminative dearomatisation of 2-naphthols to generate a variety of unprotected α-amino-β-naphthalenones **105** (Scheme 29).[76] In this transformation *O*-2,4-dinitrophenylhydroxylamine (DPH) was utilised as the aminating agent; however, the application of DPH is limited by its high price and safety concerns and so the authors subsequently reported a procedure where DPH was replaced with the safer electrophilic nitrogen source hydroxylamine-*O*-sulfonic acid (Scheme 29).[77]



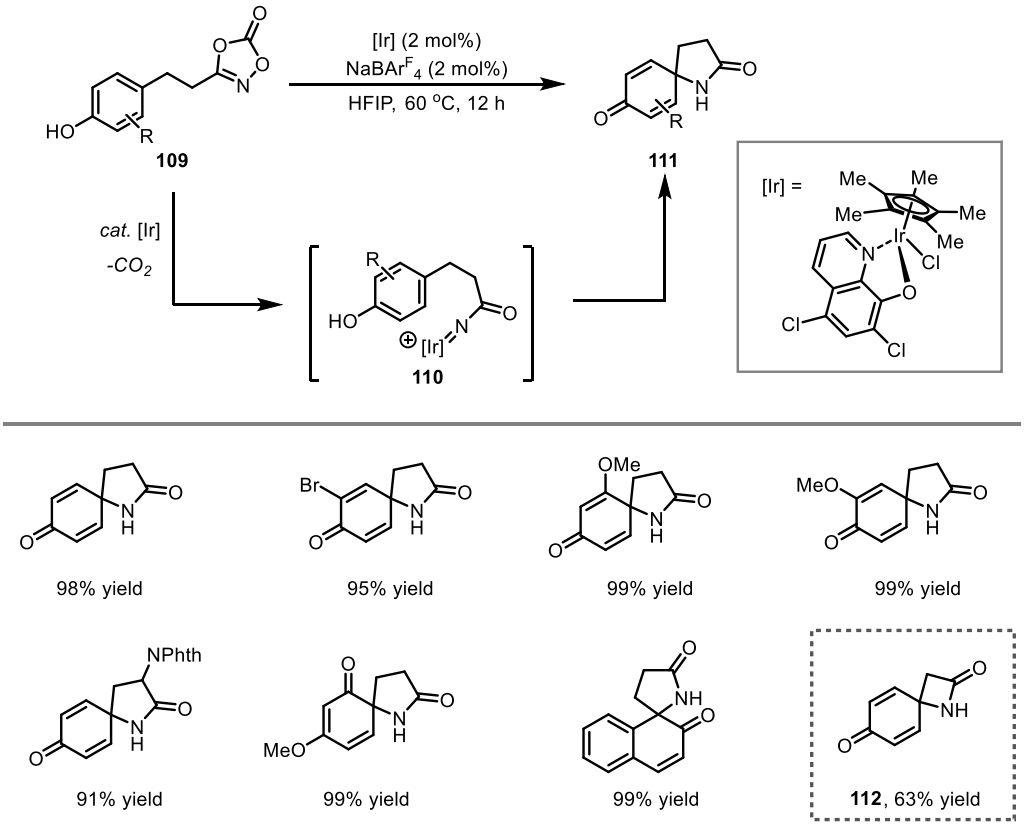
Scheme 29 *Rhodium-catalysed dearomative amination of naphthols.*[76,77]

Wang and co-workers reported a copper-catalysed dearomative amination of phenols with *O*-benzoylhydroxylamines (Scheme 30). In this transformation C-N bond formation occurs exclusively at the *ortho*-position to afford aminocyclohexa-2,4-dienones **106** under very mild conditions.[78] To rationalise the observed *ortho*-selectivity the authors proposed a mechanism as shown in Scheme 30. Oxidative addition of the amine electrophile with a copper(I)-phenol species generates amino-copper(III) complex **107**. This species may equilibrate to the corresponding *N*-centred radical/copper(II) complex **108**, and then either **107** or **108** may undergo C-N bond formation by an inner-sphere pseudo-five-membered cyclic transition state. The reaction tolerates a wide variety of cyclic *O*-benzoylhydroxylamines, such as morpholines, piperidines and piperazines.



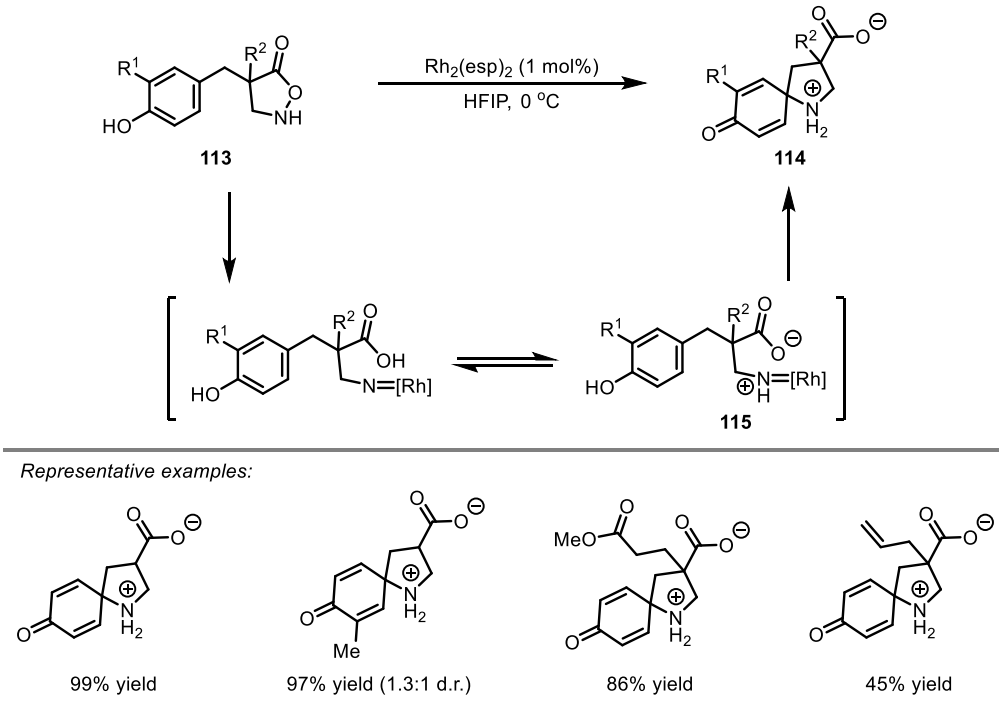
Scheme 30 *Copper-catalysed dearomative amination of phenols.*[78]

Two more related reports of metal-nitrenoid-induced C-N bond forming dearomatisation of phenols have also very recently been reported by Chang[79] and Shibasaki.[80] Chang and co-workers reported an approach to spirolactams *via* an iridium-nitrenoid intermediate **110** which was generated from dioxazolones **109** (Scheme 31).[79] Using this method, a variety of unprotected five-membered spirolactams **111** were accessed in excellent yields and the scope was also extended to the more challenging synthesis of a four membered spirolactam **112**.



Scheme 31 *Iridium-catalysed intramolecular dearomatising amination.*[79]

Shibasaki and co-workers reported a rhodium-nitrenoid-promoted dearomatising amination of *O*-acylhydroxylamines **113** to access spirocycles **114** (Scheme 32).[80] The reaction is proposed to proceed *via* the formation of a rhodium-nitrenoid species **115** with concomitant cleavage of the N-O bond. The advantage of this transformation is that by using cyclic isoxazolidin-5-ones as substrates the oxygen leaving group is retained, eliminating by-product waste.



Scheme 32 *Rhodium-catalysed dearomative amination of O-acylhydroxylamines.*[80]

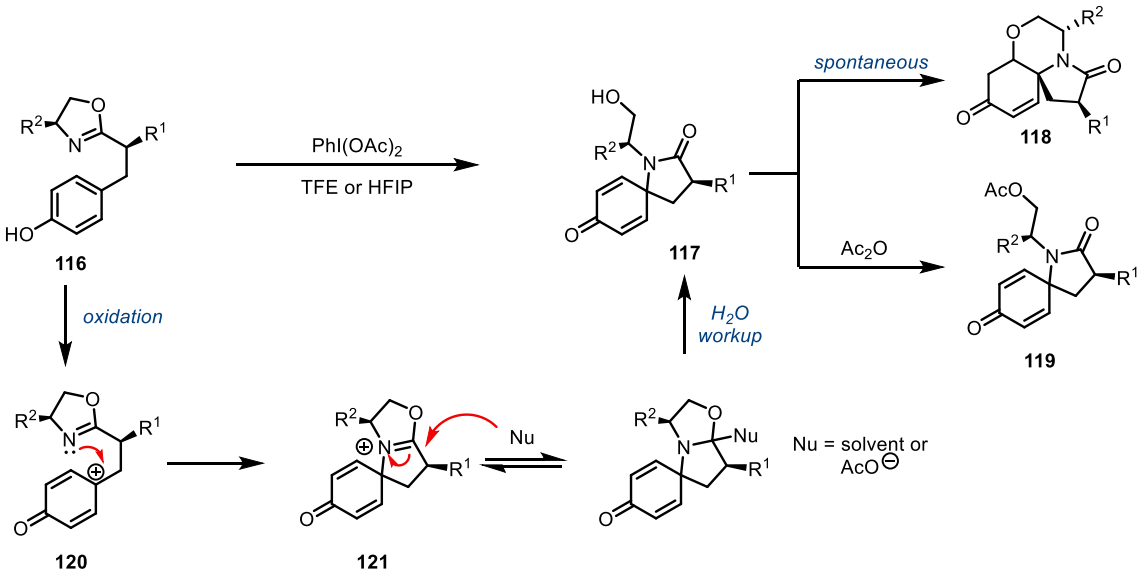
2.1.2 Oxidative dearomative amination reactions

The dearomative amination reactions described thus far rely on generating an electrophilic nitrogen source which reacts with a nucleophilic arene. Dearomative transformations which harness the more common nucleophilicity of nitrogen are also well-established. Ciufolini and co-workers have pioneered an 'oxidative amidation' approach for the conversion of phenols into spirodienones. Mechanistically, these reactions proceed *via* initial oxidation of the phenol ring to generate an electrophilic intermediate, which is then intercepted by a suitable nucleophilic nitrogen source. Typically, hypervalent iodine reagents such as DIB or PIFA serve as the external oxidant as these reagents are known to be effective oxidants for the oxidation of phenols and other arenes.[81-84]

In 1998 Ciufolini and co-workers demonstrated that oxazolines[X] **116** cyclise upon treatment with (diacetoxyiodo)benzene (DIB) in TFE or HFIP to the corresponding spirolactams **117** (Scheme 33).[85] The spirolactam products showed a strong propensity to cyclise to oxazines **118** upon chromatographic purification. This reactivity was suppressed by *in situ O*-acetylation of the crude spirolactam products and a range of spirolactams **119a-d** were obtained in modest yields *via* this two-step process (Scheme 34a). The reaction is believed to proceed *via*

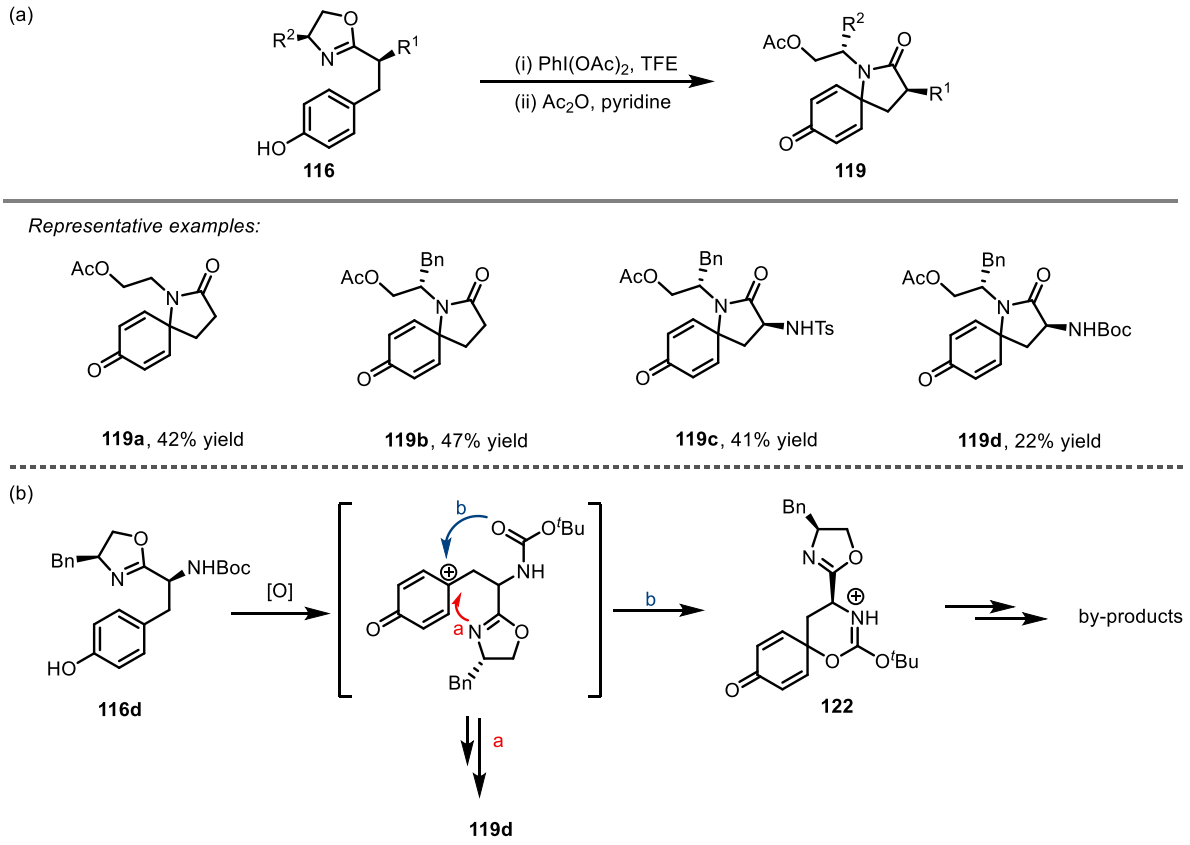
[X] Earlier work by Kita had demonstrated that amides were ineffective as substrates for this transformation due to a preference for reaction through oxygen to form spirolactones.[81]

DIB-mediated oxidation of the phenol to generate electrophile **120** which is intercepted by the oxazoline nitrogen to afford intermediate **121**. The iminium ion of **121** is then captured by another nucleophile present in the reaction mixture, such as an acetate ion or solvent molecule and the resulting intermediate affords the desired spirolactam product upon aqueous work-up.



Scheme 33 *Oxidative amidation of phenolic oxazolines.*[85]

For the cyclisation of oxaziridine **116d**, containing a carbamate functional group, a low yield of 22% was obtained (Scheme 34a). This poor result was rationalised as being due to competition between the oxazoline nitrogen and the carbonyl oxygen of the carbamate group for interception of the electrophile. Reaction *via* the carbonyl leads to formation of an unstable intermediate **122** which unravels to a variety of side products (Scheme 34b). As such, a limitation of this approach is the unsuitability of substrates containing nucleophilic functionality which may compete with the oxazoline for capture of the electrophile.

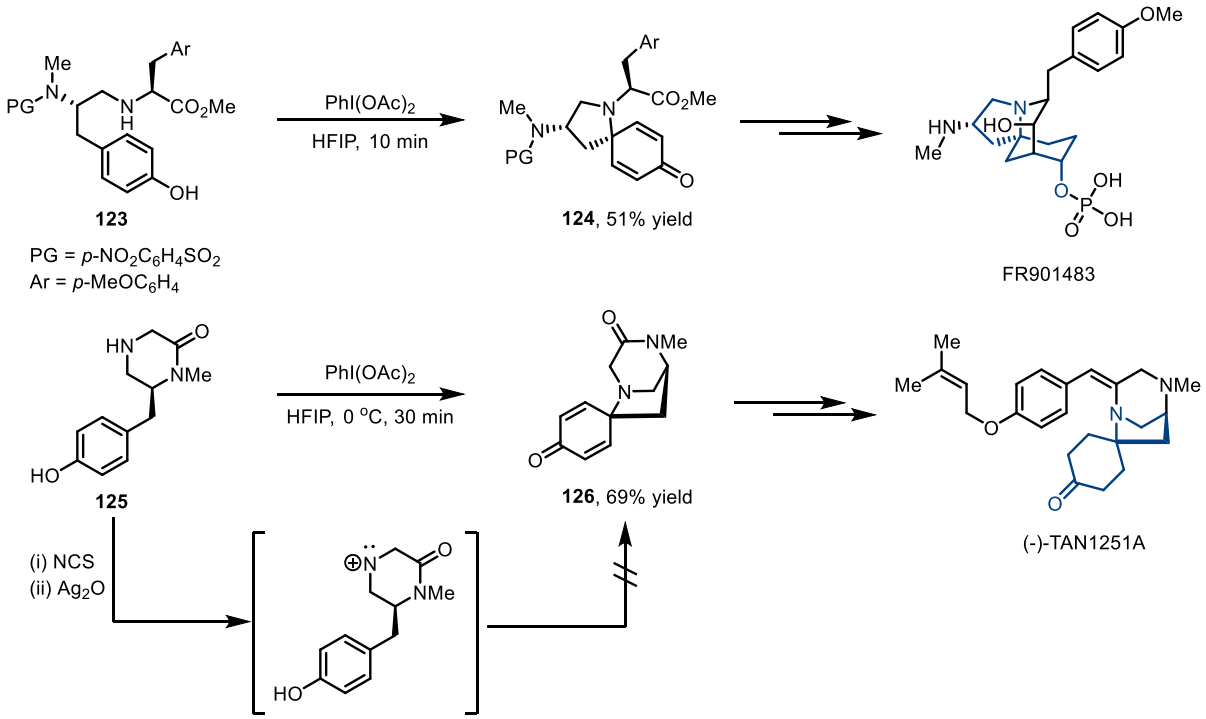


Scheme 34 *(a) Oxidative amidation of phenolic oxazolines. (b) Competitive reactive pathways of oxazoline* ***116d****.*[85]

Whilst secondary amines are generally incompatible as substrates for oxidative aminations of this type[XI] there are several instances in the literature of secondary amines undergoing successful oxidative cyclisation to form spiropyrrolidines; in these cases, the transformation represents a key step in a natural product synthesis. In 2000 Sorensen and co-workers reported a synthesis of FR901483, a fungal-derived natural product with potent immunosuppressant properties.[86] For the construction of the core azaspiro[4.5]decane motif the authors performed an oxidative amination of the tyrosine-derived compound **123** (Scheme 35). Using $PhI(OAc)_2$ in HFIP, the desired spirocyclic product **124** was obtained in good yield and subsequently transformed into the natural product. A related transformation was reported by Honda as a key step in the formal synthesis of the alkaloid natural product (-)-TAN1251A (Scheme 35).[87] Reaction of compound **125** under the same reaction conditions as used by Sorensen gave the desired spirocyclic amine **126** in 69% yield. Initially, the authors had attempted to convert **125** into the spirocompound **126** *via* formation of a nitrenium ion; however, attempted chlorination of **125** with NCS, followed by treatment with silver oxide failed to deliver the desired

[XI] This is believed to be due to the formation of acid in reactions involving DIB which protonates the amine suppressing its nucleophilicity.

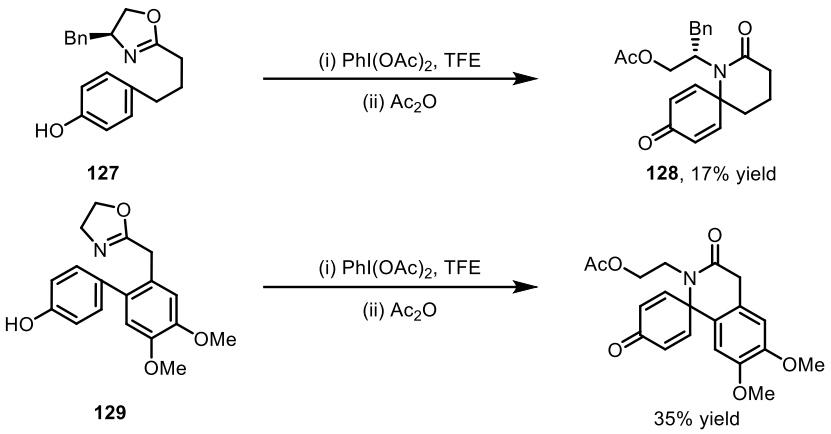
product.[XII] In both of these examples, successful oxidative cyclisation of these secondary amines is possibly due to inductive effects of the neighbouring functionality which decreases the basicity of the amines sufficiently that they remain unprotonated during the reaction and so are able to intercept the electrophilic intermediate.



Scheme 35 *Oxidative amination of secondary amines for the synthesis of natural products.*[86 87]

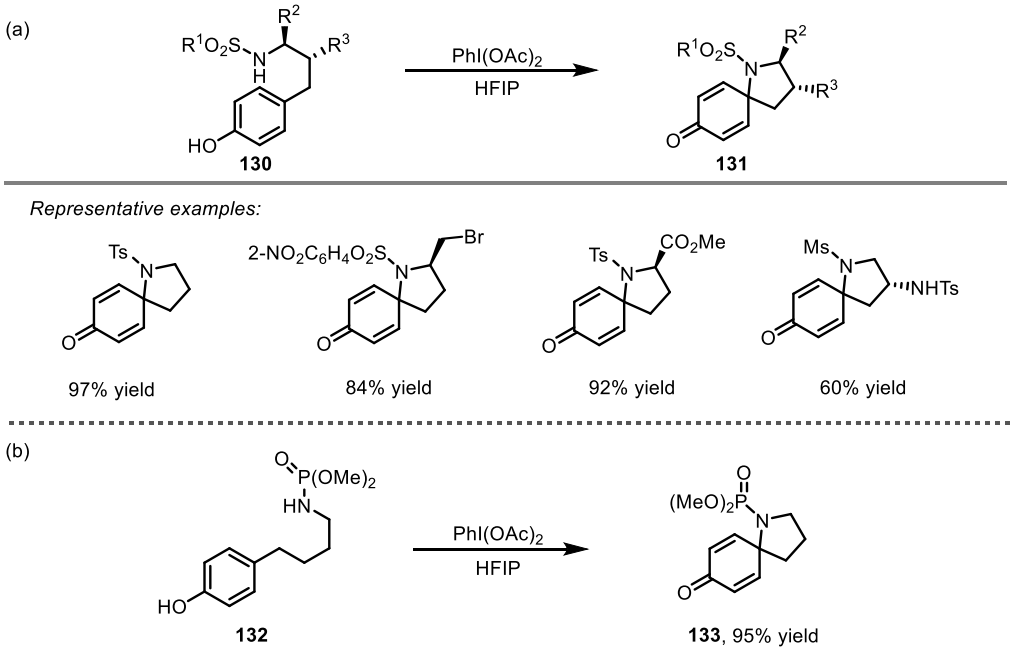
Whilst oxidative amidations are effective for constructing spirocyclic pyrrolidines, attempts to perform more challenging 6-ring cyclisations to form spirocyclic piperidines have met with less success. Ciufolini and co-workers reported the oxidative cyclisation of oxazoline **127** to afford spiropiperidine **128**, but the reaction was low yielding (Scheme 36). Higher yields were obtained with more conformationally restricted substrates such as **129**; however, this transformation remains a challenge.[88]

[XII] This is likely due to the formation of an unstable nitrenium ion.



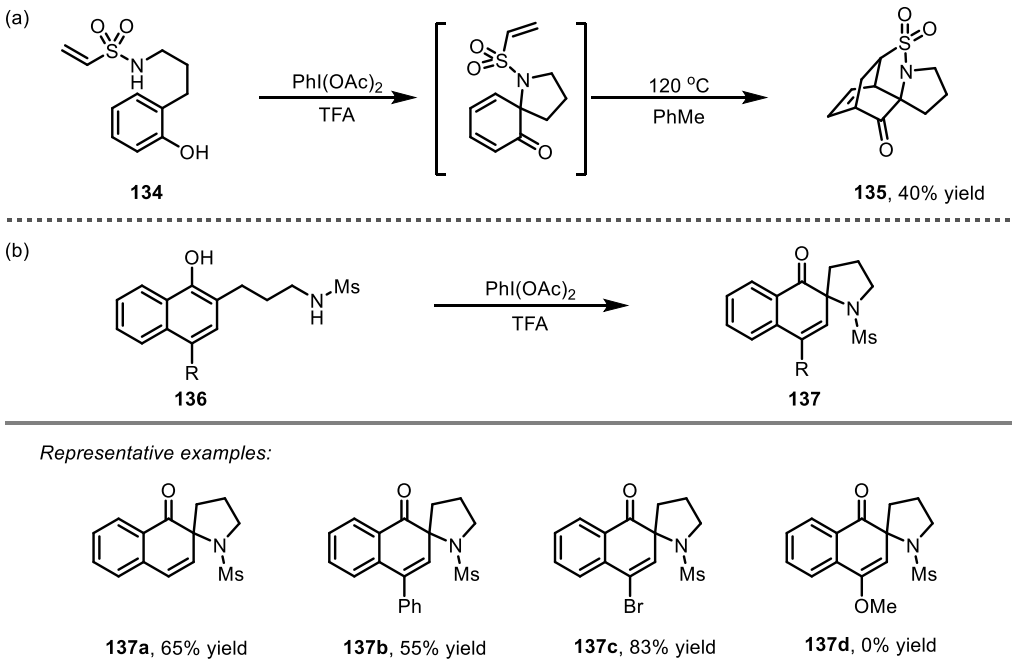
Scheme 36 *Formation of piperidines by oxidative amidation of oxazolines.*[88]

A significant improvement in the area of oxidative amidation chemistry emerged when Ciufolini and co-workers reported the oxidative dearomative cyclisation of sulfonamides. A series of sulfonamides **130** were cyclised with $PhI(OAc)_2$ in HFIP to afford the spirocyclic sulfonamide products **131** with much greater efficiency than that obtained with previous systems (Scheme 37a).[89] The choice of solvent was crucial to obtaining high yields as when TFE was used competition between the sulfonamide nitrogen and the solvent for capture of the electrophile was observed. In addition to the reaction being effective for a variety of sulfonamides, phosphonamide **132** cyclised to spirocycle **133** in excellent yield (Scheme 37b).[88]



Scheme 37 *(a) Oxidative amidation of phenolic sulfonamides.*[89] *(b) Oxidative amidation of a phosphonamide.*[88]

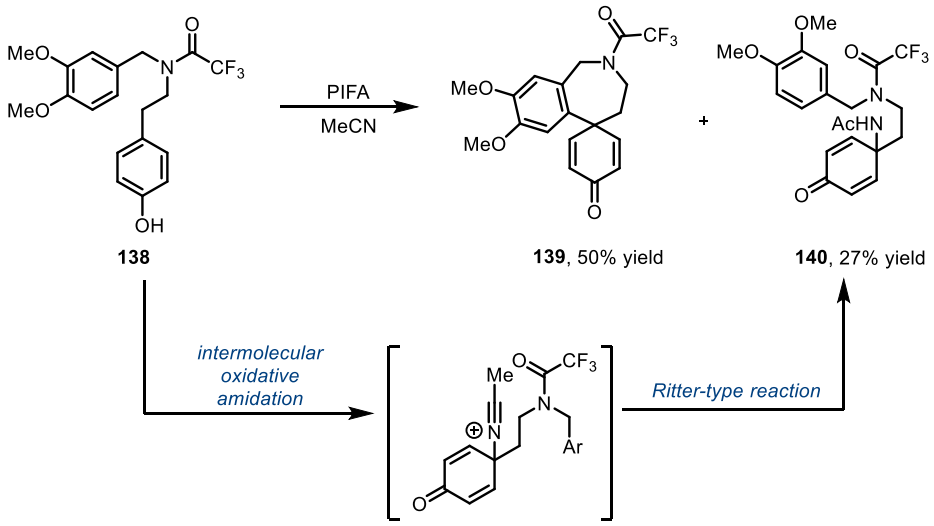
Oxidative cyclisation of *ortho*-sulfonamides, where nucleophilic attack occurs *ortho* to the phenol OH were also successfully demonstrated by Ciufolini and co-workers, although these reactions were generally less efficient than for *para*-phenol substrates. By coupling oxidative cyclisation of allylic sulfonamide **134** with a Diels-Alder reaction tetracycle **135** was obtained in good yield (Scheme 38a).[90] In addition to the dearomatisation of phenols, the scope of the reaction was also extended to the oxidative amidation of naphthols. Upon exposure to $PhI(OAc)_2$ a variety of 1-naphthols **136a-d** cyclised efficiently to the corresponding spirocyclic compounds **137a-d** (Scheme 38b).[91,XIII]



Scheme 38 *(a) Tandem oxidative amidation/Diels-Alder reaction of ortho-sulfonamide **134**.[90] (b) Oxidative amidation of naphthols.[91]*

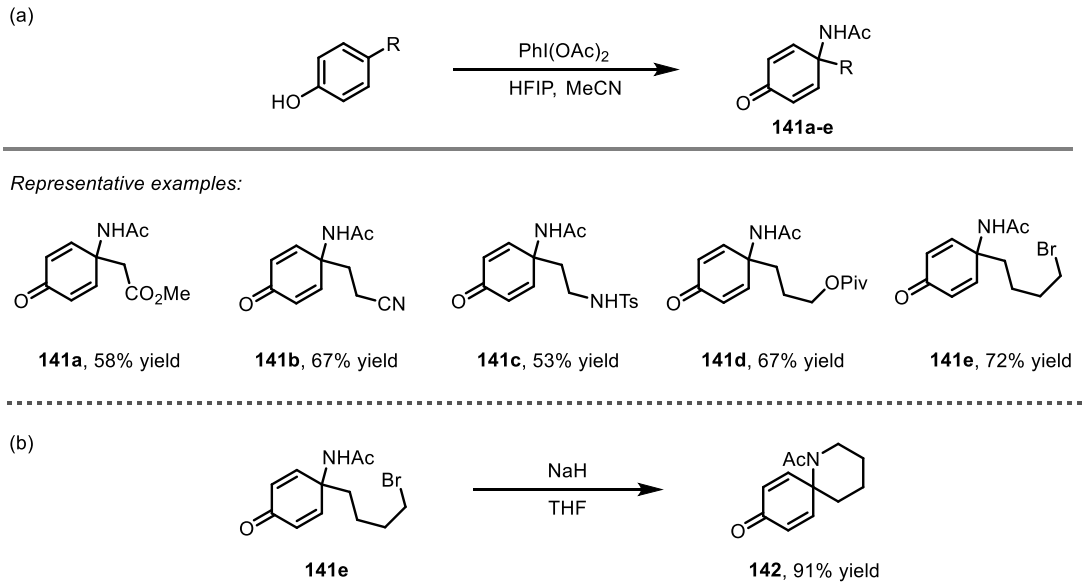
All the previous examples of oxidative cyclisation involve intramolecular reactions; however, precedence for an intermolecular oxidative amidation of phenols was set by Kita in 1996 who during the attempted oxidative cyclisation of **138** observed the competing formation of amidation product **140** in addition to the desired alkylated product **139** (Scheme 39).[92] This product likely arises by a Ritter-type reaction following initial trapping of the electrophile by a molecule of acetonitrile.

[XIII] No product was observed from the cyclisation of 1-naphthol **136d**; the authors attributed this to the instability of the corresponding product **137d**.



Scheme 39 *Observation of side product **140**, a product of intermolecular oxidative amidation.*[92]

Inspired by this result, Ciufolini developed an efficient intermolecular oxidative amidation of phenols to the corresponding dearomatised products **141a-e** using $PhI(OAc)_2$ in a 1:1 mixture of MeCN and HFIP (Scheme 40a).[93] The reaction proved compatible with a variety of functional groups including esters, nitriles, halides, sulfonamides and protected alcohols. Through treatment of compound **141e** with NaH, cyclisation to the spirocyclic piperidine **142** was achieved, allowing for an effective approach to the synthesis of spirocyclic piperidines (Scheme 40b).

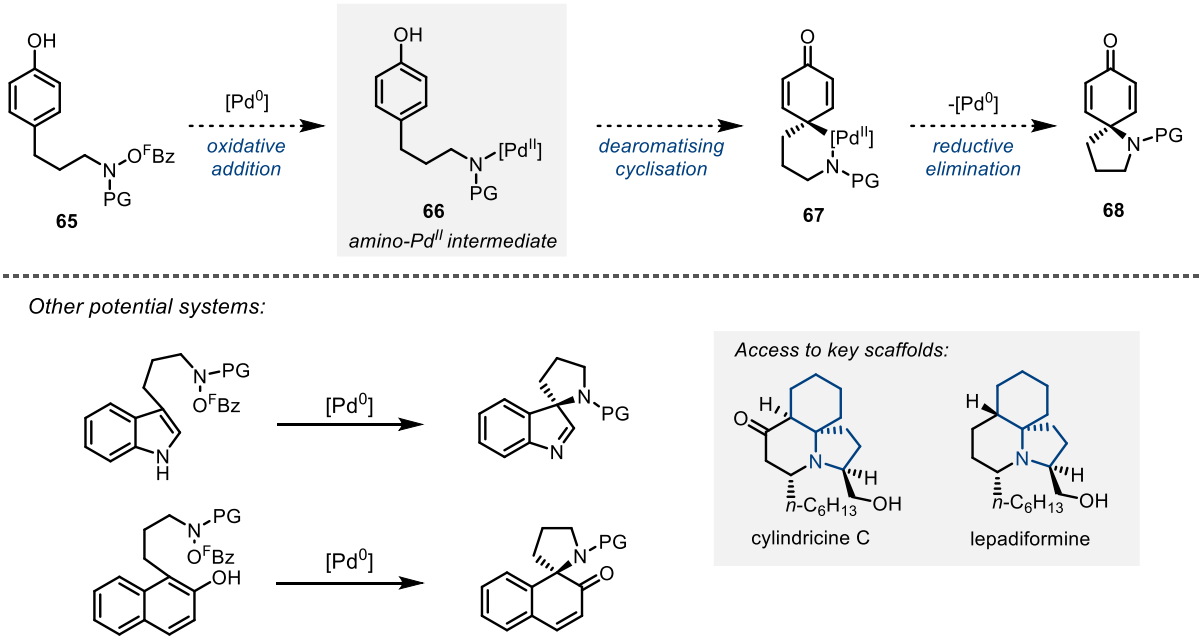


Scheme 40 *(a) Intermolecular oxidative amidation of phenols. (b) Application to the synthesis of spirocyclic piperidines.*[93]

2.2 Studies towards a palladium-catalysed dearomatising amination reaction

2.2.1 Initial results

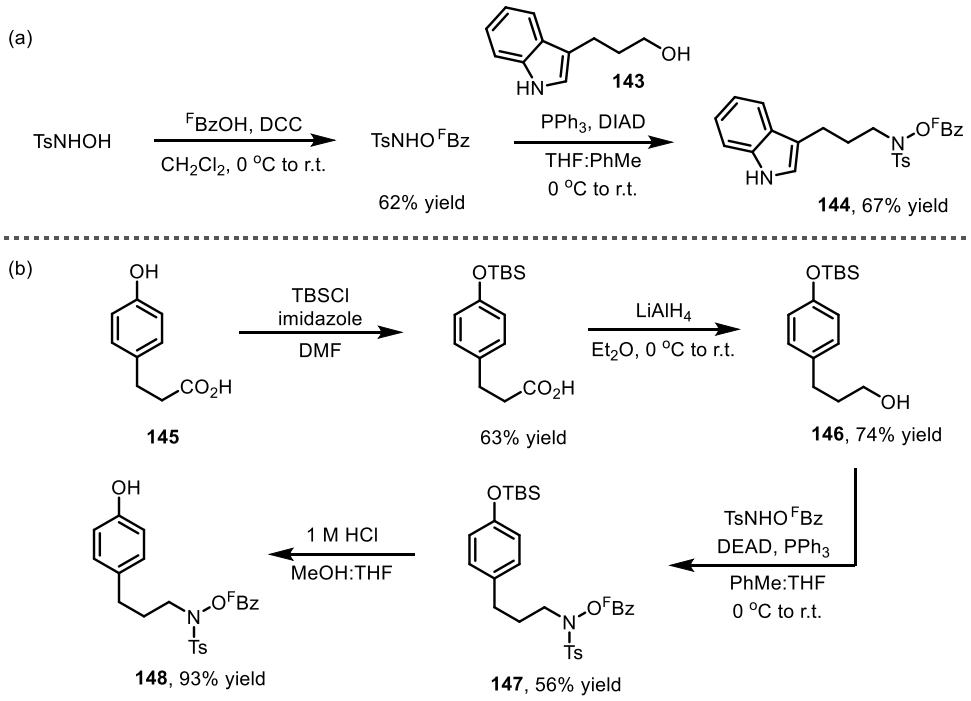
It was envisaged that the proposed dearomatising amination protocol discussed in Chapter 1 (Scheme 41) would represent (a) a mild, catalytic alternative to traditional dearomative amination approaches and (b) offer a number of additional advantages. Classical nitrenium ion-induced dearomatising amination reactions, whilst effective, are limited in scope, as typically only spirolactams with specific electron-donating *N*-protecting groups can be formed. Another advantage of the proposed approach is the lack of a requirement for oxidative conditions as the N-O bond acts as a mild internal oxidant. In the dearomatising amination approach pioneered by Ciufolini and co-workers stoichiometric amounts of external oxidants are required.[85,89,91,93-96] The strongly oxidising conditions renders oxidisable functional groups incompatible and it can lead to competing oxidation processes involving the electron-rich arene.



Scheme 41 *Proposed palladium(0)-catalysed dearomative amination.*

In order to examine the feasibility of the proposed dearomative transformation, phenolic substrate **148** was prepared. During the course of developing a dearomative amination of indoles (Section 2.3) Xiaofeng Ma (University of Bristol) demonstrated that the preactivated amino-reagent TsNHO^{F}Bz can participate in a Mitsunobu reaction to afford sulfonamide **144** in one step from alcohol **143** (Scheme 42a).[97] TsNHO^{F}Bz is itself readily prepared by an amide

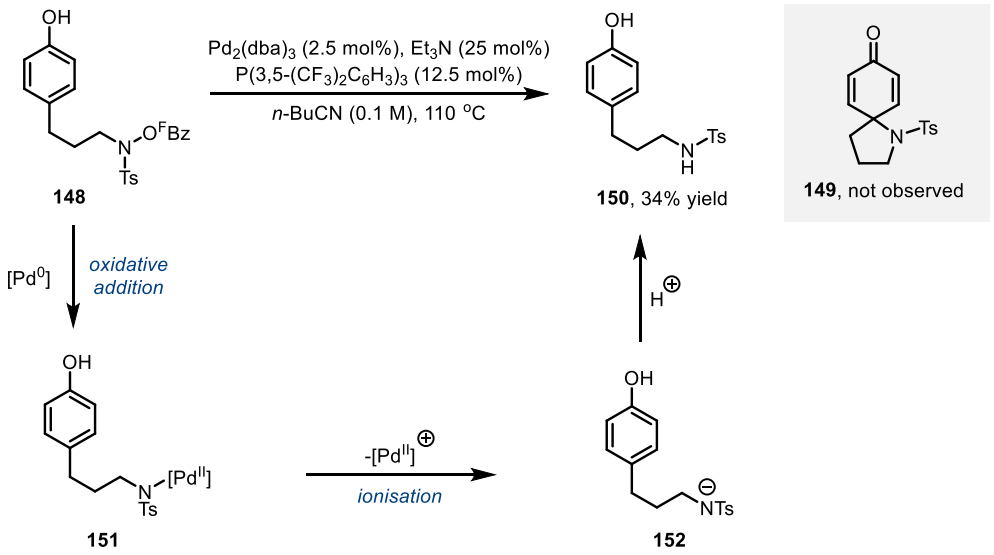
coupling reaction of TsNHOH and ^{F}BzOH. For the synthesis of **148** *via* Mitsunobu reaction, alcohol **146** was prepared in two steps from carboxylic acid **145** (Scheme 42b). To avoid potential competing side reactions during the Mitsunobu reaction, alcohol **146** was prepared with the phenol group protected as the silyl ether. Mitsunobu alkylation of TsNHO^{F}Bz with alcohol **146** afforded **147** in 56% yield. The final step was deprotection of **147** and this was performed using 1 M HCl to provide substrate **148** in excellent yield.



Scheme 42 *(a) Synthesis of sulfonamide **144** by Mitsunobu reaction.*[97] *(b) Synthesis of substrate **148**.*

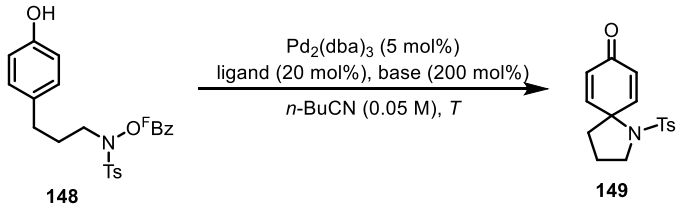
With substrate **148** in hand, the dearomatising amination reaction was investigated. When **148** was subjected to conditions previously identified as effective for aza-Heck cyclisations of *N*-acyloxysulfonamides[52] [$Pd_2(dba)_3$ (2.5 mol%), P(3,5-$(CF_3)_2(C_6H_3)_3$ (12.5 mol%), Et_3N (25 mol%), *n*-BuCN, 110 °C] the desired dearomatised product **149** was not observed (Scheme 43). Instead the major product isolated was sulfonamide **150** which was generated in 34% yield. Sulfonamide **150**, the product of reduction of the N-O bond of **148** probably occurs by protodepalladation. This most likely involves heterolytic cleavage of the Pd-N bond of **151**, formed by oxidative addition of Pd(0) into the N-O bond, followed by protonation of the ensuing nitrogen anion **152**. It is possible that these events could occur the other way around, with protonation of nitrogen preceding heterolytic cleavage. Alternatively, it is known that under certain palladium-catalysed conditions nitrogen-centred radicals are generated[98] and as

such **151** could potentially undergo homolytic cleavage to form a nitrogen-centred radical followed by hydrogen atom abstraction.



Scheme 43 *Attempted palladium(0)-catalysed dearomatising amination of substrate **148**.*

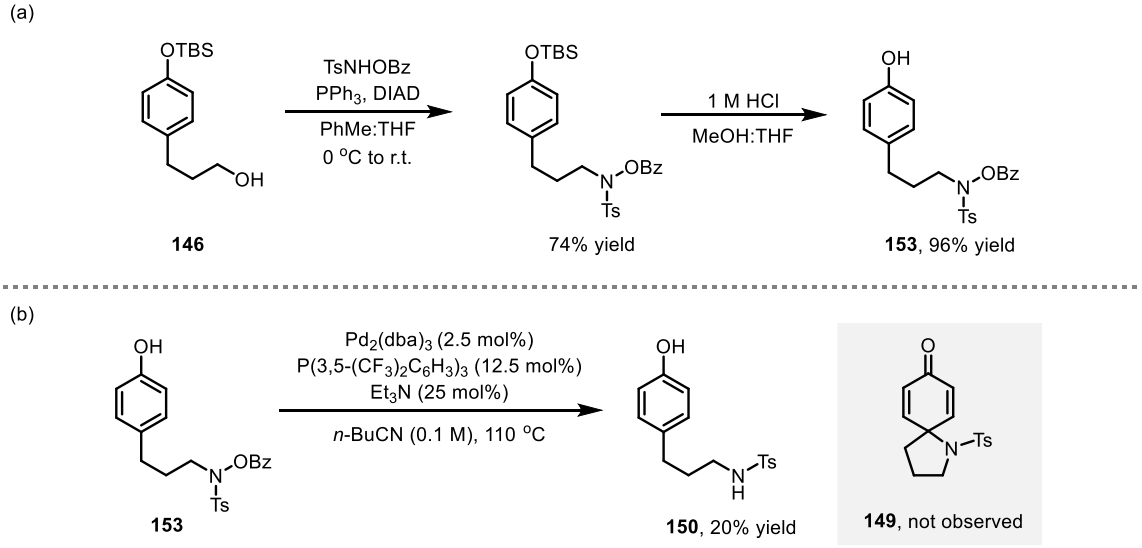
In light of this disappointing result further studies into the dearomative amination of substrate **148** were carried out (Table 1). The effects of changing the base and the use of different ligands were investigated; however, in all case no desired product was observed. The effect of temperature was also studied but increasing the temperature to 140 °C also failed to yield any desired reactivity. In the absence of base (Table 1 entry 5) a significant amount of starting material was recovered (40%) in addition to protodepalladation product **150** (27%). A series of bidentate ligands was also examined; however, these failed to induce any desired reactivity (Table 17, appendix).



Entry	*ligand*	*base*	*temperature*	*yield*
1	$P(3,5\text{-}(CF_3)_2C_6H_3)_3$	K_3PO_4	100 °C	0%
2	X-phos	K_3PO_4	100 °C	0%
3	5-nitro-1,10-phenanthroline	K_3PO_4	100 °C	0%
4	$P(3,5\text{-}(CF_3)_2C_6H_3)_3$	K_3PO_4	140 °C	0%
5	$P(3,5\text{-}(CF_3)_2C_6H_3)_3$	none	140 °C	0%
6	none	K_3PO_4	140 °C	0%

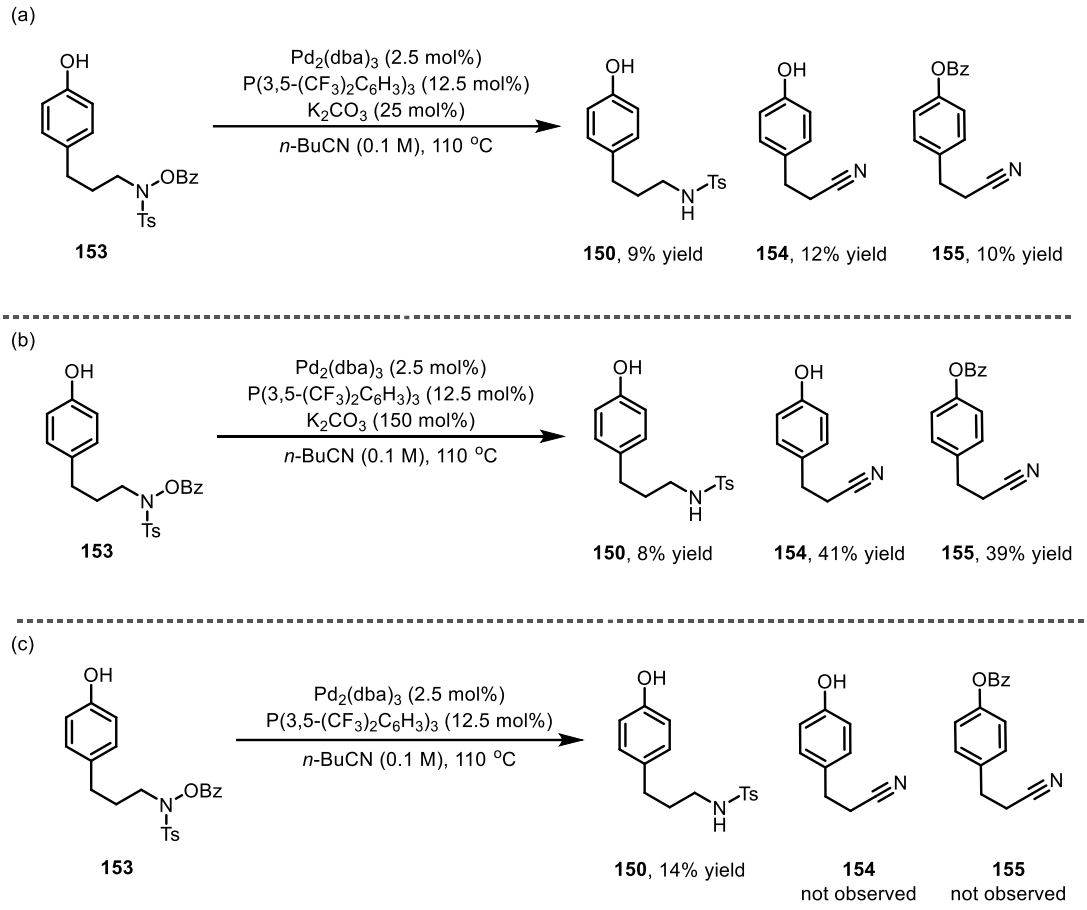
Table 1 *Attempted palladium(0)-catalysed dearomatising amination of substrate **148**.*

As the O^FBz leaving group was unsuccessful in the dearomatising amination reaction other leaving groups were examined. Substrate **153** containing an OBz group was prepared in good yield *via* Mitsunobu reaction from **146** and TsNHOBz (Scheme 43a). When **153** was subjected to the reaction conditions no dearomatised product was observed (Scheme 44b). As for substrate **148** the major product that was isolated was the protodepalladation product **150**, in addition to a significant portion of recovered starting material (51%).



Scheme 44 *(a) Synthesis of substrate **153**. (b) Attempted dearomatisation of substrate **153**.*

For substrate **153** different bases were also investigated. When **153** was reacted with the inorganic base K_2CO_3 (25 mol%) no dearomatised product was observed. Once again, the protodepalladation product **150** was observed, albeit in a reduced yield of 9%; however, under these conditions nitriles **154** and **155** were also isolated in 12% and 10% yields respectively (Scheme 45a). The yields of these products were significantly improved by increasing the loading of K_2CO_3 to 150 mol% (Scheme 45b). In contrast, in the absence of base, **154** and **155** were not observed and only protodepalladation product **150** was formed in 14% yield (in addition to the recovery of 63% starting material) (Scheme 45c).

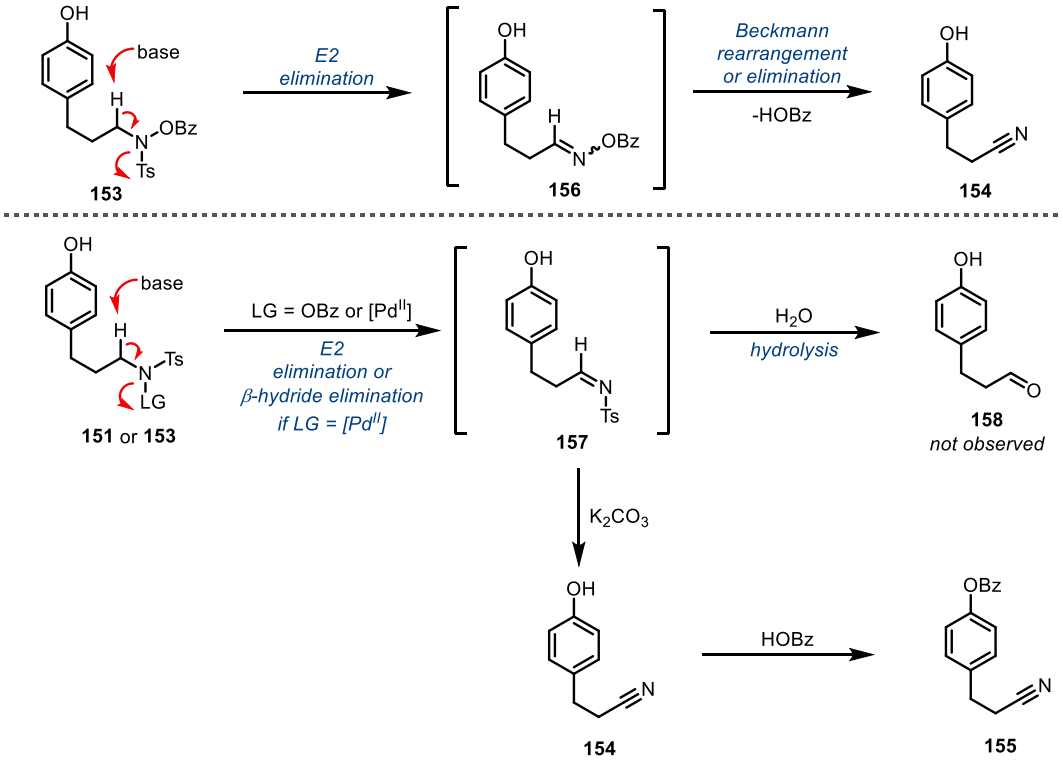


Scheme 45 *(a) Observation of side products **154** and **155** in the attempted dearomatising amination of substrate **153** using 25 mol% K_2CO_3. (b) Increased formation of **154** and **155** using 150 mol% K_2CO_3. (c) In the absence of base products **154** and **155** were not observed.*

Nitriles **154** and **155** likely result from elimination of BzOH and the tosyl group from **153**, although the order of elimination is unclear (Scheme 46). It is known that *O*-acylaldoximines can be converted to nitriles when exposed to palladium(0).[47] This is proposed to occur by Beckmann rearrangement. Alternatively, elimination of BzOH could precede elimination of the tosyl group and this could involve either a β-hydride elimination from intermediate **151** or an E2 elimination mechanism. However, **154** and **155** were still observed when **153** was heated with K_2CO_3 in *n*-BuCN in the absence of palladium, which implies palladium is not involved in this transformation. It is possible that following elimination of BzOH, the resulting imine **157** could undergo hydrolysis, to generate aldehyde **158** and $TsNH_2$.[XIV] However, neither of these products were identified in the crude reaction mixture. There is literature precedence for

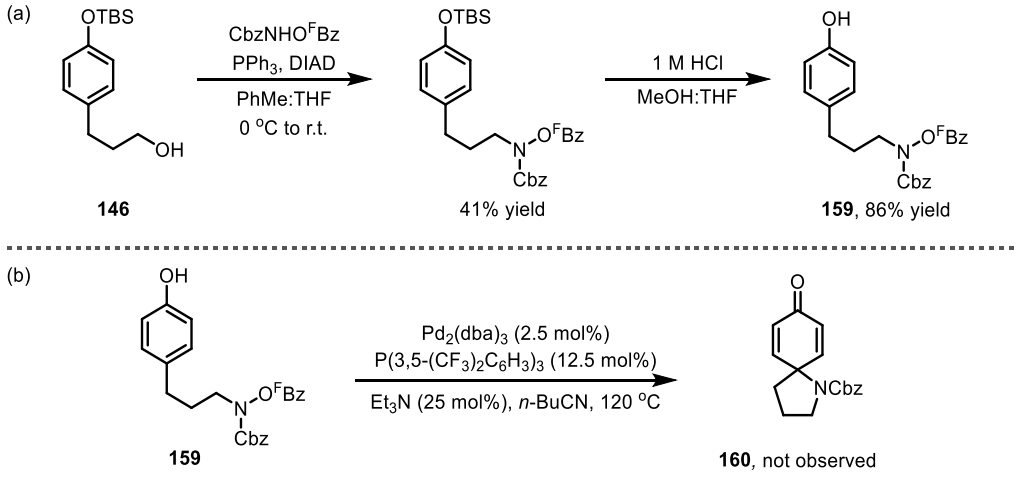
[XIV] **158** could also potentially arise from hydrolysis of **156**.

the conversion of *N*-tosylhydroxylamines to nitriles under basic conditions; however, an exact mechanism was not proposed.[99]



Scheme 46 *Possible mechanisms for the formation of nitriles **154** and **155**.*

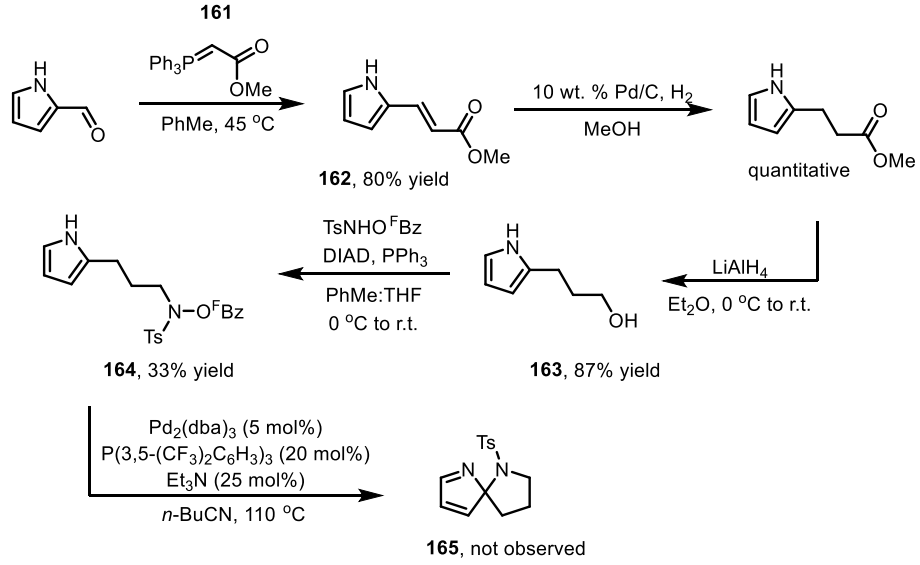
With no successful dearomatisation having occurred so far, the effect of the protecting group on nitrogen was examined next. The Cbz group was chosen as it is also electron-withdrawing but has the added benefit of being easier to remove than the tosyl group thereby improving its synthetic utility. Substrate **159** was prepared in the same manner as sulfonamide **148** but using instead CbzNHO^{F}Bz in the Mitsunobu reaction (Scheme 47a). Unfortunately, when **159** was subjected to the dearomatisation reaction conditions no cyclised product **160** was observed (Scheme 47b).



Scheme 47 *(a) Synthesis of substrate **159**. (b) Attempted dearomatisation of N-Cbz substrate **159**.*

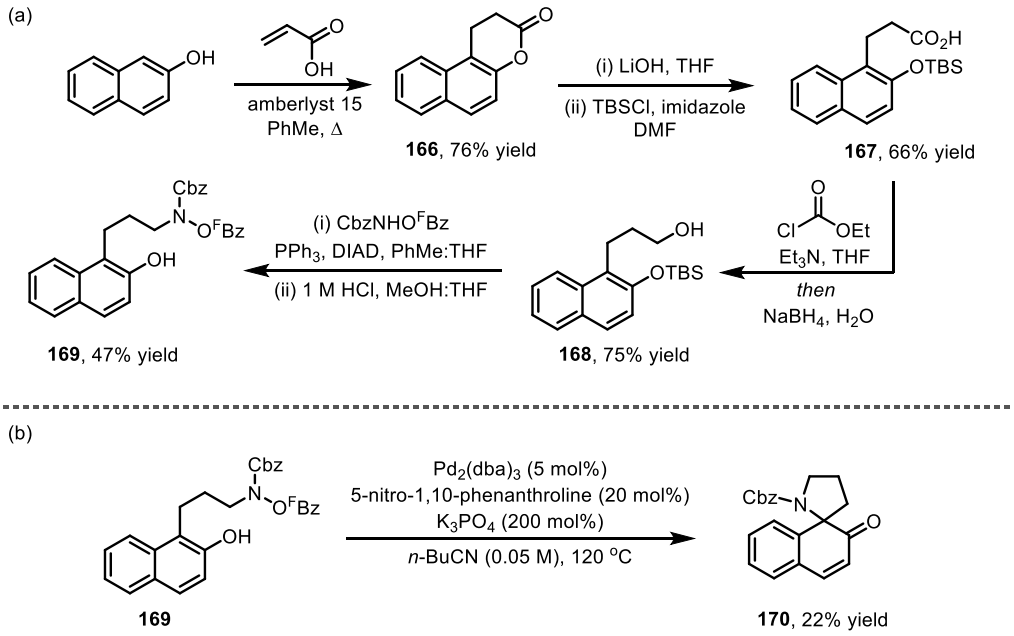
2.2.2 Studies towards a dearomatising amination reaction of naphthols and pyrroles

With phenol derivatives proving unsuccessful in the dearomative cyclisation other potentially more reactive arenes were investigated, beginning with pyrrole substrate **164** (Scheme 48). The synthesis of **164** began from 2-pyrrole aldehyde which was reacted with stabilised ylide **161** to give unsaturated ester **162**. Hydrogenation followed by reduction with $LiAlH_4$ generated alcohol **163** which then underwent Mitsunobu reaction with $TsNHO^FBz$ to give substrate **164** in a low yield of 33%. Substrate **164** was subjected to the original reaction conditions which were investigated for the phenol substrate; however, no dearomatised product **165** was observed.



Scheme 48 *Synthesis and attempted dearomatisation of substrate **164**.*

Dearomatisation of naphthols were also investigated. 2-Naphthol-derived substrate **169** was targeted, as a convenient route to its synthesis had already been identified (Scheme 49a). The synthesis began with the formation of lactone **166** by Friedel-Crafts alkylation of 2-naphthol and acrylic acid followed by spontaneous lactonisation. Lactone hydrolysis followed by TBS protection of the phenol hydroxyl group gave **167**. To obtain alcohol **168** reduction of the carboxylic acid of **167** was required. A low yield was initially obtained for this step using $LiAlH_4$ as the reductant, with deprotection of the TBS-protected phenol also occurring. However, by converting the carboxylic acid into an anhydride followed by reduction with the milder reducing agent $NaBH_4$, **168** was generated in high yield. Substrate **169** was then prepared by Mitsunobu reaction followed by TBS deprotection. When **169** was subjected to the following conditions: [$Pd_2(dba)_3$ (5 mol%), 5-nitro-1,10-phenanthroline (20 mol%), K_3PO_4 (200 mol%) in *n*-BuCN (0.05 M) at 120 °C] spirocycle **170** was generated in 22% yield (Scheme 49b). Despite this promising result, further optimisation of this reaction was abandoned in favour of alternative more successful avenues which will be discussed in the remainder of this chapter.

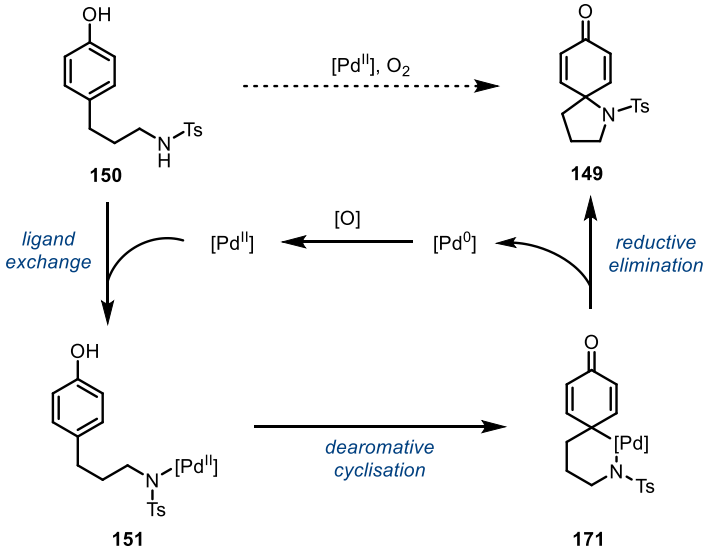


Scheme 49 *(a) Synthesis of substrate **169**. (b) Dearomatisation of substrate **169**.*

2.2.3 Studies towards a dearomatising amination reaction under oxidative conditions

As the dearomative amination reactions discussed above, where the amino-palladium(II) intermediate is accessed from an electrophile nitrogen source through oxidative addition of

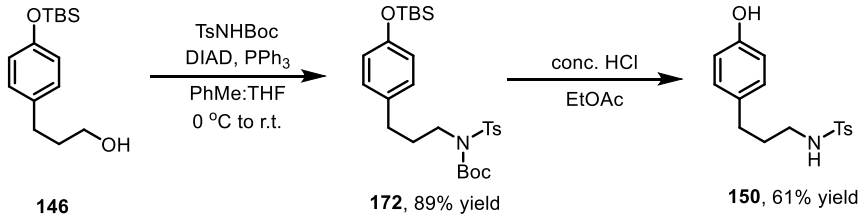
palladium(0) into the N-O bond, were proving generally unsuccessful, alternative avenues were explored. Another well-established approach to palladium-catalysed C-N bond formation is the aza-Wacker reaction, which involves the oxidative amination of alkenes with nitrogen nucleophiles.[100-102] This approach has been used to carry out intramolecular couplings of alkenes with sulfonamides to generate pyrrolidine derivatives.[103,104] In many cases, the reaction is believed to proceed through an amino-palladium(II) intermediate which is accessed through ligand displacement at the metal centre by the amine nucleophile.[105,106] It was therefore proposed that reaction of sulfonamide **150** with a palladium(II) source would result in ligand exchange to give amino-palladium(II) intermediate **151** which could then undergo dearomative amination (Scheme 50). Reductive elimination from **171** would give the dearomatised product **149** and palladium(0) which would then require re-oxidation to palladium(II) with an external oxidant to re-enter the catalytic cycle. Although this approach was not considered ideal due to the requirement for oxidative conditions, it was nevertheless investigated due to the ease of preparation of the required substrate **150**.



Scheme 50 *Proposed oxidative dearomatising amination.*

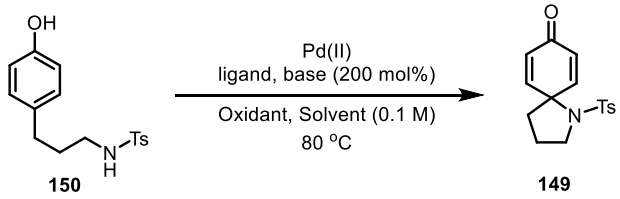
To this end substrate **150** was prepared by Mitsunobu alkylation of TsNHBoc with alcohol **146** (Scheme 51). The resulting *N*-Boc compound **172** then underwent global deprotection using concentrated HCl to afford the NH compound **150**.[XV]

[XV] Substrate **150** could not be prepared directly by Mitsunobu reaction of $TsNH_2$ as primary sulfonamides do not undergo Mitsunobu reactions.[107]



Scheme 51 *Synthesis of sulfonamide **150**.*

With sulfonamide **150** in hand, it was subjected to typical aza-Wacker conditions:[102] [$Pd(OAc)_2$ (5 mol%), pyridine (10 mol%), NaOAc (200 mol%) in PhMe (0.1 M) at 80 °C] under a balloon of oxygen. After stirring overnight, no desired dearomatised product **149** was observed and only starting material was recovered (Table 2 entry 1). A variety of bases (Table 2 entries 3-5) and solvents were examined (Table 2 entries 6-9); however, no reaction occurred under any of the conditions trialled.

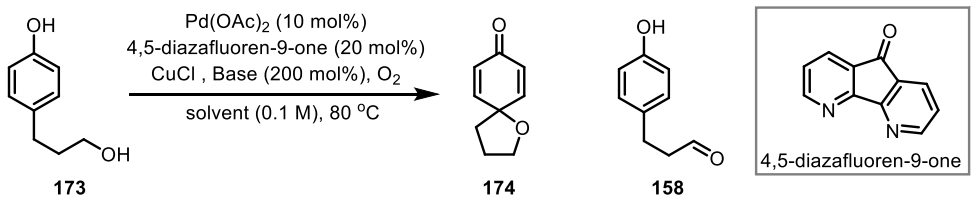


Entry	*catalyst*	*ligand*	*oxidant*	*base*	*solvent*	*yield*
1	$Pd(OAc)_2$ (5 mol%)	pyridine (10 mol%)	O_2	NaOAc	PhMe	0%
2	$Pd(OAc)_2$ (5 mol%)	pyridine (10 mol%)	$CuCl_2$	NaOAc	PhMe	0%
3	$Pd(OAc)_2$ (10 mol%)	pyridine (20 mol%)	$CuCl_2/O_2$	K_3PO_4	PhMe	0%
4	$Pd(OAc)_2$ (10 mol%)	pyridine (20 mol%)	O_2	Cs_2CO_3	PhMe	0%
5	$Pd(OAc)_2$ (10 mol%)	pyridine (20 mol%)	O_2	NaO*t*-Bu	PhMe	0%
6	$Pd(OAc)_2$ (10 mol%)	pyridine (20 mol%)	O_2	Cs_2CO_3	DMF	0%
7	$Pd(OAc)_2$ (10 mol%)	pyridine (20 mol%)	O_2	Cs_2CO_3	DMSO	0%
8	$Pd(OAc)_2$ (10 mol%)	pyridine (20 mol%)	O_2	Cs_2CO_3	MeCN	0%
9	$Pd(OAc)_2$ (10 mol%)	pyridine (20 mol%)	O_2	Cs_2CO_3	*n*-BuCN	0%

Table 2 *Attempted oxidative dearomatising amination of substrate **150**.*

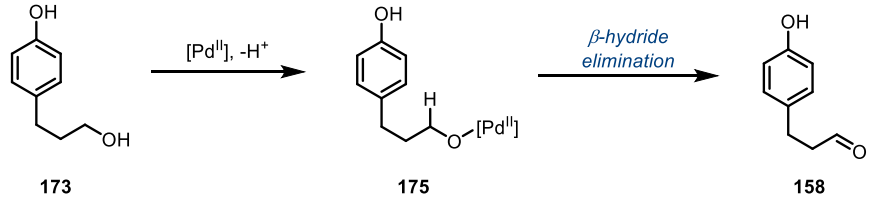
Although not an amination reaction, attempted oxidative dearomative cyclisation was also attempted with **173** as this would give rise to spirocycles such as **174** (Table 3).[XVI] When **173** was examined in the oxidative dearomative cyclisation using a variety of bases no spirocyclic product was identified. The only product, other than recovered starting material, that was obtained was aldehyde **158**, formed by oxidation of **173** presumably *via* β-hydride elimination from **175** (Scheme 52).

[XVI] Conditions for this reaction were based on a report by Lin and co-workers who developed a protocol for palladium-catalysed intramolecular oxidative dearomatisation of indoles using phenol nucleophiles.[108]



Entry	*X*	*base*	*solvent*	*yield 174*	*yield 158*
1	0	none	1,4-dioxane	0%	41%
2	10	none	1,4-dioxane	0%	not determined
3	0	none	PhMe	0%	6%
4	10	none	PhMe	0%	8%
5	10	NaOAc	1,4-dioxane	0%	15%
6	10	K_2CO_3	1,4-dioxane	0%	20%
7	10	K_3PO_4	1,4-dioxane	0%	10%
8	10	KO*t*-Bu	1,4-dioxane	0%	0%

Table 3 *Attempted oxidative dearomatisation of substrate **173**. Yields were determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture versus 1,3,5-trimethyoxybenzene as an internal standard.*



Scheme 52 *Proposed formation of aldehyde **158** by β-hydride elimination.*

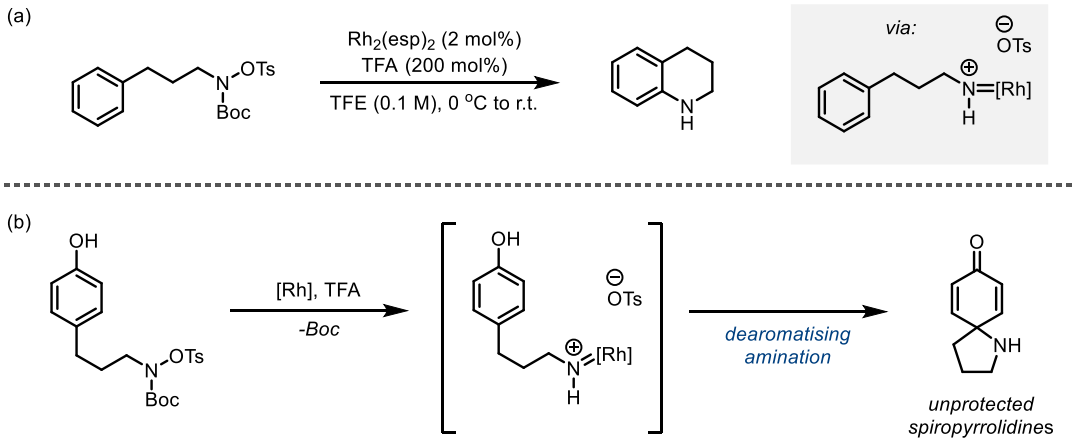
2.3 Acid-promoted dearomatising amination reactions of *N*-Boc hydroxylamines

The contents of this section have been communicated: Farndon, J, J.; Ma, X.; Bower, J. F.; *J. Am. Chem. Soc.* **2017**, *139*, 14005-14008. Parts of this section have been reproduced from this publication.

2.3.1 Introduction

Whilst the studies presented so far in this chapter were being carried out Falck and co-workers reported the dirhodium-catalysed arene amination of *O*-(sulfonyl)hydroxylamines (Scheme 53a).[33] The mildness and efficiency of this protocol in combination with there being no precedence for its use in dearomatising amination made the development of a dearomatising cyclisation based on this approach a worthwhile endeavour (Scheme 53b). It was envisaged that this approach may succeed where attempted palladium-catalysed C-N bond forming dearomatisation of *N*-acyloxysulfonamides had proved ineffective. This approach would also

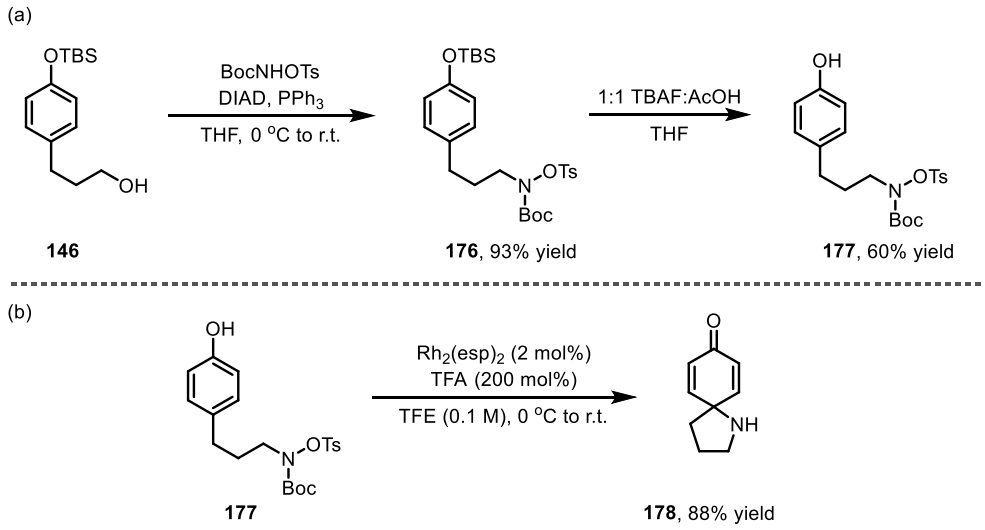
have a further benefit of allowing the direct preparation of unprotected nitrogen ring systems; this is something that is not generally possible using traditional approaches to C-N bond forming dearomatisations that harness the electrophilicity of nitrenium ions[61-65,71,73,109,110] or by the oxidative amidation approach pioneered by Ciufolini and co-workers.[85,89-91,93,94]



Scheme 53 *(a) Rhodium-catalysed intramolecular aryl C-H amination.*[33] *(b) Proposed rhodium-catalysed dearomatising amination.*

2.3.2 Reaction discovery

In order to explore a rhodium-catalysed dearomatising amination reaction of *N*-tosyloxycarbamates, phenol substrate **177** was synthesised (Scheme 54a). Using the Mitsunobu conditions developed by Falck and co-workers,[33] *N*-tosyloxycarbamate **176** was generated in 93% yield from alcohol **146**. Deprotection of the silyl ether of **176** was then required. Initial attempts using TBAF in THF resulted in poor yields of the desired phenol **177** most likely due to the basic nature of TBAF and the ease with which the tosylate group can eliminate. The poor yield of this deprotection step was ameliorated by the addition of acetic acid to the TBAF solution to counteract its basicity, and substrate **177** was generated in 60% yield using this modified approach.

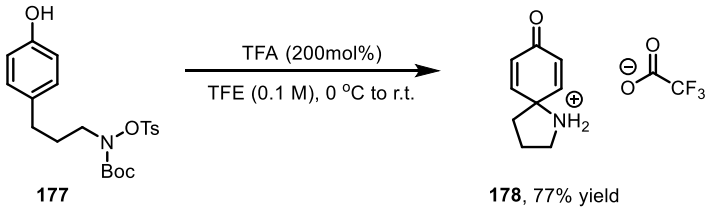


Scheme 54 *(a) Synthesis of substrate **177**. (b) Rhodium-catalysed cyclisation of substrate **177**.*

With substrate **177** in hand, the dearomatising amination reaction was investigated. Using the optimised conditions as reported by Falck and co-workers[33] [$Rh_2(esp)_2$ (2 mol%), TFA (200 mol%) in TFE (0.1 M) at 0 °C to room temperature] efficient cyclisation was observed to give the dearomatised product **178** in 88% yield (Scheme 54b).[XVII]

During reaction optimisation, it was discovered unexpectedly that the rhodium catalyst is not necessary for this reaction as when **177** was subjected to TFA in TFE, in the absence of rhodium, **178** was still obtained in 77% yield (Scheme 55). Spirocycle **178** was isolated as its TsOH salt upon completion of the reaction by removal of the solvent and other volatiles under reduced pressure. Purification was then carried out by flash column chromatography using Et_3N-washed silica to release the free base of **178**. As the free base, **178** is relatively unstable and so it was re-acidified with TFA to form the TFA salt for characterisation. In its protonated form **178** is more resistant to polymerisation and other decomposition pathways and as such this purification procedure was used in most cases, when necessary, during the investigation of substrate scope. Having established that the rhodium catalyst is not required for this reaction, with only a relatively minor reduction in yield observed in its absence, this metal-free approach was investigated further.

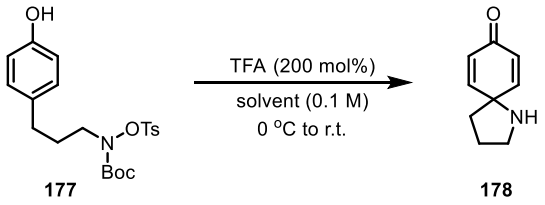
[XVII] The yield was determined by ^1H NMR analysis versus 1,3,5-trimethoxybenzene as an internal standard.



Scheme 55 *Metal-free dearomative cyclisation of substrate **177**.*

2.3.3 Reaction optimisation

Attempts at further reaction optimisation commenced with a solvent screen, the results of which highlighted the importance of TFE as the solvent for this transformation. Polar protic solvents similar to TFE, such as MeOH, EtOH and *i*-PrOH were investigated but failed to produce any desired reactivity (Table 4, entries 1-3). Less polar solvents such as THF, EtOAc and 1,4-dioxane were also unsuccessful (Table 4, entries 4-6). By contrast the aprotic and relatively non-polar solvents PhMe and CH_2Cl_2 produced **178** in modest yields of 40% and 41% respectively (Table 4, entries 7, 8). Some reactivity was also observed with MeCN as solvent, as **178** was obtained in 8% yield (Table 4 entry 9). A brief investigation into reaction concentration failed to give any improvement in yield with 0.1 M appearing to be the optimal concentration.[XVIII]

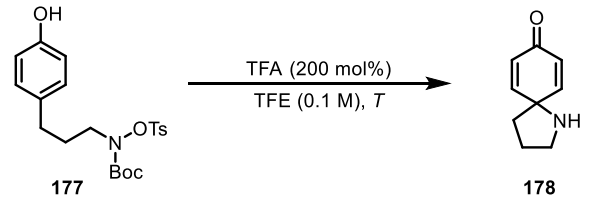


Entry	*solvent*	*yield*
1	MeOH	0%
2	EtOH	0%
3	*i*-PrOH	0%
4	THF	0%
5	EtOAc	0%
6	1,4-dioxane	0%
7	PhMe	40%
8	CH_2Cl_2	41%
9	MeCN	8%

Table 4 *Solvent screen for the dearomatising amination of **178**. Yields were determined by ^{1}H NMR analysis of the crude reaction mixture versus 1,3,5-trimethoxybenzene as an internal standard.*

[XVIII] The use of distilled TFA and TFE was also investigated; however, comparable yields were obtained with or without distillation.

The temperature of the reaction was next examined. Increasing the temperature to 40 °C had no effect on the yield of dearomatised product formed with **178** generated in 78% yield (Table 5, entry 1). However, at this higher temperature the reaction was complete in a slightly reduced time of 15 hours (versus 24 hours at room temperature). At 60 °C the reaction time was further reduced but this also led to a slight reduction in yield (Table 5, entry 2). A further increase in temperature to 80 °C led to a significant reduction in yield to 44% (Table 5, entry 3) likely due to the thermal degradation of the starting material or product at this temperature.



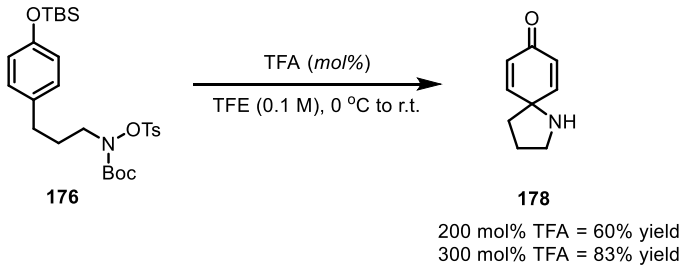
177 178

Entry	*T*	*time*	*yield*
1	40 °C	15 h	78%
2	60 °C	10 h	74%
3	80 °C	8 h	44%

Table 5 *The effect of temperature on the dearomatisation of substrate **177**. Yields were determined by ^{1}H NMR analysis of the crude reaction mixture versus 1,3,5-trimethoxybenzene as an internal standard.*

2.3.4 Tandem desilylation-dearomatisation reaction

Due to the presence of acid in the reaction conditions the possibility of *in situ* deprotection of the silyl ether was investigated as this would negate the additional deprotection step during substrate synthesis. TBS-protected phenol **176** was subjected to the dearomatisation conditions and dearomatised product **178** was formed in a reduced yield of 60% (Scheme 56). By increasing the loading of TFA to 300 mol% an improvement in yield to 83% was observed meaning that the reaction could be carried out with similar levels of efficiency as when the free phenol was used. However, for the purposes of investigating the substrate scope of this dearomative cyclisation, reactions were performed on *O*-TBS cleaved substrates.

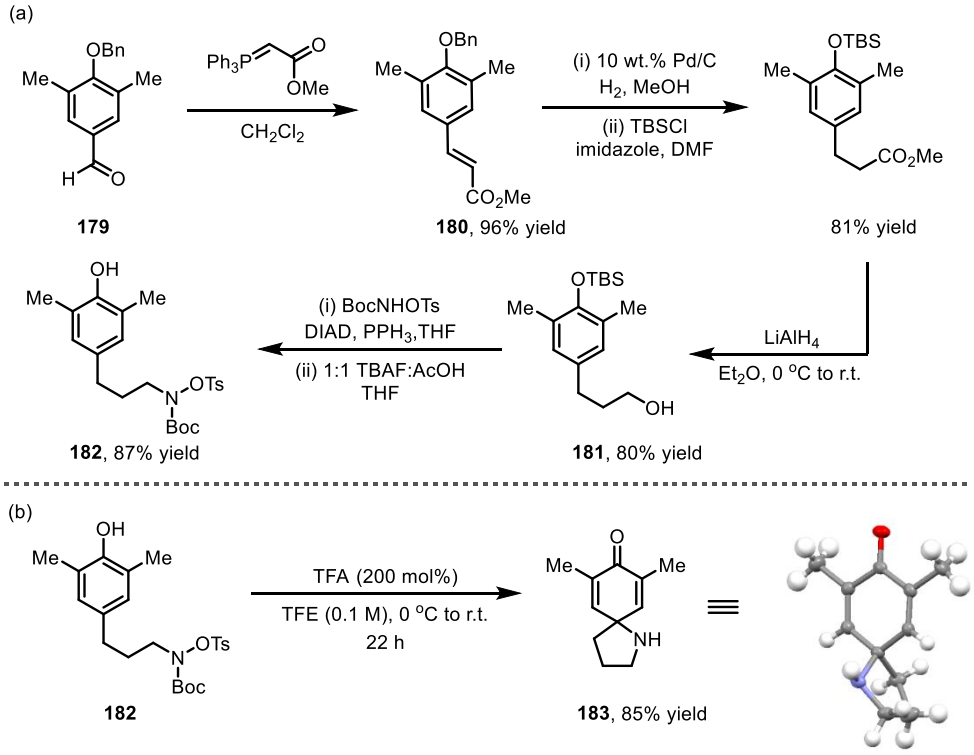


176 178

Scheme 56 *Dearomatising amination of TBS-protected substrate **176**.*

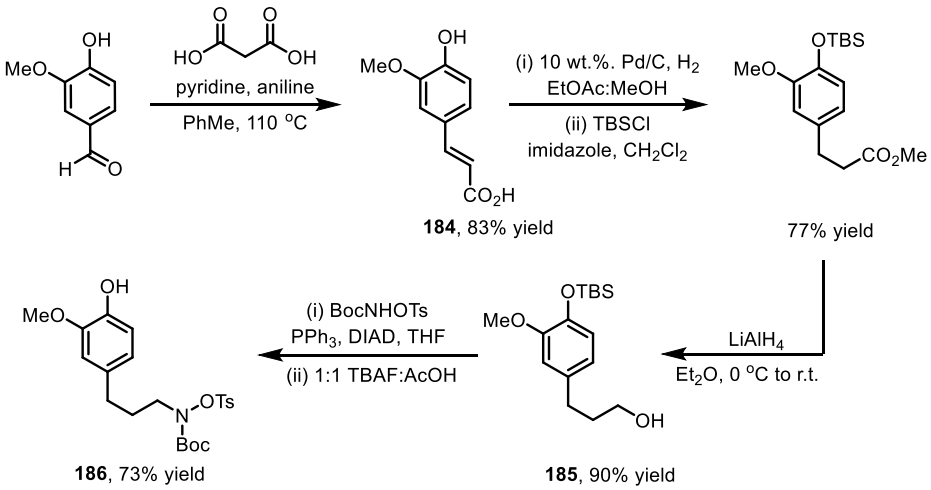
2.3.5 Dearomatising amination of *para*-phenol systems: substitution on the phenyl ring

With optimal conditions in hand, the substrate scope of the dearomatising amination reaction was examined, beginning with substitution on the phenol ring. To this end substrate **182** containing a dimethyl-substituted phenol was synthesised (Scheme 57a). The synthesis began with a Wittig reaction of the commercially available benzaldehyde **179**. The resulting unsaturated ester **180** was transformed into alcohol **181** *via* a three-step sequence, beginning with Pd/C-catalysed alkene hydrogenation with concurrent removal of the benzyl group. Reprotection of the phenol as the silyl ether and finally reduction of the ester with $LiAlH_4$ gave alcohol **181**. Mitsunobu reaction with BocNHOTs, followed by deprotection of the silyl ether with TBAF:AcOH completed the synthesis of substrate **182**, with each step occurring in high yield. When substrate **182** was subjected to the dearomatisation conditions product **183** was obtained in 85% yield (Scheme 57b). Spirocycle **183** exhibited improved stability over the parent product **178** and could be isolated as its free base. This is likely a result of the methyl substituents providing sufficient steric shielding of the sensitive unsaturated dienone group which otherwise would be highly susceptible to nucleophilic attack from another molecule of **183** leading to potential polymerisation pathways. As a result of its stability **183** was crystallised and its structure confirmed by X-ray crystallography.



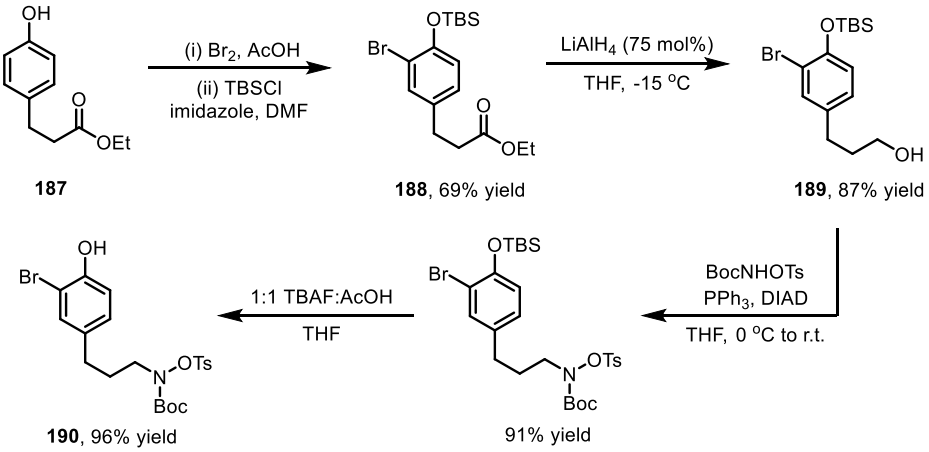
Scheme 57 *(a) Synthesis of substrate **182**. (b) Dearomative amination of substrate **182**.*

The effect of the electronics of the phenol ring on the effectiveness of the dearomatisation reaction was next examined. A series of substrates with electron-donating or electron-withdrawing substituents on the phenol ring were prepared. Substrate **186** containing a highly electron-rich methoxy-substituted phenol was prepared (Scheme 58). The synthesis began with Knoevenagel condensation between vanillin and malonic acid to give carboxylic acid **184**. In a similar sequence to the previous substrate, hydrogenation, protection of the phenol group and reduction with $LiAlH_4$ followed. From the resulting alcohol **185**, substrate **186** was synthesised by Mitsunobu reaction and deprotection of the silyl ether.



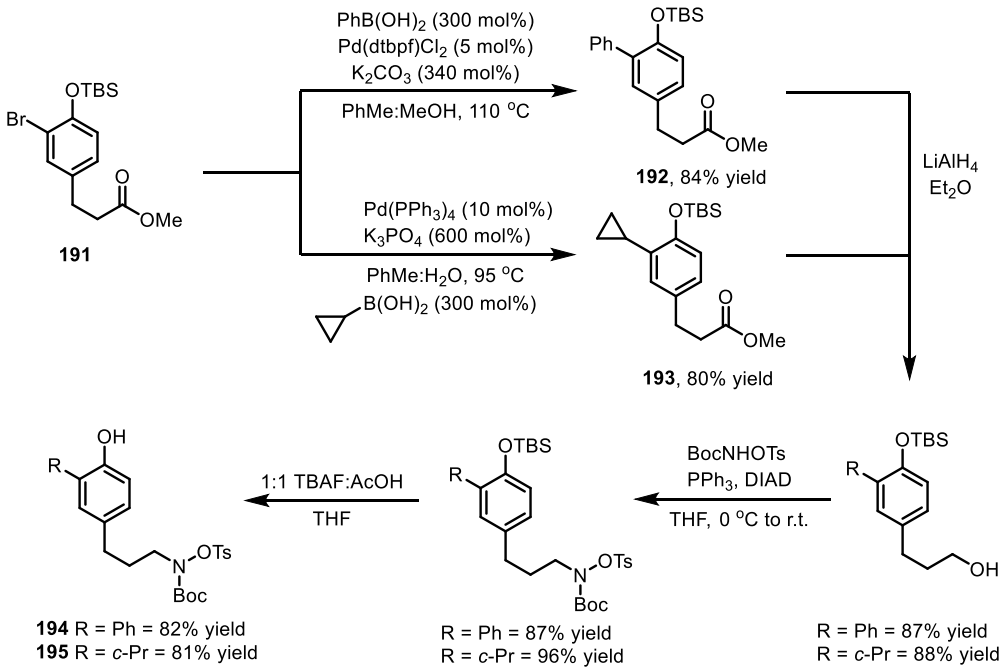
Scheme 58 *Synthesis of substrate **186**.*

Next substrate **190** containing a bromo-substituted phenol was prepared. The synthesis began by bromination of phenol **187** with bromine in AcOH (Scheme 59). Following protection of the phenol hydroxyl group with TBSCl, the ester of **188** was reduced to alcohol **189** in preparation for the Mitsunobu reaction. The use of $LiAlH_4$ (75 mol%) at -15 °C proved effective for generating alcohol **189** in 87% yield without reduction of the aryl bromide. **189** was then converted to **190** by Mitsunobu reaction and *O*-TBS deprotection.



Scheme 59 *Synthesis of substrate **190**.*

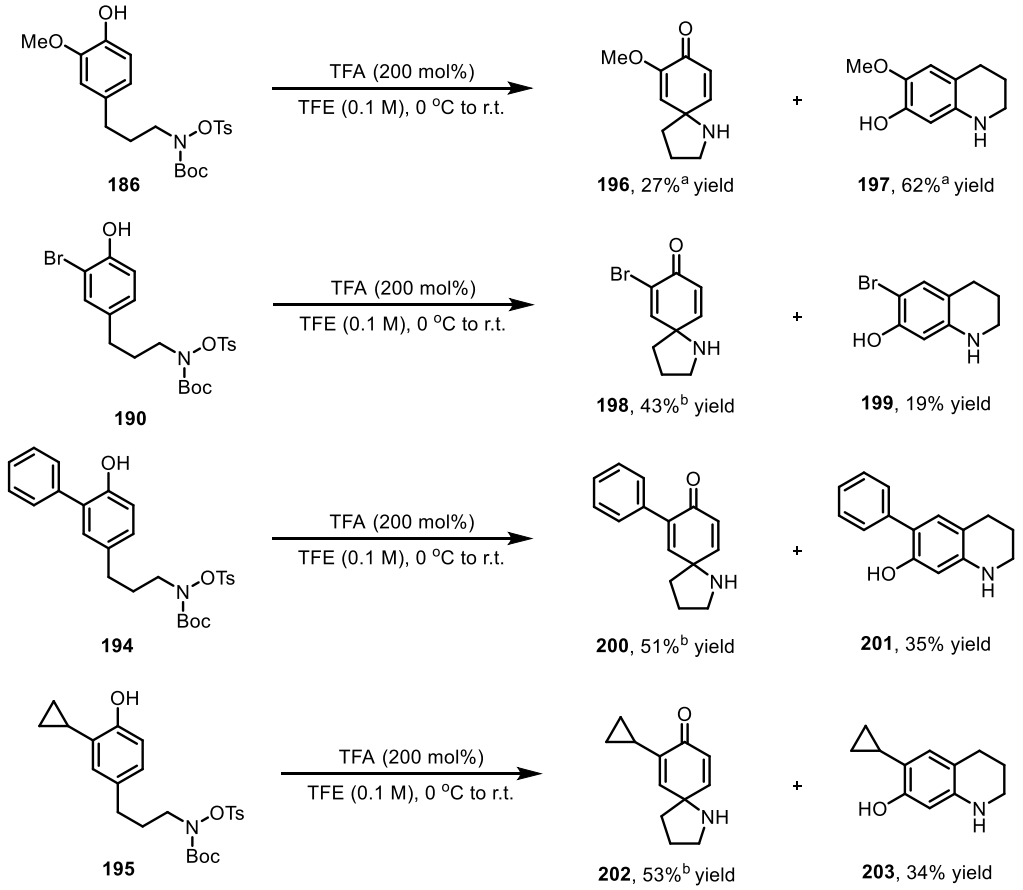
The introduction of a bromide handle allowed for further derivatives to be synthesised using metal-catalysed cross-coupling chemistry. Intermediates **192** and **193** were prepared by palladium-catalysed Suzuki cross-coupling of bromo-phenol **191** and the corresponding phenyl- and cyclopropylboronic acids (Scheme 60). After a series of optimisations, the cross-coupled products **192** and **193** were obtained in high yields. From these esters, substrates **194** and **195** were accessed using the same general approach as used for previous substrates.



Scheme 60 *Synthesis of substrates **194** and **195**.*

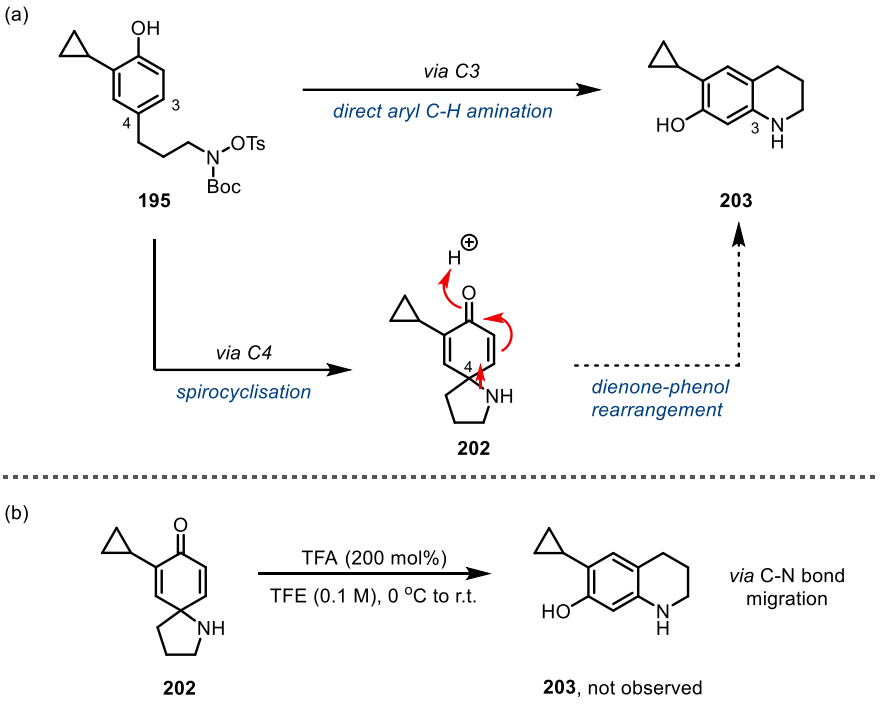
With substrates **186**, **190**, **194** and **195** in hand, they were employed in the dearomatisation reaction (Scheme 61). Although dearomatisation was accomplished in each case the yields produced were lower than for the unsubstituted parent substrate. The methoxy-substituted

example **186** was particular poor yielding producing the desired product **196** in only 27% yield. In addition, the product proved too unstable to isolate by column chromatography and as such its yield was determined by ^{1}H NMR analysis of the crude material versus an internal standard. Improved yields of 53%, 51% and 43% were observed for the bromo-, phenyl- and cyclopropyl-substituted spirocycles **198**, **200** and **202** respectively; however, these were still considerably less than the yield of 77% observed for the unsubstituted system **178**. For these systems the low yields can be attributed to the competitive formation of tetrahydroquinoline side products in addition to the desired spirocyclic targets. This was most apparent for methoxy-substituted system **186**, which cyclised to give the tetrahydroquinoline product **197** in 62% yield in addition to the 27% yield of dearomatised product **196** (Scheme 61). The phenyl- and cyclopropyl-substituted systems were more selective for formation of the spirocyclic products (**200** and **202**) but still formed the tetrahydroquinoline products **201** and **203** in yields of 35% and 34% respectively. For the bromo-substituted system only a small amount of tetrahydroquinoline product **199** was formed in addition to spirocycle **198**.



Scheme 61 *Competitive aryl C-H amination observed in the dearomatising amination of substrates **186**, **190**, **194** and **195**. [a]Yield determined by ^{1}H NMR analysis of the crude reaction mixture versus 1,3,5-trimethoxybenzene as an internal standard. [b]Compounds were isolated as the TFA salt.*

The tetrahydroquinoline products most likely form due to activation of the position *para* to the substituent resulting in a competing C-H amination pathway. No reaction *via* activation of the position *ortho* to the substituents was observed, most likely due to steric factors. The methoxy group is strongly activating which is reflected in the significant amount of tetrahydroquinoline **197** observed. The phenyl and cyclopropyl groups, whilst still electron-donating are less activating than the hydroxyl group and as such the selectivity is in favour of the spirocyclic products.



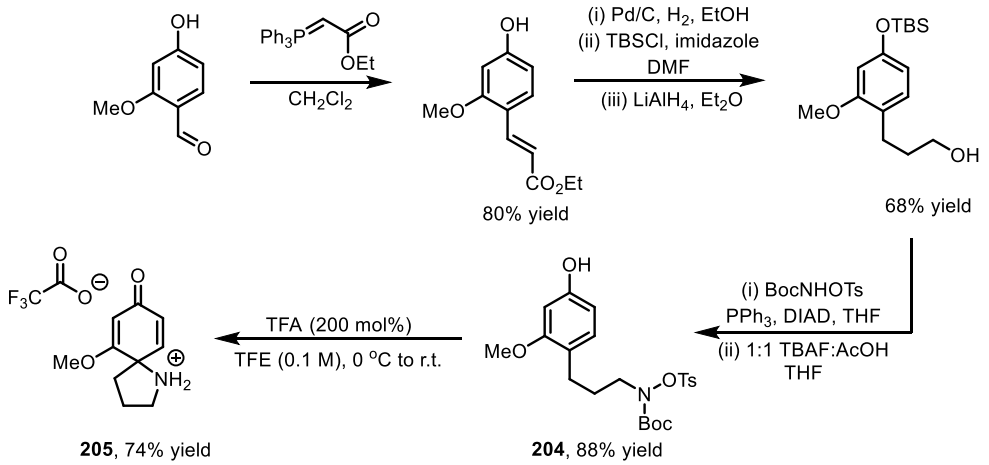
Scheme 62 *(a) Formation of **203** by either a direct aryl C-H amination or dearomatisation/rearrangement pathway. (b) Control reaction to confirm a direct aryl C-H amination pathway.*

Whilst the formation of the tetrahydroquinoline products can be rationalised by a direct aryl C-H amination pathway, these ring systems can also arise by initial spirocyclisation followed by C-N bond migration (Scheme 62a). It is well established that under acidic conditions spirodienones can undergo dienone-phenol rearrangement processes to generate the more stable phenol product.[111] In their reports on intramolecular electrophilic C-H amination Glover,[64] Kikugawa[63,112] and Cherest[113] have all described dienone-phenol rearrangements of similar aza-spirocyclic compounds.[XIX] To ascertain whether or not the tetrahydroquinoline

[XIX] Several related transformations that generate tetrahydroquinoline products *via* iridium-[79] or rhodium-nitrenoid[80] intermediates propose a mechanistic pathway involving initial spirocyclisation followed by C-C bond migration.

products were formed from the spirocyclic intermediates, spirocycle **202** was re-subjected to the standard reaction conditions but was returned unchanged and formation of tetrahydroquinoline **203** was not observed (Scheme 62b). This result confirms that tetrahydroquinoline **203** is formed *via* a direct aryl C-H amination pathway rather than by rearrangement of spirocycle **202** through a dienone-phenol rearrangement. In other cases, formation of a tetrahydroquinoline *via* a dienone-phenol rearrangement was observed and this is described in Section 2.3.15.

In order to remove the issue of selectivity, substrate **204** containing a *meta*-methoxy-substituent was synthesised (Scheme 63). In this case, both of the electron-donating substituents should serve to activate the position *para* to the hydroxyl group. Indeed, when substrate **204** was subjected to the dearomatisation reaction spirocycle **205** was formed as the sole product in 74% yield.

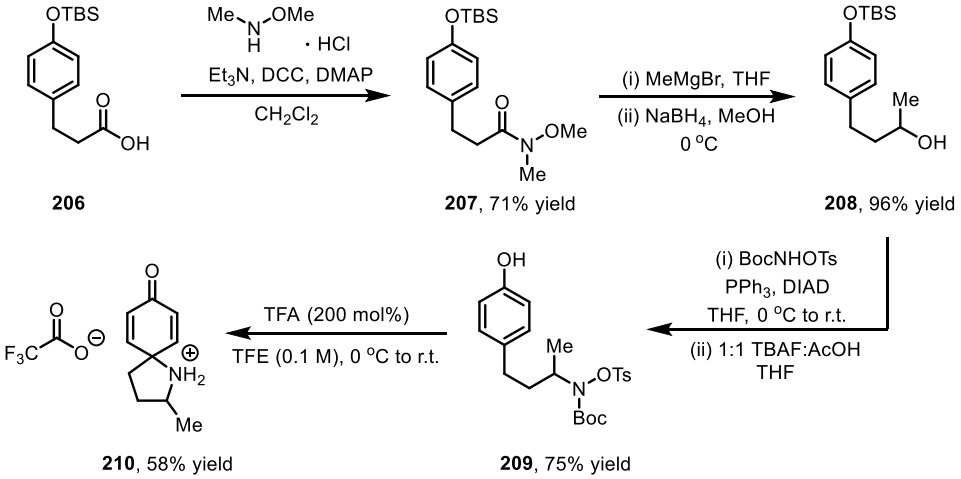


Scheme 63 *Synthesis and dearomatising amination of substrate **204**.*

2.3.6 Dearomatising amination of *para*-phenols with substitution α to nitrogen

Next the reaction scope study was expanded to investigate the effects of substitution on the carbon tether, beginning with substitution α to nitrogen. To this end, substrate **209** was prepared (Scheme 64). Carboxylic acid **206** was converted to Weinreb amide **207** by reaction with *N,O*-dimethylhydroxylamine hydrochloride. Following addition of MeMgBr and reduction of the resulting ketone with $NaBH_4$, alcohol **208** was obtained and converted to substrate **209** by Mitsunobu reaction and TBS deprotection. When **209** was subjected to the dearomatising amination reaction conditions spirocycle **210** was obtained in 58% yield (Scheme 64). The reduction in yield is possibly due to increased steric effects around the reactive nitrogen centre

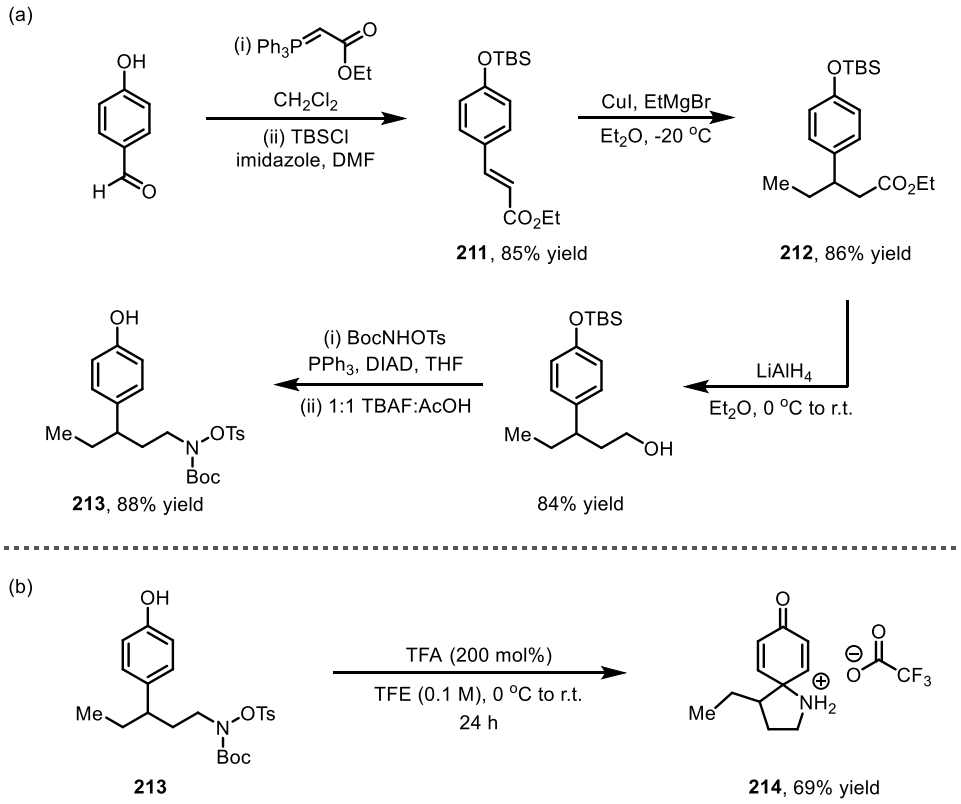
due to the introduction of an adjacent methyl group. As such the rate of reaction is slower allowing for potential competing decomposition of the substrate to occur.



Scheme 64 *Synthesis and dearomatising amination of substrate **209**.*

2.3.7 Dearomatising amination of *para*-phenols with substitution γ to nitrogen

Attention then turned to substrates containing substitution on the carbon tether γ to nitrogen. To this end, unsaturated ester **211** was synthesised by Wittig reaction of 4-hydroxybenzaldehyde, followed by protection of the phenol hydroxyl group (Scheme 65a). Reaction of **211** with EtMgBr at -20 °C in the presence of CuI led to successful 1,4-addition to afford ester **212** in 86% yield. Reduction of the ester of **212** with $LiAlH_4$, followed by Mitsunobu reaction and deprotection completed the synthesise of substrate **213**. Under the dearomatising amination reaction conditions substrate **213** cyclised to spirocycle **214** in 69% yield (Scheme 65b). This improvement in yield over the α-substituted system is likely due to the ethyl substituent being further away from the reactive nitrogen centre and as such is less of a steric hinderance to reactivity.

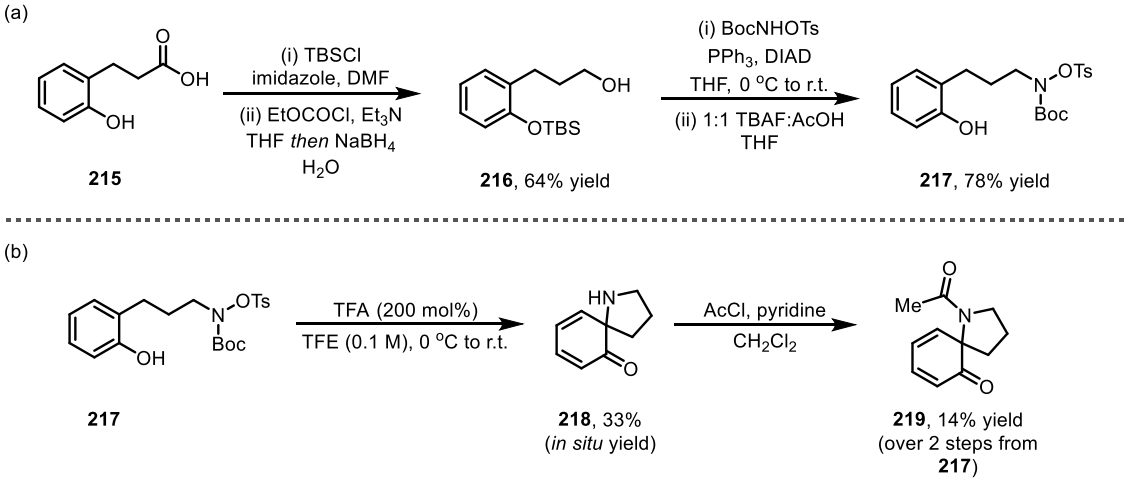


Scheme 65 *(a) Synthesis of substrate **213**. (b) Dearomatising amination of substrate **213**.*

2.3.8 Dearomatising amination of *ortho*-phenols

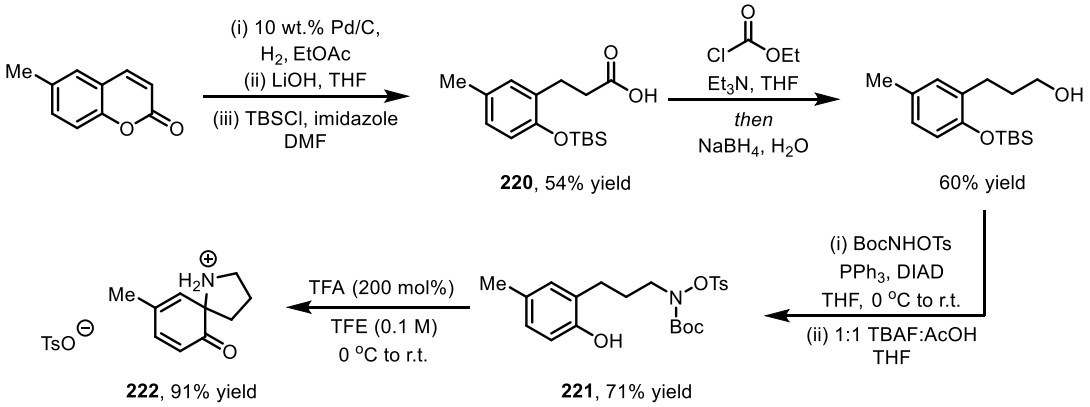
Up until this point, all the systems examined have involved formation of the C-N bond *para* to the phenol hydroxyl group. In order to expand the reaction scope, dearomatisations of *ortho*-substituted phenols were next investigated. Substrate **217** was prepared from commercially available carboxylic acid **215** (Scheme 66a). After protection of the phenol hydroxyl group, reduction of the carboxylic acid to alcohol **216** was achieved using $NaBH_4$ *via* formation of an anhydride. Following the general Mitsunobu reaction and silyl ether deprotection strategy, substrate **217** was obtained in good yield. The dearomative cyclisation of **217** was disappointing with **218** obtained in only 33% yield (Scheme 66b). The low yield can be attributed to poor stability of the dearomatised product.[XX] **218** could not be isolated following flash column chromatography and as such the yield was determined by ^{1}H NMR analysis versus 1,3,5-trimethoxybenzene as an internal standard. To enable isolation and characterisation of the dearomatised product the crude reaction mixture was treated with acyl chloride and Et_3N to provide amide **219** in 14% yield from substrate **217**.

[XX] Lower yields were generally obtained for *ortho*-cyclisations in the oxidative amidation reactions reported by Ciufolini.[95]



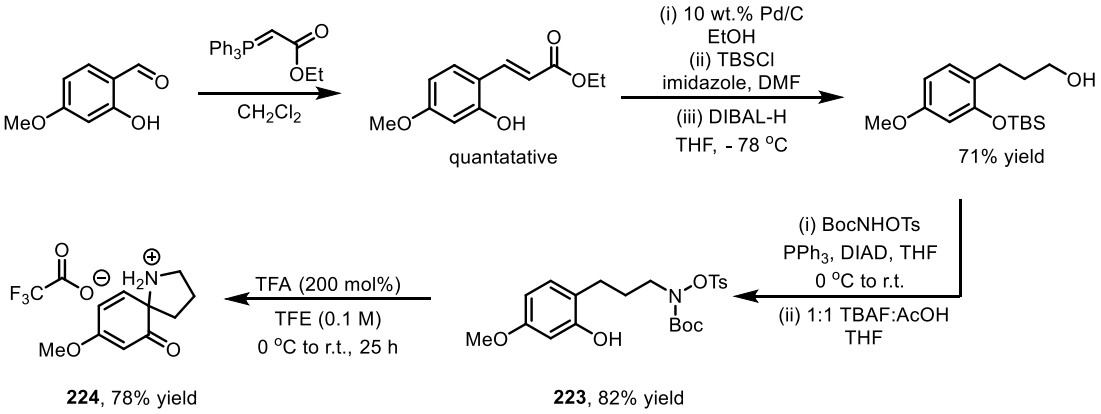
Scheme 66 *(a) Synthesis of substrate **217**. (b) Dearomatising amination of substrate **217**.*

In order to achieve a more satisfactory yield of dearomatisation from an *ortho*-phenol substrate, substrate **221** containing a methyl-substituted phenol was prepared (Scheme 67). It was proposed that the methyl group would provide a degree of steric shielding to the highly reactive dienone and as a result it would make the product more stable. The synthesis of substrate **221** began from 6-methylcoumarin. Alkene hydrogenation followed by lactone hydrolysis and protection of the resulting phenol hydroxyl group afforded carboxylic acid **220**. The synthesis of substrate **221** was completed by reduction of the carboxylic acid, followed by Mitsunobu reaction and deprotection of the phenol hydroxyl group. Substrate **221** cyclised efficiently to give spirocycle **222** in 91% yield (Scheme 67). Due to the high conversion of this substrate and the lack of side products, **222** was isolated in sufficient purity without the need for further purification. Upon completion of the reaction, the solvent and any other volatile components were removed by concentration *in vacuo* and **222** was obtained as the TsOH salt.



Scheme 67 *Synthesis and dearomatising amination of substrate **221**.*

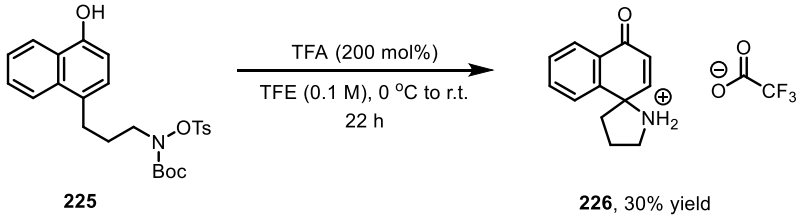
Methoxy-substituted substrate **223**, which was prepared in a similar manner as substrate **221**, was also examined (Scheme 68). When subjected to the dearomatisation conditions, substrate **223** cyclised to the dearomatised product **224** in 78% yield. In this case the dearomatised product was purified by flash column chromatography and **224** was obtained as the TFA salt upon re-acidification.



Scheme 68 *Synthesis and dearomatising amination of substrate **223**.*

2.3.9 Dearomatising amination of naphthols

To expand the scope of the dearomatisation process a further class of nucleophilic arene, naphthols, was investigated. *Para*-substituted naphthol **225**[XXI] cyclised under the standard dearomatisation conditions to form spirocycle **226** (Scheme 69); however, the yield was disappointing as **226** was isolated in only 30% yield. The exact explanation for the low yield is unclear: starting material **225** was fully consumed and no side products could be isolated. Significant decomposition of the starting material or product must therefore have occurred.

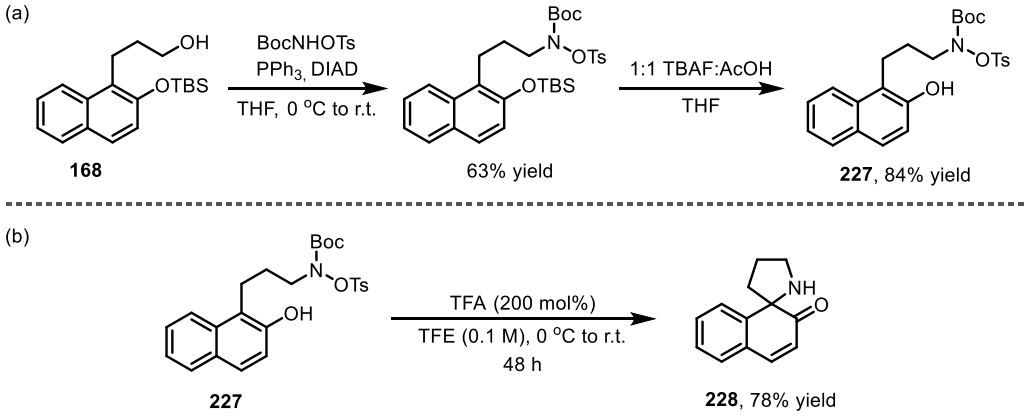


Scheme 69 *Dearomatising amination of substrate **225**.*

To extend further the scope of naphthol systems, *ortho*-naphthol substrate **227** derived from 2-naphthol was prepared. Substrate **227** was synthesised from alcohol **168** (which was prepared as described in section 2.2.2). Mitsunobu reaction of alcohol **168** with BocNHOTs followed by deprotection of the phenol hydroxyl group with 1:1 TBAF:AcOH completed the synthesis

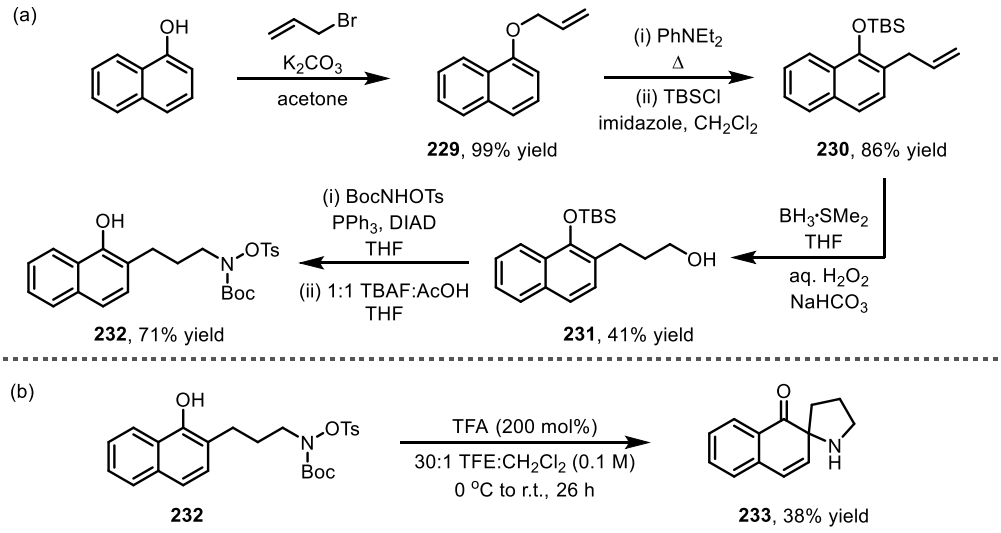
[XXI] This was prepared by Xiaofeng Ma (University of Bristol) and hence is not detailed in the experimental section.

(Scheme 70a). With **227** in hand, it was subjected to the dearomatisation conditions and the spirocyclic product **228** was obtained in 78% yield (Scheme 70b). Unlike many of the previous examples described, spirocycle **228** proved sufficiently stable for isolation and characterisation as the free base without needing to be converted to the TFA salt.



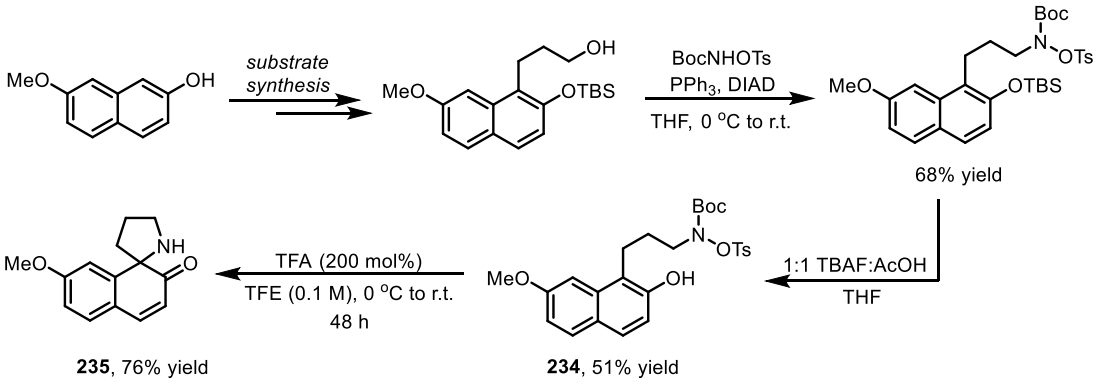
Scheme 70 *(a) Synthesis of substrate **227**. (b) Dearomatising amination of substrate **227**.*

Alcohol **231** for the synthesis of 1-naphthol-derived substrate **232** was prepared following a reported procedure (Scheme 71a).[91] Alkylation of 1-naphthol gave allyl ether **229** which upon heating underwent Claisen rearrangement to give **230** after TBS protection of the phenol. **230** was then converted to alcohol **231** *via* a hydroboration-oxidation sequence. Mitsunobu reaction, followed by TBS deprotection afforded **232**. For the dearomatisation reaction a small amount of CH_2Cl_2 was required as a co-solvent due to the poor solubility of substrate **232** in TFE. When subjected to these modified conditions spirocycle **233** was obtained in 38% yield (Scheme 71b).



Scheme 71 *(a) Synthesis of substrate **232**. (b) Dearomatising amination of substrate **232**.*

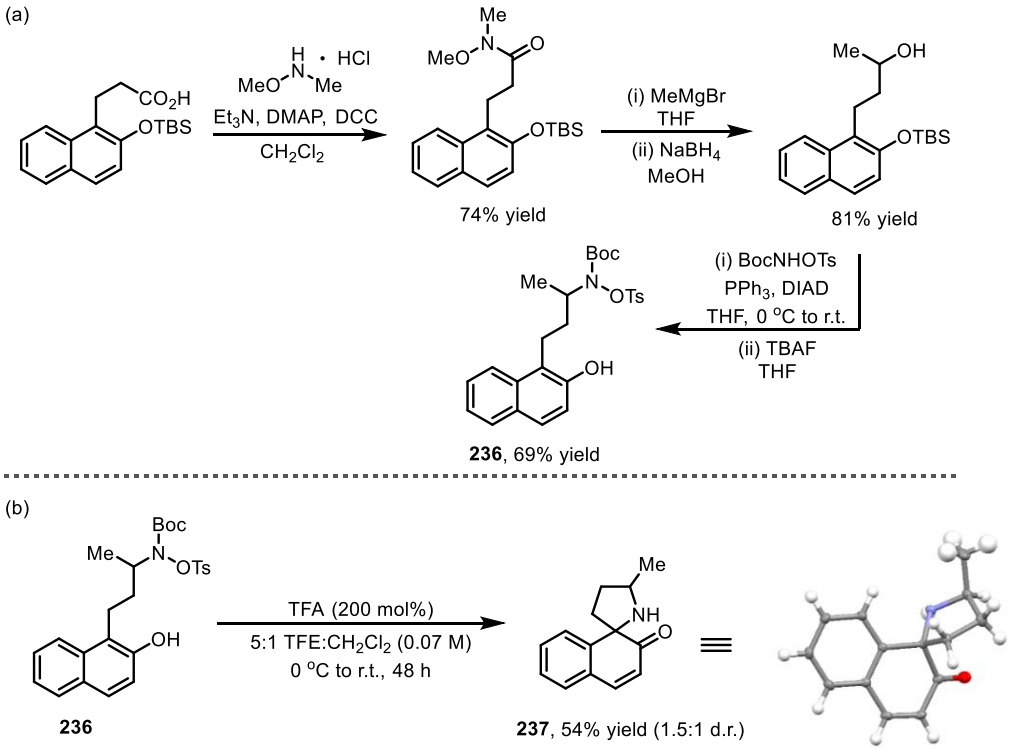
Substitution on the phenol ring was next investigated. Starting from 7-methoxynaphthalen-2-ol, substrate **234** was synthesised using the same strategy as for the unsubstituted naphthol system **227**. When subjected to the standard dearomatisation conditions, the dearomatised product **235** was generated in 76% yield (Scheme 72).



Scheme 72 *Synthesis and dearomatising amination of substrate **234**.*

2.3.10 Dearomatising amination of naphthols with substitution α to nitrogen

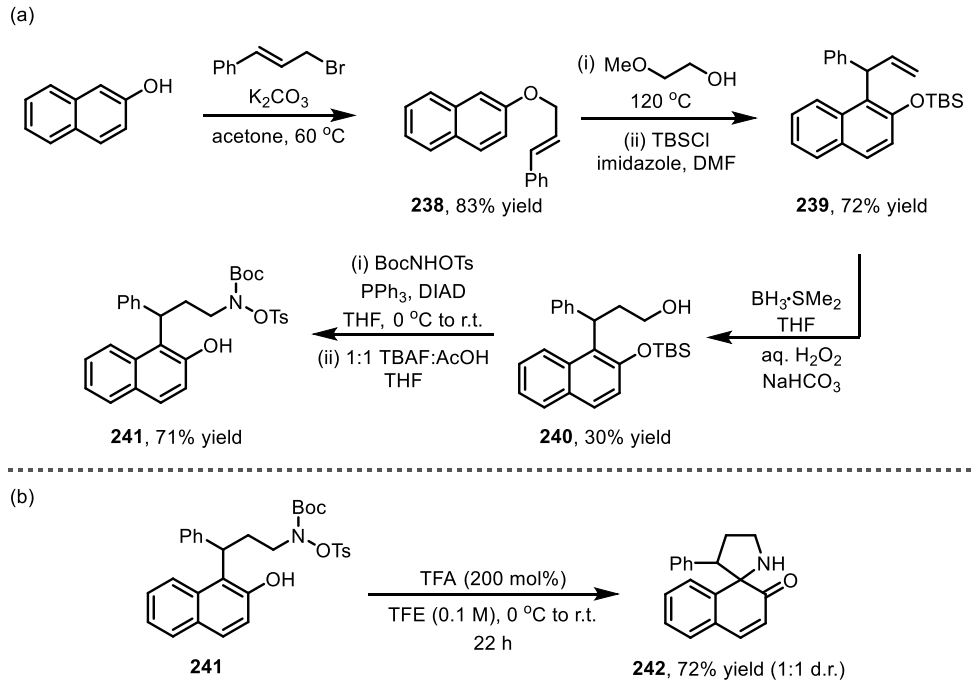
The effect of substitution adjacent to the nitrogen on the carbon tether for naphthol systems was next investigated. Substrate **236** was prepared using the same general approach as for the phenol equivalent (Scheme 73a). When substrate **236** was subjected to the dearomatising amination conditions spirocycle **237** was obtained in 54% yield (Scheme 73b). **237** was formed as an approximately 1.5:1 mixture of diastereomers indicating a lack of diastereocontrol in this reaction. The structure of **237** was confirmed by X-ray crystallography. In this case substitution α to nitrogen had a fairly negligible effect on the yield.



Scheme 73 *(a) Synthesis of substrate **236**. (b) Dearomatising amination of substrate **236**.*

2.3.11 Dearomatising amination of naphthols with substitution γ to nitrogen

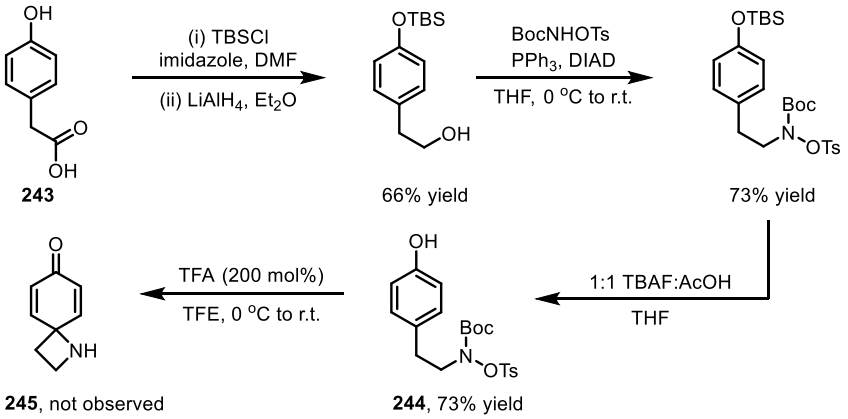
Next substitution γ to nitrogen was investigated for naphthol systems. As such, substrate **241** containing a phenyl substituent in the γ-position was prepared (Scheme 74a). 2-Naphthol was alkylated with cinnamyl bromide to generate allyl ether **238** which upon heating, underwent Claisen rearrangement; this was followed by protection of the resulting phenol hydroxyl group to give allyl substituted naphthol **239**. Alcohol **240** was then accessed *via* a hydroboration-oxidation strategy as used previously, and further transformed to substrate **241** *via* Mitsunobu reaction. Under the conditions of the dearomatisation reaction, substrate **241** cyclised to spirocycle **242** in 72% yield and as a 1:1 mixture of diastereomers (Scheme 74b).



Scheme 74 *(a) Synthesis of substrate **241**. (b) Dearomatising amination of substrate **241**.*

2.3.12 Attempted cyclisation to form 4-membered rings

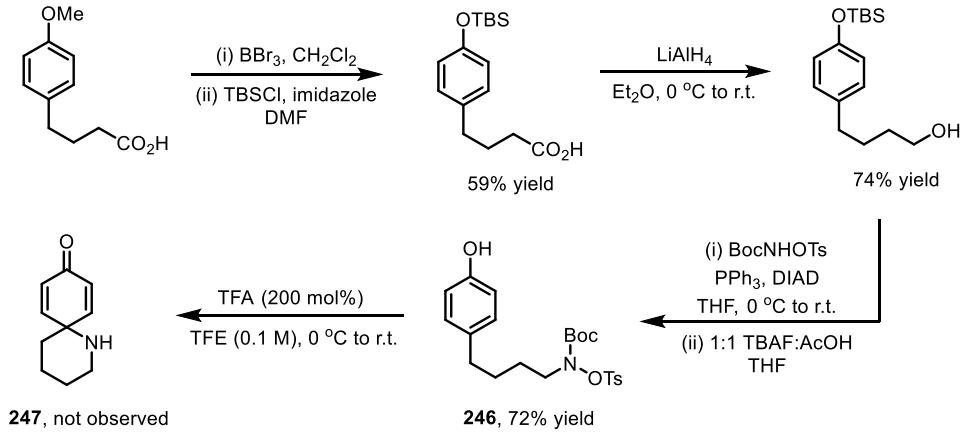
Having established that the dearomatisation reaction is effective for cyclisation to generate pyrrolidines, the synthesis of other ring sizes was investigated. If successful this would allow the preparation of other important classes of *N*-heterocycles such as azetidines and piperidines, the latter in particular are well represented in pharmaceuticals and natural products. Using the same general synthesis strategy as for the synthesis of 5-membered ring substrates, 4-membered ring substrate **244** was generated in four steps from carboxylic acid **243** (Scheme 75). When substrate **244** was subjected to the dearomatising amination conditions, azetidine **245** was not observed. Full consumption of starting material occurred, and no identifiable products were isolated from the reaction mixture. Cyclisation to form 4-membered rings is much slower than for 5-membered rings and as such it is possible that the substrate decomposes before cyclisation can occur.[114] It is also possible that the azetidine product is formed but is too unstable due to the high ring strain and as such decomposes under the reaction conditions.



Scheme 75 *Synthesis and attempted dearomatising amination of substrate **244**.*

2.3.13 Attempted cyclisation to form 6-membered rings

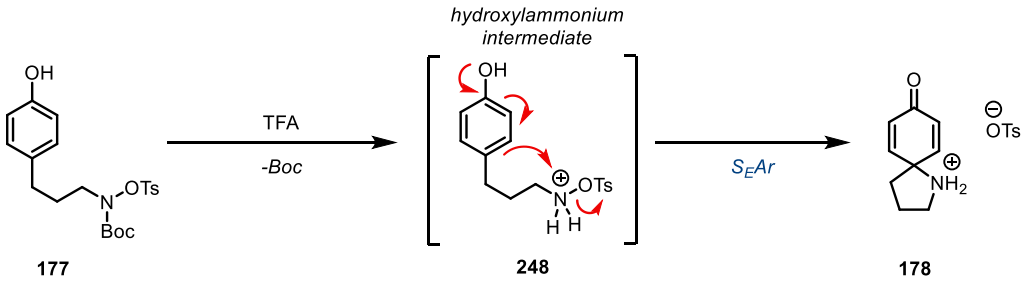
Following the unsuccessful attempt to carry out cyclisations to form 4-membered rings, the analogous 6-*exo* cyclisation was investigated (Scheme 76). Due to the significantly reduced ring strain present in piperidine rings compared to azetidines this was expected to be a more feasible transformation; however, when substrate **246** was subjected to the amination reaction conditions, none of the desired dearomatised product **247** was observed and no significant products could be isolated following flash column chromatography. The piperidine product **247** formed would not be expected to be unstable compared to the pyrrolidine equivalent, as such it is likely that the slower rate at which 6-membered rings form compared to 5-membered rings results in competing decomposition of the starting material before cyclisation can occur.



Scheme 76 *Synthesis and attempted dearomatising amination of substrate **246**.*

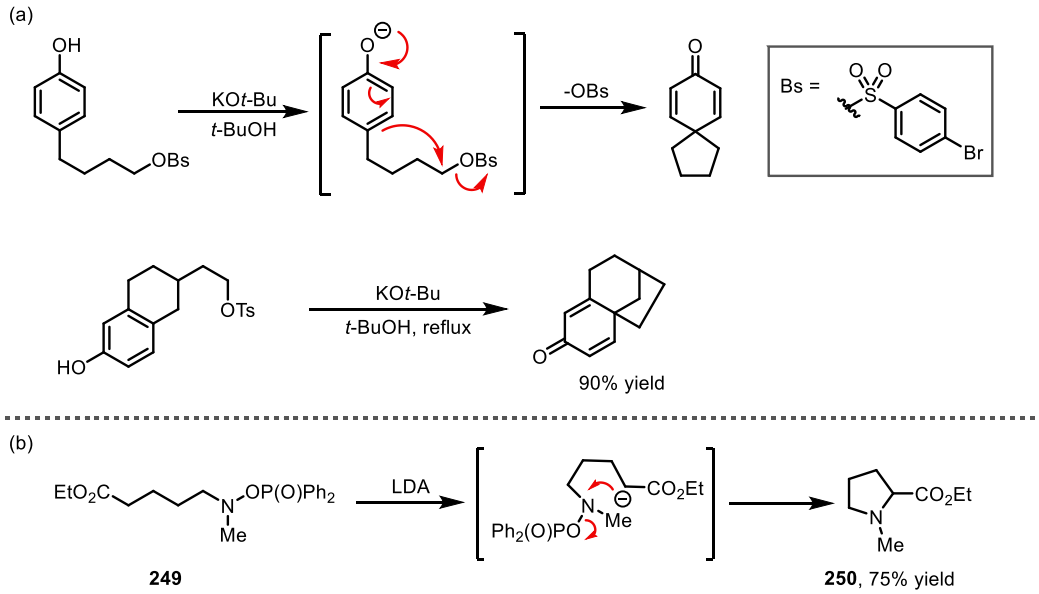
2.3.14 Mechanistic investigations

A proposed mechanism for C-N bond forming dearomatisation is presented in Scheme 77. The reaction begins with TFA-promoted Boc-deprotection of **177** which releases *O*-tosyl hydroxylammonium intermediate **248**. This electrophilic nitrogen species then induces nucleophilic attack of the tethered arene nucleophile in an S_EAr-type reaction with the release of TsOH. In this proposed mechanism the nitrogen of intermediate **248** is protonated during the C-N bond forming step as this alleviates electronic repulsion that would otherwise exist between the incoming arene nucleophile and the nitrogen lone pair of the hydroxylamine; however, it is also possible that the neutral species acts as the reactive intermediate.



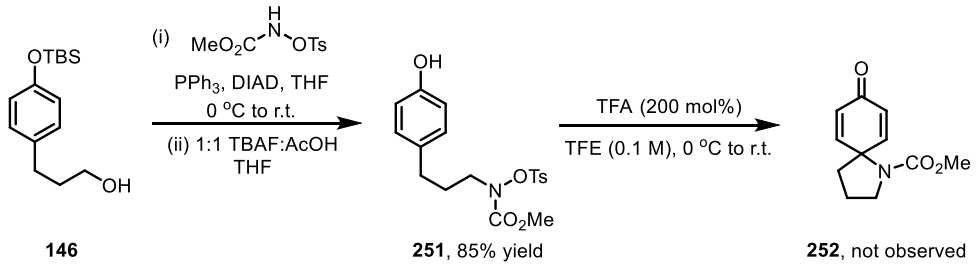
Scheme 77 *Proposed mechanism for the dearomatising amination reaction.*

Although there appears to be no direct precedent for this type of nucleophilic attack of an arene onto an electrophilic N(sp^3)-centre, a related mechanism involving attack onto a C(sp^3)-centre has been invoked in C-C bond forming dearomatisations. Both Winstein and Baird[115] and Masamune[116] have reported base-promoted dearomatisations of phenol derivatives in which an intramolecular nucleophilic attack of a phenol onto an C(sp^3)-sulfonate is invoked (Scheme 78a). In addition, intramolecular nucleophilic substitution at an N(sp^3)-centre of hydroxylamines derivatives **249** has been reported by Sheradsky and Yusupova for the synthesis of pyrrolidines **250** (Scheme 78b).[117] This transformation involves generation of an enolate which subsequently undergoes intramolecular cyclisation onto the nitrogen of a tethered *N*-diphenylphosphinyloxy derivative with expulsion of diphenylphosphinate.



Scheme 78 *(a) Dearomatisation via S_EAr-type attack on C-(sp^3) centres.*[115,116] *(b) Intramolecular nucleophilic substitution at N-(sp^3) centre of hydroxylamine derivatives.*[117]

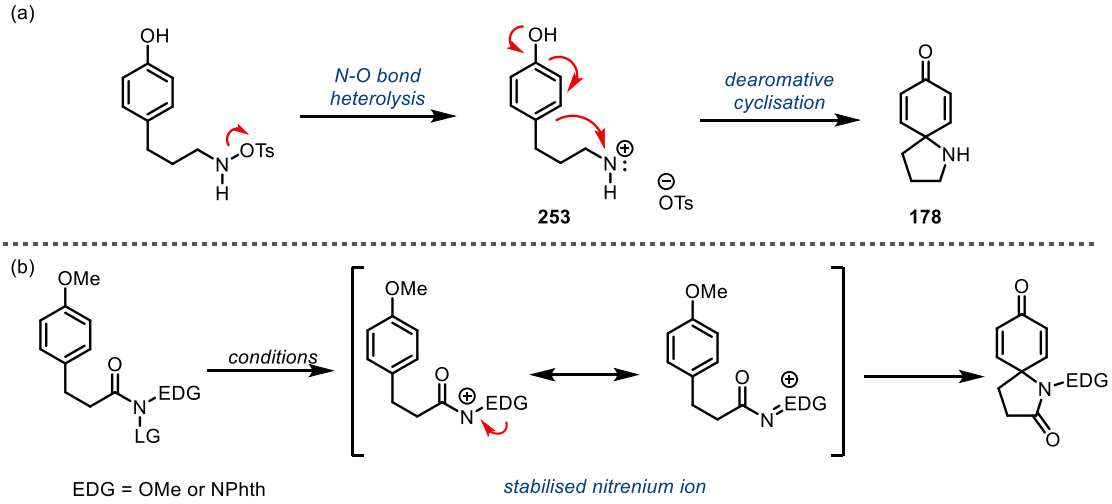
To gain more insight into the reaction mechanism, substrate **251** containing a methyl carbamate group was prepared (Scheme 79). The methyl carbamate of substrate **251** possesses similar electronic properties to the *tert*-butyl carbamate but is not cleaved under acidic conditions. When **251** was subjected to the reaction conditions, cyclisation to **252** did not occur and the starting material was recovered unchanged. This result implies that the mechanism proceeds *via* formation of an N-H hydroxylamine intermediate in which Boc deprotection occurs prior to the cyclisation event.



Scheme 79 *Attempted dearomatising amination of N-methylcarbamate **251**.*

Based on the precedent for many traditional C-N bond forming dearomatisation reactions of substrates containing N-O bonds to proceed *via* formation of a nitrenium ion, reaction *via* nitrenium ion intermediate **253** is an alternative possibility (Scheme 80a). Classical approaches towards intramolecular electrophilic aryl C-H amination and C-N bond forming dearomatisation reported by Kikugawa,[61,63,65,73,109] Glover[62,64] and others[71,110] invoke the intermediacy of nitrenium ions. However, in these examples stabilised nitrenium ions such as

N-alkoxy-*N*-acylnitrenium ions or *N*-phthalimido-*N*-acylnitrenium ions are generated in which the nitrenium ion is stabilised by delocalisation of the positive charge onto the neighbouring alkoxy or Nphth group (Scheme 80b). Moreover, the presence of a carbonyl group adjacent to the nitrenium ion is required; this is likely to prevent elimination.

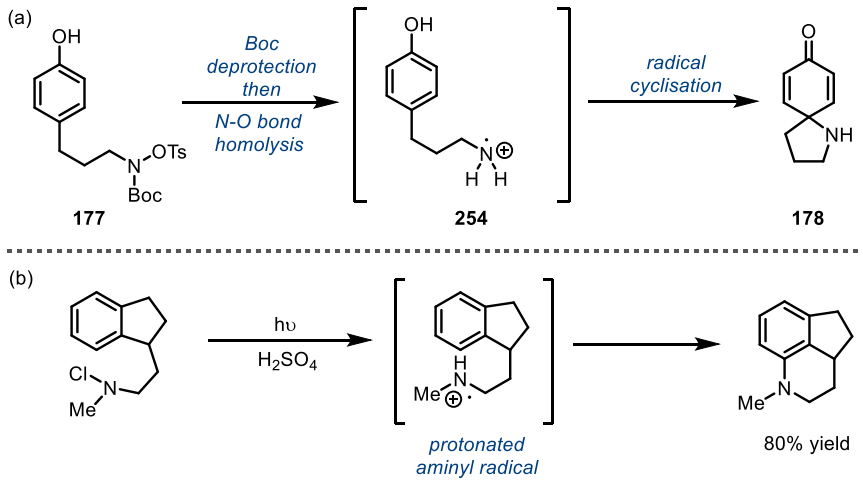


Scheme 80 *(a) Possible mechanism for the formation of **178** via an alkylnitrenium ion. (b) Classical electrophilic dearomatising aminations that invoke stabilised N-alkoxynitrenium ions.*

On the other hand, efficient cyclisations of unstabilised nitrenium ions are unknown. In circumstances where unstabilised nitrenium ions have been invoked they typically undergo isomerisation such as 1,2-alkyl or -hydride shifts.[118-120,XXII] Therefore, although dearomative cyclisation *via* formation of an alkylnitrenium ion cannot be definitively ruled out, this option is unlikely because such species would not be sufficiently stable and long-lived to undergo efficient cyclisation with the pendent arene.[XXIII]

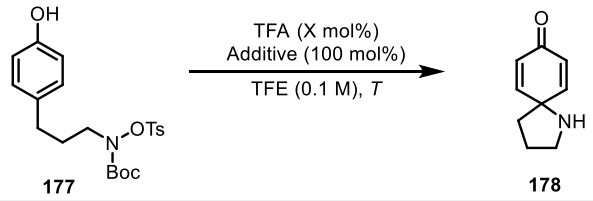
Another mechanistic possibility is that the reaction proceeds through a radical-based pathway. This would involve homolytic cleavage of the N-O bond to generate protonated aminyl radical **254**, followed by radical cyclisation with the pendent arene (Scheme 81a). In this case, reaction would likely occur through a protonated aminyl radical as these are known to be more reactive than the corresponding neutral aminyl radical.[124] Intramolecular cyclisations of aminyl radicals onto aromatic rings have been previously invoked; however, in these cases the aminyl radicals are generated from *N*-chloroamines and require photochemical or strongly acidic conditions (Scheme 81b).[125,126]

[XXII] The intermediacy of unstabilised nitrenium ions in these transformations is a source of debate.[121,122]
[XXIII] An extensive computational study into the stability of nitrenium ions, including alkylnitrenium ions has been carried out by Falvey.[123]



Scheme 81 *(a) Potential dearomatisation via a radical pathway. (b) Intramolecular cyclisation of an aminyl radical.*[125,126]

To rule out a radical pathway, a series of experiments was conducted. When the dearomatisation of **177** was performed in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), no TEMPO trapped product was observed. The addition of either TEMPO or BHT did have an inhibitory effect on the reaction, resulting in lower conversion of starting material; however, this was largely negated using slightly elevated temperatures (Table 6, entries 2-6). Moreover, when the dearomatisation of **177** was performed in the absence of light spirocycle **178** was still generated in 78% yield, excluding the possibility of light-initiated N-O bond homolysis.[XXIV]

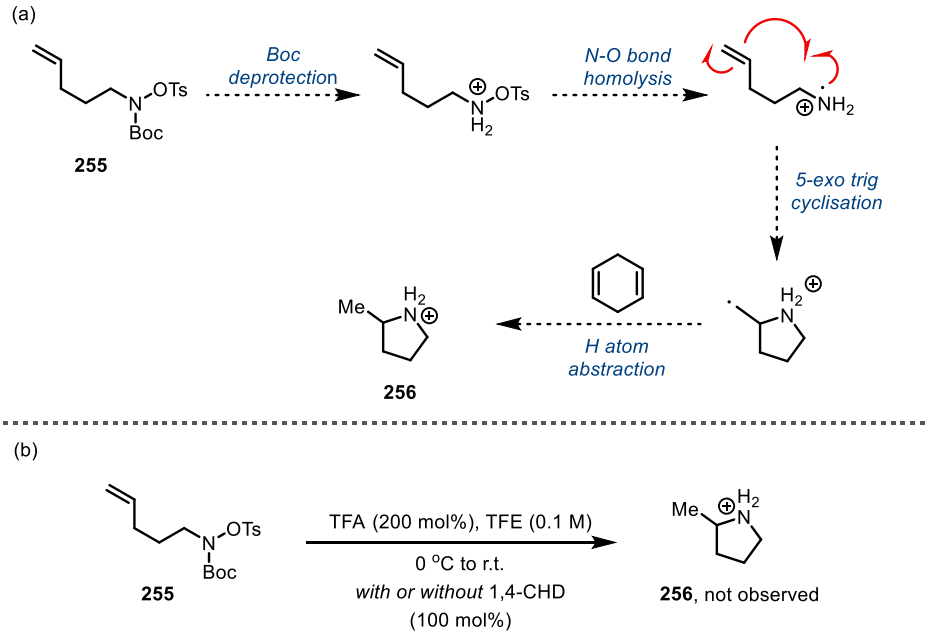


Entry	*X*	*additive*	*temperature*	*yield*
1	200	none	0 °C - r.t.	77%
2	200	TEMPO	0 °C - r.t.	14%
3	300	TEMPO	0 °C - r.t.	30%
4	300	TEMPO	40 °C	58%
5	200	BHT	0 °C - r.t.	46%
6	300	BHT	40 °C	69%

Table 6 *Dearomatising amination reaction of **177** in the presence of BHT or TEMPO. Yields were determined by ^{1}H NMR analysis of the crude reaction mixture versus 1,3,5-trimethoxybenzene as an internal standard.*

[XXIV] Computation results presented in Chapter 3 suggest that N-O bond homolysis under these reaction conditions is disfavoured on energetic grounds.

To investigate further the possibility of the reaction proceeding *via* formation of an *N*-centred radical, alkenyl system **255** was prepared (Scheme 82a). It is well-established that aminyl radicals will undergo fast 5-*exo* cyclisation onto alkenes,[127] this would generate pyrrolidine **256**. When **255** was subjected to the reaction conditions with and without the addition of the hydrogen atom donor, 1,4-cyclohexadiene (CHD), pyrrolidine **256** was not observed.



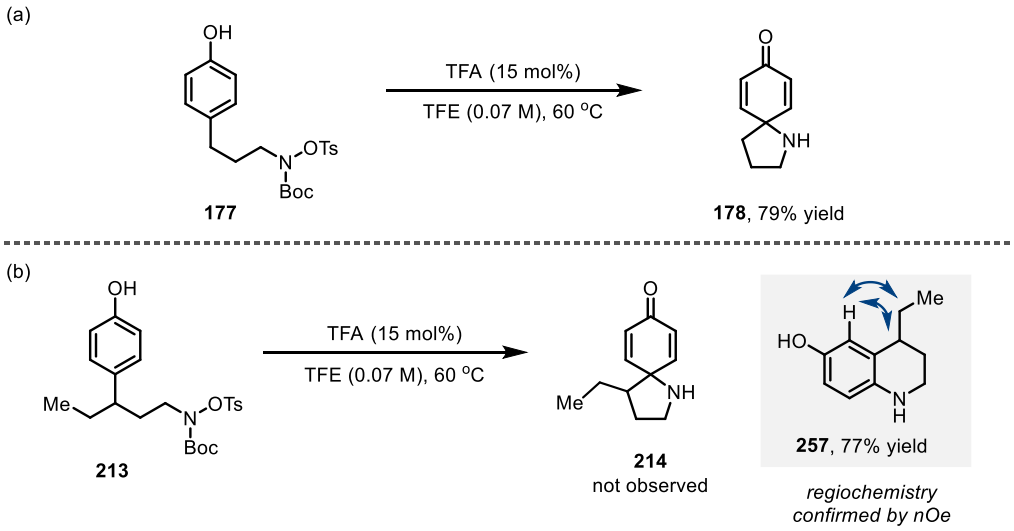
Scheme 82 *(a) Potential 5-exo cyclisation of an aminyl radical intermediate. (b) Attempted radical cyclisation of substrate **255**.*

Due to the lack of precedence for efficient cyclisations of unstabilised nitrenium ions, and with mechanistic work providing no clear evidence of a radical cyclisation, an S_EAr-like mechanism as shown in scheme 77, involving direct S_N2 attack of the arene nucleophile on an activated hydroxylammonium, is favoured at this current time.

2.3.15 Aza-dienone phenol rearrangement

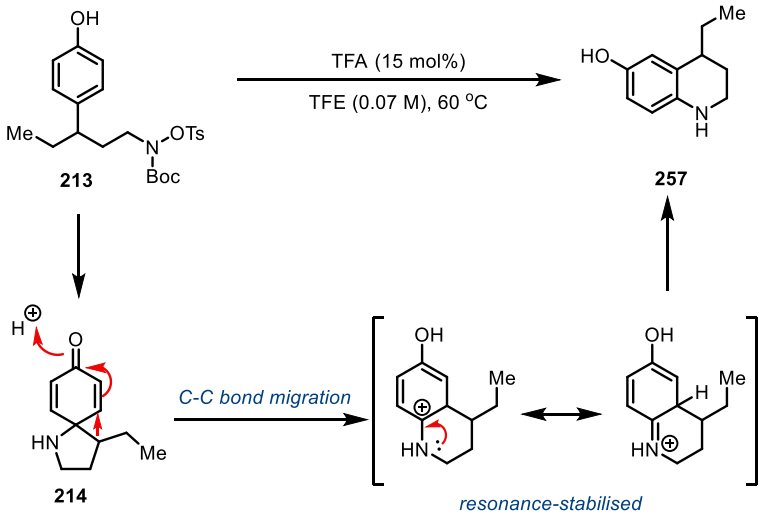
During optimisation, it was shown that the dearomative cyclisation can be performed using fewer equivalents of TFA, although a higher temperature was used to increase the rate of reaction. Using TFA (15 mol%) in TFE (0.07 M) at 60 °C, **177** cyclised to spirocycle **178** in 79% yield (Scheme 83a). When these conditions were applied to tosyloxycarbamate **213**, spirocycle **214** was not observed and instead tetrahydroquinoline **257** was generated in 77% yield (Scheme 83b). Analysis of the product using nOe analysis confirmed the structure of **257** in which skeletal rearrangement has occurred. As such, unlike the tetrahydroquinoline side products observed with other systems (section 2.3.5) which were generated *via* direct aryl-CH

amination, this reaction must proceed *via* a mechanistically distinct pathway involving skeletal rearrangement.



Scheme 83 *(a) Dearomatising amination of substrate **177** using a catalytic amount of TFA. (b) Observation of tetrahydroquinoline **257** in the dearomatising amination reaction of substrate **213**.*

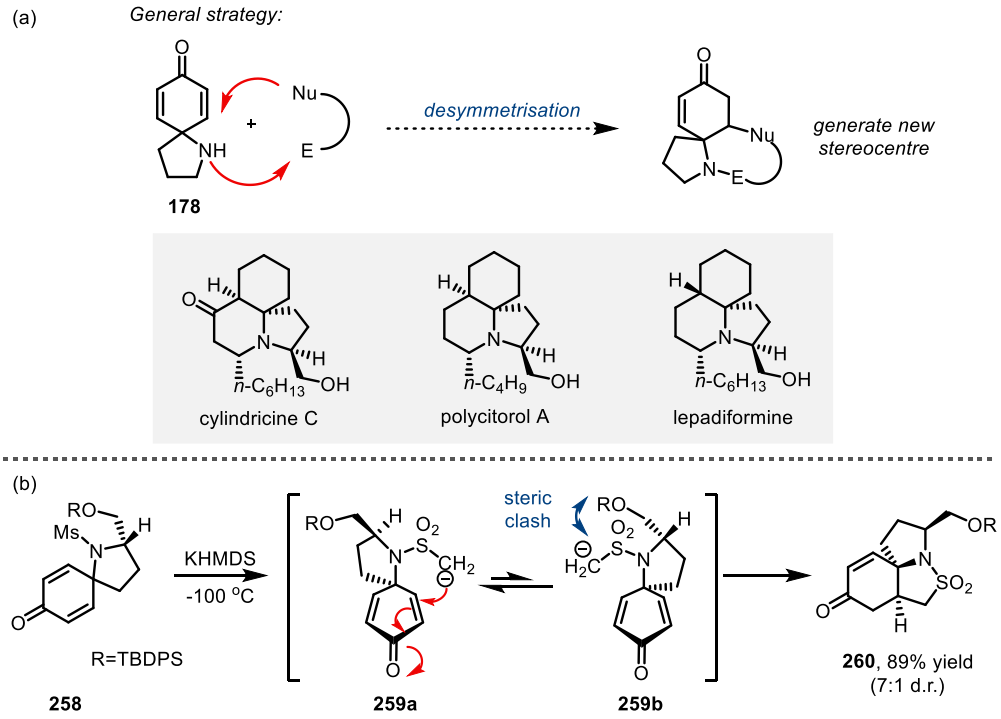
The formation of **257** likely proceeds *via* initial spirocyclisation to **214** which then undergoes a thermally promoted aza-dienone-phenol rearrangement to tetrahydroquinoline **257** (Scheme 84). Migration of the C-C bond is favoured over migration of the C-N bond as the carbocation formed is stabilised through resonance with the lone pair of the adjacent nitrogen. As a result of the lower equivalents of acid, the amine is not fully protonated and so can use its lone pair to assist C-C bond migration. This rationalises why no dienone-phenol rearrangement was observed for reaction of **213** under standard conditions (200 mol% TFA at room temperature). The presence of the ethyl substituent in this substrate is also key to observing this reaction pathway as no dienone-phenol rearrangement was observed for tosyloxycarbamate **177** under the same reaction conditions. This can be rationalised due to the increased migratory aptitude of the migrating C-C bond as a result of the *+I* inductive effect of the ethyl substituent.



Scheme 84 *Proposed formation of tetrahydroquinoline **257** by a dienone-phenol rearrangement.*

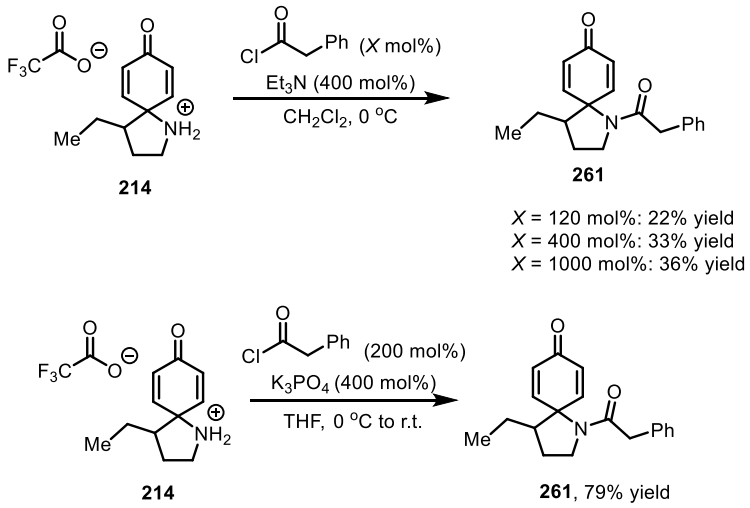
2.3.16 Annulative derivatisations of the spirocyclic pyrrolidine products

The spirocyclic pyrrolidine products generated from the dearomatising cyclisations described thus far provide many opportunities for further functionalisation. One obvious avenue for derivatisation was to exploit 1,4-addition addition of nucleophiles onto one of the diastereotopic alkenes of the cyclohexadienone ring of **178**. This approach would enable the creation of a tetrasubstituted nitrogen-bearing stereogenic carbon centre. Such carbon centres are generally difficult to access in a stereoselective manner. Through protection of the pyrrolidine nitrogen with appropriate functionality which can then acts as a nucleophile it was considered feasible to access tricyclic ring systems containing a nitrogen-bearing spirocyclic carbon centre (Scheme 85a). Related structural motifs are present in a number of alkaloid natural products including cylindricine C,[128,129] polycitorol A[130] and lepadiformine.[2,131-133] The functionalisation of spirocyclic pyrrolidines similar to those presented in this chapter have been studied by Ciufolini and co-workers as a key step in the synthesis of cyclindricine C.[134] The authors demonstrated that treatment of *N*-mesyl protected spirocycle **258**, which was prepared by oxidative amination, with KHMDS at -100 °C generated tricycle compound **260** as a 7:1 mixture of diastereomers (Scheme 85b). The diastereoselectivity observed in the cyclisation was rationalised by the steric demands of the *O*-protecting group favouring reaction *via* **259a** over the alternative conformer **259b** in which it clashes with the *N*-sulfonyl group.



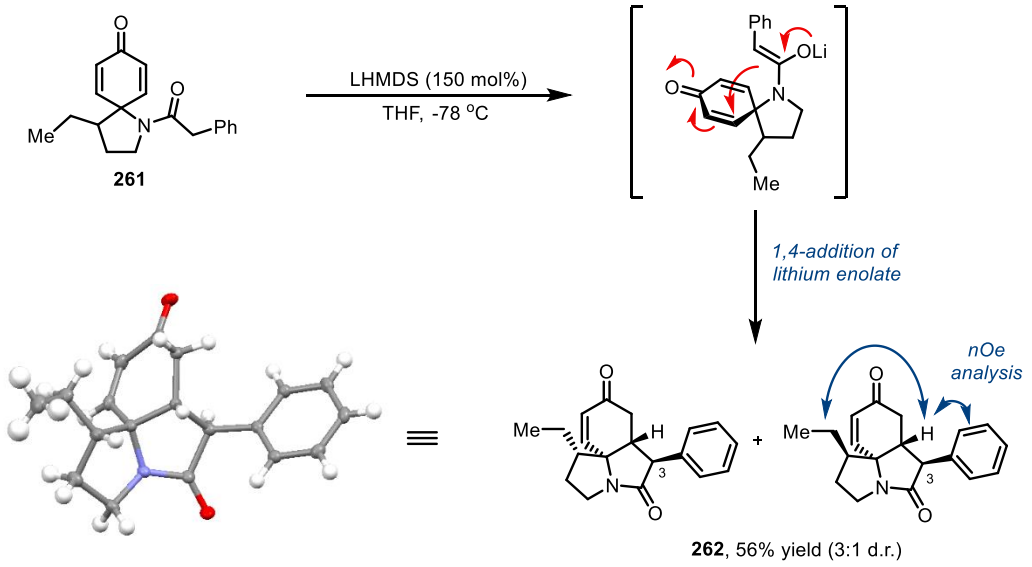
Scheme 85 *(a) Strategy for annulative derivatisations. (b) Derivatisation of spirocyclohexadienones through intramolecular 1,4-addition.*[134]

To investigate derivatisations of the spirocyclohexadienones generated by dearomatisation of *N*-tosyloxycarbamtes, **214** was acylated using phenylacetylchloride (Scheme 86). It was envisaged that upon addition of an appropriate base this would set up a 1,4-addition onto the dienone ring *via* formation of an enolate. The TFA salt of spirocycle **214** was reacted with phenylacetyl chloride (120 mol%) in the presence of Et_3N (400 mol%) at 0 °C to generate amide **261** in 22% yield. Further increasing the equivalents of phenylacetyl chloride to 400 mol% effected a slight increase in yield to 33% but any further increase of this reagent had a negligible effect. After further optimisation, it was identified that K_3PO_4 (400 mol%) in THF at 0 °C to room temperature enabled the efficient synthesis of amide **261** in 79% yield.



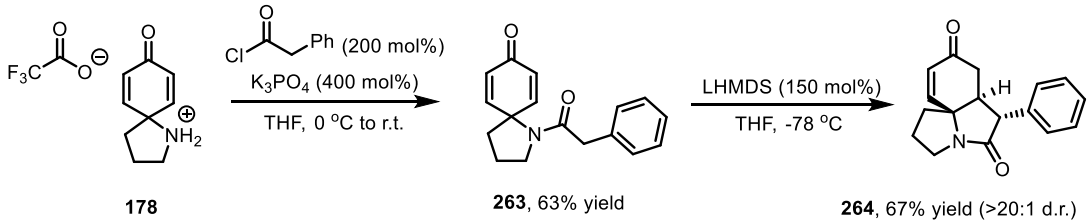
Scheme 86 *Optimisation of the acylation of spirocycle **214**.*

Pleasingly when exposed to LHMDS (150 mol%) amide **261** underwent cyclisation to generate tricyclic amide **262** in 56% yield and 3:1 d.r. (Scheme 87). The reaction proceeds *via* formation of a lithium enolate which then undergoes conjugate addition onto one of the double bonds of the dienone. The relative stereochemistry of the major diastereomer was confirmed by X-ray crystallography whilst that of the minor diastereomer was assigned using nOe analysis. **262** contains 4 contiguous stereocentres, 3 of which are formed with high diastereocontrol during the conjugate addition step. Control of the stereochemistry of the benzylic carbon centre is likely a result of epimerisation of the relatively acidic C3 proton to give the more thermodynamically stable isomer.



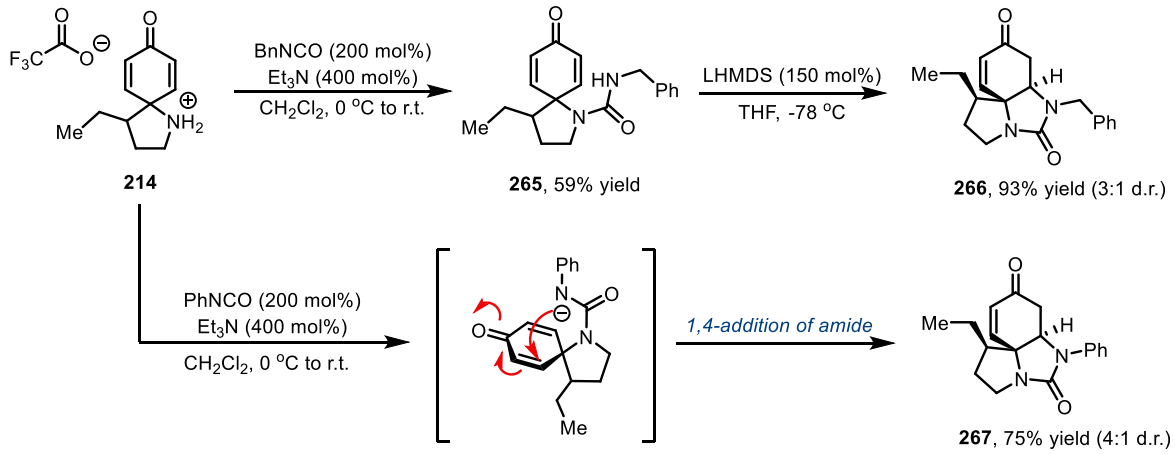
Scheme 87 *Synthesis of **262** by intramolecular 1,4-addition of **261**. The stereochemistry of the minor diastereomer of **262** was determined by nOe.*

The same transformation was also performed with spirocycle **178** (Scheme 88). Following acylation, the lithium enolate of **263** cyclised efficiently to give tricycle **264** in 67% yield and as a single diastereomer.



Scheme 88 *Synthesis of tricycle **264** from spirocycle **178**.*

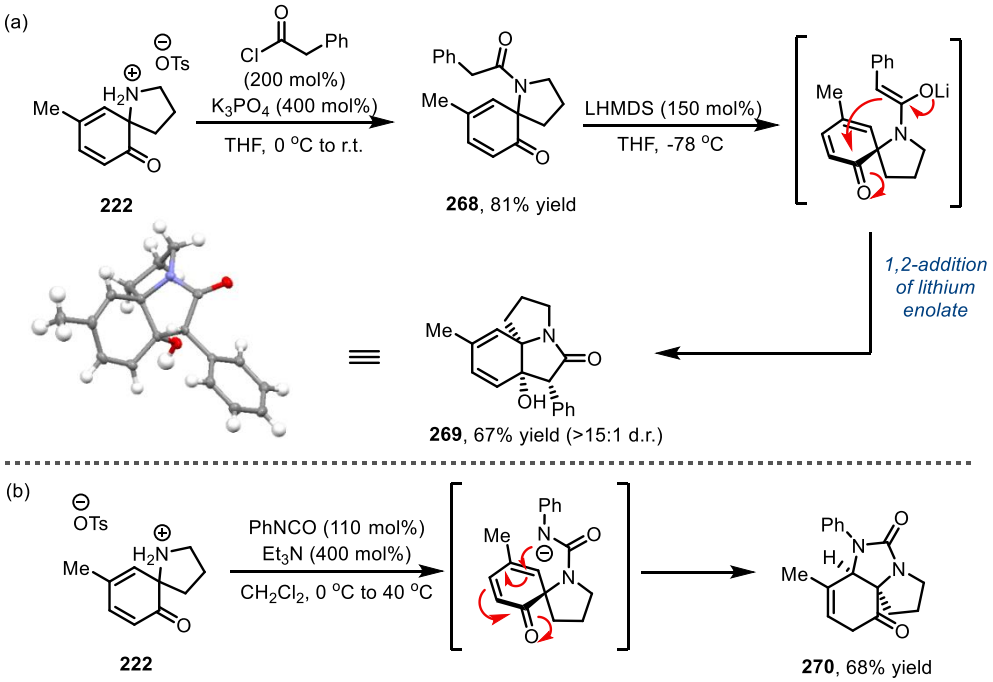
Using a similar approach, the generation of tricyclic ureas were also explored. When spirocycle **214** was reacted with benzyl isocyanate (200 mol%) and Et_3N (400 mol%) in CH_2Cl_2 urea **265** was generated in 59% yield (Scheme 89). Treatment with LHMDS then promoted intramolecular 1,4-addition of the urea NH onto the enone to give *N*-benzyl protected tricycle **266** in 93% yield and 3:1 d.r. Spirocycle **214** was also acylated with phenyl isocyanate. In this case the increased acidity of the *N*-phenyl urea versus the *N*-benzyl urea meant that Et_3N was sufficient to effect cyclisation, and tricycle **267** was generated in 75% yield and 4:1 d.r. directly from spirocycle **214**.



Scheme 89 *Synthesis of tricyclic ureas by annulative derivatisations of **214**.*

Similar derivatisation processes were also carried out on *ortho*-cyclised spirocycle **222** (Scheme 90). Following the dearomatisation reaction the crude reaction mixture containing spirocycle **222** was treated with phenylacetyl chloride using the optimised reaction conditions to generate amide **268** in 81% yield. When **268** was reacted with LHMDS, 1,2-addition onto the carbonyl of the dienone was observed to give tricycle **269** in 67% yield (Scheme 90a). The

structure and relative stereochemistry were confirmed by single crystal X-ray diffraction. In contrast, when spirocycle **222** was treated with phenyl isocyanate, 1,6-addition occurred to afford tricycle **270** as a single diastereomer (Scheme 90b).



Scheme 90 *(a) Synthesis of tricycle **269** from spirocycle **222**. (b) Synthesis of tricyclic urea **270** from spirocycle **222**.*

2.4 Base-promoted dearomatising amination reaction

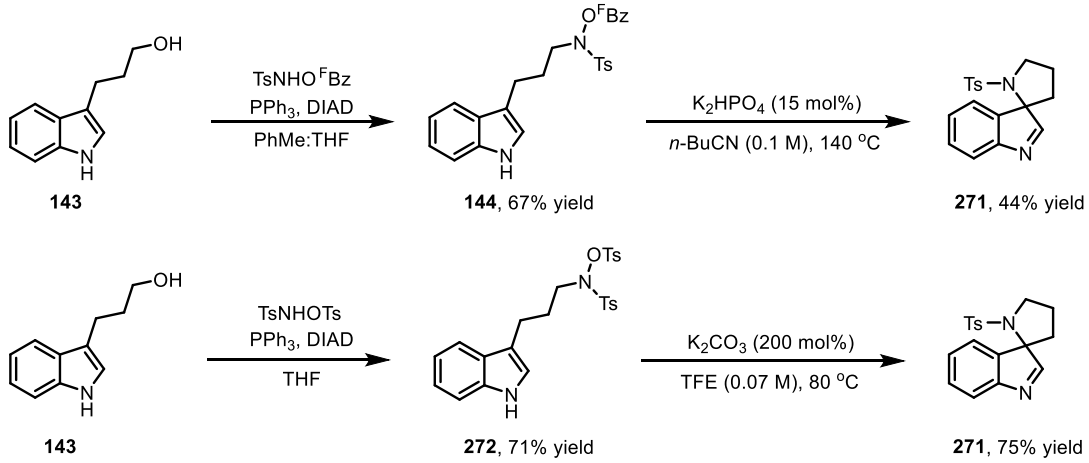
The contents of this section have been communicated: Ma, X.; Farndon, J, J.; Young, T.; Fey, N.; Bower, J. F.; *Angew. Chem. Int. Ed.* **2017**, *56*, 14531-14535. Parts of this section have been reproduced from this publication.

The results in this section were obtained by Xiaofeng Ma and hence are not detailed in the experimental section.

2.4.1 Initial results

In tandem with the development of the acid-promoted dearomatising amination of phenols and naphthols presented so far in this chapter, other classes of dearomatising aminations were also investigated. To this end, a base-promoted, metal-free C-N bond forming dearomatisation of indoles was developed. It was discovered by Xiaofeng Ma that sulfonamide **144**, which was prepared *via* Mitsunobu alkylation of TsNHO^{F}Bz with alcohol **143**, could undergo C-N bond forming dearomatisation under mild, basic conditions [K_2HPO_4 (15 mol%) in *n*-BuCN at 140 °C] to provide spirocycle **271** in 44% yield (Scheme 91). To improve the efficiency of this

process OTs substrate **272** was prepared. Following optimisation of the reaction conditions the desired dearomative transformation was achieved using a milder set of reaction conditions [K_2CO_3 (200 mol%) in TFE at 80 °C] to generate spirocycle **271** in 75% yield. The milder conditions possible for the OTs substrate **272** can be rationalised by the leaving group ability of pentafluorobenzoate versus tosylate (pK_a values in H_2O at 25 °C: ^{F}BzOH 1.75, TsOH 0.7).[135] TsOH is over 10 times more acidic than that of ^{F}BzOH reflecting the higher stability of the tosylate anion, which makes reaction of **272** relatively more facile. As this reaction proceeds under basic conditions it represents a complementary approach to the dearomatisation reaction presented previously in this chapter, and in this approach the protecting group on nitrogen is retained. Whilst C-N bond forming dearomatisations of indoles to provide spirocyclic pyrrolidines of this type have not previously been reported, Nishikawa and Isobe have reported a related dearomatisation of indoles to form spirocyclic-β-lactams using *O*-sulfonyl-hydroxylamine derivatives.[136]



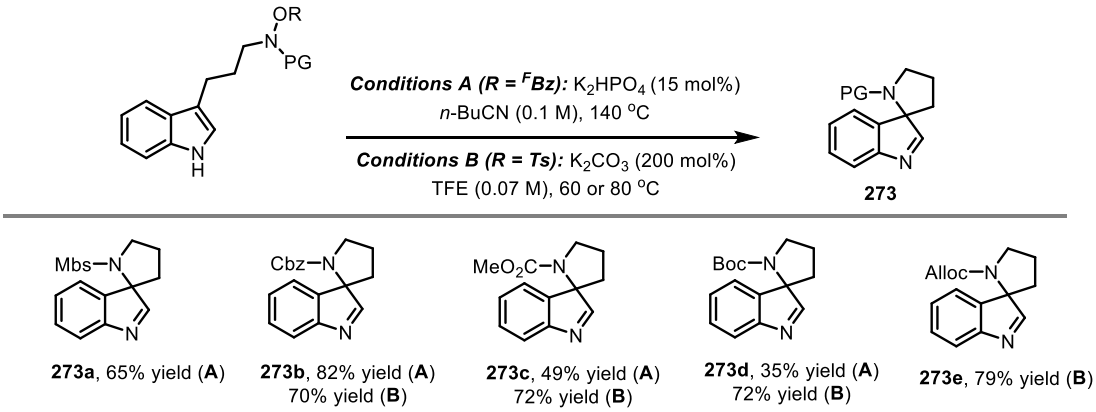
Scheme 91 *Base-promoted dearomatising amination of indole substrates **144** and **272**.*

2.4.2 Scope of the *N*-protecting group[XXV]

The dearomative aminations of indole substrates containing a wide range of *N*-protecting groups were examined (Scheme 92). These were all prepared by Mitsunobu alkylation of the corresponding amino reagent with alcohol **143**. In general, both the O^{F}Bz and OTs substrates were prepared and examined using the optimised conditions developed for each class of substrate. The reaction demonstrated good protecting group tolerance. In addition to sulfonamide based systems, including *N*-Mbs (Mbs = *p*-methoxybenzenesulfonyl) system **273a**, a variety of carbamate-based systems were also effective. By this approach spirocyclic

[XXV] The results in this section were carried out by Xiaofeng Ma (University of Bristol).

products **273b-e** containing benzyl, methyl, *tert*-butyl and allylcarbamates could also be accessed relatively efficiently. The higher reactivity of OTs systems was generally reflected in higher yields, with the exception of *N*-Cbz system **273b** where cyclisation of the O^FBz precursor was more efficient. The explanation for the higher efficiency of the O^FBz system in this case is unclear; however, in general O^FBz precursors were more stable than the OTs counterparts.

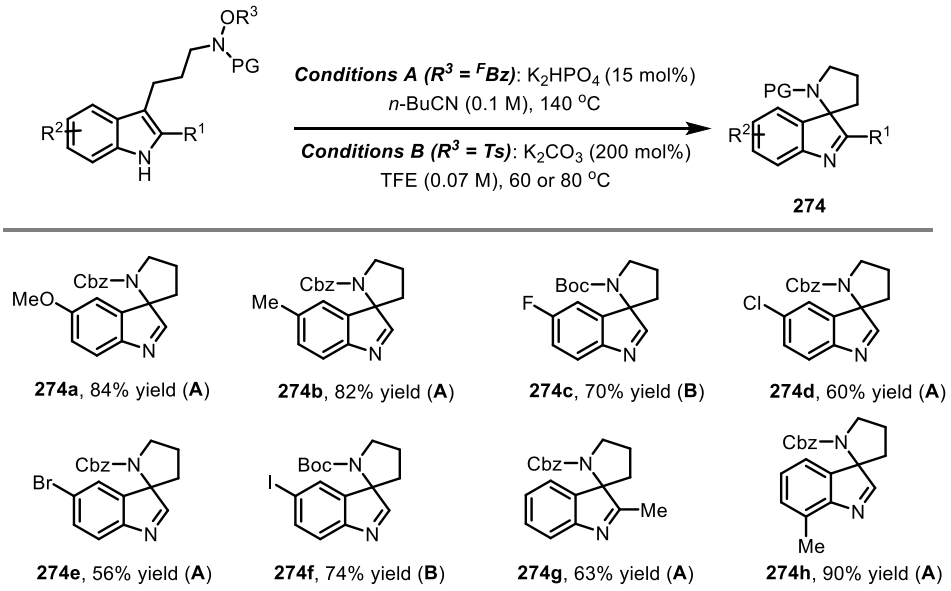


Scheme 92 *Scope of protecting group in the base promoted dearomatising amination of indoles.*

2.4.3 Scope of base-promoted dearomatisation of indoles[XXVI]

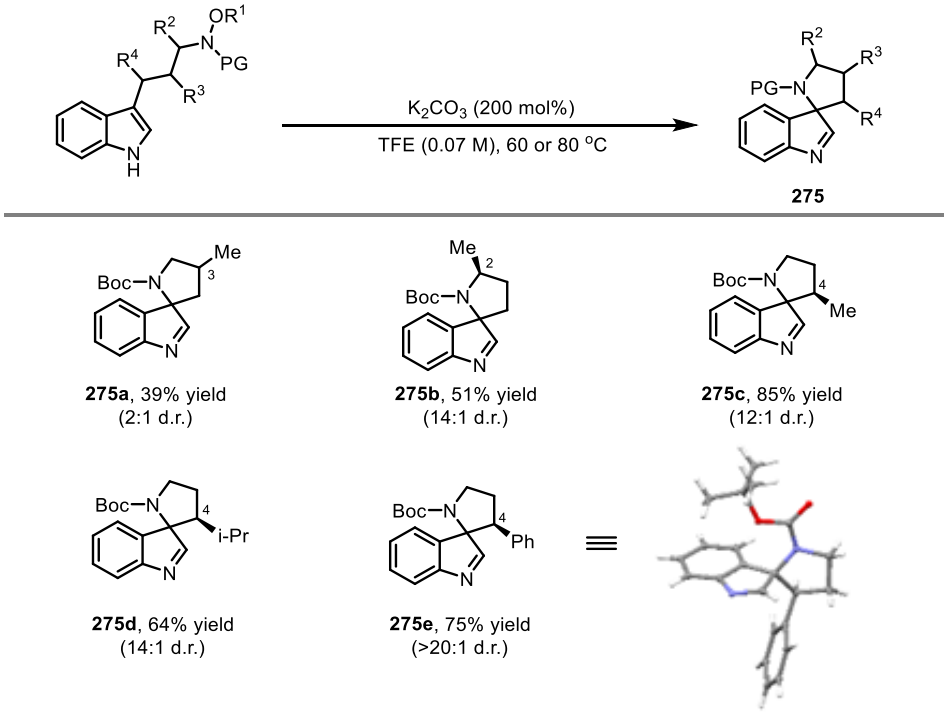
Following on from investigating the scope of the protecting group, the scope of the indole part was evaluated. A variety of substrates with substitution on the indole ring underwent dearomatisation to provide spirocycles **274a-h** in excellent yields (Scheme 93). The reaction tolerates a variety of both electron-donating and electron-withdrawing groups although in the case of electron-withdrawing halogen-substituted systems **274c-f** lower yields were generally observed.

[XXVI] The results in this section were carried out by Xiaofeng Ma (University of Bristol).



Scheme 93 *Scope of substitution on the indole ring in the base-promoted dearomatising reaction.*

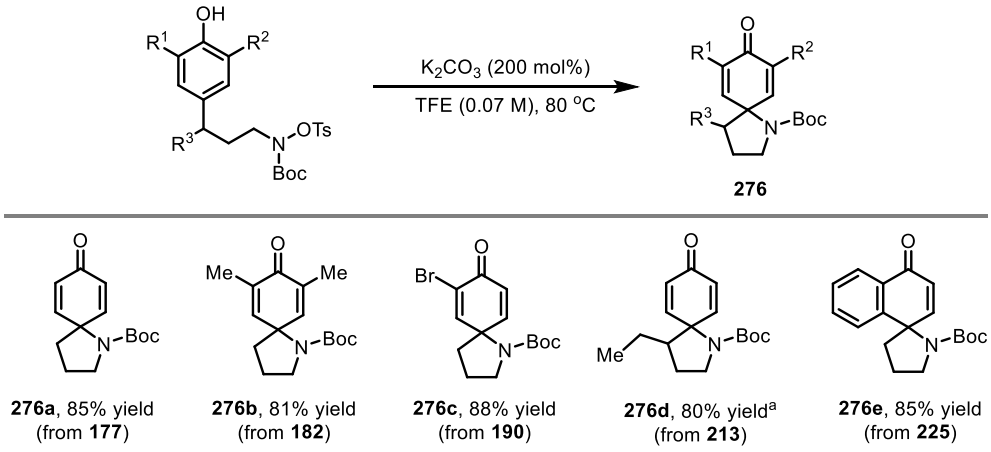
Substitution on the pyrrolidine ring was also investigated (Scheme 94). Modest diastereocontrol was observed for system **275a** with a C3-substituted methyl group; however, high levels of diastereocontrol were observed for systems with a methyl group in the C2 or C4 positions, **275b** and **275c**. As expected, improved levels of diastereocontrol were observed for systems **275d** and **275e** with bulkier substituents on the pyrrolidine ring.



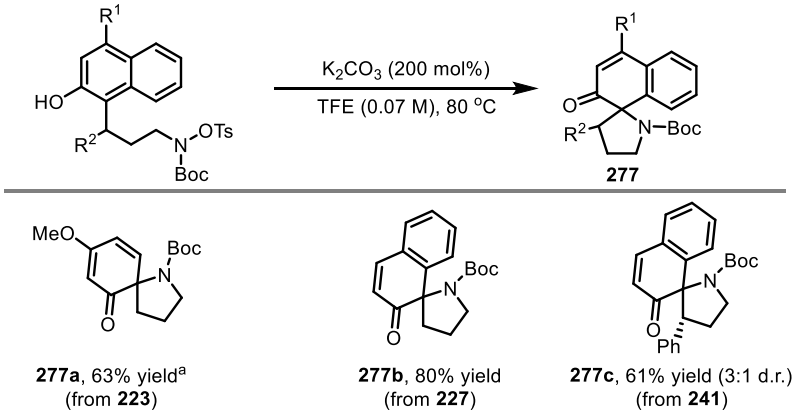
Scheme 94 *Scope of substitution on the pyrrolidine ring in the dearomatising amination reaction.*

2.4.5 Scope of base-promoted dearomatisation of phenols and naphthols[XXVII]

The scope of this base-promoted dearomatisation reaction was then extended to the cyclisation of *para*-phenols and *para*-naphthols (Scheme 95). *N*-Boc-protected systems **276a-e** were accessed in excellent yields. In addition, the base-promoted dearomatising amination conditions were also successfully applied to the reaction of *ortho*-phenols and *ortho*-naphthols (Scheme 96, **277a-c**). In general, these conditions could be applied to a wide variety of functionalised phenols and naphthols with similarly levels of efficiency observed in most cases.



Scheme 95 *Scope of base-promoted dearomatising amination of para-phenols and para-naphthols.* [a]*The reaction was carried out at 60 °C.*

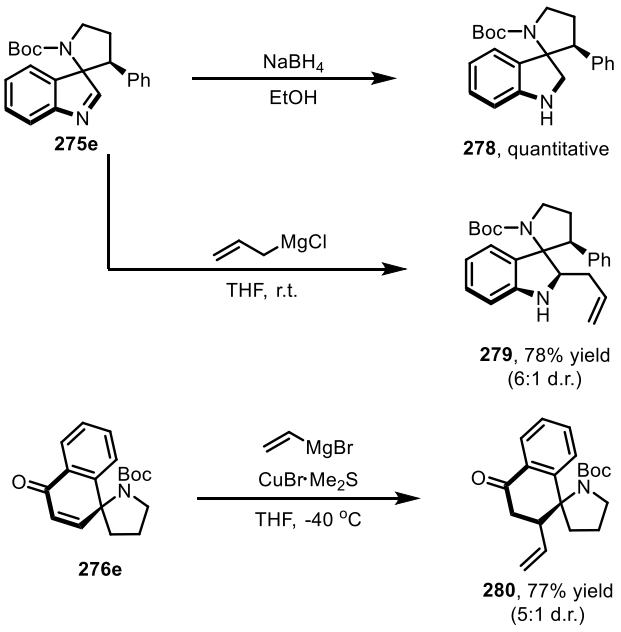


Scheme 96 *Scope of base-promoted dearomatising amination of ortho-phenols and ortho-naphthols.* [a]*The reaction was carried out at 60 °C.*

[XXVII] The results in this section were carried out by Xiaofeng Ma (University of Bristol).

2.4.6 Derivatisations of the dearomatisation products[XXVIII]

A number of derivatisations of the dearomatised products were carried out (Scheme 97). Reduction of the imine moiety of **275e** with $NaBH_4$ occurred smoothly to afford indoline **278** in quantitative yield. In addition, imine **275e** was alkylated with allyl-Grignard reagent to provide **279** in 78% yield and 6:1 d.r. with addition occurring primarily from the face opposite to the *N*-Boc group. Conjugate addition of vinyl-cuprate reagent to **276e** also occurred diastereoselectively to afford **280** in 77% yield and 5:1 d.r.



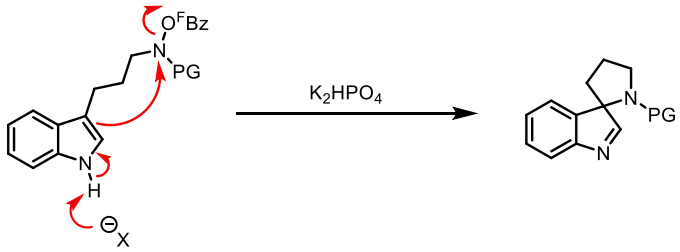
Scheme 97 *Derivatisations of the dearomatisation products.*

2.4.7 Mechanistic studies[XXIX]

Based on a series of computational and practical experiments, a proposed mechanism for this reaction is presented in Scheme 98. The proposed mechanism is very similar to that of the acid-promoted reaction, in that dearomative cyclisation occurs by direct nucleophilic attack of the arene onto the electrophilic nitrogen centre in an S_N2-like manner. However, in this case, the mild base present (K_2CO_3 or K_2HPO_4) likely increases the nucleophilicity of the aromatic unit by deprotonation either prior to or during the dearomatisation process. In the absence of base minimal conversion is observed, whilst hindered organic bases such as 2,6-di-*tert*-butylpyridine are ineffective. This suggests that the base is not merely required to sequester the TsOH or ^{F}BzOH by-products and is likely required to increase the nucleophilicity

[XXVIII] The results in this section were carried out by Xiaofeng Ma (University of Bristol).
[XXIX] The results in this section were carried out by Xiaofeng Ma (University of Bristol).

of the arene. For the O^FBz systems catalytic quantities of base can be used as the pentafluorobenzoate leaving group undergoes facile protodecarboxylation to afford pentafluorobenzene and CO_2 with regeneration of the base.[137,XXX]

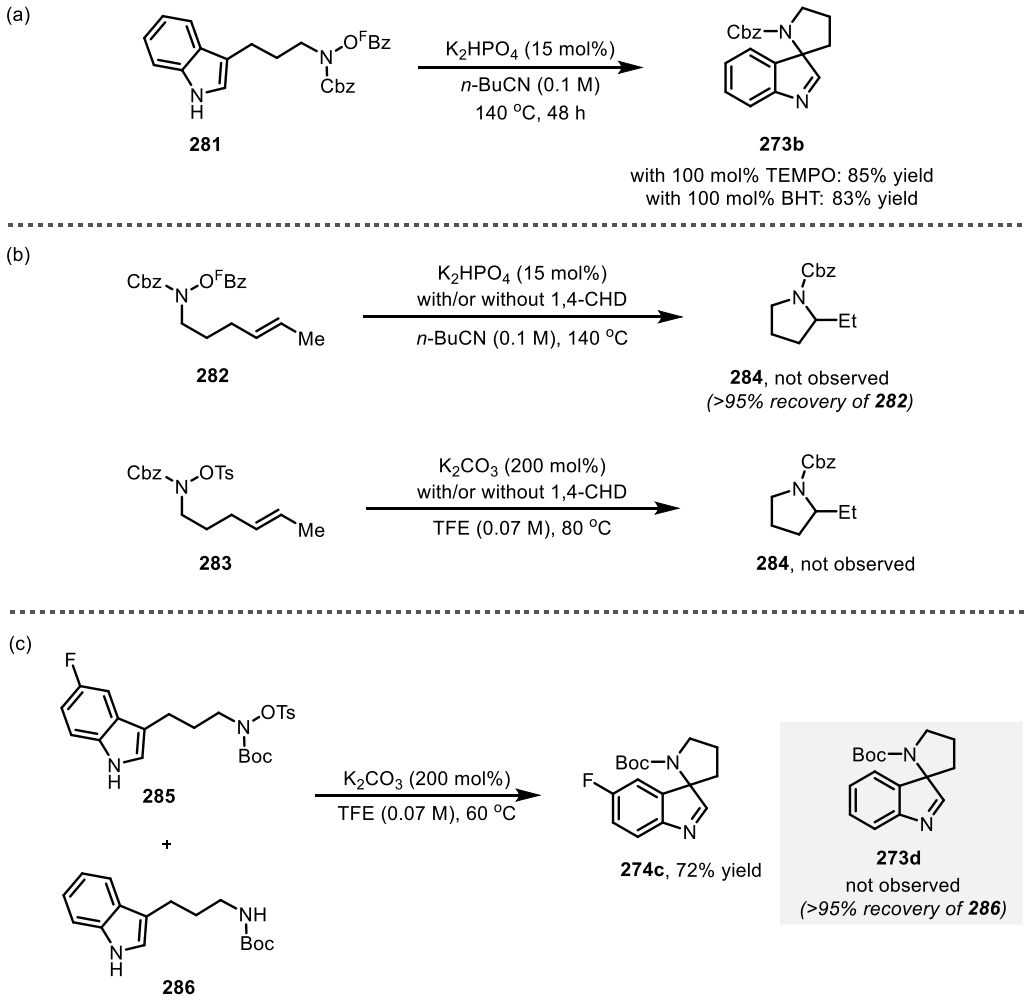


Scheme 98 *Proposed mechanism for the base-promoted dearomatising amination reaction.*

As with the acid-promoted dearomative amination reaction, a series of experiments were performed to rule out the potential of dearomatisation *via* a radical-based pathway (Scheme 99a,b). The cyclisation of **281** was not affected by the presence of TEMPO or BHT and the dearomatisation product **273b** was obtained in comparable yields to the reaction without the addition of either additive (Scheme 99a). In addition, the behaviour of alkenyl systems **282** and **283** was examined; however, when **282** and **283** were subjected to the optimised dearomatisation conditions (in the presence or absence of 1,4-cyclohexadiene) pyrrolidine **284** was not observed (Scheme 99b). This implies that an aminyl radical intermediate is not generated as this would be expected to undergo 5-*exo* cyclisation onto the pendent alkene.[127]

To further support the proposed mechanism a cross-over experiment was performed in which substrate **285** was subjected to the dearomatisation conditions in the presence of NH carbamate **286** (Scheme 99c). Dearomative cyclisation of **285** was observed in a similar yield to the reaction without **286** whilst **273d**, the product of cyclisation of **286** was not observed. This confirms that the N-O bond acts as an internal oxidant during the reaction and is not effective as an external oxidant.

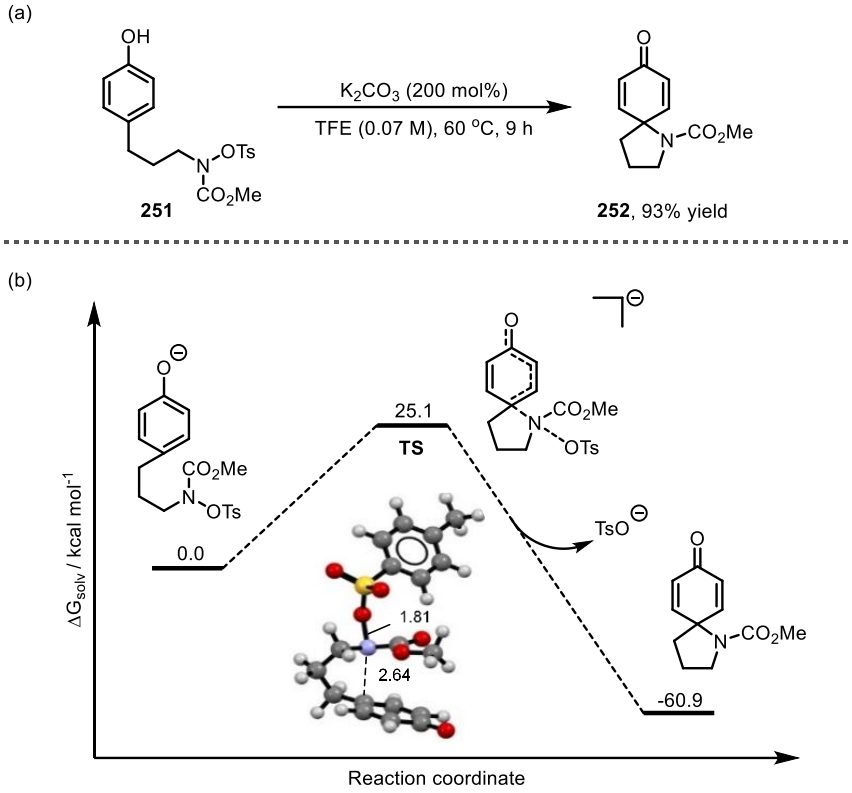
[XXX] The presence of pentafluorobenzene was confirmed by GCMS analysis of the crude reaction mixture.



Scheme 99 (*a) Base-promoted dearomatising amination of substrate **281** in the presence of TEMPO or BHT. (b) Attempted radical cyclisation of substrates **282** and **283**. (c) Base-promoted dearomatising amination of substrate **285** in the presence of **286**.*

Density functional theory (DFT) calculations were also performed to assess the viability of the proposed S_N2-like mechanism.[XXXI] For the purposes of the study the calculations were performed using tosyloxycarbamate substrate **251** which experimentally undergoes efficient dearomative cyclisation to **252** in 93% yield (Scheme 100a). When the dearomatisation of **251** was modelled for an S_N2-like mechanism, the predicted free energy barrier ($\Delta G^{\ddagger}_{solv}$) is 25.1 kcal mol^{-1} (Scheme 100b). The magnitude of this energy barrier is consistent with the reaction time required for complete conversion under the reaction conditions.

[XXXI] Computational studies were carried out by Tom Young with guidance from Dr Natalie Fey (University of Bristol).

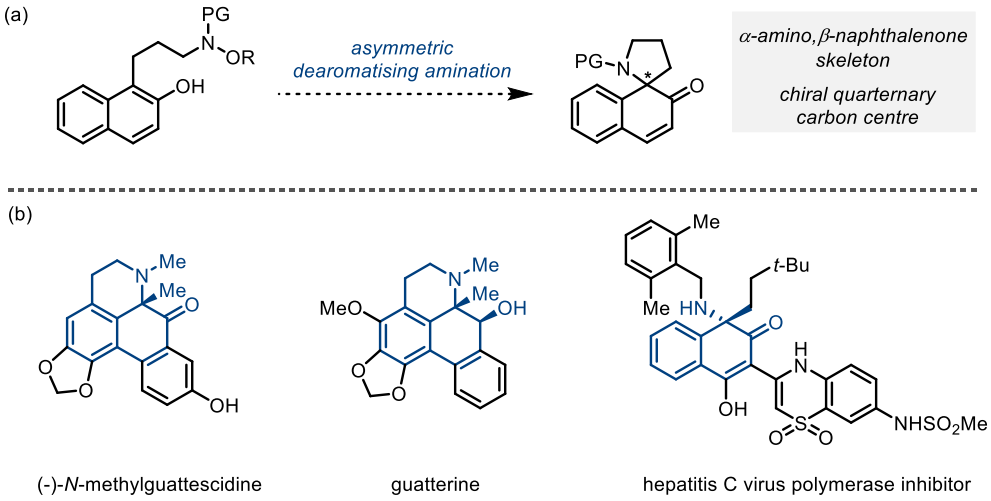


Scheme 100 (*a) Base-promoted dearomatising amination of N-methylcarbamate **251**. (b) Reaction profile for the proposed S_N2 mechanism.*

2.5 Studies towards an enantioselective dearomatising amination reaction

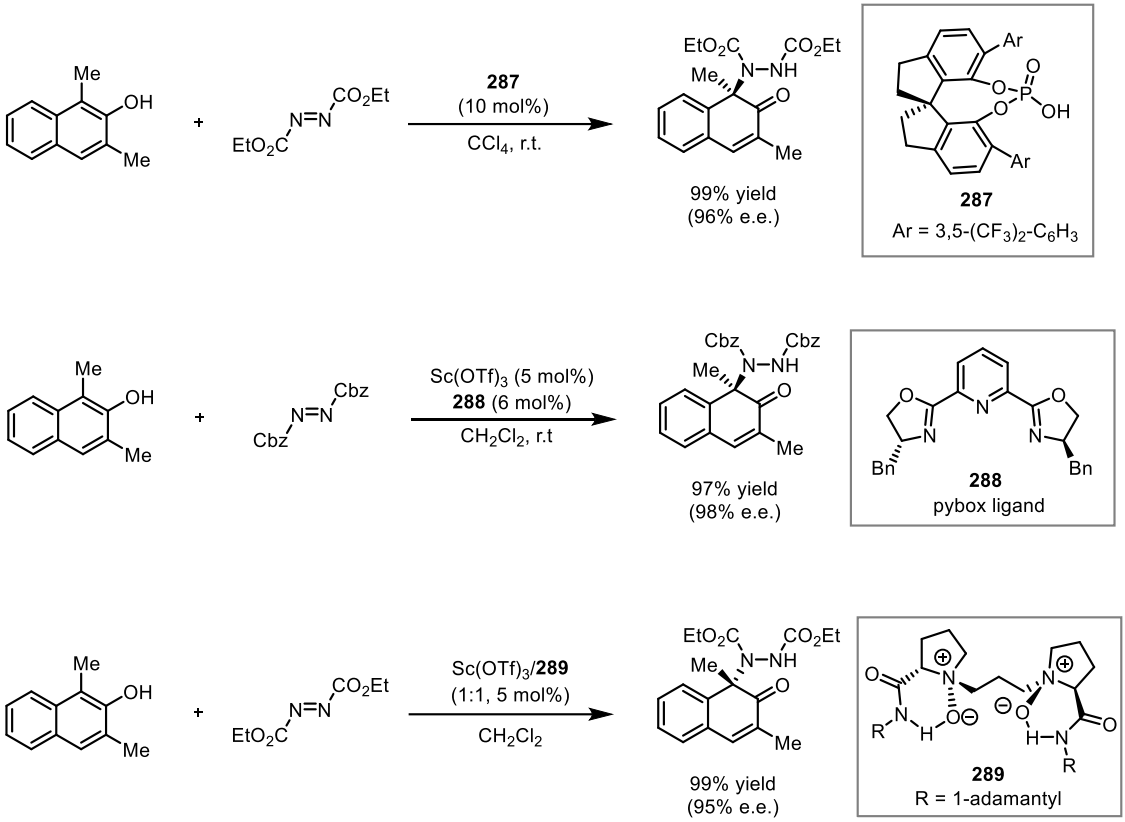
2.5.1 Introduction

The dearomatising amination reactions discussed so far allow access to complex *N*-heterocycles. Due to the importance of nitrogen heterocycles in nature particularly those with defined stereocentres adjacent to nitrogen, enantioselective dearomatising amination reactions are highly desirable and so the development of an asymmetric reaction was investigated.



Scheme 101 *(a) Proposed enantioselective dearomatising amination of naphthols. (b) Natural products and therapeutic agents containing α-amino,β-naphthalenone core.*

The enantioselective *ortho*-dearomative amination of naphthols was investigated as this would enable the formation of α-amino,β-naphthalenone structures containing a tetrasubstituted stereogenic centre (Scheme 101a). These types of motifs are important components of many biologically active natural products and therapeutic agents, including a hepatitis C virus polymerase inhibitor (Scheme 101b).[138] Also despite the importance of this motif only a few examples of asymmetric aminative dearomatisations to access these structures have been reported. These approaches typically employ azodicarboxylates as a source of electrophilic nitrogen which are activated by either Brønsted or Lewis acids (Scheme 102). You and co-workers reported an asymmetric dearomatising amination reaction of β-naphthols using chiral phosphoric acids as catalysts.[139] The reaction could be performed with loadings as low as 0.1 mol% and e.e's up to 96% were achieved using (*R*)-SPINOL-derived phosphoric acid **287**. Enantioselective dearomatising aminations of naphthols using azodicarboxylates were also reported by the Luan group.[140] A catalyst system comprising of $Sc(OTf)_3$ and a chiral pybox ligand **288** (Scheme 102) allowed for the generation of α-substituted 2-naphthols with excellent enantioselectivities of up to 98%. A related process was also developed by Feng and co-workers using a combination of $Sc(OTf)_3$ and a chiral *N*,*N*-dioxide ligand **289** to affect the dearomative amination of naphthols with high levels of enantioselectivity (Scheme 102).[141]

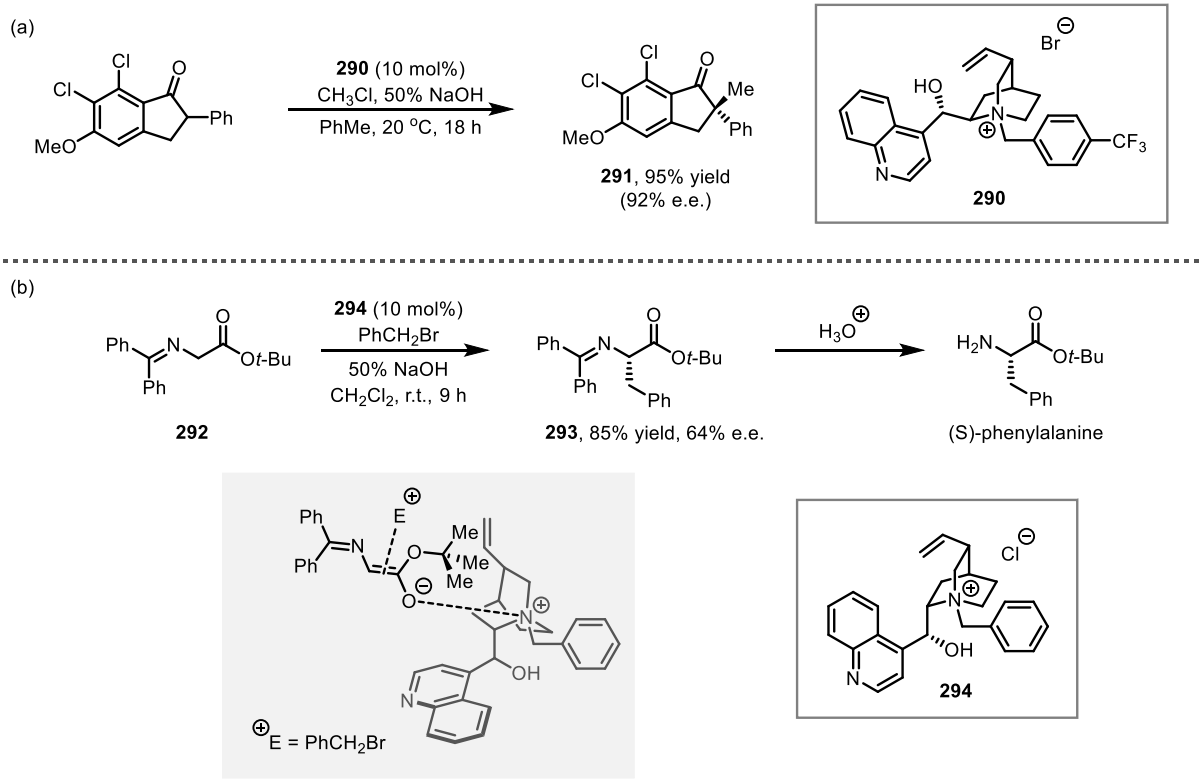


Scheme 102 *Previous examples of enantioselective dearomatising amination of β-naphthols using azodicarboxylates.*[139-141]

For the development of an enantioselective dearomatisation reaction of naphthols, the use of *Cinchona* alkaloid-derived phase transfer catalysts (PTC) was investigated. These quaternary ammonium salts were first employed as chiral phase transfer catalysts by the Merck research group in 1984 (Scheme 103a). Using *N*-*p*-trifluoromethylbenzylcinchonium bromide **290** as catalyst enantioselective methylation of phenylindanone was achieved to generate the product **291** in 92% e.e.[142] Similar *Cinchona*-derived phase transfer catalysts were used by O'Donnell and co-workers for the enantioselective alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester **292**.[143-145] The resulting alkylated product **293** was then hydrolysed to allow access to the corresponding amino acid. The origin of enantioselectivity in this reaction can be explained as shown in Scheme 103b by thinking of the quaternary ammonium salt **294** as an imaginary tetrahedron composed of the four carbons attached to the quaternary nitrogen. The enolate of **292** forms an ionic complex with the ammonium cation of the PTC. However, the *cinchona* PTC provides steric shielding that inhibits the approach of the enolate to three faces of the tetrahedron leaving only one face open to form the ionic complex. Once the ionic complex is formed, one face of the enolate is blocked by the quinoline ring of the PTC forcing the $PhCH_2Br$ electrophile to approach from the other face leading to high enantioselectivity. The commercial

availability and relatively low cost of many of these *Cinchona* PTC make them attractive catalysts for developing a variety of asymmetric reactions.

Cinchona alkaloids have been reported as effective catalysts for the enantioselective α-amination of carbonyl compounds,[146-149] whilst there have been several examples reported of their use in enantioselective alkylative and aminative dearomatisations.[150-152] As such, the use of *Cinchona* PTC to achieve an enantioselective dearomatising amination reaction was envisaged to be a feasible route to explore. [XXXII]



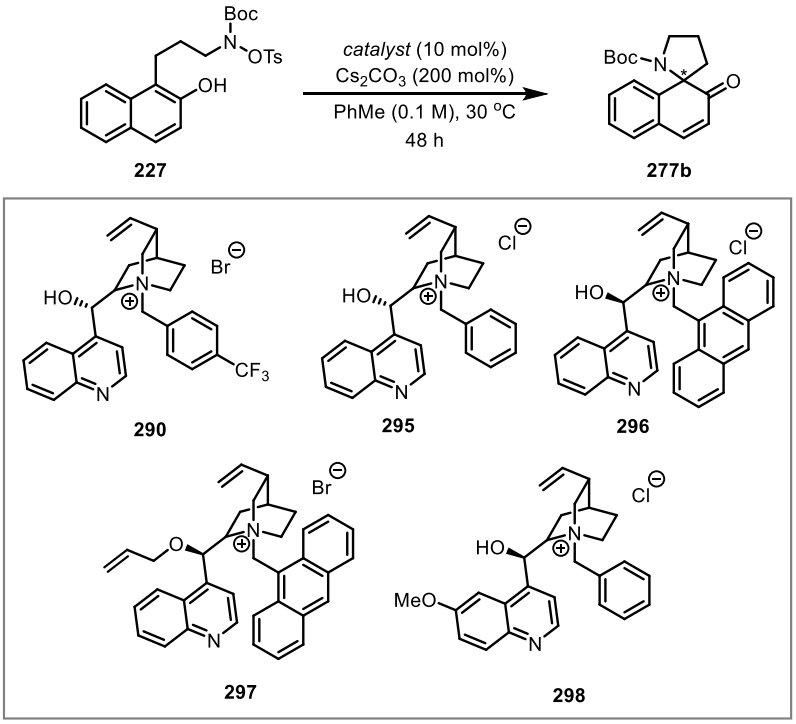
Scheme 103 *(a) Enantioselective methylation of phenylindanone using Cinchona-derived PTC.[142](b) Enantioselective alkylation using Cinchona-derived PTC.[143-145]*

2.5.2 Preliminary results

To examine the potential for an enantioselective dearomatising amination reaction, *N*-Boc protected naphthol **227** was investigated with five different commercially available *Cinchona* alkaloid-derived chiral phase transfer catalysts (Scheme 104). Using Cs_2CO_3 (200 mol%) in PhMe at 30 °C only minor enantioselectivity was observed in most cases with **295** producing the highest level of asymmetric induction to afford **277b** in 22% e.e. In contrast, for **290** no enantioselectivity was observed. The reactions were run at a lower temperature of 30 °C (versus

[XXXII] Four common *Cinchona* alkaloid-derived catalysts were examined by Luan; however, only minor enantioselectivity was observed.[140]

the optimised conditions developed for the racemic base-promoted dearomatisation reaction) with the view that this would lead to improved enantioselectivity. However, as a result, the conversion to product was quite low which is reflected in the generally low yields achieved even after performing the reactions for 48 hours.

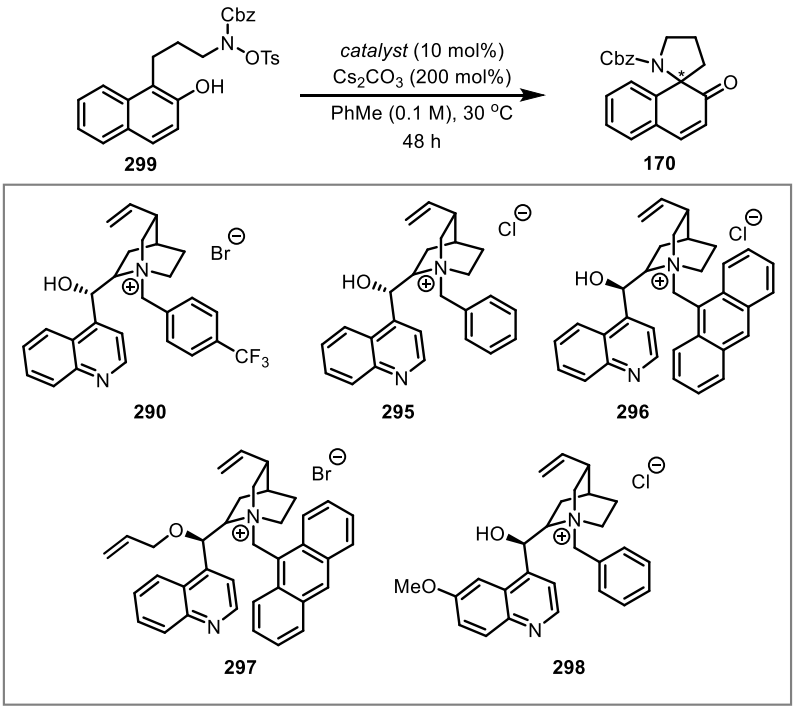


Entry	*catalyst*	*yield*	*e.e.*
1	**290**	37%	0%
2	**295**	28%	22%
3	**296**	38%	10%
4	**297**	26%	6%
5	**298**	61%	6%

Scheme 104 *Enantioselective dearomatising amination of substrate **227**.*

To explore this enantioselective reaction further, the choice of *N*-protecting group was examined. *N*-Cbz protected naphthol **299** was prepared in the same manner as for the *N*-Boc substrate with the rationale that the slightly larger protecting group (Cbz versus Boc) may translate into higher levels of enantioselectivity. **299** was then examined using the same five chiral phase transfer catalysts (Scheme 105). Under the same reaction conditions, the *N*-Cbz naphthol proved more reactive resulting in higher yields of dearomatised product **170**. This also coincided with generally much higher levels of enantioselectivity. The best result was obtained with **298** which gave the spirocyclic product in 62% yield and 54% e.e. This result shows that enantioselective dearomatising amination of naphthols using phase transfer catalysts is feasible and with further optimisation satisfactory levels of enantioselectivity might

be obtainable. Unfortunately, due to time constraints further optimisation of this enantioselective dearomatisation could not be carried out; however, additional investigations into this project will likely be carried out by other members of the group.



Entry	*catalyst*	*yield*	*e.e.*
1	**290**	40%	36%
2	**295**	41%	28%
3	**296**	43%	28%
4	**297**	42%	4%
5	**298**	62%	54%

Scheme 105 *Enantioselective dearomatising amination of substrate **299**.*

2.6 Conclusions

The development of transition metal-free dearomative C-N bond forming cyclisations of hydroxylamines for the synthesis of spirocyclic pyrrolidines has been discussed. Under acidic conditions, *in situ* deprotection of OTs activated *N*-Boc hydroxylamines generates a potent electrophilic aminating agent for the dearomative amination of phenols and naphthols. This approach provides a metal-free alternative to metal-nitrenoid-promoted amination reactions. In a complementary approach, mild, basic conditions were also shown to be effective for C-N bond forming dearomatisation of the same OTs activated hydroxylamines as well as $O^{F}Bz$ activated hydroxylamines. This protocol offers unprecedented scope versus traditional dearomatising amination approaches, encompassing indoles, phenols and naphthols as the nucleophile as well as tolerating a range of *N*-protecting groups. Another benefit over many

traditional approaches is the lack of requirement for oxidising conditions as the N-O bond acts as a mild internal oxidant which avoids any competing oxidation processes involving the arene. The spirocyclic pyrrolidine products presented in this Chapter are recognised as privileged scaffolds in drug discovery and are commonly found in the core structures of many natural products, such as cyclindricine C[128,129] and lepadiformine.[2,131-133] Preliminary studies towards an enantioselective dearomatising amination of β-naphthols using *Cinchona* alkaloid-derived chiral phase transfer catalysts were carried out, and moderate levels of enantioselectivity were obtained.

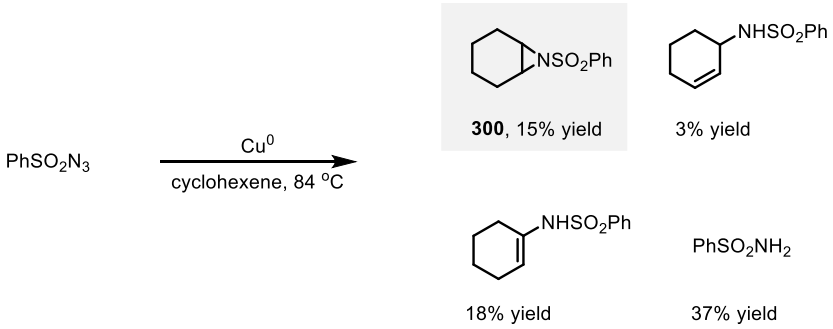
Chapter 3 - Alkene aziridinations of *N*-Boc hydroxylamines

The contents of this chapter have been communicated: Farndon, J. J.; Young, T. A.; Bower, J. F.; *J. Am. Chem. Soc.* **2018**, *140*, 17846-17850. Parts of this chapter have been reproduced from this publication.

3.1 Introduction

Following the successful development of a dearomatising amination reaction involving *N*-tosyloxycarbamates under mild, metal-free conditions, it became clear that other classes of C-N bond forming reaction that utilised electrophilic nitrogen sources may be amenable to this approach. As similar N-O donors have been effectively applied in alkene aziridination reactions, this area was deemed worthy of investigation. Before presenting the studies in this chapter related to the development of an alkene aziridination reaction of *N*-Boc hydroxylamines; it is pertinent to give a brief survey of the chemical literature relating to alkene aziridinations; in particular, methods that involve the addition of nitrenes or metal-nitrenoids to alkenes will be discussed.

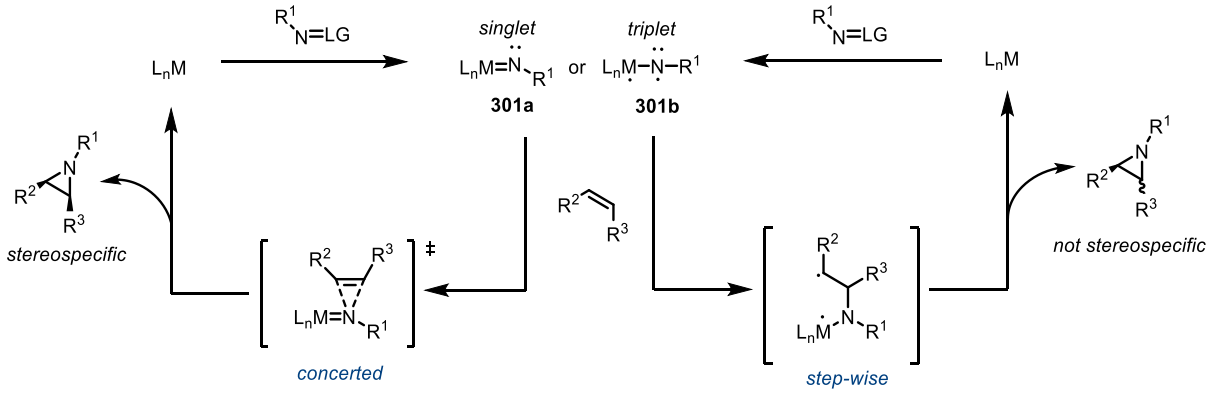
In 1967 Kwart and Khan reported the first metal-catalysed nitrogen atom transfer process for the synthesis of aziridines (Scheme 106).[153] When heated with copper powder in cyclohexene the authors observed the decomposition of benzenesulfonyl azide. Amongst the decomposition products obtained was aziridine **300** which was proposed to form *via* addition of a nitrene or nitrenoid intermediate to cyclohexene.



Scheme 106 *Copper powder-promoted alkene aziridination of benzenesulfonyl azide.*[153]

Since this initial report, metal-catalysed addition of nitrenes to alkenes has become one of the most common approaches to the synthesis of aziridines. A variety of nitrene sources have been utilised in such reactions include aryl azides, sulfonyl azides, halo amines, imino iodinanes,

and tosyloxycarbamates. In addition, a variety of transition-metal catalysts, usually in combination with ligands such as porphyrins, bis(oxazolines) and diimines, have been reported.[154] A general mechanism for metal nitrene-promoted aziridination is shown in Scheme 107. Whilst there remains some uncertainties in the mechanism, it is generally believed that aziridination can proceed *via* a singlet or triplet nitrene (**301a** and **301b** respectively) and that reaction *via* a singlet nitrene species occurs stereospecifically, with retention of the alkene's stereochemistry, whilst triplet species do not react stereospecifically.[XXXIII] It should be noted, however, that experiments on the stereospecificity of aziridinations are often substrate dependent.[154]

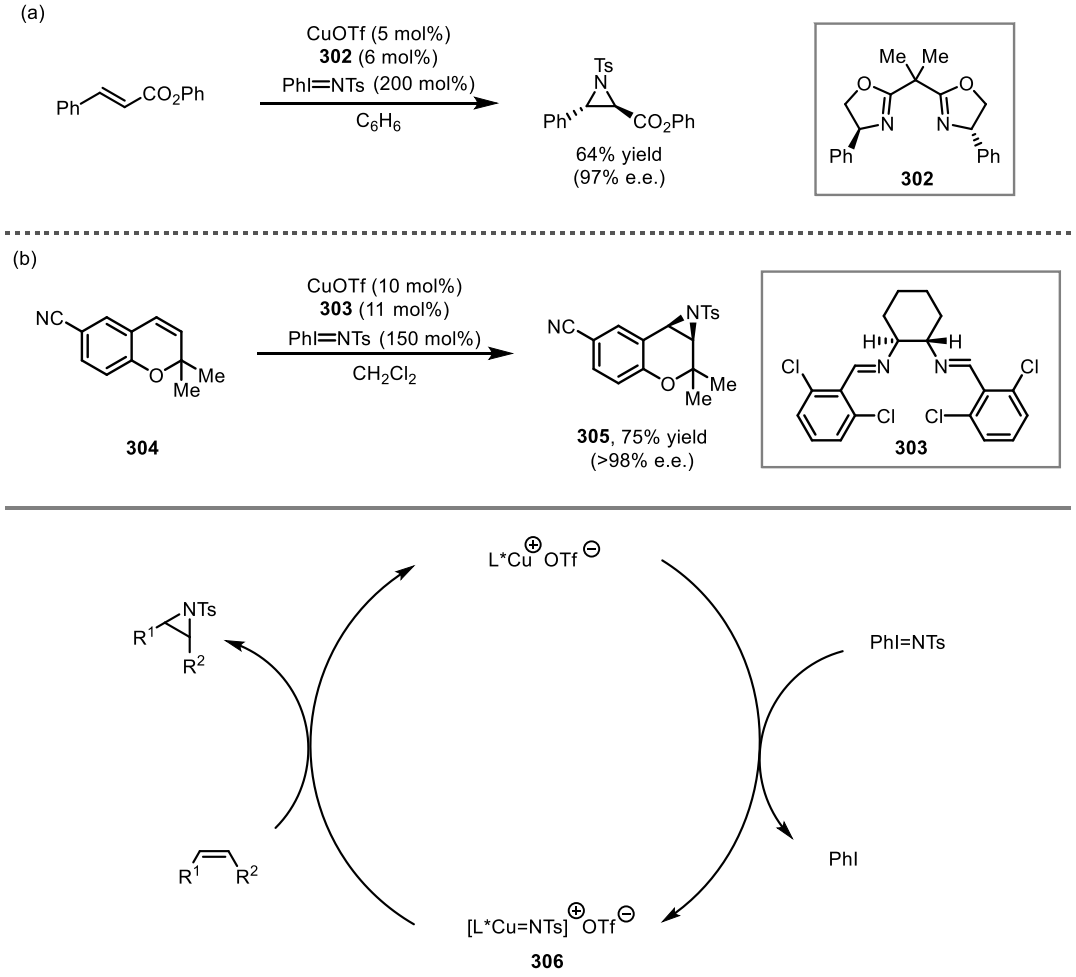


Scheme 107 *Proposed mechanistic pathways for metal nitrene-mediated aziridination.*[155]

One of the most widely used nitrene sources for alkene aziridination are sulfonyliminoiodinanes, such as *N*-(*p*-tolylsulfonyl)imino)phenyliodinane (PhI=NTs). These reactive nitrogen sources are easily generated from the corresponding sulfonyl amides. In a series of reports by Mansuy and co-workers, iron(II) or manganese(II)-porphyrin complexes were employed to catalyse the transfer of nitrogen to alkenes using PhI=NTs.[156,157] Many other groups have subsequently reported transition metal-catalysed aziridinations of alkenes using PhI=NTs as a nitrene precursor. In 1991 Evans reported that low valent copper catalysts could promote aziridinations of styrenes and aliphatic alkenes.[158,159] The use of CuOTf in combination with chiral 4,4'-disubstituted bis(oxazolines) ligand **302** enabled the first asymmetric copper-catalysed nitrene transfer to alkenes to generate *N*-tosyl aziridines in up to 97 % e.e. (Scheme 108a).[160] A related asymmetric copper(I)-catalysed aziridination was reported by Jacobsen and co-workers using chiral diamine-based ligand **303** (Scheme 108b).[161] Poor enantioselectivity was achieved using *trans*-alkenes; however, *cis*-alkenes were generally

[XXXIII]A recent report on the stereospecific aziridination of alkenes was proposed to proceed *via* a triplet copper-nitrene intermediate.[155]

more effective substrates. Stereospecific aziridination of 6-cyano-2,2-dimethylchromene **304** was achieved to afford aziridine **305** in >98% e.e. Investigation into the mechanism of (diimine)copper(I)-catalysed aziridination provided evidence to support reaction *via* a discrete copper(III)-nitrene intermediate **306**.[162] Copper-catalysed aziridinations of alkenes have also been reported by Andersson using *p*-$NO_2C_6H_4SO_2N$=IPh (PhI=NNs) as the nitrene source.[163] As well as being a more efficient for alkene aziridination than the more commonly used nitrene source, PhI=NTs, the *p*-nitroarylsulfonamide products can be cleaved more easily to the NH products than the corresponding *p*-tosylsulfonamides.

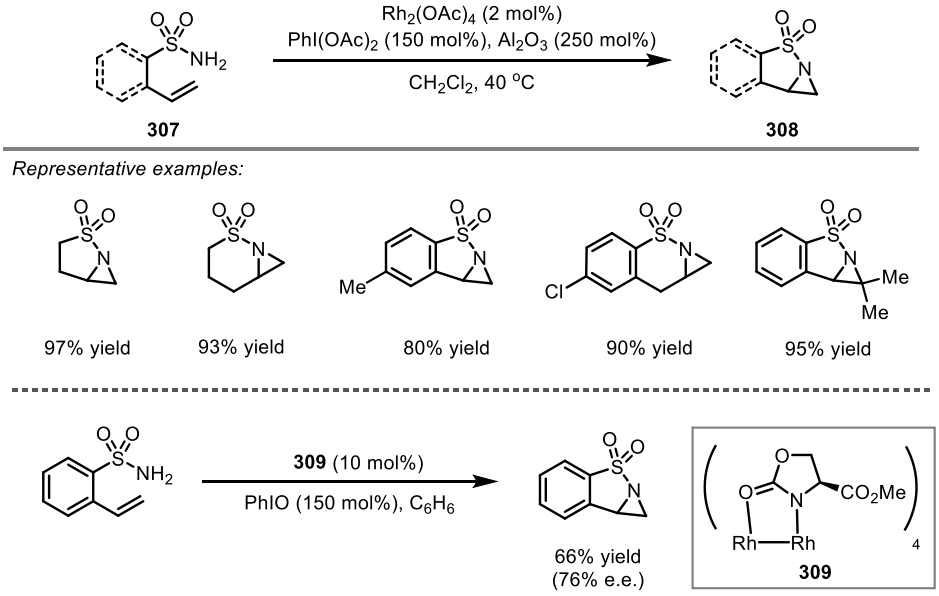


Scheme 108 *(a) Enantioselective copper-catalysed aziridination of alkenes using bis(oxazolines) ligand* ***302****.*[160] *(b) Enantioselective copper-catalysed alkene aziridination using diimine ligand* ***303****.*[161,162]

A number of other groups have reported metal-catalysed alkene aziridinations using a variety of transition metals including manganese,[164,165] silver,[166] or ruthenium.[167] Müller and co-workers demonstrated that $Rh_2(OAc)_4$ can effectively promote the aziridination of alkenes using PhI=NNs as the nitrene source.[168,169] The reaction proceeds stereospecifically with alkyl-

substituted alkenes; however, loss of stereospecificity was observed with aryl-disubstituted alkenes.

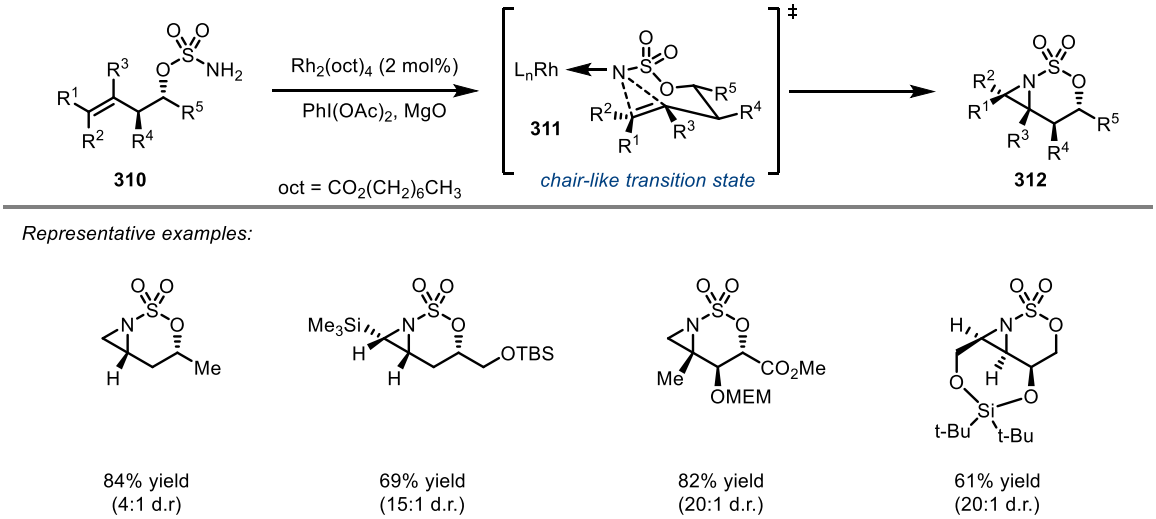
The previous examples utilise iminoiodinanes as nitrene sources; however, other aziridination protocols have since been developed in which the nitrene source is generated *in situ* by oxidation of amine derivatives such as sulfonamides or sulfamates with hypervalent iodine reagents. In 2002 Che and co-workers reported a rhodium(II)-catalysed intramolecular aziridination of unsaturated sulfonamides **307** using $PhI(OAc)_2$ as the oxidant (Scheme 109).[170] The corresponding bicyclic aziridine products **308** were obtained in generally excellent yields. An asymmetric variant of the reaction was later developed, using a chiral dirhodium(II)-complex **309** to afford the aziridine products with good levels of enantioselectivity (up to 76%).[171]



Scheme 109 *Rhodium-catalysed intramolecular aziridination of sulfonamides.*[170,171]

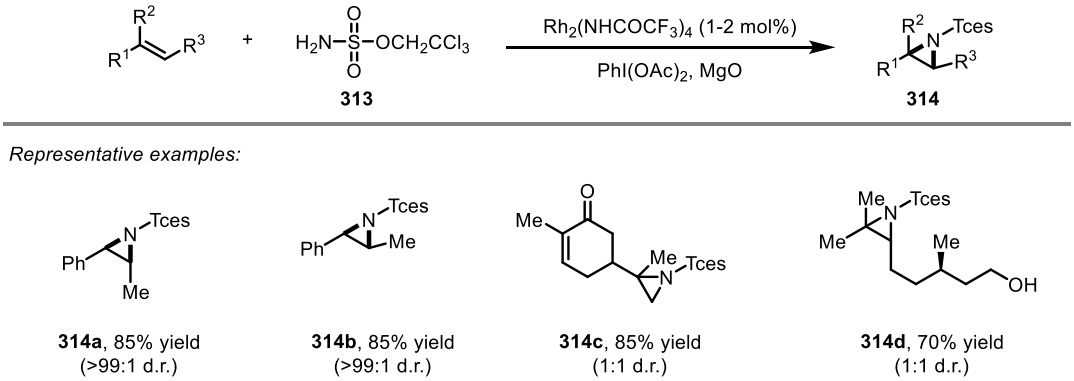
Du Bois and co-workers demonstrated the use of sulfamate esters as nitrogen donors in the aziridination of alkenes.[172] In the presence of $Rh_2(oct)_4$ and $PhI(OAc)_2$ as the oxidant, highly diastereoselective intramolecular aziridinations of alkenes **310** were achieved and a variety of bicyclic sulfamate esters **312** were obtained in good to excellent yields (Scheme 110). [XXXIV] The observed stereoselectivity is consistent with the reaction proceeding through a chair-like transition state **311** that minimises gauche and $A_{1,3}$-type interactions.

[XXXIV] The aziridination is stereospecific with respect to the alkene geometry.



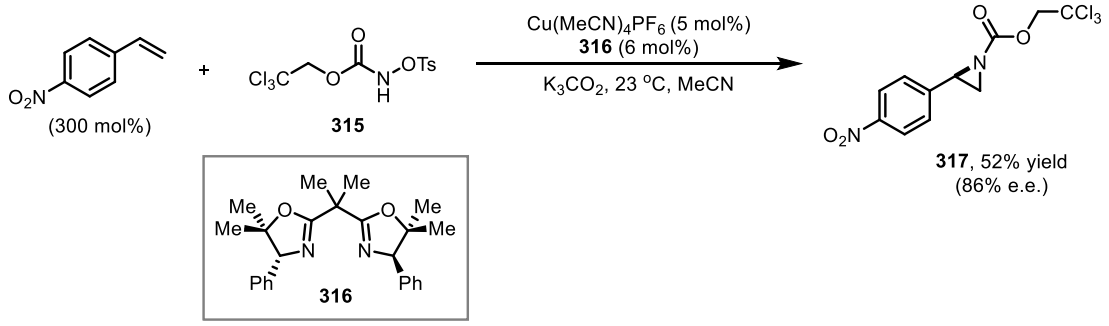
Scheme 110 *Intramolecular alkene aziridination using sulfamate esters.*[172]

This approach was also applied in an intermolecular process. Aziridination of a variety of alkenes to the corresponding aziridines **314a-d** was achieved using a trichloroethoxysulfonyl (Tces) protected amine **313** which can be cleavage under mild reductive conditions (e.g. Zn).[173] Aziridination occurs stereospecifically as demonstrated by *cis*- and *trans*-β-methylstyrene which underwent aziridination to afford aziridines **314a** and **314b** respectively as single diastereomers. (Scheme 111).



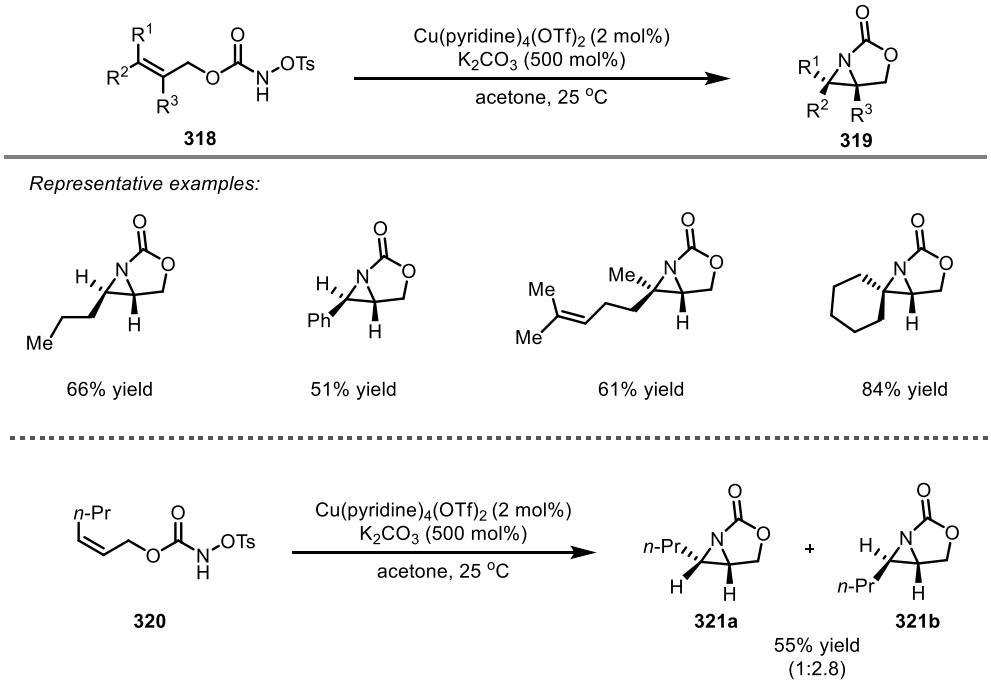
Scheme 111 *Intermolecular alkene aziridination using sulfamate esters.*[173]

Other nitrene sources that have been employed in metal-catalysed alkene aziridination are sulfonyloxycarbamates. Lebel and co-workers reported that rhodium or copper catalysts could promote the intermolecular aziridination of styrenes with tosyloxycarbamate **315** leading to aziridines **317** in good yields (Scheme 112).[174,175] Using a chiral bis(oxazoline) ligand **316** an enantioselective aziridination of styrenes was achieved.[176]



Scheme 112 *Copper-catalysed intermolecular alkene aziridination with N-tosyloxycarbamate* ***315****.*[176]

Lebel and co-workers also reported a copper or rhodium-catalysed intramolecular aziridination of *N*-tosyloxycarbamates **318** to generate bicyclic carbamates **319** in good to excellent yields (Scheme 113).[174,177] Aliphatic and aromatic (*E*)-disubstituted alkenes were shown to react stereospecifically to produce the corresponding *trans*-aziridines as single diastereomers. However, the aziridination of (*Z*)-disubstituted alkene **320** led to a mixture of *cis*- and *trans*-aziridines **321a** and **321b**. Based on this observation, the authors proposed a stepwise mechanism involving generation of a triplet nitrene intermediate.

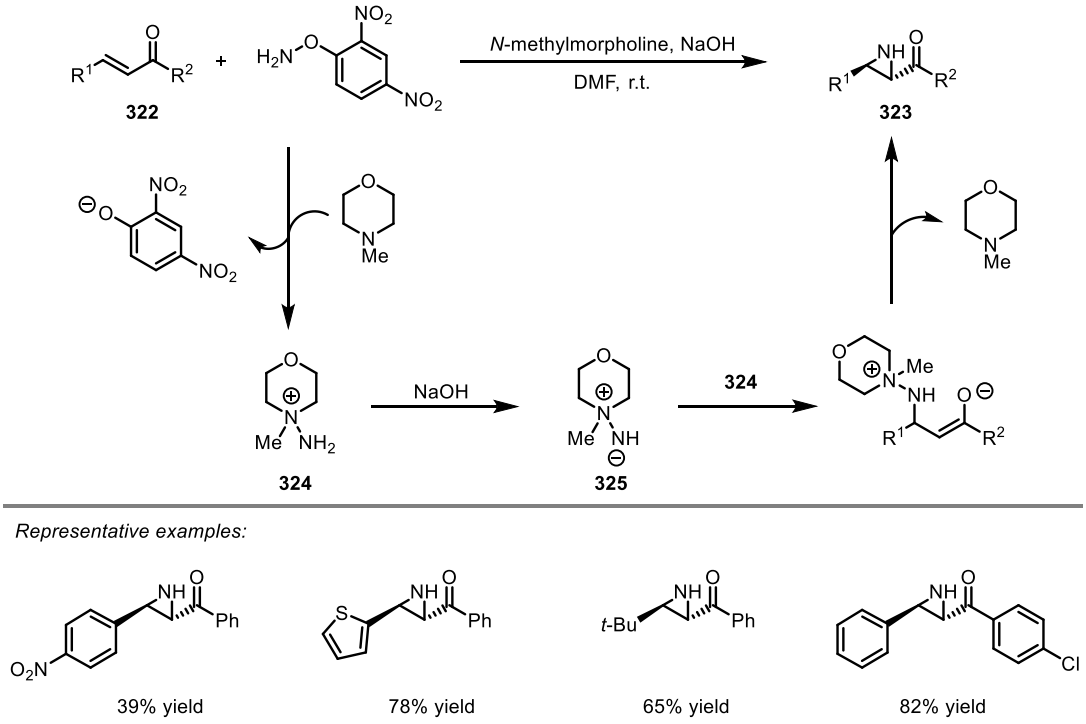


Scheme 113 *Copper-catalysed alkene aziridination with N-tosyloxycarbamates.*[174,177]

Many of the methods developed for the metal-catalysed transfer of nitrenes to alkenes are limited to the formation of aziridines bearing strongly electron-withdrawing *N*-protecting groups. Removal of these protecting groups is often difficult, requiring harsh conditions that can often result in undesired ring-opening of the aziridine ring. Methods of alkene aziridination

to access unprotected NH aziridines are less prevalent but are potentially more synthetically useful.

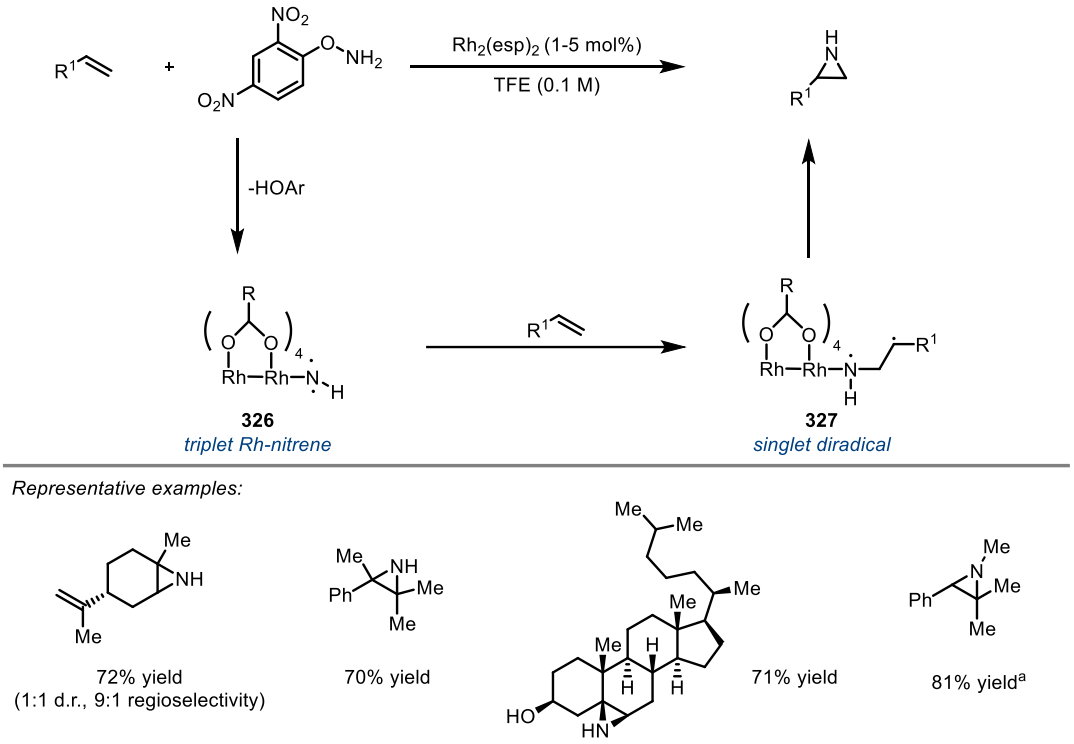
In 2012 Wang and co-workers reported an approach for the synthesis of NH aziridines **323** from α,β-unsaturated ketones **322** using DPH as a nitrogen source in combination with *N*-methylmorpholine and NaOH (Scheme 114).[178] The reaction was proposed to proceed by reaction of *N*-methylmorpholine with DPH to generate a hydrazinium salt **324**. This is then deprotonated by NaOH to form aminimide **325**, which then undergoes a conjugate addition on to the α,β-unsaturated ketone **322** followed by cyclisation to afford the aziridine product. Whilst effective for the synthesis of NH aziridines, this reaction is limited in scope to the aziridination of α,β-unsaturated ketones.



Scheme 114 *Aziridination of α,β-unsaturated ketones with O-(2,4-dinitrophenyl)-hydroxylamine.*[178]

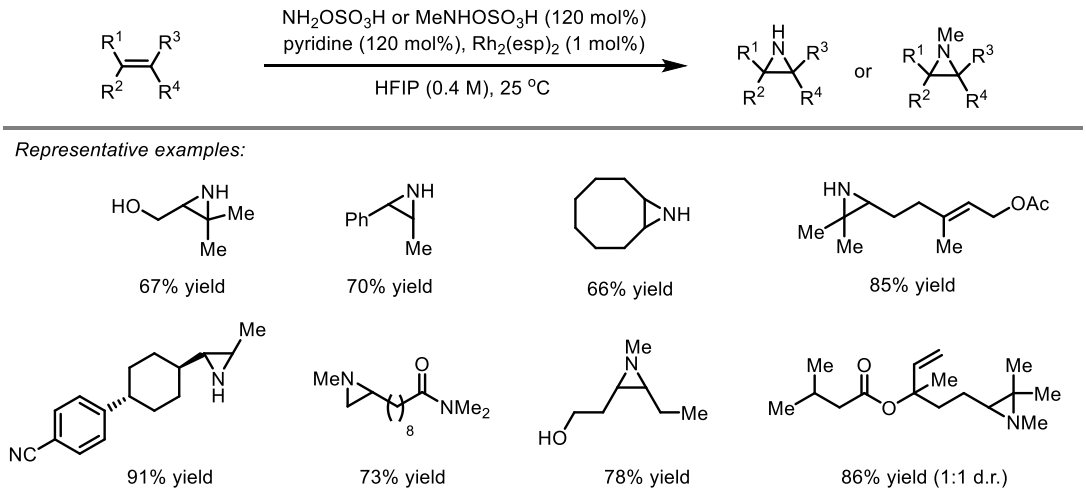
A more efficient and general protocol for stereospecific alkene aziridination that affords unprotected NH aziridines was reported by Falck and co-workers.[179] The authors demonstrated that $Rh_2(esp)_2$ in combination with DPH can effect the aziridination of a wide variety of alkenes, including tetrasubstituted alkenes, under mild reaction conditions (Scheme 115). From experimental observations and computational studies, a mechanism was proposed that involves generation of a triplet rhodium-NH-nitrenoid species **326**. This undergoes reaction with an alkene, followed by intersystem crossing to form diradical intermediate **327** from which the aziridine product is generated. As stereospecific aziridination was observed, it was rationalised

that the diradical intermediate **327** undergoes C-N bond formation without C-C bond isomerisation. The use of *N*-alkyl-DPH derivatives allowed for the generation of *N*-alkylated aziridines.



Scheme 115 *Synthesis of N-H and N-alkyl aziridines by rhodium-catalysed alkene aziridination.*[179] *[a]O-(2,4-dinitrophenyl)-N-methylhydroxylamine (140 mol%) was used.*

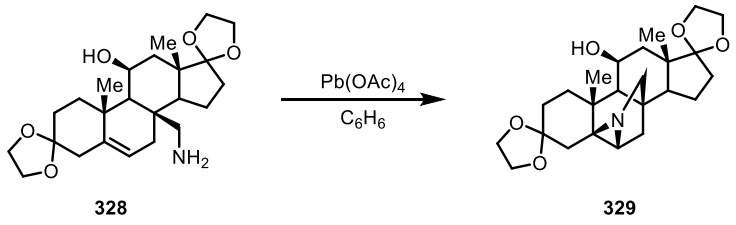
Despite its effectiveness, DPH is impractical for large scale purposes and so an improved protocol was subsequently developed by Kürti and co-workers using HOSA as the aminating agent in combination with a mild base (Scheme 116).[180] This aziridination procedure gave comparable or improved yields of aziridination of *N*-H or *N*-alkyl aziridination than the procedure developed by Falck and co-workers but was much more practical and safer for large scale reactions.



Scheme 116 *Rhodium-catalysed alkene aziridination using hydroxylamine-O-sulfonic acid or N-methyl hydroxylamine-O-sulfonic acid.*[180]

Whilst metal-nitrenoid-promoted aziridinations of alkenes are well-established, a number of transition metal-free alkene aziridinations have also been developed. These typically employ amine derivatives in the presence of an oxidant such as $Pb(OAc)_4$ or hypervalent iodine reagents.

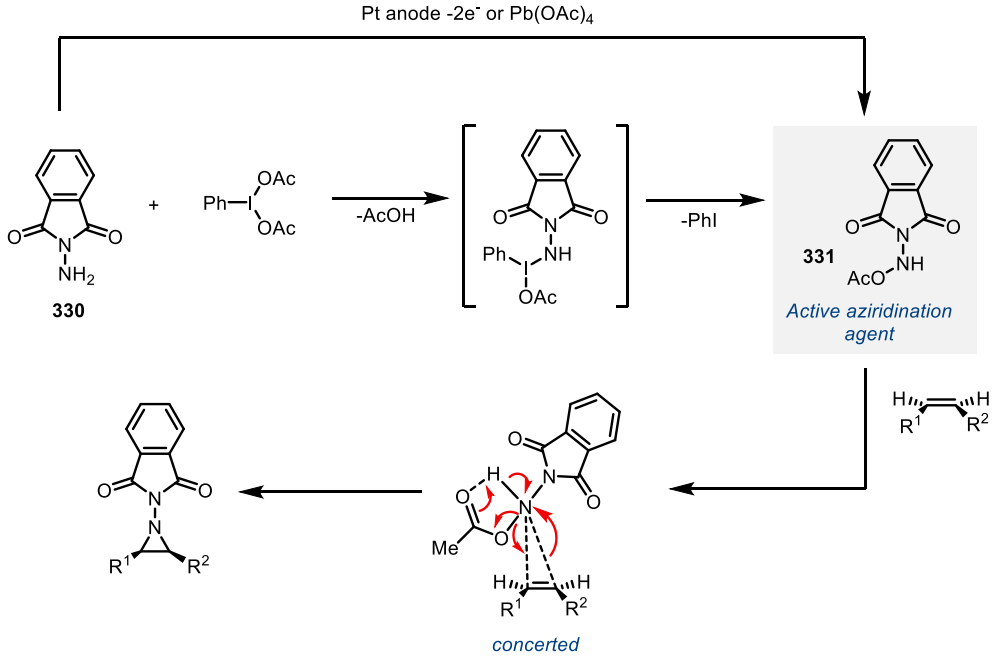
In 1967 Nagata and co-workers demonstrated that treatment of primary amine **328** with stoichiometric $Pb(OAc)_4$ yielded the bridged aziridine compound **329** (Scheme 117).[181] Cyclisation to **329** was also achieved but with less efficiency using *N*-chlorosuccinimide or HgO as the oxidant. $Pb(OAc)_4$-mediated alkene aziridination protocols have since been demonstrated by a number of groups for the synthesis of similar bridged aziridine structures.[182,183]



Scheme 117 *$Pb(OAc)_4$-promoted aziridination of **329**.*[181]

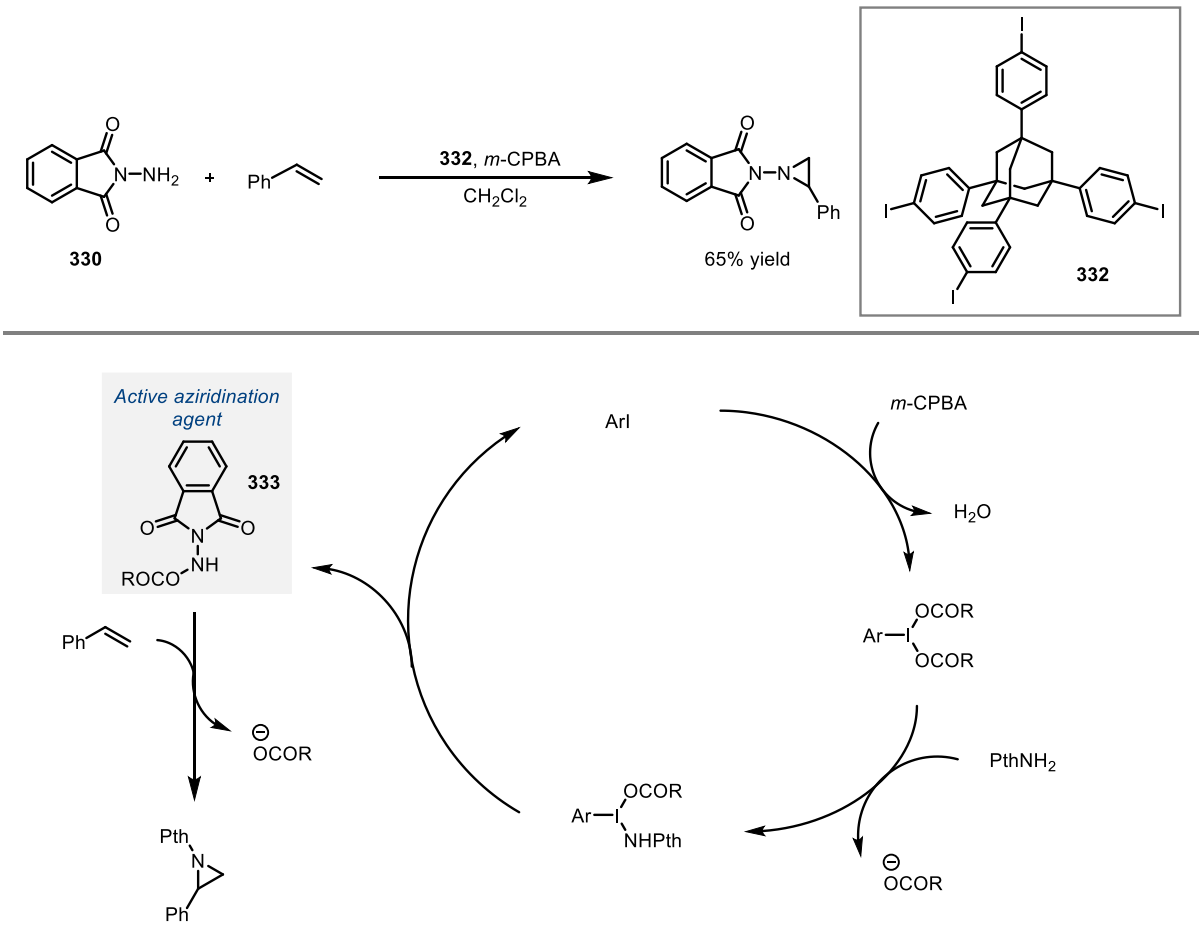
A number of groups have reported methods for alkene aziridination using *N*-aminophthalimide **330** (or *N*-aminoquinazolinones) as the nitrogen source. These are oxidised *in situ* to generate the active aziridination agent **331** (Scheme 118). Pioneering work was carried out by Atkinson and co-workers using $Pb(OAc)_4$ as the oxidant.[184-190] This method promoted the stereospecific aziridination of a range of alkenes with varying electronic properties including styrenes and

α,β-unsaturated esters. To account for the stereospecificity of the reaction the authors proposed a concerted mechanism of aziridination analogous to epoxidation of alkenes with peroxyacids (Scheme 118). Related $Pb(OAc)_4$-mediated alkene aziridinations for the synthesis of *N*-phthalimidoaziridines were reported by the Vederas[191] and Chen[192] groups. The obvious downside to these methods is the requirement for stoichiometric quantities of toxic lead-based reagents.



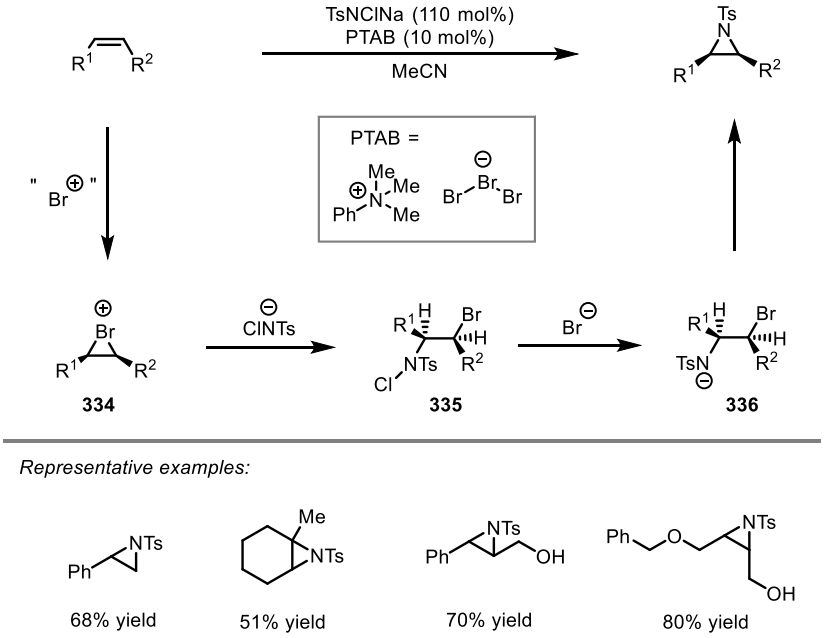
Scheme 118 *Proposed mechanism for alkene aziridination using N-aminophthalimide.*[154]

The groups of Che[193] and Yudin[194] reported alkene aziridinations using *N*-aminophthalimide **330** and $PhI(OAc)_2$ as the oxidant. A milder approach to alkene aziridination was developed by Yudin which bypassed the need for stoichiometric oxidants through the use of electrochemical conditions.[195] A related mild alkene aziridination approach was reported by Che and co-workers which used *N*-aminophthalimide **330** in combination with aryl iodide **332** and *m*-CPBA to generate the active aziridination agent **333** (Scheme 119).[196]



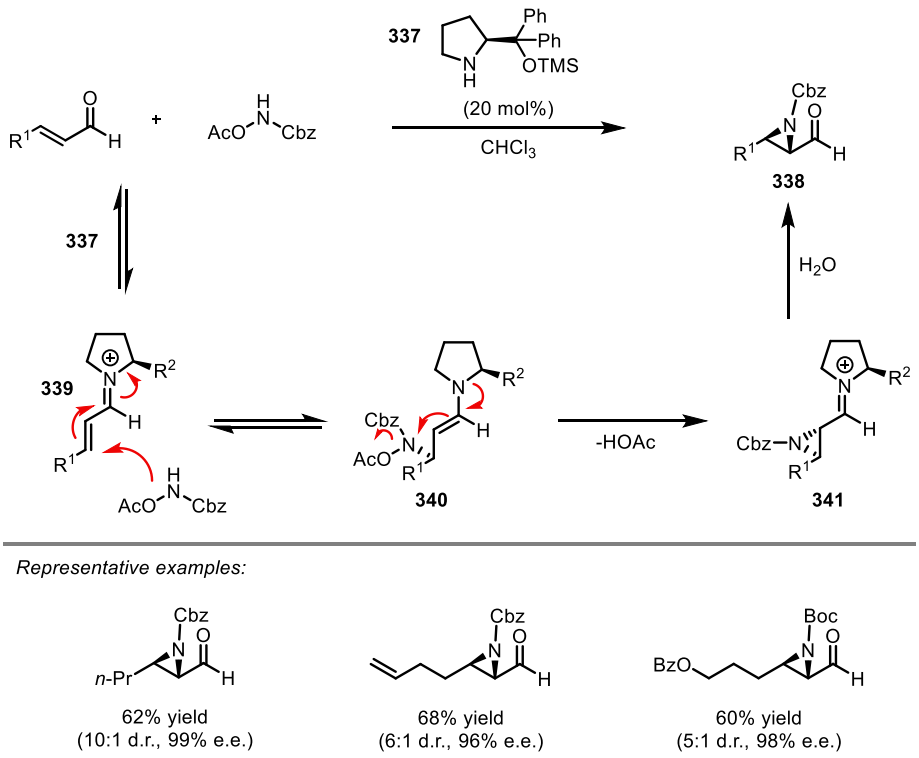
Scheme 119 *Hypervalent iodine-mediated aziridination of alkenes with N-aminophthalimide* ***330****.*[196]

A further example of a metal-free approach to alkene aziridination was reported by Sharpless and co-workers.[197] They demonstrated a bromine-catalysed procedure for the synthesis of *N*-sulfonyl aziridines using Chloramine-T (TsNClNa) as a cheap and practical nitrogen source (Scheme 120). The reaction was proposed to proceed *via* formation of bromonium ion **334** which is opened by $TsNCl^-$ to generate intermediate **335**. Cleavage of the *N*-Cl group generates nitrogen anion **336** which subsequently cyclises to the aziridine product. A variety of alkenes underwent aziridination in good yields with allylic alcohols being particularly effective substrates. A related approach for alkene aziridination was reported by Zhdankin and co-workers. This approach used TBAI to promote alkene aziridination *via* the formation of an iodonium intermediate.[198]



Scheme 120 *Bromine-catalysed aziridination of alkenes with Chloramine-T.*[197]

It is also pertinent to highlight the work of Córdova and co-workers who reported an enantioselective organocatalytic aziridination of α,β-unsaturated aldehydes employing *N*-acyl hydroxycarbamates as "nitrene" equivalents (Scheme 121).[199,200] The use of a chiral pyrrolidine-derived catalyst **337** enabled the generation of a variety of 2-formylaziridines **338** in good yields and with excellent levels of enantioselectivity (up to 99% e.e.). In the proposed mechanism unsaturated iminium ion **339** is generated and acts as a conjugate addition acceptor for the hydroxycarbamate. Asymmetry is induced by the shielding of one face of the chiral iminium intermediate by the bulky groups of the amine catalyst leading to stereoselective attack of the nucleophilic *N*-acyl hydroxycarbamate. The resulting enamine **340** then undergoes ring closure onto the now electrophilic nitrogen of the hydroxycarbamate with release of acetic acid. Hydrolysis of iminium **341** then affords the aziridine product. Hamada and co-workers reported a related enantioselective organocatalysed aziridination of α,β-unsaturated aldehydes using *N*-sulfonyloxycarbamates,[201] whilst Melchiorre extended this strategy to the aziridination of α,β-unsaturated ketones.[202]

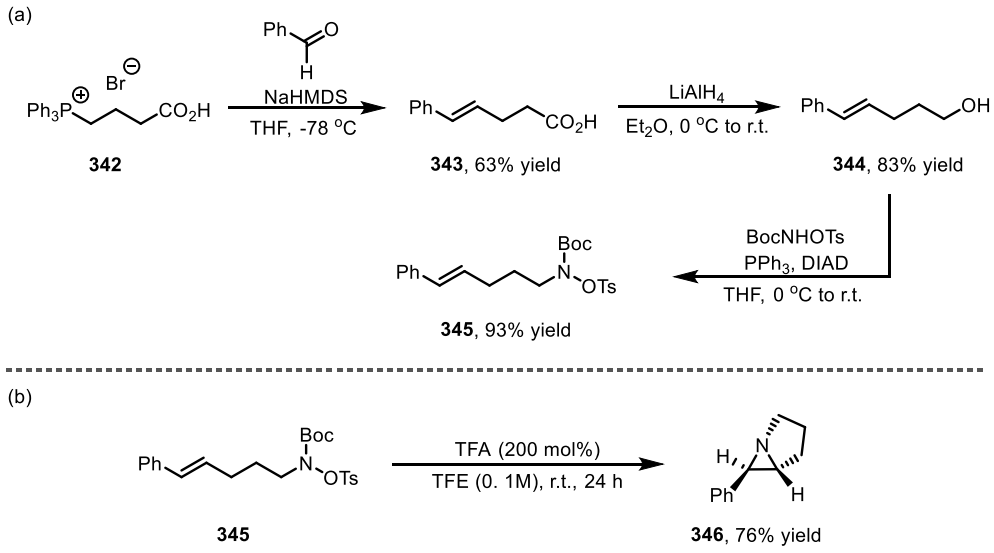


Scheme 121 *Organocatalysed aziridination of α,β-unsaturated aldehydes.*[199]

3.2 Development of an intramolecular aziridination of *N*-Boc hydroxylamines

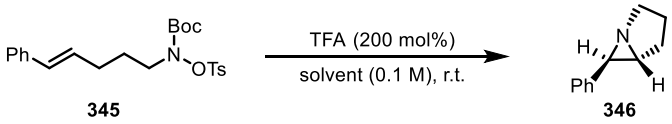
3.2.1 Initial results and reaction optimisation

To investigate the potential of carrying out an intramolecular aziridination of *N*-Boc hydroxylamines, phenyl-substituted alkene **345** was synthesised (Scheme 122a). Wittig reaction of benzaldehyde with phosphonium bromide **342** afforded carboxylic acid **343** which was subsequently reduced with $LiAlH_4$ to alcohol **344**. Substrate **345** was then obtained by Mitsunobu reaction with BocNHOTs. **345** was subjected to the acid-promoted dearomatising amination conditions [TFA (200 mol%) in TFE (0.1 M)] and bicyclic aziridine **346** was obtained in 76% yield and as a single diastereomer (Scheme 122b). Following this pleasing result further optimisation was carried out.



Scheme 122 *(a) Synthesis of substrate **345**. (b) Intramolecular aziridination of substrate **345**.*

A brief solvent screen commenced with common alcohols such as EtOH and MeOH; however, no reactivity was observed in these solvents (Table 7, entries 1-2). Other solvents such as THF, 1,4-dioxane, DMF and MeCN were also ineffective (Table 7, entries 3-6). In contrast, when the reaction was run in PhMe or CH_2Cl_2 appreciable quantities of aziridine **346** was observed (32% and 40% respectively) (Table 7, entries 7-8). The solvent screen highlights the importance of TFE as solvent for this reaction. Another fluorinated solvent α,α,α-trifluorotoluene was examined; however, under these conditions **346** was obtained in only 26% yield. (Table 7, entry 9).



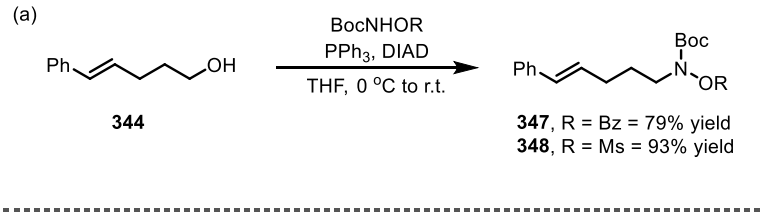
345 346

Entry	*solvent*	*yield*
1	MeOH	0%
2	EtOH	0%
3	THF	0%
4	1,4-dioxane	0%
5	DMF	0%
6	MeCN	0%
7	PhMe	32%
8	CH_2Cl_2	40%
9	α,α,α-trifluorotoluene	26%

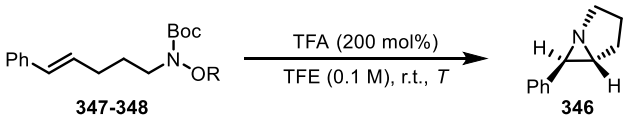
Table 7 *Solvent screen for the aziridination of substrate **345**. Yields were determined by ^{1}H NMR analysis of the crude reaction mixture versus 1,4-dinitrobenzene as an internal standard.*

At this stage a number of different hydroxylamine-derived activating groups were examined. When substrate **347** containing an OBz group was subjected to the standard reaction conditions,

no aziridination occurred (Scheme 123b). In contrast, substrate **349** containing an OMs group cyclised effectively to aziridine **346** in a slightly reduced yield versus the OTs-substrate.



(b)

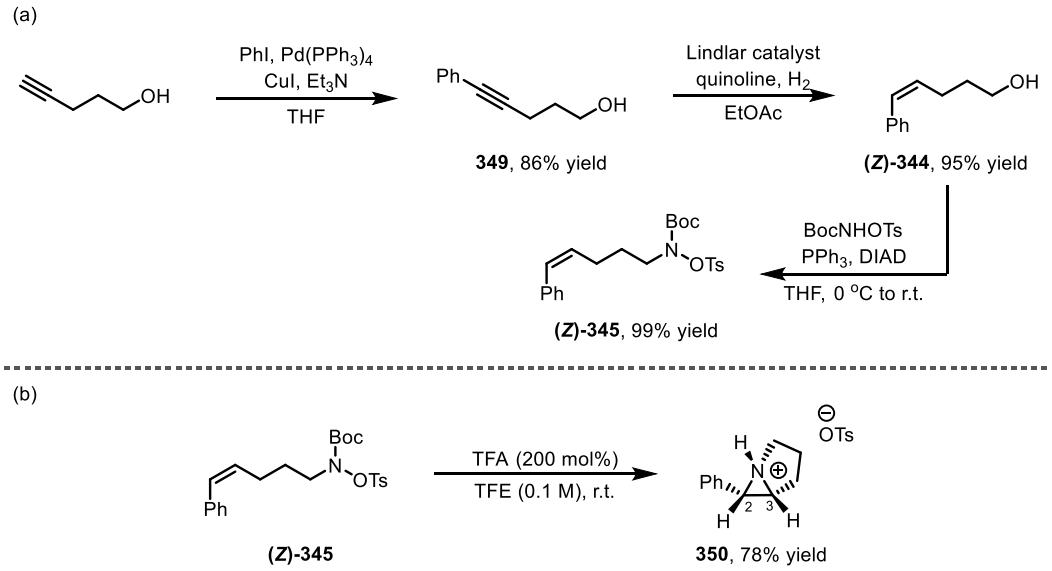


Entry	*R*	*T*	*yield*
1	Ms	48 h	69%
2	Bz	48 h	0%

Scheme 123 *(a) Synthesis of substrates **347** and **348** by Mitsunobu reaction. (b) Attempted intramolecular aziridination of substrates **347** and **348**.*

3.2.2 Aziridination of a (*Z*)-alkene

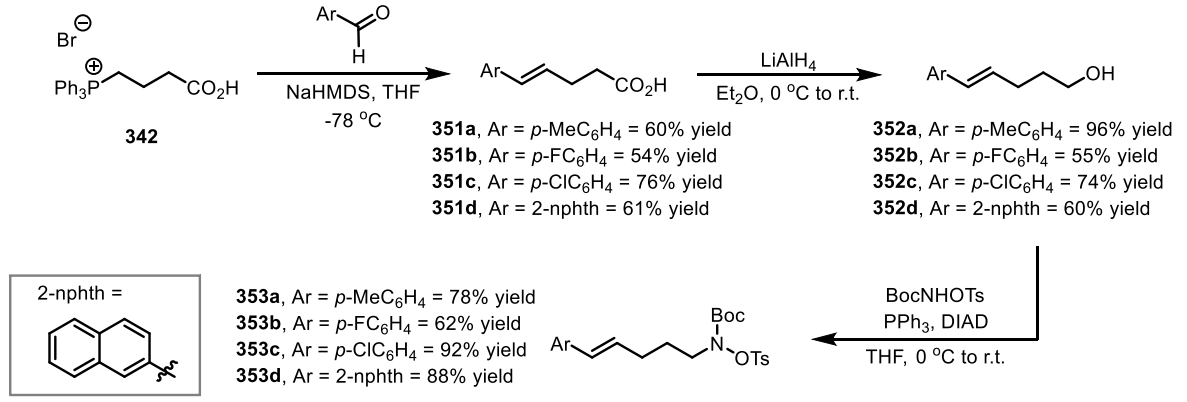
With conditions in hand, the scope of the reaction was investigated. As a starting point the stereospecificity of the reaction was first examined. To this end **(*Z*)-345**, the (*Z*)-alkene isomer of substrate **345** was prepared. The synthesis began with a Sonogashira reaction of iodobenzene and 4-pentyn-1-ol (Scheme 124a). The resulting alkyne **349** was hydrogenated to the (*Z*)-alkene using Lindlar catalyst (poisoned with quinoline to prevent over-reduction). Alcohol **(*Z*)-344** was then converted to **(*Z*)-345** by Mitsunobu reaction. **(*Z*)-345** was subjected to the standard aziridination conditions to provide aziridine **350** in 78% yield (Scheme 124b). The formation of the other diastereomer **346** was not observed. The relative stereochemistry of **350** was supported by NMR analysis of the coupling constant of the benzylic C2 proton which couples to the adjacent C3 proton with a coupling constant value of 7.8 Hz. This value is in line with typically observed values for *cis*-vicinal coupling of protons in aziridine rings.[203] In comparison for **346** the corresponding C2-C3 *trans*-coupling has a value of 2.7 Hz.



Scheme 124 *(a) Synthesis of substrate* ***(Z)-345****. (b) Intramolecular aziridination of substrate* ***(Z)-345****. Yield was obtained by* ^{1}*H NMR analysis versus 1,4-dinitrobenzene as an internal standard.*

3.2.3 Aziridination of 1,2-disubstituted alkenes

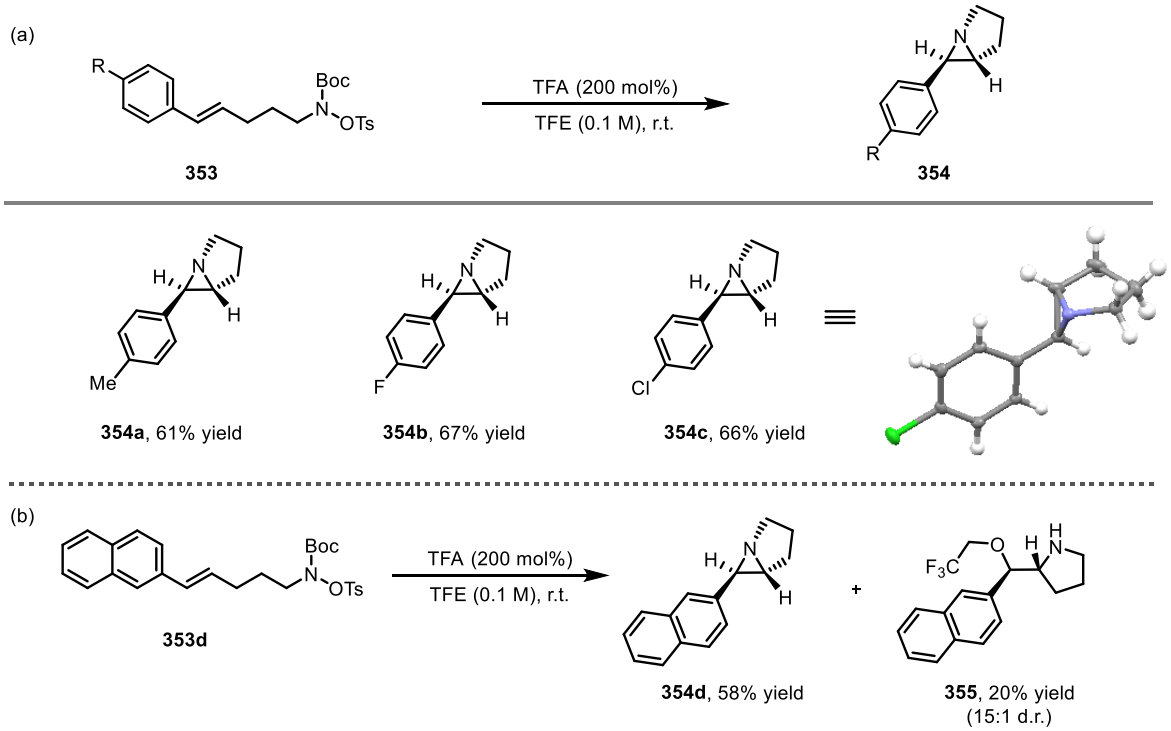
To investigate further the scope of the aziridination process a series of 1,2-disubstituted alkenes **353a-d** were prepared (Scheme 125). These substrates were accessed using the same general synthetic sequence which was used to prepare the parent substrate **345**. Wittig reaction of phosphonium bromide **342** with the corresponding aldehydes gave carboxylic acids **351a-d** in good yields.[XXXV] Reduction of the carboxylic acids to the alcohols **352a-d** with $LiAlH_4$ and Mitsunobu reaction with BocNHOTs completed the synthesis of substrates **353a-d**.



Scheme 125 *Synthesis of substrates* ***353a-d****.*

[XXXV] For carboxylic acids **351a-d** a mixture of (*E*/*Z*)-alkene isomers were obtained; these were separated by column chromatography.

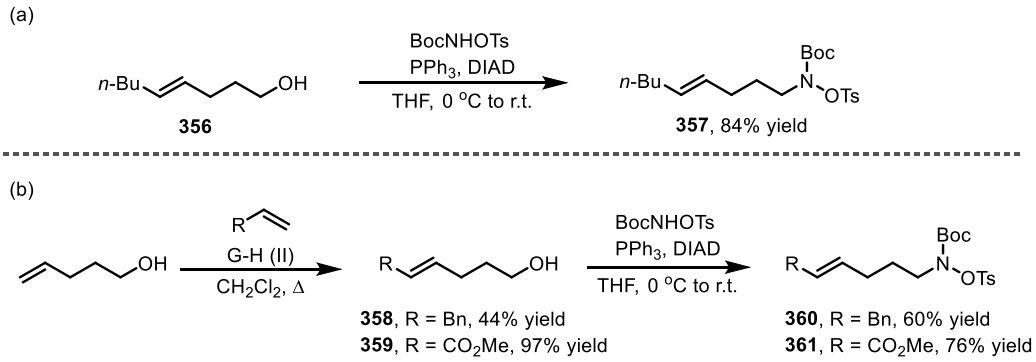
With substrates **353a-d** in hand, they were subjected to the aziridination conditions. Substrates **353a-c** cyclised effectively to generate the corresponding aziridine products **354a-c** with comparable levels of efficiency. (Scheme 126a). Aziridine **354c** was obtained as a crystalline solid and as such its structure and relative stereochemistry was confirmed by single crystal X-ray diffraction. For naphthol system **353d** cyclisation to aziridine **354d** occurred in a slightly lower yield of 58%. Here, in addition to the aziridine product, aminoether **355** was isolated in 20% yield. (Scheme 126b).



Scheme 126 *(a) Intramolecular aziridination of substrates **353a-c**. (b) Formation of aminoether **355** in the intramolecular aziridination of **353d**.*

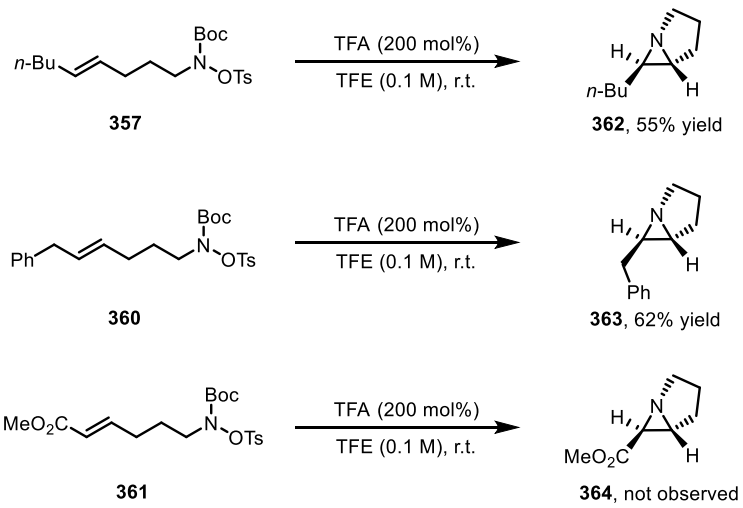
To extend the scope of the reaction beyond that of aryl-substituted alkenes, alkyl-substituted alkene substrates **357** and **360** and acyl-substituted alkene substrate **361** were prepared (Scheme 127). *n*-Butyl-substituted alkene **357** was prepared from alcohol **356** by Mitsunobu reaction.[XXXVI] Alcohols **358** and **359** were prepared in one step from pent-4-en-1-ol by alkene cross-metathesis using Hoveyda-Grubbs second generation catalyst and subsequently converted into substrates **360** and **361** by Mitsunobu reaction.

[XXXVI] Alcohol **356** was prepared by Ian Hazelden (University of Bristol) and hence is not detailed in the experimental section.



Scheme 127 *(a) Synthesis of substrate **357** by Mitsunobu reaction. (b) Synthesis of substrates **360** and **361**.*

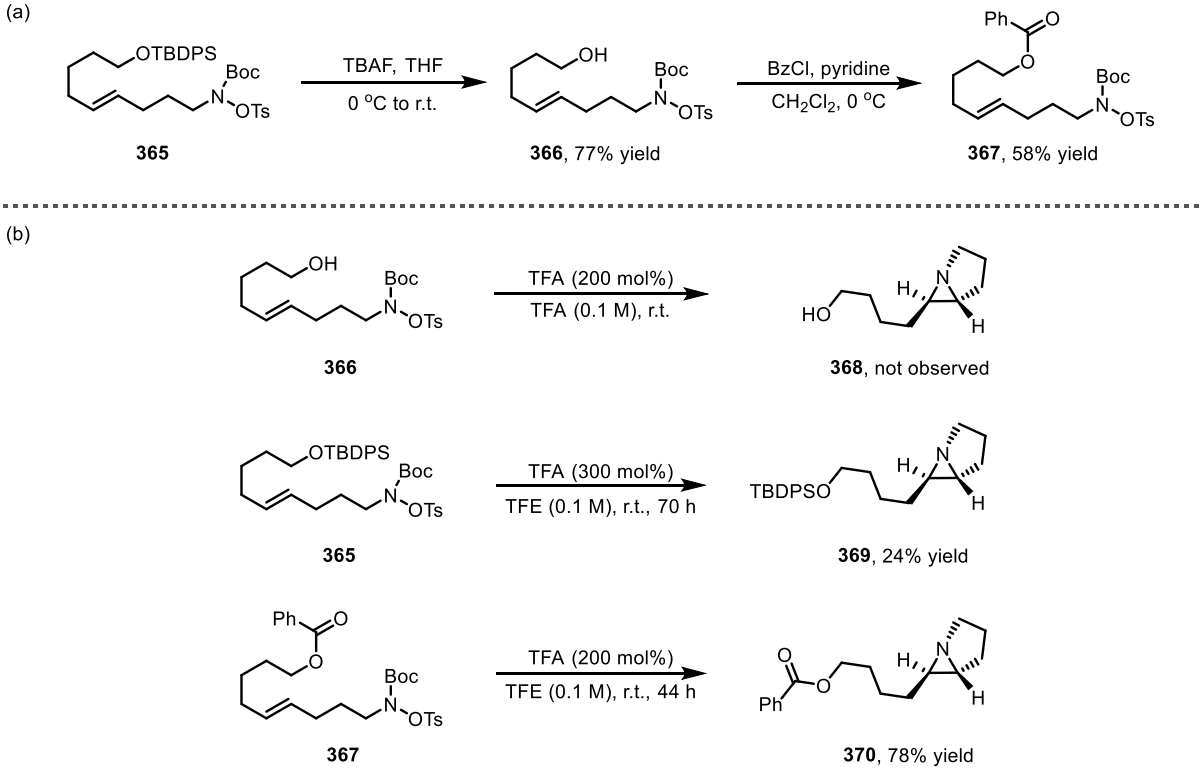
When subjected to the standard reaction conditions, substrates **357** and **360** cyclised successfully to the corresponding aziridine products **362** and **363** in 55% and 62% yields respectively (Scheme 128). Interestingly, when substrate **361** was subjected to the aziridination conditions the desired aziridine product **364** was not observed despite consumption of the starting material. As the alkene in substrate **361** is unreactive (presumably due to being electron-deficient) the starting material is instead likely consumed by other degradation pathways, although no identifiable products could be isolated. This result highlights a limitation of this reaction as electron-deficient alkenes are seemingly incompatible with the aziridination process.



Scheme 128 *Intramolecular aziridination of alkyl and acyl-substituted alkenes.*

To explore further the scope of functionality that is tolerated in the aziridination reaction substrate **366** containing an unprotected alcohol was prepared (Scheme 129a). **366** was synthesised by deprotection of *tert*-butyldiphenylsilyl (TBDPS)-protected alcohol **365** using

TBAF.[XXXVII] Unfortunately, when **366** was subjected to the aziridination conditions the desired aziridine product **368** could not be isolated (Scheme 129b). The TBDPS-protected alcohol **365** was also examined and, in this case, the desired aziridine product **369** was formed in a low yield of 24%. To define further the scope of reaction substrate **367** containing a benzoyl group was synthesised by reaction of alcohol **366** with BzCl (Scheme 129a). When **367** was exposed to the aziridination conditions, aziridine **370** was formed in 78% yield (Scheme 129b). These results highlight that although free alcohols are not tolerated in the aziridination process, bicyclic aziridine products that incorporate an alcohol functionality can be accessed through the use of a compatible protecting group.

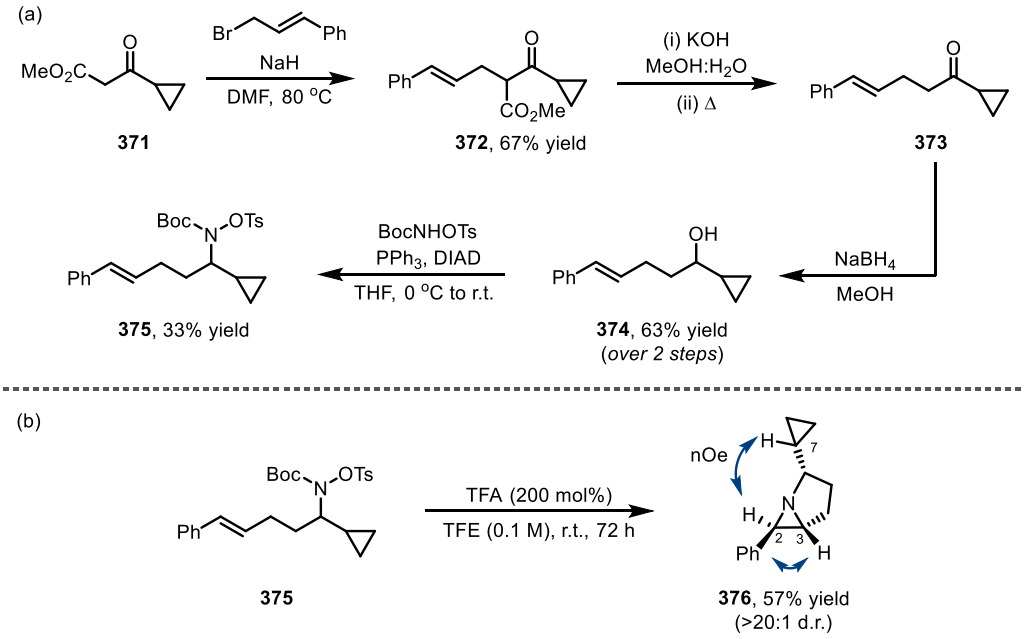


Scheme 129 *(a) Synthesis of substrates **365-367**. (b) Aziridination of substrates **365-367**.*

The effect of substitution on the carbon tether was examined next. To this end, substrate **375** containing a cyclopropyl group in the α-position (with respect to nitrogen) was synthesised (Scheme 120a). The synthesis began with alkylation of cyclopropyl-β-ketoester **371** with cinnamyl bromide. The resulting β-ketoester **372** then underwent decarboxylation and this was followed by reduction of the ketone moiety of **373** with $NaBH_4$. **375** was then accessed by

[XXXVII] TBDPS-protected alcohol **365** was prepared by Xiaofeng Ma (University of Bristol) and hence is not detailed in the experimental.

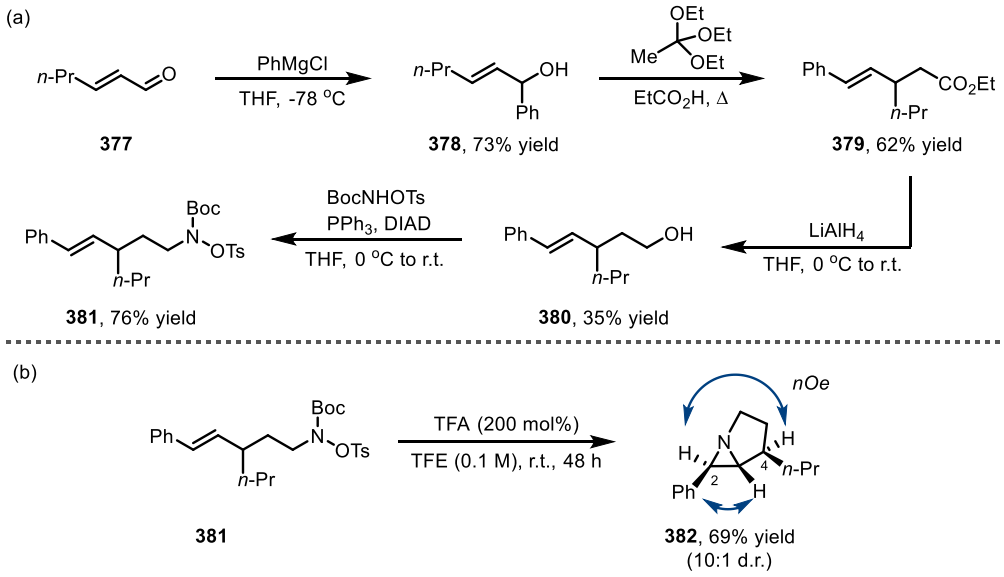
Mitsunobu reaction of alcohol **374**.[XXXVIII] **375** underwent aziridination to generate aziridine **376** in 57% yield and as a single diastereomer (Scheme 130b). The relative stereochemistry of **376** was assigned using ^{1}H NMR nOe analysis. An nOe was observed between the C7 proton of the cyclopropyl group and the C2 proton suggesting a *cis* relationship. The relationship between C3 and the phenyl group was also confirmed by nOe.



Scheme 130 *(a) Synthesis of substrate **375**. (b) Intramolecular aziridination of substrate **375**.*

Substitution in the γ-position of the carbon tether was next examined. To this end substrate **381** containing an *n*-propyl group was prepared (Scheme 131a). The synthesis began with Grignard addition of PhMgCl onto α,β-unsaturated aldehyde **377**. The resulting allylic alcohol **378** was then converted to ester **379** by Johnson-Claisen rearrangement before reduction to alcohol **380** with $LiAlH_4$. Mitsunobu reaction of alcohol **380** completed the synthesis. When substrate **381** was subjected to the aziridination conditions, aziridine **382** was formed in 69% yield and 10:1 d.r. (Scheme 131b). The relative stereochemistry of the major isomer was assigned by ^{1}H NMR nOe analysis. An nOe was observed between the C2 and C4 protons suggesting a *cis* relationship between these two protons. These results highlight that with substitution on the carbon tether highly diastereoselective aziridinations can be achieved, allowing access to highly substituted bicyclic ring systems.

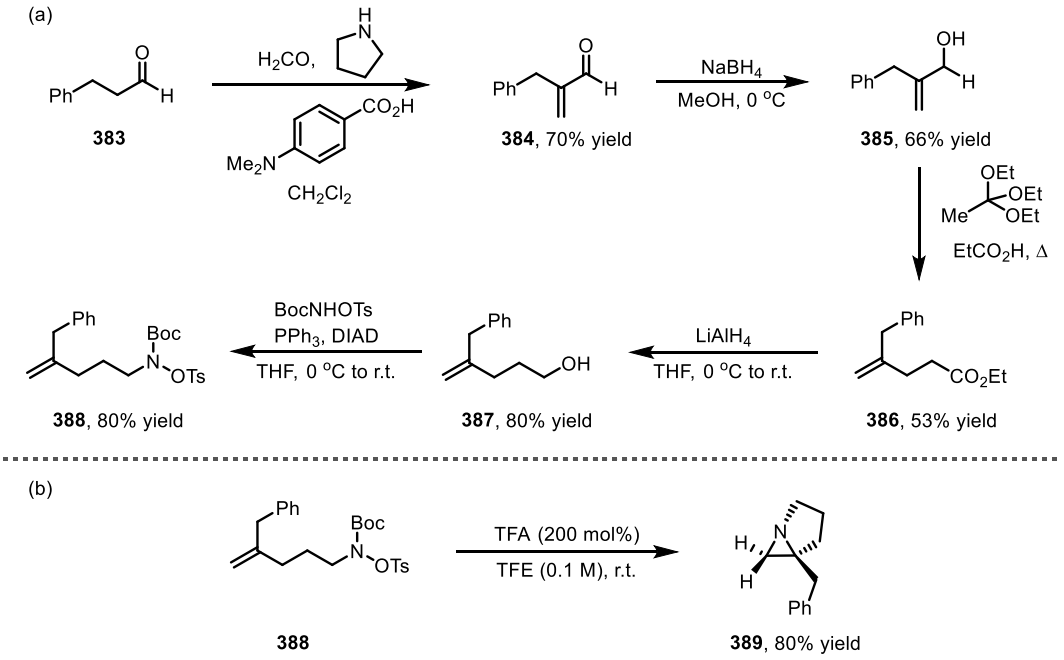
[XXXVIII] In general, secondary alcohols underwent less efficient Mitsunobu reactions with BocNHOTs than primary alcohols.



Scheme 131 *(a) Synthesis of substrate **381**. (b) Intramolecular aziridination of substrate **381**.*

3.2.4 Aziridination of 1,1-disubstituted alkenes

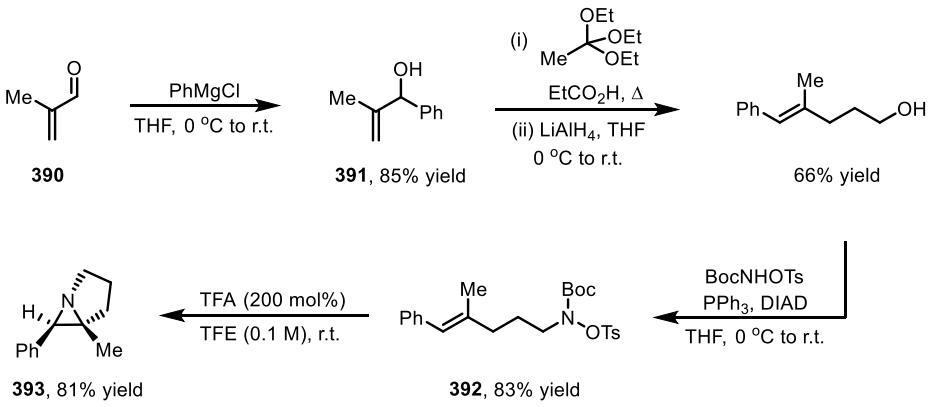
To expand the scope of aziridination of disubstituted alkenes, the reaction of 1,1-disubstituted alkene **388** was examined (Scheme 132). For the synthesis of **388**, aldehyde **383** was converted to α,β-unsaturated aldehyde **384** *via* Mannich reaction (Scheme 132a). The aldehyde was then reduced using $NaBH_4$ and the resulting alcohol **385** was converted to ester **386** by Johnson-Claisen rearrangement. Reduction with $LiAlH_4$ completed the synthesis of alcohol **387** which was then converted to substrate **388** by Mitsunobu reaction. When substrate **388** was trialled in the aziridination reaction, aziridine **389** was generated in 80% yield (Scheme 132b).



Scheme 132 *(a) Synthesis of substrate **388**. (b) Intramolecular aziridination of substrate **388**.*

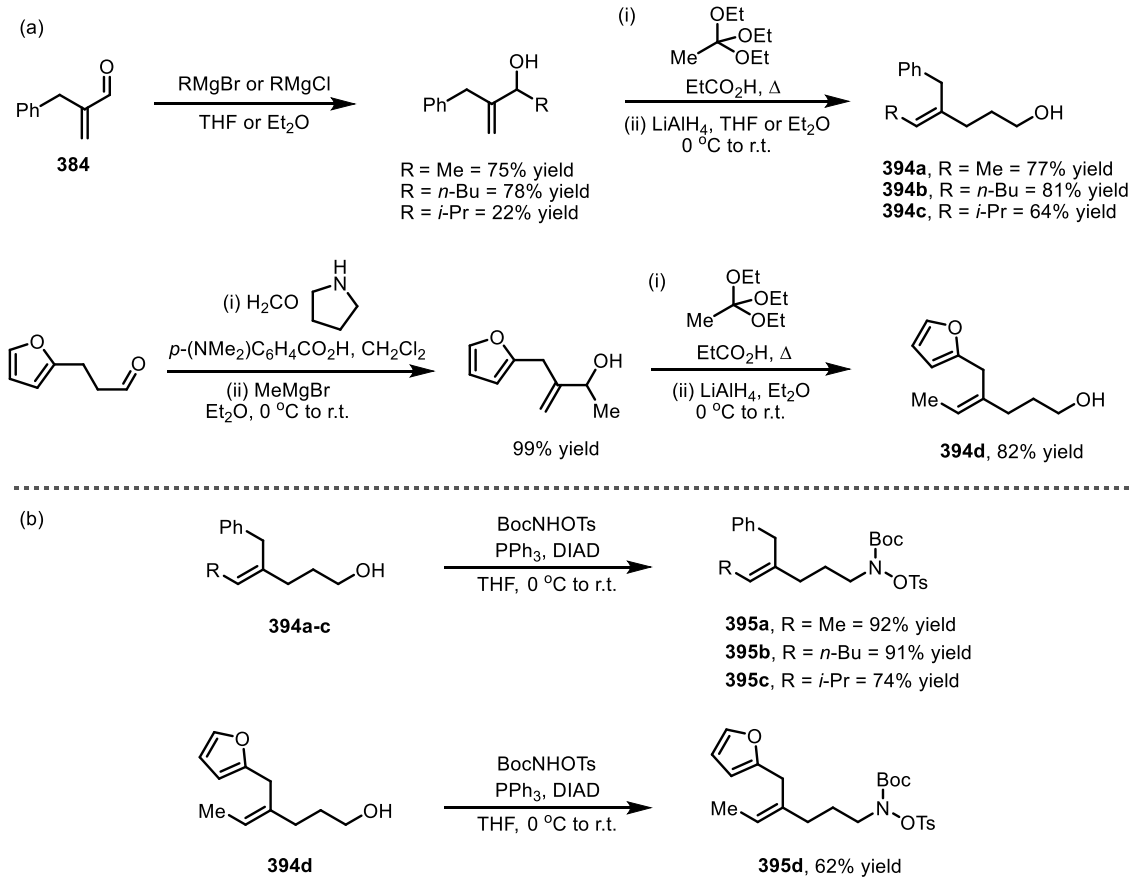
3.2.5 Aziridination of trisubstituted alkenes

Having explored the scope of the reaction of 1,1- and 1,2-disubstituted alkenes, the aziridination of trisubstituted alkenes was next examined. As a starting point trisubstituted alkene substrate **392** was targeted (Scheme 133). This was prepared from methacrolein **390** *via* 1,2-addition of PhMgCl, followed by Johnson-Claisen rearrangement of the resulting allylic alcohol **391**. Reduction with $LiAlH_4$, followed by Mitsunobu reaction completed the synthesis of substrate **392**. When employed in the aziridination reaction, **392** cyclised efficiently to generate aziridine **393** in 81% yield. This result shows that even hindered alkenes are suitable for the aziridination process, which in turn enables access to interesting and challenging heterobicyclic ring systems.



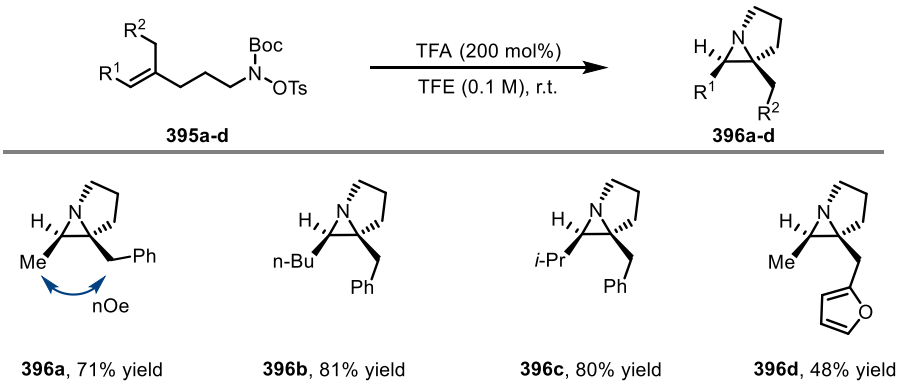
Scheme 133 *Synthesis and intramolecular aziridination of substrate **392**.*

To investigate further the scope of trisubstituted alkenes in the aziridination reaction a series of other substrates were prepared (Scheme 134). Alcohols **394a-c** were all accessed from aldehyde **384** by 1,2-addition of the appropriate organometallic reagent followed by Johnson-Claisen rearrangement and $LiAlH_4$ reduction (Scheme 134a). Alcohol **394d**, containing a furan group was also prepared by a similar route. Substrates **395a-d** where then synthesised from the corresponding alcohols **394a-d** by Mitsunobu reaction (Scheme 134b).



Scheme 134 *(a) Synthesis of alcohols **394a-d**. (b) Synthesis of substrates **395a-d** by Mitsunobu reaction.*

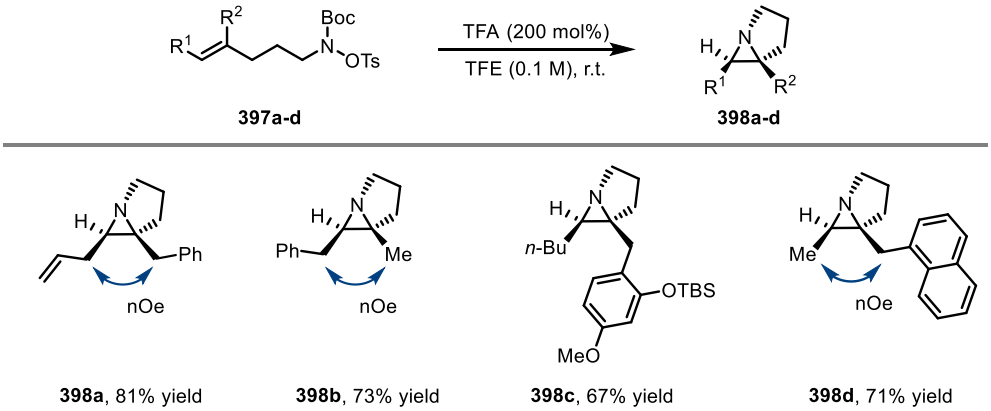
With substrates **395a-c** in hand, they were examined in the aziridination reaction. All cyclised efficiently to provide the corresponding aziridines **396a-c** in excellent yields (Scheme 135). Substrate **395d** also cyclised to the corresponding aziridine **396d**; however, the yield was much lower at 48%. The low yield in the case of the furan-substituted system is likely due to the susceptibility of furans to acid-promoted decomposition through ring opening pathways.



396a, 71% yield **396b**, 81% yield **396c**, 80% yield **396d**, 48% yield

Scheme 135 *Intramolecular aziridination of substrates **395a-d**.*

Several other trisubstituted alkenes **397a-d**[XXXIX] containing a variety of functionality were also examined in the aziridination reaction. **397a-d** underwent efficient cyclisation to the corresponding aziridine products **398a-d** (Scheme 136). Substrate **397a** is noteworthy in that it contains a skipped diene which was well tolerated in the reaction as aziridine **398a** was obtained in 81% yield and no acid-promoted isomerisation was observed. Substrate **397c**, containing an *O*-TBS protected phenol, was also compatible with the reaction conditions and cyclised to aziridine **398c** in 67% yield with the *O*-TBS protected phenol remaining intact. Where possible the relative stereochemistry of the aziridine products was confirmed by nOe analysis.



398a, 81% yield **398b**, 73% yield **398c**, 67% yield **398d**, 71% yield

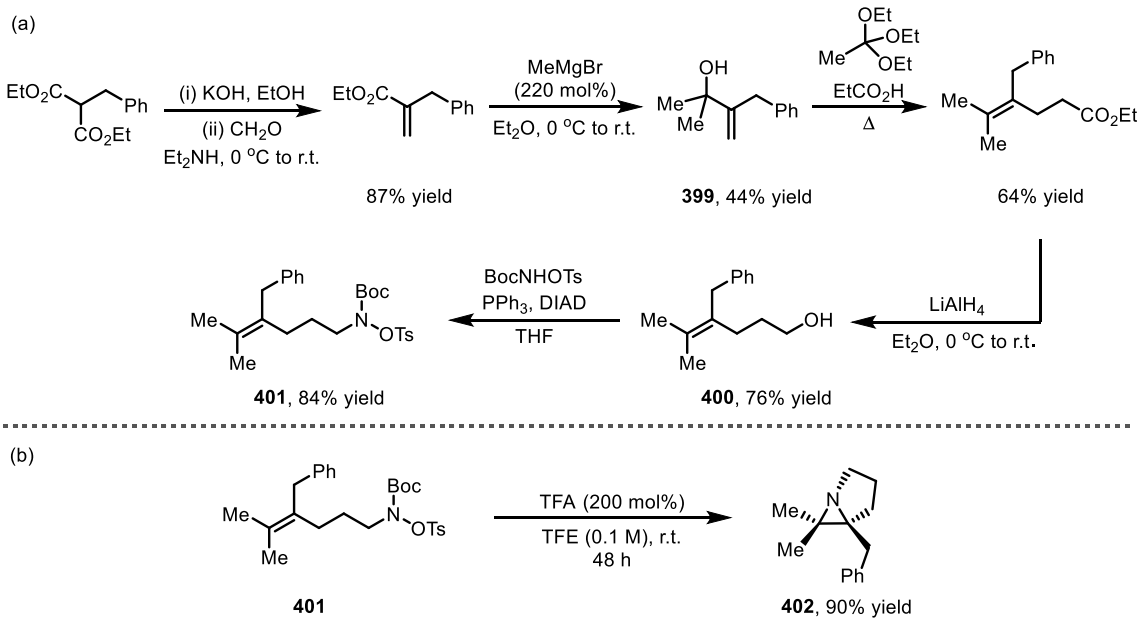
Scheme 136 *Intramolecular aziridination of substrates **397a-d**.*

3.2.6 Aziridination of tetrasubstituted alkenes

Having established that di- and trisubstituted alkenes undergo efficient aziridination the possibility of extending the scope of the reaction to tetrasubstituted alkenes was examined. To

[XXXIX] Substrates **397a-d** were prepared by Xiaofeng Ma (University of Bristol) and hence are not detailed in the experimental section.

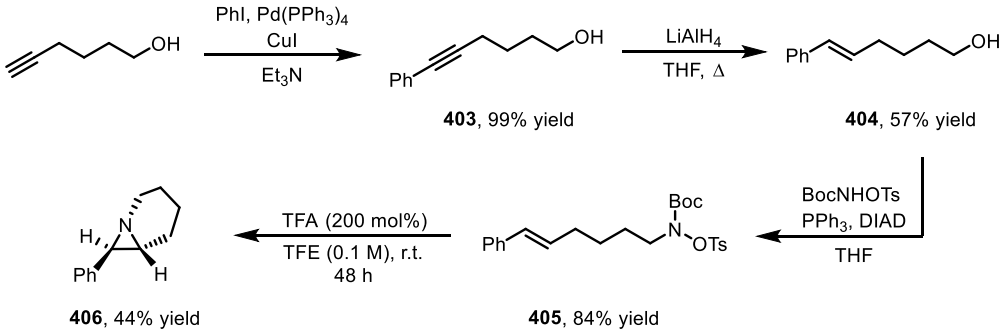
this end *gem*-dimethyl-substituted alkene substrate **401** was prepared (Scheme 137a). The route to **401** began from diethyl benzyl malonate which was converted to allylic alcohol **399** in three steps. The required alcohol **400** for Mitsunobu reaction was then prepared *via* Johnson-Claisen rearrangement followed by $LiAlH_4$ reduction. When subjected to the standard reaction conditions **401** cyclised efficiently to give aziridine **402** in 90% yield (Scheme 137b).



Scheme 137 *(a) Synthesis of tetrasubstituted alkene **401**. (b) Intramolecular aziridination of substrate **401**.*

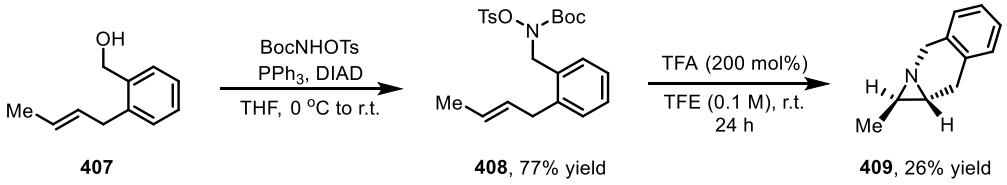
3.2.7 Cyclisation to form azabicyclo[4.1.0]heptanes

Having established that the aziridination protocol is effective for constructing azabicyclo[3.1.0]hexane ring systems, the possibility of performing aziridinations to access other ring systems such as azabicyclo[4.1.0]heptanes were investigated. To this end, phenyl-substituted alkene **405** was targeted as a suitable substrate (Scheme 138). The synthesis began from 5-hexyn-1-ol which underwent Sonogashira coupling with iodobenzene to generate **403** in excellent yield. Reduction of the alkyne of **403** with $LiAlH_4$ in refluxing THF afforded alcohol **404** which was then converted to substrate **405** by Mitsunobu reaction. When **405** was subjected to the aziridination reaction conditions cyclisation to aziridine **406** occurred in 44% yield (Scheme 138).



Scheme 138 *Synthesis and intramolecular aziridination of substrate **405**.*

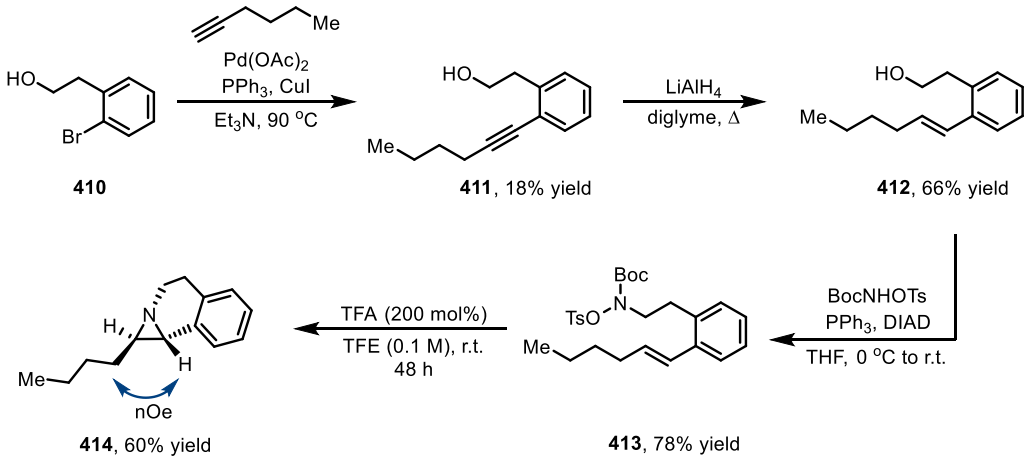
In order to achieve a more efficient aziridination other 6-ring substrates were prepared. Substrate **408** was targeted as a suitable substrate as it was hypothesised that introducing a conformational bias in the form of an arene group in the carbon tether may improve the rate of cyclisation and thus lead to an improved yield of aziridination (Scheme 139). Substrate **408** was prepared from alcohol **407** by Mitsunobu reaction.[XL] Unfortunately, when **408** was subjected to the standard aziridination reaction conditions, aziridine **413** was obtained in only 26% yield.



Scheme 139 *Synthesis and intramolecular aziridination of substrate **408**.*

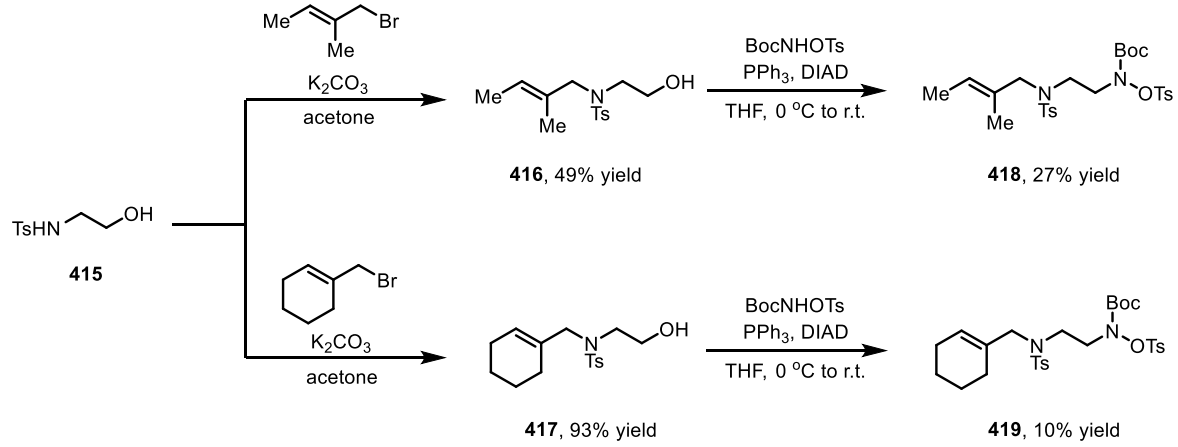
Substrate **413** containing an arene linker in the carbon tether but one carbon atom further away from the tosyloxycarbamate group (versus **408**) was also synthesised (Scheme 140). The synthesis of **413** began with a Sonogashira coupling of alcohol **410** and 1-hexyne to give alkyne **411**.[XLI] Reduction of the alkyne was performed using $LiAlH_4$ in refluxing diglyme to afford alcohol **412** which was then converted to substrate **413** by Mitsunobu reaction. **413** underwent efficient aziridination under the standard conditions to give aziridine **414** in 60% yield. This result represented a significant improvement over the previous 6-ring cyclisation substrates trialled (Scheme 140).

[XL] Alcohol **407** was prepared by Ian Hazelden (University of Bristol) and hence is not detailed in the experimental section.
[XLI] Attempted optimisation of this reaction was carried out; however, no improvement in yield was achieved.



Scheme 140 *Synthesis and intramolecular aziridination of substrate **413**.*

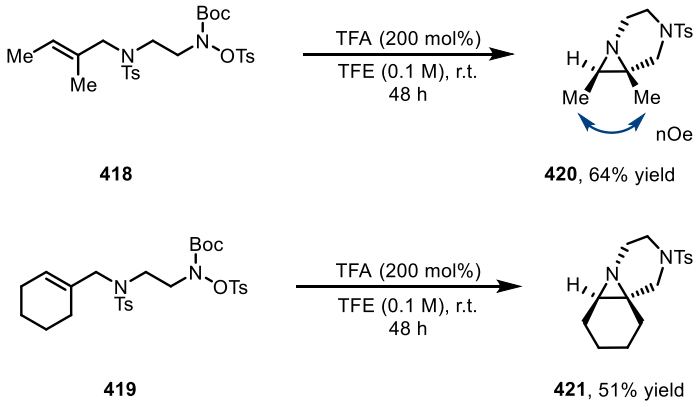
To extend further the scope of this 6-ring cyclisation, substrates **418** and **419** containing a sulfonamide in the tether were prepared as successful aziridination of these substrates would provide access to piperazines. Alcohols **416** and **417** were prepared by alkylation of sulfonamide **415** with the appropriate allyl bromide (Scheme 141). Alcohols **416** and **417** were then converted to substrates **418** and **419** by Mitsunobu reactions, although low yields of products were obtained.[XLII]



Scheme 141 *Synthesis of substrates **418** and **419**.*

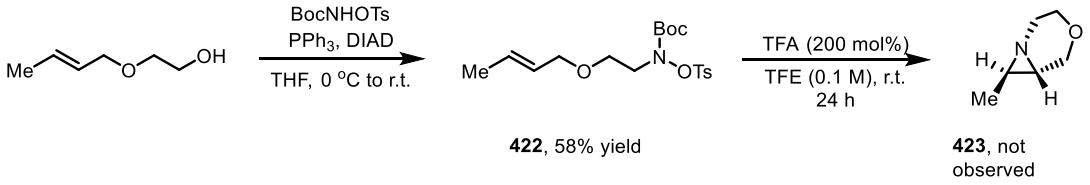
When subjected to the standard reaction conditions substrates **418** and **419** cyclised to the corresponding aziridines **420** and **421** in 51% and 64% yields respectively (Scheme 142). The effective cyclisation of substrate **419** highlights that aziridination of cyclic alkenes can be performed using this approach.

[XLII] The low yields were largely due to issues with purification of the Mitsunobu products.



Scheme 142 *Intramolecular aziridination of substrates **418** and **419**.*

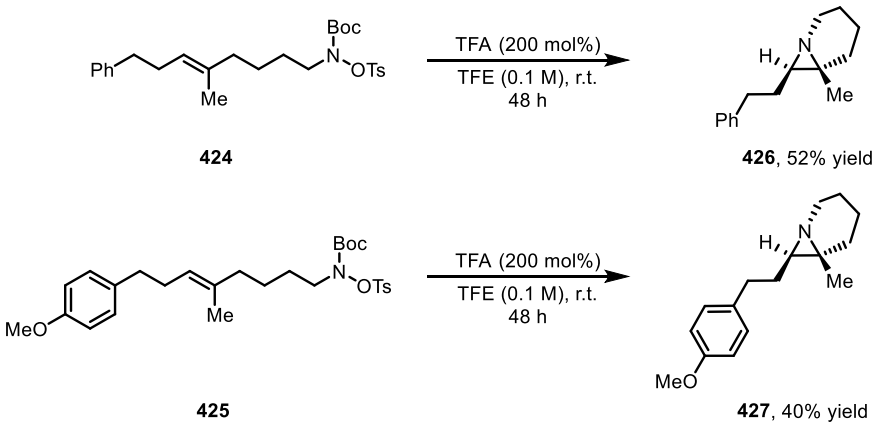
To extend the scope of heteroatoms that are compatible with this reaction, substrate **422** containing an ether group in the carbon tether was synthesised (Scheme 143). Unfortunately, when **422** was subjected to the aziridination reaction conditions the desired aziridine product **423** was not observed. It is likely that due to the electron-withdrawing nature of the ether group the alkene is insufficiently reactive to undergo cyclisation. This is consistent with earlier results which have shown that electron-rich alkenes are more effective substrates.



Scheme 143 *Synthesis and attempted aziridination of substrate **422**.*

Two final trisubstituted alkene substrates **424** and **425** were prepared and examined in the aziridination reaction (Scheme 144).[XLIII] When subjected to the standard reaction conditions, substrates **424** and **425** cyclised to the desired aziridine products **426** and **427** in 52% and 40% yields respectively.

[XLIII] These substrates were prepared by Xiaofeng Ma (University of Bristol) and hence are not detailed in the experimental.



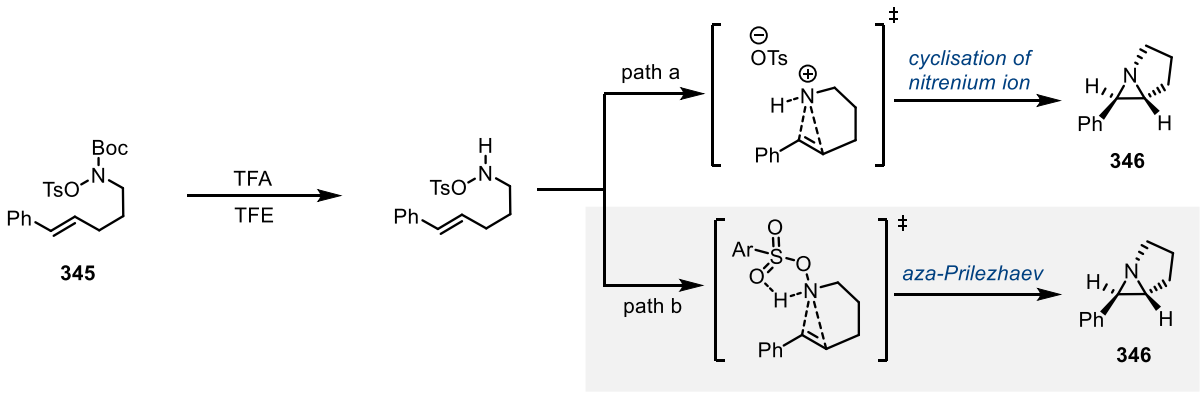
424 **426**, 52% yield

425 **427**, 40% yield

Scheme 144 *Intramolecular aziridination of substrates **424** and **425**.*

3.2.8 Mechanistic studies

Based on the observed diastereospecificity of this reaction, as demonstrated by the aziridination of the (*E*)- and (*Z*)-isomers of **345** leading to different diastereomers of product, a mechanism of aziridination is proposed as shown in Scheme 145. Following TFA promoted *N*-Boc deprotection of **345**, alkene aziridination proceeds *via* a concerted mechanism in which both new C-N bonds are formed simultaneously. Mechanistically, this could be rationalised by the formation and subsequent capture of a nitrenium ion (Scheme 145, path a) or by an aza-Prilezhaev type mechanism (path b).[XLIV]



345

Scheme 145 *Plausible mechanisms of concerted alkene aziridination. Based on available evidence an aza-Prilezhaev-type mechanism (path b) is favoured.*

To gain more of an insight into the mechanism of the aziridination reaction a series of computational studies were carried out.[XLV] The results imply that the transition state for a

[XLIV] This would resemble the aza-Prilezhaev type alkene aziridination of *N*-aminophthalimides proposed by Atkinson.[184-188]

[XLV] All computational studies were carried out by Tom Young with guidance from Natalie Fey (University of Bristol).

concerted aza-Prilezhaev-type mechanism is thermally accessible under the reaction conditions ($\Delta G^{\ddagger}_{solv}$ = 22.0 kcal mol^{-1}) and strongly resembles the spiro "butterfly" transition state involved in *m*-CPBA-mediated alkene epoxidations (Figure 3).[204,205]

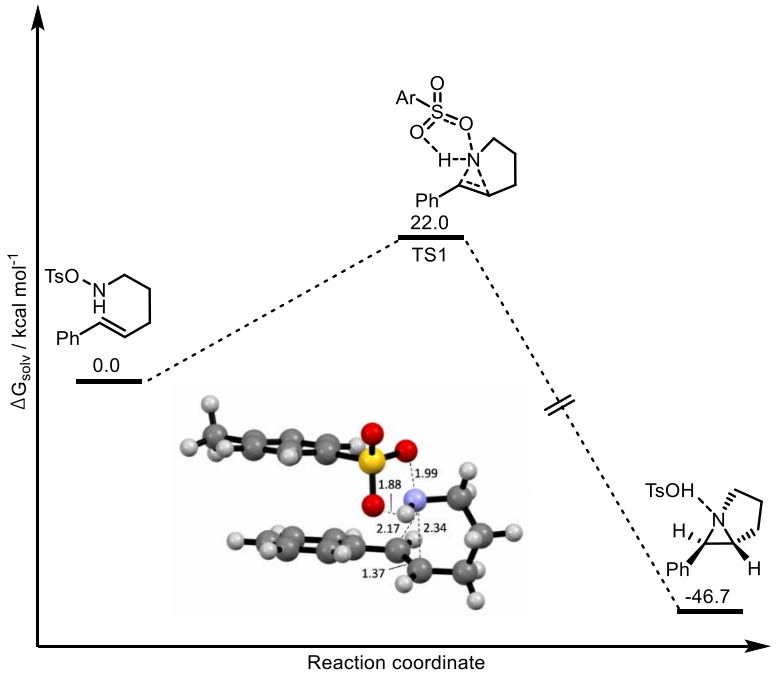
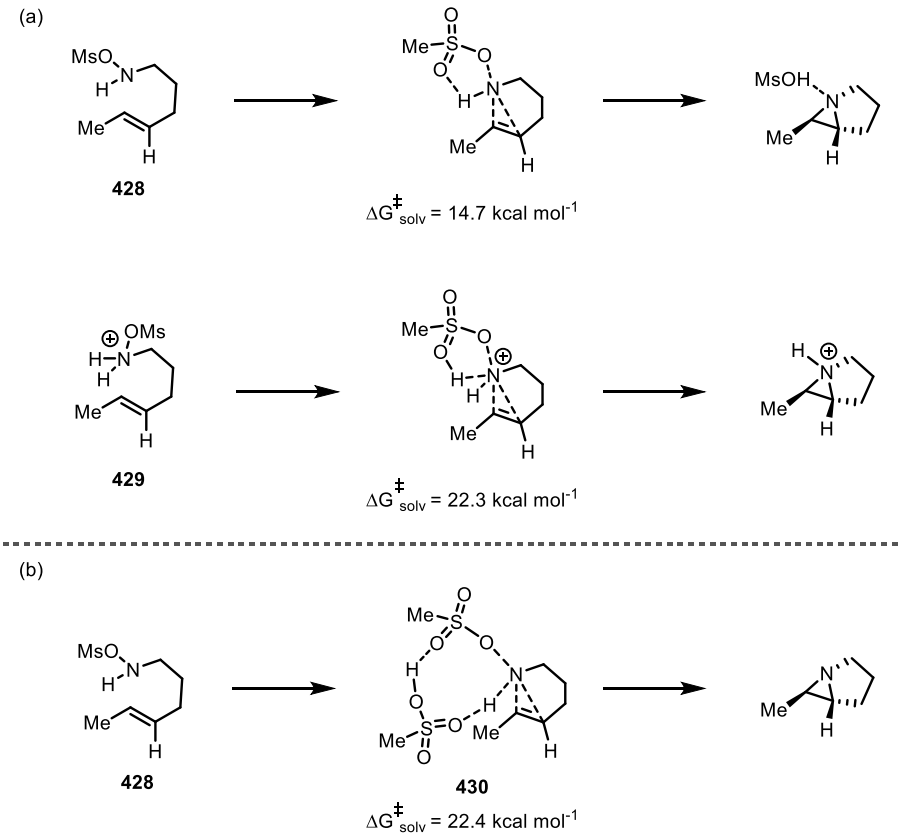


Figure 3 *Reaction profile for aziridination of **345** via an aza-Prilezhaev-type mechanism. Solvated Gibbs free energies are quoted at PBE0/6-311++G(2d,p)//PBE0-D3BJ/6-31+G(d), SMD (TFE). Free energy contributions have been calculated at 298 K.*

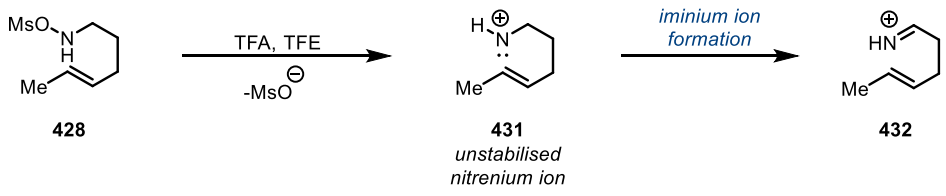
As the reaction is under acidic conditions, the effect of *N*-protonation following Boc-deprotection was also examined. For the purposes of these studies a model system **428**, containing a methyl-substituted alkene and a mesylate leaving group was used (Scheme 146).[XLVI] The results suggest that the protonated form **429** affords a considerably higher energy barrier to aziridination than the neutral form (22.3 kcal mol^{-1} versus 14.7 kcal mol^{-1}). The effect of complexation of a molecule of MsOH on the transition state stability was also examined, as this would potentially help to stabilise the developing negative charge (Scheme 146). However, the Gibbs free energy barrier of the transition state with a complexed MsOH molecule is predicted to be higher than without MsOH ($\Delta G^{\ddagger}_{solv}$ = 22.4 kcal mol^{-1} versus 14.7 kcal mol^{-1}). This difference is likely to be due to the loss of entropy which occurs upon formation of the highly ordered H-bonded transition state **430**.

[XLVI] The reaction energies are expected to differ somewhat between the actual systems and the model system.



Scheme 146 *(a) Comparison of aziridination via a protonated or non-protonated species. (b) Aziridination of* ***428*** *assisted by MsOH complexation.*

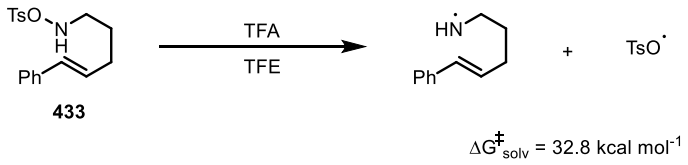
Reaction *via* the formation and subsequent capture of a nitrenium ion **431** was also examined; however, computational results imply that this is unfeasible due to the high-energy barrier to mesylate dissociation (Scheme 147). Moreover, in the event of the formation of a nitrenium ion, proton loss to afford an iminium ion **432** is expected to occur. The computational results in combination with the lack of any precedence in the literature for an efficient alkene aziridination *via* formation of an unstabilised nitrenium ion suggests that a reaction pathway of this type is unlikely.[XLVII]



Scheme 147 *Predicted reactivity of unstabilised nitrenium ion* ***431****.*

[XLVII] Zhdankin and co-workers have reported an alkene aziridination that is proposed to proceed *via* a stabilised nitrenium ion.[198]

An alternative radical-based mechanism involving initial N-O bond homolysis was also considered and examined computationally. The results suggest that this type of mechanism is also unlikely as homolysis of the N-O bond of **433** under the reaction conditions is energetically inaccessible ($\Delta G^{\ddagger}_{solv}$ = 32.8 kcal mol^{-1}) (Scheme 148). Therefore, based on the computational studies and experimental observations an aza-Prilezhaev-type mechanism is favoured for this reaction. However, reaction *via* formation and capture of a nitrenium or a radical based mechanism cannot be entirely discounted.

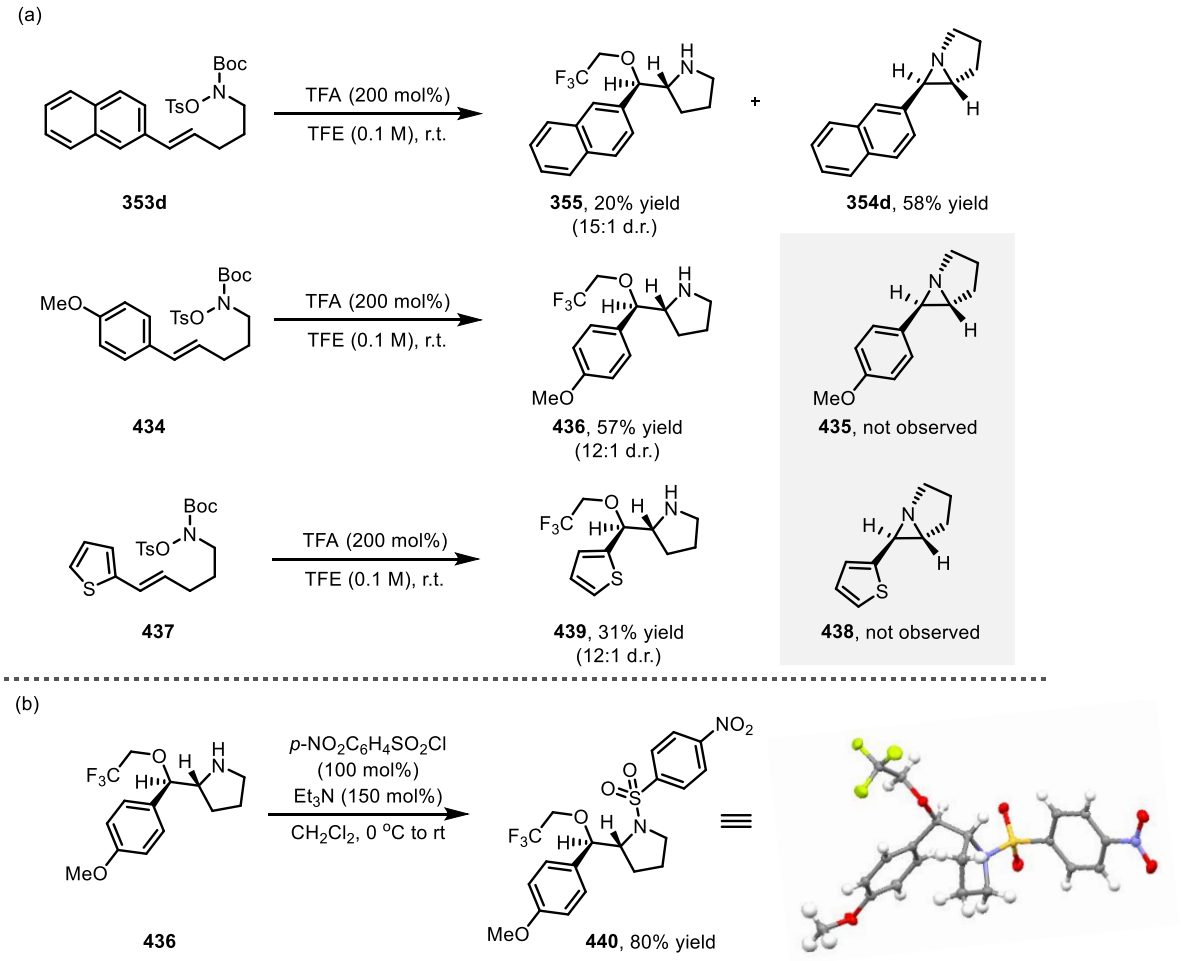


Scheme 148 *N-O bond homolysis of **433** is energetically inaccessible under the reaction conditions.*

3.2.9 Alkene aminofunctionalisations

As discussed in section 3.2.3 (Scheme 126b), when naphthyl-substituted alkene **353d** was subjected to the aziridination reaction conditions the formation of 1,2-aminoether product **355** was observed in 20% yield, in addition to aziridine product **354d**. When substrates **434** and **437**, containing highly stabilising *para*-methoxyphenyl or 2-thienyl substituents were subjected to the aziridination conditions, the expected aziridine products **435** and **438** were not observed (Scheme 149a). Instead 1,2-aminoetherification products **436** and **439** were formed exclusively in 57% and 31% yield respectively, and with good levels of diastereocontrol.[XLVIII] The stereochemistry of the major diastereomer of **436** was confirmed by single crystal X-ray diffraction following conversion of **436** to *N*-nosyl derivative **440** and subsequent recrystallisation (Scheme 149b). The stereochemistry of **355** and **439** were then assigned by comparison to **436**.

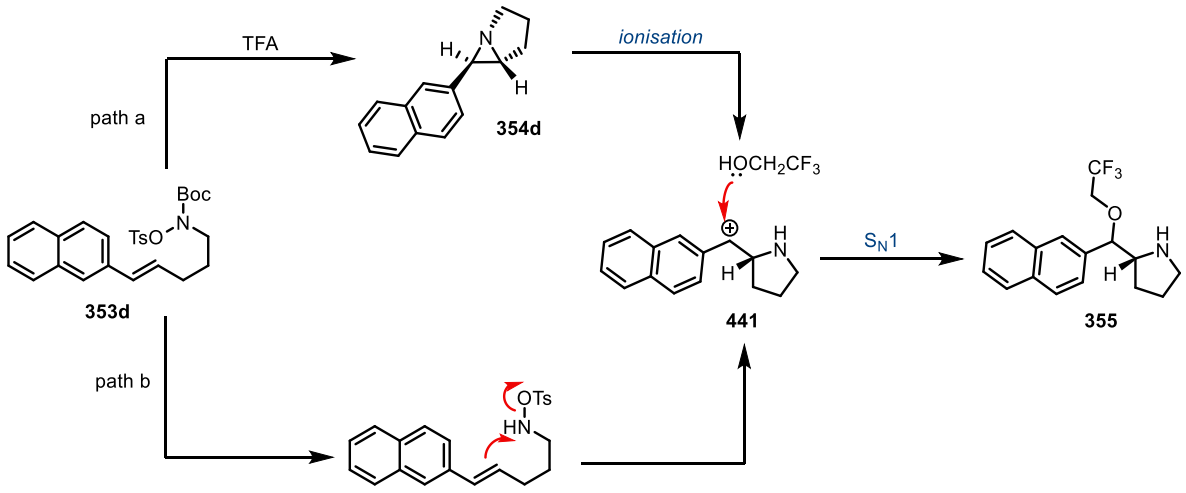
[XLVIII] 1,2-Aminoetherification products were only observed with these highly electron-rich alkenes.



Scheme 149 *(a) Formation of 1,2-aminoetherification products in the aziridination of substrates* ***353d***, ***434*** *and* ***437****. (b) Derivatisation of* ***436*** *for relative stereochemical assignment.*

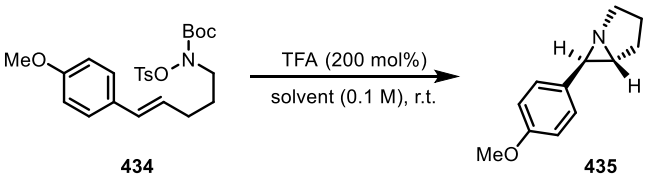
This formation of 1,2-aminoetherifcation products is consistent with an S_N1 mechanism in which acid-promoted ionisation of the initially formed aziridine generates a carbocation **441** which is subsequently captured by a molecule of solvent (Scheme 150, path a).[XLIX, L] This process is likely facilitated by the electron-rich aryl unit which helps to stabilise the adjacent carbocation. Alternatively, it is possible that the aminoether products could also form by an alternative pathway (Scheme 150, path b) that does not proceed through the formation of an aziridine intermediate and instead leads directly to the key benzylic carbocation.

[XLIX] The stereochemistry of the product in which apparent ring-opening occurs with retention, is inconsistent with ring-opening of the aziridine *via* an S_N2 mechanism.
[L] **354d** was stirred overnight in TFE with the addition of TFA/TsOH, and 1,2-aminoetherification product **355** was obtained in 10% yield.



Scheme 150 *Plausible mechanisms for formation of 1,2-aminoetherification products.*

In an attempt to suppress this ring opening reaction and obtain the aziridine products, aziridination of substrate **434** was performed in CH_2Cl_2 and PhMe as these non-nucleophilic solvents should not undergo ring-opening of the aziridine product. However, in these solvents aziridine product **435** could not be isolated (Table 8, entries 1-2). Similarly, no aziridine product was observed in HFIP, a comparable solvent to TFE but less nucleophilic (Table 8, entry 3). It is most likely that due to its sensitive nature any aziridine formed undergoes decomposition (possibly through polymerisation) under the reaction conditions.

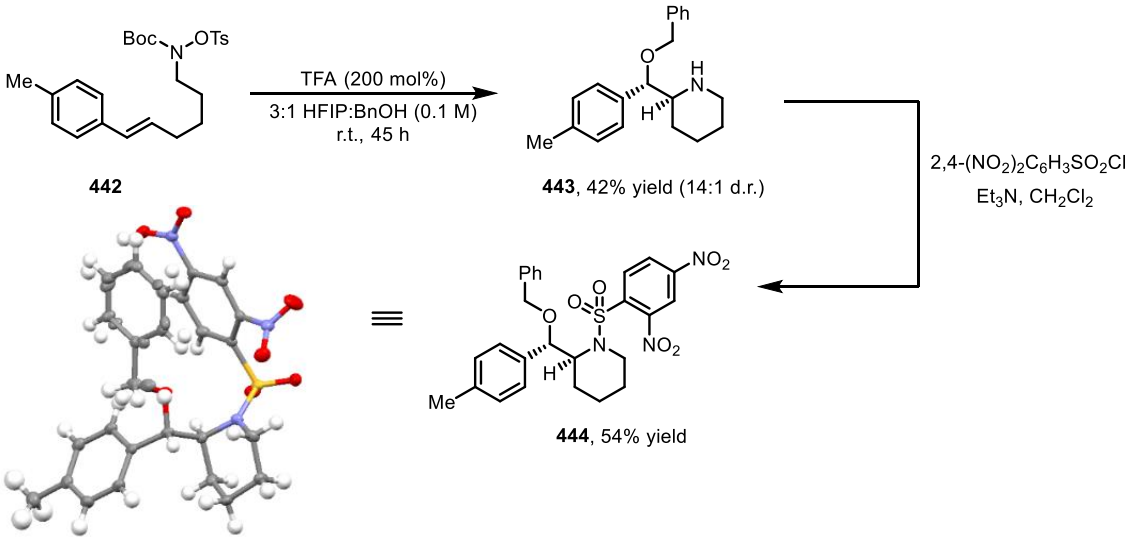


434 **435**

Entry	Acid	*solvent*	*yield*
1	TFA (200 mol%)	CH_2Cl_2	0%
2	TFA (200 mol%)	PhMe	0%
3	TFA (200 mol%)	HFIP	0%

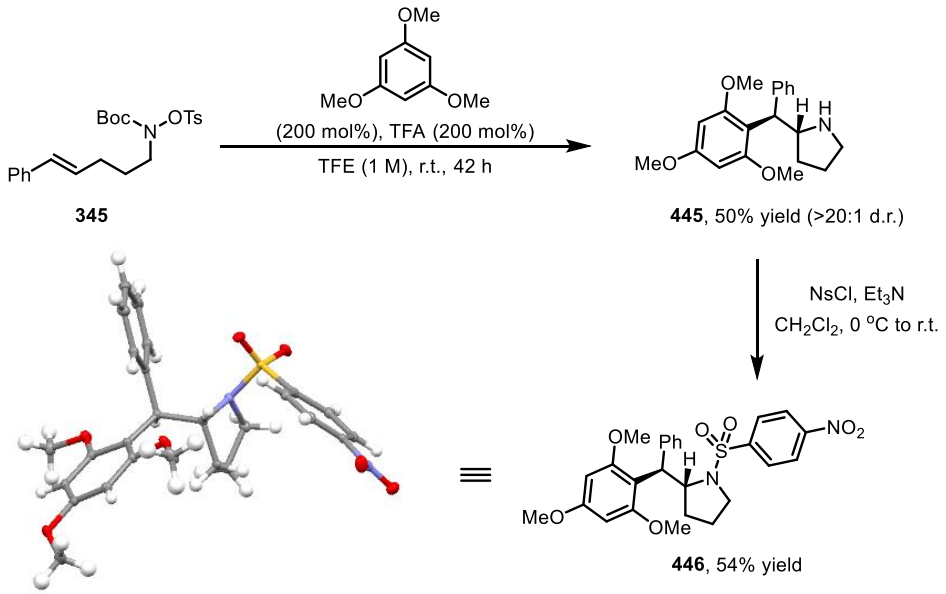
Table 8 *Attempted optimisation of the intramolecular aziridination of substrate **434**.*

The *in situ* trapping of intermediates with TFE prompted investigations into the use of other alcohol-based nucleophiles to expand the scope of 1,2-aminoetherification products that can be obtained. Following optimisation and the use of HFIP as solvent, substrate **442** was converted to 1,2-aminoether **443** in the presence of benzyl alcohol with good levels of diastereocontrol (Scheme 151). The stereochemistry of **443** was confirmed by X-ray crystallography following derivatisation to compound **444** which showed that ring opening has occurred with retention of stereochemistry.



Scheme 151 *1,2-Aminoetherification reaction of substrate **442** with BnOH. The reaction occurs with retention of stereochemistry.*

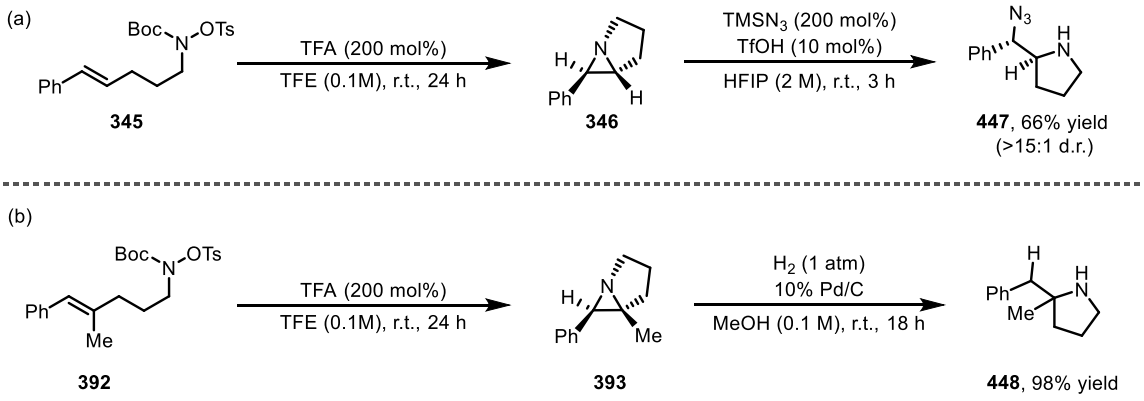
With the aziridination/ionisation sequence providing access to 1,2-aminoetherificiation products the protocol was adapted to other classes of 1,2-aminodifunctionalisations. Under optimised aziridination conditions, trimethoxybenzene functioned as an external nucleophile to enable the conversion of alkene **345** to 1,2-aminoarylation product **445** in 50% yield and as a single diastereomer (Scheme 152). The relative stereochemistry of **445** was confirmed by reaction with NsCl to generate **446** as a crystalline solid from which an X-ray crystal structure was obtained. From the X-ray crystal structure, ring opening has occurred by inversion.



Scheme 152 *1,2-Aminoarylation of substrate **345**. The reaction occurs with inversion of stereochemistry.*

3.2.10 Further derivatisations

To expand the scope of diversification a series of further derivatisations of the aziridine products was carried out. Ring-opening of aziridine **346** was achieved using $TMSN_3$ and a catalytic amount of TfOH to afford 1,2-amino-azide compound **447** in good yield and with high stereoselectivity (Scheme 153a). Aziridine **393** was subjected to hydrogenative C-N bond reduction using Pd/C and H_2 to generate pyrrolidine **448** in excellent yield (Scheme 153b).[206] This transformation represents a formal hydroamination of alkene **392**.



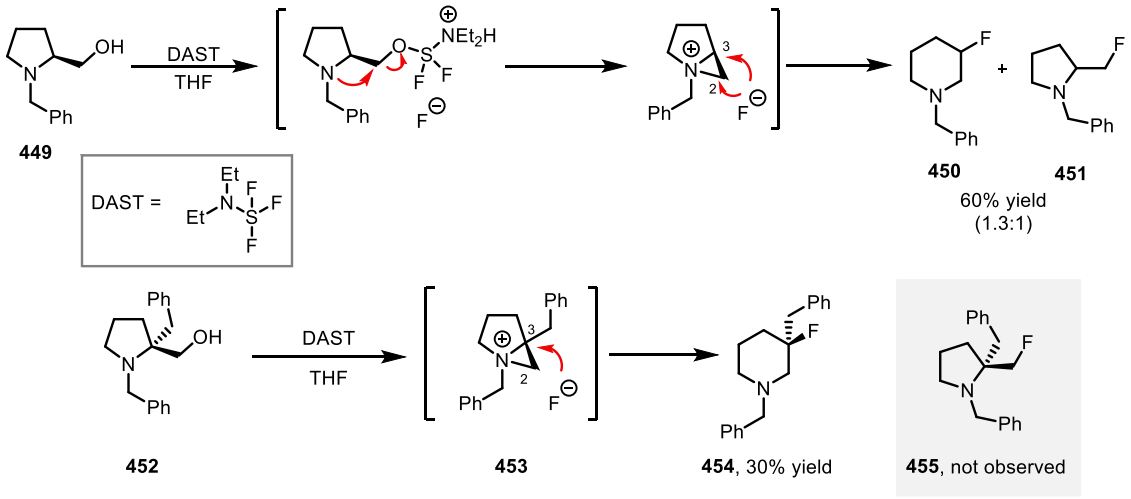
Scheme 153 *(a) Trapping of aziridine **346** with $TMSN_3$. (b) Hydrogenative C-N bond reduction of aziridine **392**.*

3.2.11 Ring expansion of azabicyclo[3.1.0]hexanes to piperidines

One of the major limitations of the dearomatising amination reaction was its inability to afford 6-membered (piperidine ring) products, with the reaction seemingly restricted to the formation of spirocyclic pyrrolidines. Piperidines are important and prevalent structures in natural products, making them attractive targets for synthesis;[207] as such, a further class of derivatisations involving ring expansion of azabicyclo[3.1.0]hexanes to piperidines was investigated. In the chemical literature bicyclic aziridinium ions that resemble the aziridine products obtained in this chapter have been invoked as intermediates in the ring expansion of pyrrolidines to piperidines.[208-214,LI] Of particular note is the work of Cossy and co-workers who have demonstrated that fluorinating reagents such as diethylaminosulfur trifluoride (DAST) can induce ring expansion of prolinols to 3-fluoropiperidines *via* an aziridinium intermediate (Scheme 154).[210] For example, through treatment with DAST, *N*-benzyl prolinol **449** was converted to 3-fluoropiperidine **450** and 2-(fluoromethyl)pyrrolidine **451** in a ratio of 1.3:1 in favour of the piperidine product. The transformation is under kinetic control and the selectivity

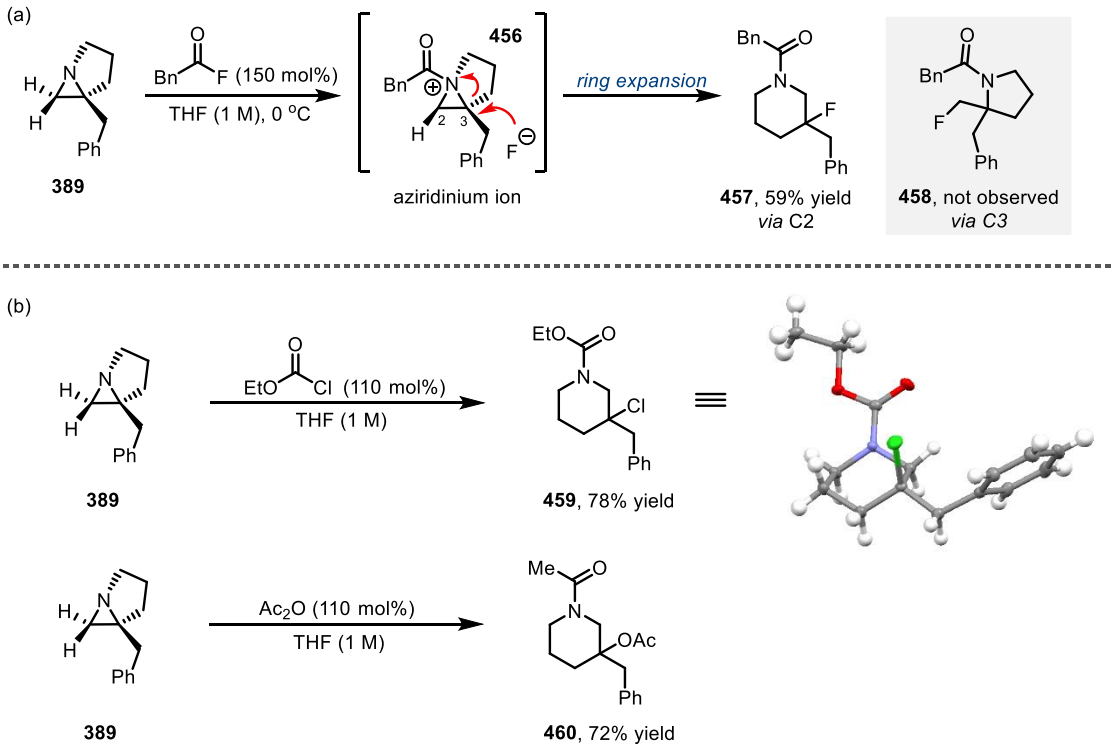
[LI] Related ring expansions of azepanes,[215] azocanes,[215] piperazines,[215] morpholines,[215] indolines[215] and ring expansions to access azepanones[216] have also been reported.

of the rearrangement is improved when the nitrogen atom of the prolinol is protected with a bulky group. Exclusive formation of the piperidine product **454** was achieved with prolinol **452** containing a quaternary centre at C3. The selective attack of fluoride at the C3 position of substituted prolinols can be rationalised due to a lengthening/weakening of the C3-N bond in aziridinium intermediate **453**. The presence of the quaternary centre at C3 results in the stabilisation of a partial positive charge at C3 and thus the fluoride attacks the more electrophilic C3 carbon to give the ring expanded product.



Scheme 154 *DAST-induced ring expansion of prolinols to piperidines.*[210]

It was envisaged that the bicyclic aziridine products obtained by the methods used in this chapter could be acylated to form an aziridinium ion which would then undergo ring expansion with an appropriate nucleophile. To this end, aziridine **389** was reacted with 2-phenylacetyl fluoride (150 mol%) in THF at 0 °C and the desired 3-fluoropiperidine product **457** was formed exclusively in 59% yield (Scheme 155a). The pyrrolidine product **458** formed by attack of the fluoride at C2 of **456** was not observed. This method proved amenable to other nucleophiles; piperidines **459** and **460** were generated in good yields from aziridine **389** by reaction with ethyl chloroformate and acetic anhydride respectively (Scheme 155b). Selectivity for formation of the piperidine product was confirmed by single crystal X-ray diffraction of **459**.

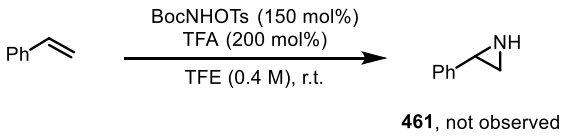


Scheme 155 *(a) Formation of 3-fluoropiperidine **457** by ring expansion of aziridine **389**. (b) Ring expansions of aziridine **389** using other nucleophiles.*

3.3 Studies towards an intermolecular aziridination reaction

3.3.1 Preliminary results

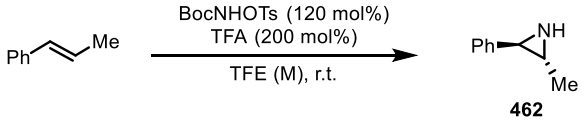
Following on from the development of an intramolecular aziridination procedure for the synthesis of aza-bicyclic structures, the potential to carry out an intermolecular aziridination was explored. As a starting point, the aziridination of styrene with BocNHOTs as the aminating agent was investigated. Unfortunately, aziridination of styrene under the following reaction conditions [BocNHOTs (150 mol%), TFA (200 mol%) in TFE (0.4 M)] failed to produce any of the desired aziridine **461** (Scheme 156).



Scheme 156 *Attempted intermolecular aziridination of styrene.*

A brief survey of other alkenes identified *trans*-β-methylstyrene as a potentially suitable alkene; aziridination of *trans*-β-methylstyrene afforded aziridine **462** in 6% yield (Table 9, entry 3). Attempts at optimising this result by varying the concentration of the reaction failed to have a significant effect on the yield although increasing the concentration to 0.5 M did

increase the yield to 12% (Table 9, entry 4). The yields were determined by ^{1}H NMR analysis of the crude reaction mixture with the addition of an internal standard as attempts to isolate aziridine **462** by flash column chromatography were unsuccessful.

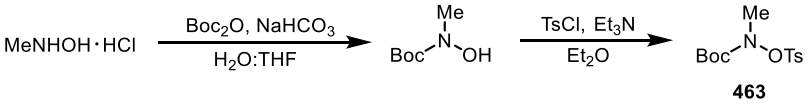


462

Entry	TFE (M)	*yield*
1	0.1 M	8%
2	0.2 M	4%
3	0.4 M	6%
4	0.5 M	12%

Table 9 *Effect of concentration on the intermolecular aziridination of trans-β-methylstyrene.*

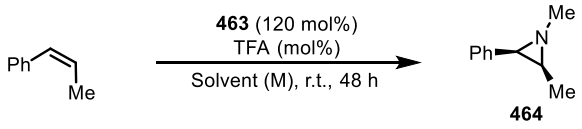
The use of an *N*-substituted aminating reagent in the reaction was investigated as this would give rise to *N*-alkylated aziridines. *N*-Methyl substituted aminating agent **463** was prepared in two steps from commercially available *N*-methyl hydroxylamine hydrochloride (Scheme 157).



463

Scheme 157 *Synthesis of N-methyl amino-reagent **463**.*

Using the previous best conditions [200 mol% TFA in TFE (0.5 M)] *cis*-β-methylstyrene underwent aziridination to afford the desired aziridine product **464** in 15% yield (Table 10 entry 1) which was improved to 21% by increasing the reaction time (48 h versus 42 h) (Table 10, entry 2). Unfortunately, further attempts at reaction optimisation failed to improve the yield further. Increasing the loading of alkene to 10 equivalents resulted in **464** being obtained in 15% yield, whilst increasing the equivalents of TFA had no effect on the yield of reaction (Table 10, entries 3 and 4). As previously observed a concentration of 0.5 M appears to be optimal with lower and higher concentrations both giving lower yields (Table 10 entries 5 and 6). In addition, changing the solvent to HFIP gave no improvement to the yield, whilst no product was observed in CH_2Cl_2 (Table 10, entry 7 and 8). The use of a lower amount of TFA (15mol%) was also ineffective (Table 10, entry 9).

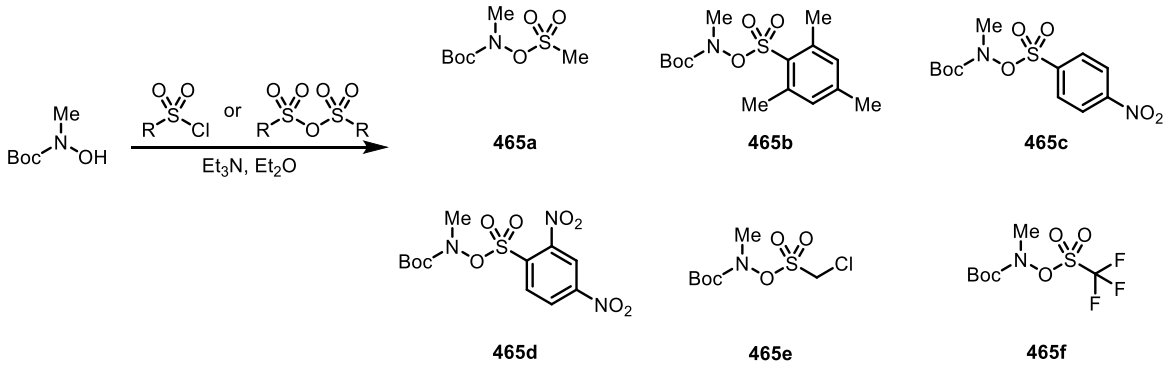


464

Entry	*TFA (X mol%)*	Solvent (M)	*yield*
1	200	TFE (0.5 M)	15%[a]
2	200	TFE (0.5 M)	21%
3	200	TFE (0.5 M)	15%[b]
4	1000	TFE (0.5 M)	17%
5	200	TFE (0.1 M)	9%
6	200	TFE (2.0 M)	11%
7	200	HFIP (0.5 M)	21%
8	200	CH_2Cl_2 (0.5 M)	0%
9	15	TFE (0.5 M)	0%

Table 10 *Attempted optimisation of the intermolecular aziridination of cis-β-methylstyrene.* [a]*Reaction time was 42 h.* [b]*100 mol% of amine used, 1000 mol% of alkene used.*

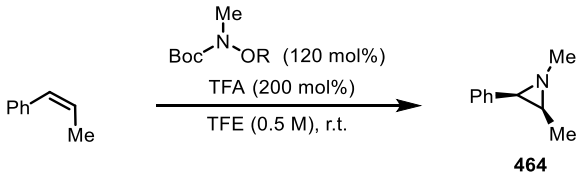
In an attempt to improve the reactivity, a range of different activated *N*-methyl hydroxylamine reagents were prepared and examined in the aziridination reaction. As for reagent **463**, compounds **465a-f** were synthesised from *tert*-butyl hydroxy(methyl)carbamate by coupling with the appropriate sulfonyl chloride or anhydride (Scheme 158).



Scheme 158 *Synthesis of N-methylhydroxylamine aminating reagents **465a-f**.*

With the reagents in hand, they were examined in the aziridination reaction. As shown in Table 11, methylsulfonyl and mesitylsulfonyl systems **465a** and **465b** were less effective in the aziridination reaction than the tosyl system (17% and 9% respectively versus 21% for the tosyl) (Table 11, entries 1 and 2). However, both the 4-nitrophenyl and 2,4-dinitrophenyl systems **465c** and **465d** were more effective, providing aziridine **464** in 35% and 38% yields respectively (Table 11, entries 3 and 4). Optimal reactivity was observed with the chloromethanesulfonyl system **465e** which gave the desired aziridine **464** in 42% yield (Table 11, entry 5). After synthesising the trifluoromethane system **465f**, and on the basis that

it was likely to be unstable to column chromatography it was used immediately in the aziridination reaction without purification, and aziridine **464** was obtained in 7% yield (Table 11, entry 6). Presumably this low yield can be attributed to hydrolysis of **465f**, before aziridination can occur.



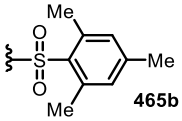
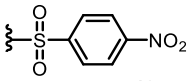
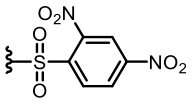
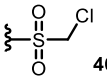
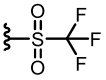
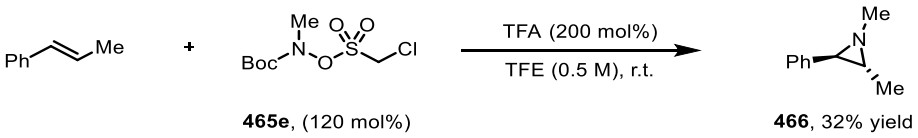
Entry	*R*	*yield*
1	 **465a**	17%
2	 **465b**	42%
3	 **465c**	7%
4	 **465d**	9%
5	 **465e**	35%
6	 **465f**	38%

Table 11 *Effect of the leaving group on the intramolecular aziridination of cis-β-methylstyrene.*

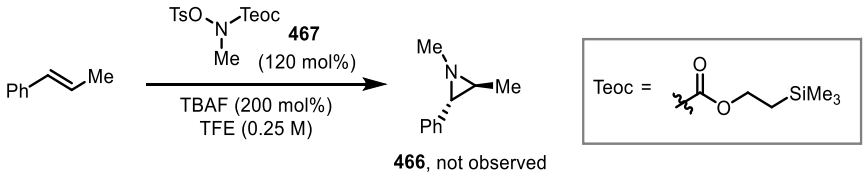
Upon repeating the aziridination of *cis*-β-methylstyrene using **465e** as the aminating reagent a 3:1 mixture of the *cis*- and *trans*-aziridine isomers was obtained. As these are only preliminary results a full mechanistic study of the intermolecular aziridination was not performed, as such it is not clear if the mechanism is analogous to that which was proposed for the intramolecular reaction or if a different mechanism is in operation. If the mechanism is the same as the intramolecular aziridination (i.e. concerted C-N bond formation) loss of stereospecificity could be due to isomerisation of the alkene or the aziridine product under the acidic reaction conditions; however, this is unconfirmed.

Aziridination of *trans*-β-methylstyrene was also examined using **465e**. When subjected to the optimised conditions, *trans*-aziridine **466** was obtained in 32% yield and as a single diastereomer. The *cis*-aziridine isomer **464** was not observed (Scheme 159).



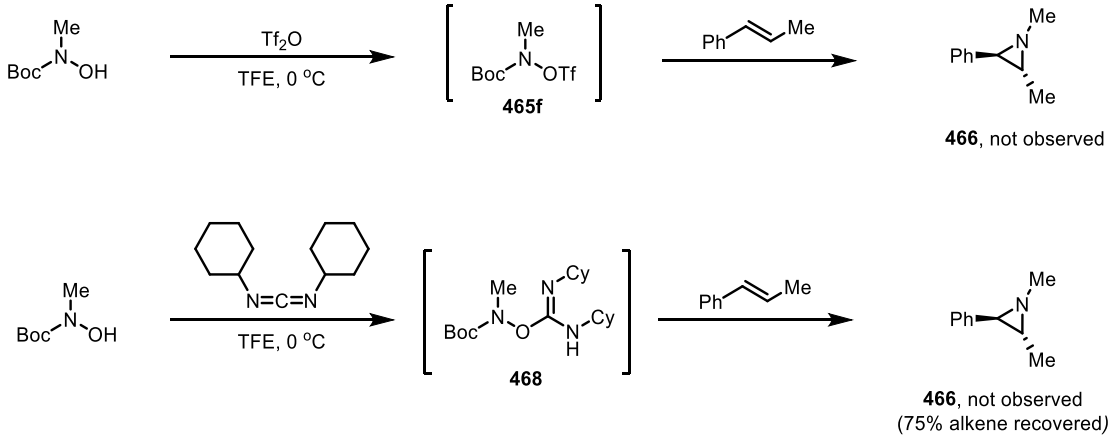
Scheme 159 *Intermolecular aziridination of trans-β-methylstyrene.*

Due to the disappointing results obtained for intermolecular aziridination a number of other approaches for generating activated hydroxylamines *in situ* were investigated. Teoc-protected hydroxylamine reagent **467** was prepared and aziridination of *trans*-β-methylstyrene was attempted using the following conditions [TBAF (200 mol%) in TFE (0.25 M)]. Unfortunately, the desired aziridine product **466** was not observed (Scheme 160).



Scheme 160 *Attempted intermolecular aziridination of trans-β-methylstyrene with Teoc-activated hydroxylamines.*

Attempts to access an activated hydroxylamine such as **465f** *in situ* from *tert*-butyl hydroxy(methyl)carbamate was also carried out. To this end *tert*-butyl hydroxy(methyl)carbamate was treated with trifluoromethanesulfonic anhydride in TFE before addition of *trans*-β-methylstyrene (Scheme 161). Unfortunately, the desired aziridine product **466** was not observed. An attempt to generate activated hydroxylamine **468** using *N*,*N*′-dicyclohexylcarbodiimide was also performed; however, this also failed to induce aziridination of *trans*-β-methylstyrene.



Scheme 161 *Attempted in situ generation of activated hydroxylamines for intramolecular aziridination.*

3.4 Conclusions

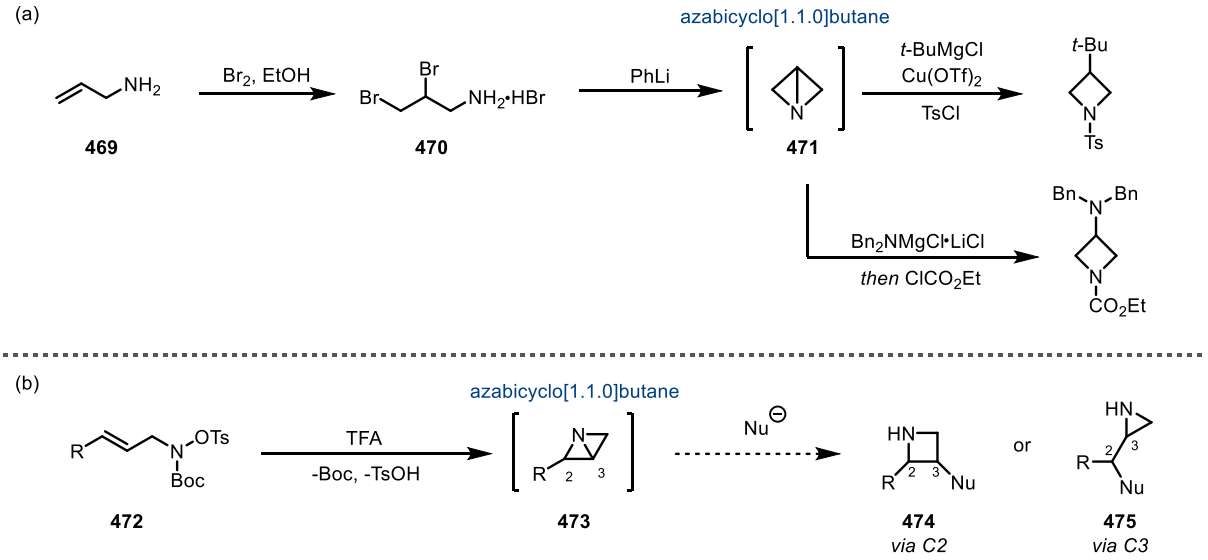
The development of a novel transition metal-free aziridination of *N*-tosyloxycarbamates was successfully achieved. Excellent yields were generally observed with substrates containing di- and trisubstituted alkenes and the methodology is also compatible with tetrasubstituted alkenes, allowing for the synthesis of highly congested *N*-heterocycles. One of the limitations of the dearomative amination reactions presented in the previous chapter is that 6-*exo* cyclisations to afford piperidine products were unsuccessful. However, through this aziridination protocol 6-ring cyclisations to afford azabicyclo[4.1.0]heptanes were possible although lower yields were generally observed versus 5-ring cyclisations. Access to 6-membered piperidine structures was also obtained by ring expansion of the azabicyclo[3.1.0]hexanes products using suitable nucleophiles. Extension of the aziridination protocol to a metal-free intermolecular reaction was attempted; however, only modest yields of aziridines were obtained.

3.5 Preliminary studies for future work

Having established an intramolecular aziridination protocol to access azabicyclo[3.1.0]hexane and azabicyclo[4.1.0]heptane motifs, the application to the formation of other aza-bicyclic ring structures such as azabicyclo[1.1.0]butanes was investigated. Very few methods exist for accessing such intermediates,[217-219] but one of the most effective methods was reported by Nagao and co-workers in which 1-azabicyclo[1.1.0]butane **471** is accessed in a two-step procedure from allylamine **469**, *via* cyclisation of 2,3-dibromopropylamine **470**.[220,221] For this transformation the use of a strong organolithium base is required. A number of groups including Nagoa,[222] Baran[223,224] and Gianatassio[225] have demonstrated that

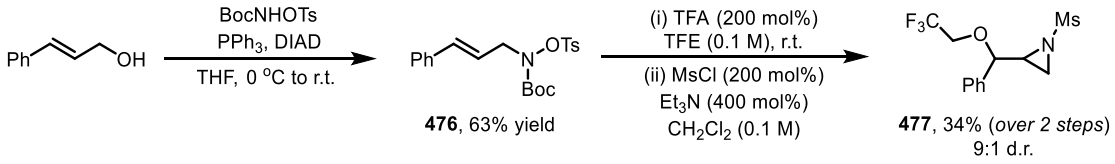
1-azabicyclo[1.1.0]butane intermediates **471** can be intercepted with a variety of nucleophiles to prepare functionalised azetidines.[226-228]

The lack of effective methods for generating azabicyclo[1.1.0]butane intermediates spurred us to investigate if alkenyl substrates such as **472** could undergo the same intramolecular aziridination process as observed for the formation of azabicyclo[3.1.0]hexane and azabicyclo[4.1.0]heptane systems, but instead lead to intermediate **473** which could be functionalised by ring-opening with an appropriate nucleophile. This could allow access to azetidine **474** or aziridine **475** products depending on the regioselectivity of the attack of the nucleophile. (Scheme 162). If successful, this approach would represent a mild alternative to traditional methods and negate the need for a strong base. Preliminary results towards harnessing the reactivity of strained azabicyclobutane intermediates are given below.



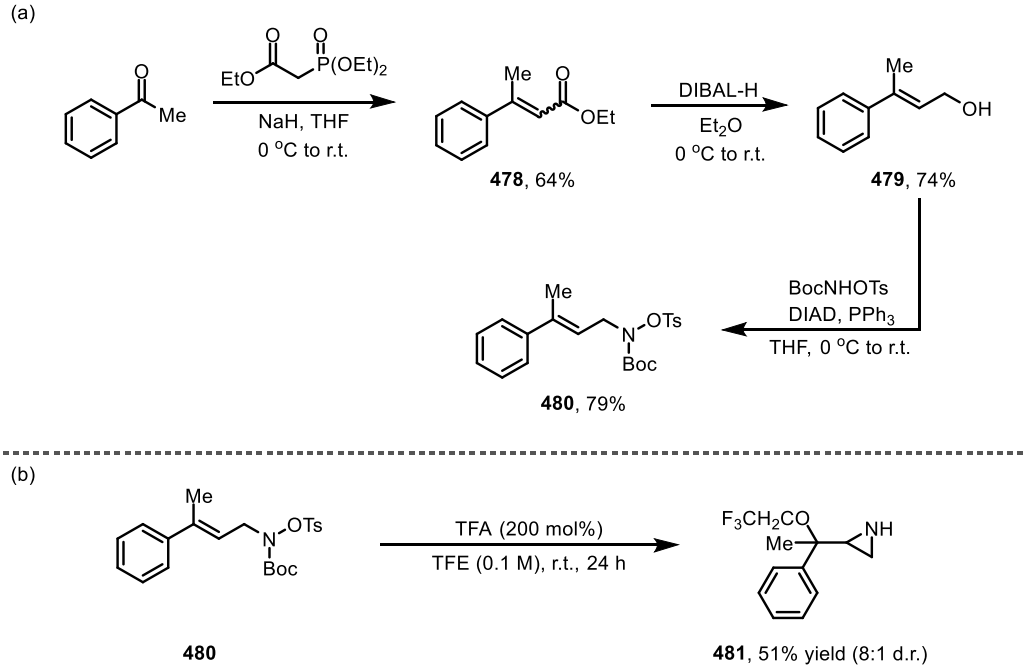
Scheme 162 *(a) Synthesis and reactions of azabicyclo[1.1.0]butanes.*[220,223-225] *(b) General strategy for harnessing the reactivity of strained aza-bicyclobutane intermediates.*

The investigation began by preparing substrate **476** which was synthesised by Mitsunobu reaction of cinnamyl alcohol (Scheme 163). Upon treatment with TFA (200 mol%) in TFE, **476** cyclised to the corresponding aziridine in 34% yield and as a 9:1 mixture of diastereomers. To improve stability and to help with isolation of the product the aziridine was isolated as sulfonamide **477** by *in situ* protection with MsCl.



Scheme 163 *Synthesis and aziridination of substrate **476**.*

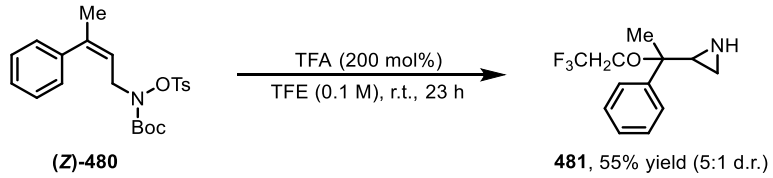
In an attempt to improve reactivity trisubstituted alkene **480** was prepared (Scheme 164a). The synthesis began with a Horner-Wadsworth-Emmons reaction to generate unsaturated ester **478** predominantly as the (*E*)-alkene isomer; however, the (*E*)- and (*Z*)-alkene isomers were separated by flash column chromatography. **478** was then reduced to allylic alcohol **479** before Mitsunobu reaction afforded the desired substrate **480** in good yield. When **480** was reacted using the aziridination conditions [TFA (200 mol%), TFE (0.1 M) at room temperature] aziridine **481** was obtained in 51% yield and as an 8:1 mixture of diastereomers (Scheme 164b). Attempts at optimising this reaction were performed (Table 18, appendix); however, no significant improvement was observed.



Scheme 164 *(a) Synthesis of substrate **480**. (b) Aziridination of substrate **480**.*

The (*Z*)-alkene isomer of **480** was also subjected to the aziridination conditions. Aziridine **481** was obtained in 55% yield and approximately 5:1 d.r. (Scheme 165). Although the relative stereochemistry of the major diastereomer of **481** was not confirmed, reaction of both **(*E*)-** and **(*Z*)-481** led to formation of the same major diastereomer. This result suggests that nucleophilic

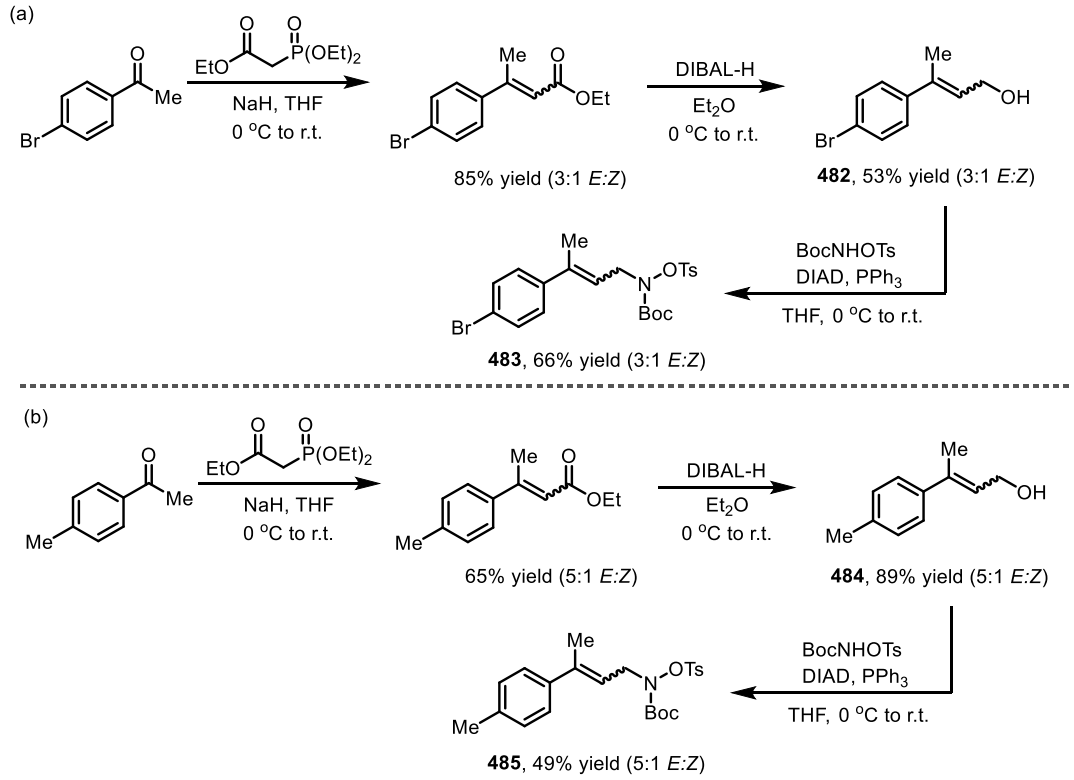
attack of the alcohol occurs *via* an S_N1 mechanism which implies the formation of a benzylic carbocation, either directly or from an azabicyclobutane intermediate.



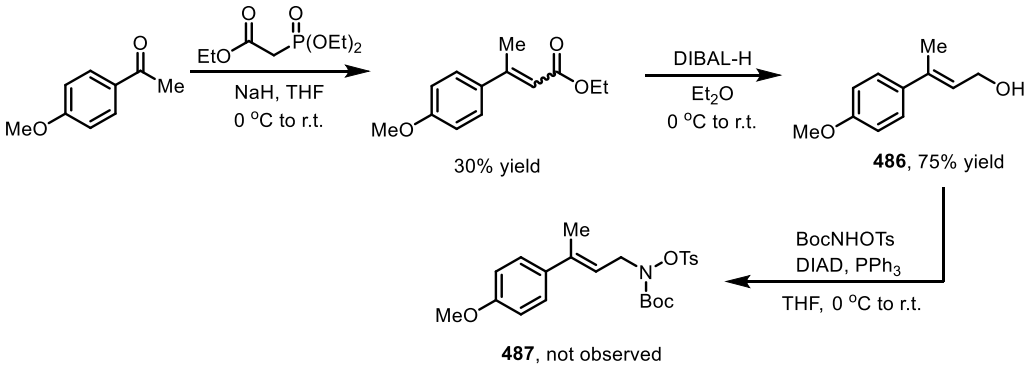
(*Z*)-480 **481**, 55% yield (5:1 d.r.)

Scheme 165 *Aziridination of* ***(Z)-480****.*

To investigate further the scope of this reaction a series of substrates with substitution in the *para* position of the phenyl group were synthesised. 4-Methyl- and 4-bromophenyl substrates **483** and **485** were synthesised using the same strategy as for the parent substrate (Scheme 166). The synthesis of 4-methoxyphenyl substrate **487** was also attempted; however, Mitsunobu reaction of alcohol **486** was unsuccessful (Scheme 167). The 4-methyl- and 4-bromophenyl substrates **483** and **485** were both obtained as a 5:1 and 3:1 mixture of (*E*/*Z*)-isomers respectively and were subjected to the aziridination conditions as isomeric mixtures.

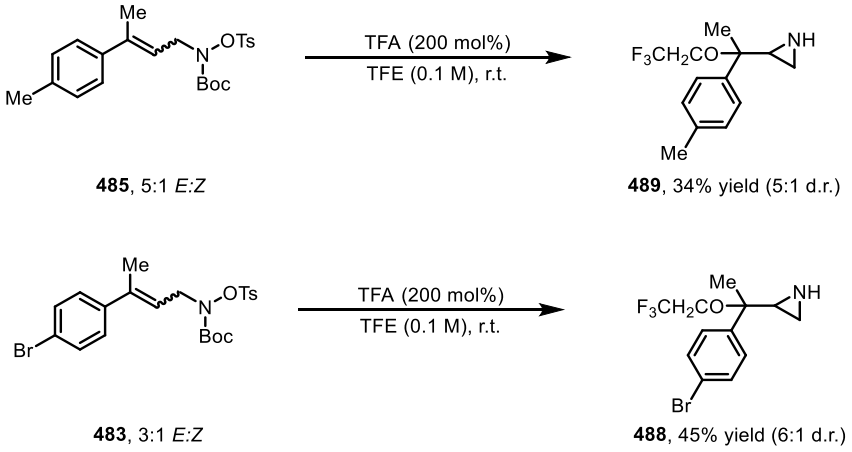


Scheme 166 *(a) Synthesis of substrate* ***483****. (b) Synthesis of substrate* ***485****.*



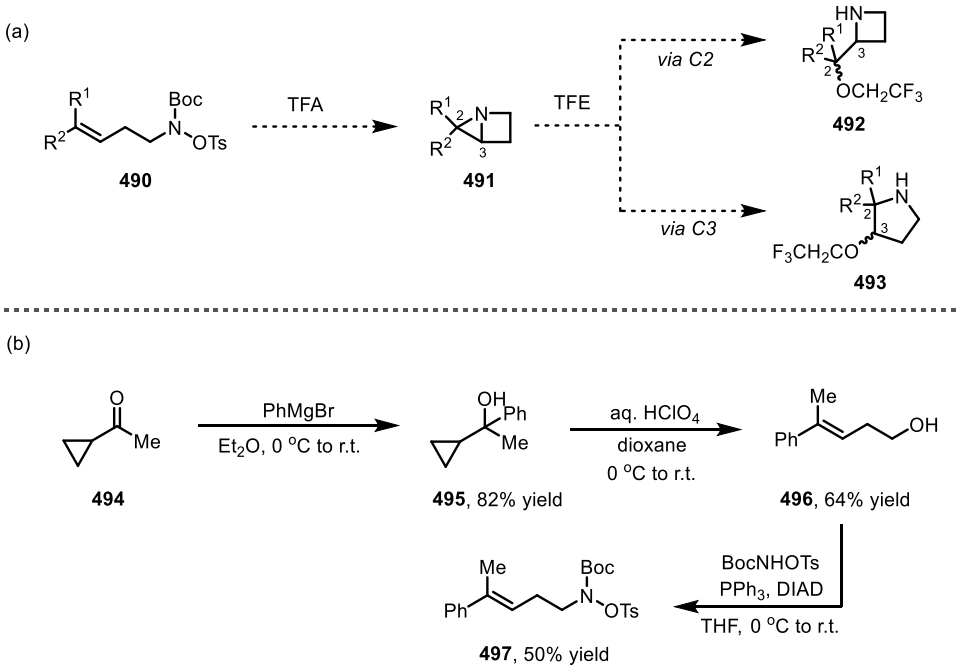
Scheme 167 *Attempted synthesis of substrate **487**.*

When **485** was examined in the aziridination reaction, aziridine **489** was formed in 34% yield and as a 5:1 mixture of diastereomers (Scheme 168). A slightly improved result was obtained for 4-bromo-phenyl substrate **483** which underwent aziridination to afford aziridine **488** in 45% yield and 6:1 d.r.



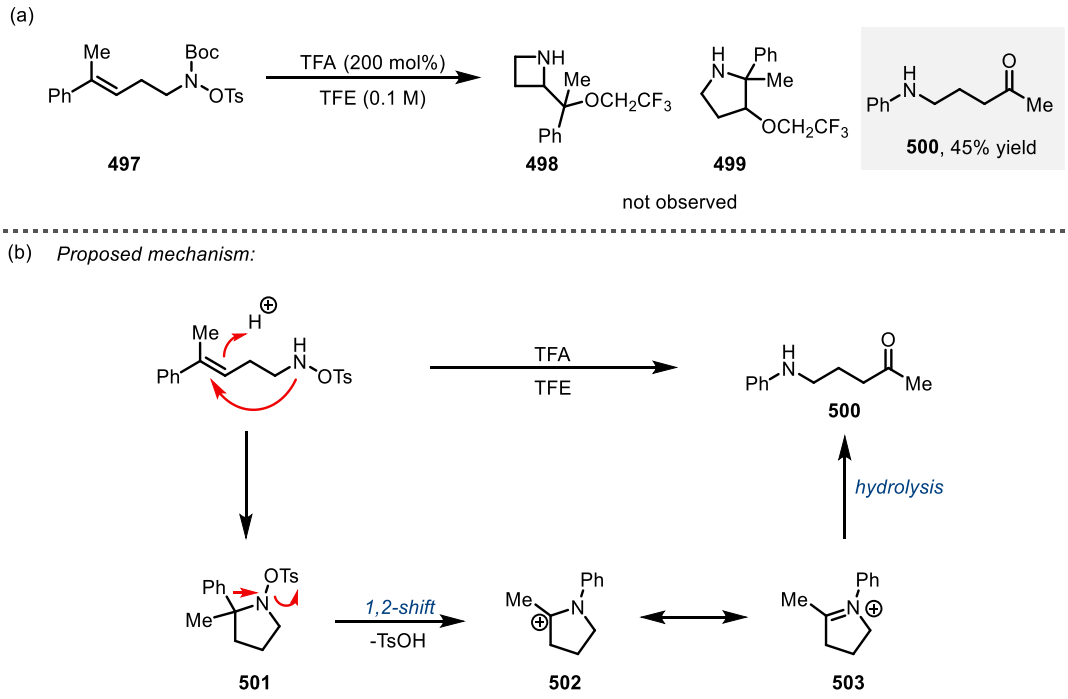
Scheme 168 *Aziridination of substrates **483** and **485**.*

It was envisaged that cyclisation of **490** would generate an 1-azabicyclo[2.1.0]pentane intermediate **491** that could undergo either ring-opening to generate an azetidine **492**, or ring expansion to form pyrrolidine **493** (Scheme 169a). Substrate **497** was synthesised in three steps from cyclopropyl ketone **494** (Scheme 169b). Addition of PhMgBr generated alcohol **495** which then under acidic conditions underwent ring opening of the cyclopropane to afford homoallylic alcohol **496**. Alcohol **496** was then converted to substrate **497** by Mitsunobu reaction.



Scheme 169 *(a) Potential ring-opening of azetidine intermediate **491**. (b) Synthesis of substrate **497**.*

When substrate **497** was subjected to the aziridination reaction conditions neither azetidine **498** or pyrrolidine **499** were formed and the only observed product was amino-ketone **500** which was isolated in 45% yield (Scheme 170a). A proposed mechanism for the formation of **500** is given in Scheme 170b. Substrate **497** undergoes acid-promoted cyclisation to generate pyrrolidine intermediate **501**. From intermediate **501**, 1,2-shift of the phenyl group can occur with loss of TsOH to generate aniline **502**. Hydrolysis of the iminium ion **503** then occurs to generate amino-ketone **500**.



Scheme 170 *(a) Observation of an amino ketone side-product **500** in the cyclisation of **497**. (b) Proposed mechanism for formation of **500**.*

In summary, preliminary results have been carried out into the use of azabicyclobutanes as reactive intermediates for the generation of nitrogen heterocycles. Thus far the use of TFE as a nucleophilic solvent has enable the synthesis of highly substituted aziridine products. Although mechanistic studies have not been performed, preliminary experimental results suggest that a benzylic cation is formed either directly from the substrate or *via* formation of an azabicyclobutane intermediate. The benzylic cation is then capture by a molecule of TFE by an S_N1 pathway to provide the 1,2-aminoether products. Further studies, including reaction optimisation and scope study will likely be carried out by other members of the group.

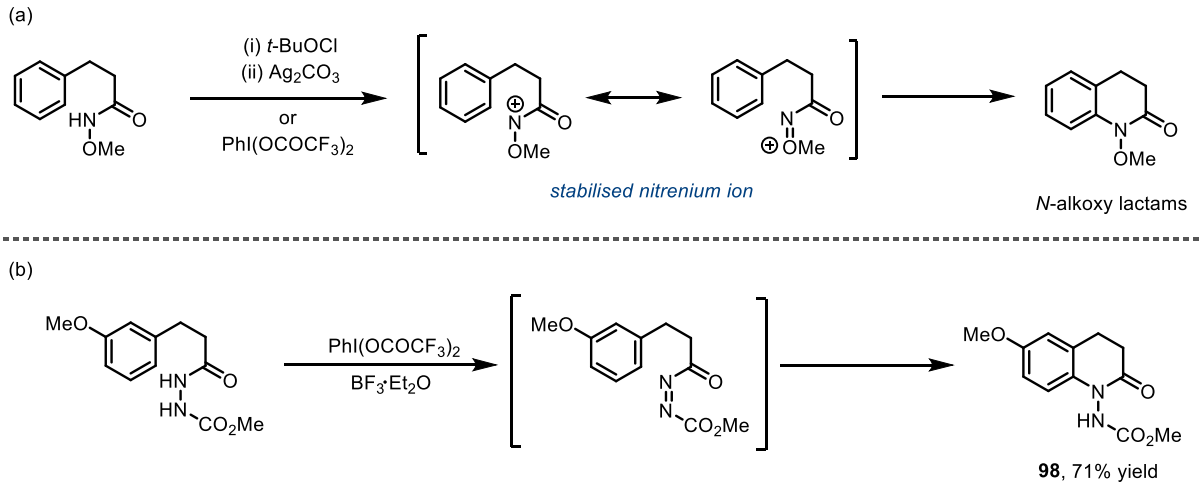
Chapter 4 - Other classes of electrophilic nitrogen-promoted aminations

4.1 Studies towards an intramolecular aryl C-H amination

4.1.1 Introduction

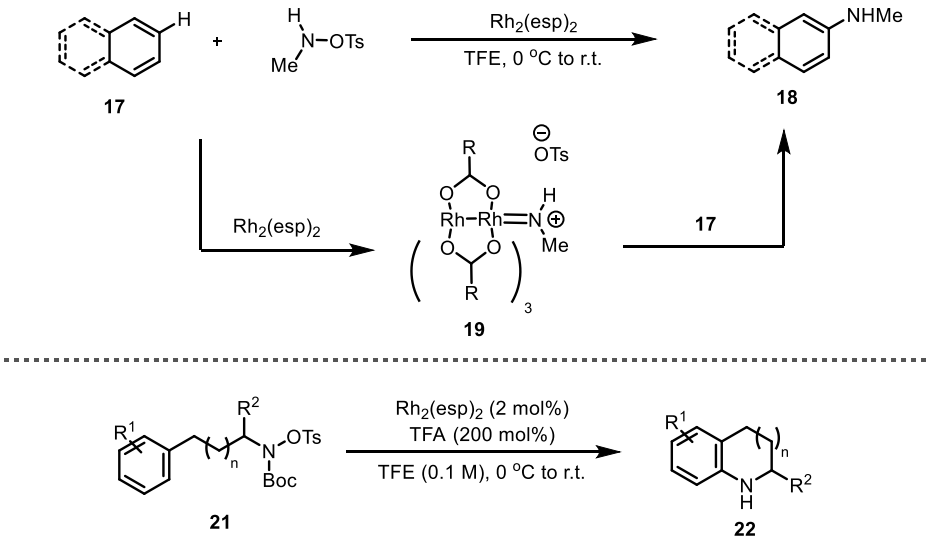
In this chapter the results of an investigation into two additional classes of amination reaction involving the use of hydroxylamine-derived electrophilic nitrogen sources are presented. The first is an intramolecular aryl C-H amination reaction to afford benzannulated products, whilst the second transformation involves the conversion of sulfoxides to sulfoximines. Before discussing the results in this section relating to the development of an intramolecular aryl C-H amination reaction of *N*-Boc hydroxylamines, a brief overview of the chemical literature relating to aryl aminations is given below.

As highlighted in Chapter 2 several groups have harnessed the reactivity of stabilised nitrenium ions for the synthesis of lactams by electrophilic aromatic substitution.[61-65,73] Typically, these highly reactive intermediates are accessed from *N*-alkoxyamides by either (a) conversion to an *N*-chloro-*N*-alkoxyamide followed by activation with silver salts or (b) by direct oxidation using a hypervalent iodine reagent. However, the effectiveness of these approaches is limited by the requirement for specific electron-donating *N*-protecting groups. A related synthesis of *N*-substituted amino dihydrocarbostyrils by Lewis acid-promoted cyclisation of azodicarbonyl compounds was reported by Prabhakar and co-workers.[74,75]



Scheme 171 *(a) Synthesis of benzo-fused lactams by nitrenium ion-promoted aryl amination.*[61-65,73] *(b) Electrophilic aryl amination using azodicarbonyls.*[74,75]

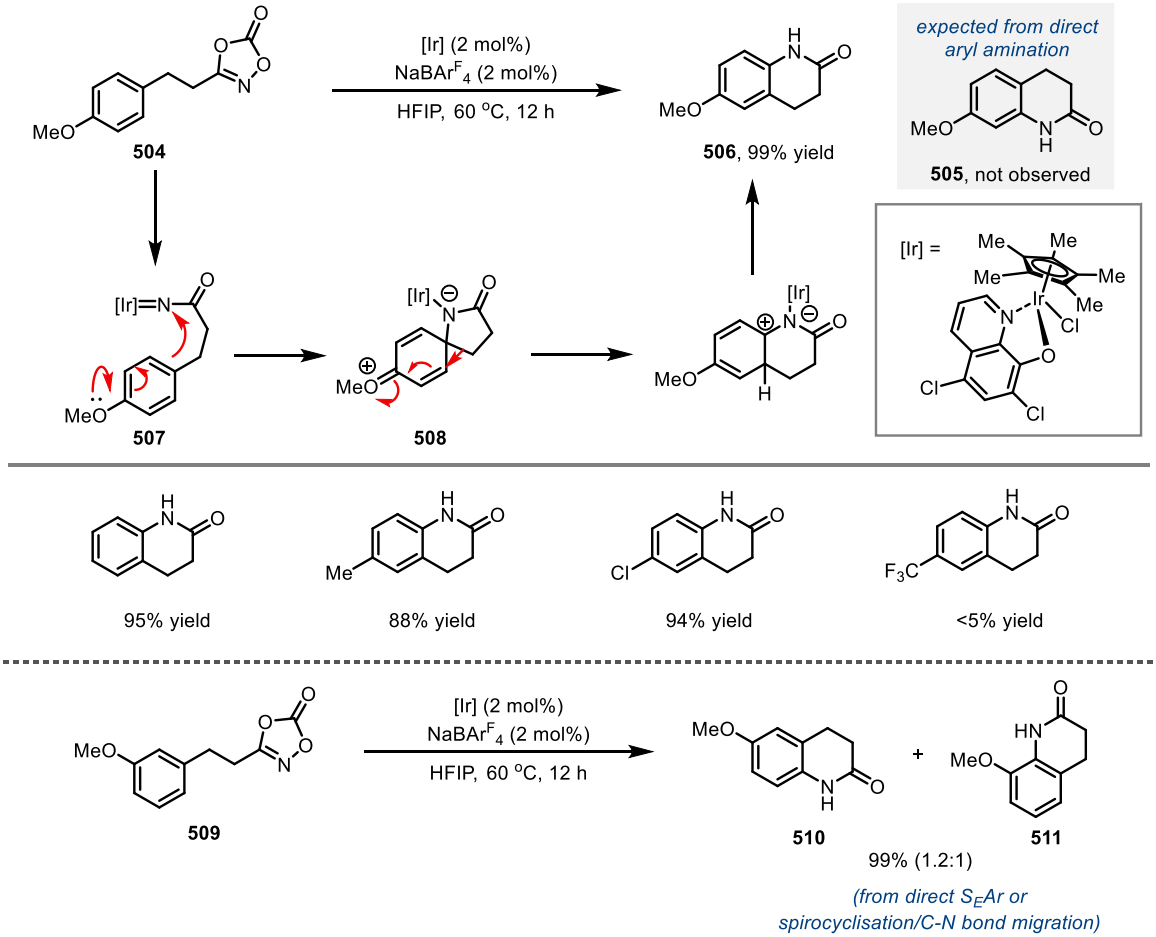
A more general approach for the synthesis of arylamines by direct aryl C-H amination was reported by Falck and co-workers.[33] The authors demonstrated that *N*-methyl-*O*-tosylhydroxylamine and other related *O*-substituted hydroxylamines in combination with $Rh_2(esp)_2$ can effect intermolecular aryl C-H amination of a variety of arenes to afford unprotected arylamine products (Scheme 172). Based on mechanistic studies the reaction is proposed to procced *via* an S_EAr mechanism from electrophilic intermediate **19**. This approach was also adapted to enable an intramolecular amination which allowed access to benzannulated products. In a later report the authors demonstrated that copper(II)-species also serve as effective catalysts for aryl amination using HOSA as the aminating agent.[34]



Scheme 172 *Rhodium-catalysed aryl C-H amination using hydroxylamine-derived reagents.*[33]

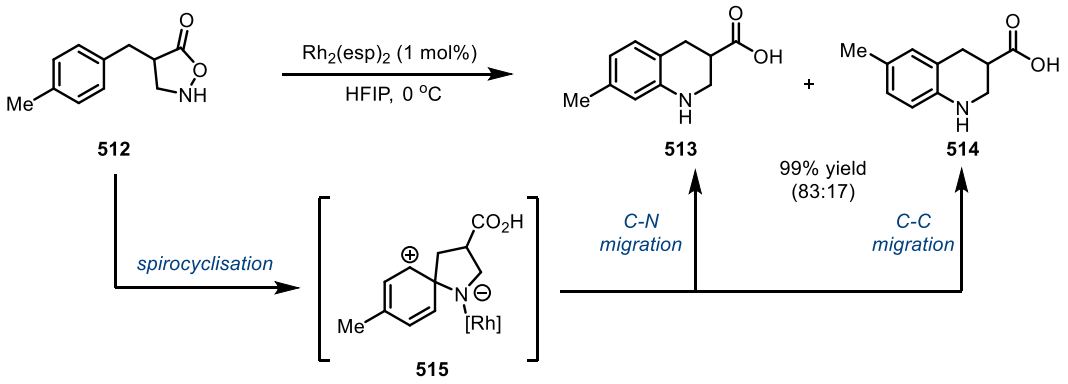
Whilst Falck and co-workers demonstrated aryl C-H aminations with compelling evidence for an S_EAr mechanism, Chang and co-workers recently reported a related iridium-catalysed synthesis of six-membered heterocycles by a mechanistically distinct pathway.[79] When attempting to carry out an aryl amidation of dioxazolone **504** the authors found that the expected δ-lactam product **505** was not formed. Instead the major product identified was the isomeric δ-lactam **506** in which a skeletal rearrangement had occurred. This suggested a different mode of reaction to the conventional S_EAr pathway was operative. To rationalise the observed regioselectivity the authors proposed a mechanism as shown in Scheme 173. Upon generation of iridium-nitrenoid intermediate **507**, spirocyclisation at the *ipso*-carbon generates spiro-amido intermediate **508**. To generate the observed lactam **506**, C-C bond migration of **508** followed by rearomatisation is proposed to occur. Evidence for the proposed mechanism was also provided by a series of DFT calculations. For other substrates such as **509**, cyclisation

occurred to provide lactam products **510** and **511** without skeletal rearrangement. In these cases, the authors were unable to distinguish whether a direct S_EAr or spirocyclisation/C-N bond migration is operative.



Scheme 173 *Iridium-catalysed arene amidation of dioxazolones.*[79]

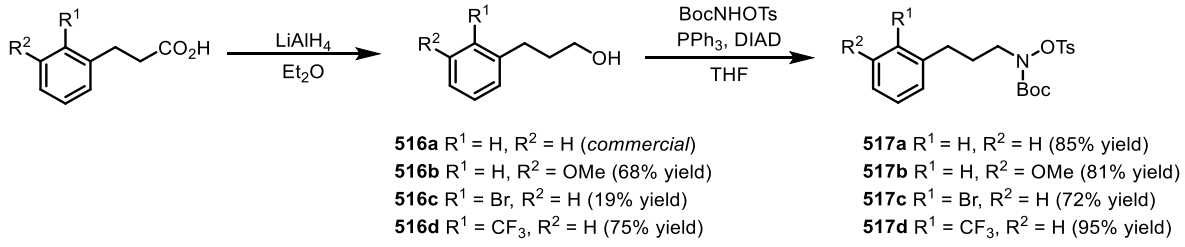
A related rhodium-catalysed electrophilic amination of isoxazolidin-5-ones **512** was reported by Shibasaki and co-workers; this enabled the synthesis of benzo-fused lactams **513** and **514**.[80] Following investigation of Hammett analysis and kinetic isotopes effects a mechanistic pathway involving spirocyclisation to **515** followed by skeletal rearrangement was proposed.



Scheme 174 *Rhodium-catalysed arene amination of isoxazolidin-5-ones.*[80]

4.1.2 Initial results

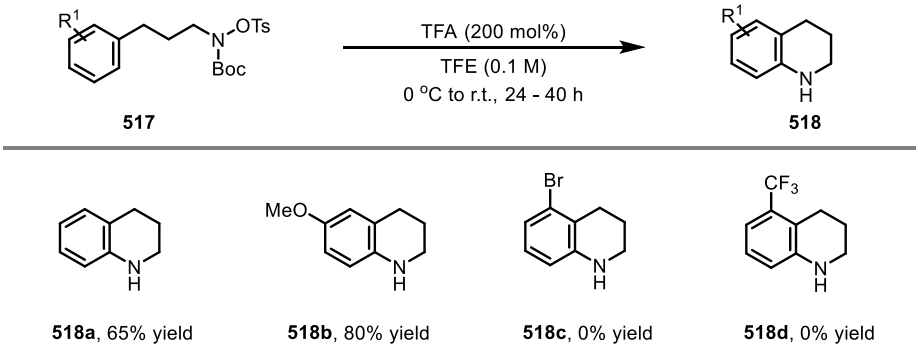
As described previously, during the development of an acid-promoted dearomative amination of phenolic tosyloxycarbamates, competing aryl C-H amination was observed for substrates containing additional activating substituents on the aromatic ring (section 2.3.5). In light of this, a scope study of aryl C-H amination reaction was undertaken. To this end, a range of phenyl tosyloxycarbamates **517a-d**, with varying electron properties of the aryl ring were synthesised (Scheme 175). The substrates were prepared by Mitsunobu reaction of the corresponding alcohols **516a-d** with the preactivated reagent BocNHOTs to generate **517a-d** in excellent yields.



Scheme 175 *Synthesis of substituted phenyl tosyloxycarbamates **517a-d**.*

With the substrates in hand, they were subjected to the reaction conditions [200 mol% TFA in 0.1 M TFE] and the results are presented in Scheme 176. For unsubstituted phenyl-system **517a** cyclisation under these conditions was relatively efficient and the tetrahydroquinoline product **518a** was formed in 65% yield. Improved reactivity was observed for the more electron-rich methoxy-phenyl-substituted **517b** which cyclised to **518b** in 80% yield. In contrast, the presence of moderately electron-withdrawing substituents on the aromatic ring resulted in a complete shutdown of the reaction, as exemplified by the Br-substituted system **517c** from which none of the desired product **518c** was isolated. The reaction also failed with substrate

517d containing a CF_3-substituted phenyl group. From these results, it is evident that the reaction is very dependent on the electronic properties of the arene and requires a sufficiently electron-rich arene for efficient cyclisation to occur. It should be noted that in Falck and co-workers report on rhodium-catalysed intramolecular amination the conditions are much less dependent on the electronic properties of the arene with high yields observed even with electron-poor substrates such as **517c** and **517d**.[33]

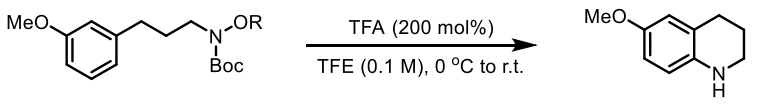


Scheme 176 *Intramolecular amination of substituted arenes.*

4.1.3 Further studies towards an intramolecular aryl C-H amination reaction

The following results in this section (3.1.2) were obtained by an MSci student Jacob Burley and hence are not detailed in the experimental section.

To further investigate a transition metal-free intramolecular aryl C-H amination reaction the nature of the hydroxylamine-derived activating group was examined. To this end, a series of hydroxylamine substrates **519a-c**, each containing a different activated hydroxylamine group were synthesised and subjected to the standard reaction conditions (Table 12). An excellent yield was obtained using the OMs substrate **519a** which cyclised to **518b** with a comparable level of efficiency to the OTs substrate **517b**. Significantly lower yields were observed with OBz and O^FBz substrates **519b** and **519c** which were converted to **518b** in 52% and 42% yields respectively. As none of these leaving groups had performed significantly more effectively than substrate **517b**, the OTs group was chosen for further evaluation of the reaction scope.

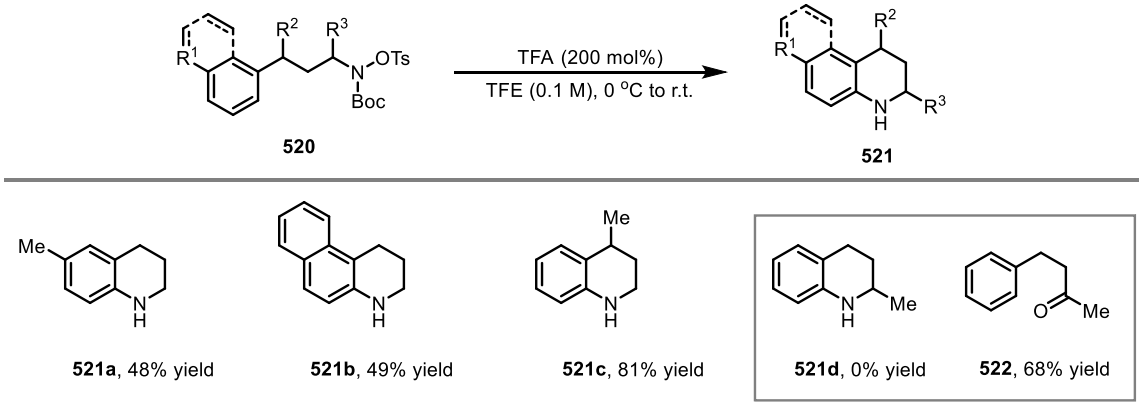


519 518b

R =	*yield*
Ms	84%
Bz	52%
^{F}Bz	42%

Table 12 *Effect of the leaving group on the intramolecular aryl C-H amination reaction.*

With an effective leaving group in hand, a further evaluation of the scope with regard to substitution on the aryl ring and carbon tether was performed. As mention previously electron-poor arenes were ineffective as substrates in the reaction and therefore electron-poor arenes were generally avoided. Following Mitsunobu reactions with the corresponding alcohols, substrates **520a-d** were obtained in high yield and examined in the aryl amination reaction (Scheme 177). Cyclisation of **520a**, containing a methyl group in the *meta*-position, cyclised effectively to **521a** although only a moderate yield of 48% was obtained. A similar level of efficiency was observed for naphthyl substrate **520b** which cyclised to tetrahydroquinoline **521b** in 49% yield. The reaction tolerates substitution at the γ-position of the carbon tether, as exemplified by substrate **520c** which cyclised to **521c** in 81% yield. On the other hand, substitution at the α-position was not tolerated. Attempted cyclisation of **520d** containing a methyl group α to nitrogen was unsuccessful and the only isolated product was ketone **522** which formed in 68% yield (Scheme 177).

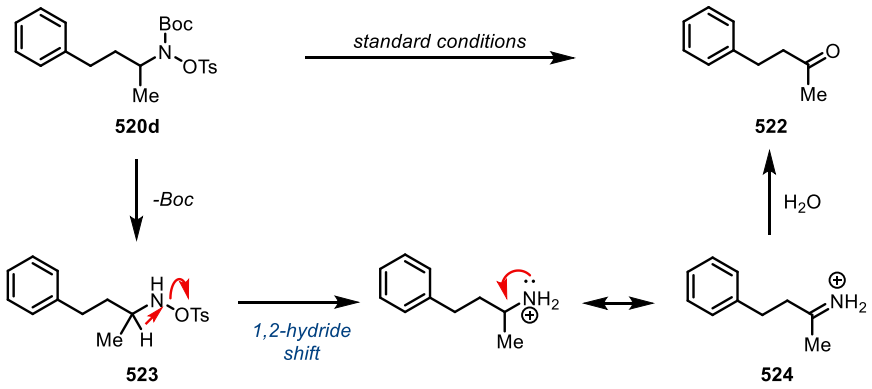


520 521

521a, 48% yield **521b**, 49% yield **521c**, 81% yield **521d**, 0% yield **522**, 68% yield

Scheme 177 *Further evaluation of the scope of aryl C-H amination: substitution on the arene and carbon tether.*

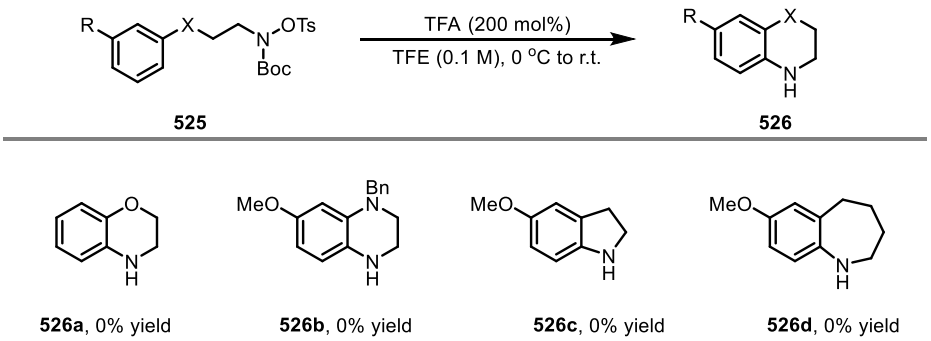
Ketone **522** likely forms by Boc deprotection of **520d** to generate intermediate **523** which undergoes 1,2-migration with expulsion of TsOH (Scheme 178). The resulting iminium ion **524** is then hydrolysed, possibly upon work up to form the corresponding ketone product. In the presence of a rhodium catalyst substrate **520d** undergoes efficient cyclisation to form tetrahydroquinoline **521d**;[33] however, in its absence it is likely that the rate of cyclisation is slower than this side reaction and so formation of ketone **522** is favoured. [LII]



Scheme 178 *Proposed mechanism for formation of ketone **522**.*

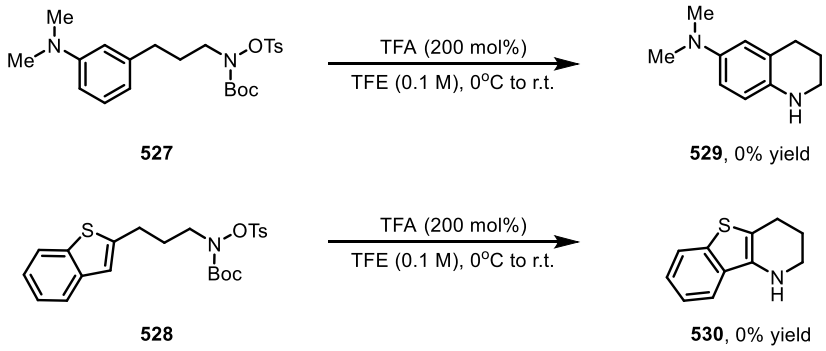
To extend the scope further, the use of heteroatoms in the tether was investigated. Substrate **525a** containing an ether group and substrate **525b** containing an amine group in the tether were synthesised and subjected to the standard reaction conditions (Scheme 179). Unfortunately, both **525a** and **525b** failed to undergo the desired cyclisation. The generation of other ring sizes was next examined. 5- and 7-ring substrates **525c** and **525d** were synthesised and subjected to the aryl C-H amination reaction; however, both substrates proved ineffective. The failure of substrate **525d** to undergo cyclisation is perhaps not surprising due to the slower rate at which 7-*exo* cyclisations occur versus 6-*exo* cyclisations; however, the failure of substrate **525c** is surprising. The formation of 5-membered rings is usually very facile compared to 6-ring cyclisations.

[LII] The increased sterics around the nitrogen likely slows down the rate of cyclisation.



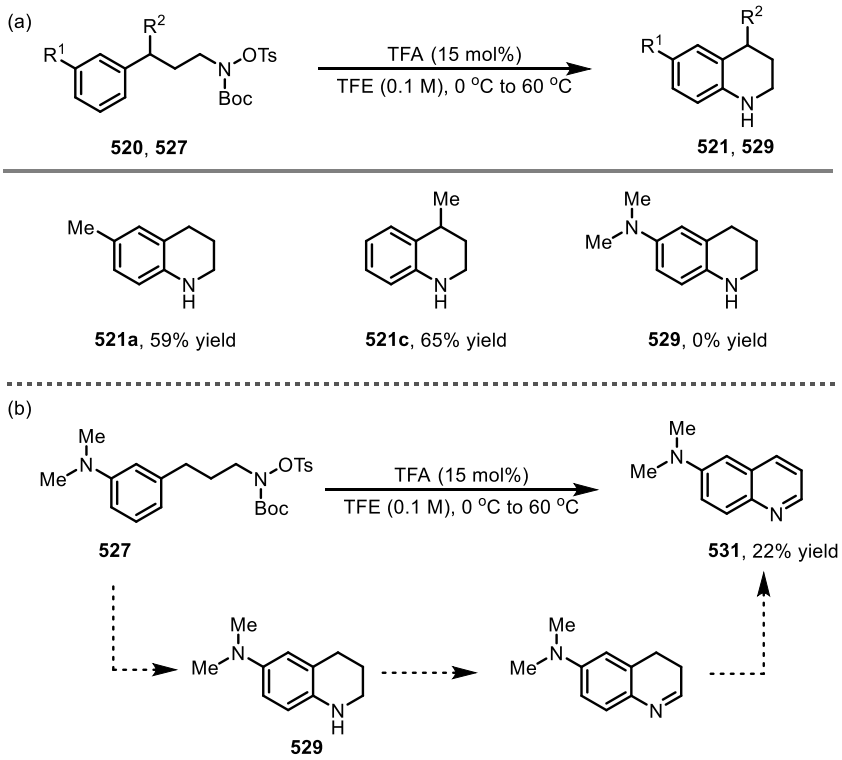
Scheme 179 *Attempted aryl C-H amination of substrates **525a-d**.*

Two additional substrates, aniline-derived **527** and benzothiophene-derived **528** were also examined in the aryl C-H amination reaction; however, both **527** and **528** failed to generate the desired cyclised products **529** and **530** (Scheme 180). In the case of the aniline substrate **527** this is most likely due to protonation of the aniline nitrogen under the acidic conditions converting the amine from an electron donating to an electron withdrawing group and, hence impeding reactivity.



Scheme 180 *Attempted aryl C-H aminations of substrates **527** and **528**.*

When the aryl C-H amination reaction was performed using lower loading of TFA (15 mol%) successful cyclisation was observed with substrates **520a** and **520c**; in the case of the former improved efficiency was observed versus the reaction under the standard conditions (Scheme 181a). Dimethyl aniline substrate **527** was also examined using these modified conditions; however, the desired tetrahydroquinoline product **529** was not obtained (Scheme 181b). Instead the fully unsaturated quinoline product **531** was isolated in 22% yield. The mechanism for the formation of **531** is unclear; however, it is likely that upon formation of tetrahydroquinoline **529** the N-O bond of a second equivalent of substrate acts as an external oxidant to oxidise **529** at least as far as the dihydroquinoline which may then be further oxidised to quinoline **531** by exposure to air.[229]



Scheme 181 *(a) Aryl C-H amination of substrates **520**, **527** under modified conditions. (b) Observation of quinoline side-product **531** in the cyclisation of substrate **527**.*

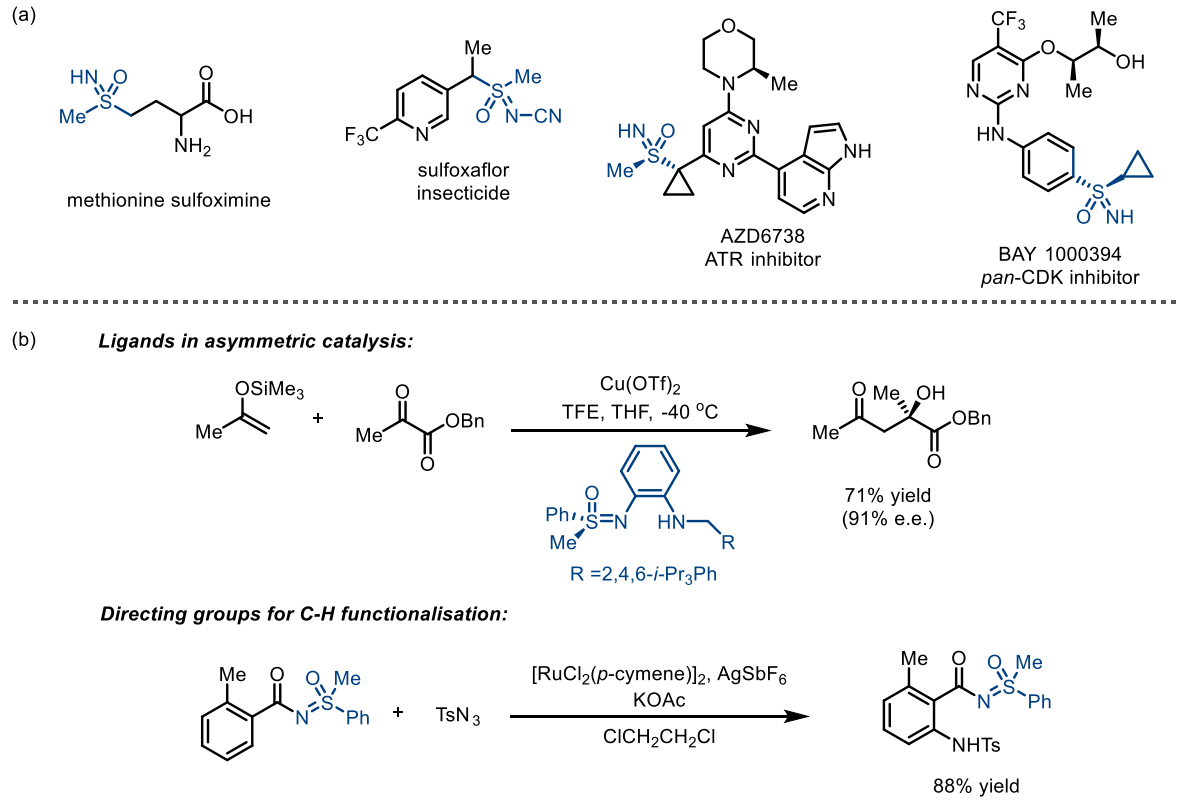
4.2 Studies towards a sulfoxide imination reaction for the synthesis of sulfoximines

The results of brief studies towards an intermolecular imination of sulfoxides to generate sulfoximines are described below. As with the previously described amination reactions the approach relies upon the generation of an electrophilic amino-reagent through the *in situ* activation of *N*-Boc-hydroxylamine reagents.

4.2.1 Introduction

In recent years sulfoximines have emerged as a valuable class of compounds, particularly in the area of medicinal chemistry, due to their versatile chemical properties and interesting bioactivities.[230,231] The sulfoximine group has a number of desirable physiochemical properties including high metabolic stability, such as stability to hydrolysis, and has both hydrogen bond acceptor and donor capabilities. Following the discovery of the first sulfoximine, methionine sulfoximine,[232] a number of bioactive sulfoximine-containing compounds have been reported. These include sulfoxaflor,[233] a commercially available insecticide and BAY1000394, a cyclin-dependent kinase inhibitor developed by Bayer, which is currently undergoing clinical trials (Scheme 182a).[234] As well as their use in medicinal chemistry sulfoximines have also

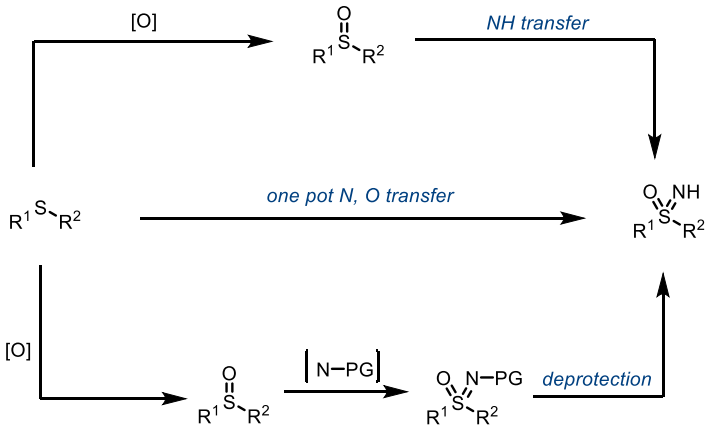
found application as chiral auxiliaries,[235-238] as ligands for asymmetric catalysis[239-242] and as directing groups for C-H functionalisation (Scheme 182b).[243-246] As such, the development of novel synthetic routes to access sulfoximines is a valuable area of research.[247] Access to unprotected sulfoximines containing a 'free' NH-group is particularly desirable as this offers potential to introduce further diversity. The functionalisation of NH-sulfoximines by arylation,[248] alkylation,[249] cyanation[250] and thioetherification[251] reactions have all been reported.



Scheme 182 *(a) Biological relevant sulfoximines.[232-234] (b) Applications of sulfoximines.[240,243]*

Over the last few decades many methodologies for the synthesis of NH-sulfoximines have been reported. Most approaches involve the transfer of nitrogen to sulfoxides, which are in turn accessed by oxidation of the corresponding sulfide (Scheme 183). In most cases a protected *N*-group is introduced and therefore an additional deprotection step is required to access the NH-sulfoximine.[LIII]

[LIII] An alternative approach to the synthesis of sulfoximines involves initial nitrogen transfer to a sulfilimine followed by an oxidation step.[252]



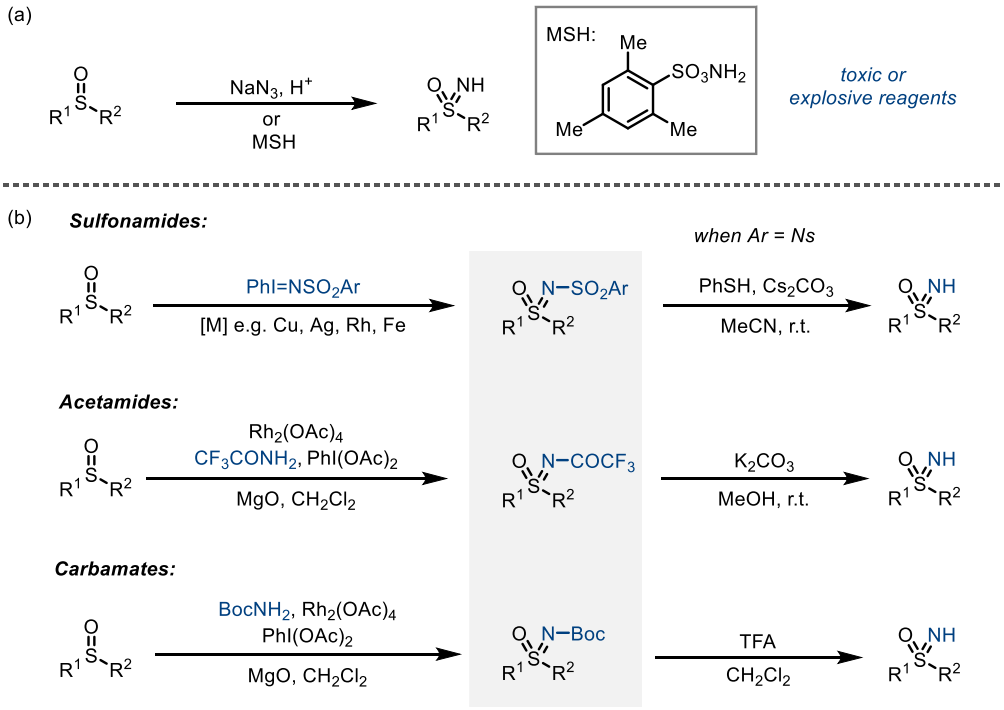
Scheme 183 *Strategies for synthesising sulfoximines from sulfides.*

Early methods for the preparation of NH-sulfoximines involved the metal-free imination of sulfoxides; however, these methods require harsh reaction conditions and toxic or explosive reagents such as a combination of NaN_3 and sulfuric acid.[253-256] Other early methods employed *O*-mesitylene sulfonylhydroxylamine (MSH) as the aminating agent[257-260] (Scheme 184a); however, the synthetic utility of this approach is limited by the use of MSH[261] which is unstable and has to be prepared directly before use.

In 1998 Müller and co-workers[262] reported a copper-catalysed imination of sulfoxides with PhI=NTs as the nitrogen source. Since then a number of transition metal-catalysed approaches for the synthesis of sulfonamide protected sulfoximines have been reported (Scheme 184b).[263,264] In particular, it is worth highlighting the work of Tye and co-workers who reported the transfer of nosyl-protected amines to sulfoxides to generate sulfoximines, which were then cleaved to the free N-H under mild conditions.[265] Other transition metal-catalysed approaches to the synthesis of sulfoximines involved the generation of the active nitrogen source by *in situ* oxidation of an appropriate amine derivative. For example, Bolm and co-workers reported a rhodium-catalysed synthesis of sulfoximines using iminoiodinanes generated from the oxidation of amides in the presence of $PhI(OAc)_2$; this approach enables the transfer of easily cleaved *N*-acyl groups to sulfoxides.[266,LIV] A related rhodium-catalysed approach to sulfoximines was reported by Bull and co-workers and enabled the generation of carbamate-protected sulfoximines, which were deprotected to the free N-H sulfoximine under acidic conditions. (Scheme 184b).[269,LV]

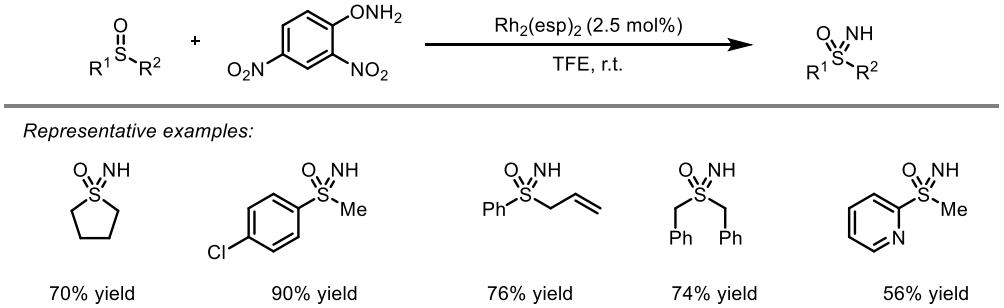
[LIV] Fe[267] and Ag[268] catalysed methodologies have also been reported.

[LV] Boc-protected sulfoximines have also been prepared from Boc-azides in the presence of an iron(II)-catalyst.[270,271]



Scheme 184 *(a) Traditional "meta-free" approaches to accessing NH-sulfoximines.*[253-260] *(b) Transition metal-catalysed synthesis and subsequent cleavage of N-protected sulfoximines.*[262-269]

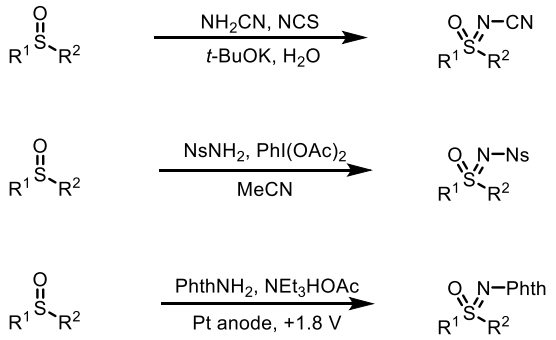
Whilst these transformations are very effective at generating protected sulfoximines, to access the NH-sulfoximine an additional deprotection step is required. A transition metal-catalysed method for the direct synthesis of NH-sulfoximines was reported by Richards and Ge using DPH as the nitrogen source and $Rh_2(esp)_2$ as the catalyst (Scheme 185).[272] This approach is compatible with sulfoxides containing alkyl, aryl, allyl and heterocyclic groups and in general the sulfoximines were obtained in good to excellent yields.



Scheme 185 *Rhodium-catalysed synthesis of NH-sulfoximines.*[272]

As the use of transition metal catalysts such as rhodium can be expensive on large scale and presents toxicological issues when used in the late-stage preparation of pharmaceuticals, a number of metal-free approaches to sulfoximines have been developed. Several groups have reported metal-free syntheses of protected sulfoximines by the metal-free transfer of amines to

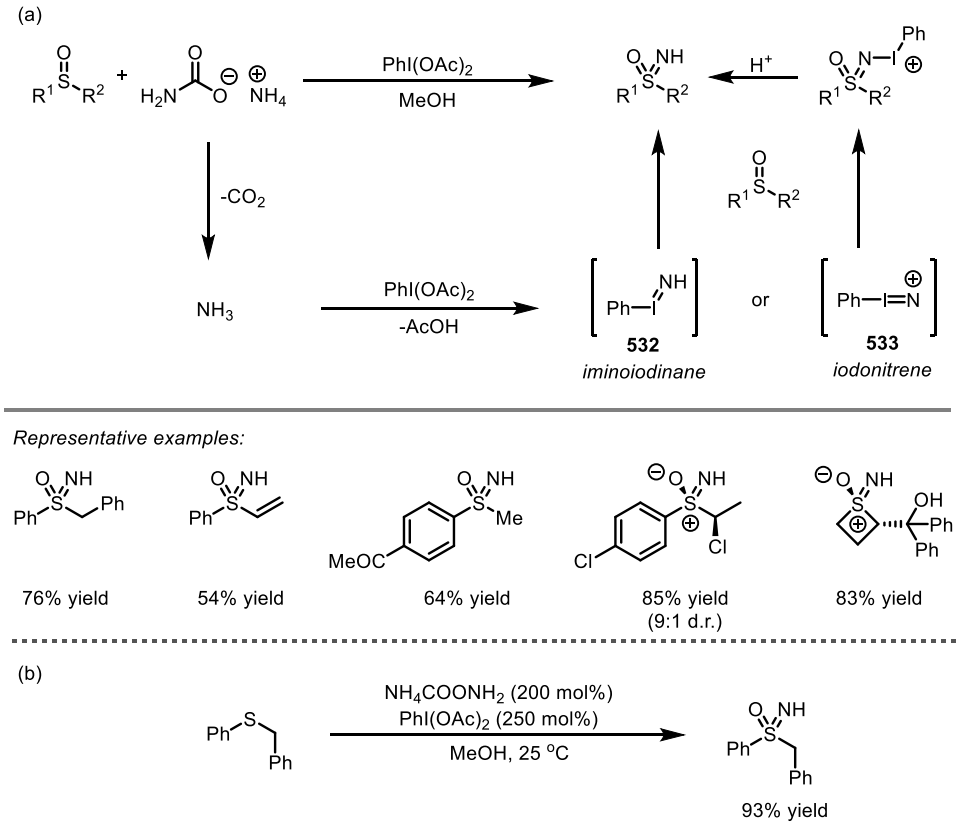
sulfoxides in the presence of an oxidant such as $PhI(OAc)_2$ or NCS (Scheme 186).[194,273,274] A very mild approach to the synthesis of sulfoximines was reported by Yudin and co-workers who developed an electrochemical approach to sulfoximines using Phth-NH_2 as the iminating agent; this method avoids the use of transition metals and stoichiometric oxidants.[275]



Scheme 186 *Selected examples of metal-free imination of sulfoxides.*[273-275]

As with most transition-metal catalysed approaches, the majority of metal-free methods for the synthesis of sulfoximines generate protected sulfoximines. To address this issue Bull and co-workers reported a metal-free approach to N-H sulfoximines using ammonium carbonate as the nitrogen source in combination with $PhI(OAc)_2$ (Scheme 187a).[276] Based on mechanistic studies the authors proposed that the ammonium carbonate provides a source of ammonia which reacts with $PhI(OAc)_2$ to form iminoiodinane **532** or iodonitrene **533**, either of which may act as the reactive nitrogen electrophile. The reaction showed excellent compatibility with a variety of functional groups including alkenes, alkynes, alkyl amines, phenols, esters, aldehydes and nitriles. Extension of the methodology to the direct synthesis of sulfoximines from the corresponding sulfides was also possible, providing an efficient route to sulfoximines under very mild reaction conditions (Scheme 187b).[277,LVI]

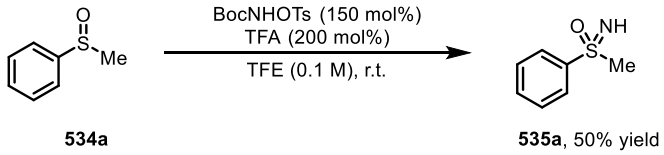
[LVI] A flow process based on this approach was recently developed by Luisi.[278]



Scheme 187 *(a) A metal-free synthesis of N-H sulfoximines by sulfoxide imination.*[276] *(b) A direct synthesis of NH-sulfoximines from sulfides.*[277]

4.2.2 Initial results and optimisation

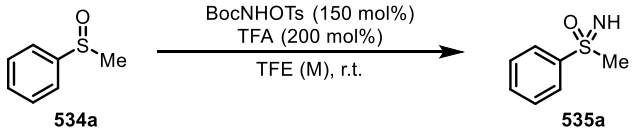
With the view to investigating a metal and oxidant-free synthesis of sulfoximines the feasibility of using the preactivated hydroxylamine reagent BocNHOTs for the amination of sulfoxides was examined. Methyl phenyl sulfoxide **534a** was chosen as substrate for initial investigation. When subjected to the reaction conditions [BocNHOTs (150 mol%), TFA (200 mol%) in TFE (0.1 M)] **534a** was converted to sulfoximine **535a** in 50% yield (Scheme 188).



Scheme 188 *Initial attempted imination of sulfoxide **534**.*

To improve the efficiency of this reaction a series of optimisations were carried out beginning with studying the effect of concentration. Lowering the concentration to 0.05 M had no effect on the yield of sulfoximine **535a** (Table 13, entry 1); however, when the yield was increased to 0.2 M a slight improvement to 57% yield was observed (Table 13, entry 2). The yield

continued to increase as the concentration was increased until an optimal yield was obtained at a concentration of 1.0 M. (Table 13, entry 5). At higher concentrations the poor solubility of BocNHOTs in TFE was an issue.

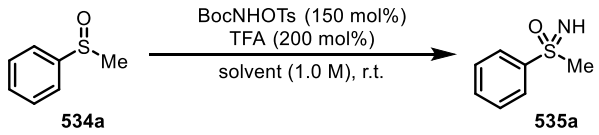


534a 535a

Entry	*TFE (M)*	*yield*
1	0.05 M	50%
2	0.2 M	57%
3	0.3 M	59%
4	0.5 M	64%
5	1.0 M	73%

Table 13 *The effect of concentration on the imination of sulfoxide **534a**.*

A solvent screen was performed, and the results are summarised in Table 14. As observed for the dearomative amination reaction, effective imination was observed in CH_2Cl_2 and PhMe (Table 13, entries 1 and 2). In this case, however, reaction in these solvents performed with similar levels of efficiency versus the reaction in TFE. A moderate yield of 51% was also achieved in MeCN (Table 14, entry 3). However, polar protic solvents such as MeOH, *i*-PrOH and EtOH did not lead to successful imination (Table 14, entries 4-5). Other common solvents such as Et_2O, THF, acetone and EtOAc were also ineffective for this reaction (Table 14, entries 7-10).

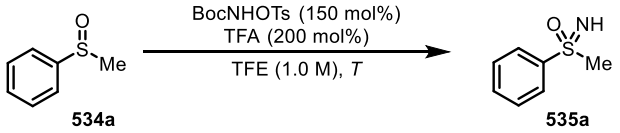


534a 535a

Entry	*solvent*	*yield*
1	CH_2Cl_2	69%
2	PhMe	73%
3	MeCN	51%
4	MeOH	0%
5	*i*PrOH	0%
6	EtOH	0%
7	Et_2O	0%
8	THF	0%
9	acetone	0%
10	EtOAc	0%

Table 14 *Solvent screen for the imination of sulfoxides **534a**.*

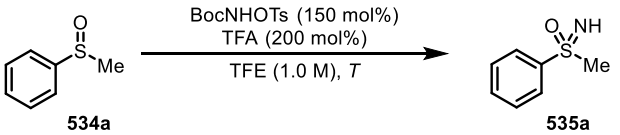
Finally, the effect of temperature was evaluated. At a higher temperature of 40 °C a reduction in yield to 62% was observed (Table 15, entry 2). At 60 °C a further decrease in yield to 48% occurred. (Table 15, entry 3).



Entry	*T*	*yield*
1	r.t.	73%
2	40 °C	62%
3	60 °C	48%

Table 15 *The effect of temperature on the imination of sulfoxide **534a** in TFE.*

As the reaction occurs with a similar level of efficiency in PhMe as in TFE, and due to the lower cost of PhMe, further optimisation was also performed in PhMe. In this solvent increasing the temperature to 40 °C also led to a reduction in yield to 55% (Table 16, entry 3). However, a slight increase in yield to 75% was obtained by performing the reaction at 30 °C (Table 16, entry 2).[LVII]



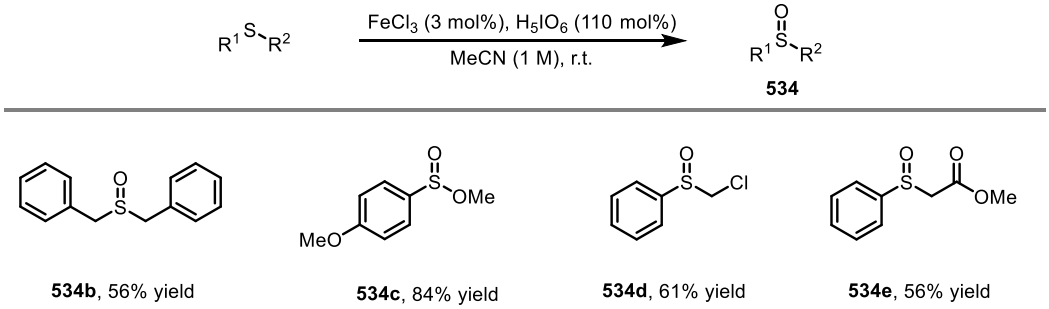
Entry	*T*	*yield*
1	r.t.	73%
2	30 °C	75%
3	40 °C	55%

Table 16 *The effect of temperature on the imination of sulfoxide **534a** in PhMe.*

4.2.2.2 Substrate scope

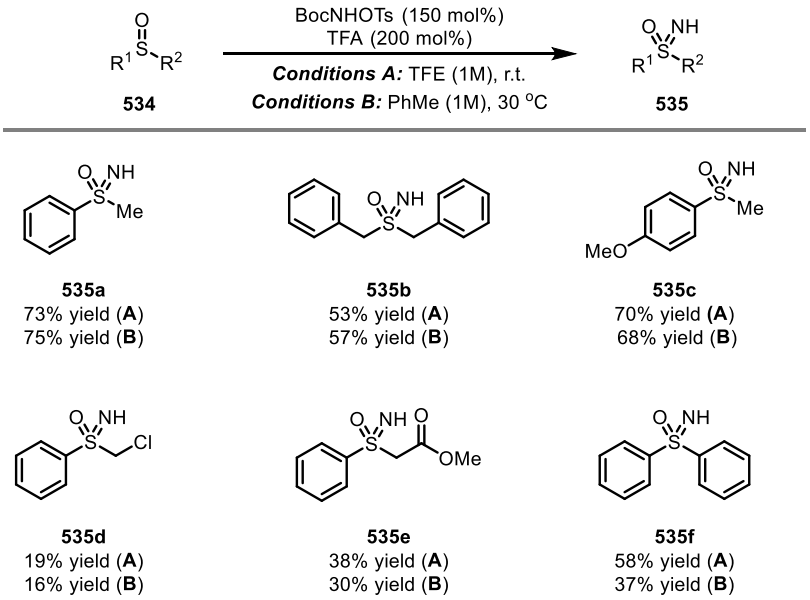
With two optimised conditions in hand, the scope of the reaction was investigated. Sulfoxides **534b-e** were synthesised from the corresponding sulfides using $FeCl_3/H_5IO_6$ (Scheme 189).[279] The required sulfoxides **534b-e** were obtained in good to excellent yields.

[LVII] Increasing the loading of BocNHOTs and TFA had a detrimental effect on the yield as did increasing or decreasing the reaction time.



Scheme 189 *Synthesis of sulfoxides **534b-e**.*

A range of sulfoxides were subjected to the optimised reaction conditions and the results are summarised in Scheme 190. Moderate yields were obtained for diphenyl and dibenzyl substituted sulfoxides **534f** and **534b** which in TFE afforded the sulfoximine products **535f** and **535b** in 58% and 53% respectively. The reaction was more efficient with *para*-methoxyphenyl-substituted **534c** which was converted to sulfoximine **535c** in 70% yield. In contrast, sulfoxides **534d** and **534e** both performed poorly in the reaction. The low yields are likely due to a reduction in nucleophilicity of the sulfoxide due to the presence of the electron-withdrawing chloro- and ester groups. The reactions were also performed using the conditions optimised for reaction in PhMe. In general, with the exception of sulfoxide **534f**, comparable yields were obtained versus reaction in TFE.



Scheme 190 *Amination of sulfoxides **534a-f**.*

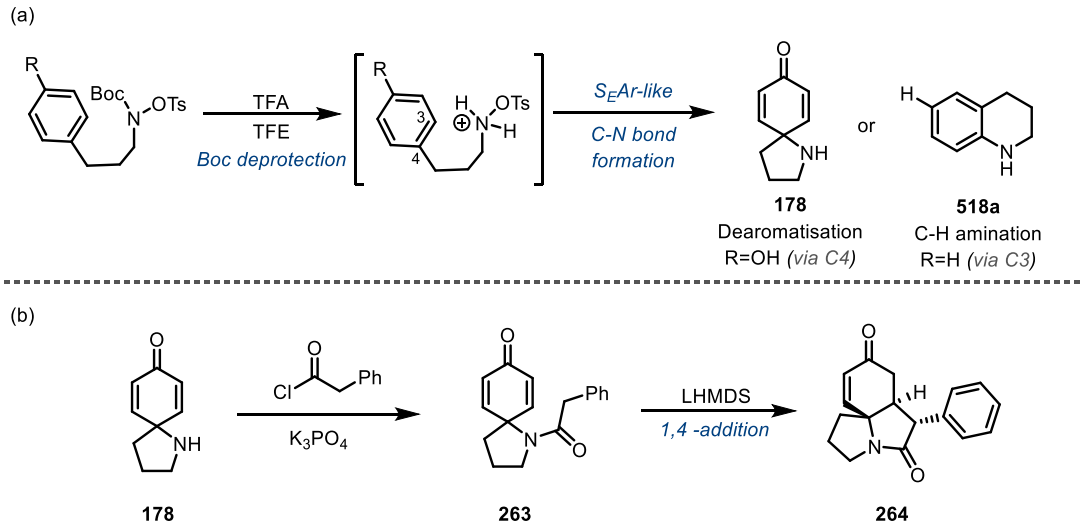
4.3 Conclusions

The application of metal-free amination reactions using activated *N*-Boc hydroxylamines has been applied to aryl C-H aminations. Electron-rich arenes undergo efficient cyclisation to afford unprotected tetrahydroquinolines. Unfortunately, the scope of this methodology is limited as many arenes failed to undergo efficient amination. In particular, electron-deficient arenes are incompatible with this reaction.

N-Boc hydroxylamines have also been applied to the synthesis of sulfoximines by sulfoxide imination. Unlike many of the approaches in the literature to sulfoximines this methodology allows efficient access to unprotected NH-sulfoximines allowing for further functionalisation. Although this approach benefits from the lack of a requirement for a transition metal catalyst or the need for an external oxidant, the poor reactivity of electron-deficient sulfoxides is a limitation of this approach.

Chapter 5 - Overall summary and conclusions

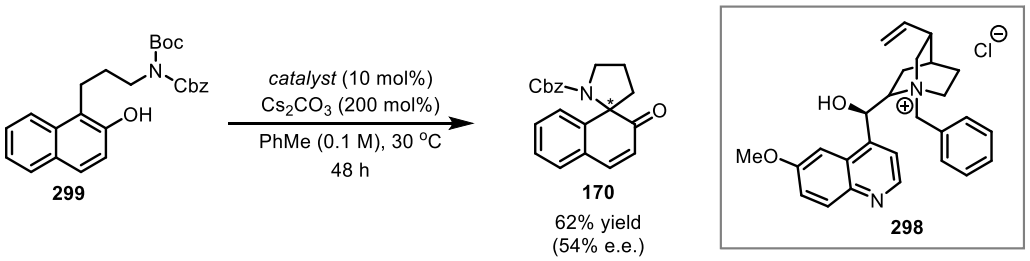
In summary, the main focus of this thesis is the development of C-N bond forming reactions of electrophilic *N*-tosyloxycarbamates and related N-O donors. In Chapter 2 the development of a dearomatising amination reaction that affords unprotected nitrogen-containing spirocyclic ring systems was described (Scheme 191a). This approach builds upon the work of Falck and co-workers who developed intramolecular aryl C-H amination processes triggered by rhodium-nitrenoids, that are generated from activated hydroxylamines.[33] These activated species are themselves accessed by *in situ* deprotection of *N*-Boc precursors which are easily prepared by Mitsunobu reaction. For the dearomative cyclisation of phenols and naphthols hydroxylammonium intermediates of this kind are sufficiently reactive for C-N bond formation to occur effectively in the absence of a transition metal catalyst. Upon treatment with trifluoroacetic acid in 2,2,2-trifluoroethanol, a potent electrophilic aminating agent is formed that reacts with pendant arenes in a S_EAr-like process to generate the dearomatised product.



Scheme 191 *(a) C-N bond forming dearomatising amination and aryl C-H amination. (b) Annulative derivatisations of the dearomatised products.*

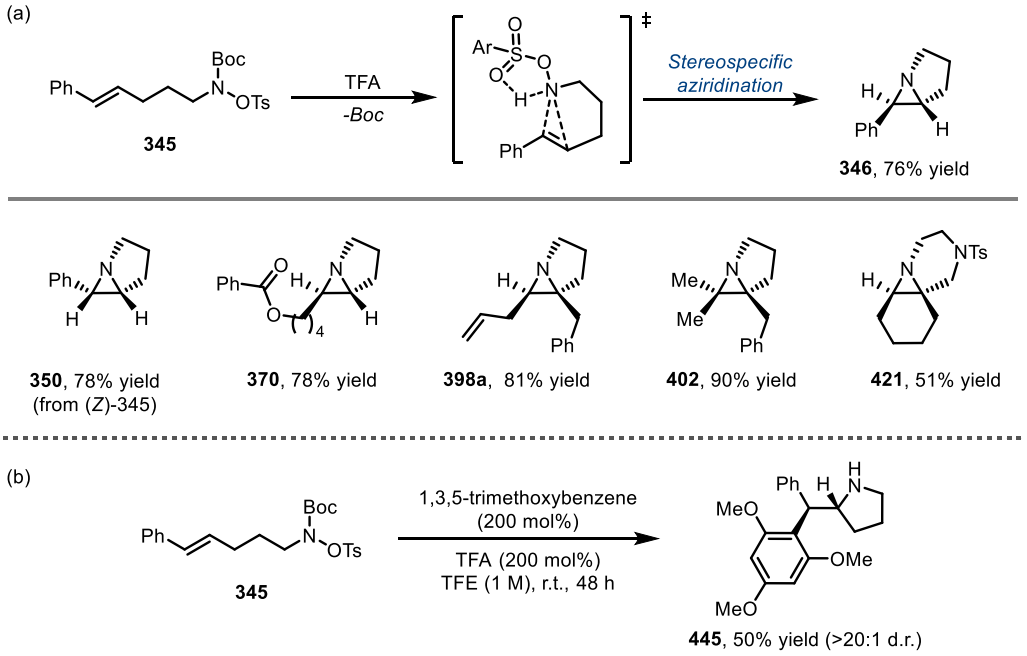
In addition to dearomatisations, this method can promote aryl C-H aminations of sufficiently electron-rich arenes, under the same metal-free conditions, to access tetrahydroquinoline structures (section 4.1). As these processes allow for the direct preparation of unprotected nitrogen ring systems, further manipulations can be achieved by direct reaction at nitrogen to access complex, natural product-like structures (Scheme 191b).

A related base-promoted dearomatising amination reaction of indoles, phenols and naphthols was developed in tandem by another member of the group, Xiaofeng Ma. This represents a complimentary approach to the formation of spirocyclic pyrrolidine products in which the *N*-protecting group is maintained in the product. Preliminary results suggest that the development of an enantioselective reaction based on this approach is feasible. In the presence of chiral phase transfer catalyst **298**, naphthol **299** cyclised to spirocycle **170** in 54% e.e. (Scheme 192).



Scheme 192 *Preliminary result in the development of an enantioselective dearomatising amination reaction.*

The application of *N*-Boc protected hydroxylamines in metal-free C-N bond forming reactions was further expanded to the synthesis of aziridines (section 3.2). Hydroxylamine-derived substrates containing a pendent alkene underwent stereospecific intramolecular aziridination to generate novel aza-bicyclic ring systems (Scheme 193a). Based on a combination of experimental observations and computational studies, aziridination is believed to occur by a concerted mechanism resembling an aza-variant of a Prilezhaev reaction. This protocol exhibits good substrate scope and is effective for the aziridination of di-, tri- and tetrasubstituted alkenes. The same alkenyl substrates can also undergo 1,2-alkene-difunctionalisations, when a suitable external nucleophile is present, to generate highly functionalised pyrrolidine and piperidine structures (Scheme 193b).



Scheme 193 *(a) Intramolecular aziridination reaction. (b) Alkene 1,2-difunctionalisations.*

Further work has shown that *N*-Boc hydroxylamine reagents also undergo metal-free imination of sulfoxides to generate NH-sulfoximines. There a very few methods in the literature for the direct synthesis of NH-sulfoximines from sulfoxides, with most methods generating a *N*-protected sulfoximine which must then be deprotected requiring an extra synthetic step. A range of NH-sulfoximines were generated using this approach in moderate to excellent yields.

Chapter 6 - Experimental

6.1 General Experimental Details

Starting materials were purchased from commercial sources (Acros, Aldrich, Alfa Aesar, Fluorochem and Strem) and used without further purification unless otherwise stated. Anhydrous 2,2,2-trifluoroethanol was obtained by drying over 4Å molecular sieves while other anhydrous solvents were obtained by distillation using standard procedures or by passage through drying columns supplied by Anhydrous Engineering Ltd. The removal of solvents *in vacuo* was achieved using both a Büchi rotary evaporator (bath temperatures up to 45 °C) at a pressure of either 15 mmHg (diaphragm pump) or 0.1 mmHg (oil pump), as appropriate, and a high vacuum line at room temperature. Reactions requiring anhydrous conditions were run under a dry atmosphere of nitrogen or argon; glassware was either flame dried immediately prior to use or placed in an oven (200 °C) for at least 2 hours and allowed to cool either in a desiccator or under an atmosphere of nitrogen or argon; liquid reagents, solutions or solvents were added via syringe through rubber septa. Flash column chromatography was performed using silica gel (Aldrich 40-63 μm, 230-400 mesh). Thin layer chromatography was performed using aluminium backed $60F_{254}$ silica plates. Visualisation was achieved by UV fluorescence or a basic $KMnO_4$ solution and heat. Proton nuclear magnetic resonance were recorded on a Varian or Jeol spectrometer at 400 MHz or 500 MHz while ^{13}C NMR spectra were recorded at 100 MHz. ^{19}F NMR spectra were recorded at 283 MHz. Chemical shifts (δ) are given in parts per million (ppm) and referenced to the appropriate residual solvent peak. Peaks are described as singlets (s), doublets (d), triplets (t), quartets (q), quintets (qn), sextet (sex), multiplets (m) and broad (br). Coupling constants (*J*) are quoted to the nearest 0.5 Hz. Assignments of ^{1}H NMR and ^{13}C NMR signals were made, where possible, using COSY, HSQC, HMBC and NOE experiments. Mixtures of isomers which could not be separated (e.g. diastereomers and/or rotamers) have been characterized together and are referred to as A and B. Numbering systems for NMR signal assignments are specified on the structure and are not related to those used for the compound names. In situ yields were determined by integration of the ^{1}H NMR of the crude material employing 1,3,5-trimethoxybenzene or 1,4-dinitrobenzene as internal standard. Mass spectra were obtained by the University of Bristol mass spectrometry service using a Bruker Daltonics FT-ICR-MS Apex 4e 7.0T FT-MS. Infrared spectra were recorded on a Perkin Elmer Spectrum Two FTIR spectrometer as either neat films or solids. Abbreviations used are: w (weak), m (medium), s (strong) and br (broad). Melting points were determined

using a Reichert melting point table and temperature controller and are uncorrected. Chiral SFC was performed on an Agilent 1260 Infinity SFC Control Module system equipped with a quaternary pump, diode array detector and column thermostat under the conditions specified. Enantiomeric excess was determined by integration of chromatogram peaks.

6.2 General procedures

General procedure A for TBS protection of phenol

To a solution of alcohol (1.0 equivalent) in DMF (*approx*. 2mL/mmol) at 0 °C was added imidazole (3.3 equivalents) and *tert*-butyldimethylsilyl chloride (2.2 equivalents). The reaction was stirred at room temperature and monitored by TLC. Upon completion, the reaction was quenched by addition of H_2O and the organic phase extracted with hexane, dried over Na_2SO_4 and concentrated *in vacuo*. To the crude reaction mixture was added MeOH (1 mL/mmol), THF (1 mL/mmol) and aqueous K_2CO_3 (2.0 equivalents) After stirring for 12 hours the reaction was quenched with 1 M HCl at 0 °C (until pH *approx*. 3). The mixture was extracted with Et_2O (3 × 20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude reaction mixture was purified by flash column chromatography.

General procedure B for reduction of carboxylic acid/ester to alcohol using $LiAlH_4$

To a solution of carboxylic acid/ester (1.0 equivalents) in anhydrous THF or Et_2O (*approx*. 5 mL/mmol) at 0 °C was added $LiAlH_4$ (*equivalents specified*) dropwise. The reaction was stirred at room temperature and monitored by TLC. Upon completion, the reaction mixture was cooled to 0 °C before addition of water (1 mL/g of $LiAlH_4$), 15% aqueous NaOH (1 mL/g $LiAlH_4$) and a final portion of water (3 mL/g of $LiAlH_4$). The mixture was filtered through Celite® and washed with CH_2Cl_2. The phases were separated, and the aqueous phase extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the crude product which was purified by flash column chromatography.

General procedure C for the preparation of *N*-acyloxysulfonamides by Mitsunobu alkylation employing DEAD or DIAD

To a solution of alcohol (1.0 equivalent), hydroxylamine-derived nucleophile (1.5 equivalents), and PPh_3 (2.0 equivalents) in anhydrous PhMe/THF (3:1, 8 mL/mmol) at 0 °C was added a solution of DEAD or DIAD (2.0 equivalents) in anhydrous PhMe (2 mL/mmol) dropwise. The reaction mixture was stirred at room temperature until completion by TLC analysis and the crude product was purified by flash column chromatography.

General procedure D for the removal of silyl protecting group with HCl

To a solution of silyl ether (1 equivalents) in MeOH (25 mL/mmol) and THF (25 mL/mmol) at 0 °C was added 1 M HCl (*amount specified*). The reaction was stirred at room temperature

overnight until completion by TLC analysis. The reaction mixture was diluted with EtOAc (20 mL) and washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*.

General procedure E for alkene hydrogenation with Pd/C

A solution of alkene (1.0 equivalent) in MeOH or EtOH or EtOAc (*approx*. 5 mL/mmol) was purged with argon before the addition of 10 wt. % Pd/C (5-10 mol%). The flask was fitted with a balloon of hydrogen and stirred at room temperature overnight and monitored by TLC. Upon completion, the reaction mixture was filtered over a bed of Celite® washing with the appropriate solvent and concentrated *in vacuo* to afford the product

General procedure F for reduction of carboxylic acids to alcohols *via* anhydride

To a solution of carboxylic acid (1.0 equivalent) and triethylamine (1.0 equivalent) in THF (10 mL/mmol) at -5 ^oC was added a solution of ethyl chloroformate (1.0 equivalent) in THF (1 mL/mmol) dropwise maintaining a temperature below 0 ^oC. The reaction was stirred at the same temperature for 1 hour and filtered to remove the white precipitate that formed, washing with THF (10 mL). The filtrate was added dropwise to a solution of $NaBH_4$ (2.5 equivalents) in H_2O (*approx*. 2 mL/mmol) at -5 ^oC. The reaction was stirred at room temperature overnight and monitored by TLC. Upon completion, the reaction was acidified to approx. pH 3 with 1 M HCl. The layers were separated, and the aqueous layer extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with aqueous 1 M NaOH (10 mL) and H_2O (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography.

General procedure G for preparation of Boc-protected hydroxylamine derivatives by Mitsunobu alkylation[33]

Diisopropyl azodicarboxylate (1.2 equivalents) was added at 0 ^oC to a stirring solution of triphenylphosphine (1.2 equivalents) in anhydrous THF (*approx*. 2mL/mmol) under a nitrogen atmosphere. After 30 minutes stirring at this temperature a solution of alcohol (1.0 equivalent) and amine nucleophile (1.2 equivalents) in anhydrous THF (*approx*. 2mL/mmol) were added. The reaction was stirred at 0 ^{o} C for 1 hour after which it was stirred at room temperature and monitored by TLC. Upon completion, the reaction mixture was concentrated *in vacuo* and purified by flash column chromatography.

General procedure H for the removal of silyl protecting group with TBAF/AcOH

To a solution of silyl ether (1.0 equivalent) in THF (*approx.* 20mL/mmol) at 0 °C was added a solution of 1:1 TBAF/AcOH (*equivalents specified*, 0.1 M in THF). The reaction mixture was stirred at room temperature and monitored by TLC. Upon completion, the reaction mixture was quenched with water (10 mL), extracted with EtOAc (2 × 10 mL), washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered and the concentrated *in vacuo*. The crude product was purified by flash column chromatography.

General procedure I for intramolecular dearomatising amination

To a stirring solution of Boc-protected amino substrate (1.0 equivalent) in anhydrous 2,2,2,-trifluoroethanol (0.1 M) at 0 °C was added trifluoroacetic acid (2.0 equivalents). After stirring for 2 hours at 0 °C the reaction was warmed to room temperature and monitored by TLC. Upon completion, the reaction mixture was concentrated *in vacuo* and purified by flash column chromatography, with a small amount of Et_3N (<1%) added to the appropriate eluent. In cases where the product was unstable the TFA salt was obtained by re-acidification with TFA.

General procedure J for formation of unsaturated esters by Wittig reaction

Aldehyde (1.0 equivalent) and methyl 2-(triphenyl-phosphaneylidene) acetate or ethyl 2-(triphenyl-phosphaneylidene) acetate (1.5 equivalents) in CH_2Cl_2 (*approx*. 1 mL/mmol) were stirred at room temperature overnight and monitored by TLC. Upon completion, the reaction mixture was concentrated *in vacuo* and purified by flash column chromatography.

General Procedure K for preparation of Weinreb amides from Carboxylic acids

To a solution of carboxylic acid (1.0 equivalent) in anhydrous CH_2Cl_2 under nitrogen at 0 °C was added *N*,*O*-dimethylhydroxylamine hydrochloride (1.4 equivalents), Et_3N (1.4 equivalents), 4-dimethylaminopyridine (1.4 equivalents), and *N*,*N*'-dicyclohexylcarbodiimide (1.4 eq.). The solution was stirred at room temperature overnight and then filtered through Celite, eluting with EtOAc. The filtrate was washed sequentially with 1 M HCl (10 mL) and saturated aqueous $NaHCO_3$ (10 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography.

General procedure L for the acylation of spirocyclic pyrrolidines with phenylacetyl chloride

A solution of spirocyclic pyrrolidine (1.0 equivalent) in anhydrous THF (5 mL/mmol) under an atmosphere of nitrogen was cooled to 0 °C and phenylacetyl chloride (2.0 equivalents) and K_3PO_4 (4.0 equivalents) were added. The reaction was warmed to room temperature and stirred overnight and monitored by TLC. Upon completion, the reaction was quenched with water (1 mL) and extracted with EtOAc (3 × 2 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography.

General procedure M for the synthesis of tricyclic amides using LiHMDS

To a solution of amide (1.0 equivalent) in anhydrous THF (1 mL) at -78 °C and under an atmosphere of nitrogen was added lithium bis(trimethylsilyl)amide (1.5 equivalents). The reaction was stirred at this temperature for the time stated. Upon completion, the reaction mixture was warmed to 0 °C and quenched with saturated aqueous NH_4Cl (0.3 mL) and extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography.

General procedure N for the synthesis of tricyclic urea compounds

A solution of spirocyclic pyrrolidine (1.0 equivalent) in anhydrous CH_2Cl_2 (0.2 M) was cooled to 0 °C and phenyl isocyanate (2.0 equivalents) and Et_3N (4.0 equivalents) were added. The reaction was stirred at this temperature for 2 hours before warming to room temperature and stirring overnight, monitoring by TLC. Upon completion, the reaction mixture was quenched with saturated aqueous NH_4Cl (1 mL) and extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*.

General procedure O for enantioselective dearomatising amination

A flame-dried resealable tube, fitted with a magnetic stirrer, was charged with cyclisation substrate (1.0 equivalent) phase-transfer catalyst (10 mol%) and Cs_2CO_3 (2.0 equivalents). The tube was fitted with a rubber septum and purged with nitrogen before solvent was added by syringe. The tube was sealed and heated at the specified time for 48 hours. The reaction mixture

was cooled to room temperature and concentrated *in vacuo*. The crude product was purified by flash column chromatography.

General procedure P for intramolecular aziridination

A flame dried re-sealable tube was charged with alkene (1.0 equivalent) and fitted with a rubber septum. The tube was purged with nitrogen before anhydrous TFE (0.1 M) and TFA (2.0 equivalents) were added *via* syringe. The tube was sealed and stirred at room temperature for the time noted. Upon completion the reaction mixture was concentrated *in vacuo* and the crude mixture was purified by flash column chromatography with addition of Et_3N (1-2 drops) to the eluent to afford the pure product.

General procedure Q for Johnson-Claisen rearrangement

A solution of propionic acid (0.2 equivalents) in triethyl orthoacetate (10.0 equivalents) was heated at 110 °C for 1 hour. After this time allylic alcohol (1.0 equivalent) was added and the reaction mixture was heated at reflux overnight. Upon cooling to room temperature, the reaction mixture was concentrated *in vacuo* to afford the crude product which was purified by flash column chromatography.

General procedure R for alkylation of sulfonamides with allylic bromides

To a solution of sulfonamide (1.0 equivalent) and K_2CO_3 (1.5 equivalents) in acetone (2 mL/mmol) was added allylic bromide (1.5 equivalents) and the reaction was stirred at room temperature overnight. Upon completion the reaction was concentrated *in vacuo* and purified by flash column chromatography.

General procedure S for formation of piperidines by ring expansion of aziridines

To a solution of aziridine (1.0 equivalent) in anhydrous THF (1 M) was added the appropriate acid halide or anhydride (*equivalents specified*) and the reaction was stirred at 0 ^oC or room temperature. Upon completion the reaction was concentrated *in vacuo* and purified by flash column chromatography.

General procedure T for the synthesis of *N*-methyl *tert*-butyl carbamate reagents

To a solution of *tert*-butyl hydroxy(methyl)carbamate (1.0 equivalent) and sulfonyl chloride (1.05 equivalents) in Et_2O (4 mL/mmol) at 0 ^oC was added Et_3N (1.05 equivalent). The reaction was warmed to room temperature and stirred overnight. The reaction mixture was filtered

through Celite®, washing with Et_2O and concentrated *in vacuo*. The crude product was purified by flash column chromatography.

General procedure U for intermolecular aziridination

A flame dried resealable tube was charged with *tert*-butyl (((chloromethyl)sulfonyl)oxy) (methyl)carbamate (1.2 equivalents) and fitted with a rubber septum. The tube was purged with nitrogen before addition of alkene (1.0 equivalent), TFE (0.5 M) and TFA (2.0 equivalents). The tube was sealed and stirred at room temperature for the stated time before being concentrated *in vacuo* and purified by flash column chromatography.

General procedure V for formation of unsaturated esters by Horner-Wadsworth-Emmons reaction

To a suspension of NaH (60 w.t.% in mineral oil, 1.5 equivalents) in anhydrous THF (5 mL/mmol) at 0 ^oC was added phosphonoacetate reagent (1.5 equivalents) dropwise. The reaction was stirred at this temperature until gas evolution had ceased at which point a solution of aldehyde (1.0 equivalent) in THF (0.5 mL/mmol) was added. The reaction was stirred at room temperature overnight. The reaction was quenched with saturated aqueous NH_4Cl (40 mL), extracted with EtOAc (20 mL) and the organic phase washed with brine (20 mL), dried, filtered and concentrated. The crude product was purified by flash column chromatography.

General procedure W for formation of aziridines by 1,2-alkene difunctionalisations

A flame dried re-sealable tube was charged with alkene (1.0 equivalent) and fitted with a rubber septum. The tube was purged with nitrogen before anhydrous TFE (0.1 M) and TFA (2.0 equivalents) were added *via* syringe. The tube was sealed and stirred at room temperature for the time noted. Upon completion the reaction mixture was concentrated *in vacuo* and the crude mixture was purified by flash column chromatography with addition of Et_3N (1-2 drops) to the eluent to afford the pure product.

General procedure X for intramolecular aryl C-H amination

To a stirring solution of Boc-protected amino substrate (1.0 equivalent) in anhydrous 2,2,2,-trifluoroethanol (0.1 M) at 0 ^oC was added trifluoroacetic acid (2.0 equivalents). After stirring for 2 hours at 0 ^oC the reaction was warmed to room temperature and monitored by

TLC. Upon completion, the reaction mixture was concentrated *in vacuo* and purified by flash column chromatography, with a small amount of Et_3N (<1%) added to the appropriate eluent.

General procedure Y synthesis of sulfoximines by amination of sulfoxides

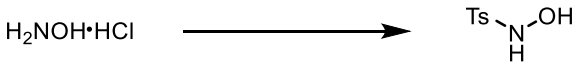
To a flame-dried reaction tube was added sulfoxide (1.0 equivalent) and amino reagent (1.5 equivalents). The tube was fitted with a suba seal and flushed with nitrogen. TFE or PhMe (1 M) was added *via* syringe followed by TFA (2.0 equivalents) and the reaction was stirred at the stated temperature and monitored by TLC. Upon completion the reaction was diluted with CH_2Cl_2 (5 mL) and washed with saturated aqueous Na_2CO_3 (5 mL) and the phases were separated, and the aqueous phase extracted with CH_2Cl_2 (2 × 5 mL). The combined organic phases were washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* before purification by flash column chromatography.

General procedure Z oxidation of sulfides to sulfoxides[279]

To a solution of sulfide (1.0 equivalent) in MeCN (1mL/mmol) was added $FeCl_3$ (3 mol%). The reaction was stirred for 5 minutes before the addition of H_5IO_6 (1.1 equivalents). After stirring at room temperature, the reaction until complete by TLC, the reaction was quenched with saturated aqueous $Na_2S_2O_3$ (4 mL/mmol) and extracted with CH_2Cl_2 (4 × 4 mL/mmol) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated in *vacuo*. Purification by flash column chromatography afford the desired sulfoxide.

6.3 Experimental procedure for the studies in Chapter 2

_N_-Hydroxy-4-methylbenzenesulfonamide

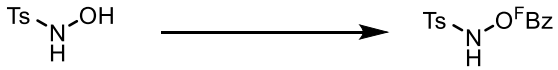


This compound was prepared according to a literature procedure.[280]

To a solution of hydroxylamine hydrochloride (10.4 g, 150 mmol) in MeOH (45 mL) and water (30 mL) was added MgO (5.1 g, 129 mmol). The reaction mixture was stirred at room temperature for 10 minutes before addition of a solution of TsCl (12.4 g, 65 mmol) in THF (450 mL) followed by another portion of MgO (2.6 g, 64.5 mmol). The reaction mixture was stirred for 1 hour before being filtered and concentrated *in vacuo*. Purification by flash column chromatography (40% EtOAc:hexane) afforded the title compound (7.6 g, 62%) as a colourless crystalline solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (2H, d, *J* = 8.5 Hz), 7.37 (2H, d, *J* = 8.5 Hz), 6.65 (1H, s), 6.05 (1H, d, *J* = 4.0 Hz), 2.46 (3H, s).

The spectroscopic properties were consistent with the data available in the literature.[281]

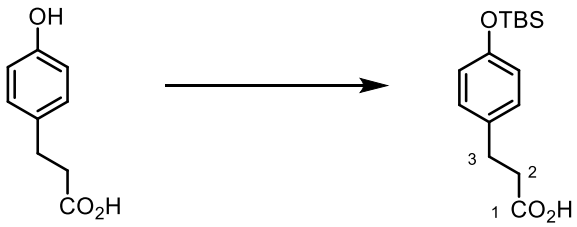
_N_-Tosyl-_O_-pentafluorobenzoyl hydroxylamine



To a suspension of *N*-tosylhydroxylamine (2.80 g, 14.4 mmol) and pentafluorobenzoic acid (3.05 g, 14.4 mmol) in CH_2Cl_2 (130 mL) at 0 °C was added a solution of *N*-*N*'-dicyclohexylcarbodiimide (3.30 g, 16.0 mmol) in CH_2Cl_2 (130 mL) dropwise. The resulting mixture was stirred at 0 °C overnight before filtration to remove the white precipitate. The filtrate was concentrated *in vacuo* and the crude mixture was purified by flash column chromatography (20% EtOAc:hexane) to give the title compound (3.48 g, 63%) as a colourless solid; ν_{max} / cm^{-1} (*solid*) 3187 (br), 1777 (s), 1653 (s), 1597 (m), 1501 (s), 1170 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (1H, br s, N<u>H</u>), 7.87 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.37 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 2.46 (3H, s, Ts C<u>H</u>$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.9 (^{F}Bz <u>C</u>=O), 146.2 (Ts Ar<u>C</u>), 132.0 (Ts Ar<u>C</u>), 130.0 (2 × Ts Ar<u>C</u>H), 128.9 (2 × Ts Ar<u>C</u>H), 21.8 (Ts <u>C</u>H$_3$). *The aromatic ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* ^{19}F NMR (377 MHz, $CDCl_3$) δ -134.7– -134.8 (2F, m), -144.1 (1F, tt, *J* = 21.0, 6.5 Hz), -158.6 – -158.8 (2F, m).

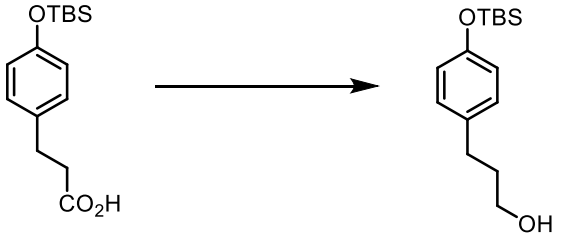
The spectroscopic properties were consistent with the data available in the literature.[52]

3-(4-((*tert*-Butyldimethylsilyl)oxy)phenyl)propanoic acid (206)



General procedure A: Carboxylic acid **145** (8.30 g, 50.0 mmol), *tert*-butyldimethylsilyl chloride (16.5 g, 110.0 mmol) and imidazole (11.25 g, 165.0 mmol) in DMF (100 mL) were employed. Purification by flash column chromatography (25% EtOAc:hexane) afforded **206** (10.8 g, 77%) as a colourless solid; m.p.: 69-71 ^{o}C (EtOAc:hexane); R_f = 0.2 (20% EtOAc:hexane); ν_{max} / cm^{-1} (*solid*) 2926 (m), 2882 (m), 2855 (m), 1714 (s), 1509 (s), 1249 (s), 1213 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.30 (1H, br s, $CO_2\underline{H}$), 7.06 (2H, d, *J* = 8.5 Hz, ArC$\underline{H}$), 6.77 (2H, d, *J* = 8.5 Hz, ArC$\underline{H}$), 2.89 (2H, t, *J* = 7.5 Hz, C**3**-$\underline{H}_2$), 2.65 (2H, t, *J* = 7.5 Hz, C**2**-$\underline{H}_2$), 0.99 (9H, s, TBS (C$\underline{H}_3$)$_3$), 0.19 (6H, s, TBS Si(C$\underline{H}_3$)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.4 (C**1**), 154.2 (Ar$\underline{C}$), 133.0 (Ar$\underline{C}$), 129.3 (2 × Ar$\underline{C}$H), 120.2 (2 × Ar$\underline{C}$H), 36.1 (C**2**), 30.0 (C**3**), 25.8 (TBS ($\underline{C}H_3$)$_3$), 18.3 (TBS Si$\underline{C}$(CH$_3$)$_3$), -4.3 (TBS Si(C$\underline{H}_3$)$_2$); HRMS (ESI$^+$) Calculated for $C_{15}H_{25}O_3Si$: 281.1567. Found [M+H]$^+$: 281.1580.

3-(4-((*tert*-Butyldimethylsilyl)oxy)phenyl)propan-1-ol (146)

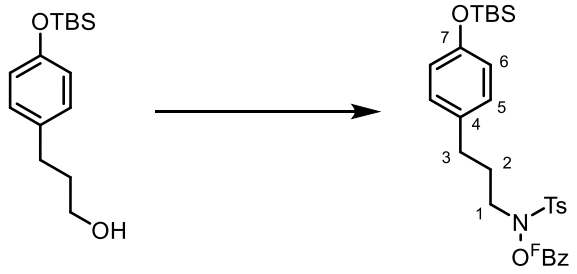


General procedure B: 3-(4-((*tert*-Butyldimethylsilyl)oxy)phenyl)propanoic acid (1.40 g, 5.0 mmol) and 2.0 equivalents of $LiAlH_4$ (1M in THF) in anhydrous Et_2O were employed. Purification by flash column chromatography (25% EtOAc:hexane) afforded **146** (990 mg, 74%) as a colourless oil R_f = 0.6 (33% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 3339 (br), 2929 (s), 2885 (s), 2858 (s), 1609 (m), 1508 (s), 1250 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (2H, d, *J* = 8.0 Hz), 6.75 (2H, d, *J* = 8.0 Hz), 3.64 – 3.68 (2H, m), 2.64 (2H, t, *J* = 7.5 Hz), 1.86 (2H,

m), 1.35 (1H, br s), 0.98 (9H, s), 0.18 (6H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.7, 134.4, 129.2, 119.9, 62.3, 34.4, 31.2, 25.7, 18.2, -4.4.

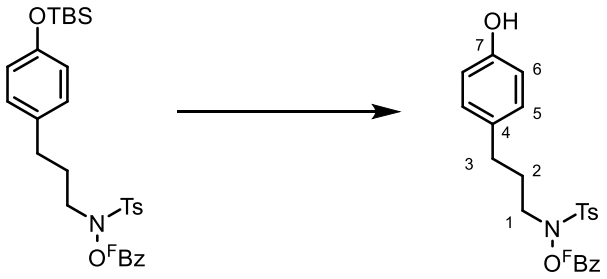
The spectroscopic properties were consistent with the data available in the literature.[282]

_N_-(3-(4-((_tert_-Butyldimethylsilyl)oxy)phenyl)propyl)-4-methyl-_N_((perfluorobenzoyl)oxy) benzenesulfonamide (147)



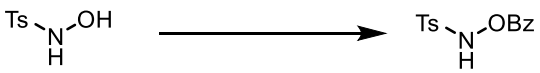
General Procedure C: Alcohol **146** (790 mg, 3.00 mmol), DEAD (0.94 mL, 6.0 mmol), $TsNHO^FBz$ (1.71 g, 4.50 mmol), and PPh_3 (1.57 g, 6.00 mmol) in anhydrous PhMe:THF (5:1, 38 mL) were employed. The reaction mixture was stirred at room temperature until completion by TLC analysis. The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (gradient, eluent: 4 – 15% EtOAc:hexane) to afford **147** (1.05 g, 56%) as an off-white solid; m.p.: 99-100 °C (Et_2O:hexane); ν_{max} / cm^{-1} (*solid*) 2929 (m), 2857 (m), 1787 (s), 1744 (s), 1508 (s), 1252 (s), 1168 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.37 (2H, d, *J* = 8.0 Hz, Ts ArC<u>H</u>), 7.00 (2H, d, *J* = 8.5 Hz, C**5**-<u>H</u>), 6.74 (2H, d, *J* = 8.5 Hz, C**6**-<u>H</u>), 3.21 (2H, br s, C**1**-<u>H</u>$_2$), 2.71 (2H, t, *J* = 7.5 Hz, C**3**-<u>H</u>$_2$), 2.46 (3H, s, Ts, C<u>H</u>$_3$), 1.83 (2H, app. quint, *J* = 7.0 Hz, C**2**-<u>H</u>$_2$), 0.97 (9H, s, TBS (C<u>H</u>$_3$)$_3$), 0.18 (6H, s, TBS Si(C<u>H</u>$_3$)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.4 (O^{F}Bz <u>C</u>=O), 153.9 (C**7**), 145.8 (Ts Ar<u>C</u>), 133.4 (Ts Ar<u>C</u>), 130.0 (C**4**), 129.9 (2 × Ts Ar<u>C</u>H), 129.6 (C**5**), 129.4 (2 × Ts Ar<u>C</u>H), 119.9 (C**6**) 51.9 (C**1**), 31.6 (C**3**), 28.6 (C**2**), 25.7 (TBS (<u>C</u>H$_3$)$_3$), 21.7 (Ts <u>C</u>H$_3$), 18.2 (TBS Si<u>C</u>(CH$_3$)$_3$), -4.5 (TBS Si(<u>C</u>H$_3$)$_2$). *The aromatic ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* ^{19}F NMR (377 MHz, $CDCl_3$) -135.8 – -135.9 (2F, m), -145.9 (1F, tt, *J* = 21.0, 5.0 Hz), -158.9 – -159.0 (2F, m); HRMS (ESI$^+$) Calculated for $C_{29}H_{32}F_5NNaO_5SSi$: 652.1583. Found $[M+Na]^+$: 652.1583.

***N*-((Benzoyl-fluoranyl)oxy)-*N*-(3-(4-hydroxyphenyl)propyl)-4-methylbenzene sulfonamide (148)**



General procedure D: *N*-acyloxysulfonamide **147** (150 mg, 0.24 mmol) and 1 M HCl (1.5 mL) in MeOH (5 mL) and THF (5 mL) were employed. The reaction was stirred at room temperature overnight until completion by TLC analysis. The crude product was purified by flash column chromatography (20% EtOAc:hexane) to afford **148** (115 mg, 93%) as a colourless solid; m.p.: 139-141 ^{o}C (EtOAc:hexane); ν_{max} / cm^{-1} (*solid*) 3506 (m), 2970 (m), 2901 (m), 1791 (s), 1517 (s), 1500 (s), 1361 (s), 1165 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (2H, d, *J* = 8.0 Hz, Ts ArC<u>H</u>), 7.37 (2H, d, *J* = 8.0 Hz, Ts ArC<u>H</u>), 7.03 (2H, d, *J* = 8.0 Hz, C**5**-<u>H</u>), 6.74 (2H, d, *J* = 8.0 Hz, C**6**-<u>H</u>), 4.64 (1H, s, O<u>H</u>), 3.20 (2H, br s, C**1**-<u>H</u>$_2$), 2.73 (2H, t, *J* = 7.5 Hz, C**3**-<u>H</u>$_2$) 2.46 (3H, s, Ts C<u>H</u>$_3$), 1.82 (2H, app. quint, *J* = 7.0 Hz, C**2**-<u>H</u>$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.9 (C**7**), 145.9 (Ts Ar<u>C</u>), 133.0 (Ts Ar<u>C</u>), 130.0 (C**4**), 129.9 (2 × Ts Ar<u>C</u>H), 129.8 (2 × Ts Ar<u>C</u>H), 129.7 (C**5**), 115.4 (C**6**) 51.9 (C**1**), 31.6 (C**3**), 28.7 (C**2**), 21.8 (Ts <u>C</u>H$_3$). *The aromatic ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* ^{19}F NMR (377 MHz, $CDCl_3$) δ -135.9 (2F, m), -145.9 (1F, m), -158.9 (2F, m); HRM,S (ESI$^+$) Calculated for $C_{23}H_{18}F_5NNaO_5S$: 538.0718. Found $[M+Na]^+$: 538.0694.

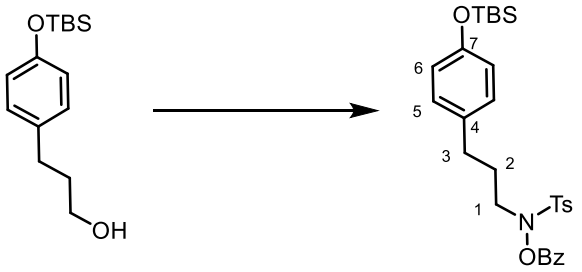
***N*-(Benzoyloxy)-4-methylbenzenesulfonamide**



To a stirred solution of TsNHOH (1.87 g, 10.0 mmol) in EtOAc (50 mL) at -5 ^{o}C was added Et_3N (1.37 mL, 9.90 mmol) dropwise. After 5 minutes benzyl chloride (1.14 mL, 9.90 mmol) was added dropwise over 15 minutes. After complete addition, the solution was warmed to room temperature and left to stir for 1.5 hours. After addition of water (25 mL) the layers were separated, and the aqueous phase extracted with EtOAc (3 × 30 mL). The combined organic

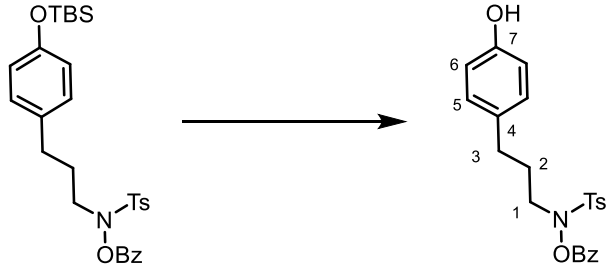
extracts were washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The resulting colourless solid (2.81 g, 97%) was used without any further purification; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.24 (1H, br s, NH), 7.91 (2H, dd, *J* = 8.5, 1.0 Hz, ArCH), 7.83 (2H, d, *J* = 8.5 Hz, Ts ArCH), 7.63 (1H, tt, *J* = 7.5, 1.0 Hz, ArCH), 7.45 (2H, dd, *J* = 8.0, 7.5 Hz, ArCH), 7.27 (2H, d, *J* = 8.5 Hz, Ts ArCH), 2.39 (3H, s, Ts CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.9, 145.7, 134.6, 132.3, 129.9, 129.6, 128.8, 128.7, 125.7, 21.7 (Ts CH_3); HRMS (ESI$^+$) Calculated for $C_{14}H_{13}NNaO_4S$: 314.0457. Found $[M+Na]^+$: 314.0454.

_N_-(Benzoyloxy)-_N_-(3-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)propyl)-4-methylbenzene sulfonamide



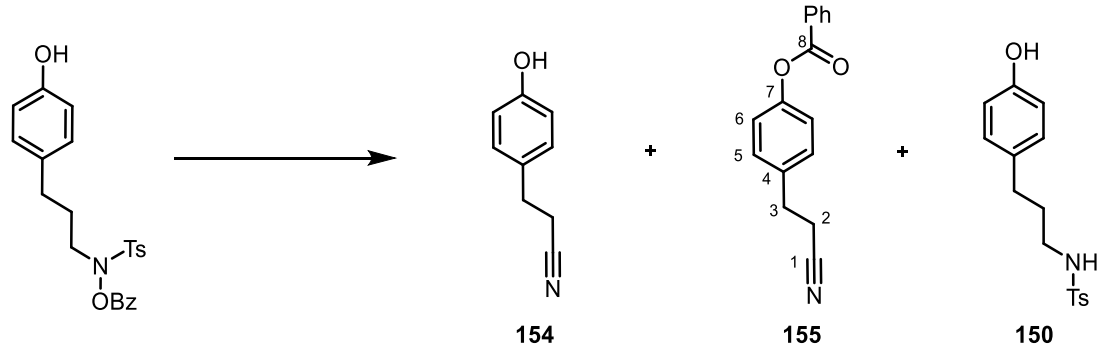
General procedure C: Alcohol **146** (532 mg, 2.00 mmol), DIAD (0.63 mL, 4.0 mmol), TsNHOBz (870 mg, 3.00 mmol) and PPh_3 (1.05 g, 4.00 mmol) in anhydrous PhMe:THF (5:1, 24 mL) were employed. The reaction mixture was stirred at room temperature until completion by TLC analysis. The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (gradient, eluent: 10 – 20% EtOAc:hexane) to afford the title compound (805 mg, 74%) as a colourless solid; m.p.: 105-107 ºC (Et_2O:hexane); ν_{max} / cm^{-1} (*solid*) 2954 (m), 2928 (m), 2900 (m), 2855 (m), 1767 (s), 1236 (s), 1168 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (2H, m, ArCH), 7.80 (2H, d, *J* = 8.5 Hz, Ts ArCH), 7.62 (1H, t, *J* = 7.5 Hz, ArCH), 7.50 – 7.44 (2H, m, ArCH), 7.38 (2H, d, *J* = 8.5 Hz, Ts ArCH), 6.99 (2H, d, *J* = 8.5 Hz, C**5**-H), 6.71 (2H, d, *J* = 8.5 Hz, C**6**-H), 3.25 (2H, br s, C**1**-H_2), 2.71 (2H, t, *J* = 7.5 Hz, C**3**-H_2), 2.48 (3H, s, Ts CH_3), 1.82 (2H, app. qn, *J* = 7.5 Hz, C**2**-H_2), 0.97 (9H, s, TBS (CH_3)$_3$), 0.17 (6H, s, TBS Si(CH_3)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.5 (OBz C=O), 153.8 (ArC), 145.4 (ArC), 133.9 (ArC), 133.7 (ArC), 130.4 (ArC), 129.9 (ArCH), 129.8 (ArCH), 129.5 (ArCH), 129.4 (ArCH), 128.7 (ArCH), 127.3 (ArCH), 119.9 (ArCH), 52.0 (C**1**), 31.8 (C**3**), 28.6 (C**2**), 25.7 (TBS (CH_3)$_3$), 21.7 (Ts CH_3), 18.2 (TBS SiC(CH_3)$_3$), -4.5 (TBS Si(CH_3)$_2$); HRMS (ESI$^+$) Calculated for $C_{29}H_{37}NNaO_5SSi$: 562.2054. Found $[M+Na]^+$: 562.2036.

***N*-(Benzoyloxy)-*N*-(3-(4-hydroxyphenyl)propyl)-4-methylbenzenesulfonamide (153)**



General procedure D: *N*-(Benzoyloxy)-*N*-(3-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)propyl) -4-methylbenzenesulfonamide (534 mg, 1.00 mmol) was employed using 1 M HCl (7 mL). The crude product was purified by flash column chromatography (20% EtOAc:hexane) to afford **153** (410 g, 96%) as a colourless solid; m.p.: 148-149 ^{o}C (Et_2O:hexane); ν_{max} / cm^{-1} (*solid*) 3432 (br), 2932 (m), 1770 (s), 1236 (s), 1167 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 – 7.94 (2H, m, ArC<u>H</u>), 7.80 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.65 – 7.60 (1H, m, ArC<u>H</u>), 7.49 – 7.44 (2H, m, ArC<u>H</u>), 7.38 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.02 (2H, d, *J* = 8.5 Hz, C**5**-<u>H</u>), 6.72 (2H, d, *J* = 8.5 Hz, C**6**-<u>H</u>), 4.86 (1H, br s, O<u>H</u>), 3.25 (2H, br s, C**1**-<u>H_2</u>), 2.71 (2H, t, *J* = 7.5 Hz, C**3**-<u>H_2</u>), 2.47 (3H, s, Ts C<u>H_3</u>), 1.81 (2H, app. qn, *J* = 7.5 Hz, C**2**-<u>H_2</u>); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.6 (OBz <u>C</u>=O), 153.8 (Ar<u>C</u>), 145.5 (Ar<u>C</u>), 133.9 (Ar<u>C</u>), 133.1 (Ar<u>C</u>), 130.3 (Ar<u>C</u>), 129.9 (Ar<u>C</u>H), 129.8 (Ar<u>C</u>H), 129.7 (Ar<u>C</u>H), 129.5 (Ar<u>C</u>H), 128.7 (Ar<u>C</u>H), 127.3 (Ar<u>C</u>H), 115.2 (Ar<u>C</u>H), 51.9 (C**1**), 31.7 (C**3**), 28.7 (C**2**), 21.7 (Ts <u>C</u>H_3); HRMS (ESI^+) Calculated for $C_{23}H_{23}NNaO_5S$: 448.1189. Found $[M+Na]^+$: 448.1181.

3-(4-Hydroxyphenyl)propanenitrile (154), 4-(2-Cyanoethyl)phenyl benzoate (155) *and* *N*-(3-(4-Hydroxyphenyl)propyl)-4-methylbenzenesulfonamide (150)



A flame-dried resealable tube, fitter with a magnetic stirrer, was charged with *N*-acyloxysulfonamide **153** (63.8 mg, 0.15 mmol), K_2CO_3 (31.1 mg, 0.225 mmol), $Pd_2(dba)_3$ (3.43 mg, 3.75 µmol) and $P(3,5\text{-}(CF_3)_2C_6H_3)_3$ (12.6 mg, 0.019 mmol). The tube was fitted with a rubber septum and purged with nitrogen before *n*-BuCN (1.5 mL) was added *via* syringe. The tube was sealed and heated at 110 ^{o}C for 24 hours. The reaction was cooled to room

temperature, filtered through a pad of Celite® and concentrated *in vacuo*. Purification by flash column chromatography afforded the title compounds.

*Data for **154**:* ν_{max} / cm^{-1} (*film*) 3379 (br), 2931 (m), 2251 (m), 1515 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 – 7.01 (2H, m), 6.79 (2H, d, *J* = 8.5 Hz), 5.15 (1H, br s), 2.89 (2H, t, *J* = 7.5 Hz), 2.58 (2H, t, *J* = 7.5 Hz).

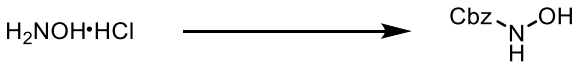
The spectroscopic properties were consistent with the data available in the literature.[283]

*Data for **155**:* ν_{max} / cm^{-1} (*film*) 2918 (m), 2849 (m), 2242 (m), 1727 (s), 1508 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 – 8.16 (2H, m, ArC<u>H</u>), 7.68 – 7.60 (1H, m, ArC<u>H</u>), 7.52 (2H, t, *J* = 7.5 Hz, ArC<u>H</u>), 7.30 (2H, d, *J* = 8.5 Hz, C**5**-<u>H</u>), 7.23 – 7.14 (2H, m, C**6**-<u>H</u>), 3.00 (2H, t, *J* = 7.5 Hz, C**3**-<u>H_2</u>), 2.65 (2H, t, *J* = 7.5 Hz, C**2**-<u>H_2</u>); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.3 (C**8**), 150.2 (C**7**), 135.8 (C**4**), 133.8 (Ar<u>C</u>H), 130.3 (Ar<u>C</u>H), 129.5 (C**5**), 128.8 (Ar<u>C</u>H), 122.3 (C**6**), 119.1 (C**1**), 31.2 (C**3**), 19.5 (C**2**).

*Data for **150**:* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (2H, d, *J* = 8.5 Hz), 7.29 (2H, d, *J* = 8.5 Hz), 6.93 (2H, d, *J* = 8.5 Hz), 6.71 (2H, d, *J* = 8.5 Hz), 2.99 – 2.90 (2H, m), 2.53 – 2.49 (2H, m), 2.42 (3H, s), 1.72 (2H, p, *J* = 7.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.1, 143.6, 136.3, 132.9, 129.9, 129.6, 127.8, 115.5, 42.8, 32.0, 31.5, 21.7.

The spectroscopic properties were consistent with the data available in the literature.[95]

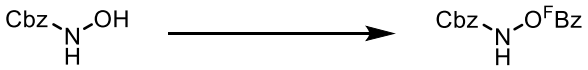
Benzyl hydroxycarbamate



A solution of hydroxylamine hydrochloride (10.4 g, 150 mmol) and K_2CO_3 (20.7 g, 150 mmol) in Et_2O (50 mL) and water (50 mL) was stirred at room temperature for 1 hour then cooled to 0 °C before the addition of CbzCl (17.0 g, 100 mmol). The reaction was stirred at room temperature for 6 hours then the reaction was filtered, and the phases were separated. The aqueous phase was extracted with Et_2O (2 × 100 mL) and the combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo* to afford the title compound (12.3 g, 74%) as a colourless crystalline solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.30 (5H, m), 5.16 (2H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.2, 135.5, 128.8, 128.7, 128.5, 68.0.

The spectroscopic properties were consistent with the data available in the literature.[284]

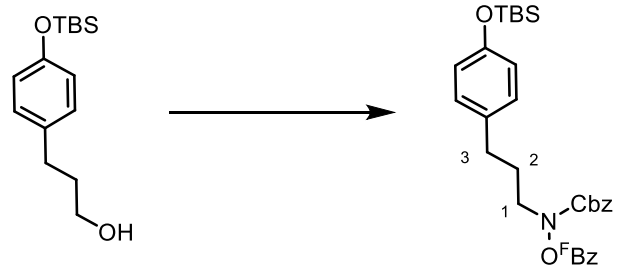
Benzyl (pentafluorobenzoyloxy)carbamate



To a suspension of benzyl hydroxycarbamate (4.20 g, 25.0 mmol) and pentafluorobenzoic acid (5.30 g, 25.0 mmol) in CH_2Cl_2 (235 mL) at 0 ^oC was added a solution of *N*-*N*'-dicyclohexylcarbodiimide (5.70 g, 27.5 mmol) in CH_2Cl_2 (235 mL) dropwise. The resulting mixture was stirred at 0 ^oC overnight before filtration to remove the white precipitate. The filtrate was concentrated *in vacuo* and the crude mixture was purified by flash column chromatography (20% EtOAc:hexane) to give the title compound (5.6 g, 64%) as a colourless solid; ν_{max} / cm^{-1} (*solid*) 3237 (s, br), 2971 (m), 2987 (m), 2901 (m), 1779 (m), 1755 (s), 1494 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (1H, br s), 7.37 (5H, s), 5.26 (2H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.7, 134.6, 128.8, 128.7, 128.4, 69.0. *The aromatic ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.*

The spectroscopic properties were consistent with the data available in the literature.[97]

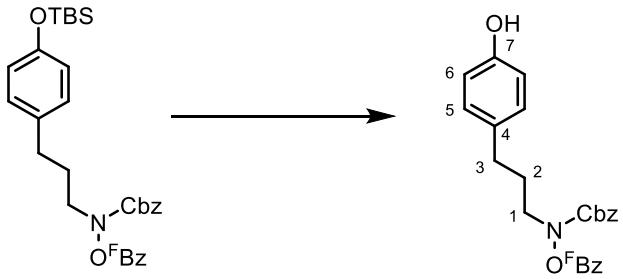
***N*-(Pentafluorobenzoyloxy)3-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)propyl)benzyl carbamate**



General procedure C: Alcohol **146** (798 mg, 3.00 mmol), DIAD (0.88 mL, 4.5 mmol), $CbzNHO^FBz$ (1.35 g, 3.90 mmol) and PPh_3 (1.17 g, 4.5 mmol) in anhydrous PhMe:THF (5:1, 32 mL) were employed. The reaction was stirred at room temperature overnight until completion by TLC analysis. The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (20% EtOAc:hexane) to afford the title compound (736 mg, 41%) as a colourless solid; m.p.: 55-57 ^oC (EtOAc:hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.32 (5H, m, ArC<u>H</u>), 7.00 (2H, d, *J* = 8.5 Hz, ArC<u>H</u>), 6.73 (2H, d, *J* = 8.5 Hz, ArC<u>H</u>), 5.21 (2H, s, Cbz C<u>H</u>$_2$), 3.76 (2H, t, *J* = 7.0 Hz, C**1**-<u>H</u>$_2$), 2.63 (2H, t, *J* = 7.5 Hz, C**3**-<u>H</u>$_2$), 1.93 (2H, app. qn, *J* = 7.5 Hz, C**2**-<u>H</u>$_2$), 0.98 (9H, s, TBS (C<u>H</u>$_3$)$_3$), 0.18 (6H, s, TBS Si(<u>C</u>H$_3$)$_2$);

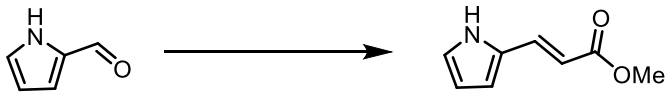
^{13}C NMR (101 MHz, $CDCl_3$) δ 157.3 (C=O), 155.4 (C=O), 153.8 (ArC), 135.2 (ArC), 133.5 (ArC), 129.2 (ArCH), 128.6 (ArCH), 128.5 (ArCH), 128.1 (ArCH), 120.0 (ArCH), 68.8 (Cbz CH_2), 50.7 (C**1**), 31.7 (C**3**), 28.7 (C**2**), 25.7 (TBS $(CH_3)_3$), 18.2 (TBS $SiC(CH_3)_3$), -4.5 (TBS $Si(CH_3)_2$). *The aromatic ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.*

_N_-(Pentafluorobenzoyloxy)-3-(4-hydroxyphenyl)propyl)benzylcarbamate (159)



General procedure D: *N*-(Pentafluorobenzoyloxy)3-(4-((*tert*-butyldimethylsilyl)oxy)phenyl) propyl) benzylcarbamate (720 mg, 1.21 mmol) and 1 M HCl (7.5 mL) in MeOH (25 mL) and THF (25 mL) were employed. The crude product was purified by flash column chromatography (20% EtOAc:hexane) to afford **159** (516 mg, 86%) as a colourless solid; ν_{max} / cm^{-1} (*solid*) 3362 (br), 1776 (s), 1698 (s), 1495 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.32 (5H, m, ArCH), 7.02 (2H, d, *J* = 8.5 Hz, C**5**-H), 6.72 (2H, d, *J* = 8.5 Hz, C**6**-H), 5.22 (2H, s, Cbz CH_2), 4.62 (1H, s, OH), 3.76 (2H, t, *J* = 7.0 Hz, C**1**-H_2), 2.63 (2H, t, *J* = 7.0 Hz, C**3**-H_2), 1.92 (2H, app. qn, *J* = 7.0 Hz, C**2**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.3 (C=O), 155.5 (C=O), 153.9 (C**7**), 135.1 (ArC), 133.0 (ArC), 129.4 (ArCH), 128.6 (ArCH), 128.5 (ArCH), 128.1 (ArCH), 115.2 (C**6**), 68.8 (Cbz CH_2), 50.6 (C**1**), 31.6 (C**3**), 28.7 (C**2**). *The aromatic ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* HRMS (ESI^+) Calculated for $C_{24}H_{18}F_5NNaO_5$: 518.0997. Found $[M+Na]^+$: 518.0997.

Methyl (*E*) 3-(1*H*-pyrrol-2-yl)acrylate (162)

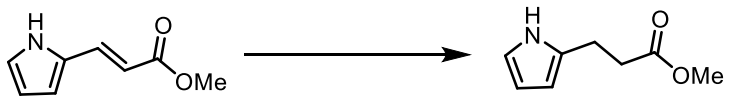


1*H*-Pyrrole-2-carboxaldehyde (1.25 g, 13.1 mmol) and methyl(triphenylphosphornaylidene) acetate **161** (4.61 g, 13.8 mmol) were heated at 45 °C in toluene (125 mL) until completion by TLC analysis (18 hours). The reaction was cooled to room temperature and concentrated *in vacuo*. Purification by flash column chromatography (20% EtOAc:hexane) afforded **162**

(1.60 g, 80%) as a colourless solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (1H, br s), 7.56 (1H, d, *J* = 16.0 Hz), 6.94 – 6.92 (1H, m), 6.58 – 6.56 (1H, m), 6.30 – 6.27 (1H, m), 5.99 (1H, d, *J* = 16.0 Hz), 3.78 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.0, 134.3, 128.3, 122.4, 114.5, 111.0, 110.8, 51.6.

The spectroscopic properties were consistent with the data available in the literature.[285]

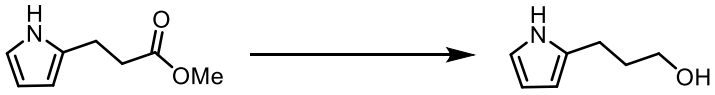
Methyl 3-(1H-pyrrol-2-yl)propanoate



General procedure E: The preceding ester **162** (3.02 g, 20 mmol) and 10 wt.% Pd/C in MeOH (150 mL) were employed. The reaction was stirred at room temperature under a hydrogen atmosphere until completion by TLC analysis (20 hours). The crude mixture was filtered over a bed of Celite® washed with MeOH (50 mL) and the solvent was removed *in vacuo* to afford the title compound (3.01 g, 100%) as a yellow oil, which required no further purification; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (1H, br s), 6.69 – 6.67 (1H, m), 6.13 – 6.10 (1H, m), 5.94 – 5.93 (1H, m), 3.71 (3H, s), 2.93 (2H, t, *J* = 7.0 Hz), 2.66 (2H, t, *J* = 7.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.5, 130.9, 116.8, 108.0, 105.5, 51.8, 34.3, 22.6.

The spectroscopic properties were consistent with the data available in the literature.[285]

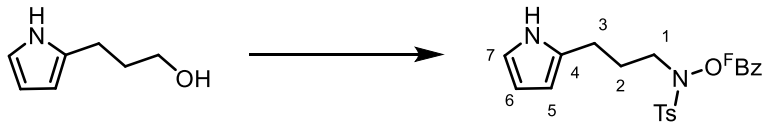
3-(1*H*-Pyrrol-2-yl)propan-1-ol (163)



General procedure B: Methyl 3-(1*H*-pyrrol-2-yl)propanoate (2.92 g, 19.1 mmol) and 1.5 equivalents of $LiAlH_4$ (1 M in THF) in anhydrous Et_2O (100 mL) were employed. The crude product was purified by flash column chromatography (33% EtOAc:hexane) to afford **163** (2.05 g, 87%) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (1H, br s), 6.69 – 6.67 (1H, m), 6.14 – 6.12 (1H, m), 5.93 – 5.92 (1H, m), 3.68 (2H, t, *J* = 6.0 Hz), 2.71 (2H, t, *J* = 7.5 Hz), 2.55 (1H, br s), 1.91 – 1.84 (2H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ 131.9, 116.5, 108.1, 105.0, 62.1, 32.3, 24.1.

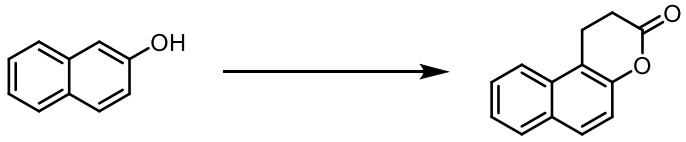
The spectroscopic properties were consistent with the data available in the literature.[286]

_N_-(3-(1_H_-Pyrrol-2-yl)propyl)-4-methyl-_N_-((perfluorobenzoyl)oxy)benzenesulfonamide (164)



General procedure C: The preceding alcohol **163** (380 mg, 3.00 mmol), DIAD (1.18 mL, 6.0 mmol), PPh_3 (1.57 g, 6.00 mmol), and $TsNHO^FBz$ (1.71 g, 4.50 mmol) in anhydrous PhMe:THF (5:1, 32 mL) were employed. The reaction mixture was stirred at room temperature until completion by TLC analysis. The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography to afford **164** (410 mg, 33%) as a brown solid; ν_{max} / cm^{-1} (*solid*) 3358 (m, br), 2974 (m), 2901 (m), 1788 (s), 1502 (s), 1168 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (1H, br s, NH), 7.78 (2H, d, *J* = 8.0 Hz, Ts ArCH), 7.38 (2H, d, *J* = 8.0 Hz, Ts ArCH), 6.71 – 6.69 (1H, m, C**7**-H), 6.14 – 6.12 (1H, m, C**6**-H), 5.93 – 5.90 (1H, m, C**5**), 3.20 (2H, br s, C**1**-H_2), 2.88 (2H, t, *J* = 7.0 Hz, C**3**-H_2), 2.47 (3H, s, Ts CH_3), 1.82 (2H, app. qn, *J* = 6.5 Hz, C**2**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.2 (Ts ArC), 131.0 (C**4**), 130.1 (2 × Ts ArCH), 130.0 (Ts ArC), 129.7 (2 × Ts ArCH), 116.8 (C**7**), 108.5 (C**6**), 105.6 (C**5**), 52.0 (C**1**), 27.5 (C**2**), 24.1 (C**3**), 21.8 (Ts CH_3). HRMS (ESI^+) Calculated for $C_{21}H_{18}F_5N_2O_4S$: 489.0902. Found $[M+H]^+$: 489.0909.

1,2-Dihydro-3*H*-benzo[f]chromen-3-one (166)

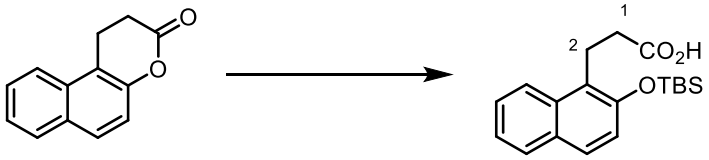


The compound was prepared according to a literature procedure.[287]

To a solution of 2-naphthol (4.33 g, 30.0 mmol) and Amberlyst 15® (3.0 g) in toluene (80 mL) was added acrylic acid (4.32 g, 60.0 mmol) and the suspension was heated at reflux for 48 hours. After cooling to room temperature, the mixture was filtered over Celite® and the filtrate was concentrated in *vacuo*. Purification by flash column chromatography (5% EtOAc:hexane) afforded **166** (4.49 g, 76%) as a yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.84 (2H, m), 7.76 (2H, d, *J* = 9.0 Hz), 7.58 (1H, app. t, *J* = 7.5 Hz), 7.47 (1H, app. t, *J* = 7.5 Hz), 7.26 – 7.21 (2H, m), 3.35 (2H, t, *J* = 7.5 Hz), 2.91 (2H, t, *J* = 7.5 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.3, 149.6, 131.1, 130.8, 128.9, 128.7, 127.1, 125.1, 122.8, 117.4, 115.5, 28.6, 19.9.

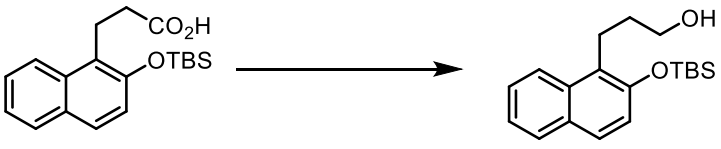
The spectroscopic properties were consistent with the data available in the literature.[287]

3-(2-((*tert*-Butyldimethylsilyl)oxy)naphthalen-1-yl)propanoic acid (167)



To a solution of the preceding lactone **166** (7.90 g, 37.0 mmol) in THF (200 mL) was added aqueous 1 M LiOH (125 mL). After stirring at room temperature overnight the pH was acidified to approx. 3 with 1 M HCl. The product was extracted with EtOAc (50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was dissolved in DMF (20 mL) and *tert*-butyldimethylsilyl chloride (12.2 g, 81.4 mmol) and imidazole (8.30 g, 122.1 mmol) were added at 0 °C. After being stirred at room temperature overnight the reaction was quenched by addition of H_2O and the product was extracted with hexane, dried over $MgSO_4$, filtered and concentrated *in vacuo*. To the crude product in MeOH (30 mL) and THF (30 mL) was added aqueous K_2CO_3 (74.0 mmol, 10.2 g in 100 mL H_2O). After stirring for 5 hours the reaction was quenched with aqueous 1 M HCl (100 mL) at 0 °C. The mixture was extracted with Et_2O, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography (20% EtOAc:hexane) afforded **167** (8.10 g, 66%) as a pale yellow solid; m.p.: 94-96 °C (EtOAc:hexane); R_f = 0.3 (33% EtOAc:hexane); ν_{max} / cm^{-1} (*solid*) 2957 (m), 2928 (m), 2900 (m), 2857 (m), 1699 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (1H, d, *J* = 8.5 Hz, ArC<u>H</u>), 7.79 (1H, d, *J* = 8.0 Hz, ArC<u>H</u>), 7.65 (1H, d, *J* = 8.5 Hz, ArC<u>H</u>), 7.51 (1H, t, *J* = 8.0 Hz, ArC<u>H</u>), 7.36 (1H, t, *J* = 7.5 Hz, ArC<u>H</u>), 7.11 (1H, d, *J* = 9.0 Hz, ArC<u>H</u>), 3.43 (2H, t, *J* = 8.5 Hz, C**2**-<u>H</u>$_2$), 2.67 (2H, t, *J* = 8.5 Hz, C**3**-<u>H</u>$_2$), 1.08 (9H, s, TBS (C<u>H</u>$_3$)$_3$), 0.31 (6H, s, TBS Si(C<u>H</u>$_3$)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.3 (<u>C</u>=O), 150.8 (Ar<u>C</u>), 133.0 (Ar<u>C</u>), 129.5 (Ar<u>C</u>), 128.6 (Ar<u>C</u>H), 127.9 (Ar<u>C</u>H), 126.5 (Ar<u>C</u>H), 123.4 (Ar<u>C</u>H), 123.1 (Ar<u>C</u>), 122.8 (Ar<u>C</u>H), 120.2 (Ar<u>C</u>H), 33.9 (C**1**), 25.8 (TBS (<u>C</u>H$_3$)$_3$), 21.0 (C**2**), 18.3 (TBS Si<u>C</u>(CH$_3$)$_3$), 3.9 (TBS Si(<u>C</u>H$_3$)$_2$); HRMS (ESI$^+$) Calculated for $C_{19}H_{26}NaO_3Si$: 353.1543. Found $[M+Na]^+$: 353.1551.

3-(2-(*tert*-Butyldimethylsilyloxy)naphthalen-1-yl)propan-1-ol (168)

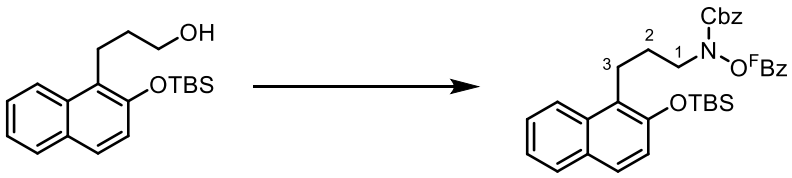


<u>General procedure F:</u> The preceding carboxylic acid **167** (1.65 g, 5.00 mmol), Et_3N (0.70 mL, 5.00 mmol), ethyl chloroformate (540 mg, 5.00 mmol) and $NaBH_4$ (470 mg, 12.5 mmol)

in THF (50 mL) and H_2O (20 mL) were employed. Purification by flash column chromatography (20% EtOAc:hexane) afforded **168** (1.19 g, 75%) as a colourless oil; R_f = 0.6 (33% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 3336 (m, br), 2953 (m), 2929 (m), 2882 (m), 2857 (m), 1622 (m), 1594 (m), 1465 (m), 1264 (m), 1241 (s), ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (1H, d, *J* = 8.0 Hz), 7.79 (1H, d, *J* = 8.5 Hz), 7.63 (1H, d, *J* = 8.5 Hz), 7.48 (1H, t, *J* = 8.0 Hz), 7.35 (1H, t, *J* = 7.0 Hz), 7.12 (1H, d, *J* = 9.0 Hz), 3.63 (2H, t, *J* = 6.0 Hz), 3.20 (2H, t, *J* = 6.5 Hz), 2.53 (1H, br s), 1.95 (2H, qn, *J* = 7.5 Hz), 1.10 (9H, s), 0.31 (6H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.6, 133.4, 129.9, 128.6, 127.4, 126.3, 124.7, 123.6, 123.5, 120.6, 62.2, 32.5, 26.0, 21.5, 18.5, -3.8.

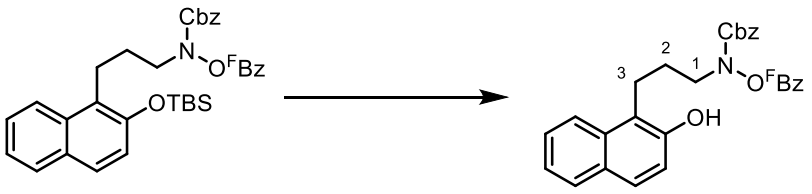
The spectroscopic properties were consistent with the data available in the literature.[91]

Benzyl(3-(2-((*tert*-butyldimethylsilyl)oxy)naphthalen-1-yl)propyl)((perfluorobenzoyl) oxy)carbamate



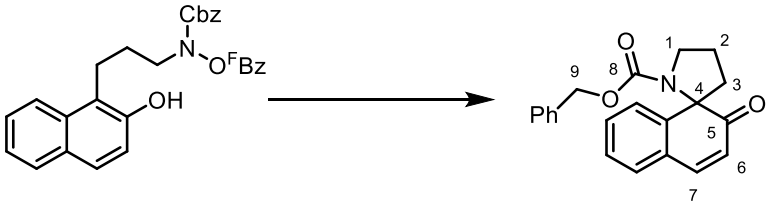
General procedure C: The preceding alcohol **168** (633 mg, 2.0 mmol), DIAD (0.82 mL, 4.2 mmol), PPh_3 (1.10 g, 4.2 mmol) and CbzNHO^{F}Bz (1.52 g, 4.2 mmol) in anhydrous PhMe:THF (5:1, 24 mL) were employed. Purification by flash column chromatography (10% EtOAc:hexane) afforded the title compound (194.2 mg, 15%) as a colourless, viscous oil; ν_{max} / cm^{-1} (*film*) 2931 (m), 2858 (m), 1782 (s), 1730 (s), 1498 (s), 1169 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (1H, d, *J* = 8.5 Hz, ArC<u>H</u>), 7.75 (1H, d, *J* = 8.0 Hz, ArC<u>H</u>), 7.60 (1H, d, *J* = 9.0 Hz, ArC<u>H</u>), 7.42 (1H, ddd, *J* = 8.5, 6.5, 1.5 Hz, ArC<u>H</u>), 7.37 – 7.26 (6H, m, ArC<u>H</u>), 7.06 (1H, d, *J* = 9.0 Hz, ArC<u>H</u>), 5.20 (s, 2H, Cbz, C<u>H_2</u>), 3.86 (2H, t, *J* = 7.5 Hz, C**1**-<u>H_2</u>), 3.21 – 2.93 (2H, m, C**3**-<u>H_2</u>), 1.98 (2H, app. qn, *J* = 7.5 Hz, C**2**-<u>H_2</u>), 1.01 (9H, s, SiC(C<u>H_3</u>)$_3$), 0.24 (6H, s, Si(C<u>H_3</u>)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6 (Cbz, <u>C</u>=O), 150.7 (Ar<u>C</u>), 135.3 (Ar<u>C</u>), 133.3 (Ar<u>C</u>), 129.6 (Ar<u>C</u>), 128.7 (Ar<u>C</u>H), 128.6 (Ar<u>C</u>H), 128.6 (Ar<u>C</u>H), 128.2 (Ar<u>C</u>H), 127.6 (Ar<u>C</u>H), 126.4 (Ar<u>C</u>H), 124.2 (Ar<u>C</u>), 123.4 (Ar<u>C</u>H), 123.2 (Ar<u>C</u>H), 120.4 (Ar<u>C</u>H), 68.9 (Cbz, C<u>H_2</u>), 51.5 (C**1**), 27.2 (C**2**), 25.9 (SiC(<u>C</u>H_3)$_3$), 22.8 (C**3**), 18.4 (Si<u>C</u>(CH_3)$_3$), -3.8 (Si(<u>C</u>H_3)$_2$). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* ^{19}F NMR (377 MHz, $CDCl_3$) δ -135.4 – -135.7 (2F, m), -144.8 – -146.6 (1F, m), -157.8 – -160.3 (2F, m). HRMS (ESI$^+$) Calculated for $C_{34}H_{35}F_5NO_5Si$: 660.2199. Found $[M+H]^+$: 660.2204.

Benzyl (3-(2-hydroxynaphthalen-1-yl)propyl)((perfluorobenzoyl)oxy)carbamate (169)



General procedure D: Benzyl (3-(2-((*tert*-butyldimethylsilyl)oxy)naphthalen-1-yl)propyl) ((perfluorobenzoyl)oxy)carbamate (279 mg, 0.41 mmol) and 1 M HCl (2.5 mL) in MeOH (10 mL) and THF (8 mL) were employed. Purification by flash column chromatography (20% EtOAc:Hex) afforded **169** (59 mg, 26%) as a colourless solid; m.p.: 129-131 ^{o}C (EtOAc:hexane); ν_{max} / cm^{-1} (*solid*) 3312 (br), 2966 (m), 1782 (s), 1698 (s), 1496 (s), 1278 (s), 1172 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (1H, d, *J* = 8.5 Hz, ArC<u>H</u>), 7.75 (1H, dd, *J* = 8.0, 1.5 Hz, ArC<u>H</u>), 7.61 (1H, d, *J* = 9.0 Hz, ArC<u>H</u>), 7.45 (1H, ddd, *J* = 8.5, 6.5, 1.5 Hz, ArC<u>H</u>), 7.38 – 7.27 (6H, m, ArC<u>H</u>), 7.05 (1H, d, *J* = 9.0 Hz, ArC<u>H</u>), 5.80 (1H, s, O<u>H</u>), 5.22 (2H, s, Cbz C<u>H</u>$_2$), 3.83 (2H, t, *J* = 6.5 Hz, C**1**-<u>H</u>$_2$), 3.16 (2H, t, *J* = 7.5 Hz, C**3**-<u>H</u>$_2$), 2.12 – 1.88 (2H, m, C**2**-<u>H</u>$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.1 (^{F}Bz <u>C</u>=O), 156.0 (Cbz <u>C</u>=O), 151.3 (Ar<u>C</u>), 135.1 (Ar<u>C</u>), 133.2 (Ar<u>C</u>), 129.5 (Ar<u>C</u>), 128.8 (Ar<u>C</u>H), 128.7 (Ar<u>C</u>H), 128.7 (Ar<u>C</u>H), 128.3 (Ar<u>C</u>H), 128.2 (Ar<u>C</u>H), 126.6 (Ar<u>C</u>H), 123.2 (Ar<u>C</u>H), 122.7 (Ar<u>C</u>H), 118.3 (Ar<u>C</u>H), 118.0 (Ar<u>C</u>), 69.2 (Cbz <u>C</u>H$_2$), 50.9 (C**1**), 26.7 (C**2**), 21.8 (C**3**). *The aromatic ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* HRMS (ESI$^+$) Calculated for $C_{28}H_{20}F_5NNaO_5$: 568.1154. Found [M+Na]$^+$: 568.1152.

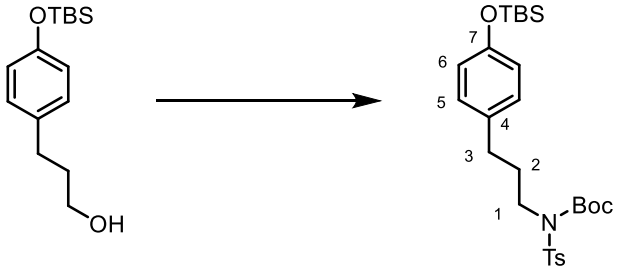
Benzyl 2-oxo-2*H*-spiro[naphthalene-1,2'-pyrrolidine]-1'-carboxylate (170)



A flame-dried resealable tube, fitter with a magnetic stirrer, was charged with *N*-acyloxysulfonamide **169** (40.9 mg, 0.075 mmol), K_3PO_4 (31.8 mg, 0.150 mmol), $Pd_2(dba)_3$ (3.43 mg, 3.75 µmol) and 5-nitro-1,10-phenanthroline (3.37 mg, 0.015 mmol). The tube was fitted with a rubber septum and purged with nitrogen before *n*-BuCN (1.5 mL) was added *via* syringe. The tube was sealed and heated at 120 ^{o}C for 66 hours. The reaction was cooled to room temperature and purified by flash column chromatography (20% EtOAc:hexane) to afford **170** (5.6 mg, 22%) as a colourless oil. *This compound exists as an approximately 3:2*

mixture of rotamers A and B; ν_{max} / cm^{-1} (*film*) 2953 (m), 1700 (s), 1671 (s), 1404 (s), 1350 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (0.4H, d, *J* = 10.0 Hz, *B*: C**7**-H), 7.38 – 7.24 (7H, m, *A*: C**7**-H, *A* and *B*: ArCH), 7.17 – 7.09 (0.6H, m, *A*: ArCH), 7.07 – 7.03 (1H, m, *A* and *B*: ArCH), 6.80 (1H, d, *J* = 7.0 Hz, *A* and *B*: ArCH), 6.22 (0.4H, d, *J* = 10.0 Hz, *B*: C**6**-H), 6.07 (0.6H, d, *J* = 10.0 Hz, *A*: C**6**-H), 5.07 (0.4H, d, *J* = 12.5 Hz, *B*: C**9**-H), 5.03 (0.4H, d, *J* = 12.5 Hz, *B*: C**9**-H'), 4.91 (0.6H, d, *J* = 12.5 Hz, *A*: C**9**-H), 4.68 (0.6H, d, *J* = 12.5 Hz, *A*: C**9**-H'), 4.07 – 3.97 (1H, m, *A* and *B*: C**1**-H), 3.92 – 3.82 (1H, m, *A* and *B*: C**1**-H'), 2.40 – 2.29 (1H, m, *A* and *B*: C**3**-H), 2.20 – 2.07 (1H, m, *A* and *B*: C**2**-H), 2.05 – 1.89 (2H, m, *A* and *B*: C**2**-H' and C**3**-H'); ^{13}C NMR (101 MHz, $CDCl_3$) δ ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.4 (*B*: C**5**), 200.3 (*A*: C**5**), 154.3 (*B*: C**8**), 154.0 (*A*: C**8**), 146.6 (*A*: ArC), 145.8 (*B*: ArC), 145.3 (*B*: C**7**), 145.0 (*A*: C**7**), 136.8 (ArC), 136.2 (ArC), 130.6 (ArCH), 130.5 (ArCH), 129.7 (ArCH), 129.6 (ArCH), 129.5 (*B*: ArC), 129.3 (*A*: ArC), 128.6 (ArCH), 128.0 (ArCH), 127.9 (ArCH), 127.6 (ArCH), 127.5 (ArCH), 127.4 (ArCH), 127.2 (ArCH), 125.0 (ArCH), 124.7 (ArCH), 124.4 (*B*: C**6**), 124.1 (*A*: C**6**), 72.3 (*B*: C**4**), 72.0 (*A*: C**4**), 67.2 (*B*: C**9**), 66.9 (*A*: C**9**), 49.7 (*A* or *B*: C**1**), 49.2 (*A* or *B*: C**1**), 42.8 (*A* or *B*: C**3**), 41.8 (*A* or *B*: C**3**), 22.7 (*A* or *B*: C**2**), 21.7 (*A* or *B*: C**2**); HRMS (ESI^+) Calculated for $C_{21}H_{19}NNaO_3$: 356.1257. Found $[M+Na]^+$: 356.1241.

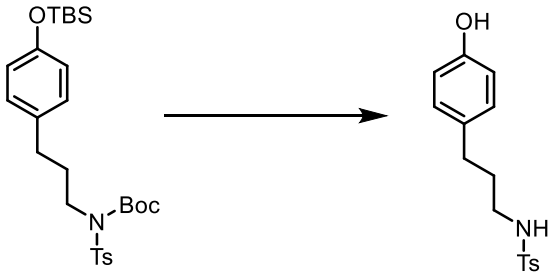
***tert*-Butyl (3-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)propyl)(tosyl)carbamate (172)**



General procedure C: Alcohol **146** (532 mg, 2.00 mmol), DIAD (0.63 mL, 4.0 mmol), TsNHBoc (813 mg, 3.00 mmol) and PPh_3 (1.05 g, 4.00 mmol) in anhydrous PhMe:THF (5:1, 24 mL) were employed. The reaction mixture was stirred at room temperature overnight until completion by TLC analysis. The reaction was concentrated *in vacuo* and purified by flash column chromatography (10% EtOAc:hexane) to afford **172** (920 mg, 89%) as a colourless solid; m.p.: 106-107 °C (EtOAc:hexane); ν_{max} / cm^{-1} (*solid*) 2981 (m), 2960 (m), 2934 (m), 2901 (m), 2862 (m), 1715 (s), 1509 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (2H, d, *J* = 8.5 Hz, Ts ArCH), 7.29 (2H, d, *J* = 8.5 Hz, Ts ArCH), 7.06 (2H, d, *J* = 8.5 Hz, C**5**-H), 6.76 (2H, d, *J* = 8.5 Hz, C**6**-H), 3.86 – 3.82 (2H, m, C**1**-H_2), 2.63 – 2.58 (2H, m, C**3**-H_2), 2.43 (3H, s, Ts CH_3), 2.05 (2H, app. qn, *J* = 8.0 Hz, C**2**-H_2), 1.32 (9H, s, Boc (CH_3)$_3$), 0.98 (9H, s, TBS

($C\underline{H}_3)_3$), 0.18 (6H, s, TBS Si($C\underline{H}_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.8 (Boc $\underline{C}$=O), 150.9 (C**7**), 144.0 (Ts Ar$\underline{C}$), 137.5 (Ts Ar$\underline{C}$), 133.8 (C**4**), 129.2 (2 × Ts Ar$\underline{C}$H), 129.1 (2 × Ts Ar$\underline{C}$H), 127.8 (C**5**), 119.9 (C**6**), 84.0 (Boc $\underline{C}(CH_3)_3$), 46.9 (C**1**), 32.2 (C**3**), 31.9 (C**2**), 27.9 (Boc ($\underline{C}H_3)_3$), 25.7 (TBS ($\underline{C}H_3)_3$), 21.6 (Ts $\underline{C}H_3$), 18.2 (TBS $\underline{C}(CH_3)_3$), -4.4 (TBS Si($\underline{C}H_3)_2$). HRMS (ESI^+) Calculated for $C_{27}H_{41}NNaO_5SSi$: 542.2367. Found $[M+Na]^+$: 542.2374.

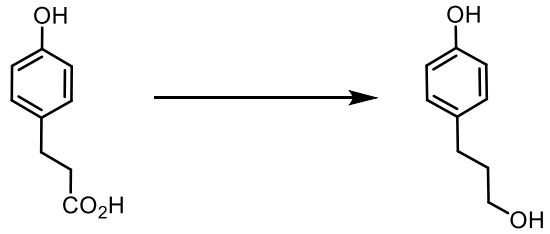
_N_-(3-(4-Hydroxyphenyl)propyl)-4-methylbenzenesulfonamide (150)



To a solution of the preceding *N*-tosylcarbamate **172** (620 mg, 1.2 mmol) in EtOAc (60 mL) at 0 ^oC was added concentrated HCl (6 mL). The reaction was stirred at room temperature until completion by TLC analysis (20 hours). To the crude reaction mixture was added Et_2O (30 mL) and the solution was washed with saturated aqueous $NaHCO_3$ (20 mL) and water (10 mL). The organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (33% EtOAc:hexane) afforded **150** (300 mg, 83%) as a colourless solid; ν_{max} / cm^{-1} (*solid*) 3317 (m, br), 3269 (m, br), 2976 (m), 2937 (m), 1514 (m), 1140 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (2H, d, *J* = 8.5 Hz), 7.30 (2H, d, *J* = 8.0 Hz), 6.94 (2H, d, *J* = 8.5 Hz), 6.72 (2H, d, *J* = 8.5 Hz), 4.73 (1H, s), 4.36 (1H, t, *J* = 6.0 Hz), 2.94 (2H, q, *J* = 6.5 Hz), 2.52 (2H, t, *J* = 7.5 Hz), 2.42 (3H, s), 1.73 (2H, app. qn, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 153.8, 143.4, 136.9, 132.9, 129.7, 129.4, 127.0, 115.2, 42.6, 31.8, 31.3, 21.5.

The spectroscopic properties were consistent with the data available in the literature.[95]

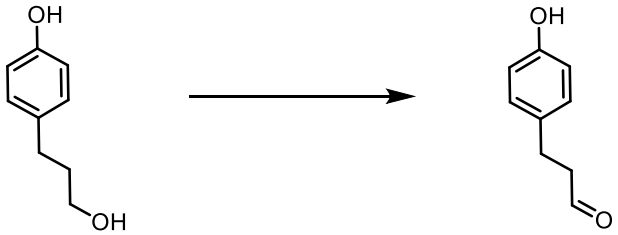
4-(3-Hydroxypropyl)phenol (173)



General procedure B: Carboxylic acid **145** (3.32 g, 20 mmol) and 1.0 equivalent of $LiAlH_4$ (2M in THF, 10 mL, 20 mmol) in anhydrous Et_2O (100 mL) were employed. Purification by flash column chromatography (50% EtOAc:hexane) afforded **173** (784 mg, 26%) as a colourless solid; m.p.: 49-51 ^oC (EtOAc:hexane) [lit: 52-53 ^oC[288]]; ^1H NMR (400 MHz, $CDCl_3$) δ 7.05 (2H, d, *J* = 8.5 Hz), 6.75 (2H, d, *J* = 8.5 Hz), 5.20 (1H, br s), 3.68 (2H, t, *J* = 6.5 Hz), 2.64 (2H, t, *J* = 7.5 Hz), 1.91 – 1.82 (2H, m), 1.45 (1H, br s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.0, 133.9, 129.6, 115.4, 62.5, 34.5, 31.3.

The spectroscopic properties were consistent with the data available in the literature.[289]

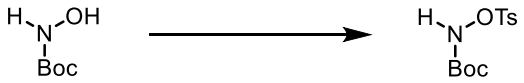
3-(4-Hydroxyphenyl)propanal (158)



A flame-dried resealable tube, fitted with a magnetic stirrer, was charged with alcohol **173** (22.8 mg, 0.15 mmol), $Pd(OAc)_2$ (3.4 mg, 10 mol%) and 4,5-diazafluoren-9-one (5.5 mg, 20 mol%). The tube was fitted with a rubber septum and purged with nitrogen before 1,4-dioxane (1.5 mL) was added by syringe. The reaction tube was fitted with a balloon of oxygen and heated at 80 ^oC for 18 hours. The reaction mixture was filtered through Celite® and washed with EtOAc. The yield of **158** (41%) was determined by ^1H NMR analysis using 1,2-dinitrobenzene as internal standard; ^1H NMR (400 MHz, $CDCl_3$) δ 7.06 (2H, d, *J* = 8.5 Hz), 6.76 (2H, d, *J* = 8.5 Hz), 2.89 (2H, t, *J* = 7.5 Hz), 2.77 – 2.72 (2H, m).

The spectroscopic properties were consistent with the data available in the literature.[290]

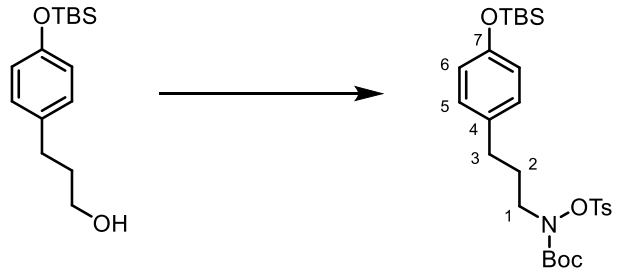
***tert*-Butyl (tosyloxy)carbamate**



The title compound was prepared according to a literature procedure.[291]

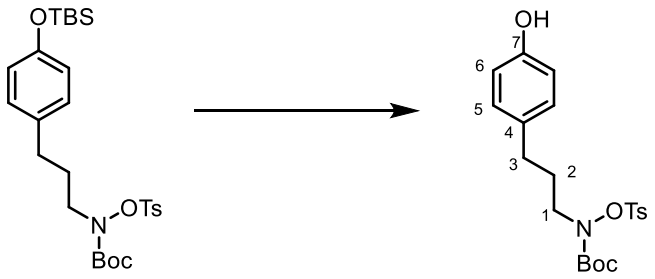
The spectroscopic properties were consistent with the data available in the literature.[291]

***tert*-Butyl (3-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)propyl)(tosyloxy)carbamate (176)**



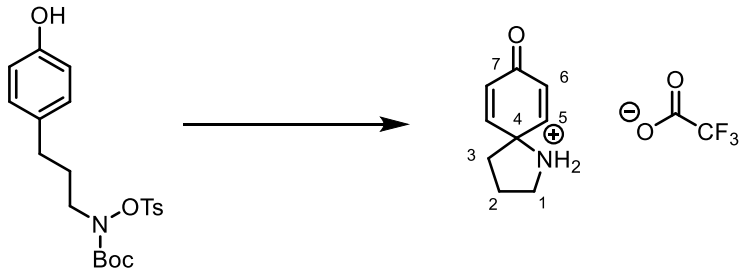
General procedure G: Alcohol **146** (0.79 g, 3.00 mmol), PPh_3 (0.94 g, 3.60 mmol), DIAD (0.71 mL, 3.60 mmol) and BocNHOTs (1.03 g, 3.60 mmol) in THF (12 mL) were employed. Purification by flash column chromatography (10% EtOAc:hexane) afforded **176** (1.49 g, 93%) as a pale yellow oil; R_f = 0.5 (20% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 2955 (m), 2930 (m), 2858 (m), 1753 (m), 1720 (s), 1509 (s), 1382 (s), 1368 (s), 1251 (s), 1178 (s), 1154 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.33 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.00 (2H, d, *J* = 8.5 Hz, C**5**-<u>H</u>), 6.74 (2H, d, *J* = 8.5 Hz, C**6**-<u>H</u>), 3.60 (2H, br s, C**1**-<u>H_2</u>), 2.52 (2H, t, *J* = 8.0 Hz, C**3**-<u>H_2</u>), 2.45 (3H, s, Ts C<u>H_3</u>), 1.95 – 1.85 (2H, m, C**2**-<u>H_2</u>), 1.22 (9H, s, Boc (C<u>H_3</u>)$_3$), 0.98 (9H, s, TBS (C<u>H_3</u>)$_3$), 0.18 (6H, s, TBS (C<u>H_3</u>)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.5 (Boc <u>C</u>=O), 153.8 (C**7**), 145.6 (Ts Ar<u>C</u>), 133.7 (C**4**), 131.3 (Ts Ar<u>C</u>), 129.6 (2 × Ts Ar<u>C</u>H), 129.5 (2 × Ts Ar<u>C</u>H), 129.1 (C**5**), 120.0 (C**6**), 83.2 (Boc <u>C</u>(CH_3)$_3$), 52.6 (C**1**), 32.0 (C**3**), 27.6 (Boc (<u>C</u>H_3)$_3$), 27.5 (C**2**), 25.7 (TBS (<u>C</u>H_3)$_3$), 21.7 (Ts <u>C</u>H_3), 18.2 (TBS Si<u>C</u>(CH_3)$_3$), -4.4 (TBS Si(<u>C</u>H_3)$_2$); HRMS (ESI^+) Calculated for $C_{27}H_{41}NNaO_6SSi$: 558.2316. Found $[M+Na]^+$: 558.2313.

***tert*-Butyl (3-(4-hydroxyphenyl)propyl)(tosyloxy)carbamate (177)**



General procedure H: The preceding *N*-tosyloxycarbamate **176** (0.69 g, 1.28 mmol) and 1:1 TBAF:HOAc solution (0.1 M in THF, 1.28 mmol) in THF (20 mL) were employed. Purification by flash column chromatography (20% EtOAc:hexane) afforded **177** (0.35 g, 60%) as a colourless solid; m.p.: 63-65 ^{o}C (EtOAc:hexane); R_f = 0.2 (20% EtOAc:hexane); ν_{max} / cm^{-1} (*solid*) 3426 (m, br), 2982 (m), 2934 (m), 1721 (s), 1515 (s), 1369 (s), 1191 (s), 1177 (s), 1152 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.32 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 6.98 (2H, d, *J* = 8.5 Hz, C**5**-<u>H</u>), 6.75 (2H, d, *J* = 8.5 Hz, C**6**-<u>H</u>), 5.75 (1H, br s, O<u>H</u>), 3.60 (2H, br s, C**1**-<u>H</u>$_2$), 2.50 (2H, t, *J* = 8.0 Hz, C**3**-<u>H</u>$_2$), 2.44 (3H, s, Ts C<u>H</u>$_3$), 1.97 – 1.80 (2H, m, C**2**-<u>H</u>$_2$), 1.23 (9H, s, Boc (C<u>H</u>$_3$)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.7 (Boc <u>C</u>=O), 154.1 (C**7**), 145.9 (Ts Ar<u>C</u>), 132.8 (C**4**), 131.0 (Ts Ar<u>C</u>), 129.6 (2 × Ts Ar<u>C</u>H), 129.5 (2 × Ts Ar<u>C</u>H), 129.3 (C**5**), 115.3 (C**6**), 83.6 (Boc <u>C</u>(CH$_3$)$_3$), 52.6 (C**1**), 31.9 (C**3**), 27.7 (C**2**), 27.6 (Boc (<u>C</u>H$_3$)$_3$), 21.7 (Ts, <u>C</u>H$_3$); HRMS (ESI$^+$) Calculated for $C_{21}H_{27}NNaO_6S$: 444.1451. Found [M+Na]$^+$: 444.1434.

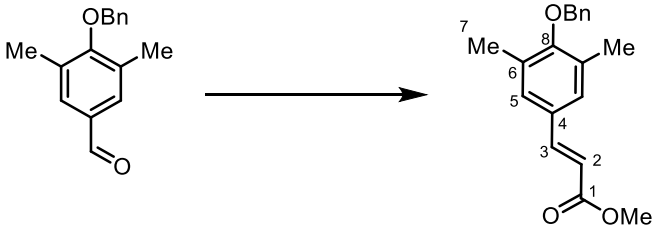
1-Azaspiro[4.5]deca-6,9-dien-8-one trifluoroacetate (178)



General procedure I: The preceding *N*-tosyloxycarbamate **177** (60.7 mg, 0.14 mmol) and TFA (22 μL, 0.28 mmol) in TFE (1.4 mL) were stirred at room temperature for 24 hours. Purification of the product by flash column chromatography (EtOAc) afforded **178** (29.0 mg, 77%) as a yellow solid; m.p.: 100-102 ^{o}C (EtOAc:hexane); R_f = 0.1 (5% MeOH:CH_2Cl_2); ν_{max} / cm^{-1} (*solid*) 1651 (s), 1633 (s), 1426 (m), 1400 (m), 1192 (s), 1175 (s), 1130 (s); ^{1}H NMR (400 MHz, CD_3OD) δ 7.11 (2H, d, *J* = 10.5 Hz, C**5**-<u>H</u>), 6.43 (2H, d, *J* = 10.5 Hz, C**6**-<u>H</u>), 3.64

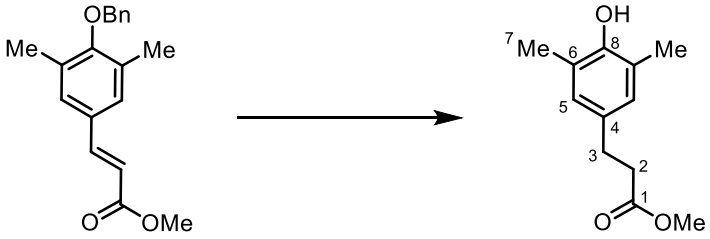
(2H, t, *J* = 7.5 Hz, C**1**-H$_2$), 2.42 – 2.34 (2H, m, C**2**-H$_2$), 2.30 – 2.25 (2H, m, C**3**-H$_2$). *The signals corresponding to the NH$_2$ were not observed.* ^{13}C NMR (101 MHz, CD_3OD) δ 185.3 (C**7**), 144.5 (C**5**), 131.7 (C**6**), 64.5 (C**4**), 46.6 (C**1**), 37.8 (C**3**), 24.8 (C**2**). *The signals corresponding to the trifluoroacetate group could not be resolved due to their weak intensity*. HRMS (ESI$^+$) Calculated for $C_9H_{12}NO$: 150.0913. Found $[M+H]^+$: 150.0908.

Methyl (*E*)-3-(4-(benzyloxy)-3,5-dimethylphenyl)acrylate (180)



General procedure J: 4-(Benzyloxy)-3,5-dimethylbenzaldehyde **179** (2.40 g, 10.0 mmol) and methyl 2-(triphenyl-phosphaneylidene) acetate (5.00 g, 15.0 mmol) in CH_2Cl_2 (15 mL) were employed. Purification by flash column chromatography (gradient, eluent: 10 – 20% EtOAc:hexane) afforded **180** (2.85 g, 96%) as a colourless oil; R_f = 0.6 (20% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 1713 (s), 1632 (m), 1434 (m), 1265 (s), 1143 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (1H, d, *J* = 16.0 Hz, C**3**-H), 7.50 – 7.46 (2H, m, ArCH), 7.46 – 7.33 (3H, m, ArCH), 7.23 (2H, s, C**5**-H), 6.36 (1H, d, *J* = 16.0 Hz, C**2**-H), 4.83 (2H, s, OCH$_2$), 3.81 (3H, s, OCH$_3$), 2.32 (6H, s, C**7**-H$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.7 (C**1**), 157.9 (C**8**), 144.8 (C**3**), 137.4 (ArC), 131.9 (C**6**), 130.2 (C**4**), 129.0 (C**5**), 128.7 (2 × ArCH), 128.2 (ArCH), 127.9 (2 × ArCH), 116.6 (C**2**), 74.2 (OCH$_2$), 51.7 (OCH$_3$), 16.6 (C**7**); HRMS (ESI$^+$) Calculated for $C_{19}H_{20}NaO_3$: 319.1305. Found $[M+Na]^+$: 319.1311.

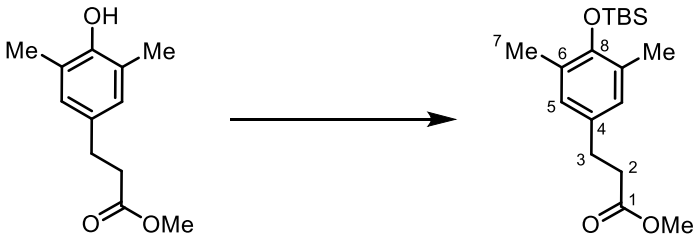
Methyl 3-(4-hydroxy-3,5-dimethylphenyl)propanoate



General procedure E: The preceding α,β-unsaturated ester **180** (2.37 g, 8.00 mmol) and 10 wt.% Pd/C (10 mol%) in MeOH (50 mL) were employed to afford the title compound (1.66 g, 99%) as a colourless solid, which was used without further purification; m.p.: 66-68 ^{o}C (EtOAc:hexane); R_f = 0.4 (20 % EtOAc:hexane); ν_{max} / cm^{-1} (*solid*) 3492 (br), 2952 (m), 2928

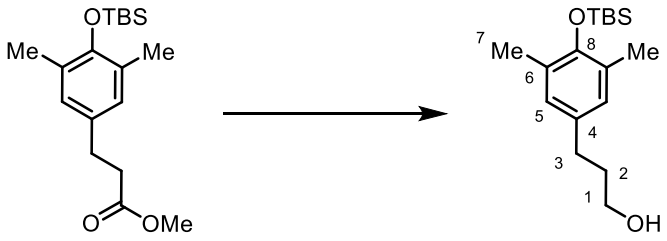
(m), 1723 (s), 1277 (s), 1174 (s), 1151 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 (2H, s, C**5**-H), 4.55 (1H, br s, OH), 3.67 (3H, s, OCH_3), 2.82 (2H, t, *J* = 8.0 Hz, C**3**-H_2), 2.58 (2H, t, *J* = 8.0 Hz, C**2**-H_2), 2.22 (6H, s, C**7**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$) 173.7 (C**1**), 150.7 (C**8**), 132.2 (C**4**), 128.5 (ArCH), 123.2 (ArCH), 51.7 (OCH_3), 36.3 (C**2**), 30.3 (C**3**), 16.0 (C**7**); HRMS (ESI^+) Calculated for $C_{12}H_{16}NaO_3$: 231.0992. Found $[M+Na]^+$: 231.1002.

Methyl 3-(4-((*tert*-butyldimethylsilyl)oxy)-3,5-dimethylphenyl)propanoate



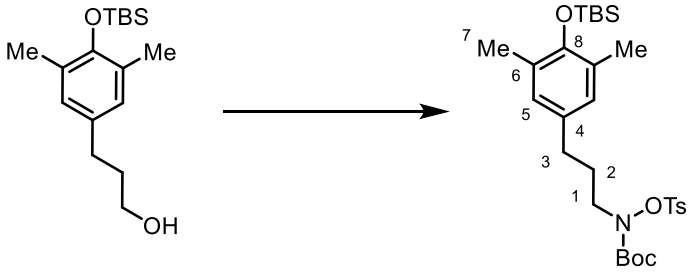
To a solution of methyl 3-(4-hydroxy-3,5-dimethylphenyl)propanoate (1.33 g, 6.00 mmol) in CH_2Cl_2 (10 mL) and DMF (12 mL) was added *tert*-butyldimethylsilyl chloride (1.8 g, 12.0 mmol) and imidazole (820 mg, 12.0 mmol) at 0 °C. The reaction was stirred at room temperature overnight and quenched with H_2O (50 mL) and the organic phase extracted with CH_2Cl_2 (3 × 15 mL), washed with brine (15 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (10% EtOAc:hexane) afforded the title compound (1.22 g, 63%) as a colourless oil; R_f = 0.6 (25% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 2953 (m), 2930 (m), 1740 (s), 1484 (m), 1473 (m), 1253 (s), 1228 (s), 1153 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.79 (2H, s, C**5**-H), 3.67 (3H, s, OCH_3), 2.81 (2H, t, *J* = 8.0 Hz, C**3**-H_2), 2.58 (2H, t, *J* = 8.0 Hz, C**2**-H_2), 2.18 (6H, s, C**7**-H_3), 1.03 (9H, s, TBS (CH_3)$_3$), 0.18 (6H, s, TBS (CH_3)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.7 (C**1**), 150.6 (C**8**), 133.1 (C**4**), 128.6 (C**5**), 128.6 (C**6**), 51.7 (OCH_3), 36.2 (C**2**), 30.3 (C**3**), 26.3 (TBS (CH_3)$_3$), 18.9 (TBS C(CH_3)$_3$), 18.0 (C**7**), -2.8 (TBS Si(CH_3)$_2$); HRMS (ESI^+) Calculated for $C_{18}H_{30}NaO_3Si$: 345.1856. Found $[M+Na]^+$: 345.1870.

3-(4-((*tert*-Butyldimethylsilyl)oxy)-3,5-dimethylphenyl)propan-1-ol (181)



General procedure B: Methyl 3-(4-((*tert*-butyldimethylsilyl)oxy)-3,5-dimethylphenyl) propanoate (960 mg, 3.0 mmol) and 2.0 equivalents of $LiAlH_4$ (1 M in THF) in anhydrous Et_2O were employed. The crude product was filtered through a plug of silica and washed with EtOAc to afford **181** (690 mg, 80%) as a pale yellow oil; R_f = 0.2 (25% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 3345 (br m), 2929 (m), 2858 (m), 1483 (s), 1472 (s), 1252 (s), 1227 (s), 1152 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.79 (2H, s), 3.66 (2H, t, *J* = 6.5 Hz), 2.57 (2H, t, *J* = 7.5 Hz), 2.18 (6H, s), 1.89 – 1.81 (2H, m), 1.29 (1H, br s), 1.03 (9H, s), 0.18 (6H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.1, 134.2, 128.6, 128.3, 62.5, 34.3, 31.2, 26.1, 18.7, 17.8, -3.0.
The *spectroscopic properties were consistent with the data available in the literature.*[292]

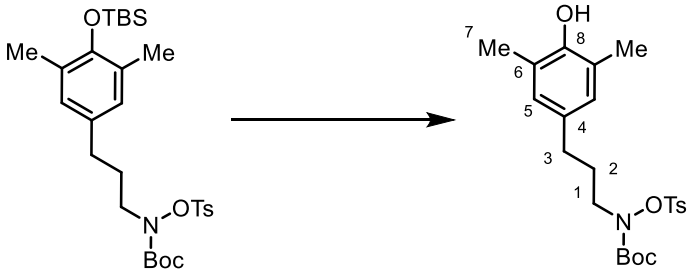
***tert*-Butyl (3-(4-((*tert*-butyldimethylsilyl)oxy)-3,5-dimethylphenyl)propyl)(tosyloxy) carbamate**



General procedure G: The preceding alcohol **181** (530 mg, 1.80 mmol), PPh_3 (580 mg, 2.20 mmol), DIAD (0.43 mL, 2.20 mmol) and BocNHOTs (630 mg, 2.20 mmol) in anhydrous THF (8 mL) were employed. Purification by flash column chromatography (10% EtOAc:hexane) afforded the title compound (880 mg, 87%) as a colourless oil; R_f = 0.55 (20% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 2955 (m), 2930 (m), 1722 (s), 1473 (m), 1483 (m), 1383 (s), 1369 (s), 1230 (s), 1191 (s), 1179 (s), 1154 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.32 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 6.75 (2H, s, C**5**-<u>H</u>), 3.61 (2H, br s, C**1**-<u>H_2</u>), 2.46 – 2.42 (5H, m, overlapping C**3**-<u>H_2</u> and Ts C<u>H_3</u>), 2.18 (6H, s, C**7**-<u>H_3</u>) 1.93 – 1.81 (2H, m, C**2**-<u>H_2</u>), 1.21 (9H, s, Boc (C<u>H_3</u>)$_3$), 1.03 (9H, s, TBS (C<u>H_3</u>)$_3$), 0.17 (6H, s, TBS Si(C<u>H_3</u>)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6 (Boc <u>C</u>=O), 150.4 (C**8**), 145.7 (Ts Ar<u>C</u>), 133.7 (C**4**), 131.4 (Ts

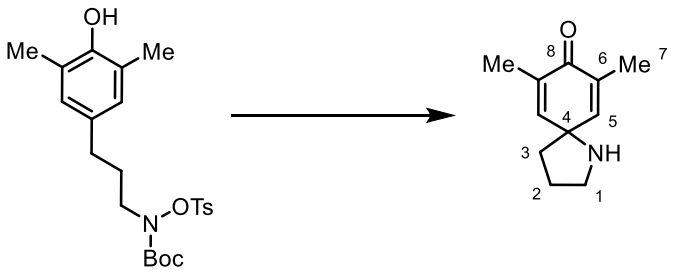
Ar<u>C</u>), 129.8 (2 × Ts Ar<u>C</u>H), 129.6 (2 × Ts Ar<u>C</u>H), 128.7 (C**5**), 128.5 (C**6**), 83.2 (Boc <u>C</u>$(CH_3)_3$), 52.9 (C**1**), 32.1 (C**3**), 27.8 (C**2**), 27.7 (Boc $(\underline{C}H_3)_3$), 26.3 (TBS $(C\underline{H}_3)_3$), 21.9 (Ts <u>C</u>H_3), 18.9 (TBS <u>C</u>$(CH_3)_3$), 18.0 (C**7**), -2.8 (TBS $(\underline{C}H_3)_2$); HRMS (ESI^+) Calculated for $C_{29}H_{45}NNaO_6SSi$: 586.2629. Found $[M+Na]^+$: 586.2648.

***tert*-Butyl (3-(4-hydroxy-3,5-dimethylphenyl)propyl)(tosyloxy)carbamate (182)**

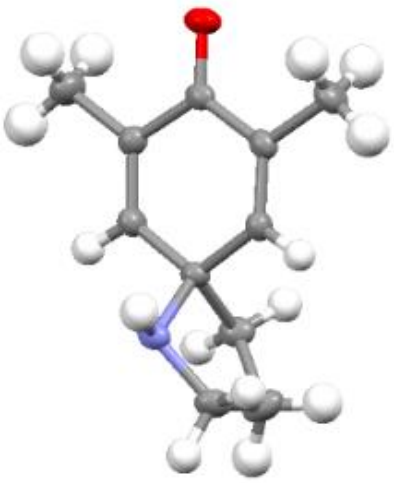


<u>General procedure H:</u> *tert*-Butyl (3-(4-((*tert*-butyldimethylsilyl)oxy)-3,5-dimethylphenyl) propyl)(tosyloxy)carbamate (450 mg, 0.80 mmol) and 1:1 TBAF:HOAc solution (0.1 M in THF, 0.88 mmol) in THF (16 mL) were employed. Purification by flash column chromatography (gradient, eluent: 20 – 33% EtOAc:hexane) afforded **182** (310 mg, 87%) as a colourless, viscous oil; R_f = 0.3 (20% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 3530 (br m), 2979 (m), 2930 (m), 1721 (s), 1597 (m), 1489 (m), 1370 (s), 1192 (s), 1177 (s), 1152 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.32 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 6.77 (2H, s, C**5**-<u>H</u>), 4.49 (1H, s, O<u>H</u>), 3.62 (2H, br s, C**1**-$\underline{H}_2$), 2.44 (5H, m, overlapping C**3**-$\underline{H}_2$ and Ts C$\underline{H}_3$), 2.21 (6H, s, C**7**-$\underline{H}_3$), 1.93 – 1.85 (2H, m, C**2**-$\underline{H}_2$), 1.20 (9H, s, Boc $(C\underline{H}_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6 (Boc <u>C</u>=O), 150.5 (C**8**), 145.8 (Ts Ar<u>C</u>), 132.8 (C**4**), 131.4 (Ts Ar<u>C</u>), 129.8 (2 × Ts Ar<u>C</u>H), 129.6 (2 × Ts Ar<u>C</u>H), 128.5 (C**5**), 123.0 (C**6**), 83.3 (Boc <u>C</u>$(CH_3)_3$), 52.8 (C**1**), 32.1 (C**3**), 27.9 (C**2**), 27.7 (Boc $(\underline{C}H_3)_3$), 21.8 (Ts <u>C</u>H_3), 16.0 (C**7**); HRMS (ESI^+) Calculated for $C_{23}H_{31}NNaO_6S$: 472.1764. Found $[M+Na]^+$: 472.1767.

7,9-Dimethyl-1-azaspiro[4.5]deca-6,9-dien-8-one (183)

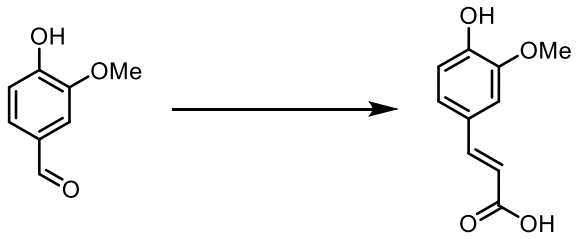


General procedure I: The preceding *N*-tosyloxycarbamate **182** (89.8 mg, 0.20 mmol) and TFA (31.0 μL, 0.40 mmol) in TFE (2 mL) were employed. After stirring at room temperature for 22 hours, purification by flash column chromatography (EtOAc) afforded **183** (30.0 mg, 85%) as a pale yellow/orange solid; m.p.: 110-113 ^{o}C (EtOAc:hexane); R_f = 0.1 (EtOAc); ν_{max} / cm^{-1} (*film*) 3318 (m), 2970 (m), 2946 (m), 2917 (m), 2882 (m), 1664 (s), 1623 (s), 1369 (m), 1222 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.60 (2H, s, C**5**-H), 3.19 (2H, t, *J* = 7.0 Hz, C**1**-H_2), 2.04 – 1.96 (2H, m, C**2**-H_2), 1.87 – 1.84 (9H, m, overlapping C**3**-H_2, C**7**-H_3 and NH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 187.2 (C**8**), 147.7 (C**5**), 132.7 (C**6**), 60.4 (C**4**), 46.1 (C**1**), 36.7 (C**3**), 25.5 (C**2**), 16.0 (C**7**); HRMS (ESI$^+$) Calculated for $C_{11}H_{16}NO$: 178.1226. Found $[M+H]^+$: 178.1228.



*X-ray crystal structure of **183**.*

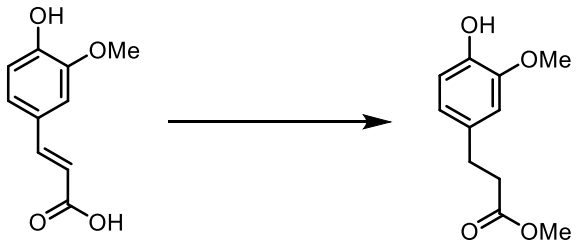
(*E*)-3-(4-Hydroxy-3-methoxyphenyl)acrylic acid (184)



Vanillin (3.04 g, 20.0 mmol) and malonic acid (2.30 g, 22.0 mmol) were added to a solution of aniline (0.22 mL, 2.36 mmol) and pyridine (2.43 mL, 30.0 mmol) in toluene (5 mL). The solution was stirred at reflux for 2 hours. The mixture was cooled to room temperature and neutralised with an aqueous 25% solution of K_2CO_3 (12 mL) followed by careful addition of concentrated HCl (until pH = 3). The resulting precipitate was filtered and washed with ice cold H_2O (10 mL) to afford **184** (3.0 g, 77%) as a yellow solid which was used without further purification; R_f = 0.5 (33% EtOAc:hexane); ^{1}H NMR (440 MHz, CD_3OD) δ 7.60 (1H, d, *J* = 16.0 Hz), 7.18 (1H, d, *J* = 2.0 Hz), 7.07 (1H, dd, *J* = 8.0, 2.0 Hz), 6.81 (1H, d, *J* = 8.0 Hz), 6.31 (1H, d, *J* = 16.0 Hz), 3.90 (3H, s); ^{13}C NMR (101 MHz, CD_3OD) δ 171.0, 150.5, 149.4, 146.9, 127.8, 123.9, 116.5, 115.9, 111.7, 56.4.

The spectroscopic properties were consistent with the data available in the literature.[293]

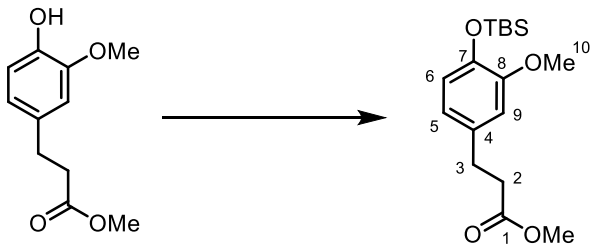
Methyl 3-(4-hydroxy-3-methoxyphenyl)propanoate



General procedure E: The preceding carboxylic acid **184** (1.94 g, 10.0 mmol) and 10 wt.% Pd/C (5 mol%) in 5:1 EtOAc:MeOH (60 mL) were employed. Purification by flash column chromatography (50% EtOAc:hexane) afforded the title compound (1.66 g, 80 %) as a yellow oil; R_f = 0.4 (33% EtOAc:hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (1H, d, *J* = 8.0 Hz), 6.72 – 6.66 (2H, m), 5.57 (1H, s), 3.86 (3H, s), 3.67 (3H, s), 2.88 (2H, t, *J* = 8.0 Hz), 2.60 (2H, t, *J* = 8.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.5, 146.4, 144.1, 132.5, 120.9, 114.5, 111.0, 55.9, 51.7, 36.2, 30.7.

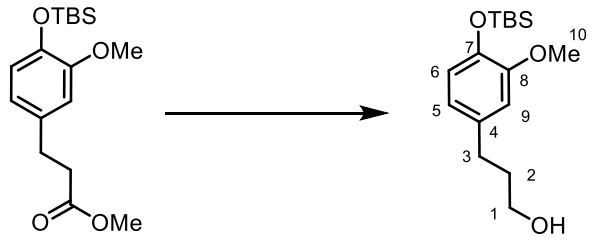
The spectroscopic properties were consistent with the data available in the literature.[294]

Methyl 3-(4-((*tert*-butyldimethylsilyl)oxy)-3-methoxyphenyl)propanoate



Methyl 3-(4-hydroxy-3-methoxyphenyl)propanoate (1.55 g, 7.40 mmol), *tert*-butyl dimethyl silyl chloride (1.34 g, 8.90 mmol) and imidazole (650 mg, 9.60 mmol) in 2.5:1 CH_2Cl_2:DMF (35 mL) were stirred at room temperature overnight and monitored by TLC. Upon completion, the reaction was quenched by addition of H_2O (50 mL), extracted with CH_2Cl_2 (3 × 20 mL), washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (gradient, eluent: 20 – 33% EtOAc:hexane) afforded the title compound (1.85 g, 77%) as a pale yellow oil; R_f = 0.7 (33% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 2952 (m), 2930 (m), 2857 (m), 1738 (s), 1512 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74 (1H, d, *J* = 8.0 Hz, C**6**-H), 6.67 (1H, d, *J* = 2.0 Hz, C**9**-H), 6.62 (1H, dd, *J* = 8.0 Hz, 2.0 Hz, C**5**-H), 3.77 (3H, s, C**10**-H_3), 3.65 (3H, s, CO_2CH_3), 2.87 (2H, t, *J* = 7.5 Hz, C**3**-H_2), 2.59 (2H, t, *J* = 7.5 Hz, C**2**-H_2), 0.98 (9H, s, TBS (CH_3)$_3$), 0.13 (6H, s, TBS Si(CH_3)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.5 (C**1**), 150.9 (C**8**), 143.5 (C**7**), 134.1 (C**4**), 120.9 (C**6**), 120.4 (C**5**) 112.5 (C**9**), 55.5 (C**10**), 51.6 (CO_2CH_3), 36.1 (C**2**), 30.8 (C**3**), 25.8 (TBS (CH_3)$_3$), 18.5 (TBS SiC(CH_3)$_3$), -4.6 (TBS Si(CH_3)$_2$). HRMS (ESI^+) Calculated for $C_{17}H_{28}NaO_4Si$: 347.1649. Found $[M+Na]^+$: 347.1661.

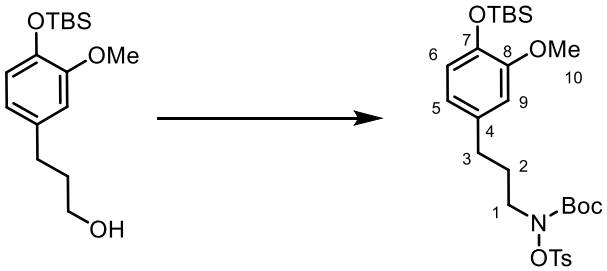
3-(4-((*tert*-Butyldimethylsilyl)oxy)-3-methoxyphenyl)propan-1-ol (185)



General procedure B: Methyl 3-(4-((*tert*-butyldimethylsilyl)oxy)-3-methoxyphenyl) propanoate (1.71 g, 5.00 mmol) and 2.0 equivalents of $LiAlH_4$ (1.0 M in THF) in anhydrous Et_2O (25 mL) were employed to afford **185** (1.34 g, 90%) as a pale yellow oil which was used without further purification; R_f = 0.3 (33% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 3357 (m br), 2930

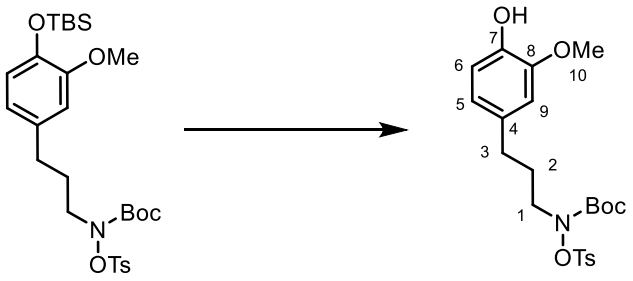
(m), 2885 (m), 2857 (m), 1511 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74 (1H, d, *J* = 8.0 Hz, C**6**-H), 6.67 (1H, d, *J* = 2.0 Hz, C**9**-H), 6.62 (1H, dd, *J* = 8.0, 2.0 Hz, C**5**-H), 3.78 (3H, s, C**10**-H_3), 3.65 (2H, t, *J* = 6.5 Hz, C**1**-H_2), 2.63 (2H, t, *J* = 7.5 Hz, C**3**-H_2), 1.89 – 1.82 (2H, m, C**2**-H_2), 0.98 (9H, s, TBS (CH_3)$_3$), 0.13 (6H, s, TBS Si(CH_3)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.8 (C**8**), 143.2 (C**7**), 135.3 (C**5**), 120.8 (C**6**), 120.5 (C**5**), 112.6 (C**9**), 62.5 (C**1**), 55.6 (C**10**), 34.4 (C**2**), 31.9 (C**3**), 25.8 (TBS (CH_3)$_3$), 18.5 (TBS SiC(CH_3)$_3$), -4.6, (TBS Si(CH_3)$_2$). HRMS (ESI$^+$) Calculated for $C_{16}H_{28}NaO_3Si$: 319.1700. Found [M+Na]$^+$: 319.1710.

***tert*-Butyl (3-(4-((*tert*-butyldimethylsilyl)oxy)-3-methoxyphenyl)propyl)(tosyloxy) carbamate**



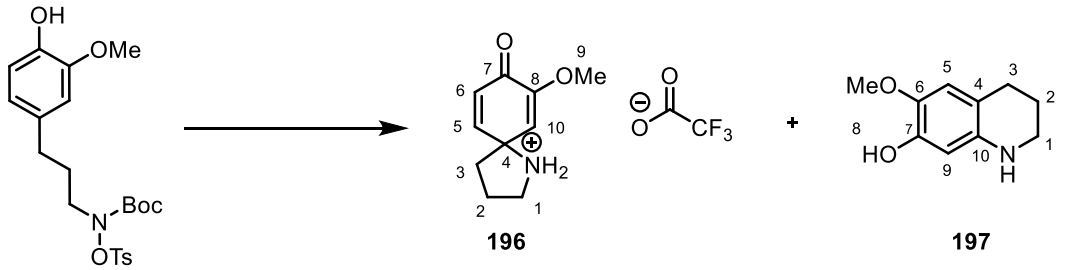
General procedure G: The preceding alcohol **185** (590 mg, 2.00 mmol), PPh_3 (630 mg, 2.40 mmol), DIAD (0.47 mL, 2.40 mmol) and BocNHOTs (690 mg, 2.40 mmol) in anhydrous THF (10 mL) were employed. Purification by flash column chromatography (10% EtOAc:hexane) afforded the title compound (940 mg, 83 %) as a colourless oil; R_f = 0.5 (20% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 2954 (m), 2930 (m), 2857 (m), 1720 (m), 1512 (s); ^{1}H NMR (400 MHz, $CDCl_3$) 7.84 (2H, d, *J* = 8.5 Hz, Ts ArCH), 7.32 (2H, d, *J* = 8.5 Hz, Ts ArCH), 6.74 (1H, d, *J* = 8.0 Hz, C**6**-H), 6.66 (1H, d, *J* = 2.0 Hz, C**9**-H), 6.59 (1H, dd, *J* = 8.0, 2.0 Hz, C**5**-H), 3.79 (3H, s, C**10**-H_3), 3.62 (2H, br s, C**1**-H_2), 2.52 (2H, t, *J* = 8.0 Hz, C**3**-H_2), 2.45 (3H, s, Ts CH_3), 1.98 – 1.87 (2H, m, C**2**-H_2), 1.22 (9H, s, Boc (CH_3)$_3$), 0.99 (9H, s, TBS (CH_3)$_3$), 0.14 (6H, s, TBS Si(CH_3)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6 (Boc C=O), 150.9 (C**8**), 145.8 (Ts ArC), 143.3 (C**7**), 134.7 (C**4**), 131.4 (Ts ArC), 129.8 (2 × Ts ArCH), 129.7 (2 × Ts ArCH), 120.8 (C**6**), 120.5 (C**5**), 122.5 (C**9**) 83.3 (Boc C(CH_3)$_3$), 55.6 (C**10**), 52.8 (C**1**), 32.6 (C**3**), 27.8 (Boc (CH$_3$)$_3$), 27.6 (C**2**), 25.9 (TBS (CH$_3$)$_3$), 21.8 (Ts CH$_3$), 18.6 (TBS SiC(CH_3)$_3$), -4.5 (TBS Si(CH$_3$)$_2$). HRMS (ESI$^+$) Calculated for $C_{28}H_{43}NNaO_7SSi$: 588.2422. Found [M+Na]$^+$: 588.2432.

***tert*-Butyl (3-(4-hydroxy-3-methoxyphenyl)propyl)(tosyloxy)carbamate (186)**



General procedure H: *tert*-Butyl (3-(4-((*tert*-butyldimethylsilyl)oxy)-3-methoxyphenyl) propyl)(tosyloxy)carbamate (570 mg, 1.0 mmol), and 1:1 TBAF:AcOH solution (0.1 M in THF, 1.0 mmol) in THF (20 mL) were employed. Purification by flash column chromatography (20% EtOAc:hexane) afforded **186** (280 mg, 62%) as a colourless solid; m.p.: 82-84 ^{o}C (EtOAc:hexane); R_f = 0.4 (33% EtOAc:hexane); ν_{max} / cm^{-1} (*solid*) 3505 (m, br), 2989 (m), 2964 (m), 2935 (m), 1749 (s), 1514 (m), 1153 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (2H, d, *J* = 8.0 Hz, Ts ArC<u>H</u>), 7.33 (2H, d, *J* = 8.0 Hz, Ts ArC<u>H</u>), 6.82 (1H, d, *J* = 8.0 Hz, C**6**-<u>H</u>), 6.69 (1H, d, *J* = 2.0 Hz, C**9**-<u>H</u>), 6.64 (1H, dd, *J* = 8.0, 2.0 Hz, C**5**-<u>H</u>), 5.47 (1H, s, O<u>H</u>), 3.89 (3H, s, C**10**-<u>H</u>$_3$), 3.60 (2H, br s, C**1**-<u>H</u>$_2$), 2.53 (2H, t, *J* = 7.5 Hz, C**3**-<u>H</u>$_2$), 2.45 (3H, s, Ts C<u>H</u>$_3$), 1.97 – 1.87 (2H, m, C**2**-<u>H</u>$_2$), 1.22 (9H, s, Boc (C<u>H</u>$_3$)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6 (Boc <u>C</u>=O), 146.5 (C**8**) 145.8, (Ts Ar<u>C</u>), 143.9 (C**7**), 133.1 (C**4**), 131.3 (Ts Ar<u>C</u>), 129.8 (2 × Ts Ar<u>C</u>H), 129.6 (2 × Ts Ar<u>C</u>H), 120.9 (C**5**), 114.3 (C**6**), 110.9 (C**9**), 83.3 (Boc <u>C</u>(CH$_3$)$_3$), 56.1 (C**10**), 52.6 (C**1**), 32.6 (C**3**), 27.7 (Boc (<u>C</u>H$_3$)$_3$), 27.7 (C**2**) 21.8 (Ts <u>C</u>H$_3$); HRMS (ESI$^+$) Calculated for $C_{22}H_{29}NNaO_7S$: 474.1557. Found [M+Na]$^+$: 474.1551.

7-Methoxy-1-azaspiro[4.5]deca-6,9-dien-8-one trifluoroacetate (196) *and* 6-Methoxy-1,2,3,4-tetrahydroquinolin-7-ol (197)



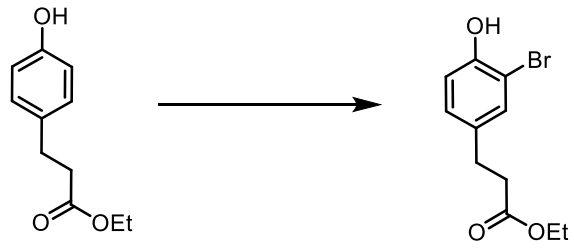
General procedure I: The preceding *N*-tosyloxycarbamate **186** (67.7 mg, 0.15 mmol) and TFA (23 μL) in TFE (1.5 mL) were stirred at room temperature for 40 hours. Upon completion, the reaction mixture was concentrated *in vacuo*. *An in situ yield was obtained by ^{1}H NMR analysis versus 1,3,5-trimethoxybenzene as an internal standard; a 27 % yield of* ***196*** *and 62 %*

*yield of **197** were observed.* Purification by flash column chromatography (EtOAc) afforded **197** (14.9 mg, 55%) as a yellow solid, however, **196** could not be isolated cleanly.

Data for **196**: *from NMR analysis of crude material:* ^{1}H NMR (400 MHz, CD_3OD) δ 7.11 (1H, dd, *J* = 10.0, 3.0 Hz, C**5**-H), 6.46 (1H, d, *J* = 10.0 Hz, C**6**-H), 6.03 (1H, d, *J* = 3.0 Hz, C**10**-H), 3.75 (3H, s, C**9**-H_3), 3.68 – 3.60 (2H, m, C**1**-H_2), 2.46 – 2.43 (2H, m, C**2**-H_2), 2.33 – 2.27 (2H, m, C**3**-H_2); ^{13}C NMR (101 MHz, CD_3OD) δ 180.8 (C**7**), 153.5 (C**8**), 144.8 (C**5**), 131.3 (C**6**), 111.5 (C**10**), 66.6 (C**4**), 56.0 (C**9**) 46.1 (C**1**) 38.2 (C**3**), 24.7 (C**2**);

Data for **197**: m.p.: 76 - 78 ^{o}C (EtOAc:hexane); R_f = 0.7 (EtOAc); ν_{max} / cm^{-1} (*solid*) 3383 (br m), 3324 (br m), 2926 (m), 1508 (s), 1464 (m), 1443 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.50 (1H, s, C**5**-H), 6.14 (1H, s, C**9**-H), 3.79 (3H, s, C**8**-H_3), 3.25 – 3.20 (2H, m, C**1**-H_2), 2.68 (2H, t, *J* = 6.5 Hz, C**3**-H_2), 1.94 – 1.88 (2H, m, C**2**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.7 (C**6**), 139.3 (C**10**), 139.1 (C**7**), 113.1 (C**5**), 112.7 (C**4**), 101.7 (C**9**), 57.0 (C**8**), 42.3 (C**1**), 26.7 (C**3**), 22.8 (C**2**); HRMS (ESI$^+$) Calculated for $C_{10}H_{14}NO_2$: 180.1019. Found $[M+H]^+$:180.1027.

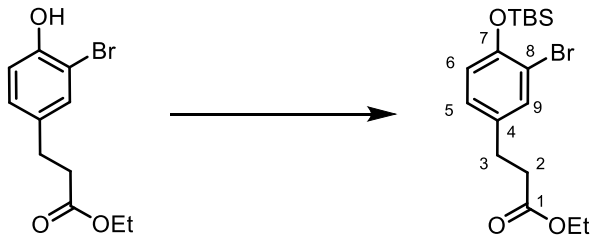
Ethyl 3-(3-bromo-4-hydroxyphenyl)propanoate



A solution of bromine (0.25 mL, 4.75 mmol) in acetic acid (20 mL) was slowly added to a stirring solution of ethyl 3-(4-hydroxyphenyl)propionate (**187**) (1.84 g, 9.50 mmol) at room temperature. The reaction mixture was stirred for 6 hours then diluted with EtOAc (80 mL) and washed with brine (2 × 30 mL). The organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (5% EtOAc:PhMe) afforded the title compound (1.14 g, 44%) as a pale yellow solid; R_f = 0.3 (5% EtOAc:PhMe); ν_{max} / cm^{-1} (*solid*) 3357 (br m), 2977 (m), 2936 (m), 1727 (s), 1704 (s), 1496 (s), 1289 (s), 1254 (s), 1180 (s), 1156 (s), 1039 (s); ^{1}H NMR (400 MHz, $CDCl_3$) 7.29 (1H, d, *J* = 2.0 Hz), 7.03 (1H, dd, *J* = 8.0, 2.0 Hz), 6.91 (1H, d, *J* = 8.0 Hz), 4.11 (2H, q, *J* = 7.0 Hz), 2.85 (2H, t, *J* = 8.5 Hz), 2.56 (2H, t, *J* = 7.5 Hz), 1.22 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.7, 150.7, 134.2, 131.6, 129.1, 116.0, 110.0, 60.5, 36.0, 29.8, 14.2.

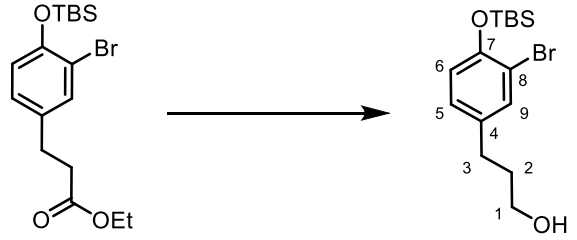
The spectroscopic properties were consistent the data available in the literature.[295]

Ethyl 3-(3-bromo-4-((*tert*-butyldimethylsilyl)oxy)phenyl)propanoate (188)



To a solution of ethyl 3-(3-bromo-4-hydroxyphenyl)propanoate (1.08 g, 3.95 mmol) in DMF (5 mL) was added *tert*-butyldimethylsilyl chloride (710 mg, 4.74 mmol) and imidazole (670 mg, 9.88 mmol) and the reaction was stirred at room temperature overnight. To the reaction was added water (25 mL) and the organic phase extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (5% EtOAc:hexane) afforded **188** (1.43 g, 93%) as a colourless oil; R_f = 0.6 (5% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 2956 (m), 2930 (m), 1734 (s), 1493 (s), 1287 (s), 1253 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (1H, d, *J* = 2.0 Hz, C**9**-H), 6.98 (1H, dd, *J* = 8.5, 2.0 Hz, C**5**-H), 6.77 (1H, d, *J* = 8.5 Hz, C**6**-H), 4.11 (2H, q, *J* = 7.0 Hz, OCH_2), 2.84 (2H, t, *J* = 7.5 Hz, C**3**-H_2), 2.56 (2H, t, *J* = 7.5 Hz, C**2**-H_2), 1.22 (3H, t, *J* = 7.0 Hz, CH_2CH_3), 1.03 (9H, s, TBS (CH_3)$_3$), 0.22 (6H, TBS (CH_3)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.8 (C**1**), 151.1 (C**7**), 134.9 (C**4**), 133.2 (C**9**), 128.2 (C**5**), 120.2 (C**6**), 115.2 (C**8**), 60.6 (OCH_2CH_3), 36.1 (C**2**), 29.9 (C**3**), 25.9 (TBS (CH_3)$_3$), 18.5 (TBS Si$C(CH_3)_3$), 14.4 (OCH_2CH_3), -4.11 (TBS Si(CH_3)$_2$); HRMS (ESI^+) Calculated for $C_{17}H_{27}{}^{79}BrNaO_3Si$: 409.0805. Found $[M+Na]^+$: 409.0816.

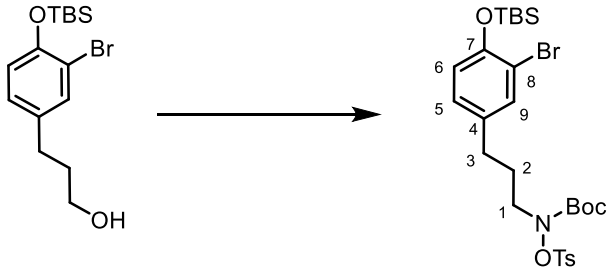
3-(3-Bromo-4-((*tert*-butyldimethylsilyl)oxy)phenyl)propan-1-ol (189)



To a solution of the preceding ester **188** (1.03 g, 2.66 mmol) in anhydrous THF (15 mL) at -15 ^oC was added 0.75 equivalents of $LiAlH_4$ (1M in THF) and the reaction was stirred at the same temperature for 25 minutes. Then to the reaction mixture was added water (0.5 mL), aqueous 1 M NaOH (0.2 mL) and water (1 mL). The reaction mixture was warmed to room temperature, filtered through Celite® and washed with CH_2Cl_2. The filtrate was dried over Na_2SO_4, filtered

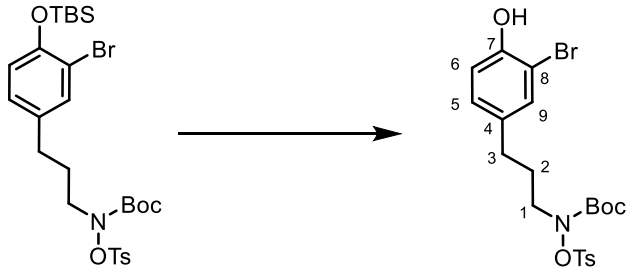
and concentrated *in vacuo*. Purification by flash column chromatography (20% EtOAc:hexane) afforded **189** (800 mg, 87%) as a colourless oil; R_f = 0.2 (20% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 3327 (br m), 2930 (m), 2858 (m), 1492 (s), 1280 (s), 1253 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (1H, d, *J* = 2.0 Hz, C**9**-H), 6.97 (1H, dd, *J* = 8.0, 2.0 Hz, C**5**-H), 6.77 (1H, dd, *J* = 8.0, 1.0 Hz, C**6**-H), 3.63 (2H, t, *J* = 6.5 Hz, C**1**-H_2), 2.60 (2H, t, *J* = 7.5 Hz, C**3**-H_2), 1.87 – 1.80 (2H, m, C**2**-H_2), 1.51 (1H, br s, OH), 1.03 (9H, s, TBS (CH_3)$_3$), 0.22 (6H, s, TBS (CH_3)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.7 (C**7**), 136.1 (C**4**), 133.2 (C**9**), 128.3 (C**5**), 120.2 (C**6**), 115.2 (C**8**), 62.1 (C**1**), 34.2 (C**2**), 31.0 (C**3**), 25.9 (TBS (CH_3)$_3$), 18.5 (TBS C(CH_3)$_3$), -4.1 (TBS Si(CH_3)$_2$); HRMS (ESI^+) Calculated for $C_{15}H_{25}{}^{79}BrNaO_2Si$: 367.0699. Found $[M+Na]^+$: 367.0701.

***tert*-Butyl (3-(3-bromo-4-((*tert*-butyldimethylsilyl)oxy)phenyl)propyl) (tosyloxy) carbamate**



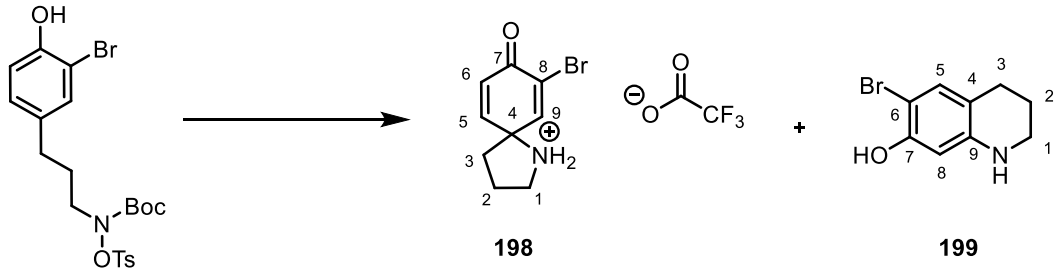
General procedure G: The preceding alcohol **189** (690 mg, 2.00 mmol), PPh_3 (630 mg, 2.40 mmol), DIAD (0.47 mL, 2.40 mmol) and BocNHOTs (690 mg, 2.40 mmol) in anhydrous THF were employed. Purification by flash column chromatography (gradient, eluent: 5% – 10% EtOAc:hexane) afforded the title compound (1.12 g, 91%) as a colourless oil; R_f = 0.6 (20% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 2955 (m), 2930 (m), 2858 (m), 1720 (s), 1493 (s), 1381 (s), 1368 (s), 1288 (s), 1254 (s), 1178 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (2H, d, *J* = 8.0 Hz, Ts ArCH), 7.32 (2H, d, *J* = 8.0 Hz, Ts ArCH), 7.29 (1H, d, *J* = 2.0 Hz, C**9**-H), 6.94 (1H, dd, *J* = 8.5, 2.0 Hz, C**5**-H), 6.77 (1H, d, *J* = 8.5 Hz, C**6**-H), 3.58 (2H, br s, C**1**-H_2), 2.49 (2H, t, *J* = 8.0 Hz, C**3**-H_2), 2.44 (3H, s, Ts CH_3), 1.95 – 1.82 (2H, m, C**2**-H_2), 1.22 (9H, s, Boc (CH_3)$_3$), 1.03 (9H, s, TBS (CH_3)$_3$), 0.23 (6H, s, TBS Si(CH_3)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6 (Boc C=O), 150.9 (C**7**), 145.8 (Ts ArC), 135.4 (C**4**), 133.1 (C**9**), 131.4 (Ts ArC), 129.8 (2 × Ts ArCH), 129.7 (2 × Ts ArCH), 128.2 (C**5**), 120.2 (C**6**), 115.2 (C**8**), 83.4 (Boc C(CH_3)$_3$), 52.6 (C**1**), 31.8 (C**3**), 27.8 (Boc (CH_3)$_3$), 27.5 (C**2**), 25.9 (TBS (CH_3)$_3$), 21.8 (Ts CH_3), 18.5 (TBS SiC(CH_3)$_3$), -4.1 (TBS Si(CH_3)$_2$); HRMS (ESI^+) Calculated for $C_{27}H_{40}{}^{79}BrNNaO_6SSi$: 636.1421. Found $[M+Na]^+$: 636.1422.

***tert*-Butyl (3-(3-bromo-4-hydroxyphenyl)propyl)(tosyloxy)carbamate (190)**



General procedure H: *tert*-Butyl (3-(3-bromo-4-((*tert*-butyldimethylsilyl)oxy)phenyl) propyl)(tosyloxy)carbamate (610 mg, 1.00 mmol) and 1:1 solution of TBAF:AcOH (0.1 M in THF, 1.00 mmol) in THF (20 mL) were employed. Purification by flash column chromatography (20% EtOAc:hexane) afforded **190** (480 mg, 96%) as a colourless solid; m.p.: 93-95 ^{o}C (EtOAc:hexane); R_f = 0.25 (20% EtOAc:hexane); ν_{max} / cm^{-1} (*solid*) 3416 (br s), 2945 (m), 1682 (s), 1371 (s), 1361 (s), 1180 (s), 1158 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (2H, d, *J* = 8.5 Hz, Ts ArC**H**), 7.32 (2H, d, *J* = 8.0 Hz, Ts ArC**H**), 7.25 (1H, d, *J* = 2.0 Hz, C**9**-**H**), 7.00 (1H, dd, *J* = 8.5, 2.0 Hz, C**5**-**H**), 6.91 (1H, d, *J* = 8.5 Hz, C**6**-**H**), 5.43 (1H, s, O**H**), 3.59 (2H, br s, C**1**-H_2), 2.50 (2H, t, *J* = 8.0 Hz, C**3**-H_2), 2.44 (3H, s, Ts CH_3), 1.91 – 1.87 (2H, m, C**2**-H_2), 1.21 (9H, s, Boc (CH_3)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6 (Boc C=O), 150.6 (C**7**), 145.9 (Ts ArC), 134.9 (C**4**), 131.6 (C**9**), 131.3 (Ts ArC), 129.8 (2 × Ts ArCH), 129.7 (2 × Ts ArCH), 129.2 (C**5**), 116.1 (C**6**), 110.1 (C**8**), 83.5 (Boc C(CH$_3$)$_3$), 52.5 (C**1**), 31.7 (C**3**), 27.8 (Boc (CH$_3$)$_3$), 27.6 (C**2**), 21.8 (Ts CH$_3$); HRMS (ESI$^+$) Calculated for $C_{21}H_{26}{}^{79}BrNO_6S$: 522.0556. Found [M+Na]$^+$: 522.0555.

7-B romo-1-azaspiro[4.5]deca-6,9-dien-8-one trifluoroacetate (198) *and* 6-Bromo-1,2,3,4-tetrahydroquinolin-7-ol (199)



198 **199**

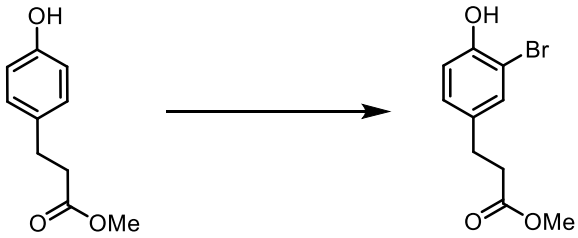
General procedure I: The preceding *N*-tosyloxycarbamate **190** (75.06 mg, 0.15 mmol) and TFA (22.9 μL, 0.30 mmol) in TFE (1.5 mL) were employed. After stirring at room temperature

for 45 hours, purification by flash column chromatography (EtOAc) afforded the title compounds **198** (22.0 mg, 43%) as a red/brown oil and **199** (8.8 mg, 19 %) as a brown oil.

Data for **198**; R_f = 0.1 (EtOAc); ν_{max} / cm^{-1} (*film*, $CDCl_3$) 2924 (m), 1675 (s), 1407 (w), 1200 (s), 1134 (m), 1066 (m); ^{1}H NMR (400 MHz, CD_3OD) δ 7.63 (1H, d, *J* = 3.0 Hz, C**9**-H), 7.14 (1H, dd, *J* = 10.0, 3.0 Hz, C**5**-H), 6.55 (1H, d, *J* = 10.1 Hz, C**6**-H), 3.64 (2H, t, *J* = 7.0 Hz, C**1**-H_2), 2.41 – 2.30 (4H, m, C**2**-H_2, C**3**-H_2). *The signals corresponding to the NH_2 were not observed.* ^{13}C NMR (101 MHz, CD_3OD) δ 178.1 (C**7**), 144.7 (C**9**), 144.6 (C**5**), 130.3 (C**6**), 128.3 (C**8**), 66.9 (C**4**), 46.7 (C**1**), 37.4 (C**3**), 24.8 (C**2**). *The signals corresponding to the trifluoroacetate group could not be resolved due to their weak intensity*. HRMS (ESI^+) Calculated for $C_9H_{11}{}^{79}BrNO$: 228.0019. Found $[M]^+$: 228.0019.

Data for **199**; R_f = 0.7 (EtOAc); ν_{max} / cm^{-1} (*film*) 3389 (m), 3197 (m), 2957 (m), 2918 (m), 2850 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (1H, s, C**5**-H), 6.16 (1H, s, C**8**-H), 3.27 – 3.24 (2H, m, C**1**-H_2), 2.66 (2H, t, *J* = 6.5 Hz, C**3**-H_2), 1.91 – 1.85 (2H, m, C**2**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.8 (C**7**), 145.1 (C**9**), 131.7 (C**5**), 115.8 (C**4**), 100.8 (C**8**), 96.6 (C**6**), 41.7 (C**1**), 26.1 (C**3**), 21.9 (C**2**). HRMS (ESI^+) Calculated for $C_9H_{11}{}^{79}BrNO$: 228.0018. Found $[M]^+$: 228.0029.

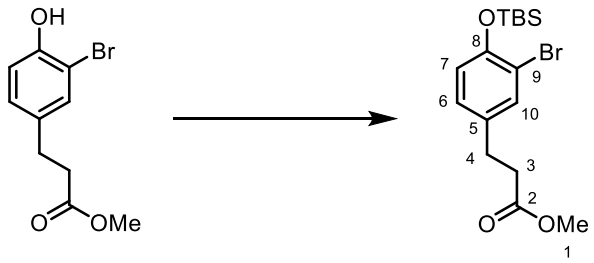
Methyl 3-(3-bromo-4-hydroxyphenyl)propanoate



To a solution of methyl 3-(4-hydroxyphenyl)propanoate (4.50 g, 25.0 mmol) in AcOH (20 mL) was slowly added a solution of Br_2 (1.3 mL, 25.0 mmol) in AcOH (15 mL). The reaction was stirred at room temperature until completion by TLC analysis. The reaction was diluted with EtOAc (20 mL) and washed with brine (20 mL), dried over Na_2SO_4, filtered, and the solvent removed *in vacuo*. Purification by flash column chromatography (20% EtOAc:hexane) afforded the title compound (2.98 g, 46%) as a colourless solid; R_f = 0.2 (20% EtOAc:hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (1H, d, *J* = 2.0 Hz), 7.05 (1H, dd, *J* = 8.5, 2.0 Hz), 6.93 (1H, d, *J* = 8.5 Hz), 3.67 (3H, s), 2.86 (2H, t, *J* = 7.5 Hz), 2.59 (2H, dd, *J* = 8.5, 6.5 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.2, 150.8, 134.3, 131.7, 129.2, 116.1, 110.1, 51.8, 35.8, 29.7.

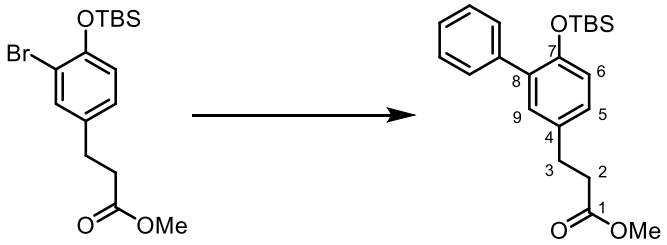
The spectroscopic properties were consistent with the data available in the literature.[296]

Methyl 3-(3-bromo-4-((*tert*-butyldimethylsilyl)oxy)phenyl)propanoate (191)



To a solution of methyl 3-(3-bromo-4-hydroxyphenyl)propanoate (2.94 g, 11.3 mmol) in DMF (5 mL) was added *tert*-butyldimethylsilyl chloride (2.05 g, 13.6 mmol) and imidazole (1.93 g, 28.4 mmol) and the reaction was stirred at room temperature overnight. To the reaction was added water (25 mL) and the organic phase was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic phases were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (20% EtOAc:hexane) afforded **191** (3.53 g, 84%) as a colourless oil; R_f = 0.4 (20% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 2952 (m), 2930 (m), 2858 (m), 1738 (s), 1492 (s), 1253 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (1H, d, *J* = 2.0 Hz, C**10**-H), 7.04 – 6.93 (1H, m, C**6**-H), 6.78 (1H, d, *J* = 8.0 Hz, C**7**-H), 3.67 (3H, s, C**1**-H_3), 2.85 (2H, t, *J* = 8.0 Hz, C**4**-H_2), 2.58 (2H, t, *J* = 8.0 Hz, C**3**-H_2), 1.03 (9H, s, TBS (CH_3)$_3$), 0.23 (6H, s, TBS Si(CH_3)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.3 (C**2**), 151.1 (C**8**), 134.8 (C**5**), 133.2 (C**10**), 128.2 (C**6**), 120.2 (C**7**), 115.3 (C**9**), 51.8 (C**1**), 35.8 (C**4**), 29.9 (C**3**), 25.9 (TBS (CH_3)$_3$), 18.5 (TBS C(CH_3)$_3$), -4.1 (TBS Si(CH_3)$_2$). HRMS (ESI$^+$) Calculated for $C_{16}H_{25}{}^{79}BrNaO_3Si$: 395.0648. Found $[M+Na]^+$: 395.0647.

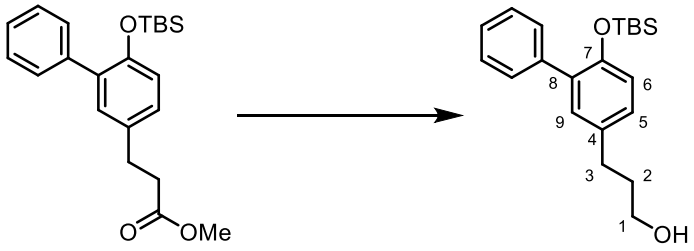
Methyl 3-(6-((*tert*-butyldimethylsilyl)oxy)-[1,1'-biphenyl]-3-yl)propanoate (192)



The preceding aryl bromide **191** (1.12 g, 3.00 mmol), phenylboronic acid (1.09 g, 9.00 mmol), K_2CO_3 (1.40 g, 10.2 mmol) and dichloro [1,1'-bis(di-*tert*butylphosphino)ferrocene] palladium(II) (Pd(dtbpf)Cl_2) (97.8 mg, 0.15 mmol) in 5:1 PhMe:MeOH (0.12 M) were heated at 110 °C overnight, under an atmosphere of N_2, and monitored by GC-MS. Upon completion, the reaction was cooled to room temperature and filtered through Celite® washing with EtOAc.

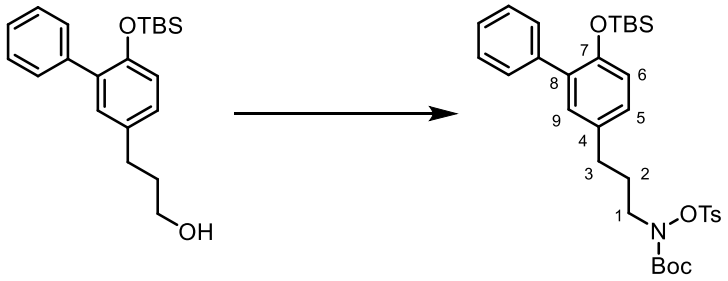
The crude reaction mixture was then washed with water and the organic layer dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography (5% EtOAc:hexane) afforded **192** (930 mg, 84%) as a pale yellow oil; R_f = 0.5 (20% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 2952 (m), 2929 (m), 2896 (m), 2857 (m), 1737 (s), 1486 (s), 1253 (s); ^1H NMR (440 MHz, $CDCl_3$) δ 7.49 – 7.45 (2H, m, ArC<u>H</u>), 7.39 – 7.33 (2H, m, ArC<u>H</u>), 7.31 – 7.26 (1H, m, ArC<u>H</u>), 7.13 (1H, d, *J* = 2.5 Hz, C**9**-<u>H</u>), 7.03 (1H, dd, *J* = 8.5, 2.5 Hz, C**5**-<u>H</u>), 6.82 (1H, d, *J* = 8.0 Hz, C**6**-<u>H</u>), 3.67 (3H, s, OC<u>H</u>$_3$), 2.93 (2H, t, *J* = 8.0 Hz, C**3**-<u>H</u>$_2$), 2.63 (2H, t, *J* = 8.0 Hz, C**2**-<u>H</u>$_2$), 0.81 (9H, s, TBS (C<u>H</u>$_3$)$_3$), -0.07 (6H, s, TBS Si(C<u>H</u>$_3$)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6 (C**1**), 151.1 (C**7**), 139.2 (C**8**), 133.6 (Ar<u>C</u>), 133.5 (C**4**), 130.8 (C**9**), 129.9 (2 × Ar<u>C</u>H), 128.1 (C**5**), 127.9 (2 × Ar<u>C</u>H), 126.9 (Ar<u>C</u>H), 120.5 (C**6**), 51.7 (O<u>C</u>H$_3$), 36.1 (C**2**), 30.4 (C**3**), 25.7 (TBS (<u>C</u>H$_3$)$_3$), 18.2 (TBS Si<u>C</u>(CH$_3$)$_3$), -4.5 (TBS Si(<u>C</u>H$_3$)$_2$); HRMS (ESI^+) Calculated for $C_{22}H_{30}NaO_{Si}$: 393.1856. Found $[M+Na]^+$: 393.1856.

3-(6-((*tert*-Butyldimethylsilyl)oxy)-[1,1'-biphenyl]-3-yl)propan-1-ol



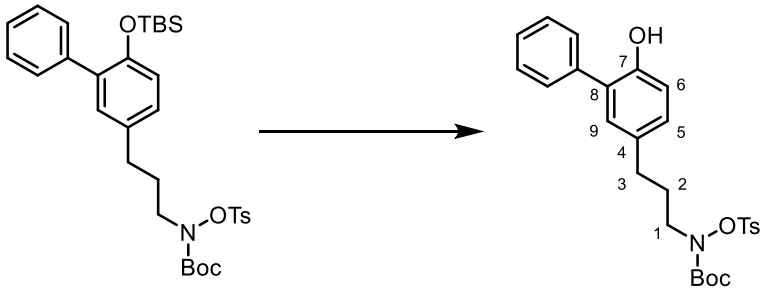
<u>General procedure B:</u> Ester **192** (740 mg, 2.00 mmol) and 2.0 equivalents of $LiAlH_4$ (1 M in THF) in anhydrous Et_2O were employed. Purification by flash column chromatography (20% EtOAc:hexane) afforded the title compound (600 mg, 87%) as a colourless oil; R_f = 0.2 (20% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 3338 (m, br), 2929 (m), 2857 (m), 2884 (m), 1485 (s), 1256 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.47 (2H, m, ArC<u>H</u>), 7.40 – 7.34 (2H, m, ArC<u>H</u>), 7.32 – 7.26 (1H, m, ArC<u>H</u>), 7.14 (1H, d, *J* = 2.5 Hz, C**9**-<u>H</u>), 7.04 (1H, dd, *J* = 8.0, 2.5 Hz, C**5**-<u>H</u>), 6.84 (1H, d, *J* = 8.0 Hz, C**6**-<u>H</u>), 3.69 (2H, t, *J* = 6.5 Hz, C**1**-<u>H</u>$_2$), 2.69 (2H, t, *J* = 7.5 Hz, C**3**-<u>H</u>$_2$), 1.94 – 1.87 (2H, m, C**3**-<u>H</u>$_2$), 1.38 (1H, br s, O<u>H</u>), 0.82 (9H, s, TBS (C<u>H</u>$_3$)$_3$), -0.06 (6H, s, TBS Si(C<u>H</u>$_3$)$_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.8 (C**7**), 139.3 (C**8**), 134.9 (C**4**), 133.4 (Ar<u>C</u>), 130.9 (C**9**), 129.9 (2 × Ar<u>C</u>H), 128.2 (C**5**), 127.9 (2 × Ar<u>C</u>H), 126.8 (Ar<u>C</u>H), 120.4 (C**6**), 62.5 (C**1**), 34.5 (C**2**), 31.4 (C**3**), 25.7 (TBS (<u>C</u>H$_3$)$_3$), 18.2 (TBS Si<u>C</u>(CH$_3$)$_3$), -4.5 (TBS Si(<u>C</u>H$_3$)$_2$); HRMS (ESI^+) Calculated for $C_{21}H_{30}NaO_2Si$: 365.1907. Found $[M+Na]^+$: 365.1924.

***tert*-Butyl(3-(6-((*tert*-butyldimethylsilyl)oxy)-[1,1'-biphenyl]-3-yl)propyl)(tosyloxy) carbamate**



General procedure G: 3-(6-((*tert*-Butyldimethylsilyl)oxy)-[1,1'-biphenyl]-3-yl)propan-1-ol (480 mg, 1.40 mmol), PPh_3 (440 mg, 1.68 mmol), DIAD (0.33 ml, 1.68 mmol) and BocNHOTs (480 mg, 1.68 mmol) in anhydrous THF (6 mL) were employed. Purification by flash column chromatography (5% EtOAc:hexane) afforded the title compound (740 mg, 87%) as a colourless solid; m.p.: 95-96 ^oC (EtOAc:hexane); R_f = 0.5 (EtOAc:hexane); ν_{max} / cm^{-1} (*solid*) 2985 (m), 2955 (m), 2937 (m), 1715 (s), 1365 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (2H, d, *J* = 8.0 Hz, Ts ArC<u>H</u>), 7.50 – 7.47 (2H, m, ArC<u>H</u>), 7.40 – 7.26 (5H, m, 3 × ArC<u>H</u>, 2 × Ts ArC<u>H</u>), 7.09 (1H, d, *J* = 2.5 Hz, C**9**-<u>H</u>), 7.01 (1H, dd, *J* = 8.0, 2.5 Hz, C**5**-<u>H</u>), 6.82 (1H, d, *J* = 8.0 Hz, C**6**-<u>H</u>), 3.64 (2H, br s, C**1**-$\underline{H}_2$), 2.57 (2H, t, *J* = 8.0 Hz, C**3**-$\underline{H}_2$), 2.44 (3H, s, Ts C$\underline{H}_3$), 2.01 – 1.88 (2H, m, C**2**-$\underline{H}_2$), 1.21 (9H, s, Boc (C$\underline{H}_3$)$_3$), 0.81 (9H, s, TBS (C$\underline{H}_3$)$_3$), -0.08 (6H, s, TBS Si(C$\underline{H}_3$)$_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.5 (Boc <u>C</u>=O), 150.9 (C**7**), 145.8 (Ts Ar<u>C</u>), 139.3 (Ar<u>C</u>), 134.2 (C**4**), 133.4 (C**8**), 131.4 (Ts Ar<u>C</u>), 130.8 (C**9**), 129.9 (2 × Ar<u>C</u>H), 129.8 (2 × Ts Ar<u>C</u>H), 129.6 (2 × Ts Ar<u>C</u>H), 128.1 (C**5**), 127.9 (2 × Ar<u>C</u>H), 126.8 (Ar<u>C</u>H), 120.4 (C**6**), 83.3 (Boc <u>C</u>(CH$_3$)$_3$), 52.8 (C**1**), 32.2 (C**3**), 27.8 (Boc (<u>C</u>H$_3$)$_3$), 27.7 (C**2**), 25.7 (TBS (<u>C</u>H$_3$)$_3$), 21.8 (Ts <u>C</u>H$_3$), 18.2 (TBS Si<u>C</u>(CH$_3$)$_3$), -4.5 (TBS Si(<u>C</u>H$_3$)$_2$); HRMS (ESI^+) Calculated for $C_{33}H_{45}NNaO_6SSi$: 634.2629. Found $[M+Na]^+$: 634.2609.

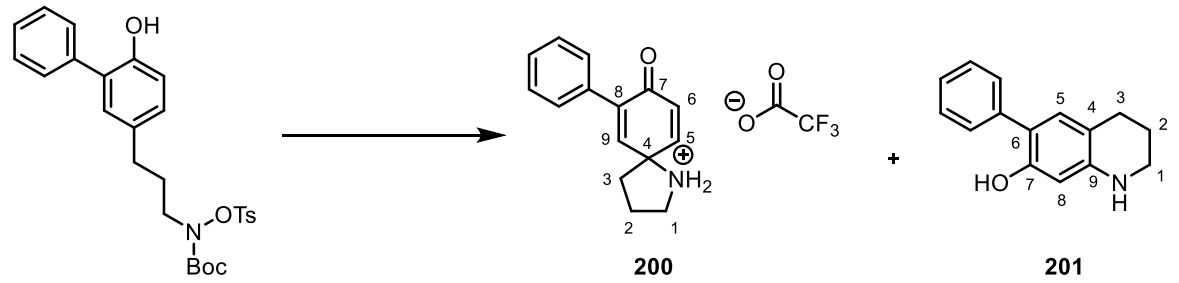
***tert*-Butyl (3-(6-hydroxy-[1,1'-biphenyl]-3-yl)propyl)(tosyloxy)carbamate (194)**



General procedure H: *tert*-Butyl(3-(6-((*tert*-butyldimethylsilyl)oxy)-[1,1'-biphenyl]-3-yl)propyl) (tosyloxy)carbamate (610 mg, 1.00 mmol) and 1:1 TBAF:AcOH solution (0.1 M in

THF, 1.00 mmol) in THF (20 mL) were employed. Purification by flash column chromatography (20% EtOAc:petroleum ether) afforded **194** (410 mg, 82%) as a colourless solid; m.p.: 108-110 °C (EtOAc:hexane); R_f = 0.2 (20% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 3467 (m, br), 2980 (m), 2930 (m), 1719 (s), 1368 (s), 1176 (s), 1151 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.51 – 7.46 (4H, m, ArC<u>H</u>), 7.42 – 7.36 (1H, m, ArC<u>H</u>), 7.32 (2H, d, *J* = 8.0 Hz, Ts ArC<u>H</u>), 7.07 – 7.03 (2H, m C**5**, C**9**-<u>H</u>), 6.90 (1H, d, *J* = 8.0 Hz, C**6**-<u>H</u>), 5.17 (1H, s, O<u>H</u>), 3.65 (2H, br s, C**1**-<u>H_2</u>), 2.57 (2H, t, *J* = 8.0 Hz, C**3**-<u>H_2</u>), 2.44 (3H, s, Ts C<u>H_3</u>), 2.01 – 1.87 (2H, m, C**2**-<u>H_2</u>), 1.22 (9H, s, Boc (C<u>H_3</u>)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6 (Boc <u>C</u>=O), 150.8 (C**7**), 145.8 (Ts Ar<u>C</u>), 137.3 (Ar<u>C</u>), 133.5 (C**4**), 131.4 (Ts Ar<u>C</u>), 130.1 (C**9**), 129.8 (2 × Ar<u>C</u>H), 129.7 (2 × Ts Ar<u>C</u>H), 129.4 (2 × Ts Ar<u>C</u>H), 129.2 (2 × Ar<u>C</u>H), 129.0 (C**5**), 128.1 (C**8**), 127.9 (Ar<u>C</u>H), 115.9 (C**6**), 83.4 (Boc <u>C</u>(CH$_3$)$_3$), 52.7 (C**1**), 32.1 (C**3**), 27.7 (Boc (<u>C</u>H$_3$)$_3$), 27.7 (C**2**), 21.8 (Ts C<u>H_3</u>); HRMS (ESI$^+$) Calculated for $C_{27}H_{31}NNaO_6S$: 520.1764. Found $[M+Na]^+$: 520.1766.

7-Phenyl-1-azaspiro[4.5]deca-6,9-dien-8-one trifluoroacetate (200) *and* 6-Phenyl-1,2,3,4-tetrahydroquinolin-7-ol (201)



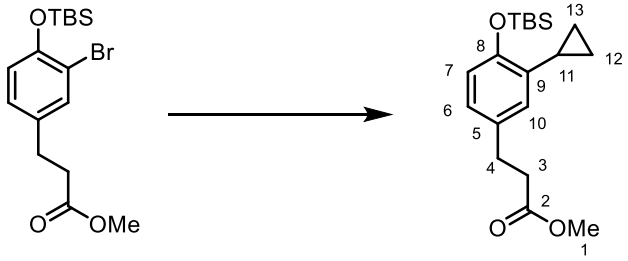
<u>General procedure I:</u> The preceding *N*-tosyloxycarbamate **194** (74.6 mg, 0.15 mmol) and TFA (23 μL, 0.30 mmol) in anhydrous TFE (1.5 mL) were employed. After stirring at room temperature for 46 hours, purification by flash column chromatography (EtOAc) afforded the title compounds **200** (26.0 mg, 51%) and **201** (11.7 mg, 35%) as yellow solids.

Data for **200**: m.p.: 136-138 °C (EtOAc:hexane); R_f = 0.1 (5% MeOH:CH_2Cl_2); ν_{max} / cm^{-1} (*film*) 3374 (m, br), 2975 (m), 1665 (s), 1640 (s); ^{1}H NMR (400 MHz, CD_3OD) δ 7.46 – 7.37 (5H, m, PhC<u>H</u>), 7.14 (1H, dd, *J* = 10.0, 3.5 Hz, C**5**-<u>H</u>), 7.09 (1H, d, *J* = 3.0 Hz, C**9**-<u>H</u>), 6.52 (1H, d, *J* = 10.0 Hz, C**6**-<u>H</u>), 3.70 – 3.63 (2H, m, C**1**-<u>H_2</u>), 2.45 – 2.30 (4H, m, C**2**-<u>H_2</u>, C**3**-<u>H_2</u>). *The signals corresponding to the N<u>H_2</u> were not observed.* ^{13}C NMR (101 MHz, CD_3OD) δ 184.4 (C**7**), 143.6 (C**5**), 142.1 (C**8**), 141.0 (C**9**), 135.6 (Ar<u>C</u>), 132.2 (C**6**), 130.0 (2 × Ar<u>C</u>H), 129.9 (Ar<u>C</u>H), 129.2 (2 × Ar<u>C</u>H), 65.2 (C**4**), 46.5 (C**1**), 37.9 (C**3**), 24.9 (C**2**). *The signals*

corresponding to the trifluoroacetate group could not be resolved due to their weak intensity. HRMS (ESI$^+$) Calculated for $C_{15}H_{16}NO$: 226.1226. Found $[M]^+$: 226.1229.

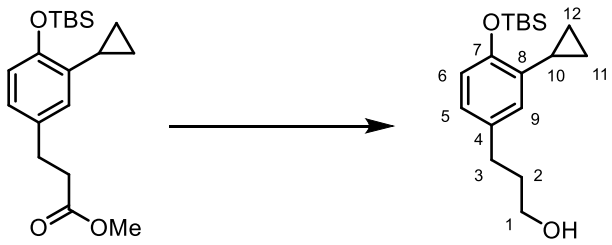
Data for **201**: m.p.: 91-94 ^oC (EtOAc:hexane); R_f = 0.4 (5% MeOH:CH_2Cl_2); ν_{max} / cm^{-1} (*solid*) 3405 (br m), 2925 (m), 2852 (m), 1622 (s), 1488 (s), 1160 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.40 (4H, m, ArC<u>H</u>), 7.33 – 7.28 (1H, m, ArC<u>H</u>), 6.84 (1H, s, C**5**-<u>H</u>), 6.11 (1H, s, C**8**-<u>H</u>), 4.98 (1H, br s), 4.04 (1H, br s), 3.32 – 3.29 (2H, m, C**1**-<u>H_2</u>), 2.73 (2H, t, *J* = 6.5 Hz, C**3**-<u>H_2</u>), 1.97 – 1.91 (2H, m, C**2**-<u>H_2</u>); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.3 (C**7**), 145.4 (C**9**), 137.7 (Ar<u>C</u>), 130.8 (C**5**), 129.1 (2 × Ar<u>C</u>H), 128.9 (2 × Ar<u>C</u>H), 126.8 (Ar<u>C</u>H), 117.3 (C**6**), 114.2 (C**4**), 100.5 (C**8**), 41.9 (C**1**), 26.2 (C**3**), 22.4 (C**2**); HRMS (ESI$^+$) Calculated for $C_{15}H_{16}NO$: 226.1226. Found $[M+H]^+$: 226.1232.

Methyl 3-(4-((*tert*-butyldimethylsilyl)oxy)-3-cyclopropylphenyl)propanoate (193)



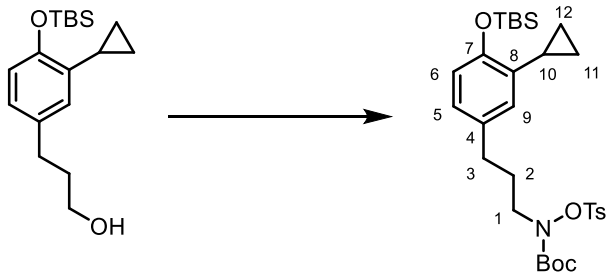
Aryl bromide **191** (1.12 g, 3.00 mmol), cyclopropylboronic acid (770 mg, 9.00 mmol), K_3PO_4 (3.82 g, 18.0 mmol) and tetrakis(triphenylphosphine)palladium (0) ($Pd(PPh_3)_4$) (346 mg, 0.30 mmol) in 20:1 toluene:H_2O (0.1 M) were heated at 95 ^oC overnight, under an atmosphere of N_2, and monitored by GC-MS. Upon completion, the reaction was cooled to room temperature and filtered through Celite® washing with EtOAc. The crude reaction mixture was then washed with water and the organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography (5% EtOAc:hexane) afforded **193** (810 mg, 80%) as a pale yellow oil; R_f = 0.5 (20% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 2953 (m), 2930 (m), 2897 (m), 2858 (m), 1739 (s), 1498 (s), 1255 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 6.85 (1H, dd, *J* = 8.0, 2.3 Hz, C**6**-<u>H</u>), 6.70 (1H, d, *J* = 8.0 Hz, C**7**-<u>H</u>), 6.62 (1H, d, *J* = 2.0 Hz, C**10**-<u>H</u>), 3.67 (3H, s, C**1**-<u>H_3</u>), 2.84 (2H, t, *J* = 8.0 Hz, C**4**-<u>H_2</u>), 2.57 (2H, t, *J* = 8.0 Hz, C**3**-<u>H_2</u>), 2.13 (1H, tt, *J* = 8.5, 5.4 Hz, C**11**-<u>H</u>), 1.03, (9H, s, TBS (C<u>H_3</u>)$_3$), 0.93 – 0.87 (2H, m, C**12**/**13**-<u>H_2</u>), 0.64 – 0.60 (2H, m, C**12**/C**13**-<u>H_2</u>), 0.23 (6H, s, TBS Si(C<u>H_3</u>)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6 (C**2**), 152.9 (C**8**), 134.2 (C**9**) , 133.2 (C**5**), 125.7 (C**6**), 124.8 (C**10**), 118.7 (C**7**), 51.7 (C**1**), 36.2 (C**3**), 30.6 (C**4**), 25.9 (TBS (<u>C</u>H_3)$_3$), 18.4 (TBS <u>C</u>(CH_3)$_3$), 10.1 (C**11**), 8.2 (C**12**,C**13**), -4.1 (TBS Si(<u>C</u>H_3)$_2$). HRMS (ESI$^+$) Calculated for $C_{19}H_{30}NaO_3Si$: 357.1856. Found $[M+Na]^+$: 357.1862.

3-(4-((*tert*-Butyldimethylsilyl)oxy)-3-cyclopropylphenyl)propan-1-ol



General procedure B: Ester **193** (670 mg, 2.00 mmol) and 2.0 equivalents of $LiAlH_4$ (1 M in THF) in anhydrous Et_2O were employed. Purification by flash column chromatography (20% EtOAc:hexane) afforded the title compound (480 mg, 78%) as a colourless oil; R_f = 0.2 (20% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 3334 (m, br), 2953 (m), 2929 (m), 2885 (m), 2857 (m), 1496 (s), 1254 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 6.84 (1H, dd, *J* = 8.0, 2.5 Hz, C**5**-H), 6.70 (1H, d, *J* = 8.0 Hz, C**6**-H), 6.61 (1H, d, *J* = 2.0 Hz, C**9**-H), 3.65 (2H, t, *J* = 6.5 Hz, C**1**-H_2), 2.59 (2H, dd, *J* = 8.5, 7.0 Hz, C**3**-H_2), 2.12 (1H, tt, *J* = 8.5, 5.5 Hz, C**10**-H), 1.88 – 1.79 (2H, m, C**2**-H_2), 1.40 (1H, br s, OH), 1.03 (9H, s, TBS (CH_3)$_3$), 0.92 – 0.88 (2H, m, C**11**/C1**2**-H_2), 0.64 – 0.60 (2H, m, C**11**/C**12**-H_2), 0.23 (6H, s, TBS Si(CH_3)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.6 (C**7**), 134.4 (C**4**), 134.1 (C**8**), 125.8 (C**5**), 124.9 (C**9**), 118.6 (C**6**), 62.5 (C**1**), 34.6 (C**2**), 31.6 (C**3**), 26.0 (TBS (CH_3)$_3$), 18.4 (TBS C(CH_3)$_3$), 10.1 (C**10**), 8.2 (C**11**, C**12**), -4.1 (TBS Si(CH_3)$_2$). HRMS (ESI^+) Calculated for $C_{18}H_{30}NaO_2Si$: 329.1907. Found $[M+Na]^+$: 329.1940.

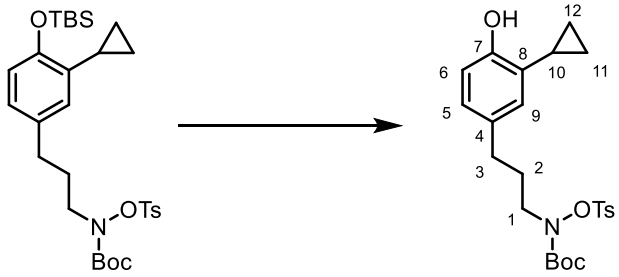
***tert*-Butyl (3-(4-((*tert*-butyldimethylsilyl)oxy)-3-cyclopropylphenyl)propyl)(tosyloxy) carbamate**



General procedure G: 3-(4-((*tert*-Butyldimethylsilyl)oxy)-3-cyclopropylphenyl)propan-1-ol (430 mg, 1.40 mmol), PPh_3 (440 mg, 1.68 mmol), DIAD (0.33 mL, 1.68 mmol) and BocNHOTs (480 mg, 1.68 mmol) in anhydrous THF (6 mL) were employed. Purification by flash column chromatography (5% EtOAc:hexane) afforded the title compound (770 mg, 96%) as a colourless solid; R_f = 0.5 (20% EtOAc:hexane); ν_{max} / cm^{-1} (*solid*) 2949 (m), 2928 (m), 2883 (m), 2857 (m), 1712 (s), 1504 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (2H, d, *J* = 8.5 Hz, Ts ArCH), 7.33 (2H, d, *J* = 8.0 H, Ts ArCH), 6.80 (1H, dd, *J* = 8.0, 2.0 Hz, C**5**-H), 6.68

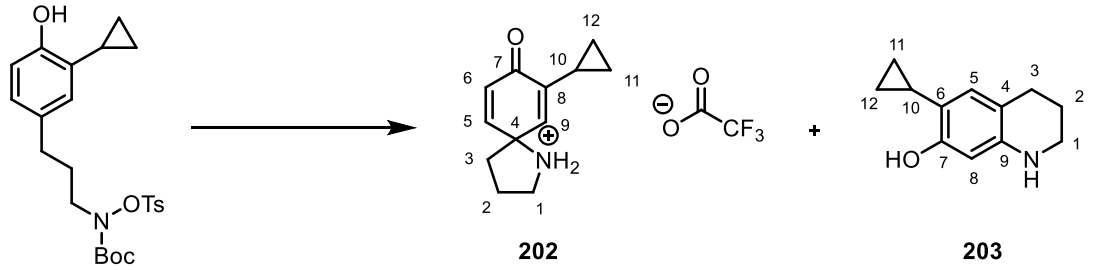
(1H, d, *J* = 8.0 Hz, C**6**-H), 6.57 (1H, d, *J* = 2.0 Hz, C**9**-H), 3.60 (2H, br s, C**1**-H_2), 2.49 – 2.44 (5H, m, C**3**-H_2 and Ts CH_3), 2.15 – 2.08 (1H, m, C**10**-H), 1.94 – 1.83 (2H, m, C**2**-H_2), 1.22 (9H, s, Boc (CH_3)$_3$), 1.03 (9H, s, TBS (CH_3)$_3$), 0.92 – 0.86 (2H, m, C**11**/C**12**-H_2), 0.64 – 0.60 (2H, m, C**11**/C**12**-H_2), 0.22 (6H, s, TBS Si(CH_3)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6 (Boc C=O), 152.7 (C**7**), 145.7 (Ts ArC), 134.1 (C**8**), 133.7 (C**4**), 131.4 (Ts ArC), 129.8 (2 × Ts CH), 129.6 (2 × Ts CH), 125.7 (C**5**), 124.8 (C**9**), 118.6 (C**6**), 83.2 (Boc C(CH_3)$_3$), 52.8 (C**1**), 32.3 (C**3**), 27.7 (C**2**), 27.7 (Boc (CH_3)$_3$) 26.0 (TBS (CH_3)$_3$), 21.8 (Ts CH_3), 18.4 (TBS C(CH_3)$_3$), 10.1 (C**10**), 8.2 (C**11**, C**12**), -4.1 (TBS Si(CH_3)$_2$). HRMS (ESI$^+$) Calculated for $C_{30}H_{45}NNaO_6SSi$: 598.2629. Found $[M+Na]^+$: 598.2615.

***tert*-Butyl (3-(3-cyclopropyl-4-hydroxyphenyl)propyl)(tosyloxy)carbamate (195)**



General procedure H: *tert*-Butyl (3-(4-((*tert*-butyldimethylsilyl)oxy)-3-cyclopropylphenyl) propyl)(tosyloxy)carbamate (580 mg, 1.00 mmol) and 1:1 TBAF:AcOH solution (0.1 M in THF, 1.00 mmol) in THF (20 mL) were employed. Purification by flash column chromatography (20% EtOAc:hexane) afforded **195** (370 mg, 81% yield) as a colourless solid; m.p.: 82-83 ^{o}C (EtOAc:hexane); R_f = 0.2 (20% EtOAc:hexane); ν_{max} / cm^{-1} (*solid*) 3472 (m, br), 2988 (m), 2930 (m), 1693 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (2H, d, *J* = 8.0 Hz, Ts ArCH), 7.33 (2H, d, *J* = 8.0 Hz, Ts ArCH), 6.90 (1H, dd, *J* = 8.0, 2.0 Hz, C**5**-H), 6.86 (1H, d, *J* = 2.0 Hz, C**9**-H), 6.76 (1H, d, *J* = 8.0 Hz, C**6**-H), 5.35 (1H, s, OH), 3.61 (2H, br s, C**1**-H_2), 2.48 (2H, t, *J* = 8.0 Hz, C**3**-H_2), 2.45 (3H, s, Ts CH_3), 1.95 – 1.84 (2H, m, C**2**-H_2), 1.83 – 1.76 (1H, m, C**10**-H), 1.21 (9H, s, Boc (CH_3)$_3$), 0.98 – 0.93 (2H, m, C**11**/C**12**-H_2), 0.66 – 0.63 (2H, m, C**11**/C**12**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6 (Boc C=O), 153.7 (C**7**), 145.8 (Ts ArC), 132.9 (C**4**), 131.4 (Ts, ArC), 129.8 (2 × Ts, ArCH), 129.6 (2 × Ts, ArCH), 128.5 (C**9**), 127.5 (C**5**), 127.5 (C**8**), 114.6 (C**6**), 83.3 (Boc C(CH_3)$_3$), 52.8 (C**1**), 32.2 (C**3**), 27.8 (C**2**), 27.7 (Boc (CH_3)$_3$), 21.8 (Ts CH_3), 9.5 (C**10**), 5.6 (C**11**, C**12**). HRMS (ESI$^+$) Calculated for $C_{24}H_{31}NNaO_6S$: 484.1764. Found $[M+Na]^+$: 484.1750.

7-Cyclopropyl-1-azaspiro[4.5]deca-6,9-dien-8-one trifluoroacetate (202) ***and*** **6-Cyclopropyl- 1,2,3,4-tetrahydroquinolin-7-ol (203)**

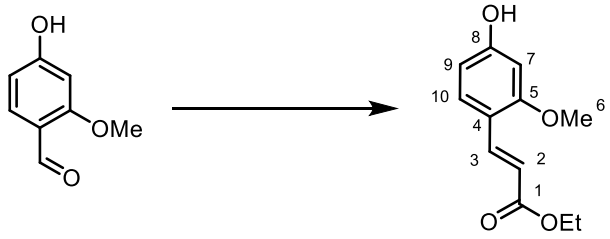


General procedure I: The preceding *N*-tosyloxycarbamate **195** (92.3 mg, 0.20 mmol) and TFA (31.0 μL, 0.40 mmol) in TFE (2 mL) were employed. After stirring at room temperature for 24 hours, purification by flash column chromatography (EtOAc) afforded the title compounds **202** (32.1 mg, 53%) and **203** (12.8 mg, 34%) as yellow solids.

Data for **202**: m.p.: 99-101 ºC (EtOAc:hexane); R_f = 0.1 (EtOAc); ν_{max} / cm^{-1} (*solid*) 2962 (m), 1667 (s), 1643 (s); ^{1}H NMR (400 MHz, CD_3OD) δ 7.07 (1H, dd, *J* = 10.0, 3.0 Hz, C**5**-H), 6.49 (1H, d, *J* = 3.0 Hz, C**9**-H), 6.43 (1H, dd, *J* = 10.0, 1.5 Hz, C**6**-H), 3.66 – 3.56 (2H, m, C**1**-H_2), 2.38 – 2.31 (2H, m, C**2**-H_2), 2.23 – 2.19 (2H, m, C**3**-H_2), 1.94 – 1.88 (1H, m, C**10**-H), 0.91 – 0.87 (2H, m, C**11**/C**12**-H_2), 0.65 – 0.62 (2H, m, C**11**/C**12**-H_2). *The signals corresponding to the NH_2 were not observed.* ^{13}C NMR (101 MHz, CD_3OD) δ 185.4 (C**7**), 144.5 (C**8**), 143.9 (C**5**), 134.6 (C**9**), 131.7 (C**6**), 64.9 (C**4**), 46.3 (C**1**), 37.8 (C**3**), 24.8 (C**2**), 10.0 (C**10**), 8.0 (C**11**/C**12**), 7.9 (C**11**/C**12**). *The signals corresponding to the trifluoroacetate group could not be resolved due to their weak intensity*. HRMS (ESI^+) Calculated for $C_{12}H_{16}NO$: 190.1226. Found $[M]^+$ 190.1230.

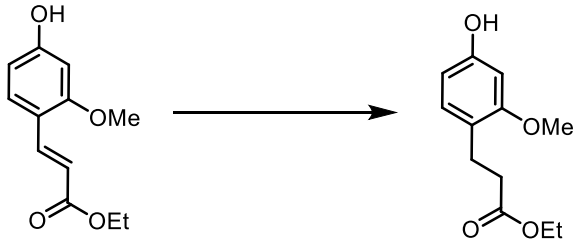
Data for **203**: m.p.: 108-110 ºC (EtOAc:hexane); R_f = 0.4 (EtOAc); ν_{max} / cm^{-1} (*solid*) 3306 (m), 2932 (m), 1614 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.68 (1H, s, C**5**-H), 6.04 (1H, s, C**8**-H), 5.10 (1H, br s, OH), 3.27 – 3.22 (2H, m, C**1**-H_2), 2.66 (2H, t, *J* = 6.5 Hz, C**3**-H_2), 1.93 – 1.87 (2H, m, C**2**-H_2), 1.69 – 1.62 (1H, m, C**10**-H), 0.89 – 0.84 (2H, m, C**11**/C**12**-H_2), 0.57 – 0.53 (2H, m, C**11**/C**12**-H_2), ^{13}C NMR (101 MHz, $CDCl_3$) 154.4 (C**7**), 144.5 (C**9**), 130.1 (C**5**), 116.3 (C**6**), 113.4 (C**4**), 100.1 (C**8**), 42.1 (C**1**), 26.4 (C**3**), 22.7 (C**2**), 8.7 (C**10**), 5.2 (C**11**,C**12**); HRMS (ESI^+) Calculated for $C_{12}H_{16}NO$: 190.1226. Found $[M+H]^+$: 190.1228.

Ethyl (*E*)-3-(4-hydroxy-2-methoxyphenyl)acrylate



General procedure J: 4-Hydroxy-2-methoxybenzaldehyde (3.04 g, 20.0 mmol) and ethyl 2-(triphenyl-phosphaneylidene) acetate (10.5 g, 30.0 mmol) in CH_2Cl_2 (20 mL) were employed. Purification by flash column chromatography (20% EtOAc:pentane) afforded the title compound (3.54 g, 80%) as a colourless solid; m.p.: 144-146 °C (EtOAc:hexane); R_f = 0.2 (20% EtOAc:hexane); ν_{max} / cm^{-1} (*solid*) 3322 (br m), 1675 (s); ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 7.88 (1H, d, *J* = 16.0 Hz, C**3**-H), 7.50 (1H, d, *J* = 8.5 Hz, C**10**-H), 6.53 (1H, d, *J* = 2.5 Hz, C**7**-H), 6.49 (1H, dd, *J* = 8.5, 2.5 Hz, C**9**-H), 6.39 (1H, d, *J* = 16.0 Hz, C**2**-H) 4.18 (2H, q, *J* = 7.0 Hz, OCH_2), 3.88 (3H, s, C**6**), 1.27 (3H, t, *J* = 7.0 Hz, CH_2CH_3); ^{13}C NMR (101 MHz, $(CD_3)_2CO$) δ 168.0 (C**1**), 162.1 (C**8**), 161.0 (C**5**), 140.5 (C**3**), 131.2 (C**10**), 115.8 (C**4**), 115.8 (C**2**), 108.9 (C**9**), 100.0 (C**7**), 60.4 (OCH_3), 56.0 (C**6**), 14.8 (CH_2CH_3); HRMS (ESI^+) Calculated for $C_{12}H_{14}NaO_4$: 245.0784. Found $[M+Na]^+$: 245.0784.

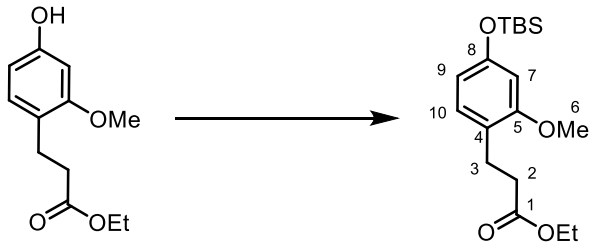
Ethyl 3-(4-hydroxy-2-methoxyphenyl)propanoate



General procedure E: Ethyl (*E*)-3-(4-hydroxy-2-methoxyphenyl)acrylate (2.22 g, 10.0 mmol) and 10 wt.% Pd/C (5 mol%) in EtOH (30 mL) were employed. Purification by flash column chromatography (20% EtOAc:hexane) afforded the title compound (1.80 g, 80%) as a colourless solid; R_f = 0.2 (20% EtOAc:hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (1H, d, *J* = 8.0 Hz), 6.38 (1H, d, *J* = 2.5 Hz), 6.31 (1H, dd, *J* = 8.0, 2.5 Hz), 4.13 (2H, q, *J* = 7.0 Hz), 3.74 (3H, s), 2.85 (2H, t, *J* = 8.0 Hz), 2.57 (2H, t, *J* = 8.0 Hz), 1.24 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.3, 158.6, 155.8, 130.4, 120.7, 106.7, 99.0, 60.6, 55.3, 34.8, 25.6, 14.30.

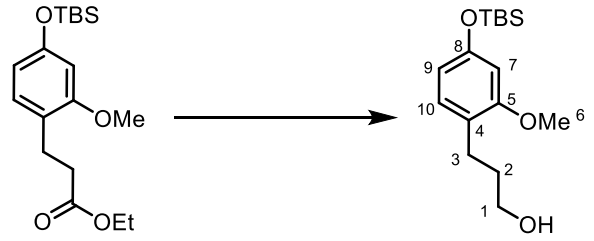
The spectroscopic properties were consistent with the data available in the literature.[297]

Ethyl 3-(4-((*tert*-butyldimethylsilyl)oxy)-2-methoxyphenyl)propanoate



To a solution of ethyl 3-(4-hydroxy-2-methoxyphenyl)propanoate (1.68 g, 7.50 mmol) in DMF (15 mL) was added *tert*-butyldimethylsilyl chloride (1.36 g, 9.00 mmol), and imidazole (1.28 g, 18.75 mmol) and the reaction was stirred at room temperature overnight. To the reaction was added water (25 mL) and the organic phases were extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (20% EtOAc:pentane) afforded the title compound (1.31 g, 52%) as a colourless oil; R_f = 0.4 (20% EtOAc:hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95 (1H, d, *J* = 8.5 Hz, C**10**-H), 6.36 – 6.32 (2H, m, C**7**-H, C**9**-H), 4.11 (2H, q, *J* = 7.0 Hz, OCH_2), 3.77 (3H, s, C**6**-H_3), 2.85 (2H, t, *J* = 8.0 Hz, C**3**-H_2), 2.55 (2H, t, *J* = 8.0 Hz, C**2**-H_2), 1.23 (3H, t, *J* = 8.0 Hz, CH_2CH_3), 0.98 (9H, s, TBS (CH_3)$_3$), 0.20 (6H, s, TBS Si(CH_3)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6 (C**1**), 158.3 (C**5**), 155.4 (C**8**), 130.1 (C**10**), 121.8 (C**4**), 111.3 (C**9**), 103.4 (C**7**), 60.3 (OCH_2), 55.3 (C**6**), 34.7 (C**2**), 25.9 (TBS (CH_3)$_3$), 25.7 (C**3**), 18.3 (TBS C(CH_3)$_3$), 14.4 (OCH_2CH_3), -4.3 (TBS Si(CH_3)$_2$); HRMS (ESI$^+$) Calculated for $C_{18}H_{30}NaO_4Si$: 361.1806. Found $[M+Na]^+$: 361.1821.

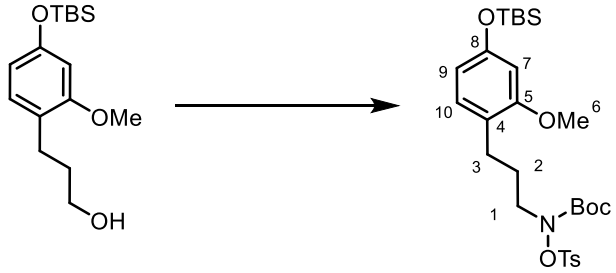
3-(4-((*tert*-Butyldimethylsilyl)oxy)-2-methoxyphenyl)propan-1-ol



General procedure B: Ethyl 3-(4-((*tert*-butyldimethylsilyl)oxy)-2-methoxyphenyl) propanoate (1.01 g, 3.00 mmol) and 1.5 equivalents of $LiAlH_4$ (1M in THF) in anhydrous Et_2O (15 mL) were employed. Purification by flash column chromatography (33% EtOAc:hexane) afforded the title compound (650 mg, 73%) as a colourless oil; R_f = 0.3 (33% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 3351 (br m), 2952 (m), 2930 (m), 2857 (m), 1607 (m), 1503 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95 (1H, d, *J* = 8.5 Hz, C**10**-H), 6.40 – 6.36 (2H, m, C**7**-H, C**9**-H), 3.79 (3H,

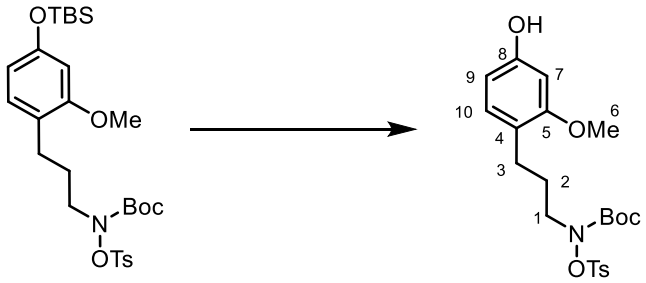
s, C**6**-H$_3$), 3.58 (2H, t, *J* = 6.0 Hz, C**1**-H$_2$), 2.64 (2H, t, *J* = 7.5 Hz, C**3**-H$_2$), 1.84 – 1.74 (3H, m, C**2**-H$_2$, OH), 0.99 (9H, s, TBS (CH$_3$)$_3$), 0.20 (6H, s, TBS Si(CH$_3$)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.2 (C**5**), 155.1 (C**8**), 130.3 (C**10**), 122.8 (C**4**), 111.8 (C**9**), 103.5 (C**7**), 62.1 (C**1**), 55.5 (C**6**), 33.2 (C**2**), 25.8, (TBS (CH$_3$)$_3$) 25.4 (C**3**), 18.3 (TBS C(CH$_3$)$_3$) , -4.3 (TBS Si(CH$_3$)$_2$); HRMS (ESI$^+$) Calculated for $C_{16}H_{28}NaO_3Si$: 319.1700. Found [M+Na]$^+$: 319.1707.

***tert*-Butyl (3-(4-((*tert*-butyldimethylsilyl)oxy)-2-methoxyphenyl)propyl)(tosyloxy) carbamate**



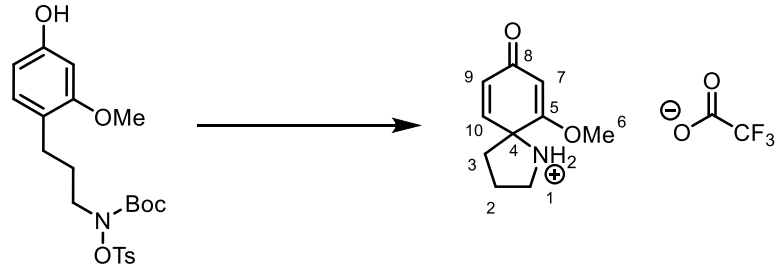
General procedure G: 3-(4-((*tert*-Butyldimethylsilyl)oxy)-2-methoxyphenyl)propan-1-ol (530 mg, 1.80 mmol), PPh_3 (560 mg, 2.16 mmol), DIAD (0.42 mL, 2.16 mmol) and BocNHOTs (620 mg, 2.16 mmol) in anhydrous THF (10 mL) were employed. Purification by flash column chromatography afforded the title compound (940 mg, 92%) as a colourless oil; R_f = 0.5 (33% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 2955 (m), 2930 (m), 1721 (s), 1504 (s), 1158 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (2H, d, *J* = 8.5 Hz, Ts ArCH), 7.32 (2H, d, *J* = 8.5 Hz, Ts ArCH), 6.90 (1H, d, *J* = 8.0 Hz, C**10**-H), 6.36 – 6.33 (2H, m, C**7**, C**9**-H), 3.75 (3H, s, C**6**-H$_3$), 3.69 – 3.48 (2H, m, C**1**-H$_2$), 2.49 (2H, t, *J* = 8.0 Hz, C**3**-H$_2$), 2.44 (3H, s, Ts CH$_3$), 1.94 – 1.78 (2H, m, C**2**-H$_2$), 1.22 (9H, s, Boc (CH$_3$)$_3$), 0.99 (9H, s, TBS (CH$_3$)$_3$), 0.20 (6H, s, TBS Si(CH$_3$)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.2 (C**5**), 155.6 (Boc C=O), 155.2 (C**8**), 145.7 (Ts ArC), 131.5 (Ts ArC), 129.8 (2 × Ts ArCH), 129.6 (2 × Ts ArCH), 122.4 (C**4**), 11.4 (C**9**), 103.5 (C**7**), 83.2 (Boc C(CH$_3$)$_3$), 55.3 (C**6**), 53.1 (C**1**), 27.8 (Boc (CH$_3$)$_3$), 26.7 (C**3**), 26.1 (C**2**), 25.9 (TBS (CH$_3$)$_3$), 21.8 (Ts CH$_3$), 18.4 (TBS C(CH$_3$)$_3$), -4.2 (TBS Si(CH$_3$)$_2$); HRMS (ESI$^+$) Calculated for $C_{28}H_{43}NNaO_7SSi$: 588.2422. Found [M+Na]$^+$: 588.2419.

***tert*-Butyl (3-(4-hydroxy-2-methoxyphenyl)propyl)(tosyloxy)carbamate (204)**



General procedure H: *tert*-Butyl (3-(4-((*tert*-butyldimethylsilyl)oxy)-2-methoxyphenyl) propyl)(tosyloxy)carbamate (560 mg, 1.00 mmol) and 1:1 TBAF:AcOH solution (0.1 M in THF, 1.00 mmol) in THF (20 mL) were employed. Purification by flash column chromatography (33% EtOAc:hexane) afforded **204** (380 mg, 84%) as a colourless viscous oil; R_f = 0.25 (33% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 3422 (br), 2936 (m), 1720 (m), 1368 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (2H, d, *J* = 8.5 Hz, Ts ArCH), 7.32 (2H, d, *J* = 8.5 Hz, Ts ArCH), 6.90 (1H, d, *J* = 8.0 Hz, C**10**-H), 6.38 (1H, d, *J* = 2.5 Hz, C**7**-H), 6.32 (1H, dd, *J* =8.0, 2.5 Hz, C**9**-H), 4.67 (1H, br s, OH), 3.76 (3H, s, C**6**-H_3), 3.70 – 3.48 (2H, m, C**1**-H_2), 2.48 (2H, t, *J* = 7.5 Hz, C**3**-H_2), 2.43 (3H, s, Ts CH_3), 1.94 – 1.78 (2H, m, C**2**-H_2), 1.22 (9H, s, Boc (CH_3)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.5 (C**5**), 155.7 (Boc C=O), 155.3 (C**8**), 145.7 (Ts ArC), 131.4 (Ts ArC), 130.1 (C**10**), 129.8 (2 × Ts ArCH), 129.6 (2 × Ts ArCH), 121.7 (C**4**), 106.6 (C**9**), 98.9 (C**7**), 83.3 (Boc C(CH_3)$_3$), 55.4 (C**6**), 53.1 (C**1**), 27.8 (Boc (CH_3)$_3$), 26.7 (C**3**), 26.1 (C**2**), 21.8 (Ts CH_3); HRMS (ESI^+) Calculated for $C_{22}H_{29}NNaO_7S$: 474.1557. Found $[M+Na]^+$: 474.1566.

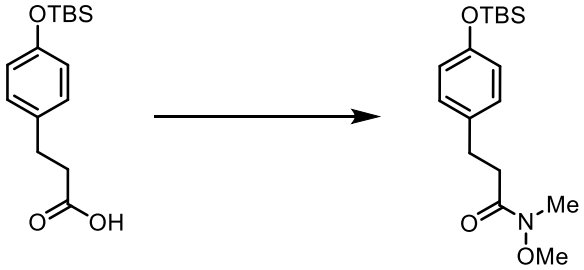
6-Methoxy-1-azaspiro[4.5]deca-6,9-dien-8-one trifluoroacetate (205)



General procedure I: The preceding *N*-tosyloxycarbamate **204** (67.7 mg, 0.15 mmol) and TFA (23 μL) in TFE (1.5 mL) were stirred at room temperature for 39 hours until completion by TLC analysis. Purification by flash column chromatography (EtOAc) afforded **205** (32.6 mg, 74%) as a viscous yellow oil; R_f = 0.1 (5% MeOH:CH_2Cl_2); ν_{max} / cm^{-1} (*film*) 2987 (m), 2901 (m), 1665 (s), 1636 (m), 1602 (s); ^{1}H NMR (400 MHz, CD_3OD) δ 6.93 (1H, d, *J* = 10.0 Hz, C**10**-H), 6.29 (1H, dd, *J* = 10.0, 1.5 Hz, C**9**-H) 5.79 (1H, d, *J* = 1.5 Hz, C**7**-H), 3.89 (3H,

s, C**6**-H$_3$), 3.66 – 3.54 (2H, m, C**1**-H$_2$), 2.53 – 2.46 (1H, m, C**3**-H), 2.40 – 2.22 (3H, m, C**3**-H', C**2**-H$_2$). *The signals corresponding to the NH$_2$ were not observed.* ^{13}C NMR (400 MHz, CD_3OD) δ 187.4 (C**8**), 171.2 (C**5**), 141.4 (C**10**), 130.0 (C**9**), 104.2 (C**7**), 65.6 (C**4**), 57.6 (C**6**), 48.7 (C**1**), 38.0 (C**3**), 26.0 (C**2**). *The signals corresponding to the trifluoroacetate group could not be resolved due to their weak intensity*. HRMS (ESI$^+$) Calculated for $C_{10}H_{14}NO_2$: 180.1019. Found $[M+H]^+$: 180.1021.

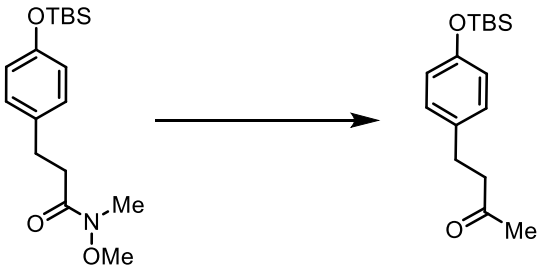
3-(4-((*tert*-Butyldimethylsilyl)oxy)phenyl)-*N*-methoxy-*N*-methylpropanamide (207)



General procedure K: Carboxylic acid **206** (2.40 g, 8.57 mmol), *N*,*O*-dimethylhydroxylamine hydrochloride (1.17 g, 12.0 mmol), Et_3N (1.67 mL, 12.0 mmol), 4-dimethylaminopyridine (1.46 g, 12.0 mmol), and *N*,*N*'-dicyclohexylcarbodiimide (2.48 g, 12.0 mmol) were employed. Purification by flash column chromatography (20% EtOAc:hexane) afforded **207** (1.97 g, 71%) as a colourless oil; R_f = 0.2 (33% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 2955 (m), 2930 (m), 2857 (m), 1665 (s), 1509 (s), 1250 (s), 1169 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (2H, d, *J* = 8.0 Hz), 6.75 (2H, d, *J* = 8.0 Hz), 3.57 (3H, s), 3.16 (3H, s), 2.88 (2H, t, *J* = 7.5 Hz), 2.71 – 2.67 (2H, m), 0.97 (9H, s), 0.17 (6H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.7, 153.8, 133.9, 129.2, 119.9, 61.1, 33.9, 32.1, 29.9, 25.6, 18.1, -4.4.

The spectroscopic properties were consistent with the data available in the literature.[298]

4-(4-((*tert*-Butyldimethylsilyl)oxy)phenyl)butan-2-one

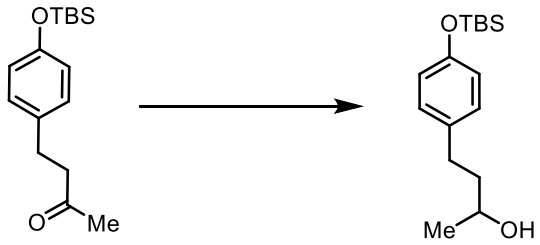


To a solution of the preceding *N*-methoxyamide **207** (690 mg, 2.15 mmol) in anhydrous THF (5 mL) at 0 °C was added methyl magnesium bromide (3 M in Et_2O, 1.43 mL, 4.30 mmol) dropwise over 5 minutes. The reaction mixture was stirred at room temperature for 1.5 hours

and then saturated aqueous NH_4Cl (5 mL) was added. The aqueous phase was extracted with EtOAc (3 × 5mL) and the combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo* to afford the title compound (600 mg, 99%) as a colourless oil, which was used without further purification; R_f = 0.6 (33% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 2955 (m), 2929 (m), 2888 (m), 2857 (m), 1716 (s), 1610 (m), 1509 (s), 1361 (m), 1251 (s), 1159 (m), 1168 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 7.02 (2H, d, *J* = 8.0 Hz), 6.75 (2H, d, *J* = 8.0 Hz), 2.85 – 2.68 (4H, m), 2.12 (3H, s), 0.98 (9H, s), 0.18 (6H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.2, 153.9, 133.6, 129.2, 120.1, 45.5, 30.2, 29.1, 25.8, 18.2, -4.3.

The spectroscopic properties were consistent with the data available in the literature. [299]

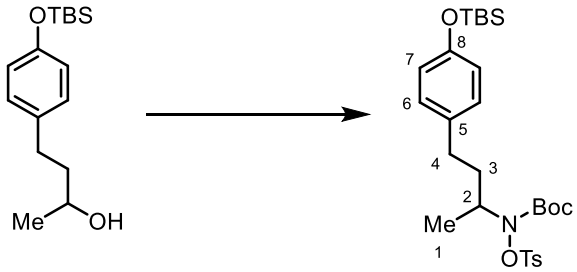
4-(4-((*tert*-Butyldimethylsilyl)oxy)phenyl)butan-2-ol (208)



To a solution of 4-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)butan-2-one (560 mg, 2.14 mmol) in MeOH (10 mL) was slowly added $NaBH_4$ (160 mg, 4.28 mmol) at 0 °C. After stirring for 45 minutes at this temperature the reaction was quenched by addition of water (10 mL) and extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford **208** (550 mg, 92%) as a colourless oil which was used without further purification; R_f = 0.5 (33% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 3339 (m, br), 2957 (m), 2929 (m), 2857 (m), 1609 (m), 1508 (s), 1250 (s), 1168 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 7.05 (2H, d, *J* = 8.5 Hz), 6.76 (2H, d, *J* = 8.5 Hz), 3.86 – 3.77 (1H, m), 2.72 – 2.57 (2H, m), 1.80 – 1.69 (2H, m), 1.65 – 1.54 (1H, br s), 1.22 (3H, d, *J* = 6.0 Hz), 0.99 (9H, s), 0.19 (6H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.6, 134.7, 129.2, 119.9, 67.5, 41.0, 31.3, 25.7, 23.6, 18.2, -4.4.

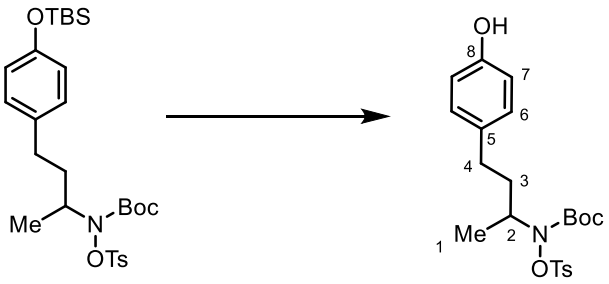
The spectroscopic properties were consistent with the data available in the literature.[300]

***tert*-Butyl (4-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)butan-2-yl)(tosyloxy)carbamate**



General procedure G: The preceding alcohol **208** (220 mg, 0.77 mmol), PPh_3 (240 mg, 0.92 mmol), DIAD (0.18 mL, 0.92 mmol) and BocNHOTs (260 mg, 0.92 mmol) in anhydrous THF (3 mL) were employed. Purification by flash column chromatography (10% EtOAc:hexane) afforded the title compound (340 mg, 75%) as a colourless oil; R_f = 0.6 (20% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 2954 (m), 2930 (m), 2857 (m), 1721 (m), 1509 (s), 1368 (m), 1251 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.32 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.01 (2H, d, *J* = 8.5 Hz, C**6**-<u>H</u>), 6.73 (2H, d, *J* = 8.5 Hz, C**7**-<u>H</u>), 3.97 (1H, app. sextet, *J* = 7.0 Hz, C**2**-<u>H</u>), 2.61 – 2.57 (2H, m, C**4**-<u>H_2</u>), 2.43 (3H, s, Ts C<u>H_3</u>), 2.06 – 1.97 (1H, m, C**3**-<u>H</u>), 1.74 – 1.66 (1H, m, C**3**-<u>H</u>'), 1.27 (9H, s, Boc (C<u>H_3</u>)$_3$), 1.21 (3H, d, *J* = 7.0 Hz, C**1**-<u>H_3</u>), 0.97 (9H, s, TBS (C<u>H_3</u>)$_3$), 0.17 (6H, s, TBS Si(C<u>H_3</u>)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.4 (Boc <u>C</u>=O), 153.8 (C**8**), 145.6 (Ts Ar<u>C</u>), 134.4 (C**5**), 131.9 (Ts Ar<u>C</u>), 129.7 (2 × Ts Ar<u>C</u>H), 129.6 (2 × Ts Ar<u>C</u>H), 129.3 (C**6**), 119.9 (C**7**), 83.4 (Boc <u>C</u>$(CH_3)_3$, 60.8 (C**2**), 32.2 (C**3**), 29.8 (C**4**), 27.8 (Boc (<u>C</u>H_3)$_3$), 25.8 (TBS (<u>C</u>H_3)$_3$), 21.8 (Ts <u>C</u>H_3), 18.3 (TBS Si<u>C</u>$(CH_3)_3$), 17.4 (C**1**), -4.4 (TBS Si(<u>C</u>H_3)$_2$); HRMS (ESI^+) Calculated for $C_{28}H_{43}NNaO_6SSi$: 572.2473. Found $[M+Na]^+$: 572.2465.

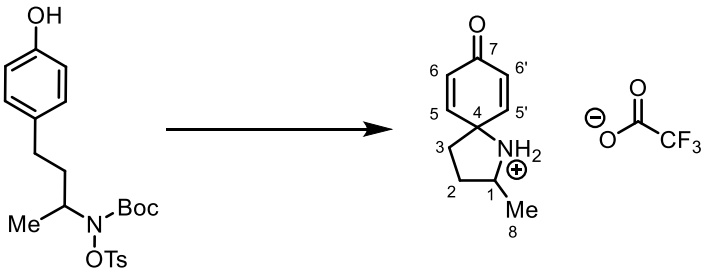
***tert*-Butyl (4-(4-hydroxyphenyl)butan-2-yl)(tosyloxy)carbamate (209)**



General procedure H: *tert*-Butyl (4-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)butan-2-yl) (tosyloxy) carbamate (320 mg, 0.58 mmol) and 1:1 TBAF:HOAc solution (0.1 M in THF, 0.58 mmol) in THF (20 mL) were employed. Purification by flash column chromatography (20% EtOAc:hexane) afforded **209** (190 mg, 75%) as a colourless oil; R_f = 0.2 (20% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 3477 (br m), 2979 (m), 1721 (s), 1515 (s), 1369 (s), 1191 (s), 1177 (s), 1156

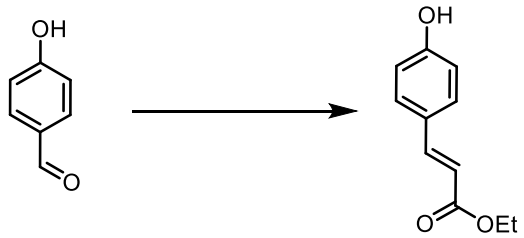
(s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.31 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.01 (2H, d, *J* = 8.0 Hz, C**6**-<u>H</u>), 6.74 (2H, d, *J* = 8.5 Hz, C**7**-<u>H</u>), 5.14 (1H, br s, O<u>H</u>), 3.97 (1H, app. sextet, *J* = 7.0 Hz, C**2**-<u>H</u>), 2.58 (2H, t, *J* = 7.5 Hz, C**4**-<u>H_2</u>), 2.42 (3H, s, Ts C<u>H_3</u>), 2.05 – 1.95 (1H, m, C**3**-<u>H</u>), 1.73 – 1.60 (1H, m, C**3**-<u>H</u>'), 1.27 (9H, s, Boc (C<u>H_3</u>)$_3$), 1.20 (3H, d, *J* = 7.0 Hz, C**1**-<u>H_3</u>); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.5 (Boc <u>C</u>=O) 153.9 (C**8**), 145.7 (Ts ArC), 133.7 (C**5**), 131.8 (Ts ArC), 129.7 (2 × Ts Ar<u>C</u>H), 129.6 (2 × Ts Ar<u>C</u>H), 129.5 (C**6**), 115.3 (C**7**), 83.6 (Boc <u>C</u>(CH_3)$_3$), 60.8 (C**2**), 36.0 (C**3**) 32.1 (C**4**), 27.8 (Boc C(<u>C</u>H_3)$_3$), 21.8 (Ts <u>C</u>H_3), 17.4 (C**1**); HRMS (ESI$^+$) Calculated for $C_{22}H_{29}NNaO_6S$: 458.1608. Found $[M+Na]^+$: 458.1597.

2-Methyl-1-azaspiro[4.5]deca-6,9-dien-8-one trifluoroacetate (210)



<u>General procedure I:</u> The preceding *N*-tosyloxycarbamate **209** (93.0 mg, 0.21 mmol) and TFA (32 μL, 0.42 mmol) in TFE (2.1 mL) were stirred at room temperature for 24 hours. Purification by flash column chromatography (EtOAc) afforded **210** (34.0 mg, 58%) as a yellow/brown oil; R_f = 0.1 (5% MeOH:CH_2Cl_2); ν_{max} / cm^{-1} (*film*, $CDCl_3$) 2922 (m), 1667 (s), 1635 (m), 1393 (m), 1173 (s), 1133 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (2H, br s, N<u>H_2</u>), 7.04 (1H, dd, *J* = 10.0, 3.0 Hz, C**5**-<u>H</u>), 6.95 (1H, dd, *J* = 10.0, 3.0 Hz, C**5**-<u>H</u>'), 6.33 – 6.32 (1H, m, C**6**-<u>H</u>), 6.31 – 6.29 (1H, m, C**6**-<u>H</u>'), 4.05 – 3.96 (1H, m, C**1**-<u>H</u>), 2.47 – 2.39 (1H, m, C**2**-<u>H</u>), 2.36 – 2.29 (1H, m, C**3**-<u>H</u>), 2.24 – 2.17 (1H, m, C**3**-<u>H</u>'), 2.08 – 1.98 (1H, m, C**2**-H'), 1.46 (3H, d, *J* = 6.5 Hz, C**8**-<u>H_3</u>); ^{13}C NMR (101 MHz, $CDCl_3$) δ 183.6 (C**7**), 143.6 (C**5**), 143.0 (C**5**), 130.5 (C**6**), 130.4 (C**6**), 63.2 (C**4**), 57.2 (C**1**), 37.1 (C**3**), 32.0 (C**2**), 17.5 (C**8**); HRMS (ESI$^+$) Calculated for $C_{10}H_{14}NO$: 164.1070. Found $[M+H]^+$: 164.1068.

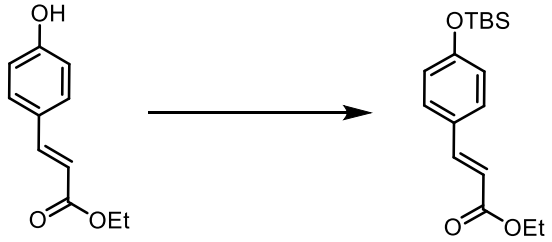
Ethyl (*E*)-3-(4-hydroxyphenyl)acrylate



General procedure J: 4-Hydroxybenzaldehyde (4.88 g, 40.0 mmol) and ethyl (triphenylphosphoranylidene)acetate (20.9 g, 60.0 mmol) in CH_2Cl_2 (40 mL) were employed. Purification by flash column chromatography (20% EtOAc:hexane) afforded the title compound (6.56 g, 85%) as a colourless solid; R_f = 0.5 (33% EtOAc:hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (1H, d, *J* = 16.0 Hz), 7.42 (2H, d, *J* = 8.5 Hz), 6.86 (2H, d, *J* = 8.5 Hz), 6.30 (1H, d, *J* = 16.0 Hz), 6.14 (1H, br s), 4.27 (2H, q, *J* = 7.0 Hz), 1.34 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (101 MHz) δ 168.1, 158.1, 144.9, 132.4, 130.1, 127.2, 116.1, 115.5, 115.1, 60.8, 14.5.

The spectroscopic properties were consistent with the data available in the literature.[301]

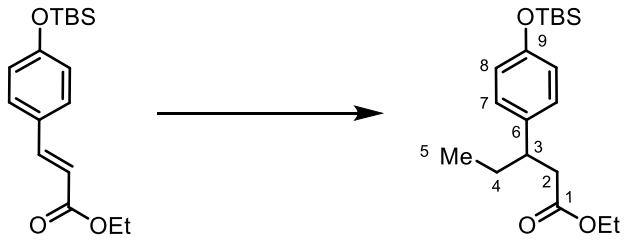
Ethyl (*E*)-3-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)acrylate (211)



To a solution of Ethyl (*E*)-3-(4-hydroxyphenyl)acrylate (3.84 g, 20.0 mmol) in DMF (20 mL) were added *tert*-butyldimethylsilyl chloride (3.60 g, 24.0 mmol) and imidazole (3.40 g, 50.0 mmol) and the reaction was stirred overnight at room temperature until completion by TLC analysis. Purification by flash column chromatography (20% EtOAc:hexane) afforded **211** (5.13 g, 84%) as a colourless oil; R_f = 0.4 (10% EtOAc:hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (1H, d, *J* = 16.0 Hz), 7.41 (2H, d, *J* = 8.5 Hz), 6.83 (2H, d, *J* =8.5 Hz), 6.30 (1H, d, *J* = 16.0 Hz), 4.25 (2H, q, *J* = 7.5 Hz), 1.33 (3H, t, *J* = 7.5 Hz), 0.98 (9H, s, TBS ($C\underline{H}_3)_3$), 0.22 (6H, s, TBS Si($C\underline{H}_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.5, 157.9, 144.4, 129.8, 127.9, 120.6, 116.1, 60.4, 25.8, 18.4, 14.5, -4.2.

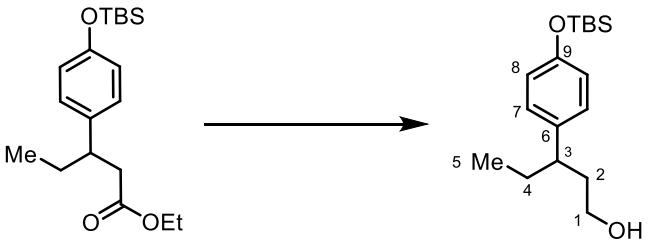
The spectroscopic properties were consistent with the data available in the literature. [302]

Ethyl 3-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)pentanoate (212)



CuI (2.86 g, 15.0 mmol) in anhydrous Et_2O (60 mL) was stirred under nitrogen at room temperature until a suspension was observed. The mixture was cooled to -20 ^oC and EtMgBr (3.0 M solution in Et_2O, 37.5 mmol) was added. After stirring for 5 minutes, a solution of the preceding α,β-unsaturated ester **211** (4.6 g, 15.0 mmol) in anhydrous Et_2O (15 mL) was added dropwise over 1 hour. After stirring at -20 ^oC for 4 hours, MeOH (15 mL) and saturated aqueous NH_4Cl (60 mL) were sequentially added and the mixture was warmed to room temperature. After extracting with Et_2O (3 × 20 mL), the combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography (20% EtOAc:hexane) afforded **212** (4.36 g, 86%) as a pale yellow oil; R_f = 0.5 (10% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 2958 (m), 2930 (m), 2858 (m), 1735 (s), 1509 (s), 1252 (s), 1165 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 7.02 (2H, d, *J* = 8.5 Hz, C**7**-H), 6.75 (2H, d, *J* = 8.5 Hz, C**8**-H), 4.02 (2H, q, *J* = 7.0 Hz, OCH_2CH_3), 2.97 – 2.89 (1H, m, C**3**-H), 2.59 (1H, dd, *J* = 15.0, 7.0 Hz, C**2**-H), 2.50 (1H, dd, *J* = 15.0, 8.5 Hz, C**2**-H'), 1.73 – 1.61 (1H, m, C**4**-H), 1.59 – 1.49 (1H, m, C**4**-H'), 1.12 (3H, t, *J* = 7.0 Hz, OCH_2CH_3), 0.97 (9H, s, TBS $(CH_3)_3$), 0.77 (3H, t *J* = 7.3 Hz, C**5**-H_3), 0.18 (6H, s, TBS $Si(CH_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.7 (C**1**), 154.1 (C**9**), 136.6 (C**6**), 128.5 (C**7**), 119.9 (C**8**), 60.2 (OCH_2CH_3), 43.4 (C**3**), 41.9 (C**2**) 29.4 (C**4**), 25.8 (TBS $(CH_3)_3$), 18.3 (TBS $SiC(CH_3)_3$), 14.3 (OCH_2CH_3), 12.0 (C**5**), -4.4 (TBS $Si(CH_3)_2$); HRMS (ESI^+) Calculated for $C_{19}H_{32}NaO_3Si$: 359.2013. Found $[M+Na]^+$: 359.2016.

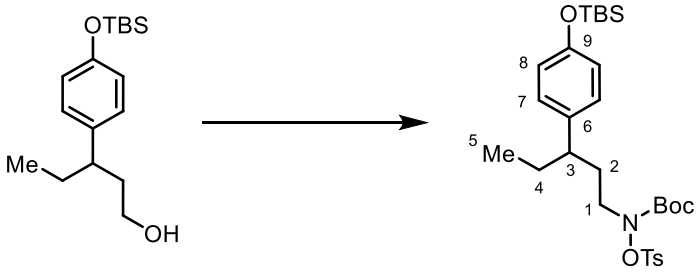
3-(4-((*tert*-Butyldimethylsilyl)oxy)phenyl)pentan-1-ol



General procedure B: The preceding ester **212** (4.10 g, 12.2 mmol), 1.0 equivalent of $LiAlH_4$ (1M in THF) and anhydrous Et_2O were employed. The title compound (3.03 g, 84%) was

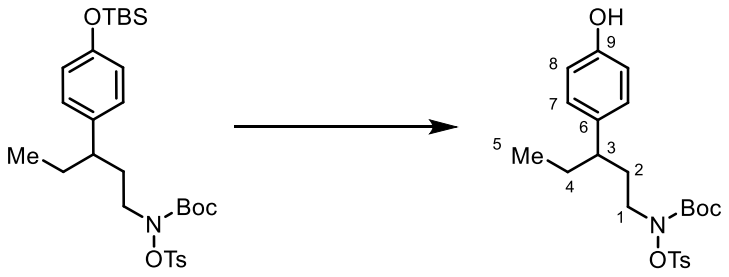
obtained as a colourless oil which was used without further purification; R_f = 0.3 (20% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 3354 (br m), 2956 (m), 2929 (m), 2858 (m), 1607 (m), 1508 (s), 1253 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (2H, d, *J* = 8.5 Hz, C**7**-H), 6.76 (2H, d, *J* = 8.5 Hz, C**8**-H), 3.55 – 3.43 (2H, m, C**1**-H_2), 2.55 – 2.47 (1H, m, C**3**-H), 1.94 – 1.87 (1H, m, C**2**-H), 1.79 – 1.72 (1H, m, C**2**-H'), 1.70 – 1.61 (1H, m, C**4**-H), 1.57 – 1.49 (1H, m, C**4**-H'), 0.98 (9H, s, TBS (CH_3)$_3$), 0.77 (3H, t, *J* = 7.4 Hz, C**5**-H_3), 0.19 (6H, s, TBS Si(CH_3)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.0 (C**9**), 137.6 (C**6**), 128.6 (C**7**), 120.0 (C**8**), 61.5 (C**1**), 43.7 (C**3**), 39.6 (C**2**), 30.1 (C**4**), 25.8 (TBS C(CH_3)$_3$), 18.3 (TBS C(CH_3)$_3$), 12.2 (C**5**), -4.3 (TBS Si(CH_3)$_2$); HRMS (ESI^+) Calculated for $C_{17}H_{30}NaO_2Si$: 317.1907. Found $[M+Na]^+$: 317.1917.

***tert*-Butyl (3-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)pentyl)(tosyloxy)carbamate**



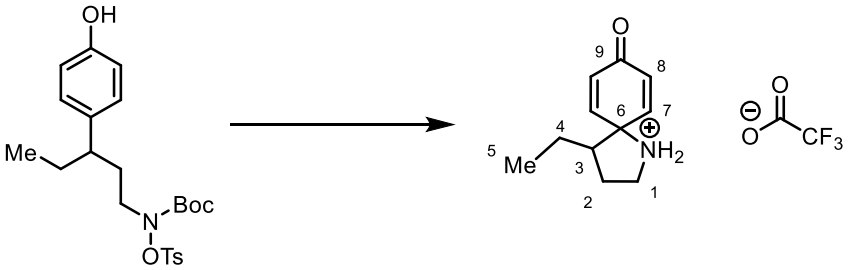
General procedure G: 3-(4-((*tert*-Butyldimethylsilyl)oxy)phenyl)pentan-1-ol (2.94 g, 10.0 mmol), PPh_3 (3.15 g, 12.0 mmol mmol), DIAD (2.36 mL, 12.0 mmol) and BocNHOTs (3.44 g, 12.0 mmol) in anhydrous THF (40 mL) were employed. Purification by flash column chromatography (5% EtOAc:hexane) afforded the title compound (5.35 g, 95%) as a colourless oil; R_f = 0.6 (20% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 2962 (m), 2931 (m), 1721 (s), 1509 (s), 1382 (s), 1369 (s), 1253 (s), 1191 (s), 1155 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (2H, d, *J* = 8.0 Hz, Ts ArCH), 7.28 (2H, d, *J* = 8.0 Hz, Ts ArCH), 6.93 (2H, d, *J* = 8.5 Hz, C**7**-H), 6.74 (2H, d, *J* = 8.5 Hz, C**8**-H), 3.48 – 3.19 (2H, m, C**1**-H_2), 2.42 (3H, s, Ts CH_3), 2.33 – 2.26 (1H, m, C**3**-H), 1.94 (1H, br s, C**2**-H), 1.76 (1H, br s, C**2**-H'), 1.66 – 1.57 (1H, m, C**4**-H), 1.53 – 1.43 (1H, m, C**4**-H'), 1.22 (9H, s, Boc (CH_3)$_3$), 0.98 (9H, s, TBS (CH_3)$_3$), 0.73 (3H, t, *J* = 7.3 Hz, C**5**-H_3), 0.18 (6H, s, TBS Si(CH_3)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) 155.5 (Boc C=O), 154.0 (C**9**), 145.7 (Ts ArC), 136.9 (C**6**), 131.4 (Ts ArC), 129.7 (2 × Ts ArCH), 129.6 (2 × Ts ArCH), 128.4 (C**7**), 120.0 (C**8**) 83.2 (Boc C(CH_3)$_3$), 52.0 (C**1**), 44.6 (C**3**), 32.0 (C**2**), 30.1 (C**4**), 27.8 (Boc (CH_3)$_3$), 25.8 (TBS C(CH_3)$_3$), 21.8 (Ts CH_3), 18.3 (TBS C(CH_3)$_3$), 12.1 (C**5**) , -4.3 (TBS Si(CH_3)$_2$); HRMS (ESI^+) Calculated for $C_{29}H_{45}NO_6SSi$: 586.2629. Found $[M+Na]^+$: 586.2628.

***tert*-Butyl (3-(4-hydroxyphenyl)pentyl)(tosyloxy)carbamate (213)**



General procedure H: *tert*-Butyl (3-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)pentyl) (tosyloxy)carbamate (2.82 g, 5.0 mmol) and 1:1 TBAF:HOAc (0.1 M in THF, 5.0 mmol) in THF (50 mL) were employed. Purification by flash column chromatography (20% EtOAc:hexane) afforded **213** (1.80 g, 80%) as a colourless solid; m.p.: 93-95 ^{o}C (EtOAc:hexane); R_f = 0.4 (33% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 3436 (br m), 2965 (m), 2930 (m), 1720 (s), 1514 (s), 1368 (s), 1191 (s), 1177 (s), 1153 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (2H, d, *J* = 8.0 Hz, Ts ArC<u>H</u>), 7.28 (2H, d, *J* = 8.0 Hz, Ts ArC<u>H</u>), 6.95 (2H, d, *J* = 8.5 Hz C**7**-<u>H</u>), 6.74 (2H, d, *J* = 8.5 Hz, C**8**-<u>H</u>), 4.93 (1H, br s, O<u>H</u>), 3.51 – 3.16 (2H, br s, C**1**-<u>H_2</u>), 2.42 (3H, s, Ts C<u>H_3</u>), 2.34 – 2.27 (1H, m, C**3**-<u>H</u>), 1.95 (1H, br s, C**2**-<u>H</u>), 1.77 (1H, br s, C**2**-<u>H</u>'), 1.66 – 1.54 (1H, m, C**4**-<u>H</u>), 1.52 – 1.43 (1H, m, C**4**-<u>H</u>'), 1.22 (9H, s, Boc (C<u>H_3</u>)$_3$), 0.73 (3H, t, *J* = 7.3 Hz, C**5**-<u>H_3</u>); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6 (Boc <u>C</u>=O), 154.1 (C**9**), 145.8 (Ts Ar<u>C</u>), 136.3 (C**6**), 131.3 (Ts Ar<u>C</u>), 129.7 (2 × Ts ArC<u>H</u>), 129.6 (2 × Ts ArC<u>H</u>), 128.7 (C**7**), 115.4 (C**8**), 83.4 (Boc <u>C</u>(CH_3)$_3$), 51.9 (C**1**), 44.5 (C**3**), 32.0 (C**2**), 30.1 (C**4**), 27.8 (Boc (<u>C</u>H_3)$_3$), 21.8 (Ts <u>C</u>H_3), 12.05 (C**5**); HRMS (ESI$^+$) Calculated for $C_{23}H_{31}NNaO_6S$: 472.1764. Found [M+H]$^+$: 472.1763.

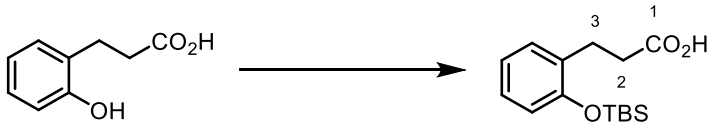
4-Ethyl-1-azaspiro[4.5]deca-6,9-dien-8-one trifluoroacetate (214)



General procedure I: The preceding *N*-tosyloxycarbamate **213** (89.9 mg, 0.20 mmol) and TFA (31 μL, 0.40 mmol) in anhydrous TFE (2 mL) were employed. Purification by flash column chromatography (EtOAc) afforded **214** (40.0 mg, 69%) as a red/brown oil; R_f = 0.1 (5% MeOH:CH_2Cl_2); ν_{max} / cm^{-1} (*film*) 2966 (m), 1673 (s), 1636 (m), 1404 (m), 1201 (s), 1134

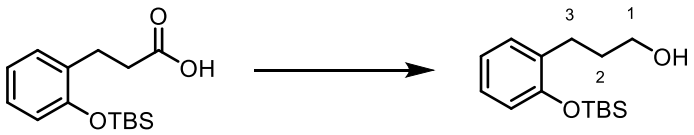
(s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (1H, dd, *J* = 10.5, 3.0 Hz, C**7**-H), 6.78 (1H, dd, *J* = 10.5, 3.0 Hz, C**7**-H'), 6.43 - 6.36 (2H, m, C**8**-H_2), 3.62 – 3.45 (2H, m, C**1**-H_2), 2.53 – 2.44 (1H, m, C**3**-H), 2.40 – 2.31 (1H, m, C**2**-H), 1.93 – 1.81 (1H, m, C**2**-H'), 1.31 – 1.23 (1H, m, C**4**-H), 1.14 – 1.05 (1H, m, C**4**-H'), 0.91 (3H, *J* = 7.5 Hz, C**5**-H_3); *The signals corresponding to the NH_2 were not observed.* ^{13}C NMR (101 MHz, $CDCl_3$) δ 183.5 (C**9**), 143.7 (C**7**), 139.6 (C**7'**), 132.4 (C**8**), 132.0 (C**8'**), 65.5 (C**6**), 50.8 (C**3**), 43.4 (C**1**), 29.3 (C**2**), 21.5 (C**4**), 12.5 (C**5**); *The signals corresponding to the trifluoroacetate group could not be resolved due to their weak intensity*. HRMS (ESI$^+$) Calculated for $C_{11}H_{16}NO^+$: 178.1226. Found $[M+H]^+$: 178.1225.

3-(2-((*tert*-Butyldimethylsilyl)oxy)phenyl)propanoic acid



General procedure A: Carboxylic acid **215** (4.15 g, 25.0 mmol), *tert*-butyldimethylsilyl chloride (8.28 g, 55.0 mmol) and imidazole (5.62 g, 82.5 mmol) in DMF (50 mL) were employed. Purification by flash column chromatography (20% EtOAc:hexane) afforded the title compound (4.40 g, 63%) as a pale yellow oil; ν_{max} / cm^{-1} (*film*) 2954 (m), 2930 (m), 2896 (m), 2858 (m), 1706 (s), 1490 (s), 1453 (m), 1250 (s), 1106 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (1H, dd, *J* = 7.5, 2.0 Hz, ArCH), 7.12 (1H, td, *J* = 7.5, 2.0 Hz, ArCH), 6.90 (1H, td, *J* = 7.5, 1.0 Hz, ArCH), 6.81 (1H, dd, *J* = 8.0, 1.0 Hz, ArCH), 2.94 (2H, t, *J* = 8.0 Hz, C**2** or C**3**), 2.67 (2H, t, *J* = 8.0 Hz, C**2** or C**3**), 1.04 (9H, s, TBS (CH_3)$_3$), 0.27 (6H, s, TBS Si(CH_3)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ179.6 (C**1**), 153.7 (ArC), 130.7 (ArC), 130.2 (ArCH), 127.5 (ArCH), 121.1 (ArCH), 118.4 (ArCH), 31.2 (C**2** or C**3**), 26.0 (C**2** or C**3**), 25.8 (TBS (CH_3)$_3$), 18.2 (TBS C(CH_3)$_3$), -4.1 (TBS Si(CH_3)$_2$).

3-(2-((*tert*-Butyldimethylsilyl)oxy)phenyl)propan-1-ol (216)

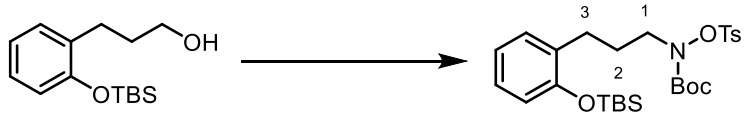


General procedure F: 3-(2-((*tert*-Butyldimethylsilyl)oxy)phenyl)propanoic acid (1.40 g, 5.00 mmol), Et_3N (0.69 mL, 5.00 mmol), ethyl chloroformate (0.48 mL, 5.00 mmol) and $NaBH_4$ (470 mg, 12.5 mmol) in THF (50 mL) and H_2O (20 mL) were employed. Purification by flash column chromatography (15% EtOAc:hexane) afforded **216** (850 mg, 64%) as a colourless oil;

ν_{max}/cm^{-1} (*film*) 3334 (m, br), 2953 (m), 2930 (m), 2884 (m), 2858 (m), 1489 (s), 1249 (s); ^{1}H NMR (400MHz, $CDCl_3$) δ 7.14 (1H, dd, *J* = 7.5, 2.0 Hz, ArC<u>H</u>), 7.08 (1H, td, *J* = 7.5, 2.0 Hz, ArC<u>H</u>), 6.89 (1H, td, *J* = 7.5, 1.0 Hz, ArC<u>H</u>), 6.80 (1H, dd, *J* = 8.0, 1.0 Hz, ArC<u>H</u>), 3.63 (2H, t, *J* = 6.5 Hz, C**1**-<u>H</u>$_2$), 2.69 (2H, t, *J* = 7.5 Hz, C**3**-<u>H</u>$_2$), 1.89 – 1.82 (2H, m, C**2**-<u>H</u>$_2$), 1.59 (1H, s, O<u>H</u>), 1.02 (9H, s, TBS (C<u>H</u>$_3$)$_3$), 0.24 (6H, s, TBS Si(C<u>H</u>$_3$)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.7 (Ar<u>C</u>), 132.4 (Ar<u>C</u>), 130.5 (Ar<u>C</u>H), 127.0 (Ar<u>C</u>H), 121.4 (Ar<u>C</u>H), 118.7 (Ar<u>C</u>H), 62.5 (C**1**), 33.2 (C**3**), 26.6 (C**2**), 25.9 (TBS (<u>C</u>H$_3$)$_3$), 18.4 (TBS <u>C</u>(CH$_3$)$_3$), -4.0 (TBS Si(<u>C</u>H$_3$)$_2$).

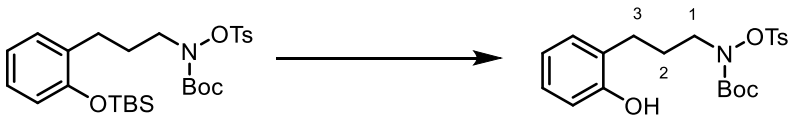
The spectroscopic properties were consistent with the data available in the literature.[303]

***tert*-Butyl (3-(2-((*tert*-butyldimethylsilyl)oxy)phenyl)propyl)(tosyloxy)carbamate**



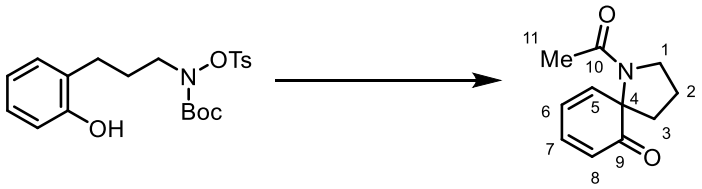
<u>General procedure G:</u> The preceding alcohol **216** (370 mg, 1.40 mmol), PPh_3 (440 mg, 1.66 mmol), DIAD (0.32 mL, 1.66 mmol) and BocNHOTs (470 mg, 1.66 mmol) in anhydrous THF (8 mL) were employed. Purification by flash column chromatography (10% EtOAc:hexane) afforded the title compound (550 mg, 73%) as a colourless oil; ν_{max} / cm^{-1} (*film*) 2954 (m), 2928 (m), 1724 (s), 1490 (s), 1366 (s), 1251 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.32 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.12 – 7.04 (2H, m, ArC<u>H</u>), 6.87 (1H, td, *J* = 7.5, 1.2 Hz, ArC<u>H</u>), 6.77 (1H, dd, *J* = 8.0, 1.0 Hz, ArC<u>H</u>), 3.55 (2H, br s, C**1**-<u>H</u>$_2$), 2.55 (2H, t, *J* = 8.0 Hz, C**3**-<u>H</u>$_2$), 2.44 (3H, s, Ts C<u>H</u>$_3$), 1.97 – 1.84 (2H, m, C**2**-<u>H</u>$_2$), 1.20 (9H, s, Boc (C<u>H</u>$_3$)$_3$), 1.01 (9H, s, TBS (C<u>H</u>$_3$)$_3$), 0.23 (6H, s, TBS Si(C<u>H</u>$_3$)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.4 (Boc <u>C</u>=O), 153.5 (Ar<u>C</u>), 145.5 (Ts Ar<u>C</u>), 131.6 (Ar<u>C</u>), 131.3 (Ar<u>C</u>), 130.0 (Ar<u>C</u>H), 129.7 (2 × Ts Ar<u>C</u>H), 129.5 (2 × Ts Ar<u>C</u>H), 127.0 (Ar<u>C</u>H), 121.0 (Ar<u>C</u>H), 118.4 (Ar<u>C</u>H), 83.1 (Boc <u>C</u>(CH$_3$)$_3$), 52.8 (C**1**), 27.6 (Boc (<u>C</u>H$_3$)$_3$, 27.5 (C**3**), 25.9 (C**2**), 25.8 (TBS (<u>C</u>H$_3$)$_3$), 21.7 (Ts <u>C</u>H$_3$), 18.2 (TBS <u>C</u>(CH$_3$)$_3$), -4.1 (TBS Si(<u>C</u>H$_3$)$_2$). HRMS (ESI$^+$) Calculated for $C_{27}H_{41}NNaO_6SSi$: 558.2316. Found [M+Na]$^+$: 558.2303.

***tert*-Butyl (3-(2-hydroxyphenyl)propyl)(tosyloxy)carbamate (217)**



General procedure H: *tert*-Butyl (3-(2-((*tert*-butyldimethylsilyl)oxy)phenyl)propyl) (tosyloxy)carbamate (530 mg, 1.00 mmol) and 1.0 equivalent of 1:1 TBAF:AcOH solution (0.1 M in THF, 10 mL, 1.00 mmol) in THF (20 mL) were employed. Purification by flash column chromatography (20% EtOAc:hexane) afforded **217** (350 mg, 83%) as a colourless solid; ν_{max} / cm^{-1} (*solid*) 3462 (m, br), 2970 (m), 2929 (m), 1723 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.33 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.10 – 7.05 (2H, m, ArC<u>H</u>), 6.85 (1H, td, *J* = 7.5, 1.0 Hz, ArC<u>H</u>), 6.75 (1H, dt, *J* = 7.5, 1.0 Hz, ArC<u>H</u>), 5.29 (1H, br s, O<u>H</u>), 3.65 (2H, br s, C**1**-<u>H_2</u>), 2.61 (2H, t, *J* = 7.5 Hz, C**3**-<u>H_2</u>), 2.45 (3H, s, Ts C<u>H_3</u>), 2.01 – 1.92 (2H, m, C**2**-<u>H_2</u>), 1.23 (9H, s, Boc (C<u>H_3</u>)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.8 (Boc <u>C</u>=O), 153.7 (Ar<u>C</u>), 145.7 (Ar<u>C</u>), 131.2 (Ar<u>C</u>), 130.1 (Ar<u>C</u>), 129.6 (2 × Ts Ar<u>C</u>H), 129.5 (2 × Ts Ar<u>C</u>H)), 127.4 (Ar<u>C</u>H), 127.2 (Ar<u>C</u>H), 120.7 (Ar<u>C</u>H), 115.5 (Ar<u>C</u>H), 83.5 (Boc <u>C</u>(CH$_3$)$_3$), 52.9 (C**1**), 27.6 (Boc (<u>C</u>H$_3$)$_3$), 27.1 (C**3**), 26.1 (C**2**), 21.7 (Ts <u>C</u>H$_3$); HRMS (ESI$^+$) Calculated for $C_{21}H_{27}NNaO_6S$: 444.1451. Found $[M+Na]^+$: 444.1463.

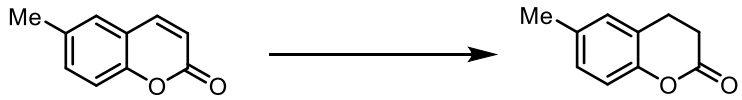
1-Acetyl-1-azaspiro[4.5]deca-7,9-dien-6-one (219)



General procedure I: The preceding *N*-tosyloxycarbamate **217** (105.4 mg, 0.25 mmol) and TFA (38.0 μL, 0.50 mmol) in anhydrous TFE (2.5 mL) were employed. The reaction mixture was concentrated *in vacuo* and to the crude mixture in anhydrous CH_2Cl_2 (10 mL) was added acetyl chloride (21 μL, 0.3 mmol) and pyridine (0.10 mL, 1.25 mmol) at 0 °C. The reaction was stirred at room temperature until completion by TLC analysis. The reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL) and the organic phase extracted with EtOAc (2 × 20 mL), washed with 1 M HCl (5 mL) and water (5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (100 % EtOAc) afforded **219** (6.6 mg, 14%) as a yellow solid; ν_{max} / cm^{-1} (*solid*) 2925 (m), 1669 (s), 1633 (s), 1413 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 – 6.96 (1H, m, C**7**-<u>H</u>), 6.24 (1H, d, *J* = 1.0 Hz, C**5**-<u>H</u>), 6.23 (1H, t, *J* = 1.0 Hz, C**6**-<u>H</u>), 6.16 (1H, dt, *J* = 10.0, 1.5 Hz, C**8**-<u>H</u>), 3.83 – 3.78 (1H, m, C**1**-<u>H</u>),

3.73 – 3.67 (1H, m, C**1**-H'), 2.29 – 2.21 (1H, m, C**2**-H), 2.12 – 2.07 (1H, m, C**3**-H), 2.06 (3H, s, C**11**-H_3), 2.05 – 1.99 (1H, m, C**2**-H'), 1.93 – 1.88 (1H, m, C**3**-H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.6 (C**9**), 168.5 (C**10**), 143.5 (C**5**), 140.7 (C**7**), 126.3 (C**8**), 120.8 (C**6**), 69.7 (C**4**), 49.2 (C**1**) 37.1 (C**3**), 23.8 (C**2**), 22.5 (C**11**); HRMS (ESI$^+$) Calculated for $C_{11}H_{13}NNaO_2$: 214.0838. Found $[M+Na]^+$: 214.0842.

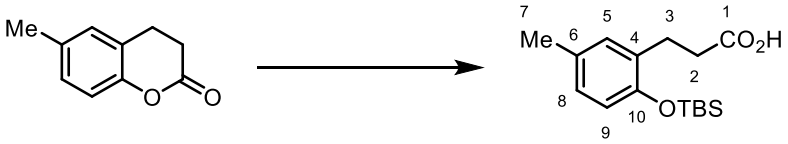
6-Methylchroman-2-one



General procedure E: 6-Methylcoumarin (4.80 g, 30.0 mmol) and 5 mol% Pd/C (10 wt. %, 1.50 mmol), in EtOAc (30 mL) were employed. Purification by flash column chromatography afforded the title compound (3.40 g, 70%) as a colourless solid; R_f = 0.4 (20% EtOAc:hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (1H, dd, *J* = 8.0, 2.0 Hz), 6.99 (1H, s), 6.93 (1H, d, *J* = 8.0 Hz), 2.98 – 2.93 (2H, m), 2.79 – 2.73 (2H, m), 2.31 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.9, 149.9, 134.0, 128.8, 128.5, 122.4, 116.7, 29.4, 23.8, 20.8.

The spectroscopic properties were consistent with the data available in the literature.[95]

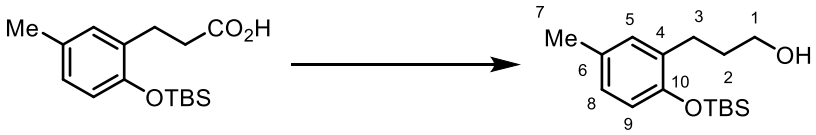
3-(2-((*tert*-Butyldimethylsilyl)oxy)-5-methylphenyl)propanoic acid (220)



To a solution of 6-methylchroman-2-one (1.74 g, 10.0 mmol) in THF (50 mL) was added a 1 M solution of aqueous LiOH (33.0 mmol, 58 mL). After stirring at room temperature overnight the pH was acidified to approx. 3 with 1 M HCl. The product was extracted with EtOAc (2 × 20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was dissolved in DMF (20 mL) and cooled to 0 °C before *tert*-butyldimethylsilyl chloride (3.32 g, 22.0 mmol) and imidazole (2.24 g, 33.0 mmol) were added. After being stirred at room temperature overnight the reaction was quenched by addition of H_2O (50 mL) and the product was extracted with hexane (3 × 20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. To the crude product in MeOH (10 mL) and THF (10 mL) was added aqueous K_2CO_3 (20.0 mmol, 2.76 g in 30 mL H_2O). After stirring at room temperature overnight the reaction was cooled to 0 °C and quenched with 1 M HCl (30 mL). The mixture was extracted with Et_2O (3

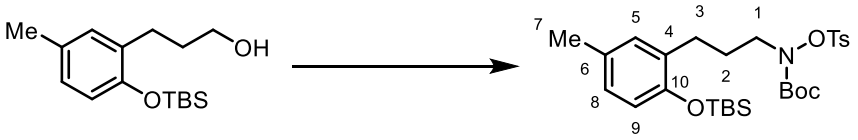
× 20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography (20% EtOAc:hexane) afforded **220** (1.60 g, 54%) as a colourless solid; m.p.: 49-51 °C (EtOAc:hexane); R_f = 0.4 (20% EtOAc:hexane); ν_{max} / cm^{-1} (*solid*) 2961 (m), 2948 (m), 2927 (m), 2900 (m), 1702 (s), 1499 (m), 1252 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 6.97 (1H, d, *J* = 2.5 Hz, C**5**-H), 6.89 (1H, dd, *J* = 8.5, 2.5 Hz, C**8**-H), 6.69 (1H, d, *J* = 8.5 Hz, C**9**-H), 2.89 (2H, t, *J* = 8.0 Hz, C**3**-H_2), 2.65 (2H, t, *J* = 8.0 Hz, C**2**-H_2), 2.26 (3H, s, C**7**-H_3), 1.01 (9H, s, TBS (CH_3)$_3$), 0.23 (6H, s, TBS Si(CH_3)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.3 (C**1**), 151.5 (C**10**), 130.9 (C**5**), 130.5 (C**4**), 130.4 (C**6**), 128.0, (C**8**) 118.3 (C**9**), 34.3 (C**2**), 26.2 (C**3**), 25.9 (TBS (CH_3)$_3$), 20.7 (C**7**), 18.4 (TBS C(CH_3)$_3$), -4.0 (TBS Si(CH_3)$_2$); HRMS (ESI^+) Calculated for $C_{16}H_{27}O_3Si$: 295.1724. Found $[M+H]^+$: 295.1739.

3-(2-((*tert*-Butyldimethylsilyl)oxy)-5-methylphenyl)propan-1-ol



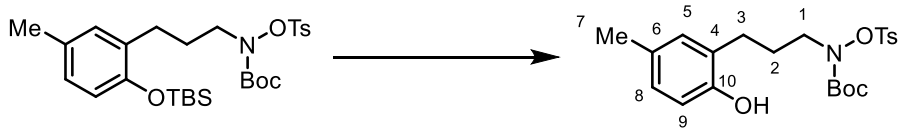
General procedure F: The preceding carboxylic acid **220** (1.25 g, 4.26 mmol), Et_3N (0.59 mL, 4.26 mmol), ethyl chloroformate (0.41 mL, 4.26 mmol) and $NaBH_4$ (400 mg, 10.60 mmol) in THF (30 mL) and H_2O (15 mL) were employed. Purification by flash column chromatography (20% EtOAc:hexane) afforded the title compound (830 mg, 60%) as a colourless oil; R_f = 0.35 (20% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 3334 (br), 2953 (m), 2929 (m), 2885 (m), 2858 (m), 1498 (s), 1253 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 6.94 (1H, d, *J* = 2.5 Hz, C**5**-H), 6.86 (1H, dd, *J* = 8.0, 2.5 Hz, C**8**-H), 6.68 (1H, d, *J* = 8.0 Hz, C**9**-H), 3.61 (2H, t, *J* = 6.5 Hz, C**1**-H_2), 2.65 (2H, t, *J* = 7.5 Hz, C**3**-H_2), 2.25 (3H, s, C**7**-H_3), 1.99 – 1.70 (2H, m, C**2**-H_2), 1.01 (9H, s, TBS (CH_3)$_3$), 0.22 (6H, s, TBS Si(CH_3)$_2$); ^{13}C NMR (400 MHz, $CDCl_3$) δ 151.3 (C**10**), 131.9 (C**4**), 131.1 (C**5**), 130.6 (C**6**), 127.4 (C**8**), 118.5 (C**9**), 62.4 (C**1**), 33.3 (C**2**), 26.6 (C**3**), 26.0 (TBS (CH_3)$_3$), 20.7 (C**7**), 18.4 (TBS C(CH_3)$_3$, -4.0 (TBS Si(CH_3)$_2$).
The spectroscopic properties were consistent with the data available in the literature.[304]

***tert*-Butyl (3-(2-((*tert*-butyldimethylsilyl)oxy)-5-methylphenyl)propyl)(tosyloxy) carbamate**



General procedure G: 3-(2-((*tert*-Butyldimethylsilyl)oxy)-5-methylphenyl)propan-1-ol (870 mg, 1.58 mmol), PPh_3 (500 mg, 1.90 mmol), DIAD (0.37 mL, 1.90 mmol) and BocNHOTs (540 mg, 1.90 mmol) were employed. Purification by flash column chromatography (10% EtOAc:hexane) afforded the title compound (710 mg, 65%) as a colourless oil; R_f = 0.6 (20% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 2957 (m), 2929 (m), 2901 (m), 2859 (m), 1721 (m), 1499 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.31 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 6.92 (1H, d, *J* = 2.5 Hz, C**5**-<u>H</u>), 6.85 (1H, dd, *J* = 8.0, 2.5 Hz, C**8**-<u>H</u>), 6.66 (1H, d, *J* = 8.0 Hz, C**9**-<u>H</u>), 3.62 (2H, br s, C**1**-<u>H_2</u>), 2.51 (2H, t, *J* = 8.0 Hz, C**3**-<u>H_2</u>), 2.43 (3H, s, Ts C<u>H_3</u>), 2.25 (3H, s, C**7**-<u>H_3</u>), 1.96 – 1.84 (2H, m, C**2**-<u>H_2</u>), 1.20 (9H, s, Boc (C<u>H_3</u>)$_3$), 1.01 (9H, s, TBS (C<u>H_3</u>)$_3$), 0.21 (6H, s, TBS Si(C<u>H_3</u>)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.5 (Boc <u>C</u>=O), 151.3 (C**10**), 145.6 (Ts Ar<u>C</u>), 131.5 (Ts Ar<u>C</u>), 131.4 (C**4**), 130.8 (C**5**), 130.2 (C**6**), 129.8 (2 × Ts ArC<u>H</u>), 129.6 (2 × Ts Ar<u>C</u>H), 127.5 (C**8**), 118.3 (C**9**), 83.1 (Boc <u>C</u>(CH$_3$)$_3$), 52.9 (C**1**), 27.7 (C**3**), 27.7 (Boc (<u>C</u>H$_3$)$_3$), 26.1 (C**2**), 25.9 (TBS (<u>C</u>H$_3$)$_3$), 21.8 (Ts <u>C</u>H$_3$), 20.6 (C**7**), 18.3 (TBS Si<u>C</u>(CH$_3$)$_3$), -4.1 (TBS Si(<u>C</u>H$_3$)$_2$); HRMS (ESI^+) Calculated for $C_{28}H_{43}NNaO_6SSi$: 572.2473. Found $[M+Na]^+$: 572.2477.

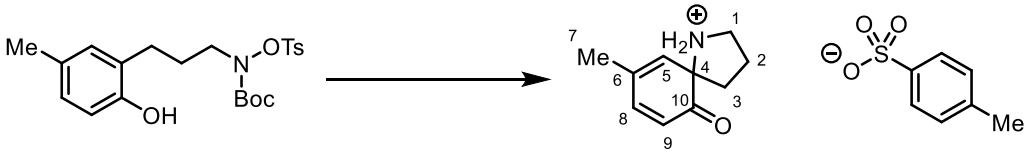
***tert*-Butyl (3-(2-hydroxy-5-methylphenyl)propyl)(tosyloxy)carbamate (221)**



General procedure H: *tert*-Butyl (3-(2-((*tert*-butyldimethylsilyl)oxy)-5-methylphenyl) propyl)(tosyloxy)carbamate (440 mg, 0.80 mmol) and 1:1 TBAF:AcOH solution (0.1 M in THF, 0.80 mmol) in THF (16 mL) were employed. Purification by flash column chromatography (gradient, eluent 20 – 33% EtOAc:hexane) afforded **221** (270 mg, 77%) as a colourless solid; m.p.: 107-108 °C (EtOAc:hexane); R_f = 0.2 (20% EtOAc:hexane); ν_{max} / cm^{-1} (*solid*) 3447 (m), 2986 (m), 1685 (s), 1509 (m), 1382 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.33 (2H, d, *J* = 8.0 Hz, Ts ArC<u>H</u>), 7.03 – 6.81 (2H, m, C**8**-<u>H</u>, C**9**-<u>H</u>), 6.64 (1H, d, *J* = 8.0 Hz, C**5**-<u>H</u>), 4.99 (1H, s, O<u>H</u>), 3.65 (2H, br s, C**1**-<u>H_2</u>), 2.56 (2H, t, *J*

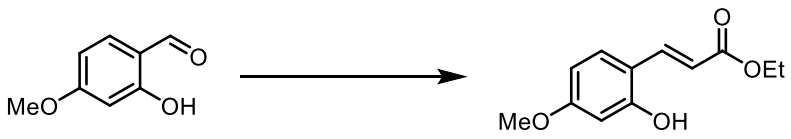
= 8.0 Hz, C**3**-H$_2$), 2.44 (3H, s, Ts CH$_3$), 2.24 (3H, s, C**7**-H$_3$), 2.00 – 1.89 (2H, m, C**2**-H$_2$), 1.21 (9H, s, Boc (CH$_3$)$_3$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 155.8 (Boc C=O), 151.4 (C**10**), 145.7 (Ts ArC), 131.3 (Ts ArC), 130.8 (C**5**), 129.9 (C**6**) 129.8 (2 × Ts ArCH), 129.6 (2 × Ts ArCH), 127.8 (C**8**), 127.0 (C**4**), 115.4 (C**9**), 83.5 (Boc C(CH$_3$)$_3$), 53.0 (C**1**), 27.7 (Boc (CH$_3$)$_3$), 27.2 (C**3**), 26.3 (C**2**), 21.8 (Ts CH$_3$), 20.6 (C**7**); HRMS (ESI$^+$) Calculated for $C_{22}H_{29}NNaO_6S$: 458.1608. Found [M+Na]$^+$: 458.1608.

9-Methyl-1-azaspiro[4.5]deca-7,9-dien-6-one tosylate (222)



General procedure I: The preceding *N*-tosyloxycarbamate **221** (25.2 mg, 0.06 mmol) and TFA (8.9 μL, 0.12 mmol) in anhydrous TFE (0.57 mL) were employed. Upon completion, the reaction mixture was concentrated *in vacuo* to afford **222** as a brown solid. *An in situ yield was obtained by ^{1}H NMR versus 1,4-dinitrobenzene as an internal standard; a yield of 91% was obtained*. R_f = 0.1 (5% MeOH:CH_2Cl_2); ν_{max} / cm^{-1} (*solid*) 3447 (m, br), 2970 (m), 2923 (m), 1673 (m), 1655 (m), 1606 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.31 (1H, br s, NH), 8.16 (1H, br s, NH), 7.71 (2H, d, *J* = 8.0 Hz, Ts ArCH), 7.18 (2H, d, *J* = 8.0 Hz, Ts ArCH), 6.83 (1H, dd, *J* = 10.0, 2.0 Hz, C**8**-H), 6.34 (1H, br s, C**5**-H), 6.07 (1H, d, *J* = 10.0 Hz, C**9**-H), 3.72 (2H, br s, C**1**-H$_2$), 2.36 (3H, s, Ts CH$_3$), 2.24 – 2.05 (4H, m, C**2**-H$_2$, C**3**-H$_2$), 1.83 (3H, s, C**7**-H$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.6 (C**10**), 147.1 (C**8**), 141.3 (Ts ArC), 140.4 (Ts ArC), 132.6 (C**6**), 131.4 (C**5**), 129.2 (2 × Ts ArCH), 126.0 (2 × Ts ArCH), 123.9 (C**9**), 72.5 (C**4**), 48.2 (C**1**), 37.2 (C**2**/C**3**), 22.6 (C**2**/C**3**), 21.5 (Ts CH$_3$), 20.9 (C**7**); HRMS (ESI$^+$) Calculated for $C_{10}H_{14}NO$: 164.1070. Found [M]$^+$: 164.1071.

Ethyl (*E*)-3-(2-hydroxy-4-methoxyphenyl)acrylate

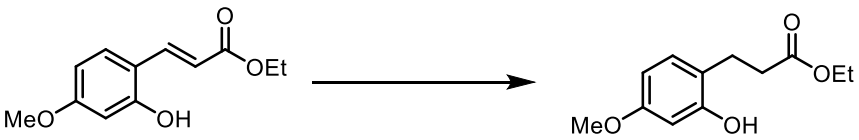


General procedure J: 2-Hydroxy-4-methoxybenzaldehyde (1.80 g, 12.0 mmol) and ethyl 2-(triphenyl-phosphaneylidene) acetate (6.27 g, 18.0 mmol) in CH_2Cl_2 (15 mL) were employed. Purification by flash column chromatography (20% EtOAc:hexane) afforded the title compound (2.73 g, quantitative) as a colourless solid; R_f = 0.3 (20% EtOAc:hexane);

^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 9.13 (1H, s), 7.93 (1H, d, *J* = 16.0 Hz), 7.54 (1H, d, *J* = 8.5 Hz), 6.53 - 6.50 (2H, m), 6.48 (1H, d, *J* = 16.0 Hz), 4.18 (2H, q, *J* = 7.0 Hz), 3.79 (3H, s), 1.27 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0, 163.6, 158.9, 140.7, 131.2, 116.1, 115.6, 107.2, 102.3, 60.4, 55.7, 14.8.

The spectroscopic properties were consistent with the data available in the literature.[305]

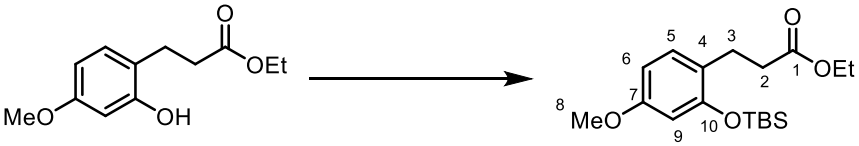
Ethyl 3-(2-hydroxy-4-methoxyphenyl)propanoate



General procedure E: Ethyl (*E*)-3-(2-hydroxy-4-methoxyphenyl)acrylate (2.22 g, 10.0 mmol) and 10 wt.% Pd/C (5 mol%) in EtOH (30 mL) were employed to afford the title compound (2.21 g, 99%) as an off-white solid; R_f = 0.2 (20% EtOAc:hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (1H, s), 6.97 (1H, d, *J* = 8.5 Hz), 6.48 - 6.40 (2H, m), 4.14 (2H, q, *J* = 7.0 Hz), 3.75 (3H, s), 2.79 – 2.89 (2H, m), 2.63 – 2.73 (2H, m), 1.24 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.1, 159.7, 155.4, 131.1, 119.7, 106.9, 102.9, 61.5, 55.4, 35.6, 24.1, 14.2.

The spectroscopic properties were consistent with the data available in the literature.[306]

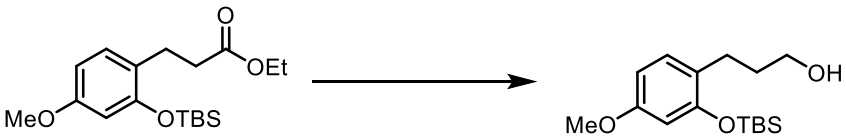
Ethyl 3-(2-((*tert*-butyldimethylsilyl)oxy)-4-methoxyphenyl)propanoate



To a solution of ethyl 3-(2-hydroxy-4-methoxyphenyl)propanoate (1.68 g, 7.50 mmol) in DMF (15 mL) were added *tert*-butyldimethylsilyl chloride (1.36 g, 9.00 mmol), and imidazole (1.28 g, 18.75 mmol) and the reaction was stirred at room temperature overnight. To the reaction was added water (25 mL) and the organic phase was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic phases were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (20% EtOAc:pentane) afforded the title compound (1.59 g, 63%) as a colourless oil; R_f = 0.5 (20% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 2955 (m), 2931 (m), 2858 (m), 1733 (s), 1611 (s), 1505 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (1H, d, *J* = 8.5 Hz, C**5**-H), 6.44 (1H, dd, *J* = 8.5, 2.5 Hz, C**6**-H), 6.38 (1H, d, *J* = 2.5 Hz, C**9**-H), 4.12 (2H, q, *J* = 7.0 Hz, OCH_2), 3.75 (3H, s, C**8**-H_3),

2.84 (2H, dd, *J* = 9.0, 7.0 Hz, C**3**-$\underline{H}_2$), 2.54 (2H, dd, *J* = 9.0, 7.0 Hz, C**2**-$\underline{H}_2$), 1.23 (3H, t, *J* = 7.0 Hz, $CH_2C\underline{H}_3$), 1.02 (9H, s, TBS ($C\underline{H}_3)_3$), 0.25 (6H, s, TBS Si($C\underline{H}_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.4 (C**1**), 159.1 (C**7**), 154.5 (C**10**), 130.4 (C**5**), 123.7 (C**4**), 105.7 (C**6**/C**9**), 105.6 (C**6**/C**9**), 60.3 ($O\underline{C}H_2$), 55.4 (C**8**), 34.9 (C**2**), 25.9 (TBS ($\underline{C}H_3)_3$), 25.8 (C**3**), 18.3 (TBS Si$\underline{C}(CH_3)_3$), 14.4 ($CH_2\underline{C}H_3$), -4.0 (TBS Si($\underline{C}H_3)_2$); HRMS (ESI$^+$) Calculated for $C_{18}H_{30}NaO_4Si$: 361.1806. Found $[M+Na]^+$: 361.1820.

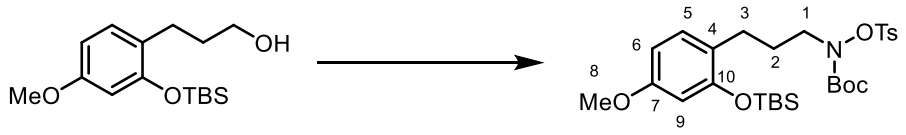
3-(2-((*tert*-Butyldimethylsilyl)oxy)-4-methoxyphenyl)propan-1-ol



A solution of ethyl 3-(2-((*tert*-butyldimethylsilyl)oxy)-4-methoxyphenyl)propanoate (1.01 g, 3.0 mmol) in anhydrous THF (15 mL) was cooled to -78 °C before 2.0 equivalents of DIBALH (1 M in CH_2Cl_2) was added dropwise to maintain the temperature of the reaction mixture below -75 °C. The reaction was stirred at this temperature for 4 hours and then warmed to 0 °C and stirred for an additional 2 hours. The reaction mixture was diluted with EtOAc (10 mL) and quenched with Rochelle's salt (10 mL). The mixture was filtered through Celite® and washed with EtOAc. The phases were separated, and the aqueous phase extracted with EtOAc (10 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography (33% EtOAc:hexane) afforded the title compound (440 mg, 50%) as a colourless oil; R_f = 0.3 (33% EtOAc:hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (1H, d, *J* = 8.5 Hz), 6.47 (1H, dd, *J* = 8.5, 2.5 Hz), 6.39 (1H, d, *J* = 2.5 Hz), 3.76 (3H, s), 3.61 (2H, t, *J* = 6.5 Hz), 2.62 (2H, t, *J* = 7.0 Hz), 1.85 – 1.77 (2H, m), 1.64 (1H, br s), 1.01 (9H, s), 0.25 (6H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.8, 154.4, 130.6, 124.7, 106.1, 105.7, 62.4, 55.4, 33.4, 25.9, 25.8, 18.4, -4.0.

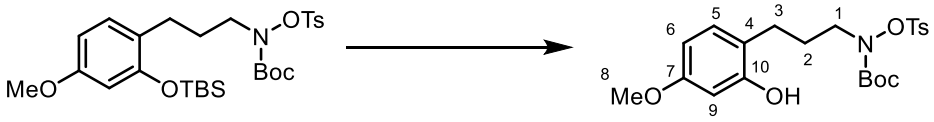
The spectroscopic properties were consistent with the data available in the literature.[307]

***tert*-Butyl (3-(2-((*tert*-butyldimethylsilyl)oxy)-4-methoxyphenyl)propyl)(tosyloxy) carbamate**



General procedure G: 3-(2-((*tert*-Butyldimethylsilyl)oxy)-4-methoxyphenyl)propan-1-ol (440 mg, 1.50 mmol), PPh_3 (470 mg, 1.80 mmol), DIAD (0.35 mL, 1.80 mmol) and BocNHOTs (520 mg, 1.80 mmol) in anhydrous THF (6 mL) were employed. Purification by flash column chromatography (10% EtOAc:hexane) afforded the title compound (820 mg, 96 %) as a colourless oil; R_f = 0.5 (33% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 2955 (m), 2931 (m), 1720 (s), 1504 (s), 1160 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.31 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.00 (1H, d, *J* = 8.5 Hz, C**5**-<u>H</u>), 6.44 (1H, dd, *J* = 8.5, 2.5 Hz, C**6**-<u>H</u>), 6.36 (1H, d, *J* = 2.5 Hz, C**9**-<u>H</u>), 3.75 (3H, s, C**8**-<u>H_3</u>), 3.71 – 3.49 (2H, m, C**1**-<u>H_2</u>), 2.49 (2H, t, *J* = 7.5 Hz, C**3**-<u>H_2</u>), 2.43 (3H, s, Ts C<u>H_3</u>), 1.95 – 1.81 (2H, m, C**2**-<u>H_2</u>), 1.21 (9H, s, Boc (C<u>H_3</u>)$_3$), 1.01 (9H, s, TBS (C<u>H_3</u>)$_3$), 0.24 (6H, s, TBS Si(C<u>H_3</u>)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.8 (C**7**), 155.5 (Boc <u>C</u>=O), 154.3 (C**10**), 145.6 (Ts Ar<u>C</u>), 131.4 (Ts Ar<u>C</u>), 130.3 (C**5**), 129.7 (2 × Ts Ar<u>C</u>H), 129.6 (2 × Ts Ar<u>C</u>H), 124.1 (C**4**), 105.7 (C**6**), 105.5 (C**9**), 83.1 (Boc <u>C</u>$(CH_3)_3$), 55.3 (C**8**), 52.8 (C**1**), 27.7 (Boc (<u>C</u>H_3)$_3$), 27.0 (C**3**), 26.2 (C**2**), 25.9 (TBS (<u>C</u>H_3)$_3$), 21.8 (Ts <u>C</u>H_3), 18.3 (TBS Si<u>C</u>$(CH_3)_3$), -4.1 (TBS Si(<u>C</u>H_3)$_2$); HRMS (ESI$^+$) Calculated for $C_{28}H_{43}NNaO_7SSi$: 588.2422. Found $[M+Na]^+$: 588.2426.

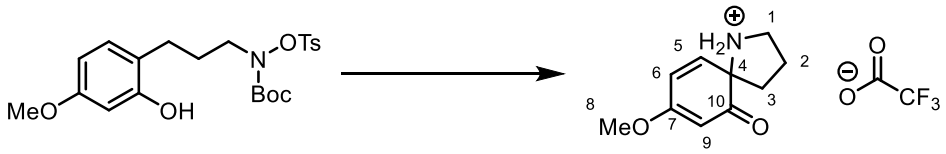
***tert*-Butyl (3-(2-hydroxy-4-methoxyphenyl)propyl)(tosyloxy)carbamate (223)**



General procedure H: *tert*-Butyl (3-(2-((*tert*-butyldimethylsilyl)oxy)-4-methoxyphenyl) propyl)(tosyloxy)carbamate (560 mg, 1.00 mmol) and 1:1 TBAF:AcOH solution (0.1 M in THF, 0.1 mmol) in THF (20 mL) were employed. Purification by flash column chromatography (33% EtOAc:hexane) afforded **223** (300 mg, 68%) as a colourless, viscous oil; R_f = 0.2 (33% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 3422 (br s), 2936 (m), 1720 (m), 1508 (m), 1368 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (2H, d, *J* = 8.0 Hz, Ts ArC<u>H</u>), 7.33 (2H, d, *J* = 8.0 Hz, Ts ArC<u>H</u>), 6.98 (1H, d, *J* =8.5 Hz, C**5**-<u>H</u>), 6.42 (1H, dd, *J* = 8.5, 2.5 Hz, C**6**-<u>H</u>), 6.36 (1H, d, *J* = 2.5 Hz, C**9**-<u>H</u>), 5.37 (1H, br s, O<u>H</u>), 3.75 (3H, s, C**8**-<u>H_3</u>), 3.72 – 3.53 (2H, m, C**1**-<u>H_2</u>), 2.54 (2H, t, *J* =

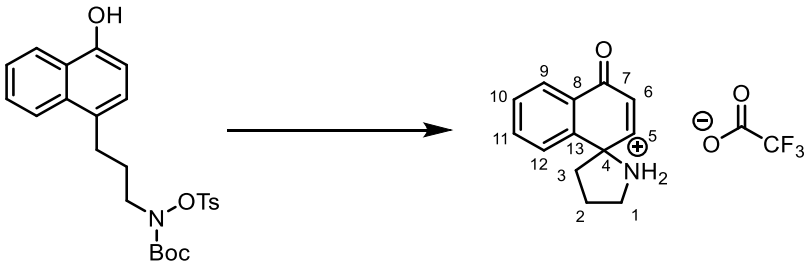
7.5 Hz, C**3**-$\underline{H}_2$), 2.44 (3H, s, Ts C$\underline{H}_3$), 1.98 – 1.85 (2H, m, C**2**-$\underline{H}_2$), 1.22 (9H, s, Boc (C$\underline{H}_3$)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3 (C**7**), 156.0 (Boc $\underline{C}$=O), 154.6 (C**10**), 145.9 (Ts Ar$\underline{C}$), 131.4 (Ts Ar$\underline{C}$), 130.7 (C**5**), 130.0 (2 × Ts Ar$\underline{C}$H), 129.7 (2 × Ts Ar$\underline{C}$H), 119.6 (C**4**), 106.1 (C**6**), 102.1 (C**9**), 83.6 (Boc $\underline{C}(CH_3)_3$), 55.5 (C**8**), 53.0 (C**1**), 27.8 (Boc ($\underline{C}H_3$)$_3$), 26.6 (C**2**/C**3**), 26.5 (C**2**/C**3**), 21.8 (Ts $\underline{C}H_3$); HRMS (ESI$^+$) Calculated for $C_{22}H_{29}NNaO_7S$: 474.1557. Found $[M+Na]^+$: 474.1560.

8-Methoxy-1-azaspiro[4.5]deca-7,9-dien-6-one trifluoroacetate (224)



General procedure I: The preceding *N*-tosyloxycarbamate **223** (67.7 mg, 0.15 mmol) and TFA (23 μL, 0.30 mmol) in TFE (1.5 mL) were stirred at room temperature for 25 hours. Purification by flash column chromatography (EtOAc) afforded **224** (34.1 mg, 78%) as a yellow oil; R_f = 0.1 (5% MeOH:CH_2Cl_2); ν_{max} / cm^{-1} (*film*) 2987 (m), 2901 (m), 1672 (s), 1634 (m); ^{1}H NMR (400 MHz, CD_3OD) δ 6.69 (1H, d, *J* = 10.0 Hz, C**5**-$\underline{H}$), 6.36 (1H, dd, *J* = 10.0, 2.0 Hz, C**6**-$\underline{H}$), 5.63 (1H, d, *J* = 2.0 Hz, C**9**-$\underline{H}$), 3.88 (3H, s, C**8**-$\underline{H}_3$), 3.69 – 3.54 (2H, m, C**1**-$\underline{H}_2$), 2.32 – 2.16 (4H, m, C**2**-$\underline{H}_2$, C**3**-$\underline{H}_2$). *The signals corresponding to the N$\underline{H}_2$ were not observed.* ^{13}C NMR (101 MHz, CD_3OD) δ 196.9 (C**10**), 173.1 (C**7**), 138.5 (C**5**), 125.5 (C**6**), 98.8 (C**9**), 71.4 (C**4**), 57.5 (C**8**), 48.5 (C**1**), 39.4 (C**3**), 24.2 (C**2**). *The signals corresponding to the trifluoroacetate group could not be resolved due to their weak intensity*. HRMS (ESI$^+$) Calculated for $C_{10}H_{14}NO_2$: 180.1019. Found $[M+H]^+$: 180.1011.

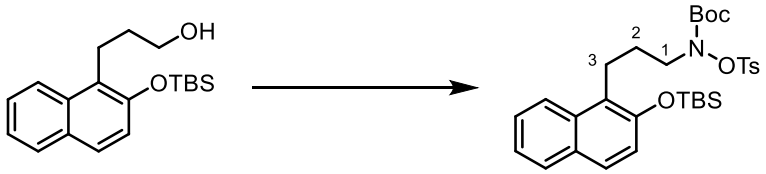
4*H*-Spiro[naphthalene-1,2'-pyrrolidin]-4-one trifluoroacetate (226)



General procedure I: *N*-Tosyloxycarbamate **225** (70.7 mg, 0.150 mmol) and TFA (23 μL, 0.30 mmol) in anhydrous TFE (1.5 mL) were stirred at room temperature for 22 hours. Purification by flash column chromatography (EtOAc) afforded **226** (14.3 mg, 30%) as a

yellow/brown solid; R_f = 0.1 (5% MeOH:CH_2Cl_2); ν_{max} / cm^{-1} (*solid*) 2987 (m), 2971 (m), 1665 (s), 1601 (m); ^{1}H NMR (400 MHz, CD_3OD) δ 8.19 (1H, d, *J* = 7.5 Hz, C**9**-H), 7.88 – 7.82 (2H, m, C**11**-H, C**12**-H), 7.67 (1H, ddd, *J* = 8.0, 6.0, 2.5 Hz, C**10**-H), 7.25 (1H, d, *J* = 10.5 Hz, C**5**-H), 6.61 (1H, d, *J* = 10.5 Hz, C**6**-H), 3.84 – 3.72 (2H, m, C**1**-H_2), 2.71 – 2.62 (1H, m, C**3**-H), 2.57 – 2.48 (3H, m, C**3**-H', C**2**-H_2). *The signals corresponding to the NH_2 were not observed.* ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.0 (C**7**), 144.5 (C**5**), 140.5 (C**13**), 135.4 (C**11**), 132.1 (C**8**), 131.1 (C**10**), 130.7 (C**6**), 128.1 (C**9**), 127.7 (C**12**), 65.9 (C**4**), 47.7 (C**1**), 41.2 (C**3**), 25.8 (C**2**). *The signals corresponding to the trifluoroacetate group could not be resolved due to their weak intensity*. HRMS (ESI$^+$) Calculated for $C_{13}H_{14}NO$: 200.1069. Found $[M+H]^+$: 200.1074.

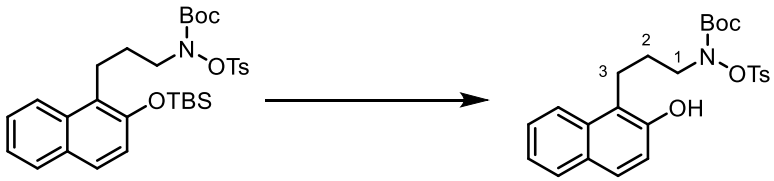
tert-Butyl (3-(2-((*tert*-butyldimethylsilyl)oxy)naphthalen-1-yl)propyl)(tosyloxy) carbamate



To a solution of alcohol **168** (630 mg, 2.00 mmol), BocNHOTs (560 mg, 3.00 mmol) and PPh_3 (1.05 g, 4.00 mmol) in anhydrous PhMe:THF (3:1, 8 mL/mmol) at 0 °C was added a solution of DIAD (0.78 mL, 4.00 mmol) in anhydrous PhMe (2 mL/mmol) dropwise. The reaction was stirred at room temperature until completion by TLC analysis (4 hours). The reaction mixture was concentrated *in vacuo* and purification by flash column chromatography (gradient 20 – 25% EtOAc:hexane) afforded the title compound (740 mg, 63%) as a colourless solid; m.p.: 79-80 °C (EtOAc:hexane); R_f = 0.7 (33% EtOAc:hexane); ν_{max} / cm^{-1} (*solid*) 2961 (m), 2927 (m), 2857 (m), 1709 (s), 1596 (m), 1466 (m), 1368 (s), 1240 (s), 1174 (s), 1164 (s), 1153 (s), 1087 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (1H, d, *J* = 8.5 Hz, ArCH), 7.82 (2H, d, *J* = 8.5 Hz, ArCH), 7.75 (1H, d, *J* = 8.0 Hz, ArCH), 7.59 (1H, d, *J* = 9.0 Hz, ArCH), 7.47 – 7.43 (1H, m, ArCH), 7.33 (1H, ddd, *J* = 8.0, 7.0, 1.0 Hz, ArCH), 7.27 (2H, d, *J* = 8.0 Hz, ArCH), 7.05 (1H, d, *J* = 9.0 Hz, ArCH), 3.71 (2H, br s, C**1**-H_2), 3.02 (2H, t, *J* = 8.0 Hz, C**3**-H_2), 2.42 (3H, s, Ts CH_3), 1.98 – 1.89 (2H, m, C**2**-H_2), 1.16 (9H, s, Boc (CH_3)$_3$), 1.07 (9H, s, TBS (CH_3)$_3$), 0.27 (6H, s, Si(CH_3)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.5 (Boc C=O), 150.6 (ArC), 145.6 (Ts ArC), 133.3 (ArC), 131.5 (Ts ArC), 129.7 (2 × Ts ArCH), 129.6 (ArC), 129.5 (2 × Ts ArCH), 128.6 (ArCH), 127.5 (ArCH), 126.4 (ArCH), 124.2 (ArC), 123.3 (ArCH), 123.2

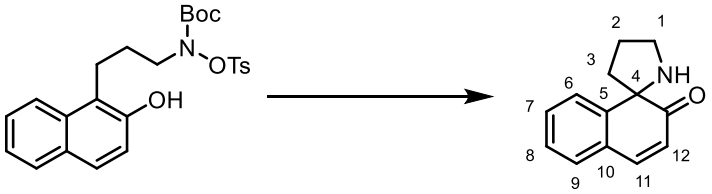
(ArCH), 120.3 (ArCH), 83.1 (Boc C(CH$_3$)$_3$), 53.1 (C**1**), 27.6 (Boc (CH$_3$)$_3$), 26.1 (C**2**), 26.0 (TBS (CH$_3$)$_3$), 22.7 (C**3**), 21.8 (Ts CH$_3$), 18.4 (TBS C(CH$_3$)$_3$), -3.8 (TBS Si(CH$_3$)$_2$); HRMS (ESI$^+$) Calculated for $C_{31}H_{43}NNaO_6SSi$: 608.2473. Found $[M+Na]^+$: 608.2456.

***tert*-Butyl (3-(2-hydroxynaphthalen-1-yl)propyl)(tosyloxy)carbamate (227)**



General procedure H: *tert*-Butyl (3-(2-((*tert*-butyldimethylsilyl)oxy)naphthalen-1-yl)propyl)(tosyloxy) carbamate (160 mg, 0.28 mmol) and 1:1 TBAF:AcOH solution (0.1 M in THF, 0.28 mmol) in THF were employed. Purification by flash column chromatography (33% EtOAc:hexane) afforded **227** (110 mg, 84%) as a pale yellow solid; m.p.: 55-57 ^{o}C (EtOAc:hexane); R_f = 0.35 (33% EtOAc:hexane); ν_{max} / cm^{-1} (*solid*) 3359 (m, br), 2931 (m), 1721 (s), 1369 (s), 1191 (s), 1178 (s), 1154 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 – 7.83 (3H, m, Ts ArCH, ArCH), 7.77 (1H, d, *J* = 8.0 Hz, ArCH), 7.62 (1H, d, *J* = 9.0 Hz, ArCH), 7.47 (1H, ddd, *J* = 8.5, 7.0, 1.5 Hz, ArCH), 7.35 – 7.29 (3H, m, Ts ArCH, ArCH), 7.07 (1H, d, *J* = 9.0 Hz, ArCH), 5.60 (1H, br s, OH), 3.79 – 3.70 (2H, m, C**1**-H$_2$), 3.07 (2H, t, *J* = 8.0 Hz, C**3**-H$_2$), 2.44 (3H, s, Ts CH$_3$), 2.08 – 1.97 (2H, m, C**2**-H$_2$), 1.20 (9H, s, Boc (CH$_3$)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.1 (Boc C=O), 151.1 (ArC), 145.9 (Ts ArC), 133.2 (ArC), 131.3 (Ts ArC), 129.7 (2 × Ts ArCH), 129.7 (2 × Ts ArCH), 129.5 (ArC), 128.8 (ArCH), 128.1 (ArCH), 126.6 (ArCH), 123.1 (ArCH), 122.8 (ArCH), 118.8 (ArC), 118.1 (ArCH), 83.6 (Boc C(CH$_3$)$_3$), 53.2 (C**1**), 27.7 (Boc (CH$_3$)$_3$), 26.4 (C**2**), 22.2 (C**3**) 21.8 (Ts CH$_3$); HRMS (ESI$^+$) Calculated for $C_{25}H_{29}NNaO_6S$: 494.1608. Found $[M+Na]^+$: 494.1598.

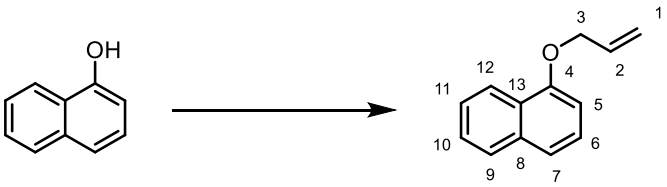
2*H*-Spiro[naphthalene-1,2'-pyrrolidin]-2-one (228)



General procedure I: The preceding *N*-tosyloxycarbamate **227** (117.9 mg, 0.25 mmol), TFA (38 μL, 0.50 mmol) and TFE (2.5 mL) were employed. After stirring at room temperature for

38 hours, purification by flash column chromatography (50% EtOAc:hexane) afforded **228** (38.8 mg, 78%) as a viscous yellow oil; R_f = 0.25 (33% EtOAc:hexane); ν_{max}/ cm^{-1} (*film*) 3339 (m), 2965 (m), 2866 (m), 1671 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (1H, dd, *J* = 7.5, 1.0 Hz, C**6**-H), 7.41 – 7.34 (2H, m, C**11**-H and C**7**-H), 7.29 – 7.21 (2H, m, C**8**-H and C**9**-H), 6.17 (1H, d, *J* = 10.0 Hz, C**12**-H), 3.45 (1H, dt, *J* = 10.5, 6.5 Hz, C**1**-H), 3.28 (1H, dt, *J* = 10.0, 6.5 Hz, C**1**-H'), 2.34 – 2.22 (1H, m, C**3**-H), 1.96 – 1.69 (3H, m, C**2**-H_2, C**3**-H'); ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.1, (C=O), 148.8 (C**5**), 144.8 (C**11**), 130.1 (C**7**), 129.2 (C**8**), 129.1 (C**10**), 127.0 (C**9**), 126.0 (C**6**), 123.6 (C**12**), 73.9 (C**4**), 49.9 (C**1**), 42.9 (C**3**), 25.6 (C**2**); HRMS (ESI^+) Calculated for $C_{13}H_{13}NNaO$: 222.0889. Found $[M+Na]^+$: 222.0883.

1-(Allyloxy)naphthalene (229)

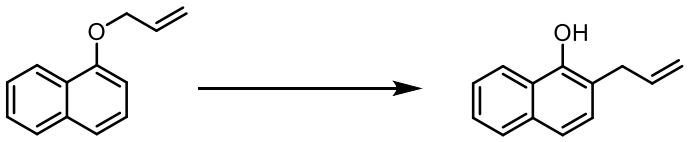


The title compound was prepared according to a literature procedure.[91]

To a solution of 1-naphthol (5.05 g, 35.0 mmol) and K_2CO_3 (5.40 g, 39.0 mmol) in acetone (40 mL) was added allyl bromide (3.3 mL, 39.0 mmol) dropwise over 20 minutes. The reaction was stirred at room temperature for 15 minutes before heating at reflux overnight. The reaction was cooled to room temperature and the concentrated *in vacuo*. To the crude residue was added H_2O (20 mL) and the organic phase was extracted with Et_2O (3 × 15 mL). The combined organic extracts were washed with brine (15 mL), dried over Na_2SO_4 and concentrated *in vacuo*. **229** (6.4 g, 99%) was obtained as an orange/brown oil and was used without purification; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 – 8.28 (1H, m, C**12**-H), 7.85 – 7.78 (1H, m, C**9**-H), 7.54 – 7.47 (2H, m, C**10**-H, C**11**-H), 7.47 – 7.35 (2H, m, C**6**-H, C**7**-H), 6.83 (1H, dd, *J* = 7.5, 1.0 Hz, C**5**-H), 6.20 (1H, ddt, *J* = 17.5, 10.5, 5.0 Hz, C**2**-H), 5.55 (1H, dq, *J* = 17.5, 1.5 Hz, C**1**-H), 5.36 (1H, dq, *J* = 10.5, 1.5 Hz, C**1**-H'), 4.80 – 4.64 (2H, m, C**3**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.5, 134.7, 133.5, 127.6 , 126.5, 125.9, 125.9 125.3, 122.2, 120.5, 117.5, 105.2, 69.1.

The spectroscopic properties were consistent with the data available in the literature.[308]

2-Allylnaphthalen-1-ol

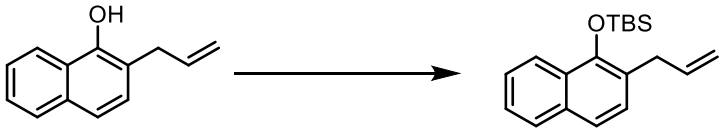


The title compound was prepared according to a literature procedure.[91]

A solution of the preceding allyl ether **229** (6.4 g, 35.0 mmol) in *N*,*N*-diethylaniline (36 mL) was heated at reflux overnight. The solution was cooled to room temperature, diluted with EtOAc (25 mL) and washed with 2M HCl (4 × 15 mL) followed by brine (15 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo to afford the title compound (6.44 g, quantitative) which was used without further purification; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 – 8.12 (1H, m), 7.79 (1H, dd, *J* = 7.5, 2.0 Hz), 7.50 – 7.45 (2H, m), 7.42 (1H, d, *J* = 8.5 Hz), 7.23 (1H, d, *J* = 8.5 Hz), 6.09 (1H, ddt, *J* = 16.5, 10.0, 6.5 Hz), 5.60 (1H, s), 5.30 – 5.23 (2H, m), 3.59 (2H, dd, *J* = 6.5, 1.5 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.7, 136.3, 133.9, 128.6, 127.7, 125.9, 125.4, 125.0, 121.5, 120.5, 118.0, 35.9.

The spectroscopic properties were consistent with the data available in the literature.[309]

((2-Allylnaphthalen-1-yl)oxy)(*tert*-butyl)dimethylsilane (230)

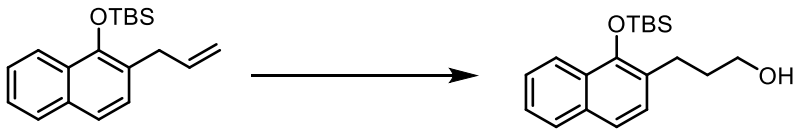


The title compound **230** was prepared according to a literature procedure.[91]

To a solution of 2-allylnaphthalen-1-ol (6.44 g, 35.0 mmol) in CH_2Cl_2 (55 mL) were added imidazole (3.1 g, 46.0 mmol) and TBSCl (6.3 g, 42.0 mmol) and the reaction was stirred at room temperature overnight. The reaction was quenched with H_2O (20 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were washed with brine (15 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash column chromatography afforded **230** (7.6 g, 73%) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 – 8.08 (1H, m), 7.83 – 7.77 (1H, m), 7.49 (1H, d, *J* = 8.5 Hz), 7.47 – 7.40 (2H, m), 7.33 (1H, d, *J* = 8.5 Hz), 6.05 – 5.94 (1H, m), 5.19 – 5.10 (2H, m), 3.59 (2H, dd, *J* = 6.5, 1.5 Hz), 1.17 (9H, s), 0.22 (6H, s).

The spectroscopic properties were consistent with the data available in the literature.[309]

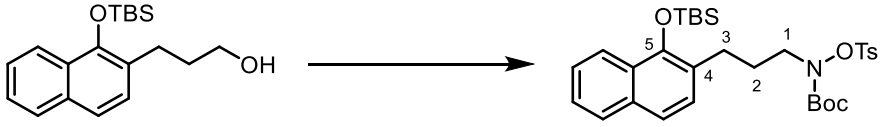
3-(1-((*tert*-Butyldimethylsilyl)oxy)naphthalen-2-yl)propan-1-ol (231)



The title compound **231** was prepared according to a literature procedure.[91]

To a solution of the preceding alkene **230** (1.5 g, 5.0 mmol) in THF (10 mL) at 0 °C was added borane-dimethyl sulfide (0.94 mL, 10.0 mmol) and the reaction was stirred at this temperature for 3 hours. Aqueous 30% H_2O_2 (1.6 mL) and $NaHCO_3$ (1.25 mL) were added and the reaction was warmed to room temperature overnight. The reaction was quenched with aqueous saturated NH_4Cl (15 mL) and extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with brine (15 mL), dried over Na_2SO_4 and concentrated in vacuo. Purification by flash column chromatography afforded **231** (650 mg, 41%) as a colourless solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 – 8.02 (1H, m), 7.78 – 7.73 (1H, m), 7.46 (1H, d, *J* = 8.5 Hz), 7.44 – 7.37 (2H, m), 7.28 (1H, d, *J* = 8.5 Hz), 3.56 (2H, t, *J* = 6.5 Hz), 2.87 (2H, t, *J* = 7.5 Hz), 1.92 – 1.85 (2H, m), 1.59 (1H, br s), 1.11 (9H, s), 0.17 (6H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.3, 133.8, 128.4, 128.2, 127.8, 126.8, 125.4, 125.0, 123.0, 122.1, 62.2, 33.3, 26.6, 26.3, 18.8, -3.1. *The spectroscopic properties were consistent with the data available in the literature.*[91]

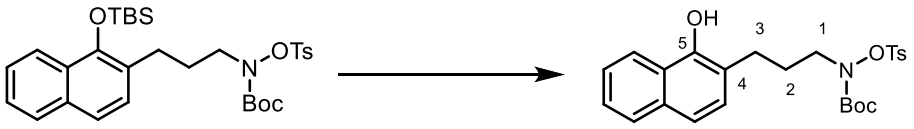
***tert*-Butyl (3-(1-((*tert*-butyldimethylsilyl)oxy)naphthalen-2-yl)propyl)(tosyloxy) carbamate**



General procedure G: The preceding alcohol **231** (470 mg, 1.50 mmol), PPh_3 (470 mg, 1.80 mmol), DIAD (0.35 mL, 1.80 mmol) and BocNHOTs (520 mg, 1.80 mmol) in anhydrous THF (8 mL) were employed. Purification by flash column chromatography (10% EtOAc:hexane) afforded the title compound as a colourless, viscous oil (670 mg, 76%); R_f = 0.4 (20% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 2955 (m), 2930 (m), 2895 (m), 2858 (m), 1720 (s), 1382 (s), 1369 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 – 8.02 (1H, m, ArC<u>H</u>), 7.80 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.78 – 7.74 (1H, m, ArC<u>H</u>), 7.46 – 7.37 (3H, m, ArC<u>H</u>), 7.28 – 7.22 (3H, m, Ts ArC<u>H</u>, ArC<u>H</u>), 3.71 – 3.43 (2H, m, C**1**-<u>H</u>$_2$), 2.73 (2H, t, *J* = 7.5 Hz, C**3**-<u>H</u>$_2$), 2.39 (3H, s, Ts C<u>H</u>$_3$), 1.99 – 1.88 (2H, m, C**2**-<u>H</u>$_2$), 1.19 (9H, s, Boc (C<u>H</u>$_3$)$_3$), 1.11 (9H, s, TBS (C<u>H</u>$_3$)$_3$), 0.17 (6H, s, TBS Si(C<u>H</u>$_3$)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6 (Boc <u>C</u>=O), 148.3 (C**5**), 145.7

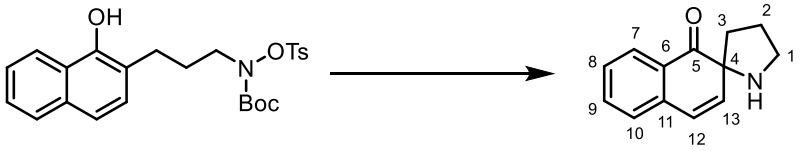
(Ts Ar<u>C</u>), 133.8 (Ar<u>C</u>), 131.4 (Ts Ar<u>C</u>), 129.7 (2 × Ts Ar<u>C</u>H) 129.6 (2 × Ts Ar<u>C</u>H), 128.2 (Ar<u>C</u>), 128.1 (Ar<u>C</u>H), 127.7 (Ar<u>C</u>H), 126.2 (C**4**), 125.4 (Ar<u>C</u>H), 124.9 (Ar<u>C</u>H), 123.2 (Ar<u>C</u>H), 121.8 (Ar<u>C</u>H), 83.3 (Boc <u>C</u>(CH_3)$_3$), 52.8 (C**1**), 27.7 (Boc (<u>C</u>H_3)$_3$), 27.6 (C**3**), 26.4 (C**2**), 26.3 (TBS (<u>C</u>H_3)$_3$), 21.8 (Ts <u>C</u>H_3), 18.9 (TBS Si<u>C</u>(CH_3)$_3$), -3.0 (TBS Si(C<u>H</u>$_3$)$_2$); HRMS (ESI^+) Calculated for $C_{31}H_{43}NNaO_6SSi$: 608.2472. Found $[M+Na]^+$: 608.2466.

***tert*-Butyl (3-(1-hydroxynaphthalen-2-yl)propyl)(tosyloxy)carbamate (232)**



<u>General procedure H:</u> *tert*-Butyl (3-(1-((*tert*-butyldimethylsilyl)oxy)naphthalen-2-yl)propyl) (tosyloxy)carbamate (560 mg, 0.97 mmol) and 1:1 TBAF:AcOH solution (0.1 M in THF, 0.97 mmol) in THF (20 mL) were employed. Purification by flash column chromatography (20% EtOAc:hexane) afforded **232** (310 mg, 68%) as a pale yellow solid; m.p.: 107-109 ^oC (EtOAc:hexane); R_f = 0.2 (20% EtOAc:hexane); ν_{max} / cm^{-1} (*solid*) 3485 (m), 2970 (m), 2942 (m), 2882 (m), 1729 (s), 1385 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 8.18 – 8.15 (1H, m, ArC<u>H</u>), 7.85 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.77 (1H, dd, *J* = 8.0, 1.5 Hz, ArC<u>H</u>), 7.49 – 7.41 (2H, m, ArC<u>H</u>), 7.39 (1H, d, *J* = 8.5 Hz, ArC<u>H</u>), 7.30 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.22 (1H, d, *J* = 8.5 Hz, ArC<u>H</u>), 6.07 (1H, br s, O<u>H</u>), 3.69 (2H, t, *J* = 6.5 Hz, C**1**-<u>H</u>$_2$), 2.81 (2H, t, *J* = 7.5 Hz, C**3**-<u>H</u>$_2$), 2.43 (3H, s, Ts C<u>H</u>$_3$), 2.10 – 2.00 (2H, m, C**2**-<u>H</u>$_2$), 1.24 (9H, s, Boc (C<u>H</u>$_3$)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.4 (Boc <u>C</u>=O), 148.8 (C**5**), 146.0 (Ts Ar<u>C</u>), 133.6 (Ar<u>C</u>), 131.3 (Ts Ar<u>C</u>), 129.8 (2 × Ts Ar<u>C</u>H), 129.7 (2 × Ts Ar<u>C</u>H), 128.8 (Ar<u>C</u>H), 127.7 (Ar<u>C</u>H), 125.7 (Ar<u>C</u>H), 125.4 (Ar<u>C</u>H), 125.0 (Ar<u>C</u>), 121.5 (Ar<u>C</u>H), 120.5 (Ar<u>C</u>H), 120.3 (Ar<u>C</u>), 84.0 (Boc <u>C</u>(CH_3)$_3$), 52.9 (C**1**), 27.7 (Boc (<u>C</u>H_3)$_3$), 27.3 (C**3**), 27.2 (C**2**), 21.8 (Ts <u>C</u>H_3); HRMS (ESI^+) Calculated for $C_{25}H_{29}NNaO_6S$: 494.1607. Found $[M+Na]^+$: 494.1614.

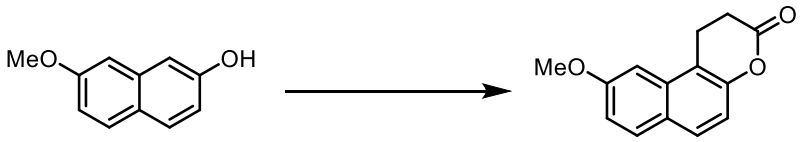
1*H*-Spiro[naphthalene-2,2'-pyrrolidin]-1-one (233)



<u>General procedure I:</u> The preceding *N*-tosyloxycarbamate **232** (70.7 mg, 0.15 mmol) and TFA (23 μL, 0.3 mmol) in 30:1 anhydrous TFE:CH_2Cl_2 (1.5 mL) were stirred at room

temperature for 26 hours. Purification by flash column chromatography (gradient, eluent: 50% EtOAc:hexane – 100% EtOAc) afforded **233** (11.4 mg, 38%) as a yellow/brown solid; m.p.: 57-60 °C (EtOAc:hexane); R_f = 0.1 (EtOAc); ν_{max} / cm^{-1} (*solid*) 2920 (m), 2851 (m), 1674 (s), 1595 (s), 1371 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (1H, d, *J* = 7.5 Hz, C**7**-H), 7.56 – 7.51 (1H, m, C**9**-H), 7.34 – 7.29 (1H, m, C**8**-H), 7.17 (1H, d, *J* = 7.5 Hz, C**10**-H), 6.43 (1H, d, *J* = 10.0 Hz, C**12**-H), 6.25 (1H, d, *J* = 10.0 Hz, C**13**-H), 3.41 – 3.33 (1H, m, C**1**-H), 3.13 – 3.05 (1H, m, C**1**-H'), 2.40 (1H, br s, NH), 2.11 – 2.06 (1H, m, C**3**-H), 1.92 – 1.78 (3H, m, C**3**-H', C**2**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.7 (C**5**), 139.8 (C**13**), 138.2 (C**11**), 134.7 (C**9**), 129.0 (C**6**), 127.9 (C**8**), 127.3 (C**7**), 127.2 (C**10**), 123.3 (C**12**), 70.2 (C**4**), 48.4 (C**1**), 38.9 (C**3**), 25.9 (C**2**); HRMS (ESI^+) Calculated for $C_{13}H_{14}NO$: 200.1069. Found $[M+H]^+$: 200.1079.

9-Methoxy-1,2-dihydro-3*H*-naphtho[*f*]chromen-3-one

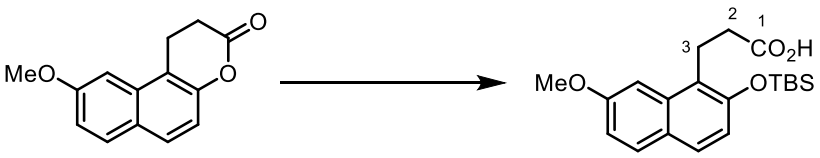


The title compound was prepared according to a literature procedure.[287]

To a solution of 7-methoxy-2-naphthol (3.48 g, 20.0 mmol) and Amberlyst 15® (2.0 g) in PhMe (50 mL) was added acrylic acid (2.88 g, 40.0 mmol) and the solution was heated at reflux for 22 hours. After cooling to room temperature, the reaction mixture was filtered over Celite® and the filtrate was concentrated *in vacuo*. Purification by flash column chromatography (gradient, eluent: 20 – 25% EtOAc:hexane) afforded the title compound (2.05 g, 44%) as a pale-yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (1H, d, *J* = 9.5 Hz), 7.69 (1H, d, *J* = 9.0 Hz), 7.15 – 7.13 (2H, m), 7.09 (1H, d, *J* = 9.0 Hz), 3.95 (3H, s), 3.31 (2H, t, *J* = 7.5 Hz), 2.92 (2H, t, *J* = 7.5 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.5, 158.9, 150.4, 132.6, 130.4, 128.7, 126.2, 117.4, 115.0, 114.4, 102.0, 55.4, 28.7, 20.2.

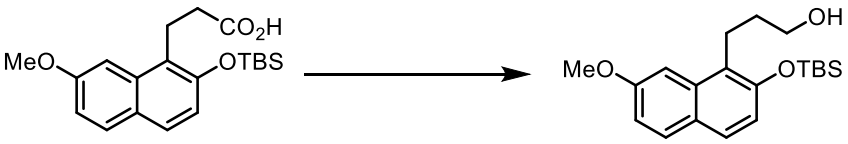
The spectroscopic properties were consistent with the data available in the literature.[310]

3-(2-((*tert*-Butyldimethylsilyl) oxy)-7-methoxynaphthalen-1-yl)propanoic acid



To a solution of 9-methoxy-1,2-dihydro-3*H*-naphtho[f]chromen-3-one (1.71 g, 7.50 mmol) in THF (75 mL) was added aqueous 1 M LiOH (44.0 mL, 24.8 mmol). After stirring at room temperature overnight the pH was acidified to approx. 3 with 1 M HCl. The product was extracted with EtOAc (50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was dissolved in DMF (15 mL) and *tert*-butyldimethylsilyl chloride (2.50 g, 16.5 mmol) and imidazole (1.68 g, 24.8 mmol) were added at 0 ^{o} C. After being stirred at room temperature overnight the reaction was quenched by addition of H_2O and the product was extracted with hexane, dried over $MgSO_4$, filtered and concentrated *in vacuo*. To the crude product in MeOH (7.5 mL) and THF (7.5 mL) was added aqueous K_2CO_3 (22 mL, 15.0 mmol). After stirring overnight at room temperature, the reaction was quenched with 1 M HCl (20 mL) at 0 ^{o}C. The organic phase was extracted with Et_2O (3 × 10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography (20% EtOAc:hexane) afforded the title compound (1.77 g, 65%) as a yellow solid; m.p.: 113-115 ^{o}C (EtOAc:hexane); R_f = 0.5 (33% EtOAc:hexane); ν_{max} / cm^{-1} (*solid*) 3675 (w), 2958 (m), 2927 (m), 1703 (s), 1627 (m), 1514 (s), 1264 (s), 1231 (s), 1037 (s); ^{1}H NMR ($CDCl_3$) δ 7.68 (1H, d, *J* = 9.0 Hz, ArC<u>H</u>), 7.56 (1H, d, *J* = 9.0 Hz, ArC<u>H</u>), 7.24 (1H, d, *J* = 2.5 Hz, ArC<u>H</u>), 7.02 (1H, dd, *J* = 9.0, 2.5 Hz, ArC<u>H</u>), 6.95 (1H, d, *J* = 9.0 Hz, ArC<u>H</u>), 3.95 (3H, s, OC<u>H</u>$_3$), 3.43 – 3.26 (2H, m, C**3**-<u>H</u>$_2$), 2.76 – 2.56 (2H, m, C**2**-<u>H</u>$_2$), 1.97 (9H, s, TBS (C<u>H</u>$_3$)$_3$), 0.29 (6H, s, TBS (Si(C<u>H</u>$_3$)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.9 (C**1**), 158.3 (Ar<u>C</u>), 151.4 (Ar<u>C</u>), 134.3 (Ar<u>C</u>), 130.1 (Ar<u>C</u>H), 127.6 (Ar<u>C</u>H), 124.8 (Ar<u>C</u>), 122.1 (Ar<u>C</u>), 117.6 (Ar<u>C</u>H), 115.7 (Ar<u>C</u>H), 101.7 (Ar<u>C</u>H), 55.3 (O<u>C</u>H$_3$), 33.5 (C**2**), 25.8 (TBS (<u>C</u>H$_3$)$_3$), 21.1 (C**3**), 18.3 (TBS Si<u>C</u>(CH$_3$)$_3$), -3.9 (TBS Si(<u>C</u>H$_3$)$_2$); HRMS (-ve ion) Calculated for $C_{20}H_{27}O_4Si$: 359.1684. Found [M-H]$^{-}$: 359.1685.

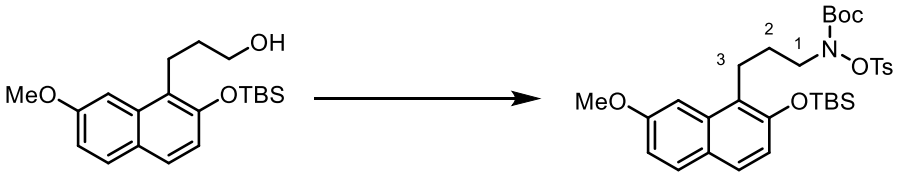
3-(2-((*tert*-Butyldimethylsilyl)oxy)-7-methoxynaphthalen-1-yl)propan-1-ol



General procedure F: 3-(2-((*tert*-Butyldimethylsilyl)oxy)-7-methoxynaphthalen-1-yl) propanoic acid (1.08 g, 3.00 mmol), ethyl chloroformate (0.29 mL, 3.00 mmol), Et_3N (0.42 mL, 3.00 mmol), and $NaBH_4$ (280 mg, 7.50 mmol) were employed. Purification by flash column chromatography (20% EtOAc:hexane) afforded the title compound (680 mg, 65%) as a pale yellow oil; R_f = 0.25 (20% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 3370 (br), 2953 (m), 2930 (m), 2884 (m), 2857 (m), 1624 (s), 1513 (s), 1461 (s), 1230 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (1H, d, *J* = 9.0 Hz), 7.53 (1H, d, *J* = 9.0 Hz), 7.27 (1H, s), 7.02 (1H, dd, *J* = 9.0, 2.5 Hz), 6.94 (1H, d, *J* = 9.0 Hz), 3.93 (3H, s), 3.59 (2H, t, *J* = 6.0 Hz), 3.14 (2H, t, *J* = 7.0 Hz), 2.06 – 1.77 (3H, m), 1.05 (9H, s), 0.27 (6H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.0, 151.2, 134.5, 130.0, 127.0, 125.1, 123.4, 117.9, 115.6, 102.5, 62.0, 55.3, 31.9, 25.9, 21.5, 18.4, -3.9; HRMS (ESI^+) Calculated for $C_{20}H_{30}NaO_3Si$: 369.1856. Found $[M+Na]^+$: 369.1855.

The spectroscopic properties were consistent with the data available in the literature.[91]

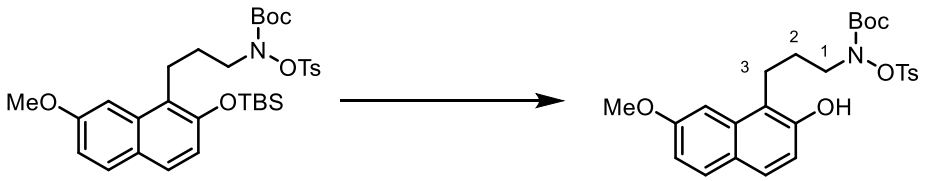
***tert*-Butyl (3-(2-((*tert*-butyldimethylsilyl)oxy)-7-methoxynaphthalen-1yl)propyl) (tosyloxy)carbamate**



General procedure G: 3-(2-((*tert*-Butyldimethylsilyl)oxy)-7-methoxynaphthalen-1-yl) propan-1-ol (400 mg, 1.15 mmol), PPh_3 (360 mg, 1.38 mmol), DIAD (0.27 mL, 1.38 mmol) and BocNHOTs (400 mg, 1.38 mmol) in anhydrous THF (5 mL) were employed. Purification by flash column chromatography (10% EtOAc:hexane) afforded the title compound (480 mg, 68%) as a colourless oil; R_f = 0.5 (20% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 2956 (m), 2930 (m), 2900 (m), 2859 (m), 1721 (s), 1623 (s), 1513 (s), 1381 (s), 1368 (s), 1231 (s), 1178 (s), 1152 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 (2H, d, *J* = 8.0 Hz, Ts ArC<u>H</u>), 7.65 (1H, d, *J* = 9.0 Hz, ArC<u>H</u>), 7.51 (1H, d, *J* = 9.0 Hz, ArC<u>H</u>), 7.30 (2H, d, *J* = 8.0 Hz, Ts ArC<u>H</u>), 7.16 (1H, d, *J* = 2.5 Hz, ArC<u>H</u>), 7.00 (1H, dd, *J* = 9.0, 2.5 Hz, ArC<u>H</u>), 6.90 (1H, d, *J* = 9.0 Hz, ArC<u>H</u>), 3.96 (3H, s, OC<u>H</u>$_3$), 3.73 (2H, br s, C**1**-<u>H</u>$_2$), 2.96 (2H, t, *J* = 8.0 Hz, C**3**-<u>H</u>$_2$), 2.42 (3H, s, Ts, C<u>H</u>$_3$),

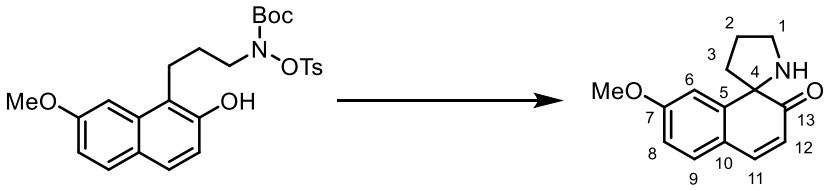
1.96 (2H, app. qn, *J* = 7.5 Hz, C**2**-$\underline{H}_2$), 1.16 (9H, s, Boc (C$\underline{H}_3$)$_3$), 1.05 (9H, s, TBS (C$\underline{H}_3$)$_3$), 0.25 (6H, s, TBS (Si(C$\underline{H}_3$)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.2 (Ar$\underline{C}$), 155.4 (Boc $\underline{C}$=O), 151.2 (Ar$\underline{C}$), 145.7 (Ts Ar$\underline{C}$), 134.5 (Ar$\underline{C}$), 131.4 (Ts Ar$\underline{C}$), 13.0 (Ar$\underline{C}$H), 129.7 (2 × Ts Ar$\underline{C}$H), 129.6 (2 × Ts Ar$\underline{C}$H), 127.2 (Ar$\underline{C}$H), 124.9 (Ar$\underline{C}$), 123.2 (Ar$\underline{C}$), 117.7 (Ar$\underline{C}$H), 116.0 (Ar$\underline{C}$H), 101.9 (Ar$\underline{C}$H), 83.2 (Boc $\underline{C}$(CH$_3$)$_3$), 55.5 (O$\underline{C}$H$_3$), 52.9 (C**1**), 27.6 (Boc ($\underline{C}$H$_3$)$_3$), 26.0 (TBS ($\underline{C}$H$_3$)$_3$), 25.8 (C**2**), 22.9 (C**3**), 21.8 (Ts $\underline{C}$H$_3$), 18.4 (TBS $\underline{C}$(CH$_3$)$_3$), -3.8 (TBS Si($\underline{C}$H$_3$)$_2$); HRMS (ESI$^+$) Calculate for $C_{32}H_{45}NNaO_7SSi$: 638.2578. Found [M+Na]$^+$: 638.2560.

***tert*-Butyl (3-(2-hydroxy-7-methoxynaphthalen-1-yl)propyl)(tosyloxy)carbamate (234)**



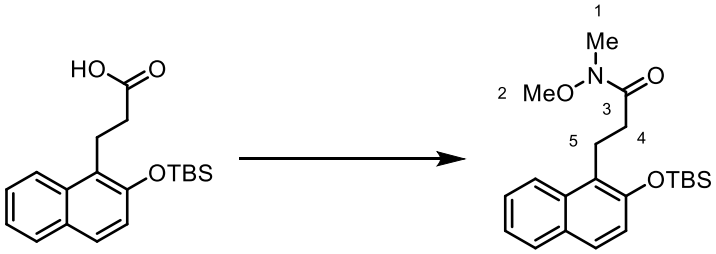
General procedure H: *tert*-Butyl (3-(2-((*tert*-butyldimethylsilyl)oxy)-7-methoxynaphthalen-1yl)propyl) (tosyloxy)carbamate (300 mg, 0.50 mmol) and 1:1 TBAF:AcOH solution (0.1 M in THF, 0.50 mmol) in THF (10 mL) were employed. Purification by flash column chromatography (gradient, eluent 20 – 33% EtOAc:hexane) afforded **234** (130 mg, 51%) as a pale yellow solid; R_f = 0.2 (20% EtOAc:hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (2H, d, *J* = 8.0 Hz, Ts ArC$\underline{H}$), 7.65 (1H, d, *J* = 9.0 Hz, ArC$\underline{H}$), 7.54 (1H, d, *J* = 8.5 Hz, ArC$\underline{H}$), 7.32 (2H, d, *J* = 8.0 Hz, Ts ArC$\underline{H}$), 7.14 (1H, d, *J* = 2.5 Hz, ArC$\underline{H}$), 6.99 (1H, dd, *J* = 9.0, 2.5 Hz, ArC$\underline{H}$), 6.89 (1H, d, *J* = 8.5 Hz, ArC$\underline{H}$), 5.34 (1H, br s, O$\underline{H}$), 3.95 (3H, s, OC$\underline{H}_3$), 3.76 (2H, br s, C**1**-$\underline{H}_2$), 3.00 (2H, t, *J* = 8.0 Hz, C**3**-$\underline{H}_2$), 2.43 (3H, s, Ts C$\underline{H}_3$), 2.07 – 2.00 (2H, m, C**2**-$\underline{H}_2$), 1.19 (9H, s, Boc (C$\underline{H}_3$)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.4 (Ar$\underline{C}$), 155.9 (Boc $\underline{C}$=O), 151.3 (Ar$\underline{C}$), 145.7 (Ts Ar$\underline{C}$), 134.3 (Ar$\underline{C}$), 131.2 (Ts Ar$\underline{C}$), 130.1 (Ar$\underline{C}$H) 129.6 (2 × Ts Ar$\underline{C}$H), 129.5 (2 × Ts Ar$\underline{C}$H), 127.7 (Ar$\underline{C}$H), 124.7 (Ar$\underline{C}$), 117.7 (Ar$\underline{C}$H), 115.4 (Ar$\underline{C}$), 115.3 (Ar$\underline{C}$H), 101.7 (Ar$\underline{C}$H), 83.5 (Boc $\underline{C}$(CH$_3$)$_3$), 55.3 (O$\underline{C}$H$_3$), 52.9 (C**1**), 27.5 (Boc ($\underline{C}$H$_3$)$_3$), 25.8 (C**2**), 22.2 (C**3**), 21.7 (Ts $\underline{C}$H$_3$); HRMS (ESI$^+$) Calculated for $C_{26}H_{31}NNaO_7S$: 524.1713. Found [M+Na]$^+$: 524.1708.

7-Methoxy-2*H*-spiro[naphthalene-1,2'-pyrrolidin]-2-one (235)



General procedure I: The preceding *N*-tosyloxycarbamate **234** (50.2 mg, 0.10 mmol), TFA (15 μL, 0.20 mmol) and TFE (1 mL) were employed. After stirring at room temperature for 48 hours, purification by flash column chromatography (gradient, eluent 50% EtOAc:hexane – EtOAc) afforded **235** (17.4 mg, 76%) as a yellow oil; R_f = 0.2 (EtOAc); ν_{max} / cm^{-1} (*film*) 3340 (m), 2963 (m), 2942 (m), 2865 (m), 1666 (s), 1601 (s), 1555 (m), 1279 (s), 1224 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (1H, d, *J* = 10.0 Hz, C**11**-H), 7.23 (1H, d, *J* = 2.5 Hz, C**6**-H), 7.19 (1H, d, *J* = 8.5 Hz, C**9**-H), 6.75 (1H, dd, *J* = 8.5, 2.5 Hz, C**8**-H), 6.03 (1H, d, *J* = 10.0 Hz, C**12**-H), 3.85 (3H, s, OCH_3), 3.44 (1H, dt, *J* = 10.0, 6.5 Hz, C**1**-H), 3.27 (1H, dt, *J* = 10.0, 6.5 Hz, C**1**-H'), 2.92 (1H, br s, NH), 2.30 – 2.23 (1H, m, C**3**-H), 1.93 – 1.72 (3H, m, C**3**-H' and C**2**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.9 (C**13**), 161.5 (C**7**), 151.2 (C**5**), 144.7 (C**11**), 130.9 (C**9**), 122.4 (C**10**), 120.8 (C**12**), 112.2 (C**6**), 112.0 (C**8**), 74.1 (C**4**), 55.4 (OCH_3), 49.9 (C**1**), 43.2 (C**3**), 25.1 (C**2**); HRMS (ESI^+) Calculated for $C_{14}H_{15}NNaO_2$: 252.0995. Found $[M+Na]^+$: 252.1002.

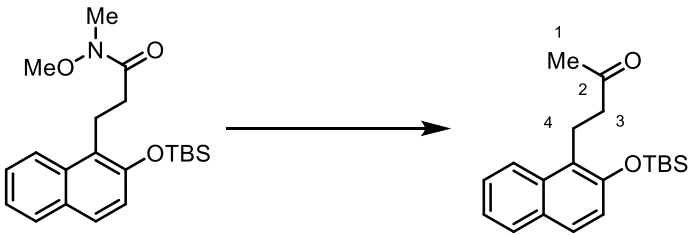
3-(2-((*tert*-Butyldimethylsilyl)oxy)naphthalen-1-yl)-*N*-methoxy-*N*-methylpropanamide



General procedure K: Carboxylic acid **167** (2.64 g, 8.00 mmol), *N*,*O*-dimethylhydroxylamine hydrochloride (1.09 g, 11.2 mmol), Et_3N (1.56 mL, 11.2 mmol), 4-dimethylaminopyridine (1.37 g, 11.2 mmol), and *N*,*N*'-dicyclohexylcarbodiimide (2.31 g, 11.2 mmol) were employed. Purification by flash column chromatography (20% EtOAc:hexane) afforded the title compound (2.20 g, 74%) as a pale yellow oil; R_f = 0.7 (33% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 2954 (m), 2930 (m), 2857 (m), 1664 (s), 1594 (m), 1466 (s), 1379 (m), 1242 (s), 1072 (m); ^{1}H NMR (400 MHz, $CDCl_3$) 8.02 (1H, d, *J* = 8.5 Hz, ArCH) δ 7.78 (1H, d, *J* = 8.5 Hz, ArCH), 7.64 (1H, d, *J* = 9.0 Hz, ArCH), 7.51 – 7.47 (1H, m, ArCH), 7.37 – 7.32 (1H, m, ArCH), 7.11

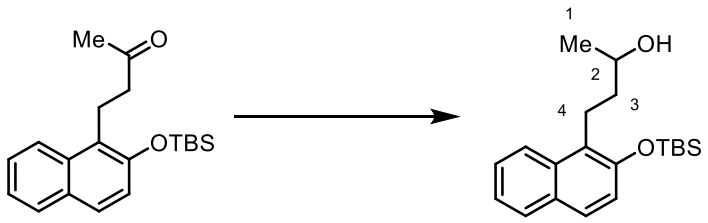
(1H, d, *J* = 9.0 Hz, ArC<u>H</u>), 3.59 (3H, s, C**2**-<u>H</u>$_3$), 3.41 (2H, t, *J* = 8.0 Hz, C**5**-<u>H</u>$_2$), 3.21 (3H, s, C**1**-<u>H</u>$_3$), 2.73 (2H, t, *J* = 8.0 Hz, C**4**-<u>H</u>$_2$), 1.07 (9H, s, TBS (C<u>H</u>$_3$)$_3$), 0.30 (6H, s, TBS Si(C<u>H</u>$_3$)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.2 (C**3**) 150.7 (Ar<u>C</u>), 133.2 (Ar<u>C</u>), 129.5 (Ar<u>C</u>), 128.5 (Ar<u>C</u>H), 127.5 (Ar<u>C</u>H), 126.3 (Ar<u>C</u>H), 124.3 (Ar<u>C</u>), 123.3 (Ar<u>C</u>H), 123.1 (Ar<u>C</u>H), 120.3 (Ar<u>C</u>H), 61.2 (C**2**), 32.3 (C**4**), 31.9 (C**1**), 25.8 (TBS (<u>C</u>H$_3$)$_3$), 20.7 (C**5**), 18.3 (TBS <u>C</u>(CH$_3$)$_3$), -3.9 (TBS Si(<u>C</u>H$_3$)$_2$); HRMS (ESI$^+$) Calculated for $C_{21}H_{31}NNaO_3Si$: 396.1965. Found [M+Na]$^+$: 396.1976.

4-(2-((*tert*-Butyldimethylsilyl)oxy)naphthalen-1-yl)butan-2-one



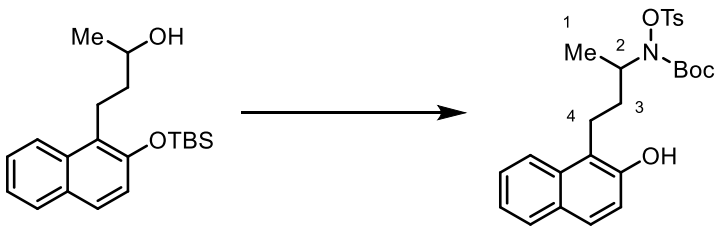
To a solution of 3-(2-((*tert*-butyldimethylsilyl)oxy)naphthalen-1-yl)-*N*-methoxy-*N*-methyl propanamide (940 mg, 2.50 mmol) in anhydrous THF (6 mL) at 0 ^{o} C was added methylmagnesium bromide (3 M in Et_2O, 1.6 mL, 5.0 mmol) dropwise over 5 minutes. The reaction mixture was stirred at room temperature for 1 hour until completion by TLC analysis. The reaction mixture was quenched by addition of saturated aqueous NH_4Cl (5 mL) and the aqueous phase was extracted with EtOAc (3 × 5mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo* to afford the title compound (610 mg, 74%) as a pale yellow oil which was used without further purification; R_f = 0.8 (33% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 2954 (m), 2929 (m), 2893 (m), 2857 (m), 1713 (s), 1622 (m), 1594 (m), 1466 (s), 1360 (m), 1242 (s), 1161 (m), 1075 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (1H, d, *J* = 8.5 Hz, ArC<u>H</u>), 7.79 (1H, d, *J* = 8.5 Hz, ArC<u>H</u>), 7.64 (1H, d, *J* = 9.0 Hz, ArC<u>H</u>), 7.49 (1H, ddd, *J* = 8.5, 7.0, 1.5 Hz, ArC<u>H</u>), 7.35 (1H, ddd, *J* = 8.0, 7.0, 1.0 Hz, ArC<u>H</u>), 7.10 (1H, d, *J* = 9.0 Hz, ArC<u>H</u>), 3.33 (2H, t, *J* = 8.0 Hz, C**4**-<u>H</u>$_2$), 2.74 (2H, t, *J* = 8.0 Hz, C**3**-<u>H</u>$_2$), 2.18 (3H, s, C**1**-<u>H</u>$_3$), 1.06 (9H, s, TBS (C<u>H</u>$_3$)$_3$), 0.29 (6H, s, TBS Si(C<u>H</u>$_3$)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.5 (C**2**), 150.6 (Ar<u>C</u>), 133.0 (Ar<u>C</u>), 129.5 (Ar<u>C</u>), 128.6 (Ar<u>C</u>H), 127.5 (Ar<u>C</u>H), 126.4 (Ar<u>C</u>H), 123.9 (Ar<u>C</u>), 123.4 (Ar<u>C</u>H), 122.9 (Ar<u>C</u>H), 120.2 (Ar<u>C</u>H), 43.5 (C**3**), 29.9 (C**1**), 25.8 (TBS (<u>C</u>H$_3$)$_3$), 19.9 (C**4**), 18.3 (TBS <u>C</u>(CH$_3$)$_3$), -3.9 (TBS Si(<u>C</u>H$_3$)$_2$); HRMS (ESI$^+$) Calculated for $C_{20}H_{28}NaO_2Si$: 351.1750. Found [M+Na]$^+$: 351.1753.

4-(2-((*tert*-Butyldimethylsilyl)oxy)naphthalen-1-yl)butan-2-ol



To a solution of 4-(2-((*tert*-butyldimethylsilyl)oxy)naphthalen-1-yl)butan-2-one (560 mg, 1.70 mmol) in MeOH (10 mL) was slowly added $NaBH_4$ (130 mg, 3.40 mmol) at 0 °C. The reaction was stirred at this temperature for 1.5 hours until complete by TLC analysis. The reaction was quenched by addition of water (10 mL) and extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered and the solvent removed *in vacuo* to afford the title compound (490 mg, 87%) as a pale yellow oil which was used without further purification; R_f = 0.6 (33% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 3360 (br), 2957 (m), 2928 (m), 2884 (m), 2857 (m), 1622 (m), 1594 (m), 1465 (m), 1241 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (1H, d, *J* = 8.5 Hz, ArC<u>H</u>), 7.78 (2H, d, *J* = 8.5 Hz, ArC<u>H</u>), 7.62 (1H, d, *J* = 9.0 Hz, ArC<u>H</u>), 7.48 (1H, ddd, *J* = 8.5, 7.0, 1.5 Hz, ArC<u>H</u>), 7.35 (1H, ddd, *J* = 8.0, 7.0, 1.0 Hz, ArC<u>H</u>), 7.10 (1H, d, *J* = 9.0 Hz, ArC<u>H</u>), 3.73 – 3.65 (1H, m, C**2**-<u>H</u>), 3.27 – 3.13 (2H, m, C**4**-<u>H</u>$_2$), 2.29 (1H, br s, O<u>H</u>), 1.87 – 1.74 (2H, m, C**3**-<u>H</u>$_2$), 1.19 (3H, d, *J* = 6.0 Hz, C**1**-<u>H</u>$_3$), 1.06 (9H, s, TBS (C<u>H</u>$_3$)$_3$), 0.29 (6H, s, TBS Si(C<u>H</u>$_3$)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.3 (Ar<u>C</u>), 133.2 (Ar<u>C</u>), 129.8 (Ar<u>C</u>), 128.5 (Ar<u>C</u>H), 127.3 (Ar<u>C</u>H), 126.2 (Ar<u>C</u>H), 124.8 (Ar<u>C</u>H), 123.5 (Ar<u>C</u>), 123.4 (Ar<u>C</u>H), 120.5 (Ar<u>C</u>H), 67.1 (C**2**), 38.9 (C**3**), 25.9 (TBS (<u>C</u>H$_3$)$_3$), 23.1 (C**4**), 21.6 (C**1**), 18.4 (TBS Si<u>C</u>(CH$_3$)$_3$), -3.9 (TBS Si(<u>C</u>H$_3$)$_2$); HRMS (ESI$^+$) Calculated for $C_{20}H_{30}NaO_2Si$: 353.1907. Found $[M+Na]^+$: 353.1894.

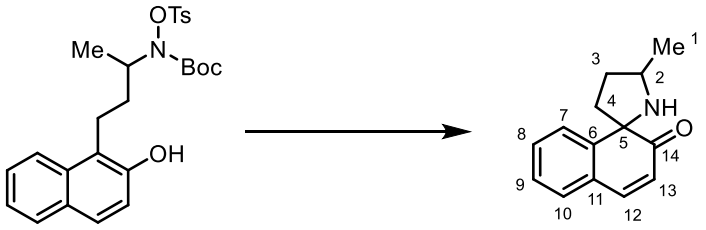
***tert*-Butyl (4-(2-hydroxynaphthalen-1-yl)butan-2-yl)(tosyloxy)carbamate (236)**



<u>General procedures G and H:</u> 4-(2-((*tert*-Butyldimethylsilyl)oxy)naphthalen-1-yl)butan-2-ol (220 mg, 0.77 mmol), PPh_3 (240 mg, 0.92 mmol), DIAD (0.18 mL, 0.92 mmol) and BocNHOTs (260 mg, 0.92 mmol) in anhydrous THF (3 mL) were employed. The desired

product could not be obtained pure so to the crude product in THF (5 mL) was added a solution of TBAF (1M in THF, 1.06 mL, 1.06 mmol) at 0 °C. The reaction mixture was stirred at this temperature for 1.5 hours until complete by TLC. The reaction mixture was quenched with saturated aqueous NH_4Cl (5 mL) and extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (gradient 20 – 33% EtOAc:hexane) afforded **236** (320 mg, 69%) as a colourless solid; R_f = 0.4 (33% EtOAc:hexane); ν_{max} / cm^{-1} (*solid*) 3461 (m, br) 2975 (m), 1688 (s), 1386 (s); ^{1}H NMR (400 MHz, CD_3OD) δ 7.83 (3H, d, *J* = 8.5, Ts ArC<u>H</u>, ArC<u>H</u>), 7.72 (1H, d, *J* = 8.0 Hz, ArC<u>H</u>), 7.58 (1H, d, *J* = 9.0 Hz, ArC<u>H</u>), 7.42 – 7.33 (3H, m, ArC<u>H</u>), 7.24 (1H, t, *J* = 7.5 Hz, ArC<u>H</u>), 7.09 (1H, d, *J* = 9.0 Hz, ArC<u>H</u>), 4.00 (1H, sextet, *J* = 7.0 Hz, C**2**-<u>H</u>), 3.03 (2H, dd, *J* = 9.5, 6.5 Hz, C**4**-<u>H_2</u>), 2.38 (3H, s, Ts C<u>H_3</u>), 1.94 – 1.83 (1H, m, C**3**-<u>H</u>), 1.77 – 1.66 (1H, m, C**3**-<u>H</u>'), 1.27 (3H, d, *J* = 6.5 Hz, C**1**-<u>H_3</u>), 1.20 (9H, s, Boc (C<u>H_3</u>)$_3$); ^{13}C NMR (101 MHz, CD_3OD) δ 157.9 (Boc <u>C</u>=O), 153.3 (Ar<u>C</u>), 147.4 (Ts Ar<u>C</u>), 134.7 (Ar<u>C</u>), 132.9 (Ar<u>C</u>), 130.8 (2 × Ts Ar<u>C</u>H), 130.7 (2 × Ts Ar<u>C</u>H), 130.4 (Ar<u>C</u>), 129.5 (Ar<u>C</u>H), 128.5 (Ar<u>C</u>H), 127.1 (Ar<u>C</u>H), 123.7 (Ar<u>C</u>H), 123.4 (Ar<u>C</u>H), 120.3 (Ar<u>C</u>), 118.6 (Ar<u>C</u>H), 84.7 (Boc <u>C</u>$(CH_3)_3$, 62.8 (C**2**), 35.2 (C**3**), 27.9 (Boc (<u>C</u>H_3)$_3$), 22.8 (C**4**), 21.6 (Ts <u>C</u>H_3), 17.8 (C**1**); HRMS (ESI^+) Calculated for $C_{26}H_{31}NNaO_6Si$: 508.1764. Found $[M+Na]^+$: 508.1756.

5'-Methyl-2*H*-spiro[naphthalene-1,2'-pyrrolidin]-2-one (237)



1.5:1 d.r.

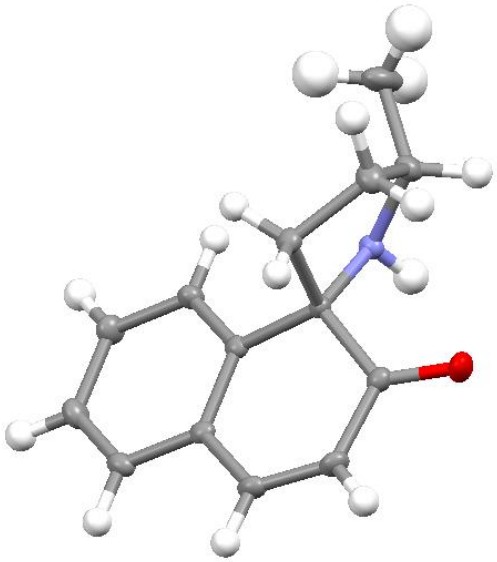
<u>General procedure I:</u> The preceding *N*-tosyloxycarbamate **236** (97.1 mg, 0.20 mmol) and TFA (30 μL, 0.4 mmol) in 5:1 TFE:CH_2Cl_2 (3 mL) were stirred at room temperature for 48 hours. Purification by flash column chromatography (20 – 33% EtOAc:hexane – 100% EtOAc) afforded **237** (23.0 mg, 54%) as a 1.5:1 mixture of diastereomers and as a yellow solid; R_f = 0.5 (2:1 EtOAc:hexane); ν_{max} / cm^{-1} (*solid*) 3337 (s), 2963 (s), 2916 (s), 2850 (s), 1668 (s), 1084 (s).

*Data for the major diastereomer **237a**:* m.p.: 89-90 °C (EtOAc:hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (1H, d, *J* = 8.0 Hz, C**7**-H), 7.41 – 7.35 (2H, m, C**8**-H, C**12**-H), 7.26 – 7.24 (2H, m, C**9**-H, C**10**-H), 6.18 (1H, d, *J* = 10.0 Hz, C**13**-H), 3.63 – 3.55 (1H, m, C**2**-H), 2.42 (1H , br s, NH) overlapping 2.45 – 2.39 (1H, ddd, *J* = 13.0, 7.0, 3.0 Hz, C**4**-H), 1.92 – 1.86 (1H, dddd, *J* = 11.5, 6.5, 5.0, 3.0 Hz, C**3**-H), 1.82 – 1.74 (1H, ddd, *J* = 13.0, 11.0, 6.0Hz, C**4**-H'), 1.42 – 1.35 (1H, m, C**3**-H') overlapping 1.39 (3H, d, *J* = 6.0 Hz, C**1**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.3 (C**14**), 149.1 (C**6**), 144.6 (C**12**), 130.4 (C**8**), 129.1 (C**10**), 128.9 (C**11**), 126.9 (C**9**), 125.8 (C**7**), 123.4 (C**13**), 74.8 (C**5**), 58.2 (C**2**), 42.9 (C**4**), 33.3 (C**3**), 20.2 (C**1**).

*Data for the minor diastereomer **237b**:*^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (1H, dd, *J* = 8.0, 1.0 Hz, C**7**-H), 7.42 – 7.32 (2H, m, C**8**-H, C**12**-H), 7.28 – 7.22 (2H, m, C**9**-H, C**10**-H), 6.15 (1H, d, *J* = 10.0 Hz, C**13**-H), 3.76 – 3.67 (1H, m, C**2**-H), 2.72 (1H, br s, NH), 2.25 (1H, ddd, *J* = 12.5, 10.0, 7.0 Hz, C**4**-H), 1.90 (1H, dddd, *J* = 12.5, 7.0, 5.5, 3.5 Hz, C**3**-H), 1.81 (1H, ddd, *J* = 12.5, 7.0, 3.5 Hz, C**4**-H'), 1.53 (1H, dddd, *J* = 12.0, 10.0, 9.0, 7.0 Hz, C**3**-H'), 1.33 (3H, d, *J* = 6.0 Hz, C**1**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.5 (C**14**), 149.2 (C**6**), 144.4 (C**12**) 130.0 (C**8**), 129.5 (C**10**), 129.2 (C**11**), 127.1 (C**9**), 126.6 (C**7**), 124.0 (C**13**), 74.0 (C**5**), 55.9 (C**2**), 42.7 (C**4**), 32.6 (C**3**), 22.3 (C**1**).

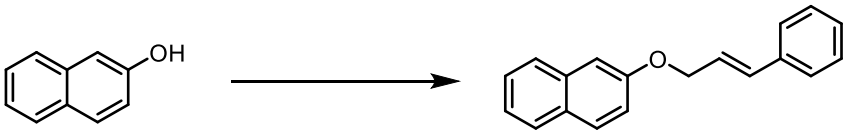
HRMS (ESI^+) Calculated for $C_{14}H_{15}NNaO$: 236.1046. Found $[M+Na]^+$: 236.1046.

The stereochemistry of the major diastereomer was determined by X-ray crystallography.



*X-ray crystal structure of **237a**.*

2-(Cinnamyloxy)naphthalene (238)

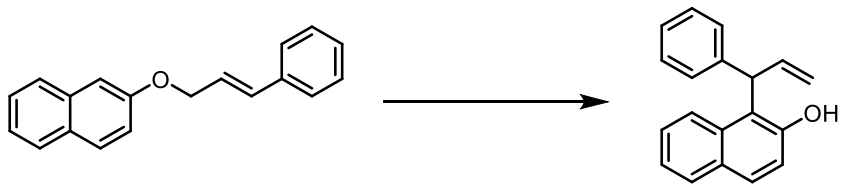


The title compound **238** was prepared according to a literature procedure.[311]

To a solution of 2-naphthol (3.6 g, 25 mmol) and K_2CO_3 (10.4 g, 75 mmol) in acetone (80 mL) was added cinnamyl bromide (3.95 g, 30 mmol) and the reaction was heated at 60 ^oC overnight. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate and water. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (5% EtOAc:hexane) afforded **238** (4.2 g, 81%) as a colourless solid; ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 – 7.73 (3H, m), 7.48 – 7.42 (3H, m), 7.38 – 7.31 (3H, m), 7.29 – 7.25 (1H, m), 7.24 – 7.19 (2H, m), 6.80 (1H, dt, *J* = 16.0, 1.5 Hz), 6.53 – 6.44 (1H, m), 4.82 (2H, dd, *J* = 6.0, 1.5 Hz).

The spectroscopic properties were consistent with the data available in the literature.[311]

1-(1-Phenylallyl)naphthalen-2-ol

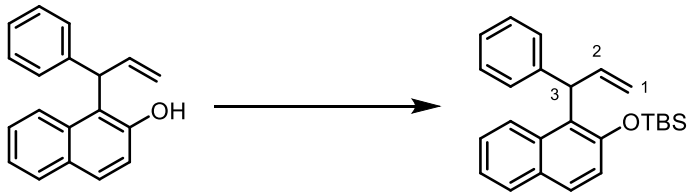


The title compound was prepared according to a literature procedure.[311]

A solution of the preceding allyl ether **238** (3.9 g, 15.0 mmol) in 2-methoxyethanol (60 mL) was heated at 120 ^oC for 48 hours. The reaction was diluted with water and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (10% EtOAc:hexane) afforded the title compound (1.8 g, 46%) as a yellow oil.

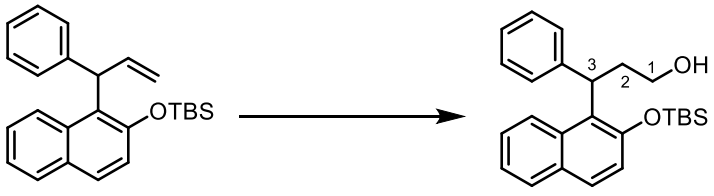
The spectroscopic properties were consistent with the data available in the literature.[312]

tert-Butyldimethyl((1-(1-phenylallyl)naphthalen-2-yl)oxy)silane (239)



To a solution of 1-(1-phenylallyl)naphthalen-2-ol (1.40 g, 5.30 mmol), in DMF (10 mL) was added *tert*-butyldimethylsilyl chloride (970 mg, 6.45 mmol) and imidazole (910 mg, 13.4 mmol) and the reaction mixture was stirred at room temperature overnight until completion by TLC analysis. The reaction was quenched with water (50 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The organic phase was washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography (4% EtOAc:hexane) afforded **239** (1.37 g, 69%) as a pale-yellow oil; R_f = 0.4 (20% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 2955 (m), 2928 (m), 1622 (m), 1586 (m), 1463 (m), 1253 (m), 1236 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (1H, d, *J* = 8.0 Hz, ArC<u>H</u>), 7.70 - 7.63 (2H, m, ArC<u>H</u>), 7.25 - 7.13 (8H, m, ArC<u>H</u>), 6.64 (1H, ddd, *J* = 17.5, 10.0, 7.5 Hz, C**2**-<u>H</u>), 5.91 (1H, d, *J* = 7.5 Hz, C**3**-<u>H</u>) 5.28 – 5.16 (2H, m, C**1**-<u>H</u>$_2$), 0.99 (9H, s, TBS (C<u>H</u>$_3$)$_3$), 0.23 (6H, d, *J* = 7.5 Hz, TBS Si(C<u>H</u>$_3$)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.4 (Ar<u>C</u>), 143.7 (Ar<u>C</u>), 138.9 (C**2**), 132.9 (Ar<u>C</u>), 130.4 (Ar<u>C</u>), 128.7 (Ar<u>C</u>H), 128.6 (Ar<u>C</u>H), 128.3 (2 × Ar<u>C</u>H), 127.6 (2 × Ar<u>C</u>H), 126.0 (Ar<u>C</u>), 125.7 (2 × Ar<u>C</u>H), 125.5 (Ar<u>C</u>H), 123.2 (Ar<u>C</u>H), 120.6 (Ar<u>C</u>H), 117.5 (C**1**), 45.4 (C**3**), 26.0 (TBS (<u>C</u>H$_3$)$_3$), 18.5 (TBS Si<u>C</u>(CH$_3$)$_3$), -3.6 (TBS Si(<u>C</u>H$_3$)$_2$); HRMS (ESI$^+$) Calculated for $C_{25}H_{31}NaOSi$: 397.1958. Found $[M+Na]^+$: 397.1972.

3-(2-((*tert*-Butyldimethylsilyl)oxy)naphthalen-1-yl)-3-phenylpropan-1-ol (240)

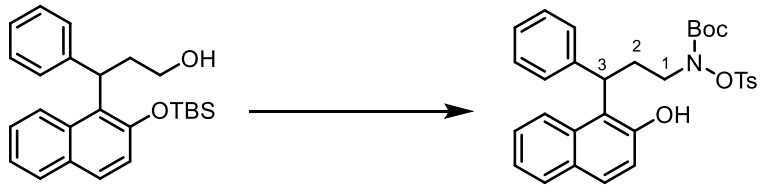


This compound **240** was prepared according to a literature procedure.[91]

To a solution of the preceding alkene **239** (790 mg, 2.0 mmol) in THF (4 mL) at 0 ^{o}C was added borane-dimethyl sulfide (0. 4 mL, 4.0 mmol) and the reaction was stirred at this temperature for 5 hours. Aqueous 30% H_2O_2 (0.6 mL) and $NaHCO_3$ (0.5 mL) were added and the reaction was warmed to room temperature overnight. The reaction was quenched with aqueous saturated NH_4Cl (15 mL) and extracted with EtOAc (3 × 15 mL). The combined

organic extracts were washed with brine (15 mL), dried over Na_2SO_4 and concentrated in vacuo. Purification by flash column chromatography afforded **240** (230 mg, 29%) as a yellow oil; ν_{max} / cm^{-1} (*film*) 3447 (m, br), 2952 (m), 2929 (m), 2857 (m), 1595 (m), 1463 (m), 1237 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 – 7.74 (1H, m, ArC<u>H</u>), 7.76 – 7.68 (1H, m, ArC<u>H</u>), 7.66 – 7.57 (1H, m, ArC<u>H</u>), 7.32 – 7.24 (5H, m, ArC<u>H</u>), 7.21 – 7.15 (3H, m, ArC<u>H</u>), 5.37 (1H, dd, *J* = 11.5, 4.5 Hz, C**3**-<u>H</u>), 3.62 – 3.53 (1H, m, C**1**-<u>H</u>), 3.37 – 3.27 (1H, m, C**1**-<u>H</u>'), 2.87 – 2.79 (1H, m, C**2**-<u>H</u>), 2.55 – 2.46 (1H, m, C**2**-<u>H</u>'), 2.28 (1H, br s, O<u>H</u>), 1.03 (9H, s, TBS (C<u>H</u>$_3$)$_3$), 0.37 (3H, s, TBS Si(C<u>H</u>$_3$)), 0.25 (3H, s, TBS Si(C<u>H</u>$_3$)); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.6 (Ar<u>C</u>), 144.6 (Ar<u>C</u>), 132.8 (Ar<u>C</u>), 130.8 (Ar<u>C</u>), 128.5 (Ar<u>C</u>), 128.8 (Ar<u>C</u>H), 128.7 (Ar<u>C</u>H), 128.3 (2 × Ar<u>C</u>H), 127.1 (2 × Ar<u>C</u>H), 125.7 (Ar<u>C</u>H), 125.7 (Ar<u>C</u>H), 125.5 (Ar<u>C</u>H), 123.5 (Ar<u>C</u>H), 120.2 (Ar<u>C</u>H) 61.5 (C**1**), 36.4 (C**3**), 34.9 (C**2**) 25.9 (TBS (<u>C</u>H$_3$)$_3$), 18.4 (TBS Si<u>C</u>(CH$_3$)$_3$), -3.44 (TBS Si(<u>C</u>H$_3$)), -3.83 (TBS Si(<u>C</u>H$_3$)); HRMS (ESI^+) Calculated for $C_{25}H_{33}NaO_2Si$: 415.2064. Found $[M+Na]^+$: 415.2061.

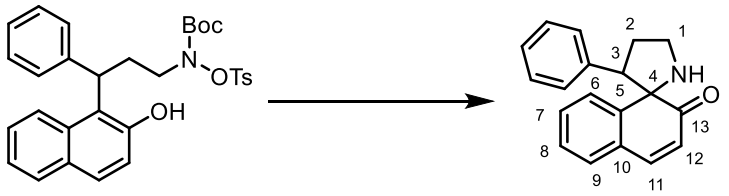
***tert*-Butyl (3-(2-hydroxynaphthalen-1-yl)-3-phenylpropyl)(tosyloxy)carbamate (241)**



<u>General procedures G and H:</u> The preceding alcohol **240** (270 mg, 0.69 mmol), PPh_3 (220 mg, 0.832 mmol), DIAD (0.16 mL, 0.83 mmol) and BocNHOTs (240 mg, 0.83 mmol) in anhydrous THF (4 mL) were employed. The product was purified by flash column chromatography (10% EtOAc:hexane) to afford the desired product (400 mg) which could not be obtained cleanly so was used crude in the next step using 1:1 TBAF:AcOH solution (0.1 M in THF, 0.60 mmol) in THF (12 mL). Purification by flash column chromatography (33% EtOAc:hexane) afforded **241** (260 mg, 71% over two steps) as an off-white solid; m.p.: 75-78 ^oC (EtOAc:hexane); R_f = 0.1 (20% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 3410 (m, br), 2978 (m), 1721 (m), 1373 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 – 7.70 (3H, m, ArC<u>H</u>), 7.66 (1H, d, *J* = 9.0 Hz, ArC<u>H</u>), 7.46 – 7.37 (1H, m, ArC<u>H</u>), 7.35 – 7.26 (9H, m, ArC<u>H</u>), 7.00 (1H, d, *J* = 9.0 Hz, ArC<u>H</u>), 5.11 (1H, br s, O<u>H</u>), 4.99 (1H, t, *J* = 8.0 Hz, C**3**-<u>H</u>), 3.73 – 3.61 (1H, m, C**1**-<u>H</u>), 3.42 – 3.15 (1H, m, C**1**-<u>H</u>'), 2.84 – 2.51 (2H, m, C**2**-<u>H</u>$_2$), 2.37 (3H, s, Ts C<u>H</u>$_3$), 1.15 (9H, s, Boc (C<u>H</u>$_3$)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6 (Boc <u>C</u>=O), 151.9 (Ar<u>C</u>), 145.7 (Ts Ar<u>C</u>), 142.9 (Ar<u>C</u>), 133.2 (Ar<u>C</u>), 131.3 (Ts Ar<u>C</u>), 129.8 (Ar<u>C</u>), 129.7 (2 × Ts Ar<u>C</u>H), 129.6 (2 × Ts ArC<u>H</u>),

129.2 (ArCH), 129.0 (ArCH), 128.9 (ArCH), 129.2 (ArCH), 127.5 (ArCH), 126.8 (ArCH), 126.6 (ArCH), 123.3 (ArCH), 121.3 (ArC), 119.2 (ArCH), 83.6 (Boc C(CH$_3$)$_3$), 52.3 (C**1**), 38.4 (C**3**), 28.0 (C**2**), 27.7 (Boc (CH$_3$)$_3$), 21.8 (Ts CH$_3$)$_3$; HRMS (ESI$^+$) Calculated for $C_{31}H_{33}NNaO_6S$: 570.1920. Found $[M+Na]^+$: 570.1912.

3'-Phenyl-2*H*-spiro[naphthalene-1,2'-pyrrolidin]-2-one (242)



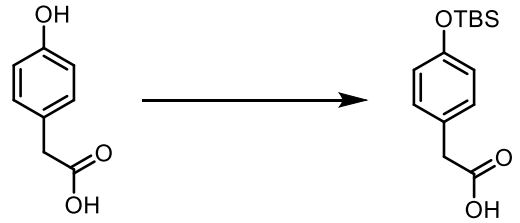
1:1 d.r.

General procedure I: The preceding *N*-tosyloxycarbamate **241** (53.2 mg, 0.097 mmol) and TFA (15.0 μL, 0.19 mmol) in anhydrous TFE (1 mL) were employed. After stirring at room temperature for 22 hours and purification by flash column chromatography (20% EtOAc:hexane) **242** (19.2 mg, 72 %) was obtained as a 1:1 mixture of diastereomers *A* and *B* and as a pale-yellow solid. *The diastereomers could not be separated by column chromatography.*

Data for mixture of diastereomers A + B: R_f = 0.5 (50% EtOAc:hexane); ν_{max} / cm^{-1} (*solid*) 2961 (m), 2864 (m), 1650 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (1H, d, *J* = 8.0 Hz, C**6**-H, *B*), 7.68 (1H, d, *J* = 8.0 Hz, C**6**-H, *A*), 7.47 (1H, td, *J* = 7.5, 1.5 Hz, C**7**-H, *B*), 7.38 (1H, td, *J* = 7.5, 1.5 Hz, C**7**-H, *A*), 7.30 – 7.25 (1H, m, C**8**-H, *B*), 7.18 – 7.09 (5H, m, 3 × ArCH, *B*, C**8**-H, *A*, C**9**-H, *B*), 7.05 – 7.00 (1H, m, ArCH, *A*), 6.93 – 6.90 (2H, m, 2 × ArCH, *A*), 6.85 – 6.81 (2H, m, C**9**-H, *A*, C**11**-H, *A*), 6.77 (1H, d, *J* = 10.0 Hz, C**11**-H, *B*), 6.71 – 6.68 (2H, m, 2 × ArCH, *B*), 6.52 – 6.48 (2H, m, 2 × ArCH, *A*), 6.03 (1H, d, *J* = 10.0 Hz, C**12**-H, *A*), 5.44 (1H, d, *J* = 10.0 Hz, C**12**-H, *B*), 3.69 (1H, ddd, *J* = 10.5, 8.0 Hz, C**1**-H, *B*), 3.56 – 3.49 (2H, m, C**1**-H$_2$, *A*), 3.40 – 3.25 (3H, m, C**3**-H, *A*+*B*, C**1**-H', *B*), 2.69 (2H, br s, NH, *A*+B), 2.57 – 2.46 (1H, m, C**2**-H, *B*), 2.44 – 2.33 (1H, m, C**2**-H, *A*), 2.22 – 1.26 (1H, m, C**2**-H', *A*), 2.04 – 1.98 (1H, m, C**2**-H', *B*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.8 (C**13**, *B*), 205.2 (C**13**, *A*), 147.7 (C**5**, *B*) , 145.9 (C**11**, *A*), 145.0 (C**5**, *A*), 143.8 (C**11**, *B*), 137.1 (ArC, *B*), 136.9 (ArC, *A*), 130.9 (C**10**, *A*), 130.5 (C**10**, *B*), 130.5 (C**7**, *B*), 129.3 (C**7**, *A*), 129.2 (2 × ArCH *A*), 128.7 (C**9**, *A*), 128.6 (2 × ArCH, *B*), 128.1 (ArCH, *B*), 128.0 (C**6**, *A*), 127.6 (2 × ArCH, *B*), 127.3 (C**8,** *B*), 127.4 (C**8**, *A*/C**9**, *B*), 127.3 (C**8**, *A*/C**9**, *B*), 127.0 (ArCH, *A*), 126.9 (2 × ArCH, *A*), 126.8 (C**6**, *B*), 124.9 (C**12**, *B*), 124.1 (C**12**, *A*), 78.1 (C**4**, *A*), 77.2 (C**4**, *B*), 64.5 (C**3**, *A*/*B*), 61.8 (C**3**, *A*/*B*), 48.3 (C**1**,

B), 47.3 (C**1**, *A*), 32.0 (C**2**, *A*), 30.0 (C**2**, *B*); HRMS (ESI$^+$) Calculated for $C_{19}H_{17}NNaO$: 298.1202. Found $[M+Na]^+$: 298.1200.

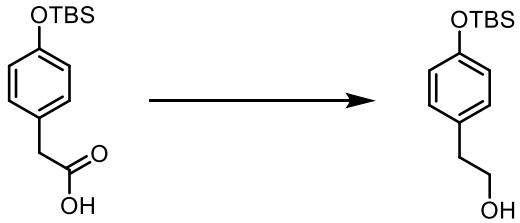
2-(4-((*tert*-Butyldimethylsilyl)oxy)phenyl)acetic acid



General procedure A: Carboxylic acid **243** (1.52 g, 10.0 mmol), *tert*-butyldimethylsilyl chloride (3.30 g, 22.0 mmol) and imidazole (2.25 g, 33.0 mmol) in DMF (20 mL) were employed. The title compound was obtained (1.45 g, 54%) as a colourless solid which was used without further purification; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 – 7.10 (2H, m), 6.78 – 6.76 (2H, m), 3.55 (2H, s), 0.98 (9H, s), 0.19 (6H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.8, 155.1, 130.5, 126.2, 120.3, 40.4, 25.8, 18.3, -4.3.

The spectroscopic properties were consistent with the data available in the literature.[313]

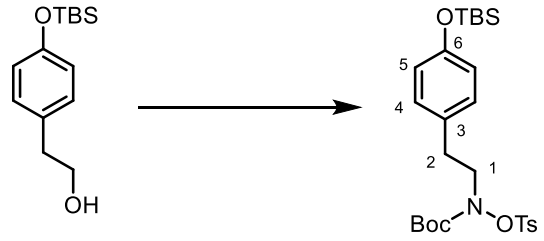
2-(4-((*tert*-Butyldimethylsilyl)oxy)phenyl)ethan-1-ol



General procedure B: 2-(4-((*tert*-Butyldimethylsilyl)oxy)phenyl)acetic acid (1.33 g, 5.00 mmol) and 2.0 equivalents of $LiAlH_4$ (1.0 M in THF, 10 mL, 10.0 mmol) in anhydrous Et_2O (25 mL) were employed. The title compound was obtained (988 mg, 78%) as a colourless oil which was used without further purification; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 – 7.06 (2H, m), 6.80 – 6.77 (2H, m), 3.79 (2H, t, *J* = 6.5 Hz), 2.79 (2H, t, *J* = 6.5 Hz), 0.99 (9H, s), 0.20 (6H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.3, 131.1, 130.0, 120.2, 63.9, 38.5, 25.8, 18.3, -4.3.

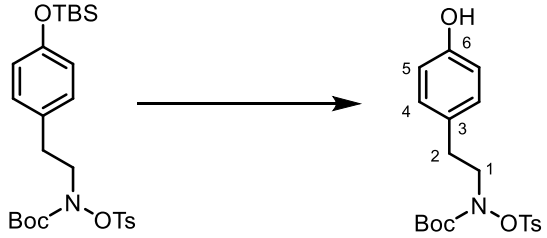
The spectroscopic properties were consistent with the data available in the literature.[314]

***tert*-Butyl (4-((*tert*-butyldimethylsilyl)oxy)phenethyl)(tosyloxy)carbamate**



General procedure G: 2-(4-((*tert*-Butyldimethylsilyl)oxy)phenyl)ethan-1-ol (370 mg, 1.40 mmol), PPh_3 (440 mg, 1.66 mmol), DIAD (0.32 mL, 1.66 mmol) and BocNHOTs (470 mg, 1.66 mmol) in anhydrous THF (8 mL) were employed. Purification by flash column chromatography (10% EtOAc:hexane) afforded the title compound (549 mg, 73%) as a colourless oil; ν_{max}/cm^{-1} (*film*) 2955 (m), 2930 (m), 1721 (s), 1509 (s), 1367 (s), 1252 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.34 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.03 (2H, d, *J* = 8.5 Hz, C**4**-<u>H</u>), 6.73 (2H, d, *J* = 8.5 Hz, C**5**-<u>H</u>), 3.81 (2H, br s, C**1**-<u>H_2</u>), 2.85 (2H, t, *J* = 7.5 Hz, C**2**-<u>H_2</u>), 2.45 (3H, s, Ts C<u>H_3</u>), 1.16 (9H, s, Boc (C<u>H_3</u>)$_3$), 0.97 (9H, s, TBS (C<u>H_3</u>)$_3$), 0.17 (6H, s, TBS Si(C<u>H_3</u>)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.2 (Boc <u>C</u>=O), 154.4 (C**6**), 145.8 (Ts Ar<u>C</u>), 131.4 (Ts Ar<u>C</u>), 130.6 (C**3**), 130.1 (2 × Ts Ar<u>C</u>H), 129.9 (2 × Ts Ar<u>C</u>H), 129.6 (C**4**), 120.2 (C**5**), 83.2 (Boc <u>C</u>(CH_3)$_3$), 54.4 (C**1**), 31.5 (C**2**), 27.7 (Boc (<u>C</u>H_3)$_3$), 25.8 (TBS (<u>C</u>H_3)$_3$), 21.8 (Ts <u>C</u>H_3), 18.3 (TBS <u>C</u>(CH_3)$_3$), -4.30 (TBS Si(<u>C</u>H_3)$_2$). HRMS (ESI$^+$) Calculated for $C_{26}H_{39}NNaO_6SSi$: 544.2160. Found [M+Na]$^+$: 544.2164.

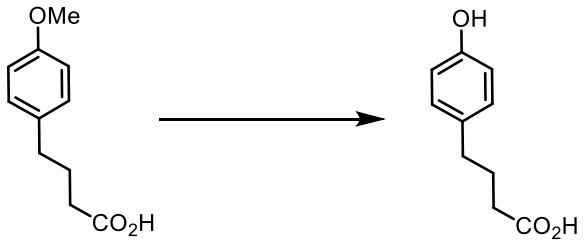
***tert*-Butyl (4-hydroxyphenethyl)(tosyloxy)carbamate (244)**



General procedure H: *tert*-Butyl (4-((*tert*-butyldimethylsilyl)oxy)phenethyl)(tosyloxy) carbamate (828 mg, 1.59 mmol) and 1.0 equivalent of 1:1 TBAF:AcOH solution (0.1 M in THF, 15.9 mL, 1.59 mmol) in THF (20 mL) were employed. Purification by flash column chromatography (33% EtOAc:hexane) afforded **244** (470 mg, 73%) as a colourless solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.34 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.05 (2H, d, *J* = 8.5 Hz, C**4**-<u>H</u>), 6.73 (2H, d, *J* = 8.5 Hz, C**5**-<u>H</u>), 3.82 (2H, br s, C**1**-<u>H_2</u>), 2.86 (2H, t, *J* = 7.5 Hz, C**2**-<u>H_2</u>), 2.45 (3H, s, Ts C<u>H_3</u>), 1.13 (9H, s, Boc (C<u>H_3</u>)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.2 (Boc <u>C</u>=O), 154.4 (C**6**), 145.9 (Ts Ar<u>C</u>), 131.3 (Ts Ar<u>C</u>), 130.4 (C**3**),

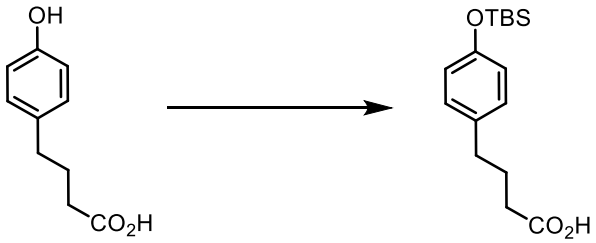
130.0 (C**4**), 129.9 (2 × Ts Ar<u>C</u>H), 129.7 (2 × Ts Ar<u>C</u>H), 115.5 (C**5**), 83.3 (Boc <u>C</u>(CH_3)$_3$), 54.2 (C**1**), 31.4 (C**2**), 27.7 (Boc (<u>C</u>H_3)$_3$), 21.9 (Ts <u>C</u>H_3); HRMS (ESI^+) Calculated for: $C_{20}H_{25}NNaO_6S$: 430.1295. Found $[M+Na]^+$: 430.1291.

4-(4-Hydroxyphenyl)butanoic acid



To a solution of 4-(4-methoxyphenyl)butanoic acid (1.94 g, 10.0 mmol) in anhydrous CH_2Cl_2 (100 mL) at 0 °C was added boron tribromide (1.0 M in CH_2Cl_2, 30 mL, 30.0 mmol) and the reaction was stirred at room temperature until completion by TLC analysis. The reaction was quenched by addition to water (200 mL) at 0 °C and the phases were separated. The aqueous phase was washed with CH_2Cl_2 (50 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography (33% EtOAc:hexane) afforded the title compound (590 mg, 33%) as a pale yellow solid; ^{1}H NMR (400 MHz, acetone-D_6) δ 10.36 (1H, br s), 8.20 (1H, br s), 7.08 – 7.00 (2H, m), 6.78 – 6.73 (2H, m), 2.59 – 2.53 (2H, m), 2.29 (2H, t, *J* = 7.5 Hz), 1.90 – 1.80 (2H, m).
The spectroscopic properties were consistent with the data available in the literature.[315]

4-(4-((*tert*-Butyldimethylsilyl)oxy)phenyl)butanoic acid

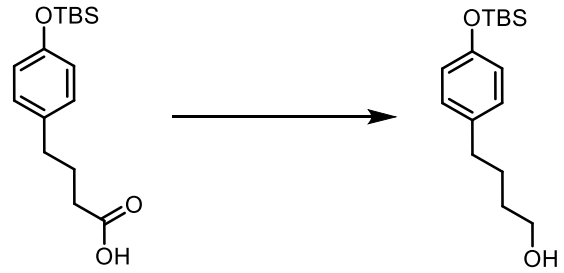


<u>General procedure A:</u> 4-(4-Hydroxyphenyl)butanoic acid (500 mg, 2.77 mmol), *tert*-butyldimethylsilyl chloride (910 mg, 6.10 mmol) and imidazole (620 mg, 9.16 mmol) in DMF (6 mL) were employed to afford the title compound (695 mg, 85%) as a yellow oil which was used without further purification; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (2H, d, *J* = 8.5 Hz), 6.76 (2H, d, *J* = 8.5 Hz), 2.60 (2H, t, *J* = 7.5 Hz), 2.36 (2H, t, *J* = 7.5 Hz), 1.93 (2H, app. qn, *J*

= 7.5 Hz), 0.98 (9H, s), 0.19 (6H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.8, 153.8, 133.8, 129.3, 119.9, 34.2, 33.3, 26.4, 25.7, 18.2, -4.4.

The spectroscopic properties were consistent with the data available in the literature.[316]

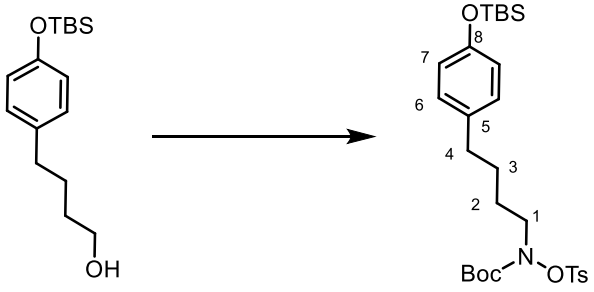
4-(4-((*tert*-Butyldimethylsilyl)oxy)phenyl)butan-1-ol



General procedure B: 4-(4-((*tert*-Butyldimethylsilyl)oxy)phenyl)butanoic acid (640 mg, 2.17 mmol) and 2.0 equivalents of $LiAlH_4$ (1.0 M in THF, 4.34 mL, 4.34 mmol) in anhydrous Et_2O (10 mL) were employed to afford the title compound (450 mg, 74%) as a colourless oil which was used without further purification; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (2H, d, *J* = 8.5 Hz), 6.75 (2H, d, *J* = 8.5 Hz), 3.64 (2H, t, *J* = 6.5 Hz), 2.57 (2H, t, *J* = 7.5 Hz), 1.70 – 1.54 (4H, m), 0.99 (9H, s), 0.19 (6H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.5, 134.9, 129.1, 119.8, 62.8, 34.8, 32.2, 27.7, 25.7, 18.2, -4.4.

The spectroscopic properties were consistent with the data available in the literature.[316]

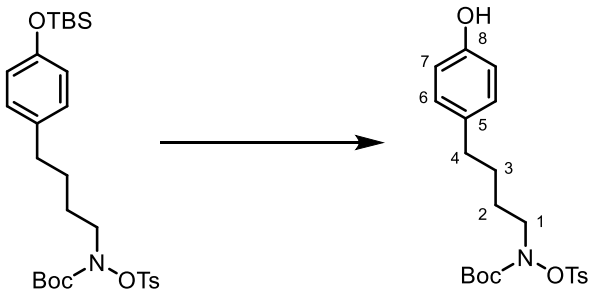
***tert*-Butyl (4-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)butyl)(tosyloxy)carbamate**



General procedure G: 4-(4-((*tert*-Butyldimethylsilyl)oxy)phenyl)butan-1-ol (350 mg, 1.25 mmol), PPh_3 (390 mg, 1.50 mmol), DIAD (0.29 mL, 1.50 mmol) and BocNHOTs (430 mg, 1.5 mmol) in anhydrous THF (5 mL) were employed. Purification by flash column chromatography (10% EtOAc:hexane) afforded the title compound (480 mg, 70%) as a colourless viscous oil containing a small impurity that was carried through to the next step; ν_{max} /cm^{-1} (*film*) 2954 (m), 2930 (m), 2858 (m), 1720 (s), 1509 (s), 1251 (s); ^{1}H NMR (400

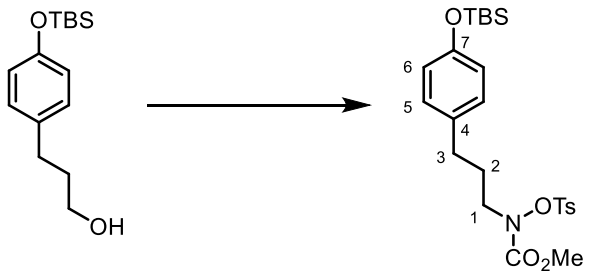
MHz, $CDCl_3$) δ 7.85 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.34 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.00 (2H, d, *J* = 8.5 Hz, C**6**-<u>H</u>), 6.74 (2H, d, *J* = 8.5 Hz, C**7**-<u>H</u>), 3.64 (2H, br s, C**1**-<u>H_2</u>), 2.53 (2H, t, *J* = 7.5 Hz, C**4**-<u>H_2</u>), 2.44 (3H, s, Ts C<u>H_3</u>), 1.69 – 1.49 (4H, m, C**2**-<u>H_2</u>, C**3**-<u>H_2</u>), 1.20 (9H, s, Boc (C<u>H_3</u>)$_3$), 0.98 (9H, s, TBS (C<u>H_3</u>)$_3$), 0.18 (6H, s, TBS Si(C<u>H_3</u>)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6 (Boc <u>C</u>=O), 153.7 (C**8**), 145.7 (Ts Ar<u>C</u>), 134.7 (C**5**), 131.4 (Ts Ar<u>C</u>), 129.8 (2 × Ts Ar<u>C</u>H), 129.6 (2 × Ts Ar<u>C</u>H), 129.2 (C**6**), 119.9 (C**7**), 83.2 (Boc <u>C</u>$(CH_3)_3$, 52.8 (C**1**), 34.6 (C**4**), 28.6 (C**3**), 27.7 (Boc (<u>C</u>H_3)$_3$), 25.8 (TBS (<u>C</u>H_3)$_3$), 25.5 (C**2**), 21.8 (Ts <u>C</u>H_3), 18.3 (TBS Si<u>C</u>$(CH_3)_3$), -4.4 (TBS Si(<u>C</u>H_3)$_2$); HRMS (ESI$^+$) Calculated for $C_{28}H_{43}NNaO_6SSi$: 572.2473. Found $[M+Na]^+$: 572.2480.

***tert*-Butyl (4-(4-hydroxyphenyl)butyl)(tosyloxy)carbamate (246)**



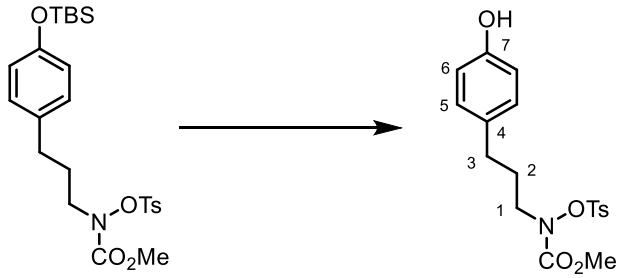
<u>General procedure H:</u> *tert*-Butyl (4-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)butyl)(tosyloxy) carbamate (470 mg, 0.86 mmol) and 1.0 equivalent of 1:1 solution of TBAF:AcOH (0.1 M in THF, 8.6 mL, 0.86 mmol) in THF (20 mL) were employed. Purification by flash column chromatography (20% EtOAc:hexane) afforded **246** (275 mg, 73%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.33 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 6.99 (2H, d, *J* = 8.5 Hz, C**6**-<u>H</u>), 6.74 (2H, d, *J* = 8.5 Hz, C**7**-<u>H</u>), 5.38 (1H, br s, O<u>H</u>), 3.63 (2H, br s, C**1**-<u>H_2</u>), 2.51 (2H, t, *J* = 7.5 Hz, C**4**-<u>H_2</u>), 2.44 (3H, s, Ts C<u>H_3</u>), 1.70 – 1.59 (2H, m, C**2**-<u>H_2</u>), 1.56 – 1.48 (2H, m, C**3**-<u>H_2</u>), 1.21 (9H, s, Boc (C<u>H_3</u>)$_3$); ^{13}C NMR (101 MHz, CDC_3) δ 155.6 (Boc <u>C</u>=O), 153.8 (C**8**), 145.7 (Ts Ar<u>C</u>), 133.9 (C**5**), 131.1 (Ts Ar<u>C</u>), 129.7 (2 × Ts Ar<u>C</u>H), 129.6 (2 × Ts Ar<u>C</u>H), 129.4 (C**6**), 115.2 (C**7**), 83.4 (Boc <u>C</u>$(CH_3)_3$), 52.7 (C**1**), 34.5 (C**4**), 28.6 (C**3**), 27.6 (Boc (<u>C</u>H_3)$_3$), 25.4 (C**2**), 21.7 (Ts <u>C</u>H_3); HRMS (ESI$^+$) Calculated for $C_{22}H_{29}NNaO_6S$: 458.1608. Found $[M+Na]^+$: 458.1603.

Methyl (3-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)propyl)(tosyloxy)carbamate



General procedure G: Alcohol **146** (530 mg, 2.00 mmol), PPh_3 (630 mg, 2.40 mmol), DIAD (0.47 mL, 2.40 mmol) and methyl (tosyloxy)carbamate (590 mg, 2.40 mmol) in anhydrous THF (8 mL) were employed. Purification by flash column chromatography (10% EtOAc:hexane) afforded the title compound (930 mg, 94%) as a colourless oil; R_f = 0.4 (20% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 2955 (m), 2930 (m), 2858 (m), 1728 (s), 1509 (s), 1253 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (2H, d, *J* = 8.0 Hz, Ts ArC<u>H</u>), 7.33 (2H, d, *J* = 8.0 Hz, Ts ArC<u>H</u>), 6.99 (2H, d, *J* = 8.0 Hz, C**5**-<u>H</u>), 6.74 (2H, d, *J* = 8.0 Hz, C**6**-<u>H</u>), 3.58 (2H, br s, C**1**-<u>H_2</u>), 3.47 (3H, s, OC<u>H_3</u>), 2.51 (2H, t, *J* = 8.0 Hz, C**3**-<u>H_2</u>), 2.45 (3H, s, Ts C<u>H_3</u>), 1.94 – 1.85 (2H, m, C**2**-<u>H_2</u>), 0.98 (9H, s, TBS (C<u>H_3</u>)$_3$), 0.18 (6H, s, TBS Si(<u>C</u>H_3)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.2 (<u>C</u>=O), 153.9 (C**7**), 146.0 (Ts Ar<u>C</u>), 133.6 (C**4**), 131.2 (Ts Ar<u>C</u>), 129.7 (2 × Ts Ar<u>C</u>H), 129.6 (2 × Ts Ar<u>C</u>H), 129.2 (C**5**), 120.1 (C**6**), 53.7 (O<u>C</u>H_3), 52.7 (C**1**), 32.0 (C**3**), 27.7 (C**2**), 25.8 (TBS (<u>C</u>H_3)$_3$), 21.9 (Ts <u>C</u>H_3), 18.3 (TBS <u>C</u>(CH_3)$_3$), -4.3 (TBS Si(<u>C</u>H_3)$_2$); HRMS (ESI^+) Calculated for $C_{24}H_{35}NNaO_6SSi$: 516.1847. Found $[M+Na]^+$: 516.1851.

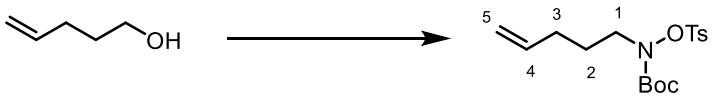
Methyl (3-(4-hydroxyphenyl)propyl)(tosyloxy)carbamate (251)



General procedure H: Methyl (3-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)propyl)(tosyloxy) carbamate (490 mg, 1.00 mmol) and 1.1 equivalents of 1:1 TBAF:AcOH solution (0.1 M in THF, 11 mL, 1.1 mmol) in THF (20 mL) were employed. Purification by flash column chromatography (gradient 20 – 33% EtOAc:hexane) afforded **251** (289 mg, 76%) as a viscous, colourless oil; R_f = 0.1 (20% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 3431 (m, br), 3023 (m), 2956

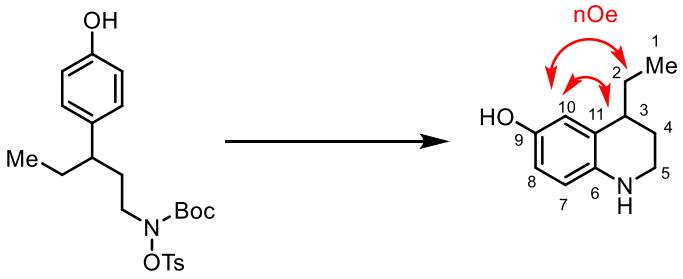
(m), 1726 (m), 1514 (m), 1175 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (2H, d, *J* = 8.0 Hz, Ts ArC<u>H</u>), 7.33 (2H, d, *J* = 8.0 Hz, Ts ArC<u>H</u>), 6.99 (2H, d, *J* = 8.0 Hz, C**5**-<u>H</u>), 6.74 (2H, d, *J* = 8.0 Hz, C**6**-<u>H</u>), 4.88 (1H, s, O<u>H</u>), 3.59 (2H, br s, C**1**-<u>H_2</u>), 2.51 (2H, t, *J* = 8.0 Hz, C**3**-<u>H_2</u>), 2.45 (3H, s, OC<u>H_3</u>), 1.95 – 1.85 (2H, m, C**2**-<u>H_2</u>); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.3 (<u>C</u>=O), 154.0 (C**7**), 146.1 (Ts Ar<u>C</u>), 133.0 (C**4**), 131.1 (Ts Ar<u>C</u>), 129.7 (2 × Ts Ar<u>C</u>H), 129.6 (2 × Ts Ar<u>C</u>H), 129.5 (C**5**), 115.4 (C**6**), 53.8 (O<u>C</u>H_3), 52.7 (C**1**), 31.9 (C**3**), 27.8 (C**2**), 21.9 (Ts <u>C</u>H_3); HRMS (ESI$^+$) Calculated for $C_{18}H_{21}NNaO_6S$: 402.0982. Found $[M+Na]^+$: 402.0984.

tert-Butyl pent-4-en-1-yl(tosyloxy)carbamate (255)



<u>General procedure G:</u> 4-Penten-1-ol (170 mg, 2.00 mmol), PPh_3 (630 mg, 2.40 mmol), DIAD (0.47 mL, 2.40 mmol) and BocNHOTs (690 mg, 2.40 mmol) in anhydrous THF (15 mL) were employed. Purification by flash column chromatography (10% EtOAc:hexane) afforded **255** (470 mg, 66%) as a colourless crystalline solid; m.p.: 47-50 ^{o}C (EtOAc:hexane); R_f = 0.5 (33% EtOAc:hexane); ν_{max} / cm^{-1} (*solid*) 2977 (m), 1715 (s), 1365 (s), 1355 (s), 1177 (s), 1154 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.34 (2H, d, *J* = 8.0 Hz, Ts ArC<u>H</u>), 5.81 – 5.71 (1H, m, C**4**-<u>H</u>), 5.05 – 4.93 (2H, m, C**5**-<u>H_2</u>), 3.62 (2H, br s, C**1**-<u>H_2</u>), 2.45 (3H, s, Ts C<u>H_3</u>), 2.07 – 2.00 (2H, m, C**3**-<u>H_2</u>), 1.77 – 1.66 (2H, m, C**2**-<u>H_2</u>), 1.22 (9H, s, Boc (C<u>H_3</u>)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6 (Boc <u>C</u>=O), 145.8 (Ts Ar<u>C</u>), 137.4 (C**4**), 131.4 (Ts Ar<u>C</u>) 129.8 (2 × Ts Ar<u>C</u>H), 129.7 (2 × Ts Ar<u>C</u>H), 115.4 (C**5**), 83.42 (Boc <u>C</u>(CH$_3$)$_3$), 52.6 (C**1**), 30.7 (C**3**), 27.7 (Boc (<u>C</u>H_3)$_3$), 25.0 (C**2**), 21.8 (Ts <u>C</u>H_3); HRMS (ESI$^+$) Calculated for $C_{17}H_{25}NNaO_5S$: 378.1346. Found $[M+Na]^+$: 378.1346.

4-Ethyl-1,2,3,4-tetrahydroquinolin-7-ol (257)

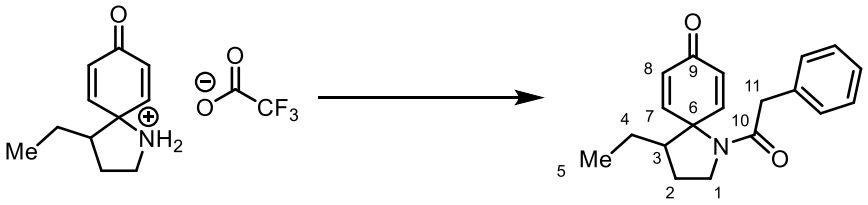


To a solution of *N*-tosyloxycarbamate **213** (67.4 mg, 0.15 mmol) in anhydrous TFE (2.3 mL, 0.07 M) at room temperature was added TFA (1.7 μL, 0.022 mmol). The reaction was heated to 60 ^{o}C and stirred overnight monitoring by TLC analysis. Purification by flash column

chromatography (gradient, eluent 33% EtOAc:hexane – 100% EtOAc (*a small amount < 1% Et_3N was added to the eluent*)) afforded **257** (20.4 mg, 77%) as a yellow oil; R_f = 0.5 (EtOAc); ν_{max} / cm^{-1} (*film*) 3145 (m, br), 2971 (m), 1618 (m), 1467 (m), 1238 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.55 (1H, s, C**10**-H), 6.49 (1H, d, *J* = 8.0 Hz, C**8**-H), 6.41 (1H, d, *J* = 8.5 Hz, C**7**-H), 4.20 (2H, br s, OH, NH), 3.28 – 3.16 (2H, m, C**5**-H_2), 2.62 – 2.56 (1H, m, C**3**-H), 1.95 – 1.87 (1H, m, C**4**-H), 1.80 – 1.67 (2H, m, C**4**-H', C**2**-H), 1.56 – 1.45 (1H, m, C**2**-H'), 0.96 (3H, t, *J* = 7.5 Hz, C**1**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.7 (C**9**), 138.1 (C**6**), 127.9 (C**11**), 116.0 (C**7**), 115.9 (C**10**), 114.2 (C**8**), 39.3 (C**5**), 37.2 (C**3**), 29.4 (C**2**), 26.2 (C**4**), 11.7 (C**1**). HRMS (ESI^+) Calculated for $C_{11}H_{16}NO$: 178.1226. Found $[M+H]^+$: 178.1227.

*The regiochemistry of the compound was confirmed by nOe analysis as shown on the compound structure. nOes were observed between C**10**-H and C**3**-H and C**10**-H and C**2**-H_2.*

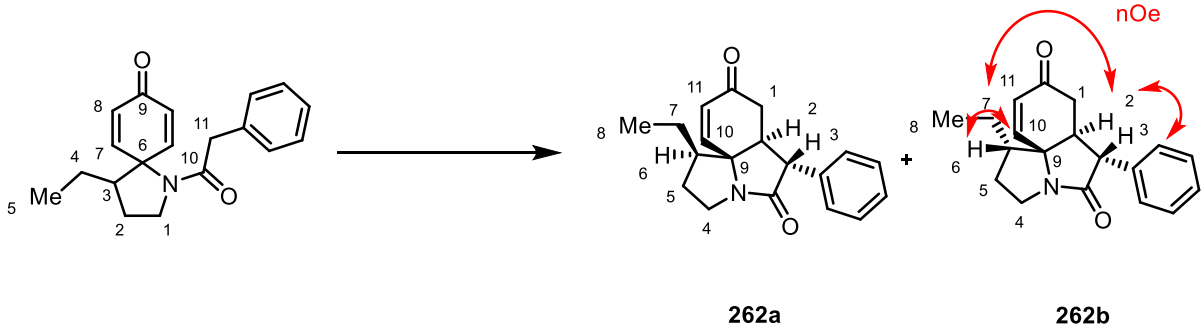
4-Ethyl-1-(2-phenylacetyl)-1-azaspiro[4.5]deca-6,9-dien-8-one (261)



General procedure L: Spirocycle **214** (23.4 mg, 0.08 mmol), phenylacetyl chloride (22 μL, 0.16 mmol) and K_3PO_4 (67.9 mg, 0.32 mmol) in anhydrous THF (0.4 mL) were employed. Purification by flash column chromatography (gradient, eluent: 50% EtOAc:pentane – 100% EtOAc) afforded **261** (18.7 mg, 79%) as a 2.3:1 mixture of rotamers *A*:*B* and a colourless oil; R_f = 0.3 (3 % MeOH:CH_2Cl_2); ν_{max} / cm^{-1} (*film*) 2962 (m), 2930 (m), 2876 (m), 1660 (s), 1623 (s), 1454 (m), 1397 (s), 1384 (s), 719 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.17 (4.40 H, m, ArCH, *A*+*B*), 7.13 – 7.10 (0.60 H, m, 2 × ArCH, *B*), 6.82 – 6.70 (0.60 H, m, 0.60 × C**7**-H, *B*), 6.67 (0.70 H, dd, *J* = 10.0, 3.0 Hz, 0.70 × C**7**-H, *A*), 6.57 (0.70 H, dd, *J* = 10.0, 3.0 Hz, 0.70 × C**7**-H', *A*), 6.40 – 6.34 (0.60 H, m, 0.60 × C**8**-H, *B*), 6.34 – 6.26 (1.40 H, m, 1.40 × C**8**-H, *A*), 4.09 (0.3 H, dd, *J* = 12.5, 8.0 Hz, 0.3 × C**1**-H), 3.82 (0.7 H, t, *J* = 9.0 Hz, 0.7 × C**1**-H), 3.65 – 3.52 (2.40 H, m, 1 × C**1**-H', 1.4 × *A*+*B*, C**11**-H_2, *A*), 3.43 (0.6 H, d, *J* = 4.5 Hz, 0.6 × C**11**-H_2, *B*), 2.31 – 2.25 (1H, m, C**2**-H, *A*+*B*), 2.23 – 2.14 (0.30 H, m, 0.30 × C**3**-H, *B*), 2.02 – 1.95 (0.70 H, m, 0.70 × C**3**-H, *A*), 1.76 – 1.64 (0.70 H, m, 0.70 × C**2**-H', *A*), 1.63 – 1.55 (0.3 H, m, 0.30 × C**2**-H', *B*), 1.27 – 1.17 (1H, m, C**4**-H, *A*+*B*), 1.06 – 0.95 (1H, m, C**4**-H', *A*+*B*), 0.93 – 0.84 (3H, m, C**5**-H_3, *A*+*B*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.8 (C**9**, *A*), 184.7 (C**9**, *B*), 170.6 (C**10**, *B*), 169.5 (C**10**, *A*), 152.1 (C**7**, *A*), 152.0 (C**7**, *B*), 147.8 (C**7'**, *B*), 146.4 (C**7'**, *A*), 134.8

(ArC, *B*), 134.1 (ArC, *A*), 130.4 (C**8**, *A*), 129.9 (C**8**, *B*), 129.6 (C**8'**, *B*), 129.3 (ArCH, *B*), 128.9 (ArCH, *A* + *B*), 128.7 (ArCH, *A* + *B*), 128.3 (ArCH, *A* + *B*), 128.2 (C**8'**, *A*), 126.9 (ArCH, *A* + *B*), 126.7 (ArCH), 65.7 (C**6**, *A*), 65.5 (C**6**, *B*), 53.5 (C**3**, *B*), 50.6 (C**3**, *A*), 47.4 (C**1**, *B*), 47.3 (C**1**, *A*), 42.5 (C**11**, *A*), 40.1 (C**11**, *B*), 29.9 (C**2**, *A*), 27.8 (C**2**, *B*), 21.3 (C**4**, *A* + *B*), 12.5 (C**5**, *A* + *B*); HRMS (ESI$^+$) Calculated for $C_{19}H_{21}NNaO_2$: 318.1464. Found $[M+Na]^+$: 318.1472.

(1*R, 6*R**, 6a*S**, 10a*S**) *and* (1*S**, 6*R**, 6a*S**, 10a*S**)-1-Ethyl-6-phenyl-2,3,6a,7-tetrahydro-1*H*,5*H*-pyrrolo[2,1-i]indole-5,8(6*H*)-dione (262a) and (1*S**,6*R**,6a*S**,10a*S**)-1-Ethyl-6-phenyl-2,3,6a,7-tetrahydro-1*H*,5*H*-pyrrolo[2,1-i]indole-5,8(6*H*)-dione (262b)**



General procedure M: The preceding amide **261** (29.5 mg, 0.100 mmol) and 1.5 equivalents of lithium bis(trimethylsilyl)amide (1 M in THF) in anhydrous THF (1 mL) were employed. The reaction was stirred at this temperature for 2 hours. Purification by flash column chromatography (50% EtOAc:hexane) afforded **262** (16.6 mg, 56%) as a 3:1 mixture of diastereomers **262a** and **262b** and as a colourless solid; R_f = 0.6 (3% MeOH:CH_2Cl_2); ν_{max} / cm ^{1} (*solid*) 2963 (m), 2929 (m), 2877 (m), 1693 (s), 1675 (s), 1394 (s).

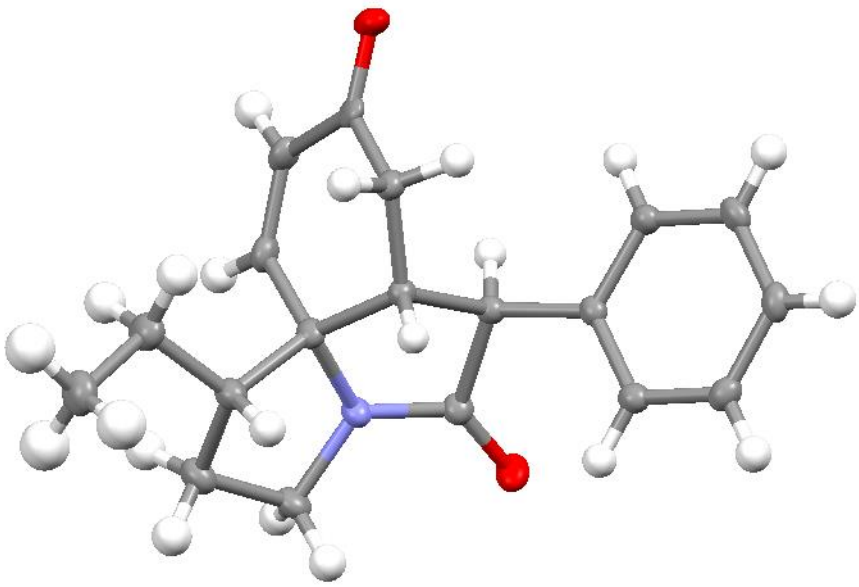
*Spectroscopic data for the major diastereomer **262a**:* m.p.: 194 ^{o}C (EtOAc:hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.32 (2H, m, ArCH), 7.30 – 7.24 (1H, m, ArCH), 7.15 – 7.12 (2H, m, ArCH), 6.62 (1H, dd, *J* = 10.5, 1.5 Hz, C**10**-H), 6.22 (1H, d, *J* = 10.5 Hz, C**11**-H), 3.77 – 3.71 (1H, m, C**4**-H), 3.68 (1H, d, *J* = 12.0 Hz, C**3**-H), 3.43 (1H, t, *J* = 10.5 Hz, C**4**-H'), 2.71 (1H, dd, *J* = 12.5, 6.0 Hz, C**2**-H), 2.65 – 2.53 (2H, m, C**1**-H, C**5**-H), 2.50 – 2.43 (1H, m, C**1**-H'), 2.10 – 1.91 (2H, m, C**6**-H, C**5**-H'), 1.62 – 1.52 (1H, m, C**7**-H), 1.37 – 1.23 (1H, m, C**7**-H'), 0.99 (3H, t, *J* = 7.5 Hz, C**8**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.3 (C=O), 171.8 (NC=O), 144.1 (C**10**), 135.8 (ArC), 129.8 (C**11**), 129.3 (2 × ArCH), 128.9 (2 × ArCH), 127.8 (ArCH), 67.7 (C**9**), 57.8 (C**3**), 51.7 (C**2**), 51.4 (C**6**), 40.5 (C**4**), 36.8 (C**1**), 32.3 (C**5**), 23.7 (C**7**), 13.0 (C**8**).

*Spectroscopic data for the minor **262b**:* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.32 (2H, m, ArCH), 7.32 – 7.28 (1H, m, ArCH), 7.14 – 7.10 (2H, m, ArCH), 6.58 (1H, dd, *J* = 10.0, 2.0

Hz, C**10**-H), 6.16 (1H, dd, *J* = 10.0, 1.0 Hz, C**11**-H), 4.05 (1H, ddd, *J* = 11.0, 7.5, 2.5 Hz, C**4**-H), 3.62 (1H, d, *J* = 12.5 Hz, C**3**-H), 3.14 – 3.06 (1H, m, C**4**-H'), 2.76 (1H, dd, *J* = 12.5, 5.5 Hz, C**2**-H), 2.56 – 2.41 (2H, m, C**1**-H_2), 2.33 – 2.25 (1H, m, C**5**-H), 2.17 – 2.08 (1H, m, C**6**-H), 1.78 – 1.68 (1H, m, C**7**-H), 1.64 – 1.55 (1H, m, C**5**-H'), 1.47 – 1.35 (1H, m, C**7**-H'), 1.03 (3H, t, *J* =7.5 Hz, C**8**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.1 (C=O), 174.6 (NC=O), 148.8 (C**10**), 135.8 (ArC), 129.4 (2 × ArCH), 129.0 (2 × ArCH), 128.2 (C**11**), 127.9 (ArCH), 66.4 (C**9**), 55.6 (C**3**), 48.9 (C**6**), 46.3 (C**2**), 42.9 (C**4**), 36.2 (C**1**), 31.9 (C**5**), 22.4 (C**7**), 13.2 (C**8**).

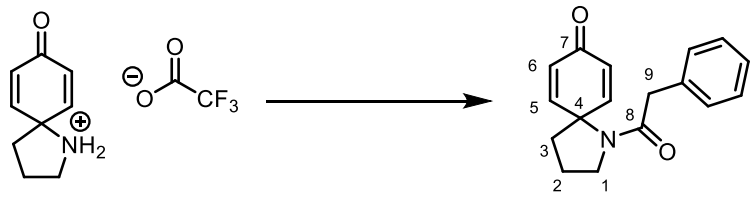
HRMS (ESI^+) Calculated for $C_{19}H_{21}NNaO_2$: 318.1464. Found $[M+Na]^+$: 318.1469.

*The relative stereochemistry of the minor diastereomer was determined by nOe experiments as indicated on the compound structure; nOes were observed between C**2**-H and C**7**-H_2 and between C**6**-H and C**10**-H. The major diastereomer was determined unambiguously by X-ray crystallography.*



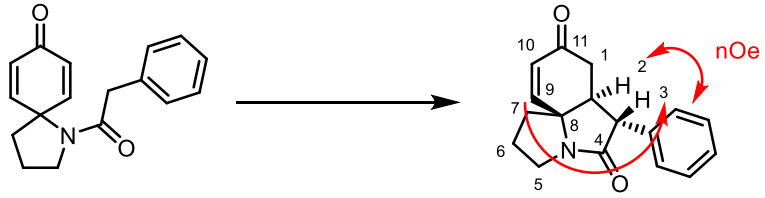
*X-ray crystal structure of **262a**.*

1-(2-Phenylacetyl)-1-azaspiro[4.5]deca-6,9-dien-8-one (263)



General procedure L: Spirocycle **178** (19.2 mg, 0.073 mmol), phenylacetyl chloride (19.4 μL, 0.147 mmol) and K_3PO_4 (62.2 mg, 0.293 mmol) in anhydrous THF (0.36 mL) were employed. Purification by flash column chromatography (gradient, eluent: 50% EtOAc:pentane – 100% EtOAc) afforded **263** (12.2 mg, 63%) as a 3:1 mixture of rotamers *A*+*B* and as a colourless, viscous oil; R_f = 0.3 (3% MeOH:CH_2Cl_2); ν_{max} / cm^{-1} (*film*) 3029 (m), 2972 (m), 2881 (m), 1659 (s), 1622 (s), 1395 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.10 (5H, m, 5 × ArC<u>H</u>, *A* + *B*), 6.95 (0.50 H, d, *J* = 10.0 Hz, 0.50 × C**5**-<u>H</u>, *B*), 6.76 (1.50 H, d, *J* = 10.0 Hz, 1.50 × C**5**-<u>H</u>, *A*), 6.32 (0.50 H, d, *J* = 10.0 Hz, 0.50 H × C**6**-<u>H</u>, *B*), 6.25 (1.50 H, d, *J* = 10.0 Hz, 1.5 × C**6**-<u>H</u>, *A*), 3.86 (0.5 H, t, *J* = 7.0 Hz, 0.50 × C**1**-<u>H_2</u>, *B*), 3.71 (1.50 H, t, *J* = 7.0 Hz, 1.50 × C**1**-<u>H_2</u>, *A*), 3.65 (1.50 H, s, 1.50 × C**9**-<u>H_2</u>, *A*), 3.43 (0.50 H, s, 0.50 × C**9**-<u>H_2</u>, *B*), 2.25 (0.50 H, t, *J* = 7.0 Hz, 0.50 × C**3**-<u>H_2</u>, *B*), 2.12 – 1.99 (3.5 H, m, 3.5 H × C**2** + C**3**-<u>H_2</u>, *A* + *B*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.4 (C**7**, *A*), 184.4 (C**7**, *B*), 170.7 (C**8**, *B*), 169.5 (C**8**, *A*), 151.2 (C**5**, *B*) 150.7 (C**5**, *A*), 134.8 (Ar<u>C</u>, *B*), 134.2 (Ar<u>C</u>, *A*), 129.4 (2 × Ar<u>C</u>H, *B*), 129.0 (2 × Ar<u>C</u>H, *A*), 128.9 (2 × Ar<u>C</u>H, *A*), 128.7 (2 × Ar<u>C</u>H, *B*), 128.5 (C**6**, *B*), 128.3 (C**6**, *A*), 127.1 (Ar<u>C</u>H, *A*), 126.9 (Ar<u>C</u>H, *B*), 62.7 (C**4**, *A*), 62.0 (C**4**, *B*), 49.0 (C**1**, *B*), 48.5 (C**1**, *A*), 42.8 (C**9**, *A*), 42.0 (C**3**, *B*), 39.9 (C**9**, *B*), 38.9 (C**3**, *A*), 24.5 (C**2**, *A*), 22.6 (C**2**, *B*); HRMS (ESI^+) Calculated for $C_{17}H_{18}NO_2$: 268.1332. Found $[M+H]^+$: 268.1325.

(6*R, 6a*S**, 10a*S**)-6-Phenyl-2,3,6a,7-tetrahydro-1*H*,5*H*-pyrrolo[2,1-i]indole-5,8(6*H*)-dione (264)**

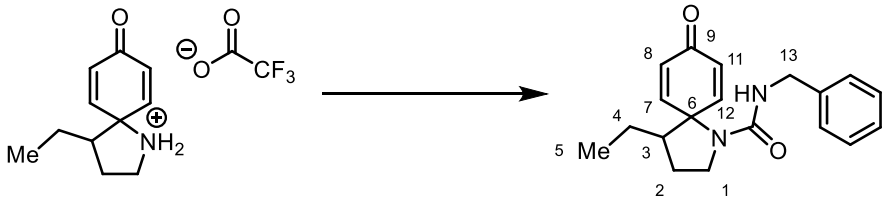


General procedure M: The preceding amide **263** (26.7 mg, 0.10 mmol) and 1.5 equivalents of lithium bis(trimethylsilyl)amide (1.0 M in THF, 0.15 mL, 0.15 mmol) in anhydrous THF (1 mL) were employed. The reaction was stirred at this temperature for 2 hours. Purification by

flash column chromatography (EtOAc) afforded **264** (17.9 mg, 67%, >20:1 d.r.) as a colourless oil; R_f = 0.4 (3% MeOH:CH_2Cl_2); ν_{max} / cm^{-1} (*film*) 2920 (m), 1677 (br s), 1395 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.27 (3H, m, ArC<u>H</u>), 7.15 – 7.11 (2H, m, ArC<u>H</u>), 6.64 (1H, dd, *J* = 10.5, 2.0 Hz, C**9**-<u>H</u>), 6.13 (1H, dd, *J* = 10.5, 1.0 Hz, C**10**-<u>H</u>), 3.97 (1H, ddd, *J* = 12.5, 7.5, 5.0 Hz, C**5**-<u>H</u>), 3.68 (1H, d, *J* =12.0 Hz, C**3**-<u>H</u>), 3.28 – 3.20 (1H, m, C**5**-<u>H</u>'), 2.71 – 2.62 (2H, m, C**2**-<u>H</u>, C**1**-<u>H</u>), 2.49 – 2.43 (1H, m, C**1**-<u>H</u>'), 2.32 – 2.21 (1H, m, C**6**-<u>H</u>), 2.19 – 2.11 (1H, m, C**6**-<u>H</u>'), 2.10 – 2.02 (2H, m, C**7**-<u>H_2</u>); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.0 (C**11**), 173.5 (C**4**), 146.9 (C**9**), 135.7 (Ar<u>C</u>), 129.2 (2 × Ar<u>C</u>H), 129.0 (2 × Ar<u>C</u>H), 128.0 (C**10**), 127.8 (Ar<u>C</u>H), 65.3 (C**8**), 56.3 (C**3**), 51.5 (C**2**), 42.7 (C**5**), 36.3 (C**1**), 35.6 (C**7**), 26.3 (C**6**). HRMS (ESI^+) Calculated for $C_{17}H_{17}NNaO_2$: 290.1151. Found $[M+Na]^+$: 290.1155.

*The relative stereochemistry of this compound was determined by nOe experiments as indicated on the compound structure. nOes were observed between C**3**-<u>H</u> and C**9**-<u>H</u>.*

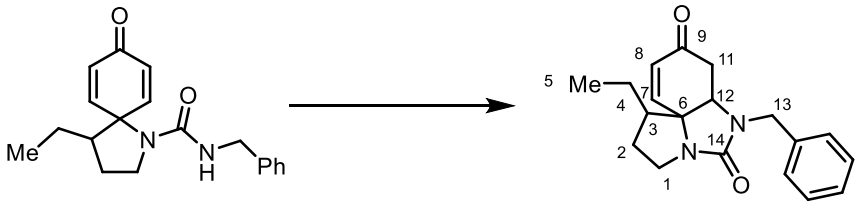
_N_-Benzyl-4-ethyl-8-oxo-1-azaspiro[4.5]deca-6,9-diene-1-carboxamide (265)



To a solution of spirocycle **214** (43.7 mg, 0.15 mmol) in anhydrous CH_2Cl_2 (1 mL) at 0 °C and under an atmosphere of nitrogen were added benzyl isocyanate (37.0 μL, 0.30 mmol) and Et_3N (84.0 μL, 0.60 mmol). The reaction mixture was stirred at 0 °C for 3 hours and then overnight at room temperature until completion by TLC analysis. The reaction mixture was quenched with saturated aqueous NH_4Cl (1 mL) and extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography (1% MeOH:CH_2Cl_2) afforded **265** (27.7 mg, 59%) as a colourless solid; ν_{max}/cm^{-1} (*solid*) 3316 (m), 2968 (m), 2929 (m), 2871 (m), 1660 (s), 1638 (s), 1528 (s), 1376 (m), 1337 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.18 (5H, m, ArC<u>H</u>), 6.77 (1H, dd, *J* = 10.0, 3.0 Hz, C**7**/C**12**-<u>H</u>), 6.70 (1H, dd, *J* = 10.5, 3.0 Hz, C**7**/C1**2**-<u>H</u>), 6.30 (2H, ddd, *J* = 10.5, 4.5, 2.0 Hz, C**8**-<u>H</u>, C**11**-<u>H</u>), 4.65 – 4.59 (1H, br s, N<u>H</u>), 4.38 – 4.28 (2H, m, C**13**-<u>H_2</u>), 3.80 (1H, t, *J* = 9.0 Hz, C**1**-<u>H</u>), 3.58 – 3.51 (1H, m, C**1**-<u>H</u>'), 2.27 (1H, dt, *J* = 12.5, 6.5 Hz, C**2**-<u>H</u>), 2.15 – 2.06 (1H, m, C**3**-<u>H</u>), 1.72 – 1.60 (1H, m, C**2**-<u>H</u>'), 1.26 – 1.16 (1H, m, C**4**-<u>H</u>), 1.07 – 0.95 (1H, m, C**4**-<u>H</u>'), 0.88 (3H, t, *J* = 7.5 Hz, C**5**-<u>H_3</u>); ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.1 (C**9**), 155.7 (N<u>C</u>=O), 153.2 (C**7**/**12**), 148.5 (C**7**/C**12**),

139.1 (Ar<u>C</u>), 130.2 (C**8**/C**11**), 129.3 (C**8**/C**11**), 128.7 (2 × Ar<u>C</u>H), 127.6 (2 × Ar<u>C</u>H), 127.4 (Ar<u>C</u>H), 64.8 (C**6**), 52.5 (C**3**), 46.5 (C**1**), 44.6 (C**13**), 29.2 (C**2**) , 21.9 (C**4**), 12.6 (C**5**); HRMS (ESI^+) Calculated for $C_{19}H_{22}N_2NaO_2$: 333.1573. Found $[M+Na]^+$: 333.1582.

6-Benzyl-1-ethyl-2,3,6a,7-tetrahydro-1*H*,5*H*-benzo[d]pyrrolo[1,2-c]imidazole-5,8(6*H*)-dione (266)



<u>General procedure M:</u> The preceding urea **265** (31.2 mg, 0.10 mmol) and lithium bis(trimethylsilyl)amide (1.0 M in THF, 0.15 mL, 0.15 mmol) in anhydrous THF (1 mL) were employed. The reaction was stirred at this temperature overnight until completion by TLC analysis. The reaction was warmed to 0 °C and quenched with saturated aqueous NH_4Cl (0.3 mL) and extracted with EtOAc (3 × 1 mL). The combined organic extracts were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography (1% MeOH:CH_2Cl_2) afforded **266** (29.0 mg, 93%) as a 3:1 mixture of diastereomers and as a colourless solid; ν_{max}/cm^{-1} (*solid*) 2963 (m), 2926 (m), 2901 (m), 2878 (m), 1683 (s, br), 1405 (m).

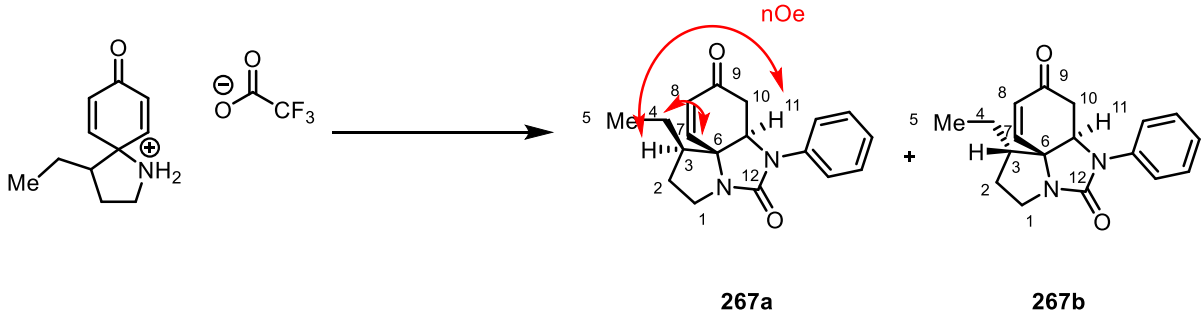
*Spectroscopic data for the major diastereomer **266a**:* ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.20 (5H, m, Ar<u>C</u>H), 6.49 (1H, d, *J* = 10.5 Hz, C**7**-<u>H</u>), 6.13 (1H, d, *J* = 10.5 Hz, C**8**-<u>H</u>), 4.80 (1H, d, *J* = 15.0 Hz, C**13**-<u>H</u>), 4.00 (1H, d, *J* = 15.0 Hz, C**13**-<u>H</u>'), 3.79 – 3.71 (1H, m, C**1**-<u>H</u>), 3.66 (1H, t, *J* = 6.5 Hz, C**12**-<u>H</u>), 3.34 (1H, ddd, *J* = 11.5, 8.5, 3.0 Hz, C**1**-<u>H</u>'), 2.67 (1H, dd, *J* = 16.0, 5.5 Hz, C**11**-<u>H</u>), 2.57 (1H, dd, *J* = 16.0, 7.0 Hz, C**11**-<u>H</u>'), 2.38 – 2.30 (1H, m, C**2**-<u>H</u>), 1.79 – 1.70 (2H, m, C**2**-<u>H</u>', C**3**-<u>H</u>), 1.33 – 1.16 (2H, m, C**4**-<u>H_2</u>), 0.83 (3H, t, *J* = 7.0 Hz, C**5**-<u>H_3</u>); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.7 (C**9**), 161.6 (C**14**), 142.8 (C**7**), 136.4 (Ar<u>C</u>), 129.4 (C**8**), 128.9 (2 × Ar<u>C</u>H), 128.3 (2 × Ar<u>C</u>H), 127.9 (Ar<u>C</u>H), 65.3 (C**6**), 57.0 (C**12**), 49.6 (C**3**), 45.4 (C**13**), 44.1 (C**1**), 39.6 (C**11**), 31.2 (C**2**), 22.5 (C**4**), 13.2 (C**5**).

*Spectroscopic data for the minor diastereomer **266b**:* ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.19 (5H, m, Ar<u>C</u>H), 6.39 (1H, d, *J* = 10.0 Hz, C**7**-<u>H</u>), 6.08 (1H, d, *J* = 10.0 Hz, C**8**-<u>H</u>), 4.76 (1H, d, *J* = 15.5 Hz, C**13**-<u>H</u>), 4.01 (1H, d, *J* = 15.5 Hz, C**13**-<u>H</u>'), 3.87 (1H, dd, *J* = 12.0, 7.0 Hz, C**1**-<u>H</u>), 3.70 (1H, s, C**12**-<u>H</u>), 3.14 (1H, td, *J* = 12.0, 5.0 Hz, C**1**-<u>H</u>'), 2.68 (1H, dd, *J* = 17.5, 2.5 Hz, C**11**-<u>H</u>'), 2.43 (1H, dd, *J* = 17.5, 4.5 Hz, C**11**-<u>H</u>'), 2.13 – 2.00 (2H, m, C**2**-<u>H</u>, C**3**-<u>H</u>), 1.55

– 1.45 (1H, m, C**4**-H), 1.32 – 1.16 (2H, m, C**2**-H', C**4**-H'), 0.95 (3H, t, *J* = 7.5 Hz, C**5**-H$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.6 (C**9**), 162.7 (C**14**), 149.5 (C**7**), 136.1 (ArC), 128.8 (2 × ArCH), 128.0 (C**8**), 128.0 (2 × ArCH), 127.7 (ArCH), 64.0 (C**6**), 56.0 (C**12**), 50.1 (C**3**) 47.5 (C**1**), 45.3 (C**13**), 36.6 (C**11**), 32.5 (C**2**), 20.9 (C**4**), 13.2 (C**5**).

HRMS (ESI$^+$) Calculated for $C_{19}H_{23}N_2O_2$: 311.1754. Found $[M+H]^+$: 311.1753.

(1*R, 6a*R**, 10a*S**) and (1*S**, 6a*R**, 10a*S**)-1-Ethyl-6-phenyl-2,3,6a,7-tetrahydro-1*H*,5*H*-benzo[d]pyrrolo[1,2-c]imidazole-5,8(6*H*)-dione (267a) and (1S*,6aR*,10aS*)-1-Ethyl-6-phenyl-2,3,6a,7-tetrahydro-1*H*,5*H*-benzo[d]pyrrolo[1,2-c]imidazole-5,8(6*H*)-dione (267b)**



General procedure N: Spirocycle **214** (45.0 mg, 0.154 mmol), phenyl isocyanate (34.0 µL, 0.308 mmol) and Et_3N (86.0 µL, 0.618 mmol) in anhydrous CH_2Cl_2 (0.77 mL, 0.2 M) were employed. The reaction was stirred at this temperature for 2 hours before warming to room temperature and stirring overnight. Purification by flash column chromatography (33% EtOAc:hexane) afforded **267** (34.1 mg, 75%) as a colourless solid. *A mixture of diastereomers **267a** and **267b** were obtained in a 4:1 ratio;* R_f = 0.6 (3% MeOH:CH_2Cl_2); ν_{max} / cm^{-1} (*solid*) 2965 (m), 2926 (m), 2885 (m), 1692 (s), 1683 (s), 1380 (s), 1309 (s).

*Data for the major diastereomer **267a**:* m.p.: 148-151 °C (EtOAc:hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.30 (4H, m, ArCH), 7.17 – 7.11 (1H, m, ArCH), 6.57 (1H, d, *J* = 10.5 Hz, C**7**-H), 6.21 (1H, d, *J* = 10.5 Hz, C**8**-H), 4.57 (1H, app. t, *J* = 6.0 Hz, C**11**-H), 3.87 – 3.78 (1H, m, C**1**-H), 3.43 – 3.35 (1H, m, C**1**-H'), 2.84 (1H, dd, *J* = 16.5, 6.0 Hz, C**10**-H), 2.66 (1H, dd, *J* = 16.5, 7.0 Hz, C**10**-H'), 2.45 – 2.36 (1H, m, C**2**-H), 2.08 – 1.98 (1H, m, C**3**-H), 1.88 – 1.76 (1H, m, C**2**-H'), 1.54 – 1.44 (1H, m, C**4**-H), 1.39 – 1.28 (1H, m, C**4**-H'), 0.99 (3H, t, *J* = 7.5 Hz, C**5**-H$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.6 (C**9**), 159.4 (C**12**), 142.4 (C**7**), 137.3 (ArC), 129.6 (C**8**), 129.3 (2 × ArCH), 125.1 (2 × ArCH), 122.2 (ArCH), 64.8 (C**6**), 58.6 (C**11**), 50.1 (C**3**), 43.9 (C**1**), 39.6 (C**10**), 30.9 (C**2**), 25.6 (C**4**), 13.2 (C**5**).

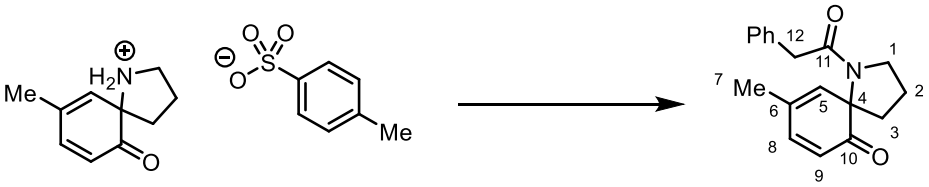
The minor diastereomer could not be isolated in a pure form.

*Spectroscopic data for the minor diastereomer **267b**: Characteristic peaks only*: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.48 (1H, d, *J* = 10.0 Hz, C**7**-H), 6.14 (1H, d, *J* = 10.0 Hz, C**8**-H), 4.51 – 4.48 (1H, m, C**11**-H), 3.94 – 3.87 (1H, m, C**1**-H), 3.20 (1H, td, *J* = 11.5, 5.0 Hz, C**1**-H'), 2.78 (1H, dd, *J* = 17.5, 3.0 Hz, C**10**-H), 2.57 (1H, dd, *J* = 17.5, 5.0 Hz, C**10**-H'), 1.05 (3H, t, *J* = 7.5 Hz, C**5**-H_3).

HRMS (ESI^+) Calculated for $C_{18}H_{20}N_2NaO_2$: 319.1417. Found $[M+Na]^+$: 319.1426.

*The relative stereochemistry of the major diastereomer of this compound was determined by nOe experiments as indicated on the compound structure. nOes were observed between C**3**-H and C**11**-H and between C**4**-H_2 and C**7**-H.*

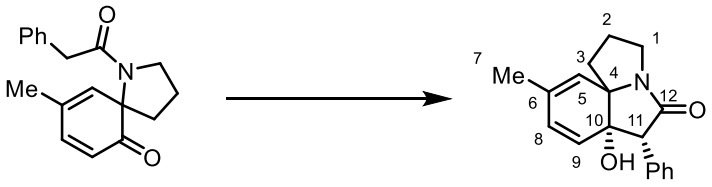
9-Methyl-1-(2-phenylacetyl)-1-azaspiro[4.5]deca-7,9-dien-6-one (268)



General procedure L: Spirocyclic amine **222** (0.150 mmol), phenylacetyl chloride (40.0 μL, 0.300 mmol) and K_3PO_4 (127.4 mg, 0.600 mmol) in anhydrous THF (0.75 mL) were employed. Purification by flash column chromatography (EtOAc) afforded **268** (34.0 mg, 81%) as a 9:1 mixture of rotamers *A*:*B* and as a yellow oil; R_f = 0.4 (3% MeOH:CH_2Cl_2); ν_{max} / cm^{-1} (*film*) 2972 (m), 2878 (m), 1675 (s), 1642 (s), 1406 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.27 (2H, m, ArCH, *A*+*B*), 7.25 – 7.20 (2.90H, m, ArCH, *A*+*B*), 7.13 – 7.09 (0.10H, m, 0.10 × ArCH, *B*), 6.93 (0.10H, dd, *J* = 10.0, 2.5 Hz, 0.10 × C**8**-H, *B*), 6.82 (0.90H, dd, *J* = 10.0, 2.5 Hz, 0.90 × C**8**-H, *A*), 6.18 – 6.09 (1.10H, m, 1.00 × C**9**-H, *A*+*B*, 0.10 × C**5**-H, *B*), 5.90 – 5.87 (0.90H, m, 0.90 × C**5**-H, *A*), 3.97 – 3.91 (0.10 H, m, 0.1 × C**1**-H, *B*), 3.78 – 3.69 (0.9H, m, 0.90 × C**1**-H, *A*), 3.67 – 3.60 (2.8H, m, 1.00 × C**1**-H', *A*+*B*, 1.80 × C**12**-H_2, *A*), 3.12 (0.20H, m, 0.20 × C**12**-H_2, *B*), 2.28 – 2.22 (0.10H, m, 0.10 × C**3**-H, *B*), 2.21 – 2.12 (1H, m, 0.90 × C**2**-H, *A*, C**3**-H', *B*), 2.10 – 1.95 (2.30 H, m, 1.00 × C**3**-H', *A*+*B*, 1.00 × C**2**-H', *A*+*B*, 0.30 × C**7**-H_3, *B*), 1.92 (2.70H, s, C**7**-H_3, *A*), 1.89 – 1.82 (1H, m, 0.90 × C**3**-H, *A*, 0.10 × C**2**-H, *B*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208. 6 (C**10**, *B*), 200.1 (C**10**, *A*), 170.3 (C**11**, *B*), 168.6 (C**11**, *A*), 145.5 (C**8**, *B*), 145.0 (C**8**, *A*), 140.3 (C**5**, *B*), 137.5 (C**5**, *A*), 134.5 (ArC, *A*+*B*), 129.6 (2 × ArCH, *B*), 129.2 (2 × ArCH, *A*), 128.7 (C**6**, *A* + *B*) 128.6 (2 × ArCH, *A*), 128.3 (2 × ArCH, *B*), 126.8 (ArCH, *A*), 126.6 (ArCH, *B*), 125.8 (C**9**), 125.1 (C**9**, *B*), 70.1 (C**4**, *B*), 69.3 (C**4**, *A*), 49.0 (C**1**, *B*), 48.8 (C**1**, *A*), 41.9 (C**12**, *A*), 40.7 (C**12**, *B*), 37.6 (C**2** or C**3**, *A* + *B*), 24.0 (C**2** or C**3** *A* + *B*),

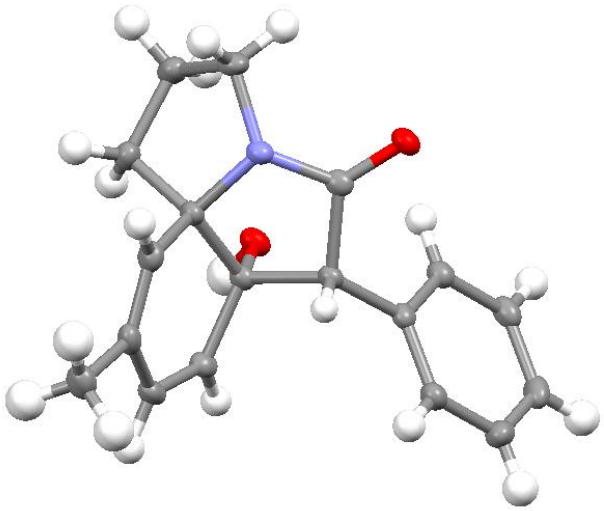
21.1 (C**7**, *A*), 20.9 (C**7**, *B*); HRMS (ESI$^+$) Calculated for $C_{18}H_{19}NNaO_2$: 304.1308. Found $[M+Na]^+$: 304.1318.

(6*R, 6a*S**)-6a-Hydroxy-9-methyl-6-phenyl-2,3,6,6a-tetrahydro-1*H*,5*H*-pyrrolo[2,1-i]indol-5-one (269)**



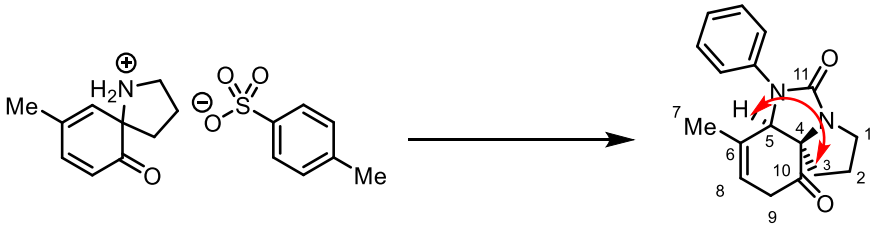
General procedure M: The preceding spirocyclic amide **268** (28.1 mg, 0.10 mmol) and 1.5 equivalents of lithium bis(trimethylsilyl)amide (1.0 M in THF) in anhydrous THF (1 mL) were employed. Purification by flash column chromatography (1% MeOH:CH_2Cl_2) afforded **269** (18.9 mg, 67%, > 15:1 d.r.) as a colourless solid; m.p.: 150-152 ^oC (EtOAc:hexane); R_f = 0.5 (3% MeOH:CH_2Cl_2); ν_{max} / cm^{-1} (*solid*) 3356 (br m), 2969 (m), 2942 (m), 2880 (m), 1673 (s), 1402 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.31 (3H, m, ArC<u>H</u>), 7.28 – 7.24 (2H, m, ArC<u>H</u>), 5.78 (1H, dd, *J* = 10.0, 1.5 Hz, C**8**-<u>H</u>), 5.53 (1H, m, C**5**-<u>H</u>), 5.38 (1H, d, *J* = 10.0 Hz, C**9**-<u>H</u>), 4.27 (1H, s, C**11**-<u>H</u>), 3.89 (1H, ddd, *J* = 12.0, 7.5, 4.5 Hz, C**1**-<u>H</u>), 3.16 (1H, ddd, *J* = 12.0, 7.5, 1.5 Hz, C**1**-<u>H</u>'), 2.54 (1H, ddd, *J* = 13.0, 8.5, 6.0 Hz, C**3**-<u>H</u>), 2.07 – 1.97 (1H, m, C**2**-<u>H</u>), 1.95 – 1.87 (1H, m, C**2**-<u>H</u>'), 1.85 (1H, d, *J* = 1.5 Hz, C**7**-<u>H</u>$_3$), 1.44 (1H, dt, *J* = 13.0, 7.5 Hz, C**3**-<u>H</u>'); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.8 (C**12**), 134.2 (2 × Ar<u>C</u>H), 131.3 (C**9**), 131.2 (Ar<u>C</u>), 128.6 (2 × Ar<u>C</u>H), 128.6 (C**6**), 128.0 (Ar<u>C</u>H), 127.0 (C**5**), 126.7 (C**8**), 79.1 (C**10**), 72.7 (C**4**), 61.6 (C**11**), 42.9 (C**1**), 30.6 (C**3**), 26.2 (C**2**), 21.2 (C**7**); HRMS (ESI$^+$) Calculated for $C_{18}H_{19}NNaO_2$: 304.1308. Found $[M+Na]^+$: 304.1322.

The relative stereochemistry of this compound was determined unambiguously using X-ray crystallography.



*X-ray crystal structure of **269**.*

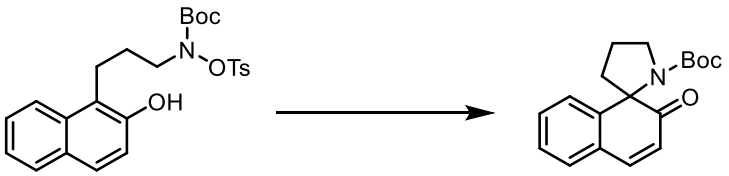
(6a*R, 10a*R**)7-Methyl-6-phenyl-2,3,6a,9-tetrahydro-1*H*,5*H*-benzo[d]pyrrolo[1,2c] imidazole-5,10(6*H*)-dione (270)**



General procedure N: Spirocyclic amine **222** (0.15 mmol), 1.1 equivalents of phenyl isocyanate (18 μL, 0.17 mmol) and Et_3N (84 μL, 0.60 mmol) in anhydrous CH_2Cl_2 (0.2 M) were employed. The reaction was stirred at this temperature for 3 hours then heated to 40 °C and stirred overnight, monitoring by TLC analysis. Purification by flash column chromatography (1% MeOH:CH_2Cl_2) afforded **270** (28.9 mg, 68%) as a colourless solid; m.p.: 110-113 °C (EtOAc:hexane); R_f = 0.6 (3% MeOH:CH_2Cl_2); ν_{max} / cm^{-1} (*solid*) 2987 (m), 2953 (m), 2923 (m), 1726 (s), 1693 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.35 (4H, m, ArC**H**), 7.21 – 7.16 (1H, m, ArC**H**), 5.59 – 5.55 (1H, m, C**8**-**H**), 4.74 (1H, s, C**5**-**H**), 3.94 – 3.87 (1H, m, C**1**-**H**), 3.68 – 3.60 (1H, m, C**9**-**H**), 2.88 (1H, ddd, *J* = 12.0, 9.0, 6.5 Hz, C**1**-**H**'), 2.79 – 2.70 (2H, m, C**9**-**H**', C**3**-**H**), 2.00 – 1.85 (2H, m, C**2**-**H**$_2$), 1.55 – 1.46 (1H, m, C**3**-**H**'), 1.41 (3H, s, C**7**-**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.6 (C**10**), 161.5 (C**11**), 138.9 (Ar**C**), 134.4 (C**6**), 129.3 (2 × Ar**C**H), 125.8 (Ar**C**H), 123.9 (2 × Ar**C**H), 121.6 (C**8**), 70.9 (C**4**), 66.5 (C**5**), 45.9 (C**1**), 36.5 (C**9**), 29.4 (C**3**), 23.7 (C**2**), 22.6 (C**7**); HRMS (ESI$^+$) Calculated for $C_{17}H_{18}N_2NaO_2$: 305.1260. Found $[M+Na]^+$: 305.1273.

*The relative stereochemistry was determined using nOe analysis as indicated on the compound structure. An nOe was observed between C**5**-H and C**3**-H$_2$.*

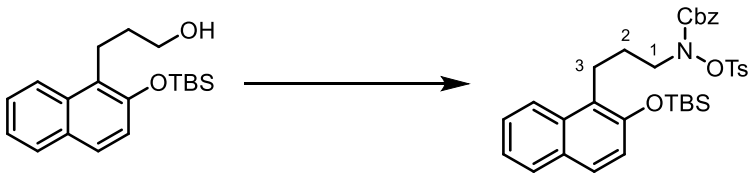
tert-Butyl 2-oxo-2*H*-spiro[naphthalene-1,2'-pyrrolidine]-1'-carboxylate (277b)



General procedure O: *N*-Tosyloxycarbamate **227** (47.2 mg, 0.1 mmol), 9-Hydroxy-1-(phenylmethyl)cinchonanium chloride **295** (4.2 mg, 10 mol%), Cs_2CO_3 (65.2 mg, 200 mol%) in anhydrous PhMe (0.1 M) were employed. The reaction was stirred at 30 ^oC for 48 hours. Purification by flash column chromatography (20% EtOAc:hexane) afforded **277b** (8.4 mg, 28%, 22% e.e.) as a colourless solid. *This compound exists as an approximately 7:2 mixture of rotamers A and B.* **SFC conditions:** *column:* CHIRALPACK IA, *elute:* 3.0% MeOH/CO_2, *detector:* 250 nm, flow rate: 2.0 mL/min, *retention times:* (major enantiomer) t_1 = 6.3 min, (minor enantiomer) t_2 = 7.2 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.34 (3H, m), 7.32 – 7.24 (2H, m), 6.18 (1H, d, *J* = 10.0 Hz), 4.00 – 3.88 (1H, m), 3.84 – 3.75 (1H, m), 2.36 – 2.25 (1H, m), 2.17 – 2.07 (1H, m), 2.01 – 1.85 (2H, m), 1.39 (2H, s), 1.00 (7H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.8, 153.3, 147.4, 146.5, 145.1, 144.9, 130.4, 129.7, 129.3, 129.1, 127.3, 124.9, 124.5, 124.4, 124.2, 80.2, 79.9, 71.9, 49.4, 48.9, 42.2, 41.8, 28.6, 27.9, 22.6, 21.7.

The spectroscopic properties were consistent with the data available in the literature.[97]

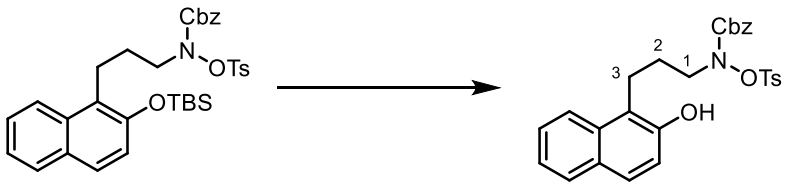
Benzyl (3-(2-((*tert*-butyldimethylsilyl)oxy)naphthalen-1-yl)propyl)(tosyloxy)carbamate



General procedure G: Alcohol **168** (1.58 g, 5.0 mmol), PPh_3 (1.57 g, 6.0 mmol), DIAD (1.18 mL, 6.0 mmol) and CbzNHOTs (1.93 g, 6.0 mmol) in anhydrous THF (20 mL) were employed. Purification by flash column chromatography (gradient, eluent: 5 – 10% EtOAc:hexane) afforded the title compound (1.64 g, 53%) as a viscous, colourless oil; ν_{max} / cm^{-1} (*film*) 2954 (m), 2929 (m), 1724 (s), 1381 (s), 1177 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (1H, d, *J* = 8.5

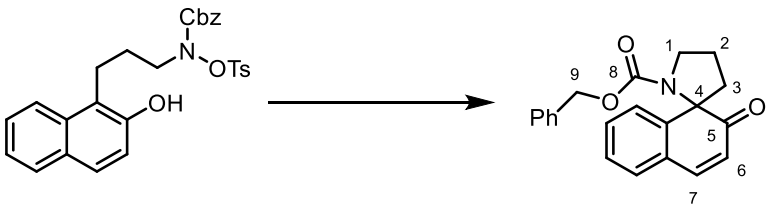
Hz, ArCH), 7.76 (1H, dd, *J* = 8.0, 1.5 Hz, ArCH), 7.72 (2H, d, *J* = 8.5 Hz, ArCH), 7.60 (1H, d, *J* = 9.0 Hz, ArCH), 7.45 (1H, ddd, *J* = 8.5, 6.5, 1.5 Hz, ArCH), 7.35 – 7.25 (4H, m, ArCH), 7.13 – 7.08 (4H, m, ArCH), 7.05 (1H, d, *J* = 9.0 Hz, ArCH), 4.87 (2H, s, Cbz CH_2), 3.75 (2H, br s, C**1**-H_2), 3.00 (2H, t, *J* = 8.0 Hz, C**3**-H_2), 2.35 (3H, s, Ts CH_3), 2.00 – 1.89 (2H, m, C**2**-H_2), 1.04 (9H, s, TBS $(CH_3)_3$), 0.25 (6H, s, $Si(CH_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.7 (Cbz C=O), 150.7 (ArC), 145.7 (ArC), 135.0 (ArC), 133.3 (ArC), 131.1 (ArC), 129.6 (ArCH), 129.5 (ArCH), 128.6 (ArC), 128.6 (ArCH), 128.5 (ArCH), 128.2 (ArCH), 127.6 (ArCH), 126.4 (ArCH), 124.1 (ArC), 123.4 (ArCH), 123.2 (ArCH), 120.4 (ArCH), 68.7 (Cbz CH_2), 53.3 (C**1**), 26.2 (C**2**) 26.0 (TBS $C(CH_3)_3$), 22.7 (C**3**), 21.9 (Ts CH_3), 18.4 (TBS $C(CH_3)_3$), -3.7 (TBS $Si(CH_3)_2$); HRMS (ESI^+) Calculated for $C_{34}H_{41}NNaO_6SSi$: 642.2316. Found $[M+Na]^+$: 642.2279.

Benzyl (3-(2-hydroxynaphthalen-1-yl)propyl)(tosyloxy)carbamate (299)



General procedure H: Benzyl (3-(2-((*tert*-butyldimethylsilyl)oxy)naphthalen-1-yl)propyl)(tosyloxy)carbamate (1.24 g, 2.0 mmol), and 1:1 TBAF:HOAc solution (0.1 M in THF, 2.0 mmol) in THF (30 mL) were employed. Purification by flash column chromatography (20% EtOA:hexane) afforded **299** (740 mg, 73%) as a pale-orange, viscous oil; ν_{max} / cm^{-1} (*film*) 3406 (br), 1722 (s), 1379 (s), 1190 (s), 1176 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (1H, d, *J* = 8.5 Hz, ArCH), 7.79 – 7.70 (3H, m, ArCH), 7.61 (1H, d, *J* = 9.0 Hz, ArCH), 7.46 (1H, ddd, *J* = 8.5, 7.0, 1.5 Hz, ArCH), 7.34 – 7.26 (4H, m, ArCH), 7.16 – 7.09 (4H, m, ArCH), 7.03 (1H, d, *J* = 9.0 Hz, ArCH), 4.90 (s, 2H, Cbz CH_2), 3.78 (2H, t, *J* = 7.0 Hz, C**1**-H_2), 3.04 (2H, t, *J* = 8.0 Hz, C**3**-H_2), 2.36 (s, 3H, Ts CH_3); 2.07 – 1.98 (2H, m, C**2**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.2 (Cbz C=O), 150.9 (ArC), 145.9 (ArC), 134.9 (ArC), 133.2 (ArC), 130.9 (ArC), 129.7 (2 × ArCH), 129.5 (2 × ArCH), 128.8 (ArC), 128.6 (2 × ArCH), 128.3 (2 × ArCH), 128.1 (ArCH), 126.7 (ArCH), 123.2 (ArCH), 122.8 (ArCH), 118.7 (ArC), 118.1 (ArCH), 68.9 (OCH_2), 53.4 (C**1**), 26.3 (C**2**), 22.2 (C**3**), 21.9 (Ts CH_3); HRMS (ESI^+) Calculated for $C_{28}H_{27}NNaO_6S$: 528.1451. Found $[M+Na]^+$: 528.14629.

Benzyl 2-oxo-2*H*-spiro[naphthalene-1,2'-pyrrolidine]-1'-carboxylate (170)

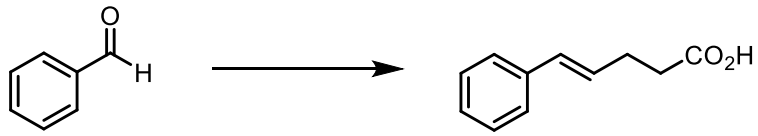


General procedure O: The preceding *N*-tosyloxycarbamate **299** (50.6 mg, 0.1 mmol), (8a,9R)-Cinchonanium,9-hydroxy-6'-methoxy-1-(phenylmethyl) chloride **298** (4.5 mg, 10 mol%), Cs_2CO_3 (65.2 mg, 200 mol%) in anhydrous PhMe (0.1 M) were employed. The reaction was stirred at 30 ^oC for 48 hours. Purification by flash column chromatography (20% EtOAc:hexane) afforded **170** (20.7 mg, 62%, 54% e.e.) as a colourless oil. *This compound exists as an approximately 3:2 mixture of rotamers A and B.* **SFC conditions:** *column:* CHIRALPACK IA, *elute:* 10.0% MeOH/CO_2, *detector:* 250 nm, flow rate: 2.0 mL/min, *retention times:* (major enantiomer) $t_1 = 8.4$ min, (minor enantiomer) $t_2 = 7.5$ min.

*Characteristic data for **170** has been provided earlier (section 6.3).*

6.4 Experimental procedure for the studies in Chapter 3

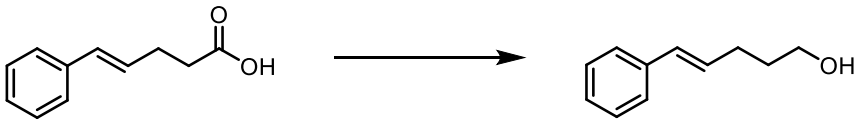
(*E*)-5-Phenylpent-4-enoic acid (343)



The title compound **343** was prepared according to a literature procedure.[317]

The spectroscopic properties were consistent with the data available in the literature.[317]

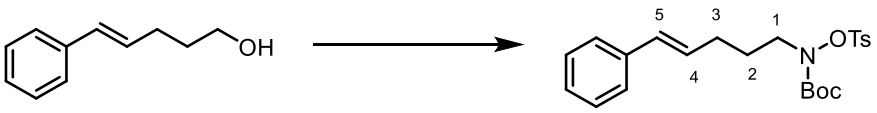
(*E*)-5-Phenylpent-4-en-1-ol (344)



General procedure B: The preceding carboxylic acid **343** (930 mg, 5.26 mmol), and 2.0 equivalents of $LiAlH_4$ (10.5 mL, 10.5 mmol, 1M in THF) in anhydrous THF (25 mL) were employed. Purification by flash column chromatography (gradient, eluent 20 – 33% EtOAc: petroleum ether) afforded **344** (710 mg, 83%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.27 (4H, m), 7.23 – 7.18 (1H, m), 6.42 (1H, d, *J* = 16.0 Hz), 6.23 (1H, dt, *J* = 16.0, 7.0 Hz), 3.72 – 3.66 (2H, m), 2.34 – 2.26 (2H, m), 1.80 – 1.71 (2H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.7, 130.5, 130.2, 128.6, 127.1, 126.1, 62.5, 32.3, 29.4.

The Spectroscopic properties were consistent with the data available in the literature.[318]

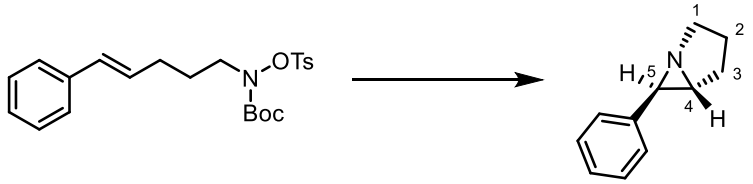
***tert*-Butyl (*E*)-(5-phenylpent-4-en-1-yl)(tosyloxy)carbamate (345)**



General procedure G: The preceding alcohol **344** (550 mg, 3.39 mmol), PPh_3 (1.07 g, 4.07 mmol), DIAD (0.79 mL, 4.07 mmol) and BocNHOTs (1.17 g, 4.07 mmol) in anhydrous THF (13 mL) were employed. Purification by flash column chromatography (5% EtOAc: petroleum ether) afforded **345** (1.36 g, 93%) as a colourless solid; R_f = 0.55 (33% EtOAc:hexane); m.p.: 61-63 °C (Et_2O:hexane); ν_{max} / cm^{-1} (*film*) 2980 (m), 2933 (m), 1749 (m), 1718 (s), 1597 (m), 1368 (s), 1177 (s), 1152 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.33 – 7.25 (6H, m, ArC<u>H</u>, Ts ArC<u>H</u>), 7.21 – 7.16 (1H, m, ArC<u>H</u>), 6.38 (1H, d, *J* = 16.0

Hz, C**5**-H), 6.18 – 6.10 (1H, m, C**4**-H), 3.65 (2H, br s, C**1**-H$_2$), 2.43 (3H, Ts CH$_3$), 2.22 – 2.15 (2H, m, C**3**-H$_2$), 1.85 – 1.75 (2H, m, C**2**-H$_2$), 1.24 (9H, s, Boc (CH$_3$)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6 (Boc C=O), 145.8 (Ts ArC), 137.7 (ArC), 131.4 (Ts ArC), 130.9 (C**5**), 129.8 (2 × Ts ArCH), 129.7 (2 × Ts ArCH), 129.3 (C**4**), 128.6 (2 × ArCH), 127.1 (2 × ArCH), 126.1 (ArCH), 83.4 (Boc C(CH$_3$)$_3$), 52.6 (C**1**), 30.1 (C**3**), 27.8 (Boc (CH$_3$)$_3$), 25.6 (C**2**), 21.8 (Ts CH$_3$); HRMS (ESI$^+$) Calculated for $C_{23}H_{29}NNaO_5S$: 454.1659. Found $[M+Na]^+$: 454.1652.

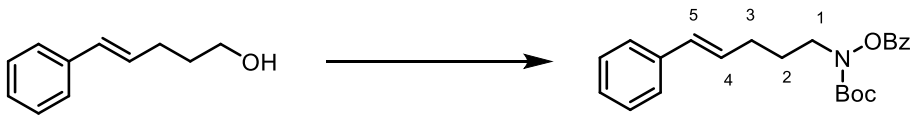
(5*S,6*S**)-6-Phenyl-1-azabicyclo[3.1.0]hexane (346)**



General procedure P: The preceding *N*-tosyloxycarbamate **345** (48.8 mg, 0.11 mmol) and TFA (17 μL, 0.23 mmol) in anhydrous TFE (1.1 mL) were employed. The reaction was stirred at room temperature for 24 hours. Purification by flash column chromatography (~0.1% Et_3N in 33% Et_2O:pentane) afforded **346** (13.7 mg, 76%) as a colourless oil; ν_{max} / cm^{-1} (*film*) 2953 (m), 2972 (m), 1605 (m), 1452 (m), 1078 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.18 (5H, m, ArCH), 3.21 (1H, ddd, *J* = 12.0, 8.5, 1.5 Hz, C**1**-H), 3.06 (1H, td, *J* = 11.5, 7.5 Hz, C**1**-H'), 2.44 (1H, dd, *J* = 5.0, 2.5 Hz, C**4**-H), 2.36 (1H, d, *J* = 2.5 Hz, C**5**-H), 2.24 (1H, ddd, *J* = 13.5, 8.5, 1.0 Hz, C**3**-H), 2.03 – 1.94 (1H, m, C**3**-H'), 1.78 – 1.70 (1H, m, C**2**-H), 1.67 – 1.56 (1H, m, C**2**-H'); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.4 (ArC), 128.4 (ArCH), 126.8 (ArCH), 126.2 (ArCH), 53.3 (C**1**), 50.9 (C**4**), 39.8 (C**5**), 26.8 (C**3**), 20.8 (C**2**); HRMS (ESI$^+$) Calculated for $C_{11}H_{14}N$: 160.1121. Found $[M+H]^+$: 160.1126.

The spectroscopic properties were consistent with the data available in the literature.[319]

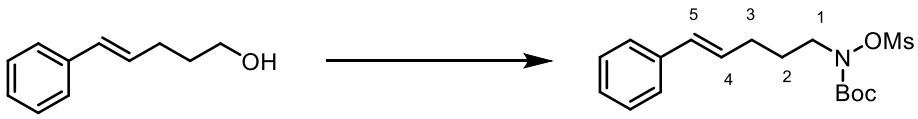
***tert*-Butyl (E)-(benzoyloxy)(5-phenylpent-4-en-1-yl)carbamate (347)**



General procedure G: Alcohol **344** (162 mg, 1.0 mmol), PPh_3 (315 mg, 1.2 mmol), DIAD (0.24 mL, 1.2 mmol) and BocNHOBz (285 mg, 1.2 mmol) in anhydrous THF (4 mL) were employed. Purification by flash column chromatography (5% EtOAc:petroleum ether) afforded **347** (300 mg, 79%) as a pale-yellow oil; ν_{max} / cm^{-1} (film) 2977 (m), 2934 (m), 1763 (s), 1711

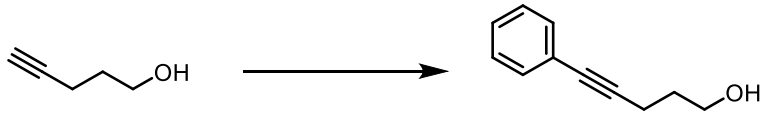
(s), 1242 (s), 1155 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 – 8.06 (2H, m, ArC<u>H</u>), 7.62 (1H, td, *J* = 7.3, 1.3 Hz, ArC<u>H</u>), 7.48 (2H, t, *J* = 7.8 Hz, ArC<u>H</u>), 7.33 – 7.25 (4H, m, ArC<u>H</u>), 7.21 – 7.16 (1H, m, ArC<u>H</u>), 6.41 (1H, d, *J* = 16.0 Hz, C**5**-<u>H</u>), 6.21 (1H, dt, *J* = 16.0, 6.5 Hz, C**4**-<u>H</u>), 3.76 (2H, t, *J* = 7.0 Hz, C**1**-<u>H_2</u>), 2.33 (2H, td, *J* = 8.0, 7.5, 6.5 Hz, C**3**-<u>H_2</u>), 1.84 (1H, app. qn, *J* = 7.4 Hz, C**2**-<u>H_2</u>), 1.47 (9H, s, Boc (C<u>H_3</u>)$_3$).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.8 (Bz, <u>C</u>=O), 155.0 (Boc <u>C</u>=O), 137.7 (Ar<u>C</u>), 133.9 (Ar<u>C</u>H), 130.8 (C**5**), 130.0 (Ar<u>C</u>H), 129.6 (C**4**), 128.8 (Ar<u>C</u>H), 128.6 (Ar<u>C</u>H), 127.8 (Ar<u>C</u>), 127.1 (Ar<u>C</u>H), 126.1 (Ar<u>C</u>H), 82.5 (Boc <u>C</u>(CH_3)$_3$), 50.3 (C**1**), 30.2 (C**3**), 28.3 (Boc (<u>C</u>H_3)$_3$), 27.2 (C**2**).

***tert*-Butyl (*E*)-((methylsulfonyl)oxy)(5-phenylpent-4-en-1-yl)carbamate (348)**



<u>General procedure G:</u> Alcohol **344** (162 mg, 1.0 mmol), PPh_3 (315 mg, 1.2 mmol), DIAD (0.24 mL, 1.2 mmol) and BocNHOMs (253 mg, 1.2 mmol) in anhydrous THF (4 mL) were employed. Purification by flash column chromatography (5% EtOAc:petroleum ether) afforded **348** (330 mg, 93%) as a colourless solid; ν_{max} / cm^{-1} (solid) 2939 (m), 1726 (s), 1361 (s), 1337 (s), 1178 (s), 1150 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.26 (4H, m, ArC<u>H</u>), 7.22 – 7.17 (1H, m, ArC<u>H</u>), 6.41 (1H, d, *J* = 16.0 Hz, C**5**-<u>H</u>), 6.18 (1H, dt, *J* = 16.0, 7.0 Hz, C**4**-<u>H</u>), 3.74 (2H, br s, C**1**-<u>H_2</u>), 3.14 (3H, s, Ms C<u>H_3</u>), 2.28 – 2.21 (2H, m, C**3**-<u>H_2</u>), 1.92 – 1.82 (2H, m, C**2**-<u>H_2</u>), 1.52 (9H, s, Boc (C<u>H_3</u>)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.7 (Boc <u>C</u>=O), 137.6 (Ar<u>C</u>), 131.0 (C**5**), 129.1 (C**4**), 128.6 (Ar<u>C</u>H), 127.2 (Ar<u>C</u>H), 126.1 (Ar<u>C</u>H), 84.3 (Boc <u>C</u>(CH_3)$_3$), 53.1 (C**1**), 37.1 (Ms <u>C</u>H_3), 30.1 (C**3**), 28.2 (Boc (<u>C</u>H_3)$_3$), 25.6 (C**2**); HRMS (ESI$^+$) Calculated for $C_{17}H_{25}NNaO_5S$: 378.1346. Found [M+Na]$^+$: 378.1336.

5-Phenylpent-4-yn-1-ol (349)

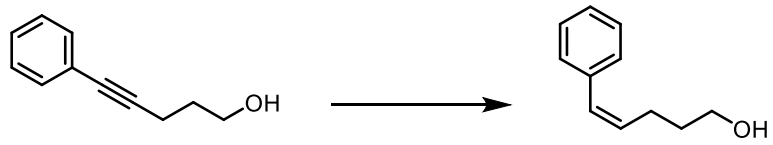


CuI (32.4 mg, 0.17 mmol) and $Pd(PPh_3)_4$ (97.1 mg, 84 μmol) were added to a solution of 4-pentyn-1-ol (0.93 mL, 10.0 mmol) and iodobenzene (2.24 mL, 20.0 mmol) in triethylamine (8 mL) and THF (20 mL) under an atmosphere of N_2. The reaction was stirred at room temperature overnight and monitored by TLC. Upon completion, the reaction mixture was

filtered through Celite® and the filtrate concentrated *in vacuo*. Purification by flash column chromatography (20% EtOAc:hexane) afforded **349** (1.38 g, 86%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.37 (2H, m), 7.30 – 7.25 (3H, m), 3.79 (2H, t, *J* = 6.0 Hz), 2.52 (2H, t, *J* = 7.0 Hz), 2.34 (1H, br s), 1.88 – 1.81 (2H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ 131.6, 128.3, 127.7, 123.8, 89.5, 81.1, 61.7, 31.4, 16.0.

The spectroscopic properties were consistent with the data available in the literature.[320]

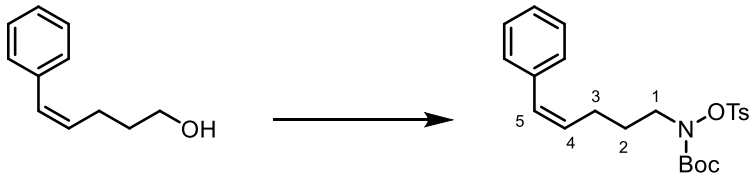
(*Z*)-5-Phenylpent-4-en-1-ol ((*Z*)-344)



To a solution of the preceding alkyne **349** (928 mg, 5.79 mmol) and quinoline (0.20 mL, 1.73 mmol) in EtOAc (15 mL) was added 5% Lindlar catalyst (153.5 mg). The reaction flask was fitted with a balloon of hydrogen and stirred at room temperature, monitoring by TLC analysis. Upon completion (~1 hour), the reaction was filtered through Celite® and concentrated *in vacuo*. Purification by flash column chromatography (CH_2Cl_2) afforded **(*Z*)-344** (895 mg, 95%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.21 (5H, m), 6.46 (1H, d, *J* = 11.5 Hz), 5.68 (1H, dt, *J* = 11.5, 7.5 Hz), 3.65 (2H, t, *J* = 6.5 Hz), 2.46 – 2.39 (2H, m), 1.76 – 1.69 (2H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.6, 132.2, 129.5, 128.8, 128.3, 126.7, 62.4, 32.9, 25.0.

The spectroscopic properties were consistent with the data available in the literature.[321]

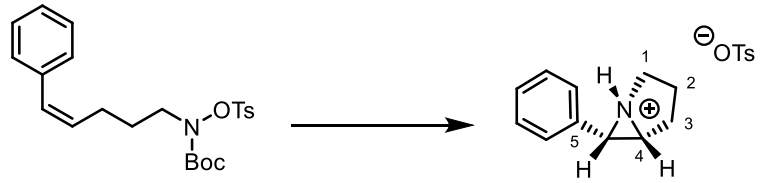
***tert*-Butyl (*Z*)-(5-phenylpent-4-en-1-yl)(tosyloxy)carbamate ((*Z*)-345)**



General procedure G: The preceding alcohol **(*Z*)-344** (687 mg, 4.24 mmol), PPh_3 (1.34 g, 5.09 mmol), DIAD (0.99 mL, 5.09 mmol) and BocNHOTs (1.46 g, 5.09 mmol) in anhydrous THF (17 mL) were employed. Purification by flash column chromatography (5% EtOAc:hexane) afforded **(*Z*)-345** (1.81 g, 99%) as a colourless solid; R_f = 0.50 (20% EtOAc:hexane); m.p.: 45-47 °C (CH_2Cl_2:hexane); ν_{max} / cm^{-1} (*solid*) 2988 (m), 2939 (m), 1714 (s), 1369 (s), 1176 (s), 1152 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (2H, d, *J* = 8.5 Hz, Ts

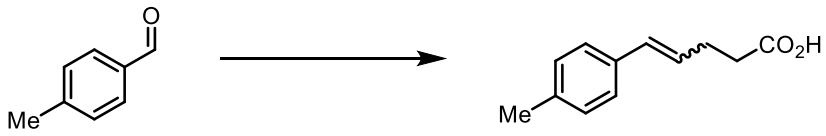
ArC<u>H</u>), 7.35 – 7.29 (4H, m, Ts ArC<u>H</u>, ArC<u>H</u>), 7.25 – 7.19 (3H, m, ArC<u>H</u>), 6.44 (1H, d, *J* = 11.5 Hz, C**5**-<u>H</u>), 5.60 (1H, dt, *J* = 11.5, 7.0 Hz, C**4**-<u>H</u>), 3.63 (2H, br s, C**1**-<u>H_2</u>), 2.44 (3H, s, Ts C<u>H_3</u>), 2.34 – 2.27 (2H, m, C**3**-<u>H_2</u>), 1.83 – 1.73 (2H, m, C**2**-<u>H_2</u>), 1.21 (9H, s, Boc (C<u>H_3</u>)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6 (Boc <u>C</u>=O), 145.8 (Ts Ar<u>C</u>), 137.5 (Ar<u>C</u>), 131.4 (Ts Ar<u>C</u>), 131.3 (C**4**), 129.9 (C**5**), 129.8 (2 × Ts Ar<u>C</u>H), 129.7 (2 × Ts Ar<u>C</u>H), 128.8 (Ar<u>C</u>H), 128.3 (Ar<u>C</u>H), 126.8 (Ar<u>C</u>H), 83.4 (Boc <u>C</u>(CH$_3$)$_3$), 52.6 (C**1**), 27.7 (Boc (<u>C</u>H_3)$_3$), 26.2 (C**2**), 25.7 (C**3**), 21.8 (Ts <u>C</u>H_3); HRMS (ESI$^+$) Calculated for $C_{23}H_{29}NNaO_5S$: 454.1659. Found [M+Na]$^+$: 454.1651.

(5*R,6*S**)-6-Phenyl-1-azabicyclo[3.1.0]hexane TsOH salt (350)**



<u>General procedure P:</u> The preceding *N*-tosyloxycarbamate **(*Z*)-345** (43.2 mg, 0.1 mmol) and TFA (15 μL, 0.2 mmol) in anhydrous TFE (1.0 mL, 0.1 M) were employed. The free base of the title compound was unstable to column chromatography and so upon completion (24 hours) the reaction mixture was concentrated *in vacuo* to afford **350** (78% yield as determined by analysis of ^{1}H NMR with addition of 1,3,5-trimethoxybenzene as an internal standard); ν_{max} / cm^{-1} (*film*) 3411 (br), 1771 (m), 1150 (s), 1121 (s); ^{1}H NMR (400 MHz, CD_3OD) δ 7.72 (2H, d, *J* = 8.0 Hz, Ts ArC<u>H</u>), 7.53 – 7.39 (5H, m, ArC<u>H</u>), 7.23 (2H, d, *J* = 8.0 Hz, Ts ArC<u>H</u>), 4.39 (1H, d, *J* = 8.0 Hz, C**5**-<u>H</u>), 4.08 – 4.04 (1H, m, C**4**-<u>H</u>), 3.60 – 3.50 (1H, m, C**1**-<u>H</u>), 3.43 – 3.35 (1H, m, C**1**-<u>H</u>'), 2.47 – 2.32 (5H, m, C**3**-<u>H_2</u>, Ts C<u>H_3</u>), 1.83 – 1.73 (1H, m, C**2**-<u>H</u>), 0.60 – 0.46 (1H, m, C**2**-<u>H</u>'); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.4 (Ts Ar<u>C</u>), 141.8 (Ts Ar<u>C</u>), 130.9 (Ar<u>C</u>H), 130.7 (Ar<u>C</u>H), 129.9 (2 × Ts Ar<u>C</u>H), 128.7 (Ar<u>C</u>H), 128.4 (Ar<u>C</u>), 126.9 (2 × Ts Ar<u>C</u>H), 51.1 (C**4**), 46.9 (C**5**), 46.7 (C**1**), 23.4 (2C, C**2** and C**3**), 21.3 (Ts <u>C</u>H_3); HRMS (ESI$^+$) Calculated for $C_{11}H_{14}N$: 160.1121. Found [M]$^+$: 160.1125.

(*E*)-5-(*p*-Tolyl)pent-4-enoic acid (351a)

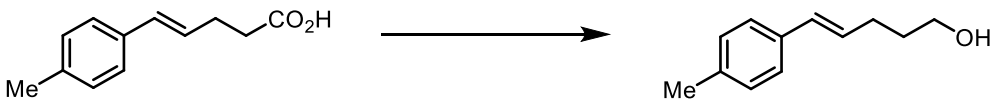


The title compound **351a** was prepared according to a literature procedure.[317]

m.p. 135-137 °C (Et_2O:petroleum ether) [lit: 142-143 (EtOAc:hexane)[317]]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (2H, d, *J* = 8.0 Hz), 7.10 (2H, d, *J* = 8.0 Hz), 6.42 (1H, d, *J* = 16.0 Hz), 6.18 – 6.13 (1H, m), 2.54 (4H, d, *J* = 3.0 Hz), 2.33 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.0, 137.1, 134.6, 131.2, 129.4, 127.1, 126.1, 33.9, 28.1, 21.3.

The spectroscopic properties were consistent with the data available in the literature.[317]

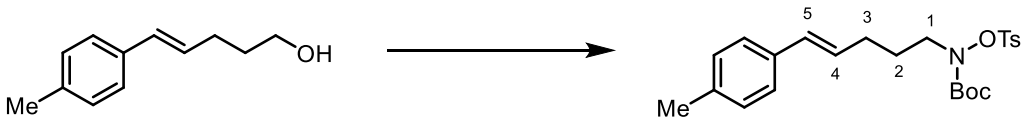
(*E*)-5-(*p*-Tolyl)pent-4-en-1-ol (352a)



General procedure B: The preceding carboxylic acid **351a** (761 mg, 4.0 mmol) and 2.0 equivalents of $LiAlH_4$ (8.0 mmol, 2 M in THF) in anhydrous Et_2O (20 mL) were employed. Purification by flash column chromatography (33% EtOAc:petroleum ether) afforded **352a** (680 mg, 96%) as a colourless solid; m.p. 35-37 °C (EtOAc:petroleum ether) [lit: 42-43 °C (EtOAc:hexane)[322]]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.22 (2H, m), 7.11 (2H, d, *J* = 8.0 Hz), 6.39 (1H, d, *J* = 16.0 Hz), 6.22 – 6.14 (1H, m), 3.70 (2H, t, *J* = 6.5 Hz), 2.34 – 2.27 (5H, m), 1.78 – 1.71 (2H, m), 1.53 (1H, br s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.8, 135.0, 130.4, 129.3, 129.1, 126.0, 62.6, 32.4, 29.4, 21.3.

The spectroscopic properties were consistent with the data available in the literature.[323]

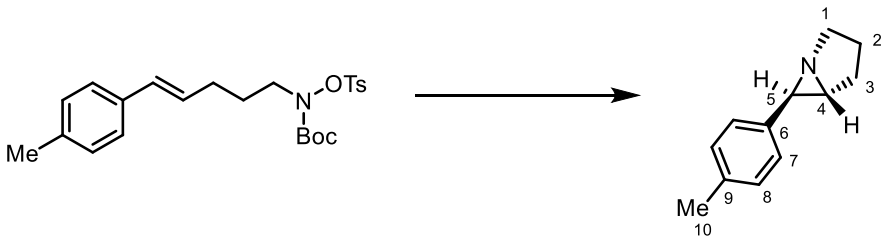
***tert*-Butyl (*E*)-(5-(*p*-tolyl)pent-4-en-1-yl)(tosyloxy)carbamate (353a)**



General procedure G: The preceding alcohol **352a** (352 mg, 2.0 mmol), PPh_3 (629 mg, 2.4 mmol), DIAD (0.47 mL, 2.4 mmol) and BocNHOTs (689 mg, 2.4 mmol) in anhydrous THF (8 mL) were employed. Purification by flash column chromatography (gradient, eluent: 5 – 20% EtOAc:petroleum ether) afforded **353a** (699 mg, 78%) as a viscous, colourless oil; R_f = 0.67 (2:1 hexane:EtOAc); ν_{max} / cm^{-1} (*film*) 3023 (m), 2981 (m), 2932 (m), 1719 (s), 1368 (s), 1191 (s), 1177 (s), 1158 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.32 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.22 (2H, d, *J* = 8.0 Hz, ArC<u>H</u>), 7.10 (2H, d, *J* = 8.0 Hz, ArC<u>H</u>), 6.35 (1H, d, *J* = 16.0 Hz, C**5**-<u>H</u>), 6.09 (1H, dt, *J* = 16.0, 7.0 Hz, C**4**-<u>H</u>), 3.64 (2H, br s, C**1**-<u>H</u>$_2$), 2.43 (3H, s, Ts C<u>H</u>$_3$), 2.32 (3H, s, C<u>H</u>$_3$), 2.21 – 2.14 (2H, m, C**3**-<u>H</u>$_2$), 1.85 – 1.75 (2H, m,

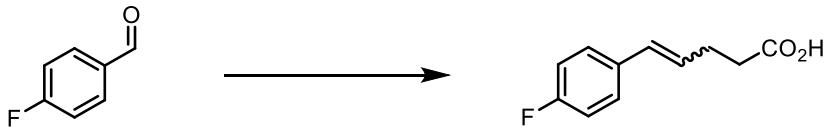
C**2**-H$_2$), 1.23 (9H, s, Boc (CH$_3$)$_3$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 155.6 (Boc C=O), 145.8 (Ts ArC), 136.8 (ArC), 134.9 (ArC), 131.4 (Ts ArC), 130.7 (C**5**), 129.8 (2 × Ts ArCH), 129.7 (2 × Ts ArCH), 129.3 (ArCH), 128.2 (C**4**), 126.0 (ArCH), 83.3 (Boc C(CH$_3$)$_3$), 52.7 (C**1**), 30.1 (C**3**), 27.8 (Boc (CH$_3$)$_3$), 25.7 (C**2**), 21.8 (Ts CH$_3$), 21.3 (CH$_3$); HRMS (ESI$^+$) Calculated for $C_{24}H_{31}NNaO_5S$: 468.1815. Found [M+Na]$^+$: 468.1822.

(5*S,6*S**)-6-(*p*-Tolyl)-1-azabicyclo[3.1.0]hexane (354a)**



General procedure P: The preceding *N*-tosyloxycarbamate **353a** (89.1 mg, 0.20 mmol) and TFA (31 μL, 0.40 mmol) in anhydrous TFE (2.0 mL) were employed. The reaction was stirred at room temperature for 24 hours. Purification by flash column chromatography (~0.1% Et$_3$N in EtOAc) afforded **354a** (21.1 mg, 61%) as a colourless oil; R_f = 0.20 (EtOAc); ν_{max} / cm^{-1} (*film*) 2946 (m), 2871 (m), 1517 (m), 1453 (m), 1078 (m); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.12 – 7.07 (4H, m, C**7** and C**8**), 3.19 (1H, ddd, *J* = 12.0, 8.5, 1.5 Hz, C**1**-H), 3.04 (1H, td, *J* = 12.0, 7.5 Hz, C**1**-H'), 2.42 (1H, dd, *J* = 5.0, 2.5 Hz, C**4**-H), 2.33 (1H, d, *J* = 2.5 Hz, C**5**-H), 2.31 (3H, s, C**10**-H$_3$), 2.23 (1H, dd, *J* = 13.5, 8.5 Hz, C**3**-H), 1.97 (1H, dddd, *J* = 13.5, 11.0, 8.5, 5.0 Hz, C**3**-H'), 1.77 – 1.68 (1H, m, C**2**-H), 1.67 – 1.56 (1H, m, C**2**-H'); ^{13}C NMR (101 MHz, CDCl$_3$) δ 137.3 (C**6**), 136.4 (C**9**), 129.0 (C**8**), 126.0 (C**7**), 53.3 (C**1**), 50.6 (C**4**), 39.6 (C**5**), 26.7 (C**3**), 21.2 (C**10**), 20.8 (C**2**); HRMS (ESI$^+$) Calculated for $C_{12}H_{16}N$: 174.1277. Found [M+H]$^+$: 174.1280.

(*E*)-5-(4-Fluorophenyl)pent-4-enoic acid (351b)



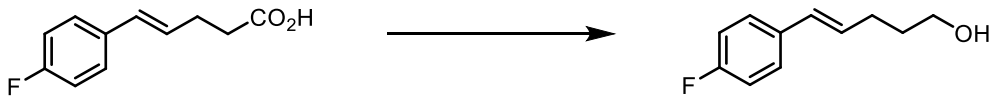
The title compound **351b** was prepared according to a literature procedure.[317]

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.32 – 7.27 (2H, m), 7.01 – 6.95 (2H, m), 6.41 (1H, d, *J* = 16.0 Hz), 6.18 – 6.08 (1H, m), 2.55 – 2.53 (4H, m); ^{13}C NMR (101 MHz, CDCl$_3$) δ 179.0, 162.2 (d,

$^{1}J_{C,F}$ = 246.5 Hz), 133.5 (d, $^{4}J_{C,F}$ = 3.5 Hz), 130.2, 127.8, 127.6 (d, $^{3}J_{C,F}$ = 8.0 Hz), 115.5 (d, $^{2}J_{C,F}$ = 21.5 Hz), 33.8, 28.0.

The spectroscopic properties were consistent with the data available in the literature.[317]

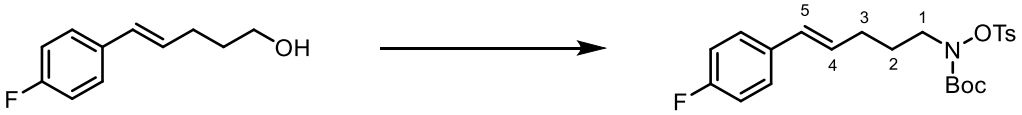
(*E*)-5-(4-Fluorophenyl)pent-4-en-1-ol (352b)



General procedure B: The preceding carboxylic acid **351b** (777 mg, 4.0 mmol) and 2.0 equivalents of. $LiAlH_4$ (8.0 mmol, 2 M in THF) in anhydrous Et_2O (20 mL) were employed. Purification by flash column chromatography (33% EtOAc:petroleum ether) afforded **352b** (396 mg, 55%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.25 (2H, m), 7.00 – 6.93 (2H, m), 6.36 (1H, d, *J* = 16.0 Hz), 6.12 (1H, dt, *J* = 16.0, 7.0 Hz), 3.68 (2H, t, *J* = 7.0 Hz), 2.31 – 2.25 (2H, m), 1.80 (1H, br s), 1.76 – 1.69 (2H, m); ^{13} C NMR (101 MHz, $CDCl_3$) δ 162.0 (d, $^{1}J_{C\text{-}F}$ = 246.0 Hz), 133.8 (d, $^{4}J_{C\text{-}F}$ = 3.0 Hz), 129.9, 129.3, 127.4 (d, $^{3}J_{C\text{-}F}$ = 8.0 Hz), 115.4 (d, $^{2}J_{C\text{-}F}$ = 22.0 Hz), 62.4, 32.3, 29.3; ^{19}F (377 MHz, $CDCl_3$) δ -115.5 (1F, m).

The spectroscopic properties were consistent with the data available in the literature.[322]

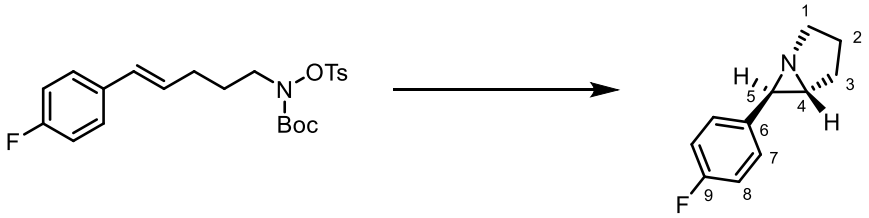
***tert*-Butyl (*E*)-(5-(4-fluorophenyl)pent-4-en-1-yl)(tosyloxy)carbamate (353b)**



General procedure G: The preceding alcohol **352b** (342 mg, 1.89 mmol), PPh_3 (598 mg, 2.28 mmol), DIAD (0.45 mL, 2.28 mmol) and BocNHOTs (655 mg, 2.28 mmol) in anhydrous THF (8 mL) were employed. Purification by flash column chromatography (10% EtOAc:petroleum ether) afforded **353b** (530 mg, 62%) as a colourless solid; R_f = 0.65 (33% EtOAc:hexane); m.p.: 52-54 ^{o}C (Et_2O:petroleum ether); ν_{max} / cm^{-1} (*solid*) 2978 (m), 2940 (m), 2983 (m), 1718 (s), 1507 (s), 1368 (s), 1178 (s), 1155 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.34 – 7.26 (4H, m, Ts ArC<u>H</u>, ArC<u>H</u>), 7.00 – 6.94 (2H, m, ArC<u>H</u>), 6.35 (1H, d, *J* = 16.0 Hz, C**5**-<u>H</u>), 6.06 (1H, dt, *J* = 16.0, 7.0 Hz, C**4**-<u>H</u>), 3.65 (2H, br s, C**1**-<u>H_2</u>), 2.43 (3H, s, Ts C<u>H_3</u>), 2.22 – 2.15 (2H, m, C**3**-<u>H_2</u>), 1.85 – 1.76 (2H, m, C**2**-<u>H_2</u>), 1.22 (9H, s, Boc (C<u>H_3</u>)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.1 (d, $^{1}J_{C\text{-}F}$ = 245.8 Hz, Ar<u>C</u>), 155.6 (Boc <u>C</u>=O), 145.8 (Ts Ar<u>C</u>), 133.8 (d, $^{4}J_{C\text{-}F}$ = 3.4, Ar<u>C</u>), 131.4 (Ts Ar<u>C</u>), 129.8 (2 × Ts Ar<u>C</u>H), 129.7 (C**5**), 129.7 (2

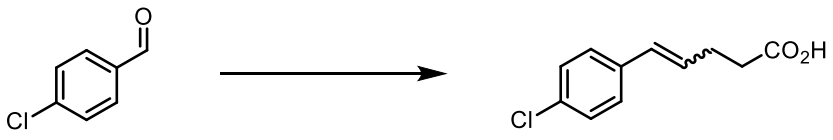
× Ts ArCH), 129.0 (C**4**), 127.6 (d, $^{3}J_{C\text{-}F}$ = 7.9 Hz, ArCH), 115.5 (d, $^{2}J_{C\text{-}F}$ = 21.4 Hz, ArCH), 83.4 (Boc C(CH$_3$)$_3$), 52.6 (C**1**), 30.0 (C**3**), 27.8 (Boc (CH$_3$)$_3$, 25.6 (C**2**), 21.8 (Ts CH$_3$); ^{19}F (377 MHz, CDCl$_3$) δ -115.4; HRMS (ESI$^+$) Calculated for $C_{23}H_{28}FNNaO_5S$: 472.1564. Found [M+Na]: 472.1550.

(5*S,6*S**)-6-(4-Fluorophenyl)-1-azabicyclo[3.1.0]hexane (354b)**



General procedure P: The preceding *N*-tosyloxycarbamate **353b** (89.9 mg, 0.20 mmol) and TFA (31 μL, 0.40 mmol) in anhydrous TFE (2.0 mL) were employed. The reaction was stirred at room temperature for 24 hours. Purification by flash column chromatography (0.1% Et$_3$N in EtOAc) afforded **354b** (23.9 mg, 67%) as a colourless oil; R_f = 0.25 (EtOAc); ν_{max} / cm^{-1} (*film*) 2963 (m), 2874 (m), 1604 (m), 1509 (s), 1226 (s), 1212 (s); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.20 – 7.14 (2H, m, C**7**-H), 6.99 – 6.92 (2H, m, C**8**-H), 3.19 (1H, ddd, *J* = 12.0, 8.5, 1.5 Hz, C**1**-H), 3.03 (1H, td, *J* = 12.0, 7.5 Hz, C**1**-H'), 2.39 (1H, dd, *J* = 5.0, 3.0 Hz, C**4**-H), 2.34 (1H, d, *J* = 3.0 Hz, C**5**-H), 2.23 (1H, dd, *J* = 13.5, 8.5 Hz, C**3**-H), 1.97 (1H, dddd, *J* = 13.5, 11.0, 8.5, 5.0 Hz, C**3**-H'), 1.78 – 1.69 (1H, m, C**2**-H), 1.66 – 1.54 (1H, m, C**2**-H'); ^{13}C NMR (101 MHz, CDCl$_3$) δ 161.8 (d, $^{1}J_{C,F}$ = 244.0 Hz, C**9**), 135.8 (d, $^{4}J_{C,F}$ = 3.0 Hz, C**6**), 127.4 (d, $^{3}J_{C,F}$ = 8.0 Hz, C**7**), 115.0 (d, $^{2}J_{C,F}$ = 21.4 Hz, C**8**), 53.1 (C**1**), 50.5 (C**4**), 39.0 (C**5**), 26.5 (C**3**), 20.7 (C**2**); ^{19}F NMR (377 MHz, CDCl$_3$) δ -116.4; HRMS (ESI$^+$) Calculated for $C_{11}H_{13}FN$: 178.1026. Found [M+H]$^+$: 178.1026.

(*E*)-5-(4-Chlorophenyl)pent-4-enoic acid (351c)

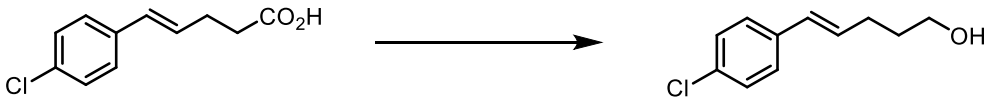


The title compound **351c** was prepared according to a literature procedure.[317]

m.p. 121-124 ºC (Et$_2$O:petroleum ether); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.26 (4H, s), 6.40 (1H, d, *J* = 16.0 Hz), 6.22 – 6.16 (1H, m), 2.56 – 2.52 (4H, m); ^{13}C NMR (101 MHz, CDCl$_3$) δ 178.7, 135.9, 133.0, 130.2, 128.9, 128.8, 127.4, 33.7, 28.0.

The spectroscopic properties were consistent with the data available in the literature.[317]

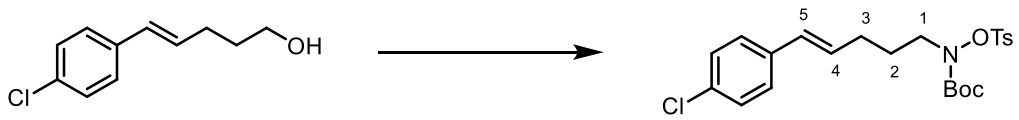
(*E*)-5-(4-Chlorophenyl)pent-4-en-1-ol (352c)



General procedure B: The preceding carboxylic acid **351c** (1.05 g, 5.0 mmol) and 1.1 equivalents of $LiAlH_4$ (5.5 mmol, 2 M in THF) in anhydrous THF (25 mL) were employed. Purification by flash column chromatography (gradient, eluent: 20% – 33% EtOAc:petroleum ether) afforded **352c** (724 mg, 74%) as a colourless solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (4H, s), 6.36 (1H, d, *J* = 16.0 Hz), 6.21 (1H, dt, *J* = 16.0, 7.0 Hz), 3.71 (2H, t, *J* = 6.5 Hz), 2.31 (2H, q, *J* = 7.0 Hz), 1.76 (2H, app. qn, *J* = 6.5 Hz), 1.43 (1H, br s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.3, 132.6, 130.9, 129.4, 128.8, 127.3, 62.5, 32.3, 29.5.

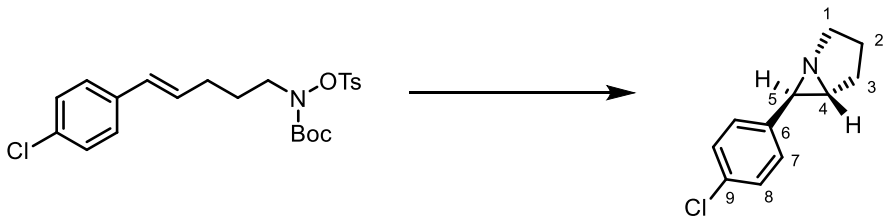
The spectroscopic properties were consistent with the data available in the literature.[324]

***tert*-Butyl (*E*)-(5-(4-chlorophenyl)pent-4-en-1-yl)(tosyloxy)carbamate (353c)**



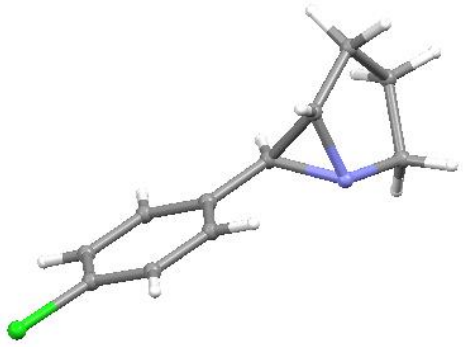
General procedure G: The preceding alcohol **352c** (295 mg, 1.50 mmol), PPh_3 (470 mg, 1.80 mmol), DIAD (0.35 mL, 1.80 mmol) and BocNHOTs (517 mg, 1.80 mmol) in anhydrous THF (6 mL) were employed. Purification by flash column chromatography (10% EtOAc:petroleum ether) afforded **353c** (643 mg, 92%) as a colourless oil; R_f = 0.6 (33% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 2981 (m), 2933 (m), 1718 (s), 1368 (s), 1191 (s), 1177 (s), 1153 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (2H, d, *J* = 8.0 Hz, Ts ArC<u>H</u>), 7.32 (2H, d, *J* = 8.0 Hz, Ts ArC<u>H</u>), 7.24 (4H, s, ArC<u>H</u>), 6.34 (1H, d, *J* = 16.0 Hz, C**5**-<u>H</u>), 6.17 – 6.08 (1H, m, C**4**-<u>H</u>), 3.65 (2H, br s, C**1**-<u>H_2</u>), 2.43 (3H, s, Ts C<u>H_3</u>), 2.23 – 2.15 (2H, m, C**3**-<u>H_2</u>), 1.87 – 1.75 (2H, m, C**2**-<u>H_2</u>), 1.22 (9H, Boc (<u>C</u>H_3)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.5 (Boc <u>C</u>=O), 145.8 (Ts Ar<u>C</u>), 136.1 (Ar<u>C</u>), 132.6 (Ar<u>C</u>), 131.3 (Ts Ar<u>C</u>), 130.0 (C**4**), 129.8 (2 × Ts Ar<u>C</u>H), 129.7 (C**5**) 129.6 (2 × Ts Ar<u>C</u>H), 128.7 (Ar<u>C</u>H), 127.3 (Ar<u>C</u>H), 83.4 (Boc <u>C</u>(CH_3)$_3$), 52.5 (C**1**), 30.0 (C**3**), 27.7 (Boc (<u>C</u>H_3)$_3$), 25.5 (C**2**), 21.8 (Ts <u>C</u>H_3); HRMS (ESI$^+$) Calculated for $C_{23}H_{28}{}^{35}ClNNaO_5S$: 488.1269. Found [M+Na]$^+$: 488.1275.

(5*S,6*S**)-6-(4-Chlorophenyl)-1-azabicyclo[3.1.0]hexane (354c)**



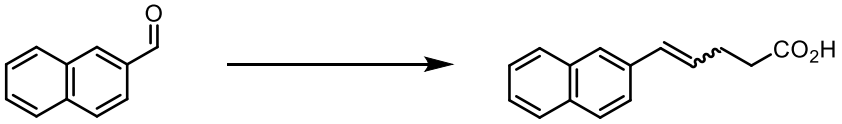
General procedure P: The preceding *N*-tosyloxycarbamate **353c** (93.2 mg, 0.2 mmol) and TFA (31 μL, 0.4 mmol) in anhydrous TFE (2.0 mL) were employed. The reaction time was 24 hours. Purification by flash column chromatography (0.1% Et_3N in EtOAc) afforded **354c** (25.7 mg, 66%) as a colourless solid; R_f = 0.35 (EtOAc); m.p.: 43-45 °C (EtOAc:hexane); ν_{max} / cm^{-1} (*solid*) 2973 (m), 2948 (m), 2922 (m), 2856 (m), 1490 (s), 1190 (m), 785 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 7.24 (2H, d, *J* = 8.5 Hz, C**7**-H), 7.14 (2H, d, *J* = 8.5 Hz, C**8**-H), 3.20 (1H, ddd, *J* = 12.0, 8.5, 1.5 Hz, C**1**-H), 3.04 (1H, td, *J* = 12.0, 7.5 Hz, C**1**-H'), 2.39 (1H, dd, 5.0, 2.5 Hz, C**4**-H), 2.33 (1H, d, *J* = 2.5 Hz, C**5**-H), 2.24 (1H, dd, *J* = 13.5, 8.5 Hz, C**3**-H), 2.03 – 1.93 (1H, m, C**3**-H'), 1.78 – 1.71 (1H, m, C**2**-H), 1.66 – 1.52 (1H, m, C**2**-H'); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.0 (C**6**), 132.4 (C**9**), 128.5 (C**7**), 127.5 (C**8**), 53.3 (C**1**), 51.0 (C**4**), 39.2 (C**5**), 26.7 (C**3**), 20.8 (C**2**); HRMS (ESI^+) Calculated for $C_{11}H_{13}{}^{35}ClN$: 194.0731. Found $[M+H]^+$: 194.0732.

*The structure and relative stereochemistry of **354c** were confirmed by X-ray crystallography after recrystallization (EtOAc:hexane).*



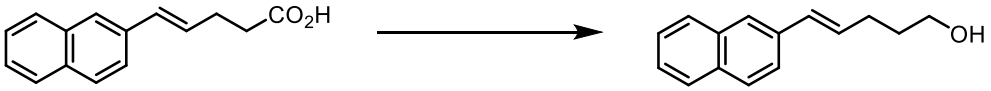
*X-ray crystal structure of **354c**.*

(*E*)-5-(Naphthalen-2-yl)pent-4-enoic acid (351d)



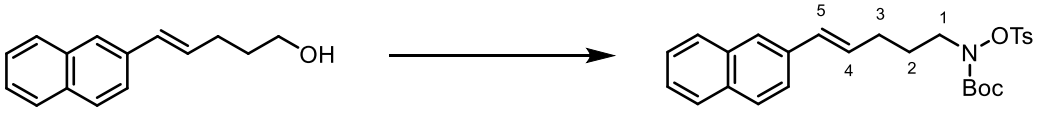
The title compound **351d** was prepared according to a literature procedure.[317]
m.p. 168-170 °C (Et_2O:petroleum ether); [lit: 173-175 °C (MeOH)[325]]; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.15 (1H, br s), 7.88 – 7.82 (3H, m), 7.78 (1H, s), 7.66 – 7.62 (1H, m), 7.51 – 7.42 (2H, m), 6.60 (1H, d, *J* = 16.0 Hz), 6.48 – 6.40 (1H, m), 2.49 - 2.41 (4H, m); ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.8, 134.7, 133.3, 132.3, 130.1, 129.9, 128.0, 127.7, 127.5, 126.3, 125.7, 125.2, 123.5, 33.4, 28.0.
The spectroscopic properties were consistent with the data available in the literature.[317]

(*E*)-5-(Naphthalen-2-yl)pent-4-en-1-ol (352d)



General procedure B: The preceding carboxylic acid **351d** (910 mg, 4.00 mmol) and 2.0 equivalents of $LiAlH_4$ (8.0 mmol, 2M in THF) in anhydrous THF (20 mL) were employed. Purification by flash column chromatography (33% EtOAc:hexane) afforded **352d** (510 mg, 60 %) as a colourless solid; m.p.: 89-91 °C (E_2O:petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 – 7.74 (3H, m), 7.67 (1H, d, *J* = 1.0 Hz), 7.56 (1H, dd, *J* = 8.5, 1.5 Hz), 7.45 – 7.38 (2H, m), 6.58 (1H, d, *J* = 16.0 Hz), 6.36 (1H, dt, *J* = 16.0, 7.0 Hz), 3.72 (2H, t, *J* = 6.5 Hz), 2.40 – 2.34 (2H, m), 1.83 – 1.76 (2H, m), 1.49 (1H, br s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.2, 133.8. 132.8, 130.6, 128.2, 127.9, 127.7, 126.3, 125.6, 124.5, 123.7, 62.6, 32.4, 29.6.
The spectroscopic properties were consistent with the data available in the literature.[322]

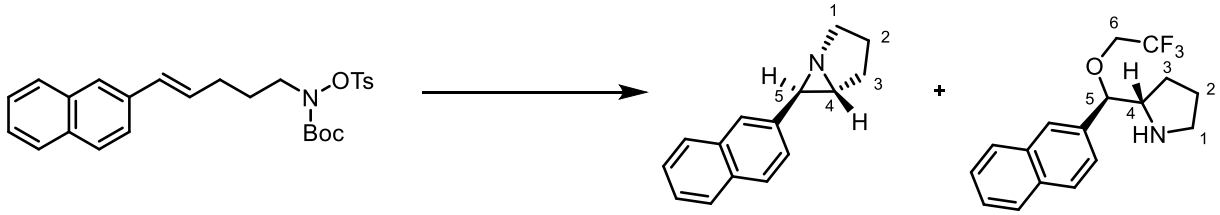
***tert*-Butyl (*E*)-(5-(naphthalen-2-yl)pent-4-en-1-yl)(tosyloxy)carbamate (353d)**



General procedure G: The preceding alcohol **352d** (320 mg, 1.50 mmol), PPh_3 (470 mg, 1.80 mmol), DIAD (0.35 mL, 1.80 mmol) and BocNHOTs (517 mg, 1.80 mmol) in anhydrous THF (6 mL) were employed. Purification by flash column chromatography (10% EtOAc:petroleum ether) afforded **353d** (640 mg, 88%) as a colourless solid; R_f = 0.75 (33% EtOAc:hexane);

m.p.: 67-69 °C (CH_2Cl_2:hexane); ν_{max} / cm^{-1} (*solid*) 2982 (m), 2954 (m), 2932 (m), 1711 (s), 1383 (s), 1368 (s), 1191 (s), 1178 (s), 1154 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.80 – 7.75 (3H, m, ArC<u>H</u>), 7.68 – 7.66 (1H, m, ArC<u>H</u>), 7.56 (1H, dd, *J* = 8.6, 1.7 Hz, ArC<u>H</u>), 7.47 – 7.39 (2H, m, ArC<u>H</u>), 7.32 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 6.55 (1H, d, *J* = 16.0 Hz, C**5**-<u>H</u>), 6.29 (1H, dt, *J* = 16.0, 7.0 Hz, C**4**-<u>H</u>), 3.67 (2H, br s, C**1**-<u>H_2</u>), 2.42 (3H, s, TsC<u>H_3</u>), 2.29 – 2.22 (2H, m, C**3**-<u>H_2</u>), 1.91 – 1.81 (2H, m, C**2**-<u>H_2</u>), 1.24 (9H, s, Boc (C<u>H_3</u>)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6 (Boc <u>C</u>=O), 145.8 (Ts Ar<u>C</u>), 135.1 (Ar<u>C</u>), 133.8 (Ar<u>C</u>), 132.9 (Ar<u>C</u>), 131.4 (Ts Ar<u>C</u>), 131.0 (C**5**), 129.8 (2 × Ts Ar<u>C</u>H), 129.8 (C**4**), 129.7 (2 × Ts Ar<u>C</u>H), 128.2 (Ar<u>C</u>H), 128.0 (Ar<u>C</u>H), 127.8 (Ar<u>C</u>H), 126.3 (Ar<u>C</u>H), 125.7 (Ar<u>C</u>H), 123.7 (Ar<u>C</u>H), 83.4 (Boc <u>C</u>(CH_3)$_3$), 52.6 (C**1**), 30.2 (C**3**), 27.8 (Boc (<u>C</u>H_3)$_3$), 25.6 (C**2**), 21.8 (Ts <u>C</u>H_3); HRMS (ESI^+) Calculated for $C_{27}H_{31}NNaO_5S$: 504.1815. Found $[M+Na]^+$: 504.1794.

(5*S,6*S**)-6-(Naphthalen-2-yl)-1-azabicyclo[3.1.0]hexane (354d) and (*S**)-2-((*R**)-Naphthalen-2-yl(2,2,2-trifluoroethoxy)methyl)pyrrolidine (355)**



354d **355**

<u>General procedure P:</u> The preceding *N*-tosyloxycarbamate **353d** (96.3 mg, 0.20 mmol) and TFA (31 μL, 0.20 mmol) in anhydrous TFE (2.0 mL) were employed. After stirring for 24 hours purification by flash column chromatography (gradient, eluent 0.1% Et_3N in 33% EtOAc:petroleum ether – EtOAc) afforded **354d** (24.6 mg, 58%) as colourless solid; m.p.: 60-62 °C (pentane:EtOAc); R_f = 0.35 (EtOAc) and **355** (12.3 mg, 20%) as a 15:1 mixture of diastereomers and as a yellow oil; R_f = 0.05 (EtOAc).

*Data for compound **354d***: ν_{max} / cm^{-1} (*film*) 2920 (m), 1369 (m), 1191 (m), 1179 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 – 7.76 (3H, m, ArC<u>H</u>), 7.71 – 7.69 (1H, m, ArC<u>H</u>), 7.46 – 7.38 (2H, m, ArC<u>H</u>), 7.34 (1H, dd, *J* = 8.5, 1.5 Hz, ArC<u>H</u>), 3.27 (1H, ddd, *J* = 12.0, 8.5, 1.5 Hz, C**1**-<u>H</u>), 3.11 (1H, td, *J* = 12.0, 7.5 Hz, C**1**-<u>H</u>'), 2.55 – 2.52 (2H, m, C**4**-<u>H</u>, C**5**-<u>H</u>), 2.29 (1H, dd, *J* = 13.5, 8.5 Hz, C**3**-<u>H</u>), 2.08 – 1.98 (1H, m, C**3**-<u>H</u>'), 1.83 – 1.74 (1H, m, C**2**-<u>H</u>), 1.71 – 1.62 (1H, m, C**2**-<u>H</u>'); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.9 (Ar<u>C</u>), 133.5 (Ar<u>C</u>), 132.7 (Ar<u>C</u>), 128.0 (Ar<u>C</u>H), 127.8 (ArC<u>H</u>), 127.7 (Ar<u>C</u>H), 126.1 (Ar<u>C</u>H), 125.4 (Ar<u>C</u>H), 124.7 (Ar<u>C</u>H), 124.6

(ArCH), 53.3 (C**1**), 51.1 (C**4**), 40.0 (C**5**), 26.8 (C**3**), 20.9 (C**2**); HRMS (ESI^+) Calculated for $C_{15}H_{16}N$: 210.1277. Found $[M+H]^+$: 210.1280.

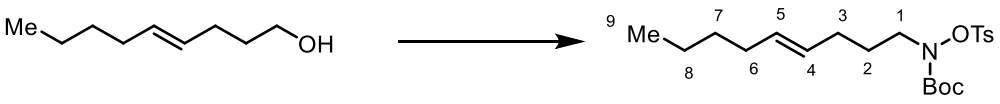
*Data for compound **355***: ν_{max} / cm^{-1} (*film*) 2931 (m), 2873 (m), 1273 (s), 1155 (s), 1121 (s), 1106 (s).

*The spectroscopic properties for the major diastereomer of **355**:* ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 – 7.81 (3H, m, ArCH), 7.75 (1H, d, *J* = 1.6 Hz, ArCH), 7.54 – 7.43 (3H, m, ArCH), 4.38 (1H, d, *J* = 8.2 Hz, C**5**-H), 3.75 – 3.66 (2H, m, C**6**-H_2), 3.45 (1H, app. q, *J* = 7.8 Hz, C**4**-H), 3.15 – 3.09 (1H, m, C**1**-H), 2.96 (1H, td, *J* = 9.1, 7.2 Hz, C**1**-H'), 2.64 (1H, br s, NH), 1.86 – 1.76 (1H, m, C**2**-H), 1.75 – 1.64 (1H, m, C**2**-H'), 1.44 – 1.38 (2H, m, C**3**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.8 (ArC), 133.6 (ArC), 133.2 (ArC), 128.9 (ArCH), 128.1 (ArCH), 127.9 (ArCH), 127.3 (ArCH), 126.6 (ArCH), 126.5 (ArCH), 124.7 (ArCH), 124.2 (q, $^1J_{C\text{-}F}$ = 278.6 Hz), 87.7 (C**5**), 66.0 (q, $^2J_{C\text{-}F}$ = 66 Hz, C**6**), 63.8 (C**4**), 46.1 (C**1**), 27.6 (C**3**), 24.3 (C**2**).

*Characteristic signals for the minor diastereomer of **355**:* ^1H NMR (400 MHz, $CDCl_3$) δ 4.48 (1H, d, *J* = 7.0 Hz).

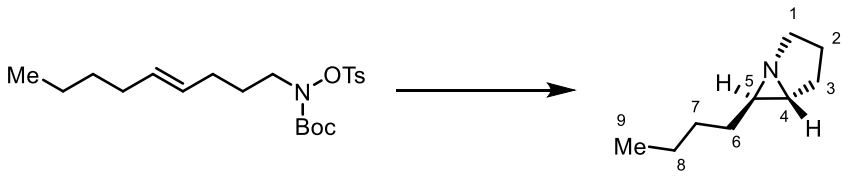
HRMS (ESI^+) Calculated for $C_{17}H_{19}F_3NO$: 310.1413. Found $[M+H]^+$: 310.1416.

tert-Butyl (*E*)-non-4-en-1-yl(tosyloxy)carbamate (357)



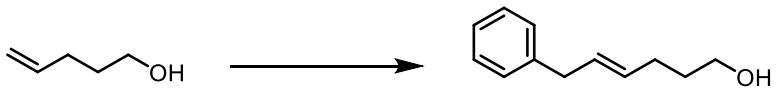
General procedure G: Alcohol **356** (284 mg, 2.0 mmol), PPh_3 (630 mg, 2.4 mmol), DIAD (0.47 mL, 2.4 mmol) and BocNHOTs (690 mg, 2.4 mmol) in anhydrous THF (8 mL) were employed. Purification by flash column chromatography (5% EtOAc:petroleum ether) afforded **357** (694 mg, 84%) as a colourless, viscous oil; R_f = 0.80 (33% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 2956 (m), 2929 (m), 2872 (m), 1720 (s), 1368 (s), 1191 (s), 1178 (s), 1154 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (2H, d, *J* = 8.0 Hz, Ts ArCH), 7.34 (2H, d, *J* = 8.0 Hz, Ts ArCH), 5.45 – 5.29 (2H, m, C**4**-H and C**5**-H), 3.59 (2H, br s, C**1**-H_2), 2.45 (3H, s, Ts CH_3), 2.00 – 1.91 (4H, m, C**3**-H_2 and C**6**-H_2), 1.72 – 1.62 (2H, m, C**2**-H_2), 1.34 – 1.24 (4H, m, C**7**-H_2 and C**8**-H_2), 1.22 (9H, s, Boc $(CH_3)_3$), 0.90 – 0.85 (3H, m, C**9**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6 (Boc C=O), 145.7 (Ts ArC), 131.7 (C**4** or C**5**), 131.4 (Ts ArC), 129.8 (2 × Ts ArCH), 129.6 (2 × Ts ArCH), 128.6 (C**4** or C**5**), 83.2 (Boc $C(CH_3)_3$), 52.8 (C**1**), 32.4 (C**3** or C**6**), 31.8 (C**7**), 29.7 (C**3** or C**6**), 27.8 (Boc $(CH_3)_3$), 25.7 (C**2**), 22.3 (C**8**), 21.8 (Ts CH_3), 14.1 (C**9**); HRMS (ESI^+) Calculated for $C_{21}H_{33}NNaO_5S$: 434.1972. Found $[M+Na]^+$: 434.1696.

(5*S,6*S**)-6-Butyl-1-azabicyclo[3.1.0]hexane (362)**



General procedure P: The preceding *N*-tosyloxycarbamate **357** (87.9 mg, 0.21 mmol) and TFA (31 μL, 0.4 mmol) in anhydrous TFE (2.0 mL) were employed. After stirring for 48 hours at room temperature purification by flash column chromatography (~0.1% Et_3N in EtOAc) afforded **362** (16.1 mg, 55%) as a colourless oil; R_f = 0.1 (EtOAc); ν_{max} / cm^{-1} (*film*) 2926 (m), 2859 (m), 1456 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 2.95 (1H, ddd, *J* = 12.0, 8.5, 1.5 Hz, C**1**-H), 2.85 (1H, td, *J* = 11.5, 7.5 Hz, C**1**-H'), 2.09 (1H, dd, *J* = 5.0, 2.5 Hz, C**4**-H), 2.06 – 1.99 (1H, m, C**3**-H), 1.87 – 1.76 (1H, m, C**3**-H'), 1.64 – 1.55 (1H, m, C**2**-H), 1.49 – 1.26 (8H, m, C**2**-H', C**5**-H, C**6**-H_2, C**7**-H_2, C**8**-H_2), 0.89 (3H, t, *J* = 7.0 Hz, C**9**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 52.8 (C**1**), 46.3 (C**4**), 38.0 (C**5**), 32.2 (C**6**), 29.8 (C**7** or C**8**), 26.1 (C**3**), 22.7 (C**7** or C**8**), 21.3 (C**2**), 14.2 (C**9**); HRMS (ESI^+) Calculated for $C_9H_{18}N$: 140.1433. Found $[M+H]^+$: 140.1435.

(*E*)-6-Phenylhex-4-en-1-ol (358)



The title compound was prepared according to a literature procedure.[52]

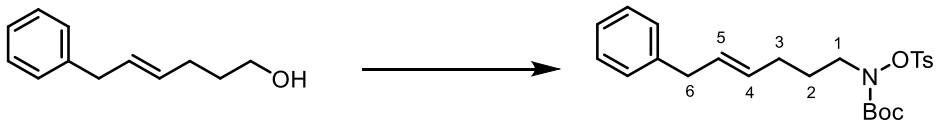
To a solution of Hoveyda-Grubbs 2nd generation catalyst (109 mg, 0.174 mmol) in anhydrous, degassed CH_2Cl_2 (80 mL) was added 4-penten-1-ol (1.2 mL, 11.6 mmol) and allyl benzene (5.8 mL, 44 mmol). The reaction was heated at reflux for 2 days before being concentrated *in vacuo* and purified by flash column chromatography (20% EtOAc:PhMe) to afford **358** (900 mg, 44%, 7:1 mixture of *E* and *Z* isomers) as a light brown oil (the colouration was due to the presence of trace amounts of Ru-impurities).

Spectroscopic data for the major E isomer: ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.28 (2H, m), 7.25 – 7.18 (3H, m), 5.64 (1H, dt, *J* = 15.0, 6.5 Hz), 5.54 (1H, dt, *J* = 15.0, 6.5 Hz), 3.66 (2H, t, *J* = 6.5 Hz), 3.35 (2H, d, *J* = 6.5 Hz), 2.16 – 2.10 (2H, m), 1.71 – 1.63 (2H, m), 1.61 (1H, br s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.9, 131.2, 129.7, 128.6, 128.5, 126.0, 62.5, 39.1, 32.4, 28.9.

Characteristic signals for the minor Z isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.44 (2H, d, *J* = 7.0 Hz), 2.29 – 2.24 (2H, m).

The spectroscopic properties were consistent with the data available in the literature.[52]

tert-Butyl (*E*)-(6-phenylhex-4-en-1-yl)(tosyloxy)carbamate (360)

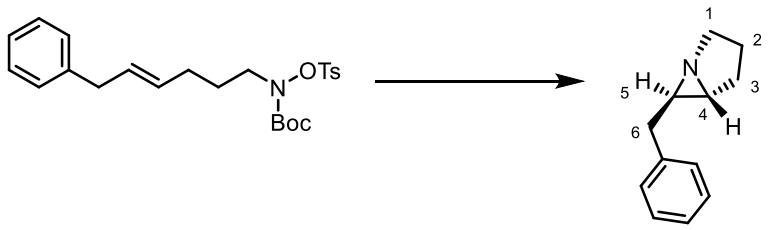


General procedure G: The preceding alcohol **358** (350 mg, 2.0 mmol), PPh_3 (630 mg, 2.4 mmol), DIAD (0.47 mL, 2.4 mmol) and BocNHOTs (690 mg, 2.4 mmol) in anhydrous THF (8 mL) were employed. Purification by flash column chromatography (10% EtOAc:petroleum ether) afforded **360** (524 mg, 60%, 7:1 mixture of *E* and *Z* isomers) as a colourless oil; R_f = 0.70 (33% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 2980 (m), 1719 (s), 1368 (s), 1191 (s), 1178 (s), 1152 (s).

Spectroscopic data for the major E isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.34 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.31 – 7.26 (2H, m, ArC<u>H</u>), 7.21 – 7.15 (3H, m, ArC<u>H</u>), 5.59 (1H, dt, *J* = 15.0, 6.5 Hz, C**5**-<u>H</u>), 5.45 (1H, dt, *J* = 15.0, 6.5 Hz, C**4**-<u>H</u>), 3.62 (2H, br s, C**1**-<u>H_2</u>), 3.32 (2H, d, *J* = 6.5 Hz, C**6**-<u>H_2</u>), 2.45 (3H, s, Ts C<u>H_3</u>), 2.03 – 1.98 (2H, m, C**3**-<u>H_2</u>), 1.78 – 1.66 (2H, m, C**2**-<u>H_2</u>), 1.22 (9H, s, Boc (C<u>H_3</u>)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6 (Boc <u>C</u>=O), 145.8 (Ts Ar<u>C</u>), 140.9 (Ar<u>C</u>), 131.4 (Ts Ar<u>C</u>), 130.4 (C**4**), 130.0 (C**5**), 129.8 (2 × Ts Ar<u>C</u>H), 129.6 (2 × Ts Ar<u>C</u>H), 128.6 (Ar<u>C</u>H), 128.5 (Ar<u>C</u>H), 126.1 (Ar<u>C</u>H), 83.3 (Boc <u>C</u>(CH$_3$)$_3$), 52.7 (C**1**), 39.1 (C**6**), 29.6 (C**3**), 27.8 (Boc (<u>C</u>H$_3$)$_3$), 25.7 (C**2**), 21.8 (Ts <u>C</u>H$_3$).

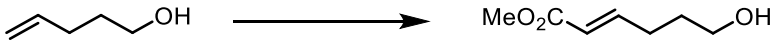
Characteristic signals for the minor Z isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.37 (2H, d, *J* = 7.0 Hz), 2.13 (2H, q, *J* = 7.0 Hz); HRMS (ESI^+) Calculated for $C_{24}H_{31}NNaO_5S$: 468.1815. Found $[M+Na]^+$: 468.1812.

(5*S,6*S**)-6-Benzyl-1-azabicyclo[3.1.0]hexane (363)**



General procedure P: The preceding *N*-tosyloxycarbamate **360** (89.11 mg, 0.20 mmol) and TFA (31 μL, 0.40 mmol) in anhydrous TFE (2.0 mL) were employed. After stirring for 24 hours, purification by flash column chromatography (~0.1% Et_3N in EtOAc) afforded **363** (21.6 mg, 62%) as a pale-yellow oil; R_f = 0.10 (EtOAc); ν_{max} / cm^{-1} (*film*) 3025 (m), 2937 (m), 2871 (m), 1494 (m), 1453 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.18 (5H, m, ArC<u>H</u>), 3.00 (1H, ddd, *J* = 12.0, 8.5, 1.5 Hz, C**1**-<u>H</u>), 2.89 (1H, td, *J* = 11.5, 7.5 Hz, C**1**-<u>H</u>'), 2.77 (1H, dd, *J* = 14.5, 6.5 Hz, C**6**-<u>H</u>), 2.57 (1H, dd, *J* = 14.5, 6.0 Hz, C**6**-<u>H</u>'), 2.28 (1H, dd, *J* = 5.0, 3.0 Hz, C**4**-<u>H</u>), 2.06 (1H, dd, *J* = 13.0, 8.5 Hz, C**3**-<u>H</u>), 1.91 – 1.80 (1H, m, C**3**-<u>H</u>'), 1.66 – 1.57 (2H, m, C**5**-<u>H</u>, C**2**-<u>H</u>), 1.47 – 1.37 (1H, m, C**2**-<u>H</u>'); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.1 (Ar<u>C</u>), 128.7 (Ar<u>C</u>H), 128.5 (Ar<u>C</u>H), 126.3 (Ar<u>C</u>H), 52.7 (C**1**), 46.3 (C**4**), 38.8 (C**6**), 38.7 (C**5**), 26.1 (C**3**), 21.2 (C**2**); HRMS (ESI^+) Calculated for $C_{12}H_{15}NNa$: 196.1097. Found $[M+Na]^+$: 196.1101.

Methyl (*E*)-6-hydroxyhex-2-enoate (359)

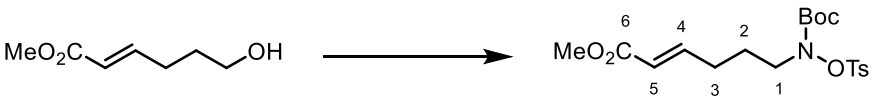


The title compound was prepared according to a literature procedure.[52]

To a solution of Hoveyda-Grubbs 2nd generation catalyst (15.7 mg, 25.0 μmol) in anhydrous, degassed CH_2Cl_2 (40 mL) was added methyl acrylate (2.25 mL, 25.0 mmol) and pent-4-en-1-ol (0.26 mL, 2.5 mmol). The reaction was heated at reflux overnight and then concentrated *in vacuo*. Purification by flash column chromatography (33% EtOAc:hexane) afforded **359** (349 mg, 97%) as a light brown oil (the colouration was due to the presence of trace amounts of Ru-impurities); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (1H, dt, *J* = 15.5, 7.0 Hz), 5.84 (1H, dt, *J* = 15.5, 1.5 Hz), 3.70 (3H, s), 3.65 (2H, t, *J* = 6.5 Hz), 2.32 – 2.26 (2H, m), 1.83 (1H, br s), 1.75 – 1.66 (2H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 148.9, 121.4, 62.0, 51.6, 31.0, 28.6.

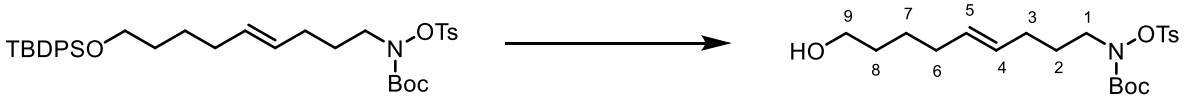
The spectroscopic properties were consistent with the data available in the literature.[52]

Methyl (*E*)-6-((*tert*-butoxycarbonyl)(tosyloxy)amino)hex-2-enoate (361)



General procedure G: The preceding alcohol **359** (288 mg, 2.0 mmol), PPh_3 (629 mg, 2.4 mmol), DIAD (0.47 mL, 2.4 mmol) and BocNHOTs (689 mg, 2.4 mmol) in anhydrous THF (8 mL) were employed. Purification by flash column chromatography (9:1 petroleum ether:EtOAc) afforded **361** (755 mg, 91%) as a colourless solid; R_f = 0.60 (33% EtOAc:hexane); m.p.: 45-47 °C (CH_2Cl_2:hexane); ν_{max} / cm^{-1} (*solid*) 2981 (m), 2953 (m), 2934 (m), 1717 (s), 1175 (s), 1159 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (2H, d, *J* = 8.5 Hz, Ts ArC**H**), 7.34 (2H, d, *J* = 8.5 Hz, Ts ArC**H**), 6.91 (1H, dt, *J* = 15.5, 7.0 Hz, C**4**-**H**), 5.83 (1H, dt, *J* = 15.5, 1.5 Hz, C**5**-**H**), 3.72 (3H, s, OCH_3), 3.62 (2H, br s, C**1**-H_2), 2.45 (3H, s, Ts CH_3), 2.23 – 2.15 (2H, m, C**3**-H_2), 1.84 – 1.74 (2H, m, C**2**-H_2), 1.22 (9H, s, Boc (CCH_3)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0 (C**6**), 155.5 (Boc C=O), 147.8 (C**4**), 145.9 (Ts ArC), 131.3 (Ts ArC), 129.8 (2 × Ts ArCH), 129.7 (2 × Ts ArCH), 121.8 (C**5**), 83.6 (Boc C(CH$_3$)$_3$), 52.4 (C**1**), 51.6 (OCH$_3$), 29.3 (C**3**), 27.7 (Boc (CH$_3$)$_3$), 24.5 (C**2**), 21.9 (Ts CH$_3$); HRMS (ESI^+) Calculated for $C_{19}H_{27}NNaO_7S$: 436.1400. Found $[M+Na]^+$: 436.1417.

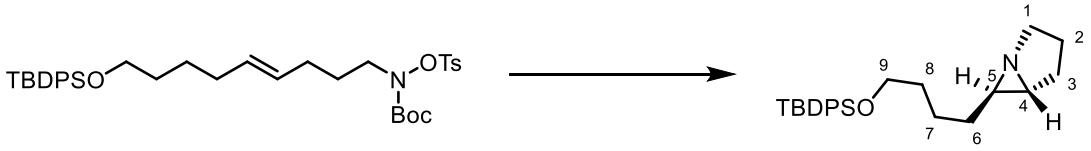
***tert*-Butyl (*E*)-(9-hydroxynon-4-en-1-yl)(tosyloxy)carbamate (366)**



To a solution of TBDPS-protected alcohol **365** (133 mg, 0.20 mmol) in THF (2.0 mL) at 0 °C was added 1.0 equivalent of TBAF (1 M in THF, 0.20 mmol) dropwise. The reaction was warmed to room temperature and stirred overnight until completion. The reaction mixture was quenched with water (5 mL), extracted with EtOAc (2 × 5 mL), washed with saturated aqueous $NaHCO_3$ (5 mL) and brine (5 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography (33% EtOAc:hexane) afforded **366** (65.8 mg, 77%) as a colourless viscous oil; R_f = 0.01 (20% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 3392 (br m), 2983 (m), 2931 (m), 2860 (m), 1723 (s), 1368 (s), 1191 (s), 1178 (s), 1153 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (2H, d, *J* = 8.5 Hz, Ts ArC**H**), 7.34 (2H, d, *J* = 8.5 Hz, Ts ArC**H**), 5.45 – 5.32 (2H, m, C**4**-**H** and C**5**-**H**), 3.72 – 3.52 (4H, m, C**1**-H_2 and C**9**-H_2), 2.45 (3H, s, Ts CH_3), 2.04 – 1.94 (4H, m, C**3**-H_2 and C**6**-H_2), 1.74 – 1.64 (2H, m, C**2**-H_2), 1.60 – 1.53 (2H, m, C**8**-H_2), 1.45 – 1.36 (2H, m, C**7**-H_2), 1.21 (9H, s, Boc (CH_3)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ

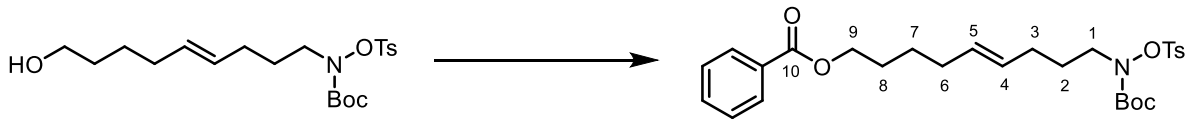
155.6 (Boc C=O), 145.8 (Ts ArC), 131.4 (Ts ArC), 131.2 (C**5**), 129.8 (2 × Ts ArCH), 129.6 (2 × Ts ArCH), 129.2 (C**4**), 83.3 (Boc $C(CH_3)_3$), 63.0 (C**9**), 52.6 (C**1**), 32.3 (C**6**), 32.3 (C**8**), 29.6 (C**3**), 27.7 (Boc $C(CH_3)_3$), 25.6 (C**7**), 25.6 (C**2**) 21.8 (Ts CH_3); HRMS (ESI^+) Calculated for $C_{21}H_{33}NNaO_6S$: 450.1921. Found $[M+Na]^+$: 450.1919.

(5*S,6*S**)-6-(4-((*tert*-Butyldiphenylsilyl)oxy)butyl)-1-azabicyclo[3.1.0]hexane (369)**



General procedure P: TBDPS-Protected alcohol **365** (66.6 mg, 0.10 mmol) and TFA (23 μL, 0.30 mmol) in TFE (1.0 mL) were employed. After stirring for 70 hours at room temperature purification by flash column chromatography (~0.1% Et_3N in EtOAc) afforded **369** (9.4 mg, 24%) as a yellow oil; R_f = 0.01 (EtOAc); ν_{max} / cm^{-1} (*film*) 2938 (m), 2864 (m), 1681 (m), 1426 (m), 1108 (s), 1091 (s), 907 (s), 729 (s), 700 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 – 7.65 (4H, m, ArCH), 7.43 – 7.35 (6H, m, ArCH), 3.66 (2H, t, *J* = 6.5 Hz, C**9**-H_2), 2.99 – 2.84 (2H, m, C**1**-H_2), 2.16 – 2.11 (1H, m, C**4**-H), 2.06 – 2.00 (1H, m, C**3**-H'), 1.88 – 1.78 (1H, m, C**3**-H'), 1.66 – 1.55 (3H, m, C**2**-H, C**8**-H_2), 1.48 – 1.39 (3H, m, C**2**-H', C**7**-H_2), 1.36 – 1.25 (3H, m, C**5**-H, C**6**-H_2), 1.04 (9H, s, $SiC(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.7 (ArCH), 134.3 (ArC), 129.6 (ArCH), 127.7 (ArCH), 64.1 (C**9**), 52.5 (C**1**), 46.4 (C**4**), 38.2 (C**5**), 32.6 (C**8**), 32.1 (C**6**), 27.0 ($SiC(CH_3)_3$), 26.0 (C**3**), 23.8 (C**7**), 21.2 (C**2**), 19.4 (SiC); HRMS (ESI^+) Calculated for $C_{25}H_{36}NOSi$: 394.2560. Found $[M+H]^+$: 394.2576.

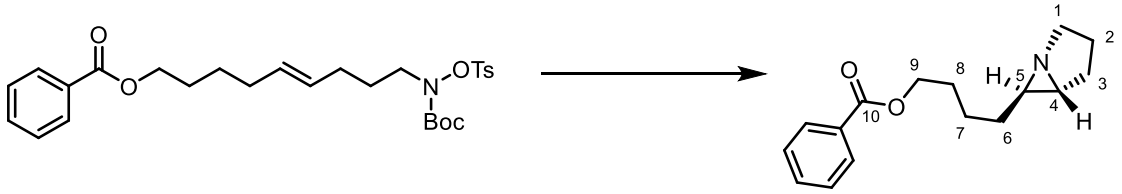
(*E*)-9-((*tert*-Butoxycarbonyl)(tosyloxy)amino)non-5-en-1-yl benzoate (367)



To a solution of alcohol **366** (70.5 mg, 0.165 mmol) and pyridine (29 μL, 0.36 mmol) in anhydrous CH_2Cl_2 (1.0 mL) at 0 °C was added benzoyl chloride (17 μL, 0.15 mmol). The reaction stirred at room temperature for 2 hours and quenched with H_2O (1 mL). The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organic extracts were washed with saturated aqueous NH_4Cl (1 mL), saturated aqueous $NaHCO_3$ (1 mL) and brine (1 mL), filtered and concentrated *in vacuo*. Purification by flash column chromatography (gradient, eluent: 10

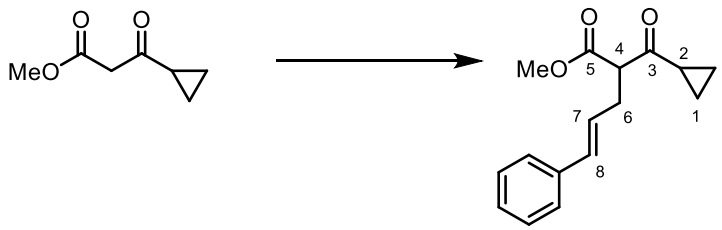
– 20% EtOAc:hexane) afforded **367** (51.0 mg, 58%) as a colourless oil; R_f = 0.45 (33% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 2929 (m), 2852 (m), 1719 (s), 1382 (m), 1369 (m), 1274 (s), 1191 (s), 1179 (s), 713 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 – 8.02 (2H, m, ArC<u>H</u>), 7.85 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.57 – 7.52 (1H, m, ArC<u>H</u>), 7.46 – 7.41 (2H, m, ArC<u>H</u>), 7.34 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 5.47 – 5.34 (2H, m, C**4**-<u>H</u> and C**5**-<u>H</u>), 4.31 (2H, t, *J* = 6.5 Hz, C**9**-<u>H_2</u>), 3.61 (2H, br s, C**1**-<u>H_2</u>), 2.44 (3H, s, Ts C<u>H_3</u>), 2.08 – 2.03 (2H, m, C**6**-<u>H_2</u>), 1.99 – 1.94 (2H, m, C**3**-<u>H_2</u>), 1.80 – 1.64 (4H, m, C**8**-<u>H_2</u>, C**2**-<u>H_2</u>), 1.54 – 1.47 (2H, m, C**7**-<u>H_2</u>), 1.20 (9H, s, Boc (C<u>H_3</u>)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8 (C**10**), 155.5 (Boc <u>C</u>=O), 145.7 (Ts Ar<u>C</u>), 132.9 (Ar<u>C</u>H), 131.4 (Ts Ar<u>C</u>), 130.9 (C**5**), 130.6 (Ar<u>C</u>), 129.8 (2 × Ts Ar<u>C</u>H), 129.7 (Ar<u>C</u>H), 129.6 (2 × Ts Ar<u>C</u>H), 129.4 (C**4**), 128.4 (Ar<u>C</u>H), 83.2 (Boc <u>C</u>(CH_3)$_3$), 65.1 (C**9**), 52.7 (C**1**), 32.2 (C**6**), 29.6 (C**3**), 28.3 (C**8**), 27.7 (Boc (<u>C</u>H_3)$_3$), 26.0 (C**7**), 25.7 (C**2**), 21.8 (Ts <u>C</u>H_3); HRMS (ESI^+) Calculated for $C_{28}H_{37}NNaO_7S$: 554.2183. Found $[M+Na]^+$: 554.2185.

4-((5*S,6*S**)-1-Azabicyclo[3.1.0]hexan-6-yl)butyl benzoate (370)**



<u>General procedure P:</u> The preceding *N*-tosyloxycarbamate **367** (48.8 mg, 0.092 mmol), and TFA (14 μL, 0.184 mmol) in anhydrous TFE (0.1 M) were employed. After stirring for 44 hours purification by flash column chromatography (eluent: ~0.1% Et_3N in EtOAc) afforded **370** (18.5 mg, 78%) as a pale-yellow oil; R_f = 0.01 (EtOAc); ν_{max} / cm^{-1} (*film*) 2936 (m), 2870 (m), 1715 (s), 1451 (m), 1270 (s), 1110 (s), 710 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 – 8.02 (2H, m, ArC<u>H</u>), 7.57 – 7.52 (1H, m, ArC<u>H</u>), 7.46 – 7.41 (2H, m, ArC<u>H</u>), 4.32 (2H, t, *J* = 6.5 Hz, C**9**-<u>H_2</u>), 2.97 (1H, ddd, *J* = 12.0, 8.5, 1.5 Hz, C**1**-<u>H</u>), 2.86 (1H, td, *J* = 11.5, 7.5 Hz, C**1**-<u>H</u>'), 2.11 (1H, dd, *J* = 5.0, 3.0 Hz, C**4**-<u>H</u>), 2.04 (1H, dd, *J* = 13.0, 8.5 Hz, C**3**-<u>H</u>), 1.87 – 1.76 (3H, m, C**3**-<u>H</u>', C**8**-<u>H_2</u>), 1.64 – 1.38 (6H, m, C**2**-<u>H_2</u>, C**6**-<u>H_2</u>, C**7**-<u>H_2</u>), 1.35 – 1.30 (1H, m, C**5**-<u>H</u>); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8 (C**10**), 132.9 (Ar<u>C</u>H), 130.6 (Ar<u>C</u>), 129.7 (Ar<u>C</u>H), 128.5 (Ar<u>C</u>H), 65.2 (C**9**), 52.8 (C**1**), 46.2 (C**4**), 37.7 (C**5**), 32.2 (C**6**), 28.8 (C**8**), 26.1 (C**3**), 24.2 (C**7**), 21.2 (C**2**); HRMS (ESI^+) Calculated for $C_{16}H_{22}NO_2$: 260.1645. Found $[M+H]^+$: 260.1657.

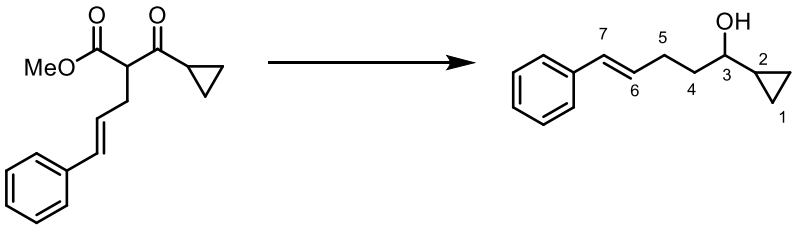
Methyl (*E*)-2-(cyclopropanecarbonyl)-5-phenylpent-4-enoate (372)



The title compound was prepared following a literature procedure.[52]

β-Ketoester **371** (1.70 g, 12.0 mmol) was added dropwise to a suspension of NaH (60% weight in mineral oil, 480 mg, 12.0 mmol) in anhydrous DMF (23 mL). The reaction mixture was stirred at room temperature for 1 hour before addition of 3-bromo-1-phenyl-1-propene (1.57 g, 8.0 mmol) and heated at 80 ^{o}C overnight. The reaction mixture was cooled to room temperature before addition of saturated aqueous NH_4Cl (30 mL) and extraction with Et_2O (3 × 30 mL). The organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (gradient, eluent: 5 – 7% EtOAc:hexane) to afford **372** (1.39, 67%) as a pale yellow oil; R_f = 0.30 (20% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 3025 (m), 2952 (m), 1738 (s), 1698 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.23 (4H, m, ArC<u>H</u>), 7.20 – 7.16 (1H, ArC<u>H</u>), 6.44 (1H, d, *J* = 16.0 Hz, C**8**-<u>H</u>), 6.10 (1H, ddd, *J* = 16.0, 7.5, 6.5 Hz, C**7**-<u>H</u>), 3.76 – 3.70 (4H, m, C**4**-<u>H</u>, OC<u>H</u>$_3$), 2.79 – 2.74 (2H, m, C**6**-<u>H</u>$_2$), 2.09 – 2.03 (1H, m, C**2**-<u>H</u>), 1.11 – 1.03 (2H, m, C**1**-<u>H</u>$_2$), 0.96 – 0.87 (2H, m, C**1**'-<u>H</u>$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.6 (C**3**), 169.9 (C**5**), 137.2 (Ar<u>C</u>), 132.7 (C**8**), 128.6 (Ar<u>C</u>H), 127.4 (Ar<u>C</u>H), 126.3 (Ar<u>C</u>H), 126.0 (C**7**), 59.7 (C**4**), 52.6 (O<u>C</u>H$_3$), 31.8 (C**6**), 20.2 (C**2**), 12.0 (C**1**), 11.9 (C**1**'); HRMS (ESI$^+$) Calculated for $C_{16}H_{18}NaO_3$: 281.1148. Found [M+Na]$^+$: 281.1156.

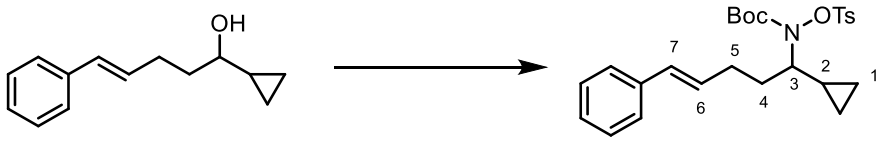
(*E*)-1-Cyclopropyl-5-phenylpent-4-en-1-ol (374)



To a solution of the preceding β-ketoester **372** (1.03 g, 4.0 mmol), in MeOH:water (5:3, 16 mL) was added KOH (898 mg, 16.0 mmol). The reaction mixture was stirred at room temperature for 45 minutes before addition of 2 M HCl (11 mL) and extraction with Et_2O (3 × 30 mL). The organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The crude

mixture was dissolved in EtOAc (13 mL) and heated to reflux for 4 hours before being concentrated *in vacuo*. The resulting oil was dissolved in MeOH (10 mL) and cooled to 0 °C before addition of $NaBH_4$ (151 mg, 4.0 mmol). The reaction mixture was stirred at this temperature for 90 minutes before addition of 1 M HCl (20 mL) and extraction with Et_2O (3 × 30 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash column chromatography (20% EtOAc:petroleum ether) afforded **374** (508 mg, 63%) as a colourless oil; R_f = 0.40 (20% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 3387 (br m), 3001 (m), 2930 (m), 1447 (m), 963 (s), 692 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.26 (4H, m, ArC<u>H</u>), 7.21 – 7.18 (1H, m, ArC<u>H</u>), 6.43 (1H, d, *J* = 16.0 Hz, C**7**-<u>H</u>), 6.25 (1H, dt, *J* = 16.0, 7.0 Hz, C**6**-<u>H</u>), 2.93 (1H, dt, *J* = 8.5, 6.0 Hz, C**3**-<u>H</u>), 2.46 – 2.30 (2H, m, C**5**-<u>H_2</u>), 1.83 – 1.77 (2H, m, C**4**-<u>H_2</u>), 1.62 (1H, br s, O<u>H</u>), 0.98 – 0.89 (1H, m, C**2**-<u>H</u>), 0.59 – 0.48 (2H, m, C**1**-<u>H_2</u>), 0.32 – 0.21 (2H, m, C**1**'-<u>H_2</u>); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.8 (Ar<u>C</u>), 130.6 (C**6**), 130.2 (C**7**), 128.6 (Ar<u>C</u>H), 127.0 (Ar<u>C</u>H), 126.0 (Ar<u>C</u>H), 76.4 (C**3**), 36.8 (C**4**), 29.4 (C**5**), 18.1 (C**2**), 2.9 (C**1**), 2.7 (C**1**'); HRMS (ESI^+) Calculated for $C_{14}H_{18}NaO$: 225.1250. Found $[M+Na]^+$: 225.1247.

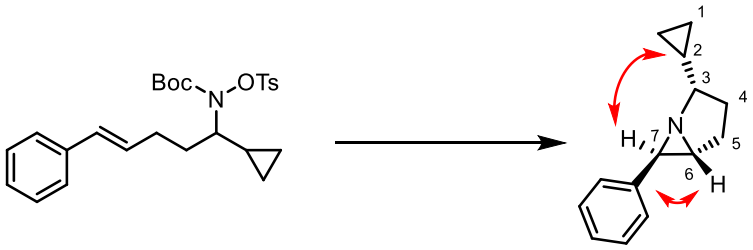
***tert*-Butyl (*E*)-(1-cyclopropyl-5-phenylpent-4-en-1-yl)(tosyloxy)carbamate (375)**



<u>General procedure G:</u> The preceding alcohol **374** (303 mg, 1.50 mmol), PPh_3 (472 mg, 1.80 mmol), DIAD (0.35 mL, 1.80 mmol) and BocNHOTs (517 mg, 1.80 mmol) in anhydrous THF (6.0 mL) were employed. Purification by flash column chromatography (gradient, eluent: 2 – 5% EtOAc:hexane) afforded **375** (231 mg, 33%) as a colourless, viscous oil; R_f = 0.65 (20% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 2980 (m) 1721 (s), 1369 (s), 1191 (s), 1178 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.34 – 7.25 (6H, m, Ts ArC<u>H</u>, ArC<u>H</u>), 7.20 – 7.15 (1H, m, ArC<u>H</u>), 6.38 (1H, d, *J* = 16.0 Hz, C**7**-<u>H</u>), 6.18 (1H, dt, *J* = 16.0, 7.0 Hz, C**6**-<u>H</u>), 3.15 – 3.08 (1H, m, C**3**-<u>H</u>), 2.42 (3H, s, Ts C<u>H_3</u>), 2.36 – 2.29 (2H, m, C**5**-<u>H_2</u>), 2.10 – 1.99 (1H, m, C**4**-<u>H</u>), 1.88 – 1.76 (1H, m, C**4**-<u>H</u>'), 1.25 (9H, s, Boc C(C<u>H_3</u>)$_3$), 1.17 – 1.09 (1H, m, C**2**-<u>H</u>), 0.63 – 0.55 (1H, m, C**1**-<u>H</u>), 0.50 – 0.40 (2H, m, C**1**-<u>H_2</u>, C**1**'-<u>H_2</u>), 0.25 – 0.18 (1H, m, C**1**-<u>H</u>'); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.6 (Boc <u>C</u>=O), 145.6 (Ts Ar<u>C</u>), 137.9 (Ar<u>C</u>), 131.9 (Ts Ar<u>C</u>), 130.5 (C**7**), 130.1 (C**6**), 129.8 (2 × Ts Ar<u>C</u>H), 129.6 (2 × Ts Ar<u>C</u>H), 128.6 (Ar<u>C</u>H) 127.0 (Ar<u>C</u>H), 126.1 (Ar<u>C</u>H), 83.4 (Boc <u>C</u>(CH_3)$_3$), 70.9 (C**3**), 32.8 (C**4**) 30.3 (C**5**),

27.8 (Boc C(<u>C</u>H$_3$)$_3$), 21.8 (Ts <u>C</u>H$_3$), 14.0 (C**2**), 5.3 (C**1**), 3.4 (C**1**'); HRMS (ESI$^+$) Calculated for $C_{26}H_{33}NNaO_5S$: 494.1972. Found $[M+Na]^+$: 494.1985.

(2*S,5*R**,6*R**)-2-Cyclopropyl-6-phenyl-1-azabicyclo[3.1.0]hexane (376)**

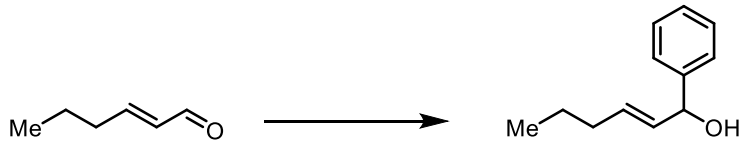


>20:1 d.r.

<u>General procedure P:</u> The preceding *N*-tosyloxycarbamate **375** (47.9 mg, 0.10 mmol) and TFA (15 μL, 0.2 mmol) in anhydrous TFE (1.0 mL) were employed. After stirring at room temperature for 72 hours, purification by flash column chromatography (~0.1% Et_3N in 33% EtOAc:pentane) afforded **376** (11.4 mg, 57%) as a >20:1 mixture of diastereomers and as a pale-yellow oil; R_f = 0.20 (20% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 3002 (m), 2955 (m), 2879 (m), 1453 (m), 1087 (m), 740 (s), 697 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.18 (5H, m, ArC<u>H</u>), 2.75 – 2.69 (1H, m, C**3**-<u>H</u>), 2.61 (1H, d, *J* = 2.5 Hz, C**7**-<u>H</u>), 2.42 (1H, dd, *J* = 5.0, 2.5 Hz, C**6**-<u>H</u>), 2.23 (1H, dd, *J* = 13.5, 8.0 Hz, C**5**-<u>H</u>), 2.03 – 1.98 (1H, m, C**5**-<u>H</u>'), 1.74 (1H, ddd, *J* = 13.5, 8.5, 7.0 Hz, C**4**-<u>H</u>), 1.38 (1H, dtd, *J* = 13.5, 11.0, 8.0 Hz, C**4**-<u>H</u>'), 0.88 – 0.78 (1H, m, C**2**-<u>H</u>), 0.51 – 0.41 (3H, m, 2 × C**1**-<u>H</u>, 1 × C**1**'-<u>H</u>), 0.22 – 0.14 (1H, m, C**1**'-<u>H</u>'); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.6 (Ar<u>C</u>), 128.3 (Ar<u>C</u>H), 126.8 (Ar<u>C</u>H), 126.6 (Ar<u>C</u>H), 69.4 (C**3**), 49.7 (C**6**), 36.2 (C**7**), 27.2 (C**5**), 26.1 (C**4**), 13.0 (C**2**), 4.1 (C**1**), 2.8 (C**1**'); HRMS (ESI$^+$) Calculated for $C_{14}H_{18}N$: 200.1433. Found $[M+H]^+$: 200.1441.

*The relative stereochemistry was assigned by nOe experiments as indicated on the compound structure. nOe correlations were observed between C**6**-<u>H</u> and ArC<u>H</u> and between C**7**-<u>H</u> and C**2**-<u>H</u>. No nOe correlation was observed between C**7**-<u>H</u> and C**3**-<u>H</u>.*

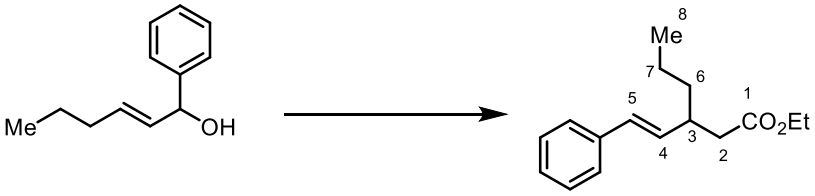
(*E*)-1-Phenylhex-2-en-1-ol (378)



To a solution of α,β-unsaturated aldehyde **377** (2.3 mL, 20.0 mmol) in anhydrous THF (40 mL) at – 78 °C was added PhMgCl (2M in THF, 16.0 mL, 32.0 mmol) dropwise. The reaction was warmed to room temperature and stirred for 2 hours before addition of a solution of saturated aqueous NH_4Cl (20 mL) and extraction with EtOAc (2 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash column chromatography (20% EtOAc:hexane) afforded **378** (2.56 g, 73%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.22 (5H, m), 5.79 – 5.70 (1H, m), 5.69 – 5.60 (1H, m), 5.14 (1H, d, *J* = 6.5 Hz), 2.13 – 1.82 (3H, m), 1.45 – 1.35 (2H, m), 0.89 (3H, t, *J* = 7.5 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.5, 132.7, 132.5, 128.6, 127.6, 126.3, 75.3, 34.4, 22.4, 13.8.

The spectroscopic properties were consistent with the data available in the literature.[326]

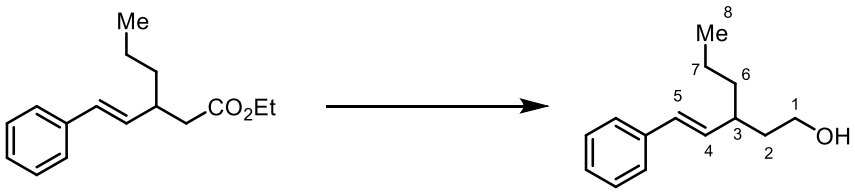
Ethyl (*E*)-3-styrylhexanoate (379)



General procedure Q: The preceding alcohol **378** (441 mg, 2.5 mmol), propionic acid (37 μL, 0.5 mmol) and triethyl orthoacetate (4.6 mL, 25 mmol) were employed. The reaction time was 16 hours. Purification by flash column chromatography (5% EtOAc:hexane) afforded **379** (379 mg, 62%) as a colourless oil containing an unknown impurity which was used in the next step; R_f = 0.40 (10% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 2958 (m), 2929 (m), 1732 (s), 1235 (s), 1161 (s), 965 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.16 (5H, m, ArC<u>H</u>), 6.39 (1H, d, *J* = 16.0 Hz, C**5**-<u>H</u>), 6.00 (1H, dd, *J* = 16.0 Hz, C**4**-<u>H</u>), 4.09 (2H, q, *J* = 7.0 Hz, OC<u>H</u>$_2$CH$_3$), 2.74 – 2.65 (1H, m, C**3**-<u>H</u>), 2.46 – 2.32 (2H, m, C**2**-<u>H</u>$_2$), 1.47 – 1.28 (4H, m, C**6**-<u>H</u>$_2$, C**7**-<u>H</u>$_2$), 1.20 (3H, t, *J* = 7.0 Hz, OCH$_2$C<u>H</u>$_3$), 0.89 (3H, t, *J* = 7.0 Hz, C**8**-<u>H</u>$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.6 (C**1**), 137.6 (Ar<u>C</u>), 133.1 (C**4**), 130.5 (C**5**), 128.6 (Ar<u>C</u>H), 127.2 (Ar<u>C</u>H), 126.2 (Ar<u>C</u>H), 60.4

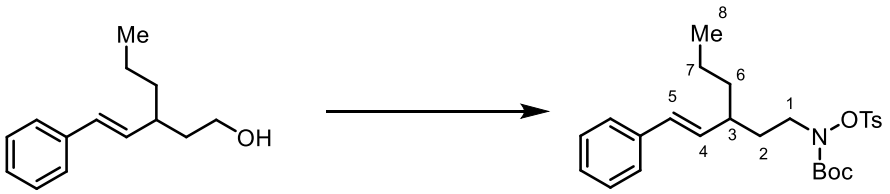
(O<u>C</u>H$_2$CH$_3$), 40.7 (C**2**), 39.9 (C**3**), 37.3 (C**6**), 20.4 (C**7**), 14.4 (OCH$_2$<u>C</u>H$_3$), 14.2 (C**8**); HRMS (ESI$^+$) Calculated for $C_{16}H_{22}NaO_2$: 269.1512. Found [M+Na]$^+$: 269.1514.

(*E*)-3-Styrylhexan-1-ol (380)



<u>General procedure B:</u> The preceding ester **379** (325 mg, 1.32 mmol) and 0.8 equivalents $LiAlH_4$ (1.06 mL, 1 M in THF) in anhydrous THF (5 mL) were employed. Purification by flash column chromatography (20% EtOAc:hexane) afforded **380** (95 mg, 35%); R_f = 0.2 (20% EtOAc:hexane);ν_{max} / cm^{-1} (*film*) 3332 (br m), 2955 (m), 2927 (m), 1449 (m), 965 (s), 747 (s), 691 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.29 (4H, m, ArC<u>H</u>), 7.23 – 7.19 (1H, m, ArC<u>H</u>), 6.39 (1H, d, *J* = 16.0 Hz, C**5**-<u>H</u>), 5.98 (1H, dd, *J* = 16.0, 9.0 Hz, C**4**-<u>H</u>), 3.73 – 3.62 (2H, m, C**1**-<u>H</u>$_2$), 2.38 – 2.28 (1H, m, C**3**-<u>H</u>), 1.80 – 1.72 (1H, m, C**2**-<u>H</u>), 1.63 – 1.51 (2H, m, O<u>H</u>, C**2**-<u>H</u>'), 1.49 – 1.27 (4H, m, C**6**-<u>H</u>$_2$, C**7**-<u>H</u>$_2$), 0.91 (3H, t, *J* = 7.0 Hz, C**8**-<u>H</u>$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.6 (Ar<u>C</u>), 134.9 (C**4**), 130.2 (C**5**), 128.6 (Ar<u>C</u>H), 127.1 (Ar<u>C</u>H), 126.1 (Ar<u>C</u>H), 61.4 (C**1**), 40.2 (C**3**), 38.4 (C**2**), 38.0 (C**6**), 20.5 (C**7**), 14.2 (C**8**); HRMS (ESI$^+$) Calculated for $C_{14}H_{20}NaO$: 227.1406. Found [M+Na]$^+$: 227.1407.

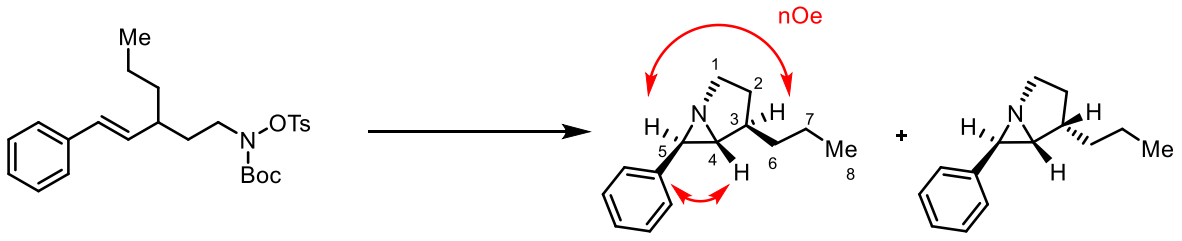
***tert*-Butyl (*E*)-(3-styrylhexyl)(tosyloxy)carbamate (381)**



<u>General procedure G:</u> The preceding alcohol **380** (307 mg, 1.50 mmol), PPh_3 (472 mg, 1.80 mmol), DIAD (0.35 mL, 1.80 mmol) and BocNHOTs (517 mg, 1.80 mmol) in anhydrous THF (6.0 mL) were employed. Purification by flash column chromatography (gradient, eluent: 5 – 10% EtOAc:hexane) afforded **381** (542 mg, 76%) as a pale yellow, viscous oil; R_f = 0.70 (20% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 2958 (m), 2930 (m), 1719 (s), 1368 (s), 1191 (s), 1178 (s), 732 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.34 – 7.24 (6H, m, ArC<u>H</u>, Ts ArC<u>H</u>), 7.22 – 7.17 (1H, m, ArC<u>H</u>), 6.31 (1H, d, *J* = 16.0 Hz, C**5**-<u>H</u>), 5.87 (1H, dd, *J* = 16.0, 9.0 Hz, C**4**-<u>H</u>), 3.53 (2H, br s, C**1**-<u>H</u>$_2$), 2.38 (3H, s, Ts C<u>H</u>$_3$), 2.15 – 2.06 (1H, m,

C**3**-H), 1.85 – 1.71 (1H, m, C**2**-H), 1.65 – 1.52 (1H, m, C**2**-H'), 1.43 – 1.24 (4H, m, C**6**-H_2 and C**7**-H_2), 1.23 (9H, s, Boc (CH_3)$_3$), 0.87 (3H, t, *J* = 7.0 Hz, C**8**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6 (Boc C=O), 145.7 (Ts ArC), 137.6 (ArC), 133.8 (C**4**), 131.4 (Ts ArC), 130.7 (C**5**), 129.8 (2 × Ts ArCH), 129.6 (2 × Ts ArCH), 128.6 (ArCH), 127.2 (ArCH), 126.2 (ArCH), 83.3 (Boc C(CH_3)$_3$), 51.7 (C**1**), 40.9 (C**3**), 37.7 (C**6**), 31.0 (C**2**), 27.8 (Boc (CH_3)$_3$), 21.8 (Ts CH_3), 20.4 (C**7**), 14.2 (C**8**); HRMS (ESI$^+$) Calculated for $C_{26}H_{35}NNaO_5S$: 496.2128. Found [M+Na]$^+$: 496.2134.

(4*R,5*R**,6*R**)-6-Phenyl-4-propyl-1-azabicyclo[3.1.0]hexane (382a) and (4*S**,5*R**,6*R**)-6-Phenyl-4-propyl-1-azabicyclo[3.1.0]hexane (382b)**



General procedure P: The preceding *N*-tosyloxycarbamate **381** (94.7 mg, 0.20 mmol) and TFA (31 μL, 0.40 mmol) in anhydrous TFE (2.0 mL) were employed. After stirring for 48 hours purification by flash column chromatography (eluent: ~0.1% Et_3N in 33% EtOAc:pentane) afforded **382** (27.9 mg, 69%) as a 10:1 mixture of diastereomers and as a pale-yellow oil; R_f = 0.35 (20% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 2955 (m), 2925 (m), 2873 (m), 1453 (m), 737 (s), 696 (s).

*Spectroscopic properties for the major diastereomer **382a**:* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.23 (2H, m, ArCH), 7.21 – 7.16 (3H, m, ArCH), 3.14 – 3. 07 (2H, m, C**1**-H_2), 2.47 – 2.40 (1H, m, C**3**-H), 2.33 (1H, d, *J* = 2.5 Hz, C**5**-H), 2.25 (1H, d, *J* = 2.5 Hz, C**4**-H), 1.82 – 1.70 (1H, m, C**2**-H), 1.50 –1.29 (5H, m, C**2**-H', C**6**-H_2, C**7**-H_2), 0.92 (3H, t, *J* = 7.0 Hz, C**8**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.4 (ArC), 128.3 (ArCH), 126.8 (ArCH), 126.1 (ArCH), 55.6 (C**4**), 52.0 (C**1**), 41.0 (C**5**), 39.5 (C**3**), 37.0 (C**6**), 27.3 (C**2**), 21.0 (C**7**), 14.3 (C**8**).

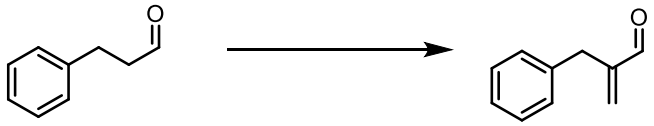
In $CDCl_3$ the signals for the minor diastereomer were overlapped by the major diastereomer however in $(CD_3)_2CO$ some of the minor peaks could be observed allowing for the d.r. to be determined.

*Characteristic signals for the minor diastereomer **382b**:* ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 2.55 (1H, d, *J* = 2.5 Hz), 2.22 (1H, dd, *J* = 4.5, 2.5 Hz).

HRMS (ESI$^+$) Calculated for $C_{14}H_{20}N$: 202.1590. Found $[M+H]^+$: 202.1591.

*The relative stereochemistry was determined by nOe experiments as indicated on the compound structure. nOe correlations were observed between C**4**-H and ArCH and between C**3**-H and C**5**-H.*

2-Benzylacrylaldehyde (384)

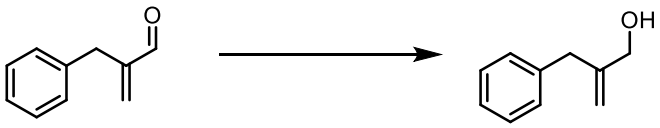


This compound was prepared according to a literature procedure.[327]

To a solution of 4-(dimethylamino)benzoic acid (830 mg, 5.0 mmol) and pyrrolidine (0.21 mL, 2.5 mmol) in CH_2Cl_2 (25 mL) were added formaldehyde (37% solution in H_2O, 2.0 mL, 25 mmol) and 3-phenylpropanal (**383**) (3.35 mg, 25.0 mmol) at room temperature. The reaction was heated at 45 ^oC and stirred for 2 hours. The reaction mixture was added to saturated aqueous $NaHCO_3$ (20 mL) and the resulting mixture was extracted with CH_2Cl_2 (3 × 20mL). The combined organic extracts were then washed with brine (20 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash column chromatography (20% EtOAc:hexane) afforded **384** (2.56 g, 70%) as a yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 9.61 (1H, s), 7.33 – 7.15 (5H, m), 6.11 (1H, s), 6.07 (1H, s), 3.57 (2H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.9, 149.9, 138.2, 135.3, 129.3, 128.7, 126.6, 34.3.

The spectroscopic properties were consistent with the data available in the literature.[327]

2-Benzylprop-2-en-1-ol (385)



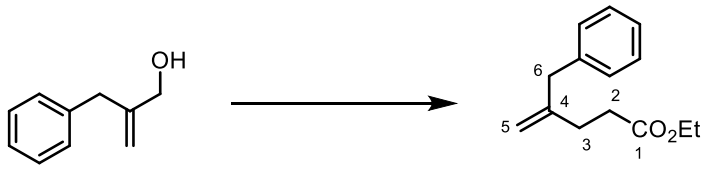
The title compound was prepared according to a literature procedure.[137]

To a solution of aldehyde **384** (2.50 g, 17.0 mmol) in MeOH (8.5 mL) at 0 ^oC was added $NaBH_4$ (680 mg, 17.85 mmol) portion wise and the reaction was stirred for 30 minutes. The reaction mixture was quenched with saturated aqueous NH_4Cl (8.5 mL), diluted with H_2O (17 mL) and extracted with Et_2O (3 × 35 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash column chromatography (gradient, eluent 10 – 20% EtOAc:petroleum ether) afforded **385** (1.67 g, 66%) as a colourless oil; ^1H NMR (400

MHz, $CDCl_3$) δ 7.32 – 7.17 (5H, m), 5.14 – 5.11 (1H, m), 4.93 – 4.89 (1H, m), 4.04 (2H, s), 3.41 (2H, s), 1.73 (1H, br s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.3, 139.2, 129.0, 128.5, 126.4, 111.6, 65.4, 40.0.

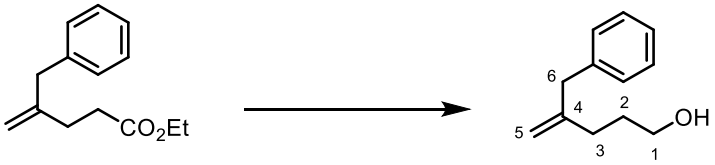
The spectroscopic properties were consistent with the data available in the literature.[137]

Ethyl 4-benzylpent-4-enoate (386)



General procedure Q: The preceding alcohol **385** (1.46 g, 10 mmol), propionic acid (0.15 mL, 2.0 mmol) and triethyl orthoacetate (18.3 mL, 100 mmol) were employed. Purification by flash column chromatography (5% EtOAc:petroleum ether) afforded **386** (1.15 g, 53%) as a colourless oil; R_f = 0.70 (20% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 2980 (m), 2906 (m), 1732 (s), 1155 (s), 698 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.26 (2H, m, ArC**H**), 7.23 – 7.17 (3H, m, ArC**H**), 4.85 – 4.83 (1H, m, C**5**-**H**), 4.81 – 4.79 (1H, m, C**5**-**H**'), 4.12 (2H, q, *J* = 7.0 Hz, OC**H**$_2$CH$_3$), 3.37 (2H, s, C**6**-**H**$_2$), 2.48 – 2.42 (2H, m, C**2**-**H**$_2$), 2.34 – 2.28 (2H, m, C**3**-**H**$_2$), 1.24 (3H, t, *J* = 7.0 Hz, OCH$_2$C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.3 (C**1**), 147.4 (C**4**), 139.4 (Ar**C**), 129.1 (Ar**C**H), 128.5 (Ar**C**H), 126.3 (Ar**C**H), 111.7 (C**5**), 60.5 (O**C**H$_2$CH$_3$), 43.3 (C**6**), 32.7 (C**2**), 30.4 (C**3**), 14.3 (OCH$_2$**C**H$_3$); HRMS (ESI^+) Calculated for $C_{14}H_{18}NaO_2$: 241.1199. Found $[M+Na]^+$: 241.1199.

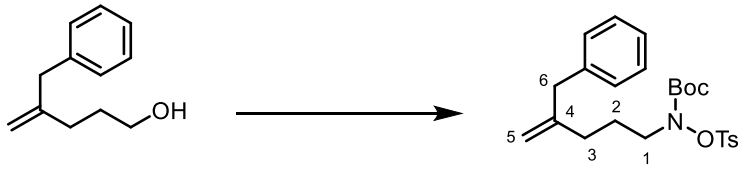
4-Benzylpent-4-en-1-ol (387)



General procedure B: The preceding ester **386** (873 mg, 4.0 mmol) and 0.8 equivalents of $LiAlH_4$ (121 mg, 3.2 mmol) in THF (20 mL) were employed. Purification by flash column chromatography (20% EtOAc:petroleum ether) afforded **387** (556 mg, 80%) as a colourless oil; R_f = 0.20 (20% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 3327 (br m), 2937 (m), 697 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.26 (2H, m, ArC**H**), 7.22 – 7.16 (3H, m, ArC**H**), 4.87 – 4.85 (1H, m, C**5**-**H**), 4.79 – 4.77 (1H, m, C**5**-**H**'), 3.61 (2H, t, *J* = 6.5 Hz, C**1**-**H**$_2$), 3.35 (2H, s, C**6**-**H**$_2$), 2.04 (2H, t, *J* = 7.5 Hz, C**3**-**H**$_2$), 1.74 – 1.66 (2H, m, C**2**-**H**$_2$), 1.50 (1H, br s, O**H**); ^{13}C NMR

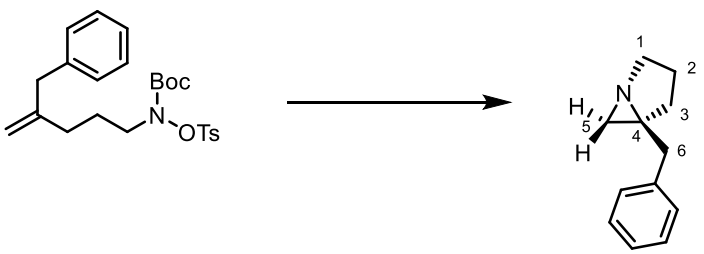
(101 MHz, $CDCl_3$) δ 148.6 (C**4**), 139.7 (Ar<u>C</u>), 129.1 (Ar<u>C</u>H), 128.4 (Ar<u>C</u>H), 126.3 (Ar<u>C</u>H), 111.6 (C**5**), 62.8 (C**1**), 43.2 (C**6**), 31.7 (C**3**), 30.7 (C**2**); HRMS (ESI^+) Calculated for $C_{12}H_{16}NaO$: 199.1093. Found $[M+Na]^+$: 199.1098.

***tert*-Butyl (4-benzylpent-4-en-1-yl)(tosyloxy)carbamate (388)**



<u>General procedure G:</u> The preceding alcohol **387** (441 mg, 2.5 mmol), PPh_3 (787 mg, 3.0 mmol), DIAD (0.59 mL, 3.0 mmol) and BocNHOTs (862 mg, 3.0 mmol) in anhydrous THF (10 mL) were employed. Purification by flash column chromatography (10% EtOAc:hexane) afforded **388** (895 mg, 80%) as a colourless solid; R_f = 0.4 (20% EtOAc:hexane); m.p.: 84-86 °C (Et_2O:pentane); ν_{max} / cm^{-1} (*solid*) 2980 (m), 1711 (s), 1370 (s), 1342 (s), 1176 (s), 1150 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.33 (2H, d, *J* = 8.0 Hz, Ts ArC<u>H</u>), 7.30 – 7.36 (2H, m, ArC<u>H</u>), 7.22 – 7.14 (3H, m, ArC<u>H</u>), 4.84 – 4.81 (1H, m, C**5**-<u>H</u>), 4.78 – 4.76 (1H, m, C**5**-<u>H</u>'), 3.57 (2H, br s, C**1**-<u>H_2</u>), 3.32 (2H, s, C**6**-<u>H_2</u>), 2.45 (3H, s, Ts C<u>H_3</u>), 1.93 (2H, t, *J* = 7.5 Hz, C**3**-<u>H_2</u>), 1.82 – 1.71 (2H, m, C**2**-<u>H_2</u>), 1.21 (9H, s, Boc (C<u>H_3</u>)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6 (Boc <u>C</u>=O), 147.6 (C**4**), 145.8 (Ts Ar<u>C</u>), 139.6 (Ar<u>C</u>), 131.4 (Ts Ar<u>C</u>), 129.8 (2 × Ts Ar<u>C</u>H), 129.7 (2 × Ts Ar<u>C</u>H), 129.1 (Ar<u>C</u>H), 128.5 (Ar<u>C</u>H), 126.3 (Ar<u>C</u>H), 111.9 (C**5**), 83.3 (Boc <u>C</u>(CH_3)$_3$), 52.8 (C**1**), 43.1 (C**6**), 32.2 (C**3**), 27.7 (Boc C(<u>C</u>H_3)$_3$), 23.7 (C**2**), 21.8 (Ts <u>C</u>H_3); HRMS (ESI^+) Calculated for $C_{24}H_{31}NNaO_5S$: 468.1815. Found $[M+Na]^+$: 468.1806.

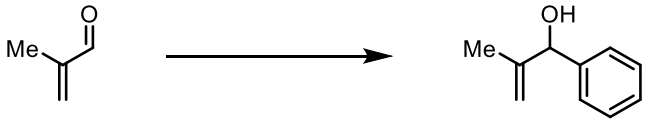
5-Benzyl-1-azabicyclo[3.1.0]hexane (389)



<u>General procedure P:</u> The preceding *N*-tosyloxycarbamate **388** (89.1 mg, 0.2 mmol) and TFA (31 μL, 0.4 mmol) in anhydrous TFE (2.0 mL) were employed. After stirring for 42 hours at room temperature purification by flash column chromatography (~0.1% Et_3N in EtOAc)

afforded **389** (27.8 mg, 80%) as a yellow oil; R_f = 0.1 (EtOAc); ν_{max} / cm^{-1} (*film*) 2925 (m), 1673 (m), 1453 (m), 700 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.18 (5H, m, ArC<u>H</u>), 2.99 – 2.89 (3H, m, C**1**-<u>H</u>$_2$, C**6**-<u>H</u>), 2.80 (1H, d, *J* = 14.0 Hz, C**6**-<u>H</u>'), 1.96 (1H, dd, *J* = 12.5, 8.0 Hz, C**3**-<u>H</u>), 1.71 – 1.56 (3H, m, C**2**-<u>H</u>, C**3**-<u>H</u>', C**5**-<u>H</u>), 1.54 – 1.43 (2H, m, C**2**-<u>H</u>', C**5**-<u>H</u>'); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.2 (Ar<u>C</u>), 129.4 (Ar<u>C</u>H), 128.4 (Ar<u>C</u>H), 126.3 (Ar<u>C</u>H), 53.1 (C**1**), 50.4 (C**4**), 41.9 (C**6**), 32.2 (C**5**), 29.2 (C**3**), 21.5 (C**2**); HRMS (ESI^+) Calculated for $C_{12}H_{16}N$: 174.1277. Found $[M+H]^+$: 174.1283.

2-Methyl-1-phenylprop-2-en-1-ol (391)

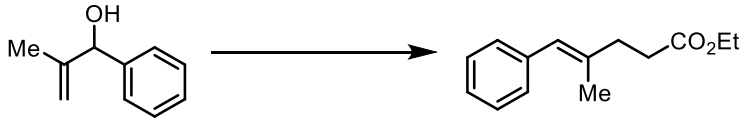


This compound was prepared according to a literature procedure.[328]

To a solution of methacrolein (**390**) (2.8 g, 40.0 mmol) in anhydrous THF (18 mL) at 0 °C was added PhMgBr (3.0 M in Et_2O, 13.6 mL, 41.0 mmol) dropwise. The reaction was warmed to room temperature and stirred for 1.5 hours. The reaction was quenched with a solution of saturated aqueous NH_4Cl (50 mL) and diluted with H_2O (100 mL). The layers were separated, and the organic phase was extracted with Et_2O (2 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4 and concentrated *in vacuo*. **391** was obtained as a yellow oil (5.02 g, 85%) and was used without further purification; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.26 (5H, m), 5.22 – 5.20 (1H, m), 5.13 (1H, s), 4.97 – 4.95 (1H, m), 2.19 (1H, br s), 1.62 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.9, 142.1, 128.5, 127.7, 126.6, 111.3, 78.0, 18.4.

The spectroscopic properties were consistent with the data available in the literature.[329]

Ethyl (*E*)-4-methyl-5-phenylpent-4-enoate

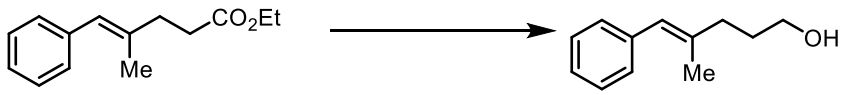


<u>General procedure Q:</u> The preceding alcohol **391** (3.71 g, 25.0 mmol), propionic acid (0.37 mL, 5.0 mmol) and triethyl orthoacetate (46 mL, 250 mmol) were employed. Purification by flash column chromatography (3% EtOAc:petroleum ether) afforded the title compound (3.38 g, 62%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.30 (2H, m), 7.24 – 7.18 (3H, m), 6.31 (1H, s), 4.15 (2H, q, *J* = 7.0 Hz), 2.54 – 2.50 (4H, m), 1.87 (3H, s), 1.27 (3H, t,

J = 7.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.3, 138.3, 137.2, 128.9, 128.2, 126.2, 125.7, 60.5, 35.8, 33.3, 17.8, 14.4.

The spectroscopic properties were consistent with the data available in the literature.[322]

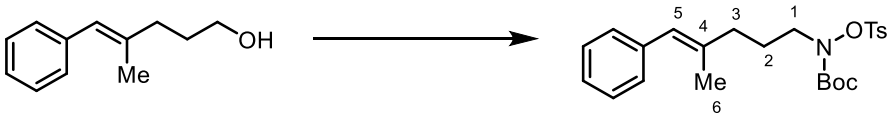
(*E*)-4-Methyl-5-phenylpent-4-en-1-ol



General procedure B: Ethyl (*E*)-4-methyl-5-phenylpent-4-enoate (3.30 g, 15.2 mmol) and 0.8 equivalents of $LiAlH_4$ (1M in THF) in anhydrous THF (50 mL) were employed. Purification by flash column chromatography (20% EtOAc:petroleum ether) afforded the title compound (1.88 g, 70%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.29 (2H, m), 7.26 – 7.16 (3H, m), 6.32 (1H, s), 3.71 (2H, t, *J* = 6.5 Hz), 2.27 (2H, t, *J* = 7.5 Hz), 1.88 (3H, s), 1.85 – 1.77 (2H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.6, 138.5, 128.9, 128.2, 126.1, 125.3, 62.8, 37.1, 31.0, 17.9.

The spectroscopic properties were consistent with the data available in the literature.[322]

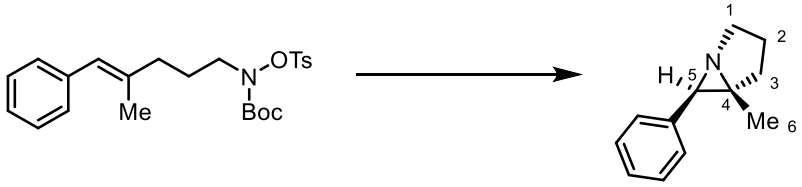
***tert*-Butyl (*E*)-(4-methyl-5-phenylpent-4-en-1-yl)(tosyloxy)carbamate (392)**



General procedure G: (*E*)-4-Methyl-5-phenylpent-4-en-1-ol (1.76 g, 10.0 mmol), PPh_3 (3.15 g, 12.0 mmol), DIAD (2.36 mL, 12.0 mmol) and BocNHOTs (3.40 g, 12.0 mmol) in anhydrous THF (40 mL) were employed. Purification by flash column chromatography (10% EtOAc:petroleum ether) afforded **392** (3.70 g, 83%) as a colourless solid; R_f = 0.7 (50% EtOAc:hexane); m.p.: 74-76 °C (CH_2Cl_2:hexane); ν_{max} / cm^{-1} (*solid*) 2980 (m), 2958 (m), 2948 (m), 1709 (s), 1369 (s), 1348 (s), 1174 (s), 1151 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.36 – 7.28 (4H, m, Ts ArC<u>H</u> and ArC<u>H</u>), 7.24 – 7.16 (3H, m, ArC<u>H</u>), 6.26 (1H, s, C**5**-<u>H</u>), 3.64 (2H, br s, C**1**-<u>H_2</u>), 2.44 (3H, s, Ts C<u>H_3</u>), 2.18 – 2.12 (2H, m, C**3**-<u>H_2</u>), 1.90 – 1.79 (5H, m, C**2**-<u>H_2</u> and C**6**-<u>H_3</u>), 1.24 (9H, s, Boc (C<u>H_3</u>)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6 (Boc <u>C</u>=O), 145.8 (Ts Ar<u>C</u>), 138.4 (Ar<u>C</u>), 137.6 (C**4**), 131.4 (Ts Ar<u>C</u>), 129.9 (2 × Ts Ar<u>C</u>H), 129.7 (2 × Ts Ar<u>C</u>H), 129.0 (Ar<u>C</u>H), 128.2 (Ar<u>C</u>H), 126.1 (Ar<u>C</u>H), 125.7 (C**5**), 83.4

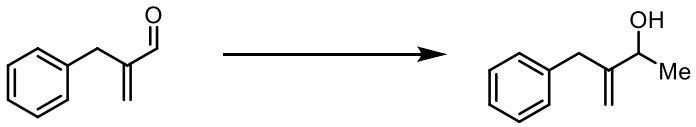
(Boc C(CH$_3$)$_3$), 52.8 (C**1**), 37.6 (C**3**), 27.8 (Boc (CH$_3$)$_3$), 24.1 (C**2**), 21.9 (Ts CH$_3$), 17.7 (C**6**); HRMS (ESI$^+$) Calculated for $C_{24}H_{31}NNaO_5S$: 468.1815. Found [M+Na]+: 468.1814.

(5*S,6*S**)-5-Methyl-6-phenyl-1-azabicyclo[3.1.0]hexane (393)**



General procedure P: The preceding *N*-tosyloxycarbamate **392** (89.1 mg, 0.2 mmol) and TFA (31 μL, 0.4 mmol) in anhydrous TFE (2.0 mL) were employed. After stirring for 48 hours purification by flash column chromatography (0.1% Et$_3$N in EtOAc) afforded **393** (28.1 mg, 81%) as a yellow oil; R_f = 0.50 (EtOAc); ν_{max} / cm^{-1} (*film*) 2951 (m), 2925 (m), 2874 (m), 1498 (m), 1449 (m), 1063 (m); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.31 – 7.26 (4H, m, ArCH), 7.23 – 7.18 (1H, m, ArCH), 3.17 – 3.12 (2H, m, C**1**-H$_2$), 2.65 (1H, s, C**5**-H), 2.27 – 2.21 (1H, m, C**3**-H), 1.88 – 1.81 (1H, m, C**3**-H'), 1.80 – 1.65 (2H, m, C**2**-H$_2$), 1.06 (3H, s, C**6**-H$_3$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 138.4 (ArC), 128.0 (ArCH), 127.8 (ArCH), 126.5 (ArCH), 53.7 (C**1**), 53.3 (C**4**), 44.4 (C**5**), 33.4 (C**3**), 22.1 (C**2**), 16.3 (C**6**); HRMS (ESI$^+$) Calculated for $C_{12}H_{16}N$: 174.1277. Found [M+H]$^+$: 174.1277.

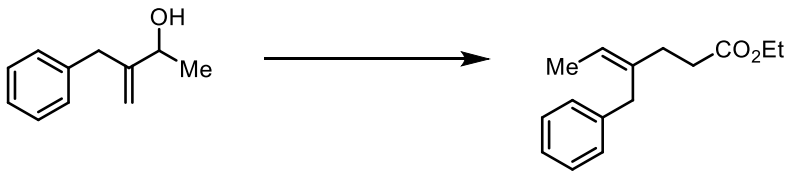
3-Benzylbut-3-en-2-ol



To a solution of MeMgBr (3.0 M in Et$_2$O, 20 mL, 60 mmol) in anhydrous Et$_2$O (50 mL) at 0 ^{o}C was added 2-benzylacrylaldehyde (**384**) (5.85 g, 40 mmol) dropwise. The reaction mixture was stirred for 1 hour at room temperature before addition of saturated aqueous NH$_4$Cl (50 mL). The phases were separated, and the aqueous phase extracted with Et$_2$O (2 × 50 mL). The combined organic extracts were dried over Na$_2$SO$_4$, filtered and concentrated *in vacuo* to afford the title compound (4.85 g, 75%) as a pale-yellow oil, which was used without further purification; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.33 – 7.27 (2H, m), 7.24 – 7.19 (3H, m), 5.16 – 5.14 (1H, m), 4.76 – 4.74 (1H, m), 4.25 (1H, q, *J* = 6.5 Hz), 3.48 (1H, d, *J* = 15.5 Hz), 3.36 (1H, d, *J* = 15.5 Hz), 1.67 (1H, br s), 1.31 (3H, d, *J* = 6.5 Hz); ^{13}C NMR (101 MHz, CDCl$_3$) δ 152.7, 139.5, 129.3, 128.5, 126.3, 111.0, 70.3, 39.1, 22.3.

The spectroscopic properties were consistent with the data available in the literature.[52]

Ethyl (*Z*)-4-benzylhex-4-enoate

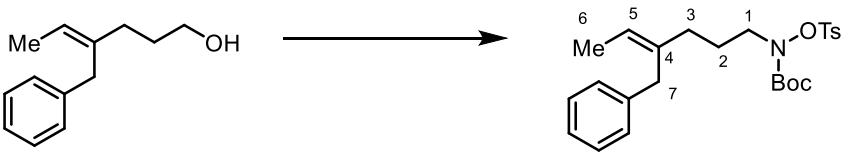


General procedure Q: 3-Benzylbut-3-en-2-ol (4.06 g, 25.0 mmol), propionic acid (0.37 mL, 5.0 mmol) and triethyl orthoacetate (46 mL, 250 mmol) were employed. Purification by flash column chromatography (10% EtOAc:petroleum ether) afforded the title compound (3.50 g, 60%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.24 (2H, m), 7.21 – 7.14 (3H, m), 5.45 (1H, q, *J* = 6.5 Hz), 4.09 (2H, q, *J* = 7.0 Hz), 3.42 (2H, s), 2.39 – 2.32 (2H, m), 2.29 – 2.23 (2H, m), 1.72 (3H, d, *J* = 6.5 Hz), 1.23 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.5, 140.0, 137.0, 128.6, 128.5, 126.1, 121.1, 60.3, 35.8, 33.2, 31.9, 14.4, 13.8.
The spectroscopic properties were consistent with the data available in the literature.[52]

(*Z*)-4-Benzylhex-4-en-1-ol (394a)

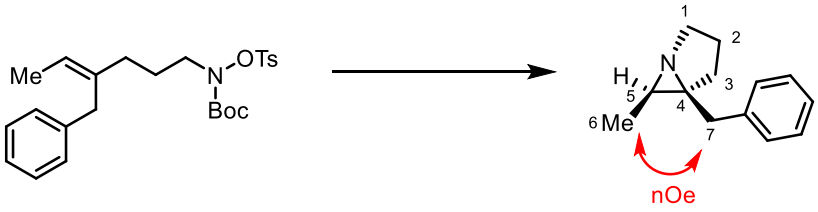
General procedure B: Ethyl (*Z*)-4-benzylhex-4-enoate (2.32 g, 10.0 mmol) and 0.8 equivalents of $LiAlH_4$ (304 mg) in anhydrous Et_2O (50 mL) were employed. **394a** (1.79 g, 94%) was obtained as a colourless oil which was used without further purification; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.24 (2H, m), 7.22 – 7.15 (3H, m), 5.46 (1H, q, *J* = 7.0 Hz), 3.58 (2H, t, *J* = 6.5 Hz), 3.42 (2H, s), 2.03 – 1.97 (2H, m), 1.74 (3H, d, *J* = 7.0 Hz), 1.67 – 1.60 (2H, m), 1.45 (1H, br s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.3, 138.2, 128.6, 128.5, 126.0, 120.7, 62.8, 35.7, 32.9, 31.0, 13.8.
The spectroscopic properties were consistent with the data available in the literature.[52]

***tert*-Butyl (*Z*)-(4-benzylhex-4-en-1-yl)(tosyloxy)carbamate (395a)**



General procedure G: The preceding alcohol **394a** (290 mg, 1.50 mmol), PPh_3 (470 mg, 1.80 mmol), DIAD (0.35 mL, 1.80 mmol) and BocNHOTs (520 mg, 1.80 mmol) in anhydrous THF (6 mL) were employed. Purification by flash column chromatography (10% EtOAc:petroleum ether) afforded **395a** (630 mg, 92%) as a viscous, colourless oil; R_f = 0.80 (20% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 3027 (m), 2980 (m), 2932 (m), 1720 (s), 1380 (s), 1368 (s), 1191 (s), 1178 (s), 1152 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.33 (2H, d, *J* = 8.0 Hz, Ts ArC<u>H</u>), 7.29 – 7. 24 (2H, m, ArC<u>H</u>), 7.20 – 7.12 (3H, m, ArC<u>H</u>), 5.41 (1H, q, *J* = 6.5 Hz, C**5**-<u>H</u>), 3.53 (2H, br s, C**1**-<u>H_2</u>), 3.38 (2H, s, C**7**-<u>H_2</u>), 2.45 (3H, s, Ts C<u>H_3</u>), 1.87 (2H, t, *J* = 7.5 Hz, C**3**-<u>H_2</u>), 1.75 – 1.66 (5H, m, C**2**-<u>H_2</u>, C**6**-<u>H_3</u>), 1.20 (9H, s, Boc (C<u>H_3</u>)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6 (Boc <u>C</u>=O), 145.7 (Ts Ar<u>C</u>), 140.1 (Ar<u>C</u>), 137.3 (C**4**), 131.4 (Ts Ar<u>C</u>), 129.8 (2 × Ts Ar<u>C</u>H), 129.6 (2 × Ts Ar<u>C</u>H), 128.6 (Ar<u>C</u>H), 128.5 (Ar<u>C</u>H), 126.0 (Ar<u>C</u>H), 120.9 (C**5**), 83.2 (Boc <u>C</u>(CH$_3$)$_3$), 52.9 (C**1**), 35.6 (C**7**), 33.4 (C**3**), 27.7 (Boc (<u>C</u>H$_3$)$_3$), 24.0 (C**2**), 21.8 (Ts <u>C</u>H$_3$), 13.8 (C**6**); HRMS (ESI^+) Calculated for $C_{25}H_{33}NNaO_5S$: 482.1972. Found $[M+Na]^+$: 482.1974.

(5*R,6*S**)-5-Benzyl-6-methyl-1-azabicyclo[3.1.0]hexane (396a)**

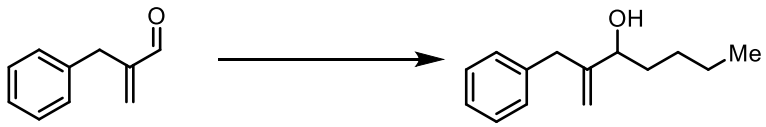


General procedure P: The preceding *N*-tosyloxycarbamate **395a** (91.9 mg, 0.20 mmol), and TFA (31 μL, 0.4 mmol) in anhydrous TFE (2.0 mL) were employed. After stirring at room temperature for 48 hours purification by flash column chromatography (~0.1% Et_3N in EtOAc) afforded **396a** (26.5 mg, 71%) as a colourless oil; R_f = 0.31 (EtOAc); ν_{max} / cm^{-1} (*film*) 2955 (m), 2871 (m), 1495 (m), 1453 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.18 (5H, m, ArC<u>H</u>), 3.03 – 2.91 (2H, m, C**1**-<u>H_2</u>), 2.89 (2H, s, C**7**-<u>H_2</u>), 1.89 (1H, dd, *J* = 12.5, 8.5 Hz, C**3**-<u>H</u>), 1.71 – 1.62 (2H, m, C**5**-<u>H</u>, C**3**-<u>H</u>'), 1.60 – 1.43 (2H, m, C**2**-<u>H_2</u>) 1.28 (3H, d, *J* = 6.0 Hz, C**6**-<u>H_3</u>); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.7 (Ar<u>C</u>), 129.3 (Ar<u>C</u>H), 128.4 (Ar<u>C</u>H), 126.2 (Ar<u>C</u>H), 54.2

(C**4**), 53.2 (C**1**), 37.3 (C**7**), 36.8 (C**5**), 30.5 (C**2**), 22.2 (C**3**), 14.4 (C**6**); HRMS (ESI$^+$) Calculated for $C_{13}H_{18}N$: 188.1433. Found $[M+H]^+$: 188.1438.

*The relative stereochemistry of this compound was determined by nOe experiments as indicated on the compound structure. An nOe correlation was observed between C**7**-H$_2$ and C**6**-H$_3$. There was no nOe observed between C**7**-H$_2$ and C**5**-H.*

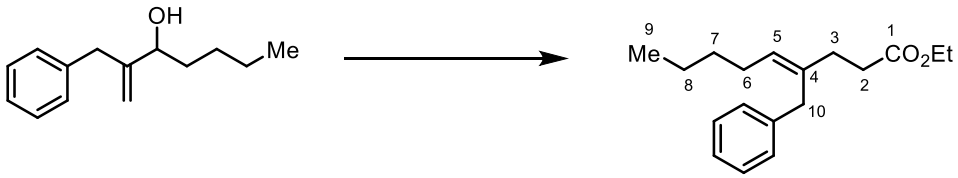
2-Benzylhept-1-en-3-ol



To a solution of 2-benzylacrylaldehyde (**384**) (1.17 g, 8.0 mmol) in anhydrous THF (26 mL) at -78 ^oC was added *n*-BuLi (2.5 M in hexanes, 3.84 mL, 9.6 mmol) dropwise. The reaction mixture was stirred at this temperature for 1 hour then warmed to 0 ^oC before addition of water (20 mL). The phases were separated, and the aqueous phase was extracted with Et_2O (3 × 20 mL) and the combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography (20% EtOAc:petroleum ether) afforded the title compound (1.28 g, 78%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.27 (2H, m), 7.24 – 7.18 (3H, m), 5.12 (1H, s), 4.75 (1H, t, *J* = 1.5 Hz), 4.09 (1H, m), 3.47 (1H, d, *J* = 15.5 Hz), 3.32 (1H, d, *J* = 15.5 Hz), 1.67 – 1.50 (2H, m), 1.41 – 1.23 (4H, m), 0.90 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.6, 139.6, 129.4, 128.5, 126.3, 112.1, 74.9, 38.7, 35.3, 27.9, 22.8, 14.2.

The spectroscopic properties were consistent with the data available in the literature.[330]

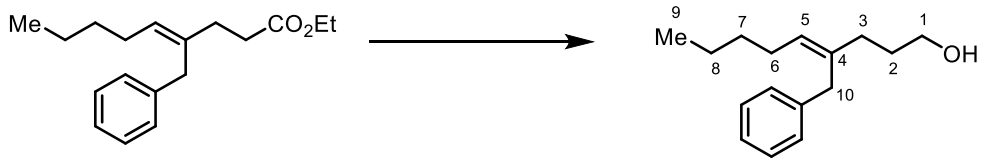
Ethyl (*Z*)-4-benzylnon-4-enoate



General procedure Q: 2-Benzylhept-1-en-3-ol (1.02 g, 5.0 mmol), propionic acid (75 μL, 1.0 mmol) and triethyl orthoacetate (9.2 mL, 50 mmol) were employed. Purification by flash column chromatography (5% EtOAc:hexane) afforded the title compound (1.04 g, 76%) as a colourless oil.; R_f = 0.35 (5% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 2956 (m), 2927 (m), 1733 (s), 1452 (m), 1164 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.24 (2H, m, ArC<u>H</u>), 7.21 – 7.14

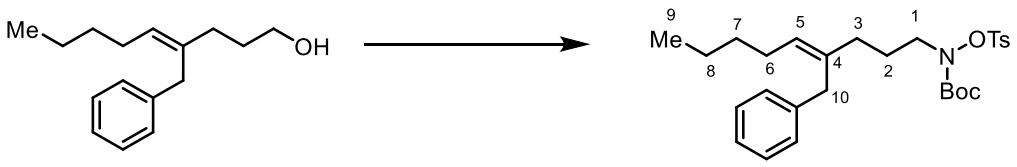
(3H, m, ArC<u>H</u>), 5.36 (1H, t, *J* = 7.5 Hz, C**5**-<u>H</u>), 4.09 (2H, q, *J* = 7.0 Hz, OC<u>H</u>$_2$CH$_3$), 3.41 (2H, s, C**10**-<u>H</u>$_2$), 2.40 – 2.33 (2H, m, C**2**-<u>H</u>$_2$), 2.29 – 2.22 (2H, m, C**3**-<u>H</u>$_2$), 2.17 – 2.10 (2H, m, C**6**-<u>H</u>$_2$), 1.42 – 1.29 (4H, m, C**7**-<u>H</u>$_2$, C**8**-<u>H</u>$_2$), 1.23 (3H, t, *J* = 7.0 Hz, OCH$_2$C<u>H</u>$_3$), 0.91 (3H, t, *J* = 7.0 Hz, C**9**-<u>H</u>$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.5 (C**1**), 140.0 (Ar<u>C</u>), 135.9 (C**4**), 128.6 (Ar<u>C</u>H), 128.5 (Ar<u>C</u>H), 127.6 (C**5**), 126.1 (Ar<u>C</u>H), 60.3 (O<u>C</u>H$_2$CH$_3$), 36.2 (C**10**), 33.3 (C**2**), 32.3 (C**7** or C**8**), 31.8 (C**3**), 27.9 (C**6**), 22.5 (C**7** or C**8**), 14.4 (OCH$_2$<u>C</u>H$_3$), 14.2 (C**9**); HRMS (ESI$^+$) Calculated for $C_{18}H_{27}O_2$: 275.2006. Found $[M+H]^+$: 275.2008.

(*Z*)-4-Benzylnon-4-en-1-ol (394b)



<u>General procedure B:</u> Ethyl (*Z*)-4-benzylnon-4-enoate (960 mg, 3.5 mmol) and 0.8 equivalents of $LiAlH_4$ (2M in THF) in anhydrous Et_2O (7 mL) were employed. Purification by flash column chromatography (20% EtOAc:hexane) afforded **394b** (700 mg, 86%) as a colourless oil; R_f = 0.5 (20% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 3328 (br s), 2954 (m), 2927 (m), 1494 (m), 1452 (m), 1055 (m), 1029 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.23 (2H, m, ArC<u>H</u>), 7.20 – 7.14 (3H, m, ArC<u>H</u>), 5.37 (1H, t, *J* = 7.0 Hz, C**5**-<u>H</u>), 3.57 (2H, t, *J* = 6.5 Hz, C**1**-<u>H</u>$_2$), 3.40 (2H, s, C**10**-<u>H</u>$_2$), 2.19 – 2.12 (2H, m, C**6**-<u>H</u>$_2$), 2.00 – 1.95 (2H, m, C**3**-<u>H</u>$_2$), 1.67 – 1.60 (2H, m, C**2**-<u>H</u>$_2$), 1.54 – 1.29 (5H, m, O<u>H</u>, C**7**-<u>H</u>$_2$, C**8**-<u>H</u>$_2$), 0.91 (3H, t, *J* = 7.0 Hz, C**9**-<u>H</u>$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.3 (Ar<u>C</u>), 137.0 (C**4**), 128.7 (Ar<u>C</u>H), 128.4 (Ar<u>C</u>H), 127.3 (C**5**), 126.0 (ArC<u>H</u>), 62.9 (C**1**), 36.0 (C**10**), 32.8 (C**3**), 32.4 (C**7** or C**8**), 31.0 (C**2**), 28.0 (C**6**), 22.6 (C**7** or C**8**), 14.2 (C**9**); HRMS (ESI$^+$) Calculated for $C_{16}H_{24}NaO$: 255.1719. Found $[M+Na]^+$: 255.1726.

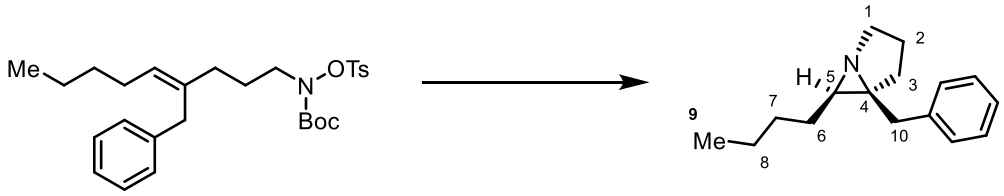
***tert*-Butyl (*Z*)-(4-benzylnon-4-en-1-yl)(tosyloxy)carbamate (395b)**



<u>General procedure G:</u> The preceding alcohol **394b** (465 mg, 2.0 mmol), PPh_3 (629 mg, 2.4 mmol), DIAD (0.47 mL, 2.4 mmol), and BocNHOTs (689 mg, 2.4 mmol) in anhydrous THF (8.0 mL) were employed. Purification by flash column chromatography (gradient, eluent: 5 – 20% EtOAc:petroleum ether) afforded **395b** (911 mg, 91%) as a colourless solid; R_f = 0.55

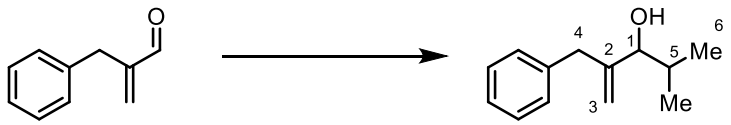
(20% EtOAc:hexane); m.p.: 36-38 °C (Et_2O:petroleum ether); ν_{max} / cm^{-1} (*solid*) 2925 (m), 2855 (m), 1719 (s), 1377 (s), 1176 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.32 (2H, d, *J* = 8.0 Hz, Ts ArC<u>H</u>), 7.28 – 7.23 (2H, m, ArC<u>H</u>), 7.19 – 7.12 (3H, m, ArC<u>H</u>), 5.32 (1H, t, *J* = 7.0 Hz, C**5**-<u>H</u>), 3.52 (2H, br s, C**1**-<u>H_2</u>), 3.37 (2H, s, C**10**-<u>H_2</u>), 2.44 (3H, s, Ts C<u>H_3</u>), 2.16 – 2.09 (2H, m, C**6**-<u>H_2</u>), 1.85 (2H, t, *J* = 7.5 Hz, C**3**-<u>H_2</u>), 1.75 – 1.64 (2H, m, C**2**-<u>H_2</u>), 1.41 – 1.30 (4H, m, C**7**-<u>H_2</u>, C**8**-<u>H_2</u>), 1.20 (9H, s, Boc (C<u>H_3</u>)$_3$), 0.91 (3H, t, *J* = 7.0 Hz, C**9**-<u>H_3</u>); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6 (Boc <u>C</u>=O), 145.7 (Ts Ar<u>C</u>), 140.2 (Ar<u>C</u>), 136.1 (C**4**), 131.5 (Ts Ar<u>C</u>), 129.8 (2 × Ts Ar<u>C</u>H), 129.6 (2 × Ts Ar<u>C</u>H), 128.6 (ArC<u>H</u>), 128.5 (ArC<u>H</u>), 127.5 (C**5**), 126.0 (ArC<u>H</u>), 83.2 (Boc <u>C</u>(CH$_3$)$_3$), 53.0 (C**1**), 35.9 (C**10**), 33.4 (C**3**), 32.4 (C**7** or C**8**), 28.0 (C**6**), 27.7 (Boc (<u>C</u>H$_3$)$_3$), 24.0 (C**2**), 22.6 (C**7** or C**8**), 21.8 (Ts <u>C</u>H$_3$), 14.2 (C**9**); HRMS (ESI^+) Calculated for $C_{28}H_{39}NNaO_5S$: 524.2441. Found $[M+Na]^+$: 524.2441.

(5*R,6*S**)-5-Benzyl-6-butyl-1-azabicyclo[3.1.0]hexane (396b)**



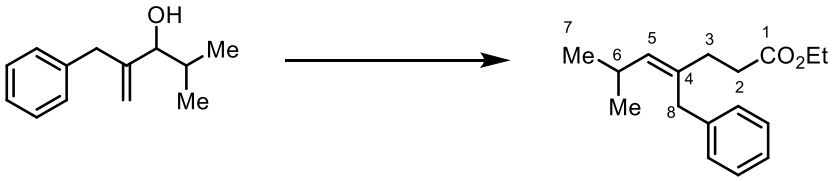
<u>General procedure P:</u> The preceding *N*-tosyloxycarbamate **395b** (100.3 mg, 0.2 mmol), TFA (31 μL, 0.4 mmol) in anhydrous TFE (2.0 mL) were employed. The reaction was stirred at room temperature for 22 hours. Purification by flash column chromatography (~0.1% Et_3N in EtOAc) afforded **396b** (37.2 mg, 81%) as a colourless oil.; R_f = 0.30 (EtOAc); ν_{max} / cm^{-1} (*film*) 2955 (m), 2931 (m), 2870 (m), 1687 (m), 1453 (m), 1180 (m), 701 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.18 (5H, m, ArC<u>H</u>), 3.05 – 3.00 (2H, m, C**1**-<u>H_2</u>), 2.98 (1H, d, *J* = 14.5 Hz, C**10**-<u>H</u>), 2.92 (1H, d, *J* = 14.5 Hz, C**10**-<u>H</u>'), 1.92 (1H, dd, *J* = 13.0, 8.0 Hz, C**3**-<u>H</u>), 1.75 – 1.33 (10H, m, C**2**-<u>H_2</u>, C**3**-<u>H</u>', C**5**-<u>H</u>, C**6**-<u>H_2</u>, C**7**-<u>H_2</u>, C**8**-<u>H_2</u>), 0.92 (3H, t, *J* = 7.0 Hz, C**9**-<u>H_3</u>); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.1 (Ar<u>C</u>), 129.4 (Ar<u>C</u>H), 128.5 (Ar<u>C</u>H), 126.3 (Ar<u>C</u>H), 54.9 (C**4**), 52.9 (C**1**), 42.9 (C**5**), 37.0 (C**10**), 30.4 (C**3**), 30.3 (C**7** or C**8**), 28.5 (C**6**), 22.8 (C**7** or C**8**), 22.1 (C**2**), 14.2 (C**9**); HRMS (ESI^+) Calculated for $C_{16}H_{24}N$: 230.1903. Found $[M+H]^+$: 230.1907.

2-Benzyl-4-methylpent-1-en-3-ol



To a solution of 2-benzylacrylaldehyde (**384**) (1.17 g, 8.0 mmol) in anhydrous THF (18 mL) at 0 °C was added *i*-PrMgCl (2 M in THF, 4.4 mL, 8.8 mmol) dropwise. After stirring at this temperature for 1 hour the reaction was quenched with a saturated aqueous Rochelle's salt (3 mL). The phases were separated, and the aqueous phase was extracted with Et_2O (3 × 20 mL) and the combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography (gradient, eluent: 10 – 20% EtOAc:petroleum ether) afforded the title compound (335 mg, 22%) as a colourless oil; R_f = 0.60 (20% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 3427 (br), 2958 (m), 1453 (m), 1012 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.27 (2H, m, ArC<u>H</u>), 7.24 – 7.18 (3H, m, ArC<u>H</u>), 5.09 (1H, t, *J* = 1.0 Hz, C**3**-<u>H</u>), 4.75 (1H, q, *J* = 1.5 Hz, C**3**-<u>H</u>'), 3.80 (1H, d, *J* = 6.5 Hz, C**1**-<u>H</u>), 3.46 (1H, d, *J* = 15.5 Hz, C**4**-<u>H</u>), 3.29 (1H, d, *J* = 15.5 Hz, C**4**-<u>H</u>'), 1.93 – 1.83 (1H, m, C**5**-<u>H</u>), 1.59 (1H, br s, O<u>H</u>), 0.96 (3H, d, *J* = 7.0 Hz, C**6**-<u>H_3</u>), 0.91 (3H, d, *J* = 7.0 Hz, C**6**'-<u>H_3</u>); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.7 (C**2**), 139.5 (Ar<u>C</u>), 129.5 (Ar<u>C</u>H), 128.5 (Ar<u>C</u>H), 126.3 (Ar<u>C</u>H), 113.1 (C**3**), 80.5 (C**1**), 38.7 (C**4**), 31.3 (C**5**), 19.8 (C**6**), 17.4 (C**6**'); HRMS (ESI^+) Calculated for $C_{13}H_{18}NaO$: 213.1250. Found $[M+Na]^+$: 213.1260.

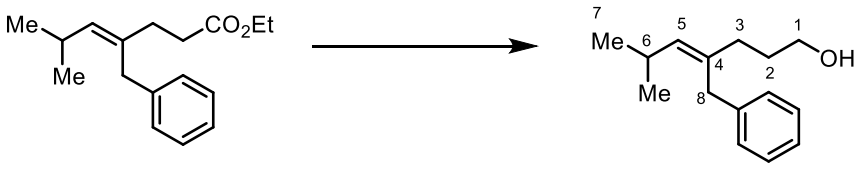
Ethyl (*Z*)-4-benzyl-6-methylhept-4-enoate



<u>General procedure Q:</u> 2-Benzyl-4-methylpent-1-en-3-ol (287 mg, 1.51 mmol), propionic acid (22 μL, 0.30 mmol) and triethyl orthoacetate (2.77 mL, 15.1 mmol) were employed. Purification by flash column chromatography (2% EtOAc:petroleum ether) afforded the title compound (200 mg, 51%) as a pale-yellow oil; R_f = 0.70 (10% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 2956 (m), 1733 (s), 1452 (m), 1154 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.24 (2H, m, ArC<u>H</u>), 7.20 – 7.13 (3H, m, ArC<u>H</u>), 5.16 (1H, d, *J* = 9.5 Hz, C**5**-<u>H</u>), 4.08 (2H, q, *J* = 7.0 Hz, OC<u>H_2</u>CH_3), 3.40 (2H, s, C**8**-<u>H_2</u>), 2.69 – 2.59 (1H, m, C**6**-<u>H</u>), 2.37 – 2.31 (2H, m, C**2**-<u>H_2</u>), 2.22 – 2.17 (2H, m, C**3**-<u>H_2</u>), 1.22 (3H, t, *J* = 7.0 Hz, OCH_2C<u>H_3</u>), 0.97 (6H, d, *J* = 6.5 Hz, C**7**-<u>H_3</u>);

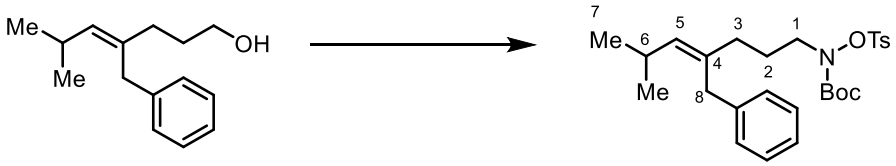
^{13}C NMR (101 MHz, $CDCl_3$) δ 173.5 (C**1**), 140.0 (Ar<u>C</u>), 135.2 (C**5**), 133.4 (C**4**), 128.6 (Ar<u>C</u>H), 128.5 (Ar<u>C</u>H), 126.1 (Ar<u>C</u>H), 60.3 (O<u>C</u>H$_2$CH$_3$), 36.3 (C**8**), 33.4 (C**2**), 31.6 (C**3**), 27.4 (C**6**), 23.5 (C**7**), 14.4 (OCH$_2$<u>C</u>H$_3$); HRMS (ESI$^+$) Calculated for $C_{17}H_{24}NaO_2$: 283.1669. Found $[M+Na]^+$:283.1676.

(*Z*)-4-Benzyl-6-methylhept-4-en-1-ol (394c)



<u>General procedure B</u>: Ethyl (*Z*)-4-benzyl-6-methylhept-4-enoate (198 mg, 0.76 mmol) and 0.8 equivalents of $LiAlH_4$ (2M in THF) in anhydrous Et_2O (2.0 mL) were employed. Purification by flash column chromatography (gradient, eluent: 10 – 25% EtOAc:petroleum ether) afforded **394c** (127 mg, 77%) as a colourless oil; R_f = 0.4 (20% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 3336 (br m), 2953 (m), 2856 (m), 1452 (m), 728 (m), 697 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.26 (2H, m, ArC<u>H</u>), 7.22 – 7.16 (3H, m, ArC<u>H</u>), 5.20 (1H, d, *J* = 9.5 Hz, C**5**-<u>H</u>), 3.57 (2H, t, *J* = 6.5 Hz, C**1**-<u>H</u>$_2$), 3.43 (2H, s, C**8**-<u>H</u>$_2$), 2.74 – 2.64 (1H, m, C**6**-<u>H</u>), 1.98 – 1.93 (2H, m, C**3**-<u>H</u>$_2$), 1.82 – 1.60 (3H, m, C**2**-<u>H</u>$_2$, O<u>H</u>), 1.02 (6H, d, *J* = 6.5 Hz, C**7**-<u>H</u>$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.2 (Ar<u>C</u>), 134.8 (C**5**), 134.5 (C**4**), 128.6 (Ar<u>C</u>H), 128.4 (Ar<u>C</u>H), 126.0 (Ar<u>C</u>H), 63.8 (C**1**), 36.1 (C**8**), 32.6 (C**3**), 30.9 (C**2**), 27.3 (C**6**), 23.6 (C**7**); HRMS (ESI$^+$) Calculated for $C_{15}H_{22}NaO$: 241.1563. Found $[M+Na]^+$: 241.1564.

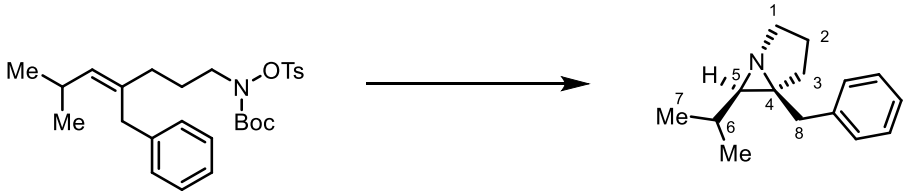
***tert*-Butyl (*Z*)-(4-benzyl-6-methylhept-4-en-1-yl)(tosyloxy)carbamate (395c)**



<u>General procedure G:</u> The preceding alcohol **394c** (120 mg, 0.55 mmol), PPh_3 (173 mg, 0.66 mmol), DIAD (0.13 mL, 0.66 mmol) and BocNHOTs (189 mg, 0.66 mmol) in anhydrous THF (3.0 mL) were employed. Purification by flash column chromatography (5% EtOAc:hexane) afforded **395c** (198 mg, 74%) as a colourless solid; m.p.: 64-66 ^{o}C (CH_2Cl_2:hexane); ν_{max} / cm^1 (*solid*) 2964 (m), 2953 (m), 2934 (m), 1716 (s), 1365 (s), 1175 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.32 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.29 – 7.24 (2H, m, ArC<u>H</u>), 7.20 – 7.12 (3H, m, ArC<u>H</u>), 5.14 (1H, d, *J* = 9.5 Hz, C**5**-<u>H</u>), 3.52 (2H, br s, C**1**-<u>H</u>$_2$),

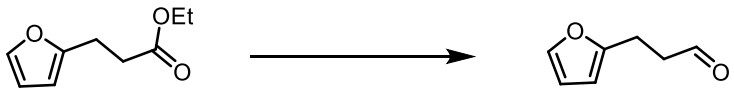
3.38 (2H, s, C**8**-H$_2$), 2.72 – 2.59 (1H, m, C**6**-H), 2.44 (3H, s, Ts CH$_3$), 1.84 – 1.80 (2H, m, C**3**-H$_2$), 1.76 – 1.63 (2H, m, C**2**-H$_2$), 1.21 (9H, s, Boc (CH$_3$)$_3$), 0.99 (6H, d, *J* = 6.5 Hz, C**7**-H$_3$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 155.9 (Boc C=O), 145.7 (Ts ArC), 140.1 (ArC), 135.1 (C**5**), 133.6 (C**4**), 131.4 (Ts ArC), 129.8 (2 × Ts ArCH), 129.6 (2 × Ts ArCH), 128.6 (ArCH), 128.5 (ArCH), 126.0 (ArCH), 83.2 (Boc C(CH$_3$)$_3$), 52.9 (C**1**), 36.0 (C**8**), 33.2 (C**3**), 27.7 (Boc (CH$_3$)$_3$), 27.4 (C**6**), 23.9 (C**2**), 23.6 (C**7**), 21.8 (Ts CH$_3$); HRMS (ESI$^+$) Calculated for $C_{27}H_{37}NNaO_5S$: 510.2285. Found [M+Na]$^+$: 510.2291.

(5*R,6*S**)-5-Benzyl-6-isopropyl-1-azabicyclo[3.1.0]hexane (396c)**



General procedure P: The preceding *N*-tosyloxycarbamate **395c** (97.5 mg, 0.2 mmol) and TFA (31 μL, 0.4 mmol) in anhydrous TFE (2.0 mL) were employed. After stirring for 46 hours purification by flash column chromatography (~0.1% Et$_3$N in EtOAc) afforded **396c** (34.6 mg, 80%) as a colourless oil; ν_{max} / cm^{-1} (*film*) 2957 (m), 2868 (m), 1494 (m), 1453 (s), 1181 (m), 1063 (m); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.32 – 7.25 (4H, m, ArCH), 7.22 – 7.17 (1H, m, ArCH), 2.99 – 2.87 (4H, m, C**1**-H$_2$, C**8**-H$_2$), 1.94 – 1.87 (1H, m, C**3**-H), 1.69 – 1.49 (4H, m, C**2**-H$_2$, C**3**-H', C**6**-H), 1.23 (1H, d, *J* = 9.5 Hz, C**5**-H), 1.10 (3H, d, *J* = 6.5 Hz, C**7**-H$_3$), 0.93 (3H, d, *J* = 6.5 Hz, C**7**'-H$_3$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 139.6 (ArC), 129.7 (ArCH), 128.3 (ArCH), 126.2 (ArCH), 54.6 (C**4**), 53.7 (C**1**), 49.6 (C**5**), 36.9 (C**8**), 30.1 (C**3**), 28.5 (C**6**), 22.3 (C**2**), 21.5 (C**7**), 20.6 (C**7**'); HRMS (ESI$^+$) Calculated for $C_{15}H_{22}N$: 216.1746. Found [M+H]$^+$: 216.1747.

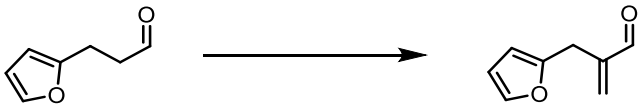
3-(Furan-2-yl)propanal



The title compound was prepared according to a literature procedure.[331]

^{1}H NMR (400 MHz, CDCl$_3$) δ 9.82 (1H, t, *J* = 1.5 Hz), 7.30 (1H, dd, *J* = 2.0, 1.0 Hz), 6.28 (1H, dd, *J* = 3.0, 2.0 Hz), 6.02 (1H, dd, *J* = 3.0, 1.0 Hz), 2.98 (2H, t, *J* = 7.5 Hz), 2.85 – 2.68 (2H, m).

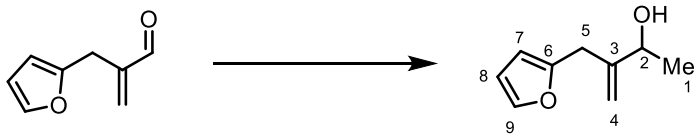
2-(Furan-2-ylmethyl)acrylaldehyde



The title compound was prepared according to a literature procedure.[327]

To a solution of pyrrolidine (54 µL, 0.64 mmol) and 4-(dimethylamino)benzoic acid (213 mg, 1.28 mmol) in dichloromethane (6.44 mL) were added formaldehyde (37% solution in H_2O, 0.51 mL, 6.44 mmol) and 3-(furan-2-yl)propanal (800 mg, 6.44 mmol) at room temperature. The reaction mixture was rapidly heated to 45 °C and stirred for 1 hour. The reaction mixture was then added to saturated aqueous $NaHCO_3$ (10 mL) and the resulting mixture extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were then washed with brine (10 mL), dried over Na_2SO_4, and concentrated *in vacuo* to obtain the crude product (896 mg, quantitative), which was used for the next step without further purification; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.58 (1H, s), 7.32 – 7.30 (1H, m), 6.30 – 6.28 (1H, m), 6.22 – 6.20 (1H, m), 6.10 -6.09 (1H, m), 6.08 – 6.06 (1H, m), 3.59 – 3.56 (2H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.5, 151.6, 146.7, 141.7, 135.4, 110.4, 107.0, 26.6.

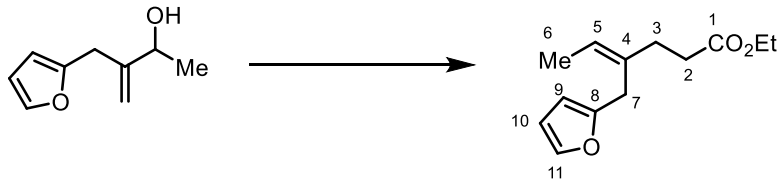
3-(Furan-2-ylmethyl)but-3-en-2-ol



To a solution of MeMgBr (3.0 M in Et_2O, 2.95 mL, 8.85 mmol) in anhydrous Et_2O (10 mL) at 0 °C was added 3-(furan-2-yl)but-3-enal (809 mg, 5.90 mmol) dropwise. The reaction mixture was stirred for 45 minutes at room temperature before addition of saturated aqueous NH_4Cl (10 mL). The phases were separated, and the aqueous phase extracted with Et_2O (2 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the title compound (873 mg, 97%) as a pale-yellow oil, which was used without further purification; ν_{max} / cm^{-1} (*film*) 3357 (br m), 2975 (m), 2899 (m), 1505 (m), 1071 (s), 1010 (s), 896 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (1H, dd, *J* = 2.0, 1.0 Hz, C**9**-H), 6.29 (1H, dd, *J* = 3.0, 2.0 Hz, C**8**-H), 6.08 – 6.06 (1H, m, C**7**-H), 5.14 – 5.12 (1H, m, C**4**-H'), 4.84 – 4.81 (1H, m, C**4**-H), 4.27 (1H, q, *J* = 6.5 Hz, C**2**-H), 3.43 (2H, q, *J* = 16.5 Hz, C**5**-H_2), 2.12 (1H, br s, OH), 1.28 (3H, d, *J* = 6.5 Hz, C**1**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ

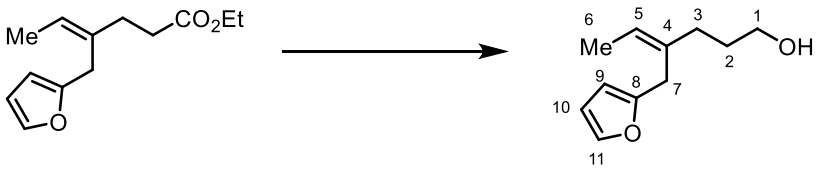
153.2 (C**6**), 149.5 (C**3**), 141.2 (C**9**), 111.0 (C**4**), 110.2 (C**8**), 106.4 (C**7**), 70.0 (C**2**), 30.9 (C**5**), 21.7 (C**1**); HRMS (APCI$^+$) Calculated for $C_9H_{12}O_2$: 153.0910. Found $[M+H]^+$: 153.0911.

Ethyl (*Z*)-4-(furan-2-ylmethyl)hex-4-enoate



General procedure Q: 4-(Furan-2-yl)pent-4-en-2-ol (873 mg, 5.70 mmol), propionic acid (86 μL, 1.15 mmol) and triethyl orthoacetate (10.4 mL, 57.0 mmol) were employed. The title compound was obtained as an orange oil (983 mg, 76%) which was used without further purification; ν_{max} / cm^{-1} (*film*) 2980 (m), 2931 (m), 1732 (s), 1160 (s), 1148 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (1H, dd, *J* = 2.0, 1.0 Hz, C**11**-H), 6.26 (1H, dd, *J* = 3.0, 2.0 Hz, C**10**-H), 5.97 (1H, dd, *J* = 3.0, 1.0 Hz, C**9**-H), 5.45 – 5.38 (1H, m, C**5**-H), 4.10 (2H, q, *J* = 7.0 Hz, $COCH_2CH_3$), 3.37 (2H, s, C**7**-H_2), 2.40 – 2.28 (4H, m, C**2**-H_2 and C**3**-H_2), 1.67 (3H, dd, *J* = 6.5 Hz, C**6**-H_3), 1.23 (3H, t, *J* = 7.0 Hz, $COCH_2CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.4 (C**1**), 153.7 (C**8**), 141.2 (C**11**), 134.5 (C**4**), 122.0 (C**5**), 110.3 (C**10**), 105.8 (C**9**), 60.3 (CH_2CH_3), 33.2 (C**3**), 32.2 (C**2**), 28.9 (C**7**), 14.3 (CH_2CH_3), 13.5 (C**6**); HRMS (APCI$^+$) Calculated for $C_{13}H_{19}O_3$: 223.1329. Found $[M+H]^+$: 223.1322.

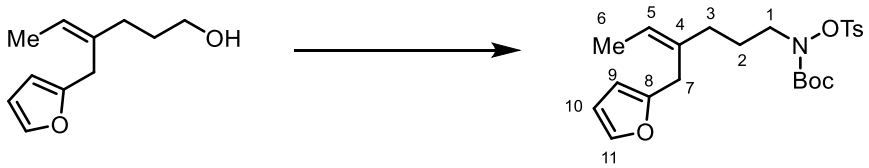
(*Z*)-4-(Furan-2-ylmethyl)hex-4-en-1-ol (394d)



General procedure B: Ethyl (*Z*)-4-(furan-2-ylmethyl)hex-4-enoate (983 mg, 4.42 mmol) and 0.8 equivalents of $LiAlH_4$ (3.54 mmol, 2 M in THF) in anhydrous Et_2O (20 mL) were employed. **394d** was obtained as a yellow oil (697 mg, 87%) which was used without further purification; R_f = 0.20 (20% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 3336 (br m), 2922 (m), 1505 (m), 1147 (m), 1055 (s), 1009 (s), 725 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (1H, dd, *J* = 2.0, 1.0 Hz, C**11**-H), 6.27 (1H, dd, *J* = 3.0, 2.0 Hz, C**10**-H), 5.98 (1H, dd, *J* = 3.0, 1.0 Hz, C**9**-H), 5.46 – 5.41 (1H, m, C**5**-H), 3.60 (2H, t, *J* = 6.5 Hz, C**1**-H_2), 3.38 (2H, s, C**7**-H_2), 2.10 – 2.06 (2H, m, C**3**-H_2), 1.70 – 1.61 (5H, m, C**2**-H_2, C**6**-H_3), 1.26 (1H, br s, OH); ^{13}C NMR (101 MHz,

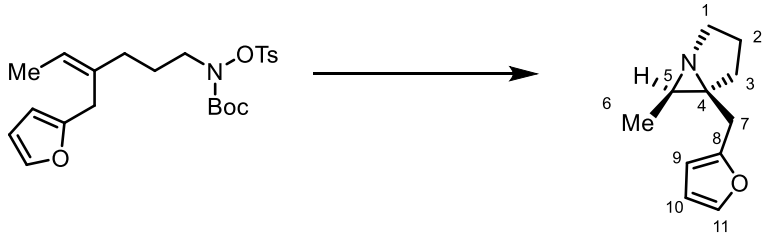
$CDCl_3$) δ 154.1 (C**8**), 141.2 (C**11**), 135.7 (C**4**), 121.6 (C**5**), 110.3 (C**10**), 105.8 (C**9**), 62.9 (C**1**), 33.4 (C**3**), 31.1 (C**2**), 28.9 (C**7**), 13.6 (C**6**).

***tert*-Butyl (*Z*)-(4-(furan-2-ylmethyl)hex-4-en-1-yl)(tosyloxy)carbamate (395d)**



General procedure G: The preceding alcohol **394d** (697 mg, 3.87 mmol), PPh_3 (1.22 g, 4.64 mmol), DIAD (0.91 mL, 4.64 mmol) and BocNHOTs (1.33 g, 4.64 mmol) in anhydrous THF (15 mL) were employed. Purification by flash column chromatography (gradient, eluent: 5 – 10% EtOAc:hexane) afforded **395d** (1.07 g, 62%) as a viscous, colourless oil; R_f = 0.55 (20% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 2986 (m), 2931 (m), 1719 (s), 1379 (s), 1368 (s), 1191 (s), 1178 (s), 1152 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.34 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.29 (1H, dd, *J* = 2.0, 1.0 Hz, C**11**-<u>H</u>), 6.26 (1H, dd, *J* = 3.0, 2.0 Hz, C**10**-<u>H</u>), 5.96 (1H, dd, *J* = 3.0, 1.0 Hz, C**9**-<u>H</u>), 5.41 – 5.36 (1H, m, C**5**-<u>H</u>), 3.54 (2H, br s, C**1**-<u>H_2</u>), 3.35 (2H, s, C**7**-<u>H_2</u>), 2.45 (3H, s, Ts C<u>H_3</u>), 1.97 – 1.92 (2H, m, C**3**-<u>H_2</u>), 1.75 – 1.66 (5H, m, C**2**-<u>H_2</u>, C**6**-<u>H_3</u>), 1.21 (9H, s, Boc (C<u>H_3</u>)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6 (Boc <u>C</u>=O), 153.9 (C**8**), 145.8 (Ts Ar<u>C</u>), 141.2 (C**11**), 134.8 (C**4**), 131.4 (Ts Ar<u>C</u>), 129.8 (2 × Ts Ar<u>C</u>H), 129.6 (2 × Ts Ar<u>C</u>H), 121.7 (C**5**), 110.3 (C**10**), 105.8 (C**9**), 83.3 (Boc <u>C</u>(CH_3)$_3$), 52.9 (C**1**), 33.9 (C**3**), 28.8 (C**7**), 27.8 (Boc (<u>C</u>H_3)$_3$), 24.0 (C**2**), 21.8 (Ts <u>C</u>H_3), 13.5 (C**6**); HRMS (ESI^+) Calculated for $C_{23}H_{31}NNaO_6S$: 472.1764. Found $[M+Na]^+$: 472.1772.

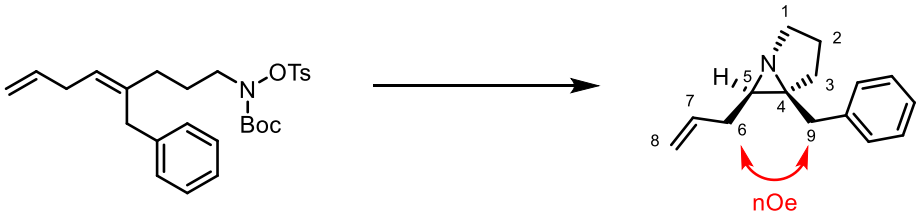
(5*S,6*R**)-5-(Furan-2-ylmethyl)-6-methyl-1-azabicyclo[3.1.0]hexane (396d)**



General procedure P: The preceding *N*-tosyloxycarbamate **395d** (89.9 mg, 0.2 mmol), and TFA (31 μL, 0.4 mmol) in anhydrous TFE (0.1 M) were employed. After stirring for 48 hours purification by flash column chromatography (~0.1% Et_3N in 33% EtOAc:hexane) afforded **396d** (17.1 mg, 48%) as a colourless oil; R_f = 0.01 (EtOAc); ν_{max} / cm^{-1} (*film*) 2958 (m), 2876 (m), 1505 (m), 1146 (s), 1009 (s), 731 (s), 723 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (1H,

dd, *J* = 2.0, 1.0 Hz, C**11**-H), 6.29 (1H, dd, *J* = 3.0, 2.0 Hz, C**10**-H), 6.06 (3.0, 1.0 Hz, C**9**-H), 3.01 – 2.83 (4H, m, C**1**-H$_2$, C**7**-H$_2$), 2.02 (1H, dd, *J* = 13.0, 8.5 Hz, C**3**-H), 1.78 – 1.69 (1H, m, C**3**-H'), 1.68 – 1.59 (2H, m, C**2**-H, C**5**-H), 1.58 – 1.46 (1H, m, C**2**-H'), 1.21 (3H, d, *J* = 6.0 Hz, C**6**-H$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.7 (C**8**), 141.2 (C**11**), 110.3 (C**10**), 106.3 (C**9**), 53.2 (C**1**), 52.6 (C**4**), 36.7 (C**5**), 30.9 (C**3**), 30.5 (C**7**), 22.4 (C**2**), 14.1 (C**6**); HRMS (ESI$^+$) Calculated for $C_{11}H_{16}NO$: 178.1226. Found $[M+H]^+$: 178.1219.

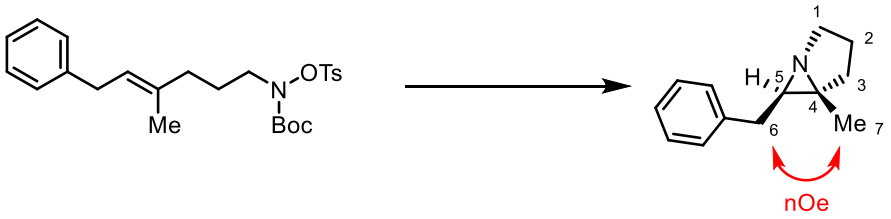
(5*R,6*S**)-6-Allyl-5-benzyl-1-azabicyclo[3.1.0]hexane (398a)**



General procedure P: *N*-Tosyloxycarbamate **397a** (94.3 mg, 0.195 mmol) and TFA (31 μL, 0.4 mmol) in anhydrous TFE (2.0 mL) were employed. After stirring at room temperature for 41 hours purification by flash column chromatography (0.1% Et_3N in EtOAc) afforded **398a** (33.6 mg, 81%) as a colourless oil; R_f = 0.30 (EtOAc); ν_{max} / cm^{-1} (*film*) 2959 (m), 2935 (m), 2871 (m), 1640 (m), 1494 (m), 1453 (m), 909 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.26 (4H, m ArCH), 7.25 – 7.19 (1H, m, ArCH), 5.95 (1H, ddt, *J* = 16.5, 10.0, 6.5 Hz, C**7**-H), 5.18 – 5.06 (2H, m, C**8**-H$_2$), 3.06 – 2.89 (4H, m, C**1**-H$_2$, C**9**-H$_2$), 2.38 – 2.32 (2H, m, C**6**-H$_2$), 1.94 (1H, dd, *J* = 12.5, 8.5 Hz, C**3**-H), 1.73 – 1.51 (4H, m, C**2**-H$_2$, C**3**-H', C**5**-H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.4 (ArC), 136.3 (C**7**), 129.5 (ArCH), 128.4 (ArCH), 126.2 (ArCH), 115.9 (C**8**), 54.2 (C**4**), 53.5 (C**1**), 41.2 (C**5**), 37.3 (C**9**), 33.6 (C**6**), 30.4 (C**3**), 22.2 (C**2**); HRMS (ESI$^+$) Calculated for $C_{15}H_{19}N$: 214.1590. Found $[M+H]^+$: 214.1590.

*The relative stereochemistry of this compound was determined by nOe experiments as indicated on the compound structure. An nOe correlation was observed between C**6**-H$_2$ and C**9**-H$_2$.*

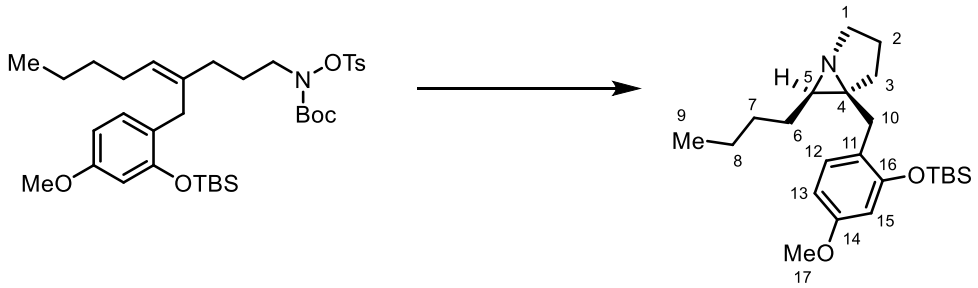
(5*S,6*S**)-6-Benzyl-5-methyl-1-azabicyclo[3.1.0]hexane (398b)**



General procedure P: *N*-Tosyloxycarbamate **397b** (91.9 mg, 0.2 mmol) and TFA (31 μL, 0.4 mmol) in anhydrous TFE (2.0 mL) were employed. The reaction was stirred at room temperature for 24 hours. Purification by flash column chromatography (~0.1% Et_3N in EtOAc) afforded **398b** (27.3 mg, 73%) as a pale-yellow oil; R_f = 0.15 (EtOAc); ν_{max} / cm^{-1} (*film*) 2950 (m), 2873 (m), 1493 (m), 1453 (m), 730 (s), 697 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.24 (4H, m, ArC**H**), 7.23 – 7.18 (1H, m, ArC**H**), 3.04 – 2.95 (2H, m, C**1**-H$_2$), 2.81 (1H, dd, *J* = 15.0, 6.5 Hz, C**6**-H), 2.68 (1H, dd, 15.0, 6.0 Hz, C**6**-H'), 2.09 (1H, dd, *J* = 12.5, 8.5 Hz, C**3**-H), 1.76 – 1.60 (3H, m, C**3**-H', C**5**-H, C**2**-H), 1.58 – 1.48 (1H, m, C**2**-H'), 1.37 (3H, s, C**7**-H$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.5 (Ar**C**), 128.6 (Ar**C**H), 128.5 (Ar**C**H), 126.2 (Ar**C**H), 53.4 (C**1**), 50.1 (C**4**), 42.8 (C**5**), 35.4 (C**6**), 33.2 (C**3**), 22.4 (C**2**), 17.3 (C**7**); HRMS (ESI^+) Calculated for $C_{13}H_{18}N$: 188.1434. Found $[M+H]^+$: 188.1439.

*The relative stereochemistry of this compound was determined by nOe experiments as indicated on the compound structure. nOe correlations were observed between C**6**-H$_2$ and C**7**-H$_3$, and C**7**-H$_3$ and ArCH.*

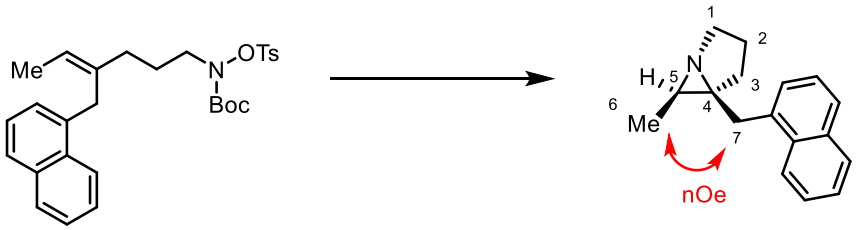
(5*R,6*S**)-6-Butyl-5-(2-((*tert*-butyldimethylsilyl)oxy)-4-methoxybenzyl)-1-azabicyclo [3.1.0]hexane (398c)**



General procedure P: *N*-Tosyloxycarbamate **397c** (66.2 mg, 0.1 mmol) and 3.0 equivalents of TFA (23 μL) in anhydrous TFE (1.0 mL) were employed. Purification by flash column chromatography (~0.1% Et_3N in EtOAc) afforded **398c** (26.3 mg, 67%) as a yellow oil; R_f = 0.60 (EtOAc); ν_{max} / cm^{-1} (*film*) 2954 (m), 2929 (m), 1609 (m), 1504 (s), 1161 (s), 837 (s), 778

(s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (1H, d, *J* = 8.5 Hz, C**12**-H), 6.48 (1H, dd, *J* = 8.5, 2.5 Hz, C**13**-H), 6.37 (1H, d, *J* = 2.5 Hz, C**15**-H), 3.76 (3H, s, C**17**-H_3), 2.98 – 2.74 (4H, m, C**1**-H_2, C**10**-H_2), 1.96 – 1.90 (1H, m, C**3**-H), 1.67 – 1.30 (10H, m, C**3**-H', C**2**-H_2, C**6**-H_2, C**7**-H_2, C**8**-H_2, C**5**-H), 1.01 (9H, s, TBS SiC(CH_3)$_3$), 0.91 (3H, t, *J* = 7.0 Hz, C**9**-H_3), 0.22 (3H, s, TBS SiCH_3), 0.22 (3H, s, TBS SiCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.6 (C**14**), 154.6 (C**16**), 130.7 (C**12**), 122.6 (C**11**), 106.0 (C**13**), 105.4 (C**15**), 55.4 (C**17**), 54.2 (C**4**), 53.5 (C**1**), 42.3 (C**5**), 30.6 (C**6** or C**7** or C**8**), 30.6 (C**3**), 29.5 (C**10**), 28.9 (C**6** or C**7** or C**8**), 26.0 (TBS SiC(CH_3)$_3$), 22.9 (C**6** or C**7** or C**8**), 22.3 (C**2**), 18.4 (TBS SiC(CH_3)$_3$), 14.3 (C**9**), -3.9 (TBS SiCH_3), -4.0 (TBS SiCH_3); HRMS (ESI$^+$) Calculated for $C_{23}H_{40}NO_2Si$: 390.2822. Found $[M+H]^+$: 390.2826.

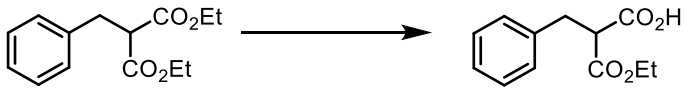
(5*R,6*S**)-6-Methyl-5-(naphthalen-1-ylmethyl)-1-azabicyclo[3.1.0]hexane (398d)**



General procedure P: *N*-Tosyloxycarbamate **397d** (101.9 mg, 0.2 mmol), and TFA (31 μL, 0.4 mmol) in anhydrous TFE (0.1 M) were employed. After stirring for 48 hours purification by flash column chromatography (~0.1% Et_3N in 33% EtOAc:hexane) afforded **398d** (33.5 mg, 71%) as a yellow oil; R_f = 0.1 (EtOAc); ν_{max} / cm^{-1} (*film*) 2955 (m), 2929 (m), 2869 (m), 791 (s), 778 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (1H, d, *J* = 8.5 Hz, ArCH), 7.85 (1H, dd, *J* = 8.0, 1.5 Hz, ArCH), 7.74 (1H, d, *J* = 8.0 Hz, ArCH), 7.56 – 7.40 (4H, m, ArCH), 3.46 (1H, d, *J* = 15.5 Hz, C**7**-H), 3.31 (1H, d, *J* = 15.5 Hz, C**7**-H'), 3.06 – 2.90 (2H, m, C**1**-H_2), 1.99 – 1.92 (1H, m, C**3**-H), 1.81 (1H, q, *J* = 6.0 Hz, C**5**-H), 1.58 – 1.46 (3H, m, C**2**-H_2, C**3**-H'), 1.31 (3H, d, *J* = 6.0 Hz, C**6**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.9 (ArC), 133.8 (ArC), 132.7 (ArC), 128.7 (ArCH), 126.9 (ArCH), 126.7 (ArCH), 126.0 (ArCH), 125.6 (ArCH), 125.5 (ArCH), 124.7 (ArCH), 53.3 (C**4**), 52.8 (C**1**), 37.1 (C**5**), 34.2 (C**7**), 30.2 (C**3**), 22.3 (C**2**), 14.1 (C**6**); HRMS (ESI$^+$) Calculated for $C_{17}H_{20}N$: 238.1590. Found $[M+H]^+$: 238.1593.

*The relative stereochemistry of this compound was determined by nOe experiments as indicated on the compound structure. nOe correlations were observed between C**6**-H_3 and C**7**-H_2.*

2-Benzyl-3-ethoxy-3-oxopropanoic acid

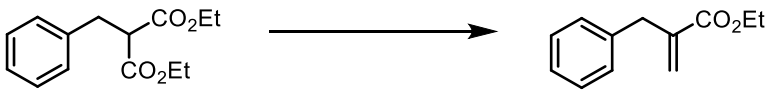


This compound was prepared according to a literature procedure.[332]

To a solution of diethyl 2-benzylmalonate (12.5 g, 50.0 mmol) in EtOH (45 mL) was added a solution of KOH (2.80 g, 50.0 mmol) in EtOH (45 mL) and the reaction was stirred overnight. The reaction was concentrated *in vacuo*, diluted with ice-cold H_2O and extracted with Et_2O. The aqueous solution was acidified to pH 2 with concentrated HCl and extracted with Et_2O, dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (8.75 g, 79%) which was used without further purification; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (1H, br s), 7.31 – 7.19 (5H, m), 4.17 (2H, q, *J* = 7.0 Hz), 3.70 (1H, t, *J* = 7.5 Hz), 3.24 (2H, d, *J* = 7.5 Hz), 1.20 (3H, t, *J* = 7.0 Hz).

The spectroscopic properties were consistent with the data available in the literature.[333]

Ethyl 2-benzylacrylate

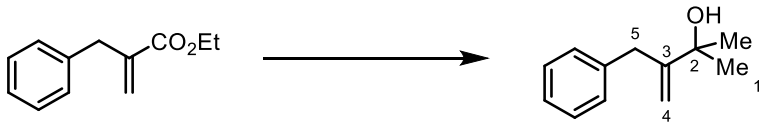


This compound was prepared based on a literature procedure.[332]

To a solution of 2-benzyl-3-ethoxy-3-oxopropanoic acid (8.73 g, 39.3 mmol) in diethylamine (4.2 mL) and CH_2Cl_2 (5 mL) at 0 °C was added formaldehyde (37% aqueous solution, 4.1 mL) and the reaction was stirred at room temperature overnight. The reaction was extracted with Et_2O (3 × 50 mL) and washed with aqueous 2 M HCl (50 mL) and then a saturated aqueous solution of $NaHCO_3$ (50 mL) and finally brine (50 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The title compound (7.14 g, 96%) was obtained as a colourless oil which was used without further purification; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.28 (2H, m), 7.23 – 7.20 (3H, m), 6.25 – 6.24 (1H, m), 5.47 – 5.45 (1H, m), 4.19 (2H, q, *J* = 7.0 Hz), 3.65 (2H, s), 1.27 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0, 140.5, 138.9, 129.2, 128.5, 126.4, 126.1, 60.8, 38.2, 14.3.

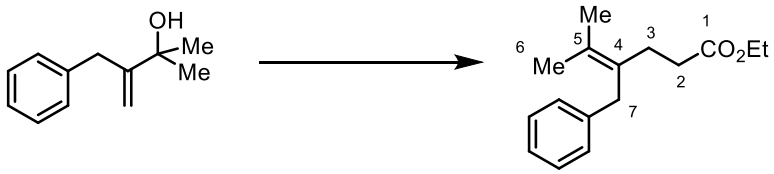
The spectroscopic properties were consistent with the data available in the literature.[334]

3-Benzyl-2-methylbut-3-en-2-ol (399)



A solution of ethyl 2-benzylacrylate (3.80 g, 20.0 mmol) in anhydrous Et_2O (25 mL) was cooled to 0 °C before addition of MeMgBr (3.0 M in Et_2O, 14.6 mL, 44.0 mmol) dropwise over 30 minutes. The reaction was stirred at room temperature for 1 hour then quenched with saturated aqueous NH_4Cl (20 mL). The layers were separated, and the aqueous phase extracted with Et_2O (3 × 50 mL) and the combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography (20% EtOAc:petroleum ether) afforded **399** (1.54 g, 44%) as a colourless oil; Rf = 0.40 (20% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 3388 (br s), 2976 (m), 1128 (s), 904 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.28 (2H, m, ArC<u>H</u>), 7.23 – 7.18 (3H, m, ArC<u>H</u>), 5.21 – 5.20 (1H, m, C**4**-<u>H</u>), 4.59 – 4.58 (1H, m, C**4**-<u>H</u>'), 3.47 (2H, s, C**5**-<u>H_2</u>), 1.51 (1H, br s, O<u>H</u>), 1.39 (6H, s, C**1**-<u>H_3</u>); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.7 (C**3**), 140.3 (Ar<u>C</u>), 129.4 (Ar<u>C</u>H), 128.5 (Ar<u>C</u>H), 126.2 (Ar<u>C</u>H), 110.7 (C**4**), 73.6 (C**2**), 38.5 (C**5**), 29.7 (C**1**); HRMS (ESI^+) Calculated for $C_{12}H_{15}$: 159.1168. Found $[M+H-H_2O]^+$: 159.1170.

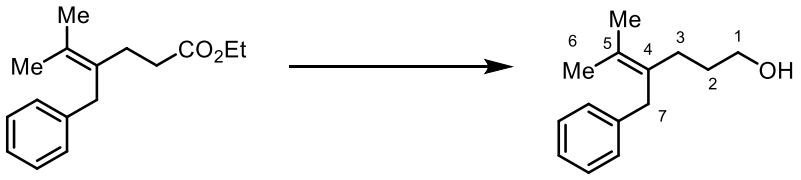
Ethyl 4-benzyl-5-methylhex-4-enoate



<u>General procedure Q:</u> The preceding allylic alcohol **399** (1.32 g, 7.5 mmol), propionic acid (0.11 mL, 1.50 mmol) and triethyl orthoacetate (13.7 mL, 75 mmol) were employed. Purification by flash column chromatography (5% EtOAc:petroleum ether) afforded the title compound (1.18 g, 64%) as a colourless oil; R_f = 0.70 (20% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 2981 (m), 2927 (m), 1732 (s), 1162 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.25 (2H, m, ArC<u>H</u>), 7.20 – 7.13 (3H, m, ArC<u>H</u>), 4.09 (2H, q, *J* = 7.0 Hz, $CO_2C\underline{H}_2CH_3$), 3.43 (2H, s, C**7**-<u>H_2</u>), 2.37 – 2.31 (2H, m, C**3**-<u>H_2</u>), 2.30 – 2.25 (2H, m, C**2**-<u>H_2</u>), 1.78 (6H, s, C**6**-<u>H_3</u>), 1.23 (3H, t, *J* = 7.0 Hz, $CO_2CH_2C\underline{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6 (C**1**), 140.7 (Ar<u>C</u>), 129.2 (C**4** or C**5**), 128.5 (Ar<u>C</u>H), 128.4 (Ar<u>C</u>H), 128.4 (C**4** or C**5**), 125.9 (Ar<u>C</u>H), 60.4 ($CO_2\underline{C}H_2CH_3$), 37.7

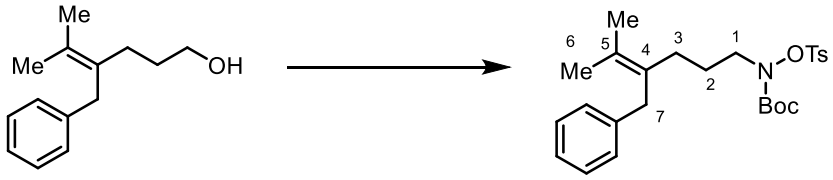
(C**7**), 33.4 (C**2**), 27.7 (C**3**), 21.1 (C**6**), 20.5 (C**6**'), 14.3 ($CO_2CH_2\underline{C}H_3$); HRMS (ESI^+) Calculated for $C_{16}H_{22}NaO_2$: 269.1512. Found $[M+Na]^+$: 269.1526.

4-Benzyl-5-methylhex-4-en-1-ol (400)



General procedure B: Ethyl 4-benzyl-5-methylhex-4-enoate (932 mg, 3.78 mmol) and 0.8 equivalents of $LiAlH_4$ (1M in THF) in anhydrous Et_2O (20 mL) were employed. Purification by flash column chromatography (20% EtOAc:petroleum ether) afforded **400** (584 mg, 76%) as a colourless oil; R_f = 0.20 (20% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 3330 (br s), 2918 (m), 2853 (m), 1493 (m), 1451 (m), 1057 (m), 1030 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.24 (2H, m, ArC$\underline{H}$), 7.20 – 7.13 (3H, m, ArC$\underline{H}$), 3.56 (2H, t, *J* = 6.5 Hz, C**1**-$\underline{H}_2$), 3.44 (2H, s, C**7**-$\underline{H}_2$), 2.06 (2H, dd, *J* = 9.5, 6.5 Hz, C**3**-$\underline{H}_2$), 1.79 (3H, s, C**6**-$\underline{H}_3$), 1.77 (3H, s, C**6**'-$\underline{H}_3$), 1.63 (1H, br s, O$\underline{H}$), 1.62 – 1.54 (2H, m, C**2**-$\underline{H}_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.0 (Ar$\underline{C}$), 130.4 (C**4**), 128.6 (Ar$\underline{C}$H), 128.4 (Ar$\underline{C}$H), 127.3 (C**5**), 125.9 (Ar$\underline{C}$H), 63.2 (C**1**), 37.9 (C**7**), 31.7 (C**2**), 28.4 (C**3**), 21.0 (C**6**), 20.5 (C**6**'); HRMS (ESI^+) Calculated for $C_{14}H_{20}NaO$: 227.1406. Found $[M+Na]^+$: 227.1397.

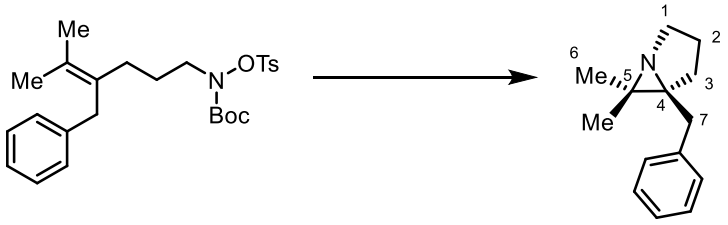
***tert*-Butyl (4-benzyl-5-methylhex-4-en-1-yl)(tosyloxy)carbamate (401)**



General procedure G: The preceding alcohol **400** (409 mg, 2.0 mmol), PPh_3 (629 mg, 2.4 mmol), DIAD (0.47 mL, 2.4 mmol) and BocNHOTs (689 mg, 2.4 mmol) in anhydrous THF (8 mL) were employed. Purification by flash column chromatography (10% EtOAc:petroleum ether) afforded **401** (791 mg, 84%) as a colourless, viscous oil; R_f = 0.4 (4:1 hexane:EtOAc); ν_{max} / cm^{-1} (*film*) 2981 (m), 2929 (m), 1720 (s), 1379 (s), 1368 (s), 1191 (s), 1177 (s), 1156 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (2H, d, *J* = 8.5 Hz, Ts ArC$\underline{H}$), 7.32 (2H, d, *J* = 8.5 Hz, Ts ArC$\underline{H}$), 7.28 – 7.22 (2H, m, ArC$\underline{H}$), 7.18 – 7.10 (3H, m, ArC$\underline{H}$), 3.52 (2H, br s, C**1**-$\underline{H}_2$), 3.39 (2H, s, C**7**-$\underline{H}_2$), 2.44 (3H, s, Ts C$\underline{H}_3$), 1.92 (2H, t, *J* = 8.0 Hz, C**3**-$\underline{H}_2$), 1.76 (3H, s, C**6**-$\underline{H}_3$), 1.72 (3H, s, C**6**'-$\underline{H}_3$), 1.68 – 1.59 (2H, m, C**2**-$\underline{H}_2$), 1.19 (9H, s, Boc ($\underline{C}H_3)_3$); ^{13}C NMR (101 MHz,

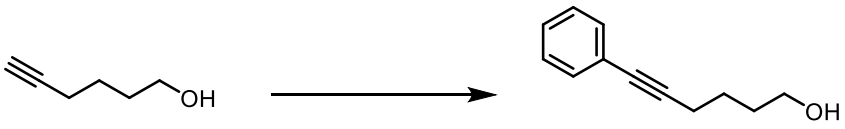
$CDCl_3$) δ 155.6 (Boc C=O), 145.7 (Ts ArC), 140.9 (ArC), 131.5 (Ts ArC), 129.9 (C**4** or C**5**), 129.8 (2 × Ts ArCH), 129.6 (2 × Ts ArCH), 128.6 (ArCH), 128.4 (ArCH), 127.5 (C**4** or C**5**), 125.9 (ArCH), 83.2 (Boc $C(CH_3)_3$), 53.1 (C**1**), 37.6 (C**7**), 29.0 (C**3**), 27.7 (Boc $(CH_3)_3$), 24.8 (C**2**), 21.8 (Ts CH_3), 21.0 (C**6**), 20.6 (C**6**'); HRMS (ESI^+) Calculated for $C_{26}H_{35}NNaO_5S$: 496.2128. Found $[M+Na]^+$: 496.2112.

5-Benzyl-6,6-dimethyl-1-azabicyclo[3.1.0]hexane (402)



General procedure P: The preceding *N*-tosyloxycarbamate **401** (94.7 mg, 0.2 mmol) and TFA (31 μL, 0.4 mmol) in anhydrous TFE (2 mL) were employed. After stirring for 48 hours purification by flash column chromatography (~0.1% Et_3N in EtOAc) afforded **402** (36.2 mg, 90%) as a colourless oil; R_f = 0.05 (EtOAc); ν_{max} / cm^{-1} (*film*) 2951 (m), 2924 (m), 2878 (m), 1494 (m), 1452 (m), 1114 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.17 (5H, m, ArCH), 3.23 (1H, ddd, *J* = 13.0, 10.20, 6.0 Hz, C**1**-H), 2.97 (1H, d, *J* = 15.0 Hz, C**7**-H), 2.88 (1H, d, *J* = 15.0 Hz, C**7**-H'), 2.70 (1H, ddd, *J* = 13.0, 9.5, 5.5 Hz, C**1**-H'), 1.97 – 1.85 (1H, m, C**2**-H), 1.83 – 1.71 (2H, m, C**3**-H_2), 1.68 – 1.57 (1H, m, C**2**-H'), 1.31 (3H, s, C**6**-H_3), 1.09 (3H, s, C**6**'-H_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.1 (ArC), 129.0 (ArCH), 128.4 (ArCH), 126.0 (ArCH), 59.7 (C**4**), 49.8 (C**1**), 44.3 (C**5**), 39.6 (C**7**), 30.0 (C**2**), 29.7 (C**3**), 24.6 (C**6**), 15.9 (C**6**'); HRMS (ESI^+) Calculated for $C_{14}H_{20}N$: 202.1590. Found $[M+H]^+$: 202.1598.

6-Phenylhex-5-yn-1-ol (403)



The title compound was prepared according to a literature procedure.[335]

To a stirred solution of iodobenzene (2.04 g, 10.0 mmol) in Et_3N (20 mL) under an atmosphere of nitrogen were added $Pd(PPh_3)_2Cl_2$ (105.3 mg, 0.15 mmol) and CuI (57.1 mg, 0.3 mmol). The reaction was stirred at room temperature for 10 minutes then 5-hexyn-1-ol (1.21 mL, 11.0 mmol) was added and then reaction was stirred at room temperature overnight. The reaction mixture was poured into a saturated aqueous solution of NH_4Cl (20 mL) and extracted with

Et_2O. The organic extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash column chromatography (gradient, eluent: 20 – 33% EtOAc:petroleum ether) afforded **403** (1.74 g, 99%) as a brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.36 (2H, m), 7.29 – 7.24 (3H, m), 3.70 (2H, t, *J* = 6.0 Hz), 2.45 (2H, t, *J* = 6.5 Hz), 1.85 (1H, br s), 1.78 – 1.65 (4H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ 131.7, 128.3, 127.7, 124.0, 90.0, 81.1, 62.6, 32.0, 25.1, 19.3.

The spectroscopic properties were consistent with the data available in the literature.[336]

(*E*)-6-Phenylhex-5-en-1-ol (404)

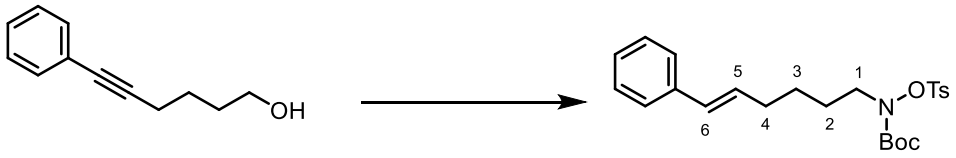
To a solution of the preceding alkyne **403** (1.59 g, 9.13 mmol) in THF (15 mL) at 0 °C was added 3.5 equivalents of $LiAlH_4$ (16 mL, 2 M in THF). After stirring at 0 °C for 20 minutes the reaction was heated to reflux and stirred overnight. Upon completion, the reaction mixture was cooled to 0 °C before addition of water (1 mL/g of $LiAlH_4$), 15% aqueous NaOH (1 mL/g $LiAlH_4$) and a final portion of water (3 mL/g of $LiAlH_4$). The mixture was filtered through Celite® and washed with CH_2Cl_2. The phases were separated, and the aqueous phase extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography (gradient, eluent: 20 – 33% EtOAc:petroleum ether) afforded **404** (920 mg, 57%, 10:1 mixture of *E* and *Z* isomers) as a colourless oil.

Spectroscopic data for the major E isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.17 (5H, m), 6.40 (1H, dt, *J* = 16.0, 1.5 Hz), 6.22 (1H, dt, *J* = 16.0, 7.0 Hz), 3.68 (2H, t, *J* = 6.5 Hz), 2.25 (2H, qd, *J* = 7.0, 1.5 Hz), 1.66 - 1.53 (4H, m), 1.49 (1H, br s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.9, 130.7 , 130.3, 128.6, 127.0, 126.1, 63.0, 32.9, 32.4, 25.6.

Characteristic signals for the minor Z isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.66 (1H, dt, *J* = 11.5, 7.0 Hz), 3.63 (2H, t, *J* = 6.5 Hz), 2.37 (2H, qd, *J* = 7.5, 2.0 Hz).

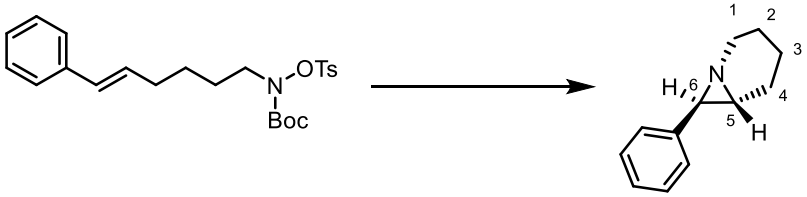
The spectroscopic properties were consistent with the data available in the literature.[337]

***tert*-Butyl (*E*)-(6-phenylhex-5-en-1-yl)(tosyloxy)carbamate (405)**



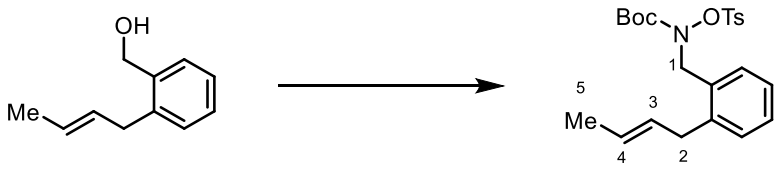
General procedure G: The preceding alcohol **404** (260 mg, 1.50 mmol), PPh_3 (470 mg, 1.80 mmol), DIAD (0.35 mL, 1.80 mmol) and BocNHOTs (520 mg, 1.80 mmol) in anhydrous THF (6 mL) were employed. Purification by flash column chromatography (5% EtOAc:petroleum ether) afforded **405** (560 mg, 84%) as a viscous, colourless oil; R_f = 0.40 (20% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 2933 (m), 1719 (s), 1368 (s), 1191 (s), 1177 (s), 1152 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.36 – 7.27 (6H, m, ArC<u>H</u>, Ts ArC<u>H</u>), 7.21 – 7.16 (1H, m, ArC<u>H</u>), 6.37 (1H, d, *J* = 16.0 Hz, C**6**-<u>H</u>), 6.17 (1H, dt, *J* = 16.0, 7.0 Hz, C**5**-<u>H</u>), 3.64 (2H, br s, C**1**-<u>H</u>$_2$), 2.45 (3H, s, Ts C<u>H</u>$_3$), 2.24 – 2.17 (2H, m, C**4**-<u>H</u>$_2$), 1.74 – 1.63 (2H, m, C**2**-<u>H</u>$_2$), 1.49 – 1.40 (2H, m, C**3**-<u>H</u>$_2$), 1.22 (9H, s, Boc (C<u>H</u>$_3$)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.7 (Boc <u>C</u>=O), 145.8 (Ts Ar<u>C</u>), 137.8 (Ar<u>C</u>), 131.4 (Ts Ar<u>C</u>), 130.5 (C**6**), 130.3 (C**5**), 129.8 (2 × Ts Ar<u>C</u>H), 129.7 (2 × Ts Ar<u>C</u>H), 128.6 (Ar<u>C</u>H), 127.0 (Ar<u>C</u>H), 126.1 (Ar<u>C</u>H), 83.3 (Boc <u>C</u>(CH$_3$)), 52.8 (C**1**), 32.7 (C**4**), 27.8 (Boc (<u>C</u>H$_3$)), 26.4 (C**3**), 25.5 (C**2**), 21.8 (Ts <u>C</u>H$_3$); HRMS (ESI$^+$) Calculated for $C_{24}H_{31}NNaO_5S$: 468.1815. Found [M+Na]$^+$: 468.1823.

(6*S,7*S**)-7-Phenyl-1-azabicyclo[4.1.0]heptane (406)**



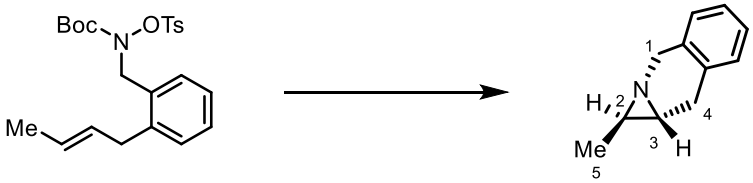
General procedure P: The preceding *N*-tosyloxycarbamate **405** (66.8 mg, 0.15 mmol) and 2.0 equivalents of TFA (23 μL, 0.3 mmol) in anhydrous TFE (1.5 mL) were employed. After stirring for 48 hours purification by flash column chromatography (~0.1% Et_3N in EtOAc) afforded **406** (11.5 mg, 44%) as a pale-yellow oil; R_f = 0.30 (EtOAc); ν_{max} / cm^{-1} (*film*) 2932 (m), 2852 (m), 1602 (m), 1498 (m), 1450 (m), 1161 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.25 (2H, m, ArC<u>H</u>), 7.22 – 7.16 (3H, m, ArC<u>H</u>), 3.49 – 3.41 (1H, m, C**1**-<u>H</u>), 2.96 – 2.88 (1H, m, C**1**-<u>H</u>'), 2.56 (1H, d, *J* = 3.0 Hz, C**6**-<u>H</u>), 2.20 – 2.16 (1H, m, C**5**-<u>H</u>), 2.08 – 2.00 (2H, m, C**4**-<u>H</u>$_2$), 1.54 – 1.39 (4H, m, C**2**-<u>H</u>$_2$, C**3**-<u>H</u>$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.4 (Ar<u>C</u>), 128.4 (Ar<u>C</u>H), 126.8 (Ar<u>C</u>H), 125.9 (Ar<u>C</u>H), 48.7 (C**1**), 45.6 (C**6**), 42.1 (C**5**), 22.1 (C**4**), 21.4 (C**2**), 18.4 (C**3**); HRMS (ESI$^+$) Calculated for $C_{12}H_{16}N$: 174.1277. Found [M+H]$^+$: 174.1279.

***tert*-Butyl (*E*)-(2-(but-2-en-1-yl)benzyl)(tosyloxy)carbamate (408)**



General procedure G: Alcohol **407** (243 mg, 1.50 mmol), PPh_3 (472 mg, 1.80 mmol), DIAD (0.35 mL, 1.80 mmol) and BocNHOTs (517 mg, 1.80 mmol) in anhydrous THF (6 mL) were employed. Purification by flash column chromatography (10% EtOAc:petroleum ether) afforded **408** (499 mg, 77%) as colourless solid; R_f = 0.36 (10% EtOAc:petroleum ether); m.p.: 77-78 °C (CH_2Cl_2:hexane); ν_{max} / cm^{-1} (solid) 2977 (m), 1723 (s), 1368 (s), 1175 (s), 1191 (s), 1152 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.32 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.23 – 7.18 (2H, m, ArC<u>H</u>), 7.16 – 7.11 (2H, m, ArC<u>H</u>), 5.56 – 5.48 (1H, m, C**3**-<u>H</u>), 5.44 – 5.34 (1H, m, C**4**-<u>H</u>), 4.86 (2H, br s, C**1**-<u>H_2</u>), 3.33 (2H, d, *J* = 6.0 Hz, C**2**-<u>H_2</u>), 2.45 (3H, s, Ts C<u>H_3</u>), 1.66 (3H, dd, *J* = 6.0, 1.5 Hz, C**5**-<u>H_3</u>), 1.22 (9H, s, Boc (C<u>H_3</u>)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.5 (Boc <u>C</u>=O), 145.8 (Ts Ar<u>C</u>), 139.2 (Ar<u>C</u>), 133.4 (Ar<u>C</u>), 131.5 (Ts Ar<u>C</u>), 129.9 (Ar<u>C</u>H), 129.8 (2 × Ts Ar<u>C</u>H), 129.7 (2 × Ts ArC<u>H</u>), 129.3 (C**3**) 128.4 (Ar<u>C</u>H), 128.0 (Ar<u>C</u>H), 126.7 (C**4**), 126.5 (Ar<u>C</u>H), 83.6 (Boc <u>C</u>(CH$_3$)$_3$), 53.0 (C**1**) 36.0 (C**2**), 27.7 (Boc (<u>C</u>H$_3$)$_3$), 21.9 (Ts <u>C</u>H$_3$), 18.1 (C**5**); HRMS (ESI^+) Calculated for $C_{23}H_{29}NNaO_5S$: 454.1659. Found $[M+Na]^+$: 454.1660.

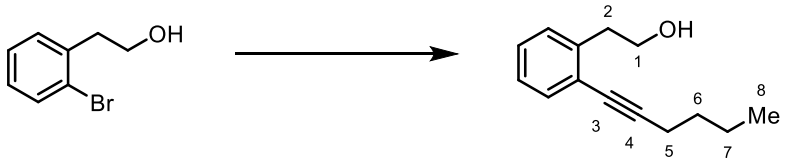
(1S*,8aS*)-1-Methyl-1,3,8,8a-tetrahydroazirino[1,2-b]isoquinoline (409)



General procedure P: The preceding *N*-tosyloxycarbamate **408** (86.3 mg, 0.20 mmol) and TFA (31 μL, 0.40 mmol) in anhydrous TFE (2.0 mL) were employed. After stirring for 24 hours, purification by flash column chromatography (gradient, eluent: ~ 0.1% Et_3N in 33% EtOAc:petroleum ether – ~ 0.1% Et_3N in EtOAc) afforded **409** (8.3 mg, 26%) as a colourless oil; R_f = 0.1 (EtOAc); ν_{max} / cm^{-1} (film) 2956 (m), 2923 (m), 2849 (m), 1494 (m), 1456 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 7.21 – 7.14 (2H, m, ArC<u>H</u>), 7.05 – 7.01 (1H, m, ArC<u>H</u>), 6.99 – 6.95 (1H, m, ArC<u>H</u>), 4.17 (1H, d, *J* = 16.0 Hz, C**1**-<u>H</u>), 4.04 (1H, d, *J* = 16.0 Hz, C**1**-<u>H</u>'), 3.11 – 3.08 (2H, m, C**4**-<u>H_2</u>), 2.18 – 2.14 (1H, m, C**3**-<u>H</u>), 1.59 – 1.53 (1H, m, C**2**-<u>H</u>), 1.13 (3H, d, *J*

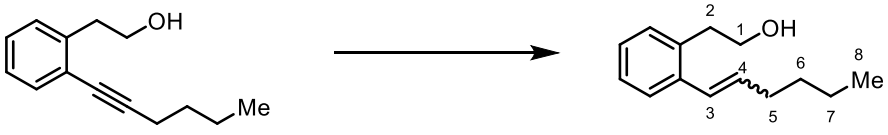
= 5.5 Hz, C**5**-H$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.0 (ArC), 132.9 (ArC), 128.1 (ArCH), 127.3 (ArCH), 127.2 (ArCH), 127.0 (ArCH), 50.9 (C**1**), 38.6 (C**3**), 29.0 (C**2**), 27.3 (C**4**), 17.2 (C**5**); HRMS (ESI$^+$) Calculated for $C_{11}H_{14}N$: 160.1121. Found $[M+H]^+$: 160.1127.

2-(2-(Hex-1-yn-1-yl)phenyl)ethan-1-ol (411)



To a solution of alcohol **410** (2.01 g, 10.0 mmol) in Et_3N (20 mL) under an atmosphere of N_2 was added CuI (114.3 mg, 0.6 mmol), $Pd(OAc)_2$ (134.7 mg, 0.6 mmol), PPh_3 (262.3 mg, 1.0 mmol) and hex-1-yne (1.26 mL, 11.0 mmol). The reaction mixture was heated to 90 °C and stirred for 48 hours. The reaction was poured into a saturated aqueous solution of NH_4Cl (20 mL) and extracted with Et_2O (2 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (20% EtOAc:petroleum ether) to afford **411** (358 mg, 18%) as a light brown oil; R_f = 0.3 (33% EtOAc:petroleum ether); ν_{max} / cm^{-1} (*film*) 3337 (br m), 2956 (m), 2930 (m), 2871 (m), 1484 (m), 1447 (m), 1041 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (1H, dd, *J* = 7.5, 1.5 Hz, ArCH), 7.23 – 7.13 (3H, m, ArCH), 3.92 – 3.84 (2H, m, C**1**-H$_2$), 3.04 (2H, t, *J* = 7.0 Hz, C**2**-H$_2$), 2.44 (2H, t, *J* = 7.0 Hz, C**5**-H$_2$), 1.68 – 1.55 (3H, m, OH, C**6**-H$_2$), 1.54 – 1.44 (2H, m, C**7**-H$_2$), 0.96 (3H, t, *J* = 7.5 Hz, C**8**-H$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.2 (ArC), 132.6 (ArCH), 129.7 (ArCH), 127.8 (ArCH), 126.5 (ArCH), 124.0 (ArC), 94.5 (C**4**), 79.2 (C**3**), 63.1 (C**1**), 38.1 (C**2**), 31.0 (C**6**), 22.2 (C**7**), 19.3 (C**5**), 13.8 (C**8**); HRMS (ESI$^+$) Calculated for $C_{14}H_{18}NaO$: 225.1250. Found $[M+Na]^+$: 225.1242.

(*E*)-2-(2-(Hex-1-en-1-yl)phenyl)ethan-1-ol (412)



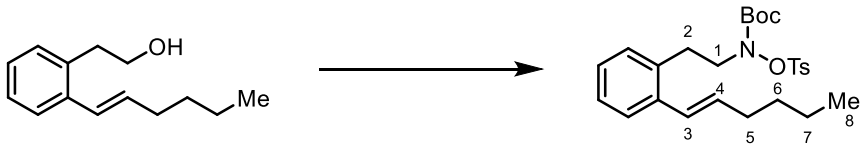
A solution of the preceding alkyne **411** (506 mg, 2.5 mmol) in diglyme (15 mL) under an atmosphere of nitrogen was cooled to 0 °C before addition of $LiAlH_4$ (569 mg, 15 mmol). The solution was then heated to reflux until completion by TLC analysis (1 hour). Upon completion the reaction was cooled to room temperature before addition of water (1 mL), 15% aqueous NaOH (1 mL) and a final portion of water (3 mL). The resulting mixture was filtered through

Celite® and washed with Et_2O. The phases were separated, and the aqueous phase extracted with Et_2O. The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was dissolved in pentane and washed with water to remove diglyme before purification by flash column chromatography (20% EtOAc:petroleum ether) to afford **412** (337 mg, 66% as an 8:1 mixture of *E* and *Z* isomers) as a pale-yellow oil; R_f = 0.60 (33% EtOAc:hexane) ν_{max} / cm^{-1} (*film*) 3416 (br m), 2928 (m), 1718 (s), 1028 (s).

Spectroscopic data for the major E isomer: ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.43 (1H, m, ArC<u>H</u>), 7.22 – 7.15 (3H, m, ArC<u>H</u>), 6.64 (1H, dt, *J* = 15.5, 1.5 Hz, C**3**-<u>H</u>), 6.10 (1H, dt, *J* = 15.5, 7.0 Hz, C**4**-<u>H</u>), 3.82 (2H, t, *J* = 7.0 Hz, C**1**-<u>H_2</u>), 2.96 (2H, t, *J* = 7.0 Hz, C**2**-<u>H_2</u>), 2.27 – 2.21 (2H, m, C**5**-<u>H_2</u>), 1.51 – 1.35 (5H, m, C**6**-<u>H_2</u>, C**7**-<u>H_2</u>, O<u>H</u>), 0.94 (3H, t, *J* = 7.0 Hz, C**8**-<u>H_3</u>); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.5 (Ar<u>C</u>), 135.1 (Ar<u>C</u>), 133.6 (C**4**), 130.4 (Ar<u>C</u>H), 127.2 (C**3**), 127.1 (Ar<u>C</u>H), 127.0 (Ar<u>C</u>H), 126.4 (Ar<u>C</u>H), 63.2 (C**1**), 36.7 (C**2**), 33.1 (C**5**), 31.7 (C**6** or C**7**), 22.4 (C**6** or C**7**), 14.1 (C**8**).

Characteristic signals for the minor Z isomer: ^1H NMR (400 MHz, $CDCl_3$) δ 6.51 (1H, dt, *J* = 11.5, 1.5 Hz), 5.74 (1H, dt, *J* = 11.5, 7.5 Hz), 3.79 (2H, t, *J* = 7.0 Hz), 2.89 (2H, t, *J* = 7.0 Hz), 2.13 (2H, qd, *J* = 7.5, 1.5 Hz); HRMS (ESI^+) Calculated for $C_{14}H_{20}NaO$: 227.1406. Found $[M+Na]^+$: 227.1411.

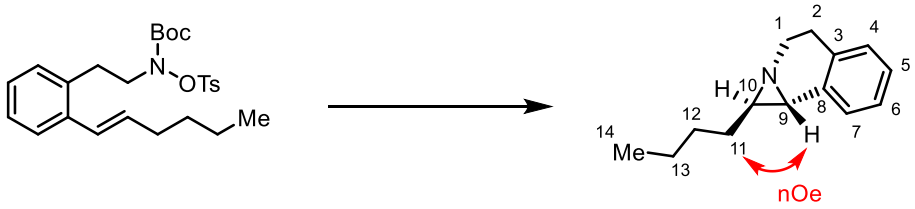
tert-Butyl (*E*)-(2-(hex-1-en-1-yl)phenethyl)(tosyloxy)carbamate (413)



<u>General procedure G:</u> The preceding alcohol **412** (245 mg, 1.2 mmol), PPh_3 (377 mg, 1.44 mmol), DIAD (0.28 mL, 1.44 mmol) and BocNHOTs (413 mg, 1.44 mmol) in anhydrous THF (5.0 mL) were employed. Purification by flash column chromatography (5% EtOAc:petroleum ether) afforded **413** (445 mg, 78%) as a colourless, viscous oil; R_f = 0.70 (20% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 2957 (m), 2930 (m), 1720 (s), 1368 (s), 1178 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.43 – 7.40 (1H, m, ArC<u>H</u>), 7.34 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.18 – 7.10 (3H, m, ArC<u>H</u>), 6.64 (1H, d, *J* = 15.5 Hz, C**3**-<u>H</u>), 6.12 (1H, dt, *J* = 15.5, 7.0 Hz, C**4**-<u>H</u>), 3.79 (2H, br s, C**1**-<u>H_2</u>), 3.04 – 2.96 (2H, m, C**2**-<u>H_2</u>), 2.44 (3H, s, Ts C<u>H_3</u>), 2.29 – 2.22 (2H, m, C**5**-<u>H_2</u>), 1.52 – 1.44 (2H, m, C**6**-<u>H_2</u>), 1.43 – 1.34 (2H, m, C**7**-<u>H_2</u>), 1.16 (9H, s, Boc (C<u>H_3</u>)$_3$), 0.94 (3H, t, *J* = 7.0 Hz, C**8**-<u>H_3</u>); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.1 (Boc <u>C</u>=O), 145.8 (Ts Ar<u>C</u>), 137.5 (Ar<u>C</u>), 134.6 (Ar<u>C</u>), 133.8 (C**4**), 131.4 (Ts Ar<u>C</u>), 130.4 (Ar<u>C</u>H), 129.9

(ArCH), 129.9 (2 × Ts ArCH), 129.6 (2 × Ts ArCH), 127.1 (ArCH), 126.7 (C**3**), 126.1 (ArCH), 83.2 (Boc C(CH$_3$)$_3$), 53.4 (C**1**), 33.1 (C**5**), 31.7 (C**6**), 29.8 (C**2**), 27.7 (Boc (CH$_3$)$_3$), 22.5 (C**7**), 21.8 (Ts CH$_3$), 14.1 (C**8**); HRMS (ESI$^+$) Calculated for $C_{26}H_{35}NNaO_5S$: 496.2128. Found $[M+Na]^+$: 496.2121.

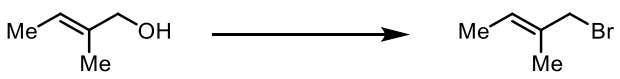
(1*S,8b*S**)-1-Butyl-1,3,4,8b-tetrahydroazirino[2,1-a]isoquinoline (414)**



General procedure P: The preceding *N*-tosyloxycarbamate **413** (47.4 mg, 0.1 mmol) and 2.0 equivalents of TFA (15 μL, 0.2 mmol) in anhydrous TFE (1.0 mL) were employed. After stirring for 48 hours purification by flash column chromatography (~0.1% Et$_3$N in EtOAc) afforded **414** (12.0 mg, 60%) as a pale-yellow oil; Rf = 0.40 (EtOAc); ν_{max} / cm^{-1} (*film*) 2954 (m), 2927 (s), 2858 (m), 1494 (m), 1463 (m), 752 (s), 736 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (1H, dd, *J* = 7.5, 1.5 Hz, C**7**-H), 7.23 – 7.18 (1H, m, C**6**-H), 7.15 (1H, td, *J* = 7.5, 1.5 Hz, C**5**-H), 7.05 (1H, d, *J* = 7.5 Hz, C**4**-H), 3.43 (1H, ddd, *J* = 13.0, 6.0, 2.0 Hz, C**1**-H), 2.89 – 2.81 (1H, m, C**1**-H'), 2.70 (1H, d, *J* = 2.5 Hz, C**9**-H), 2.65 – 2.50 (2H, m, C**2**-H$_2$), 2.10 (1H, td, *J* = 6.0, 2.5 Hz, C**10**-H), 1.57 – 1.48 (2H, m, C**11**-H$_2$), 1.46 – 1.31 (4H, m, C**12**-H$_2$, C**13**-H$_2$), 0.91 (3H, t, *J* = 7.0 Hz, C**14**-H$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.9 (C**8**), 131.9 (C**3**), 128.5 (C**4**), 128.1 (C**7**), 126.5 (C**6**), 125.9 (C**5**), 42.9 (C**1**), 40.8 (C**9**), 38.7 (C**10**), 32.9 (C**11**), 29.6 (C**12** or C**13**), 24.5 (C**2**), 22.7 (C**12** or C**13**), 14.3 (C**14**); HRMS (ESI$^+$) Calculated for $C_{14}H_{20}N$: 202.1590. Found $[M+H]^+$: 202.1589.

*The relative stereochemistry of this compound was determined by nOe experiments as indicated on the compound structure. An nOe correlation was observed between C**9**-H and C**11**-H$_2$. No nOe was observed between C**9**-H and C**10**-H.*

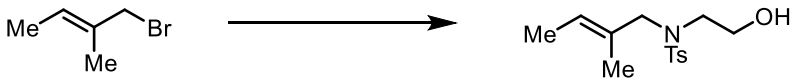
(*E*)-1-Bromo-2-methylbut-2-ene



The title compound was prepared according to a literature procedure.[49]

The spectroscopic properties were consistent with the data available in the literature.[49]

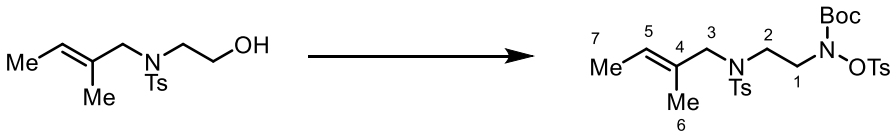
(*E*)-*N*-(2-hydroxyethyl)-4-methyl-*N*-(2-methylbut-2-en-1-yl)benzenesulfonamide (416)



General procedure R: *N*-(2-Hydroxyethyl)-4-methylbenzenesulfonamide **415** (2.15 g, 10.0 mmol), K_2CO_3 (2.07 g, 15.0 mmol) and (*E*)-1-bromo-2-methylbut-2-ene (1.72 mL, 15.0 mmol) in acetone (20 mL) were employed. Purification by flash column chromatography (gradient, eluent: 33 – 50% EtOAc:petroleum ether) afforded **416** (1.40 g, 49%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (2H, d, *J* = 8.0 Hz), 7.31 (2H, d, *J* = 8.0 Hz), 5.38 (1H, q, *J* = 6.5 Hz), 3.70 – 3.60 (4H, m), 3.14 (2H, t, *J* = 5.5 Hz), 2.42 (3H, s), 2.37 (1H, br s), 1.63 – 1.56 (6H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.6, 136.1, 131.4, 129.9, 127.4, 124.7, 61.4, 58.3, 50.2, 21.6, 13.8, 13.6.

The spectroscopic properties were consistent with the data available in the literature.[338]

***tert*-Butyl (*E*)-(2-((4-methyl-*N*-(2-methylbut-2-en-1-yl)phenyl)sulfonamido)ethyl)(tosyloxy)carbamate (418)**



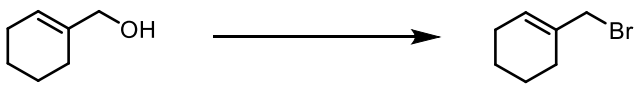
General procedure G: The preceding alcohol **416** (708 mg, 2.5 mmol), PPh_3 (789 mg, 3.0 mmol), DIAD (0.59 mL, 3.0 mmol) and BocNHOTs (860 mg, 3.0 mmol) in anhydrous THF (10 mL) were employed. Purification by flash column chromatography (10% EtOAc:petroleum ether) followed by (gradient, eluent: 50% CH_2Cl_2:PhMe – CH_2Cl_2) afforded **418** (373 mg, 27%) as a pale-yellow, viscous oil; R_f = 0.70 (33% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 3029 (m), 2981 (m), 2925 (m), 2862 (m), 1723 (m), 1370 (s), 1339 (s), 1192 (s), 1178 (s), 1155 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.68 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.34 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.30 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 5.47 – 5.40 (1H, m, C**5**-<u>H</u>), 3.71 (2H, br s, C**1**-<u>H</u>$_2$), 3.60 (2H, s, C**3**-<u>H</u>$_2$), 3.25 – 3.19 (2H, m, C**2**-<u>H</u>$_2$), 2.45 (3H, s, Ts C<u>H</u>$_3$), 2.42 (3H, s, Ts C<u>H</u>$_3$), 1.60 (3H, d, *J* = 6.5 Hz, C**7**-<u>H</u>$_3$), 1.56 (3H, s, C**6**-<u>H</u>$_3$), 1.23 (9H, s, Boc (C<u>H</u>$_3$)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.7 (Boc <u>C</u>=O), 145.9 (Ts Ar<u>C</u>), 143.4 (Ts Ar<u>C</u>), 136.3 (Ts Ar<u>C</u>), 131.0 (Ts Ar<u>C</u>), 130.3 (C**4**), 129.8 (2 ×Ts Ar<u>C</u>H), 129.7 (2 ×Ts Ar<u>C</u>H), 129.6 (2 ×Ts Ar<u>C</u>H), 127.3 (2 × Ts Ar<u>C</u>H), 125.7 (C**5**), 83.7 (Boc <u>C</u>(CH$_3$)$_3$), 57.5 (C**3**), 51.3 (C**1**), 42.8 (C**2**), 27.6 (Boc (<u>C</u>H$_3$)$_3$), 21.8 (Ts <u>C</u>H$_3$), 21.6 (Ts <u>C</u>H$_3$), 13.7 (C**6**), 13.6 (C**7**); HRMS (ESI$^+$) Calculated for $C_{26}H_{36}N_2NaO_7S_2$: 575.1856. Found [M+Na]$^+$: 575.1872.

(6*S,7*S**)-6,7-Dimethyl-4-tosyl-1,4-diazabicyclo[4.1.0]heptane (420)**

General procedure P: The preceding *N*-tosyloxycarbamate **418** (55.3 mg, 0.1 mmol) and 2.0 equivalents of TFA (15 μL, 0.2 mmol) in anhydrous TFE (1.0 mL) were employed. After stirring for 48 hours purification by flash column chromatography (~0.1% Et_3N in EtOAc) afforded **420** (18.0 mg, 64%) as a colourless oil; R_f = 0.10 (EtOAc); ν_{max} / cm^{-1} (*film*) 2926 (m), 2871 (m), 1597 (m), 1457 (m), 1340 (s), 1162 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.33 (2H, d, *J* = 8.0 Hz, Ts ArC<u>H</u>), 3.77 (1H, dd, *J* = 12.0, 1.5 Hz, C**3**-<u>H</u>), 3.41 (1H, dddd, *J* = 12.0, 6.0, 2.5, 1.5 Hz, C**2**-<u>H</u>), 3.31 (1H, ddd, *J* = 13.0, 5.0, 3.0 Hz, C**1**-<u>H</u>), 2.88 (1H, ddd, *J* = 13.0, 11.0, 6.0 Hz, C**1**-<u>H</u>'), 2.66 (1H, d, *J* = 12.0 Hz, C**3**-<u>H</u>'), 2.48 – 2.40 (4H, m, C**2**-<u>H</u>' and Ts C<u>H</u>$_3$), 2.05 (1H, q, *J* = 5.5 Hz, C**6**-<u>H</u>), 1.10 (3H, d, *J* = 5.5 Hz, C**7**-<u>H</u>$_3$), 1.05 (3H, s, C**5**-<u>H</u>$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.9 (Ts Ar<u>C</u>), 133.3 (Ts Ar<u>C</u>), 129.9 (2 × Ts Ar<u>C</u>H), 127.7 (2 × Ts Ar<u>C</u>H), 48.5 (C**3**), 48.1 (C**1**), 42.7 (C**2**), 42.3 (C**6**), 39.3 (C**4**), 21.7 (Ts <u>C</u>H_3), 18.6 (C**5**), 14.0 (C**7**); HRMS (ESI^+) Calculated for $C_{14}H_{20}N_2NaO_2S$: 303.1138. Found $[M+Na]^+$: 303.1141.

*The relative stereochemistry of this compound was determined by nOe experiments as indicated on the compound structure. An nOe correlation was observed between C**5**-<u>H</u>$_3$ and C**7**-<u>H</u>$_3$.*

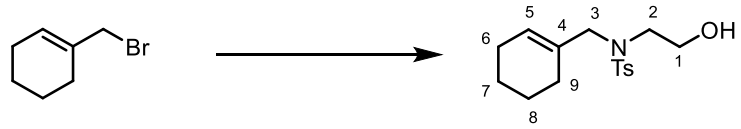
1-(Bromomethyl)cyclohex-1-ene



To a solution of cyclohex-1-en-1-ylmethanol (550 mg, 4.9 mmol) in Et_2O (25 mL) at 0 °C was added PBr_3 (667 mg, 2.5 mmol) and the reaction was warmed to room temperature and monitored by TLC. Upon completion of the reaction, the solution was poured into an ice-cold solution of K_2CO_3 (677 mg, 4.9 mmol) and the phases were separated. The aqueous phase was extracted with Et_2O (2 × 10 mL) and the combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the title compound (650 mg, 76%) as a colourless oil which was used without further purification.

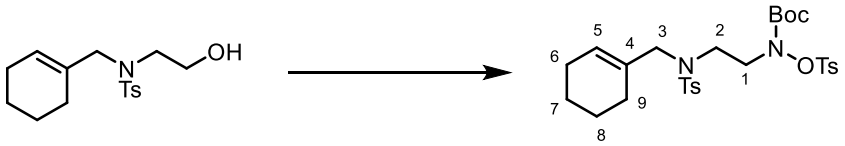
The spectroscopic properties were consistent with the data available in the literature.[49]

_N_-(Cyclohex-1-en-1-ylmethyl)-_N_-(2-hydroxyethyl)-4-methylbenzenesulfonamide (417)



General procedure R: _N_-(2-Hydroxyethyl)-4-methylbenzenesulfonamide **415** (540 mg, 2.50 mmol), K_2CO_3 (520 mg, 3.77 mmol) and 1-(bromomethyl)cyclohex-1-ene (660 mg, 3.77 mmol) in acetone (5 mL) were employed. Purification by flash column chromatography (33% EtOAc:petroleum ether) afforded **417** (719 mg, 93%) as a colourless oil; R_f = 0.40 (50% petroleum ether:EtOAc); ν_{max} / cm^{-1} (*film*) 3438 (br m), 2926 (m), 1328 (s), 1154 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (2H, d, *J* = 8.0 Hz, Ts ArC<u>H</u>), 7.30 (2H, d, *J* = 8.0 Hz, Ts ArCH), 5.60 – 5.56 (1H, m, C**5**-<u>H</u>), 3.68 – 3.62 (4H, m, C**1**-<u>H_2</u>, C**3**-<u>H_2</u>), 3.16 (3H, t, *J* = 5.5 Hz, C**2**-<u>H_2</u>), 2.42 (3H, s, Ts C<u>H_3</u>), 2.32 (1H, br s, O<u>H</u>), 2.01 – 1.91 (4H, m, C**6**-<u>H_2</u>, C**9**-<u>H_2</u>), 1.63 – 1.49 (4H, m, C**7**-<u>H_2</u>, C**8**-<u>H_2</u>); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.6 (Ts Ar<u>C</u>), 136.1 (Ts Ar<u>C</u>), 133.3 (C**4**), 129.8 (2 × Ts Ar<u>C</u>H), 127.4 (2 × Ts Ar<u>C</u>H), 127.2 (C**5**), 61.4 (C**1**), 56.9 (C**3**), 50.4 (C**2**), 26.1 (C**6** or C**9**), 25.3 (C**6** or C**9**), 22.5 (C**7** or C**8**), 22.3 (C**7** or C**8**), 21.6 (Ts <u>C</u>H_3); HRMS (ESI^+) Calculated for $C_{16}H_{23}NNaO_3S$: 332.1291. Found $[M+Na]^+$: 332.1279.

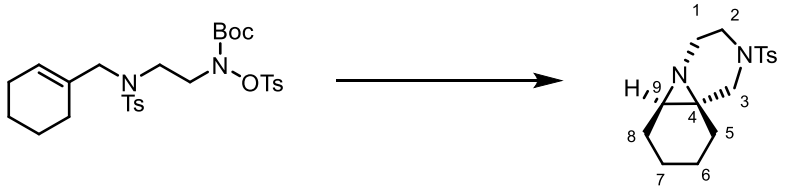
***tert*-Butyl (2-((_N_-(cyclohex-1-en-1-ylmethyl)-4-methylphenyl)sulfonamido)ethyl) (tosyloxy)carbamate (419)**



General procedure G: The preceding alcohol **417** (619 mg, 2.0 mmol), PPh_3 (629 mg, 2.4 mmol), DIAD (0.47 mL, 2.4 mmol) and BocNHOTs (689 mg, 2.4 mmol) in anhydrous THF (8 mL) were employed. Purification by flash column chromatography (gradient, eluent: 10 – 20% EtOAc:petroleum ether, then 4% EtOAc:toluene) afforded **419** (121 mg, 10%) as a viscous, colourless oil; R_f = 0.40 (4% EtOAc:toluene); ν_{max} / cm^{-1} (*film*) 2929 (m), 2837 (m), 1722 (m), 1369 (s), 1340 (s), 1192 (s), 1178 (s), 1156 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.67 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.33 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.29 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 5.65 – 5.61 (1H, m, C**5**-<u>H</u>), 3.74 (2H, br s, C**1**-<u>H_2</u>), 3.59 (2H, s, C**3**-<u>H_2</u>), 3.22 (2H, t, *J* = 7.5 Hz, C**2**-<u>H_2</u>), 2.44 (3H, s, Ts C<u>H_3</u>), 2.42 (3H, s, Ts C<u>H_3</u>), 2.06 – 2.00

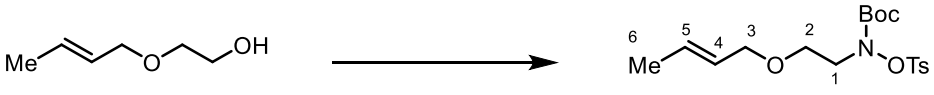
(2H, m, C**6**-H$_2$), 1.92 – 1.86 (2H, m, C**9**-H$_2$), 1.63 – 1.51 (4H, m, C**7**-H$_2$ and C**8**-H$_2$), 1.24 (9H, s, Boc (CH$_3$)$_3$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 154.8 (Boc C=O), 145.9 (Ts ArC), 143.4 (Ts ArC), 136.4 (Ts ArC), 132.4 (C**4**), 131.1 (Ts ArC), 129.8 (4 × Ts ArCH), 129.7 (Ts ArCH), 128.2 (C**5**), 127.3 (Ts ArCH), 83.8 (Boc C(CH$_3$)$_3$), 56.2 (C**3**), 51.6 (C**1**), 43.1 (C**2**), 27.7 (Boc (CH$_3$)$_3$), 26.1 (C**9**), 25.3 (C**6**), 22.5 (C**7** or C**8**), 22.2 (C**7** or C**8**), 21.8 (Ts CH$_3$), 21.6 (Ts CH$_3$); HRMS (ESI$^+$) Calculated for $C_{28}H_{38}N_2NaO_7S_2$: 601.2013. Found [M+Na]$^+$: 601.1986.

(5a*S,9a*S**)-2-Tosyloctahydro-7*H*-benzo[2,3]azirino[1,2-*a*]pyrazine (421)**



General procedure P: The preceding *N*-tosyloxycarbamate **419** (57.9 mg, 0.1 mmol) and 2.0 equivalents of TFA (15 μL, 0.2 mmol) in anhydrous TFE (1.0 mL) were employed. After stirring for 48 hours purification by flash column chromatography (0.1% Et$_3$N in EtOAc) afforded **421** (15.5 mg, 51%) as a yellow oil; R_f = 0.30 (EtOAc); ν_{max} / cm^{-1} (*film*) 2929 (m), 2855 (m), 1339 (m), 1159 (s); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.63 (2H, d, *J* = 8.0 Hz, Ts ArCH), 7.33 (2H, d, *J* = 8.0 Hz, Ts ArCH), 3.84 (1H, dd, *J* = 12.0, 1.5 Hz, C**3**-H), 3.43 (1H, dddd, *J* = 12.0, 6.0, 3.0, 1.5 Hz, C**2**-H), 3.32 (1H, ddd, *J* = 13.0, 5.0, 3.0 Hz, C**1**-H), 2.89 (1H, ddd, *J* = 13.0, 11.0, 6.0 Hz, C**1**-H'), 2.60 (1H, d, *J* = 13.0 Hz, C**3**-H'), 2.45 – 2.34 (4H, m, C**2**-H' and Ts CH$_3$), 2.15 (1H, dd, *J* = 4.5, 2.0 Hz, C**9**-H), 1.77 – 1.70 (2H, m, C**8**-H$_2$), 1.67 – 1.59 (1H, m, C**5**-H), 1.45 – 1.08 (5H, m, C**5**-H', C**6**-H$_2$ and C**7**-H$_2$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 143.9 (Ts ArC), 133.2 (Ts ArC), 129.9 (2 × Ts ArCH), 127.7 (2 × Ts ArCH), 48.4 (C**1**), 47.9 (C**3**), 42.8 (C**2**), 42.7 (C**9**), 38.9 (C**4**), 29.5 (C**5**), 24.4 (C**8**), 21.7 (Ts CH$_3$), 20.7 (C**7**), 20.4 (C**6**); HRMS (ESI$^+$) Calculated for $C_{16}H_{23}N_2O_2S$: 307.1475. Found [M+H]$^+$: 307.1490.

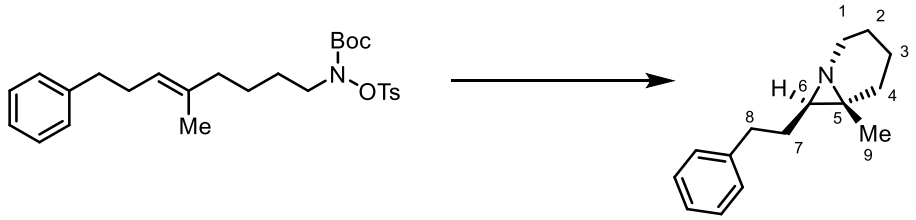
***tert*-Butyl (*E*)-(2-(but-2-en-1-yloxy)ethyl)(tosyloxy)carbamate (422)**



General procedure G: (*E*)-2-(But-2-en-1-yloxy)ethan-1-ol (188 mg, 1.62 mmol), PPh$_3$ (509 mg, 1.94 mmol), DIAD (0.38 mL, 1.94 mmol), and BocNHOTs (558 mg, 1.94 mmol) in anhydrous THF (6.5 mL) were employed. Purification by flash column chromatography (5% EtOAc:petroleum ether) afforded **422** (365 mg, 58%) as a viscous, colourless oil; ^{1}H NMR

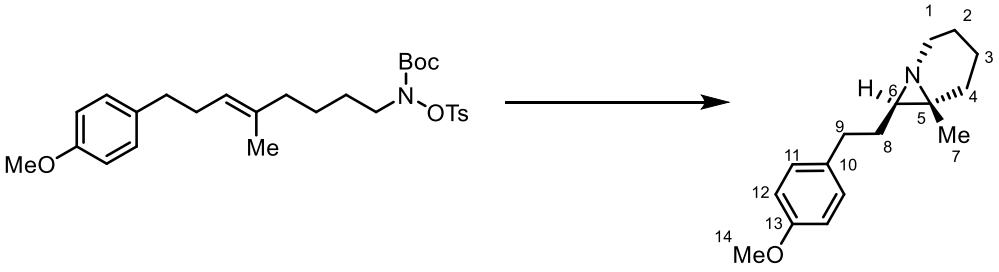
(400 MHz, $CDCl_3$) δ 7.85 (2H, d, *J* = 8.0 Hz, Ts ArC<u>H</u>), 7.33 (2H, d, *J* = 8.0 Hz, Ts ArC<u>H</u>), 5.71 – 5.61 (1H, m, C**5**-<u>H</u>), 5.53 – 5.45 (1H, m, C**4**-<u>H</u>), 4.16 – 3.44 (4H, m, C**1**-<u>H_2</u> and C**2**-<u>H_2</u>), 3.86 (2H, dd, *J* = 6.0, 1.0 Hz, C**3**-<u>H_2</u>), 2.44 (3H, s, Ts C<u>H_3</u>), 1.66 (3H, d, *J* = 6.5 Hz, C**6**-<u>H_3</u>), 1.19 (9H, s, Boc (C<u>H_3</u>)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.8 (Boc <u>C</u>=O), 145.8 (Ts Ar<u>C</u>), 131.2 (Ts Ar<u>C</u>), 129.9 (2 × Ts Ar<u>C</u>H), 129.6 (C**5**), 129.6 (2 × Ts Ar<u>C</u>H), 127.5 (C**4**), 83.1 (Boc <u>C</u>(CH_3)$_3$), 71.8 (C**3**), 64.5 (C**2**), 52.0 (C**1**), 27.7 (Boc (<u>C</u>H_3)$_3$), 21.8 (Ts <u>C</u>H_3), 17.8 (C**6**).

(6*S,7*S**)-6-Methyl-7-phenethyl-1-azabicyclo[4.1.0]heptane (426)**



<u>General procedure P:</u> *N*-Tosyloxycarbamate **424** (48.8 mg, 0.1 mmol), TFA (15 μL, 0.2 mmol) in anhydrous TFE (1.0 mL) were employed. After stirring for 48 hours, purification by flash column chromatography (~0.1% Et_3N in EtOAc) afforded **426** (11.3 mg, 52%) as a colourless oil; R_f = 0.05 (EtOAc); ν_{max} / cm^{-1} (*film*) 2928 (m), 2856 (m), 1452 (m), 749 (s), 697 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.25 (2H, m, ArC<u>H</u>), 7.22 – 7.15 (3H, m, ArC<u>H</u>), 3.35 – 3.29 (1H, m, C**1**-<u>H</u>), 2.79 (1H, dt, *J* = 14.5, 7.5 Hz, C**8**-<u>H</u>), 2.72 – 2.58 (2H, m, C**1**-<u>H</u>', C**8**-<u>H</u>'), 1.84 (1H, dt, *J* = 11.5, 5.5 Hz, C**4**-<u>H</u>), 1.76 – 1.56 (3H, m, C**4**-<u>H</u>', C**7**-<u>H_2</u>), 1.46 – 1.38 (1H, m, C**3**-<u>H</u>), 1.38 – 1.24 (3H, m, C**2**-<u>H_2</u>, C**3**-<u>H</u>'), 1.03 (3H, s, C**9**-<u>H_3</u>); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.3 (Ar<u>C</u>), 128.7 (Ar<u>C</u>H), 128.4 (Ar<u>C</u>H), 125.9 (Ar<u>C</u>H), 49.1 (C**1**), 47.8 (C**6**), 38.9 (C**5**), 34.3 (C**8**), 31.6 (C**7**), 29.4 (C**4**), 21.9 (C**9**), 21.1 (C**2**), 18.1 (C**3**); HRMS (ESI$^+$) Calculated for $C_{15}H_{22}N$: 216.1747. Found $[M+H]^+$: 216.1748.

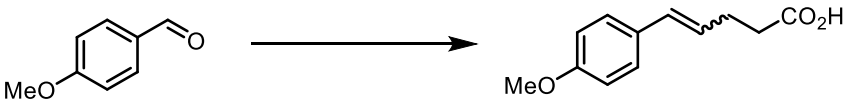
(6*S,7*S**)-7-(4-Methoxyphenethyl)-6-methyl-1-azabicyclo[4.1.0]heptane (427)**



<u>General procedure P:</u> *N*-Tosyloxycarbamate **425** (51.8 mg, 0.1 mmol) and TFA (15 μL, 0.2 mmol) in anhydrous TFE (1.0 mL) were employed. The reaction was stirred at room temperature for 48 hours. Purification by flash column chromatography (~0.1% Et_3N in

EtOAc) afforded **427** (9.9 mg, 40%) as a pale-yellow oil; R_f = 0.05 (EtOAc); ν_{max} / cm^{-1} (*film*) 2928 (m), 2856 (m), 1611 (m), 1511 (s), 1244 (s), 1036 (m); ^{1}H NMR (440 MHz, $CDCl_3$) δ 7.12 (2H, d, *J* = 8.5 Hz, C**11**-H), 6.82 (2H, d, *J* = 8.5 Hz, C**12**-H), 3.78 (3H, s, C**14**-H_3), 3.34 – 3.27 (1H, m, C**1**-H), 2.73 (1H, ddd, *J* = 14.5, 8.5, 6.5 Hz, C**9**-H), 2.66 – 2.57 (2H, m, C**1**-H', C**9**-H'), 1.87 – 1.81 (1H, m, C**4**-H), 1.70 – 1.54 (4H, m, C**4**-H', C**6**-H, C**8**-H_2), 1.46 – 1.24 (4H, m, C**2**-H_2, C**3**-H_2), 1.03 (3H, s, C**7**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.8 (C**13**), 134.4 (C**10**), 129.5 (C**11**), 113.8 (C**12**), 55.4 (C**14**), 49.1 (C**1**), 47.8 (C**6**), 38.7 (C**5**), 33.4 (C**9**), 31.9 (C**8**), 29.4 (C**4**), 22.0 (C**7**), 21.2 (C**2** or C**3**), 18.1 (C**2** or C**3**); HRMS (ESI^+) Calculated for $C_{16}H_{24}NO$: 246.1852. Found $[M+H]^+$: 246.1856.

(*E*)-5-(4-Methoxyphenyl)pent-4-enoic acid

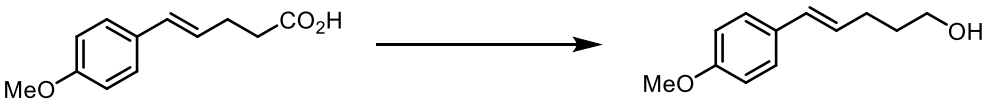


The title compound was prepared according to a literature procedure.[317]

m.p. 137-139 °C (Et_2O:petroleum ether); [lit: 144-145 °C (EtOAc:hexane)[317]]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (2H, d, *J* = 9.0 Hz), 6.84 (2H, d, *J* = 8.5 Hz), 6.39 (1H, d, *J* = 16.0 Hz), 6.12 – 6.02 (1H, m), 3.80 (3H, s), 2.54 – 2.50 (4H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.6, 159.1, 130.7, 130.2, 127.3, 126.0, 114.1, 55.4, 34.0, 28.1.

The spectroscopic properties were consistent with the data available in the literature.[317]

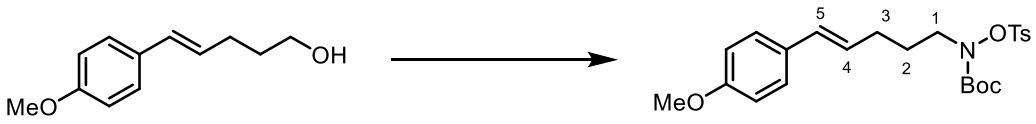
(*E*)-5-(4-Methoxyphenyl)pent-4-en-1-ol



General procedure B: (*E*)-5-(4-Methoxyphenyl)pent-4-enoic acid (820 mg, 4.00 mmol) and 2.0 equivalents of $LiAlH_4$ (8.0 mmol, 2M in THF) in anhydrous THF (20 mL) were employed. Purification by flash column chromatography (50% petroleum ether:EtOAc) afforded the title compound (520 mg, 67%) as a colourless solid; m.p.: 69-72 °C (Et_2O:petroleum ether) [lit: 71-73 °C (EtOAc:hexane)[322]]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (2H, d, *J* = 9.0 Hz), 6.82 (2H, d, *J* = 9.0 Hz), 6.35 (1H, d, *J* = 15.5 Hz), 6.11 – 6.04 (1H, m), 3.79 (3H, s), 3.69 (2H, t, *J* = 6.5 Hz), 2.31 – 2.25 (2H, m), 1.77 – 1.70 (2H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.9, 130.6, 129.9, 128.0, 127.2, 114.1, 62.6, 55.4, 32.5, 29.4.

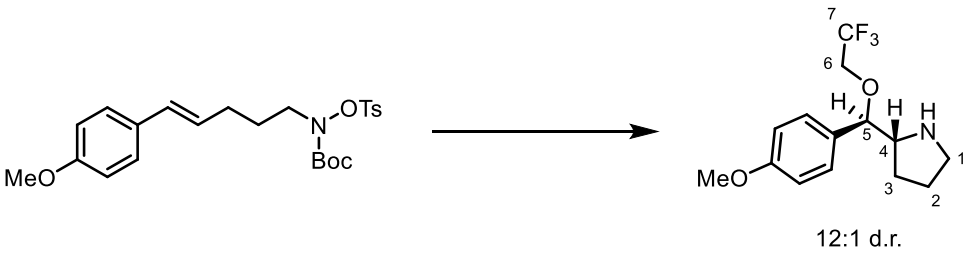
The spectroscopic properties were consistent with the data available in the literature.[323]

***tert*-Butyl (*E*)-(5-(4-methoxyphenyl)pent-4-en-1-yl)(tosyloxy)carbamate (434)**



General procedure G: (*E*)-5-(4-Methoxyphenyl)pent-4-en-1-ol (290 mg, 1.50 mmol), PPh_3 (470 mg, 1.80 mmol), DIAD (0.35 mL, 1.80 mmol) and BocNHOTs (517 mg, 1.80 mmol) in anhydrous THF (6 mL) were employed. Purification by flash column chromatography (gradient, eluent: 10 – 20% EtOAc:petroleum ether) afforded **434** (680 mg, 99 %) as a colourless solid; R_f = 0.60 (33% EtOAc:hexane); m.p. 57-59 °C (EtOAc:hexane); ν_{max} / cm^{-1} (*solid*) 2995 (m), 2977 (m), 2961 (m), 2935 (m), 2865 (m), 1711 (s), 1367 (s), 1173 (s), 1152 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.32 (2H, d, *J* = 8.5 Hz, Ts Ar<u>C</u>H), 7.26 (2H, d, *J* = 8.5 Hz, ArC<u>H</u>), 6.83 (2H, d, *J* = 8.5 Hz, ArC<u>H</u>), 6.32 (1H, d, *J* = 16.0 Hz, C**5**-<u>H</u>), 6.00 (1H, dt, *J* = 16.0, 7.0 Hz, C**4**-<u>H</u>), 3.79 (3H, s, OC<u>H</u>$_3$), 3.63 (2H, br s, C**1**-<u>H</u>$_2$), 2.43 (3H, s, Ts C<u>H</u>$_3$), 2.20 – 2.13 (2H, m, C**3**-<u>H</u>$_2$), 1.83 – 1.75 (2H, m, C**2**-<u>H</u>$_2$), 1.23 (9H, s, Boc (C<u>H</u>$_3$)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.9 (Ar<u>C</u>), 155.6 (Boc <u>C</u>=O), 145.8 (Ts Ar<u>C</u>), 131.4 (Ts Ar<u>C</u>), 130.5 (Ar<u>C</u>), 130.2 (C**5**), 129.8 (2 × Ts Ar<u>C</u>H), 129.6 (2 × Ts Ar<u>C</u>H), 127.2 (Ar<u>C</u>H), 127.1 (C**4**), 114.0 (Ar<u>C</u>H), 83.3 (Boc <u>C</u>(CH$_3$)$_3$), 55.4 (O<u>C</u>H$_3$), 52.6 (C**1**), 30.0 (C**3**), 27.7 (Boc (<u>C</u>H$_3$)$_3$), 25.7 (C**2**), 21.8 (Ts <u>C</u>H$_3$); HRMS (ESI^+) Calculated for $C_{24}H_{31}NNaO_6S$: 484.1763. Found $[M+Na]^+$: 484.1768.

(*R)-2-((*R**)-(4-Methoxyphenyl)(2,2,2-trifluoroethoxy)methyl)pyrrolidine (436)**



12:1 d.r.

To a solution of the preceding *N*-tosyloxycarbamate **434** (92.3 mg, 0.2 mmol) in anhydrous TFE (2.0 mL) was added TFA (31 μL, 0.4 mmol). After stirring overnight at room temperature, the reaction mixture was concentrated *in vacuo*. To the crude reaction mixture was added EtOAc (5 mL) and saturated aqueous $NaHCO_3$ (5 mL) and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 2 mL) and the combined organic phases were washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography (eluent: EtOAc) afforded **436** (32.9 mg, 57%) as a 12:1

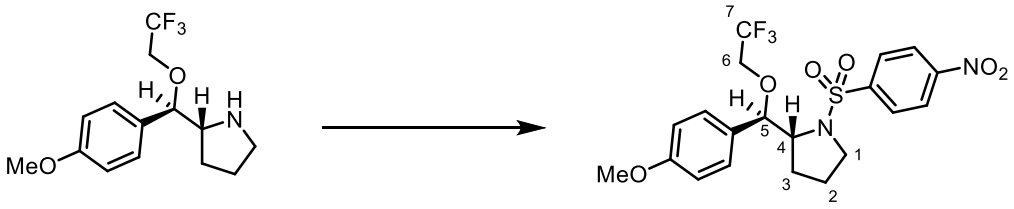
mixture of diastereomers **436a** and **436b** and as a yellow oil; R_f = 0.05 (EtOAc); ν_{max} / cm^{-1} (*film*) 3417 (br w), 2943 (m), 1671 (s), 1168 (s), 1123 (s).

*Spectroscopic properties for the major diastereomer **436a**:* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (2H, d, *J* = 8.5 Hz, ArC<u>H</u>), 6.89 (2H, d, *J* = 8.5 Hz, ArC<u>H</u>), 4.13 (1H, d, *J* = 8.5 Hz, C**5**-<u>H</u>), 3.81 (3H, s, OC<u>H</u>$_3$), 3.63 (2H, q, *J* = 8.8 Hz, C**6**-<u>H</u>$_2$), 3.29 (1H, q, *J* = 8.2 Hz, C**4**-<u>H</u>), 3.10 – 3.03 (1H, m, C**1**-<u>H</u>), 2.95 – 2.88 (1H, m, C**1**-<u>H</u>'), 2.63 (1H, br s, N<u>H</u>) 1.81 – 1.62 (2H, m, C**2**-<u>H</u>$_2$), 1.44 – 1.25 (2H, m, C**3**-<u>H</u>$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.9 (Ar<u>C</u>), 130.5 (Ar<u>C</u>), 128.8 (Ar<u>C</u>H), 124.2 (q, $^1J_{C\text{-}F}$ = 278.5 Hz, C**7**), 114.2 (Ar<u>C</u>H), 87.2 (C**5**), 65.7 (q, $^2J_{C\text{-}F}$ = 34.0 Hz, C**6**), 63.9 (C**4**), 55.4 (O<u>C</u>H$_3$), 46.0 (C**1**), 27.6 (C**3**), 24.3 (C**2**).

*Characteristic signals for the minor diastereomer **436b**:* ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.23 (1H, d, *J* = 7.0 Hz).

HRMS (ESI^+) Calculated for $C_{14}H_{19}F_3NO_2$: 290.1362. Found $[M+H]^+$: 290.1376.

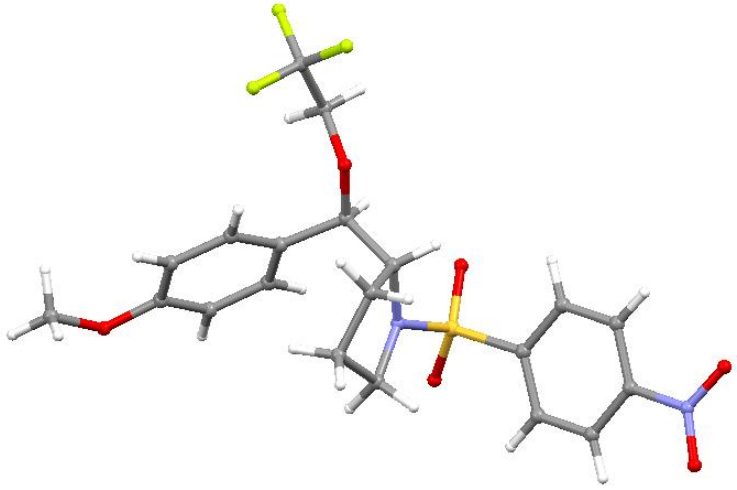
(*R)-2-((*R**)-(4-Methoxyphenyl)(2,2,2-trifluoroethoxy)methyl)-1-((4-nitrophenyl) sulfonyl)-pyrrolidine (440)**



To a solution of pyrrolidine **436** (65.2 mg, 0.225 mmol) and Et_3N (47 μL, 0.338 mmol) in CH_2Cl_2 (0.9 mL) at 0 °C was added 4-nitrobenzenesulfonyl chloride (49.9 mg, 0.225 mmol). The reaction was warmed to room temperature and stirred overnight. To the reaction was added CH_2Cl_2 (5 mL) and aqueous 1 M HCl (1 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic extracts were washed with water (5 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash column chromatography (20% EtOAc:petroleum ether) afforded **440** (84.9 mg, 80%) as a colourless solid; R_f = 0.80 (EtOAc); m.p. 83-85 °C (CH_2Cl_2:hexane); ν_{max} / cm^{-1} (*solid*) 2883 (m), 2953 (m)1607 (m), 1533 (s), 1350 (s), 1164 (s), 1145 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (2H, d, *J* = 8.5 Hz, ArC<u>H</u>), 8.06 (2H, d, *J* = 8.5 Hz, ArC<u>H</u>), 7.34 (2H, d, *J* = 8.5 Hz, ArC<u>H</u>), 6.92 (2H, d, *J* = 8.5 Hz, ArC<u>H</u>), 4.92 (1H, d, *J* = 4.5 Hz, C**5**-<u>H</u>), 4.04 – 3.99 (1H, m, C**4**-<u>H</u>), 3.90 – 3.80 (4H, m, OC<u>H</u>$_3$, C**6**-<u>H</u>), 3.78 – 3.69 (1H, m, C**6**-<u>H</u>'), 3.06 – 2.96 (2H, m, C**1**-<u>H</u>$_2$), 1.94 – 1.86 (1H, m, C**3**-<u>H</u>), 1.56 – 1.46 (1H, m, C**3**-<u>H</u>'), 1.31 – 1.21 (1H, m, C**2**-<u>H</u>), 0.91 – 0.80 (1H, m, C**2**-<u>H</u>'); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.0 (Ar<u>C</u>), 150.3 (Ar<u>C</u>), 143.1 (Ar<u>C</u>), 129.0

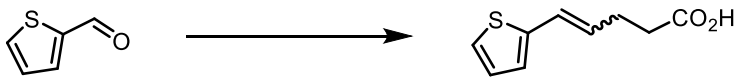
(ArCH), 128.9 (ArCH), 127.2 (ArC), 124.5 (ArCH) 123.5 (q, $^{1}J_{C\text{-}F}$ = 279.5 Hz, C**7**), 114.1 (ArCH), 83.3 (C**5**), 66.6 (q, $^{2}J_{C\text{-}F}$ = 34.2 Hz, C**6**), 63.2 (C**4**), 55.4 (OCH_3), 49.5 (C**1**), 26.2 (C**3**), 23.9 (C**2**); HRMS (ESI^+) Calculated for $C_{20}H_{21}F_3N_2NaO_6S$: 497.0965. Found $[M+Na]^+$: 497.0970.

The structure and relative stereochemistry of this compound was confirmed by X-ray crystallography after recrystallization (Et_2O:hexane).



*X-ray crystal structure of **440**.*

(*E*)-5-(Thiophen-2-yl)pent-4-enoic acid

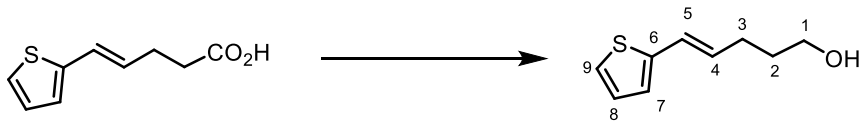


The title compound was prepared according to a literature procedure.[317]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (1H, d, *J* = 5.0 Hz), 6.96 – 6.89 (2H, m), 6.58 (1H, d, *J* = 15.5 Hz), 6.10 – 6.01 (1H, m), 2.54 – 2.51 (4H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.9, 142.5, 128.0, 127.4, 125.0, 124.6, 123.8, 33.7, 27.9.

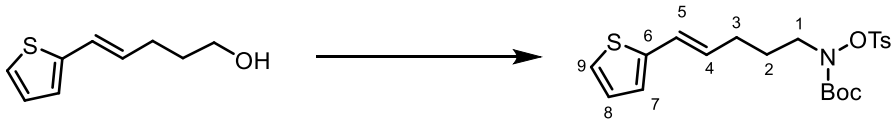
The spectroscopic properties were consistent with the data available in the literature.[317]

(*E*)-5-(Thiophen-2-yl)pent-4-en-1-ol



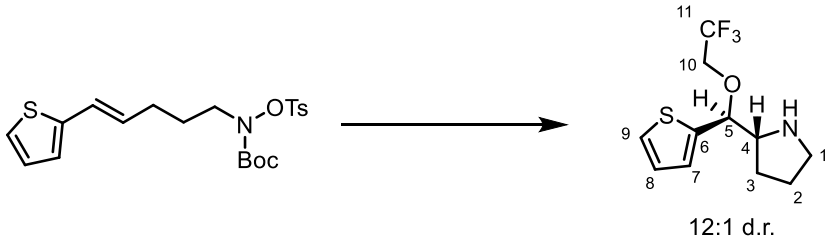
General procedure B: (*E*)-5-(Thiophen-2-yl)pent-4-enoic acid (910 mg, 5.0 mmol) and 2.0 equivalents of $LiAlH_4$ (10.0 mmol, 2M in THF) in anhydrous THF (25 mL) were employed. Purification by flash column chromatography (33% EtOAc:hexane) afforded the title compound (580 mg, 69 %) as a pale-yellow oil; R_f = 0.50 (33% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 3373 (br), 2935 (m), 1037 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (1H, d, *J* = 5.0 Hz, C**9**-H), 6.94 – 6.92 (1H, m, C**8**-H), 6.87 (1H, d, *J* = 2.4 Hz, C**7**-H), 6.55 (1H, d, *J* = 15.6 Hz, C**5**-H), 6.07 (1H, dt, *J* = 15.6, 7.0 Hz, C**4**-H), 3.70 (2H, t, *J* = 6.5 Hz, C**1**-H_2), 2.31 – 2.25 (2H, m, C**3**-H_2), 1.77 – 1.70 (2H, m, C**2**-H_2), 1.59 (1H, br s, OH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.9 (C**6**), 130.1 (C**4**), 127.3 (C**8**), 124.5 (C**7**), 123.8 (C**5**), 123.4 (C**9**), 62.4 (C**1**), 32.2 (C**2**), 29.2 (C**3**).

***tert*-Butyl (*E*)-(5-(thiophen-2-yl)pent-4-en-1-yl)(tosyloxy)carbamate (437)**



General procedure G: (*E*)-5-(Thiophen-2-yl)pent-4-enoic acid (252 mg, 1.50 mmol), PPh_3 (470 mg, 1.80 mmol), DIAD (0.35 mL, 1.80 mmol) and BocNHOTs (517 mg, 1.80 mmol) in anhydrous THF (6 mL) were employed. Purification by flash column chromatography (10% EtOAc:petroleum ether) afforded **437** (505 mg, 77%) as a pale-yellow oil; R_f = 0.80 (33% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 2981 (m), 2933 (m), 1718 (s), 1368 (s), 1191 (s), 1177 (s), 1152 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (2H, d, *J* = 8.5 Hz, Ts ArCH), 7.33 (2H, d, *J* = 8.5 Hz, Ts ArCH), 7.09 (1H, dd, *J* = 5.0, 1.0 Hz, C**9**-H), 6.93 (1H, dd, *J* = 5.0, 3.5 Hz, C**8**-H), 6.87 (1H, d, *J* = 3.5 Hz, C**7**-H), 6.51 (1H, d, *J* = 15.5 Hz, C**5**-H), 5.99 (1H, dt, *J* = 15.5, 7.0 Hz, C**4**-H), 3.62 (2H, br s, C**1**-H_2), 2.43 (3H, s, Ts CH_3), 2.19 – 2.12 (2H, m, C**3**-H_2), 1.86 – 1.73 (2H, m, C**2**-H_2), 1.24 (9H, s, Boc $(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6 (Boc C=O), 145.8 (Ts ArC), 142.8 (C**6**), 131.4 (Ts ArC), 129.8 (2 × Ts ArCH), 129.7 (2 × Ts ArCH), 129.1 (C**4**), 127.3 (C**8**), 124.7 (C**7**), 124.1 (C**5**), 123.5 (C**9**), 83.4 (Boc $C(CH_3)_3$), 52.5 (C**1**), 29.9 (C**3**), 27.8 (Boc $(CH_3)_3$), 25.5 (C**2**), 21.8 (Ts CH_3); HRMS (ESI^+) Calculated for $C_{21}H_{27}NNaO_5S_2$: 460.1223. Found $[M+Na]^+$: 460.1232.

(*R)-2-((*S**)-Thiophen-2-yl(2,2,2-trifluoroethoxy)methyl)pyrrolidine (439)**



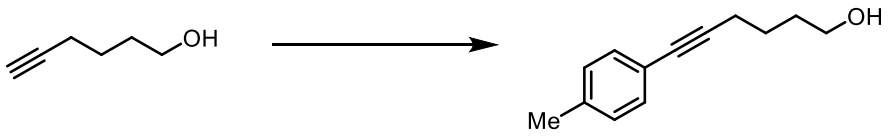
To a solution of the preceding *N*-tosyloxycarbamate **437** (87.5 mg, 0.2 mmol) in anhydrous TFE (2.0 mL, 0.1 M) was added TFA (31 μL, 0.4 mmol). After stirring for 24 hours at room temperature, the reaction mixture was concentrated *in vacuo*. To the crude reaction mixture was added EtOAc (5 mL) and saturate aqueous $NaHCO_3$ (5 mL) and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 2 mL) and the combined organic phases were washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography (5% MeOH: CH_2Cl_2) afforded **439** (16.3 mg, 31%) as a 12:1 mixture of diastereomers **439a** and **439b** and as a yellow oil; R_f = 0.1 (EtOAc); ν_{max} / cm^{-1} (*film*) 3362 (br), 2936 (m), 1276 (s), 1158 (s).

*Spectroscopic data for the major diastereomer **439a**:* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (1H, dd, *J* = 5.0, 1.0 Hz, C**9**-H), 7.09 (1H, dd, *J* = 3.5, 1.5 Hz, C**7**-H), 7.01 (1H, dd, *J* = 5.0, 3.5 Hz, C**8**-H), 4.69 (1H, d, *J* = 9.0 Hz, C**5**-H), 4.41 (1H, br s, NH), 3.87 (1H, dq, *J* = 11.5, 8.5 Hz, C**10**-H), 3.73 (1H, dq, *J* = 11.5, 8.5 Hz, C**10**-H'), 3.61 – 3.55 (1H, m, C**4**-H), 3.24 – 3.09 (2H, m, C**1**-H_2), 1.93 – 1.75 (2H, m, C**2**-H_2), 1.69 – 1.62 (1H, m, C**3**-H), 1.51 – 1.42 (1H, m, C**3**-H'); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.5 (C**6**), 127.6 (C**7**), 127.0 (C**9**), 126.9 (C**8**), 123.9 (q, $^1J_{C\text{-}F}$ = 278.3 Hz, C**11**) 81.2 (C**5**), 65.6 (q, $^2J_{C\text{-}F}$ = 34.6 Hz, C**10**) 64.1 (C**4**), 46.2 (C**1**), 28.0 (C**3**), 24.3 (C**2**); ^{19}F NMR (377 MHz, $CDCl_3$) δ -73.6 (3H, t, *J* = 8.5 Hz).

*Characteristic signals for the minor diastereomer **439b**:* ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.84 (1H, d, *J* = 6.0 Hz).

HRMS (ESI^+) Calculated for $C_{11}H_{15}F_3NOS$: 266.0821. Found $[M+H]^+$: 266.0822.

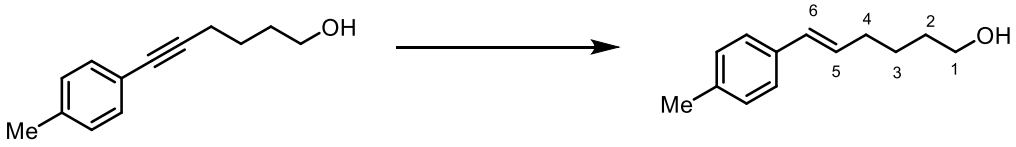
6-(*p*-Tolyl)hex-5-yn-1-ol



To a solution of 4-iodotolune (2.18 g, 10.0 mmol) in Et_3N (20 mL) under an atmosphere of N_2 was added $Pd(PPh_3)_2Cl_2$ (105 mg, 0.15 mmol) and CuI (57 mg, 0.3 mmol). The reaction was stirred at room temperature for 10 minutes and 5-hexyn-1-ol (1.21 mL, 11.0 mmol) was added. The reaction was stirred at room temperature overnight then poured into saturated aqueous NH_4Cl (20 mL) and extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash column chromatography (33% EtOAc:petroleum ether) afforded the title compound (1.95 g, quantitative) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (2H, d, *J* = 8.0 Hz), 7.08 (2H, d, *J* = 8.0 Hz), 3.73 – 3.68 (2H, m), 2.45 (2H, td, *J* = 7.0, 1.0 Hz), 2.33 (3H, s), 1.79 – 1.65 (4H, m), 1.60 (1H, br s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.7, 131.5, 129.1, 121.0, 89.2, 81.1, 62.6, 32.1, 25.2, 21.5, 19.3.

The spectroscopic properties were consistent with the data available in the literature.[339]

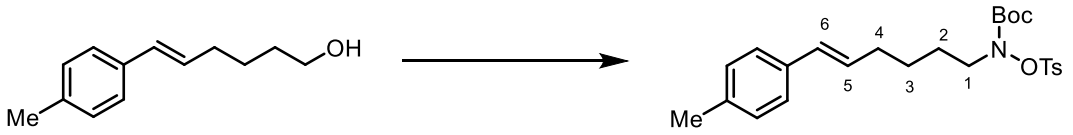
(*E*)-6-(*p*-Tolyl)hex-5-en-1-ol



To a solution of 6-(*p*-tolyl)hex-5-yn-1-ol (508 mg, 2.70 mmol) in diglyme (15 mL) at 0 °C was added 3.5 equivalents of $LiAlH_4$ (610 mg, 16.1 mmol). After stirring at 0 °C for 20 minutes the reaction was heated to reflux and stirred for 1 hour. Upon completion, the reaction mixture was cooled to 0 °C before addition of water (1 mL/g of $LiAlH_4$), 15% aqueous NaOH (1 mL/g $LiAlH_4$) and a final portion of water (3 mL/g of $LiAlH_4$). The mixture was filtered through Celite® and washed with CH_2Cl_2. The phases were separated, and the aqueous phase extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography (20% EtOAc:petroleum ether) afforded the title compound (281 mg, 55%) as a pale-yellow oil; ν_{max} / cm^{-1} (*film*) 3335 (br m), 2930 (m), 2858 (m), 1512 (m), 964 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (2H, d, *J* = 8.0 Hz, ArC<u>H</u>), 7.10 (2H, d, *J* = 8.0 Hz, ArC<u>H</u>), 6.36 (1H, d, *J* = 16.0 Hz, C**6**-<u>H</u>), 6.16 (1H, dt,

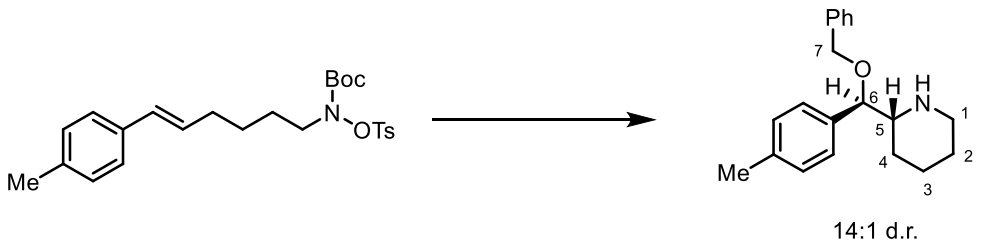
J = 16.0, 7.0 Hz, C**5**-H), 3.67 (2H, t, *J* = 6.5 Hz, C**1**-H_2), 2.32 (3H, s, CH_3), 2.28 – 2.20 (2H, m, C**4**-H_2), 1.67 – 1.51 (4H, m, C**2**-H_2, C**3**-H_2), 1.31 (1H, br s, OH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.4 (ArC), 134.8 (ArC), 129.8 (C**6**), 129.3 (C**5**), 129.0 (ArCH), 125.6 (ArCH), 62.7 (C**1**), 32.5 (C**4**), 32.1 (C**2**), 25.4 (C**3**), 20.9 (CH_3); HRMS (ESI$^+$) Calculated for $C_{13}H_{18}NaO$: 213.1250. Found $[M+Na]^+$: 213.1250.

tert-Butyl (*E*)-(6-(*p*-tolyl)hex-5-en-1-yl)(tosyloxy)carbamate (442)



General procedure G: (*E*)-6-(*p*-Tolyl)hex-5-en-1-ol (228 mg, 1.2 mmol), PPh_3 (377 mg, 1.44 mmol), DIAD (0.28 mL, 1.44 mmol) and BocNHOTs (413 mg, 1.44 mmol) in anhydrous THF (5 mL) were employed. Purification by flash column chromatography (gradient, eluent: 10-20% EtOAc:petroleum ether) afforded **442** (508 mg, 92%) as a colourless, crystalline solid; R_f = 0.50 (20% EtOAc:hexane); m.p.: 54-57 °C (EtOAc:petroleum ether) ν_{max} / cm^{-1} (*film*) 2932 (m), 1716 (s), 1366 (s), 1351 (s), 1177 (s), 1155 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (2H, d, *J* = 8.0 Hz, Ts ArCH), 7.34 (2H, d, *J* = 8.0 Hz, Ts ArCH), 7.22 (2H, d, *J* = 8.0 Hz, ArCH), 7.09 (2H, *J* = 8.0 Hz, ArCH), 6.34 (1H, d, *J* = 16.0 Hz, C**6**-H), 6.11 (1H, dt, *J* = 16.0, 7.0 Hz, C**5**-H), 3.64 (2H, br s, C**1**-H_2), 2.45 (3H, s, Ts CH_3), 2.32 (3H, s, CH_3), 2.22 – 2.17 (2H, m, C**4**-H_2), 1.73 – 1.63 (2H, m, C**2**-H_2), 1.47 – 1.39 (2H, m, C**3**-H_2), 1.22 (9H, s, Boc C(CH_3)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.7 (Boc C=O), 145.8 (ArC), 136.7 (ArC), 135.1 (ArC), 131.4 (ArC), 130.3 (C**6**), 129.8 (ArCH), 129.7 (ArCH), 129.3 (ArCH), 129.2 (C**5**), 126.0 (ArCH), 83.3 (Boc C(CH_3)$_3$), 52.8 (C**1**), 32.7 (C**4**), 27.8 (Boc C(CH_3)$_3$), 26.5 (C**3**), 25.5 (C**2**), 21.9 (Ts CH_3), 21.3 (CH_3); HRMS (ESI$^+$) Calculated for $C_{25}H_{33}NNaO_5S$: 482.1972. Found $[M+Na]^+$: 482.1977.

(*R)-2-((*R**)-(Benzyloxy)(*p*-tolyl)methyl)piperidine (443)**



14:1 d.r.

An oven dried re-sealable tube, fitted with a magnetic stirrer, was charged with the preceding *N*-tosyloxycarbamate **442** (45.9 mg, 0.1 mmol). The tube was fitted with a rubber septum and

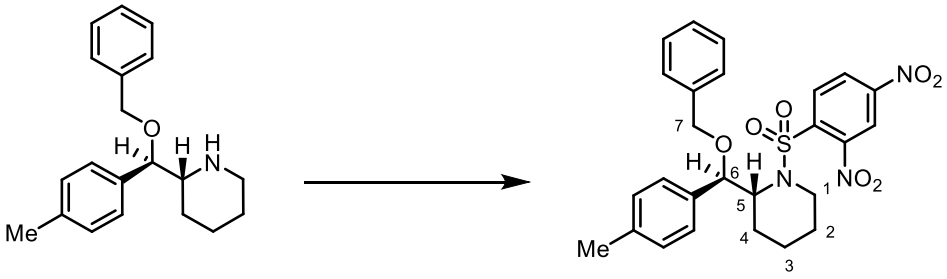
purged with nitrogen before addition of BnOH (0.25 mL), HFIP (0.75 mL) and TFA (15 μL). The tube was sealed and stirred at room temperature for 45 hours. The solvent was removed *in vacuo* and purification by flash column chromatography (~0.1% Et_3N in EtOAc) afforded **443** (12.5 mg, 42%) as a 14:1 mixture of diastereomers **443a** and **443b** and as a yellow oil; R_f = 0.05 (EtOAc); ν_{max} / cm^{-1} (*film*) 3345 (m), 2928 (m), 2855 (m), 1065 (s), 812 (s).

*Spectroscopic data for the major diastereomer **443a**:* ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.16 (9H, m, ArC<u>H</u>), 4.33 (1H, d, *J* = 11.0 Hz, C**7**-<u>H</u>), 4.24 (1H, d, *J* = 11.0 Hz, C**7**-<u>H</u>'), 4.12 (1H, d, *J* = 8.5 Hz, C**6**-<u>H</u>), 3.12 – 3.05 (1H, m, C**1**-<u>H</u>), 2.72 – 2.65 (1H, m, C**5**-<u>H</u>), 2.60 (1H, td, *J* = 12.0, 3.0 Hz, C**1**-<u>H</u>'), 2.37 (3H, s, C<u>H</u>$_3$), 1.70 – 1.63 (1H, m, C**3**-<u>H</u>), 1.60 – 1.52 (1H, m, C**2**-<u>H</u>), 1.51 – 1.38 (1H, m, C**2**-<u>H</u>'), 1.18 – 1.04 (3H, m, C**3**-<u>H</u>', C**4**-<u>H</u>$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.5 (Ar<u>C</u>), 137.8 (Ar<u>C</u>), 136.5 (Ar<u>C</u>), 129.2 (Ar<u>C</u>H), 128.5 (Ar<u>C</u>H), 128.3 (Ar<u>C</u>H), 128.0 (Ar<u>C</u>H), 127.8 (Ar<u>C</u>H), 86.7 (C**6**), 70.9 (C**7**), 62.1 (C**5**), 46.8 (C**1**), 28.5 (C**4**), 26.1 (C**2**), 24.6 (C**3**), 21.4 (<u>C</u>H$_3$).

*Characteristic signals for the minor diastereomer **443b**:* ^1H NMR (400 MHz, $CDCl_3$) δ 4.43 (1H, d, *J* = 11.5 Hz)

HRMS (ESI^+) Calculated for $C_{20}H_{26}NO$: 296.2009. Found $[M+H]^+$: 296.2002.

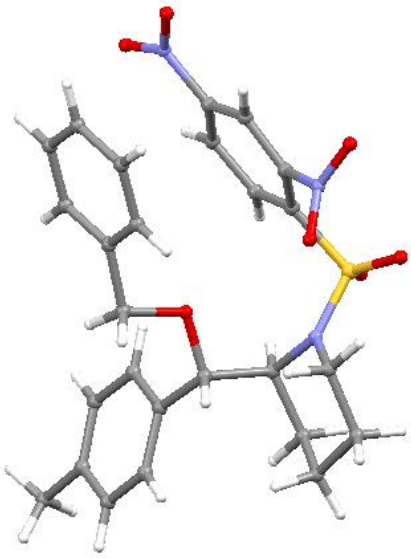
(*R)-2-((*R**)-(Benzyloxy)(*p*-tolyl)methyl)-1-((2,4-dinitrophenyl)sulfonyl)piperidine (444)**



To a solution of piperidine **443** (29.8 mg, 0.1 mmol) and Et_3N (21 μL, 0.15 mmol) in CH_2Cl_2 (0.4 mL) at 0 °C was added 2,4-dinitrobenzenesulfonyl chloride (24.0 mg, 0.09 mmol) and the reaction was stirred at room temperature overnight. To the reaction mixture was added CH_2Cl_2 (5 mL) and 1 M HCl (1 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 2 mL) and the combined organic extracts were washed with water (2 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash column chromatography (10% EtOAc:pentane) afforded **444** (25.5 mg, 54%) as a yellow solid; R_f = 0.50 (20% EtOAc:hexane); m.p.: 137-140 °C (CH_2Cl_2:Et_2O); ν_{max} / cm^{-1} (*solid*) 2926 (m), 2855 (m), 1548 (s), 1535 (s), 1344 (s), 1161 (s), 750 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 8.17 (1H, d, *J* = 8.5

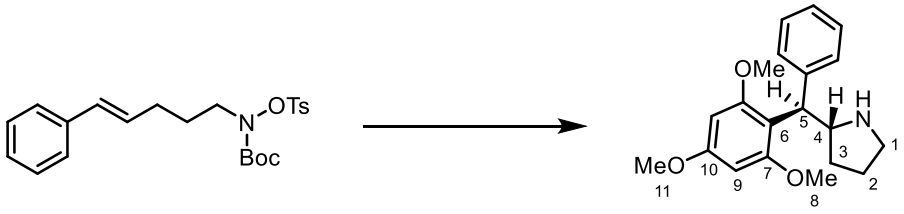
Hz, ArCH), 8.02 (1H, dd, *J* = 8.5, 2.5 Hz, ArCH), 7.86 (1H, d, *J* = 2.5 Hz, ArCH), 7.24 – 7.18 (4H, m, ArCH), 7.15 – 7.06 (3H, m, ArCH), 6.83 – 6.77 (2H, m, ArCH), 4.63 (1H, d, *J* = 10.5 Hz, C**6**-H), 4.25 – 4.19 (1H, m, C**5**-H), 4.11 – 4.05 (1H, m, C**1**-H), 3.97 (1H, d, *J* = 10.5 Hz, C**7**-H), 3.89 (1H, d, *J* = 10.5 Hz, C**7**-H'), 3.35 – 3.26 (1H, m, C**1**-H'), 2.38 (3H, s, CH_3), 1.86 – 1.78 (1H, m, C**2**-H), 1.68 – 1.55 (4H, m, C**2**-H', C**3**-H_2, C**4**-H), 1.35 – 1.22 (1H, m, C**4**-H'); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.5 (ArC), 147.2 (ArC), 140.9 (ArC), 138.9 (ArC), 137.2 (ArC), 135.6 (ArC), 132.8 (ArCH), 129.8 (ArCH), 128.4 (ArCH), 128.1 (ArCH), 127.6 (ArCH), 125.3 (ArCH), 119.4 (ArCH), 78.5 (C**6**), 71.0 (C**7**), 59.2 (C**5**), 42.6 (C**1**), 26.6 (C**2**), 26.2 (C**4**), 21.4 (CH_3), 19.4 (C**3**); HRMS (ESI$^+$) Calculated for $C_{26}H_{27}N_3NaO_7S$: 548.1462. Found $[M+Na]^+$: 548.1454.

The structure and relative stereochemistry of this compound was confirmed by X-ray crystallography after recrystallization (CH_2Cl_2:hexane).



*Crystal structure of **444**.*

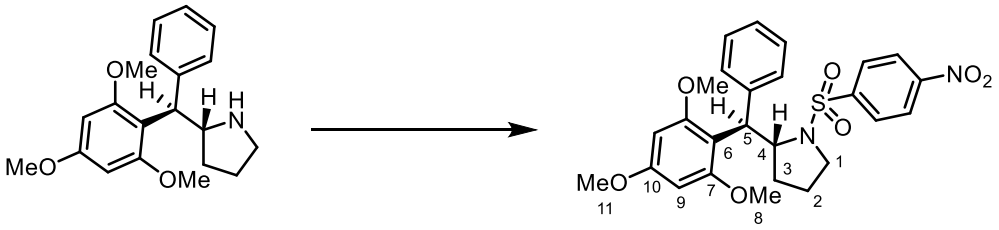
(*R)-2-((*R**)-Phenyl(2,4,6-trimethoxyphenyl)methyl)pyrrolidine (445)**



To a re-sealable tube was added *N*-tosyloxycarbamate **345** (43.2 mg, 0.10 mmol) and 1,3,5-trimethoxybenzene (33.6 mg, 0.20 mmol). The tube was fitted with a rubber septum and purged with nitrogen before addition of TFE (0.1 mL) and TFA (15 μL, 0.20 mmol). The tube was

sealed and stirred at room temperature for 42 hours before being concentrated *in vacuo*. The crude reaction mixture was purified by flash column chromatography (~0.1% Et_3N in EtOAc) to afford **445** (16.5 mg, 50%) as a >20:1 mixture of diastereomers and as a yellow oil; R_f = 0.05 (EtOAc); ν_{max} / cm^{-1} (*film*) 2937 (m), 2836 (m), 1602 (s), 1589 (s), 1452 (s), 1202 (s), 1148 (s), 1115 (s), 730 (s), 698 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.44 (2H, m, ArC<u>H</u>), 7.24 – 7.18 (2H, m, ArC<u>H</u>), 7.12 – 7.07 (1H, m, ArC<u>H</u>), 6.08 (2H, s, C**9**-<u>H</u>), 4.44 (1H, d, *J* = 10.5 Hz, C**5**-<u>H</u>), 4.32 (1H, ddd, *J* = 10.5, 7.6, 6.1 Hz, C**4**-<u>H</u>), 3.76 (9H, s, C**8**-<u>H_3</u>, and C**11**-<u>H_3</u>), 3.03 (1H, ddd, *J* = 10.0, 7.5, 5.2 Hz, C**1**-<u>H</u>), 2.89 (1H, dt, *J* = 10.1, 7.4 Hz, C**1**-<u>H</u>'), 2.39 (1H, br s, N<u>H</u>), 1.83 – 1.64 (3H, m, C**2**-<u>H_2</u>, C**3**-<u>H</u>), 1.34 – 1.25 (1H, m, C**3**-<u>H</u>'); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.6 (C**10**), 159.0 (C**7**), 144.3 (Ar<u>C</u>), 128.9 (Ar<u>C</u>H), 128.0 (Ar<u>C</u>H), 125.7 (Ar<u>C</u>H), 113.6 (C**6**), 91.2 (C**9**), 59.6 (C**4**), 55.8 (C**8**), 55.3 (C**11**), 46.8 (C**5**), 46.5 (C**1**), 30.4 (C**3**), 25.1 (C**2**); HRMS (ESI^+) Calculated for $C_{20}H_{26}NO_3$: 328.1913. Found $[M+H]^+$: 328.1905.

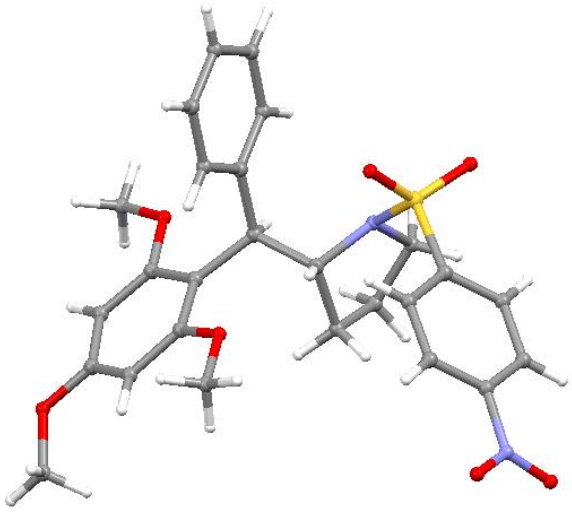
(*R)-1-((4-Nitrophenyl)sulfonyl)-2-((*R**)-phenyl(2,4,6-trimethoxyphenyl)methyl) pyrrolidine (446)**



To a solution of pyrrolidine **445** (16.5 mg, 0.05 mmol) and Et_3N (10.5 μL, 0.075 mmol) in CH_2Cl_2 (0.2 mL) at 0 °C was added 4-nitrobenzenesulfonyl chloride (11.1 mg, 0.05 mmol). The reaction was warmed to room temperature and stirred overnight. The reaction was diluted with CH_2Cl_2 (5 mL) and 1 M HCl (1 mL) was added. The phases were separated, and the aqueous layer extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were washed with H_2O, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (20% EtOAc:petroleum ether) to afford **446** (13.9 mg, 54%) as a yellow solid; R_f = 0.75 (EtOAc); m.p.: 201-203 °C (EtOAc); ν_{max} / cm^{-1} (*solid*) 2940 (m), 2839 (m), 1604 (s), 1587 (s), 1526 (s), 1348 (s), 1149 (s), 1121 (s), 734 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 8.08 – 8.03 (2H, m, Ns ArC<u>H</u>), 7.44 – 7.37 (4H, m, Ns ArC<u>H</u>, ArC<u>H</u>), 7.14 – 7.09 (3H, m, ArC<u>H</u>), 6.08 (2H, s, C**9**-<u>H</u>), 5.58 (1H, ddd, *J* = 11.0, 7.0, 2.0 Hz, C**4**-<u>H</u>), 4.35 (1H, d, *J* = 11.0 Hz, C**5**-<u>H</u>), 3.93 – 3.67 (10H, m, C**1**-<u>H</u>, C**8**-<u>H_3</u>, C**8**-<u>H_3</u>', C**11**-<u>H_3</u>), 3.30 (1H, ddd, *J* = 11.5, 8.5, 5.5 Hz, C**1**-<u>H</u>'), 1.97 – 1.80 (2H, m, C**2**-<u>H_2</u>), 1.76 – 1.65 (1H, m, C**3**-<u>H</u>), 1.64 – 1.57 (1H, m, C**3**-<u>H</u>'); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.1 (C**10**), 158.8 (C**7**), 149.4

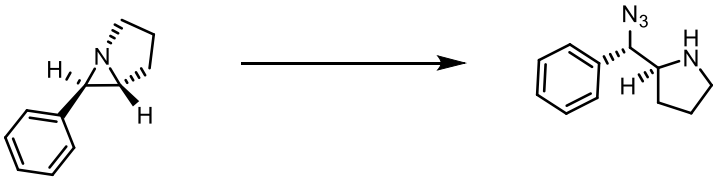
(Ns ArC), 146.6 (Ns ArC), 143.0 (ArC), 129.6 (ArCH), 128.2 (2 × Ns ArCH), 128.0 (ArCH), 126.2 (ArCH), 123.8 (2 × Ns ArCH), 111.5 (C**6**), 91.2 (C**9**), 63.6 (C**4**), 55.4 (C**8**, C**11**), 47.1 (C**1**), 45.3 (C**5**), 30.1 (C**3**), 24.6 (C**2**); HRMS (ESI$^+$) Calculated for $C_{26}H_{28}N_2NaO_7S$: 535.1509. Found $[M+Na]^+$: 535.1503.

The structure and relative stereochemistry were confirmed by single crystal X-ray diffraction after recrystallisation ($CHCl_3$:hexane).



*X-ray crystal structure of **446**.*

(*S)-2-((*S**)-Azido(phenyl)methyl)pyrrolidine (447)**



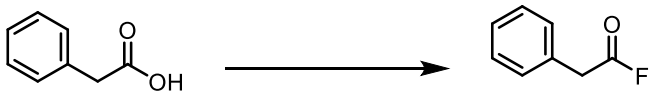
To a solution of 1-azabicyclo[3.1.0]hexane **346** (23.9 mg, 0.15 mmol) and $TMSN_3$ (39.8 µL, 0.30 mmol) in HFIP (75 µL, 2 M) was added TfOH (1.3 µL, 10 mol%) and the reaction was stirred at room temperature for 3 hours. After completion the crude mixture was concentrated *in vacuo* and purified by flash column chromatography (EtOAc) to afford **447** (20.0 mg, 66%) as a >15:1 mixture of diastereomers and as a pale-yellow oil; ν_{max} / cm^{-1} (*film*) 2964 (m), 2870 (m), 2093 (s), 1452 (m), 1243 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.27 (5H, m), 4.39 (1H, d, *J* = 7.5 Hz), 3.35 (1H, q, *J* = 7.2 Hz), 2.98 (1H, ddd, *J* = 10.0, 7.2, 5.2 Hz), 2.84 (1H, ddd, *J* = 9.9, 7.5, 6.5 Hz), 2.02 (1H, br s), 1.96 – 1.63 (4H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.2, 128.8, 128.4, 127.4, 70.1, 62.9, 46.5, 28.2, 25.0; HRMS (ESI$^+$) Calculated for $C_{11}H_{15}N_4$: 203.1299. Found $[M+H]^+$: 203.1297.

The spectroscopic properties were consistent with the data available in the literature.[340]
The relative stereochemistry was determined by comparison to the literature data.

2-Benzyl-2-methylpyrrolidine (448)

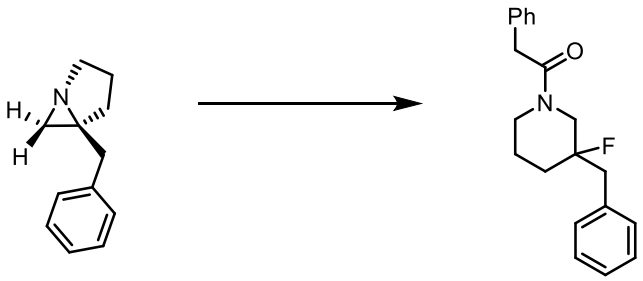
To solution of 1-azabicyclo[3.1.0]hexane **393** (16.9 mg, 0.098 mmol) in MeOH (1 mL) was added 5 % Pd/C (1.69 mg, 10 wt.%). The reaction flask was fitted with a hydrogen balloon and stirred overnight at room temperature. Upon completion the reaction mixture was filtered through Celite® and concentrated *in vacuo* to afford **448** (16.8 mg, 98%) as a colourless oil; R_f = 0.01 (5% MeOH:CH_2Cl_2); ν_{max} / cm^{-1} (*film*) 3328 (br m), 2959 (m), 699 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.17 (5H, m, ArC<u>H</u>), 3.00 (2H, t, *J* = 7.0 Hz, C**1**-<u>H_2</u>), 2.73 (2H, q, *J* = 13.0 Hz, C**5**-<u>H_2</u>), 2.03 (1H, br s, N<u>H</u>), 1.87 – 1.67 (3H, m, C**2**-<u>H_2</u>, C**3**-<u>H</u>), 1.49 (1H, ddd, *J* = 12.5, 8.5, 5.5 Hz, C**3**-<u>H</u>'), 1.08 (3H, s, C**6**-<u>H_3</u>); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.9 (Ar<u>C</u>), 130.4 (Ar<u>C</u>H), 128.2 (Ar<u>C</u>H), 126.3 (Ar<u>C</u>H), 62.3 (C**4**), 46.9 (C**5**), 45.4 (C**1**), 37.4 (C**3**), 26.3 (C**6**), 25.1 (C**2**); HRMS (ESI^+) Calculated for $C_{12}H_{18}N$: 176.1434. Found $[M+H]^+$: 176.1436.

2-Phenylacetyl fluoride



The title compound was prepared according to a literature procedure.[341]
The title compound was used immediately in the next step without purification.

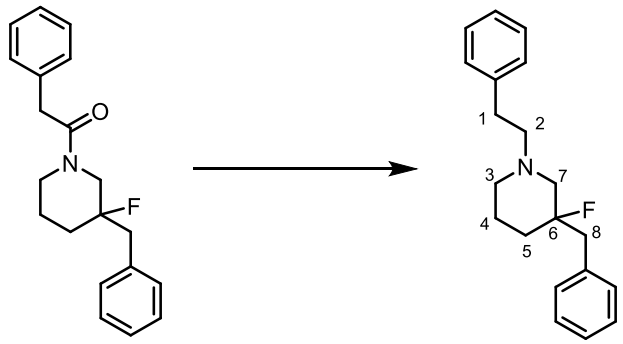
1-(3-Benzyl-3-fluoropiperidin-1-yl)-2-phenylethan-1-one (457)



General procedure S: 1-Azabicyclo[3.1.0]hexane **389** (27.9 mg, 0.16 mmol) and 2-phenylacetyl fluoride (33.2 mg, 0.24 mmol) in anhydrous THF (0.16 mL) were employed. The reaction was stirred at 0 °C for 3 h before being concentrated *in vacuo*. The crude product was purified twice by flash column chromatography (20% EtOAc:PhMe then gradient, eluent: 20 – 33% EtOAc:pentane) to afford **457** (29.2 mg, 59%) as a colourless oil; R_f = 0.25 (33% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 3029 (m), 2929 (m), 1638 (s), 1454 (s), 1438 (s), 1159 (m); HRMS (ESI^+) Calculated for $C_{20}H_{22}FNNaO$: 334.1578. Found $[M+Na]^+$: 334.1584.

*The complex exists as an approximately 3:2 mixture of rotamers. The amide of **457** was reduced to allow nmr assignment, details of this are given below.*

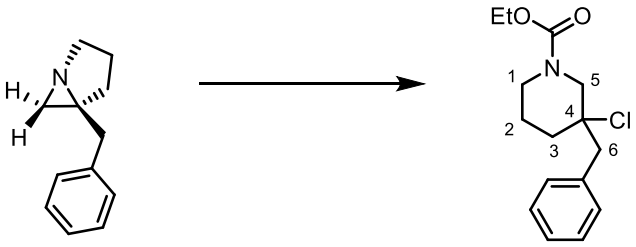
3-Benzyl-3-fluoro-1-phenethylpiperidine



General procedure B: The preceding piperidine **457** (49.9 mg, 0.17 mmol) and 2.0 equivalents of $LiAlH_4$ (0.34 mmol, 0.34 mL, 1M in THF) in anhydrous THF (1 mL) were employed. Purification by flash column chromatography (20% EtOAc:pentane) afforded the title compound (20.6 mg, 41%) as a colourless oil; R_f = 0.60 (33% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 2942 (m), 2802 (m), 1495 (m), 1453 (m), 1115 (m); ^{1}H NMR (400 MHz, CD_3CN) δ 7.31 – 7.14 (10H, m, ArC<u>H</u>), 3.04 – 2.86 (2H, m, C**8**-<u>H_2</u>), 2.80 – 2.68 (2H, m, C**1**-<u>H_2</u>), 2.60 – 2.33 (6H, m, C**2**-<u>H_2</u>, C**3**-<u>H_2</u>, C**7**-<u>H_2</u>), 1.76 – 1.51 (4H, m, C**4**-<u>H_2</u>, C**5**-<u>H_2</u>); ^{13}C NMR (101 MHz, CD_3CN) δ 141.9 (Ar<u>C</u>), 137.5 (Ar<u>C</u>), 131.5 (Ar<u>C</u>H), 129.8 (Ar<u>C</u>H), 129.2 (Ar<u>C</u>H), 128.9

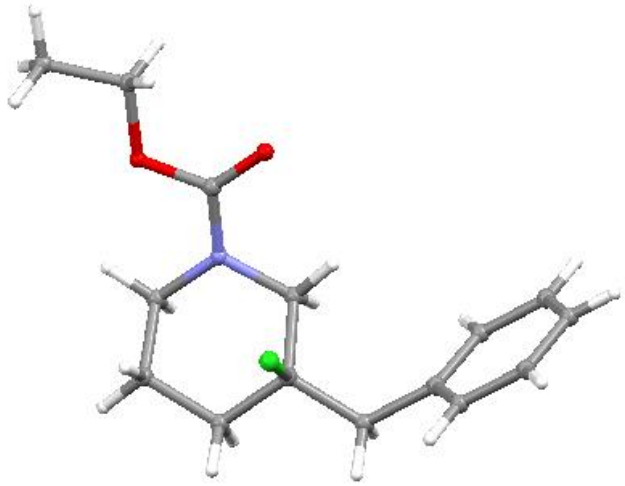
(Ar<u>C</u>H), 127.4 (Ar<u>C</u>H), 126.8 (Ar<u>C</u>H), 94.8 (d, $^{1}J_{C\text{-}F}$ = 174.5 Hz, C**6**), 61.4 (d, $^{2}J_{C\text{-}F}$ = 23.5 Hz, C**7**), 60.9 (C**2**), 53.6 (C**3**), 44.1 (d, $^{3}J_{C\text{-}F}$ = 21.0 Hz, C**8**), 34.3 (d, $^{2}J_{C\text{-}F}$ = 21.5 Hz, C**5**), 33.8 (C**1**), 23.0 (d, $^{3}J_{C\text{-}F}$ = 6.0 Hz, C**4**); ^{19}F NMR (377 MHz, CD_3CN) δ -151.9; HRMS (ESI^+) Calculated for $C_{20}H_{25}FN$: 298.1966. Found $[M+H]^+$: 298.1979.

Ethyl 3-benzyl-3-chloropiperidine-1-carboxylate (459)



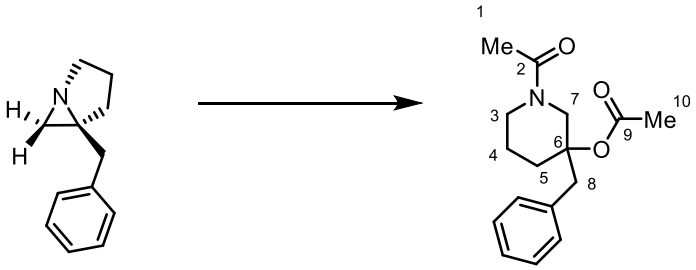
<u>General procedure S:</u> 1-Azabicyclo[3.1.0]hexane **389** (17.3 mg, 0.1 mmol) and ethyl chloroformate (10.5 μL, 0.11 mmol) in anhydrous THF (0.1 mL) were employed. The reaction time was 18 hours. Purification by flash column chromatography (33% EtOAc:hexane) afforded **459** (22.0 mg, 78%) as a colourless solid; R_f = 0.60 (33% EtOAc:hexane), m.p. 100-103 °C; ν_{max} / cm^{-1} (*solid*) 2983 (m), 2932 (m), 2954 (m), 1679 (s), 1439 (s), 1244 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.25 (5H, m, Ar<u>C</u>H), 4.15 (2H, q, *J* = 7.0 Hz, <u>C</u>$H_2$$CH_3$), 4.12 – 3.93 (1H, m, C**5**-<u>H</u>), 3.89 (1H, dt, *J* = 13.5, 4.0 Hz, C**1**-<u>H</u>), 3.32 – 3.18 (1H, m, C**5**-<u>H</u>'), 3.13 (1H, d, *J* = 14.0 Hz, C**6**-<u>H</u>), 3.08 (1H, d, *J* = 14.0 Hz, C**6**-<u>H</u>'), 3.04 – 2.92 (1H, m, C**1**-<u>H</u>'), 1.96 – 1.85 (2H, m, C**2**-<u>H</u>, C**3**-<u>H</u>), 1.82 – 1.72 (1H, m, C**3**-<u>H</u>'), 1.63 – 1.55 (1H, m, C**2**-<u>H</u>'), 1.26 (3H, t, *J* = 7.0 Hz, CH_2<u>C</u>H_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.8 (<u>C</u>=O), 135.4 (Ar<u>C</u>), 131.1 (Ar<u>C</u>H), 128.2 (Ar<u>C</u>H), 127.2 (Ar<u>C</u>H), 70.7 (C**4**), 61.6 (<u>C</u>$H_2$$CH_3$), 55.0 (C**5**), 47.3 (C**6**), 43.7 (C**1**), 37.4 (C**3**), 21.9 (C**2**), 14.8 (CH_2<u>C</u>H_3); HRMS (ESI^+) Calculated for $C_{15}H_{20}{}^{35}ClNNaO_2$: 304.1074. Found $[M+Na]^+$: 304.1083.

*The structure of **459** was confirmed by X-ray crystallography after recrystallisation (CH_2Cl_2:hexane).*



*X-ray crystal structure of **459**.*

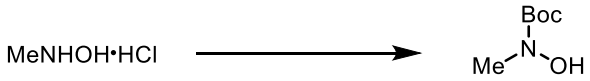
1-Acetyl-3-benzylpiperidin-3-yl acetate (460)



General procedure S: 1-Azabicyclo[3.1.0]hexane (**389**) (17.6 mg, 0.10 mmol) and acetic anhydride (10.4 μL, 0.11 mmol) in anhydrous THF (0.1 mL) were employed. The reaction time was 18 hours. Purification by flash column chromatography (gradient, eluent: 33% EtOAc:hexane – EtOAc) afforded **460** (19.8 mg, 72%) as a colourless oil. *This compound exists as an approximately 3:1 mixture of rotamers A and B.* R_f = 0.10 (33% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 2931 (m), 2850 (m), 1728 (s), 1631 (s), 1438 (s), 1236 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.05 (5H, m, *A* and *B*: ArC<u>H</u>), 4.58 (0.25H, d, *J* = 14.0 Hz, *B*: C**7**-<u>H</u>), 4.45 – 4.38 (0.75H, m, *A*: C**3**-<u>H</u>), 4.27 (0.75H, d, *J* = 13.5 Hz, *A*: C**7**-<u>H</u>), 3.61 – 3.54 (0.25H, m, *B*: C**3**-<u>H</u>), 3.34 (0.25H, d, *J* = 14.0 Hz, *B*: C**8**-<u>H</u>), 3.27 (0.75H, d, *J* = 14.0 Hz, *A*: C**8**-<u>H</u>), 3.16 – 3.02 (2H, m, *B*: C**3**-<u>H</u>', *A*: C**7**-<u>H</u>', *A* + *B*: C**8**-<u>H</u>'), 2.95 (0.25H, d, *J* = 13.5 Hz, *B*: C**7**-<u>H</u>'), 2.61 – 2.52 (0.75H, m, *A*: C**3**-<u>H</u>'), 2.36 – 2.25 (1H, m, *A* + *B*: C**5**-<u>H</u>), 2.06 (0.75H, s, *B*: C**1**-<u>H_3</u>), 2.00 – 1.94 (4.50H, m, *A*: C**1**-<u>H_3</u> + C**10**-<u>H_3</u>), 1.91 (0.75H, s, *B*: C**10**-<u>H_3</u>), 1.63 – 1.41 (3H, m, *A* + *B*: C**4**-<u>H_2</u> + C**5**-<u>H</u>'); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.3 (*A*: C**9**), 170.8 (*B*: C**9**), 170.1 (*A*: C**2**), 169.5 (*B*: C**2**), 135.9 (*B*: Ar<u>C</u>), 135.5 (*A*: Ar<u>C</u>), 130.5 (*B*: Ar<u>C</u>H), 130.3 (*A*: Ar<u>C</u>H), 128.5 (*A*: Ar<u>C</u>H), 128.4 (*B*: Ar<u>C</u>H), 127.1 (*A*: Ar<u>C</u>H), 126.8 (*B*: Ar<u>C</u>H), 80.7 (*A*: C**6**), 80.6 (*B*: C**6**), 53.2

(*A*: C**7**), 48.3 (*B*: C**7**), 46.5 (*B*: C**3**), 41.7 (*A*: C**3**), 41.1 (*B*: C**8**), 41.0 (*A*: C**8**), 33.1 (*A*: C**5**), 32.6 (*B*: C**5**), 22.4 (*A*: C**10**), 22.0 (*B*: C**10**), 21.7 (*B*: C**1**), 21.3 (*A*: C**1**), 20.8 (*A* + *B*: C**4**); HRMS (ESI$^+$) Calculated for $C_{16}H_{21}NNaO_3$: 298.1414. Found $[M+Na]^+$: 298.1424.

***tert*-Butyl hydroxy(methyl)carbamate**

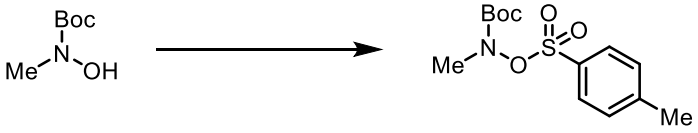


The title compound was prepared according to a literature procedure.[342]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (1H, s), 3.10 (3H, s), 1.43 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.7, 81.6, 38.0, 28.3.

The spectroscopic properties were consistent with the data available in the literature.[342]

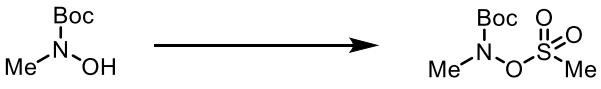
***tert*-Butyl methyl(tosyloxy)carbamate (463)**



General procedure T: *tert*-Butyl hydroxy(methyl)carbamate (8.97 g, 61.0 mmol), 4-toluenesulfonyl chloride (12.2 g, 64.0 mmol) and Et_3N (8.9 mL, 64.0 mmol) in Et_2O (250 mL) were employed. Purification by flash column chromatography (10% EtOAc:petroleum ether) afforded **463** (9.02 g, 49%) as a colourless solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (2H, d, *J* = 8.5 Hz), 7.35 (2H, d, *J* = 8.5 Hz), 3.24 (3H, s), 2.45 (3H, s), 1.21 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.2, 145.8, 131.2, 129.8, 129.7, 83.4, 40.3, 27.7, 21.8; HRMS (ESI$^+$) Calculated for $C_{13}H_{19}NNaO_5S$: 324.0876. Found $[M+Na]^+$: 324.0875.

The spectroscopic properties were consistent with the data available in the literature.[343]

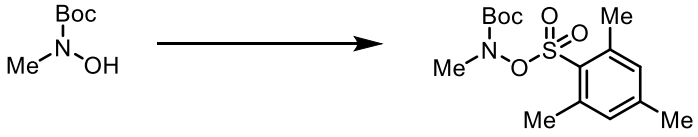
***tert*-Butyl methyl((methylsulfonyl)oxy)carbamate (465a)**



General procedure T: *tert*-Butyl hydroxy(methyl)carbamate (736 mg, 5.0 mmol), methanesulfonylchloride (0.41 mL, 5.25 mmol) and Et_3N (0.73 mL, 5.25 mmol) in Et_2O (20 mL) were employed. Purification by flash column chromatography (10% EtOAc:petroleum ether) afforded **465a** (680 mg, 60%) as a colourless oil; ν_{max} / cm^{-1} (*film*) 2981 (m), 1726 (s),

1367 (s), 1322 (s), 1181 (s), 1145 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.31 (3H, s, NC<u>H</u>$_3$), 3.13 (3H, s, Ms C<u>H</u>$_3$), 1.51 (9H, s, Boc (C<u>H</u>$_3$)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.2 (Boc <u>C</u>=O), 84.5 (Boc <u>C</u>(CH$_3$)$_3$), 40.7 (N<u>C</u>H$_3$), 36.8 (Ms <u>C</u>H$_3$), 28.2 (Boc (<u>C</u>H$_3$)$_3$); HRMS (ESI$^+$) Calculated for $C_7H_{15}NNaO_5S$: 248.0563. Found $[M+Na]^+$: 248.0567.

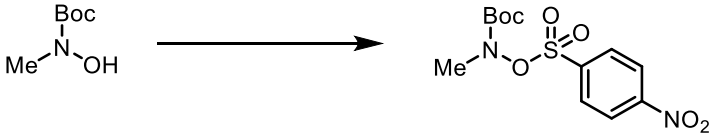
tert-Butyl ((mesitylsulfonyl)oxy)(methyl)carbamate (465b)



<u>General procedure T:</u> *tert*-Butyl hydroxy(methyl)carbamate (1.47 g, 10.0 mmol), 2-mesitylenesulfonyl chloride (2.30 g, 10.5 mmol) and Et_3N (1.46 mL, 10.5 mmol) in Et_2O (40 mL) were employed. Purification by flash column chromatography (10% EtOAc:petroleum ether) followed by recrystallisation (from hexane) afforded **465b** (645 mg, 20%) as a colourless solid; m.p. 69-70 °C (CH_2Cl_2:hexane) [lit: 67-69 °C (hexane)[344]]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (2H, s), 3.22 (3H, s), 2.64 (6H, s), 2.30 (3H, s), 1.25 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.4, 144.3, 142.1, 131.8, 129.6, 83.5, 40.4, 27.8, 23.5, 21.2; HRMS (ESI$^+$) Calculated for $C_{15}H_{23}NNaO_5S$: 352.1189. Found $[M+Na]^+$: 352.1191.

The spectroscopic properties were consistent with the data available in the literature.[344]

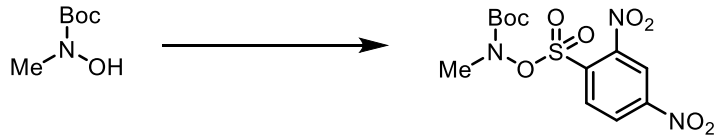
tert-Butyl methyl(((4-nitrophenyl)sulfonyl)oxy)carbamate (465c)



<u>General procedure T:</u> *tert*-Butyl hydroxy(methyl)carbamate (1.47 g, 10.0 mmol), 4-nitrobenzenesulfonyl chloride (2.33 g, 10.5 mmol) and Et_3N (1.46 mL, 10.5 mmol) in Et_2O (40 mL) were employed. Purification by flash column chromatography (10% EtOAc:petroleum ether) afforded **465c** (1.44 g, 43%) as a pale-yellow solid; m.p.: 98-99 °C (CH_2Cl_2/hexane); ν_{max} / cm^{-1} (*solid*) 3115 (m), 2984 (m), 2934 (m), 1736 (s), 1535 (s), 1383 (s), 1371 (s), 1133 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (2H, d, *J* = 8.7 Hz, ArC<u>H</u>), 8.20 (2H, d, *J* = 8.7 Hz, ArC<u>H</u>), 3.29 (3H, s, NC<u>H</u>$_3$), 1.23 (9H, s, Boc (C<u>H</u>$_3$)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.7 (Boc <u>C</u>=O), 151.3 (Ar<u>C</u>), 140.0 (Ar<u>C</u>), 131.3 (Ar<u>C</u>H), 124.0 (Ar<u>C</u>H), 84.3 (Boc <u>C</u>(CH$_3$)$_3$), 40.9

(N<u>C</u>H$_3$), 27.8 (Boc (<u>C</u>H$_3$)$_3$); HRMS (ESI$^+$) Calculated for $C_{12}H_{16}N_2NaO_7S$: 355.0570. Found [M+Na]$^+$: 355.0573.

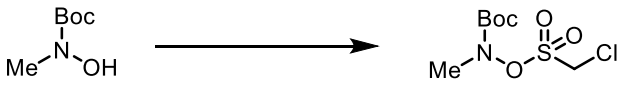
***tert*-Butyl (((2,4-dinitrophenyl)sulfonyl)oxy)(methyl)carbamate (465d)**



<u>General procedure T:</u> *tert*-Butyl hydroxy(methyl)carbamate (1.47 g, 10.0 mmol), 2,4-dinitrobenzenesulfonyl chloride (2.79 g, 10.5 mmol) and Et$_3$N (1.46 mL, 10.5 mmol) in Et$_2$O (40 mL) were employed. Purification by flash column chromatography (20% EtOAc:petroleum ether) afforded **465d** (335 mg, 9%) as a colourless solid; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.61 (1H, d, *J* = 2.0 Hz), 8.54 (1H, dd, *J* = 8.5, 2.0 Hz), 8.41 (1H, d, *J* = 8.5 Hz), 3.32 (3H, s), 1.30 (9H, s); ^{13}C NMR (101 MHz, CDCl$_3$) δ 155.5, 150.1, 149.4, 134.7, 133.1, 126.0, 120.1, 84.9, 41.2, 27.9.

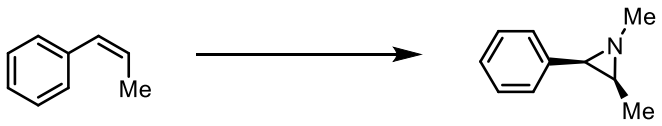
The spectroscopic properties were consistent with the data available in the literature.[342]

***tert*-Butyl (((chloromethyl)sulfonyl)oxy)(methyl)carbamate (465e)**



<u>General procedure T:</u> *tert*-Butyl hydroxy(methyl)carbamate (1.47 g, 10.0 mmol), chloromethane sulfonyl chloride (0.95 mL, 10.5 mmol) and Et$_3$N (1.46 mL, 10.5 mmol) in Et$_2$O (40 mL) were employed. Purification by flash column chromatography (10% EtOAc: petroleum ether) afforded **465e** (1.27 g, 49%) as an off-white solid; m.p.: 49-51 ^{o}C (CH_2Cl_2:hexane); ν_{max} / cm^{-1} (*solid*) 3030 (m), 2978 (m), 2963 (m), 1722 (s), 1384 (s), 1371 (s), 1147 (s); ^{1}H NMR (400 MHz, CDCl$_3$) δ 4.79 (2H, s, C<u>H</u>$_2$Cl), 3.34 (3H, s, NC<u>H</u>$_3$), 1.53 (9H, s, Boc (C<u>H</u>$_3$)$_3$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 156.1 (Boc <u>C</u>=O), 85.2 (Boc <u>C</u>(CH$_3$)$_3$), 53.7 (<u>C</u>H$_2$Cl), 41.1 (N<u>C</u>H$_3$), 28.2 (Boc C(<u>C</u>H$_3$)$_3$); HRMS (ESI$^+$) Calculated for $C_7H_{14}Cl_{35}NNaO_5S$: 282.0173. Found [M+Na]$^+$: 282.0175.

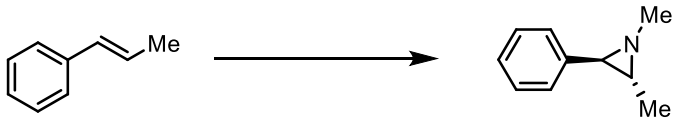
(2*S,3*R**)-1,2-Dimethyl-3-phenylaziridine (464)**



General procedure U: *tert*-Butyl (((chloromethyl)sulfonyl)oxy)(methyl)carbamate **465e** (155.8 mg, 0.6 mmol), *cis*-β-methylstyrene (65 μL, 0.5 mmol) and TFA (77 μL, 2.0 mmol) in TFE (1.0 mL, 0.5 M) were employed. The reaction was stirred at room temperature for 48 hours. After completion the solvent was removed *in vacuo* and purification by flash column chromatography (~0.1% Et_3N in 10% EtOAc:pentane) afforded **464** (31.0 mg, 42%) as a colourless oil; R_f = 0.40 (20% EtOAc:hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.27 (4H, m), 7.24 – 7.19 (1H, m), 2.51 (3H, s), 2.45 (1H, d, *J* = 6.5 Hz), 1.70 (1H, dq, *J* = 6.5, 5.5 Hz), 0.93 (3H, d, *J* = 5.5 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.7, 128.0, 127.9, 126.6, 47.8, 47.7, 43.1, 12.8.

The spectroscopic properties were consistent with the data available in the literature.[345]

(2*R,3*R**)-1,2-Dimethyl-3-phenylaziridine (466)**



3:1 mixture of invertomers

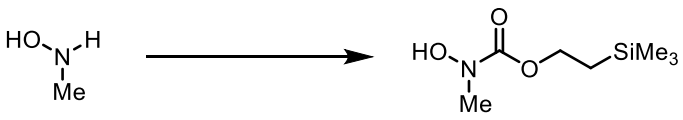
General procedure U: *tert*-Butyl (((chloromethyl)sulfonyl)oxy)(methyl)carbamate **465e** (155.8 mg, 0.6 mmol), *trans*-β-methylstyrene (65 μL, 0.5 mmol) and TFA (77 μL, 2.0 mmol) in TFE (1.0 mL, 0.5 M) were employed. The reaction was stirred at room temperature for 48 hours and concentrated *in vacuo*. Purification by flash column chromatography (~0.1% Et_3N in 20% EtOAc:pentane) afforded **466** (23.7 mg, 32%) as an approximately 3:1 mixture of invertomers (at 298 K) and as a pale-yellow oil.

Spectroscopic data for the major invertomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.19 (5H, m), 2.55 (3H, s), 2.15 – 2.10 (1H, m), 2.09 – 2.07 (1H, m), 1.37 (3H, d, *J* = 6.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.9, 128.4, 126.8, 126.0, 49.7, 42.7, 38.4, 10.9.

Characteristic signals for the minor invertomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.86 (1H, d, *J* = 3.5 Hz), 2.05 (3H, s), 1.99 – 1.93 (1H, m), 1.32 (3H, d, *J* = 5.5 Hz); ^{13}C NMR (101 MHz), δ 134.4, 130.3, 128.0, 127.5, 47.2, 39.8, 39.0, 18.3.

The spectroscopic properties were consistent with the data available in the literature.[346]

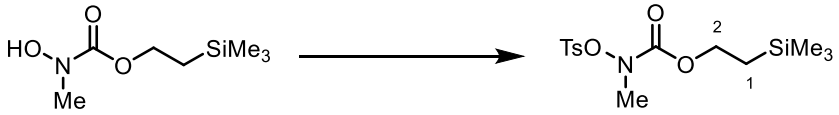
2-(Trimethylsilyl)ethyl hydroxy(methyl)carbamate



To *N*-methylhydroxylamine hydrochloride (169 mg, 2.02 mmol) in MeOH (20 mL) was added a solution of KOH (20 mL, 0.1 M in MeOH) and *N*-[2-(trimethylsilyl)ethoxy carbonyloxy]succinimide (500 mg, 1.93 mmol) and the reaction was stirred at room temperature overnight. The solvent was removed in *vacuo* and the residue was dissolved in EtOAc (30 mL) and washed with saturated aqueous $NaHCO_3$ (3 × 15 mL) and brine (15 mL), dried over Na_2SO_4, filtered and concentrated in *vacuo*. The resulting colourless oil (318 mg, 86%) was used without further purification; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.27 – 4.22 (2H, m), 3.20 (3H, s), 1.59 (1H, br s), 1.06 – 1.01 (2H, m), 0.05 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.2, 65.2, 37.7, 17.9, -1.4.

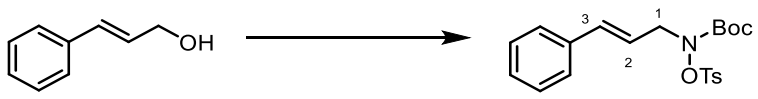
The spectroscopic properties were consistent with the data available in the literature.[347]

2-(Trimethylsilyl)ethyl methyl(tosyloxy)carbamate (467)



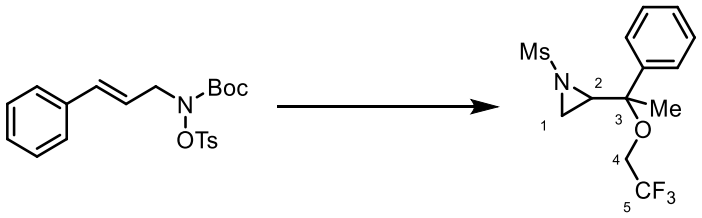
To a solution of 2-(trimethylsilyl)ethyl hydroxy(methyl)carbamate (318 mg, 1.66 mmol) in CH_2Cl_2 (5 mL) cooled to 0 °C were added Et_3N (0.25 mL) and TsCl (349 mg, 1.83 mmol). The reaction was warmed to room temperature and stirred overnight. The reaction was quenched with 1M aqueous HCl (5 mL) and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (5 mL) and the combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated in *vacuo*. Purification by flash column chromatography (10% EtOAc:hexane) afforded **467** (480 mg, 84%) as a colourless solid; m.p.: 68-70 °C (CH_2Cl_2); ν_{max} / cm^{-1} (*solid*) 2960 (m), 1722 (s), 1375 (s), 1172 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.34 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 3.98 – 3.92 (2H, m, C**2**-<u>H</u>$_2$), 3.24 (3H, s, NC<u>H</u>$_3$), 2.45 (3H, s, Ts C<u>H</u>$_3$), 0.75 – 0.68 (2H, m, C**1**-<u>H</u>$_2$), -0.01 (9H, s, Si(C<u>H</u>$_3$)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.6 (<u>C</u>=O), 145.9 (Ts Ar<u>C</u>), 131.3 (Ts Ar<u>C</u>), 129.8 (2 × Ts Ar<u>C</u>H), 129.7 (2 × Ts Ar<u>C</u>H), 65.9 (C**2**), 40.3 (N<u>C</u>H$_3$), 21.9 (Ts <u>C</u>H$_3$), 17.5 (C**1**), -1.51 (Si(<u>C</u>H$_3$)$_3$); HRMS (ESI$^+$) Calculated for $C_{14}H_{23}NNaO_5SSi$: 368.0958. Found $[M+Na]^+$: 368.0966.

***tert*-Butyl cinnamyl(tosyloxy)carbamate (476)**



General procedure G: Cinnamyl alcohol (671 mg, 5.0 mmol), PPh_3 (1.57 g, 6.0 mmol), DIAD (1.17 mL, 6.0 mmol) and BocNHOTs (1.72 g, 6.0 mmol) in anhydrous THF (20 mL) were employed. Purification by flash column chromatography (gradient, eluent: 5 – 10% EtOAc:hexane) afforded **476** (1.28 g, 63%) as a colourless solid; m.p.: 77-79 ^{o}C (CH_2Cl_2/hexane); ν_{max}/cm^{-1} (solid) 1715 (s), 1379 (s), 1344 (s), 1190 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (2H, d, *J* = 8.0 Hz, Ts ArC<u>H</u>), 7.38 – 7.13 (7H, m, Ts ArC<u>H</u>, ArC<u>H</u>), 6.54 (1H, d, *J* = 16.0 Hz, C**3**-<u>H</u>), 6.17 (1H, dt, *J* = 16.0, 6.5 Hz, C**2**-<u>H</u>), 4.31 (2H, br s, C**1**-<u>H_2</u>), 2.42 (3H, s, Ts C<u>H_3</u>), 1.23 (9H, s, Boc (C<u>H_3</u>)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6 (Boc <u>C</u>=O), 145.9 (Ts Ar<u>C</u>), 136.4 (Ar<u>C</u>), 135.3 (C**3**), 131.4 (Ts Ar<u>C</u>), 129.8 (Ts Ar<u>C</u>H), 129.7 (Ts Ar<u>C</u>H), 128.7 (Ar<u>C</u>H), 128.1 (Ar<u>C</u>H), 126.7 (Ar<u>C</u>H), 121.4 (C**2**) 83.7 (Boc <u>C</u>(CH_3)$_3$), 55.4 (C**1**), 27.8 (Boc (<u>C</u>H_3)$_3$), 21.8 (Ts <u>C</u>H_3); HRMS (ESI$^+$) Calculated for $C_{21}H_{25}NaNO_5S$: 426.1346. Found [M+Na]$^+$: 426.1329.

1-(Methylsulfonyl)-2-(phenyl(2,2,2-trifluoroethoxy)methyl)aziridine (477)



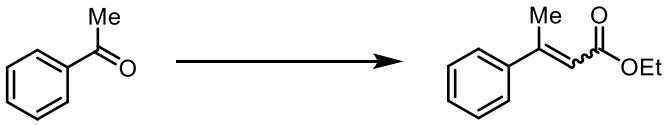
To a solution of the preceding *N*-tosyloxycarbamate **476** (202 mg, 0.5 mmol) in anhydrous TFE (0.1 M) under an atmosphere of nitrogen was added TFA (77 µL, 1.0 mmol). The reaction was stirred at room temperature for 26 h and concentrated *in vacuo*. The crude reaction mixture was dissolved in anhydrous CH_2Cl_2 (5 mL) and cooled to 0 ^{o}C. To the reaction was added methanesulfonyl chloride (77 µL, 1.0 mmol) and Et_3N (0.28 mL, 2.0 mmol). The reaction was allowed to warm to room temperature and stirred overnight before being quenched with saturated aqueous NH_4Cl (5 mL). The phases were separated, and the aqueous phase extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (gradient, eluent: 20% – 33% hexane:EtOAc) afforded **477** (52.4 mg, 34 %) as a 9:1 mixture of diastereomers and as a yellow oil.

*Spectroscopic properties for the major diastereomer **477a**:* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.32 (5H, m, ArC<u>H</u>), 4.17 (1H, d, *J* = 7.5 Hz, C**3**-<u>H</u>), 3.87 – 3.67 (2H, m, C**4**-<u>H_2</u>), 3.05 (3H, s, Ms C<u>H_3</u>), 2.98 (1H, td, *J* = 7.5, 4.5 Hz, C**2**-<u>H</u>), 2.66 (1H, dd, *J* = 7.5, 1.0 Hz, C**1**-<u>H</u>), 2.31 (1H, dd, *J* = 4.5, 1.0 Hz, C**1**-<u>H</u>'); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.1 (Ar<u>C</u>), 129.6 (ArC<u>H</u>), 129.4 (Ar<u>C</u>H), 127.1 (Ar<u>C</u>H), 123.9 (q, *J* = 278.5 Hz, C**5**), 83.2 (C**3**), 66.1 (q, *J* = 34.5 Hz, C**4**) 44.3 (C**2**), 39.4 (Ms <u>C</u>H_3), 29.1 (C**1**).

*Characteristic signals for the minor diastereomer **477b**:* ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.35 (1H, d, *J* = 6.0 Hz), 2.72 (1H, d, *J* = 7.0 Hz).

HRMS (MALDI^{+}) Calculated for: $C_{12}H_{14}NaNO_3F_3S$: 332.0539. Found $[M+Na]^{+}$: 332.0548.

Ethyl (*E*)-3-phenylbut-2-enoate (478)

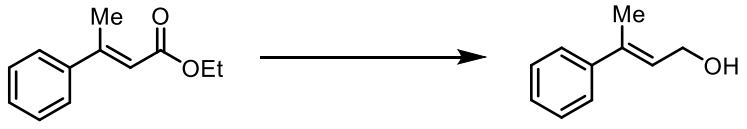


<u>General procedure V:</u> Acetophenone (2.40 g, 20 mmol), triethyl phosponoacetate (6.73 g, 30 mmol) and NaH (60 w.t.% in mineral oil, 1.22 g, 30 mmol) in anhydrous THF (100 mL) were employed. The title compound was obtained as a 5:1 mixture of *E:Z* alkene isomers which were separated by flash column chromatography (5% EtOAc:hexane) to obtain **(*E*)-478** (1.99 g, 52%) as a colourless oil and **(*Z*)-478** (430 mg, 11%) as a colourless oil.

*Spectroscopic properties for **(E)-478**:* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.45 (2H, m), 7.40 – 7.35 (3H, m), 6.14 (1H, q, *J* = 1.5 Hz), 4.22 (2H, q, *J* = 7.0 Hz), 2.58 (3H, d, *J* = 1.5 Hz), 1.32 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0, 155.7, 142.4, 129.1, 128.6, 126.4, 117.3, 59.9, 18.1, 14.5.

The spectroscopic properties were consistent with the data available in the literature.[348]

(*E*)-3-Phenylbut-2-en-1-ol (479)

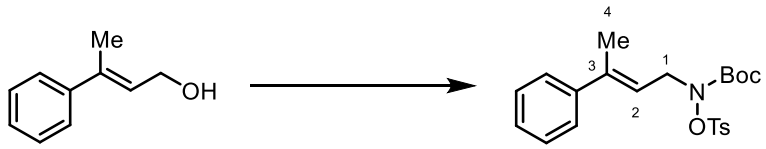


To a solution of the preceding ester **(*E*)-478** (1.54 g, 8.0 mmol) in anhydrous Et_2O (18 mL) at 0 ^{o}C was added DIBAL-H (1M in hexanes, 17.6 mL) dropwise over 15 min. The reaction was stirred at room temperature until completion by TLC analysis (2.5 hours). Upon completion

the reaction was cooled to 0 °C and water (10 mL) was added then brine (10 mL). The white solid formed was partially dissolved by the addition of aqueous HCl (1 M) and the layers were separated. The aqueous layer was extracted with Et_2O and the combined organic extracts were dried, filtered and concentrated under reduced pressure. Purification by flash column chromatography (33% EtOAc:hexane) afforded **479** (873 mg, 74%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.38 (2H, m), 7.35 – 7.30 (2H, m), 7.28 – 7.23 (1H, m), 6.00 – 5.95 (1H, m), 4.36 (2H, d, *J* = 6.5 Hz), 2.08 (3H, s), 1.72 (1H, br s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.8, 137.2, 128.4, 127.3, 126.4, 125.9, 60.1, 16.2.

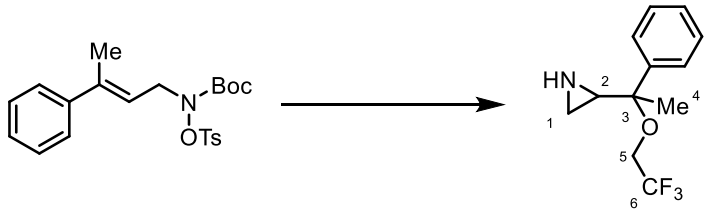
The spectroscopic properties were consistent with the data available in the literature.[349]

tert-Butyl (*E*)-(3-phenylbut-2-en-1-yl)(tosyloxy)carbamate (480)



General procedure G: The preceding alcohol **479** (445 mg, 3.0 mmol), PPh_3 (940 mg, 3.6 mmol), DIAD (0.71 mL, 3.6 mmol) and BocNHOTs (1.03 g, 3.6 mmol) in anhydrous THF (12 mL) were employed. Purification by flash column chromatography (gradient 5 – 10% EtOAc:hexane) afforded **480** (985 mg, 79%) as an off-white solid; ν_{max}/cm^{-1} (solid) 2985 (m), 1746 (s), 1721 (s), 1365 (s), 1147 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 – 7.84 (2H, m, Ts ArC**H**), 7.37 – 7.22 (7H, m, ArC**H**, Ts ArC**H**), 5.79 (1H, td, *J* = 7.0, 1.5 Hz, C**2**-**H**), 4.39 (2H, s, C**1**-H_2), 2.43 (3H, s, Ts CH_3), 2.08 (3H, d, *J* = 1.5 Hz, C**4**-H_3), 1.22 (9H, s, Boc (CH_3)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.8 (Boc **C**=O), 145.8 (Ts Ar**C**), 143.0 (C**3**), 140.7 (Ar**C**), 131.4 (Ts Ar**C**), 129.8 (2 × Ts Ar**C**H), 129.7 (2 × Ts Ar**C**H), 128.4 (Ar**C**H), 127.5 (Ar**C**H), 126.1 (Ar**C**H), 119.6 (C**2**), 83.6 (Boc **C**(CH$_3$)$_3$), 51.5 (C**1**), 27.7 (Boc (**C**H$_3$)$_3$), 21.8 (Ts **C**H$_3$), 16.4 (C**4**); HRMS (ESI$^+$) Calculated for $C_{22}H_{27}NaNO_5S$: 440.1502. Found [M+Na]$^+$: 440.1494.

2-(1-Phenyl-1-(2,2,2-trifluoroethoxy)ethyl)aziridine (481)



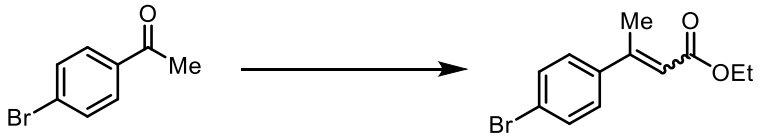
General procedure W: The preceding *N*-tosyloxycarbamate **480** (125 mg, 0.3 mmol) and TFA (46 µL, 0.6 mmol) in anhydrous TFE (3 mL, 0.1 M) were employed. The reaction was stirred at room temperature for 24 hours. Purification by flash column chromatography with ~0.1 % Et_3N added to the eluent (33% EtOAc:hexane) afforded **481** (37.4 mg, 51%) as an 8:1 mixture of diastereomers and as a colourless oil; ν_{max} / cm^{-1} (*film*) 2936 (m), 1275 (s), 1150 (s), 1109 (s).

*Spectroscopic properties for the major diastereomer **481a**:* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.29 (5H, m), 3.82 – 3.63 (2H, m, C**5**-$\underline{H}_2$), 2.32 (1H, dd, *J* = 6.0, 3.5 Hz, C**2**-$\underline{H}$), 1.74 (1H, d, *J* = 6.0 Hz, C**1**-$\underline{H}$), 1.60 (1H, d, *J* = 3.5 Hz, C**1**-$\underline{H}$'), 1.53 (3H, s, C**4**-$\underline{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.1 (Ar$\underline{C}$), 128.7 (Ar$\underline{C}$H), 128.1 (Ar$\underline{C}$H), 126.3 (Ar$\underline{C}$H), 124.3 (q, *J* = 277.6 Hz, C**6**), 78.9 (C**3**), 61.6 (q, *J* = 34.5 Hz, C**5**), 38.5 (C**2**), 22.1 (C**1**), 20.8 (C**4**); ^{19}F NMR (377 MHz, $CDCl_3$) δ -74.00 (t, *J* = 8.5 Hz).

*Characteristic signals for the minor diastereomer **481b**:* ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.19 (1H, dd, *J* = 6.0, 3.5 Hz), 1.84 (1H, d, *J* = 3.5 Hz).

HRMS (ESI^+) Calculated for $C_{12}H_{15}NOF_3$: 246.1100. Found $[M+H]^+$: 246.1093.

Ethyl (*E*)-3-(4-bromophenyl)but-2-enoate



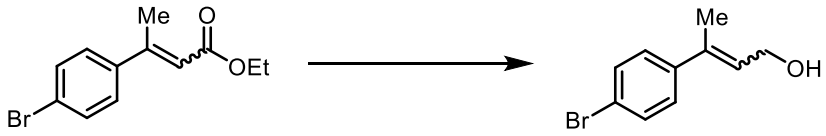
General procedure V: 4-Bromoacetophenone (3.00 g, 20 mmol), triethyl phosphonoacetate (6.73 g, 30 mmol) and NaH (60 w.t.% in mineral oil, 1.22 g, 30 mmol) in anhydrous THF (100 mL) were employed. The title compound was obtained as a 3:1 mixture of *E:Z* alkene isomers which was purified by flash column chromatography (5% EtOAc:hexane) to obtain the title compound (4.55 g, 56%, 3:1 *E:Z*) as a colourless oil.

Spectroscopic properties of the major E isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.47 (2H, m), 7.36 – 7.31 (2H, m), 6.12 – 6.10 (1H, m), 4.21 (2H, q, *J* = 7.0 Hz), 2.54 (3H, d, *J* =

1.5 Hz), 1.31 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.7, 154.2, 141.2, 131.8, 128.0, 123.3, 117.7, 60.1, 17.9, 14.4.

The spectroscopic properties were consistent with the data available in the literature.[350]

(*E*)-3-(4-Bromophenyl)but-2-en-1-ol (482)



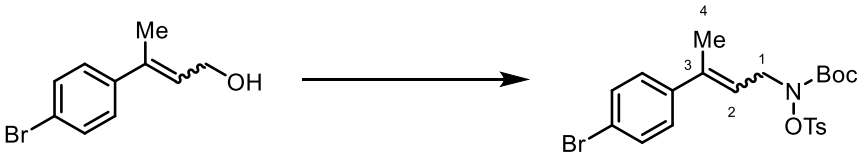
To a solution of the proceeding compound (2.15 g, 8.0 mmol, 3:1 *E:Z*) in Et_2O (18 mL) at 0 °C was added DIBAL-H (17.6 mL, 1 M in hexanes) dropwise. The reaction was stirred at room temperature overnight. The reaction was cooled to 0 °C and quenched with H_2O (0.04 mL/mmol DIBAL-H), 2M NaOH (0.04 mL/mmol DIBAL-H) and H_2O (0.1 mL/mmol DIBAL-H). The reaction mixture was warmed to room temperature and stirred for 15 minutes before being dried over Na_2SO_4 and stirred for a further 30 minutes. The resulting solid was filtered, and the filtrate concentrated *in vacuo*. Purification by flash column chromatography (33% EtOAc:hexane) afforded **482** (968 mg, 53%, 3:1 mixture of *E:Z* isomers) as a colourless oil.

Spectroscopic data for the major E isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (2H, d, *J* = 8.5 Hz), 7.26 (2H, d, *J* = 9.0 Hz), 5.98 – 5.92 (1H, m), 4.35 (2H, d, *J* = 6.5 Hz), 2.04 (3H, d, *J* = 1.0 Hz), 1.38 (1H, br s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.8, 136.8, 131.4, 127.5, 127.2, 121.3, 60.0, 16.0.

The spectroscopic properties were consistent with the data available in the literature.[351]

Spectroscopic data for the minor Z isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (2H, d, *J* = 8.5 Hz), 7.04 (1H, d, *J* = 8.5 Hz), 5.71 (1H, tq, *J* = 7.0, 1.5 Hz), 4.03 (1H, d, *J* = 7.0 Hz), 2.05 (2H, d, *J* = 1.5 Hz).

***tert*-Butyl (*E*)-(3-(4-bromophenyl)but-2-en-1-yl)(tosyloxy)carbamate (483)**

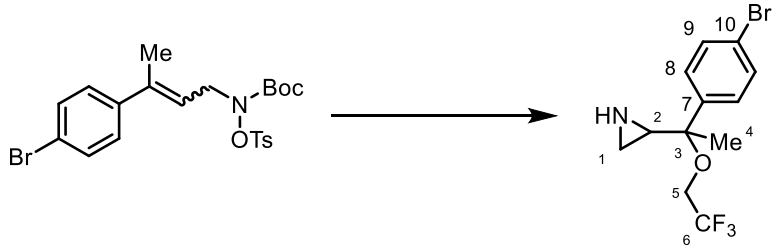


General procedure G: The preceding alcohol **482** (3:1 *E:Z*, 681 mg, 3.0 mmol), PPh_3 (940 mg, 3.6 mmol), DIAD (0.71 mL, 3.6 mmol) and BocNHOTs (1.03 g, 3.6 mmol) in anhydrous

THF (12 mL) were employed. Purification by flash column chromatography (5% EtOAc:hexane) afforded **483** (3:1 *E:Z*, 989 mg, 66%) as a pale-yellow solid; mp. 90-92 °C (CH_2Cl_2/hexane); ν_{max} / cm^{-1} (*solid*) 2981 (m), 1746 (s), 1370 (s), 1180 (s), 1152 (s).

Spectroscopic data for the major E isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (2H, d, *J* = 8.0 Hz, Ts ArC<u>H</u>), 7.43 (2H, d, *J* = 8.5 Hz, ArC<u>H</u>), 7.34 (2H, d, *J* = 8.0 Hz, Ts ArC<u>H</u>), 7.22 (2H, d, *J* = 8.5 Hz, ArC<u>H</u>), 5.79 (1H, td, *J* = 7.0, 1.5 Hz, C**2**-<u>H</u>), 4.39 (2H, br s, C**1**-<u>H_2</u>), 2.45 (3H, s, Ts C<u>H_3</u>), 2.07 (3H, s, C**4**-<u>H_3</u>), 1.22 (9H, s, Boc C(C<u>H_3</u>)$_3$), ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.8 (Boc <u>C</u>=O), 145.9 (Ts Ar<u>C</u>), 141.8 (Ar<u>C</u>), 139.6 (C**3**), 131.5 (ArC<u>H</u>), 131.4 (Ts Ar<u>C</u>), 129.9 (2 × Ts Ar<u>C</u>H), 129.7 (2 × Ts Ar<u>C</u>H), 127.7 (ArC<u>H</u>), 121.5 (Ar<u>C</u>), 120.2 (C**2**), 83.7 (Boc <u>C</u>(CH_3)$_3$), 51.4 (C**1**), 27.7 (Boc C(<u>C</u>H_3)$_3$), 21.8 (Ts <u>C</u>H_3), 16.3 (C**4**); HRMS (ESI$^+$) Calculated for $C_{22}H_{26}NaNO_5SBr$: 518.0607. Found $[M+Na]^+$: 518.0605.

2-(1-(4-Bromophenyl)-1-(2,2,2-trifluoroethoxy)ethyl)aziridine (488)



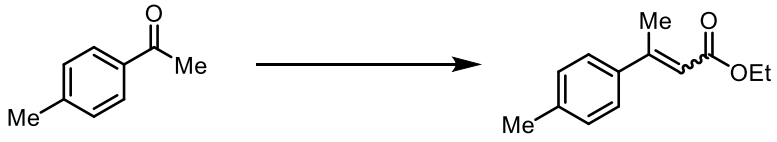
<u>General procedure W:</u> The proceeding compound **483** (3:1 *E:Z*, 149 mg, 0.3 mmol) and TFA (46 µL, 0.6 mmol) in anhydrous TFE (3 mL) were employed. The reaction was stirred at room temperature for 24 hours. Purification by flash column chromatography with the addition of ~0.1% Et_3N to the eluent (33% EtOAc:hexane) afforded **488** (44 mg, 45 %, 6:1 mixture of diastereomers) as a colourless oil; ν_{max} / cm^{-1} (*film*) 2938 (m), 1487 (m), 1277 (s), 1153 (s).

*Spectroscopic data for the major diastereomer **488a**:* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (2H, d, *J* = 8.5 Hz, C**9**-<u>H</u>), 7.31 (2H, d, *J* = 8.5 Hz, C**8**-<u>H</u>), 3.87 – 3.61 (2H, m, C**5**-<u>H_2</u>), 2.28 (1H, m, C**2**-<u>H</u>), 1.76 (1H, d, *J* = 6.0 Hz, C**1**-<u>H</u>), 1.59 – 1.54 (1H, m, C**1**-<u>H</u>'), 1.48 (3H, s, C**4**-<u>H_3</u>); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.4 (C**7**), 131.8 (C**9**), 128.1 (C**8**), 124.1 (d, *J* = 277.5 Hz, C**6**), 122.2 (C**10**), 78.7 (C**3**) 61.6 (q, *J* = 34.5 Hz, C**5**-<u>H_2</u>), 38.0 (C**2**), 22.0 (C**1**), 20.6 (C**4**); ^{19}F NMR (377 MHz, $CDCl_3$) δ -74.02 (t, *J* = 8.5 Hz).

*Characteristic signals for the minor isomer **488b**:* ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.20 – 2.14 (1H, m).

HRMS (ESI$^+$) Calculated for $C_{12}H_{14}BrF_3NO$: 324.0205. Found $[M+H]^+$: 324.0201.

Ethyl (*E*)-3-(*p*-tolyl)but-2-enoate



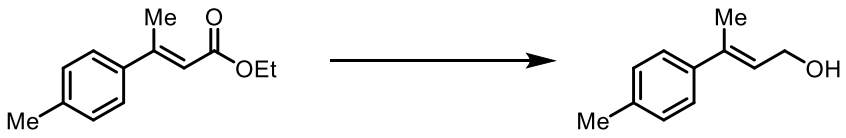
General procedure V: 4-Methylacetophenone (2.99 g, 22.3 mmol), triethyl phosphonoacetate (4.8 mL, 26.8 mmol) and NaH (60 w.t.% in mineral oil, 1.06 g, 26.8 mmol) in anhydrous THF (25 mL) were employed. Purification by flash column chromatography afforded the title compound (2.93 g, 5:1 *E:Z*) as a colourless oil.

Spectroscopic data for the major E isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (2H, d, *J* = 8.0 Hz), 7.17 (2H, d, *J* = 8.0 Hz), 6.14 – 6.11 (1H, m), 4.20 (2H, q, *J* = 7.0), 2.56 (3H, s), 2.36 (3H, s), 1.30 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 155.6, 139.4, 139.3, 129.3, 126.4, 116.4, 59.9, 21.3, 17.9, 14.5.

Spectroscopic data for the minor Z isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 – 7.09 (4H, m), 5.87 (1H, q, *J* = 1.5 Hz), 4.01 (2H, q, *J* = 7.0 Hz), 2.34 (3H, s), 2.15 (3H, d, *J* = 1.5 Hz), 1.11 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2, 155.7, 137.9, 137.8, 128.7, 127.0, 117.5, 59.9, 27.3, 21.4, 14.2.

The spectroscopic properties were consistent with the data available in the literature.[352]

(*E*)-3-(*p*-Tolyl)but-2-en-1-ol (484)

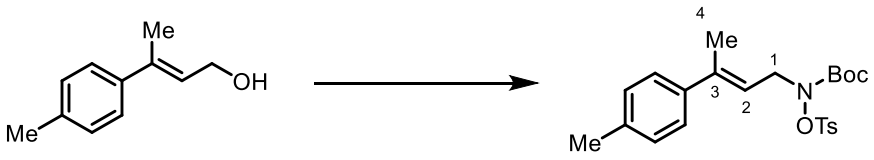


To a solution of the proceeding compound (5:1 *E:Z*, 1.63 g, 8.0 mmol) in anhydrous Et_2O (18 mL) at 0 °C was added DIBAL-H (17.6 mL, 1M in THF) dropwise. The reaction was warmed to room temperature and stirred for 2 hours until completion. The reaction was cooled to 0 °C and quenched with H_2O (0.04 mL/mmol DIBAL-H), 2M NaOH (0.04 mL/mmol DIBAL-H) and H_2O (0.1 mL/mmol DIABL-H). To the crude reaction mixture was then added Rochelle's salt (20 mL) and the reaction was stirred overnight. Et_2O (20 mL) was added and the layers were separated. The aqueous phase was extracted with Et_2O (20 mL) and the combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography (2:1 hexane:EtOAc) afforded **484** (1.16 g, 89%, 5:1 mixture of *E:Z* isomer) as a colourless oil.

Spectroscopic data for the major E isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (2H, d, *J* = 8.0 Hz), 7.13 (2H, d, *J* = 8.0 Hz), 5.95 (1H, t, *J* = 6.5, Hz), 4.34 (2H, t, *J* = 6.0 Hz), 2.33 (3H, s), 2.06 (3H, s).

The spectroscopic properties were consistent with the data available in the literature.[353]

tert-Butyl (*E*)-(3-(*p*-tolyl)but-2-en-1-yl)(tosyloxy)carbamate (485)



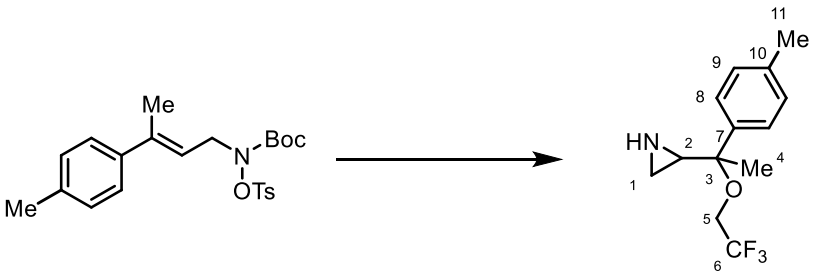
General procedure G: The proceeding compound **484** (5:1 *E:Z*, 487 mg, 3.0 mmol), PPh_3 (940 mg, 3.6 mmol), DIAD (0.71 mL, 3.6 mmol) and BocNHOTs (1.03 g, 3.6 mmol) in anhydrous THF (12 mL) were employed. Purification by flash column chromatography (5% EtOAc:hexane) afforded **485** (633 mg, 49%, 5:1 mixture of *E:Z*) as a pale yellow oil; ν_{max} / cm ^{1} (*solid*) 2977 (s), 1746 (s), 1370 (s), 1179 (s), 1153 (s).

Spectroscopic data for major E isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.32 (2H, d, *J* = 8.0 Hz, Ts ArC<u>H</u>), 7.25 (2H, d, *J* = 8.0 Hz, ArC<u>H</u>) 7.11 (2H, d, *J* = 8.0 Hz, ArC<u>H</u>), 5.80 – 5.74 (1H, m, C**2**-<u>H</u>), 4.38 (2H, br s, C**1**-<u>H_2</u>), 2.43 (3H, s, Ts C<u>H_3</u>), 2.32 (3H, s, C<u>H_3</u>), 2.06 (3H, s, C**4**-<u>H_3</u>), 1.22 (9H, s, Boc (C<u>H_3</u>)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.8 (Boc, <u>C</u>=O), 145.7 (Ts Ar<u>C</u>), 140.4 (Ar<u>C</u>), 140.0 (C**3**), 137.2 (Ar<u>C</u>), 131.4 (Ts Ar<u>C</u>), 129.8 (2 × Ts Ar<u>C</u>H), 129.6 (2 × Ts Ar<u>C</u>H), 129.0 (Ar<u>C</u>H), 125.9 (<u>ArCH</u>), 118.7 (C**2**), 83.5 (Boc <u>C</u>(CH$_3$)$_3$), 51.5 (C**1**), 27.7 (Boc (<u>C</u>H$_3$)$_3$), 21.8 (Ts <u>C</u>H$_3$), 21.2 (<u>C</u>H$_3$), 16.4 (C**4**).

Spectroscopic data for minor Z isomer: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.72 (d, *J* = 8.0 Hz, 2H), 7.01 (d, *J* = 8.0 Hz, 2H), 5.47 – 5.42 (m, 2H), 2.40 (s, 3H), 2.35 (s, 3H), 1.99 (s, 3H), 1.24 (s, 9H).

HRMS (ESI^{+}) Calculated for $C_{23}H_{29}NaNO_5S$: 454.1659. Found [M+Na]$^{+}$: 454.1654.

2-(1-(*p*-Tolyl)-1-(2,2,2-trifluoroethoxy)ethyl)aziridine (489)



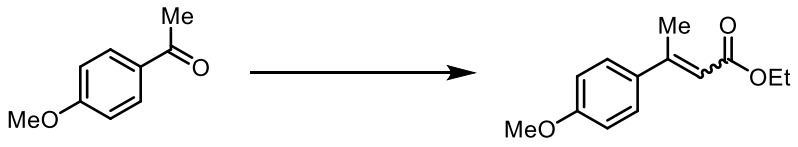
General procedure W: The proceeding compound **485** (130 mg, 0.3 mmol) and TFA (46 µL, 0.6 mmol) in anhydrous TFE (3 mL) were employed. The reaction was stirred for 23 hours. Purification by flash column chromatography with the addition of ~0.1 % Et_3N to the eluent (33% EtOAc: hexane) afforded **489** (26.2 mg, 34 %, 5:1 mixture of diastereomers) as a colourless oil; ν_{max} / cm^{-1}: (*film*) 2927 (m), 1275 (s), 1153 (s).

*Spectroscopic data for the major diastereomer **489a**:* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (2H, d, *J* = 8.0 Hz, C**8**-H), 7.18 (2H, d, *J* = 8.0 Hz, C**9**-H), 3.79 – 3.58 (2H, m, C**5**-H_2), 2.34 (3H, s, C**11**-H_3), 2.32 – 2.27 (1H, m, C**2**-H), 1.72 (1H, d, *J* = 6.0 Hz, C**1**-H), 1.62 – 1.55 (1H, m, C**1**-H'), 1.52 (3H, s, C**4**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.8 (C**7**), 137.9 (C**10**), 129.3 (C**9**), 126.4 (C**8**), 124.3 (q, *J* = 277.4 Hz, C**6**), 78.8 (C**3**), 61.5 (q, *J* = 34.0 Hz, C**5**-H_2), 38.6 (C**2**), 22.1 (C**1**), 21.2 (C**11**), 20.9 (C**4**); ^{19}F NMR (377 MHz, $CDCl_3$) -73.97 (t, *J* = 8.5 Hz).

*Characteristic signals for the minor isomer **489b**:* ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.55 – 3.45 (1H, m), 2.20 – 1.25 (1H, m), 1.82 (1H, d, *J* = 4.0 Hz), 1.63 (3H, s).

HRMS (ESI$^+$) Calculated for $C_{13}H_{17}F_3NO$: 260.1260. Found $[M+H]^+$: 260.1252.

Ethyl (*E*)-3-(4-methoxyphenyl)but-2-enoate

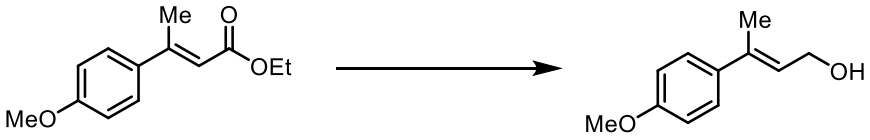


General procedure V: 4-Methoxyacetophenone (3.0 g, 20.0 mmol), triethyl phosphonoacetate (6.73 g, 30.0 mmol) and NaH (60 w.t.% in mineral oil, 1.22 g, 30.0 mmol) in anhydrous THF (100 mL) were employed. The title compound was obtained as a 4:1 mixture of (*E:Z*) alkene isomers which were separated by flash column chromatography (5% EtOAc:hexane) to obtain ethyl (*E*)-3-(4-methoxyphenyl)but-2-enoate (1.95 g, 30%) and ethyl (*Z*)-3-(4-methoxyphenyl)but-2-enoate (609 mg, 9%) as colourless oils.

Spectroscopic properties for the major E isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (2H, d, *J* = 9.0 Hz), 6.89 (2H, d, *J* = 9.0 Hz), 6.12 – 6.09 (1H, m), 4.20 (2H, q, *J* = 7.0 Hz), 3.83 (3H, s), 2.56 (3H, d, *J* = 1.5 Hz), 1.31 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 160.5, 155.0, 134.4, 127.8, 115.4, 113.9, 59.8, 55.5, 17.8, 14.5.

The spectroscopic properties were consistent with the data available in the literature.[348]

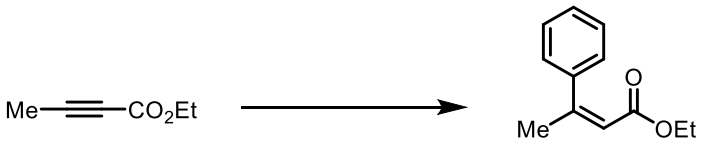
(*E*)-3-(4-Methoxyphenyl)but-2-en-1-ol (486)



To a solution of ethyl (*E*)-3-(4-methoxyphenyl)but-2-enoate (1.39 g, 6.30 mmol) in anhydrous Et_2O (14 mL) at 0 °C was added a solution of DIBAL-H (13.9 mL, 1M in hexanes) dropwise. The reaction was stirred at room temperature overnight. The reaction was cooled to 0 °C and quenched with H_2O (0.04 mL/mmol DIBAL-H), 2M NaOH (0.04 mL/mmol DIBAL-H) and H_2O (0.1 mL/mmol DIBAL-H). The reaction mixture was warmed to room temperature and stirred for 15 minutes before being dried over Na_2SO_4 and stirred for a further 30 minutes. The resulting solid was filtered, and the filtrate concentrated *in vacuo*. Purification by flash column chromatography (gradient, eluent: 33 – 50 % EtOAc:hexane) afforded **486** (839 mg, 75%) as a colourless solid; ^{1}H NMR (101 MHz, $CDCl_3$) δ 7.36 (2H, d, *J* = 8.5 Hz), 6.87 (2H, d, *J* = 8.5 Hz), 5.92 (1H, dt, *J* = 7.0, 1.0 Hz), 4.35 (2H, d, *J* = 7.0 Hz), 3.81 (3H, s), 2.06 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1, 137.5, 135.4, 127.0, 125.0, 113.7, 60.1, 55.4, 16.1.

The spectroscopic properties were consistent with the data available in the literature.[354]

Ethyl (*Z*)-3-phenylbut-2-enoate



The title compound was prepared following a literature procedure.[355]

CuI (85.7 mg, 5 mol%) and LiCl (38.2 mg, 10 mol%) were suspended in anhydrous THF (60 mL) in a flame-dried flask under nitrogen and stirred for 1.5 hours until completely dissolved. The flask was then cooled to -78 °C before addition of ethyl but-2-ynoate (1.00 g, 9.0 mmol) and TMSOTf (2.1 g, 9.45 mmol). The reaction was stirred at this temperature for 5 minutes and then PhMgBr (10.8 mL, 1M in THF) was added dropwise. The reaction was then stirred at

-78 °C for 1 hour at which point TFA (0.83 mL, 10.8 mmol) was added and the reaction was warmed to room temperature and stirred for 1 hour. The reaction was quenched by addition of a saturated aqueous solution of $NaHCO_3$ (80 mL) and extracted with Et_2O (3 × 25 mL). The combined organic extracts were washed sequentially with H_2O (25 mL) and a saturated aqueous solution of NH_4Cl (25 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The title compound was obtained as a 5:1 mixture of *Z:E* alkene which was purified by flash column chromatography (5% EtOAc:hexane) to afford the title compound (1.10 g, >99:1 *Z:E*) as a pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.26 (3H, m), 7.22 – 7.16 (2H, m), 5.90 (1H, q, *J* = 1.5 Hz), 3.99 (2H, q, *J* = 7.0 Hz), 2.17 (3H, d, *J* = 1.5 Hz), 1.07 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1, 155.5, 141.0, 128.0, 127.9, 126.9, 117.9, 59.9, 27.3, 14.1.

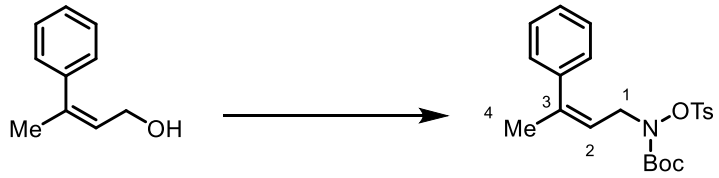
The spectroscopic properties were consistent with the data available in the literature.[356]

(*Z*)-3-Phenylbut-2-en-1-ol

To a solution of ethyl (*Z*)-3-phenylbut-2-enoate (951 mg, 5.0 mmol) in anhydrous Et_2O (11 mL) at 0 °C was added DIBAL-H (11.0 mL, 1M in THF) dropwise. The reaction was warmed to room temperature and stirred for 3.5 h until completion. The reaction was cooled to 0 °C and quenched with H_2O (0.04 mL/mmol DIBAL-H), 2M NaOH (0.04 mL/mmol DIBAL-H) and H_2O (0.1 mL/mmol DIABL-H). The reaction was warmed to room temperature and stirred for 15 minutes. The reaction was dried over Na_2SO_4 and stirred for 30 minutes then filtered and concentrated *in vacuo*. Purification by flash column chromatography (20% EtOAc:hexane) afforded the title compound (597 mg, 81%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$ δ 7.37 – 7.29 (2H, m), 7.29 – 7.23 (1H, m), 7.20 – 7.12 (2H, m), 5.73 – 5.68 (1H, m), 4.10 – 4.02 (2H, m), 2.08 (3H, d, *J* = 1.5 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.9, 140.5, 128.3, 127.9, 127.4, 126.2, 60.0, 25.0.

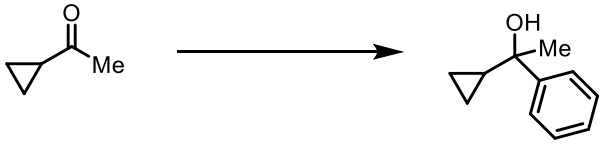
The spectroscopic properties were consistent with the data available in the literature.[356]

***tert*-Butyl (*Z*)-(3-phenylbut-2-en-1-yl)(tosyloxy)carbamate ((*Z*)-480)**



General procedure G: (*Z*)-3-Phenylbut-2-en-1-ol (445 mg, 3.0 mmol), PPh_3 (944 mg, 3.6 mmol), DIAD (0.70 mL, 3.6 mmol) and BocNHOTs (1.03 g, 3.6 mmol) in anhydrous THF (12 mL) were employed. Purification by flash column chromatography (10% EtOAc:hexane) afforded **(*Z*)-480** (704 mg, 56%) as a colourless solid; ν_{max} / cm^{-1} (*solid*) 2977 (m), 1748 (s), 1374 (s), 1367 (s), 1179 (s), 1150 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.36 – 7.30 (2H, m, Ts ArC<u>H</u>), 7.29 – 7.20 (3H, m, ArC<u>H</u>), 7.20 – 7.07 (2H, m, ArC<u>H</u>), 5.48 (1H, m, C**2**-<u>H</u>), 3.98 (2H, br s, C**1**-<u>H_2</u>), 2.40 (3H, s, Ts C<u>H_3</u>), 2.02 (3H, s, C**4**-<u>H_3</u>), 1.24 (9H, s, Boc (C<u>H_3</u>)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.9 (Boc <u>C</u>=O), 145.5 (Ts Ar<u>C</u>), 142.4 (Ar<u>C</u>), 140.7 (C**3**), 131.5 (Ts Ar<u>C</u>), 129.6 (2 × Ts Ar<u>C</u>H), 129.6 (2 × Ts Ar<u>C</u>H), 128.4 (Ar<u>C</u>H), 127.9 (Ar<u>C</u>H), 127.3 (Ar<u>C</u>H), 119.3 (C**2**), 83.6 (Boc <u>C</u>(CH$_3$)$_3$), 51.9 (C**1**), 27.8 (Boc (<u>C</u>H$_3$)$_3$), 25.8 (C**4**), 21.8 (Ts <u>C</u>H$_3$); HRMS (ESI$^+$) Calculated for $C_{22}H_{27}NaNO_5S$: 440.1502. Found $[M+Na]^+$: 440.1495.

1-Cyclopropyl-1-phenylethan-1-ol (495)



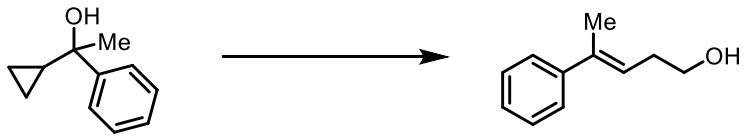
The title compound was prepared based on a literature procedure.[353]

To a solution of PhMgBr (1 M in THF, 12 mmol, 12 mL) in anhydrous Et_2O at 0 °C under nitrogen was added a solution of ketone (**494**) (0.99 mL, 10 mmol) in anhydrous Et_2O (10 mL) dropwise maintaining the temperature at 0 °C. The reaction was warmed to room temperature and stirred overnight. The reaction was cooled to 0 °C and diluted with *tert*-butyl methyl ether (15 mL) and H_2O (15 mL) and stirred for 15 minutes. The resulting precipitate which was formed was removed by filtration and the layers were separated. The aqueous layer was extracted with Et_2O (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography (20% EtOAc:hexane) afforded **495** (1.33 g, 82%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.50 (2H, m), 7.34 (2H, dd, *J* = 8.5, 7.0 Hz), 7.28 – 7.21 (1H, m), 1.66 (1H, br s), 1.49 (3H, s), 1.26 (1H, tt, *J* = 8.0, 5.5 Hz), 0.56

– 0.36 (4H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.2, 128.2, 126.9, 125.3, 73.3, 28.6, 22.9, 2.1, 1.2.

The spectroscopic properties were consistent with the data available in the literature.[353]

(*E*)-4-Phenylpent-3-en-1-ol (496)

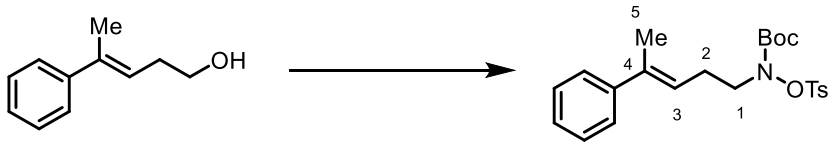


The title compound was prepared following a literature procedure.[353]

A solution of the preceding alcohol **495** (811 mg, 5.0 mmol) in dioxane was cooled to 0 ^{o}C (the reaction was required to warm slightly as the dioxane had frozen). A solution of 20% aqueous $HClO_4$ (3 mL) was added dropwise over 15 minutes and the reaction was warmed to room temperature and stirred overnight. Upon completion the reaction was diluted with H_2O (15 mL) and extracted with EtOAc (4 × 20 mL). The combined organic extracts were washed sequentially with saturated aqueous $NaHCO_3$ (3 × 15 mL) and brine (15 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography (gradient, eluent: 20 – 33% EtOAc:hexane) afforded **496** (519 mg, 64%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.35 (2H, m), 7.33 – 7.27 (2H, m), 7.27 – 7.18 (1H, m), 5.80 – 5.75 (1H, m), 3.74 (2H, q, *J* = 6.0 Hz), 2.53 – 2.46 (2H, m), 2.07 (3H, s), 1.43 (1H, br s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.6, 137.8, 128.3, 126.9, 125.7, 123.9, 62.4, 32.4, 16.1.

The spectroscopic properties were consistent with the data available in the literature.[353]

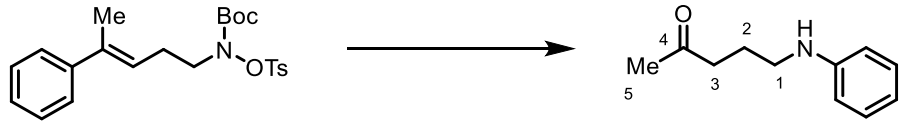
***tert*-Butyl (*E*)-(4-phenylpent-3-en-1-yl)(tosyloxy)carbamate (497)**



General procedure G: The preceding alcohol **496** (325 mg, 2.0 mmol), PPh_3 (629 mg, 2.4 mmol), DIAD (0.47 mL) and BocNHOTs (690 mg, 3,6 mmol) in anhydrous THF (8 mL) were employed. Purification by flash column chromatography (10% EtOAc:hexane) afforded **497** (431 mg, 50%) as a viscous, colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (2H, d, *J* = 8.5 Hz, Ts ArC<u>H</u>), 7.37 – 7.31 (4H, m, ArC<u>H</u>, Ts ArC<u>H</u>), 7.30 – 7.23 (2H, m, ArC<u>H</u>), 7.22 – 7.16 (1H, m, ArC<u>H</u>), 5.69 – 5.62 (1H, m, C**3**-<u>H</u>), 3.73 (2H, br s, C**1**-<u>H_2</u>), 2.54 (2H, q, *J* = 7.5 Hz, C**2**-<u>H_2</u>), 2.44 (3H, s, Ts C<u>H_3</u>), 2.03 (3H, s, C**5**-<u>H_3</u>), 1.14 (9H, s, Boc (C<u>H_3</u>)$_3$); ^{13}C NMR (101

MHz, $CDCl_3$) δ 155.5 (Boc C=O), 145.8 (Ts ArC), 143.5 (ArC), 137.9 (C**4**), 131.3 (Ts ArC), 129.9 (2 × Ts ArCH), 129.7 (2 × Ts ArCH), 128.3 (ArCH), 127.0 (ArCH), 125.8 (ArCH), 123.2 (C**3**), 83.3 (Boc $C(CH_3)_3$), 52.1 (C**1**), 27.7 (Boc $C(CH_3)_3$), 25.7 (C**2**), 21.9 (Ts CH_3), 15.9 (C**5**); HRMS (ESI^+) Calculated for $C_{23}H_{29}NO_5SK$: 470.1417. Found $[M+K]^+$: 470.1404.

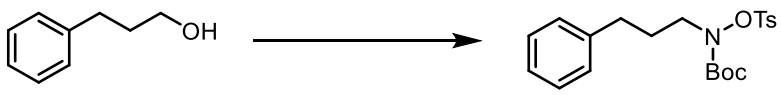
5-(Phenylamino)pentan-2-one (500)



General procedure W: The proceeding *N*-tosyloxycarbamate **497** (64.7 mg, 0.15 mmol) and TFA (23 µL, 0.3 mmol) in anhydrous TFE (1.5 mL) were employed. The reaction was stirred at room temperature for 18 hours. Purification by flash column chromatography with the addition of 0.1 % Et_3N to the eluent (EtOAc) afforded **500** (11.7 mg, 44 %) as a unstable colourless oil; ν_{max} / cm^{-1}: (*film*) 3394 (br), 2929 (m), 1709 (s), 1602 (s), 1506 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 7.16 (2H, dd, *J* = 8.5, 7.0 Hz, ArCH), 6.68 (1H, t, *J* = 7.0 Hz, ArCH), 6.58 (2H, d, *J* = 8.0 Hz, ArCH), 3.12 (2H, t, *J* = 7.0 Hz, C**1**-H_2), 2.56 (2H, t, *J* = 7.0 Hz, C**3**-H_2), 2.14 (3H, s, C**5**-H_3), 1.89 (2H, app. qn, *J* = 7.0 Hz,C**2**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.8 (C**4**), 148.4 (ArC), 129.4 (ArCH), 117.5 (ArCH), 112.8 (ArCH), 43.5 (C**1**), 41.3 (C**3**), 30.2 (C**5**), 23.5 (C**2**); HRMS (ESI^+) Calculated for $C_{11}H_{16}NO$: 178.1226. Found $[M+H]^+$: 178.1225.

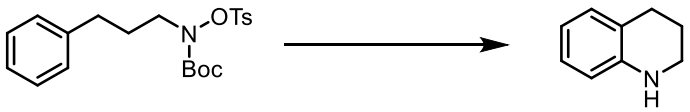
6.5 Experimental procedures for Chapter 4

tert-Butyl (3-phenylpropyl)(tosyloxy)carbamate (517a)



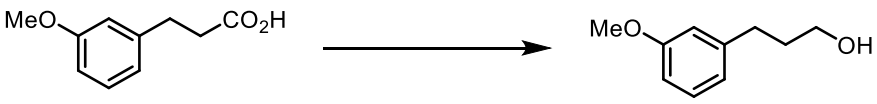
General procedure G: Alcohol **516a** (200 mg, 1.50 mmol), PPh_3 (470 mg, 1.80 mmol), DIAD (0.36 mL, 1.80 mmol) and BocNHOTs (520 mg, 1.80 mmol) in anhydrous THF (6 mL) were employed. Purification by flash column chromatography (10% EtOAc:hexane) afforded **517a** (520 mg, 85%) as a viscous colourless oil; R_f = 0.7 (33% EtOAc:hexane); ν_{max} / cm^{-1} (*film*) 2981 (m), 2932 (m), 2865 (m), 1718 (s), 1598 (m), 1454 (m), 1368 (s), 1294 (m), 1191 (s), 1151 (s), 1177 (s), 1089 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (2H, d, *J* = 8.5 Hz), 7.35 – 7.31 (2H, m), 7.31 – 7.26 (2H, m), 7.22 – 7.15 (3H, m), 3.63 (2H, br s), 2.60 (2H, t, *J* = 8.0 Hz), 2.45 (3H, s), 2.02 – 1.91 (2H, m), 1.23 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.4, 145.7, 141.1, 131.2, 129.7, 129.5, 128.4, 128.3, 126.0, 83.2, 52.6, 32.8, 27.6, 27.4, 21.7.
The spectroscopic properties were consistent with the data available in the literature.[33]

1,2,3,4-Tetrahydroquinoline (518a)



General procedure X: The preceding *N*-tosyloxycarbamate **517a** (120 mg, 0.30 mmol) and TFA (46.0 μL, 0.60 mmol) in TFE (3 mL) were employed. After stirring at room temperature for 24 hours, purification by flash column chromatography (33% Et_2O:hexane) afforded **518a** (26.0 mg, 65%) as a yellow oil; R_f = 0.7 (33% EtOAc:hexane); ν_{max} / cm^{-1} (*film*); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 – 6.95 (2H, m), 6.62 (1H, t, *J* = 7.5 Hz), 6.48 (1H, d, *J* = 8.0 Hz), 3.80 (1H, br s), 3.31 (2H, t, *J* = 5.5 Hz), 2.78 (2H, t, *J* = 6.5 Hz), 2.01 – 1.90 (2H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.8, 129.5, 126.7, 121.4, 116.9, 114.2, 41.9, 26.9, 22.2.
The spectroscopic properties were consistent with the data available in the literature.[33]

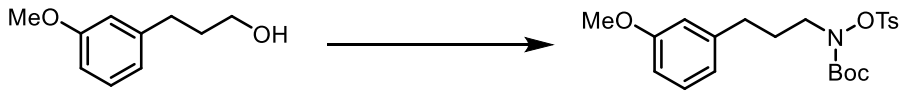
3-(3-Methoxyphenyl)propan-1-ol (516b)



General procedure B: 3-(3-Methoxyphenyl)propanoic acid (540 mg, 3.00 mmol) and 2.0 equivalents of $LiAlH_4$ (1 M in THF) in anhydrous Et_2O were employed to afford **516b** (340 mg, 68%) as a pale yellow oil which was used without further purification; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 – 7.19 (1H, m), 6.82 – 6.79 (1H, m), 6.77 – 6.73 (2H, m), 3.80 (3H, s), 3.66 (2H, t, *J* = 6.5 Hz), 2.71 – 2.67 (2H, m), 2.14 (1H, br s), 1.92 – 1.85 (2H, m).

The spectroscopic properties were consistent with the data available in the literature.[33]

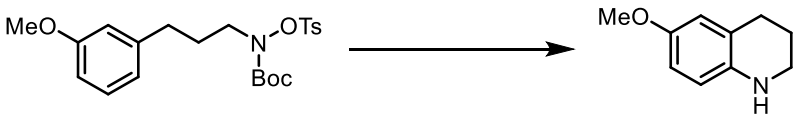
***tert*-Butyl (3-(3-methoxyphenyl)propyl)(tosyloxy)carbamate (517b)**



General procedure G: The preceding alcohol **516b** (240 mg, 1.50 mmol), PPh_3 (470 mg, 1.80 mmol), DIAD (0.35 mL, 1.80 mmol) and BocNHOTs (517 mg, 1.80 mmol) in anhydrous THF (8 mL) were employed. Purification by flash column chromatography (gradient, eluent: 5 – 10% EtOAc:hexane) afforded **517b** (530 mg, 81%) as a colourless, viscous oil; R_f = 0.5 (33% EtOAc:hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (2H, d, *J* = 8.5 Hz), 7.32 (2H, d, *J* = 8.5 Hz), 7.19 (1H, t, *J* = 8.0 Hz), 6.80 – 6.69 (3H, m), 3.79 (3H, s), 3.62 (2H, br s), 2.57 (2H, t, *J* = 8.0 Hz), 2.44 (3H, s), 1.95 (2H, br s), 1.21 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.7, 155.4, 145.7, 142.7, 131.2, 129.7, 129.5, 129.4, 120.7, 113.9, 111.4, 83.2, 55.1, 52.6, 32.8, 27.6, 27.3, 21.7.

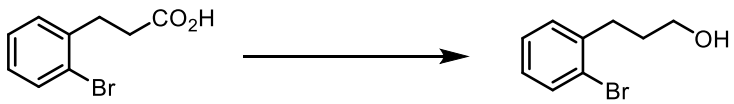
The spectroscopic properties were consistent with the data available in the literature.[33]

6-Methoxy-1,2,3,4-tetrahydroquinoline (518b)



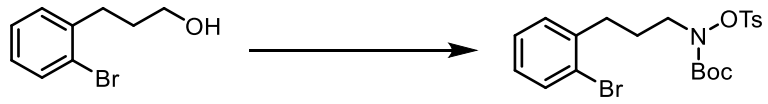
General procedure X: The preceding *N*-tosyloxycarbamate (**517b**) (87.1 mg, 0.20 mmol), TFA (31.0 μL, 0.40 mmol) in TFE (2 mL) were employed. After stirring at room temperature for 40 hours, purification by flash column chromatography (gradient, eluent: 10 – 25% EtOAc:hexane) afforded **518b** (26.0 mg, 80%) as a pale yellow oil; R_f = 0.45 (33% EtOAc:hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.63 – 6.54 (2H, m), 6.46 (1H, d, *J* = 8.5 Hz), 3.73 (3H, s), 3.37 (1H, br s), 3.27 – 3.24 (2H, m), 2.76 (2H, t, *J* = 6.5 Hz), 1.97 – 1.89 (2H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.9, 138.8, 122.9, 115.6, 114.9, 112.9, 55.8, 42.3, 27.2, 22.4.
The spectroscopic properties were consistent with the data available in the literature.[33]

3-(2-Bromophenyl)propan-1-ol (516c)



To a solution of ethyl 3-(2-bromophenyl)propanoic acid (920 mg, 4.00 mmol) in anhydrous THF (20 mL) at -10 °C was added 0.75 equivalents of $LiAlH_4$ (1 M in THF) and the reaction was stirred at the same temperature for 30 minutes. To the reaction mixture was added water (0.5 mL), aqueous 1 M NaOH (0.2 mL) and a further portion of water (1 mL). The reaction mixture was warmed to room temperature, filtered through Celite® and washed with CH_2Cl_2. The phases were separated, and the aqueous phase washed with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford **516c** as a colourless oil (160 mg, 19%) which was used without further purification; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (1H, d, *J* = 8.0 Hz), 7.26 – 7.21 (2H, m), 7.09 – 7.02 (1H, m), 3.70 (2H, t, *J* = 6.5 Hz), 2.83 (2H, t, *J* = 8.0 Hz), 1.94 – 1.85 (2H, m), 1.54 (1H, br s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.1, 132.8, 130.4, 127.6, 127.5, 124.4, 62.1, 32.7, 32.4.
The spectroscopic properties were consistent with the data available in the literature.[33]

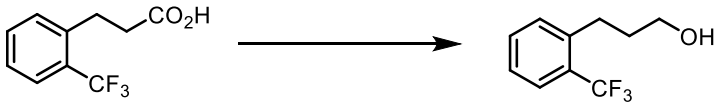
***tert*-Butyl(3-(2-bromophenyl)propyl)(tosyloxy)carbamate (517c)**



General procedure G: The preceding alcohol **516c** (160 mg, 0.74 mmol), PPh_3 (230 mg, 0.88 mmol), DIAD (0.17 mL, 0.88 mmol) and BocNHOTs (250 mg, 0.88 mmol) in anhydrous THF (4 mL) were employed. Purification by flash column chromatography (10 % EtOAc:hexane) afforded **517c** (260 mg, 72%) as a colourless solid; R_f = 0.6 (20 % EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (2H, d, *J* = 8.5 Hz), 7.52 (1H, dd, *J* = 8.0, 1.0 Hz), 7.33 (2H, d, *J* = 8.0 Hz), 7.24 – 7.19 (2H, m), 7.06 (1H, ddd, *J* = 8.0, 6.5, 2.5 Hz), 3.66 (2H, br s), 2.71 (2H, t, *J* = 8.0 Hz), 2.45 (3H, s), 1.99 – 1.90 (2H, m), 1.23 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.5, 145.8, 140.6, 132.9, 131.4, 130.3, 129.8, 129.7, 127.9, 127.6, 124.5, 83.4, 52.7, 33.3, 27.8, 26.2, 21.9.

The spectroscopic properties were consistent with the data available in the literature.[33]

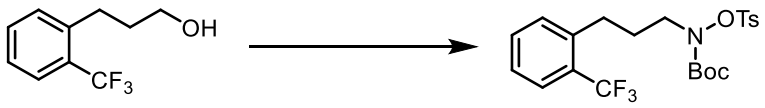
3-(2-(Trifluoromethyl)phenyl)propan-1-ol (516d)



General procedure B: 3-(2-(Trifluoromethyl)phenyl)propanoic acid (550 mg, 2.50 mmol) and 1.0 equivalents of $LiAlH_4$ (1.0 M in THF) in anhydrous THF were employed to afford **516d** (380 mg, 75%) as a colourless oil which was used without further purification; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (1H, d, *J* = 8.0 Hz), 7.45 (1H, t, *J* = 7.5 Hz), 7.34 (1H, d, *J* = 7.5 Hz), 7.27 (1H, t, *J* = 7.5 Hz), 3.71 (2H, t, *J* = 6.5 Hz), 2.87 (2H, t, *J* = 8.0 Hz), 1.93 (1H, br s), 1.92 – 1.85 (2H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.7, 131.7, 131.0, 128.5, 125.9, 123.3, 120.6, 62.2, 34.5, 28.9.

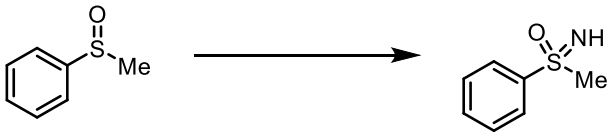
The spectroscopic properties were consistent with the data available in the literature.[33]

tert-Butyl (tosyloxy)(3-(2-(trifluoromethyl)phenyl)propyl)carbamate (517d)



General procedure G: The preceding alcohol **516d** (200 mg, 1.00 mmol), PPh_3 (320 mg, 1.20 mmol), DIAD (0.24 mL, 1.20 mmol) and BocNHOTs (350 mg, 1.20 mmol) in anhydrous THF (5 mL) were employed. Purification by flash column chromatography (10% EtOAc:hexane) afforded **517d** (450 mg, 95%) as a colourless oil; R_f = 0.5 (20% EtOAc:hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (2H, d, *J* = 8.5 Hz), 7.60 (1H, d, *J* = 8.0 Hz), 7.47 (1H, t, *J* = 7.5 Hz), 7.33 (2H, d, *J* = 8.5 Hz), 7.31 – 7.27 (2H, m), 3.67 (2H, br s), 2.75 (2H, t, *J* = 8.0 Hz), 2.44 (3H, s), 2.01 – 1.90 (2H, m), 1.23 (9H, s); ^{13}C NMR (101 MHz, $CDCl_2$) δ 155.5, 145.8, 140.1, 132.0, 131.3, 130.9, 129.8, 129.7, 128.5, 126.3, 126.1, 124.6, 83.5, 52.9, 29.7, 27.9, 27.7, 27.5, 21.8. *The spectroscopic properties were consistent with the data available in the literature*.[33]

Imino(methyl)(phenyl)- λ^6-sulfanone (535a)

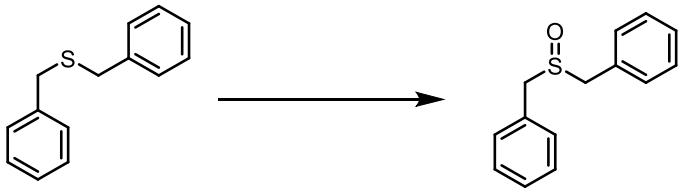


General procedure Y: Sulfoxide **534a** (21.03 mg, 0.15 mmol), TFA (23 µL, 0.30 mmol), BocNHOTs (64.6 mg, 0.225 mmol) in PhMe (0.15 mL, 1.0 M) were employed. The reaction was heated at 30 ^{o}C for 22 hours. Purification by flash column chromatography (gradient, eluent: 50% hexane:EtOAc - EtOAc) afforded **535a** (17.4 mg, 75%) as a pale-yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 – 8.00 (2H, m, ArC<u>H</u>), 7.64 – 7.53 (3H, m, ArC<u>H</u>), 3.10 (3H, s, SC<u>H</u>$_3$); ^{13}CNMR (101 MHz, $CDCl_3$) δ 143.6, 133.2, 129.4, 127.8, 46.3.

The spectroscopic properties were consistent with the data available in the literature.[357]

Using the other optimised conditions: TFE (1.0 M) at room temperature a yield of 73% was obtained.

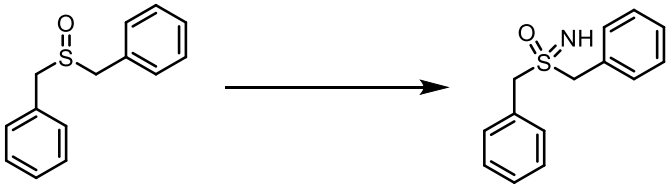
(Sulfinylbis(methylene))dibenzene



General procedure Z: Dibenzyl sulphide (1.07 g, 5.0 mmol), $FeCl_3$ (24.3 mg, 0.15 mmol) and H_5IO_6 (1.25 g, 5.5 mmol) in MeCN (5 mL, 1.0 M) were employed. The reaction time was 10 minutes. Purification by flash column chromatography (gradient, eluent: 50% hexane:EtOAc – 100% EtOAc) afforded **534b** (647 mg, 56%) as a colourless solid; m.p.: 131-132 °C (EtOAc:hexane) [lit: 130-132 °C (*no recrystallisation solvent given*)[358]]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.27 (10H, m), 3.93 (2H, d, *J* = 13.0 Hz), 3.87 (2H, d, *J* = 13.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 130.3, 129.1, 128.5, 57.4.

The spectroscopic properties were consistent with the data available in the literature.[359]

Dibenzyl(imino)-λ^6-sulfanone (535b)

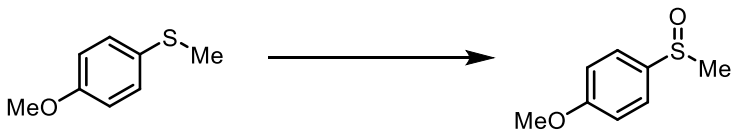


General procedure Y: The preceding sulfoxide **534b** (34.5 mg, 0.15 mmol), TFA (23 µL, 0.30 mmol) and BocNHOTs (64.6 mg, 0.225 mmol) in PhMe (0.15 mL, 1.0 M) were employed. The reaction was stirred at 30 °C for 23 hours. Purification by flash column chromatography (gradient, eluent: 33% hexane:EtOAc – EtOAc) afforded **535b** (20.8 mg, 57%) as a colourless solid; m.p.: 167-168 °C (EtOAc:hexane) [lit 167-168 °C (EtOH:H_2O)[360]]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (10H, s, ArC<u>H</u>), 4.27 (2H, d, *J* = 13.0 Hz, SC<u>H</u>$_2$), 4.15 (2H, d, *J* = 13.0 Hz, SC<u>H</u>$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 131.3, 129.2, 129.1, 128.0, 60.7.

The spectroscopic properties were consistent with the data available in the literature.[277]

Using the other optimised conditions: TFE (1.0 M) at room temperature a yield of 53% was obtained.

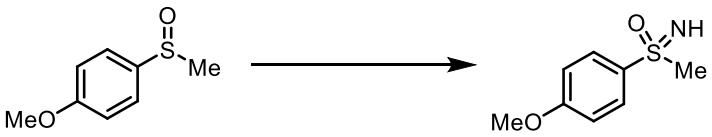
1-Methoxy-4-(methylsulfinyl)benzene (534c)



General procedure Z: 4-Methoxythioanisole (770 mg, 5.0 mmol), $FeCl_3$ (24.3 mg, 0.15 mmol) and H_5IO_6 (1.25 g, 5.5 mmol) in MeCN (5 mL, 1.0 M) were employed. The reaction time was 5 minutes. Purification by flash column chromatography (gradient, eluent: 50% hexane:EtOAc – 100% EtOAc) afforded **534c** (716 mg 84%) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 – 7.55 (2H, m), 7.02 – 6.98 (2H, m), 3.83 (3H, s), 2.67 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.1, 136.7, 125.5, 114.9, 55.6, 44.1.

The spectroscopic properties were consistent with the data available in the literature.[361]

Imino(4-methoxyphenyl)(methyl)-λ^6-sulfanone (535c)

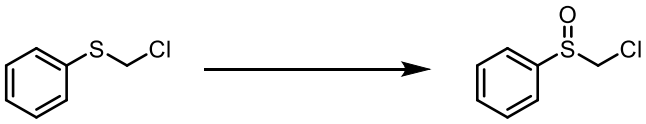


General procedure Y: The preceding sulfoxide **534c** (25.5 mg, 0.15 mmol), TFA (23 µL, 0.30 mmol) and BocNHOTs (64.6 mg, 0.225 mol) in PhMe (0.15 mL, 1.0 M) were employed. The reaction was stirred at 30 ^{o}C for 23 hours. Purification by flash column chromatography (gradient, eluent: 50% hexane:EtOAc – 100% EtOAc) afforded **535c** (18.9 mg, 68%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (2H, d, *J* = 9.0 Hz), 7.00 (2H, d, *J* = 9.0 Hz), 3.87 (3H, s), 3.08 (3H, s), 2.41 (1H, br s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.5, 135.2, 129.9, 114.5, 55.8, 46.7.

The spectroscopic properties were consistent with the data available in the literature.[362]

Using the other optimised conditions: TFE (1.0 M) at room temperature a yield of 70% was obtained.

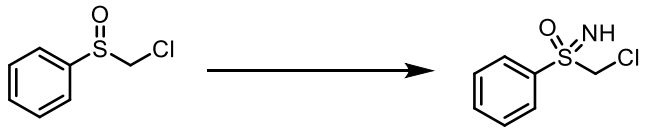
((Chloromethyl)sulfinyl)benzene (534d)



General procedure Z: Chloromethyl phenyl sulfide (670 mg, 5.0 mmol), $FeCl_3$ (24.3 mg, 0.15 mmol) and H_5IO_6 (1.25 g, 5.5 mmol) in MeCN (5 mL, 1.0 M) were employed. The reaction time was 30 minutes. Purification by flash column chromatography (gradient, eluent: 50% hexane:EtOAc – 100% EtOAc) afforded **534d** (530 mg, 61%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 – 7.69 (2H, m), 7.59 – 7.55 (3H, m), 4.39 (2H, d, *J* = 2.5 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.1, 132.3, 129.5, 125.0, 61.4.

The spectroscopic properties were consistent with the data available in the literature.[363]

(Chloromethyl)(imino)(phenyl)-λ^6-sulfanone (535d)

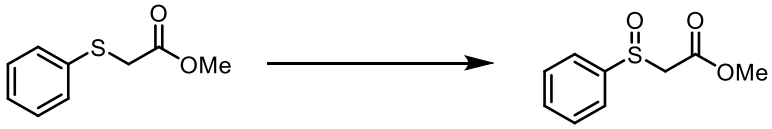


General procedure Y: The preceding sulfoxide **534d** (26.2 mg, 0.15 mmol), TFA (26 µL, 0.30 mmol) and BocNHOTs (64.6 mg, 0.225 mmol) in TFE (0.15 mL, 1.0 M) were employed. The reaction was stirred at room temperature for 23 hours. Purification by flash column chromatography (33% EtOAc:hexane) afforded **535d** (5.4 mg, 19%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 – 8.03 (2H, m, ArC<u>H</u>), 7.72 – 7.67 (1H, m, ArC<u>H</u>), 7.63 – 7.57 (2H, m, Ar<u>C</u>H), 4.57 (2H, s, SC<u>H</u>$_2$), 3.11 (1H, s, N<u>H</u>); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.7, 134.2, 129.5, 129.4, 61.4.

The spectroscopic properties were consistent with the data available in the literature.[364]

Using the other optimised conditions: PhMe (1.0 M) at 30 °C a yield of 16% was obtained.

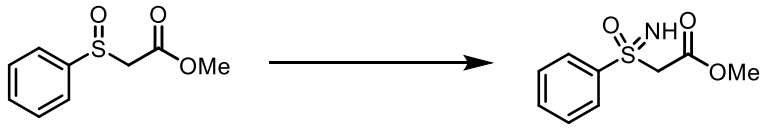
Methyl 2-(phenylsulfinyl)acetate (354e)



The title compound was prepared according to a literature procedure.[365]

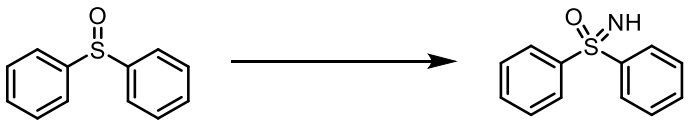
To a solution of 1-(phenylthio)propan-2-one (365 mg, 2.0 mmol) in CH_3CN (10 mL) was added 30% aq. H_2O_2 (0.4 mL, 4.0 mmol) and TMSCl (0.25 mL, 2.0 mmol). The reaction was stirred at room temperature for 3 hours, quenched with H_2O (10 mL) and extracted with EtOAc (4 × 5 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography (33% EtOAc:hexane) afforded **354e** (203 mg, 56%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.64 (2H, m), 7.55 – 7.50 (3H, m), 3.83 (1H, d, *J* = 13.5 Hz), 3.69 (3H, s), 3.66 (1H, d, *J* = 13.5 Hz).
The spectroscopic properties were consistent with the data available in the literature.[365]

Methyl 2-(phenylsulfonimidoyl)acetate (535e)



General procedure Y: The preceding sulfoxide **354e** (29.7 mg, 0.15 mmol), TFA (23 µL, 0.30 mmol) and BocNHOTs (67.8 mg, 0.225 mmol) in TFE (0.15 mL, 1.0 M) were employed. The reaction was stirred at room temperature for 22 hours. Purification by flash column chromatography (50% PhMe:EtOAc) afforded a mixture of the title compound **535e** and the starting sulfoxide **534e** (11.1 mg) as a colourless oil. The yield of the title compound was obtained as 38% as determined by ^{1}H NMR analysis with the addition of 1,4-dinitrobenzene as internal standard; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 – 7.99 (2H, m), 7.67 – 7.62 (1H, m), 7.58 – 7.51 (2H, m) 4.16 – 4.08 (2H, m), 3.72 (3H, s), 3.29 (1H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.6, 140.5, 133.9, 129.3, 128.8, 63.2, 53.2.
The spectroscopic properties were consistent with the data available in the literature.[366]

Iminodiphenyl-λ^6-sulfanone (535f)



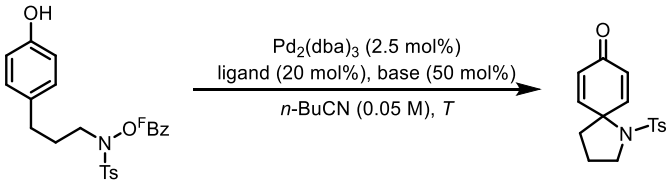
General procedure Y: Diphenyl sulfoxide (30.3 mg, 0.15 mmol), TFA (23 µL, 0.30 mmol) and BocNHOTs (64.6 mg, 0.225 mmol) in TFE (0.15 mL, 1.0 M) were employed. The reaction was stirred at room temperature for 22 hours. Purification by flash column chromatography (33% EtOAc:hexane) afforded **535f** (18.7 mg, 58%) as a colourless solid; mp: 97-98 °C (EtOAc:hexane) [lit: 102-104 °C (*no recrystallisation solvent given*)[367]]; ^{1}H NMR (400 MHz,

$CDCl_3$) δ 8.06 – 8.03 (4H, m, ArC<u>H</u>), 7.54 – 7.45 (6H, m, ArC<u>H</u>), 3.04 (1H, br s, N<u>H</u>); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.6, 132.7, 129.3, 128.1.

The spectroscopic properties were consistent with the data available in the literature.[366]

Using the other optimised conditions: PhMe (1.0 M) at 30 °C a yield of 37% was obtained.

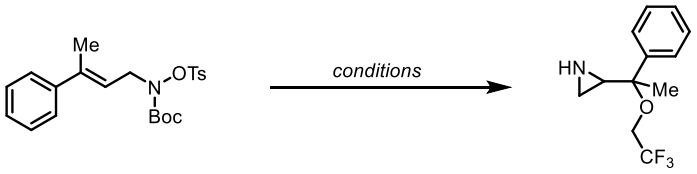
Appendix



148 149

Entry	*ligand*	*base*	*temperature*	*yield*
1	Xantphos	Et_3N	120 °C	0%
2	*N*-Xantphos	Et_3N	120 °C	0%
3	*t*-Bu-Xantphos	Et_3N	120 °C	0%
4	dppb	Et_3N	120 °C	0%
5	DPEphos	Et_3N	120 °C	0%
6	dppf	Et_3N	120 °C	0%

Table 17 *Attempted dearomatising amination using bidentate ligands.*



480 481

Entry	*TFA (mol%)*	*Solvent (M)*	*temperature*	*yield*[a]
1	200	TFE (0.1)	r.t.	58%
2	200	TFE (0.2)	r.t.	58%
3	200	TFE (0.5)	r.t.	53%
4	200	TFE (0.05)	r.t.	58%
5	50	TFE (0.1)	r.t.	61%
6	100	TFE (0.1)	r.t.	57%
7	500	TFE (0.1)	r.t.	55%
8	200	TFE (0.1)	60 °C	25%
9	15	TFE (0.1)	60 °C	38%

[a]major isomer

Table 18 *Attempted optimisation of the aziridination of substrate **480**.*

References

1. McGrath, N. A.; Brichacek, M.; Njardarson, J. T. *J. Chem. Educ.* **2010,** *87*, 1348-1349.
2. Nishikawa, K.; Yamauchi, K.; Kikuchi, S.; Ezaki, S.; Koyama, T.; Nokubo, H.; Matsumura, K.; Kodama, T.; Kumagai, M.; Morimoto, Y. *Chem. Eur. J.* **2017**, *23*, 9535-9545.
3. Ku, A. F.; Cuny, G. D. *J. Org. Chem.* **2016**, *81*, 10062-10070.
4. Snider, B. B.; Lin, H. *J. Am. Chem. Soc.* **1999**, *121*, 7778-7786.
5. Snider, B. B.; Lin, H. *Org. Lett.* **2000**, *2*, 643-646.
6. Nugent, T. C.; El-Shazly, M. *Adv. Synth. Catal.* **2010**, *352*, 753-819.
7. Surry, D. S.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 6338-6361.
8. Surry, D. S.; Buchwald, S. L. *Chem. Sci.* **2011**, *2*, 27-50.
9. Hartwig, J. F. *Acc. Chem. Res.* **2008**, *41*, 1534-1544.
10. Chan, D. M. T.; Monaco, K. L.; Wang, R.-P.; Winters, M. P. *Tetrahedron Lett.* **1998**, *39*, 2933-2936.
11. Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Chan, D. M. T.; Combs, A. *Tetrahedron Lett.* **1998**, *39*, 2941-2944.
12. Qiao, J. X.; Lam, P. Y. S. *Synthesis* **2011**, 829-856.
13. Ciganek, E., Electrophilic Amination of Carbanions, Enolates, and Their Surrogates. In *Organic Reactions*, **2009**, *72*.
14. Barker, T. J.; Jarvo, E. R. *Synthesis* **2011**, 3954-3964.
15. Corpet, M.; Gosmini, C. *Synthesis* **2014**, *46*, 2258-2271.
16. Yan, X.; Yang, X.; Xi, C. *Catal. Sci. Technol.* **2014**, *4*, 4169-4177.
17. Dong, X.; Liu, Q.; Dong, Y.; Liu, H. *Chem. Eur. J.* **2017**, *23*, 2481-2511.
18. Brown, H. C.; Heydkamp, W. R.; Breuer, E.; Murphy, W. S. *J. Am. Chem. Soc.* **1964**, *86*, 3565-3566.
19. Brown, H. C.; Kim, K.-W.; Srebnik, M.; Bakthan, S. *Tetrahedron* **1987**, *43*, 4071-4078.
20. Rangaishenvi, M. V.; Singaram, B.; Brown, H. C. *J. Org. Chem.* **1991**, *56*, 3286-3294.
21. Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem. Int. Ed.* **2012**, *51*, 3642-3645.
22. Rucker, R. P.; Whittaker, A. M.; Dang, H.; Lalic, G. *Angew. Chem. Int. Ed.* **2012**, *51*, 3953-3956.
23. Zhu, C.; Li, G.; Ess, D. H.; Falck, J. R.; Kürti, L. *J. Am. Chem. Soc.* **2012**, *134*, 18253-18256.
24. Ou, L.; Shao, J.; Zhang, G.; Yu, Y. *Tetrahedron Lett.* **2011**, *52*, 1430-1431.
25. Xiao, Q.; Tian, L.; Tan, R.; Xia, Y.; Qiu, D.; Zhang, Y.; Wang, J. *Org. Lett.* **2012**, *14*, 4230-4233.
26. Voth, S.; Hollett, J. W.; McCubbin, J. A. *J. Org. Chem.* **2015**, *80*, 2545-2553.
27. Sun, H.-B.; Gong, L.; Tian, Y.-B.; Wu, J.-G.; Zhang, X.; Liu, J.; Fu, Z.; Niu, D. *Angew. Chem. Int. Ed.* **2018**, *57*, 9456-9460.
28. Berman, A. M.; Johnson, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 5680-5681.
29. Berman, A. M.; Johnson, J. S. *J. Org. Chem.* **2005**, *70*, 364-366.
30. Berman, A. M.; Johnson, J. S. *J. Org. Chem.* **2006**, *71*, 219-224.
31. Berman, A. M.; Johnson, J. S. *Synlett* **2005**, *2005*, 1799-1801.
32. Campbell, M. J.; Johnson, J. S. *Org. Lett.* **2007**, *9*, 1521-1524.
33. Paudyal, M. P.; Adebesin, A. M.; Burt, S. R.; Ess, D. H.; Ma, Z. W.; Kurti, L.; Falck, J. R. *Science* **2016**, *353*, 1144-1147.
34. Munnuri, S.; Anugu, R. R.; Falck, J. R. *Org. Lett.* **2019**, *21*, 1926-1929.

35. Liu, J.; Wu, K.; Shen, T.; Liang, Y.; Zou, M.; Zhu, Y.; Li, X.; Li, X.; Jiao, N. *Chem. Eur. J.* **2017**, *23*, 563-567.
36. Legnani, L.; Prina Cerai, G.; Morandi, B. *ACS Catal.* **2016**, *6*, 8162-8165.
37. D'Amato, E. M.; Börgel, J.; Ritter, T. *Chem. Sci.* **2019**, *10*, 2424-2428.
38. Ortiz, G. X.; Hemric, B. N.; Wang, Q. *Org. Lett.* **2017**, *19*, 1314-1317.
39. Hironori, T.; Koichi, N. *Chem. Lett.* **1999**, *28*, 45-46.
40. Hironori, T.; Mitsuru, K.; Koichi, N. *Bull. Chem. Soc. Jpn.* **2002,** *75*, 1451-1460.
41. Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009-3066.
42. Tan, Y.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 3676-3677.
43. Hong, W. P.; Iosub, A. V.; Stahl, S. S. *J. Am. Chem. Soc.* **2013**, *135*, 13664-13667.
44. Race, N. J.; Hazelden, I. R.; Faulkner, A.; Bower, J. F. *Chem. Sci.* **2017**, *8*, 5248-5260.
45. Kitamura, M.; Zaman, S.; Narasaka, K. *Synlett* **2001**, 974-976.
46. Shazia, Z.; Mitsuru, K.; Koichi, N. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 1055-1062.
47. Faulkner, A.; Bower, J. F. *Angew. Chem. Int. Ed.* **2012**, *51*, 1675-1679.
48. Hanley, P. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2011**, *133*, 15661-15673.
49. Faulkner, A.; Scott, J. S.; Bower, J. F. *Chem. Commun.* **2013**, *49*, 1521-1523.
50. Race, N. J.; Bower, J. F. *Org. Lett.* **2013**, *15*, 4616-4619.
51. Race, N. J.; Faulkner, A.; Fumagalli, G.; Yamauchi, T.; Scott, J. S.; Rydén-Landergren, M.; Sparkes, H. A.; Bower, J. F. *Chem. Sci.* **2017,** *8*, 1981-1985.
52. Hazelden, I. R.; Ma, X.; Langer, T.; Bower, J. F. *Angew. Chem. Int. Ed.* **2016**, *55*, 11198-11202.
53. Hazelden, I. R.; Carmona, R. C.; Langer, T.; Pringle, P. G.; Bower, J. F. *Angew. Chem. Int. Ed.* **2018**, *57*, 5124-5128.
54. Shuler, S. A.; Yin, G.; Krause, S. B.; Vesper, C. M.; Watson, D. A. *J. Am. Chem. Soc.* **2016**, *138*, 13830-13833.
55. Xu, F.; Shuler, S. A.; Watson, D. A. *Angew. Chem. Int. Ed.* **2018**, *57*, 12081-12085.
56. Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147-168.
57. Walters, W. P.; Green, J.; Weiss, J. R.; Murcko, M. A. *J. Med. Chem.* **2011**, *54*, 6405-6416.
58. Lovering, F.; Bikker, J.; Humblet, C. *J. Med. Chem.* **2009**, *52*, 6752-6756.
59. Rousseaux, S.; García-Fortanet, J.; Del Aguila Sanchez, M. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2011**, *133*, 9282-9285.
60. Xu, R.-Q.; Gu, Q.; Wu, W.-T.; Zhao, Z.-A.; You, S.-L. *J. Am. Chem. Soc.* **2014**, *136*, 15469-15472.
61. Kikugawa, Y.; Kawase, M. *J. Am. Chem. Soc.* **1984**, *106*, 5728-5729.
62. Glover, S. A.; Goosen, A.; McCleland, C. W.; Schoonraad, J. L. *J. Chem. Soc., Perkin Trans.1* **1984**, 0, 2255-2260.
63. Kawase, M.; Kitamura, T.; Kikugawa, Y. *J. Org. Chem.* **1989**, *54*, 3394-3403.
64. Glover, S. A.; Goosen, A.; McClei, C. V.; Schoonraad, J. L. *Tetrahedron* **1987**, *43*, 2577-2592.
65. Yasuo, K.; Masami, K. *Chem. Lett* **1990**, *19*, 581-582.
66. Wardrop, D. J.; Basak, A. *Org. Lett.* **2001**, *3*, 1053-1056.
67. Wardrop, D. J.; Landrie, C. L.; Ortíz, J. A. *Synlett* **2003**, 1352-1354.
68. Wardrop, D. J.; Zhang, W.; Landrie, C. L. *Tetrahedron Lett.* **2004,** *45*, 4229-4231.
69. Wardrop, D. J.; Burge, M. S. *Chem. Commun.* **2004**, 1230-1231.
70. Wardrop, D. J.; Zhang, W. *Org. Lett.* **2001**, *3*, 2353-2356.
71. Wardrop, D. J.; Burge, M. S. *J. Org. Chem.* **2005**, *70*, 10271-10284.
72. Wardrop, D. J.; Burge, M. S.; Zhang, W.; Ortíz, J. A. *Tetrahedron Lett.* **2003**, *44*, 2587-2591.

73. Kikugawa, Y.; Nagashima, A.; Sakamoto, T.; Miyazawa, E.; Shiiya, M. *J. Org. Chem.* **2003**, *68*, 6739-6744.
74. Clemente, D.-T. V.; Lobo, A. M.; Prabhakar, S.; Marcelo-Curto, M. J. *Tetrahedron Lett.* **1994**, *35*, 2043-2046.
75. Prata, J. V.; Clemente, D.-T. S.; Prabhakar, S.; Lobo, A. M.; Mourato, I.; Branco, P. S. *J. Chem. Soc., Perkin Trans. 1* **2002**, 513-528.
76. Yi, J.-C.; Tu, H.-F.; You, S.-L. *Org. Biomol. Chem.* **2018**, *16*, 8700-8703.
77. Yi, J.-C.; Wu, Z.-J.; You, S.-L. *Eur. J. Org. Chem.* **2019**, 5736-5739.
78. Yao, Z.-L.; Wang, L.; Shao, N.-Q.; Guo, Y.-L.; Wang, D.-H. *ACS Catal.* **2019**, *9*, 7343-7349.
79. Hwang, Y.; Park, Y.; Kim, Y. B.; Kim, D.; Chang, S. *Angew. Chem. Int. Ed.* **2018**, *57*, 13565-13569.
80. Yu, J.-S.; Espinosa, M.; Noda, H.; Shibasaki, M. *J. Am. Chem. Soc.* **2019**, *141*, 10530-10537.
81. Tamura, Y.; Yakura, T.; Haruta, J.; Kita, Y. *J. Org. Chem.* **1987**, *52*, 3927-3930.
82. Kita, Y.; Tohma, H.; Kikuchi, K.; Inagaki, M.; Yakura, T. *J. Org. Chem.* **1991**, *56*, 435-438.
83. Pelter, A.; Elgendy, S. *Tetrahedron Lett.* **1988**, *29*, 677-680.
84. Barret, R.; Daudon, M. *Tetrahedron Lett.* **1991**, *32*, 2133-2134.
85. Braun, N. A.; Ciufolini, M. A.; Peters, K.; Peter, E.-M. *Tetrahedron Lett.* **1998**, *39*, 4667-4670.
86. Scheffler, G.; Seike, H.; Sorensen, E. J. *Angew. Chem. Int. Ed.* **2000**, *39*, 4593-4596.
87. Mizutani, H.; Takayama, J.; Soeda, Y.; Honda, T. *Tetrahedron Lett.* **2002**, *43*, 2411-2414.
88. Ciufolini, M. A.; Braun, N. A.; Canesi, S.; Ousmer, M.; Chang, J.; Chai, D. *Synthesis* **2007**, 3759-3772.
89. Canesi, S.; Belmont, P.; Bouchu, D.; Rousset, L.; Ciufolini, M. A. *Tetrahedron Lett.* **2002**, *43*, 5193-5195.
90. Liang, H.; Ciufolini, M. A. *Org. Lett.* **2010**, *12*, 1760-1763.
91. Jain, N.; Ciufolini, M. A. *Synlett* **2015**, *26*, 631-634.
92. Kita, Y.; Takada, T.; Gyoten, M.; Tohma, H.; Zenk, M. H.; Eichhorn, J. *J. Org. Chem.* **1996**, *61*, 5857-5864.
93. Canesi, S.; Bouchu, D.; Ciufolini, M. A. *Org. Lett.* **2005**, *7*, 175-177.
94. Braun, N. A.; Ousmer, M.; Bray, J. D.; Bouchu, D.; Peters, K.; Peters, E.-M.; Ciufolini, M. A. *J. Org. Chem.* **2000**, *65*, 4397-4408.
95. Liang, H.; Ciufolini, M. A. *Chem. Eur. J.* **2010**, *16*, 13262-13270.
96. Liang, H.; Ciufolini, M. A. *Tetrahedron* **2010**, *66*, 5884-5892.
97. Ma, X.; Farndon, J. J.; Young, T. A.; Fey, N.; Bower, J. F. *Angew. Chem. Int. Ed.* **2017**, *56*, 14531-14535.
98. Race, N. J.; Faulkner, A.; Shaw, M. H.; Bower, J. F. *Chem Sci* **2016**, *7*, 1508-1513.
99. Di Pietro, O.; Vicente-García, E.; Taylor, M. C.; Berenguer, D.; Viayna, E.; Lanzoni, A.; Sola, I.; Sayago, H.; Riera, C.; Fisa, R.; Clos, M. V.; Pérez, B.; Kelly, J. M.; Lavilla, R.; Muñoz-Torrero, D., *Eur. J. Med. Chem.* **2015**, *105*, 120-137.
100. Hegedus, L. S.; Allen, G. F.; Waterman, E. L. *J. Am. Chem. Soc.* **1976,** *98*, 2674-2676.
101. Hegedus, L. S.; Allen, G. F.; Bozell, J. J.; Waterman, E. L. *J. Am. Chem. Soc.* **1978,** *100*, 5800-5807.
102. Kotov, V.; Scarborough, C. C.; Stahl, S. S. *Inorg. Chem.* **2007**, *46*, 1910-1923.
103. Minatti, A.; Muñiz, K. *Chem. Soc. Rev.* **2007**, *36*, 1142-1152.
104. Rogers, M. M.; Wendlandt, J. E.; Guzei, I. A.; Stahl, S. S. *Org. Lett.* **2006**, *8*, 2257-2260.

105. Brice, J. L.; Harang, J. E.; Timokhin, V. I.; Anastasi, N. R.; Stahl, S. S. *J. Am. Chem. Soc.* **2005**, *127*, 2868-2869.
106. Liu, G.; Stahl, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 6328-6335.
107. Henry, J. R.; Marcin, L. R.; McIntosh, M. C.; Scola, P. M.; Davis Harris, G.; Weinreb, S. M. *Tetrahedron Lett.* **1989**, *30*, 5709-5712.
108. Fang, X.; Gao, S.; Wu, Z.; Yao, H.; Lin, A. *Org. Chem. Front.* **2017**, *4*, 292-296.
109. Miyazawa, E.; Sakamoto, T.; Kikugawa, Y. *Heterocycles* **2003**, *59*, 149-160.
110. Liang, D.; Yu, W.; Nguyen, N.; Deschamps, J. R.; Imler, G. H.; Li, Y.; MacKerell, A. D.; Jiang, C.; Xue, F. *J. Org. Chem.* **2017**, *82*, 3589-3596.
111. Arnold, R. T.; Buckley, J. S.; Richter, J. *J. Am. Chem. Soc.* **1947**, *69*, 2322-2325.
112. Kawase, M.; Kikugawa, Y. *Chem. Pharm. Bull* **1981**, *29*, 1615-1623.
113. Cherest, M.; Lusinchi, X. *Tetrahedron Lett.* **1989**, *30*, 715-718.
114. Galli, C.; Illuminati, G.; Mandolini, L.; Tamborra, P. *J. Am. Chem. Soc.* **1977**, *99*, 2591-2597.
115. Winstein, S.; Baird, R. *J. Am. Chem. Soc.* **1957**, *79*, 756-757.
116. Masamune, S. *J. Am. Chem. Soc.* **1961**, *83*, 1009-1010.
117. Sheradsky, T.; Yusupova, L. *Tetrahedron Lett.* **1995**, *36*, 7701-7704.
118. Gassman, P. G.; Cryberg, R. L. *J. Am. Chem. Soc.* **1969**, *91*, 5176-5177.
119. Gassman, P. G., Nitrenium ions. *Acc. Chem. Res.* **1970**, *3*, 26-33.
120. Gassman, P. G.; Hartman, G. D. *J. Am. Chem. Soc.* **1973**, *95*, 449-454.
121. Hoffman, R. V.; Kumar, A.; Buntain, G. A. *J. Am. Chem. Soc.* **1985**, *107*, 4731-4736.
122. Henry-Riyad, H.; Kobayashi, S.; Tidwell, T. T. *Arkivoc* **2005**, 266-276.
123. Falvey, D. E. *ACS Omega.* **2018**, *3*, 10418-10432.
124. Zard, S. Z. *Chem. Soc. Rev.* **2008**, *37*, 1603-1618.
125. Minisci, F.; Galli, R. *Tetrahedron Lett.* **1966**, *7*, 2531-2533.
126. Anderson, P. S.; Lundell, G. F.; Cias, J. L.; Robinson, F. M. *Tetrahedron Lett.* **1971**, *12*, 2787-2790.
127. Stella, L. *Angew. Chem. Int. Ed.* **1983**, *22*, 337-350.
128. Li, C.; Blackman, A. *Aust. J. Chem.* **1994**, *47*, 1355-1361.
129. Molander, G. A.; Rönn, M. *J. Org. Chem.* **1999**, *64*, 5183-5187.
130. Issa, H. H.; Tanaka, J.; Rachmat, R.; Setiawan, A.; Trianto, A.; Higa, T. *Mar. Drugs* **2005**, *3*, 78-83.
131. Biard, J. F.; Guyot, S.; Roussakis, C.; Verbist, J. F.; Vercauteren, J.; Weber, J. F.; Boukef, K. *Tetrahedron Lett.* **1994**, *35*, 2691-2694.
132. Abe, H.; Aoyagi, S.; Kibayashi, C. *Angew. Chem. Int. Ed.* **2002**, *41*, 3017-3020.
133. Abe, H.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc.* **2000**, *122*, 4583-4592.
134. Canesi, S.; Bouchu, D.; Ciufolini, M. A. *Angew. Chem. Int. Ed.* **2004**, *43*, 4336-4338.
135. *Handbook of Chemistry and Physics*. 97th ed.; CRC Press: Boca Raton, FL, 2017.
136. Nishikawa, T.; Kajii, S.; Isobe, M. *Synlett* **2004**, 2025-2027.
137. Faulkner, A.; Scott, J. S.; Bower, J. F. *J. Am. Chem. Soc.* **2015**, *137*, 7224-7230.
138. Randolph, J. T.; Flentge, C. A.; Huang, P. P.; Hutchinson, D. K.; Klein, L. L.; Lim, H. B.; Mondal, R.; Reisch, T.; Montgomery, D. A.; Jiang, W. W.; Masse, S. V.; Hernandez, L. E.; Henry, R. F.; Liu, Y.; Koev, G.; Kati, W. M.; Stewart, K. D.; Beno, D. W. A.; Molla, A.; Kempf, D. J. *J. Med. Chem.* **2009**, *52*, 3174-3183.
139. Wang, S.-G.; Yin, Q.; Zhuo, C.-X.; You, S.-L. *Angew. Chem. Int. Ed.* **2015**, *54*, 647-650.
140. Nan, J.; Liu, J.; Zheng, H.; Zuo, Z.; Hou, L.; Hu, H.; Wang, Y.; Luan, X. *Angew. Chem. Int. Ed.* **2015**, *54*, 2356-2360.
141. Lian, X.; Lin, L.; Wang, G.; Liu, X.; Feng, X. *Chem. Eur. J.* **2015**, *21*, 17453-17458.
142. Dolling, U. H.; Davis, P.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1984**, *106*, 446-447.

143. Lipkowitz, K. B.; Cavanaugh, M. W.; Baker, B.; O'Donnell, M. J. *J. Org. Chem.* **1991**, *56*, 5181-5192.
144. O'Donnell, M. J.; Wu, S.; Huffman, J. C. *Tetrahedron* **1994**, *50*, 4507-4518.
145. O'Donnell, M. J.; Bennett, W. D.; Wu, S. *J. Am. Chem. Soc.* **1989**, *111*, 2353-2355.
146. Saaby, S.; Bella, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 8120-8121.
147. Cheng, L.; Liu, L.; Wang, D.; Chen, Y.-J. *Org. Lett.* **2009**, *11*, 3874-3877.
148. Qian, Z.-Q.; Zhou, F.; Du, T.-P.; Wang, B.-L.; Ding, M.; Zhao, X.-L.; Zhou, J. *Chem. Commun.* **2009**, 6753-6755.
149. Bui, T.; Borregan, M.; Barbas, C. F. *J. Org. Chem.* **2009**, *74*, 8935-8938.
150. Qi, J.; Beeler, A. B.; Zhang, Q.; Porco, J. J. A. *J. Am. Chem. Soc.* **2010**, *132*, 13642-13644.
151. Gu, Q.; You, S.-L. *Org. Lett.* **2011**, *13*, 5192-5195.
152. Gu, Q.; You, S.-L. *Chem. Sci.* **2011**, *2*, 1519-1522.
153. Kwart, H.; Khan, A. A. *J. Am. Chem. Soc.* **1967**, *89*, 1951-1953.
154. Degennaro, L.; Trinchera, P.; Luisi, R. *Chem. Rev.* **2014**, *114*, 7881-7929.
155. Maestre, L.; Sameera, W. M. C.; Díaz-Requejo, M. M.; Maseras, F.; Pérez, P. J. *J. Am. Chem. Soc.* **2013**, *135*, 1338-1348.
156. Mansuy, D.; Mahy, J.-P.; Dureault, A.; Bedi, G.; Battioni, P. *J. Chem. Soc., Chem. Commun.* **1984**, 1161-1163.
157. Mahy, J.-P.; Bedi, G.; Battioni, P.; Mansuy, D. *J. Chem. Soc., Perkin Trans. 2.* **1988**, 1517-1524.
158. Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Org. Chem.* **1991**, *56*, 6744-6746.
159. Evans, D. A.; Bilodeau, M. T.; Faul, M. M. *J. Am. Chem. Soc.* **1994**, *116*, 2742-2753.
160. Evans, D. A.; Faul, M. M.; Bilodeau, M. T.; Anderson, B. A.; Barnes, D. M. *J. Am. Chem. Soc.* **1993**, *115*, 5328-5329.
161. Li, Z.; Conser, K. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1993**, *115*, 5326-5327.
162. Li, Z.; Quan, R. W.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5889-5890.
163. Södergren, M. J.; Alonso, D. A.; Bedekar, A. V.; Andersson, P. G. *Tetrahedron Lett.* **1997**, *38*, 6897-6900.
164. Noda, K.; Hosoya, N.; Irie, R.; Ito, Y.; Katsuki, T. *Synlett* **1993**, 469-471.
165. Nishikori, H.; Katsuki, T. *Tetrahedron Lett.* **1996**, *37*, 9245-9248.
166. Cui, Y.; He, C. *J. Am. Chem. Soc.* **2003**, *125*, 16202-16203.
167. Au, S.-M.; Huang, J.-S.; Yu, W.-Y.; Fung, W.-H.; Che, C.-M. *J. Am. Chem. Soc.* **1999**, *121*, 9120-9132.
168. Müller, P.; Baud, C.; Jacquier, Y. *Tetrahedron* **1996**, *52*, 1543-1548.
169. Müller, P.; Baud, C.; Jacquier, Y. *Can. J. Chem.* **1998**, *76*, 738-750.
170. Liang, J.-L.; Yuan, S.-X.; Chan, P. W. H.; Che, C.-M. *Org. Lett.* **2002**, *4*, 4507-4510.
171. Liang, J.-L.; Yuan, S.-X.; Chan, P. W. H.; Che, C.-M. *Tetrahedron Lett.* **2003**, *44*, 5917-5920.
172. Guthikonda, K.; Wehn, P. M.; Caliando, B. J.; Du Bois, J. *Tetrahedron* **2006**, *62*, 11331-11342.
173. Guthikonda, K.; Du Bois, J. *J. Am. Chem. Soc.* **2002**, *124*, 13672-13673.
174. Lebel, H.; Lectard, S.; Parmentier, M. *Org. Lett.* **2007**, *9*, 4797-4800.
175. Lebel, H.; Spitz, C.; Leogane, O.; Trudel, C.; Parmentier, M. *Org. Lett.* **2011**, *13*, 5460-5463.
176. Lebel, H.; Parmentier, M.; Leogane, O.; Ross, K.; Spitz, C. *Tetrahedron* **2012**, *68*, 3396-3409.
177. Lebel, H.; Huard, K.; Lectard, S. *J. Am. Chem. Soc.* **2005**, *127*, 14198-14199.
178. Wang, J.-J.; Lao, J.-H.; Li, X.-M.; Lu, R.-J.; Miao, H.; Yan, M. *Synth. Commun.* **2012**, *42*, 1577-1584.

179. Jat, J. L.; Paudyal, M. P.; Gao, H.; Xu, Q.-L.; Yousufuddin, M.; Devarajan, D.; Ess, D. H.; Kürti, L.; Falck, J. R. *Science* **2014**, *343*, 61-65.
180. Ma, Z.; Zhou, Z.; Kürti, L. *Angew. Chem. Int. Ed.* **2017**, *56*, 9886-9890.
181. Nagata, W.; Hirai, S.; Kawata, K.; Aoki, T. *J. Am. Chem. Soc.* **1967**, *89*, 5045-5046.
182. Shibanuma, Y.; Okamoto, T. *Chem. Pharm. Bull* **1985**, *33*, 3187-3194.
183. Roy, A.; Roberts, F. G.; Wilderman, P. R.; Zhou, K.; Peters, R. J.; Coates, R. M. *J. Am. Chem. Soc.* **2007**, *129*, 12453-12460.
184. Atkinson, R. S.; Kelly, B. J. *J. Chem. Soc., Chem. Commun.* **1988**, 624-625.
185. S. Atkinson, R.; Ulukanli, S.; J. Williams, P. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2121-2128.
186. Atkinson, R. S.; Meades, C. K. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1518-1527.
187. Atkinson, R. S.; Fawcett, J.; Lochrie, I. S. T.; Ulukanli, S.; Claxton, T. A. *J. Chem. Soc., Perkin Trans. 2* **2002**, 819-828.
188. Atkinson, R. S.; Draycott, R. D.; Hirst, D. J.; Parratt, M. J.; Raynham, T. M. *Tetrahedron Lett.* **2002**, *43*, 2083-2085.
189. Atkinson, R. S.; Grimshire, M. J.; Kelly, B. J. *Tetrahedron* **1989**, *45*, 2875-2886.
190. Atkinson, R. S.; Jones, D. W.; Kelly, B. J. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1344-1346.
191. Kapron, J. T.; Santarsiero, B. D.; Vederas, J. C. *J. Chem. Soc., Chem. Commun.* **1993**, 1074-1076.
192. Yang, K.-S.; Chen, K. *Org. Lett.* **2002**, *4*, 1107-1109.
193. Li, J.; Liang, J.-L.; Chan, P. W. H.; Che, C.-M. *Tetrahedron Lett.* **2004**, *45*, 2685-2688.
194. Krasnova, L. B.; Hili, R. M.; Chernoloz, O. V.; Yudin, A. K. *Arkivoc* **2005**, 26-38.
195. Siu, T.; Yudin, A. K. *J. Am. Chem. Soc.* **2002**, *124*, 530-531.
196. Li, J.; Chan, P. W. H.; Che, C-M. *Org. Lett.* **2005**, *7*, 5801-5804.
197. Jeong, J. U.; Tao, B.; Sagasser, I.; Henniges, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1998**, *120*, 6844-6845.
198. Yoshimura, A.; Middleton, K. R.; Zhu, C.; Nemykin, V. N.; Zhdankin, V. V. *Angew. Chem. Int. Ed.* **2012**, *51*, 8059-8062.
199. Vesely, J.; Ibrahem, I.; Zhao, G.-L.; Rios, R.; Córdova, A., *Angew. Chem. Int. Ed.* **2007**, *46*, 778-781.
200. Deiana, L.; Dziedzic, P.; Zhao, G.-L.; Vesely, J.; Ibrahem, I.; Rios, R.; Sun, J.; Córdova, A. *Chem. Eur. J.* **2011**, *17*, 7904-7917.
201. Arai, H.; Sugaya, N.; Sasaki, N.; Makino, K.; Lectard, S.; Hamada, Y. *Tetrahedron Lett.* **2009**, *50*, 3329-3332.
202. Pesciaioli, F.; De Vincentiis, F.; Galzerano, P.; Bencivenni, G.; Bartoli, G.; Mazzanti, A.; Melchiorre, P. *Angew. Chem. Int. Ed.* **2008**, *47*, 8703-8706.
203. Brois, S. J.; Beardsley, G. P.*Tetrahedron Lett.* **1966**, *7*, 5113-5119.
204. Bach, R. D.; Canepa, C.; Winter, J. E.; Blanchette, P. E. *J. Org. Chem.* **1997**, *62*, 5191-5197.
205. Kim, C.; Traylor, T. G.; Perrin, C. L. *J. Am. Chem. Soc.* **1998**, *120*, 9513-9516.
206. Hu, X. E. *Tetrahedron* **2004**, *60*, 2701-2743.
207. Laschat, S.; Dickner, T. *Synthesis* **2000**, 1781-1813.
208. Fuson, R. C.; Zirkle, C. L. *J. Am. Chem. Soc.* **1948**, *70*, 2760-2762.
209. Gomez Pardo, D.; Cossy, J. *Chem. Eur. J.* **2014**, *20*, 4516-4525.
210. Déchamps, I.; Gomez Pardo, D.; Cossy, J. *Synlett* **2007**, 0263-0267.
211. Rioton, S.; Orliac, A.; Antoun, Z.; Bidault, R.; Gomez Pardo, D.; Cossy, J. *Org. Lett.* **2015**, *17*, 2916-2919.
212. Lam, Y.-H.; Houk, K. N.; Cossy, J.; Gomez Pardo, D.; Cochi, A. *Helv. Chim. Acta.* **2012**, *95*, 2265-2277.

213. Jarvis, S. B. D.; Charette, A. B. *Org. Lett.* **2011**, *13*, 3830-3833.
214. Nagata, W.; Hirai, S.; Kawata, K.; Okumura, T. *J. Am. Chem. Soc.* **1967,** *89*, 5046-5048.
215. Anxionnat, B.; Robert, B.; George, P.; Ricci, G.; Perrin, M.-A.; Gomez Pardo, D.; Cossy, J. *J. Org. Chem.* **2012**, *77*, 6087-6099.
216. Dupas, A.; Lhotellier, P.-A.; Guillamot, G.; Meyer, C.; Cossy, J. *Org. Lett.* **2019**, *21*, 3589-3593.
217. Funke, W. *Angew. Chem. Int. Ed.* **1969**, *8*, 70-71.
218. Dave, P. R. *J. Org. Chem.* **1996**, *61*, 5453-5455.
219. Bartnik, R.; Cal, D.; Marchand, A. P.; Alihodzic, S.; Devasagayaraj, A. *Synth. Commun.* **1998**, *28*, 3949-3954.
220. Hayashi, K.; Sato, C.; Hiki, S.; Kumagai, T.; Tamai, S.; Abe, T.; Nagao, Y. *Tetrahedron Lett.* **1999**, *40*, 3761-3764.
221. Hayashi, K.; Ikee, Y.; Goto, S.; Shiro, M. *Chem. Pharm. Bull.* **2004**, *52*, 89-94.
222. Ikee, Y.; Hashimoto, K.; Kamino, M.; Nakashima, M.; Hayashi, K.; Sano, S.; Shiro, M.; Nagao, Y. *Chem. Pharm. Bull.* **2008**, *56*, 346-356.
223. Gianatassio, R.; Lopchuk, J. M.; Wang, J.; Pan, C.-M.; Malins, L. R.; Prieto, L.; Brandt, T. A.; Collins, M. R.; Gallego, G. M.; Sach, N. W.; Spangler, J. E.; Zhu, H.; Zhu, J.; Baran, P. S. *Science* **2016**, *351*, 241-246.
224. Lopchuk, J. M.; Fjelbye, K.; Kawamata, Y.; Malins, L. R.; Pan, C.-M.; Gianatassio, R.; Wang, J.; Prieto, L.; Bradow, J.; Brandt, T. A.; Collins, M. R.; Elleraas, J.; Ewanicki, J.; Farrell, W.; Fadeyi, O. O.; Gallego, G. M.; Mousseau, J. J.; Oliver, R.; Sach, N. W.; Smith, J. K.; Spangler, J. E.; Zhu, H.; Zhu, J.; Baran, P. S. *J. Am. Chem. Soc.* **2017**, *139*, 3209-3226.
225. Gianatassio, R.; Kadish, D. *Org. Lett.* **2019**, *21*, 2060-2063.
226. Marchand, A.; Alihodzić, S.; Bartnik, R.; Mloston, G. *Heterocycles* **1999**, *50*, 131.
227. Mlostoń, G.; Celeda, M. *Helv. Chim. Acta.* **2005**, *88*, 1658-1663.
228. Mlostoń, G.; Woźnicka, M.; Drabowicz, J.; Linden, A.; Heimgartner, H. *Helv. Chim. Acta*. **2008**, *91*, 1419-1429.
229. Dauphinee, G. A.; Forrest, T. P. *Can. J. Chem.* **1978**, *56*, 632-634.
230. Sirvent, J. A.; Lücking, U. *ChemMedChem* **2017**, *12*, 487-501.
231. Lücking, U. *Angew. Chem. Int. Ed.* **2013**, *52*, 9399-9408.
232. Sellinger, O. Z.; Weiler, P. *Biochem. Pharmacol.* **1963**, *12*, 989-1000.
233. Zhu, Y.; Loso, M. R.; Watson, G. B.; Sparks, T. C.; Rogers, R. B.; Huang, J. X.; Gerwick, B. C.; Babcock, J. M.; Kelley, D.; Hegde, V. B.; Nugent, B. M.; Renga, J. M.; Denholm, I.; Gorman, K.; DeBoer, G. J.; Hasler, J.; Meade, T.; Thomas, J. D. *J. Agric. Food Chem.* **2011**, *59*, 2950-2957.
234. Lücking, U.; Jautelat, R.; Krüger, M.; Brumby, T.; Lienau, P.; Schäfer, M.; Briem, H.; Schulze, J.; Hillisch, A.; Reichel, A.; Wengner, A. M.; Siemeister, G. *ChemMedChem* **2013**, *8*, 1067-1085.
235. Koep, S.; Gais, H.-J.; Raabe, G. *J. Am. Chem. Soc.* **2003**, *125*, 13243-13251.
236. Shen, X.; Miao, W.; Ni, C.; Hu, J. *Angew. Chem. Int. Ed.* **2014**, *53*, 775-779.
237. Nagatomo, M.; Yoshioka, S.; Inoue, M. *Chem. Asian. J.* **2015,** *10*, 120-123.
238. Shen, X.; Liu, Q.; Zhang, W.; Hu, J. *Eur. J. Org. Chem.* **2016**, *2016*, 906-909.
239. Bolm, C.; Verrucci, M.; Simic, O.; Cozzi, P. G.; Raabe, G.; Okamura, H. *Chem. Commun.* **2003**, 2826-2827.
240. Langner, M.; Bolm, C. *Angew. Chem. Int. Ed.* **2004**, *43*, 5984-5987.
241. Frings, M.; Atodiresei, I.; Wang, Y.; Runsink, J.; Raabe, G.; Bolm, C. *Chem. Eur. J.* **2010**, *16*, 4577-4587.
242. Langner, M.; Rémy, P.; Bolm, C. *Chem. Eur. J.* **2005**, *11*, 6254-6265.

243. Yadav, M. R.; Rit, R. K.; Sahoo, A. K. *Org. Lett.* **2013**, *15*, 1638-1641.
244. Yadav, M. R.; Rit, R. K.; Sahoo, A. K. *Chem. Eur. J.* **2012**, *18*, 5541-5545.
245. Rit, R. K.; Yadav, M. R.; Ghosh, K.; Shankar, M.; Sahoo, A. K. *Org. Lett.* **2014**, *16*, 5258-5261.
246. Cheng, Y.; Dong, W.; Parthasarathy, K.; Bolm, C. *Org. Lett.* **2017**, *19*, 726-729.
247. Bull, J. A.; Degennaro, L.; Luisi, R. *Synlett* **2017**, *28*, 2525-2538.
248. Sedelmeier, J.; Bolm, C. *J. Org. Chem.* **2005**, *70*, 6904-6906.
249. Cheng, Y.; Dong, W.; Wang, L.; Parthasarathy, K.; Bolm, C. *Org. Lett.* **2014**, *16*, 2000-2002.
250. Teng, F.; Yu, J.-T.; Zhou, Z.; Chu, H.; Cheng, J. *J. Org. Chem.* **2015**, *80*, 2822-2826.
251. Zhu, H.; Yu, J.-T.; Cheng, J. *Chem. Commun.* **2016**, *52*, 11908-11911.
252. Gilchrist, T. L.; Moody, C. J. *Chem. Rev.* **1977**, *77*, 409-435.
253. Whitehead, J. K.; Bentley, H. R. *J. Chem. Soc.* **1952**, 1572-1574.
254. Johnson, C. R.; Haake, M.; Schroeck, C. W. *J. Am. Chem. Soc.* **1970**, *92*, 6594-6598.
255. Stoss, P.; Satzinger, G. *Angew. Chem. Int. Ed.* **1971**, *10*, 76-76.
256. Rynbrandt, R. H.; Balgoyen, D. P. *J. Org. Chem.* **1978**, *43*, 1824-1825.
257. Tamura, Y.; Sumoto, K.; Minamikawa, J.; Ikeda, M. *Tetrahedron Lett.* **1972**, *13*, 4137-4140.
258. Tamura, Y.; Minamikawa, J.; Sumoto, K.; Fujii, S.; Ikeda, M. *J. Org. Chem.* **1973**, *38*, 1239-1241.
259. Johnson, C. R.; Kirchhoff, R. A.; Corkins, H. G. *J. Org. Chem.* **1974**, *39*, 2458-2459.
260. Allenmark, S.; Claeson, S.; Löwendahl, C. *Tetrahedron: Asymmetry* **1996**, *7*, 361-364.
261. Mendiola, J.; Rincón, J. A.; Mateos, C.; Soriano, J. F.; de Frutos, Ó.; Niemeier, J. K.; Davis, E. M., *Org. Process Res. Dev.* **2009**, *13*, 263-267.
262. Müller, J. F. K.; Vogt, P. *Tetrahedron Lett.* **1998**, *39*, 4805-4806.
263. Lacôte, E.; Amatore, M.; Fensterbank, L.; Malacria, M., *Synlett* **2002**, 0116-0118.
264. Mancheño, O. G.; Dallimore, J.; Plant, A.; Bolm, C. *Org. Lett.* **2009**, *11*, 2429-2432.
265. Cren, S.; Kinahan, T. C.; Skinner, C. L.; Tye, H. *Tetrahedron Lett.* **2002**, *43*, 2749-2751.
266. Okamura, H.; Bolm, C. *Org. Lett.* **2004**, *6*, 1305-1307.
267. Mancheño, O. G.; Bolm, C. *Org. Lett.* **2006**, *8*, 2349-2352.
268. Cho, G. Y.; Bolm, C. *Org. Lett.* **2005**, *7*, 4983-4985.
269. Zenzola, M.; Doran, R.; Luisi, R.; Bull, J. A. *J. Org. Chem.* **2015**, *80*, 6391-6399.
270. Bach, T.; Korber, C. *Tetrahedron Lett.* **1998**, *39*, 5015-5016.
271. Bach, T.; Körber, C. *Eur. J. Org. Chem.* **1999**, 1033-1039.
272. Miao, J.; Richards, N. G. J.; Ge, H. *Chem. Commun.* **2014**, *50*, 9687-9689.
273. Dannenberg, C. A.; Fritze, L.; Krauskopf, F.; Bolm, C. *Org. Biomol. Chem.* **2017,** *15*, 1086-1090.
274. Cho, G. Y.; Bolm, C. *Tetrahedron Lett.* **2005**, *46*, 8007-8008.
275. Siu, T.; Yudin, A. K. *Org. Lett.* **2002**, *4*, 1839-1842.
276. Zenzola, M.; Doran, R.; Degennaro, L.; Luisi, R.; Bull, J. A. *Angew. Chem. Int. Ed.* **2016**, *55*, 7203-7207.
277. Tota, A.; Zenzola, M.; Chawner, S. J.; John-Campbell, S. S.; Carlucci, C.; Romanazzi, G.; Degennaro, L.; Bull, J. A.; Luisi, R. *Chem. Commun.* **2017**, *53*, 348-351.
278. Degennaro, L.; Tota, A.; De Angelis, S.; Andresini, M.; Cardellicchio, C.; Capozzi, M. A.; Romanazzi, G.; Luisi, R. *Eur. J. Org. Chem.* **2017**, *2017*, 6486-6490.
279. Kim, S. S.; Nehru, K.; Kim, S. S.; Kim, D. W.; Jung, H. C. *Synthesis* **2002**, 2484-2486.
280. Porcheddu, A.; De Luca, L.; Giacomelli, G. *Synlett* **2009**, 2149-2153.
281. Shigeru, O.; Koichi, S.; Ken, F.; Hae, K. Y. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 775-784.
282. Rauniyar, V.; Hall, D. G. *J. Org. Chem.* **2009**, *74*, 4236-4241.

283. Moriya, T.; Shoji, K.; Yoneda, S.; Ikeda, R.; Konakahara, T.; Sakai, N. *Synthesis* **2013**, *45*, 3233-3238.
284. Harris, L.; Mee, S. P. H.; Furneaux, R. H.; Gainsford, G. J.; Luxenburger, A. *J. Org. Chem.* **2011**, *76*, 358-372.
285. Krajcovicova, S.; Stankova, J.; Dzubak, P.; Hajduch, M.; Soural, M.; Urban, M. *Chem. Eur. J.* **2018**, *24*, 4957-4966.
286. Hansen, A. M.; Sewell, A. L.; Pedersen, R. H.; Long, D.; Gadegaard, N.; Marquez, R. *Tetrahedron* **2013**, *69*, 8527-8533.
287. Sudo, A.; Zhang, Y.; Endo, T. *J. Polym. Sci., Part A: Polym. Chem.* **2011**, *49*, 619-624.
288. Han, C.; Huang, Z.; Zheng, C.; Wan, L.; Lai, Y.; Peng, S.; Ding, K.; Ji, H.; Zhang, Y. *Eur. J. Med. Chem.* **2013**, *66*, 82-90.
289. McLane, R. D.; Le Cozannet-Laidin, L.; Boyle, M. S.; Lanzillotta, L.; Taylor, Z. L.; Anthony, S. R.; Tranter, M.; Onorato, A. J. *Bioorg. Med. Chem. Lett.* **2018**, *28*, 334-338.
290. Zheng, Y.; Ghazvini Zadeh, E. H.; Yuan, Y. *Eur. J. Org. Chem.* **2016**, 2115-2119.
291. Masruri; Willis, A. C.; McLeod, M. D. *J. Org. Chem.* **2012**, *77*, 8480-91.
292. Angle, S. R.; Arnaiz, D. O.; Boyce, J. P.; Frutos, R. P.; Louie, M. S.; Mattson-Arnaiz, H. L.; Rainier, J. D.; Turnbull, K. D.; Yang, W. J. *J. Org. Chem.* **1994**, *59*, 6322-6337.
293. Prachayasittikul, S.; Suphapong, S.; Worachartcheewan, A.; Lawung, R.; Ruchirawat, S.; Prachayasittikul, V. *Molecules* **2009**, *14*, 850-867.
294. Snyder, S. A.; Kontes, F. *J. Am. Chem. Soc.* **2009**, *131*, 1745-1752.
295. Xing, X. C.; Padmanaban, D.; Yeh, L. A.; Cuny, G. D. *Tetrahedron* **2002**, *58*, 7903-7910.
296. Garcia, J.; Franci, G.; Pereira, R.; Benedetti, R.; Nebbioso, A.; Rodriguez-Barrios, F.; Gronemeyer, H.; Altucci, L.; de Lera, A. R. *Bioorg. Med. Chem.* **2011**, *19*, 3637-3649.
297. Sasaki, S.; Kitamura, S.; Negoro, N.; Suzuki, M.; Tsujihata, Y.; Suzuki, N.; Santou, T.; Kanzaki, N.; Harada, M.; Tanaka, Y.; Kobayashi, M.; Tada, N.; Funami, M.; Tanaka, T.; Yamamoto, Y.; Fukatsu, K.; Yasuma, T.; Momose, Y. *J. Med. Chem.* **2011**, *54*, 1365-1378.
298. Beaulieu, M. A.; Sabot, C.; Achache, N.; Guerard, K. C.; Canesi, S. *Chem. Eur. J.* **2010,** *16*, 11224-11228.
299. Trader, D. J.; Carlson, E. E. *J. Org. Chem.* **2013**, *78*, 7349-7355.
300. Jones, G. B.; Heaton, S. B. *Tetrahedron Asymmetry* **1993**, *4*, 261-272.
301. Zhang, H.; Huang, X. L. *Adv. Synth. Catal.* **2016**, *358*, 3736-3742.
302. Boschi, D.; Tron, G. C.; Lazzarato, L.; Chegaev, K.; Cena, C.; Di Stilo, A.; Giorgis, M.; Bertinaria, M.; Fruttero, R.; Gasco, A. *J. Med. Chem.* **2006**, *49*, 2886-2897.
303. Devi, R.; Das, J.; Sarma, B.; Das, S. K. *Org. Biomol. Chem.* **2018**, *16*, 5846-5858.
304. Trost, B. M.; Shen, H. C.; Dong, L.; Surivet, J.-P.; Sylvain, C. *J. Am. Chem. Soc.* **2004**, *126*, 11966-11983.
305. Chaabouni, S.; Simonet, F.; François, A.; Abid, S.; Galaup, C.; Chassaing, S. *Eur. J. Org. Chem.* **2017**, 271-277.
306. Bourke, D. G.; Collins, D. J. *Tetrahedron* **1997**, *53*, 3863-3878.
307. Lu, H.; Zhang, F.-M.; Pan, J.-L.; Chen, T.; Li, Y.-F. *J. Org. Chem.* **2014**, *79*, 546-558.
308. Hemming, D. S.; Talbot, E. P.; Steel, P. G. *Tetrahedron Lett.* **2017**, *58*, 17-20.
309. Schünemann, K.; Furkert, D. P.; Connelly, S.; Fraser, J. D.; Sperry, J.; Brimble, M. A. *Eur. J. Org. Chem.* **2014**, 122-128.
310. Posakony, J.; Hirao, M.; Stevens, S.; Simon, J. A.; Bedalov, A. *J. Med. Chem.* **2004**, *47*, 2635-2644.
311. Huang, J.; Wang, W.; He, H.-Y.; Jian, L.; Fu, H.-Y.; Zheng, X.-L.; Chen, H.; Li, R.-X. *J. Org. Chem.* **2017**, *82*, 2523-2534.

312. Li, C.; Breit, B. *Chem. Eur. J.* **2016,** *22*, 14655-14663.
313. Brümmer, O.; Hoffman, T. Z.; Chen, D.-W.; Janda, K. D. *Chem. Commun.* **2001**, 19-20.
314. Toop, H. D.; Don, A. S.; Morris, J. C. *Org. Biomol. Chem.* **2015**, *13*, 11593-11596.
315. Morin, M. D.; Wang, Y.; Jones, B. T.; Su, L.; Surakattula, M. M.; Berger, M.; Huang, H.; Beutler, E. K.; Zhang, H.; Beutler, B.; Boger, D. L. *J. Med. Chem.* **2016**, *59*, 4812-4830.
316. Trost, B. M.; Yeh, V. S.; Ito, H.; Bremeyer, N. *Org. Lett.* **2002**, *4*, 2621-2623.
317. Tan, C. K.; Zhou, L.; Yeung, Y. Y. *Org. Lett.* **2011**, *13*, 2738-2741.
318. Yalavac, I.; Lyons, S. E.; Webb, M. R.; Procter, D. J. *Chem. Commun.* **2014**, *50*, 12863-12866.
319. Zhou, L.; Tay, D. W.; Chen, J.; Leung, G. Y. C.; Yeung, Y.-Y. *Chem. Commun.* **2013**, *49*, 4412-4414.
320. Ferrand, L.; Tang, Y.; Aubert, C.; Fensterbank, L.; Mouriès-Mansuy, V.; Petit, M.; Amatore, M. *Org. Lett.* **2017**, *19*, 2062-2065.
321. Semba, K.; Fujihara, T.; Xu, T.; Terao, J.; Tsuji, Y. *Adv. Synth. Catal.* **2012**, *354*, 1542-1550.
322. Logan, A. W. J.; Parker, J. S.; Hallside, M. S.; Burton, J. W. *Org. Lett.* **2012**, *14*, 2940-2943.
323. Ohtsuki, A.; Sakurai, S.; Tobisu, M.; Chatani, N. *Chem. Lett.* **2016**, *45*, 1277-1279.
324. Bélanger, G.; Lévesque, F.; Pâquet, J.; Barbe, G. *J. Org. Chem.* **2005**, *70*, 291-296.
325. Itoh, K.; Hamaguchi, N.; Miura, M.; Nomura, M. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2833-2835.
326. Wang, D.; Chen, D.; Haberman, J. X.; Li, C.-J. *Tetrahedron* **1998**, *54*, 5129-5142.
327. Erkkilä, A.; Pihko, P. M. *Eur. J. Org. Chem.* **2007**, 4205-4216.
328. Deshong, P.; Dicken, C. M.; Staib, R. R.; Freyer, A. J.; Weinreb, S. M. *J. Org. Chem.* **1982**, *47*, 4397-4403.
329. Sudhakar, G.; Satish, K. *Chem. Eur. J.* **2015**, *21*, 6475-6480.
330. Schmidt, Y.; Breit, B. *Chem. Eur. J.* **2011**, *17*, 11780-11788.
331. Zúñiga, A.; Pazos, G.; Besada, P.; Fall, Y. *Tetrahedron Lett.* **2012**, *53*, 4293-4295.
332. Neustadt, B. R.; Smith, E. M.; Nechuta, T. L.; Bronnenkant, A. A.; Haslanger, M. F.; Watkins, R. W.; Foster, C. J.; Sybertz, E. J. *J. Med. Chem.* **1994**, *37*, 2461-2476.
333. Doni, E.; Mondal, B.; O'Sullivan, S.; Tuttle, T.; Murphy, J. A. *J. Am. Chem. Soc.* **2013**, *135*, 10934-10937.
334. Kawashima, S.; Aikawa, K.; Mikami, K. *Eur. J. Org. Chem.* **2016**, 3166-3170.
335. Qiu, Y.-F.; Yang, F.; Qiu, Z.-H.; Zhong, M.-J.; Wang, L.-J.; Ye, Y.-Y.; Song, B.; Liang, Y.-M. *J. Org. Chem.* **2013**, *78*, 12018-12028.
336. Chenniappan, V. K.; Rahaim, R. J. *Org. Lett.* **2016**, *18*, 5090-5093.
337. Mikhaylov, A. A.; Dilman, A. D.; Novikov, R. A.; Khoroshutina, Y. A.; Struchkova, M. I.; Arkhipov, D. E.; Nelyubina, Y. V.; Tabolin, A. A.; Ioffe, S. L. *Tetrahedron Lett.* **2016**, *57*, 11-14.
338. Venning, A. R. O.; Kwiatkowski, M. R.; Roque Peña, J. E.; Lainhart, B. C.; Guruparan, A. A.; Alexanian, E. J. *J. Am. Chem. Soc.* **2017**, *139*, 11595-11600.
339. D'Oyley, J. M.; Aliev, A. E.; Sheppard, T. D. *Angew. Chem. Int. Ed.* **2014,** *53*, 10747-10750.
340. Vinayagam, P.; Vishwanath, M.; Kesavan, V. *Tetrahedron Asymmetry* **2014**, *25*, 1252.
341. O'Sulliva, A. C.; Struber, F.; Ley, S. V. *J. Org. Chem.* **1999**, *64*, 6252-6256.
342. Cecere, G.; König, C. M.; Alleva, J. L.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2013**, *135*, 11521-11524.

343. John, O. R. S.; Killeen, N. M.; Knowles, D. A.; Yau, S. C.; Bagley, M. C.; Tomkinson, N. C. O. *Org. Lett.* **2007**, *9*, 4009-4012.
344. Tamura, Y.; Ikeda, H.; Morita, I.; Tsubouchi, H.; Ikeda, M. *Chem. Pharm. Bull.* **1982**, *30*, 1221-1224.
345. Cruz, A.; Padilla-Martínez, I. I.; García-Báez, E. V. *Tetrahedron Asymmetry* **2010**, *21*, 909-913.
346. Affortunato, F.; Florio, S.; Luisi, R.; Musio, B. *J. Org. Chem.* **2008**, *73*, 9214-9220.
347. Agarwal, P.; van der Weijden, J.; Sletten, E. M.; Rabuka, D.; Bertozzi, C. R. *Proc. Natl. Acad. Sci. U.S.A.* **2013**, *110*, 46-51.
348. Nguyen, T. N. T.; Thiel, N. O.; Pape, F.; Teichert, J. F. *Org. Lett.* **2016**, *18*, 2455-2458.
349. Arai, N.; Sato, K.; Azuma, K.; Ohkuma, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 7500-7504.
350. Skhiri, A.; Salem, R. B.; Soulé, J.-F.; Doucet, H. *Synthesis* **2016,** *48*, 3097-3106.
351. Mogensen, J. P.; Sauerberg, P.; Bury, P. S.; Jeppesen, L.; Pettersson, I. *Compounds, their preparation and use*. 2001.
352. Metternich, J. B.; Gilmour, R. *J. Am. Chem. Soc.* **2015**, *137*, 11254-11257.
353. Bernasconi, M.; Ramella, V.; Tosatti, P.; Pfaltz, A. *Chem. Eur. J.* **2014**, *20*, 2440-2444.
354. Griesbeck, A. G.; Brautigam, M.; Kleczka, M.; Raabe, A. *Molecules* **2017**, *22*.
355. Mueller, A. J.; Jennings, M. P. *Org. Lett.* **2007**, *9*, 5327-5329.
356. Miller, D. J.; Yu, F.; Young, N. J.; Allemann, R. K. *Org. Biomol. Chem.* **2007**, *5*, 3287-3298.
357. Lai, C.; Mathieu, G.; Gabrielli Tabarez, L. P.; Lebel, H. *Chem. Eur. J.* **2019**, *25*, 9423-9426.
358. Li, X.; Du, J.; Zhang, Y.; Chang, H.; Gao, W.; Wei, W. *Org. Biomol. Chem.* **2019**, *17*, 3048-3055.
359. Selmi, A.; Aydi, R.; Mosset, P.; Gree, R.; Kammoun, M. *Arkivoc* **2019**, 108-120.
360. Tamura, Y.; Bayomi, S. M.; Tsunekawa, M.; Ikeda, M. *Chem. Pharm. Bull.* **1979**, *27*, 2137-2142.
361. Gayakwad, E. M.; Patil, V. V.; Shankarling, G. S. *New. J. Chem.* **2016**, *40*, 223-230.
362. Kim, J.; Ok, J.; Kim, S.; Choi, W.; Lee, P. H. *Org. Lett.* **2014**, *16*, 4602-4605.
363. Bulman Page, P. C.; Buckley, B. R.; Elliott, C.; Chan, Y.; Dreyfus, N.; Marken, F. *Synlett* **2016**, *27*, 80-82.
364. Hua, Y.; Zhang, W.; Wang, X.; Ge, Z.; Li, R. *Tetrahedron* **2017**, *73*, 4387-4391.
365. Bahrami, K.; Khodaei, M. M.; Yousefi, B. H.; Arabi, M. S. *Tetrahedron Lett.* **2010**, *51*, 6939-6941.
366. Yu, H.; Li, Z.; Bolm, C. *Angew. Chem. Int. Ed.* **2018**, *57*, 324-327.
367. Hanchate, V.; Muniraj, N.; Prabhu, K. R. *J. Org. Chem.* **2019**, *84*, 8248-8255.