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Title:
C–C bond activation of strained ring systems

C–C Bond Activation of Strained Ring Systems

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A thesis submitted to the University of Bristol in accordance with the requirements for award of the degree of PhD in the Faculty of Science

School of Chemistry, December 2020

(95,244 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 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.

Signed: OLGA SOKOLOVA

Date: 17-December-2020

Abstract

Studies towards C-C bond activation-based methodologies involving strained ring systems are presented. The work aims to develop further directing group-assisted cyclisations developed in Bristol. Specifically, aminocyclopropane-based and related ring systems were examined to identify suitable substrates for directed transition metal-catalysed ring cleavage and subsequent transformations.

Rare examples of carbonylative rearrangements of aminocyclopropanes using a temporary directing group have been discovered. The process involves an unusual ring contraction and can be used to provide a range of γ-lactams. The method is conceptually unique compared to other temporary directing group strategies used in C-C bond activation.

Investigations into substrates for intramolecular nucleophilic addition to C-C bond activation derived metallacycles identified aminocyclopropanes equipped with anilines as suitable substrates. These cyclopropanes undergo carbonylative cyclisation to form 8-membered *N*-heterocycles. Studies were also undertaken to evaluate a range of alternative substrates with tethered nucleophiles under carbonylative conditions.

A novel (3+1+2) cycloaddition between aminocyclopropanes, CO and tethered π-unsaturates has been developed. An extensive study of the reaction scope was undertaken, and conditions for asymmetric cycloadditions were identified. This methodology provides the first examples of highly enantioselective C-C bond activations of aminocyclopropanes.

Additionally, the reactivity of various homologated aminocyclopropanes was investigated. A previously developed carbonylative rearrangement of aminomethylcyclopropanes to α-aminocyclopentanones was re-evaluated. Second-generation conditions were optimised and these offered enhanced efficiencies for certain substrates. The carbonylative rearrangement was integrated into cascade and tandem processes to access various polycyclic products (e.g. spirocycles and indoles).

Efforts to achieve challenging C-C bond activation-triggered transformations of aminocyclobutanes are described. Several representative aminocyclobutane-based substrates were evaluated under transition metal-catalysed conditions, but these failed to deliver the desired targets.

Acknowledgements

I would first like to thank my supervisor, Prof John Bower, for all of the guidance and support that he has provided throughout my PhD. John's hard-working attitude and incredible chemistry knowledge created a competitive and nurturing environment that made me a better chemist. I am grateful to have had the chance to work on so many interesting projects and I will look back fondly on the time spent in his group. Since my first internship in Bristol in 2014, I knew that John would be one of the leading professionals in chemistry and he has continuously proved me right. I wish him all the best with his new position in Liverpool and I look forward to seeing more of his highly creative chemistry.

My research would not have been possible without all of the technical staff at Bristol. In particular, I am grateful to Prof Craig Butts for his help with NMR, and Paul Lawrence, who was always patient and willing to help me with complex NMR experiments. I would like to thank Dr Hazel Sparkes and Dr Natalie Pridmore for running my X-ray crystal structures.

I was lucky to be a part of a great team, and I am grateful to all the members of the Bower group I had the pleasure of working with. I would like to thank Andrew Dalling, Ben Jones, Madelene Waldron and Lauren O'Neil, who had the unfortunate experience of proof-reading my chapter drafts. I thank Giacomo Crisenza, who co-supervised me during the C-H activation project and made me (naively) think that doing a PhD would be a breeze. I also learned a lot from Dr Adam Calow and Dr Gang-Wei Wang, who worked on individual projects in collaboration with me. I am grateful to summer and undergraduate students, Hector Christodoulou and Matthew Curley, who contributed to the research presented in this thesis.

A special acknowledgement goes to people who made my off-lab time in Bristol so enjoyable. Maddy, thank you for all the bubble tea and bookish conversations we shared, I'm looking forward to seeing your name on a book cover one day. I thank Adam and Lucas for encouraging me to come out of my shell, organising numerous get-togethers and making sure I had a good time. I am also grateful to Katya for showing me great cafés around Bristol and providing a much-needed opportunity to fume over things.

I cannot thank Olya the Hamster enough for coming over to the UK many times and being a great friend from high school, and through till now. I am also lucky to have Nadya, who provided me with friendship and many good memories throughout my studies. A huge thanks goes to Fedor, whose constant care and help makes my life much better in many ways.

Finally, I would like to thank my Mum, Granny and Grandpa, who provided me with unconditional love and support. I couldn't have done it without you.

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Abbreviations

BARF	tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
BHT	3,5-di-tert-butyl-4-hydroxytoluene
DAST	diethylaminosulfur trifluoride
DBU	1,8-diazabicyclo(5.4.0)undec-7-ene
1,2-DCB	1,2-dichlorobenzene
DCC	*N*,*N*′-dicyclohexylcarbodiimide
d^fppb	1,2-bis[bis(pentafluorophenyl)phosphino]butane
d^fppe	1,2-bis[bis(pentafluorophenyl)phosphino]ethane
DIBAL	diisobutylaluminium hydride
DIPA	diisopropylamine
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
HOBt	hydroxybenzotriazole
LDA	lithium diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide
m-CPBA	*m*-chloroperoxybenzoic acid
NCS	*N*-chlorosuccinimide
PCC	pyridinium chlorochromate
py	pyridyl
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl
TFAA	trifluoroacetic anhydride
TMEDA	tetramethylethylenediamine

Standard abbreviations are not stated here.

CHAPTER 1

Introduction

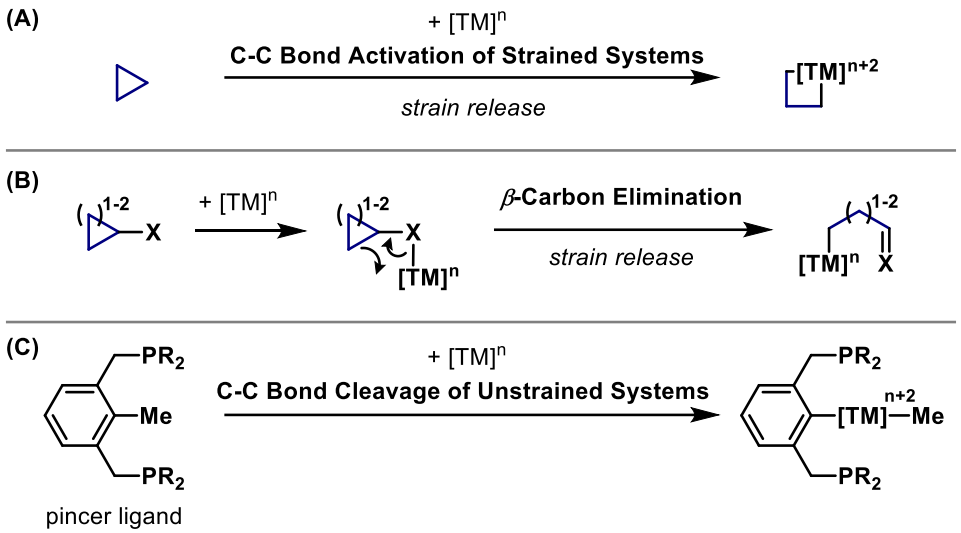
Aspects of this Chapter have been adapted from a review article.

(Sokolova, O. O.; Bower, J. F. *Chem. Rev.* **2021**, *In press*)

1.1 Transition metal-assisted C-C single-bond cleavage

Catalytic processes involving oxidative addition of a transition metal into a C-C bond ("C-C bond activation") allow the atom economical assembly of complex scaffolds.[1-4] Examples of stoichiometric C-C bond cleavage by transition metals have been known since 1955,[5,6] but the catalytic application of this process has gained traction only in the last few decades. This can be attributed to the challenging nature of C-C bond activation.[7] Competing C-H bond activation is usually favoured due to greater orbital availability, the statistical abundance of C-H bonds (vs. C-C bonds), and the lower activation energy barrier (0-9 kcal/mol for C-H insertion vs. 13-27 kcal/mol for C-C insertion of second row late transition metals).[8,9] These considerations mean that C-C bond activation is usually a kinetically unfavoured process. Moreover, oxidative insertion of transition metals into relatively stable C-C bonds (approximate bond energy of 90 kcal/mol) is thermodynamically unfavoured because two weak metal-carbon bonds (approximate bond energies of 20–30 kcal/mol) are formed instead.[10] Nonetheless, C-C bond activation methodologies remain highly attractive from a synthetic viewpoint as they offer a direct and unconventional approach towards target molecules that might otherwise require multistep synthesis.

The focus of the work presented in this dissertation is on C-C bond activation-based methodologies involving strained ring systems. This introduction aims to cover key early investigations into carbonylative processes involving C-C bond cleavage of cyclopropanes via oxidative addition of transition metals (Scheme 1A). Recent developments in C-C bond activation of cyclopropylamines are of particular interest to the research contained within this dissertation and are reviewed in depth here. An overview of asymmetric methodologies involving C-C bond activation is provided in Chapter 4. Processes involving C-C bond activation of cyclobutane-based systems are discussed in Chapter 6. It should be noted that transition metal-catalysed $C(sp^3)$-$C(sp^3)$ bond cleavage can also be achieved via β-carbon elimination (Scheme 1B)[11,12] or the activation of specialised unstrained compounds (e.g. pincer ligands, Scheme 1C);[13,14] these kinds of processes are not discussed in detail here because they are not directly relevant to studies described later.



Scheme 1: Strategies for transition metal-catalysed C(sp^3)-C(sp^3) bond cleavage.

1.2 Carbonylative C-C bond activation of cyclopropanes

Small ring systems, in particular cyclopropanes, play an important role in C-C bond activation as the release of ring strain, in addition to high orbital availability, facilitates metal insertion.[7,15] The desirable bond angle for sp^3 hybridised carbons is 109.5°, but the strained structure of cyclopropane forces internal bond angles to be 60°. This difference means the C-C bonds bend outward, leading to partial rehybridisation and increased p character. Indeed, calculations show that the natural hybrid orbitals of cyclopropane C-C bonds are $sp^{3.46}$ hybridised (*vs*. $sp^{2.56}$ for ethane). [16,17] To some extent, this makes the HOMO and LUMO of cyclopropane similar to π and π* orbitals of alkenes and, as a result, bonding with transition metals is highly favoured for cyclopropane-based systems compared to linear alkanes (Figure 1).

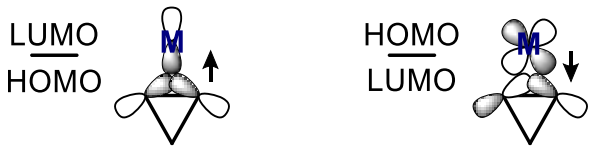
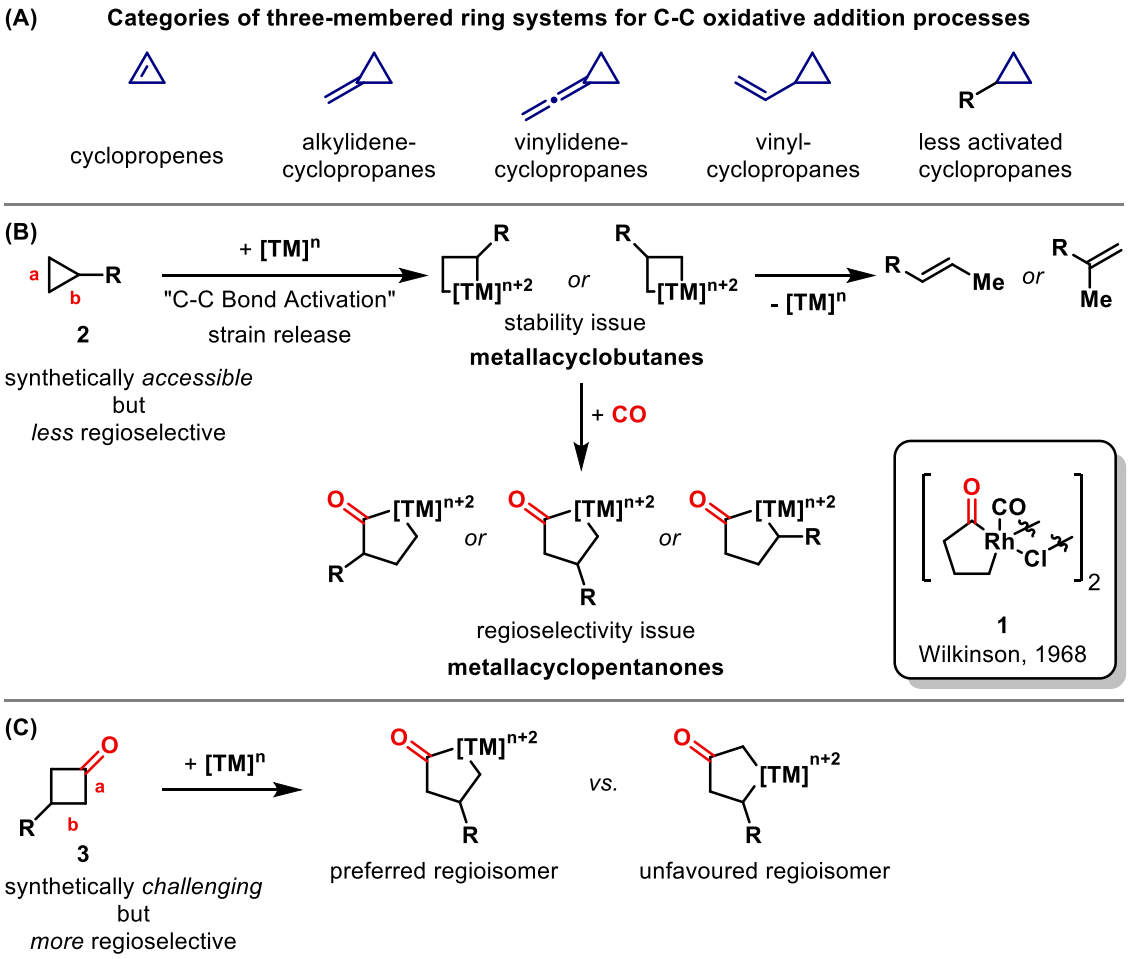


Figure 1: Walsh model for metal-cyclopropane orbital interaction.

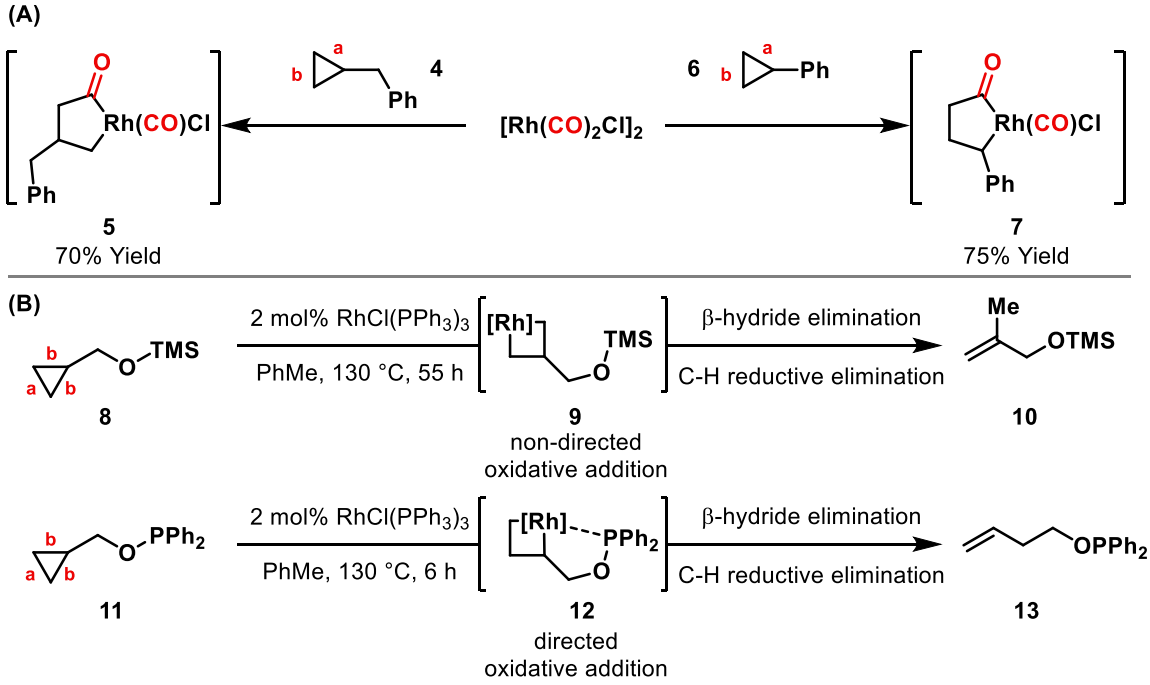
Early reports on C-C bond activation focused on the use of activated cyclopropane-based rings, such as cyclopropenes, alkylidene cyclopropanes, vinylidene cyclopropanes and vinyl cyclopropanes (Scheme 2A).[2,18-23] More recent methodologies have enabled the routine exploitation of less activated cyclopropane-based substrates in reaction design. As discussed above, the intrinsic ring strain of cyclopropanes facilitates metal insertion into their C-C bond. However, the instability of the resulting metallacyclobutanes, which are prone to β-elimination, limits their use in reaction design (Scheme 2B). A viable strategy for making productive use of cyclopropane derived metallacyclobutanes is to trap them with CO, as the CO insertion process is

fast compared to β-hydride elimination. The resulting metallacyclopentanones are less strained and much more stable. In 1968, Wilkinson and co-workers[24] showed, through stoichiometric studies, that rhodacyclopentanone **1** (which is dimeric via chloride bridging) can be generated by exposure of cyclopropane to $[Rh(CO)_2Cl]_2$. For substituted cyclopropanes **2**, the regioselectivity of transition metal oxidative addition and CO migratory insertion is uncertain, and can, in principle, lead to multiple regioisomers of the rhodacyclopentanone (Scheme 2B, top). Rhodacyclopentanones can also be accessed by C-C bond activation of cyclobutanones **3** (Scheme 2C). Usually oxidative insertion of a transition metal to cyclobutanones occurs at bond **a**, adjacent to the carbonyl, allowing more precise regiocontrol. This process has underpinned many methodologies, with significant contributions from the groups of Murakami[25-28] and, later, Cramer[29-31] and Dong[32-35] (for details of some processes involving C-C activation of cyclobutanones, see Chapter 4, Schemes 60-62). Despite the improved regioselectivity, the shortcoming of cyclobutanone-based processes is that synthetic routes to the starting material are less flexible compared to cyclopropanes.



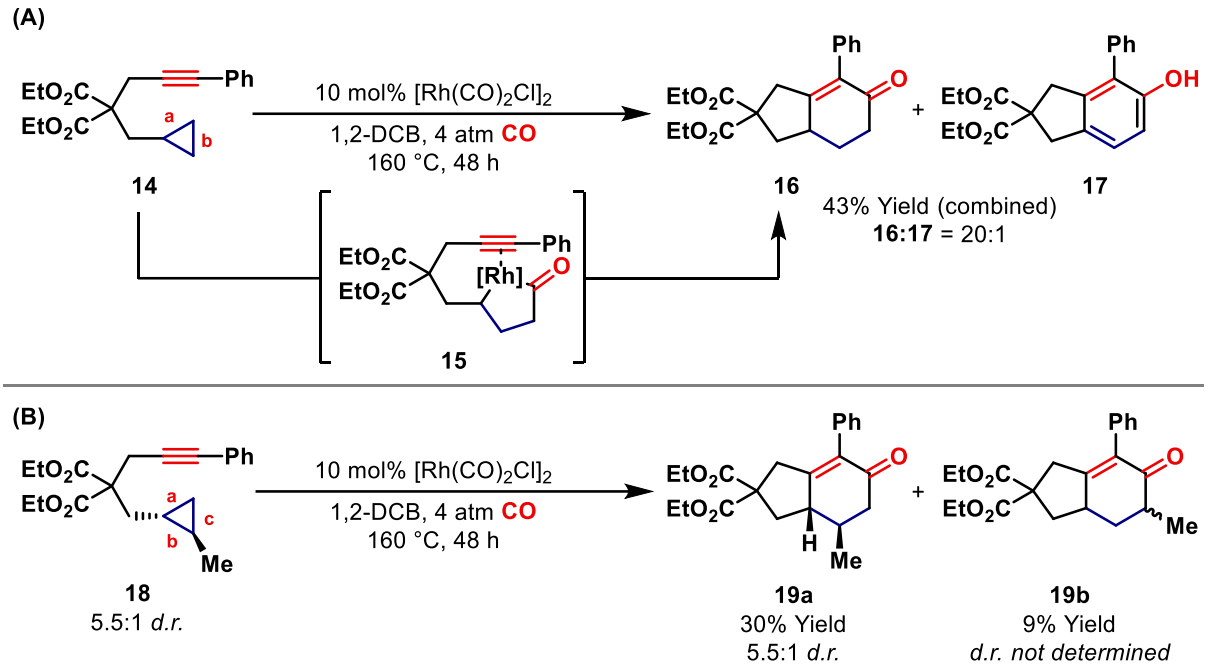
Scheme 2: (A) Three-membered ring systems used in C-C oxidative addition processes; (B) and (C) Cleavage of cyclopropanes and cyclobutanones by C−C bond activation.

McQuillin and Powell[36,37] have examined the regioselectivity of carbonylative C-C bond activation of substituted cyclopropanes through stoichiometric studies, which revealed that this aspect is substrate dependent (Scheme 3A). For benzylcyclopropane **4**, oxidative insertion into the more sterically accessible bond **b** gave **5**, whereas phenylcyclopropane **6** delivered **7** via cleavage of more hindered but also more activated bond **a**. The issue of enforcing the regioselectivity of transition metal oxidative addition of substituted cyclopropanes was addressed by Chirik and co-workers.[38] They studied the C-C bond cleavage of cyclopropanes **8** and **11**, which contain coordinating and non-coordinating substituents, respectively (Scheme 3B). It was found that branched olefin **10** formed when cyclopropane **8** was used. Mechanistically, oxidative addition of Rh into less sterically hindered distal bond **a** provides rhodacyclobutane **9**, which undergoes β-hydride elimination and C-H reductive elimination to give branched alkene **10**. When the O-substituent was switched to a coordinating phosphinite, the reaction efficiency dramatically increased and complete conversion of starting cyclopropane **11** was observed in 6 h (as opposed to 55 h for **8**). The reaction regioselectivity also switched, and this was attributed to the phosphinite directing metal insertion into the more hindered proximal bond **b,** thereby favouring the formation of rhodacyclobutane **12**. From this intermediate, β-hydride elimination and C-H reductive elimination affords linear alkene **13**. Accordingly, directing groups can have a strong influence on reaction rate and regioselectivity in transition metal-catalysed C-C bond activations of cyclopropanes.



Scheme 3: (A) C-C bond activation regioselectivity studies with substituted cyclopropanes. (B) Non-directed and directed C-C bond activation of a cyclopropane.

Other types of directing group strategy have been employed for accessing rhodacyclopentanones by carbonylative C-C bond activation. Narasaka and Koga used cyclopropane **14** to obtain bicyclic products via an intramolecular (3+1+2) cycloaddition[39] that is superficially similar to the Pauson-Khand reaction (Scheme 4A).[40-42] The selective formation of rhodacyclopentanone **15** is governed by the tethered alkyne, which directs oxidative addition of the pre-coordinated Rh catalyst into the less sterically accessible cyclopropane bond **a**. This is followed by CO insertion (to **15**), alkyne insertion and C-C reductive elimination to generate cycloadduct **16** along with a small amount of oxidised product **17**. The reactivity of *trans*-disubstituted cyclopropane **18** was studied as well: C-C bond activation-triggered cycloaddition of **18** delivered regioisomers **19a** and **19b**, resulting from insertion into bond **a** and **b**, respectively (Scheme 4B). The products were formed in a 3:1 ratio favouring **19a**, which indicates a preference for cleavage of the less sterically hindered bond **a**. In these studies, products arising from cleavage of bond **c** were not observed, emphasizing the role of the alkyne in directing oxidative addition.

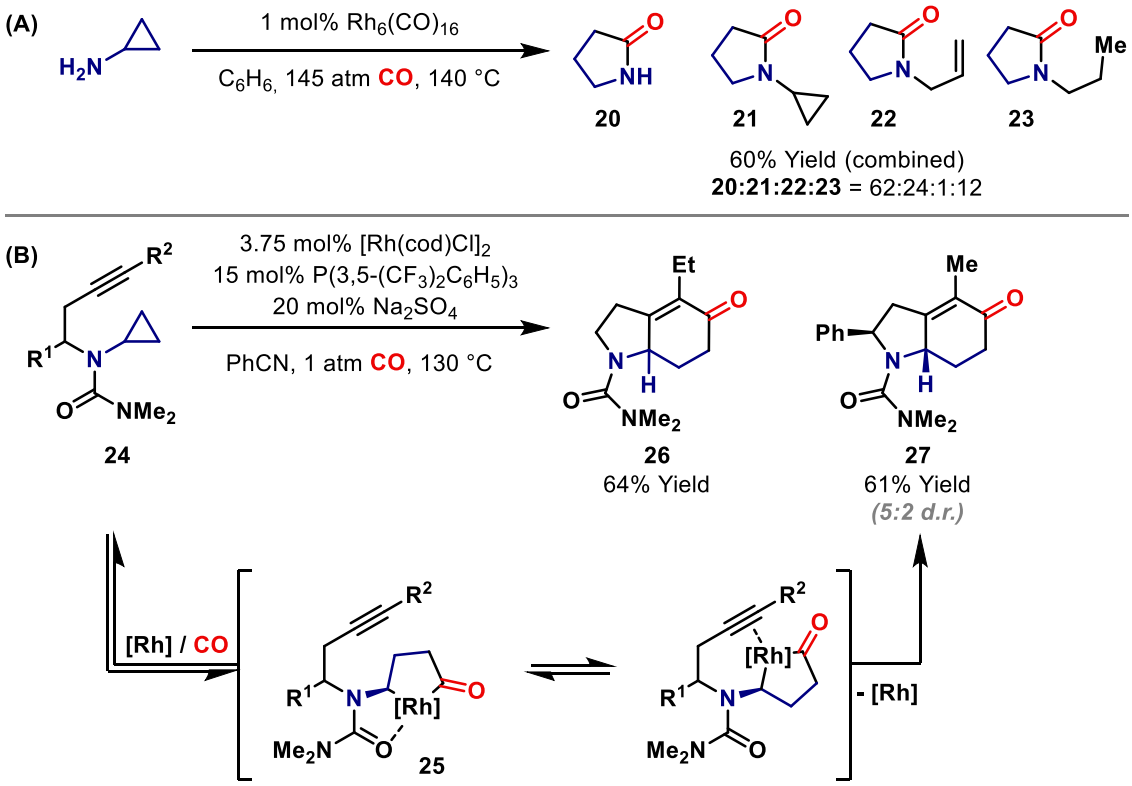


Scheme 4: Alkyne-directed carbonylative (3+1+2) cycloadditions of cyclopropanes.

1.3 Directed C-C bond activation of cyclopropylamines

An alternative strategy for achieving regiocontrol during the formation of metallacyclopentanones is to use a nitrogen-based directing group. Rhodium-catalysed carbonylation of simple cyclopropylamine to give γ-lactams was reported by Iqbal in 1971 (Scheme 5A).[43] Here, major lactam product **20** was formed alongside other lactams **21-23**. A mechanism was not advanced for these processes, but product **20** could conceivably form via the directed formation of a rhodacyclopentanone.

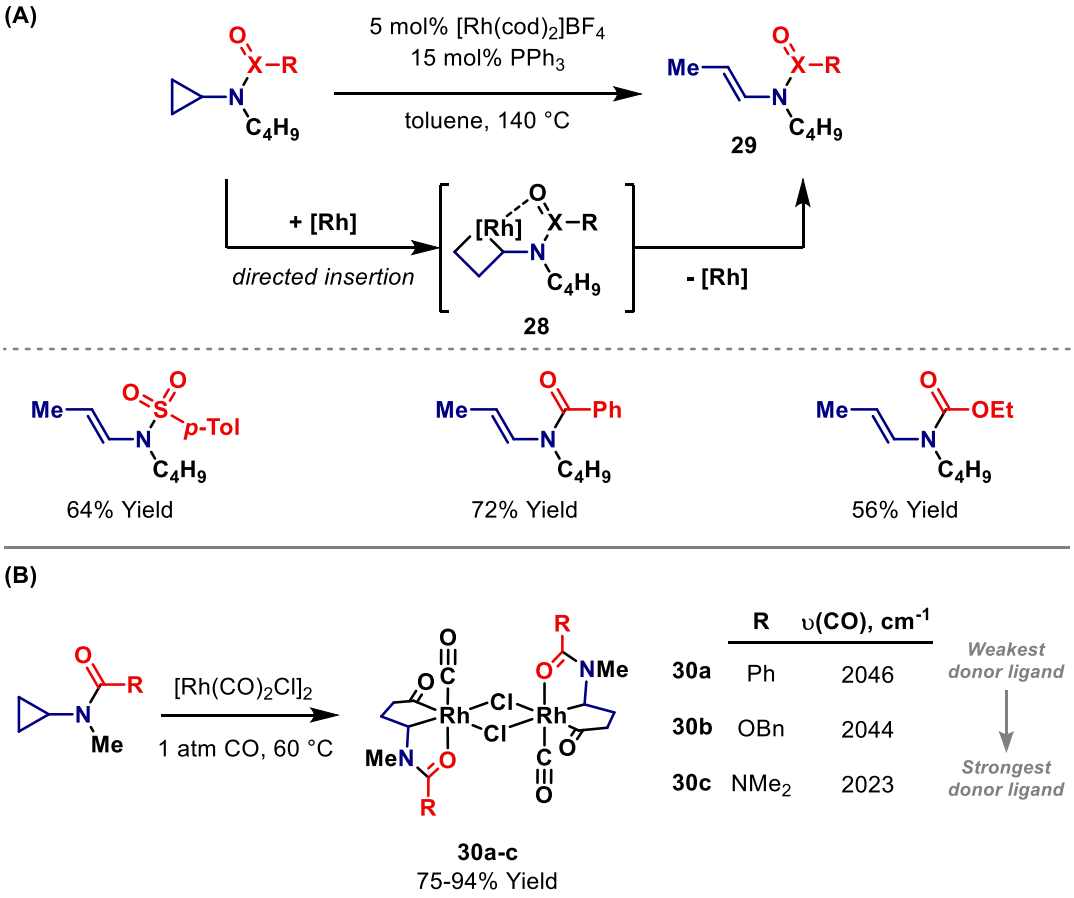
Further developments in this area occurred much later when directing-group promoted C-C bond activations of cyclopropylamines were developed in Bristol.[2,44,45] Early work focused on a prototype (3+1+2) cycloaddition process for the preparation of bicyclic products, such as **26** and **27** (Scheme 5B).[46] These studies were inspired by the seminal work from Narasaka and Koga (see Scheme 4),[39] where a tethered alkyne unit was used to direct insertion of Rh into the cyclopropane C-C bond. In contrast, the process in Scheme 5 uses the urea directing group of **24** to enhance the rate and control the regioselectivity of rhodacyclopentanone (**25**) formation. Directing group dissociation, alkyne insertion and C-C reductive elimination then leads to the targets. Subsequent studies showed that, under specific conditions and for certain substrates, replacement of $[Rh(cod)Cl]_2$ with $[Rh(cod)_2]OTf$ leads to higher yields and shorter reaction times.[47]



Scheme 5: (A) First examples of the carbonylation of aminocyclopropane; (B) Rh-catalysed carbonylative (3+1+2) cycloadditions of aminocyclopropanes and alkynes.

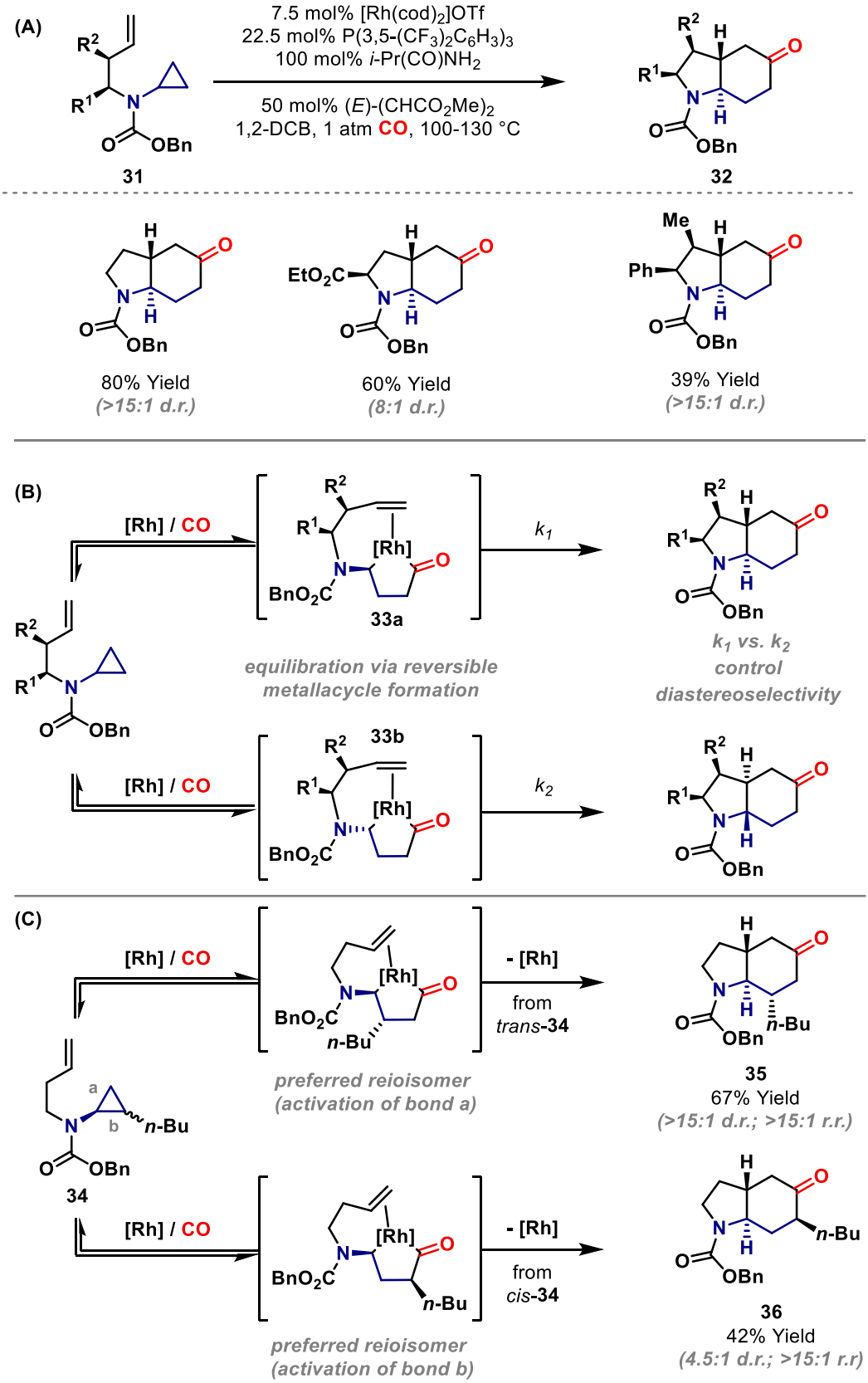
The process in Scheme 5B was underpinned by detailed studies on the directed C-C bond activation step. Under non-carbonylative conditions, different directing groups (e.g. sulfonamides, amides and carbamates) were evaluated for their ability to direct formation of the key rhodacyclobutane (**28**). In the event, sufonamides, amides and carbamates were all effective, as evidenced by the formation (via β-hydride elimination and C-H reductive elimination) of linear N-alkenyl products **29** (Scheme 6A). Model rhodacyclopentanones **30a-c** could also be isolated and analysis of their CO stretching frequencies revealed that urea directing groups are stronger donors than carbamates or amides (Scheme 6B). For the process in Scheme 5B, a urea is required to

outcompete the alkyne for coordination to Rh(I) prior to C-C oxidative addition of the cyclopropane.



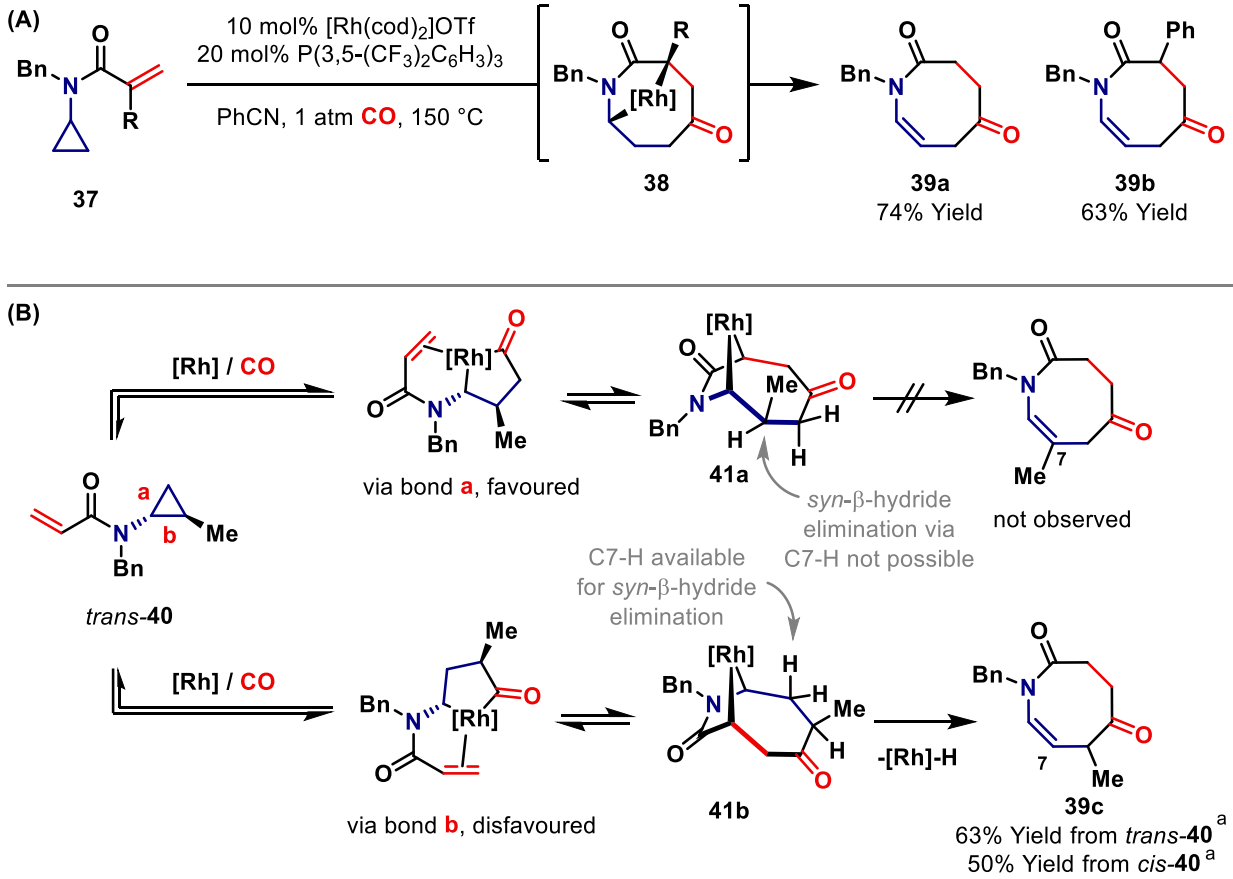
Scheme 6: Mechanistic studies on the directed C-C bond activation of protected aminocyclopropanes.

Alkenes coordinate less strongly to Rh(I) than alkynes, and so for alkene-based (3+1+2) cycloadditions, less strongly coordinating carbamate directing groups can be used.[48] This enables efficient Cbz-directed cycloadditions of **31** to provide interesting *trans*-fused heterocycles **32** (Scheme 7A). High yields required the addition of *i*-Pr(CO)NH_2 and dimethyl fumarate; the Lewis basicity of *i*-Pr(CO)NH_2 may assist with stabilisation of the Rh-catalyst and dimethyl fumarate is a labile electron-deficient ligand that may accelerate alkene insertion and/or reductive elimination.[49] An interesting feature of these processes is the high diastereoselectivity that is achieved with respect to the new stereocentre adjacent to nitrogen. Stoichiometric studies support a mechanism wherein *non-selective and reversible* generation of diastereomeric rhodacyclopentanones **33a** and **33b** precedes diastereo-determining alkene insertion (Scheme 7B). Geometry dependent regioselectivity was observed for 1,2-disubstituted aminocyclopropanes: cycloaddition of *trans*-**34** provided **35**, whereas cycloaddition of *cis*-**34** generated **36** (Scheme 7C). As confirmed by stoichiometric studies, these product regioselectivies reflect the inherent regiochemical preference of directed rhodacyclopentanone formation.



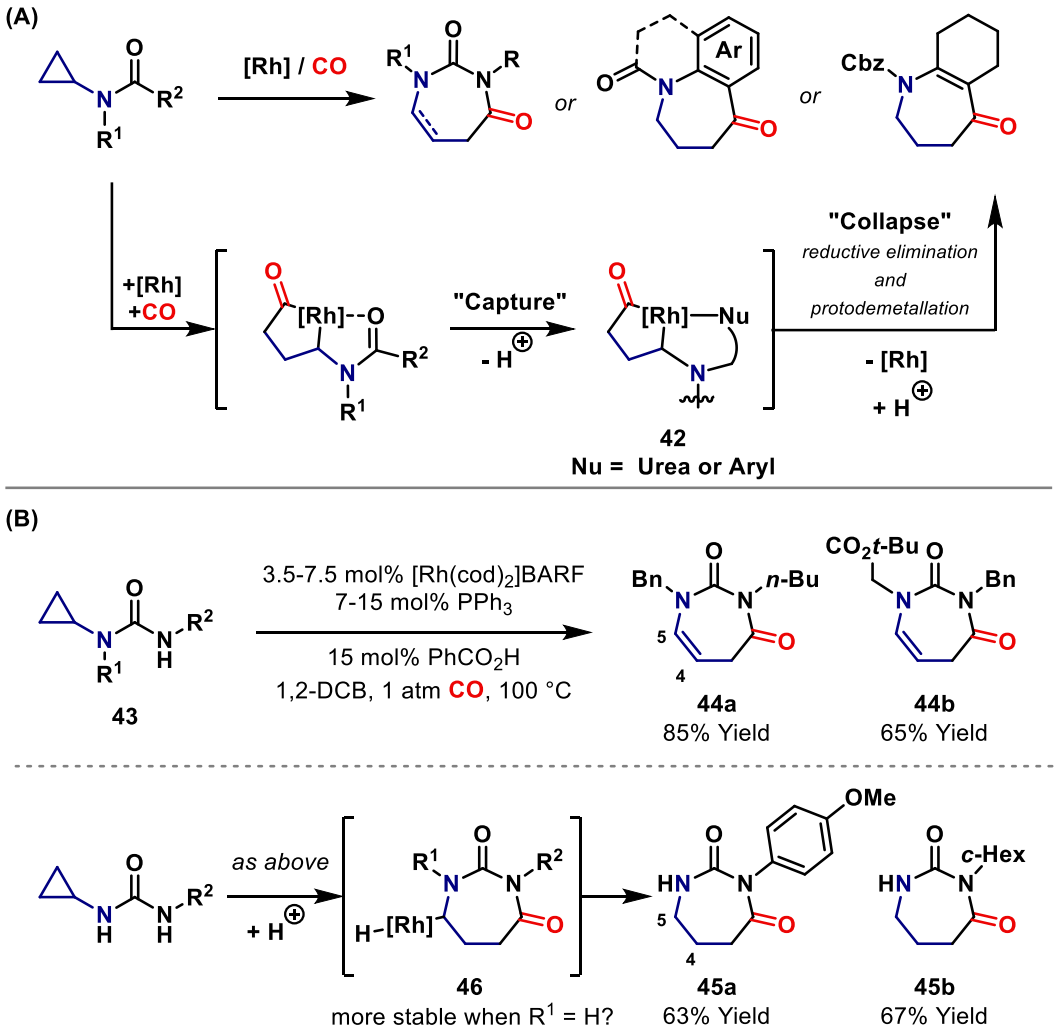
Scheme 7: Rh-catalysed carbonylative (3 + 1 + 2) cycloadditions of aminocyclopropanes and alkenes.

Acrylamide-based systems **37** undergo a distinct reaction pathway leading to synthetically challenging 8-membered rings **39** (Scheme 8A).[50] Here, insertion of the alkene into the rhodacyclopentanone generates metallabicycle **38**, which undergoes β-hydride elimination (via C**7**) and C-H reductive elimination to provide the targets. This pathway is supported by deuterium labelling studies. An unusual aspect is that both *trans*- and *cis*-1,2-disubstituted cyclopropanes (e.g. *trans*-**40** and *cis*-**40**) delivered the same regioisomer of the product (**39c**) as a result of Rh(I) oxidative addition into the more hindered cyclopropane bond **b** (Scheme 8B). While previous studies from Bristol demonstrated that this regioselectivity is typical for *cis*-1,2-disubstituted cyclopropanes, the outcome for *trans*-1,2-disubstituted cyclopropanes was rationalised by invoking β-hydride elimination from **41** as the first irreversible step in the reaction pathway. Regioisomer **41a** arising from insertion into sterically accessible bond **a** possesses a *cis*-Me substituent at C**7** and C**7**-H is not available for *syn*-β-hydride elimination. However, insertion into less favoured bond **b** gives rise to intermediate **41b**, in which *syn*-β-hydride elimination is possible and, following C-H reductive elimination, provides **39c**.



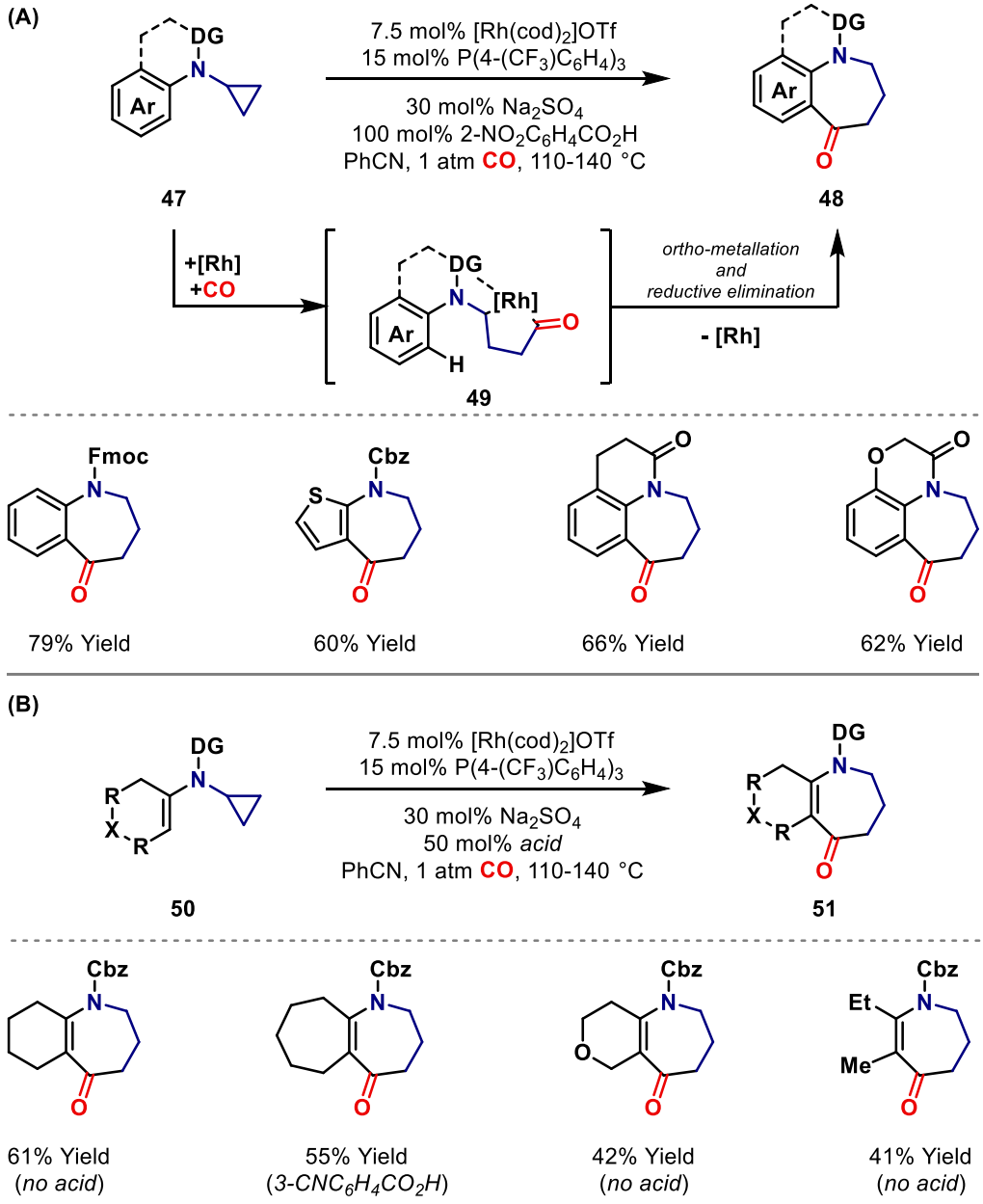
Scheme 8: Rh-catalysed carbonylative (7 + 1) cycloadditions of aminocyclopropanes and alkenes. [a] 10 mol% $[Rh(cod)_2]BARF$ and 10 mol% $P(4\text{-}(CN)C_6H_4)_3$ were employed.

Rhodacyclopentanones generated by directed carbonylative C-C bond activation of aminocyclopropanes are sufficiently electrophilic at the Rh-centre to engage conventional tethered protic nucleophiles (Scheme 9A). This "capture" event generates intermediate **42** which undergoes C-N or C-C bond forming reductive elimination and protodemetallation ("collapse") to provide challenging ring sizes (7- or 8-membered). Here, the relief of cyclopropane ring strain and the templating effect of the metallabicyclic intermediate (**42**) address the thermodynamic and entropic barriers that are typical of medium ring closures.[51,52] In a prototype study, this approach was used to access 1,3-diazepanes from NH ureas **43** (Scheme 9B).[53] C**4**-C**5** unsaturated systems **44** were generated selectively for systems with substituents at R^1. Conversely, saturated products **45** formed preferentially when R^1=H, presumably due to the increased stability of protonated Rh(III)-hydride **46**, such that β-hydride elimination to C**4**-C**5** unsaturated product occurs slower and C-H reductive elimination to **45** is preferred.



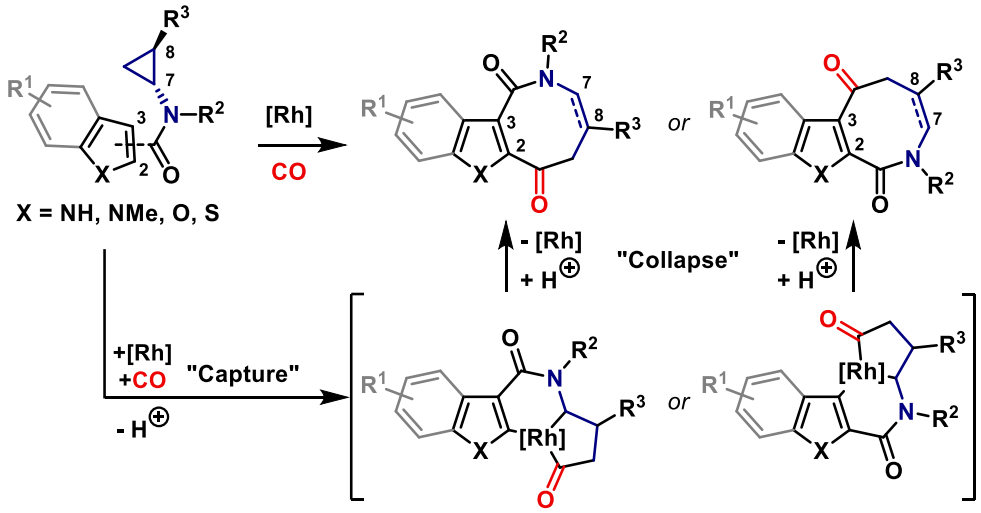
Scheme 9: Rh-catalysed carbonylative formation of 7-membered heterocycles from aminocyclopropanes.

The "capture-collapse" strategy extends to carbon-based nucleophiles. *N*-Aryl aminocyclopropanes **47** undergo efficient carbonylative ring expansion to provide pharmaceutically relevant benzazepines **48** (Scheme 10A).[54] Here the key rhodacyclopentanone intermediate (**49**) is used to effect *ortho*-metallation of the aryl unit in advance of the "collapse" sequence. Mechanistic studies suggest that all steps up to C-C reductive elimination are reversible. A relatively nucleophilic arene is required for metallation at the stage of **49**, suggesting that this process proceeds via an electrophilic aromatic substitution type mechanism. Based on this, investigations into other C-based nucleophiles were undertaken, and these studies showed that *N*-vinyl units (**50**) are also competent nucleophiles (Scheme 10B). This then allows access to non-benzofused azepines **51** in a direct manner.

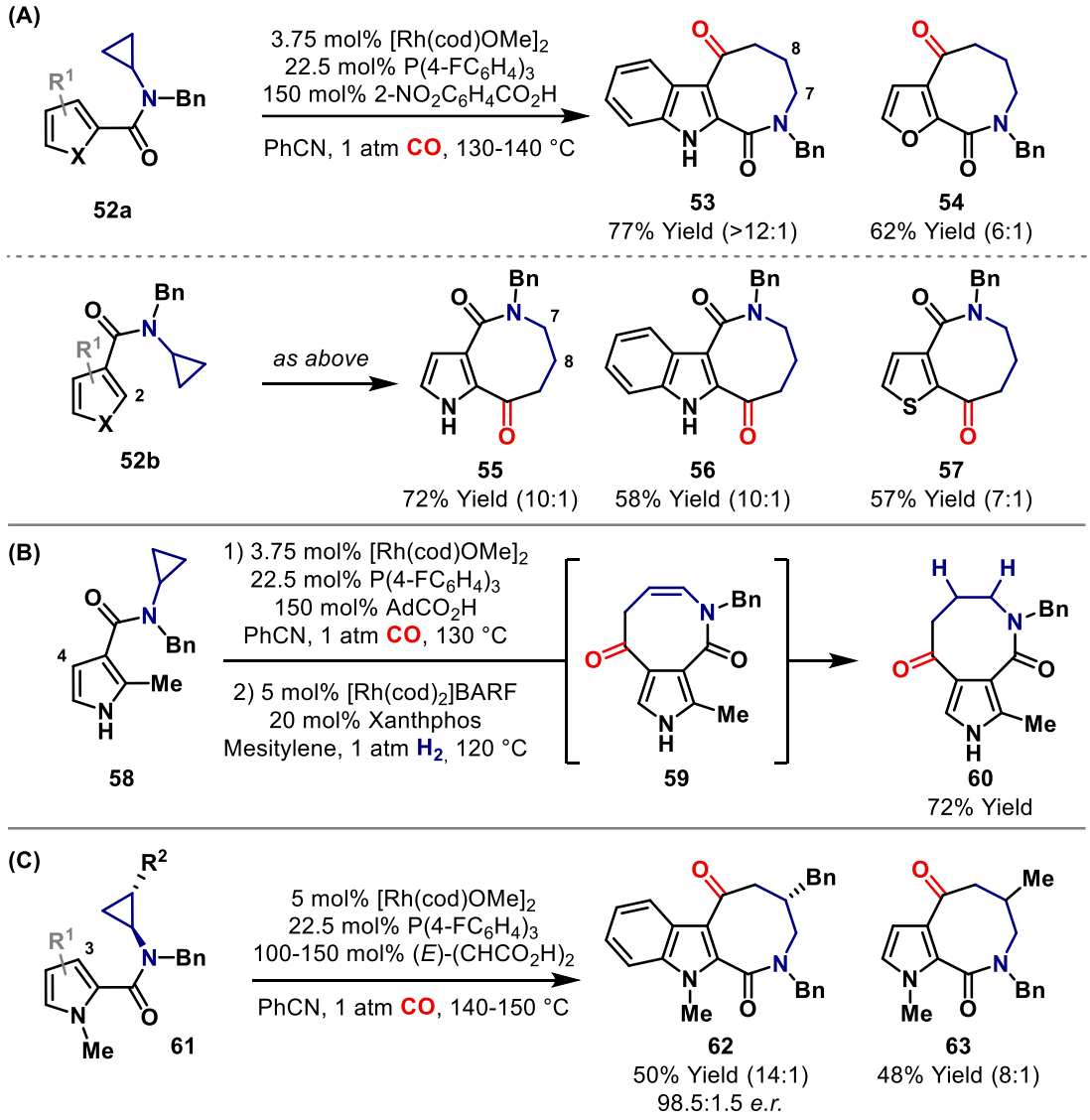


Scheme 10: Rh-catalysed carbonylative formation of azepines from (A) *N*-aryl cyclopropylamines; (B) *N*-vinyl cyclopropylamines.

The process described above is limited to the synthesis of 7-membered rings; however, if the substrate is redesigned so as the directing group and nucleophile are part of the same unit, then access to more challenging 8-membered rings is possible (Scheme 11).[55] Using this strategy, a variety of electron rich heteroarenes **52** underwent carbonylative heterocyclization via either C3 or C2 to provide challenging 8-membered heterocycles (e.g. **53-57**) (Scheme 12A). Extensive studies were undertaken to establish conditions that gave high selectivity for the C7-C8 saturated products over the corresponding unsaturated variants. Cyclization via C4 of pyrrole **58** was also demonstrated and this provided **59** and **60** in a 3:4 ratio (Scheme 12B). The low selectivity was resolved by using a separate hydrogenation step, which converted **59** to **60**. Processes involving substituted aminocyclopropanes provided access to adducts **62** (98.5:1.5 e.r.) and **63**; the former is derived from enantioenriched starting material and demonstrates that the process is enantiospecific (Scheme 12C). It should be noted, that for substituted aminocyclopropanes, N-H heterocyclic systems such as **52a,b** were inefficient and so *N*-Me heterocycles **61** were used instead.

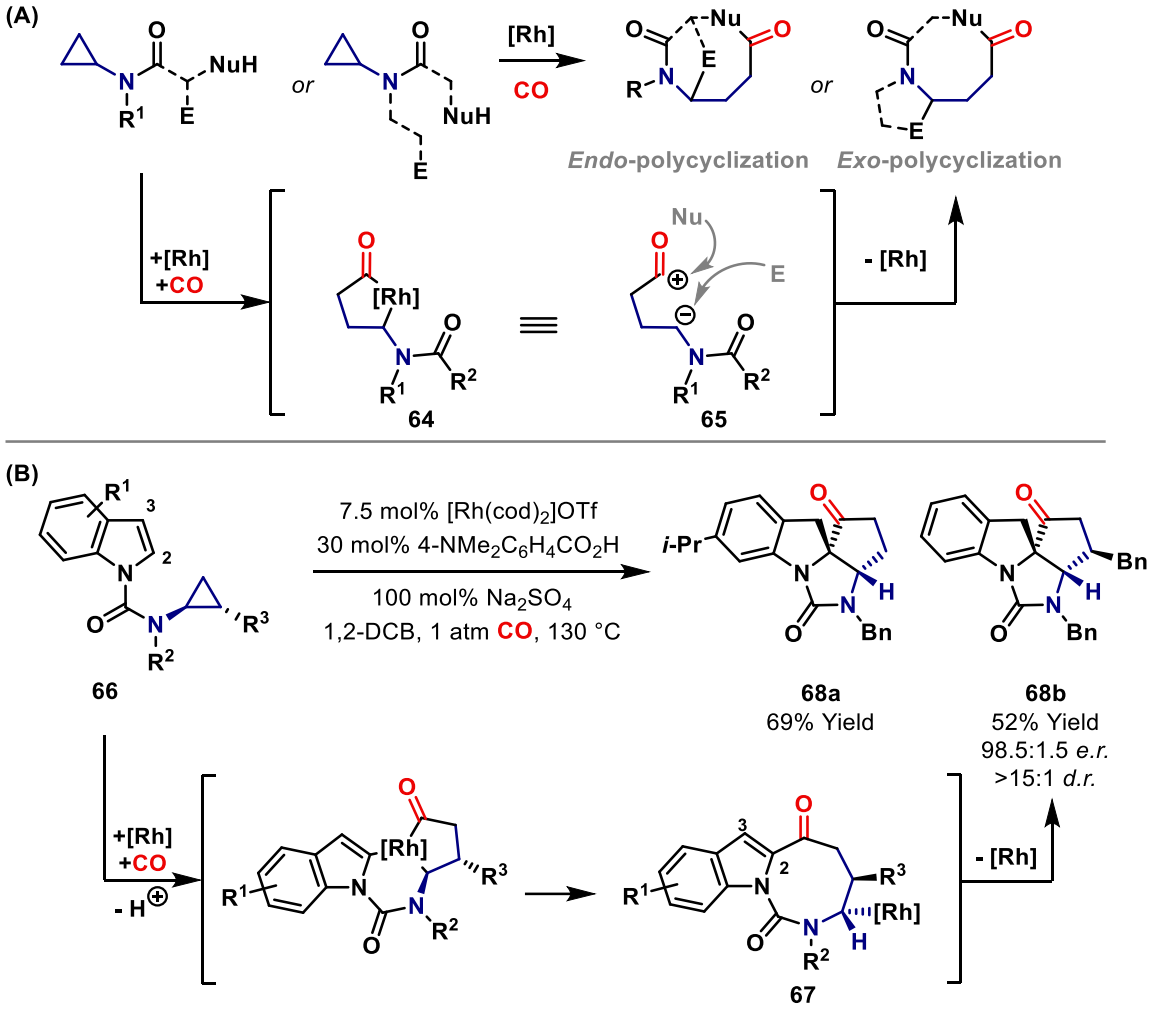


Scheme 11: Strategy to generate 8-membered *N*-heterocycles by C-C bond activation of aminocyclopropanes.



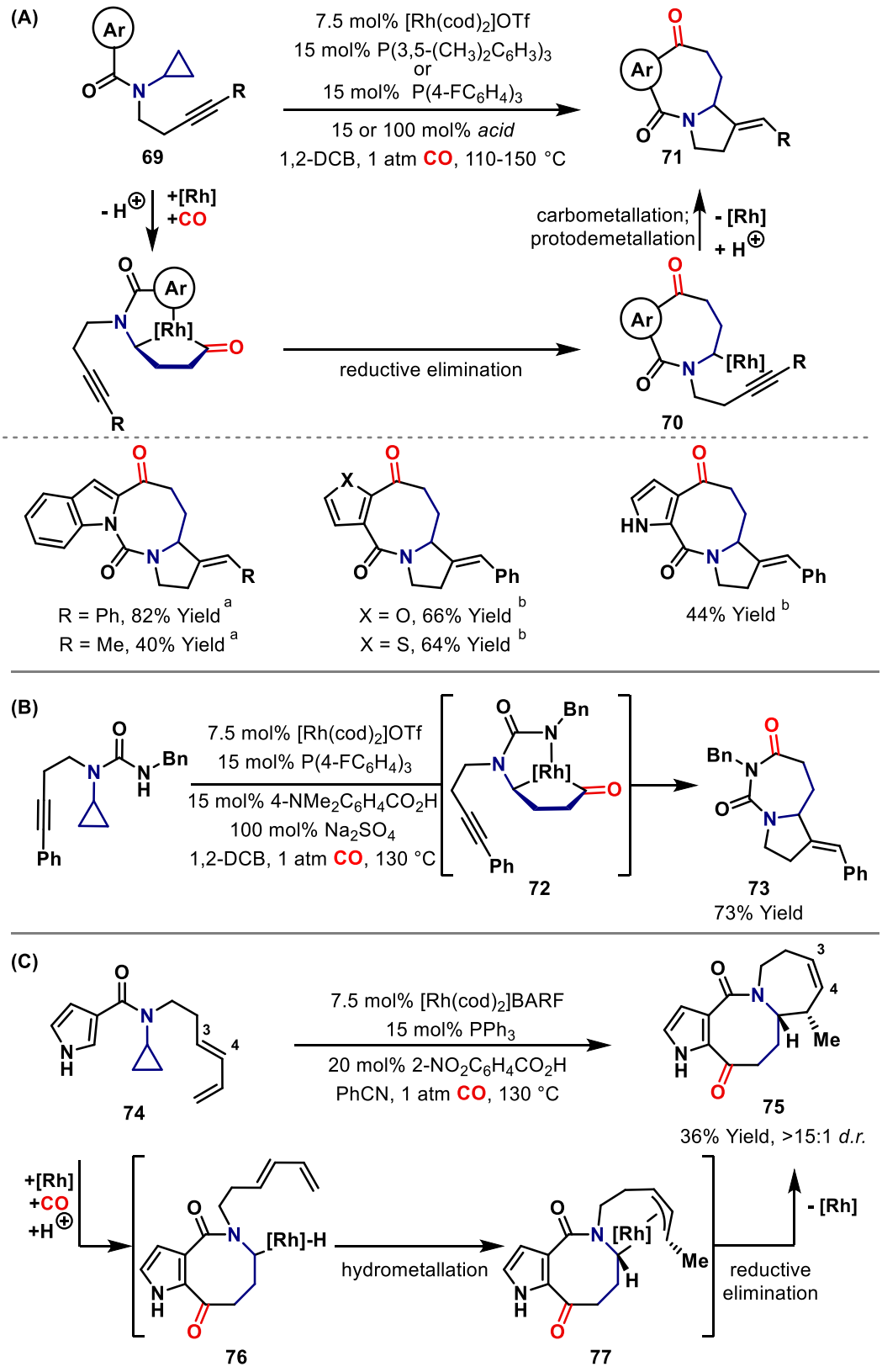
Scheme 12: Carbonylative C-C bond activation of aminocyclopropanes to generate 8-membered *N*-heterocycles.

The "capture-collapse" strategy can be extended to the formation of multiple ring systems by delaying the final protodemetallation step (see Scheme 9A). In this approach, C-Nu bond forming reductive elimination is followed by carbometallation of a formally electrophilic component prior to protodemetallation (Scheme 13A).[56] This approach offers high flexibility and uses the rhodacyclopentanone **64** as a synthetic equivalent to ambiphilic synthon **65**, thereby allowing the assembly of two rings instead of one. In one example of this methodology, it was shown that indoles **66** are competent nucleophiles leading to intermediates **67**. From here, carbometallation of the indole C2-C3 π-system is followed by protodemetallation to give complex polycycles **68** (Scheme 13B). The mechanism of this process was probed experimentally and by DFT studies.



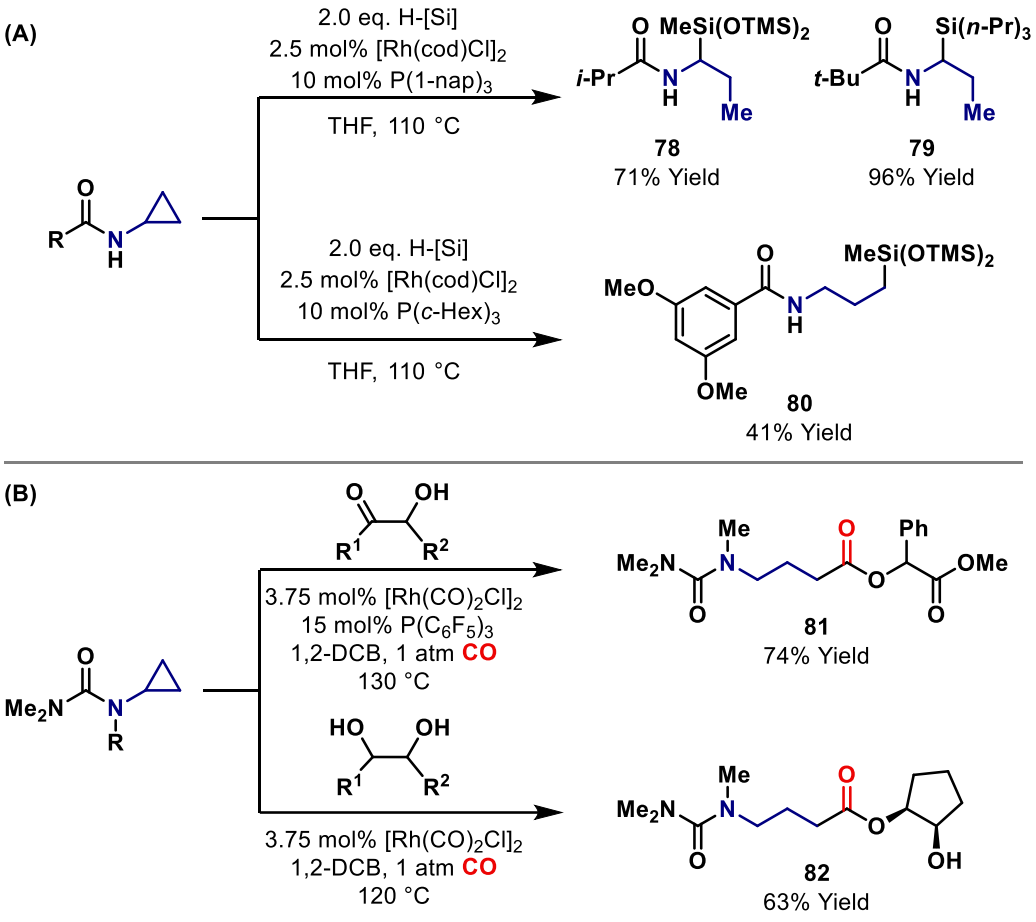
Scheme 13: Polycyclisations via rhodacyclopentanone intermediates.

Exo-selective polycyclizations can also be achieved (Scheme 14). For systems **69**, C-C reductive elimination generates **70** and this is followed by *syn*-stereospecific carbometallation of the alkyne prior to protodemetallation. A wide variety of electron-rich arenes participate efficiently, providing access to polycycles **71** (Scheme 14A). A related process gives access to bicyclic 1,3-diazepane **73** - here the first ring forms by C-N reductive elimination from **72** (Scheme 14B). Further studies on systems similar to **73** are discussed in Chapter 2. Other classes of electrophile can be used to initiate the second cyclization event (Scheme 14C). For the conversion of dienyl system **74** to polycycle **75**, a distinct mechanism was proposed involving protonation to Rh(III)-hydride **76** in advance of diene hydrometalation and C-C reductive elimination. The formation of Rh-π-allyl **77** prior to C-C reductive elimination accounts for the geometry switch observed at C3-C4.[57,58]



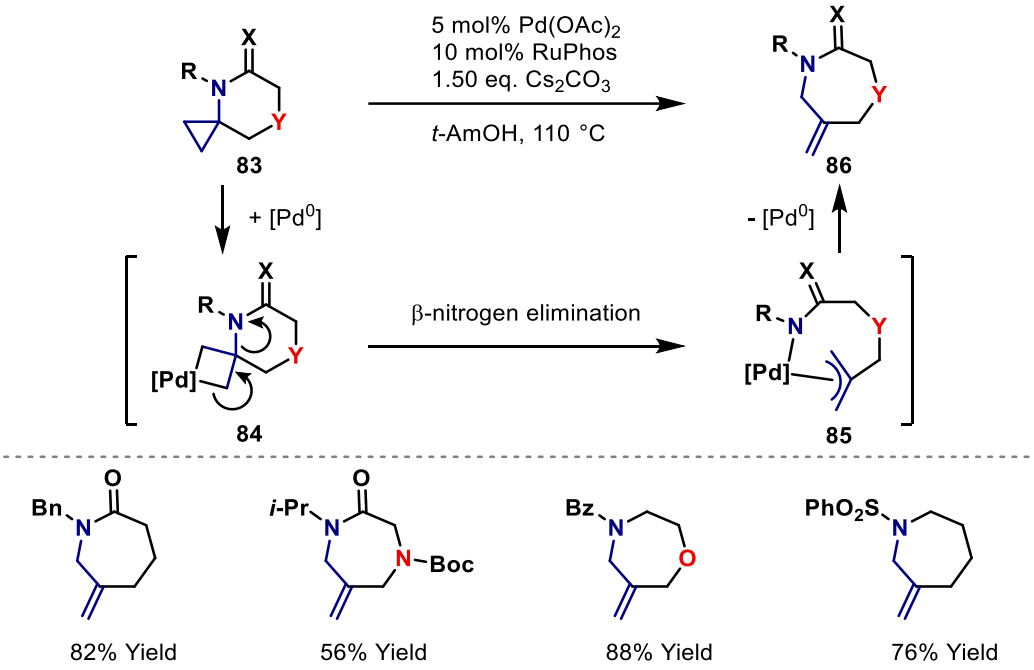
Scheme 14: Rh-catalysed *exo*-polycyclizations. [a]15 mol% 4-$NMe_2C_6H_4CO_2H$; [b]100 mol% 2-$NO_2C_6H_4CO_2H$

The methodologies developed in Bristol (Schemes 5-14) are intramolecular transformations. Under certain conditions Rh-catalysed directed C-C bond activation of aminocyclopropanes can be used for intermolecular processes. For example, the Yamaguchi group[59] reported regiodivergent Rh-catalysed hydrosilylations of protected aminocyclopropanes under non-carbonylative conditions (Scheme 15A). Branched products (e.g. **78** and **79**) were favoured when tri-1-naphthylphosphine (P(1-nap)$_3$) was used as ligand. Conversely, by using tricyclohexylphosphine, a more electron-rich and bulky ligand, the regioselectivity switched to give linear products such as **80**. Wang and co-workers[60] have shown that aminocyclopropane derived rhodacyclopentanones can be trapped by α-hydroxy carbonyl compounds or 1,2-diols to give esters, such as **81** and **82** (Scheme 15B); mechanistically, these processes are similar to the "capture-collapse" sequence shown in the Scheme 9A. It should be noted, that unsymmetrical diols gave poor regioselectivity and that the methodology is limited by the requirement for a non-labile urea directing group.



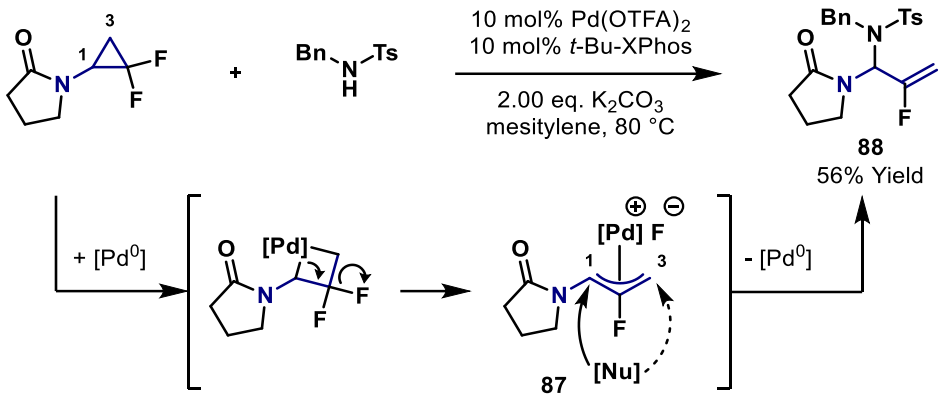
Scheme 15: Rh-catalysed transformations of aminocyclopropanes to linear products.

The processes described above employ Rh-based complexes as catalysts, but for certain systems Pd-catalysed processes have also been demonstrated. For example, uncommon regioselectivity for Pd-catalysed aminocyclopropane C-C bond cleavage was observed by Rene and co-workers[61] in the context of spiro-fused cyclopropanes **83** (Scheme 16). In this case, experimental and DFT studies supported Pd-insertion into the less hindered distal bond of the cyclopropylamine unit to give palladacyclobutane **84**. Collapse of this by β-nitrogen elimination generates π-allyl intermediate **85**, which undergoes C-N bond forming reductive elimination to provide the targets. The methodology provides access to interesting 7-membered *N*-heterocycles **86**, including examples containing multiple heteroatoms.



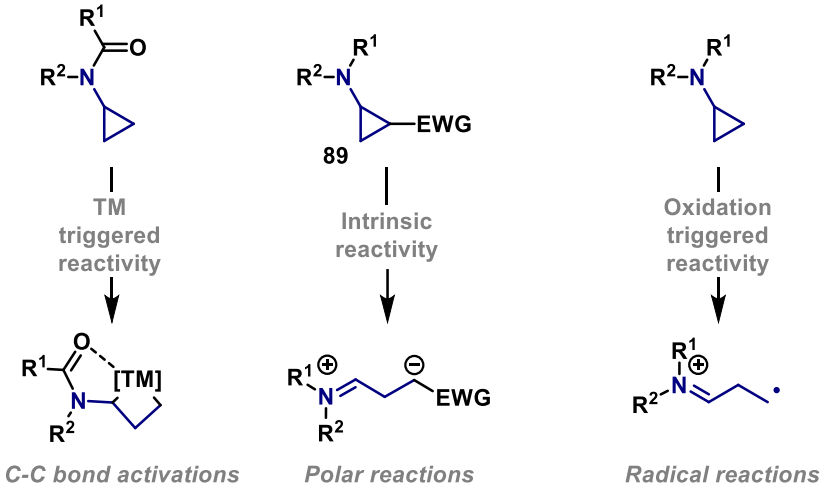
Scheme 16: Pd-catalysed cleavage of the distal bond of cyclopropylamine-based systems.

An isolated example of Pd-catalyzed C-C bond cleavage of a difluorocyclopropylamine derivative was reported by the Fu group (Scheme 17).[62] The proposed mechanism starts with insertion of palladium into the lengthened C**1**-C**3** bond of the cyclopropane.[63] Then, β-fluorine elimination from the palladacyclobutane gives π-allyl complex **87**, which is susceptible to attack by an external nucleophile. In this case, the preferred site of nucleophilic attack was at C**1**, generating branched product **88**. Interestingly, for other classes of difluorinated cyclopropane, the process led to alternate regioselectivity, where the nucleophile attacked at C**3**.



Scheme 17: Pd-catalysed cleavage of the C-C bond of a difluorocyclopropylamine.

The processes discussed in Section 1.3 involve cleavage of strained cyclopropylamine C-C bonds by oxidative addition of transition metal complexes. It is important to note that a range of alternate mechanistic options exist for promoting ring cleavage (Scheme 18). The N-lone pair of cyclopropylamines provides a "push", which means that cyclopropane rings are often relatively electron rich and can behave as competent nucleophiles in certain cases. This behaviour is present in donor−acceptor (DA) based systems **89**, which possess a highly labile cyclopropane C−C bond and have found wide use in reaction design.[64,65] The drawback of this approach is the prerequisite for an electron-withdrawing substituent on the cyclopropane ring. In addition to polar reaction pathways, oxidation to *N*-centred radicals can be used to trigger β-scission en route to reactive carbon-centred radicals.[66] This strategy has recently been employed to great effect in the development of cycloaddition reactions.[67-74]. For a detailed discussion of these and other processes, the reader is directed to the comprehensive review article cited at the beginning of this chapter.



Scheme 18: Ring cleavage modes available to aminocyclopropane derivatives.

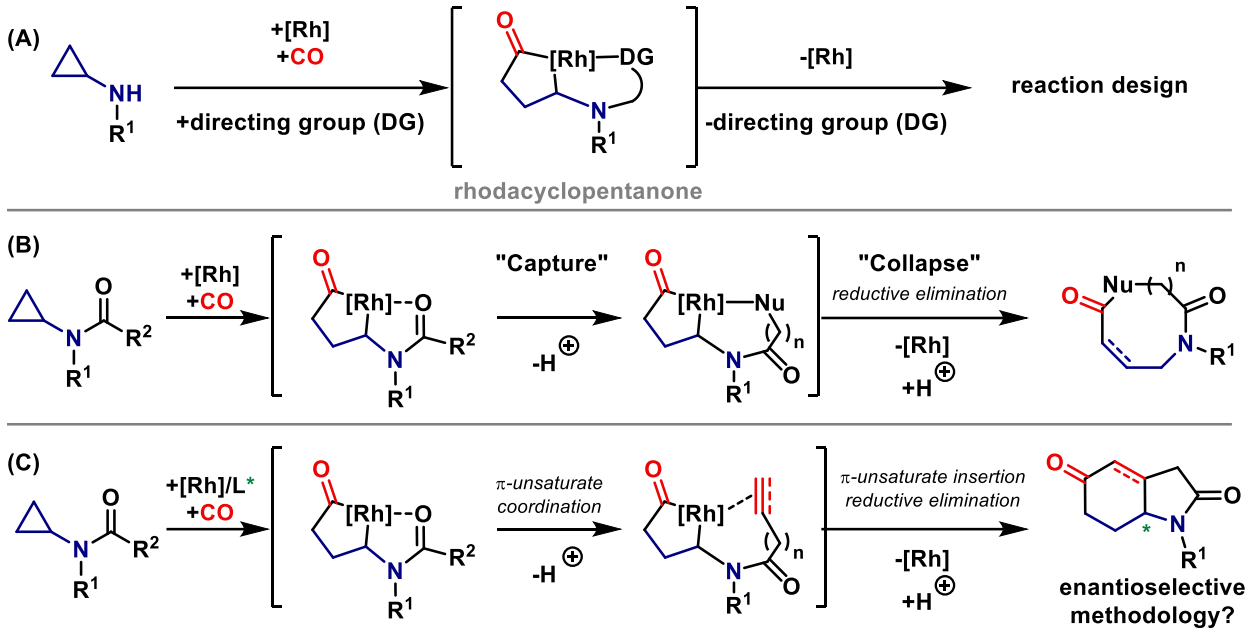
1.4 Project aims and thesis overview

Section 1.3 outlines a summary of previous work at Bristol on the use of aminocyclopropanes to form rhodacyclopentanone-based intermediates. The research contained within this dissertation explores further the carbonylative C-C bond activation of aminocyclopropanes and homologated structures (aminomethylcyclopropanes and aminocyclobutanes). The general aim of the studies was to exemplify Rh(I)-catalysed C-C activation with a variety of strained ring systems. The majority of reported methodologies involving C-C bond cleavage use activated substrates, which are often challenging to synthesise. Accordingly, the evaluation of readily available systems (e.g. aminocyclopropane derivatives) was prioritised. Specific research projects are described over five Chapters, and each Chapter is contextualised with a specific introductory section.

Known C-C bond activation processes involving aminocyclopropanes typically rely on a directing group to direct oxidative addition. As a result, the directing group becomes integrated into the reaction product. The work described in Chapter 2 details studies on the development of carbonylative transformation that employs a temporary directing group to generate the rhodacyclopentanone intermediate (Scheme 19A). Here, the temporary directing group is not incorporated into the final product, and the aim was to use such a process in a variety of cascade protocols.

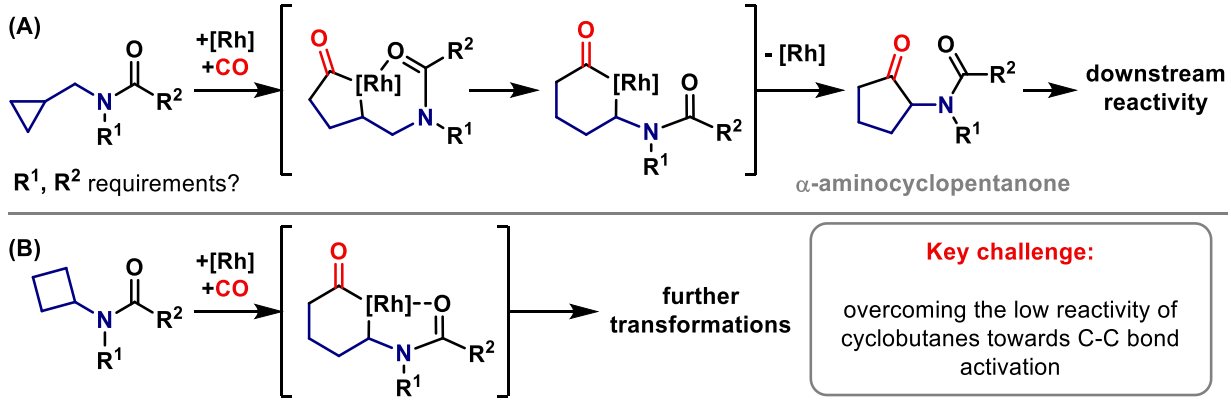
The goal of Chapter 3 was to demonstrate that rhodacyclopentanones can be trapped by various heteroatom-based nucleophiles (Scheme 19B). This work was inspired by seminal work from Bristol on the "capture" of rhodacyclopentanones with tethered urea-based nucleophiles.[53] Attempts were undertaken to develop a general set of conditions for the synthesis of 8-membered ring systems from cyclopropylamines bearing tethered anilines. Additionally, studies aimed at identifying alternate substrates bearing tethered nucleophiles are presented.

Chapter 4 describes studies aimed at developing a new class of substrate for intramolecular (3+1+2) cycloadditions between cyclopropylamines, CO and tethered π-unsaturates (Scheme 19C).[46,48] A key objective was to develop an asymmetric (3+1+2) cycloaddition, as such processes had not previously been realised. The studies described in this chapter represent the first highly enantioselective C-C bond activations of cyclopropylamines.



Scheme 19: Overview of the research described in Chapters 2-4.

The research described in Chapters 5 and 6 was conducted prior to Chapters 2-4, and focuses on generating and exploiting rhodacyclohexanones as key intermediates. Chapter 5 describes the use of these in a cyclopentanone forming reaction. The process is enabled by C-C bond activation of aminomethylcyclopropanes and builds upon previous studies at Bristol (Scheme 20A).[75] Finally, Chapter 6 details the synthesis of a range of cyclobutanes in pursuit of the first cyclobutane-based C-C bond activation process (Scheme 20B).



Scheme 20: Overview of the research described in Chapters 5 and 6.

CHAPTER 2

Temporary directing group-enabled C-C bond activation of aminocyclopropanes

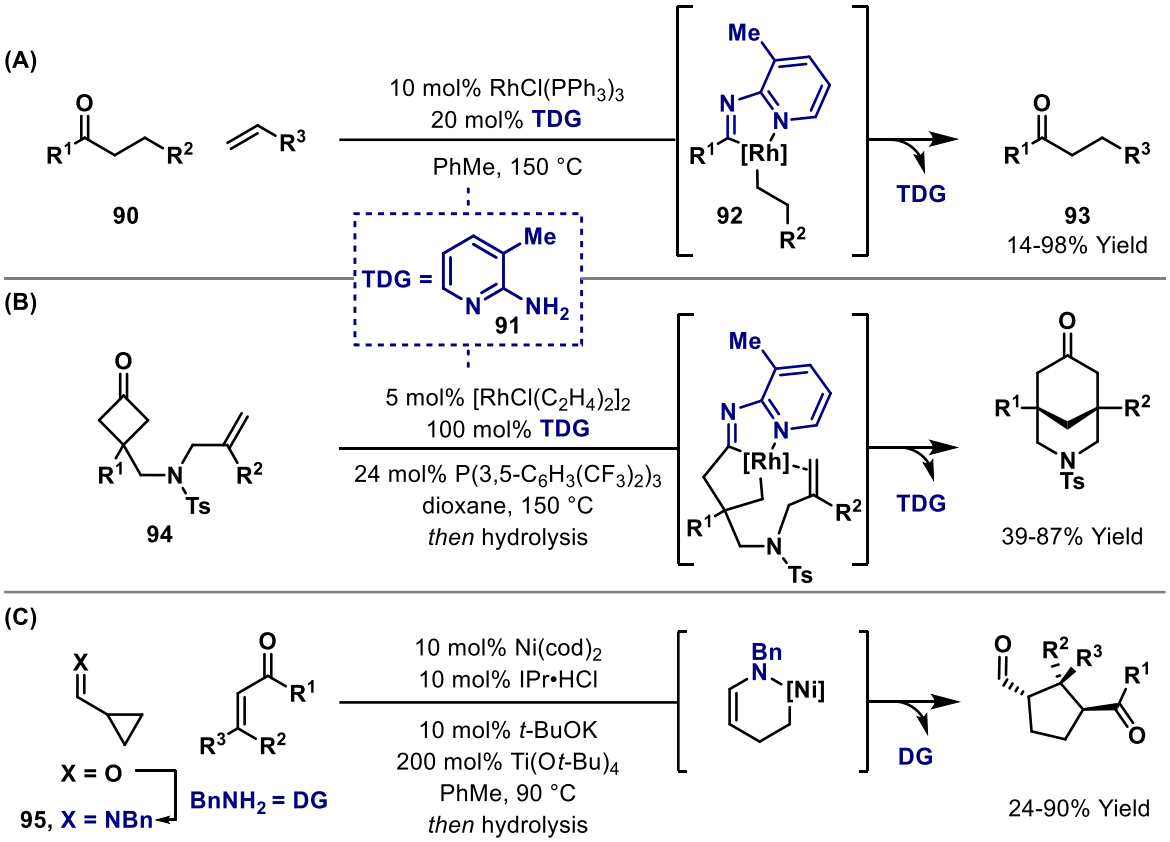
Aspects of this Chapter have been adapted from a communication.

(Wang, G.-W.†; Sokolova, O. O.†; Young, T. A.; Christodoulou, E. M. S.; Butts, C. P.; Bower, J. F. *J. Am. Chem. Soc.* **2020**, *142*, 19006. †G.-W. Wang and O. O. Sokolova contributed equally)

2.1 Introduction

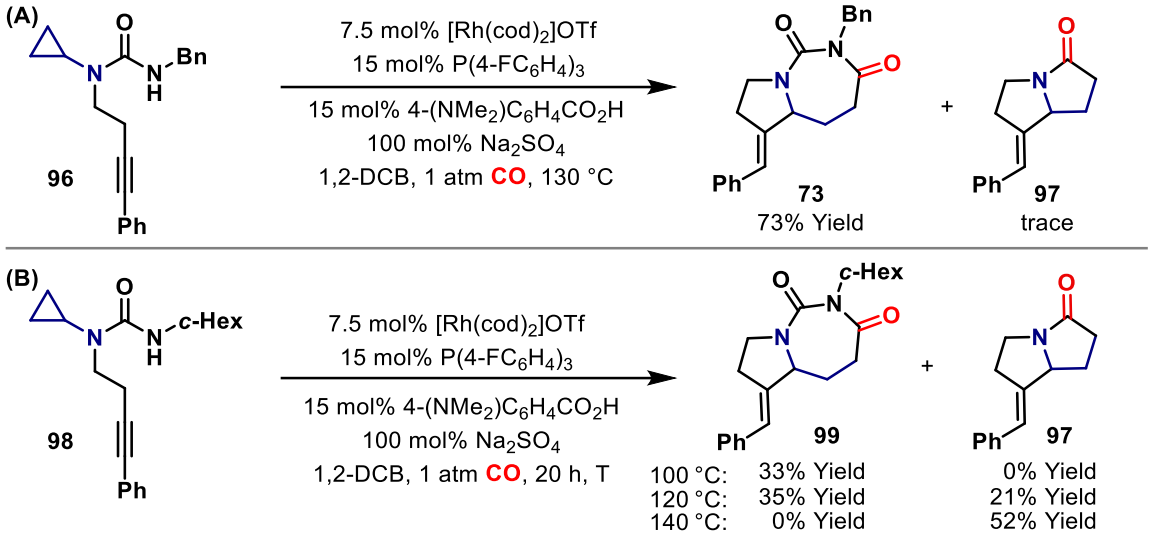
Methods based on catalytic C-C bond activation commonly require directing groups to accelerate the rate and control the regioselectivity of metal insertion.[1-4,12,76-78] "Permanent" directing groups have been used to facilitate the activation of a relatively broad range of C-C bonds.[38,79-92] Section 1.3 outlines the directing group (DG) strategy developed in Bristol for the Rh-catalysed C-C bond activation of aminocyclopropanes. A key feature of such processes is the use of an *N*-carbonyl-based directing group, which either becomes part of the new ring system or, in some cases (e.g. *N*-Cbz), can be removed after the C-C bond activation process. On the other hand, "temporary" directing groups (TDGs) are potentially more powerful because they can avoid the need for discrete DG installation and removal steps. Jun's seminal works[93-95] achieved activations of ketone-based substrates such as **90** via condensation with 2-amino-3-picoline **91** to generate the corresponding imines (Scheme 21A). Pyridine-directed C-C bond activation of these delivers intermediate **92** which, after β-hydride elimination, alkene hydrometallation and C-C reductive elimination affords linear ketones **93**. More recently, this strategy has been developed significantly by Dong and co-workers,[96-99] who used the 2-amino-3-picoline-derived TDG for the activation of small cyclic ketones. Of particular relevance to the research discussed in this chapter are examples involving 4-membered ring systems **94**, based on cyclobutanones (Scheme 21B).[32] By contrast, the use of TDGs for the activation of 3-membered carbocycles (e.g. cyclopropanes) is virtually unknown. Perhaps the closest precedent is Montgomery's use of cyclopropanal-derived imines **95** in Ni-catalysed (3+2) cycloadditions (Scheme 21C).[100,101] Here, discrete steps were required for DG installation and removal, although there is evident potential for refinement to a "full" TDG-based protocol. An impediment in this area is that, until recently, most C-C bond activation methodologies involving 3-membered carbocycles required highly activated or specialized variants (e.g. spirocyclopropanes, cyclopropenes, alkylidene cyclopropanes).[2] These systems are usually unstable and not easily adapted to TDG-based settings. Thus, the identification

of a suitable system for TDG-assisted C-C bond activation of unactivated cyclopropanes is highly desirable.



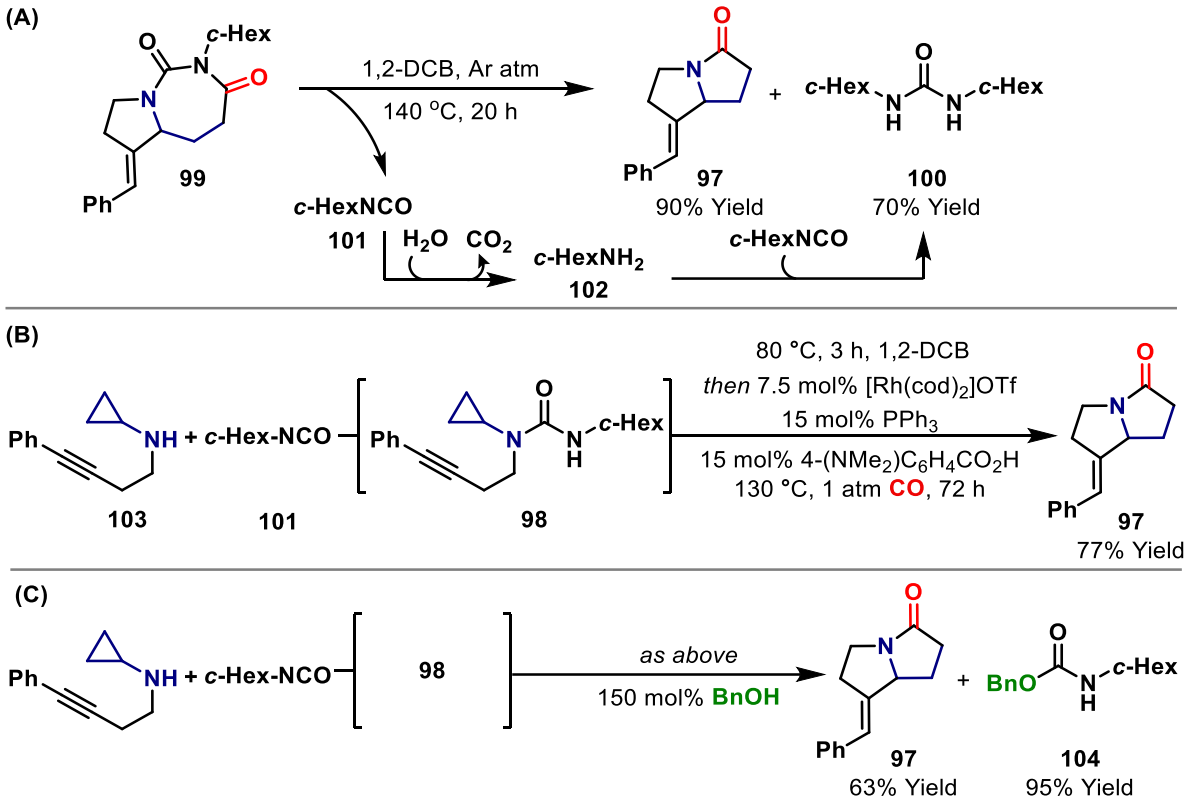
Scheme 21: Known temporary directing groups used in C-C bond activation.

Initial studies on this research topic were undertaken by Dr Gang-Wei Wang, a postdoctoral researcher in the Bower group. Upon prolonged heating of urea-protected substrate **96** under Rh-catalysed carbonylative conditions, he observed the formation of trace amounts of γ-lactam **97** in addition to expected product **73** (Scheme 22A); the formation of **73** is described in detail in section 1.3 (Scheme 14B).[56] When the *N*-benzyl substituent of **96** was changed to a cyclohexyl unit, 5,5-fused ring system **97** was generated as the major product and its yield increased when the temperature was raised (Scheme 22B); for example, at 120 °C **97** was obtained in 21% yield, whereas at 140 °C the yield increased to 52%.



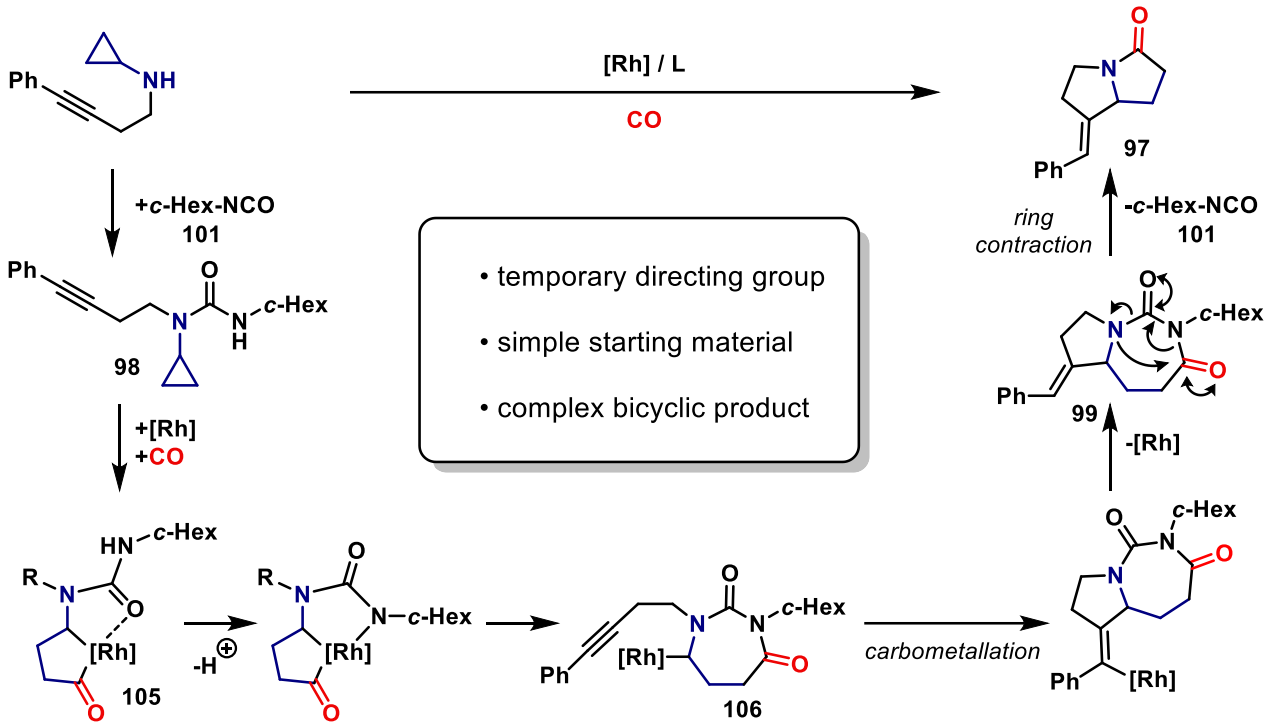
Scheme 22: Preliminary results for the formation of the 5,7-fused ring systems obtained by Wang.

A control experiment was performed in which diazepane **99** was isolated and heated to 140 °C in 1,2-dichlorobenzene. This provided γ-lactam **97** in excellent yield along with urea **100**. It was reasoned that the formation of **100** may be due to cyclohexyl isocyanate **101** being generated in the course of the reaction. Hydrolysis of **101** would form amine **102**, which could react with a second equivalent of isocyanate to provide urea **100** (Scheme 23A). The starting material **98** can be prepared in high yield by heating amine **103** in the presence of cyclohexyl isocyanate **101**. This allowed Dr Wang to develop a streamlined two-step one-pot procedure, where urea **98** is formed *in situ* prior to the C-C bond activation induced cascade (Scheme 23B). To prove further that isocyanate is released under these conditions, benzyl alcohol was used as an additive. In this experiment, carbamate **104** was obtained in high yield, which is consistent with the attack of benzyl alcohol onto isocyanate **101** (Scheme 23C).



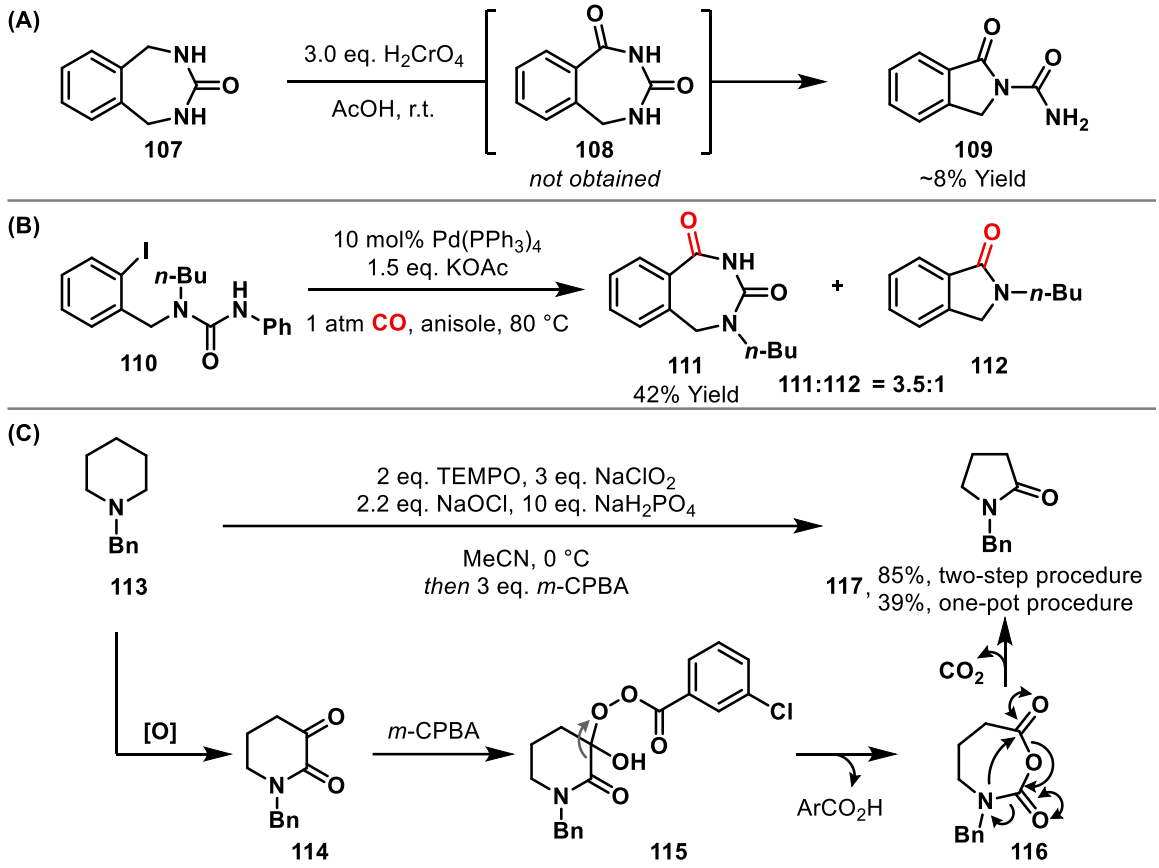
Scheme 23: Mechanistic investigations of the ring contraction cascade and a one-pot procedure developed by Wang.

Based on the observations outlined above, a plausible mechanism for the formation of **97** is presented on Scheme 24. The process commences with the formation of urea **98**, and this allows directed Rh(I) oxidative insertion into the cyclopropane prior to migratory insertion of CO, which delivers rhodacyclopentanone **105**. After directing group dissociation, the pendent nucleophilic N-H group coordinates to the cationic Rh(III) complex and, following deprotonation, C-N reductive elimination generates alkyl-Rh(I) species **106**. Carbometallation of the tethered alkyne forms the second 5-membered ring, and protodemetallation affords **99**. From here, intramolecular nucleophilic attack of nitrogen induces the ring contraction with concomitant expulsion of isocyanate **101** to deliver the target **97**. Thus, the directing group is appended and then "disappears" over the course of the reaction.



Scheme 24: Plausible mechanism for the ring contraction cascade.

Ring contractions related to **99** to **97** are unusual, and only a few examples have been reported (Scheme 25). In 1968, Felix and Fryer attempted the synthesis of 2,4-benzodiazepane-1,3-dione **108** by oxidation of compound **107**.[102] The desired product could not be isolated and, after evaluating various oxidation conditions, only compound **109** was obtained (Scheme 25A). Later, Ferraccioli and co-workers described Pd(0)-catalysed carbonylative cyclisation of urea **110** (Scheme 25B).[103] This provided significant quantities of ring contraction product **111** in addition to expected product **112**. The formation of **109** and **112** can both be rationalised by expulsion of an isocyanate. A related deconstructive lactamisation with carbon dioxide as a leaving group has been reported recently by the Sartillo-Piscil group (Scheme 25C).[104] In this two-step methodology, sequential oxidation of piperidine derivatives, such as **113**, delivers piperidine-2,3-dione **114** and then seven-membered cycle **116** via intermediate **115**. From here, decarboxylative cyclisation gives lactam **117**.



Scheme 25: Known ring contractions leading to γ-lactam-containing products.

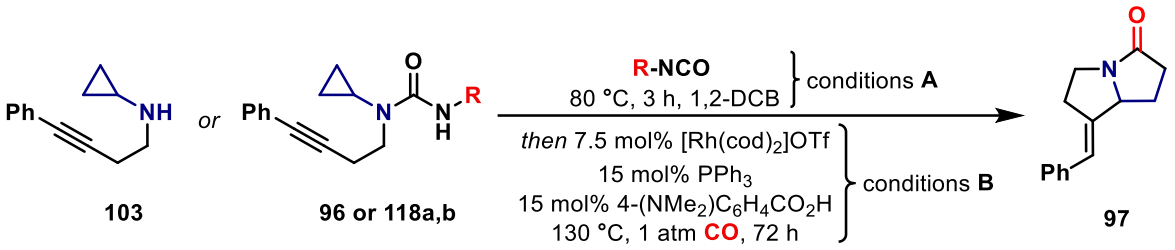
As demonstrated above, the state-of-art of TDGs in C-C bond activation is limited to carbonyl-containing starting materials (Scheme 21). Additionally, none of the ring contractions in Scheme 25 use a transient directing group or C-C bond activation to access γ-lactam scaffolds. The process discovered in Bristol (Scheme 23) demonstrates the unprecedented use of TDG-assisted C-C bond activation of aminocyclopropanes for the formation of γ-lactams. With a suitable system for the ring contraction cascade identified, further developments were directed at showcasing the strategy.

2.2 Further developments of the temporary directing group enabled C-C bond activation of aminocyclopropanes

2.2.1 Further mechanistic considerations

The effect of different isocyanates on the ring contraction was investigated further to identify an optimal *N*-substituent (Table 1). The **R** substituent was evaluated using ureas **96** and **118a,b** under Rh-catalysed carbonylative conditions (7.5 mol% $[Rh(cod)_2]OTf$, 15 mol% PPh_3, 1,2-DCB, 130 °C, "conditions **B**"). Alternatively, the urea unit was installed on amine **103** *in situ* by reaction with the isocyanate at 80 °C in 1,2-DCB ("conditions **A**"), followed by addition of the components required for the carbonylative heterocyclisation/ring contraction sequence

("conditions **B**"). It was found that reaction of *N*-benzyl-substituted **96** gave a moderate yield of the desired γ-lactam **97** at elevated temperature, while *N*-phenyl-substituted urea **118a** caused a significant decrease of yield (Table 1, Entries 1 and 2). Installing tertiary *N*-substituents on the urea, e.g. *tert*-butyl and 1-adamantyl proved to be completely inefficient, indicating that there is a fine balance in the overall reaction with respect to the **R** substituent's steric bulk (Table 1, Entries 3 and 4). Secondary isocyanates, such as isopropyl isocyanate, worked well for the ring contraction in general. However, isocyanates with cyclic substituents, such as cyclopentyl or cyclohexyl isocyanate performed better than those possessing acyclic groups (Table 1, Entries 5-7). Although both cyclopentyl and cyclohexyl isocyanate gave comparable yields of **97** (78-80%), the reaction conditions in Entry 7 were identified as "optimal" because cyclohexyl isocyanate is much cheaper than the cyclopentyl analogue (£0.03/mmol vs. £3.09/mmol).[105]



Entry	Conditions	Starting material	R	Yield of 97[a] (%)
1	**B**[b,c]	**96**	Bn	57
2	**B**[c]	**118a**	Ph	<20
3	**B**[c]	**118b**	*t*-Bu	0
4	**A**, then **B**	**103**	1-Adamantyl	0
5	**A**, then **B**	**103**	*i*-Pr	65
6	**A**, then **B**	**103**	*c*-Pent	80
7	**A**, then **B**[c]	**103**	*c*-Hex	78 (77)

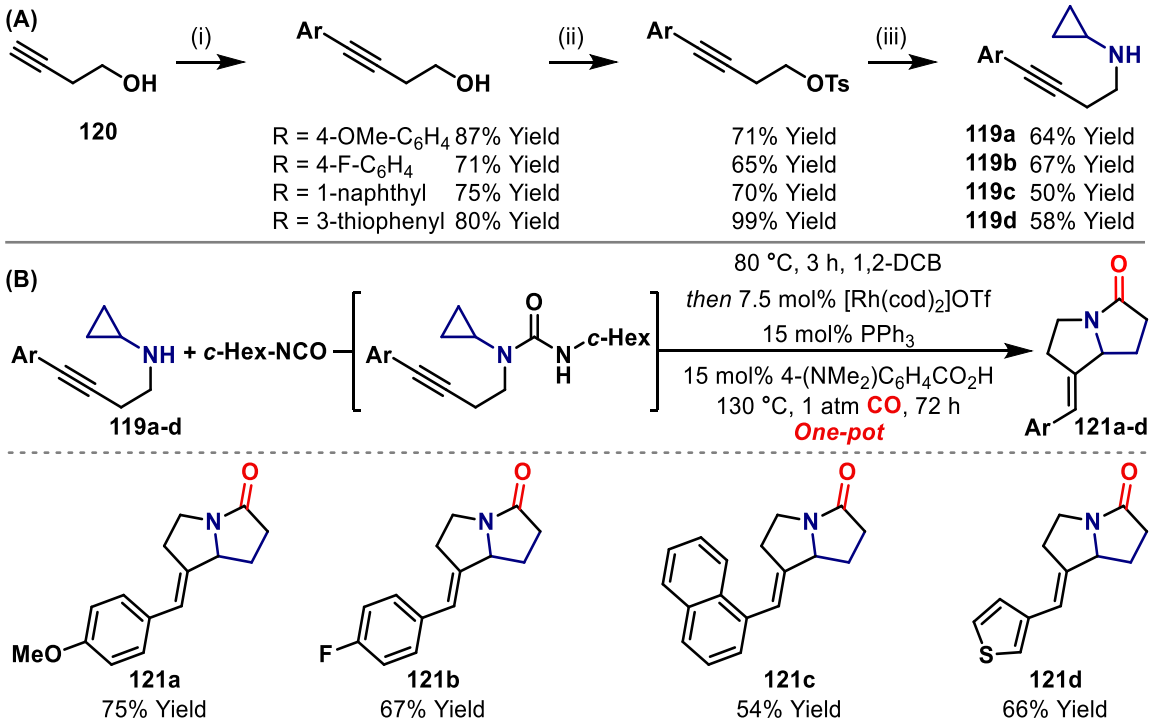
Table 1: Directing group substituent studies for the ring contraction cascade. [a] Yields were determined by ^{1}H NMR spectroscopy using 1,4-dinitrobenzene as a standard. Isolated yields are given in parentheses. [b] Reaction performed at 140 °C. [c] Result obtained by Wang.

2.2.2 Scope of the alkyne in the cascade reaction

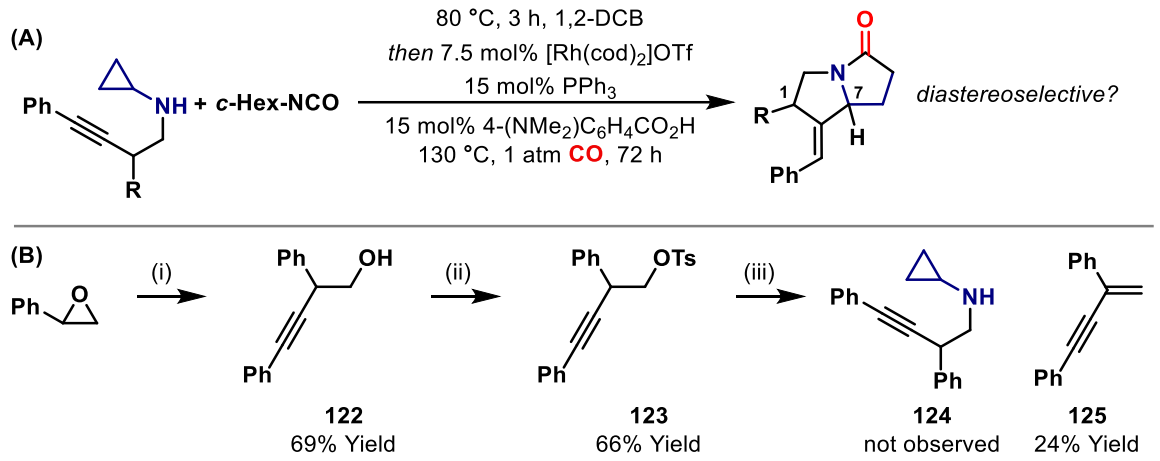
As discussed earlier (Section 2.1), Wang had discovered an efficient diazepane formation-ring contraction cascade for substrate **103** (cf. Scheme 23B). To evaluate scope, a range of cyclopropylamines **119a-d** containing tethered alkynes with different aromatic substituents at the terminal position was synthesised. This was achieved from alkyne **120** via sequential Sonogashira reaction, alcohol tosylation and nucleophilic substitution with cyclopropylamine (Scheme 26A). Pleasingly, these substrates all performed well under the standard reaction conditions regardless

of the substituent's electronics, delivering γ-lactams **121a-d** in high to moderate yields (Scheme 26B).

Next, the effect of α-substitution on the alkyne was evaluated. The key question was whether the reaction would exhibit innate control over the stereorelationship between C1 and C7 (Scheme 27A). To this end, the synthesis of α-phenyl-substituted starting material **124** was attempted. Tosylate **123** was generated via regioselective alkynylation of styrene oxide with triisopropoxy titanium acetylide,[106] followed by treatment of the resulting alcohol **122** with TsCl. Unfortunately, the subsequent alkylation of cyclopropylamine with **123** was problematic and target **124** was not observed (Scheme 27B). Instead, elimination predominated to provide alkene **125**; the facility of this competing process can be rationalised by the steric hinderance around the electrophilic centre, as well as the favourable formation of a new conjugated π-bond.



Scheme 26: Synthesis and reactivity of cyclopropylamines **119a-d**. *Reagents and conditions*: (i) $PdCl_2(PPh_3)_2$, CuI, Ar-I or Ar-Br, Et_3N, r.t. or 60 °C; (ii) TsCl, Et_3N, DMAP, DCM, 0 °C to r.t.; (iii) cyclopropylamine, MeCN, reflux.



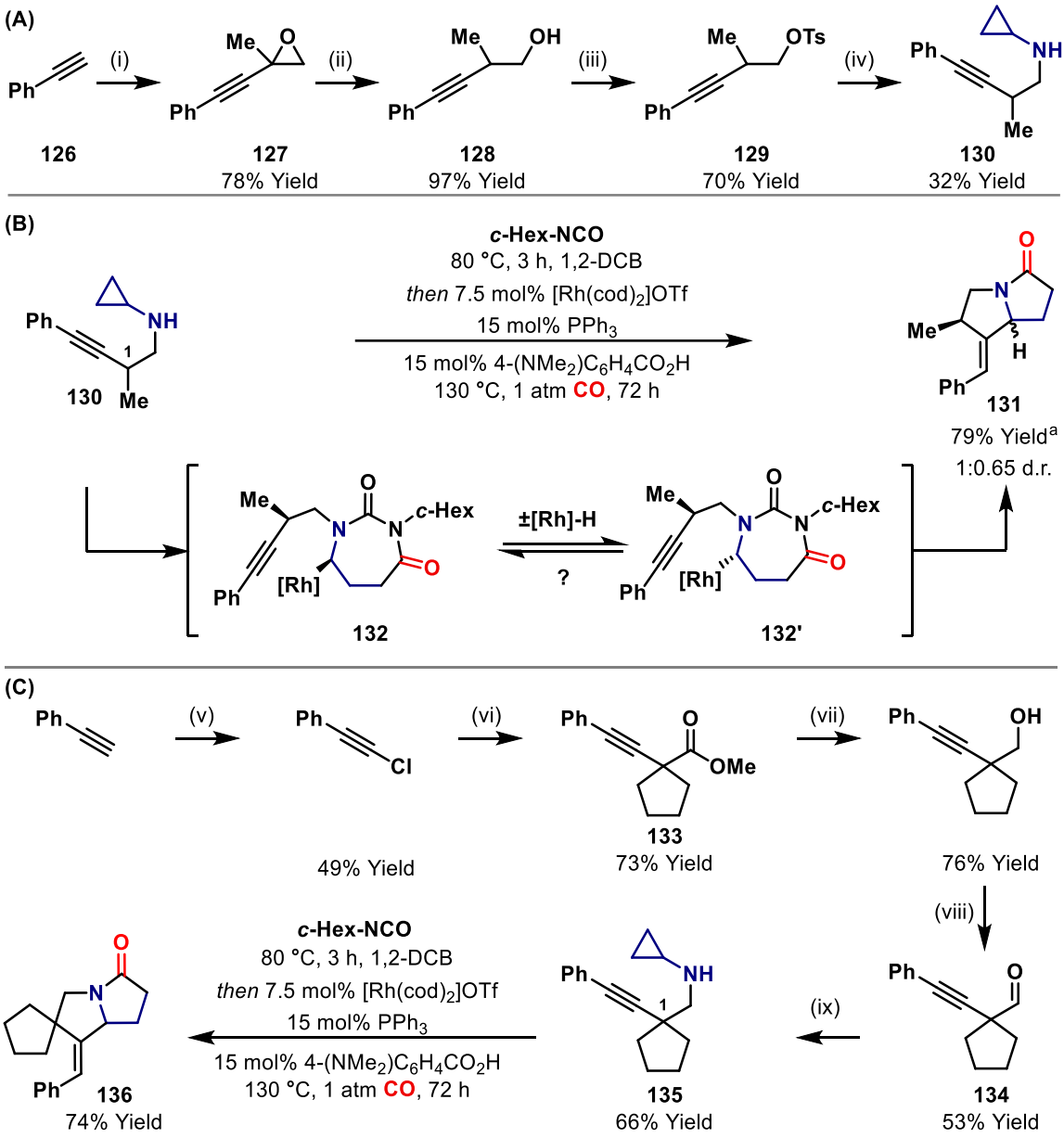
Scheme 27: Attempted synthesis of **122**. *Reagents and conditions*: (i) (a) Ti(O*i*-Pr)$_4$, TiCl$_4$, hexane, r.t.; (b) *n*-BuLi, phenylacetylene, THF, 0 °C to r.t., then ClTi(O*i*-Pr)$_3$, styrene oxide, -41 °C to r.t.; (ii) TsCl, Et$_3$N, DMAP, DCM, 0 °C to r.t.; (iii) cyclopropylamine, MeCN, reflux;

Subsequently, substrate **130** containing an α-methyl substituent was targeted (Scheme 28A). The synthesis commenced with Darzens reaction of phenylacetylene **126** with chloroacetone to give **127**. Regioselective reductive oxirane opening[107] using DIBAL-H gave alcohol **128**, which was converted to tosylate **129**. This product was used for the alkylation of cyclopropylamine to give target amine **130** in moderate yield.

When amine **130** was subjected to optimised carbonylative conditions, γ-lactam **131** was formed as a 1:0.65 mixture of diastereomers, thereby demonstrating poor diastereocontrol (Scheme 28B). The lack of diastereocontrol is not surprising if oxidative addition of the Rh(I)-catalyst into cyclopropane is the stereodetermining step; in this scenario, high diastereocontrol requires the substituent at C1 to bias Rh-insertion into one of the two diastereotopic cyclopropane C-C bonds. Based on earlier diastereoselective C-C bond activation protocols developed in Bristol,[48,108] it may be assumed that the d.r. of **131** depends on the stereochemistry of alkyl Rh(I)-intermediate **132**. It is possible that equilibration of **132** and **132'** can occur via reversible β-hydride elimination, this would provide a mechanism for achieving diastereocontrol. The low diastereoselectivity observed for **130** to **131** therefore indicates that either (a) the rates of carbometallation from **132** and **132'** are comparable or (b) reversible β-hydride elimination does not occur and diastereoselectivity is solely governed by the carbonyl-directed C-C oxidative addition step, which generates **132** and **132'** in nearly equal amounts.

To circumvent the issue of poor diastereoselectivity, *spiro*-cyclopentyl-containing amine **135** was synthesised. This was achieved by a sequence of electrophilic alkynylation of methyl cyclopentanecarboxylate, a two-step conversion of ester **133** to aldehyde **134**, and reductive amination with cyclopropylamine (Scheme 28C). Pleasingly, *spiro*-substituted amine **135** gave

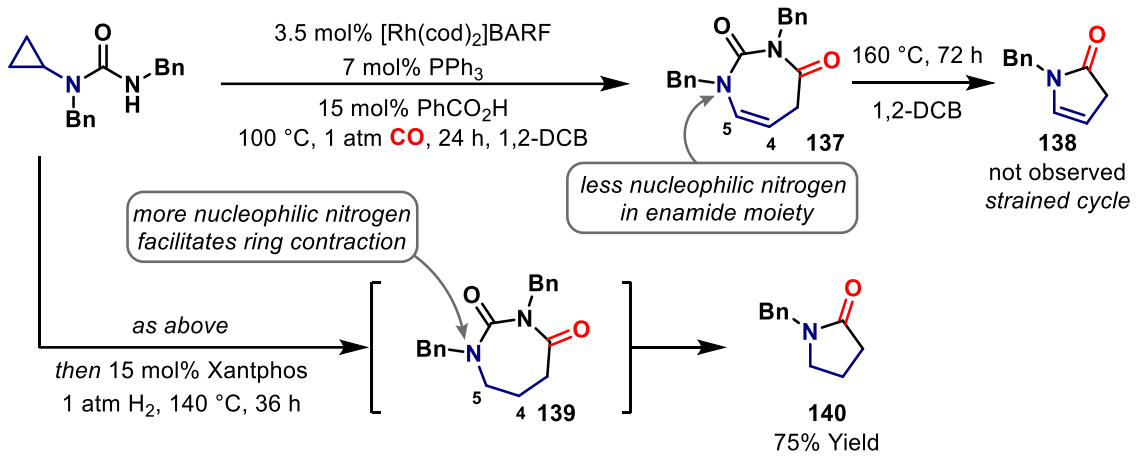
tricyclic product **136** in high yield, indicating that the reaction is relatively insensitive to the steric effects of substitution at C1.



Scheme 28: Synthesis and reactivity of cyclopropylamines **130** and **135**. [a]Yield was determined by ^{1}H NMR spectroscopy using 1,4-dinitrobenzene as a standard. *Reagents and conditions*: (i) *n*-BuLi, chloroacetone, THF, -41 °C to -78 °C to r.t.; (ii) DIBAL-H; THF, -20 °C to r.t.; (iii) TsCl, Et_3N, DMAP, DCM, 0 °C to r.t.; (iv) cyclopropylamine, MeCN, reflux; (v) *n*-BuLi, NCS, THF, -78 °C to r.t.; (vi) methyl cyclopentanecarboxylate, LDA, THF, -78 °C to r.t.; (vii) DIBAL-H, THF, -78 °C to 0 °C; (viii) PCC, silica gel, DCM, r.t.; (ix) cyclopropylamine, $MgSO_4$, DCM, r.t., then $NaBH_4$, MeOH, 0 °C to r.t.

2.2.3 Hydrogenation - ring contraction cascade of diazepanes and computational studies

The possibility of ring contractions of unsaturated 7-membered rings was also examined. Wang attempted the thermal ring contraction of unsaturated diazepane **137**, which can easily be synthesised by the group's previously developed catalytic methodology,[53] but did not obtain dihydropyrrol-2-one **138** (Scheme 29). The failure of this process may be due to the increased strain of **138** vs. **140** and/or the lower nucleophilicity of the nitrogen centre of **137** vs. **139** (as a result of cross-conjugation with the adjacent C4-C5 π-bond). To circumvent this issue, after carbonylative cyclisation, the C4-C5 double bond of **137** was hydrogenated to give **139**, which, under the high reaction temperature, contracted to give lactam **140**. The carbonylative cyclisation and hydrogenation steps were achieved using the same Rh(I)-source; after completion of the first step, Xantphos ligand and H_2 were added to facilitate the reduction process.



Scheme 29: Hydrogenation - ring contraction sequence developed by Wang.

The ring contraction of diazepanes to γ-lactams is unusual and has not previously been interrogated mechanistically. Accordingly, DFT studies were performed by Tom A. Young, a collaborator from the University of Oxford. Using simplified system **141a**, an energetically feasible concerted pathway was found for expulsion of methyl isocyanate. In this process, the C2-N1 bond cleaves as attack of N6 onto C2 occurs (Figure 2). The energy barrier of 33.5 kcal/mol for **TS1a** is consistent with the reaction conditions (150 ºC, ~1 day). A more conventional stepwise addition-elimination mechanism was discounted because tetrahedral **TS2** could not be located on the potential energy surface and is > 100 kcal/mol less stable than **141a**. The concerted nature of the ring contraction process is similar to recently reported ring contractions of cyclic *N*-carboxyanhydrides (cf. Scheme 25C).[104] In the process outlined in Figure 2, the nucleophilicity of the N6 center is key: ring contraction of unsaturated system **141b**, where cross-conjugation with the alkene likely diminishes the nucleophilicity of the nitrogen lone pair, has a higher energy

barrier (**TS1b**, $\Delta G^{\ddagger}$ = 39.7 kcal mol^{-1}). This result is consistent with the observation that unsaturated **141b** does not undergo ring contraction to *dehydro*-**142**.

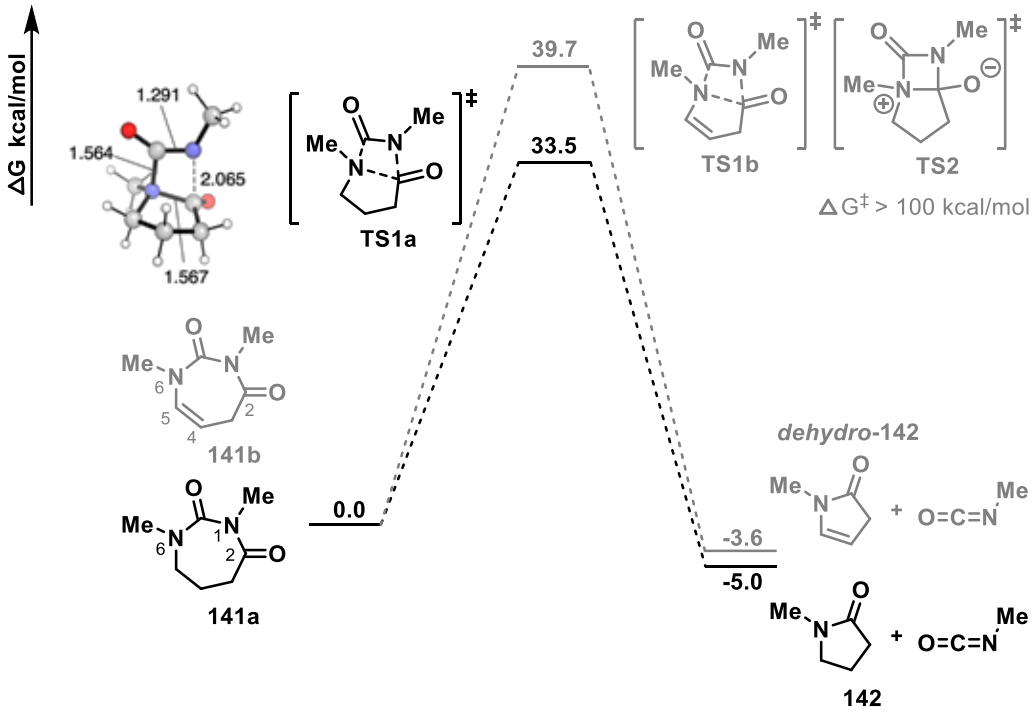
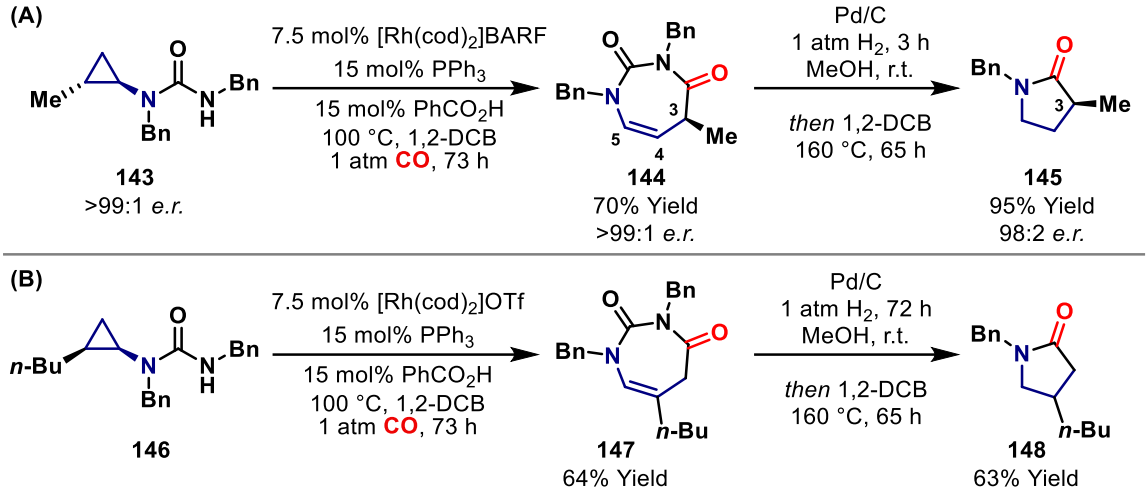


Figure 2: Free energy profiles computed at SMD(DCB)-DLPNO-CCSD(T)/def2-TZVPP//PBE0-D3BJ/def2-TZVP, 423.15 K. 3D geometries with key distances are quoted in Å.

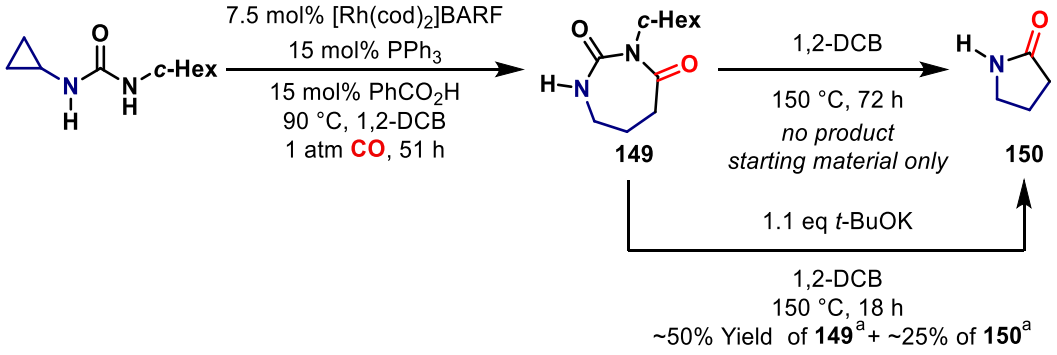
Unfortunately, the Rh-mediated hydrogenation conditions used for **137** to **139** were not compatible with the more hindered methyl-substituted diazepane **144**, which was accessed from urea **143** (>99:1 e.r.) using previously established methodology;[53] here, only trace amounts of hydrogenated product were formed (Scheme 30A). Consequently, a modified two-step procedure was developed: hydrogenation using Pd/C reduced the C4-C5 unsaturation, and this product (not depicted) was isolated prior to thermally promoted ring contraction, which provided **145** in 95% yield. It is important to note that the ring contraction step did not result in significant epimerization of the C3 stereocentre. The hydrogenation-ring contraction cascade offers an alternative approach to challenging enantioenriched α-substituted γ-lactams, which typically require multistep synthesis.[109]

To evaluate the scope of the hydrogenation-ring contraction sequence further, butyl-analogue **147** was targeted (Scheme 30B). Following the developed at Bristol methodology,[53] carbonylative cyclisation of urea **146** provided **147** in 64% yield. The more hindered alkene of **147** rendered the hydrogenation step more sluggish and necessitated a prolonged reaction time. Nonetheless, the subsequent ring contraction proceeded smoothly, giving butyl-substituted lactam **148** in 63% yield.



Scheme 30: Hydrogenation - ring contraction sequence of more complex substrates.

To examine a secondary nitrogen as the potential nucleophile, diazepane **149**[53] was trialled. Interestingly, **149** did not undergo thermally promoted ring contraction (Scheme 31); a possible explanation for this is the lowered nucleophilicity of the nitrogen centre due to the poorly electron-donating hydrogen substituent. On the other hand, conversion to target lactam **150** was feasible when a slight excess of base (*t*-BuOK) was used. Here, computational studies performed by Young suggest that the model substrate may be deprotonated to generate **151** with a sufficiently nucleophilic nitrogen to form a tetrahedral intermediate **152** (Figure 3). This intermediate then collapses to give the ring contracted product **150'** upon loss of isocyanate. This is in contrast to the concerted reaction mechanism for *N*-alkyl substituted variant **141a**, where a tetrahedral intermediate is energetically unfeasible (Figure 2 vs. Figure 3).



Scheme 31: Base-promoted ring contraction of diazepane **149**. [a]Yield was determined by ^{1}H NMR spectroscopy using 1,4-dinitrobenzene as a standard.

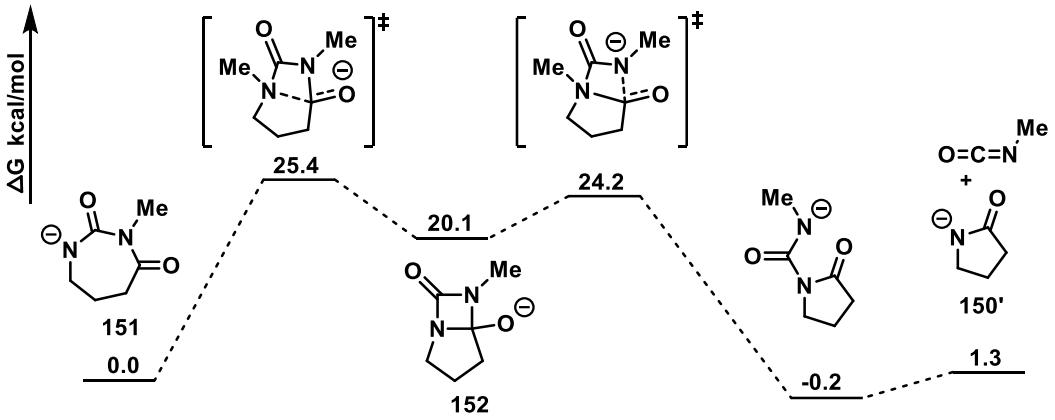
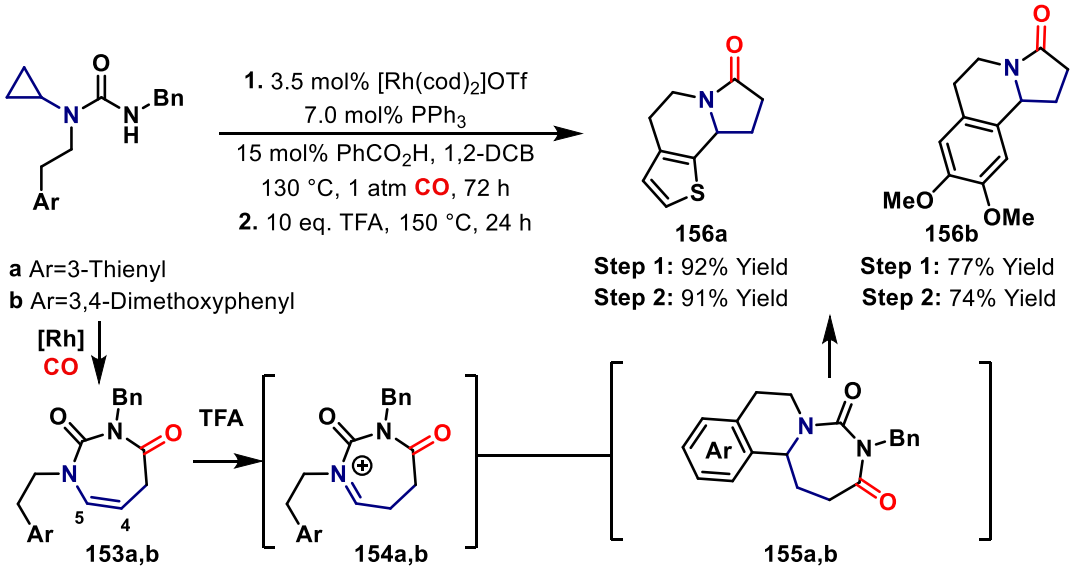


Figure 3: Free energy profile computed at SMD(DCB)-DLPNO-CCSD(T)/def2-TZVPP//PBE0-D3BJ/def2-TZVP.

2.2.4 Pictet-Spengler cyclisation - ring contraction cascade of diazepanes

This part of the project was conducted with the assistance of Ektor Christodoulou, a summer student in the Bower group, and studies conducted by Christodoulou are highlighted in the text.

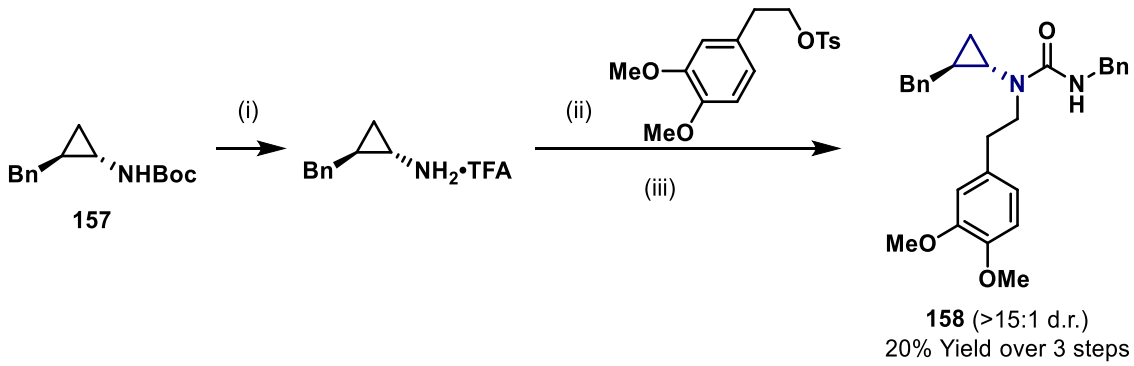
The DFT studies outlined in Section 2.2.3 show that ring contraction only occurs for diazepanes that possess C4-C5 saturation. It was envisaged that processes that exploit removal of the easily installed C4-C5 unsaturation in further bond formations could be used as a method to "activate" unsaturated 7-membered rings. Previous studies in the Bower group[53] showed that carbonylative C-C bond activation product **153** can undergo Pictet-Spengler cyclisation at 60 °C via iminium ion **154** to give tricyclic products **155** (Scheme 32). Dr Wang found that when the TFA-promoted cyclisation step was carried out at higher temperature (150 vs. 60 °C), the corresponding ring contraction products **156a,b** were obtained instead.



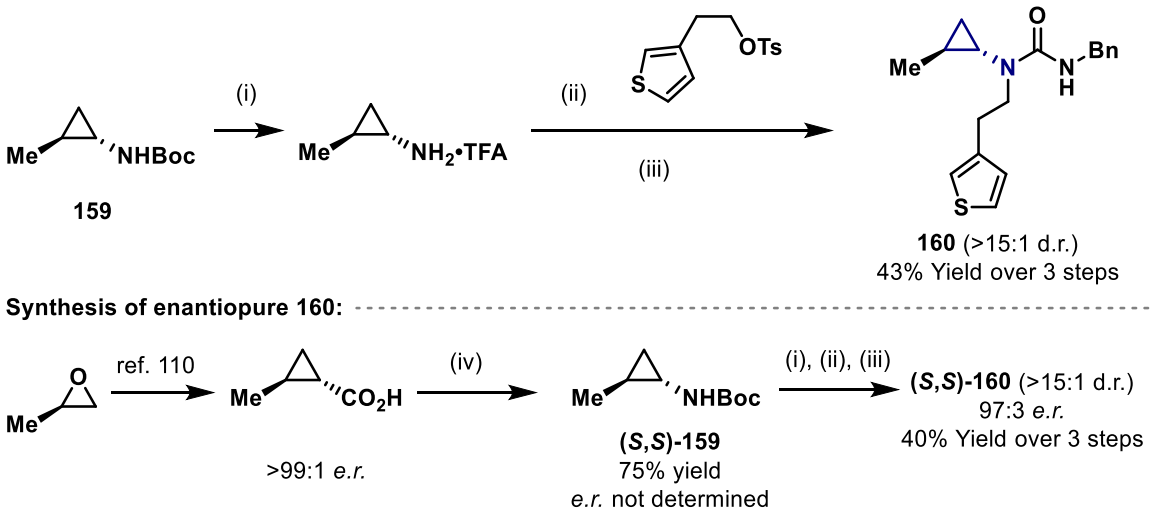
Scheme 32: Initial studies on Pictet-Spengler cyclisation - ring contraction sequence.

To extend further the scope of this cascade to more challenging substrates, benzyl-substituted substrate **158** bearing a tethered dimethoxyphenyl moiety was made from **157** by Boc deprotection, alkylation and urea formation (Scheme 33). Christodoulou used the same approach to convert **159** to racemic methyl-substituted substrate **160**, which bears a tethered thienyl substituent (Scheme 34). Enantioenriched **(*S*,*S*)-159** was prepared from (*R*)-propylene oxide by a known two-step sequence[53,110] and transformed to enantioenriched **(*S*,*S*)-160** (>97:3 e.r.) in a similar manner to racemic **160**.

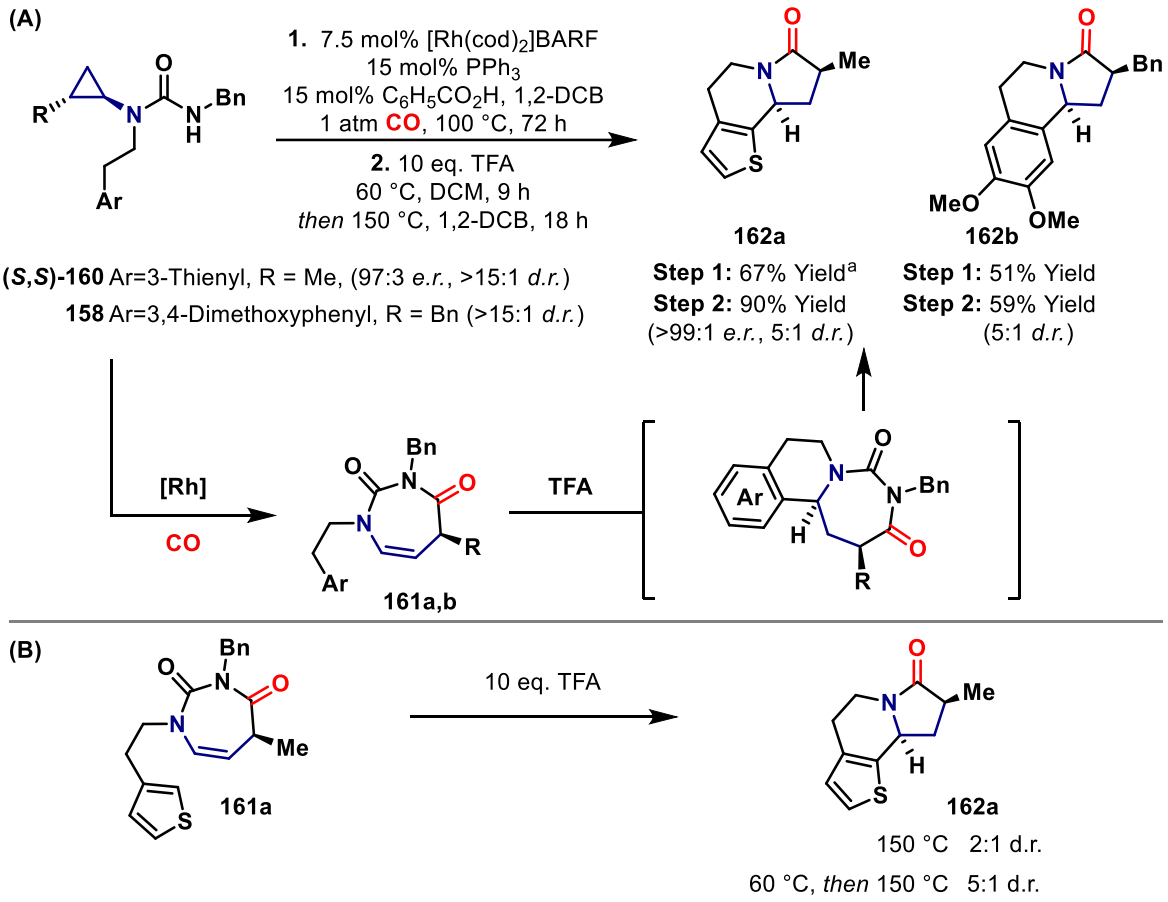
Pleasingly, by applying conditions previously developed for *trans*-disubstituted urea-protected cyclopropylamines,[53] both substrates delivered seven-membered products **161a,b** (Scheme 35). When the conditions for the one-pot Pictet-Spengler cyclisation - ring contraction process were applied to diazepane **161a**, the desired tricyclic product **162a** was obtained in poor diastereoselectivity (2:1 d.r.) (Scheme 35B). Lowering the temperature to 60 °C for the TFA-promoted ring formation and then heating up to 150 °C in the absence of TFA for the subsequent ring contraction improved the d.r. to 5:1. The improvement in d.r. at lower temperatures suggests that this is the kinetic outcome of the Pictet-Spengler-like reaction. Cyclopropanes **158** and **160** both gave good yields of γ-lactams **162a,b** with the established conditions (Scheme 35A). Selective nOe studies confirmed the relative stereochemistry of the major diastereomer (depicted). It is also worth pointing out that the absolute stereochemistry of enantioenriched thiophene-substituted cyclopropane **(*S*,*S*)-160** was retained through the C-C activation, cyclisation and ring contraction steps, which makes this methodology potentially attractive for total syntheses.



Scheme 33: Synthesis of **158**. *Reagents and conditions*: (i) TFA, DCM, r.t.; (ii) K_2CO_3, MeCN, 90 °C; (iii) benzyl isocyanate, NEt_3, DCM, 0 °C to r.t.



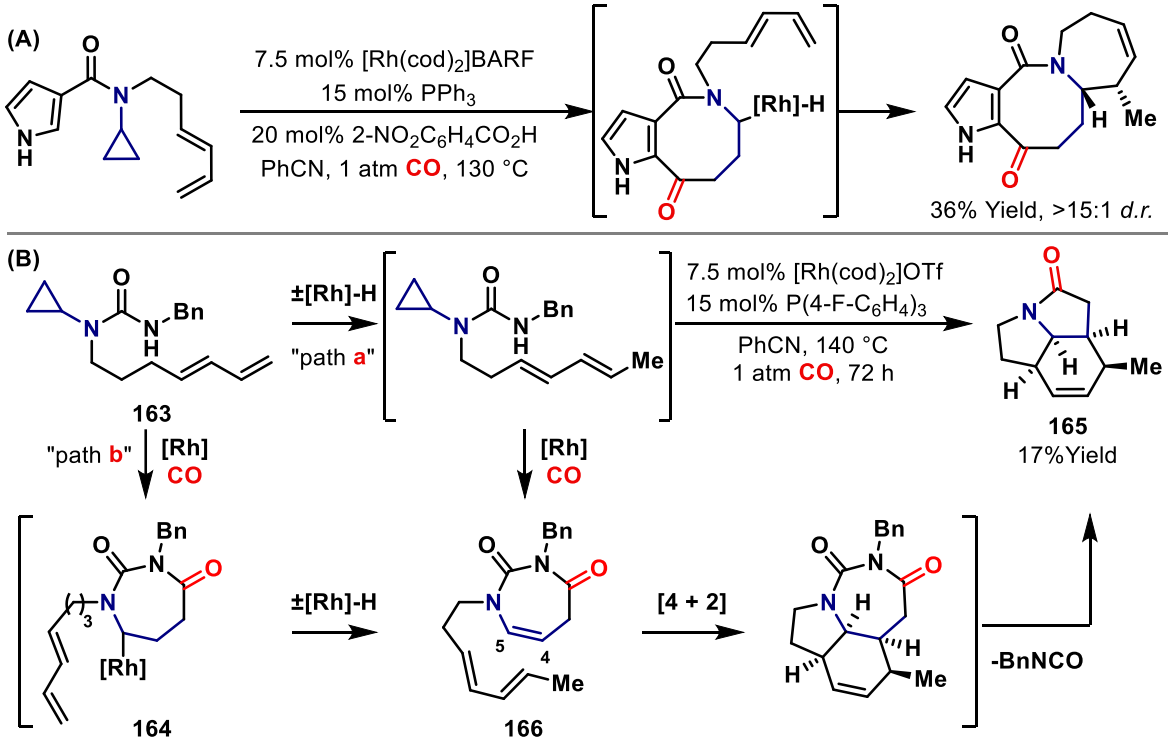
Scheme 34: Synthesis of **160** and **(*S*,*S*)-160**. *Reagents and conditions*: (i) TFA, DCM, r.t.; (ii) K_2CO_3, MeCN, 90 °C; (iii) benzyl isocyanate, DCM, 0 °C to r.t.; (iv) DPPA, NEt_3, *t*-BuOH, 80 °C.



Scheme 35: Reactivity of cyclopropylamines **158** and **160** and optimisation of the cyclisation step. [a] Result obtained by Christodoulou.

2.2.5 Diels-Alder cyclisation - ring contraction cascade of diazepanes

Having established the Pictet-Spengler cyclisation - ring contraction cascade to access tricyclic scaffolds, other cascades forming complex products were sought. It was found that aminocyclopropanes **163** equipped with tethered dienes offer the possibility of effecting Diels-Alder-based cascades (Scheme 36B). Wang's original idea was to trigger an additional cyclisation via diene carbometallation from intermediate **164**; a similar sequence had been demonstrated in the group's earlier work (Scheme 36A).[56] Unexpectedly, trace amounts of tricyclic compound **165** were isolated; it was suggested that this may form via inverse electron-demand Diels-Alder reaction of enamide **166** with an isomerised diene unit. The isomerisation process may be facilitated by hydrometallation of the diene[111,112] either before (Scheme 36B, "path **a**") or after (Scheme 36B, "path **b**") formation of the 7-membered ring. The Diels-Alder process removes the C**4**-C**5** unsaturation from cyclic enamide **166**, thereby triggering ring contraction to **165**. This serendipitous discovery suffered from a poor yield, and so further reaction optimisation was required.

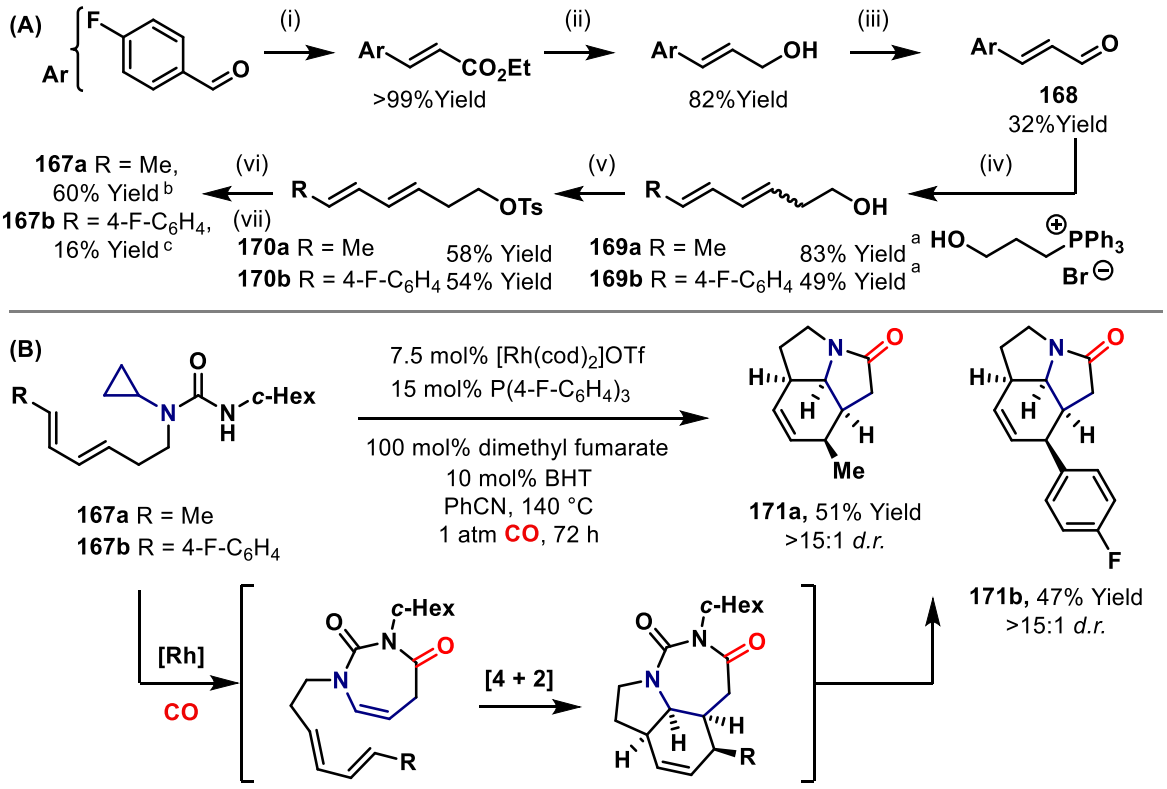


Scheme 36: Previously known reaction, developed in the group and reactivity study of **163**, performed by Wang.

Based on the preliminary results from Scheme 36B, diene-bearing substrates **167a** and **167b** were suggested as suitable starting materials (Scheme 37). These compounds have the previously optimised cyclohexyl group on the urea moiety and the diene is correctly positioned for the Diels-Alder cycloaddition. The synthesis of **167a** started with commercially available *trans*-crotylaldehyde, whereas **167b** was derived from known[113] aldehyde **168** (Scheme 37A). Wittig olefination delivered a mixture of *cis*/*trans*-dienes **169a,b**. The alcohols were then tosylated

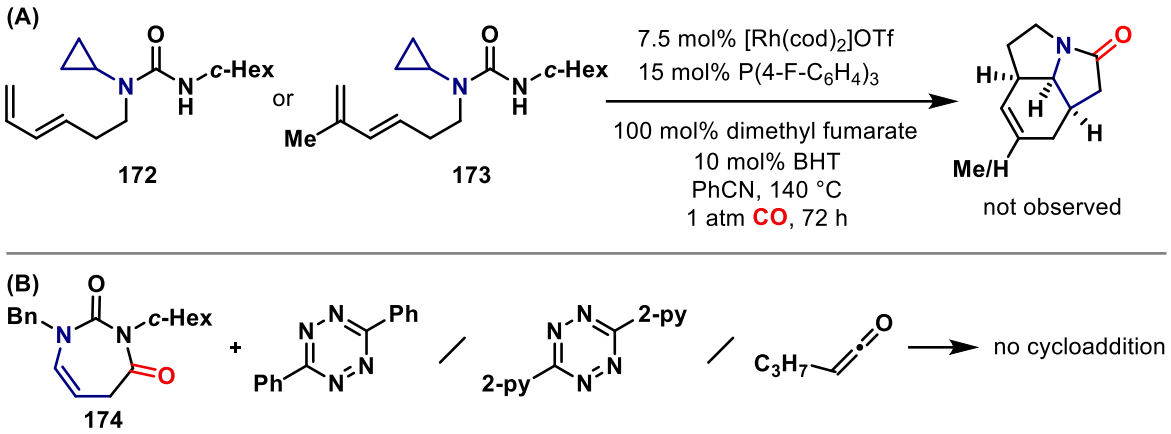
and tosylates **170a,b** were used to alkylate cyclopropylamine. Finally, urea formation with cyclohexyl isocyanate gave the desired starting materials **167a,b**.

With **167a,b** in hand, the Diels-Alder cyclisation - ring contraction cascade was attempted. The substrates performed poorly under the conditions outlined in Scheme 36, giving **171a** and **171b** in low yield (<30%, as determined by ^{1}H NMR analysis of the reaction mixture). Nonetheless, this was deemed a promising result that seemed to validate the mechanistic hypothesis for transformation of diene **163** into **165**. It was thought that using BHT as an additive may help to suppress radical polymerization of the diene substrate during the reaction.[28,114] A weakly coordinating electron-deficient dimethyl fumarate ligand was used as well because it was found to be beneficial in previously reported C-C bond activation methodologies.[48,49] Under the reaction conditions from Scheme 36, modified with the aforementioned additives, tricyclic lactams **171a** and **171b** were obtained in 51% and 47% yield, respectively (Scheme 37B). The relative stereochemistry of tricyclic lactam **171a** was determined by nOe-distance analysis[115] in collaboration with Prof. Craig Butts (see the Experimental for further details). Overall, this multistep process involves C-C activation, carbonylation, C-N bond formation, Diels-Alder reaction and ring contraction in the course of just one transformation. Even mid-range yields are impressive when accounting for the complexity of the resulting tricyclic products.



Scheme 37: Synthesis and reactivity of **167a,b**. *Reagents and conditions*: (i) triethyl phosphonoacetate, DME, 0 °C to r.t.; (ii) DIBAL-H, THF, -78 °C or 0 °C; (iii) PCC, silica gel, DCM, r.t.; (iv) *n*-BuLi, THF, 0 °C; (v) TsCl, Et_3N, DMAP, DCM, 0 °C to r.t.; (vi) cyclopropylamine, K_2CO_3, MeCN, 90 °C; (vii) cyclohexyl isocyanate, DCM, 0 °C to r.t.; [a] *E*/*Z* = 4:1; [b] *E*/*Z* = 10:1; [c] *E*/*Z* > 15:1.

Systems equipped with other types of tethered dienes were also tested: the less sterically hindered diene **172** and the methyl-substituted diene **173**, where the methyl substituent may help the diene to adopt the s-*cis* conformation required for the Diels-Alder cycloaddition (Scheme 38A). Unfortunately, diene **172** did not undergo the carbonylative cyclisation cascade, which may be due to its susceptibility to competitive hydrometallation under the reaction conditions. Electron-rich diene **173** was also not suitable; this is in line with the notion that inverse electron demand Diels-Alder reactions prefer more electron-poor dienes. Therefore *intermolecular* inverse electron demand Diels-Alder reactions between enamide **174** and tetrazines, which are typical partners for related [4+2] cycloadditions,[116] were also investigated, but no cycloaddition was observed. Attempts to use ketenes in a [2+2] cycloaddition with **174** were also not fruitful.



Scheme 38: Failed diene substrates and other attempted cycloadditions.

2.3 Conclusions

The studies outlined in this chapter have demonstrated that a range of different cascades can be employed to trigger a ring contraction in diazepane systems; these are obtained from urea-protected cyclopropylamines by Rh(I)-catalysed carbonylative cyclisation. Substrates with tethered alkynes and dienes engage in subsequent cyclisations or cycloadditions in the course of the C-C bond activation reaction. C-C bond activation products bearing appropriately positioned electron-rich aromatics were used to perform Pictet-Spengler-like cyclisations and this enabled ring contraction to give γ-lactams. Similarly, hydrogenation of unsaturated diazepanes can be used to trigger ring contractions. The processes are stereospecific, which allows the absolute stereochemistry of the cyclopropylamine precursors to be transferred to the products. In broader terms, these studies validate a conceptually unique TDG-based strategy for C-C bond activation. Specifically, the processes are the first in this area that do not harness carbonyl condensation and imine hydrolysis for TDG installation and removal.

CHAPTER 3

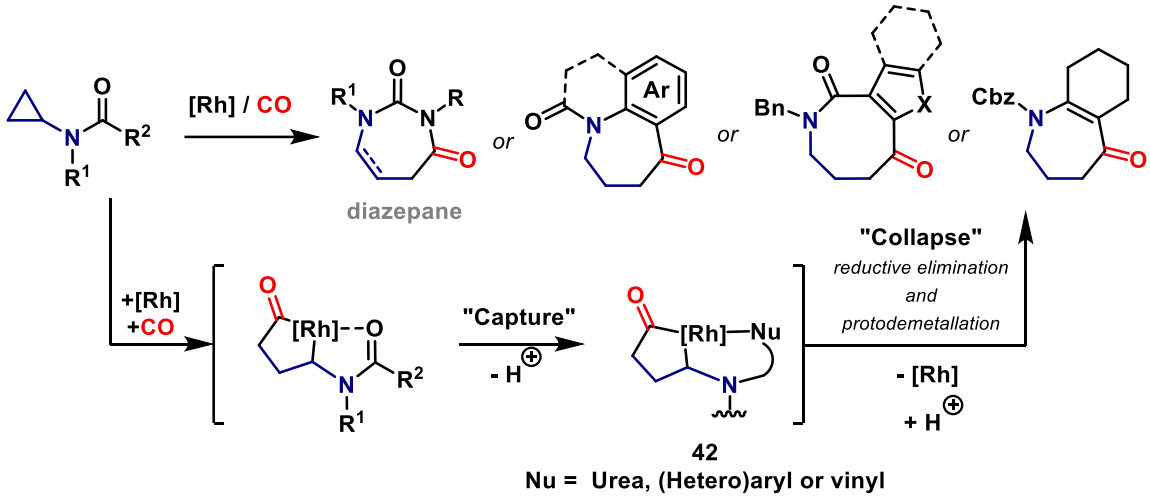
New substrates for intramolecular nucleophilic addition to rhodacyclopentanones

Aspects of this Chapter have been adapted from a paper.

(Boyd, O.[†]; Wang, G.-W.[†]; Sokolova, O. O.; Calow, A. D. J.; Bertrand, S. M.; Bower, J. F. *Angew. Chem. Int. Ed.* **2019**, *58*, 18844. [†]O. Boyd and G.-W. Wang contributed equally)

3.1 Introduction

As outlined in section 1.3, early investigations into nucleophilic addition to rhodacyclopentanones via intermediate **42** demonstrated that urea-protected aminocyclopropanes can undergo a (6+1) carbonylative cyclisation to give a range of diazepanes (Scheme 39). The scope of nucleophiles that can trap out the rhodacyclopentanone intermediate was then extended to carbon-based systems. Aromatic, vinylic and heterocyclic units, such as indoles, pyrroles and furans were demonstrated to provide challenging 7- and 8-membered rings.

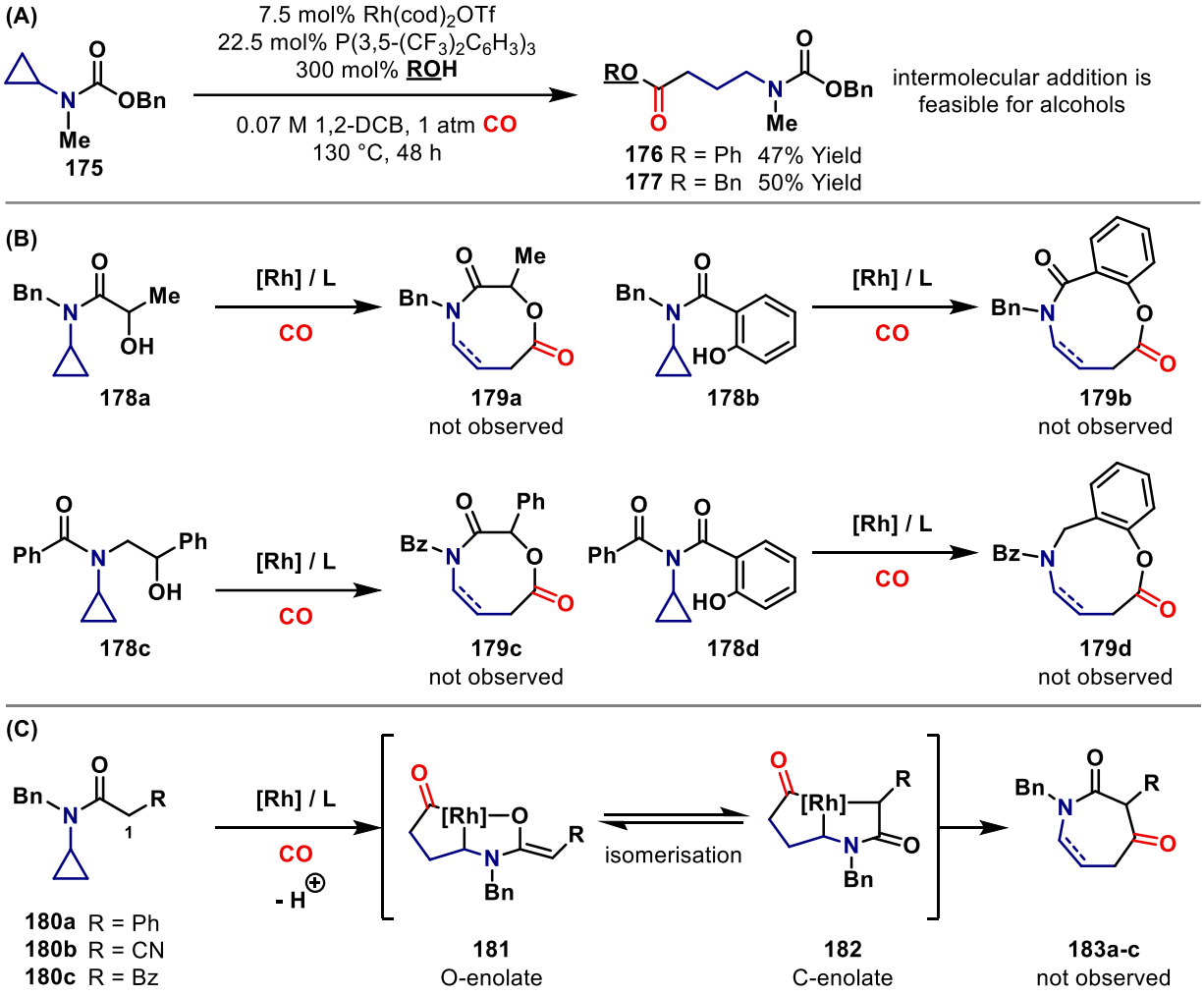


Scheme 39: Successful nucleophilic additions to rhodacyclopentanones.

3.1.1 Prior studies carried out in Bristol

In pursuit of new protected aminocyclopropane-based systems that can "capture" rhodacyclopentanones, Dr. McCreanor and Dr. Stanton tested various systems containing oxygen, carbon and nitrogen-based nucleophiles.[75,117] Oxygen-based nucleophiles were efficient in intermolecular transformations. Subjection of cyclopropylamine **175** to carbonylative conditions in the presence of PhOH or BnOH gave linear adducts **176** and **177** in 47 and 50% yield, respectively (Scheme 40A). However, when an oxygen-based nucleophile was incorporated into aminocyclopropane-bearing substrates **178a-d**, none of the desired cycloadducts **179a-d** were

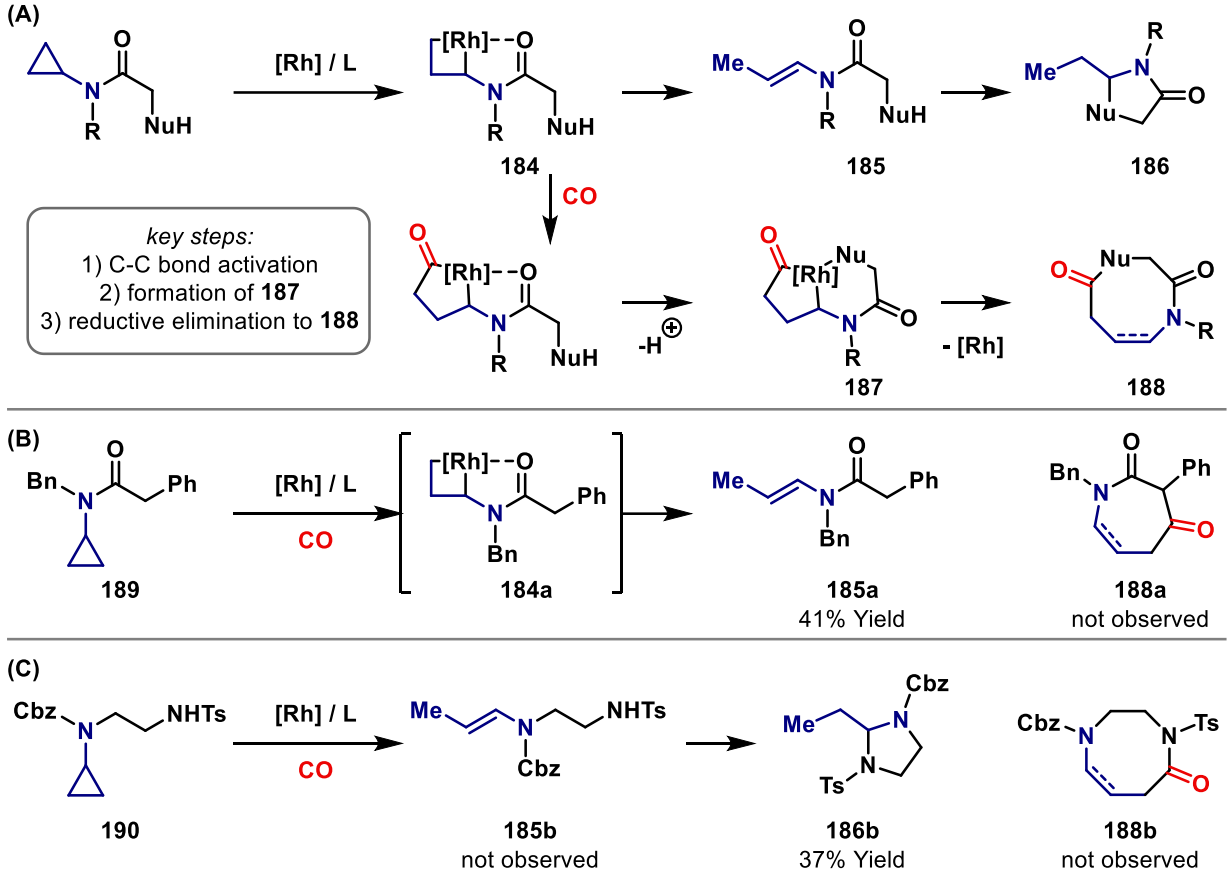
observed (Scheme 40B). With respect to carbon-based nucleophiles, it was envisaged that substrates **180a-c** may be nucleophilic due to the presence of enolisable C1-H protons (Scheme 40C). It was proposed that these substrates may form an O-bound Rh(III)-enolate **181** which isomerises to C-bound Rh(III)-enolate **182**. Subsequent C-C bond forming reductive elimination would then give 7-membered products **183a-c**. However, the desired products were not observed under various catalytic conditions.



Scheme 40: Other systems trialled in nucleophilic additions to rhodacyclopentanones.

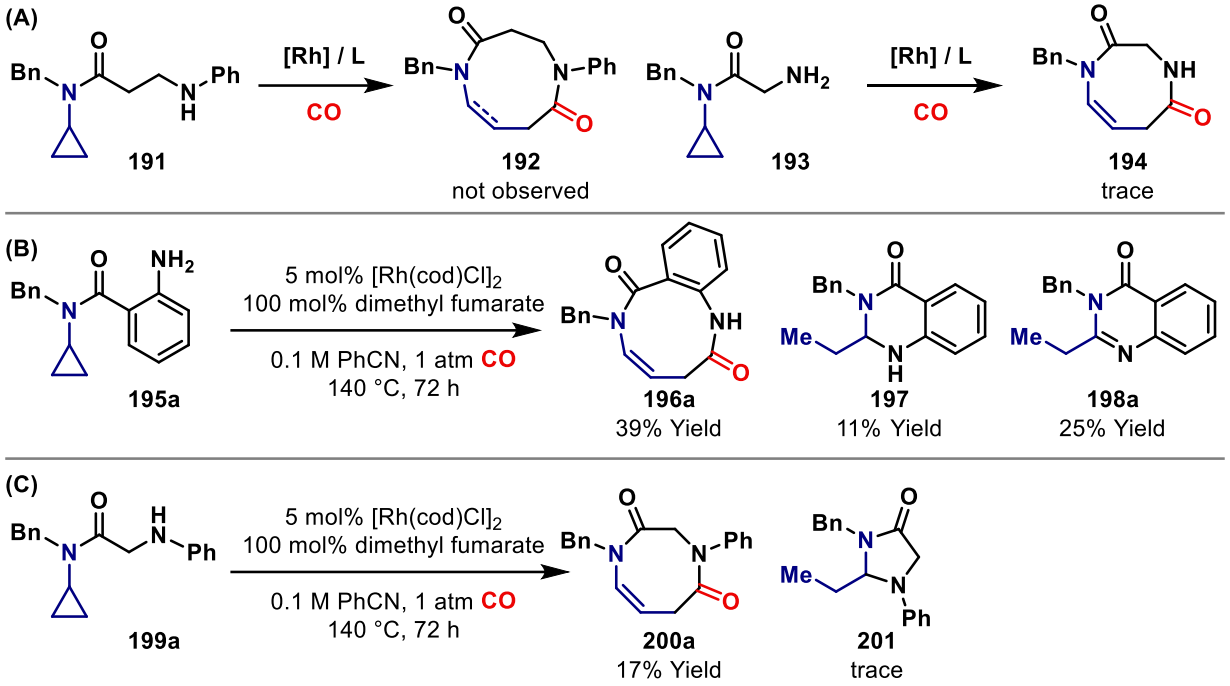
Although the studies in Scheme 40 were largely unsuccessful, linear side products **185** were observed in some cases (Scheme 41A). Side products **185** likely arise via directed formation of rhodacyclobutane **184**, which then undergoes β-hydride elimination and C-H reductive elimination. For example, substrate **189** gave enamide **185a** in 41% yield, and this presumably arises via rhodacyclobutane **184a** (Scheme 41B). Cyclic structures **186**, formed by intramolecular nucleophilic addition to enamide **185**, were also observed. When aminocyclopropane **190**, which bears a nitrogen-based nucleophile, was used, enamides **185b** or **188b** were not observed but 5-membered cyclic product **186b** was isolated instead in 37% yield. This result can be rationalized

via a directed C-C bond activation pathway, involving conversion of **185b** to **186b** (Scheme 41C). The formation of side products **185a** and **186b** indicates that directed C-C bond activation had occurred, but, presumably, either the formation of intermediate **187** or the reductive elimination process are problematic, such that the target products **188** do not form.



Scheme 41: Typical side products resulting from failed nucleophilic additions to rhodacyclopentanones.

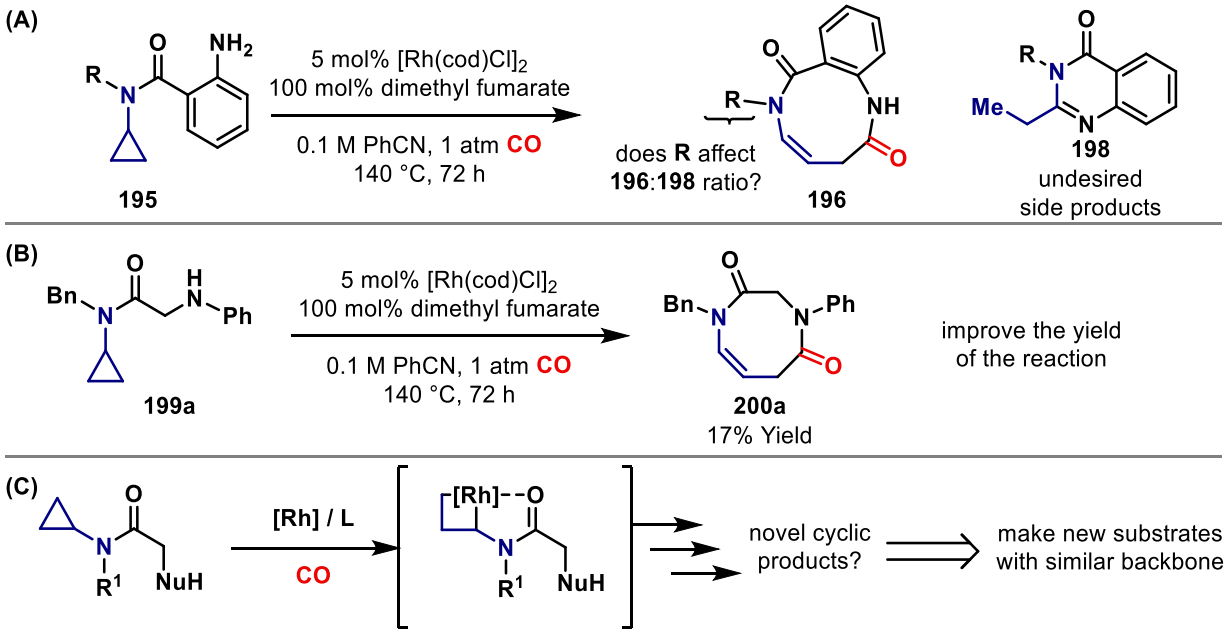
Further studies on nucleophilic addition to rhodacyclopentanones were carried out by Dr Adam Calow. As there are several examples known in the literature[118-121] where nitrogen incorporated in the starting material directs Rh(I)-catalysed transformations, Dr Calow investigated various substrates containing tethered nitrogen-based nucleophiles (Scheme 42A). With protected aminocyclopropane **191**, no target 9-membered product **192** could be obtained. On the other hand, the transformation of similar substrate **193** delivered trace amounts of 8-membered product **194**. Encouraged by this result, similar substrates were made. When substrate **195a**, containing an unprotected aniline was used, diazonine **196a** was obtained in 39% yield; side products **197** and **198a** were also formed (Scheme 42B). Unfortunately, attempts to suppress the formation of 6-membered adducts **197** and **198a** and improve the yield of **196a** were unsuccessful. Finally, substrate **199a**, containing a monosubstituted aniline, underwent Rh(I)-catalysed transformation to **200a** in 17% yield; here, only traces of adduct **201** were observed (Scheme 42C). This promising result prompted further investigation of parent substrate **199a**.



Scheme 42: Investigations by Dr. Calow on nucleophilic addition to rhodacyclopentanones.

3.2 Further work on nucleophilic addition to rhodacyclopentanones

The initial aims of the work described in this section were to screen different substitution patterns on general substrate **195** in order to suppress the formation of undesired side products (e.g. **198a**) (Scheme 43A) and improve the yield of 8-membered product **200a** (Scheme 43B). Related substrates for the carbonylative rearrangement were also proposed (Scheme 43C). For the screening studies described below, several parameters were evaluated: Rh(I) precatalyst (cationic – $[Rh(cod)_2]BARF$, $[Rh(cod)_2]BF_4$ or $[Rh(cod)_2]OTf$; neutral – $[Rh(cod)Cl]_2$ or $[Rh(cod)OMe]_2$), phosphine ligand (PPh_3 and its derivatives with various electronics), reaction solvent (coordinating PhCN or non-coordinating 1,2-DCB) and reaction temperature (100-160 °C).

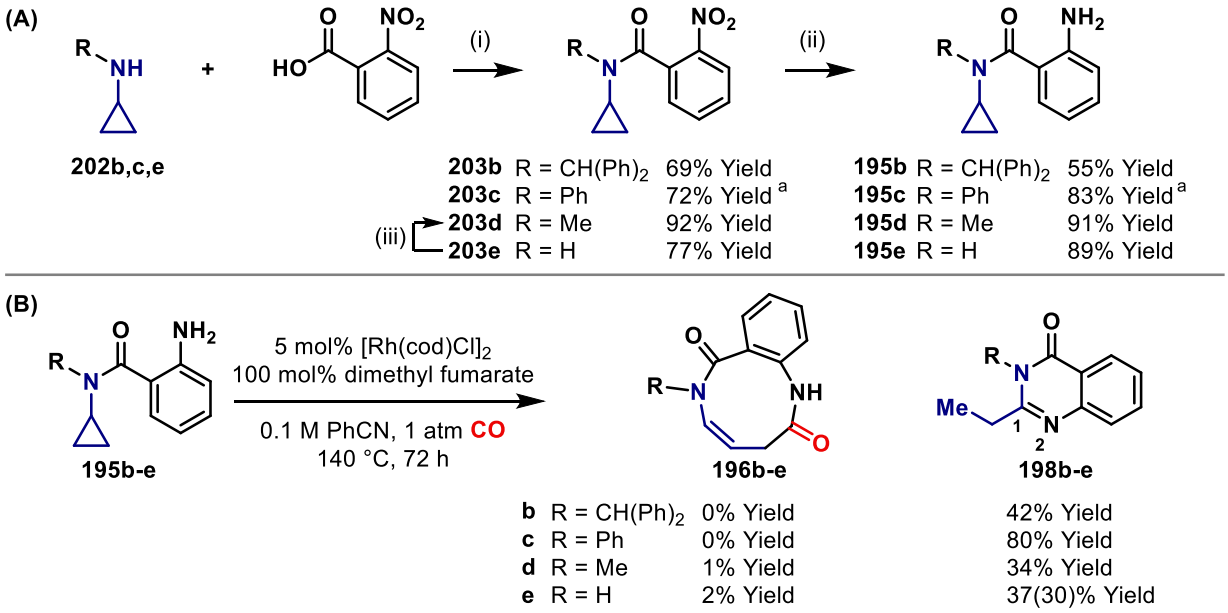


Scheme 43: Further work on the "capture-collapse" strategy - project aims.

3.2.1 Substrate evaluation for the formation of 9-membered cycloadducts

To assess the effect of sterics on the formation of 9-membered product **196** and 6-membered adduct **198**, substrates **195b-e**, with different R-substituents, were made via a two-step sequence. Amide coupling of amines **202b,c,e** with 2-nitrobenzoic acid provided amides **203b,c,e**. Subsequent reduction of the nitro group with iron in acetic acid delivered aniline derivatives **195b,c,e**. Methyl-substituted compound **195d** was synthesised by the methylation of **203e** under basic conditions (methyl iodide, base) to give **203d** followed by nitro group reduction to **195d**.

When substrates **195b-e** were exposed to carbonylative reaction conditions, at most, only traces of target material **196b-e** were observed in the ^{1}H NMR spectrum of the crude reaction mixture. Instead, C1-N2 unsaturated adducts **198b-e** were obtained; in particular, **198e** was isolated in 30% yield. The yields of **198b-d** were determined by ^{1}H NMR analysis of the crude reaction mixture and were not isolated. These results indicate that the reaction outcome is highly dependent on the R-substituent, such that only benzyl substituted **195a** is suitable for efficient carbonylative cyclisation (to **196a**).



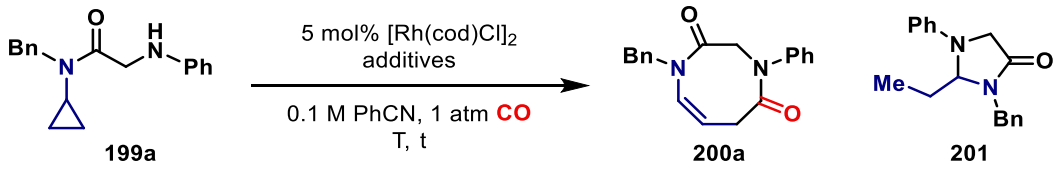
Scheme 44: Synthesis and reactivity of substrates with different substituents on nitrogen. *Reagents and conditions*: (i) EDCI, DMAP, DCM, 0 °C to r.t., 18 h; (ii) Fe, AcOH, EtOH, 85-90 °C, 2-18 h; [a] This compound was made by Dr Calow. Yields in (B) were determined by ^{1}H NMR spectroscopy using 1,4-dinitrobenzene as a standard. An isolated yield for **198e** is given in parentheses.

3.2.2 Optimisation of the carbonylative heterocyclisation process

To improve the yield of the carbonylative heterocyclisation of **199a**, an extensive evaluation of reaction conditions was carried out (>250 sets of conditions), and selected results are shown in Table 2. Raising the reaction temperature to 150 or 160 °C did not give a substantial

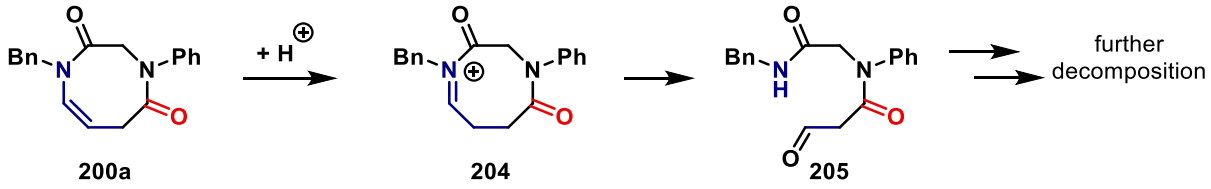
increase in yield and mass recovery was poor (Table 2, Entries 1-3). Using a combination of dimethyl fumarate as a π-acidic ligand and 20 mol% of a Na_2SO_4 as a desiccant improved the yield to 43% (Table 2, Entry 4). Both dimethyl fumarate and Na_2SO_4 proved necessary to achieve this moderate yield, and using only Na_2SO_4 gave **200a** in 21% yield (Table 2, Entry 5). Increasing the reaction time led to greater consumption of starting material, but gave **200a** in 35% yield (Table 2, Entry 6). This result may indicate that the product is unstable under the reaction conditions and longer reaction times facilitate decomposition. A possible pathway involves protonation of enamide **200a** to give iminium **204** which can then hydrolyse to aldehyde **205**; this behaviour is consistent with related 7- and 8-membered structures in the literature (Scheme 45).[122,123]

To avoid the formation of presumed iminium ion **204**, different basic additives were screened. However, the reaction demonstrated high sensitivity towards these, and 30 mol% of the base (e.g. NaOAc) was enough to completely prevent formation of target **200a** (Table 2, Entry 7). Nevertheless, an improved yield was obtained by using the same molar concentration of base as Rh-catalyst (5 mol% NaOAc) (Table 2, Entry 8). By switching to a stronger base (NaO*t*-Bu) and increasing the reaction temperature to 160 °C, **200a** was formed in 46% yield (Table 2, Entries 9, 10). Further screening of reaction conditions did not improve the yield of **200a** and efforts turned to an evaluation of the reaction's scope. As the results with 20 mol% Na_2SO_4 (Table 2, Entry 4) and 5 mol% NaO*t*-Bu (Table 2, Entry 10) were comparable, both sets of conditions were used for this endeavour.



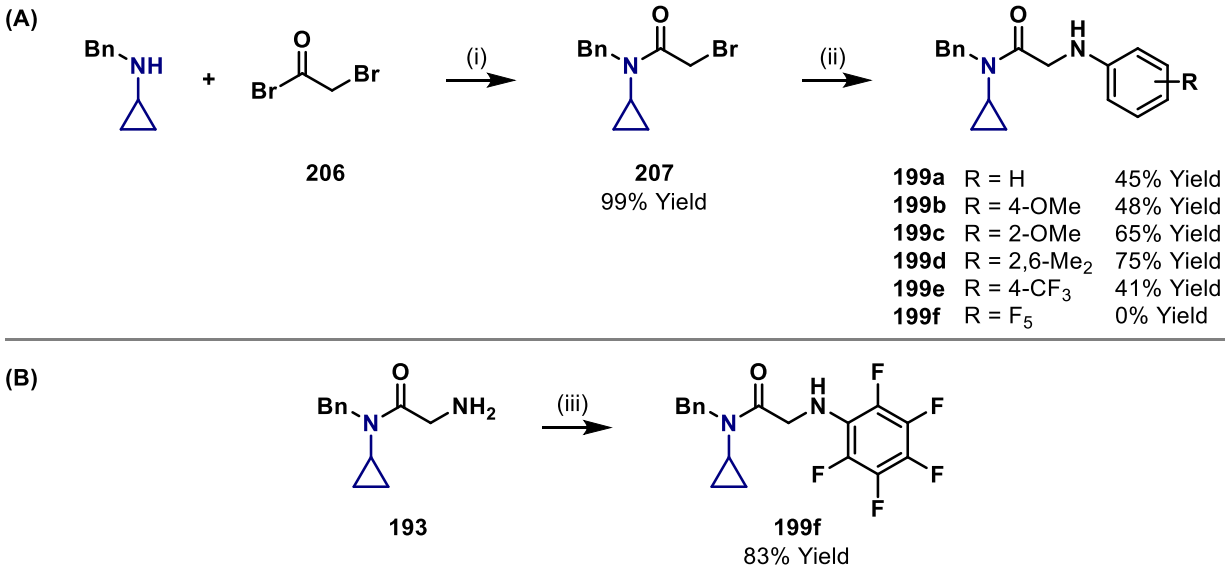
Entry	Additives (mol %)	T (°C)	Time (h)	199a (%)	200a (%)	201 (%)
1	DF (100)	140	24	82	17	trace
2	DF (100)	**150**	72	25	25	8
3	DF (100)	**160**	72	trace	37-38	8
4	DF (100), **Na_2SO_4 (20)**	150	72	20	47 (43)	6
5	**Na_2SO_4 (20)**	150	72	33	21	9
6	DF (100), Na_2SO_4 (20)	150	**96**	9	35	6
7	DF (100), **NaOAc (30)**	150	72	86	0	0
8	DF (100), **NaOAc (5)**	150	72	25	39	trace
9	DF (100), **NaO*t*-Bu (5)**	150	72	31	44	4
10	DF (100), NaO*t*-Bu (5)	**160**	72	11	51 (46)	6

Table 2: Optimization studies for the formation of **200a**. Yields were determined by ^{1}H NMR spectroscopy using 1,4-dinitrobenzene as a standard. Isolated yields are given in parentheses. DF = dimethyl fumarate.



Scheme 45: Proposed pathway for the decomposition of **200a**.

In order to explore the effect of different electronics on the aniline unit, substrates **199a-f** were targeted (Scheme 46A). The syntheses commenced with condensation of bromoacetyl bromide **206** and *N*-benzylcyclopropanamine to give 2-bromoacetamide **207** in quantitative yield. **207** was then used to alkylate a range of anilines, delivering **199a-e** in 41-75% yield. The formation of **199f** did not occur under these alkylation conditions, presumably due to the low nucleophilicity of pentafluoroaniline. An alternative approach, where C_6F_6 underwent S_NAr reaction with primary amine **193** provided **199f** in 83% yield (Scheme 46B).



Scheme 46: Synthesis of substrates **199a-f**. *Reagents and conditions*: (i) bromoacetyl bromide, K_2CO_3, DCM, 0 °C to r.t., 18 h; (ii) corresponding aniline, K_2CO_3, toluene, 90 °C, 2-18 h; (iii) DMSO, C_6F_6, KF, 100 °C, 18 h.

Substrates **199a-f** were then exposed to the optimised carbonylative reaction conditions (Table 3). It was observed that aminocyclopropanes **199b-d**, possessing electron-rich substituents on the aniline, cyclized to provide 1,4-diazocanes **200b-d** in moderate and similar yields (30-42%). The structure of *o*-methoxy-substituted 1,4-diazocane **200c** was confirmed by single-crystal X-ray diffraction. It was proposed that substrates equipped with electron-poor anilines (4-CF_3 and F_5) might enhance the reaction rate by reducing coordinative saturation of Rh by *N*-coordination[124,125] and also by electronically facilitating C-N reductive elimination at the stage of **187** (see

Scheme 41).[126-128] However, substrates **199e,f** were less efficient at delivering the desired adducts **200e,f** (12-17% yield). Overall, these results suggest that efficient generation of metallabicyclic intermediate **187** is the key factor, and more nucleophilic anilines facilitate this.

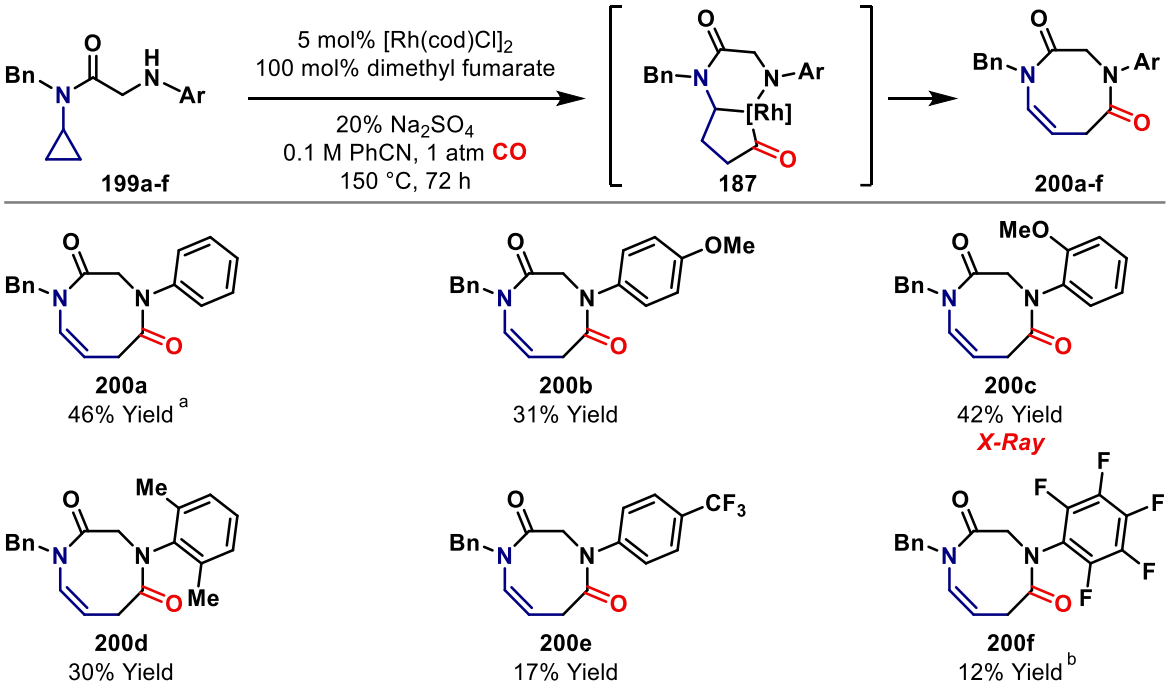
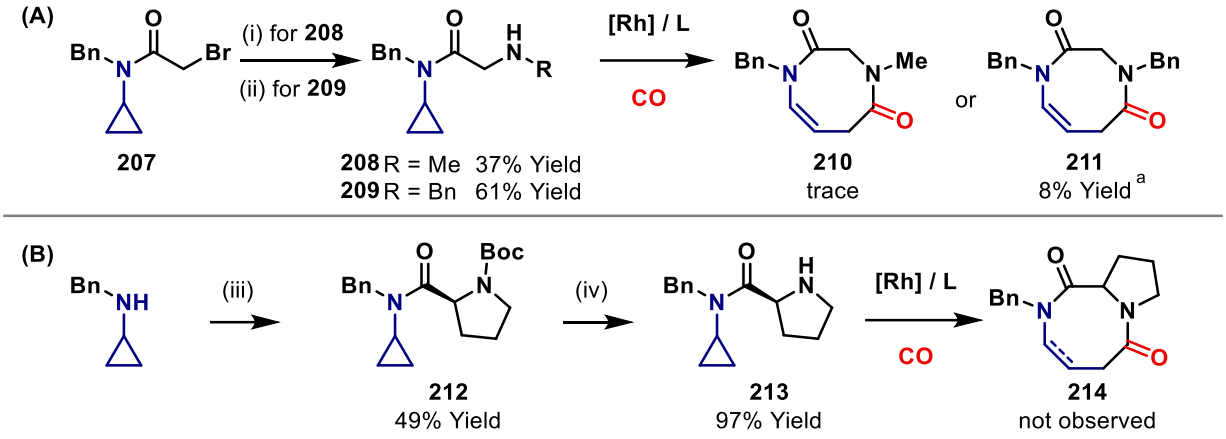


Table 3: Scope of the aniline component. [a] 5% NaO^{t}Bu instead of 20% Na_2SO_4, 160°C. [b] Yield was determined by ^{1}H NMR spectroscopy using 1,4-dinitrobenzene as a standard.

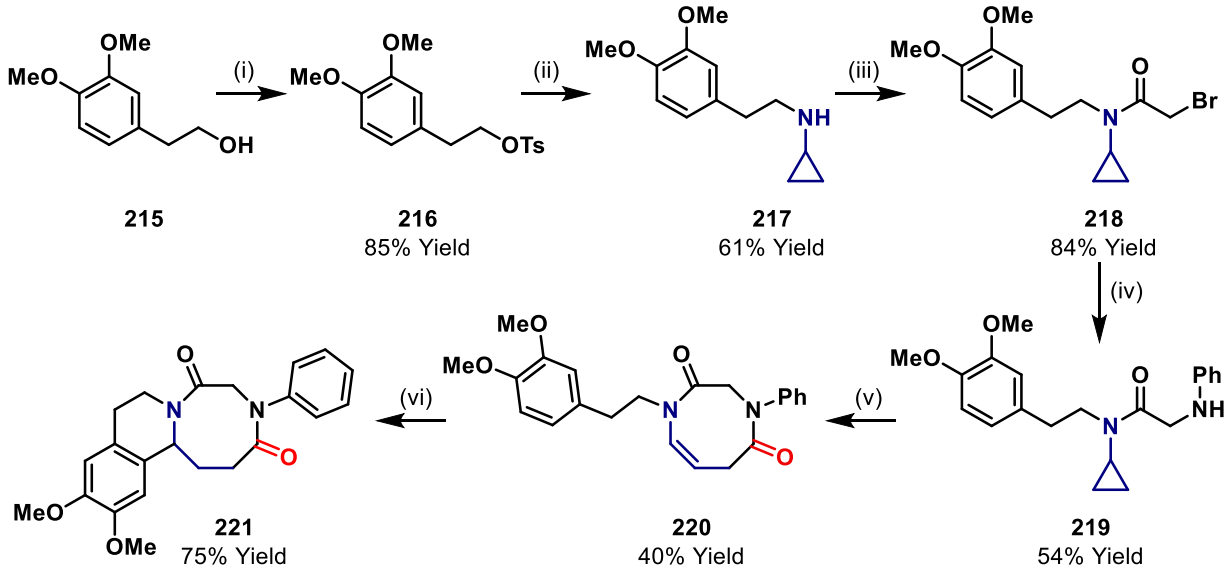
Moving away from aniline nucleophiles, other *N*-based nucleophiles were trialled with limited success. More nucleophilic amines were expected to perform better in the transformation because electron-poor anilines **199e** and **199f** gave **200e,f** in only 12-17% yield. To address this, methylamine and benzylamine were alkylated with 2-bromoacetamide **207** to provide **208** and **209**, respectively (Scheme 47A). Subjection of these substrates to the Rh(I)-catalysed carbonylative conditions led predominantly to decomposition, although trace quantities of target products **210** and **211** were observed in the ^{1}H NMR spectrum of the crude reaction mixture. Pyrrolidine-derived substrate **213** was accessed via **212** by amide coupling of *N*-Boc-proline and *N*-benzylcyclopropanamine followed by Boc deprotection (Scheme 47B). Subjection of **213** to a range of catalytic conditions led to starting material degradation and the formation of bicyclic structure **214** did not occur. The poor performance of these cyclisations indicates that aniline-substituted substrates are uniquely suitable for the transformation. For the substrates depicted in Scheme 47, the strongly Lewis basic amine moieties may outcompete the weakly coordinating amide directing group and prevent directed C-C bond activation.[129]



Scheme 47: Synthesis and reactivity of substrates **208**, **209** and **213**. *Reagents and conditions*: (i) 40% aq. $MeNH_2$, EtOH, 65 °C, 18 h; (ii) benzylamine, K_2CO_3, toluene, 80 °C, 18 h; (iii) *N*-Boc-proline, EDCI, DMAP, DCM, 0 °C to r.t., 18 h; (iv) TFA, DCM, 1 h. [a] Yield was determined by ^1H NMR spectroscopy using 1,4-dinitrobenzene as a standard.

3.2.3 Further product derivatisation via Pictet-Spengler cyclisation

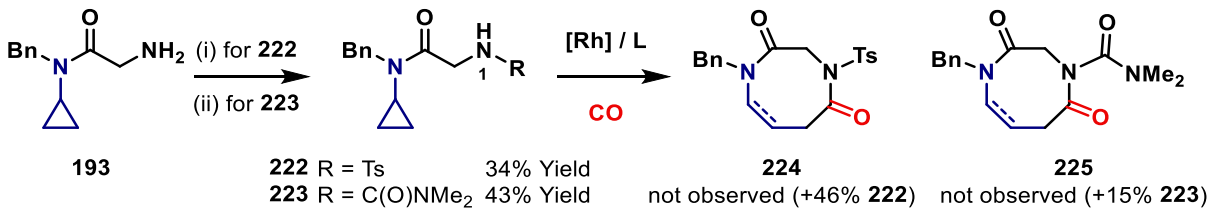
To demonstrate the use of the Rh(I)-catalysed cyclisation products in further transformations, enamide **220** was made (Scheme 48). It was envisaged that the tethered electron-rich aromatic ring might be amenable to Pictet-Spengler-like cyclisation.[130,131] First, alcohol **215** was converted to tosylate **216**, and this was used to provide **217** via alkylation of aminocyclopropane. Amine **217** was alkylated with bromoacetyl bromide to give **218** in 84% yield. Next, reaction of **218** with aniline provided heterocyclisation substrate **219**. Exposure of **219** to the optimised carbonylative conditions delivered 8-membered product **220** in 40% yield. Finally, **220** was treated with TFA to deliver complex tricycle **221** in 75% yield. This result showcases the reactivity of the enamide moiety of the carbonylative heterocyclization product.



Scheme 48: Synthesis of Pictet-Spengler product **221**. *Reagents and conditions*: (i) TsCl, Et_3N, DMAP, DCM, r.t., 4 h; (ii) cyclopropylamine, MeCN, 90 °C, 18 h; (iii) bromoacetyl bromide, K_2CO_3, DCM, 0 °C to r.t., 18 h; (iv) aniline, K_2CO_3, toluene, 90 °C, 4 h; (v) $[Rh(cod)Cl]_2$ (5 mol%), dimethyl fumarate (100 mol%), Na_2SO_4 (20 mol%), PhCN (0.1 M), CO (1 atm), 150 °C, 72 h; (vi) TFA, DCM, 60 °C, 24 h.

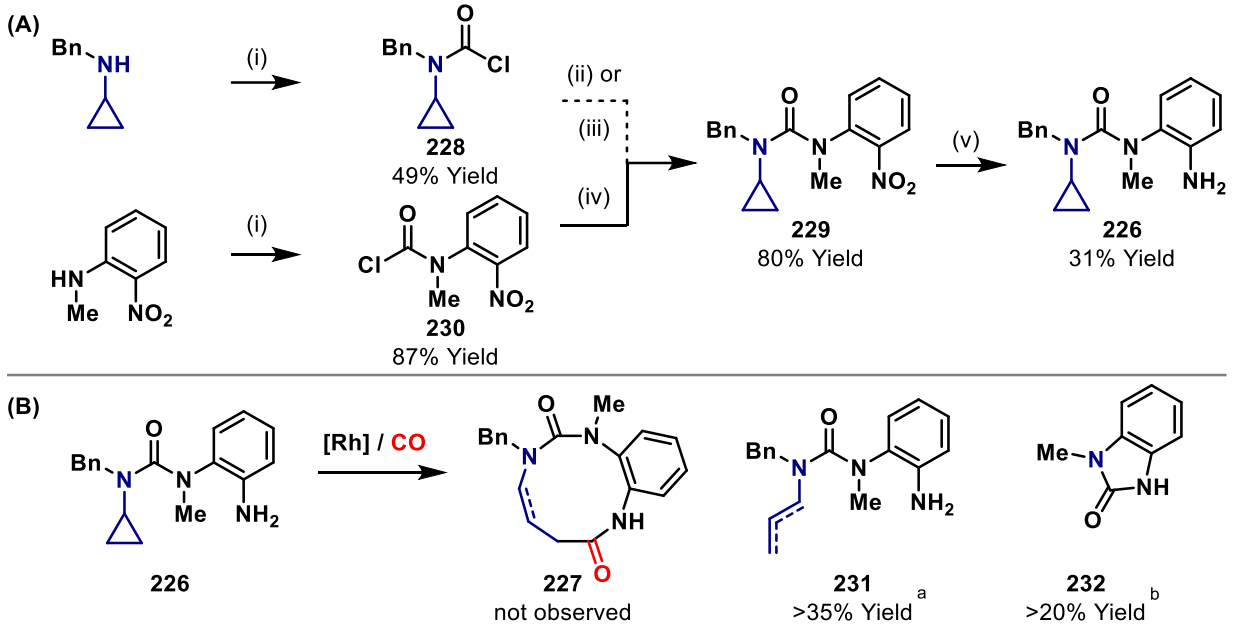
3.2.4 Evaluation of alternative systems with tethered nucleophiles

Having established that 8-membered rings can be accessed using aniline nucleophiles, efforts were undertaken to identify other suitable substrate classes. *N*-Alkyl amines **208** and **209** were inefficient for the cyclisation (Scheme 47A), so substrates containing less basic sulfonamide and urea units were targeted next. Protection of primary amine **193** with either tosyl chloride or dimethylcarbamoyl chloride delivered **222** and **223**, respectively (Scheme 49). Both of these substrates, which contain *N*-based nucleophiles to "capture" the rhodacyclopentanone intermediate, did not undergo the desired carbonylative rearrangement and adducts **224**, **225** were not observed upon exposure to various Rh(I) catalysed conditions. In the case of sulfonamide **222**, only starting material was recovered, while urea **223** decomposed under the reaction conditions. It may be that the nucleophilicity of the N1-unit is insufficient to promote the heterocyclisation of **224** and **225**.



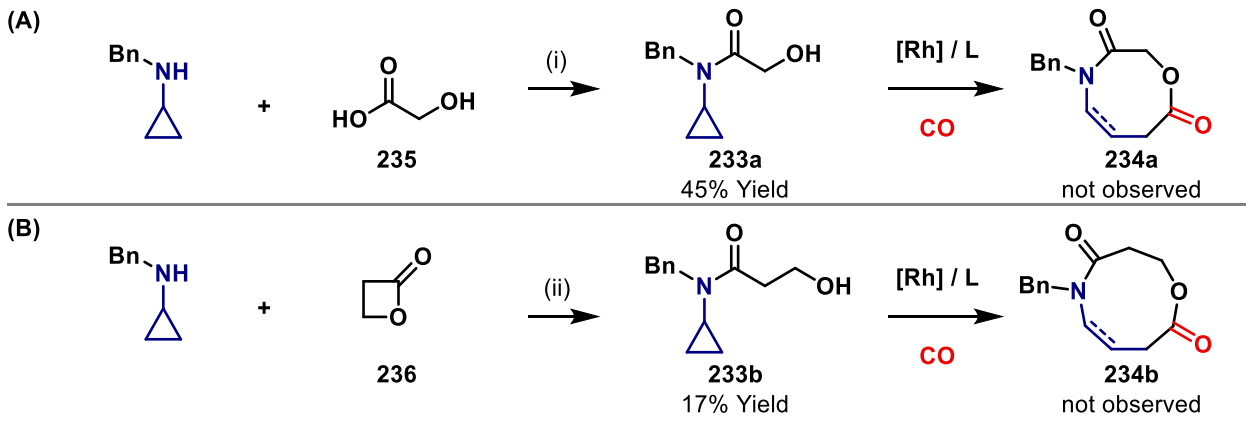
Scheme 49: Synthesis and reactivity of *N*-substituted substrates **222** and **223**. *Reagents and conditions*: (i) TsCl, pyridine, DMAP, DCM, 0 °C to r.t., 18 h; (ii) dimethylcarbamyl chloride, TEA, DCM, 0 °C to r.t., 18 h.

In concurrent studies, urea-derived substrate **226** was designed in an attempt to access larger 10-membered products like **227** (Scheme 50). The first approach to **226**, starting with the condensation of carbamoyl chloride **228** with the 2-nitroaniline, did not deliver any of intermediate urea **229** (Scheme 50A). An alternative approach, where 2-nitroaniline was transformed into its corresponding carbamoyl chloride **230** and then reacted with *N*-benzylcyclopropanamine, gave **229** in 80% yield. Finally, the reduction of the nitro group of **229** with stannous chloride provided urea **226**. Unfortunately, under various Rh-catalysed reaction conditions, the formation of **227** did not occur (Scheme 50B). Depending on the reaction conditions, β-hydride elimination product **231** or cyclisation to **232** could be observed in the ^{1}H NMR spectrum of the crude reaction mixture. This implies that the C-C bond activation step takes place, but that degradation of the intermediate occurs prior to either nucleophilic trapping of the rhodacyclopentanone or C-N reductive elimination (cf. Scheme 41A).



Scheme 50: Synthesis and reactivity of **226**. *Reagents and conditions*: (i) triphosgene, pyridine, DCM, 0 °C to r.t., 4 h; (ii) 2-nitroaniline, DMAP, DCM, 0 °C to r.t., 18 h; (iii) 2-nitroaniline, NaH, THF, 0 °C to r.t. to 60 °C, 18 h; (iv) *N*-benzylcyclopropanamine, DMAP, DCM, 0 °C to r.t., 18 h; (v) $SnCl_2$•$2H_2O$, EtOAc, 50 °C, 6 h. [a] $[Rh(cod)Cl]_2$ (5 mol%), dimethyl fumarate (100 mol%), PhCN (0.1 M), CO (1 atm), 140 °C, 48 h. [b] $[Rh(cod)_2]$BARF (5 mol%), PPh_3 (10 mol%), $PhCO_2H$ (30 mol%), 1,2-DCB (0.1 M), CO (1 atm), 100 °C, 48 h.

Substrates **233a** and **233b** were also made to explore the possibility of carbonylative heterocyclisations with tethered *O*-based nucleophiles. The synthesis of **233a** involved HOBt-assisted amide coupling with glycolic acid **235** (Scheme 51A). Upon exposure of **233a** to various Rh-catalysed carbonylative conditions, decomposition of the starting material occurred, and oxazocane **234a** did not form. Similar reactivity was observed with alcohol **233b**, which was obtained by the nucleophilic ring opening of β-propiolactone **236** with *N*-benzylcyclopropanamine (Scheme 51B). The target 9-membered product **234b** was not formed, and, instead, starting material **233b** degraded under the reaction conditions. The inability of substrates **233a** and **233b** to deliver cyclisation products **234a** and **234b** may be due to the lower nucleophilicity of tethered alcohols compared to tethered anilines. The intrinsically challenging nature of C-O reductive elimination may also contribute to the failure of these reactions.[132]

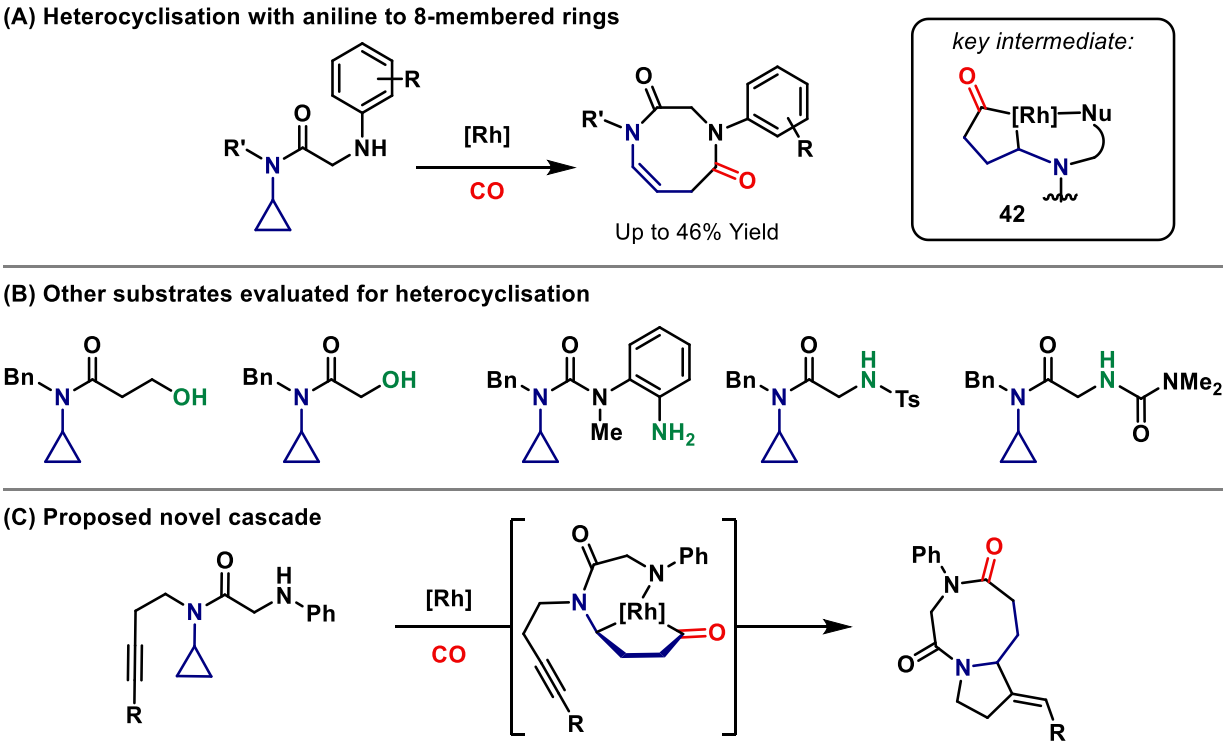


Scheme 51: Synthesis and reactivity of **233a,b**. *Reagents and conditions*: (i) EDCI, HOBt, *N*-methylmorpholine, DMF, r.t., 18 h; (ii) β-propiolactone, toluene, 105 °C, 15 min.

3.3 Conclusions

The studies in this chapter have demonstrated that 8-membered rings can be accessed in moderate yield when anilines are used as the nucleophilic component in capture-collapse heterocyclisations (Scheme 52A). A range of other substrates with tethered *N*- and *O*-based nucleophiles was examined, but no suitable systems were identified (Scheme 52B). The success of the carbonylative cyclisation is highly dependent on the electronics of the incoming nucleophile and, so far, only anilines have proved suitable for the transformation. The key challenge is to ensure that formation of the nucleophile-bound rhodacyclic intermediate **42** and subsequent C-Nu reductive elimination step are efficient enough to prevent competitive degradation pathways.

Future work in this area could focus on further evaluation of various substrates with tethered nucleophiles. For example, the studies outlined in Chapter 2 demonstrated that nucleophilic addition of ureas to rhodacyclopentanones may be followed by intramolecular carbometalation of an alkyne. The possibility of similar aniline-based cascades could be explored (Scheme 52C).



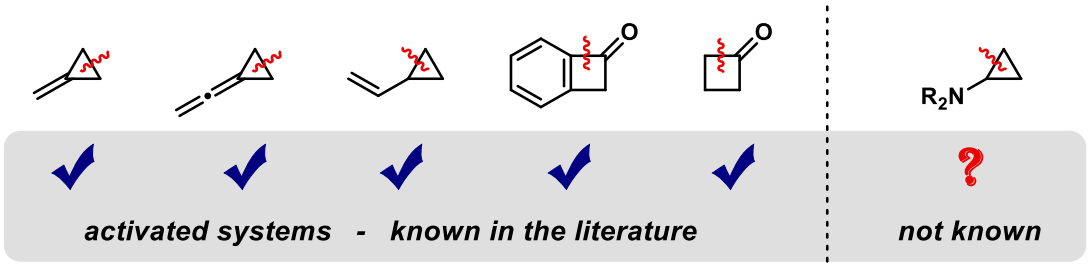
Scheme 52

CHAPTER 4

Asymmetric C-C bond activation of cyclopropylamines

4.1 Introduction

Achieving high levels of enantioselectivity under C-C bond activation conditions is challenging because such reactions often require high temperatures. However, enantioselective methodologies involving the C-C bond activation of activated cyclopropanes, such as alkylidenecyclopropanes, vinylidenecyclopropanes, vinylcyclopropanes, and 4-ring systems, such as benzocyclobutenones and cyclobutanones, have been developed. To date, enantioselective transformations involving non-activated aminocyclopropane systems have not been reported. (Scheme 53).



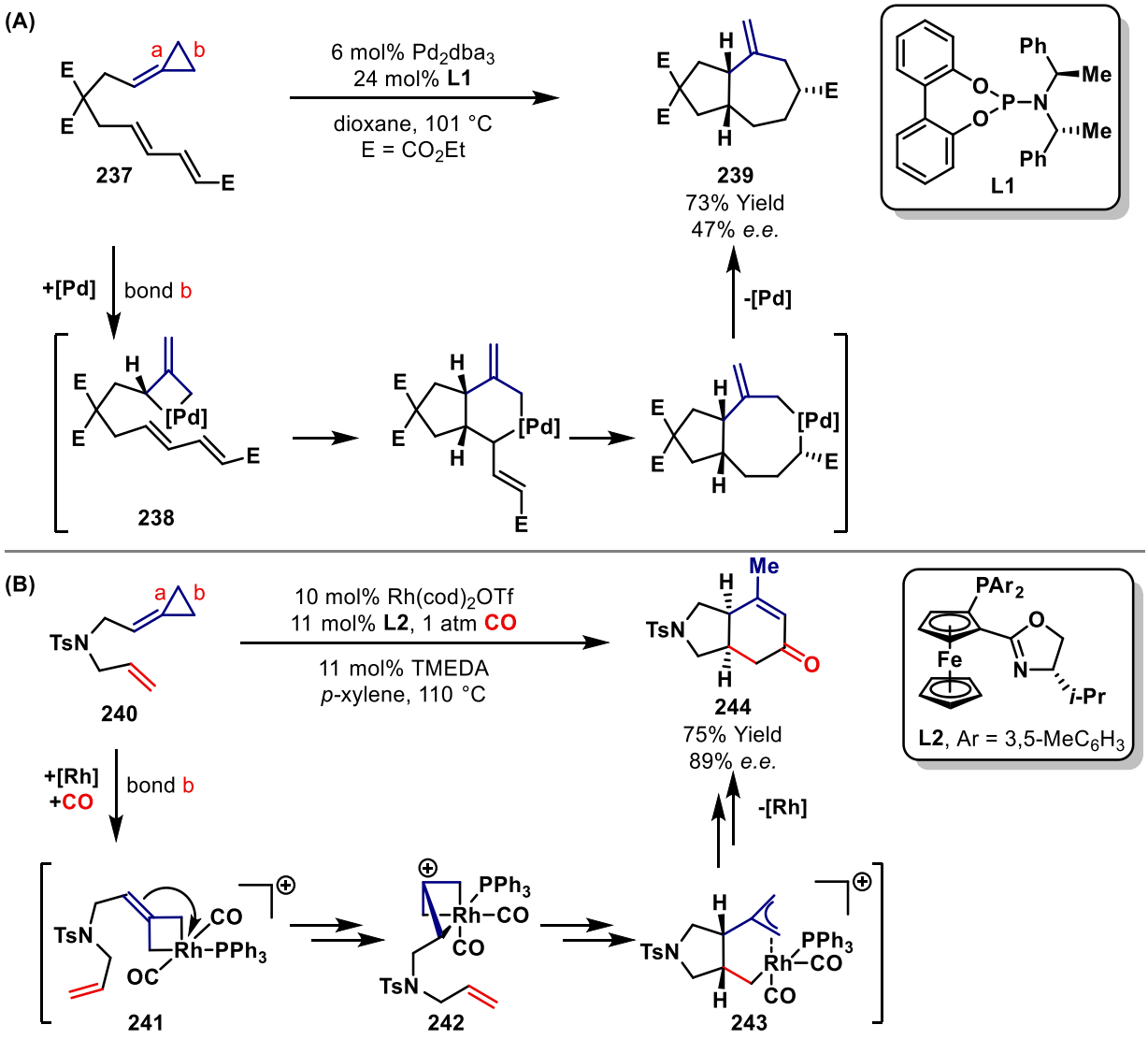
Scheme 53: Different systems for enantioselective transformations via C-C bond activation.

Alkylidenecyclopropanes (approximate strain energy of 40 kcal/mol) are highly reactive towards transition-metal-catalysed C-C oxidative addition due to the strain release during formation of the metallacycle.[133] As a result, many cycloaddition methodologies use alkylidenecyclopropane motifs.[2] Although this area has been explored for over 50 years,[134] only two reports demonstrate asymmetric induction in the course of the C-C bond activation process.

In 2007, Mascareñas and co-workers reported[135] the first example of a Pd-catalysed enantioselective intramolecular cycloaddition involving an alkylidenecyclopropane **237**. Exposure of alkylidenecyclopropane **237** to a catalyst system derived from Pd(0) and phosphoramidite ligand **L1** afforded carbocycle **239** in 73% yield and 43% e.e. (Scheme 54A). In this process, the Pd(0)-catalyst was proposed to insert into the distal bond "b", and the resulting palladacyclobutane subsequently undergoes allylic rearrangement to give palladacycle **238**. This is followed by ring-forming diastereoselective carbopalladation, allylic isomerisation and C-C reductive elimination to afford the target cycloadduct **239**. A more efficient set of conditions has been developed subsequently by the same group.[136]

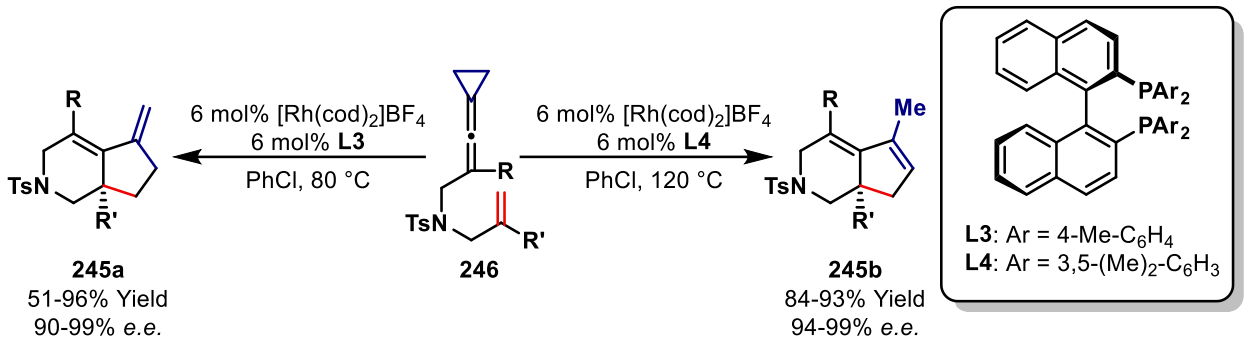
Building upon the work of Mascareñas, Evans and co-workers[137] reported a Rh(I)-catalysed enantioselective transformation involving alkylidenecyclopropane **240** (Scheme 54B). In this process, high enantioselectivity was achieved through the use of bidentate *P*,*N*-ligand **L2**. Here, a

strong preference for rhodium insertion into the distal bond "**b**" over proximal bond "**a**" was observed, leading to rhodacyclobutane **241**. Computational studies revealed that an unusual six-coordinate 18-electron Rh(III)-trimethylenemethane complex **242** is formed upon isomerisation of **241**. Subsequent alkene insertion affords η^3-allyl complex **243**, which, after CO migratory insertion, C-C reductive elimination and alkene isomerisation, provided the target structure **244** in high enantiopurity. To date, this is the only example of an enantioselective *carbonylative* C-C bond activation process known in the literature.[2,138]



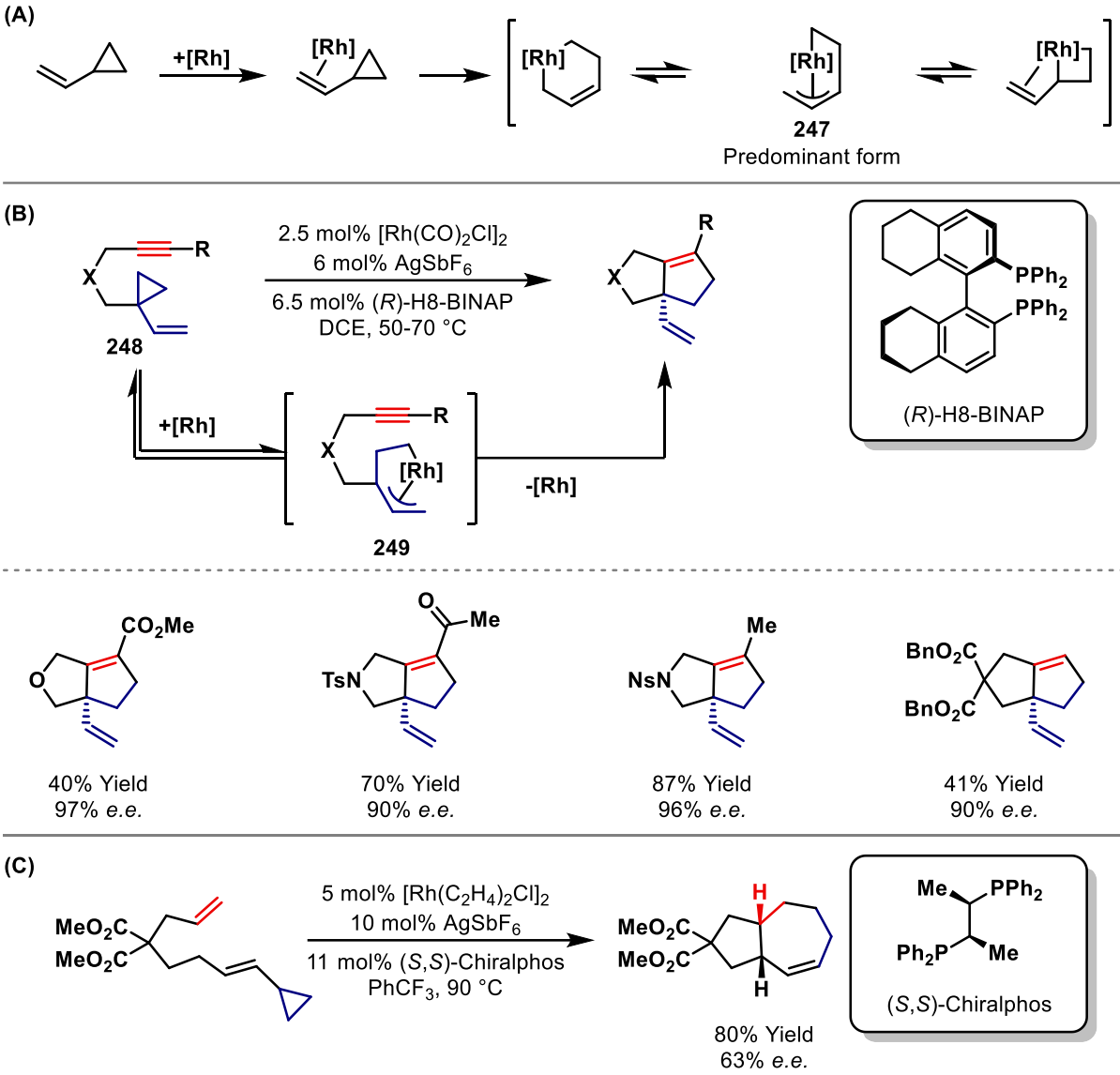
Scheme 54: Enantioselective transformations involving alkylidenecyclopropane derivatives.

Aside from alkylidenecyclopropanes, vinylidenecyclopropanes have also been employed in asymmetric transformations.[139-141] For example Wei, Shi and co-workers demonstrated that regiochemical cycloadducts **245a** and **245b** can be obtained from vinylidenecyclopropane **246** through judicious choice of BINAP-derived ligands **L3,4** (Scheme 55).[141] Control experiments suggested that **245a** and **245b** do not interconvert, indicating that different mechanistic pathways occur for their formation, and that the distinct outcomes are not down to alkene isomerisation at the stage of the cycloadduct.



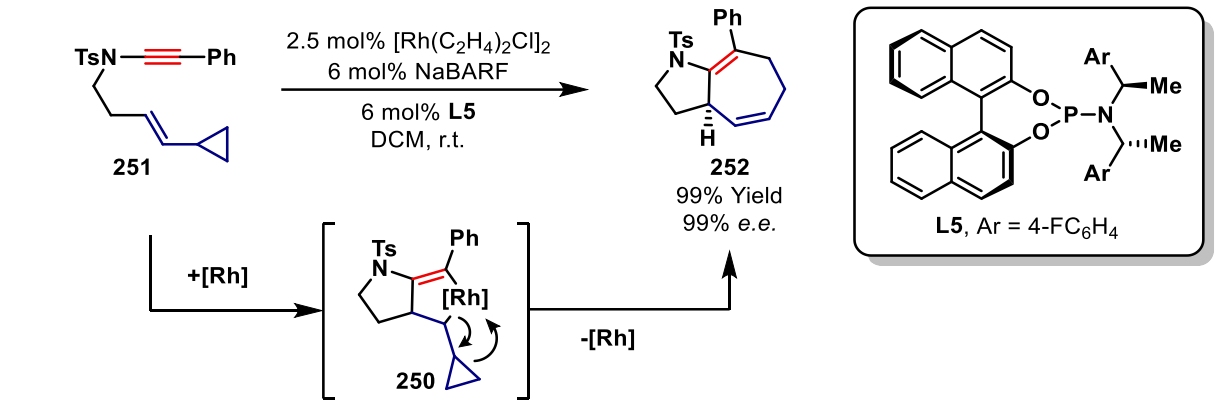
Scheme 55: Enantioselective transformations of vinylidenecyclopropane derivatives.

Another reactive strained system that has been successfully used in enantioselective C-C bond cleavage is based on the vinylcyclopropane (VCP) core. Although less strained than alkylidenecyclopropanes (approximate strain energies of 28 vs 40 kcal/mol),[133] vinylcyclopropanes are nonetheless highly reactive towards transition metal-catalysed ring cleavage. Here, the vinyl unit brings the Rh(I)-catalyst into close proximity of the cyclopropane and promotes the formation of π-allyl rhodacycle **247** (Scheme 56A). Utilising this type of C-C bond activation process, the Yu group has reported an enantioselective intramolecular (3+2) cycloaddition involving vinylcyclopropane **248**, where the metallacycle is trapped by tethered alkynes (Scheme 56B).[142] High enantioselectivity was achieved with a cationic rhodium catalyst, which was formed *in situ* from $[Rh(CO)_2Cl]_2$, $AgSbF_6$ and (*R*)-H8-BINAP. Computational calculations suggested that reversible formation of rhodacycle **249** from **248** is followed by irreversible rate determining and stereodetermining alkyne insertion. Asymmetric (5+2) annulations have also been studied. The first example, published by Wender and co-workers, demonstrated moderate enantioselectivity with (*S*,*S*)-Chiralphos as the ligand (Scheme 56C).[143] Later, the enantioselectivity of this cycloaddition was improved by using different chiral ligands.[144,145]

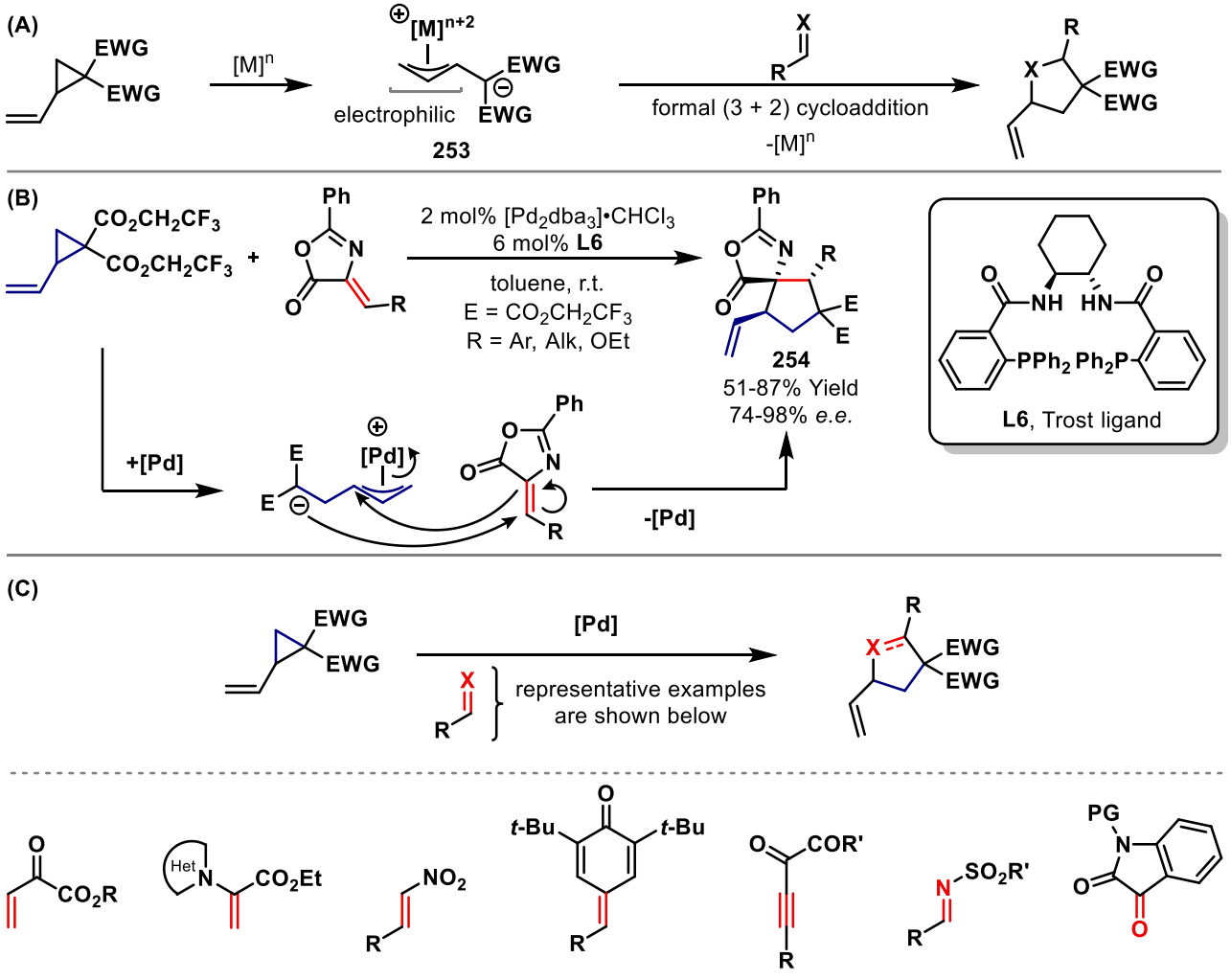


Scheme 56: Enantioselective transformations involving vinylcyclopropane derivatives.

Usually, C-C bond cleavage in VCPs occurs prior to C-C bond formation (Scheme 56A).[146] Mechanistically distinct transformations, involving oxidative coupling (to **250**) prior to β-carbon elimination and C-C reductive elimination were reported by the Anderson group (Scheme 57).[147] Exposure of ynamide substrates, such as **251**, to a cationic Rh(I)-catalyst and phosphoramidite ligand **L5** provided [5.3.0]-azabicyclic structures, such as **252**, in excellent yield and with high enantioselectivity. The reaction conditions are notably mild, with room temperature being sufficient for high turnover. This may reflect that cleavage of the cyclopropane unit occurs via β-carbon elimination instead of C-C oxidative addition.



Scheme 57: Enantioselective (5+2) cycloaddition of ynamide substrates.



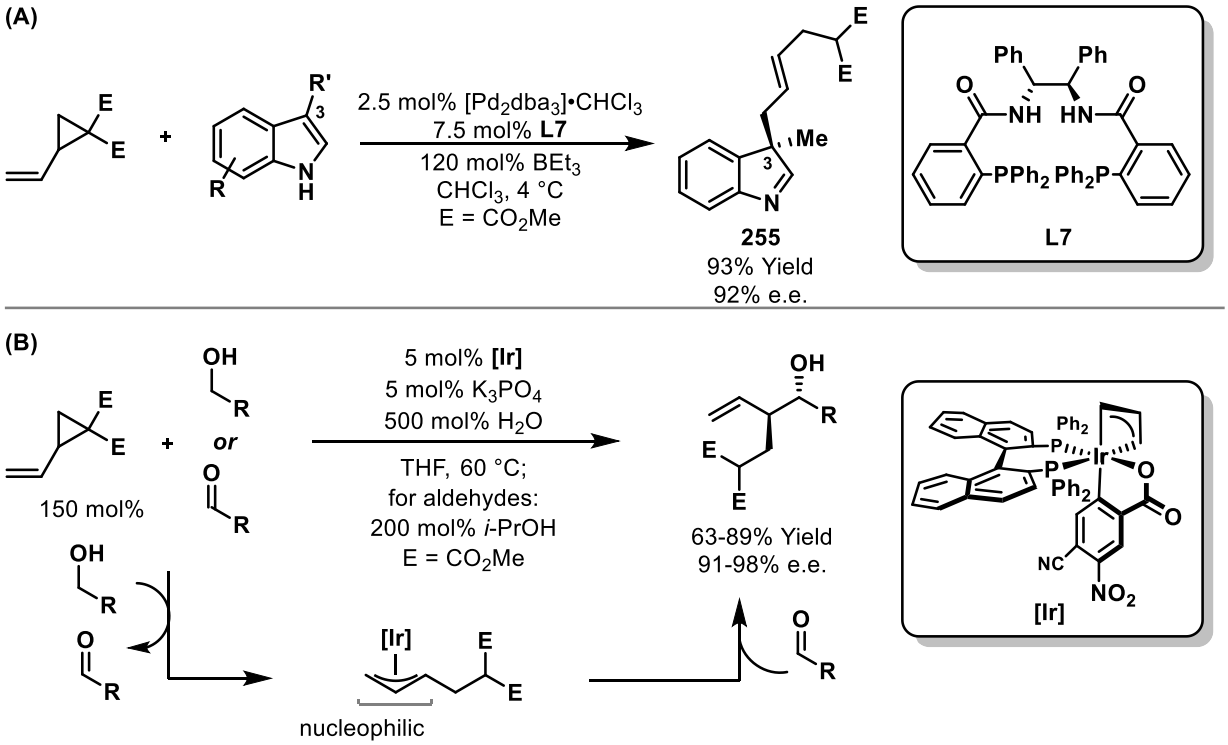
Scheme 58: Dynamic kinetic asymmetric (3 + 2) cycloadditions of vinylcyclopropanes.

Vinylcyclopropanes bearing electron withdrawing groups can form electrophilic zwitterionic η^3-allyl complexes, such as **253**, in the presence of a chiral transition metal catalyst (Scheme 58A). This complex adds in an enantioselective manner across electron-poor olefins to give various (3+2) cycloadducts, a reactivity mode first demonstrated by Trost and co-

workers.[148,149] Using the classic Trost ligand **L6**, the group was able to use alkylidene azlactones as two-carbon components yielding highly substituted five-membered cyclic systems **254** in high e.e. (Scheme 58B). Following this, many other π-unsaturates have been used in Pd(0)-catalysed asymmetric (3+2) cycloadditions, e.g. β,γ-unsaturated α-keto esters,[150] α-heterocycle-substituted acrylates,[151] nitroolefins,[152-154] *p*-quinone methides,[155] electron-deficient alkynes,[156] imines,[157-159] and isatins (Scheme 58C).[160]

Linear products with well-defined stereochemistry are also accessible using VCPs. For example, Pd-catalysed asymmetric alkylations of 3-substituted indoles was disclosed by the Trost group using modified Trost ligand **L7** (Scheme 59A).[161] Here, unlike with electron-deficient olefins (cf. Scheme 58), the initially formed 1,3-dipole first acts as an electrophile. This allows quaternary centres to be installed (e.g. **255**) by alkylation of 3-substituted indoles. In these processes, the π-nucleophilicity of the indole is enhanced by using triethylborane as additive.[162]

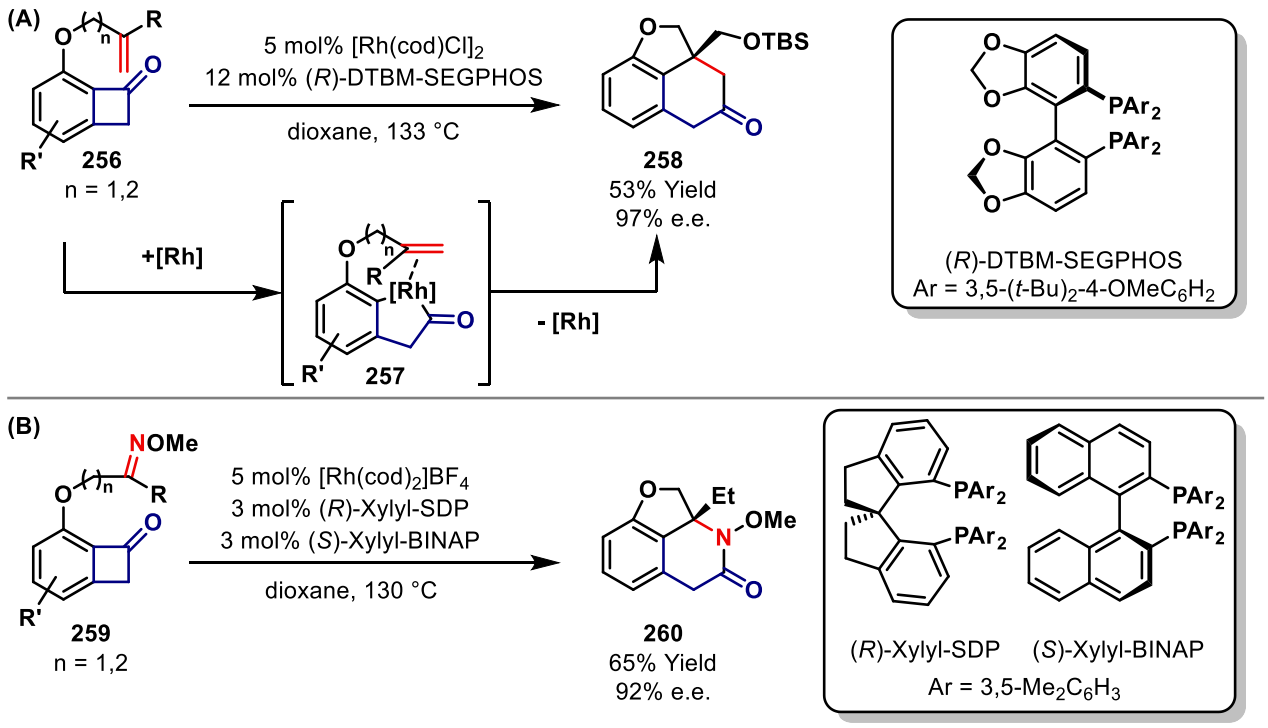
Recently, Krische and co-workers reported[163] an umpolung process, where a donor-acceptor VCP and the cyclometalated Krische Ir-catalyst was used to generate an unusual nucleophilic π-allyl intermediate (Scheme 59B). This was able to engage in efficient asymmetric carbonyl allylation. The coupling partner in the process is either an aldehyde with a sacrificial equivalent of isopropanol as reductant, or an alcohol, which is converted to an aldehyde in situ.



Scheme 59: Asymmetric transformations of vinylcyclopropanes giving linear products.

Four-membered systems, namely cyclobutanone derivatives, have also been employed in asymmetric transformations. Dong and co-workers have published several methodologies in which benzocyclobutenones undergo Rh-catalysed C-C bond activation. Following C-C oxidative

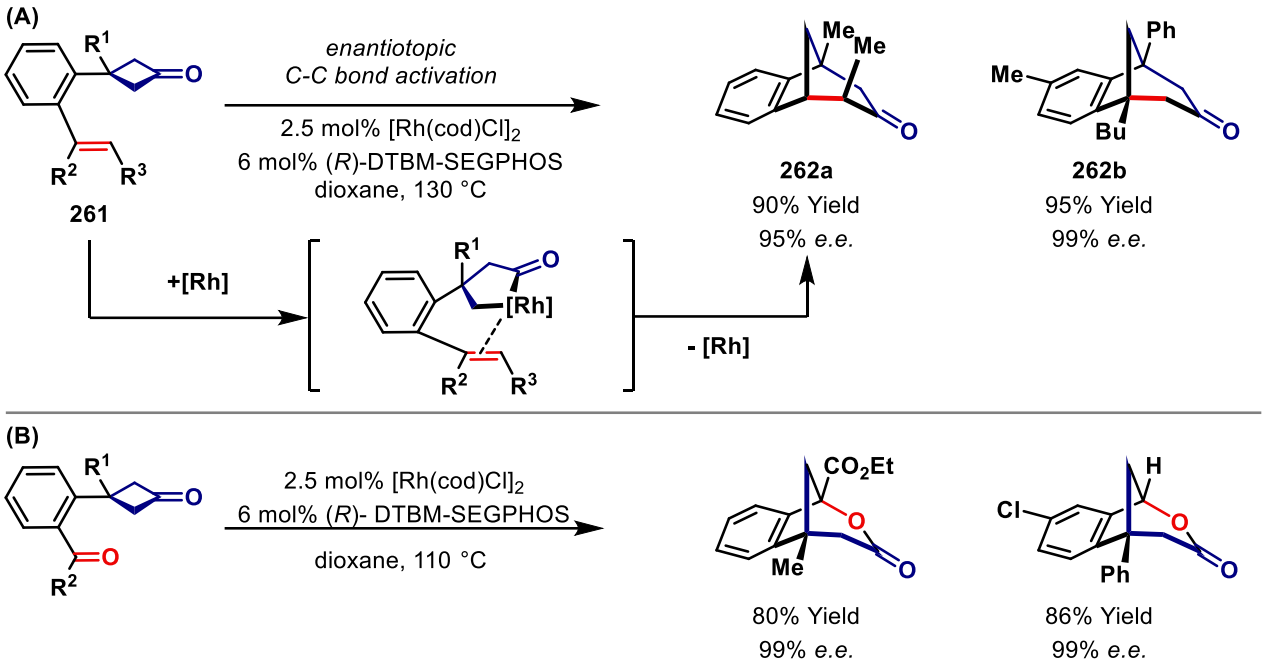
addition of the cyclobutanone (e.g. **256**), the rhodabenzocyclopentenone intermediate is trapped by a tethered π-unsaturate (Scheme 60). First, it was shown that rhodacycle **257**, formed upon regioselective insertion of rhodium into cyclobutenone **256**, can undergo enantiodetermining migratory insertion of the tethered alkene to give tricyclic products like **258** by using a bulky and electron-rich SEGPHOS-based ligand (Scheme 60A).[164] Subsequently, the group showcased the methodology in the total synthesis of (−)-cycloclavine.[165] Later, it was shown that oximes **259** can function as the inserting π-unsaturate to provide lactams **260** (Scheme 60B).[166] Interestingly, a mixed-ligand catalyst system was necessary: while (*R*)-Xylyl-SDP gave higher enantiomeric excess than (*S*)-Xylyl-BINAP (98 vs. 92% e.e.), the yield was higher for the latter (53 vs 79%). Combining both ligands resulted in prolonged catalytic activity and high enantioselectivity.



Scheme 60: Asymmetric transformations of benzocyclobutenones.

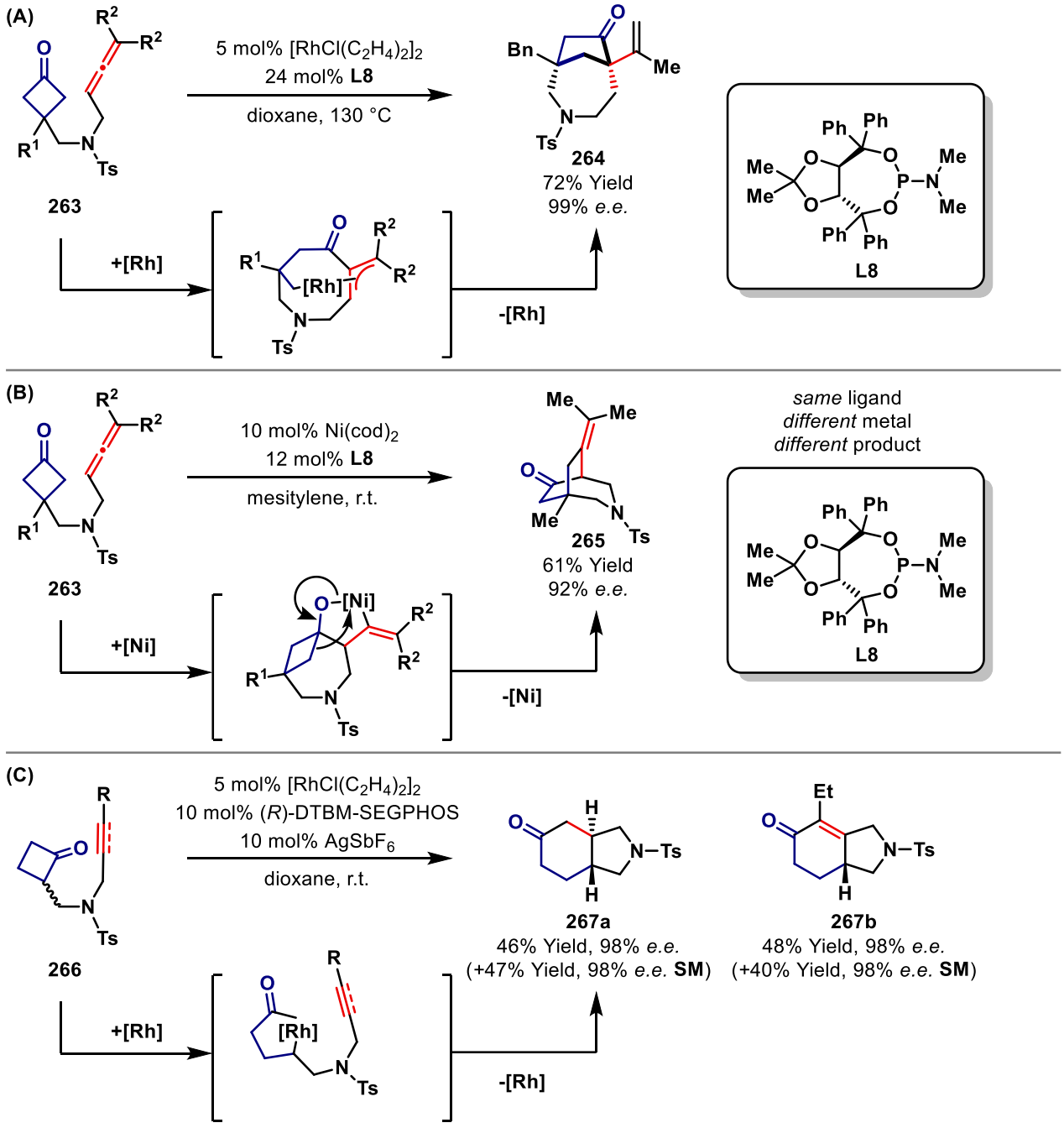
Aside from benzocyclobutenones, less strained cyclobutanone derivatives have also been used in asymmetric C-C bond activations and related processes. In particular, there are several publications that demonstrate the use of an aromatic tether between the cyclobutanone unit and the inserting π-unsaturate. Building upon research from Murakami and co-workers,[167] the Cramer group have demonstrated Rh(I)-catalysed C-C bond activation of cyclobutanone derivatives **261** (Scheme 61A).[29] Highly enantioselective C-C bond activation occurs when (*R*)-DTBM-SEGPHOS (cf. Scheme 60A) is used. The researchers propose that the initial coordination of the inserting alkene and the cyclobutanone carbonyl to Rh provides a highly ordered transition state, which makes the C-C cleavage step more enantioselective. As a result, different complex bicyclic

ketones such as **262a** and **262b** are formed efficiently after migratory insertion and reductive elimination. An analogous process, using ketones and aldehydes in place of the alkene component, has also been published (Scheme 61B).[31]



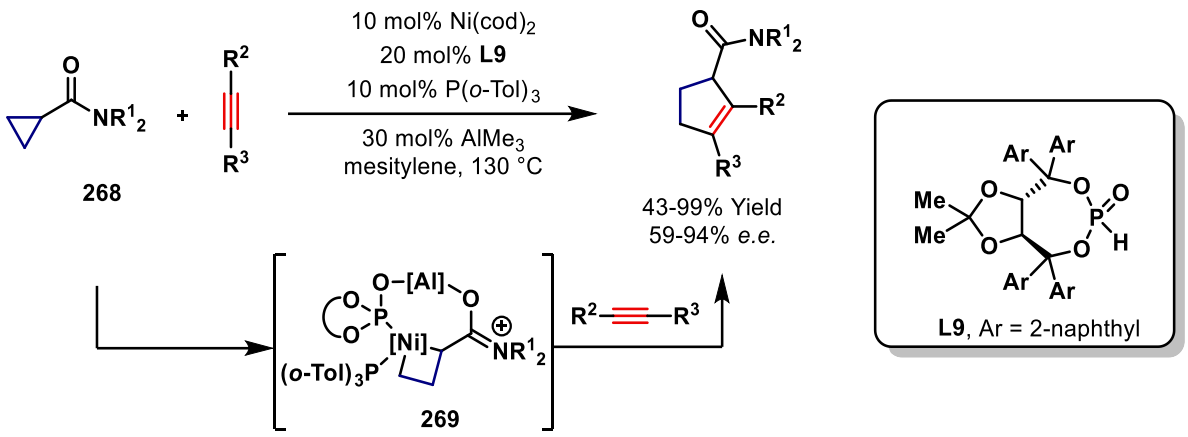
Scheme 61: Asymmetric transformations of cyclobutanones, tethered to an aromatic ring.

Finally, recent publications from Dong and co-workers have explored the possibility of asymmetric transformations of cyclobutanones using π-unsaturates that are attached by an aliphatic (rather than aromatic) linker. For allene-derived substrate **263**, regiochemically distinct cycloadducts **264** and **265** can be obtained using either Rh- or Ni-based catalyst systems (Scheme 62A vs. Scheme 62B).[33,35] Cyclobutanones **266** with tethered alkynes or terminal alkenes have been shown to participate in Rh(I)-catalysed kinetic resolutions at room temperature, giving fused bicyclic products **267** (Scheme 62C).[168]



Scheme 62: Asymmetric transformations and kinetic resolutions of cyclobutanones.

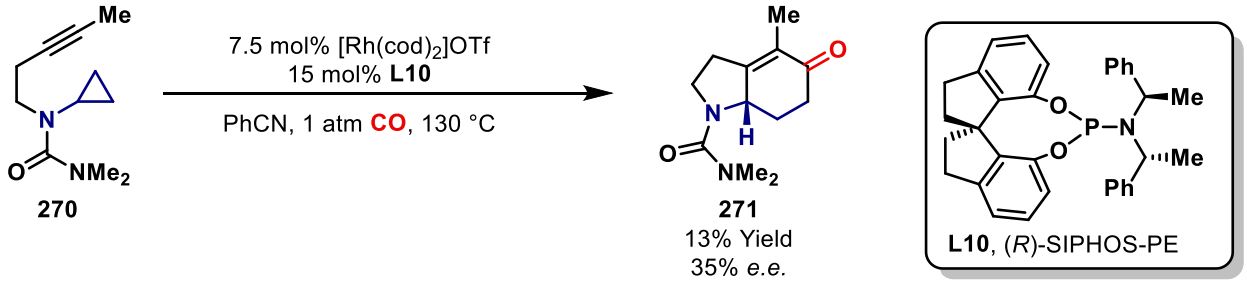
A single report of enantioselective C-C bond activations using less activated 3-ring systems has been disclosed by Ye and co-workers. Here, a ligand-enabled bimetallic strategy was employed to allow enantioselective intermolecular (3+2) cycloadditions between cyclopropyl carboxamides **268** and alkynes (Scheme 63).[169] In this process, ligand **L9** is ligated to both a Ni-catalyst and an aluminium-based Lewis acid; the latter, coordinates to the carbonyl unit of **268**, which facilitates the formation and stabilisation of nickelacycle **269**. An additional achiral phosphine ligand (P(*o*-Tol)$_3$) further stabilises the nickelacycle and is proposed to assist with the initial oxidative addition event.



Scheme 63: Asymmetric transformation of cyclopropyl carboxamides.

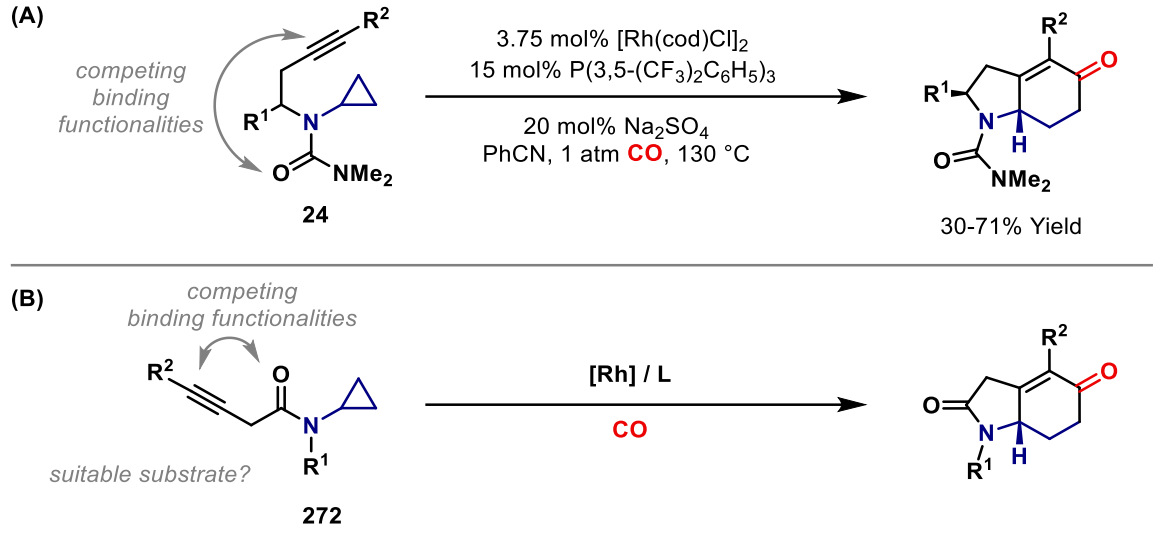
4.2 Reaction design

The processes described above encompass enantioselective transformations that are possible via C-C bond cleavage of small ring systems. However, achieving high levels of enantioselectivity in C-C bond activation processes involving simple, non-activated cyclopropane-based systems is highly challenging due to the lower reactivity of such motifs. To date, there are no reported highly asymmetric processes involving aminocyclopropanes. Early investigations conducted at Bristol by Dr. Shaw sought to address this issue, and the urea-directed C-C activation protocol involving protected aminocyclopropane **270** was screened with various chiral ligands (see also Section 1.3, Scheme 5B).[123] An encouraging level of enantioselectivity was achieved using phosphoramidite ligand **L10**, which afforded **271** in 35% e.e., albeit in low yield (Scheme 64).



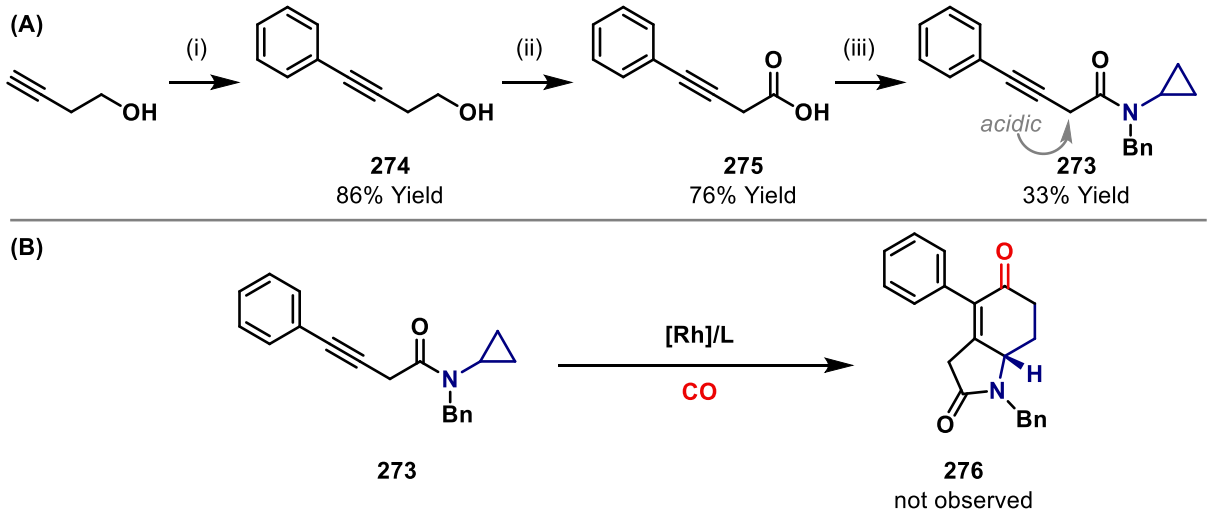
Scheme 64: Early study towards enantioselective (3+1+2) cycloadditions in the Bower group.

As a result of this preliminary study, efforts were directed towards finding other substrate classes suitable for an enantioselective C-C bond activation-based methodology. Extensive efforts were made to render the (3+1+2) cycloaddition process involving substrate **270** highly enantioselective, but no further improvements were forthcoming. Accordingly, substrate modification was deemed an attractive direction of research (Scheme 65A). Initial studies on urea-based substrates highlighted the importance of a strong directing group (urea) to outcompete the alkyne for coordination to Rh(I) prior to C-C oxidative addition of the cyclopropane. However, system **272** was considered as an alternative to **24** (Scheme 65B). It was proposed that the requirement for the strong directing group might be alleviated by tethering the alkyne moiety to the directing group unit; here, inductive effects should decrease the alkyne's donor ability. Additionally, in this design, the R^1 substituent on nitrogen can be varied, which offers more diversity versus the approach in Scheme 65A.



Scheme 65: Relevant work from the Bower group and starting material design.

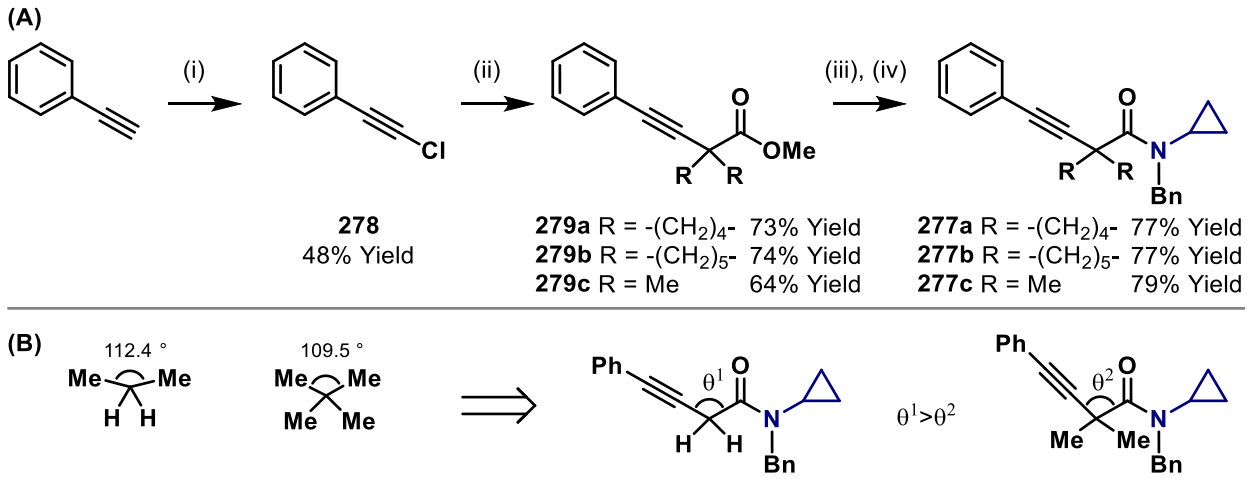
With the design in Scheme 65B in hand, amide **273** was synthesised (Scheme 66A). This was achieved by Sonogashira cross-coupling of 3-butyn-1-ol with phenyl iodide to form **274**, Jones oxidation (to **275**) and amide formation via the corresponding acid chloride. Subjection of **273** to >10 sets of Rh(I)-catalysed conditions resulted only in degradation of starting material and cycloadduct **276** was not observed (Scheme 66B). It was reasoned that this might be due to the acidic and enolisable propargylic CH_2 group of substrate **273**.



Scheme 66: Synthesis and reactivity of cyclopropylamide **273**. *Reagents and conditions*: (i) $PdCl_2(PPh_3)_2$, CuI, PhI, Et_3N, r.t.; (ii) CrO_3, H_2SO_4, H_2O, acetone, 0 °C; (iii) oxalyl chloride, DCM, r.t., then *N*-benzylcyclopropanamine, DCM, 0 °C to r.t.

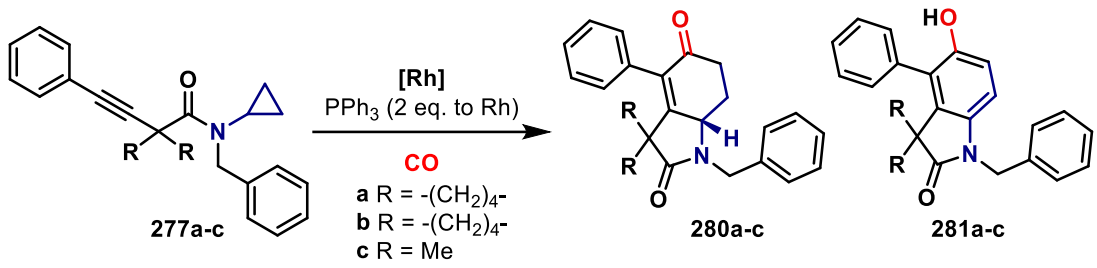
An easy way to prevent enolisation at the α-position of **273** is to change the C-H bonds to two identical substituents. Synthesis of substrates **277a-c** was achieved by electrophilic alkynylation of various *gem*-disubstituted methyl esters with alkynyl chloride **278** to form esters **279a-c** (Scheme 67A).[170-172] Subsequent ester hydrolysis and amide coupling of the resulting

carboxylic acids delivered target substrates **277a-c**. Substrates **277a-c** may also benefit from the Thorpe-Ingold effect: bulky substituents at the tetrahedral centre can compress the angle between the other two reacting substituents ($\theta^1>\theta^2$) (and/or more strongly favour the reactive conformer, *vide infra*), and this effect can accelerate alkyne insertion (Scheme 67B).[173,174]



Scheme 67: Synthesis of cyclopropylamides **277a-c** and a rationalisation of the Thorpe-Ingold effect. *Reagents and conditions*: (i) *n*-BuLi, NCS, THF, -78 °C to r.t.; (ii) corresponding methyl ester, LDA, THF, -78 °C to r.t.; (iii) 4.0 M aq. NaOH, MeOH, r.t.; (iv) *N*-benzylcyclopropanamine, EDCI, DMAP, DCM, 0 °C to r.t.

Initial studies to test the feasibility of the proposed transformation were undertaken with cyclopentyl derivative **277a** (Table 4). First, cationic and neutral Rh(I) sources modified with PPh_3 were screened in either coordinating or non-coordinating solvents (Table 4, Entries 1-4). Pleasingly, cyclohexenone **280a** was isolated in 71% yield utilising a cationic precatalyst ($[Rh(cod)_2]OTf$) and non-coordinating solvent (1,2-DCB) (Table 4, Entry 4). The use of other cationic Rh(I) sources and electron-rich or electron-poor triphenylphosphine derivatives was detrimental to the reaction yield (not shown in Table 4). With the first-generation conditions in hand, other disubstituted derivatives were evaluated. Cyclohexyl derivative **277b** performed much worse than its cyclopentyl homologue **277a** and a significant amount of phenol side product **281b** was obtained (Table 4, Entry 5). This side product may be the result of further oxidation of cyclohexenone **280b**, suggesting that under these conditions cycloaddition of substrate **277b** is faster. Lowering the temperature or reaction time gave comparable yields and suppressed formation of the phenol side product **281b** (Table 4, Entries 6 and 7); for convenience, further optimisation was pursued using a reaction time of 48 h. Pleasingly, reducing the loading of $[Rh(cod)_2]OTf$ from 10 to 5 mol% did not appreciably change yields of **280a-c** (Table 4, Entries 8-10).



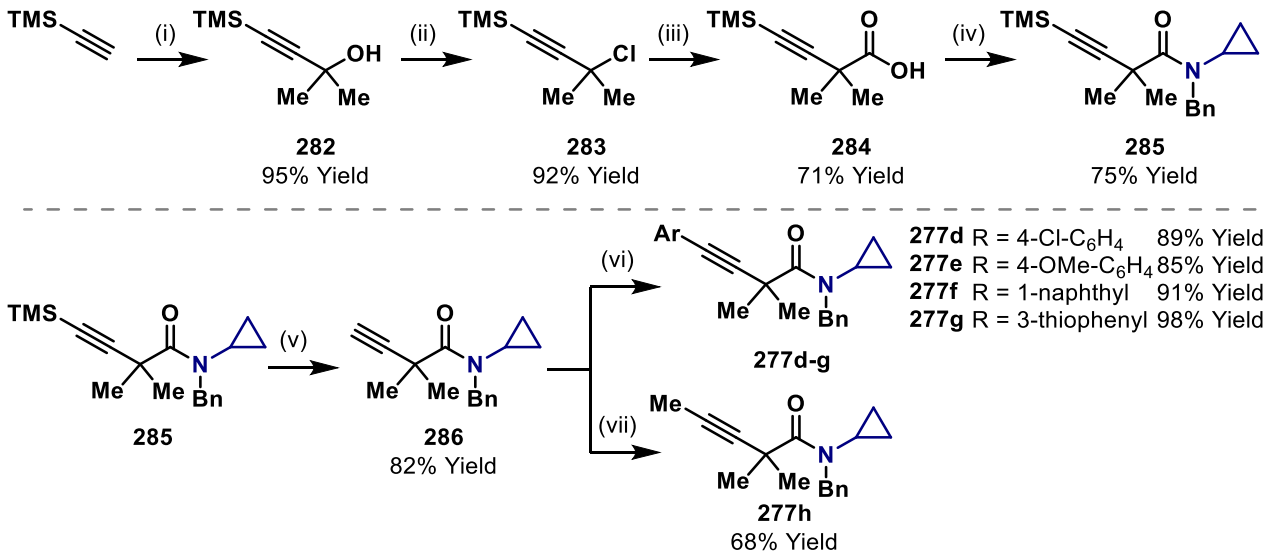
Entry	Rh^{I} (mol %)	R	Solvent (M)	T (°C)	Time (h)	Yield of 280[a] (%)	Yield of 281[a] (%)
1	$[Rh(cod)Cl]_2$ (5)	$-(CH_2)_4-$	1,2-DCB (0.1)	130	72	0	0
2	$[Rh(cod)Cl]_2$ (5)	$-(CH_2)_4-$	**PhCN (0.1)**	130	72	12	0
3	**$[Rh(cod)_2]OTf$ (10)**	$-(CH_2)_4-$	PhCN (0.1)	130	72	37	0
4	$[Rh(cod)_2]OTf$ (10)	$-(CH_2)_4-$	**1,2-DCB (0.1)**	130	72	73 (71)	trace
5	$[Rh(cod)_2]OTf$ (10)	$-(CH_2)_5-$	1,2-DCB (0.1)	130	72	31 (26)	35 (20)
6	$[Rh(cod)_2]OTf$ (10)	$-(CH_2)_5-$	1,2-DCB (0.1)	**120**	72	80	trace
7	$[Rh(cod)_2]OTf$ (10)	$-(CH_2)_5-$	1,2-DCB (0.1)	130	**48**	82	trace
8	**$[Rh(cod)_2]OTf$ (5)**	$-(CH_2)_5-$	1,2-DCB (0.1)	130	48	81 (78)	trace
9	$[Rh(cod)_2]OTf$ (5)	**$-(CH_2)_4-$**	1,2-DCB (0.1)	130	48	79 (75)	0
10	$[Rh(cod)_2]OTf$ (5)	**Me**	1,2-DCB (0.1)	130	48	80 (77)	trace

Table 4: Optimisation studies for the new (3+1+2) cycloaddition. [a]Yields were determined by ^1H NMR spectroscopy using 1,4-dinitrobenzene as a standard. Isolated yields are given in parentheses.

4.3 Reaction scope

4.3.1 Scope of the substitution on the alkyne component

With the optimised reaction conditions established, efforts focused on defining the scope of the transformation. To vary the alkyne component, a different approach to the synthesis of the substrates was employed (Scheme 68, cf. Scheme 67A). The synthesis of **277d-h** commenced with alkynylation of acetone to give tertiary alcohol **282** in good yield, which was treated with HCl to form alkyl chloride **283** in excellent yield. Grignard formation followed by a quench with dry ice afforded carboxylic acid **284**, and subsequent amide coupling gave amide **285**. TMS deprotection led to terminal alkyne **286**, which was cross-coupled with various aromatic halides giving **277d-g** in excellent yield (85-98%). Alternatively, deprotonation of alkyne **286** with *n*-BuLi and alkylation of the resulting anion with methyl iodide afforded **277h**.



Scheme 68: Synthesis of cyclopropylamides **277d-h**. *Reagents and conditions*: (i) *n*-BuLi, acetone, THF, -78 °C to r.t.; (ii) conc. HCl, 0 °C to r.t.; (iii) Mg, THF, 0 °C to r.t., then CO_2 (dry ice); (iv) *N*-benzylcyclopropanamine, EDCI, DMAP, DCM, 0 °C to r.t.; (v) K_2CO_3, MeOH, 0 °C to r.t.; (vi) $PdCl_2(PPh_3)_2$, CuI, Ar-Hal, Et_3N, r.t. or 60 °C; (vii) *n*-BuLi, MeI, -78 °C to r.t.

Cyclopropanes **277a-h** were used under the optimised Rh(I)-catalysed conditions and good yields were obtained regardless of the electronics of the alkyne component (52-88% yield) (Table 5). Both electron-poor (**280d**) and electron-rich (**280e**) aromatic substituents were tolerated, as well as heteroaromatic functionality (**280g**) and alkyl substituents (**280h**). The structure of *para*-methoxyphenyl-substituted cyclohexenone **280e** was confirmed by X-ray crystallography (see Table 5).

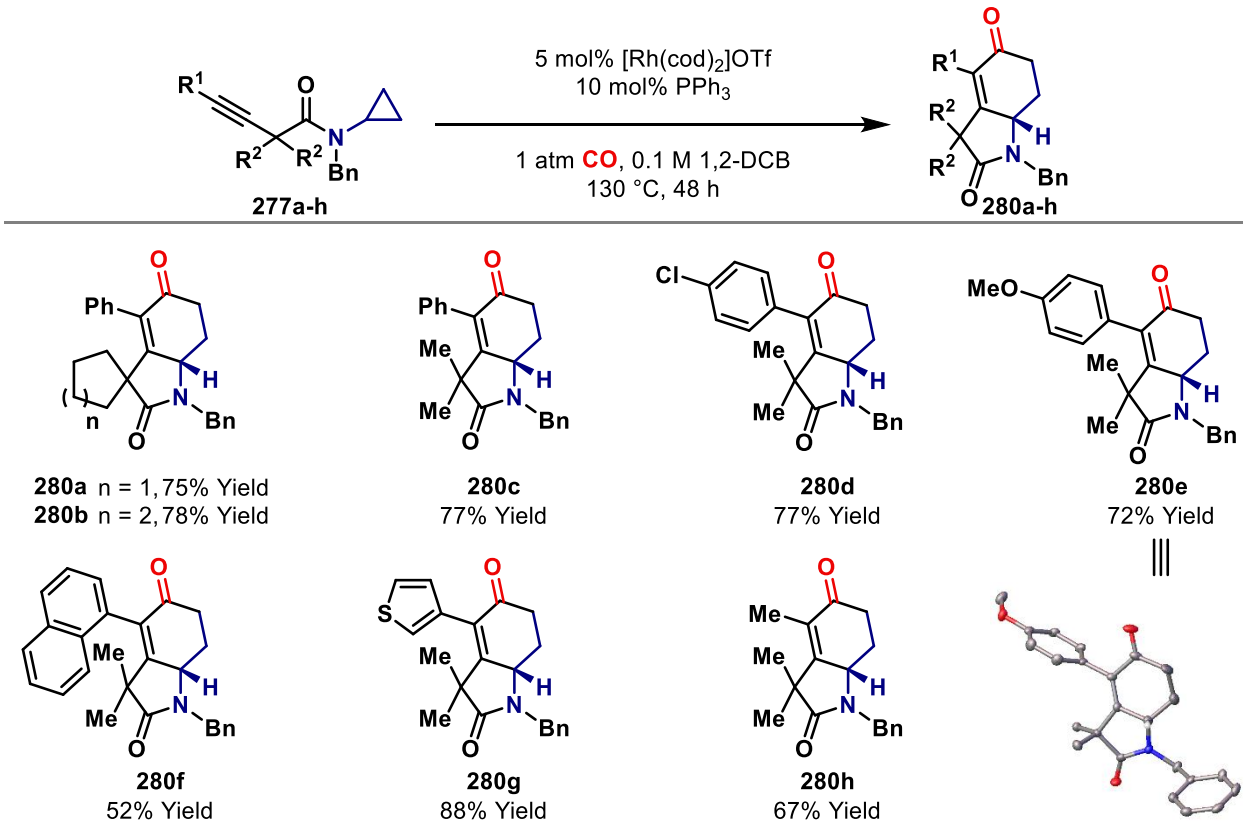
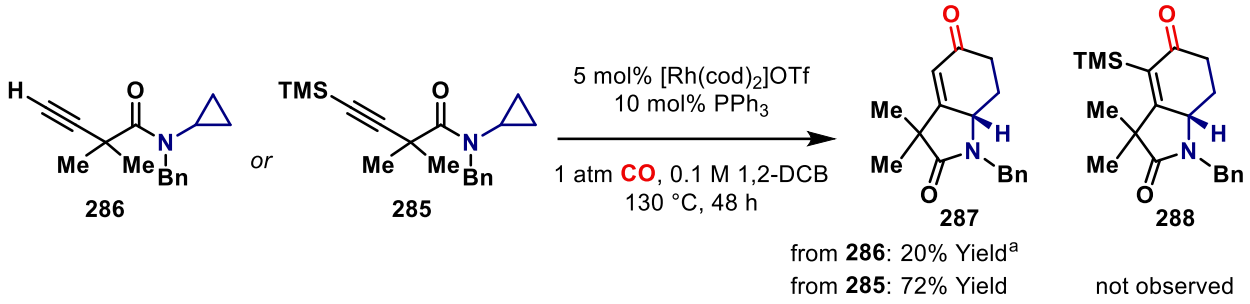


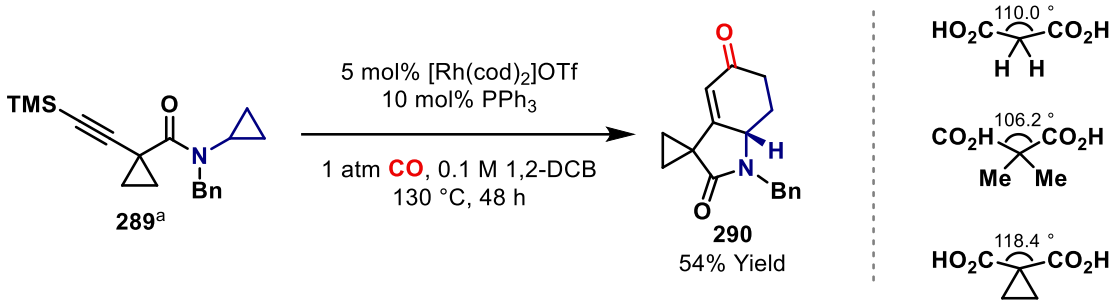
Table 5: Scope of the (3+1+2) cycloaddition with respect to the alkyne containing unit.

Substrate **286**, bearing a terminal alkyne, and TMS-protected alkyne **285** were also evaluated under the reaction conditions (Scheme 69). Substrate **286** gave **287** in poor yield, which may be rationalised by the competing formation of inactive Rh-vinylidene species.[175,176] Interestingly, when silyl-protected alkyne **285** was used in the reaction instead, the product (**287**) that had been expected from the cycloaddition of **286** was obtained and silylated analogue **288** was not observed. It is unclear at which stage desilylation occurs. In one scenario, slow release of the unprotected terminal alkyne **286** prevents catalyst poisoning, or, alternatively, desilylation occurs to deliver **287** after formation of TMS-bearing cyclohexenone **288**. If the latter is operative, the process must be relatively facile as **288** was not observed in the ^{1}H NMR spectrum of the crude reaction mixture.



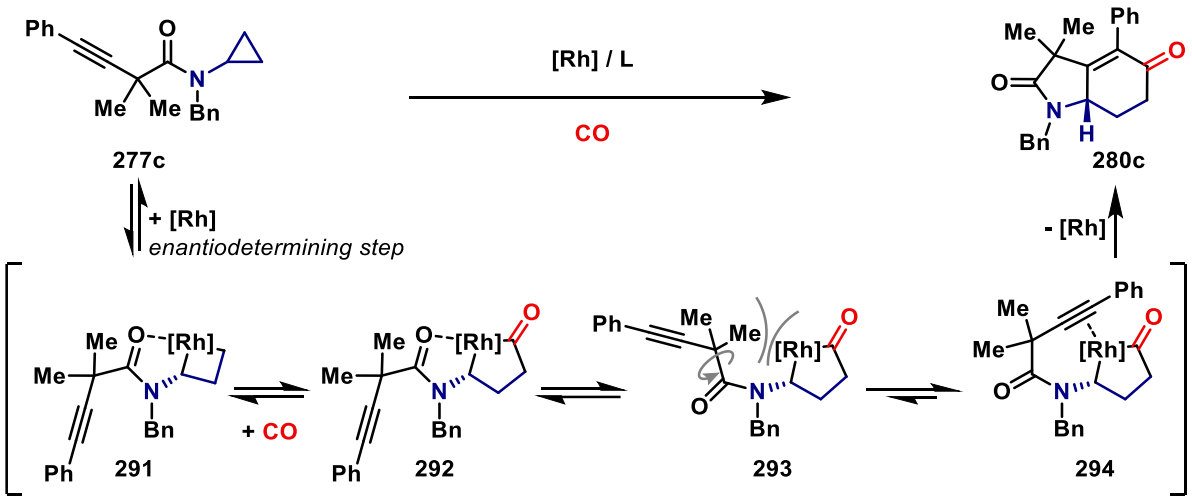
Scheme 69: Reactivity of cyclopropylamides **285** and **286**. [a]Yield was determined by ^{1}H NMR spectroscopy using 1,4-dinitrobenzene as a standard.

The design of the *gem*-disubstituted substrates used so far was, in part, driven by the idea that angle compression might facilitate cycloaddition (see Scheme 67B). To probe this further, substrate **289**, which has a cyclopropane as the *gem*-disubstituting unit, was synthesised. Exposure of this to optimised conditions provided cycloaddition product **290** in 54% yield (Scheme 70). The fact that the yield of **290** is comparable to parent system **285** helps distinguish the two commonly invoked explanations for the *gem*-disubstituent effect: "angle compression upon substitution" and the "reactive rotamer effect".[173,177] If the former is operative, then switching the dimethyl substituents of e.g. **285** to a cyclopropyl moiety (**289**) would increase the angle between the alkyne and cyclopropane-bearing units of the molecule and this would be expected to significantly decrease reaction efficiency. Related bond angle changes have been confirmed by X-ray analysis of substituted malonic acids (Scheme 70, right);[178] note how the angle is increased to 118.4° in the case of the cyclopropyl system. Hence, the commonly invoked explanation for the "Thorpe-Ingold effect" does not account for the high efficiency of the conversion of **289** to **290**; instead, the "reactive rotamer effect" provides a more compelling explanation. The successful conversion of **289** to **290** is notable also because it shows that there is a strong preference for oxidative insertion of Rh(I) into the cyclopropylamine C-C bond over the more electron poor α-cyclopropyl unit.



Scheme 70: Cycloaddition involving cyclopropylamide **289**. [a]Amide **289** was synthesised by Curley.

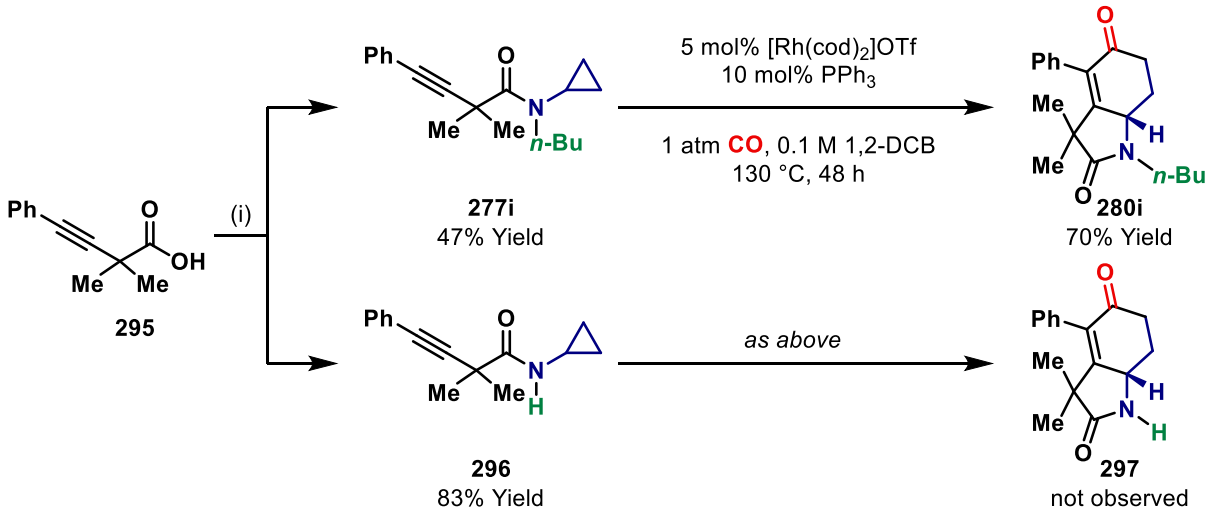
A plausible mechanism for the (3+1+2) cycloaddition is outlined in Scheme 71. First, amide-directed formation of rhodacyclopentanone **292** occurs from substrate **277c** via rhodacyclobutane **291**. Then, after directing group dissociation, access to π-complex **294** is facilitated by the greater conformational population of the "reactive" rotamer: steric clashes between the *gem*-disubstituents and the Rh(III)-centre in **293** shifts the equilibrium more towards **294**. This facilitates alkyne coordination and leads to migratory insertion and reductive elimination to give the target cyclohexenone **280c**. The migratory insertion step could involve either the Rh-acyl bond or the Rh-C(sp^3) bond – these options have not been distinguished experimentally.



Scheme 71: Proposed reaction mechanism.

4.3.2 Scope of the nitrogen substituent

To evaluate further the scope of the carbonylative cycloaddition, cyclopropylamides **277i** and **296**, containing two different substituents on the nitrogen were made by amide coupling with acid **295** (Scheme 72). Substrate **277i**, containing an *n*-butyl group, performed well in the reaction, giving **280i** in 70% yield. When secondary amide **296** was tested, only degradation of the starting material occurred with no target material **297** observed in the ^{1}H NMR spectrum of the crude mixture or by TLC analysis. The lack of productive reactivity can be attributed to side reactions, possibly involving inter- or intramolecular addition of the amide across the alkyne.[179] Unfortunately, the process resulted in a complex mixture of products, and so a precise rationalisation for its failure cannot be advanced.



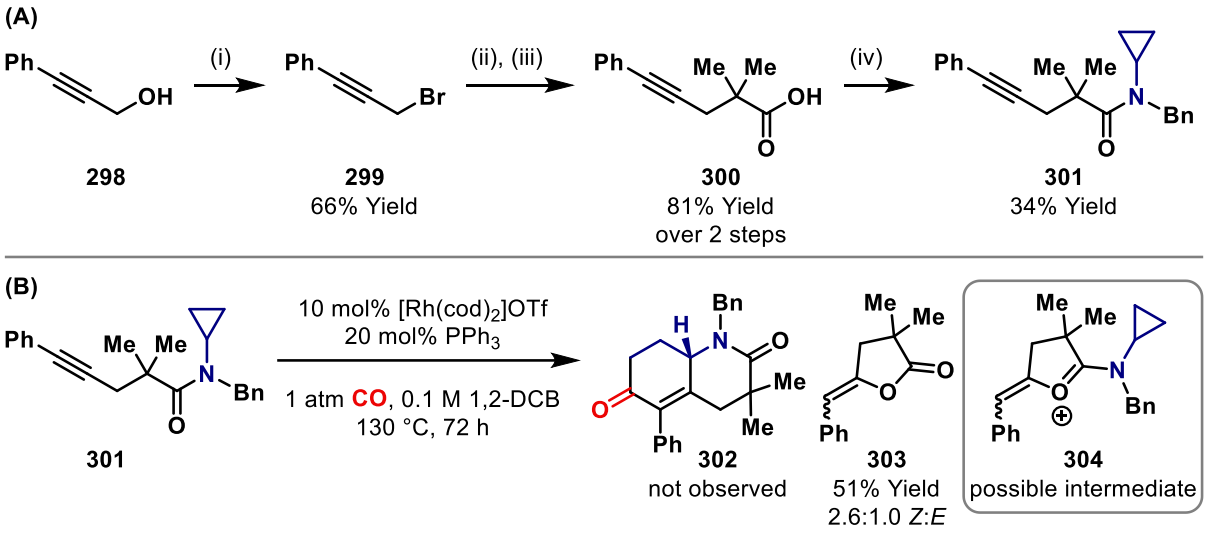
Scheme 72: Evaluation of substrates with different substituents on the nitrogen. *Reagents and conditions*: (i) corresponding cyclopropanamine, EDCI, DMAP, DCM, 0 °C to r.t.

4.3.3 Synthesis and evaluation of substrates with different alkyne tether lengths

With the successful cycloaddition of one class of substrates demonstrated (cf. Table 5), attention turned to finding other amenable systems. Ultimately, a wide pool of suitable substrates would increase the chances of finding a suitable system for a subsequent asymmetric protocol.

Substrates similar to the working system, but with different linker lengths between the alkyne and the directing group were tested under various Rh(I)-catalysed carbonylative conditions. To test whether another CH_2 group could be inserted into the linker, amide **301** was synthesised via a four-step protocol (Scheme 73A). First, Appel reaction with propargylic alcohol **298** afforded bromide **299**, which was used as an alkylating reagent with the enolate of methyl isobutyrate. The resulting ester was saponified to carboxylic acid **300** in good overall yield. Finally, amide coupling between carboxylic acid **300** and *N*-benzylcyclopropanamine provided the desired amide **301**.

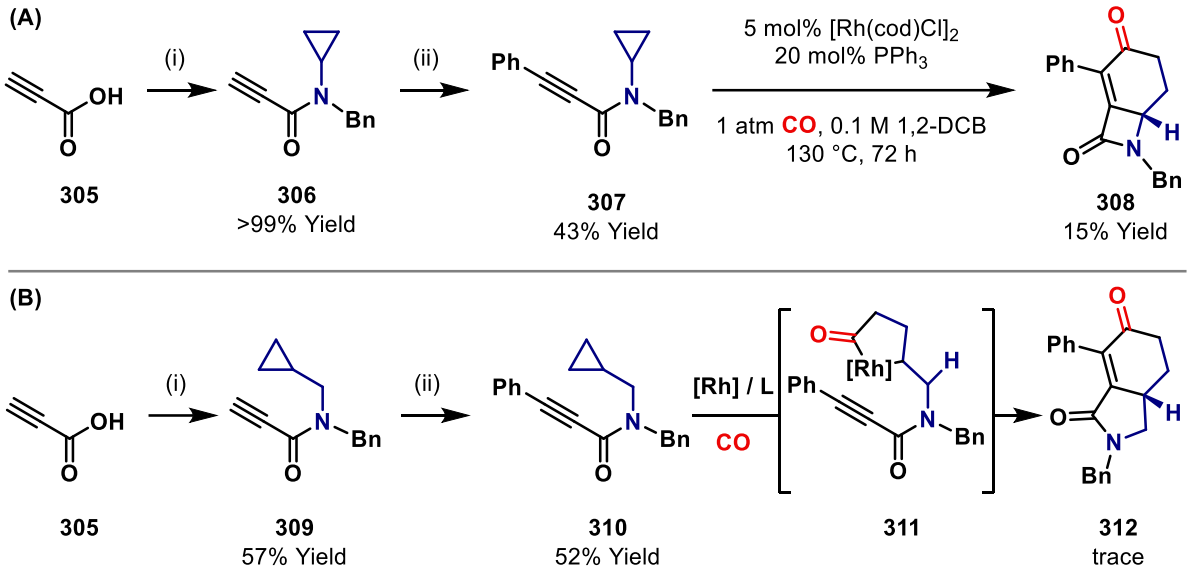
Unfortunately, exposure of amide **301** to the optimised cycloaddition protocol did not result in the formation of expected bicyclic product **302**. Instead, lactone **303** was isolated as a mixture of geometric isomers (Scheme 73B). This outcome may be rationalised by attack of the amide carbonyl onto the alkyne to give intermediate **304**. Subsequent hydrolysis would afford **303**. In this case, Rh(I) may act as a Lewis acid, promoting the intramolecular cyclisation.



Scheme 73: Synthesis and reactivity of cyclopropylamide **301**. *Reagents and conditions*: (i) PPh_3, Br_2, DCM, 0 °C, then *n*-pentane, r.t.; (ii) DIPA, *n*-BuLi, methyl isobutyrate, THF, -78 °C to r.t.; (iii) 4.0 M aq. NaOH, MeOH, r.t.; (iv) *N*-benzylcyclopropanamine, EDCI, DMAP, DCM, 0 °C to r.t.

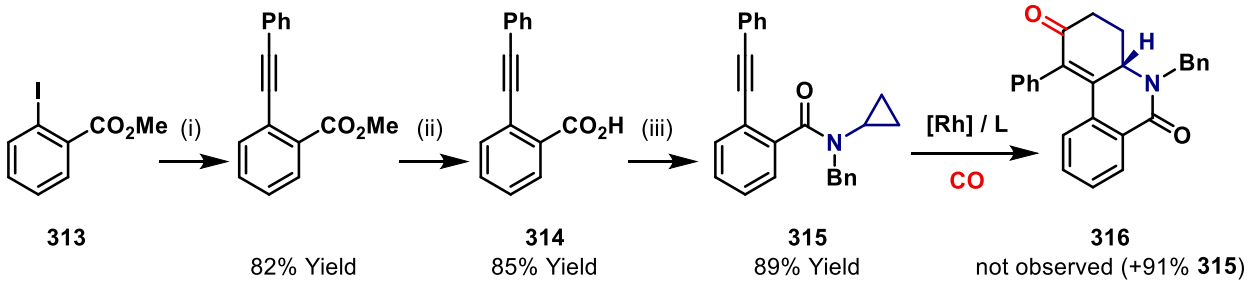
Moving forward, analogue **307**, which possesses a shorter alkyne tether, was also synthesised (Scheme 74A). To do this, amide coupling of **305** with *N*-benzylcyclopropanamine provided **306**, which was subjected to a Sonogashira cross-coupling with iodobenzene to provide **307**. Studies were undertaken to examine the feasibility of the carbonylative cycloaddition of **307**. The standard conditions from Table 5 were not suitable, but an interesting result was observed using a neutral Rh(I) precatalyst; under these conditions, cycloadduct **308** containing a β-lactam was isolated in 15% yield. This demonstrates that the methodology can even access highly strained four membered rings. Attempts to improve the yield of the reaction by varying the reaction time, temperature, solvent, Rh(I)-precatalyst and ligand were not successful.

To see if other classes of cyclopropane might be suitable, aminomethylcyclopropane system **310** was made from **305** by a method similar to that used for **307** (Scheme 74B). Under a range of conditions, no significant formation of cycloaddition product **312** was observed and only decomposition occurred. The cyclopropane unit of substrate **310** is considerably less nucleophilic compared to the one in **307**, making Rh(I) C−C oxidative addition more challenging. Additionally, upon formation of rhodacyclopentanone **311** and DG dissociation, facile exocyclic β-hydride elimination can occur, which, in turn, leads to decomposition.



Scheme 74: Synthesis and reactivity of cyclopropanes **307** and **310**. *Reagents and conditions*: (i) corresponding amine, DCC, DCM, 0 °C to r.t.; (ii) $PdCl_2(PPh_3)_2$, CuI, PhI, Et_3N, 80 °C.

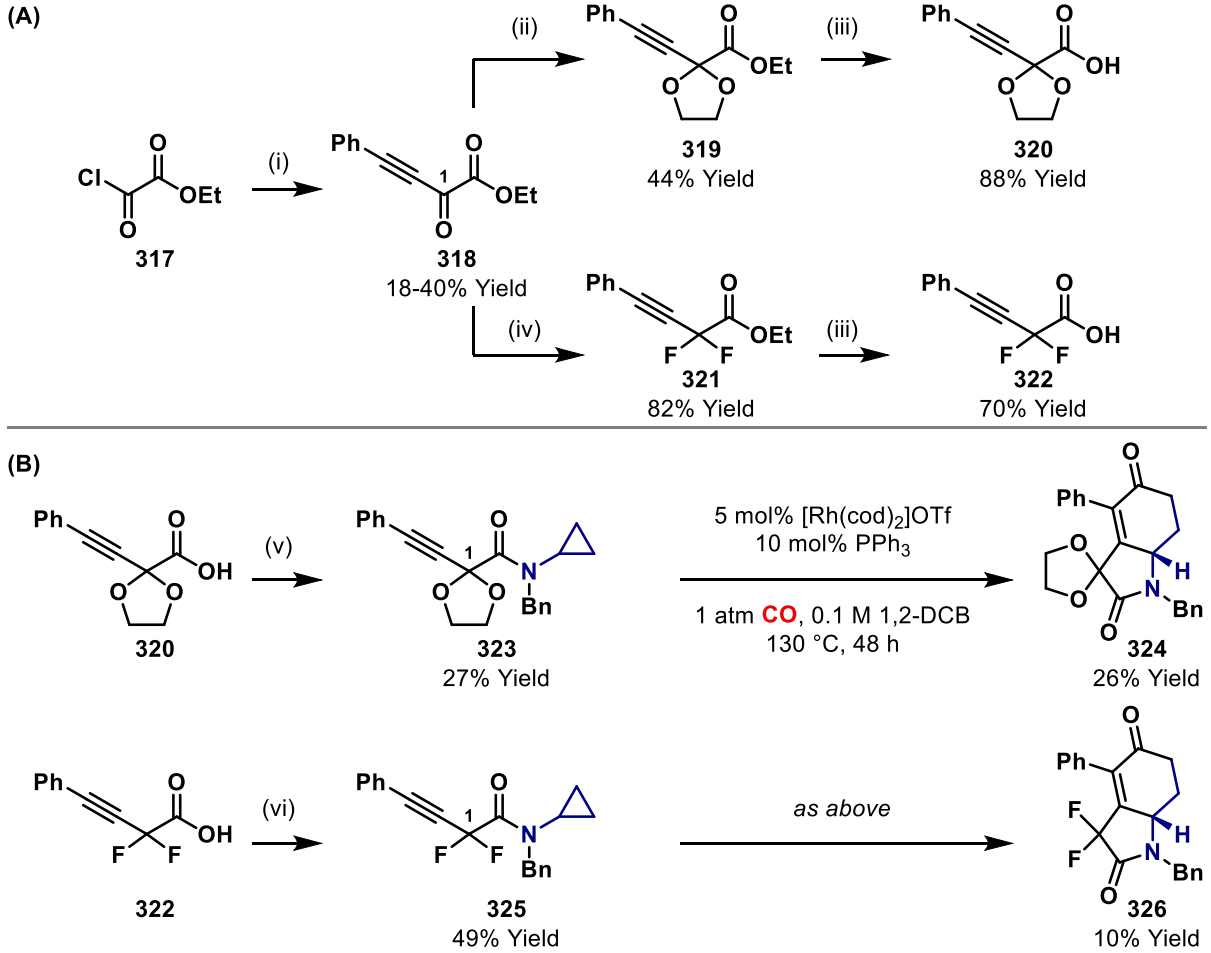
Further attempts to achieve 6-ring cycloadditions focused on substrates that possess a high degree of conformational bias. Accordingly, system **315** was targeted, as it was anticipated that the aromatic linker would facilitate the formation of benzofused system **316** (Scheme 75). Carboxylic acid **314**, which was prepared from ester **313** using a literature procedure,[180] was coupled with *N*-benzylcyclopropanamine to provide **315** in 89% yield. Subsequently, cycloaddition of **315** was evaluated under Rh(I)-catalysed carbonylative conditions, but target **316** was not observed and **315** was recovered. In this case, it may be that competing amide direct aryl C-H activation prevents C-C bond activation.[181]



Scheme 75: Synthesis and reactivity of cyclopropylamide **315**. *Reagents and conditions*: (i) $PdCl_2(PPh_3)_2$, CuI, phenylacetylene, Et_3N, THF, reflux; (ii) 4.0 M aq. NaOH, MeOH, r.t.; (iii) *N*-benzylcyclopropanamine, EDCI, DMAP, DCM, 0 °C to r.t.

At this stage, it had been determined that the new cycloaddition protocol is suitable for 5-ring cyclisations involving systems where R^2 is carbon-based (cf. Table 5). To explore scope further and to assess the effects of electronic factors, substrates **323** and **325**, containing heteroatoms at R^2 were evaluated. For this purpose, a divergent synthetic approach was used, starting from common intermediate **318** (Scheme 76A). This was accessed by copper-catalysed addition of phenylacetylene to acyl chloride **317**. The yield of this process varied depending on scale (18% at 20 mmol vs. 40% at 5 mmol); diminished yields at higher scale are attributed to

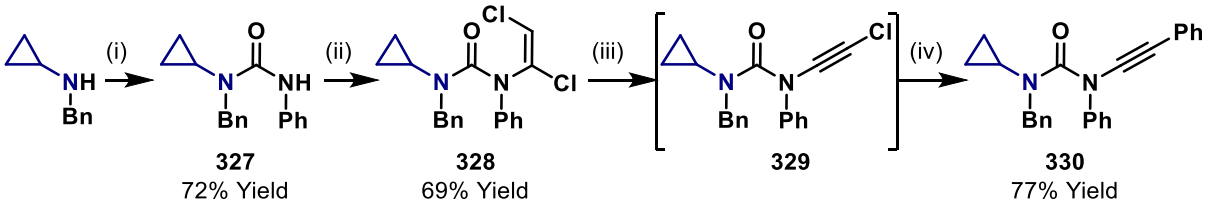
poorer control of reaction exotherms. **318** was converted to **320** and **322** by two distinct sequences. For the former, **318** was protected as 1,3-dioxolane derivative **319**, which, upon saponification, provided acid **320**. The synthesis of **322** required the conversion of the C1 carbonyl unit to a *gem*-difluoride, and this was readily achieved using diethylaminosulfur trifluoride (DAST). As before, saponification of the ester provided target acid **322**. Acids **320** and **322** were converted to amides **323** and **325** using EDCI-promoted coupling with *N*-benzylcyclopropanamine (Scheme 76B). With difluoro acid **322**, the EDCI mediated amide coupling did not give useful amounts of product **325**, so an alternative approach, proceeding via the corresponding acid chloride, was used. Amides **323** and **325** were evaluated under the standard Rh(I)-catalysed carbonylative conditions, and both delivered the desired cycloaddition product (**324** and **326**, respectively), but in low yields. Brief attempts were made to optimise these reactions by varying the ligand and the Rh(I) source, but improvements in yield were not achieved. Accordingly, the process does not tolerate inductively withdrawing substituents at C1. These would be expected to decrease the coordinating ability of both the amide DG and the alkyne, and both aspects may be detrimental to cycloaddition efficiency.



Scheme 76: Synthesis and reactivity of cyclopropylamides **323** and **325**. *Reagents and conditions*: (i) CuI, phenylacetylene, TMEDA, Et_3N, r.t.; (ii) ethane-1,2-diol, BF_3•Et_2O, MeCN, r.t.; (iii) 4.0 M aq. NaOH, MeOH, r.t.; (iv) DAST, DCM, 0 °C to r.t.; (v) *N*-benzylcyclopropanamine, EDCI, DMAP, DCM, 0 °C to r.t.; (vi) oxalyl chloride, DCM, r.t., then *N*-benzylcyclopropanamine, DCM, 0 °C to r.t.

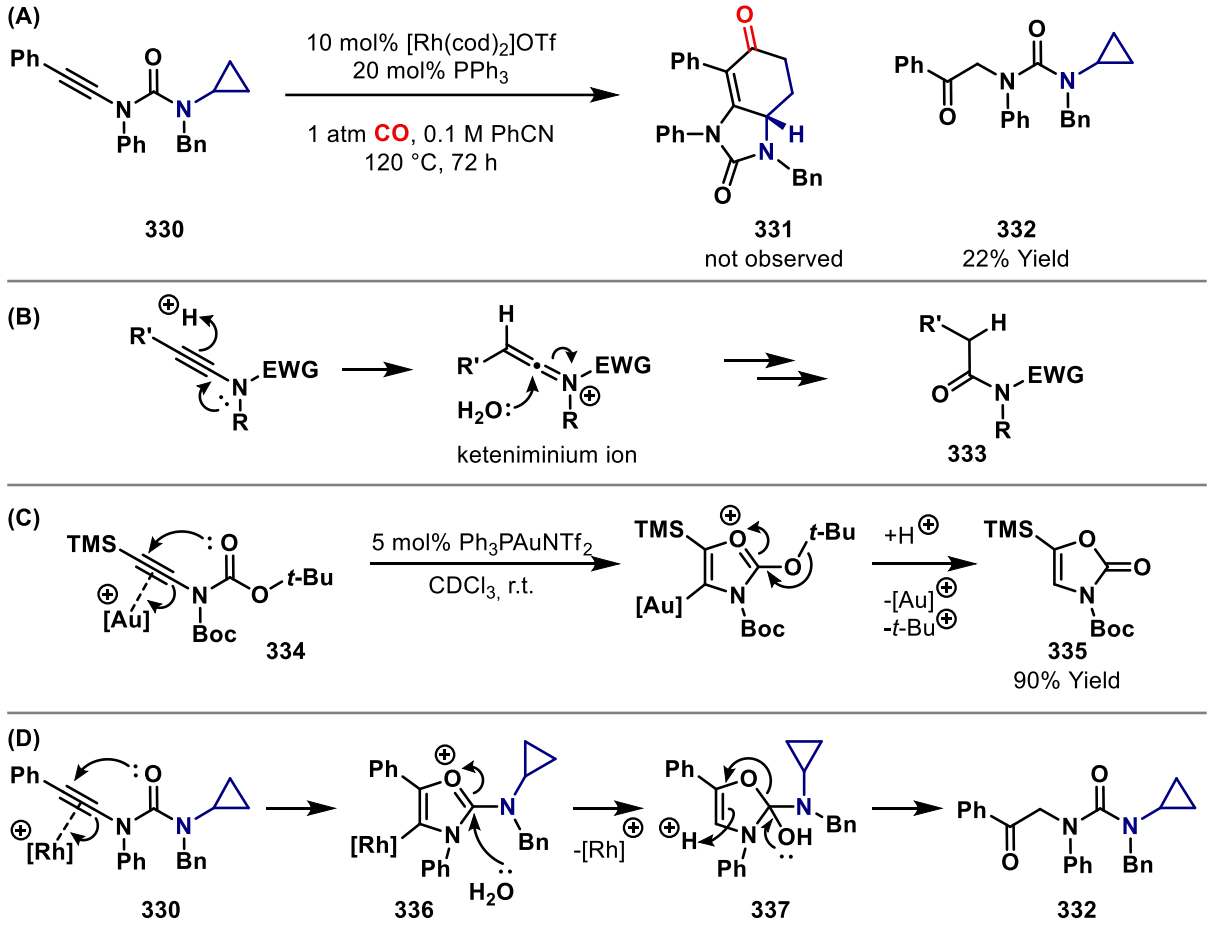
4.3.4 Synthesis and evaluation of other substrates

As outlined above, the (3+1+2) cycloaddition allows the synthesis of fused lactams from protected aminocyclopropanes. Further, distinct systems were evaluated to assess the possibility of accessing alternative cyclic products. Substrate **330**, containing a ynamide unit, was synthesised based on modified methodology from the Anderson group (Scheme 77A).[182] First, vinylation of urea **327** with trichloroethylene afforded **328**. Treatment of **328** with LiHMDS resulted in elimination of HCl to afford chloroynamide **329**. This underwent copper(I)-catalysed coupling with freshly formed diphenylzinc to give **330**.



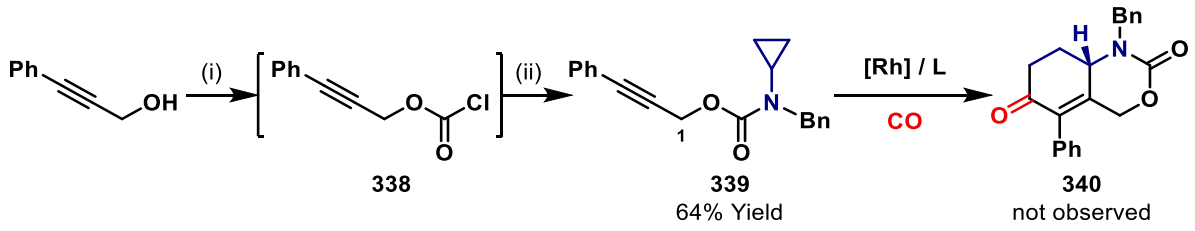
Scheme 77: Synthesis of ynamide **330**. *Reagents and conditions*: (i) PhNCO, Et_3N, DCM, 0 °C to r.t.; (ii) (*n*-Bu)$_4$N(HSO$_4$), KOH, toluene, H_2O, 60 °C, then trichloroethylene, 60 °C to r.t.; (iii) LiHMDS, Et_2O, 0 °C; (iv) PhMgBr, $ZnCl_2$, TMEDA, toluene, r.t., then CuCN•2LiCl.

Exposure of **330** to Rh(I)-catalysed cycloaddition conditions at 130 °C only led to the decomposition of starting material; no desired cycloaddition product **331** was formed. When the reaction temperature was lowered to 120 °C, the formation of ketourea **332**, a formal hydration product of **330**, was observed (Scheme 78A). The observed regioselectivity for hydration is not typical for ynamides - usually amides of type **333** are formed because ynamide protonation leads preferentially to a keteniminium ion (Scheme 78B).[183,184] It is likely that the Rh-catalyst promotes hydration of **330** by adventitious water. A related gold-catalysed process has been reported – here, Au(I) coordinates to the triple bond of **334**, which promotes attack of the Boc-carbonyl group to form **335** after loss of the *tert*-butyl group (Scheme 78C).[185] In a similar manner, Rh(I) may coordinate to the alkyne of **330** and assist the formation of oxazolium ion **336** (Scheme 78D). Attack of water and protodemetalation gives **337**, which opens to ketourea **332**.



Scheme 78: (A) Reactivity of ynamide **330**; (B) General regioselectivity in ynamide hydrolysis. (C, D) Related gold-catalysed process and the mechanism for the formation of **332**.

To test whether a carbamate may act as a suitable directing group in a similar (3+1+2) cycloaddition process, substrate **339** was made (Scheme 79). Commercially available 3-phenyl-2-propyn-1-ol was converted to chloroformate **338**, and this was exposed to *N*-benzylcyclopropanamine to provide **339**. Exposure of the resulting carbamate to the Rh-catalysed cycloaddition conditions failed to deliver any of the target product **340** and decomposition of starting material occurred. It is possible that the C1-O bond ionises to give a Rh-propargyl species and this prevents the desired reaction pathway.[186]

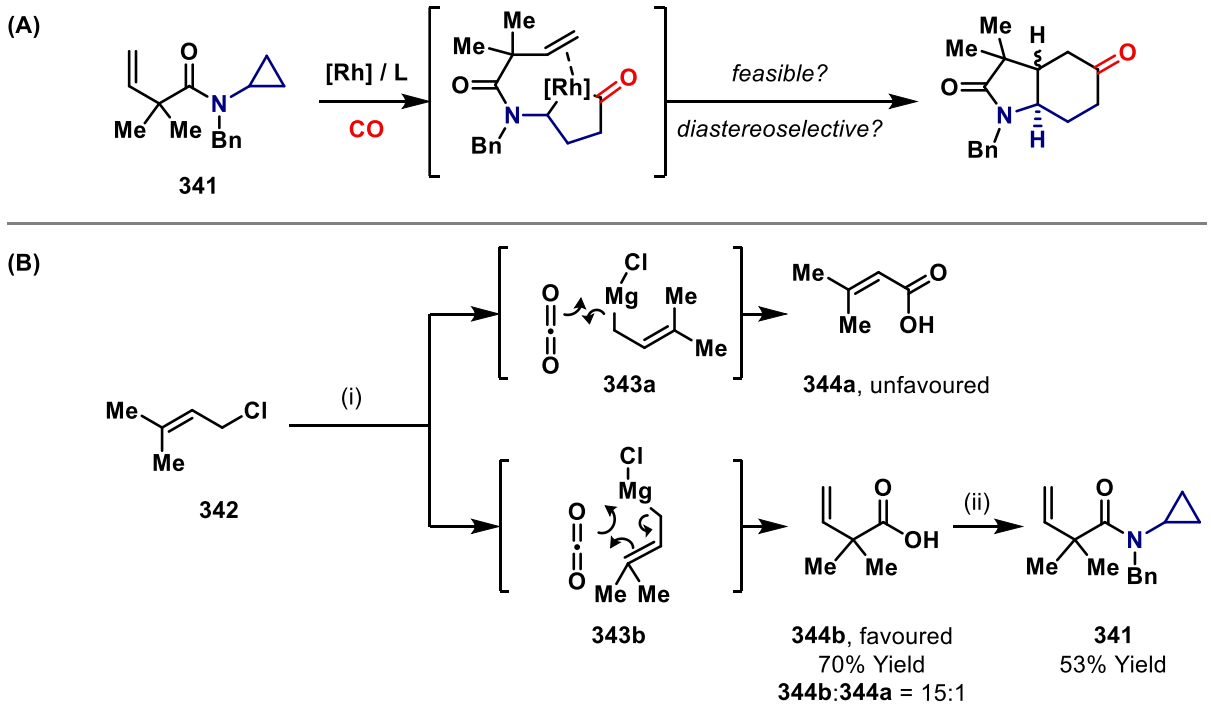


Scheme 79: Synthesis and reactivity of carbamate **339**. *Reagents and conditions*: (i) triphosgene, activated charcoal, Et_2O, 0 °C; (ii) *N*-benzylcyclopropanamine, Et_3N, DCM, 0 °C to r.t.

4.4 Extension of the methodology to alkenes

4.4.1 Reaction discovery and optimisation

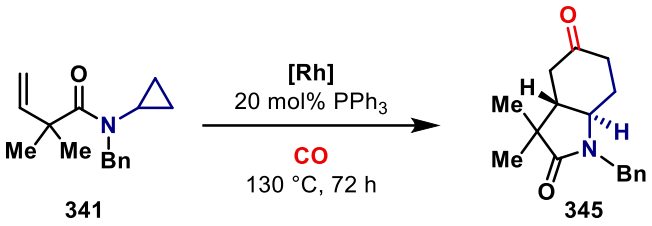
Section 4.3 outlines intramolecular (3+1+2) cycloadditions where alkynes are used as π-unsaturated component. Based upon previously reported[48] methodologies from Bristol, whereby substrates bearing alkenes have been used as a "2"-component (cf. Section 1.3, Scheme 7), system **341** was proposed (Scheme 80A). The resulting bicyclic product would contain one extra stereocenter and is more "sp^3-rich" than the alkyne-derived products obtained so far. To evaluate the possibility of using alkenes, amide **341** was synthesised in two steps from **342** (Scheme 80B). In the first step, **342** was converted to the corresponding allyl Grignard reagent and this was exposed to CO_2 to give acid **344b**. The regiochemical outcome of this process can be rationalised via 6-membered transition state **343b**, wherein allylic inversion of the sterically favoured, primary σ-allyl Grignard reagent leads to γ-addition product **344b**.[187] Subsequent amide coupling provided target amide **341** in 53% yield.



Scheme 80: Reaction design and synthesis of model cyclopropylamide **341**. *Reagents and conditions*: (i) Mg, THF, r.t. to 0 °C, then CO_2 (dry ice); (ii) *N*-benzylcyclopropanamine, EDCI, DMAP, DCM, 0 °C to r.t.

Amide **341** was evaluated under different Rh-catalysed carbonylative cycloaddition conditions. Pleasingly, the conditions optimised for alkyne **277** provided **345** in 33% yield (Table 6, Entry 1). **345** was formed as a single diastereomer, and the relative stereochemistry of the ring junction was determined as *trans* by nOe studies. Efforts to optimise this process focussed on solvent and Rh-source, and selected results are presented in Table 6. By changing the solvent from 1,2-DCB to PhCN, the yield of **345** could be improved to 58% (Table 6, Entry 2). Interestingly,

[Rh(cod)Cl]$_2$, a neutral Rh(I) precatalyst, gave a much higher yield when PhCN was used instead of 1,2-DCB (80% vs. 29%, Table 6, Entries 3 and 4). These conditions were carried forward to define the scope of this new alkene-based cycloaddition.



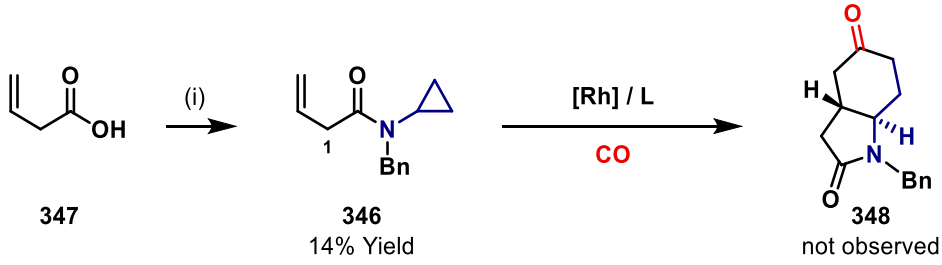
Entry	Rh^I (mol %)	Solvent (M)	Yield of 345[a] (%)
1	[Rh(cod)$_2$]OTf (10)	1,2-DCB (0.1)	33
2	[Rh(cod)$_2$]OTf (10)	PhCN (0.1)	58
3	[Rh(cod)Cl]$_2$ (5)	1,2-DCB (0.1)	29
4	[Rh(cod)Cl]$_2$ (5)	PhCN (0.1)	**80 (73)**

Table 6: Optimisation studies for the new (3+1+2) cycloaddition with an alkene. [a]Yields were determined by ^{1}H NMR spectroscopy using 1,4-dinitrobenzene as a standard. Isolated yields are given in parentheses.

4.4.2 Scope of the alkene component

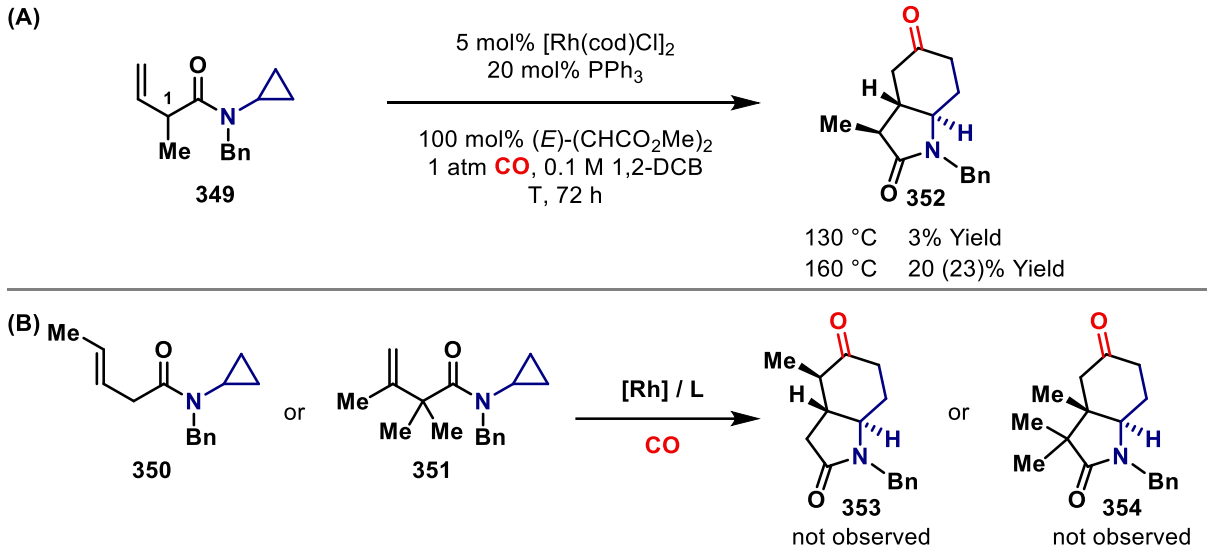
This part of the project was conducted with the assistance of Matthew Curley, an MSci student in the Bower group, and studies conducted by Curley are highlighted in the text.

To find out whether *gem*-disubstitution at C1 of **341** is necessary for cycloaddition to occur, amide **346** was made from the corresponding carboxylic acid **347** in 14% yield (Scheme 81). The low yield reflects purification difficulties rather than inefficient reaction. Employing substrate **346** in the Rh(I)-catalysed cycloaddition protocol failed to afford **348**, and only decomposition was observed. This result emphasises that substitution α to the carbonyl is crucial for the transformation.



Scheme 81: Synthesis and reactivity of cyclopropylamide **348**. *Reagents and conditions*: (i) *N*-benzylcyclopropanamine, EDCI, DMAP, DCM, 0 °C to r.t.

To investigate further the scope of the alkene component, Curley synthesised amides **349**-**351** and evaluated them under the optimised cycloaddition conditions (Scheme 82).[188] For substrate **349**, which bears only one methyl substituent at C1, it was found that the transformation is feasible at 160 °C, and **352** was formed in 23% yield (major diastereomer). The process was highly diastereoselective (>10:1 d.r.) and the relative stereochemistry of the major diastereomer was supported by nOe studies. Other diastereomers were observed in the ^{1}H NMR of the crude reaction mixture, but these could not be isolated cleanly for full characterisation. A high reaction temperature was required to afford cyclohexanone **352**; at 130 °C only traces were observed (Scheme 82A). The use of dimethyl fumarate as an electron deficient ligand was also important; its role may be to accelerate alkene insertion and/or reductive elimination.[49] A similar effect has been observed for previous alkene-based cycloadditions developed in the Bower group.[48] Substrates **350** and **351**, bearing 1,2- and 1,1-disubstituted alkenes, did not deliver cycloaddition products **353** and **354**; the failure of these systems can be attributed to the increased steric bulk of the alkene, which presumably hinders coordination to the Rh(III)-centre of the rhodacyclopentanone intermediate (Scheme 82B).



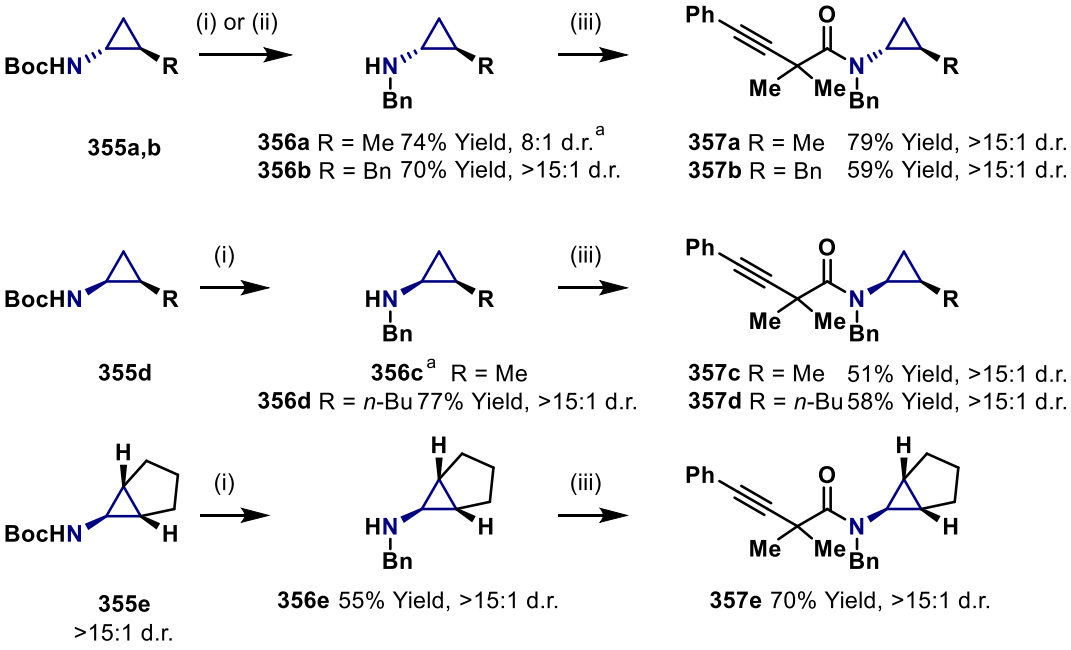
Scheme 82: Evaluation of a range of alkene tether substitution conducted by Curley. Yields were determined by ^{1}H NMR spectroscopy using 1,4-dinitrobenzene as a standard. Isolated yields are given in parentheses.

4.5 (3+1+2) Cycloadditions of polysubstituted cyclopropanes

The newly discovered system enables the transformation of simple racemic starting materials into complex cyclic products. The enantiospecificity of the (3+1+2) cycloaddition was studied next, focussing specifically on the use of more highly substituted and enantioenriched cyclopropanes. To test this, and to explore the tolerance of the reaction towards increased steric bulk on the cyclopropane ring, several substrates with di/trisubstituted cyclopropanes were synthesised.

4.5.1 Cycloadditions of polysubstituted cyclopropanes with alkynes

Substrates **357a-e**, with an alkyne as the π-unsaturated moiety, were made from *N*-Boc-protected cyclopropylamines **355a-e**, which were synthesised according to well-established synthetic routes.[48] TFA-promoted Boc deprotection followed by reductive amination gave amines **356a-e**, which underwent subsequent amide coupling to **357a-e** (Scheme 83).

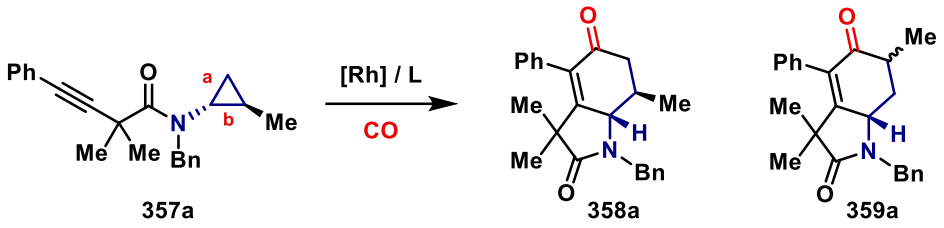


Scheme 83: Synthesis of polysubstituted cyclopropylamides **357a-e**. *Reagents and conditions*: (i) (a) TFA, DCM, r.t.; (b) benzaldehyde, $MgSO_4$, toluene, r.t., then $NaBH_4$, MeOH, 0 °C to r.t.; (ii) *for* **355a** *only* (a) TFA, DCM, r.t.; (b) benzaldehyde, $NaHCO_3$, MeOH, reflux, then $NaBH_4$, 0 °C to r.t.; (iii) 2,2-dimethyl-4-phenylbut-3-ynoic acid **295**, EDCI, DMAP, DCM, 0 °C to r.t. [a] *trans*-**356a** and *cis*-**356c** were separated by column chromatography.

When cyclopropylamide **357a** was submitted to the optimised reaction conditions ([Rh(cod)$_2$]OTf/PPh$_3$, 1,2-DCB, 130 °C), only trace amounts of a complex mixture of regio- and diastereoisomers was obtained (Table 7, Entry 1). The exact amount of remaining starting material **357a** was hard to quantify due to its highly rotameric nature. To improve efficiency, combinations of neutral ([Rh(cod)Cl]$_2$) or cationic ([Rh(cod)$_2$]OTf) sources of rhodium(I) and coordinating or non-coordinating (PhCN or 1,2-DCB) solvents were evaluated (Table 7, Entries 1-4). Based upon these results, the conditions from Entry 3 ([Rh(cod)Cl]$_2$/PPh$_3$, PhCN) were brought forward as they gave the highest yield of **358a** and **359a** (30% combined yield). Upon prolonged heating at 150 °C, a significant improvement in the yield of **358a** was observed (63% yield), alongside smaller amounts of **359a** (22% yield, 1.2:1 d.r.).

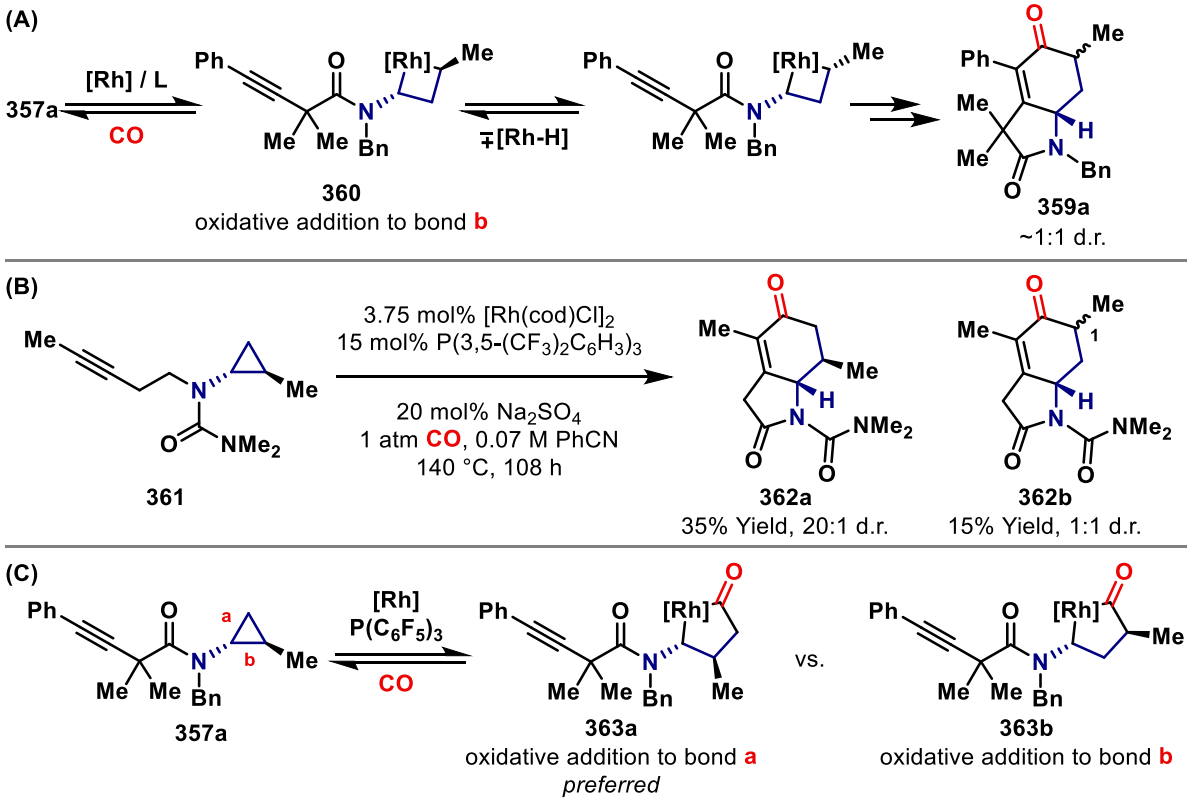
The factors governing the poor diastereoselectivity of cyclohexenone **359a** are unclear. It may be that cycloadduct **359a** epimerises under the reaction conditions, or, alternatively, epimerisation may occur at an earlier stage. For example, a reversible β-hydride elimination-hydrometallation sequence at the stage of rhodacyclobutane **360** could also result in epimerisation (Scheme 84A). It should be noted that the effect of *trans*-substitution on the cyclopropane ring has been evaluated in Bristol on other related systems and similar results were obtained. For example, (3+1+2) cycloaddition of **361** occurred in low yield and regioselectivity, with minor product **362b** formed as a 1:1 mixture of diastereomers (Scheme 84B).[123] In this case, control experiments indicate that epimerisation of C1 occurs by epimerisation of **362b**.

Further optimisation was still required as it was challenging to separate one of the diastereomers of **359a** from the main product **358a**. Accordingly, a range of triphenylphosphine-based ligands was screened (several examples are shown in Table 7, Entries 6-8). The use of more electron-rich P(4-OMeC$_6$H$_4$)$_3$ did not significantly affect the reaction outcome (Table 7, Entry 6), but electron-poor ligands suppressed the formation of **358a** (Table 7, Entries 7 and 8). P(C$_6$F$_5$)$_3$ was especially selective, and full conversion of **357a** into cyclohexenone **358a** was possible. This highly electron-deficient ligand may enforce kinetic C-C bond activation selectivity (via bond **a**) by enhancing coordination or accelerating migratory insertion of the alkene at the stage of rhodacyclopentanone **363** (Scheme 84C). If either of these processes are slow, then reversible rhodacyclopentanone formation can erode regiochemical fidelity by competitive activation of bond **b**.



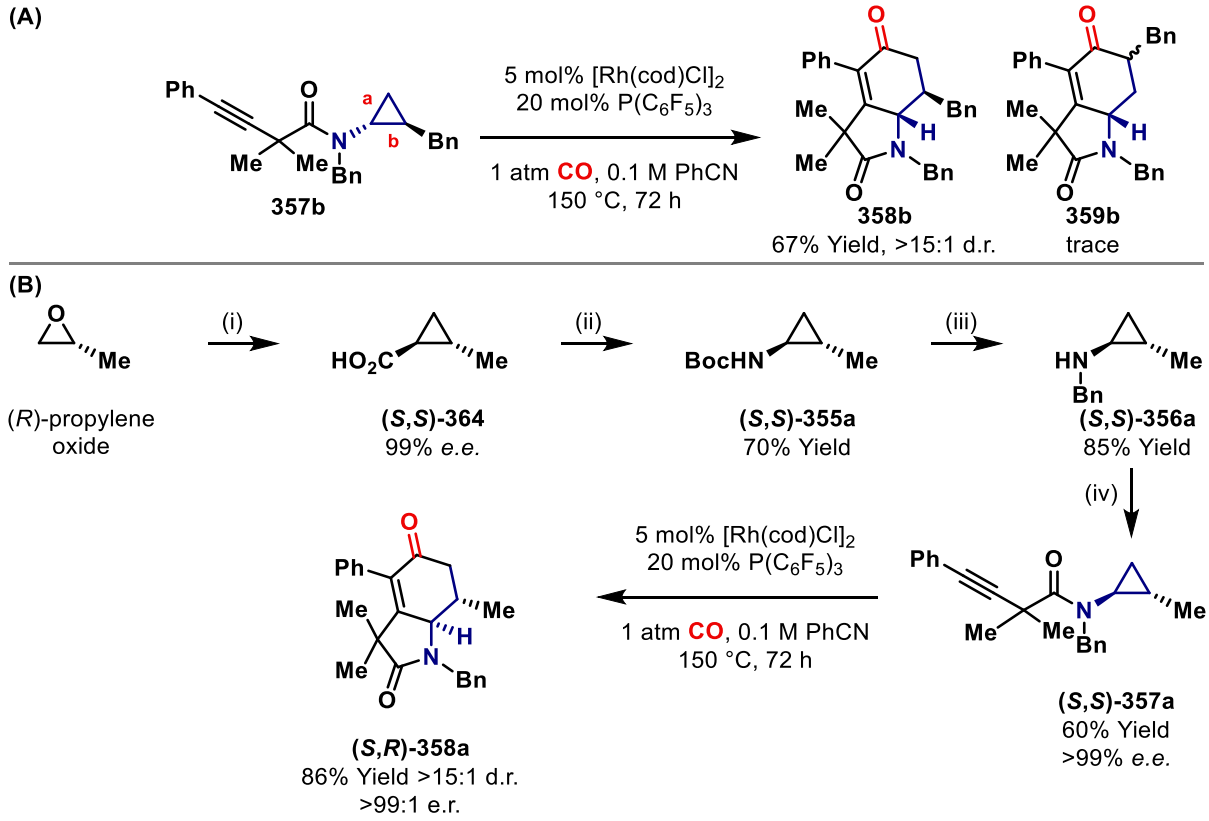
Entry	Rh^{I} (mol %)	Ligand (mol %)	Solvent (M)	Time (h)	T (°C)	358a[a] (%)	359a[a] (%)
1	$[Rh(cod)_2]OTf$ (5)	PPh_3, 10	1,2-DCB, 0.1	48	130	5	10 (1:1 d.r.)
2	**$[Rh(cod)Cl]_2$ (5)**	PPh_3, 20	1,2-DCB, 0.1	48	130	11	trace
3	$[Rh(cod)Cl]_2$ (5)	PPh_3, 20	**PhCN, 0.1**	48	130	6	24 (1:1 d.r.)
4	**$[Rh(cod)_2]OTf$ (5)**	PPh_3, 10	PhCN, 0.1	48	130	15	5 (1:1 d.r.)
5	$[Rh(cod)Cl]_2$ (5)	PPh_3, 20	PhCN, 0.1	**72**	**150**	63	22 (1.2:1 d.r.)
6	$[Rh(cod)Cl]_2$ (5)	**$P(4\text{-}OMeC_6H_4)_3$, 20**	PhCN, 0.1	72	150	62	4 (2:1 d.r.)
7	$[Rh(cod)Cl]_2$ (5)	**$P(3,4,5\text{-}F_3C_6H_4)_3$, 20**	PhCN, 0.1	72	150	57	trace
8	$[Rh(cod)Cl]_2$ (5)	**$P(C_6F_5)_3$, 20**	PhCN, 0.1	72	150	86 (84)	trace

Table 7: Optimisation studies for the (3+1+2) cycloaddition with a *trans*-disubstituted cyclopropanamide. [a]Yields were determined by ^1H NMR spectroscopy using 1,4-dinitrobenzene as a standard. Isolated yields are given in parentheses.



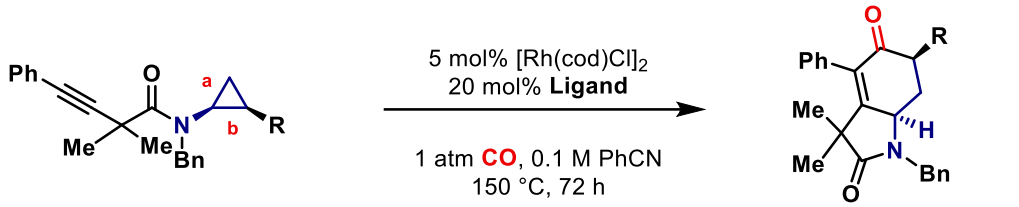
Scheme 84: Mechanistic considerations for systems with *trans*-disubstituted cyclopropanes.

The conditions from Table 7, Entry 8 were employed with benzyl-substituted cyclopropylamide **357b** and delivered desired product **358b** in 67% yield (Scheme 85A). As with **357a**, only traces of product **359b** resulting from C-C bond activation of bond **b** were observed. Accordingly, the optimised protocol appears to be generally applicable to *trans*-1,2-disubstituted cyclopropanes. Next, an enantioenriched sample of methyl-substituted cyclopropylamide **(*S*,*S*)-357a** was made from commercially available (*R*)-propylene oxide (Scheme 85B). The synthesis commenced with the known enantioretentive Horner−Wadsworth−Emmons cyclopropanation reaction, which gave acid **(*S*,*S*)-364** in 99% e.e. after saponification of the crude ester.[110] **(*S*,*S*)-364a** was then transformed to *N*-Boc-protected cyclopropylamine **(*S*,*S*)-355a** by Curtius rearrangement.[189] Boc deprotection followed by reductive amination provided secondary amine **(*S*,*S*)-356a**, which was used in an amide coupling reaction to give the enantioenriched cyclopropylamide **(*S*,*S*)-357a** (>98% e.e.). Carbonylative rearrangement of **(*S*,*S*)-357a** proceeded with complete retention of both stereocenters, forming the target cycloadduct **(*S*,*R*)-358a** in >99% e.e. This result confirms that the process is enantiospecific, such that no epimerisation occurs during the course of the reaction.



Scheme 85: Synthesis and reactivity of other *trans*-disubstituted cyclopropanes with tethered alkyne. *Reagents and conditions*: (i) (a) triethylphosphonoacetate, *n*-BuLi, 2-MeTHF; (b) NaOH, H_2O, 100 °C; (ii) diphenylphosphoryl azide, Et_3N, *t*-BuOH, 80 °C; (iii) (a) TFA, DCM, r.t.; (b) benzaldehyde, $MgSO_4$, toluene, r.t., then $NaBH_4$, MeOH, 0 °C to r.t. (iv) 2,2-dimethyl-4-phenylbut-3-ynoic acid, EDCI, DMAP, DCM, 0 °C to r.t.

To determine whether the catalytic conditions for *trans*-disubstituted cyclopropylamides could also be used for the *cis*-disubstituted cyclopropylamides, methyl-substituted substrate **357c** was exposed to the conditions outlined in Scheme 85A. Under these conditions, regioisomer **359c**, which is derived from C-C bond activation of more hindered bond **b**, was formed in 9% yield and as a single diastereomer; the mass balance consisted of unidentified degradation products (Table 8, Entry 1). The regiochemical outcome of this process reflects earlier work from Bristol.[48] Bond **b** is more electron rich than bond **a**, and the *cis*-configuration of **357c** alleviates steric hindrance compared to *trans*-system **357a**. Accordingly, the Rh-catalyst can preferentially coordinate to bond **b** and this leads the observed C-C bond activation selectivity.[190] Further exploration of the electronics of the triarylphosphine ligand (Table 8, Entries 2-5) revealed that electron-rich $P(4\text{-}OMeC_6H_5)_3$ is most suitable and this modification provided **359c** in 50% yield as a single diastereomer.



357c R = Me
357d R = n-Bu

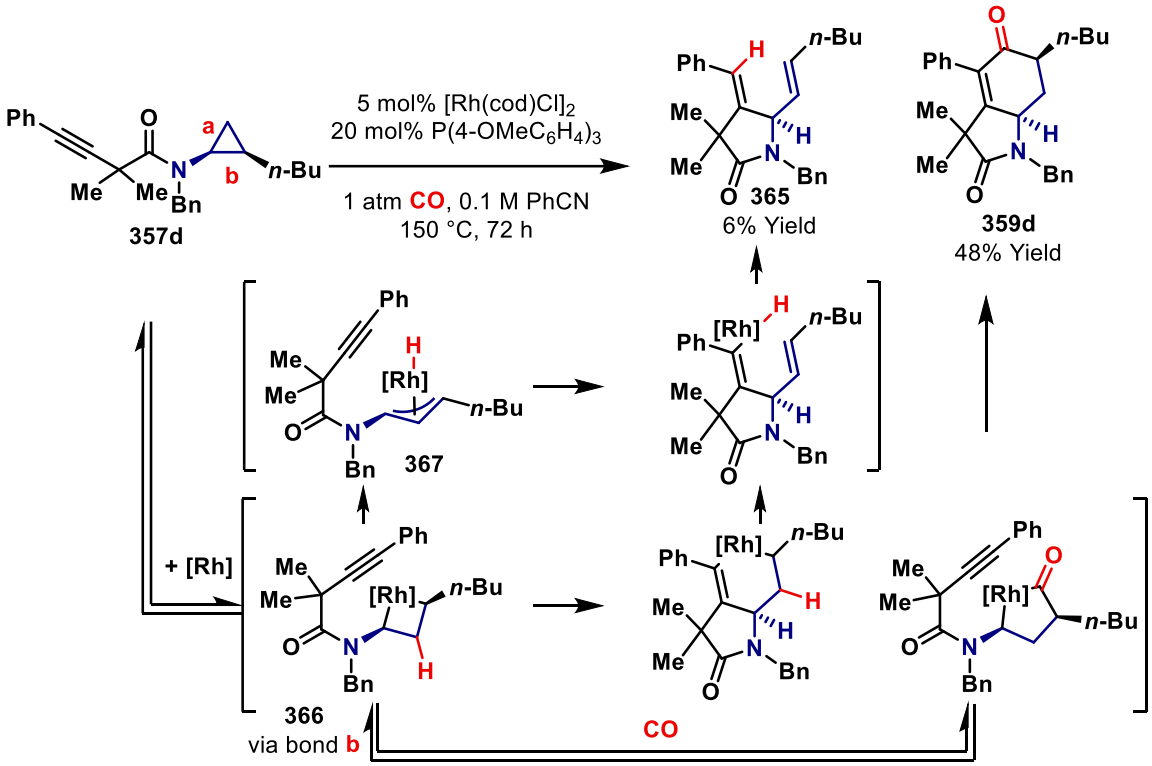
359c R = Me, >15:1 d.r.
359d R = n-Bu, >15:1 d.r.

Entry	R	Ligand	359 (%)
1	Me	$P(C_6F_5)_3$	9
2	Me	PPh_3	22
3	Me	$P(3,5\text{-}Me_2C_6H_3)_3$	28
4	Me	$P(4\text{-}OMeC_6H_4)_3$	**51 (50)**
5	Me	$P((2,4,6\text{-}OMe)_3C_6H_2)_3$	<10
6	*n*-Bu	$P(4\text{-}OMeC_6H_4)_3$	**45 (48)**
7	*n*-Bu	$P(3,5\text{-}Me_2\text{-}4\text{-}OMeC_6H_2)_3$	35

Table 8: Optimisation studies for (3+1+2) cycloaddition with *cis*-disubstituted cyclopropanamides. [a]Yields were determined by ^1H NMR spectroscopy using 1,4-dinitrobenzene as a standard. Isolated yields are given in parentheses.

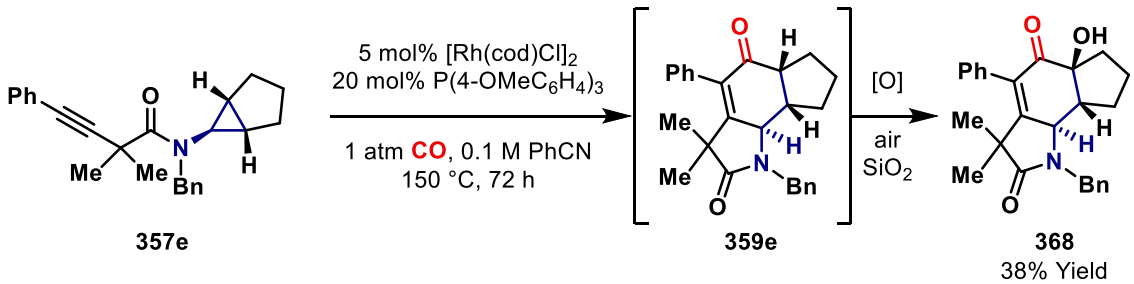
The conditions optimised for **357c** also transferred to *n*-butyl analogue **357d**, which was formed in 48% yield (Table 8, Entry 6). In this case, dienyl side product **365** also formed in 6% yield. Several pathways can account for the formation of **365** (Scheme 86). One possibility

involves β-hydride elimination from rhodacyclobutane **366** to generate Rh-allyl **367**. This can then engage in alkyne carbometallation and C-H reductive elimination. An alternative mechanism involves alkyne migratory insertion into rhodacyclobutane **366**, followed by β-hydride elimination from the resulting metallacycle and C-H reductive elimination.



Scheme 86: Cycloaddition of a *cis*-disubstituted cyclopropylamide with a tethered alkyne and a plausible mechanism.

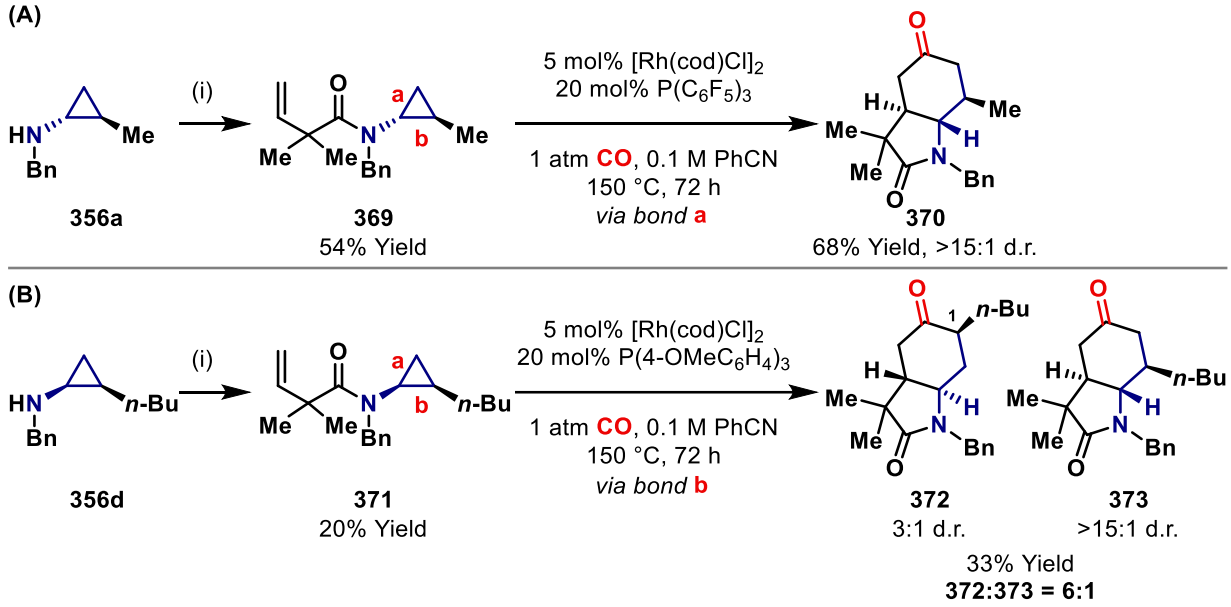
Finally, when *trans*-trisubstituted cyclopropylamide **357e** was evaluated in the cycloaddition protocol, unexpected product **368** was isolated (Scheme 87). This α-hydroxycyclohexenone was not observed in the ^{1}H NMR of the crude reaction material and is presumably a result of aerobic oxidation of expected cycloadduct **359e** during purification. Although the exact mechanism and rationale for this transformation is unclear, precedence for metal-free aerobic C-H oxidation of cyclic enones exists in the literature.[191]



Scheme 87: Cycloaddition of a trisubstituted cyclopropylamide with a tethered alkyne.

4.5.2 Cycloadditions of polysubstituted cyclopropanes with alkenes

With cycloaddition conditions optimised for polysubstituted systems bearing alkynes, the effect of substitution on the cyclopropane moiety in processes involving alkenes was studied next. In these cases, the cycloaddition products contain an extra stereocentre, offering a facile entry to more complex, sp^3-rich scaffolds. Accordingly, methyl-substituted substrate **369** and *n*-butyl substituted substrate **371** were made from amines **356a** and **356d** by amide coupling reactions (Scheme 88, cf. Scheme 83).



Scheme 88: Synthesis and reactivity of disubstituted cyclopropylamides **369** and **371**. *Reagents and conditions*: (i) 2,2-dimethylbut-3-enoic acid, EDCI, DMAP, DCM, 0 °C to r.t.

The catalytic conditions established for cycloadditions of *trans*-disubstituted cyclopropanes with alkynes transferred efficiently to system **369**, and gave target **370** as a single diastereomer and regioisomer (68% yield, >20:1 d.r.) (Scheme 86A). However, when the conditions optimised for cycloadditions of *cis*-disubstituted cyclopropanes (*vide supra*, Scheme 86) alkynes were applied to substrate **371**, a complex mixture of **372** and **373** was isolated. Similarly to alkynes **357c** and **357d**, product **372**, derived from C-C bond activation of bond **b**, predominated and epimerisation of the C1 stereocentre occurred (Scheme 88B, cf. Table 8). Attempts to improve the yield by lowering the temperature, or changing the ligand or Rh(I) source were not fruitful.

4.6 Asymmetric (3+1+2) cycloadditions

The focus then shifted to finding suitable conditions to render the new (3+1+2) cycloaddition asymmetric. It should be noted that, because rhodacyclopentanone formation can be highly reversible, there are several stages in the cycloaddition that might be enantiodetermining. One of these involves oxidative addition of the rhodium into one of the two enantiotopic proximal cyclopropylamine bonds. The studies described in this section provide circumstantial evidence that this is indeed the enantiodetermining step.

4.6.1 Ligand screen for alkyne-based cycloadditions

In collaboration with Curley, a representative range of commercially available chiral ligands was screened by adapting the non-enantioselective conditions optimised for alkyne system **277c** (Table 9). Generally, bidentate ligands, including *P*,*P*-, *N*,*N*- and *P*,*N*-variants, were detrimental for this reaction in terms of yield and e.e. (Table 9, Row 1). Given that the Rh(I) catalyst requires a vacant coordination site for oxidative addition and alkyne insertion, it is important that active intermediates are not coordinatively saturated. Indeed, chiral monodentate ligands gave higher yields, but low to minimal enantioinduction was observed in most cases (21-38% Yield, 0-14% e.e.) (Table 9, Row 2). A derivative of (*R*)-SEGPHOS has been shown to be very efficient for the kinetic resolution of cyclobutanones via rhodacyclopentanone formation (cf. Scheme 62), but, in this case, (*R*)-SEGPHOS gave only 4% e.e.. Nonetheless, as higher yields were observed with monodentate ligands, screening of these continued, focussing particularly on variation of the ligand backbone.

To date, most Rh(I)-based enantioselective catalytic systems employ chiral bidentate ligands.[192-194] In recent years, more attention has been drawn to monodentate systems, in particular ligands bearing spirocyclic backbones.[195] (*R*)-SIPHOS-PE, a phosphoramidite ligand with a SPINOL-derived structure, had previously been identified as the most promising for urea-directed (3+1+2) cycloadditions (cf. Scheme 64).[123] When applied to **277c**, this ligand gave a moderate yield and lower enantioselectivity (12% vs. 35% e.e.). Zhou and co-workers have demonstrated the use of two other SPINOL-based monodentate ligands, ShiP and FuP-tBu, for Rh(I)-catalysed asymmetric arylation[196] and hydrogenation,[197] respectively. Although none of these ligands gave a significant enantiomeric excess, the 17% e.e. with (*S*)-ShiP was the best result achieved so far (Table 9, Row 3). This result highlighted that the ligand needs a backbone with a large dihedral angle. Pleasingly, the geometrically similar, but more electron rich (*S*)-SITCP, gave **280c** in excellent yield and enantioselectivity (86% e.e.). This result constitutes the first highly enantioselective carbonylative higher order cycloaddition of a "simple" cyclopropane.

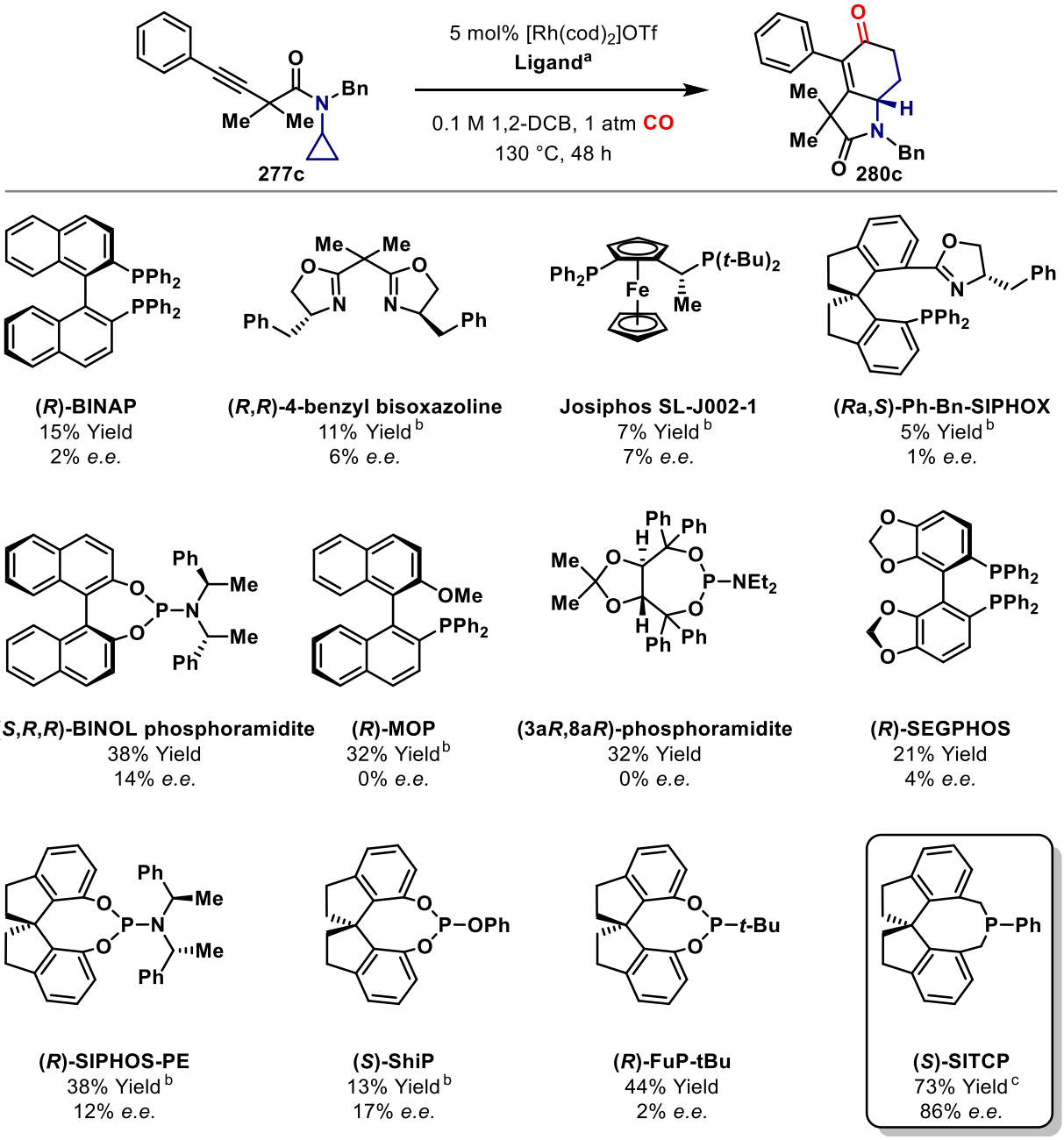


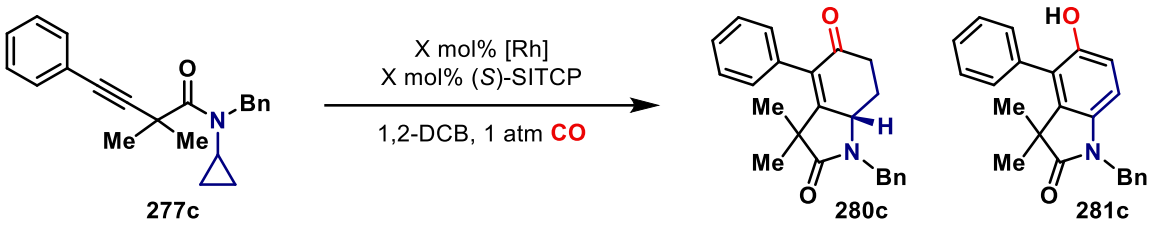
Table 9: Survey of chiral ligands for asymmetric (3+1+2) cycloaddition of cyclopropylamide **277c**. Yields were determined by ^{1}H NMR spectroscopy using 1,4-dinitrobenzene as a standard. [a] Bidentate ligands: 5 mol%, monodentate ligands: 10 mol%. [b] Reaction carried out by Curley. [c] 48% Yield, 78% *e.e.* if reaction is heated for 72 h.[188]

4.6.2 Enantioselective reaction optimisation

The result with (*S*)-SITCP was optimised further for enantioselectivity by screening Rh(I) sources, reaction time, temperature, and concentration - an abridged summary is represented in Table 10. Neutral Rh(I) precatalysts, such as $[Rh(cod)Cl]_2$, did not generate cyclohexenone **280c**, whilst $[Rh(cod)_2]BF_4$ performed considerably worse than $[Rh(cod)_2]OTf$ (Table 10, Entries 1-3). Increasing the dilution provided **280c** in excellent yield but decreased the enantioselectivity of the

process (Table 10, Entry 4). Pleasingly, when the reaction was run for 72 h at a lower temperature of 115 °C, **280c** was formed in 66% yield and 90% enantiomeric excess (Table 10, Entry 5).

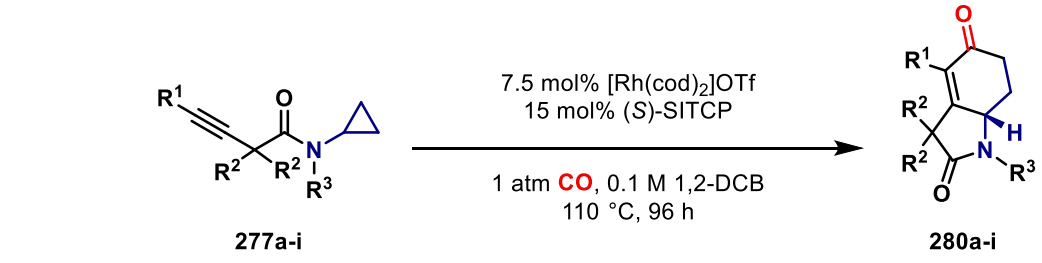
Further studies focused on improving the yield while maintaining the high enantioselectivity. Increasing the loading of the rhodium catalyst lowered the e.e., but full conversion as observed at 115 °C (Table 10, Entry 6). Finally, when the reaction was heated to 110 °C for 96 h using 7.5 mol% [Rh] and 15 mol% (*S*)-SITCP, a combination of good yield and (76%) excellent enantioselectivity (90% e.e.) was achieved (Table 10, Entry 7). It should be noted, that one equivalent of the chiral ligand relative to Rh is sufficient to achieve high enantioselectivity (Table 10, Entries 8-10). This suggests that the second equivalent is sacrificial, and may only be required due to ligand degradation (by hydrolysis or oxidation) over the course of the reaction.



Entry	Rh[I] (mol %)	(*S*)-SITCP (mol %)	1,2-DCB (M)	Time (h)	T (°C)	Yield of 280c[a] (%)	277c [a] (%)	e.e. (%)
1	[Rh(cod)$_2$]OTf (5)	10	0.1	48	130	73	0 (+21% **281c**)	86
2	**[Rh(cod)Cl]$_2$ (5)**	20	0.1	48	130	0	>99	-
3	**[Rh(cod)$_2$]BF$_4$ (5)**	10	0.1	48	130	47	0	40
4	[Rh(cod)$_2$]OTf (5)	10	**0.05**	48	130	92	0 (+7% **281c**)	84
5	[Rh(cod)$_2$]OTf (5)	10	0.1	**72**	**115**	66	32	90
6	**[Rh(cod)$_2$]OTf (7.5)**	15	0.1	72	115	83	trace	80
7	[Rh(cod)$_2$]OTf (7.5)	15	0.1	**96**	110	78 (76)	7	90
8	[Rh(cod)$_2$]OTf (7.5)	**11.25**	0.1	96	110	66	-	89
9	[Rh(cod)$_2$]OTf (7.5)	**7.5**	0.1	96	110	68	-	82
10	[Rh(cod)$_2$]OTf (7.5)	**18.75**	0.1	96	110	63	-	90

Table 10: Optimisation studies for the asymmetric (3+1+2) cycloaddition. [a]Yields were determined by ^{1}H NMR spectroscopy using 1,4-dinitrobenzene as a standard. Isolated yields are given in parentheses.

The conditions from Table 10, Entry 7 were carried forward and applied to a wide range of substrates and Table 11 summarises the results obtained. In general, good yields and enantiomeric ratios were observed regardless of the substrate's electronics. For example, *para*-chlorophenyl and 3-thienyl analogues **280d** and **280g** were both formed in 93:7 e.r. Similarly, variation of substitution α to the amide had only a minor effect (cf. **280a** vs. **280c**). For compound **280f**, rotation around the C1-C2 bond is sufficiently restricted that atropisomers are formed; chiral SFC analysis revealed that both of these diastereomers were generated with similar levels of enantioselectivity. The absolute stereochemistry of **280d** was determined by single crystal X-ray diffraction, and the absolute stereochemistries of the other cyclohexenones were assigned by analogy.



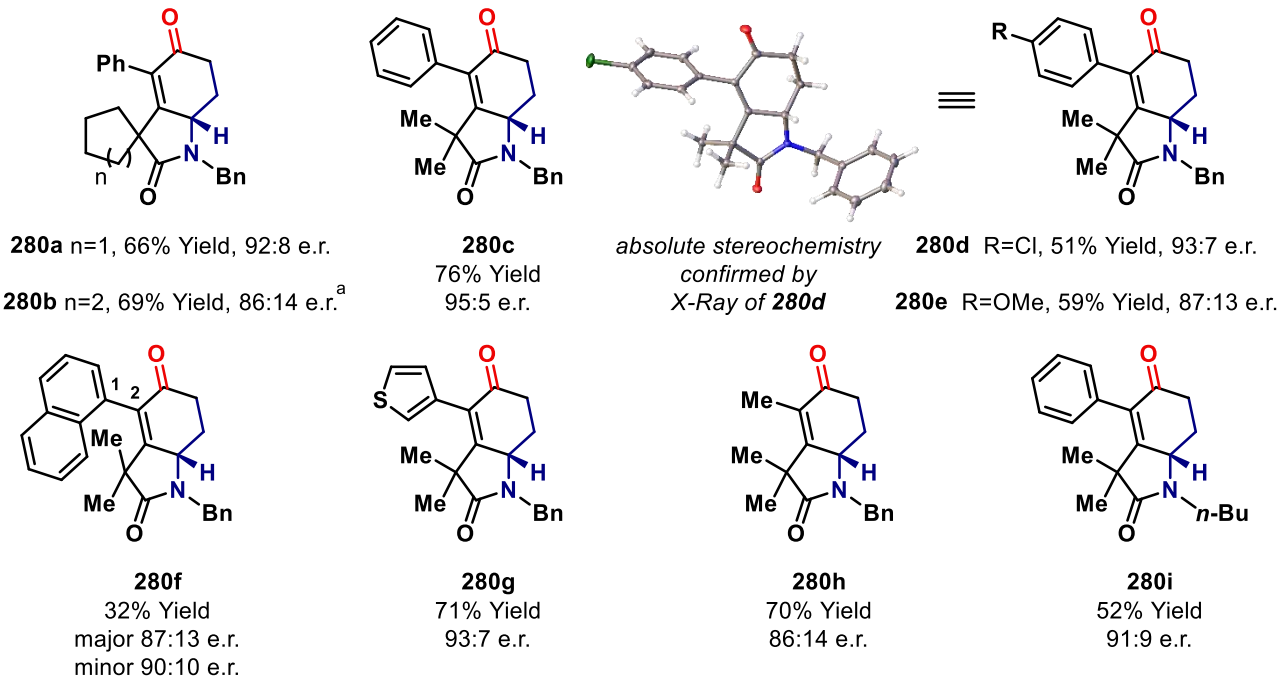
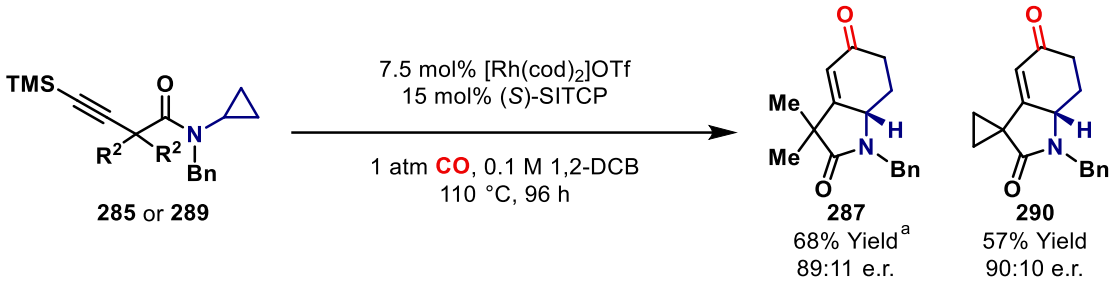
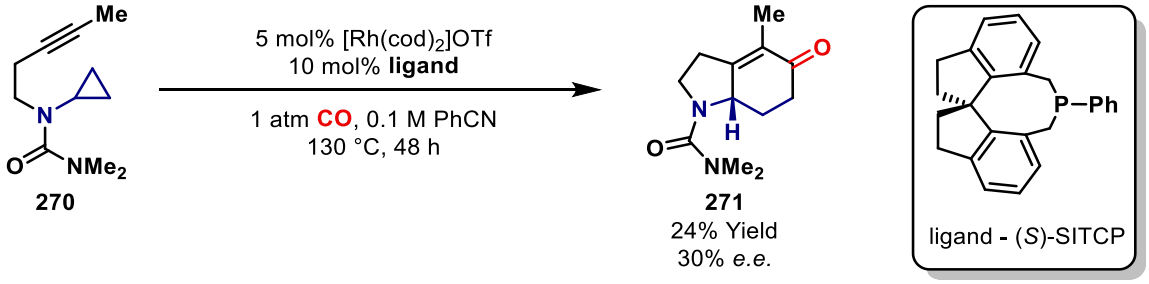


Table 11: The scope for the asymmetric (3+1+2) cycloaddition using (*S*)-SITCP. [a] The reaction was run at 120 °C.

Substrates with TMS-protected alkynes **285** and **289** also engaged in the asymmetric cycloaddition. As observed previously (see Scheme 69), the silyl unit "disappeared" over the course of the reaction and products **287** and **290** were formed in a highly asymmetric manner (Scheme 89). The optimised conditions using the (*S*)-SITCP ligand were also examined on cyclopropylamine **270** (Scheme 90). Compared to previously established conditions (see Scheme 64), a higher yield was obtained and the enantioselectivity was similar. Thus, the conditions appear to be specific for the substrate class developed here.



Scheme 89: (3+1+2) Cycloadditions of TMS-protected alkynes **287** and **290**. [a] The reaction was run at 120 °C.



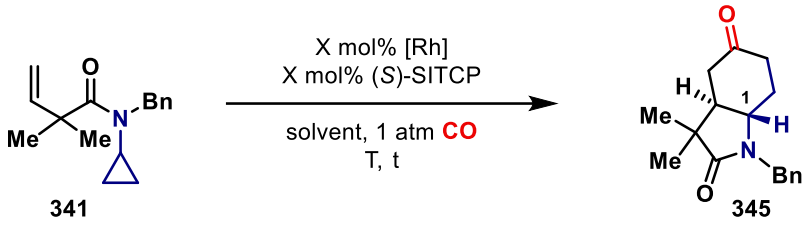
Scheme 90: (3+1+2) cycloaddition of the urea-based system **270** under optimised conditions.

4.6.3 Enantioselective alkene-based cycloadditions

It was also of interest to assess whether the newly identified chiral ligand system would perform well with alkene-bearing substrates, as this would allow the formation of two contiguous stereocentres in an enantioselective and diastereoselective manner. Further, in these processes, (a) trapping of the rhodacyclopentanone is expected to be slower because the alkene is a less good ligand than the alkynes used previously, and (b) the sterics of the alkene unit are distinct from alkyne substrates. Thus, if high enantioselectivities are still achieved, then it would offer circumstantial evidence that the primary enantiodetermining step in these cycloadditions is the C-C bond activation process.

Cycloaddition of system **341** to **345** was explored using (*S*)-SITCP under the conditions previously optimised for the non-asymmetric transformation ($[Rh(cod)Cl]_2$ in PhCN). This

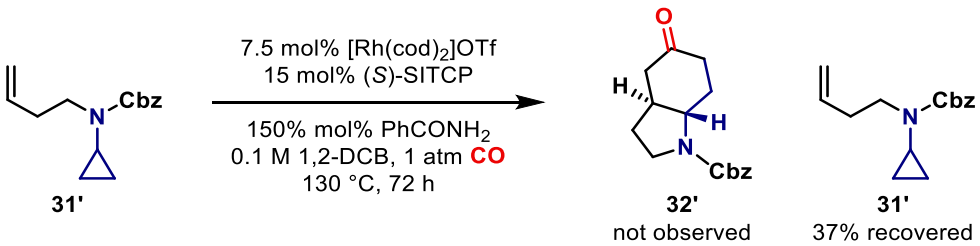
experiment led only to the recovery of starting material (Table 12, Entry 1). Pleasingly, conditions optimised for the alkyne-bearing substrates ([Rh(cod)$_2$]OTf in 1,2-DCB) transferred efficiently to cyclopropylamine **341**, and cyclohexanone **345** was isolated as a single diastereomer in 63% yield and 78% e.e. (Table 12, Entry 2). The enantioselectivity observed here is similar to that obtained for **277** to **280**, which, in turn, suggests that C-C bond activation is enantiodetermining.



Entry	Rh^{I} (mol %)	(*S*)-SITCP (mol %)	Solvent (M)	Time (h)	T (°C)	Yield of 345[a] (%)	341[a] (%)	e.r.
1	[Rh(cod)Cl]$_2$ (5)	20	PhCN, 0.1	72	130	0	>99	-
2	[Rh(cod)$_2$]OTf (7.5)	15	1,2-DCB, 0.1	96	110	70 (63)	0	89:11

Table 12: Optimisation studies on an alkene-based asymmetric (3+1+2) cycloaddition. [a]Yields were determined by ^{1}H NMR spectroscopy using 1,4-dinitrobenzene as a standard. Isolated yields are given in parentheses. The absolute configuration of **345** at C1 was tentatively assigned as (*S*) by analogy with **280d**.

The (*S*)-SITCP ligand was also evaluated on the previously established Cbz-directed cycloaddition of substrate **31'** to **32'** (Scheme 91, cf. Section 1.3, Scheme 7).[48] The expected product **32'** was not observed, and only some starting material **31'** was recovered. The poor mass balance is attributed to decomposition of the starting material and no further studies were undertaken on this reaction.

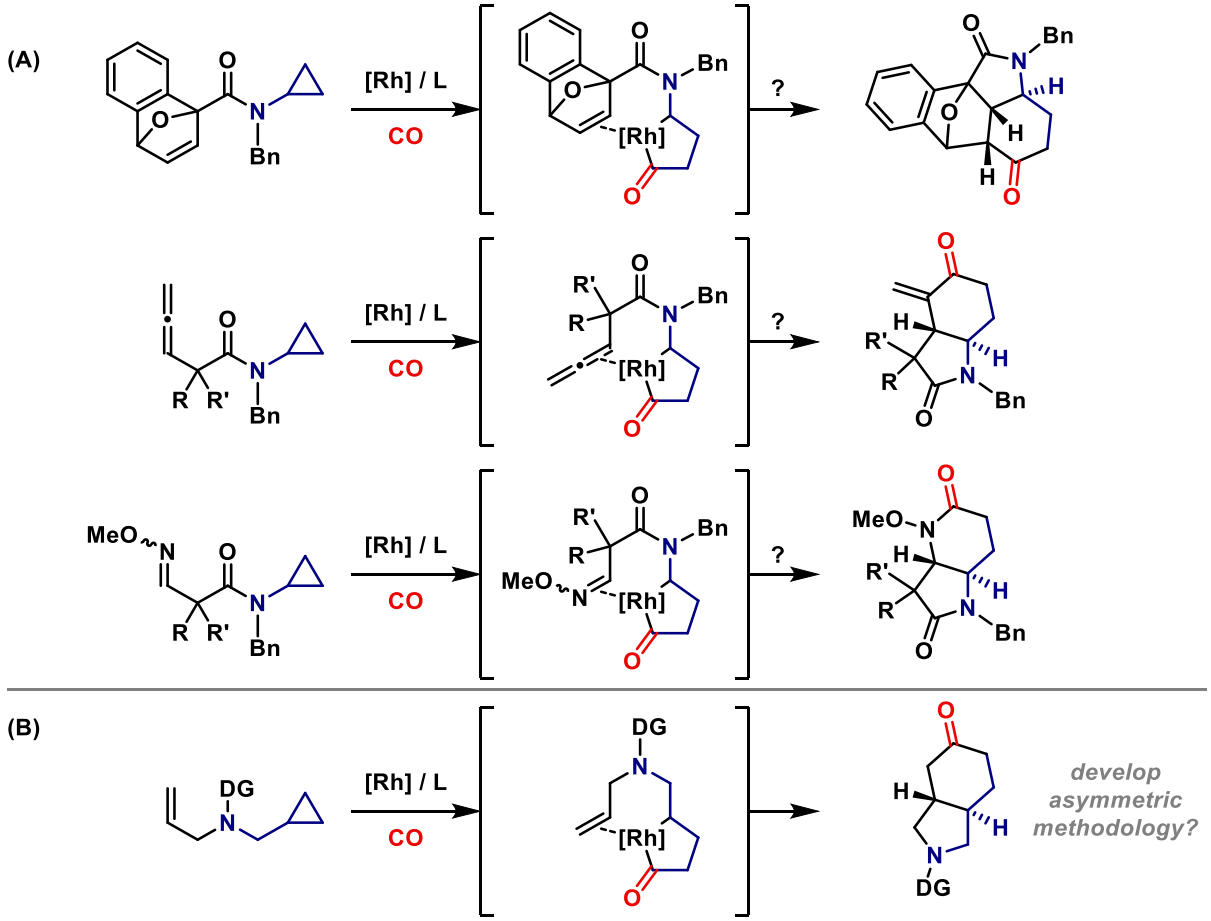


Scheme 91: Attempted enantioselective cycloaddition of **31'**.

4.7 Conclusions and future directions

To summarise, novel carbonylative (3+1+2) cycloadditions of aminocyclopropanes bearing tethered alkynes or alkenes have been developed. An extensive study of the scope and limitations of the reaction has been undertaken. The first asymmetric C-C bond activation of aminocyclopropanes has been realised and exemplified. The complementary transformation giving racemic products was studied with respect to polysubstituted cyclopropanes. For enantioenriched cyclopropane units, the enantiospecific nature of the Rh(I)-catalysed C-C bond activation process has been established. The studies described here add to a growing body of enantioselective C-C bond activations,[2,138] and provide rare examples of enantioselective carbonylative C-C bond activations.[137] Within this context, these are the first examples of highly enantioselective higher order (multicomponent) cycloadditions that use "simple" non-activated cyclopropanes.

Future studies should focus on ligand design to improve the enantioselectivity of the process. Other tethered π-unsaturates, such as bicyclic alkenes[198], *N*-oximes[166] and allenes[33] could also be tested under C-C bond activation conditions and the possibility of making these cycloadditions asymmetric can be explored (Scheme 92A). Additionally, C-C bond activation methodologies previously established in the Bower group should be re-examined using the newly developed enantioselective conditions (e.g. Scheme 92B).[108]



Scheme 92: Proposed substrates for (3+1+2) cycloadditions.

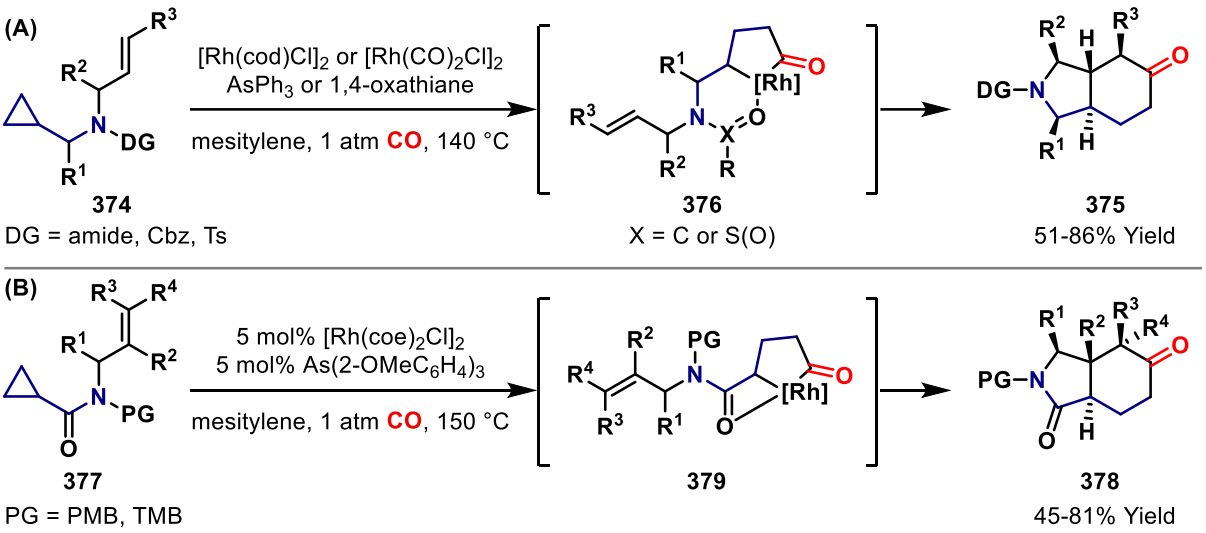
CHAPTER 5

C-C Bond activation of aminomethylcyclopropanes

5.1 Introduction

5.1.1 Directed C-C bond activation in aminocyclopropane homologues

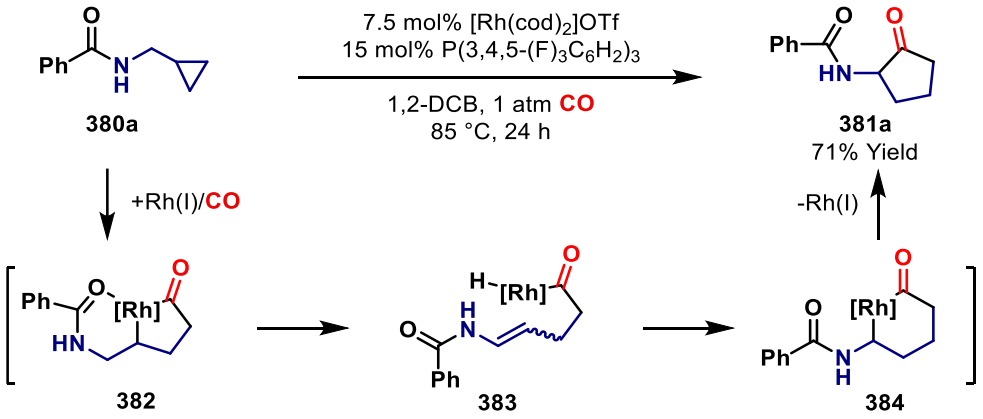
In general, C-C bond activation processes employing cyclopropane derivatives either require activated variants[137,199-201] or rely on the incoming π-unsaturate to direct C-C activation,[202] thereby limiting further application of the initiation mode. The studies at Bristol are therefore significant because relatively unactivated cyclopropanes can be used in a range or processes. Aside from aminocyclopropanes, several related classes of cyclopropane can also undergo amide-directed C-C bond activation. Previous research has demonstrated that electronically distinct aminomethylcyclopropanes **374** undergo directed carbonylative C-C bond activation to form a wide range of (3+1+2) cycloaddition products **375** (Scheme 93A).[108] This transformation proceeds through a relatively unstable 6-ring chelate **376**, which adds an additional challenge as facile exocyclic β-hydride elimination can occur upon dissociation of the directing group. The process also employs an electron neutral nonactivated cyclopropane instead of the more electron-rich aminocyclopropane. The less nucleophilic cyclopropane of **374** makes C-C oxidative addition to form intermediate **376** more difficult. Systems containing an electron-poor cyclopropylamide unit (**377**) are even more challenging and required the design of a specific hemilabile arsine ligand ($As(2\text{-}OMeC_6H_4)_3$, Scheme 93B).[203] Here, control experiments showed that directed C-C activation of **377** to **378** is less favourable than for **374** to **375**; this is likely due to a combination of the electronics of the cyclopropane and the generation of a relatively strained 4-membered chelate **379** (vs. 6-membered chelate **376**). The studies outlined in Scheme 93 demonstrate that directed C-C bond activation can occur regardless of the cyclopropane electronics; however, the more electron-poor the cyclopropane unit, the more challenging the process is.



Scheme 93: Rhodium-catalysed (3 + 1 + 2) cycloadditions of aminocyclopropane homologues.

5.1.2 Preliminary investigations into aminomethylcyclopropane ring expansions

During further studies on the reactivity of aminomethylcyclopropane derivatives, Dr. Niall McCreanor discovered that α-aminocyclopentanone **381a** can be obtained from **380a** under carbonylative conditions (Scheme 94).[75] A plausible mechanism for the formation of **381a** commences with amide directed formation of rhodacyclopentanone **382**. Subsequent directing group dissociation and β-hydride elimination from **382** forms Rh(III)-acyl hydride species **383**. Hydrometallation of the resultant enamide generates rhodacyclohexanone **384**, a metallacycle which is scarcely presented in the literature. Finally, $C(sp^3)$-$C(sp^2)$ reductive elimination affords cyclopentanone adduct **381a**. The process represents an unusual example of a C-C bond activation triggered alkene hydroacylation and also offers the option of exploring further the chemistry of unusual metallacycle **384**.



Scheme 94: Proposed mechanism for carbonylative ring expansion of aminomethylcyclopropane **380a**.

Optimisation studies carried out by McCreanor on aminomethylcyclopropane **380a** revealed that neutral Rh-precatalysts (e.g. $[Rh(cod)Cl]_2$) are less active than cationic $[Rh(cod)_2]OTf$, and that strongly coordinating solvents (benzonitrile, *N*,*N*-dimethylformamide) suppress cyclisation, whilst weakly coordinating variants (anisole, 1,2-DCB) are more effective. For example, **381a** was obtained in 9% yield using PhCN as a solvent, whereas in 1,2-DCB the yield increased to 71%. Electron-deficient monodentate ligands increased the yield, and $P(3,4,5\text{-}(F)_3C_6H_2)_3$ was found to be the optimum ligand for this transformation. Electron-deficient bidentate P-ligands such as d^fppe and d^fppb were also examined; however, they proved ineffective at promoting the carbonylative cyclisation. Later, it was found by Dr. Gabriele Fumagalli that the addition of 20 mol% $PhCO_2H$ has a positive effect on the yield of the reaction. Under the optimised conditions shown in Table 13, a range of substituted aminomethylcyclopropanes **380a-i** with varying directing groups were evaluated. Amide based systems **380a-e** cyclised in moderate to excellent yield, whereas sulfonamide (**380f**), carbamate (**380g**) and urea-based systems (**380h**) were ineffective. In these cases, only starting material was recovered.

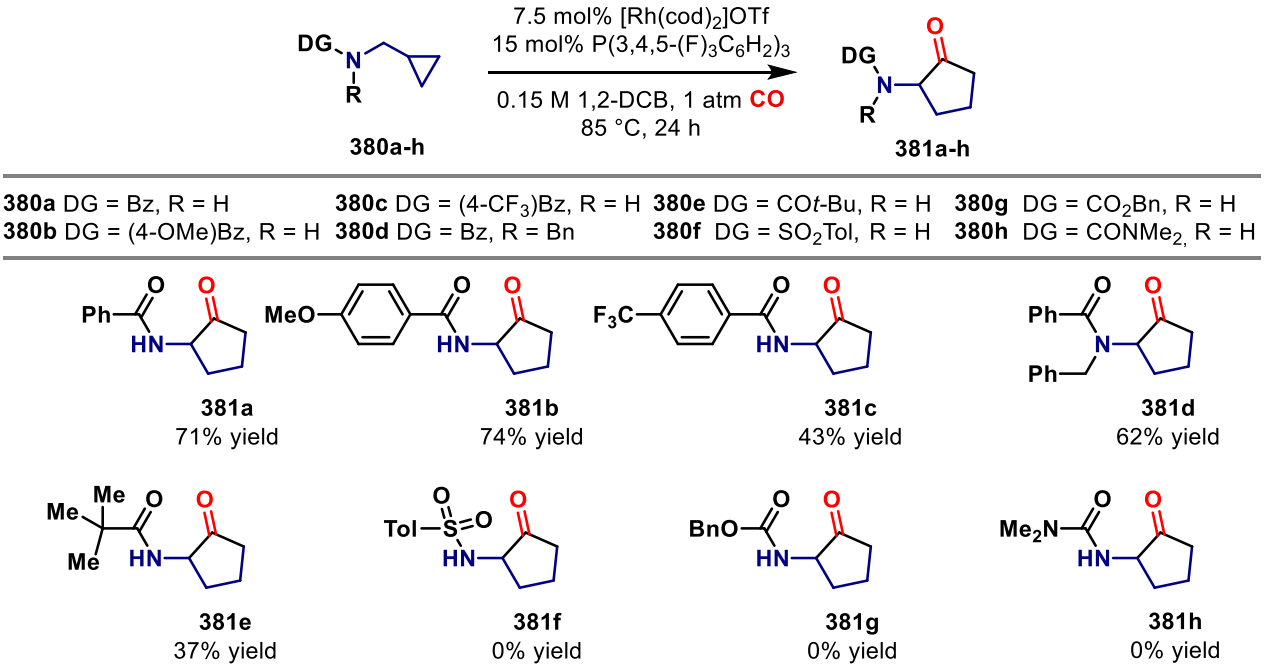


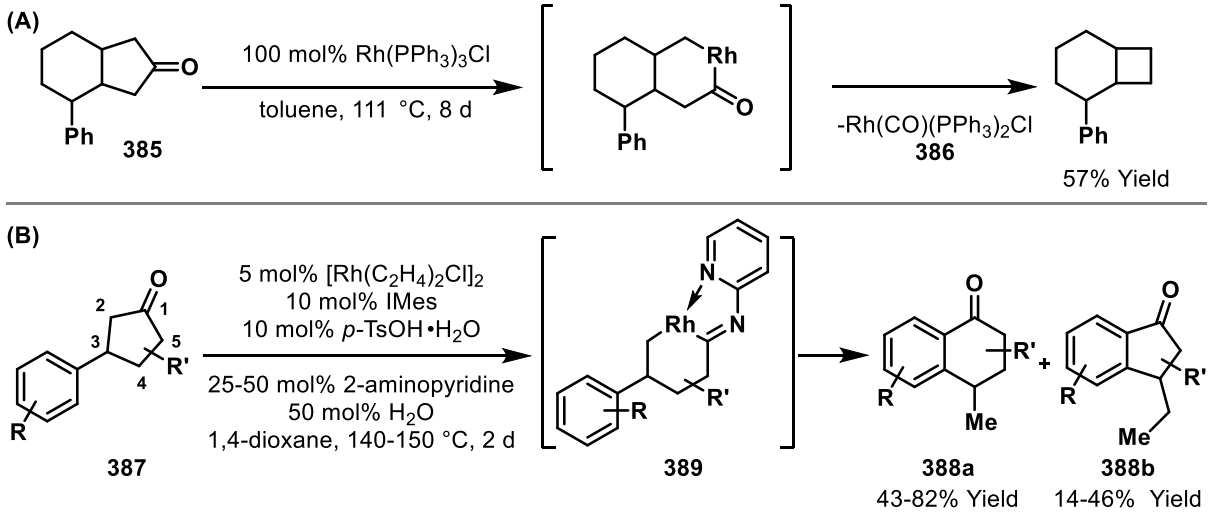
Table 13: Selected examples of carbonylative cyclisation of aminomethylcyclopropanes to α-aminocyclopentanones. For **381a**, 20 mol% of $PhCO_2H$ was used as an additive; for **381d**, 15 mol% $P(3,5\text{-}(CF_3)_2C_6H_3)_3$ was used as a ligand and the reaction was stirred for 48 h. [a]Compound **381a** was obtained in 81% yield at 110 °C.

5.1.3 Known systems proceeding via rhodacyclohexanone intermediates

Section 5.1.2 demonstrates rare examples of a transformation proceeding via the formation of a rhodacyclohexanone (**384**). In principle, rhodacyclohexanones can be formed by C-C bond activation of cyclopentanones; however, this is a challenging process. In contrast to three-membered rings, cyclopentanones lack sufficient thermodynamic driving force to favour oxidative

addition of a transition metal, with the reverse process being energetically preferred.[204] Thus, the catalytic C-C activation of non-strained rings, such as cyclopentanones, is underdeveloped.

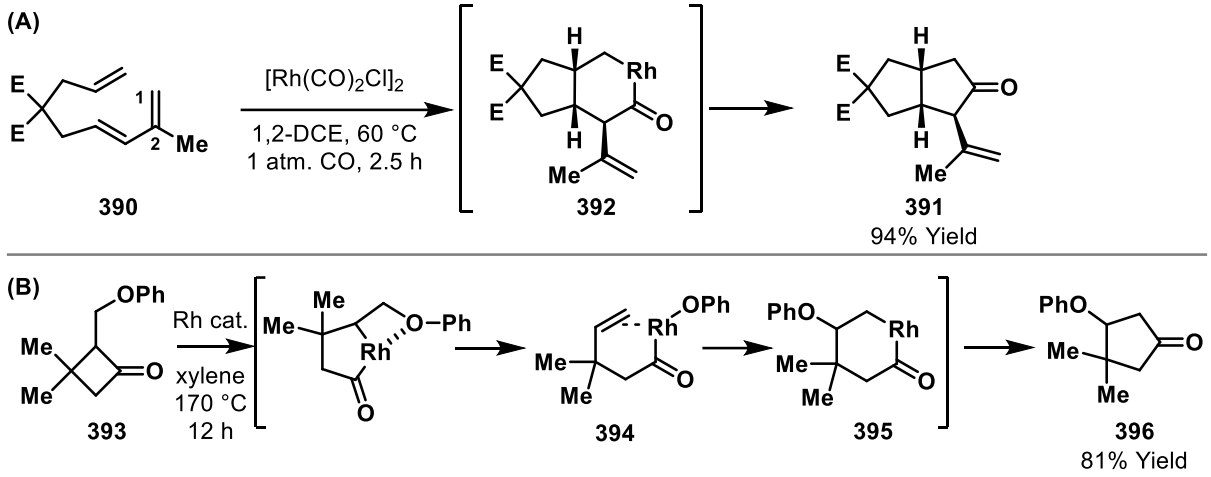
In 1994, rhodium-mediated decarbonylation of cyclopentanone **385** was described by Murakami and co-workers (Scheme 95A).[205] However, this process requires stoichiometric amounts of a Rh(I)-complex and showed low overall efficiency, primarily because the released rhodium carbonyl complex **386** does not turnover.[206] Dong has shown that the problem of low reactivity can be solved by merging an unfavourable C-C bond activation with a tandem sp^2 C-H functionalisation - this enables an overall thermodynamically favoured transformation (Scheme 95B).[96] Installation an aryl group at the C3 position of the cyclopentanone allows the transient C-C bond activation intermediate to undergo intramolecular *ortho*-C-H activation. Several 3-arylcyclopentanones **387** were employed and gave rise to two products, α-tetralones **388a**, which were formed as a result of the cleavage of the more hindered C1-C2 bond, and α-indanones **388b**, generated from the cleavage of the less hindered C1-C5 bond. This reaction is further enhanced by using a transient pyridyl imine as a directing group for the formation of **389**; consequently, the reaction does not proceed via rhodacyclohexanone. Overall, cyclopentanones show low reactivity and undergo highly reversible C-C bond insertion by rhodium species, which makes it hard to exploit rhodacyclohexanone intermediates in catalysis.



Scheme 95: (A) Rhodium-mediated decarbonylation of a cyclopentanone; (B) C-C activation of 3-arylcyclopentanones via tandem sp^2 C-H functionalisation.

Interestingly, less commonly exploited substrates can also lead to the formation of rhodacyclohexanones. For example, diene-enes **390** undergo a Rh(I)-catalysed (2+2+1) reaction to provide hexahydropentalen-2-ones **391** (Scheme 96A).[207] Computational studies revealed that this process proceeds through a rhodacyclohexanone intermediate **392**.[208] The study found that the presence of the additional C1-C2 π-based fragment in the diene moiety is crucial, and this allows

the metal to be coordinatively saturated during the critical oxidative coupling step. Furthermore, cyclobutanone **393**, which contains a phenoxymethyl side chain, can also undergo C-C bond activation leading to the formation of the olefin-coordinated acylrhodium intermediate **394**. This intermediate forms through successive cleavage of C-C and C-O bonds (Scheme 96B).[27] Subsequent recyclisation of **394** leads to rhodacyclohexanone **395** by 6-*endo* aryloxymetallation. C-C reductive elimination of **395** then gives cyclopentanone **396**.



Scheme 96: (A) Diene-ene (2+2+1) carbocyclisation; (B) Successive cleavage of C-C and C-O bonds of a cyclobutanone system; E = CO_2Me; Rh cat. = $[Rh(nbd)(dppp)]PF_6$; nbd - norborna-2,5-diene; dppp - 1,3-bis(diphenylphosphino)propane.

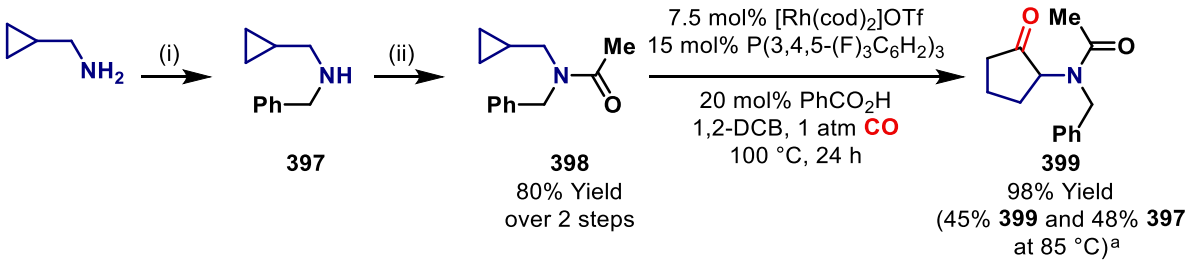
The processes above are rare examples of the intermediacy of rhodacyclohexanones (or related species) in catalysis. The newly discovered transformation of aminomethylcyclopropanes **380** shown in Scheme 94 offers a simple entry to the rhodacyclohexanone intermediates. Furthermore, the process provides an unconventional approach to the synthesis of protected α-aminocyclopentanones **381**. As such, further studies into this and related transformations were warranted.

5.2 C-C Bond activation-triggered hydroacylation of aminomethylcyclopropanes

5.2.1 Synthesis and reactivity of *N*-benzyl-*N*-(cyclopropylmethyl)acetamide

Previously developed conditions[75] allowed the successful cyclisation of benzoyl protected substrate **380a** in good yield, but the yields decreased when tertiary amides (e.g. **380d**) were used (i.e. R ≠ H, see Table 13). Although cyclopropane **380d** bearing a benzyl group on the nitrogen did form the desired cyclopentanone **381d** in 62% yield, all further attempts to increase the yield were not fruitful. It was envisaged desirable to optimise this process, because appendage of additional units to the *N*-centre may allow the design of processes that divert the rhodacyclohexanone intermediate into other pathways.

Acyl-protected amide **398** was readily synthesised by reductive amination of cyclopropylmethanamine with benzaldehyde to give amine **397**, which was acetylated using acetic anhydride to give **398** in 80% overall yield (Scheme 97). When amide **398** was exposed to the developed catalytic system at 85 °C, starting material **398** and target material **399** were observed in a 1:1 ratio, and no other significant products were formed. Pleasingly, cyclopentanone **399** could be delivered in excellent yield (98%) simply by raising the temperature to 110 °C (Scheme 97).



397

398
80% Yield
over 2 steps

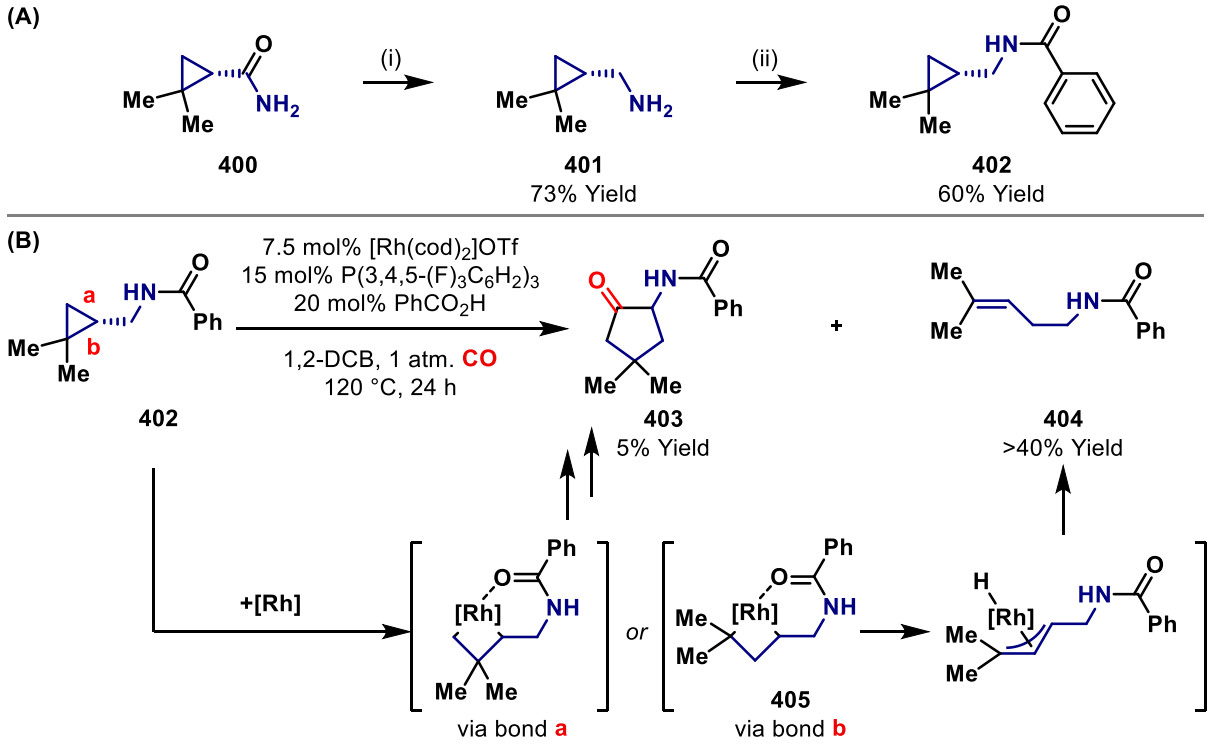
399
98% Yield
(45% **399** and 48% **397**
at 85 °C)[a]

Scheme 97: Synthesis and Rh-catalysed carbonylative cyclisation of *N*-benzyl-*N*-(cyclopropylmethyl)acetamide. *Reagents and conditions:* (i) (a) benzaldehyde, $NaHCO_3$, MeOH, reflux, 3 h; (b) $NaBH_4$, 0 °C to r.t., 4 h; (ii) acetic anhydride, TEA, DCM, 0 °C to r.t., 16 h. [a] Yields were determined by ^1H NMR spectroscopy using 1,4-dinitrobenzene as an internal standard.

5.2.2 Carbonylative rearrangement of substituted aminomethylcyclopropanes

With high yielding conditions in hand, further studies with respect to substitution on the cyclopropane unit were conducted. For this purpose, 2,2-dimethylcyclopropyl derivative **402** was synthesised. The amide unit of commercially available **400** was reduced with $LiAlH_4$ to generate amine **401**, and this was protected with benzoyl chloride to deliver cyclopropane **402** (Scheme 98A). Dimethylcyclopropane **402** was subjected to the optimised reaction conditions (7.5 mol% $[Rh(cod)_2]OTf$, 15 mol% $P(3,4,5\text{-}F_3C_6H_2)_3$, 20 mol% benzoic acid, 0.15 M 1,2-DCB, 1 atm CO,

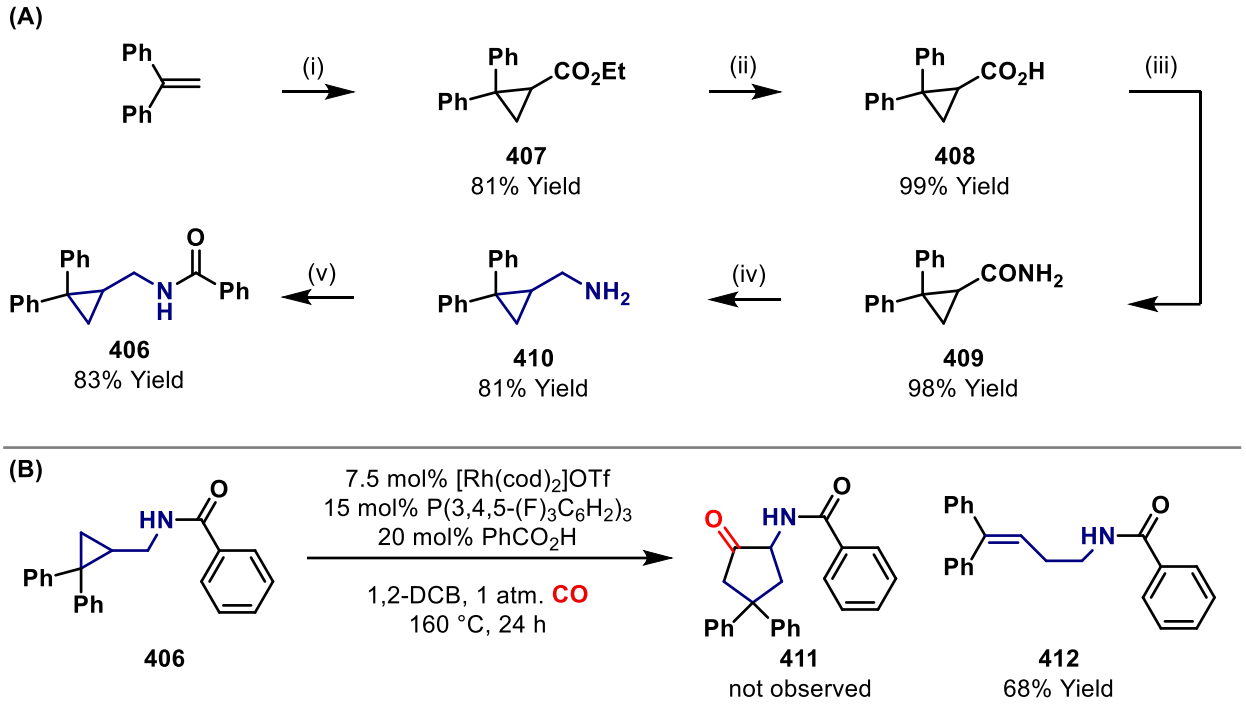
85 °C) but target product **403** was not observed. To address this, temperature (85 to 160 °C), catalyst loading (7.5 to 15 mol%) and reaction time (24 to 48 h) were all varied. It was found that cyclopropane **402** generally remained unreacted at low temperatures, but, at 120 °C, some reactivity was observed, and cyclopentanone **403** was isolated in 5% yield (Scheme 98B). Alkene **404** was observed as the major product of the reaction, and this likely forms via β-hydride elimination from the initially generated rhodacyclobutane **405**. It is worth noting that cyclopentanone **403** results from metal insertion into the less hindered C-C bond **a** of cyclopropane **402**, whereas **404** arises from insertion into the more hindered bond **b**. Raising the reaction temperature further to 140 or 160 °C led to a complex mixture of cyclopropane **402**, alkenyl product **404** and its isomers, and cyclopentanone **403** was not observed.



Scheme 98: Synthesis and reactivity of (dimethylcyclopropyl)methylbenzamide **402**. *Reagents and conditions:* (i) $LiAlH_4$, THF, 0 °C to reflux, 16 h; (ii) BzCl, TEA, DCM, 0 °C to r.t., 16 h.

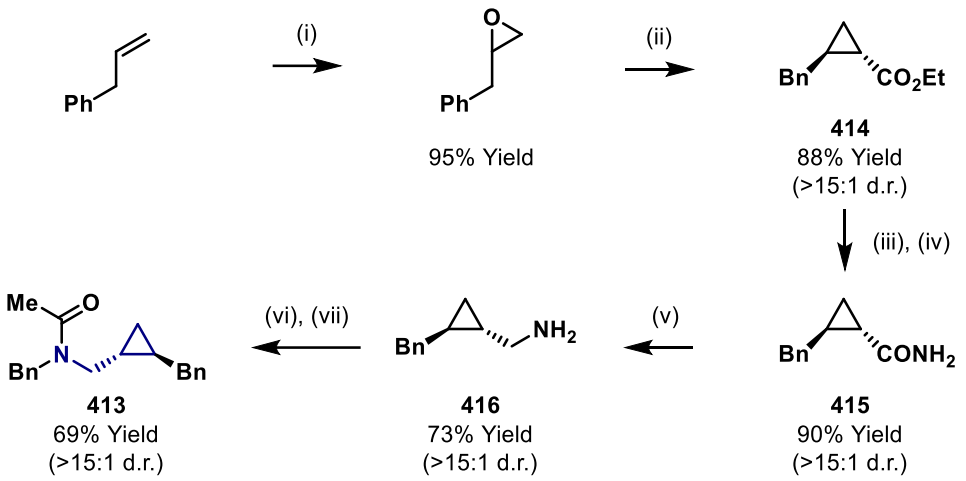
In an attempt to avoid the β-hydride elimination pathway, diphenyl-substituted cyclopropane **406** was synthesised (Scheme 99A). It was anticipated that this system might undergo C-C bond activation at lower temperature as a result of benzylic activation of the C-C bond. Initial Rh-catalysed cyclopropanation of 1,1-diphenylethylene produced cyclopropane ester **407**. Subsequent saponification to acid **408** was followed by reaction of the corresponding acyl chloride with ammonia to produce amide **409**. Reduction of amide **409** with $LiAlH_4$ generated amine **410**, which was protected with benzoyl chloride to deliver cyclopropane **406**.

When diphenylcyclopropane **406** was subjected to the conditions that proved optimal for **398** (see Scheme 97), only starting material was recovered. At elevated temperatures, the reaction led to degradation of the rhodacyclic intermediate by β-hydride elimination, as evidenced by the formation of **412**. Indeed, increasing the temperature to 160 °C resulted in formation of alkene **412** in 68% yield and product **411** was not observed (Scheme 99B). This result indicates that insertion into sterically bulky aminomethylcyclopropane **406** is extremely slow and, upon formation of the rhodacyclic intermediate, degradation occurs in preference to either (reversible) CO insertion or acyl-C reductive elimination.



Scheme 99: Synthesis and reactivity of (diphenylcyclopropyl)methylbenzamide **406**. *Reagents and conditions:* (i) $Rh_2(OAc)_4$, ethyl diazoacetate, Et_2O, 8 h; (ii) KOH, 1,4-dioxane:H_2O 1:1, reflux, 80 °C, 4 h; (iii) oxalyl chloride, DCM, r.t., then NH_3, THF, 0 °C, 1.5 h; (iv) $LiAlH_4$, THF, 0 °C to reflux, 16 h; (v) BzCl, TEA, DCM, 0 °C to r.t., 16 h.

The results with 2,2-disubstituted cyclopropanes **402** and **406** suggested that switching to a less hindered system might suppress undesired β-hydride elimination. Benzyl-substituted cyclopropane **413**, which is equipped with a directing group analogous to efficient system **398** (cf. Section 5.2.1), was synthesised in 7 steps *via* the synthetic route depicted in Scheme 100. Allylbenzene was treated with *m*-CPBA to deliver the corresponding epoxide. Subsequent Horner–Wadsworth–Emmons cyclopropanation generated ester **414** as a single *trans*-diastereomer.[209,210] Hydrolysis of ester **414** and treatment of the corresponding acid chloride with ammonia delivered amide **415**, which was reduced to amine **416** in the presence of $LiAlH_4$. Finally, reductive amination followed by acylation afforded *trans*-1,2-disubstituted methylcyclopropane **413**.

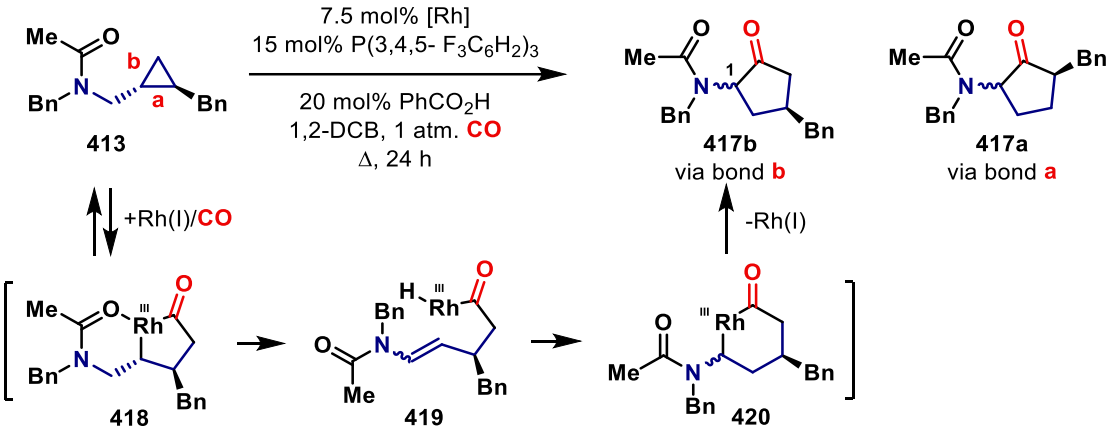


Scheme 100: Synthesis of *trans*-1,2-disubstituted aminomethylcyclopropane **413**. *Reagents and conditions*: (i) *m*-CPBA, DCM, 0 °C to r.t., 18 h; (ii) triethylphosphonoacetate, *n*-BuLi, DME, 130 °C, 16 h; (iii) 4.0 M aq. NaOH, MeOH, r.t., 3 h; (iv) oxalyl chloride, DCM, r.t., then NH_3, THF, 0 °C, 1.5 h; (v) $LiAlH_4$, THF, 0 °C to reflux, 16 h; (vi) (a) benzaldehyde, $NaHCO_3$, MeOH, reflux, 3 h; (b) $NaBH_4$, 0 °C to r.t., 4 h; (vii) acetic anhydride, TEA, DCM, 0 °C to r.t., 16 h.

Carbonylative rearrangement of cyclopropane **413** under standard conditions yielded **417b** as a mixture of diastereomers (~2:1) in less than 5% yield (Table 14, Entry 1). Cyclopentanone **417b** is a result of oxidative addition of the Rh(I)-catalyst into the less hindered proximal C-C bond **b** leading to rhodacyclopentanone **418**. Mechanistically, the lack of diastereocontrol is unsurprising. If hydrometallation is the stereodetermining step for this process, enamide isomerisation may occur upon the formation of Rh(III)-acyl hydride species **419**, thus delivering a mixture of diastereomeric rhodacyclohexenones **420** (Table 14, top). Even if a geometrically defined enamide is formed, hydroacylation can occur via either face of intermediate **419**, which would also lead to a mixture of diastereomers. Finally, the C1 stereocenter of **417b** is potentially labile and may epimerise under the reaction conditions.

Although poor diastereisomeric ratios (approx. 2:1) were observed for **417b**, studies were undertaken to improve the yield. It was found that increasing the reaction time and temperature led to the formation of **417b** in approximately 30% yield (Table 14, Entries 2-3). Although no starting material was observed in the reaction mixture, acetamide **413** was converted into a complex mixture of undesired products (Table 14, Entry 3). As a result, a range of cationic Rh(I)-sources, with various counterions (OTf, BF_4, SbF_6 and BARF), was evaluated (Table 14, Entries 3-6). A Rh(I)-precatalyst with a highly dissociating counteranion, $[Rh(cod)_2]$BARF, suppressed the formation of by-products and cyclopentanone **417b** was isolated in 52% yield (Table 14, Entry 6). Increasing the reaction temperature in this case did not increase the yield (Table 14, Entry 7). Interestingly, longer reaction times resulted in the formation of trace quantities of alternate

regioisomer **417a**, which arises from Rh insertion into the more hindered C-C bond **a** (Table 14, Entry 8). Electron-rich or -neutral P-ligands, as well as sterically bulky and bidentate P-ligands, were all detrimental to the yield of the reaction. None of the ligands assessed displayed a significant advantage over P(3,4,5-(F)$_3$C$_6$H$_2$)$_3$. Although the overall yield of transformation was significantly improved, further investigations failed to enhance the levels of diastereoselectivity.



Entry	Catalyst	T, °C	Time, h	413 left, %	Yield of 417b[a], %	d.r.
1	[Rh(cod)$_2$]OTf	100	24	68	<5	-
2	[Rh(cod)$_2$]OTf	120	24	24	32 (27)[b]	1:1.5
3	[Rh(cod)$_2$]OTf	130	48	0	34	1:1.3
4	[Rh(cod)$_2$]BF$_4$	120	72	82	<10	-
5	[Rh(cod)$_2$]SbF$_6$	120	72	28	52 (38)[b]	1.5:1
6	[Rh(cod)$_2$]BARF	120	24	22	56 (52)[b]	2.2:1
7	[Rh(cod)$_2$]BARF	140	24	15	48	1.6:1
8	[Rh(cod)$_2$]BARF	120	48	15	65 (68)[b,c]	2.0:1

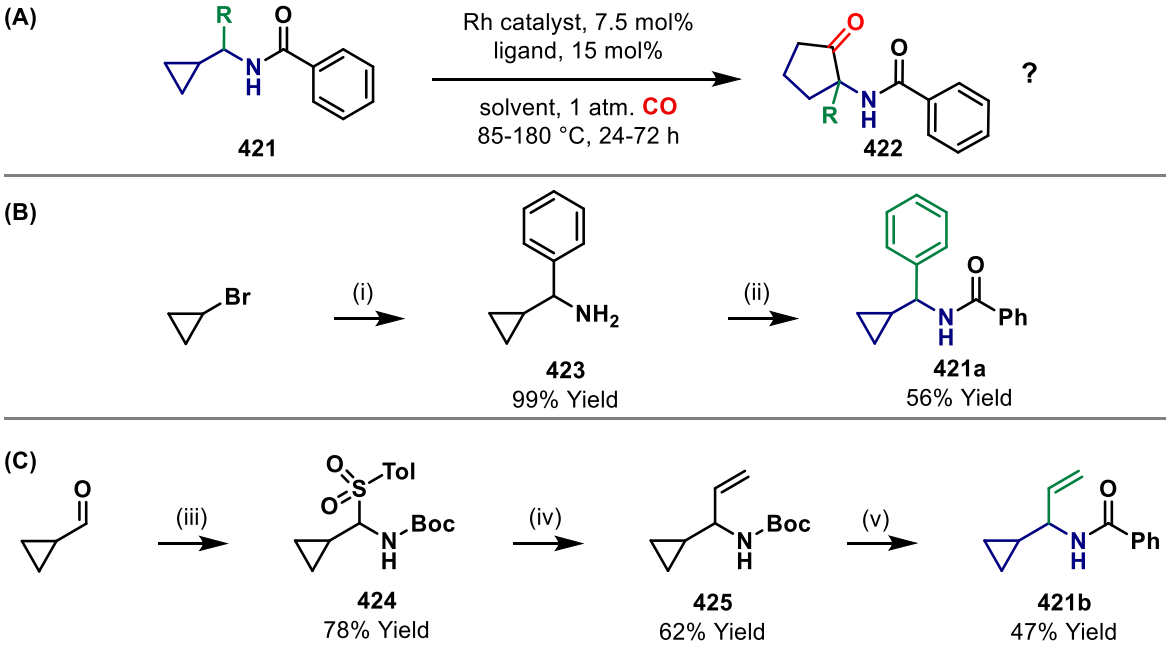
Table 14: Proposed mechanism and selected conditions for Rh-catalysed carbonylative ring expansion of *trans*-1,2-disubstituted aminomethylcyclopropane **413**. [a]Yields were determined by ^{1}H NMR analysis of the crude reaction mixture against an internal standard (1,4-dinitrobenzene). Isolated yields are given in parentheses. [b] Isolated as a mixture of diastereomers. [c] Isolated as an approx. 3:1 mixture of regioisomers.

5.2.3 α-Substituted *N*-(cyclopropylmethyl)benzamides

The generality of the carbonylative cyclopentanone **422** synthesis was next examined by evaluating α-substituted *N*-(cyclopropylmethyl)benzamides **421** (Scheme 101A). To this end, phenyl and vinyl substituted cyclopropanes **421a** and **421b** were synthesised. Compound **421a** was obtained through a two-step sequence (Scheme 101B). Firstly, PhCN was treated with freshly formed cyclopropylmagnesium bromide to give the corresponding imine, which was immediately

reduced with $NaBH_4$ to provide amine **423** in quantitative yield. This was subsequently reacted with benzoyl chloride to give the target starting material **421a**. The synthesis of α-vinyl substituted substrate **421b** was achieved using an alternative route (Scheme 101C). Condensation of cyclopropanecarboxaldehyde with *tert*-butyl carbamate and sodium *p*-toluenesulfinate afforded sulfone **424**. This was then treated with an excess of Grignard reagent to convert **424** into the corresponding imine which then reacted with another equivalent of vinylmagnesium bromide to give addition product **425** in 62% yield.[211] Boc-deprotection using trifluoroacetic acid, and amide formation with benzoyl chloride provided cyclopropane **421b**.

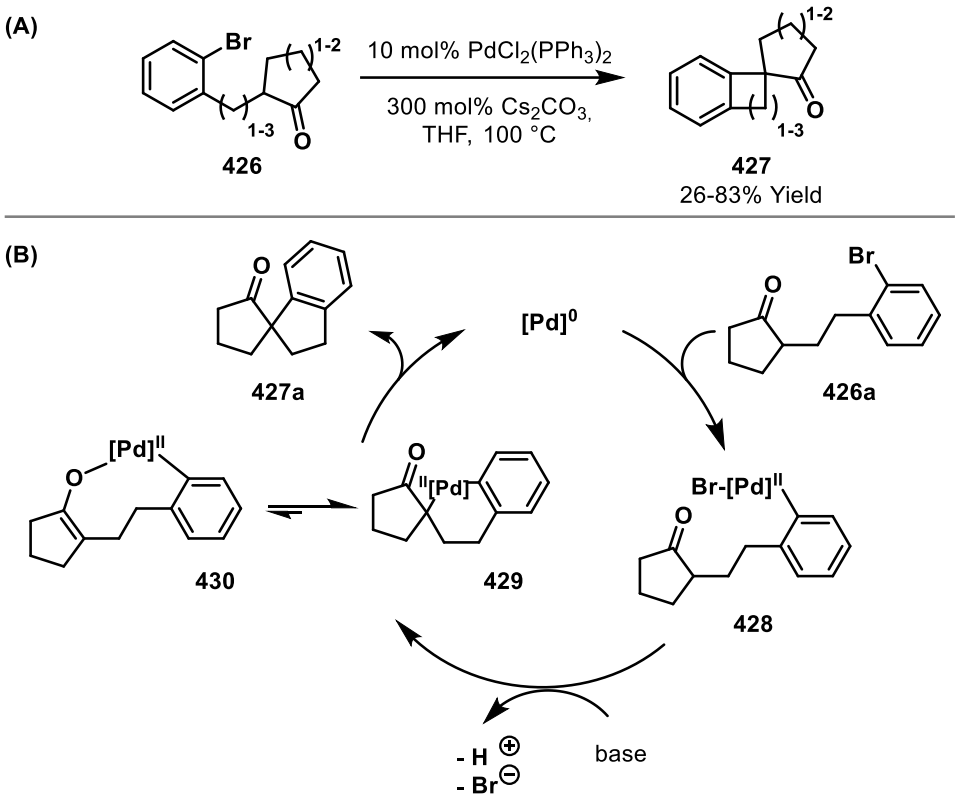
Cyclopropanes **421a** and **421b** were exposed to a range of catalytic conditions, employing neutral (PPh_3), electron-deficient ($P(3,5\text{-}CF_3C_6H_3)_3$, $P(3,4,5\text{-}F_3C_6H_2)_3$) and electron-rich ($P(4\text{-}OMeC_6H_4)_3$) monodentate ligands, and neutral ($[Rh(cod)Cl]_2$) and cationic ($[Rh(cod)_2]OTf$) Rh-precatalysts. Non-coordinating (1,2-DCB and mesitylene) and strongly coordinating solvents (benzonitrile), different temperatures (85-180 °C) and reaction times of up to 3 days were investigated. However, for **421a** only starting material was recovered, whereas for **421b** consumption of starting material was observed, but target product **422** could not be isolated. The failure of these systems might suggest that additional substitution at C1 suppresses β-hydride elimination (cf. Scheme 92, **383** to **383**) and/or enamide hydrometallation (**383** to **384**). Alternatively, C-C bond activation of these sterically demanding substrates may be inefficient.



Scheme 101: (A) Proposed Rh-catalysed cyclisation of α-substituted *N*-(cyclopropylmethyl)benzamides. (B) Synthesis of *N*-[cyclopropyl(phenyl)methyl]benzamide **421a**. (C) Synthesis of *N*-(1-cyclopropylallyl)benzamide **421b**. *Reagents and conditions:* (i) (a) Mg, benzonitrile, THF, 0 °C, 6 h; (b) $NaBH_4$, MeOH, 0 °C to r.t., 16 h; (ii) BzCl, TEA, DCM, 0 °C to r.t., 16 h; (iii) *tert*-butyl carbamate, sodium *p*-toluenesulfinate, HCO_2H, H_2O:MeOH 2:1, r.t., 2 d; (iv) vinylmagnesium bromide, THF, -78 °C to r.t., 2 h; (v) (a) TFA, DCM, r.t., then (b) BzCl, TEA, DCM, 0 °C to r.t., 16 h.

5.2.4 *ortho*-Halogenated *N*-(cyclopropylmethyl)benzamides

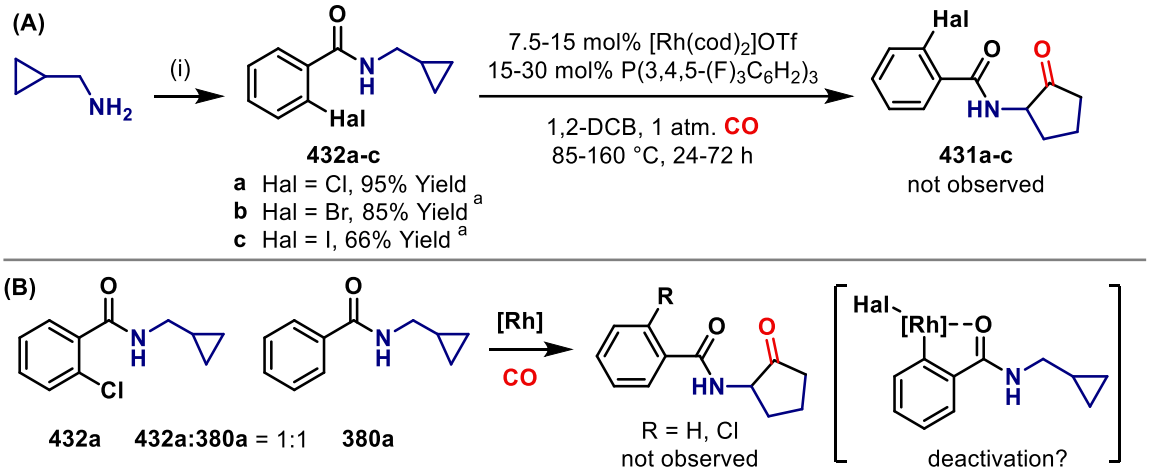
In 1997, Muratake and Natsume reported the synthesis of spirobicycles **427** via the Pd-catalysed intramolecular α-arylation of cyclic ketones **426** (Scheme 102A).[212] A catalytic cycle for cyclopentanone α-arylation is shown in Scheme 102B.[213] Initially, oxidative addition of aryl halide **426a** to the Pd(0) complex forms arylpalladium(II) complex **428**. Substitution of the coordinated halide by an enolate nucleophile and reductive elimination from the resulting C-bound palladium enolate σ-complex **429**, which is preferred over O-bound palladium enolate σ-complex **430**,[214-216] gives aryl ketone **427a** and regenerates the Pd(0) complex.



Scheme 102: Pd-catalysed intramolecular α-arylation of α-substituted cyclic ketones as demonstrated by Muratake and Natsume and a generic α-arylation mechanism.

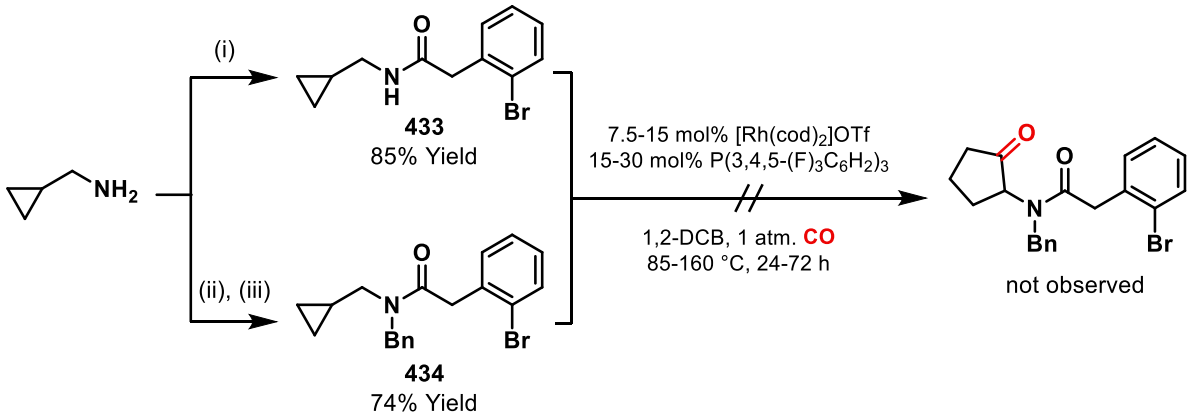
Subsequently, intramolecular α-arylations of this type have proved to be a powerful synthetic method for constructing α-arylated compounds.[217] In theory, this approach could be applied in the further functionalisation of α-aminocyclopentanones **431a-c** (Scheme 103A). In order to test the intramolecular cyclisation, a range of *ortho*-halogenated cyclopropylmethylbenzamides **432a-c** were synthesised from the corresponding substituted benzoyl chlorides. Unfortunately, the desired cyclopentanones **431a-c** were not observed when **432a-c** were exposed to a variety of Rh-catalysed carbonylation conditions. Even with increased reaction times, catalyst loading and elevated temperature, only starting material remained in the

reaction mixture. To test if the *ortho*-halide causes catalyst deactivation, a 1:1 mixture of unsubstituted cyclopropylmethylbenzamide **380a** and *ortho*-chloro-substituted cyclopropylmethylbenzamide **432a** was subjected to catalytic reaction conditions using 7.5 mol% of [Rh] at 100 °C (Scheme 103B). After 24 h, only the starting cyclopropanes were observed. A plausible explanation for the low reactivity of *ortho*-halogenated derivatives is that Rh insertion into the C-Hal bond of **432a-c** occurs, which then inhibits C-C bond activation.



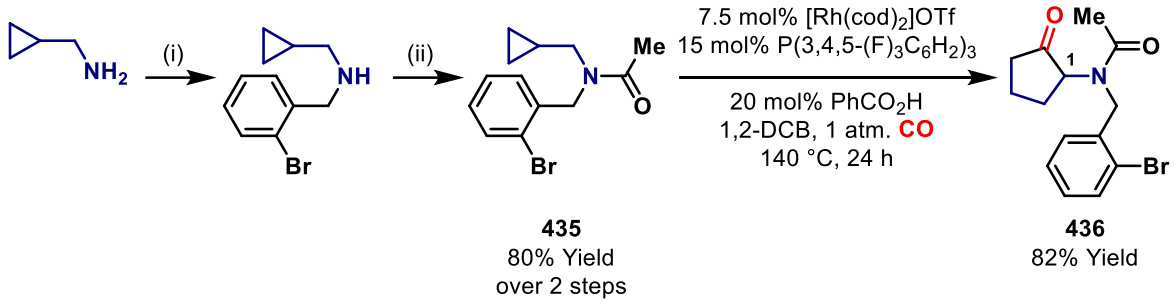
Scheme 103: Synthesis of *ortho*-halogenated cyclopropylmethylbenzamides and attempted Rh-catalysed ring expansion. *Reagents and conditions:* (i) ArCOCl, TEA, DCM, 0 °C to r.t., 16 h. [a]This compound was prepared by Dr. Fumagalli

It was proposed that increasing the distance between the amide directing group and *ortho*-halogenated aromatic ring would lower the chance of catalyst deactivation. To test this hypothesis, secondary amide **433** and tertiary amide **434** were synthesised (Scheme 104); however, both substrates were unreactive under the standard catalytic conditions. Similarly, when exposed to harsher reactions conditions no product was observed in an analogous manner to systems **432a-c**.



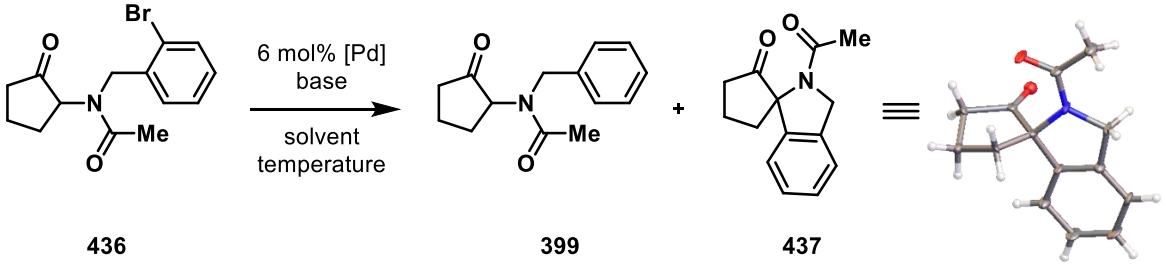
Scheme 104: Synthesis of amides **433** and **434**. *Reagents and conditions*: (i) 2-bromophenylacetic acid, EDCI, DMAP, DCM, 0 °C to r.t.; (ii) (a) benzaldehyde, $NaHCO_3$, MeOH, reflux, 18 h; (b) $NaBH_4$, 0 °C to r.t., 18 h; (iii) 2-(2-bromophenyl)acetyl chloride, TEA, DCM, 0 °C to r.t., 16 h.

The efficiency of the *N*-benzyl-*N*-(cyclopropylmethyl)acetamide system **398** (Section 5.2.1, Scheme 97) prompted evaluation of systems where *ortho*-halogenation is incorporated into the *N*-benzyl group instead of the benzamide unit (cf. **432a-c**). Acetamide **435** was readily synthesised in two steps in an analogous manner to **398** (*vide supra*) and exposed to the standard catalytic system (Scheme 105). At 85 °C, no conversion of the starting material was observed. However, in contrast to other systems, where the *ortho*-substituted aromatic ring was within the amide directing moiety (see Schemes 103 and 104), amide **435** does not deactivate the catalyst and the carbonylative rearrangement is feasible at elevated temperatures. At 140 °C, cyclopentanone **436** was formed in 82% yield, which then makes further functionalisation of C1 possible.



Scheme 105: Synthesis and Rh-catalysed carbonylative rearrangement of **435**. *Reagents and conditions:* (i) (a) 2-bromobenzaldehyde, $NaHCO_3$, MeOH, reflux, 3 h; (b) $NaBH_4$, 0 °C to r.t., 4 h; (ii) acetic anhydride, TEA, DCM, 0 °C to r.t., 16 h.

A typical procedure for the cross-coupling of a nucleophilic enolate and electrophilic aryl halide employs a Pd catalyst and a base (Table 15). Products of this reaction contain a new carbon-carbon bond at the α-carbon of the carbonyl compound. Buchwald and co-workers have demonstrated a general approach for the α-arylation of a wide variety of substrates using sodium or lithium *tert*-butoxide as the base.[218,219] Unfortunately, this strategy was inefficient for the proposed intramolecular arylation (Table 15, Entries 1-3) and led predominantly to dehalogenated species **399**, along with the target spirobicycle **437**. Conditions from the pioneering study by Muratake and Natsume[212] employ caesium carbonate as the base and THF or 1,4-dioxane as the solvent. These conditions were more promising (Table 15, Entries 4, 5), and, by switching to toluene as the solvent, **437** was formed in 47% yield and with good selectivity over dehalogenated product **399** (Table 15, Entry 6). A number of different bases were screened (Table 15, Entries 7, 8), but none of them were as effective as caesium carbonate. Finally, an 81% yield of target **437** was obtained by using $PdCl_2(PPh_3)_2$ as the precatalyst with 200mol% Cs_2CO_3 (Table 15, Entry 9 vs Entry 6); under these conditions, minimal amounts of dehalogenated side product **399** were observed. The structure of novel spirobicyle **437** was unambiguously determined by single crystal X-ray diffraction.

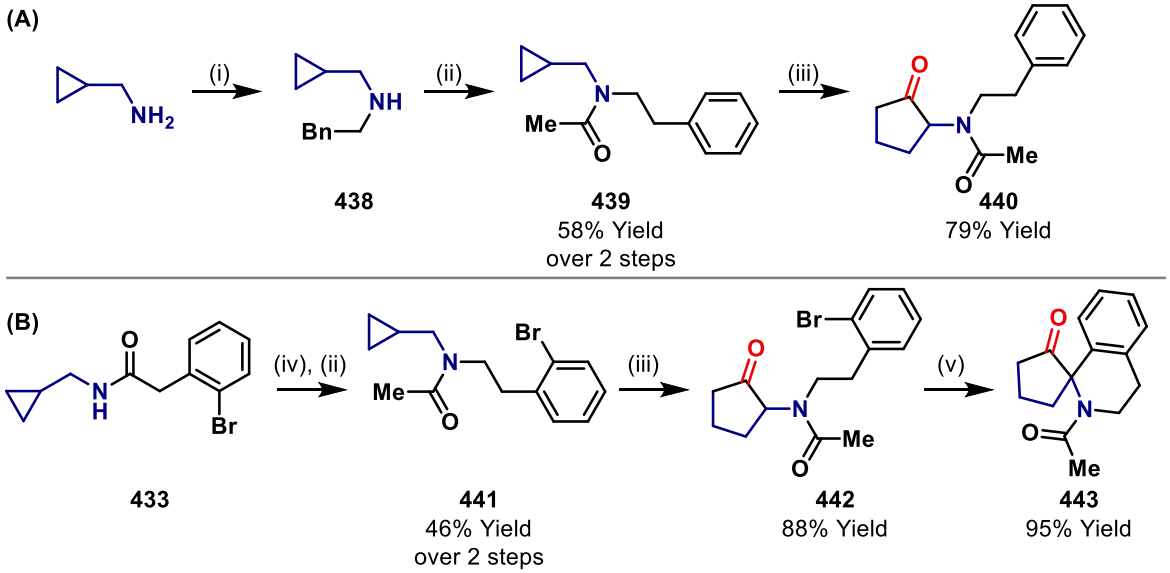


436 **399** **437**

Entry	Catalyst	Base, mol%	Solvent, M	T, °C	437:399	Yield of 437[a], %
1	$Pd_2(dba)_3$/ DavePhos	NaO*t*-Bu, 200	1,4-dioxane:THF 1:1, 0.2	100	1 : 0.00	<5
2	$Pd_2(dba)_3$/ 2 × PPh_3	LiO*t*-Bu, 200	toluene, 0.1	110	1 : 0.20	15
3	$Pd_2(dba)_3$/ 2 × PPh_3	KO*t*-Bu, 200	toluene,0.1	110	1 : 0.33	53
4	$PdCl_2{\cdot}(CH_3CN)_2$/ 2 × PPh_3	Cs_2CO_3, 300	THF, 0.1	100	1 : 0.25	31[b,c]
5	$PdCl_2(PPh_3)_2$	Cs_2CO_3, 300	1,4-dioxane, 0.1	100	1 : 0.31	55
6	$PdCl_2(PPh_3)_2$	Cs_2CO_3, 300	toluene, 0.1	110	1 : 0.17	47[b]
7	$PdCl_2(PPh_3)_2$	LiO*t*-Bu, 200	toluene, 0.1	110	1 : 0.15	25
8	$PdCl_2(PPh_3)_2$	KO*t*-Bu, 200	toluene, 0.1	110	1 : 0.32	78
9	$PdCl_2(PPh_3)_2$	Cs_2CO_3, 200	toluene, 0.1	110	1 : 0.09	81[b]

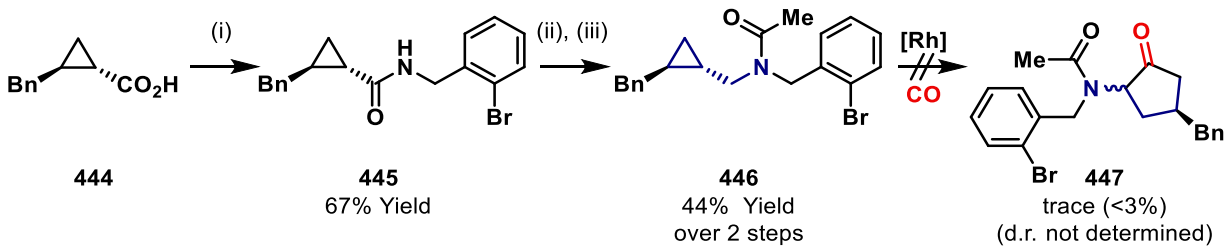
Table 15: Selected conditions for Pd-catalysed intramolecular α-arylation of cyclopentanone **436**. [a]Yields were determined by ^{1}H NMR analysis of the crude reaction mixture against an internal standard (1,4-dinitrobenzene). [b]Isolated yield. [c]10 mol% of $PdCl_2{\cdot}(CH_3CN)_2$ were used.

To test whether larger spirobicycles can be accessed with this methodology, homologated substrate **439** was made (Scheme 106A). The requisite *N*-substituents of **439** were easily installed by a reductive amination-acetylation sequence. Conditions optimised for the carbonylative cyclisation of benzylacetamide **398** were efficient for this system and cyclopentanone **440** was generated in 79% yield. *Ortho*-halogenated cyclopropane **441** was prepared from amide **433** by a sequence of borane reduction and acetylation. When the optimised conditions for the carbonylative rearrangement were applied to **441** desired product **442** was formed in 88% yield (Scheme 106B). Finally, the optimised protocol for Pd-catalysed intramolecular α-arylation delivered acetamide **443**, bearing spiro-fused five and six-membered rings.



Scheme 106: Synthesis of *N*-(cyclopropylmethyl)-*N*-phenethylacetamide **439**, its *ortho*-halogenated derivative **441** and the subsequent carbonylative rearrangement and α-arylation. *Reagents and conditions*: (i) (a) phenylacetaldehyde, MeOH, -78°C, 3 min; (b) $NaBH_4$, -78 to 0 °C, 2 h; (ii) acetic anhydride, TEA, DCM, 0 °C to r.t., 16 h; (iii) 7.5 mol% $[Rh(cod)_2]OTf$, 15 mol% $P(3,4,5\text{-}(F)_3C_6H_2)_3$, 20 mol% $PhCO_2H$, 0.15 M 1,2-DCB, 1 atm CO, 110 °C, 24 h; (iv) (a) BH_3•THF, THF, 0 °C to reflux, 20 h; (b) 2.0 M aq. HCl, 85 °C, 1 h; (v) 6 mol% $PdCl_2(PPh_3)_2$, 200 mol% Cs_2CO_3, toluene, 110 °C, 18 h.

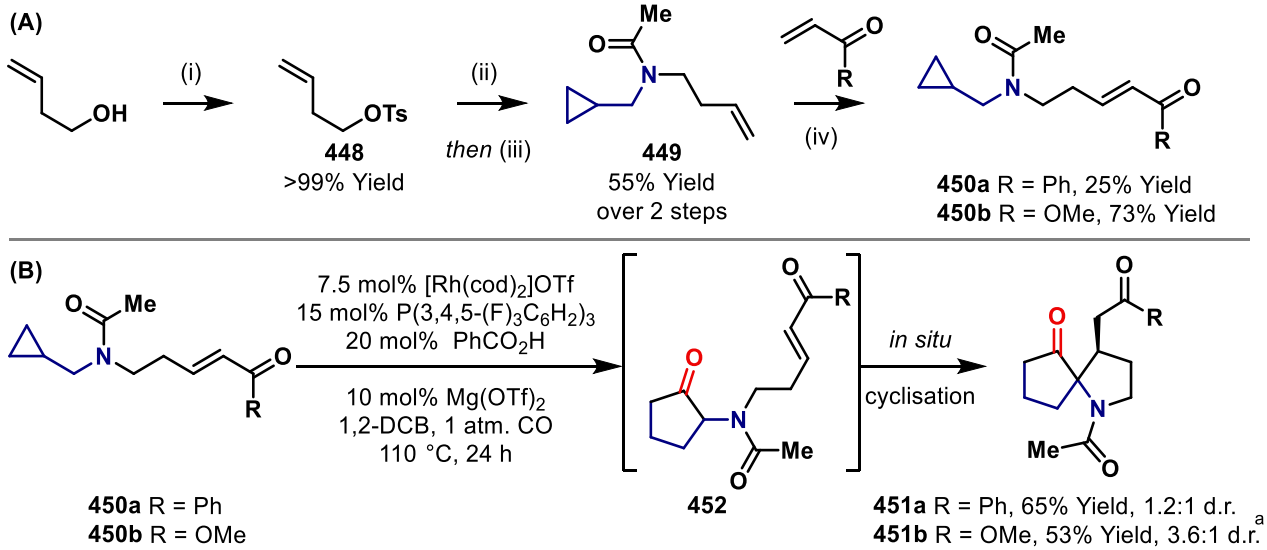
To test whether a more elaborate sp^3-rich spirobicyclic system could be accessed via the same synthetic pathway, benzyl-substituted cyclopropane **446** was synthesised. Acid **444** was converted to the corresponding acid chloride and this was reacted with 2-bromobenzylamine to produce amide **445**. Subsequent reduction and acylation gave *trans*-1,2-disubstituted aminomethylcyclopropane **446** in an overall yield of 30% (Scheme 107). Under the best conditions found for **413** to **417b** (see Table 14), **446** provided only trace amounts of target **447**. The low yield could be due to competitive oxidative insertion into the C-Br bond, which would lead to catalyst deactivation. A variety of harsher reaction conditions were evaluated (e.g. heating to 180 °C, running the reaction at 1.0 M concentration or using 15 mol% $[Rh(cod)_2]BARF$), but they did not facilitate the carbonylative rearrangement of **447**. This result indicates that the relative facility of C-C versus C-Br bond activation is finely balanced.



Scheme 107: Synthesis and reactivity of *trans*-1,2-disubstituted methylcyclopropane **446**. *Reagents and conditions:* (i) oxalyl chloride, DCM, r.t., then 2-bromobenzylamine hydrochloride, TEA, DCM, 0 °C to r.t., 16 h; (ii) (a) benzaldehyde, $NaHCO_3$, MeOH, reflux, 3 h; (b) $NaBH_4$, 0 °C to r.t., 4 h; (iii) acetic anhydride, TEA, DCM, 0 °C to r.t., 16 h. *Rh-catalysed conditions*: 7.5 mol% $[Rh(cod)_2]OTf$ *or* $[Rh(cod)_2]BARF$, 15 mol% $P(3,4,5\text{-}(F)_3C_6H_2)_3$, 20 mol% $PhCO_2H$, 0.15 M 1,2-DCB, 1 atm CO, 110-160 °C, 24-72 h.

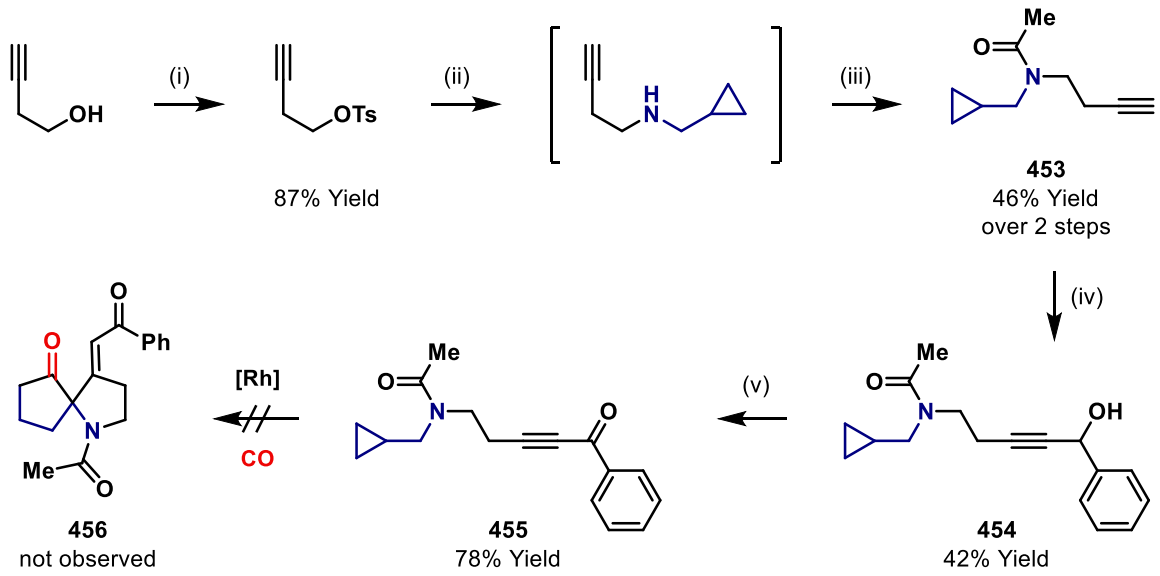
5.2.5 Evaluation of other enolate-based spirocyclisation processes.

The possibility of employing the cyclopentanone ketone product as a nucleophile in other spirocyclisations was investigated next. Specifically, a carbonylative rearrangement-conjugate addition cascade was envisaged using **450a** or **450b**. The synthesis of these substrates commenced with the known two-step alkylation-protection procedure (Scheme 108A).[48] Alkylation of aminomethylcyclopropane with tosylate **448** delivered secondary amine, which was protected with acetic anhydride to afford **449** in 55% yield. Amide **449** was converted to **450a** or **450b** by alkene metathesis between **449** and the corresponding enone or acrylate. **450a** was exposed to carbonylative cyclisation conditions (Scheme 108B); pleasingly, at 130 °C 5-*exo*-*trig* ring closure of in situ generated cyclopentanone **452** occurred directly to provide spirobicycle **451a** in 41% yield and as an approximately 1:1 mixture of diastereomers. A Lewis acid additive screen ($Zn(OTf)_2$, $La(OTf)_3$, $Eu(OTf)_3$, $Mg(OTf)_2$, MoO_3, $ZnCl_2$) was undertaken in the hope of promoting diastereoselective conjugate addition *via* coordination to both oxygens of intermediate **452**, but improvements in d.r. were not forthcoming. However, the yield of **451a** was improved to 65% when the reaction temperature was lowered from 130 °C to 110 °C and 10 mol% $Mg(OTf)_2$ was used as an additive. When methyl acrylate **450b** was examined under these conditions, compound **451b** was isolated in 30% yield and in a 2:1 diastereomeric ratio. This initial result was irreproducible, with diminished yields and large amounts of intermediate **452** often observed in the crude reaction mixture on repeated runs. The variances in the yield were attributed to trace amounts of base present in the reaction tube. Subsequently, the crude reaction mixture was treated with an excess of K_2CO_3 at room temperature prior to the purification by silica gel column chromatography. This gave **451b** in a reproducible 53% yield and 3.6:1 d.r.



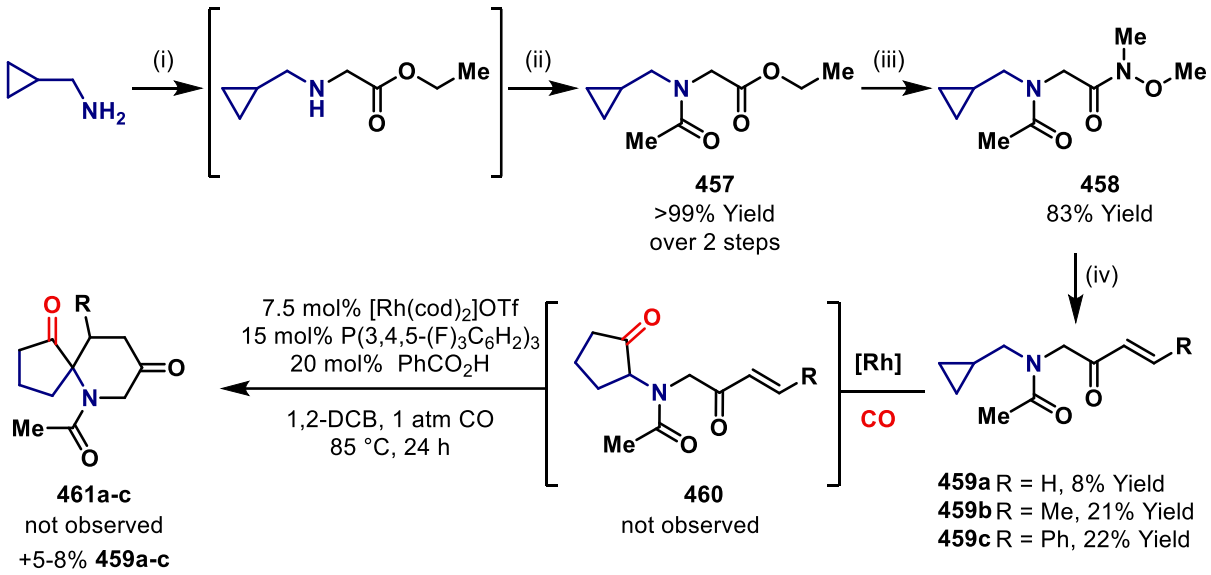
Scheme 108: (A) Synthesis of **451a,b**. *Reagents and conditions*: (i) TsCl, Et_3N, DCM, r.t., 18 h; (ii) aminomethylcyclopropane, MeCN, reflux, 18 h; (iii) acetic anhydride, TEA, DCM, 0 °C to r.t., 16 h; (iv) DCM, Hoveyda-Grubbs Catalyst 2nd Gen., r.t., 18 h. (B) Carbonylative rearrangement-conjugate addition cascade of **451a,b**. [a] 2 equiv. of K_2CO_3 were used.

Ynone **455** was proposed as a more reactive conjugate acceptor compared to **450a,b**. Amide **453** was synthesised in 46% yield by the two-step alkylation-protection procedure. Deprotonation of the alkyne **453** with *n*-BuLi and addition of the resulting Li-acetylide to benzaldehyde provided alcohol **454**. This was subjected to PDC oxidation to furnish ynone **455** in 78% yield (Scheme 109). Unfortunately, carbonylative rearrangement of **455** under standard catalytic conditions and at elevated temperatures was unsuccessful. In most cases, degradation of starting material was observed and the formation of **456** did not occur. It is possible that strong coordination of Rh to the alkyne unit inhibits the desired amide-directed C-C bond activation pathway.



Scheme 109: Synthesis and attempted Rh-catalysed ring expansion of ynone **455**. *Reagents and conditions*: (i) TsCl, Et_3N, DCM, r.t., 18 h; (ii) methyaminocyclopropane, MeCN, reflux, 18 h; (iii) acetic anhydride, TEA, DCM, 0 °C to r.t., 16 h; (iv) (a) *n*-BuLi, THF, 0 °C, 30 min; (b) benzaldehyde, 0 °C to r.t., 2 h; (v) pyridinium dichromate, DCM, r.t., 2 h.

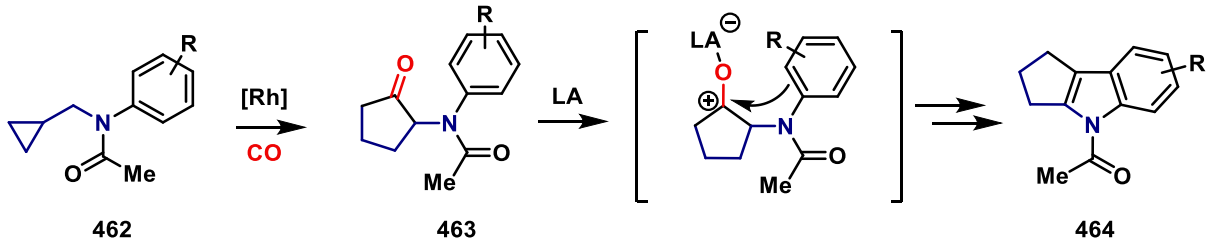
Analogous 6-*endo-trig* ring closures of enones **459a-c** were investigated next (Scheme 110). Ethyl ester **457** was synthesised by the two-step alkylation-protection procedure and then transformed into a Weinreb amide **458**. This was treated with the appropriate Grignard reagent to provide enones **459a-c** in low yields. These were exposed to conditions optimised for **450a,b** to **451a,b** (see Scheme 108), but, unfortunately, neither bicycle **461a-c** or cyclopentanone **450** were observed. Only trace amounts of starting material were present in the crude reaction mixtures of the carbonylative reaction after 24 h when heated to 85 °C, which may indicate that enones **459a-c** are unstable under the reaction conditions.



Scheme 110: Synthesis and attempted carbonylative rearrangement-conjugate addition cascade of **459a-c**. *Reagents and conditions*: (i) ethyl bromoacetate, MeCN, 0 °C to r.t., 1 h; (ii) acetic anhydride, TEA, DCM, 0 °C to r.t., 16 h; (iii) Me_2AlCl, MeNHOMe·HCl, 16 h; (iv) Grignard reagent, THF, -78 °C, 2.5 h.

5.2.6 One-pot synthesis of indoles and dihydroisoquinolines

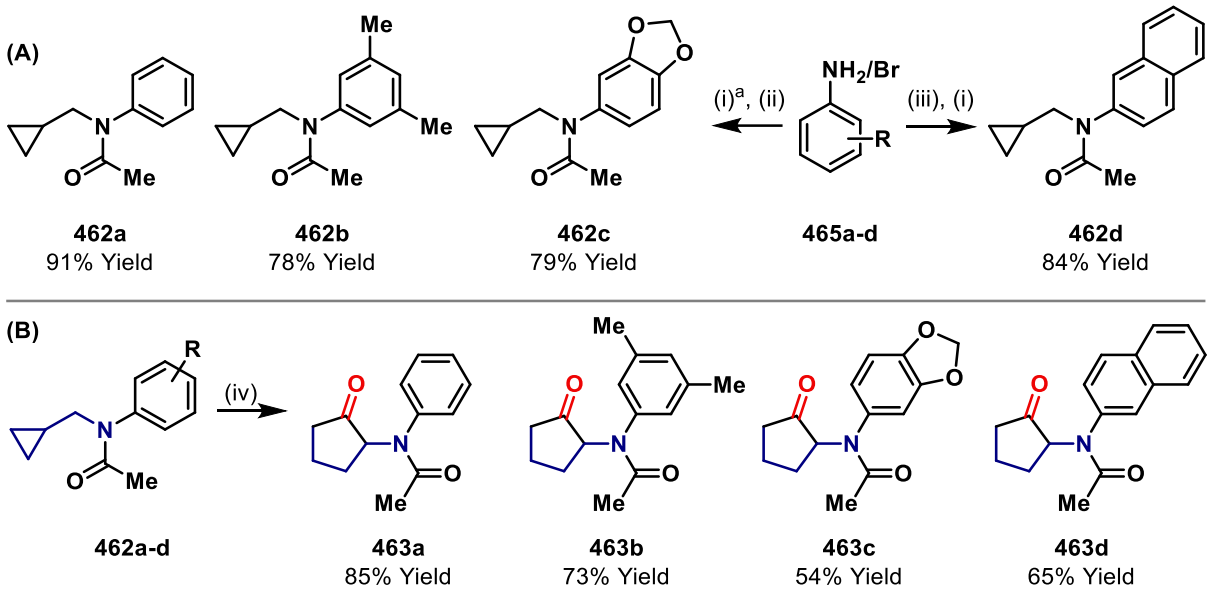
The studies outlined above demonstrated that the amide-directed carbonylative rearrangement process can be used with a wide variety of substrates, including systems that allow subsequent α-functionalisation of the ketone product. In this section, subsequent transformations involving direct reaction at the carbonyl unit of the product cyclopentanone are explored. The development of a carbonylative rearrangement of *N*-aryl aminomethylcyclopropanes **462** into cyclopentanones **463** could, in principle, enable a subsequent Lewis acid-catalysed pathway to novel indole scaffolds **464** (Scheme 111).



Scheme 111: Proposed transformation of derivatised *N*-aryl α-aminocyclopentanones **463** to *N*-acetylindoles **464**.

To investigate the proposal in Scheme 111, N-phenylated system **462a** and more electron-rich analogues **462b-d** were synthesised. This was achieved either by alkylation of the respective acetanilides with cyclopropylmethyl bromide (**462a-c**) or by Buchwald–Hartwig amination and subsequent acetylation (**462d**) (Scheme 112A).

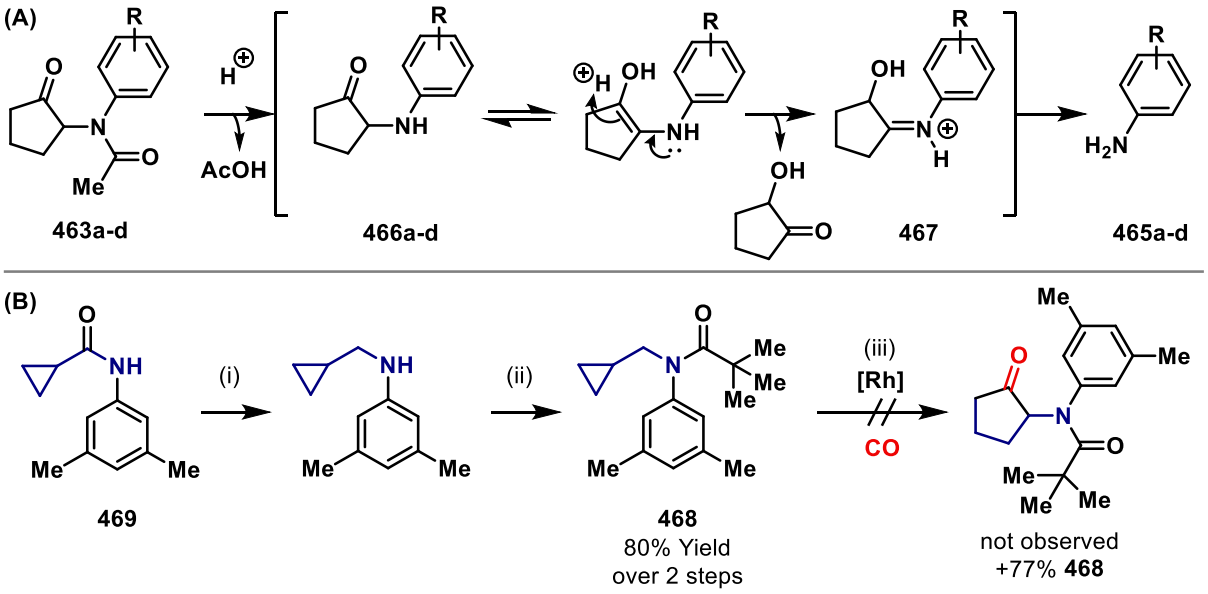
Aminomethylcyclopropanes **462a-d** were exposed to the standard catalytic conditions to assess the scope of the reaction with respect to the aryl component. Pleasingly, all systems were tolerated and cyclopentanones **463a-d** were isolated in good yields (Scheme 112B). The resulting cyclopentanones **463a-d** were exposed to a variety of Brønsted and Lewis acids to promote the envisaged intramolecular cyclisation. Conditions included refluxing in TFA for 3 days, heating to 130 °C in neat polyphosphoric acid, heating in 1,2-dichlorobenzene with $AlCl_3$ or $FeCl_3$, heating in dimethoxyethane with $MgCl_2$, $ZnCl_2$, or $BF_3{\cdot}Et_2O$. The target material **464**, bearing an indole scaffold, was not observed under these reaction conditions and starting material (or a complex mixture in the case of polyphosphoric acid) was recovered.



Scheme 112: (A) Synthesis and (B) carbonylative rearrangements of arylacetamides **463a-d**. *Reagents and conditions*: (i) corresponding substituted aniline and Ac_2O or AcCl, [a] prepared according to the literature procedures; (ii) (a) NaH, THF, 0 °C to r.t., 1 h; (b) cyclopropylmethyl bromide, r.t. to 50 °C, 18 h; (iii) 2-bromonaphthalene, aminomethylcyclopropane, sodium *tert*-amoxide, $Pd_2(dba)_3$, BrettPhos, toluene, 80 °C, 16 h; (iv) 7.5 mol% $[Rh(cod)_2]OTf$, 15 mol% $P(3,4,5\text{-}(F)_3C_6H_2)_3$, 20 mol% $PhCO_2H$, 0.15 M 1,2-DCB, 1 atm CO, 110 °C, 18 h.

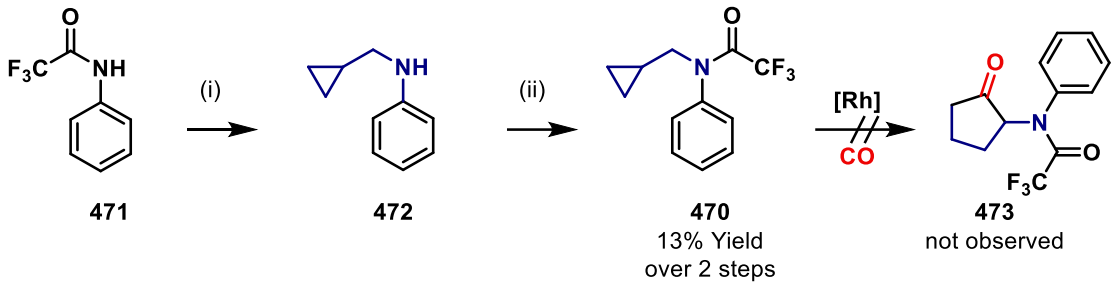
To promote the cyclisation, attempts were made to remove the acetyl group of acetanilides **463a-d** and give the more electron rich NH anilines **466a-d**. Under forcing basic conditions (40 eq. NaOH, water:1,4-dioxane:MeOH 1:1:1, 135 °C, 72 h) starting material decomposed, whereas acidic conditions (conc. HCl:EtOH 1:1, 120 °C, 72 h) yielded the corresponding unsubstituted anilines **465a-d**, where the cyclopentanone unit has been lost (Scheme 113A). A possible mechanistic pathway involves acid-catalysed deacetylation to give the desired amine **466a-d**. At this stage, iminium ion formation (**467**) and hydrolysis leads to the corresponding aniline and an α-hydroxy ketone, which is unstable in the presence of a strong acid.

Next, to evaluate alternative amine protecting groups, pivalamide **468** was prepared in 80% yield from amide **469** by the reduction-protection strategy (Scheme 113B). Unfortunately, under the carbonylative conditions from Scheme 112, only starting material **468** was observed in the ^{1}H NMR spectrum of the crude reaction mixture. Overall, the results in Scheme 113 suggested that a protecting group that is more labile that *N*-acetyl but less bulky than *N*-pivaloyl would be beneficial.



Scheme 113: (A) Studies evaluating the deacetylation of **463a-d**. Proposed mechanism for the formation of anilines. (B) Synthesis and reactivity of pivalamide **468**. *Reagents and conditions*: (i) $LiAlH_4$, THF, 0 °C to reflux, 16 h; (ii) pivaloyl chloride, TEA, DCM, 0 °C to r.t., 16 h; (iii) 7.5 mol% $[Rh(cod)_2]OTf$, 15 mol% $P(3,4,5\text{-}(F)_3C_6H_2)_3$, 20 mol% $PhCO_2H$, 0.15 M 1,2-DCB, 1 atm CO, 110 °C, 18 h.

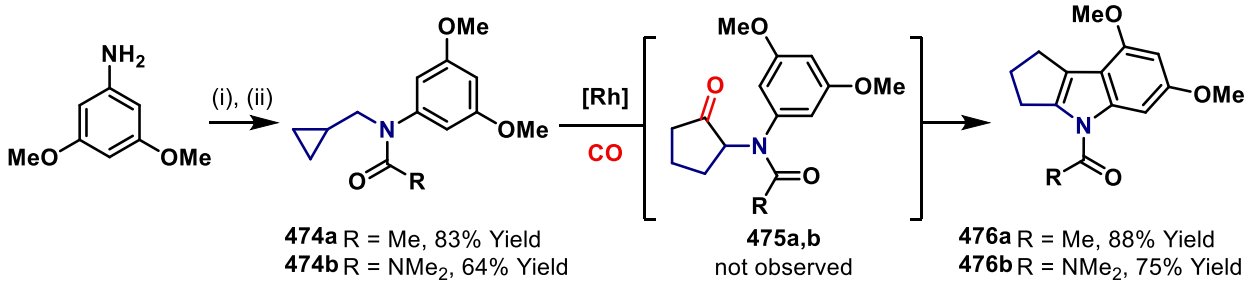
To address this, trifluoroacetamide **470** was targeted (Scheme 114). Alkylation of trifluoroacetyl-protected anilide **471** with cyclopropylmethyl bromide provided secondary aniline **472**, where the trifluoroacetyl group has been removed. This was reinstalled by treatment with trifluoroacetic anhydride. Trifluoroacetamide **470** was subjected to the standard catalytic conditions, but the desired cyclopentanone **473** was not formed, and only starting material was observed. This result indicates that the *N*-trifluoroacetyl directing group is not sufficiently Lewis basic to promote the carbonylative transformation.



Scheme 114: Synthesis and evaluation of trifluoroacetamide **470**. *Reagents and conditions*: (iii) (a) NaH, THF, 0 °C to r.t., 1 h; (b) cyclopropylmethyl bromide, r.t. to 50 °C, 18 h; (iv) trifluoroacetic anhydride, TEA, DCM, 0 °C to r.t., 16 h. *Catalytic conditions:* 7.5 mol% $[Rh(cod)_2]OTf$, 15 mol% $P(3,4,5\text{-}(F)_3C_6H_2)_3$, 20 mol% $PhCO_2H$, 0.15 M 1,2-DCB, 1 atm CO, 85°C or 110 °C, 18 h

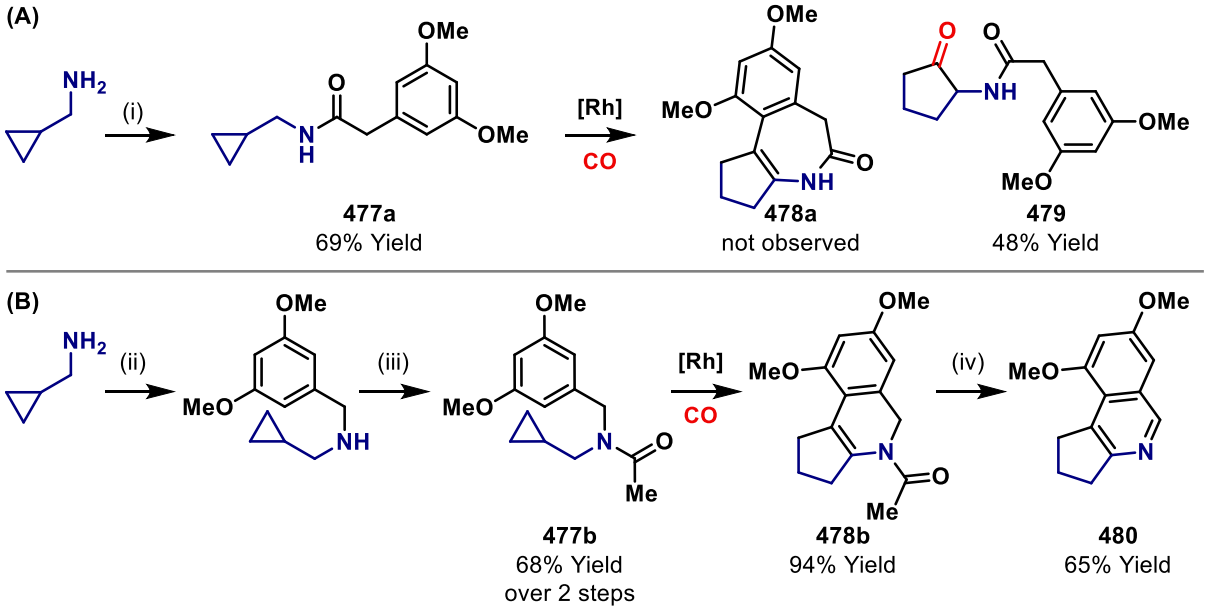
A literature search of condensation reactions related to the idea proposed in Scheme 111 revealed that 3,5-dimethoxy-substituted anilides might be suitable.[220,221] To enable the investigation of this electron-rich system, cyclopropane **474a** was synthesised by alkylation with cyclopropylmethyl bromide in a manner analogous to acetanilides **462a-c** (Scheme 115). To assess the possible benefits of a stronger *N*-directing group in the Rh-catalysed carbonylative rearrangement, cyclopropane **474b**, bearing a dimethylurea directing group, was also synthesised.

Cyclopropanes **474a,b** were exposed to the optimised cationic catalytic conditions and, pleasingly, carbonylative rearrangement and one-pot condensation delivered the desired indoles **476a,b** in excellent yield (Scheme 115). This result demonstrates that acid activation is not required for intramolecular condensations involving 3,5-dimethoxy-substituted systems. Interestingly, cyclopentanones **475a,b** were not observed in the ^1H NMR spectrum of the crude reaction mixture, indicating that cyclocondensation occurs spontaneously.



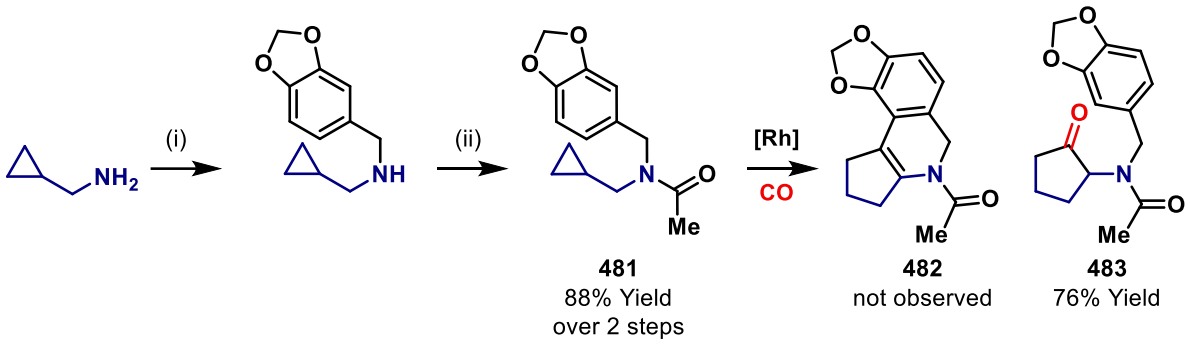
Scheme 115: Synthesis of cyclopropanes **474a,b** and a one-pot indole synthesis. *Reagents and conditions*: (i) acetic anhydride or dimethylcarbamyl chloride; (ii) (a) NaH, THF, 0 °C to r.t., 1 h; (b) cyclopropylmethyl bromide, r.t. to 50 °C, 18 h; *Catalysis conditions*: 7.5 mol% $[Rh(cod)_2]OTf$, 15 mol% $P(3,4,5\text{-}F_3C_6H_2)_3$, 20 mol% $PhCO_2H$, 0.15M 1,2-DCB, 1 atm CO, 110 °C, 18 h.

With an optimised system in hand, further studies focused on evaluating the scope of the reaction. To do this, homologated amide **477a** was prepared from the corresponding acid chloride, whereas aminomethylcyclopropane **477b** was prepared by reductive amination and subsequent acetylation (Scheme 116). Substrate **477a** failed to provide the desired heterocycle **478a** under the carbonylative C-C bond activation conditions and instead cyclopentanone **479** was isolated in 48% yield. When acetamide **477b** was used, the desired 1,2-dihydroisoquinoline **478b** was delivered in 94% yield. Subsequent acid-promoted deacetylation of substrate **478b** provided isoquinoline **480** after spontaneous aerobic oxidation. **480** is a pharmacologically significant heterocyclic scaffold, as isoquinoline-based drugs find many applications, including as anaesthetics and vasodilators.[222]



Scheme 116: Synthesis and evaluation of systems containing a 3,5-dimethoxyphenyl unit. *Reagents and conditions*: (i) 2-(3,5-dimethoxyphenyl)acetyl chloride, TEA, DCM, 0 °C to r.t., 16 h; (ii) (a) 3,5-dimethoxybenzaldehyde, $NaHCO_3$, MeOH, reflux, 3 h; (b) $NaBH_4$, 0 °C to r.t., 4 h; (iii) acetic anhydride, TEA, DCM, 0 °C to r.t., 16 h; (iv) 1,4-dioxane:H_2O:conc.HCl 1:1:1, reflux, 2 h; *Catalysis conditions*: 7.5 mol% $[Rh(cod)_2]OTf$, 15 mol% $P(3,4,5\text{-}(F)_3C_6H_2)_3$, 20 mol% $PhCO_2H$, 0.15M 1,2-DCB, 1 atm CO, 110 °C, 18 h.

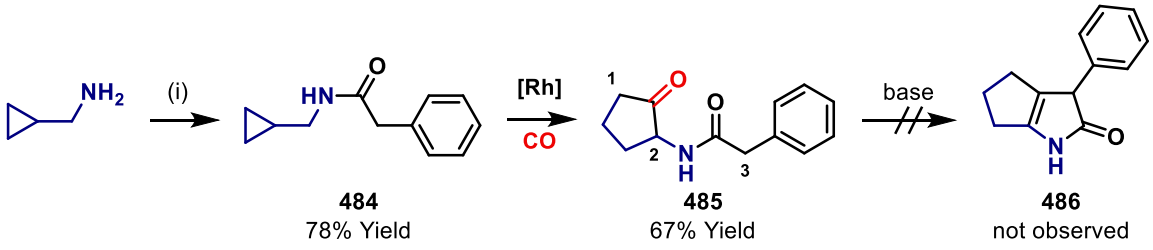
The success of the process in Scheme 116B is finely balanced, and is critically dependent on the substitution pattern of the arene. When 3,4-methylenedioxy-substituted substrate **481** was employed, target dihydroisoquinoline **482** was not observed and cyclopentanone **483** was isolated in 76% yield (Scheme 117). In an effort to promote cyclocondensation, **483** was heated at reflux in TFA for 3 days, but this did not lead to the formation of the desired heterocycle.



Scheme 117: Synthesis and carbonylative rearrangement of a system containing a 3,4-methylenedioxyphenyl unit. *Reagents and conditions*: (i) (a) piperonal, $NaHCO_3$, MeOH, reflux, 3 h; (b) $NaBH_4$, 0 °C to r.t., 4 h; (ii) acetic anhydride, TEA, DCM, 0 °C to r.t., 16 h; *Catalysis conditions*: 7.5 mol% $[Rh(cod)_2]OTf$, 15 mol% $P(3,4,5\text{-}(F)_3C_6H_2)_3$, 20 mol% $PhCO_2H$, 0.15M 1,2-DCB, 1 atm CO, 110 °C, 18 h.

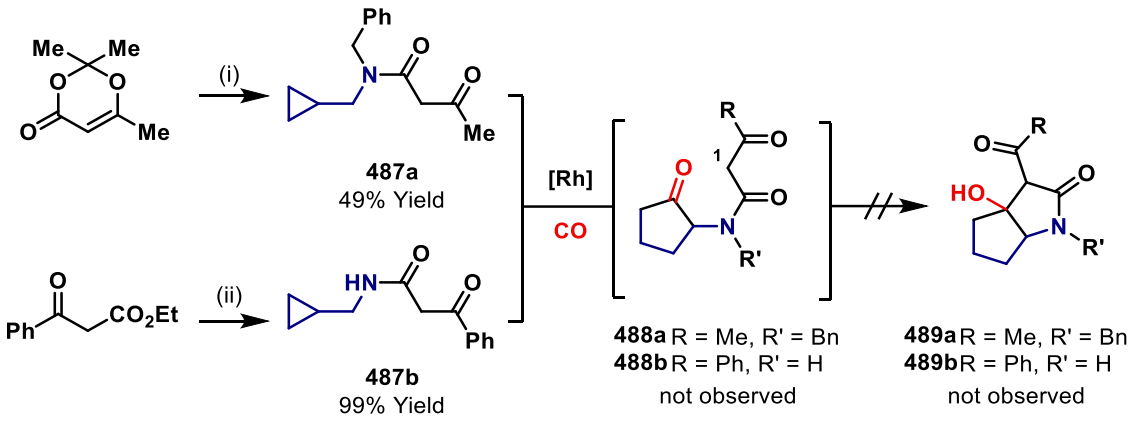
5.2.7 Evaluation of substrates for cascade cyclisations

In addition to the systems described in Section 5.2.6, alternative substrates were examined where the carbonyl group of the resulting cyclopentanone can act as an electrophile and induce further cyclisations. Amide **484** was prepared from aminomethylcyclopropane and phenylacetyl chloride, which was then exposed to the optimised conditions for the Rh-catalysed carbonylative rearrangement to provide cyclopentanone **485** in 67% yield (Scheme 118). Upon treatment with base (NaOH or KO*t*-Bu), no formation of the desired pyrrol-2-one **486** was observed. More forcing conditions to deprotonate C3 (e.g. LiHMDS)[223] were not screened due to the presence of competitive sites for deprotonation at C1 and C2 of cyclopentanone **485**.



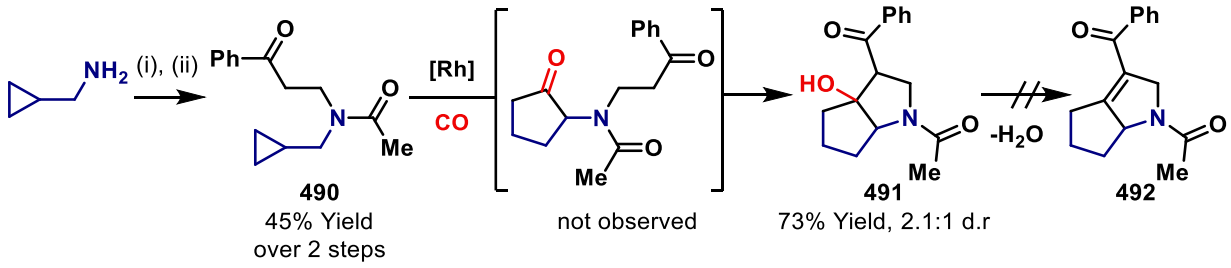
Scheme 118: Synthesis and carbonylative rearrangement of amide **484**. *Reagents and conditions*: (i) phenylacetyl chloride, TEA, DCM, 0 °C to r.t., 16 h; *Catalysis conditions*: 7.5 mol% $[Rh(cod)_2]OTf$, 15 mol% $P(3,4,5\text{-}F_3C_6H_2)_3$, 20 mol% $PhCO_2H$, 0.15M 1,2-DCB, 1 atm CO, 110 °C, 18 h.

Cyclopropanes **487a,b** bearing β-ketoamide directing groups were also investigated (Scheme 119). Carbonylative rearrangements of **487a,b** under standard catalytic conditions and at elevated temperatures were unsuccessful, presumably due to strong coordination of the Rh(I)-catalyst to the acac-like 1,3-diketone moiety. No traces of cyclopentanone **488a,b** or fused bicycle **489a,b** were observed by ^1H NMR analysis of the crude reaction mixtures.



Scheme 119: Synthesis and attempted carbonylative rearrangement of β-ketoamides **487a,b**. *Reagents and conditions*: (i) *N*-benzyl-1-cyclopropylmethylamine, toluene, reflux, 4 h; (ii) aminomethylcyclopropane, pyridine, xylenes, 120 °C, 2.5 h; *Catalysis conditions*: 7.5 mol% $[Rh(cod)_2]OTf$, 15 mol% $P(3,4,5\text{-}F_3C_6H_2)_3$, 20 mol% $PhCO_2H$, 0.15M 1,2-DCB, 1 atm CO, 110 -160 °C, 18 h.

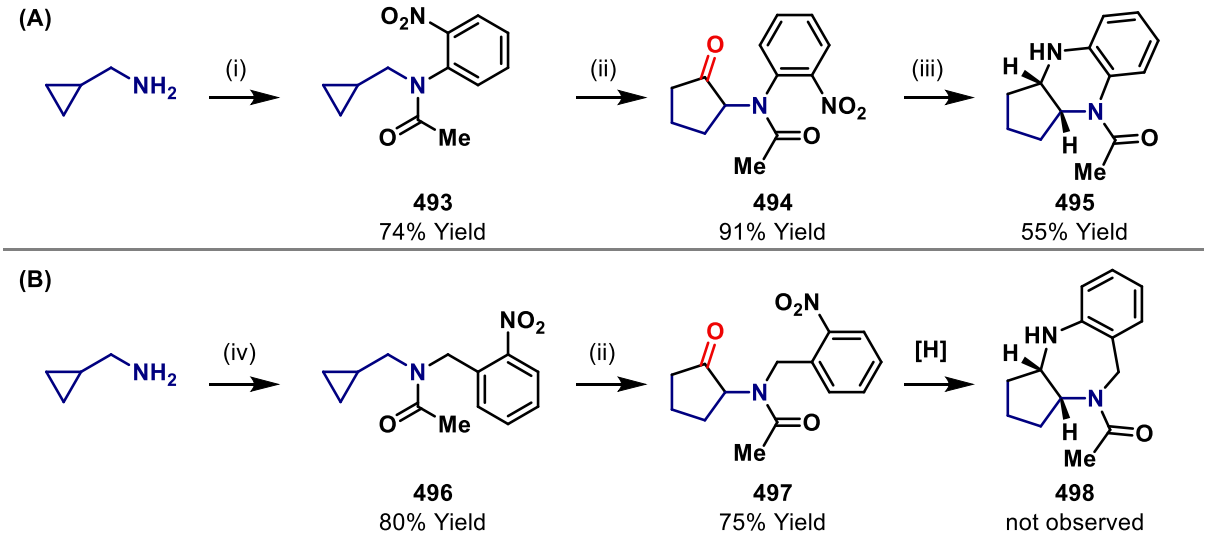
It was envisaged that 1,2-addition of the C1 enolate of **488** to the ketone may be reversible. To circumvent this, less stabilised enolates were also explored. Acetamide **490** was readily prepared in two steps, and exposure of this to carbonylative rearrangement conditions resulted in spontaneous nucleophilic addition to the ketone to give fused bicyclic structure **491** in 73% yield and as a 2:1 mixture of diastereoisomers (Scheme 120). Attempts to promote dehydration of β-hydroxyketone **491** by screening over 10 sets of conditions (e.g. TFAA/DBU, Burgess reagent,[224] $POCl_3$/pyridine, conc. H_2SO_4, MsCl/Et_3N, MsCl/DMAP/H_2O[225]) were unsuccessful; this result is surprising but can be rationalised by the unfavourable increase in strain of the resulting unsaturated product **492**.



Scheme 120: Synthesis and carbonylative rearrangement of acetamide **490**. *Reagents and conditions*: (i) 3-chloropropiophenone, TEA, DCM, 0 °C to r.t., 6 h; (ii) acetic anhydride, TEA, DCM, 0 °C to r.t., 16 h; *Catalysis conditions*: 7.5 mol% $[Rh(cod)_2]OTf$, 15 mol% $P(3,4,5\text{-}F_3C_6H_2)_3$, 20 mol% $PhCO_2H$, 0.15M 1,2-DCB, 1 atm CO, 110 °C, 18 h.

Finally, substrates equipped with latent nucleophilic functionality were evaluated, as outlined in Scheme 121. Aromatic nucleophilic substitution of 1-fluoro-2-nitrobenzene with aminomethylcyclopropane, followed by acylation of the resulting amine gave **493** in 74% yield. Acetamide **493** underwent carbonylative rearrangement to give cyclopentanone **494**. Upon

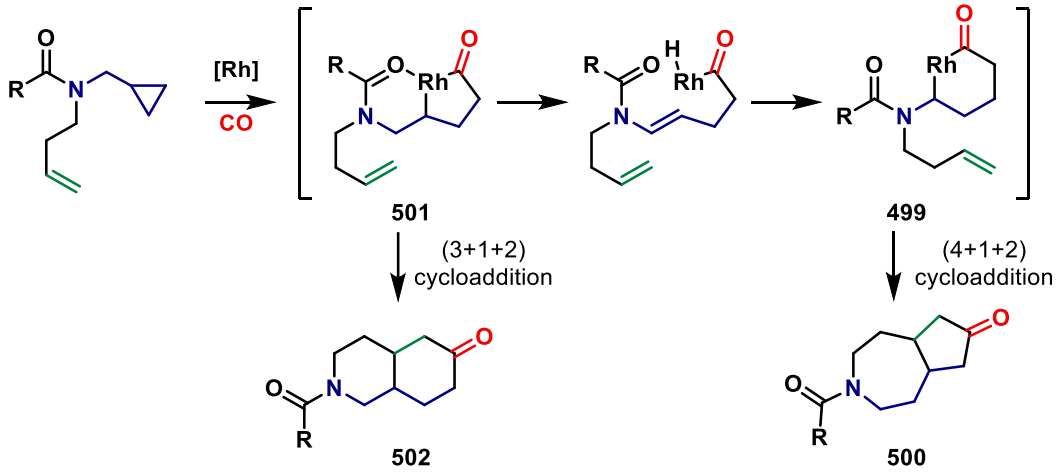
reduction of the nitro group of **494**, cyclisation of the intermediate aniline onto the cyclopentanone and subsequent imine hydrogenation occurred, affording **495** as a single diastereomer in 55% yield. This result encouraged the synthesis of acetamide **496**, which was formed in 80% yield via a reductive amination-acylation sequence. C-C bond activation-triggered rearrangement provided **497** in 75% yield, but its conversion to 7-membered target **498** was not observed under a range of reductive conditions (Pd/C, H_2; Fe/AcOH; $SnCl_2$). This result shows that the formation of larger fused ring systems is more challenging and that, in such cases, alternative decomposition pathways predominate. The corresponding uncyclised aniline was not observed, although conversion of starting material **497** to a complex mixture of products occurred under several of the evaluated conditions.



Scheme 121: Synthesis, carbonylative rearrangement and reductive cyclisation of cyclopropanes **493** and **496**. *Reagents and conditions*: (i) (a) 1-fluoro-2-nitrobenzene, K_2CO_3, DMF, r.t., 4 h; (b) Ac_2O, conc. H_2SO_4, 50 to 80 °C, 3 h, then MeOH, 0 °C, 2 h; (ii) 7.5 mol% $[Rh(cod)_2]OTf$, 15 mol% $P(3,4,5\text{-}(F)_3C_6H_2)_3$, 20 mol% $PhCO_2H$, 0.15 M 1,2-DCB, 1 atm CO, 110 °C, 24 h; (iii) Pd/C, 1 atm H_2, MeOH, r.t., 8 h; (iv) (a) 2-nitrobenzaldehyde, MeOH, reflux, 3 h; (b) $NaBH_4$, 0 °C to r.t., 4 h; (c) acetic anhydride, TEA, DCM, 0 °C to r.t., 16 h.

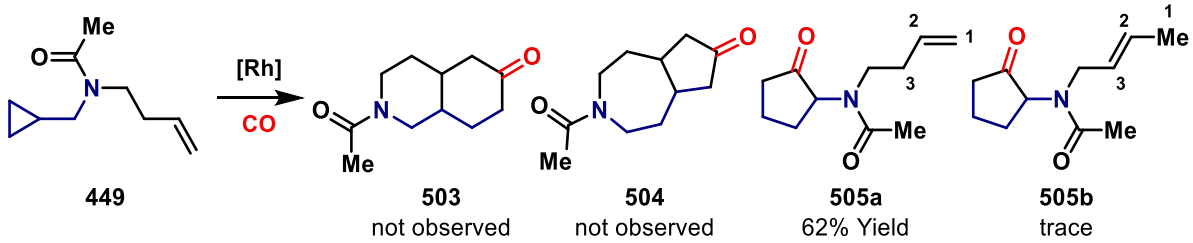
5.3 Synthesis and reactivity of aminomethylcyclopropanes with tethered alkenes

Previous research at Bristol demonstrated that rhodacyclopentanones, formed under carbonylative conditions, can be trapped by tethered π-unsaturates to provide a multitude of (3+1+2) cycloaddition products (see Chapter 1, Schemes 5,7 and Chapter 4). It was envisaged that it might be feasible to integrate the carbonylative rearrangement process into multicomponent cycloadditions of this type, thereby delivering analogous stereochemically complex *N*-heterobicyclic scaffolds (Scheme 122). Here, trapping of rhodacyclohexanone **499** with tethered π-unsaturates (e.g. alkene or alkyne) would lead to fused bicyclic systems **500** via a formal (4+1+2) cycloaddition. An alternative (3+1+2) pathway would involve direct trapping of rhodacyclopentanone **501** to provide saturated isoquinolinone-type structures **502**.



Scheme 122: Proposed cycloadditions between aminomethylcyclopropanes, CO and tethered alkene.

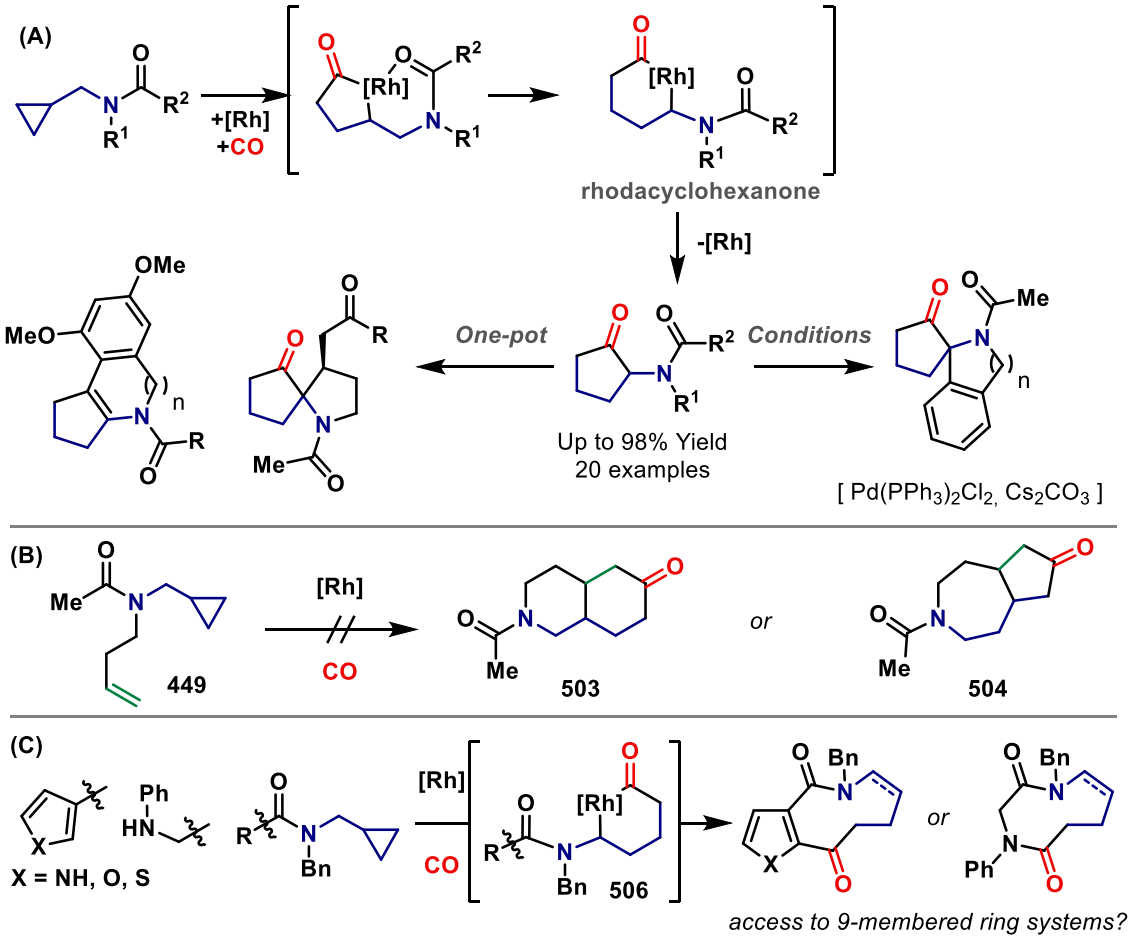
To investigate the proposed multicomponent cycloaddition, amide **449** (see Scheme 108A) was subjected to the standard Rh-catalysed carbonylative conditions. Cycloaddition products **503** and **504** did not form and only cyclopentanone **505** was isolated in 62% yield (Scheme 123). Along with the main C1-C2 unsaturated product **505a**, traces of C2-C3 unsaturated system **505b** were also observed; this presumably arises from isomerisation of the alkene under the reaction conditions. This result shows that rearrangement of the rhodacyclopentanone into rhodacyclohexanone occurs, but reductive elimination is preferred over coordination and insertion of the alkene.



Scheme 123: Carbonylative rearrangement of **449**. *Catalysis conditions*: 7.5 mol% $[Rh(cod)_2]OTf$, 15 mol% $P(3,4,5\text{-}F_3C_6H_2)_3$, 20 mol% $PhCO_2H$, 0.15M 1,2-DCB, 1 atm CO, 110 °C, 18 h.

5.4 Conclusions

Directing group optimisation and second-generation conditions have been developed for the C-C bond activation triggered hydroacylation of aminomethylcyclopropanes. This process provides an unusual and direct entry to α-amino cyclopentanones. The scope of the protocol was investigated with a range of substituted aminocyclopropanes. The Rh-catalysed carbonylative rearrangement can be followed by intramolecular Pd-catalysed α-arylation to create spiro compounds (Scheme 124A). Furthermore, one-pot indole and dihydroisoquinoline syntheses were discovered. Other cascade processes, leading to (a) spiro compounds and (b) tricyclic products have also been investigated. Attempts to adapt previously developed (3+1+2) cycloadditions to aminomethylcyclopropane system **449** were unsuccessful and cycloadducts **503** or **504** were not be obtained (Scheme 124B). Further studies could focus on trapping intermediates of type **506** with other reactive units that have been shown to engage rhodacyclopentanones. For example, the possibility of accessing 9-membered ring systems could be explored by using systems containing heterocycles or anilines as a nucleophile (Scheme 124C).[55]



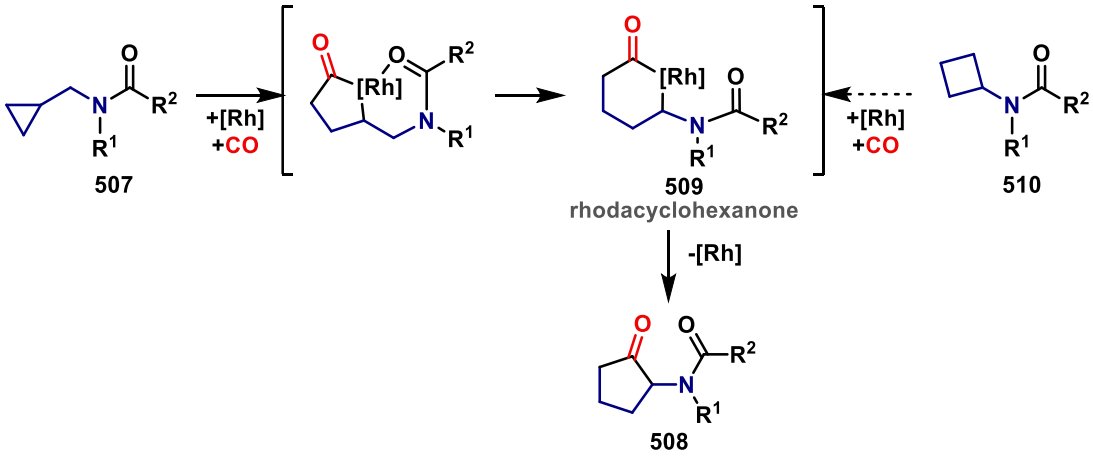
Scheme 124: Summary and proposed further studies on the carbonylative rearrangement of aminomethylcyclopropanes.

CHAPTER 6

Studies towards the C-C bond activation of cyclobutanes

6.1 Introduction

The studies in Chapter 5 outline the carbonylative rearrangement of aminomethylcyclopropanes **507** to cyclopentanones **508** via rhodacyclohexanone intermediate **509**. In theory, C-C bond activation of cyclobutane **510** could lead to the formation of the same rhodacyclic intermediate (Scheme 125). However, there is no precedent for forming rhodacyclohexanone **509** intermediates via the C-C bond activation of cyclobutanes.



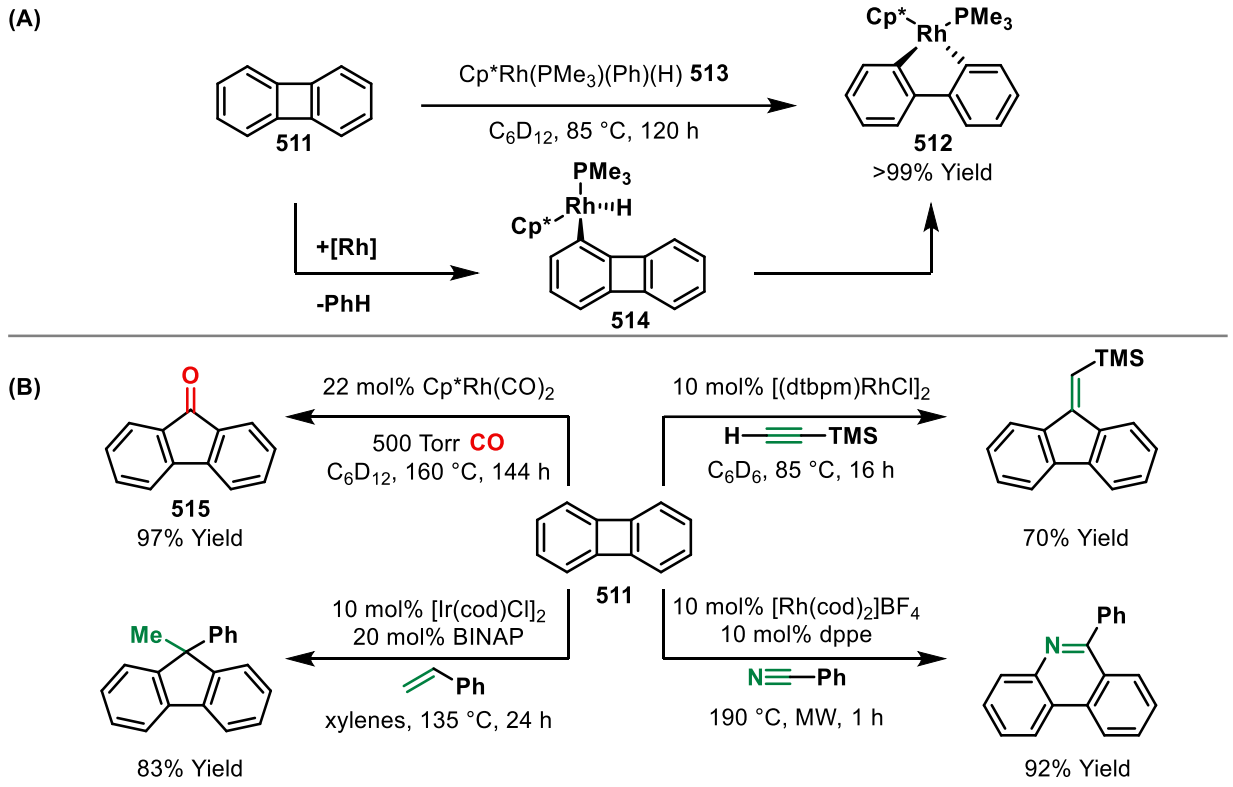
Scheme 125: Proposed formation of rhodacyclohexanones from cyclobutane **510**.

Compared to three-membered rings, there are far fewer examples of catalytic ring expansions for four-membered rings. The primary reason for this difference may simply be that there are not many reliable methods to synthesize four-membered rings, whereas there are numerous ways to access three-membered rings. Cyclobutane is only slightly less strained than cyclopropane (approximate strain energies of 26 vs 29 kcal/mol),[226] but it is much less reactive under C-C bond activation conditions. Such a difference in reactivity is likely reflective of different orbital availability, which is lower for cyclobutanes in comparison to cyclopropanes (Figure 4).

Figure 4: Orbital models for metal-cyclopropane and metal-cyclobutane interactions.

C-C bond activations of cyclobutanones, i.e. four-membered cyclic ketones, is a well-known process (see also Section 1.2, Scheme 2C).[29-35,168,227,228] On the other hand, examples of direct C-C bond activation of simpler cyclobutanes (i.e. those not bearing an endocyclic carbonyl group) are scarce in the literature. Aside from cyclobutanones, biphenylene **511** is the most

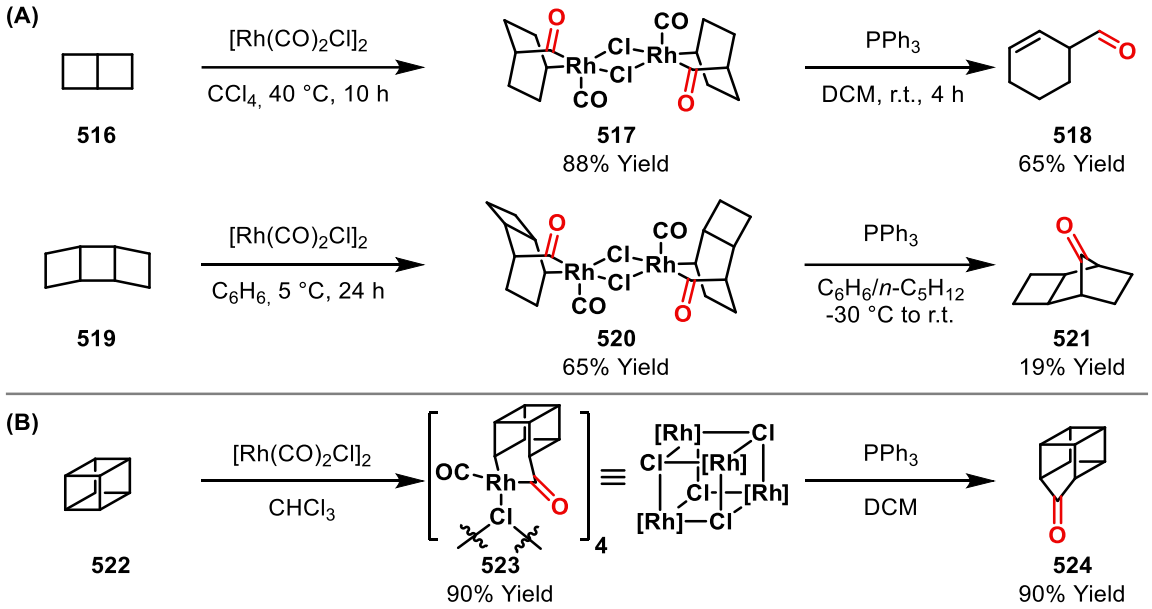
common four-membered cycle that readily allows insertion of Rh into its C-C bond. In 1994, Perthuisot and Jones demonstrated[229] the formation of rhodacycle **512** upon treatment of biphenylene with complex **513** (Scheme 126A). The reaction proceeds through the formation of kinetic C-H activated product **514** (as observed by NMR spectroscopy), which then rearranges to give thermodynamic product **512**. This kind of oxidative addition process has given rise to diverse reactivity. It has been long known[230] that exposure of biphenylene to Rh-carbonyl complexes gives trace amounts of **515**. More recently, a high-yielding Rh-catalysed carbonylation of biphenylene to give fluorenone **515** has been reported,[231] although the reaction takes 6 days to proceed to completion (Scheme 126B). Following this, intermolecular cycloadditions of biphenylene with alkynes,[232,233] alkenes[232,234] and nitriles[233,235] have been demonstrated (Scheme 126B).



Scheme 126: (A) Formation of rhodacycle **512** from biphenylene; (B) Carbonylation and cycloadditions of biphenylene with alkynes, alkenes and nitriles; dtbpm = bis(di-tert-butylphosphino)methane), dppe = 1,2-bis(diphenylphosphino)ethane.

Other four-membered carbocycles show limited reactivity in C-C bond activation processes. Stoichiometric carbonylations using $[Rh(CO)_2Cl]_2$ have been demonstrated for several strained saturated systems. Bicyclo-[2.2.0]hexane **516** and *syn*-tricyclo[4.2.0.0]octane **519** give bridged dimers **517** and **520** (Scheme 127A).[236] Treatment of complex **517** with excess PPh_3 results in aldehyde **518,** which forms via a sequence of β-hydride elimination, rearrangement and C-H reductive elimination. In contrast, reaction of complex **520** with PPh_3 results in C-C reductive elimination, which gives ketone **521** in a low yield of 19%. Cubane **522** demonstrates similar

behaviour when exposed to $[Rh(CO)_2Cl]_2$ (Scheme 127B);[237] tetramer **523** is formed first (with chloride as a triply bridging ligand), and then phosphine-induced reductive elimination leads to **524**.



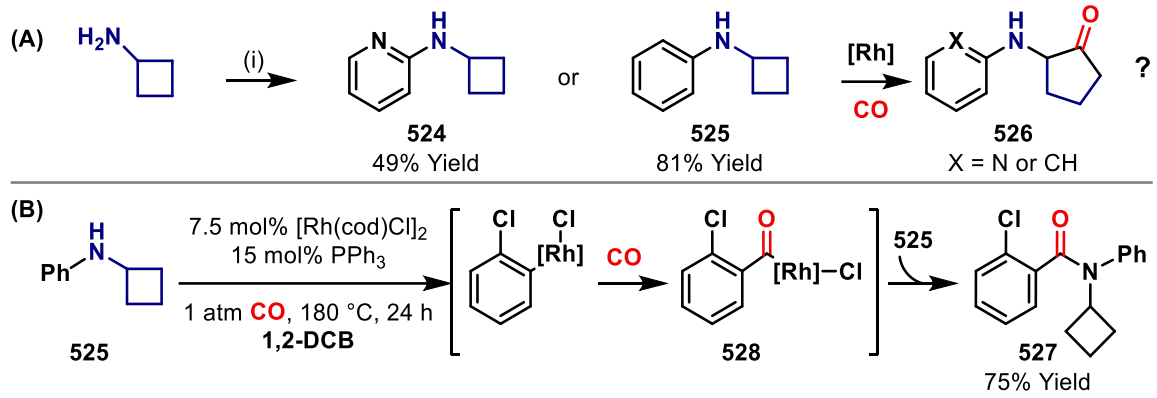
Scheme 127: Carbonylation of (A) bicyclo-[2.2.0]hexane, *syn*-tricyclo[4.2.0.0]octane and (B) cubane.

To date, efficient C-C bond activations of simple cyclobutanes, where all carbons are sp^3-hybridised, have not been developed. This limitation stimulated investigations at Bristol. The research presented in the following sections is focused on the synthesis and reactivity of substituted aminocyclobutanes, which might, in principle, form rhodacyclohexanones **509** upon carbonylative C-C bond activation. Subsequent C-C reductive elimination would then deliver cyclopentanones **508** (see Scheme 125). Alternatively, rhodacyclohexanone **509** might be amenable to diversion via other reaction pathways, leading to other types of scaffold.

6.2 Synthesis and reactivity of aminocyclobutanes

The low reactivity of cyclobutanes towards C-C bond activation calls for careful design of a suitable system. The possibility of C-C bond activation of cyclobutanes containing different nitrogen-based directing groups was investigated first. Aminocyclobutanes **524** and **525** were synthesised via Buchwald-Hartwig cross-coupling (Scheme 128A), and exposed to a range of Rh-catalysed carbonylation conditions. Cyclobutane **524** failed to deliver any of desired product **526**, and only starting material was recovered. When cyclobutane **525** was used, the formation of amide **527** occurred in 75% yield (Scheme 128B). This product presumably results from aminocarbonylation of the 1,2-dichlorobenzene solvent, via a sequence involving oxidative

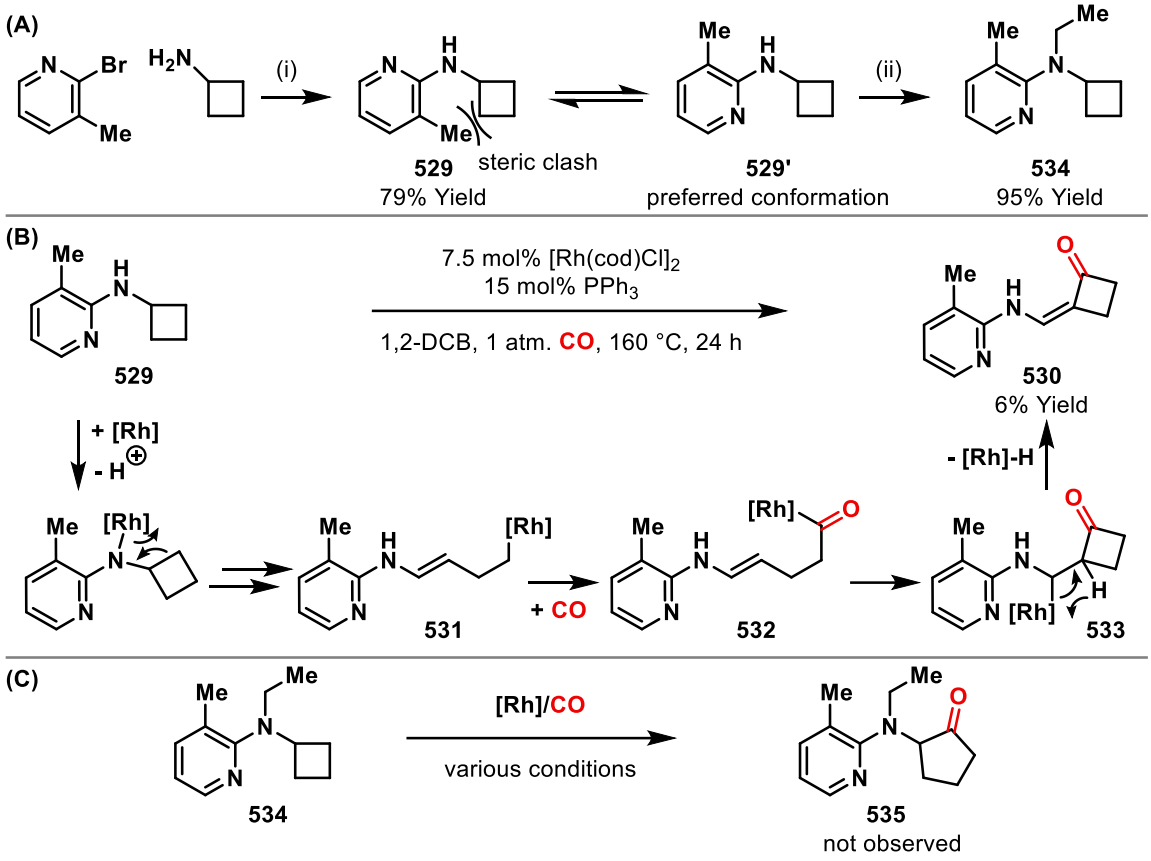
addition of Rh into the C-Cl bond and CO insertion. The resulting acylmetal species **528** is intercepted by the nucleophilic *N*-center of **525** prior to C-N reductive elimination.



Scheme 128: (A) Synthesis of *N*-substituted aminocyclobutanes. *Reagents and conditions:* (i) 2-Bromopyridine or iodobenzene, sodium *tert*-amoxide, $Pd_2(dba)_3$, BrettPhos, 80 °C, 16 h; (B) Proposed mechanism for the formation of amide **527** from amine **525**.

Having established that aminocyclobutanes **524** and **525** are not suitable for the envisaged C-C bond activation process, modified substrates were considered. It was envisaged that addition of a methyl group to the pyridine ring in **529** would facilitate nitrogen-directed insertion of Rh into the C-C bond. This idea was based on the notion that the methyl group should bias the preferred conformation towards **529'**, in which the pyridine nitrogen is appropriately positioned to direct Rh insertion into the C-C bond (for the use of the 2-picoline-based directing group in C-C bond activation methodologies, see Chapter 2, Scheme 21).[238] **529** was accessed in 79% yield by Buchwald-Hartwig cross-coupling of 2-bromo-3-methylpyridine and cyclobutylamine (Scheme 129A). Surprisingly, when **529** was exposed to $[Rh(cod)_2]OTf/PPh_3$ at 160 °C in 1,2-DCB under 1 atm of CO, vinylogous amide **530** was isolated in low yield (Scheme 129B). It should be noted, that in all other cases only starting material was recovered under different Rh-catalysed carbonylation conditions.

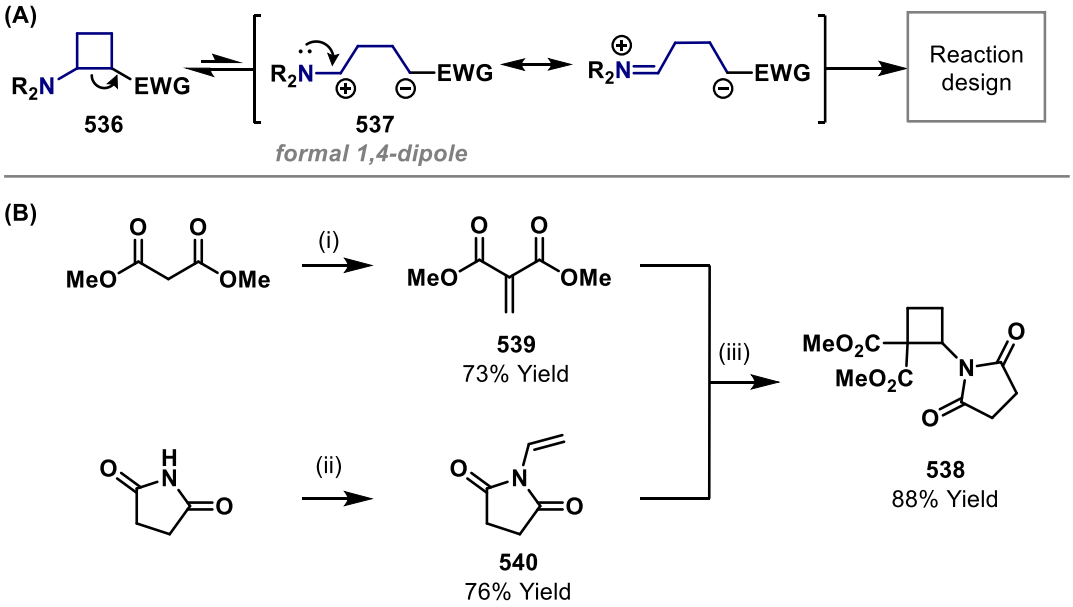
The mechanism for the formation of **530** may proceed via insertion of Rh into the N-H bond of **529** to give intermediate **531** after β-carbon elimination (Scheme 129B). At this stage, migratory insertion of CO would give **532**, which can undergo 1,2 acyl-metallation of the enamine to give **533**. β-Hydride elimination would then release product **530**. To avoid insertion of Rh into the N-H bond, tertiary amine **534** was synthesised by reductive amination of amine **529** with acetaldehyde. Unfortunately, despite an extensive screening of carbonylative conditions (>20 sets of conditions), only starting material was recovered using substrate **534** and cyclopentanone **535** did not form (Scheme 129C).



Scheme 129: (A) Synthesis of aminocyclobutanes **529** and **534**. *Reagents and conditions:* (i) sodium *tert*-amoxide, $Pd_2(dba)_3$, BrettPhos, 80 °C, 16 h; (ii) acetaldehyde, $NaBH(OAc)_3$, 1,2-dichloroethane, r.t., 4 h; (B) Proposed mechanism for the formation of vinylogous amide **530** from amine **529**. (C) Attempted C-C bond activation of **534**.

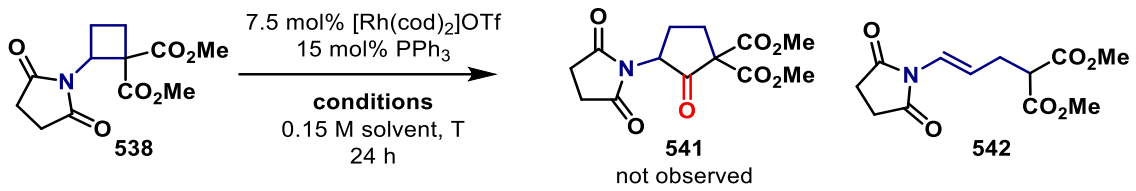
6.3 Synthesis and reactivity of donor-acceptor cyclobutanes

One way to enhance aminocyclobutane reactivity is to add an electron-withdrawing substituent to the ring.[239] The nitrogen of aminocyclobutane in **536** acts as an electron-donating group, such that the vicinal C-C bond is strongly polarized and prone to cleavage under a range of conditions to give a 1,4-dipole **537** (Scheme 130A). In this context, donor-acceptor cyclobutane **538** was synthesised in 88% yield by iron-catalysed [2+2] cycloaddition between **539** and **540** (Scheme 130B).[240]



Scheme 130: (A) Cleavage of the C-C bond in donor-acceptor aminocyclobutane derivatives. (B) Synthesis of β-succinimide dicarboxylic ester **538**. *Reagents and conditions:* (i) *i*-Pr_2NH·TFA, TFA, paraformaldehyde, THF, reflux, 7 h; (ii) $Na_2[PdCl_4]$, vinyl acetate, reflux, 3 d; (iii) $FeCl_3$, DCM, r.t., 18 h.

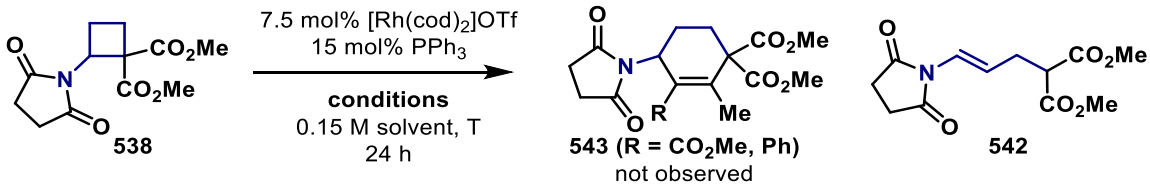
Cyclobutane **538** was subjected to a range of catalytic conditions, encompassing various phosphine ligands, neutral ($[Rh(cod)Cl]_2$) and cationic ($[Rh(cod)_2]OTf$) Rh-precatalysts, non-coordinating (1,2-DCB and decalin) and strongly coordinating solvents (benzonitrile), different temperatures (100-190 °C), carbon monoxide pressures (1, 5 atm) and reaction times of up to 2 days. Under these conditions, cyclobutane **538** remained mainly unreacted and target cyclopentanone **541** was not formed (Table 16, Entries 1-5). The only observable product was alkene **542** (Table 16, Entries 2-4).



Entry	Solvent	T, °C	Conditions	Yield of 542, %[a]
1	1,2-DCB	100	CO, 1 atm	0
2	1,2-DCB	140	CO, 1 atm	19
3	1,2-DCB	180	CO, 1 atm	89
4	PhCN	180	CO, 1 atm	trace
5	Decalin	190	CO, 1 atm	0

Table 16: Selected conditions for cyclobutane **538** ring opening. [a] Yields were determined by ^{1}H NMR analysis of the crude reaction mixture against an internal standard (1,4-dinitrobenzene).

The formation of alkene **542** merited further investigation. It was found that cyclobutane **538** remained unreacted over the course of 2 days when heated at 180 °C in 1,2-DCB in the absence of catalyst (Table 17, Entry 1). This implies that the formation of alkene **542** is facilitated by Rh, and this may occur via a sequence of C-C bond activation, β-hydride elimination and C-H reductive elimination. Alternatively, the Rh catalyst may act as a Lewis acid and coordinate to ester groups of cyclobutane **538**, thereby facilitating ring cleavage. Alkene **542** also formed under non-carbonylative conditions using a Rh-based catalytic system (Table 17, Entry 2). On the presumption that a rhodacyclohexanone intermediate may be forming, the possibility of alkyne insertion (Table 17, Entries 3, 4) was investigated, but the envisaged cycloadducts **543** were not observed.

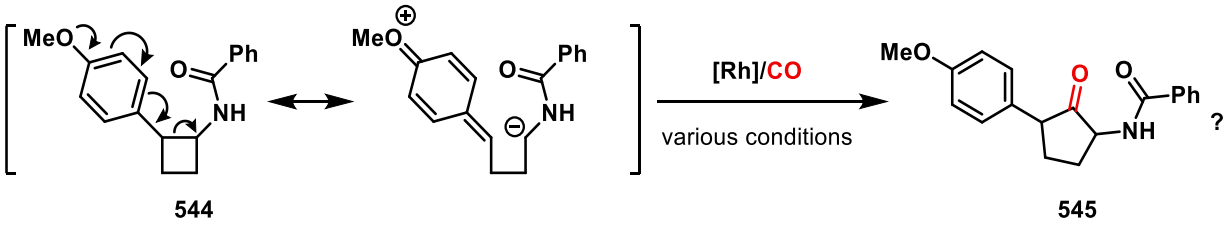


Entry	Solvent	T, °C	Conditions	Yield of 542, %[a]
1	1,2-DCB	180	no CO, no [Rh]/PPh_3	0 (+96% **538**)
2	1,2-DCB	180	no CO	33 [a]
3	1,2-DCB	180	Me—≡—CO_2Me, 1,5 eq.	0
4	1,2-DCB	180	Me—≡—Ph, 1.5 eq.	0

Table 17: Selected conditions for ring opening of cyclobutane **538**. [a]Yields were determined by ^{1}H NMR analysis of the crude reaction mixture against an internal standard (1,4-dinitrobenzene). [a] Isolated yield.

6.4 Synthesis and reactivity of *para*-methoxyphenyl cyclobutane

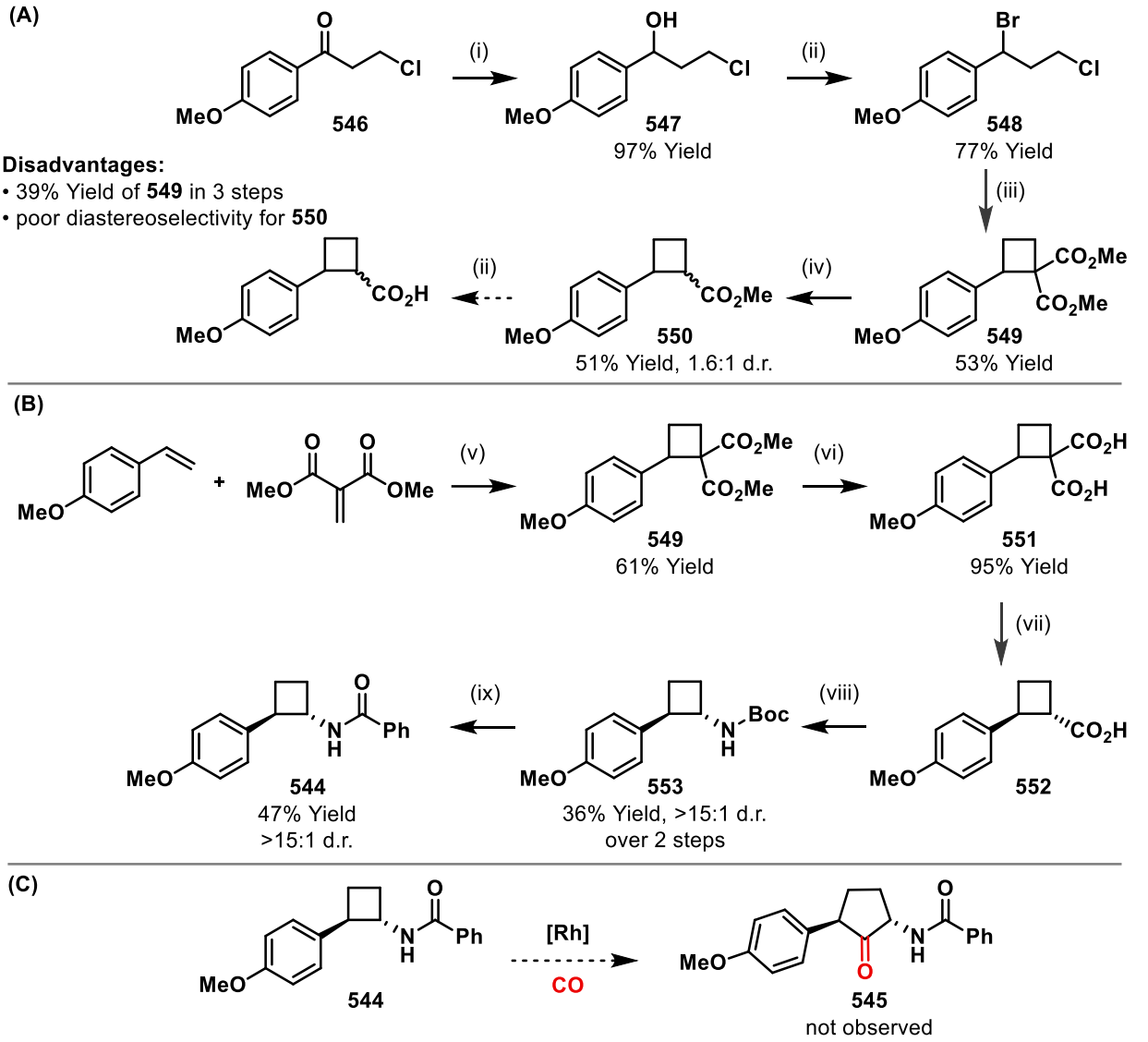
In efforts to facilitate the C-C bond activation of cyclobutanes, more highly activated variants were sought. It was proposed that π-donation from an aromatic ring to the σ*-antibonding orbital of the C-C bond of the cyclobutane could weaken the C-C bond and facilitate Rh insertion. Substrate **544** was identified as a suitable starting material to probe the formation of cyclopentanone **545** under Rh-catalysed carbonylative conditions (Scheme 131). C-C bond insertion into **544** should be facilitated by a relatively electron-rich aromatic ring and the amide-based directing group.



544 **545**

Scheme 131: Proposed transformation of cyclobutane **544** to cyclopentanone **545**.

The first synthetic pathway to **544** was via acid intermediate **550** and is depicted in Scheme 132A. 1,3-Dihalogenated alkane **548**, which was synthesised from 3-chloropropiophenone **546** via alcohol **547** according to a literature procedure,[241] was used for sequential alkylation of dimethyl malonate. This delivered diester **549** in 52% yield, which is equivalent to a 39% yield for **549** over three steps. This was followed by Krapcho decarboxylation to afford ester **550** as a 1.6:1 mixture of diastereomers. The poor diastereoselectivity and lower overall yield made the approach outlined in Scheme 132A unfavourable. An alternative synthetic pathway was then used; here, dicarboxylate precursor **549** was accessed in 61% yield by employing a [2+2] cycloaddition protocol (Scheme 132B, cf. 39% yield of **549** over three steps, Scheme 132A).[242] Saponification of ester **549** and thermally promoted decarboxylation of the corresponding diacid **551** gave *trans*-**552**. Subsequent Curtius rearrangement of acid **552** delivered *N*-Boc aminocyclobutane **553**. Finally, Boc-deprotection and acylation with benzoyl chloride provided target cyclobutane **544** in 47% yield. Unfortunately, despite trialling a number of Rh-catalysed carbonylation conditions, cyclobutane **544** did not deliver C-C bond activation derived products such as **545** and only starting material was observed (Scheme 132C).

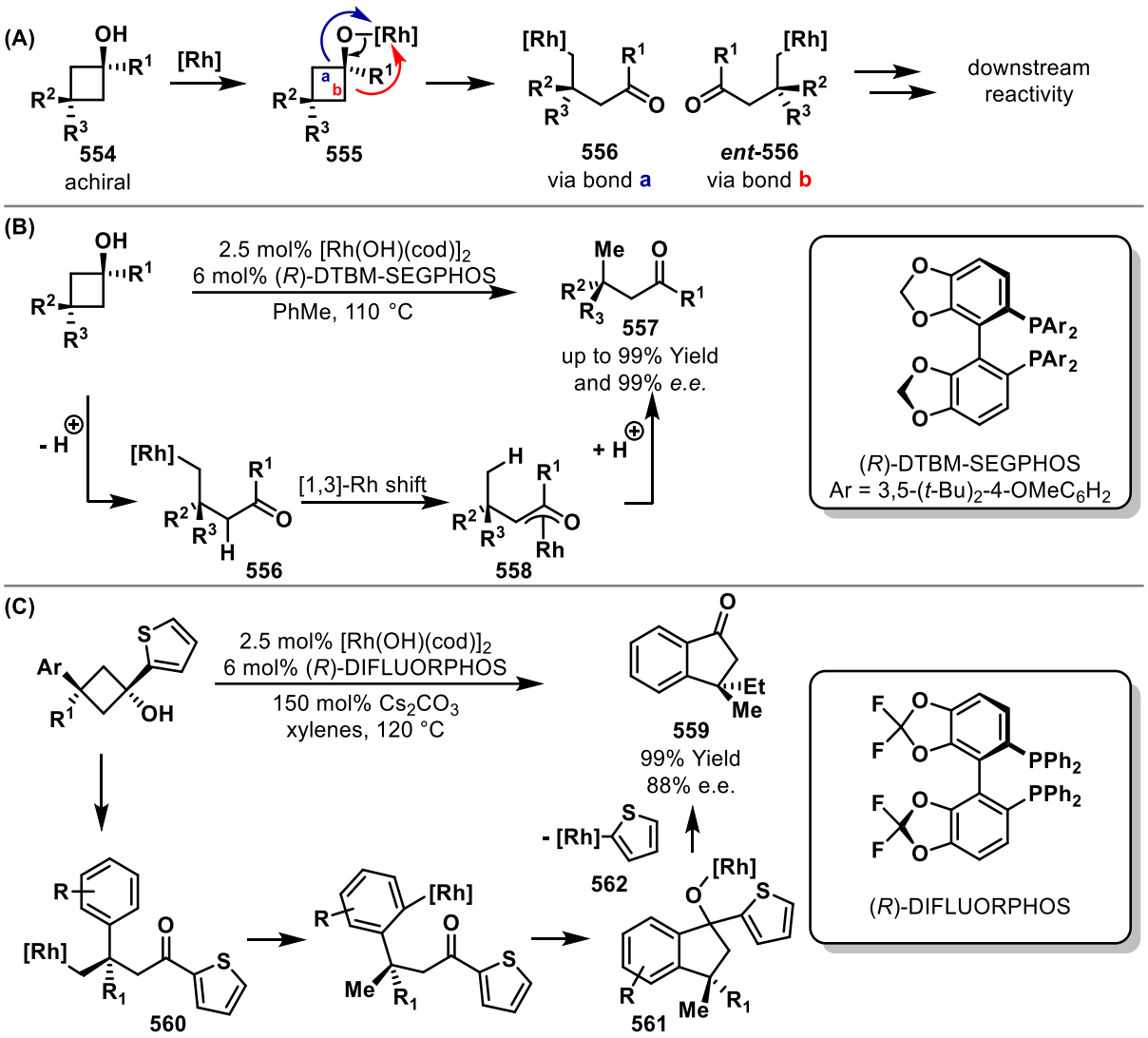


Scheme 132: (A) Initial approach towards **550**. *Reagents and conditions:* (i) $NaBH_4$, MeOH, 0 °C, 30 min; (ii) HBr, H_2O, r.t., 3 h; (iii) dimethyl malonate, NaH, 1,4-dioxane, reflux, 18 h; (iv) LiCl, H_2O, DMSO, 180 °C, 2 h. (B) An alternative synthesis of cyclobutane benzamide **544**. *Reagents and conditions:* (v) dry $ZnBr_2$, DCM, -130 to -78 °C, 3 h; (vi) KOH, 1,4-dioxane: H_2O 1:1, reflux, 80 °C, 4 h; (vii) DMF, reflux, 3 h; (viii) diphenylphosphoryl azide, NEt_3, *t*-BuOH, 80 °C, 17 h; (ix) (a) TFA, DCM, r.t., then (b) BzCl, TEA, DCM, 0 °C to r.t., 16 h. (C) Attempted C-C bond activation of **544**.

6.5 Combining the C-C bond activation of cyclopropanes with ring-opening of larger carbocycles

6.5.1 Known methods for β-carbon elimination in cyclobutanes

As described in Sections 6.2-6.4, little to no reactivity was observed when direct C-C bond activations of cyclobutanes were attempted. However, β-carbon elimination is a well-known process for ring-opening cyclobutanes, with cyclobutanol being the most common unit employed in such reactions.[243-250] The commonly accepted mechanism of this ring opening involves ligand exchange between cyclobutanol **554** and the catalyst to give **555** (Scheme 133A). Alkoxide **555** then undergoes C-C bond cleavage by β-carbon elimination to generate intermediate **556**, which is able to engage in subsequent processes. In certain cases, defined quaternary stereocentres can be generated if a chiral ligand is used. For example, Cramer and Seiser showed that the enantioselective generation of ketones **557** is possible using a $[Rh(OH)(cod)]_2$/DTBM-SEGPHOS system (Scheme 133B).[244] Deuterium labelling studies demonstrated that methyl substituted ketones **557** are obtained via protonation of Rh-enolate **558** rather than via direct protodemetallation of alkyl-metal intermediate **556**. Another example is depicted in Scheme 133C. Based on earlier works on the synthesis of indanols,[245,246] Cramer and co-workers developed[247] an asymmetric synthesis of indanones, such as **559**. This process uses two consecutive β-carbon eliminations. First, cyclobutanol ring-opening gives **560**, which undergoes a [1,4]-Rh shift and intramolecular 1,2-addition to yield alkoxide **561**. A second β-carbon elimination forms **559** and Rh-thienyl species **562**, which likely undergoes protodemetallation to regenerate the active catalyst.



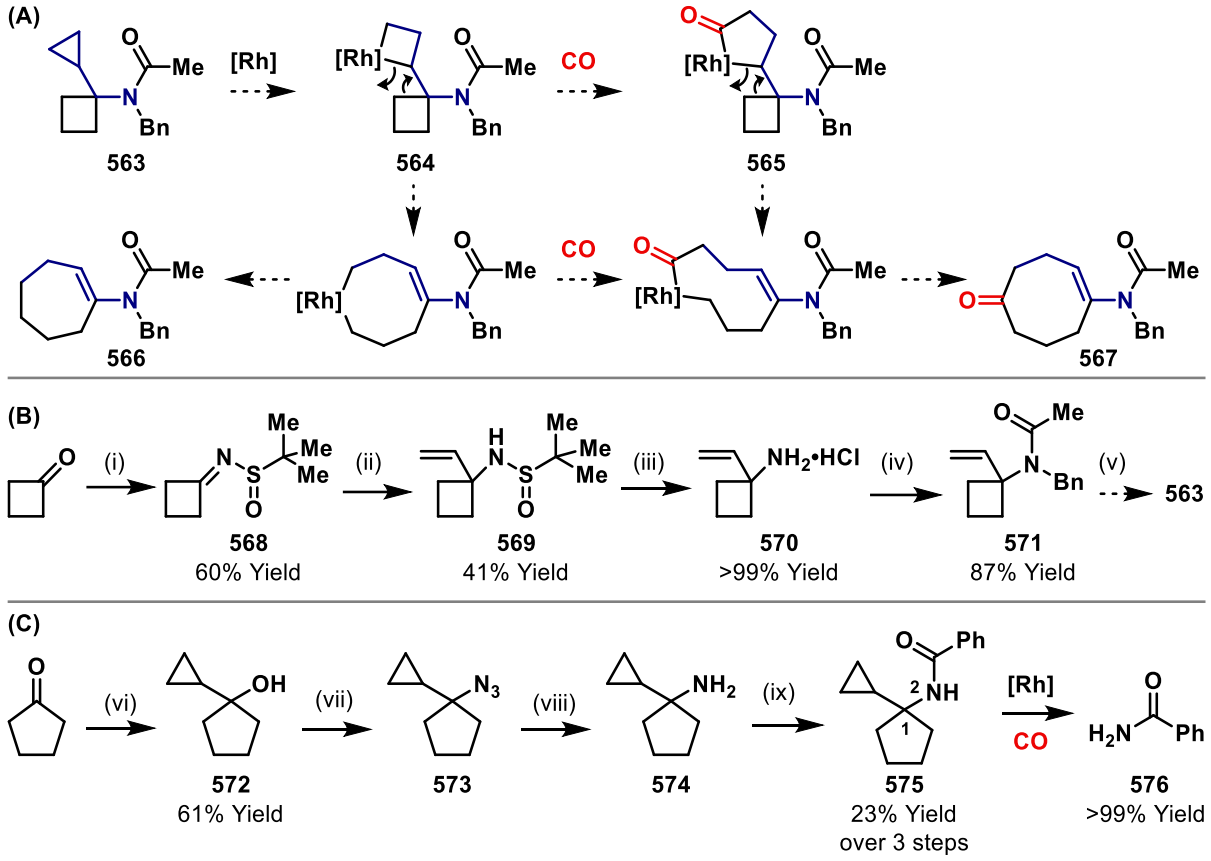
Scheme 133: (A) β-Carbon elimination triggered ring opening of cyclobutanols; (B) Enantioselective synthesis of linear compounds with methyl substituted quaternary centres; (C) Enantioselective synthesis of indanones.

6.5.2 Studies on C-C bond activation-triggered β-carbon elimination

Taking the previous developments in the area into account, a novel method was proposed which combines C-C bond activation and β-carbon elimination. Cyclopropyl cyclobutane **563** was considered a suitable starting material to form rhodacyclobutane **564** or rhodacyclopentanone **565** (Scheme 134A). It was thought that either of these intermediates might undergo β-carbon elimination of the strained 4-membered ring in advance of C-C reductive elimination to enamide **566** or **567**.

The synthesis of **563** started with the formation of racemic Ellman's sulfinamide **568** from cyclobutanone (Scheme 134B).[251,252] Vinyl Grignard addition to **568** gave vinyl cyclobutane **569**, which underwent quantitative deprotection (HCl, MeOH) to give amine **570** as its HCl salt. Following this, a reductive amination-acylation sequence furnished *N*-benzyl acetamide **571** in 87% yield. Various methods for Simmons-Smith cyclopropanation[253-255] of **571** were trialled. Under certain conditions **563** was observed, but the reaction was extremely sensitive to scale, difficult to purify and full conversion of **571** to cyclopropane **563** could not be achieved.

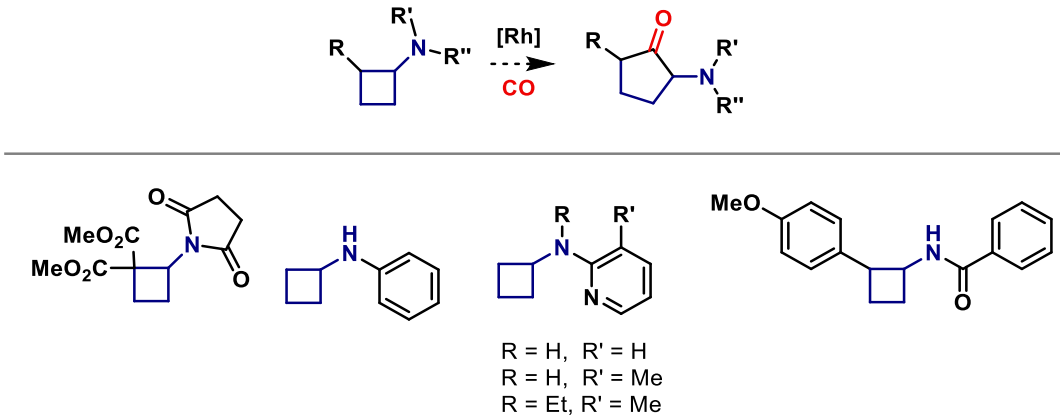
Concurrently, cyclopropyl cyclopentane **572** was made to see whether the C-C bond activation/β-carbon elimination strategy is feasible for five-membered rings (Scheme 134C). The route commenced with the addition of lithiated cyclopropane to cyclopentanone to give tertiary alcohol **573** in 61% yield. Nucleophilic substitution of the alcohol with sodium azide afforded **573**, which was immediately reduced using $LiAlH_4$.[256] The resulting crude amine **574** was then reacted with benzoyl chloride to provide amide **575** in 23% yield over the three steps. When cyclopropane **575** was subjected to Rh-catalysed carbonylative conditions ($[Rh(cod)_2]OTf/P(3,4,5\text{-}(F)_3C_6H_2)_3$, 1,2-DCB, 1 atm. CO, 110 °C), no evidence for the C-C bond activation triggered ring-opening cascade could be obtained. Instead, benzamide **576** formed in quantitative yield. It is unclear at which stage of the catalytic cycle the reaction fails. One of the possibilities is that the C1-N2 bond undergoes facile cleavage under the reaction conditions due to the formation of a relatively stable tertiary cyclopentyl carbocation. This explanation is supported by the successful S_N1-type transformation of alcohol **572** to azide **573**, which presumably proceeds via acid-promoted formation of a cyclopropane-stabilised tertiary carbocation.



Scheme 134: (A) Proposed reactivity mode for cyclobutane **563**; (B) Attempted synthesis of aminocyclobutane **563**; (C) Synthesis and reactivity of cyclopentane **575**. *Reagents and conditions:* (i) *t*-Butanesulfinamide, $Ti(OEt)_4$, THF, r.t., 18 h; (ii) vinylmagnesium bromide, THF, -78 °C to r.t., 18 h; (iii) HCl, MeOH, Et_2O, 0 °C to r.t., 1 h; (iv) (a) benzaldehyde, $NaHCO_3$, MeOH, reflux, 3 h; (b) $NaBH_4$, 0 °C to r.t., 4 h; (c) acetic anhydride, TEA, DCM, 0 °C to r.t., 16 h; (v) Et_2Zn, CH_2I_2, DCE or Et_2Zn, CH_2I_2, TFA, DCM; (vi) cyclopropyl bromide, *t*-BuLi, Et_2O, -78 °C, 4 h then r.t., 18 h; (vii) NaN_3, TFA, PhMe, 0 °C, 4 h; (viii) $LiAlH_4$, THF, 0 °C to rt, 16 h then 50 °C, 1 h; (ix) benzoyl chloride, TEA, DCM, 0 °C to r.t., 16 h.

6.6 Conclusions

4-Membered rings are considerably more challenging systems for C-C bond activation than cyclopropanes. In particular, such process have not previously been demonstrated for relatively unstrained all sp^3-hybridised cyclobutanes. Inspired by this deficiency, studies have been undertaken to assess whether cyclopentanones can be accessed by carbonylative C-C bond activation of cyclobutanes. A donor-acceptor cyclobutane, aminocyclobutanes bearing *N*-based directing groups, and an arene activated cyclobutane were synthesised (Scheme 135). These were subjected to a range of carbonylative C-C bond activation conditions, but, in most cases, the cyclobutanes remained unreacted and the target cyclopentanones were not observed. An alternative β-carbon elimination approach to the ring-opening of small carbocycles was also unsuccessful.

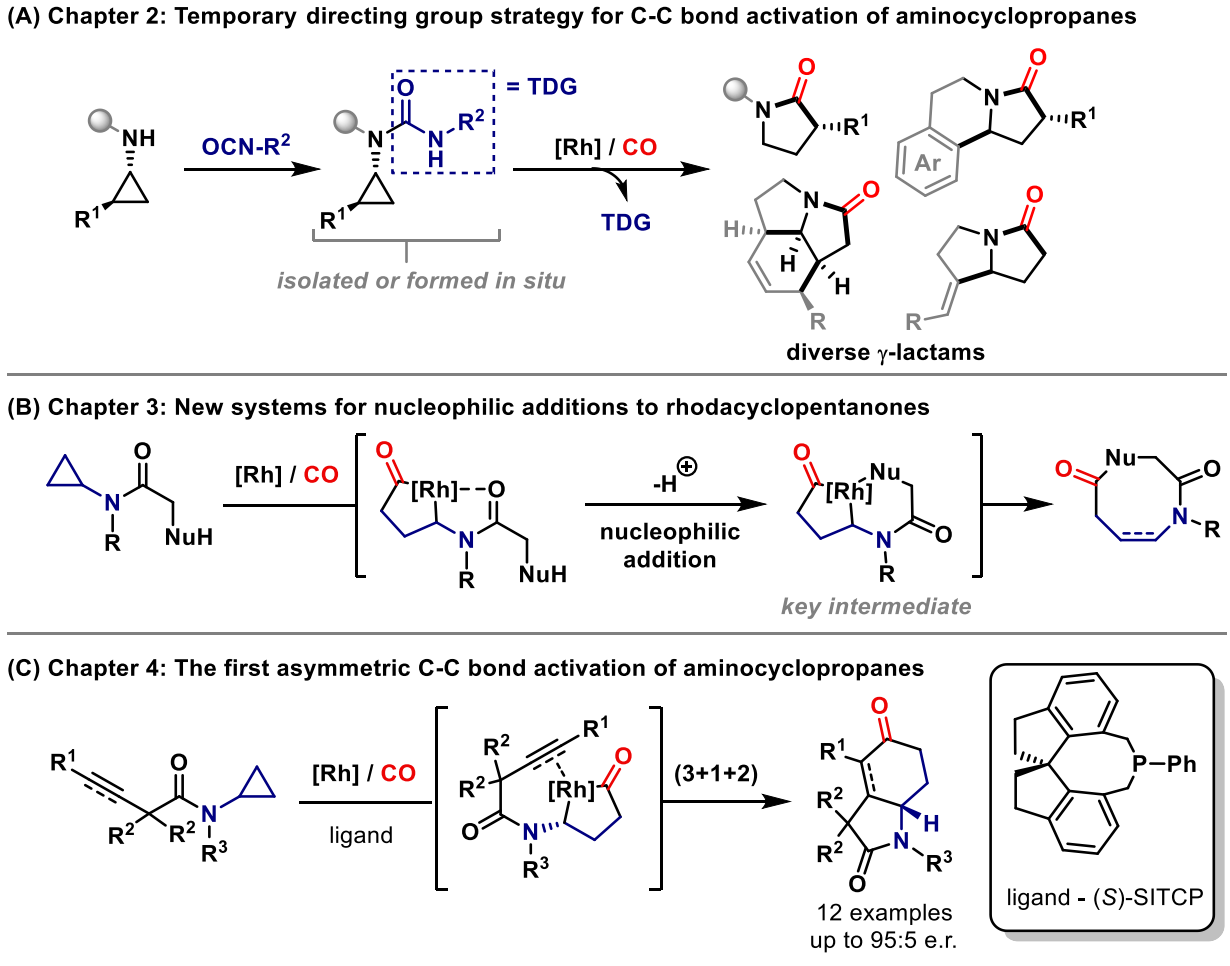


Scheme 135: Attempted Rh-catalysed ring expansion of cyclobutanes.

CHAPTER 7

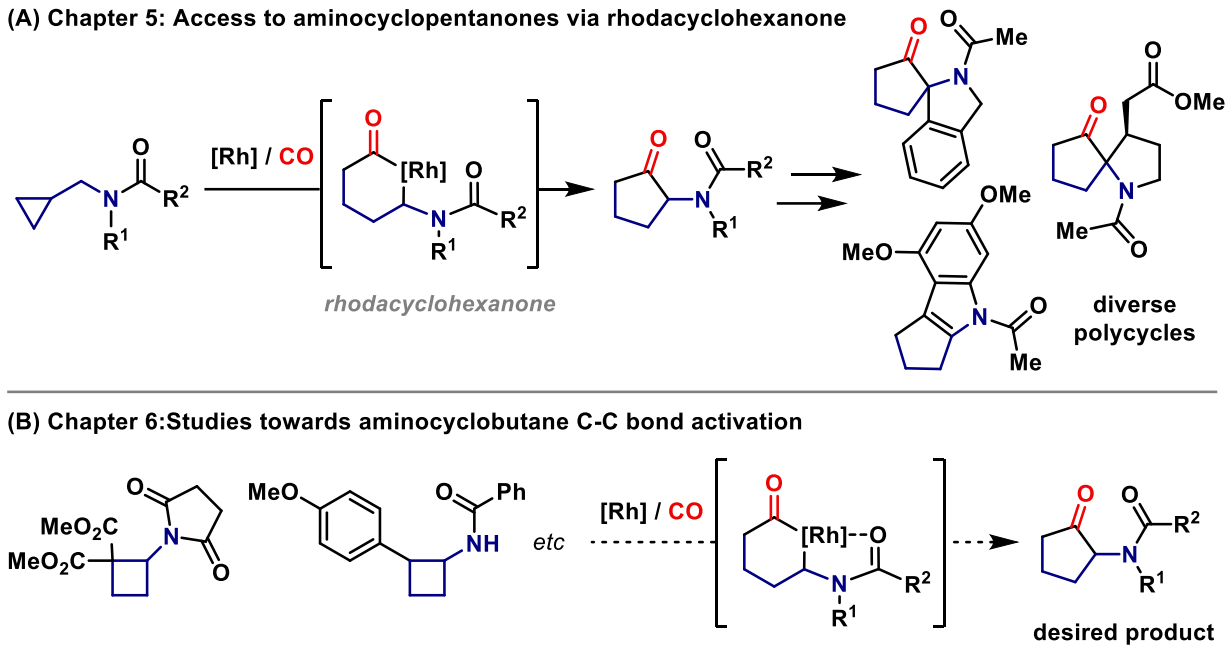
Overall summary and conclusions

The work presented in this thesis has established several C-C bond activation methodologies. Chapter 2 summarises the development of a ring contraction cascade to access diverse γ-lactams from aminocyclopropanes (Scheme 136A). Unlike the previously known methods for directed oxidative addition of transition metals to aminocyclopropanes, this transformation uses an isocyanate-based temporary directing group which can easily be installed in a one-pot manner. Chapter 3 investigates new systems for nucleophilic additions to rhodacyclopentanones (Scheme 136B). Substrates with aniline-based nucleophiles were identified as promising precursors to 8-membered heterocycles; several alternative substrates with pendent nucleophiles were trialled with limited success. Studies in Chapter 4 resulted in the discovery of a novel asymmetric (3+1+2) cycloaddition between aminocyclopropanes, CO and tethered π-unsaturates (Scheme 136C). This transformation constitutes the first highly enantioselective aminocyclopropane-based C-C bond activation methodology. The identified catalytic system is expected to encourage further development of asymmetric C-C bond activations in Bristol.



Scheme 136

Chapter 5 demonstrates unique examples of processes where aminomethylcyclopropane C-C bond activation leads to rhodacyclohexanone intermediates (Scheme 137A). These undergo reductive elimination to provide α-aminocyclopentanones, which were employed in tandem and cascade processes to obtain distinct polycyclic products. Finally, the possibility of aminocyclobutane C-C bond activation was investigated in Chapter 6 with a variety of systems (Scheme 137B). Unfortunately, the desired reactivity was not observed and the cyclobutanes remained mainly unreacted. Nonetheless, these studies demonstrated that several cyclobutane-based systems are not suitable, and the results will guide further efforts in this area.



Scheme 137

To summarise, this thesis has advanced the field of C-C bond activation through studies on the chemistry of aminocyclopropanes and related strained ring systems. The developed methodologies offer efficient and atom-economical entries to complex heterocyclic scaffolds, and highlight the power of using C-C bond activation of cyclopropanes as a by-product free reaction initiation mode. The new methods provide compounds that are challenging to synthesise using conventional approaches. A particular highlight of the work described here is the realisation of enantioselective carbonylative C-C bond activations of aminocyclopropane-based substrates. This will set the stage for future studies that harness cyclopropanes as readily available C3 units for accessing enantioenriched compounds.

CHAPTER 8

Experimental

8.1 General experimental details

All materials for which a synthetic route is not described or referenced were purchased from commercial sources (Sigma-Aldrich, Alfa Aesar, Fluorochem and Strem) and used as received unless otherwise stated. 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 40 °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. Catalytic reactions were carried out inside oven/flame dried glass reaction tubes equipped with a Suba-Seal® and a balloon of inert gas (or carbon monoxide in the case of carbonylation reactions). Petrol refers to petroleum ether consisting of aliphatic hydrocarbons boiling in the range 40–60 °C. Flash column chromatography (FCC) was performed using silica gel (Aldrich 40-63 μm, 230-400 mesh). Thin layer chromatography was performed using aluminium backed 60 F_{254} silica plates. Visualisation was achieved by UV fluorescence or a basic $KMnO_4$ solution and heat. Proton nuclear magnetic resonance spectra (NMR) were recorded on the following spectrometers: JEOL ECS400, JEOL ECZ400, Varian 400-MR, Bruker Nano400, Varian VNMR 500, and Bruker Avance III HD 500 Cryoprobe. ^{1}H NMR spectra were recorded at 400 MHz or 500 MHz as stated. ^{13}C NMR spectra were recorded at 101 MHz or 126 MHz as stated. Chemical shifts (δ) are given in parts per million (ppm). Peaks are described as singlets (s), doublets (d), triplets (t), quartets (q), septets (sept), multiplets (m) and broad (br.). Coupling constants (*J*) are quoted to the nearest 0.5 Hz. All assignments of NMR spectra were based on 2D NMR data (COSY, HSQC, HMBC, TOCSY, and nOe experiments where appropriate). Where compounds were isolated as a mixture of isomers (e.g. rotamers), they are referred as A and B. NMR yields were determined by employing 1,4-dinitrobenzene as an internal standard. Mass spectra were recorded using the following instruments: Bruker Daltonics FT-ICR-MS Apex 4e 7.0T FT-MS or Bruker Daltonics micrOTOF II (ESI), Shimadzu GCMS QP2010+ or Thermo Scientific Orbitrap Elite (EI), Bruker ultrafleXtreme 2 (MALDI), Thermo Scientific Orbitrap Elite (APCI) and Waters Synapt G2S (Nanospray). Infrared spectra were recorded on a Perkin Elmer Spectrum Two FT-IR spectrometer as thin films or solids compressed on a diamond plate. Melting points were determined using Reichert melting point apparatus. Optical rotations were measured using an ADP440+ polarimeter at the concentration and temperature stated. Enantiomeric excess was determined using an Agilent 1290 Infinity chiral SFC under the conditions noted for each compound.

8.2 General procedures

General procedure A for the *N*-alkylation of primary amines

To a reaction tube containing the appropriate tosylate (1.00 eq) in MeCN (0.4 M) was added cyclopropylamine (4.00 eq). The tube was sealed and heated to reflux for 16 h. The reaction mixture was cooled to r.t. and concentrated *in vacuo*. Sat. aq. $NaHCO_3$ (10 mL/mmol) and DCM (5 mL/mmol) were added, the layers were separated and the aqueous portion was further extracted with DCM (2 × 5 mL/mmol). The organic extracts were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography, under the conditions noted, to afford the desired *N*-substituted amine.

General procedure B for tosylation of alcohols

To a solution of alcohol (1.00 eq) in DCM (0.5 M) was added Et_3N (1.20 eq), DMAP (0.20 eq) and TsCl (1.20 eq) at 0 °C. The reaction was warmed to r.t. and stirred for 16 h. Water (5 mL/mmol) was added and the solution was extracted with DCM (3 × 5 mL/mmol). The organic extracts were combined, washed with brine (5 mL/mmol), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography, under the conditions noted, to provide the desired tosylate.

General Procedure C for the traceless directing group enabled C-C activation of aminocyclopropanes

To an oven dried reaction tube, fitted with a magnetic stirrer, was added amine substrate (100 mol%), cyclohexyl isocyanate (100 mol%) and anhydrous 1,2-DCB (0.10 M) under argon. The mixture was then heated at 80 °C for 3 hours. The reaction was cooled to room temperature, $[Rh(cod)_2]OTf$ (7.5 mol%), PPh_3 (15 mol%), 4-(dimethylamino)benzoic acid (15 mol%) and anhydrous 1,2-DCB (0.05 M) were added to the tube under argon. The reaction vessel was purged with CO for 10 minutes and then the solution was sparged with CO for approx. 20 seconds. The mixture was heated at 130 °C for 72 hours, under a CO atmosphere (1 atm). The mixture was cooled to room temperature, concentrated *in vacuo* and the residue was purified by flash column chromatography, under the conditions noted, to afford the desired product.

General Procedure D for preparation of protected amines

To a stirring solution of cyclopropylamine (1.00 eq) and NEt_3 (1.20 eq) in DCM (0.20 M) was added the corresponding acid chloride/sulfonyl chloride/anhydride (1.20 eq) dropwise at 0 °C over a period of 10 minutes under an atmosphere of nitrogen. The mixture was warmed to r.t. and for

18 h. The mixture was diluted with water (10 mL/mmol) and extracted with DCM (3 × 10 mL/mmol). The organic extracts were combined, washed with brine (10 mL/mmol), dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash column chromatography, under the conditions noted, afforded the corresponding substituted amine.

General procedure E for the alkylation of anilines with 2-bromoacetamide-substituted substrates

A solution of the specified 2-bromoacetamide (1.00 eq), specified aniline (5.00 eq) and K_2CO_3 (1.20 eq) in toluene (1.0 M) was heated at 90 °C for 5 h. The reaction mixture was concentrated *in vacuo* and then sat. aq. $NaHCO_3$ (10 mL/mmol) was added. The solution was extracted with EtOAc (3 × 5 mL/mmol) and then the organic extracts were combined, washed with brine (5 mL/mmol), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by recrystallisation or by flash column chromatography, under the conditions noted, to afford the title compound.

General procedure F for carbonylative ring expansions of aniline tethered aminocyclopropane substrate

An oven dried reaction tube, fitted with a magnetic stirrer, was charged with aminocyclopropane substrate (100 mol%), $[Rh(cod)Cl]_2$ (5 mol%) and dimethyl fumarate (100 mol%). The tube was fitted with a rubber septum and purged with argon. Anhydrous PhCN (0.1 M) was added *via* syringe. The reaction mixture was sparged with CO for approx. 10 seconds, then heated at 150 °C under a CO atmosphere (1 atm) for 72 h. The mixture was cooled to r.t., concentrated *in vacuo* and purified by flash column chromatography, under the conditions noted, to afford the title compound.

General procedure G for the amide coupling with EDCI

To a solution of acid (1.00 eq) in DCM (0.3 M), EDCI (1.10 eq) was added at 0 °C and the reaction was stirred for 10 min. Then, the specified amine (1.00 eq) and DMAP (10 mol%) were added at 0 °C and the reaction was slowly warmed to r.t., stirred for 18 h and then concentrated in vacuo. 1.0 M aq. NaOH (5 mL/mmol) was added and the solution was extracted with EtOAc (3 × 3 mL/mmol). The organic extracts were combined, washed with 1.0 M aq. HCl (5 mL/mmol) and brine (5 mL/mmol), dried over $MgSO_4$ and concentrated *in vacuo*. The product was purified by flash column chromatography, under the conditions noted, to afford the target amide.

General procedure H for the preparation of aryl-substituted alkyne substrates via Sonogashira reaction

An oven-dried reaction tube, fitted with a magnetic stirrer, was charged with terminal alkyne (1.00 eq) and aryl halide (1.10-1.20 eq as noted). The tube was fitted with a rubber septum and purged with argon. Anhydrous Et_3N (1.0 M) was added and the solution was sparged with argon for approx. 5 min. $Pd(PPh_3)_4$ (2 mol%) and CuI (2 mol%) were added, the tube was sealed and stirred (at r.t., 60 or 80 °C as noted) for 2-16 h. The mixture was concentrated *in vacuo*. The residue was purified by flash column chromatography, under the conditions noted, to afford the desired aryl-substituted alkyne.

General procedure I for carbonylative ring expansion of protected alkynyl aminocyclopropanes to cyclohexenones

An oven dried reaction tube, fitted with a magnetic stirrer, was charged with aminocyclopropane substrate (100 mol%), PPh_3 (10 mol%) and $[Rh(cod)_2]OTf$ (5 mol%). The tube was fitted with a rubber septum, evacuated and backfilled with nitrogen three times and anhydrous 1,2-DCB (0.1 M) was added via syringe. The reaction mixture was sparged with CO for approx. 10 seconds, then heated at 130 °C under a CO atmosphere (1 atm, balloon) for 48 h. The mixture was cooled to r.t., concentrated *in vacuo* and purified by flash column chromatography, under the conditions noted, to afford the target cyclohexenone.

General procedure J for asymmetric carbonylative ring expansion of protected alkynyl aminocyclopropanes to cyclohexenones

An oven dried reaction tube, fitted with a magnetic stirrer, was charged with aminocyclopropane substrate (100 mol%) and $[Rh(cod)_2]OTf$ (7.5 mol%). In the glovebox, (*S*)-SITCP (15 mol%) was added. The tube was fitted with a rubber septum, taken out of the glovebox and anhydrous 1,2-DCB (0.1 M) was added via syringe. The reaction mixture was sparged with CO for ca. 10 seconds, then heated at 110 °C under a CO atmosphere (1 atm, balloon) for 96 h. The mixture was cooled to r.t., concentrated *in vacuo* and purified by flash column chromatography, under the conditions noted, to afford the target cyclohexenone.

General procedure K for the reduction of amides by $LiAlH_4$

A solution of $LiAlH_4$ in THF (1.0 M, 1.50 eq) was added dropwise to a solution of amide (1.00 eq) in dry THF (0.50 M) over a period of 5 mins at 0 °C. The mixture was warmed to r.t. and then heated to reflux for 16 h. The reaction was diluted with Et_2O, cooled to 0 °C and subsequently quenched with H_2O (0.04 mL per mmol of $LiAlH_4$), 15% NaOH (0.04 mL per mmol of $LiAlH_4$) and H_2O (3 × 0.04 mL per mmol of $LiAlH_4$). The crude mixture was warmed to r.t. and stirred for 10 min. Anhydrous magnesium sulphate was added and the solution was stirred for 5 min. The precipitate was filtered off and the resulting solution was concentrated *in vacuo* to yield title compound.

General procedure L for the synthesis of primary amides from carboxylic acids

To a solution of carboxylic acid (1.00 eq) in DCM (0.5 mL/mmol), stirring under a nitrogen atmosphere at room temperature, oxalyl chloride (2.00 eq) was added dropwise. Evolution of gas was immediately observed and the reaction was stirred until gas effervescence stopped. DCM and an excess of oxalyl chloride were removed *in vacuo* and the corresponding acyl chlorides were used in the next step without purification. Ammonia was bubbled through the solution of the acyl chloride (1.00 eq) in dry THF (0.3 mL/mmol) at 0 °C stirring under a nitrogen atmosphere for 15 minutes. The solvent was removed *in vacuo* and the resulting precipitate was washed abundantly with water.

General procedure M for the synthesis of *N, N*-disubstituted amides via a two-step reductive amination-protection method

A solution of primary amine (1.00 eq), aldehyde (1.05 eq) and $NaHCO_3$ (1.5 eq) in MeOH (0.5 M) was heated at 40 °C for 3 h. The reaction mixture was cooled to 0 °C and $NaBH_4$ (1.50 eq. or 2.00 eq) was added portionwise. The solution was warmed to r.t. and stirred for 4 h. The reaction mixture was concentrated *in vacuo* and then sat. aq. $NaHCO_3$ (10 mL/mmol) was added. The solution was extracted with DCM (3 × 5 mL/mmol) and then the organic extracts were combined, washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the secondary amine intermediate. To a stirring solution of secondary cyclopropylmethylamine (1.00 eq) in dry DCM (3 mL/mmol), TEA (1.20 eq) and a corresponding acid chloride/anhydride (1.20 eq) were added at 0 °C under nitrogen. The solution was warmed to r.t. and stirred for 16 h. Sat. aq. $NaHCO_3$ (10 mL/mmol) was added and the aqueous layer was extracted with DCM (3 × 5 mL/mmol). The combined organic extracts were washed with brine (10 mL/mmol), dried over $MgSO_4$ and concentrated *in vacuo*. The product was purified by flash column chromatography, under the conditions noted, to afford the title compound.

General Procedure N for Rh-catalysed carbonylative rearrangement of amide protected methylaminocyclopropanes to cyclopentanones

An oven dried reaction tube, fitted with a magnetic stirrer, was charged with the starting material (1.00 eq), benzoic acid (20 mol%), Rh catalyst (7.5 mol%) and ligand (15 mol%). The tube was fitted with a rubber septum and purged with argon. Dry and degassed 1,2-DCB (1.5 M) was added via syringe. The reaction mixture was sparged with CO for approximately 10 seconds, then heated to the specified temperature under a CO atmosphere (1 atm) for the specified reaction time (18 – 48 h as noted). The mixture was cooled to r.t., concentrated *in vacuo* and purified by silica gel column chromatography, under the conditions noted.

General procedure O for Buchwald–Hartwig amination

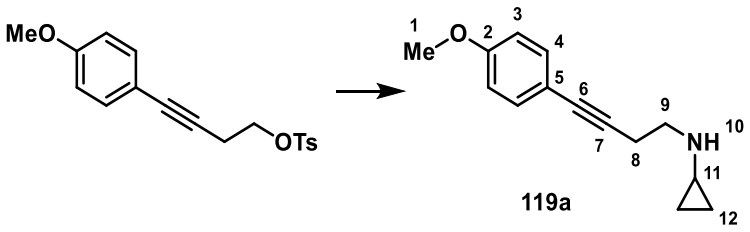
A flame dried reaction tube, fitted with a magnetic stirrer, was charged with sodium *tert*-amoxide (1.50 eq), $Pd_2(dba)_3$ (0.01 eq) and BrettPhos (0.03 eq). The tube was fitted with a rubber septum and purged with argon. Anhydrous toluene (2 mL/mmol) followed by aromatic halide (1.00 eq) and amine of choice (1.20 eq) were then added to the reaction mixture. The tube was sealed and heated at 80 °C for 16 h. The reaction mixture was cooled to r.t., diluted with diethyl ether, filtered through a pad of silica and concentrated *in vacuo*. The residue was purified by flash column chromatography, under the conditions noted, to afford the title compound.

General procedure P for the *N*-alkylation of secondary amides

To a solution of NaH (2.00 eq, 60 % dispersion in mineral oil) in THF (1.0 M) was added a solution of protected aminomethylcyclopropane (1.00 eq) of choice in THF (2.0 M) at 0 °C and the reaction was stirred at r.t. for 1 h. Cyclopropylmethyl bromide (2.00 eq) was added dropwise over 5 minutes and the reaction was heated to 50 °C for 18 h. Water (5 mL/mmol) was added and the mixture was extracted with Et_2O (3 × 2 mL/mmol). The organic extracts were combined, washed with brine (5 mL/mmol), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography under the conditions noted to yield the desired product.

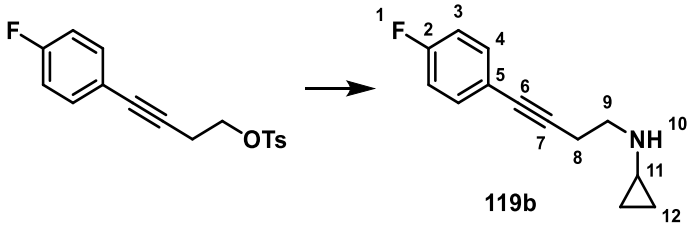
8.3 Experimental procedures for the studies in Chapter 2

N-(4-(4-Methoxyphenyl)but-3-yn-1-yl)cyclopropanamine (119a)



General procedure A: 4-(4-Methoxyphenyl)but-3-yn-1-yl 4-methylbenzenesulfonate (1.98 g, 6.00 mmol, prepared according to the literature procedure[257] from 4-iodoanisole and 3-butyn-1-ol) was employed. Flash column chromatography (50% EtOAc/hexane) afforded the title compound **119a** (0.83 g, 64%) as a pale yellow oil; ν_{max} / cm^{-1}: 2932 (w), 2836 (w), 1606 (m), 1508 (s), 1288 (m), 1243 (s), 1172 (m), 1032 (m), 830 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.36 – 7.32 (m, 2H, 2 × C**4**-H), 6.84 – 6.79 (m, 2H, 2 × C**3**-H), 3.80 (s, 3H, C**1**-H_3), 2.92 (t, *J* = 6.6 Hz, 2H, C**9**-H_2), 2.60 (t, *J* = 6.6 Hz, 2H, C**8**-H_2), 2.19 (tt, *J* = 6.6, 3.6 Hz, 1H, C**11**-H), 1.88 (br. s, 1H, N**10**-H), 0.48 – 0.41 (m, 2H, C**12**-H_2), 0.40 – 0.34 (m, 2H, C**12**-H_2); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 159.3 (C**2**), 133.1 (C**4**), 115.9 (C**5**), 113.9 (C**3**), 86.5 (C**7**), 81.6 (C**6**), 55.4 (C**1**), 48.1 (C**9**), 29.9 (C**11**), 20.6 (C**8**), 6.5 (C**12**);HRMS: (ESI^+) calculated for $C_{14}H_{18}NO$: 216.1383, found $[M+H]^+$: 216.1380.

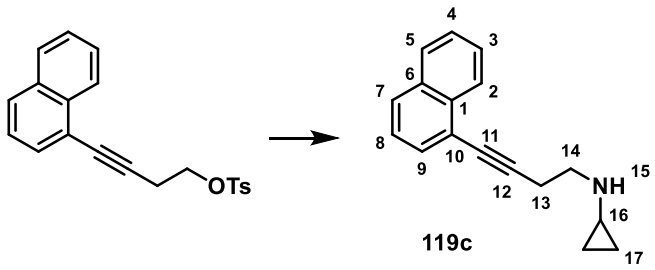
N-(4-(4-Fluorophenyl)but-3-yn-1-yl)cyclopropanamine (119b)



General procedure A: 4-(4-Fluorophenyl)but-3-yn-1-yl 4-methylbenzenesulfonate (1.91 g, 6.00 mmol, prepared according to the literature procedure[257] from 4-fluoroiodobenzene and 3-butyn-1-ol) was employed. Flash column chromatography (40% EtOAc/hexane) afforded the title compound **119b** (0.82 g, 67%) as a pale yellow oil; ν_{max} / cm^{-1}: 2928 (m), 1506 (s), 1220 (s), 1156 (m), 1093 (m), 1014 (m), 834 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.40 – 7.34 (m, 2H, 2 × C**4**-H), 7.02 – 6.94 (m, 2H, 2 × C**3**-H), 2.92 (t, *J* = 6.7 Hz, 2H, C**9**-H_2), 2.60 (t, *J* = 6.6 Hz, 2H, C**8**-H_2), 2.19 (tt, *J* = 6.6, 3.6 Hz, 1H, C**11**-H), 1.87 (br. s, 1H, N**10**-H), 0.49 – 0.43 (m, 2H, C**12**-H_2), 0.40 – 0.34 (m, 2H, C**12**-H_2); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 162.3 (d, *J* = 248.2 Hz, C**2**), 133.5 (d, *J*

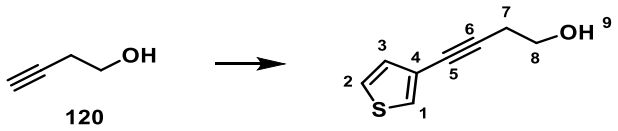
= 8.2 Hz, C**4**), 119.9 (d, *J* = 3.4 Hz, C**5**), 115.6 (d, *J* = 22.1 Hz, C**3**), 87.9 (d, *J* = 1.4 Hz, C**7**), 80.8 (C**6**), 48.0 (C**9**), 29.8 (C**11**), 20.6 (C**8**), 6.5 (C**12**); ^{19}F NMR ($CDCl_3$, 376 MHz): -111.87 (tt, *J* = 8.6, 5.4 Hz, F**1**); HRMS: (ESI^+) calculated for $C_{13}H_{15}FN$: 204.1183, found $[M+H]^+$: 204.1183.

***N*-(4-(Naphthalen-1-yl)but-3-yn-1-yl)cyclopropanamine (119c)**



General procedure A: 4-(naphthalen-1-yl)but-3-yn-1-yl 4-methylbenzenesulfonate (2.10 g, 6.00 mmol, prepared according to the literature procedure[257] from 1-iodonaphthalene and 3-butyn-1-ol) was employed. Flash column chromatography (30-40% EtOAc/hexane) afforded the title compound **119c** (0.70 g, 50%) as a pale yellow oil; ν_{max} / cm^{-1}: 3006 (m), 2926 (m), 2830 (m), 2222 (w), 1586 (m), 1396 (m), 1015 (m), 799 (s), 773 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.33 (d, *J* = 8.2 Hz, 1H, C**2**-H), 7.84 (d, *J* = 7.9 Hz, 1H, C**5**-H), 7.79 (d, *J* = 8.3 Hz, 1H, C**7**-H), 7.64 (d, *J* = 7.1 Hz, 1H, C**9**-H), 7.58 – 7.48 (m, 2H, C**3**-H and C**4**-H), 7.40 (t, *J* = 7.7 Hz, 1H, C**8**-H), 3.05 (t, *J* = 6.6 Hz, 2H, C**14**-H_2), 2.79 (t, *J* = 6.6 Hz, 2H, C**13**-H_2), 2.26 (tt, *J* = 6.6, 3.6 Hz, 1H, C**16**-H), 1.85 (br. s, 1H, N**15**-H), 0.52 – 0.45 (m, 2H, C**17**-H_2), 0.44 – 0.38 (m, 2H, C**17**-H_2); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 133.6, 133.3 (C**1** and C**6**), 130.3 (C**9**), 128.4 (C**5**), 128.3 (C**7**), 126.7, 126.4 (C**3** and C**4**), 126.4 (C**2**), 125.3 (C**8**), 121.5 (C**10**), 93.3 (C**12**), 79.9 (C**11**), 48.2 (C**14**), 29.9 (C**16**), 21.0 (C**13**), 6.5 (C**17**); HRMS: (ESI^+) calculated for $C_{17}H_{18}N$: 236.1434, found $[M+H]^+$: 236.1428.

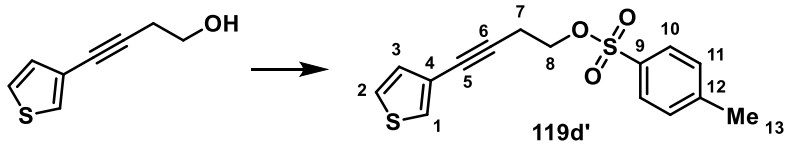
4-(Thiophen-3-yl)but-3-yn-1-ol



A solution containing but-3-yn-1-ol **120** (1.51 mL, 20 mmol) and 3-bromothiophene (2.06 mL, 22 mmol) in dry triethylamine (25 mL) was purged with argon. $Pd(PPh_3)_2Cl_2$ (280.8 mg, 0.4 mmol) and CuI (76.2 mg, 0.4 mmol) were added and the solution was heated to 60 °C for 16 h. The reaction mixture was cooled to r.t., filtered through Celite® and silica gel with DCM and concentrated *in vacuo*. The residue was purified by flash column chromatography (10-20%

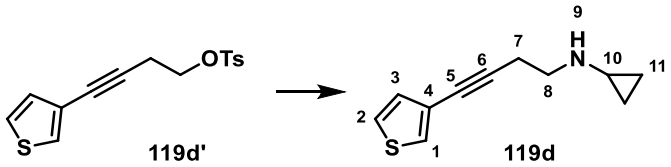
EtOAc/hexane) to afford the alcohol (2.44 g, 80%) as a yellow oil; ν_{max} / cm^{-1}: 3362 (m), 3106 (m), 2885 (m), 1668 (m), 1413 (m), 1046 (s), 782 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.39 (dd, *J* = 3.0, 1.2 Hz, 1H, C**1**-H), 7.24 (dd, *J* = 5.0, 3.0 Hz, 1H, C**2**-H), 7.08 (dd, *J* = 5.0, 1.2 Hz, 1H, C**3**-H), 3.80 (t, *J* = 6.2 Hz, 2H, C**8**-H_2), 2.67 (t, *J* = 6.2 Hz, 2H, C**7**-H_2), 1.84 (br. s, 1H, O**9**-H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 130.1 (C**3**), 128.4 (C**1**), 125.3 (C**2**), 122.4 (C**4**), 86.0 (C**6**), 77.7 (C**5**), 61.3 (C**8**), 23.9 (C**7**). The spectroscopic properties of this compound were consistent with the data available in the literature.[258]

4-(Thiophen-3-yl)but-3-yn-1-yl 4-methylbenzenesulfonate (119d')



General procedure B: 4-(Thiophen-3-yl)but-3-yn-1-ol (2.44 g, 16.03 mmol) was employed. Flash column chromatography (100% toluene) afforded the tosylate (3.12 g, 99%) as an off-white solid; m.p. 51-53 °C (DCM); ν_{max} / cm^{-1}: 2959 (w), 1356 (s), 1189 (s), 1172 (s), 973 (s), 897 (s), 782 (s), 763 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.84 – 7.79 (m, 2H, 2 × C**10**-H), 7.35 – 7.29 (m, 3H, 2 × C**11**-H and C**1**-H), 7.23 (dd, *J* = 5.0, 3.0 Hz, 1H, C**2**-H), 7.01 (dd, *J* = 5.0, 1.2 Hz, 1H, C**3**-H), 4.17 (t, *J* = 7.1 Hz, 2H, C**8**-H_2), 2.76 (t, *J* = 7.1 Hz, 2H, C**7**-H_2), 2.43 (s, 3H, C**13**-H_3); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 145.1 (C**9**), 133.0 (C**12**), 130.0, 130.0 (C**3** and C**11**), 128.7 (C**1**), 128.1 (C**10**), 125.3 (C**2**), 122.1 (C**4**), 83.5 (C**6**), 77.9 (C**5**), 67.8 (C**8**), 21.8 (C**13**), 20.5 (C**7**); HRMS: (ESI^+) calculated for $C_{15}H_{15}O_3S_2$: 307.0457, found $[M+H]^+$: 307.0452.

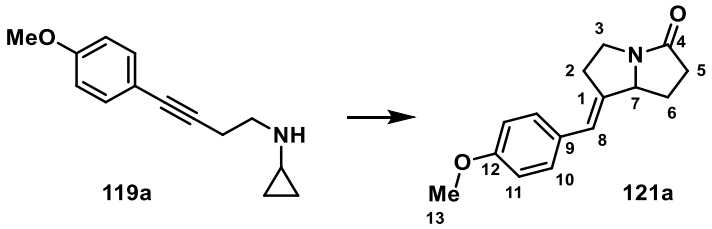
***N*-(4-(Thiophen-3-yl)but-3-yn-1-yl)cyclopropanamine (119d)**



General procedure A: 4-(Thiophen-3-yl)but-3-yn-1-yl 4-methylbenzenesulfonate **119d'** (1.53 g, 5.00 mmol) was employed. Flash column chromatography (30-40% EtOAc/ hexane) afforded the title compound **119d** (0.56 g, 58%) as a pale yellow oil; ν_{max} / cm^{-1}: 2926 (m), 1435 (m), 1346 (s), 1013 (s), 778 (s); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.36 (dd, *J* = 3.0, 1.2 Hz, 1H, C**1**-H), 7.23 (dd, *J* = 5.0, 3.0 Hz, 1H, C**2**-H), 7.08 (dd, *J* = 5.0, 1.2 Hz, 1H, C**3**-H), 2.92 (t, *J* = 6.7 Hz, 2H, C**8**-H_2),

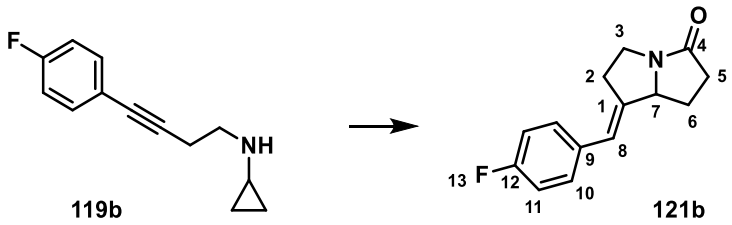
2.60 (t, *J* = 6.7 Hz, 2H, C**7**-H$_2$), 2.19 (tt, *J* = 6.6, 3.6 Hz, 1H, C**10**-H), 1.87 (br. s, 1H, N**9**-H), 0.48 – 0.42 (m, 2H, C**11**-H$_2$), 0.38 – 0.34 (m, 2H, C**11**-H$_2$); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 130.1 (C**3**), 128.0 (C**1**), 125.2 (C**2**), 122.8 (C**4**), 87.8 (C**6**), 76.8 (C**5**), 48.0 (C**8**), 29.8 (C**10**), 20.6 (C**7**), 6.5 (C**11**); HRMS: (ESI$^+$) calculated for $C_{11}H_{14}NS$: 192.0841, found $[M+H]^+$: 192.0835.

(*E*)-7-(4-Methoxybenzylidene)hexahydro-3*H*-pyrrolizin-3-one (121a)



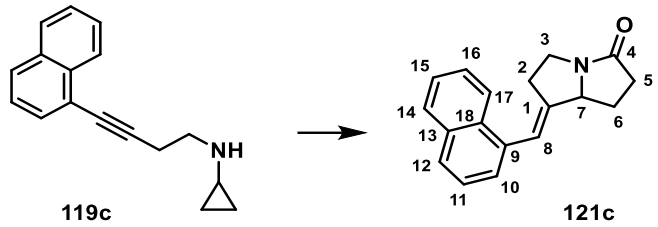
General procedure C: *N*-(4-(4-Methoxyphenyl)but-3-yn-1-yl)cyclopropanamine **119a** (32.3 mg, 0.15 mmol) and cyclohexyl isocyanate (19 μL, 0.15 mmol) were employed. Flash column chromatography (10% MeCN/DCM) afforded the title compound **121a** (27.3 mg, 75%) as a pale brown oil; ν_{max} / cm^{-1}: 2938 (w), 1699 (s), 1606 (m), 1512 (s), 1406 (m), 1249 (s), 1177 (m); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.22 (d, *J* = 8.8 Hz, 2H, 2 × C**10**-H), 6.88 (d, *J* = 8.8 Hz, 2H, 2 × C**11**-H), 6.27 (dd, *J* = 2.5, 2.5 Hz, 1H, C**8**-H), 4.55 (td, *J* = 7.6, 1.9 Hz, 1H, C**7**-H), 4.03 (ddd, *J* = 11.8, 7.4, 4.6 Hz, 1H, C**3**-H$_a$H$_b$), 3.81 (s, 3H, C**13**-H$_3$), 3.15 – 3.03 (m, 1H, C**3**-H$_a$H$_b$), 2.93 – 2.85 (m, 2H, C**2**-H$_2$), 2.73 (dddd, *J* = 16.5, 10.9, 8.9, 1.4 Hz, 1H, C**5**-H$_a$H$_b$), 2.52 (dddd, *J* = 12.5, 9.2, 7.3, 1.9 Hz, 1H, C**6**-H$_a$H$_b$), 2.42 (ddd, *J* = 16.5, 9.2, 2.0 Hz, 1H, C**5**-H$_a$H$_b$), 1.93 (dddd, *J* = 12.5, 10.9 9.5, 7.6 Hz, 1H, C**6**-H$_a$H$_b$); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 175.6 (C**4**), 158.6 (C**12**), 140.5 (C**1**), 129.9 (C**9**), 129.6 (C**10**), 121.7 (C**8**), 114.0 (C**11**), 65.0 (C**7**), 55.4 (C**13**), 41.7 (C**3**), 34.1 (C**5**), 31.7 (C**2**), 28.1 (C**6**); HRMS: (ESI$^+$) calculated for $C_{15}H_{18}NO_2$: 244.1332, found $[M+H]^+$: 244.1333. *This compound is unstable and was stored as a frozen matrix in benzene.*

(*E*)-7-(4-Fluorobenzylidene)hexahydro-3*H*-pyrrolizin-3-one (121b)



General procedure C: *N*-(4-(4-Fluorophenyl)but-3-yn-1-yl)cyclopropanamine **119b** (30.5 mg, 0.15 mmol) and cyclohexyl isocyanate (19 μL, 0.15 mmol) were employed. Flash column chromatography (10% MeCN/DCM) afforded the title compound **119b** (23.3 mg, 67%) as a pale brown oil; ν_{max} / cm^{-1}: 2932 (w), 1691 (s), 1601 (m), 1508 (s), 1407 (m), 1224 (s), 1159 (m), 832 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.23 (dd, *J* = 8.5, 5.0 Hz, 3H, 2 × C**10**-H), 7.07 – 6.99 (m, 2H, 2 × C**11**-H), 6.29 (d, *J* = 2.7 Hz, 1H, C**8**-H), 4.55 (t, *J* = 7.6 Hz, 1H, C**7**-H), 4.04 (ddd, *J* = 11.8, 7.0, 4.8 Hz, 1H, C**3**-H_aH_b), 3.15 – 3.03 (m, 1H, C**3**-H_aH_b), 2.91 – 2.83 (m, 2H, C**2**-H_2), 2.73 (ddd, *J* = 16.5, 9.9, 9.5 Hz, 1H, C**5**-H_aH_b), 2.58 – 2.47 (m, 1H, C**6**-H_aH_b), 2.42 (ddd, *J* = 16.5, 9.4, 1.9 Hz, 1H, C**5**-H_aH_b), 1.99 – 1.86 (m, 1H, C**6**-H_aH_b); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 175.6 (C**4**), 161.70 (d, *J* = 247.3 Hz, C**12**), 142.6 (C**1**), 133.2 (d, *J* = 3.2 Hz, C**9**), 129.9 (d, *J* = 8.0 Hz, C**10**), 121.2 (C**8**), 115.5 (d, *J* = 21.5 Hz, C**11**), 64.9 (C**7**), 41.7 (C**3**), 34.0 (C**5**), 31.7 (C**2**), 28.0 (C**6**); ^{19}F NMR ($CDCl_3$, 376 MHz): -114.54 (tt, *J* = 8.6, 5.5 Hz, F**13**); HRMS: (ESI^+) calculated for $C_{14}H_{15}NOF$: 232.1132, found $[M+H]^+$: 232.1132.

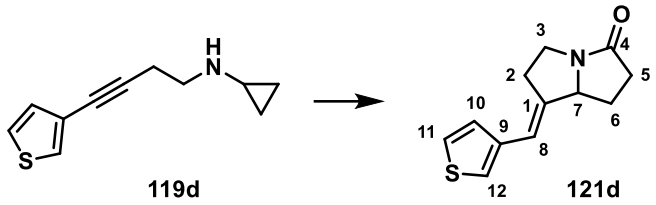
(*E*)-7-(Naphthalen-1-ylmethylene)hexahydro-3*H*-pyrrolizin-3-one (121c)



General procedure C: *N*-(4-(Naphthalen-1-yl)but-3-yn-1-yl)cyclopropanamine **119c** (35.3 mg, 0.15 mmol) and cyclohexyl isocyanate (19 μL, 0.15 mmol) were employed. Flash column chromatography (10% MeCN/DCM) afforded the title compound **121c** (21.3 mg, 54%) as a pale brown oil; ν_{max} / cm^{-1}: 2928 (w), 1692 (s), 1412 (m), 1395 (m), 1280 (m), 783 (s); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.97 – 7.94 (m, 1H, C**12**-H), 7.89 – 7.85 (m, 1H, Ar-H), 7.78 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.55 – 7.43 (m, 3H, Ar-H), 7.39 – 7.35 (m, 1H, Ar-H), 6.93 (d, *J* = 2.5 Hz, 1H, C**8**-H), 4.69 (td, *J* = 7.6, 1.9 Hz, 1H, C**7**-H), 3.94 (dt, *J* = 12.1, 6.2, 6.0 Hz, 1H, C**3**-H_2), 3.13 – 3.05 (m, 1H, C**3**-H_2), 2.86 – 2.75 (m, 3H, C**2**-H_2 and C**5**-H_aH_b), 2.65 (dddd, *J* = 12.5, 9.0, 7.3, 1.8 Hz, 1H, C**6**-

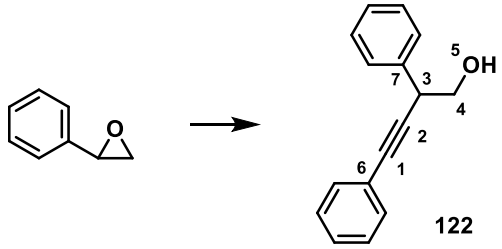
H$_2$), 2.51 (ddd, *J* = 16.5, 9.4, 1.8 Hz, 1H, C**5**-H$_a$H$_b$), 2.11 (dddd, *J* = 12.5, 11.3, 9.4, 7.9 Hz, 1H, C**6**-H$_2$); ^{13}C NMR (CDCl$_3$, 126 MHz): δ 175.7 (C**4**), 145.1, 134.1, 133.7, 131.7, 128.8, 127.9, 126.2, 126.1, 126.0, 126.0, 125.4 (3 × Ar-C, 7 × Ar-CH and C**1**), 124.3 (C**8**), 64.6 (C**7**), 41.6 (C**3**), 34.3 (C**5**), 31.5 (C**2**), 28.3 (C**6**); HRMS: (ESI$^+$) calculated for $C_{18}H_{18}NO$: 264.1383, found [M+H]$^+$: 264.1385. *This compound is unstable and was stored as a frozen matrix in benzene.*

(*E*)-7-(Thiophen-3-ylmethylene)hexahydro-3H-pyrrolizin-3-one (121d)



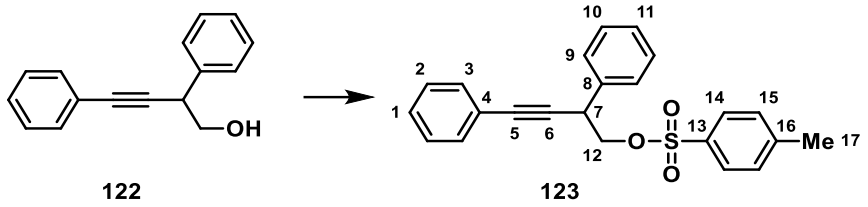
General procedure C: *N*-(4-(thiophen-3-yl)but-3-yn-1-yl)cyclopropanamine **119d** (28.7 mg, 0.15 mmol) and cyclohexyl isocyanate (19 μL, 0.15 mmol) were employed. Flash column chromatography (10% MeCN/DCM) afforded the title compound **121d** (21.7 mg, 66%) as a colourless oil; ν_{max} / cm^{-1}: 2931 (w), 1684 (s), 1415 (m), 1279 (m), 777 (m), 637 (m); ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.31 (dd, *J* = 5.0, 2.9 Hz, 1H, C**11**-H), 7.15 – 7.12 (m, 1H, C**12**-H), 7.10 (dd, *J* = 5.0, 1.3 Hz, 1H, C**10**-H), 6.39 – 6.35 (m, 1H, C**8**-H), 4.55 (td, *J* = 7.6, 2.1 Hz, 1H, C**7**-H), 4.08 (ddd, *J* = 11.9, 7.1, 4.9 Hz, 1H, C**3**-H$_a$H$_b$), 3.17 – 3.08 (m, 1H, C**3**-H$_a$H$_b$), 2.93 – 2.85 (ddt, *J* = 8.3, 4.7, 2.3 Hz, 2H, C**2**-H$_2$), 2.74 (dddd, *J* = 16.4, 10.7, 9.0, 1.5 Hz, 1H, C**5**-H$_a$H$_b$), 2.53 (dddd, *J* = 12.4, 9.0, 7.4, 2.1 Hz, 1H, C**6**-H$_a$H$_b$), 2.42 (ddd, *J* = 16.4, 9.4, 2.1 Hz, 1H, C**5**-H$_a$H$_b$), 1.93 (dddd, *J* = 12.4, 10.8, 9.4, 7.6 Hz, 1H, C**6**-H$_a$H$_b$); ^{13}C NMR (CDCl$_3$, 101 MHz): δ 175.5 (C**4**), 141.9 (C**1**), 138.7 (C**9**), 127.9 (C**10**), 125.7 (C**11**), 122.7 (C**12**), 116.4 (C**8**), 64.7 (C**7**), 41.6 (C**3**), 34.0 (C**5**), 32.1 (C**2**), 27.9 (C**6**); HRMS: (ESI$^+$) calculated for $C_{12}H_{14}NOS$: 220.0791, found [M+H]$^+$: 220.0780.

2,4-Diphenylbut-3-yn-1-ol (122)



This compound was prepared according to the modified literature procedure.[106] To a solution of $Ti(O^iPr)_4$ (7.76 mL, 30.0 mmol) in dry hexane (40 mL) under a nitrogen atmosphere, $TiCl_4$ (1.10 mL, 10.0 mmol) was added dropwise at room temperature and the solution was stirred for 1 h, allowing the exothermic formation of $ClTi(O^iPr)_3$. In a separate flame-dried flask, *n*-BuLi (25.16 mL, 40.0 mmol, 1.59 M in hexanes) was added dropwise to a solution of phenylacetylene (4.39 mL, 40.0 mmol) in dry THF (20 mL) at 0 °C and the solution was stirred for 30 min. The solution was concentrated *in vacuo* at 0 °C, redissolved in dry THF (40 mL), and cooled down to -41 °C (acetonitrile/dry ice bath). A solution of triisopropyloxytitanium chloride (40.0 mmol in 40 mL of hexanes) was added *via* syringe. After 30 min, styrene oxide (2.28 mL, 20.0 mmol) was slowly added dropwise at -41 °C. The solution was warmed to room temperature and stirred for 15 h. 2.0 M aq. HCl (150 mL) was added and the solution was extracted with Et_2O (3 × 75 mL). The organic extracts were combined, washed with brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (10% EtOAc/hexane) to afford the title compound **122** (3.07 g, 69%) as a brown oil; ν_{max} / cm^{-1}: 3371 (br. m), 1598 (m), 1490 (s), 1453 (m), 1058 (s), 755 (s), 692 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.50 – 7.45 (m, 4H, 4 × Ar-H), 7.41 – 7.35 (m, 2H, 2 × Ar-H), 7.34 – 7.30 (m, 4H, 4 × Ar-H), 4.10 (t, *J* = 6.8 Hz, 1H, C**3**-H), 3.86 (t, *J* = 6.9 Hz, 2H, C**4**-H_2), 1.92 (t, *J* = 7.0 Hz, 1H, O**5**-H); ^{13}C NMR ($CDCl_3$,101 MHz): δ 138.1 (C**7**), 131.9 (Ar-CH), 128.9 (Ar-CH), 128.4 (Ar-CH), 128.3 (Ar-CH), 128.1 (Ar-CH), 127.6 (Ar-CH), 123.2 (C**6**), 88.3 (C**2**), 85.0 (C**1**), 67.9 (C**4**), 42.2 (C**3**). The spectroscopic properties of this compound were consistent with the data available in the literature.[259]

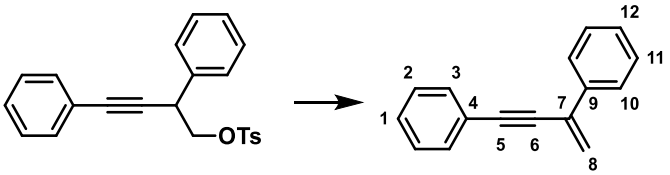
2,4-Diphenylbut-3-yn-1-yl 4-methylbenzenesulfonate (123)



122 123

General procedure B: 2,4-Diphenylbut-3-yn-1-ol **122** (3.00 g, 13.50 mmol) was employed. Flash column chromatography (100% toluene) afforded the title compound **123** (3.33 g, 66%) as an orange oil; ν_{max} / cm^{-1}: 1491 (m), 1361 (s), 1189 (s), 1175 (s), 971 (s), 757 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.70 (d, *J* = 8.1 Hz, 2H, 2 × C**14**-H), 7.44 – 7.22 (m, 12H, 2 × C**2**-H, 2 × C**3**-H, 2 × C**9**-H, 2 × C**10**-H, 2 × C**15**-H, C**1**-H and C**11**-H), 4.34 – 4.15 (m, 3H, C**7**-H and C**12**-H_2), 2.42 (s, 3H, C**17**-H_3); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 144.8 (C**13**), 136.6, 133.0 (C**8** and C**16**), 131.9, 129.9, 128.9, 128.4, 128.4, 128.2, 128.0, 128.0 (14 × **Ar**-CH), 122.9 (C**4**), 86.5 (C**6**), 85.0 (C**5**), 72.9 (C**12**), 38.6 (C**7**), 21.8 (C**17**); HRMS: (MALDI) calculated for $C_{23}H_{20}NaO_3S$: 399.1025, found $[M+Na]^+$: 399.1019.

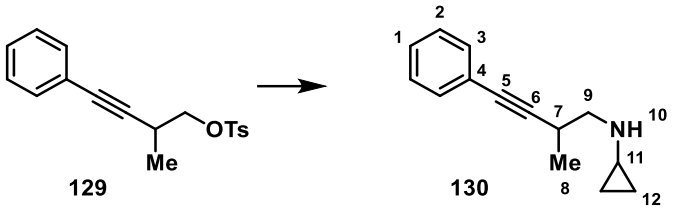
But-3-en-1-yne-1,3-diyldibenzene (125)



123 125

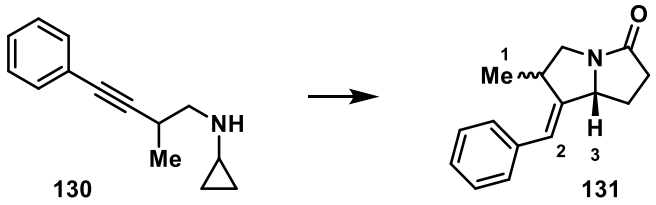
General procedure A: 2,4-Diphenylbut-3-yn-1-yl 4-methylbenzenesulfonate **123** (1.00 g, 2.66 mmol) was employed. Flash column chromatography (0-20% EtOAc/hexane) afforded the side product **125** (0.13 g, 24%) as a yellow oil; ν_{max} / cm^{-1}: 3056 (w), 2198 (w), 1597 (m), 1490 (s), 1443 (m), 908 (m), 754 (s), 690 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.78 – 7.73 (m, 2 × **Ar**-CH), 7.59 – 7.54 (m, 2 × **Ar**-CH), 7.44 – 7.33 (m, 6 × **Ar**-CH), 6.01 (d, *J* = 1.2 Hz, C**8**-H_aH_b), 5.79 (d, *J* = 1.2 Hz, C**8**-H_aH_b); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 137.4 (C**7**), 131.8 (C**3**), 130.7 (C**9**), 128.6, 128.5, 126.2 (C**2**, C**10** and C**11**), 128.1, 128.0 (C**1** and C**12**), 123.2 (C**4**), 120.8 (C**8**), 90.9 (C**5**), 88.7 (C**6**). The spectroscopic properties of this compound were consistent with the data available in the literature.[260]

***N*-(2-Methyl-4-phenylbut-3-yn-1-yl)cyclopropanamine (130)**



General procedure A: 2-Methyl-4-phenylbut-3-yn-1-yl 4-methylbenzenesulfonate **129** (0.50 g, 1.59 mmol, prepared according to the **General procedure B** from the corresponding alcohol, prepared according to the literature procedure[261] from phenyl acetylene) was employed. Flash column chromatography (40% EtOAc/hexane) afforded the title compound **130** (102.4 mg, 32%) as a pale yellow oil; ν_{max} / cm^{-1}: 2968 (m), 2932 (m), 2226 (w), 1490 (m), 1442 (m), 1371 (m), 1343 (m), 1014 (m), 755 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.43 – 7.39 (m, 2H, 2 × C**3**-H), 7.31 – 7.25 (m, 3H, C**1**-H and 2 × C**2**-H), 2.92 (q, *J* = 6.9 Hz, 1H, C**7**-H), 2.78 (d, *J* = 6.9 Hz, 2H, C**9**-H_2), 2.23 – 2.17 (m, 1H, C**11**-H), 1.88 (br. s, 1H, N**10**-H), 1.25 (d, *J* = 6 .9 Hz, 3H, C**8**-H_3), 0.48 – 0.42 (m, 2H, C**12**-H_2), 0.40 – 0.35 (m, 2H, C**12**-H_2); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 131.8 (C**3**), 128.3 (C**2**), 127.8 (C**1**), 123.8 (C**4**), 93.0 (C**6**), 81.8 (C**5**), 55.2 (C**7**), 29.9 (C**11**), 27.2 (C**9**), 18.9 (C**8**), 6.7 (C**12**), 6.4 (C**12**); HRMS: (ESI^+) calculated for $C_{14}H_{18}N$: 200.1434, found $[M+H]^+$: 200.1429.

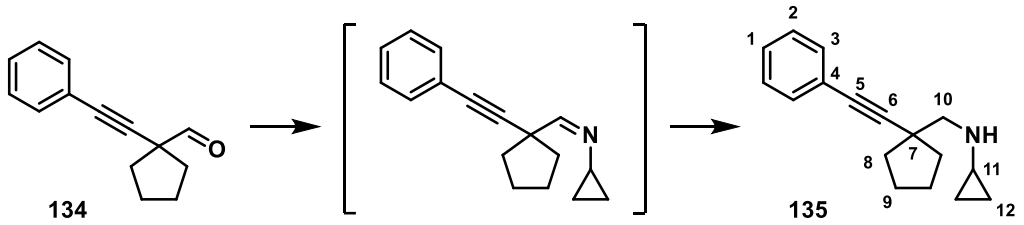
7-((*E*)-Benzylidene)-6-methylhexahydro-3*H*-pyrrolizin-3-one (131)



General procedure C: *N*-(2-methyl-4-phenylbut-3-yn-1-yl)cyclopropanamine **130** (29.9 mg, 0.15 mmol) and cyclohexyl isocyanate (19 μL, 0.15 mmol) were employed. An *in situ* yield (79%) was obtained by using 1,4-dinitrobenzene as an internal standard for ^{1}H NMR spectroscopy.

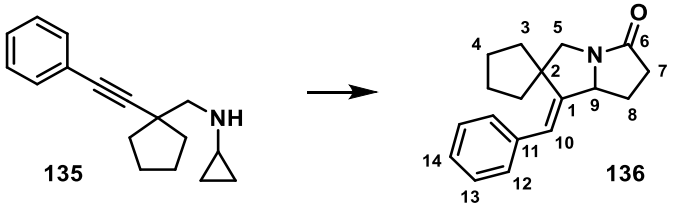
^{1}H NMR ($CDCl_3$, 400 MHz, *characteristic signals only, mixture of diastereomers A:B = 1:0.65*): δ 6.28 (s, 1H, C**2**-H, *B*), 6.21 (s, 1H, C**2**-H, *A*), 4.58 (t, *J* = 7.3 Hz, 1H, C**3**-H, *A*), 4.53 (td, *J* = 8.0, 1.7 Hz, 1H, C**3**-H, *B*), 1.16 (d, *J* = 7.0 Hz, 3H, C**1**-H_3, *A*), 1.09 (d, *J* = 7.1 Hz, 3H, C**1**-H_3, *B*).

***N*-((1-(Phenylethynyl)cyclopentyl)methyl)cyclopropanamine (135)**



A solution of 1-(phenylethynyl)cyclopentane-1-carbaldehyde **134** (0.26 g, 1.31 mmol, prepared according to the literature procedure[262]), cyclopropylamine (0.18 mL, 2.63 mmol) and $MgSO_4$ (0.63 g, 5.26 mmol) in DCM (5 mL) was stirred at r.t. for 16 h. The resulting slurry was filtered, rinsed with DCM (2 × 5 mL) and concentrated *in vacuo*. The imine was redissolved in MeOH (10 mL), cooled to 0°C and then $NaBH_4$ (74.3 mg, 1.97 mmol) was added at once. The reaction was warmed up to r.t., concentrated *in vacuo*, water (20 mL) was added and the solution was extracted with DCM (3 × 10 mL). The organic extracts were combined, washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Flash column chromatography (0-10% EtOAc/hexane) afforded the title compound **135** (206.7 mg, 66% over two steps) as a colourless oil; ν_{max} / cm^{-1}: 2954 (m), 1491 (m), 1442 (m), 1014 (m), 754 (s), 691 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.41 – 7.36 (m, 2H, 2 × C**3**-H), 7.31 – 7.24 (m, 3H, 2 × C**2**-H and C**1**-H), 2.76 (s, 2H, C**10**-H_2), 2.23 (tt, *J* = 6.6, 3.6 Hz, 1H, C**11**-H), 2.01 – 1.63 (m, 8H, 2 × C**8**-H_2 and 2 × C**9**-H_2), 0.47 – 0.32 (m, 4H, 2 × C**12**-H_2); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 131.7 (C**3**), 128.3 (C**2**), 127.6 (C**1**), 124.1 (C**4**), 96.4 (C**6**), 81.5 (C**5**), 58.5 (C**10**), 44.1 (C**7**), 38.9 (C**8**), 31.0 (C**11**), 24.8 (C**9**), 6.7 (C**12**); HRMS: (ESI^+) calculated for $C_{17}H_{22}N$: 240.1747, found $[M+H]^+$: 240.1738.

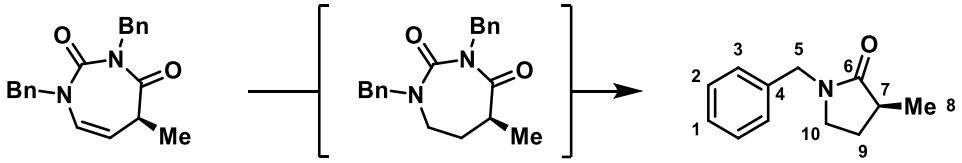
(*E*)-1'-Benzylidenetetrahydro-3'*H*,5'*H*-spiro[cyclopentane-1,2'-pyrrolizin]-5'-one (136)



General procedure C: Amine **135** (35.9 mg, 0.15 mmol) was employed and the residue was purified by flash column chromatography (10-20% MeCN/DCM) to yield the title compound **136** (29.8 mg, 74%) as a colourless oil; ν_{max} / cm^{-1}: 2939 (m), 2870 (m), 1690 (s), 1448 (m), 1401 (s), 1281 (m), 1247 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.34 – 7.27 (m, 2H, 2 × C**12**-H), 7.26 – 7.16 (m, 3H, C**14**-H and 2 × C**13**-H), 6.44 (s, 1H, C**10**-H), 4.59 (td, *J* = 7.9, 2.0 Hz, 1H, C**9**-H), 3.80 (d, *J* = 11.2 Hz, 1H, C**5**-H_aH_b), 2.72 (d, *J* = 11.2 Hz, 1H, C**5**-H_aH_b), 2.78 – 2.65 (m, 1H, C**7**-H_aH_b),

2.57 – 2.48 (m, 1H, C**8**-$\underline{H}_aH_b$), 2.44 (ddd, *J* = 16.2, 9.1, 1.4 Hz, 1H, C**7**-$H_a\underline{H}_b$), 1.98 – 1.81 (m, 2H, C**8**-$H_a\underline{H}_b$ and C**3**-$\underline{H}_aH_b$), 1.76 – 1.65 (m, 3H, C**3'**-$\underline{H}_2$ and C**4**-$\underline{H}_aH_b$), 1.63 – 1.35 (m, 3H, C**4'**-$\underline{H}_2$ and C**4**-$H_a\underline{H}_b$), 1.32 – 1.21 (m, 1H, C**3**-$H_a\underline{H}_b$); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 176.2 (C**6**), 151.5 (C**1**), 137.1 (C**11**), 129.0 (C**13**), 128.1 (C**12**), 127.0 (C**14**), 122.6 (C**10**), 66.4 (C**9**), 57.2 (C**5**), 55.8 (C**2**), 40.8 (C**3'**), 34.0 (C**3**), 33.6 (C**7**), 30.1 (C**8**), 25.5 (C**4'**), 25.4 (C**4**); HRMS: (ESI^+) calculated for $C_{18}H_{22}NO$: 268.1696, found $[M+H]^+$: 268.1698.

(*S*)-1-Benzyl-3-methylpyrrolidin-2-one (145)



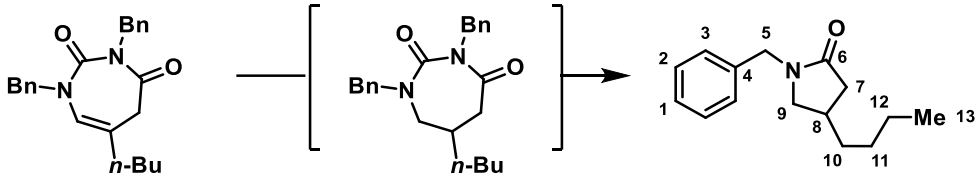
144 **145**

A solution of (*S*)-1,3-dibenzyl-6-methyl-3,6-dihydro-1*H*-1,3-diazepine-2,7-dione **144** (10 mg, 0.03 mmol, prepared according to the literature procedure[53]) in MeOH (2 mL) was added to Pd on carbon (10 mg, 10% w/w) under nitrogen. The reaction was stirred at r.t. under 1 atm of H_2 for 3 h and then filtered through Celite® and concentrated *in vacuo*. The crude was redissolved in 1,2-DCB (0.5 mL), stirred at 160 °C for 65 h and concentrated *in vacuo*. The residue was purified by flash column chromatography (50% EtOAc/hexane) to afford lactam **145** (5.6 mg, 95%) as a colourless oil; ν_{max} / cm^{-1}: 2929 (m), 2871 (m), 1683 (s), 1454 (m), 1358 (s), 740 (s), 713 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.34 – 7.20 (m, 5H, 2 × C**2**-$\underline{H}$, 2 × C**3**-$\underline{H}$ and C**1**-$\underline{H}$), 4.45 (d, *J* = 14.7 Hz, 1H, C**5**-$\underline{H}_aH_b$), 4.40 (d, *J* = 14.7 Hz, 1H, C**5**-$H_a\underline{H}_b$), 3.19 – 3.12 (m, 2H, C**10**-$\underline{H}_2$), 2.55 – 2.44 (m, 1H, C**7**-$\underline{H}$), 2.19 (dddd, *J* = 12.9, 8.7, 6.2, 4.7 Hz, 1H, C**9**-$\underline{H}_aH_b$), 1.64 – 1.51 (m, 1H, C**9**-$H_a\underline{H}_b$), 1.22 (d, *J* = 7.1 Hz, 3H, C**8**-$\underline{H}_3$); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 177.5 (C**6**), 136.8 (C**4**), 128.8, 128.2, 127.6 (C**1**, C**2** and C**3**), 46.9 (C**5**), 44.8 (C**10**), 36.9 (C**7**), 27.2 (C**9**), 16.6 (C**8**). The spectroscopic properties of this compound were consistent with the data available in the literature.[263]

The enantiopurity of this compound was determined by chiral SFC against a racemic standard (prepared as described above from 1,3-dibenzyl-6-methyl-3,6-dihydro-1*H*-1,3-diazepine-2,7-dione, prepared according to the literature procedure[53]).

Chiral SFC: (DAICEL CHIRALPAK-IA column (25 cm), CO_2:MeOH 92:8, 2 mL/min, 140 bars, 40 °C). Retention times: major diastereomer – 3.6 minutes (major), 4.0 minutes (minor), e.r. = 98:2.

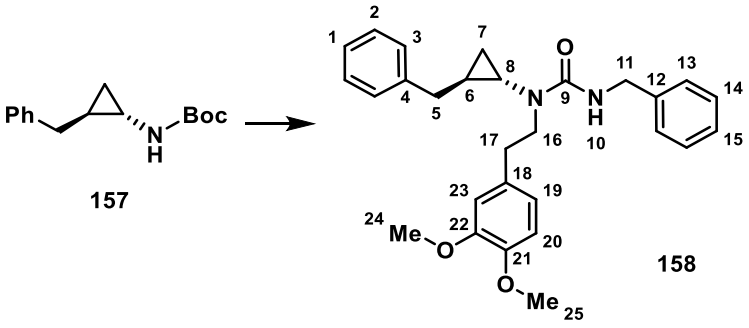
1-Benzyl-4-butylpyrrolidin-2-one (148)



147 148

A solution of 1,3-dibenzyl-5-butyl-3,6-dihydro-1*H*-1,3-diazepine-2,7-dione **147** (10 mg, 0.03 mmol, prepared according to the literature procedure[53]) in MeOH (2 mL) was added to Pd on carbon (10 mg, 10% w/w) under nitrogen. The reaction was stirred at r.t. under 1 atm of H_2 for 24 h and then filtered through Celite® and concentrated *in vacuo*. This was repeated two more times and then the crude was redissolved in 1,2-DCB (0.5 mL), stirred at 160 °C for 65 h and concentrated *in vacuo*. The residue was purified by flash column chromatography (50% EtOAc/hexane) to afford lactam **148** (4.0 mg, 63%) as a pale yellow oil; ν_{max} / cm^{-1}: 2925 (m), 1690 (s), 1425 (m), 1268 (m), 701 (m); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.35 – 7.21 (m, 5H, 2 × C**2**-H, 2 × C**3**-H and C**1**-H), 4.47 (d, *J* = 14.7 Hz, 1H, C**5**-H_aH_b), 4.41 (d, *J* = 14.7 Hz, 1H, C**5**-H_aH_b), 3.33 (dd, *J* = 9.7, 8.0 Hz, 1H, C**9**-H_aH_b), 2.87 (dd, *J* = 9.7, 6.7 Hz, 1H, C**9**-H_aH_b), 2.57 (dd, *J* = 16.6, 8.7 Hz, 1H, C**7**-H_aH_b), 2.32 – 2.2 (m, 1H, C**8**-H), 2.12 (dd, *J* = 16.6, 7.9 Hz, 1H, C**7**-H_aH_b), 1.44 – 1.34 (m, 2H, C**10**-H_2), 1.31 – 1.17 (m, 4H, C**11**-H_2 and C**12**-H_2), 0.87 (t, *J* = 7.1 Hz, 3H, C**13**-H_3); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 174.7 (C**6**), 136.8 (C**4**), 128.8, 128.3 (C**2** and C**3**), 127.7 (C**1**), 52.6 (C**9**), 46.6 (C**5**), 37.9 (C**7**), 34.6 (C**10**), 31.9 (C**8**), 29.7 (C**11**), 22.8 (C**12**), 14.1 (C**13**); HRMS: (ESI^+) calculated for $C_{15}H_{22}NO$: 232.1696, found $[M+H]^+$: 232.1687.

3-Benzyl-1-((1*S,2*S**)-2-benzylcyclopropyl)-1-(3,4-dimethoxyphenethyl)urea (158)**

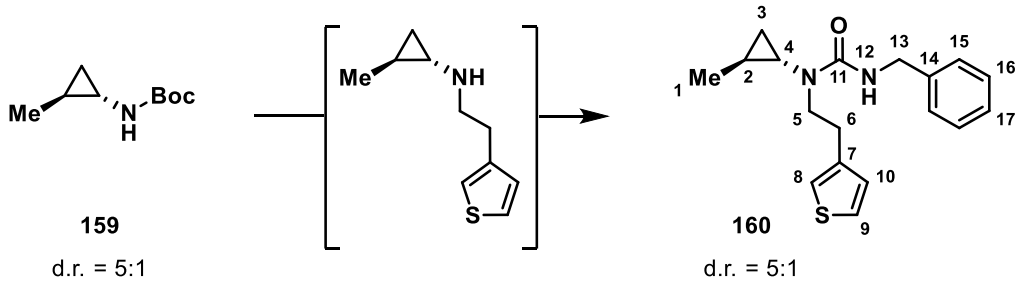


157 158

To a solution of the Boc-protected cyclopropylamine **157** (1.20 g, 4.85 mmol, prepared according to the literature procedure[46]) in DCM (5 mL) was added trifluoroacetic acid (3.72 mL, 48.52 mmol) and the reaction was stirred at r.t. for 3 h. The reaction mixture was concentrated *in vacuo*, water (15 mL) was added and the solution was extracted with DCM (15 mL). The aqueous portion was

adjusted to pH 12 by addition of 2.0 M aq. NaOH and then extracted with DCM (3 × 10 mL). The organic extracts were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was dissolved in MeCN (10 mL) and transferred to a sealed tube. K_2CO_3 (1.01 g, 7.28 mmol) and a solution of 3,4-dimethoxyphenethyl 4-methylbenzenesulfonate (1.63 g, 4.85 mmol, prepared according to the literature procedure[50]) in MeCN (2 mL) were added. The tube was sealed and the reaction was heated to 90 °C for 18 h. The reaction was cooled to r.t. and concentrated *in vacuo*. The residue was dissolved in DCM (20 mL), washed with water (30 mL) and the aqueous portion was further extracted with DCM (2 × 20 mL). The organic extracts were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was dissolved in dry DCM (10 mL) and cooled down to 0 °C. Triethylamine (0.60 mL, 4.85 mmol) and benzyl isocyanate (0.68 mL, 4.85 mmol) were added at 0 °C, the reaction mixture was warmed to r.t. and stirred for 18 h. The solution was diluted with DCM (10 mL) and washed with water (20 mL), aq. 1.0 M HCl (20 mL), sat. aq. $NaHCO_3$ (20 mL) and brine (20 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (30% EtOAc/hexane) to afford the title compound **158** (0.43 g, 20% over 3 steps) as a colourless oil; ν_{max} / cm^{-1}: 3441 (w), 2933 (w), 1651 (m), 1511 (s), 1453 (m), 1261 (s), 1235 (s), 1028 (s), 699 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.32 – 7.10 (m, 10H, 2 × C**2**-H, 2 × C**3**-H, 2 × C**13**-H, 2 × C**14**-H, C**1**-H and C**15**-H), 6.77 (d, *J* = 8.1 Hz, 1H, C**20**-H), 6.69 (d, *J* = 1.9 Hz, 1H, C**23**-H), 6.64 (dd, *J* = 8.1, 2.0 Hz, 1H, C**19**-H), 5.07 (br. t, *J* = 5.9 Hz, 1H, N**10**-H), 4.14 (dd, *J* = 15.1, 6.0 Hz, 1H, C**11**-H_aH_b), 4.07 (dd, *J* = 15.1, 6.0 Hz, 1H, C**11**-H_aH_b), 3.86 (s, 3H, C**24**-H_3 or C**25**-H_3), 3.82 (s, 3H, C**24**-H_3 or C**25**-H_3), 3.54 (ddd, *J* = 13.6, 9.0, 6.2 Hz, 1H, C**16**-H_aH_b), 3.35 (ddd, *J* = 13.6, 9.0, 6.2 Hz, 1H, C**16**-H_aH_b), 2.93 – 2.85 (m, 1H, C**17**-H_aH_b), 2.80 – 2.65 (m, 2H, C**5**-H_2), 2.27 – 2.23 (m, 1H, C**6**-H), 2.16 (dd, *J* = 14.3, 9.0 Hz, 1H, C**17**-H_aH_b), 1.37 – 1.27 (m, 1H, C**8**-H), 0.88 (ddd, *J* = 9.2, 5.1, 3.7 Hz, 1H, C**7**-H_aH_b), 0.77 – 0.70 (m, 1H, C**7**-H_aH_b); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 158.5 (C**9**), 148.9 (C**22**), 147.5 (C**21**), 140.1, 140.0 (C**4** and C**12**), 132.5 (C**18**), 129.1, 128.6, 128.5, 127.3 (C**2**, C**3**, C**13** and C**14**), 127.0, 126.9 (C**1** and C**15**), 120.9 (C**19**), 112.3 (C**23**), 111.2 (C**20**), 56.0, 56.0 (C**24** and C**25**), 49.2 (C**16**), 44.3 (C**11**), 38.7 (C**17**), 34.4, 34.4 (C**5** and C**6**), 24.4 (C**8**), 15.7 (C**7**); HRMS: (ESI^+) calculated for $C_{28}H_{33}N_2O_3$: 445.2486, found $[M+H]^+$: 445.2478.

3-Benzyl-1-((1*S,2*S**)-2-methylcyclopropyl)-1-(2-(thiophen-3-yl)ethyl)urea (160)**



*Starting cyclopropylamine **159** and 2-(thiophen-3-yl)ethyl 4-methylbenzenesulfonate were synthesised by Christodoulou.* To a solution of the Boc-protected cyclopropylamine **159** (0.34 g, 2.00 mmol, prepared according to the literature procedure[53]) in DCM (2 mL) was added trifluoroacetic acid (1.53 mL, 20.00 mmol) and the reaction was stirred at r.t. for 3 h. The reaction mixture was concentrated *in vacuo*, water (15 mL) was added and the solution was extracted with DCM (15 mL). The aqueous portion was adjusted to pH 12 by addition of 2.0 M aq. NaOH and then extracted with DCM (3 × 10 mL). The organic extracts were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was dissolved in MeCN (7 mL) and transferred to a sealed tube. K_2CO_3 (0.41 g, 3.00 mmol) and a solution of 2-(thiophen-3-yl)ethyl 4-methylbenzenesulfonate (0.56 g, 2.00 mmol, prepared according to the literature procedure[53]) in MeCN (2 mL) were added. The tube was sealed and the reaction was heated to 90 °C for 18 h. The reaction was cooled to r.t. and concentrated *in vacuo*. The residue was dissolved in DCM (20 mL), washed with water (30 mL) and the aqueous portion was further extracted with DCM (2 × 20 mL). The organic extracts were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was dissolved in dry DCM (5 mL) and cooled down to 0 °C. Triethylamine (0.28 mL, 2.00 mmol) and benzyl isocyanate (0.25 mL, 2.00 mmol) were added at 0 °C, the reaction mixture was warmed to r.t. and stirred for 18 h. The solution was diluted with DCM (10 mL) and washed with water (10 mL), aq. 1.0 M HCl (10 mL), sat. aq. $NaHCO_3$ (10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (30-40% EtOAc/hexane) to afford the title compound **160** (0.29 g, 43% over 3 steps, d.r. = 5:1) as a colourless oil.

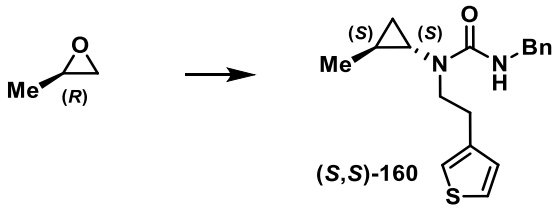
Data for the mixture of compounds: ν_{max} / cm^{-1}: 2952 (w), 1643 (s), 1509 (s), 1452 (m), 1285 (s), 728 (s), 698 (s); HRMS: (ESI^+) calculated for $C_{18}H_{23}N_2OS$: 315.1526, found $[M+H]^+$: 315.1518.

Data for the major *trans*-diastereomer: ^1H NMR ($CDCl_3$, 400 MHz): δ 7.35 – 7.20 (m, 6H, 2 × C**15**-H, 2 × C**16**-H, C**17**-H and C**9**-H), 7.01 – 6.96 (m, 2H, C**8**-H and C**10**-H), 5.37 (t, *J* = 5.8 Hz, 1H, N**12**-H), 4.48 – 4.43 (m, 2H, C**13**-H_2), 3.62 (ddd, *J* = 14.4, 8.0, 6.6 Hz, 1H, C**5**-H_aH_b), 3.52 (ddd, *J* = 14.4, 8.0, 6.6 Hz, 1H, C**5**-H_aH_b), 2.94 – 2.88 (m, 2H, C**6**-H_2), 2.01 – 1.94 (m, 1H, C**4**-

H), 1.02 – 0.93 (m, 4H, C**2**-H and C**1**-H$_3$), 0.80 – 0.73 (m, 1H, C**3**-H$_a$H$_b$), 0.55 – 0.48 (m, 1H, C**3**-H$_a$H$_b$); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 158.5 (C**11**), 140.0 (C**7**), 139.7 (C**14**), 128.6 (C**10**), 128.5, 127.3, 127.1, 125.3 (C**9**, C**15**, C**16** and C**17**), 121.1 (C**8**), 47.7 (C**5**), 44.6 (C**13**), 35.4 (C**4**), 29.0 (C**6**), 16.9, 16.8, 16.4 (C**1**, C**2** and C**3**).

Data for the minor *cis*-diastereomer: *Characteristic signals only*: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.46 (t, *J* = 6.0 Hz, 1H, N**12**-H), 3.87 (ddd, *J* = 14.0, 9.1, 6.6 Hz, 1H, C**5**-H$_a$H$_b$), 3.35 (ddd, *J* = 14.0, 8.9, 5.7 Hz, 1H, C**5**-H$_a$H$_b$), 2.38 – 2.32 (m, 1H, C**4**-H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 159.1 (C**11**).

3-Benzyl-1-((1*S*,2*S*)-2-methylcyclopropyl)-1-(2-(thiophen-3-yl)ethyl)urea ((*S*,*S*)-160)

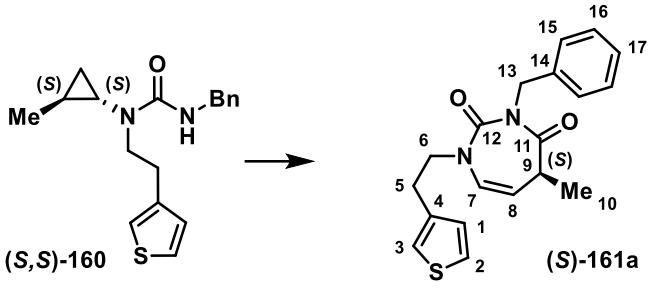


*Cyclopropylamine **(S,S)-160** was synthesised by Christodoulou.* Enantioenriched substrate **(*S*,*S*)-160** (97:3 e.r.) was synthesised starting from commercially available (*R*)-propylene oxide according to the literature procedure in a similar to **160** way.[53,110]

$[\alpha]_D^{23.7}$ = +39.4 (c = 0.22, $CHCl_3$).

The enantiopurity of this compound was determined by chiral SFC analysis against a racemic standard. Chiral SFC: DAICEL CHIRALPAK-IA column (25 cm), CO_2:MeOH 88:12, 2 mL/min, 140 bars, 40 °C. Retention times: 7.4 minutes (minor), 8.0 minutes (major), e.r. = 97:3.

(*S*)-1-Benzyl-6-methyl-3-(2-(thiophen-3-yl)ethyl)-3,6-dihydro-1*H*-1,3-diazepine-2,7-dione ((*S*)-161a)

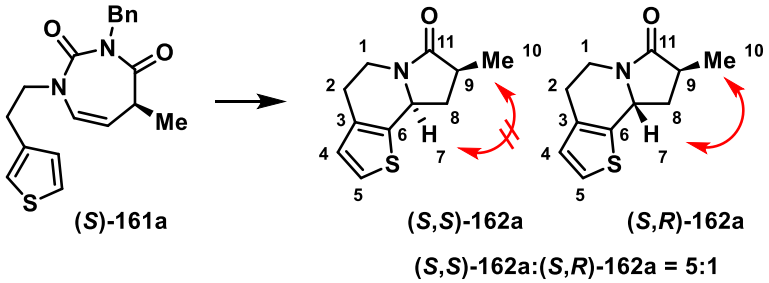


An oven dried reaction tube, fitted with a magnetic stirrer, was charged with cyclopropylamine **(*S*,*S*)-160** (47.2 mg, 0.15 mmol), PPh_3 (5.9 mg, 0.02 mmol) and $PhCO_2H$ (2.7 mg, 0.02 mmol). The tube was fitted with a rubber septum and purged with argon. Anhydrous 1,2-DCB (0.75 mL) was added via syringe. The reaction vessel was purged with CO for 10 minutes and then the solution was sparged with CO for approx. 20 seconds. The mixture was heated at 100 °C for 72 hours, under a CO atmosphere (1 atm). The mixture was cooled to room temperature, concentrated *in vacuo* and the residue was purified by flash column chromatography (30% EtOAc/hexane) to afford the title compound **(*S*)-161a** (34.3 mg, 67%) as a pale brown oil; ν_{max} / cm^{-1}: 2936 (w), 1698 (m), 1645 (s), 1405 (m), 1289 (m), 1189 (m), 723 (m), 697 (m); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.31 – 7.20 (m, 6H, 2 × C**15**-H, 2 × C**16**-H, C**17**-H and C**2**-H), 6.86 (dd, *J* = 5.0, 1.3 Hz, 1H, C**1**-H), 6.79 – 6.77 (m, 1H, C**3**-H), 5.72 (dd, *J* = 6.9, 2.0 Hz, 1H, C**7**-H), 5.17 (dd, *J* = 14.7 Hz, 1H, C**13**-H_aH_b), 5.08 (dd, *J* = 6.9, 6.0 Hz, 1H, C**8**-H), 4.89 (d, *J* = 14.7 Hz, 1H, C**13**-H_aH_b), 4.00 (ddd, *J* = 13.5, 7.4, 7.4 Hz, 1H, C**6**-H_aH_b), 3.60 (ddd, *J* = 13.5, 7.1, 6.0 Hz, 1H, C**6**-H_aH_b), 3.00 – 2.75 (m, 3H, C**5**-H_2 and C**9**-H), 1.28 (d, *J* = 6.8 Hz, 3H, C**10**-H_3); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 172.6 (C**11**), 153.8 (C**12**), 138.4, 138.0 (C**4** and C**14**), 129.1, 128.5, 128.1, 128.1, 127.3, 126.0 (C**1**, C**2**, C**7**, C**15**, C**16** and C**17**), 122.0 (C**3**), 120.2 (C**8**), 50.8 (C**6**), 48.2 (C**13**), 37.9 (C**9**), 28.8 (C**5**), 13.7 (C**10**); HRMS: (ESI^+) calculated for $C_{19}H_{21}N_2O_2S$: 341.1318, found $[M+H]^+$: 342.1316.

$[\alpha]_D^{23.2}$ = +192 (c = 0.21, $CHCl_3$).

The enantiopurity of this compound was determined by chiral SFC analysis against a racemic standard (prepared from racemic starting material **160** by using the same method as above). Chiral SFC: DAICEL CHIRALPAK-IB column (25 cm), CO_2:MeOH 96:4, 2 mL/min, 140 bars, 40 °C. Retention times: 18.3 minutes (minor), 18.9 minutes (major), e.r. > 99:1.

(8*S*,9a*S*)-8-Methyl-4,8,9,9a-tetrahydrothieno[3,2-g]indolizin-7(5*H*)-one ((*S*,*S*)-162a) *and* (8*S*,9a*R*)-8-methyl-4,8,9,9a-tetrahydrothieno[3,2-g]indolizin-7(5*H*)-one ((*S*,*R*)-162a)



A reaction tube with a solution of diazepane **(*S*)-161a** (50.0 mg, 0.15 mmol) and TFA (0.11 mL, 1.47 mmol) in DCM (1.5 mL) was fitted with a rubber septum and heated to 60 °C for 9 h. The reaction was cooled to r.t., concentrated *in vacuo*, redissolved in 1,2-DCB (1.5 mL) and heated to 150 °C for 24 h. The mixture was cooled to room temperature, concentrated *in vacuo* and the residue was purified by flash column chromatography (66% EtOAc/hexane) to afford the title compound **162a** (27.5 mg, 90%, 5:1 d.r.) as a pale brown oil.

Data for the mixture of compounds: ν_{max} / cm^{-1}: 2928 (w), 1628 (s), 1452 (m), 1419 (s), 1360 (m), 1299 (m), 865 (m), 723 (m); HRMS: (ESI^+) calculated for $C_{11}H_{14}NOS$: 208.0791, found $[M+H]^+$: 208.0789.

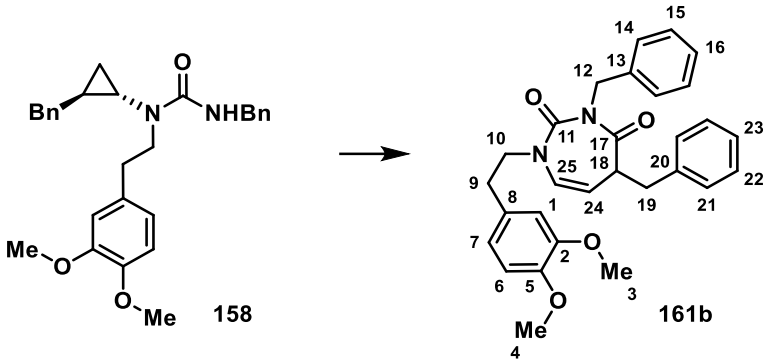
Data for the major compound **(*S*,*S*)-162a**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.18 (d, *J* = 5.0 Hz, 1H, C**5**-H), 6.79 (d, *J* = 5.0 Hz, 1H, C**4**-H), 4.75 (dd, *J* = 9.1, 6.6 Hz, 1H, C**7**-H), 4.46 – 4.35 (m, 1H, C**1**-H_aH_b), 3.02 – 2.91 (m, 1H, C**1**-H_aH_b), 2.82 – 2.54 (m, 4H, C**2**-H_2, C**8**-H_aH_b and C**9**-H), 1.50 (ddd, *J* = 11.4, 9.4, 9.4 Hz, 1H, C**8**-H_aH_b), 1.21 (d, *J* = 6.9 Hz, 3H, C**10**-H_3); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 175.3 (C**11**), 136.2 (C**6**), 133.3 (C**3**), 127.3 (C**4**), 123.5 (C**5**), 53.9 (C**7**), 37.8, 37.7 (C**8** and C**9**), 37.0 (C**1**), 25.6 (C**2**), 15.8 (C**10**). *The relative stereochemistry of this compound was corroborated by nOe experiments (as indicated on the compound structure). No nOe was observed between C**7**-H and C**10**-H_3.*

Data for the minor compound **(*S*,*R*)-162a**: *Characteristic signals only*: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.88 (t, *J* = 7.3 Hz, 1H, C**7**-H), 2.24 – 2.11 (m, 1H, C**8**-H_aH_b), 1.28 (d, *J* = 7.3 Hz, 1H, C**10**-H_3). *The relative stereochemistry of this compound was corroborated by nOe experiments (as indicated on the compound structure). A strong nOe was observed between C**7**-H and C**10**-H_3.*

The enantiopurity of this compound was determined by chiral SFC against a racemic standard (prepared from racemic **161a** by the same method as above).

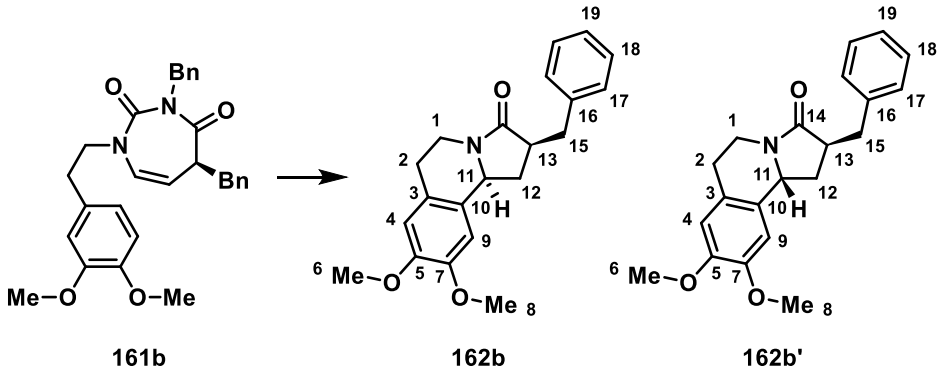
Chiral SFC: DAICEL CHIRALPAK-IC column (25 cm), CO_2:MeOH 92:8, 2 mL/min, 140 bars, 40 °C. Retention times: major diastereomer – 13.1 minutes (minor), 14.2 minutes (major), e.r. >99:1; minor diastereomer – 12.2 minutes (major), 13.7 minutes (minor), e.r. >99:1.

1,6-Dibenzyl-3-(3,4-dimethoxyphenethyl)-3,6-dihydro-1*H*-1,3-diazepine-2,7-dione (161b)



An oven dried reaction tube, fitted with a magnetic stirrer, was charged with cyclopropylamine **158** (66.7 mg, 0.15 mmol), PPh_3 (5.9 mg, 0.02 mmol) and $PhCO_2H$ (2.7 mg, 0.02 mmol). The tube was fitted with a rubber septum and purged with argon. Anhydrous 1,2-DCB (0.75 mL) was added via syringe. The reaction vessel was purged with CO for 10 minutes and then the solution was sparged with CO for approx. 20 seconds. The mixture was heated at 100 °C for 72 hours, under a CO atmosphere (1 atm). The mixture was cooled to room temperature, concentrated *in vacuo* and the residue was purified by flash column chromatography (30% EtOAc/hexane) to afford the title compound **161b** (36.0 mg, 51%) as a pale yellow oil; ν_{max} / cm^{-1}: 2936 (w), 1698 (s), 1649 (s), 1515 (s), 1453 (m), 1406 (s), 1261 (s), 1237 (s), 1029 (s), 699 (s); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.31 – 7.11 (m, 10H, 2 × C**14**-H, 2 × C**15**-H, 2 × C**21**-H, 2 × C**22**-H, C**16**-H and C**23**-H), 6.66 – 6.62 (m, 2H, C**1**-H and C**6**-H), 6.47 (dd, *J* = 8.1, 2.1 Hz, 1H, C**7**-H), 5.78 (dd, *J* = 7.0, 1.9 Hz, 1H, C**25**-H), 5.20 (dd, *J* = 7.0, 6.1 Hz, 1H, C**24**-H), 5.13 (d, *J* = 14.6 Hz, 1H, C**12**-H_aH_b), 4.92 (d, *J* = 14.6 Hz, 1H, C**12**-H_aH_b), 3.93 (ddd, *J* = 13.5, 7.7 Hz, 7.7 Hz, 1H, C**10**-H_aH_b), 3.82 (s, 3H, C**3**-H_3 or C**4**-H_3), 3.80 (s, 3H, C**3**-H_3 or C**4**-H_3), 3.59 (ddd, *J* = 13.5, 7.2, 6.1 Hz, 1H, C**10**-H_aH_b), 3.32 (dd, *J* = 14.3, 6.5 Hz, 1H, C**19**-H_aH_b), 3.14 – 3.06 (m, 1H, C**18**-H), 2.89 (dd, *J* = 14.3, 8.3 Hz, 1H, C**19**-H_aH_b), 2.78 – 2.72 (m, 2H, C**9**-H_2); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 171.2 (C**17**), 153.7 (C**11**), 149.1, 147.9 (C**2** and C**5**), 138.8, 137.9 (C**13** and C**20**), 130.5, 129.7, 129.2, 128.7, 128.5, 128.0, 127.3, 126.6 (C**8**, C**14**, C**15**, C**16**, C**21**, C**22**, C**23** and C**25**), 121.0 (C**7**), 118.3 (C**24**), 111.9, 111.3 (C**6** and C**1**), 56.0, 56.0 (C**3** and C**4**), 51.5 (C**10**), 48.4 (C**12**), 44.9 (C**18**), 34.3 (C**19**), 34.0 (C**9**); HRMS: (ESI^+) calculated for $C_{29}H_{30}N_2NaO_4$: 493.2098, found $[M+Na]^+$: 493.2083.

(2*S,10b*S**)-2-Benzyl-8,9-dimethoxy-1,5,6,10b-tetrahydropyrrolo[2,1-a]isoquinolin-3(2*H*)-one (162b)** ***and*** **(2*S**,10b*R**)-2-Benzyl-8,9-dimethoxy-1,5,6,10b-tetrahydropyrrolo[2,1-a]isoquinolin-3(2*H*)-one (162')**



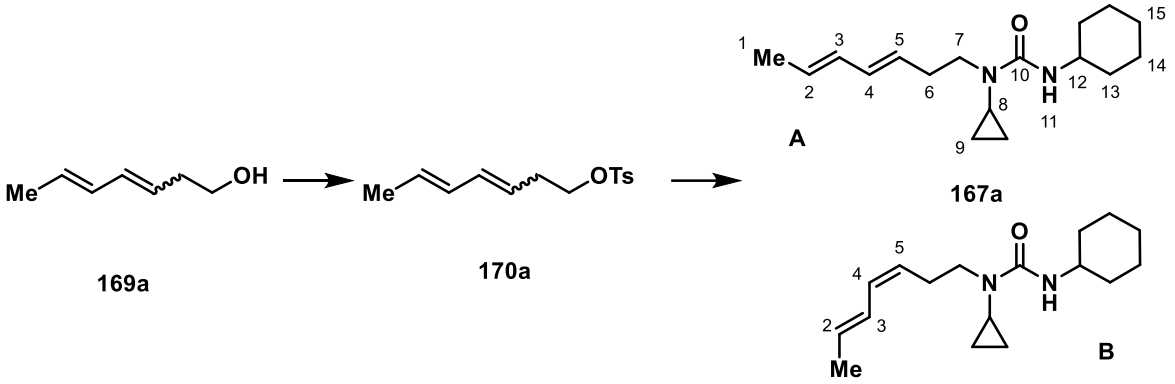
A reaction tube with a solution of diazepane **161b** (30.0 mg, 0.06 mmol) and TFA (50 µL, 0.64 mmol) in DCM (0.6 mL) was fitted with a rubber septum and heated to 60 °C for 9 h. The reaction was cooled to r.t., concentrated *in vacuo*, redissolved in 1,2-DCB (0.6 mL) and heated to 150 °C for 24 h. The mixture was cooled to room temperature, concentrated *in vacuo* and the residue was purified by flash column chromatography (66% EtOAc/hexane) to afford the title compound **162b** (12.8 mg, 59%, 5:1 d.r.) as a pale brown oil.

Data for the mixture of compounds: ν_{max} / cm^{-1}: 2932 (w), 1681 (s), 1512 (s), 1453 (s), 1429 (s), 1254 (s), 1227 (s), 1116 (s), 731 (s); HRMS: (ESI^+) calculated for $C_{21}H_{23}NNaO_3$: 360.1570, found $[M+Na]^+$: 360.1567.

Data for the major compound **162b**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35 – 7.15 (m, 5H, 2 × C**17**-H, 2 × C**18**-H and C**19**-H), 6.59 (s, 1H, C**9**-H), 6.47 (s, 1H, C**4**-H), 4.56 (dd, *J* = 9.6, 6.4 Hz, 1H, C**11**-H), 4.39 – 4.25 (m, 1H, C**1**-H_aH_b), 3.84 (s, 3H, C**6**-H_3), 3.81 (s, 3H, C**8**-H_3), 3.43 (dd, *J* = 13.9, 3.8 Hz, 1H, C**15**-H_aH_b), 3.06 – 2.80 (m, 3H, C**1**-H_aH_b, C**13**-H and C**2**-H_aH_b), 2.72 – 2.53 (m, 2H, C**2**-H_aH_b and C**12**-H_aH_b), 2.47 (dd, *J* = 13.9, 10.8 Hz, 1H, C**15**-H_aH_b), 1.48 (ddd, *J* = 11.7, 9.6, 9.6 Hz, 1H, C**12**-H_aH_b); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 174.0 (C**14**), 148.2, 148.0 (C**5** and C**7**), 139.9 (C**16**), 129.1, 128.9, 128.6, 126.4, 125.5 (C**3**, C**10**, C**17**, C**18** and C**19**), 111.8 (C**9**), 107.7 (C**4**), 56.2, 56.0 (C**6** and C**8**), 54.7 (C**11**), 45.1 (C**13**), 37.2 (C**1**), 37.1 (C**15**), 35.3 (C**2**), 28.3 (C**12**).

Data for the minor compound **162b'**: *Characteristic signals only*: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.56 (s, 1H, C**9**-H), 6.44 (s, 1H, C**4**-H), 3.82 (s, 3H, C**6**-H_3), 3.80 (s, 3H, C**8**-H_3).

3-Cyclohexyl-1-cyclopropyl-1-((3*E*,5*E*)-hepta-3,5-dien-1-yl)urea (167a)



General procedure B: Hepta-3,5-dien-1-ol **169a** (mixture of geometric isomers (3*E*,5*E*):(3*Z*,5*E*) = 4:1, 1.62 g, 14.44 mmol, prepared according to the literature procedure[264] from *trans*-crotonaldehyde) was employed. Flash column chromatography (100% toluene) afforded the corresponding tosylate **170a** (2.23 g, 58%) as a colourless oil; ν_{max} / cm^{-1}: 2916 (w), 1359 (s), 1189 (s), 1176 (s), 988 (s). This compound is unstable and was used in subsequent reaction without further characterisation.

In a sealed reaction tube, a solution of cyclopropylamine (1.04 mL, 15.02 mmol) and tosylate **170a** (1.00 g, 3.75 mmol) in MeCN (10 mL) was heated to 90 °C for 18 h. The reaction was cooled to r.t., trifluoroacetic acid (0.43 mL, 5.63 mmol) was added (due to intermediate amine's volatility) and the mixture was concentrated *in vacuo*. The residue was dissolved in dry DCM (50 mL) and cooled down to 0 °C. Triethylamine (1.05 mL, 7.50 mmol) and cyclohexyl isocyanate (0.48 mL, 3.75 mmol) were added at 0 °C, the reaction mixture was warmed to r.t. and stirred for 18 h. The solution was washed with water (20 mL), aq. 1.0 M HCl (20 mL), sat. aq. $NaHCO_3$ (20 mL) and brine (20 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (20% EtOAc/hexane) to afford the title compound **167a** (0.62 g, 60% over 2 steps, mixture of geometric isomers A:B = 10:1) as a colourless oil.

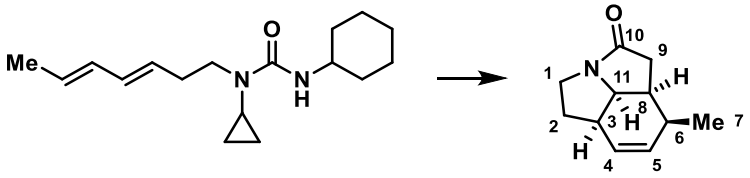
Data for the mixture of geometric isomers: ν_{max} / cm^{-1}: 2928 (s), 2853 (m), 1644 (s), 1508 (s), 1450 (m), 987 (m); HRMS: (ESI^+) calculated for $C_{17}H_{29}N_2O$: 277.2274, found $[M+H]^+$: 277.2270.

Data for the major geometric isomer **A**: ^1H NMR ($CDCl_3$, 400 MHz): δ 6.09 – 5.94 (m, 2H, C**3**-H and C**4**-H), 5.63 – 5.47 (m, 2H, C**2**-H and C**5**-H), 5.08 (br. d, *J* = 8.1 Hz, 1H, N**11**-H), 3.71 – 3.59 (m, 1H, C**12**-H), 3.35 (t, *J* = 7.2 Hz, 2H, C**7**-H_2), 2.48 – 2.39 (m, 1H, C**8**-H), 2.35 – 2.26 (m, 2H, C**6**-H_2), 1.98 – 1.85 (m, 2H, 2 × C**13**-H_aH_b), 1.80 – 1.54 (m, 7H, 2 × C**14**-H_aH_b, C**15**-H_2 and C**1**-H_3), 1.44 – 1.31 (m, 2H, 2 × C**14**-H_aH_b), 1.24 – 1.06 (m, 2H, 2 × C**13**-H_aH_b), 0.84 – 0.78 (m, 2H, 2 × C**9**-H_aH_b), 0.71 – 0.65 (m, 2H, 2 × C**9**-H_aH_b); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 158.2 (C**10**), 132.1 (C**4**), 131.7 (C**3**), 128.9 (C**5**), 127.5 (C**2**), 49.0 (C**12**), 46.7 (C**7**), 34.1 (C**13**), 31.9 (C**6**), 27.6

(C**8**), 25.9 (C**15**), 25.1 (C**14**), 18.1 (C**1**), 8.8 (C**9**) *This compound is unstable and was stored as a frozen matrix in benzene.*

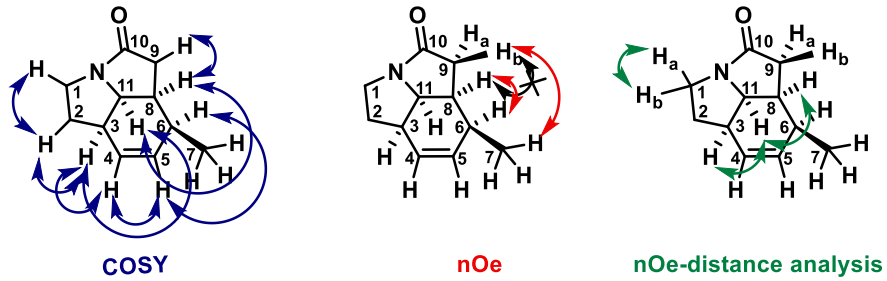
Data for the minor geometric isomer **B**: *Characteristic signals only*: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.43 – 6.26 (m, 2H, C**3**-H and C**4**-H), 5.77 – 5.64 (m, 2H, C**2**-H and C**5**-H).

(3^{1}*R,5a*R**,8*S**,8a*S**)-8-Methyl-3^{1},4,5,5a,8,8a-hexahydropyrrolo[3,2,1-*hi*]indol-2(1*H*)-one (171a)**



167a **171a**

An oven dried reaction tube, fitted with a magnetic stirrer, was charged with protected cyclopropylamine **167a** (27.6 mg, 0.10 mmol), P(4-F-C_6H_4)$_3$ (4.7 mg, 15 mol%), [Rh(cod)$_2$]OTf (3.5 mg, 7.5 mol%), dimethyl fumarate (14.4 mg, 0.10 mmol) and BHT (2.2 mg, 0.01 mmol). The tube was fitted with a rubber septum and purged with argon. Anhydrous PhCN (1.00 mL) was added via syringe. The reaction vessel was purged with CO for 10 minutes and then the solution was sparged with CO for approx. 20 seconds. The mixture was heated at 140 °C for 72 hours, under a CO atmosphere (1 atm). The mixture was cooled to room temperature, concentrated *in vacuo* and the residue was purified by flash column chromatography (20% MeCN/DCM) to afford the title compound **171a** (9.1 mg, 51%, single diastereomer) as a pale yellow oil; ν_{max} / cm^{-1}: 2957 (w), 2930 (w), 1683 (s), 1408 (s), 1285 (m), 692 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.59 (ddd, *J* = 9.7, 3.2, 3.2 Hz, 1H, C**4**-H), 5.50 – 5.43 (m, 1H, C**5**-H), 4.17 – 4.10 (m, 1H, C**11**-H), 3.60 (ddd, *J* = 11.7, 8.3, 8.3 Hz, 1H, C**1**-H$_a$H$_b$), 3.03 – 2.93 (m, 1H, C**1**-H$_a$H$_b$), 2.77 – 2.67 (m, 1H, C**8**-H), 2.57 (dd, *J* = 17.7, 10.4 Hz, 1H, C**9**-H$_a$H$_b$), 2.46 – 2.39 (m, 1H, C**3**-H), 2.34 – 2.14 (m, 3H, C**2**-H$_a$H$_b$, C**6**-H and C**9**-H$_a$H$_b$), 2.02 – 1.92 (m, 1H, C**2**-H$_a$H$_b$), 1.08 (d, *J* = 7.2 Hz, 3H, C**7**-H$_3$); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 177.3 (C**10**), 134.9 (C**4**), 132.5 (C**5**), 66.0 (C**11**), 41.3 (C**1**), 35.9 (C**3**), 35.2 (C**9**), 33.6 (C**8**), 32.7 (C**2**), 30.7 (C**6**), 17.6 (C**7**); HRMS: (ESI^{+}) calculated for $C_{11}H_{16}NO$: 178.1226, found [M+H]$^{+}$: 178.1224.



*The structure of **171a** was corroborated by HH Cosy experiments (as indicated on the compound structure. HH Cosy correlations were observed between C**1**-H and C**2**-H, C**2**-H and C**3**-H, C**3**-H and C**4**-H, C**4**-H and C**5**-H, C**5**-H and C**6**-H, C**6**-H and C**7**-H, C**8**-H and C**9**-H, C**8**-H and C**11**-H, C**3**-H and C**11**-H.*

*The relative stereochemistry of C**11**-H, C**8**-H and C**3**-H of **171a** was corroborated by using quantifiable nOe analysis. In quantifiable nOe analysis, the determination of the interproton distances is based on the comparison of relative nOe intensities instead of absolute intensities. The advantage of this method is the minimisation of the perturbations that affect all of the spins. The relative stereochemistry of C**8**-H and C**6**-H of **171a** was corroborated by nOe experiments (as indicated on the compound structure). nOe was observed between C**7**-H_3 and C**9**-H_b, C**8**-H and C**6**-H; at the same time, no nOe was observed between C**9**-H_b and C**8**-H.*

Quantifiable nOe analysis

1-Dimensional transient nOe spectra were acquired on a 500MHz Bruker Avance IIIHD NMR spectrometer equipped with a DCH ^{13}C-optimised cryoprobe. Chemical-shift-selective filter nOe pulse sequence ('selcssfnozs') from the Bruker Top Spin library was used with a 500ms nOe mixing time and otherwise using the same spectrum parameters as for ^{1}H spectra.

nOe-distance Analysis was carried out in collaboration with Prof. Craig Butts at Bristol. nOe-distance analysis on **171a** confirmed the relative stereochemistry of C**3**-H, C**8**-H and C**11**-H using the relationship between nOe intensity and internuclear distance in transient nOe experiments. The underpinning method used is based on that described by Butts *et al*[115] which assumes that all interproton distances between nuclei X and Y (r_{XY}) are related to the intensity of the nOe signal between them (η_{XY}) by the relationship: $\eta_{XY} \alpha r_{XY}^{-6}$, and that the effects of differential relaxation between all nuclei in the molecule can be corrected for by measuring nOe integrals relative to the intensity of the irradiated peak–the so-called PANIC method.[265]

In this case the PANIC-corrected nOe intensities from irradiation of C**11**-H to C**3**-H and C**8**-H, gave rise to almost identical internuclear distances, which were established to be ~2.3Å after calibration against the known nOe-distance for C**1**-H_a-C**1**-H_b (~1.83Å). Molecular mechanics

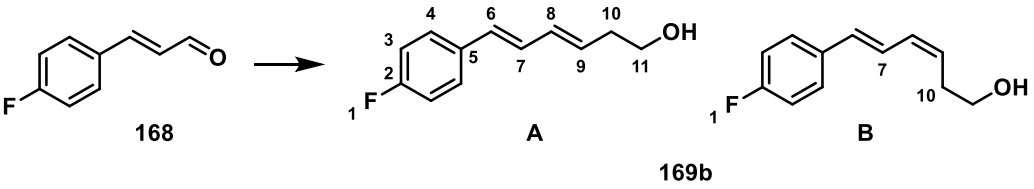
modelling on **171a** found a single low energy conformer with C**11**-H-C**3**-H and C**11**-H-C**8**-H distances of 2.53Å and 2.34Å respectively, which are within the expected error limits of nOe-distance analysis (For comparison, an nOe-distance of >3Å would have been expected for C**3**-H or C**8**-H in alternative diastereomers (trans relationship)). Other measurable nOe-distances were also found to fit with the proposed structure, however the absolute intensities of the nOes in the datasets for compound **171a** were weak.

nOe integrals and nOe-distance analysis for 171a

nOe from	nOe to	Integral	Relative distance	nOe-Distance /Å	Model Distance /Å	Error
C11-H	C3-H	4.77	1.259	2.30	2.53	8.92%
C11-H	C8-H	4.88	1.254	2.30	2.34	1.90%
C1-H_a[a]	C1-H_b	**19.01**	**1.000**	**1.83**	**1.83**	**0.00%**

[a] C1-H_a-C1-H_b (methylene) was used as the reference distance, with measured C11-H nOe-distances established relative to this. See reference 115 for details.

(3*E*,5*E*)-6-(4-Fluorophenyl)hexa-3,5-dien-1-ol (169b)



169b

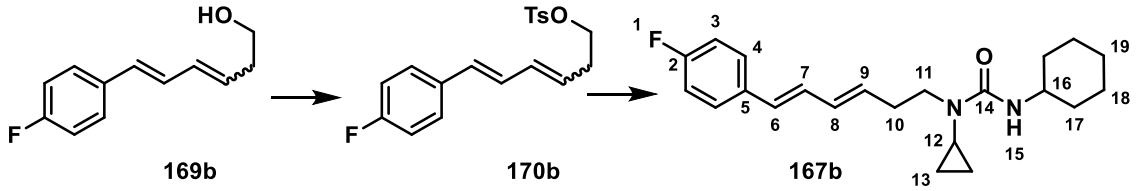
A suspension of (3-hydroxypropyl)triphenylphosphonium bromide (4.82 g, 12.00 mmol, prepared according to the literature procedure[266]) in dry THF (25 mL) was cooled to 0 °C and *n*-BuLi (16.7 mL, 1.44 M in hexanes) was added dropwise. The solution was stirred at 0 °C for 30 min and then (*E*)-3-(4-fluorophenyl)acrylaldehyde (1.80 g, 12.00 mmol, prepared according to the literature procedure[267] from 4-fluorobenzaldehyde) in dry THF (8 mL) was added dropwise and the solution was stirred at 0 °C for 2.5 h. The reaction was diluted with Et_2O (30 mL) and washed with sat. aq. NH_4Cl (30 mL) and brine (30 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (20-40% EtOAc/hexane) afforded the title compound **169b** (1.13 g, 49%, mixture of geometric isomers A:B = 4:1) as a colourless oil.

Data for the mixture of geometric isomers: ν_{max} / cm^{-1}: 3270 (br. m), 2945 (m), 1508 (s), 1248 (s), 1050 (s), 982 (s), 834 (m); HRMS: (ESI^+) calculated for $C_{12}H_{13}FO$: 193.1023, found $[M+H]^+$: 193.1019.

Data for the major geometric isomer **A**: ^1H NMR ($CDCl_3$, 400 MHz): δ 7.37 – 7.31 (m, 2H, 2 × C**4**-H), 7.04 – 6.95 (m, 2H, 2 × C**3**-H), 6.67 (dd, *J* = 15.7, 10.4 Hz, 1H, C**7**-H), 6.45 (d, *J* = 15.7 Hz, 1H, C**6**-H), 6.30 (dd, *J* = 15.3, 10.4 Hz, 1H, C**8**-H), 5.79 (dt, *J* = 15.3, 7.2 Hz, 1H, C**9**-H), 3.77 – 3.69 (m, 2H, C**11**-H_2), 2.46 – 2.39 (m, 2H, C**10**-H_2); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 162.3 (d, *J* = 246.8 Hz, C**2**), 133.7 (d, *J* = 3.2 Hz, C**5**), 133.4 (C**8**), 130.9 (C**9**), 130.1 (C**6**), 128.7 (d, *J* = 2.4 Hz, C**7**), 127.8 (d, *J* = 7.9 Hz, C**4**), 115.68 (d, *J* = 21.7 Hz, C**3**), 62.1 (C**11**), 36.4 (C**10**); ^{19}F NMR ($CDCl_3$, 376 MHz): -114.48 (td, *J* = 8.8, 4.5 Hz, F**1**).

Data for the minor geometric isomer **B**: *Characteristic signals only*: δ 6.52 (d, *J* = 15.6 Hz, 1H, C**7**-H), 2.60 – 2.52 (m, 2H, C**10**-H_2); ^{19}F NMR ($CDCl_3$, 376 MHz): -114.10 (td, *J* = 8.8, 4.5 Hz, F**1**)

3-Cyclohexyl-1-cyclopropyl-1-((3*E*,5*E*)-6-(4-fluorophenyl)hexa-3,5-dien-1-yl)urea (167a)

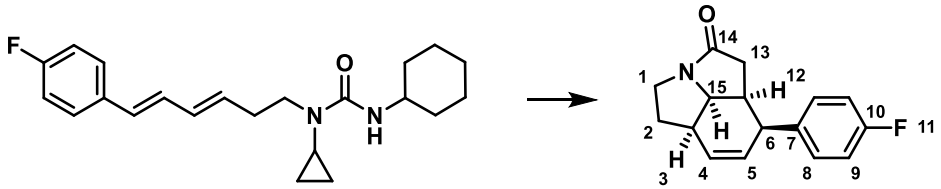


General procedure B: 6-(4-Fluorophenyl)hexa-3,5-dien-1-ol **169b** (mixture of geometric isomers A:B = 4:1, 1.13 g, 5.88 mmol) was employed. Flash column chromatography (100% toluene) afforded the corresponding tosylate **170b** (1.10 g, 54%) as a colourless oil. This compound is unstable and was used in subsequent reaction without further characterisation.

In a sealed reaction tube, a solution of cyclopropylamine (0.40 mL, 6.93 mmol) and tosylate **170b** (0.60 g, 1.73 mmol) in MeCN (5 mL) was heated to 90 °C for 18 h. The reaction was cooled to r.t. and concentrated *in vacuo*. The residue was diluted with DCM (10 mL) and washed with sat. aq. $NaHCO_3$ (20 mL). The organic layer was dried over $MgSO_4$ and cooled down to 0 °C. Triethylamine (0.48 mL, 3.46 mmol) and cyclohexyl isocyanate (0.22 mL, 1.73 mmol) were added at 0 °C, the reaction mixture was warmed to r.t. and stirred for 18 h. The solution was washed with water (20 mL), aq. 1.0 M HCl (20 mL), sat. aq. $NaHCO_3$ (20 mL) and brine (20 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (30% EtOAc/hexane) to afford the title compound **167b** as a single isomer (101.0 mg, 16%) as a colourless oil; ν_{max} / cm^{-1}: 2928 (m), 2853 (w), 1651 (m), 1507 (s), 1228 (m), 987

(w), 834 (w); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.34 – 7.30 (m, 2H, 2 × C**4**-H), 6.98 (t, *J* = 8.7 Hz, 2H, 2 × C**3**-H), 6.65 (dd, *J* = 15.7, 10.4 Hz, 1H, C**7**-H), 6.39 (d, *J* = 15.7 Hz, 1H, C**6**-H), 6.22 (dd, *J* = 15.0, 10.4 Hz, 1H, C**8**-H), 5.80 (dt, *J* = 15.0, 7.3 Hz, 1H, C**9**-H), 5.10 (d, *J* = 8.0 Hz, 1H, N**15**-H), 3.70 – 3.61 (m, 1H, C**16**-H), 3.41 (t, *J* = 7.0 Hz, 2H, C**11**-H_2), 2.47 – 2.37 (m, 3H, C**12**-H and C**10**-H_2), 1.96 – 1.89 (m, 2H, 2 × C**17**-H_aH_b), 1.70 – 1.58 (m, 3H, C**19**-H_aH_b and 2 × C**18**-H_aH_b), 1.43 – 1.32 (m, 2H, 2 × C**18**-H_aH_b), 1.22 – 1.07 (m, 3H, C**19**-H_aH_b and 2 × C**17**-H_aH_b), 0.85 – 0.80 (m, 2H, 2 × C**13**-H_aH_b), 0.72 – 0.68 (m, 2H, 2 × C**13**-H_aH_b); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 162.21 (d, *J* = 246.6 Hz, C**2**), 158.3 (C**14**), 133.86 (d, *J* = 3.2 Hz, C**5**), 132.8 (C**9**), 132.1 (C**8**), 129.3 (C**6**), 129.14 (d, *J* = 2.4 Hz, C**7**), 127.73 (d, *J* = 7.9 Hz, C**4**), 115.62 (d, *J* = 21.6 Hz, C**3**), 49.1 (C**16**), 46.6 (C**11**), 34.1 (C**17**), 32.3 (C**10**), 27.7 (C**12**), 25.9 (C**19**), 25.1 (C**18**), 8.8 (C**13**); ^{19}F NMR ($CDCl_3$, 376 MHz): -114.79 (tt, *J* = 9.0, 5.3 Hz, F**1**); HRMS: (ESI^+) calculated for $C_{22}H_{30}FN_2O$: 357.2337, found $[M+H]^+$: 357.2336. *This compound is unstable and was stored as a frozen matrix in benzene.*

8-(4-Fluorophenyl)-3^{1},4,5,5a,8,8a-hexahydropyrrolo[3,2,1-*hi*]indol-2(1*H*)-one (171b)

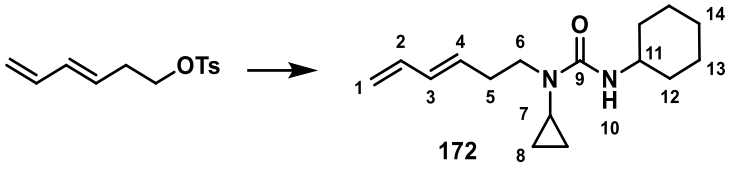


167b **171b**

An oven dried reaction tube, fitted with a magnetic stirrer, was charged with protected cyclopropylamine **167b** (35.6 mg, 0.10 mmol), P(4-F-C_6H_4)$_3$ (4.7 mg, 15 mol%), [Rh(cod)$_2$]OTf (3.5 mg, 7.5 mol%), dimethyl fumarate (14.4 mg, 0.10 mmol) and BHT (2.2 mg, 0.01 mmol). The tube was fitted with a rubber septum and purged with argon. Anhydrous PhCN (1.00 mL) was added via syringe. The reaction vessel was purged with CO for 10 minutes and then the solution was sparged with CO for approx. 20 seconds. The mixture was heated at 140 °C for 72 hours, under a CO atmosphere (1 atm). The mixture was cooled to room temperature, concentrated *in vacuo* and the residue was purified by flash column chromatography (20% MeCN/DCM, then 90% EtOAc/hexane) to afford the title compound **171b** (12.1 mg, 47%) as a pale yellow oil; ν_{max} / cm^{-1}: 2928 (w), 1687 (s), 1510 (s), 1410 (m), 1222 (s), 1160 (w), 822 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.20 (dd, *J* = 8.5, 5.3 Hz, 2H, 2 × C**8**-H), 7.04 (dd, *J* = 8.5, 8.5 Hz, 2H, 2 × C**9**-H), 6.11 (dt, *J* = 9.8, 2.8 Hz, 1H, C**4**-H), 5.68 (d, *J* = 9.8 Hz, 1H, C**5**-H), 4.27 (dd, *J* = 8.4, 6.4 Hz, 1H, C**15**-H), 3.62 (dt, *J* = 11.7, 8.6 Hz, 1H, C**1**-H_aH_b), 3.56 – 3.51 (m, 1H, C**6**-H), 3.08 – 2.94 (m, 2H, C**12**-H and C**1**-H_aH_b), 2.62 – 2.56 (m, 1H, C**3**-H), 2.40 – 2.28 (m, 2H, C**2**-H_aH_b and C**13**-H_aH_b),

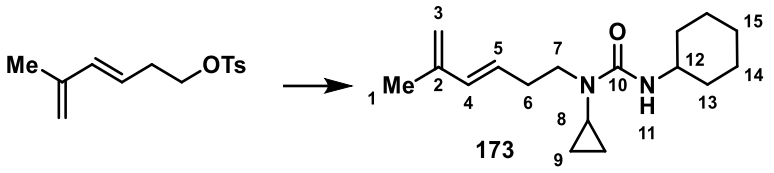
2.17 – 2.02 (m, 2H, C**2**-$H_a\underline{H}_b$ and C**13**-$H_a\underline{H}_b$); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 176.6 (C**14**), 161.8 (d, *J* = 245.3 Hz, C**10**), 137.4 (d, *J* = 3.3 Hz, C**7**), 133.7 (C**5**), 131.2 (C**4**), 129.6 (d, *J* = 7.9 Hz, C**8**), 115.7 (d, *J* = 21.2 Hz, C**9**), 64.9 (C**15**), 41.3, 41.2 (C**1** and C**6**), 36.3 (C**3**), 35.9, 34.92 (d, *J* = 1.2 Hz), 32.8 (C**2**, C**12** and C**13**); ^{19}F NMR ($CDCl_3$, 376 MHz): -116.15 (tt, *J* = 9.2, 5.2 Hz, F**11**); HRMS: (ESI^+) calculated for $C_{16}H_{17}NOF$: 258.1289, found $[M+H]^+$: 258.1283. *The relative stereochemistry of this compound was assigned by analogy to that of* **171a**.

(*E*)-3-Cyclohexyl-1-cyclopropyl-1-(hexa-3,5-dien-1-yl)urea (172)



In a sealed reaction tube, a solution of cyclopropylamine (1.10 mL, 15.85 mmol) and (*E*)-hexa-3,5-dien-1-yl 4-methylbenzenesulfonate (1.00 g, 3.96 mmol, prepared according to the literature procedure[268]) in MeCN (10 mL) was heated to 90 °C for 18 h. The reaction was cooled to r.t. and concentrated *in vacuo*. The residue was diluted with DCM (10 mL) and washed with sat. aq. $NaHCO_3$ (20 mL). The organic layer was dried over $MgSO_4$ and cooled down to 0 °C. Triethylamine (2.21 mL, 15.84 mmol) and cyclohexyl isocyanate (1.01 mL, 7.92 mmol) were added at 0 °C, the reaction mixture was warmed to r.t. and stirred for 18 h. The solution was washed with water (20 mL), aq. 1.0 M HCl (20 mL), sat. aq. $NaHCO_3$ (20 mL) and brine (20 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Flash column chromatography (20% EtOAc/hexane) of the crude afforded the title compound **172** (1.20 g, 58% over two steps) as a pale yellow oil; ν_{max} / cm^{-1}: 2928 (s), 2853 (m), 1645 (s), 1510 (s), 1451 (m), 1356 (m), 1279 (m), 1258 (m), 1003 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.30 (ddd, *J* = 16.6, 10.2, 10.2 Hz, 1H, C**2**-$\underline{H}$), 6.09 (dd, *J* = 15.1, 10.2 Hz, 1H, C**3**-$\underline{H}$), 5.68 (dt, *J* = 15.1, 7.3 Hz, 1H, C**4**-$\underline{H}$), 5.08 (d, *J* = 16.6 Hz, 1H, C**1**-$\underline{H}_{trans}$), 5.08 (s, 1H, N**10**-$\underline{H}$), 4.96 (d, *J* = 10.1 Hz, 1H, C**1**-$\underline{H}_{cis}$), 3.70 – 3.59 (m, 1H, C**11**-$\underline{H}$), 3.36 (t, *J* = 7.0 Hz, 2H, C**6**-$\underline{H}_2$), 2.42 (tt, *J* = 6.9, 3.8 Hz, 1H, C**7**-$\underline{H}$), 2.38 – 2.30 (m, 2H, C**5**-$\underline{H}_2$), 1.97 – 1.88 (m, 2H, 2 × C**12**-$\underline{H}_aH_b$), 1.72 – 1.54 (m, 3H, C**14**-$\underline{H}_aH_b$ and 2 × C**13**-$\underline{H}_aH_b$), 1.44 – 1.31 (m, 2H, 2 × C**13**-$H_a\underline{H}_b$), 1.26 – 1.07 (m, 3H, C**14**-$H_a\underline{H}_b$ and 2 × C**12**-$H_a\underline{H}_b$), 0.84 – 0.78 (m, 2H, 2 × C**8**-$\underline{H}_aH_b$), 0.71 – 0.65 (m, 2H, 2 × C**8**-$H_a\underline{H}_b$); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 158.2 (C**9**), 137.3 (C**2**), 132.7 (C**3**), 132.4 (C**4**), 115.4 (C**1**), 49.0 (C**11**), 46.5 (C**6**), 34.1 (C**12**), 31.9 (C**5**), 27.6 (C**7**), 25.9 (C**14**), 25.1 (C**13**), 8.8 (C**8**); HRMS: (ESI^+) calculated for $C_{16}H_{27}N_2O$: 263.2118, found $[M+H]^+$: 263.2115.

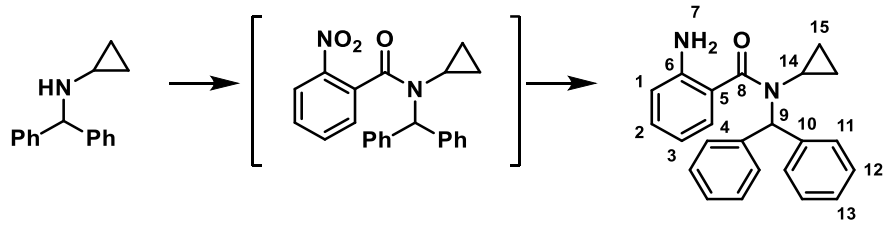
(*E*)-3-Cyclohexyl-1-cyclopropyl-1-(5-methylhexa-3,5-dien-1-yl)urea (173)



In a sealed reaction tube, a solution of cyclopropylamine (1.14 mL, 16.52 mmol) and (*E*)-5-methylhexa-3,5-dien-1-yl 4-methylbenzenesulfonate (1.10 g, 4.13 mmol, prepared according to the literature procedure[269]) in MeCN (10 mL) was heated to 90 °C for 18 h. The reaction was cooled to r.t. and concentrated *in vacuo*. The residue was diluted with DCM (10 mL) and washed with sat. aq. $NaHCO_3$ (20 mL). The organic layer was dried over $MgSO_4$ and cooled down to 0 °C. Triethylamine (1.15 mL, 8.26 mmol) and cyclohexyl isocyanate (0.53 mL, 4.13 mmol) were added at 0 °C, the reaction mixture was warmed to r.t. and stirred for 18 h. The solution was washed with water (20 mL), aq. 1.0 M HCl (20 mL), sat. aq. $NaHCO_3$ (20 mL) and brine (20 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Flash column chromatography (20% EtOAc/hexane) of the crude afforded the title compound **173** (428.0 mg, 37% over two steps) as a colourless oil; ν_{max} / cm^{-1}: 2927 (s), 2853 (m), 1642 (s), 1508 (s), 1451 (m), 1280 (m), 1257 (m), 966 (m); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.18 (d, *J* = 15.4 Hz, 1H, C**4**-H), 5.64 (dt, *J* = 15.4, 7.2 Hz, 1H, C**5**-H), 5.09 (br. d, *J* = 7.9j Hz, 1H, N**11**-H), 4.86 (s, 2H, C**3**-H_2), 3.70 – 3.59 (m, 1H, C**12**-H), 3.39 (t, *J* = 7.2 Hz, 2H, C**7**-H_2), 2.45 – 2.32 (m, 3H, C**8**-H and C**6**-H_2), 1.97 – 1.87 (m, 2H, 2 × C**13**-H_aH_b), 1.82 (s, 3H, C**1**-H_3), 1.72 – 1.54 (m, 3H, C**15**-H_aH_b and 2 × C**14**-H_aH_b), 1.44 – 1.31 (m, 2H, 2 × C**14**-H_aH_b), 1.24 – 1.07 (m, 3H, C**15**-H_aH_b and 2 × C**13**-H_aH_b), 0.85 – 0.78 (m, 2H, 2 × C**9**-H_aH_b), 0.71 – 0.66 (m, 2H, 2 × C**9**-H_aH_b); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 158.2 (C**10**), 142.3 (C**2**), 134.6 (C**4**), 128.1 (C**5**), 114.8 (C**3**), 49.1 (C**12**), 46.6 (C**7**), 34.0 (C**13**), 32.1 (C**6**), 27.6 (C**8**), 25.9 (C**15**), 25.1 (C**14**), 18 .8 (C**1**), 8.8 (C**9**); HRMS: (ESI^+) calculated for $C_{17}H_{29}N_2O$: 277.2274, found $[M+H]^+$: 277.2261.

8.4 Experimental procedures for the studies in Chapter 3

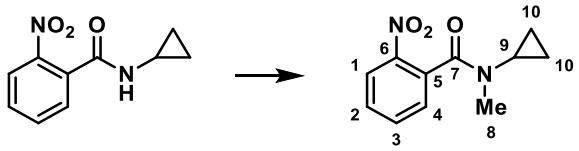
2-Amino-*N*-benzhydryl-*N*-cyclopropylbenzamide (195b)



202b **203b** **195b**

General procedure D: *N*-Benzhydrylcyclopropanamine **202b** (1.80 g, 8.06 mmol, prepared according to the literature procedure[270]) and 2-nitrobenzoyl chloride (1.28 mL, 9.67 mmol) were employed to afford amide **203b** (2.08 g, 69%) which was used in the next step without further purification. Amide **203b** (2.08 g, 5.59 mmol) was dissolved in AcOH:EtOH (1:2, 15:30 mL) and iron (0.78 g, 13.96 mmol) was added at r.t. The reaction mixture was heated to 85 °C for 18 h, cooled to r.t. and concentrated *in vacuo*. 1.0 M aq. NaOH was added to adjust pH to ~10 and the solution was extracted with EtOAc (3 × 30 mL). The organic extracts were combined, washed with brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Flash column chromatography (3-10% EtOAc/pentane) afforded the title compound **195b** (1.05 g, 55%) as a colourless solid; m.p. 150-151 °C (DCM/hexane); ν_{max} / cm^{-1}: 3448 (br. w), 3356 (br. w), 3027 (w), 1617 (s), 1589 (s), 1493 (s), 1394 (s), 1326 (m), 1268 (m), 1031 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38 – 7.27 (m, 10H, 2 × C**11**-H, 2 × C**12**-H and C**13**-H), 7.17 (dd, *J* = 7.6, 1.6 Hz, 1H, C**4**-H), 7.14 (td, *J* = 7.9, 1.6 Hz, 1H, C**2**-H), 6.78 (s, 1H, C**9**-H), 6.72 (dd, *J* = 7.9, 1.0 Hz, 1H, C**1**-H), 6.66 (td, *J* = 7.6, 1.0 Hz, 1H, C**3**-H), 4.40 (br. s, 2H, N**7**-H_2), 2.23 (tt, *J* = 7.0, 4.0 Hz, 1H, C**14**-H), 0.65 – 0.59 (m, 2H, 2 × C**15**-H_aH_b), 0.34 – 0.27 (m, 2H, 2 × C**15**-H_aH_b); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 173.3 (C**8**), 145.6 (C**6**), 139.6 (C**10**), 130.3 (C**2**), 129.1 (C**12**), 128.2 (C**11**), 127.6 (C**4**), 127.3 (C**13**), 122.2 (C**5**), 117.1 (C**3**), 116.6 (C**1**), 65.0 (C**9**), 31.2 (C**14**), 9.6 (C**15**); HRMS: (ESI^+) calculated for $C_{23}H_{23}N_2O$: 343.1805, found $[M+H]^+$: 343.1802.

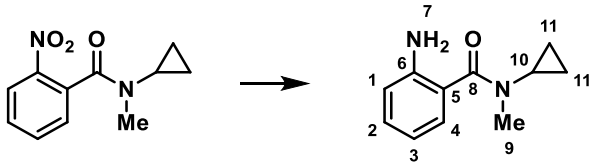
N-Cyclopropyl-*N*-methyl-2-nitrobenzamide (203d)



203e **203d**

N-Cyclopropyl-2-nitrobenzamide **203e** (0.60 g, 2.91 mmol, prepared according to the literature procedure[271]) was dissolved in dry THF (7 mL) and the solution was cooled to 0 °C. NaH (0.58 g, 14.55 mmol, 60% dispersion in mineral oil) was added batchwise and the reaction was stirred at 0 °C for 1 h. Methyl iodide (0.91 mL, 14.55 mmol) was added dropwise, the solution was warmed to r.t. and stirred for 18 h. Water (30 mL) was added and the solution was extracted with Et_2O (3 × 20 mL). The organic extracts were combined, washed with brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (3-10% EtOAc/hexane) to afford the title compound **203d** (0.59 g, 92%, 1:0.18 mixture of rotamers *A*:*B*) as a colourless oil; ν_{max} / cm^{-1}: 1641 (s), 1523 (s), 1344 (s), 1288 (m), 1032 (m), 851 (m), 713 (s); ^{1}H NMR ($CDCl_3$, 400 MHz, major rotamer only): δ 8.14 (dd, *J* = 8.3, 1.3 Hz, 1H, C**1**-H), 7.68 (td, *J* = 7.5, 1.1 Hz, 1H, C**4**-H), 7.56 – 7.50 (m, 1H, C**2**-H), 7.40 (dd, *J* = 7.5, 1.3 Hz, 1H, C**3**-H), 3.12 (s, 3H, C**8**-H_3), 2.49 – 2.42 (m, 1H, C**9**-H), 0.53 – 0.41 (m, 4H, 2 × C**10**-H_2); ^{13}C NMR ($CDCl_3$, 101 MHz, major rotamer only): δ 169.7 (C**7**), 145.2 (C**6**), 134.5 (C**5**), 134.0 (C**4**), 129.5 (C**2**), 128.6 (C**3**), 124.4 (C**1**), 34.4 (C**8**), 31.7 (C**9**), 8.6 (C**10**); HRMS: (ESI^+) calculated for $C_{11}H_{15}N_2O$: 191.1179, found $[M+H]^+$: 191.1175.

2-Amino-*N*-cyclopropyl-*N*-methylbenzamide (195d)

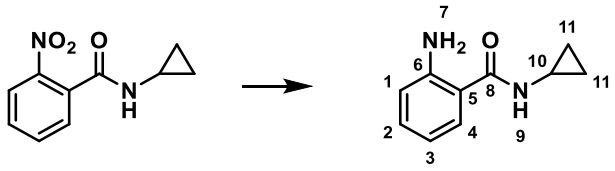


203d **195d**

Amide **203d** (0.50 g, 2.27 mmol) was dissolved in AcOH:EtOH (1:2, 5:10 mL) and iron (0.32 g, 5.68 mmol) was added at r.t. The reaction mixture was heated to 90 °C for 2 h, cooled to r.t., stirred for 16 h and concentrated *in vacuo*. 1.0 M aq. NaOH was added to adjust pH to ~10 and the solution was extracted with EtOAc (3 × 20 mL). The organic extracts were combined, washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Flash column chromatography (40% EtOAc/pentane) afforded the title compound **195d** (0.39 g, 91%) as a pale yellow oil; ν_{max} / cm^{-1}: 3449 (br. w), 3348 (br. w), 3008 (br. w), 1615 (s), 1586 (s), 1384 (s), 1362 (s); ^{1}H NMR ($CDCl_3$,

400 MHz): δ 7.18 (dd, *J* = 8.0, 1.6 Hz, 1H, C**2**-H or C**4**-H), 7.13 (td, *J* = 7.6, 1.6 Hz, 1H, C**2**-H or C**4**-H), 6.71 – 6.65 (m, 2H, C**1**-H and C**3**-H), 4.42 (br. s, 2H, N**7**-H_2), 3.06 (s, 3H, C**9**-H_3), 2.79 (tt, *J* = 7.0, 4.0 Hz, 1H, C**10**-H), 0.66 – 0.49 (m, 4H, 2 × C**1**-H_2); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 172.6 (C**8**), 145.7 (C**6**), 130.4, 128.1 (C**2** and C**4**), 121.2 (C**5**), 116.9, 116.5 (C**1** and C**3**), 35.3 (C**9**), 32.7 (C**10**), 8.7 (C**11**); HRMS: (ESI$^+$) calculated for $C_{11}H_{14}N_2NaO$: 213.0998, found $[M+H]^+$: 213.1006.

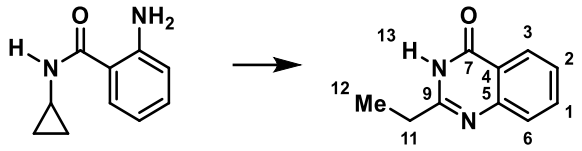
2-Amino-*N*-cyclopropylbenzamide (195e)



203e **195e**

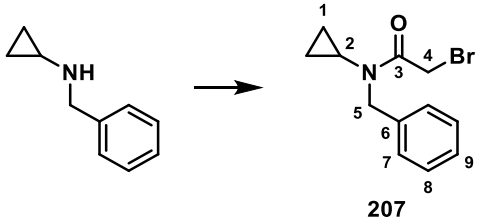
N-Cyclopropyl-2-nitrobenzamide **203e** (1.10 g, 5.33 mmol, mmol, prepared according to the literature procedure[271]) was dissolved in AcOH:EtOH (1:2, 8:16 mL) and iron (0.74 g, 13.30 mmol) was added at r.t. The reaction mixture was heated to 90 °C for 2 h, cooled to r.t. and concentrated *in vacuo*. 1.0 M aq. NaOH was added to adjust pH to ~10 and the solution was extracted with EtOAc (3 × 20 mL). The organic extracts were combined, washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by recrystallization (DCM/hexane, 2 crops) to afford the title compound **195e** (0.84 g, 89%) as a colourless solid; m.p. 147-148 °C (DCM/hexane); ν_{max} / cm^{-1}: 3422 (br. m), 3301 (s), 1634 (m), 1620 (s), 1588 (m), 1523 (s), 1303 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.23 (dd, *J* = 7.9, 1.5 Hz, 1H, C**4**-H), 7.18 (ddd, *J* = 8.5, 7.2, 1.5 Hz, 1H, C**2**-H), 6.66 (dd, *J* = 8.3, 1.1 Hz, 1H, C**1**-H), 6.60 (ddd, *J* = 8.1, 7.2, 1.2 Hz, 1H, C**3**-H), 6.18 (br. s, 1H, N**9**-H), 5.56 (br. s, 2H, N**7**-H_2), 2.83 (tt, *J* = 7.0, 3.8 Hz, 1H, C**10**-H), 0.88 – 0.81 (m, 2H, 2 × C**11**-H_aH_b), 0.62 – 0.56 (m, 2H, 2 × C**11**-H_aH_b); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 170.8 (C**8**), 148.8 (C**5**), 132.3 (C**2**), 127.0 (C**4**), 117.3 (C**1**), 116.4 (C**3**), 115.6 (C**7**), 22.8 (C**10**), 6.7 (C**11**); HRMS: (ESI$^+$) calculated for $C_{10}H_{13}N_2O$: 177.1022, found $[M+H]^+$: 100.1030.

2-Ethylquinazolin-4(3*H*)-one (198e)



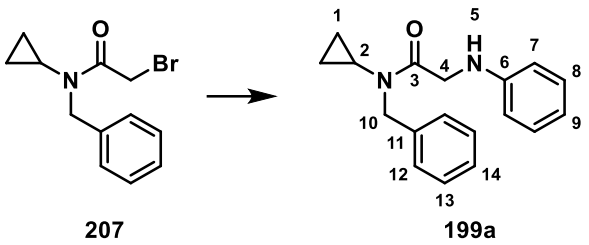
General procedure F: *In a modification to the general procedure, the reaction was heated to 140 °C.* 2-Amino-*N*-cyclopropylbenzamide **195e** (17.6 mg, 0.10 mmol) was employed. Flash column chromatography (20-30% EtOAc/hexane) afforded the title compound **198e** (5.2 mg, 30%) as a colourless solid; m.p. 230-231 °C (DCM/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 11.80 (br. s, 1H, N**13**-H), 8.29 (dd, *J* = 8.0, 1.3 Hz, 1H, C**3**-H), 7.77 (ddd, *J* = 8.2, 7.0, 1.3 Hz, 1H, C**1**-H), 7.70 (d, *J* = 8.2 Hz, 1H, C**6**-H), 7.47 (ddd, *J* = 8.0, 7.0, 1.2 Hz, 1H, C**2**-H), 2.87 (q, *J* = 7.3 Hz, 2H, C**11**-H_2), 1.46 (t, *J* = 7.3 Hz, 3H, C**12**-H_3); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 164.4 (C**7**), 157.7 (C**9**), 149.5 (C**5**), 134.8, 127.2, 126.4, 126.3 (C**1**, C**2**, C**3**, and C**6**), 120.5 (C**4**), 29.2 (C**11**), 11.6 (C**12**). The spectroscopic properties of this compound were consistent with the data available in the literature.[272]

***N*-Benzyl-2-bromo-*N*-cyclopropylacetamide (207)**



To a solution of *N*-benzylcyclopropanamine (2.00 g, 13.61 mmol, prepared according to the literature procedure[50]) and potassium carbonate (2.57 g, 16.33 mmol) in dry DCM (30 mL) under a nitrogen atmosphere, bromoacetyl bromide (1.42 mL, 16.33 mmol) was added dropwise at 0 °C. The reaction was warmed to room temperature and stirred for 18 h. Water (30 mL) was added and the solution was extracted with DCM (3 × 30 mL). The organic extracts were combined, washed with brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford 2-bromoacetamide **207** (3.63, 99%) as a pale yellow oil which was used in the following step without further purification; ν_{max} / cm^{-1}: 1652 (s), 1428 (m), 1400 (s), 1372 (m), 1212 (m), 1031 (m), 696 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35 – 7.23 (m, 5H, 2 × C**7**-H, 2 × C**8**-H and C**9**-H), 4.62 (s, 2H, C**5**-H_2), 4.18 (s, 2H, C**4**-H_2), 2.70 (tt, *J* = 6.8, 4.2 Hz, 1H, C**2**-H), 0.92 – 0.84 (m, 4H, 2 × C**1**-H_2); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 169.5 (C**3**), 137.5 (C**6**), 128.7, 128.0 (C**7** and C**8**), 127.5 (C**9**), 50.4 (C**5**), 30.3 (C**2**), 27.5 (C**4**), 9.2 (C**1**); HRMS: (ESI^+) calculated for $C_{12}H_{15}NOBr$: 268.0332, found $[M+H]^+$: 238.0334.

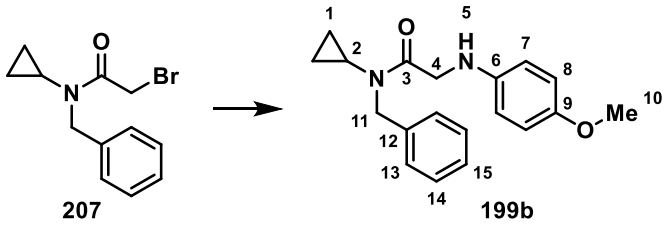
***N*-Benzyl-*N*-cyclopropyl-2-(phenylamino)acetamide (199a)**



207 **199a**

General procedure E: *In a modification to the general procedure, toluene (10 mL) and aniline (40 mL) were used.* *N*-Benzyl-2-bromo-*N*-cyclopropylacetamide **207** (6.37 g, 23.76 mmol) was employed and the reaction was stirred at 80 °C for 18 h. The residue was purified twice by recrystallization (DCM/hexane) to afford the title compound **199a** (2.98 g, 45%) as a colourless solid; m.p. 109-110 °C (DCM/hexane); ν_{max} / cm^{-1}: 3388 (br. w), 1660 (s), 1604 (s), 1507 (s), 1404 (s), 750 (m), 694 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35 – 7.17 (m, 7H, 2 × C**8**-H, 2 × C**12**-H, 2 × C**13**-H and C**14**-H), 6.73 (t, *J* = 7.3 Hz, 1H, C**9**-H), 6.66 (d, *J* = 7.9 Hz, 2H, 2 × C**7**-H), 4.91 (br. s, 1H, N**5**-H), 4.66 (s, 2H, C**10**-H_2), 4.12 (s, 2H, C**4**-H_2), 2.61 (tt, *J* = 6.8, 4.1 Hz, 1H, C**2**-H), 0.97 – 0.81 (m, 4H, 2 × C**1**-H_2); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 172.4 (C**3**), 147.7 (C**6**), 137.8 (C**11**), 129.4 (C**8**), 128.7, 127.9 (C**12** and C**13**), 127.5 (C**14**), 117.7 (C**9**), 113.1 (C**7**), 50.4 (C**4**), 46.5 (C**10**), 29.0 (C**2**), 8.8 (C**1**); HRMS: (ESI^+) calculated for $C_{18}H_{21}N_2O$: 281.1648, found $[M+H]^+$: 281.1651.

***N*-Benzyl-*N*-cyclopropyl-2-((4-methoxyphenyl)amino)acetamide (199b)**

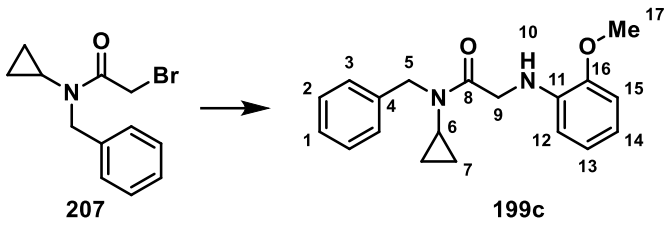


207 **199b**

General procedure E: *N*-Benzyl-2-bromo-*N*-cyclopropylacetamide **207** (1.00 g, 3.73 mmol) and *p*-anisidine (2.30 g, 18.65 mmol) were employed and the reaction was stirred at 90 °C for 3 h. The residue was purified by flash column chromatography (30% EtOAc/toluene) to afford the title compound **199b** (0.51 g, 48%) as an off-white solid; m.p. 88-89 °C (DCM/hexane); ν_{max} / cm^{-1}: 3372 (br. w), 2935 (br. w), 2831 (w), 1659 (s), 1513 (s), 1396 (m), 1234 (s), 1036 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.33 – 7.21 (m, 5H, 2 × C**13**-H, 2 × C**14**-H and C**15**-H), 6.80 (d, *J* = 8.8 Hz, 2H, 2 × C**7**-H), 6.63 (d, *J* = 8.8 Hz, 2H, 2 × C**8**-H), 4.65 (s, 2H, C**11**-H_2), 4.63 (br. s, 1H, N**5**-H),

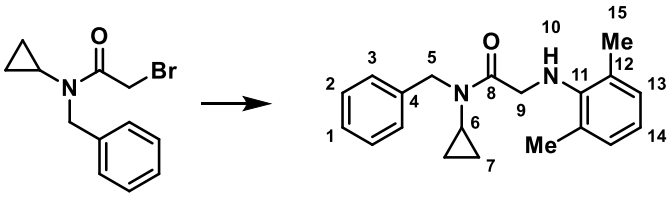
4.09 (s, 2H, C**4**-H$_2$), 3.75 (s, 3H, C**10**-H$_3$), 2.60 (tt, *J* = 6.9, 4.0 Hz, 1H, C**2**-H), 0.94 – 0.81 (m, 4H, 2 × C**1**-H$_2$); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 172.6 (C**3**), 152.3 (C**9**), 142.0 (C**6**), 137.7 (C**12**), 128.6 (C**14**), 127.8 (C**13**), 127.3 (C**15**), 114.9 (C**7**), 114.3 (C**8**), 55.8 (C**10**), 50.2 (C**11**), 47.3 (C**4**), 28.9 (C**2**), 8.7 (C**1**); HRMS: (ESI$^+$) calculated for $C_{19}H_{23}N_2O_2$: 311.1754, found [M+H]$^+$: 311.1765.

***N*-Benzyl-*N*-cyclopropyl-2-((2-methoxyphenyl)amino)acetamide (199c)**



General procedure E: *N*-Benzyl-2-bromo-*N*-cyclopropylacetamide **207** (1.00 g, 3.73 mmol) and *o*-anisidine (2.30 g, 18.65 mmol) were employed and the reaction was stirred at 90 °C for 5 h. The residue was purified by recrystallization (DCM/hexane) to afford the title compound **199c** (0.75 g, 65%) as a colourless solid; m.p. 134-135 °C (DCM/hexane); ν_{max} / cm^{-1}: 3407 (br. w), 1657 (s), 1601 (s), 1515 (s), 1401 (s), 1245 (m), 1221 (s), 1027 (s); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.36 – 7.25 (m, 5H, C**1**-H, 2 × C**2**-H and 2 × C**3**-H), 6.92 – 6.87 (m, 1H, C**13**-H), 6.84 – 6.80 (m, 1H, C**12**-H), 6.75 – 6.70 (m, 1H, C**14**-H), 6.56 (d, *J* = 7.6 Hz, 1H, C**15**-H), 5.41 (br. s, 1H, N**10**-H), 4.69 (s, 2H, C**5**-H$_2$), 4.17 (d, *J* = 3.9 Hz, 2H, C**9**-H$_2$), 3.89 (s, 3H, C**17**-H$_3$), 2.64 (tt, *J* = 6.7, 4.2 Hz, 1H, C**6**-H), 0.98 – 0.84 (m, 4H, 2 × C**7**-H$_2$); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 172.5 (C**8**), 147.4 (C**11**), 138.0, 137.8 (C**4** and C**16**), 128.7, 128.0 (C**2** and C**3**), 127.4 (C**1**), 121.2 (C**13**), 117.0 (C**14**), 110.0 (C**15**), 109.7 (C**12**), 55.6 (C**17**), 50.3 (C**5**), 46.4 (C**9**), 29.0 (C**6**), 8.8 (C**7**); HRMS: (ESI$^+$) calculated for $C_{19}H_{23}N_2O_2$: 311.1754, found [M+H]$^+$: 311.1752.

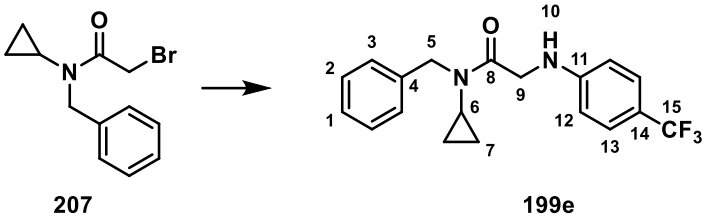
***N*-Benzyl-*N*-cyclopropyl-2-((2,6-dimethylphenyl)amino)acetamide (199d)**



207 **199d**

General procedure E: *N*-Benzyl-2-bromo-*N*-cyclopropylacetamide **207** (1.00 g, 3.73 mmol) and 3,5-xylidine (2.26 g, 18.65 mmol) were employed and the reaction was stirred at 90 °C for 2 h. The residue was purified by flash column chromatography (5-20% EtOAc/hexane) to afford the title compound **199d** (0.86 g, 75%) as a pale yellow oil; ν_{max} / cm^{-1}: 3357 (br. w), 2940 (w), 1657 (s), 1476 (m), 1398 (s), 1265 (s), 1030 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.33 – 7.20 (m, 5H, C**1**-H, 2 × C**2**-H and 2 × C**3**-H), 6.99 (d, *J* = 7.4 Hz, 2H, 2 × C**13**-H), 6.80 (t, *J* = 7.5 Hz, 1H, C**14**-H), 4.76 (br. s, 1H, N**10**-H), 4.64 (s, 2H, C**5**-H_2), 4.05 (s, 2H, C**9**-H_2), 2.49 (tt, *J* = 6.8, 4.0 Hz, 1H, C**6**-H), 2.36 (s, 6H, 2 × C**15**-H_3), 0.86 – 0.73 (m, 4H, 2 × C**7**-H_2); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 173.6 (C**8**), 147.1 (C**11**), 137.8 (C**4**), 128.8 (C**13**), 128.6 (C**2** or C**3**), 128.2 (C**12**), 127.8 (C**2** or C**3**), 127.3 (C**1**), 121.2 (C**14**), 51.0 (C**9**), 50.3 (C**5**), 28.8 (C**6**), 19.1 (C**15**), 8.5 (C**7**); HRMS: (ESI^+) calculated for $C_{20}H_{25}N_2O$: 309.1961, found $[M+H]^+$: 309.1955.

***N*-Benzyl-*N*-cyclopropyl-2-((4-(trifluoromethyl)phenyl)amino)acetamide (199e)**

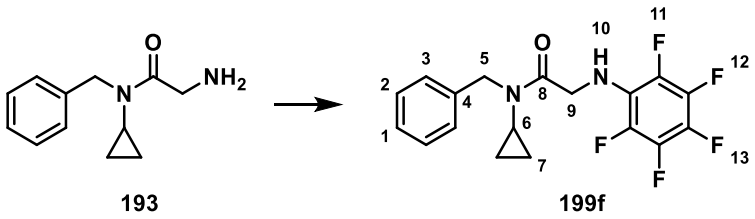


207 **199e**

General procedure E: *N*-Benzyl-2-bromo-*N*-cyclopropylacetamide **207** (0.99 g, 3.69 mmol) and 4-(trifluoromethyl)aniline (0.60 g, 3.69 mmol) were employed and the reaction was stirred at 90 °C for 5 h. The residue was purified by recrystallization (DCM/hexane) to afford the title compound **199e** (0.51 g, 41%) as a colourless solid; m.p. 147-148 °C (DCM/hexane); ν_{max} / cm^{-1}: 3350 (m), 1657 (s), 1616 (s), 1406 (m), 1330 (s), 1290 (m), 1097 (s), 1066 (s), 727 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.42 (d, *J* = 8.3 Hz, 2H, 2 × C**13**-H), 7.36 – 7.22 (m, 5H, C**1**-H, 2 × C**2**-H and 2 × C**3**-H), 6.64 (d, *J* = 8.3 Hz, 2H, 2 × C**12**-H), 5.30 (br. s, 1H, N**10**-H), 4.67 (s, 2H, C**5**-H_2), 4.13 (d, *J* = 4.3 Hz, 2H, C**9**-H_2), 2.62 (tt, *J* = 6.9, 4.0 Hz, 1H, C**6**-H), 0.99 – 0.84 (m, 4H, 2 × C**7**-H_2); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 171.69 (C**8**), 149.85 (C**11**), 137.66 (C**4**), 128.80, 127.93 (C**2** and C**3**), 127.58 (C**1**), 126.79 (q, *J* = 3.7 Hz, C**13**), 125.12 (q, *J* = 270.3 Hz, C**15**), 119.14 (q, *J* =

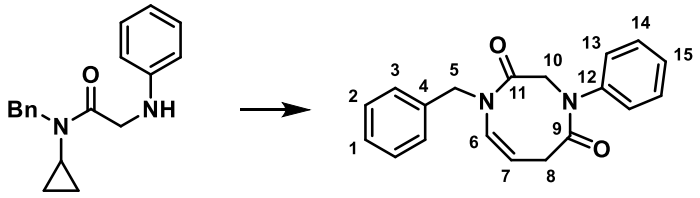
32.6 Hz, C**14**), 112.21 (C**12**), 50.49 (C**5**), 45.82 (C**9**), 29.02 (C**6**), 8.81 (C**7**); ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.40; HRMS: (ESI^+) calculated for $C_{19}H_{19}F_3N_2NaO$: 371.1342, found $[M+Na]^+$: 371.1349.

***N*-Benzyl-*N*-cyclopropyl-2-((perfluorophenyl)amino)acetamide (199f)**



To a sealed tube containing a solution of primary amine **193** (0.30 g, 1.47 mmol, provided by Dr Calow) in dimethyl sulfoxide (1.5 mL), hexafluorobenzene (0.16 mL, 1.40 mmol) and potassium fluoride (0.08 g, 2.20 mmol) were added. The tube was sealed and heated to 100 °C for 18 h. The solution was cooled to r.t. and water (10 mL) and EtOAc (10 mL) were added. The layers were separated and the organic portion was washed with water (3 × 5 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (40% EtOAc/hexane) to afford the title compound **199f** (0.43 g, 83%) as a yellow oil; ν_{max} / cm^{-1}: 3358 (br. w), 1664 (s), 1522 (s), 1405 (s), 1267 (m), 1025 (s), 965 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35 – 7.20 (m, 5H, C**1**-H, 2 × C**2**-H and 2 × C**3**-H), 4.95 (br. s, 1H, N**10**-H), 4.64 (s, 2H, C**5**-H_2), 4.34 (s, 2H, C**9**-H_2), 2.56 (tt, *J* = 7.2, 4.1 Hz, 1H, C**6**-H), 0.95 – 0.77 (m, 4H, 2 × C**7**-H_2); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 171.9 (C**8**), 137.6 (C**4**), 128.8 (C**2**), 127.9 (C**3**), 127.6 (C**1**), 50.5 (C**5**), 48.0 (C**9**), 28.9 (C**6**), 8.8 (C**7**); *The aromatic signals corresponding to the pentafluorophenyl group could not be resolved due to their weak intensity*; ^{19}F NMR ($CDCl_3$, 376 MHz): δ -159.94 – -160.07 (m, F**11**), -164.46 – -164.62 (m, F**12**), -172.09 (tt, *J* = 22.0, 6.7 Hz, F**13**); HRMS: (ESI^+) calculated for $C_{18}H_{15}F_5N_2NaO$: 393.0997, found $[M+Na]^+$: 393.0988.

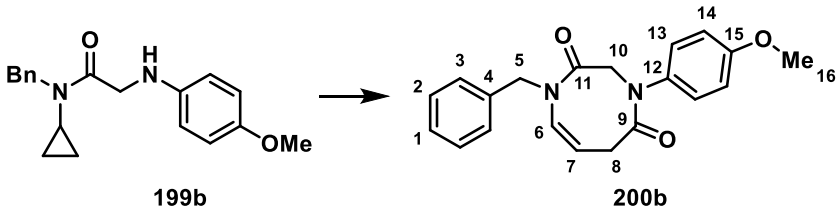
(*Z*)-1-Benzyl-4-phenyl-1,3,4,6-tetrahydro-1,4-diazocine-2,5-dione (200a)



199a **200a**

General procedure F: *In a modification to the general procedure, sodium tert-butoxide (5 mol%) was used and the reaction was stirred at 160 °C.* *N*-Benzyl-*N*-cyclopropyl-2-(phenylamino)acetamide **199a** (28.0 mg, 0.10 mmol) was employed. Flash column chromatography (5-10% acetone/toluene) afforded the title compound **200a** (14.2 mg, 46%) as a light brown oil; ν_{max} / cm^{-1}: 1653 (s), 1493 (m), 1454 (m), 1402 (s), 1216 (s), 724 (s), 698 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.42 – 7.23 (m, 10H, 2 × C**2**-H, 2 × C**3**-H, 2 × C**13**-H, 2 × C**14**-H, C**1**-H and C**15**-H), 6.39 (d, *J* = 7.2 Hz, 1H, C**6**-H), 5.59 (td, *J* = 8.1, 7.2 Hz, 1H, C**7**-H), 4.68 (s, 2H, C**5**-H_2), 4.42 (s, 2H, C**10**-H_2), 3.05 (dd, *J* = 8.2, 1.1 Hz, 2H, C**8**-H_2); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 166.8 (C**11**), 166.5 (C**9**), 145.2 (C**12**), 135.7 (C**4**), 132.7 (C**6**), 129.4 (C**14**), 129.0, 128.9 (C**3** and C**2**), 128.3, 127.3 (C**1** and C**15**), 126.8 (C**13**), 116.8 (C**7**), 56.8 (C**10**), 50.2 (C**5**), 36.8 (C**8**); HRMS: (ESI^+) calculated for $C_{19}H_{19}N_2O_2$: 307.1441, found $[M+H]^+$: 307.1444.

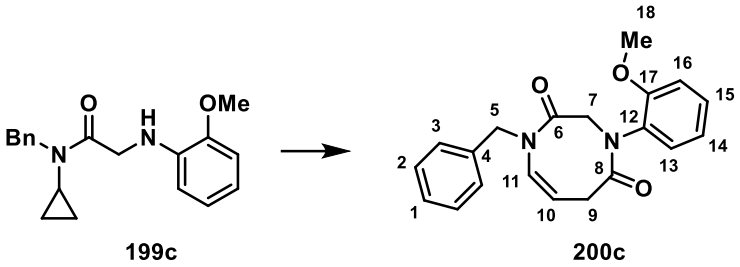
(*Z*)-1-Benzyl-4-(4-methoxyphenyl)-1,3,4,6-tetrahydro-1,4-diazocine-2,5-dione (200b)



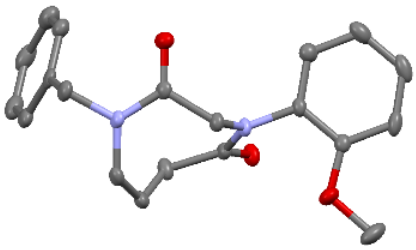
199b **200b**

General procedure F: *N*-Benzyl-*N*-cyclopropyl-2-((4-methoxyphenyl)amino)acetamide **199b** (31.0 mg, 0.10 mmol) was employed. Flash column chromatography (5-10% acetone/toluene) afforded the title compound **200b** (10.4 mg, 31%) as a light brown oil; ν_{max} / cm^{-1}: 2940 (br. w), 1658 (s), 1499 (s), 1455 (s), 1407 (s), 1266 (m), 1242 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.39 – 7.27 (m, 5H, 2 × C**2**-H, 2 × C**3**-H and C**1**-H), 7.22 – 7.17 (m, 2H, 2 × C**13**-H), 6.92 – 6.87 (m, 2H, 2 × C**14**-H), 6.37 (d, *J* = 7.2 Hz, 1H, C**6**-H), 5.57 (td, *J* = 8.1, 7.2 Hz, 1H, C**7**-H), 4.67 (s, 2H, C**5**-H_2), 4.39 (s, 2H, C**10**-H_2), 3.80 (s, 3H, C**16**-H_3), 3.04 (dd, *J* = 8.1, 1.1 Hz, 2H, C**8**-H_2); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 166.9 (C**11**), 166.7 (C**9**), 158.5 (C**15**), 138.1 (C**12**), 135.8 (C**4**), 132.6 (C**6**), 129.0 (C**3**), 128.9 (C**2**), 128.3 (C**1**), 127.8 (C**13**), 116.9 (C**7**), 114.7 (C**14**), 57.1 (C**10**), 55.6 (C**16**), 50.2 (C**5**), 36.7 (C**8**); HRMS: (ESI^+) calculated for $C_{20}H_{20}N_2NaO_3$: 359.1366, found $[M+Na]^+$: 359.1360.

(*Z*)-1-Benzyl-4-(2-methoxyphenyl)-1,3,4,6-tetrahydro-1,4-diazocine-2,5-dione (200c)

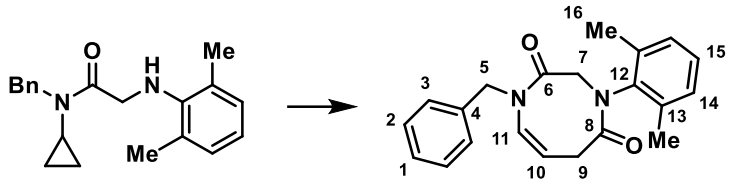


General procedure F: *N*-Benzyl-*N*-cyclopropyl-2-((2-methoxyphenyl)amino)acetamide **199c** (31.0 mg, 0.10 mmol) was employed. Flash column chromatography (5% acetone/toluene) afforded the title compound **200c** (14.1 mg, 42%) as a colourless solid; m.p. 139-140 °C (DCM/Et_2O/hexane); ν_{max} / cm^{-1}: 2938 (br. w), 1658 (s), 1499 (s), 1455 (s), 1405 (s), 1266 (m), 1241 (m), 1214 (m); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.38 – 7.24 (m, 7H, C**1**-H, C**13**-H, C**15**-H, 2 × C**2**-H and 2 × C**3**-H), 6.97 (td, *J* = 7.6, 1.2 Hz, 1H, C**14**-H), 6.93 (dd, *J* = 8.2, 1.2 Hz, 1H, C**16**-H), 6.35 (d, *J* = 7.3 Hz, 1H, C**11**-H), 5.58 (td, *J* = 8.1, 7.3 Hz, 1H, C**10**-H), 4.86 (br. s, 1H, C**5**-H_2), 4.59 (br. s, 1H, C**7**-H_2), 4.50 (br. s, 1H, C**5**-H_2), 4.00 (br. s, 1H, C**7**-H_2), 3.80 (s, 3H, C**18**-H_3), 3.06 (d, *J* = 8.1 Hz, 2H, C**9**-H_2); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 167.0 (C**6**), 166.6 (C**8**), 154.5 (C**17**), 135.9 (C**4**), 133.9 (C**12**), 132.4 (C**11**), 129.1, 129.0 (C**13** and C**15**), 129.0, 128.9 (C**2** and C**3**), 128.2 (C**1**), 121.3 (C**14**), 116.9 (C**10**), 112.1 (C**16**), 56.4 (C**7**), 55.9 (C**18**), 50.1 (C**5**), 36.5 (C**9**); HRMS: (ESI^+) calculated for $C_{20}H_{21}N_2O_3$: 337.1547, found $[M+H]^+$: 337.1551. *The structure of **200c** was determined unambiguously by X-ray crystallography*.



Crystal image of **200c** generated in Olex2, ellipsoids at 50% probability, hydrogen atoms omitted for clarity; Crystal data for **200c**: $C_{20}H_{20}N_2O_3$, MW = 336.38, orthorhombic, space group $P2_12_12_1$, a = 7.7872(10) Å, b = 9.6572(12) Å, c = 22.965(3) Å, V = 1727.1(4) $Å^3$, α = 90.00°, β = 90.00°, γ = 90.00°, Z = 4, D_c = 1.294 g/cm^3, Mo-Kα radiation, λ = 0.71073 Å, μ = 0.088 mm^{-1}, T = 100 K; colourless block, crystal size 0.35 × 0.305 × 0.2 mm^3, Bruker Apex II diffractometer, 8460 reflections were collected, 4057 were unique, R_{int} = 0.0312; refinement on F^2 gave R_1 = 0.0422 and wR_2 = 0.0881, GOF = 1.028 for 227 refined parameters.

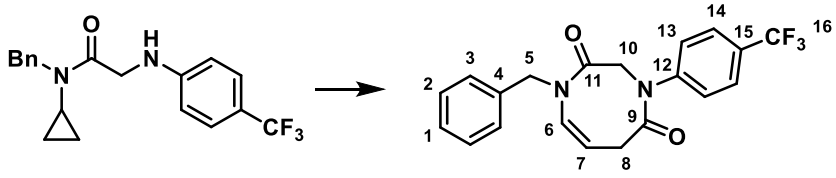
(*Z*)-1-Benzyl-4-(2,6-dimethylphenyl)-1,3,4,6-tetrahydro-1,4-diazocine-2,5-dione (200d)



199d **200d**

General procedure F: *N*-Benzyl-*N*-cyclopropyl-2-((2,6-dimethylphenyl)amino)acetamide **199d** (30.8 mg, 0.10 mmol) was employed. Flash column chromatography (5-10% acetone/toluene) afforded the title compound **200d** (10.0 mg, 30%) as a light brown oil; ν_{max} / cm^{-1}: 2924 (br. w), 1656 (s), 1456 (m), 1405 (s), 1212 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.39 – 7.30 (m, 5H, C**1**-H, 2 × C**2**-H and 2 × C**3**-H), 7.15 – 7.07 (m, 3H, C**15**-H and 2 × C**14**-H), 6.42 (d, *J* = 7.1 Hz, 1H, C**11**-H), 5.62 (td, *J* = 8.3, 7.1 Hz, 1H, C**10**-H), 4.69 (s, 2H, C**5**-H_2), 4.17 (s, 2H, C**7**-H_2), 3.06 (dd, *J* = 8.3, 1.1 Hz, 2H, C**9**-H_2), 2.23 (s, 6H, 2 × C**16**-H_3); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 166.3 (C**6**), 165.7 (C**8**), 142.9 (C**12**), 135.6 (C**4**), 135.1 (C**13**), 132.7 (C**11**), 129.0, 128.9 (C**2** and C**3**), 128.8 (C**14**), 128.3 (C**1**), 128.1 (C**15**), 116.8 (C**10**), 56.1 (C**7**), 50.2 (C**5**), 36.1 (C**9**), 18.0 (C**16**); HRMS: (ESI^+) calculated for $C_{21}H_{22}N_2NaO_2$: 357.1573, found $[M+Na]^+$: 357.1569.

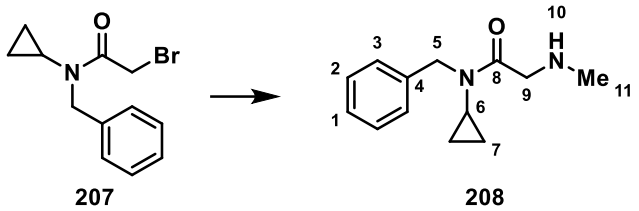
(*Z*)-1-Benzyl-4-(4-(trifluoromethyl)phenyl)-1,3,4,6-tetrahydro-1,4-diazocine-2,5-dione (200e)



199e **200e**

General procedure F: *N*-Benzyl-*N*-cyclopropyl-2-((4-(trifluoromethyl)phenyl)-amino)-acetamide **199e** (34.8 mg, 0.10 mmol) was employed. Flash column chromatography (5% acetone/toluene) afforded the title compound **200e** (6.4 mg, 17%) as a pale brown oil; ν_{max} / cm^{-1}: 1659 (s), 1401 (m), 1321 (s), 1163 (s), 1108 (s), 1066 (m), 722 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.67 – 7.63 (m, 2H, 2 × C**14**-H), 7.48 – 7.44 (m, 2H, 2 × C**13**-H), 7.39 – 7.31 (m, 5H, C**1**-H, 2 × C**2**-H and 2 × C**3**-H), 6.42 (dt, *J* = 7.2, 1.2 Hz, 1H, C**6**-H), 5.60 (td, *J* = 8.1, 7.2 Hz, 1H, C**7**-H), 4.69 (s, 2H, C**5**-H_2), 4.44 (s, 2H, C**10**-H_2), 3.05 (dd, *J* = 8.1, 1.2 Hz, 2H, C**8**-H_2); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 166.6, 166.5 (C**9** and C**11**), 148.0 (C**12**), 135.6 (C**4**), 133.0 (C**6**), 129.21 (q, *J* = 32.8 Hz, C**15**), 129.0, 129.0 (C**2** and C**3**), 128.4 (C**1**), 127.2 (C**13**), 126.53 (q, *J* = 3.7 Hz, C**14**), 123.98 (q, *J* = 271.7 Hz, C**16**), 116.7 (C**7**), 56.3 (C**10**), 50.3 (C**5**), 36.8 (C**8**); ^{19}F NMR (376 MHz, $CDCl_3$) δ -60.87; HRMS: (ESI^+) calculated for $C_{20}H_{18}F_3N_2O_2$: 375.1315, found $[M+H]^+$: 375.1317.

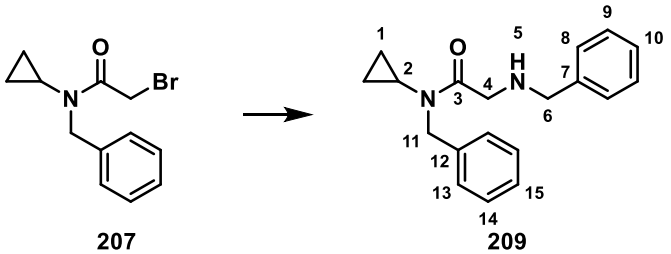
***N*-Benzyl-*N*-cyclopropyl-2-(methylamino)acetamide (208)**



207 **208**

To a sealed tube containing a solution of 2-bromoacetamide **207** (1.00 g, 1.47 mmol) in ethanol (5 mL), methylamine solution (40% in H_2O, 5 mL) was added. The tube was sealed and heated to 65 °C for 18 h. The solution was cooled to r.t., the solvent was removed *in vacuo* and the residue was redissolved in EtOAc (20 mL) and washed with sat. aq. $NaHCO_3$ (20 mL). The aqueous portion was further extracted with EtOAc (2 × 10 mL) and the organic extracts were combined, washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (0-10% MeOH/EtOAc) to afford the title compound **208** (0.30 g, 37%) as a yellow oil; ν_{max} / cm^{-1}: 3337 (br. w), 2940 (w), 1652 (s), 1402 (s), 1374 (s), 1264 (s), 1031 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.33 – 7.20 (m, 5H, C**1**-H, 2 × C**2**-H and 2 × C**3**-H), 4.62 (s, 2H, C**5**-H_2), 3.62 (s, 2H, C**9**-H_2), 2.52 (tt, *J* = 7.1, 4.2 Hz, 1H, C**6**-H), 2.47 (s, 3H, C**11**-H_3), 2.31 (s, 1H, N**10**-H), 0.87 – 0.73 (m, 4H, 2 × C**7**-H_2); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 174.1 (C**8**), 138.1 (C**4**), 128.6 (C**2**), 127.9 (C**3**), 127.3 (C**1**), 53.3 (C**9**), 50.1 (C**5**), 36.6 (C**11**), 29.1 (C**6**), 9.0 (C**7**); HRMS: (ESI^+) calculated for $C_{13}H_{19}N_2O$: 219.1492, found $[M+H]^+$: 219.1497.

***N*-Benzyl-2-(benzylamino)-*N*-cyclopropylacetamide (209)**

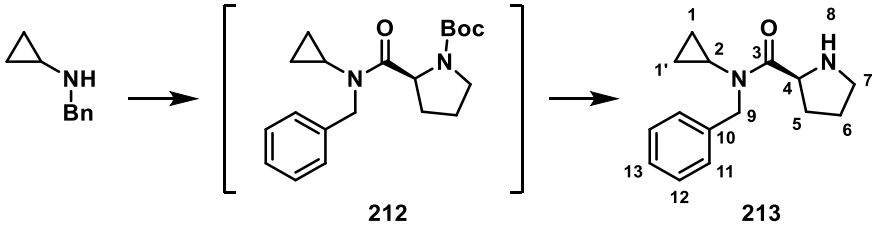


207 **209**

To a solution of *N*-Benzyl-2-bromo-*N*-cyclopropylacetamide **207** (0.76 g, 2.83 mmol) in toluene (30 mL), benzylamine (1.24 mL, 11.34 mmol) and K_2CO_3 (1.65 g, 11.90 mmol) were added. The reaction mixture was heated at 80 °C for 18 h, concentrated *in vacuo* and then water (30 mL) was added. The solution was extracted with EtOAc (3 × 30) and then the organic extracts were combined, washed with brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (80% EtOAc/hexane) to afford the title compound **209** (0.51 g, 61%) as a colourless oil; ν_{max} / cm^{-1}: 3328 (br. w), 1653 (s), 1453 (m), 1404 (s), 1264

(m), 1030 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38 – 7.21 (m, 10H, 2 × C**8**-H, 2 × C**9**-H, 2 × C**13**-H, 2 × C**14**-H, C**10**-H and C**15**-H), 4.62 (s, 2H, C**11**-H_2), 3.84 (s, 2H, C**6**-H_2), 3.66 (s, 2H, C**4**-H_2), 2.47 (tt, *J* = 6.8, 4.2 Hz, 1H, C**2**-H), 0.81 – 0.67 (m, 4H, 2 × C**1**-H_2); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 174.3 (C**3**), 140.1 (C**7**), 138.2 (C**12**), 128.6, 128.5, 128.4, 127.9, 127.3, 127.1 (C**8**, C**9**, C**10**, C**13**, C**14** and C**15**), 53.8 (C**6**), 50.6 (C**4**), 50.1 (C**11**), 29.1 (C**2**), 8.9 (C**1**); HRMS: (ESI$^+$) calculated for $C_{19}H_{23}N_2O$: 295.1805, found $[M+H]^+$: 295.1809.

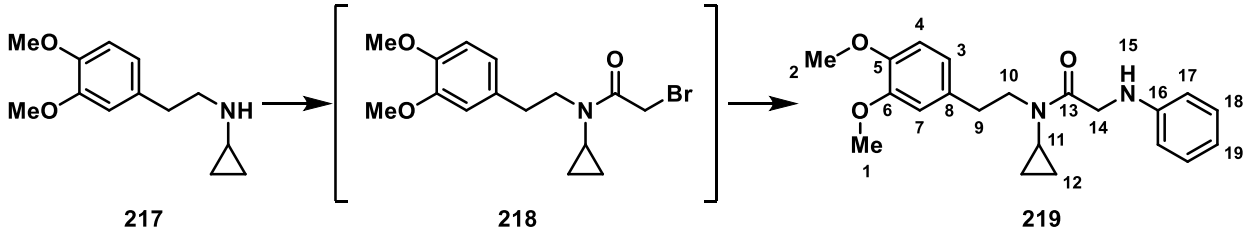
***N*-Benzyl-*N*-cyclopropylpyrrolidine-2-carboxamide (213)**



To a solution of *N*-(*tert*-butoxycarbonyl)-proline (1.46 g, 6.79 mmol) in DCM (0.3 M), EDCI (1.43 g, 7.47 mmol) was added and the reaction was stirred at r.t. for 10 min. Then, *N*-benzylcyclopropanamine (1.00 g, 6.79 mmol) and 4-dimethylaminopyridine (0.08 g, 0.68 mmol) were added and the reaction was stirred at r.t. for 18 h, washed with 2.0 M aq. HCl (30 mL), water (30 mL), sat. aq. $NaHCO_3$ (30 mL), and brine (30 mL). Organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The resulting amide **212** was isolated as a colourless solid (1.15 g, 49%) and used in the next step without purification. *tert*-Butyl 2-(benzyl(cyclopropyl)carbamoyl)-pyrrolidine-1-carboxylate **212** (0.60 g, 1.74 mmol) in DCM (3 mL) was treated with TFA (1.3 mL, 17.41 mmol) and the solvent was removed *in vacuo* after 1h. The residue was dissolved in DCM (30 mL), water (30 mL) and K_2CO_3 (approx. 1.0 g) were added and layers were separated. The aqueous portion was further extracted with DCM (2 × 20 mL) and the organic extracts were combined, washed with brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (1% MeOH/DCM) to afford the title compound **213** (0.41 g, 97%) as a colourless oil; ν_{max} / cm^{-1}: 3430 (br. w), 2969 (br. m), 1649 (s), 1451 (s), 1400 (s), 1373 (s), 1200 (s), 1173 (s), 1127 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.33 – 7.17 (m, 5H, 2 × C**11**-H, 2 × C**12**-H and C**13**-H), 5.45 (br. s, 1H, N**8**-H), 4.89 (d, *J* = 14.6 Hz, 1H, C**9**-H_aH_b), 4.72 (dd, *J* = 8.4, 7.0 Hz, 1H, C**4**-H), 4.31 (d, *J* = 14.6 Hz, 1H, C**9**-H_aH_b), 3.28 (dt, *J* = 11.1, 6.6 Hz, 1H, C**7**-H_aH_b), 3.11 (dt, *J* = 11.1, 7.0 Hz, 1H, C**7**-H_aH_b), 2.57 – 2.50 (m, 1H, C**2**-H), 2.29 (dtd, *J* = 12.5, 8.4, 6.2 Hz, 1H, C**5**-H_aH_b), 2.03 – 1.81 (m, 2H, C**6**-H_2), 1.78 – 1.68 (m, 1H, C**5**-H_aH_b), 0.99 – 0.89 (m, 2H, C**1**-H_2), 0.86 – 0.77 (m, 2H, C**1'**-H_2); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 175.0 (C**3**), 137.6 (C**10**), 128.8, 127.8 (C**11** and C**12**), 127.5 (C**13**), 58.8 (C**4**), 50.8 (C**9**), 47.3 (C**7**), 30.2

(C**5**), 29.6 (C**2**), 26.1 (C**6**), 10.1 (C**1**), 8.3 (C**1'**); HRMS: (ESI$^+$) calculated for $C_{15}H_{21}N_2O$: 245.1648, found $[M+H]^+$: 245.1642.

N-Cyclopropyl-*N*-(3,4-dimethoxyphenethyl)-2-(phenylamino)acetamide (219)

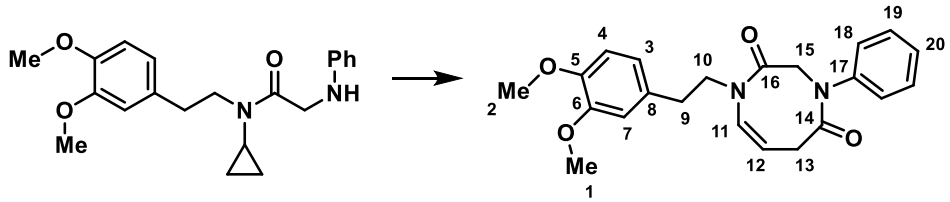


217 **218** **219**

To a solution of *N*-(3,4-dimethoxyphenethyl)cyclopropanamine **217** (1.50 g, 6.78 mmol, prepared according to the literature procedure[50]) and potassium carbonate (1.12 g, 8.13 mmol) in dry DCM (15 mL) under a nitrogen atmosphere, bromoacetyl bromide (0.71 mL, 8.13 mmol) was added dropwise at 0 °C. The reaction was warmed to room temperature and stirred for 18 h. Water (30 mL) was added and the solution was extracted with DCM (3 × 20 mL). The organic extracts were combined, washed with brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford 2-bromoacetamide **218** (1.96, 84%) as a brown oil which was used in the following step without further purification.

General procedure E: 2-Bromo-*N*-cyclopropylacetamide **218** (1.50 g, 4.38 mmol) and aniline (15 mL) were employed and the reaction was stirred at 90 °C for 4 h. The residue was purified by flash column chromatography (20-40% EtOAc/hexane) to afford the title compound **219**(0.83 g, 54%) as an off-white solid; m.p. 122-123 °C; ν_{max} / cm^{-1}: 3383 (br. w), 1655 (s), 1602 (s), 1508 (s), 1406 (s), 1260 (s), 1235 (s), 1027 (s), 750 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.20 (dd, *J* = 8.5, 7.3 Hz, 2H, 2 × C**18**-H), 6.81 – 6.70 (m, 4H, C**4**-H, C**7**-H and 2 × C**17**-H), 6.67 – 6.61 (m, 2H, C**3**-H and C**19**-H), 4.87 (br. s, 1H, N**15**-H), 4.02 (s, 2H, C**14**-H_2), 3.86 (s, 3H, C**1**-H_3 or C**2**-H_3), 3.86 (s, 3H, C**1**-H_3 or C**2**-H_3), 3.65 (t, *J* = 7.5 Hz, 2H, C**10**-H_2), 2.84 (t, *J* = 7.5 Hz, 2H, C**9**-H_2), 2.49 (tt, *J* = 6.9, 4.1 Hz, 1H, C**11**-H), 0.93 – 0.86 (m, 2H, 2 × C**12**-H_aH_b), 0.74 – 0.69 (m, 2H, 2 × C**12**-H_aH_b); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 172.1 (C**13**), 149.1, 147.8, 147.7 (C**5**, C**6** and C**16**), 131.9 (C**8**), 129.4 (C**18**), 120.9, 117.7 (C**3** and C**19**), 113.1 (C**17**), 112.2, 111.4 (C**4** and C**7**), 56.0 (C**1** and C**2**), 49.2 (C**10**), 46.4 (C**14**), 34.0 (C**9**), 29.4 (C**11**), 8.9 (C**12**); HRMS: (ESI$^+$) calculated for $C_{21}H_{27}N_2O_3$: 355.2016, found $[M+H]^+$: 355.2019.

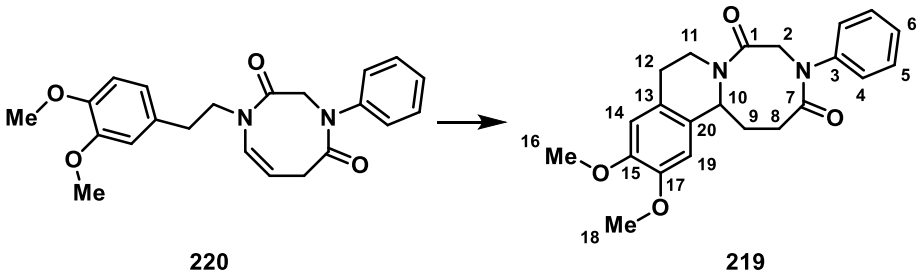
(*Z*)-1-(3,4-Dimethoxyphenethyl)-4-phenyl-1,3,4,6-tetrahydro-1,4-diazocine-2,5-dione (220)



219 **220**

General procedure F: Acetamide **219** (35.4 mg, 0.10 mmol) was employed. Flash column chromatography (1-10% acetone/toluene) afforded the title compound **220** (15.1 mg, 40%) as a brown oil; ν_{max} / cm^{-1}: 2934 (w), 1658 (s), 1515 (s), 1453 (m), 1405 (s), 1262 (s), 1236 (s), 1215 (s), 1154 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.42 – 7.36 (m, 2H, 2 × C**19**-H), 7.31 – 7.24 (m, 3H, C**20**-H and 2 × C**18**-H), 6.82 – 6.73 (m, 3H, C**3**-H, C**4**-H and C**7**-H), 6.31 (d, *J* = 7.3 Hz, 1H, C**11**-H), 5.60 (q, *J* = 7.9 Hz, 1H, C**12**-H), 4.36 (s, 2H, C**15**-H_2), 3.88 (s, 3H, C**1**-H_3 or C**2**-H_3), 3.86 (s, 3H, C**1**-H_3 or C**2**-H_3), 3. 76 (t, *J* = 7.7 Hz, 2H, C**10**-H_2), 3.24 (d, *J* = 8.1 Hz, 2H, C**13**-H_2), 2.87 (t, *J* = 7.7 Hz, 2H, C**9**-H_2); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 166.8 (C**16**), 166.4 (C**14**), 149.2 (C**5** or C**6**), 148.0 (C**5** or C**6**), 145.1 (C**17**), 133.2 (C**11**), 130.6 (C**8**), 129.4 (C**19**), 127.3 (C**20**), 126.7 (C**18**), 120.8 (C**3**), 116.1 (C**12**), 112.0 (C**7**), 111.4 (C**4**), 56.8 (C**15**), 56.1 (C**1** or C**2**), 56.0 (C**1** or C**2**), 48.1 (C**10**), 37.1 (C**13**), 33.7 (C**9**); HRMS: (ESI^+) calculated for $C_{22}H_{24}N_2NaO_4$: 403.1628, found $[M+Na]^+$: 403.1636.

11,12-Dimethoxy-4-phenyl-1,4,5,8,9,13b-hexahydro-2*H*-[1,4]diazocino[8,1-*a*]isoquinoline-3,6-dione (221)

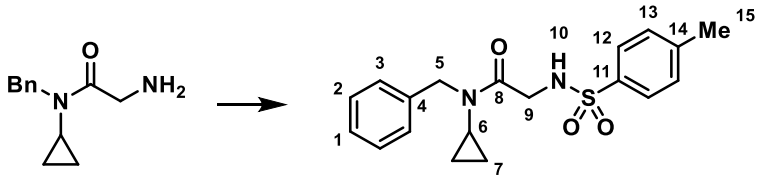


220 **219**

A solution of compound **220** (57.1 mg, 0.15 mmol) and TFA (0.12 mL, 1.50 mmol) in DCM (1.5 mL) was heated in a sealed tube at 60 °C for 24 h. The reaction mixture was cooled to r.t. and sat. aq. $NaHCO_3$ (20 mL) was added. The solution was extracted with DCM (3 × 10 mL) and the organic extracts were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (100% EtOAc) to yield the title compound **219** (42.8 mg, 75%) as a colorless solid; m.p. 242-243 °C (DCM/hexane); ν_{max} / cm^{-1}: 2935 (w), 1644 (s), 1518

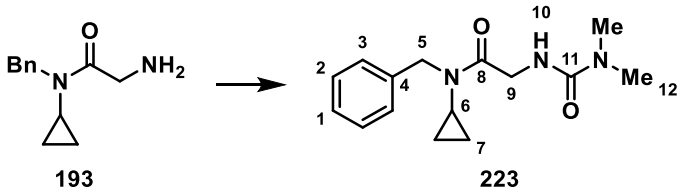
(s), 1443 (s), 1256 (s), 1210 (s), 1123 (s); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.44 – 7.39 (m, 2H, 2 × C**5**-H), 7.32 – 7.26 (m, 3H, C**6**-H and 2 × C**4**-H), 6.66 (s, 1H, C**19**-H), 6.59 (s, 1H, C**14**-H), 5.29 (br. s, 1H, C**10**-H), 4.67 (br. s, 2H, C**2**-H_2), 4.41 (br, s, 1H, C**12**-H_aH_b), 3.88 (s, 3H, C**16**/**18**-H_3), 3.87 (s, 3H C**16**/**18**-H_3), 3.37 – 3.25 (br. m, 1H, C**12**-H_aH_b), 2.93 – 2.75 (m, 4H, C**9**-H_2 and C**11**-H_2), 2.35 – 2.18 (m, 2H, C**8**-H_2); ^{13}C NMR (DMSO-*d*$_6$, 126 MHz, 80 °C): δ 172.4 (C**7**), 168.1 (C**1**), 147.8, 147.7 (C**15** and C**17**), 143.2 (C**3**), 128.7 (C**20**), 128.2 (C**5**), 126.7, 126.7 (C**4** and C**13**), 125.9 (C**6**), 112.0 (C**19**), 111.3 (C**14**), 56.3, 55.9 (C**16** and C**18**), 55.6 (C**2**), 54.2 (C**10**), 38.6 (C**12**), 35.6 (C**11**), 34.2 (C**8**), 27.0 (C**9**); HRMS: (ESI$^+$) calculated for $C_{22}H_{25}N_2O_4$: 381.1809, found $[M+H]^+$: 381.1815.

***N*-Benzyl-*N*-cyclopropyl-2-((4-methylphenyl)sulfonamido)acetamide (222)**



To a solution of amine **193** (0.20 g, 0.98 mmol, provided by Dr Calow), pyridine (0.12 mL, 1.47 mmol) and DMAP (12 mg, 0.10 mmol) in dry DCM (3 mL), tosyl chloride (0.22 g, 1.17 mmol) was added at 0 °C. The reaction was stirred for 24 h at r.t. Water (10 mL) was added and the solution was extracted with Et_2O (3 × 10 mL). The organic extracts were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (40% EtOAc/hexane) to afford the title compound **222** (0.12 g, 34%) as a colourless solid; m.p. 115-116 °C (DCM/hexane); ν_{max} / cm^{-1}: 3224 (br. w), 1652 (s), 1398 (s), 1374 (s), 1334 (s), 1160 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.77 (d, *J* = 8.3 Hz, 2H, 2 × C**12**-H), 7.33 – 7.22 (m, 5H, C**1**-H, 2 × C**2**-H and 2 × C**13**-H), 7.07 – 7.02 (m, 2H, 2 × C**3**-H), 5.72 (t, *J* = 4.5 Hz, 1H, N**10**-H), 4.49 (s, 2H, C**5**-H_2), 3.99 (d, *J* = 4.5 Hz, 2H, C**9**-H_2), 2.43 (s, 3H, C**15**-H_3), 2.42 – 2.37 (m, 1H, C**6**-H), 0.86 – 0.80 (m, 2H, 2 × C**7**-H_aH_b), 0.70 – 0.64 (m, 2H, 2 × C**7**-H_aH_b); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 170.1 (C**8**), 143.7 (C**14**), 137.3 (C**4**), 136.2 (C**11**), 129.8 (C**13**), 128.7 (C**2**), 127.7 (C**3**), 127.5 (C**1**), 127.4 (C**12**), 50.4 (C**5**), 44.7 (C**9**), 28.8 (C**6**), 21.7 (C**15**), 8.7 (C**7**); HRMS: (MALDI) calculated for $C_{19}H_{22}N_2NaO_3S$: 381.1243, found $[M+Na]^+$: 381.1249.

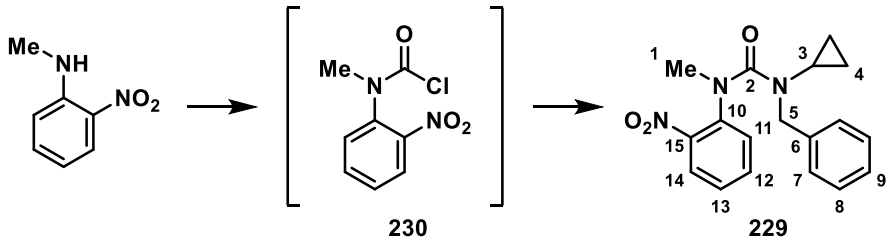
***N*-Benzyl-*N*-cyclopropyl-2-(3,3-dimethylureido)acetamide (223)**



193 223

To a solution of amine **193** (0.50 g, 2.45 mmol, provided by Dr Calow) and Et_3N (0.51 mL, 3.67 mmol) in dry DCM (3 mL), dimethylcarbamyl chloride (0.34 mL, 3.67 mmol) was added at 0 °C. The reaction was stirred for 24 h at r.t. Water (10 mL) was added and the solution was extracted with DCM (3 × 10 mL). The organic extracts were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (50-100% EtOAc/hexane, then 5% MeOH/EtOAc) to afford the title compound **223** (0.29 g, 43%) as a colourless oil; ν_{max} / cm^{-1}: 3351 (br. w), 2931 (br. w), 1642 (s), 1532 (s), 1413 (s), 1267 (m), 1218 (m); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.33 – 7.17 (m, 5H, C**1**-H, 2 × C**2**-H and 2 × C**3**-H), 5.50 (br. t, *J* = 4.1 Hz, 1H, N**10**-H), 4.61 (s, 2H, C**5**-H_2), 4.28 (d, *J* = 4.1 Hz, 2H, C**9**-H_2), 2.94 (s, 6H, 2 × C**12**-H_3), 2.57 (tt, *J* = 6.9, 4.0 Hz, 1H, C**6**-H), 0.92 – 0.76 (m, 4H, 2 × C**7**-H_2); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 172.7 (C**8**), 158.4 (C**11**), 137.8 (C**4**), 128.7 (C**2**), 127.7 (C**3**), 127.4 (C**1**), 50.4 (C**5**), 44.0 (C**9**), 36.3 (C**12**), 29.2 (C**6**), 8.8 (C**7**); HRMS: (ESI^+) calculated for $C_{15}H_{22}N_3O_2$: 276.1707, found $[M+H]^+$: 276.1720.

1-Benzyl-1-cyclopropyl-3-methyl-3-(2-nitrophenyl)urea (229)

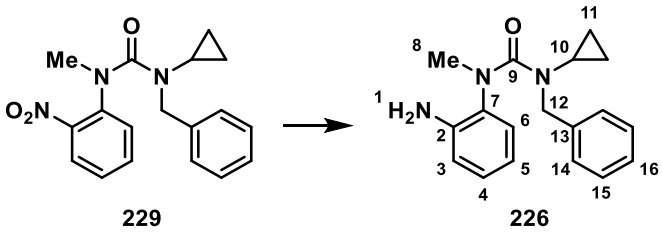


230 229

To a solution of triphosgene (2.93 g, 9.86 mmol) in dry DCM (25 mL) was added pyridine (3.19 mL, 39.43 mmol) dropwise at 0 °C. The reaction was stirred for 10 min and then *N*-methyl-2-nitroaniline (3.00 g, 19.72 mmol) in DCM (25 ml) was added. The reaction mixture was warmed to r.t. and stirred for 4 h. The solution was washed with 1.0 M aq. HCl (3 × 30 mL), water (40 mL), dried over $MgSO_4$ and then concentrated *in vacuo* to afford carbamic chloride **230** (3.70 g, 87%) as a brown oil which was used without further purification. Carbamic chloride **230** (1.50 g, 6.99 mmol) was dissolved in dry DCM (25 mL), then *N*-benzylcyclopropanamine (1.03 g, 6.99 mmol) and DMAP (1.71 g, 13.98 mmol) were added and the reaction was stirred for 18 h at r.t.

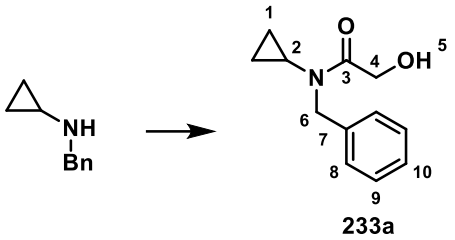
The solution was washed with 1.0 M aq. HCl (30 mL), sat. aq. $NaHCO_3$ (30 mL), water (30 mL), brine (30 mL), dried over $MgSO_4$ and then concentrated *in vacuo*. The residue was purified by flash column chromatography (50% EtOAc/hexane) to afford the title compound **229** (1.82 g, 80%) as a bright yellow oil; ν_{max} / cm^{-1}: 2924 (w), 1651 (s), 1604 (m), 1526 (s), 1358 (s), 1294 (m), 702 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.92 (dd, *J* = 8.2, 1.6 Hz, 1H, C**14**-H), 7.44 (ddd, *J* = 7.8, 7.8, 1.6 Hz, 1H, C**12**-H), 7.32 – 7.19 (m, 6H, C**13**-H, C**9**-H, 2 × C**7**-H and 2 × C**8**-H), 7.10 (dd, *J* = 7.8, 1.4 Hz, 1H, C**11**-H), 4.26 (s, 2H, C**5**-H_2), 3.29 (s, 3H, C**1**-H_3), 1.74 (tt, *J* = 6.7, 3.9 Hz, 1H, C**3**-H), 0.66 – 0.58 (m, 2H, 2 × C**4**-H_aH_b), 0.45 – 0.38 (m, 2H, 2 × C**11**-H_aH_b); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 161.0 (C**2**), 145.0 (C**15**), 140.1 (C**10**), 137.8 (C**6**), 133.9 (C**12**), 129.1 (C**11**), 128.7, 128.6, 127.4, 126.4 (C**7**, C**8**, C**9** and C**13**), 126.0 (C**14**), 53.2 (C**5**), 40.0 (C**1**), 30.8 (C**3**), 9.5 (C**4**); HRMS: (ESI^+) calculated for $C_{18}H_{19}N_3NaO_3$: 348.1319, found $[M+H]^+$: 348.1331.

1-(2-Aminophenyl)-3-benzyl-3-cyclopropyl-1-methylurea (226)



To a solution of **229** (1.87 g, 5.75 mmol) in EtOAc (40 mL), stannous chloride dihydrate (6.49 g, 6.49 mmol) was added and the reaction was stirred a 50 °C for 6 h. The reaction mixture was cooled to r.t., sat. aq. $NaHCO_3$ (100 mL) was added and the mixture was stirred at r.t. for 40 min. Then, the solution was extracted with EtOAc (3 × 70 mL). The organic extracts were combined, washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (30-50% EtOAc/pentane) to afford the title compound **226** (0.52 g, 31%) as a colourless oil; ν_{max} / cm^{-1}: 3453 (br. w), 3342 (br. m), 1621 (s), 1502 (s), 1425 (s), 1388 (s), 1310 (s), 1113 (m), 1029 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.34 – 7.22 (m, 5H, 2 × C**14**-H, 2 × C**15**-H and C**16**-H), 6.99 (ddd, *J* = 8.0, 7.3, 1.5 Hz, 1H, C**4**-H), 6.71 (dd, *J* = 3.4, 1.5 Hz, 1H, C**3**-H), 6.69 (dd, *J* = 3.2, 1.5 Hz, 1H, C**6**-H), 6.57 (td, *J* = 7.6, 1.5 Hz, 1H, C**5**-H), 4.37 (br. s, 2H, C**12**-H_2), 3.78 (br. s, 2H, N**1**-H_2), 3.06 (s, 3H, C**8**-H_3), 1.83 (tt, *J* = 6.7, 3.9 Hz, 1H, C**10**-H), 0.65 – 0.56 (m, 2H, 2 × C**11**-H_aH_b), 0.54 – 0.48 (m, 2H, 2 × C**11**-H_aH_b); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 163.2 (C**9**), 142.0 (C**2**), 138.6 (C**13**), 131.8 (C**7**), 128.5, 128.4 (C**14** and C**15**), 127.5 (C**4**), 127.2 (C**16**), 127.0 (C**6**), 118.7 (C**5**), 116.1 (C**3**), 53.0 (C**12**), 37.4 (C**8**), 30.7 (C**10**), 9.3 (C**11**); HRMS: (ESI^+) calculated for $C_{18}H_{22}N_3O$: 296.1757, found $[M+H]^+$: 296.1764.

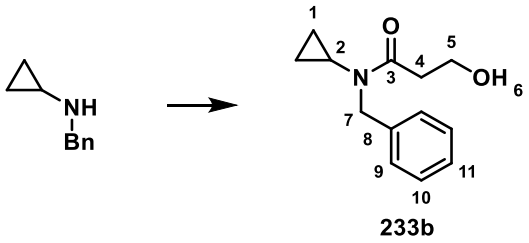
***N*-Benzyl-*N*-cyclopropyl-2-hydroxyacetamide (233a)**



233a

To a solution of glycolic acid (0.62 g, 8.15 mmol) in DMF (12 mL), EDCI (1.95 g, 10.19 mmol) was added and the reaction mixture was stirred at r.t. for 10 min. HOBt (1.66 g, 10.19 mmol, 20 wt.% H_2O), *N*-methylmorpholine (2.24 mL, 20.38 mmol) and *N*-benzylcyclopropanamine (1.00 g, 6.79 mmol) were added and the reaction mixture was stirred at r.t. for 18 h. Water (30 mL) was added and aqueous layer was extracted with DCM (3 × 30 mL). The organic extracts were combined, washed with 1.0 M aq. HCl (30 mL), brine (40 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (30-40% EtOAc/pentane) to afford the title compound **233a** (0.62 g, 45%) as a colourless oil; ν_{max} / cm^{-1}: 3432 (br. m), 2927 (w), 1652 (s), 1375 (s), 1292 (s), 1097 (s), 1081 (s), 1031 (s); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.35 – 7.22 (m, 5H, 2 × C**8**-H, 2 × C**9**-H and C**10**-H), 4.64 (s, 2H, C**6**-H_2), 4.38 (d, *J* = 4.5 Hz, 2H, C**4**-H_2), 3.56 (t, *J* = 4.5 Hz, 1H, O**5**-H), 2.47 (tt, *J* = 6.9, 4.1 Hz, 1H, C**2**-H), 0.87 – 0.74 (m, 4H, 2 × C**1**-H_2); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 175.2 (C**3**), 137.5 (C**7**), 128.8, 128.0 (C**8** and C**9**), 127.6 (C**10**), 61.1 (C**4**), 50.5 (C**6**), 28.1 (C**2**), 8.2 (C**1**); HRMS: (ESI^+) calculated for $C_{12}H_{16}NO_2$: 206.1176, found $[M+H]^+$: 206.1179.

***N*-Benzyl-*N*-cyclopropyl-3-hydroxypropanamide (233b)**

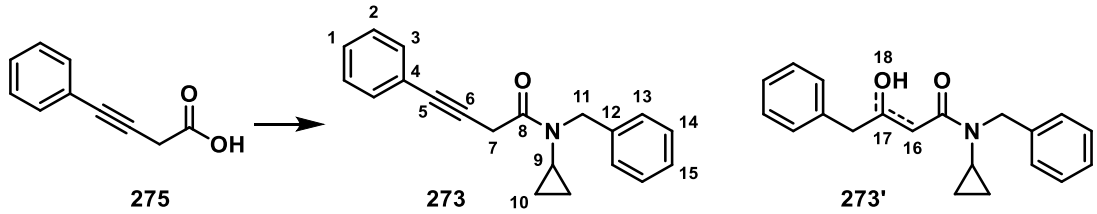


233b

A solution of *N*-benzylcyclopropanamine (0.50 g, 3.40 mmol) and β-propiolactone (0.75 mL, 11.80 mmol) in toluene (7 mL) was heated to 105 °C for 15 min. The reaction was cooled to r.t. and concentrated *in vacuo*. Et_2O (20 mL) and water (20 mL) were added, the layers were separated and the organic portion was further washed with water (2 × 10 mL). The organic extract was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (1-2% MeOH/DCM) to afford the title compound **233b** (0.13 g, 17%) as a colourless oil; ν_{max} / cm^{-1}: 3417 (br. m), 2939 (w), 1630 (s), 1407 (s), 1373 (s), 1032 (s); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.34 – 7.20 (m, 5H, 2 × C**9**-H, 2 × C**10**-H and C**11**-H), 4.61 (s, 2H, C**7**-H_2), 3.92 (q, *J* = 5.7 Hz, 2H, C**5**-H_2), 3.49 (t, *J* = 6.6 Hz, 1H, O**6**-H), 2.81 (t, *J* = 5.3 Hz, 2H, C**4**-H_2), 2.55 (tt, *J* = 7.0, 4.1 Hz, 1H, C**2**-H), 0.89 – 0.75 (m, 4H, 2 × C**1**-H_2); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 176.0 (C**3**), 138.1 (C**8**), 128.7, 127.7 (C**9** and C**10**), 127.3 (C**11**), 58.9 (C**5**), 49.8 (C**7**), 36.4 (C**4**), 30.1 (C**2**), 9.3 (C**1**); HRMS: (ESI^+) calculated for $C_{13}H_{17}NNaO_2$: 242.1151, found $[M+Na]^+$: 242.1143.

8.5 Experimental procedures for the studies in Chapter 4

***N*-Benzyl-*N*-cyclopropyl-4-phenylbut-3-ynamide (273)**

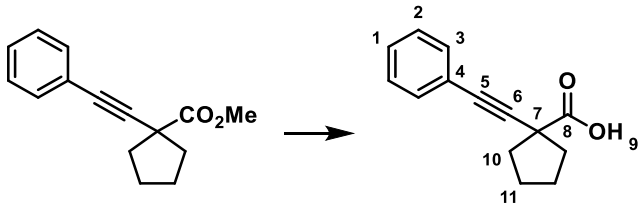


4-Phenylbut-3-ynoic acid (0.50 g, 3.12 mmol, prepared according to the literature procedure[273]) was dissolved in DCM (6 mL), treated with oxalyl chloride (0.30 mL, 3.44 mmol), a drop of DMF and stirred at r.t. for 1 h. DCM and an excess of oxalyl chloride were removed in vacuo and the corresponding acyl chloride was dissolved in DCM (2 mL). The solution was added dropwise to *N*-benzylcyclopropanamine (0.51 g, 3.44 mmol) and TEA (0.48 mL, 3.44 mmol) in DCM (4 mL) at 0 °C, the reaction was warmed to r.t. and stirred for 18 h. Sat. aq. $NaHCO_3$ (20 mL) and DCM (10 mL) were added, the layers were separated and the aqueous portion was further extracted with DCM (2 × 15 mL). The organic extracts were combined, washed with 1.0 M aq. HCl (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (5-10% EtOAc/hexane) to afford the title compound **273** (0.30 g, 33%, 1:0.88 mixture of rotamers *A*:*B*) as an orange oil; ν_{max} / cm^{-1}: 1720 (m), 1654 (s), 1566 (s), 1453 (s), 1403 (s), 1369 (s), 1269 (s), 1029 (m), 753 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.44 – 7.05 (m, 20H, C**1**-H, C**15**-H, 2 × C**2**-H, 2 × C**3**-H, 2 × C**13**-H and 2 × C**14**-H, *A*+*B*), 4.65 (s, 2H, C**11**-H_2, *B*), 4.60 (s, 2H, C**11**-H_2, *A*), 3.86 (s, 2H, C**7**-H_2, *B*), 3.79 (s, 2H, C**7**-H_2, *A*), 2.79 – 2.72 (m, 1H, C**9**-H, *B*), 2.45 – 2.37 (m, 1H, C**9**-H, *A*), 0.94 – 0.61 (m, 8H, 2 × C**10**-H_2, *A*+*B*); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 170.2 (C**8**, *B*), 170.0 (C**8**, *A*), 138.0 (C**12**, *B*), 137.8 (C**12**, *A*), 131.8, 129.8, 129.5, 129.0, 128.7, 128.6, 128.5, 128.3, 128.2, 128.2, 128.0, 127.9, 127.4, 127.3 (C**1**, C**2**, C**3**, C**4**, C**13**, C**14** and C**15**, *A*+*B*), 93.9 (C**5**, *B*), 89.7 (C**5**, *A*), 83.6 (C**6**, *B*), 82.7 (C**6**, *A*), 50.5 (C**7**, *B*), 50.3 (C**11**, *B*), 50.1 (C**11**, *A*), 48.7 (C**11**, *A*), 30.5 (C**9**, *A*), 30.4 (C**9**, *B*), 9.4 (C**10**, *B*), 9.1 (C**10**, *A*); HRMS: (ESI^+) calculated for $C_{20}H_{20}NO$: 290.1539, found $[M+H]^+$: 290.1532.

*Analysis of the NMR spectra also indicated trace amounts of unseparable impurity **273'**.*

Data for **273'** *(characteristic signals only)*: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 14.62 (s, 1H, O**18**-H), 5.47 (s, 1H, C**16**-H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 202.7 (C**17**).

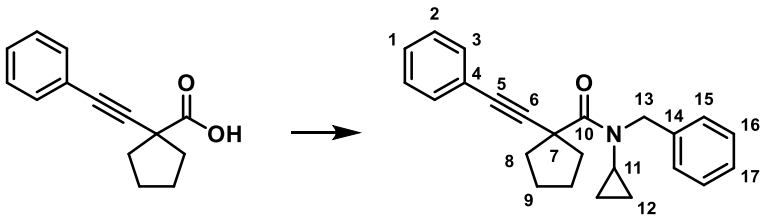
1-(Phenylethynyl)cyclopentane-1-carboxylic acid (279a')



279a **279a'**

To a solution of ester **279a** (1.00 g, 4.38 mmol, prepared according to the literature procedure[262]) in MeOH (8 mL) was added 4.0 M aq. NaOH (5.5 mL) and the reaction was stirred at r.t. for 16 h. The reaction mixture was concentrated *in vacuo*, diluted with water (20 mL) and extracted with Et_2O (20 mL). The aqueous portion was adjusted to pH 2 by addition of 6.0 M aq. HCl and then extracted with Et_2O (3 × 20 mL). The organic extracts were combined, dried over $MgSO_4$ and concentrated *in vacuo* to afford the title compound **279a'** (0.92 g, 98%) as a colourless solid; m.p. 78-79 °C (DCM/hexane); ν_{max} / cm^{-1}: 2957 (br. m), 1703 (s), 1273 (m), 755 (m), 690 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.41 (br. s, 1H, O**9**-H), 7.45 – 7.40 (m, 2H, 2 × C**3**-H), 7.32 – 7.27 (m, 3H, C**1**-H and 2 × C**2**-H), 2.40 – 2.27 (m, 2H, 2 × C**10**-H_aH_b), 2.23 – 2.09 (m, 2H, 2 × C**10**-H_aH_b), 1.98 – 1.75 (m, 4H, 2 × C**11**-H_2); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 179.6 (C**8**), 131.9 (C**3**), 128.3 (C**2**), 128.2 (C**1**), 123.2 (C**4**), 90.7 (C**6**), 82.9 (C**5**), 48.9 (C**7**), 39.5 (C**10**), 25.1 (C**11**); HRMS: (ESI$^-$) calculated for $C_{14}H_{13}O_2$: 213.0916, found [M-H]$^-$: 213.0909.

***N*-Benzyl-*N*-cyclopropyl-1-(phenylethynyl)cyclopentane-1-carboxamide (277a)**

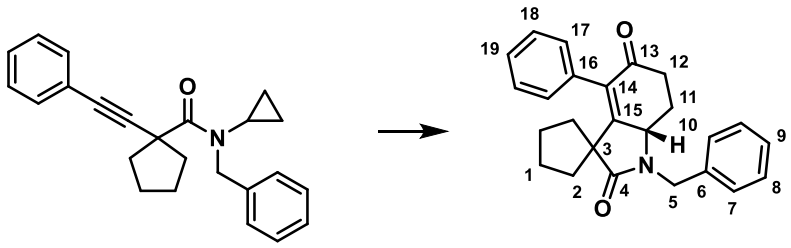


279a' **277a**

General procedure G: *N*-Benzylcyclopropanamine (0.34 g, 2.31 mmol) and acid **279a'** (0.50 g, 2.33 mmol) were employed and the residue was purified by flash column chromatography (5% EtOAc/hexane) to afford the title compound **277a** (0.61 g, 77%) as a colourless oil; ν_{max} / cm^{-1}: 2955 (m), 1645 (s), 1491 (m), 1453 (m), 1389 (s), 756 (s), 692 (s); ^{1}H NMR (DMSO-d_6, 500 MHz, 80 °C): δ 7.34 – 7.19 (m, 10H, C**1**-H, C**17**-H, 2 × C**2**-H, 2 × C**3**-H, 2 × C**15**-H and 2 × C**16**-H), 4.73 (br. s, 2H, C**13**-H_2), 3.06 – 2.93 (br. m, 1H, C**11**-H), 2.41 – 2.33 (m, 2H, 2 × C**8**-H_aH_b), 2.19 – 2.10 (m, 2H, 2 × C**8**-H_aH_b), 1.88 – 1.78 (m, 2H, 2 × C**9**-H_aH_b), 1.76 – 1.66 (m, 2H, 2 × C**9**-H_aH_b), 0.79 – 0.69 (m, 4H, 2 × C**12**-H_2); ^{13}C NMR (DMSO-d_6, 126 MHz, 80 °C): δ 172.39 (C**10**),

138.15 (C**14**), 130.68, 128.02, 127.89, 127.70, 126.31, 126.25 (C**1**, C**2**, C**3**, C**15**, C**16** and C**17**), 122.36 (C**4**), 92.71 (C**5**), 82.57 (C**6**), 49.54 (C**7**), 48.08 (C**13**), 38.87 (C**8**), 30.30 (C**11**), 23.97 (C**9**), 7.40 (C**12**); HRMS: (ESI$^+$) calculated for $C_{24}H_{26}NO$: 344.2009, found $[M+H]^+$: 344.1998.

1'-benzyl-4'-phenyl-1',6',7',7a'-tetrahydrospiro[cyclopentane-1,3'-indole]-2',5'-dione (280a)



277a **280a**

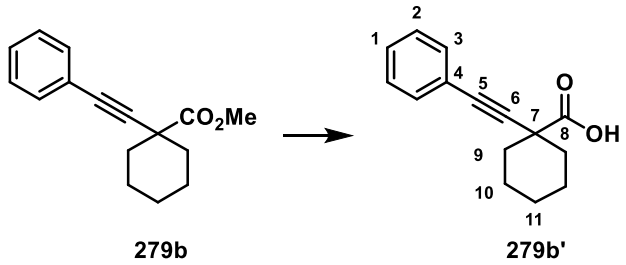
General procedure I: Amide **277a** (34.3 mg, 0.10 mmol) was employed. Flash column chromatography (30% EtOAc/hexane) afforded the title compound **280a** (27.9 mg, 75%) as a pale brown oil; ν_{max} / cm^{-1}: 2947 (m), 1693 (s), 1674 (s), 1443 (m), 1417 (s), 1313 (m), 1269 (m), 1174 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.41 – 7.27 (m, 8H, C**9**-H, C**19**-H, 2 × C**7**-H, 2 × C**8**-H and 2 × C**18**-H), 7.06 – 7.00 (m, 2H, 2 × C**17**-H), 5.09 (d, *J* = 14.9 Hz, 1H, C**5**-H_aH_b), 4.23 (dd, *J* = 11.8, 4.2 Hz, 1H, C**10**-H), 4.11 (d, *J* = 14.9 Hz, 1H, C**5**-H_aH_b), 2.73 (ddd, *J* = 17.8, 4.5, 2.2 Hz, 1H, C**12**-H_aH_b), 2.51 – 2.43 (m, 1H, C**11**-H_aH_b), 2.43 – 2.32 (m, 1H, C**12**-H_aH_b), 2.15 – 2.07 (m, 1H, C**2**-H_aH_b), 1.96 – 1.48 (m, 7H, C**1**-H_2, C**1'**-H_aH_b, C**2'**-H_2, C**2**-H_aH_b and C**11**-H_aH_b), 0.74 – 0.61 (m, 1H, C**1'**-H_aH_b); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 196.9 (C**13**), 178.9 (C**4**), 163.5 (C**15**), 136.2 (C**6**), 134.9 (C**14**), 134.1 (C**16**), 130.2 (C**17**), 129.1, 128.2, 128.1 (C**7**, C**8** and C**18**), 128.0, 128.0 (C**9** and C**19**), 56.9 (C**10**), 54.9 (C**3**), 44.1 (C**5**), 42.1 (C**2**), 35.9 (C**12**), 34.2 (C**2'**), 28.2 (C**11**), 27.4 (C**1'**), 27.2 (C**1**); HRMS: (ESI$^+$) calculated for $C_{25}H_{26}NO_2$: 372.1958, found $[M+H]^+$: 372.1948.

General procedure J: Amide **277a** (34.3 mg, 0.10 mmol) was employed. Flash column chromatography (50% EtOAc/hexane) afforded the title compound **(*S*)-280a** (24.5 mg, 66%) as a colourless oil. The enantiopurity of this compound was determined by chiral SFC against a racemic standard.

$[\alpha]_D^{23.8}$ = -48.1 (c = 0.11, $CHCl_3$).

Chiral SFC: (DAICEL CHIRALPAK-IB column (25 cm), CO_2:MeOH 80:20, 2 mL/min, 140 bars, 40 °C). Retention times: 9.6 minutes (major), 11.0 minutes (minor), e.r. = 92:8.

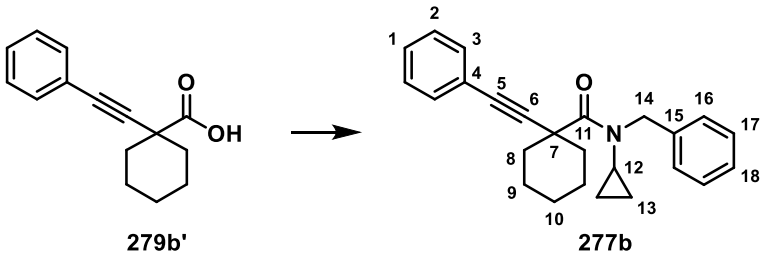
1-(Phenylethynyl)cyclohexane-1-carboxylic acid (279b')



279b **279b'**

To a solution of ester **279b** (2.08 g, 8.58 mmol, prepared according to the literature procedure[262]) in MeOH (17 mL) was added 4.0 M aq. NaOH (10.7 mL) and the reaction was stirred at r.t. for 16 h. The reaction mixture was concentrated *in vacuo*, diluted with water (20 mL) and extracted with Et_2O (20 mL). The aqueous portion was adjusted to pH 2 by addition of 6.0 M aq. HCl and then extracted with Et_2O (3 × 20 mL). The organic extracts were combined, dried over $MgSO_4$ and concentrated *in vacuo* to afford the title compound **279b'** (1.65 g, 84%) as a colourless solid; m.p. 72-73 °C ($CDCl_3$); ν_{max} / cm^{-1}: 2933 (m), 1704 (s), 1444 (m), 1284 (m), 1258 (m), 755 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.49 – 7.43 (m, 2H, 2 × C**3**-H), 7.33 – 7.27 (m, 3H, C**1**-H and 2 × C**2**-H), 2.11 – 2.01 (m, 2H, 2 × C**9**-H_aH_b), 1.93 – 1.61 (m, 7H, 2 × C**9**-H_aH_b, 2 × C**10**-H_2 and C**11**-H_aH_b), 1.36 – 1.22 (m, 1H, C**11**-H_aH_b); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 179.6 (C**8**), 131.9 (C**3**), 128.3 (C**2**), 128.3 (C**1**), 123.2 (C**4**), 89.1 (C**6**), 85.0 (C**5**), 44.4 (C**7**), 34.8 (C**9**), 25.5 (C**11**), 22.6 (C**10**); HRMS: (ESI^-) calculated for $C_{15}H_{15}O_2$: 227.1072, found $[M-H]^-$: 227.1081.

***N*-Benzyl-*N*-cyclopropyl-1-(phenylethynyl)cyclohexane-1-carboxamide (277b)**

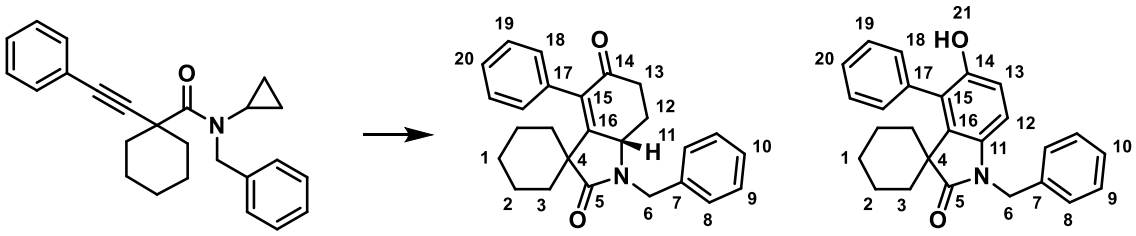


279b' **277b**

General procedure G: *N*-Benzylcyclopropanamine (0.36 g, 2.45 mmol) and acid **279b'** (0.56 g, 2.45 mmol) were employed and the residue was purified by flash column chromatography (5% EtOAc/hexane) to afford the title compound **277b** (0.67 g, 77%) as a pale yellow oil; ν_{max} / cm^{-1}: 2932 (m), 1651 (s), 1386 (m), 756 (m), 692 (m); ^{1}H NMR (DMSO-d_6, 500 MHz, 110 °C): δ 7.34 – 7.19 (m, 10H, C**1**-H, C**18**-H, 2 × C**2**-H, 2 × C**3**-H, 2 × C**16**-H and 2 × C**17**-H), 4.81 (s, 2H, C**14**-H_2), 3.03 – 2.95 (m, 1H, C**12**-H), 2.10 – 2.02 (m, 2H, 2 × C**8**-H_aH_b), 1.95 – 1.87 (m, 2H, 2 × C**8**-H_aH_b), 1.82 – 1.71 (m, 2H, 2 × C**9**-H_aH_b), 1.70 – 1.61 (m, 3H, 2 × C**9**-H_aH_b and C**10**-H_aH_b), 1.34

– 1.23 (m, 1H, C**10**-$H_a\underline{H_b}$), 0.73 – 0.69 (m, 2H, 2 × C**13**-$\underline{H_2}$); ^{13}C NMR (DMSO-d_6, 126 MHz, 110 °C): δ 172.8 (C**11**), 138.0 (C**15**), 130.4, 127.8, 127.6, 127.5, 126.2, 126.0 (C**1**, C**2**, C**3**, C**16**, C**17** and C**18**), 122.2 (C**4**), 90.4 (C**6**), 86.1 (C**5**), 49.8 (C**14**), 43.1 (C**7**), 34.9 (C**8**), 30.3 (C**12**), 24.5 (C**10**), 21.6 (C**9**), 7.1 (C**13**); HRMS: (ESI$^+$) calculated for $C_{25}H_{28}NO$: 358.2165, found $[M+H]^+$: 358.2159.

1'-Benzyl-4'-phenyl-1',6',7',7a'-tetrahydrospiro[cyclohexane-1,3'-indole]-2',5'-dione (280b) and 1'-benzyl-5'-hydroxy-4'-phenylspiro[cyclohexane-1,3'-indolin]-2'-one (281b)



General procedure I: *In a modification to the general procedure, 10 mol% [Rh(cod)$_2$]OTf and 20 mol% PPh$_3$ were used and the reaction was heated for 72 h.* Amide **277b** (35.8 mg, 0.10 mmol) was employed. Flash column chromatography (30% EtOAc/hexane) afforded cyclohexenone **280b** (10.2 mg, 26%) and phenol **281b** (7.5 mg, 20%) as pale yellow oils.

General procedure I: Amide **277b** (35.8 mg, 0.10 mmol) was employed. Flash column chromatography (30% EtOAc/hexane) afforded the title compound **280b** (29.9 mg, 78%) as a pale brown oil.

Data for **280b**: ν_{max} / cm^{-1}: 2924 (m), 1674 (s), 1414 (m), 1258 (m), 1078 (m), 910 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.41 – 7.23 (m, 8H, C**10**-$\underline{H}$, C**20**-$\underline{H}$, 2 × C**8**-$\underline{H}$, 2 × C**9**-$\underline{H}$ and 2 × C**19**-$\underline{H}$), 7.04 – 6.99 (m, 2H, 2 × C**18**-$\underline{H}$), 5.11 (d, *J* = 14.9 Hz, 1H, C**6**-$\underline{H_a}H_b$), 4.18 (dd, *J* = 11.7, 4.2 Hz, 1H, C**11**-$\underline{H}$), 4.06 (d, *J* = 14.9 Hz, 1H, C**6**-$H_a\underline{H_b}$), 2.71 (ddd, *J* = 17.9, 4.5, 2.3 Hz, 1H, C**13**-$\underline{H_a}H_b$), 2.49 – 2.42 (m, 1H, C**12**-$\underline{H_a}H_b$), 2.40 – 2.20 (m, 2H, C**2**-$\underline{H_a}H_b$ and C**13**-$H_a\underline{H_b}$), 1.97 – 1.47 (m, 6H, C**1**-$\underline{H_2}$, C**2'**-$\underline{H_2}$, C**3**-$\underline{H_a}H_b$ and C**12**-$H_a\underline{H_b}$), 1.45 – 1.36 (m, 1H, C**3'**-$\underline{H_a}H_b$), 1.24 – 1.15 (m, 1H, C**2**-$H_a\underline{H_b}$), 1.09 (td, *J* = 13.2, 4.7 Hz, 1H, C**3'**-$H_a\underline{H_b}$), 0.86 – 0.72 (m, 1H, C**3**-$H_a\underline{H_b}$); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 197.2 (C**14**), 176.5 (C**5**), 162.5 (C**16**), 136.3 (C**7**), 135.6 (C**15**), 134.3 (C**17**), 130.1 (C**18**), 129.1, 128.1, 128.0 (C**8**, C**9**, C**10**, C**19** and C**20**), 55.6 (C**11**), 48.6 (C**4**), 43.6 (C**6**), 35.8 (C**13**), 35.1 (C**1**), 30.1 (C**3**), 28.2 (C**12**), 25.1 (C**3'**), 21.6 (C**2**), 20.9 (C**2'**); HRMS: (ESI$^+$) calculated for $C_{26}H_{28}NO_2$: 386.2115, found $[M+H]^+$: 386.2112.

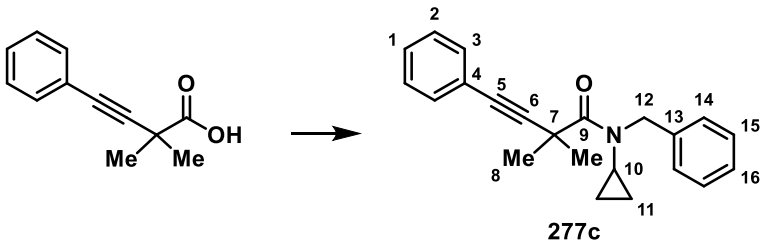
General procedure J: *In a modification to the general procedure, the reaction was heated to 120 °C.* Amide **277b** (35.8 mg, 0.10 mmol) was employed. Flash column chromatography (40% EtOAc/hexane) afforded the title compound **(*S*)-280b** (26.8 mg, 69%) as a yellow oil. The enantiopurity of this compound was determined by chiral SFC against a racemic standard.

$[\alpha]_D^{23.9}$ = -20.5 (c = 0.57, $CHCl_3$).

Chiral SFC: (DAICEL CHIRALPAK-IB column (25 cm), CO_2:MeOH 88:12, 2 mL/min, 140 bars, 40 °C). Retention times: 16.7 minutes (major), 21.3 minutes (minor), e.r. = 86:14.

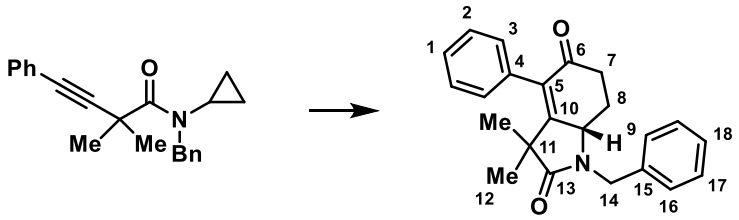
Data for **281b**: ν_{max} / cm^{-1}: 3356 (br. m), 2924 (s), 1675 (s), 1613 (s), 1458 (s), 1340 (s), 1075 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.49 – 7.16 (m, 10H, C**10**-H, C**20**-H, 2 × C**8**-H, 2 × C**9**-H, 2 × C**18**-H and 2 × C**19**-H), 6.69 (d, *J* = 8.4 Hz, 1H, C**12**-H), 6.52 (d, *J* = 8.4 Hz, 1H, C**13**-H), 4.81 (s, 2H, C**6**-H_2), 4.16 (s, 1H, O**21**-H), 2.18 – 2.03 (m, 2H, 2 × C**2**-H_aH_b), 1.62 – 1.53 (m, 5H, C**1**-H_aH_b and 2 × C**3**-H_2), 1.34 – 1.26 (m, 2H, 2 × C**2**-H_aH_b), 0.69 – 0.55 (m, 1H, C**1**-H_aH_b); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 179.9 (C**5**), 149.4 (C**14**), 136.6, 135.3, 132.8, 132.8, 131.5, 129.2, 129.1, 128.9, 127.6, 127.3, 126.6 (C**7**, C**8**, C**9**, C**10**, C**11**, C**15**, C**16**, C**17**, C**18**, C**19** and C**20**), 113.3 (C**12**), 109.1 (C**13**), 48.8 (C**4**), 43.2 (C**6**), 32.4 (C**3**), 25.3 (C**1**), 20.5 (C**2**); HRMS: (ESI^+) calculated for $C_{26}H_{26}NO_2$: 384.1958, found $[M+H]^+$: 384.1956.

***N*-Benzyl-*N*-cyclopropyl-2,2-dimethyl-4-phenylbut-3-ynamide (277c)**



General procedure G: *N*-Benzylcyclopropanamine (0.61 g, 4.12 mmol) and 2,2-dimethyl-4-phenylbut-3-ynoic acid (0.78 g, 4.12 mmol, prepared according to the literature procedure[274]) was employed. Flash column chromatography (30% EtOAc/hexane) afforded the title compound **277c** (1.04 g, 79%) as a colourless solid; m.p. 47-48 °C (DCM/hexane); ν_{max} / cm^{-1}: 2985 (m), 1643 (s), 1394 (s), 1361 (m), 756 (s), 691 (s); ^{1}H NMR (DMSO-d_6, 500 MHz, 110 °C): δ 7.34 – 7.19 (m, 10H, C**1**-H, C**16**-H, 2 × C**2**-H, 2 × C**3**-H, 2 × C**14**-H and 2 × C**15**-H), 4.79 (s, 2H, C**12**-H_2), 3.08 – 3.00 (m, 1H, C**10**-H), 1.60 (s, 6H, 2 × C**8**-H_3), 0.78 – 0.71 (m, 4H, 2 × C**11**-H_2); ^{13}C NMR (DMSO-d_6, 126 MHz, 110 °C): δ 172.9 (C**9**), 138.0 (C**13**), 130.4, 127.7, 127.7, 127.5, 126.1, 126.0 (C**1**, C**2**, C**3**, C**14**, C**15** and C**16**), 122.2 (C**4**), 92.7 (C**6**), 82.8 (C**5**), 49.8 (C**12**), 37.3 (C**7**), 30.5 (C**10**), 28.1 (C**8**), 7.2 (C**11**); HRMS: (ESI^+) calculated for $C_{22}H_{24}NO$: 318.1852, found $[M+H]^+$: 318.1847.

1-Benzyl-3,3-dimethyl-4-phenyl-1,6,7,7a-tetrahydro-2*H*-indole-2,5(3*H*)-dione (280c)



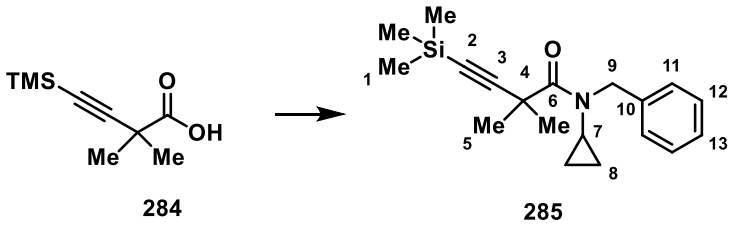
General procedure I: Amide **277c** (31.7 mg, 0.10 mmol) was employed. Flash column chromatography (40% EtOAc/hexane) afforded the title compound **277c** (26.5 mg, 77%) as a colourless oil; ν_{max} / cm^{-1}: 2930 (w), 1697 (s), 1674 (s), 1418 (m), 1242 (m), 701 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.40 – 7.25 (m, 8H, C**1**-H, C**18**-H, 2 × C**2**-H, 2 × C**16**-H and 2 × C**17**-H), 7.05 – 7.00 (m, 2H, 2 × C**3**-H), 5.11 (d, *J* = 14.9 Hz, 1H, C**14**-H_aH_b), 4.23 (dd, *J* = 11.7, 4.4 Hz, 1H, C**9**-H), 4.11 (d, *J* = 14.9 Hz, 1H, C**14**-H_aH_b), 2.73 (ddd, *J* = 17.7, 4.4, 2.4 Hz, 1H, C**7**-H_aH_b), 2.50 (dtd, *J* = 11.7, 4.8, 2.4 Hz, 1H, C**8**-H_aH_b), 2.38 (ddd, *J* = 17.7, 14.1, 4.8 Hz, 1H, C**7**-H_aH_b), 1.82 (dtd, *J* = 14.1, 11.7, 4.4 Hz, 1H, C**8**-H_aH_b), 1.34 (s, 3H, C**12**-H_3), 0.82 (s, 3H, C**12'**-H_3); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 196.8 (C**6**), 177.4 (C**13**), 162.4 (C**10**), 136.1, 136.0 (C**5** and C**15**), 134.1 (C**4**), 129.9 (C**3**), 129.1, 128.1, 128.1, 128.1 (C**1**, C**2**, C**16**, C**17** and C**18**), 55.8 (C**9**), 46.0 (C**11**), 44.1 (C**14**), 35.8 (C**7**), 28.4 (C**8**), 26.2 (C**12**), 21.9 (C**12'**); HRMS: (ESI^+) calculated for $C_{23}H_{24}NO_2$: 346.1802, found $[M+H]^+$: 346.1786.

General procedure J: Amide **279c** (31.7 mg, 0.10 mmol) was employed. Flash column chromatography (40% EtOAc/hexane) afforded the title compound **(*S*)-277c** (26.3 mg, 76%) as a colourless oil. The enantiopurity of this compound was determined by chiral SFC against a racemic standard.

$[\alpha]_D^{23.7}$ = -22.9 (c = 0.41, $CHCl_3$).

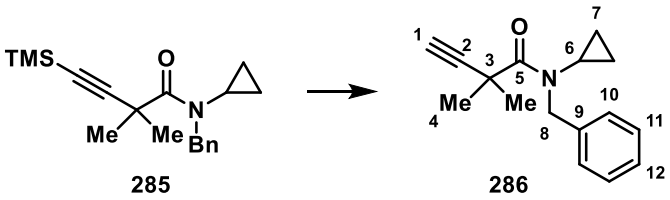
Chiral SFC: (DAICEL CHIRALPAK-IB column (25 cm), CO_2:MeOH 88:12, 2 mL/min, 140 bars, 40 °C). Retention times: 13.4 minutes (major), 15.0 minutes (minor), e.r. = 95:5.

***N*-benzyl-*N*-cyclopropyl-2,2-dimethyl-4-(trimethylsilyl)but-3-ynamide (285)**



General procedure G: *N*-Benzylcyclopropanamine (2.96 g, 20.07 mmol) and 2,2-dimethyl-4-(trimethylsilyl)but-3-ynoic acid **284** (3.70 g, 20.07 mmol, prepared according to the literature procedure[275]) were employed and the residue was purified by flash column chromatography (20% EtOAc/hexane) to afford the title compound **285** (4.69 g, 75%) as a colourless solid; m.p. 57-58 °C (DCM/hexane); ν_{max} / cm^{-1}: 2959 (w), 2155 (w), 1650 (s), 1395 (m), 1249 (m), 878 (m), 840 (s); ^{1}H NMR (DMSO-*d*$_6$, 500 MHz, 110 °C): δ 7.35 – 7.30 (m, 2H, 2 × C**11**-H or 2 × C**12**-H), 7.26 – 7.20 (m, 3H, C**13**-H and 2 × C**11**-H or 2 × C**12**-H), 4.75 (s, 2H, C**9**-H$_2$), 3.03 – 2.96 (br. m, 1H, C**7**-H), 1.49 (s, 6H, 2 × C**5**-H$_3$), 0.72 – 0.67 (m, 4H, 2 × C**8**-H$_2$), 0.05 (s, 9H, 3 × C**1**-H$_3$); ^{13}C NMR (DMSO-*d*$_6$, 126 MHz, 110 °C): δ 172.6 (C**6**), 137.9 (C**10**), 127.6, 126.1 (C**11** and C**12**), 126.0 (C**13**), 109.4 (C**2**), 86.9 (C**3**), 49.6 (C**9**), 37.5 (C**4**), 30.4 (C**7**), 27.9 (C**5**), 7.2 (C**8**), -0.9 (C**1**); HRMS: (ESI$^+$) calculated for $C_{19}H_{28}NOSi$: 314.1935, found $[M+H]^+$: 314.1933.

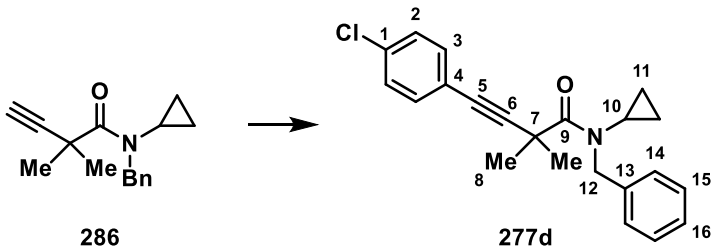
***N*-Benzyl-*N*-cyclopropyl-2,2-dimethylbut-3-ynamide (286)**



Trimethylsilyl alkyne **285** (3.50 g, 11.16 mmol) was dissolved in MeOH (22 mL) and the solution was cooled to 0°C. Potassium carbonate (4.63 g, 33.49 mmol) was added at once, the reaction was warmed to r.t. and stirred for 2 h. The reaction mixture was concentrated *in vacuo*, diluted with 1M HCl (50 mL) and extracted with EtOAc (3 × 30 mL). The organic extracts were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (10% EtOAc/hexane) to afford the title compound **286** (2.21 g, 82%) as a colourless oil; ν_{max} / cm^{-1}: 3288 (w), 3235 (w), 2987 (w), 1644 (s), 1396 (s), 1168 (w), 1029 (m), 698 (m); ^{1}H NMR (DMSO-*d*$_6$, 500 MHz, 110 °C): δ 7.33 – 7.29 (m, 2H, 2 × C**11**-H), 7.24 – 7.19 (m, 3H, C**12**-H and 2 × C**10**-H), 4.70 (s, 2H, C**8**-H$_2$), 3.02 – 2.97 (br. m, 1H, C**6**-H), 2.90 (br. s, 1H, C**1**-H), 1.50 (s, 6H, 2 × C**4**-H$_3$), 0.72 – 0.68 (m, 4H, 2 × C**7**-H$_2$); ^{13}C NMR (DMSO-*d*$_6$, 126

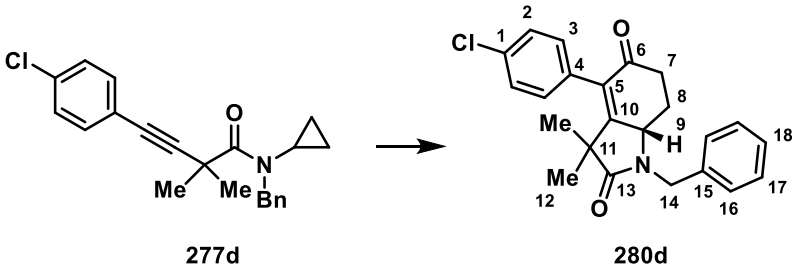
MHz, 110 °C): δ 172.7 (C**5**), 138.0 (C**9**), 127.6 (C**11**), 126.1 (C**10**), 126.0 (C**12**), 86.9 (C**2**), 73.2 (C**1**), 49.6 (C**8**), 36.6 (C**3**), 30.5 (C**6**), 28.0 (C**4**), 7.3 (C**7**); HRMS: (ESI^+) calculated for $C_{16}H_{20}NO$: 242.1529, found $[M+H]^+$: 242.1547.

***N*-Benzyl-4-(4-chlorophenyl)-*N*-cyclopropyl-2,2-dimethylbut-3-ynamide (277d)**



General procedure H: Aminocyclopropane **286** (200.0 mg, 0.83 mmol) and 1-chloro-4-iodobenzene (217.0 mg, 0.91 mmol) were employed and the reaction was stirred for 2 h at r.t. Flash column chromatography (10% EtOAc/hexane) afforded alkyne **277d** (261.4 mg, 89%) as an orange solid; m.p. 83-84 °C (DCM/hexane); ν_{max} / cm^{-1}: 2986 (w), 1646 (s), 1490 (m), 1397 (s), 1089 (m), 828 (m); ^1H NMR (DMSO-d_6, 500 MHz, 110 °C): δ 7.35 – 7.29 (m, 4H, 2 × C**2**-H and 2 × C**3**-H), 7.25 – 7.19 (m, 5H, 2 × C**14**-H, 2 × C**15**-H and C**16**-H), 4.78 (s, 2H, C**12**-H_2), 2.98 (br. s, overlapped by water, 1H, C**10**-H), 1.59 (s, 6H, 2 × C**8**-H_3), 0.74 – 0.70 (m, 4H, 2 × C**11**-H_2); ^{13}C NMR (DMSO-d_6, 126 MHz, 110 °C): δ 172.8 (C**9**), 138.0 (C**14**), 132.6 (C**1**), 132.2, 128.0, 127.8, 126.1 (C**2**, C**3**, C**14** and C**15**), 126.1 (C**16**), 121.0 (C**4**), 93.9 (C**6**), 81.7 (C**5**), 49.9 (C**12**), 37.3 (C**7**), 30.5 (C**10**), 28.0 (C**8**), 7.3 (C**11**); HRMS: (ESI^+) calculated for $C_{22}H_{23}{}^{35}ClNO$: 352.1463, found $[M+H]^+$: 352.1471.

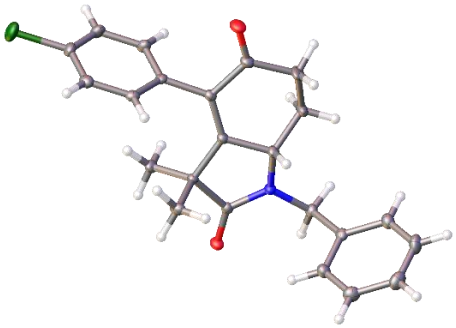
1-Benzyl-4-(4-chlorophenyl)-3,3-dimethyl-1,6,7,7a-tetrahydro-2*H*-indole-2,5(3*H*)-dione (280d)



General procedure I: Amide **277d** (35.2 mg, 0.10 mmol) was employed. Flash column chromatography (30% EtOAc/hexane) afforded the title compound **280d** (29.2 mg, 77%) as a pale yellow oil; ν_{max} / cm^{-1}: 2929 (w), 1695 (s), 1674 (s), 1418 (m), 1242 (m), 1088 (m), 728 (s), 702

(s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.39 – 7.28 (m, 5H, C**18**-H, 2 × C**17**-H and 2 × C**16**-H), 7.28 – 7.23 (m, 2H, 2 × C**2**-H), 6.99 – 6.93 (m, 2H, 2 × C**3**-H), 5.10 (d, *J* = 14.9 Hz, 1H, C**14**-H_aH_b), 4.21 (dd, *J* = 11.7, 4.4 Hz, 1H, C**9**-H), 4.09 (d, *J* = 14.9 Hz, 1H, C**14**-H_aH_b), 2.71 (ddd, *J* = 17.8, 4.4, 2.4 Hz, 1H, C**7**-H_aH_b), 2.52 – 2.45 (m, 1H, C**8**-H_aH_b), 2.36 (ddd, *J* = 17.8, 14.3, 4.9 Hz, 1H, C**7**-H_aH_b), 1.80 (dtd, *J* = 14.3, 11.7, 4.4 Hz, 1H, C**8**-H_aH_b), 1.32 (s, 3H, C**12**-H_3), 0.85 (s, 3H, C**12'**-H_3); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 196.5 (C**6**), 177.1 (C**13**), 163.1 (C**10**), 135.9 (C**15**), 135.0 (C**5**), 134.3 (C**4**), 132.5 (C**1**), 131.3 (C**3**), 129.1, 128.5, 128.1, 128.1 (C**2**, C**16**, C**17** and C**18**), 55.8 (C**9**), 46.0 (C**11**), 44.2 (C**14**), 35.8 (C**7**), 28.4 (C**8**), 26.2 (C**12**), 22.1 (C**12'**); HRMS: (ESI^+) calculated for $C_{23}H_{22}{}^{35}ClNNaO_2$: 402.1231, found $[M+Na]^+$: 402.1240.

General procedure J: Amide **277d** (35.2 mg, 0.10 mmol) was employed. Flash column chromatography (40% EtOAc/hexane) afforded the title compound **(*S*)-280d** (19.5 mg, 51%) as a colourless solid, m.p. 214-215 °C (DCM/hexane). The enantiopurity of this compound was determined by chiral SFC against a racemic standard. The structure and absolute configuration of this compound was determined unambiguously by X-ray crystallography.

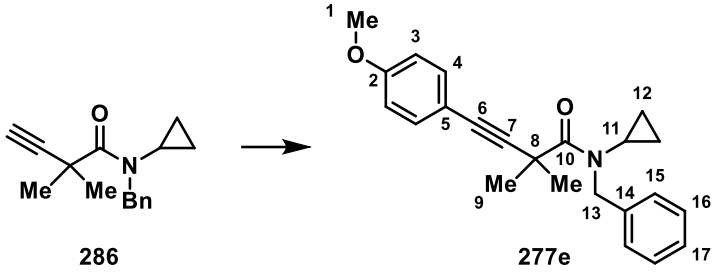


Crystal image of **(*S*)-280d** generated in Olex2, ellipsoids at 50% probability; Crystal data for **(*S*)-280d**: $C_{23}H_{22}ClNO_2$, MW = 379.86, orthorhombic, space group $P2_12_12_1$, a = 8.9513(2) Å, b = 11.5502(3) Å, c = 18.9200(4) Å, V = 1956.13(8) Å^3, α = 90.00°, β = 90.00°, γ = 90.00°, Z = 4, D_c = 1.290 g/cm^3 , Mo-Kα radiation, λ = 0.71073 Å, μ = 0.213 mm^{-1}, T = 100 K; colourless block, crystal size 0.467 × 0.378 × 0.256 mm^3, Bruker Apex II diffractometer, 44550 reflections were collected, 5790 were unique, R_{int} = 0.0445; refinement on F^2 gave R_1 = 0.0330 and wR_2 = 0.0822, GOF = 1.030 for 246 refined parameters; flack parameter -0.04(2).

$[\alpha]_D^{24.2}$ = -30.8 (c = 0.26, $CHCl_3$).

Chiral SFC: (DAICEL CHIRALPAK-IB column (25 cm), CO_2:MeOH 88:12, 2 mL/min, 140 bars, 40 °C). Retention times: 14.9 minutes (minor), 15.6 minutes (major), e.r. = 93:7.

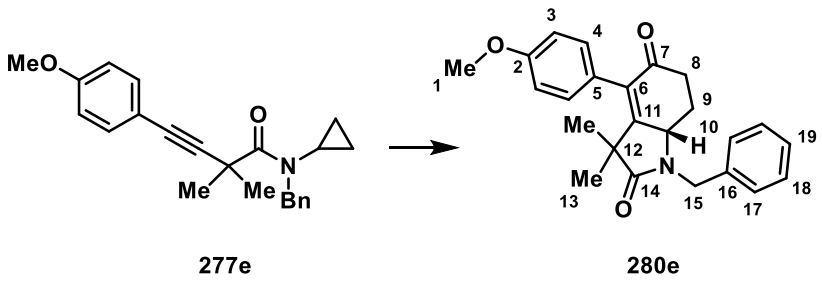
***N*-Benzyl-*N*-cyclopropyl-4-(4-methoxyphenyl)-2,2-dimethylbut-3-ynamide (277e)**



286 **277e**

General procedure H: Aminocyclopropane **286** (200.0 mg, 0.83 mmol) and 4-iodoanisole (213.4 mg, 0.91 mmol) were employed and the reaction was stirred for 2 h at r.t. Flash column chromatography (10% EtOAc/hexane) afforded alkyne **277e** (246.1 mg, 85%) as an orange solid; m.p. 60-61 °C (DCM/hexane); ν_{max} / cm^{-1}: 2935 (w), 1645 (s), 1509 (s), 1247 (s), 1167 (s), 1029 (m), 831 (s); ^{1}H NMR (DMSO-d_6, 500 MHz, 110 °C): δ 7.33 – 7.20 (m, 5H, 2 × C**15**-H, 2 × C**16**-H and C**17**-H), 7.18 – 7.13 (m, 2H, 2 × C**4**-H), 6.87 – 6.83 (m, 2H, 2 × C**3**-H), 4.79 (s, 2H, C**13**-H_2), 3.77 (s, 3H, C**1**-H_3), 3.07 – 3.00 (br. m, 1H, C**11**-H), 1.59 (s, 6H, 2 × C**9**-H_3), 0.76 – 0.69 (m, 4H, 2 × C**12**-H_2); ^{13}C NMR (DMSO-d_6, 126 MHz, 110 °C): δ 173.1 (C**10**), 158.9 (C**2**), 138.0 (C**14**), 131.9 (C**4**), 127.6, 126.1 (C**15** and C**16**), 126.0 (C**17**), 114.3 (C**5**), 113.7 (C**3**), 91.1 (C**7**), 82.7 (C**6**), 54.8 (C**1**), 49.8 (C**13**), 37.3 (C**8**), 30.4 (C**11**), 28.1 (C**9**), 7.2 (C**12**); HRMS: (ESI^+) calculated for $C_{23}H_{26}NO_2$: 348.1958, found $[M+H]^+$: 348.1953.

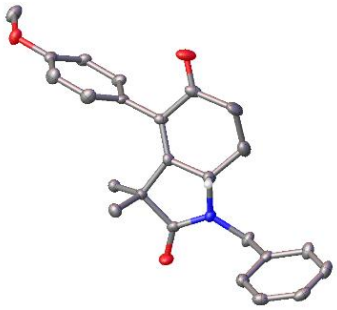
1-Benzyl-4-(4-methoxyphenyl)-3,3-dimethyl-1,6,7,7a-tetrahydro-2*H*-indole-2,5(3*H*)-dione (280e)



277e **280e**

General procedure I: Amide **277e** (34.7 mg, 0.10 mmol) was employed. Flash column chromatography (30% EtOAc/hexane) afforded the title compound **280e** (27.1 mg, 72%) as a colourless solid; m.p. 160-161 °C (DCM/hexane); ν_{max} / cm^{-1}: 2931 (w), 1694 (s), 1673 (s), 1510 (s), 1418 (m), 1243 (s), 1173 (s), 726 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.39 – 7.23 (m, 5H, C**19**-H, 2 × C**17**-H and 2 × C**18**-H), 6.96 – 6.85 (m, 4H, 2 × C**3**-H and 2 × C**4**-H), 5.09 (d, *J* = 14.9 Hz, 1H, C**15**-H_aH_b), 4.20 (dd, *J* = 11.7, 4.4 Hz, 1H, C**10**-H), 4.09 (d, *J* = 14.9 Hz, 1H, C**15**-H_aH_b), 3.80 (s, 3H, C**1**-H_3), 2.71 (ddd, *J* = 17.8, 4.4, 2.3 Hz, 1H, C**8**-H_aH_b), 2.51 – 2.43 (m, 1H, C**9**-H_aH_b),

2.35 (ddd, *J* = 17.8, 14.2, 4.9 Hz, 1H, C**8**-H_aH_b), 1.85 – 1.72 (m, 1H, C**9**-H_aH_b), 1.33 (s, 3H, C**13**-H_3), 0.85 (s, 3H, C**13'**-H_3); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 197.1 (C**7**), 177.5 (C**14**), 162.6 (C**11**), 159.4 (C**2**), 136.0 (C**16**), 135.7 (C**6**), 131.0 (2 signals, C**4** and C**19**), 129.1, 128.1 (C**17** and C**18**), 126.1 (C**5**), 113.6 (C**3**), 55.8 (C**10**), 55.3 (C**1**), 46.0 (C**12**), 44.1 (C**15**), 35.8 (C**8**), 28.4 (C**9**), 26.2 (C**13**), 22.0 (C**13'**); HRMS: (ESI^+) calculated for $C_{24}H_{25}NNaO_3$: 398.1727, found $[M+Na]^+$: 398.1725. The structure and relative stereochemistry of this compound was determined unambiguously by X-ray crystallography.



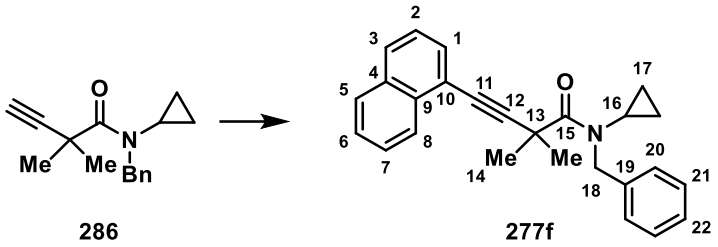
Crystal image of **280e** generated in Olex2, ellipsoids at 50% probability, hydrogen atoms and the water solvent molecule omitted for clarity; Crystal data for **280e**: $C_{24}H_{27}NO_4$, MW = 393.46, orthorhombic, space group $P2_1/c$, a = 9.4740(7) Å, b = 11.4261(8) Å, c = 19.3296(16) Å, V = 2037.0(3) $Å^3$, α = 90.00°, β = 103.220(5)°, γ = 90.00°, Z = 4, D_c = 1.283 g/cm^3 , Mo-Kα radiation, λ = 0.71073 Å, μ = 0.087 mm^{-1}, T = 100 K; colourless plate, crystal size 0.419 × 0.344 × 0.149 mm^3, Bruker Apex II diffractometer, 18092 reflections were collected, 4836 were unique, R_{int} = 0.0727; refinement on F^2 gave R_1 = 0.0583 and wR_2 = 0.1673, GOF = 1.012 for 268 refined parameters.

General procedure J: Amide **277e** (34.7 mg, 0.10 mmol) was employed. Flash column chromatography (40% EtOAc/hexane) afforded the title compound **(*S*)-280e** (22.1 mg, 59%) as a colourless oil. The enantiopurity of this compound was determined by chiral SFC against a racemic standard.

$[\alpha]_D^{23.9}$ = -55.1 (c = 0.13, $CHCl_3$).

Chiral SFC: (DAICEL CHIRALPAK-IA column (25 cm), CO_2:MeOH 88:12, 2 mL/min, 140 bars, 40 °C). Retention times: 7.7 minutes (minor), 8.4 minutes (major), e.r. = 87:13.

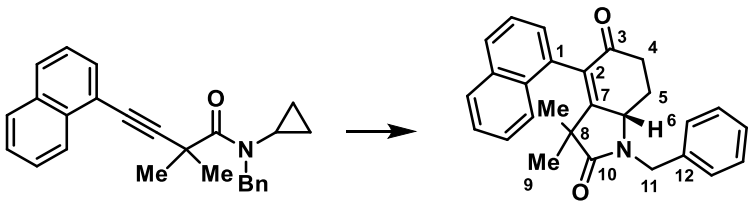
***N*-Benzyl-*N*-cyclopropyl-2,2-dimethyl-4-(naphthalen-1-yl)but-3-ynamide (277f)**



286 **277f**

General procedure H: Aminocyclopropane **286** (200.0 mg, 0.83 mmol) and 1-iodonaphthalene (231.2 mg, 0.91 mmol) were employed and the reaction was stirred for 3 h at r.t. Flash column chromatography (10% EtOAc/hexane) afforded alkyne **277f** (277.1 mg, 91%) as an orange oil; ν_{max} / cm^{-1}: 2984 (w), 1643 (s), 1394 (s), 1165 (m), 799 (s), 774 (s); ^{1}H NMR (DMSO-*d*$_6$, 500 MHz, 110 °C): δ 8.15 (br. d, *J* = 8.3 Hz, 1H, C**8**-H), 7.95 – 7.91 (m, 1H, C**5**-H), 7.89 (br. d, *J* = 8.0 Hz, 1H, C**3**-H), 7.61 – 7.53 (m, 2H, C**1**-H and C**7**-H), 7.47 – 7.40 (m, 2H, C**2**-H and C**6**-H), 7.30 – 7.17 (m, 5H, 2 × C**20**-H, 2 × C**21**-H and C**22**-H), 4.83 (s, 2H, C**18**-H$_2$), 3.11 (br. s, 1H, C**16**-H), 1.72 (s, 6H, 2 × C**14**-H$_3$), 0.80 – 0.70 (m, 4H, 2 × C**17**-H$_2$); ^{13}C NMR (DMSO-*d*$_6$, 126 MHz, 110 °C): δ 173.0 (C**15**), 138.0 (C**19**), 132.4, 132.2 (C**4** and C**9**), 129.4, 128.0, 127.8, 127.7, 126.4, 126.2, 126.1, 125.9, 124.8, 124.7 (C**1**, C**2**, C**3**, C**5**, C**6**, C**7**, C**8**, C**20**, C**21** and C**22**), 119.6 (C**10**), 97.8 (C**12**), 81.0 (C**11**), 49.8 (C**18**), 37.8 (C**13**), 30.6 (C**16**), 28.3 (C**14**), 7.3 (C**17**); HRMS: (ESI$^+$) calculated for $C_{26}H_{26}NO$: 368.2009, found $[M+H]^+$: 368.2013.

1-Benzyl-3,3-dimethyl-4-(naphthalen-1-yl)-1,6,7,7a-tetrahydro-2*H*-indole-2,5(3*H*)-dione (280f)



277f **280f**

General procedure I: Amide **277f** (36.7 mg, 0.10 mmol) was employed. Flash column chromatography (30-40% EtOAc/hexane) afforded the title compound **280f** (20.7 mg, 52%) as a colourless oil. The product was obtained as a mixture of diastereomers (*A*:*B*, 1:2.6) due to restricted rotation around the C**1**-C**2** bond; ν_{max} / cm^{-1}: 1696 (s), 1673 (s), 1644 (m), 1418 (m), 1242 (m), 801 (m), 777 (m), 733 (m), 709 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.89 – 7.84 (m, 4H, 2 × Ar-H, *A*+*B*), 7.51 – 7.28 (m, 18H, 9 × Ar-H, *A*+*B*), 7.18 (d, *J* = 7.0 Hz, 1H, Ar-H, *B*), 7.14 (d, *J* = 7.2 Hz, 1H, Ar-H, *A*), 5.17 (d, *J* = 14.9 Hz, 1H, C**11**-H$_a$H$_b$, *B*), 5.17 (d, *J* = 14.9 Hz, C**11**-H$_a$H$_b$, *A*),

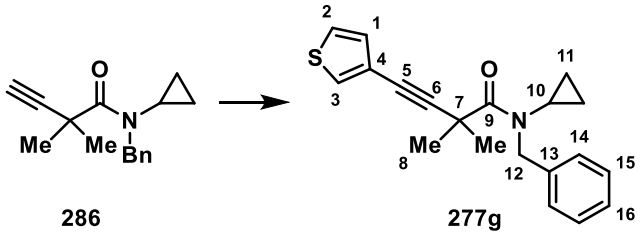
4.40 – 4.28 (m, 2H, C**6**-H, *A*+*B*), 4.16 – 4.09 (m, 2H, C**11**-H_aH_b, *A*+*B*), 2.89 – 2.75 (m, 2H, C**4**-H_aH_b, *A*+*B*), 2.66 – 2.53 (m, 2H, C**5**-H_aH_b, *A*+*B*), 2.52 – 2.40 (m, 2H, C**4**-H_aH_b, *A*+*B*), 2.09 – 1.89 (m, 2H, C**5**-H_aH_b, *A*+*B*), 1.36 (s, 3H, C**9**-H_3, *B*), 0.98 (s, 3H, C**9**-H_3, *A*), 0.82 (s, 3H, C**9'**-H_3, *A*), 0.56 (s, 3H, C**9'**-H_3, *B*); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 196.6 (C**3**, *A*), 196.3 (C**3**, *B*), 177.5 (C**10**, *A*), 177.4 (C**10**, *B*), 164.0 (C**7**, *B*), 163.7 (C**7**, *A*), 136.0 (C**12**, *A*), 136.0 (C**12**, *B*), 134.7, 134.2, 133.7, 133.4, 132.6, 132.4, 132.0, 131.3, 129.2, 129.0, 128.7, 128.6, 128.2, 128.2, 128.2, 128.1, 127.8, 126.5, 126.1, 126.0, 125.5, 125.3, 125.1, 125.0 (2 × Ar-C, 10 × Ar-CH, C**1** and C**2**, *A*+*B*), 56.1 (C**6**, *B*), 55.9 (C**6**, *A*), 46.2 (C**8**, *A*), 46.1 (C**8**, *B*), 44.2 (C**11**, *B*), 44.2 (C**11**, *A*), 36.0 (C**4**, *A*), 35.9 (C**4**, *B*), 28.6 (C**5**, *B*), 28.3 (C**5**, *A*), 26.0 (C**9**, *B*), 23.8 (C**9**, *A*), 23.1 (C**9'**, *A*), 20.7 (C**9'**, *B*); HRMS: (ESI$^+$) calculated for $C_{27}H_{26}NO_2$: 396.1958, found $[M+H]^+$: 396.1968.

General procedure J: Amide **277f** (36.7 mg, 0.10 mmol) was employed. Flash column chromatography (40% EtOAc/hexane) afforded the title compound **(*S*)-280f** (12.8 mg, 32%) as a colourless oil. The product was obtained as a mixture of diastereomers (*A*:*B*, 1:2). The enantiopurity of this compound was determined by chiral SFC against a racemic standard.

$[\alpha]_D^{23.8}$ = -6.93 (c = 0.47, $CHCl_3$, mixture of diastereomers).

Chiral SFC: (DAICEL CHIRALPAK-IA column (25 cm), CO_2:MeOH 88:12, 2 mL/min, 140 bars, 40 °C). Retention times: major diastereomer – 11.2 minutes (minor), 16.0 minutes (major), e.r. = 87:13; minor diastereomer – 10.3 minutes (minor), 16.0 minutes (major), e.r. = 90:10.

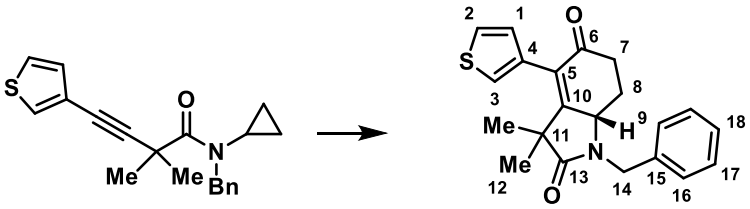
***N*-Benzyl-*N*-cyclopropyl-2,2-dimethyl-4-(thiophen-3-yl)but-3-ynamide (277g)**



General procedure H: Aminocyclopropane **286** (200.0 mg, 0.83 mmol) and 3-bromothiophene (85 μL, 0.91 mmol) were employed and the reaction was stirred for 16 h at 60 °C. Flash column chromatography (10% EtOAc/hexane) afforded alkyne **277g** (263.1 mg, 98%) as an orange solid; m.p. 74-75 °C (DCM/hexane); ν_{max} / cm^{-1}: 2985 (w), 1644 (s), 1396 (s), 1361 (m), 783 (m); ^{1}H NMR (DMSO-*d*$_6$, 500 MHz, 110 °C): δ 7.47 – 7.42 (m, 2H, C**2**-H and C**3**-H), 7.34 – 7.20 (m, 5H, 2 × C**14**-H, 2 × C**15**-H and C**16**-H), 6.92 (dd, *J* = 4.9, 1.3 Hz, 1H, C**1**-H), 4.78 (s, 2H, C**12**-H_2), 3.00 (br. s, overlapped by water, 1H, C**10**-H), 1.58 (s, 6H, 2 × C**8**-H_3), 0.75 – 0.70 (m, 4H, 2 × C**11**-H_2); ^{13}C NMR (DMSO-*d*$_6$, 126 MHz, 110 °C): δ 173.0 (C**9**), 138.0 (C**13**), 128.8, 128.1, 127.7,

126.2, 126.1, 125.6 (C**1**, C**2**, C**3**, C**14**, C**15** and C**16**), 121.1 (C**4**), 91.9 (C**6**), 78.3 (C**5**), 49.9 (C**12**), 37.3 (C**7**), 30.5 (C**10**), 28.1 (C**8**), 7.3 (C**11**); HRMS: (ESI^+) calculated for $C_{20}H_{22}NOS$: 324.1417, found $[M+H]^+$: 324.1424.

1-Benzyl-3,3-dimethyl-4-(thiophen-3-yl)-1,6,7,7a-tetrahydro-2*H*-indole-2,5(3*H*)-dione (280g)



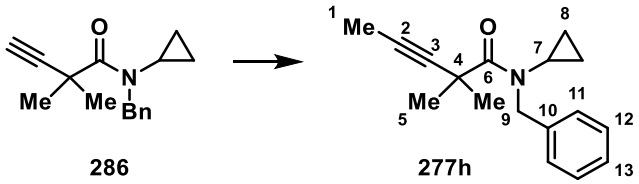
General procedure I: Amide **277g** (32.3 mg, 0.10 mmol) was employed. Flash column chromatography (40% EtOAc/hexane) afforded the title compound **280g** (30.9 mg, 88%) as a yellow oil; ν_{max} / cm^{-1}: 1694 (s), 1673 (s), 1645 (m), 1417 (s), 1241 (m), 1196 (m), 732 (s), 697 (s); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.39 – 7.22 (m, 6H, C**2**-H, C**18**-H, 2 × C**16**-H and 2 × C**17**-H), 7.00 (dd, *J* = 2.9, 1.3 Hz, 1H, C**3**-H), 6.81 (dd, *J* = 5.0, 1.3 Hz, 1H, C**1**-H), 5.09 (d, *J* = 15.0 Hz, 1H, C**14**-H_aH_b), 4.20 (dd, *J* = 11.7, 4.4 Hz, 1H, C**9**-H), 4.08 (d, *J* = 15.0 Hz, 1H, C**14**-H_aH_b), 2.76 – 2.65 (m, 1H, C**7**-H_aH_b), 2.51 – 2.42 (m, 1H, C**8**-H_aH_b), 2.41 – 2.28 (m, 1H, C**7**-H_aH_b), 1.86 – 1.72 (m, 1H, C**8**-H_aH_b), 1.36 (s, 3H, C**12**-H_3), 0.88 (s, 3H, C**12'**-H_3); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 196.5 (C**6**), 177.4 (C**13**), 163.8 (C**10**), 135.9 (C**15**), 133.6 (C**4**), 131.2 (C**5**), 129.4 (C**2**), 129.1, 128.1, 128.0 (C**16**, C**17** and C**18**), 125.3 (C**1**), 124.7 (C**3**), 56.0 (C**9**), 46.0 (C**11**), 44.1 (C**14**), 35.8 (C**7**), 28.4 (C**8**), 26.3 (C**12**), 21.4 (C**12'**); HRMS: (ESI^+) calculated for $C_{21}H_{21}NNaO_2S$: 374.1185, found $[M+Na]^+$: 374.1196.

General procedure J: Amide **277g** (32.3 mg, 0.10 mmol) was employed. Flash column chromatography (40% EtOAc/hexane) afforded the title compound **(*S*)-280g** (25.0 mg, 71%) as a colourless oil. The enantiopurity of this compound was determined by chiral SFC against a racemic standard.

$[\alpha]_D^{23.7}$ = -27.4 (c = 0.38, $CHCl_3$).

Chiral SFC: (DAICEL CHIRALPAK-IA column (25 cm), CO_2:MeOH 88:12, 2 mL/min, 140 bars, 40 °C). Retention times: 7.5 minutes (minor), 10.6 minutes (major), e.r. = 93:7.

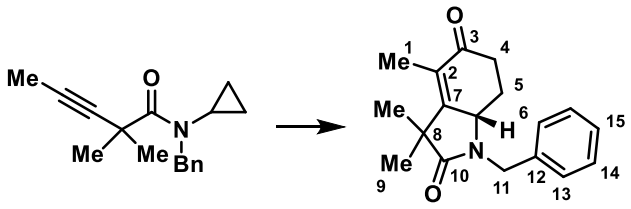
***N*-Benzyl-*N*-cyclopropyl-2,2-dimethylpent-3-ynamide (277h)**



286 **277h**

To a solution of terminal alkyne **286** (200.0 mg, 0.83 mmol) in THF (0.1 M) at -78 °C was added *n*-BuLi (1.00 mmol, 1.5 M in hexanes) and the solution was stirred for 1 h under nitrogen. Methyl iodide (103 μL, 1.66 mmol) was added and the reaction was slowly warmed to r.t. and stirred for 16 h. Sat. aq. NH_4Cl (20 mL) was added and the solution was extracted with EtOAc (3 × 10 mL). The organic extracts were combined, washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Flash column chromatography (10% EtOAc/hexane) afforded alkyne **277h** (144.5 mg, 68%) as a colourless oil; ν_{max} / cm^{-1}: 2983 (m), 2935 (m); 1643 (s), 1454 (m), 1394 (s), 1237 (s), 1167 (m), 1027 (m), 1001 (s), 727 (s), 670 (s); ^{1}H NMR (DMSO-d_6, 500 MHz, 110 °C): δ 7.36 – 7.19 (m, 5H, 2 × C**11**-H, 2 × C**12**-H and C**13**-H), 4.75 (s, 2H, C**9**-H_2), 2.96 (br. s, 1H, C**7**-H), 1.63 (s, 3H, C**1**-H_3), 1.45 (s, 6H, 2 × C**5**-H_3), 0.70 – 0.66 (m, 4H, 2 × C**8**-H_2); ^{13}C NMR (DMSO-d_6, 126 MHz, 110 °C): δ 173.5 (C**6**), 138.2 (C**10**), 127.7, 126.1 (C**11** and C**12**), 126.0 (C**13**), 82.2 (C**3**), 78.7 (C**2**), 49.7 (C**9**), 36.7 (C**7**), 30.4 (C**4**), 28.2 (C**5**), 7.0 (C**8**), 2.3 (C**1**); HRMS: (ESI^+) calculated for $C_{17}H_{22}NO$: 256.1696, found $[M+H]^+$: 256.1691.

1-Benzyl-3,3,4-trimethyl-1,6,7,7a-tetrahydro-2*H*-indole-2,5(3*H*)-dione (280h)



277h **280h**

General procedure I: Amide **277h** (25.5 mg, 0.10 mmol) was employed. Flash column chromatography (30-40% EtOAc/hexane) afforded the title compound **280h** (19.1 mg, 67%) as a colourless oil; ν_{max} / cm^{-1}: 1698 (s), 1670 (s), 1652 (s), 1419 (m), 1316 (m), 1246 (m), 704 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35 – 7.19 (m, 5H, C**15**-H, 2 × C**13**-H and 2 × C**14**-H), 5.01 (d, *J* = 15.0 Hz, 1H, C**11**-H_aH_b), 4.10 (d, *J* = 15.0 Hz, 1H, C**11**-H_aH_b), 4.02 – 3.95 (m, 1H, C**6**-H), 2.59 (ddd, *J* = 18.0, 4.6, 2.1 Hz, 1H, C**4**-H_aH_b), 2.38 – 2.29 (m, 1H, C**5**-H_aH_b), 2.20 (ddd, *J* = 18.0, 14.1, 5.0 Hz, 1H, C**4**-H_aH_b), 1.86 (d, *J* = 2.1 Hz, 3H, C**1**-H_3), 1.68 – 1.56 (m, 1H, C**5**-H_aH_b), 1.54 (s, 3H, C**9**-H_3), 1.34 (s, 3H, C**9'**-H_3); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 197.5 (C**3**), 177.8 (C**10**), 160.5

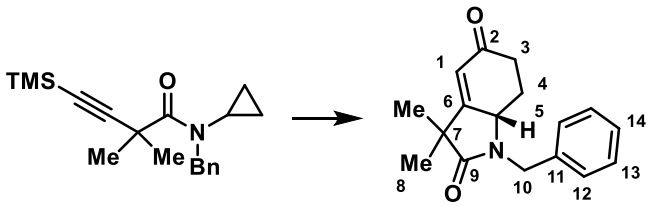
(C**7**), 136.0 (C**12**), 129.7 (C**2**), 129.0, 128.0, 128.0 (C**13**, C**14** and C**15**), 56.0 (C**6**), 45.3 (C**8**), 44.2 (C**11**), 35.5 (C**4**), 28.4 (C**5**), 23.1 (C**9**), 22.8 (C**9'**), 10.9 (C**1**); HRMS: (ESI$^+$) calculated for $C_{18}H_{21}NNaO_2$: 306.1465, found [M+Na]$^+$: 306.1470.

General procedure J: Amide **277h** (25.5 mg, 0.10 mmol) was employed. Flash column chromatography (50% EtOAc/hexane) afforded the title compound **(*S*)-280h** (19.9 mg, 70%) as a colourless oil. The enantiopurity of this compound was determined by chiral SFC against a racemic standard.

$[\alpha]_D^{24.2}$ = -72.1 (c = 0.23, $CHCl_3$).

Chiral SFC: (DAICEL CHIRALPAK-IB column (25 cm), CO_2:MeOH 94:6, 2 mL/min, 140 bars, 40 °C). Retention times: 11.9 minutes (minor), 12.5 minutes (major), e.r. = 86:14.

1-Benzyl-3,3-dimethyl-1,6,7,7a-tetrahydro-2*H*-indole-2,5(3*H*)-dione (287)



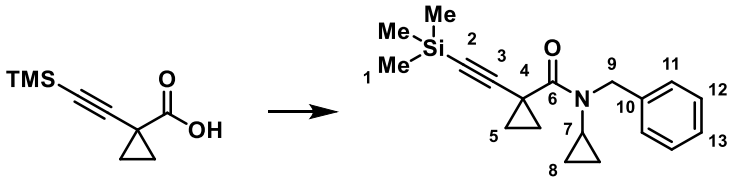
General procedure I: Amide **285** (31.4 mg, 0.10 mmol) was employed. Flash column chromatography (50% EtOAc/hexane) afforded the title compound **287** (19.3 mg, 72%) as a pale yellow oil; ν_{max} / cm^{-1}: 2967 (w), 1676 (s), 1413 (m), 1233 (m), 1191 (m), 703 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.37 – 7.21 (m, 5H, 2 × C**12**-H, 2 × C**13**-H and C**14**-H), 5.90 (d, *J* = 1.2 Hz, 1H, C**1**-H), 5.07 (d, *J* = 15.0 Hz, 1H, C**10**-H_aH_b), 4.09 (ddd, *J* = 11.7, 4.7, 2.3 Hz, 1H, C**5**-H), 4.01 (d, *J* = 15.0 Hz, 1H, C**10**-H_aH_b), 2.58 – 2.50 (m, 1H, C**3**-H_aH_b), 2.39 (dtd, *J* = 11.7, 4.7, 2.3 Hz, 1H, C**4**-H_aH_b), 2.25 (ddd, *J* = 17.6, 14.3, 4.7 Hz, 1H, C**3**-H_aH_b), 1.71 – 1.59 (m, 1H, C**4**-H_aH_b), 1.35 (s, 3H, C**8**-H_3), 1.28 (s, 3H, C**8'**-H_3); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 197.4 (C**2**), 177.0 (C**9**), 169.2 (C**6**), 135.9 (C**11**), 129.1, 129.1, 128.1 (C**12**, C**13** and C**14**), 121.1 (C**1**), 55.1 (C**5**), 44.8 (C**7**), 44.1 (C**10**), 35.7 (C**3**), 28.8 (C**4**), 25.3 (C**8**), 21.5 (C**8'**); HRMS: (ESI$^+$) calculated for $C_{17}H_{19}NNaO_2$: 292.1308, found [M+Na]$^+$: 292.1308.

General procedure J: *In a modification to the general procedure, the reaction was heated to 120 °C.* Amide **285** (31.4 mg, 0.10 mmol) was employed. Flash column chromatography (50% EtOAc/hexane) afforded the title compound **(*S*)-287** (18.4 mg, 68%) as a yellow oil. The enantiopurity of this compound was determined by chiral SFC against a racemic standard.

$[\alpha]_D^{23.6}$ = -51.3 (c = 0.07, $CHCl_3$).

Chiral SFC: (DAICEL CHIRALPAK-IB column (25 cm), CO_2:MeOH 88:12, 2 mL/min, 140 bars, 40 °C). Retention times: 5.2 minutes (minor), 6.1 minutes (major), e.r. = 89:11.

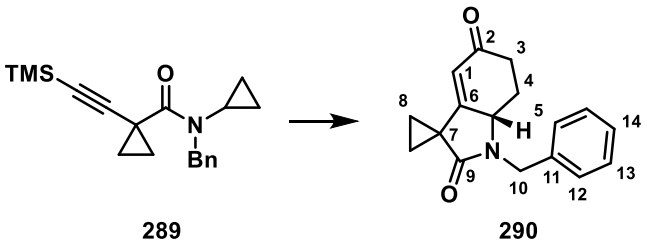
_N_-Benzyl-_N_-cyclopropyl-1-((trimethylsilyl)ethynyl)cyclopropane-1-carboxamide (289)



289' **289**

*Aminocyclopropane **289** was prepared by Curley.* **General procedure G:** *N*-Benzylcyclopropanamine (0.49 g, 3.30 mmol) and acid **289'** (0.60 g, 3.30 mmol, prepared according to the literature procedure[276]) were employed and the residue was purified by flash column chromatography (20% EtOAc/hexane) to afford the title compound **289** (0.51, 50%) as a colourless oil; ν_{max} / cm^{-1}: 2956 (m), 2831 (m), 1633 (m), 1406 (m), 1249 (m), 1026 (s), 841(s), 697 (m); ^{1}H NMR (DMSO-d_6, 500 MHz, 110 °C): δ 7.35 – 7.19 (m, 5H, 2 × C**11**-H, 2 × C**12**-H and C**13**-H), 4.62 (s, 2H, C**9**-H_2), 2.98 – 2.92 (m, 1H, C**7**-H), 1.44 – 1.36 (m, 2H, 2 × C**5**-H_aH_b), 1.21 – 1.15 (m, 2H, 2 × C**5**-H_aH_b), 0.86 – 0.76 (m, 4H, 2 × C**8**-H_2), 0.09 (s, 9H, 3 × C**1**-H_3); ^{13}C NMR (DMSO-d_6, 126 MHz, 110 °C): 169.5 (C**6**), 137.8 (C**10**), 127.8, 126.5, 126.3 (C**11**, C**12** and C**13**), 107.0 (C**2**), 82.8 (C**3**), 50.0 (C**9**), 30.8 (C**7**), 17.7 (C**4**), 17.2 (C**5**), 8.2 (C**8**), -0.7 (C**1**); HRMS: (ESI^+) calculated for $C_{19}H_{26}NOSi$: 312.1767, found $[M+H]^+$: 312.1754.

1'-Benzyl-1',6',7',7a'-tetrahydrospiro[cyclopropane-1,3'-indole]-2',5'-dione (290)



289 **290**

General procedure I: Amide **289** (31.2 mg, 0.10 mmol) was employed. Flash column chromatography (50% EtOAc/hexane) afforded the title compound **290** (14.4 mg, 54%) as a pale yellow oil; ν_{max} / cm^{-1}: 2925 (w), 1657 (s), 1672 (s), 1435 (m), 1411 (m), 1353 (m), 1231 (m), 1193 (m), 733 (s), 702 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38 – 7.24 (m, 5H, 2 × C**12**-H, 2 × C**13**-H and C**14**-H), 5.53 (dd, *J* = 2.5, 1.0 Hz, 1H, C**1**-H), 4.95 (d, *J* = 15.0 Hz, 1H, C**10**-H_aH_b), 4.27 (d, *J* = 15.0 Hz, 1H, C**10**-H_aH_b), 4.24 (ddd, *J* = 11.8, 4.4, 2.4 Hz, 1H, C**5**-H), 2.60 – 2.53 (m,

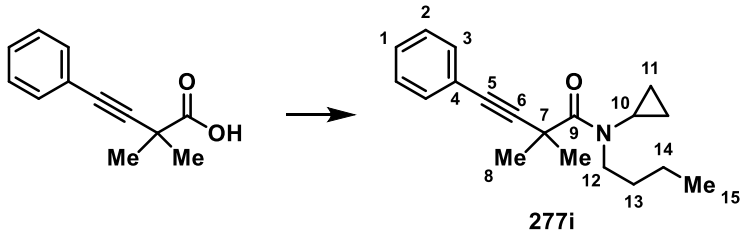
1H, C**3**-$\underline{H}_aH_b$), 2.38 (dtd, *J* = 11.8, 4.7, 2.4 Hz, 1H, C**4**-$\underline{H}_aH_b$), 2.24 (ddd, *J* = 17.7, 13.9, 4.7 Hz, 1H, C**3**-$H_a\underline{H}_b$), 1.86 – 1.69 (m, 3H, C**4**-$H_a\underline{H}_b$, C**8**-$\underline{H}_aH_b$, C**8'**-$\underline{H}_aH_b$), 1.31 (d, *J* = 4.4 Hz, 2H, C**8**-$H_a\underline{H}_b$, C**8'**-$H_a\underline{H}_b$); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 196.7 (C**2**), 174.1 (C**9**), 166.8 (C**6**), 136.2 (C**11**), 129.1, 128.2, 128.1 (C**12**, C**13** and C**14**), 116.2 (C**1**), 57.9 (C**5**), 45.1 (C**10**), 36.2 (C**3**), 29.0 (C**4**), 28.0 (C**7**), 23.7 (C**8**), 17.5 (C**8'**); HRMS: (ESI^+) calculated for $C_{17}H_{18}NO_2$: 268.1332, found $[M+H]^+$: 268.1332.

General procedure J: Amide **289** (31.2 mg, 0.10 mmol) was employed. Flash column chromatography (50% EtOAc/hexane) afforded the title compound **(*S*)-290** (15.4 mg, 57%) as a yellow oil. The enantiopurity of this compound was determined by chiral SFC against a racemic standard.

$[\alpha]_D^{23.8}$ = -9.0 (c = 0.25, $CHCl_3$).

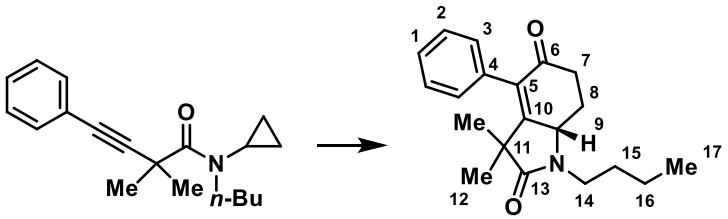
Chiral SFC: (DAICEL CHIRALPAK-IB column (25 cm), CO_2:MeOH 88:12, 2 mL/min, 140 bars, 40 °C). Retention times: 9.7 minutes (minor), 10.4 minutes (major), e.r. = 90:10.

***N*-Butyl-*N*-cyclopropyl-2,2-dimethyl-4-phenylbut-3-ynamide (277i)**



General procedure G: *N*-Butylcyclopropanamine (0.18 g, 1.59 mmol) and 2,2-dimethyl-4-phenylbut-3-ynoic acid (0.30 g, 1.59 mmol, prepared according to the literature procedure[274]) were employed and the residue was purified by flash column chromatography (5-10% EtOAc/hexane) to afford the title compound **277i** (0.21 g, 47%) as a colourless oil; ν_{max} / cm^{-1}: 2957 (m), 2934 (m), 1648 (s), 1465 (m), 1399 (s), 1289 (m), 756 (s), 692 (s); ^{1}H NMR (DMSO-d_6, 500 MHz, 110 °C): δ 7.38 – 7.33 (m, 5H, 2 × C**2**-H, 2 × C**3**-H and C**1**-H), 3.49 (t, *J* = 7.6 Hz, 2H, C**12**-$\underline{H}_2$), 2.94 (br. s, 1H, C**10**-H), 1.62 – 1.55 (m, 2H, C**13**-$\underline{H}_2$), 1.52 (s, 6H, 2 × C**8**-$\underline{H}_3$), 1.32 – 1.24 (m, 2H, C**14**-$\underline{H}_2$), 0.88 – 0.80 (m, 5H, C**15**-$\underline{H}_3$ and 2 × C**11**-$\underline{H}_aH_b$), 0.71 – 0.65 (m, 2H, 2 × C**11**-$H_a\underline{H}_b$); ^{13}C NMR (DMSO-d_6, 126 MHz, 110 °C): δ 172.3 (C**9**), 130.5, 128.0 (C**2** and C**3**), 127.6 (C**1**), 122.4 (C**4**), 93.0 (C**6**), 82.4 (C**5**), 46.2 (C**12**), 37.1 (C**7**), 29.7 (C**13**), 29.4 (C**10**), 28.0 (C**8**), 19.0 (C**14**), 12.9 (C**15**), 7.3 (C**11**); HRMS: (ESI^+) calculated for $C_{19}H_{26}NO$: 284.2009, found $[M+H]^+$:284.2009.

1-Butyl-3,3-dimethyl-4-phenyl-1,6,7,7a-tetrahydro-2*H*-indole-2,5(3*H*)-dione (280i)



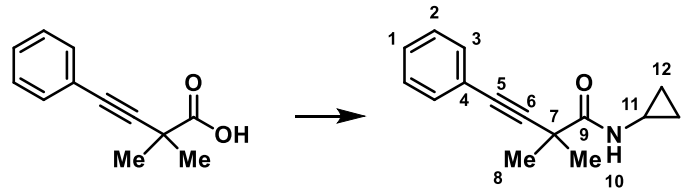
General procedure I: Amide **277i** (28.3 mg, 0.10 mmol) was employed. Flash column chromatography (35% EtOAc/hexane) afforded the title compound **280i** (21.9 mg, 70%) as a pale yellow oil; ν_{max} / cm^{-1}: 2957 (m), 2930 (m), 2871 (m), 1694 (s), 1674 (s), 1644 (m), 1462 (m), 1422 (m), 1241 (m), 1201 (m), 755 (m), 705 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.39 – 7.32 (m, 3H, 2 × C**2**-H and C**1**-H), 7.06 – 7.00 (m, 2H, 2 × C**3**-H), 4.43 (dd, *J* = 11.6, 4.1 Hz, 1H, C**9**-H), 3.69 (ddd, *J* = 13.8, 8.7, 7.3 Hz, 1H, C**14**-H_aH_b), 3.09 (ddd, *J* = 13.8, 8.5, 5.2 Hz, 1H, C**14**-H_aH_b), 2.85 – 2.76 (m, 1H, C**7**-H_aH_b), 2.61 – 2.46 (m, 2H, C**7**-H_aH_b and C**8**-H_aH_b), 1.91 – 1.78 (m, 1H, C**8**-H_aH_b), 1.65 – 1.48 (m, 2H, C**15**-H_2), 1.41 – 1.31 (m, 2H, C**16**-H_2), 1.30 (s, 3H, C**12**-H_3), 0.95 (t, *J* = 7.3 Hz, 3H, C**17**-H_3), 0.74 (s, 3H, C**12'**-H_3); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 196.9 (C**6**), 177.0 (C**13**), 163.0 (C**10**), 136.0 (C**5**), 134.1 (C**4**), 129.9 (C**3**), 128.1 (C**1** and C**2**), 56.3 (C**9**), 46.0 (C**11**), 39.9 (C**14**), 35.9 (C**7**), 29.5 (C**15**), 28.6 (C**8**), 26.4 (C**12**), 21.9 (C**12'**), 20.2 (C**16**), 13.9 (C**17**); HRMS: (ESI^+) calculated for $C_{20}H_{26}NO_2$: 312.1958, found $[M+H]^+$: 312.1958.

General procedure J: Amide **277i** (28.3 mg, 0.10 mmol) was employed. Flash column chromatography (40% EtOAc/hexane) afforded the title compound **(*S*)-280i** (16.1 mg, 52%) as a colourless oil. The enantiopurity of this compound was determined by chiral SFC against a racemic standard.

$[\alpha]_D^{24.2}$ = 16.7 (c = 0.23, $CHCl_3$).

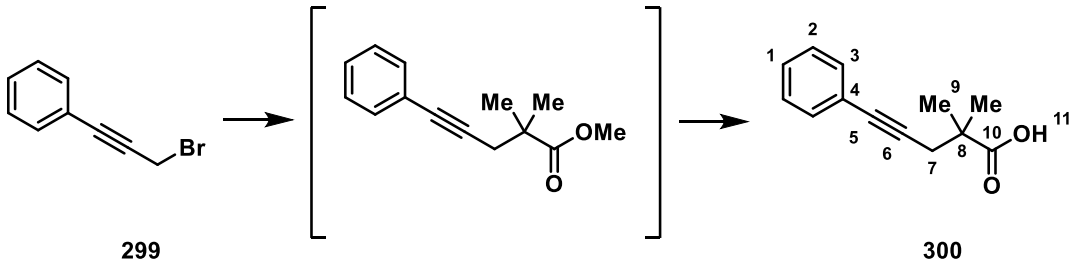
Chiral SFC: (DAICEL CHIRALPAK-IB column (25 cm), CO_2:MeOH 94:6, 2 mL/min, 140 bars, 40 °C). Retention times: 12.9 minutes (major), 13.5 minutes (minor), e.r. = 91:9.

***N*-Cyclopropyl-2,2-dimethyl-4-phenylbut-3-ynamide (296)**



General procedure G: Cyclopropylamine (0.11 mL, 1.59 mmol) and 2,2-dimethyl-4-phenylbut-3-ynoic acid **295** (0.30 g, 1.59 mmol) were employed and the residue was purified by recrystallization from DCM/hexane (two crops) to afford the title compound **296** (0.30 g, 83%) as a colourless solid; m.p. 57-58 °C (DCM/hexane); ν_{max} / cm^{-1}: 3328 (br. w), 2977 (m), 1659 (s), 1490 (s), 1269 (m), 1024 (m), 755 (s), 691 (s); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.43 – 7.38 (m, 2H, 2 × C**3**-H), 7.35 – 7.30 (m, 3H, 2 × C**2**-H and C**1**-H), 6.77 (br. s, 1H, N**10**-H), 2.76 – 2.70 (m, 1H, C**11**-H), 1.51 (s, 6H, 2 × C**8**-H_3), 0.81 – 0.75 (m, 2H, 2 × C**12**-H_aH_b), 0.55 – 0.48 (m, 2H, 2 × C**12**-H_aH_b); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 175.0 (C**9**), 131.7, 128.6, 128.5 (C**2**, C**3** and C**4**), 122.6 (C**1**), 92.4 (C**6**), 84.9 (C**5**), 39.3 (C**7**), 27.7 (C**8**), 23.1 (C**11**), 6.8 (C**12**); HRMS: (ESI^+) calculated for $C_{15}H_{18}NO$: 228.1383, found $[M+H]^+$: 228.1375.

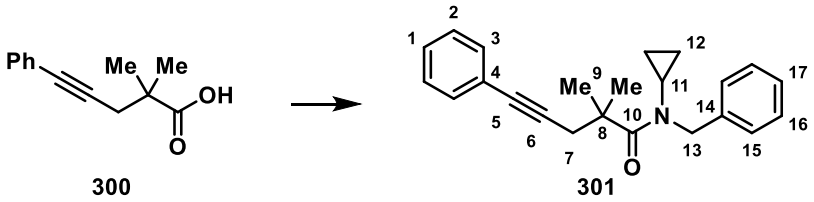
2,2-Dimethyl-5-phenylpent-4-ynoic acid (300)



Dry diisopropylamine (1.11 mL, 7.84 mmol) was dissolved in dry THF (20 mL) and cooled to -78 °C and *n*-BuLi (5.41 mL, 1.45 M solution in hexanes) was added dropwise. The mixture was stirred 30 min at -78 °C. Methyl isobutyrate (0.88 mL, 7.69 mmol) was added dropwise and the reaction was stirred for 45 min at -78 °C. (3-Bromoprop-1-yn-1-yl)benzene **299** (1.80 g, 9.23 mmol, prepared according to the literature procedure[277]) was added dropwise and then the mixture was warmed up to r.t. and stirred for 18 h. Sat. aq. NH_4Cl (30 mL) was added, the layers were separated and the aqueous portion was further extracted with Et_2O (3 × 20 mL). The organic extracts were combined, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was dissolved in MeOH (14 mL), 4.0 M aq. NaOH (9 mL) was added and the reaction was stirred at r.t. for 3 h. The reaction mixture was concentrated *in vacuo*, diluted with water (20 mL) and

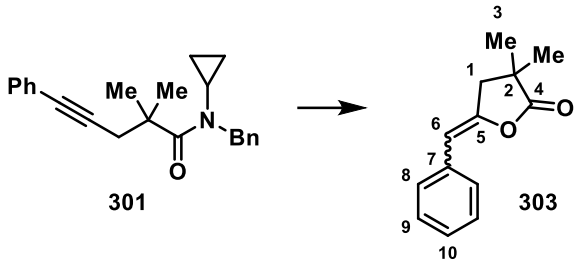
extracted with Et_2O (20 mL). The aqueous portion was adjusted to pH 2 by addition of 6.0 M aq. HCl and then extracted with Et_2O (3 × 20 mL). The organic extracts were combined, dried over $MgSO_4$ and concentrated *in vacuo* to afford the title compound **300** (1.27 g, 81% over two steps) as a colourless solid; ν_{max} / cm^{-1}: 2928 (m), 1699 (s); 1491 (m), 1473 (m), 1227 (m), 1160 (m), 755 (s), 691 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.40 – 7.36 (m, 2H, 2 × C**3**-H), 7.28 – 7.24 (m, 3H, 2 × C**2**-H and C**1**-H), 2.68 (s, 2H, C**7**-H_2), 1.37 (s, 6H, 2 × C**9**-H_3); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 183.0 (C**10**), 131.8, 128.3 (C**2** and C**3**), 127.9 (C**1**), 123.7 (C**4**), 86.4 (C**6**), 83.1 (C**5**), 42.5 (C**7**), 30.4 (C**8**), 24.6 (C**9**). The spectroscopic properties of this compound were consistent with the data available in the literature.[278]

***N*-Benzyl-*N*-cyclopropyl-2,2-dimethyl-5-phenylpent-4-ynamide (301)**



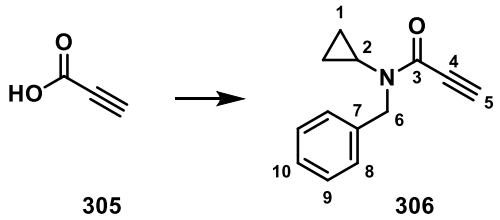
General procedure G: *N*-Benzylcyclopropanamine (0.92 g, 6.30 mmol) and acid **300** (1.27 g, 6.30 mmol) were employed. Flash column chromatography (5% EtOAc/hexane) afforded the title compound **301** (0.72 g, 34%) as a pale yellow oil; ν_{max} / cm^{-1}: 2969 (w), 1628 (s), 1392 (m), 1363 (s), 1249 (m), 1030 (m), 756 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.42 – 7.36 (m, 2H, 2 × C**3**-H), 7.31 – 7.26 (m, 3H, 2 × C**2**-H and C**1**-H), 7.23 – 7.16 (m, 5H, 2 × C**15**-H, 2 × C**16**-H and C**17**-H), 4.69 (s, 2H, C**13**-H_2), 2.88 (s, 2H, C**7**-H_2), 2.87 – 2.78 (m, 1H, C**11**-H), 1.51 (s, 6H, 2 × C**9**-H_3), 0.86 – 0.76 (m, 4H, 2 × C**12**-H_2); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 179.0 (C**10**), 138.6 (C**14**), 131.8 (C**3**), 128.6, 128.3, 127.8, 127.1, 127.0 (C**1**, C**2**, C**15**, C**16** and C**17**), 123.9 (C**4**), 88.0 (C**6**), 82.8 (C**5**), 52.3 (C**13**), 44.2 (C**8**), 32.6 (C**7**), 31.6 (C**11**), 26.1 (C**9**), 9.8 (C**12**); HRMS: (ESI^+) calculated for $C_{23}H_{26}NO$: 332.2009, found $[M+H]^+$: 332.2020.

5-Benzylidene-3,3-dimethyldihydrofuran-2(3*H*)-one (303)



An oven dried reaction tube, fitted with a magnetic stirrer, was charged with aminocyclopropane substrate **301** (33.1 mg, 0.10 mmol), $[Rh(cod)_2]OTf$ (4.7 mg, 0.01 mmol) and PPh_3 (5.2 mg, 0.02 mmol). The tube was fitted with a rubber septum and purged with argon. Argon sparged anhydrous 1,2-DCB (1.0 mL) was added and the reaction was sparged with CO for ca. 10 seconds. The tube was heated to 130 °C, under a CO atmosphere (1 balloon) and stirred for 72 h. The mixture was cooled to r.t. and concentrated *in vacuo*. An *in situ* yield (55%) was obtained by using 1,4-dinitrobenzene as an internal standard for ^{1}H NMR spectroscopy. The residue was purified by flash column chromatography (10% EtOAc/hexane) to afford a mixture of (*E*)- and (*Z*)-**303** (10.3 mg, 51%, (*E*):(*Z*)=1:2.6) as a colourless oil; ν_{max} / cm^{-1}: 1798 (s), 1690 (m), 1551 (s), 1340 (m), 1068 (s), 938 (m); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.60 – 7.57 (m, 2H, 2 × C**8**-H, (*E*)- and (*Z*)-**303**), 7.39 –7.19 (m, 3H, 2 × C**9**-H and C**10**-H, (*E*)- and (*Z*)-**303**), 6.38 (t, *J* = 2.1 Hz, 1H, C**6**-H, (*E*)-**303**), 5.58 (t, *J* = 1.6 Hz, 1H, C**6**-H, (*Z*)-**303**), 3.03 (d, *J* = 2.1 Hz, 2H, C**1**-H_2, (*E*)-**303**), 2.87 (d, *J* = 1.6 Hz, 2H, C**1**-H_2, (*Z*)-**303**), 1.38 (s, 3H, C**3**-H_3, (*Z*)-**303**), 1.37 (s, 3H, C**3**-H_3, (*E*)-**303**); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 180.3 (C**4**, (*Z*)-**303**), 179.7 (C**4**, (*E*)-**303**), 149.0 (C**5**, (*E*)-**303**), 146.2 (C**5**, (*Z*)-**303**), 134.6 (C**7**, (*E*)-**303**), 134.1 (C**7**, (*Z*)-**303**), 128.8, 128.6, 128.5, 128.0, 126.9, 126.8 (C**8**, C**9** and C**10**, (*E*)- and (*Z*)-**303**), 107.7 (C**6**, (*E*)-**303**), 105.4 (C**6**, (*Z*)-**303**), 42.4 (C**1**, (*Z*)-**303**), 40.8 (C**1**, (*E*)-**303**), 40.1 (C**2**, (*E*)-**303**), 39.4 (C**2**, (*Z*)-**303**), 25.2 (C**3**, (*E*)-**303**), 24.8 (C**3**, (*Z*)-**303**); MS: (APCI$^+$) 203.11 ([M+H]$^+$, 100%).The spectroscopic properties of (*Z*)-**303** were consistent with the data available in the literature.[279]

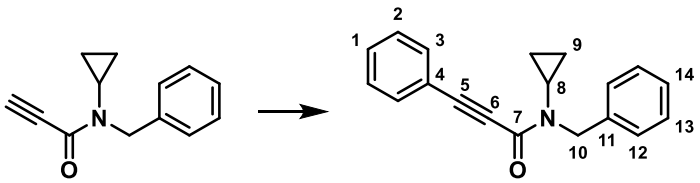
***N*-Benzyl-*N*-cyclopropylpropiolamide (306)**



305 **306**

To a stirring solution of *N*-Benzylcyclopropanamine (1.47 g, 10.0 mmol), DCC (2.27 g, 11.0 mmol) and DMAP (1.2 mg, 0.01 mmol) in DCM (30 mL) at 0 °C was added acid **305** (0.67 mL, 10.8 mmol) in DCM (10 mL). The reaction was stirred for 2 h before being filtered through a pad of celite, washing with DCM (2 × 10 mL). The organic solution was concentrated *in vacuo*. FCC (15% EtOAc/hexane) provided the title compound (2.00 g, quantitative, 3:1 mixture of rotamers A:B) as a pale yellow solid; m.p. 102–105 °C ($CHCl_3$); ν_{max} / cm^{-1}: 3206 (m), 2096 (m), 1615 (s), 1395 (m), 1303 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38–7.25 (10H, m, C**8**-H, C**9**-H, C**10**-H, A+B), 4.77 (2H, s, C**6**-H_2, B), 4.60 (2H, s, C**6**-H_2, A), 3.20 (1H, s, C**5**-H, A), 3.08 (1H, s, C**5**-H, B), 2.66 (1H, m, C**2**-H, A), 2.52 (1H, m, C**2**-H, B), 0.88–0.87 (4H, m, C**1**-H_2, A), 0.82 (2H, m, C**1**-H_2, B), 0.69 (2H, m, C**1**-H_2, B); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 155.9 (C**3**, A), 155.2 (C**3**, B), 136.9 (C**7**, A), 136.8 (C**7**, B), 128.8, 128.6, 128.0, 127.8, 127.5, 127.2 (C**8**, C**9**, C**10**, A+B), 80.2 (C**5**, A), 78.7 (C**4**, A), 77.1 (C**5**, B), 76.6 (C**4**, B), 53.4 (C**6**, B), 49.8 (C**6**, A), 30.3 (C**2**, A), 28.1 (C**2**, B), 9.2 (C**1**, A), 7.1 (C**1**, B); HRMS: (ESI^+) Calculated for $C_{13}H_{14}NO$: 200.1070. Found $[M + H]^+$: 200.1064.

***N*-Benzyl-*N*-cyclopropyl-3-phenylpropiolamide (307)**

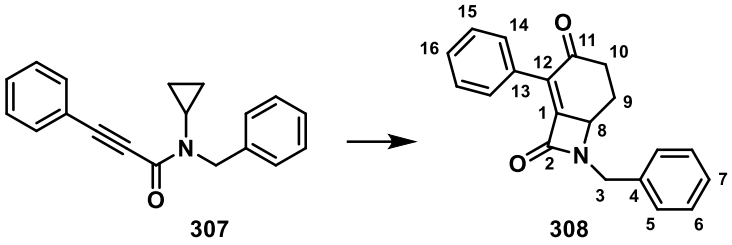


306 **307**

An oven dried reaction tube, fitted with a magnetic stirrer, was charged with amide **306** (1.00 g, 5.00 mmol) and iodobenzene (0.67 mL, 6.00 mmol) were dissolved in dry TEA (10 mL) and the solution was sparged with argon. $Pd(PPh_3)_2Cl_2$ (70.2 mg, 2 mol%) and CuI (19.1 mg, 2 mol%) were added, the tube was sealed and the reaction mixture was heated at 80 °C for 16 h. The mixture was cooled to r.t., filtered through a pad of silica, rinsed with DCM (30 mL) and concentrated *in vacuo*. Flash column chromatography (20% EtOAc/hexane) afforded the title compound **307** (0.59 g, 43%, 1:0.33 mixture of rotamers *A*:*B*) as a yellow oil; ν_{max} / cm^{-1}: 2216 (m), 1628 (s), 1490 (m),

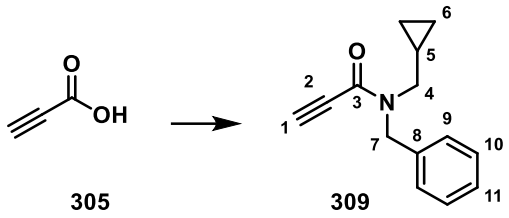
1399 (s), 1303 (m), 758 (m), 690 (m); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.58 – 7.54 (m, 2H, 2 × C**3**-H, *A*), 7.48 – 7.26 (m, 18H, 2 × C**3**-H, *B* and 2 × C**2**-H, 2 × C**12**-H, 2 × C**13**-H, C**1**-H, C**14**-H, *A*+*B*), 4.84 (s, 2H, C**10**-H_2, *B*), 4.66 (s, 2H, C**10**-H_2, *A*), 2.73 (tt, *J* = 6.8, 4.1 Hz, 1H, C**8**-H, *A*), 2.59 (tt, *J* = 7.1, 4.2 Hz, 1H, C**8**-H, *B*), 0.98 – 0.90 (m, 4H, 2 × C**9**-H_2, *A*), 0.87 – 0.82 (m, 2H, 2 × C**9**-H_aH_b, *B*), 0.75 – 0.71 (m, 2H, 2 × C**9**-H_aH_b, *B*); ^{13}C NMR ($CDCl_3$,126 MHz): δ 157.2 (C**7**, *A*), 156.6 (C**7**, *B*), 137.4 (C**11**, *A*+*B*), 132.6 (C**3**, *A*+*B*), 130.2, 130.1, 128.9, 128.7, 128.7, 128.6, 128.2, 127.8, 127.5, 127.4 (C**1**, C**2**, C**12**, C**13** and C**14**, *A*+*B*), 121.1 (C**4**, *A*), 120.6 (C**4**, *B*), 91.5 (C**5**, *A*), 90.0 (C**5**, *B*), 83.2 (C**6**, *A*), 82.6 (C**6**, *B*), 53.8 (C**10**, *B*), 49.9 (C**10**, *A*), 30.5 (C**8**, *A*), 28.4 (C**8**, *B*), 9.2 (C**9**, *A*), 7.4 (C**9**, *B*); HRMS: (ESI$^+$) calculated for $C_{19}H_{18}NO$: 276.1383, found $[M+H]^+$: 276.1377.

7-Benzyl-2-phenyl-7-azabicyclo[4.2.0]oct-1-ene-3,8-dione (308)



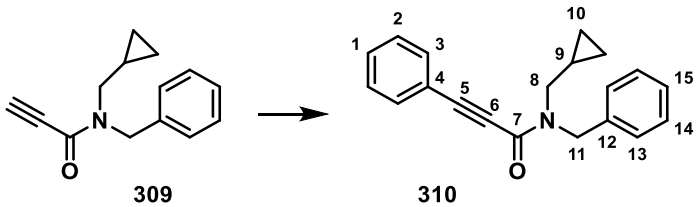
An oven dried reaction tube, fitted with a magnetic stirrer, was charged with aminocyclopropane substrate **307** (27.5 mg, 0.10 mmol), $[Rh(cod)Cl]_2$ (2.5 mg, 0.005 mmol) and PPh_3 (5.2 mg, 0.02 mmol). The tube was fitted with a rubber septum and purged with argon. Anhydrous 1,2-DCB (1.0 mL) was added and the reaction was sparged with CO for ca. 10 seconds. The tube was heated to 130 °C, under a CO atmosphere (1 balloon) and stirred for 72 h. The mixture was cooled to r.t. and concentrated *in vacuo*. The residue was purified by flash column chromatography (10-25% EtOAc/hexane) to afford **308** (4.7 mg, 15%) as a yellow oil; ν_{max} / cm^{-1}: 2925 (w), 1746 (s), 1684 (s), 1379 (m), 1139 (m), 741 (m), 694 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.72 – 7.66 (m, 2H, 2 × C**14**-H), 7.45 – 7.30 (m, 8H, C**7**-H, C**16**-H, 2 × C**5**-H, 2 × C**6**-H and 2 × C**15**-H), 4.64 (d, *J* = 14.8 Hz, 1H, C**3**-H_aH_b), 4.51 (d, *J* = 14.8 Hz, 1H, C**3**-H_aH_b), 4.12 (dd, *J* = 11.4, 4.6 Hz, 1H, C**8**-H), 2.70 (ddd, *J* = 18.9, 4.9, 2.0 Hz, 1H, C**10**-H_aH_b), 2.43 (ddd, *J* = 18.9, 13.9, 4.9 Hz, 1H, C**10**-H_aH_b), 2.10 (dtd, *J* = 11.8, 4.6, 2.0 Hz, 1H, C**9**-H_aH_b), 1.74 (dtd, *J* = 13.9, 11.4, 4.9 Hz, 1H, C**9**-H_aH_b); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 196.6 (C**11**), 160.6 (C**2**), 154.6 (C**1**), 135.2 (C**4**), 132.7 (C**13**), 130.4 (C**12**), 130.3 (C**14**), 129.8, 129.2, 128.8, 128.5, 128.4 (C**5**, C**6**, C**7**, C**15** and C**16**), 56.3 (C**8**), 46.7 (C**3**), 36.8 (C**10**), 28.2 (C**9**); HRMS: (ESI$^+$) calculated for $C_{20}H_{18}NO_2$: 304.1332, found $[M+H]^+$: 304.1322.

***N*-Benzyl-*N*-(cyclopropylmethyl)propiolamide (309)**



To a stirring solution of *N*-benzyl-1-cyclopropylmethanamine (0.81 g, 5.0 mmol) and DCC (1.24 g, 6.0 mmol) in DCM (50 mL) at 0 °C was added acid **305** (0.37 mL, 6.0 mmol). The reaction was allowed to slowly warm up to r.t. while being stirred for 2 h. The organic solution was washed with 2.0 M aq. HCl (10 mL), then with sat. aq. $NaHCO_3$ (30 mL), the layers were separated and the aqueous portion was further extracted with DCM (3 × 10 mL). The organic extracts were combined, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Flash column chromatography (20% EtOAc/hexane) afforded the title compound **309** (0.61 g, 57%, 1:1 mixture of rotamers *A*:*B*) as a yellow oil; ν_{max} / cm^{-1}: 3213 (w), 2100 (m), 1621 (s), 1425 (s), 1244 (m), 729 (s), 696 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38 – 7.18 (m, 10H, C**11**-H, 2 × C**9**-H and 2 × C**10**-H, *A*+*B*), 4.91 (s, 2H, C**7**-H_2, *A* or *B*), 4.74 (s, 2H, C**7**-H_2, *A* or *B*), 3.38 (d, *J* = 6.9 Hz, 2H, C**4**-H_2, *A* or *B*), 3.20 (d, *J* = 7.0 Hz, 2H, C**4**-H_2, *A* or *B*), 3.12 (s, 1H, C**1**-H, *A* or *B*), 3.09 (s, 1H, C**1**-H, *A* or *B*), 1.04 – 0.86 (m, 2H, C**5**-H, *A*+*B*), 0.57 – 0.40 (m, 4H, 2 × C**6**-H_aH_b, *A*+*B*), 0.27 – 0.19 (m, 2H, 2 × C**6**-H_aH_b, *A* or *B*), 0.18 – 0.11 (m, 2H, 2 × C**6**-H_aH_b, *A* or *B*); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 153.8, 153.6 (C**3**, *A*+*B*), 136.5, 136.3 (C**8**, *A*+*B*), 128.9, 128.7, 128.1, 127.9, 127.6, 127.4 (C**9**, C**10** and C**11**, *A*+*B*), 79.3, 79.0 (C**1**, *A*+*B*), 76.2, 76.1 (C**2**, *A*+*B*), 52.5 (C**4**, *A*), 52.4 (C**7**, *A*), 48.1 (C**4**, *B*), 47.3 (C**7**, *B*), 10.2, 9.1 (C**5**, *A*+*B*), 3.9, 3.7 (C**6**, *A*+*B*); HRMS: (ESI^+) calculated for $C_{14}H_{16}NO$: 214.1226, found $[M+H]^+$: 214.1236.

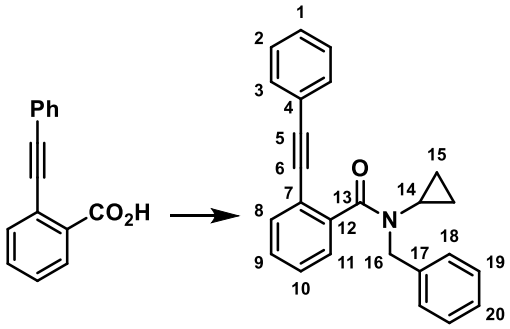
***N*-Benzyl-*N*-(cyclopropylmethyl)-3-phenylpropiolamide (310)**



General procedure H: Amide **309** (0.40 g, 1.88 mmol) and phenyl iodide (0.25 mL, 2.25 mmol) were employed and the reaction was stirred for 16 h at 80 °C. Flash column chromatography (10% EtOAc/hexane) afforded alkyne **310** (0.28 g, 52%, 1:1.03 mixture of rotamers *A*:*B*) as an orange oil; ν_{max} / cm^{-1}: 2213 (m), 1620 (s), 1490 (m), 1449 (m), 1421 (s), 1274 (m), 756 (s), 730 (s), 689

(s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.56 – 7.51 (m, 2H, 2 × C**3**-H, *A*), 7.49 – 7.45 (m, 2H, 2 × C**3**-H, *B*), 7.45 – 7.21 (m, 16H, C**1**-H, C**15**-H, 2 × C**2**-H, 2 × C**13**-H and 2 × C**14**-H, *A*+*B*), 4.98 (s, 2H, C**11**-H_2, *A*), 4.80 (s, 2H, C**11**-H_2, *B*), 3.46 (d, *J* = 6.9 Hz, 2H, C**8**-H_2, *A*), 3.27 (d, *J* = 7.0 Hz, 2H, C**8**-H_2, *B*), 1.11 – 0.90 (m, 2H, C**9**-H, *A*+*B*), 0.59 – 0.43 (m, 4H, 2 × C**10**-H_aH_b, *A*+*B*), 0.31 – 0.15 (m, 4H, 2 × C**10**-H_aH_b, *A*+*B*); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 155.0, 154.9 (C**7**, *A*+*B*), 136.8, 136.8 (C**12**, *A*+*B*), 132.5, 132.4, 130.2, 130.1, 128.9, 128.7, 128.7, 128.6, 128.1, 127.9, 127.6, 127.5 (C**1**, C**2**, C**3**, C**13**, C**14** and C**15**, *A*+*B*), 120.7, 120.6 (C**4**, *A*+*B*), 90.5, 90.3 (C**5**, *A*+*B*), 82.0, 82.0 (C**6**, *A*+*B*), 52.7 (C**8**, *A*), 52.6 (C**11**, *A*), 48.3 (C**8**, *B*), 47.4 (C**11**, *B*), 10.3, 9.3 (C**9**, *A*+*B*), 4.0, 3.8 (C**10**, *A*+*B*); HRMS: (ESI$^+$) calculated for $C_{20}H_{20}NO$: 290.1539, found $[M+H]^+$: 290.1532.

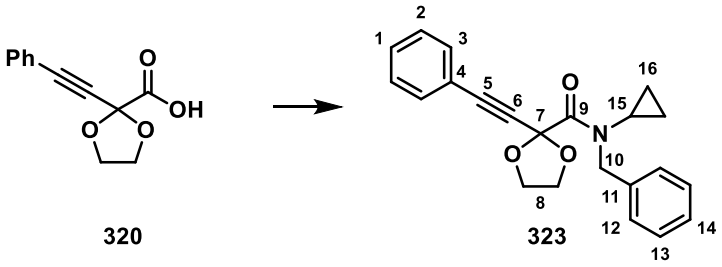
N-Benzyl-*N*-cyclopropyl-2-(phenylethynyl)benzamide (315)



314 **315**

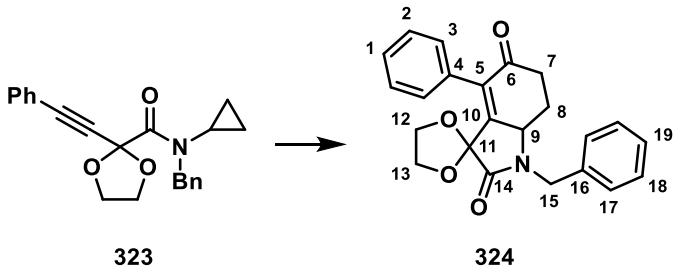
General procedure G: *N*-Benzylcyclopropanamine (0.66 g, 4.50 mmol) and acid **314** (1.00 g, 4.50 mmol, prepared according to the literature procedure[180]) were employed and the residue was purified by flash column chromatography (20% EtOAc/pentane) to afford the title compound **315** (1.41 g, 89%, 1:0.15 mixture of rotamers *A*:*B*) as a yellow oil; ν_{max} / cm^{-1}: 1644 (s), 1494 (m), 1444 (m), 1403 (s), 1373 (m), 756 (s); ^{1}H NMR (DMSO-d_6, 500 MHz, *major rotamer A only*): δ 7.64 – 7.08 (m, 14H, C**1**-H, C**8**-H, C**9**-H, C**10**-H, C**11**-H, C**20**-H, 2 × C**2**-H, 2 × C**3**-H, 2 × C**18**-H and 2 × C**19**-H), 4.72 (br. s, 2H, C**16**-H_2), 2.70 (tt, *J* = 7.2, 3.9 Hz, 1H, C**14**-H), 0.50 (br. s, 2H, 2 × C**15**-H_aH_b), 0.41 – 0.33 (m, 2H, 2 × C**15**-H_aH_b); ^{13}C NMR (DMSO-d_6, 126 MHz, *major rotamer A only*): 171.1 (C**13**), 141.0 (C**12**), 138.1 (C**17**), 132.0 (C**8**), 131.4 (C**3**), 129.0, 128.9, 128.7, 128.6, 128.3, 127.5, 126.8, 126.6, 121.9, 118.8 (C**1**, C**2**, C**4**, C**7**, C**9**, C**10**, C**11**, C**18**, C**19** and C**20**), 92.0 (C**6**), 87.3 (C**5**), 49.3 (C**16**), 30.7 (C**14**), 8.4 (C**15**); HRMS: (ESI$^+$) calculated for $C_{25}H_{22}NO$: 352.1696, found $[M+H]^+$: 352.1683. *High temperature NMR (100 °C, DMSO-d_6) resulted in partial coalescence of the signals for rotamers A and B. However, the low signal intensity of the resulting ^{13}C spectre did not allow a full characterisation.*

***N*-Benzyl-*N*-cyclopropyl-2-(phenylethynyl)-1,3-dioxolane-2-carboxamide (323)**



General procedure G: *N*-Benzylcyclopropanamine (0.26 g, 1.80 mmol) and acid **320** (0.39 g, 1.80 mmol, prepared according to the literature procedure[280]) were employed and the residue was purified by flash column chromatography (50% EtOAc/hexane) to afford the title compound **323** (0.17 g, 27%) as a colourless oil; ν_{max} / cm^{-1}: 2896 (m), 2229 (m), 1663 (s), 1490 (m), 1404 (m), 1148 (s), 1016 (s), 987 (s), 757 (s), 691 (s); ^{1}H NMR (DMSO-*d*$_6$, 500 MHz, 110 °C): δ 7.45 – 7.20 (m, 10H, 2 × C**2**-H, 2 × C**3**-H, 2 × C**12**-H, 2 × C**13**-H, C**1**-H and C**14**-H), 4.71 (br. s, 2H, C**10**-H$_2$), 4.18 – 4.10 (m, 2H, 2 × C**8**-H$_a$H$_b$), 4.08 – 3.99 (m, 2H, 2 × C**8**-H$_a$H$_b$), 2.87 (s, 1H, C**15**-H), 0.85 – 0.68 (m, 4H, 2 × C**16**-H$_2$); ^{13}C NMR (DMSO-*d*$_6$, 126 MHz, 110 °C): δ 166.0 (C**9**), 137.6 (C**11**), 131.0, 128.9, 128.1, 127.7, 126.4, 126.3 (C**1**, C**2**, C**3**, C**12**, C**13** and C**14**), 120.2 (C**4**), 98.9, 85.7, 84.5 (C**5**, C**6** and C**7**), 64.5 (C**8**), 49.8 (C**10**), 29.9 (C**15**), 7.1 (C**16**); HRMS: (ESI$^+$) calculated for $C_{22}H_{22}NO_3$: 348.1594, found [M+H]$^+$: 348.1585.

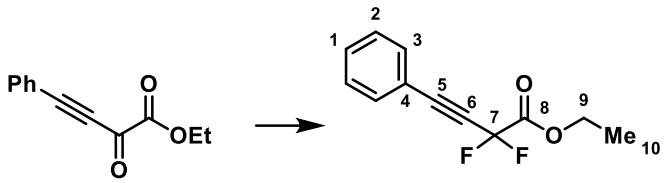
1-Benzyl-4-phenyl-1,6,7,7a-tetrahydrospiro[indole-3,2'-[1,3]dioxolane]-2,5-dione (324)



General procedure I: Amide **323** (34.7 mg, 0.10 mmol) was employed. Flash column chromatography (40% EtOAc/hexane) afforded the title compound **324** (9.9 mg, 26%) as a yellow oil; ν_{max} / cm^{-1}: 1710 (s), 1683 (s), 1443 (m), 1242 (s), 1177 (s), 1031 (m), 997 (m), 730 (m), 699 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.40 – 7.23 (m, 8H, C**1**-H, C**19**-H, 2 × C**2**-H, 2 × C**17**-H and 2 × C**18**-H), 7.16 – 7.11 (m, 2H, 2 × C**3**-H), 4.99 (d, *J* = 15.0 Hz, 1H, C**15**-H$_a$H$_b$), 4.35 – 4.28 (m, 2H, C**9**-H and C**12**-H or C**13**-H), 4.22 (d, *J* = 15.0 Hz, 1H, C**15**-H$_a$H$_b$), 4.08 (ddd, *J* = 7.0, 7.0, 4.2 Hz, 1H, C**12**-H or C**13**-H), 3.97 (ddd, *J* = 7.4, 6.6, 4.2 Hz, 1H, C**12**-H or C**13**-H), 2.91 – 2.84 (m, 1H, C**12**-H or C**13**-H), 2.80 – 2.71 (m, 1H, C**7**-H$_a$H$_b$), 2.47 – 2.36 (m, 2H, C**7**-H$_a$H$_b$ and C**8**-H$_a$H$_b$), 1.91 – 1.78 (m, 1H, C**8**-H$_a$H$_b$); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 196.5 (C**6**), 170.3 (C**14**), 149.0

(C**10**), 139.2 (C**5**), 135.3 (C**16**), 132.9 (C**4**), 129.8 (C**3**), 129.2, 128.3, 128.2, 128.1, 127.6 (C**1**, C**2**, C**17**, C**18** and C**19**), 102.7 (C**11**), 67.0, 66.4 (C**12** and C**13**), 54.7 (C**9**), 44.3 (C**15**), 35.9 (C**7**), 28.4 (C**8**); HRMS: (ESI$^+$) calculated for $C_{23}H_{21}NNaO_4$: 398.1363, found $[M+Na]^+$: 398.1345.

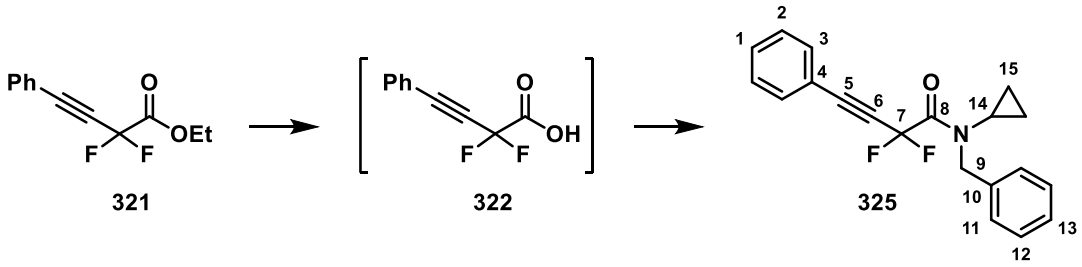
Ethyl 2,2-difluoro-4-phenylbut-3-ynoate (321)



318 **321**

To a solution of ethyl 2-oxo-4-phenylbut-3-ynoate **318** (1.00 g, 4.95 mmol, prepared according to the literature procedure[280]) in DCM (10 mL), DAST (1.63 mL, 12.36 mmol) was added dropwise at 0 °C, the reaction mixture was warmed up to r.t. and stirred for 90 min. The crude reaction was poured into crushed ice and stirred for 2 h. The resulting suspension was extracted with DCM (3 × 20 mL) and the organic extracts were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (10% Et_2O/pentane) to afford the title compound **321** (0.91 g, 82%) as a colourless oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.56 – 7.34 (m, 5H, 2 × C**2**-H, 2 × C**3**-H and C**1**-H), 4.40 (q, *J* = 7.1 Hz, 2H, C**9**-H_2), 1.39 (t, *J* = 7.1 Hz, 3H, C**10**-H_3); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 161.6 (C**8**, t, *J* = 34.1 Hz), 132.4 (C**4**, t, *J* = 2.4 Hz), 130.5, 128.5, 119.3 (C**1**, C**2** and C**3**), 104.9 (C**7**, t, *J* = 241.1 Hz), 89.6 (C**5**, t, *J* = 6.3 Hz), 78.3 (C**6**, t, *J* = 37.7 Hz), 63.8 (C**9**), 13.9 (C**10**). The spectroscopic properties of this compound were consistent with the data available in the literature.[281]

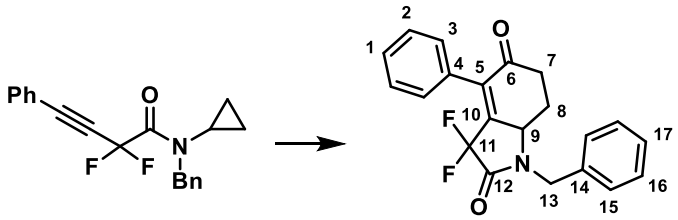
***N*-Benzyl-*N*-cyclopropyl-2,2-difluoro-4-phenylbut-3-ynamide (325)**



To a solution of ester **321** (0.91, 4.06 mmol) in MeOH (8 mL) was added 4.0 M aq. NaOH (5.5 mL) and the reaction was stirred at r.t. for 16 h. The reaction mixture was concentrated *in vacuo*, diluted with water (20 mL) and extracted with Et_2O (20 mL). The aqueous portion was adjusted to pH 2 by addition of 6.0 M aq. HCl and then extracted with Et_2O (3 × 20 mL). The organic extracts were combined, dried over $MgSO_4$ and concentrated *in vacuo* to afford the title compound **322** (0.56 g, 70%) as a colourless solid which was used in next step without further purification.

Acid **322** was dissolved in DCM (6 mL), treated with oxalyl chloride (0.24 mL, 2.85 mmol), a drop of DMF and stirred at r.t. for 1 h. DCM and an excess of oxalyl chloride were removed in vacuo and the corresponding acyl chloride was dissolved in DCM (2 mL). The solution was added dropwise to *N*-benzylcyclopropanamine (0.44 g, 2.99 mmol) and TEA (0.79 mL, 0.58 mmol) in DCM (4 mL) at 0 °C, the reaction was warmed to r.t. and stirred for 18 h. Sat. aq. $NaHCO_3$ (20 mL) and DCM (10 mL) were added, the layers were separated and the aqueous portion was further extracted with DCM (2 × 15 mL). The organic extracts were combined, washed with 1.0 M aq. HCl (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (10% EtOAc/hexane) to afford the title compound **325** (0.45 g, 49%) as a pale yellow oil; ν_{max} / cm^{-1}: 2237 (m), 1682 (s), 1409 (m), 1138 (s), 1078 (s), 757 (s), 690 (m); ^{1}H NMR (DMSO-d_6, 500 MHz, 110 °C): δ 7.57 – 7.50 (m, 3H, 3 × Ar-H), 7.49 – 7.43 (m, 2H, 2 × Ar-H), 7.36 – 7.31 (m, 2H, 2 × Ar-H), 7.29 – 7.24 (m, 3H, 3 × Ar-H), 4.70 (s, 2H, C**9**-H_2), 2.92 (br. s, 1H, C**14**-H), 0.95 – 0.82 (m, 4H, 2 × C**10**-H_2); ^{13}C NMR (DMSO-d_6, 126 MHz, 110 °C): δ 137.5 (C**10**), 132.5, 131.4, 129.4, 128.9, 127.6, 127.5, 127.4 (C**1**, C**2**, C**3**, C**4**, C**11**, C**12** and C**13**), 107.32 (C**7**, t, *J* = 242.0 Hz), 91.14 (C**5**, t, *J* = 6.6 Hz), 79.83 (C**6**, t, *J* = 37.6 Hz), 31.1 (C**14**), 8.5 (C**15**); signal corresponding to C**8** was not observed due to its weak intensity; ^{19}F NMR ($CDCl_3$, 376 MHz, 25 °C, 2:1 mixture of rotamers *A*:*B*): δ -84.3 (*A*), -84.5 (*B*); HRMS: (ESI^+) calculated for $C_{20}H_{18}F_2NO$: 326.1351, found $[M+H]^+$: 326.1349.

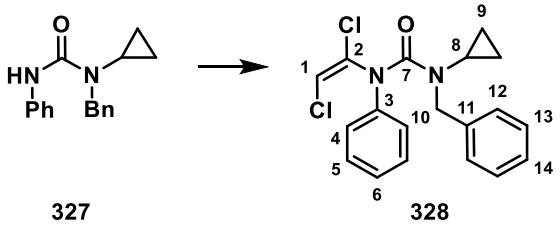
1-Benzyl-3,3-difluoro-4-phenyl-1,6,7,7a-tetrahydro-2*H*-indole-2,5(3*H*)-dione (326)



325 **326**

General procedure I: Amide **325** (32.5 mg, 0.10 mmol) was employed. Flash column chromatography (40% EtOAc/hexane) afforded the title compound **326** (3.5 mg, 10%) as a pale brown oil; ν_{max} / cm^{-1}: 1731 (s), 1693 (s), 1445 (m), 1241 (s), 1172 (s), 1071 (s), 732 (s), 698 (s); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.46 – 7.19 (m, 10H, C**1**-H, C**17**-H, 2 × C**2**-H, 2 × C**3**-H, 2 × C**15**-H and 2 × C**16**-H), 5.12 (d, *J* = 15.0 Hz, 1H, C**13**-H_aH_b), 4.34 (dt, *J* = 11.7, 3.9 Hz, 1H, C**9**-H), 4.25 (d, *J* = 15.0 Hz, 1H, C**13**-H_aH_b), 2.90 – 2.80 (m, 1H, C**7**-H_aH_b), 2.58 – 2.42 (m, 2H, C**8**-H_aH_b and C**7**-H_aH_b), 1.96 – 1.83 (m, 1H, C**8**-H_aH_b); $^{13}C\{^{1}H,^{19}F\}$ NMR ($CDCl_3$, 101 MHz): δ 195.4 (C**6**), 162.8 (C**12**), 141.4 (C**10**), 140.5 (C**5**), 134.3 (C**14**), 130.8, 129.8, 129.5, 129.4, 128.7, 128.2, 128.1 (C**1**, C**2**, C**3**, C**4** ,C**15**, C**16** and C**17**), 111.2 (C**11**), 53.8 (C**9**), 44.8 (C**13**), 35.7 (C**7**), 28.0 (C**8**); ^{19}F NMR ($CDCl_3$, 376 MHz) δ -89.9 (dd, *J* = 302.3, 3.4 Hz), -117.7 (d, *J* = 302.3 Hz); HRMS: (ESI^+) calculated for $C_{21}H_{18}F_2NO_2$: 354.1300, found $[M+H]^+$: 354.1286.

(*E*)-1-Benzyl-1-cyclopropyl-3-(1,2-dichlorovinyl)-3-phenylurea (328)

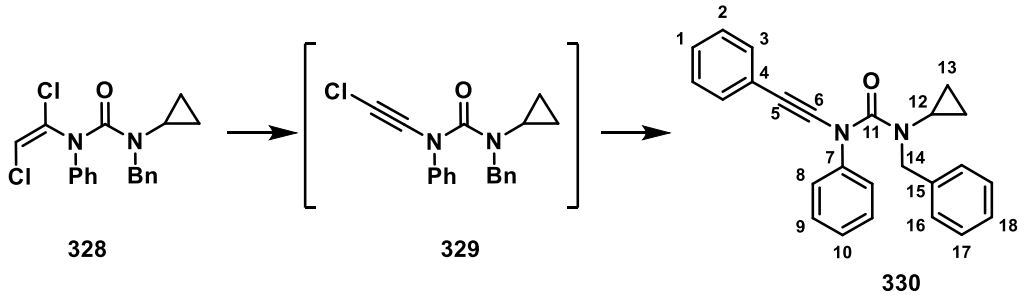


327 **328**

This compound was prepared according to the literature procedure.[182] Urea **327** (1.00 g, 3.75 mmol, prepared according to the literature procedure[53]) and tetrabutylammonium hydrogensulfate (0.32 g, 0.94 mmol) were dissolved in toluene (38 mL). The flask was purged with argon using a balloon and outlet needle. Then, 50% w/v KOH aqueous solution (17 mL) was added and the reaction was heated to 60 °C for 10 min. Trichloroethylene (1.00 mL, 11.25 mmol) was added dropwise over 5 min and the mixture was stirred at 60 °C for 2 h. The reaction was cooled to r.t. and then water (50 mL) was added. The solution was extracted with Et_2O (3 × 50 mL) and the organic extracts were combined, washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by recrystallization (DCM/Et_2O, 2 crops) to afford the title

compound **328** (0.93 g, 69%) as a colourless solid; m.p. 130-131 °C (DCM/Et_2O); ν_{max} / cm^{-1}: 3675 (w), 2989 (m), 1666 (s), 1492 (m), 1393 (s), 1256 (s), 1066 (s), 805 (m), 805 (m); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.38 – 7.21 (m, 7H, 2 × C**5**-H, 2 × C**12**-H, 2 × C**13**-H and C**14**-H), 7.19 – 7.12 (m, 1H, C**6**-H), 7.06 – 6.99 (m, 2H, 2 × C**4**-H), 6.25 (s, 1H, C**1**-H), 4.55 (s, 2H, C**10**-H_2), 1.81 (tt, *J* = 7.0, 3.9 Hz, 1H, C**8**-H), 0.94 – 0.85 (m, 2H, 2 × C**9**-H_aH_b), 0.55 – 0.47 (m, 2H, 2 × C**9**-H_aH_b); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 157.3 (C**7**), 140.7 (C**3**), 137.4 (C**11**), 133.8 (C**2**), 129.2, 129.0, 128.6, 127.7 (C**5**, C**12**, C**13** and C**14**), 126.4 (C**6**), 125.2 (C**4**), 113.3 (C**1**), 53.3 (C**10**), 31.1 (C**8**), 10.4 (C**9**); HRMS: (ESI^+) calculated for $C_{19}H_{19}{}^{35}Cl_2N_2O$: 361.0869, found $[M+H]^+$: 361.0869.

1-Benzyl-1-cyclopropyl-3-phenyl-3-(phenylethynyl)urea (330)



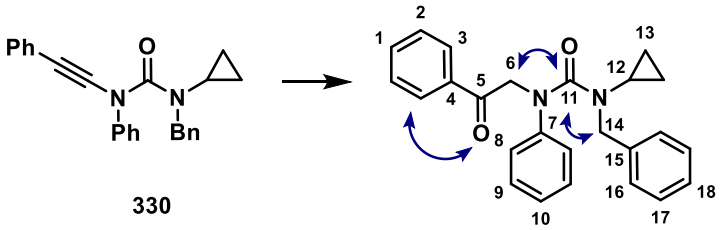
This compound was prepared according to the modified literature procedure.[182] To a solution of (*E*)-1-benzyl-1-cyclopropyl-3-(1,2-dichlorovinyl)-3-phenylurea **328** in dry Et_2O (8 mL), LiHMDS (0.66 mL, 1.00 mmol, 1.5 M in THF) was added dropwise at 0 °C. The reaction was stirred for 2 h at 0 °C and then warmed to r.t. to allow the formation of chloroynamide **329**.

In a second flask, dry toluene (2.5 mL) was added to zinc(II) chloride (0.17 g, 1.25 mmol, dried by fusing on Bunsen burner prior to use). Phenylmagnesium bromide (2.49 mL, 2.49 mmol, 1.0 M in THF) was added dropwise to the resulting suspension at r.t and the mixture stirred for 5 minutes. To this was added dry TMEDA (1.25 mL, 8.30 mmol) dropwise at r.t. and the solution stirred for 5 minutes to allow the formation of diphenylzinc.

To the previously prepared solution of chloroynamide **329**, CuCN•2LiCl (10 μL, 0.01 mmol, 1.0 M in THF) was added at r.t., followed by the previously prepared diphenylzinc solution. The reaction was stirred for 30 minutes at r.t. and then sat. aq. NH_4Cl (30 mL) was added. The solution was extracted with Et_2O (3 × 20 mL) and the organic extracts were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (10% EtOAc/petrol) to afford the title compound **330** (0.23 g, 77%) as a pale yellow oil; ν_{max} / cm^{-1}: 2240 (m), 1645 (s), 1494 (m), 1389 (s), 1249 (m), 753 (m), 691 (m); ^1H NMR ($CDCl_3$, 400 MHz):

δ 7.43 – 7.24 (m, 14H, 2 × C**2**-H, 2 × C**3**-H, 2 × C**8**-H, 2 × C**9**-H, 2 × C**16**-H, 2 × C**17**-H, C**1**-H and C**18**-H), 7.20 – 7.14 (m, 1H, C**10**-H), 4.71 (s, 2H, C**14**-H_2), 2.70 (tt, *J* = 6.7, 4.2 Hz, 1H, C**12**-H), 0.88 – 0.78 (m, 4H, 2 × C**13**-H_2); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 158.5 (C**11**), 141.0 (C**7**), 137.4 (C**15**), 130.8, 129.1, 128.8, 128.5, 128.3, 127.6, 127.5 (C**1**, C**2**, C**3**, C**9**, C**16**, C**17** and C**18**), 125.2 (C**10**), 123.6 (C**4**), 121.9 (C**8**), 83.9 (C**6**), 71.8 (C**5**), 53.0 (C**14**), 31.5 (C**12**), 9.8 (C**13**); HRMS: (ESI$^+$) calculated for $C_{25}H_{23}N_2O$: 367.1805, found [M+H]$^+$: 367.1815.

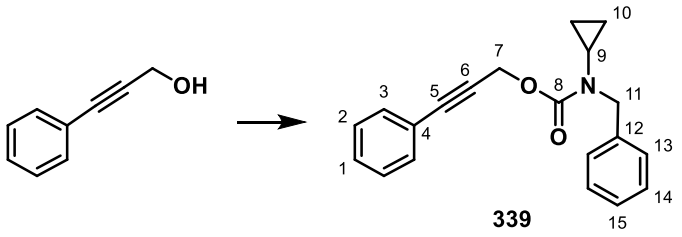
1-Benzyl-1-cyclopropyl-3-(2-oxo-2-phenylethyl)-3-phenylurea (332)



An oven dried reaction tube, fitted with a magnetic stirrer, was charged with ynamide substrate **330** (36.6 mg, 0.10 mmol), $[Rh(cod)_2]OTf$ (4.7 mg, 0.01 mmol) and PPh_3 (5.2 mg, 0.02 mmol). The tube was fitted with a rubber septum and purged with argon. Anhydrous PhCN (1.0 mL) was added and the reaction was sparged with CO for ca. 10 seconds. The tube was heated to 120 °C, under a CO atmosphere (1 balloon) and stirred for 72 h. The mixture was cooled to r.t. and concentrated *in vacuo*. The residue was purified by flash column chromatography (20% EtOAc/hexane) to afford the title compound **332** (8.5 mg, 22%) as an orange oil; ν_{max} / cm^{-1}: 2923 (w), 1699 (s), 1636 (s), 1596 (s), 1494 (s), 1414 (s), 1220 (s), 750 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.00 – 7.97 (m, 2H, 2 × C**3**-H), 7.60 – 7.55 (m, 1H, C**1**-H), 7.49 – 7.44 (m, 2H, 2 × C**2**-H), 7.36 – 7.34 (m, 4H, 4 × Ar-H), 7.32 – 7.27 (m, 1H, Ar-H), 7.21 – 7.15 (m, 2H, 2 × Ar-H), 7.08 – 7.01 (m, 3H, 2 × Ar-H and C**18**-H), 5.16 (s, 2H, C**6**-H_2), 4.50 (s, 2H, C**14**-H_2), 1.61 (tt, *J* = 6.7, 3.8 Hz, 1H, C**12**-H), 1.02 – 0.96 (m, 2H, 2 × C**13**-H_aH_b), 0.44 – 0.38 (m, 2H, 2 × C**13**-H_aH_b); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 195.5 (C**5**), 160.4 (C**11**), 145.6 (C**7**), 138.1 (C**15**), 135.5 (C**4**), 133.6 (C**1**), 129.0, 128.9, 128.8, 128.5, 128.1, 127.4, 125.3 (C**2**, C**3**, C**8**, C**9**, C**10**, C**16** and C**17**), 125.1 (C**18**), 59.0 (C**6**), 53.1 (C**14**), 31.3 (C**12**), 10.9 (C**13**); HRMS: (ESI$^+$) calculated for $C_{25}H_{25}N_2O_2$: 385.1911, found [M+H]$^+$: 385.1914.

The structure of product **332** was confirmed by HMBC analysis (as indicated on the compound structure).

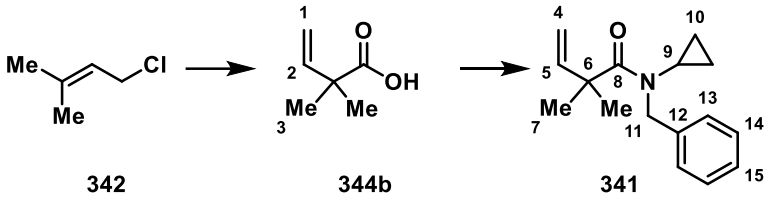
3-Phenylprop-2-yn-1-yl benzyl(cyclopropyl)carbamate (339)



339

This compound was prepared according to the modified literature procedure.[282] To a solution of triphosgene (1.48 g, 5.00 mmol) in dry ether (20 mL), activated charcoal (0.05 g) was added and stirred for 1 h at room temperature. The solution was cooled to 0 °C and 3-phenyl-2-propyn-1-ol (1.23 mL, 10.00 mmol) was added dropwise. The reaction was stirred for 12 h and filtered through a pad of celite. The crude was concentrated *in vacuo* and dry DCM (20 mL) was added. The reaction was cooled to 0 °C and *N*-benzylcyclopropanamine (1.47 g, 10.00 mmol) was added, followed by triethylamine (2.09 mL, 15 mmol). The reaction was warmed to r.t. and stirred for 16 h. 1.0 M aq. HCl (20 mL) was added, the layers were separated and the organic portion was further washed with sat. aq. $NaHCO_3$ (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (10% EtOAc/hexane) to afford the title compound **339** (1.95 g, 64%) as a pale yellow oil; ν_{max} / cm^{-1}: 3030 (w), 1702 (s), 1405 (s), 1268 (s), 1227 (s), 1121 (s), 1060 (s), 755 (s), 690 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.48 – 7.43 (m, 2H, 2 × C**3**-H), 7.35 – 7.23 (m, 8H, C**1**-H, C**15**-H, 2 × C**2**-H, 2 × C**13**-H and 2 × C**14**-H), 4.99 (s, 2H, C**7**-H_2), 4.52 (s, 2H, C**11**-H_2), 2.54 (br. s, 1H, C**9**-H), 0.81 – 0.68 (m, 4H, 2 × C**10**-H_2); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 157.3 (br. s, C**8**), 138.2 (C**12**), 132.0 (C**3**), 128.7, 128.6, 128.4, 127.8, 127.4 (C**1**, C**2**, C**13**, C**14** and C**15**), 122.6 (C**4**), 86.2 (C**5**), 84.0 (C**6**), 53.9 (C**7**), 51.8 (C**11**), 29.3 (br. s, C**9**), 8.3 (br. s, C**10**); HRMS: (ESI^+) calculated for $C_{20}H_{19}NNaO_2$: 328.1308, found $[M+Na]^+$: 328.1313.

***N*-Benzyl-*N*-cyclopropyl-2,2-dimethylbut-3-enamide (341)**

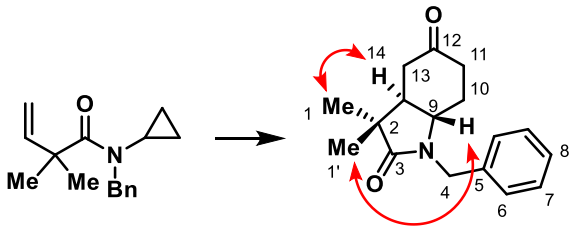


342 344b 341

2,2-Dimethylbut-3-enoic acid **344b** was prepared according to a literature procedure.[283] 1-Chloro-3-methyl-2-butene **342** was added dropwise to a stirred suspension of magnesium (4.65 g, 191.24 mmol) in dry THF (60 mL) at room temperature. Once an exotherm was observed, the reaction mixture was cooled to 0 °C and the rest of 1-chloro-3-methyl-2-butene (10.78 mL in total, 95.62 mmol) was added dropwise. The reaction was warmed to r.t., stirred for 2 h and the reaction mixture was cannulated into dry ice (approx. 200 g). After stirring for 3 h at r.t., 1.0 M HCl (100 mL) was added and the solution was extracted with Et_2O (3 × 50 mL). The combined organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to afford the acid **344b** (7.69 g, 70%, 15:1 mixture of regioisomers) as a pale yellow oil which was used in the next step without further purification; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.05 (dd, *J* = 17.4, 10.6 Hz, 1H, C**2**-H), 5.15 (dd, *J* = 17.4, 0.8 Hz, 1H, C**1**-H$_{trans}$), 5.11 (dd, *J* = 10.6, 0.8 Hz, 1H, C**1**-H$_{cis}$), 1.33 (s, 6H, 2 × C**3**-H$_3$);The spectroscopic properties of this compound were consistent with the data available in the literature.[283]

N-Benzyl-*N*-cyclopropyl-2,2-dimethylbut-3-enamide **341** was prepared according to **general procedure G**. *N*-Benzylcyclopropanamine (1.29 g, 8.76 mmol) and acid **344** (1.00 g, 8.76 mmol) were employed and the residue was purified by flash column chromatography (10% EtOAc/hexane) to afford the title compound **341** (1.13 g, 53%) as a colourless oil; ν_{max} / cm^{-1}: 2975 (w), 1630 (s), 1545 (m), 1388 (s), 995 (m), 913 (m), 698 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.34 – 7.13 (m, 5H, 2 × C**13**-H, 2 × C**14**-H and C**15**-H), 6.10 (dd, *J* = 17.6, 10.6 Hz, 1H, C**5**-H), 5.09 (d, *J* = 17.6 Hz, 1H, C**4**-H$_{trans}$), 5.05 (d, *J* = 10.6 Hz, 1H, C**4**-H$_{cis}$), 4.58 (s, 2H, C**11**-H$_2$), 2.69 (br. s, 1H, C**9**-H), 1.37 (s, 6H, 2 × C**7**-H$_3$), 0.73 – 0.58 (m, 4H, 2 × C**10**-H$_2$); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 178.5 (C**8**), 143.9 (C**5**), 138.5 (br., C**12**), 128.6, 127.1, 126.9 (C**13**, C**14** and C**15**), 112.2 (C**4**), 51.4 (br., C**11**), 46.0 (C**6**), 30.8 (br., C**9**), 26.9 (C**7**), 8.7 (br., C**10**); HRMS: (ESI$^+$) calculated for $C_{16}H_{22}NO$: 244.1696, found [M+H]$^+$: 244.1691.

1-Benzyl-3,3-dimethylhexahydro-2*H*-indole-2,5(3*H*)-dione (345)



341 **345**

An oven dried reaction tube, fitted with a magnetic stirrer, was charged with aminocyclopropane substrate **341** (24.3 mg, 0.10 mmol), $[Rh(cod)Cl]_2$ (2.5 mg, 0.005 mmol) and PPh_3 (5.2 mg, 0.02 mmol). The tube was fitted with a rubber septum and purged with argon. Anhydrous PhCN (1.0 mL) was added and the reaction was sparged with CO for approx. 10 seconds. The tube was heated to 130 °C, under a CO atmosphere (1 balloon) and stirred for 72 h. The mixture was cooled to r.t. and concentrated *in vacuo*. An *in situ* yield (80%) was obtained by using 1,4-dinitrobenzene as an internal standard for ^{1}H NMR spectroscopy. The residue was purified by flash column chromatography (50% EtOAc/hexane) to afford **345** (19.7 mg, 73%) as a pale yellow oil; ν_{max} / cm^{-1}: 2952 (m), 1688 (s), 1405 (m), 1267 (m), 1177 (w), 753 (w), 703 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.34 – 7.23 (m, 3H, 2 × C**7**-H and C**8**-H), 7.22 – 7.17 (m, 2H, 2 × C**6**-H), 4.92 (d, *J* = 15.0 Hz, 1H, C**4**-H_aH_b), 4.05 (d, *J* = 15.0 Hz, 1H, C**4**-H_aH_b), 3.26 – 3.15 (m, 1H, C**9**-H), 2.54 – 2.46 (m, 1H, C**11**-H_aH_b), 2.43 – 2.36 (m, 1H, C**13**-H_aH_b), 2.31 – 2.16 (m, 3H, C**10**-H_aH_b, C**11**-H_aH_b, C**13**-H_aH_b), 1.85 – 1.74 (m, 1H, C**14**-H), 1.60 – 1.47 (m, 1H, C**10**-H_aH_b), 1.18 (s, 3H, C**1**-H_3), 0.97 (s, 3H, C**1'**-H_3); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 207.9 (C**12**), 180.5 (C**3**), 136.9 (C**5**), 128.9, 128.0 (C**6** and C**7**), 127.8 (C**8**), 56.5 (C**9**), 50.8 (C**14**), 44.4 (C**4**), 42.7 (C**2**), 39.8 (C**13**), 39.3 (C**11**), 28.4 (C**10**), 23.0 (C**1**), 17.0 (C**1'**); HRMS: (ESI$^+$) calculated for $C_{17}H_{22}NO_2$: 272.1645, found $[M+H]^+$: 272.1651.

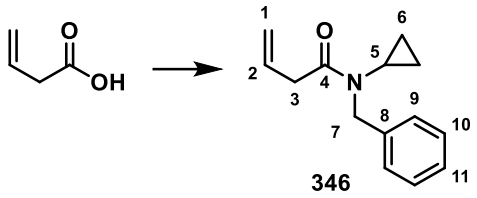
The relative stereochemistry of this compound was corroborated by nOe experiments (as indicated on the compound structure). A strong nOe was observed between C**14**-H and C**1**-H_3. A strong nOe was observed between C**9**-H and C**1'**-H_3. No significant nOe was observed between C**9**-H and C**14**-H.

General procedure J: Amide **341** (24.3 mg, 0.10 mmol) was employed. Flash column chromatography (50% EtOAc/hexane) afforded the title compound **(*R*,*S*)-345** (17.2 mg, 63%) as a yellow oil. The enantiopurity of this compound was determined by chiral SFC against a racemic standard. The absolute stereochemistry in **(*R*,*S*)-345** was assigned by analogy with **(*S*)-380c**.

$[\alpha]_D^{24.2}$ = -14.4 (c = 0.50, $CHCl_3$).

Chiral SFC: (DAICEL CHIRALPAK-IB column (25 cm), CO_2:MeOH 94:6, 2 mL/min, 140 bars, 40 °C). Retention times: 10.8 minutes (minor), 12.1 minutes (major), e.r. = 89:11.

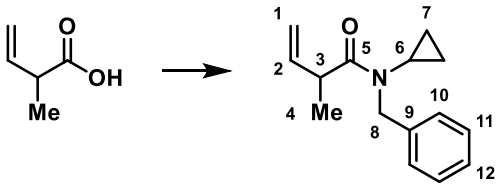
***N*-Benzyl-*N*-cyclopropylbut-3-enamide (346)**



346

General procedure G: *N*-Benzylcyclopropanamine (1.00 g, 6.79 mmol) and but-3-enoic acid (0.58 g, 6.79 mmol) were employed and the residue was purified by flash column chromatography (20% EtOAc/hexane) to afford the title compound **346** (0.21 g, 14%) as a colourless oil; 0.71 g of title compound containing ~10% of unidentified impurity was also isolated; ν_{max} / cm^{-1}: 1652 (s), 1398 (m), 1259 (w), 1031 (w), 916 (w), 701 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.33 – 7.20 (m, 5H, 2 × C**9**-H, 2 × C**10**-H and C**11**-H), 6.05 (ddt, *J* = 17.1, 10.5, 6.7 Hz, 1H, C**2**-H), 5.20 – 5.12 (m, 2H, C**1**-H_2), 4.60 (s, 2H, C**7**-H_2), 3.41 (d, *J* = 6.7, 2H, C**3**-H_2), 2.61 – 2.53 (m, 1H, C**5**-H), 0.89 – 0.76 (m, 4H, 2 × C**6**-H_2); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 174.0 (C**4**), 138.5 (C**8**), 132.2 (C**2**), 128.6, 128.0 (C**9** and C**10**), 127.2 (C**11**), 117.8 (C**1**), 49.9 (C**7**), 39.6 (C**3**), 30.2 (C**5**), 9.4 (C**6**); HRMS: (ESI^+) calculated for $C_{14}H_{18}NO$: 216.1383, found $[M+H]^+$: 216.1378.

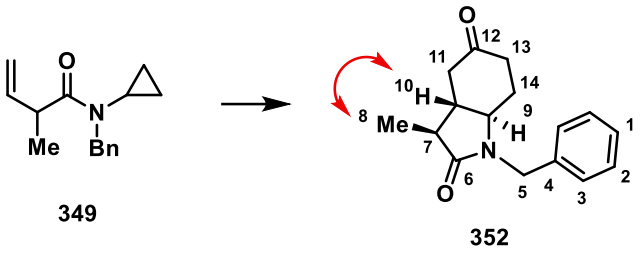
***N*-Benzyl-*N*-cyclopropyl-2-methylbut-3-enamide (349)**



349

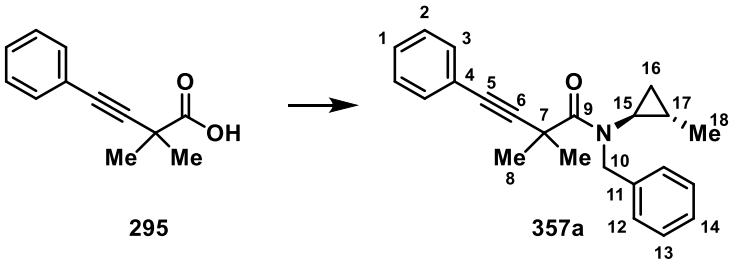
*Aminocyclopropane **349** was prepared by Curley.* **General procedure G:** *N*-Benzylcyclopropanamine (1.00 g, 6.80 mmol) and 2-methylbut-3-enoic acid (0.68 g, 6.80 mmol, prepared according to the literature procedure[284]) were employed and the residue was purified by flash column chromatography (20% EtOAc/hexane) to afford the title compound **349** (0.61 g, 39%) as a colourless oil; ν_{max} / cm^{-1}: 1651 (s), 1634 (s), 1395 (s), 1454 (m), 1249 (m), 1030 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.34 – 7.14 (m, 5H, 2 × C**10**-H, 2 × C**11**-H and C**12**-H), 5.91 (ddd, *J* = 17.1, 10.2, 8.0 Hz, 1H, C**2**-H), 5.17 – 5.00 (m, 2H, C**1**-H_2), 4.69 (d, *J* = 14.6 Hz, 2H, C**8**-H_aH_b), 4.50 (d, *J* = 14.6 Hz, 2H, C**8**-H_aH_b), 4.03 – 3.90 (m, 1H, C**3**-H), 2.62 – 2.52 (m, 1H, C**6**-H), 1.26 (d, *J* = 6.8 Hz, 3H, C**4**-H_3), 0.91 – 0.70 (m, 4H, 2 × C**7**-H_2); ^{13}C NMR ($CDCl_3$, 101 MHz): 177.2 (C**5**), 139.0 (C**9**), 138.5 (C**2**), 128.5, 127.8, 127.1 (C**10**, C**11** and C**12**), 115.5 (C**1**), 49.9 (C**8**), 41.7 (C**3**), 29.8 (C**6**), 18.2 (C**4**), 9.9 (C**7**), 9.1 (C**7'**); HRMS: (ESI^+) calculated for $C_{15}H_{20}NO$: 230.1539, found $[M+H]^+$: 230.1539.

(3*S,3a*S**,7a*R**)-1-benzyl-3-methylhexahydro-2*H*-indole-2,5(3*H*)-dione (352)**



*Cyclohexanone **352** was prepared by Curley.* An oven dried reaction tube, fitted with a magnetic stirrer, was charged with aminocyclopropane **349** (22.9 mg, 0.10 mmol), $[Rh(cod)Cl]_2$ (2.5 mg, 0.005 mmol), dimethyl fumarate (14.4 mg, 0.1 mmol) and PPh_3 (5.2 mg, 0.02 mmol). The tube was fitted with a rubber septum and purged with argon. Anhydrous PhCN (1.0 mL) was added and the reaction was sparged with CO for approx. 10 seconds. The tube was heated to 130 °C, under a CO atmosphere (1 balloon) and stirred for 72 h. The mixture was cooled to r.t. and concentrated *in vacuo*. An *in situ* yield (20%) was obtained by using 1,4-dinitrobenzene as an internal standard for ^{1}H NMR spectroscopy. The residue was purified by flash column chromatography (70% EtOAc/hexane) to afford **345** (5.9 mg, 23%) as a pale yellow oil; ν_{max} / cm^{-1}: 1688 (s), 1406 (s), 1454 (m), 1375 (m), 1302 (m), 1194 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35 – 7.19 (m, 5H, 2 × C**3**-H, 2 × C**2**-H and C**1**-H), 4.90 – 4.80 (d, *J* = 14.9 Hz, 1H, C**5**-H_aH_b), 4.22 – 4.13 (d, *J* = 14.9 Hz, 1H, C**5**-H_aH_b), 3.28 – 3.17 (m, 1H, C**9**-H), 2.69 – 2.63 (m, 1H, C**11**-H_aH_b), 2.59 – 2.51 (m, 1H, C**13**-H_aH_b), 2.34 – 2.16 (m, 4H, C**11**-H_aH_b, C**13**-H_aH_b, C**14**-H_aH_b and C**7**-H), 1.69 (dddd, *J* = 14.0, 11.5, 9.9, 3.8 Hz, 1H, C**10**-H), 1.60 – 1.52 (m, 1H, C**14**-H_aH_b) 1.24 (d, *J* = 6.9 Hz, 3H, C**8**-H_3); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 207.3 (C**12**), 177.7 (C**6**), 136.9 (C**4**), 128.9, 128.0, 127.7 (C**1**, C**2** and C**3**), 59.0 (C**9**), 48.4 (C**10**), 44.6 (C**5**), 43.2 (C**11**), 42.9 (C**7**), 39.2 (C**13**), 28.2 (C**14**), 13.0 (C**8**). The spectroscopic properties of this compound were consistent with the data available in the literature.[285] The relative stereochemistry of this compound was corroborated by nOe experiments (as indicated on the compound structure). A strong nOe was observed between C**10**-H and C**8**-H_3. No nOe was observed between C**9**-H and C**8**-H_3 or C**9**-H and C**10**-H.

***N*-Benzyl-2,2-dimethyl-*N*-((1*S**,2*S**)-2-methylcyclopropyl)-4-phenylbut-3-ynamide (357a)**



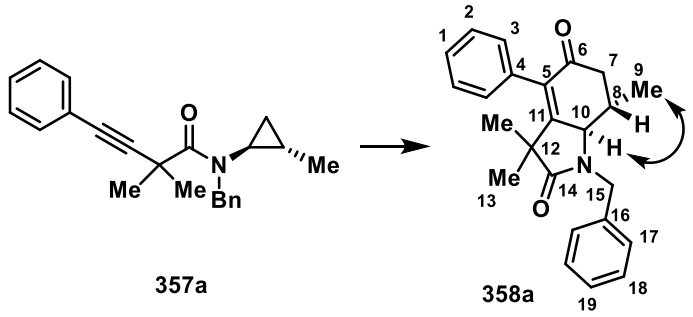
General procedure G: (1*S**,2*S**)-*N*-Benzyl-2-methylcyclopropan-1-amine (0.43 g, 2.66 mmol, prepared according to the literature procedure[48]) and 2,2-dimethyl-4-phenylbut-3-ynoic acid (0.50 g, 2.66 mmol) were employed and the residue was purified by flash column chromatography (5% EtOAc/hexane) to afford the title compound **357a** (0.69 g, 79%) as a colourless solid; m.p. 75-76 °C (DCM/hexane); ν_{max} / cm^{-1}: 2988 (m), 1651 (s), 1492 (m), 1454 (m), 1394 (s), 1169 (m), 1077 (m), 756 (s), 692 (s); ^{1}H NMR (DMSO-d_6, 500 MHz, 110 °C): δ 7.34 – 7.19 (m, 10H, 2 × C**2**-H, 2 × C**3**-H, 2 × C**12**-H, 2 × C**13**-H, C**1**-H and C**14**-H), 4.81 (s, 2H, C**10**-H_2), 2.63 (br. s, 1H, C**15**-H), 1.59 (s, 6H, 2 × C**8**-H_3), 1.11 – 1.02 (m, 1H, C**17**-H), 0.93 (d, J = 6.1 Hz, 3H, C**18**-H_3), 0.91 – 0.85 (m, 1H, C**16**-H_aH_b), 0.51 – 0.46 (m, 1H, C**16**-H_aH_b); ^{13}C NMR (DMSO-d_6, 126 MHz, 110 °C): δ 172.8 (C**9**), 137.8 (C**11**), 130.5, 127.8, 127.7, 127.6, 126.3, 126.1 (C**1**, C**2**, C**3**, C**12**, C**13** and C**14**), 122.2 (C**4**), 92.7 (C**6**), 82.8 (C**5**), 50.1 (C**10**), 37.9 (C**15**), 37.2 (C**7**), 28.1 (C**8**), 27.9 (C**8'**), 16.5 (C**18**), 15.1 (C**17**), 14.8 (C**16**); HRMS: (ESI^+) calculated for $C_{23}H_{25}NO$: 332.2009, found $[M+H]^+$: 332.2000.

Data for enantioenriched **(*S*,*S*)-357a** (prepared from (*R*)-propylene oxide[110]):

$[\alpha]_D^{23.5}$ = +19.8 (c = 0.33, $CHCl_3$).

Chiral SFC: (DAICEL CHIRALPAK-IB column (25 cm), CO_2:*i*-PrOH 98:2, 2 mL/min, 100 bars, 40 °C). Retention times: 27.0 minutes (major), e.r. > 99:1.

(7*S,7a*R**)-1-Benzyl-3,3,7,7a-tetramethyl-4-phenyl-1,6,7,7a-tetrahydro-2*H*-indole-2,5(3*H*)-dione (358a)**



An oven dried reaction tube, fitted with a magnetic stirrer, was charged with aminocyclopropane substrate **357a** (27.5 mg, 0.10 mmol), $[Rh(cod)Cl]_2$ (2.5 mg, 0.005 mmol) and $P(C_6F_5)_3$ (10.6 mg, 0.02 mmol). The tube was fitted with a rubber septum and purged with argon. Anhydrous PhCN (1.0 mL) was added and the reaction was sparged with CO for ca. 10 seconds. The tube was heated to 150 °C, under a CO atmosphere (1 balloon) and stirred for 72 h. The mixture was cooled to r.t. and concentrated *in vacuo*. The residue was purified by flash column chromatography (10-25% EtOAc/hexane) to afford **358a** (30.3 mg, 84%) as a colourless oil, the product was isolated as a single diastereomer (>15:1 d.r.); ν_{max} / cm^{-1}: 1697 (s), 1673 (s), 1410 (s), 1295 (m), 1239 (m), 919 (m), 730 (s), 700 (s); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.41 – 7.27 (m, 6H, 2 × C**2**-H, 2 × C**18**-H, C**1**-H and C**19**-H), 7.22 – 7.17 (m, 2H, 2 × C**17**-H), 7.08 – 7.00 (m, 2H, 2 × C**3**-H), 5.17 (d, *J* = 15.6 Hz, 1H, C**15**-H_aH_b), 4.50 (d, *J* = 15.6 Hz, 1H, C**15**-H_aH_b), 4.11 (d, *J* = 9.9 Hz, 1H, C**10**-H), 2.59 (dd, *J* = 17.1, 3.6 Hz, 1H, C**7**-H_aH_b), 2.40 – 2.27 (m, 1H, C**8**-H), 2.21 (dd, *J* = 17.1, 13.1 Hz, 1H, C**7**-H_aH_b), 1.34 (s, 3H, C**13**-H_3), 1.24 (d, *J* = 6.3 Hz, 3H, C**9**-H_3), 0.88 (s, 3H, C**13'**-H_3); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 197.0 (C**6**), 179.4 (C**14**), 162.3 (C**11**), 136.6, 136.3 (C**5** and C**16**), 134.0 (C**4**), 130.0 (C**3**), 129.0, 128.1, 128.1, 127.7, 127.4 (C**1**, C**2**, C**17**, C**18** and C**19**), 63.1 (C**10**), 46.6 (C**15**), 45.8 (C**7**), 45.5 (C**12**), 38.1 (C**8**), 26.5 (C**13**), 22.7 (C**13'**), 20.8 (C**9**); HRMS: (ESI^+) calculated for $C_{20}H_{26}NO_2$: 360.1958, found $[M+H]^+$: 360.1949.

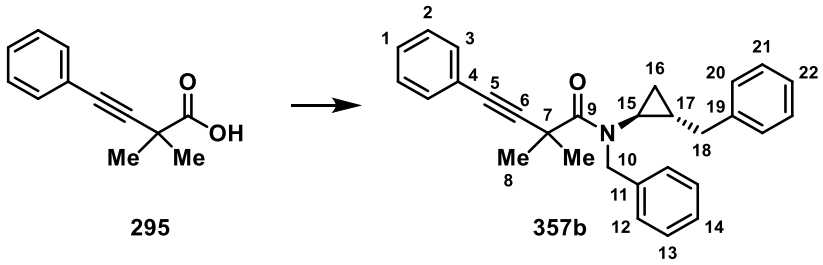
The relative stereochemistry of this compound was corroborated by nOe experiments (as indicated on the compound structure). A strong nOe was observed between C**10**-H and C**9**-H_3. No significant nOe was observed between C**10**-H and C**8**-H.

Data for enantioenriched **(*S*,*R*)-358a** (obtained from enantioenriched amide **(*S*,*S*)-357a**):

$[\alpha]_D^{23.4}$ = +61.4 (c = 0.15, $CHCl_3$).

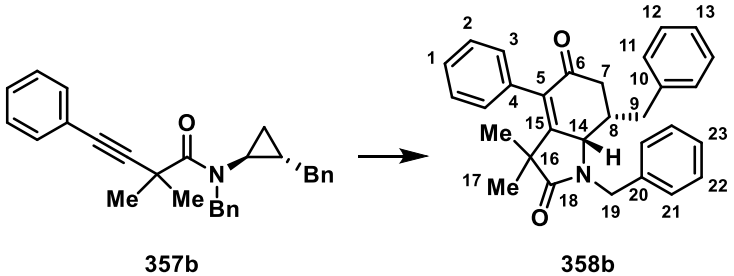
Chiral SFC: (DAICEL CHIRALPAK-IB column (25 cm), CO_2:MeOH 88:12, 2 mL/min, 140 bars, 40 °C). Retention times: 13.7 minutes (minor), 17.3 minutes (major), e.r. > 99:1.

***N*-Benzyl-*N*-((1*S**,2*S**)-2-benzylcyclopropyl)-2,2-dimethyl-4-phenylbut-3-ynamide (357b)**



General procedure G: (1*S**,2*S**)-*N*,2-dibenzylcyclopropan-1-amine (0.25 g, 1.05 mmol, prepared according to the literature procedure[48]) and acid **295** (0.20 g, 1.05 mmol) were employed and the residue was purified by flash column chromatography (5% EtOAc/hexane) to afford the title compound **357b** (0.25 g, 59%) as a pale yellow oil; ν_{max} / cm^{-1}: 2986 (m), 1644 (s), 1495 (m), 1454 (m), 1394 (s), 1167 (m), 1029 (m), 756 (s), 728 (s), 691 (s); ^{1}H NMR (DMSO-d_6, 500 MHz, 110 °C): δ 7.33 – 7.11 (m, 13H, 2 × C**2**-H, 2 × C**3**-H, 2 × C**12**-H, 2 × C**13**-H, 2 × C**21**-H, C**1**-H, C**14**-H and C**22**-H), 7.07 – 7.04 (m, 2H, 2 × C**20**-H), 4.85 (d, *J* = 16.0 Hz, 1H, C**10**-H_aH_b), 4.74 (d, *J* = 16.0 Hz, 1H, C**10**-H_aH_b), 2.85 (br. s, 1H, C**15**-H), 2.75 (dd, *J* = 14.5, 5.3 Hz, 1H, C**18**-H_aH_b), 2.25 (dd, *J* = 14.5, 8.1 Hz, 1H, C**18**-H_aH_b), 1.59 (s, 3H, C**8**-H_3), 1.59 (s, 3H, C**8'**-H_3), 1.41 – 1.33 (m, 1H, C**17**-H), 0.97 – 0.89 (m, 1H, C**16**-H_aH_b), 0.71 – 0.65 (m, 1H, C**16**-H_aH_b); ^{13}C NMR (DMSO-d_6, 126 MHz, 110 °C): δ 172.8 (C**9**), 139.7 (C**19**), 137.8 (C**11**), 130.5, 127.8, 127.8, 127.7, 127.6, 127.5, 126.2, 126.1, 125.3 (C**1**, C**2**, C**3**, C**12**, C**13**, C**14**, C**20**, C**21** and C**22**), 122.1 (C**4**), 92.7 (C**6**), 82.9 (C**5**), 50.0 (C**10**), 37.2 (C**7**), 36.8 (C**18**), 36.7 (C**15**), 28.1 (C**8**), 28.0 (C**8'**), 21.0 (C**17**), 14.1 (C**16**); HRMS: (ESI$^+$) calculated for $C_{29}H_{30}NO$: 408.2322, found $[M+H]^+$: 408.2323.

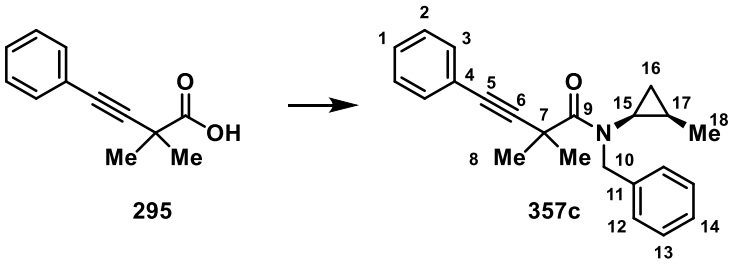
(7*R,7aS*)-1,7-Dibenzyl-3,3-dimethyl-4-phenyl-1,6,7,7a-tetrahydro-2*H*-indole-2,5(3*H*)-dione (358b)**



An oven dried reaction tube, fitted with a magnetic stirrer, was charged with aminocyclopropane substrate **357b** (40.8 mg, 0.10 mmol), $[Rh(cod)Cl]_2$ (2.5 mg, 0.005 mmol) and $P(C_6F_5)_3$ (10.6 mg, 0.02 mmol). The tube was fitted with a rubber septum and purged with argon. Anhydrous PhCN (1.0 mL) was added and the reaction was sparged with CO for ca. 10 seconds. The tube was heated

to 150 °C, under a CO atmosphere (1 balloon) and stirred for 72 h. The mixture was cooled to r.t. and concentrated *in vacuo*. The residue was purified by flash column chromatography (10-25% EtOAc/hexane) to afford **358b** (29.4 mg, 67%) as a pale yellow oil, the product was isolated as a single diastereomer (>15:1 d.r.); ν_{max} / cm^{-1}: 1698 (s), 1672 (s), 1495 (m), 1409 (m), 1243 (m), 911 (m), 728 (s), 699 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.44 – 7.14 (m, 11H, 2 × C**2**-H, 2 × C**11**-H, 2 × C**12**-H, 2 × C**22**-H, C**1**-H, C**13**-H and C**23**-H), 7.05 – 6.97 (m, 2H, 2 × C**21**-H), 6.87 – 6.80 (m, 2H, 2 × C**3**-H), 5.05 (d, *J* = 16.0 Hz, 1H, C**19**-H_aH_b), 4.83 (d, *J* = 16.0 Hz, 1H, C**19**-H_aH_b), 4.32 (d, *J* = 9.8 Hz, 1H, C**14**-H), 3.50 (dd, *J* = 12.7, 3.1 Hz, 1H, 1H, C**9**-H_aH_b), 2.50 – 2.25 (m, 3H, C**8**-H, C**7**-H_aH_b, C**9**-H_aH_b), 2.10 – 1.98 (m, 1H, C**7**-H_aH_b), 1.37 (s, 3H, C**17**-H_3), 0.91 (s, 3H, C**17'**-H_3); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 196.7 (C**6**), 179.8 (C**18**), 162.1 (C**15**), 137.6 (C**20**), 136.9 (C**5**), 136.6 (C**10**), 133.9 (C**4**), 130.0, 129.2, 129.1, 128.8, 128.2, 128.1, 127.8, 127.2, 126.8 (C**1**, C**2**, C**3**, C**11**, C**12**, C**13**, C**21**, C**22** and C**23**), 62.7 (C**14**), 47.6 (C**19**), 45.4 (C**16**), 44.5 (C**8**), 41.8 (C**7**), 40.1 (C**9**), 26.6 (C**17**), 22.9 (C**17'**); HRMS: (ESI^+) calculated for $C_{30}H_{30}NO_2$: 436.2271, found $[M+H]^+$: 436.2247.

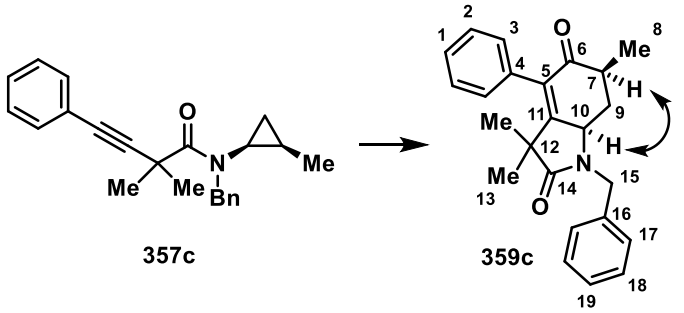
***N*-Benzyl-2,2-dimethyl-N-((1*S**,2*R**)-2-methylcyclopropyl)-4-phenylbut-3-ynamide (357c)**



General procedure G: (1*S**,2*R**)-*N*-Benzyl-2-methylcyclopropan-1-amine (0.30 g, 1.86 mmol, prepared according to the literature procedure[48]) and acid **295** (0.35 g, 1.86 mmol) were employed and the residue was purified by flash column chromatography (5% EtOAc/hexane) to afford the title compound **357c** (0.31 g, 51%) as a colourless solid; m.p. 53-54 °C (DCM/hexane); ν_{max} / cm^{-1}: 2986 (m), 2258 (w), 1647 (s), 1395 (s), 1233 (m), 1162 (m), 755 (s), 691 (s); ^{1}H NMR (DMSO-d_6, 500 MHz, 110 °C): δ 7.31 – 7.11 (m, 10H, 2 × C**2**-H, 2 × C**3**-H, 2 × C**12**-H, 2 × C**13**-H, C**1**-H and C**14**-H), 5.45 (d, *J* = 16.2 Hz, 1H, C**10**-H_aH_b), 4.42 (d, *J* = 16.2 Hz, 1H, C**10**-H_aH_b), 2.74 (br. s, 1H, C**15**-H), 1.56 (s, 6H, 2 × C**8**-H_3), 1.07 – 0.93 (m, 4H, C**17**-H and C**18**-H_3), 0.73 – 0.64 (m, 1H, C**16**-H_aH_b), 0.39 (s, 1H, C**16**-H_aH_b); ^{13}C NMR (DMSO-d_6, 126 MHz, 110 °C): δ 173.8 (C**9**), 137.6 (C**11**), 130.5, 127.8, 127.8, 127.6, 126.5, 126.2 (C**1**, C**2**, C**3**, C**12**, C**13** and C**14**), 122.1 (C**4**), 92.6 (C**6**), 82.9 (C**5**), 51.2 (C**10**), 37.4 (C**7**), 34.5 (C**15**), 28.3 (C**8**), 28.0 (C**8'**), 13.4

(C**17**), 12.3 (C**16**), 11.7 (C**18**); HRMS: (ESI$^+$) calculated for $C_{23}H_{26}NO$: 332.2009, found $[M+H]^+$: 332.2014.

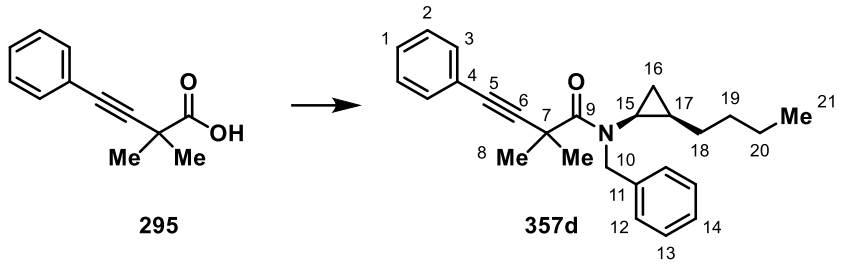
(6*S,7a*R**)-1-Benzyl-3,3,6-trimethyl-4-phenyl-1,6,7,7a-tetrahydro-2*H*-indole-2,5(3*H*)-dione (359c)**



An oven dried reaction tube, fitted with a magnetic stirrer, was charged with aminocyclopropane substrate **357c** (33.1 mg, 0.10 mmol), $[Rh(cod)Cl]_2$ (2.5 mg, 0.005 mmol) and $P(4\text{-}OMeC_6H_4)_3$ (7.0 mg, 0.02 mmol). The tube was fitted with a rubber septum and purged with argon. Anhydrous PhCN (1.0 mL) was added and the reaction was sparged with CO for ca. 10 seconds. The tube was heated to 150 °C, under a CO atmosphere (1 balloon) and stirred for 72 h. The mixture was cooled to r.t. and concentrated *in vacuo*. The residue was purified by flash column chromatography (10-25% EtOAc/hexane) to afford **359c** (18.0 mg, 50%) as a colourless oil, the product was isolated as a single diastereomer (>15:1 d.r.); ν_{max} / cm^{-1}: 2931 (m), 1677 (s), 1401 (m), 1208 (m), 910 (m), 729 (s), 699 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35 – 7.19 (m, 8H, 2 × C**2**-H, 2 × C**17**-H, 2 × C**18**-H, C**1**-H and C**19**-H), 6.98 – 6.91 (m, 2H, 2 × C**3**-H), 5.07 (d, *J* = 15.0 Hz, 1H, C**15**-H_aH_b), 4.21 (dd, *J* = 11.5, 4.3 Hz, 1H, C**10**-H), 3.99 (d, *J* = 15.0 Hz, 1H, C**15**-H_aH_b), 2.41 (ddd, *J* = 11.6, 4.3, 4.3 Hz, 1H, C**9**-H_aH_b), 2.36 – 2.25 (m, 1H, C**7**-H), 1.58 (ddd, *J* = 13.3, 11.6, 11.5 Hz, 1H, C**9**-H_aH_b), 1.27 (s, 3H, C**13**-H_3), 1.17 (d, *J* = 6.8 Hz, 3H, C**8**-H_3), 0.73 (s, 3H, C**13''**-H_3); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 199.2 (C**6**), 177.6 (C**14**), 161.6 (C**11**), 136.0 (C**16**), 135.7 (C**5**), 134.3 (C**4**), 130.0 (br., C**3**), 129.1, 128.1, 128.0, 128.0 (C**1**, C**2**, C**17**, C**18** and C**19**), 55.5 (C**10**), 46.0 (C**12**), 44.0 (C**15**), 40.3 (C**7**), 36.7 (C**9**), 26.1 (C**13**), 21.8 (C**13'**), 16.3 (C**8**); HRMS: (ESI$^+$) calculated for $C_{24}H_{26}NO_2$: 360.1958, found $[M+H]^+$: 360.1960.

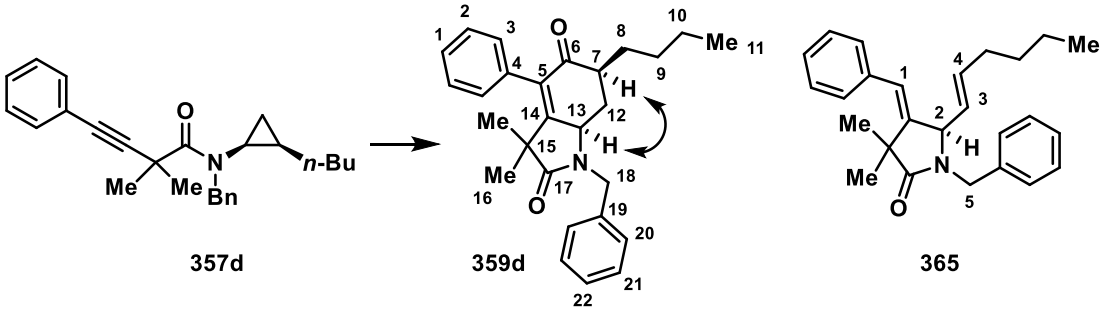
The relative stereochemistry of this compound was corroborated by nOe experiments (as indicated on the compound structure). A strong nOe was observed between C**10**-H and C**7**-H.

***N*-Benzyl-*N*-((1*S**,2*R**)-2-butylcyclopropyl)-2,2-dimethyl-4-phenylbut-3-ynamide (357d)**



General procedure G: (1*S**,2*R**)-*N*-Benzyl-2-butylcyclopropan-1-amine (0.40 g, 1.97 mmol, prepared according to the literature procedure[53]) and acid **295** (0.37 g, 1.97 mmol) were employed and the residue was purified by flash column chromatography (10% EtOAc/hexane) to afford the title compound **357d** (0.43 g, 58%) as a colourless oil; ν_{max} / cm^{-1}: 2928 (m), 1650 (s), 1454 (m), 1394 (s), 1232 (m), 1162 (m), 1030 (m), 755 (s), 690 (s); ^{1}H NMR (DMSO-d_6, 500 MHz, 110 °C): δ 7.33 – 7.19 (m, 8H, 2 × C**2**-H, 2 × C**12**-H, 2 × C**13**-H, C**1**-H, C**14**-H), 7.16 – 7.11 (m, 2H, 2 × C**3**-H), 5.48 (d, *J* = 16.3 Hz, 1H, C**10**-H_aH_b), 4.44 (d, *J* = 16.3 Hz, 1H, C**10**-H_aH_b), 2.78 (br. s, 1H, C**15**-H), 1.57 (s, 3H, C**8**-H_3), 1.56 (s, 3H, C**8'**-H_3), 1.52 – 1.42 (m, 1H, C**18**-H_aH_b), 1.39 – 1.24 (m, 4H, C**19**-H_2 and C**20**-H_2), 1.06 – 0.91 (m, 2H, C**18**-H_aH_b and C**17**-H), 0.85 (t, *J* = 7.2 Hz, 3H, C**21**-H_3), 0.71 – 0.63 (m, 1H, C**16**-H_aH_b), 0.46 – 0.39 (m, 1H, C**16**-H_aH_b); ^{13}C NMR (DMSO-d_6, 126 MHz, 110 °C): δ 173.6 (C**9**), 137.6 (C**11**), 130.5 (C**3**), 127.8, 127.7, 127.6, 126.4, 126.2 (C**1**, C**2**, C**12**, C**13** and C**14**), 122.1 (C**4**), 92.5 (C**6**), 82.8 (C**5**), 51.1 (C**10**), 37.3 (C**7**), 34.5 (C**15**), 30.7 (C**19**), 28.2, 28.0 (C**8** and C**8'**), 26.3 (C**18**), 21.4 (C**20**), 19.2 (C**17**), 13.1 (C**21**), 11.0 (C**16**); HRMS: (ESI^+) calculated for $C_{26}H_{32}NO$: 374.2478, found $[M+H]^+$: 374.2481.

(6*S,7a*R**)-1-Benzyl-6-butyl-3,3-dimethyl-4-phenyl-1,6,7,7a-tetrahydro-2*H*-indole-2,5(3*H*)-dione (359d) and (R)-1-benzyl-4-((E)-benzylidene)-5-((E)-hex-1-en-1-yl)-3,3-dimethylpyrrolidin-2-one (365)**



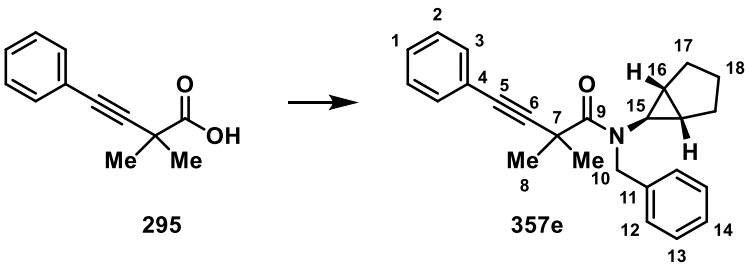
An oven dried reaction tube, fitted with a magnetic stirrer, was charged with aminocyclopropane substrate **357d** (37.4 mg, 0.10 mmol), $[Rh(cod)Cl]_2$ (2.5 mg, 0.005 mmol) and $P(4\text{-}OMeC_6H_4)_3$ (7.0 mg, 0.02 mmol). The tube was fitted with a rubber septum and purged with argon. Anhydrous

PhCN (1.0 mL) was added and the reaction was sparged with CO for ca. 10 seconds. The tube was heated to 150 °C, under a CO atmosphere (1 balloon) and stirred for 72 h. The mixture was cooled to r.t. and concentrated *in vacuo*. The residue was purified by flash column chromatography (20% EtOAc/hexane) to afford **357d** (19.1 mg, 48%, isolated as a single diastereomer, >15:1 d.r.) and **365** (2.2 mg, 6%) as colourless oils.

Data for **359d**: ν_{max} / cm^{-1}: 2957 (m), 2930 (m), 2863 (m), 1698 (s), 1672 (s), 1418 (s), 1360 (m), 1310 (m), 1238 (m), 734 (s), 701 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.41 – 7.27 (m, 8H, 2 × C**2**-H, 2 × C**20**-H, 2 × C**21**-H, C**1**-H and C**22**-H), 7.03 – 6.98 (m, 2H, 2 × C**3**-H), 5.15 (d, *J* = 14.9 Hz, 1H, C**18**-H_aH_b), 4.23 (dd, *J* = 11.6, 4.3 Hz, 1H, C**13**-H), 4.08 (d, *J* = 14.9 Hz, 1H, C**18**-H_aH_b), 2.50 (ddd, *J* = 11.6, 4.3, 4.3 Hz, 1H, C**12**-H_aH_b), 2.29 – 2.20 (m, 1H, C**7**-H), 1.96 – 1.87 (m, 1H, C**8**-H_aH_b), 1.60 (ddd, *J* = 13.4, 11.6, 11.6 Hz, 1H, C**12**-H_aH_b), 1.55 – 1.47 (m, 1H, C**8**-H_aH_b), 1.36 – 1.23 (m, 7H, C**16**-H_3, C**9**-H_2 and C**10**-H_2), 0.91 (t, *J* = 7.0 Hz, 3H, C**11**-H_3), 0.81 (s, 3H, C**16'**-H_3); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 199.0 (C**6**), 177.6 (C**17**), 161.2 (C**14**), 136.1 (C**19**), 134.5 (C**5**), 130.0 (br., C**3**), 129.1, 128.1, 128.1, 128.1, 128.0, 128.0 (C**1**, C**2**, C**4**, C**20**, C**21** and C**22**), 55.7 (C**13**), 45.9 (C**15**), 45.0 (C**7**), 44.1 (C**18**), 33.7 (C**12**), 30.1 (C**8**), 28.9 (C**9**), 26.1 (C**16**), 22.9 (C**10**), 21.9 (C**16'**), 14.1 (C**11**); HRMS: (ESI^+) calculated for $C_{27}H_{31}NNaO_2$: 424.2247, found $[M+Na]^+$: 424.2240. The relative stereochemistry of this compound was corroborated by nOe experiments (as indicated on the compound structure). A strong nOe was observed between C**7**-H and C**13**-H. No significant nOe was observed between C**8**-H_2 and C**13**-H.

Data for **365** *(characteristic signals only)*: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.45 (d, *J* = 2.2 Hz, 1H, C**1**-H), 5.44 (dt, *J* = 15.3, 6.9 Hz, 1H, C**4**-H), 5.11 (d, *J* = 15.0 Hz, 1H, C**5**-H_aH_b), 5.00 (ddt, *J* = 15.3, 8.8, 1.4 Hz, 1H, C**3**-H), 4.75 (dd, *J* = 8.8, 2.2 Hz, 1H, C**2**-H), 3.89 (d, *J* = 15.0 Hz, 1H, C**5**-H_aH_b).

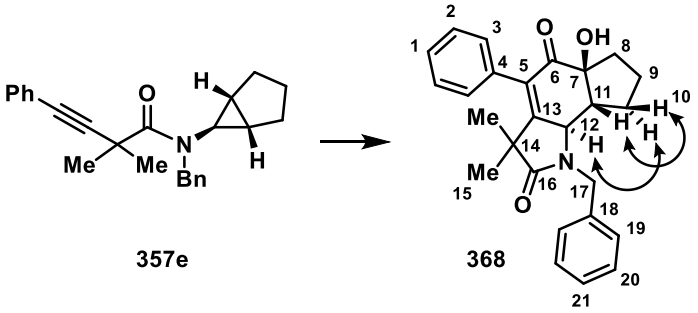
N-Benzyl-*N*-((1*R**,5*S**,6*r*)-bicyclo[3.1.0]hexan-6-yl)-2,2-dimethyl-4-phenylbut-3-ynamide (357e)



General procedure G: (1*R**,5*S**,6*r*)-*N*-benzylbicyclo[3.1.0]hexan-6-amine (0.30 g, 1.60 mmol, prepared according to the literature procedure[53]) and acid **295** (0.30 g, 1.60 mmol) were employed

and the residue was purified by flash column chromatography (10% EtOAc/hexane) to afford the title compound **357e** (0.40 g, 70%) as a colourless oil; ν_{max} / cm^{-1}: 2934 (m), 1643 (s), 1492 (m), 1393 (s), 1356 (m), 1165 (m), 755 (s), 691 (s); ^{1}H NMR (DMSO-d_6, 500 MHz, 110 °C): δ 7.32 – 7.17 (m, 10H, 2 × C**2**-H, 2 × C**3**-H, 2 × C**12**-H, 2 × C**13**-H, C**1**-H and C**14**-H), 4.76 (s, 2H, C**10**-H_2), 2.70 (br. s, 1H, C**15**-H), 1.67 – 1.54 (m, 12H, 2 × C**17**-H_2, 2 × C**8**-H_3, C**18**-H_2), 1.49 – 1.39 (m, 1H, C**16**-H), 0.95 – 0.82 (m, 1H, C**16**-H); ^{13}C NMR (DMSO-d_6, 126 MHz, 110 °C): δ 172.6 (C**9**), 137.9 (C**11**), 130.4, 127.8, 127.6, 127.5, 126.3, 126.0 (C**1**, C**2**, C**3**, C**12**, C**13** and C**14**), 122.2 (C**4**), 92.8 (C**6**), 82.9 (C**5**), 49.8 (C**10**), 37.7 (C**15**), 37.3 (C**7**), 28.0 (C**8**), 26.6, 26.2 (C**17** and C**18**), 20.7 (C**16**); HRMS: (ESI$^+$) calculated for $C_{25}H_{28}NO$: 358.2165, found $[M+H]^+$: 358.2164.

1-Benzyl-5a-hydroxy-3,3-dimethyl-4-phenyl-5a,6,7,8,8a,8b-hexahydrocyclopenta-[*g*]idole-2,5(1*H*,3*H*)-dione (368)

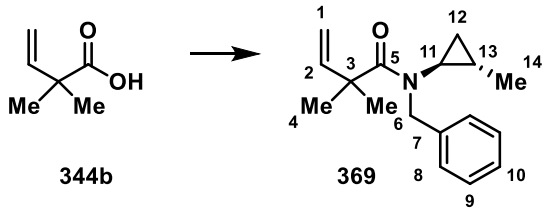


An oven dried reaction tube, fitted with a magnetic stirrer, was charged with aminocyclopropane substrate **357e** (35.8 mg, 0.10 mmol), $[Rh(cod)Cl]_2$ (2.5 mg, 0.005 mmol) and $P(4\text{-}OMeC_6H_4)_3$ (7.0 mg, 0.02 mmol). The tube was fitted with a rubber septum and purged with argon. Anhydrous PhCN (1.0 mL) was added and the reaction was sparged with CO for ca. 10 seconds. The tube was heated to 150 °C, under a CO atmosphere (1 balloon) and stirred for 72 h. The mixture was cooled to r.t. and concentrated *in vacuo*. The residue was purified by flash column chromatography (10-25% EtOAc/hexane) to afford **368** (15.3 mg, 38%) as a pale yellow oil, the product was isolated as a single diastereomer (>15:1 d.r.); ν_{max} / cm^{-1}: 3406 (br. m), 2969 (m), 2932 (m), 1695 (s), 1680 (s), 1416 (m), 1074 (m), 910 (m), 731 (s), 700 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.43 – 7.27 (m, 6H, 2 × C**2**-H, 2 × C**20**-H, C**1**-H and C**21**-H), 7.21 – 7.16 (m, 2H, 2 × C**19**-H), 7.14 – 7.09 (m, 2H, 2 × C**3**-H), 5.16 (d, *J* = 16.0 Hz, 1H, C**17**-H_aH_b), 4.31 (d, *J* = 16.0 Hz, 1H, C**17**-H_aH_b), 4.20 (d, *J* = 9.6 Hz, 1H, C**12**-H), 3.42 (s, 1H, C**7**-OH), 2.61 – 2.54 (m, 1H, C**11**-H), 2.30 – 2.17 (m, 1H, C**10**-H_aH_b), 2.01 – 1.82 (m, 3H, C**10**-H_aH_b, C**8**-H_aH_b, C**9**-H_aH_b), 1.76 – 1.59 (m, 2H, C**8**-H_aH_b, C**9**-H_aH_b), 1.45 (s, 3H, C**15**-H_3), 0.80 (s, 3H, C**15'**-H_3); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 198.6 (C**6**), 177.9 (C**16**), 161.6 (C**13**), 136.0, 133.8, 133.3 (C**4**, C**5** and C**18**), 130.3, 129.1, 128.5, 128.1, 127.7,

127.1 (C**1**, C**2**, C**3**, C**19**, C**20** and C**21**), 82.7 (C**7**), 58.1 (C**12**), 52.3 (C**11**), 46.1 (C**14**), 44.6 (C**17**), 37.2 (C**8**), 29.8 (C**10**), 26.6 (C**15**), 21.7, 21.7 (C**9** and C**15'**); HRMS: (ESI$^+$) calculated for $C_{26}H_{28}NO_3$: 402.2064, found $[M+H]^+$: 402.2052.

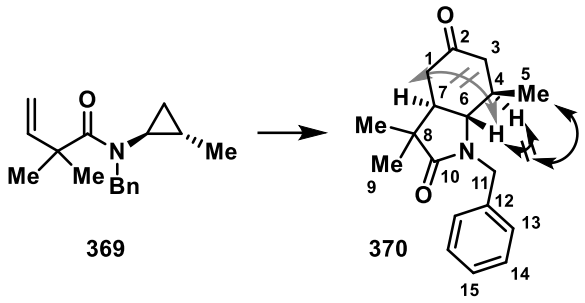
The relative stereochemistry of this compound was corroborated by nOe experiment (as indicated on the compound structure). An nOe was observed between C**11**-H and C**10**-H_aH_b. An nOe was observed between C**12**-H and C**10**-H_aH_b.

***N*-Benzyl-2,2-dimethyl-*N*-((1*S**,2*S**)-2-methylcyclopropyl)but-3-enamide (369)**



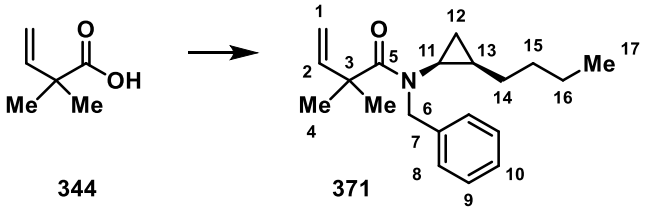
General procedure G: (1*S**,2*S**)-*N*-Benzyl-2-methylcyclopropan-1-amine (0.71 g, 4.38 mmol, prepared according to the literature procedure[48]) and acid **344b** (0.50 g, 4.38 mmol) were employed and the residue was purified by flash column chromatography (10% EtOAc/hexane) to afford the title compound **369** (0.61 g, 54%) as a pale yellow oil; ν_{max} / cm^{-1}: 2974 (w), 1644 (s), 1630 (s), 1388 (m), 1173 (m), 912 (m), 998 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.34 – 7.12 (m, 5H, 2 × C**8**-H, 2 × C**9**-H and C**10**-H), 6.09 (dd, *J* = 17.6, 10.7 Hz, 1H, C**2**-H), 5.13 – 5.01 (m, 2H, C**1**-H_2), 4.59 (d, *J* = 15.9 Hz, 1H, C**6**-H_aH_b), 4.53 (d, *J* = 15.9 Hz, 1H, C**6**-H_aH_b), 2.29 (br. s, 1H, C**11**-H), 1.36 (s, 6H, 2 × C**4**-H_3), 1.00 – 0.87 (m, 4H, C**13**-H and C**14**-H_3), 0.73 (br. s, 1H, C**12**-H_aH_b), 0.45 – 0.38 (m, 1H, C**12**-H_aH_b); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 178.2 (C**5**), 144.0 (C**2**), 138.2 (br., C**7**), 128.6, 127.1, 127.1 (C**8**, C**9** and C**10**), 112.4 (C**1**), 51.6 (br., C**6**), 45.9 (C**3**), 38.2 (br., C**11**), 26.9 (C**4**), 26.9 (C**4'**), 17.4 (C**14**), 16.3 (br., C**12**), 16.2 (C**13**); HRMS: (ESI$^+$) calculated for $C_{17}H_{24}NO$: 258.1852, found $[M+H]^+$: 258.1844.

(3a*R,7*R**,7a*S**)-1-Benzyl-3,3,7-trimethylhexahydro-2*H*-indole-2,5(3*H*)-dione (370)**



An oven dried reaction tube, fitted with a magnetic stirrer, was charged with aminocyclopropane substrate **369** (25.7 mg, 0.10 mmol), $[Rh(cod)Cl]_2$ (2.5 mg, 0.005 mmol) and $P(C_6F_5)_3$ (10.6 mg, 0.02 mmol). The tube was fitted with a rubber septum and purged with argon. Anhydrous PhCN (1.0 mL) was added and the reaction was sparged with CO for ca. 10 seconds. The tube was heated to 150 °C, under a CO atmosphere (1 balloon) and stirred for 72 h. The mixture was cooled to r.t. and concentrated *in vacuo*. The residue was purified by flash column chromatography (60-70% EtOAc/hexane) to afford **370** (19.4 mg, 68%) as a pale yellow oil, the product was isolated as a single diastereomer (>15:1 d.r.); ν_{max} / cm^{-1}: 2961 (m), 1687 (s), 1399 (m), 1315 (m), 1260 (m), 1137 (m), 733 (m), 701 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.34 – 7.20 (m, 3H, 2 × C**14**-H and C**15**-H), 7.15 – 7.09 (m, 2H, 2 × C**13**-H), 4.85 (d, *J* = 16.0 Hz, 1H, C**11**-H_aH_b), 4.51 (d, *J* = 16.0 Hz, 1H, C**11**-H_aH_b), 3.13 (dd, *J* = 9.6, 9.6 Hz, 1H, C**6**-H), 2.49 – 2.22 (m, 3H, C**1**-H_2 and C**3**-H_aH_b), 2.08 – 1.87 (m, 3H, C**3**-H_aH_b, C**4**-H and C**7**-H), 1.21 (s, 3H, C**9**-H_3), 1.06 – 1.02 (m, 6H, C**5**-H_3 and C**9'**-H_3); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 207.7 (C**2**), 181.7 (C**10**), 137.3 (C**12**), 128.8 (C**14**), 127.3 (C**13**), 126.9 (C**15**), 63.6 (C**6**), 50.3 (C**7**), 49.1 (C**3**), 45.9 (C**11**), 42.2 (C**8**), 39.3 (C**1**), 37.0 (C**4**), 23.2 (C**9**), 21.1 (C**9'**), 17.6 (C**5**); HRMS: (ESI^+) calculated for $C_{18}H_{23}NNaO_2$: 308.1621, found $[M+Na]^+$: 308.1616. The relative stereochemistry of this compound was corroborated by nOe experiments (as indicated on the compound structure) and assigned in analogy with **345**. No nOe was observed between C**6**-H and C**7**-H or between C**6**-H and C**4**-H. An nOe was observed between C**6**-H and C**5**-H_3.

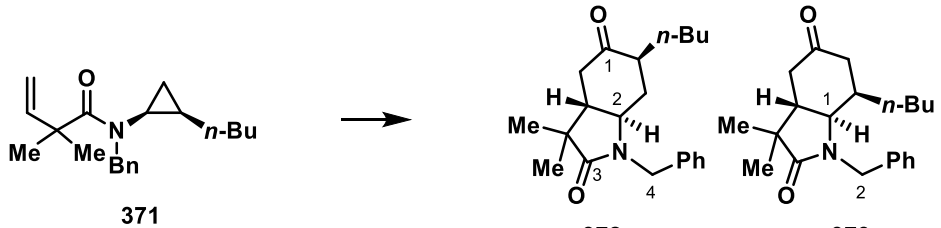
***N*-Benzyl-*N*-((1*S**,2*R**)-2-butylcyclopropyl)-2,2-dimethylbut-3-enamide (371)**



344 **371**

General procedure G: (1*S**,2*R**)-*N*-Benzyl-2-butylcyclopropan-1-amine (0.40 g, 1.97 mmol, prepared according to the literature procedure[53]) and acid **344** (0.22 g, 1.97 mmol) were employed and the residue was purified by flash column chromatography (10% EtOAc/hexane) to afford the title compound **371** (0.12 g, 20%) as a colourless oil; ν_{max} / cm^{-1}: 2958 (m), 2928 (m), 1647 (s), 1631 (s), 1467 (m), 1454 (m), 1389 (s), 713 (m), 696 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.34 – 7.28 (m, 2H, 2 × C**9**-H), 7.27 – 7.21 (m, 1H, C**10**-H), 7.15 (d, *J* = 6.9 Hz, 2H, 2 × C**8**-H), 6.09 (dd, *J* = 17.6, 10.7 Hz, 1H, C**2**-H), 5.14 – 5.08 (m, 2H, C**6**-H_aH_b and C**1**-H_{trans}), 5.05 (d, *J* = 10.7 Hz, 1H, C**1**-H_{cis}), 4.07 (d, *J* = 16.2 Hz, 1H, C**6**-H_aH_b), 2.69 (br. s, 1H, C**11**-H), 1.64 – 1.52 (m, 1H, C**14**-H_aH_b), 1.43 – 1.26 (m, 10H, 2 × C**4**-H_3, C**15**-H_2, C**16**-H_2), 1.08 – 0.95 (m, 1H, C**13**-H), 0.93 – 0.77 (m, 4H, C**14**-H_aH_b and C**17**-H_3), 0.70 – 0.57 (m, 1H, C**12**-H_aH_b), 0.19 (br. s, 1H, C**12**-H_aH_b); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 178.9 (C**5**), 144.1 (C**2**), 138.2 (C**7**), 128.6 (C**9**), 127.1 (C**10**), 127.0 (C**8**), 112.5 (C**1**), 52.2 (br., C**6**), 46.1 (C**3**), 35.0 (C**11**), 31.9 (C**15**), 27.8 (C**14**), 27.4 (C**4**), 26.4 (C**4'**), 22.8 (C**16**), 20.4 (C**13**), 14.3 (C**17**), 11.9 (br., C**12**); HRMS: (ESI^+) calculated for $C_{20}H_{30}NO$: 300.2322, found $[M+H]^+$: 300.2321.

(3a*S,7a*R**)-1-Benzyl-6-butyl-3,3-dimethylhexahydro-2*H*-indole-2,5(3*H*)-dione (372) and (3a*S**,7*R**,7a*R**)-1-benzyl-7-butyl-3,3-dimethylhexahydro-2*H*-indole-2,5(3*H*)-dione (373)**



371

372 3:1 d.r. **373** >20:1 d.r.

372:**373** = 6:1

An oven dried reaction tube, fitted with a magnetic stirrer, was charged with aminocyclopropane substrate **371** (29.9 mg, 0.10 mmol), $[Rh(cod)Cl]_2$ (2.5 mg, 0.005 mmol) and $P(4\text{-}OMeC_6H_4)_3$ (7.0 mg, 0.02 mmol). The tube was fitted with a rubber septum and purged with argon. Anhydrous PhCN (1.0 mL) was added and the reaction was sparged with CO for ca. 10 seconds. The tube was heated to 150 °C, under a CO atmosphere (1 balloon) and stirred for 72 h. The mixture was cooled

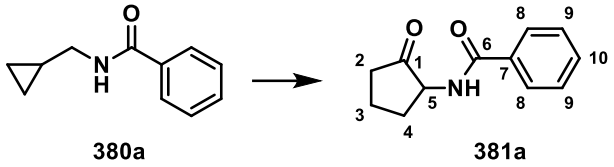
to r.t. and concentrated *in vacuo*. The residue was purified by flash column chromatography (10-25% EtOAc/hexane) to afford an unseparable mixture of **372** and **373** (10.8 mg, 33%, 6:1 r.r.) as a pale yellow oil.

NMR data for **372** (3:1 mixture of major **A** and minor **B** diastereomers, *characteristic signals only*): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.08 (d, *J* = 14.7 Hz, 1H, C**4**-$\underline{H}_aH_b$, **B**), 4.94 (d, *J* = 15.0 Hz, 1H, C**4**-$\underline{H}_aH_b$, **A**), 4.04 (d, *J* = 15.0 Hz, 1H, C**4**-$H_a\underline{H}_b$, **A**), 3.78 (d, *J* = 14.7 Hz, 1H, C**4**-$H_a\underline{H}_b$, **B**), 3.27 (ddd, *J* = 11.6, 10.2, 3.5 Hz, 1H, C**2**-$\underline{H}$, **A**), 3.20 (ddd, *J* = 11.9, 10.3, 4.2 Hz, 1H, C**2**-$\underline{H}$, **B**); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 209.1 (C**1**, **A**), 180.6 (C**3**, **A**), 56.6 (C**2**, **A**); HRMS: (ESI^+) calculated for $C_{21}H_{30}NO_2$: 328.2271, found $[M+H]^+$: 328.2275.

NMR data for **373** (>15:1 d.r., *characteristic signals only*): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.95 (d, *J* = 14.8 Hz, 1H, C**2**-$\underline{H}_aH_b$), 3.99 (d, *J* = 14.8 Hz, 1H, C**2**-$H_a\underline{H}_b$), 3.34 (dd, *J* = 10.8, 3.8 Hz, 1H, C**1**-$\underline{H}$).

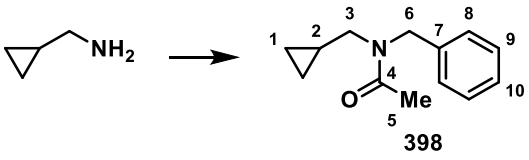
8.6 Experimental procedures for the studies in Chapter 5

N-(2-Oxocyclopentyl)benzamide (381a)



General procedure N: *N*-(Cyclopropylmethyl)benzamide **380a** (26.3 mg, 0.15 mmol, prepared according to the literature procedure[108]), $[Rh(cod)_2]OTf$ (5.3 mg, 0.01 mmol, 7.5 mol%), $P(3,4,5\text{-}F_3C_6H_2)_3$ (9.5 mg, 0.02 mmol, 15 mol%) and benzoic acid (3.7 mg, 0.03 mmol, 20 mol%) were employed and the reaction was stirred for 24 h at 110 °C. The crude mixture was purified by silica gel column chromatography (40% EtOAc/hexane) to yield the title compound **381a** (21.7 mg, 71%) as a yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, *J* = 7.0 Hz, 2H, 2 × C**8**-H), 7.44 (m, 1H, C**10**-H), 7.38 – 7.34 (m, 2H, 2 × C**9**-H), 4.24 (dddd, *J* = 12.5, 8.0, 5.5, 1.0 Hz, 1H, C**5**-H), 2.73 (m, 1H, C**4**-H_2), 2.41 (ddd, *J* = 20.0, 10.0, 1.0 Hz, 1H, C**2**-H_2), 2.20 (m, 1H, C**2**-H_2), 2.06 (m, 1H, C**3**-H_2), 1.87 (m, 1H, C**3**-H_2), 1.62 (m, 1H, C**4**-H_2); ^{13}C NMR ($CDCl_3$, 101 MHz,): δ 215.2 (C**1**), 167.7 (C**6**), 133.7 (C**7**), 131.8 (C**10**), 128.6 (C**9**), 127.1 (C**8**), 58.6 (C**5**), 34.9 (C**2**), 30.3 (C**4**), 18.1 (C**3**). The spectroscopic properties of this compound were consistent with the data available in the literature.[286] This compound was also obtained by Dr. McCreanor during the preliminary studies towards carbonylative cyclisation of **380a**.

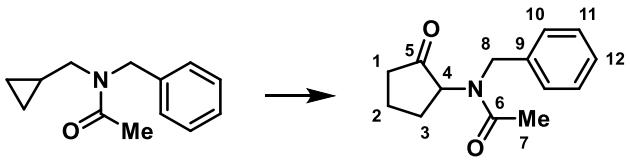
N-Benzyl-*N*-(cyclopropylmethyl)acetamide (398)



General procedure M: Cyclopropylmethylamine (0.21 g, 3.00 mmol), benzaldehyde (0.38 g, 3.60 mmol) and acetic anhydride (0.31 g, 3.60 mmol) were employed and the reaction was stirred at r.t. for 16 h. Flash column chromatography (40% EtOAc/hexane) afforded the title compound **398** (0.49 g, 80%, 1:1 mixture of rotamers *A*:*B*) as a pale yellow oil; ν_{max} / cm^{-1}: 3003 (m), 2926 (m), 1639 (s), 1420 (s), 1357 (m), 1249 (s), 1020 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): 7.38-7.13 (m, 10H, 2 × C**8**-H, 2 × C**9**-H, C**10**-H, *A*+*B*), 4.72 (s, 2H, C**6**-H_2, *A*), 4.64 (s, 2H, C**6**-H_2, *B*), 3.28 (d, *J* = 7.0 Hz, 2H, C**3**-H_2, *A*), 3.09 (d, *J* = 6.6 Hz, 2H, C**3**-H_2, *B*), 2.20 (s, 3H, C**5**-H_3, *A*), 2.11 (s, 3H, C**5**-H_3, *B*), 1.02-0.83 (m, 2H, C**2**-H, *A*+*B*), 0.56-0.49 (m, 2H, C**1**-H_2, *A*), 0.48-0.40 (m, 2H, C**1**-H_2, *B*), 0.20-0.10 (m, 4H, C**1**-H_2, *A*+*B*); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 171.1 (C**4**, *B*), 170.5 (C**4**, *A*),

137.7 (C**7**, *A*), 137.0 (C**7**, *B*), 128.8, 128.5, 127.8, 127.4, 127.1, 126.2 (C**7**, C**8** and C**9**, *A*+*B*), 52.0 (C**3**, *B*), 51.8 (C**6**, *B*), 49.8 (C**3**, *A*), 47.9 (C**6**, *A*), 21.8 (C**5**, *B*), 21.7 (C**5**, *A*), 10.0, 9.6 (C**2**, *A*+*B*), 3.7, 3.6 (C**1**, *A*+*B*); HRMS: (ESI$^+$) calculated for $C_{13}H_{18}NO$: 204.1383, found $[M+H]^+$: 204.1379.

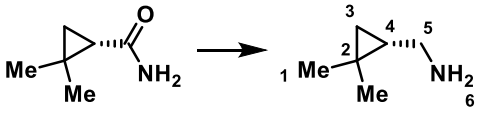
N-Benzyl-*N*-(2-oxocyclopentyl)acetamide (399)



398 399

General procedure N: Compound **36** (30.5 mg, 0.15 mmol), $[Rh(cod)_2]OTf$ (5.3 mg, 0.011 mmol, 7.5 mol%) and $P(3,4,5\text{-}F_3C_6H_2)_3$ (9.5 mg, 0.023 mmol, 15 mol%) were employed and the reaction was stirred for 18 h at 110 °C. The crude mixture was purified by silica gel column chromatography (40% EtOAc/hexane) to yield the title compound **37** (34.0 mg, 98%) as a colourless solid; m.p. 124-125 °C; ν_{max} / cm^{-1}: 2964 (m), 1742 (s), 1636 (s), 1429 (s), 1363 (s), 1251 (s), 1153 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.40-7.26 (m, 5H, 2 × C**10**-H, 2 × C**11**-H, C**12**-H), 4.57 (s, 2H, C**8**-H_2), 3.53 (t, *J* = 9.8 Hz, 1H, C**4**-H), 2.48 (ddd, *J* = 18.4, 11.9, 9.2 Hz, 1H, C**1**-H_aH_b), 2.26-1.94 (m, 4H, C**1**-H_aH_b, C**2**-H_aH_b, 2 × C**3**-H_2), 2.11 (s, 3H, C**7**-H_3), 1.68-1.53 (m, 1H, C**2**-H_aH_b); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 213.4 (C**5**), 170.1 (C**6**), 136.6 (C**9**), 128.9 (C**11**), 127.8 (C**12**), 126.6 (C**10**), 64.4 (C**4**), 53.7 (C**8**), 35.8 (C**1**), 27.0 (C**3**), 21.6 (C**7**), 19.1 (C**2**); HRMS: (ESI$^+$) calculated for $C_{14}H_{18}NO_2$: 232.1332, found $[M+H]^+$: 232.1333.

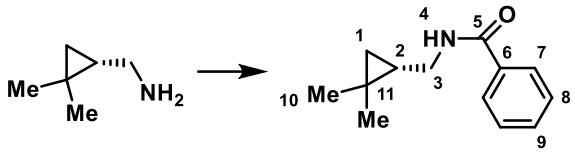
(2,2-Dimethylcyclopropyl)methanamine (401)



400 401

General procedure B: Amide **400** (1.00 g, 8.84 mmol) was employed. The title compound **401** (0.640 g, 73 %) was isolated as a colourless oil and used in the next step without purification; ν_{max} / cm^{-1}: 2946 (m), 2926 (m), 1656 (m), 1626 (m), 1455 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.71-2.55 (m, 2H, C**5**-H_2), 1.06 (s, 3H, C**1**-H_3), 1.04 (s, 3H, C**1**-H_3), 0.69 (dddd, *J* = 8.5, 7.6, 6.9, 5.3 Hz, 1H, C**4**-H), 0.40 (dd, *J* = 8.5, 4.3 Hz, 1H, C**3**-H), -0.01 (app. t, *J* = 4.8 Hz, 1H, C**3**-H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 42.0 (C**5**), 27.1 (C**1**), 24.9 (C**4**), 19.8 (C**3**), 18.8 (C**2**); HRMS: (ESI$^+$) calculated for $C_6H_{14}N$: 100.1121, found $[M+H]^+$: 100.1118

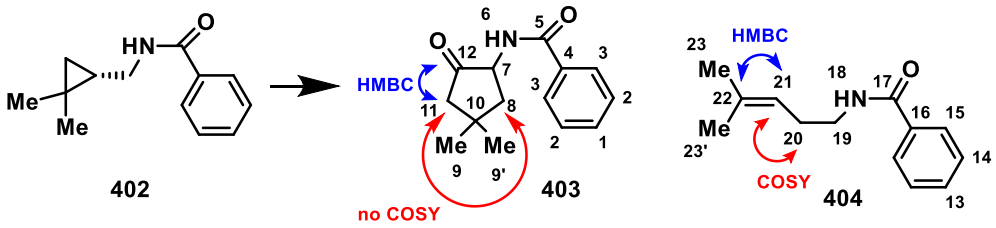
(*S*)-*N*-((2,2-Dimethylcyclopropyl)methyl)benzamide (402)



400 401

General procedure D: Amine (0.30 g, 3.02 mmol) and benzoyl chloride (0.51 g, 3.62 mmol) were employed and the reaction was stirred at r.t. for 16 h. Flash column chromatography (20% EtOAc/hexane) afforded the title compound **402** (0.369 g, 60%) as a colourless solid; m.p. 58-59 °C; ν_{max} / cm^{-1}: 3310 (m), 2944 (m), 1635 (s), 1539 (s), 1310 (m), 1593 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): 7.79-7.75 (m, 2H, 2 × C**7**-H), 7.53-7.41 (m, 3H, C**9**-H, and 2 × C**8**-H), 6.10 (br. s, 1H, N**4**-H), 3.55-3.35 (m, 2H, C**3**-H_2), 1.15 (s, 3H, C**10**-H_3), 1.09 (s, 3H, C**10**-H_3), 0.90-0.82 (m, 1H, C**2**-H), 0.58-0.50 (m, 1H, C**1**-H), 0.23-0.14 (m, 1H, C**1**-H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 167.3 (C**5**), 134.9 (C**6**), 131.3 (C**9**), 128.5 (C**8**), 126.8 (C**7**), 41.2 (C**3**), 27.2 (C**10**), 23.7 (C**2**), 20.0 (C**1**), 18.9 (C**10**), 16.0 (C**11**); HRMS: (ESI^+) calculated for $C_{13}H_{18}CNO$: 204.1383, found $[M+H]^+$: 204.1388.

***N*-(4,4-Dimethyl-2-oxocyclopentyl)benzamide (403) and *N*-(4-Methylpent-3-en-1-yl)benzamide (404)**



402 403 404

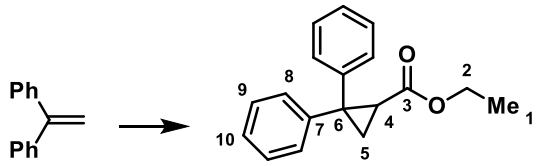
General procedure N: (*S*)-*N*-((2,2-Dimethylcyclopropyl)methyl)benzamide (30.49 mg, 0.15 mmol), $[Rh(cod)_2]OTf$ (5.3 mg, 0.011 mmol, 7.5 mol%), $P(3,4,5\text{-}F_3C_6H_2)_3$ (9.5 mg, 0.023 mmol, 15 mol%) and benzoic acid (3.7 mg, 0.030 mmol, 20 mol%) were employed and the reaction was stirred at 120 °C for 24 h. Flash column chromatography (2-20% EtOAc/hexane) afforded compounds **403** (1.6 mg, 5%) and **404** (8.2 mg, a mixture with starting material and other by-products) as colourless oils. *Alkene **404** could not be readily separated from the starting material and other alkene isomers, the structure of the alkene products was determined by analysis of the ^{1}H NMR spectrum of the reaction mixture and corroborated by HMBC, HSQC and COSY data.*

Data for compound **403**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.81-7.76 (2H, m, 2 × C**3**-H), 7.54-7.48 (2H, m, C**1**-H), 7.47-7.41 (2H, m, 2 × C**2**-H), 6.50 (br. s, 1H, N**6**-H), 4.53 (ddd, *J* = 12.3, 8.5, 5.7 Hz, 1H, C**7**-H), 2.55 (ddd, *J* = 12.3, 8.5, 2.2 Hz, 1H, C**8**-H), 2.39-2.31 (m, 1H, C**11**-H), 2.22 (d, *J* = 19.0 Hz, 1H, C**11**-H), 1.71 (app. t, *J* = 12.3 Hz, 1H, C**8**-H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ

215.1 (C**12**), 171.8 (C**5**), 31.8 (C**1**), 128.6 (C**3**), 127.0 (C**2**), 57.5 (C**7**), 50.4 (C**11**), 43.8 (C**12**), 32.5 (C**8**), 30.3 (C**9**), 31.9 (C**10**), 28.8 (C**9**); HRMS: (ESI^+) calculated for $C_{14}H_{17}NNaO_2$: 254.1151, found $[M+Na]^+$: 254.1155.

Data for compound **404**: ^1H NMR ($CDCl_3$, 400 MHz, *characteristic signals only*): δ 6.16 (br. s, 1H, N**18**-H), 5.16 (dddd, *J* = 7.3, 5.9, 2.9, 1.5 Hz, 1H, C**21**-H), 2.37-2.28 (m, 2H, C**20**-H_2), 1.73 (s, 3H, C**23**-H_3), 1.65 (s, 3H, C**23**-H_3); ^{13}C NMR ($CDCl_3$, 101 MHz, *characteristic signals only*): δ 167.4 (C**17**), 134.9 (C**22**), 131.4 (C**13**), 128.8 (C**14**), 126.9 (C**15**), 120.7 (C**21**), 39.8 (C**19**), 28.1 (C**20**), 25.8 (C**23**), 17.9 (C**23**).

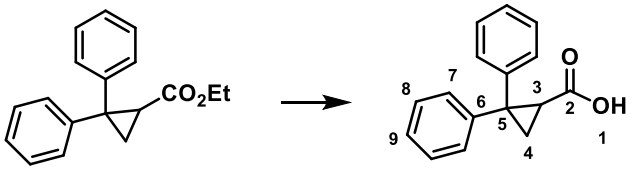
Ethyl 2,2-diphenylcyclopropane-1-carboxylate (407)



407

To a solution of $Rh_2(OAc)_4$ (36.78 mg, 0.003 eq) and 1,1-diphenylethylene (5.00 g, 27.74 mmol) in anhydrous Et_2O (70 mL) was added a solution of ethyl diazoacetate (4.75 g, 41.61 mmol) in Et_2O (12 mL) dropwise by syringe pump over 8 h. The reaction mixture was diluted with petrol (50 mL), filtered through a pad of silica and concentrated *in vacuo*. The crude mixture was purified by silica gel column chromatography (5% EtOAc/hexane) to yield the title compound **407** (5.99 g, 81%) as a yellow oil; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.36–7.18 (m, 10H, 2 ×C**10**-H, 4 × C**9**-H and 4 × C**8**-H), 3.91 (m, 2H, C**2**-H_2), 2.54 (dd, *J* = 8.2, 5.9 Hz, 1H, C**5**-H_2), 2.17 (dd, *J* = 5.9, 4.8 Hz, 1H, C**4**-H), 1.59 (dd, *J* = 8.2, 4.8 Hz, 1H, C**5**-H_2), 1.01 (t, *J* = 7.1 Hz, 3H, C**1**-H_3); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 170.73 (C**3**), 144.99 (C**7**), 140.38 (C**7**), 129.88 (C**9**), 128.55 (C**9**), 128.38 (C**8**), 127.69 (C**8**), 127.06 (C**10**), 126.61 (C**10**), 60.53 (C**2**), 39.91 (C**6**), 29.16 (C**4**), 20.21 (C**5**), 14.12 (C**1**). The spectroscopic properties of this compound were consistent with the data available in the literature.[17]

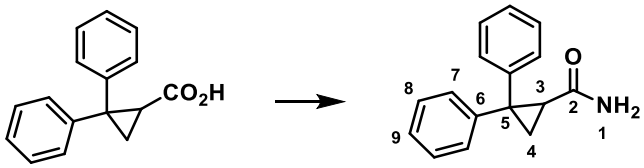
2,2-Diphenylcyclopropane-1-carboxylic acid (30)



407 **408**

Ester **407** (5.00 g, 18.77 mmol) was dissolved in a mixture of 1,4-dioxane and water (1:1, 80 mL), then potassium hydroxide pellets (5.26 g, 93.87 mmol) were added and the reaction mixture was stirred at 80 °C for 4h. The reaction mixture was concentrated *in vacuo*, diluted with water (100 mL) and extracted with Et_2O (50 mL). The aqueous portion was adjusted to pH 2 by addition of 2.0 M aq. HCl and then extracted with Et_2O (3 × 50 mL). The organic extracts were combined, washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the title compound **408** (4.48 g, 99%) as a colourless solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.9 (br. s, 1H, O**1**-H), 7.19-7.38 (m, 10H, 2 ×C**9**-H, 4 × C**8**-H and 4 × C**7**-H), 2.52 (dd, *J* = 8.0, 5.8 Hz, 1H, C**4**-H_2), 2.15 (dd, *J* = 5.8, 4.9 Hz, 1H, C**3**-H), 1.70 (dd, J = 8.0, 4.9 Hz, 1H, C**4**-H_2); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 176.9 (C**2**), 144.5 (C**6**), 139.7 (C**6**), 129.5 (C**8**), 128.5 (C**8**), 128.3 (C**7**), 127.5 (C**7**), 127.0 (C**9**), 126.6 (C**9**), 41.0 (C**5**), 28.5 (C**3**), 20.7 (C**4**). The spectroscopic properties of this compound were consistent with the data available in the literature.[18]

2,2-Diphenylcyclopropane-1-carboxamide (409)



408 **409**

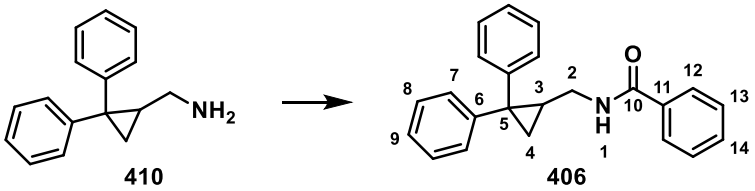
General procedure L: Acid **408** (2.00 g, 8.39 mmol) and oxalyl chloride (1.48 mL, 16.78 mmol) were employed. The title compound **409** (1.95 g, 98%) was isolated as a colourless solid; ^{1}H NMR ($CDCl_3$, 400 MHz): 7.40-7.12 (m, 10H, 2 ×C**9**-H, 4 × C**8**-H and 4 × C**7**-H), 5.36 (br. s, 2H, N**1**-H_2), 2.35 (dd, *J* = 8.3, 6.0 Hz, 1H, C**4**-H_2), 2.12 (dd, *J* = 6.0, 5.0 Hz, 1H, C**3**-H), 1.64 (dd, *J* = 8.3, 5.0 Hz, 1H, C**4**-H_2); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 171.5 (C**2**), 145.1, 139.8, 129.8, 128.5, 127.3, 127.1, 126.5 (C**6**, C**7**, C**8** and C**9**), 39.20 (C**5**), 30.620 (C**3**), 20.20 (C**4**). The spectroscopic properties of this compound were consistent with the data available in the literature.[19]

(2,2-Diphenylcyclopropyl)methanamine (410)

409 **410**

General procedure K: Amide **409** (1.00 g, 4.21 mmol) and $LiAlH_4$ (0.26 g, 6.85 mmol) were employed. The title compound **410** (0.76 g, 81 %) was isolated as a yellow oil and used in the next step without purification; ν_{max} / cm^{-1}: 3056 (m), 3023 (m), 1598 (m), 1494 (s), 1445 (s), 1308 (m), 1028 (m); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.39-7.14 (m, 10H, 2 ×C**9**-H, 4 × C**8**-H and 4 × C**7**-H), 2.63 (dd, *J* = 13.1, 7.0 Hz, 1H, C**2**-H_2), 2.40 (dd, *J* = 13.1, 7.0 Hz, 1H, C**2**-H_2), 1.86 (dtd, *J* = 8.8, 7.0, 5.9 Hz, 1H, C**3**-H), 1.35 (dd, *J* = 5.9, 4.9 Hz, 1H, C**4**-H_2), 1.28 (br. s, 2H, N**1**-H_2), 1.25 (dd, *J* = 8.8, 4.9 Hz, 1H, C**4**-H_2); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 146.7 (C**6**), 141.4 (C**6**), 130.1 (C**8**), 128.3 (C**8**), 128.2 (C**7**), 127.9 (C**7**), 126.4 (C**9**), 125.8 (C**9**), 43.5 (C**2**), 34.4 (C**5**), 29.1 (C**3**), 18.9 (C**4**); HRMS: (ESI^+) calculated for $C_{16}H_{18}N$: 224.1434, found $[M+H]^+$: 224.1430.

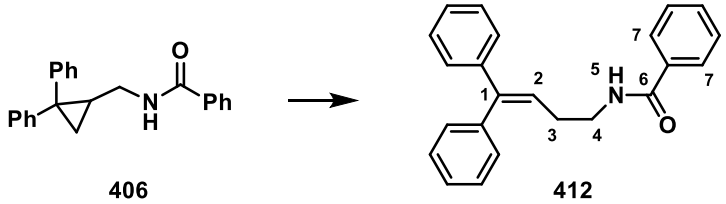
***N*-((2,2-Diphenylcyclopropyl)methyl)benzamide (406)**



410 **406**

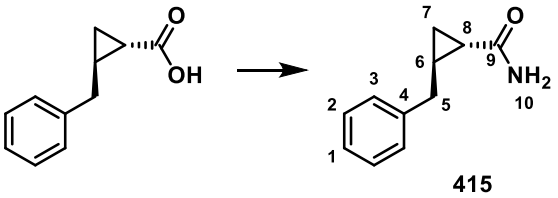
General procedure D: Amine **410** (0.76 g, 3.40 mmol) and benzoyl chloride (0.47 mL, 4.08 mmol) were employed. The crude mixture was purified by silica gel column chromatography (20-40% EtOAc/hexane) to yield the title compound **406** (0.92 g, 83%) as a colourless solid; m.p. 102-103 °C; ν_{max} / cm^{-1}: 3312 (m), 3059 (m), 3025 (m), 1634 (s), 1538 (s), 1491 (s), 1294 (m), 1035 (m); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.73-7.68 (m, 2H, 2 ×C**12**-H), 7.56-7.14(m, 13H, 2 ×C**9**-H, 4 × C**8**-H, 4 × C**7**-H, 2 × C**13**-H and C**14**-H), 6.05(br. s, 1H, N**1**-H), 3.35 (dd, *J* = 7.1, 5.8 Hz, 2H, C**2**-H_2), 2.12 (dtd, *J* = 8.8, 7.1, 5.8 Hz, 1H, C**3**-H), 1.50 (m, 1H, C**4**-H_2), 1.32 (dd, *J* = 8.8, 5.0 Hz, 1H, C**4**-H_2); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 167.2 (C**10**), 146.0 (C**6**), 141.0 (C**6**), 134.6 (C**11**), 131.4, 130.1, 128.7, 128.6, 128.3, 127.8, 126.9, 126.8, 126.1(C**7**, C**8**, C**9**, C**12**, C**13** and C**14**), 41.1 (C**2**), 35.2 (C**5**), 25.1 (C**3**), 18.9 (C**4**); HRMS: (ESI^+) calculated for $C_{23}H_{23}NO$: 328.1696, found $[M+H]^+$: 328.1704.

***N*-(4,4-Diphenylbut-3-en-1-yl)benzamide (412)**



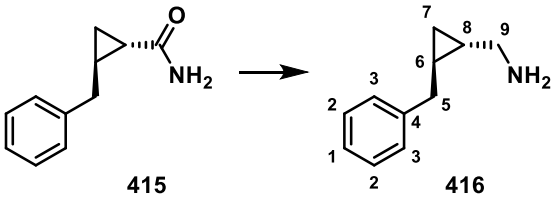
General procedure N: Amide **406** (49.1 mg, 0.15 mmol), $[Rh(cod)_2]OTf$ (5.3 mg, 0.011 mmol, 7.5 mol%), $P(3,4,5\text{-}F_3C_6H_2)_3$ (9.5 mg, 0.023 mmol, 15 mol%) and benzoic acid (3.70 mg, 0.030 mmol, 20 mol%) were employed and the reaction was stirred at 160 °C for 24 h. Flash column chromatography (20-40% EtOAc/hexane) afforded compound **412** (33.2 mg, 68%) as a colourless solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.70 (d, *J* = 6.9 Hz, 2H, 2 × C**7**-H), 7.52-7.10 (m, 13 H, Ar-H), 6.11 (t, *J* = 7.5 Hz, 1H, C**2**-H), 6.10 (br. s, 1H, N**5**-H), 3.56 (app. q, *J* = 6.8 Hz, 2H, C**4**-H_2), 2.46 (app. q, *J* = 7.1 Hz, 2H, C**3**-H_2); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 167.5 (C**6**), 144.3(C**1**), 142.2, 139.7, 134.3, 131.2, 129.6, 128.4, 128.3, 128.1, 127.4, 127.3, 126.8 (Ar-C), 125.6 (C**2**), 39.9 (C**4**), 30.0 (C**3**). The spectroscopic properties of this compound were consistent with the data available in the literature.[20]

(1*S,2*R**)-2-Benzylcyclopropane-1-carboxamide (415)**



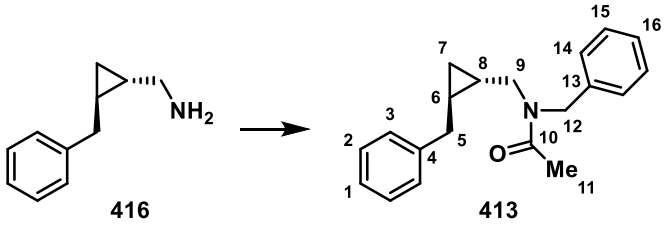
General procedure L: (1*R**,2*S**)-2-Benzylcyclopropane-1-carboxylic acid (1.65 g, 9.36 mmol, prepared according to the literature procedure[48]) and oxalyl chloride (1.65 mL, 18.73 mmol) were employed. The title compound **415** (1.64 g, 99%) was isolated as a colourless solid; m.p. 114-115 °C (DCM/hexane); ν_{max} / cm^{-1}: 3333 (br. m), 3166 (br. m), 1651 (s), 1620 (s), 1454 (s), 1428 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.32-7.18 (m, 5H, C**1**-H, 2 × C**2**-H and 2 × C**3**-H), 5.50 (br. s, 1H, N**10**-H_2), 5.27 (br. s, 1H, N**10**-H_2), 2.71 (dd, *J* = 14.6, 6.8 Hz, 1H, C**5**-H_2), 2.65 (dd, *J* = 14.6, 6.9 Hz, 1H, C**5**-H_2), 1.76-1.65 (m, 1H, C**6**-H), 1.32-1.22 (m, 2H, C**7**-H_aH_b and C**8**-H), 0.83-0.76 (m, 1H, C**7**-H_aH_b); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 175.5 (C**9**), 140.2 (C**4**), 128.4, 128.3 (C**2** and C**3**), 126.2 (C**1**), 38.4 (C**5**), 22.1 (C**8**), 21.4 (C**6**), 14.7 (C**7**); HRMS: (ESI^+) calculated for $C_{11}H_{14}NO$: 176.1070, found $[M+H]^+$: 176.1071.

((1*S,2*R**)-2-Benzylcyclopropyl)methanamine (416)**



General procedure K: Amide **415** (1.50 g, 8.56 mmol) and was employed. The title compound **416** (1.00 g, 73 %) was isolated as a pale yellow oil and used in the next step without purification; ν_{max} / cm^{-1}: 3026 (m), 2997 (m), 2912 (m), 2849 (m), 1574 (s), 1495 (s), 1453 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.32-7.16 (m, 5H, C**1**-H, 2 × C**2**-H and 2 × C**3**-H), 2.64-2.50 (m, 4H, C**5**-H_2 and C**9**-H_2), 0.89-0.77 (m, 2H, C**6**-H and C**8**-H), 0.41 (ddd, *J* = 15.7, 8.0, 4.9 Hz, 2H, C**7**-H_2); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 142.0 (C**4**), 128.3, 128.3 (C**2** and C**3**), 125.9 (C**1**), 46.5 (C**9**), 39.6 (C**5**), 22.4 (C**8**), 18.6 (C**6**), 10.5 (C**7**); HRMS: (ESI^+) calculated for $C_{11}H_{16}N$: 162.1277, found $[M+H]^+$: 162.1280.

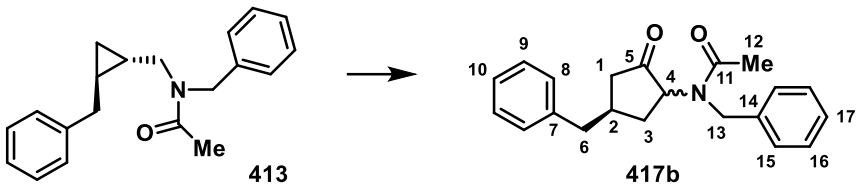
***N*-Benzyl-*N*-(((1*S**,2*R**)-2-benzylcyclopropyl)methyl)acetamide (413)**



General procedure M: Amine **416** (1.99 g, 12.34 mmol), benzaldehyde (1.38 g, 12.96 mmol) and acetic anhydride (1.40 mL, 14.81 mmol) were employed and the reaction was stirred at r.t. for 18 h. Flash column chromatography (30% EtOAc/pentane) afforded the title compound **413** (2.49 g, 69%, 1:1.3 mixture of rotamers *A*:*B*) as a colourless oil; ν_{max} / cm^{-1}: 3026 (br. m), 2998 (br. m), 2917 (br. m), 1641 (s), 1419 (s), 1246 (s), 1028 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.37 – 7.04 (m, 20H, 2 × C**1**-H, 2 × C**2**-H, C**3**-H, 2 × C**14**-H, 2 × C**15**-H, C**16**-H, *A*+*B*), 4.66 (d, *J* = 15.1 Hz, 1H, C**12**-H_2, *A*), 4.46 (d, *J* = 15.1 Hz, 1H, C**12**-H_2, *A*), 4.35 (d, *J* = 17.2 Hz, 1H, C**12**-H_2, *B*), 4.29 (d, *J* = 17.2 Hz, 1H, C**12**-H_2, *B*), 3.51 (dd, *J* = 14.0, 5.5 Hz, 1H, C**5**-H_2, *B*), 3.25 (dd, *J* = 15.1, 5.4 Hz, 1H, C**5**-H_2, *A*), 3.08 – 2.92 (m, 2H, C**5**-H_2, *A*+*B*), 2.65 (dd, *J* = 14.4, 5.8 Hz, 1H, C**9**-H_2, *B*), 2.56 – 2.48 (m, 2H, C**9**-H_2, *A*), 2.38 – 2.30 (m, 1H, C**9**-H_2, *B*), 2.17 (s, 3H, C**11**-H_3, *A*), 2.04 (s, 3H, C**11**-H_3, *B*), 0.96 – 0.76 (m, 4H, C**6**-H and C**8**-H, *A*+*B*), 0.53 – 0.35 (m, 4H, C**7**-H, *A*+*B*); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 171.0 (C**10**, *B*), 170.3 (C**10**, *A*), 141.9 (C**4**, *A*), 141.1 (C**4**, *B*), 137.7 (C**13**, *A*), 136.9 (C**13**, *B*), 128.8, 128.5, 128.4, 128.4, 128.3, 128.2, 127.8, 127.4, 127.1, 126.2,

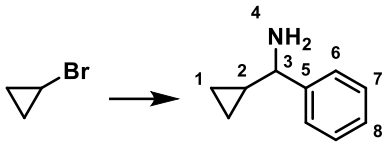
126.1, 125.9 (C**1**, C**2**, C**3**, C**14**, C**15** and C**16**, *A*+*B*), 51.3 (C**12**, *B*), 51.3 (C**5**, *A*), 48.8 (C**5**, *B*), 47.7 (C**12**, *A*), 39.5 (C**9**, *B*), 39.2 (C**9**, *A*), 21.7 (C**11**, *B*), 21.7 (C**11**, *A*), 19.7 (C**6**, *A*), 19.4 (C**6**, *B*), 17.5 (C**8**, *A*), 17.0 (C**8**, *B*), 10.7 (C**7**, *A*+*B*); HRMS: (ESI$^+$) calculated for $C_{20}H_{24}NO$: 294.1852, found $[M+H]^+$: 294.1865.

N-Benzyl-*N*-((4*R**)-4-benzyl-2-oxocyclopentyl)acetamide (417b)



General procedure N: Compound **413** (44.0 mg, 0.15 mmol), $[Rh(cod)_2]BARF$ (13.3 mg, 0.011 mmol, 7.5 mol%) and $P(3,4,5\text{-}F_3C_6H_2)_3$ (9.5 mg, 0.023 mmol, 15 mol%) were employed and the reaction was stirred for 24 h at 120 °C. The crude mixture was purified by silica gel column chromatography (1% MeOH/DCM) to yield the title compound **417b** (25.1 mg, 52%, 1:2.2 mixture of diastereomers *A*:*B*) as a light brown oil; ν_{max} / cm^{-1}: 2922 (br. w), 1747 (s), 1643 (s), 1453 (s), 1432 (s), 740 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.43 – 7.01 (m, 20H, 2 × C**8**-H, 2 × C**9**-H, C**10**-H, 2 × C**15**-H, 2 × C**16**-H, C**17**-H, *A*+*B*), 4.61 – 4.47 (m, 4H, C**13**-H_2, *A*+*B*), 3.55 – 3.44 (m, 2H, C**4**-H, *A*+*B*), 2.82 – 2.67 (m, 3H, C**3**-H_2, *B* and C**2**-H, *A*), 2.56 – 2.52 (m, 2H, C**3**-H_2, *A*), 2.35 – 1.96 (m, 5H, C**1**-H_2, *A*+*B* and C**2**-H, *B*), 2.12 (s, 3H, C**7**-H_3, *B*), 2.11 (s, 3H, C**7**-H_3, *A*); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 213.0 (C**5**, *A*), 212.0 (C**5**, *B*), 170.1 (C**11**, *B*), 170.0 (C**11**, *A*), 140.0 (C**7**, *B*), 139.7 (C**7**, *A*), 136.4 (C**14**, *B*), 136.3 (C**14**, *A*), 129.0, 128.9, 128.8, 128.6, 128.4, 128.4, 127.9, 127.8, 126.8, 126.6, 126.2, 126.2 (C**8**, C**9**, C**10**, C**15**, C**16** and C**17**, *A*+*B*), 65.2 (C**4**, *B*), 62.1 (C**4**, *A*), 54.1 (C**13**, *A*), 53.8 (C**13**, *B*), 42.6 (C**3**, *B*), 42.5 (C**3**, *A*), 41.7 (C**1**, *B*), 41.5 (C**1**, *A*), 35.0 (C**2**, *B*), 34.3 (C**2**, *A*), 33.1 (C**6**, *B*), 32.5 (C**6**, *A*), 21.6 (C**12**, *B*), 21.5 (C**12**, *A*); HRMS: (ESI$^+$) calculated for $C_{21}H_{24}NO_2$: 322.1802, found $[M+H]^+$: 322.1812.

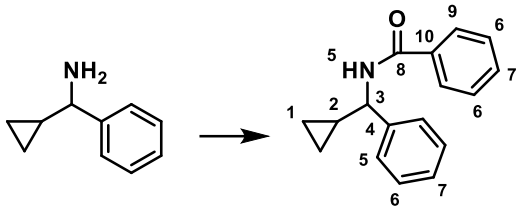
Cyclopropyl(phenyl)methanamine (423)



423

The title compound was prepared following a literature procedure.[287] A flame-dried flask was charged with a stirring bar and Mg turnings (0.73 g, 30 mmol, 4.00 eq), heated with a heatgun under high vacuum and then the turnings were suspended in 50 ml of dry THF. Bromocyclopropane (3.59 mL, 45 mmol, 4.50 eq) was added dropwise at 0 °C, the reaction was warmed to r.t. and stirred for ~1 h until complete consumption of Mg turnings. The resulting solution was added dropwise to the solution of benzonitrile (1.10 mL, 10 mmol, 1.00 eq) in dry THF (10 mL) at 0 °C over a period of 10 minutes under nitrogen atmosphere. The reaction was stirred at 0 °C for 5 h, then 30 mL of MeOH was added dropwise and $NaBH_4$ (0.80 g, 20.9 mmol, 2.10 eq) was added batchwise. The mixture was warmed to r.t. and stirred for 18 h. The solution was concentrated *in vacuo* the and then water (5 mL/mmol) and chloroform (5 mL/mmol) were added. The resulting solution was adjusted to pH 2 by addition of aq. 2 M HCl and phases were separated. The aqueous layer was extracted with chloroform (3 × 5 mL/mmol), then adjusted to pH 9 by addition of aq. 10% NaOH and again extracted with chloroform (3 × 5 mL/mmol). The organic extracts were combined, washed with brine (5 mL/mmol), dried over $MgSO_4$ and concentrated *in vacuo* to afford the title compound **423** as a pale yellow oil (1.47 g, 99%) which was used in the following step without further purification; ν_{max} / cm^{-1}: 3077 (m), 3001 (m), 1602 (m), 1492 (m), 1452 (m) 1046 (m), 1017 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.42-7.39 (m, 2H, 2 × C**6**-H), 7.37-7.31 (m, 2H, 2 × C**7**-H), 7.28-7.23 (m, 1H, C**8**-H), 3.21 (d, *J* = 8.6 Hz, 1H, C**3**-H), 1.66 (br. s, 2H, N**4**-H_2), 1.15-1.05 (m, 1H, C**2**-H), 0.64-0.56 (m, 1H, C**1**-H_aH_b), 0.52-0.43 (m, 1H, C**1**-H_aH_b), 0.37-0.24 (m, 2H, C**1**-H_2); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 145.4 (C**5**), 128.4 (C**7**), 127.0 (C**6**), 126.5 (C**8**), 60.8 (C**3**), 19.7 (C**2**), 4.0 (C**1**), 3.2 (C**1**); m/z (EI^+): 147 ($[M]^+$, 10%), 119 ($[M-C_2H_4]^+$, 40%), 106 ($[M-C_3H_5]^+$, 100%).

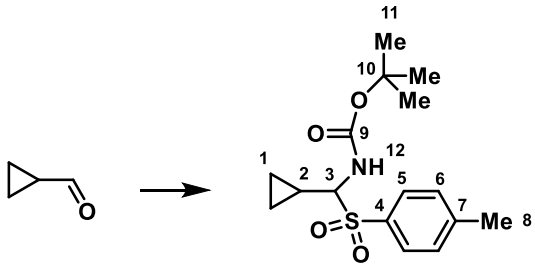
***N*-[Cyclopropyl(phenyl)methyl]benzamide (421a)**



423 **421a**

General procedure D: Amine **423** (0.73 g, 5.00 mmol) and benzoyl chloride (0.70 mL, 6.00 mmol) were employed and the reaction was stirred at r.t. for 16 h. The residue was purified by recrystallization (EtOAc/hexane) to afford the title compound **421a** (0.65 g, 56%) as a crystalline colourless solid; m.p. 107-108 °C; ν_{max} / cm^{-1}: 3338 (m), 3074 (m), 2999 (m), 1630 (s), 1521 (s), 1490 (s), 1317 (m), 1018 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.84-7.77 (m, 2H, 2 × C**9**-H), 7.54-7.24 (m, 8H, 2 × C**5**-H, 4 × C**6**-H, 2 × C**7**-H), 6.50 (d, *J* = 7.9 Hz, 1H, N**5**-H), 4.66 (app. t, *J* = 8.3 Hz, 1H, C**3**-H), 1.32-1.21 (m, 1H, C**2**-H), 0.71-0.52 (m, 3H, C**1**-H_aH_b and 2 × C**1**-H_2), 0.50-0.42 (m, 1H, C**1**-H_aH_b); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 168.5 (C**8**), 142.0 (C**4**), 131.5 (C**10**), 128.6, 128.5, 127.3, 127.3, 126.9, 126.7 (10 × Ar-CH), 57.5 (C**3**), 16.8 (C**2**), 4.1 (C**1**), 3.7 (C**1**); HRMS: (ESI^+) calculated for $C_{17}H_{17}NNaO$: 274.1202, found $[M+Na]^+$: 274.1202.

***tert*-Butyl [cyclopropyl(tosyl)methyl]carbamate (424)**

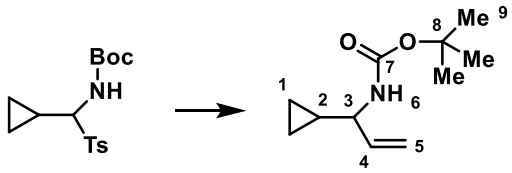


424

The title compound was prepared following a literature procedure.[288] To a stirring solution of *tert*-butyl carbamate (0.70 g, 5.98 mmol) and sodium *p*-toluenesulfinate (1.18 g, 6.62 mmol) in H_2O/MeOH (2:1 v/v, 30 mL) cyclopropanecarboxaldehyde (0.50 mL, 3.97 mmol) and formic acid (0.89 mL, 23.50 mmol) were added at room temperature. The mixture was stirred for 48 h. The resulting off-white precipitate was filtered off, triturated with copious amounts of 10% DCM in petroleum spirit and dried under high vacuum to afford pure α-amido sulfone (3.94 g, 78%) as a colourless solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.82 (d, *J* = 8.0 Hz, 2H, 2 × C**5**-H), 7.35 (d, *J* = 8.0 Hz, 2H, 2 × C**6**-H), 5.17 (d, *J* = 11.5 Hz, 1H, N**12**-H), 4.34 (app. t, *J* = 10.0 Hz, 1H, C**3**-H),

2.42 (s, 3H, C**8**-H$_3$), 1.39-1.32 (m, 1H, C**2**-H), 1.25 (s, 9H, 3 × C**11**-H$_3$), 0.83-0.74 (m, 1H, C**1**-H$_a$H$_b$–C**1**-H$_a$H$_b$), 0.70-0.61 (m, 1H, C**1**-H$_a$H$_b$–C**1**-H$_a$H$_b$), 0.61-0.53 (m, 1H, C**1**-H$_a$H$_b$–C**1**-H$_a$H$_b$), 0.45-0.37 (m, 1H, C**1**-H$_a$H$_b$–C**1**-H$_a$H$_b$); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 153.8 (C**9**), 145.0 (C**7**), 134.5 (C**4**), 129.6 (C**6**), 129.2 (C**5**), 80.5 (C**3**), 74.3 (C**10**), 27.7 (C**11**), 21.3 (C**8**), 9.0 (C**2**), 4.2 (C**1**), 2.0 (C**1**); The spectroscopic properties of this compound were consistent with the data available in the literature.[289]

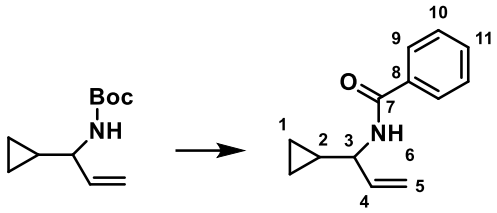
tert-Butyl (1-cyclopropylallyl)carbamate (425)



424 **425**

The title compound was prepared following an adapted literature procedure.[288] To a stirring solution of **424** (3.90 g, 12.00 mmol) in dry THF, vinylmagnesium bromide (28 mL, 1.0 M in THF, 28.00 mmol) was added dropwise over 10 min at -78 °C. The reaction mixture was warmed to r.t. and stirred for 2 h. The reaction was quenched with sat. aq. NH_4Cl (2 mL/mmol) at 0 °C and warmed to r.t. The solution was extracted with Et_2O (3 × 75 mL) and the organic extracts were combined, washed with brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (20% EtOAc/hexane) to afford the title compound **425** (1.47 g, 62%) as a colourless oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.80 (ddd, *J* = 17.0, 10.5, 5.0 Hz, 1H, C**4**-H), 5.21-5.06 (m, 2H, C**5**-H$_2$), 4.61 (app. br. s, 1H, C**3**-H), 3.58 (br. s, 1H, N**6**-H), 1.43 (s, 9H, 3 × C**9**-H$_3$), 0.85 (dtt, *J* = 8.1, 8.1, 5.0 Hz, 1H, C**2**-H), 0.53-0.45 (m, 2H, C**1**-H$_2$), 0.41-0.33 (m, 1H, C**1**-H$_a$H$_b$), 0.27-0.22 (m, 1H, C**1**-H$_a$H$_b$); ^{13}C NMR ($CDCl_3$, 101 MHz,): δ 155.3 (C**7**), 137.9 (C**4**), 114.4 (C**5**), 79.2 (C**8**), 56.3 (C**3**), 28.4 (C**9**), 15.6 (C**2**), 2.7 (C**1**); The spectroscopic properties of this compound were consistent with the data available in the literature.[289]

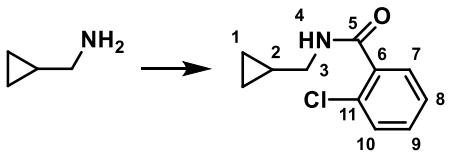
***N*-(1-Cyclopropylallyl)benzamide (401)**



400 **401**

To a stirring solution of Boc-protected amine **400** (0.40 g, 2.03 mmol) in DCM (10 mL), TFA (1.50 mL, 20.30 mmol) was added and the solvent was removed *in vacuo*. The residue was dissolved in dry DCM, then TEA (1.41 mL, 10.15 mmol) and benzoyl chloride (0.70 mL, 6.09 mmol) were added dropwise at 0°C under nitrogen. The reaction was warmed to r.t. and stirred for 16 h. The reaction mixture was concentrated *in vacuo* and then distilled water and DCM were added. The aqueous portion was further extracted with DCM (2 × 5 mL/mmol) and the organic extracts were combined washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (16% EtOAc/hexane) to afford the title compound **401** (193 mg, 47%) as a colourless solid; m.p. 96-97 °C; ν_{max} / cm^{-1}: 3278 (m), 3080 (m), 3006 (m), 1624 (s), 1545 (s), 1335 (m), 1292 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.82-7.78 (m, 2H, 2 × C**9**-H), 7.54-7.41 (m, 3H, C**11**-H and 2 × C**10**-H), 6.20 (br. s, 1H, N**6**-H), 5.93 (ddd, *J* = 17.2, 10.5, 5.1 Hz, 1H, C**4**-H), 5.30 (dd, *J* = 17.2, 1.5 Hz, 1H, C**5**-$H_{2,\ trans}$), 5.17 (dd, *J* = 10.5, 1.5 Hz, 1H, C**5**-$H_{2,\ cis}$), 4.18-4.10 (m, 1H, C**3**-H), 1.05-0.95 (m, 1H, C**2**-H), 0.65-0.43 (m, 3H, 3 × C**1**-H_2), 0.41-0.34 (m, 1H, C**1**-H_2); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 166.7 (C**7**), 137.3 (C**4**), 134.7 (C**8**), 131.5 (C**11**), 128.6 (C**10**), 126.9 (C**9**), 115.1 (C**5**), 55.6 (C**3**), 15.5 (C**2**), 3.1 (C**1**), 3.0 (C**1**); HRMS: (ESI^+) calculated for $C_{13}H_{15}NNaO$: 224.1046, found $[M+Na]^+$: 224.1050.

2-Chloro-*N*-(cyclopropylmethyl)benzamide (432a)



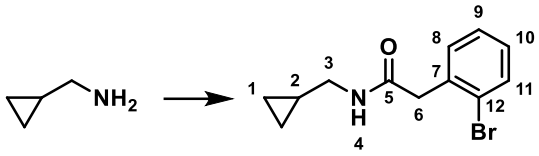
432a

General procedure D: Cyclopropylmethylamine (0.42 g, 3.00 mmol) and 2-chlorobenzoyl chloride (0.91 mL, 3.60 mmol) were employed and the reaction was stirred at r.t. for 16 h. Flash column chromatography (30-40% EtOAc/hexane) afforded the title compound **432a** (1.26 g, 95%) as a colourless solid; m.p. 82-83 °C; ν_{max} / cm^{-1}: 3277 (m), 3080 (m), 1637 (s), 1530 (s) 1433 (s), 1302 (s), 1265 (s), 1156 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.57-7.52 (m, 1H, C**7**-H), 7.37-7.31

(m, 3H, C**8**-H, C**9**-H, C**10**-H), 6.23 (br. s, 1H, N**4**-H), 3.23 (dd, *J* = 7.2, 5.4 Hz, 2H, C**3**-H_2), 1.04-0.91 (m, 1H, C**2**-H), 0.50-0.42 (m, 2H, C**1**-H_2), 0.22-0.15 (m, 2H, C**1**-H_2); ^{13}C NMR ($CDCl_3$, 101 MHz,): δ 166.4 (C**5**), 135.4 (C**11**), 131.1 (C**9**), 130.6 (C**6**), 130.2, 130.1 (C7 and C10), 127.0 (C**8**), 44.9 (C**3**), 10.8 (C**2**), 3.5 (C**1**); HRMS: (ESI^+) calculated for $C_{11}H_{13}ClNO$: 210.0680, found $[M+H]^+$: 210.0684.

*Compounds **432b** and **432c** were prepared by Dr. Gabrielle Fumagalli.*

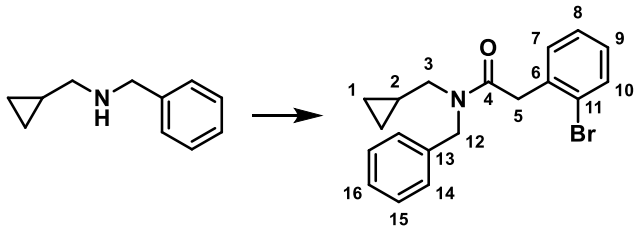
2-(2-Bromophenyl)-*N*-(cyclopropylmethyl)acetamide (433)



433

To a solution of cyclopropylmethylamine (1.78 g, 25.00 mmol), EDCI (4.46 g, 28.75 mmol) and DMAP (0.31 g, 2.50 mmol) in DCM (0.5 M) at 0 °C was added 2-bromophenylacetic acid (5.91 g, 27.50 mmol). The reaction was warmed to r.t., stirred for 18 h and then concentrated *in vacuo*. 1.0 M aq. NaOH (5 mL/mmol) was added and the solution was extracted with EtOAc (3 × 3 mL/mmol). The organic extracts were combined, washed with 1.0 M aq. HCl (5 mL/mmol) and brine (5 mL/mmol), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by recrystallisation (EtOAc/hexane) to afford the title compound **433** (5.68 g, 85%) as a colourless solid; m.p. 107-108 °C (EtOAc/hexane); ν_{max} / cm^{-1}: 3298 (s), 3077 (m), 3010 (m), 2917 (m), 1641 (s), 1549 (s), 1240 (s), 1026 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.58 (dd, *J* = 7.9, 1.3 Hz, 1H, C**11**-H), 7.38 – 7.26 (m, 2H, C**8**-H and C**9**-H), 7.15 (td, *J* = 7.9, 1.9 Hz, 1H, C**10**-H), 5.63 (br. s, 1H, N**4**-H), 3.69 (s, 2H, C**6**-H_2), 3.09 (dd, *J* = 7.1, 5.5 Hz, 2H, C**3**-H_2), 0.95 – 0.83 (m, 1H, C**2**-H), 0.49 – 0.39 (m, 2H, C**1**-H_aH_b), 0.17 – 0.10 (m, 2H, C**1**-H_aH_b); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 169.4 (C**5**), 135.0 (C**7**), 133.1 (C**11**), 131.7 (C**8**-H or C**9**-H), 129.0 (C**10**), 127.9 (C**8**-H or C**9**-H), 124.9 (C**12**), 44.4 (C**3**), 44.0 (C**6**), 10.6 (C**2**), 3.2 (C**1**); HRMS: (ESI^+) calculated for $C_{12}H_{15}{}^{79}BrNO$: 268.0332, found $[M+H]^+$: 268.0330.

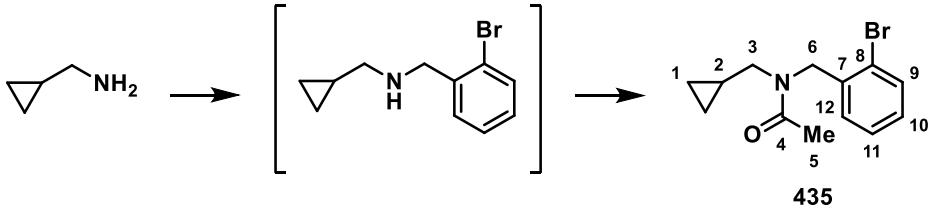
***N*-Benzyl-2-(2-bromophenyl)-*N*-(cyclopropylmethyl)acetamide (434)**



434

To a solution of 2-bromophenylacetic acid (0.70 g, 3.26 mmol) in DCM (1 mL), stirring under a nitrogen atmosphere at room temperature, oxalyl chloride (0.34 mL, 3.91 mmol) and a drop of *N*,*N*-dimethylformamide were added. The reaction was stirred until gas effervescence stopped. DCM and an excess of oxalyl chloride were removed *in vacuo* and the resulting acyl chloride was adder dropwise to a mixture of *N*-benzyl-1-cyclopropylmethanamine (0.53 g, 3.26 mmol, prepared according to the literature procedure[290]) and TEA (0.54 mL, 3.91 mmol) at 0 °C. The mixture was warmed to r.t. and stirred for 18 h. The mixture was diluted with water (30 mL) and extracted with DCM (3 × 20 mL). The organic extracts were combined, washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (20% EtOAc/petrol) to afford the title compound **434** (0.87 g, 74%, 1.04:1 mixture of rotamers *A*:*B*) as a colourless oil; ν_{max} / cm^{-1}: 3063 (w), 3003 (w), 1642 (s), 1440 (s), 1427 (s), 1026 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.57 (dd, *J* = 8.0, 1.3 Hz, 1H, C**10**-H, *A*), 7.54 (dd, *J* = 8.0, 1.3 Hz, 1H, C**10**-H, *B*), 7.39 – 7.21 (m, 14H, C**7**-H, C**8**-H, C**10**-H, C**16**-H, 2 × C**14**-H and 2 × C**15**-H, *A*+*B*), 7.16 – 7.08 (m, 2H, C**9**-H, *A*+*B*), 4.78 (s, 2H, C**12**-H_2, *A*), 4.69 (s, 2H, C**12**-H_2, *B*), 3.94 (s, 2H, C**5**-H_2, *A*), 3.82 (s, 2H, C**5**-H_2, *B*), 3.35 (d, *J* = 7.0 Hz, 2H, C**3**-H_2, *A*), 3.15 (d, *J* = 6.6 Hz, 1H, C**3**-H_2, *B*), 1.08 – 0.87 (m, 2H, C**2**-H, *A*+*B*), 0.58 – 0.50 (m, 2H, C**1**-H_aH_b, *A*), 0.50 – 0.42 (m, 2H, C**1**-H_aH_b, *B*), 0.25 – 0.12 (m, 4H, C**1**-H_aH_b, *A*+*B*); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 170.4 (C**4**, *A*), 169.9 (C**4**, *B*), 137.7, 136.9, 135.5, 135.4, 132.7, 132.7, 131.1, 130.9, 128.8, 128.5, 128.5, 128.0, 127.6, 127.5, 127.5, 127.2, 126.4, 125.1, 124.8, 124.7 (C**6**, C**7**, C**8**, C**9**, C**10**, C**11**, C**13**, C**14**, C**15** and C**16**, *A*+*B*), 51.4 (C**3**, *B*), 51.3 (C**12**, *B*), 50.2 (C**3**, *A*), 48.3 (C**12**, *A*), 41.0 (C**5**, *B*), 40.9 (C**5**, *A*), 10.0 (C**2**, *A*), 9.5 (C**2**, *B*), 3.9 (C**1**, *A*), 3.6 (C**1**, *B*); HRMS: (ESI^+) calculated for $C_{19}H_{21}{}^{79}BrNO$: 358.0801, found $[M+H]^+$: 358.0810.

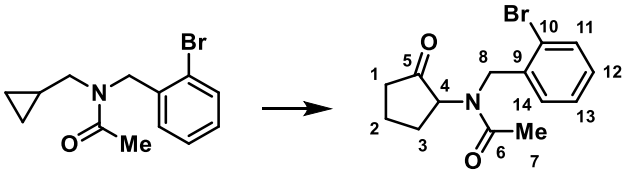
***N*-(2-Bromobenzyl)-*N*-(cyclopropylmethyl)acetamide (435)**



435

General procedure M: Cyclopropylmethylamine (0.23 mL, 2.60 mmol), 2-bromobenzaldehyde (0.51 g, 2.73 mmol) and acetic anhydride (0.26 g, 2.50 mmol) were employed and the reaction was stirred at r.t. for 16 h. Flash column chromatography (20-30% EtOAc/hexane) afforded the title compound **435** (0.48 g, 65%, 1:1.25 mixture of rotamers *A*:*B*) as a colourless oil; ν_{max} / cm^{-1}: 3003 (m), 2929 (m), 1651 (s), 1440 (s), 1421 (s), 1252 (m), 1024 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.57 (dd, *J* = 7.8, 1.2 Hz, 1H, C**9**-H, *A*), 7.52 (dd, *J* = 7.9, 1.2 Hz, 1H, C**9**-H, *B*), 7.35-7.06 (m, 6H, C**10**-H, C**11**-H and C**12**-H, *A*+*B*), 4.81 (s, 2H, C**6**-H_2, *B*), 4.65 (s, 2H, C**6**-H_2, *A*), 3.31 (d, *J* = 7.0 Hz, 2H, C**3**-H_2, *A*), 3.16 (d, *J* = 6.7 Hz, 2H, C**3**-H_2, *B*), 2.24 (s, 3H, C**5**-H_3, *B*), 2.06 (s, 3H, C**5**-H_3, *A*), 1.02-0.87 (m, 2H, C**2**-H, *A*+*B*), 0.57-0.42 (m, 4H, C**1**-H_aH_b, *A*+*B*), 0.23-0.14 (m, 4H, C**1**-H_aH_b, *A*+*B*); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 171.3 (C**4**, *B*), 170.7 (C**4**, *A*), 136.6 (C**7**, *A*), 135.9 (C**7**, *B*), 133.0 (C**9**, *A*), 132.7 (C**9**, *B*), 128.9, 128.5, 128.5, 127.8, 127.5, 126.9 (C**10**, C**11** and C**12**, *A*+*B*), 123.2, 122.5 (C**8**, *A*+*B*), 52.9 (C**3**, *B*), 52.4 (C**6**, *A*), 50.3 (C**3**, *A*), 48.5 (C**6**, *B*), 21.6 (C**5**, *A*+*B*), 10.2, 9.6 (C**2**, *A*+*B*), 3.7 (C**1**, *B*), 3.6 (C**1**, *A*); HRMS: (ESI^+) calculated for $C_{13}H_{17}{}^{79}BrNO$: 282.0488, found $[M+H]^+$: 282.0495.

***N*-(2-Bromobenzyl)-*N*-(2-oxocyclopentyl)acetamide (436)**

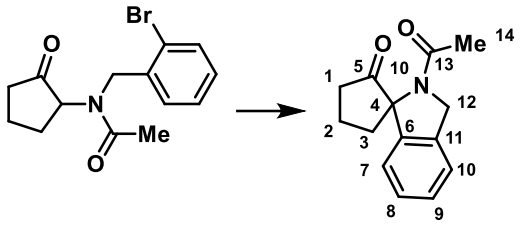


435 **436**

General procedure N: Compound **435** (42.3 mg, 0.15 mmol), $[Rh(cod)_2]OTf$ (5.3 mg, 0.011 mmol, 7.5 mol%) and $P(3,4,5\text{-}F_3C_6H_2)_3$ (9.5 mg, 0.023 mmol, 15 mol%) were employed and the reaction was stirred for 24 h at 140 °C. The crude mixture was purified by silica gel column chromatography (30% EtOAc/hexane) to yield the title compound **436** (38.3 mg, 82%) as a brown oil; ν_{max} / cm^{-1}: 2964 (m), 2880 (m), 1745 (s), 1647 (s), 1425 (s), 1253 (s), 1025 (s); ^{1}H NMR ($CDCl_3$, 400 MHz,): δ 7.61 (d, *J* = 7.7 Hz, 1H, C**11**-H), 7.56 (d, *J* = 7.9 Hz, 1H, C**14**-H), 7.38 (dd, *J* = 7.7, 7.5 Hz, 1H, C**12**-H), 7.21-7.15 (m, 1H, C**13**-H), 4.67 (d, *J* = 17.8 Hz, 1H, C**8**-H_aH_b), 4.49

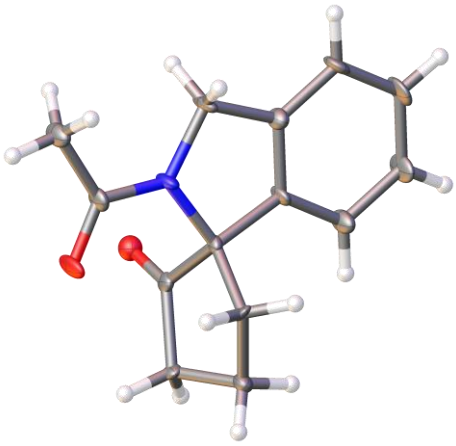
(d, *J* = 17.8 Hz, 1H, C**8**-$H_a\underline{H_b}$), 3.52 (t, *J* = 9.7 Hz, 1H, C**4**-$\underline{H}$), 2.52 (ddd, *J* = 18.5, 11.9, 9.3 Hz, 1H, C**1**-$\underline{H_a}H_b$), 2.29-2.08 (m, 4H, C**1**-$H_a\underline{H_b}$, C**2**-$\underline{H_a}H_b$, 2 × C**3**-$\underline{H_2}$), 2.06 (s, 3H, C**7**-$\underline{H_3}$), 1.73-1.57 (m, 1H, C**2**-$H_a\underline{H_b}$); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 213.1 (C**5**), 170.4 (C**6**), 135.4 (C**9**), 132.9 (C**14**), 129.2 (C**13**), 128.0, 128.0 (C**11** and C**12**), 122.5 (C**10**), 64.6 (C**4**), 53.9 (C**8**), 35.9 (C**1**), 26.9 (C**3**), 21.4 (C**7**), 19.1 (C**2**); HRMS: (ESI^+) calculated for $C_{14}H_{17}{}^{79}BrNO_2$: 310.0437, found $[M+H]^+$: 310.0426.

2'-Acetylspiro[cyclopentane-1,1'-isoindolin]-2-one (437)



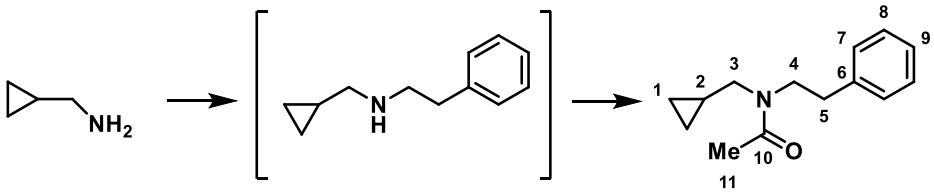
436 **437**

An oven-dried Schlenk flask, fitted with a magnetic stirrer, was charged with $PdCl_2(PPh_3)_2$ (4.2 mg, 6 mol%) and Cs_2CO_3 (65.2 mg, 2.00 eq). The flask was fitted with a rubber septum, evacuated and backfilled with nitrogen three times. Then, a solution of cyclopentanone **436** (31.0 mg, 0.10 mmol) in dry and degassed toluene (0.10 M) was added *via* syringe. The flask was sealed and the reaction mixture was heated at 110 °C for 18 h. The mixture was cooled to r.t. and concentrated *in vacuo*. The residue was purified by flash column chromatography (40% EtOAc/pentane) to afford the title compound **40** (18.5 mg, 81%) as a colourless solid; m.p. 177-178 °C (DCM/hexane); ν_{max} / cm^{-1}: 2960 (m), 2924 (m), 2860 (m), 1746 (s), 1645 (s), 1410 (s), 1355 (m), 1147 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.34-7.24 (m, 3H, C**8**-$\underline{H}$, C**9**-$\underline{H}$ and C**10**-$\underline{H}$), 7.16-7.09 (m, 1H, C**7**-$\underline{H}$), 4.94 (d, *J* = 13.5 Hz, 1H, C**12**-$\underline{H_a}H_b$), 4.82 (d, *J* = 13.5 Hz, 1H, C**12**-$H_a\underline{H_b}$), 2.94-2.78 (m, 2H, C**1**-$\underline{H_2}$ and C**2**-$\underline{H_2}$), 2.55-2.46 (m, 1H, C**1**-$\underline{H_2}$), 2.43-2.33 (m, 1H, C**3**-$\underline{H_2}$), 2.23-2.08 (m, 2H, C**2**-$\underline{H_2}$ and C**3**-$\underline{H_2}$), 2.15 (s, 3H, C**14**-$\underline{H_3}$); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 215.0 (C**5**), 168.6 (C**13**), 142.3 (C**6**), 135.7 (C**11**), 128.5, 128.2, 122.8 (C**8**, C**9**, C**10**), 121.4 (C**7**), 75.9 (C**4**), 53.8 (C**12**), 36.4 (C**1**), 35.6 (C**2**), 22.5 (C**14**), 19.0 (C**3**); HRMS: (ESI^+) calculated for $C_{14}H_{16}NO_2$: 230.1176, found $[M+H]^+$: 230.1179. *The structure of **437** was determined unambiguously by X-ray crystallography*.



Crystal image of **437** generated in Olex2, ellipsoids at 50% probability; Crystal data for **437**: $C_{14}H_{15}NO_2$, MW = 229.27, orthorhombic, space group Pnma, a = 16.1606(16) Å, b = 6.8731(7) Å, c = 9.9963(9) Å, V = 1110.32(19) $Å^3$, α = 90.00°, β = 90.00°, γ = 90.00°, Z = 4, D_c = 1.372 g/cm^3, Mo-Kα radiation, λ = 0.71073 Å, μ = 0.092 mm^{-1}, T = 100 K; colourless plate, crystal size 0.564 × 0.306 × 0.17 mm^3, Bruker Apex II diffractometer, 7747 reflections were collected, 1109 were unique, R_{int} = 0.0868; refinement on F^2 gave R_1 = 0.0914 and wR_2 = 0.2225, GOF = 1.214 for 122 refined parameters.

N-(Cyclopropylmethyl)-*N*-phenethylacetamide (439)



439

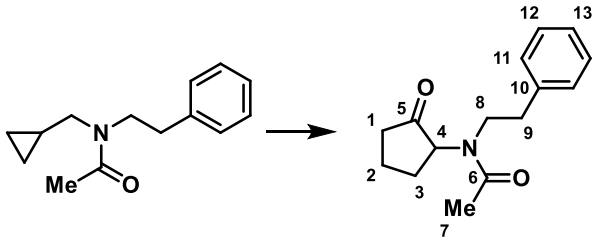
Phenylacetaldehyde (0.70 mL, 6.05 mmol, 1.05 eq) was added dropwise to the solution of cyclopropylmethylamine (0.5 mL, 5.77 mmol, 1.00 eq) in MeOH (0.5 M) at -78 °C and the reaction was stirred for 3 min. $NaBH_4$ (0.44 g, 2.00 eq) was added portionwise, the solution was warmed to 0 °C and stirred for 2 h.

Note: It is important to reduce the imine promptly, otherwise it self-polymerises in less than 10 min.

The reaction mixture was concentrated *in vacuo* and then sat. aq. $NaHCO_3$ (10 mL/mmol) was added. The solution was extracted with DCM (3 × 5 mL/mmol) and then the organic extracts were combined, washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the secondary amine intermediate.

To a stirring solution of secondary cyclopropylmethylamine (1.00 g, 5.71 mmol, 1.00 eq) in dry DCM (5 mL), TEA (0.95 mL, 1.20 eq) and acetic anhydride (0.65 mL, 1.20 eq) were added at 0 °C under nitrogen. The solution was warmed to r.t. and stirred for 16 h. Sat. aq. $NaHCO_3$ (50 mL) was added and the aqueous layer was extracted with DCM (3 × 20 mL). The combined organic extracts were washed with brine (70 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (20-40% EtOAc/hexane) to afford the title compound **439** (0.77 g, 58% over two steps, 1:1 mixture of rotamers *A*:*B*) as a colorless oil; ν_{max} / cm^{-1}: 3002 (w), 2930 (br. w), 1639 (s), 1453 (s), 1421 (s) ,1020 (m); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.37-7.12 (m, 10H, 2 × C**7**-H, 2 × C**8**-H and C**9**-H, *A*+*B*), 3.65-3.54 (m, 4H, C**4**-H_2, *A*+*B*), 3.29 (d, *J* = 6.9 Hz, 2H, C**3**-H_2, *A*), 3.06 (d, *J* = 6.6 Hz, 2H, C**3**-H_2, *B*), 2.93-2.82 (m, 4H, C**5**-H_2, *A*+*B*), 2.12 (s, 3H, C**11**-H_3, *A*), 1.96 (s, 3H, C**11**-H_3, *B*), 1.07-0.97 (m, 1H, C**2**-H, *A*), 0.96-0.85 (m, 1H, C**2**-H, *B*), 0.62-0.49 (m, 4H, 2 × C**1**-H_aH_b, *A*+*B*), 0.29-0.24 (m, 2H, 2 × C**1**-H_aH_b, *A*), 0.23-0.17 (m, 2H, 2 × C**1**-H_aH_b, *B*); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 170.4 (C**10**, *A*), 170.0 (C**10**, *B*), 139.5 (C**6**, *A*), 138.3 (C**6**, *B*), 128.8, 128.8 (C**8**, *A*+*B*), 128.7, 128.4 (C**7**, *A*+*B*), 126.70, 126.2 (C**9**, *A*+*B*), 53.7 (C**3**, *B*), 50.3 (C**4**, *A*), 49.5 (C**3**, *A*), 48.1 (C**4**, *B*), 35.3, 34.1 (C**5**, *A*+*B*), 21.9 (C**11**, *A*), 21.3 (C**11**, *B*), 10.5 (C**2**, *B*), 9.8 (C**2**, *A*), 3.8 (C**1**, *A*+*B*); HRMS: (ESI^+) calculated for $C_{14}H_{20}NO$: 218.1539, found $[M+H]^+$: 218.1537.

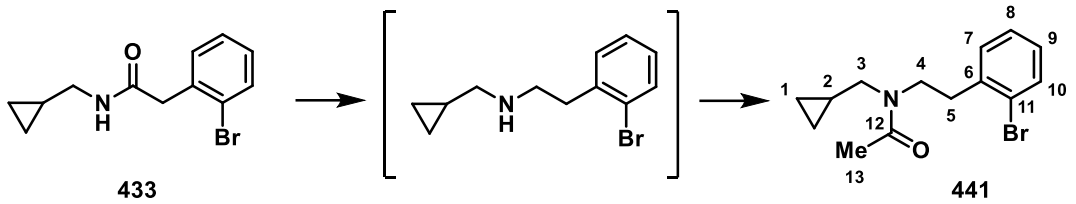
***N*-(2-Oxocyclopentyl)-*N*-phenethylacetamide (440)**



439 **440**

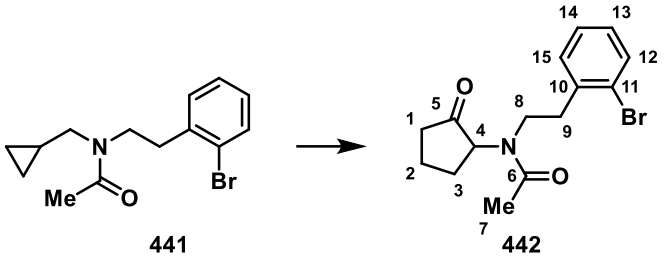
General procedure N: Compound **439** (32.6 mg, 0.15 mmol), $[Rh(cod)_2]OTf$ (5.3 mg, 0.011 mmol, 7.5 mol%) and $P(3,4,5\text{-}F_3C_6H_2)_3$ (9.5 mg, 0.023 mmol, 15 mol%) were employed and the reaction was stirred for 18 h at 110 °C. The crude mixture was purified by silica gel column chromatography (40% EtOAc/hexane) to yield the title compound **440** (29.1 mg, 79%) as a yellow oil; ν_{max} / cm^{-1}: 2959 (m), 2912 (br. m), 1744 (s), 1632 (s), 1430 (s), 1153 (m), 1102 (m); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.34-7.15 (m, 5H, 2 × C**11**-H, 2 × C**12**-H and C**13**-H), 3.61-3.46 (m, 2H, C**8**-H_2), 3.40 (t, *J* = 9.6 Hz, 1H, C**4**-H), 2.96-2.80 (m, 2H, C**9**-H_2), 2.55 (ddd, *J* = 18.2, 11.8, 9.3 Hz, 1H, C**1**-H), 2.35-2.06 (m, 4H, 2 × C**3**-H_2, C**1**-H and C**2**-H), 1.84 (s, 3H, C**7**-H_3), 1.79-1.62 (m, 1H, C**2**-H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 213.5 (C**5**), 169.4 (C**6**), 138.0 (C**10**), 128.8, 128.8 (C**11** and C**12**), 126.8 (C**13**), 64.9 (C**4**), 52.9 (C**8**), 36.0 (C**9**), 35.8 (C**1**), 27.2 (C**3**), 21.0 (C**7**), 19.4 (C**2**); HRMS: (ESI^+) calculated for $C_{15}H_{20}NO_2$: 246.1489, found $[M+H]^+$: 246.1491.

***N*-(2-Bromophenethyl)-*N*-(cyclopropylmethyl)acetamide (441)**



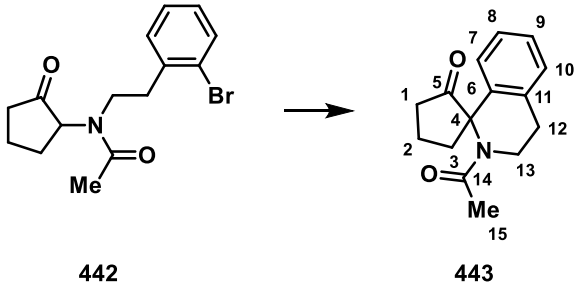
Compound **433** (0.50 g, 1.86 mmol) was dissolved in dry THF (10 mL) and the reaction vessel was cooled to 0 °C. Borane-THF complex solution (1 M in THF, 9.30 mmol, 5.00 eq) was added dropwise. The solution was warmed to room temperature and then heated to reflux for 20 h. The reaction was allowed to cool to room temperature, 40 mL of 2.0 M aq. HCl was added and the solution was heated to 85 °C for 1 h. The solution was washed with Et_2O (2 × 20 mL) and adjusted to pH 10 with 2.0 M aq. NaOH. The aqueous portion was diluted with water (50 mL) and extracted with Et_2O (3 × 20 mL). The organic extracts were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The resulting secondary amine (0.23 g, 0.90 mmol) was acylated according to the **general procedure D** with acetic anhydride (0.10 mL, 1.09 mmol) and the residue was purified by flash column chromatography (15-20% EtOAc/petrol) to afford the title compound **441** (254 mg, 46% over two steps, 1:1.04 mixture of rotamers *A*:*B*) as a colourless oil; ν_{max} / cm^{-1}: 3003 (w), 2932 (w), 1642 (s), 1472 (m), 1420 (s), 1023 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.56 (dd, *J* = 8.0, 1.3 Hz, 1H, C**10**-H, *A*), 7.52 (dd, *J* = 8.0, 1.3 Hz, 1H, C**10**-H, *B*), 7.32-7.17 (m, 4H, C**7**-H and C**8**-H, *A*+*B*), 7.15-7.05 (m, 2H, C**9**-H, *A*+*B*), 3.65 – 3.57 (m, 4H, C**4**-H_2, *A*+*B*), 3.30 (d, *J* = 6.9 Hz, 2H, C**3**-H_2, *B*), 3.07 (d, *J* = 6.6 Hz, C**3**-H_2, 2H, *A*), 3.05 – 2.99 (m, 4H, C**5**-H_2, *A*+*B*), 2.12 (s, 3H, C**13**-H_3, *A*), 2.03 (s, 3H, C**13**-H_3, *B*), 1.08 – 0.99 (m, 1H, C**2**-H, *A*), 0.96 – 0.88 (m, 1H, C**2**-H, *B*), 0.59 – 0.49 (m, 4H, C**1**-H_aH_b, *A*+*B*), 0.31 – 0.25 (m, 2H, C**1**-H_aH_b, *A*), 0.25 – 0.20 (m, 2H, C**1**-H_aH_b, *B*); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 170.5, 170.2 (C**12**, *A*+*B*), 138.8, 137.6 (C**6**, *A*+*B*), 133.0 (C**10**, *A*), 132.7 (C**10**, *B*), 131.3, 131.0, 128.6, 128.0 (C**7** and C**8**, *A*+*B*), 127.9, 127.6 (C**9**, *A*+*B*), 124.4, 124.3 (C**11**, *A*+*B*), 53.6 (C**3**, *A*), 49.6 (C**3**, *B*), 48.3, 46.2 (C**4**, *A*+*B*), 35.6, 34.2 (C**5**, *A*+*B*), 21.8 (C**13**, *A*), 21.4 (C**13**, *B*), 10.4 (C**2**, *B*), 9.8 (C**2**, *A*), 3.7, 3.7 (C**1**, *A*+*B*); HRMS: (ESI^+) calculated for $C_{14}H_{19}{}^{79}BrNO$: 296.0645, found $[M+H]^+$: 296.0638.

***N*-(2-Bromophenethyl)-*N*-(2-oxocyclopentyl)acetamide (442)**



General procedure N: Compound **441** (44.4 mg, 0.150 mmol), $[Rh(cod)_2]OTf$ (5.3 mg, 0.011 mmol, 7.5 mol%) and $P(3,4,5\text{-}F_3C_6H_2)_3$ (9.5 mg, 0.023 mmol, 15 mol%) were employed and the reaction was stirred for 24 h at 110 °C. The crude mixture was purified by silica gel column chromatography (20-40% EtOAc/petrol) to yield the title compound **442** (43.1 mg, 88%) as a yellow oil; ν_{max} / cm^{-1}: 2964 (w), 1745 (s), 1635 (s), 1472 (m), 1431 (s), 1154 (m), 1024 (m); ^1H NMR (400 MHz, $CDCl_3$): δ 7.56 (dd, *J* = 7.9.0, 1.5 Hz, 1H, C**12**-H), 7.35-7.27 (m, 2H, C**14**-H and C**15**-H), 7.13 (td, *J* = 7.9, 1.8 Hz, 1H, C**13**-H), 3.65 – 3.44 (m, 3H, C**4**-H and C**8**-H_2), 3.07 – 3.00 (m, 2H, C**9**-H_2), 2.58 (ddd, *J* = 18.3, 11.9, 9.4 Hz, 1H, C**1**-H_aH_b), 2.37 – 2.11 (m, 4H, C**1**-H_aH_b, C**2**-H_aH_b, 2 × C**3**-H_2), 1.94 (s, 3H, C**7**-H_3), 1.82 – 1.66 (m, 1H, C**2**-H_aH_b); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 213.5 (C**5**), 169.5 (C**6**), 137.2 (C**10**), 133.0 (C**15**), 131.4 (C**14**), 128.7, 127.9 (C**12** and C**13**), 124.3 (C**11**), 64.9 (C**4**), 50.7 (C**8**), 36.5 (C**1**), 35.9 (C**9**), 27.2 (C**3**), 21.0 (C**7**), 19.4 (C**2**); HRMS: (ESI^+) calculated for $C_{15}H_{19}{}^{79}BrNO_2$: 324.0594, found $[M+H]^+$: 324.0607.

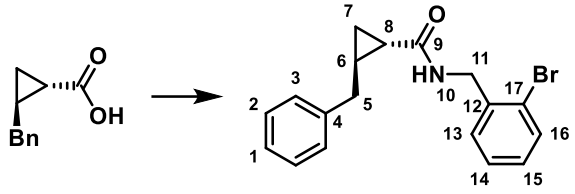
2'-Acetyl-3',4'-dihydro-2'*H*-spiro[cyclopentane-1,1'-isoquinolin]-2-one (443)



An oven-dried Schlenk flask, fitted with a magnetic stirrer, was charged with $PdCl_2(PPh_3)_2$ (4.2 mg, 6 mol%) and Cs_2CO_3 (65.2 mg, 0.20 mmol, 2.00 eq). The flask was fitted with a rubber septum, evacuated and backfilled with nitrogen three times. Then, a solution of cyclopentanone **442** (32.4 mg, 0.10 mmol) in dry and degassed toluene (0.10 M) was added *via* syringe. The flask was sealed and the reaction mixture was heated at 110 °C for 18 h. The mixture was cooled to r.t. and concentrated *in vacuo*. The residue was purified by flash column chromatography (40% EtOAc/petrol) to afford the title compound **443** (23.1 mg, 95%) as a colourless solid; m.p. 151-

152 °C (DCM/hexane); ν_{max} / cm^{-1}: 2954 (w), 1740 (s), 1633 (s), 1416 (s), 1149 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.23 – 7.14 (m, 3H, C**8**-H, C**9**-H and C**10**-H), 7.00 – 6.95 (m, 1H, C**7**-H), 3.74 (ddd, *J* = 12.2, 7.3, 4.0 Hz, 1H, C**13**-H_aH_b), 3.60 (ddd, *J* = 12.0, 7.8, 3.8 Hz, 1H, C**13**-H_aH_b), 3.04 (ddt, *J* = 15.9, 7.8, 4.0 Hz, 1H, C**12**-H_aH_b), 2.99 – 2.93 (m, 1H, C**2**-H_aH_b), 2.94 – 2.82 (m, 1H, C**12**-H_aH_b), 2.68 – 2.59 (m, 1H, C**1**-H_aH_b), 2.50 – 2.41 (m, 1H, C**2**-H_aH_b), 2.32 – 2.16 (m, 2H, C**3**-H_aH_b and C**1**-H_aH_b), 2.15 (s, 3H, C**15**-H_3), 2.03 – 1.92 (m, 1H, C**3**-H_aH_b); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 214.7 (C**12**), 169.0 (C**14**), 138.1 (C**6**), 135.0 (C**11**), 128.3, 127.1, 127.0 (C**8**, C**9**, C**10**), 125.5 (C**7**), 68.1 (C**4**), 44.3 (C**13**), 39.2 (C**1**), 36.7 (C**2**), 30.4 (C**12**), 22.6 (C**15**), 18.7 (C**3**); HRMS: (ESI^+) calculated for $C_{15}H_{17}NNaO_2$: 266.1151, found $[M+Na]^+$: 266.1146.

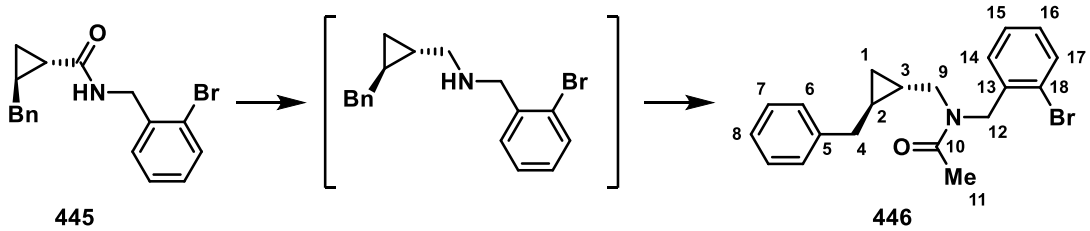
(1*S,2*R**)-2-Benzyl-*N*-(2-bromobenzyl)cyclopropane-1-carboxamide (445)**



444 **445**

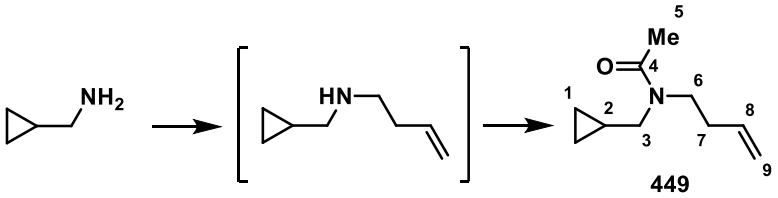
To a solution of (1*R**,2*S**)-2-benzylcyclopropane-1-carboxylic acid **444** (1.20 g, 6.81 mmol, prepared according to the literature procedure[48]) in DCM (1 mL), stirring under a nitrogen atmosphere at room temperature, oxalyl chloride (0.88 mL, 10.21 mmol) was added. The reaction was stirred until gas effervescence stopped. DCM and an excess of oxalyl chloride were removed *in vacuo* and the resulting acyl chloride was adder dropwise to a mixture of 2-bromobenzylamine hydrochloride (1.59 g, 7.15 mmol) and TEA (2.08 mL, 14.98 mmol) at 0 °C. The mixture was warmed to r.t. and stirred for 18 h. The mixture was diluted with water (50 mL) and extracted with DCM (3 × 40 mL). The organic extracts were combined, washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by recrystallization (DCM/hexane) to afford the title compound **445** (1.57 g, 67%) as a colourless solid; m.p. 138-139 °C (DCM/hexane); ν_{max} / cm^{-1}: 3282 (br. m), 2920 (br. w), 1643 (s), 1543 (s), 1440 (s), 1239 (s), 1028 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.55 (dd, *J* = 8.0, 1.3 Hz, 1H, C**16**-H), 7.36 – 7.11 (m, 8H, C**1**-H, C**13**-H, C**14**-H, C**15**-H, 2 × C**2**-H and 2 × C**3**-H), 6.01 (br. m, 1H, N**4**-H), 4.51 (d, *J* = 6.0 Hz, 2H, C**11**-H_2), 2.68 (d, *J* = 3.4 Hz, 1H, C**5**-H_2), 2.66 (d, *J* = 3.4 Hz, 1H, C**5**-H_2), 1.75 – 1.66 (m, 1H, C**6**-H), 1.30 – 1.21 (m, 2H, C**7**-H_aH_b and C**8**-H), 0.75 (ddd, *J* = 7.2, 6.3, 3.6 Hz, 1H, C**7**-H_aH_b); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 172.7 (C**9**), 140.3 (C**4**), 137.5 (C**12**), 132.7 (C**16**), 130.3, 129.1, 128.4, 128.3, 127.7, 126.1 (C**1**, C**2**, C**3**, C**13**, C**14** and C**15**), 123.7 (C**17**), 44.0 (C**11**), 38.4 (C**5**), 22.2 (C**6**), 21.7 (C**8**), 14.3 (C**7**); HRMS: (ESI^+) calculated for $C_{18}H_{19}{}^{79}BrNO$: 344.0645, found $[M+H]^+$: 344.0649.

***N*-(((1*S**,2*R**)-2-Benzylcyclopropyl)methyl)-*N*-(2-bromobenzyl)acetamide (444)**



Compound **445** (1.00 g, 2.90 mmol) was dissolved in dry THF (10 mL) and the reaction vessel was cooled to 0 °C. Borane-THF complex solution (1 M in THF, 14.52 mmol, 5.00 eq) was added dropwise. The solution was warmed to room temperature and then heated to reflux for 24 h. The reaction was allowed to cool to room temperature, 50 mL of 2.0 M aq. HCl was added and the solution was heated to 85 °C for 1 h. The solution was washed with Et_2O (2 × 20 mL) and adjusted to pH 10 with 2.0 M aq. NaOH. The aqueous portion was diluted with water (50 mL) and extracted with Et_2O (3 × 30 mL). The organic extracts were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The resulting secondary amine was acylated according to the **general procedure D** with acetic anhydride (0.33 mL, 3.48 mmol) and the residue was purified by flash column chromatography (4.5/4.5/1 DCM/hexane/acetone) to afford the title compound **446** (0.48 g, 44% over two steps, 1.55:1 mixture of rotamers *A*:*B*) as a colourless oil; ν_{max} / cm^{-1}: 2997 (w), 2918 (br. w), 1647 (s), 1439 (s), 1420 (s), 1248 (m), 1025 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.56 (dd, *J* = 8.0, 1.2 Hz, 1H, C**17**-H, *A*), 7.52 (dd, *J* = 8.0, 1.2 Hz, 1H, C**17**-H, *B*), 7.32 – 7.04 (m, 16H, C**8**-H, C**14**-H, C**15**-H, C**16**-H, 2 × C**6**-H and 2 × C**7**-H, *A*+*B*), 4.75 (d, *J* = 16.1 Hz, 1H, C**12**-H_2, *B*), 4.68 (d, *J* = 16.1 Hz, 1H, C**12**-H_2, *B*), 4.41 (s, 2H, C**12**-H_2, *A*), 3.48 (dd, *J* = 14.0, 5.6 Hz, 1H, C**4**-H_2, *A*), 3.29 (dd, *J* = 15.2, 5.9 Hz, 1H, C**4**-H_2, *B*), 3.12 (dd, *J* = 14.0, 7.5 Hz, 1H, C**4**-H_2, *A*), 3.05 (dd, *J* = 15.2, 7.0 Hz, 1H, C**4**-H_2, *B*), 2.64 – 2.35 (m, 4H, C**9**-H_2, *A*+*B*), 2.21 (s, 3H, C**11**-H_3, *B*), 1.97 (s, 3H, C**11**-H_3, *A*), 1.01 – 0.79 (m, 4H, C**2**-H and C**3**-H, *A*+*B*), 0.52 – 0.37 (m, 4H, C**1**-H, *A*+*B*); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 171.3 (C**10**, *A*), 170.6 (C**10**, *B*), 141.7 (C**5**, *A*), 141.1 (C**5**, *B*), 136.6 (C**13**, *B*), 135.9 (C**13**, *A*), 133.1 (C**17**, *A*), 132.7 (C**17**, *B*), 128.9, 128.7, 128.6, 128.4, 128.3, 128.3, 127.8, 127.6, 127.0, 126.2, 125.9 (C**8**, C**14**, C**15**, C**16**, C**7** and C**6**, *A*+*B*), 123.3 (C**18**, *B*), 122.5 (C**18**, *A*), 52.2 (C**4**, *B*), 52.2 (C**12**, *A*), 49.4 (C**4**, *A*), 48.4 (C**12**, *B*), 39.4 (C**9**, *A*), 39.1 (C**9**, *B*), 21.6 (C**11**, *B*), 21.6 (C**11**, *A*), 19.5 (C**2**, *B*), 19.2 (C**2**, *A*), 17.7 (C**3**, *B*), 17.1 (C**3**, *A*), 10.8 (C**1**, *A*), 10.7 (C**1**, *B*); HRMS: (ESI^+) calculated for $C_{20}H_{23}{}^{79}BrNO$: 372.0958, found $[M+H]^+$: 372.0975.

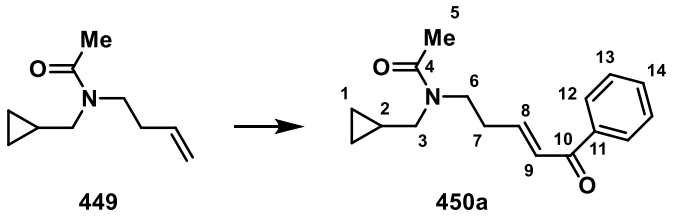
***N*-(but-3-en-1-yl)-*N*-(cyclopropylmethyl)acetamide (449)**



To a solution of but-3-en-1-yl 4-methylbenzenesulfonate (3.39 g, 15.00 mmol, prepared according to the literature procedure[48]) and K_2CO_3 (2.07 g, 15.00 mmol) in MeCN (3 mL) in a sealed tube was added a solution of cyclopropylmethylamine (1.07 g, 15.00 mmol) in MeCN (15 mL). The tube was sealed and the reaction was heated to 90 °C for 18 h. The reaction mixture was cooled to r.t. and then the solution was concentrated *in vacuo*. Water (50 mL) was added and the solution was extracted with DCM (3 × 30 mL). The organic extracts were combined, washed with brine (40 mL), dried over $MgSO_4$ and concentrated *in vacuo* to yield the secondary amine intermediate.

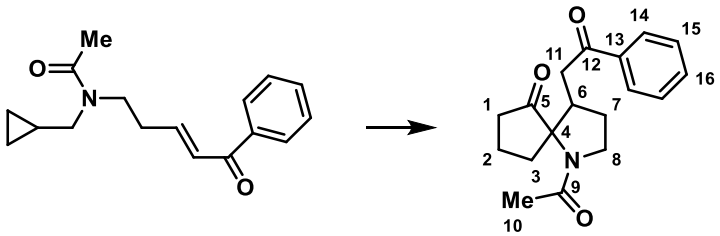
To a stirring solution of secondary amine in dry DCM (5 mL), TEA (5.98 mL, 3.00 eq) and acetic anhydride (4.05 mL, 3.00 eq) were added at 0 °C under nitrogen. The solution was warmed to r.t. and stirred for 16 h. Sat. aq. $NaHCO_3$ (30 mL) was added and the aqueous layer was extracted with DCM (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by silica gel column chromatography (20-40% EtOAc/hexane) to yield the title compound **449** (1.39 g, 55% over two steps, 1:1 mixture of rotamers *A*:*B*) as a yellow oil; ν_{max} / cm^{-1}: 2978 (m), 2930 (m), 1636 (s), 1422 (s), 1019 (m), 996 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.79 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 2H, C**8**-H, *A*+*B*), 5.17-4.99 (m, 4H, C**9**-H_2, *A*+*B*), 3.49 (t, *J* = 7.5 Hz, 2H, C**6**-H_2, *A*), 3.43 (t, *J* = 7.7 Hz, 2H, C**6**-H_2, *B*), 3.28 (d, *J* = 6.9 Hz, 2H, C**3**-H_2, *A*), 3.18 (d, *J* = 6.5 Hz, 2H, C**3**-H_2, *B*), 2.40-2.30 (m, 4H, C**7**-H_2, *A*+*B*), 2.13 (s, 3H, C**5**-H_3, *A*), 2.12(s, 3H, C**5**-H_3, *B*), 1.07-0.89 (m, 2H, C**2**-H, *A*+*B*), 0.64-0.58 (m, 2H, 2 × C**1**-H_aH_b, *B*), 0.55-0.48 (m, 2H, 2 × C**1**-H_aH_b, *A*), 0.28-0.21 (m, 4H, 2 × C**1**-H_aH_b, *A*+*B*); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 170.3, 170.0 (C**4**, *A*+*B*), 135.7, 134.4 (C**8**, *A*+*B*), 117.4, 116.3 (C**9**, *A*+*B*), 53.3 (C**3**, *B*), 49.5 (C**3**, *A*), 48.1 (C**6**, *B*), 45.4 (C**6**, *A*), 33.2, 32.2 (C**7**, *A*+*B*), 21.8, 21.6 (C**5**, *A*+*B*), 10.5, 9.8 (C**2**, *A*+*B*), 3.8 (C**1**, *B*), 3.7 (C**1**, *A*); HRMS: (ESI^+) calculated for $C_{10}H_{18}NO$: 168.1383, found $[M+H]^+$: 168.1385.

***(E)*-*N*-(Cyclopropylmethyl)-*N*-(5-oxo-5-phenylpent-3-en-1-yl)acetamide (450a)**



A flame-dried flask was charged with alkene **449** (0.70 g, 4.19 mmol) and 1-phenylprop-2-en-1-one (1.66 g, 12.56 mmol, prepared according to the literature procedure[291]). Dry DCM (0.1 M) and Hoveyda-Grubbs Catalyst™ 2nd Generation (40 mg, 1.5 mol%) were added and the solution was stirred at r.t. for 18 h. A few drops of DMSO were added, the crude was concentrated *in vacuo* and the residue was purified by silica gel column chromatography (20-50% EtOAc/petrol) to yield the title compound **90a** (0.28 g, 25%, 1:1.83 mixture of rotamers *A*:*B*) as a brown oil; ν_{max} / cm^{-1}: 3004 (w), 292 (br. w), 1669 (s), 1691 (s), 1448 (m), 1262 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.94 – 7.90 (m, 4H, 2 × C**12**-H, *A*+*B*), 7.60 – 7.44 (m, 6H, C**14**-H and 2 × C**13**-H, *A*+*B*), 7.04 – 6.90 (m, 4H, C**8**-H and C**9**-H, *A*+*B*), 3.62 – 3.53 (m, 4H, C**6**-H_2, *A*+*B*), 3.29 (d, *J* = 6.9 Hz, 2H, C**3**-H_2, *A*), 3.18 (d, *J* = 6.6 Hz, 2H, C**3**-H_2, *B*), 2.67 – 2.58 (m, 4H, C**7**-H_2, *A*+*B*), 2.13 (s, 3H, C**5**-H_3, *A*), 2.12 (s, 3H, C**5**-H_3, *B*), 1.04 – 0.88 (m, 2H, C**2**-H, *A*+*B*), 0.64 – 0.58 (m, 2H, 2 × C**1**-H_aH_b, *B*), 0.55 – 0.50 (m, 2H, 2 × C**1**-H_aH_b, *A*), 0.29 – 0.21 (m, 4H, 2 × C**1**-H_aH_b, *A*+*B*); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 190.7 (C**10**, *B*), 190.0 (C**10**, *A*), 170.3 (C**4**, *B*), 170.3 (C**4**, *A*), 146.0 (C**8**, *B*), 144.1 (C**8**, *A*), 137.7 (C**11**, *B*), 137.5 (C**11**, *A*), 133.0 (C**14**, *A*), 132.7 (C**14**, *B*), 128.7, 128.6, 128.6, 128.5(C**12** and C**13**, *A*+*B*), 127.9 (C**9**, *A*), 127.4 (C**9**, *B*), 53.8 (C**3**, *B*), 49.7 (C**3**, *A*), 47.3 (C**6**, *A*), 45.1 (C**6**, *B*), 32.4 (C**7**, *A*), 31.2 (C**7**, *B*), 21.8 (C**5**, *B*), 21.6 (C**5**, *A*), 10.6 (C**2**, *B*), 9.8 (C**2**, *A*), 3.9 (C**1**, *B*), 3.8 (C**1**, *A*); HRMS: (ESI^+) calculated for $C_{17}H_{22}NO_2$: 272.1645, found $[M+H]^+$: 272.1653.

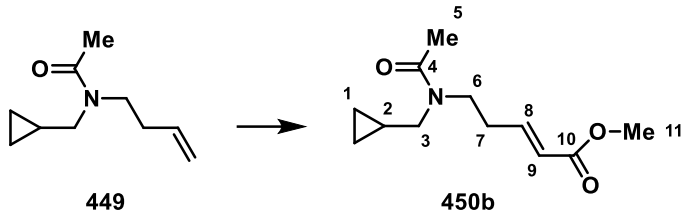
1-acetyl-4-(2-oxo-2-phenylethyl)-1-azaspiro[4.4]nonan-6-one (451a)



450a **451a**

General procedure N: Compound **450a** (40.7 mg, 0.150 mmol), $[Rh(cod)_2]OTf$ (5.3 mg, 0.011 mmol, 7.5 mol%), and $P(3,4,5\text{-}F_3C_6H_2)_3$ (9.5 mg, 0.023 mmol, 15 mol%) *and* $Mg(OTf)_2$ (4.8 mg, 0.015 mmol, 10 mol%) were employed and the reaction was stirred for 24 h at 110 °C. The crude mixture was purified by silica gel column chromatography (40% EtOAc/ *n*-pentane) to yield the title compound **451a** (29.0 mg, 65%, 1:1.5 mixture of diastereomers *A*:*B*) as a brown oil; ν_{max} / cm^{-1}: 2965 (w), 1740 (s), 1683 (s), 1631 (s), 1448 (s), 1415 (s), 1216 (s); ^1H NMR ($CDCl_3$, 400 MHz): δ 8.00 – 7.86 (m, 4H, 2 × C**14**-H, *A*+*B*), 7.59 – 7.39 (m, 6H, 2 × C**15**-H and C**16**-H, *A*+*B*), 3.69 – 3.44 (m, 4H, C**8**-H_2, *A*+*B*), 3.12 (dd, *J* = 16.6, 5.9 Hz, 1H, C**11**-H_aH_b, *B*), 2.98 (dd, *J* = 16.6, 8.4 Hz, 1H, C**11**-H_aH_b, *B*), 3.04 – 2.47 (m, 3H, C**6**-H, *A*+*B* and C**11**-H_2, *A*), 2.41 – 2.03 (m, 10H, C**1**-H_2, C**2**-H_aH_b, C**3**-H_aH_b and C**7**-H_aH_b, *A*+*B*), 2.02 (s, 3H, C**10**-H_3, *B*), 1.97 (s, 3H, C**10**-H_3, *A*), 1.96 – 1.45 (m, 6H, C**2**-H_aH_b, C**3**-H_aH_b and C**7**-H_aH_b, *A*+*B*); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 216.8, 216.1 (C**5**, *A*+*B*), 198.8, 197.4 (C**12**, *A*+*B*), 168.2, 168.1 (C**9**, *A*+*B*), 136.8, 136.2 (C**13**, *A*+*B*), 133.5, 133.2 (C**16**, *A*+*B*), 128.8, 128.6 (C**14**, *A*+*B*), 128.0, 127.9 (C**15**, *A*+*B*), 72.1, 71.1 (C**4**, *A*+*B*), 47.3, 47.1 (C**8**, *A*+*B*), 42.4, 42.3 (C**6**, *A*+*B*), 38.6, 37.5 (C**11**, *A*+*B*), 37.0, 36.2 (C**7**, *A*+*B*), 35.6, 31.0 (C**3**, *A*+*B*), 30.4, 29.9 (C**1**, *A*+*B*), 22.7, 22.1(C**10**, *A*+*B*), 19.2, 18.9 (C**2**, *A*+*B*); HRMS: (ESI^+) calculated for $C_{18}H_{21}NNaO_3$: 322.1414, found $[M+H]^+$: 322.1424.

Methyl (*E*)-5-(*N*-(cyclopropylmethyl)acetamido)pent-2-enoate (450b)

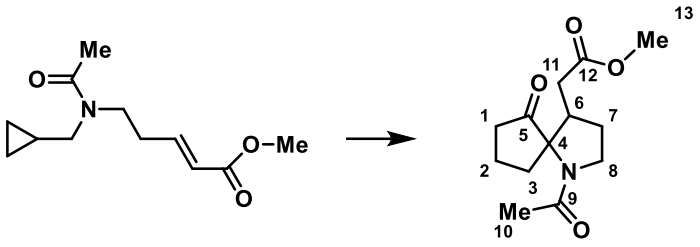


449 **450b**

A flame-dried flask was charged with alkene **449** (0.30 g, 1.79 mmol) and methyl acrylate (0.46 g, 5.38 mmol). Dry DCM (6 mL) and Hoveyda-Grubbs Catalyst™ 2nd Generation (0.05 g, 5 mol%) were added and the solution was stirred at r.t. for 18 h. A few drops of DMSO were added, the crude was concentrated *in vacuo* and the residue was purified by silica gel column chromatography

(20-50% EtOAc/petrol) to yield the title compound **450b** (0.30 g, 73%, 1:1.79 mixture of rotamers *A*:*B*) as a brown oil; ν_{max} / cm^{-1}: 3002 (w), 2951 (w), 1720 (s), 1634 (s) 1423 (s), 1273 (s), 1200 (s), 1174 (s), 1021 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ δ 6.92 (dt, *J* = 15.6, 7.2 Hz, 1H, C**8**-H, *B*), 6.89 (dt, *J* = 15.7, 7.3 Hz, C**8**-H, 1H, *A*), 5.89 (dt, *J* = 15.7, 1.4 Hz, 1H, C**9**-H, *A*), 5.85 (dt, *J* = 15.6, 1.5 Hz, C**9**-H, 1H, *B*), 3.73 (s, 3H, C**11**-H_3, *A*), 3.71 (s, 3H, C**11**-H_3, *B*), 3.53 – 3.46 (m, 4H, C**6**-H_2, *A*+*B*), 3.25 (d, *J* = 6.9 Hz, 2H, C**3**-H_2, *A*), 3.15 (d, *J* = 6.5 Hz, 2H, C**3**-H_2, *B*), 2.52 – 2.47 (m, 4H, C**7**-H_2, *A*+*B*), 2.10 (s, 3H, C**5**-H_3, *B*), 2.10 (s, 3H, C**5**-H_3, *B*), 1.01 – 0.86 (m, 2H, C**2**-H, *A*+*B*), 0.62 – 0.56 (m, 2H, 2 × C**1**-H_aH_b, *B*), 0.53 – 0.48 (m, 2H, 2 × C**1**-H_aH_b, *A*), 0.25 – 0.19 (m, 4H, 2 × C**1**-H_aH_b, *A*+*B*); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 170.2 (C**4**, *B*), 170.2 (C**4**, *A*), 166.8 (C**10**, *B*), 166.4 (C**10**, *A*), 146.0 (C**8**, *B*), 144.3 (C**8**, *A*), 123.4 (C**9**, *A*), 122.5 (C**9**, *B*), 53.8 (C**3**, *B*), 51.6 (C**11**, *A*), 51.5 (C**11**, *B*), 49.6 (C**3**, *A*), 47.1 (C**6**, *A*), 45.0 (C**6**, *B*), 31.8 (C**7**, *A*), 30.7 (C**7**, *B*), 21.8 (C**5**, *B*), 21.6 (C**5**, *A*), 10.5 (C**2**, *B*), 9.8 (C**2**, *A*), 3.8 (C**1**, *B*), 3.8 (C**1**, *A*); HRMS: (ESI^+) calculated for $C_{12}H_{19}NNaO_3$: 248.1257, found $[M+Na]^+$: 248.1263.

Methyl 2-(1-acetyl-6-oxo-1-azaspiro[4.4]nonan-4-yl)acetate (451b)

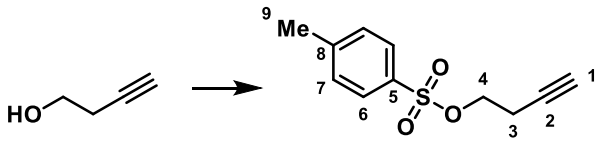


450b **451b**

General procedure N: Compound **450b** (33.8 mg, 0.15 mmol), $[Rh(cod)_2]OTf$ (5.3 mg, 0.011 mmol, 7.5 mol%), and $P(3,4,5\text{-}F_3C_6H_2)_3$ (9.5 mg, 0.023 mmol, 15 mol%) *and* $Mg(OTf)_2$ (4.8 mg, 0.015 mmol, 10 mol%) were employed and the reaction was stirred for 24 h at 110 °C. The crude mixture was purified by silica gel column chromatography (40% EtOAc/ *n*-pentane) to yield the title compound **451b** (20.0 mg, 53%, 1:3.6 mixture of diastereomers *A*:*B*) as a brown oil; ν_{max} / cm^{-1}: 2954 (w), 1736 (s), 1627 (s), 1418 (s), 1203 (s), 1168 (s), 1145 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.65 (s, 3H, C**13**-H_3, *B*), 3.63 (s, 3H, C**13**-H_3, *A*), 3.62 – 3.31 (m, 4H, C**8**-H_2, *A*+*B*), 2.81 (dt, *J* = 18.7, 10.6 Hz, 1H, C**1**-H_aH_b, *B*), 2.70 – 2.47 (m, 4H, C**1**-H_aH_b and C**11**-H_aH_b, *A*; C**6**-H, *A*+*B*), 2.42 (dd, *J* = 15.8, 6.0 Hz, 1H, C**11**-H_aH_b, *B*), 2.35 (dd, *J* = 15.7, 9.2 Hz, 1H, C**11**-H_aH_b, *B*), 2.32 – 2.04 (m, 9H, C**11**-H_aH_b, *A*; C**1**-H_aH_b, C**2**-H_aH_b, C**3**-H_2, *A*+*B*), 2.00 (s, 3H, C**10**-H_3, *A*), 1.96 (s, 3H, C**10**-H_3, *B*), 1.92 – 1.49 (m, 6H, C**2**-H_aH_b and C**7**-H_2, *A*+*B*); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 216.6 (C**5**, *B*), 215.6 (C**5**, *A*), 172.8 (C**12**, *A*), 171.6 (C**12**, *B*), 168.2 (C**10**, *A*), 167.9 (C**10**, *B*), 71.8 (C**4**, *A*), 70.9 (C**4**, *B*), 51.8 (C**13**, *B*), 51.7 (C**13**, *A*), 47.1 (C**8**, *B*), 46.9 (C**8**, *A*), 43.5 (C**6**, *A*),

42.8 (C**6**, *B*), 37.0 (C**1**, *A*), 36.2 (C**1**, *B*), 35.3 (C**3**, *A*), 34.1 (C**11**, *A*), 33.1 (C**11**, *B*), 30.7 (C**7**, *A*), 30.4 (C**7**, *B*), 29.7 (C**3**, *B*), 22.7 (C**10**, *A*), 22.1 (C**10**, *B*), 18.9 (C**2**, *B*), 18.8 (C**2**, *A*); HRMS: (ESI^+) calculated for $C_{13}H_{20}NO_4$: 254.1387, found $[M+H]^+$: 254.1388.

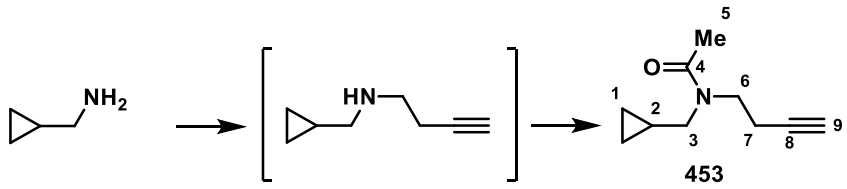
But-3-yn-1-yl 4-methylbenzenesulfonate (453')



453'

To a solution of 3-butyn-1-ol (3.00 g, 42.80 mmol) and Et_3N (5.97 mL, 42.80 mmol) in DCM (40 mL) was added tosyl chloride (7.42 g, 38.91 mmol) and the reaction was stirred for 18 h at r.t. Water (80 mL) was added and the solution was extracted with DCM (3 × 40 mL). The organic extracts were combined, dried over $MgSO_4$ and concentrated *in vacuo* to provide the title compound **453'** (8.35 g, 87%) as a colourless oil; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.84-7.80 (m, 2H, 2 × C**6**-H), 7.39-7.35 (m, 2H, 2 × C**7**-H), 4.11 (t, 2H, *J* = 7.0 Hz, C**4**-H_2), 2.57 (td, *J* = 7.0, 2.5 Hz, 2H, C**3**-H_2), 2.47 (s, 3H, C**9**-H_3), 1.98 (t, *J* = 2.5 Hz, 1H, C**1**-H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 145.0 (C**8**), 132.8 (C**5**), 129.9 (C**7**), 128.0 (C**6**), 78.3 (C**2**), 70.7 (C**1**), 67.4 (C**4**), 21.6 (C**9**), 19.4 (C**3**). The spectroscopic properties of this compound were consistent with the data available in the literature.[292]

***N*-(But-3-yn-1-yl)-*N*-(cyclopropylmethyl)acetamide (453)**

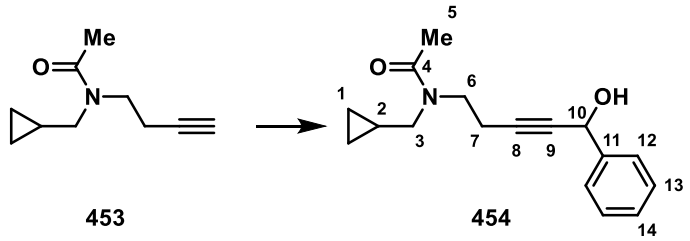


453

To a sealed tube containing **453'** (2.24 g, 10.00 mmol) in MeCN (15 mL) was added a cyclopropylmethylamine (3.47 mL, 40.00 mmol). The tube was sealed and the reaction was heated to 90 °C for 18 h. The reaction mixture was cooled to r.t., trifluoroacetic acid (1.15 mL, 15.00 mmol) was added and then the solution was concentrated *in vacuo*. The residue was dissolved in DCM (50 mL) and washed with sat. aq. $NaHCO_3$ (100 mL). The aqueous portion was extracted with DCM (3 × 30 mL). The organic extracts were combined, washed with brine (40 mL), dried over $MgSO_4$ and concentrated *in vacuo* to yield the secondary amine intermediate.

To a stirring solution of secondary amine in dry DCM (30 mL), TEA (11.15 mL, 80.00 mmol) and acetic anhydride (3.77 mL, 40.00 mmol) were added at 0 °C under nitrogen. The solution was warmed to r.t. and stirred for 16 h. Sat. aq. $NaHCO_3$ (30 mL) was added and the aqueous layer was extracted with DCM (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by silica gel column chromatography (20-40% EtOAc/pentane) to yield the title compound **453** (0.75 mg, 46% over two steps, 1:1.4 mixture of rotamers *A*:*B*) as a pale yellow oil; ν_{max} / cm^{-1}: 3296 (m), 3237 (m), 3003 (m), 1634 (s), 1421 (s), 1250 (m), 1011 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.57 (t, *J* = 7.1 Hz, 4H, C**6**-$\underline{H}_2$, *A*+*B*), 3.30-3.24 (m, 4H, C**3**-$\underline{H}_2$, *A*+*B*), 2.52-2.44 (m, 4H, C**7**-$\underline{H}_2$, *A*+*B*), 2.16 (s, 3H, C**5**-$\underline{H}_3$, *A*), 2.11 (s, 3H, C**5**-$\underline{H}_3$, *B*), 2.03 (t, *J* = 3.2 Hz, 1H, C**9**-$\underline{H}$, *A*), 1.95 (t, *J* = 2.7 Hz, 1H, C**9**-$\underline{H}$, *B*), 1.03-0.88 (m, 2H, C**2**-$\underline{H}$, *A*+*B*), 0.63-0.56 (m, 2H, 2 × C**1**-$\underline{H}_aH_b$, *B*), 0.54-0.48 (m, 2H, 2 × C**1**-$\underline{H}_aH_b$, *A*), 0.29-0.20 (m, 4H, 2 × C**1**-$H_a\underline{H}_b$, *A*+*B*); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 170.3, 170.3 (C**4**, *A*+*B*), 82.2, 80.5 (C**8**, *A*+*B*), 70.7 (C**9**, *A*), 69.4 (C**9**, *B*), 54.0 (C**3**, *B*), 49.3 (C**3**, *A*), 46.9 (C**6**, *A*), 45.1 (C**6**, *B*), 21.7(C**5**, *A*+*B*), 18.8 (C**7**, *A*), 17.6 (C**7**, *B*), 10.5 (C**2**, *B*), 9.7 (C**2**, *A*), 3.7 (C**1**, *A*+*B*); HRMS: (ESI^+) calculated for $C_{10}H_{15}NNaO$: 188.1046, found $[M+Na]^+$: 188.1055.

***N*-(Cyclopropylmethyl)-*N*-(5-hydroxy-5-phenylpent-3-yn-1-yl)acetamide (454)**

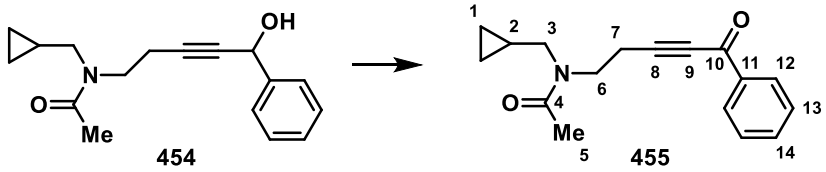


453 454

To a solution of **453** (1.00 g, 6.05 mmol) in dry THF (1 M) was added *n*-BuLi (3.47 mL, 5.55 mmol, 1.6 M in hexanes) dropwise over 5 minutes at 0 °C and the reaction was stirred at this temperature for 30 min. Then, benzaldehyde (0.51 mL, 5.04 mmol) was added dropwise over 5 minutes and the reaction mixture was warmed to r.t. and stirred for 2 h. Sat. aq. NH_4Cl (100 mL) was added and the solution was extracted with EtOAc (3 × 50 mL). The organic extracts were combined, washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (20-40% EtOAc/petrol) to afford the title compound **454** (580 mg, 42%, 1:1.5 mixture of rotamers *A*:*B*) as an orange oil; ν_{max} / cm^{-1}: 3335 (br. m), 1618 (s), 1450 (s), 1421 (s), 1131 (m), 1261 (s), 1011 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.53-7.48 (m, 4H, 2 × C**13**-$\underline{H}$, *A*+*B*), 7.41-7.29 (m, 6H, 2 × C**12**-$\underline{H}$ and C**14**-$\underline{H}$, *A*+*B*), 5.45 (br. s, 1H, C**10**-$\underline{H}$,

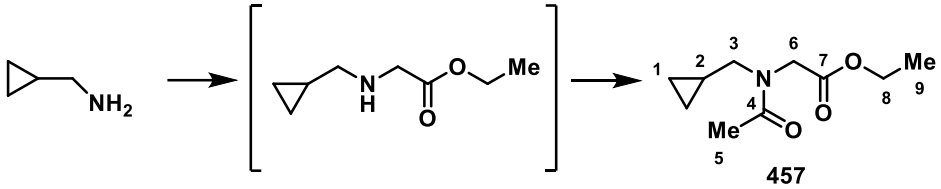
A), 5.43 (s, 1H, C**10**-H, *B*), 3.58 (t, *J* = 7.3 Hz, 2H, C**6**-H_2, *B*), 3.57 (t, *J* = 7.8 Hz, 2H, C**6**-H_2, *A*), 3.27 (d, *J* = 6.9 Hz, 2H, C**3**-H_2, *A*), 3.19 (d, *J* = 6.6 Hz, 2H, C**3**-H_2, *B*), 2.59-2.54 (m, 4H, C**7**-H_2, *A*+*B*), 2.12 (s, 3H, C**5**-H_3, *A*), 2.09 (s, 3H, C**5**-H_3, *B*), 1.03-0.84 (m, 2H, C**2**-H, *A*+*B*), 0.61-0.53 (m, 2H, C**1**-H_aH_b, *B*), 0.54-0.46 (m, 2H, C**1**-H_aH_b, *A*), 0.26-0.16 (m, 4H, 2 × C**1**-H_aH_b, *A*+*B*); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 170.7 (C**4**, *A*), 170.6 (C**4**, *B*), 141.3 (C**11**, *B*), 141.0 (C**11**, *A*), 128.6 (C**13**, *A*), 128.5 (C**13**, *B*), 128.2 (C**14**, *A*), 128.1 (C1**4**, *B*), 126.5 (C**12**, *B*), 126.5 (C**12**, *A*), 84.6 (C**8**, *B*), 82.9 (C**8**, *A*), 82.7 (C**9**, *A*), 81.6 (C**9**, *B*), 64.5 (C**10**, *A*+*B*), 53.8 (C**3**, *B*), 49.4 (C**3**, *A*), 46.9 (C**6**, *A*), 45.0 (C**6**, *B*), 21.7 (C**5**, *A*+*B*), 19.2 (C**7**, *A*), 18.0 (C**7**, *B*), 10.4 (C**2**, *B*), 9.7 (C**2**, *A*), 3.7 (C**1**, *A*+*B*); HRMS: (ESI^+) calculated for $C_{17}H_{21}NNaO_2$: 294.1464, found $[M+Na]^+$: 294.1467.

N-(Cyclopropylmethyl)-*N*-(5-oxo-5-phenylpent-3-yn-1-yl)acetamide (455)



To a stirring solution of **454** (0.20 g, 0.47 mmol) in DCM (10 mL), a spatula of celite and pyridinium dichromate (0.42 g, 1.11 mmol, 1.50 eq) were added and the mixture was stirred at r.t. for 2 h. The reaction was filtered through a pad of celite, a filtrate was evaporated to dryness *in vacuo* and purified by flash column chromatography (40% EtOAc/petrol) to afford the title compound **455** (156 mg, 78%, 1:2.94 mixture of rotamers *A*:*B*) as a yellow oil; ν_{max} / cm^{-1}: 3004 (br. w), 2235 (m), 1637 (s), 1597 (m), 1449 (m), 1419 (m), 1262 (S); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.14 – 8.07 (m, 4H, 2 × C**12**-H, *A*+*B*), 7.64 – 7.57 (m, 2H, C**14**-H, *A*+*B*), 7.52 – 7.44 (m, 4H, 2 × C**13**-H, *A*+*B*), 3.74 – 3.66 (m, 4H, C**6**-H_2, *A*+*B*), 3.33 (d, *J* = 6.9 Hz, 2H, C**3**-H_2, *A*), 3.28 (d, *J* = 6.6 Hz, 2H, C**3**-H_2, *B*), 2.83 (t, *J* = 7.1 Hz, 2H, C**7**-H_2, *B*), 2.80 (t, *J* = 7.2 Hz, 2H, C**7**-H_2, *A*), 2.19 (s, 3H, C**5**-H_3, *A*), 2.14 (s, 3H, C**5**-H_3, *B*), 1.03 – 0.85 (m, 2H, C**2**-H, *A*+*B*), 0.66 – 0.57 (m, 2H, C**1**-H_aH_b, *B*), 0.56 – 0.51 (m, 2H, C**1**-H_aH_b, *A*), 0.30 – 0.23 (m, 4H, 2 × C**1**-H_aH_b, *A*+*B*); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 178.0 (C**10**, *B*), 177.7 (C**10**, *A*), 170.5 (C**4**, *B*), 170.3 (C**4**, *A*), 136.7 (C**11**, *B*), 136.4 (C**11**, *A*), 134.3 (C**14**, *A*), 134.0 (C**14**, *B*), 129.6, 129.5, 128.6, 128.5 (C**12** and C**13**, *A*+*B*), 93.7 (C**8**, *B*), 91.4 (C**8**, *A*), 81.1 (C**9**, *A*), 80.4 (C**9**, *B*), 54.2 (C**3**, *B*), 49.5 (C**3**, *A*), 46.4 (C**6**, *A*), 44.6 (C**6**, *B*), 21.7 (C**5**, *B*), 21.7 (C**5**, *A*), 19.7 (C**7**, *A*), 18.4 (C**7**, *B*), 10.5 (C**2**, *B*), 9.8 (C**2**, *A*), 3.8 (C**1**, *A*), 3.8 (C**1**, *B*); HRMS: (ESI^+) calculated for $C_{17}H_{20}NO_2$: 270.1489, found $[M+H]^+$: 270.1488.

***N*-(Cyclopropylmethyl)-*N*-(2-oxobutyl)acetamide (457)**

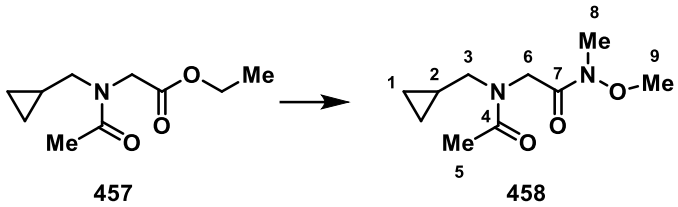


457

To a stirring solution of cyclopropylmethylamine (7.00 mL, 80.00 mmol) in dry acetonitrile (40 mL) was added ethyl bromoacetate (2.21 mL, 20.00 mmol) at 0 °C under nitrogen. The solution was warmed to r.t. and stirred for 1 h. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in DCM (40 mL). 3.0 M aq. NaOH solution (15 mL) was added and the aqueous portion was extracted with DCM (3 × 30 mL). The organic extracts were combined, dried over $MgSO_4$ and concentrated *in vacuo* until the concentration was reduced to *ca*. 2 mL/mmol.

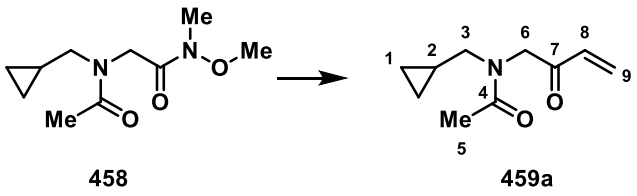
To the resulting solution of secondary amine in DCM, TEA (5.58 mL, 40.00 mmol) and acetic anhydride (3.77 mL, 40.00 mmol) were added at 0 °C under nitrogen. The solution was warmed to r.t. and stirred for 16 h. Water (50 mL) was added and the aqueous layer was extracted with DCM (3 × 20 mL). The combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by silica gel column chromatography (20-50% EtOAc/petrol) to yield the title compound **457** (3.94 g, quantitative over 2 steps, 1:2.4 mixture of rotamers *A*:*B*) as a colourless oil; ν_{max} / cm^{-1}: 2984 (br. m), 1745 (s), 1646 (s), 1425 (s), 1258 (m), 1190 (s), 1023 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.25-4.10 (m, 8H, C**6**-$\underline{H}_2$ and C**8**-$\underline{H}_2$, *A*+*B*), 3.31 (d, *J* = 7.0 Hz, 2H, C**3**-$\underline{H}_2$, *A*), 3.26 (d, *J* = 6.7 Hz, 2H, C**3**-$\underline{H}_2$, *B*), 2.17 (s, 3H, C**5**-$\underline{H}_3$, *B*), 2.06 (s, 3H, C**5**-$\underline{H}_3$, *A*), 1.31-1.24 (m, 6H, C**9**-$\underline{H}_3$, *A*+*B*), 0.98-0.84 (m, 2H, C**2**-$\underline{H}$, *A*+*B*), 0.62-0.54 (m, 2H, C**1**-$\underline{H}_a$$H_b$, *B*), 0.52-0.45 (m, 2H, C**1**-$\underline{H}_a$$H_b$, *A*), 0.21-0.16 (m, 4H, 2 × C**1**-$H_a\underline{H}_b$, *A*+*B*); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 170.9 (C**4**, *A*), 170.7 (C**4**, *B*), 169.5 (C**7**, *B*), 169.4 (C**7**, *A*), 61.5 (C**8**, *A*), 61.0 (C**8**, *B*), 53.9 (C**3**, *B*), 50.8 (C**3**, *A*), 50.2 (C**6**, *A*), 46.9 (C**6**, *B*), 21.6 (C**5**, *A*), 21.3 (C**5**, *B*), 14.2 (C**9**, *A*+*B*), 9.9 (C**2**, *B*), 9.2 (C**2**, *A*), 3.6 (C**1**, *B*), 3.5 (C**1**, *A*); HRMS: (ESI^+) calculated for $C_{10}H_{18}NO_3$: 200.1281, found $[M+H]^+$: 200.1282.

2-(*N*-(Cyclopropylmethyl)acetamido)-*N*-methoxy-*N*-methylacetamide (458)



To a suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (1.96 g, 20.01 mmol) in 40 mL of dry DCM, Me_2AlCl (1 M in hexanes, 20 mL) was added at 0 °C. The mixture was warmed to r.t. and stirred for 1 h. Then, a solution of ester **457** in 10 mL of dry DCM was added dropwise and the reaction was stirred at r.t. for 16 h. The solution was cooled to 0 °C, sat. aq. $NaHCO_3$ (50 mL) was added dropwise and the crude was filtered through Celite®. The filtrate was extracted with DCM (3 × 50 mL). The organic extracts were combined, washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the title compound **458** (1.49 g, 83%, 3:1 mixture of rotamers *A*:*B*) as a colourless oil which was used without further purification; ν_{max} / cm^{-1}: 3496 (br. w), 3001 (br. m), 2940 (br. m), 1641 (s), 1423 (s), 1388 (s), 988 (s); ^1H NMR ($CDCl_3$, 400 MHz): δ 4.36 (s, 2H, C**6**-$\underline{H}_2$, *A*), 4.29 (s, 2H, C**6**-$\underline{H}_2$, *B*), 3.74 (s, 2H, C**9**-$\underline{H}_2$, *A*), 3.71 (s, 2H, C**9**-$\underline{H}_2$, *B*), 3.30 – 3.24 (m, 4H, C**3**-$\underline{H}_2$, *A*+*B*), 3.19 (s, 2H, C**8**-$\underline{H}_2$, *B*), 3.15 (s, 2H, C**8**-$\underline{H}_2$, *A*), 2.15 (s, 2H, C**5**-$\underline{H}_2$, *A*), 2.01 (s, 2H, C**5**-$\underline{H}_2$, *B*), 0.97 – 0.84 (m, 2H, C**2**-$\underline{H}$, *A*+*B*), 0.58 – 0.52 (m, 2H, 2 × C**1**-$\underline{H}_a$$H_b$, *A*), 0.49 – 0.43 (m, 2H, 2 × C**1**-$\underline{H}_a$$H_b$, *B*), 0.19 – 0.13 (m, 4H, 2 × C**1**-$H_a$$\underline{H}_b$, *A*+*B*); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 171.4 (C**4**, *B*), 171.0 (C**4**, *A*), 169.7 (br. s, C**7**, *A*+*B*), 61.5 (C**9**, *B*), 61.3 (C**9**, *A*), 53.9 (C**3**, *A*), 50.7 (C**3**, *B*), 48.9 (C**6**, *B*), 45.7 (C**6**, *A*), 32.6 (C**8**, *B*), 32.3 (C**8**, *A*), 21.6 (C**5**, *B*), 21.4 (C**5**, *A*), 9.9 (C**2**, *A*), 9.3 (C**2**, *B*), 3.6 (C**1**, *A*), 3.5 (C**1**, *B*); HRMS: (ESI^+) calculated for $C_{10}H_{19}N_2O_3$: 215.1390, found $[M+H]^+$: 215.1384.

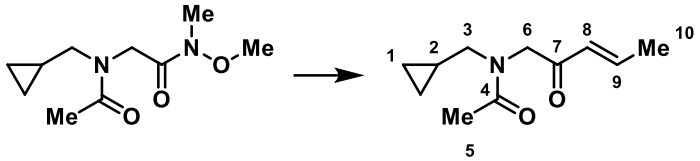
***N*-(Cyclopropylmethyl)-*N*-(2-oxobut-3-en-1-yl)acetamide (459a)**



Vinylmagnesium bromide (13.8 mL, 1.0 M in THF, 3.0 eq) was added dropwise to a solution of Weinreb amide **458** (984 mg, 4.59 mmol) in dry THF (25 mL) at -78 °C. The reaction was stirred at this temperature for 2.5 h (monitored by TLC, 8:2 EtOAc:petrol) and then poured into an ice-cold sat. aq. NH_4Cl. The mixture was extracted with Et_2O (3 × 20 mL). The organic extracts were combined, washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude

mixture was purified by silica gel column chromatography (50% EtOAc/petrol) to yield the title compound **459a** (66 mg, 8%, 1:3.7 mixture of rotamers *A*:*B*) as a colourless oil; ν_{max} / cm^{-1}: 3457 (br. w), 3003 (br. w), 2926 (br. w), 1697 (s), 1643 (s), 1427 (s), 988 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.51 – 6.27 (m, 4H, C**9**-H$_{2,cis}$ and C**8**-H, *A*+*B*), 5.92 (dd, *J* = 10.4, 1.2 Hz, 1H, C**9**-H$_{2,trans}$, *A*), 5.84 (dd, *J* = 10.3, 1.4 Hz, 1H, C**9**-H$_{2,trans}$, *B*), 4.47 (s, 2H, C**6**-H$_2$, *B*), 4.38 (s, 2H, C**6**-H$_2$, *A*), 3.27 (d, *J* = 7.0 Hz, 2H, C**3**-H$_2$, *A*), 3.22 (d, *J* = 6.7 Hz, 2H, C**3**-H$_2$, *B*), 2.17 (s, 3H, C**5**-H$_3$, *B*), 1.95 (s, 3H, C**5**-H$_3$, *A*), 0.95 – 0.79 (m, 2H, C**2**-H, *A*+*B*), 0.59 – 0.42 (m, 4H, 2 × C**1**-H$_a$H$_b$, *A*+*B*), 0.17 – 0.10 (m, 4H, 2 × C**1**-H$_a$H$_b$, *A*+*B*); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 195.0 (C**7**, *B*), 194.6 (C**7**, *A*), 171.0 (C**4**, *A*), 170.6 (C**4**, *B*), 133.8 (C**8**, *B*), 133.1 (C**8**, *A*), 129.9 (C**9**, *A*), 129.0 (C**9**, *B*), 55.8 (C**6**, *A*), 53.9 (C**3**, *B*), 52.6 (C**6**, *B*), 50.9 (C**3**, *A*), 21.5 (C**5**, *A*), 21.3 (C**5**, *B*), 9.9 (C**2**, *B*), 9.3 (C**2**, *A*), 3.7 (C**1**, *B*), 3.6 (C**1**, *A*); HRMS: (ESI^+) calculated for $C_{10}H_{15}NO_2$: 182.1176, found $[M+H]^+$: 182.1181.

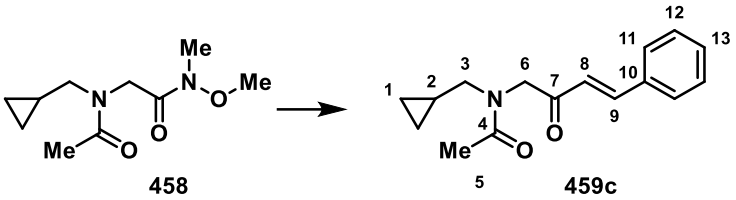
(*E*)-*N*-(Cyclopropylmethyl)-*N*-(2-oxopent-3-en-1-yl)acetamide (459b)



458 **459b**

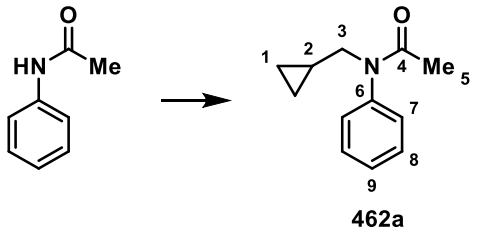
1-Propenylmagnesium bromide (5.6 mL, 0.5 M in THF, 2.0 eq) was added dropwise to a solution of Weinreb amide **458** (300 mg, 1.4 mmol) in dry THF (2 mL) at -78 °C. The reaction was stirred at this temperature for 2.5 h (monitored by TLC, 8:2 EtOAc:petrol) and then poured into an ice-cold sat. aq. NH_4Cl. The mixture was extracted with Et_2O (3 × 20 mL). The organic extracts were combined, washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by silica gel column chromatography (30-50% EtOAc/petrol) to yield the title compound **459b** (57 mg, 21%, 1:2.9 mixture of rotamers *A*:*B*) as a yellow oil; ν_{max} / cm^{-1}: 3003 (br. w), 2934 (br. w), 1684 (s), 1634 (s), 1428 (s), 1207 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.91 – 6.75 (m, 2H, C**9**-H, *A*+*B*), 6.09 (dq, *J* = 15.8, 1.7 Hz, C**8**-H, *A*), 6.03 (dq, *J* = 15.8, 1.7 Hz, 1H, C**8**-H, *B*), 4.28 (s, 2H, C**6**-H$_2$, *B*), 4.18 (s, 2H, C**6**-H$_2$, *A*), 3.13 (d, *J* = 7.0 Hz, 2H, C**3**-H$_2$, *A*), 3.08 (d, *J* = 6.7 Hz, 2H, C**3**-H$_2$, *B*), 2.03 (s, 3H, C**5**-H$_3$, *B*), 1.81 (s, 3H, C**5**-H$_3$, *A*), 1.81 – 1.79 (dd, *J* = 7.0, 1.7 Hz, 3H, C**10**-H$_3$, *A*), 1.76 (dd, *J* = 6.9, 1.7 Hz, 3H, C**10**-H$_3$, *B*), 0.74 (m, 2H, C**2**-H, *A*+*B*), 0.43 – 0.37 (m, 2H, 2 × C**1**-H$_a$H$_b$, *B*), 0.34 – 0.28 (m, 2H, 2 × C**1**-H$_a$H$_b$, *A*), 0.03 – -0.03 (m, 4H, 2 × C**1**-H$_a$H$_b$, *A*+*B*); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 194.5 (C**7**, *B*), 194.0 (C**7**, *A*), 171.1 (C**4**, *A*), 170.6 (C**4**, *B*), 144.8 (C**9**, *A*), 143.6 (C**9**, *B*), 129.0 (C**8**, *B*), 128.2 (C**8**, *A*), 56.0 (C**6**, *A*), 53.8 (C**3**, *B*), 52.6 (C**6**, *B*), 50.9 (C**3**, *A*), 21.5 (C**5**, *A*), 21.3 (C**5**, *B*), 18.5 (C**10**, *B*), 18.4 (C**10**, *A*), 9.9 (C**2**, *B*), 9.3 (C**2**, *A*), 3.6 (C**1**, *B*), 3.5 (C**1**, *A*); HRMS: (ESI^+) calculated for $C_{11}H_{17}NNaO_2$: 218.1151, found $[M+Na]^+$: 218.1162.

(*E*)-*N*-(cyclopropylmethyl)-*N*-(2-oxo-4-phenylbut-3-en-1-yl)acetamide (459c)



Styrylmagnesium bromide (5.6 mL, 0.55 M in THF, 2.0 eq, freshly prepared from β-bromostyrene[27]) was added dropwise to a solution of Weinreb amide **458** (300 mg, 1.4 mmol) in dry THF (2 mL) at -78 °C. The reaction was stirred at this temperature for 2.5 h (monitored by TLC, 8:2 EtOAc:petrol) and then poured into an ice-cold sat. aq. NH_4Cl. The mixture was extracted with Et_2O (3 × 20 mL). The organic extracts were combined, washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by silica gel column chromatography (20-40% EtOAc/petrol) to yield the title compound **459c** (53 mg, 22%, 1:3.0 mixture of rotamers *A*:*B*) as a yellow oil; ν_{max} / cm^{-1}: 3003 (w), 2925 (w), 1639 (s), 1612 (s), 1449 (m), 1426 (m), 1188 (m); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.70 (d, *J* = 16.1 Hz, 1H, C**9**-H, *A*), 7.64 (d, *J* = 16.2 Hz, 1H, C**9**-H, *B*), 7.58 – 7.51 (m, 4H, 2 × C**11**, *A*+*B*), 7.43 – 7.36 (m, 6H, C**13** and 2 × C**12**, *A*+*B*), 6.84 (d, *J* = 16.1 Hz, 1H, C**8**-H, *A*), 6.78 (d, *J* = 16.2 Hz, 1H, C**8**-H, *B*), 4.54 (s, 2H, C**6**-H_2, *B*), 4.43 (s, 2H, C**6**-H_2, *A*), 3.33 (d, *J* = 6.9 Hz, 2H, C**3**-H_2, *A*), 3.27 (d, *J* = 6.7 Hz, 2H, C**3**-H_2, *B*), 2.20 (s, 3H, C**5**-H_3, *B*), 2.01 (s, 3H, C**5**-H_3, *A*), 0.96 – 0.85 (m, 2H, C**2**-H, *A*+*B*), 0.60 – 0.53 (m, 2H, 2 × C**1**-H_aH_b, *B*), 0.51 – 0.45 (m, 2H, 2 × C**1**-H_aH_b, *A*), 0.20 – 0.15 (m, 4H, 2 × C**1**-H_aH_b, *A*+*B*); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 194.8 (C**7**, *B*), 194.4 (C**7**, *A*), 171.1 (C**4**, *A*), 170.7 (C**4**, *B*), 144.4 (C**9**, *A*), 143.4 (C**9**, *B*), 134.3 (C**10**, *B*), 133.9 (C**10**, *A*), 131.16 (C**13**, *A*), 130.7 (C**13**, *B*), 129.1 (C**12**, *A*), 128.9 (C**12**, *B*), 128.5 (C**11**, *A*), 128.4 (C**11**, *B*), 123.2 (C**8**, *B*), 121.8 (C**8**, *A*), 56.8 (C**6**, *A*), 53.9 (C**3**, *B*), 53.4 (C**6**, *B*), 51.0 (C**3**, *A*), 21.6 (C**5**, *A*), 21.3 (C**5**, *B*), 10.0 (C**2**, *B*), 9.4 (C**2**, *A*), 3.7 (C**1**, *B*), 3.6 (C**1**, *A*); HRMS: (ESI^+) calculated for $C_{16}H_{20}NO_2$: 258.1489, found $[M+H]^+$: 258.1493.

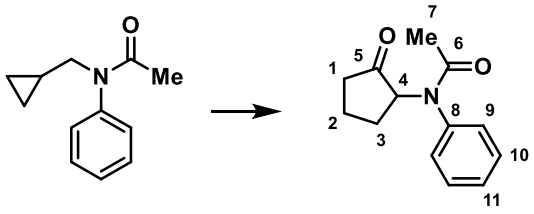
***N*-(Cyclopropylmethyl)-*N*-phenylacetamide (462a)**



462a

General procedure P: Acetanilide (1.88 g, 13.91 mmol) was employed. Flash column chromatography (10-20% EtOAc/petrol) afforded the title compound **462a** (2.40 g, 91%) as a pale pink solid; m.p. 44-45 °C (EtOAc/hexane); ν_{max} / cm^{-1}: 3005 (br. w), 1654 (s), 1595 (s), 1496 (s), 1396 (s), 1290 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.45 – 7.31 (m, 3H, C**9**-H and 2 × C**8**-H), 7.24 – 7.19 (m, 2H, 2 × C**7**-H), 3.57 (d, *J* = 7.2 Hz, 2H, C**3**-H_2), 1.83 (s, 3H, C**5**-H_3), 1.01 – 0.87 (m, 1H, C**2**-H), 0.45 – 0.38 (m, 2H, C**1**-H_aH_b), 0.14 – 0.08 (m, 2H, C**1**-H_aH_b); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 170.2 (C**4**), 143.3 (C**6**), 129.5 (C**8**), 128.4 (C**7**), 127.8 (C**9**), 53.2 (C**3**), 22.8 (C**5**), 9.9 (C**2**), 3.6 (C**1**); HRMS: (ESI^+) calculated for $C_{12}H_{16}NO$: 190.1226, found $[M+H]^+$: 190.1230.

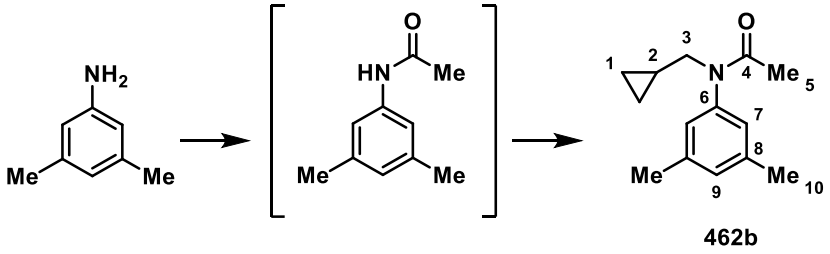
***N*-(2-Oxocyclopentyl)-*N*-phenylacetamide (463a)**



462a **463a**

General procedure N: Compound **462a** (28.4 mg, 0.15 mmol), $[Rh(cod)_2]OTf$ (5.3 mg, 0.011 mmol, 7.5 mol%) and $P(3,4,5\text{-}F_3C_6H_2)_3$ (9.5 mg, 0.023 mmol, 15 mol%) were employed and the reaction was stirred for 24 h at 110 °C. The crude mixture was purified by silica gel column chromatography (30% EtOAc/petrol) to yield the title compound **463a** (27.7 mg, 85%) as an off-white solid; m.p. 77-78 °C (DCM/hexane); ν_{max} / cm^{-1}: 2965 (br. w), 1746 (s), 1652 (s), 1595 (s), 1493 (s), 1399 (s), 1328 (s), 1257 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.42 – 7.30 (m, 3H, C**11**-H and 2 × C**10**-H), 7.26 – 7.22 (m, 2H, 2 × C**9**-H), 4.20 – 4.12 (m, 1H, C**4**-H), 2.42 – 2.01 (m, 5H, C**2**-H_aH_b, C**3**-H_2 and C**1**-H_2), 1.82 (s, 3H, C**7**-H_3), 1.78 – 1.64 (m, 1H, C**2**-H_aH_b); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 213.4 (C**5**), 170.0 (C**6**), 142.6 (C**8**), 129.8 (C**10**), 128.5 (C**9**), 128.3 (C**11**), 66.3 (C**4**), 35.9, 26.7 (C**1** and C**3**), 22.5 (C**7**), 18.9 (C**2**); HRMS: (ESI^+) calculated for $C_{13}H_{15}NNaO_2$: 240.0995, found $[M+Na]^+$: 240.1002.

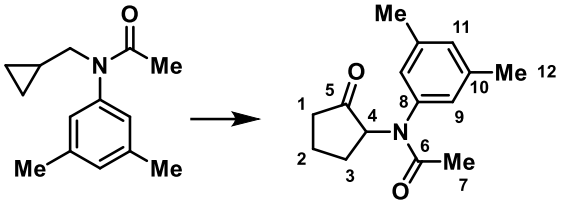
***N*-(Cyclopropylmethyl)-*N*-(3,5-dimethylphenyl)acetamide (462b)**



462b

General procedure P: *N*-(3,5-Dimethylphenyl)acetamide (1.25 g, 7.66 mmol, prepared according to the literature procedure[293] from 3,5-dimethylaniline) was employed. Flash column chromatography (15-20% EtOAc/petrol) afforded the title compound **462b** (1.29 g, 78% over two steps) as a pale yellow oil; ν_{max} / cm^{-1}: 3004 (br. w), 2919 (br. w), 1657 (s), 1595 (s), 1378 (s), 1305 (s); ^1H NMR ($CDCl_3$, 400 MHz): δ 6.96 (s, 1H, C**9**-H), 6.82 (br. s, 2H, 2 × C**7**-H), 3.53 (d, *J* = 7.1 Hz, 2H, C**3**-H_2), 2.39 – 2.26 (m, 6H, 2 × C**10**-H_3), 1.83 (s, 3H, C**5**-H_3), 1.02 – 0.87 (m, 1H, C**2**-H), 0.45 – 0.37 (m, 2H, C**1**-H_aH_b), 0.16 – 0.11 (m, 2H, C**1**-H_aH_b); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 170.2 (C**4**), 143.2 (C**6**), 139.1 (C**8**), 129.3 (C**9**), 125.9 (C**7**), 53.2 (C**3**), 22.7 (C**5**), 21.2 (C**10**), 10.00 (C**2**), 3.6 (C**1**); HRMS: (ESI^+) calculated for $C_{14}H_{19}NNaO$: 240.1359, found $[M+Na]^+$: 240.1370.

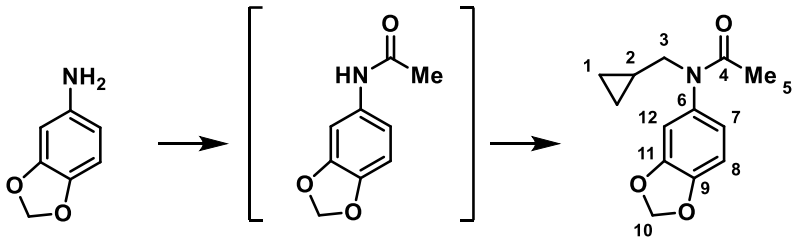
***N*-(3,5-Dimethylphenyl)-*N*-(2-oxocyclopentyl)acetamide (463b)**



462b 463b

General procedure N: Compound **462b** (32.6 mg, 0.15 mmol), $[Rh(cod)_2]OTf$ (5.3 mg, 0.011 mmol, 7.5 mol%) and $P(3,4,5\text{-}F_3C_6H_2)_3$ (9.5 mg, 0.023 mmol, 15 mol%) were employed and the reaction was stirred for 24 h at 110 °C. The crude mixture was purified by silica gel column chromatography (30% EtOAc/petrol) to yield the title compound **463b** (26.9 mg, 73%) as a pale yellow oil; ν_{max} / cm^{-1}: 2964 (br. w), 2919 (w), 1747 (s), 1657 (s), 1596 (s), 1398 (s), 1327 (s); ^1H NMR ($CDCl_3$, 400 MHz): δ 6.97 (br. s, 1H, C**11**-H), 6.86 (br. s, 2H, 2 × C**9**-H), 4.05 (t, *J* = 10.0 Hz, 1H, C**4**-H), 2.41 (ddd, *J* = 18.5, 11.8, 9.2 Hz, 1H, C**1**-H_aH_b), 2.32 (s, 6H, 2 × C**12**-H_3), 2.30 – 2.19 (m, 3H, C**1**-H_aH_b and C**3**-H_2), 2.14 – 2.04 (m, 1H, C**2**-H_aH_b), 1.84 (s, 3H, C**7**-H_3), 1.78 – 1.63 (m, 1H, C**2**-H_aH_b); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 213.5 (C**5**), 169.9 (C**6**), 142.7 (C**8**), 139.6 (C**10**), 129.8 (C**11**), 125.8 (C**9**), 66.5 (C**4**), 35.9 (C**1**), 26.8 (C**3**), 22.4 (C**7**), 21.1 (C**12**), 19.0 (C**2**); HRMS: (ESI^+) calculated for $C_{15}H_{20}NO_2$: 246.1489, found $[M+H]^+$: 246.1498.

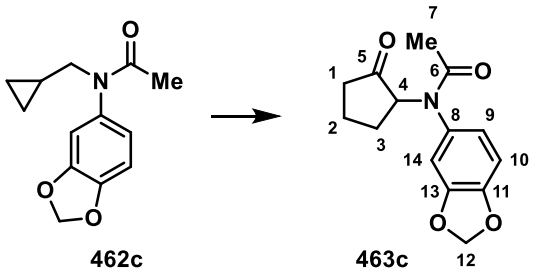
***N*-(Benzo[*d*][1,3]dioxol-5-yl)-*N*-(cyclopropylmethyl)acetamide (462c)**



462c

General procedure P: *N*-(Benzo[*d*][1,3]dioxol-5-yl)acetamide (1.00 g, 5.58 mmol, prepared according to the literature procedure[294] from 3,4-(methylenedioxy)aniline) was employed. Flash column chromatography (40% EtOAc/petrol) afforded the title compound **462c** (1.06 g, 79% over two steps) as a pale brown solid; m.p. 71-72 °C (DCM/hexane); ν_{max} / cm^{-1}: 2908 (br. w), 1655 (s), 1485 (s), 1214 (s), 1034 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.82 – 6.78 (m, 1H, C**7**-H), 6.70 – 6.66 (m, 2H, C**8**-H and C**12**-H), 6.02 (s, 2H, C**10**-H_2), 3.51 (d, *J* = 7.2 Hz, 2H, C**3**-H_2), 1.85 (s, 3H, C**5**-H_3), 0.99 – 0.88 (m, 1H, C**2**-H), 0.46 – 0.38 (m, 2H, C**1**-H_aH_b), 0.16 – 0.10 (m, 2H, C**1**-H_aH_b); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 170.5 (C**4**), 148.2 (C**11**), 147.0 (C**9**), 137.1 (C**6**), 121.8 (C**12**), 109.2 (C**8**), 108.4 (C**7**), 101.7 (C**10**), 53.3 (C**3**), 22.6 (C**5**), 9.9 (C**2**), 3.7 (C**1**); HRMS: (ESI^+) calculated for $C_{13}H_{15}NNaO_3$: 256.0944, found $[M+Na]^+$: 256.0953.

***N*-(Benzo[*d*][1,3]dioxol-5-yl)-*N*-(2-oxocyclopentyl)acetamide (463c)**

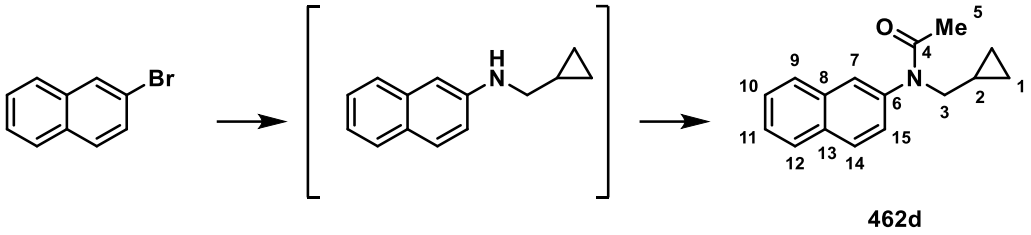


462c **463c**

General procedure N: Compound **462c** (35.0 mg, 0.15 mmol), $[Rh(cod)_2]OTf$ (5.3 mg, 0.011 mmol, 7.5 mol%) and $P(3,4,5\text{-}F_3C_6H_2)_3$ (9.5 mg, 0.023 mmol, 15 mol%) were employed and the reaction was stirred for 18 h at 110 °C. The crude mixture was purified by silica gel column chromatography (30-40% EtOAc/hexane) to yield the title compound **463c** (21.3 mg, 54%) as a pale yellow oil; ν_{max} / cm^{-1}: 2965 (br. w), 2906 (br. w), 1745 (s), 1655 (s), 1484 (s), 1215 (s), 1034 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.78 (dd, *J* = 7.9, 0.6 Hz, 1H, C**9**-H), 6.74 – 6.69 (m, 2H, C**10**-H and C**14**-H), 6.00 (s, 2H, C**12**-H_2), 4.23 (t, *J* = 9.6 Hz, 1H, C**4**-H), 2.39 – 2.01 (m, 5H, C**1**-H_2, C**3**-H_2, C**2**-H_aH_b), 1.86 (s, 3H, C**7**-H_3), 1.81 – 1.66 (m, 1H, C**2**-H_aH_b); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 213.5 (C**5**), 170.4 (C**6**), 148.3, 147.4 (C**11** and C**13**), 136.2 (C**8**), 122.1 (C**9**), 109.4 (C**10**),

108.5 (C**14**), 101.8 (C**12**), 66.1 (C**4**), 35.8 (C**1**), 26.6 (C**3**), 22.4 (C**7**), 18.9 (C**2**); HRMS: (ESI$^+$) calculated for $C_{14}H_{16}NO_4$: 262.1074, found $[M+H]^+$: 262.1069.

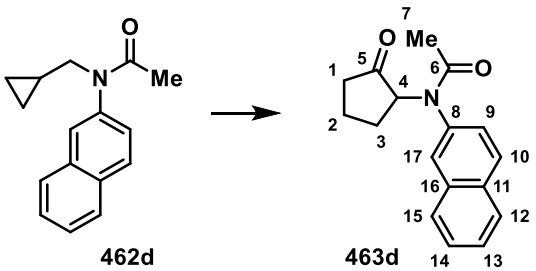
N-(Cyclopropylmethyl)-*N*-(naphthalen-2-yl)acetamide (462d)



462d

The secondary amine intermediate was prepared according to the **general procedure O** from 2-bromonaphthalene (0.62 g, 3.00 mmol) and cyclopropylmethylamine (0.39 mL, 4.50 mmol). Flash column chromatography (2% EtOAc/petrol) afforded the secondary amine (0.51 g, 86%) as a pale yellow oil which was acylated according to the **general procedure D** using acetic anhydride (0.29 mL, 3.10 mmol). Flash column chromatography (20% EtOAc/petrol) afforded the title compound **462d** (0.61 g, 98%) as a colourless oil; ν_{max} / cm^{-1}: 3003 (br. w), 1653 (s), 1627 (s), 1597 (m), 1397 (s), 1286 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.92 – 7.82 (m, 3H, Ar-C<u>H</u>), 7.70 (d, *J* = 2.1 Hz, 1H, Ar-C<u>H</u>), 7.57 – 7.51 (m, 2H, Ar-C<u>H</u>), 7.33 (dd, *J* = 8.6, 2.1 Hz, 1H, Ar-C<u>H</u>), 3.67 (d, *J* = 7.2 Hz, 2H, C**3**-<u>H$_2$</u>), 1.88 (s, 3H, C**5**-<u>H$_3$</u>), 1.05 – 0.94 (m, 1H, C**2**-<u>H</u>), 0.46 – 0.39 (m, 2H, C**1**-<u>H$_a$</u>H$_b$), 0.16 – 0.09 (m, 2H, C**1**-H$_a$<u>H$_b$</u>); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 170.3 (C**4**), 140.7 (C**6**), 133.6 (C**8**), 132.4, 129.5, 127.9, 127.8, 126.9, 126.8, 126.6, 126.4 (C**7**, C**9**, C**10**, C**11**, C**12**, C**13**, C**14** and C**15**), 53.4 (C**3**), 22.9 (C**5**), 10.0 (C**2**), 3.7 (C**1**); HRMS: (ESI$^+$) calculated for $C_{16}H_{17}NNaO$: 262.1202, found $[M+Na]^+$: 262.1203.

N-(Naphthalen-2-yl)-*N*-(2-oxocyclopentyl)acetamide (463d)

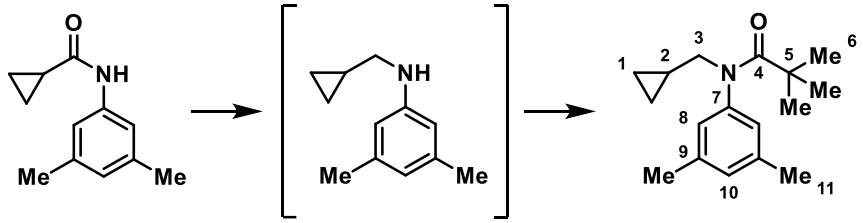


462d **463d**

General procedure N: Compound **462d** (35.9 mg, 0.15 mmol), $[Rh(cod)_2]OTf$ (5.3 mg, 0.011 mmol, 7.5 mol%) and $P(3,4,5\text{-}F_3C_6H_2)_3$ (9.5 mg, 0.023 mmol, 15 mol%) were employed and the reaction was stirred for 24 h at 110 °C. The crude mixture was purified by silica gel column chromatography (30% EtOAc/petrol) to yield the title compound **463d** (26.1 mg, 65%) as a pale

brown oil; ν_{max} / cm^{-1}: 2965 (br. w), 1747 (s), 1658 (s), 1629 (s), 1401 (m), 1326 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.91 – 7.82 (m, 3H, Ar-C<u>H</u>), 7.75 (d, *J* = 2.1 Hz, 1H, C**17**-<u>H</u>), 7.57 – 7.51 (m, 2H, Ar-C<u>H</u>), 7.36 (dd, *J* = 8.6, 2.1 Hz, 1H, C**9**-<u>H</u>), 4.34 – 4.24 (m, 1H, C**4**-<u>H</u>), 2.44 – 2.18 (m, 4H, C**1**-<u>H_2</u> and C**3**-<u>H_2</u>), 2.14 – 2.03 (m, 1H, C**2**-<u>H_a</u>H_b), 1.88 (s, 3H, C**7**-<u>H_3</u>), 1.82 – 1.68 (m, 1H, C**2**-H_a<u>H_b</u>); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 213.5 (C**5**), 170.2 (C**6**), 139.9 (C**8**), 133.6, 132.6 (C**11** and C**16**), 129.9, 128.0, 127.7 (C**10**, C**12** and C**15**), 127.1 (C**17**), 126.9, 126.9 (C**13** and C**14**), 126.4 (C**9**), 66.4 (C**4**), 35.9 (C**1**), 26.8 (C**3**), 22.7 (C**7**), 19.0 (C**2**); HRMS: (ESI^+) calculated for $C_{17}H_{17}NNaO_2$: 290.1151, found $[M+Na]^+$: 290.1139.

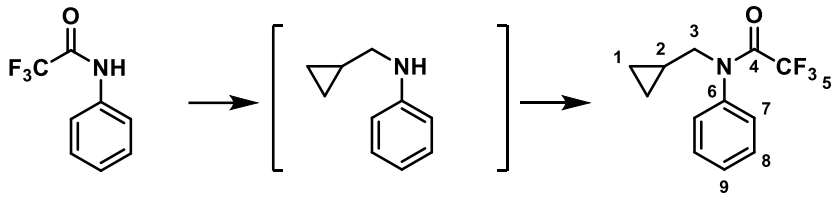
***N*-(Cyclopropylmethyl)-*N*-(3,5-dimethylphenyl)pivalamide (468)**



469 468

Amide **469** (2.00 g, 10.57 mmol, prepared according to the literature procedure[294] from 3,5-dimethylaniline) was reduced according to the **general procedure K**. The resulting secondary amine was protected according to the **general procedure D** with pivaloyl chloride (1.56 mL, 12.68 mmol) and the residue was purified by flash column chromatography (10% EtOAc/petrol) to afford the title compound **468** (2.18 g, 80% over two steps) as a pale yellow oil; ν_{max} / cm^{-1}: 2997 (br. w), 2958 (br. w), 2919 (br. w), 1636 (s), 1593 (s), 1480 (m), 1185 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.95 – 6.93 (br. m, 1H, C**10**-<u>H</u>), 6.85 – 6.84 (br. m, 2H, 2 × C**8**-<u>H</u>), 3.46 (d, *J* = 7.1 Hz, 2H, C**3**-<u>H_2</u>), 2.36 – 2.26 (m, 6H, 2 × C**11**-<u>H_3</u>), 1.03 (s, 9H, 2 × C**6**-<u>H_3</u>), 1.01 – 0.94 (m, 1H, C**2**-<u>H</u>), 0.43 – 0.36 (m, 2H, C**1**-<u>H_a</u>H_b), 0.12 – 0.06 (m, 2H, C**1**-H_a<u>H_b</u>);^{13}C NMR ($CDCl_3$, 101 MHz): δ 177.5 (C**4**), 143.6 (C**7**), 138.3 (C**9**), 129.1 (C**10**), 127.6 (C**8**), 56.9 (C**3**), 41.1 (C**5**), 29.6 (C**6**), 21.2 (C**11**), 9.7 (C**2**), 3.6 (C**1**); HRMS: (ESI^+) calculated for $C_{17}H_{26}NO$: 260.2009, found $[M+H]^+$: 260.2019.

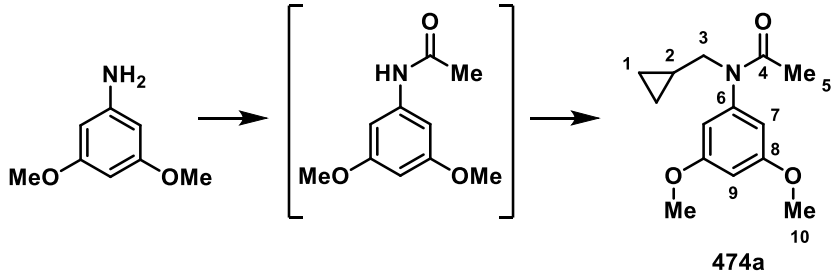
***N*-(cyclopropylmethyl)-2,2,2-trifluoro-*N*-phenylacetamide (470)**



471 470

Acetamide **471** (2.00 g, 12.58 mmol, prepared according to the literature procedure[295] from aniline) was alkylated according to the **general procedure P**. Trifluoroacetyl group was removed under these reaction conditions. The resulting secondary amine (0.55 g, 3.74 mmol) was protected according to the **general procedure D** with trifluoroacetic anhydride (0.55 mL, 3.92 mmol) and the residue was purified by flash column chromatography (0-5% diethyl ether/petrol) to afford the title compound **470** (0.41 g, 13% over two steps) as a yellow oil; ν_{max} / cm^{-1}: 3084 (br. w), 3010 (br. w), 1691 (s), 1495 (m), 1194 (s), 1144 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.46 – 7.39 (m, 3H, C**9**-H, 2 × C**8**-H), 7.30 – 7.25 (m, 2H, 2 × C**7**-H), 3.63 (d, *J* = 7.3 Hz, 2H, C**3**-H_2), 1.06 – 0.94 (m, 1H, C**2**-H), 0.55 – 0.44 (m, 2H, C**1**-H_aH_b), 0.22 – 0.14 (m, 2H, C**1**-H_aH_b);^{13}C NMR (126 MHz, $CDCl_3$): δ 156.71 (q, *J* = 35.3 Hz, C**4**), 139.2 (C**6**), 129.2 (C**8**), 129.0 (C**7**), 128.7 (C**9**), 116.48 (q, *J* = 288.5 Hz, C**5**), 56.1 (C**3**), 9.1 (C**2**), 3.7 (C**1**); ^{19}F NMR ($CDCl_3$, 376 MHz): -67.1(C**5**-F_3); HRMS: (ESI^+) calculated for $C_{12}H_{13}F_3NO$: 244.0944, found $[M+H]^+$: 244.0941.

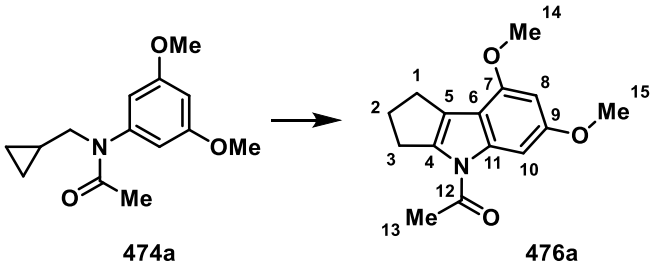
***N*-(Cyclopropylmethyl)-*N*-(3,5-dimethoxyphenyl)acetamide (474a)**



474a

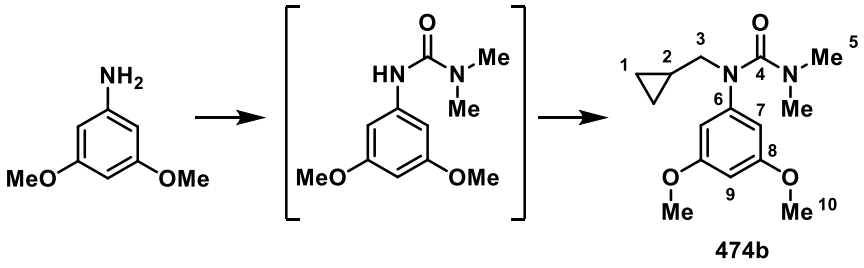
General procedure P: *N*-(3,5-Dimethoxyphenyl)acetamide (1.50 g, 7.68 mmol, prepared according to the literature procedure[296] from 3,5-dimethoxyaniline) was employed. Flash column chromatography (20-30% EtOAc/pentane) afforded the title compound **474a** (1.59 g, 83% over two steps) as a pale yellow oil; ν_{max} / cm^{-1}: 3003 (br. w), 2937 (br. w), 1656 (s), 1589 (s), 1205 (s), 1152 (s), 1061 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.44 (t, *J* = 2.3 Hz, 1H, C**9**-H), 6.37 (d, *J* = 2.3 Hz, 2H, 2 × C**7**-H), 3.79 (s, 6H, 2 × C**10**-H_3), 3.54 (d, *J* = 7.1 Hz, 2H, C**3**-H_2), 1.89 (s, 3H, C**5**-H_3), 1.04 – 0.92 (m, 1H, C**2**-H), 0.47 – 0.40 (m, 2H, 2 × C**1**-H_aH_b), 0.18 – 0.12 (m, 2H, 2 × C**1**-H_aH_b); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 170.1 (C**4**), 161.2 (C**8**), 145.1 (C**6**), 106.7 (C**7**), 99.6 (C**9**), 55.5 (C**10**), 53.1 (C**3**), 22.6 (C**5**), 10.0 (C**2**), 3.7 (C**1**); HRMS: (ESI^+) calculated for $C_{14}H_{20}NO_3$: 250.1438, found $[M+H]^+$: 250.1444.

1-(6,8-dimethoxy-2,3-dihydrocyclopenta[*b*]indol-4(1*H*)-yl)ethan-1-one (476a)



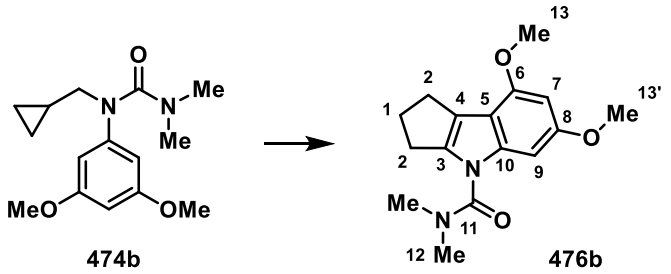
General procedure N: Compound **474a** (37.4 mg, 0.15 mmol), [Rh(cod)$_2$]OTf (5.3 mg, 0.011 mmol, 7.5 mol%) and P(3,4,5-F$_3$C$_6$H$_2$)$_3$ (9.5 mg, 0.023 mmol, 15 mol%) were employed and the reaction was stirred for 24 h at 110 °C. The crude mixture was purified by silica gel column chromatography (10% EtOAc/pentane) to yield the title compound **61a** (34.2 mg, 88%) as a colourless solid; m.p. 183-184 °C (DCM/hexane); ν_{max} / cm^{-1}: 2967 (m), 2928 (br. m), 1696 (s), 1609 (s), 1583 (s), 1425 (s), 1379 (s), 1301 (s), 1287 (s), 1111 (s); ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.69 (s, 1H, C**8**-H), 6.35 (s, 1H, C**10**-H), 3.85 (s, 3H, C**14**-H$_3$ or C**15**-H$_3$), 3.84 (s, 3H, C**14**-H$_3$ or C**15**-H$_3$), 3.06 – 2.99 (m, 2H, C**3**-H$_2$), 2.90 – 2.83 (m, 2H, C**1**-H$_2$), 2.53 (s, 3H, C**13**-H$_3$), 2.51 – 2.44 (m, 3H, C**2**-H$_2$); ^{13}C NMR (CDCl$_3$, 126 MHz,): δ 169.5 (C**12**), 158.6, 152.6 (C**7** and C**9**), 142.1 (C**11**), 138.2 (C**4**), 126.0 (C**5**), 111.2 (C**6**), 95.2 (C**10**), 94.4 (C**8**), 55.8, 55.5 (C**14** and C**15**), 30.1 (C**3**), 28.0 (C**2**), 25.5 (C**1**), 25.2 (C**13**); HRMS: (ESI$^+$) calculated for $C_{15}H_{18}NO_3$: 260.1281, found [M+H]$^+$: 260.1286.

1-(Cyclopropylmethyl)-1-(3,5-dimethoxyphenyl)-3,3-dimethylurea (474b)



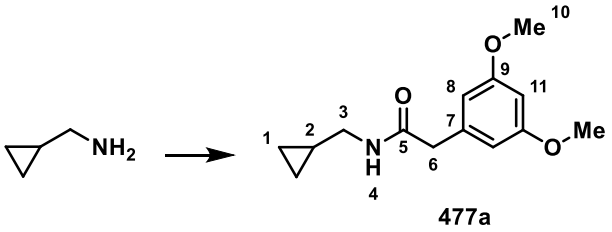
General procedure P: 3-(3,5-Dimethoxyphenyl)-1,1-dimethylurea (0.30 g, 1.34 mmol, prepared according to the literature procedure[297] from 3,5-dimethoxyaniline) was employed. Flash column chromatography (10-30% EtOAc/petrol) afforded the title compound **474b** (0.22 g, 64% over two steps) as a pale brown oil; ν_{max} / cm^{-1}: 2936 (br. m), 1648 (m), 1592 (s), 1376 (m), 1206 (s), 1153 (m), 1063 (m); ^{1}H NMR (CDCl$_3$, 400 MHz): δ 6.24 – 6.19 (m, 3H, C**9**-H and 2 × C**7**-H), 3.76 (s, 6H, 2 × C**10**-H$_3$), 3.48 (d, *J* = 6.8 Hz, 2H, C**3**-H$_2$), 2.72 (s, 6H, 2 × C**5**-H$_3$), 1.18 – 1.06 (m, 1H, C**2**-H), 0.45 – 0.37 (m, 2H, 2 × C**1**-H$_a$H$_b$), 0.19 – 0.13 (m, 2H, 2 × C**1**-H$_a$H$_b$); ^{13}C NMR (CDCl$_3$, 101 MHz): δ 161.4 (C**4**), 161.2 (C**8**), 147.9 (C**6**), 102.8 (C**7**), 95.9 (C**9**), 56.3 (C**3**), 55.4 (C**10**), 37.9 (C**5**), 10.8 (C**2**), 3.7 (C**1**); HRMS: (ESI$^+$) calculated for $C_{15}H_{22}N_2NaO_3$: 301.1523, found [M+Na]$^+$: 301.1526.

6,8-Dimethoxy-*N*,*N*-dimethyl-2,3-dihydrocyclopenta[*b*]indole-4(1*H*)-carboxamide (476b)



General procedure N: Compound **474b** (41.8 mg, 0.15 mmol), $[Rh(cod)_2]OTf$ (5.3 mg, 0.011 mmol, 7.5 mol%) and $P(3,4,5\text{-}F_3C_6H_2)_3$ (9.5 mg, 0.023 mmol, 15 mol%) were employed and the reaction was stirred for 24 h at 110 °C. The crude mixture was purified by silica gel column chromatography (20% EtOAc/petrol) to yield the title compound **476b** (32.3 mg, 75%) as a brown oil; ν_{max} / cm^{-1}: 2940 (br. m), 1684 (s), 1611 (s), 1453 (s), 1388 (s), 1152 (s); ^1H NMR ($CDCl_3$, 400 MHz): δ 6.59 (d, *J* = 2.0 Hz, 1H, C**7**-H), 6.25 (d, *J* = 2.0 Hz, 1H, C**9**-H), 3.86 (s, 3H, C**13**-H_3), 3.82 (s, 3H, C**13'**-H_3), 3.04 (s, 6H, 2 × C**12**-H_3), 2.90 – 2.82 (m, 4H, 2 × C**2**-H_2), 2.50 – 2.42 (m, 2H, C**1**-H_2); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 157.4 (C**6** or C**8**), 155.3 (C**11**), 153.2(C**6** or C**8**), 141.5 (C**10**), 140.8 (C**3**), 121.7 (C**4**), 110.8 (C**5**), 93.0, 90.4 (C**7** and C**9**), 55.8 (C**13**), 55.5 (C**13'**), 38.2 (C**12**), 28.3 (C**1**), 26.6 (C**2**), 25.7 (C**2**); HRMS: (ESI^+) calculated for $C_{16}H_{21}N_2O_3$: 289.1547, found $[M+H]^+$: 289.1558.

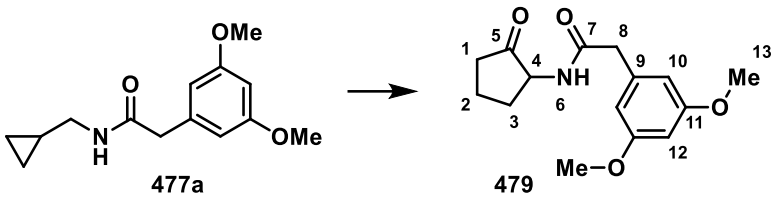
***N*-(Cyclopropylmethyl)-2-(3,5-dimethoxyphenyl)acetamide (477a)**



To a solution of (3,5-dimethoxyphenyl)acetic acid (0.75 g, 3.82 mmol) in DCM (1 mL), stirring under a nitrogen atmosphere at room temperature, oxalyl chloride (0.40 mL, 4.59 mmol) and a drop of *N*,*N*-dimethylformamide were added. The reaction was stirred until gas effervescence stopped. DCM and an excess of oxalyl chloride were removed *in vacuo* and the resulting acyl chloride was adder dropwise to a mixture of cyclopropylmethylamine (0.40 mL, 4.59 mmol) and TEA (0.64 mL, 4.59 mmol) at 0 °C. The mixture was warmed to r.t. and stirred for 18 h. The mixture was diluted with water (30 mL) and extracted with DCM (3 × 20 mL). The organic extracts were combined, washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by recrystallisation (Et_2O/DCM/hexane, 2 crops) to afford the title compound

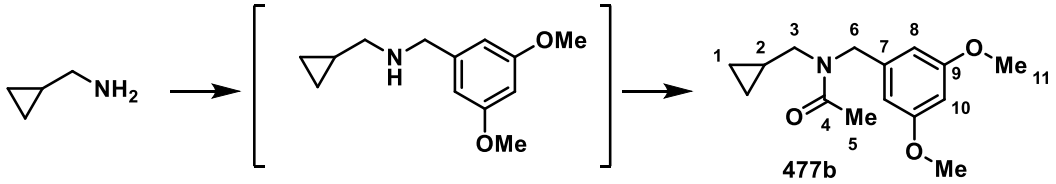
477a (0.66 g, 69%) as a colourless solid; m.p. 93-94 °C (Et_2O/DCM/hexane); ν_{max} / cm^{-1}: 3295 (br. s), 3008 (br. w), 2960 (br. w), 1640 (s), 1596 (s), 1548 (m), 1205 (s), 1151 (s); ^1H NMR ($CDCl_3$, 400 MHz): δ 6.42 – 6.37 (m, 3H, C**11**-H and 2 ×C**8**-H), 5.60 (br. s, 1H, N**4**-H), 3.78 (s, 3H, C**10**-H_3), 3.49 (s, 2H, C**6**-H_2), 3.07 (dd, *J* = 6.3, 6.3 Hz, 1H, C**3**-H), 0.92 – 0.81 (m, 1H, C**2**-H), 0.47 – 0.39 (m, 2H, 2 × C**1**-H_aH_b), 0.15 – 0.09 (m, 2H, 2 ×C**1**-H_aH_b); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 170.5 (C**5**), 161.2 (C**9**), 137.2 (C**7**), 107.4 (C**8**), 99.3 (C**11**), 55.4, 55.3 (C**10**), 44.3 (C**3**), 44.2 (C**6**), 10.6 (C**2**), 3.2 (C**1**); HRMS: (ESI^+) calculated for $C_{14}H_{20}NO_3$: 250.1438, found $[M+H]^+$: 250.1439.

2-(3,5-Dimethoxyphenyl)-*N*-(2-oxocyclopentyl)acetamide (479)



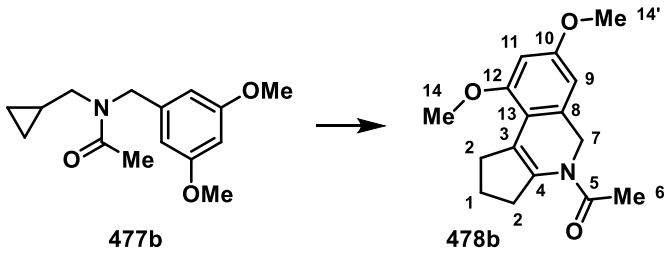
General procedure N: Compound **477a** (37.4 mg, 0.15 mmol), $[Rh(cod)_2]OTf$ (5.3 mg, 0.011 mmol, 7.5 mol%) and $P(3,4,5\text{-}F_3C_6H_2)_3$ (9.5 mg, 0.023 mmol, 15 mol%) were employed and the reaction was stirred for 18 h at 110 °C. The crude mixture was purified by silica gel column chromatography (40-50% EtOAc/hexane) to yield the title compound **479** (20.1 mg, 48%) as a pale yellow oil; ν_{max} / cm^{-1}: 3285 (br. w), 2962 (br. w), 1747 (s), 1647 (s), 1595 (s), 1460 (s), 1204 (s), 1150 (s); ^1H NMR ($CDCl_3$, 400 MHz): δ 6.43 – 6.41 (m, 2H, 2 × C**10**-H), 6.37 (t, *J* = 2.3 Hz, 1H, C**12**-H), 5.92 (br. d, *J* = 6.0 Hz, 1H, N**6**-H), 4.08 (dddd, *J* = 12.4, 7.9, 6.2, 1.2 Hz, 1H, C**4**-H), 3.78 (s, 6H, 2 × C**13**-H_3), 3.53 (s, 2H, C**8**-H_2), 2.62 – 2.52 (m, 1H, C**3**-H_aH_b), 2.42 – 2.32 (m, 1H, C**2**-H_aH_b), 2.22 – 2.09 (m, 1H, C**2**-H_aH_b), 2.08 – 1.98 (m, 1H, C**1**-H_aH_b), 1.83 (tddd, *J* = 13.0, 10.9, 9.0, 6.2 Hz, 1H, C**1**-H_aH_b), 1.63 – 1.49 (m, 1H, C**3**-H_aH_b); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 214.8 (C**5**), 171.0 (C**7**), 161.2 (C**11**), 136.6 (C**9**), 107.3 (C**10**), 99.4 (C**12**), 58.1 (C**4**), 55.4 (C**13**), 43.7 (C**8**), 34.9 (C**2**), 29.8 (C**3**), 18.1 (C**1**); HRMS: (ESI^+) calculated for $C_{15}H_{20}NO_4$: 278.1387, found $[M+H]^+$: 278.1387.

***N*-(Cyclopropylmethyl)-*N*-(3,5-dimethoxybenzyl)acetamide (477b)**



General procedure M: Cyclopropylmethylamine (1.00 g, 14.06 mmol), 3,5-dimethoxybenzaldehyde (2.45 g, 14.76 mmol) and acetic anhydride (1.72 g, 16.87 mmol) were employed and the reaction was stirred at r.t. for 16 h. Flash column chromatography (40-50% EtOAc/petrol) afforded the title compound **477b** (2.52 g, 68%, 1:1.11 mixture of rotamers *A*:*B*) as a pale yellow oil; ν_{max} / cm^{-1}: 3001 (w), 2938 (br. w), 1641 (s), 1595 (s), 1420 (s), 1203 (s), 1153 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.39 – 6.29 (m, 6H, C**10**-H and 2 × C**8**-H, *A*+*B*), 4.66 (s, 2H, C**6**-H_2, *A*), 4.57 (s, 2H, C**6**-H_2, *B*), 3.77 (s, 6H, 2 × C**11**-H_3, *B*), 3.76 (s, 6H, 2 × C**11**-H_3, *A*), 3.29 (d, *J* = 7.0 Hz, 2H, C**3**-H_2, *B*), 3.10 (d, *J* = 6.6 Hz, 2H, C**3**-H_2, *B*), 2.20 (s, 3H, C**5**-H_3, *A*), 2.11 (s, 3H, C**5**-H_3, *B*), 1.03 – 0.86 (m, 2H, C**2**-H, *A*+*B*), 0.58 – 0.51 (m, 2H, C**1**-H_aH_b, *A*), 0.49 – 0.43 (m, 2H, C**1**-H_aH_b, *B*), 0.22 – 0.13 (m, 4H, C**1**-H_aH_b, *A*+*B*); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 171.1 (C**4**, *B*), 170.4 (C**4**, *A*), 161.3 (C**9**, *B*), 160.9 (C**9**, *A*), 140.2 (C**7**, *A*), 139.8 (C**7**, *B*), 105.9 (C**8**, *A*), 104.2 (C**8**, *B*), 99.0 (C**10**, *B*), 98.9 (C**10**, *A*), 55.4 (C**11**, *B*), 55.3 (C**11**, *A*), 51.9 (C**3**, *A*), 51.9 (C**6**, *B*), 50.0 (C**3**, *B*), 48.0 (C**6**, *A*), 21.8 (C**5**, *B*), 21.7 (C**5**, *A*), 10.0 (C**2**, *A*), 9.6 (C**2**, *B*), 3.7 (C**1**, *A*), 3.6 (C**1**, *B*); HRMS: (ESI^+) calculated for $C_{15}H_{22}NO_3$: 264.1594, found $[M+H]^+$: 264.1606.

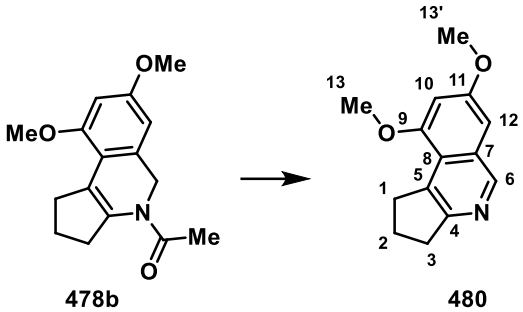
1-(7,9-dimethoxy-1,2,3,5-tetrahydro-4*H*-cyclopenta[*c*]isoquinolin-4-yl)ethan-1-one (478b)



General procedure N: Compound **477b** (39.5 mg, 0.15 mmol), $[Rh(cod)_2]OTf$ (5.3 mg, 0.011 mmol, 7.5 mol%) and $P(3,4,5\text{-}F_3C_6H_2)_3$ (9.5 mg, 0.023 mmol, 15 mol%) were employed and the reaction was stirred for 24 h at 110 °C. The crude mixture was purified by silica gel column chromatography (20% EtOAc/petrol) to yield the title compound **478b** (38.5 mg, 94%) as a brown oil; ν_{max} / cm^{-1}: 2957 (br. w), 2939 (br. w), 1652 (m), 1604 (s), 1574 (s), 1199 (s), 1156 (s), 1070 (s); ^{1}H NMR (DMSO-d_6, 500 MHz, 100 °C, *all signals are very broad at r.t., heating to 100 °C caused the formation of trace amounts of isoquinoline **480***: δ 6.49 (s, 1H, C**9**-H), 6.45 (s, 1H, C**11**-

H), 4.63 (s, 2H, C**7**-H$_2$), 3.76 (s, 3H, C**14**-H$_3$), 3.75 (s, 3H, C**14'**-H$_3$), 2.80 (dt, *J* = 14.0, 7.4 Hz, 4H, 2 × C**2**-H$_2$), 2.09 (s, 3H, C**6**-H$_3$), 1.94 (p, *J* = 7.4 Hz, 2H, C**1**-H$_2$); ^{13}C NMR ($CDCl_3$, 101 MHz, *some signals were elucidated by HMBC correlation*): δ 169.3 (C**5**), 159.6 (C**12**), 156.1 (C**10**), 134.9 (C**4**), 129.4 (C**8**), 126.1 (C**3**), 114.5 (C1**3**), 102.7 (C**9**), 97.3 (C**11**), 55.4 (C**14** and **C14'**, broad), 47.0 (C**7**), 34.0 (C**2**), 32.1 (C**2**), 29.7 (C**1**), 23.7 (C**6**); HRMS: (ESI$^+$) calculated for $C_{16}H_{20}NO_3$: 274.1438, found $[M+H]^+$: 274.1436.

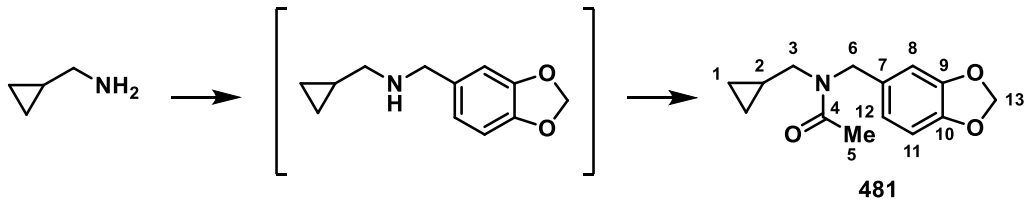
7,9-dimethoxy-2,3-dihydro-1*H*-cyclopenta[*c*]isoquinoline (480)



478b **480**

This compound was prepared using an adapted literature procedure.[298] The solvent of the crude catalytic reaction mixture containing **478b** (~0.15 mmol, not purified, obtained according to **General procedure C**) was taken off *in vacuo*. The residue was dissolved in 2 mL of 1,4-dioxane, 2 ml of deionized water and 2 mL of conc. aq. HCl. The reaction was heated to reflux for 2 h and then concentrated *in vacuo*, Water (5 mL) and EtOAc (5 mL) were added, the layers were basified with K_2CO_3, separated and the aqueous portion was further extracted with EtOAc (2 × 5 mL). The organic extracts were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (1-5% MeOH/DCM) to afford the title compound **480** (22.4 mg, 65%) as a brown oil; ν_{max} / cm^{-1}: 2926 (br. m), 1626 (m), 1576 (s), 1453 (m), 1206 (m), 1158 (s), 1049 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.84 (s, 1H, C**6**-H), 6.77 (d, *J* = 2.3 Hz, 1H, C**10**-H), 6.58 (d, *J* = 2.3 Hz, 1H, C**12**-H), 3.91 (s, 3H, C**13**-H$_3$), 3.89 (s, 3H, C**13'**-H$_3$), 3.47 (ddd, *J* = 7.8, 7.0, 1.1 Hz, 2H, C**3**-H$_2$), 3.10 (t, *J* = 7.8 Hz, 2H, C**1**-H$_2$), 2.16 (dt, *J* = 15.0, 7.8 Hz, 2H, C**2**-H$_2$); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 158.0 (C**9**), 157.0 (C**11**), 156.2 (C**4**), 148.8 (C**6**), 129.7 (C**5**), 129.4 (C**8**), 123.5 (C**7**), 101.8 (C**12**), 97.2 (C**10**), 55.5 (C**13**), 55.4 (C**13'**), 33.6 (C**1**), 32.8 (C**3**), 22.9 (C**2**); HRMS: (ESI$^+$) calculated for $C_{14}H_{16}NO_2$: 230.1176, found $[M+H]^+$: 230.1185.

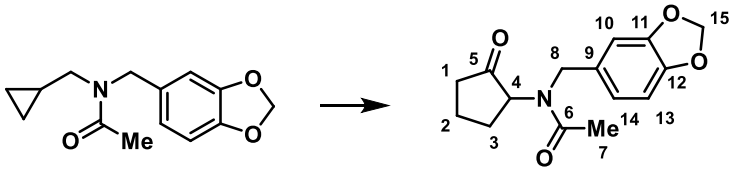
***N*-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-*N*-(cyclopropylmethyl)acetamide (481)**



481

General procedure M: Cyclopropylmethylamine (1.22 mL, 14.06 mmol), piperonal (2.22 g, 14.76 mmol) and acetic anhydride (1.59 mL, 16.87 mmol) were employed and the reaction was stirred at r.t. for 18 h. Flash column chromatography (10-40% EtOAc/petrol) afforded the title compound **481** (3.05 g, 88%, 1:1.13 mixture of rotamers *A*:*B*) as a colourless oil; ν_{max} / cm^{-1}: 3002 (br. m), 2899 (br. m), 1638 (s), 1489 (s), 1440 (s), 1422 (s), 1238 (s), 1036 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.79 – 6.59 (m, 6H, C**8**-H, C**11**-H and C**12**-H, *A*+*B*), 5.94 (s, 2H, C**13**-H_2, *A*), 5.91 (s, 2H, C**13**-H_2, *B*), 4.61 (s, 2H, C**6**-H_2, *B*), 4.53 (s, 2H, C**6**-H_2, *A*), 3.25 (d, *J* = 6.9 Hz, 2H, C**3**-H_2, *A*), 3.08 (d, *J* = 6.6 Hz, 2H, C**3**-H_2, *B*), 2.18 (s, 3H, C**5**-H_3, *B*), 2.11 (s, 3H, C**5**-H_3, *A*), 1.01 – 0.83 (m, 2H, C**2**-H, *A*+*B*), 0.58 – 0.49 (m, 2H, C**1**-H_aH_b, *B*), 0.49 – 0.41 (m, 2H, C**1**-H_aH_b, *A*), 0.20 – 0.11 (m, 4H, C**1**-H_aH_b, *A*+*B*); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 170.9 (C**4**, *A*), 170.4 (C**4**, *B*), 148.2, 147.9, 147.0, 146.7 (C**9** and C**10**, *A*+*B*), 131.7 (C**7**, *B*), 130.9 (C**7**, *A*), 121.1, 119.4, 108.5, 108.4, 108.0, 106.7 (C**8**, C**11** and C**12**, *A*+*B*), 101.2 (C**13**, *A*), 100.9 (C**13**, *B*), 51.7 (C**3**, *B*), 51.6 (C**6**, *A*), 49.6 (C**3**, *A*), 47.7 (C**6**, *B*), 21.8 (C**5**, *A*), 21.7 (C**5**, *B*), 10.0 (C**2**, *B*), 9.6 (C**2**, *A*), 3.8 (C**1**, *B*), 3.6 (C**1**, *A*); HRMS: (ESI^+) calculated for $C_{14}H_{17}NNaO_3$: 270.1101, found $[M+Na]^+$: 270.1114.

***N*-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-*N*-(2-oxocyclopentyl)acetamide (483)**

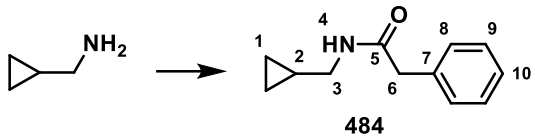


481 483

General procedure N: Compound **481** (37.1 mg, 0.15 mmol), $[Rh(cod)_2]OTf$ (5.3 mg, 0.011 mmol, 7.5 mol%) and $P(3,4,5\text{-}F_3C_6H_2)_3$ (9.5 mg, 0.023 mmol, 15 mol%) were employed and the reaction was stirred for 18 h at 110 °C. The crude mixture was purified by silica gel column chromatography (30-50% EtOAc/petrol) to yield the title compound **483** (31.4 mg, 76%) as a pale brown oil; ν_{max} / cm^{-1}: 2966 (br. m), 2883 (br. m), 1743 (s), 1637 (s), 1490 (s), 1437 (s), 1248 (s), 1236 (s), 1034 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.81 – 6.73 (m, 3H, C**10**-H, C**13**-H and C**14**-H), 5.96 (s, 2H, C**15**-H_2), 4.47 (s, 2H, C**8**-H_2), 3.54 – 3.46 (m, 1H, C**4**-H), 2.49 (ddd, *J* = 18.4, 12.0, 9.2 Hz, 1H, C**1**-H_aH_b), 2.26 – 1.93 (m, 4H, C**1**-H_aH_b, C**2**-H_aH_b, C**3**-H_2), 2.12 (s, 3H, C**7**-H_3), 1.70 – 1.56 (m, 1H, C**2**-H_aH_b); ^{13}C NMR (101 MHz, $CDCl_3$) δ 213.4 (C**5**), 169.9 (C**6**), 148.2,

147.2 (C**11** and C**12**), 130.3 (C**9**), 120.0 (C**14**), 108.5 (C**10**), 107.2 (C**13**), 101.2 (C**15**), 64.2 (C**4**), 53.6 (C**8**), 35.8 (C**1**), 27.0 (C**3**), 21.6 (C**7**), 19.2 (C**2**); HRMS: (ESI$^+$) calculated for $C_{15}H_{18}NO_4$: 276.1230, found $[M+H]^+$: 276.1235.

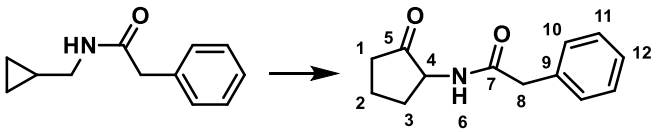
N-(Cyclopropylmethyl)-2-phenylacetamide (484)



484

General procedure D: Cyclopropylmethylamine (1.00 g, 14.06 mmol) and phenylacetyl chloride (2.23 mL, 16.87 mmol) were employed and the reaction was stirred at r.t. for 16 h. The residue was purified by recrystallisation (EtOAc/hexane) to afford the title compound **484** (2.07 g, 78%) as a colourless solid; m.p. 85-86 °C (DCM/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.39-7.25 (m, 5H, C**10**-H, 2 × C**9**-H and 2 × C**8**-H), 5.45 (br. s, 1H, N**4**-H), 3.58 (s, 2H, C**6**-H_2), 3.08 (dd, *J* = 7.1, 5.7 Hz, 2H, C**3**-H_2), 0.92-0.80 (m, 1H, C**2**-H), 0.48-0.39 (m, 2H, C**1**-H_aH_b), 0.12 (dt, *J* = 5.7, 4.6 Hz, 2H, C**1**-H_aH_b); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 170.8 (C**5**), 135.1 (C**7**), 129.4 (C**8**), 129.0 (C**9**), 127.3 (C**10**), 44.3 (C**3**), 43.9 (C**6**), 10.6 (C**2**), 3.2 (C**1**). The spectroscopic properties of this compound were consistent with the data available in the literature.[299]

N-(2-Oxocyclopentyl)-2-phenylacetamide (485)

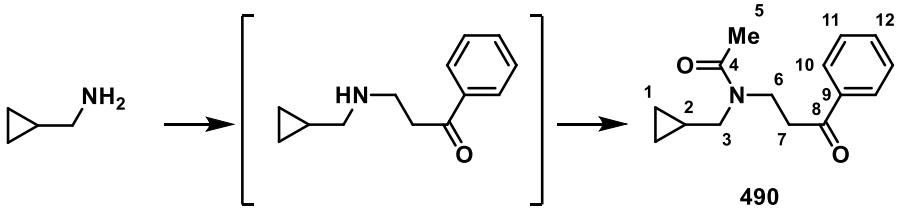


484 **485**

General procedure N: Compound **484** (28.4 mg, 0.15 mmol), $[Rh(cod)_2]OTf$ (5.3 mg, 0.011 mmol, 7.5 mol%), and $P(3,4,5\text{-}F_3C_6H_2)_3$ (9.5 mg, 0.023 mmol, 15 mol%) were employed and the reaction was stirred for 18 h at 110 °C. The crude mixture was purified by silica gel column chromatography (40% EtOAc/ *n*-pentane) to yield the title compound **485** (21.7 mg, 67%) as an off-white solid; m.p. 113-114 °C; ν_{max} / cm^{-1}: 3257 (br. m), 3067 (m), 2968 (m), 1745 (s), 1640 (s), 1558 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38-7.32 (m, 2H, 2 × C**10**-H), 7.31-7.25 (m, 3H, 2 × C**11**-H and C**12**-H), 5.86 (br. s, 1H, N**6**-H), 4.07 (dddd, *J* = 12.4, 7.8, 6.2, 1.2 Hz, 1H, C**4**-H), 3.59 (s, 2H, C**8**-H_2), 2.59 (dddd, *J* = 15.4, 8.1, 5.1, 1.7 Hz, 1H, C**3**-H_aH_b), 2.37 (ddd, *J* = 19.2, 9.2, 1.7 Hz, 1H, C**1**-H_aH_b), 2.14 (ddd, *J* = 19.2, 10.8, 9.2 Hz, 1H, C**1**-H_aH_b), 2.08-1.96 (m, 1H, C**2**-H_aH_b), 1.90-1.77 (m, 1H, C**2**-H_aH_b), 1.54 (m, 1H, C**3**-H_aH_b); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 214.9

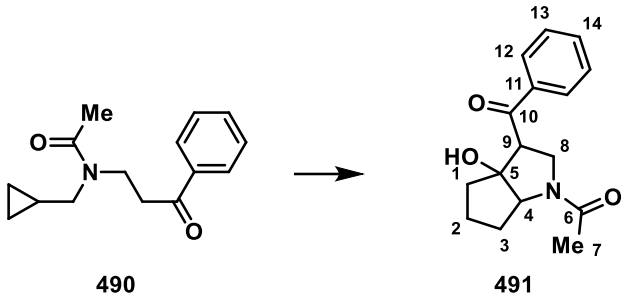
(C**5**), 171.3 (C**7**), 134.5 (C**9**), 129.4 (C**11**), 129.0 (C**10**), 127.4 (C**12**), 58.1 (C**4**), 43.4 (C**8**), 34.9 (C**1**), 29.9 (C**3**), 18.0 (C**2**); HRMS: (ESI^+) calculated for $C_{13}H_{16}NO_2$: 218.1176, found $[M+H]^+$: 218.1186.

N-(Cyclopropylmethyl)-*N*-(3-oxo-3-phenylpropyl)acetamide (490)



To a solution of 3-chloropropiophenone (3.00 g) and TEA (7.40 mL) in dry DCM (45 mL), cyclopropylmethylamine (1.41 mL) was added dropwise at 0 °C. The solution was warmed to r.t. and stirred for 6 h. Water (75 mL) was added and the organic layer was washed with water (2 × 50 mL) and brine (50 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to afford the secondary amine intermediate. The resulting secondary amine was protected according to the **general procedure D** with acetic anhydride (2.00 mL) and the residue was purified by flash column chromatography (20-50% EtOAc/petrol) to afford the title compound **490** (2.43 g, 56% over two steps, 1:2.7 mixture of rotamers *A*:*B*) as a pale yellow oil; ν_{max} / cm^{-1}: 3003 (br. w), 1635 (s), 1448 (s), 1423 (s), 11210 (s); ^1H NMR ($CDCl_3$, 400 MHz): δ 8.01-7.93 (m, 4H, 2 × C**10**-H, *A*+*B*), 7.63-7.42 (m, 6H, 2 × C**11**-H and C**12**-H, *A*+*B*), 3.87-3.82 (m, 2H, C**6**-H_2, *A*), 3.79 (t, *J* = 7.0 Hz, 2H, C**6**-H_2, *B*), 3.35 (t, *J* = 7.0 Hz, 2H, C**7**-H_2, *B*), 3.33-3.25 (m, 4H, C**3**-H_2 and C**7**-H_2, *A*), 3.25 (d, *J* = 6.6 Hz, 2H, C**3**-H_2, *B*), 2.16 (s, 3H, C**5**-H_3, *A*), 2.11 (s, 3H, C**5**-H_3, *B*), 1.07-0.90 (m, 2H, C**2**-H, *A*+*B*), 0.62-0.55 (m, 2H, 2 × C**1**-H_aH_b, *B*), 0.55-0.47 (m, 2H, 2 × C**1**-H_aH_b, *A*), 0.30-0.23 (m, 4H, 2 × C**1**-H_aH_b, *A*+*B*); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 199.3 (C**8**, *B*), 197.8 (C**8**, *A*), 170.5 (C**4**, *B*), 170.3 (C**4**, *A*), 136.7 (C**9**, *B*), 136.4 (C**9**, *A*), 133.6 (C**12**, *A*), 133.2 (C**12**, *B*), 128.8 (C**11**, *A*), 128.6 (C**11**, *B*), 128.1 (C**10**, *B*), 127.9 (C**10**, *A*), 54.3 (C**3**, *B*), 49.6 (C**3**, *A*), 43.6 (C**6**, *A*), 42.7 (C**6**, *B*), 37.7 (C**7**, *A*), 37.3 (C**7**, *B*), 21.8 (C**5**, *B*), 21.6 (C**5**, *A*), 10.6 (C**2**, *B*), 9.8 (C**2**, *A*), 3.8 (C**1**, *A*), 3.7 (C**1**, *B*); HRMS: (ESI^+) calculated for $C_{15}H_{19}NNaO_2$: 268.1308, found $[M+Na]^+$: 268.1320.

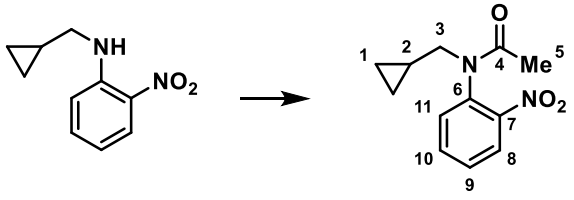
1-(3-benzoyl-3a-hydroxyhexahydrocyclopenta[*b*]pyrrol-1(2*H*)-yl)ethan-1-one (491)



490 **491**

General procedure N: Compound **490** (36.8 mg, 0.150 mmol), $[Rh(cod)_2]OTf$ (5.3 mg, 0.011 mmol, 7.5 mol%), and $P(3,4,5\text{-}F_3C_6H_2)_3$ (9.5 mg, 0.023 mmol, 15 mol%) were employed and the reaction was stirred for 18 h at 110 °C. The crude mixture was purified by silica gel column chromatography (1-5% MeOH/DCM) to yield the title compound **491** (30.1 mg, 73%, 2.1:1 mixture of diastereomers *A:B*) as a brown oil; ν_{max} / cm^{-1}: 3355 (br. m), 2961 (br. m), 1678 (m), 1616 (s), 1597 (s), 1448 (s), 1229 (s); ^1H NMR ($CDCl_3$, 400 MHz): δ 8.07 – 8.03 (m, 1H, 2 × C**12**-H, *A*), 7.95 – 7.89 (m, 2H, 2 × C**12**-H, *B*), 7.65 – 7.39 (m, 6H, 2 × C**13**-H and C**14**-H, *A*+*B*), 4.17 (dd, *J* = 8.1, 4.8 Hz, 1H, C**4**-H, *A*), 4.08 (dd, *J* = 7.6, 4.9 Hz, 1H, C**4**-H, *B*), 4.07 – 4.01 (m, 1H, C**9**-H, *A*), 4.00 – 3.83 (m, 5H, C**9**-H, *B* and C**8**-H_2, *A*+*B*), 2.39 – 2.28 (m, 2H, C**3**-H_aH_b, *A*+*B*), 2.04 (s, 3H, C**7**-H_3, *B*), 2.00 (s, 3H, C**7**-H_3, *A*), 1.99 – 1.74 (m, 8H, C**1**-H_2 and C**2**-H_2, *A*+*B*), 1.72 – 1.62 (m, 2H, C**3**-H_aH_b, *A*+*B*); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 201.3 (C**10**, *B*), 200.1 (C**10**, *A*), 169.9 (C**6**, *B*), 169.3 (C**6**, *A*), 136.7 (C**11**, *A*), 135.9 (C**11**, *B*), 134.2 (C**14**, *B*), 134.1 (C**14**, *A*), 128.9 (C**13**, *B*), 128.6 (C**12**, *B*), 128.5 (C**13**, *A*), 128.2 (C**12**, *A*), 90.3 (C**5**, *B*), 89.0 (C**5**, *A*), 69.9 (C**4**, *B*), 69.8 (C**4**, *A*), 51.3 (C**9**, *A*), 50.7 (C**8**, *A*), 49.9 (C**9**, *B*), 48.8 (C**8**, *B*), 37.8 (C**1**, *B*), 37.7 (C**1**, *A*), 33.2 (C**3**, *B*), 31.5 (C**3**, *A*), 24.0 (C**2**, *B*), 23.9 (C**2**, *A*), 22.3 (C**7**, *A*), 21.9 (C**7**, *B*); HRMS: (ESI^+) calculated for $C_{16}H_{20}NO_3$: 274.1438, found $[M+H]^+$: 274.1442.

***N*-(Cyclopropylmethyl)-*N*-(2-nitrophenyl)acetamide (493)**

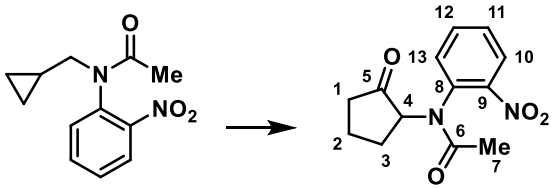


493

To a solution of *N*-(cyclopropylmethyl)-2-nitroaniline (2.00 g, 10.40 mmol, prepared according to the literature procedure[300]) in acetic anhydride (10.40 mL) and 5 drops of conc. H_2SO_4 were added at r.t. and the reaction mixture was heated to 50 °C for 2 h and then to 80 °C for 45 min. Then

MeOH (6.90 mL) was added at 0 °C and the solution was stirred for 20 min. Neat K_2CO_3 was added to the reaction mixture until the effervescence was no longer observed. Water (50 mL) was added and the solution was extracted with DCM (3 × 30 mL). The organic extracts were combined, washed with brine (40 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (50% EtOAc/hexane) to yield the title compound **493** (1.80 g, 74%, 9:1 mixture of isomers *A*:*B*) as a bright yellow oil; ν_{max} / cm^{-1}: 1664 (s), 1601 (m), 1525 (s), 1379 (m), 1348 (s), 1286 (m), 785 (m); ^{1}H NMR ($CDCl_3$, 400 MHz, main isomer only): δ 7.98 (dd, *J* = 8.2, 1.6 Hz, 1H, C**8**-H), 7.68 (ddd, *J* = 7.8, 7.6, 1.6 Hz, 1H, C**10**-H), 7.55 (ddd, *J* = 8.2, 7.6, 1.4 Hz, 1H, C**9**-H), 7.42 (dd, *J* = 7.8, 1.4 Hz, 1H, C**11**-H), 3.66 (dd, *J* = 14.1, 7.2 Hz, 1H, C**3**-H_aH_b), 3.34 (dd, *J* = 14.1, 7.2 Hz, 1H, C**3**-H_aH_b), 1.84 (s, 3H, C**5**-H_3), 0.88 – 0.74 (m, 1H, C**2**-H), 0.42 – 0.32 (m, 2H, C**1**-H_aH_b), 0.06 – -0.05 (m, 2H, C**1**-H_aH_b); ^{13}C NMR ($CDCl_3$, 101 MHz, main isomer only): δ 170.1 (C**4**), 147.7 (C**7**), 136.5 (C**6**), 134.1 (C**10**), 132.4 (C**11**), 129.6 (C**9**), 125.6 (C**8**), 53.5 (C**3**), 22.8 (C**5**), 9.6 (C**2**), 4.0 (C**1**), 3.6 (C**1'**); HRMS: (ESI^+) calculated for $C_{12}H_{14}N_2NaO_3$: 257.0897, found $[M+Na]^+$: 257.0898.

***N*-(2-nitrophenyl)-*N*-(2-oxocyclopentyl)acetamide (494)**

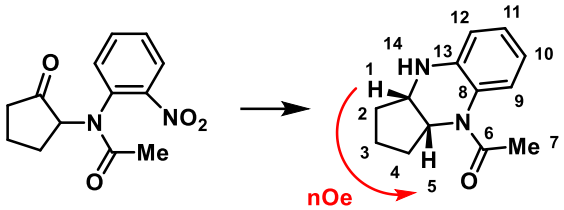


493 **494**

General procedure N: Compound **493** (35.1 mg, 0.15 mmol), $[Rh(cod)_2]OTf$ (5.3 mg, 0.011 mmol, 7.5 mol%) and $P(3,4,5\text{-}F_3C_6H_2)_3$ (9.5 mg, 0.023 mmol, 15 mol%) were employed and the reaction was stirred for 24 h at 110 °C. The crude mixture was purified by silica gel column chromatography (5% acetone/DCM) to yield the title compound **494** (35.7 mg, 91%, 1:2.7 mixture of atropisomers *A*:*B*) as a yellow oil; ν_{max} / cm^{-1}: 1747 (m), 1667 (s), 1527 (s), 1399 (m), 1354 (m), 1325 (m), 1303 (m); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.95 (dd, *J* = 8.1, 1.6 Hz, 1H, C**10**-H, *A*), 7.91 (dd, *J* = 8.1, 1.5 Hz, 1H, C**10**-H, *B*), 7.75 – 7.49 (m, 6H, C**11**-H, C**12**-H and C**13**-H, *A*+*B*), 5.18 (dd, *J* = 13.2, 8.1 Hz, 1H, C**4**-H, *A*), 3.48 (dd, *J* = 11.3, 8.9 Hz, 1H, C**4**-H, *B*), 2.62 – 2.50 (m, 4H, C**1**-H_aH_b and C**3**-H_aH_b, *A*+*B*), 2.37 – 2.09 (m, 5H, C**1**-H_aH_b and C**3**-H_aH_b, *A*+*B*; C**2**-H_aH_b, *A*), 2.04 – 1.93 (m, 1H, C**2**-H_aH_b, *B*), 1.92 (s, 3H, C**7**-H_3, *A*), 1.81 (s, 3H, C**7**-H_3, *B*), 1.73 – 1.59 (m, 4H, C**2**-H_aH_b, *B*), 1.45 – 1.33 (m, 1H, C**2**-H_aH_b, *A*); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 213.7 (C**5**, *B*), 213.1 (C**5**, *A*), 170.8 (C**6**, *A*), 169.4 (C**6**, *B*), 137.0 (C**9**, *B*), 134.6, 134.3, 133.6, 133.1, 132.3 (C**9**, *A*; C**11** and C**13**, *A*+*B*), 130.2 (C**12**, *A*), 129.8 (C**12**, *B*), 125.4 (C**10**, *A*), 125.0 (C**10**, *B*), 68.8 (C**4**,

B), 64.1 (C**4**, *A*), 35.8 (C**1**, *B*), 35.4 (C**1**, *A*), 26.6 (C**3**, *B*), 26.0 (C**3**, *A*), 22.6 (C**7**, *A*), 22.4 (C**7**, *B*), 19.4 (C**2**, *B*), 18.3 (C**2**, *A*); HRMS: (ESI$^+$) calculated for $C_{13}H_{15}N_2O_4$: 263.1026, found $[M+H]^+$: 263.1029. High temperature NMR (DMSO-d_6, 100 °C) did not result in coalescence of the signals for isomers *A* and *B*; this suggests that these are atropisomers rather than rotamers.

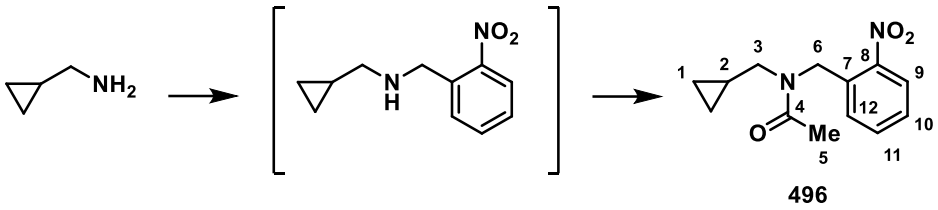
1-((3a*R,9a*S**)-1,2,3,3a,9,9a-Hexahydro-4*H*-cyclopenta[*b*]quinoxalin-4-yl)ethan-1-one (495)**



494 **495**

Compound **494** (50.0 mg, 0.19 mmol) was dissolved in MeOH (5 mL) and Pd on carbon (10 mg, 10% w/w) was added. The reaction tube was sealed, sparged with H_2 for 1 min and stirred under an atmosphere of H_2 for 8 h. The solution was filtered through Celite® (rinsing with MeOH) and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (5% acetone/DCM) to yield the title compound **495** (22.8 mg, 55%) as a pale brown oil; ν_{max} / cm^{-1}: 3340 (m), 2956 (m), 1631 (s), 1502 (s), 1388 (s), 1314 (s), 730 (s); ^{1}H NMR ($CDCl_3$, 500 MHz, 50 °C): δ 7.13 – 6.96 (m, 3H, C**9**-H, C**10**-H and N**14**-H), 6.67 (ddd, *J* = 7.6, 7.7, 1.4 Hz, 1H, C**11**-H), 6.58 (dd, *J* = 7.7, 1.5 Hz, 1H, C**12**-H), 5.31 (br. s, 1H, C**5**-H), 3.87 (ddd, *J* = 7.0, 5.0, 2.4 Hz, 1H, C**1**-H), 2.22 (s, 3H, C**7**-H_3), 1.97 – 1.87 (m, 2H, C**2**-H_aH_b and C**4**-H_aH_b), 1.80 – 1.69 (m, 1H, C**3**-H_aH_b), 1.65 – 1.51 (m, 2H, C**2**-H_aH_b, C**3**-H_aH_b), 1.35 – 1.24 (m, 1H, C**4**-H_aH_b); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 169.5 (C**6**), 126.3, 125.6 (C**9** and C**10**), 117.0 (C**11**), 114.3 (C**12**), 56.5 (C**1**), 33.5 (C**2**), 27.3 (C**4**), 22.9 (C**7**), 21.7 (C**3**); signals corresponding to C**5**, C**8** and C**13** were not observed due to their weak intensity; HRMS: (ESI$^+$) calculated for $C_{13}H_{17}N_2O$: 217.1335, found $[M+H]^+$: 217.1337. The relative stereochemistry of this compound was corroborated by nOe experiments (as indicated on the compound structure). A strong nOe was observed between C**1**-H and C**5**-H.

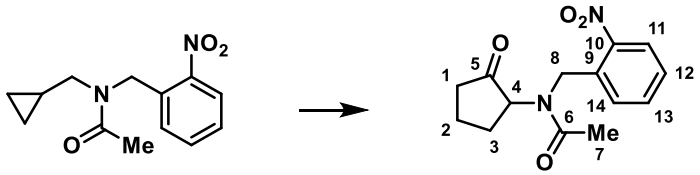
***N*-(Cyclopropylmethyl)-*N*-(2-nitrosobenzyl)acetamide (496)**



496

General procedure M: Cyclopropylmethylamine (1.22 mL, 14.06 mmol), 2-nitrobenzaldehyde (2.22 g, 14.76 mmol) and acetic anhydride (1.59 mL, 16.87 mmol) were employed and the reaction was stirred at r.t. for 18 h. Flash column chromatography (20-50% EtOAc/pentane) afforded the title compound **496** (2.78 g, 80%, 1:1.07 mixture of rotamers *A*:*B*) as a dark yellow oil; ν_{max} / cm^{-1}: 1643 (s), 1521 (s), 1421 (m), 1339 (s), 1253 (m), 857 (m), 789 (m), 726 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.15 (dd, *J* = 8.1, 1.3 Hz, 1H, C**9**-H, *A*), 8.00 (dd, *J* = 8.2, 1.3 Hz, 1H, C**9**-H, *B*), 7.66 (td, *J* = 7.6, 1.3 Hz, 1H, C**11**-H, *A*), 7.55 (td, *J* = 7.6, 1.3 Hz, 1H, C**11**-H, *B*), 7.48 (t, *J* = 8.1 Hz, 1H, C**10**-H, *A*), 7.41 – 7.35 (m, 2H, C**10**-H, *B* and C**12**-H, *A*), 7.33 – 7.29 (m, 1H, C**12**-H, *B*), 5.03 (s, 4H, C**6**-H_2, *A*+*B*), 3.31 (d, *J* = 7.0 Hz, 2H, C**3**-H_2, *A*), 3.21 (d, *J* = 6.7 Hz, 2H, C**3**-H_2, *B*), 2.26 (s, 3H, C**5**-H_3, *B*), 2.05 (s, 3H, C**5**-H_3, *A*), 1.01 – 0.84 (m, 2H, C**2**-H, *A*+*B*), 0.55 – 0.41 (m, 4H, 2 × C**1**-H_aH_b, *A*+*B*), 0.21 – 0.10 (m, 4H, 2 × C**1**-H_aH_b, *A*+*B*); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 171.6 (C**4**, *A*), 171.1 (C**4**, *B*), 148.5 (C**8**, *A*), 147.9 (C**8**, *B*), 134.3 (C**11**, *A*), 133.6 (C**7**, *B*), 133.6 (C**7**, *A*), 133.5 (C**11**, *B*), 128.6 (C**12**, *B*), 128.5 (C**10**, *A*), 127.8, 127.6 (C**12**, *A* and C**10**, *B*), 125.8 (C**9**, *A*), 125.0 (C**9**, *B*), 54.0 (C**3**, *B*), 50.7 (C**3**, *A*), 50.0 (C**6**, *A*), 46.5 (C**6**, *B*), 21.7 (C**5**, *A*+*B*), 10.4 (C**2**, *B*), 9.7 (C**2**, *A*), 3.9 (C**1**, *B*), 3.8 (C**1**, *A*); HRMS: (ESI^+) calculated for $C_{13}H_{17}N_2O_3$: 249.1234, found $[M+H]^+$: 249.1233.

***N*-(2-Nitrobenzyl)-*N*-(2-oxocyclopentyl)acetamide (497)**

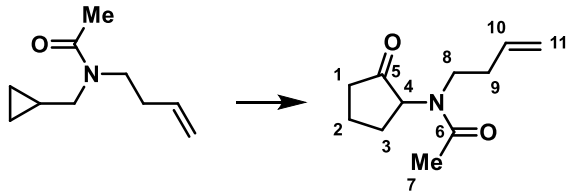


496 **497**

General procedure N: Compound **496** (37.2 mg, 0.15 mmol), $[Rh(cod)_2]OTf$ (5.3 mg, 0.011 mmol, 7.5 mol%) and $P(3,4,5\text{-}F_3C_6H_2)_3$ (9.5 mg, 0.023 mmol, 15 mol%) were employed and the reaction was stirred for 18 h at 110 °C. The crude mixture was purified by silica gel column chromatography (30-50% EtOAc/petrol) to yield the title compound **497** (31.1 mg, 75%) as a pale brown solid; m.p. 106-107 °C (DCM/hexane); ν_{max} / cm^{-1}: 2968 (br. w), 1744 (m), 1645 (s), 1523 (s), 1424 (m), 1338 (s), 1258 (m), 729 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.14 (dd, *J* = 8.2, 1.3 Hz, 1H, C**11**-H), 8.09 (dd, *J* = 7.9, 1.3 Hz, 1H, C**14**-H), 7.78 – 7.71 (m, 1H, C**13**-H), 7.53 – 7.47

(m, 1H, C**12**-H), 5.08 (d, *J* = 18.9 Hz, 1H, C**8**-$\underline{H}_aH_b$), 4.80 (d, *J* = 18.9 Hz, 1H, C**8**-$H_a\underline{H}_b$), 3.37 (t, *J* = 9.6 Hz, 1H, C**4**-H), 2.57 (ddd, *J* = 18.5, 11.9, 9.3 Hz, 1H, C**1**-$\underline{H}_aH_b$), 2.30 – 2.06 (m, 4H, C**1**-$H_a\underline{H}_b$, C**2**-$\underline{H}_aH_b$, C**3**-H_2), 2.02 (s, 3H, C**7**-H_3), 1.72 – 1.57 (m, 1H, C**2**-$H_a\underline{H}_b$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 213.0 (C**5**), 170.5 (C**6**), 147.7 (C**10**), 134.8 (C**13**), 132.9 (C**9**), 128.8, 128.6 (C**12** and C**14**), 125.7 (C**11**), 65.0 (C**4**), 51.4 (C**8**), 36.1 (C**1**), 27.0 (C**3**), 21.4 (C**7**), 19.4 (C**2**); HRMS: (ESI$^+$) calculated for $C_{14}H_{16}N_2NaO_4$: 299.1002, found $[M+Na]^+$: 299.0996.

***N*-(But-3-en-1-yl)-*N*-(2-oxocyclopentyl)acetamide (505a)**

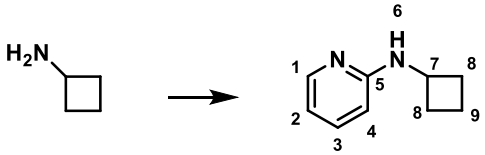


449 **505a**

General procedure N: Compound **449** (25.1 mg, 0.15 mmol), $[Rh(cod)_2]OTf$ (5.3 mg, 0.011 mmol, 7.5 mol%), and $P(3,4,5\text{-}F_3C_6H_2)_3$ (9.5 mg, 0.023 mmol, 15 mol%) were employed and the reaction was stirred for 18 h at 110 °C. The crude mixture was purified by silica gel column chromatography (30-50% EtOAc/pentane) to yield the title compound **505a** (18.2 mg, 62%) as a brown oil; ν_{max} / cm^{-1}: 2967 (br. w), 2921 (br. w), 1744 (s), 1631 (s), 1431 (s), 1154 (m), 1001 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.73 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 1H, C**10**-$\underline{H}$), 5.11 – 5.02 (m, 2H, C**11**-$\underline{H}_2$), 3.35 – 3.26 (m, 3H, C**4**-$\underline{H}$ and C**8**-$\underline{H}_2$), 2.48 (ddd, *J* = 18.3, 11.8, 9.4 Hz, 1H, C**1**-$\underline{H}_aH_b$), 2.33-2.25 (m, 2H, C**9**-$\underline{H}_2$), 2.25 – 2.04 (m, 4H, C**1**-$H_a\underline{H}_b$, C**2**-$\underline{H}_aH_b$ and C**3**-$\underline{H}_2$), 2.01 (s, 3H, C**7**-$\underline{H}_3$), 1.69 – 1.59 (m, 1H, C**2**-$H_a\underline{H}_b$); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 213.4 (C**5**), 169.3 (C**6**), 134.1 (C0**1**), 117.8 (C**11**), 64.7 (C**4**), 50.7 (C**8**), 35.8 (C**1**), 33.9 (C**9**), 27.3 (C**3**), 21.4 (C**7**), 19.4 (C**2**); HRMS: (ESI$^+$) calculated for $C_{11}H_{18}NO_2$: 196.1336, found $[M+H]^+$: 196.1332.

8.7 Experimental procedures for the studies in Chapter 6

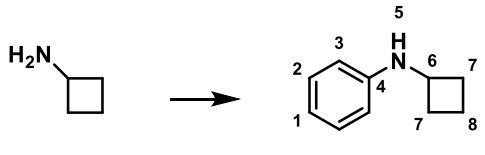
***N*-Cyclobutylpyridin-2-amine (524)**



524

General procedure O: 2-Bromopyridine (0.20 mL, 2.00 mmol) and cyclobutylamine (0.20 mL, 2.40 mmol) were employed. Flash column chromatography (9% EtOAc/hexane) afforded the title compound **524** (0.15 g, 49 %) as a yellow solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.06 (dt, *J* = 4.8, 1.4 Hz, 1H, C**1**-H), 7.42 (m, 1H, C**3**-H), 6.56 (ddd, *J* = 7.2, 5.1, 1.0 Hz, 1H, C**2**-H), 6.31 (d, *J* = 8.4 Hz, 1H, C**4**-H), 4.68 (br. s, 1H, N**6**-H), 4.12 (h, *J* = 7.5 Hz, 1H, C**7**-H), 2.51-2.36 (m, 2H, C**9**-H_2), 1.90-1.74 (m, 4H, 2 × C**8**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 158.0 (C**5**), 148.3 (C**1**), 137.8 (C**3**), 113.0 (C**2**), 106.5 (C**4**), 47.5 (C**7**), 31.5 (C**8**), 15.4 (C**9**). The spectroscopic properties of this compound were consistent with the data available in the literature.[301]

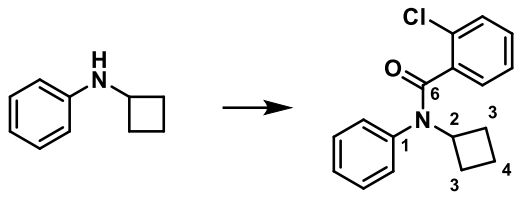
***N*-Cyclobutylaniline (525)**



525

General procedure O: Iodobenzene (0.36 mL, 3.20 mmol) and cyclobutylamine (0.33 mL, 3.84 mmol) were employed. Flash column chromatography (2% EtOAc/hexane) afforded the title compound **525** (0.38 g, 81 %) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21 (ddd, *J* = 8.7, 7.3, 1.6 Hz, 2H, 2 × C**2**-H), 6.75-6.67 (m, 1H, C**1**-H), 6.59 (dt, J = 8.7, 1.3 Hz, 2H, 2 × C**3**-H), 3.98-3.89 (m, 1H, C**6**-H), 3.82 (br. s, 1H, N**5**-H), 2.43-2.24 (m, 2H, C**8**-H_2), 1.84-1.62 (m, 4H, 2 × C**7**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 147.2 (C**4**), 129.3 (C**2**), 117.40 (C**1**), 113.06 (C**3**), 49.04 (C**6**), 31.28 (C**7**), 15.30 (C**8**). The spectroscopic properties of this compound were consistent with the data available in the literature.[301]

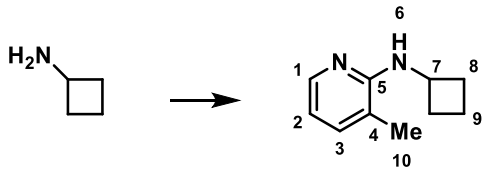
2-Chloro-*N*-cyclobutyl-*N*-phenylbenzamide (527)



527

General procedure N: *N*-Cyclobutylaniline (14.72 mg, 0.10 mmol), $[Rh(cod)Cl]_2$ (3.70 mg, 0.008 mmol, 7.5 mol%), PPh_3 (3.93 mg, 0.015 mmol, 15 mol%) were employed and the reaction was stirred at 180 °C for 24 h. *No benzoic acid was used*. Flash column chromatography (20% EtOAc/hexane) afforded compound **527** (21.3 mg, 75%) as a colourless oil; ν_{max} / cm^{-1}: 2987 (m), 2947 (m), 1652 (s), 1594 (m), 1495 (s), 1395 (m), 1346 (s), 1280 (m).^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28-6.95 (m, 9H, Ar-H), 5.23 (app. p, *J* = 8.7 Hz, 1H, C**2**-H), 2.33-2.30 (m, 2H, 2 × C**3**-H_aH_b), 1.96-1.83 (m, 2H, 2 × C**3**-H_aH_b), 1.75-1.63 (m, 1H, C**4**-H_aH_b), 1.62-1.49 (m, 1H, C**4**-H_aH_b); ^{13}C NMR (101 MHz, $CDCl_3$): δ 167.6 (C**6**), 138.5 (C**1**), 137.2, 129.8, 129.3, 129.2, 128.6, 128.3, 127.9, 126.0 (Ar-C), 50.7 (C**2**), 28.8 (C**4**), 15.3 (C**5**); HRMS: (ESI^+) calculated for $C_{17}H_{17}ClNO$: 286.0993, found $[M+H]^+$: 286.1001.

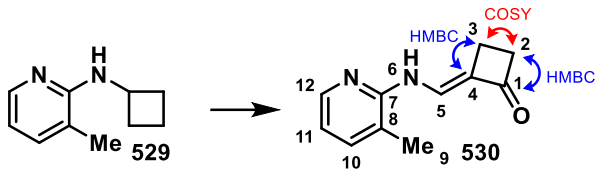
***N*-Cyclobutyl-3-methylpyridin-2-amine (529)**



529

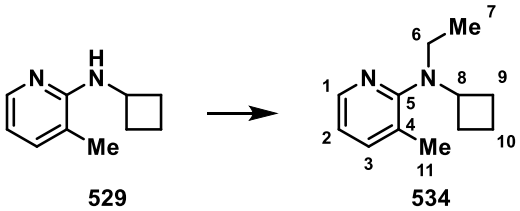
General procedure O: 2-Bromo-3-methylpyridine (0.90 mL, 8.00 mmol) and cyclobutylamine (0.82 mL, 9.60 mmol) were employed. Flash column chromatography (9% EtOAc/hexane) afforded the title compound **529** (1.02 g, 79 %) as a crystalline colourless solid; m.p. 77-78 °C; ν_{max} / cm^{-1}: 2969 (m), 2938 (m), 1598 (s). 1582 (s), 1494 (s), 1467 (s), 1413 (m), 1340 (m), 1253 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.00 (dd, *J* = 5.2, 1.8 Hz, 1H, C**1**-H), 7.19 (ddq, *J* = 7.1, 1.8, 0.9 Hz, 1H, C**3**-H), 6.50 (dd, *J* = 7.1, 5.2 Hz, 1H, C**2**-H), 4.63-4.52 (m, 1H, C**7**-H), 4.24 (br. s, 1H, N**6**-H), 2.52-2.44 (m, 2H, 2 × C**8**-H_2), 2.07 (s, 3H, C**10**-H_3), 1.92-1.71 (m, 4H, 2 × C**8**-H_2 and C**9**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 156.0 (C**5**), 145.5 (C**1**), 136.8 (C**3**), 116.2 (C**4**), 112.5 (C**2**), 46.7 (C**7**), 32.2 (C**8**), 17.0 (C**10**), 15.1 (C**9**); HRMS: (ESI^+) calculated for $C_{10}H_{15}N_2$: 163.1230, found $[M+H]^+$: 163.1229.

(*E*)-2-(((3-Methylpyridin-2-yl)amino)methylene)cyclobutan-1-one (530)



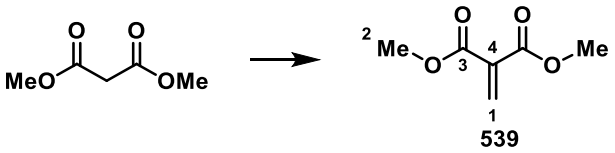
General procedure N: Amine **529** (19.0 mg, 0.10 mmol), $[Rh(cod)_2]OTf$ (3.5 mg, 0.0075 mmol, 7.5 mol%) and PPh_3 (3.9 mg, 0.015 mmol, 15 mol%) were employed and the reaction was stirred at 160 °C for 24 h. *No benzoic acid was used*. Preparative thin layer chromatography (10% MeOH/DCM) afforded title compound **530** (1.1 mg, 6%) as a colourless oil; ν_{max} / cm^{-1}: 3419 (m), 3402 (m), 2917 (m), 1695 (s), 1645 (s), 1590 (s), 1524 (s), 1413 (s), 1113 (m); ^1H NMR (400 MHz, $CDCl_3$): δ 8.16-8.12 (dd, *J* = 5.0, 1.8 Hz, 1H, C**12**-H), 7.91 (t, *J* = 3.2 Hz, 1H, C**5**-H), 7.35 (dd, *J* = 7.3, 1.8, 1H, C**10**-H), 6.72 (dd, *J* = 7.3, 5.0 Hz, 1H, C**11**-H), 6.69 (br. s, 1H, N**6**-H), 2.73-2.68 (m, 2H, C**3**-H_2), 2.48-2.45 (m, 2H, C**2**-H_2), 2.26 (s, 3H, C**9**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 204.9 (C**1**), 152.7 (C**7**), 145.3 (C**12**), 138.1 (C**4**), 137.6 (C**10**), 133.6 (C**5**), 118.4 (C**8**), 115.5 (C**11**), 32.4 (C**2**), 24.6 (C**3**), 16.9 (C**9**); HRMS: (ESI^+) calculated for $C_{11}H_{13}N_2O$: 189.1022, found $[M+H]^+$: 189.1028.

***N*-Cyclobutyl-*N*-ethyl-3-methylpyridin-2-amine (534)**



Amine **529** (0.50 g, 3.08 mmol) and acetaldehyde (0.35 mL, 6.16 mmol) in dry 1,2-dichloroethane (5 mL) were stirred at r.t. for 15 min. Sodium triacetoxyborohydride (1.63 g, 7.70 mmol) was added and the reaction was stirred at r.t. for 4 h. The reaction mixture was quenched with 2.0 M aq. HCl and adjusted to neutral pH by the addition of sat. aq. $NaHCO_3$. The solution was extracted with DCM (3 × 15 mL) and then the organic extracts were combined, washed with brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (20% EtOAc/hexane) to afford the title compound **534** (0.56 g, 95%) as a bright yellow oil; ν_{max} / cm^{-1}: 2969 (s), 2936 (m), 2869 (m), 1586 (m), 1449 (s), 1422 (s), 1337 (m), 1256 (m), 1105 (s); ^1H NMR (400 MHz, $CDCl_3$): δ 8.16 (dd, *J* = 5.2, 1.9 Hz, 1H, C**1**-H), 7.39 (ddq, *J* = 6.7, 1.9, 1.0 Hz, 1H, C**3**-H), 6.84-6.79 (m, 1H, C**2**-H), 4.06 (tt, *J* = 8.8, 6.8 Hz, 1H, C**8**-H), 3.15 (q, *J* = 7.1 Hz, 2H, C**6**-H_2), 2.26 (s, 3H, C**11**-H_3), 2.19-2.08 (m, 2H, C**9**-H_2), 1.91-1.77 (m, 2H, C**9**-H_2), 1.70-1.60 (m, 2H, C**10**-H_2), 0.89 (t, *J* = 7.1 Hz, 3H, C**7**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 160.6 (C**5**), 145.3 (C**1**), 138.9 (C**3**), 127.4 (C**4**), 117.8 (C**2**), 54.9 (C**8**), 42.6 (C**6**), 28.9 (C**9**), 18.7 (C**11**), 15.0 (C**10**), 12.3 (C**7**); HRMS: (ESI^+) calculated for $C_{12}H_{19}N_2$: 191.1543, found $[M+H]^+$: 191.1549.

Dimethyl 2-methylenemalonate (539)

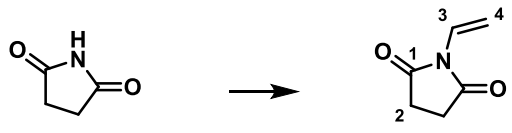


539

The title compound was prepared following a literature procedure.[302] TFA (7.70 mL, 100 mmol) was added dropwise to a stirred solution of diisopropylamine (10.10 g, 100 mmol) in Et_2O (100 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 10 min and then filtered to obtain the white precipitate. The filter cake was washed with Et_2O and dried under high vacuum to obtain diisopropylamine 2,2,2-trifluoroacetate as colourless crystals (20.73 g, 96%).

Dimethyl malonate (10.00 mL, 87.50 mmol), diisopropylamine 2,2,2-trifluoroacetate (18.83 g, 87.50 mmol), paraformaldehyde (5.26 g, 175 mmol) and trifluoroacetic acid (0.67 mL, 8.75 mmol) in dry THF (130 mL) were heated to reflux and stirred for 2 h. Paraformaldehyde (5.26 g, 175 mmol) was added and the reflux was restarted for 5 h. The reaction was cooled to room temperature and THF was removed under reduced pressure (50 mbar at 40°C). The crude mixture was dissolved in diethyl ether (50 mL) and filtered through a paper filter. The organic layer was washed with 2.0 M HCl (2 × 20 mL). The aqueous layers were combined and extracted with diethyl ether (25 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude oil was purified by distillation. Compound **539** (9.22 g, 73%) was collected as a colourless oil between 45 °C at 1.5 mbar and 50 °C at 1 mbar. Due to an unstable nature, the product was stored under nitrogen in a glovebox freezer. ^{1}H NMR ($CDCl_3$, 400 MHz): 6.58 (s, 2H, C**1**-$\underline{H}_2$), 3.83 (s, 6H, 2 × C**2**-$\underline{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 167.0 (C**3**), 135.3 (C**1**), 134.5 (C**4**), 52.70 (C**2**). The spectroscopic properties of this compound were consistent with the data available in the literature.[302]

1-Vinylpyrrolidine-2,5-dione (43)

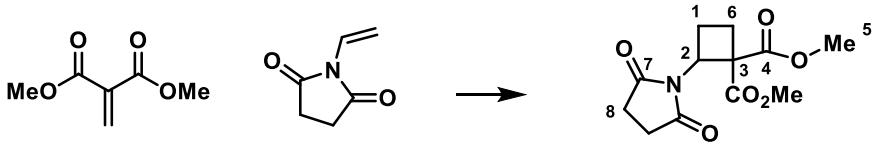


540

The title compound was prepared following a literature procedure.[240] To a stirred solution of pyrrolidine-2,5-dione (1.00 g, 10.10 mmol) in vinyl acetate (25 mL), Na_2PdCl_4 (59.0 mg, 0.20 mmol) was added. The reaction was heated to reflux and stirred for 72h. The residue was purified

by flash column chromatography (20-40% EtOAc/hexane) to provide **540** (0.96 g, 76%) as a yellow solid; m.p. 48-49 °C (DCM/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.50 (dd, *J* = 16.4, 9.9 Hz, 1H, C**3**-H), 5.88 (d, *J* = 16.4 Hz, 1H, C**4**-H_2), 4.87 (d, *J* = 9.9 Hz, 1H, C**4**-H_2), 2.57 (s, 4H, 2 × C**2**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 175.4 (C**1**), 124.3 (C**3**), 106.6 (C**4**), 27.8 (C**2**). The spectroscopic properties of this compound were consistent with the data available in the literature.[240]

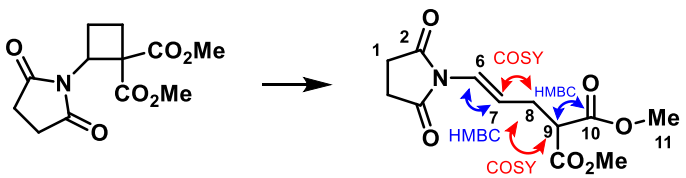
Dimethyl 2-(2,5-dioxopyrrolidin-1-yl)cyclobutane-1,1-dicarboxylate (538)



539 **540** **538**

The title compound was prepared following a literature procedure.[240] To a stirred solution of iron trichloride (0.13 g, 0.80 mmol) in dry DCM (5 mL), 1-vinylpyrrolidine-2,5-dione **540** (0.50 g, 4.00 mmol) and dimethyl 2-methylenemalonate **539** (1.15 g, 8.00 mmol) in dry dichloromethane (10 mL) were added dropwise at 0 °C under nitrogen. The reaction was warmed to r.t. and stirred for 18 h. The reaction mixture was diluted with dichloromethane, filtered through a pad of silica and concentrated *in vacuo*. The residue was purified by flash column chromatography (4-50% EtOAc/hexane) to provide cyclobutane **538** (0.95 g, 88%) as a colourless oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.32-5.23 (m, 1H, C**2**-H), 3.71 (s, 3H, C**5**-H_3), 3.67 (s, 3H, C**5**-H_3), 3.14-3.01 (m, 1H, C**6**-H_2), 2.95-2.85 (m, 1H, C**6**-H_2), 2.74-2.56 (m, 4H, 2 × C**8**-H_2), 2.24-2.09 (m, 2H, C**1**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 177.2 (C**7**), 170.5 (C**4**), 168.6 (C**4**), 57.8 (C**3**), 53.1 (C**5**), 52.9 (C**5**), 48.2 (C**2**), 28.0 (C**8**), 24.8 (C**6**), 20.7 (C**1**). The spectroscopic properties of this compound were consistent with the data available in the literature.[240]

Dimethyl (*E*)-2-(3-(2,5-dioxopyrrolidin-1-yl)allyl)malonate (542)

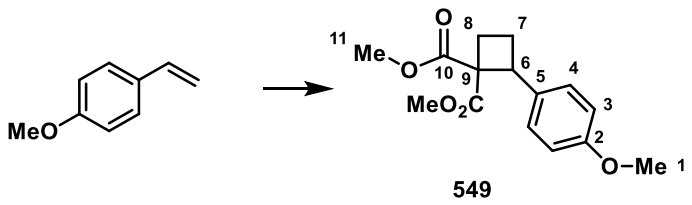


538 **542**

General procedure N: *In a modification to the general procedure, no benzoic acid was used and the reaction was run under an atmosphere of argon*. Cyclobutane **538** (40.4 mg, 0.15 mmol), $[Rh(cod)_2]OTf$ (5.27 mg, 0.011 mmol, 7.5 mol%) and PPh_3 (5.90 mg, 0.023 mmol, 15 mol%) were

employed and the reaction was stirred at 180 °C for 24 h. Flash column chromatography (40% EtOAc/hexane) afforded compound **542** (13.2 mg, 33%) as a colourless oil; ν_{max} / cm^{-1}: 2956 (m), 2924 (m), 2853 (m), 1730 (s), 1701 (s), 1436 (m), 1385 (s), 1201 (s), 1152 (s), 1101 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.62-6.52 (m, 1H, C**7**-H and d, *J* = 14.6 Hz, 1H, C**6**-H), 3.74 (s, 6H, 2 × C**11**-H_3), 3.47 (t, *J* = 7.5 Hz, 1H, C**9**-H), 2.73-2.68 (m, 2H, C**8**-H_2), 2.71 (s, 4H, 2 × C**1**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 175.2 (C**2**), 169.0(C**10**), 120.7 (C**6**), 119.2 (C**7**), 52.7 (C**11**), 51.7 (C**9**), 30.5 (C**8**), 27.8 (C**1**); HRMS: (ESI^+) calculated for $C_{12}H_{15}NNaO_6$: 292.0792, found $[M+Na]^+$: 292.0793.

Dimethyl 2-(4-methoxyphenyl)cyclobutane-1,1-dicarboxylate (549)

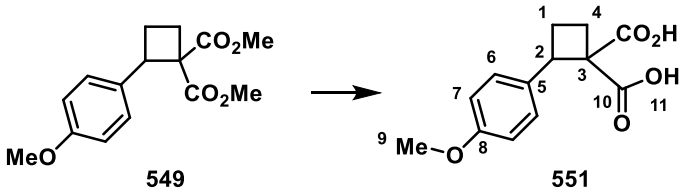


549

The title compound was prepared following a modified literature procedure.[242] In the glovebox, a flame-dried flask was charged with previously fused and dried on the oil pump for 18 h $ZnBr_2$ (1.32 g, 5.90 mmol), fitted with a rubber septum, removed from the glovebox and placed under an atmosphere or Ar. Dry DCM (20 mL) was added and the flask was cooled to -130 °C in a pentane/liquid N_2 bath. A solution of dimethyl 2,2-methylidene malonate (1.70 g, 11.8 mmol) in dry DCM (10 mL) and a solution of 1-methoxy-4-vinylbenzene (0.78 mL, 5.90 mmol) in dry DCM (10 mL) were prepared and cooled to -130 °C in a pentane/liquid N_2 bath. Dimethyl 2,2-methylidene malonate solution followed by 1-methoxy-4-vinylbenzene solution were added to the flask containing $ZnBr_2$ via syringe over a period of 5 min at -130 °C. The reaction was warmed to -78 °C in an isopropanol/dry ice bath and stirred for 3 h. A solution of pyridine (2 ml) in wet DCM (15 mL) pre-cooled to -78 °C was added to the reaction via syringe. The reaction was warmed to room temperature, washed with saturated aq. Na_2EDTA (2 x 60 mL), dried over Mg_2SO and concentrated *in vacuo*. The residue was purified by flash column chromatography (4% EtOAc/hexane) to afford the title compound **549** (1.00 g, 61%) as a colourless solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21 (d, *J* = 8.8 Hz, 2H, 2 × C**4**-H), 6.82 (d, *J* = 8.8 Hz, 2H, 2 × C**3**-H), 4.31 (t, J = 9.5 Hz, 1H, C**6**-H), 3.78 (s, 3H, C**10**-H_3), 3.77 (s, 3H, C**11**-H_3), 3.28 (s, 3H, C**1**-H_3), 2.71 – 2.65 (m, 1H, C**8**-H_2), 2.62-2.51 (m, 1H, C**8**-H_2), 2.28-2.19 (m, 1H, C**7**-H_2), 2.18-2.11 (m, 1H, C**7**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.1 (C**10**), 169.8 (C**10**), 158.6 (C**2**), 131.3 (C**5**), 128.7 (C**4**), 113.4 (C**3**), 59.8 (C**9**), 55.2 (C**1**), 52.4 (C**11**), 51.8 (C**11**), 44.7 (C**6**), 25.5 (C**8**), 21.0 (C**7**); The

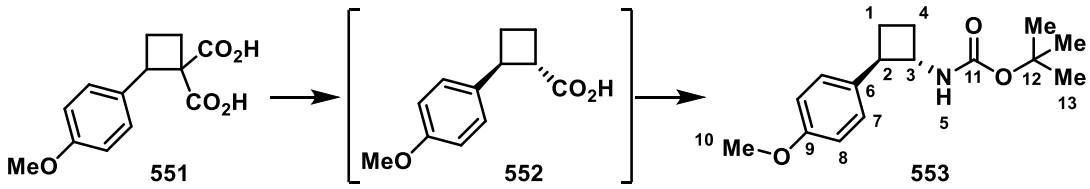
spectroscopic properties of this compound were consistent with the data available in the literature.[242]

2-(4-Methoxyphenyl)cyclobutane-1,1-dicarboxylic acid (551)



Dicarboxylate **549** (3.23 g, 11.60 mmol) was dissolved in a mixture of 1,4-dioxane and water (1:1, 200 mL), then potassium hydroxide pellets (6.50 g, 116 mmol) were added and the reaction mixture was stirred at 80 °C for 16 h. The reaction mixture was concentrated *in vacuo*, diluted with water (100 mL) and extracted with Et_2O (50 mL). The aqueous portion was adjusted to pH 2 by addition of 2.0 M aq. HCl and then extracted with Et_2O (3 × 50 mL). The organic extracts were combined, washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford pure title compound **551** (2.75 g, 95%) as a colourless solid; m.p. 118-119 °C; ν_{max} / cm^{-1}: 2953 (m), 1729 (s), 1708 (s), 1611 (m), 1513 (s), 1245 (s), 1175 (s), 1033 (s); ^{1}H NMR (400 MHz, MeOD): δ 7.27 (d, *J* = 8.7 Hz, 2H, 2 × C**6**-H), 6.85 (d, *J* = 8.7 Hz, 2H, 2 × C**7**-H), 4.88 (br. s, 2H, O**11**-H), 4.28 (t, *J* = 9.3 Hz, 1H, C**2**-H), 3.78 (s, 3H, C**9**-H_3), 2.67-2.51 (m, 2H, C**1**-H_2 and C**4**-H_2), 2.36-2.11 (m, 2H, C**1**-H_2 and C**4**-H_2); ^{13}C NMR (101 MHz, MeOD): δ 174.17 (C**10**), 171.69 (C**10**), 158.61 (C**8**), 131.65 (C**5**), 128.43 (C**6**), 112.91 (C**7**), 59.68 (C**3**), 54.19 (C**9**), 44.57 (C**2**), 25.32 (C**4**), 20.51 (C**1**); HRMS: (ESI^-) calculated for $C_{13}H_{13}O_5$: 249.0768, found $[M-H]^-$: 249.0770.

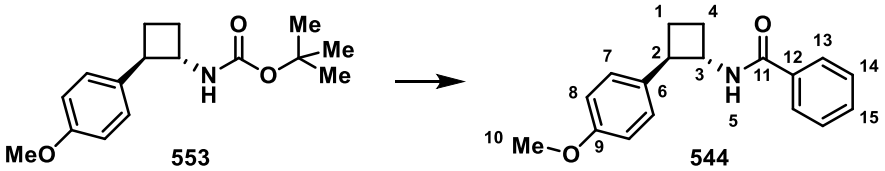
***tert*-Butyl (2-(4-methoxyphenyl)cyclobutyl)carbamate (552)**



Dicarboxylic acid **551** (1.75 g, 7.00 mmol) was dissolved in DMF (50 mL) and heated to reflux for 3 hours before being co-evaporated with toluene to dryness *in vacuo*. The crude was taken up in EtOAc (50 mL). The solution was washed with water (3 × 20 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude decarboxylated product **552**. To a solution of carboxylic acid and Et_3N (0.98 mL, 7.00 mmol) in anhydrous *t*-BuOH (60 mL) was added diphenylphosphoryl azide (1.66 mL, 7.70 mmol) dropwise. The reaction was heated to 80 °C and stirred for 24 h before cooling to r.t. The reaction mixture was concentrated *in vacuo* and

the residue was dissolved in Et_2O (50 mL). Water (50 mL) was added and the aqueous portion was further extracted with Et_2O (3 × 30 mL). The organic extracts were combined, washed with sat. aq. $NaHCO_3$ (50 mL) and brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (1-7% EtOAc/hexane) to afford the title compound **553** (0.70 g, 36%, single diastereomer) as a colourless solid; m.p. 102-103 °C (Et_2O); ν_{max} / cm^{-1}: 3361 (m), 2975 (m), 2931 (m), 2857 (m), 1710 (s), 1513 (s), 1456 (m), 1366 (s), 1247 (s), 1173 (s), 1041 (s); ^1H NMR (400 MHz, $CDCl_3$): δ 7.17 (d, *J* = 8.6 Hz, 2H, 2 × C**7**-H), 6.87-6.82 (m, 2H, 2 × C**8**-H), 4.83 (br. s, 1H, N**5**-H), 4.21-4.07 (m, 1H, C**3**-H), 3.78 (s, 3H, C**10**-H_3), 3.27-3.12 (m, 1H, C**2**-H), 2.36-2.25 (m, 1H, C**4**-H_aH_b), 2.15-2.05 (m, 1H, C**1**-H_aH_b), 1.85-1.60 (m, 2H, C**1**-H_aH_b and C**4**-H_aH_b), 1.42 (br. s, 9H, 3 × C**12**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 158.1 (C**9**), 154.7 (C**11**), 134.8 (C**6**), 127.5 (C**7**), 113.7 (C**8**), 79.2 (C**12**), 55.3 (C**10**), 51.8 (C**3**), 48.8 (C**2**), 28.4 (C**13**), 28.0 (C**4**), 22.53(C**1**); HRMS: (ESI^+) calculated for $C_{16}H_{23}NNaO_3$: 300.1570, found $[M+Na]^+$: 300.1578. *The relative stereochemistry of this compound was corroborated by nOe experiments. No significant nOe was observed between C**2**-H and C**3**-H.*

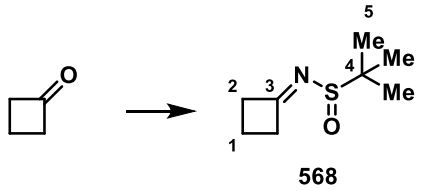
N-(2-(4-Methoxyphenyl)cyclobutyl)benzamide (544)



To a solution of protected amine **553** (0.10 g, 0.36 mmol) in DCM (5 mL) was added TFA (0.28 mL, 3.60 mmol) and the reaction mixture was stirred at r.t. for 10 min. The solvent was removed *in vacuo* and the residue was redissolved in DCM (10 mL) and washed with sat. aq. $NaHCO_3$ (10 mL/mmol). The aqueous portion was further extracted with DCM (2 × 5 mL) and the organic extracts were combined, washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo* until the concentration was reduced to approx. 15 mL/mmol. The solution was cooled to 0 °C and Et_3N (0.47 mmol, 50 μL) and benzoyl chloride (0.59 mmol, 35 μL) were added. The reaction was warmed to r.t. and stirred for 8 h under nitrogen. Water (5 mL) was added to the reaction mixture and the solution was extracted with DCM (3 × 5 mL). The organic extracts were combined, washed with brine (10 mL), dried over MgSO4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (20-50% EtOAc/hexane) to afford the title compound **544** (47.0 mg, 47%) as a colourless solid; m.p. 142-143 °C; ν_{max} / cm^{-1}: 3304 (m), 2978 (m), 2947 (m), 1635 (s), 1534 (s), 1513 (s), 1294 (m), 1249 (s); ^1H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 7.2 Hz, 2H, 2 × C**13**-H), 7.51-7.40 (m, 3H, C**15**-H and 2 × C**14**-H), 7.22 (d, *J* = 8.5 Hz, 2H, 2 × C**7**-H), 6.85 (d, *J* = 8.5 Hz, 2H, 2 × C**8**-H), 6.32 (br. d, *J* = 7.8 Hz, 1H, N**5**-H), 4.73 (app. p, *J* = 8.7 Hz, 1H, C**3**-

H), 3.78 (s, 3H, C**9**-H$_3$), 3.43-3.38 (m, 1H, C**2**-H), 2.45 (m, 1H, C**4**-H$_a$H$_b$), 2.23 (app. q, J = 9.2 Hz, 1H, C**1**-H$_a$H$_b$), 1.92 (app. p, J = 9.8 Hz, 1H, C**4**-H$_a$H$_b$), 1.85-1.73 (m, 1H, C**1**-H$_a$H$_b$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.5 (C**11**), 157.9 (C**9**), 134.5, 134.4 (C**6** and C**12**), 131.4 (C**15**), 128.5 (C**14**), 127.5 (C**7**), 126.9 (C**13**), 113.9 (C**8**), 55.3 (C**10**), 50.8 (C**3**), 48.7 (C**2**), 28.0 (C**4**), 23.1 (C**1**); HRMS: (ESI$^+$) calculated for $C_{18}H_{20}NO_2$: 282.1489, found [M+H]$^+$: 282.1490.

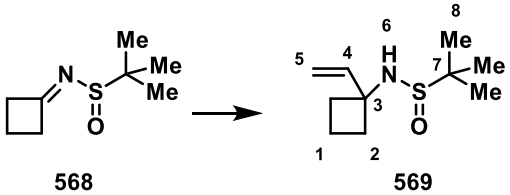
N-Cyclobutylidene-2-methylpropane-2-sulfinamide (568)



568

The title compound was prepared following a slightly modified literature procedure.[303] A mixture of titanium (IV) ethoxide (22.4 mL, 107.0 mmol) and cyclobutanone (5.37 mL, 71.0 mmol) in dry tetrahydrofuran (120 mL) was stirred for 10 minutes. *tert*-Butanesulfinamide (7.17 g, 59.0 mmol) was added and the reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was poured over stirring brine (130 ml), Celite® was added and the slurry was diluted with EtOAc (200 ml). The slurry was filtered, washed with EtOAc (3 × 50 ml) and the filtrate was charged into a separatory funnel and the organic layer was separated. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (10% EtOAc/petrol) to afford the title compound **568** (7.53 g, 60%) as a colorless oil; ν_{max} / cm^{-1}: 2959 (m), 1661 (s), 1362 (m), 1116 (s), 1078 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.51 – 3.39 (m, 1H, C**2**-H$_2$), 3.28 – 3.16 (m, 1H, C**2**-H$_2$), 3.14 – 2.97 (m, 2H, C**2**-H$_2$), 2.10 – 2.00 (m, 2H, C**1**-H$_2$), 1.20 (s, 9H, 3 × C**5**-H$_3$); ^{13}C NMR ($CDCl_3$,101 MHz): δ 186.8 (C**3**), 56.7 (C**4**), 40.5 (C**2**), 39.9 (C**2**), 22.2 (C**5**), 15.0 (C**1**). The spectroscopic properties of this compound were consistent with the data available in the literature.[303]

2-Methyl-*N*-(1-vinylcyclobutyl)propane-2-sulfinamide (569)

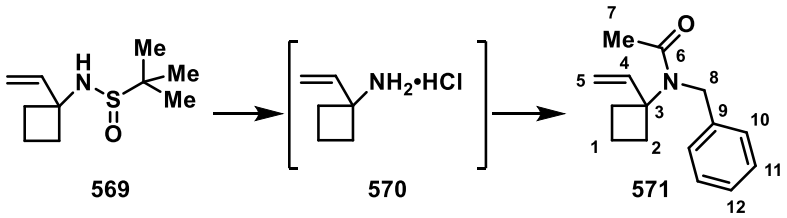


568 **569**

A solution of **568** (3.00 g, 17.31 mmol) in dry THF was *quickly* added to vinylmagnesium bromide (1 M in THF, 86.6 mL, 5.0 eq) in one batch at -78 °C and the reaction mixture was stirred at room

temperature for 18 hours. The reaction was cooled to -78 °C and sat. aq. NH_4Cl (50 mL) was added. The solution was extracted with Et_2O (3 × 75 mL) and the organic extracts were combined, washed with brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (30% EtOAc/petrol) to afford the title compound **569** (2.08 g, 41%) as a colorless oil; ν_{max} / cm^{-1}: 3206 (br. w), 2982 (m), 2950 (m), 1363 (m), 1150 (m), 1051 (s), 914 (m); ^1H NMR ($CDCl_3$, 400 MHz): δ 6.02 (dd, *J* = 17.3, 10.5 Hz, 1H, C**4**-H), 5.30 (dd, *J* = 17.3, 0.8 Hz, 1H, C**5**-$H_{2,\ trans}$), 5.19 (dd, *J* = 10.5, 0.8 Hz, 1H, C**5**-$H_{2,\ cis}$), 3.37 (br. s, 1H, N**6**-H), 2.33 – 2.16 (m, 4H, 2 × C**2**-H_2), 1.91 – 1.80 (m, 1H, C**1**-H_2), 1.73 (dp, *J* = 10.9, 8.6 Hz, 1H, C**1**-H_2), 1.20 (s, 9H, 3 × C**8**-H_3); ^{13}C NMR ($CDCl_3$,101 MHz): δ 141.8 (C**4**), 113.4 (C**5**), 60.8 (C**3**), 55.5 (C**7**), 34.5 (C**2**), 33.7 (C**2**), 22.5 (C**8**), 14.0 (C**1**); HRMS: (ESI^+) calculated for $C_{10}H_{19}NNaOS$: 224.1080, found $[M+Na]^+$: 224.1078.

***N*-Benzyl-*N*-(1-vinylcyclobutyl)acetamide (571)**

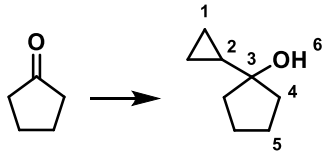


569 570 571

To a solution of **569** (2.78 g, 13.81 mmol) in dry Et_2O (15 mL), MeOH (5.59 mL, 138.08 mmol) and then HCl (2 M in Et_2O, 7.1 mL) were added via syringe at 0 °C. The reaction mixture was warmed to r.t., stirred for 1 h and then the precipitated was separated by filtration, washed with Et_2O:hexane = 1:2 (3 × 15 mL) and dried under the high vacuum to afford amine hydrochloride **570** (1.85 g, >99%). To a suspension of amine salt **570** (1.85 g, 13.85 mmol) in dry toluene (20 mL) over 3 Å molecular sieves, Et_3N (2.03 mL, 14.54 mmol) was added at r.t. and the reaction mixture was stirred for 1 h. Benzaldehyde (1.47 mL, 14.54 mmol) was added at r.t. and the reaction was stirred for further 16 h at r.t. The resulting mixture was filtered, rinsed with toluene and concentrated *in vacuo*. The residue was dissolved in MeOH (20 mL), cooled to 0 °C and $NaBH_4$ (0.63 g, 16.61 mmol) was added portionwise. The solution was warmed to r.t. and stirred for 6 h. The reaction mixture was concentrated *in vacuo* and then sat. aq. $NaHCO_3$ (30 mL) was added. The solution was extracted with DCM (3 × 30 mL) and then the organic extracts were combined, washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the secondary amine intermediate. The obtained amine was dissolved in DCM (15 mL), Et_3N (2.31 mL, 16.61 mmol) and acetic anhydride (1.57 mL, 16.61 mmol) were added at 0 °C under nitrogen. The solution was warmed to r.t. and stirred for 16 h. Sat. aq. $NaHCO_3$ (40 mL) was added and the

aqueous layer was extracted with DCM (3 × 30 mL). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Flash column chromatography (20% EtOAc/petrol) afforded the title compound **571** (2.76 g, 87%, 1.12:1 mixture of rotamers *A*:*B*) as a pale yellow oil; ν_{max} / cm^{-1}: 2986 (w), 2946 (w), 1645 (s), 1398 (s), 1349 (m), 708 (m); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.42 – 7.18 (m, 10H, 2 × C**10**-H, 2 × C**11**-H and C**12**-H, *A*+*B*), 6.22 (dd, *J* = 17.1, 10.7 Hz, 1H, C**4**-H, *B*), 6.17 (dd, *J* = 17.1, 10.5 Hz, 1H, C**4**-H, *A*), 5.20 – 5.04 (m, 4H, C**5**-H_2, *A*+*B*), 4.47 (br. s, 2H, C**8**-H_2, *A*), 4.34 (s, 2H, C**8**-H_2, *B*), 2.54 – 2.09 (m, 8H, 2 × C**2**-H_2, *A*+*B*), 2.02 (s, 3H, C**7**-H_3, *A*), 1.95 (s, 3H, C**7**-H_3, *B*), 1.89 – 1.57 (m, 4H, C**1**-H_2, *A*+*B*); ^{13}C NMR ($CDCl_3$,101 MHz): δ 172.5, 171.0 (C**3**, *A*+*B*), 139.8, 139.3, 138.8, 138.8 (C**4** and C**9**, *A*+*B*), 129.0, 128.6, 127.3, 126.7 (2 signals), 125.8 (C**10**, C**11** and C**12**, *A*+*B*), 112.2, 111.6 (C**5**, *A*+*B*), 64.4, 63.8 (C**3**, *A*+*B*), 49.3, 48.4 (C**8**, *A*+*B*), 34.6, 32.7 (C**2**, *A*+*B*), 23.4, 23.1 (C**7**, *A*+*B*), 14.7, 14.0 (C**1**, *A*+*B*); HRMS: (ESI^+) calculated for $C_{15}H_{19}NNaO$: 252.1359, found $[M+Na]^+$: 252.1361.

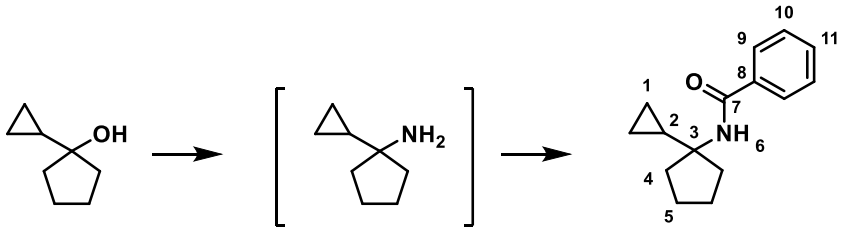
1-Cyclopropylcyclopentan-1-ol (572)



572

The title compound was prepared following a literature procedure.[304] To a solution of bromocyclopropane (2.54 mL, 31.7 mmol) in diethyl ether (50 mL) at -78 °C. under nitrogen was added, dropwise, tert-butyllithium (18.2 mL of a 1.7 M solution in pentane, 31 mmol). Diethyl ether (30 mL) was added and the mixture was stirred for 1 hour at -78 °C. A solution of cyclopentanone (2.74 mL, 34 mmol) in diethyl ether (40 mL) was then added dropwise. The reaction was stirred for 4 hours at -78 °C. and was then allowed to warm to room temperature over 16 hours. Water (40 mL) was added, the solution was extracted with Et_2O (3 × 25 mL) and the organic extracts were combined, dried over $MgSO_4$ and concentrated *in vacuo.* The residue was purified by flash column chromatography (100% DCM) to afford the title compound **572** (2.45 g, 61%) as a colorless oil; ν_{max} / cm^{-1}: 3422 (br. m), 2959 (m), 2926 (m), 1455 (m), 1391 (m), 1051 (s), 1023 (s); ^1H NMR ($CDCl_3$, 400 MHz): δ 1.86 – 1.74 (m, 2H, C**5**-H_2), 1.67 – 1.48 (m, 6H, C**5**-H_2 and 2 × C**4**-H_2), 1.14 (br. s, 1H, O**6**-H), 1.09 (tt, *J* = 8.4, 5.5 Hz, 1H, C**2**-H), 0.45 – 0.39 (m, 2H, 2 × C**1**-H_aH_b), 0.33 – 0.28 (m, 2H, 2 × C**1**-H_aH_b); ^{13}C NMR ($CDCl_3$,101 MHz): δ 82.3 (C**3**), 38.6 (C**4**), 23.9 (C**5**), 20.1 (C**2**), 1.5 (C**1**). The spectroscopic properties of this compound were consistent with the data available in the literature.[304]

***N*-(1-Cyclopropylcyclopentyl)benzamide (575)**



572 **574** **575**

The amine intermediate was prepared following a slightly literature procedure.[305] To a solution of sodium azide (1.12 g, 17.12 mmol) in toluene (8 mL) under nitrogen at room temperature was added trifluoroacetic acid (1.31 mL, 17.12 mmol). The mixture was cooled to 0° C and a solution of 1-cyclopropylcyclopentan-1-ol **572** (1.08 g, 8.56 mmol) in toluene (2 ml) was added dropwise. The mixture was stirred for 4 hours at 0 °C and allowed to warm to room temperature. Concentrated ammonium hydroxide solution (8 mL) was then added and the toluene layer was separated, washed with water (2 × 5 mL) and dried over $MgSO_4$. The resulting solution was added dropwise to a solution of $LiAlH_4$ (2 M in THF, 8.56 mL) in tetrahydrofuran (8 ml) at 0 °C under nitrogen. The mixture was stirred at room temperature for 16 h and then heated to 50 °C for 1 h. The reaction mixture was cooled to 0 °C, water (0.68 ml) was added dropwise, followed by 2.0 M aq. NaOH solution (1.28 ml) and water (2.05 ml). The mixture was stirred for 15 minutes, filtered and evaporated under reduced pressure to a volume of approx. 20 mL. The solution was washed with sat. aq. $NaHCO_3$ (20 ml) and dried over $MgSO_4$. Half of the resulting solution (approx. 8.56 mmol of amine **574**) was used in the next step without further purification. The amine **574** was converted to an amide **575** according to the **General Procedure D** using benzoyl chloride (0.75 mL, 6.42 mmol) and the residue was purified by flash column chromatography (5-10% EtOAc/hexane) to afford the title compound **575** (230.3 mg, approx. 23% over three steps) as a colourless solid; m.p. 106-107 °C (DCM/hexane); ν_{max} / cm^{-1}: 3356 (m), 2954 (m), 1634 (s), 1532 (s), 1490 (m), 1309 (m), 1295 (m), 709 (m), 691 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.75 – 7.70 (m, 2H, 2 × C**9**-H), 7.51 – 7.38 (m, 3H, 2 × C**10**-H and C**11**-H), 5.97 (br. s, 1H, N**6**-H), 2.16 – 2.07 (m, 2H, 2 × C**4**-H_aH_b), 1.86 – 1.73 (m, 2H, 2 × C**5**-H_aH_b), 1.71 – 1.52 (m, 5H, 2 × C**4**-H_aH_b, 2 × C**5**-H_aH_b and C**2**-H), 0.52 – 0.44 (m, 2H, 2 × C**1**-H_aH_b), 0.38 – 0.32 (m, 2H, 2 × C**1**-H_aH_b); ^{13}C NMR ($CDCl_3$,101 MHz): δ 167.1 (C**7**), 136.2 (C**8**), 131.2 (C**11**), 128.6 (C**10**), 126.9 (C**9**), 65.3 (C**3**), 35.6 (C**4** and C**7**), 24.3 (C**5** and C**6**), 18.8 (C**2**), 2.0 (C**1**); HRMS: (ESI^+) calculated for $C_{15}H_{19}NNaO$: 252.1359, found $[M+Na]^+$: 252.1361.

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