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*A thesis submitted in part fulfilment of the requirements of the degree
of Doctor of Philosophy*

Advances in Palladium Catalysed Wacker-Type Oxidative Transformations

Darren S. Lee

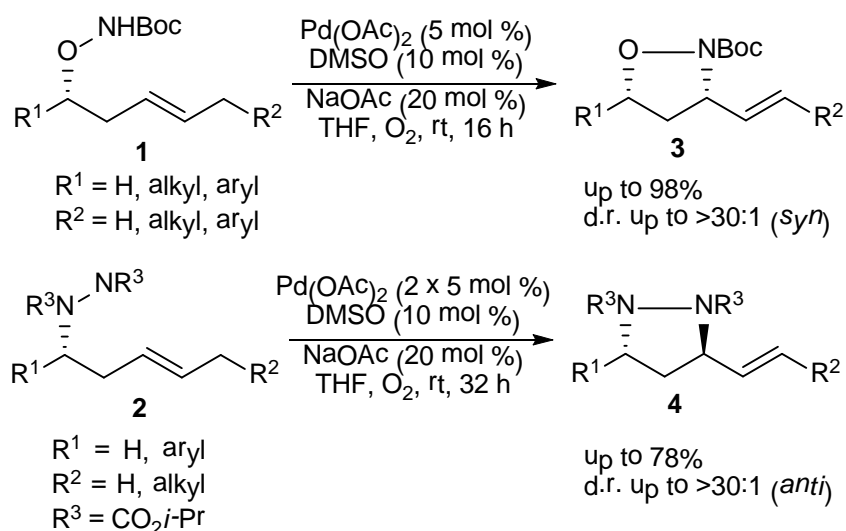


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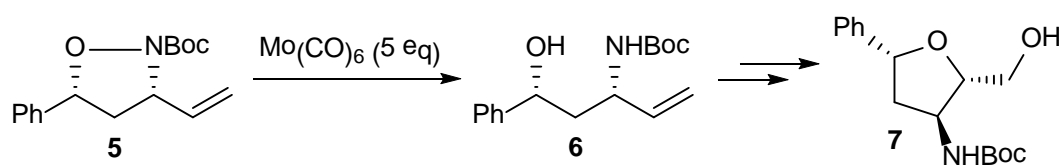
Thesis abstract

The development and optimisation of conditions for oxidative Wacker-type cyclisations followed by establishing the reaction scope are reported. Building upon the achievements in the field of oxidative Wacker-type reactions that has recently gathered interest, hydroxylamines **1** and hydrazines **2** were converted to isoxazolidines **3** and pyrazolidines **4** respectively (Scheme 1).



Scheme 1

Secondary hydroxylamines cyclised yielding *syn*-isoxazolidines with excellent diastereoselectivities, whereas secondary hydrazines cyclised yielding *anti*-pyrazolidines but still maintained a high level of diastereoselectivity. Isoxazolidine **5** was successfully transformed to the corresponding amino alcohol **6**, which was further converted to amino sugar derivatives **7** (Scheme 2).



Scheme 2

Acknowledgements

I would like to thank my supervisor Prof. Andrei Malkov for giving me an interesting project, the opportunity to join his group and the chance to go Estonia. Thanks to Prof. Jones, Dr. Pritchard, Dr. Weaver, Dr. Buckley and Dr. Christie for all their help, guidance and their relaxed group meetings(!). Thanks to all the support staff in the chemistry department who have assisted me during my studies. Thanks to Al Daley for his encyclopedia like knowledge and his rapid response as a technician. Special thanks go to Marc Kimber for all his mentoring, advice, for being a great friend, the trips to FND and for all the single malt.

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List of abbreviations

$[\alpha]_D$ – Optical rotation

$^{\circ}\text{C}$ – Degrees centigrade

^{13}C – Carbon-13

^1H – Hydrogen (Proton)

Alk – Alkyl

AP – Aminopalladation

Ar – Aryl

BINAP – 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl

Bn – Benzyl

Boc – *tert*-Butylcarbonate

Bz – Benzoyl

c – Concentration

Cbz – Carboxybenzyl

Cy – Cyclohexyl

d – Day(s), Doublet (Spectral)

D – Deuterium

d.r. – Diastereoisomer ratio

dba – Dibenzylideneacetone

DIPEA – Diisopropylethylamine

DMAP – 4-Dimethylaminopyridine

DMPU– 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone

DMSO – Dimethylsulfoxide

DPE-Phos – Bis[(2-diphenylphosphino)phenyl] ether

dppf – 1,1'-Bis(diphenylphosphino)ferrocene

ee – Enantiomeric excess

eq – Stoichiometric equivalents

Et – Ethyl

EWG – Electron withdrawing group

g – Gram

h – Hour(s)

HRMS – High resolution mass spectrometry

IMes – 1,3-Bis(2,4,6-trimethylphenyl)imidazol-2-ylidene

i-Pr – *iso*-propyl

IR – Infra red

L – Litre, Ligand

M – Metal

M – Molar concentration

m.p. – Melting point

Me – Methyl

Mes – Mesityl, 1,3,5-trimethylbenzene

min – Minute(s)

mL – Millilitre

mol – Mole

MS – Molecular sieves

n-Bu – Normal butyl

NFBS – N-fluorobenzenesulfonimide

NHC – N-heterocyclic carbene

NHP – *N*-Hydroxyphthalimide

NMR – Nuclear magnetic resonance

NP – Nucleopalladation

NPhth – Phthalimide

Ns – Nosyl (4-nitrobenzenesulfonyl)

Nuc – Nucleophile

OAc/Ac – Acetate

oct – Octet (Spectral)

OP – Oxypalladation

PG – Protecting group

Ph – Phenyl

Pr – Propyl

py – Pyridine

q – Quartet (Spectral)

quin – Quintet (Spectral)

R – Any atom (not H)

rt – Room Temperature

s – Second(s), Singlet (Spectral)

sep – Septet (Spectral)

sex – Sextet (Spectral)

SM – Starting material

t – Triplet (Spectral)

t-Bu – Tertiary butyl

TFA – Trifluoroacetic acid

THF – Tetrahydrofuran

TLC – Thin layer chromatography

tol – *p*-toluyl

TPP – Tetraphenyl porphyrin

Ts – Tosyl (4-toluenesulfonyl)

X – Halogen, Ligand

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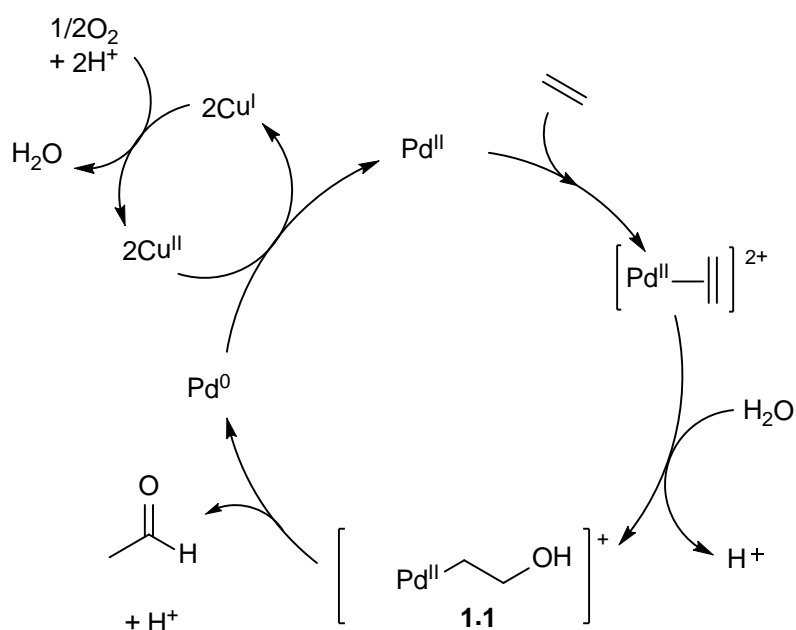
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1. Literature Review

1.1. Introduction

Electron-rich alkenes are typically unsusceptible to nucleophilic attack; complexation to an electrophilic transition metal, such as Pt^{II} , Pd^{II} or Fe^{II} , unlocks the potential for such a nucleophilic attack to occur. Palladium, which can exist in 3 interconvertible oxidation states: Pd^0 , Pd^{II} and Pd^{IV} , is known for its role in a range of well established reactions and is more often than not the first choice for activating unsaturated alkenes.¹ Palladium is a versatile metal with its unique properties derived from the ability to form both d^8 and d^{10} complexes at the +2 and 0 oxidation states respectively.²

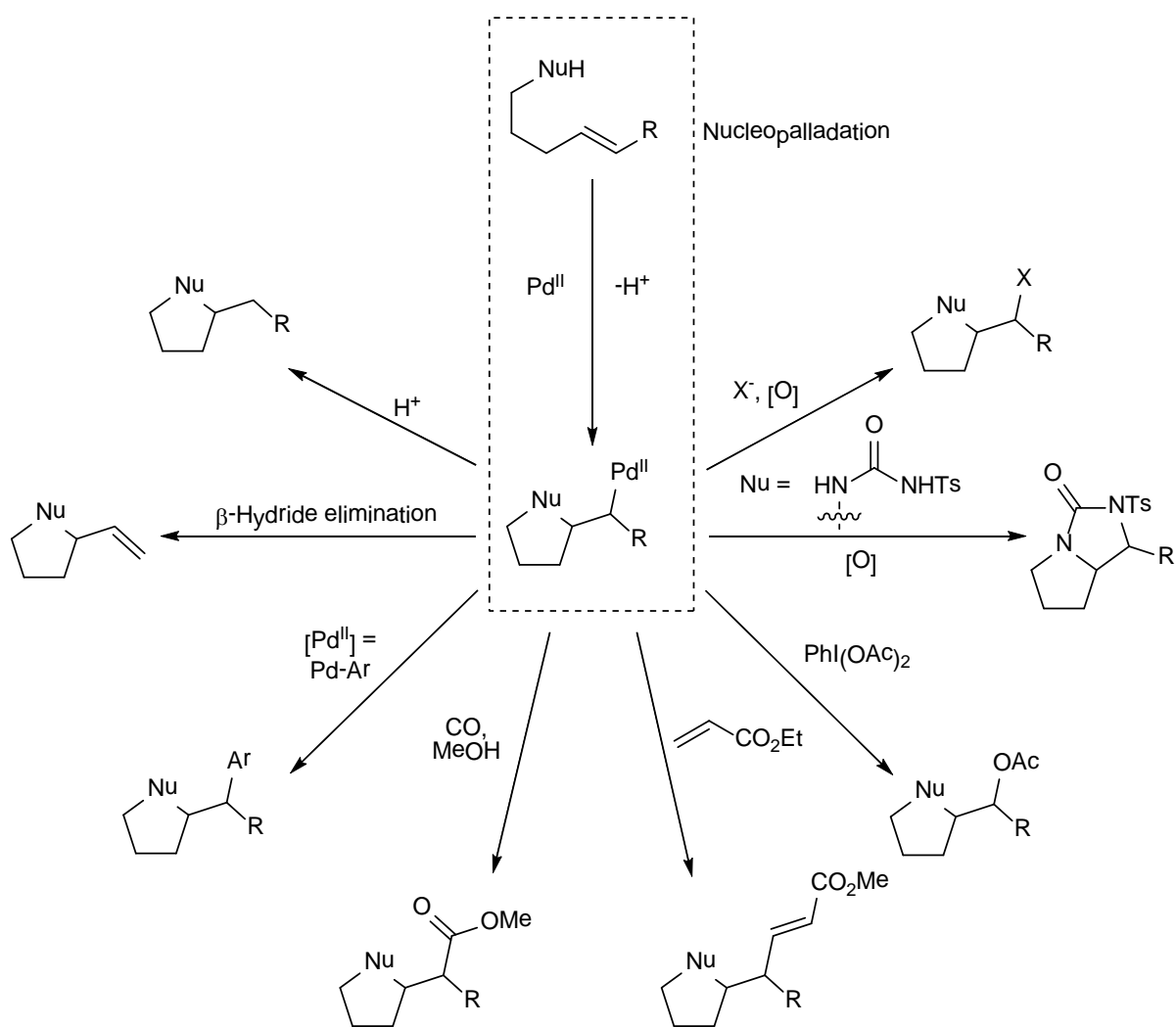


Scheme 1.1

The Wacker process, in which ethylene is converted to acetaldehyde by a Pd catalysed aerobic oxidation (Scheme 1.1), was developed in 1959 at Wacker Chemie.³ Many regard this development as the starting point for decades of research and development into many other Pd catalysed reactions. Whilst the Wacker process is regarded the origin of this field of chemistry, the discovery really dates back to 1894 when Phillips observed a stoichiometric

oxidation of ethylene using aqueous Pd^{II} salts.⁴ However, it was the Wacker process that really set the precedent for this chemistry with the use of a Cu^{II} co-catalyst in the presence of molecular oxygen, allowing for the use of catalytic amounts of palladium.

The reaction proceeds via a β -hydroxyethyl-Pd^{II} intermediate **1.1** (Scheme 1.1) formed from the addition of hydroxide and palladium across the C-C double bond. This addition across the double bond has been labelled “Nucleopalladation”, where the nucleo represents the nucleophile; a label which is often changed to fit the nucleophile in use. In the case of the Wacker oxidation, the term is hydroxypalladation as hydroxide is the nucleophile.

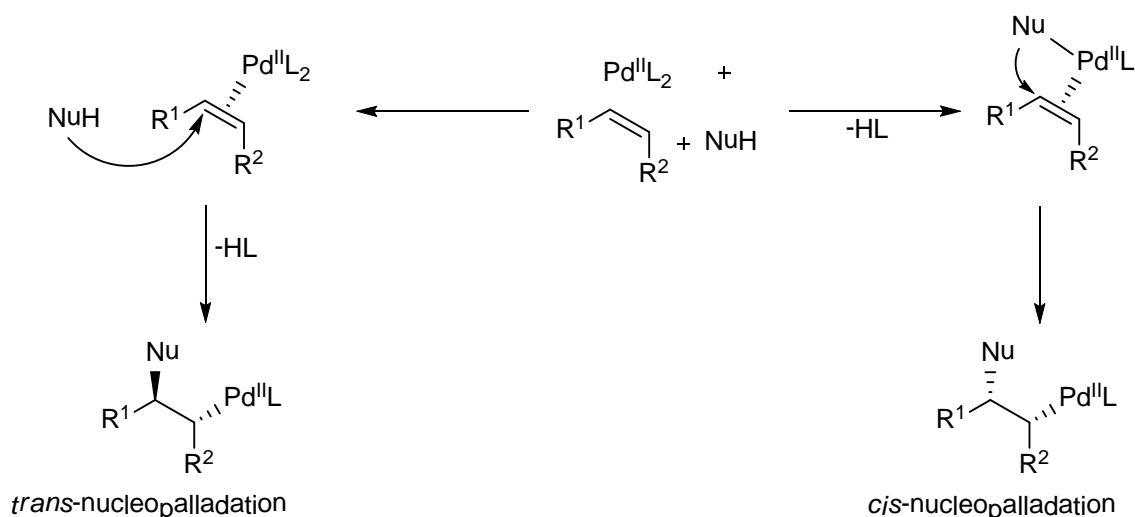


Since the Wacker process was established there have been numerous examples demonstrating that Pd^{II} can catalyse the addition of different nucleophiles to alkenes. These demonstrate a range of intermolecular and intramolecular transformations, the most common being oxidative and non-oxidative C-O, C-N and C-C bond forming reactions.⁵ Research groups have also taken advantage of the highly reactive Pd^{II}-alkyl intermediates, demonstrating the ability of the moiety to subsequently participate in a wide range of reactions (Scheme 1.2).⁵

The large range of nucleophiles, coupled with the possibility for further functionalisation allow for access to a range of synthetically useful building blocks. This area of synthetic organic chemistry has developed vastly over the past half century and still remains very much active today. New methodology is being developed, with research groups striving for lower catalyst loadings, milder conditions and stereochemical control over newly formed bonds.

1.2. Mechanism of Aminopalladation

Mechanistically, the nucleopalladation step is not as simple as it may first appear. It has been shown that two pathways exist, in which the addition of palladium and a nucleophile across a double bond can occur (Scheme 1.3).



Scheme 1.3

The difference in the two pathways stem from whether the nucleophile coordinates to the Pd, before the addition takes place, or not. In the case of *trans*-nucleopalladation, the nucleophile does not coordinate before the addition step, it approaches from the opposite face to the Pd^{II}. After the addition takes place the newly formed bonds are *trans*- (*anti*-) with respect to each other. As for *cis*-nucleopalladation, the nucleophile coordinates to the Pd catalyst before the addition takes place. The nucleophile bound Pd then interacts with the alkene, and now the addition across the double bond occurs. The nucleophile migrates from the Pd to the alkene, and the resulting alkyl-Pd species has the newly formed bonds in a *cis*- (*syn*-) configuration.

Understanding these two pathways is important from a stereochemical standpoint; control over the nucleopalladation step could have a big influence on the stereochemistry of newly formed bonds. In some cases both pathways have been shown to operate in parallel, when the energy barriers associated with each manifold are extremely similar.⁶

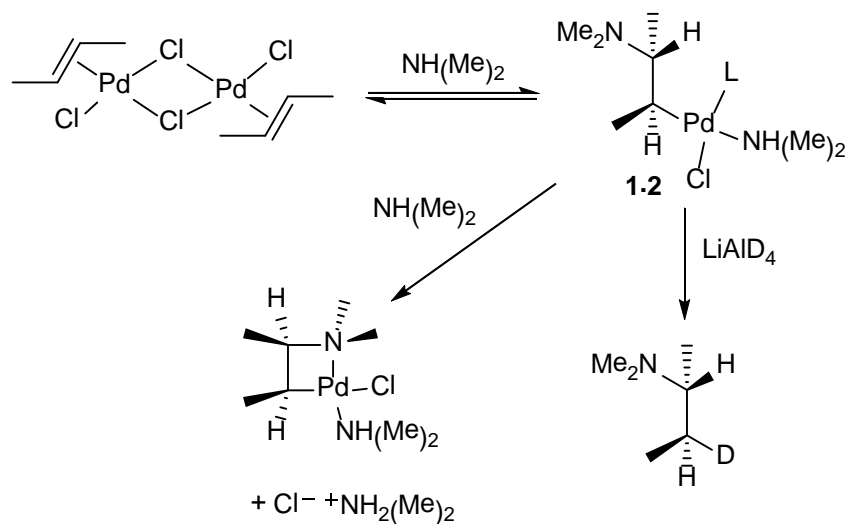
1.2.1. Early Studies

Early studies into the hydroxypalladation step of the Wacker process were carried out by Henry, providing evidence for a *cis*-hydroxypalladation pathway.⁷ Based upon kinetic analysis and rate law determination of the reaction, Henry suggested that hydroxide bound to palladium (*cis*) would undergo the alkene addition faster than that of the Pd-alkene species (*trans*).⁷

Soon after these initial findings, several groups observed that under modified Wacker conditions the pathway would primarily proceed via *trans*-hydroxypalladation.⁸ These studies were designed to yield products that could easily be analysed based on stereochemical outcome. Henry and co-workers later reported that the change in reaction conditions led to the change in stereochemical pathway.⁹ Recent computational studies have provided further evidence for this theory.¹⁰

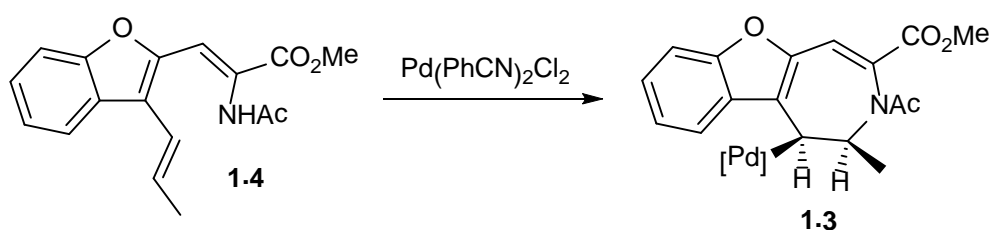
Around the same time as the studies into hydroxypalladation of the Wacker and related reactions, various research groups began to study the stereochemical pathways involved in palladium catalysed amination reactions. Åkermark, Bäckvall and Zetterberg reacted secondary amines with 2-butene. The aminated Pd-alkyl species **1.2** could be reacted further with NH(Me)₂ or LiAlD₄ to yield products that could be isolated and subjected to deuterium

studies to determine what stereochemical course was taken. They found that *trans*-AP was operating (Scheme 1.4).¹¹



Scheme 1.4

Taniguchi and co-workers isolated a Pd-alkyl intermediate **1.3** via an intramolecular alkene addition of enamide **1.4**. The tricyclic product was isolated with stereochemistry indicative of a *cis*-AP mechanism. β -Hydride elimination is prevented as the Pd and β -H are in a *trans*-configuration (Scheme 1.5).¹²



Scheme 1.5

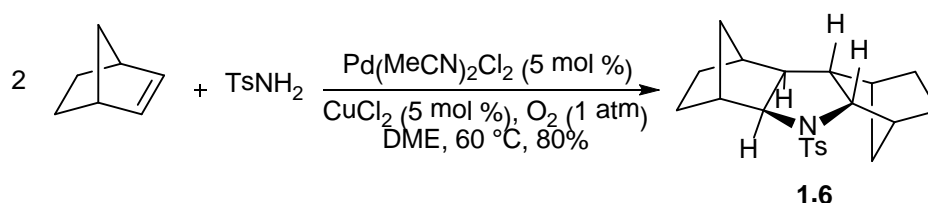
These early studies into nucleopalladation are important and show how the pathway can easily be altered. However, taking into account the sensitive nature of the nucleopalladation step, these earlier studies could not provide an accurate account of what transpires in a catalytic process.

Recently however, studies into catalytic amination reactions have gathered momentum. Recent studies have been primarily focused on understanding the mechanistic aspects of the catalytic aminopalladation step and how it is influenced by different factors, i.e. conditions, catalysts and the nature of the substrates.

1.2.2. Oxidative Wacker-type Amination

Oxidative amination is the sequence where an alkene undergoes aminopalladation and subsequent β -hydride elimination to furnish a product that contains a new C-N bond but retains the alkene functionality, albeit in a different position. Catalysed by an electrophilic Pd^{II} species, the aminopalladation step in this type of transformation can be unpredictable. Several groups have attempted to gain an understanding of what governs the two pathways.

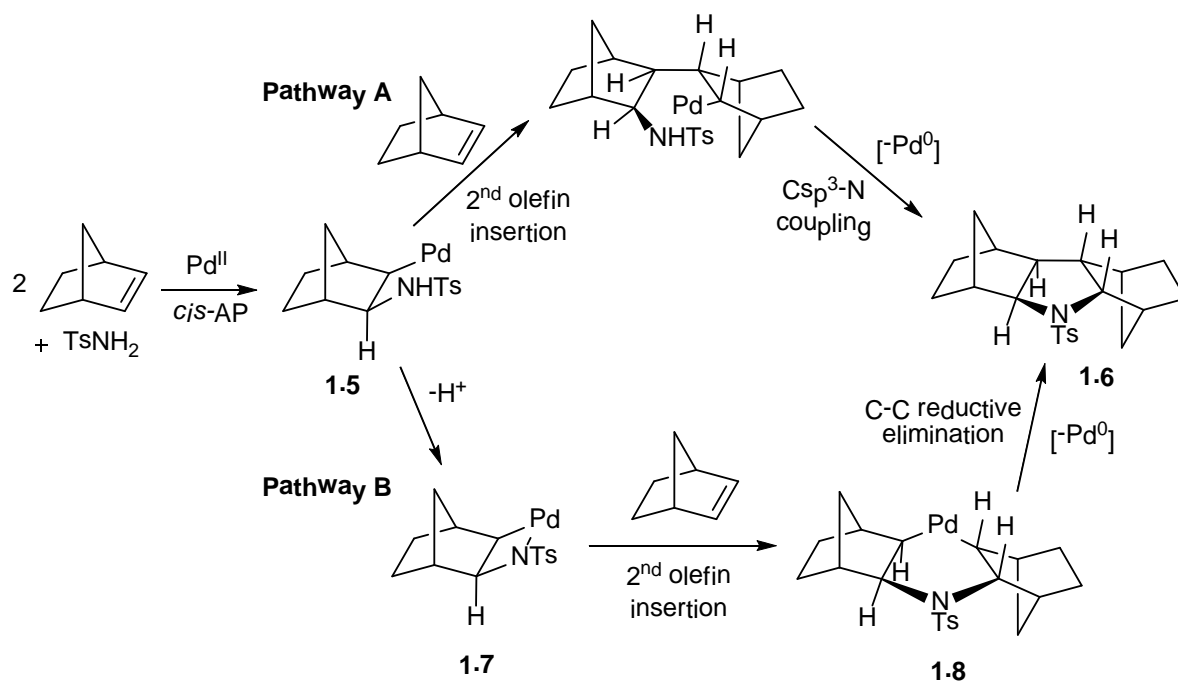
Stahl and co-workers reported the synthesis of a C₂-symmetrical pyrrolidine via a palladium catalysed oxidative amination of norbornene and TsNH₂ (Scheme 1.6).¹³



Scheme 1.6

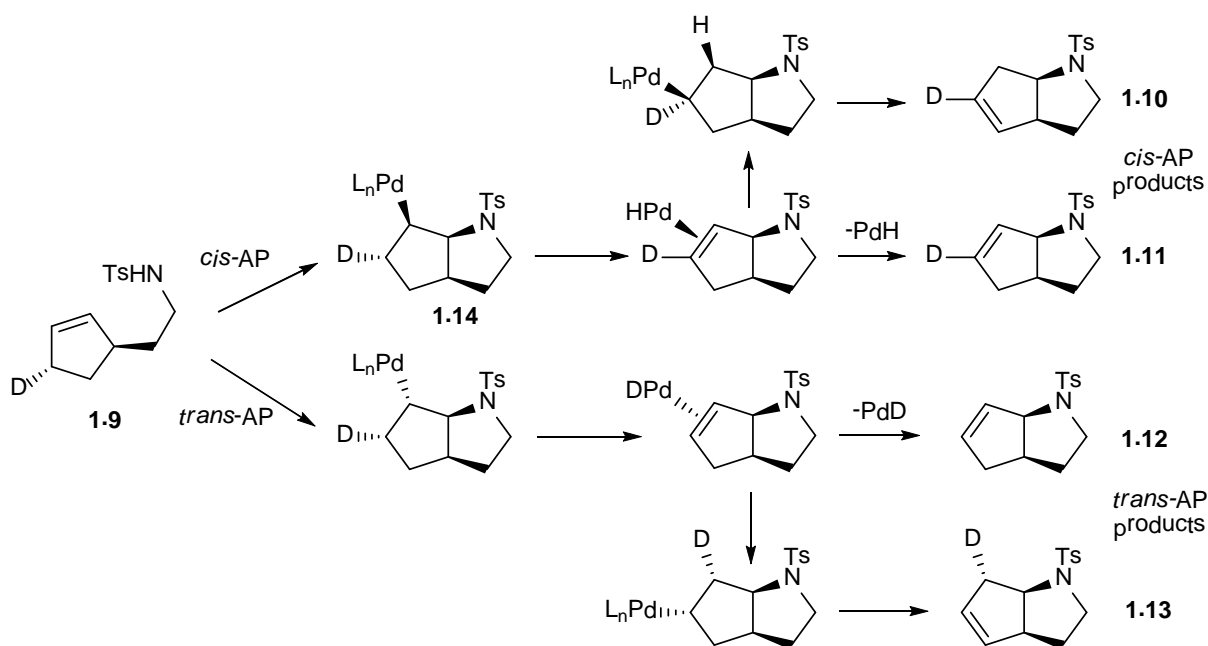
Through X-ray crystallography the group found that the pyrrolidine contained the nitrogen atom in a *cis*-configuration on the *exo*-faces of the alkenes. They suggested that intermediate **1.5** could be formed via a *cis*-AP on the first equivalent of norbornene, and then proposed a mechanistic pathway, leading to the formation of **1.6** (Scheme 1.7, pathway A). Pathway A involves a Heck-type addition of the Pd-alkyl intermediate **1.5** into the alkene of a second norbornene equivalent, followed by C-N coupling with elimination of palladium to furnish **1.6**. In a recent review, Stahl suggested an alternate pathway that could also give rise to **1.6** (Scheme 1.7, pathway B).¹⁴ Pathway B proceeds slightly differently with a 4-membered Pd-N intermediate **1.7** forming before the insertion of the second norbornene molecule. Addition of

the second olefin to the Pd-N bond yields a 6-membered intermediate **1.8**, containing both Pd and N bridging atoms. Subsequent C-C reductive elimination leads to the product **1.6**. Both pathways are mechanistically viable and both account for the formation of product **1.6** from a *cis*-aminopalladation.



Two years after this report, Liu and Stahl published findings on the mechanistic studies of an intramolecular aminopalladation. Using a range of known oxidative amination conditions, they set out to determine the effect of different catalyst systems on the aminopalladation pathway.¹⁵ A deuterated substrate **1.9** was designed to probe different aminopalladation pathways. The product structures **1.10-1.13** could easily be identified to determine the dominant aminopalladation route (Scheme 1.8). During the *cis*-AP pathway in Scheme 1.8, **1.11** is formed from β -hydride elimination of **1.14**, and **1.10** is formed from β -hydride elimination, reinsertion of Pd-H and another β -hydride elimination. As the Pd and β -D atoms are in an *anti*-conformation as a result of *cis*-AP, the D atom remains unchanged. For the *trans*-AP pathway, the Pd and β -D are in a *syn*-configuration, so this time β -deuteride elimination can occur. The two products **1.12** and **1.13** are then formed via the same way as for the *cis*-AP pathway, with loss and shift of D respectively.

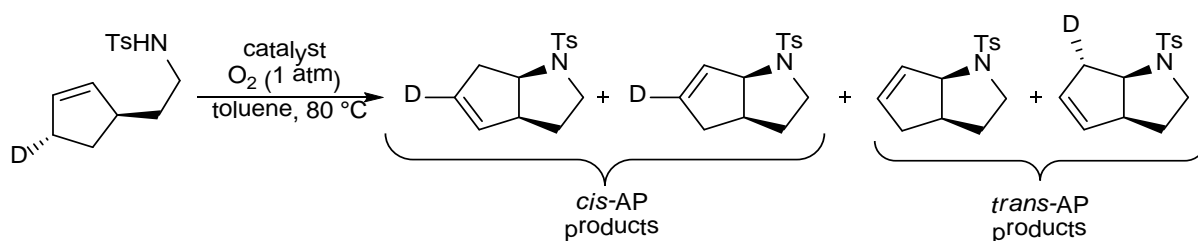
When the substrate **1.9** was submitted to the different catalyst systems, the results showed that *cis*-AP is dominant (Table 1.1, entries 1-4), with the exception of the NHC catalyst system of Pd(IMes)(TFA)₂/BzOH (Table 1.1, entry 5), which showed a 1:1 mixture of *cis*- and *trans*-pathway products. It was observed that this system was the only one operating under acidic conditions, in the presence of BzOH, whereas the others are under basic conditions, from either exogenous base or a basic anionic ligand.



Scheme 1.8

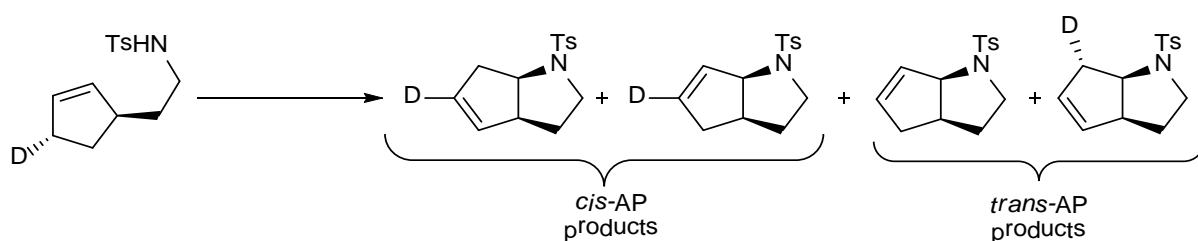
With this observation came the hope of seemingly being able to direct the course of the aminopalladation pathway. So with this they screened various acid and base additives with the NHC catalyst system (Table 1.2).

Table 1.1



Catalyst		Yield (%)	Product ratios - <i>cis:trans</i>	
1	Pd(OAc) ₂ /DMSO	70	100 (100:0)	: 0
2	Pd(OAc) ₂ /py	84	100 (98:2)	: 0
3	Pd(TFA) ₂ /py	85	100 (88:12)	: 0
4	Pd(TFA) ₂ /(-)-sparteine	37	100 (59:41)	: 0
5	Pd(IMes(TFA) ₂)/BzOH	60	51 (43:8)	: 49 (37:12)

Table 1.2



Additive (pKa)	Yield (%) of <i>cis</i> -AP (ratio of products)	Yield (%) of <i>trans</i> -AP (ratio of products)
1 None	39 (38:10)	20 (26:6)
2 AcOH (4.76)	36 (49:8)	26 (34:7)
3 BzOH (4.20)	31 (43:8)	29 (37:12)
4 CF ₃ CO ₂ H (-0.25)	4 (ND)	9 (ND)
5 NaOAc	68 (87:13)	0
6 Na ₂ CO ₃	71 (89:11)	0

Reaction conditions: **1.9** (0.05 mmol), (IMes)Pd-(O₂CCF₃)₂(OH₂) (2.5 μmol), additive (AcOH and BzOH, 20 mol %; CF₃CO₂H, 1 eq.; Na₂CO₃, 2 eq.), O₂ (1 atm), toluene (0.5 mL), 80 °C, 72 h. ND = Not determined.

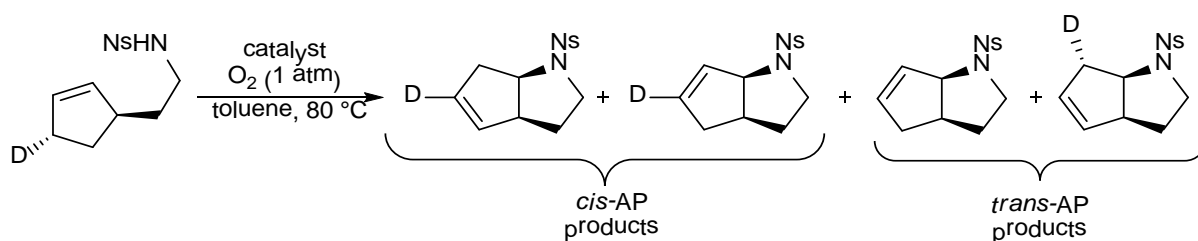
In the absence of additives both *cis*- and *trans*-AP products were obtained, favouring the *cis*-products 2:1 (Table 1.2, entry 1). With increase in the strength of the added acid, the relative ratio of *cis*: *trans*-AP decreases, from 1.5:1 for AcOH to 1:2 for TFA (Table 1.2, entries 2-4). When base was used as the additive the *cis*-AP pathway was operating exclusively and the products were achieved in an improved yield (Table 1.2, entries 5-6). These observations seem to suggest that the dominant aminopalladation pathway is influenced by the pH of the reaction mixture.

Following this, Stahl and co-workers investigated how the acidity of the nitrogen nucleophile tethered to the substrate would affect the stereochemical course of the reaction. With the pKa of TsNH₂ ≈ 15.1, NsNH₂ ≈ 13.9 and RCONHTs ≈ 9 (all in DMSO), it was expected that substrates bearing more acidic nitrogen atoms would show a different preference for stereochemical outcome of the aminopalladation step (Figure 1.1).



Figure 1.1

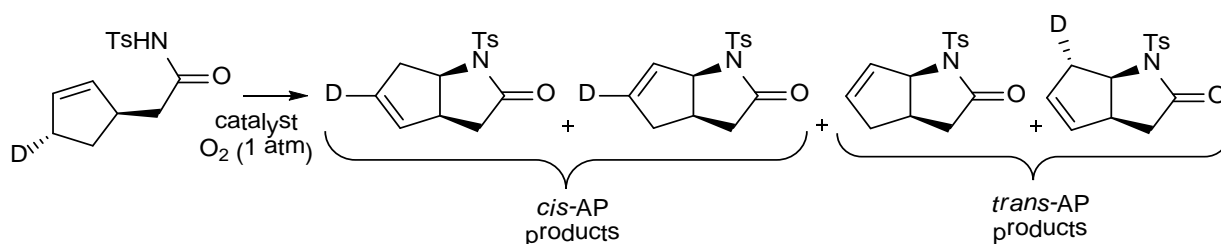
First the Ns derivative **1.15** was subjected to the catalyst screen (Table 1.3), which gave exclusively *cis*-AP products for all catalyst systems, including the acidic NHC/BzOH system. From this observation it would seem that increasing the acidity of the nucleophile increases the preference for *cis*-AP.

Table 1.3^a

	Catalyst	Yield (%)	Product ratios - <i>cis:trans</i> ^b	
1	Pd(OAc) ₂ /DMSO	74	100 (100:0)	: 0
2	Pd(OAc) ₂ /py	91	100 (100:2)	: 0
3	Pd(TFA) ₂ /py	86	100 (90:10)	: 0
4 ^c	Pd(IMes(TFA) ₂)/BzOH	78	100 (82:18)	: 0

(a) Reaction conditions: 5 mol % Pd, 33 μmol scale, 80 °C, 24 h. (b) Determined by ¹H NMR spectroscopy (c) 32 h.

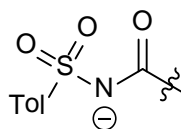
However, an even more acidic sulfonamide **1.16** gave rise to a more complex and unexpected set of results (Table 1.4).

Table 1.4^a

	Catalyst	Yield (%)	Product ratios - <i>cis:trans</i> ^b	
1	Pd(OAc) ₂ /DMSO	73	0	: 100 (100:0)
2	Pd(OAc) ₂ /py	47	89 (85:4)	: 11 (4:7)
3	Pd(TFA) ₂ /py	83	84 (78:6)	: 16 (14:2)
4 ^c	Pd(IMes(TFA) ₂)/BzOH	74	54 (41:13)	: 46 (22:24)
5 ^c	Pd(IMes(TFA) ₂)/Na ₂ CO ₃	34	67 (65:2)	: 33 (32:1)

(a) Reaction conditions: 5 mol % Pd, 33 μmol scale, 80 °C, 24 h. (b) Determined by ¹H NMR spectroscopy (c) 32 h.

The Pd(OAc)₂/DMSO system (Table 1.4, entry 1) which had previously given solely *cis*-AP products gave 100% *trans*-AP with this substrate. The two systems with exogenous pyridine (Table 1.4, entries 2-3) that previously gave predominantly *cis*-AP products now contained small amounts of the *trans*-AP products too. The NHC catalyst with BzOH (Table 1.4, entry 4) gave 1:1 *cis:trans* products whereas substituting BzOH with Na₂CO₃ (Table 1.4, entry 5) favoured the *cis* products 2:1. They speculated that these observations could originate from the anion of amide **1.17** being more stable in DMSO than the corresponding Pd-N intermediate, thus leading to a more readily dissociated Pd-N bond and resulting ultimately in an increase in *trans*-AP (Figure 1.2).

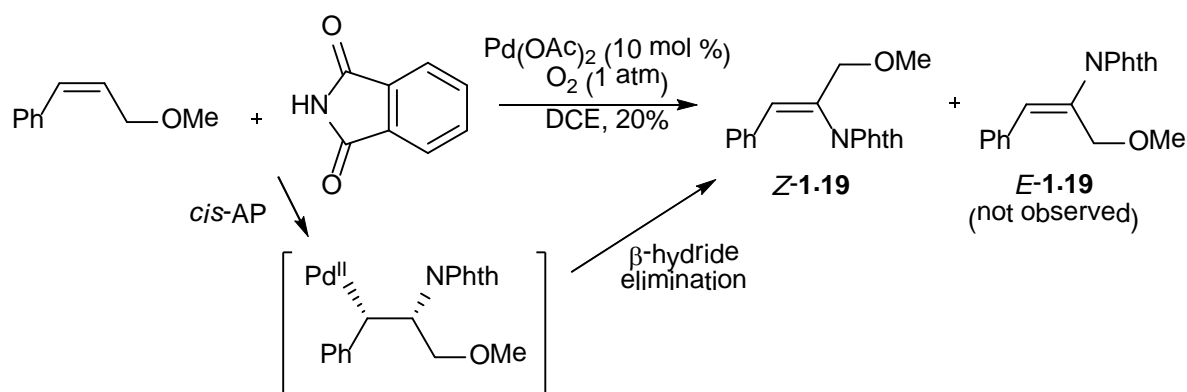


1.17

Figure 1.2

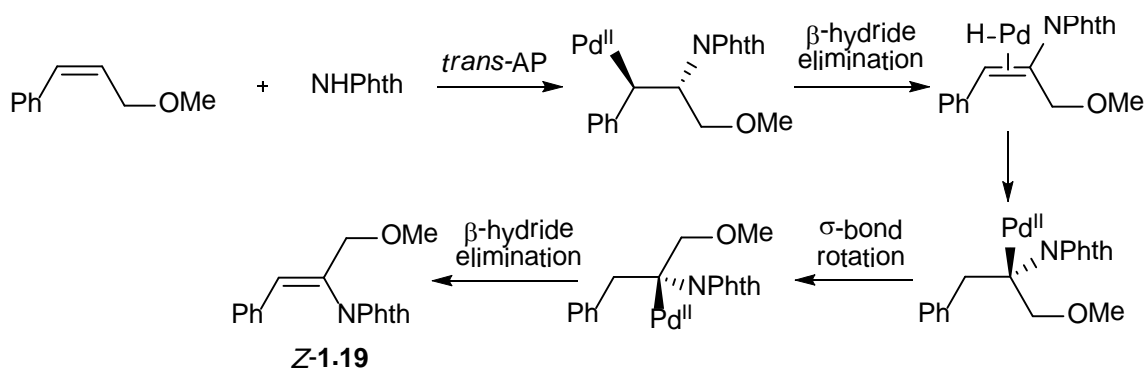
In the case of the Pd(OAc)₂/DMSO system Stahl suggested that the anionic acetate is a strong enough base to deprotonate the sulfonimide **1.16** and in the polar solvent DMSO, stabilisation of the anion does not require a metal centre. Essentially acetate deprotonates, DMSO stabilises the anion and palladium does not interact with the nitrogen at all, thus favouring *trans*-AP exclusively. This study by Stahl is perhaps the most important carried out in the field as it emphasises the fine balance between the nature of the catalyst, substrate identity and the influence of external additives, and how altering one factor can drastically change the stereochemical course of the reaction.

Stahl and co-workers also reported an intermolecular oxidative amination, reacting phthalimide, as the nucleophile, with a *Z*-alkene.¹⁶ A product *Z*-**1.19** that indicated a *cis*-AP pathway was obtained (Scheme 1.9).



Scheme 1.9

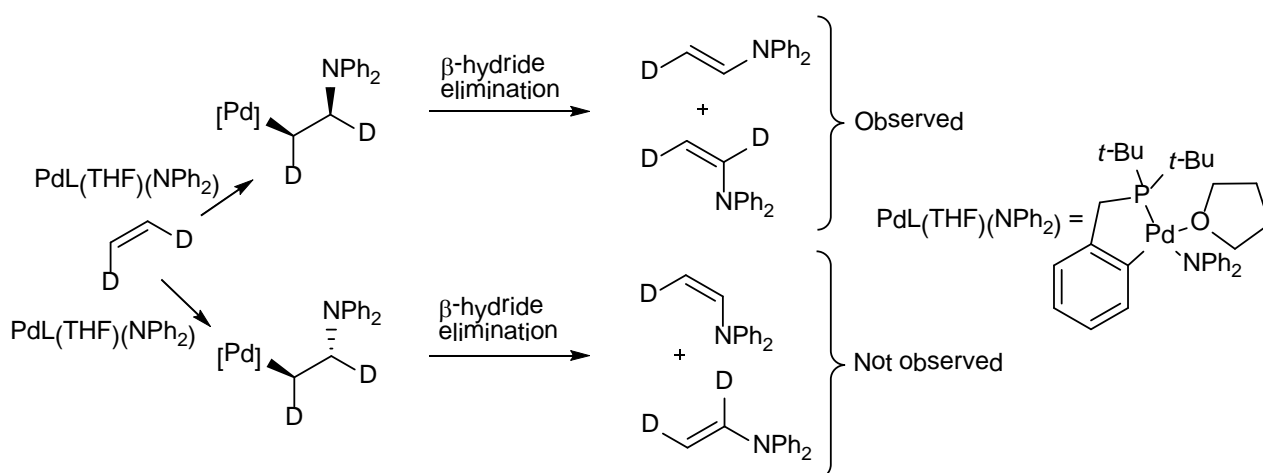
The product *E*-1.19 that would arise from a *trans*-AP was not observed. This is unexpected given that the previous findings suggest that more acidic nucleophiles favoured *trans*-AP.¹⁶ Stahl later hypothesised that in fact *trans*-AP could occur and *E*-1.19 is formed but reinsertion of Pd-H, followed by σ-bond rotation ultimately yields Z-1.19 (Scheme 1.10). This process would have to be thermodynamically more favourable.¹⁴



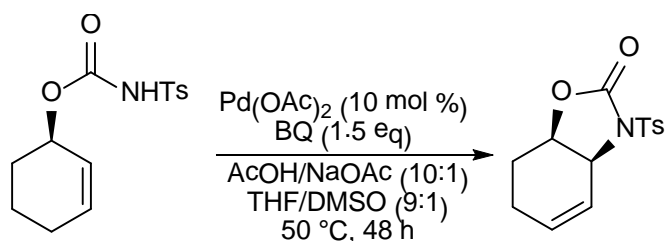
Scheme 1.10

Whilst this alternate hypothesis is viable, it could simply be that *cis*-AP is dominant due to the lack of a polar solvent. The stabilisation that a polar solvent, such as DMSO, would provide to the phthalimide anion would mean that coordination to Pd is not necessary. This would lead to a decrease in Pd-N species formed, and as a result lead to an increase in *trans*-AP.

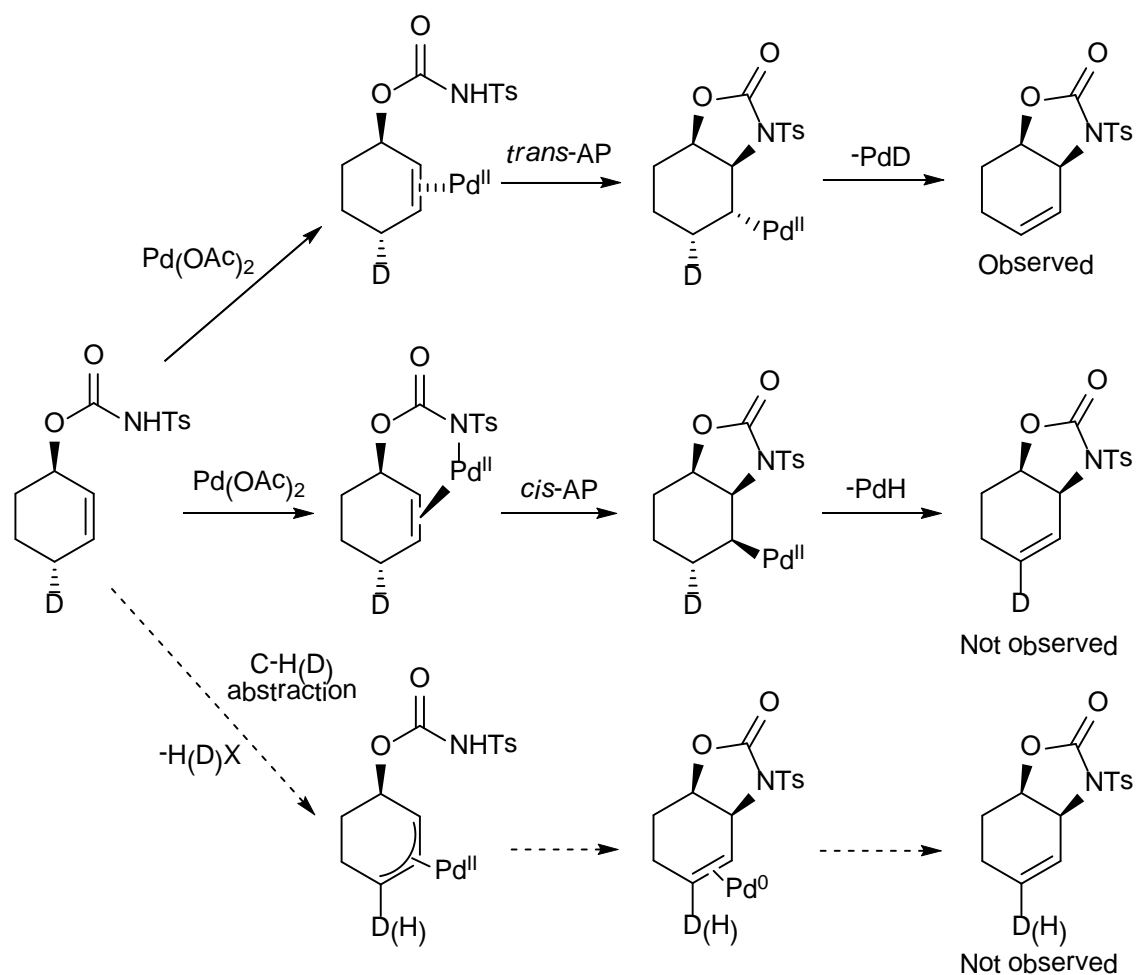
The Hartwig group published a report on intermolecular insertion of alkenes into a Pd-amide species.¹⁷ Using a variety of preformed Pd-N complexes exposed to ethylene or octene, an aminopalladation/ β -hydride elimination sequence took place. It was discovered that complexes with electron-rich amides reacted faster than those with electron-poor amides. Evidence for a *cis*-AP pathway was provided with deuterium studies on *Z*-ethylene-d₂ (Scheme 1.11), however it was only carried out for electron-rich amides, more electron-deficient amides could proceed via a different mechanism.



In 2012, Bäckvall reported a Pd^{II} catalysed oxidative cyclisation of allylic tosyl carbamates (Scheme 1.12).¹⁸



Bäckvall proposed that the reaction could proceed via 3 different pathways; *cis*- or *trans*-AP or a C-H activation pathway. Only the product arising from *trans*-AP was observed in the deuterium labelling studies carried out (Scheme 1.13).

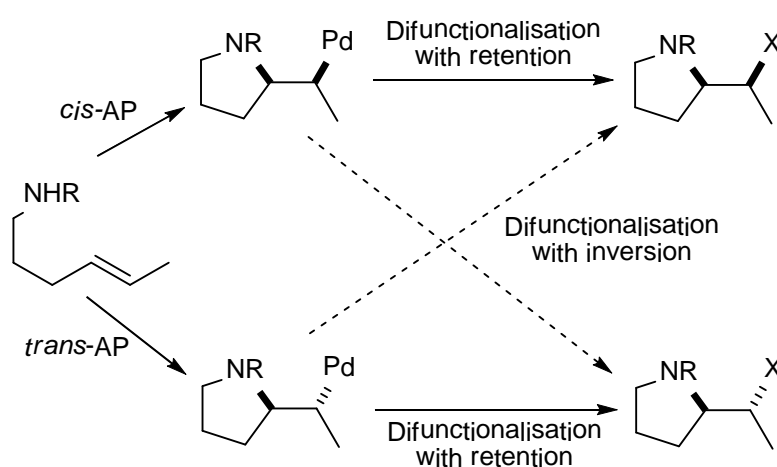


Scheme 1.13

This key observation provides support to the initial hypothesis by Stahl. *Trans*-AP is dominant when an acidic nucleophile, in this case a carbamate, is in the presence of anionic acetate and DMSO, allowing easy deprotonation of the nucleophile. Stabilisation of the resulting anion comes from the polar solvent and does not require coordination to a metal centre.

1.2.3. Aminoarylation

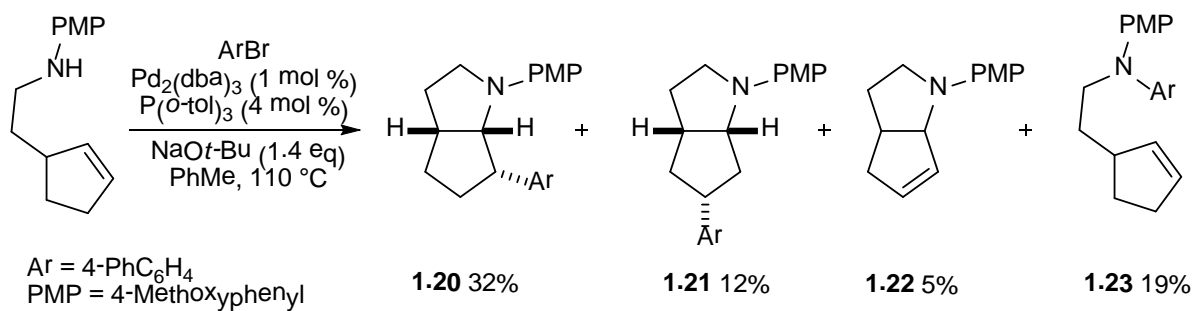
Alkene difunctionalisation is the sequence by which aminopalladation and C-X insertion are taking place to yield a di-substituted product. A range of different functional groups can be introduced depending on the reactants. However, with this comes a new problem in determining the stereochemical course of the aminopalladation step, as the Pd-alkyl species then can be further functionalised either with retention or inversion of stereochemistry with respects to the Pd-C bond (Scheme 1.14).



Scheme 1.14

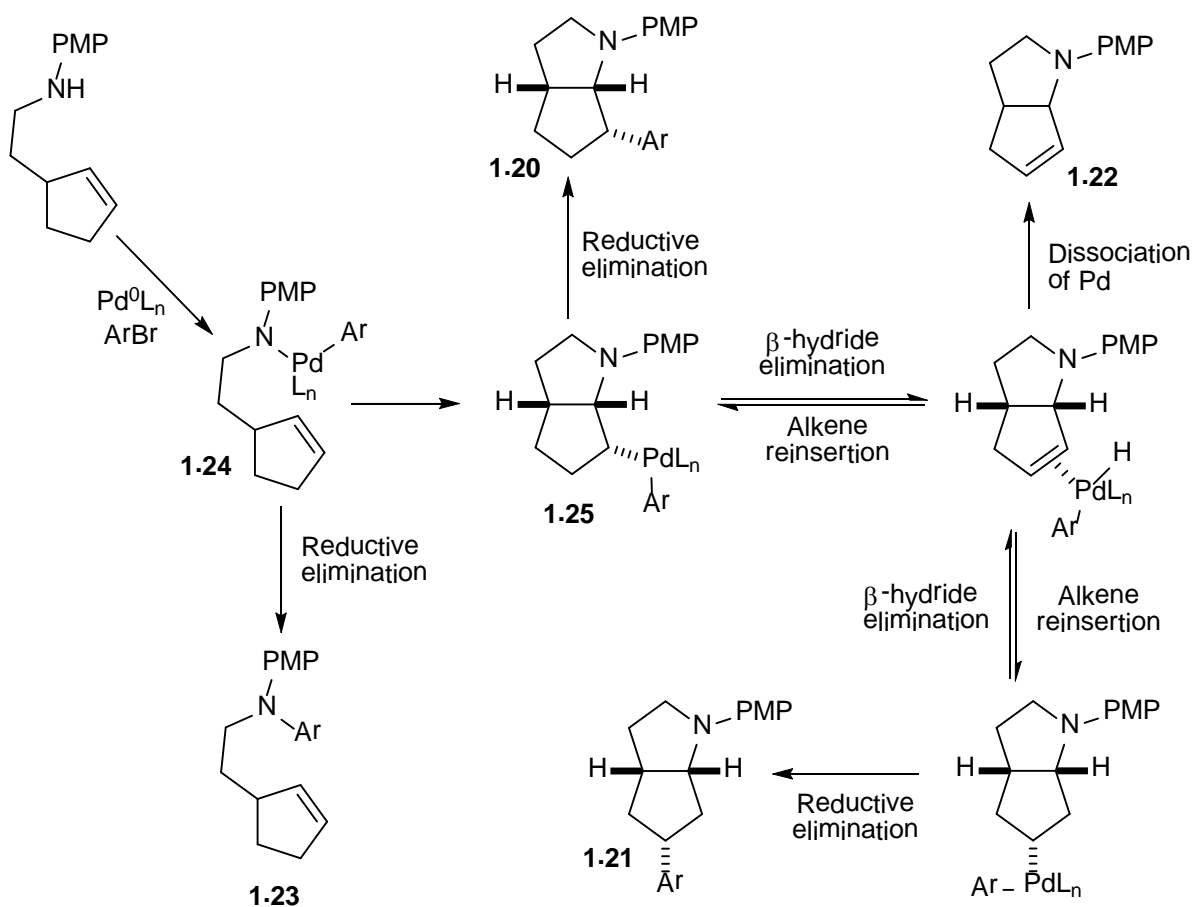
Perhaps the most documented of the amination/functionalisation reactions is aminoarylation, where a Pd-aryl species is formed by oxidative addition of an aryl halide to Pd⁰ followed by aminopalladation and C-C reductive elimination of the resultant alkyl-Pd-aryl species.

Wolfe and co-workers reported that pyrrolidines could be synthesised from γ -(*N*-arylamino)alkenes and aryl halides (Scheme 1.15).¹⁹ They observed that 4 different products were formed in the reaction and proposed a *cis*-AP mechanism that accounts for all 3 cyclised products **1.20-1.22** and, in part, for the observed *N*-Ar product **1.23** (Scheme 1.16). Oxidative addition of ArBr to Pd gives the ArPdBr species which forms a Pd-N bond to give **1.24**. This undergoes *cis*-AP to yield **1.25**, now two pathways arise; i) where C-C reductive elimination yields **1.20**, ii) where β -hydride elimination occurs to give **1.22**. **1.21** is formed by the reinsertion of Pd-H into the C-C double bond, followed by C-C reductive elimination.



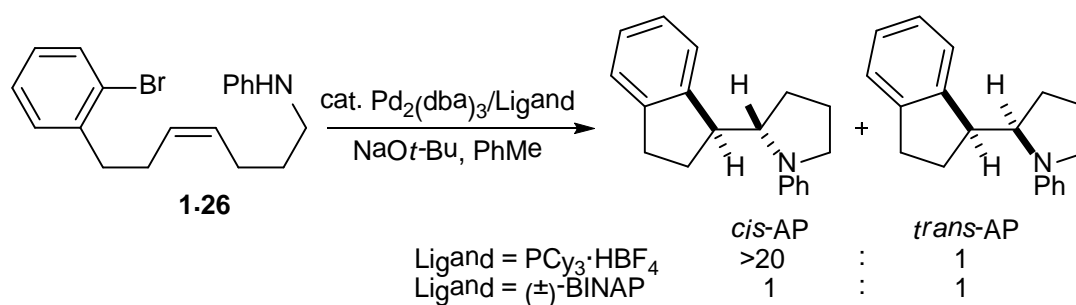
Scheme 1.15

The formation of **1.23** is what gives the most support to the claim of a *cis*-AP mechanism. The aryl group has undergone C-N reductive elimination to furnish this product, the only way this could occur is if an Ar-Pd-N species **1.24** existed before the aminopalladation step took place. A *trans*-AP mechanism would most likely not see this compound being formed.



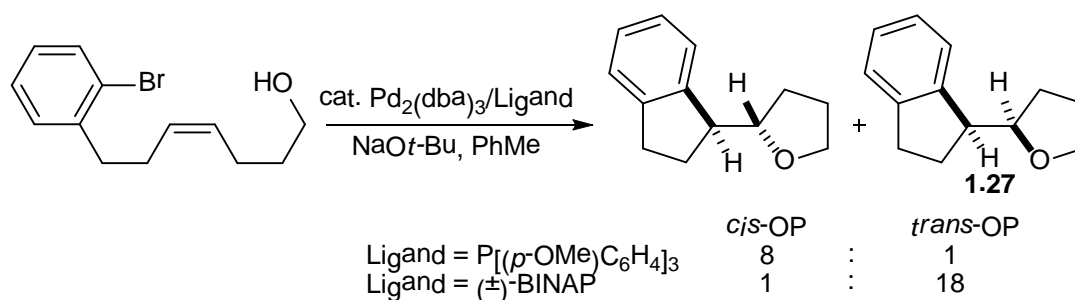
Scheme 1.16

Wolfe and co-workers obtained additional evidence to support the theory that aminoarylation proceeds via *cis*-AP when they studied the intramolecular bicyclisation of a tethered aryl bromide and amine across a *Z*-alkene **1.26** (Scheme 1.17).²⁰



Scheme 1.17

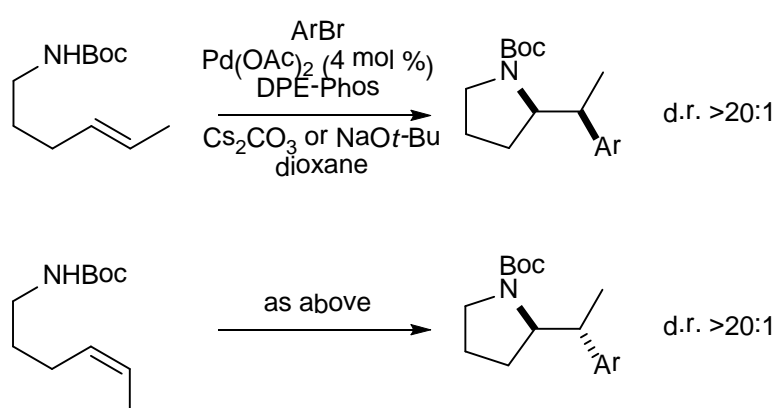
Using PCy₃·HBF₄ as the ligand, almost entirely *cis*-AP was observed, however changing the ligand to (±)-BINAP gave a 1:1 mixture of *cis*- and *trans*-AP products. The authors suggest that in the case of (±)-BINAP, the amine is more readily deprotonated and less likely to coordinate to Pd. It is possible that this bulky bidentate ligand may not allow room for Pd-N formation. In an analogous reaction using alcohol as the nucleophile (±)-BINAP gives a majority of *trans*-OP product **1.27** (Scheme 1.18).



Scheme 1.18

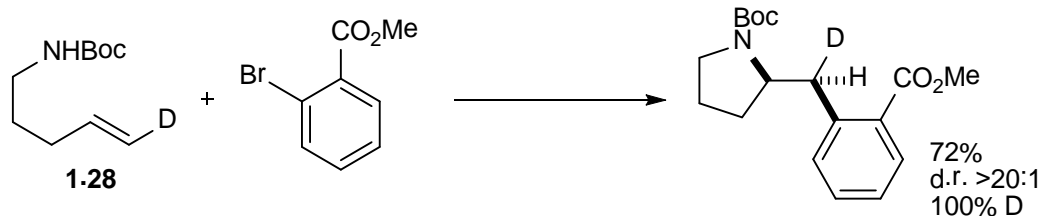
The fact that this more acidic oxygen favours *trans*-AP compared to the less acidic nitrogen supports the theory, proposed by Stahl, that the acidity of the nucleophile can alter the predominant aminopalladation pathway when using a set catalyst system.¹⁵

Further studies into aminoarylation and the effects played by different external bases in the AP step were carried out by Wolfe.²¹ *N*-Boc amines were cyclised to yield pyrrolidines with high diastereoselectivity, which is indicative of a preference for one AP pathway (Scheme 1.19).



Scheme 1.19

Regardless of the base that was used the stereochemical outcome in both cases suggest a *cis*-AP. This was also confirmed using a deuterated alkene **1.28**, which gave a single diastereoisomer, resulting from *cis*-AP (Scheme 1.20).



Scheme 1.20

It is possible that Pd can form a complex **1.29** with the amine and the adjoining Boc group, this stabilised intermediate is formed after N-H deprotonation facilitated by the base (Figure 1.3).

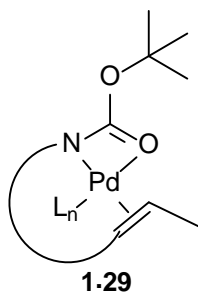
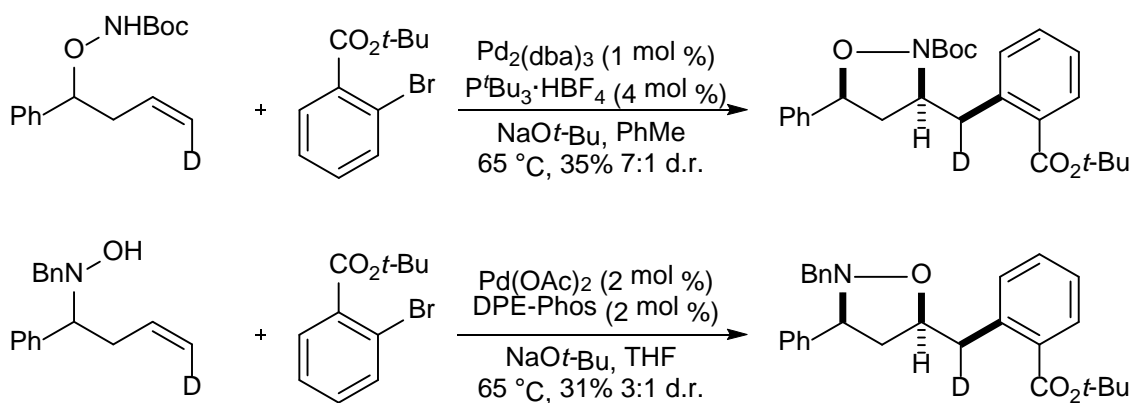
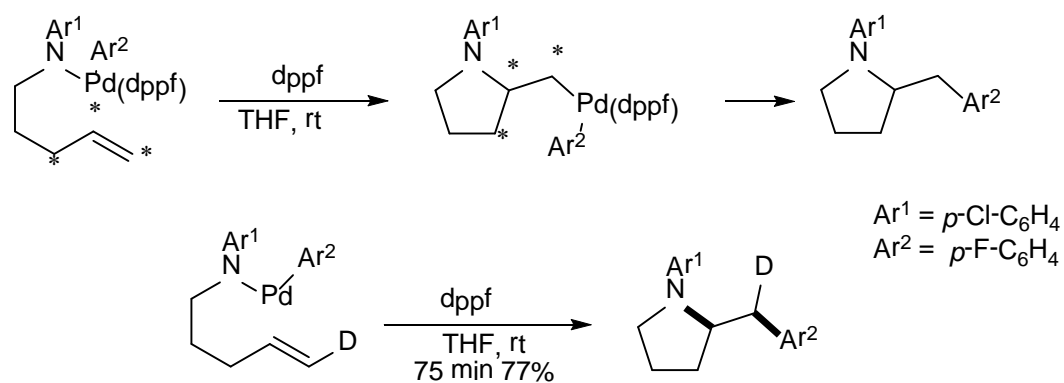


Figure 1.3

Wolfe and co-workers investigated intramolecular aminoarylation, in the synthesis of isoxazolidines²² and pyrrolidines.²³ Deuterium and ¹³C labelling was used to prove the mode of aminopalladation. Once again a *cis*-AP pathway was shown to be dominant (Scheme 1.21²² and 1.22²³).

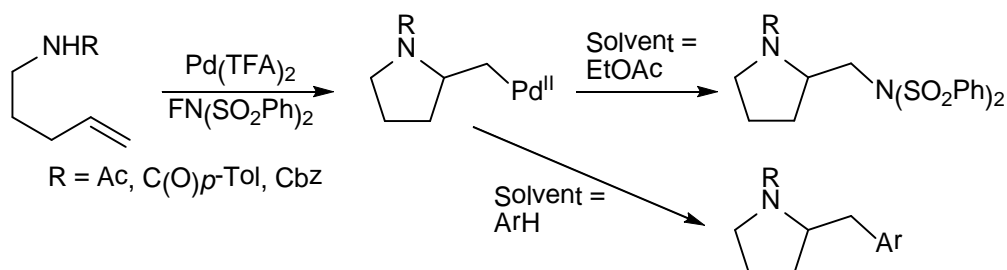


Scheme 1.21



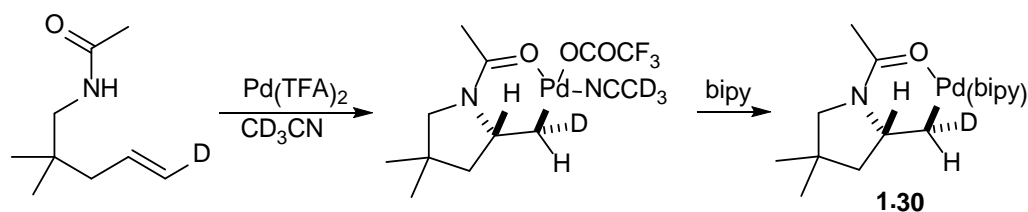
Scheme 1.22

Michael and co-workers reported intramolecular aminoarylation and diamination reactions promoted by *N*-fluorobenzenesulfonamide (Scheme 1.23).²⁴



Scheme 1.23

The stereochemical pathway was studied²⁵ by trapping the Pd-alkyl intermediate with bipyridine **1.30** (Scheme 1.24). The isolated structure suggests that the mechanism proceeds via a *trans*-AP. The authors justify this preference by the type of nucleophile used, stating that the acidic conditions along with an N-H bond that is difficult to deprotonate promote *trans*-AP. However as previously mentioned more acidic nucleophiles, such as phthalimide and sulfonamide, prefer to undergo *trans*-AP and as acetamide is less acidic in comparison, it would be expected that *cis*-AP would be favourable in this case. This observation once again highlights the importance of the balance between nitrogen acidity and pH of the reaction mixture.



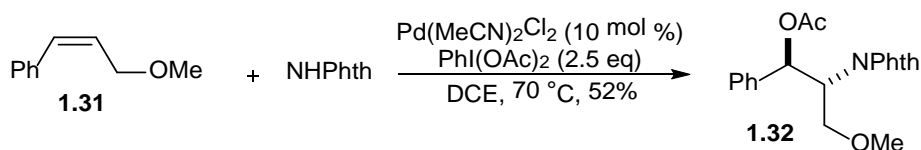
Scheme 1.24

This observation has proved to be somewhat contradictory to the findings of other research groups and needs to be investigated further to determine the factors causing this preference for *trans*-AP. A mechanism was proposed, whereby the Pd^{II}-alkyl intermediate formed by *trans*-AP can undergo oxidation by FN(SO₂Ph)₂ to form a Pd^{IV} intermediate, Pd^{IV} may then be substituted by Ar or N(SO₂Ph)₂ in an S_N2 like fashion, yielding a product whose stereochemistry would indicate a *cis*-AP pathway.

Whilst aminoarylation is a well documented procedure, the stereochemical course of aminopalladation in these reactions is less so. The work by Wolfe has outlined that whilst *cis*-AP seems to be dominant, it is not exclusive. These studies have also provided support to the mechanistic hypothesis by Stahl that were discussed earlier.

1.2.4. Intermolecular Alkene Difunctionalisation

This area has been a subject of much interest, however the mechanistic aspects have mostly been focused on intramolecular aminoarylation. However, following on from the previously discussed intramolecular variant, Lui and Stahl reported an intermolecular aminoacetoxylation of an alkene **1.31** with phthalimide (Scheme 1.25).¹⁶

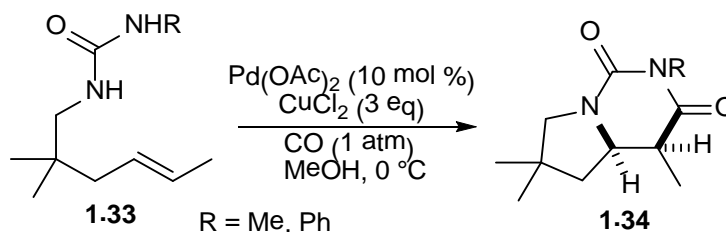


Scheme 1.25

The difunctionalised product **1.32** was obtained in an *anti*-configuration, however the authors proposed that the mechanism goes via *cis*-AP. The Pd^{II}-alkyl intermediate can be oxidised to a Pd^{IV} intermediate by PhI(OAc)₂. The Pd^{IV} may then be substituted in an S_N2 type substitution that would furnish the observed *anti*-configuration in **1.32**.

1.2.5. Aminocarbonylation

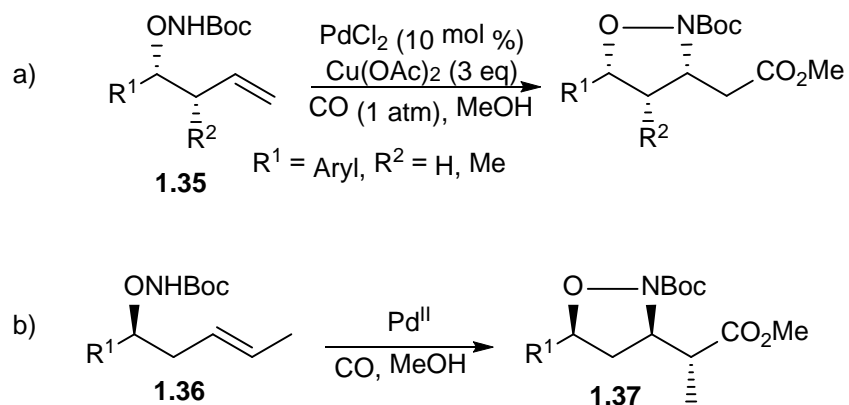
In 1988, Tamaru and co-workers reported that alkylamines, in the presence of Pd^{II} and CO could undergo catalytic intramolecular aminocarbonylation.²⁶ In this case AP takes place, then CO inserts into the Pd-C bond of the Pd-alkyl intermediate. Reductive elimination with MeOH furnishes an ester. In the case of ureas **1.33**, C-N reductive elimination can also occur yielding a cyclic amide **1.34** (Scheme 1.26).



Scheme 1.26

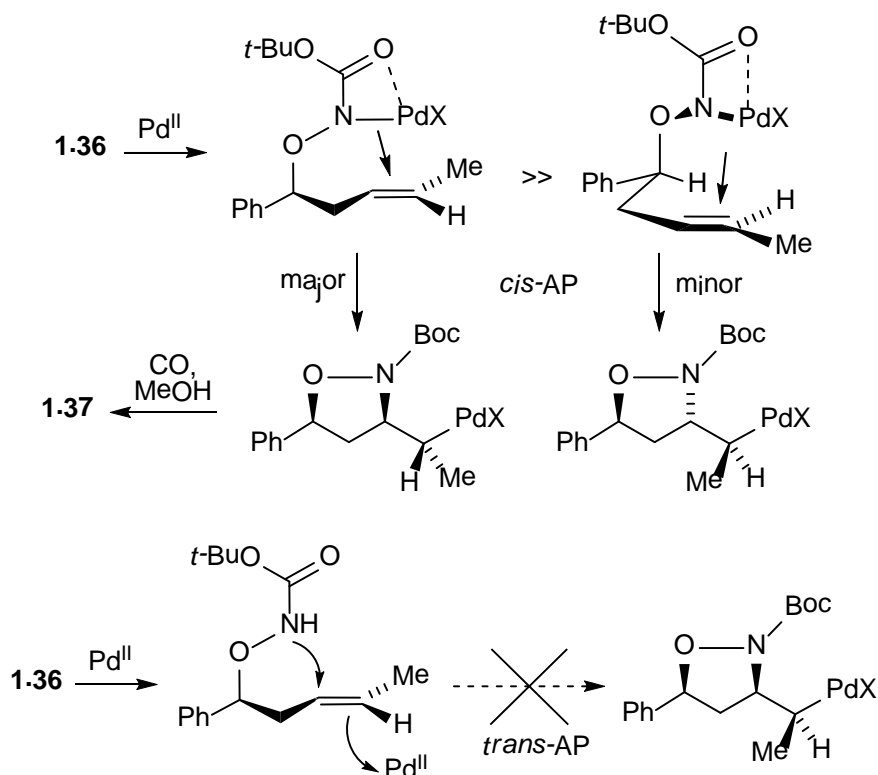
It is documented that carbonylation of a Pd-C bond usually results in retention of configuration,²⁷ therefore the stereochemistry observed in this instance is evident of *trans*-AP taking place.

Recently Malkov *et al.* reported on a stereoselective Pd^{II} catalysed aminocarbonylation of *N*-Boc alkoxyamines **1.35**, **1.36** (Scheme 1.27a).²⁸



Scheme 1.27

In order to gain an insight into the mechanistic pathways occurring in these reactions a substrate with an internal double bond was employed, which upon aminocarbonylation would, through stereochemistry of the product, cast light on the pathway involved (Scheme 1.27b). Analysis of the product by X-ray crystallography indicated formation of *syn*, *anti*-isoxazolidine **1.37**. To rationalise the observed stereochemistry, it was suggested that the carbamate group would coordinate the Pd^{II} catalyst, followed by *syn*-addition across the alkene (Scheme 1.28).



Scheme 1.28

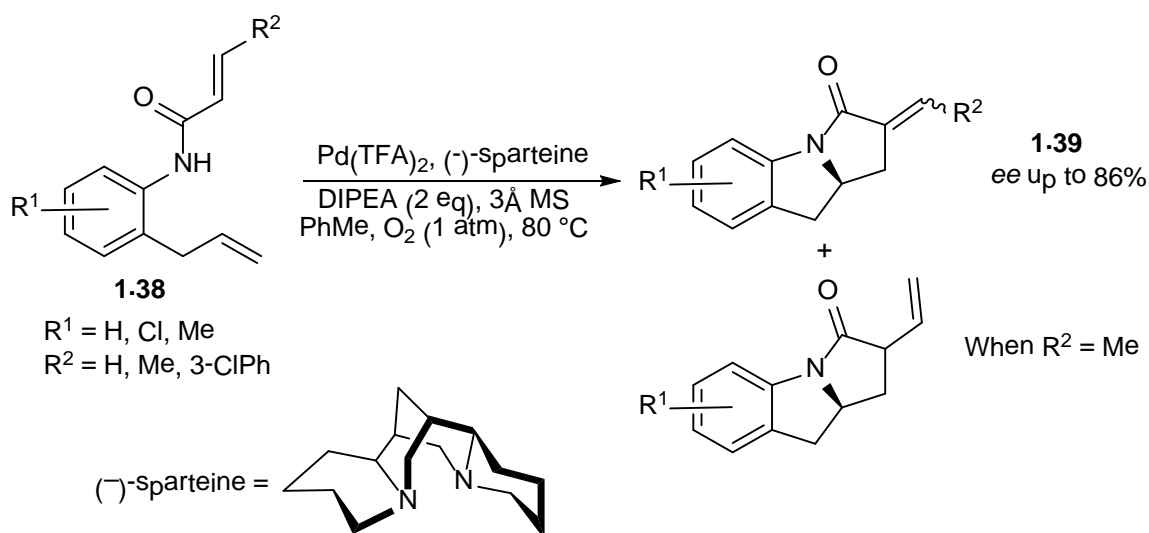
The Pd-alkyl species can attack either face of the alkene, where formation of the *syn*-isomer takes preference over the *anti*-isomer, due to the increased allylic strain in the latter. The product that would arise from *trans*-AP is not observed, therefore this manifold can be ruled out.

These studies into the aminopalladation step have provided a basis of understanding as to why one pathway may be dominant over another. The acidity and coordination ability of the nucleophile, along with the types of additives, play the most important roles in determining which pathway prevails.

1.2.6. Enantioselective Intramolecular Amination

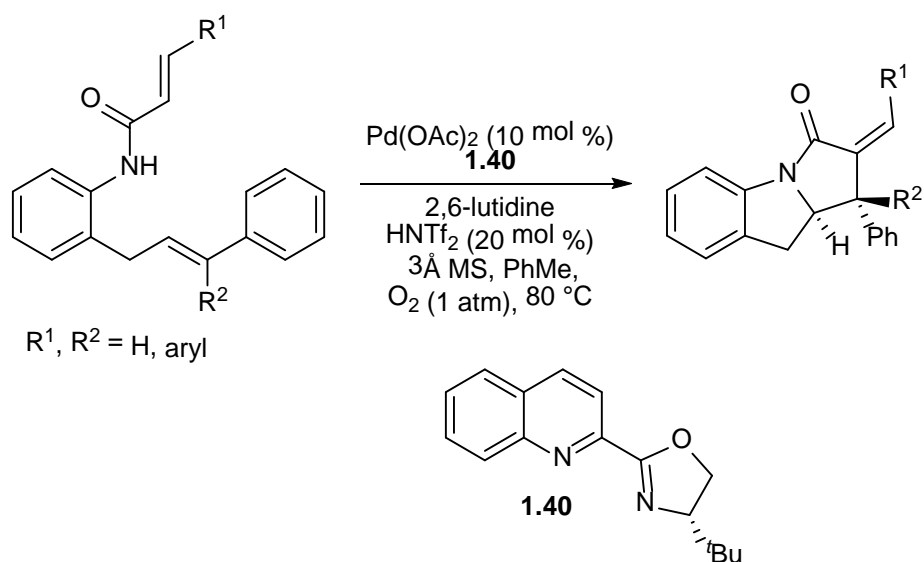
Whilst intramolecular amination reactions are quite well documented, enantioselective variants have not been explored to the same extent. The ambiguity of the AP step and the lack of known ligands for this type of transformation are the barriers that hold back progress in this area. However, some research groups have shown that these reactions can indeed be achieved with simple ligands and under mild conditions.

Yang and co-workers reported that in the presence of Pd(TFA)₂ and (–)-sparteine, amines **1.38** undergo carboamination to yield tricyclic products **1.39** (Scheme 1.29).²⁹



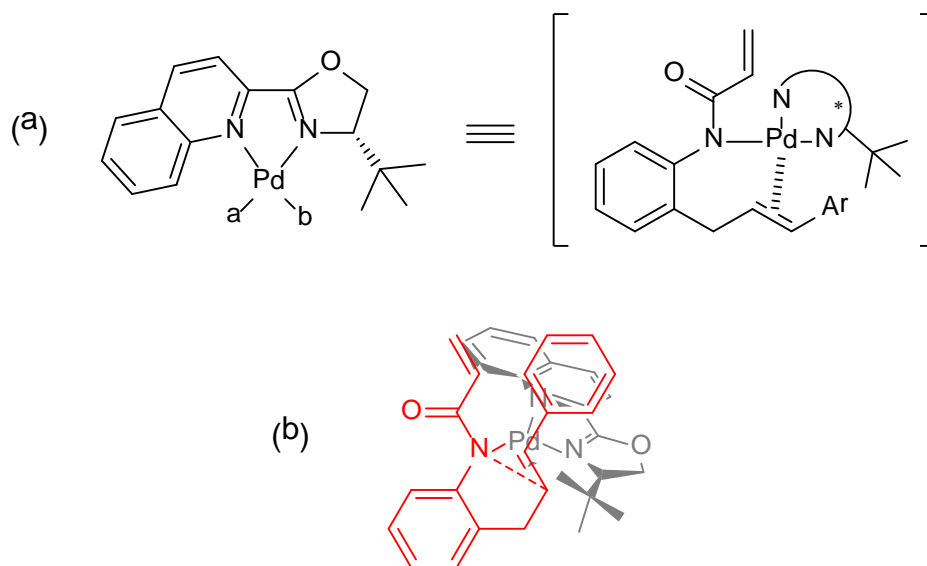
Scheme 1.29

As only one enantiomer of sparteine exists in nature, the researchers sought more efficient ligands that could be synthesised in both enantiomeric forms. In 2009, a similar carboamination reaction was reported, employing a chiral quinolineoxazoline **1.40** (Scheme 1.30).³⁰ Formation of a single diastereoisomer by a *cis*-AP route was observed. The stereochemistry was explained by suggesting a transition state model, in which the ligand coordinates to Pd in a bidentate model. The other two vacant sites are filled with the alkene and nitrogen. The authors state that for the observed stereochemistry, the N atom of the acrylamide and the alkene occupy site a and b respectively (Scheme 1.31a).



Scheme 1.30

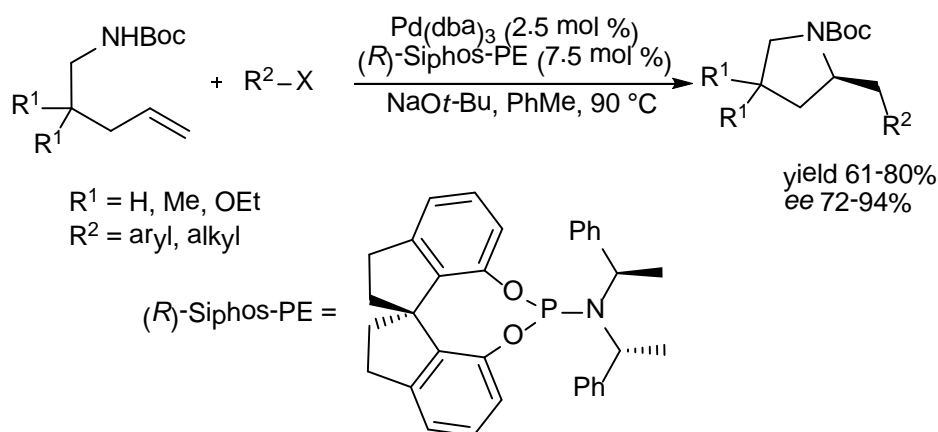
The *si*-face cyclisation shown in Scheme 1.31b is the mostly likely path leading to the observed stereochemistry, as others are hindered by steric repulsion of bulky groups in close proximity.



Scheme 1.31

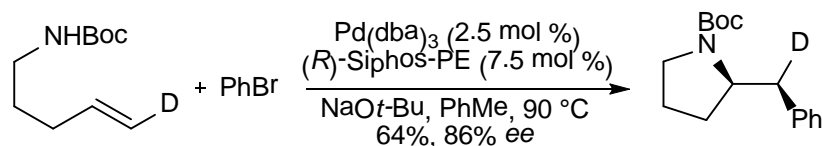
The *cis*-AP pathway plays an important role in forming a sterically congested reactive intermediate, whereas the chiral ligand determines the enantiofacial selectivity of the reaction, thus both contributing the stereochemical outcome of the newly formed bonds.

Mai and Wolfe reported a synthesis of enantioenriched pyrrolidines via an aminoarylation from *N*-Boc alkenylamines and aryl halides.³¹ The chiral monodentate ligand (*R*)-Siphos-PE was found to provide moderate to excellent enantioselectivity in this reaction (Scheme 1.32).



Scheme 1.32

Based upon their previous studies into aminoarylation²¹ they expected a *cis*-AP pathway, which was confirmed by deuterium labelling studies (Scheme 1.33).



Scheme 1.33

It was noticed that altering the Pd:ligand ratio to 1:1 and 1:2 had no effect on enantioselectivity, which suggested the formation of a monoligated Pd complex. Whilst the intermediate structure in the reaction is not totally clear, it is evident that monodentate

ligands take precedence over chelating ones in this instance. With bis-phosphine ligands a decline in enantioselectivity was observed, which was credited to the loss of “one arm” of the chelate upon coordination to substrate (Figure 1.4).

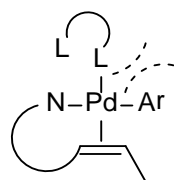
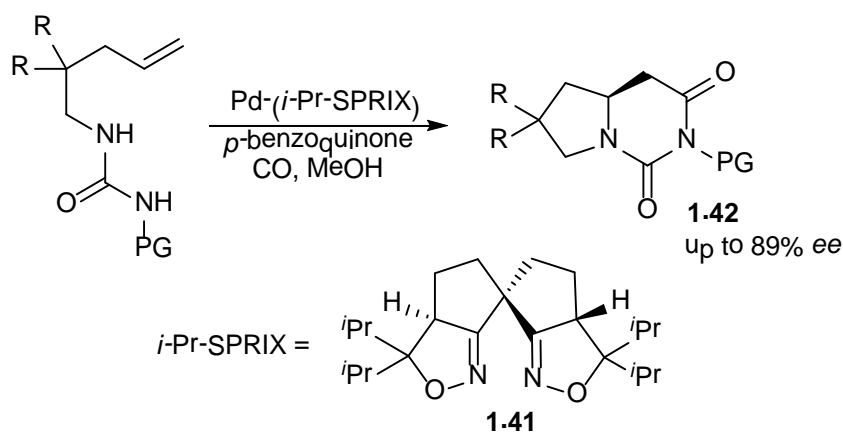


Figure 1.4

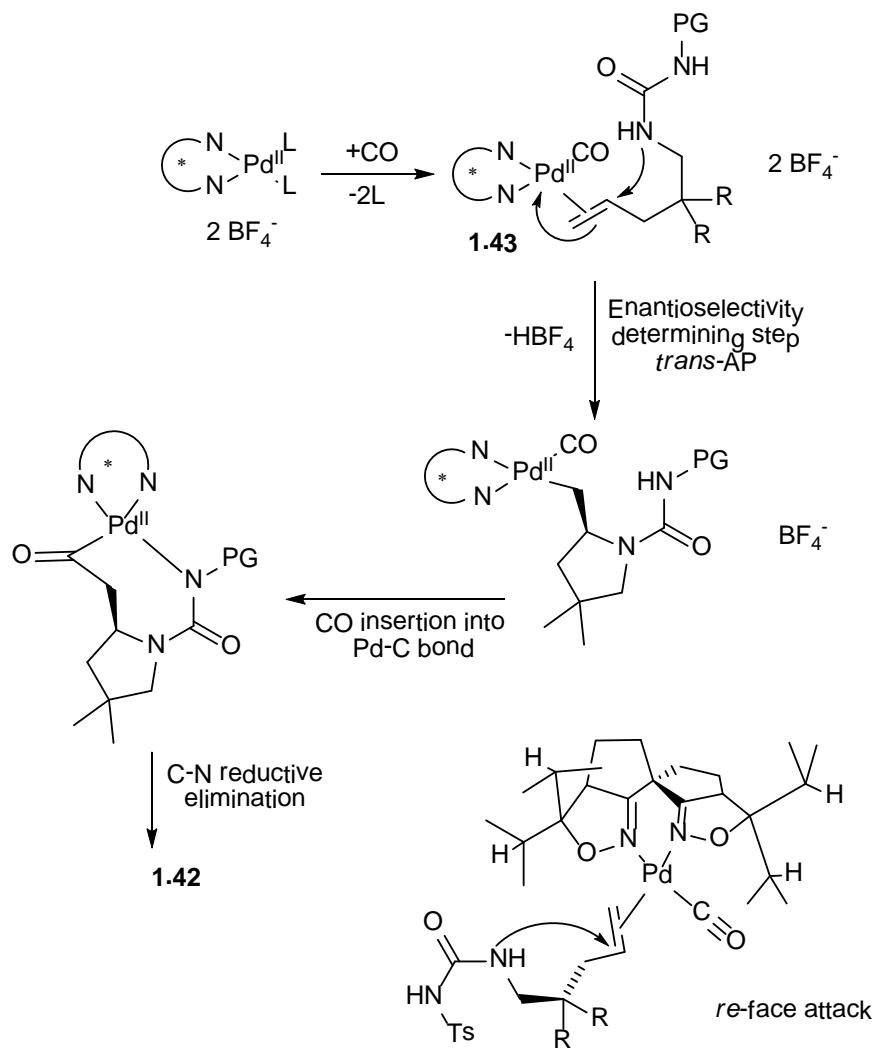
Sasai and colleagues reported an enantioselective amination/carbonylation using a chiral spiro bis(isoxazoline) ligand **1.41** (Scheme 1.34).³² The reactions yielded bicyclic products **1.42** in practical *ee*'s (up to 89%).



Scheme 1.34

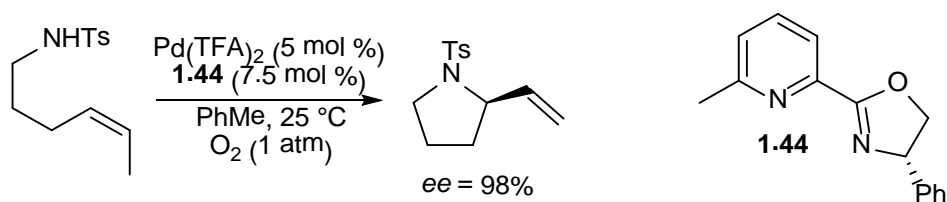
The reaction was thought to proceed via *trans*-AP, enforced by the steric bulk of the *i*-Pr groups of ligands that led to a *re*-facial attack (Scheme 1.35). In this case it appears that the chelated Pd complex **1.43** with CO takes preference over forming a Pd-N species. Interestingly this shows that *cis*-AP is not exclusive for enantioselective reactions, and that

both pathways are still viable. In this case *trans*-AP is favoured due to the steric bulk of the ligand.



Scheme 1.35

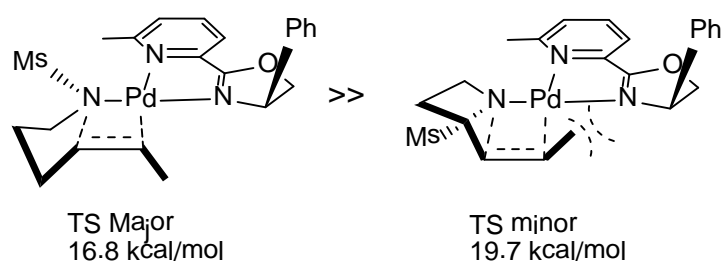
In 2011, Stahl reported a mild enantioselective oxidative amidation of alkenes, employing a Pd(TFA)₂/pyrox catalyst system (Scheme 1.36).³³



Scheme 1.36

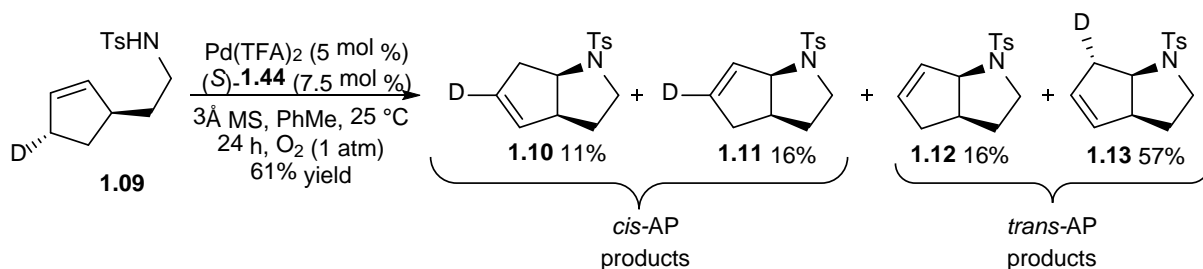
It was observed that when using Pd(OAc)₂ as the Pd^{II} source the *ee* observed was severely diminished, for reasons not fully understood at this stage. Based on earlier results with the Pd(OAc)₂/py, Pd(TFA)₂/py and Pd(TFA)₂/(-)-sparteine catalyst systems,¹⁵ the reaction was expected to proceed via a *cis*-AP mechanism. Transition state energies were calculated under the assumption of the *cis*-AP pathway being dominant (Scheme 1.37). However, further investigation was required to unravel the mechanistic pathways of this reaction.

A year later, Weinstein and Stahl attempted to establish a direct correlation between the stereochemistry of nucleopalladation and enantioselectivity of the reaction.³⁴



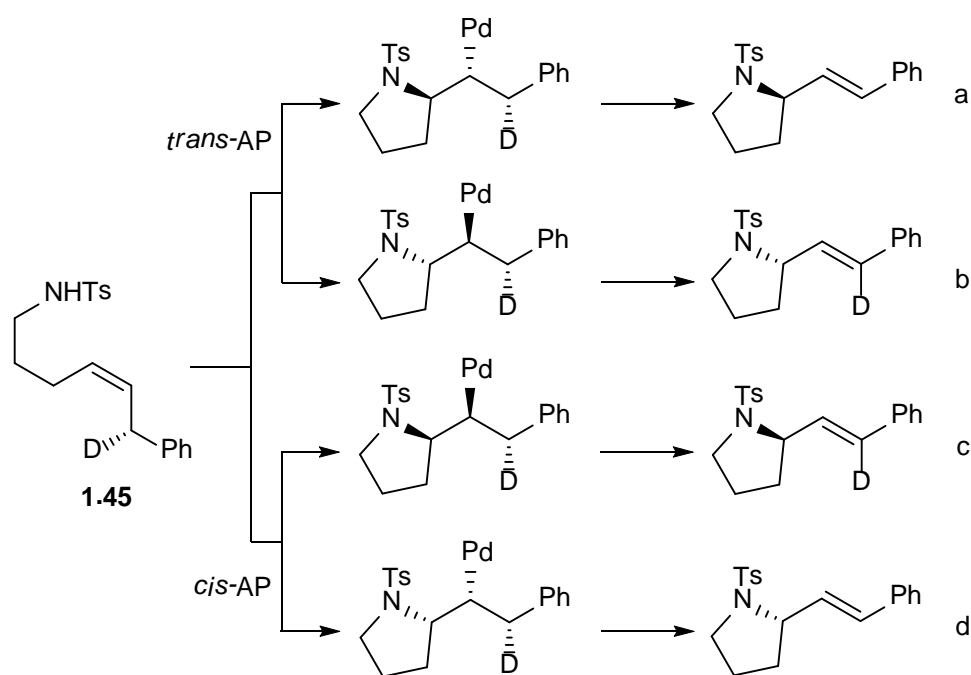
Scheme 1.37

They used the previously mentioned deuterated substrate **1.09** (See Scheme 1.8) to probe the avenue of AP. Under the new reaction conditions with the pyrox ligand, an unexpected mixture of products **1.10-1.13** were observed, where the *trans*-AP pathway was dominant, however a significant amount of *cis*-AP products were also isolated (Scheme 1.38).



Scheme 1.38

The 3:1 ratio of *trans*/*cis*-AP products was surprising as a *cis*-AP mechanism was expected to be the main pathway, if not exclusive. To imitate the conditions that gave the high enantioselectivity, they used an acyclic substrate **1.45** that would resemble the substrates used in the original reaction (Scheme 1.39). When **1.45** was submitted to the enantioselective amination conditions, *trans*-AP was again found to be favoured, this time 91:9, and the yield and *ee* were consistent with that previously observed, 90% and 96% respectively (Table 1.5, entry 1). It was noted that the difference in the enantioselectivities of the two substrates could be attributed directly to the AP step. In the cyclic example, *trans*-AP:*cis*-AP is 3:1 and the *ee* is poor, where as in the acyclic substrate *trans*-AP:*cis*-AP is 9:1 and the *ee* is excellent. This proved that the ambiguity of the AP step is the biggest drawback in developing this type of reaction.



Scheme 1.39

Table 1.5

	Pd ^{II}	Ligand	Yield (%)	<i>ee</i> (%)	Ratio of products ^a
					<i>trans</i> -AP(a+b): <i>cis</i> -AP(c+d)
1	Pd(TFA) ₂	(<i>S</i>)- 144	90	96	91:9 (91+0):(7+2)
2	Pd(OAc) ₂	(<i>S</i>)- 144	48	20	10:90 (9+1):(51+39)
3	Pd(TFA) ₂	none	55	0	1:6
4	Pd(OAc) ₂	none	15	0	<1:9

(a) Products outlined in Scheme 1.39.

When the Pd^{II} source was changed to Pd(OAc)₂, which in their original paper gave poor enantioselectivity, *cis*-AP was the main pathway in a ratio of 9:1 (Table 1.5, entry 2). The breakdown of products shows that the *trans*-AP still maintains high enantioselectivity (9:1), where as the *cis*-AP products are more even mixture (51:39). The main conclusion drawn from this observation is that *trans*-AP is required for any significant enantioselectivity to occur, at least for this catalyst, ligand and substrate combination. When the ligand was removed from the system, rather unexpectedly both Pd^{II} sources exhibited preference for *cis*-

AP (Table 1.5, entries 3-4). This means that the ligand plays a crucial role in enforcing the *trans*-AP pathway with Pd(TFA)₂ as the Pd^{II} source. However this is contrary to the previous hypothesis where anionic carboxylate ligands acting as a weak base would mediate *cis*-AP, instead it appears that the combination of anionic trifluoroacetate and neutral-donor pyrox ligands results in *trans*-AP. The substitution of TFA by the substrate alkene is more favoured than Pd-N formation (Figure 1.5).

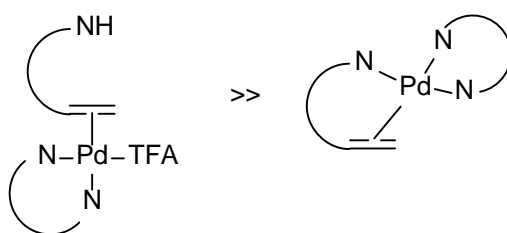


Figure 1.5

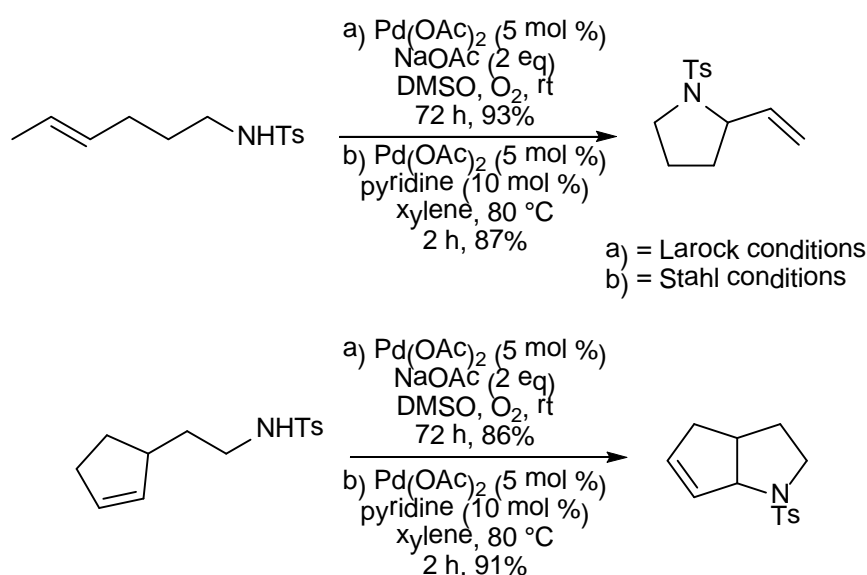
It is clear from these studies that both aminopalladation pathways can give good stereoselectivity, however to obtain a high *ee* a single pathway must be dominant. It has been shown that in some cases *cis*-AP gives little or no stereoselectivity and *trans*-AP is required for the high *ee* observed, however this *trans*-AP is only obtained by the presence of the chiral ligand. Without the ligand, *cis*-AP is dominant again. This area has a lot left to be explored but the difficulty in predicting and controlling the AP pathways, coupled with only a small library of ligands available make this a difficult subject to approach. The studies carried out by Stahl have laid the groundwork for understanding the factors dictating the aminopalladation pathway.

1.3. Synthetic Examples of Intramolecular Amination

There has been little, albeit important, exploration into the mechanistic aspects of this field; however the reactions in this area are diverse and well documented. There have been many examples of intramolecular amination reactions furnishing a range of heterocycles.

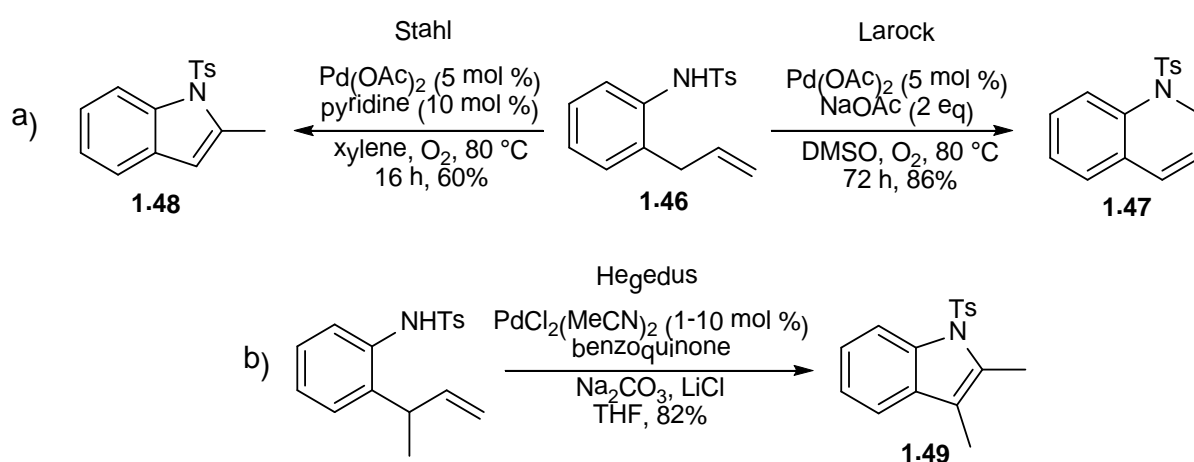
1.3.1. Synthesis of Pyrrolidines and Related Derivatives

Several groups have reported the synthesis of functionalised pyrrolidines from the cyclisation of simple cyclic and acyclic aminoalkenes (Scheme 1.40). Larock³⁵ used a Pd(OAc)₂/DMSO system in the presence of O₂ over 72 h, however, Stahl³⁶ reported that the same transformations could be furnished in just 2 h with Pd(OAc)₂/pyridine in an atmosphere of O₂. Stahl's mechanistic studies revealed that the reoxidation of Pd by O₂ was the limiting factor in the Pd/DMSO system.³⁷ He reported that pyridine and other imine donor ligands could improve efficiency compared to neat DMSO and are required for direct oxidation of Pd by O₂.³⁸



Scheme 1.40

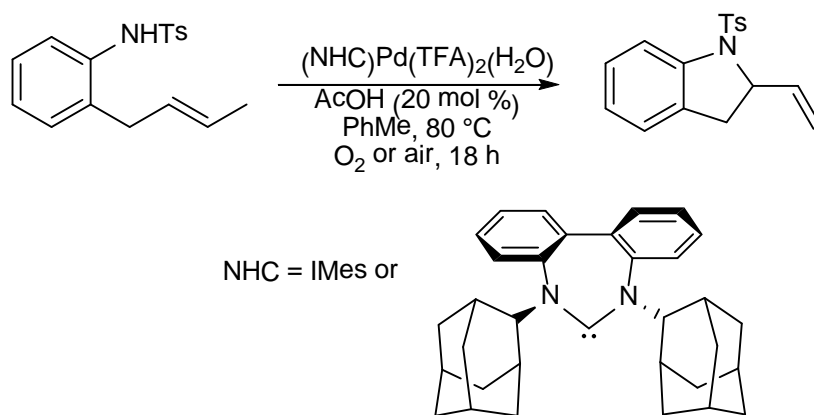
Various aryl amines with tethered alkenes were cyclised giving indoles, with little difference in reactivity between the two catalyst systems. Interestingly the use of an aryl amine containing a tethered terminal alkene **1.46** seems to prefer forming a six-membered ring **1.47** under Larock's conditions (Scheme 1.41a). Stahl reported that the same substrate cyclised to yield 2-methylindole **1.48**. It would appear that the product observed by Larock could arise from π -allyl complex formation rather than aminopalladation. Larock's findings contrast, whereas Stahl's work compliment the results by Hegedus, where indoles **1.49** were formed exclusively when catalytic $\text{PdCl}_2(\text{MeCN})_2$ was used (Scheme 1.41b).³⁹



Scheme 1.41

Indoles **1.48** and **1.49** most likely arise from the re-insertion of Pd-H followed by another β -hydride elimination.

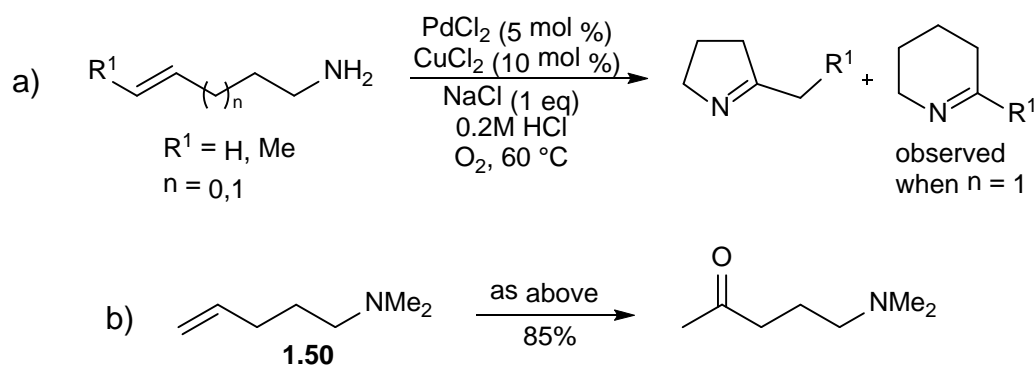
Later, Stahl and co-workers reported that pyrrolidines can be synthesised using a $\text{Pd}(\text{TFA})_2/\text{NHC}$ catalyst system under an atmosphere of O_2 or air (Scheme 1.42).⁴⁰



Scheme 1.42

Various substituted amines were cyclised giving pyrrolidines in excellent yields. Terminal alkenes gave aminopalladation products similar to **1.48** and **1.49**. The addition of a carboxylic acid additive increases the stability of the catalyst and enables the use of air as the source of O_2 .

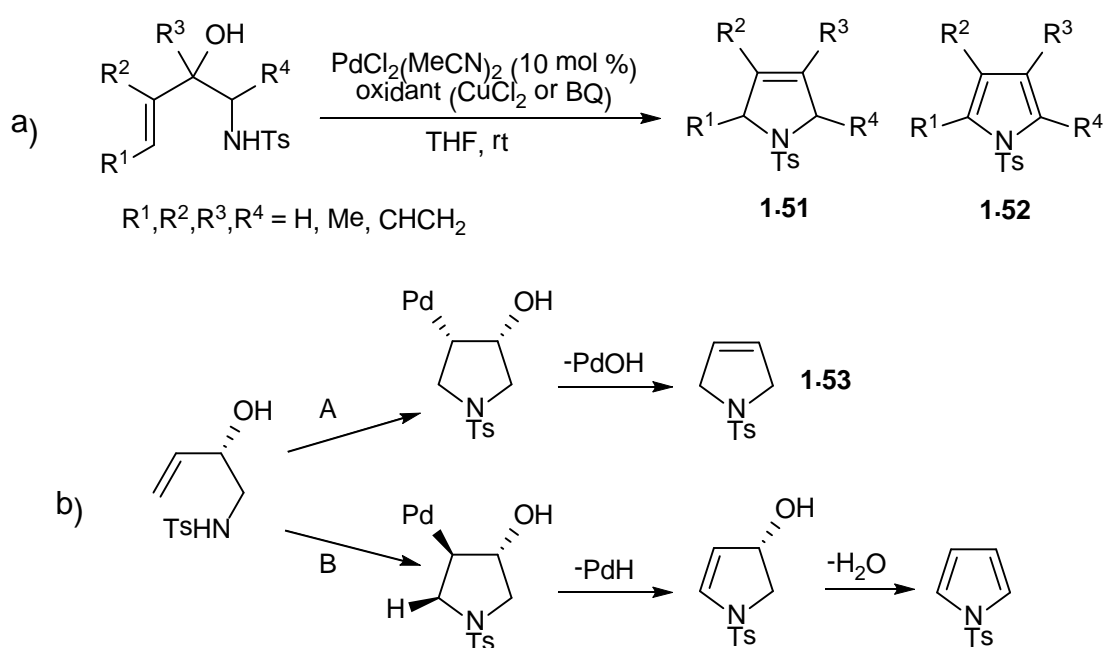
Pugin and Venanzi reported that aminoalkenes and their salts underwent intramolecular cyclisations when subjected to conditions similar to those in the original Wacker reaction, with catalytic PdCl_2 and a CuCl_2/O_2 reoxidation system.⁴¹ 1-Pyrroline products most likely arose from an aminopalladation pathway followed by β -hydride elimination, alkene reinsertion and another β -hydride elimination to yield the presumably more stable cyclic imine products over forming vinylpyrrolidines (Scheme 1.43a).



Scheme 1.43

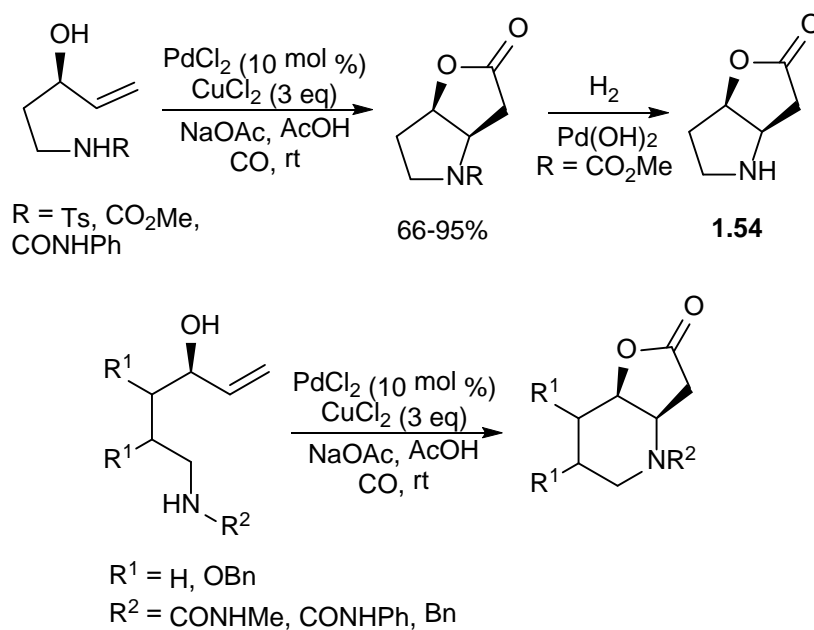
When tertiary nitrogen nucleophile **1.50** was used, no cyclisation took place and aminoketones were isolated instead (Scheme 1.43b). The tertiary nitrogen will neither form a Pd-N species for *cis*-AP or act as a nucleophile for *trans*-AP, the traditional Wacker oxidation observed is hardly surprising.

Tamaru and co-workers⁴² demonstrated that pyrrolines **1.51** and pyrroles **1.52** can be synthesised from homoallylic amines, by the means of two different aminopalladation pathways operating in tandem (Scheme 1.44a). If aminopalladation forms the new Pd-C bond *syn* to the alcohol group then Pd-hydroxide elimination leads to the formation of pyrrolines **1.53** (Scheme 1.44b, pathway A). However pyrroles are formed when aminopalladation leaves the new Pd-C bond *anti* with respects to the position of the OH group, in this case β -hydride elimination occurs, followed by aromatisation with the loss of water (Scheme 1.44b, pathway B). Unfortunately the reaction conditions do not differentiate very well between the two pathways and the two products are formed in varying ratios, from 2:1 to 15:1 (pyrroline:pyrrole) depending on substituents.



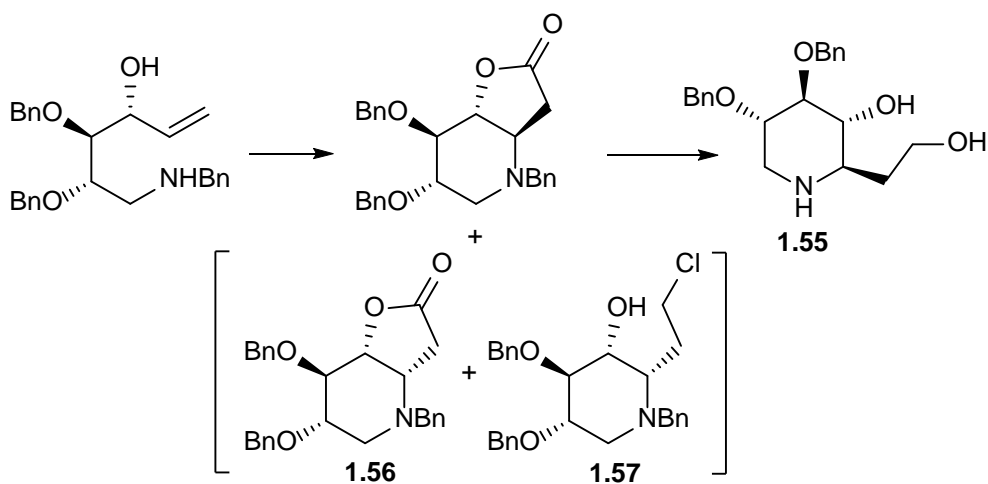
Scheme 1.44

Bicyclic lactones can be synthesised from the Pd-alkyl intermediate formed after intramolecular aminopalladation forms a new nitrogen containing heterocycle. Yoshida,^{43,44} Takahata⁴⁵ and Gracza^{46,47} have all reported syntheses of lactones in this manner. Yoshida initially reported the development of the conditions and reported an extensive substrate scope which led to Takahata applying this methodology to the synthesis of the optically active Geissman-Waiss lactone **1.54** (Scheme 1.45). Gracza attempted to apply the methodology to pyrrolidine containing natural products, such as 1-deoxynojirimycin **1.55** (Scheme 1.46). However, the desired lactone could not be synthesised exclusively and varying amounts of diastereoisomer **1.56** were found along with a small quantity of chloro derivative **1.57**. Assuming that **1.57** was formed from the excess of CuCl₂ present in the reaction, they discovered that **1.57** could be synthesised exclusively if CO was omitted from the reaction.



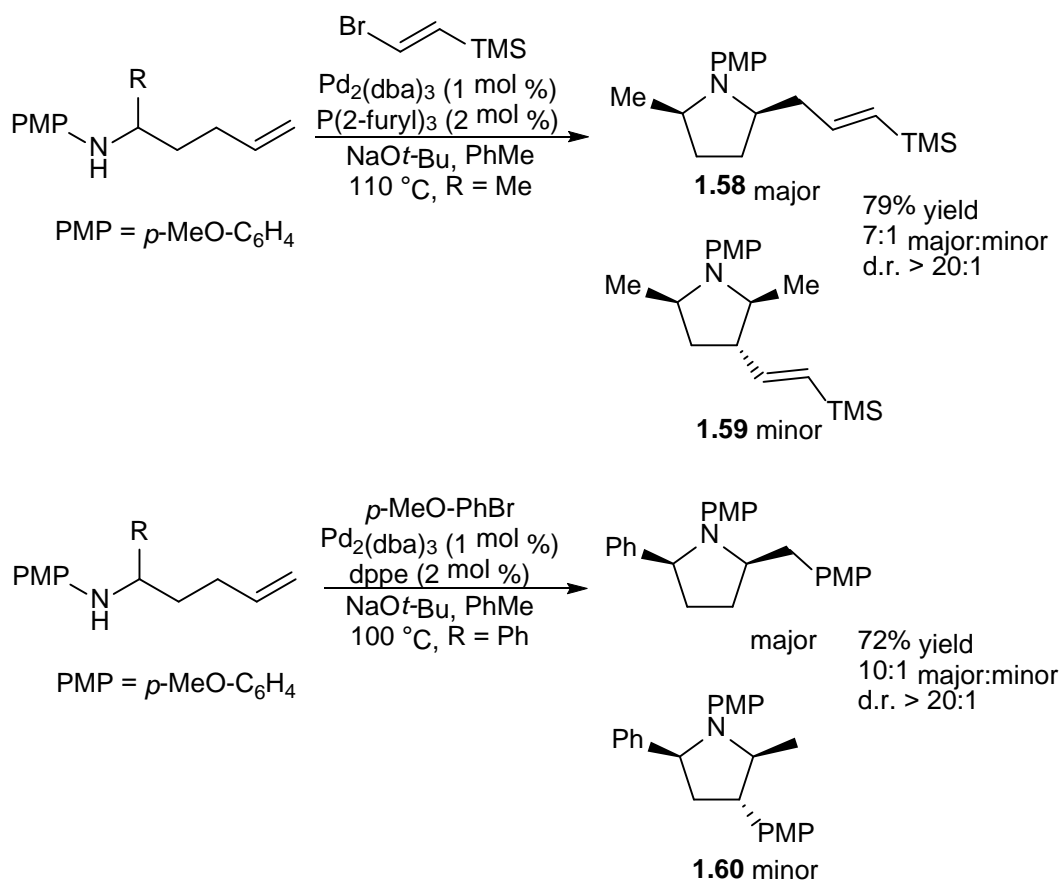
Scheme 1.45

The methodology reported by these groups is a great example of how this type of palladium transformation can be used to form multiple bonds in one step and essentially streamline a synthesis towards a synthetically valuable intermediate or target.



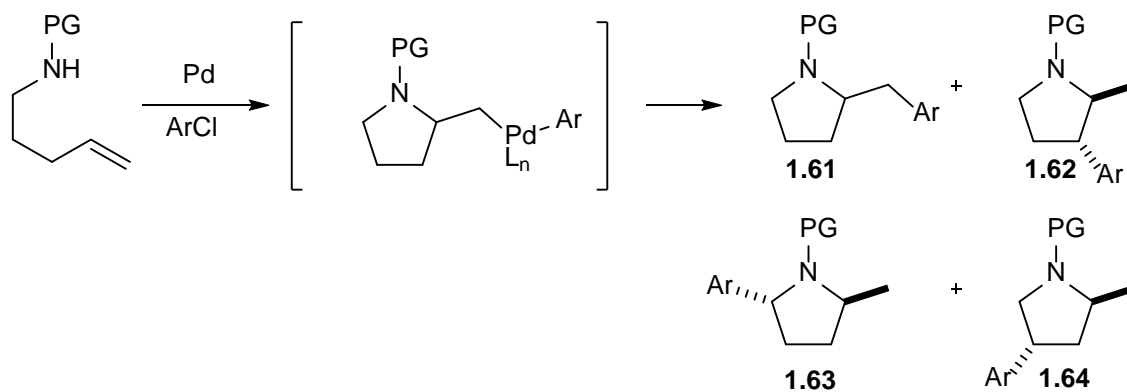
Scheme 1.46

Wolfe and co-workers reported a stereoselective synthesis of *N*-aryl pyrrolidines from γ -(*N*-arylamino)alkenes with aryl and vinyl bromides (Scheme 1.47).^{19,48} The major product **1.58** from the reaction is as expected, the minor is yet another example of side products being formed from β -hydride elimination and Pd-H reinsertion into the alkene. However this time instead of β -hydride elimination, C-C reductive elimination furnished the pyrrolidine with the vinyl **1.59** or aryl **1.60** in the alternated position. The diastereoselectivities obtained were excellent which is an indication that only one AP pathway is operating.



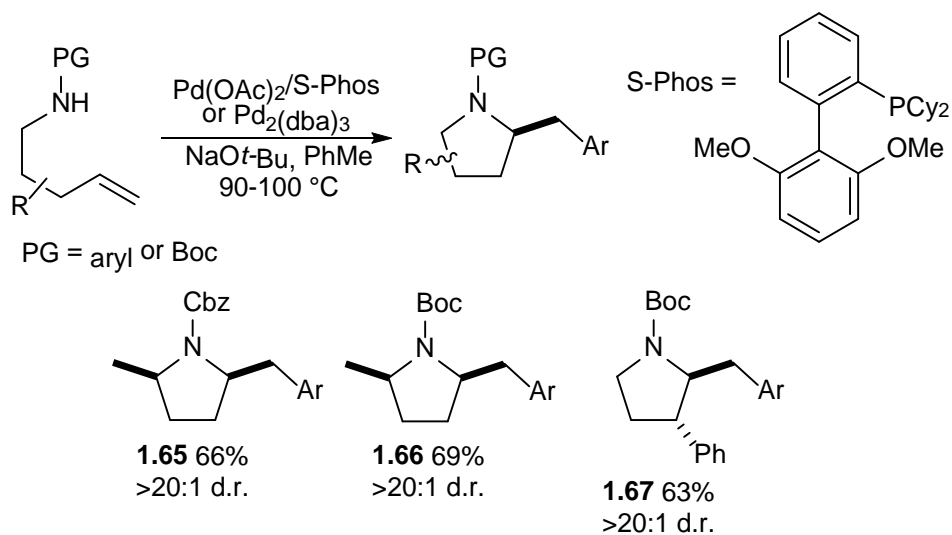
Scheme 1.47

Wolfe found that whilst aryl bromides could be coupled with ease, the cheaper alternative of aryl chlorides could not. Aryl chlorides are generally deemed less reactive than their bromide counterparts and remain unactivated by the Pd/ligand system outlined in Scheme 1.47. Wolfe strived to develop a system that could provide the same efficient coupling with inexpensive aryl chlorides. When they used their previous conditions with the ligand P(*t*-Bu)₂Me·HBF₄ the desired product was obtained but with a significant amount of regioisomers in a 11:1:1:3 (1.61:1.62:1.63:1.64) mixture (Scheme 1.48).⁴⁹



Scheme 1.48

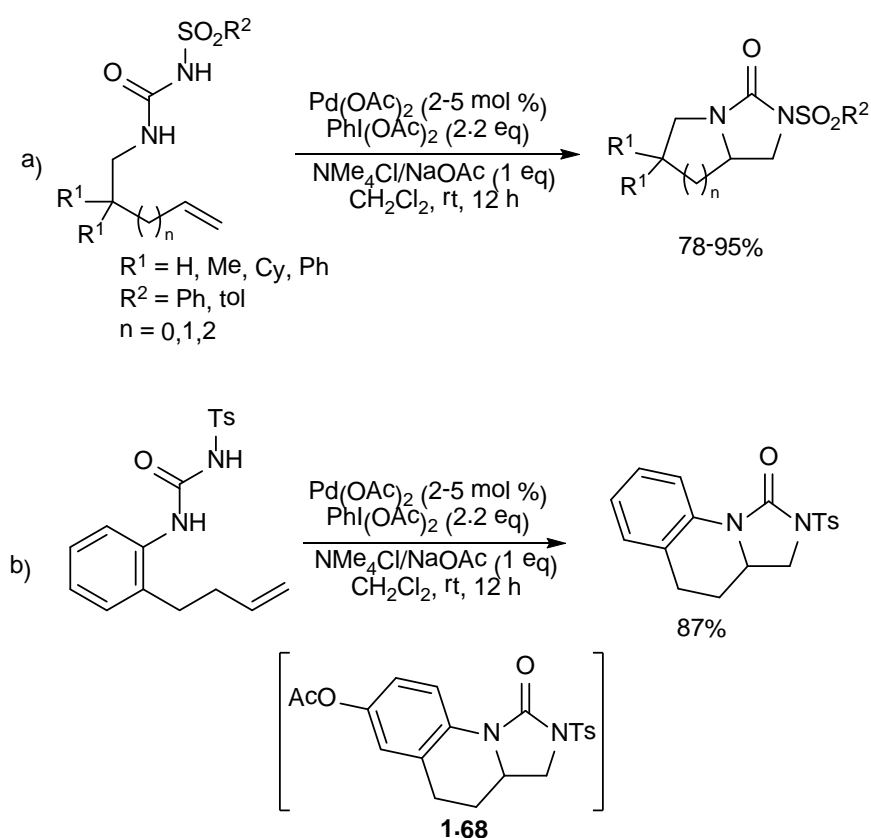
The problem was that an electron-rich ligand was required for Pd, however the use of such ligands are known to slow the rate of C-C reductive elimination.⁵⁰ They found that using S-Phos was optimal, leading to acceptable yields of the desired products and maintaining the high level of diastereoselectivity observed with the aryl bromide system (Scheme 1.49).



Scheme 1.49

2,5-Disubstituted pyrrolidines **1.65** and **1.66** were formed in a *cis*-configuration, where as those with a 2,3-motif **1.67** were formed *trans*, which is mostly likely due to steric repulsion between the substituent and the PdAr species in the Pd-alkyl intermediate.

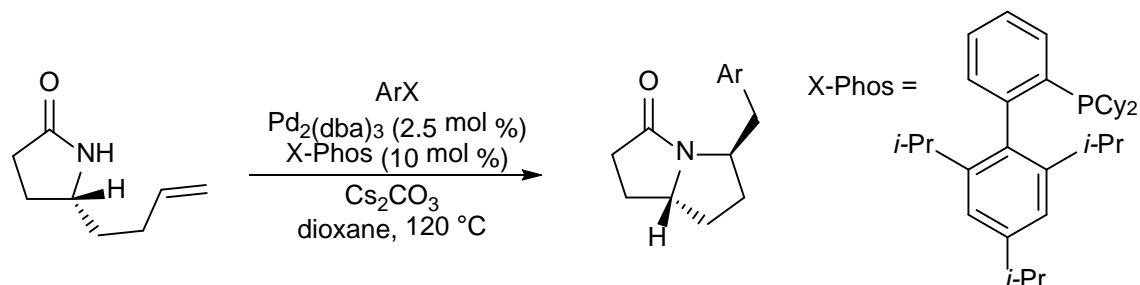
Muñiz and colleagues synthesised bicyclic nitrogen heterocycles in a single step diamination reaction (Scheme 1.50a).⁵¹ Utilising alkene tethered ureas, they demonstrated the scope of this reaction, varying the substituents bound to the alkene chain. They also varied the length of the alkene chain resulting in different sizes of the ring formed from the initial aminopalladation; 5-, 6- and 7-membered rings were formed.



Scheme 1.50

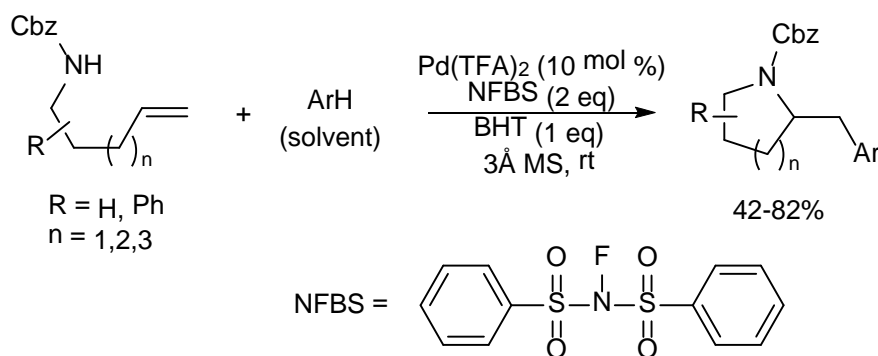
They also demonstrated that tricyclic heterocycles could be synthesised in the same manner (Scheme 1.50b). Omitting the base from the reaction led to a diminishment in yield as well as leading to the production of an almost equal amount of the acetyl substituted compound **1.68**, which the authors attribute to a Pd-catalysed oxidation of the arene ring.⁵²

Pyrrolidine fused lactams can also be synthesised from alkene chain containing lactams and aryl bromides, chlorides and triflates using a Pd/X-Phos catalyst (Scheme 1.51).⁵³



Scheme 1.51

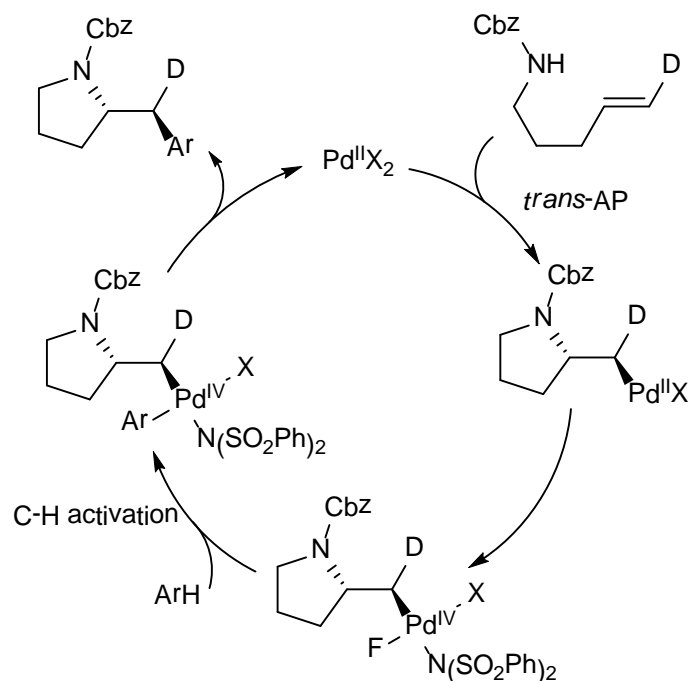
Michael and co-workers reported an unconventional aminoarylation reaction, whereby 5-, 6- and 7-membered nitrogen heterocycles were formed and coupled with aromatic solvents in one step (Scheme 1.52).⁵⁴



Scheme 1.52

The authors claimed that this reaction proceeds through a $\text{Pd}^{\text{II}}/\text{Pd}^{\text{IV}}$ cycle with *trans*-AP, as opposed to conventional aminoarylation which proceeds through a $\text{Pd}^0/\text{Pd}^{\text{II}}$ cycle with ArX electrophiles and often *cis*-AP.⁵⁵ They reported that first *trans*-AP occurs, followed by oxidation of Pd^{II} to Pd^{IV} , which is facilitated by NFBS. The Pd^{IV} -alkyl species can then undergo arene C-H activation, followed by C-C reductive elimination to relinquish the

product (Scheme 1.53). The inclusion of BHT in the reaction mixture is to prevent isomerisation reactions.



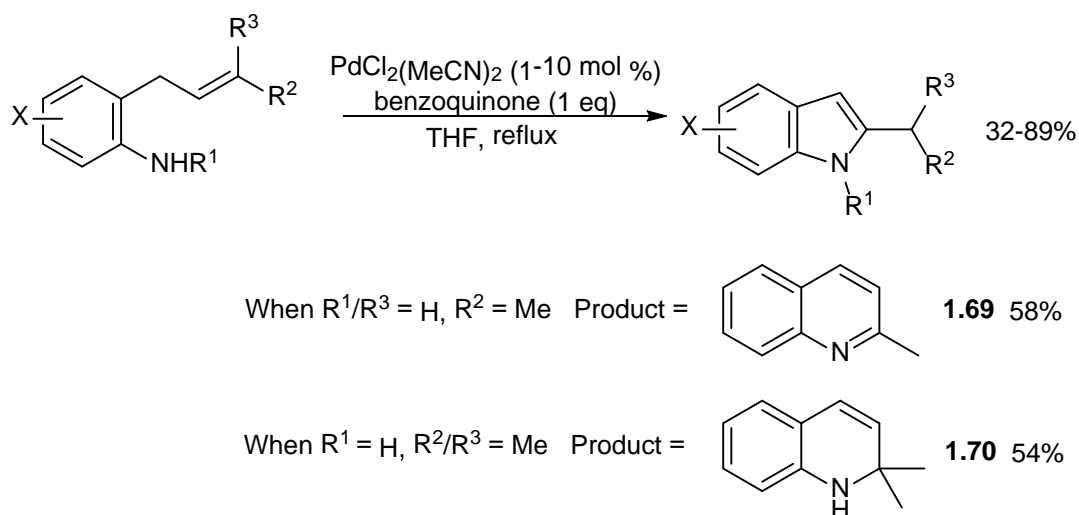
Scheme 1.53

Pyrrolidines are possibly the most reported of all the products obtained by these Wacker-type palladium transformations and whilst they are synthetically valuable, the scope of these transformations is by no means limited to synthesising pyrrolidines.

1.3.2. Synthesis of Indoles and Related Derivatives

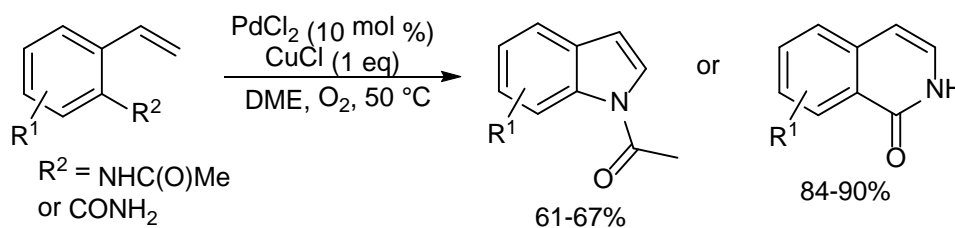
Alkene containing aniline derivatives have been shown to be capable of undergoing oxidative Wacker-type conditions to yield functionalised indoles. Hegedus and co-workers showed that 2-methylindoles⁵⁶ and indoloquinones⁵⁷ could be synthesised using stoichiometric $\text{PdCl}_2(\text{MeCN})_2$. With the correct substituents the Pd-alkyl intermediate could be trapped with no β -hydrogen present, and coupled with CO/MeOH or an alkene in a Heck-type coupling.

They reported catalytic reactions, using 1-10 mol % Pd to synthesise functionalised indoles.⁵⁸ However, if an internal *E*-alkene is reacted, the observed product is a quinoline **1.69** or the corresponding derivative **1.70** (scheme 1.54).



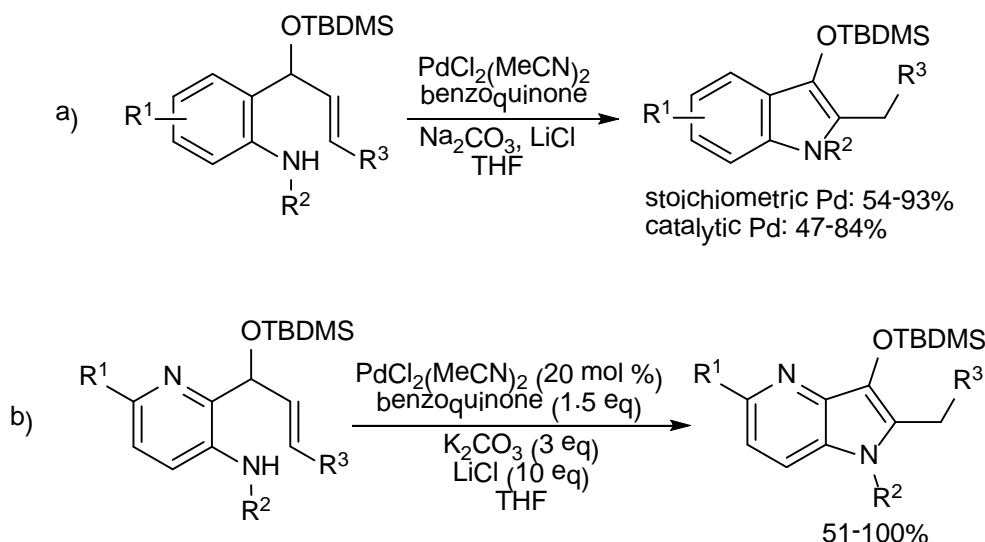
Scheme 1.54

Izumi *et al.* demonstrated a similar transformation (Scheme 1.55).⁵⁹



Scheme 1.55

Lau reported the synthesis of indoles⁶⁰ (Scheme 1.56a) and azaindoles⁶¹ (Scheme 1.56b) using catalytic PdCl₂(MeCN)₂. The catalytic transformations took place in near identical yields when compared to the same reaction using stoichiometric Pd.

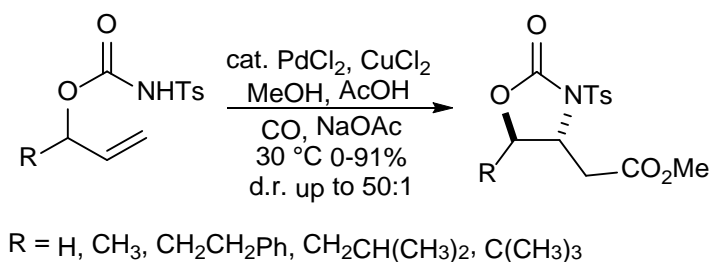


Scheme 1.56

1.3.3. Synthesis of Oxazolidinones, Isoxazolidines and Related Derivatives

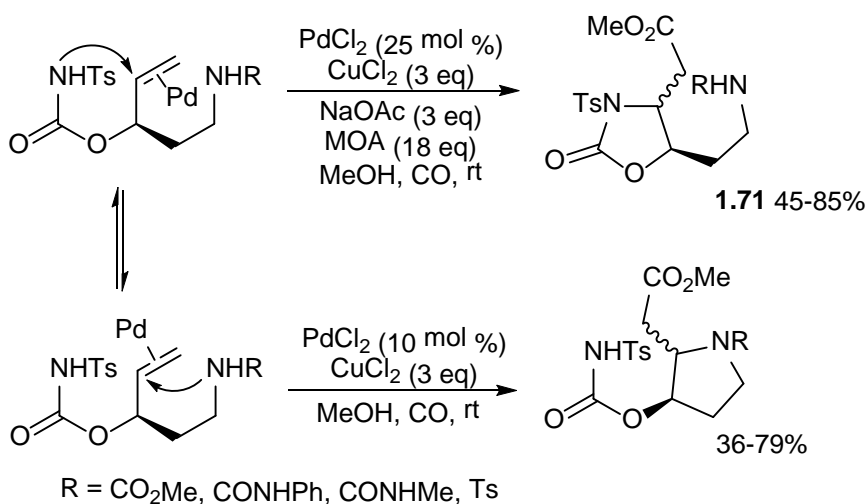
Oxazolidinones are interesting and synthetically valuable heterocycles, furthermore they can be rapidly transformed into valuable 1,2-amino alcohols, a motif that is present in a range of biologically important compounds.

Allylic *N*-tosyl carbamates can be cyclised under carbonylative conditions to yield oxazolidinones. Tamaru and colleagues⁶² synthesised oxazolidinones using standard conditions, they found that *N*-Ts carbamates gave the best results and that bulky R groups gave poor yields which were slightly improved by the inclusion of methyl orthoacetate (Scheme 1.57). Moderate d.r.'s were obtained for the secondary carbamates; R = Me 7:1, R = CH₂*i*-Pr 10:1, R = CH₂CH₂Ph 3:1*. When R = *t*-Bu, the diastereoselectivity was greatly increased to 50:1*. (* with the inclusion of methyl orthoacetate).



Scheme 1.57

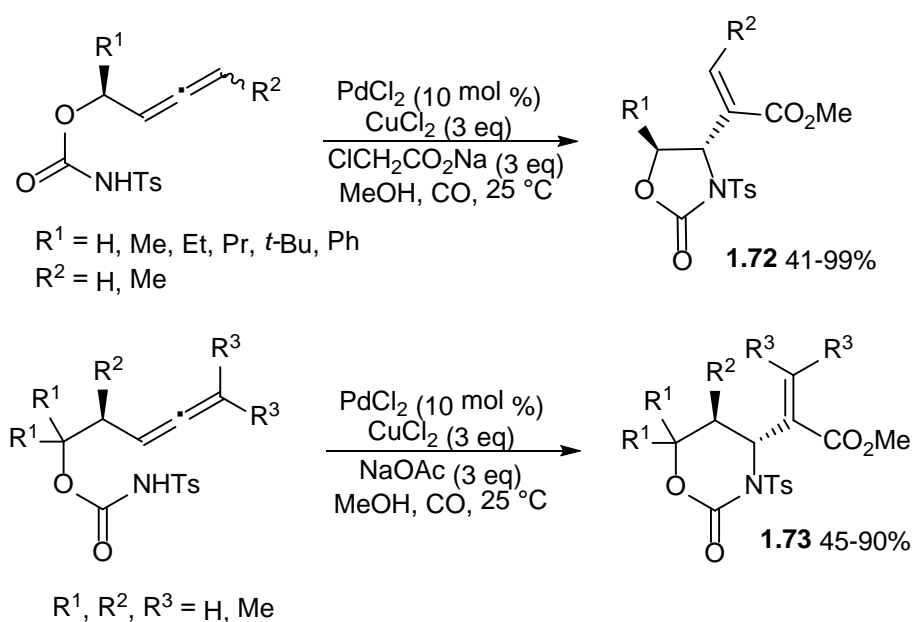
Five years later Tamaru reported another aminocarbonylation, this time with an alkene containing two tethered amines.^{63,64} Each amine could be cyclised independently depending on the conditions used (Scheme 1.58).



Scheme 1.58

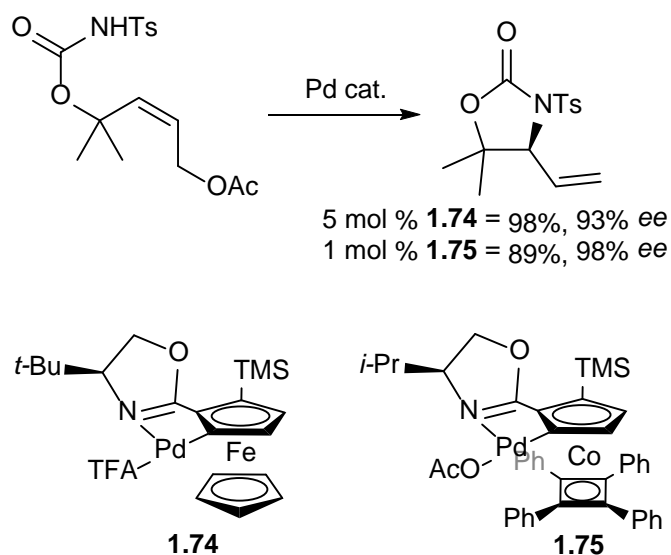
This is a good example of how different additives (mainly acid and base) and the type of nitrogen nucleophile are linked and play an important role in this type of reaction. In this instance, the acidic conditions favoured the cyclisation of the 'exo'-nitrogen, whereas the conditions that are buffered with methyl orthoacetate (MOA) and NaOAc lead exclusively to the formation of the oxazolidone **1.71**. It is unclear what aminopalladation pathway is operating in each of these cases, but the change in reaction conditions could be an indication that the operating pathway has changed.

Allenes can be employed in carbonylation reactions leading to 5- and 6-membered cyclic carbamates. Tamaru⁶⁵ reported the stereoselective synthesis of **1.72** and **1.73** derivatives (Scheme 1.59). Interestingly these reactions proceeded without the need for any MOA that previously played a vital role in the reactions that were outlined in scheme 1.58.



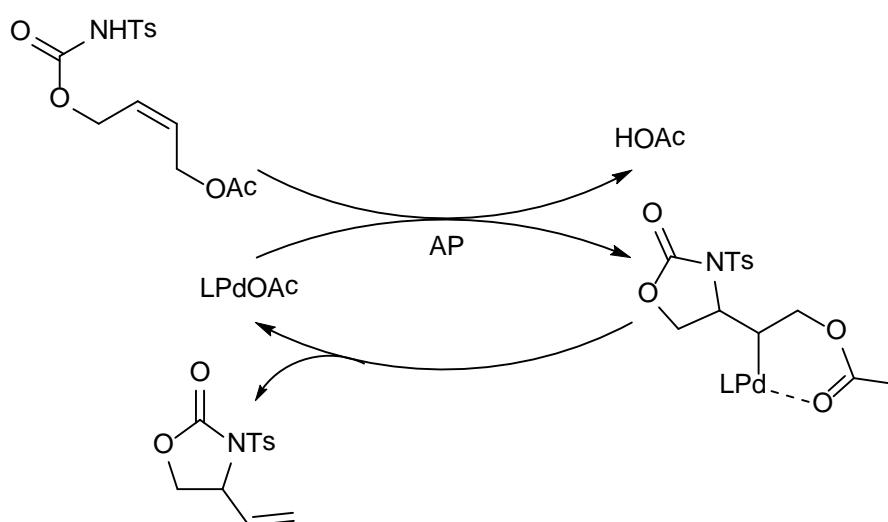
Scheme 1.59

Overman and Remarchuk demonstrated an enantioselective synthesis of oxazolidinones using chiral Pd catalysts (Scheme 1.60).⁶⁶



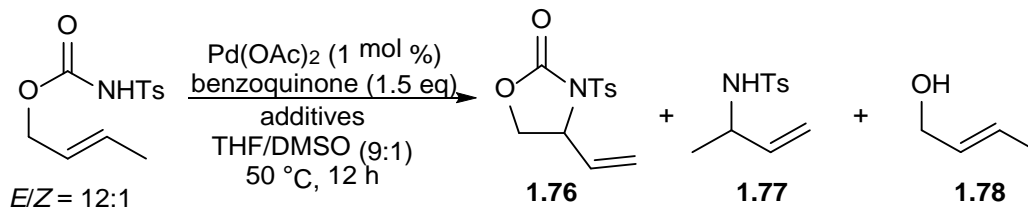
Scheme 1.60

Utilising a substrate with an acetate leaving group, allows for an efficient catalytic cycle where by upon formation of the Pd-alkyl, an equivalent of HOAc is released, the acetate anion coming from the catalyst (Scheme 1.61). The active catalyst is then regenerated by β -acetate elimination with Pd, yielding the product in excellent yield and enantiomeric excess. It was not discussed in the report, but a more traditional allylic substitution mechanism cannot be completely ruled out.



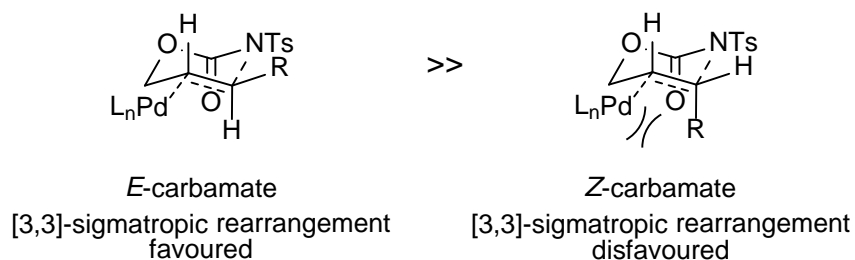
Scheme 1.61

In 2012, Bäckvall reported the synthesis of oxazolidinones from allylic tosylcarbamates.¹⁸ Initially, they observed a mixture of three different products from the reaction (Scheme 1.62).



Scheme 1.62

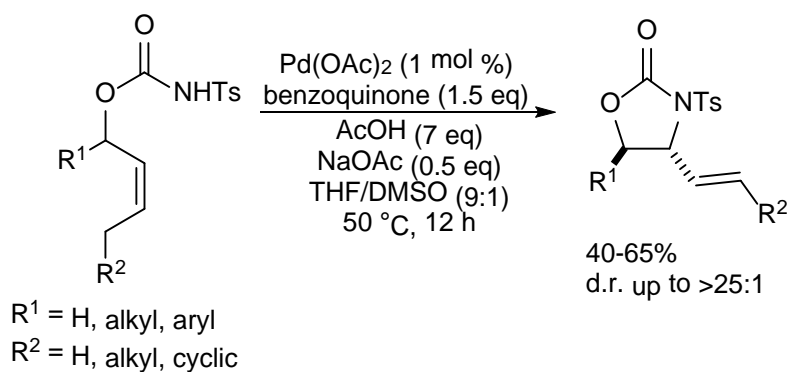
Products **1.76**, **1.77** and **1.78** were obtained initially in a ratio of 45:5:50 respectively using 0.5 eq HOAc, the ratio changed to 40:20:40 by replacing HOAc with NaOAc. Using a 2:1 ratio of HOAc:NaOAc gave a 75:20:5 mixture. A 7:0.5 mixture of HOAc:NaOAc proved optimal, giving a product ratio of 85:10:5 (**1.76:1.77:1.78**). The allylic rearrangement product was not unexpected as Overman has reported such rearrangements in the past.⁶⁷ However, it was noticed that it could be suppressed to just trace amounts using *Z*-alkenes instead of the *E*-isomers. They rationalised this observation looking at the 6-membered transition states, stating that the rearrangement is disfavoured in *Z*-alkenes because of steric interactions between Pd and the pseudo-axial R group (Scheme 1.63).



Scheme 1.63

Their optimal conditions tolerated a range of substituents on both the alkene and at the carbon containing the carbamate group (Scheme 1.64). Secondary carbamates cyclised with excellent

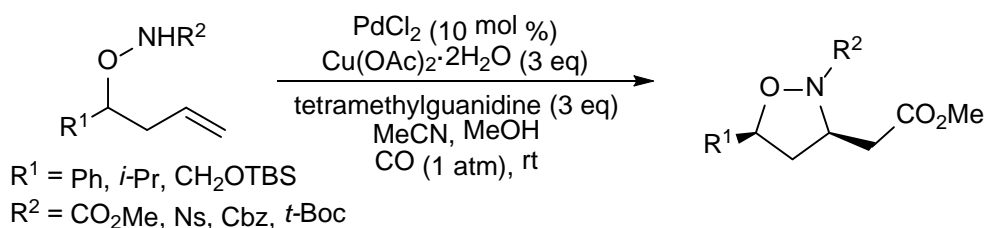
diastereoselectivities (>20:1), however these required 5 mol % of Pd(OAc)₂ in order to obtain practical yields. In the case of cyclohexene substituted carbamate the d.r. was >25:1, however this required 10 mol % Pd(OAc)₂ and 48 h.



Scheme 1.64

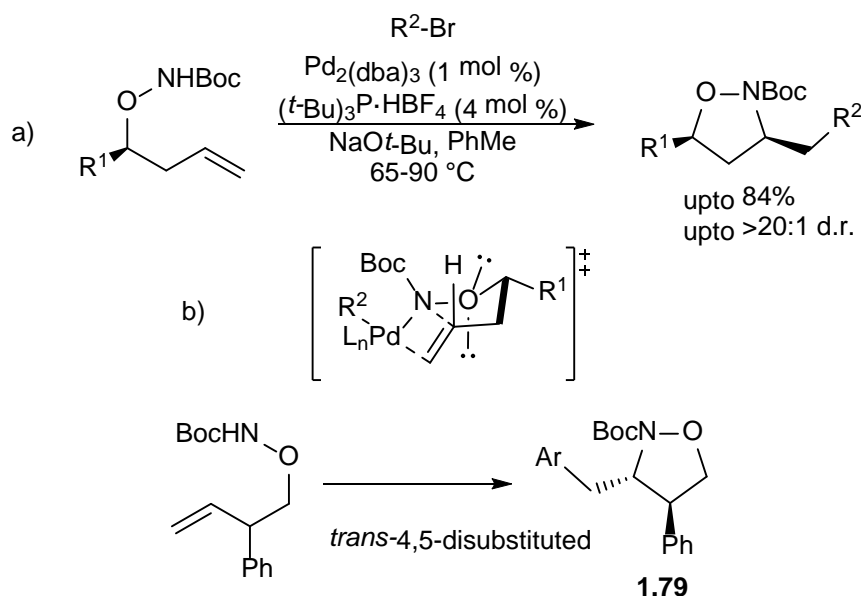
They synthesised a six-membered ring in this manner from a homoallylic carbamate. However this required a 10 mol % catalyst loading and 48 h reaction time, and yielded just 46% of the product, which was isolated as the *N*-tosylamino alcohol derivative due to difficulties in purification.

Isoxazolidines are often used as precursors to 1,3-amino alcohols, which are a motif that is present in a range of biologically active compounds.⁶⁸ Bates and Sa-Ei published an aminocarbonylation using novel *O*-homoallylic hydroxylamines (Scheme 1.65).⁶⁹ They found that an electron withdrawing group on the nitrogen atom was necessary for a successful cyclisation to occur. C-1 trisubstituted substrates formed the isoxazolidines in a diastereomerically pure *syn*-configuration.



Scheme 1.65

Wolfe and co-workers recently reported that *N*-Boc-*O*-homoallylic hydroxylamines can be cyclised and functionalised with aryl bromides under aminoarylation conditions (Scheme 1.66a).²²

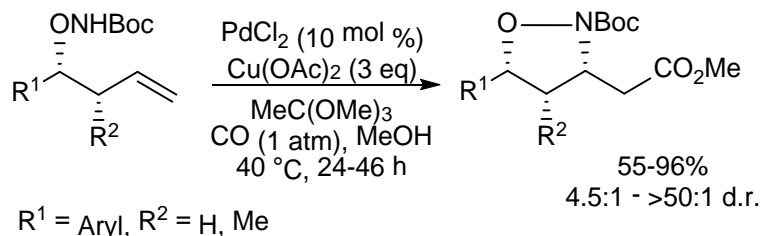


Scheme 1.66

Their transition states suggest that high diastereoselectivities observed with the 3,5-disubstituted rings arise from a *cis*-AP, with the carbamate group and alkene methyl group pointing away from each other (Scheme 1.66b). *Trans*-4,5-disubstituted rings **1.79** can also be synthesised, from C-2 functionalised starting hydroxylamines. The *trans*-configuration observed most likely arises from steric interaction with Pd as the *cis*-AP step occurs.

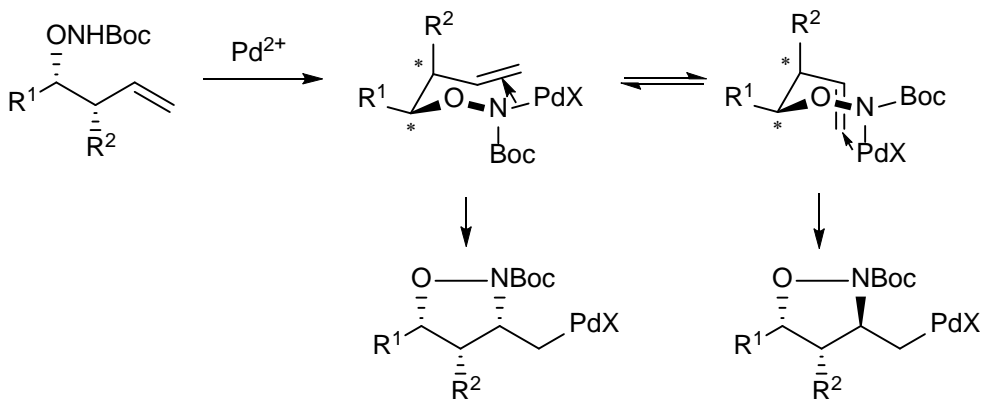
As previously mentioned, Malkov and Kočovský reported a stereoselective carbonylative amidation of *N*-Boc homoallylic hydroxylamines.²⁸ Using methodology developed in the

Malkov group for obtaining chiral homoallylic alcohols,⁷⁰ they synthesised enantioenriched hydroxylamines similar to the those used by Bates⁶⁹ and Wolfe²² (Scheme 1.67).



Scheme 1.67

These cyclised without problems and tolerated a range of functionalities without much change in diastereoselectivity. The exception is when $\text{R}^2 = \text{Me}$, for these substrates the d.r. is quite low at around 5:1, as opposed to the >50:1 observed for some substrates that have $\text{R}^2 = \text{H}$. It is possible this methyl group causes some steric interactions in the transition state that are unfavoured, leading to the mixture of isomers (Scheme 1.68).

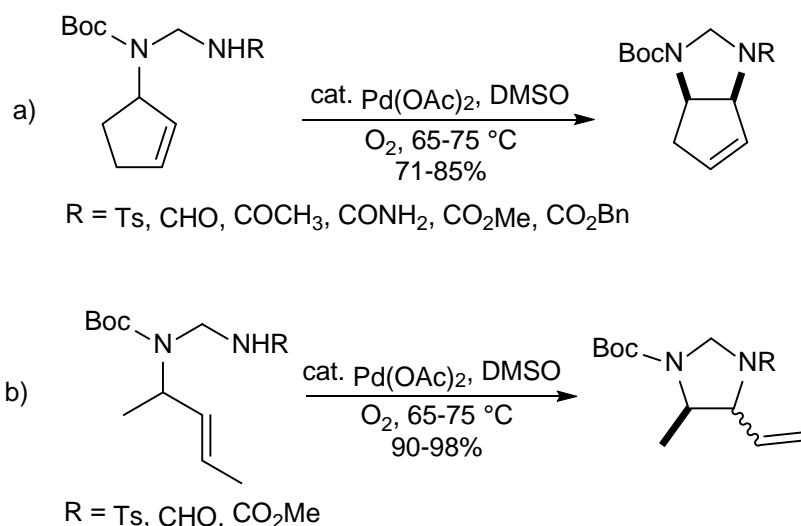


Scheme 1.68

1.3.4. Synthesis of Imidazolidines, Pyrazolidines and Related Derivatives

Heterocycles containing two nitrogen atoms are useful intermediate building blocks, and as with oxazolidinones and isoxazolidines, they can be easily converted into vicinal 1,2- or 1,3-diamines.

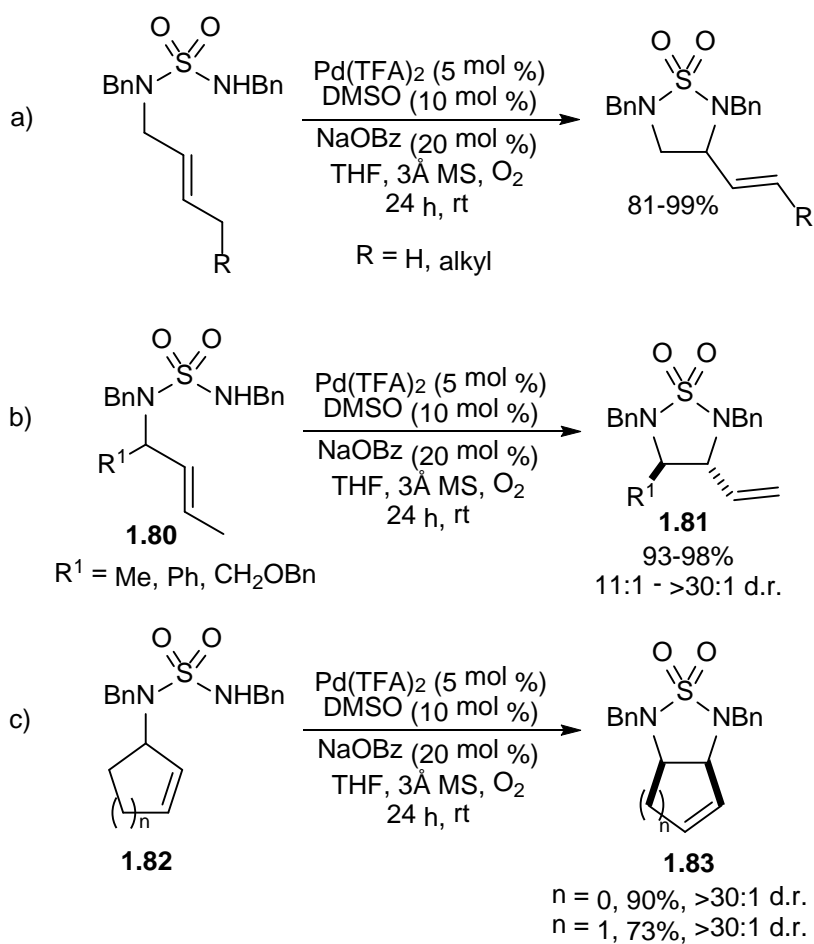
Cyclisation of cyclic and acyclic amins with Pd^{II} was demonstrated by Hiemstra and colleagues.⁷¹ Cyclic amins were cyclised with ease, yielding *syn*-imidazolidines (Scheme 1.69a). Acyclic amins cyclised more efficiently. However, the downside of using these substrates is the lack of diastereoselectivity (\approx 1:1) in the aminopalladation step, which is unusual for this type of cyclisation (Scheme 1.69b).



Scheme 1.69

They also found that acid/base hydrolysis would not convert the imidazolidines to the desired diamines. In order to cleave the amination and obtain the diamine they had to employ a 3-step process of first removing protecting group R, electrochemical oxidation to an amidine and then finally hydrolysis could take place yielding the diamine.

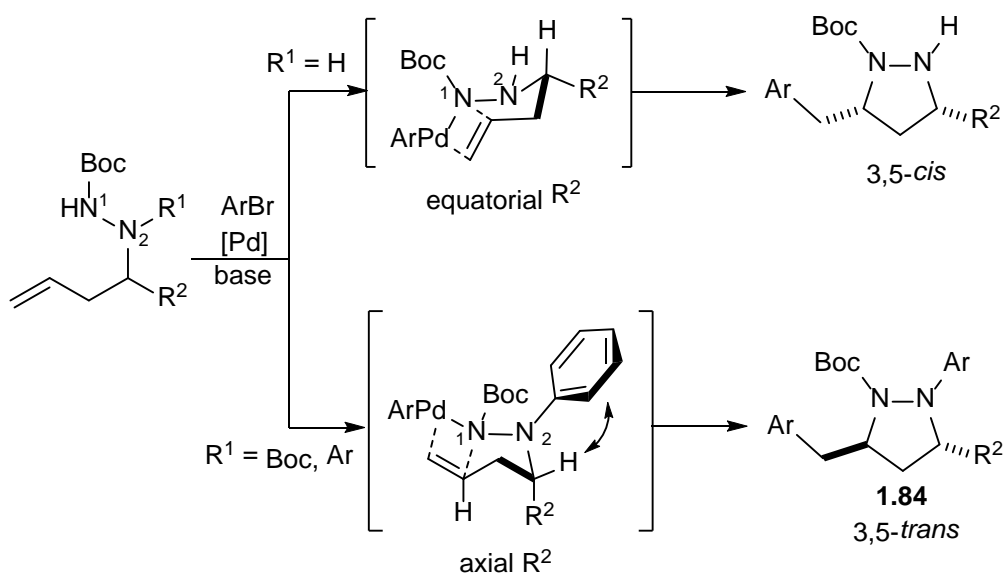
Sulfamides have been shown to cyclise under Wacker-type conditions, Stahl showed that cyclic sulfamides could be obtained with excellent diastereoselectivity and easily converted to vicinal diamines (Scheme 1.70).⁷²



Scheme 1.70

The catalyst system was developed from previously reported reactions using a Pd^{II}/DMSO/O₂ mixture. The presence of base NaOBz was necessary for efficient conversion, however only a catalytic amount was required (20 mol %). It was found that by changing the solvent to THF enabled the synthesis to be carried out at room temperature rather than the 80°C required by toluene and 1,4-dioxane. Most importantly however is the Pd^{II}/DMSO ratio, and if DMSO is used as the solvent the reaction yield is diminished by 50%. The optimal ratio was found to be 1:2 Pd^{II}/DMSO. Stahl has recently established that DMSO can act as a ligand to Pd and can in fact be coordinated by both oxygen and sulfur.⁷³ Excellent diastereoselectivities can be obtained using secondary substrates **1.80** which cyclise giving a *trans*-motif **1.81** (Scheme 72b), and using the cyclic sulfamides **1.82** which yields *cis*-diamines **1.83** (Scheme 1.70c). The sulfone bridge between nitrogen atoms can easily be removed using a straightforward LiAlH₄ reduction.

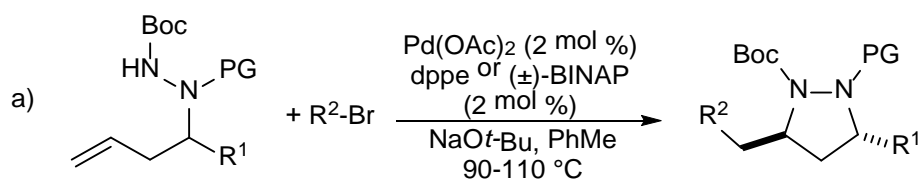
Wolfe once again reported an aminoarylation, though this time using homoallylic hydrazines that were cyclised to pyrazolidines.⁷⁴ Secondary homoallylic diamines were cyclised in decent yields, however interesting results were obtained when the functionality on the *N*-homoallyl nitrogen atom was changed. Wolfe observed that when N-2 was not functionalised, the resulting pyrazolidines were obtained with a *cis*-3,5-motif, however functionalisation at N-2 with Boc or an aryl group led to *trans*-3,5-disubstituted pyrazolidines being formed. Wolfe rationalised these observations with transition state models, outlined in scheme 1.71.



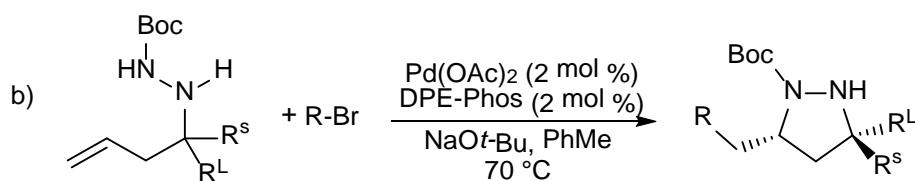
Scheme 1.71

When $R^1 = H$ there is little steric interaction with the adjoining R^2 group, which is situated equatorially, in this favoured position the two substituents at 3- and 5- positions sit *cis* to each other. When $R^1 = Boc$ or aryl, then there is a large steric interaction with R^2 , therefore R^2 is forced into an axial position with the hydrogen near the Boc/Ar group to minimise steric interaction. This lower energy conformation leads to the *3,5-trans* product **1.84**. A range of *trans*-3,5-disubstituted pyrazolidines were synthesised with excellent diastereoselectivities (Table 1.6).

Table 1.6



	PG	R ¹	R ²	Yield (%)	d.r. (crude)
1	Ph	Ph	4-BzC ₆ H ₄	74	20:1 (11:1)
2	PMP	Pr	4-NCC ₆ H ₄	63	>20:1 (>20:1)
3	Boc	Ph	2-naphthyl	55	>20:1 (>20:1)
4	Boc	Pr	3-F ₃ CC ₆ H ₄	81	>20:1 (>20:1)

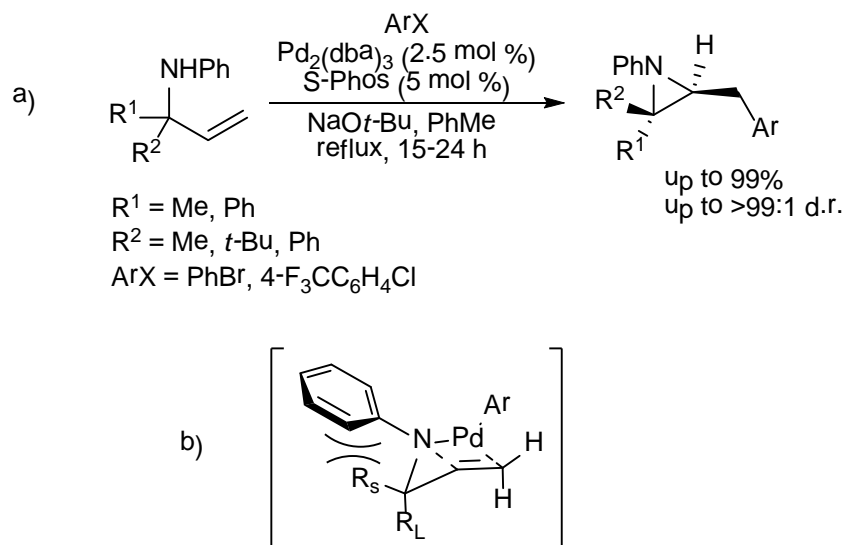


	R ^S	R ^L	R	Yield (%)	d.r. (crude)
5	H	Pr	4-ClC ₆ H ₄	70	>20:1 (7:1)
6	H	Ph	3-MeC ₆ H ₄	66	13:1 (10:1)
7	Me	Ph	4-PhC ₆ H ₄	83	6:1 (6:1)

Switching R^S to a methyl group resulted in a diminished diastereoselectivity (Table 1.6, entry 7), this is probably due to the two groups R^S and R^L flipping between the equatorial and axial positions, thus leading to a greater mixture of the two stereoisomers.

1.3.5. Synthesis of Other Nitrogen Heterocycles

Hayashi, Yorimitsu and Oshima reported that functionalised aziridines could be synthesised with high stereoselectivity from allylic amines under aminoarylation conditions (Scheme 1.72a).⁷⁵ The reaction proceeded surprisingly efficiently and with no Heck-type coupling by-products, that were observed in the analogous synthesis of epoxides.⁷⁶

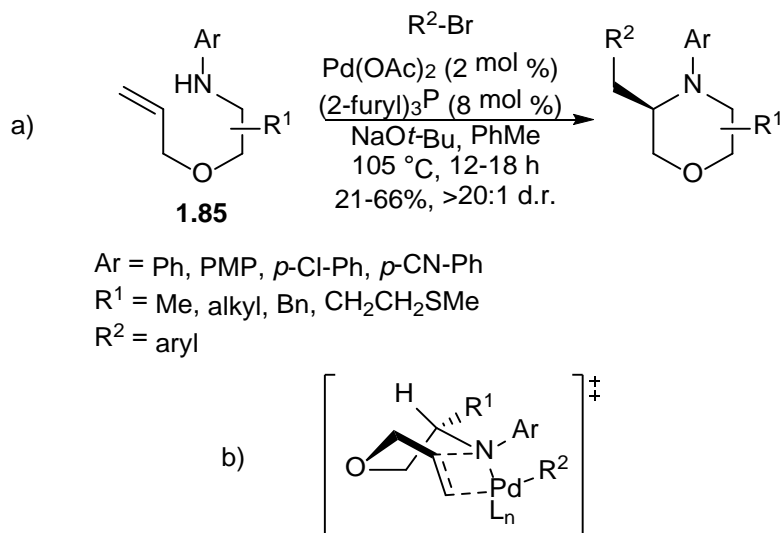


Scheme 1.72

They carried out deuteration studies to establish that *cis*-AP was the operating pathway; from this they suggested an intermediate that justified the excellent stereoselectivity observed (Scheme 1.72b). The larger R^{L} group sits axially, whilst the smaller R^{S} sits equatorially nearer the aryl group, ultimately the strain is minimalised in this conformation as the steric repulsion is less between Ph and R^{S} .

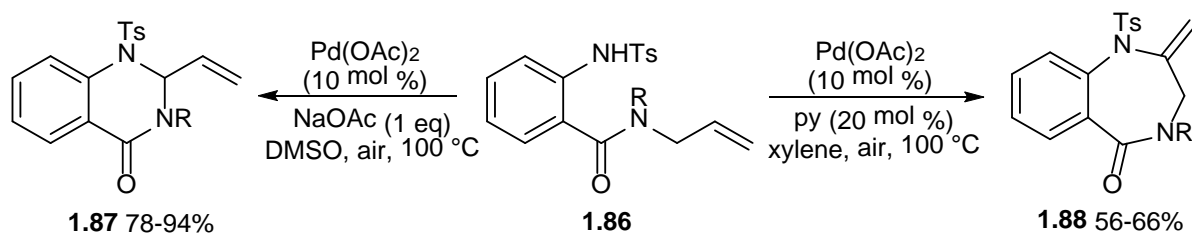
Morpholines are found in a range of biologically active molecules, and new synthetic routes to these building blocks are always welcome. Wolfe reported the stereoselective aminoarylation of amines containing allyl ethers **1.85** (Scheme 1.73a).⁷⁷ Using aryl bromides and a phosphine ligand, morpholines were synthesised with >20:1 diastereoselectivity. Wolfe assumed a *cis*-AP based on his previous studies with pyrrolidines, piperazines and other nitrogen heterocycles. He proposed a boat like transition state to account for the observed

stereochemistry (Scheme 1.73b). In this conformation, the steric repulsion between Ar and R¹ is minimalised.



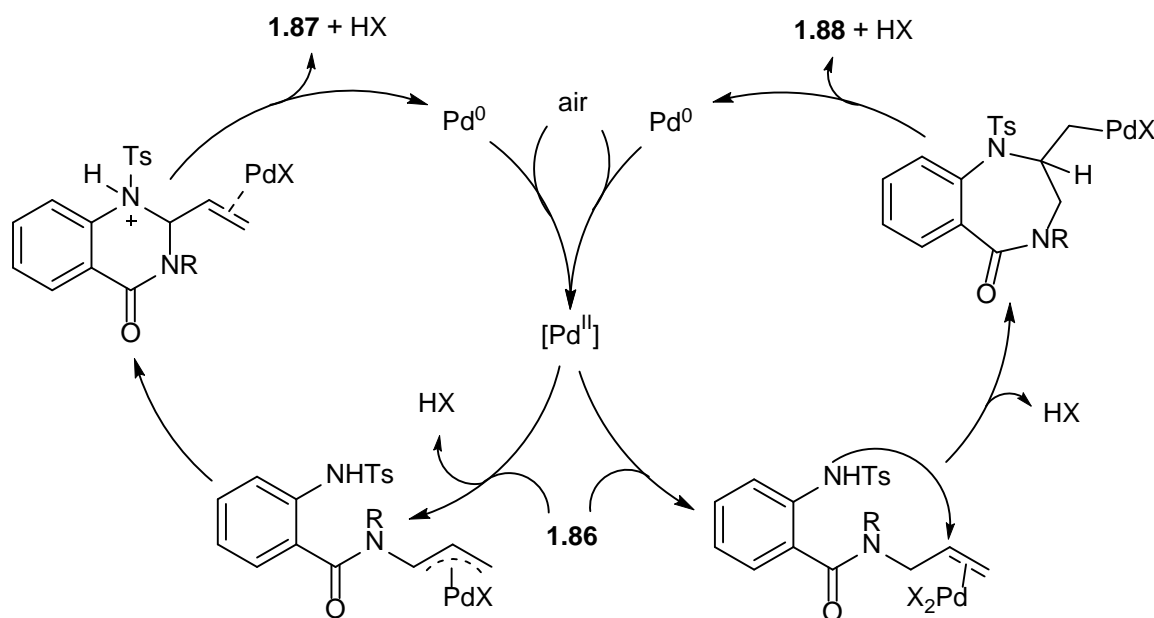
Scheme 1.73

Broggini and co-workers reported that from aniline derivatives containing tethered allylic amides **1.86**, quinazolin-4-ones **1.87** and 1,4-benzodiazepin-5-ones **1.88** can be formed.⁷⁸ **1.87** is formed when Pd(OAc)₂ in DMSO with NaOAc is used, whereas Pd(OAc)₂ with 20 mol % pyridine gives **1.88** exclusively (Scheme 1.74).



Scheme 1.74

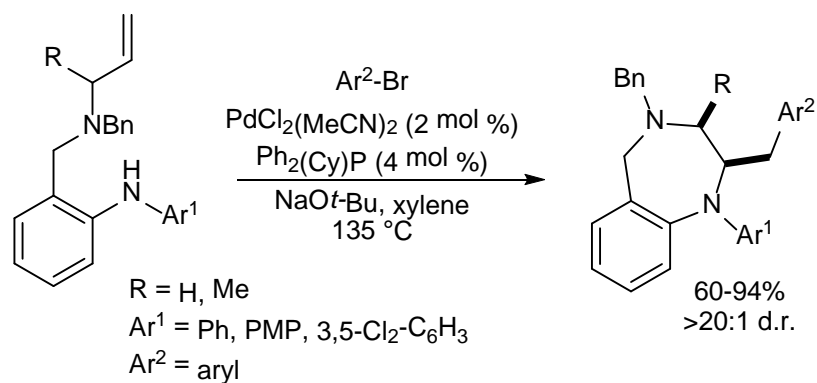
The authors proposed that **1.87** is most likely formed by **1.86** forming a π -allyl complex with Pd, then N-nucleophilic attack and Pd-dissociation. Formation of **1.88** is likely to follow an aminopalladation and β -hydride elimination mechanism (Scheme 1.75).



Scheme 1.75

The π -allyl mechanism that forms **1.87**, with the Pd/DMSO catalyst, is unexpected, however not unusual. White has used Pd/sulfoxide catalysts to facilitate a range of reactions involving the attack of a nucleophile to a π -allyl intermediate.^{79,80} She has shown that oxazolidinones⁸¹ and oxazinanones⁸² can be synthesised efficiently via this π -allyl/C-H activation methodology.

Wolfe also applied his aminoarylation methodology to the synthesis of 1,4-benzodiazepines, using Pd^{II} and a phosphine ligand (Scheme 1.76).⁸³ Once again his methodology proved straightforward, reliable and able to tolerate varying substituents.



Scheme 1.76

As with his work on morpholines, Wolfe assumed a *cis*-AP mechanism is in operation and accounted for the high level of stereoselectivity by proposing a transition state **1.89** (Figure 1.6). A boat-like transition state was proposed, where R sits equatorial in the position of least steric interaction. The methyl of the alkene is positioned away from the bulky Ar group attached to the nitrogen atom.

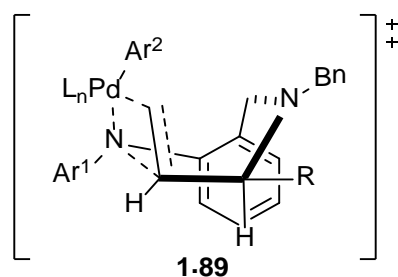


Figure 1.6

These examples show the range of substrates that are available for use in aza-Wacker type transformations. Different ring sizes can be synthesised with varying functionalities and the reactive Pd-alkyl intermediate can further couple with more reagents, expanding the scope for functionalisation.

1.4. Concluding Remarks

There has been a great deal of advances in the past five decades, since the initial report of the Wacker process in 1959. Amongst the vast library of examples are those that are stereoselective, the key to which lie in the aminopalladation step. The studies into the mechanistic aspects of these Wacker-type oxidative amination reactions have proved invaluable in understanding the difference between the two modes of aminopalladation. The work carried out by Stahl is by far the most important as it not only highlights the difference in pathways, but how the additives and even the nature of the substrate nucleophile play a crucial role in determining which aminopalladation pathway operates primarily. The studies by Stahl show how unpredictable and how complex controlling aminopalladation can be, for example *cis*-AP is observed under neutral conditions, whereas *trans*-AP appears to favour acidic conditions. Increasing acidity increases the *trans*:*cis*-AP ratio. However, what seems to play a more important role is the acidity of the nucleophile; using a more acidic nucleophile can lead to a complete preference for *cis*-AP, even under acidic reaction conditions. Matters are further complicated when the nucleophile acidity is increased again leading to mixtures of *cis* and *trans*-AP products, and in the case of Pd(OAc)₂/DMSO (which had shown exclusively *cis*-AP products for the previous two substrates) *trans*-AP was observed exclusively. These observations are explained in full in chapter 1.2, but this brief highlight shows how complex planning a stereoselective aza-Wacker transformation can be. That being said, many research groups have found compatible conditions and substrates, obtaining some excellent diastereoselectivities. Enantioselective Wacker-type reactions, which are known to be troublesome, are possible and only a handful of examples exist in the literature.

The vast range of heterocycles that can be synthesised shows how versatile this type of Pd catalysis can be, especially when coupled with the ability to harness the reactivity of the Pd-alkyl intermediate formed from aminopalladation. Formation of multiple bonds under catalytic conditions in a single step is an attractive prospect and with correct reaction planning, these transformations can be employed to streamline routes to functionalised heterocyclic compounds.

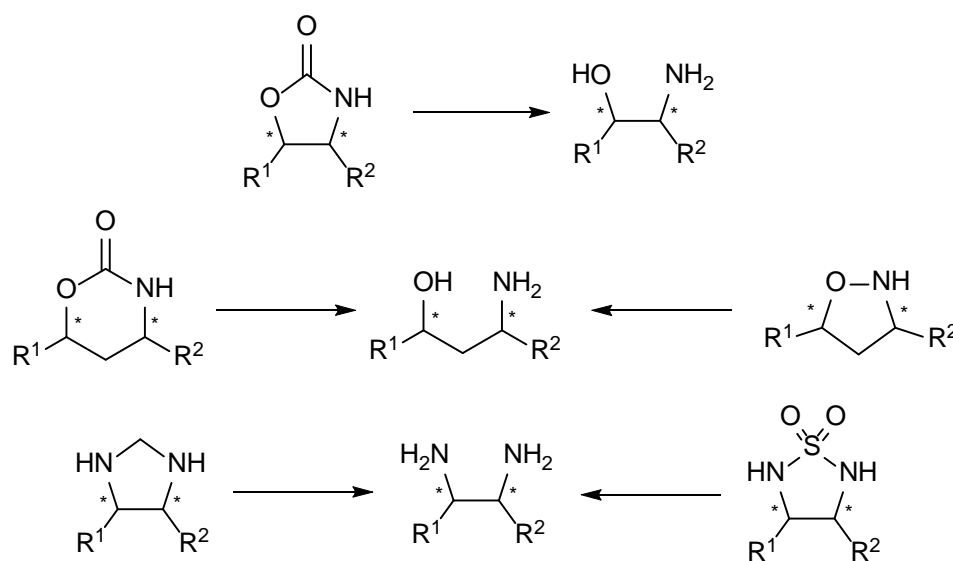
The future of this chemistry has three avenues; the first being the development of more economical conditions. Ultimately being able to carry out this chemistry with lower loadings of Pd without a loss in reactivity or a significant increase in reaction time is desirable. Using air as the reoxidant would be extremely ideal, negating the need for expensive oxidants or

highly reactive and explosive pure oxygen. The second avenue is the development of simple and readily accessible ligands for enantioselective amination reactions. The third avenue is controlling the aminopalladation step. Ideally, to assist the design of new reactions of this kind, a set of rules could be set out that help predict the outcome of aminopalladation, depending on catalyst, substrate and conditions. This may seem quite distant, but we are now some way towards understanding the aminopalladation step, however there are still a lot more contributing factors to identify.

2. Results and Discussion

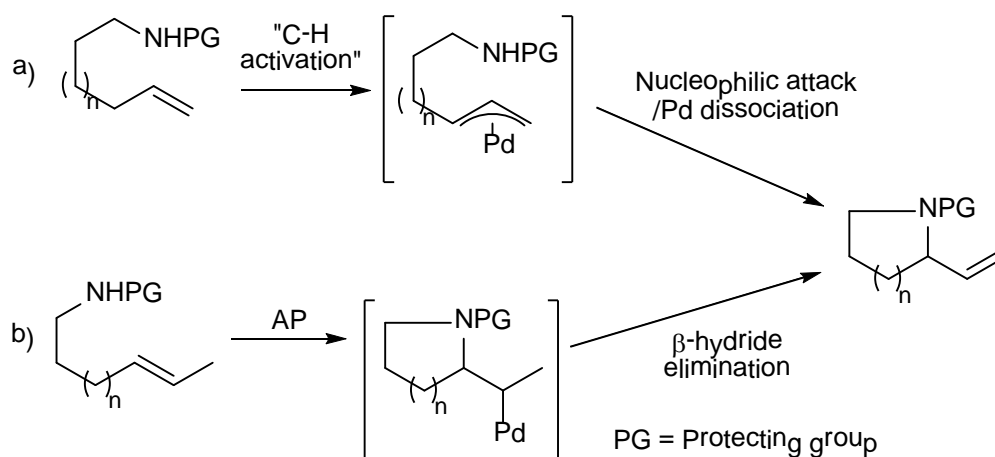
2.1. Introduction

Many pharmaceuticals and natural products feature C-N and C-O bonds in 1,2- and 1,3- relative positions. A wide range of precursors for 1,2 and 1,3-amino alcohols and diamines exist (Scheme 2.1).



Scheme 2.1

Pd^{II} has been shown to catalyse allylic amination reactions, via two different pathways (Scheme 2.2). Pathway A, proceeds via a π -allyl intermediate and only works well with terminal alkenes. Internal alkenes have shown poor reactivity. Pathway B, is an aminopalladation and subsequent β -hydride elimination. Internal alkenes are required in this case. Terminal alkenes can be used in pathway B, however a coupling reagent must be used in this instance to release Pd from the Pd-alkyl intermediate.



Scheme 2.2

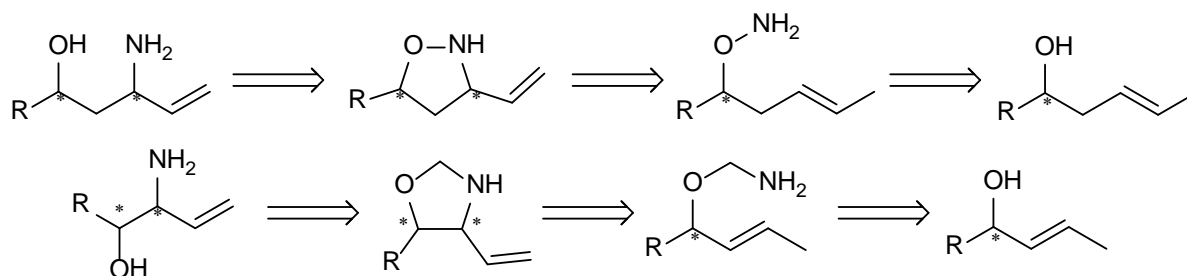
1,2- and 1,3-amino alcohol and diamine motifs can generally exist as *syn/anti* isomers, however from a synthetic point of view, single diastereoisomers are often desired. White and co-workers have shown that oxazolidinones⁸⁰ and isoxazolidines⁸¹ can be synthesised using Pd^{II} catalysed allylic C-H activation. However there are apparent drawbacks to using this methodology, often poor to moderate diastereoselectivity is observed in these reactions meaning that diastereoisomers must first be chromatographically separated. Secondly, there is usually a need for a stoichiometric external oxidant, whereas many reactions that proceed via aminopalladation can utilise molecular O₂ and in some cases even air. There is a necessity for elevated temperatures and often long reaction times are required for substantial yields to be obtained. Many of the catalytic amination reactions that proceed via an aminopalladation mechanism often yield new heterocycles with excellent diastereoselectivities. However, whilst there has been a lot of work synthesising 1,2 and 1,3 motifs using aminopalladation/coupling reactions, at the time of starting this project there were no examples of these kind of heterocycles being synthesised using aminopalladation/ β -hydride elimination methodology. Recently however, Bäckvall¹⁸ and Stahl⁷² have demonstrated the synthesis of 1,2-amino alcohols and 1,2-diamines respectively, but still there have been no reports on the synthesis of 1,3-derivatives in this manner.

Our goal was to establish a robust and reliable diastereoselective method for intramolecular allylic C-H amination to give heterocycles serving as the precursors to 1,2 and 1,3-amino alcohols and diamines.

2.2. Isoxazolidines & Pyrazolidines; Precursors to 1,3-Amino Alcohols and 1,3-Diamines

2.2.1. Substrate Design and Development

The study began by focusing on the synthesis of amino alcohols. From the start, it was decided that 5-membered heterocyclic rings would be our target. The reason for this choice is as follows: 5-membered rings are the easiest to form. In contrast 6-membered rings, despite being more stable, are less kinetically favourable than 5-membered rings, therefore are often slow to form.⁸⁴ Compounds containing an internal C-C double bond were selected to avoid competing reactions via π -allyl complexes (as discussed in the previous section).^{80,81} In addition, internal alkenes possess hydrogen atoms in the necessary positions to facilitate β -hydride elimination. The retrosynthetic routes outlined in Scheme 2.3 show that allylic and homoallylic alcohols are an ideal starting point for synthesising the desired substrates. We decided to centre our attention on synthesising isoxazolidines as the group already had methodology in place to synthesise enantioenriched secondary homoallylic alcohols.⁷⁰

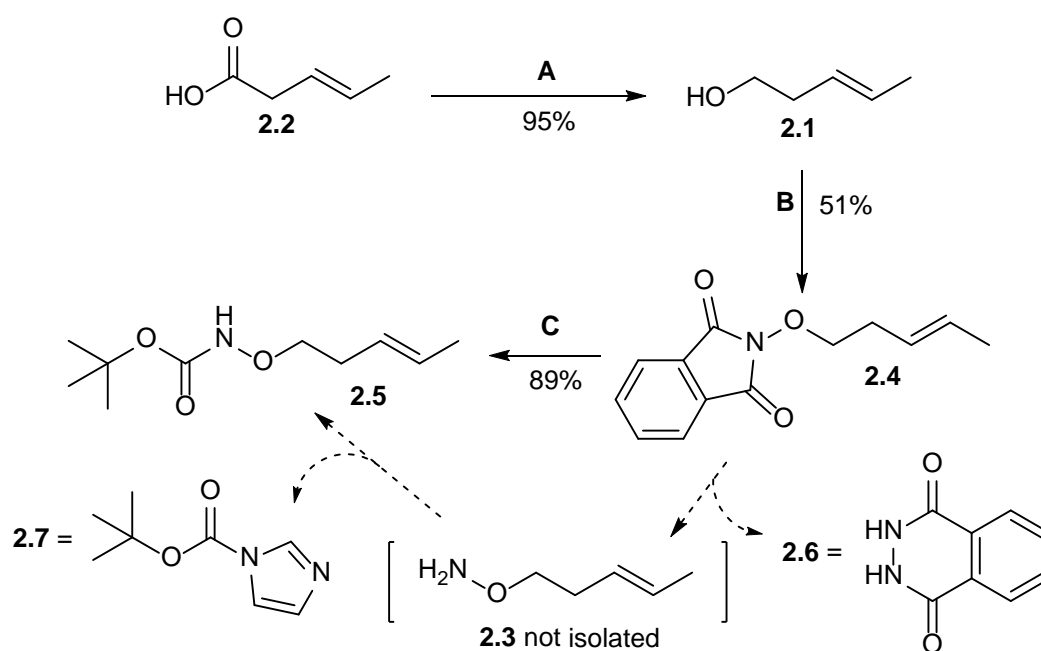


Scheme 2.3

We planned to accomplish the transformation of homoallylic alcohols to hydroxylamines via Mitsunobu protocol using *N*-hydroxyphthalimide as the nucleophile (Scheme 2.4).^{69,85} The desired *O*-alkyl hydroxylamines can be obtained by cleaving the phthalimide group with hydrazine; this is usually a straight forward and relatively quick reaction. Finally the nitrogen atom of the hydroxylamine is protected as a carbamate. There are two reasons for using a protecting group; firstly to prevent further reaction of the amine, in both the hydroxylamine and oxazolidine form. Secondly, having a carbamate group present would promote Pd-N

formation by providing coordination through the carbamate to Pd and hence favour a *cis*-AP route.

For screening reaction conditions, (*E*)-pent-3-en-1-ol **2.1** was chosen as a model substrate. Commercially available (*E*)-pent-3-enoic acid **2.2** was reduced to the corresponding alcohol using LiAlH₄ (Scheme 2.4, step A).⁸⁶ The alcohol was obtained in a respectable yield (95%), however care should be taken during isolation due to the volatility of the product.



A. LiAlH₄ (1.2 eq), THF, rt, overnight **B.** *N*-hydroxyphthalimide (1.2 eq), PPh₃ (1.2 eq), DIAD (1.2 eq), THF, rt, overnight **C.** i) N₂H₄·H₂O (5 eq), CH₂Cl₂, rt, 3 h ii) Boc₂O (1.2 eq), NaOH (2 eq), CH₂Cl₂/H₂O (9:1), rt, overnight iii) imidazole (5 eq), CHCl₃ (or CH₂Cl₂), rt, 30 min.

Scheme 2.4

Using the Mitsunobu protocol developed earlier in the group (Scheme 2.4, step B),⁸⁷ the alcohol was reacted overnight and after consumption of starting material which was observed using TLC, hydrazine was added to cleave the phthalimide, leaving the free hydroxylamine **2.3**. Following this sequence, after chromatographic purification, the resulting hydroxylamine contained significant amounts of Ph₃PO, which were co-eluting with the product. It was decided that phthalimide derivative **2.4** should be isolated before the addition of hydrazine, as

it is less polar than hydroxylamine **2.3** and PPh_3O (Fig 2.1), thus leading to an easier purification.

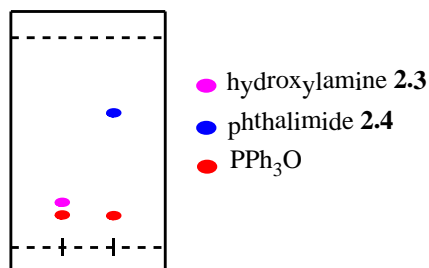


Figure 2.1

Due to volatility of hydroxylamine **2.3**, it was decided to carry out the Boc protection step immediately without isolation. The cleavage of **2.4** with hydrazine was completed after 3 hours stirring at room temperature. A white precipitate of phthalhydrazide **2.6** was removed by filtration and the solution of hydroxylamine containing excess hydrazine was reacted directly with Boc_2O (Scheme 2.4).

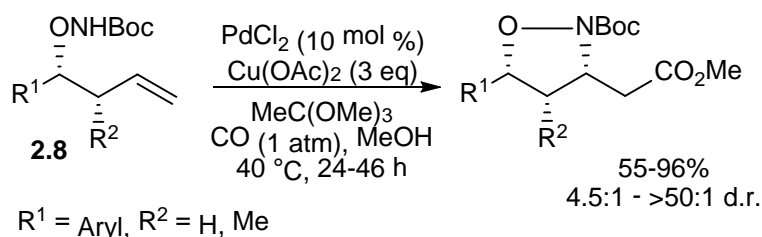
The Boc protection step^{87,88} proceeded with 100% conversion, however purification caused some issue. After column chromatography, the isolated **2.5** according to ^1H NMR spectroscopy contained a considerable amount of unreacted Boc_2O . Further chromatography proved unsuccessful in removing this impurity, so an alternate strategy was employed. Imidazole has been shown to readily react with Boc_2O at room temperature, and the high polarity of the product **2.7** allows for easy separation from the target compound.⁸⁹ Five equivalents of imidazole were added to the mixture of **2.5** and Boc_2O in CH_2Cl_2 or CHCl_3 . After the excess Boc_2O was consumed (monitored by TLC developing with vanillin dye), any leftover imidazole was removed by an aqueous wash. The *N*-Boc-hydroxylamine **2.5** was isolated with ease by column chromatography. Scheme 2.4 outlines the final procedure for generating the desired *N*-Boc-hydroxylamine **2.5** from a commercially available acid **2.2**.

With the optimal conditions for synthesising model compounds in place and the substrate in hand, focus was now be turned to screening reaction conditions.

2.2.2. Screening Conditions for Wacker-Type Oxidative Amination

As outlined in chapter 1, it is evident that a range of different conditions can be used to facilitate Wacker-type oxidative cyclisations. A source of Pd^{II} is required, often in conjunction with a ligand, in order to successfully proceed via an aminopalladation mechanism. Often, different additives are employed taking on different roles, e.g. buffering pH or promoting β -hydride elimination. Most commonly, toluene and THF are used as the solvents for these reactions, for their elevated temperature tolerance and compatibility with organometallic compounds respectively.

Table 2.1 outlines the development of the optimal conditions for Wacker-type oxidative cyclisation of **2.5**. As a starting point, the conditions developed by the Malkov group used in the carbonylative cyclisation of **2.8** (Scheme 2.5) were used without the atmosphere of CO, MeOH and MeC(OMe)₃ (Table 2.1, entry 1).^{28,87}

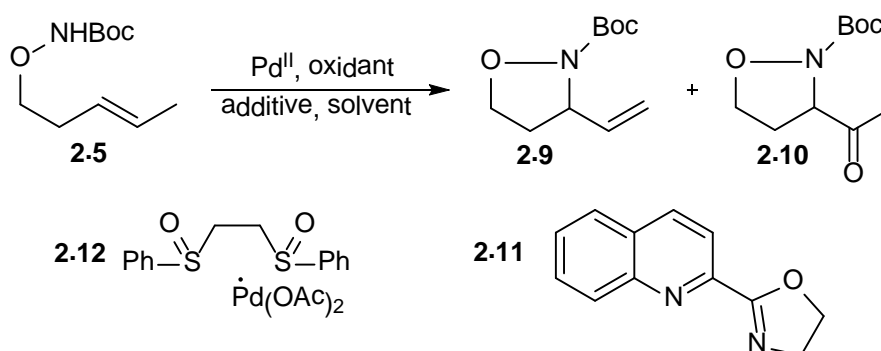


Scheme 2.5

Pd(OAc)₂ (10 mol %) and Cu(OAc)₂ (3 eq) were heated to 60 °C with **2.5** in MeCN under an inert atmosphere. The reaction was run overnight for 16 h. The ¹H NMR spectrum of the crude mixture was surprisingly clean, indicating the presence of **2.9** in 95% conversion, the remaining material was the starting hydroxylamine **2.5**. Column chromatography yielded isoxazolidine **2.9** (85%) isolated as a clear oil. It was a good start, however drawbacks such as the incomplete conversion had to be addressed. Furthermore, using 10 mol % of Pd^{II} and 3 equivalents of Cu^{II} salts is not ideal should the reaction be scaled up for industrial purposes. Although an elevated temperature is not impractical it is often preferable to be avoided. Running the reaction at room temperature (entry 2), slowed the conversion significantly (11% after 16 h), however no Pd black was observed and the catalyst remained active albeit slow.

Lowering the loading of Cu(OAc)₂ oxidant to 30 mol % (entry 3) gave a better result, however conversion still remained slow (69% after 16 h). Oxygen (1 atm) was introduced into the system (entry 4), to speed up the re-oxidation process, similar to the known Wacker processes.³ Surprisingly, ketone **2.10** was obtained as the sole product (20% after 16 h), it was unclear whether the product of Wacker oxidation was formed after β-hydride elimination with the free alkene or before with the Pd-alkyl intermediate. Using Pd(MeCN)₂Cl₂ and QUINOX ligand **2.11** led to an increase in the amount of **2.10** formed (entry 5). Submitting cyclised alkene **2.9** to the conditions in entry 5 gave a very slow conversion to ketone **2.10** (<5% after 16 h), which indicated that the active Pd species involved in forming ketone **2.10** are formed during the cyclisation of **2.5**. It was clear that the combination of Cu^{II} and O₂ was leading to the formation of this undesired ketone, so in an attempt to avoid from this side reaction, molecular oxygen was used as the sole oxidant. This also addressed the high loading of Cu^{II} in the reaction. Reverting back to the initial conditions and exchanging Cu for O₂ (entry 6) yielded poor results. Using toluene at 80 °C (entry 7) had no great effect on the conversion, even when NaOAc was introduced to promote Pd-N formation.¹⁵ In DMSO and THF (entries 8-9) the conversion showed little change.

Table 2.1.^(a)



	Pd^{II} (mol %)	Oxidant (eq)^(b)	Solvent	Additive (eq)	Temp. (°C)	Conv. (%)^(c)
1	Pd(OAc) ₂ (10)	Cu(OAc) ₂ (3)	MeCN	None	60	2.9 95 ^(d)
2	Pd(OAc) ₂ (10)	Cu(OAc) ₂ (3)	MeCN	None	rt	2.9 11
3	Pd(OAc) ₂ (10)	Cu(OAc) ₂ (0.3)	MeCN	None	60	2.9 69
4	Pd(OAc) ₂ (10)	Cu(OAc) ₂ (0.3)/O ₂	MeCN	None	60	2.10 20
5	Pd(MeCN) ₂ Cl ₂ (5)	Cu(OAc) ₂ (0.3)/O ₂	MeCN	2.11 (0.4)	60	2.10 50
6	Pd(OAc) ₂ (10)	O ₂	MeCN	None	60	2.9 29
7	Pd(OAc) ₂ (10)	O ₂	PhMe	NaOAc (0.2)	80	2.9 34
8	Pd(OAc) ₂ (10)	O ₂	DMSO	NaOAc (0.2)	60	2.9 37
9	Pd(OAc) ₂ (10)	O ₂	THF	NaOAc (0.2)	60	2.9 36
10	Pd(OAc) ₂ (5)	O ₂	THF	NaOAc (0.2)/ DMSO (0.1)	rt	2.9 100 ^(e)
11	2.12 (10)	O ₂	THF	NaOAc (0.2)	rt	2.9 39
12	Pd(OAc) ₂ (5)	O ₂	THF	NaOAc (0.2)/ DMF (0.1)	rt	2.9 52
13	Pd(OAc) ₂ (5)	O ₂	MeCN	NaOAc(0.2)/ DMSO (0.1)	rt	2.9 35

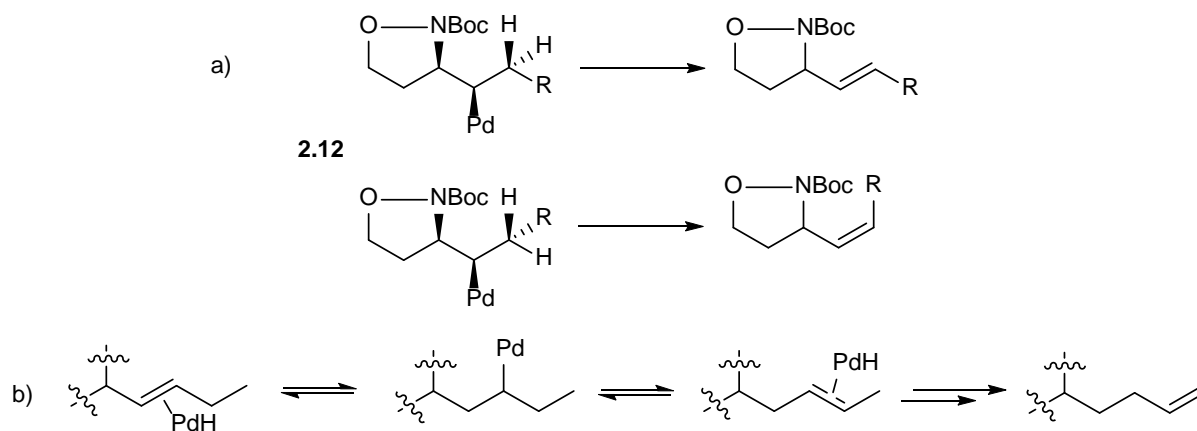
(a) Conditions: **2.5** (0.25 mmol), solvent 3 mL, 16 h. (b) The flask was flushed with O₂, before a balloon (1 atm) of O₂ was applied. (c) Conversion was estimated using ¹H NMR and the ratio of SM **2.5**: product **2.9(2.10)**. (d) Isolated yield 85%. (e) Isolated yield 98%.

The best results were obtained with the introduction of DMSO (10 mol %) as an additive (entry 10), resulting in a clean, complete conversion and an isolated yield of 98%. The complex $\text{Pd}(\text{DMSO})_2(\text{OAc})_2$ has been studied by Stahl.⁹⁰ DMSO, as a ligand to Pd, in this catalyst system has been shown to promote the oxidation of Pd^0 to Pd^{II} by molecular O_2 . Interestingly when DMSO was used as a solvent, the reactivity dropped considerably. Hence, the excess DMSO deactivates the catalytic system to some extent, creating the necessity for correct stoichiometry. Use of the bis-sulfoxide catalyst **2.11** introduced by White gave an inferior conversion (entry 11). Replacing DMSO with DMF (entry 12) and THF with MeCN (entry 13) also proved detrimental.

The conditions outlined in entry 10 were taken as the optimal, fitting the desired criteria of a low Pd loading, use of molecular O_2 as an oxidant, with the reaction proceeding cleanly overnight at room temperature. With these conditions in hand, we set to establish the scope and the limitations of the intramolecular cyclisation of *N*-Boc homoallylic hydroxylamines.

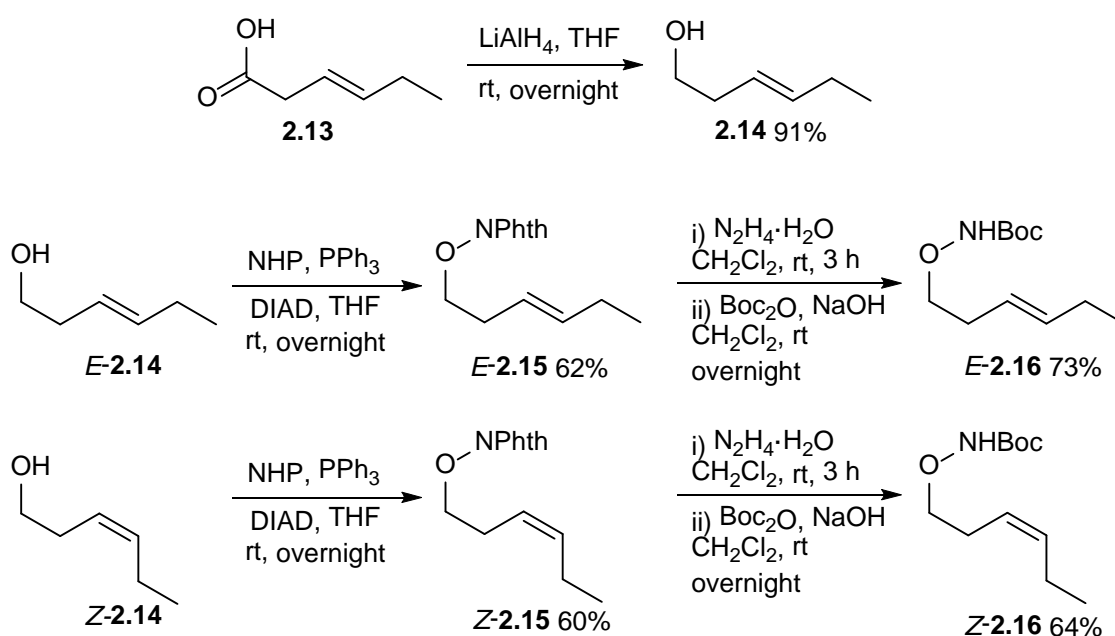
2.2.3. Investigating Longer and Functionalised Alkyl Chains

Our model substrate contained an internal alkene that produced a terminal alkene once the substrate had cyclised and undergone β -hydride elimination. As a further extension of the method, substrates that would yield internal alkenes after β -hydride elimination were investigated next where the formation of different isomers can be envisioned (Scheme 2.6).



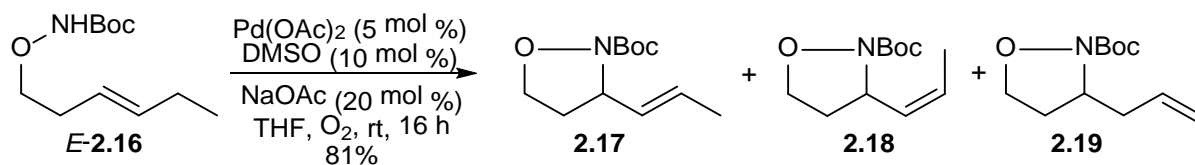
First, there is the possibility of reforming the C=C double bond in either *E* or *Z* configuration (Scheme 2.6a). In the intermediate **2.12**, C-C bond rotation is fast, so there is the chance for β -hydride elimination to yield one of two isomers. The *E*-isomer is likely favoured as it does not suffer the steric interactions that *Z*-isomer does. Secondly, re-addition/elimination of Pd-H can lead to a shift of the double bond. The combination of these two isomerisation pathways could potentially give rise to a large amount of undesired side products.

First, substrate *E*-**2.16** was tested. It was synthesised from commercially available (*E*)-hex-3-enoic acid **2.13** as shown in Scheme 2.7 following the protocol developed earlier for the model substrate.



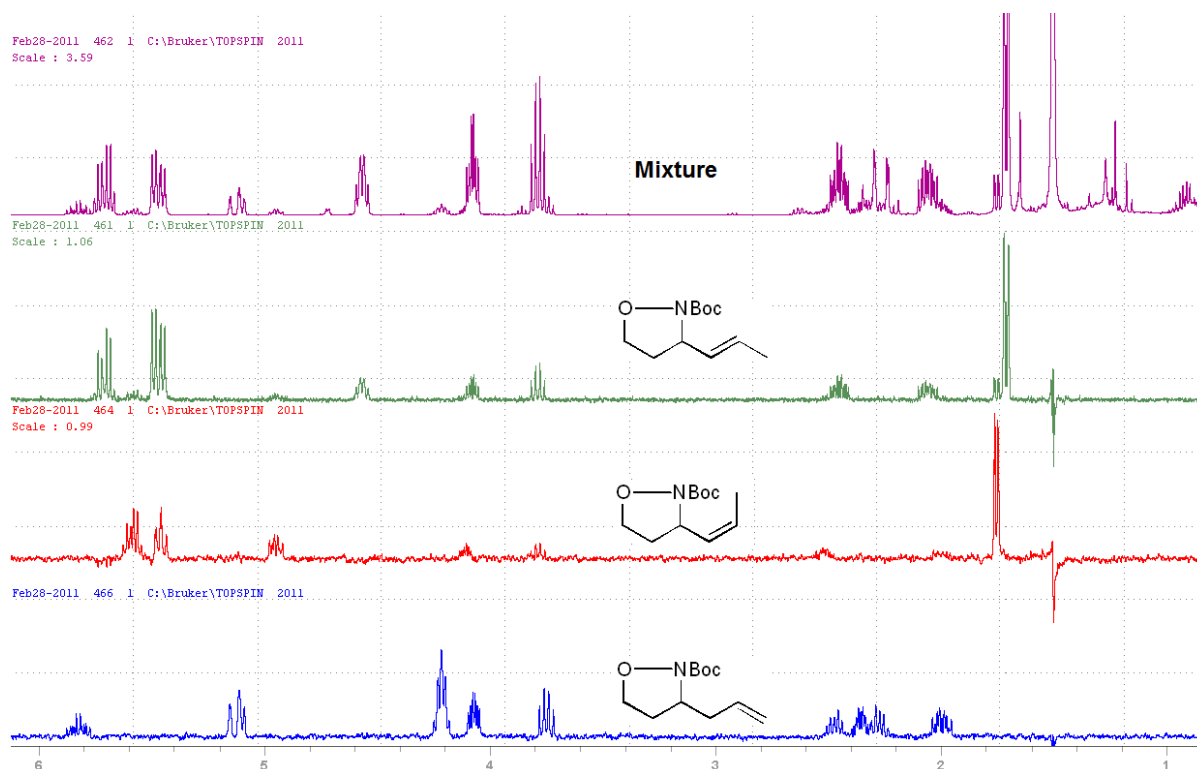
Scheme 2.7

E-**2.13** was submitted to the optimal reaction conditions and a mixture of isomers **2.17-2.19** was isolated as a single fraction by column chromatography in 81% overall yield. Initial analysis of the ^1H NMR showed both major and minor signals in both the alkane and alkene regions, the major signals were indicative of an internal alkene, whereas the minor signals suggested the presence of a terminal alkene and another internal alkene (Scheme 2.8).



Scheme 2.8

Using TOCSY (Total Correlation Spectroscopy) NMR spectroscopy the major and minor signals were separated into separate spectra, which were used to confirm the structures of the 3 isomers (Figure 2.2).



* The *t*-Boc peaks are not shown, as the resonance effect between the irradiated proton and the C(CH₃)₃ part of the *t*-Boc group is diluted.

Figure 2.2

The major isomer corresponds to the isoxazolidine **2.17**, the minor components were confirmed as the isoxazolidines **2.18** and a terminal alkene **2.19**. Using integrations of the peaks corresponding to C-4/5 in each of the isomers, an approximation of the ratio of products was determined as 22:1.7:1 (*E*:*Z*:terminal) (Figure 2.3).

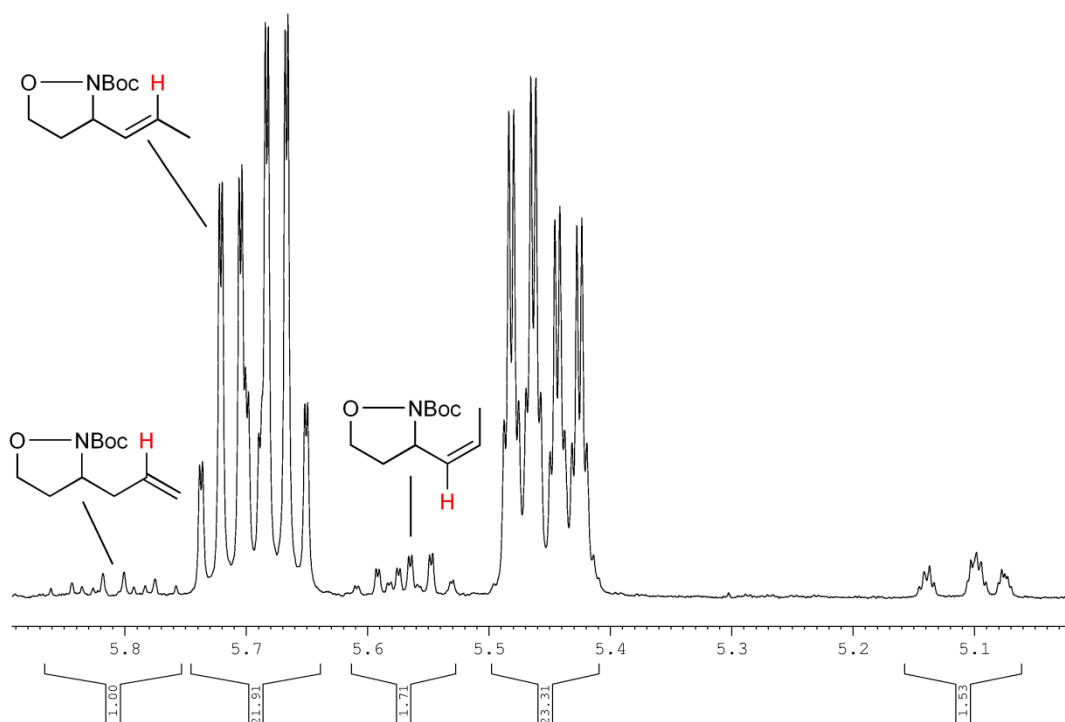


Figure 2.3

The isomer ratios depending on the Pd sources used in the reaction are shown in Table 2.2.

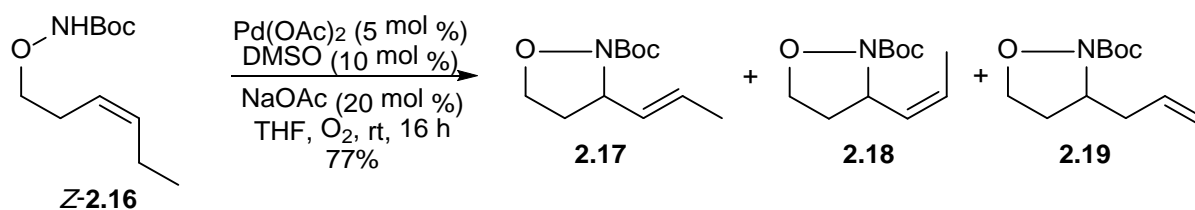
Table 2.2

	Pd^{II} source (5 mol %)	Isolated yield (%)	Ratio of isomers (<i>E</i>:<i>Z</i>:terminal)
1	Pd(OAc) ₂	81	13:1:trace
2	PdCl ₂	54	3:trace:2
3	Pd(TFA) ₂	79	13:1:trace

Changing to Pd(TFA)₂ (entry 3), gave similar results to the initial observation, however changing the Pd source to PdCl₂ (entry 2) produced a 3:2 ratio of the *E*-isomer and the terminal alkene, in 54% yield. It may suggest that Pd-H in this instance does not dissociate

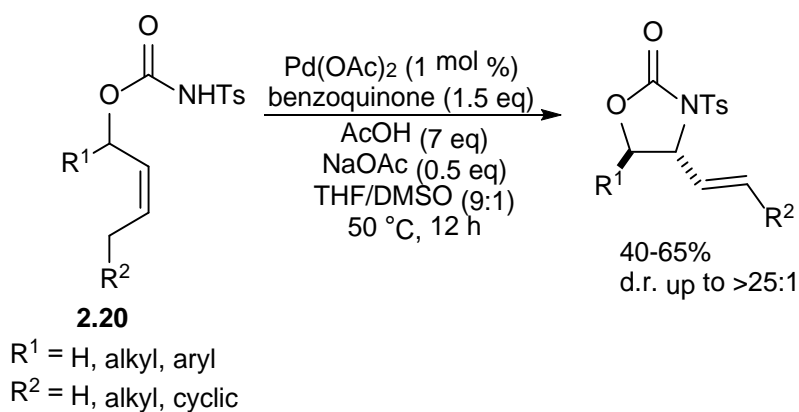
from the newly formed alkene as quickly as it does when Pd(OAc)₂ or Pd(TFA)₂ are used, hence reinsertion and subsequent β-hydride elimination yields the shifted alkene. The reason PdCl₂ facilitates this transformation is unclear, however potentially the problem could be that Pd⁰ species formed from PdCl₂ is not oxidised as fast as that from Pd(OAc)₂, hence the lifetime of PdH is longer, leading to an increased probability of it being reinserted into the alkene. This hypothesis is supported by the fact that the overall conversion was poor, assuming the Pd oxidation step is the limiting factor.

The next step was to test whether *Z*-alkenes yielded the same major products. The corresponding *Z*-homoallylic hydroxylamine **Z-2.16** was synthesised in the usual manner from commercially available (*Z*)-hex-3-en-1-ol **Z-2.14** (See Scheme 2.7). When this substrate was submitted to the oxidative amination conditions, the conversion was complete overnight. Analysis by ¹H NMR spectroscopy revealed that the ratio of products **2.17-2.19** was exactly the same as that obtained for the *E*-substrate (22:1.7:1, *E*:*Z*:terminal) (Scheme 2.9).



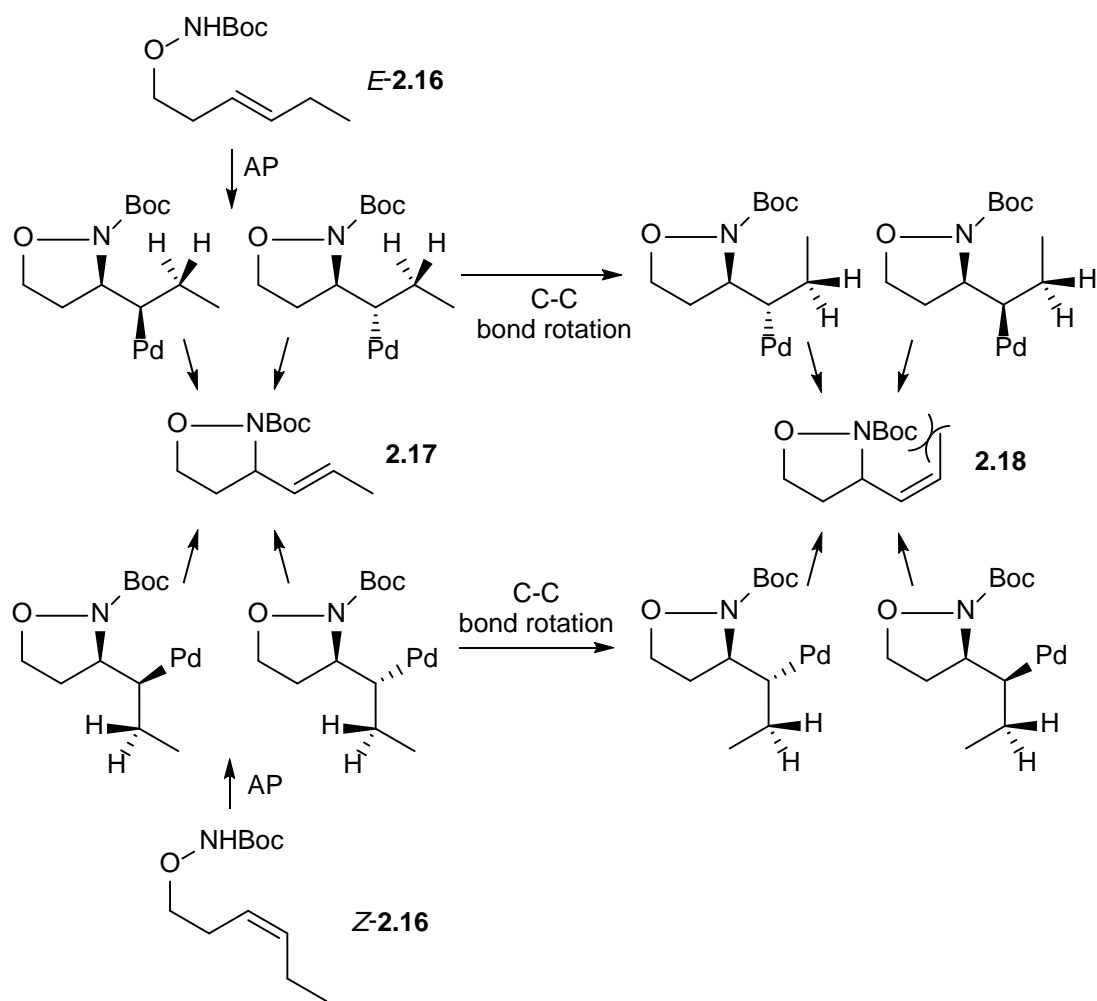
Scheme 2.9

The reaction conditions tolerate both *E* and *Z* alkenes without any major deterioration in yield, unlike allylic tosylcarbamates **2.20** reported by Bäckvall that only show practical reactivity with *Z*-alkenes (Scheme 2.10).¹⁸



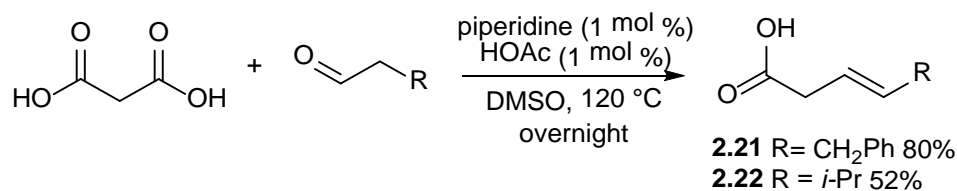
Scheme 2.10

The preference for forming the *trans*-alkene **2.17** can be rationalised by observing the positions of the hydrogen atoms relative to Pd in each case (Scheme 2.11). As is well known, Pd and H must be on the same face for β -hydride elimination to occur. When *E*-**2.16** and *Z*-**2.16** are cyclised both *E*- and *Z*-isoxazolidines can be formed regardless of aminopalladation pathway. The preference for the formation of **2.17** is likely from the increased stability of the *E*-isomer over the *Z*. Secondly the conformation for β -hydride elimination that gives **2.17** is less sterically congested than that of **2.18**, which suffers from interactions between the Boc and Me groups.



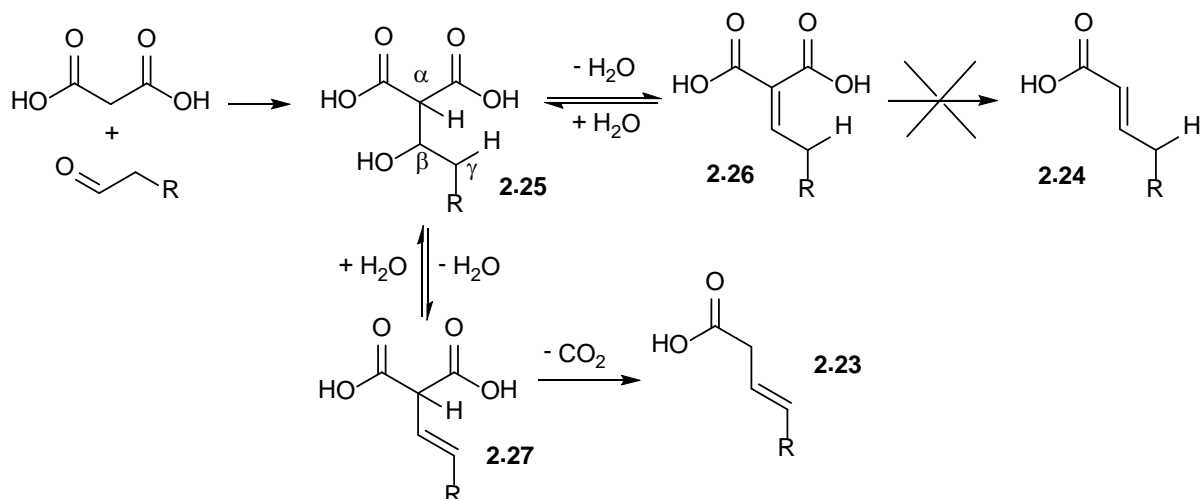
Scheme 2.11

After investigating the effect of β -hydride elimination on *E* and *Z* alkenes, it was decided to examine substrates that are sterically encumbered around the β -hydrogen to determine how it would affect the β -hydride elimination step. Using a modified Knoevenagel condensation, (*E*)-3-alkenoic acids could be synthesised from malonic acid and the desired aldehyde (Scheme 2.12).⁹¹



Scheme 2.12

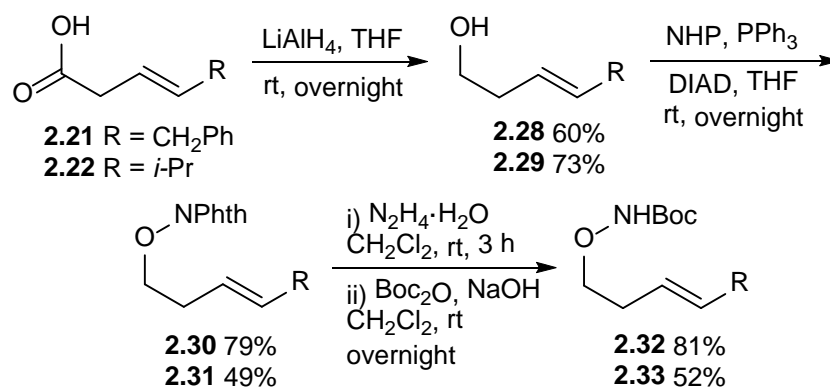
The Knoevenagel condensation proceeded without any problems and no by-products were observed. Ragoussis proposed a mechanism to explain why β,γ -acid **2.23** is formed in preference over α,β -acid **2.24** (Scheme 2.13).^{91b} Piperidine and acetic acid form piperidinium acetate which facilitates the reversible dehydration of **2.25**, leading to the formation of **2.26** and **2.27**. The α,β -malonic acid **2.26** cannot in this case undergo decarboxylation, but is instead isomerised to **2.27** through rehydration. At an elevated temperature (>100 °C) β,γ -malonic acid **2.27** can undergo irreversible decarboxylation yielding the desired β,γ -acid **2.23**.



Scheme 2.13

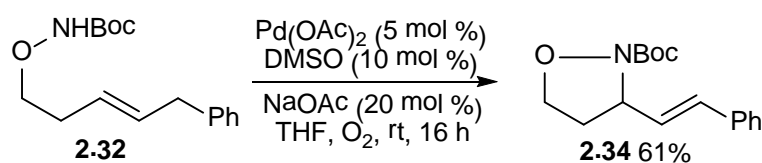
The desired acids, which were isolated in modest to excellent yields, were then subjected to the usual transformations that yielded the substrates required for oxidative amination (Scheme 2.14).

The phenyl substrate **2.32** was chosen due to its position relative to the β -hydrogens. Having the aromatic ring in conjugation with this position could affect the β -hydride elimination step.



Scheme 2.14

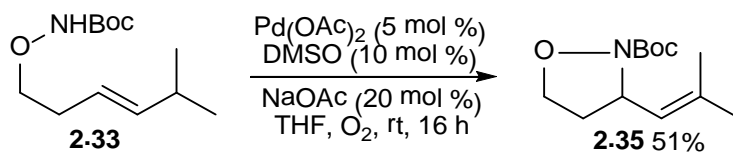
Submitting **2.32** to the amination conditions for 16 h yielded the expected product **2.34**, isolated in a moderate yield (61%) (Scheme 2.15). The remaining material may have suffered from decomposition as no remaining starting material or by-products were observed in the ¹H NMR spectrum of the reaction mixture. This slower conversion is perhaps the result of steric interactions between Pd and the nearby Ph group.



Scheme 2.15

The second of these bulkier substrates investigated contains an *iso*-propyl group, the hydrogen atom of which is in the β -position with respect to where Pd addition will occur. This substrate was exposed to the amination conditions, and after 16 h the expected product **2.35** was obtained (isolated yield 51%) (Scheme 2.16). Once again, the reaction suffered

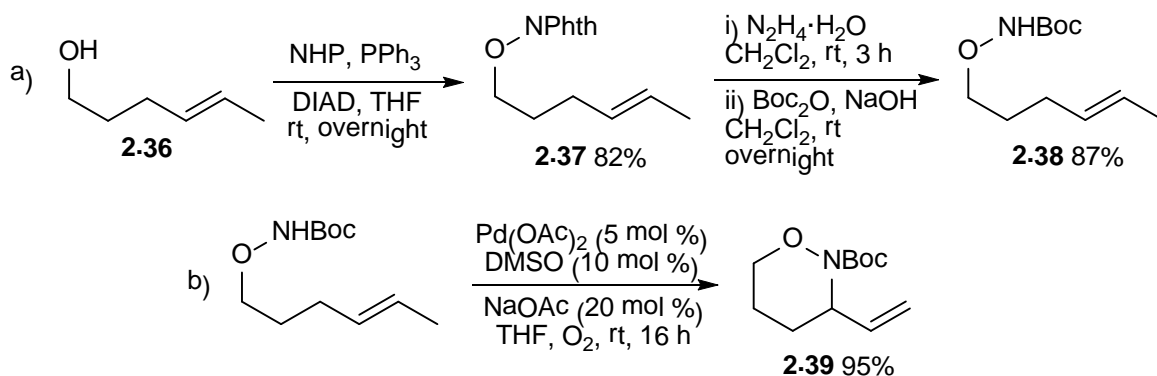
deterioration in conversion, no left over starting material or by-products were observed in the ^1H NMR spectrum of the crude reaction mixture.



Scheme 2.16

The Pd-alkyl intermediate that arises from **2.33** contains a significant amount of steric bulk around the Pd atom, and it does only contain only one β -hydrogen (Scheme 2.16). The increased steric bulk around the β -hydrogen can suffer interactions with the Boc group.

In the final modification to the alkyl chain, the position of the double bond within the chain was altered. Moving the alkene further along the chain could potentially open up a route to larger ring sizes, and in turn give amino alcohols with greater distance between OH and NH_2 . Using commercially available (*E*)-hex-4-en-1-ol **2.36**, the relevant hydroxylamine **2.38** was synthesised via the usual methodology (Scheme 2.17a) and submitted to the oxidative amination conditions for 16 h (Scheme 2.17b).

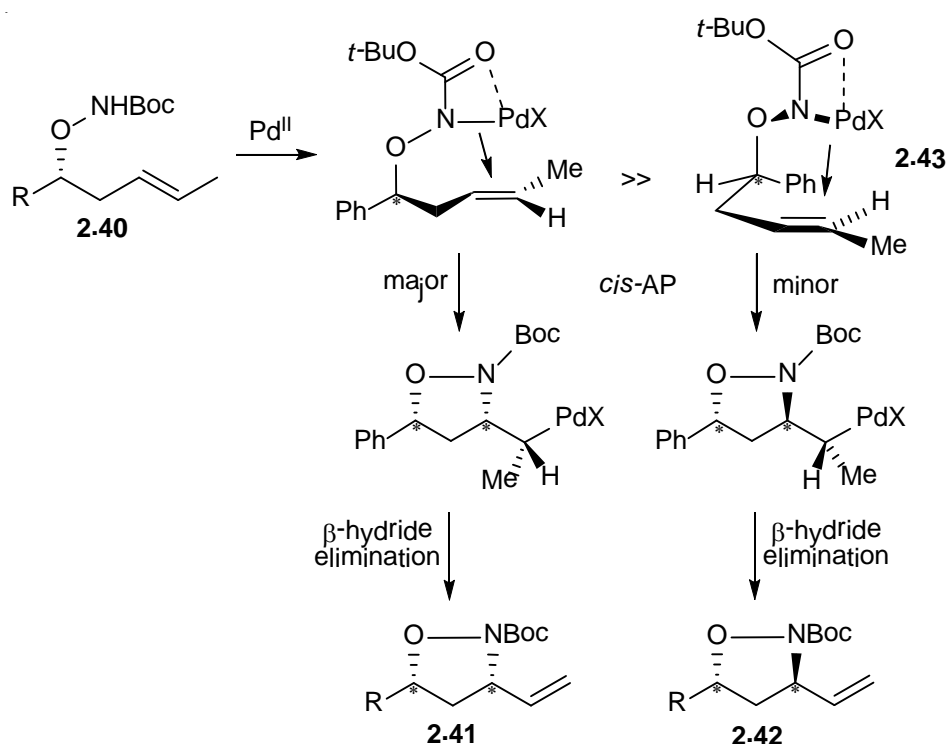


Scheme 2.17

Analysis of the crude reaction mixture after 16 h revealed a complete and clean conversion to the expected tetrahydro-1,2-oxazine **2.39**, which after chromatography was isolated in 95% yield. This outstanding result opened up the possibility of synthesising 1,4-amino alcohol precursors. This reaction, with its excellent conversion, highlighted the preference for the formation of terminal alkenes in this type of substrate. Interestingly only a few examples of similar type cyclisations yielding 1,4-substrates exist in the literature,⁹² however none of these methods use a Pd catalysed Wacker-type cyclisation. Overall, this result means there is the possibility that rings larger than 6 can be synthesised in this manner, however 7, 8 and 9 membered rings are harder to form. Also, when forming larger rings, reactive intermediates run the risk of reacting with another molecule of substrate before the intramolecular cyclisation can be completed. Problems aside, there is a great deal of future work that could be explored here.

2.2.4. Investigating Diastereoselectivity and Mechanistic Aspects

It is well documented that these types of Pd transformations can yield high diastereoselectivities. This is often the result of a single aminopalladation pathway operating within the reaction system. In order to investigate this further, enantioenriched secondary substrates **2.40** (Scheme 2.18) were selected. The cyclisation of these substrates can in theory produce two isomers; *syn* **2.41** and *anti* **2.42**.

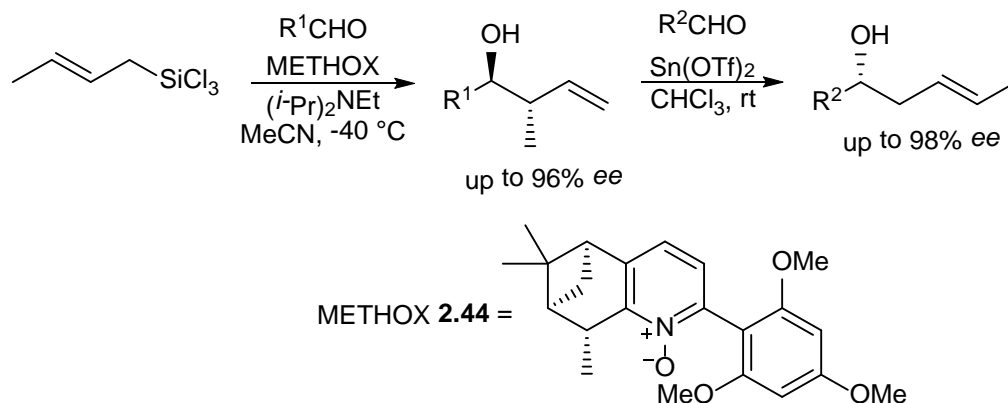


Scheme 2.18

Looking at transition state models of the two possible configurations of **2.40** reveals that the formation of *syn* **2.41** is favoured and cyclisation on the opposite face **2.43** generates a 1,3-strain in the molecule (Scheme 2.18).

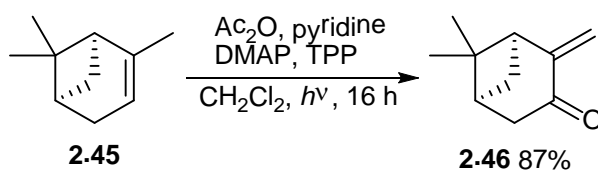
In order to synthesise the desired chiral *N*-Boc homoallylic hydroxylamines **2.40**, a route to chiral homoallylic alcohols was required. The Malkov group has also developed a route to (*E*)-homoallylic alcohols, utilising a combination of asymmetric crotylation followed by a Lewis acid catalysed allyl transfer (Scheme 2.19).^{70b} Pyridine *N*-oxide catalysts developed by

Malkov and Kočovský have proved successful in asymmetric allylation reactions.⁹³ This method was initially chosen for synthesising chiral (*E*)-homoallylic alcohols, however it did prove troublesome in several areas.



Scheme 2.19

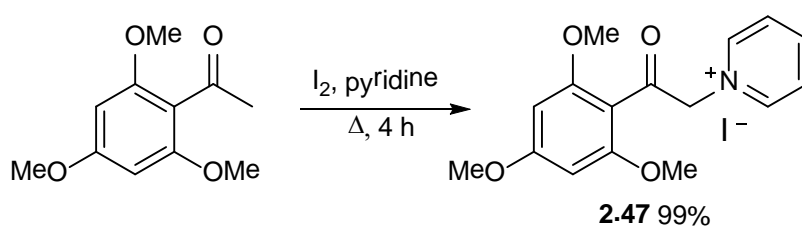
The requisite chiral pyridine *N*-oxide catalyst METHOX **2.44** for the asymmetric allylation step had to be synthesised from commercially available (+)- α -pinene **2.45** employing a 5 step protocol. In the first step (+)- α -pinene **2.45** was converted to pinacarvone **2.46** using a singlet oxygen reaction (Scheme 2.20).



Scheme 2.20

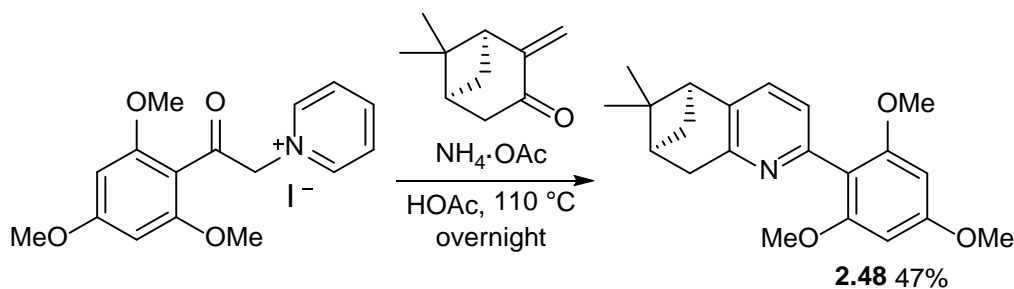
Initially this reaction was carried out in a custom glass reaction vessel, which had a cold water jacket to cool the reaction mixture. However this method proved tiresome as the reaction required constant monitoring, due to rapid evaporation of dichloromethane from the vessel caused by the intense heat given off by the 400W lamp. Reaction conversion was

monitored by ^1H NMR spectroscopy, and starting material was no longer present after 12 h. The isolated yield of **2.46** was a disappointing 21%. A vast improvement to this method was achieved by using a custom continuous flow system. The reaction mixture saturated by a gentle stream of oxygen was pumped around the system in a loop passing through a ‘cold’ lamp, which provided irradiation. This method did not require any attention once it was running and proved to be a lot safer, as the lamps did not generate any significant heat, and the volume of material passing through the light was kept to a minimum. The isolated yield of **2.46** was greatly increased when using this method (87%).



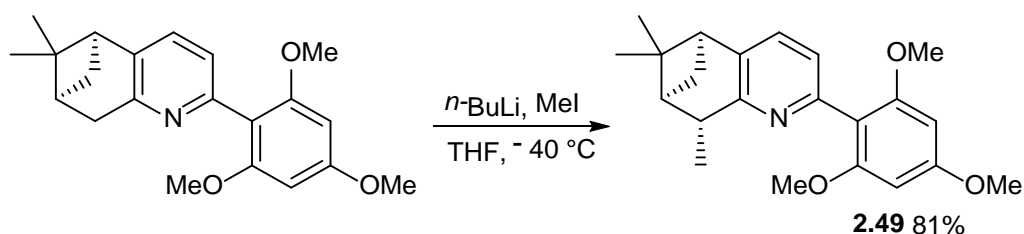
Scheme 2.21

The second step was the preparation of Kröhnke salt **2.47**. This step proceeded without any trouble and the salt was prepared in quantitative yield after 4 h (Scheme 2.21). With **2.46** and **2.47** in hand, they were combined to form the desired pyridine using Kröhnke conditions (Scheme 2.22). Purification of the reaction mixture proved to be a lengthy process, due to the presence of several complex by-products formed by the harsh reaction conditions. The pyridine **2.48** was eventually isolated in 47% yield.



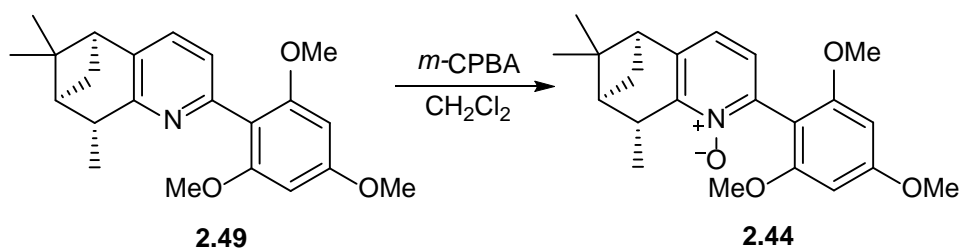
Scheme 2.22

Introducing a methyl group onto the pinene portion of the molecule is again a step that proved to be more difficult than the literature suggested. Deprotonating pyridine **2.48** with LDA and treating with MeI, is a relatively straight forward approach in theory, however in practice the reaction was suffering from an incredibly poor yield (10%). The remaining material contained mostly unreacted starting material and some complex by-products. It was suspected that the starting pyridine **2.48** contained traces of water that was neutralising LDA, so several measures were introduced to ensure all moisture was removed from the reaction. Pyridine **2.48** was placed in toluene and evaporated to dryness 3 times to azeotropically remove water. MeI was stirred in dry THF with molecular sieves for 3 h before use. Diisopropylamine was distilled over CaH before it was used to form LDA *in situ*. However even with these measures, no increase in yield was observed. Using commercially obtained LDA gave no improvement in yield. It was noted that LDA formed *in situ* was made by a mixture of diisopropylamine and *n*-BuLi (1:1.1), the leftover 0.1 eq of *n*-BuLi may be responsible for deprotonating the pyridine leading to the constantly observed 10% yield. When straight *n*-BuLi (1.1 eq) was used in the reaction, then the desired methylated pyridine **2.49** was obtained as the major product (isolated yield 81%) (Scheme 2.23).



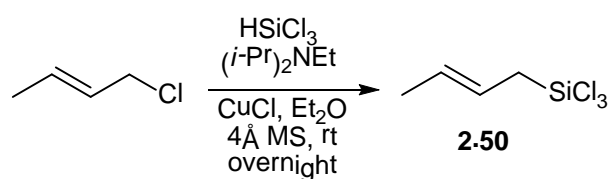
Scheme 2.23

The final step was to oxidise the pyridine **2.49** to a pyridine *N*-oxide with *m*-CPBA, this proceeded as expected with a moderate yield of 46% (Scheme 2.24).



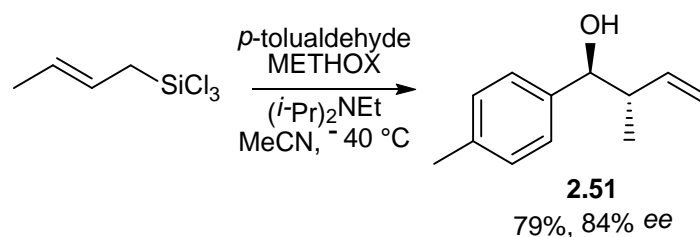
Scheme 2.24

After the synthesis of METHOX **2.44**, crotyl trichlorosilane **2.50** was synthesised from crotyl chloride (Scheme 2.25). Once again this synthesis was not straight forward as the silane **2.50** is extremely moisture sensitive. HSiCl_3 was added to a dried flask of crotyl chloride, Hünig's base, CuCl and 4Å MS, the reaction was left overnight.



Scheme 2.25

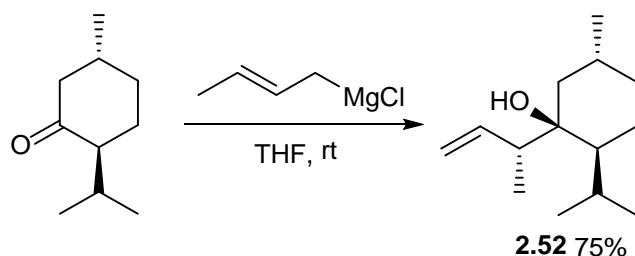
Once the starting material had been consumed (monitored by ^1H NMR spectroscopy), the reaction mixture was transferred to a separate dry flask via cannula to remove any solids. The reaction mixture was placed under a gentle vacuum to remove the excess Et_2O , and then heated lightly to separate the crotyl silane **2.50** from the excess HSiCl_3 and base (isolated yield was not recorded, instead the distilled silane was used in slight excess immediately). With METHOX and crotyl trichlorosilane in hand, the asymmetric allylation reaction could take place. Using *p*-tolualdehyde, the allylation took place with little problem and the desired alcohol **2.51** was isolated in 79% (Scheme 2.26).



Scheme 2.26

However, when **2.51** was submitted for chiral GC the observed *ee* was moderate and poorer than expected, compared to the literature (98% *ee*). The recovered METHOX had also been reduced back to the pyridine by the presence of trace amounts of HSiCl_3 . This disappointing result prompted a change in route, as synthesising METHOX was a lengthy process, and the allylation suffered a deteriorated *ee*.

An alternate route was found in the literature where the synthesis of enantioenriched secondary (*E*)-homoallylic alcohols was carried out by allyl transfer from an allyl menthol derivative **2.52** (Scheme 2.27).⁹⁴

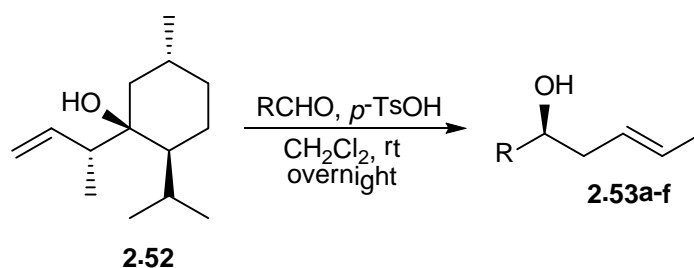


Scheme 2.27

This route only takes one step to form the chiral transfer reagent **2.52** and uses relatively cheap starting materials; crotyl chloride and (–)-menthone. However, the drawback of this method is that it requires a 2:1 stoichiometry of allyl transfer reagent to aldehyde, compared to the method reported by Malkov which takes place catalytically. The chiral transfer reagent was synthesised with ease, after forming crotyl magnesium chloride *in situ* and treating with (–)-menthone. The major diastereoisomer **2.52** was separated from any minor isomers and

impurities with column chromatography, and was isolated in 75% yield. With **2.52** in hand, the desired (*E*)-homoallylic alcohols could be synthesised. A range of aliphatic and aromatic aldehydes were converted into the corresponding homoallylic alcohols via a *p*-TsOH catalysed allyl transfer (Table 2.3). Aromatic aldehydes containing electron donating groups were avoided as they are known to cause racemisation during the Mitsunobu step.²⁸

Table 2.3

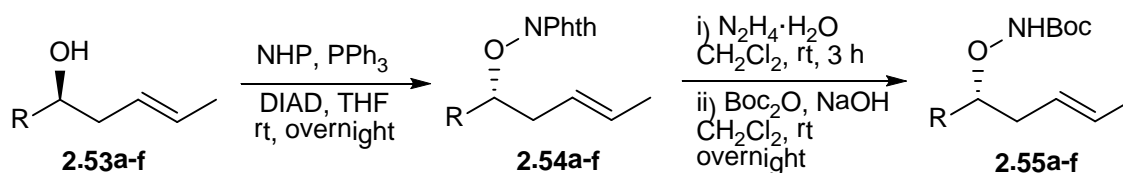


Entry	2.53	R =	Yield (%)	<i>ee</i> ^(a)
1	a	Ph	64	96
2	b	Bn	80	92
3	c	CH ₂ CH ₂ Ph	86	94
4	d	Cy	63	97
5	e	CH(Et) ₂	77	94
6	f	<i>n</i> -C ₆ H ₁₃	27	92

(a) Enantiomeric excess was determined by chiral HPLC (entry 1-2), chiral GC (entry 3-6) and by comparison to literature.^{70b, 94}

The allyl transfer reactions proceeded with good yields and gave excellent *ee*'s. The exception was **2.53f** which gave an unusually poor yield, however as the *ee* was sufficient and the amount of obtained material was enough to carry out subsequent transformations, it was decided that no further optimisation was necessary. The alcohol derivatives were then successfully converted into the corresponding hydroxylamines using the established methodology (Table 2.4).

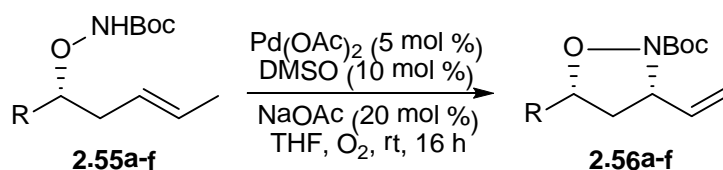
Table 2.4



Entry	R =	Phthalimide derivatives (2.54)	Yield (%)	Hydroxylamine derivatives (2.55)	Yield (%)
1	Ph	2.54a	51	2.55a	59
2	Bn	2.54b	57	2.55b	44
3	CH ₂ CH ₂ Ph	2.54c	40	2.55c	56
4	Cy	2.54d	29	2.55d	39
5	CH(Et) ₂	2.54e	19	2.55e	63
6	ⁿ C ₆ H ₁₃	2.54f	45	2.55f	43

Phthalimide derivatives **2.54a-f** were synthesised in moderate yields, with some of the alkyl derivatives (**2.54d-e**) suffering poor yields. The Mitsunobu reaction proceeds via an S_N2 mechanism, meaning that hydroxyphthalimide substitutes the hydroxyl group with inversion of stereochemistry. Malkov reported that the inversion of stereochemistry proceeds with extremely little or no loss in *ee*.^{28,87} The preservation of optical activity in compounds **2.54a-f** seemed to confirm that. Finally, the phthalimides **2.54a-f** were converted into the corresponding *N*-Boc hydroxylamines **2.55a-f**, which were obtained in moderate yields (Table 2.4). With these substrates finally available, the diastereoselectivity of the amination was tested.

Table 2.5



Entry	Isoxazolidine	R =	Yield (%)	d.r. ^{a,b}
	2.56			
1	a	Ph	98	>30:1
2	b	Bn	96	≈18:1
3	c	CH ₂ CH ₂ Ph	96	>30:1
4	d	Cy	96	>30:1
5	e	CH(Et) ₂	93	>30:1
6	f	ⁿ C ₆ H ₁₃	95	>30:1

(a) Ratio of *syn* and *anti* diastereoisomers was determined by ¹H NMR spectroscopy

(b) Ratios of >30:1 refer to instances in which the minor diastereoisomer could not be distinguished from the baseline of the ¹H NMR spectra.

The cyclisation of *N*-Boc hydroxylamines **2.55a-f** proceeded smoothly and with excellent yields (Table 2.5); as outlined previously the formation of terminal alkenes appears favoured over the formation of the internal ones. Analysis of ¹H NMR spectrum of the crude reaction mixture revealed the presence of only one diastereoisomer for the majority of the examples (the minor diastereoisomer could not be detected amongst the baseline noise) (Figure 2.4a). However, benzyl substituted isoxazolidine **2.56b** (Table 2.5, entry 2) showed a reduced but still credible 18:1 ratio of diastereoisomers (Figure 2.4b).

The formation of *syn*-isoxazolidines was confirmed by nOe (see appendix 5.3) and can be rationalised by looking at all possible modes of aminopalladation and the transition states involved with each. Each diastereoisomer can be formed by both *cis*- and *trans*-AP pathways, however based on the earlier results in the group and by others, *cis*-AP is most likely to be in operation (Scheme 2.28).^{21,22,28,31} It is speculated that the carbonyl adjacent to nitrogen is involved in the coordination of Pd to nitrogen, thus disfavouring the *trans*-AP approach.

Additionally, Stahl has provided evidence that suggests *trans*-AP is favoured in acidic reaction conditions, in which nitrogen deprotonation and Pd-N formation are not favoured.

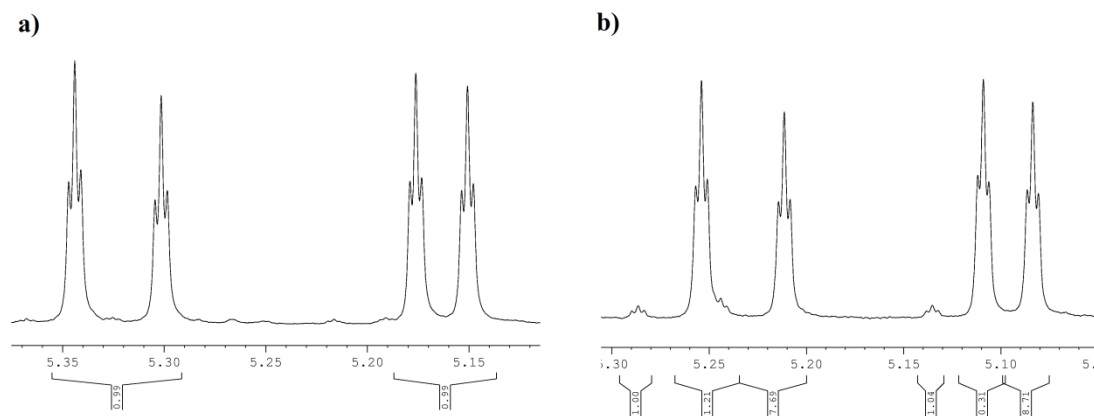
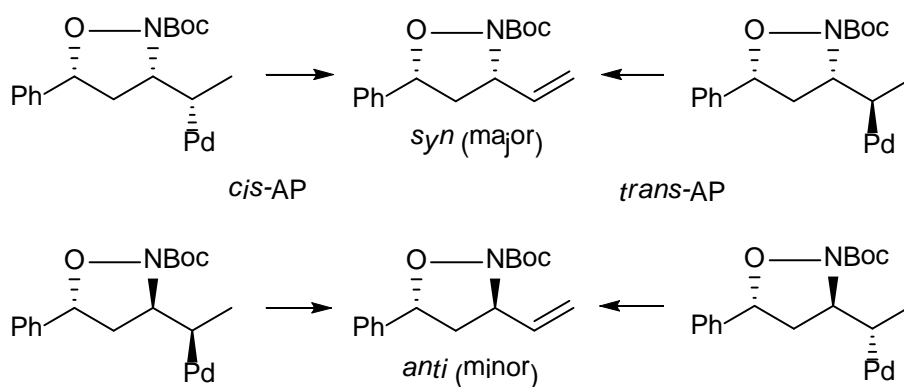
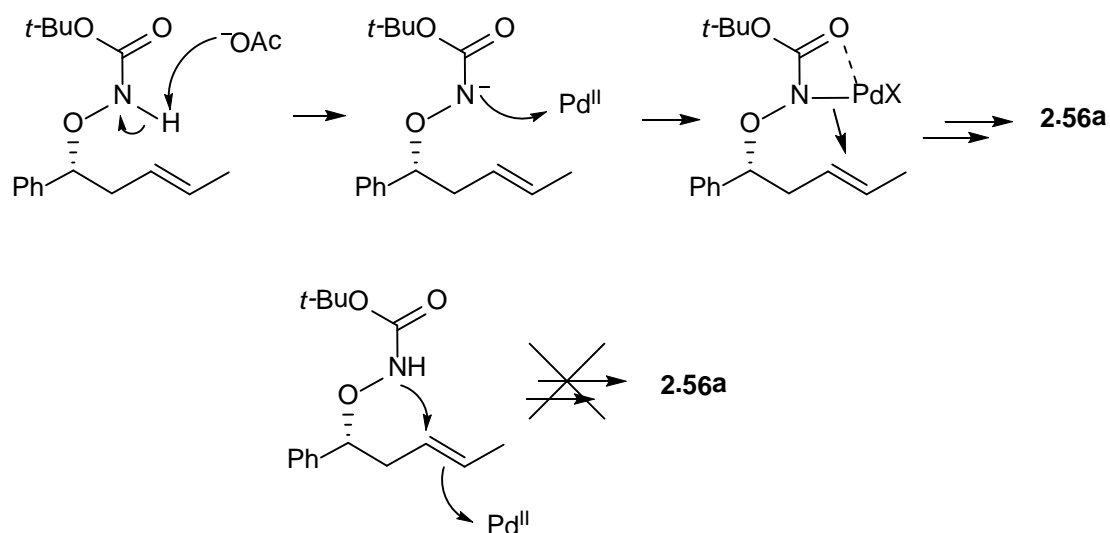


Figure 2.4. a) ^1H NMR showing single isomer, b) ^1H NMR showing 18:1 mixture



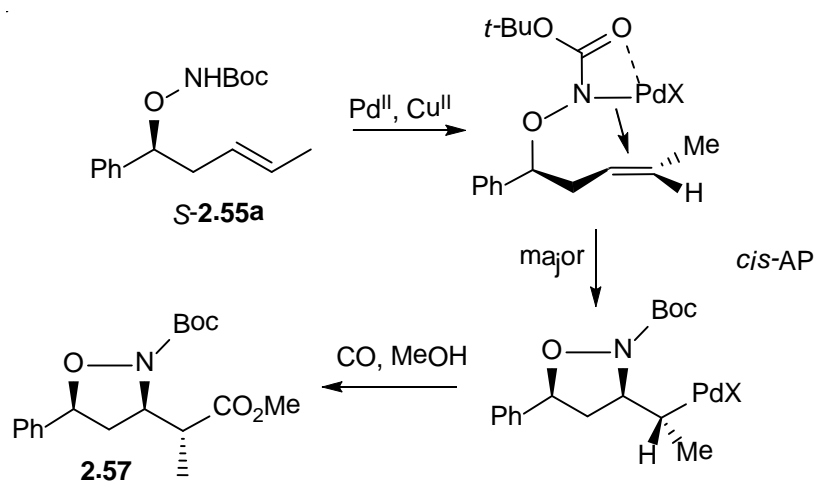
Scheme 2.28

The reaction developed in this study operates under mildly basic conditions, with the presence of NaOAc, which facilitates the deprotonation of the nitrogen nucleophile, and in turn leads to the formation of the Pd-N intermediate (Scheme 2.29). DMSO serves as a ligand to Pd and is necessary for the oxidation of Pd^0 by O_2 . Stahl has shown that $\text{Pd}(\text{OAc})_2$ and DMSO can form $\text{Pd}(\text{DMSO})_2(\text{OAc})_2$ *in situ*, where DMSO can be *O*- and/or *S*-bound. The more labile *O*-bound DMSO is likely to enable weakly coordinating L-type ligands access to the coordination sphere of Pd, i.e. in this case the carbonyl group of the Boc group. For the oxidation of Pd^0 , Stahl speculates that *S*-bound DMSO can coordinate to Pd^0 and essentially stabilise it by inhibiting aggregation into Pd black, thus allowing O_2 to oxidise back to Pd^{II} .^{90c}



Scheme 2.29. Proposed *cis*-AP reaction mechanism

A *cis*-AP pathway has been proved for carbonylative cyclisation of the same substrate **S-2.55a**, trapping the intermediate with CO and forming ester **2.57** (Scheme 2.30).²⁸

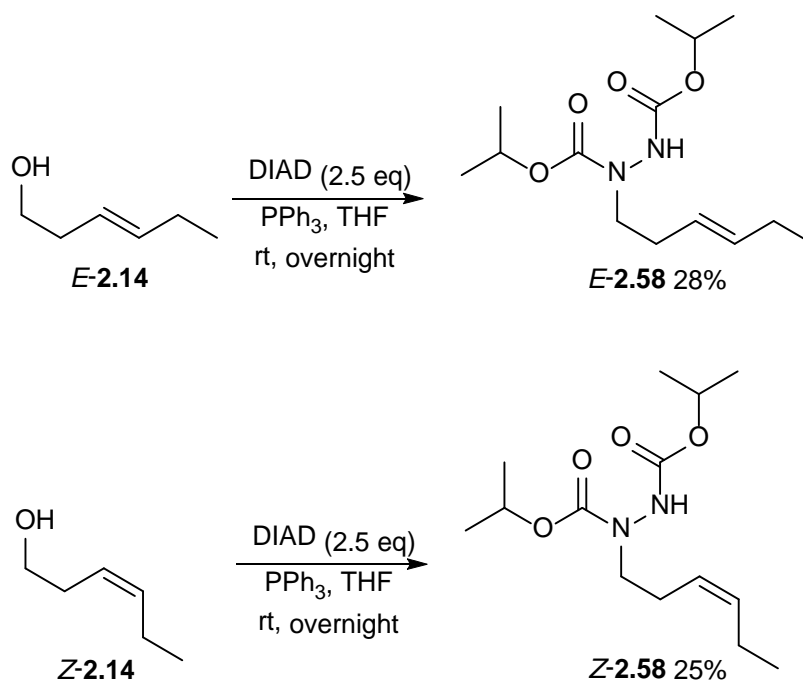


Scheme 2.30

In conclusion, *syn*-isoxazolidines have been obtained with high diastereoselectivities and excellent yields.

2.2.5. Pyrazolidines

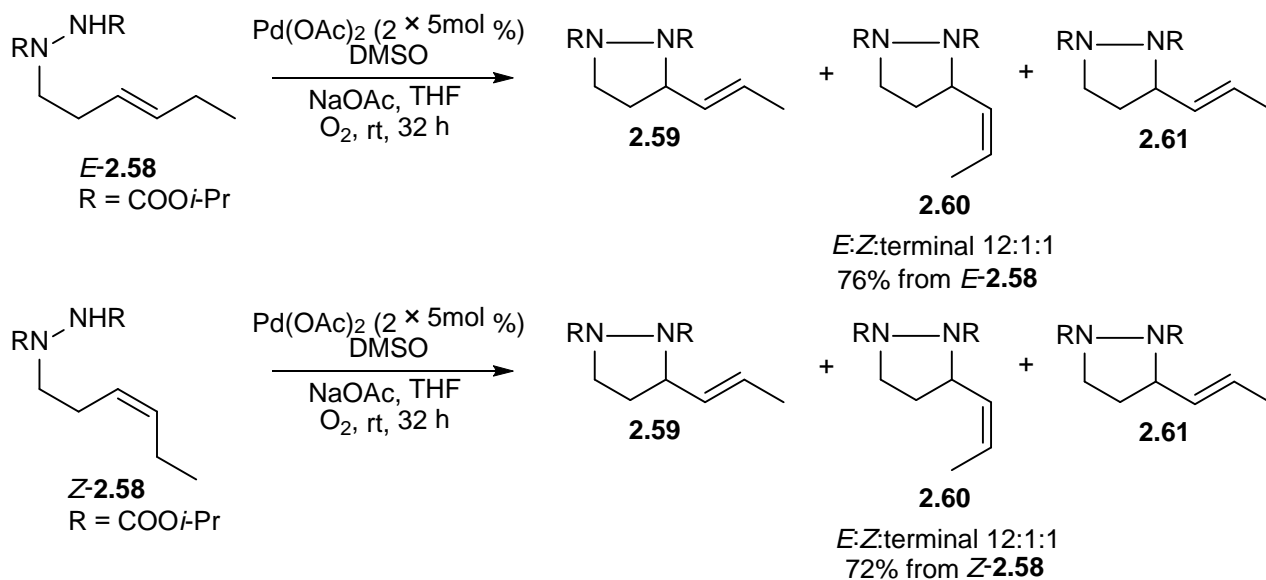
Building upon the success achieved with isoxazolidines, it was envisaged that dinitrogen analogues could be cyclised in a similar manner to yield functionalised pyrazolidines. Again starting from (*E*)-homoallylic alcohols and using the Mitsunobu protocol, the desired diamine substrates could be synthesised in one step (Scheme 2.31).



Scheme 2.31

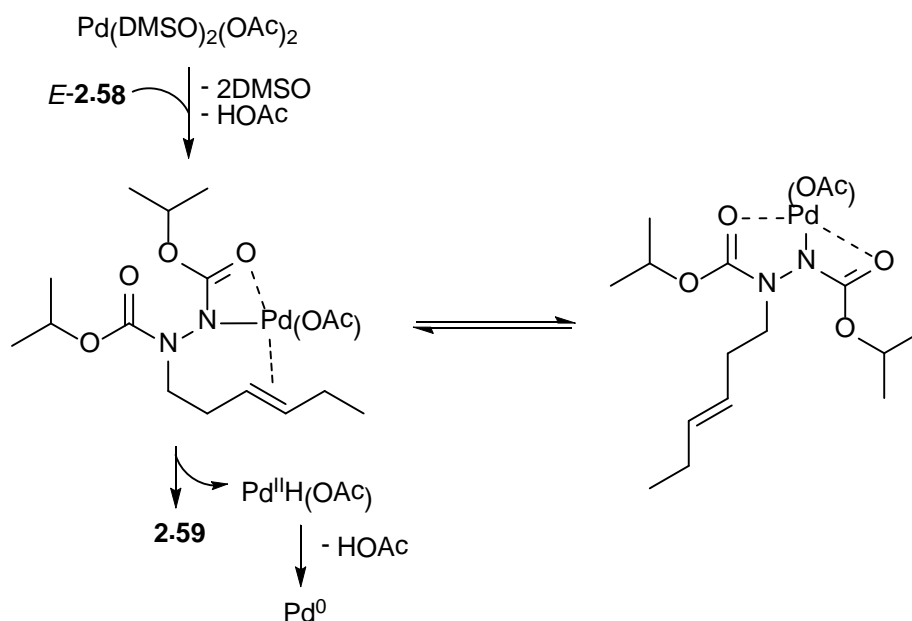
Using an excess of DIAD in place of a nucleophile allowed for the addition of the hydrazine moiety to the alkyl chain. The *E* and *Z* alkenes explored previously were chosen once again so that the isomerisation effect could be observed with this new substrate. The yields obtained were relatively low, but the isolated material was sufficient to proceed with. The ¹H NMR spectra of each suffered from some peak broadening due to rotamers. Both diamines were subjected to the reaction conditions for 16 h, however after this time a significant amount of starting material remained (≈50%). To improve the conversion, a second batch of Pd(OAc)₂ (5 mol %) was added to the reaction mixture, which was left to stir for a further 16 h (Scheme 2.32). After this time, the conversion was sufficient enough (SM < 5%) and the pyrazolidines were purified and analysed with NMR spectroscopy. Interestingly the

pyrazolidines isomers **2.59-2.61** were obtained in similar ratios to analogous isoxazolidines (**2.17-2.19**); *E:Z*:terminal 12:1:1.



Scheme 2.32

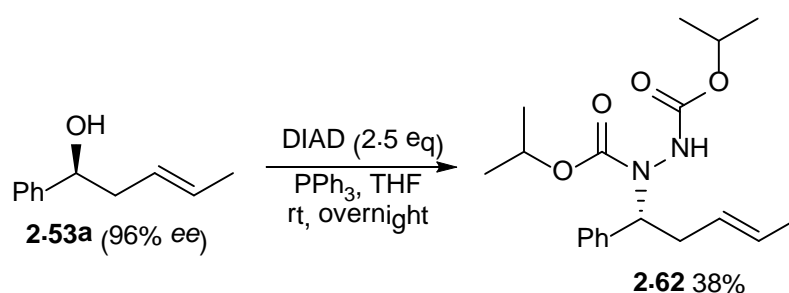
It is difficult to identify the primary cause for the loss of reactivity in this reaction, when compared to the analogous hydroxylamine. The increased steric bulk of having a second carbamate group, the lower acidity of NH and the coordinating nature of the second carbamate group (Scheme 2.33) may all contribute in the drop in reactivity.



Scheme 2.33

After the initial 16 h, adding a second portion of $\text{Pd}(\text{OAc})_2$ (5 mol %) and reacting for a further 16 h enabled a more efficient conversion of the product **2.59** (Scheme 2.32).

A secondary hydrazine substrate was synthesised to see if these substrates maintained similar diastereoselectivity to that observed with oxyamines (Scheme 2.34).

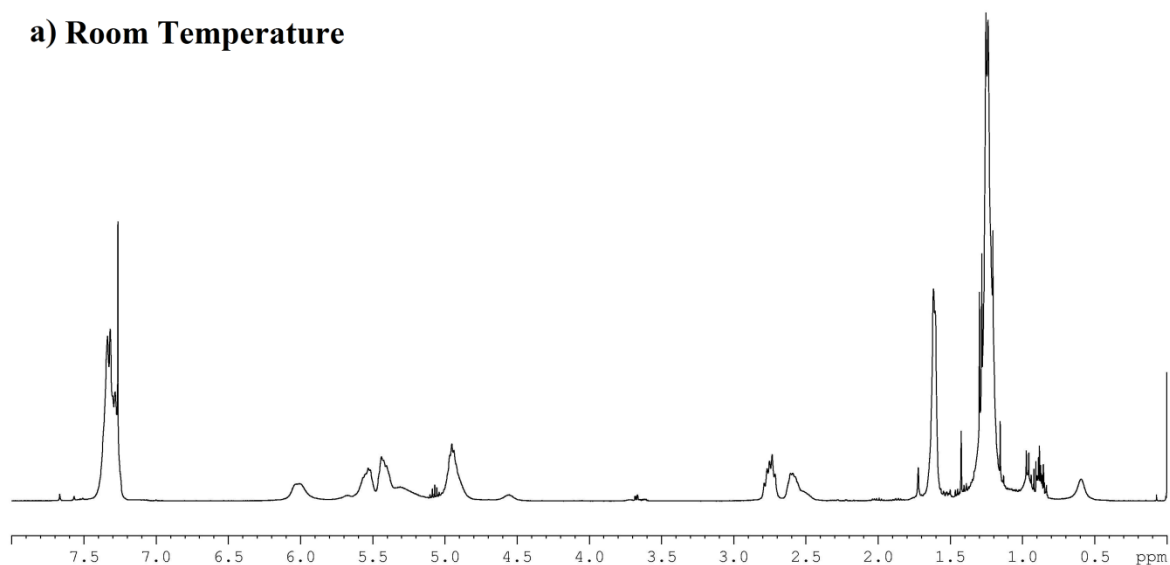


Scheme 2.34

2.62 Was synthesised in the same manner as the previous two hydrazine substrates and was obtained in 38% yield. A broad ^1H NMR spectra was obtained at room temperature (Figure

2.5a), at 115 °C in DMSO-d₆ sharper peaks were obtained (Figure 2.5b). Slow bond rotation at room temperature causes the appearance of broad peaks which is the result of the same atoms or groups of atoms being observed in multiple positions at one time, throughout different molecules in the mixture. The elevated temperature causes an increase in bond rotation, which has the effect of ‘averaging out’ these poorly defined peaks, meaning that atoms are observed in the same position throughout the molecules in the mixture. Hence sharper peaks are obtained.

a) Room Temperature



b) High Temperature (115 °C)

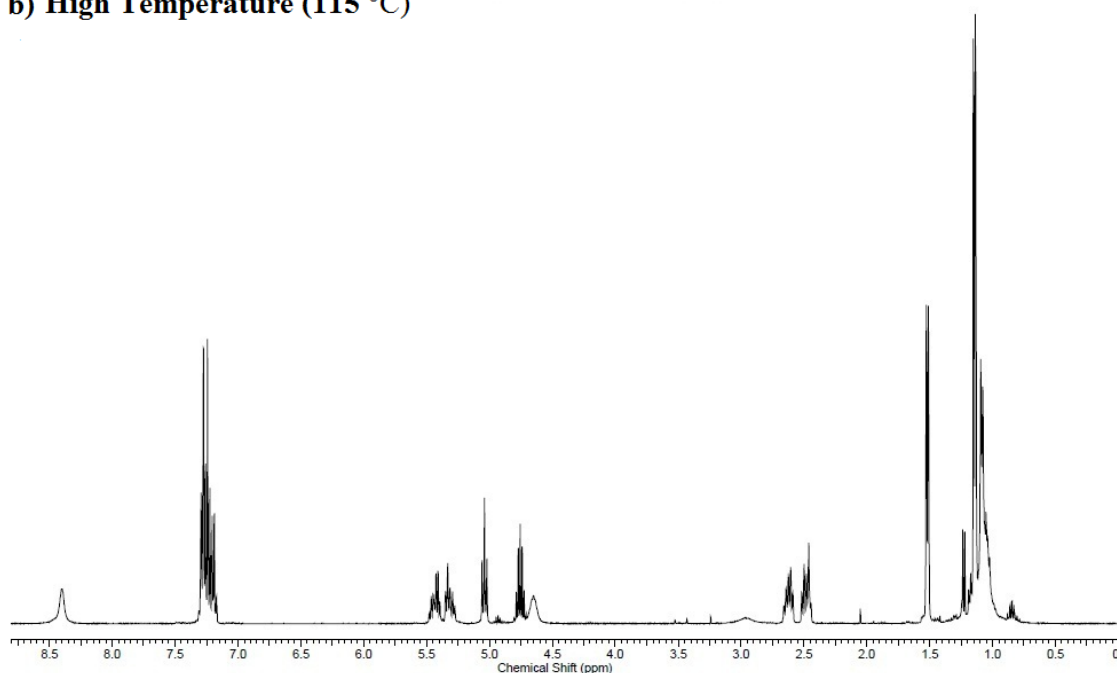
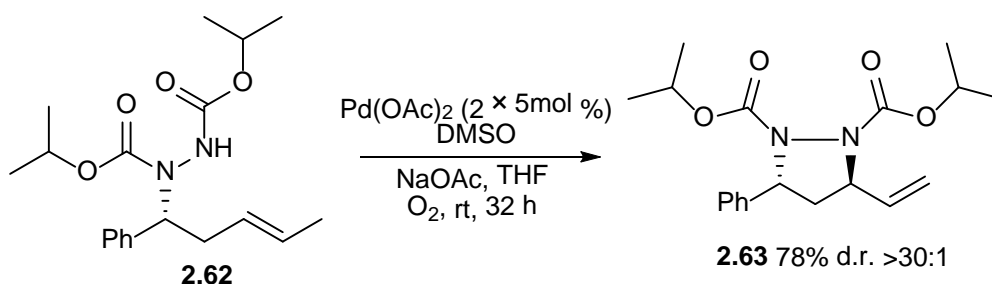


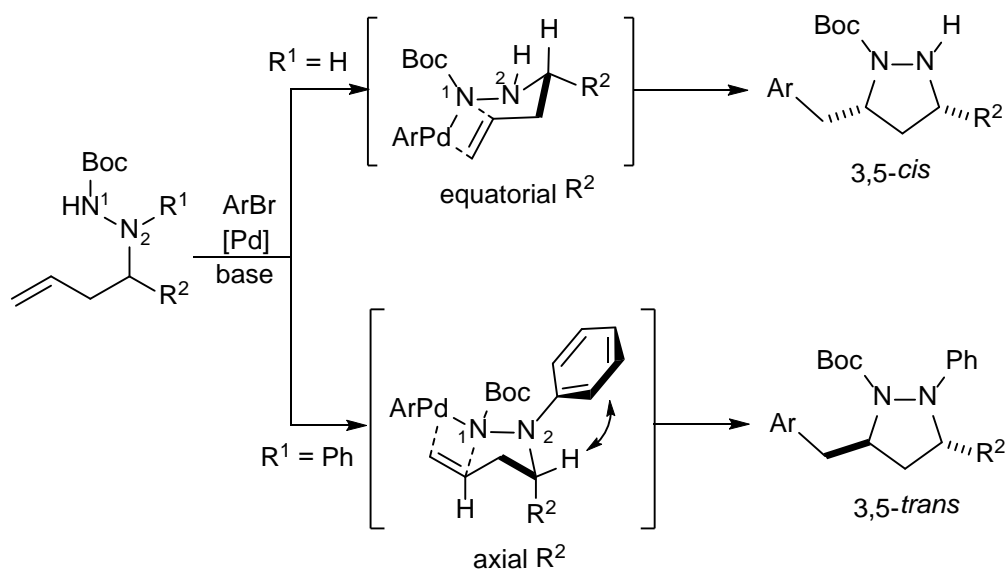
Figure 2.5

Substrate **2.62** was cyclised using the modified oxidative amination conditions that were used for the previous hydrazine compounds (Scheme 2.35). **2.63** was isolated in 78% yield and showed a d.r. of >30:1, however it could not be assumed that the *syn*-pyrazolidine was formed.



Scheme 2.35

As outlined by Wolfe in his synthesis of pyrazolidines via an oxidative aminoarylation, the substituent on N-2 plays a crucial role in determining the stereochemical outcome of the newly formed C-N bond (Scheme 2.36).⁷⁴



Scheme 2.36

Bulkier substituents at N-2 cause a degree of steric repulsion between the bulky group and the substituents of the neighbouring carbon atom, as a consequence R² sits axially forcing the molecule to adopt a conformation that favours *anti*-pyrazolidine formation. With small groups at N-2, there is little steric interaction with the neighbouring substituents, therefore R² can sit equatorially and the molecule adopts a conformation favouring *syn*-pyrazolidine formation. With the bulky carbamate group it could be assumed that **2.63** was in the *anti*-conformation. This was confirmed by nOe studies (see appendix 5.2) and by single crystal X-ray. The single crystal was grown by vapour diffusion using diethyl ether/hexane over several days. The ring structure was shown to be in a twisted *anti*-conformation that positioned the carbamate groups on opposing faces with respect to each other and to the neighbouring substituents at C-3 and C-5 (Figure 2.6, see also appendix 5.1).

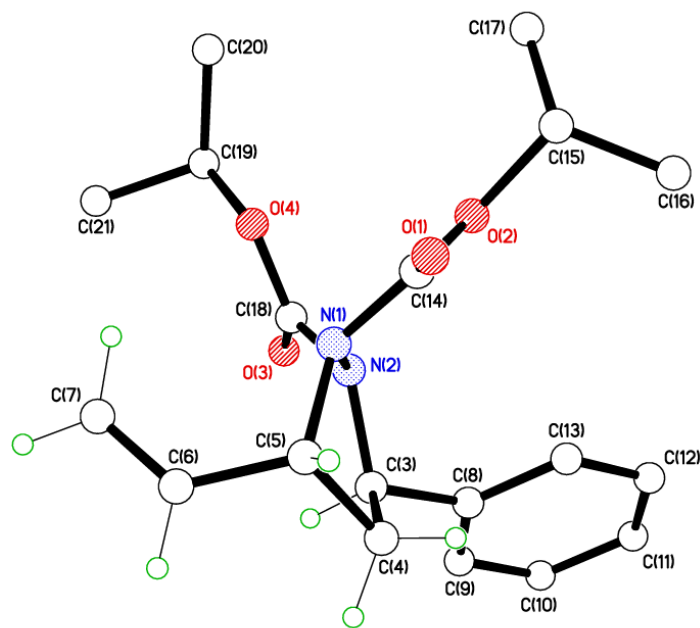
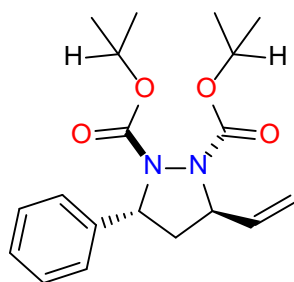
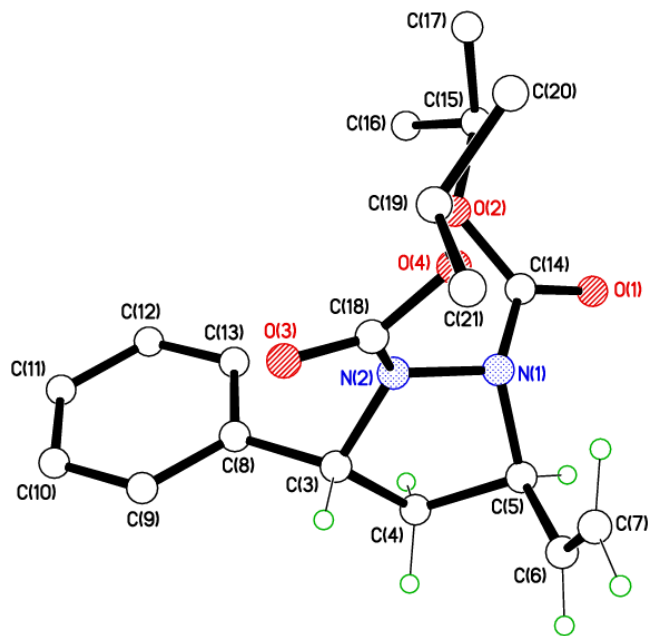
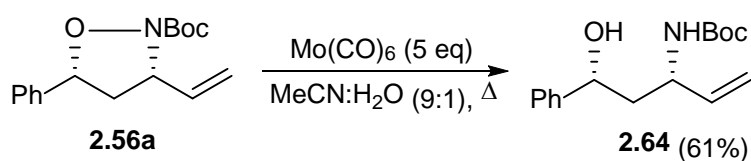


Figure 2.6

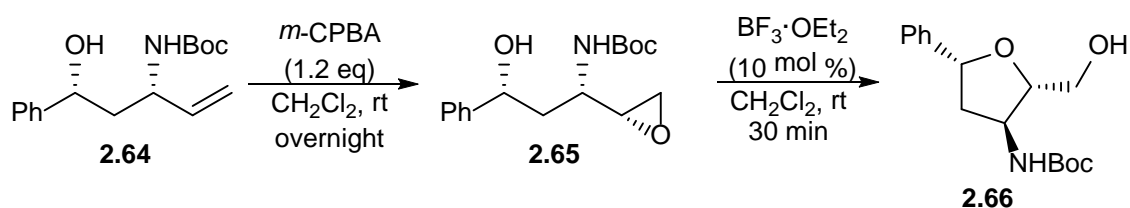
2.2.6. Applications of Isoxazolidines and Pyrazolidines

Amino acids and their derivatives often show useful pharmacological properties,⁹⁶ such as allosedridine.⁹⁷ Amino acids can be accessed directly from 1,3-amino alcohols. Transforming isoxazolidines into amino alcohols was an essential step in the applications of the chemistry developed in this study. Using MoCO_6 , isoxazolidine **2.56a** was transformed into corresponding amino alcohol **2.64**, in 61% yield, as outlined in scheme 2.37.



Scheme 2.37

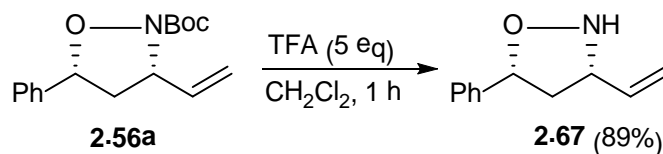
Unnatural sugar derivatives in the form of 3-amino-tetrahydrofurans were synthesised by a colleague at Glasgow University, and can be obtained in 2 steps from the amino alcohol **2.64**. The amino alcohol was submitted to oxidation conditions using *m*-CPBA, which formed epoxide **2.65** in 68% yield and 7:1 d.r. (Scheme 2.38). Amino sugar derivative **2.66** was obtained in 68% yield after cyclisation with $\text{BF}_3 \cdot \text{OEt}_2$.⁸⁷



Scheme 2.38

Attempts to isolate a single crystal of **2.56a** failed, so the next logical step was to remove the Boc protecting group and attempt to grow a crystal from the amine or corresponding amine salt. Deprotection of **2.56a** was carried out with trifluoroacetic acid,⁸⁸ yielding the free amine

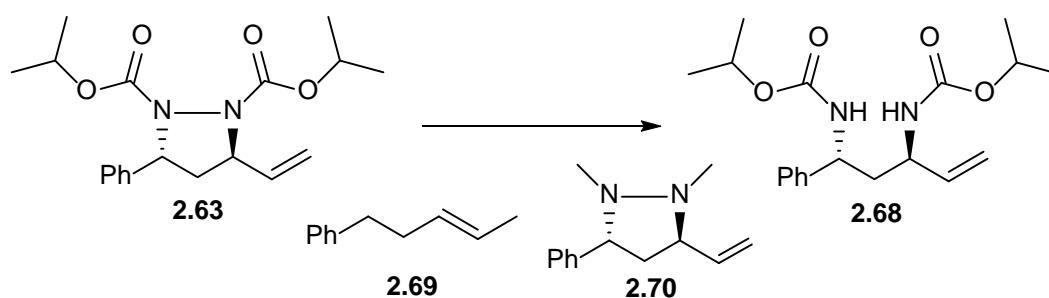
2.67 (Scheme 2.39), however attempts to isolate a single crystal of the amine or the corresponding salt failed.



Scheme 2.39

1,3-Diamines **2.68** are also valuable targets so the ability to cleave the N-N bond of pyrazolidines was required. Wolfe has reported the successful cleavage of N-N bonds in pyrazolidines using SmI_2 .¹⁹ However, attempts to repeat this procedure and cleave the N-N bond of **2.63** proved unsuccessful. A few other methods were carried out in an attempt to cleave the N-N bond, however were still unsuccessful (Table 2.6); SmI_2 returned unreacted starting material, both when made *in situ* and when used as a commercial reagent. Li/NH_3 completely cleaved the hydrazine component and yielded internal alkene **2.69**, whereas LiAlH_4 yielded methyl amine **2.70**.

Table 2.6



Entry	Conditions	Product
1	SmI_2 (Prepared <i>in situ</i>)	SM
2	SmI_2 (Commercial)	SM
3	Li/NH_3	2.69
4	LiAlH_4	2.70

It may be a case of altering the protecting groups to allow SmI_2 to react with the N-N bond,⁷⁵ however due to time constraints this could not be explored further.

2.2.7. Attempted Enantioselective Variant

Attempts were made to develop an enantioselective version of the Wacker-type amination process. The idea was to take the achiral model substrate **2.5** and induce enantioselectivity in the newly formed bond using a chiral ligand for Pd^{II} . Several different ligands (Figure 2.7), Pd^{II} sources and conditions were tested (Table 2.7).

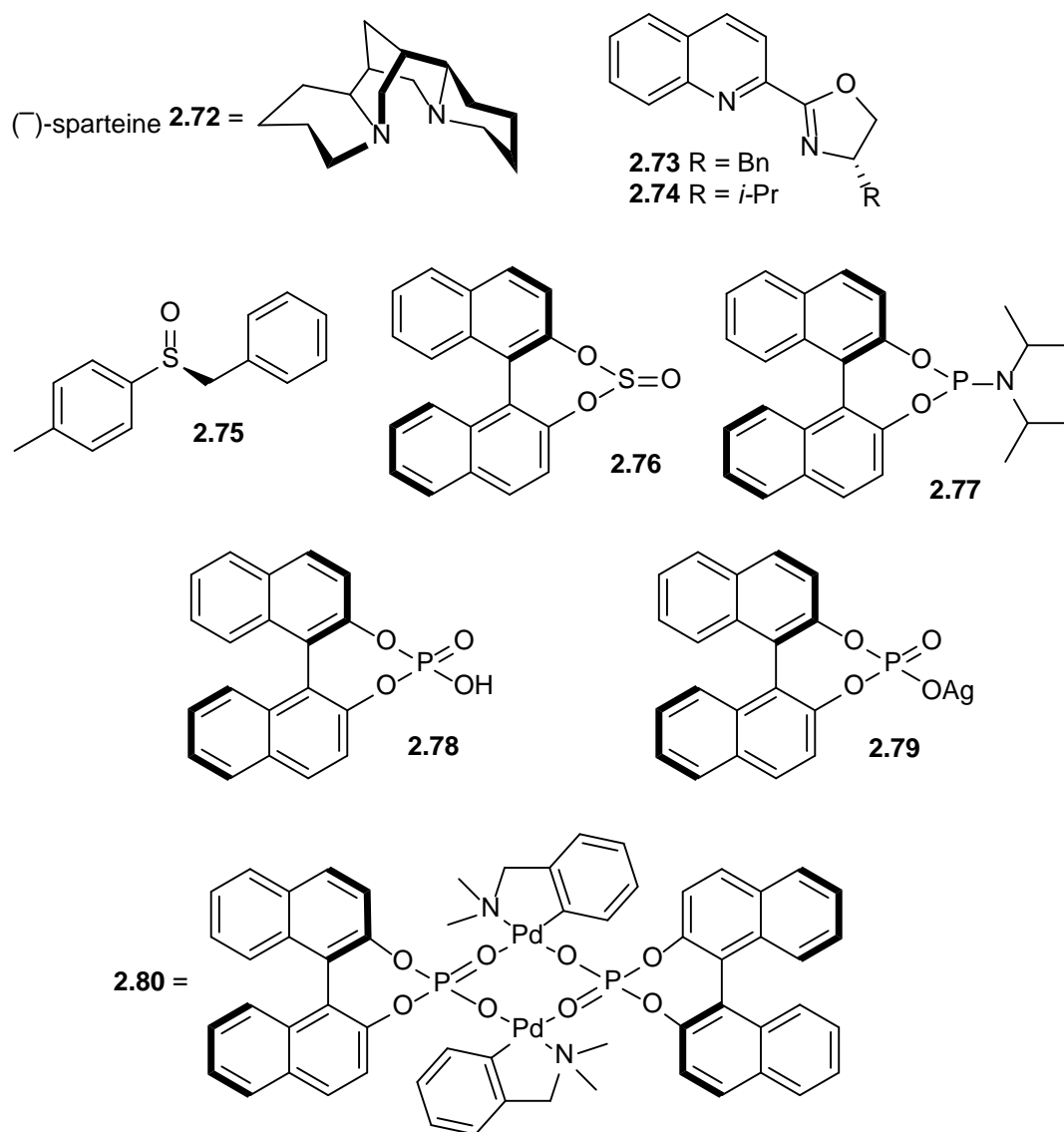
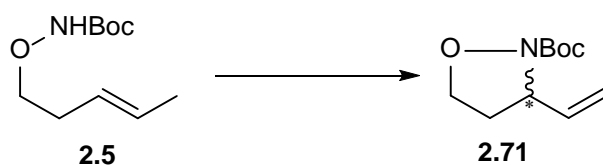


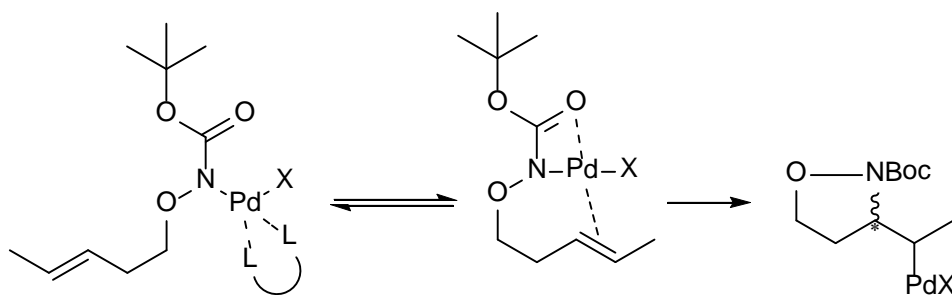
Figure 2.7

Table 2.7^a

Entry	Pd ^{II} (mol %)	Ligand (mol %)	Additives ^b (mol %)	Time	Yield ^c (%)	ee ^d (%)
1	Pd(OAc) ₂ (5)	(-)-Sparteine 2.72 (15)	DMSO (10), NaOAc (20), O ₂	5 days	50	0
2	Pd(OAc) ₂ (5)	Bn-QUINOX 2.73 (15)	DMSO (10), NaOAc (20), O ₂	3 days	47	0
3	Pd(OAc) ₂ (5)	<i>i</i> -Pr-QUINOX 2.74 (15)	DMSO (10), NaOAc (20), O ₂	5 days	65	0
4	PdCl ₂ (5)	<i>i</i> -Pr-QUINOX 2.74 (15)	DMSO (10), NaOAc (20), O ₂	5 days	78	0
5	Pd(TFA) ₂ (5)	<i>i</i> -Pr-QUINOX 2.74 (15)	DMSO (10), NaOAc (20), O ₂	16 h	66	0
6	Pd(OAc) ₂ (5)	2.75 (10)	NaOAc (20), O ₂	16 h	42	0
7	Pd(OAc) ₂ (5)	2.76 (10)	NaOAc (20), O ₂	16 h	55	0
8	Pd(OAc) ₂ (5)	2.77 (20)	DMSO (10), NaOAc (20), O ₂	16 h	51	0
9	Pd(OAc) ₂ (5)	(<i>R</i>)-BNPPA 2.78 (5)	DMSO (10), NaOAc (20), O ₂	16 h	21	0
10	Pd(OAc) ₂ (5)	(<i>R</i>)-BNPPA-Ag salt 2.79 (5)	DMSO (10), NaOAc (20), O ₂	16 h	36	0
11	2.80 (5)	None	DMSO (10), NaOAc (20), O ₂	16 h	10	5

(a) Conditions: **2.5** (0.25 mmol), solvent 3 mL, rt. (b) The flask was flushed with O₂, before a balloon (1 atm) of O₂ was applied. (c) Yields are of isolated **2.71**. (d) *ee*'s were determined by HPLC; Chiracel IB column, 98:2 hexane: propan-2-ol, 0.75 mL min⁻¹, 220 nm detector, retention time = 12.02 min, 13.87 min.

Initially the conditions were kept the same but with the addition of a chiral ligand. Using (-)-sparteine **2.72** and QUINOX ligands **2.73** and **2.74** (Table 2.7, entries 1-3) gave sluggish reactivity, and took 3-5 days to obtain a respectable yield. However, no enantiomeric excess was observed. Changing the Pd^{II} source to PdCl₂ (Table 2.7, entry 4), gave a slight improvement in yield but still no *ee*. Changing to Pd(TFA)₂ (Table 2.7, entry 5) sped up the reaction dramatically, resulting in a 66% yield after 16 h, though the isoxazolidine **2.71** was still racemic. As DMSO is acting as a ligand to Pd, the sluggish reactivity and lack of *ee* could be attributed to a competition effect between the two ligands. Chiral sulfoxides **2.75** and **2.76** were used in place of DMSO (Table 2.7, entries 6-7), however once again no *ee* was observed. A similar result was obtained for phosphoramidite **2.77** (Table 2.7, entry 8). To understand the lack of enantioselectivity, the mechanism of the reaction was analysed (Scheme 2.40).

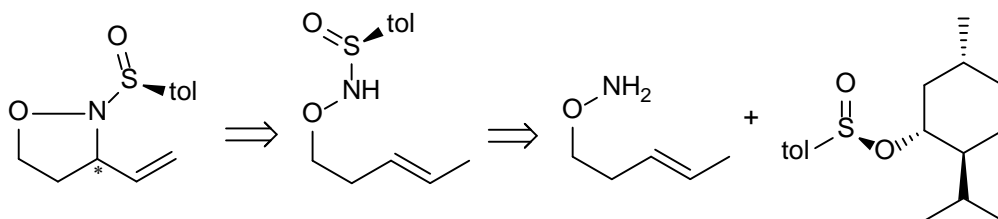


Scheme 2.40

Because of the coordination from the carbonyl and the alkene that is required for *cis*-AP, there is simply no room in the Pd coordination sphere for a donating ligand. The sluggish reactivity could potentially come from slow exchange between the carbonyl/alkene and the chiral bidentate ligand. The lack of *ee* also provides further evidence for a *cis*-AP mechanism; if *trans*-AP was in operation, then some of the Pd coordination sphere would be accessible for ligands and some *ee* should be observed. In the key intermediate for *cis*-AP there is only the one counter-ion remaining bound to Pd. A strategy to make a chiral counter-ion for Pd was attempted, using phosphoric acid **2.78** and its silver salt **2.79** (Table 2.7, entries 9-10). Once again, no *ee* was observed. Using a premade Pd complex **2.80** (Table 2.7, entry 11) gave a poor yield of 10%, but showed a small amount of enantiomeric induction

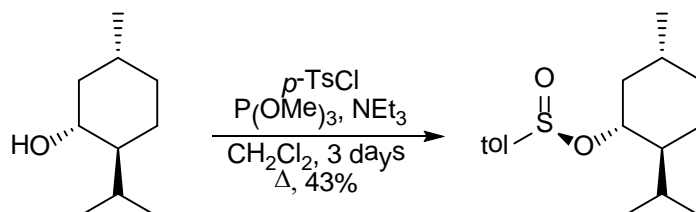
(5%). In light of Stahl's report,³⁴ outlining the effects of the different aminopalladation modes on enantioselectivity, this study was abandoned as it was evident that *cis*-AP does not favour chiral induction through a ligand.

Briefly, an attempt was made to induce enantioselectivity by substituting the *t*-Boc of the substrate for a chiral sulfoxide alternative (Scheme 2.41).



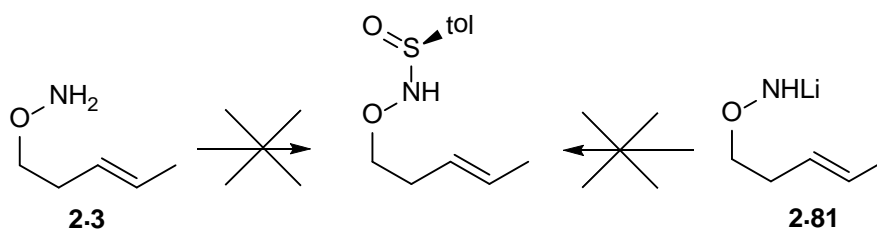
Scheme 2.41

(*S*)-(-)-menthyl *p*-toluene-sulfinate was synthesised from L-menthol and *p*-TsCl in moderate yield (Scheme 2.42).⁹⁸



Scheme 2.42

It was planned to substitute menthol with hydroxylamine **2.3**. However, this could not be achieved with either the free hydroxylamine or its corresponding lithium salt **2.81** (Scheme 2.43).



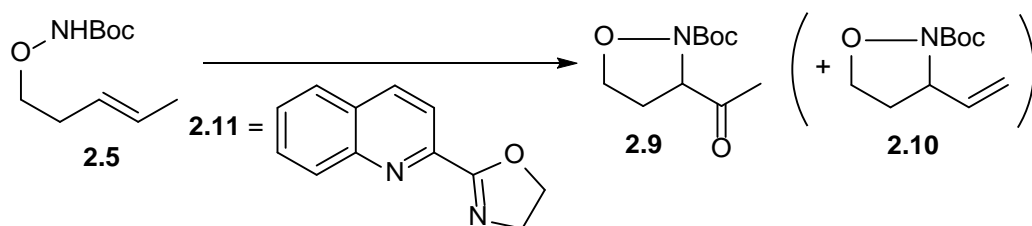
Scheme 2.43

2.2.8. Optimisation of Tandem Cyclisation/Wacker Oxidation Conditions

It was decided to examine further the competition between formation of alkene **2.9** and ketone **2.10** during the oxidative Wacker-type amination that was mentioned earlier (Section 2.2.2., Table 2.1, entries 4-5). We aimed to investigate whether the reaction conditions leading to the formation of ketone **2.10** could be optimised further (Table 2.8).

Using 2,2'-bipyridine as a ligand gave a reduction in ketone **2.10** (Table 2.8, entry 3). QUINOX **2.11** was used as the ligand again and after 72 h a 62% conversion (Table 2.8, entry 4) was obtained. Carrying out the reaction in the presence of water (Table 2.8, entry 5) or under anhydrous conditions (Table 2.8, entry 6) gave similar yields. Changing oxidant to *p*-benzoquinone (Table 2.8, entry 7) gave no change in conversion. Removal of the co-oxidant gave the best result (Table 2.8, entry 8), 85% conversion and 81% yield.

Table 2.8.^a

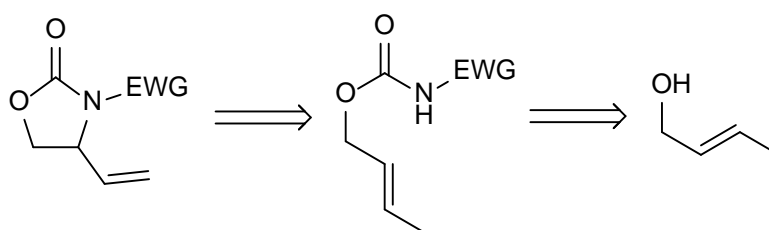


Entry	Pd ^{II} (mol %)	Oxidant ^b (mol %)	Ligand (mol %)	Solvent	Conv. ^{c,d} 2.10 (%)	Conv. ^c 2.9 (%)
1	Pd(OAc) ₂ (10)	Cu(OAc) ₂ (30)/ O ₂	None	MeCN	20	0
2	Pd(MeCN) ₂ Cl ₂	Cu(OAc) ₂ (30)/ O ₂	2.11 (40)	MeCN	50	0
(5)						
3	Pd(MeCN) ₂ Cl ₂	Cu(OAc) ₂ (30)/ O ₂	bipy (40)	MeCN	25	0
(5)						
4^e	Pd(MeCN) ₂ Cl ₂	Cu(OAc) ₂ (30)/ O ₂	2.11 (40)	MeCN	62	22
(5)						
5	Pd(MeCN) ₂ Cl ₂	Cu(OAc) ₂ (30)/ O ₂	2.11 (40)	MeCN/ 5% H ₂ O	65	17
(5)						
6	Pd(MeCN) ₂ Cl ₂	CuCl (30)/ O ₂	2.11 (40)	MeCN	56	0
(5)						
7	Pd(MeCN) ₂ Cl ₂	BQ (30)/ O ₂	2.11 (40)	MeCN	56	0
(5)						
8	Pd(MeCN) ₂ Cl ₂	O ₂	2.11 (40)	MeCN	85 (81)	15 ^c
(5)						
9	Pd(MeCN) ₂ Cl ₂	O ₂	2.11 (40)	DMPU	44	13
(5)						

(a) Conditions: **2.5** (0.25 mmol), solvent 3 mL, 60 °C, 16 h. (b) The flask was flushed with O₂, before a balloon (1 atm) of O₂ was applied. (c) Conversion was determined using ¹H NMR and the ratio of SM:product(s). (d) Isolated yields are in parenthesis. (e) This reaction was run for 72 h. BQ = *p*-benzoquinone, BIPY = 2,2'-bipyridine.

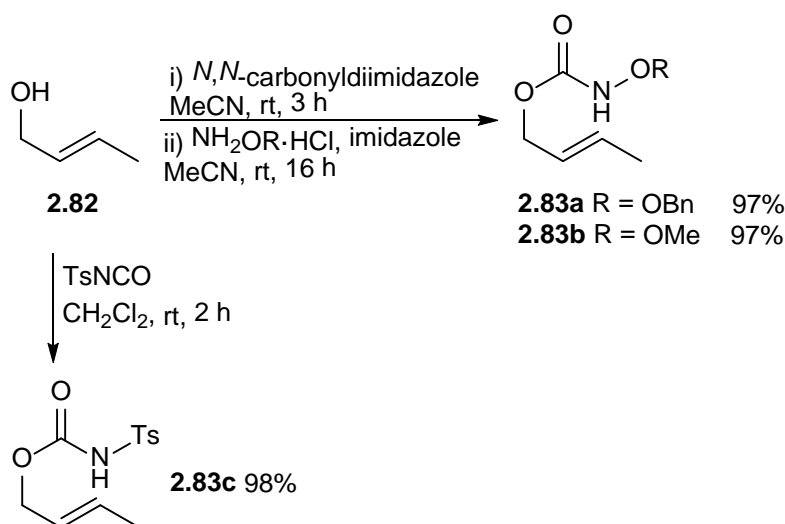
2.3. Oxazolidinones; an Attempted Synthesis of 1,2-Amino Alcohol Precursors

Oxazolidinones are ideal precursors to 1,2-amino alcohols as the carbonyl can easily be hydrolysed to yield the amine and hydroxyl groups. Alongside the synthesis of isoxazolidines, a Pd^{II} catalysed oxidative cyclisation strategy was envisioned. A brief retrosynthetic analysis revealed that the desired oxazolidinones could be accessed from allylic carbamates, which in turn could be synthesised from allylic alcohols (Scheme 2.44).



Scheme 2.44

Using a similar design to that used for 1,3-amino alcohols, the nitrogen nucleophile would contain an electron-withdrawing group that would hopefully enable a *cis*-AP pathway. Several substrates bearing different electron withdrawing groups were synthesised,^{100,101} which were used in the optimisation of conditions (Scheme 2.45).



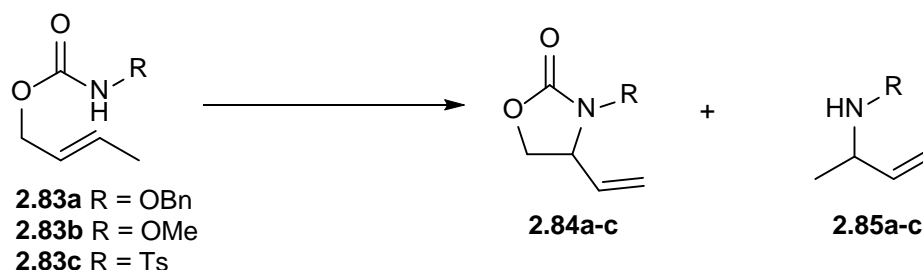
Scheme 2.45

As a starting point, conditions similar to those developed in the group for the synthesis of isoxazolidines via an oxidative cyclisation/carbonylation were chosen.²⁹ From this starting point, several conditions and substrates were screened as outlined in table 2.9.

A mixture of compounds was obtained in the reaction of **2.83a** (Table 2.9, entry 1), the desired oxazolidinone **2.84a** was obtained along with the product of an allylic rearrangement **2.85a**. This type of rearrangement is not uncommon.⁶⁷ The remainder of the material with the near 1:1 mixture of **2.84a** and **2.85a** obtained with starting material. Switching the reaction solvent to toluene and DMSO (Table 2.9, entry 2-3) gave complex mixtures. Going back to MeCN, but using the substrate **2.83b** gave a similar result to that obtained with **2.83a** (Table 2.9, entry 4). In an attempt to suppress the allylic rearrangement the substrate was switched to one containing a more electron withdrawing Ts group **2.83c**. However the cyclisation with these conditions led to the decomposition of the compound and the isolated material was mainly TsNH₂. It was speculated that the double bond could be shifted by Pd, leading to CO₂ and TsNH₂ evolution. Adding ground pH 7.0 buffer tablet to the reaction suppressed this decomposition somewhat, however trace amounts of TsNH₂ were still observed (Table 2.9, entry 6). Switching to *N,N*-diisopropylethylamine (Table 2.9, entry 7) in an attempt to promote nitrogen deprotonation and Pd-N formation led to slight increase of both **2.84c** and **2.85c**. The introduction of an oxygen atmosphere into the system (Table 2.9, entry 8) provided the best result, obtaining 65% conversion of **2.84c**, however a greater amount of

TsNH₂ was obtained in this reaction. Submitting **2.83c** to the amination conditions used for the synthesis of 1,3-substrates returned unreacted starting material (Table 2.9, entry 9).

Table 2.9.^a



Entry	Substrate 2.83 (R =)	Pd ^{II} (mol %)	Oxidant (eq)	Additive (eq)	Solvent	Yield 2.84 (2.85) ^d
1	a (OBn)	PdCl ₂ (10)	Cu(OAc) ₂ (3)	MOA (1)	MeCN	20 (18)
2	a (OBn)	PdCl ₂ (10)	Cu(OAc) ₂ (3)	MOA (1)	Toluene	0 ^e
3	a (OBn)	PdCl ₂ (10)	Cu(OAc) ₂ (3)	MOA (1)	DMSO	0 ^e
4	b (OMe)	PdCl ₂ (10)	Cu(OAc) ₂ (3)	MOA (1)	MeCN	14 (15)
5	c (Ts)	PdCl ₂ (10)	Cu(OAc) ₂ (3)	MOA (1)	MeCN	0 ^f
6	c (Ts)	PdCl ₂ (10)	Cu(OAc) ₂ (3)	MOA (1) ^c	MeCN	22 (15) ^g
7	c (Ts)	PdCl ₂ (10)	Cu(OAc) ₂ (3)	DIPEA (1) ^c	MeCN	37 (25) ^g
8	c (Ts)	Pd(OAc) ₂ (10)	Cu(OAc) ₂ (3)/O ₂ ^b	DIPEA (1) ^c	MeCN	65 (17) ^h
9	c (Ts)	Pd(OAc) ₂ (5)	DMSO/O ₂ ^b	NaOAc	THF	SM

(a) Conditions: substrate **2.83a-c** (0.38 mmol), solvent 3 mL, 60 °C, 3 days (b) The flask was flushed with O₂, before a balloon (1 atm) of O₂ was applied. (c) 0.1g ground pH 7.0 buffer tablet was added. (d) Remaining material is starting carbamate unless stated otherwise. (e) A complex mixture was obtained. (f) Isolated material was predominately TsNH₂. (g) Trace amounts of TsNH₂ were observed. (h) ≈15% TsNH₂ was isolated. MOA = methyl orthoacetate, DIPEA = *N,N*-diisopropylethylamine.

Ultimately, efforts to optimise these conditions were halted in favour of the more successful isoxazolidines that do not suffer from a competing rearrangement reaction. Bäckvall and co-workers¹⁸ (see page 49) later provided an insight into this reaction and found that in fact the cyclisation is operating via a *trans*-AP pathway (see page 13-14).

2.4. Conclusion

During this study, conditions have been identified for the successful transformations of hydroxylamines and hydrazines to isoxazolidines and pyrazolidines respectively. The role of each component of the reaction conditions have been outlined in the proposed *cis*-AP reaction mechanism. DMSO is essential for the enabling the re-oxidation of Pd⁰ by molecular O₂ and preventing Pd-black formation. NaOAc in the reaction mixture and the presence *N*-Boc group on the substrate are required for the successful formation of the Pd-N species for *cis*-AP. The range of substrates can be extended to substituted alkene, secondary substrates and even those leading to the formation of larger rings. Substrates that are functionlised on the alkyl chain can be cyclised efficiently, however substrates with steric bulk around the the β-hydrogen give a slower conversion. *syn*-Isoxazolidines can be formed with excellent diastereoselectivities (up to >30:1), whilst maintaining the efficient and mild reaction conditions. Side products have been observed in the form of keto-isoxazolidine **2.10**, the conditions leading to this by-product have been optimised. Hydrazine substrates have shown similar reactivity to that observed for hydroxylamines. Attempts into developing an enantioselective variant proved unsuccessful with chiral ligands as, in line with recent literature,³⁴ Pd in a *cis*-AP intermediate cannot support donating type ligands and a *trans*-AP pathway or a chiral counter ion is required for enantioselective induction to take place. Studies into optimising conditions leading to oxazolidinones was less successful due to a competing 3,3'-allylic rearrangement, that could not be productively suppressed. Isoxazolidines were successfully transformed into the corresponding 1,3-amino alcohols, proving the validity of this chemistry as a gateway for synthetically valuable amino alcohols building blocks. Ultimately, this study is a valuable addition to the ever growing field of Wacker-type palladium transformations.

2.5. Future Work

Ideally, for industrial purposes, the catalysis conditions would contain as little Pd as possible. Efforts into lowering the Pd loading to 1% or lower whilst maintaining a decent reactivity are highly desirable. Additionally utilising air instead of O₂ would be beneficial, cutting costs of obtaining the pure gas and removing the risks associated with pure oxygen. With regards to the substrates, the example leading to 1,4-amino alcohol precursor oxazine **2.39** could be further expanded, opening up a whole new substrate scope, with diastereoselectivity being chief amongst them. Attempts can be made to synthesise larger ring sizes, however there is the possibility that these may suffer a loss in reactivity as forming larger rings becomes unfavourable. Expanding the scope of the hydrazine substrates is another avenue to be further explored. By removing or replacing the carbamate (with something non-coordinating) on the alkyl tethered amine, perhaps the reactivity can be brought into line with that observed for hydroxlamines. The coordination effect that appears to be inhibiting Pd would be removed and the cyclisation could take place faster and without the need for additional Pd. Also, in line with the reports by Wolfe,⁷⁵ perhaps the *syn*- or *anti*-ring configuration can be tuned by the size of this group. Removing one, or both of the protecting groups from the pyrazolidines, may be the key to cleaving the N-N bond yielding the desired 1,3-diamines. Further studies into tuning the enantioselective conditions should be carried out. Employing more acidic conditions and altering the substrate so that a *trans*-AP is favoured would be the key to successfully inducing enantioselectivity with a donating ligand. Additionally, further studies into finding a suitable chiral counter-ion could enable some stereochemical induction whilst maintaining the *cis*-AP pathway. Finally, applications of this chemistry could be explored, first by coupling the cyclisation with different substrates, such as those seen in aminoarylation, aminocarbonylation, etc. Secondly applying the chemistry to natural product or a target orientated synthesis.

3. Experimental

3.1. General Considerations

All infrared spectra were obtained using a Perkin-Elmer, spectrum 65 FT-IR spectrophotometer; spectra for liquids were acquired as a thin film using sodium chloride plates or in the case of solids, as a KBr disc.

All ^1H and ^{13}C NMR spectra were measured at 400 and 100 MHz respectively using a Bruker DPX 400 MHz spectrometer. The solvent used for NMR spectroscopy was chloroform- d_1 (δ 7.26, ^1H ; δ 77.0, ^{13}C) using TMS (tetramethylsilane) as the internal reference, unless stated otherwise. Chemical shifts are given in parts per million (ppm) and J values are given in Hertz (Hz). Various 2D-techniques and DEPT experiments were used to establish the structures and to assign the signals.

The mass spectra were recorded using a Thermoscientific exactive (Orbi) ESI (Ethanol) via nanomate (Advion) and by the EPSRC national mass spectrometry service at the University of Wales, Swansea, utilising electrospray (ES).

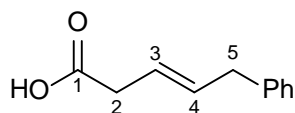
All chromatographic manipulations used silica gel as the adsorbent. Reactions were monitored using thin layer chromatography (TLC) on aluminium backed plates with Merck TLC 60 F₂₅₄ silica gel. TLC visualised by UV radiation at a wavelength of 254 nm, or stained by exposure to an ethanolic solution of vanillin (acidified with concentrated sulphuric acid) or an ethanolic solution of Phosphomolybdic acid, followed by charring where appropriate. Purification by column chromatography using Apollo ZEOprep 60/ 40-63 micron silica gel.

The reactions requiring anhydrous conditions were carried out using flame dried glassware, under a nitrogen atmosphere unless otherwise stated. Reaction solvents were used as obtained commercially. Tetrahydrofuran (THF) was distilled under an argon atmosphere from the sodium/benzophenone ketyl radical.

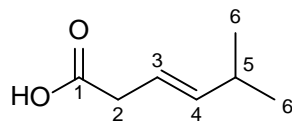
3.2. Experimental Data

3.2.1. General Procedure for Knoevenagel Condensation⁹¹

Acetic acid (0.017g, 0.29 mmol) was added dropwise to a solution of piperidine (0.025 g, 0.29 mmol) in DMSO (2 mL) and stirred at room temperature for 5 minutes. Malonic acid (3.1 g, 29.8 mmol) and the desired aldehyde (1 g, 14.9 mmol) in DMSO (15 mL) was added and stirred at room temperature for 15 minutes. The mixture was then heated to 120 °C and stirred at this temperature overnight. CO₂ evolution was observed upon heating. Once the reaction was complete, the mixture was cooled and extracted with diethyl ether (2 × 10 mL). The combined fractions were washed with water (15 mL) and dried over anhydrous Na₂SO₄ and evaporated under reduced pressure. The crude oil was purified using column chromatography (light petroleum: EtOAc, 10:1) to yield the pure carboxylic acid.



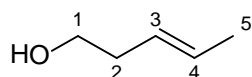
(E)-5-Phenylpent-3-enoic acid (2.21).¹⁰¹ Clear oil, (80%): ¹H NMR (400 MHz; CDCl₃) δ 3.09 (d, *J* = 6.8 Hz, 2H, H-2), 3.37 (d, *J* = 6.8 Hz, 2H, H-5), 5.56 – 5.64 (m, 1H, H-3), 5.69 – 5.77 (m, 1H, H-4), 7.15 – 7.20 (m, 3H), 7.25 – 7.29 (m, 2H), 11.93 (br s, OH); ¹³C NMR (100 MHz, CDCl₃) δ 37.8 (CH₂, C-2), 39.0 (CH₂, C-5), 122.4 (CH, C-3), 126.2 (CH, Ph), 128.5 (CH × 2, Ph), 128.6 (CH × 2, Ph), 133.9 (CH, C-4), 140.0 (C), 178.8 (CO); IR (NaCl) ν 3028, 2671, 1710, 1494, 1416, 1289, 1223, 970, 699, 489 cm⁻¹; HRMS (ESI) 199.0729 (C₁₁H₁₂O₂Na requires 199.0730).



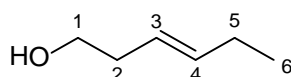
(E)-5-Methylhex-3-enoic acid (2.22).¹⁰² Clear oil, (52%): ¹H NMR (400 MHz; CDCl₃) δ 0.99 (d, *J* = 6.8 Hz, 6H, H-6), 2.30 (oct, *J* = 6.8 Hz, 1H, H-5), 3.06 (d, *J* = 7.6 Hz, 2H, H-2), 5.43 – 5.59 (m, 2H, H-3/4), 11.97 (br s, OH); ¹³C NMR (100 MHz, CDCl₃) δ 22.1 (CH₃ × 2, C-6), 31.0 (CH, C-5), 37.8 (CH₂, C-2), 118.0 (CH, C-3/4), 142.2 (CH, C-3/4), 179.0 (CO); IR (NaCl) ν 2961, 2668, 1713, 1416, 1288, 1223, 970, 625, 472 cm⁻¹; HRMS (ESI) 151.0730 (C₇H₁₂O₂Na requires 151.0730).

3.2.2. General Procedure for LiAlH₄ Reduction of Acids to Alcohols⁸⁶

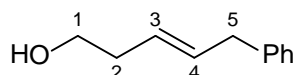
THF (20 mL) was added to a 250 mL round bottom flask charged with LiAlH₄ (0.13 g, 3.41 mmol) under an atmosphere of nitrogen. The mixture was cooled to 0 °C and the acid (0.5 g, 2.84 mmol) in THF (10 mL) was added dropwise and the mixture was allowed to warm to room temperature and left to stir overnight. Sodium sulphate decahydrate was added portion wise at 0 °C, until any excess LiAlH₄ was quenched. The resultant mixture was filtered through a thin pad of celite to remove the magnesium salts. The solvent was removed from the filtrate *in vacuo*, to yield the crude alcohol. Purification with column chromatography (light petroleum: EtOAc 10:1) yielded the pure alcohol.



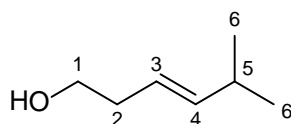
(E)-Pent-3-en-1-ol (2.1).⁸⁶ Clear oil, was used without purification (95%): ¹H NMR (400 MHz; CDCl₃) δ 1.67 (d, *J* = 6.4 Hz, 3H, H-5), 1.80 (br s, OH), 2.25 (q, *J* = 6.4 Hz, 2H, H-2), 3.62 (t, *J* = 6.4 Hz, 2H, H-1), 5.37 – 5.45 (m, 1H, H-3), 5.52 – 5.61 (m, 1H, H-4); ¹³C NMR (100 MHz, CDCl₃) δ 18.0 (CH₃, C-5), 35.9 (CH₂, C-2), 62.0 (CH₂, C-1), 127.1 (CH, C-3), 128.4 (CH, C-4); IR (NaCl) ν 3340, 2936, 2920, 1449, 1378, 1045, 966 cm⁻¹; HRMS (ESI) 87.0804 (C₅H₁₁O requires 87.0808).



(E)-Hex-3-en-1-ol (E-2.14).¹⁰³ Clear oil, was used without purification (91%): ¹H NMR (400 MHz; CDCl₃) δ 0.99 (t, *J* = 6.7 Hz, 3H, H-6), 2.04 (quin, *J* = 6.7 Hz, 2H, H-5), 2.27 (q, *J* = 6.7 Hz, 2H, H-2), 3.63 (t, *J* = 6.7 Hz, 2H, H-1), 5.38 (dt, *J* = 15.2, 6.7 Hz, 1H, H-3), 5.60 (dt, *J* = 15.2, 6.7 Hz, 1H, H-4); ¹³C NMR (100 MHz, CDCl₃) δ 13.7 (CH₃, C-6), 25.6 (CH₂, C-5), 35.9 (CH₂, C-2), 62.0 (CH₂, C-1), 124.8 (CH, C-3), 135.6 (CH, C-4); IR (NaCl) ν 3341, 2962, 2932, 1459, 1048, 968 cm⁻¹; HRMS (ESI) 101.0962 (C₆H₁₃O requires 101.0961).



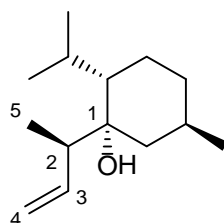
(E)-5-Phenylpent-3-en-1-ol (2.28).¹⁰⁴ Clear oil, (60%): ¹H NMR (500 MHz; CDCl₃) δ 2.06 (br s, OH), 2.27 (q, *J* = 6.5 Hz, 2H, H-2), 3.34 (d, *J* = 7.0 Hz, 2H, H-5), 3.61 (t, *J* = 6.5 Hz, 2H, H-1), 5.44 – 5.51 (m, 1H, H-3), 5.69 (dtt, *J* = 15.5, 7.0, 1.5 Hz, 1H, H-4), 7.16 – 7.20 (m, 3H), 7.26 – 7.29 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 36.0 (CH₂, C-2), 39.2 (CH₂, C-5), 62.1 (CH₂, C-1), 126.1 (CH, Ph), 127.6 (CH, C-3), 128.4 (CH × 2, Ph), 128.5 (CH × 2, Ph), 132.3 (CH, C-4), 140.6 (C); IR (NaCl) ν 3342, 3027, 2928, 1494, 1453, 1046, 969, 746, 698 cm⁻¹; HRMS (ESI) 185.0937 (C₁₁H₁₄ONa requires 185.0937).



(E)-5-Methylhex-3-en-1-ol (2.29).¹⁰⁵ Clear oil, (73%): ¹H NMR (500 MHz; CDCl₃) δ 0.98 (d, *J* = 7.0 Hz, 6H, H-6), 2.05 (br s, OH), 2.23 – 2.31 (m, 3H, CH & CH₂, H-2/5), 3.62 (t, *J* = 6.5 Hz, 2H, H-1), 5.31 – 5.37 (dtd, *J* = 15.2, 6.5, 1.2 Hz, 1H, H-3), 5.50 – 5.55 (ddt, *J* = 15.2, 6.5, 1.2 Hz, 1H, H-4); ¹³C NMR (125 MHz, CDCl₃) δ 22.5 (CH₃ × 2, C-6), 31.1 (CH, C-5), 35.9 (CH₂, C-2), 62.1 (CH₂, C-1), 122.7 (CH, C-3), 141.2 (CH, C-4); IR (NaCl) ν 3342, 2958, 2929, 2870, 1466, 1048, 970 cm⁻¹; HRMS (ESI) 137.0936 (C₇H₁₄ONa requires 137.0937).

3.2.3. Preparation of Chiral Allyl Donor 2.52 from (-)-menthone^{94b}

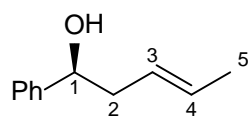
A flame dried flask was charged with magnesium turnings (0.71 g, 30 mmol) and THF (40 mL). The mixture was cooled to 0 °C and crotyl chloride (2.65 g, 30 mmol) in THF (10 mL) was added dropwise via syringe. The mixture was stirred at 0 °C for 30 minutes or until the exothermic reaction had subsided, before being warmed to room temperature to be stirred for 24 hours or until all of the magnesium had dissolved. The Grignard solution was transferred to a new sealed flask via cannula to remove any excess magnesium. The solution was cooled to 0 °C and a solution of (-)-menthone (3 g, 19.5 mmol) in THF (20 mL) was added dropwise via syringe. The reaction mixture was maintained at 0 °C stirring for a further 2 hours. Upon completion, the reaction mixture was partitioned between brine (30 mL) and EtOAc (40 mL), the organic layer was washed with 1M HCl (30 mL), dried with MgSO₄ and the solvent removed *in vacuo*. A crude yellow oil was obtained which was purified using column chromatography (light petroleum: EtOAc 30:1).



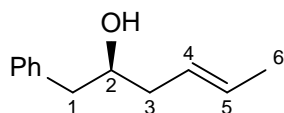
(1R,2S,5R)-1-((R)-But-3-en-2-yl)-2-isopropyl-5-methylcyclohexanol (2.52).^{94b} Clear oil, (75%): $[\alpha]_D +9.8$ (*c* 1.3, CHCl₃); ¹H NMR (400 MHz; CDCl₃) δ 0.75 – 1.02 (m, 2H), 0.85 (d, *J* = 6.4 Hz, 3H), 0.91 (d, *J* = 7.2 Hz, 3H), 0.92 (d, *J* = 7.2 Hz, 3H), 0.96 (d, *J* = 7.2 Hz, 3H), 1.32 – 1.34 (m, 1H), 1.33 – 1.35 (m, 1H), 1.46 – 1.53 (m, 2H), 1.57 (br s, OH), 1.67 – 1.79 (m, 2H), 2.09 (sep, *J* = 6.8 Hz, 1H), 2.60 (quin, *J* = 7.2 Hz, 1H), 5.10 – 5.15 (m, 2H, H-4), 5.88 (ddd, *J* = 16.8, 10.4, 8.0 Hz, 1H, H-3); ¹³C NMR (100 MHz, CDCl₃) δ 14.7, 18.0, 20.6, 22.6, 23.4, 25.0, 27.6, 35.2, 41.5, 45.2, 45.9, 76.2, 116.7, 140.8; IR (NaCl) ν 3574, 2952, 2917, 2848, 1457, 1378, 1007, 942, 913, 742 cm⁻¹; HRMS (ESI) 233.1896 (C₁₄H₂₆ONa requires 233.1896).

3.2.4. General Procedure for *p*-TsOH Catalysed Allyl Transfer^{94b}

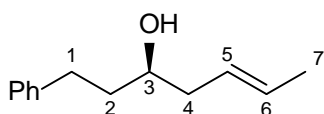
To a mixture of (1*R*,2*S*,5*R*)-1-((*R*)-but-3-en-2-yl)-2-isopropyl-5-methylcyclohexanol **2.52** (0.5 g, 2.4 mmol) and the desired aldehyde (0.13 g, 1.2 mmol) in dichloromethane (5 mL) was added *p*-toluenesulfonic acid monohydrate (23 mg, 0.12 mmol). The reaction mixture was stirred overnight and a yellow colour change was observed. Once the reaction was complete, saturated NaHCO₃ solution (10 mL) was added. The organic layer was separated and dried over MgSO₄, filtered and the solvent removed *in vacuo*. The resultant crude yellow oil was purified using column chromatography (light peteroelum: EtOAc 20:1).



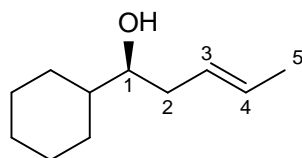
(*S,E*)-1-Phenylpent-3-en-1-ol (2.53a).^{94a} Clear liquid (64%): [α]_D -59.0 (*c* 1.0, CHCl₃); literature gives [α]_D -66.4 (*c* 1.0 CHCl₃); ¹H NMR (400 MHz; CDCl₃) δ 1.67 (dd, *J* = 6.4, 1.2 Hz, 3H, H-5), 2.23 (br s, OH), 2.36 – 2.47 (m, 2H, H-2), 4.65 (dd, *J* = 8.0, 5.2 Hz, 1H, H-1), 5.37 – 5.45 (m, 1H, H-3), 5.53 – 5.62 (m, 1H, H-4), 7.23 – 7.29 (m, 1H), 7.30 – 7.35 (m, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 18.1 (CH₃, C-5), 42.8 (CH₂, C-2), 73.5 (CH, C-1), 125.9 (CH \times 2, Ph), 126.9 (CH, C-3), 127.4 (CH, Ph), 128.4 (CH \times 2, Ph), 129.4 (CH, C-4), 144.1 (C); IR (NaCl) ν 3383, 3028, 2916, 1494, 1453, 1041, 967, 758, 699, 551 cm⁻¹; HRMS (ESI) 185.0936 (C₁₁H₁₄ONa requires 185.0937); chiral HPLC (Chiralcel IB column, hexane: 2-propanol = 98:2, 0.75 mL min⁻¹) showed 96% *ee* (*t*_R = 13.68 min, *t*_S = 17.59 min).



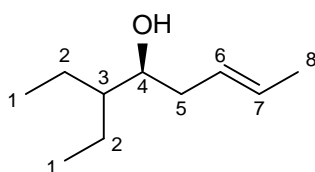
(*S,E*)-1-Phenylhex-4-en-2-ol (2.53b).^{70b} Clear liquid (80%): $[\alpha]_D +11.0$ (*c* 1.0, CHCl_3); ^1H NMR (400 MHz; CDCl_3) δ 1.60 (dd, $J = 6.4, 1.2$ Hz, 3H, H-6), 1.80 (br s, OH), 1.99 – 2.07 (m, 1H, H-3), 2.11 – 2.17 (m, 1H, H-3), 2.60 (dd, $J = 13.6, 7.8$ Hz, 1H, H-1), 2.69 (dd, $J = 13.6, 4.8$ Hz, 1H, H-1), 3.70 (dddd, $J = 7.8, 4.8$ Hz, 1H, H-2), 5.32 – 5.40 (m, 1H, H-4), 5.42 – 5.51 (m, 1H, H-5), 7.10 – 7.15 (m, 3H), 7.18 – 7.22 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 18.2 (CH_3 , C-6), 40.0 (CH_2 , C-3), 43.3 (CH_2 , C-1), 72.1 (CH , C-2), 126.4 (CH , Ph), 127.1 (CH , C-4), 128.5 ($\text{CH} \times 2$, Ph), 128.9 (CH , C-5), 129.5 ($\text{CH} \times 2$, Ph), 138.7 (C); IR (NaCl) ν 3401, 3027, 2917, 1601, 1496, 1453, 1080, 1031, 742, 700, 602, 555, 505 cm^{-1} ; HRMS (ESI) 199.1092 ($\text{C}_{12}\text{H}_{16}\text{ONa}$ requires 199.1093); chiral HPLC (Chiralcel IB column, hexane: 2-propanol = 98:2 0.75 mL min^{-1}) showed 92% *ee* ($t_R = 13.6$ min, $t_S = 11.5$ min).



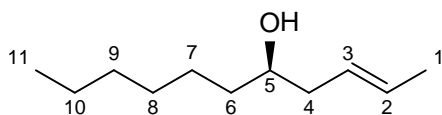
(*R,E*)-1-Phenylhept-5-en-3-ol (2.53c).^{94b} Clear liquid (86%): $[\alpha]_D +23.0$ (*c* 1.0, CHCl_3); ^1H NMR (400 MHz; CDCl_3) δ 1.68 (dd, $J = 6.0, 0.8$ Hz, 3H, H-7), 1.73 – 1.78 (m, 2H, H-2), 1.85 (br s, OH), 2.06 – 2.13 (m, 1H, H-4), 2.20 – 2.27 (m, 1H, H-4), 2.67 (dt, $J = 13.6, 8.4$ Hz, 1H, H-1), 2.80 (dt, $J = 13.6, 8.4$ Hz, 1H, H-1), 3.57 – 3.63 (m, 1H, H-3), 5.39 – 5.45 (m, 1H, H-5), 5.51 – 5.59 (m, 1H, H-6), 7.15 – 7.22 (m, 3H), 7.25 – 7.29 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 18.1 (CH_3 , C-7), 32.1 (CH_2 , C-1), 38.4 (CH_2 , C-2), 40.9 (CH_2 , C-4), 70.3 (CH , C-3), 125.8 (CH , Ph), 127.0 (CH , C-5), 128.4 ($\text{CH} \times 2$, Ph), 128.5 ($\text{CH} \times 2$, Ph), 129.1 (CH , C-6), 142.2 (C); IR (NaCl) ν 3368, 3026, 2930, 2856, 1603, 1496, 1454, 1046, 968, 746, 699 cm^{-1} ; HRMS (ESI) 213.1247 ($\text{C}_{13}\text{H}_{18}\text{ONa}$ requires 213.1250); chiral GC (Supelco γ -DEX column, oven for 2 min at 120 $^\circ\text{C}$, then 0.5 $^\circ\text{C} \text{min}^{-1}$) showed 94% *ee* ($t_R = 44.8$ min, $t_S = 47.9$ min).



(*S,E*)-1-Cyclohexylpent-3-en-1-ol (2.53d).¹⁰⁶ Clear liquid (63%): $[\alpha]_{\text{D}} -1.18$ (c 4.0, CHCl_3); ^1H NMR (400 MHz; CDCl_3) δ 0.84 – 1.41 (m, 7H, Cy), 1.65 – 1.81 (m, 7H, $2 \times \text{CH}_2$, Cy & CH_3 , H-5), 2.05 (dt, $J = 14.0, 8.0$ Hz, 1H, H-2), 2.22 – 2.28 (m, 1H, H-2), 3.30 – 3.34 (m, 1H, H-1), 5.40 – 5.48 (m, 1H, H-3), 5.51 – 5.58 (m, 1H, H-4); ^{13}C NMR (100 MHz, CDCl_3) δ 18.0 (CH_3 , C-5), 26.2 (CH_2 , Cy), 26.3 (CH_2 , Cy), 26.4 (CH_2 , Cy), 28.2 (CH_2 , Cy), 29.1 (CH_2 , 29.1), 37.5 (CH_2 , C-2), 43.0 (CH, Cy), 75.0 (CH, C-1), 127.7 (CH, C-3), 128.6 (CH, C-4); IR (NaCl) ν 3390, 2925, 2853, 1449, 1031, 969, 892 cm^{-1} ; HRMS (ESI) 191.1404 ($\text{C}_{11}\text{H}_{20}\text{ONa}$ requires 191.1406); chiral GC (Supelco α -DEX column, oven for 30 min at 105 $^\circ\text{C}$, then 0.5 $^\circ\text{C min}^{-1}$) showed 97% *ee* ($t_{\text{R}} = 30.1$ min, $t_{\text{S}} = 31.0$ min).



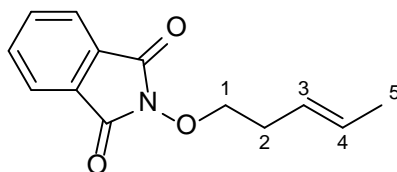
(*S,E*)-3-Ethyl-oct-6-en-4-ol (2.53e).^{94a} Clear liquid (77%): $[\alpha]_{\text{D}} -0.73$ (c 3.0, CHCl_3); ^1H NMR (400 MHz; CDCl_3) δ 0.91 (t, $J = 7.6$ Hz, 6H, H-1), 1.21 – 1.50 (m, 5H, H-2/3), 1.52 (br s, OH), 1.70 (d, $J = 6.4$ Hz, 3H, H-8), 2.06 (dt, $J = 14.0, 8.8$ Hz, 1H, H-5), 2.19 – 2.24 (m, 1H, H-5), 3.55 – 3.62 (m, 1H, H-4), 5.40 – 5.48 (m, 1H, H-6), 5.52 – 5.59 (m, 1H, H-7); ^{13}C NMR (100 MHz, CDCl_3) δ 11.6 ($2 \times \text{CH}_3$, C-1), 18.1 (CH_3 , C-8), 21.3 (CH_2 , C-2), 21.9 (CH_2 , C-2), 37.5 (CH_2 , C-5), 46.0 (CH, C-3), 72.1 (CH, C-4), 127.9 (CH, C-6), 128.8 (CH, C-7); IR (NaCl) ν 3391, 2962, 2934, 2875, 1461, 1378, 968 cm^{-1} ; HRMS (ESI) 179.1404 ($\text{C}_{10}\text{H}_{20}\text{ONa}$ requires 179.1406); chiral GC (Supelco α -DEX column, oven for 2 min at 65 $^\circ\text{C}$, then 0.5 $^\circ\text{C min}^{-1}$) showed 94% *ee* ($t_{\text{R}} = 36.0$ min, $t_{\text{S}} = 36.6$ min).



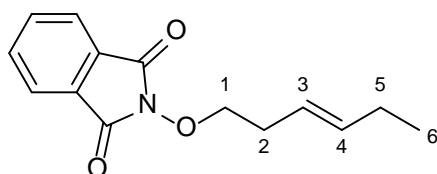
(*R,E*)-Undec-2-en-5-ol (2.53f).^{70b} Clear liquid (27%): $[\alpha]_D +1.7$ (c 1.0, CHCl_3); ^1H NMR (400 MHz; CDCl_3) δ 0.89 (t, $J = 6.4$ Hz, 3H, H-11), 1.26 – 1.36 (m, 8H, $4 \times \text{CH}_2$, H-7/8/9/10), 1.41 – 1.47 (m, 3H, OH & CH_2 , H-6), 1.69 (dd, $J = 6.0, 0.8$ Hz, 3H, H-1), 2.05 (dt, $J = 14.8, 8.0$ Hz, 1H, H-4), 2.19 – 2.25 (m, 1H, H-4), 3.55 – 3.59 (m, 1H, H-5), 5.39 – 5.47 (m, 1H, H-3), 5.51 – 5.60 (m, 1H, H-2); ^{13}C NMR (100 MHz, CDCl_3) δ 14.1 (CH_3 , C-11), 18.0 (CH_3 , C-1), 22.6 (CH_2 , C-7/8/9/10), 25.7 (CH_2 , C-7/8/9/10), 29.4 (CH_2 , C-7/8/9/10), 31.8 (CH_2 , C-7/8/9/10), 36.8 (CH_2 , C-6), 40.7 (CH_2 , C-4), 71.0 (CH, C-5), 127.2 (CH, C-3), 128.8 (CH, C-2); IR (NaCl) ν 3360, 2957, 2929, 2857, 1455, 967 cm^{-1} ; HRMS (ESI) 169.1587 ($\text{C}_{11}\text{H}_{21}\text{O}$ requires 169.1587); chiral GC (Supelco γ -DEX column, oven for 2 min at 120 $^\circ\text{C}$, then 0.5 $^\circ\text{C min}^{-1}$) showed 92% *ee* ($t_R = 28.2$ min, $t_S = 31.0$ min).

3.2.5. General Procedure for the Synthesis of Phthalimide Protected Hydroxylamines

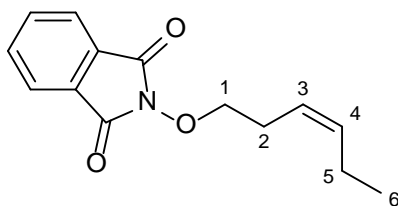
To a flame dried flask with an inert atmosphere, was added PPh₃ (3.4 g, 1.3 mmol) and *N*-hydroxyphthalimide (2.2 g, 1.3 mmol). THF (30 mL) was added and the mixture stirred until all the solids had dissolved. The desired alcohol (1.2 g, 1.2 mmol) was added via syringe and the mixture cooled to 0 °C. DIAD (2.6 mL, 1.3 mmol) was added dropwise via syringe. The reaction was stirred overnight at room temperature. Upon completion the THF was evaporated and the mixture was partitioned between saturated NaHCO₃ solution (30 mL) and light petroleum: EtOAc (1:1, 30 mL), the organic layer separated and washed further with sat. NaHCO₃ solution (2 × 30 mL) and with brine (30 mL). The mixture was dried with MgSO₄, filtered and the solvent removed *in vacuo*. The resultant yellow oil (sometimes solidifies on standing) was purified using column chromatography (light petroleum: EtOAc 10:1) to the yield the pure phthalimide derivative.



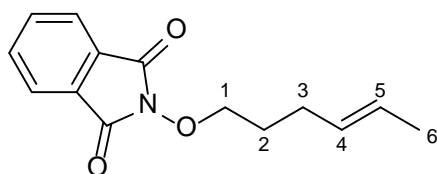
(*E*)-2-(Pent-3-enyloxy)isoindoline-1,3-dione (2.4). Colourless oil, (51%): ¹H NMR (400 MHz; CDCl₃) δ 1.66 (dd, *J* = 6.2, 1.4 Hz, 3H, H-5), 2.47 – 2.53 (m, 2H, H-2), 4.22 (t, *J* = 7.0 Hz, 2H, H-1), 5.44 – 5.52 (m, 1H, H-3), 5.57 – 5.64 (m, 1H, H-4), 7.73 – 7.78 (m, 2H), 7.80 – 7.86 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 18.0 (CH₃, C-5), 31.5 (CH₂, C-2), 77.8 (CH₂, C-1), 123.5 (CH × 2, Phth), 125.4 (CH, C-3), 128.3 (CH, C-4), 129.0 (C), 134.5 (CH × 2, Phth), 163.6 (CO); IR (NaCl) ν 2942, 1789, 1733, 1467, 1374, 1245, 1187, 1127, 877, 700 cm⁻¹; HRMS (ESI) 254.0784 (C₁₃H₁₂NO₃ requires 254.0788).



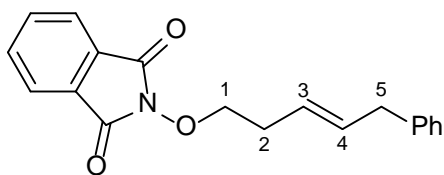
(E)-2-(Hex-3-enyloxy)isoindoline-1,3-dione (E-2.15). Colourless oil, (62%): ^1H NMR (400 MHz; CDCl_3) δ 0.96 (t, $J = 7.6$ Hz, 3H, H-6), 2.01 (quin, $J = 7.6$ Hz, 2H, H-5), 2.49 – 2.54 (m, 2H, H-2), 4.22 (t, $J = 8.0$ Hz, 2H, H-1), 5.41 – 5.49 (m, 1H, H-3), 5.60 – 5.67 (m, 1H, H-4), 7.74 – 7.77 (m, 2H), 7.82 – 7.85 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 13.6 (CH_3 , C-6), 25.6 (CH_2 , C-5), 31.5 (CH_2 , C-2), 77.9 (CH_2 , C-1), 123.1 (CH, C-3), 123.5 (CH \times 2, Phth), 129.0 (C), 134.5 (CH \times 2, Phth), 135.4 (CH, C-4), 163.6 (CO); IR (NaCl) ν 2962, 1790, 1733, 1467, 1373, 1187, 877, 700 cm^{-1} ; HRMS (ESI) 268.0944 ($\text{C}_{14}\text{H}_{15}\text{NO}_3\text{Na}$ requires 268.0940).



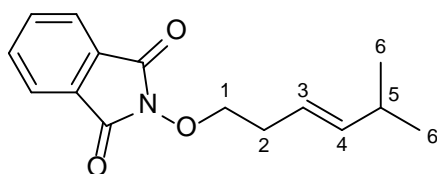
(Z)-2-(Hex-3-enyloxy)isoindoline-1,3-dione (Z-2.15). Colourless oil, (60%): ^1H NMR (400 MHz; CDCl_3) δ 0.98 (t, $J = 7.5$ Hz, 3H, H-6), 2.09 (quin, $J = 7.5$ Hz, 2H, H-5), 2.55 – 2.60 (m, 2H, H-2), 4.20 (t, $J = 7.2$ Hz, 2H, H-1), 5.38 – 5.44 (m, 1H, H-3), 5.50 – 5.56 (m, 1H, H-4), 7.73 – 7.78 (m, 2H), 7.82 – 7.87 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 14.2 (CH_3 , C-6), 20.7 (CH_2 , C-5), 26.4 (CH_2 , C-2), 77.7 (CH_2 , C-1), 122.7 (CH, C-3), 123.5 (CH \times 2, Phth), 129.0 (C), 134.5 (CH \times 2, Phth), 134.9 (CH, C-4), 163.6 (CO); IR (NaCl) ν 2963, 1783, 1727, 1465, 1377, 1187, 987, 699 cm^{-1} ; HRMS (ESI) 268.0943 ($\text{C}_{14}\text{H}_{15}\text{NO}_3\text{Na}$ requires 268.0944).



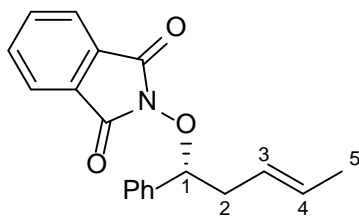
(E)-2-(Hex-4-enyloxy)isoindoline-1,3-dione (2.37). White solid (82%): mp 44 - 46°C; ^1H NMR (400 MHz; CDCl_3) δ 1.65 (dd, $J = 6.0, 1.2$ Hz, 3H, H-6), 1.85 (quin, $J = 6.9$ Hz, 2H, H-2), 2.16 – 2.22 (m, 2H, H-3), 4.21 (t, $J = 6.9$ Hz, 2H, H-1), 5.43 – 5.51 (m, 2H, H-4/5), 7.74 – 7.77 (m, 2H), 7.82 – 7.85 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 17.9 (CH_3 , C-6), 28.0 (CH_2 , C-2), 28.5 (CH_2 , C-3), 78.0 (CH_2 , C-1), 123.5 ($\text{CH} \times 2$, Phth), 126.2 (CH , C-4/5), 129.0 (C), 129.8 (CH , C-4/5), 134.4 ($\text{CH} \times 2$, Phth), 163.7 (CO); IR (NaCl) ν 2940, 1789, 1732, 1372, 1186, 1127, 1016, 877, 700 cm^{-1} ; HRMS (ESI) 268.0940 ($\text{C}_{14}\text{H}_{15}\text{NO}_3\text{Na}$ requires 268.0944).



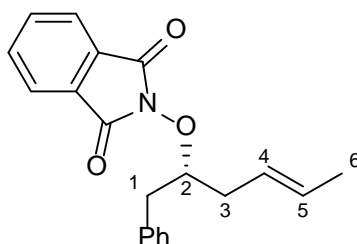
(E)-2-(5-Phenylpent-3-enyloxy)isoindoline-1,3-dione (2.30). Colourless oil, (79%): ^1H NMR (400 MHz; CDCl_3) δ 2.54 (q, $J = 6.9$ Hz, 2H, H-2), 3.33 (d, $J = 6.8$ Hz, 2H, H-5), 4.23 (t, $J = 6.9$ Hz, 2H, H-1), 5.53 – 5.61 (m, 1H, H-3), 5.72 – 5.79 (m, 1H, H-4), 7.15 – 7.18 (m, 3H), 7.24 – 7.28 (m, 2H), 7.70 – 7.73 (m, 2H), 7.79 – 7.82 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 31.1 (CH_2 , C-2), 39.2 (CH_2 , C-5), 77.7 (CH_2 , C-1), 123.8 ($\text{CH} \times 2$, Phth), 125.9 (CH , Ph), 126.0 (CH , C-3), 128.4 ($\text{CH} \times 2$, Ph), 128.5 ($\text{CH} \times 2$, Ph), 129.0 (C), 132.3 (CH , C-4), 134.5 ($\text{CH} \times 2$, Phth), 140.4 (C), 163.6 (CO); IR (NaCl) ν 3027, 2950, 2896, 1788, 1738, 1603, 1372, 1187, 1128, 991, 706, 518 cm^{-1} ; HRMS (ESI) 330.1092 ($\text{C}_{19}\text{H}_{17}\text{NO}_3\text{Na}$ requires 330.1101).



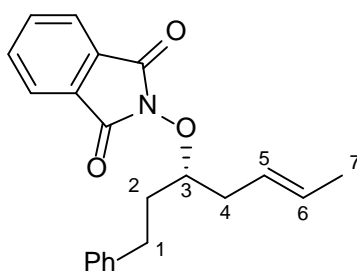
(E)-2-(5-Methylhex-3-enyloxy)isoindoline-1,3-dione (2.31). Clear colourless oil, (49%): ^1H NMR (400 MHz; CDCl_3) δ 0.85 (d, $J = 6.4$ Hz, 6H, H-6), 2.12 – 2.17 (m, 1H, H-5), 2.41 (q, $J = 7.0$ Hz, 2H, H-2), 4.12 (t, $J = 7.0$ Hz, 2H, H-1), 5.28 – 5.35 (m, 1H, H-3), 5.44 – 5.49 (m, 1H, H-4), 7.66 – 7.69 (m, 2H), 7.72 – 7.76 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 22.4 (CH_3 , C-6), 31.0 (CH, C-5), 31.4 (CH_2 , C-2), 77.9 (CH_2 , C-1), 121.1 (CH, C-3), 123.4 ($\text{CH} \times 2$, Phth), 128.9 (C), 131.4 ($\text{CH} \times 2$, Phth), 140.8 (CH, C-4), 163.5 (CO); IR (NaCl) ν 2958, 1790, 1735, 1467, 1373, 1187, 1128, 977, 878, 701 cm^{-1} ; HRMS (ESI) 282.1095 ($\text{C}_{15}\text{H}_{17}\text{NO}_3\text{Na}$ requires 282.1101).



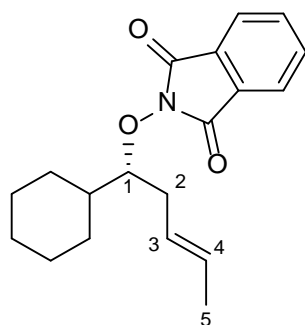
(R,E)-2-(1-Phenylpent-3-enyloxy)isoindoline-1,3-dione (2.54a). Colourless oil (51%): $[\alpha]_{\text{D}} +120.0$ (c 1.0, CHCl_3); ^1H NMR (400 MHz; CDCl_3) δ 1.59 – 1.61 (dd, $J = 6.4, 1.2$ Hz, 3H, H-5), 2.62 – 2.70 (m, 1H, H-2), 2.84 – 2.94 (m, 1H, H-2), 5.33 – 5.36 (t, $J = 7.0$ Hz, 1H, H-1), 5.34 – 5.41 (m, 1H, H-3), 5.51 – 5.59 (m, 1H, H-4), 7.23 – 7.35 (m, 3H), 7.45 – 7.47 (m, 2H), 7.74 – 7.76 (m, 2H), 7.83 – 7.85 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 18.0 (CH_3 , C-5), 38.0 (CH_2 , C-2), 88.8 (CH, C-1), 123.3 ($\text{CH} \times 2$, Phth), 123.5 ($\text{CH} \times 2$, Phth), 125.3 (CH, C-3), 128.2 ($\text{CH} \times 2$, Ph), 128.2 ($\text{CH} \times 2$, Ph), 128.7 (CH, C-4), 128.8 (C), 129.0 (CH, Ph), 137.7 (C), 163.7 (CO); IR (NaCl) ν 2981, 2935, 1789, 1733, 1467, 1379, 1188, 1015, 878, 700 cm^{-1} ; HRMS (ESI) 330.1095 ($\text{C}_{19}\text{H}_{17}\text{NO}_3\text{Na}$ requires 330.1101).



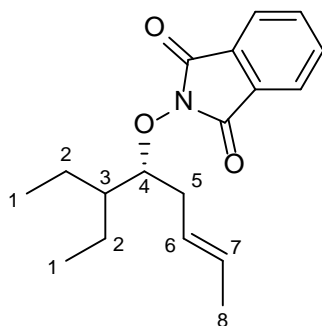
(*R,E*)-2-(1-Phenylhex-4-en-2-yloxy)isoindoline-1,3-dione (2.54b). Colourless oil (57%): $[\alpha]_D -12.0$ (c 1.0, CHCl_3); $^1\text{H NMR}$ (400 MHz; CDCl_3) δ 1.54 (d, $J = 5.2$ Hz, 3H, H-6), 2.30 – 2.32 (m, 2H, H-3), 2.01 (qd, $J = 14.4, 6.2$ Hz, 2H, H-1), 4.55 (quin, $J = 6.2$ Hz, 1H, H-2), 5.39 – 5.52 (m, 2H, H-4/5), 7.04 – 7.08 (m, 1H), 7.13 – 7.18 (m, 4H), 7.61 – 7.64 (m, 2H), 7.67 – 7.71 (m, 2H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 18.0 (CH_3 , C-6), 35.6 (CH_2 , C-3), 38.9 (CH_2 , C-1), 87.6 (CH, C-2), 123.4 ($\text{CH} \times 2$, Phth), 125.7 (CH, C-4/5), 126.4 (CH, Ph), 128.3 ($\text{CH} \times 2$, Ph), 128.7 (CH, C-4/5), 129.0 (C), 129.3 ($\text{CH} \times 2$, Ph), 134.4 ($\text{CH} \times 2$, Phth), 137.3 (C), 164.1 (CO); IR (NaCl) ν 3028, 2934, 1789, 1736, 1454, 1375, 1188, 1127, 975, 878, 700 cm^{-1} ; HRMS (ESI) 344.1257 ($\text{C}_{20}\text{H}_{19}\text{NO}_3\text{Na}$ requires 344.1255).



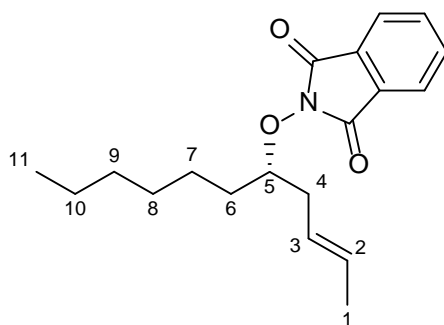
(*S,E*)-2-(1-Phenylhept-5-en-3-yloxy)isoindoline-1,3-dione (2.54c). Colourless oil (40%): $[\alpha]_D -52.0$ (c 1.0, CHCl_3); $^1\text{H NMR}$ (400 MHz; CDCl_3) δ 1.62 (d, $J = 5.2$ Hz, 3H, H-7), 1.93 – 2.07 (m, 2H, H-2), 2.40 – 2.48 (m, 2H, H-4), 2.85 – 2.96 (m, 2H, H-1), 4.32 (quin, $J = 5.9$ Hz, 1H, H-3), 5.44 – 5.58 (m, 2H, H-5/6), 7.16 – 7.20 (m, 1H), 7.25 – 7.31 (m, 4H), 7.72 – 7.77 (m, 2H), 7.81 – 7.86 (m, 2H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 18.0 (CH_3 , C-7), 31.3 (CH_2 , C-1), 34.3 (CH_2 , C-2), 36.1 (CH_2 , C-4), 87.0 (CH, C-3), 123.5 ($\text{CH} \times 2$, Phth), 125.5 (CH, C-5/6), 125.9 (CH, Ph), 128.4 ($\text{CH} \times 2$, Ph), 128.5 ($\text{CH} \times 2$, Phth), 128.6 (CH, C-5/6), 129.0 (C), 134.4 ($\text{CH} \times 2$, Phth), 142.0 (C), 164.3 (CO); IR (NaCl) ν 2934, 1789, 1734, 1374, 1188, 1124, 976, 878, 700 cm^{-1} ; HRMS (ESI) 358.1414 ($\text{C}_{21}\text{H}_{21}\text{NO}_3\text{Na}$ requires 358.1412).



(*R,E*)-2-(1-Cyclohexylpent-3-enyloxy)isoindoline-1,3-dione (2.54d). Colourless oil (29%): $[\alpha]_D -29.3$ (c 1.5, CHCl_3); $^1\text{H NMR}$ (400 MHz; CDCl_3) δ 1.13 – 1.29 (m, 8H, Cy), 1.58 (d, $J = 5.6$ Hz, 3H, H-5), 1.64 – 1.74 (m, 1H), 1.76 – 1.83 (m, 1H), 1.85 – 1.97 (m, 1H), 2.33 – 2.43 (m, 2H, H-2), 4.11 (q, $J = 4.0$ Hz, 1H, H-1), 5.46 – 5.60 (m, 2H, H-3/4), 7.72 – 7.76 (m, 2H), 7.80 – 7.84 (m, 2H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 18.0 (CH_3 , C-5), 26.2 ($\text{CH}_2 \times 2$, Cy), 26.5 (CH_2 , Cy), 28.1 (CH_2 , Cy), 28.2 (CH_2 , Cy), 32.9 (CH_2 , C-2), 39.8 (CH , Cy), 91.2 (CH , C-1), 123.3 ($\text{CH} \times 2$, Phth), 126.6 (CH , C-3/4), 127.5 (CH , C-3/4), 129.1 (C), 134.3 ($\text{CH} \times 2$, Phth), 164.3 (CO); IR (NaCl) ν 2928, 2853, 1790, 1734, 1450, 1374, 1188, 1122, 977, 878, 702 cm^{-1} ; HRMS (ESI) 336.1570 ($\text{C}_{19}\text{H}_{23}\text{NO}_3\text{Na}$ requires 336.1568).



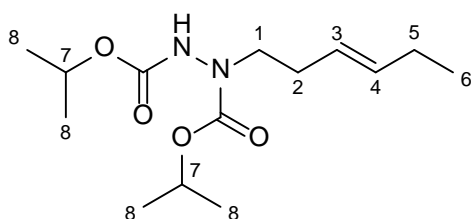
(*R,E*)-2-(3-Ethyl-oct-6-en-4-yloxy)isoindoline-1,3-dione (2.54e). Colourless oil (19%): $[\alpha]_D -26.9$ (c 10.0, CHCl_3); $^1\text{H NMR}$ (400 MHz; CDCl_3) δ 0.94 (t, $J = 6.3$ Hz, 3H, H-1), 1.00 (t, $J = 6.3$ Hz, 3H, H-1), 1.21 – 1.28 (m, 2H, H-2), 1.46 – 1.58 (m, 5H, H-2/3/8), 1.74 – 1.83 (m, 1H, H-2), 2.36 – 2.40 (m, 2H, H-5), 4.36 (dt, $J = 8.9, 3.0$ Hz, 1H, H-4), 5.48 – 5.53 (m, 2H, H-6/7), 7.72 – 7.76 (m, 2H), 7.80 – 7.84 (m, 2H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 11.8 (CH_3 , C-1), 12.0 (CH_3 , C-1), 17.9 (CH_3 , C-8), 21.5 (CH_2 , C-2), 21.8 (CH_2 , C-2), 32.9 (CH_2 , C-5), 43.3 (CH , C-3), 88.8 (CH , C-4), 123.3 ($\text{CH} \times 2$, Phth), 126.9 (CH , C-6/7), 127.4 (CH , C-6/7), 129.1 (C), 134.3 ($\text{CH} \times 2$, Phth), 164.3 (CO); IR (NaCl) ν 2963, 2935, 1790, 1735, 1374, 1188, 976, 878, 701 cm^{-1} ; HRMS (ESI) 324.1565 ($\text{C}_{18}\text{H}_{23}\text{NO}_3\text{Na}$ requires 324.1570).



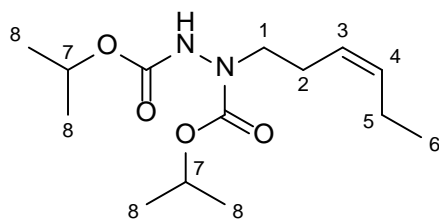
(*S,E*)-2-(Undec-2-en-5-yloxy)isoindoline-1,3-dione (2.54f). Colourless oil (45%): $[\alpha]_D -16.5$ (*c* 2.0, CHCl_3); $^1\text{H NMR}$ (400 MHz; CDCl_3) δ 0.89 (t, $J = 6.6$ Hz, 3H, H-11), 1.26 – 1.36 (m, 6H, H-8/9/10), 1.52 (quin, $J = 7.4$ Hz, 2H, H-7), 1.62 (d, $J = 4.8$ Hz, 3H, H-1), 1.64 – 1.71 (m, 2H, H-6), 2.40 (t, $J = 5.6$ Hz, 2H, H-4), 4.27 (quin, $J = 5.6$ Hz, 1H, H-5), 5.45 – 5.57 (m, 2H, H-2/3), 7.72 – 7.76 (m, 2H), 7.80 – 7.85 (m, 2H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 14.1 (CH_3 , C-11), 18.0 (CH_3 , C-1), 22.6 (CH_2 , C-8/9/10), 25.0 (CH_2 , C-7), 29.3 (CH_2 , C-8/9/10), 31.7 (CH_2 , C-8/9/10), 32.3 (CH_2 , C-6), 36.0 (CH_2 , C-4), 87.6 (CH, C-5), 123.4 (CH \times 2, Phth), 125.8 (CH, C-2/3), 128.2 (CH, C-2/3), 129.1 (C), 134.4 (CH \times 2, Phth), 164.3 (CO); IR (NaCl) ν 2929, 2856, 1790, 1734, 1374, 1188, 976, 701 cm^{-1} ; HRMS (ESI) 338.1727 ($\text{C}_{19}\text{H}_{25}\text{NO}_3\text{Na}$ requires 338.1724).

3.2.6. General Procedure for the Synthesis of Homoallylic Hydrazines

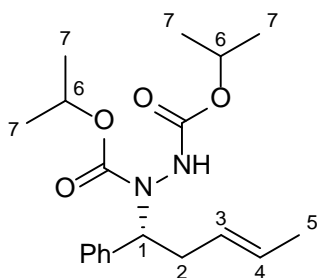
To a flame dried flask with an inert atmosphere was added PPh₃ (0.58 g, 2.2 mmol) and THF (40 mL), the mixture was stirred until all the solids had dissolved. The alcohol (0.2 g, 2.0 mmol) was added via syringe and the mixture cooled to 0 °C. DIAD (0.8 mL, 5 mmol) was added dropwise via syringe. The reaction was stirred overnight at room temperature. Upon completion saturated NaHCO₃ solution (20 mL) was added and the mixture extracted with light petroleum: EtOAc (1:1, 50 mL), the organic layer separated and washed further with sat. NaHCO₃ solution (2 × 30 mL) and brine (20 mL). The mixture was dried with MgSO₄, filtered and the solvent removed *in vacuo*. The resultant yellow oil (sometimes solidifies on standing) was purified using column chromatography (light petroleum: EtOAc 10:1) to the yield the pure diamine derivative.



(E)-Diisopropyl 1-(hex-3-enyl)hydrazine-1,2-dicarboxylate (E-2.58). Colourless oil (28%): ¹H NMR (400 MHz; CDCl₃) δ 0.94 (t, *J* = 7.2 Hz, 3H, H-6), 1.25 (d, *J* = 6.4 Hz, 12H, H-8), 1.99 (quin, *J* = 7.2 Hz, 2H, H-5), 2.25 (q, *J* = 5.2 Hz, 2H, H-2), 3.45 – 2.55 (m, 2H, H-1), 4.90 – 4.97 (m, 2H, H-7), 5.31 – 5.40 (m, 1H, H-3), 5.48 – 5.55 (m, 1H, H-4), 6.48 (s, NH); ¹³C NMR (100 MHz, CDCl₃) δ 13.7 (CH₃, C-6), 22.0 (CH₃ × 4, C-8), 25.6 (CH₂, C-5), 30.8 (CH₂, C-2), 49.5 (CH₂, C-1), 69.6 (CH, C-7), 70.0 (CH, C-7), 125.4 (CH, C-3), 134.4 (CH, C-4), 160.0 (CO), 164.5 (CO); IR (NaCl) ν 3309, 2982, 2937, 2876, 1811, 1748, 1715, 1615, 1499, 1467, 1385, 1376, 1259, 1181, 1096, 903, 764 cm⁻¹; HRMS (ESI) 309.1781 (C₁₄H₂₆N₂O₄Na requires 309.1796).



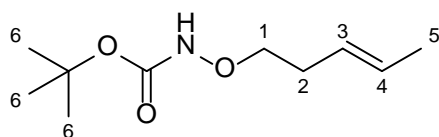
(Z)-Diisopropyl 1-(hex-3-enyl)hydrazine-1,2-dicarboxylate (Z-2.58). Colourless oil (25%): ^1H NMR (400 MHz; CDCl_3) δ 0.97 (t, $J = 7.5$ Hz, 3H, H-6), 1.26 (d, $J = 5.6$ Hz, 12H, H-8), 2.05 (quin, $J = 7.5$ Hz, 2H, H-5), 2.33 (q, $J = 5.3$ Hz, 2H, H-2), 3.46 – 3.54 (m, 2H, H-1), 4.88 – 5.00 (m, 2H, H-7), 5.25 – 5.35 (m, 1H, H-3), 5.42 – 5.52 (m, 1H, H-4), 6.46 (s, NH); ^{13}C NMR (100 MHz, CDCl_3) δ 14.3 (CH_3 , C-6), 20.5 (CH_2 , C-2), 22.0 ($\text{CH}_3 \times 4$, C-8), 25.6 (CH_2 , C-5), 49.6 (CH_2 , C-1), 69.7 (CH, C-7), 69.9 (CH, C-7), 125.0 (CH, C-3), 134.1 (CH, C-4), 156.1 (CO), 156.4 (CO); IR (NaCl) ν 3303, 2981, 2936, 2877, 1713, 1511, 1467, 1413, 1302, 1256, 1203, 1109, 1049, 763 cm^{-1} ; HRMS (ESI) 309.1777 ($\text{C}_{14}\text{H}_{26}\text{N}_2\text{O}_4\text{Na}$ requires 309.1796).



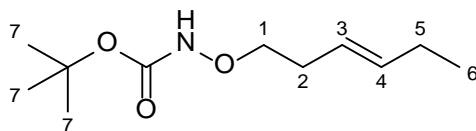
(*R,E*)-Diisopropyl 1-(1-phenylpent-3-enyl)hydrazine-1,2-dicarboxylate (2.62). Colourless oil (36%): $[\alpha]_D +32.8$ (*c* 5.0, CHCl_3); $^1\text{H NMR}$ (400 MHz; CDCl_3 at 25°C) δ 1.25 (d, broad, $J = 6.0$ Hz, 12H, H-7), 1.61 – 1.62 (s, broad, 3H, H-5), 2.46 – 2.64 (m, broad, 1H, H-2), 2.72 – 2.79 (m, broad, 1H, H-2), 4.88 – 5.01 (m, broad, 2H, H-6), 5.35 – 5.47 (m, broad, 2H, H-1/3), 5.49 – 5.60 (m, broad, 1H, H-4), 7.27 – 7.34 (m, broad, 5H); $^1\text{H NMR}$ (400 MHz; DMSO-d_6 at 115°C) δ 1.08 (d, $J = 6.4$ Hz, 6H, H-7), 1.14 (d, $J = 6.4$ Hz, 6H, H-7), 1.52 (d, $J = 6.2$ Hz, 3H, H-5), 2.45 – 2.52 (m, 1H, H-2), 2.59 – 2.66 (m, 1H, H-2), 4.60 – 4.70 (m, 1H, H-6), 4.76 (quin, $J = 6.4$ Hz, 1H, H-6), 5.04 (t, $J = 7.2$ Hz, 1H, H-1), 5.23 – 5.35 (m, 1H, H-3), 5.40 – 5.46 (m, 1H, H-4), 7.17 – 7.31 (m, 5H), 8.40 (s, NH); $^{13}\text{C NMR}$ (100 MHz, DMSO-d_6) δ 17.7 (CH_3 , C-5), 21.9 ($\text{CH}_3 \times 4$, C-7), 34.0 (CH_2 , C-2), 61.2 (CH, C-1), 69.5 (CH, C-6), 70.1 (CH, C-6), 127.5 (CH, C-3), 127.6 (CH, C-4), 128.1 (CH \times 2, Ph), 128.2 (CH \times 3, Ph), 139.2 (C), 155.6 (CO), 156.2 (CO); IR (NaCl) ν 3293, 2980, 2936, 1709, 1403, 1385, 1300, 1259, 1230, 1109, 1035, 968, 759, 699 cm^{-1} ; HRMS (ESI) 371.1937 ($\text{C}_{19}\text{H}_{28}\text{N}_2\text{O}_4\text{Na}$ requires 371.1941).

3.2.7. General Procedure for the Synthesis of *N*-Boc Hydroxylamines

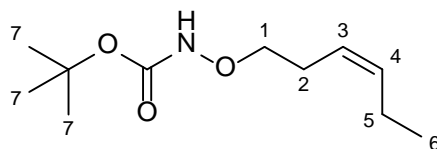
Hydrazine hydrate (62 mg, 1.95 mmol) was added to a solution of the desired phthalimide protected hydroxylamine (0.12 g, 0.4 mmol) in CH₂Cl₂ (20 mL) and stirred at room temperature. A white precipitate is formed throughout the reaction. More CH₂Cl₂ can be added if the precipitate begins to hinder stirring. The reaction was monitored by TLC and after consumption of the starting material the precipitate was filtered off. The filtrate was collected and Boc₂O (0.1 g, 0.47 mmol) was added along with a solution of NaOH (30 mg, 0.78 mmol) in H₂O (5 mL). The mixture was vigorously stirred overnight or until complete consumption of the amine was observed. The reaction mixture was added to a separating funnel and the organic layer isolated, dried over MgSO₄, filtered and the solvent was removed *in vacuo*. The resultant crude oil was purified using column chromatography (10:1, light petroleum: EtOAc) to yield the pure *N*-Boc hydroxylamine. To remove any unreacted Boc₂O that has co-eluted with the carbamate, the mixture was dissolved in CHCl₃ and stirred with imidazole (5 eq, 1.95 mmol) for 30 min. The mixture was washed with H₂O, dried with MgSO₄ and the solvent removed *in vacuo*. The pure *N*-Boc hydroxylamine could then be isolated using flash chromatography (light petroleum: EtOAc 4:1).



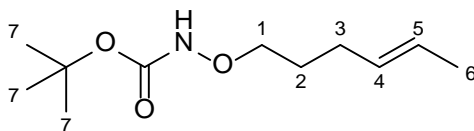
(*E*)-tert-Butyl pent-3-enyloxycarbamate (2.5). Colourless oil (89%): ¹H NMR (400 MHz; CDCl₃) δ 1.41 (s, 9H, H-6), 1.59 (dq, *J* = 6.4, 1.2 Hz, 3H, H-5), 2.26 (qt, *J* = 6.8, 1.2 Hz, 2H, H-2), 3.79 (t, *J* = 6.8 Hz, 2H, H-1), 5.31 – 5.39 (m, 1H, H-3), 5.43 – 5.52 (m, 1H, H-4), 7.06 (s, NH); ¹³C NMR (100 MHz, CDCl₃) δ 18.0 (CH₃, C-5), 28.2 (CH₃ × 3, C-6), 31.4 (CH₂, C-2), 76.2 (CH₂, C-1), 81.6 (C), 126.7 (CH, C-3), 127.5 (CH, C-4), 156.9 (CO); IR (NaCl) ν 3295, 2978, 2935, 1719, 1479, 1455, 1368, 1251, 1168, 967, 774 cm⁻¹; HRMS (ESI) 224.1256 (C₁₀H₁₉NO₃Na requires 224.1257).



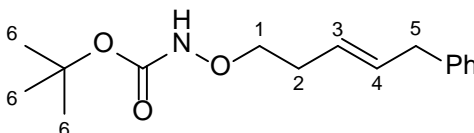
(E)-tert-Butyl hex-3-enyloxycarbamate (E-2.16). Colourless oil (73%): ^1H NMR (400 MHz; CDCl_3) δ 0.97 (t, $J = 7.4$ Hz, 3H, H-6), 1.48 (s, 9H, H-7), 1.97 – 2.05 (m, 2H, H-5), 2.34 (qd, $J = 6.5, 1.2$ Hz, 2H, H-2), 3.86 (t, $J = 6.5$ Hz, 2H, H-1), 5.39 (dt, $J = 15.2, 6.5, 1.2$ Hz, 1H, H-3), 5.57 (dt, $J = 15.2, 6.5, 1.2$ Hz, 1H, H-4), 7.20 (s, NH); ^{13}C NMR (100 MHz, CDCl_3) δ 13.7 (CH_3 , C-6), 25.6 (CH_2 , C-5), 28.2 ($\text{CH}_3 \times 3$, C-7), 31.4 (CH_2 , C-2), 76.3 (CH_2 , C-1), 81.6 (C), 124.4 (CH, C-3), 134.7 (CH, C-4), 156.9 (CO); IR (NaCl) ν 3291, 2965, 2933, 1719, 1457, 1392, 1368, 1250, 1170, 1112, 968, 773 cm^{-1} ; HRMS (ESI) 238.1414 ($\text{C}_{11}\text{H}_{21}\text{NO}_3\text{Na}$ requires 238.1414).



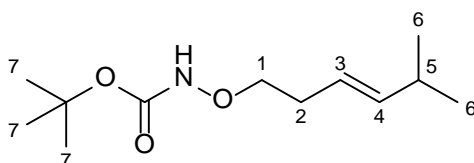
(Z)-tert-Butyl hex-3-enyloxycarbamate (Z-2.16). Colourless oil (64%): ^1H NMR (400 MHz; CDCl_3) δ 0.97 (t, $J = 7.6$ Hz, 3H, H-6), 1.49 (s, 9H, H-7), 2.06 (quind, $J = 7.2, 1.6$ Hz, 2H, H-5), 2.41 (qd, $J = 7.2, 1.6$ Hz, 2H, H-2), 3.85 (t, $J = 7.2$ Hz, 2H, H-1), 5.35 (dt, $J = 10.8, 7.2, 1.6$ Hz, 1H, H-3), 5.49 (dt, $J = 10.8, 7.2, 1.6$ Hz, 1H, H-4), 7.46 (s, NH); ^{13}C NMR (100 MHz, CDCl_3) δ 14.1 (CH_3 , C-6), 20.5 (CH_2 , C-5), 26.2 (CH_2 , C-2), 28.2 ($\text{CH}_3 \times 3$, C-7), 76.0 (CH_2 , C-1), 81.4 (C), 124.0 (CH, C-3), 134.0 (CH, C-4), 157.0 (CO); IR (NaCl) ν 3291, 2967, 2934, 1720, 1479, 1457, 1392, 1251, 1113, 1015, 774 cm^{-1} ; HRMS (ESI) 238.1412 ($\text{C}_{11}\text{H}_{21}\text{NO}_3\text{Na}$ requires 238.1414).



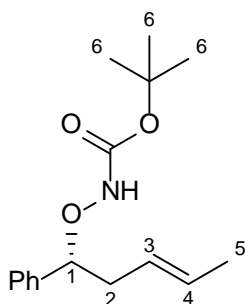
(E)-tert-Butyl hex-4-enyloxycarbamate (2.38). Colourless oil (87%): ^1H NMR (400 MHz; CDCl_3) δ 1.48 (s, 9H, H-7), 1.64 – 1.71 (m, 5H, H-2/6), 2.04 – 2.09 (m, 2H, H-3), 3.85 (t, J = 6.6 Hz, 2H, H-1), 5.37 – 5.49 (m, 2H, H-4/5), 7.12 (s, NH); ^{13}C NMR (100 MHz, CDCl_3) δ 17.9 (CH_3 , C-6), 27.9 (CH_2 , C-2), 28.2 ($\text{CH}_3 \times 3$, C-7), 28.8 (CH_2 , C-3), 76.3 (CH_2 , C-1), 81.6 (C), 125.5 (CH , C-4/5), 130.3 (CH , C-4/5), 156.9 (CO); IR (NaCl) ν 3294, 2978, 2935, 1720, 1479, 1455, 1368, 1251, 1170, 1113, 966 cm^{-1} ; HRMS (ESI) 238.1410 ($\text{C}_{11}\text{H}_{21}\text{NO}_3\text{Na}$ requires 238.1414).



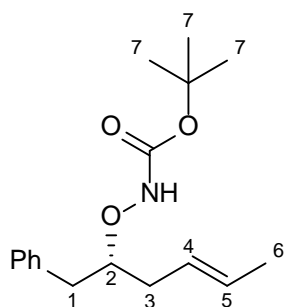
(E)-tert-Butyl 5-phenylpent-3-enyloxycarbamate (2.32). Colourless oil (81%): ^1H NMR (400 MHz; CDCl_3) δ 1.48 (s, 9H, H-6), 2.39 (q, J = 6.7 Hz, 2H, H-2), 3.34 (d, J = 6.7 Hz, 2H, H-5), 3.89 (t, J = 6.7 Hz, 2H, H-1), 5.48 – 5.55 (m, 1H, H-3), 5.65 – 5.72 (m, 1H, H-4), 7.17 – 7.21 (m, 3H), 7.26 – 7.30 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 28.2 ($\text{CH}_3 \times 3$, C-6), 31.4 (CH_2 , C-2), 39.1 (CH_2 , C-5), 76.1 (CH_2 , C-1), 81.7 (C), 126.0 (CH , Ph), 127.1 (CH , C-3), 128.4 ($\text{CH} \times 2$, Ph), 128.5 ($\text{CH} \times 2$, Ph), 131.5 (CH , C-4), 140.5 (C), 156.9 (CO); IR (NaCl) ν 3294, 2977, 2932, 1719, 1454, 1368, 1250, 1167, 1111, 969, 699 cm^{-1} ; HRMS (ESI) 300.1570 ($\text{C}_{16}\text{H}_{23}\text{NO}_3\text{Na}$ requires 300.1570).



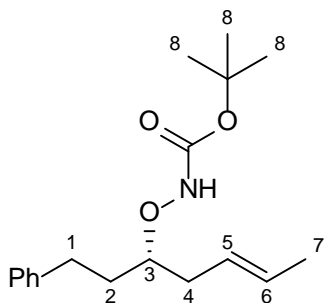
(E)-tert-Butyl 5-methylhex-3-enyloxycarbamate (2.33). Colourless oil (52%): ^1H NMR (400 MHz; CDCl_3) δ 0.96 (d, $J = 6.7$ Hz, 6H, H-6), 1.48 (s, 9H, H-7), 2.25 (sex, $J = 6.7$ Hz, 1H, H-5), 2.33 (q, $J = 6.7$ Hz, 2H, H-2), 3.86 (t, $J = 6.7$ Hz, 2H, H-1), 5.35 (dtd, $J = 15.6, 6.7, 1.2$ Hz, 1H, H-3), 5.49 (ddt, $J = 15.2, 6.7, 1.2$ Hz, 1H, H-4), 7.08 (s, NH); ^{13}C NMR (100 MHz, CDCl_3) δ 22.5 ($\text{CH}_3 \times 2$, C-6), 28.2 ($\text{CH}_3 \times 3$, C-7), 31.0 (CH, C-5), 31.4 (CH_2 , C-2), 76.4 (CH_2 , C-1), 81.6 (C), 122.3 (CH, C-3), 140.2 (CH, C-4), 156.9 (CO); IR (NaCl) ν 3294, 2960, 2928, 1719, 1458, 1368, 1250, 1168, 1110, 971 cm^{-1} ; HRMS (ESI) 252.1570 ($\text{C}_{12}\text{H}_{23}\text{NO}_3\text{Na}$ requires 252.1570).



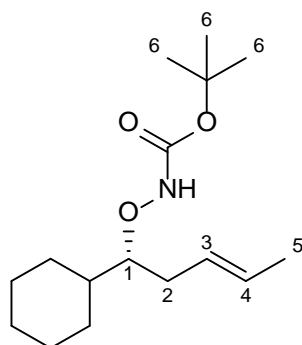
(R,E)-tert-Butyl 1-phenylpent-3-enyloxycarbamate (2.55a). Colourless oil (59%): $[\alpha]_{\text{D}} +23.3$ (c 1.0, CHCl_3); ^1H NMR (400 MHz; CDCl_3) δ 1.45 (s, 9H, H-6), 1.62 (dd, $J = 6.2, 1.4$ Hz, 3H, H-5), 2.38 – 2.45 (m, 1H, H-2), 2.62 – 2.70 (m, 1H, H-2), 4.74 (t, $J = 7.0$ Hz, 1H, H-1), 5.34 – 5.42 (m, 1H, H-3), 5.45 – 5.54 (m, 1H, H-4), 6.87 (s, NH), 7.29 – 7.39 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3) δ 18.0 (CH_3 , C-5), 28.2 ($\text{CH}_3 \times 3$, C-6), 38.5 (CH_2 , C-2), 81.6 (C), 87.6 (CH, C-1), 126.1 (CH, C-3), 127.3 ($\text{CH} \times 2$, Ph), 128.1 (CH, C-4), 128.2 (CH, Ph), 128.5 ($\text{CH} \times 2$, Ph), 140.0 (C), 156.4 (CO); IR (NaCl) ν 3303, 2978, 2917, 2850, 1747, 1716, 1699, 1454, 1368, 1247, 1167, 1104, 1009, 968, 758 cm^{-1} ; HRMS (ESI) 300.1569 ($\text{C}_{16}\text{H}_{23}\text{NO}_3\text{Na}$ requires 300.1570).



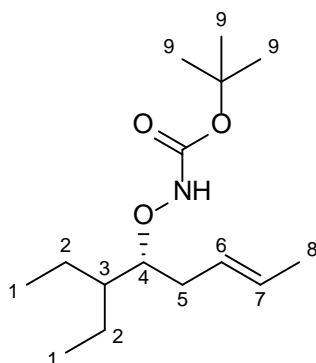
(*R,E*)-tert-Butyl 1-phenylhex-4-en-2-ylloxycarbamate (2.55b). Colourless oil (44%): $[\alpha]_D -10.8$ (c 5.0, CHCl_3); $^1\text{H NMR}$ (400 MHz; CDCl_3) δ 1.47 (s, 9H, H-7), 1.66 – 1.68 (m, 3H, H-6), 2.25 – 2.29 (m, 2H, H-3), 2.79 (dd, $J = 13.9, 7.0$ Hz, 1H, H-1), 2.98 (dd, $J = 13.9, 6.0$ Hz, 1H, H-1), 3.99 (quin, $J = 6.0$ Hz, 1H, H-2), 5.48 – 5.51 (m, 2H, H-4/5), 6.97 (s, NH), 7.18 – 7.22 (m, 3H), 7.26 – 7.29 (m, 2H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 18.1 (CH_3 , C-6), 28.2 ($\text{CH}_3 \times 3$, C-7), 35.2 (CH_2 , C-3), 38.6 (CH_2 , C-1), 81.6 (C), 86.3 (CH, C-2), 126.2 (CH, Ph), 126.6 (CH, C-4/5), 128.0 (CH, C-4/5), 128.4 (CH \times 2, Ph), 129.4 (CH \times 2, Ph), 138.3 (C), 157.1 (CO); IR (NaCl) ν 3303, 2978, 2933, 1718, 1695, 1454, 1368, 1248, 1165, 1104, 1009, 969, 744 cm^{-1} ; HRMS (ESI) 314.1727 ($\text{C}_{17}\text{H}_{25}\text{NO}_3\text{Na}$ requires 314.1727).



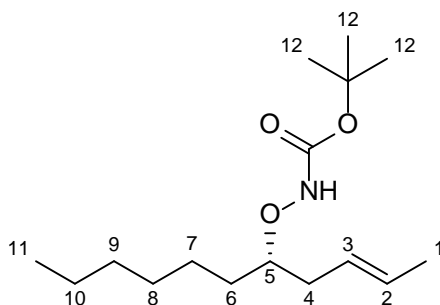
(*S,E*)-tert-Butyl 1-phenylhept-5-en-3-ylloxycarbamate (2.55c). Colourless oil (56%): $[\alpha]_D -34.0$ (c 1.0, CHCl_3); $^1\text{H NMR}$ (400 MHz; CDCl_3) δ 1.49 (s, 9H, H-8), 1.66 (dd, $J = 5.8, 1.0$ Hz, 3H, H-7), 1.76 – 1.92 (m, 2H, H-2), 2.24 – 2.31 (m, 1H, H-4), 2.33 – 2.42 (m, 1H, H-4), 2.66 – 2.73 (m, 1H, H-1), 2.81 – 2.88 (m, 1H, H-1), 3.79 (quin, $J = 5.8$ Hz, 1H, H-3), 5.43 – 5.56 (m, 2H, H-5/6), 6.94 (s, NH), 7.16 – 7.21 (m, 3H), 7.26 – 7.29 (m, 2H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 18.0 (CH_3 , C-7), 28.3 ($\text{CH}_3 \times 3$, C-8), 31.7 (CH_2 , C-1), 33.9 (CH_2 , C-2), 35.8 (CH_2 , C-4), 81.6 (C), 84.7 (CH, C-3), 125.8 (CH, Ph), 126.5 (CH, C-5/6), 128.0 (CH, C-5/6), 128.3 (CH \times 2, Ph), 128.4 (CH \times 2, Ph), 142.3 (C), 157.1 (CO); IR (NaCl) ν 3300, 2925, 1751, 1718, 1695, 1454, 1367, 1246, 1165, 1104, 968, 699 cm^{-1} ; HRMS (ESI) 328.1883 ($\text{C}_{18}\text{H}_{27}\text{NO}_3\text{Na}$ requires 328.1883).



(*R,E*)-tert-Butyl 1-cyclohexylpent-3-enyloxycarbamate (2.55d). Colourless oil (39%): $[\alpha]_D -24.5$ (c 10.0, CHCl_3); $^1\text{H NMR}$ (400 MHz; CDCl_3) δ 0.83 – 1.35 (m, 8H, Cy), 1.49 (s, 9H, H-6), 1.54 – 1.61 (m, 1H, Cy), 1.63 – 1.76 (m, 5H, H-5 + Cy), 2.22 – 2.34 (m, 2H, H-2), 3.52 (q, $J = 4.3$ Hz, 1H, H-1), 5.45 – 5.56 (m, 2H, H-3/4), 7.01 (s, NH); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 18.1 (CH_3 , C-5), 26.3 (CH_2 , Cy), 26.4 (CH_2 , Cy), 26.6 (CH_2 , Cy), 28.3 ($\text{CH}_3 \times 3$, C-6), 28.5 (CH_2 , Cy), 28.6 (CH_2 , Cy), 32.6 (CH_2 , C-2), 39.3 (CH , Cy), 81.4 (C), 89.7 (CH , C-1), 127.2 (CH , C-3/4), 127.4 (CH , C-3/4), 157.0 (CO); IR (NaCl) ν 3300, 2978, 2927, 2853, 1752, 1694, 1367, 1246, 1169, 1104, 1009, 968, 771 cm^{-1} ; HRMS (ESI) 306.2037 ($\text{C}_{16}\text{H}_{29}\text{NO}_3\text{Na}$ requires 306.2040).



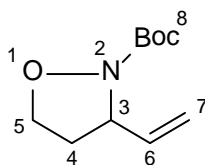
(*R,E*)-tert-Butyl 3-ethyloct-6-en-4-yloxycarbamate (2.55e). Colourless oil (63%): $[\alpha]_D -38.7$ (c 1.5, CHCl_3); $^1\text{H NMR}$ (400 MHz; CDCl_3) δ 0.90 (t, $J = 7.4$ Hz, 6H, H-1), 1.21 – 1.32 (m, 2H, H-2), 1.34 – 1.59 (m, 12H, H-2/3/9), 1.67 (dd, $J = 3.4, 1.0$ Hz, 3H, H-8), 2.24 – 2.27 (m, 2H, H-5), 3.75 (q, $J = 6.0$ Hz, 1H, H-4), 5.46 – 5.56 (m, 2H, H-6/7), 6.93 (s, NH); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 11.8 (CH_3 , C-1), 12.0 (CH_3 , C-1), 18.1 (CH_3 , C-8), 21.6 (CH_2 , C-2), 21.7 (CH_2 , C-2), 28.3 ($\text{CH}_3 \times 3$, C-9), 32.5 (CH_2 , C-5), 42.4 (CH , C-3), 81.4 (C), 87.3 (CH , C-4), 127.1 (CH , C-6/7), 127.8 (CH , C-6/7), 156.9 (CO); IR (NaCl) ν 3305, 2964, 2934, 1752, 1694, 1457, 1367, 1168, 1102 cm^{-1} ; HRMS (ESI) 294.2039 ($\text{C}_{15}\text{H}_{29}\text{NO}_3$ requires 294.2040).



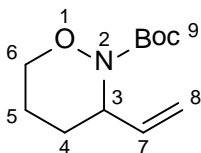
(*S,E*)-tert-Butyl undec-2-en-5-yloxycarbamate (2.55f). Colourless oil (43%): $[\alpha]_D -40.5$ (c 2.0, CHCl_3); $^1\text{H NMR}$ (400 MHz; CDCl_3) δ 0.88 (t, $J = 6.6$ Hz, 3H, H-11), 1.26 – 1.37 (m, 8H, H-7/8/9/10), 1.40 – 1.56 (m, 11H, H-6/12), 1.67 (d, $J = 5.6$ Hz, 3H, H-1), 2.21 – 2.34 (m, 2H, H-4), 3.73 (quin, $J = 5.8$ Hz, 1H, H-5), 5.40 – 5.55 (m, 2H, H-2/3), 6.95 (s, NH); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 14.1 (CH_3 , C-11), 18.0 (CH_3 , C-1), 22.6 (CH_2 , C-7/8/9/10), 25.3 (CH_2 , C-7/8/9/10), 28.2 ($\text{CH}_3 \times 3$, C-12), 29.5 (CH_2 , C-7/8/9/10), 31.8 (CH_2 , C-6), 32.0 (CH_2 , C-7/8/9/10), 35.7 (CH_2 , C-4), 81.4 (C), 85.4 (CH , C-5), 126.8 (CH , C-2/3), 127.6 (CH , C-2/3), 157.1 (CO); IR (NaCl) ν 3299, 2956, 2931, 1720, 1696, 1456, 1367, 1246, 1169, 1104, 1010, 967 cm^{-1} ; HRMS (ESI) 308.2192 ($\text{C}_{16}\text{H}_{31}\text{NO}_3\text{Na}$ requires 308.2196).

3.2.8. General Procedure for Palladium Catalyzed Intramolecular Amination of *N*-Boc Hydroxylamines

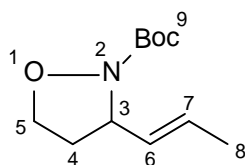
A flask was charged with palladium acetate (2.8 mg, 0.013 mmol) and sodium acetate (4.1 mg, 0.05 mmol) and flushed with O₂. DMSO (1.8 μL, 0.025 mmol) in THF (2 mL) was added and a balloon of O₂ applied. The desired substrate (50 mg, 0.25 mmol) in THF (1 mL) was added to the flask via syringe and stirred at room temperature overnight. The mixture was filtered through a pad of celite, washing with ethyl acetate, and the solvent removed *in vacuo* to yield a brown oil. The crude oil was purified using column chromatography (10:1, light petroleum: EtOAc).



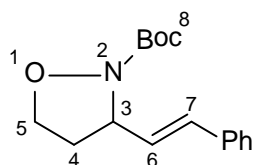
***tert*-Butyl 3-vinylisoxazolidine-2-carboxylate (2.9).** Colourless oil (98%): ¹H NMR (400 MHz; CDCl₃) δ 1.50 (s, 9H, H-8), 2.04 – 2.13 (m, 1H, H-4), 2.44 – 2.52 (m, 1H, H-4), 3.80 (dt, *J* = 8.1, 7.2 Hz, 1H, H-5), 4.08 (td, *J* = 8.1, 4.3 Hz, 1H, H-5), 4.58 – 4.63 (m, 1H, H-3), 5.14 (dt, *J* = 10.2, 1.2 Hz, 1H, H-7), 5.28 (dt, *J* = 16.8, 1.2 Hz, 1H, H-7), 5.83 (ddd, *J* = 16.8, 10.2, 6.4 Hz, 1H, H-6); ¹³C NMR (100 MHz, CDCl₃) δ 28.2 (CH₃ × 3, C-8), 35.2 (CH₂, C-4), 61.0 (CH, C-3), 68.6 (CH₂, C-5), 81.9 (C), 116.0 (CH₂, C-7), 137.5 (CH, C-6), 157.1 (CO); IR (NaCl) ν 2980, 1733, 1705, 1368, 1324, 1165, 1065, 990, 923 cm⁻¹; HRMS (ESI) 222.1101 (C₁₀H₁₇NO₃Na requires 222.1101).



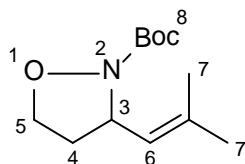
tert-Butyl 3-vinylmorpholine-2-carboxylate (2.39). Colourless oil (95%): ^1H NMR (400 MHz; CDCl_3) δ 1.47 – 1.50 (m, 10H, H-5/9), 1.75 – 1.80 (m, 1H, H-4), 1.89 – 2.03 (m, 2H, H-4/5), 3.85 – 3.91 (m, 1H, H-6), 4.02 – 4.06 (m, 1H, H-6), 4.67 – 4.72 (m, 1H, H-3), 5.23 (dt, $J = 10.6, 1.6$ Hz, 1H, H-8), 5.26 (dt, $J = 17.5, 1.6$ Hz, 1H, H-8), 6.02 (ddd, $J = 17.5, 10.6, 5.4$ Hz, 1H, H-7); ^{13}C NMR (100 MHz, CDCl_3) δ 20.3 (CH_2 , C-5), 26.5 (CH_2 , C-4), 28.3 ($\text{CH}_3 \times 3$, C-9), 56.4 (CH, C-3), 71.4 (CH_2 , C-6), 81.3 (C), 116.6 (CH_2 , C-8), 135.4 (CH, C-7), 155.1 (CO); IR (NaCl) ν 2977, 1727, 1697, 1391, 1367, 1309, 1171, 1094, 897, 759 cm^{-1} ; HRMS (ESI) 236.1254 ($\text{C}_{11}\text{H}_{19}\text{NO}_3\text{Na}$ requires 236.1257).



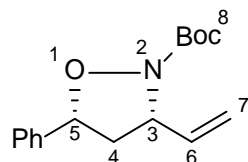
(E)-tert-Butyl 3-(prop-1-enyl)isoxazolidine-2-carboxylate (2.17). Colourless oil, isolated as a mixture of 22:1.7:1 of *E*:*Z*:Terminal isomers respectively (81% from *E*-**2.16**, 77% from *Z*-**2.16**): ^1H NMR (400 MHz; CDCl_3) δ ***E* isomer**: 1.49 (s, 9H, H-9), 1.70 (ddd, $J = 6.6, 1.6, 1.2$ Hz, 3H, H-8), 2.00 – 2.09 (m, 1H, H-4), 2.40 – 2.48 (m, 1H, H-4), 3.77 (dt, $J = 8.2, 7.2$ Hz, 1H, H-5), 4.07 (td, $J = 8.2, 4.0$ Hz, 1H, H-5), 4.56 (q, $J = 7.6$ Hz, 1H, H-3), 5.46 (ddq, $J = 15.2, 7.6, 1.6$ Hz, 1H, H-6), 5.70 (dq, $J = 15.2, 6.6, 1.2$ Hz, 1H, H-7); ***Z* isomer**: 1.74 (dd, $J = 6.8, 1.6$ Hz, 3H, CH_3), 4.94 (dt, $J = 8.8, 5.2$ Hz, 1H), 5.42 – 5.49 (m, 1H), 5.53 – 5.61 (m, 1H); **Terminal isomer**: 5.07 – 5.15 (m, 2H), 5.76 – 5.87 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 17.6 (CH_3 , C-8), 28.2 ($\text{CH}_3 \times 3$, C-9), 35.5 (CH_2 , C-4), 60.7 (CH, C-3), 68.6 (CH_2 , C-5), 81.7 (C), 127.2 (CH, C-7), 130.6 (CH, C-6), 157.3 (CO); IR (NaCl) ν 2978, 1732, 1705, 1367, 1321, 1167, 1061, 964, 851, 767 cm^{-1} ; HRMS (ESI) 236.1257 ($\text{C}_{11}\text{H}_{19}\text{NO}_3\text{Na}$ requires 236.1257).



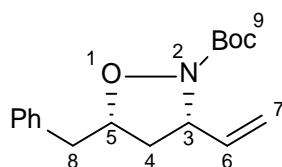
(E)-tert-Butyl 3-styrylisoxazolidine-2-carboxylate (2.34). Colourless oil (61%): ^1H NMR (400 MHz; CDCl_3) δ 1.50 (s, 9H, H-8), 2.13 – 2.21 (m, 1H, H-4), 2.52 – 2.60 (m, 1H, H-4), 3.84 (dt, $J = 8.4, 7.4$ Hz, 1H, H-5), 4.14 (td, $J = 7.4, 4.0$ Hz, 1H, H-5), 4.75 – 4.80 (br q, $J = 7.4$ Hz, 1H, H-3), 6.17 (dd, $J = 16.0, 7.4$ Hz, 1H, H-6), 6.60 (d, $J = 16.0$ Hz, 1H, H-7), 7.21 – 7.39 (m, 5H, Ph); ^{13}C NMR (100 MHz, CDCl_3) δ 28.3 ($\text{CH}_3 \times 3$, C-8), 35.8 (CH_2 , C-4), 60.8 (CH, C-3), 68.8 (CH_2 , C-5), 82.0 (C), 126.5 (CH \times 2, Ph), 127.7 (CH, Ph), 128.6 (CH \times 2, Ph), 128.8 (CH, C-6), 131.0 (CH, C-7), 136.5 (C), 157.1 (CO); IR (NaCl) ν 2979, 2930, 1730, 1705, 1367, 1322, 1165, 1071, 965, 750, 694 cm^{-1} ; HRMS (ESI) 298.1411 ($\text{C}_{16}\text{H}_{21}\text{NO}_3\text{Na}$ requires 298.1414).



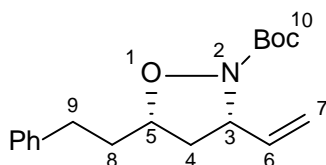
tert-Butyl 3-(2-methylprop-1-enyl)isoxazolidine-2-carboxylate (2.35).^{92d} Colourless oil (51%): ^1H NMR (400 MHz; CDCl_3) δ 1.49 (s, 9H, H-8), 1.73 (dd, $J = 7.6, 1.2$ Hz, 6H, H-7), 1.93 – 2.01 (m, 1H, H-4), 2.43 – 2.50 (m, 1H, H-4), 3.73 – 3.79 (m, 1H, H-5), 4.09 (td, $J = 8.0, 4.0$ Hz, 1H, H-5), 4.85 (dt, $J = 8.6, 4.8$ Hz, 1H, H-3), 5.16 – 5.22 (br dsep, $J = 8.6, 1.2$ Hz, 1H, H-6); ^{13}C NMR (100 MHz, CDCl_3) δ 18.0 (CH_3 , C-7), 25.7 (CH_3 , C-7), 28.3 ($\text{CH}_3 \times 3$, C-8), 36.1 (CH_2 , C-4), 57.1 (CH, C-3), 68.7 (CH_2 , C-5), 81.7 (C), 125.3 (CH, C-6), 134.1 (C), 157.4 (CO); IR (NaCl) ν 2977, 2930, 1732, 1704, 1367, 1322, 1167, 1060, 853, 770 cm^{-1} ; HRMS (ESI) 250.1413 ($\text{C}_{12}\text{H}_{21}\text{NO}_3\text{Na}$ requires 250.1414).



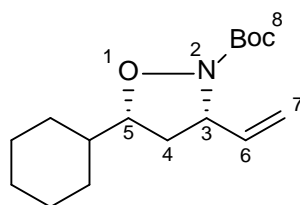
(3*S*,5*R*)-tert-butyl 5-phenyl-3-vinylisoxazolidine-2-carboxylate (2.56a). Colourless oil (98%): $[\alpha]_D -3.8$ (*c* 5.0, CHCl_3); $^1\text{H NMR}$ (400 MHz; CDCl_3) δ 1.52 (s, 9H, H-8), 2.07 – 2.14 (m, 1H, H-4), 2.84 – 2.91 (m, 1H, H-4), 4.78 (q, $J = 7.0$ Hz, 1H, H-3), 4.90 (dd, $J = 10.0, 6.5$ Hz, 1H, H-5), 5.17 (dt, $J = 10.0, 1.2$ Hz, 1H, H-7), 5.33 (dt, $J = 17.0, 1.2$ Hz, 1H, H-7), 5.93 (ddd, $J = 17.0, 10.0, 7.0$ Hz, 1H, H-6), 7.30 – 7.40 (m, 5H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 28.3 ($\text{CH}_3 \times 3$, C-8), 43.7 (CH_2 , C-4), 62.7 (CH, C-3), 82.0 (C), 82.7 (CH, C-5), 115.6 (CH_2 , C-7), 126.8 (CH \times 2, Ph), 128.5 (CH, Ph), 128.5 (CH \times 2, Ph), 137.2 (C), 137.9 (CH, C-6), 157.6 (CO); IR (NaCl) ν 2879, 2931, 1731, 1705, 1456, 1368, 1326, 1255, 1165, 1091, 1034 cm^{-1} ; HRMS (ESI) 298.1411 ($\text{C}_{16}\text{H}_{21}\text{NO}_3\text{Na}$ requires 298.1414).



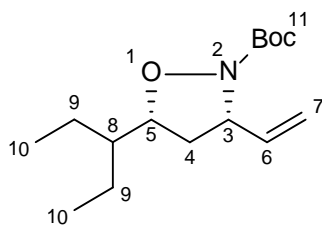
(3*S*,5*S*)-tert-Butyl 5-benzyl-3-vinylisoxazolidine-2-carboxylate (2.56b). Colourless oil (96%): $[\alpha]_D -2.5$ (*c* 0.5, CHCl_3); $^1\text{H NMR}$ (400 MHz; CDCl_3) δ 1.48 (s, 9H, H-8), 1.76 – 1.83 (m, 1H, H-4), 2.44 – 2.51 (m, 1H, H-4), 2.83 (dd, $J = 14.2, 6.5$ Hz, 1H, H-8), 3.14 (dd, $J = 14.2, 6.2$ Hz, 1H, H-8), 4.14 (dq, $J = 10.0, 6.5$ Hz, 1H, H-5), 4.55 – 4.61 (m, 1H, H-3), 5.10 (dt, $J = 10.2, 1.2$ Hz, 1H, H-7), 5.24 (dt, $J = 17.2, 1.2$ Hz, 1H, H-7), 5.81 (ddd, $J = 17.2, 10.2, 7.2$ Hz, 1H, H-6), 7.20 – 7.31 (m, 5H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 28.2 ($\text{CH}_3 \times 3$, C-9), 38.5 (CH_2 , C-8), 40.9 (CH_2 , C-4), 62.3 (CH, C-3), 81.5 (CH, C-5), 115.4 (CH_2 , C-7), 126.6 (CH, Ph), 128.5 (CH \times 2, Ph), 129.1 (CH \times 2, Ph), 137.2 (C), 138.0 (CH, C-6), 157.6 (CO); IR (NaCl) ν 2977, 2926, 1731, 1706, 1455, 1368, 1328, 1255, 1166, 1082, 920, 853, 753, 700 cm^{-1} ; HRMS (ESI) 312.1568 ($\text{C}_{17}\text{H}_{23}\text{NO}_3\text{Na}$ requires 312.1570).



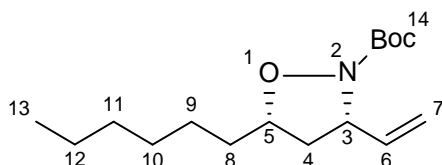
(3*S*,5*S*)-*tert*-Butyl 5-phenethyl-3-vinylisoxazolidine-2-carboxylate (2.56c). Colourless oil (96%): $[\alpha]_D -34.7$ (c 3.0, CHCl_3); $^1\text{H NMR}$ (400 MHz; CDCl_3) δ 1.50 (s, 9H, H-10), 1.71 (ddd, $J = 17.6, 12.0, 9.6$ Hz, 1H, H-4), 1.84 – 1.93 (m, 1H, H-8), 1.99 – 2.08 (m, 1H, H-8), 2.52 (ddd, $J = 17.6, 14.4, 8.4$ Hz, 1H, H-4), 2.68 – 2.84 (m, 2H, H-9), 3.84 – 3.91 (m, 1H, H-5), 4.58 – 4.63 (m, 1H, H-3), 5.11 (dt, $J = 10.0, 1.2$ Hz, 1H, H-7), 5.25 (dt, $J = 17.0, 1.2$ Hz, 1H, H-7), 5.84 (ddd, $J = 17.0, 10.0, 6.8$ Hz, 1H, H-6), 7.18 – 7.22 (m, 3H), 7.26 – 7.30 (m, 2H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 28.3 ($\text{CH}_3 \times 3$, C-10), 32.3 (CH_2 , C-9), 34.3 (CH_2 , C-8), 41.2 (CH_2 , C-4), 62.2 (CH, C-3), 80.2 (CH, C-5), 81.8 (C), 115.4 (CH_2 , C-7), 126.1 (CH, Ph), 128.4 (CH \times 2, Ph), 128.5 (CH \times 2, Ph), 138.1 (CH, C-6), 141.2 (C), 157.5 (CO); IR (NaCl) ν 2978, 2931, 1730, 1704, 1454, 1367, 1330, 1254, 1165, 1082, 988, 920, 852, 749, 700 cm^{-1} ; HRMS (ESI) 326.1727 ($\text{C}_{18}\text{H}_{25}\text{NO}_3\text{Na}$ requires 326.1727).



(3*S*,5*R*)-*tert*-Butyl 5-cyclohexyl-3-vinylisoxazolidine-2-carboxylate (2.56d). Colourless oil (96%): $[\alpha]_D -67.4$ (c 4.0, CHCl_3); $^1\text{H NMR}$ (400 MHz; CDCl_3) δ 0.95 – 1.34 (m, 4H, Cy), 1.48 – 1.76 (m, 16H, H-4/8/Cy), 1.97 – 2.02 (m, 1H, Cy), 2.48 (ddd, $J = 12.0, 8.8, 5.8$ Hz, 1H, H-4), 3.59 (ddd, $J = 10.0, 7.6, 5.8$ Hz, 1H, H-5), 4.57 – 4.62 (m, 1H, H-3), 5.10 (dt, $J = 10.2, 1.2$ Hz, 1H, H-7), 5.24 (dt, $J = 17.0, 1.2$ Hz, 1H, H-7), 5.83 (ddd, $J = 17.0, 10.2, 6.8$ Hz, 1H, H-6); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 25.6 (CH_2 , Cy), 25.8 (CH_2 , Cy), 26.3 (CH_2 , Cy), 28.2 ($\text{CH}_3 \times 3$, C-8), 28.8 (CH_2 , Cy), 29.9 (CH_2 , Cy), 39.1 (CH_2 , C-4), 40.5 (CH, Cy), 62.2 (CH, C-3), 81.5 (C), 85.5 (CH, C-5), 115.07 (CH_2 , C-7), 138.3 (CH, C-6), 157.7 (CO); IR (NaCl) ν 2977, 2927, 2854, 1735, 1708, 1392, 1367, 1254, 1170, 1083, 987, 918, 853, 774 cm^{-1} ; HRMS (ESI) 304.1881 ($\text{C}_{16}\text{H}_{27}\text{NO}_3\text{Na}$ requires 304.1883).



(3*S*,5*R*)-*tert*-Butyl 5-(pentan-3-yl)-3-vinylisoxazolidine-2-carboxylate (2.56e). Colourless oil (93%): $[\alpha]_D^{25} +19.6$ (c 1.0, CHCl_3); $^1\text{H NMR}$ (400 MHz; CDCl_3) δ 0.85 – 0.93 (m, 6H, H-10), 1.22 – 1.33 (m, 2H, H-9), 1.42 – 1.45 (m, 2H, H-9), 1.49 (s, 9H, H-11), 1.51 – 1.56 (m, 1H, H-8), 1.74 (ddd, $J = 13.7, 10.4, 6.8$ Hz, 1H, H-4), 2.51 (ddd, $J = 13.7, 8.8, 5.6$ Hz, 1H, H-4), 3.74 (ddd, $J = 12.4, 10.4, 5.6$ Hz, 1H, H-5), 4.59 – 4.65 (m, 1H, H-3), 5.10 (dt, $J = 10.1, 1.3$ Hz, 1H, H-7), 5.25 (dt, $J = 16.9, 1.3$ Hz, 1H, H-7), 5.83 (ddd, $J = 16.9, 10.1, 6.8$ Hz, 1H, H-6); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 10.3 (CH_3 , C-10), 11.0 (CH_3 , C-10), 22.0 (CH_2 , C-9), 28.2 ($\text{CH}_3 \times 3$, C-11), 29.7 (CH_2 , C-9), 39.4 (CH_2 , C-4), 42.7 (CH , C-8), 62.2 (CH , C-3), 81.6 (C), 83.8 (CH , C-5), 115.1 (CH_2 , C-7), 138.3 (CH , C-6), 157.9 (CO); IR (NaCl) ν 2966, 2934, 2877, 1734, 1709, 1459, 1368, 1326, 1254, 1168, 1119, 1074, 919, 852, 775 cm^{-1} ; HRMS (ESI) 292.1883 ($\text{C}_{15}\text{H}_{27}\text{NO}_3\text{Na}$ requires 292.1883).



(3*S*,5*S*)-*tert*-Butyl 5-hexyl-3-vinylisoxazolidine-2-carboxylate (2.56f). Colourless oil (95%): $[\alpha]_D -5.9$ (*c* 1.0, CHCl_3); $^1\text{H NMR}$ (400 MHz; CDCl_3) δ 0.88 (t, $J = 6.8$ Hz, 3H, H-13), 1.26 – 1.45 (m, 8H, H-9/10/11/12), 1.49 (s, 9H, H-14), 1.53 – 1.77 (m, 3H, H-4/8), 2.54 (ddd, $J = 12.0, 8.4, 5.6$ Hz 1H, H-4), 3.83 – 3.90 (m, 1H, H-5), 4.57 – 4.62 (m, 1H, H-3), 5.10 (d, $J = 10.0$ Hz, 1H, H-7), 5.24 (d, $J = 16.8$ Hz, 1H, H-7), 5.84 (ddd, $J = 16.8, 10.0, 6.8$ Hz, 1H, H-6); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 14.1 (CH_3 , C-13), 22.6 (CH_2 , C-9/10/11/12), 26.0 (CH_2 , C-9/10/11/12), 28.2 ($\text{CH}_3 \times 3$, C-14), 29.2 (CH_2 , C-9/10/11/12), 31.7 (CH_2 , C-9/10/11/12), 32.4 (CH_2 , C-8), 41.3 (CH_2 , C-4), 62.2 (CH, C-3), 81.3 (CH, C-5), 81.6 (C), 115.2 (CH_2 , C-7), 138.2 (CH, C-6), 157.5 (CO); IR (NaCl) ν 2956, 2931, 2859, 1734, 1708, 1457, 1392, 1367, 1330, 1170, 1090, 987, 919, 853 cm^{-1} ; HRMS (ESI) 306.2033 ($\text{C}_{16}\text{H}_{29}\text{NO}_3\text{Na}$ requires 306.2040).

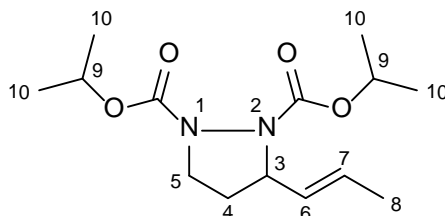
3.2.9. Alternate Conditions for Cyclisation of 2.5

Conditions outlined in Table 2.1, entry 1.

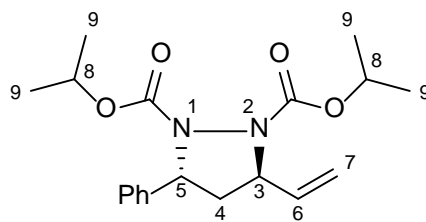
A flask was charged with Pd(OAc)₂ (5.6 mg, 0.025 mmol) and Cu(OAc)₂·H₂O (0.15 g, 0.75 mmol), flushed with N₂ and then sealed with a balloon of N₂. **2.5** (50 mg, 0.25 mmol) in MeCN (3 mL) was added via syringe. The mixture was heated to 60°C and stirred for 16 h. Upon consumption of starting material, the mixture was cooled and partitioned between EtOAc (10 mL) and sat. NaHCO₃ solution (10 mL), the aqueous layer was extracted further with EtOAc (10 mL). The combined organic fractions were washed with brine (10 mL), dried with MgSO₄ and the solvent removed *in vacuo*. The crude oil was purified using column chromatography (10:1, light petroleum : EtOAc).

3.2.10. General Procedure for Palladium Catalyzed Intramolecular Amination of Hydrazines

A flask was charged with palladium acetate (1.5 mg, 0.007 mmol) and sodium acetate (2 mg, 0.028 mmol) and flushed with O₂. DMSO (1 mg, 0.014 mmol) in THF (2 mL) was added and a balloon of O₂ applied. The desired substrate (50 mg, 0.14 mmol) in THF (1 mL) was added to the flask via syringe and stirred at room temperature overnight. Another portion of palladium acetate (1.5 mg, 0.007 mmol) was added to the reaction mixture and left to stir for a further 24 h. The mixture was filtered through a pad of celite with ethyl acetate and the solvent removed *in vacuo* to yield a brown oil. The crude oil was purified using column chromatography (10:1, light petroleum: EtOAc).



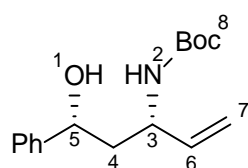
(E)-Diisopropyl 3-(prop-1-enyl)pyrazolidine-1,2-dicarboxylate (2.59). Colourless oil, isolated as a mixture of 12:1:1 of *E*:*Z*:Terminal isomers respectively (76% from *E*-**2.58**, 72% from *Z*-**2.58**): ¹H NMR (400 MHz; CDCl₃) δ *E* isomer: 1.24 – 1.29 (m, 12H, H-10), 1.68 (dt, *J* = 6.4, 1.5 Hz, 3H, H-8), 1.86 (ddt, *J* = 12.4, 8.0, 5.2 Hz, 1H, H-4), 2.21 (ddt, *J* = 12.4, 8.0, 5.2 Hz, 1H, H-4), 3.19 – 3.25 (m, 1H, H-5), 3.92 – 3.98 (m, 1H, H-5), 4.65 – 4.69 (m, 1H, H-3), 4.91 – 5.02 (m, 2H, H-9), 5.33 (ddq, *J* = 15.2, 5.8, 1.5 Hz, 1H, H-6), 5.74 (dq, *J* = 15.2, 6.4, 1.2 Hz, 1H, H-7); *Z* isomer: 4.94 – 5.02 (m, 1H), 5.25 – 5.34 (m, 1H), 5.54 – 5.65 (m, 1H); **Terminal isomer**: 5.10 – 5.15 (m, 2H), 5.77 – 5.85 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 17.5 (CH₃, C-8), 21.8 (CH₃, C-10), 22.0 (CH₃ × 3, C-10), 32.3 (CH₂, C-4), 46.4 (CH₂, C-5), 60.1 (CH, C-3), 69.8 (CH, C-9), 69.9 (CH, C-9), 126.8 (CH, C-7), 129.4 (CH, C-6), 157.2 (CO); IR (NaCl) ν 2980, 2935, 1701, 1407, 1375, 1318, 1180, 1108, 964, 922, 762 cm⁻¹; HRMS (ESI) 307.1622 (C₁₄H₂₄N₂O₄Na requires 307.1628).



(3*R*,5*S*)-Diisopropyl 3-phenyl-5-vinylpyrazolidine-1,2-dicarboxylate (2.63). Colourless oil (78%): $[\alpha]_D +8.4$ (c 9.0, CHCl_3); $^1\text{H NMR}$ (400 MHz; CDCl_3) δ 1.21 – 1.30 (m, 12H, H-9), 2.30 – 2.37 (m, 1H, H-4), 2.41 – 2.47 (m, 1H, H-4), 4.85 (m, 1H, H-3), 4.94 – 5.06 (m, 2H, H-8), 5.17 (dt, $J = 10.4, 1.5$ Hz, 1H, H-7), 5.27 (t, $J = 7.2$ Hz, 1H, H-5), 5.42 (dt, $J = 15.8, 1.5$ Hz, 1H, H-7), 5.78 (ddd, $J = 15.8, 10.4, 4.4$ Hz, 1H, H-6), 7.21 – 7.37 (m, 5H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 22.0 ($\text{CH}_3 \times 4$, C-9), 40.7 (CH_2 , C-4), 60.7 (CH , C-3), 62.1 (CH , C-5), 70.0 (CH , C-8), 70.1 (CH , C-8), 115.9 (CH_2 , C-7), 125.9 ($\text{CH} \times 2$, Ph), 127.3 (CH , Ph), 128.5 ($\text{CH} \times 2$, Ph), 135.7 (CH , C-6), 140.8 (C), 156.9 (CO), 157.0 (CO); IR (NaCl) ν 2981, 2935, 1767, 1704, 1455, 1373, 1308, 1179, 1108, 921 cm^{-1} ; HRMS (ESI) 369.1782 ($\text{C}_{19}\text{H}_{26}\text{N}_2\text{O}_4\text{Na}$ requires 369.1785).

3.2.11. Reduction of Vinylisoxazolidine 2.56a with Mo(CO)₆

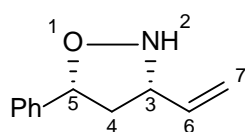
A solution of the isoxazolidine **2.56a** (0.15 g, 0.55 mmol) in a 9:1 mixture of CH₃CN and H₂O (8 mL) was added to Mo(CO)₆ (0.72 g, 2.73 mmol) and the resulting solution was heated to reflux (~90 °C) for 2 h, during which time the colour had changed from white to black. The mixture was then cooled to room temperature, filtered through celite, and the filtrate was evaporated. The residue was purified by column chromatography (gradient 9:1 to 2:1, light petroleum: EtOAc).



tert-Butyl (3S,5R)-5-hydroxy-5-phenylpent-1-en-3-ylcarbamate (2.64). Colourless oil (61%): [α]_D +24.8 (*c* 5.0, CHCl₃); ¹H NMR (400 MHz; CDCl₃) δ 1.44 (s, 9H, H-8), 1.82 – 1.93 (br. m, 1H, H-4), 2.00 (dt, *J* = 14.0, 8.0 Hz, 1H, H-4), 2.45 – 2.58 (m, 1H), 4.22 – 4.32 (m, 1H, H-3), 4.66 – 4.75 (m, 1H), 4.80 (dd, *J* = 8.0, 4.4 Hz, 1H, H-5), 5.13 (d, *J* = 10.4 Hz, 1H, H-7), 5.21 (d, *J* = 17.6 Hz, 1H, H-7), 5.75 – 5.83 (m, 1H, H-6), 7.28 – 7.38 (m, 5H); ¹³CNMR (100 MHz, CDCl₃) δ 28.4 (CH₃ \times 3, C-8), 31.6 (CH, C-3), 44.3 (CH₂, C-4), 72.3 (CH, C-5), 79.6 (C), 115.0 (CH₂, C-7), 125.8 (CH \times 2, Ph), 127.7 (CH, Ph), 128.6 (CH \times 2, Ph), 138.6 (CH, C-6), 144.4 (C), 156.8 (CO); IR ν 3347, 2977, 2927, 1691, 1504, 1454, 1391, 1366, 1249, 1170, 1024, 700 cm⁻¹; HRMS (ESI) 300.1570 (C₁₆H₂₃NO₃Na requires 300.1570).

3.2.12. Removal of *t*-Boc Group from Vinylisoxazolidine 2.56a

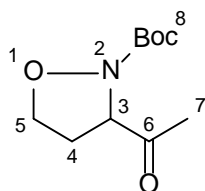
To a solution of **2.56a** (150 mg, 0.85 mmol) in CH₂Cl₂ (2 mL), TFA (1.5 mL, 20 mmol) was added slowly at 0 °C. The reaction mixture was stirred for 1 h at 0 °C. Upon consumption of the starting material, the excess TFA was neutralised with slow additions of sat. NaHCO₃ solution. Once effervescence subsided and the solution tested basic, the mixture was extracted with CH₂Cl₂ (10 mL), dried with MgSO₄ and the solvent removed *in vacuo*. The residue was purified by column chromatography (4:1, light petroleum: EtOAc).



(3*S*,5*R*)-5-Phenyl-3-vinylisoxazolidine (2.67). Colourless oil (89%): [α]_D +24.8 (*c* 5.0, CHCl₃); ¹H NMR (400 MHz; CDCl₃) δ 2.06 (dt, *J* = 12.4, 7.6 Hz, 1H, H-4), 2.90 (dt, *J* = 12.4, 7.6 Hz, 1H, H-4), 4.05 – 4.16 (br m, 1H), 4.92 – 5.30 (br m, 1H), 5.20 (br d, *J* = 9.6 Hz, 1H, H-7), 5.31 (br d, *J* = 16.8 Hz, 1H, H-7), 5.78 – 5.96 (br m, 1H, H-6), 7.27 – 7.38 (br m, 5H); IR (NaCl) ν 3209, 3030, 2980, 2925, 1711, 1642, 1603, 1493, 1451, 1424, 1029, 989, 920, 758, 699 cm⁻¹; HRMS (ESI) 198.0889 (C₁₁H₁₃NONa requires 198.0889).

3.2.13. Optimal Conditions for Oxidative Cyclisation/Wacker-Oxidation

A flask was charged with Pd(MeCN)₂Cl₂ (3.4 mg, 0.013 mmol), QUINOX ligand **2.11** (20mg, 0.1 mmol) and MeCN (2 mL). O₂ was bubbled through the solution for 2 mins. **2.5** (50 mg, 0.25 mmol) in MeCN (1 mL) was added via syringe and the reaction heated to 60 °C and stirred for 16 h. Upon consumption of starting material the reaction mixture was cooled to room temperature and filtered through a pad of celite with EtOAc (5 mL). The solvent was removed from the filtrate *in vacuo*, the crude oil that remained was purified by column chromatography (10:1, EtOAc: light petroleum).

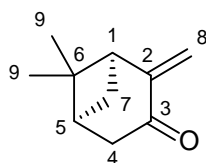


tert-Butyl 3-acetylisoxazolidine-2-carboxylate (2.10). Colourless oil (81%): ¹H NMR (400 MHz; CDCl₃) δ 1.52 (s, 9H, H-8), 2.29 (s, 3H, H-7), 2.39 – 2.56 (m, 2H, H-4), 3.75 (dt, *J* = 8.4, 7.6 Hz, 1H, H-5), 4.09 (tdd, *J* = 8.4, 4.0, 0.8 Hz, 1H, H-5), 4.61 (dd, *J* = 9.2, 5.2 Hz, 1H, H-3); ¹³C NMR (100 MHz, CDCl₃) δ 26.3 (CH₃, C-7), 28.2 (CH₃ × 3, C-8), 30.7 (CH₂, C-4), 66.6 (CH, C-3), 69.1 (CH₂, C-5), 83.0 (C), 157.2 (CO), 206.9 (CO); IR (NaCl) ν 3479, 3377, 2979, 2917, 1721, 1457, 1369, 1255, 1162, 1070, 847, 732 cm⁻¹; HRMS (ESI) 238.1051 (C₁₀H₁₇NO₄Na requires 238.1050).

3.2.14. Synthesis of METHOX

Oxidation of (+)- α -pinene^{70a}

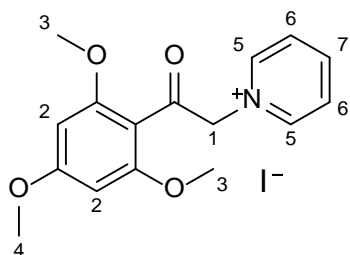
(+)- α -pinene (15 g, 110 mmol), acetic anhydride (10 mL, 110 mmol), pyridine (6 mL, 73 mmol), DMAP (3.4 g, 28mmol) and TPP (7 mg, 0.011 mmol) were placed in a custom reaction vessel. CH₂Cl₂ (80 mL) was added and the mixture was pumped through a continuous flow system. O₂ was bubbled through the system at a steady rate (c.a. 100 bubbles min⁻¹). The reaction mixture was irradiated with a 24W lamp. The reaction was monitored by ¹H NMR; CH₂Cl₂ was topped up as necessary. After 16 h, the starting material was consumed. The solution was transferred to a separating funnel, sat. NaHCO₃ was added until the solution became basic. The organic extract was then washed with 1M HCl to yield a green solution. The organic layer was further washed with sat. CuSO₄ solution and brine, dried with MgSO₄, filtered and the solvent removed *in vacuo* to yield a red/brown oil, which was distilled on a kugelrohr and yielded a clear oil.



(1S,5S)-6,6-Dimethyl-2-methylenebicyclo[3.1.1]heptan-3-one (2.46).^{70a} Viscous colourless oil (87%): [α]_D -35 (*c* 4.0, CHCl₃); ¹H NMR (400 MHz; CDCl₃) δ 0.82 (s, 3H, H-9), 1.31 (d, *J* = 10.4 Hz, 1H, H-7), 1.37 (s, 3H, H-9), 2.27 (sep, *J* = 3.0 Hz, 1H, H-5), 2.54 (dd, *J* = 19.2, 3.0 Hz, 1H, H-4), 2.66 – 2.72 (m, 2H, H-4/7), 2.78 (t, *J* = 5.6 Hz, 1H, H-1), 5.02 (d, *J* = 1.6 Hz, 1H, H-8), 5.97 (d, *J* = 1.6 Hz, 1H, H-8); ¹³C NMR (100 MHz, CDCl₃) δ 21.6 (CH₃, C-9), 26.0 (CH₃, C-9), 32.4 (CH₂, C-7), 38.5 (CH, C-5), 40.8 (C), 42.5 (CH₂, C-4), 48.2 (CH₂, C-1), 117.5 (CH₂, C-8), 149.1 (C), 200.2 (CO); IR (NaCl) ν 3398, 2930, 1706, 1625, 1464, 1397, 1370, 1329, 1284, 1263, 1101, 1060, 925 cm⁻¹; HRMS (ESI) 173.0936 (C₁₀H₁₄ONa requires 173.0937).

Preparation of Kröhnke salt^{70a}

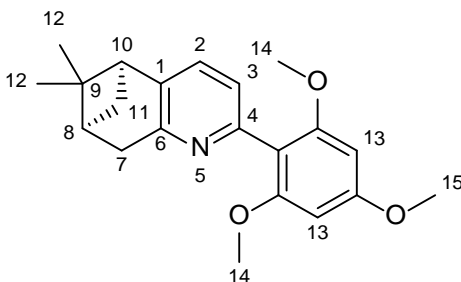
To a solution of iodine (11.6 g, 45.7 mmol) in pyridine (20 mL), 2,4,6-trimethoxyacetophenone (8 g, 38 mmol) was added in one portion, and mixture heated to reflux. After 4 h the mixture was cooled and the resulting precipitate was filtered and washed with pyridine (3 × 15 mL), and dried in a desiccator. The resulting brown solid was used without further purification.



1-(2-Oxo-2-(2,4,6-trimethoxyphenyl)ethyl)pyridinium iodide (2.47).^{70a} Brown solid (99%): mp 200 – 203°C; ¹H NMR (400 MHz; DMSO-d₆) δ 3.86 (s, 6H, H-3), 3.91 (s, 3H, H-4), 6.02 (s, 2H, H-1), 6.37 (s, 2H, H-2), 8.23 (dd, *J* = 7.8, 6.2 Hz, 2H, H-6), 8.71 (t, *J* = 7.8 Hz, 1H, H-7), 8.93 (d, *J* = 6.2 Hz, 2H, H-5); ¹³C NMR (100 MHz, DMSO-d₆) δ 55.8 (CH₃), 56.3 (CH₃ × 2), 69.4 (CH₂), 91.2 (CH × 2), 107.3 (C), 127.8 (CH × 2), 146.1 (CH × 2), 146.2 (CH), 160.5 (C × 2), 164.5 (C), 190.3 (CO); IR (KBr) ν 3398, 3120, 2947, 2839, 2793, 1708, 1581, 1415, 1126, 759 cm⁻¹; HRMS (ESI) 288.1226 (C₁₆H₁₈NO₄ requires 288.1230).

Kröhnke Annulation of **2.46** and **2.47**^{70a}

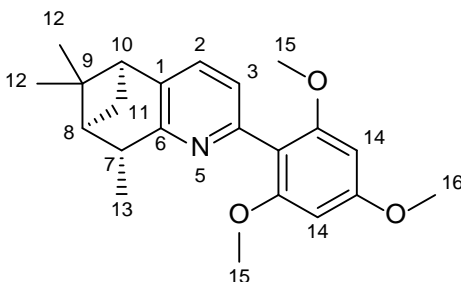
Ammonium acetate (70 g) was dissolved in AcOH (70 mL), heated to 110 °C and stirred until dissolved. Kröhnke salt **2.47** (12 g, 28.9 mmol) was added and stirred at 110 °C until dissolved leaving a red/orange solution. Pinacarvone **2.46** (4 g, 26.3 mmol) was added turning the mixture brown in colour. The mixture was left to reflux at 110 °C overnight. Water (20 mL) was added, the mixture was then basified with sat. NaOH solution. The aqueous media was then extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were dried with MgSO₄ and the solvent removed *in vacuo*. A crude brown solid was isolated. Column chromatography using 9:1 petroleum ether: EtOAc was used to purify the compounds.



(+)-5-(2',4',6'-Trimethoxyphenyl)-10,10-dimethyl-6-aza-tricyclo[7.1.1.0^{2,7}]undeca-2(7),3,5-triene (2.48**).**^{70a} Brown solid (47%): [α]_D +42.0 (*c* 1.0, CHCl₃); ¹H NMR (400 MHz; CDCl₃) δ 0.71 (s, 3H, H-12), 1.39 (d, *J* = 9.4 Hz, 1H, H-10), 1.42 (s, 3H, H-12), 2.37 (sep, *J* = 2.8 Hz, 1H, H-8), 2.68 (dt, *J* = 9.4, 5.8 Hz, 1H, H-11), 2.77 (t, *J* = 5.8 Hz, 1H, H-11), 3.15 (d, *J* = 2.8 Hz, 2H, H-7), 3.70 (s, 6H, H-14), 3.85 (s, 3H, H-15), 6.20 (s, 2H, H-13), 6.95 (d, *J* = 7.6 Hz, 1H, H-2/3), 7.22 (d, *J* = 7.6 Hz, 1H, H-2/3); ¹³C NMR (100 MHz, CDCl₃) δ 21.4 (CH₃, C-12), 26.1 (CH₃, C-12), 31.8 (CH₂, C-10), 36.6 (CH₂, C-7), 39.6 (C), 40.3 (CH, C-8), 46.4 (CH, C-11), 55.4 (CH₃, C-15), 56.0 (CH₃ × 2, C-14), 91.0 (CH × 2, C-13), 113.1 (C), 122.7 (CH, C-2/3), 132.6 (CH, C-2/3), 139.2 (C), 151.2 (C), 156.0 (C), 159.0 (C × 2), 161.0 (C); IR (NaCl) ν 2934, 1609, 1587, 1453, 1223, 1204, 1156, 1127, 1042, 948, 810, 729 cm⁻¹; HRMS (ESI) 340.1902 (C₂₁H₂₆NO₃ requires 340.1907).

Methylation of Pyridine 2.48^{70a}

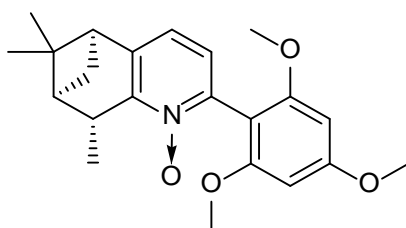
A solution of pyridine derivative **2.48** (2.3 g, 6.8 mmol) in THF (40 mL) was cooled to -40 °C. ⁿBuLi (2.2M in hexane, 3.4 mL, 7.45 mmol) was added dropwise turning the mixture a deep red colour. The solution was stirred at -40 °C for 1 h. A solution of MeI (1.06 g, 7.45 mmol) in THF (5 mL) was added dropwise. After the addition the mixture was allowed to warm to room temperature and left to stir overnight. Water (30 mL) was added to quench the reaction. The mixture was extracted with CH₂Cl₂ (3 × 30 mL), the combined organic fractions were washed with brine (2 × 30 mL), dried with MgSO₄ and the solvent removed *in vacuo* to yield a brown solid. Column chromatography was used to purify the compound (4:1, light petroleum: EtOAc).



(1S,8R,9S)-8,10,10-Trimethyl-5-(2,4,6-trimethoxyphenyl)-6-zatricyclo[7.1.1.0^{2,7}]undeca-2,4,6-triene (2.49).^{70a} Brown solid (81%): $[\alpha]_D +1.05$ (*c* 5.0, CHCl₃); ¹H NMR (400 MHz; CDCl₃) δ 0.62 (s, 3H, H-12), 1.31 (d, *J* = 7.2 Hz, 3H, H-13), 1.35 (s, 3H, H-12), 2.08 (td, *J* = 6.0, 2.4 Hz, 1H, H-8), 2.48 (dt, *J* = 10.0, 6.0 Hz, 2H, H-11), 2.69 (t, *J* = 6.0 Hz, 1H, H-10), 3.17 (qd, *J* = 7.2, 2.4 Hz, 1H, H-7), 3.64 (s, 6H, H-15), 3.77 (s, 3H, H-16), 6.14 (s, 2H, H-14), 6.89 (d, *J* = 7.4 Hz, 1H, H-2/3), 7.12 (d, *J* = 7.4 Hz, 1H, H-2/3); ¹³C NMR (100 MHz, CDCl₃) δ 18.6 (CH₃, C-12), 21.4 (CH₃, C-13), 26.4 (CH₃, C-12), 28.6 (CH₂, C-11), 39.6 (CH, C-7), 41.5 (C), 47.0 (CH, C-8), 47.1 (CH, C-10), 55.4 (CH₃, C-16), 56.2 (CH₃ × 2, C-15), 91.5 (CH × 2, C-14), 113.4 (C), 122.8 (CH, C-2/3), 132.5 (CH, C-2/3), 138.9 (C), 151.0 (C), 159.1 (C × 2), 159.8 (C), 161.0 (C); IR (NaCl) ν 2931, 1609, 1587, 1465, 1334, 1223, 1204, 1156, 1128, 1037, 811, 730 cm⁻¹; HRMS (ESI) 354.2056 (C₂₂H₂₈NO₃Na requires 354.2064).

Oxidation of **2.49**^{70a}

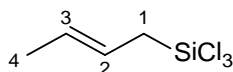
To a solution of the methylated pyridine derivative **2.49** (0.3 g, 0.81 mmol) in CH₂Cl₂ (10 mL), *m*-CPBA (0.3 g, 0.89 mmol) in CH₂Cl₂ (10 mL) was added in four portions via syringe. The reaction was stirred for 2 h. Et₂O (10 mL) was added and washed with sat. NaHCO₃ solution (10 mL) and with brine (10 mL). The organic phase was dried with MgSO₄, filtered and the solvent removed *in vacuo* to yield a pale yellow solid. The pure pyridine *N*-oxide was purified using column chromatography (light petroleum: EtOAc, 10:1).



(+)-5-(2',4',6'-Trimethoxyphenyl)-8,10,10-trimethyl-6-azatricyclo[7.1.1.0^{2,7}]undeca-2,4,6-triene 6-Oxide (2.44).^{70a} Pale yellow solid (46%): ¹H NMR (400 MHz; CDCl₃) δ 0.59 (s, 3H), 1.34 (s, 3H), 1.42 (d, *J* = 6.8 Hz, 3H), 2.01 – 2.04 (m, 1H), 2.03 – 2.10 (m, 1H), 2.47 (dt, *J* = 9.6, 6.0 Hz, 1H), 2.70 (t, *J* = 5.6 Hz, 1H), 3.31 – 3.38 (m, 1H), 3.64 (s, 3H), 3.66 (s, 3H), 3.76 (s, 3H), 6.12 (s, 2H), 6.76 (d, *J* = 7.6 Hz, 1H), 6.94 (d, *J* = 7.6 Hz, 1H).

3.2.15. Preparation of (*E*)-crotyl trichlorosilane

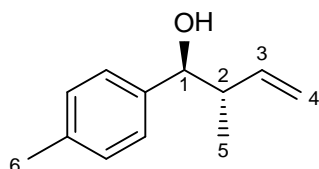
CuCl (0.55 g, 5.5 mmol) was weighed out under a stream of nitrogen and placed into a flame dried flask containing powdered 4Å MS. Et₂O (40 mL) was added to the flask via syringe. Crotyl chloride (1 g, 11.0 mmol) was added in one portion, followed by Hünigs base (4.8 mL, 27.6 mmol) in one portion. The mixture was cooled to 0°C and HSiCl₃ (2.2 mL, 22.1 mmol) was added slowly via syringe. The mixture was allowed to warm to room temperature and left to stir overnight or until the starting material was consumed (monitored by ¹H NMR). The reaction has been observed changing colours to a range including yellow, green, blue, brown or also remaining an off white colour. Once the reaction was complete stirring was stopped and any solid particles were left to settle. The solution was transferred to an anhydrous distillation kit to using a cannula. Any Et₂O was removed under a stream of nitrogen, then the crotyl trichlorosilane was distilled off under vacuum and heating. The pure silane was used immediately.



(*E*)-But-2-enyltrichlorosilane (2.50).¹⁰⁷ Clear liquid: ¹H NMR (400 MHz; CDCl₃) δ1.69 (d, *J* = 4.4 Hz, 3H, H-4), 2.23 (d, *J* = 7.6, 2H, H-1), 5.35 (1H, m), 5.57 (1H, m).

3.2.16. Preparation of Allyl Transfer Reagent **2.51**^{70b}

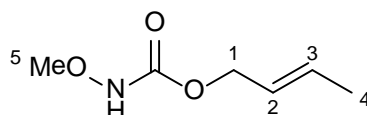
To a solution of METHOX (0.1 g, 0.3 mmol) in freshly distilled MeCN (30 mL) was added *i*-Pr₂NEt (11.4 g, 88.0 mmol) and *p*-tolualdehyde (0.7 g, 5.9 mmol). The reaction vessel was cooled to -40 °C and freshly prepared crotyl trichlorosilane **2.50** (2.2 g, 11.7 mmol) was added dropwise via syringe. The reaction was maintained at -40 °C until consumption of the starting material was observed by TLC. After consumption of the starting material, the reaction was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with sat. NaHCO₃ (30 mL) and brine (30 mL), then dried with MgSO₄. The solvent was evaporated to yield the crude product as a yellow oil. Column chromatography was used to purify the compound using 95:5 petroleum ether: ethyl acetate.



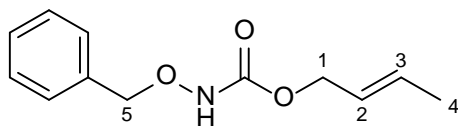
(1*S*,2*S*)-2-Methyl-1-*p*-tolylbut-3-en-1-ol (2.51).^{70b} Pale yellow oil (79%): ¹H NMR (400 MHz; CDCl₃) δ 0.87 (d, *J* = 6.8 Hz, 3H, H-5), 2.08 – 2.18 (m, OH), 2.34 (s, 3H, H-6), 2.43 – 2.52 (m, 1H, H-2), 4.31 (d, *J* = 8.0 Hz, H-1), 5.15 – 5.22 (m, 2H), 5.81 (ddd, *J* = 17.2, 10.4, 8.0 Hz, 1H, H-3), 7.13 – 7.23 (m, 5H); ¹³C NMR (100 MHz, CDCl₃) δ 16.6 (CH₃, C-5), 21.1 (CH₃, C-6), 46.2 (CH, C-2), 77.8 (CH, C-1), 116.6 (CH₂, C-4), 126.8 (CH × 2, Ph), 128.9 (CH × 2, Ph), 137.3 (C), 139.5 (C), 140.9 (CH, C-3); IR (NaCl) ν 3415, 2975, 2926, 2870, 1638, 1514, 1455, 1416, 1030, 1017, 913, 812 cm⁻¹; HRMS (ESI) 199.1092 (C₁₂H₁₆ONa requires 199.1093); chiral GC (Supelco γ-DEX column, oven for 2 min at 100 °C, then 0.5 °C min⁻¹) showed 84% *ee* (*t*_R = 49.5 min, *t*_S = 50.0 min).

3.2.17. Synthesis of Allylic *N*-alkyloxy and *N*-aryloxy Carbamates¹⁰¹

To a flask of *N,N*-carbonyldiimidazole (1.7 g, 10.4 mmol) in MeCN (c.a. 5 mL/mmol) under an atmosphere of N₂, the allylic alcohol was added (0.5 g, 6.9 mmol) and the mixture stirred at room temperature until all of the allylic alcohol is used up (c.a. 3 h). Imidazole (1.9 g, 27.7 mmol) and hydroxylamine derivative (2.9g, 34.7 mmol) were added and the mixture stirred for a further 12 h. The solvent was removed *in vacuo* to yield a white solid, this was partitioned between EtOAc (20 mL) and 1M HCl (20 mL) and extracted further with more EtOAc (20 mL). The combined organic fractions were dried with MgSO₄, filtered and the solvent removed *in vacuo* to yield the allylic carbamate. Compounds were purified by column chromatography (3:2, petroleum ether: EtOAc).



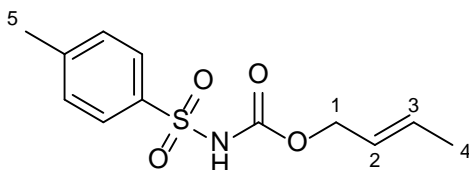
(*E*)-But-2-enyl methoxycarbamate (2.83b). Colourless oil (97%): ¹H NMR (400 MHz; CDCl₃) δ 1.72 (d, *J* = 6.4 Hz, 3H, H-4), 3.73 (s, 3H, H-5), 4.58 (d, *J* = 6.4 Hz, 2H, H-1), 5.55 – 5.65 (m, 1H, H-2), 5.77 – 5.87 (m, 1H, H-3), 8.00 (s, 1H, NH); ¹³C NMR (100 MHz, CDCl₃) δ 17.7 (CH₃, C-4), 64.5 (CH₃, C-5), 66.4 (CH₂, C-1), 124.9 (CH, C-2), 131.8 (CH, C-3), 157.6 (CO); IR (NaCl) ν 3272, 2941, 1723, 1484, 1338, 1256, 1117, 1032, 968, 772, 560 cm⁻¹; HRMS (ESI) 168.0630 (C₆H₁₁NO₃Na requires 168.0631).



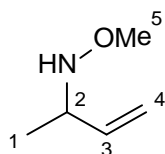
(E)-But-2-enyl benzyloxycarbamate (2.83a). Colourless oil (97%): ^1H NMR (400 MHz; CDCl_3) δ 1.71 (d, $J = 6.4$ Hz, 3H, H-4), 4.56 (d, $J = 6.4$ Hz, 2H, H-1), 4.86 (s, 2H, H-5), 5.53 – 5.63 (m, 1H, H-2), 5.75 – 5.85 (m, 1H, H-3), 7.32 – 7.40 (m, 5H), 7.53 (br. s, 1H, NH); ^{13}C NMR (100 MHz, CDCl_3) δ 17.8 (CH_3 , C-4), 66.5 (CH_2 , C-1), 78.6 (CH_2 , C-5), 124.9 (CH, C-2), 128.5 ($\text{CH} \times 2$, Ph), 128.6 (CH, Ph), 129.2 ($\text{CH} \times 2$, Ph), 132.0 (CH, C-3), 135.5 (C), 157.4 (CO); IR (NaCl) ν 3261, 2939, 1716, 1454, 1257, 1109, 969, 745, 698 cm^{-1} ; HRMS (ESI) 244.0938 ($\text{C}_{12}\text{H}_{15}\text{NO}_3\text{Na}$ requires 244.0944).

3.2.18. Synthesis of Allylic *N*-tosyl Carbamate¹⁰²

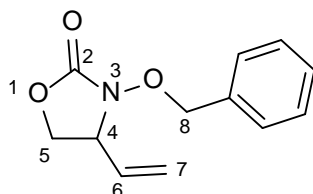
p-Tosyl isocyanate (5.6 g, 28.3 mmol) was added slowly to a cooled to 0°C solution of allylic alcohol (2 g, 25.7 mmol) in CH₂Cl₂ (20 mL), and the resulting solution was allowed to warm to room temperature. The mixture was stirred for c.a. 3 h, after which the solvent was removed *in vacuo* to yield the carbamate, which was used without further purification.



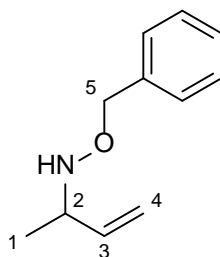
(*E*)-But-2-enyl tosylcarbamate (2.83c).¹⁰⁸ Viscous colourless oil (98%): ¹H NMR (400 MHz; CDCl₃) δ 1.68 (ddt, *J* = 6.4, 1.6, 1.0 Hz, 3H, H-4), 2.44 (s, 3H, H-5), 4.49 (dt, *J* = 6.8, 1.0 Hz, 2H, H-1), 5.44 – 5.52 (m, 1H, H-2), 5.70 – 5.79 (m, 1H, H-3), 7.34 (d, *J* = 8.0 Hz, 2H), 7.93 (d, *J* = 8.0 Hz, 2H), 8.05 (br. s, 1H, NH); ¹³C NMR (100 MHz, CDCl₃) δ 17.8 (CH₃, C-4), 21.7 (CH₃, C-5), 67.6 (CH₂, C-1), 123.9 (CH, C-2), 128.4 (CH × 2, Ph), 129.6 (CH × 2, Ph), 132.9 (CH, C-3), 135.5 (C), 145.1 (C), 150.5 (CO); IR (NaCl) ν 3241, 1748, 1597, 1447, 1348, 1220, 1161, 1090, 967, 856, 663, 583, 547 cm⁻¹; HRMS (ESI) 292.0610 (C₁₂H₁₅NO₄SNa requires 292.0614).



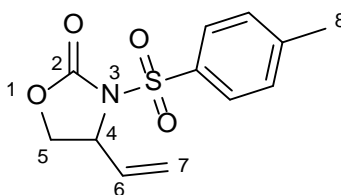
***N*-(But-3-en-2-yl)-*O*-methylhydroxylamine (2.85b).** Colourless oil (15%): ^1H NMR (400 MHz; CDCl_3) δ 1.26 (d, $J = 7.2$ Hz, 3H, H-1), 3.65 (s, 3H, H-5), 4.50 – 4.59 (m, 1H, H-2), 5.08 (dt, $J = 10.4, 1.2$ Hz, 1H, H-4), 5.13 (dt, $J = 17.6, 1.2$ Hz, 1H, H-4), 5.87 (ddd, $J = 17.6, 10.4, 6.4$ Hz, 1H, H-3); ^{13}C NMR (100 MHz, CDCl_3) δ 16.4 (CH_3 , C-1), 57.5 (CH , C-2), 64.4 (CH_3 , C-5), 116.2 (CH_2 , C-4), 137.2 (CH , C-3), 157.6 (CO); IR (NaCl) ν 2976, 2939, 1734, 1710, 1389, 1282, 1089, 1064, 967, 925, 768 cm^{-1} ; HRMS (ESI) 123.0666 ($\text{C}_5\text{H}_{10}\text{NONa}$ requires 123.0655).



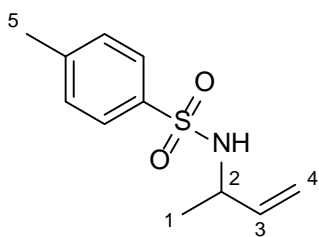
3-(Benzyloxy)-4-vinyloxazolidin-2-one (2.84a). Colourless oil (20%): ^1H NMR (400 MHz; CDCl_3) δ 3.85 (t, $J = 8.4$ Hz, 1H, H-5), 4.10 (q, $J = 8.4$ Hz, 1H, H-4), 4.24 (t, $J = 8.4$ Hz, 1H, H-5), 4.84 (d, $J = 10.6$ Hz, 1H, H-8), 4.95 (d, $J = 10.6$ Hz, 1H, H-8), 5.24 (d, $J = 10.0$ Hz, 1H, H-7), 5.31 (d, $J = 17.0$ Hz, 1H, H-7), 5.53 (ddd, $J = 17.0, 10.0, 8.4$ Hz, 1H, H-6), 7.26 – 7.36 (m, 5H); HRMS (ESI) 242.0785 ($\text{C}_{12}\text{H}_{13}\text{NO}_3\text{Na}$ requires 242.0788).



O-Benzyl-N-(but-3-en-2-yl)hydroxylamine (2.85a). Colourless oil (18%): ^1H NMR (400 MHz; CDCl_3) δ 1.26 (d, $J = 6.8$ Hz, 3H, H-1), 4.54 – 4.63 (m, 1H, H-2), 4.80 (s, 1H, H-5), 4.81 (s, 1H, H-5), 5.09 (d, $J = 10.4$ Hz, 1H, H-4), 5.15 (d, $J = 17.2$ Hz, 1H, H-4), 5.90 (ddd, $J = 17.2, 10.4, 6.0$ Hz, 1H, H-3), 7.25 – 7.35 (m, 5H); HRMS (ESI) 200.1047 ($\text{C}_{12}\text{H}_{15}\text{NONa}$ requires 200.1046).



3-Tosyl-4-vinyloxazolidin-2-one (2.84c).¹⁸ Colourless oil (65%): ^1H NMR (400 MHz; CDCl_3) δ 2.45 (s, 3H, H-8), 4.05 (dd, $J = 8.4, 4.0$ Hz, 1H, H-5), 4.50 (t, $J = 8.4$ Hz, 1H, H-5), 4.92 (td, $J = 8.4, 4.0$ Hz, 1H, H-4), 5.39 (d, $J = 10.0$ Hz, 1H, H-7), 5.49 (d, $J = 16.8$ Hz, 1H), 5.82 (ddd, $J = 16.8, 10.0, 8.4$ Hz, 1H, H-6), 7.34 (d, $J = 8.0$ Hz, 2H), 7.93 (d, $J = 8.0$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 21.7 (CH_3 , C-8), 59.6 (CH, C-4), 68.1 (CH_2 , C-5), 120.9 (CH_2 , C-7), 128.7 (CH \times 2, Ph), 129.7 (CH \times 2, Ph), 133.6 (CH, C-6), 135.0 (C), 145.6 (C), 151.9 (CO); IR (NaCl) ν 3303, 1783, 1373, 1173, 1124, 1054, 815, 756, 665, 602 cm^{-1} ; HRMS (ESI) 290.0453 ($\text{C}_{12}\text{H}_{13}\text{NO}_4\text{SNa}$ requires 290.0457).



***N*-(But-3-en-2-yl)-4-methylbenzenesulfonamide (2.85c).**¹⁰⁹ Colourless oil (25%): ¹H NMR (400 MHz; CDCl₃) δ 1.18 (d, *J* = 6.8 Hz, 3H, H-1), 2.43 (s, 3H, H-5), 3.86 – 3.96 (m, 1H, H-2), 4.99 (dt, *J* = 10.4, 1.2 Hz, 1H, H-4), 5.06 (dt, *J* = 17.2, 1.2 Hz, 1H, H-4), 5.64 (ddd, *J* = 17.2, 10.4, 6.0 Hz, 1H, H-3), 7.29 (d, *J* = 7.8 Hz, 2H), 7.75 (d, *J* = 7.8 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 21.5 (CH₃, C-1), 21.6 (CH₃, C-5), 51.6 (CH, C-2), 115.2 (CH₂, C-4), 127.2 (CH × 2, Ph), 129.6 (CH × 2, Ph), 138.0 (C), 139.0 (CH, C-3), 143.8 (C); IR (NaCl) ν 3278, 2925, 1736, 1598, 1360, 1327, 1158, 1091, 814, 672 cm⁻¹; HRMS (ESI) 248.0711 (C₁₁H₁₅NO₂SNa requires 248.0716).

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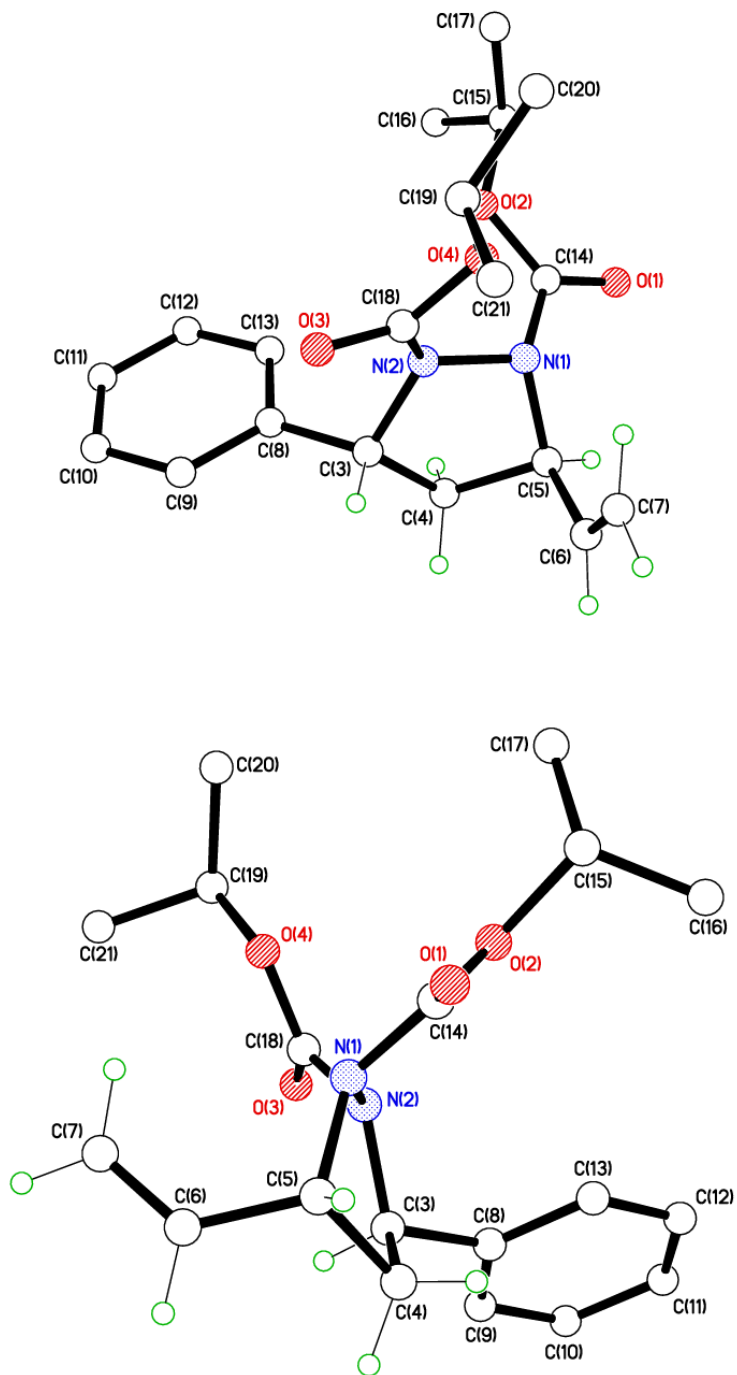
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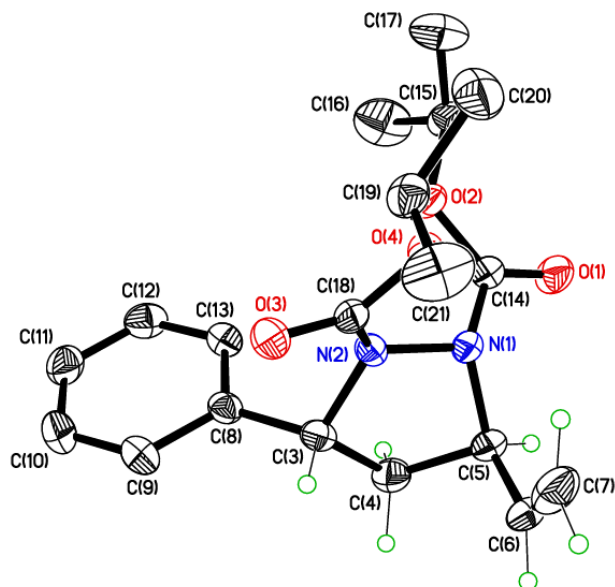
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5. Appendix

5.1. Crystal Data for 2.63





Crystal data

$C_{19}H_{26}N_2O_4$	$F(000) = 372$
$M_r = 346.42$	$D_x = 1.207 \text{ Mg m}^{-3}$
Monoclinic, $P2_1$	Mo $K\alpha$ radiation, $\lambda = 0.71073 \text{ \AA}$
$a = 11.1404 (18) \text{ \AA}$	Cell parameters from 4923 reflections
$b = 8.0196 (13) \text{ \AA}$	$\theta = 3.1\text{--}28.1^\circ$
$c = 11.1622 (18) \text{ \AA}$	$\mu = 0.09 \text{ mm}^{-1}$
$\beta = 107.072 (2)^\circ$	$T = 150 \text{ K}$
$V = 953.3 (3) \text{ \AA}^3$	Block, colourless
$Z = 2$	$0.41 \times 0.29 \times 0.25 \text{ mm}$

Data collection

Bruker APEX 2 CCD diffractometer	4049 reflections with $I > 2\sigma(I)$
Radiation source: fine-focus sealed tube	$R_{\text{int}} = 0.058$
ω rotation with narrow frames scans	$\theta_{\text{max}} = 28.4^\circ$, $\theta_{\text{min}} = 1.9^\circ$
Absorption correction: multi-scan TWINABS v2012/1, Sheldrick, G.M., (2012)	$h = -14 \rightarrow 14$
$T_{\text{min}} = 0.966$, $T_{\text{max}} = 0.979$	$k = -10 \rightarrow 10$
17201 measured reflections	$l = -14 \rightarrow 14$
4577 independent reflections	

Refinement

Refinement on F^2	Secondary atom site location: difference Fourier map
Least-squares matrix: full	Hydrogen site location: difference Fourier map
$R[F^2 > 2\sigma(F^2)] = 0.038$	Only H-atom coordinates refined
$wR(F^2) = 0.096$	$w = \frac{1}{[\sigma^2(F_o^2) + (0.0567P)^2]}$ where $P = (F_o^2 + 2F_c^2)/3$
$S = 1.08$	$(\Delta/\sigma)_{\max} < 0.001$
4577 reflections	$\Delta_{\max} = 0.20 \text{ e } \text{\AA}^{-3}$
327 parameters	$\Delta_{\min} = -0.16 \text{ e } \text{\AA}^{-3}$
16 restraints	Absolute structure: Flack x determined using 1663 quotients [(I+)-(I-)]/[(I+)+(I-)] (Parsons and Flack (2004), Acta Cryst. A60, s61). Flack x via hole-in-one method gives 0.230(999).
Primary atom site location: structure-invariant direct methods	Flack parameter: 1.0 (7). Could not be reliably determined.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (\AA^2)

	x	y	z	$U_{\text{iso}}^*/U_{\text{eq}}$
N1	0.19893 (15)	0.9726 (2)	0.32609 (15)	0.0221 (3)
N2	0.25192 (14)	0.8306 (2)	0.28546 (15)	0.0219 (3)
C3	0.36959 (18)	0.8747 (3)	0.25585 (18)	0.0240 (4)
H3	0.440 (2)	0.827 (3)	0.319 (2)	0.018 (5)*
C4	0.3745 (2)	1.0655 (3)	0.2721 (2)	0.0307 (5)
H4A	0.461 (2)	1.104 (3)	0.303 (2)	0.026 (6)*
H4B	0.337 (2)	1.119 (4)	0.200 (3)	0.038 (7)*
C5	0.30169 (19)	1.0958 (3)	0.3672 (2)	0.0271 (4)
H5	0.271 (2)	1.207 (3)	0.358 (2)	0.023 (6)*
C6	0.3824 (2)	1.0612 (3)	0.4993 (2)	0.0350 (5)
H6	0.458 (2)	1.127 (4)	0.521 (3)	0.046 (8)*
C7	0.3580 (3)	0.9571 (4)	0.5790 (2)	0.0420 (6)
H7A	0.280 (3)	0.896 (4)	0.564 (3)	0.050 (8)*
H7B	0.416 (2)	0.944 (3)	0.658 (2)	0.034 (7)*
C8	0.36914 (17)	0.8173 (3)	0.12673 (18)	0.0237 (4)
C9	0.4686 (2)	0.7237 (3)	0.1118 (2)	0.0316 (5)
H9	0.538 (2)	0.697 (3)	0.184 (3)	0.032 (6)*
C10	0.4712 (2)	0.6746 (3)	-0.0067 (2)	0.0388 (5)
H10	0.537 (3)	0.611 (4)	-0.015 (3)	0.046 (8)*
C11	0.3745 (2)	0.7209 (3)	-0.1111 (2)	0.0373 (5)
H11	0.380 (3)	0.678 (4)	-0.188 (3)	0.048 (8)*

C12	0.2750 (2)	0.8136 (3)	-0.0975 (2)	0.0336 (5)
H12	0.207 (3)	0.846 (4)	-0.168 (3)	0.042 (7)*
C13	0.27169 (19)	0.8605 (3)	0.02092 (19)	0.0270 (4)
H13	0.204 (2)	0.924 (3)	0.030 (2)	0.026 (6)*
C14	0.08331 (18)	1.0278 (3)	0.24990 (18)	0.0239 (4)
O1	0.04204 (14)	1.1641 (2)	0.26171 (15)	0.0341 (4)
O2	0.02419 (13)	0.90933 (19)	0.17165 (15)	0.0317 (4)
C15	-0.10419 (19)	0.9454 (3)	0.0936 (2)	0.0350 (5)
H15	-0.132 (3)	1.044 (4)	0.131 (3)	0.043 (8)*
C16	-0.1009 (3)	0.9788 (5)	-0.0366 (3)	0.0575 (8)
H16A	-0.192 (2)	0.991 (6)	-0.086 (3)	0.086*
H16B	-0.071 (4)	0.875 (4)	-0.069 (4)	0.086*
H16C	-0.054 (3)	1.085 (4)	-0.046 (4)	0.086*
C17	-0.1821 (3)	0.7979 (5)	0.1054 (3)	0.0557 (8)
H17A	-0.181 (4)	0.778 (6)	0.192 (4)	0.090 (14)*
H17B	-0.156 (4)	0.695 (6)	0.067 (4)	0.085 (13)*
H17C	-0.273 (3)	0.817 (5)	0.059 (3)	0.070 (10)*
C18	0.24242 (17)	0.6777 (3)	0.33648 (17)	0.0225 (4)
O3	0.30908 (13)	0.56129 (18)	0.32784 (14)	0.0284 (3)
O4	0.14892 (13)	0.67313 (18)	0.38916 (13)	0.0257 (3)
C19	0.1221 (2)	0.5097 (3)	0.4342 (2)	0.0288 (4)
H19	0.136 (2)	0.428 (3)	0.376 (2)	0.027 (6)*
C20	-0.0122 (3)	0.5174 (3)	0.4362 (3)	0.0425 (6)
H20A	-0.072 (3)	0.538 (4)	0.349 (2)	0.057 (9)*
H20B	-0.019 (3)	0.599 (4)	0.503 (3)	0.059 (9)*
H20C	-0.039 (3)	0.410 (3)	0.465 (3)	0.054 (9)*
C21	0.2141 (3)	0.4760 (4)	0.5615 (3)	0.0513 (7)
H21A	0.304 (3)	0.484 (4)	0.560 (3)	0.049 (8)*
H21B	0.195 (3)	0.562 (4)	0.616 (3)	0.041 (7)*
H21C	0.200 (4)	0.370 (5)	0.593 (4)	0.076 (11)*

Geometric parameters (Å, °)

N1—C14	1.391 (2)	C12—H12	0.95 (3)
N1—N2	1.417 (2)	C13—H13	0.95 (2)
N1—C5	1.479 (3)	C14—O1	1.208 (3)
N2—C18	1.369 (3)	C14—O2	1.327 (2)
N2—C3	1.486 (2)	O2—C15	1.469 (2)
C3—C8	1.512 (3)	C15—C16	1.488 (4)
C3—C4	1.539 (3)	C15—C17	1.496 (4)

C3—H3	0.96 (2)	C15—H15	0.98 (3)
C4—C5	1.532 (3)	C16—H16A	1.01 (2)
C4—H4A	0.97 (2)	C16—H16B	1.01 (2)
C4—H4B	0.90 (3)	C16—H16C	1.02 (2)
C5—C6	1.511 (3)	C17—H17A	0.98 (4)
C5—H5	0.95 (3)	C17—H17B	1.01 (4)
C6—C7	1.305 (4)	C17—H17C	1.00 (4)
C6—H6	0.96 (3)	C18—O3	1.214 (2)
C7—H7A	0.96 (3)	C18—O4	1.338 (2)
C7—H7B	0.94 (3)	O4—C19	1.466 (2)
C8—C9	1.388 (3)	C19—C20	1.504 (3)
C8—C13	1.393 (3)	C19—C21	1.512 (3)
C9—C10	1.388 (3)	C19—H19	0.97 (3)
C9—H9	0.97 (3)	C20—H20A	1.02 (2)
C10—C11	1.386 (4)	C20—H20B	1.01 (2)
C10—H10	0.91 (3)	C20—H20C	1.00 (2)
C11—C12	1.379 (3)	C21—H21A	1.01 (3)
C11—H11	0.94 (3)	C21—H21B	0.98 (3)
C12—C13	1.385 (3)	C21—H21C	0.95 (4)
C14—N1—N2	117.27 (15)	C12—C13—H13	119.8 (14)
C14—N1—C5	118.05 (17)	C8—C13—H13	119.6 (15)
N2—N1—C5	106.19 (14)	O1—C14—O2	126.05 (19)
C18—N2—N1	119.75 (15)	O1—C14—N1	122.36 (18)
C18—N2—C3	119.16 (16)	O2—C14—N1	111.45 (17)
N1—N2—C3	110.92 (15)	C14—O2—C15	117.27 (17)
N2—C3—C8	112.53 (16)	O2—C15—C16	108.44 (19)
N2—C3—C4	102.35 (17)	O2—C15—C17	106.3 (2)
C8—C3—C4	113.90 (18)	C16—C15—C17	114.2 (3)
N2—C3—H3	109.1 (13)	O2—C15—H15	106.4 (16)
C8—C3—H3	110.2 (13)	C16—C15—H15	111.6 (16)
C4—C3—H3	108.4 (14)	C17—C15—H15	109.3 (16)
C5—C4—C3	103.38 (18)	C15—C16—H16A	104 (2)
C5—C4—H4A	111.8 (13)	C15—C16—H16B	108 (2)
C3—C4—H4A	110.7 (15)	H16A—C16—H16B	106 (3)
C5—C4—H4B	110.1 (17)	C15—C16—H16C	114 (2)
C3—C4—H4B	111.9 (19)	H16A—C16—H16C	109 (3)
H4A—C4—H4B	109 (2)	H16B—C16—H16C	115 (3)
N1—C5—C6	111.40 (19)	C15—C17—H17A	112 (3)
N1—C5—C4	101.42 (16)	C15—C17—H17B	111 (2)

C6—C5—C4	111.28 (19)	H17A—C17—H17B	112 (4)
N1—C5—H5	111.6 (14)	C15—C17—H17C	111 (2)
C6—C5—H5	111.9 (14)	H17A—C17—H17C	105 (3)
C4—C5—H5	108.8 (15)	H17B—C17—H17C	106 (3)
C7—C6—C5	126.8 (2)	O3—C18—O4	125.93 (19)
C7—C6—H6	121.4 (18)	O3—C18—N2	122.12 (17)
C5—C6—H6	111.8 (18)	O4—C18—N2	111.87 (16)
C6—C7—H7A	123.9 (19)	C18—O4—C19	116.00 (16)
C6—C7—H7B	119.5 (16)	O4—C19—C20	105.77 (17)
H7A—C7—H7B	117 (2)	O4—C19—C21	109.40 (19)
C9—C8—C13	118.89 (19)	C20—C19—C21	113.3 (2)
C9—C8—C3	120.01 (18)	O4—C19—H19	106.7 (15)
C13—C8—C3	121.08 (18)	C20—C19—H19	113.1 (14)
C10—C9—C8	120.6 (2)	C21—C19—H19	108.3 (15)
C10—C9—H9	120.2 (15)	C19—C20—H20A	111.6 (17)
C8—C9—H9	119.2 (15)	C19—C20—H20B	109.3 (18)
C11—C10—C9	119.8 (2)	H20A—C20—H20B	115 (3)
C11—C10—H10	120.8 (18)	C19—C20—H20C	111.2 (18)
C9—C10—H10	119.4 (18)	H20A—C20—H20C	106 (3)
C12—C11—C10	120.2 (2)	H20B—C20—H20C	103 (3)
C12—C11—H11	124.6 (19)	C19—C21—H21A	111.9 (17)
C10—C11—H11	115.1 (19)	C19—C21—H21B	104.0 (17)
C11—C12—C13	120.0 (2)	H21A—C21—H21B	112 (3)
C11—C12—H12	121.8 (17)	C19—C21—H21C	111 (2)
C13—C12—H12	118.3 (17)	H21A—C21—H21C	110 (3)
C12—C13—C8	120.6 (2)	H21B—C21—H21C	108 (3)
C14—N1—N2—C18	-100.6 (2)	C3—C8—C9—C10	-178.0 (2)
C5—N1—N2—C18	124.97 (18)	C8—C9—C10—C11	0.7 (4)
C14—N1—N2—C3	114.44 (18)	C9—C10—C11—C12	-0.8 (4)
C5—N1—N2—C3	-20.04 (19)	C10—C11—C12—C13	0.0 (4)
C18—N2—C3—C8	87.0 (2)	C11—C12—C13—C8	1.1 (3)
N1—N2—C3—C8	-127.73 (17)	C9—C8—C13—C12	-1.2 (3)
C18—N2—C3—C4	-150.30 (17)	C3—C8—C13—C12	177.1 (2)
N1—N2—C3—C4	-5.06 (19)	N2—N1—C14—O1	-164.79 (19)
N2—C3—C4—C5	27.0 (2)	C5—N1—C14—O1	-35.7 (3)
C8—C3—C4—C5	148.78 (17)	N2—N1—C14—O2	19.3 (2)
C14—N1—C5—C6	143.74 (18)	C5—N1—C14—O2	148.38 (17)
N2—N1—C5—C6	-82.21 (19)	O1—C14—O2—C15	-1.2 (3)
C14—N1—C5—C4	-97.8 (2)	N1—C14—O2—C15	174.51 (18)

N2—N1—C5—C4	36.3 (2)	C14—O2—C15—C16	105.0 (3)
C3—C4—C5—N1	-38.8 (2)	C14—O2—C15—C17	-131.7 (2)
C3—C4—C5—C6	79.8 (2)	N1—N2—C18—O3	-162.53 (16)
N1—C5—C6—C7	-11.1 (3)	C3—N2—C18—O3	-20.4 (3)
C4—C5—C6—C7	-123.5 (3)	N1—N2—C18—O4	20.6 (2)
N2—C3—C8—C9	-128.1 (2)	C3—N2—C18—O4	162.73 (16)
C4—C3—C8—C9	116.0 (2)	O3—C18—O4—C19	-3.2 (3)
N2—C3—C8—C13	53.7 (3)	N2—C18—O4—C19	173.52 (16)
C4—C3—C8—C13	-62.3 (3)	C18—O4—C19—C20	-156.27 (18)
C13—C8—C9—C10	0.4 (3)	C18—O4—C19—C21	81.3 (2)

Hydrogen-bond geometry (Å, °)

<i>D</i> —H... <i>A</i>	<i>D</i> —H	H... <i>A</i>	<i>D</i> ... <i>A</i>	<i>D</i> —H... <i>A</i>
C19—H19...O1 ⁱ	0.97 (3)	2.53 (3)	3.343 (3)	141.4 (18)

Symmetry code: (i) *x*, *y*-1, *z*.

Computing details

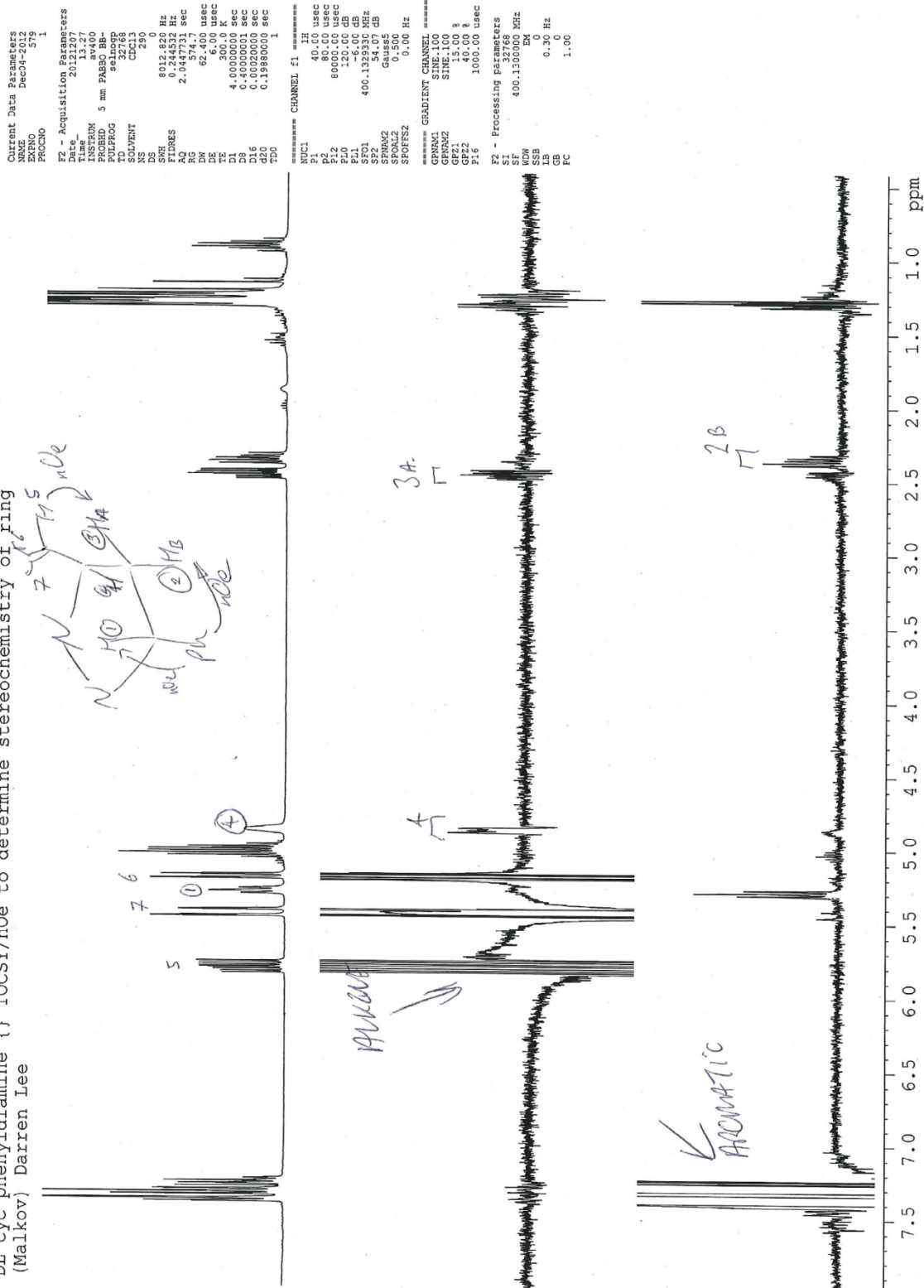
Data collection: Bruker *APEX 2*; cell refinement: Bruker *SAINT*; data reduction: Bruker *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL2012* (Sheldrick, 2012); molecular graphics: Bruker *SHELXTL*; software used to prepare material for publication: Bruker *SHELXTL*.

Special details

Geometry. All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

5.2. NOE Spectra for 2.63

DL cyc phenyldiamine {} TOCSY/NOE to determine stereochemistry of ring
(Malkov) Darren Lee



5.3. NOE Spectra for 2.56a

