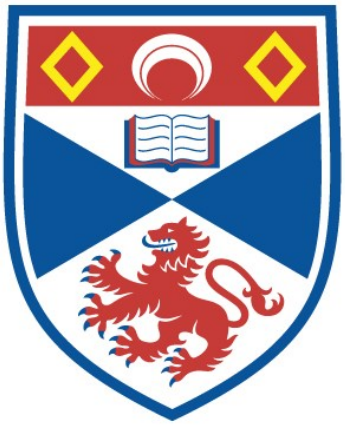
Synthesis of chiral nitrogen heterocycles using hydroformylation – cyclisation reactions

Nina Jeffrey

A thesis submitted for the degree of PhD
at the
University of St Andrews



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"Sometimes I lie awake at night, and I ask, 'Where have I gone wrong?' Then a voice says to me, 'This is going to take more than one night'."
Charles M. Schulz

Acknowledgements

It is said that to owe your supervisor a debt of thanks is a joyous debt to have for it means that they have invested time and effort in you, and I certainly owe Matt a debt of thanks for all his time, patience and effort over the course of this PhD.

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Abstract:

This thesis concerns the investigation of hydroformylation-cyclisation reactions for the synthesis of chiral, saturated nitrogen heterocycles.

The first chapter is a literature review that details the work that has previously been carried out in this area, much of which is focussed on linear regioselective hydroformylation reactions and hence these do not include any introduction of enantioselectivity from the hydroformylation reaction. A few examples use dual catalysts in order to refine the enantiomeric excess after the hydroformylation step, but the examples that introduce enantioselectivity in the hydroformylation step are recent ones and are primarily from the Zhang group and the Clarke group. These are discussed in the most detail.

The second chapter is a discussion of the experimental work on the use of hydroformylation-cyclisation reactions with a Rh/ BOBPHOS catalyst for the synthesis of piperidines. Here it is established that the use of BOBPHOS is necessary for obtaining high branched regioselectivity as well as high enantioselectivity with these unbiased substrates. It is also clearly presented that the use of a sulfonamide protecting group on the nitrogen is key to balancing the nucleophilicity of the nitrogen lone pair with the stability of the hemi-aminal intermediate, which can then be reduced in a one-pot procedure to the piperidine. Expansion of this methodology to substituted piperidines is also discussed.

The third chapter focusses on the formation of 3-methylpyrrolidine through hydroformylation-cyclisation to form the tosyl-protected derivative, followed by a one-pot reduction and subsequent isolation from the crude reaction mixture. Deprotection of such a small, volatile amine as well as measurement of the enantiomeric excess proved challenging and that is also discussed here. Preliminary steps for extending the reactivity of this methodology for the synthesis of an ant venom component, Leptothoracine, through a second HAM reaction of a 1,1-disubstituted alkene are also presented.

The fourth chapter summarises the main outcomes of these results and contextualises the advances that have been made, whilst the final chapter contains the experimental procedures and compound data. Two appendixes are also included: the first describing palladium-catalysed carbonylation reactions for the synthesis of pyrrolidinones and piperidinones; the second appendix contains data for selected key compounds whose synthesis has been discussed within this thesis.

Abbreviations:

µL – Microlitre

µW - Microwave

Å – Angstrom

Ac - Acetyl

AcOH - Acetic acid

AHF – Asymmetric hydroformylation

AZADO - 2-Azaadamantane-*N*-oxyl

Bn - Benzyl

Boc – *tert*-butyloxycarbonyl

Bpy - 2,2′ -Bipyridine

Bz - Benzoyl

cat. – Catalyst

CBz – Benzyl carbamate

CO – Carbon monoxide

COD – Cyclooctadiene

CSA – Chiral solvating agent

CDA – Chiral derivatising agent

DCC – *N*, *N*′ -Dicyclohexylcarbodiimide

DCE - Dichloroethane

DCM - Dichloromethane

DIAD - Diisopropyl azodicarboxylate

DMAP - 4-Dimethylaminopyridine

DMF - *N*, *N*-Dimethyl formamide

DMSO - Dimethyl sulfoxide

dr - Diastereomeric ratio

EDG - Electron Donating Group

ee - Enantiomeric excess

EPSRC - Engineering and Physical Sciences Research Council

equiv - Equivalent

EWG - Electron Withdrawing Group

Et_2O - Diethyl ether

FTIR - Fourier Transform Infrared Spectroscopy

HAM – Hydroaminomethylation

HF – Hydroformylation

HPLC – High performance liquid chromatography

hr - Hours

HRMS - High Resolution Mass Spectrometry

Hz – Hertz

IR - Infrared

LA - Lewis Acid

LDA - Lithium Diisopropylamide

M – Molar

Mandyphos: (*S*, *S*)-(+)-2,2'-Bis[(*R*)-(*N*, *N*-dimethylamino)(phenyl)methyl]-1,1'-bis(dicyclohexylphosphino)ferrocene, for (*S*, *S*) enantiomer

MeCN – Acetonitrile

MeOH - Methanol

mg - Milligrammes

MHz - Megahertz

min - Minutes

mmol - Millimole

mol - Moles

mL - Millilitres

MS - Molecular sieves

Ms – Methanesulfonyl

MTBE – Methyl *tert*butylether

MW - Microwave

NEt_3 - Triethylamine

nm - Nanometre

NMR - Nuclear Magnetic Resonance

Ns – Nosyl, 2-nitrobenzenesulfonyl

Nu – Nucleophile

PCC – Pyridinium chlorochromate

p-cymene - 1-Isopropyl-4-methylbenzene

PG - Protecting Group

Ph-BPE - (+)-1,2-Bis((2*S*, 5*S*)-2,5-diphenylphospholano)ethane, for (*S*, *S*) enantiomer.

Phth – Phthalimide

PMB - *Para*-methoxybenzyl

PMP – *Para*-methoxyphenyl

ppm - Parts per million

PPTS - Pyridinium *p*-toluenesulfonate

rt - Room temperature

segphos - (*R*)-(+)-5,5'-Bis(diphenylphosphino)-4,4'-bi-1,3-benzodioxole, for (*R*) enantiomer

TBAF - Tetra-n-butylammonium fluoride

TBDPS – *tert*-butyldiphenylsilyl

TBS – *tert*-butyldimethylsilyl

TBSCl - *tert*-butyldimethylsilyl chloride

Tf - Triflate, trifluoromethanesulfonate

TFA - Trifluoroacetic acid

THF - Tetrahydrofuran

TLC - Thin Layer Chromatography

Trityl – Triphenylmethylsilyl

Ts – Tosyl, 4-methylbenzenesulfonyl

TsCl – Tosyl chloride

TsOH – Tosylsulfonic acid

UV - Ultraviolet

Contents

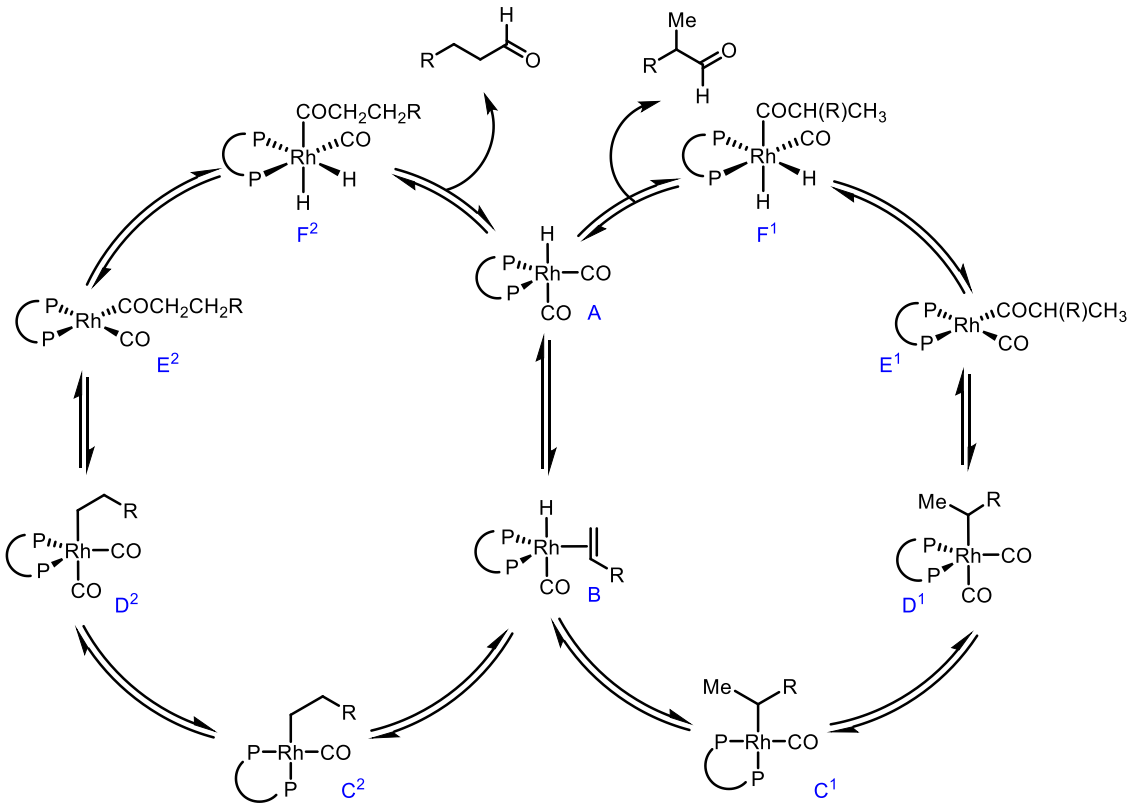
Chapter 1: Introduction

The synthesis of chiral nitrogen containing compounds is lacking in facile, accessible routes: the limitations of current methods include the reliance on reagents that create waste, the use of chiral auxiliaries or classical resolution procedures. Hydroformylation of amine functionalised alkenes offers a route to form chiral nitrogen containing compounds in a simple, atom efficient and catalytic process.

Tandem reactions are defined as those "in which multiple reactions are combined into one synthetic operation"; whilst domino and cascade reactions are "closely coupled individual reactions that often yield a product difficult to obtain by a single process".[1] One-pot sequential reactions, which are domino reactions where some reagents have to be added after one of the steps, can rapidly increase the complexity of a reaction or molecule whilst also minimising purification steps and solvent use. Due to the compatibility of hydroformylation conditions with a wide variety of functional groups and molecules, it is an ideal reaction for use in tandem, domino or cascade methodologies. Asymmetric hydroformylation to yield the branched product allows for the introduction of a stereocentre with potentially high enantioselectivity. Formation of the correct enantiomer in high enantiomeric excess is absolutely critical for the pharmaceutical industry in particular, and this is common knowledge ever since the prominent disaster of the racemic phthalidomide morning sickness drug, from which the inactive enantiomer caused birth defects.

Rhodium Catalysed Hydroformylation

Rhodium catalysed hydroformylation has been much researched and can now be used under carefully selected conditions to induce linear or branched selectivity for a variety of substrates. The control for the regioselectivity is influenced by the sterics and electronics of the substrate as well as the choice of ligand, Scheme 1.

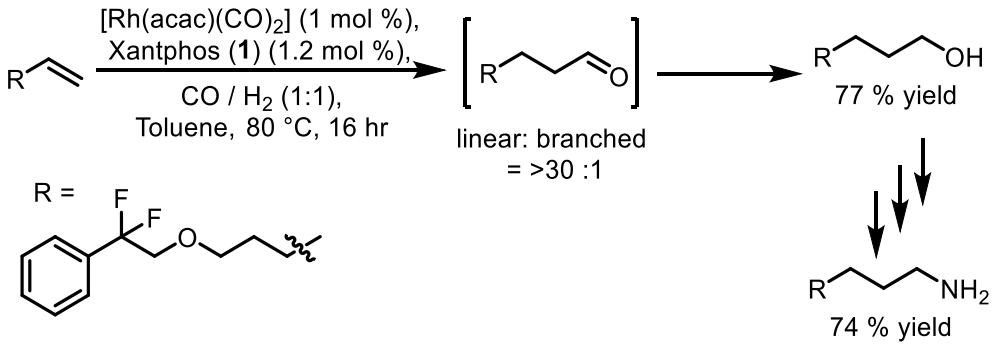


Scheme 1: Hydroformylation catalytic cycle depicting both branched and linear pathways

The compatibility of hydroformylation reaction conditions with a range of alkene substituents bearing various functional groups have led to the investigation of using HF with tandem, domino, cascade and one pot reactions in order to build molecular complexity in a variety of efficient ways.

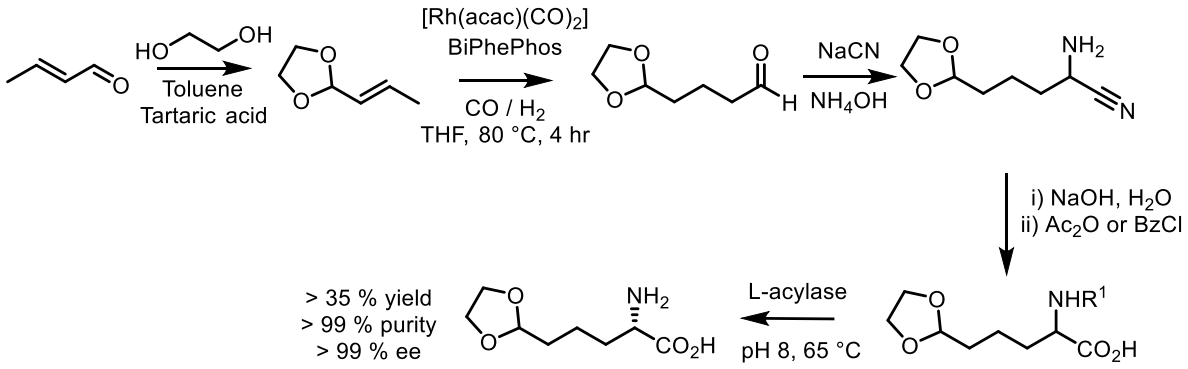
Hydroformylation reactions can be used to make nitrogen compounds in a direct manner via one-pot procedures such as hydroaminomethylation (HAM) reactions, but also with added reagents after the hydroformylation step. This review will start with examples of standard hydroformylation reactions before discussing hydroaminomethylation reactions in more detail.

Recently a hydroformylation reaction for the synthesis of the lipophilic part of the drug molecule known commercially as Abediterol was used, before reducing the aldehyde to an alcohol and carrying out a Mitsunobu reaction to insert the amine moiety, Scheme 2.[2] This had the advantages of removing the need for the use of hydrazine in the synthesis, as well as avoiding using large excesses of other reagents. The selectivity for the linear product was achieved by using the bidentate phosphine ligand, Xantphos (**2**).



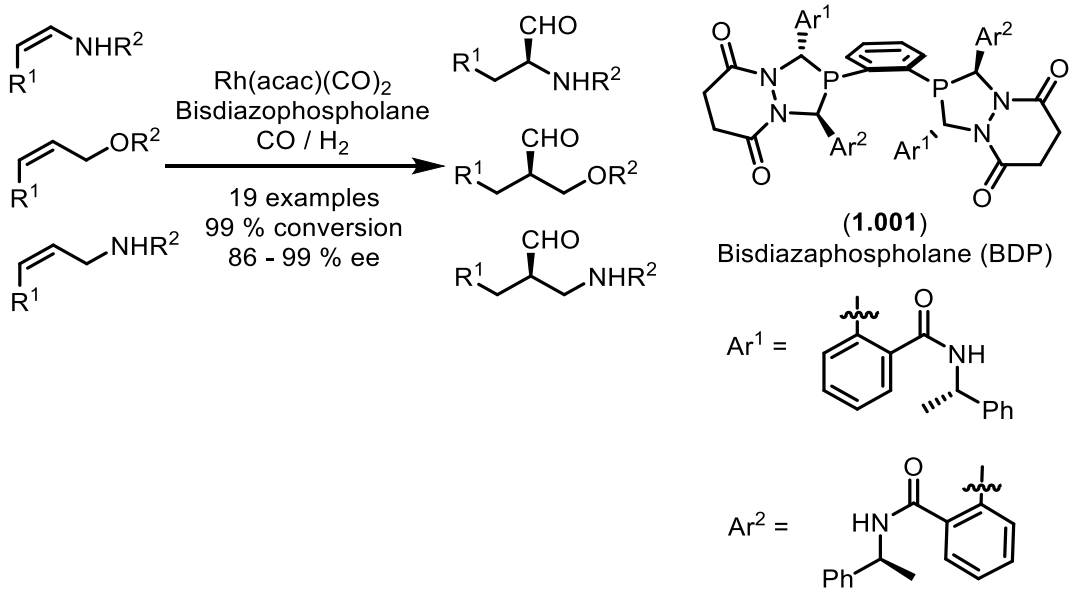
Scheme 2: Synthesis of intermediate for Abediterol using HF.[2]

In another example, the use of a hydroformylation reaction in conjunction with an enzyme enables the large-scale formation of a chiral amine, Scheme 3.[3] The cheap starting material is first protected before isomerisation of the internal alkene to a terminal alkene occurs, next linear regioselective hydroformylation using the ligand BiPhePhos (**7**) takes place and then finally the amine function introduced by use of a Strecker reaction on the crude hydroformylation reaction mixture. The material is then subjected to further steps before finally carrying out an amine deprotection with L-acylase to yield the desired enantiomer. The unwanted enantiomer can be recycled through the system to get higher ee values and it was found that up to > 98 % of the rhodium can be retrieved from the work up, to up to 300 L scale.



Scheme 3: Hydroformylation as a key component of a large-scale synthesis.[3]

It is possible to induce enantioselectivity within the HF step through the use of an enantioselective ligand. One such work to do this was that by Stahl, Landis and co-workers who have achieved high enantioselectivities, between 86-99 % ee, for the hydroformylation of functionalised alkenes, although regioselectivity depended on the electronic preference of the R^1 substituent for formation of the correct regioisomer, Scheme 4.[4]

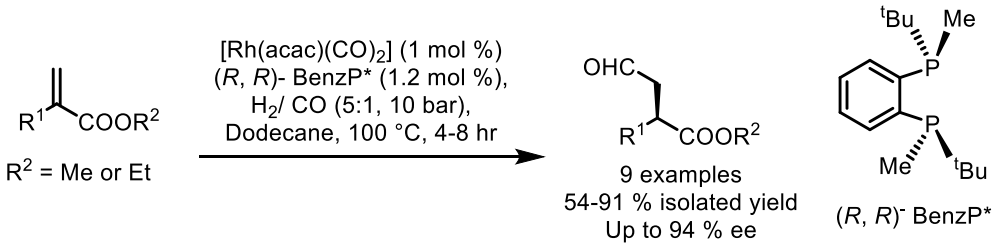


Scheme 4: Asymmetric hydroformylation of nitrogen containing compounds.[4]

1,1-Disubstituted Alkenes:

There are specific challenges associated with the hydroformylation of 1,1-disubstituted alkenes. The first is that regioselectivity is significantly pre-determined by the substrate: the steric affects of the 1,1-disubstitution mean that, apart from in certain cases, the linear regioisomer is formed. This is often so absolute that in 1948 Keuleman's rule was published which ascertained this.[5] The notable exceptions to this are typically α,β-unsaturated esters: the electron withdrawing properites and coordinating functional group mean that this class of substrates can be regioselective for the branched isomer. Regardless of the regioselectivity, in an unsymmetrical 1,1-disubstituted alkene a new stereocentre upon hydroformylation and the development of catalysts that can do this with good enantioselectivity has been slow until recently. Part of the reason that this transformation has proven so difficult is not only the control of chemo, regio and enantioselectivity that is inherent to all hydroformylation reactions, but that the difference in the two C1 centres is so small that most catalysts struggle to differentiate between them for enantioselective results, as is seen in other enantioselective reactions concerning these substrates, such as hydrogenations.

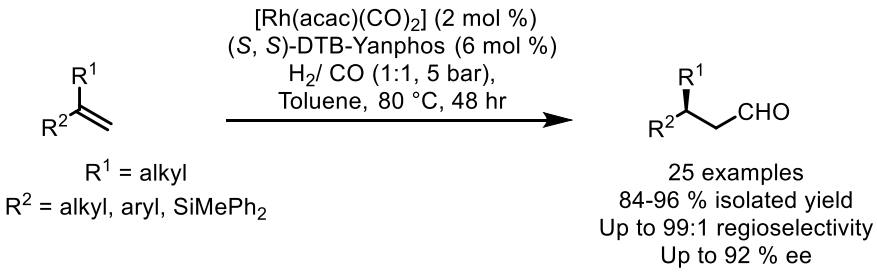
The first prominent paper in this area was the report of the AHF of α-alkylacrylates with high selectivities by Wang and Buchwald, Scheme 5.[6]



Scheme 5: Enantioselective hydroformylation of α-alkylacrylates.[6]

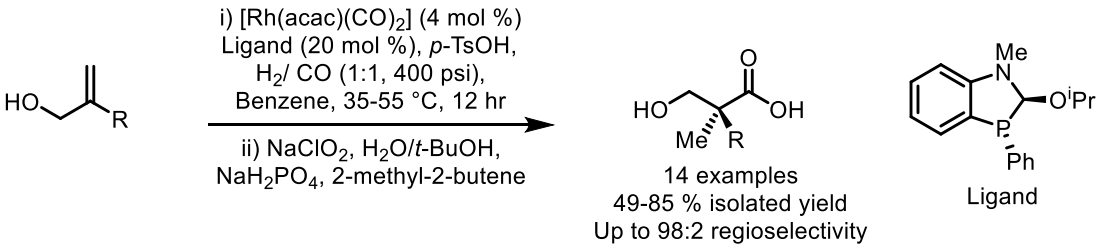
Within this paper they disclose the use of chiral phosphine ligands for the AHF of these substrates as being particularly important for achieving this, the hypothesis the authors put forward is that by containing the chiral information on the phosphorus that is directly bonded to the rhodium centre, combined with the rigid backbone of the ligand, this allows for enantiomeric induction during the AHF. Furthermore, careful control of the ratio and pressure of CO and H_2 is needed in order to suppress formation of the side product arising from hydrogenation of the starting substrate, whilst the side product arising from formation of the branched aldehyde was also observed in some cases.

Later in 2018, Zhang and co-workers published procedure that used a new chiral ligand to achieve AHF of 1,1-disubstituted alkenes.[7] Here it was found that it was crucial to use a ligand with (*S*, *S*) axial chirality as opposed to the traditional (*S*, *R*) axial chirality that Yanphos is normally synthesised. Furthermore, use of significant steric hindrance on the phosphine groups is required to help differentiate between the two achiral faces of the substrate and introduce enantioselectivity, Scheme 6.



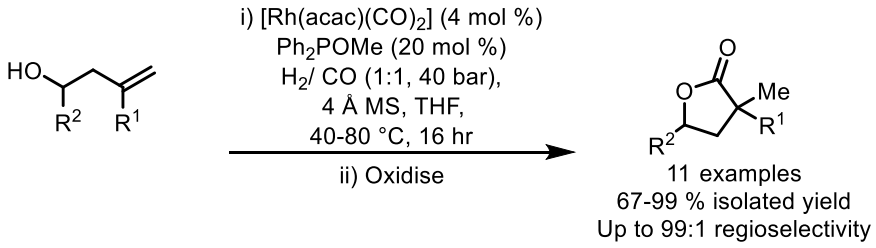
Scheme 6: Enantioselective hydroformylation with a Yanphos derivative.[7]

Tan and co-workers have demonstrated one example of directing the regioselectivity of the hydroformylation of a disubstituted alkene through a scaffolding ligand that binds to both the substrate and the catalyst, Scheme 7.[8]



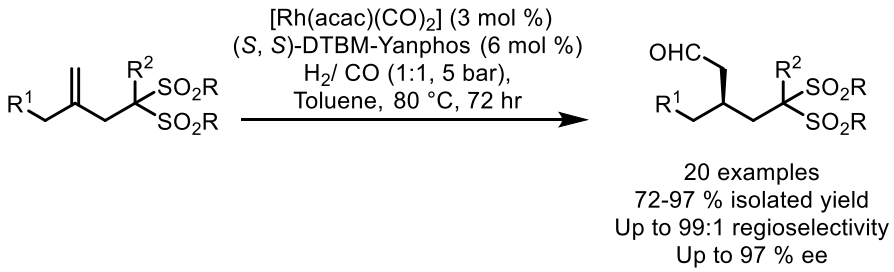
Scheme 7: Enantioselective hydroformylation with coordinating alcohol and specialised ligand.[8]

The scaffolding ligand exchanges the isopropanol group with the substrate before binding to the catalyst and then directing the hydroformylation for the formation of a quaternary carbon centre. Formation of quaternary carbon centres through hydroformylation are exceedingly difficult and if triphenyl phosphine is used as the ligand instead of the scaffolding ligand or the alcohol on the substrate is changed to an ether, then no conversion to the target molecule is observed. This demonstrates the requirement of the scaffolding ligand for achieving this transformation and further control experiments established that the starting substrate had a slightly stronger binding affinity for the ligand compared to the product, thus assisting with exchange between the two. The product could not be isolated as the aldehyde as it was unstable to purification, hence it was oxidised to the carboxylic acid, further losses in yield were due to a small amount of the dimerised product forming. A wide range of aryl groups could be tolerated but a significant drop in regioselectivity was observed when a methyl group was used instead.



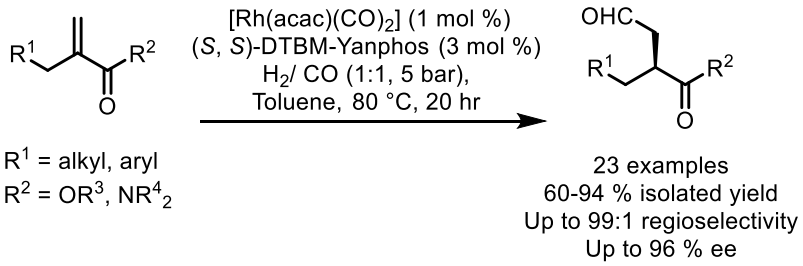
Scheme 8: Hydroformylation of 1,1-disubstituted alkenes with reversibly bound directing group.[9]

Another paper that was able to form quaternary carbon centres through hydroformylation of a disubstituted alkene was work by Breit and co-workers.[9] Again this used a reversibly bound directing group in catalytic quantities, here a diphenylphosphite that can coordinate to the alcohol of the substrate prior to coordination to the catalyst. A selection of functional groups could be tolerated for the hydroformylation reaction with the lactone product given after a one-pot oxidation, Scheme 8. Furans could also be synthesised by carrying out a one-pot reduction after the hydroformylation reaction.



Scheme 9: Hydroformylation of a 1,1-disubstituted alkene with an auxiliary group.[10]

Building on their previous work concerning the AHF of 1,1-disubstituted alkenes, the use of an auxiliary group for the regio- and enantioselective hydroformylation was published by Zhang and co-workers.[10] This work specifically addressed the limitation of their previous work in the AHF of alkyl-alkyl substituted alkenes by using an auxiliary group that could be easily removed once the AHF reaction had taken place, Scheme 9. A control reaction without this chiral auxiliary gave only 62 % ee compared to a substrate with the auxiliary which had an ee of 97 %. The starting substrates were not commercially available and had to be synthesised but a wide range of functionalities were tolerated during the AHF. Further reactions and cleavage of the auxiliary after the AHF to produce a chiral alcohol, amine and carboxylic acid in 22-25 % yields over 3 steps from the starting substrate were also demonstrated.

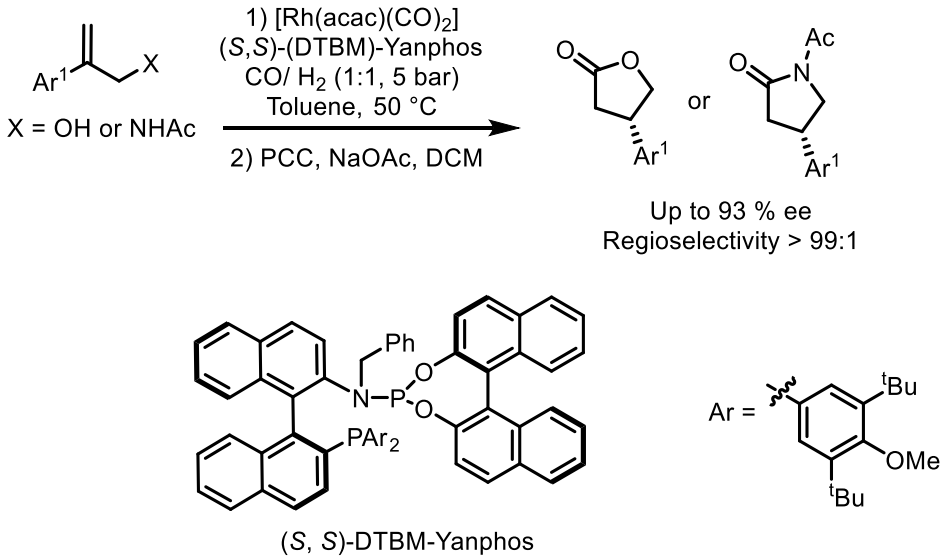


Scheme 10: Asymmetric hydroformylation of α,β-unsaturated compounds.[11]

Whilst it is known that α,β-unsaturated esters typically disobey Keulemans' rule to give quaternary carbon centres upon hydroformylation, a recent work from Zhang and co-workers has reversed this selectivity.[11] Using the Yanphos catalysts that are developed within their group, this methodology tolerated a wide range of functionalities with the limits being the steric hindrance on the ester or amide group, Scheme 10. It was found that increasing this steric hindrance lead to an increase in the ee up to a point, beyond this too significant steric hindrance stopped coordination of the group and lead to a drop in selectivity.

In addition to this Zhang and co-workers developed a methodology for the synthesis of pyrrolidinones through the AHF of 1,1-disubstituted alkenes, again with a Rh/ YanPhos catalyst.[12] The scope was

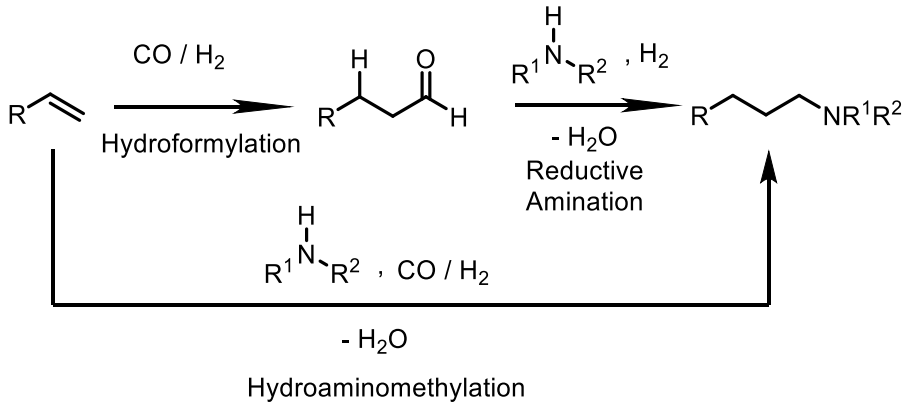
limited to the formation of pyrrolidinones and lactams but the use of 1,1-disubstituted alkenes had the advantage of also protecting the newly formed stereocentre from racemisation through the imine/ enamine pathway, Scheme 11.



Scheme 11: Asymmetric hydroformylation-cyclisation of 1,1-disubstituted alkenes.[12]

Hydroaminomethylation

Hydroaminomethylation (HAM) is a specific type of tandem reaction involving the treatment of an alkene or alkyne first with a hydroformylation reaction, followed by a subsequent reductive amination to yield an amine product. Within a HAM reaction, often the same catalyst that carries out the hydroformylation of the alkene also carries out the hydrogenation of the imine or enamine intermediate, Scheme 12. This is a particularly desirable reaction since it affords a simple pathway from cheap olefins to value added amines, which can be used as starting materials for pharmaceuticals, fine chemicals and other purposes. This tandem reaction is a good example of green chemistry since it is atom economical, catalytic and avoids the stoichiometric use of metal or halide salts.



Scheme 12: Synthetic steps involved in linear regioselective hydroaminomethylation.

There are challenges that must be met for this reaction to be useful: for example, the hydroformylation step must be much faster than the possible hydrogenation of the alkene or aldehyde to avoid the competing hydrogenation reaction pathway dominating the outcome.[13] As a result of these difficulties, much research has taken place in finding the ideal operating conditions and the ligands that facilitate this.

The first known HAM used acetylenic compounds, carbon monoxide and ammonia to form a mixture of products, one of which was an amine.[14] The reaction has since then been greatly improved to become catalytic, selective and operational under far more benign conditions and pressures. In particular, rhodium catalysts are favoured on account of their high activity and ability to efficiently catalyse both the hydroformylation and hydrogenation step. Furthermore, phosphine ligands are often favoured due to their literature precedent, stability and tuneable electronic and steric properties Figure 1.

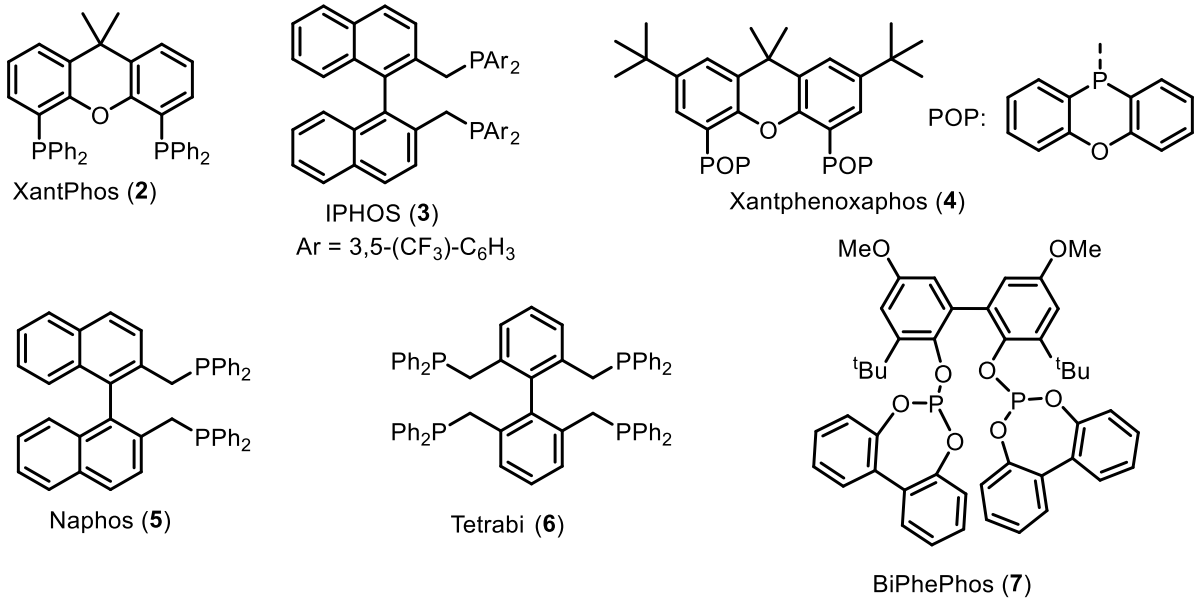
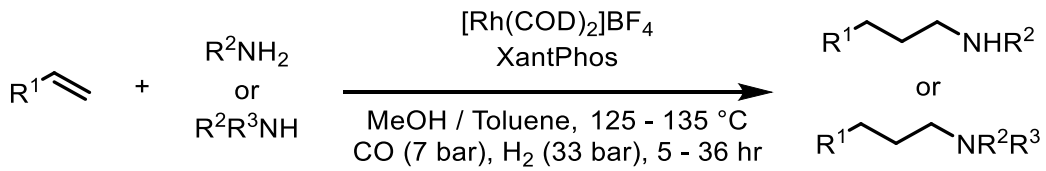


Figure 1: Common ligands for linear-selective hydroformylation reactions

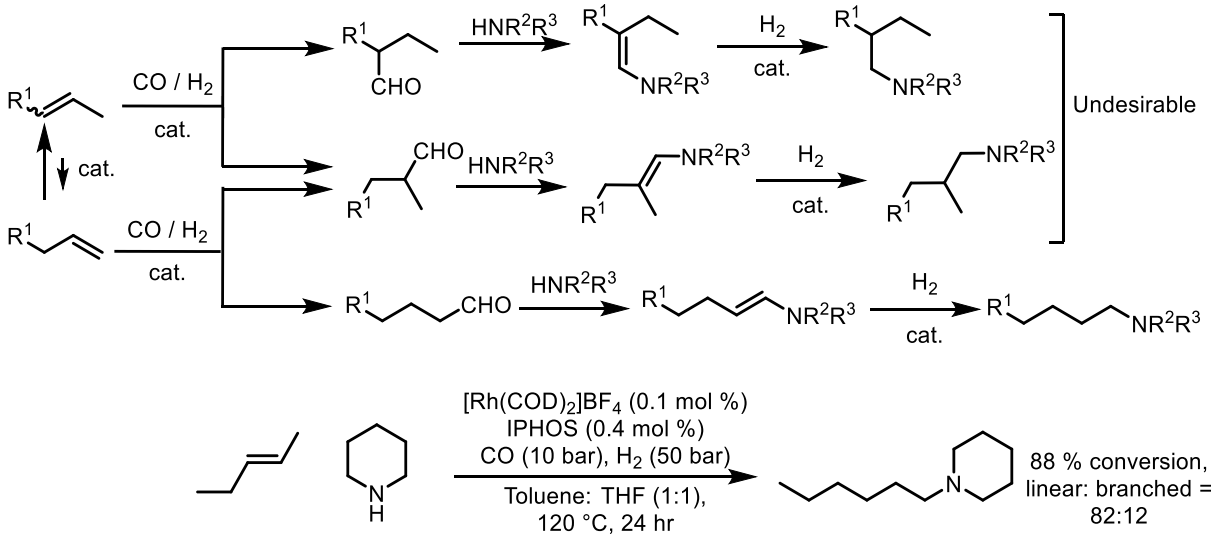
Beller and co-workers have produced pioneering work on the linear selective HAM reaction, Scheme 13; they induced linear regioselectivity through a bidentate ligand, XantPhos in the reaction of predominantly long-chain alkyl alkene substrates.[15] The bidentate ligand is of particular importance: it has a large bite angle and offers significant steric hindrance, raising the regioselectivity by favouring the formation of the linear aldehyde and hence linear amine; a drop in regioselectivity was observed when using triphenylphosphine as the ligand. Most of the substrates used were generally R^1 = alkyl, thus the inherent electronic preference was to prefer linear regioselectivity giving linear to branched ratios of up to 99:1. However, for styrene and *p*-chlorostyrene, substrates whose inherent electronic preference is for branched regioselectivity, this paper was the first reported linear selective HAM, with linear to branched selectivity of 82:12 and 80:20 respectively.



Scheme 13: First general linear selective HAM[15]

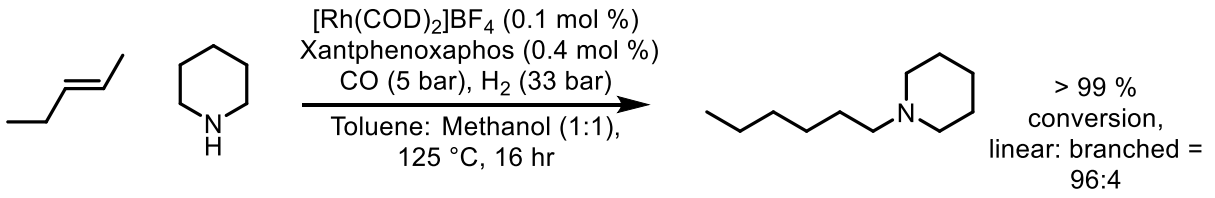
One of the other notable studies from this group reports the use of not only terminal olefins but also internal alkenes to selectively synthesise linear, terminal amines through HAM reactions.[16] The authors characterised the problems to be addressed as follows: the catalyst must affect fast isomerization between internal and terminal olefins; it must also be selective for linear hydroformylation of the terminal olefin compared to the internal olefin; it must be active and selective for enamine, or imine, hydrogenation, Scheme 14. The authors postulated that the main problem with

the reaction was the low isomerization activity of the rhodium catalyst in the presence of strong σ-donor ligands, for example amines, and hence the use of an electron withdrawing bidentate ligand, IPHOS, was employed. The substrates used were linear, long-chain, internal alkenes.



Scheme 14: Linear selective HAM from internal olefins[16]

Improved results were obtained with a return to a XantPhos-like ligand, Xantphenoxaphos, (**4**), that could also affect the isomerization of internal olefins to external olefins, even within mixtures of olefins, and thus selectively provide linear amines, Scheme 15.[17] Within this study the mechanism was also explored by monitoring the reaction via high pressure IR. This was possible for this reaction since different components, the aldehyde, enamine and aldol condensation product from an unwanted side reaction, all had strong and distinct absorbance bands.



Scheme 15: Improved conditions for linear selective HAM of internal olefins.[17]

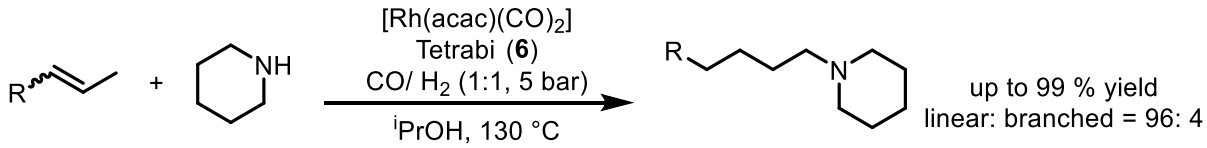
From this study, it was determined that enamine formation occurred much faster than the hydroformylation step under HAM conditions. In addition, the relative concentrations of aldehyde and enamine have a dramatic influence on the hydrogenation activity of the catalyst: in all instances the hydrogenation reaction that was tested for the enamine substrates alone was slower than the rate of the HAM reaction when the enamines were generated in situ. This is confirmed by monitoring the HAM reaction since no IR absorbances relating to the aldehyde or the enamine were observed, indicating that the reactions of these species, including the hydrogenation, are fast and not rate

determining under the HAM conditions. The reaction was also monitored by high pressure IR when determining the solvent effects and it was found that these played a non-nominal role: 2-Me-THF made hydrogenation of the enamine less efficient, leading to a greater formation of aldol side products. More polar solvents such as methanol increased the hydrogenation activity, thus supressing the formation of the side products.

With these insights the group were then able to apply their best HAM conditions a wide range of substrates. However, a limitation of this methodology was that when using primary amines under these conditions the major product obtained was an imine. It is therefore likely that the rate determining step of the reaction is highly dependent on the choice of substrates and conditions.

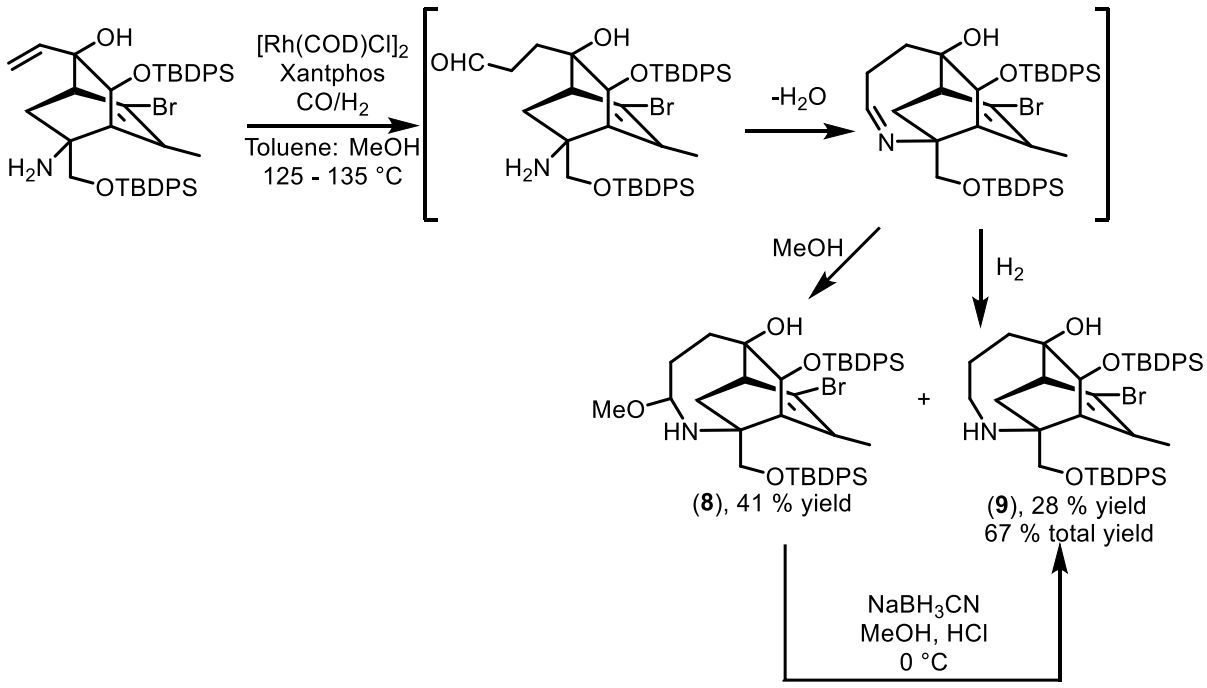
In addition, the conditions were applied to an industrial mixture of octenes to successfully give linear amines with high chemo- and regioselectivities.

Another group that had achieved the regioselective HAM of terminal olefins from internal olefins is that of Zhang and Wu, Scheme 16.[18] This used the Tetrabi ligand, (**6**), to achieve high selectivity for the linear aldehyde and subsequently the tertiary amine.



Scheme 16: Linear selective HAM of internal olefins[18]

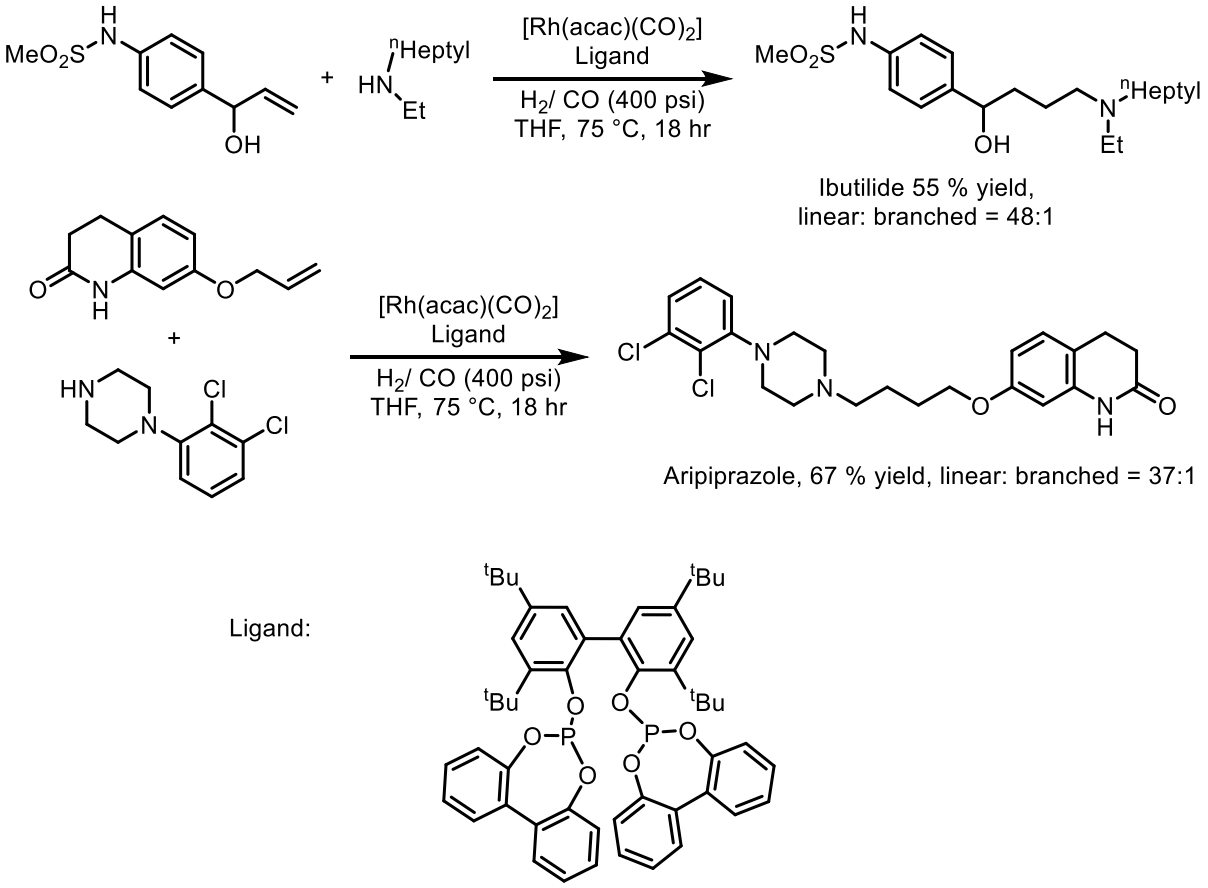
One example of an intramolecular HAM strategy is the synthesis of the azacyclooctane moiety from the *Lycopodium* alkaloid Lycopladine H.[19] This utilised a $[Rh(COD)_2]BF_4$ precursor with the ligand Xantphos (**2**) to chemoselectively hydroformylate a somewhat hindered terminal alkene over an internal alkene and form the linear aldehyde which undergoes intramolecular attack from the intramolecular amine nucleophile. The imine formed is not isolated and is either hydrogenated in-situ or subject to competing attack by the methanol solvent, so the N,O-acetal, (**8**), is then reduced to the azacyclooctane target molecule, (**9**), by the addition of hydrogen chloride and sodium cyanoborohydride, Scheme 17.



Scheme 17: Intramolecular HAM for the synthesis of an azacyclooctane.[19]

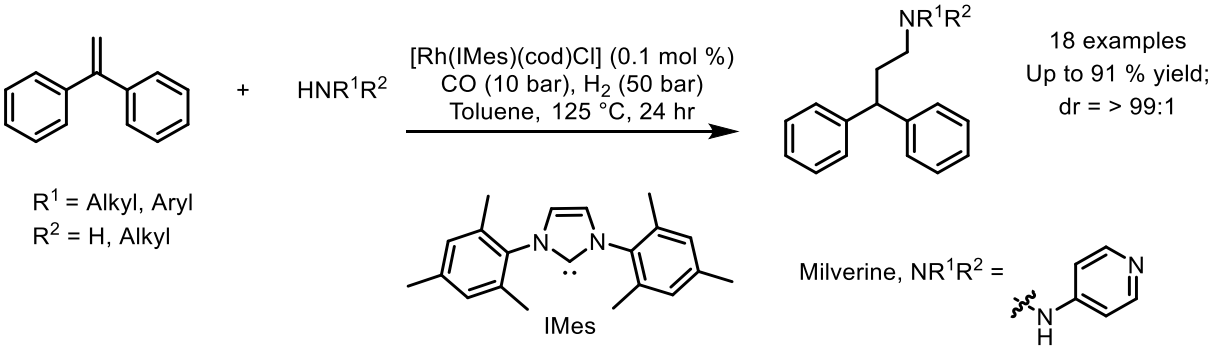
Here, a switch to the rhodium precursor $[Rh(COD)_2]BF_4$ and increasing the catalyst loading from 1 mol % to 2 mol %, as well as making the solvent mixture of equal parts toluene and hexafluoroisopropanol, HFIPA, meant that none of the N,O-acetal was formed and only the azocane product was observed in 75 % yield, without the need for the addition of sodium cyanoborohydride.

The use of HAM for the synthesis of other biologically active amines was also achieved in a simple step; various functional groups were tolerated without the need for derivatisation after the HAM reaction, Scheme 18.[20]



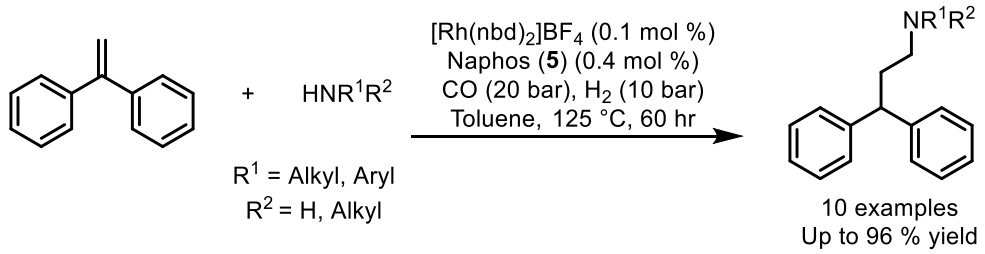
Scheme 18: Synthesis of biologically active amines via HAM[20]

Even somewhat sterically demanding alkenes are tolerated for HAM reactions such as a set of pharmaceutically active 3,3-diarylpropylamines, known as pheniramines, to give the linear aldehyde product which on reaction with the chosen amine yields a selection of biologically active compounds. The most efficient synthesis of this is that by Beller and co-workers, developing a fast route to these compounds with low catalyst loadings and high regioselectivity, utilising a novel rhodium-NHC complex as the catalyst: this was the first one pot synthesis of milverine, Scheme 19.[21] The HAM of olefins using a rhodium carbene catalyst had previously been published by Beller et al and this paper demonstrated the applicability of the catalyst system in a specific substrate synthesis.[22]



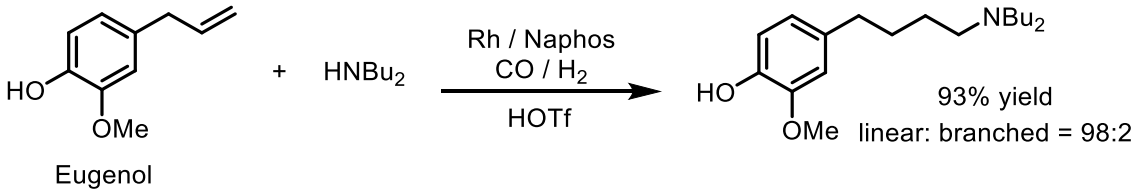
Scheme 19: First one pot synthesis of Milverine[21]

A more traditional catalyst system was later employed by Zhang and co-workers to synthesis the same compounds, utilising the wide-angle bidentate phosphine ligand Naphos, (**5**), Scheme 20.[23] Again, high regioselectivity was observed due to the steric hindrance of the starting alkene, the largest side product detected was from the hydrogenation of this alkene to the alkane. High yields were observed and a range of amines, both primary and secondary, were tolerated.



Scheme 20: HAM of sterically hindered alkene.[23]

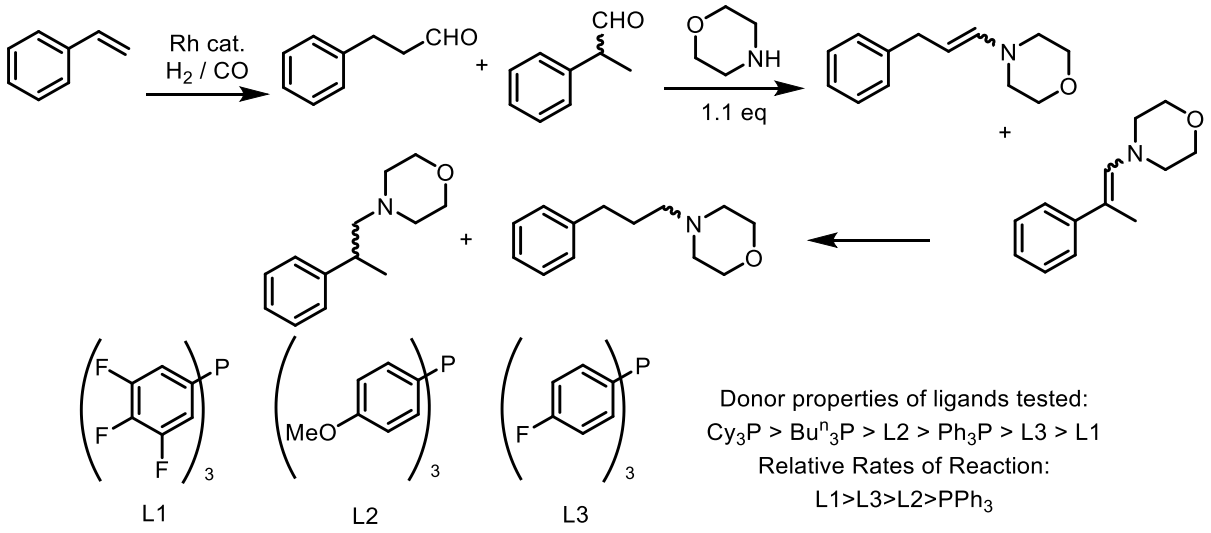
In some cases, it has been found to be beneficial to use acidic additives to promote the formation of the desired amine product as opposed to the imine or enamine. An investigation into 3 different strong Brønsted acids: sulfuric acid, *para*-toluenesulfonic acid, HOTs, and trifluoromethanesulfonic acid, HOTf, on the HAM reaction of eugenol with di-n-butylamine differed the pKa, the counterion and the coordination ability, Scheme 21.[24]



Scheme 21: HAM with acid additive for improved yield.[24]

The lead for the inclusion of an acid additive in this work came from work by Routaboul et al. who used HBF_4 to promote their HAM reaction: the hypothesis being that the acid would promote the enamine or imine species and this corresponding salt would then more readily undergo hydrogenation.[25] Alternatively, Behr et al. used ammonium salts instead of an amine, by varying the acid they could conclude that it had the effect of forming a cationic rhodium species that facilitated the hydrogenation of the enamine or imine.[26] The work in reference 25 however found that the coordination ability proved critical: the less able the acid was to coordinate, the more efficiently the reaction proceeded. This is in support of the conclusions drawn by Behr et al. yet does not rule out the former hypothesis regarding protonation of the enamine or imine. Here in the study on eugenol, HOTf is found to be the best promotor of the reaction and is more stable than HBF_4.

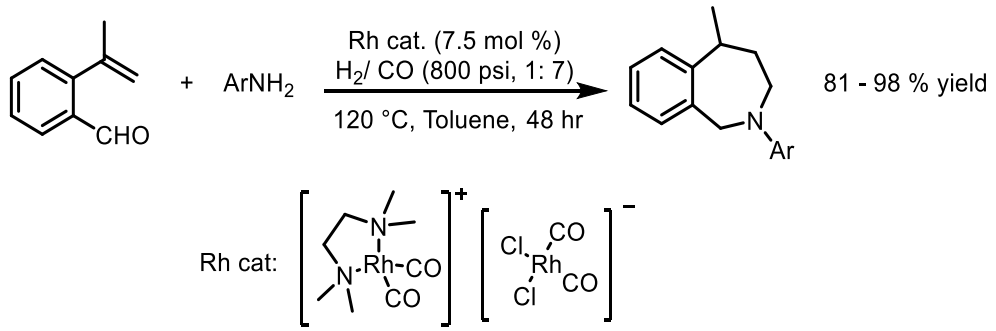
It is known that hydroformylation reactions on the whole benefit from ligands bearing an electron poor phosphine, whilst alkene hydrogenation is normally accelerated by electron rich ligands. An investigation into the ligand effects found that electron donating ligands were not found to reduce enamines, but electron poor ones did, thus supporting the conclusions drawn by Behr et al., Scheme 22.[27]



Scheme 22: Investigation into donor properties of monodentate phosphine ligands.[27]

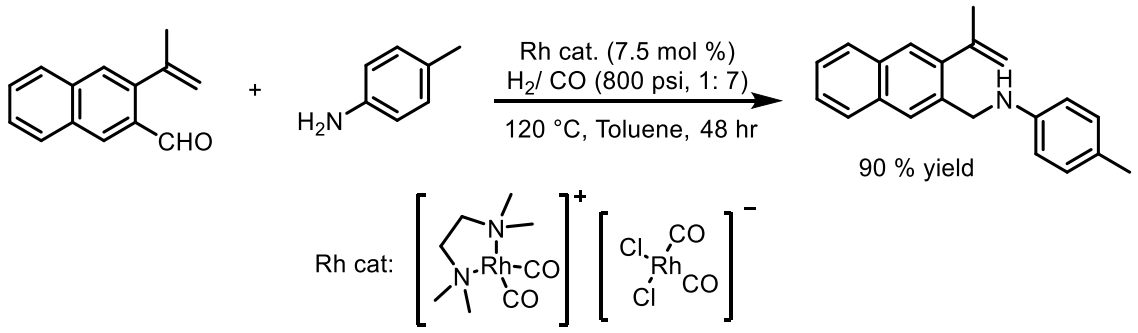
There were two possible mechanistic scenarios to explain this, either the ligand effects differ when using syngas as opposed to pure hydrogen gas; or that the high activity of rhodium complexes with electron rich phosphines for alkene hydrogenation doesn't extend to a number of enamine substrates. Further investigations found that the second scenario is correct, and thus electron poor monodentate phosphines are best for a number of enamine hydrogenations. Utilising DFT calculations it was found that the rhodium α-adduct has an additional Rh-N contact to form a 3 membered chelate ring, stabilising this intermediate by at least 50 $kJmol^{-1}$. This intermediate is so stable that the subsequent reductive elimination step has a high barrier, and thus this is the rate determining step. By comparison, in normal alkene hydrogenations the rate determining step is the initial hydride transfer.

So far most examples in this review have used phosphine ligands which undoubtedly lead to greater control and activity over the hydroformylation step. However, under the forcing conditions shown in Scheme 23, this step can be accomplished with a range of rhodium species.[28]



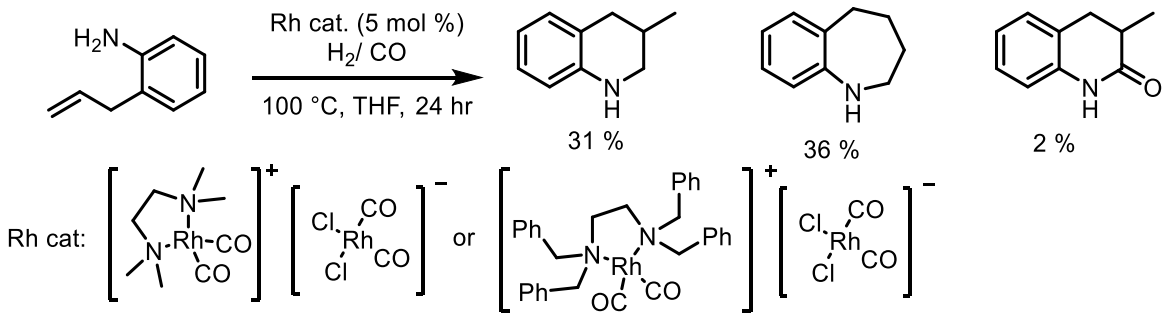
Scheme 23: Novel rhodium catalysts for the formation of benzazepines through HAM.[28]

This reaction produced a range of benzazepines through what was predicted to be an initial intermolecular reductive amination, then hydroformylation, then intramolecular reductive amination. The evidence for this arises from the reaction of a different alkene substrate which did not undergo hydroformylation, most likely due to steric hindrance, Scheme 24.



Scheme 24: Evidence for the initial step of the reaction being reductive amination as opposed to hydroformylation.[28]

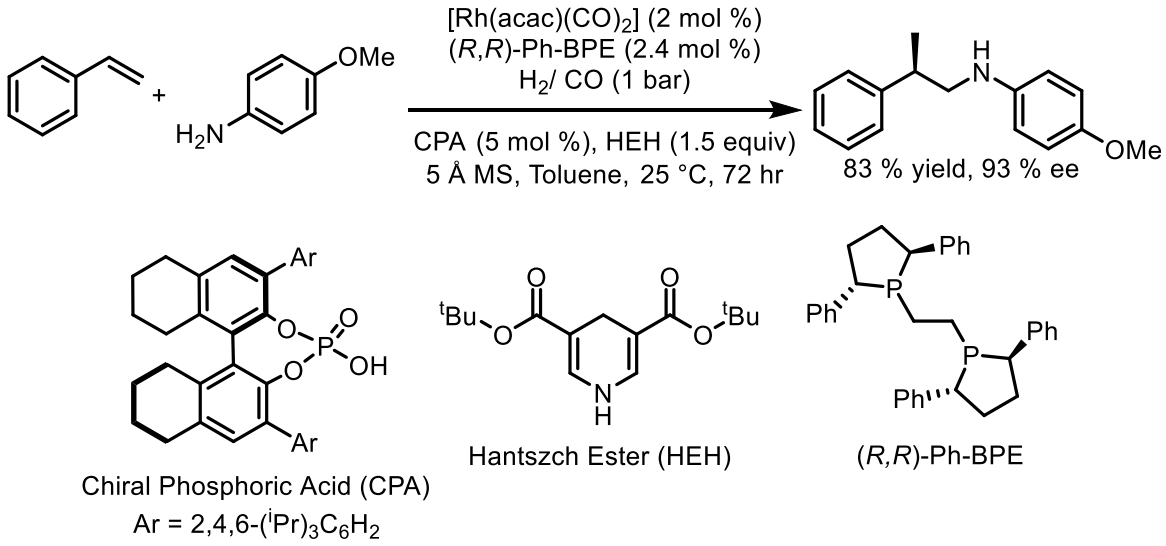
Further investigations were carried out with these catalysts but unfortunately this reaction was not particularly selective and produced 3 different products, Scheme 25.[29]



Scheme 25: Intramolecular HAM with novel rhodium catalysts.[29]

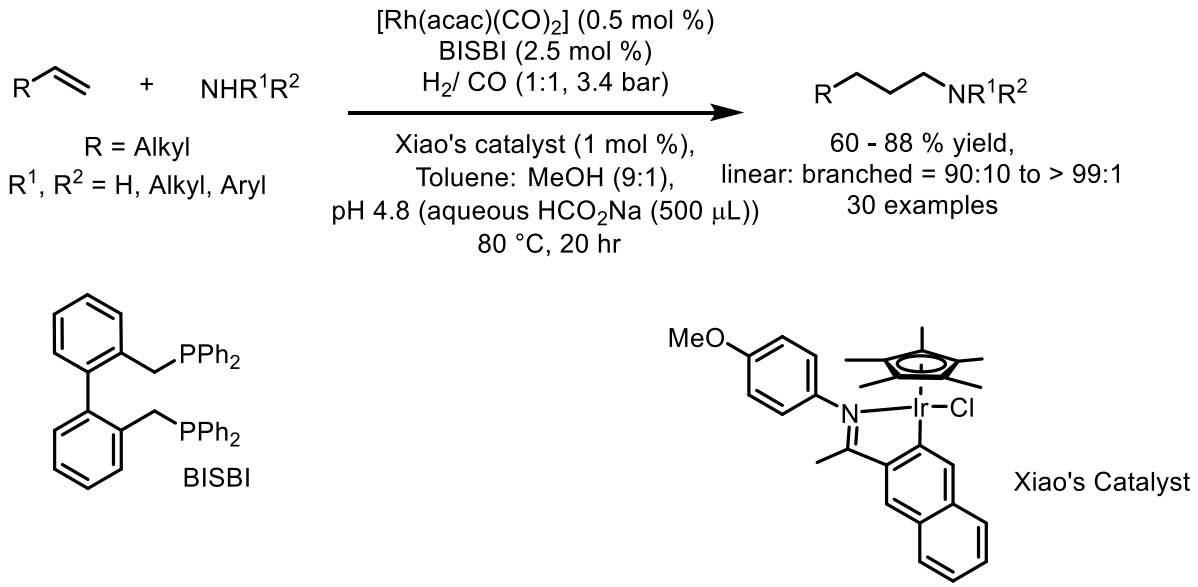
Enantioselective HAM has been carried out on olefins using hydroformylation and Brønsted acid relay catalysis, Scheme 26.[30] This work utilised the bidentate ligand Ph-BPE for the hydroformylation reaction and then a Chiral Phosphoric Acid, (CPA) as the Brønsted acid controls the enantioselectivity during the iminium ion reduction step. The source of hydrogen for the hydrogenation step however

was a Hanztsch ester, which is not atom efficient compared to dihydrogen for example. The substrate scope dealt majorly with aryl alkenes, as alkyl alkene substrates were found to be poorly tolerated by the system giving low yields of the desired product. Furthermore, quite high catalyst loadings of the CPA (5 mol %) are also required.



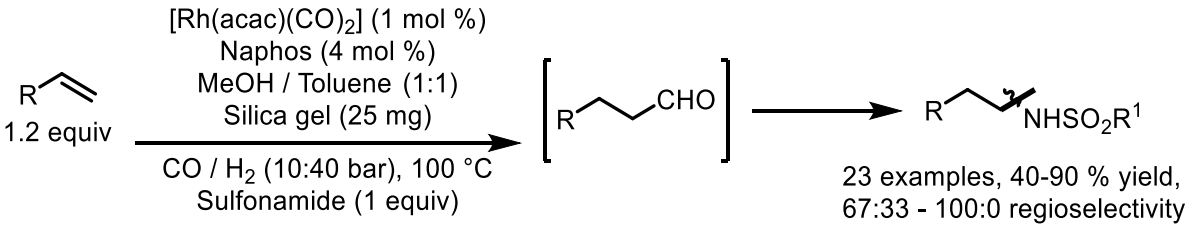
Scheme 26: Enantioselective HAM through coupling with a chiral phosphoric acid.[30]

A different approach to carrying out a hydroaminomethylation reaction came recently from Hartwig and co-workers, Scheme 27.[31] This work hypothesised that since no single catalyst complex had been identified that could carry out both the hydroformylation step and the reductive amination step in high yields and selectivity without requiring high temperatures and gas pressures, the use of two different catalysts working in sequence could solve this. They proposed that the reductive amination step is often inhibited by carbon monoxide coordination to the catalytic complex, hence by picking a catalyst that worked by a different mechanism such as transfer hydrogenation, it would not be inhibited. This guided the development of this methodology and from the catalysts that were investigated a rhodium/ diphosphine catalyst and Xiao's iridium catalyst were chosen as the most active and selective. Optimisation of the reaction conditions lead to the use of aqueous sodium formate buffer at pH 4.8 as the reducing agent. A wide substrate scope was investigated, changing both the alkene and the amine counterpart, with no obvious drop in linear selectivity or activity, including when using amines that can chelate to metals through a second nitrogen site. The temperature and pressure used here are significantly lower than in many of the examples discussed earlier.



Scheme 27: HAM through a dual catalyst system.[31]

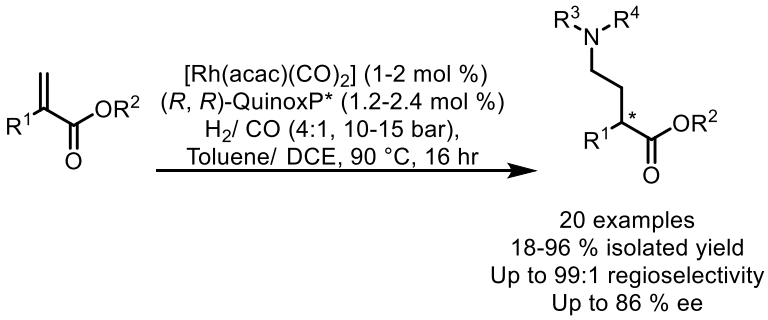
Amines are not the only nitrogen containing groups that can be introduced via hydroformylation reactions; recently a novel tandem hydroformylation with reductive sulfonamidation, termed hydrosulfonamidomethylation, was reported, Scheme 28.[32]



Scheme 28: Hydrosulfonamidomethylation[32]

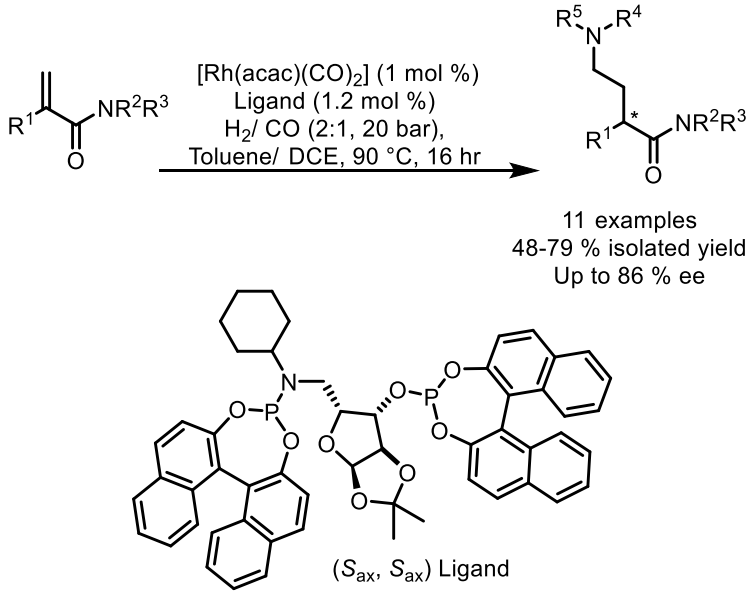
The Naphos ligand, (**5**), was required for the best combination of selectivity and yield, whilst the solvent mixture was found to be optimal for the highest yield, as well as the addition of silica gel improved the yield further.

The most recent papers in developing the asymmetric HAM of 1,1-disubstituted alkenes come from the Godard group. The first used QuinoxP* as the ligand, as well as a directing group in the form of acrylate alkenes to obtain a series of chiral γ-aminobutyric esters, Scheme 29.[33]



Scheme 29: Asymmetric HAM of 1,1-disubstituted alkenes.[33]

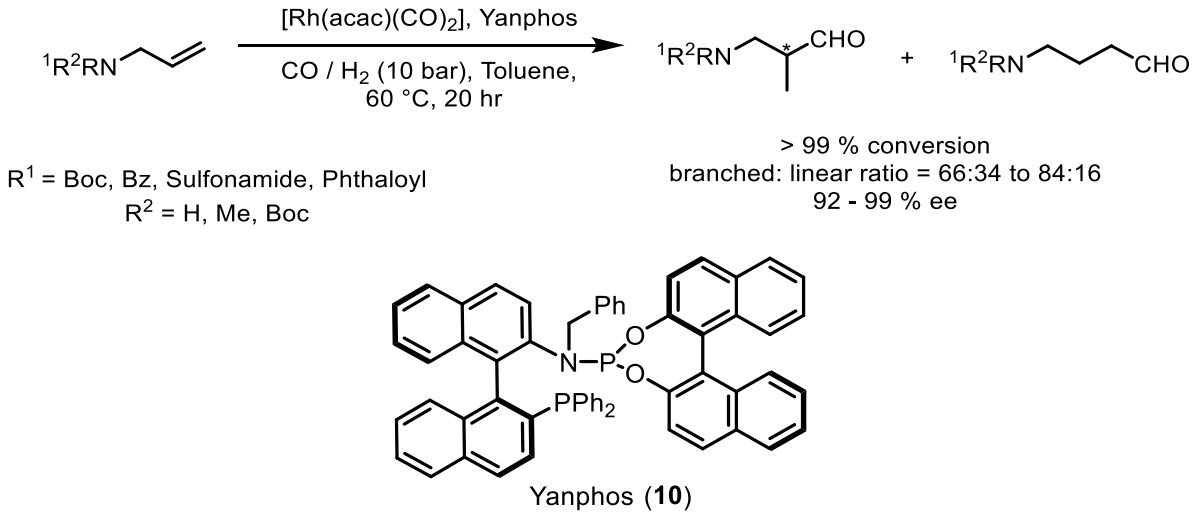
The next paper from the Godard group focussed on the design and implementation of a new chiral phosphite-phosphoramide ligand for the rhodium-catalyzed asymmetric HF and HAM of α-substituted acrylamides, Scheme 30.[34] This culminated in the efficient synthesis of an RWAY inhibitor. Similar to Zhang et al, the (*S*, *S*) axial chirality of the ligand was important for achieving high enantioselectivity within this reaction.



Scheme 30: Asymmetric HAM using a phosphite-phosphoramide ligand.[34]

Hydroformylation of Alkenes with Nitrogen Functionalities

The use of the ligand Yanphos, (**10**), has also had literature precedent in the asymmetric hydroformylation of *N*-allylamides, Scheme 31.[35] Within the hydroformylation reaction, phosphine directing groups can be used to coordinate to the rhodium centre and influence regioselectivity. Later, it was then noted that the carbonyl function of an amide could also bond to the rhodium centre and serve as a directing group to influence the regioselectivity of the reaction.[36] Building on this, the investigation into the asymmetric hydroformylation of *N*-allylamides was carried out by Zhang et al. with promising results.



Scheme 31: Hydroformylation of N-allylamides.[35]

Observations from the differing protecting groups were that little difference was found in the effect on the enantioselectivity, whilst electron rich groups promoted higher branched regioselectivity. Furthermore, different functional groups instead of the *N*-allylamide were investigated under the same conditions, Scheme 32. Here it was again found that the group had no effect on the enantioselectivity but greatly affected the regioselectivity. It should be considered however that all these substrates are prone to isomerization from terminal alkenes to internal, thus complicating the understanding of the selectivity of the catalyst. No examples with a further CH_2 between the nitrogen and alkene were reported.

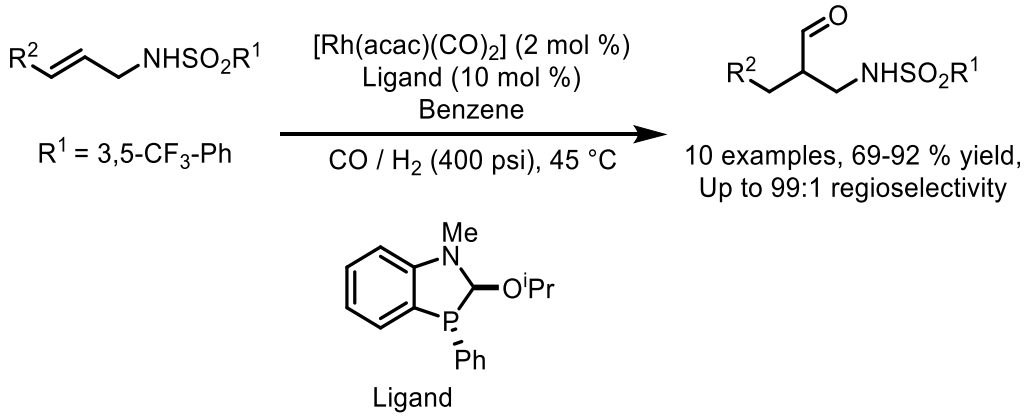
branched: linear = 71:29, 94 % ee | branched: linear = 30:70, 94 % ee | branched: linear = 72:28, 94 % ee | branched: linear = 42:58, 94 % ee

Scheme 32: Other allyl compounds studied for hydroformylation under the above conditions.[35]

Almost all hydroformylation catalysts favour the linear aldehyde more than the branched in the absence of directing group (e.g. aryl, amide, CF_3, CH_2-amide, CH_2-nitrile or CH_2CF_3). In 2012 a catalyst was reported that overcomes this limitation and it's application in the use of hydroformylation cyclisation methodology is discussed later in this review.[37]

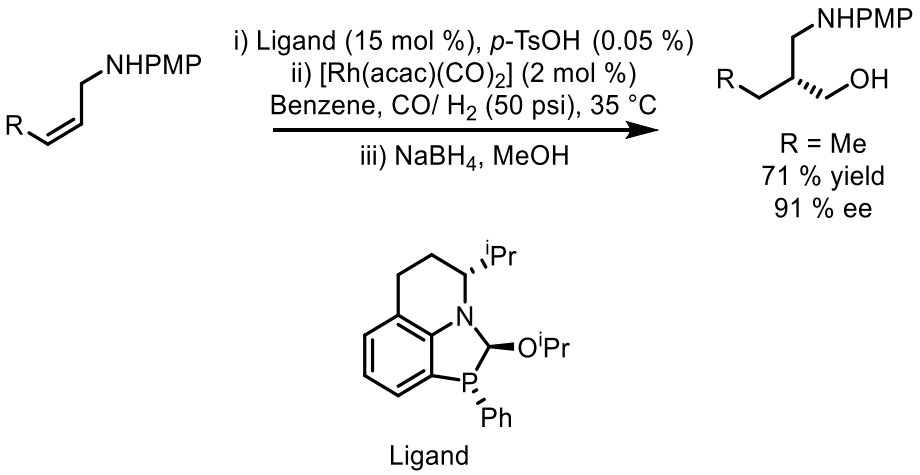
An innovative use of the sulfonamide functionality was described by Tan and co-workers in 2009 whereby the alkene substrate contained a sulfonamide that bound to the ligand prior to coordination with the rhodium centre.[38] This allowed for high regioselectivity under mild operating conditions, with the key steps being the initial precomplexation of the ligand and substrate prior to the addition of the rhodium precursor, and then a high pressure of syngas, Scheme 33. The ligand behaves somewhat like

a chiral auxiliary but as the binding to the substrate is reversible it can be used in catalytic quantities in the reaction. Despite the chirality of the phosphorus moiety in the ligand, no enantioselectivity was observed in the product.



Scheme 33: Hydroformylation of sulfonamides with a specialised ligand.[38]

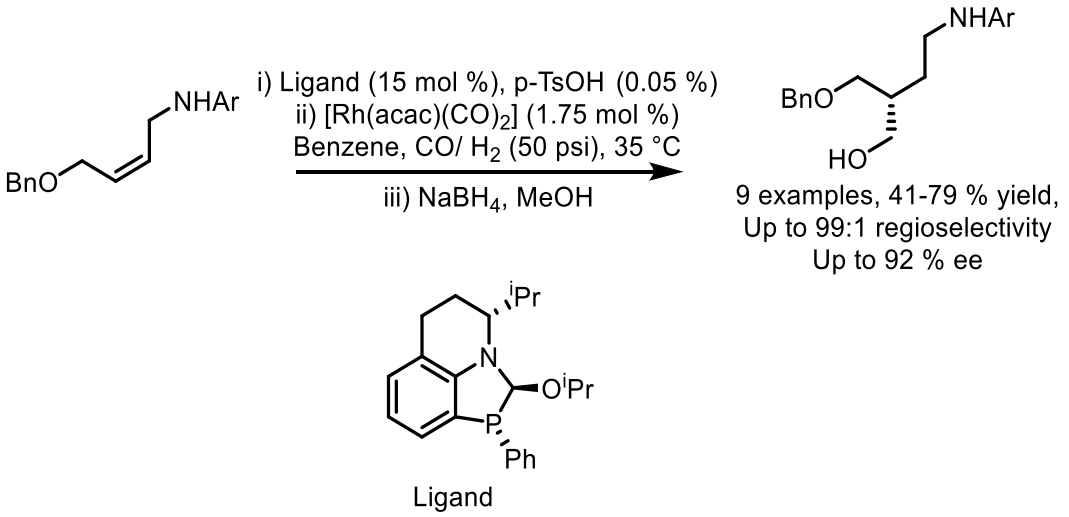
An enantioselective variant of this methodology was later developed through the use of *p*-methoxyphenyl protected aminoalkenes as substrate and a derivatised ligand, Scheme 34.[39] Especially important in the design of the ligand was the introduction of the third ring and the stereocentre on it, this stopped the epimerisation of the chiral phosphorus and the stereocentre adjacent to it by providing thermodynamic control for the preference of one diastereomer. A wide range of functional groups were tolerated in the substrate but the (*Z*) isomer of the alkene repeatedly gave higher enantiomeric excesses than the (*E*) isomer, 91 % ee versus 80 % ee respectively.



Scheme 34: Enantioselective hydroformylation using a specialised ligand.[39]

A further update to this methodology included the use of anilines as substrates, Scheme 35.[40] Here the anilines were particularly important both for the initial exchange to bind to the ligand and also the hydroformylation reaction. Upon investigation, electron poor anilines were found to have a lower

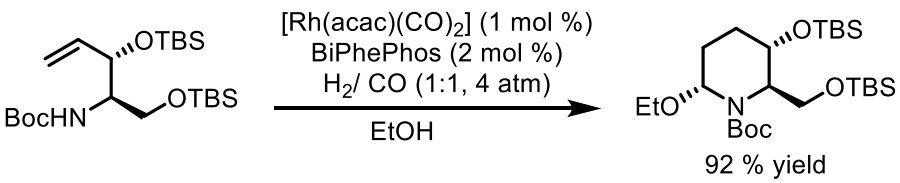
binding ability than electron rich anilines, which in turn lead to lower yields and enantioselectivities being obtained for these substrates. The others postulated that this might be a result of catalyst decomposition before full conversion was achieved when such substrates are used.



Scheme 35: Hydroformylation of aniline substrates using a specialised ligand.[40]

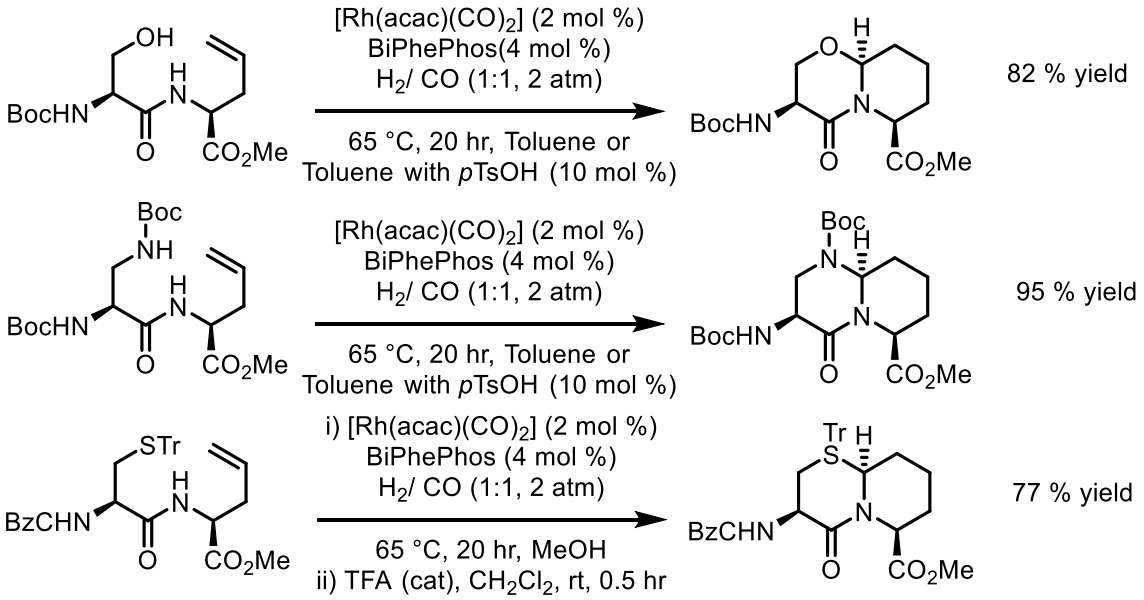
Hydroformylation-Cyclisation Sequences Producing *N*-Heterocycles

Cyclocarbonylation reactions are normally the coupling of a carbonylation component, such as an aldehyde or ketone, with a cyclisation component, normally one that contains an unsaturated system such as a π-bond or heteroatom in the presence of a transition metal catalyst.[41] Pioneered by Ojima, hydroformylation-cyclisation reactions are one type of cyclohydrocarbonylation.[42] One of the first works to include an amine was published in 1998 and focussed on the synthesis of (+)-prosopinine and (-)-deoxoprosophylline, Scheme 36.[43] This utilised the ligand BiPhePhos to achieve linear selective hydroformylation. Depending on the choice of solvent, different products could then be achieved. Without the use of a nucleophilic alcohol solvent to trap the reactive intermediate, a further hydrogenation of the enamine is required in order to reach the desired product. This methodology was also applied for the synthesis of pipecolic acid derivatives.[44]



Scheme 36: Hydroformylation and cyclisation followed by trapping of intermediate with ethanol.[43]

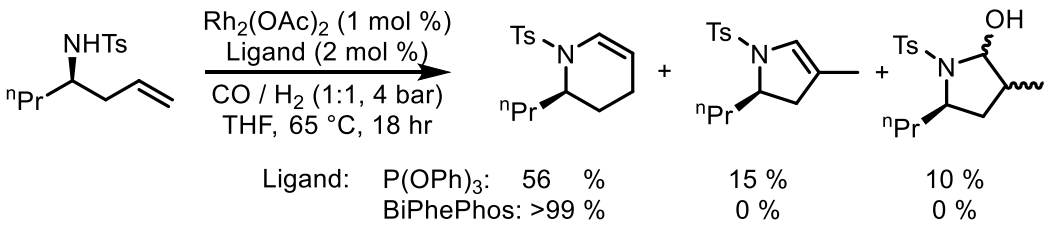
One of the most prominent works to be published was the efficient synthesis of azabicyclo[x.y.0.] alkane amino acids, Scheme 37, substrates that are of interest for screening for pharmaceutical purposes, through cyclohydrocarbonylation reactions.[45]



Scheme 37: Formation of azabicycloalkane amino acids through cyclohydrocarbonylation.[45]

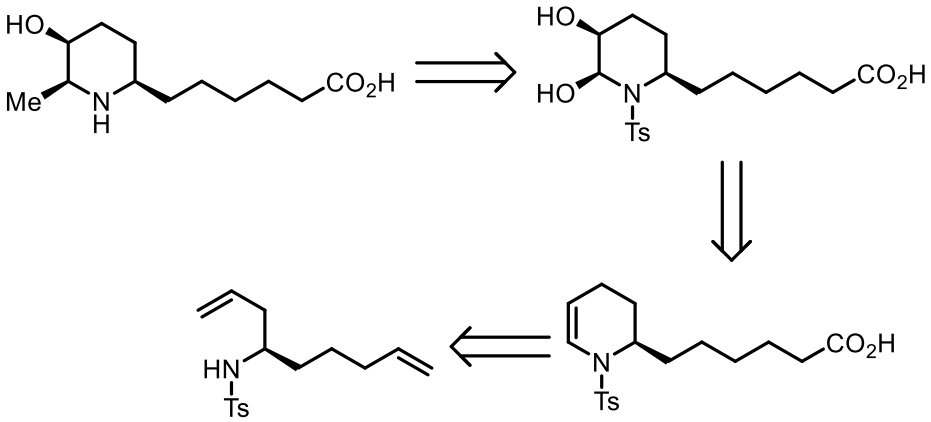
It is worth noting that cyclisation was not observed in THF or toluene with DMAP (10 mol %). Furthermore, the nature of the substituent at C10 exerts a critical effect on the direction of the second cyclization and generation of the stereochemistry at C6. For the reactions involving *S*-Trityl, the sulfur protecting group was required to avoid S-S bond formation, but this then required a change of *N*-protecting group from Boc to CBz since Boc would not survive the conditions to remove the Trityl group. It was also noted that the second cyclization step should be kinetically controlled and influenced by the directing groups and sterics. Lastly, it is observed that the 1,3-diaxial strain is more restricting and has a higher energy barrier than the 1,3-allylic strain.

In 2011, the synthesis of pseudoconhydrine and its epimers was achieved by the hydroformylation-cyclisation of a chiral alkenyl amine to give the linear aldehyde regioisomer intermediate, which cyclised to give a 6 membered ring, Scheme 38.[46] The formation of the desired pseudoconhydrine could be achieved by using the ligand BiPhePhos, (**7**): this gave full conversion to the target material. Use of $P(OPh)_3$ gave mixtures of three products, with an increased ligand loading diminishing the formation of the hemi-aminal. The starting material here already contained a stereogenic centre which was preserved through the hydroformylation and cyclisation.



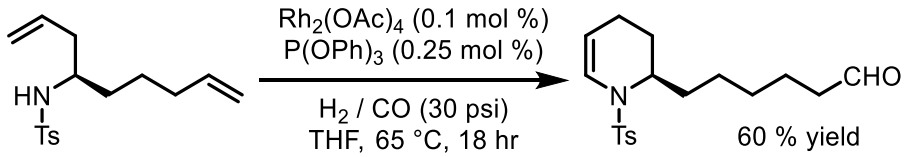
Scheme 38: Formation of pseudoconhydrine through hydroformylation.[46]

The use of $P(OPh)_3$ as a ligand was later utilised by Bates and Kasinathan in the synthesis of azimic acid to achieve dual, linear selective hydroformylation-cyclisation.[47] The retrosynthetic analysis of the synthesis is shown below, Scheme 39, and this differs from most common approaches in that the largest challenge is the installation of 3 stereocentres, the majority of which are normally installed prior to the formation of the piperidine ring.



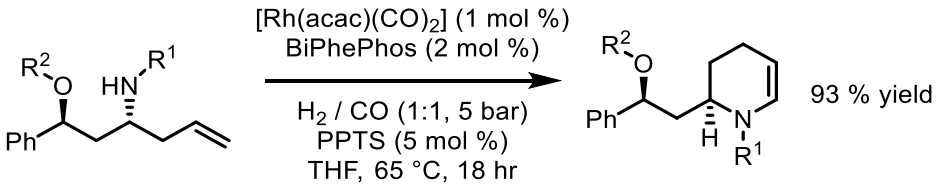
Scheme 39: Proposed retrosynthetic route to azimic acid using dual, linear selective hydroformylation.[47]

The hydroformylation-cyclisation step proceeded smoothly under the following conditions, Scheme 40. However, one drawback is that the starting material is not readily available and requires a multi-step synthesis.



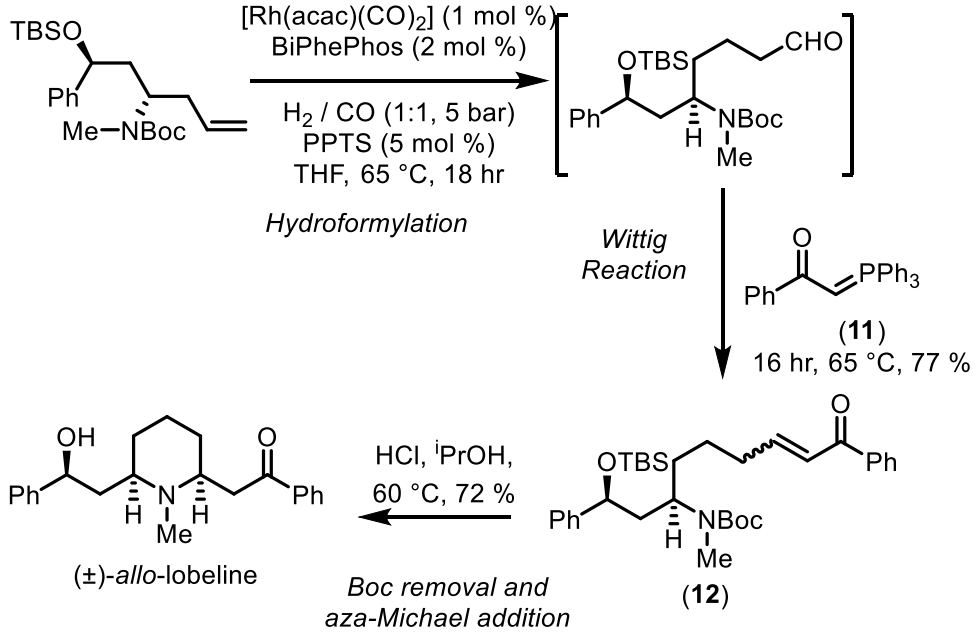
Scheme 40: Dual, linear selective hydroformylation conditions.[47]

Another synthesis that utilised BiPhePhos (**7**) in one pot reactions was that by Mann and co-workers for the quick synthesis of (±)-*allo*-Sedamine and (±)-*allo*-Lobeline in a one pot process of hydroformylation followed by an aza-Sakuri-Hosoni reaction, Scheme 42.[48] The chosen methodology for the synthesis of the target materials provides a viable alternative to the more commonly used ruthenium catalysed metathesis approach, which requires more forcing conditions than those reported for the rhodium catalysed hydroformylation, Scheme 41.



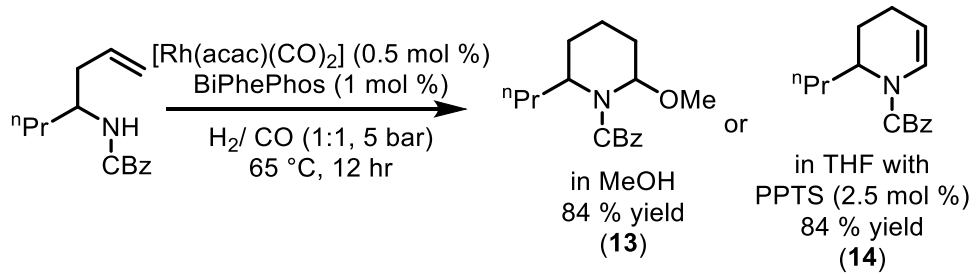
Scheme 41: Hydroformylation-cyclisation for substituted piperidine core for synthesis of alkaloids.[48]

This methodology was then applied in the synthesis of the target molecules and a Wittig reaction was used to further furnish the target molecule, Scheme 42. Attempts to incorporate the Wittig reaction into a domino sequence by including the phosphonium ylide, (**11**), from the beginning found that under the hydroformylation conditions the conjugated alkene in compound (**12**) was reduced. This would stop the subsequent cyclisation reaction, hence the Wittig reaction had to be carried out in a one pot, sequential manner by adding the reagent after the hydroformylation was complete.



Scheme 42: Synthetic route to (±)-allo-lobeline.[48]

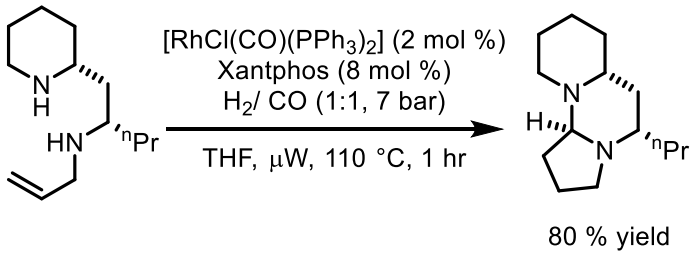
Further to this work, Mann and co-workers also demonstrated concise methods for the synthesis of piperidines, quinolizidines and related alkaloids through hydroformylation-cyclisation reactions.[49] The first undertakings found that using an alcohol solvent that could serve as an O-nucleophile, such as methanol, gave the hemi-aminal (**13**) compared to the ene-carbamate (**14**) that was observed when the same reaction was carried out in THF, Scheme 43.



Scheme 43: Different products formed from the use of different solvents.[49]

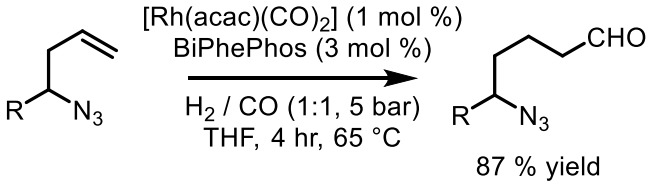
Understanding the propensity of the intermediate to come under nucleophilic attack led to the use of carefully constructed starting materials that, when hydroformylated, underwent cascade

intramolecular cyclisation to yield a 3-ring system. Intriguingly here, microwaves are used to promote the reaction so that the overall reaction time is only 1 hour, Scheme 44.



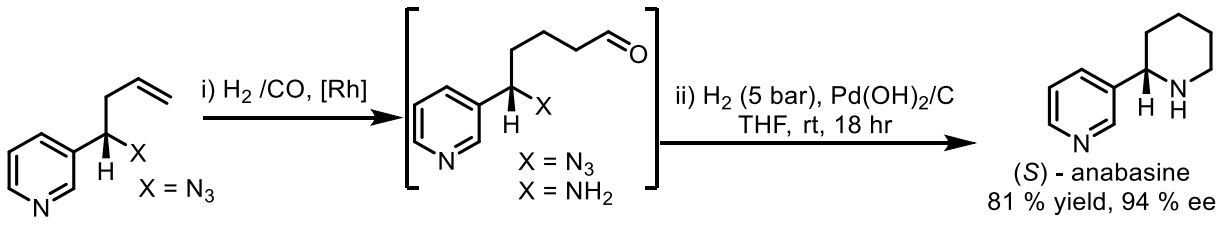
Scheme 44: Use of microwaves to improve the efficiency of the hydroformylation reaction.[49]

Alkaloids are a selection of natural products initially isolated from plants that contain a minimum of one nitrogen atom; one approach to their synthesis was attempted by the group of Mann and utilised the methodology of a hydroformylation of a homoallylic azide, which when converted to the amine could then undergo a cyclisation or intramolecular reaction to furnish the final product, Scheme 45.[50]



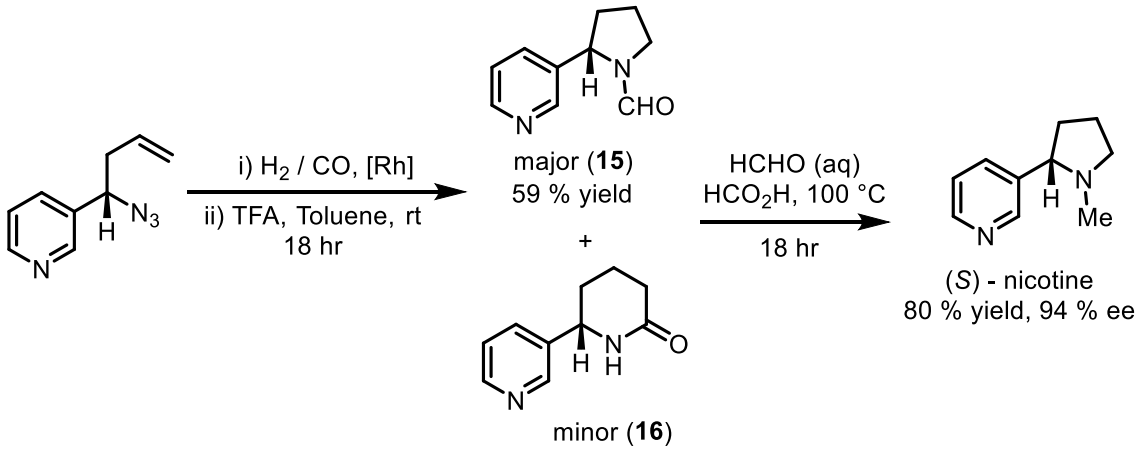
Scheme 45: Hydroformylation of azide alkenes.[50]

Here the use of the BiPhePhos ligand, (**7**), was important not only because it favours a high linear to branched ratio, but also because phosphites are more electron deficient than phosphines and so are less reactive with azides. Azides are commonly considered as being less suitable for large scale synthesis and even lab scale synthesis due to the explosiveness of HN_3, although azides have in recent times often been incorporated into flow chemistry processes to generate and use in situ.[51] Here the authors note that: "Preparations of [substrates] 1a-1h were uneventful using standard methods." Further functionalisation of these hydroformylated compounds was then possible to yield the desired alkaloids: (±)-sedamine, (*S*)-anabasine and (*S*)-nicotine. For (*S*)-anabasine all that was required was hydrogenation of the azide intermediate to give a primary amine, which cyclises with the aldehyde and is then reduced to the target molecule in one sequence, Scheme 46.



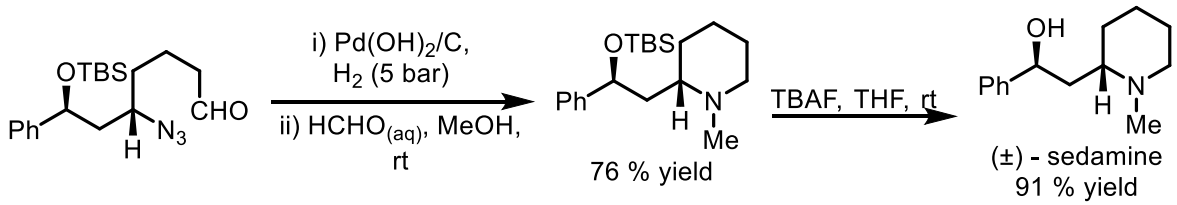
Scheme 46: Synthesis of (S)-anabasine via hydroformylation.[50]

For (*S*)-nicotine the hydroformylation proceeded as above followed by cyclisation and an acid promoted Schmidt rearrangement to give the 5-membered pyrrolidine ring, (**15**), as the major product, with trace amounts of the lactam, (**16**), observed.[50] Subsequent treatment with formaldehyde and formic acid completed the synthesis of the desired alkaloid, Scheme 47.



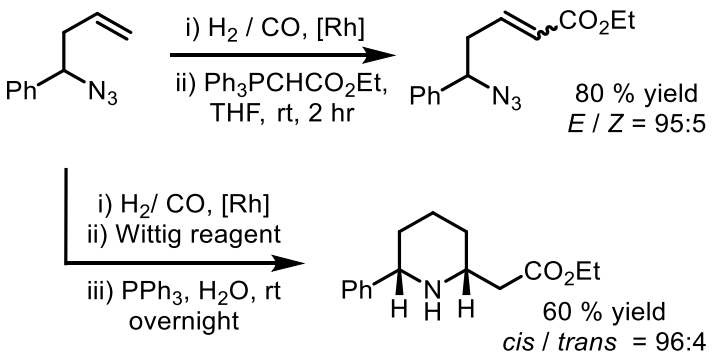
Scheme 47: Hydroformylation-cyclisation with an acid promoted Schmidt rearrangement and then subsequent reaction to give (S)-nicotine.[50]

For (±)-sedamine a different starting material was subjected to the same hydroformylation conditions before completing the cyclisation and deprotection of the alcohol, Scheme 48.



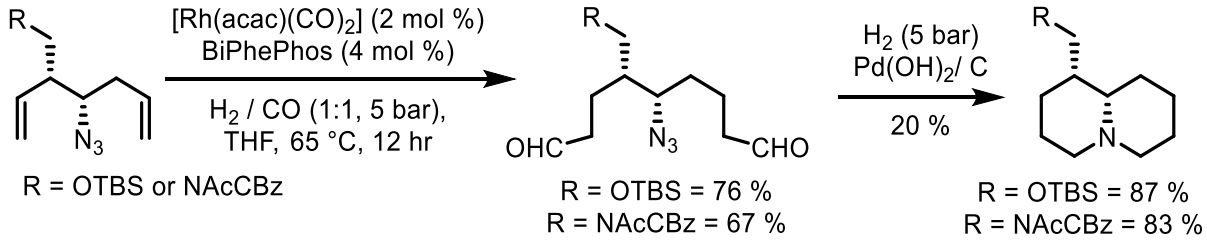
Scheme 48: Simple synthesis of (±) – sedamine through same methodology.[50]

Included in this work was the methodology for the first reported sequential one pot HF / Wittig olefination / Staudinger reaction / Michael addition, Scheme 49. This supplied the desired target material in moderate yield with simple synthetic steps.



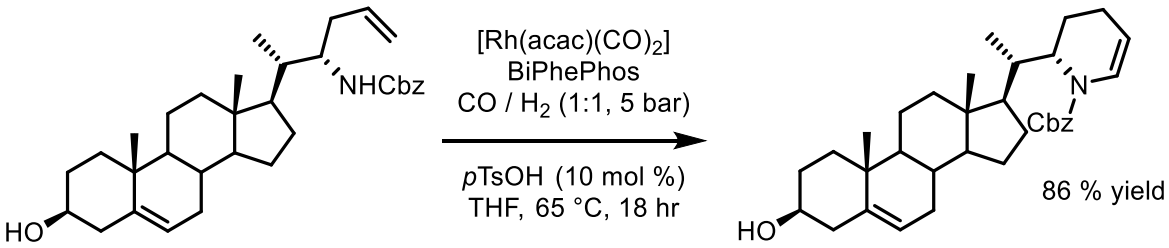
Scheme 49: One-pot hydroformylation and subsequent functionalisation.[50]

A short synthesis of (+)-lupinine and (+)-epiquinamide through a double hydroformylation reaction builds on the previous approach.[52] One of the downfalls of this synthetic strategy is the enantiopure starting material requires 8 or 9 steps to synthesise it, but none the less delivers the desired products in 15 % yield for (+)-lupinine and 29 % yield for (+)-epiquinamide, Scheme 50.



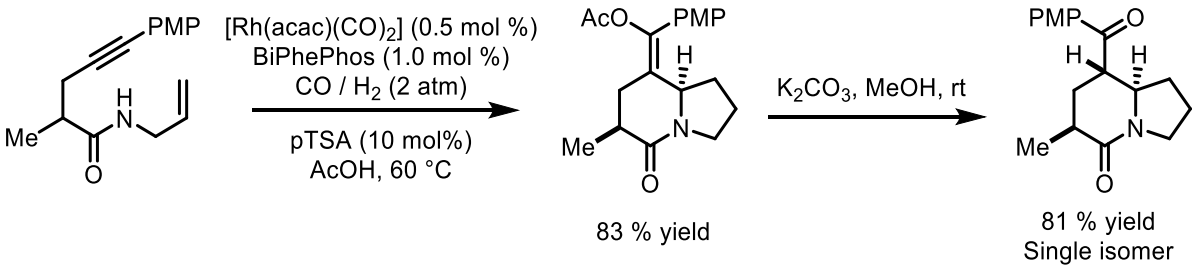
Scheme 50: Formation of octahydroquinolizines through double hydroformylation.[52]

Another natural product synthesis published by Mann and co-workers in 2011 that contained a 6-membered ring formed by hydroformylation was that of desmethylvermaline.[53] This utilised the same ligand, BiPhePhos, (**7**), to achieve linear selective hydroformylation and then subsequent cyclisation from the intramolecular amine was so rapid no aldehyde intermediate was observed, Scheme 51. This reaction demonstrates the utility of this technique by leaving the stereocentres, alcohol group and internal double bond untouched. In addition, under these conditions and, for this substrate only, the reaction was completely regioselective for the linear aldehyde product, none of the branched was observed at any time. The use of hydrogen and palladium on carbon with a reaction time of two days was required however to completely hydrogenate the enamine, though again the other internal alkene remained untouched.



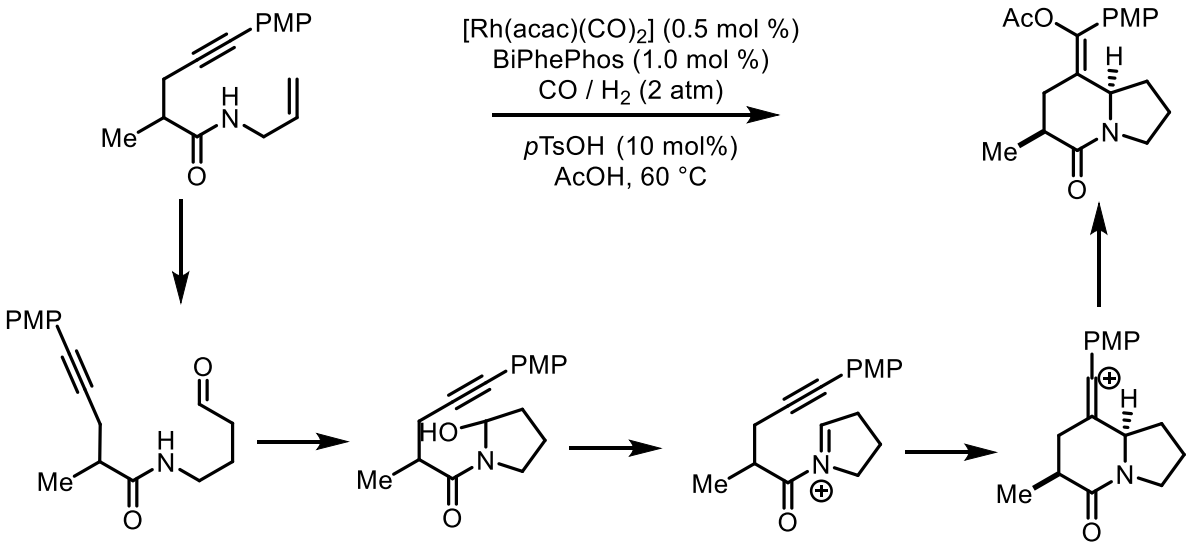
Scheme 51: Selective hydroformylation of terminal alkene.[53]

In previous examples, Schemes 44, 46, 48 and 50, the initial stereocentres are preserved; it is also known for the formation of a new stereocentre to occur upon cyclisation, Scheme 52. Mechanistic insights into the *syn* / *anti* preference of attack for the formation of cyclic products arising from domino HF / cyclisation reactions for indolizidine derivatives has been carried out by Chiou and co-workers.[54]



Scheme 52: Formation of indolizidine derivatives through hydroformylation.[54]

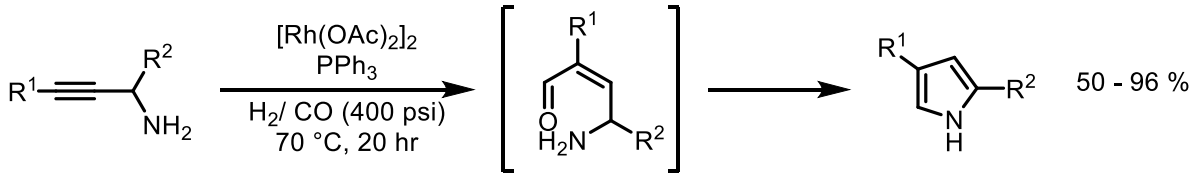
This found that selective hydroformylation of the alkene over the alkyne meant that attack of the amine into the aldehyde formed the first 5 membered ring, whilst subsequent attack of the alkyne into the iminium ion then forms the 6 membered ring which can be trapped by nucleophilic attack of the solvent, Scheme 53. In addition to the experimental observations, computational methods were also utilised to determine the preferred attack of the alkyne in the formation of the joined rings. This found that there was a higher energy barrier to *syn* attack of the imine by the alkyne compared to *anti* attack, although both were energetically accessible. This was observed experimentally, and the *anti*-product was preferentially formed setting the stereocentre between the two rings as such.



Scheme 53: Proposed mechanism for formation of rings.[54]

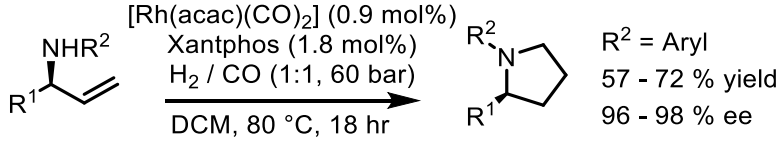
It was found that use of the *para*-methoxyphenyl group on the alkyne was necessary to achieve high yields; without this electron donating group, complex mixtures of side products were obtained from the hydroformylation reactions. Furthermore, it was found that C2 and C5 were stereogenic centres and affected the overall product outcome, whilst the E enolate was formed preferentially to the Z enolate after the first hydroformylation. In addition, increasing the alkyne chain length by one carbon still lead to the formation of cyclised product upon hydroformylation, yet in much smaller yield.

Another example utilising an alkyne starting material is the formation of β-substituted pyrroles through hydroformylation, which gave good yields and required no further additives or reactions to achieve the desired target material, Scheme 54.[55]



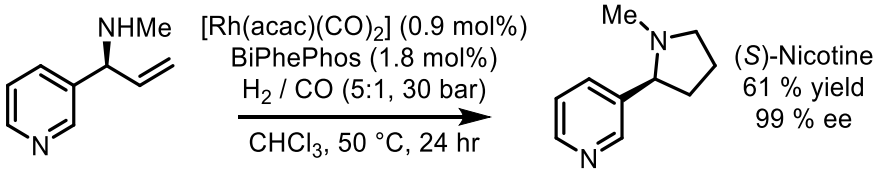
Scheme 54: Hydroformylation of alkyne.[55]

A notable example of the formation of a chiral natural product using rhodium catalysts derived from BiPhePhos, (**7**), is that of (*S*)-nicotine by Helmchen et al, Scheme 55.[56] This study formed the chiral starting material in high ee through an Ir catalysed allylic amination to form the homoallylic amine.[57] From here, subsequent intramolecular hydroaminomethylation gave the 2-subsituted pyrrolidines in moderate yields (57-72 %) with preservation of high ee (96 – 98 %). Initial attempts to synthesise (*S*)-Nicotine found that the use of a methyl group as R^2 led to low yields and the side formation of the lactam. Switching to an aryl group in the position R^2 allowed the formation of the desired product in reasonable yields.



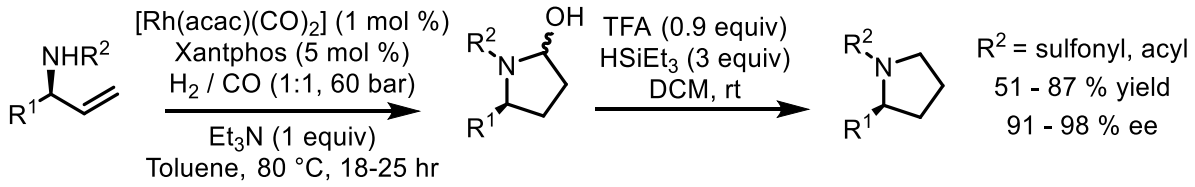
Scheme 55: Linear selective hydroformylation and cyclisation for pyrrolidine rings.[56]

Once this had been achieved, returning to a methyl group in the position R^2 and then optimisation of the reaction conditions, notably a change in ligand from Xantphos to BiPhePhos, meant the desired (*S*)-Nicotine product was synthesised in good yield, Scheme 56.



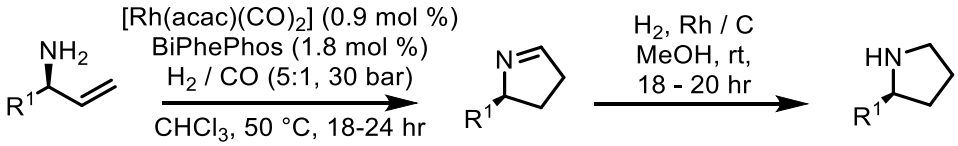
Scheme 56: Application of hydroformylation system in the synthesis of (S)-Nicotine.[56]

If a sulfonamide or amide protecting group was used instead of an alkyl or aryl group, then the hemi-aminal was formed and a further reduction was necessary to yield the target molecule, Scheme 57.



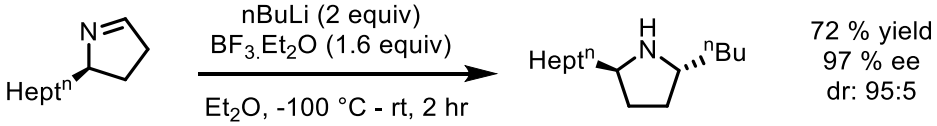
Scheme 57: Change of conditions to tolerate a change in the substrate.[56]

Unprotected primary allylamines showed low yields when used under the conditions shown above, Scheme 48, with Xantphos as the ligand, whilst the switch to the conditions shown below, Scheme 58, found good yields. This was attributed to the higher activity of BiPhePhos, yet despite this a separate hydrogenation was also required with these substrates in order to arrive at the amine and not imine product. The hydrogenation was also found to decrease the ee's: from 98 % to 96 % for the Rh/C system, whilst Pd/C went from 98 % to 90 %.



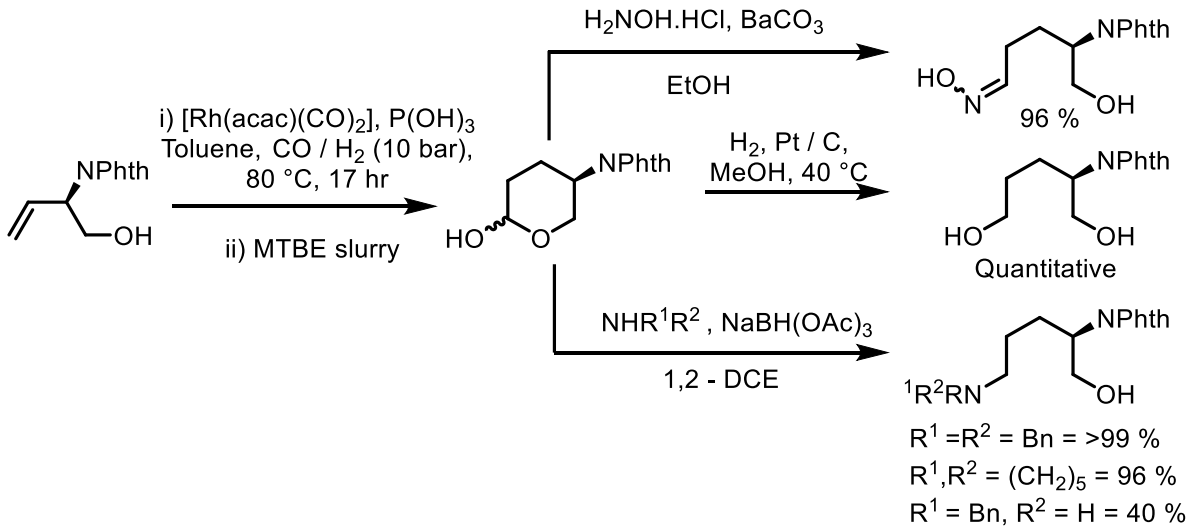
Scheme 58: Hydroformylation and cyclisation of primary amines.[56]

The imine product could be intercepted however to functionalise at C5 with high enantioselectivity and good yields, though under very specific conditions, Scheme 59. Here the use of solvent was paramount to selectivity: utilising toluene as opposed to diethyl ether resulted in a low diastereomeric ratio of 66:34.



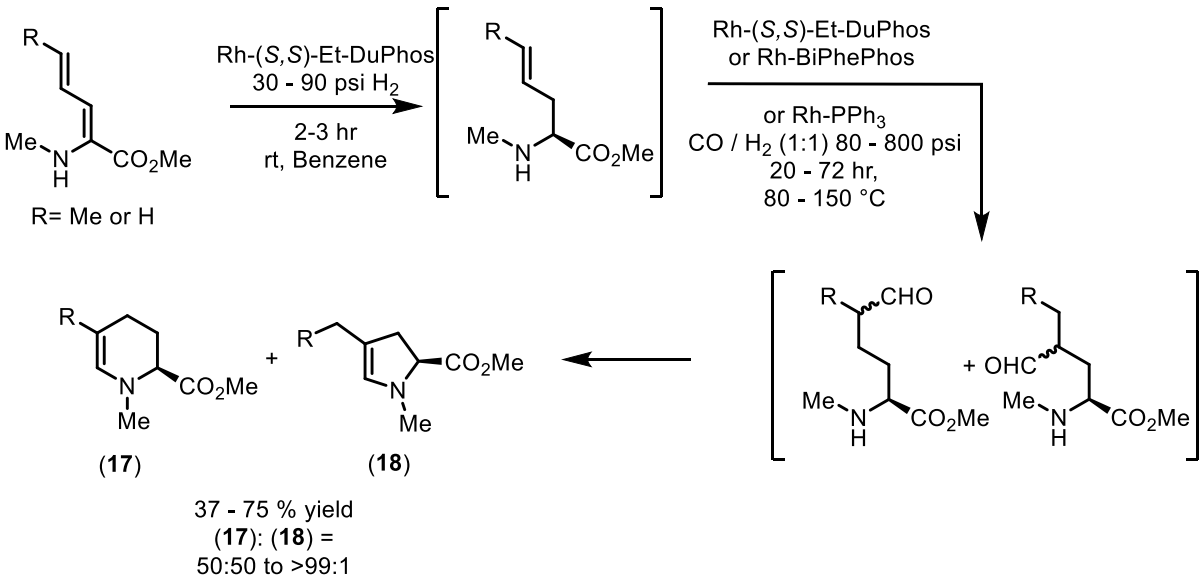
Scheme 59: Functionalisation of the imine product.[56]

Whilst the majority of the investigations carried out have worked to synthesise specific enantiomeric targets such as alkaloids, one group took the hydroformylation approach to create a trifunctionalised protected C5 synthon that could then be utilised for further synthetic applications, Scheme 60.[58] This paper saw a return to $P(OPh)_3$ as the most useful ligand for the highest combination of conversion and linear selectivity. It was noted during the study that switching from the alcohol to the mesylate derivative proceeded with a drop in regioselectivity, indicating that the alcohol group has a potential interaction with the catalyst system that aids selectivity for the linear regioisomer. However, the system requires high catalyst loadings in order to achieve the desired target material in good conversion.



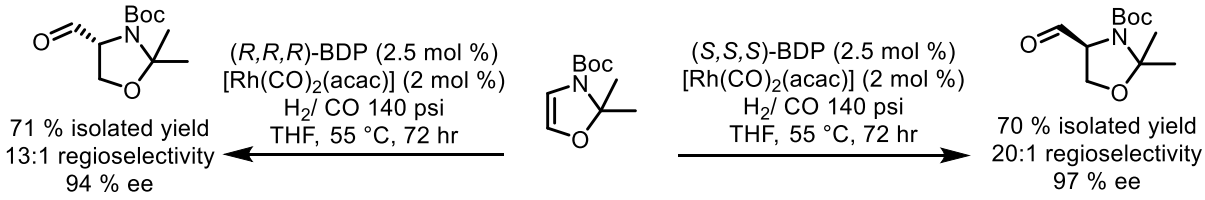
Scheme 60: Hydroformylation and functionalisation of synthon.[58]

Another way to install chirality within the molecule was described by Robinson et al. This utilised a rhodium catalyst to first enantioselectively hydrogenate one of the alkene functions, then a regioselective hydroformylation-cyclisation to form the desired product, Scheme 61.[59] The asymmetric hydrogenation gave excellent enantioselectivity which was then maintained through the hydroformylation reaction. Using the same catalyst system for the hydrogenation as for the hydroformylation meant that more forcing conditions were required to obtain similar conversion compared to switching to a catalyst system more suited to hydroformylation such as those using triphenylphosphine or BiPhePhos ligands. When using these ligands for the hydroformylation step, the temperature and time of reaction could be lowered. However, independent of the ligand system chosen, when the hydroformylation was completely regioselective for the linear product then cyclisation was not complete and the intermediate aldehydes were observed, and low yields were obtained.



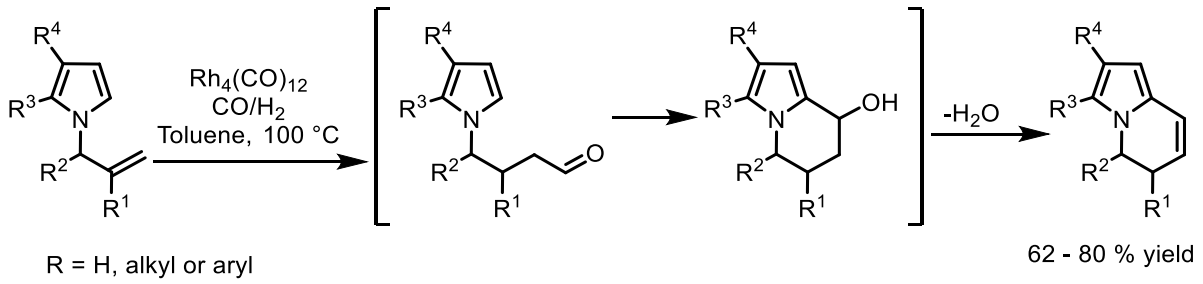
Scheme 61: Hydrogenation then hydroformylation and cyclisation.[59]

To introduce enantioselectivity succinctly to a preformed heterocycle the synthesis of Garner's aldehyde was undertaken by asymmetric HF using bis(diazaphospholane) (BDP) ligands, Scheme 62.[60] In this work, high enantioselectivity and regioselectivity were achieved in the synthesis of this common building block. It should also be noted that both enantiomers of Garner's aldehyde can be easily synthesised from the commercially available D- or L-seine.



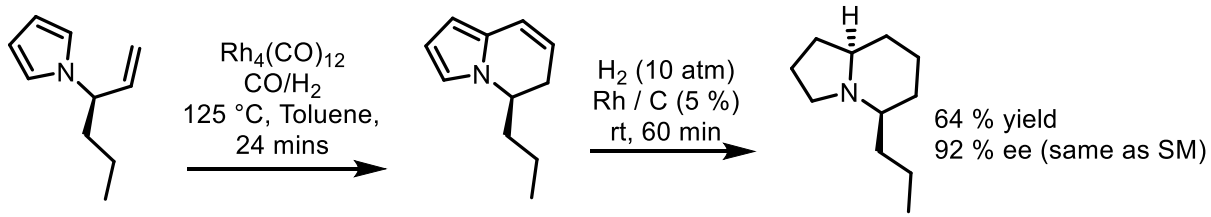
Scheme 62: Formation of Garner's aldehyde through hydroformylation.[60]

Domino reactions to carry out a cyclisation to form the product are common within hydroformylation systems, and methodology to which this is no exception are the works undertaken by the group of Lazzaroni. In these investigations a hydroformylation reaction is followed by a cyclization using a heterocycle as a C nucleophile, instead of an amine or alcohol, then either a dehydration or hydrogenation to provide the target compound. The first of these investigations reported were into a facile synthesis of 5,6-dihydroindolizines.[61] This process begins with the linear selective hydroformylation of the alkene, followed by intramolecular attack of the aldehyde by the pyrrolidine ring and then elimination of water to give the alkene product, Scheme 63.



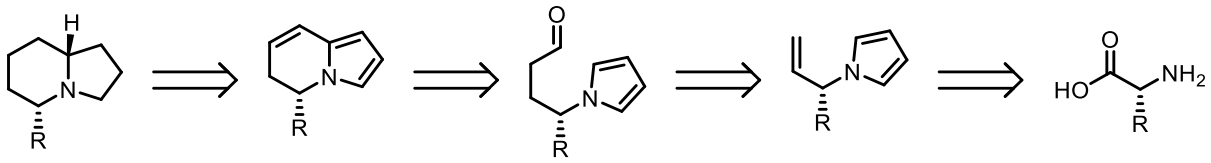
Scheme 63: Investigation into the synthesis of indolizine derivatives through hydroformylation.[61]

The next development was to use similar methodology to rapidly synthesise the natural product (-) – Indolizidine 167B with good yield and enantioselectivity, Scheme 64.[62]



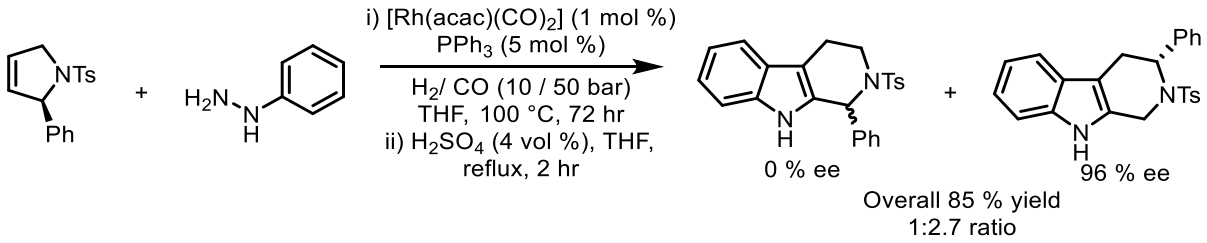
Scheme 64: Application of hydroformylation method in the synthesis of a specific natural product.[62]

The most recent hydroformylation work from the group of Lazzaroni is on the synthesis of indolizidines from optically pure α-amino acids.[63] Whilst this paper is presented as a review, the only work considered and reported is from the group of the authors. The retrosynthetic analysis for the target molecules was proposed as follows, Scheme 65, and the forward reactions were carried out in a one pot process. The hydroformylation step proceeds regioselectively to give the linear aldehyde, despite not using any ligand to enforce a preference for this, and the final products have the same ee as the starting materials.



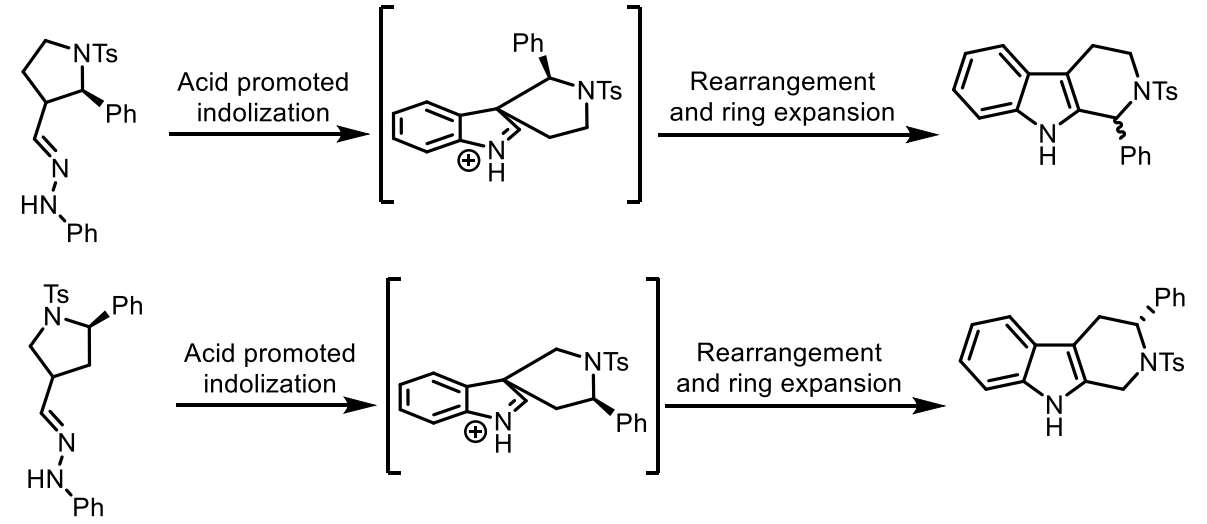
Scheme 65: Retrosynthetic analysis for formation of indolizidines.[63]

The synthesis of tetrahydro-β-carbolines via a one-pot HF/ Fischer indole synthesis produced the desired products in moderate yields, however it was observed that the 1-substituted carbolines racemised during cyclisation whereas the 3-substituted carbolines did not, Scheme 66.[64]



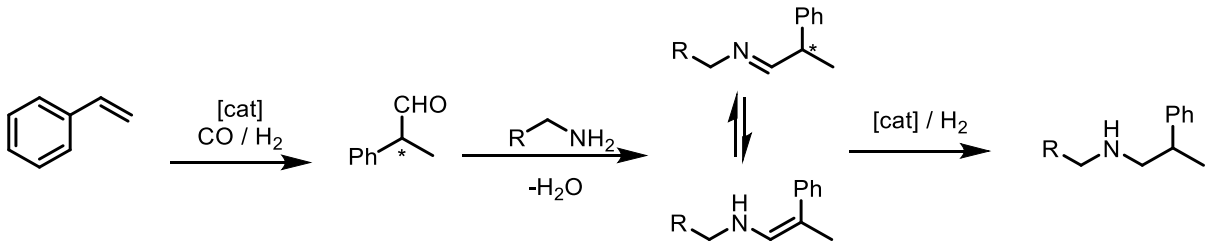
Scheme 66: Formation of carbolines through one-pot hydroformylation and Fischer indole synthesis.[64]

This work utilises an unselective hydroformylation of the aryl pyrrolidine starting material which is then attacked by the phenyl hydrazine to give the hydrazone product, this undergoes acid promoted, intramolecular indolization to give the carboline product. Within the scope of the study, it was found that there was preferential formation of the aldehyde at the C4 position of the pyrrolidine ring, which on completion of the cascade reaction lead to a higher ratio of the 3-substituted carboline being formed. In addition, the rearrangement and ring expansion saw racemisation of the stereocentre on formation of the 1-substituted carboline product from the C2 hydroformylation product, whereas this was not observed for the rearrangement of the 3-substituted carboline product, Scheme 67.



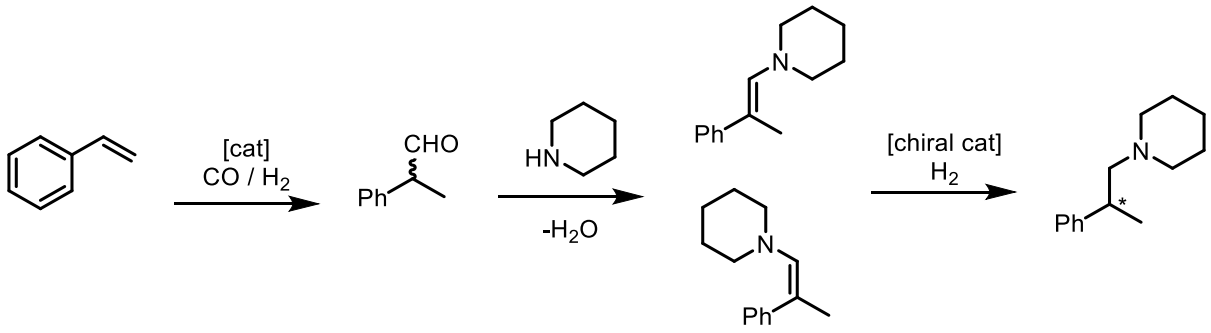
Scheme 67: Proposed explanation for retention of stereocentre or lack of.[64]

Work to achieve enantioselective HAM is particularly difficult due to racemisation via imine/ enamine, where any enantioselectivity introduced in the formation of the aldehyde is lost at this stage of the reaction, Scheme 68.



Scheme 68: Racemisation through imine / enamine pathway.

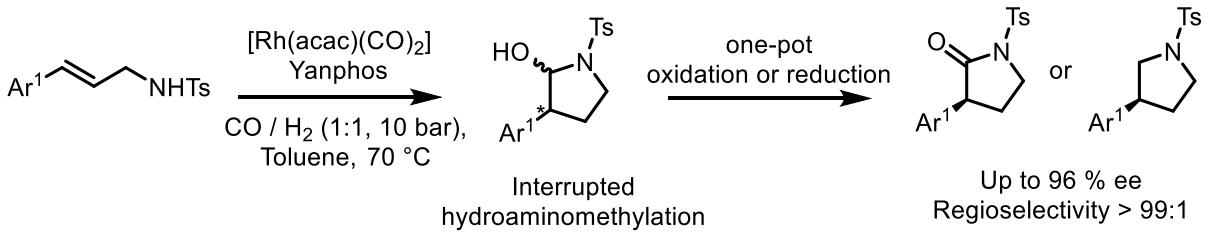
If enantioselectivity is instead attempted to be introduced by hydrogenation of the enamine intermediate, the two pathways are of such similar energy differences that no enantioselectivity has been induced thus far, Scheme 69.



Scheme 69: Lack of enantioselectivity on enamine hydrogenation during HAM.

This was comprehensively investigated by Kalck and co-workers through experimental reactions, high pressure NMR mechanistic insights and computational modelling.[65] The lack of enantioselectivity in their system was postulated, and supporting evidence provided, as arising from the low difference in energy states at the rate determining step, thereby allowing a build of both the *E* and *Z* enamine through H transfer allowing for racemisation and thus no specific enamine conformer could be selectively formed. Whilst asymmetric imine hydrogenation is reasonably achievable, asymmetric enamine hydrogenation is much more challenging, especially under tandem reaction conditions.

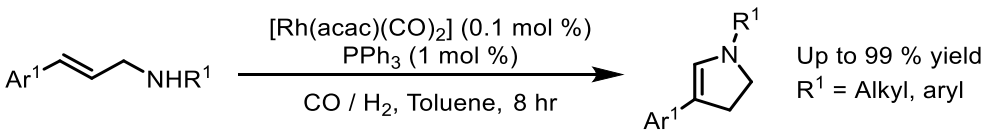
In spite of this, arguably the current most prominent work in this field is that by Zhang et al. which reports the first asymmetric hydroformylation-cyclisation, termed 'interrupted hydroaminomethylation' in the paper, which leads to the formation of chiral, five membered, nitrogen heterocycles.[66] This reaction utilises a rhodium catalyst with a Yanphos ligand to undergo the tandem hydroformylation-cyclisation reaction to give a cyclic hemi-aminal, followed by a one pot oxidation or reduction to complete the methodology, Scheme 70. The use of an internal alkene and an aryl substitution ensured that selectivity for the desired regioisomer was more easily achieved, and the chiral catalyst leads to the intermediate aldehyde in high ee which is immediately trapped as the hemi-aminal.



Scheme 70: First asymmetric hydroformylation-cyclisation.[66]

Since racemisation occurs through isomerisation of the chiral iminium to the non-chiral enamine, Zhang et al. proposed that by forming the stable five-membered hemi-aminal the interrupted hydroaminomethylation could take place, and then subsequent conversion to the valuable pyrrolidine or pyrrolidinone could be achieved through oxidation or reduction. More readily available, *trans* disubstituted 1,2 alkene isomers are known to be more challenging substrates than *cis* alkene isomers for hydroformylation reactions, but it was found that starting from either isomer had no effect on the final ee values. The limitation of this catalyst was that only aryl groups were well tolerated by the reaction – using an alkyl group meant a drop in the yield, with 28 % of the other regioisomer which was the uncyclized aldehyde chain recovered after the oxidation. No terminal alkenes were reported and it would be expected that these would not give the chiral regioisomer under these conditions. A reduction in the catalyst loading was also possible for this larger scale reaction. On account of the good yields and enantioselectivity of the pyrrolidine and pyrrolidinone cores formed, novel synthetic routes to the drug targets venakalant and Enablex were proposed.

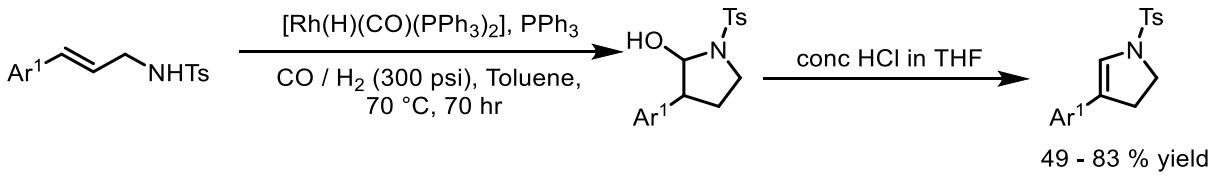
This work builds on previous investigations by Zhang and co-workers that synthesised 4-aryl-2,3-dihydropyrroles through an intramolecular hydroformylation-cyclisation reaction.[67] These substrates showed an electronic preference for the formation of one regioisomer and hence only triphenylphosphine was used as the ligand to deliver racemic aldehydes that cyclised but then eliminated water, delivering the enamine as the final product, Scheme 71. Interestingly, the bidentate ligands tested showed no or poor yields of the desired products, and a decrease in the loading of the rhodium precursor from 0.2 mol % to 0.1 mol % increased the yield.



Scheme 71: Hydroformylation and cyclisation of internal olefins.[67]

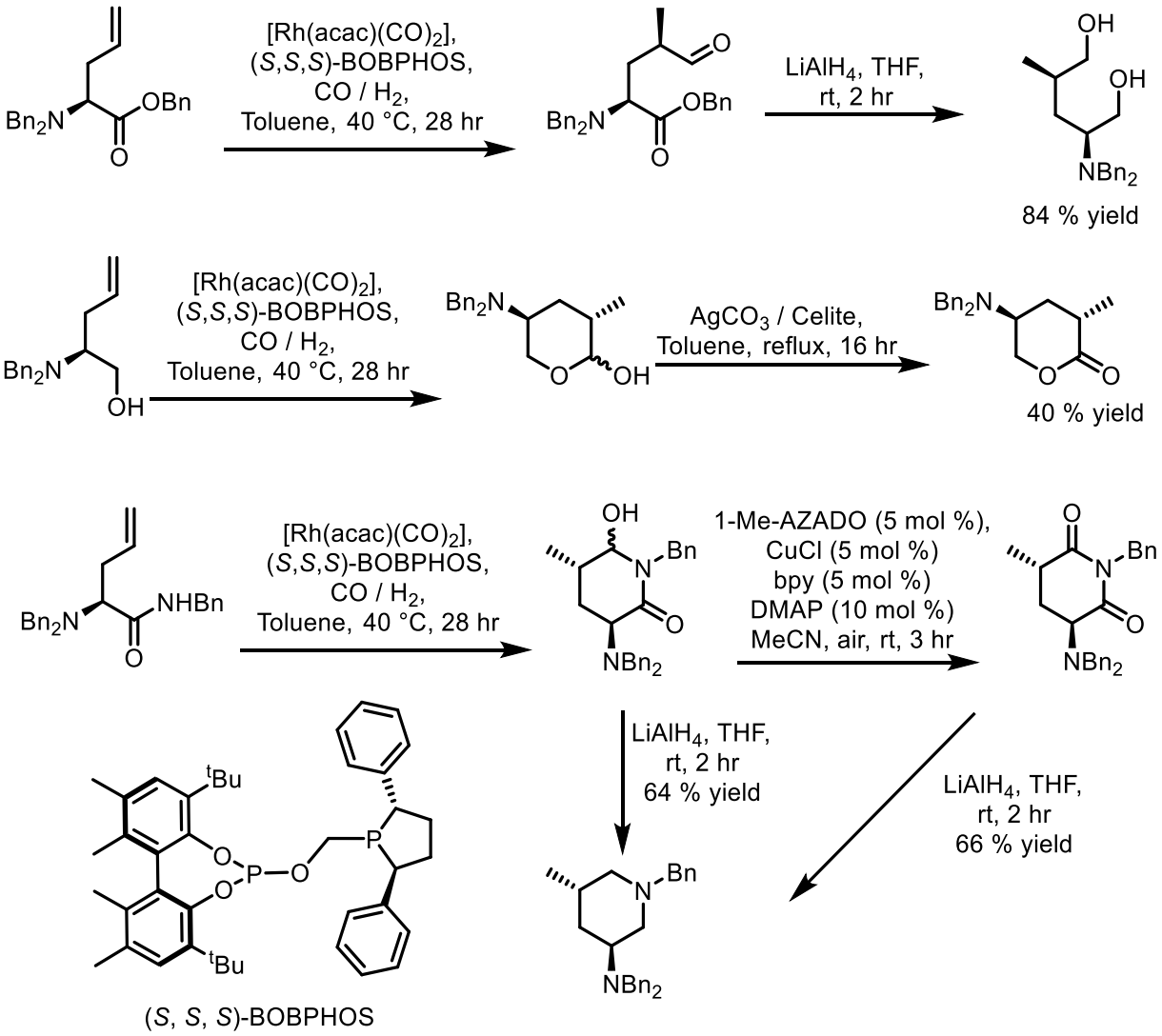
This study in itself has its origins in work by Busacca and Dong from 1996, in which similar compounds were hydroformylated and then further reacted in order to reach the same dihydropyrrole products,

Scheme 72.[68] Again, excellent regioselectivity was observed due to the electronic preference of a substrate with aryl directing group, as well as moderate to high yields.



Scheme 72: Development of hydroformylation conditions such that hemiaminal intermediate is observed.[68]

At the same time as the work by Zhang et al. on interrupted hydroaminomethylation was published, work within our group was being carried out on developing a shorter synthetic route to the antibiotic nemonoxacin using hydroformylation-cyclisation.[69] This utilised allylglycine derivatives to selectively form branched aldehydes. The position and chirality of the amine function was already established prior to carrying out the hydroformylation reaction, but a new stereocentre was formed from the branched selective hydroformylation, Scheme 73. The reaction proceeded utilising the ligand BOBPHOS, since other ligands for asymmetric hydroformylation were found to have lower activities and branched selectivity.



Scheme 73: Asymmetric synthesis of nemonoxacin intermediate.[69]

Once the aldehyde had been formed, the enantiomer was reduced with retention of stereochemistry. This enabled the asymmetric synthesis of the target carbamate through more efficient methodology than the current synthesis towards the antibiotic, nemonoxacin. BOBPHOS remains the only ligand for introducing both enantioselectivity and branched regioselectivity to an alkyl alkene substrate within a hydroformylation reaction.

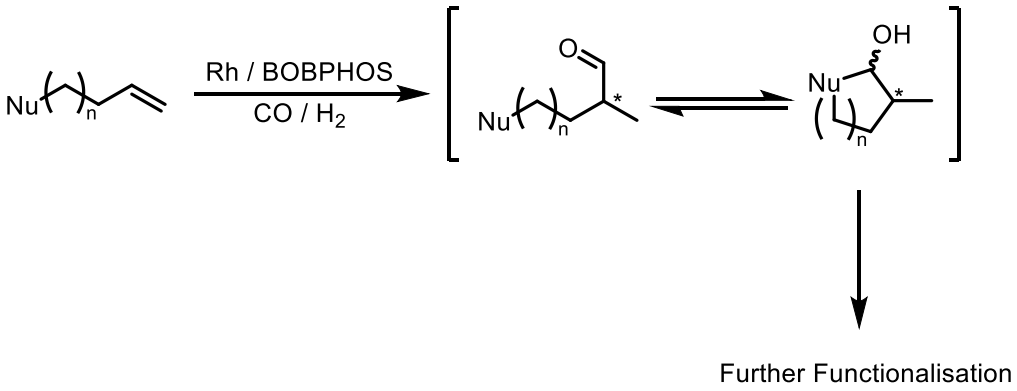
Summary:

The use of linear-selective hydroformylation- reductive amination reactions have seen great amounts of research due to their use in industry, with examples as shown here in the synthesis of complex products. The use of these reactions to generate the desired product in high yields under mild, tolerant reaction conditions has been well established, yet the generation and preservation of a new stereocentre during hydroformylation-cyclisations is far less explored. There are just a few examples

of asymmetric hydroformylation-cyclisation reactions, and using the Rh/ BOBPHOS catalysts, an opportunity exists to significantly develop this approach to chiral heterocycles.

Aims:

The aim of this PhD was to develop the hydroformylation-cyclisation methodology using Rh/ BOBPHOS catalysts and exploit their unique reactivity on substrates that would otherwise show linear selectivity in hydroformylation.



Scheme 74: Generic scheme of hydroformylation-cyclisation.

By control of the chain length and electronics, a cyclic hemi-aminal intermediate would be obtained, Scheme 74. Through subsequent functionalisation of this hemi-aminal intermediate, an efficient route to a range of small, chiral nitrogen heterocycles will be investigated.

Chapter 2: Asymmetric Hydroformylation-Cyclisation For Piperidines

Hydroformylation-Cyclisation Introduction:

As discussed in chapter one, asymmetric hydroformylation (AHF) provides a simple way to access enantioenriched aldehydes, a privileged class of compounds which can then easily be reacted further to give alcohols, amines or carboxylic acids, for example. Many factors make AHF feasible for an industrial process: the atom efficiency of the reaction, the wide tolerance of functional groups to the reaction conditions and the easily accessible alkene substrates. The factors hindering the use of AHF are not only achieving high enantioselectivity, but also high regioselectivity for the branched isomer in the first instance regardless of the substrate used.

There has been much progress made on this problem in recent years and one of the most prominent catalysts in this area are the Rh/ BOBPHOS catalysts, developed within the Clarke group.[27] These catalysts provide both high regioselectivity and enantioselectivity over a broad range of substrates, not only those alkenes which exhibit an inherent electronic preference to form the branched regioisomer, such as styrene, but also those with no electronic interference, such as hex-1-ene. Whilst branched selective hydroformylation shows great promise for use industrially, such as in the synthesis of commodity chemicals, there also exists the opportunity to use it for the synthesis of added value fine chemicals such as bioactive compounds for agrochemicals, drug intermediates or natural products. Some examples of possible targets for which the 3-methyl group of a pyrrolidine or piperidine could be installed through an asymmetric hydroformylation-cyclisation reaction are depicted, Figure 2.

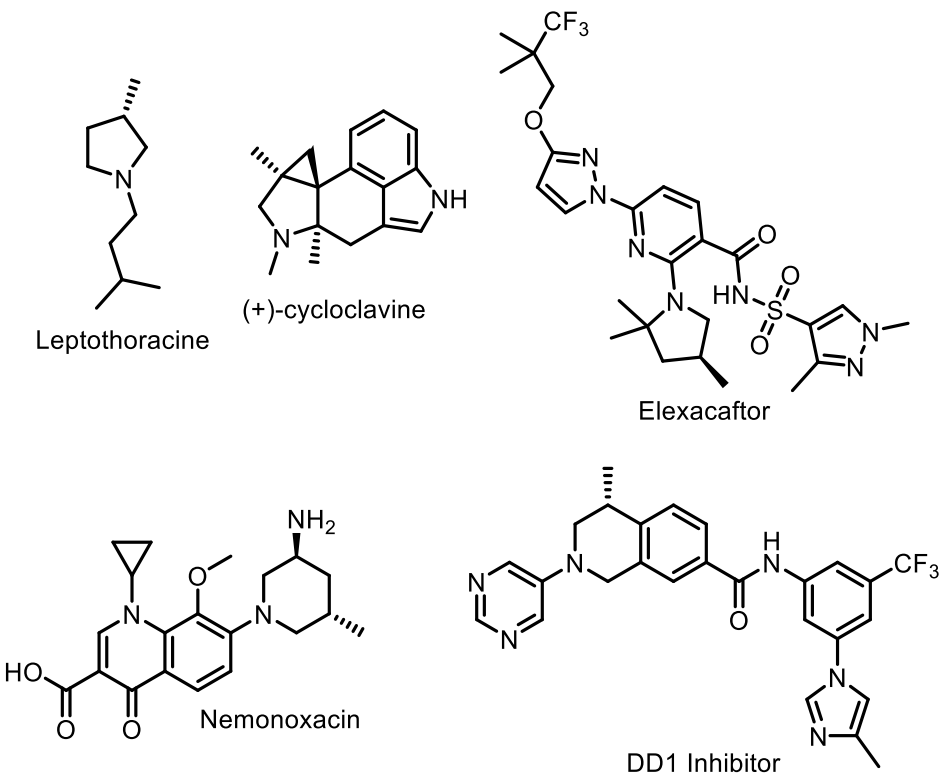


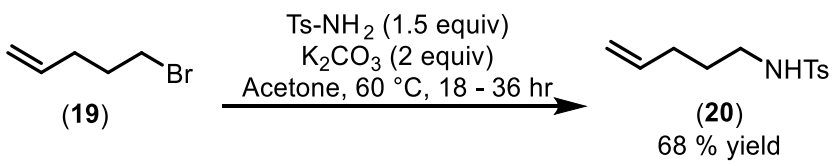
Figure 2: Possible targets containing 3-methylpyrrolidine rings

Previous prominent work in this area is outlined in chapter 1. As discussed previously, the limitations of this method were the requirement of an aryl group as a substituent of the 1,2-alkene. This chapter focuses on the attempt to develop a general methodology that would be applicable for forming a range of substituted and unsubstituted 3-methylpiperidines, as opposed to a two-pot process for a specific drug[69] or an aryl directed process.[66]

This chapter begins with a discussion on finding the most suitable protecting group for the alkyl alkene substrate, followed by optimisation of the hydroformylation conditions. Subsequent sections discuss the synthesis of a fluorinated derivative, an aryl substituted derivative and steps towards the starting material for formation of a spirocyclic substrate. The final section concerns reactions carried out on the hemi-aminal intermediate to generate new substitution patterns.

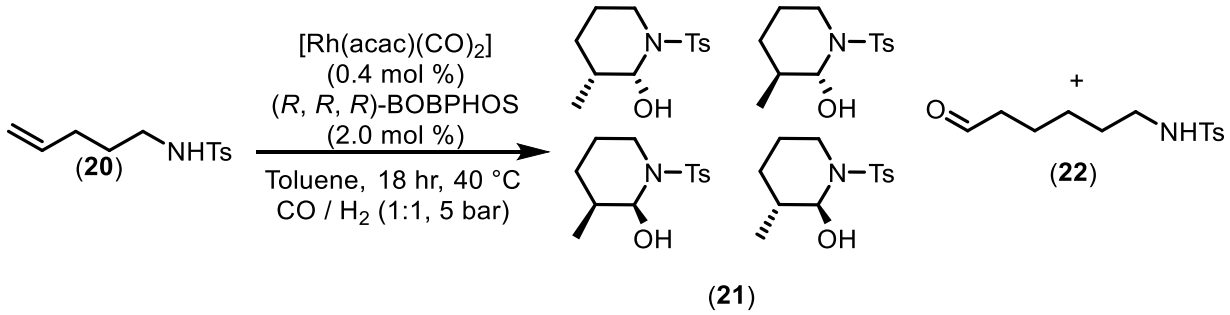
Optimisation of the Hydroformylation-Cyclisation Reaction:

The first substrate was synthesised by nucleophilic substitution of 5-bromo-1-pentene with 4-methylbenzenesulfonamide under basic conditions and in good yield, Scheme 75.



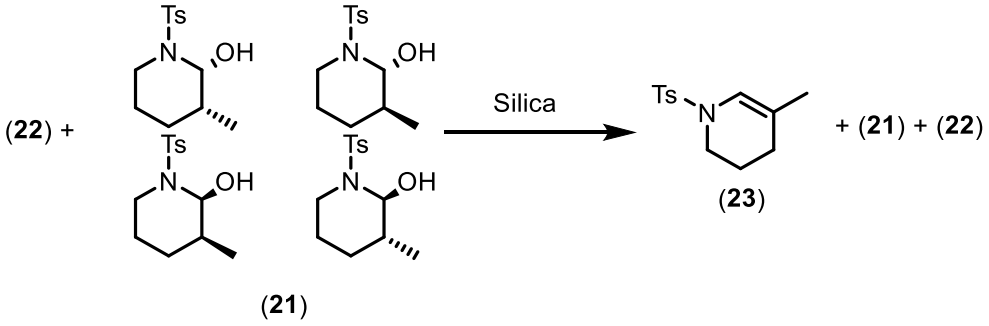
Scheme 75: Synthesis of N-(pent-4-en-1-yl)-4-methylbenzenesulfonamide

The substrate was then subjected to the hydroformylation conditions that had been previously established for the synthesis of the nemonoxacin intermediate. On analysing the reaction mixture by ^{1}H NMR after the hydroformylation, it was observed that the branched regioisomer had undergone cyclisation to give the hemi-aminal as four enantiomers, observable in the NMR spectrum as two diastereomers, whilst the linear regioisomer remained acyclic as the aldehyde, Scheme 76.



Scheme 76: Products from the AHF of N-(pent-4-en-1-yl)-4-methylbenzenesulfonamide

This mixture of compounds formed after the initial hydroformylation reaction could not be analysed accurately on account of the lack of unique, distinct peaks to attribute to the starting material, the two diastereomers of the hemi-aminal arising from the branched regioisomer product and the linear regioisomer aldehyde. Attempts to isolate the hemi-aminal diastereomers lead to partial elimination of water on the silica column, giving the enamine product which further complicated the analysis, Scheme 77. An analytically pure sample of the enamine was prepared by a different method, Scheme 82, and characterised.

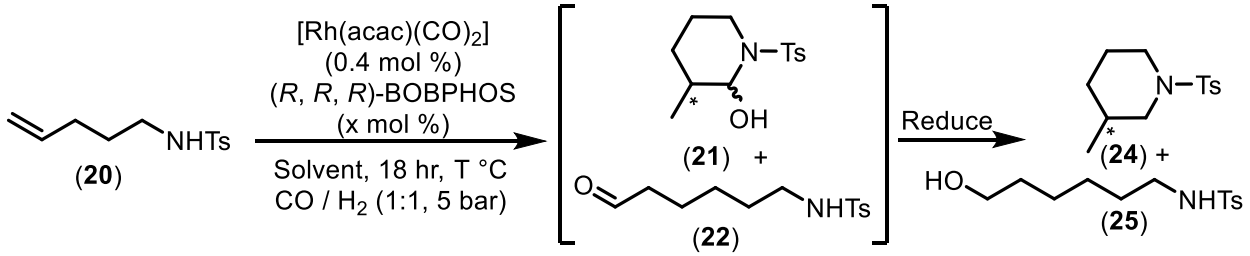


Scheme 77: Degradation of hemi-aminal on silica column chromatography

As a result of this, a one-pot reduction was carried out immediately after the hydroformylation reaction, with precedence from Zhang et al.[66] Accurate analysis of the conversion, regioselectivity and enantioselectivity could then be carried out on the *N*-tosyl-3-methylpiperidine, derived from the branched regioisomer, and the corresponding alcohol, derived from the linear regioisomer. Measurement of the enantiomeric excess of the *N*-tosyl-3-methylpiperidine was carried out by HPLC and by using the products formed from each enantiomer of the BOBPHOS catalyst to develop the HPLC

method. Whilst it is normally preferred to use an achiral ligand, such as triphenyl phosphine, to form a racemic product and then develop a HPLC method, this was not possible in this case. The reason was that the use of triphenyl phosphine gave too small an amount of the branched isomer to isolate and analyse, due to low conversions and the lack of any inherent electronic preference of the substrate for branched regioselectivity, thus forming the linear aldehyde in equal amounts, Table 1, entry 1. After the HPLC method had been developed using the method of opposite enantiomers, a small amount of racemic sample of *N*-tosyl-3-methylpiperidine was prepared by hydroformylation with Rh/triphenylphosphine and analysed via the HPLC method to confirm the validity of this method.

From here, optimisation was carried out on this reaction, Table 1.



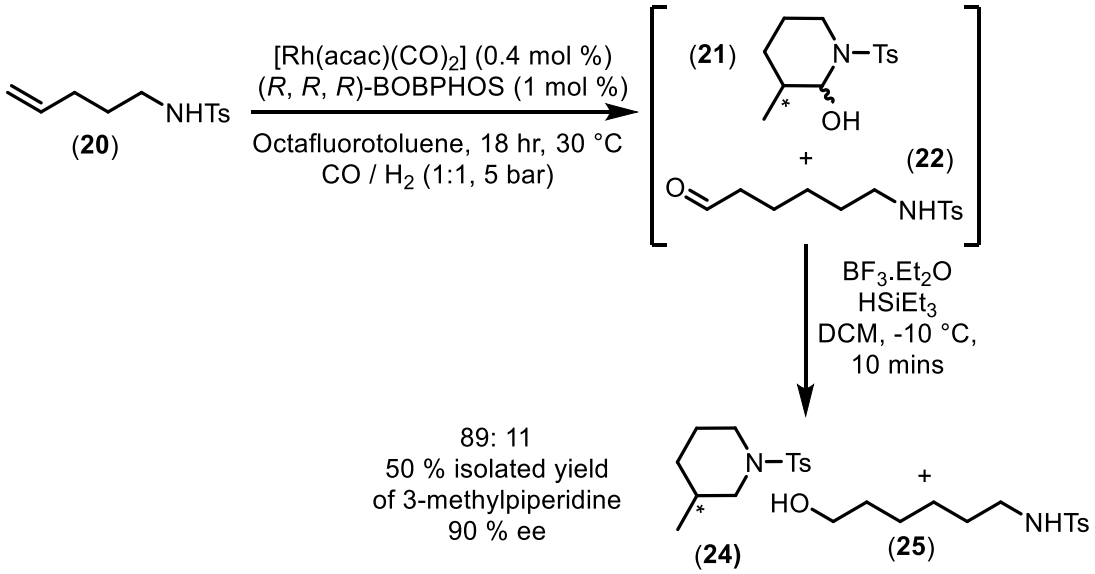
Entry [a]	Ligand	Solvent	Temperature / °C	Conversion	Branched : linear	ee[b]
1	(*R*, *R*, *R*)-BOBPHOS (0.5 mol %)	Toluene	40	95 %[c]	76:24	37 %
2	(*R*, *R*, *R*)-BOBPHOS (1.0 mol %)	Toluene	40	> 99 %	80:20	53 %
3	(*R*, *R*, *R*)-BOBPHOS (1.5 mol %)	Toluene	40	> 99 %	80:20	53 %
4	(*R*, *R*, *R*)-BOBPHOS (2.0 mol %)	Toluene	40	> 99 %	83:17	64 %
5	Ph-BPE (1.0 mol %)	Toluene	40	61 %[c]	54: 46	13 %
6	PPh_3 (1.0 mol %)	Toluene	40	37 %[c]	55: 45	N/A
7	(*R*, *R*, *R*)-BOBPHOS (1.0 mol %)	Toluene	30	95 %	77:23	85 %
8	(*R*, *R*, *R*)-BOBPHOS (1.0 mol %)	Octafluorotoluene	30	> 99 %	88: 12	84 %
9	(*R*, *R*, *R*)-BOBPHOS (1.0 mol %)	Heptane	30	95 %	87: 13	45 %
10	(*R*, *R*, *R*)-BOBPHOS (1.0 mol %)	Hexafluorobenzene	30	90 %	89:11	56 %
11	(*R*, *R*, *R*)-BOBPHOS (2.0 mol %)	Octafluorotoluene	30	> 99 %	86: 14	88 %
12	(*R*, *R*, *R*)-BOBPHOS (1.0 mol %)	Octafluorotoluene	40	> 99 %	89: 11	72 %
13	(*R*, *R*, *R*)-BOBPHOS (1.0 mol %)	Octafluorotoluene	20 (24 hr)	98 %	92: 8	85 %

[a]Standard reaction conditions: substrate (0.50 mmol), $[Rh(acac)(CO)_2]$ = 0.4 mol %, L = 1.0 mol %. Measurements made by ^1H NMR after one-pot reduction with $HSiEt_3$ (3 equiv, 1.5 mmol) and BF_3Et_2O (3 equiv, 1.5 mmol) in DCM (-15 °C, 15 mins). See SI for details. [b] Enantioselectivity measured by chiral HPLC. [c] Unknown impurity present, predicted to be isomerised starting material.

Table 1: Optimisation of hydroformylation-cyclisation reaction conditions

Considering Table 1, pronounced effects on the enantioselectivity were observed on lowering the temperature, entries 2 and 7, and changing the solvent to octafluorotoluene led to an increase in regioselectivity. The chiral phosphine ligand (*S*, *S*)-1,2-bis(2,5-diphenylphospholano)ethane, known here on as Ph-BPE, was first reported in 2003 as a ligand for hydrogenation reactions.[70] It is commercially available and was noted in 2005 for delivering high enantioselectivity in branched products when used in AHF reactions.[71] The original investigation used activated substrates such as styrene or vinyl acetate that have an electronic preference for the formation of predominantly the

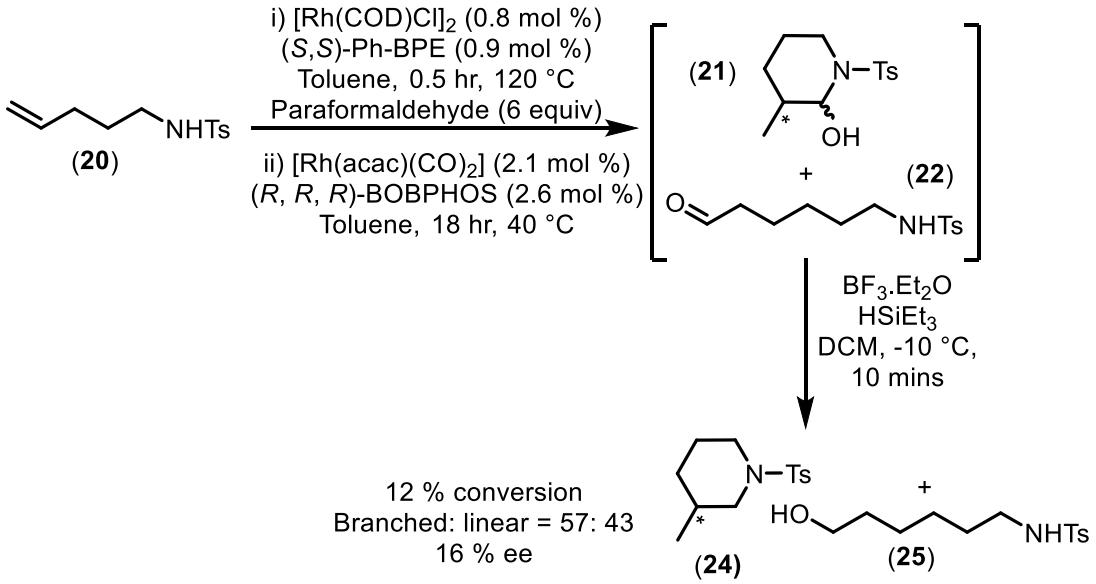
branched product, more recent investigations have shown branched regioselectivity can be achieved when using this ligand with more electronically biased substrates such as allylic ethers.[72] Here it gave no control over the regioselectivity and of the branched regioisomer that was formed, very little enantioselectivity was observed, entry 5. This, along with literature precedent, established that the use of BOBPHOS as the ligand was required for the key combination of regioselectivity and enantioselectivity. The ligand loading could be dropped from 2 mol %, which is 5 equivalents of ligand to 1 equivalent of rhodium precursor, to 1 mol %, 2.5:1 ligand to rhodium ratio, with minimal differences observed. The pressure was not altered since enough prior research has been carried out in the group to know that a good operating pressure for the BOBPHOS/ rhodium catalyst is 5 bar. The final optimised conditions were as shown below, Scheme 78.



Scheme 78: Synthesis of chiral 3-methylpiperidine through hydroformylation-cyclisation and one-pot reduction.

Asymmetric Transfer Hydroformylation:

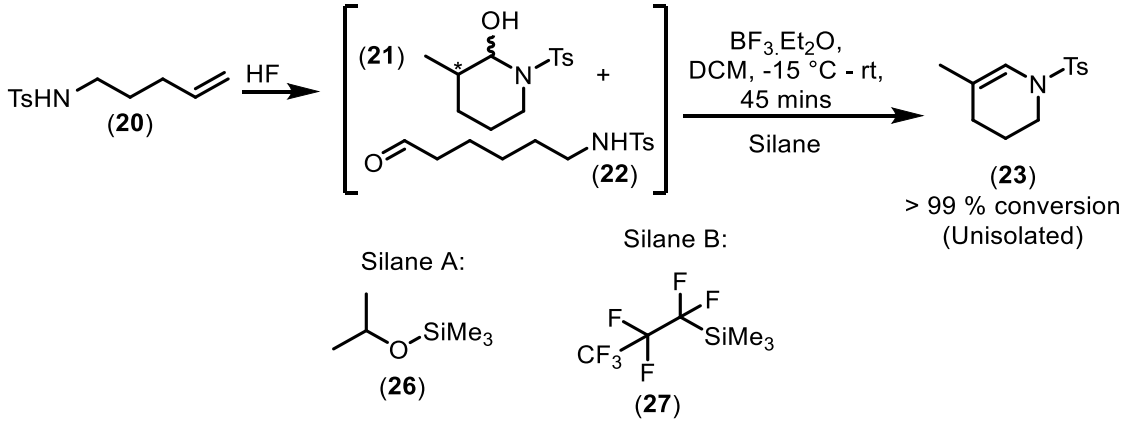
Previously within the group, conditions for an asymmetric transfer hydroformylation had been developed with the aim of providing methodology that did not require the use of carbon monoxide, hydrogen gas and pressure vessels such as autoclaves.[72] The use of dual catalysts was investigated in order to optimise both the cracking of the paraformaldehyde to give the carbon monoxide and dihydrogen gas components and also the hydroformylation reaction. It was found that the most efficient catalyst to crack the paraformaldehyde is a Rh/ Ph-BPE complex, whilst the other catalyst that carries out the hydroformylation with the desired regio- and enantioselectivity is Rh/ BOBPHOS. As proven in the literature, control experiments have shown that the catalyst based on Rh/ Ph-BPE does not interfere with the asymmetric transfer hydroformylation reaction. In this reaction, it was found that the substrate did not undergo complete conversion and that the enantioselectivity was poor, Scheme 79. No tosyl amines had been previously studied in this reaction hence it is possible that this type of substrate is not efficiently reacted under these optimised conditions.



Scheme 79: Attempted ATHF under literature conditions

Investigations into Reactions on the Hemi-Aminal Intermediate:

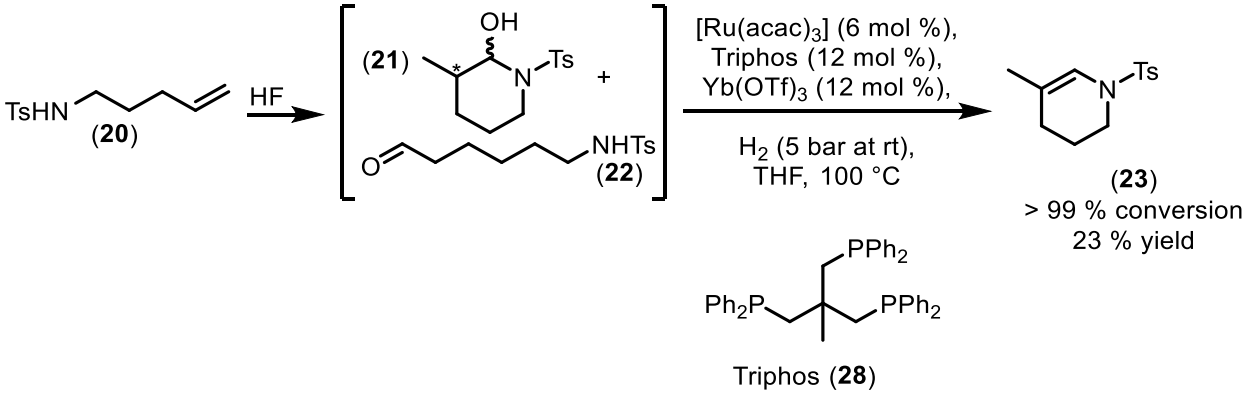
Reactions on hemi-acetals and hemi-aminals have long been studied, partly owing to the interest from carbohydrate chemistry.[73] Literature precedent for reactions on the hemi-aminal intermediate had also been previously set by Zhang et al. in their work from 2016.[66] Here we were able to successfully adapt these conditions on our substrates, albeit with lower diastereoselectivity. On investigation of other silanes it was found that no addition occurred, only elimination of water to give the enamine as the product, Scheme 80. This meant the loss of the chiral centre and suggests that the Lewis acid was capable of activating the OH for removal but that attack by the silyl reagent was too slow to intercept, and the iminium ion formed then converted to the enamine.



Scheme 80: Attempted addition with different silanes

Whilst the use of triethylsilane and a Lewis acid gives the desired reduced product, and in the case of the allylsilane, allows for diversification from the hemi-aminal hydroformylation-cyclisation product, it would be more atom efficient and greener to use a catalyst and dihydrogen gas to carry out a

hydrogenation of the hemi-aminal intermediate to give the saturated piperidine whilst avoiding racemisation of the β-stereocentre. The majority of the literature in this area focuses on the complete reduction of amides to the corresponding alcohols and amines, with cleavage of the C-N bond occurring via the hemi-aminal intermediate. In this instance, this would lead to the ring-opened, branched alcohol product which would be detrimental to the aim of the synthetic route for the formation of saturated heterocycles. Hence attention focussed on the published conditions for the reduction of cyclic amides to amines and it is these conditions that were investigated in a test reaction.[73] Unfortunately, this also showed full conversion to the enamine as the product, Scheme 81.

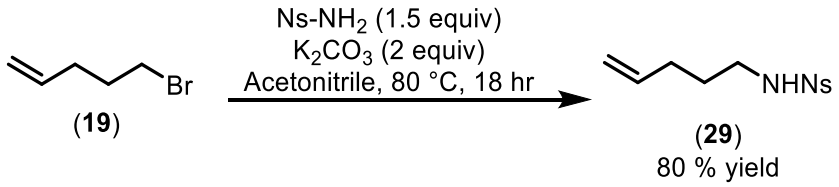


Scheme 81: Attempted reduction with dihydrogen gas

Nitrogen Protecting Group Investigation

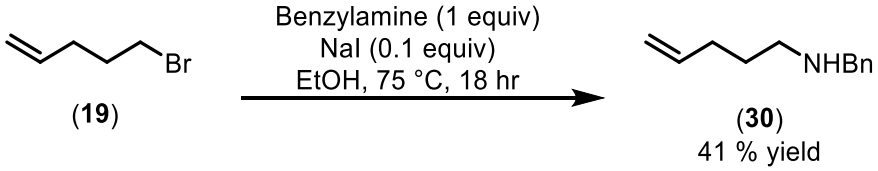
Once the reaction conditions had been optimised, an investigation into the nitrogen protecting group was undertaken. Different nitrogen protecting groups offer different properties, such as acidity, stability and nucleophilicity of the nitrogen lone pair. Of equal importance is the ease of access to the protecting group when carrying out the original protection, and then also the ease of removing the group must be considered if using the substrate in multi-step syntheses.

The tosyl protected starting material was prepared as previously discussed, Scheme 75, and these conditions were replicated for the synthesis of the nosyl protected compound. Unfortunately, at the end of the reaction time limited conversion had been obtained and the di-substituted compound was the major product. A solvent switch to acetonitrile was undertaken and this allowed for the synthesis of the desired monosubstituted compound in high isolated yield, Scheme 82.



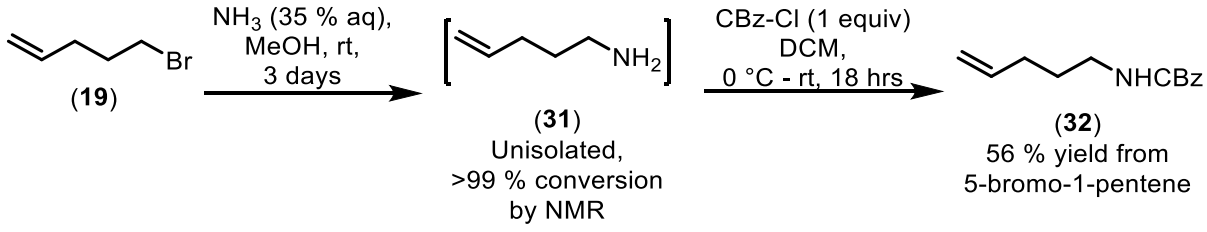
Scheme 82: Synthesis of N-(pent-4-en-1-yl)-2-nitrobenzenesulfonamide

As an electron rich protecting group, the benzyl group was chosen. The synthesis of the benzylamine product was obtained via a literature procedure and purified by distillation under reduced pressure without incident, Scheme 83.



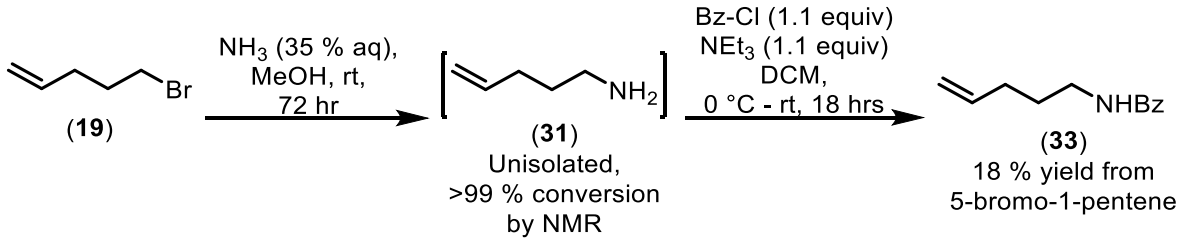
Scheme 83: Synthesis of N-pent-4-enebenzylamine

The next protecting group chosen was a benzoyl carbamate protecting group, whilst the tert-butyloxycarbonyl protecting group is the more commonly used carbamate protecting group, it lacks a significant chromophore which would be required for measurement by UV-vis detection of HPLC for the enantioselectivity of the hydroformylation reaction. Using an adapted literature procedure the desired substrate was synthesised in a moderate yield. Owing to the rotational flexibility of this group and also the propensity for hydrogen bonding, the NMR of the clean material contained broadened peaks, a phenomenon that was further heightened after hydroformylation of the substrate to form the hemi-aminal and aldehyde intermediate. Other examples of this are available within the literature.[74] The substrate was synthesised in a two-step procedure, Scheme 84.



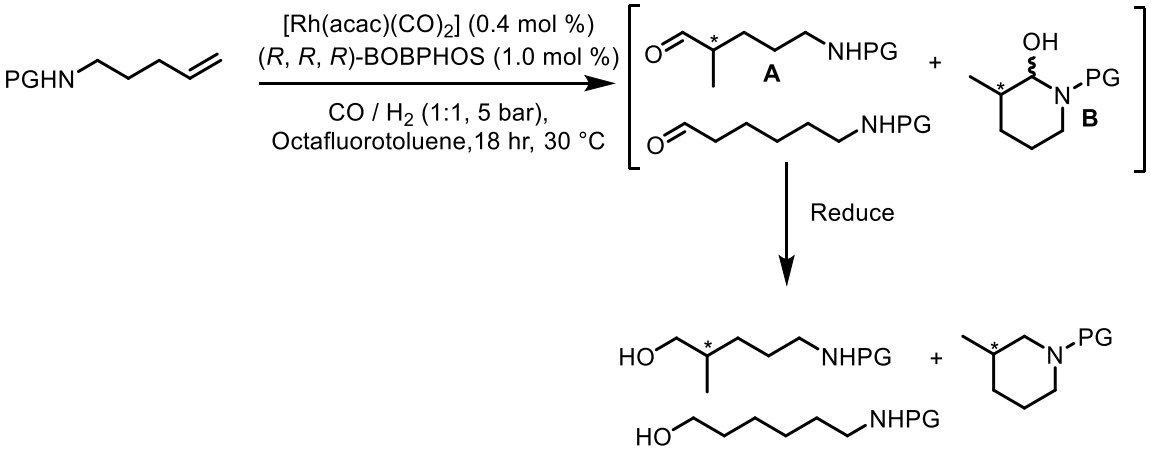
Scheme 84: Synthesis of carbamate protected substrate

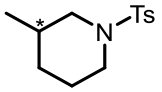
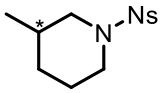
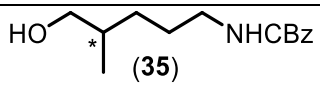
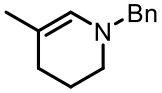
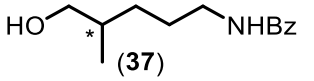
The final protecting group was a benzoate protecting group and was prepared in a two-step procedure as for compound **32**, Scheme 85.



Scheme 85: Synthesis of benzoate protected substrate

A range of protecting groups were thus chosen for the investigation of the hydroformylation-cyclisation reaction under the optimised conditions. The results are outlined in the table below, Table 2.



Entry[a]	Protecting Group	Conversion	Branched (A+ B): linear	Aldehyde (A): Hemi-aminal (B)	Yield and Product after Reduction	ee[b]
1	Tosyl	> 99 %	88: 12	0: 100	 (**24**) 46 %	84 %
2	Nosyl	> 99 %	85: 15	0: 100	 (**34**) 23 %	88 %
3	CBz	95 %	75: 25	54: 46	 (**35**) N/A	n.d.
4	Benzyl	70 %	81: 19	0:100 (enamine)	 (**36**) N/A	n.d.
5	Benzoyl	98 %	72: 28	100: 0	 (**37**) 29 %	75 %

[a]Standard reaction conditions: substrate (0.50 mmol), $[Rh(acac)(CO)_2]$ = 0.4 mol %, L = 1.0 mol %. Measurements made by ^1H NMR after one-pot reduction with $HSiEt_3$ (3 equiv, 1.5 mmol) and BF_3Et_2O (3 equiv, 1.5 mmol) in DCM (-15 °C, 15 mins). See SI for details. [b] Enantioselectivity measured by chiral HPLC.

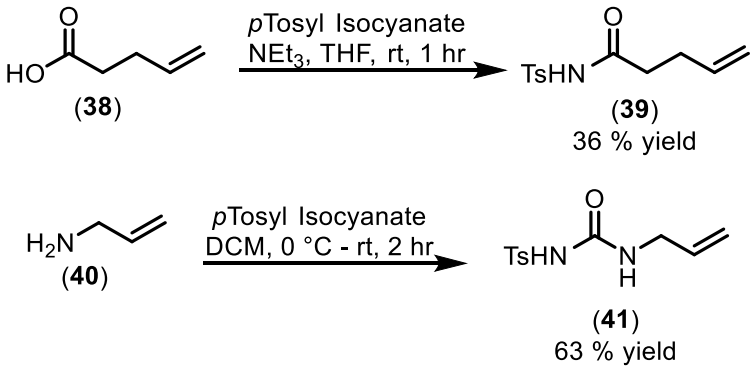
Table 2: Investigation into different nitrogen protecting groups

As can be seen from the results, the most electron donating protecting group benzyl not only cyclised to the hemi-aminal but also eliminated the hydroxy group, forming first the iminium ion, then the enamine, Table 2, entry 4. This immediate loss of the newly formed chiral centre renders this protecting group useless for making chiral heterocycles but has actually been used under slightly different conditions as an efficient synthesis of cyclic enamines. In the opposite direction, the benzoyl carbamate protecting group and the benzoyl protecting group, entries 3 and 5, were not nucleophilic

enough to allow for complete cyclisation to the hemi-aminal, a prerequisite for the formation of chiral nitrogen heterocycles. The benzoyl carbamate formed a mixture of the aldehyde and hemi-aminal, but on reduction the carbamate group was lost and this further complicated matters for isolation and measurement of these compounds. As a result of this investigation, the sulfonamide protecting groups were established as clearly being optimal for this methodology.

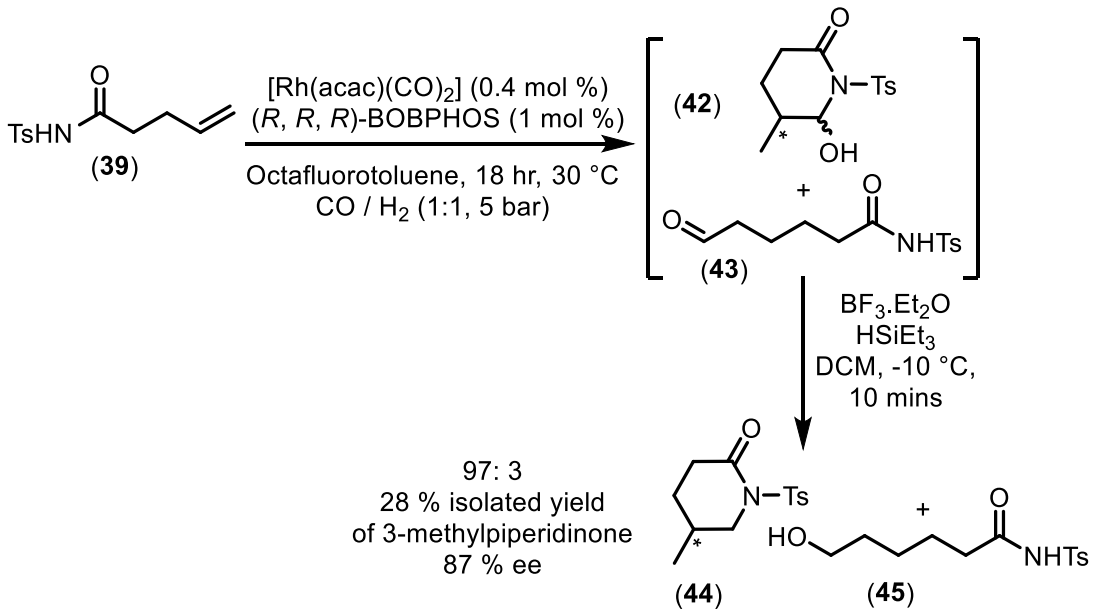
Investigation of Different Substitution Patterns in the Alkene

The alkene chain of the substrate was then diversified and the use of a tosyl protecting group used with an amide and a urea substrate. These were prepared according to literature procedures, Scheme 86.



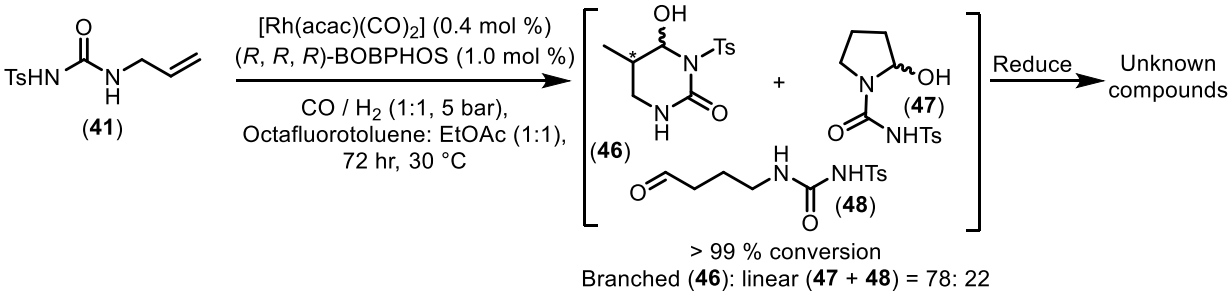
Scheme 86: Synthesis of amide and urea substrates

Hydroformylation of the amide substrate proceeded with high regioselectivity and enantioselectivity, as measured on the reduced piperidinone product, Scheme 87.



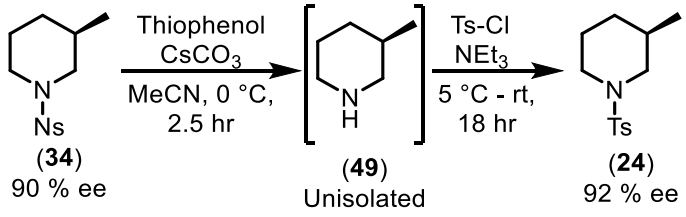
Scheme 87: AHF of amide substrate under optimised conditions

For the urea however, there were issues with finding a solvent that both suitably solvated the substrate but did also not have a detrimental effect on the activity or selectivity of the hydroformylation reaction. A one-to-one mixture of ethyl acetate and octafluorotoluene along with an extended reaction time was used which gave full conversion of the substrate to the hemi-aminal intermediates. Cyclisation was observed to give both the piperidine and pyrrolidine species but on carrying out the one-pot reduction, degradation to unknown compounds was observed, Scheme 89. On account of the low mass balance recovered, it was assumed that ring opening and elimination of the tosyl protecting group was the main pathway. As a result, no stable compounds could be isolated from the reaction mixture since the hemi-aminals are prone to degrading to the enamines as discussed previously, Scheme 77, and the reduction conditions facilitated degradation to unknown, volatile compounds.



Scheme 88: AHF of urea under optimised conditions

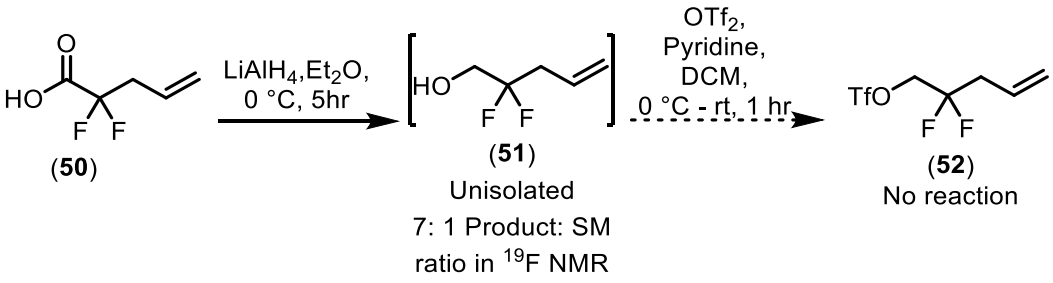
In order to confirm that the enantioselective hydroformylation-cyclisation methodology could be used in an asymmetric synthesis a clean sample of the *N*-nosyl-3-methylpiperidine was deprotected using a literature procedure, then re-protected with a tosyl protecting group and the enantioselectivity measured again, Scheme 89.[75] The near identical enantiomeric excess gave assurances that no racemisation of the β-stereocentre had taken place.



Scheme 89: Deprotection and reprotection of 3-methylpiperidine

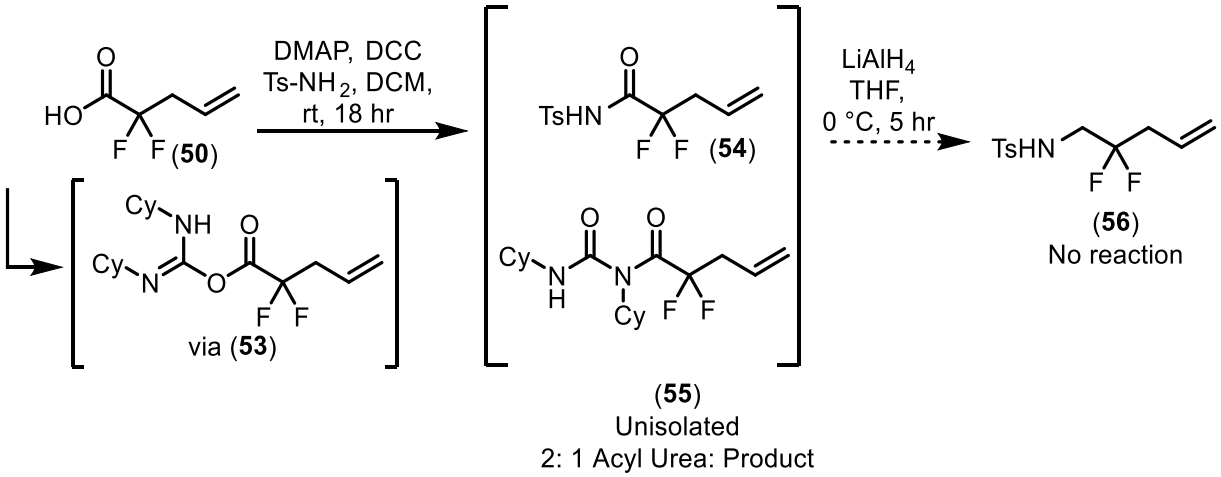
The use of a fluorine functional group in agrochemicals or medicinal chemistry has a strong prevalence owing to the interesting change in biological properties, such as lipophilicity or metabolic stability, that occur when switching from hydrogen atoms to fluorine. As a result of this, and also because of the differing electronic effect it would have on the substrate for the hydroformylation reaction, a substrate incorporating fluorine was chosen. The substrate synthesis started from the commercially available 2,2-difluoropent-4-enoic acid and the initial attempt to obtain a tosyl-protected amine

focussed on first reducing the carboxylic acid to the alcohol; protecting the alcohol with a triflate group to turn it into a better leaving group; then a substitution with 4-methylbenzenesulfonamide would be carried out to furnish the desired amine substrate, Scheme 90. Owing to the volatility, and in some cases instability, of each of these intermediates then minimal purification was carried out until the final tosyl protected amine had been reached.



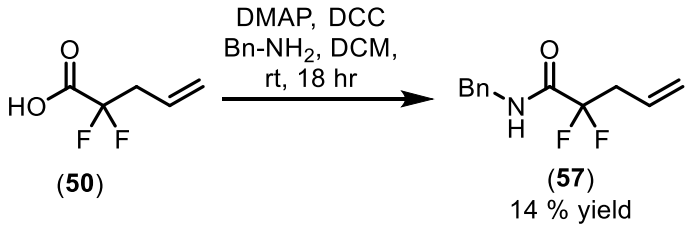
Scheme 90: Initial attempt for synthesis of fluorinated substrate.

Unfortunately, whilst the reduction was carried out with an acceptable conversion, the triflate protection of the alcohol was unsuccessful and no appropriate peak was visible in the ^{19}F NMR. Hence a second approach was attempted, to first form the amide through a standard amide coupling and then to reduce this to the amine, Scheme 91. The largest component that was isolated from the amide coupling was the N-acyl urea product, leaving the reaction for a longer length of time or carrying out the reaction at a higher temperature had no effect on increasing the amount of amide observed. On taking the amide through to the reduction step, no amine was ever isolated.



Scheme 91: Second proposed synthesis of substrate

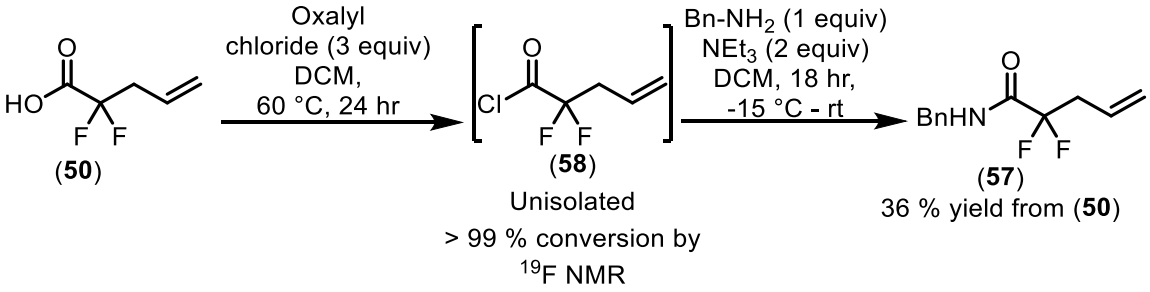
Carrying out the amide coupling reaction with benzylamine as opposed to 4-methylbenzenesulfonamide was predicted to be more successful owing to the higher nucleophilicity of benzylamine but still lead to the isolation of the N-acyl urea product as the largest component of the reaction, Scheme 92.



Scheme 92: Attempted amide coupling reaction

Hence an alternative synthetic route was considered: first the carboxylic acid would be turned into the acid chloride and then it would be reacted with the appropriate amine and the resulting amide would then be used as the substrate for the hydroformylation reaction. Again, owing to the volatility of the intermediate this was to be carried out as a one-pot procedure with minimal purification. Initially the synthesis of the acid chloride was attempted with thionyl chloride as the chlorinating agent but despite a prolonged reaction time there was no conversion to the acid chloride.

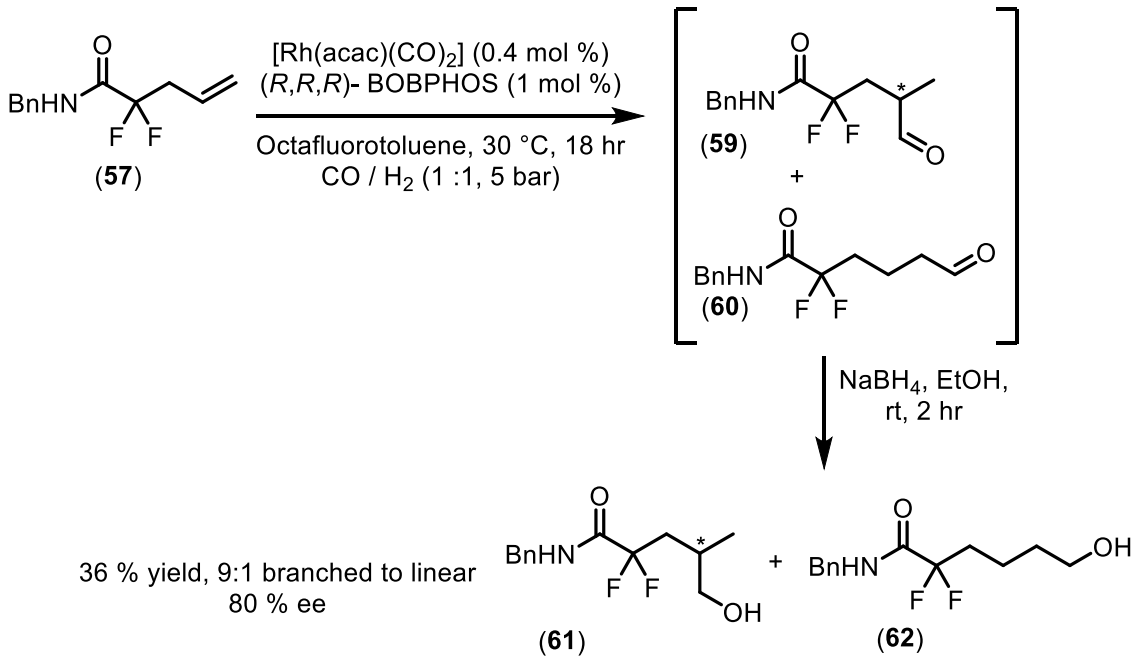
Oxalyl chloride was chosen as the next chlorinating agent and initially showed a conversion of 8 % after 4 hours, however leaving the reaction overnight gave no further conversion and dried the reaction out. These conditions were then improved upon by performing the reaction in a sealed microwave vial and increasing the equivalents of the oxalyl chloride, Scheme 93.



Scheme 93: Synthesis of 2,2-difluoropent-4-enoyl chloride

This allowed full conversion of the carboxylic acid to the acid chloride, which was unisolated and taken onto the next step without further purification. The amine component was chosen as benzylamine again and the final product isolated in 36 % yield with respect to the original amount of carboxylic acid.

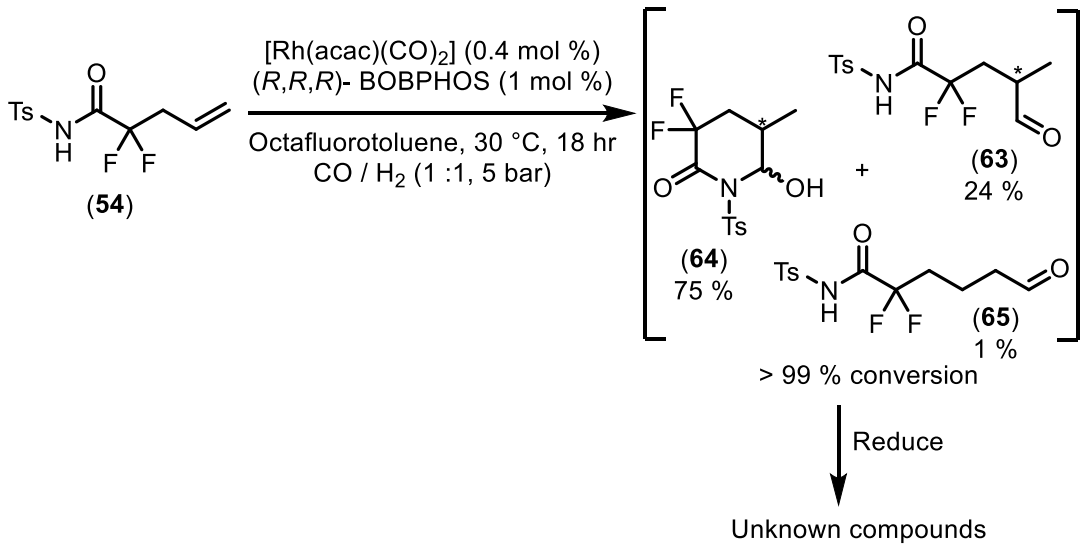
This was then subjected to the hydroformylation conditions identified in the optimisation of 3-methylpiperidine. Full conversion and a branched to linear ratio of 9:1 were observed, however there was no cyclisation and so the branched and linear aldehydes were reduced to the alcohols in a one-pot reaction with sodium borohydride, Scheme 94.



Scheme 94: Hydroformylation-cyclisation followed by one-pot reduction of N-benzyl-2,2-difluoropent-4-enamide

The racemic was prepared from a hydroformylation reaction with triphenyl phosphine as the ligand and then the enantiomeric excess determined by chiral HPLC. The use of triphenyl phosphine as the ligand was possible in this case since the electron withdrawing effect of the gem-difluoro group gives a higher branched to linear ratio than a similar substrate without this group.

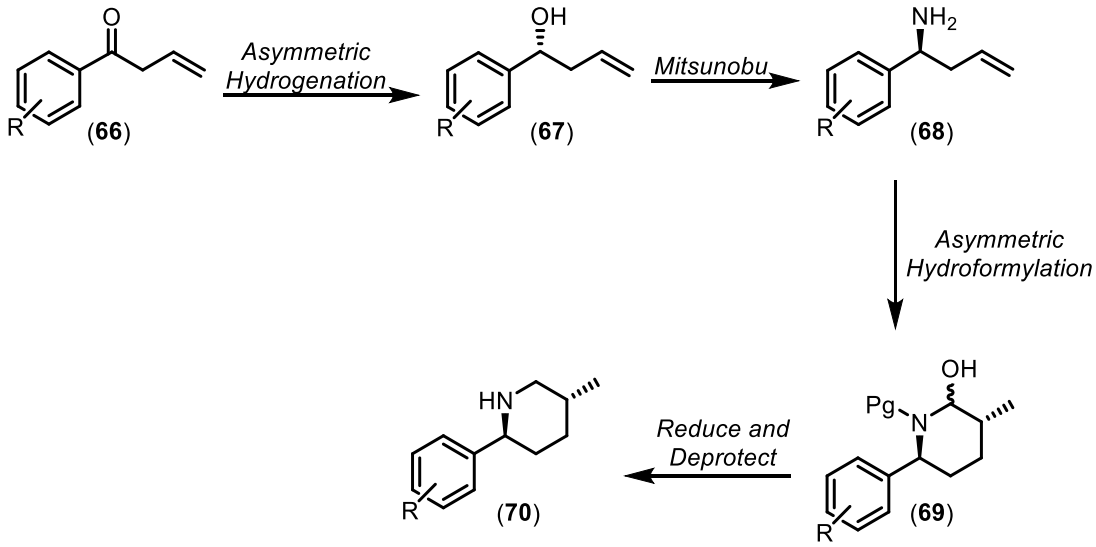
A tosyl protected derivative could be prepared by the same methodology as depicted in Scheme 94 in 16 % yield and then successfully hydroformylated to give excellent regioselectivity with a mixture of aldehyde and hemi-aminal branched products. Unfortunately, on attempting to reduce these products to the corresponding alcohol and piperidinone, the sample degraded into unidentifiable compounds, Scheme 95. As a result of this, without a stable sample reliable measurement of the enantioselectivity and full characterisation could not be undertaken.



Scheme 95: AHF of N-tosyl-2,2-difluoropent-4-en-1-amide

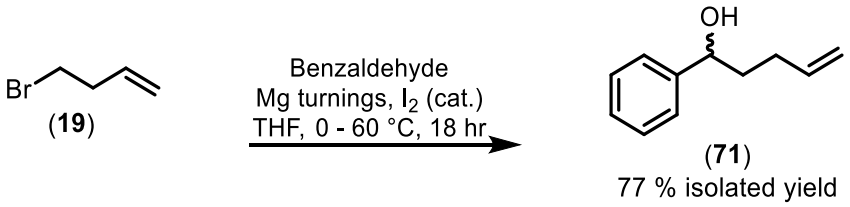
Synthesis of Enantiomerically Pure Substituted Substrates using Manganese Catalysed Reduction:

This synthetic route to substituted piperidines was initially identified by a previous PhD student but never optimised.[76] The suggested route is outlined below, Scheme 96.



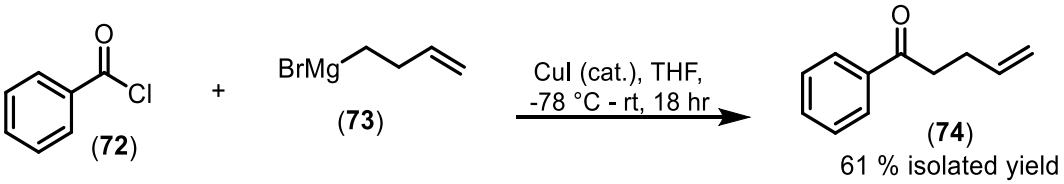
Scheme 96: Proposed methodology for synthesis of chiral piperidines

Work actually began by synthesising a racemic alcohol through a Grignard reaction, a commonplace reaction that is tolerant to a range of functional groups, since the racemic product offered a route to exploring the subsequent hydroformylation and other reactions without considering the enantioselectivity. This reaction proceeded with good yields from readily available starting materials, Scheme 97.[77]



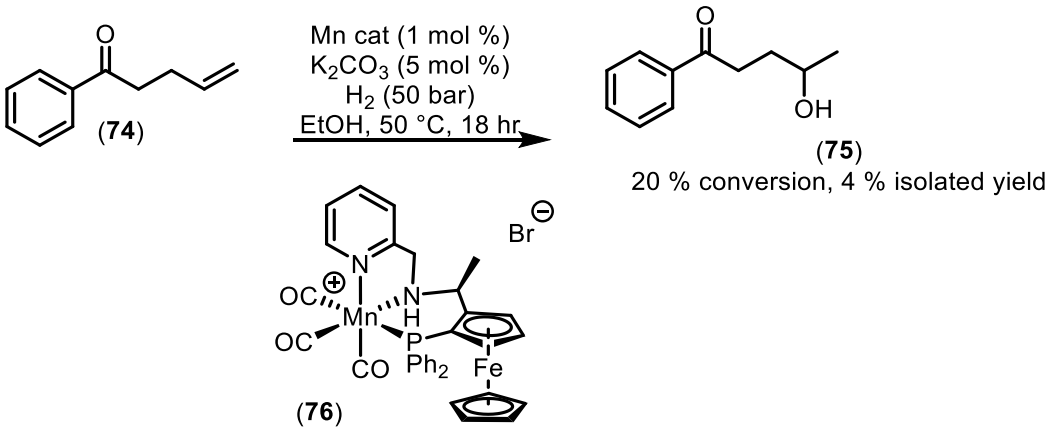
Scheme 97: Synthesis of racemic alcohol substrates

Next a route to the ketone was required and a Gilman's reaction was utilised to form the desired product from the previous bromoalkene used for the racemic alcohol, Scheme 98.[78] This Gilman's reaction was suitable to be scaled up to a 25 mmol scale with no issues.



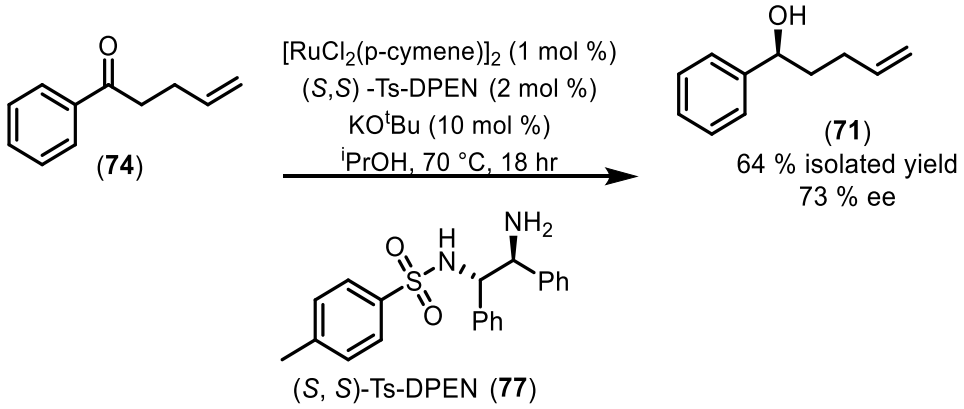
Scheme 98: Synthesis of ketone substrates

From here methodology was investigated to asymmetrically hydrogenate the ketone.[79] Manganese catalysts have now been shown in the literature to be as effective, or in some cases more, as precious metal catalysts, though use of higher catalyst loadings is often required. Not only because of the lower cost, the use of a manganese catalyst is also preferential to ruthenium as manganese is more abundant and also requires less stringent metal recovery from pharmaceutical processes; there is a higher ppm value tolerated within industry guidelines as it is not as harmful within the body. The Clarke group reported the first enantioselective hydrogenation of prochiral ketones in 2017 using a manganese catalyst that was developed in house with a *P*, *N*, *N* ligand. This catalyst was more active than achiral manganese catalysts at the time and was also successful in the hydrogenation of esters to alcohols, but had not been extensively studied for the reduction of unsaturated ketones. Initial attempts to perform an asymmetric hydrogenation of the ketone substrate used this manganese catalyst, compound (**76**), and hydrogen gas in an autoclave, Scheme 99.



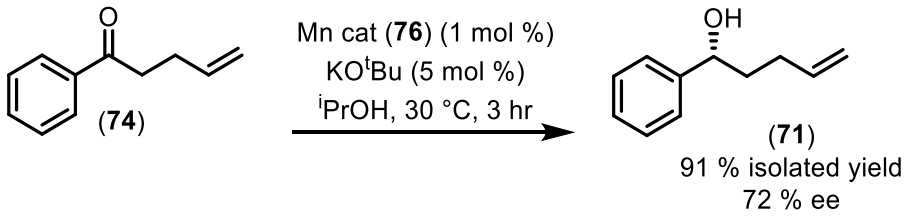
Scheme 99: Asymmetric Hydrogenation conditions

Low conversion to an undesired product was obtained and repeating this experiment lead to low conversion to the target molecule or no conversion at all. Hence no optimisation was carried out on this hydrogenation as significant improvements were envisaged with further development of the methodology. As an alternative asymmetric transfer hydrogenation (ATH) was attempted. This utilises a hydrogen source other than hydrogen gas, in this case from the isopropanol also used as solvent. Firstly, a Noyori ATH was considered since it was reliable and established, and this was undertaken with the following conditions, Scheme 100.[80]



Scheme 100: Noyori Asymmetric Transfer Hydrogenation conditions

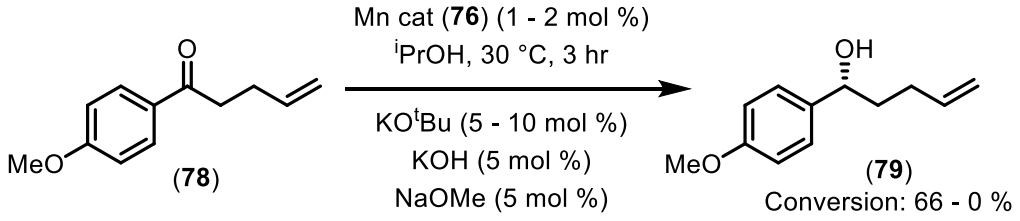
Once it was established that the substrate could undergo this transformation in good yields, a return to the manganese catalyst was undertaken and conditions for ATH that had been tested for with some other substrates were adapted for use with this substrate, Scheme 101.



Scheme 101: Manganese Asymmetric Transfer Hydrogenation Conditions

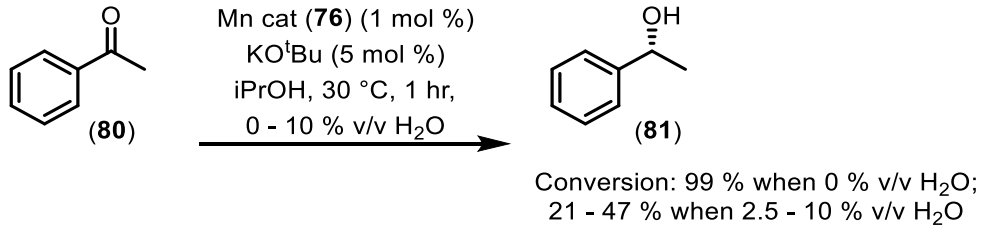
Since the manganese ATH was found to produce a comparable yield and enantiomeric excess as the Noyori ATH, this was considered when switching to the next substrate: 1-(4'-methoxyphenyl)pent-4-en-1-one.

This followed the same procedures as outlined above for the unsubstituted phenyl, and comparable yields were found in the synthesis of the racemic alcohol and the ketone. With the ATH however, the increased electron density at the carbonyl carbon meant that there was reduced activity and the conversion of the manganese catalysed ATH fell from >99 % to approximately 66 % by NMR. Optimisation was then attempted by considering the base and catalyst loadings, as well as the source of base, Scheme 102. However, as the reactions were carried out it was found that in some cases the reaction seemed to fail completely suggesting a problem with this substrate.



Scheme 102: Optimisation of conditions for Manganese ATH with methoxy substrate

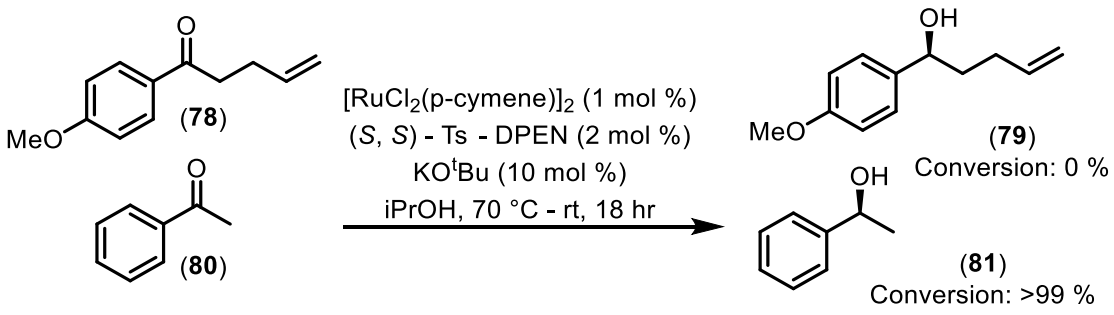
The complete lack of conversion on altering the conditions was unexpected. Initially it was considered that residual moisture was prohibiting formation of the active catalytic species and causing the failed reactions. In order to investigate the effect of water on the manganese catalysed ATH the following reactions were undertaken with acetophenone, Scheme 103.



Scheme 103: Effect of water spiking on ATH of acetophenone

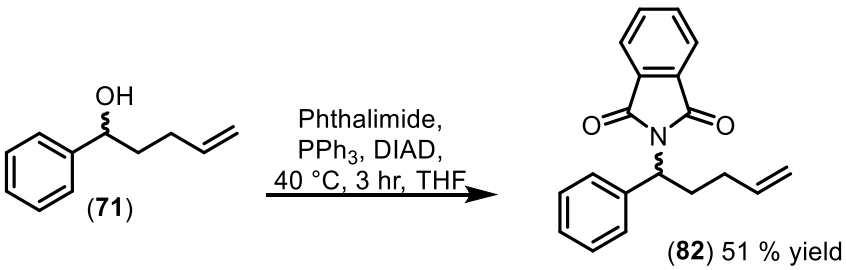
From these reactions it was determined that in completely dry conditions the reaction gave optimal conversion; but that water could be tolerated by the reaction up to 10 % v/v, albeit with a drop in the activity. Hence it appears that residual moisture is not the cause of the failed reactions and it is not yet clear why the ATH reaction with these alkenone substrates is less robust than other molecules. Subsequent to this work, other co-workers also found the manganese catalysed transfer hydrogenation, unlike the pressure hydrogenation, to be very substrate specific.[81]

The Noyori ATH of the methoxy substrate was attempted and it was found the conversions were also persistently low: between 8 – 17 % conversion by NMR. To determine if this was due to substrate inhibition or low activity of the substrate, a reaction containing a one to one mixture of methoxy substrate and acetophenone was undertaken and it was found that the acetophenone substrate underwent full conversion to the secondary alcohol, whilst the methoxy substrate remained unreacted, Scheme 104. This is therefore most consistent with the inhibition caused by the pentene chain; rather than poisoning of the catalyst.



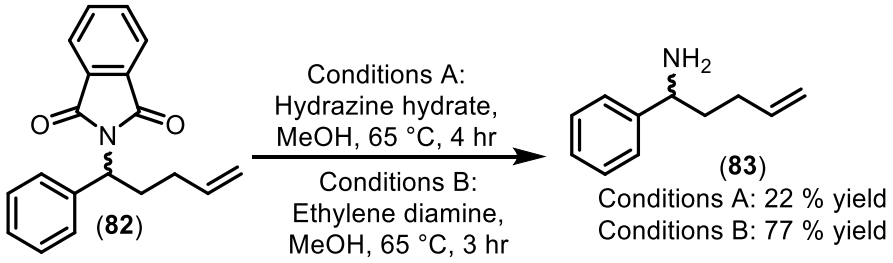
Scheme 104: Substrate comparison of Noyori ATH

For the formation of chiral amines, a Mitsunobu reaction with phthalimide on an enantioenriched alcohol would generate the protected amine without any loss of stereochemistry. It was found that the initial test reaction with the racemic alcohol, carried out on a small scale (0.5 mmol), was successful but subsequent reactions were carried out on a larger scale and these reactions did not yield good results initially.[82] By carrying out an optimisation it was found that heating the reaction to 40 °C provided a more reliable yield and pushed the reaction to completion within 3 hours, Scheme 105.



Scheme 105: Mitsunobu reaction conditions

From here, the deprotection was first investigated with hydrazine hydrate and refluxing in methanol.[82] However, low yields meant the reaction required optimisation. In addition, it is preferable to use greener reagents than hydrazine hydrate and pleasingly ethylene diamine was found to give good results for this deprotection, Scheme 106.[83]



Scheme 106: Deprotection of phthalimide group

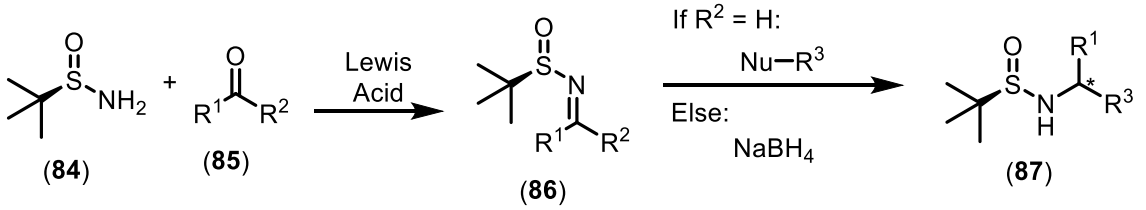
Since the manganese hydrogenation of the desired substrate failed to facilitate an enantioenriched alcohol that could be used for the formation of the amine, a different method for the preparation of these substrates was considered.

Ellman's Chiral Auxiliary for Chiral Substituted Substrates:

In an alternative method, the use of Ellman's chiral auxiliary to induce another chiral centre has long had literature precedent. First reported in 1999, Ellman's chiral auxiliary has had a strong presence since then both in academia and industry for the synthesis of chiral amines.[84] It's prevalence stems from the ease of access of the commercially available tert-butanesulfinamide, available as either enantiomer and available reasonably cheaply, as well as the tolerance of different methods to a wide range of approaches and functional groups. Furthermore, that the sulfinamide group serves both to induce chirality and as a protecting group gives it a dual purpose that makes it even more cost and time efficient within multistep synthesises.

The primary method of utilising the tert-butanesulfinamide group is to react it with an aldehyde or ketone, forming an imine intermediate. These intermediates are often stable enough to be isolated before being reacted with a range of nucleophiles which, in the presence of the tert-

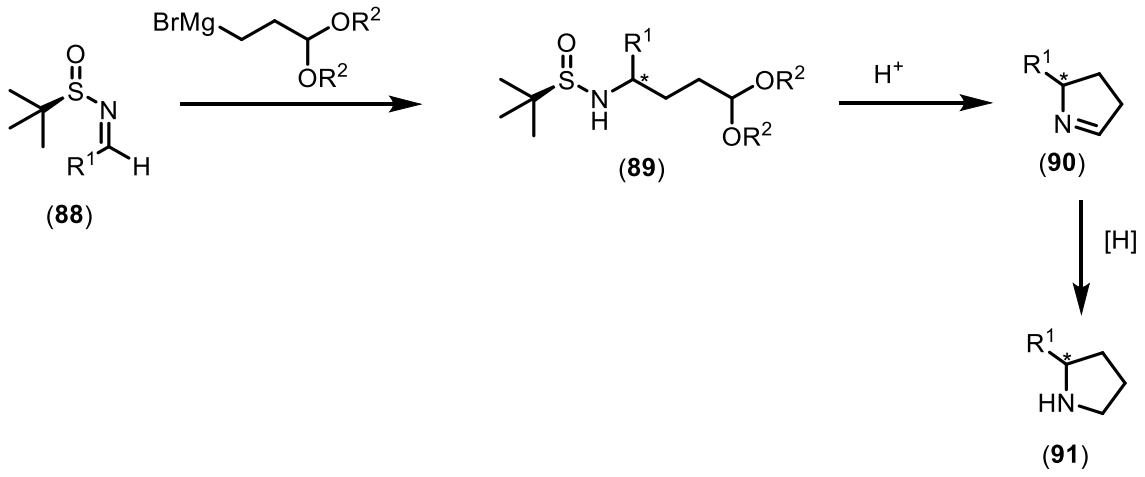
butanesulfinamide group as a chiral directing agent, proceed with high diastereoselectivity, Scheme 107.



Scheme 107: Schematic of use of Ellman's chiral auxiliary with aldehydes or ketones

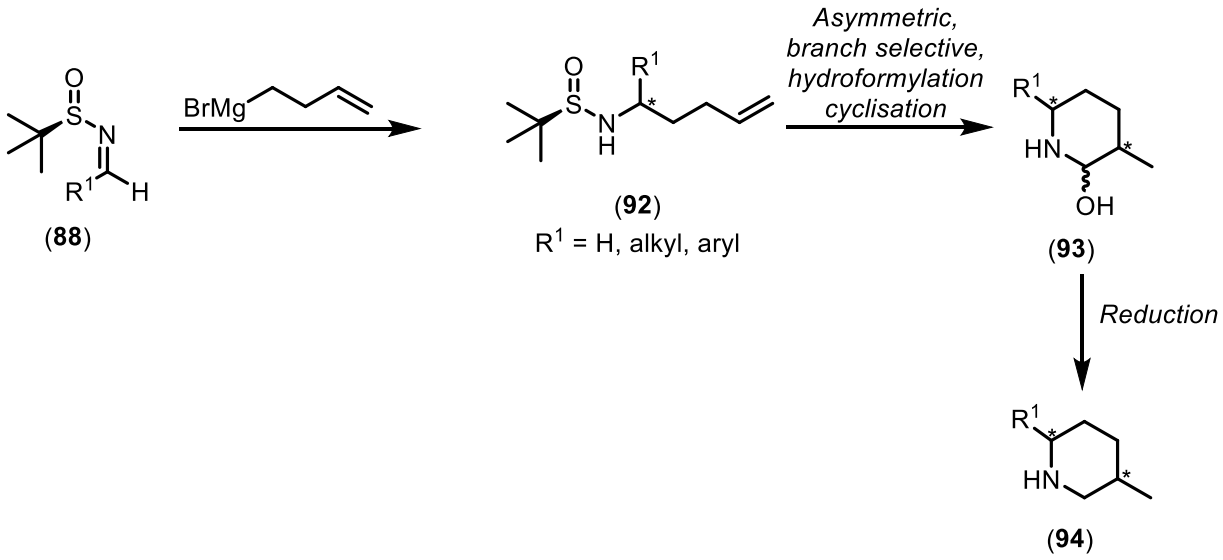
There have also been studies on cleavage and recyclability of the tert-butanesulfone group, which can then be reacted again to regenerate the tert-butanesulfinamide with no loss of enantiopurity. Whilst Ellman's chiral auxiliary has been used for the synthesis of chiral alcohols, esters, amides and carboxylic acids, here the interest was in using it specifically for the generation of chiral amines.

One of the general approaches for using tert-butanesulfinamide to form a chiral centre in an amine is to form an imine and then add in a Grignard reagent, ideally with a high diastereomeric ratio as induced by the tert-butanesulfinamide group and under low temperatures. In 2005, this approach of using Ellman's chiral auxiliary was used to synthesis 2-aryl pyrrolidines through the deprotection of an acetal group, leading to attack by the nitrogen to form the pyrrolidine core, Scheme 108.[85]



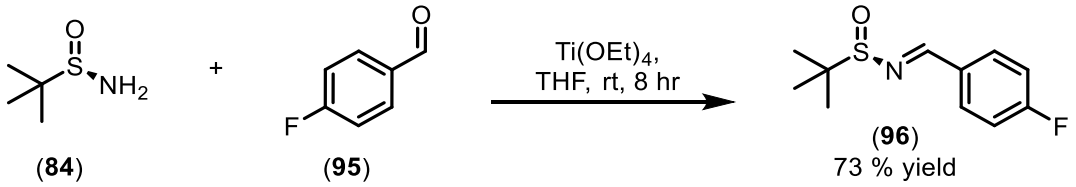
Scheme 108: Literature precedent for methodology of forming chiral substituted pyrrolidines.

Using the hydroformylation-cyclisation methodology, it would be possible to add in another chiral centre through branched, asymmetric hydroformylation, Scheme 109. This would also use a simpler, more readily available alkene Grignard reagent compared to the acetal used above in Scheme 109. In addition, the introduction of an extra carbon through the AHF reaction would mean the final product would be a piperidine rather than a pyrrolidine heterocycle core.



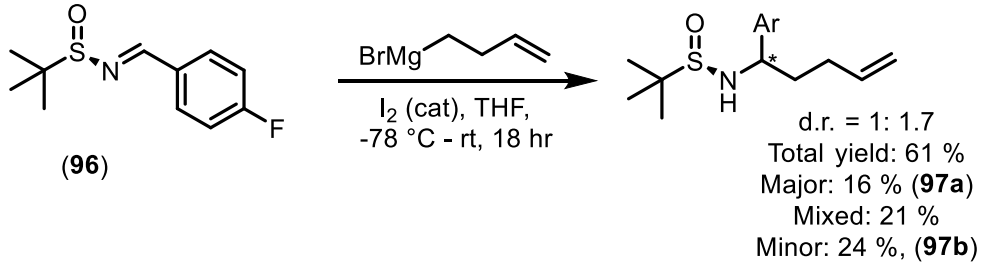
Scheme 109: Proposed route to formation of substituted chiral piperidines.

Work began by reaction of the (*S*)-*N*-tertbutanesulfinamide with 4-fluorobenzaldehyde to give an imine, Scheme 110. This proceeded with good yields and was isolated without degradation of the reactive imine species.[86]



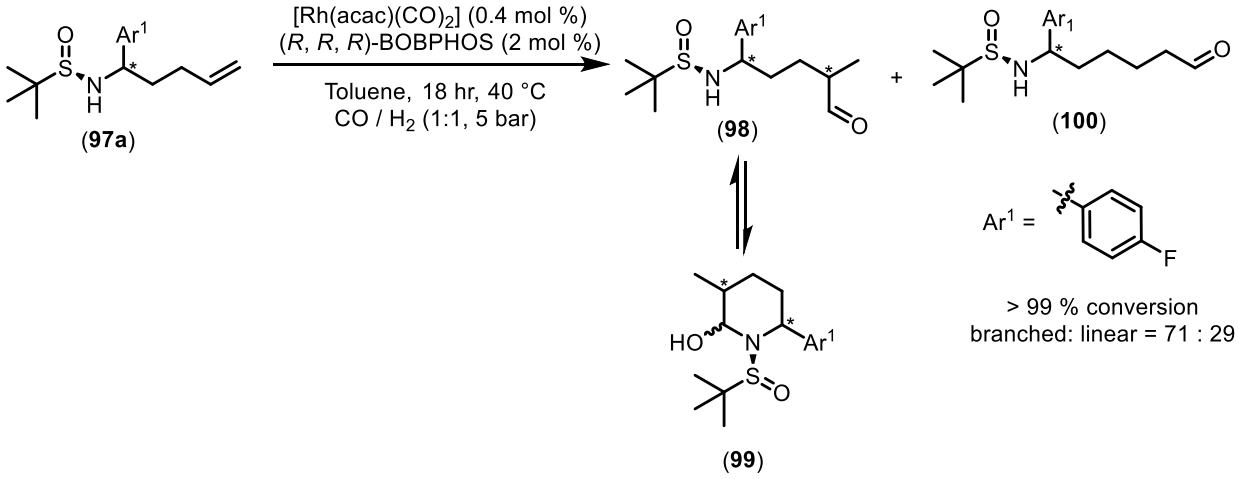
Scheme 110: Formation of N-tertbutanesulfinimine.

This imine product was then used with a Grignard reaction to furnish the intermediate with the butene chain for the desired diastereomer, Scheme 111.[85] The diastereoisomer ratio, which was lower than expected, was determined from the crude NMR and the diastereomers separated by silica column chromatography. Literature precedent suggests that the major diastereomer is expected to bear the same stereocentre as the sulfinamide group, here it would be (*S*)- in each case.



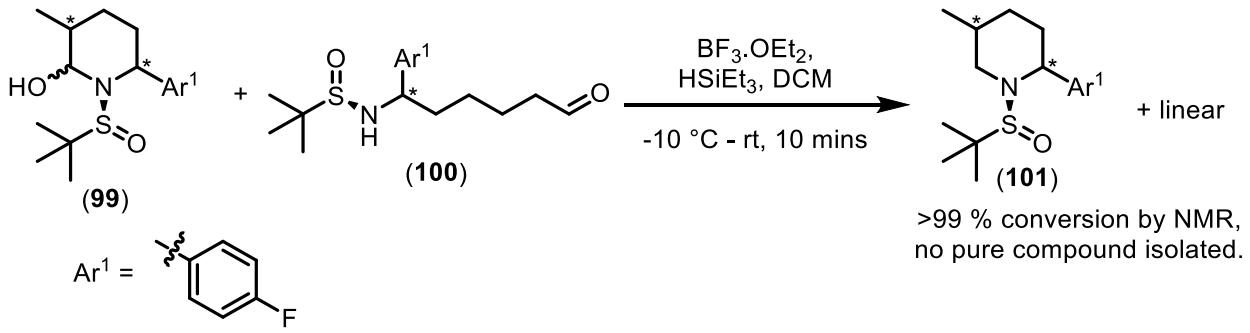
Scheme 111: Grignard reaction for formation of substrate.

The major diastereomer was then hydroformylated using the prior established conditions, Scheme 112. It was found that full conversion of starting material was obtained and it was observed in the crude NMR that the branched aldehyde preferentially cyclised to give the 6-membered hemi-aminal, whilst the linear remained uncyclized as the aldehyde.



Scheme 112: Asymmetric, branch selective hydroformylation using Rh/ BOBPHOS catalyst.

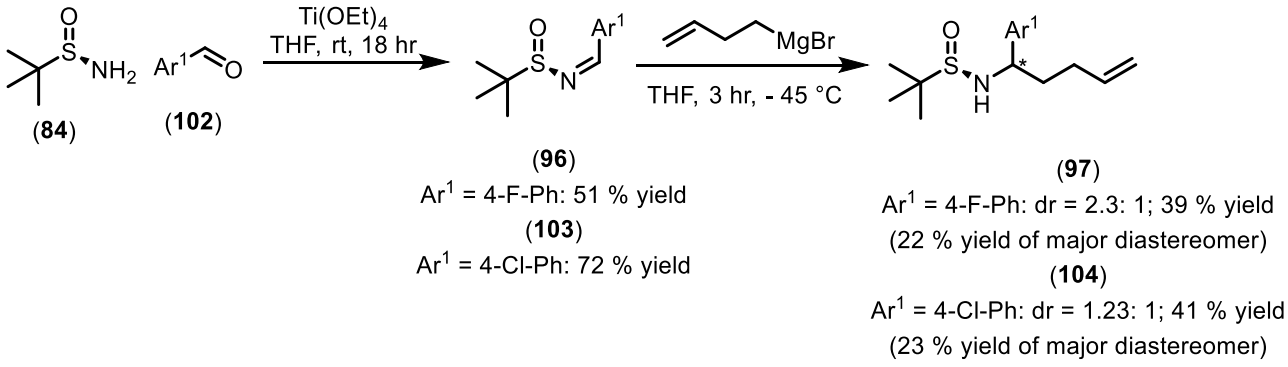
Next the hemi-aminal was reduced using conditions that had been identified in the literature for similar substrates, Scheme 113.[66]



Scheme 113: Reduction of hemiaminal to piperidine.

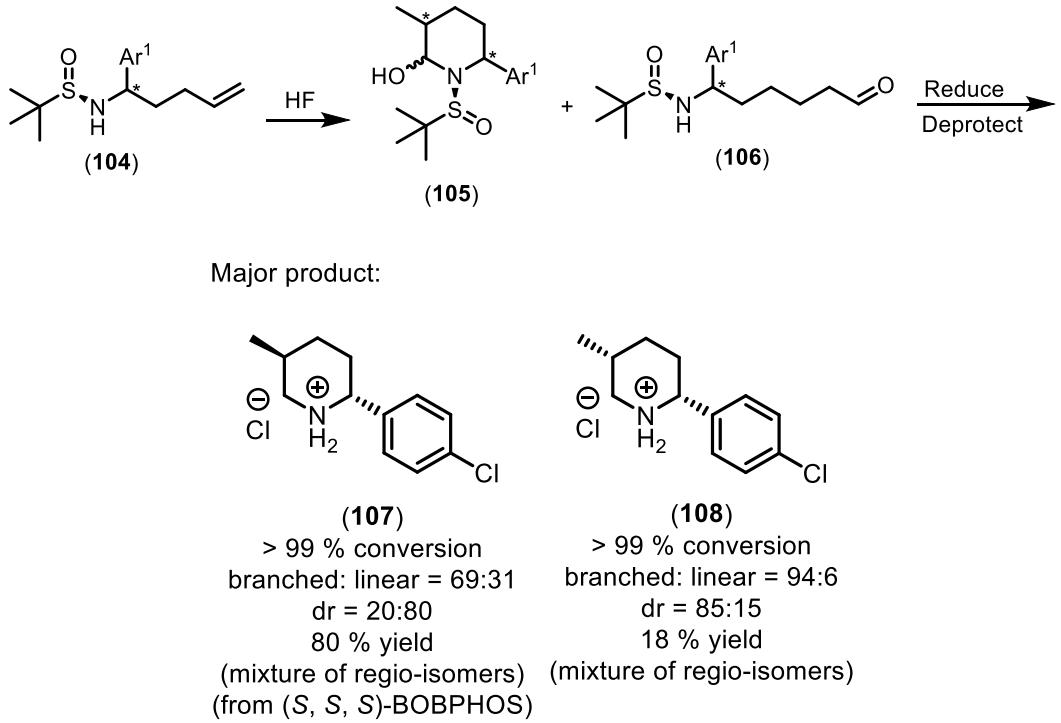
Upon attempts to isolate this compound however, it was found that the product was strongly sticking to the silica and a very low yield was obtained. Eventually it was determined that the protecting group was being lost from the nitrogen within the reduction reaction conditions and potentially also by purification.

Other aryl substituents were synthesised and low diastereoselectivity was still observed for the Grignard addition step, Scheme 114. Despite attempts to optimise the reaction no improvements could be made.



Scheme 114: Initial synthesis of arylaminoalkenes

One of these two compounds was then reacted under the optimised AHF reaction conditions. This was followed by a one-pot reduction and deprotection, finishing at the chloride salt of the piperidine. The results are outlined below, Scheme 115.



Scheme 115: Hydroformylation, reduction and deprotection of substituted substrates.

To assist with peak assignments the 4-chlorophenyl substituted substrate was hydroformylated with the opposite enantiomer of BOBPHOS to give predominantly the opposite diastereomer. Interestingly, though only a small difference in the diastereomer ratio was observed, there was a large difference in the branched to linear regioselectivity. This indicates that there is some favourable matching effect between the enantiomer of ligand and the enantiomer of the substrate.

Summary

In this chapter it has been established that the correct choice of protecting group on the nitrogen is key to obtaining the cyclic, stable hemi-aminal intermediate through regio- and enantio-selective

hydroformylation-cyclisation reactions. The use of a sulfonamide protecting group prohibits elimination of water to form the enamine, thereby losing the β-stereocentre, whilst still being nucleophilic enough to avoid ring opening to the aldehyde product. Decreasing the electron density at the nitrogen by introduction of an adjacent carbonyl group still gave full cyclisation of the branched regioisomer; further decreases by the introduction of a difluoro- group gave unstable products with a tosyl protecting group or the ring opened product with a benzyl protecting group. Owing to the complexity of the crude reaction mixture, it was necessary to carry out a one-pot reduction in all cases before reliable analysis could be obtained.

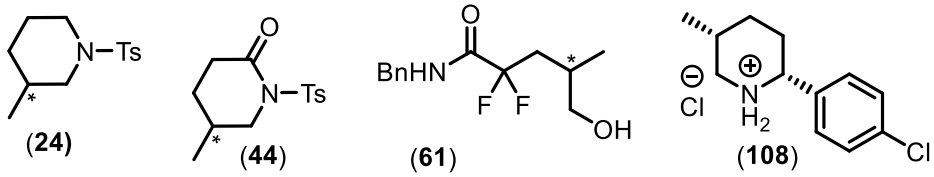


Figure 3: Selected compounds from this chapter.

The use of an ATHF gave poor conversion and enantioselectivity on the standard substrate. Experiments exploring the reactivity of the hemi-aminal intermediate yielded no promising results: the literature experiments could be repeated but expanding this to other silanes gave only the enamine. Similarly, a reduction of the hemi-aminal intermediate to an amine with hydrogen gas and a ruthenium catalyst gave only the enamine.

The synthesis of unsaturated amines from chiral alcohols was studied. Asymmetric transfer hydrogenation of this substrate proceeded unreliably under conditions that work well for related saturated substrates and through investigations it was found that the likely cause of this was due to coordination of the pentenyl chain to the catalyst, which prohibited conversion of the ketone to the alcohol. Asymmetric pressure hydrogenation was also found to be unreliable in this instance and since the Mitsunobu reaction was not overly efficient, a chiral auxiliary approach was used. The use of Ellman's chiral auxiliary as a protecting group eventually allowed for the synthesis of substituted piperidine rings. This synthesis was not as facile as described in the literature with disappointing diastereomeric ratios initially obtained, but the product could undergo AHF to yield a substituted piperidine with high diastereoselectivity when matching the enantiomer of catalyst to enantiomer of substrate. A one-pot reduction and deprotection was required to arrive at a stable product that could then be accurately analysed.

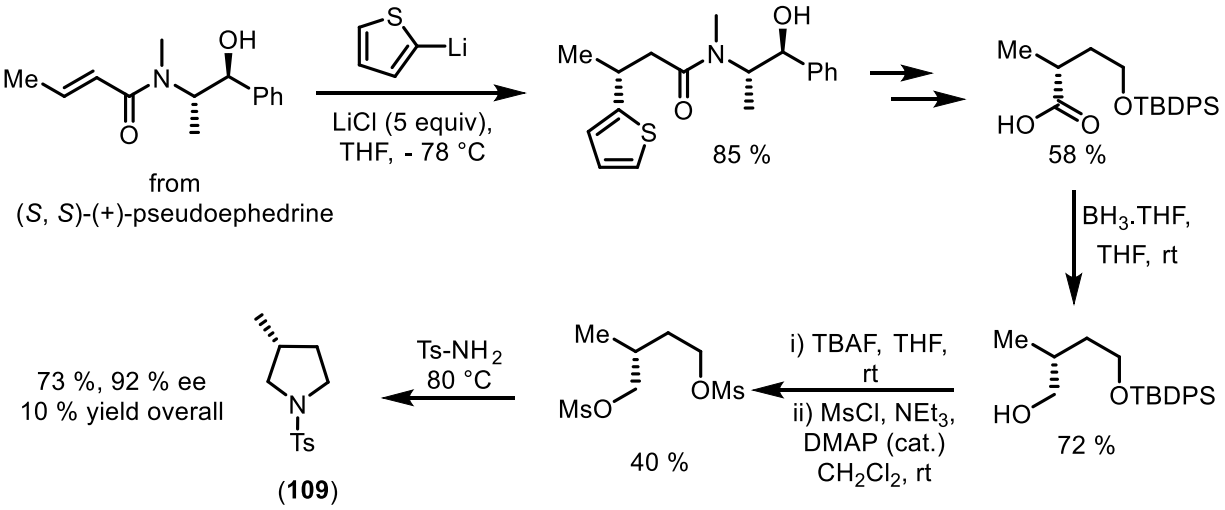
A small selection of chiral piperidines were made with high enantioselectivity or diastereoselectivity and good regioselectivity, Figure 3. These promising results led us to seek to extend the methodology to the formation of 3-methylpyrrolidine and this is discussed in chapter 3.

Chapter 3: Chiral Pyrrolidines from Asymmetric Hydroformylation-Cyclisation Reactions

Introduction:

In the previous chapter the synthesis of chiral piperidines through hydroformylation-cyclisation reactions was discussed. In this chapter, the extension of that methodology to the synthesis of chiral pyrrolidines is demonstrated, in addition to the development of a hydroaminomethylation reaction specifically for 1,1-alkenes as an approach to a natural product.

Forming a stereocentre α to an amino group is well known and can be done in a number of ways, such as additions to imines or imine hydrogenation, yet forming a stereocentre β to the nitrogen has far fewer efficient reactions. Strategies using directing groups have enabled selective functionalisation of this position, whilst other methods rely on enantiopure starting materials. It was envisaged that the methodology described in chapter 2 would be extendable to making pyrrolidines with β-methyl centres. Of particular interest would be 3-methylpyrrolidine since 2-methylpyrrolidine is synthesised relatively easily from cheap proline and is widely used as a building block in medicinal chemistry.[87] It would be envisaged that should it be available, 3-methylpyrrolidine would also be used in a similar way, but there are no efficient, cheap methods to make it. A literature synthesis of *N*-tosyl-3-methylpyrrolidine takes place over more than 6 steps from an enantiopure starting material that had to be synthesised and arrives at the chiral product in 10 % yield for the (*R*)-isomer, Scheme 116.[88]

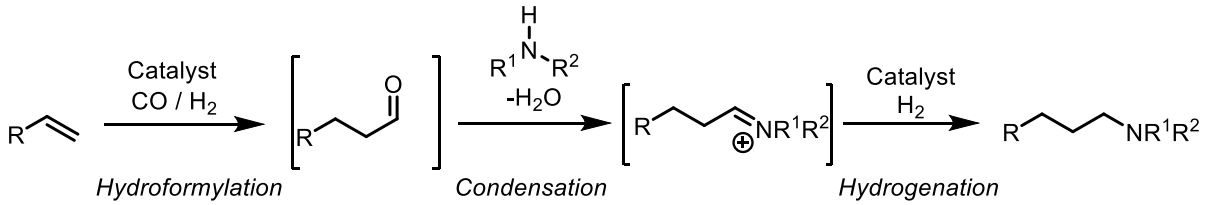


Scheme 116: Literature preparation of 3-methylpyrrolidine.[88]

This demonstrates a clear need for more efficient methodology for the formation of chiral 3-methylpyrrolidine and efforts to do this through AHF-cyclisation will be discussed here. The proposed route to compound (**109**) would be a two-step synthesis from cheap, fundamental starting materials.

In addition to this target, also of interest was using this product in a very direct natural product synthesis using a hydroaminomethylation of 3-methylpyrrolidine with 1,1-alkenes.

As discussed in chapter 1, hydroaminomethylation reactions involve dual catalytic cycles as the catalyst first carries out the hydroformylation reaction on the alkene, then when the resulting aldehyde is attacked by the amine that is present in solution to form either an imine or an enamine, the same catalyst carries out the hydrogenation of this intermediate to give the final amine product. This atom efficient reaction has only water as the by-product but requires careful control to achieve the desired chemo-, regio- and enantioselectivity, Scheme 117.



Scheme 117: Synthetic steps involved in a hydroaminomethylation reaction

1,1-alkenes are available from feedstock chemicals and biomass but are often underutilised in synthetic methodology due to specific challenges associated with their increased steric hindrance when compared to terminal, monosubstituted alkenes. For hydroaminomethylation reactions, the regioselectivity is close to completely selective for the formation of the linear aldehyde. However, control of the enantioselectivity for this newly formed stereocentre is often low. In recent years more ligands have been designed that specialise in formation of this stereocentre, including the use of bulky chiral ligands or directing groups on the alkene.[61, 62, 63, 65, 69] There still exists scope for exploring new ligands that efficiently catalyse this reaction and provide the desired amine with high selectivity. In particular, there was interest in combining the use of the AHF-cyclisation methodology for the formation of 3-methylpyrrolidine with a HAM of a 1,1-disubstituted alkene for the efficient and selective formation of a natural product isolated from ant venom, Leptothoracine, Figure 4. This chapter contains a discussion of developing AHF-cyclisation for protected 3-methylpyrrolidine; a synthetic route to the pyrrolidine component of the drug Elexacaftor and lastly investigations into hydroaminomethylation of 1,1-disubstituted alkenes as a route to Leptothoracine.

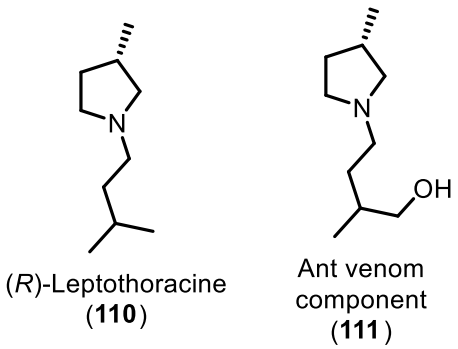
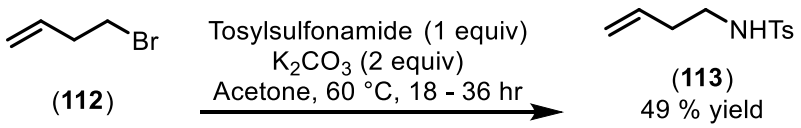


Figure 4: Possible ant venom targets

Initial Studies of Hydroformylation-Cyclisation Reaction:

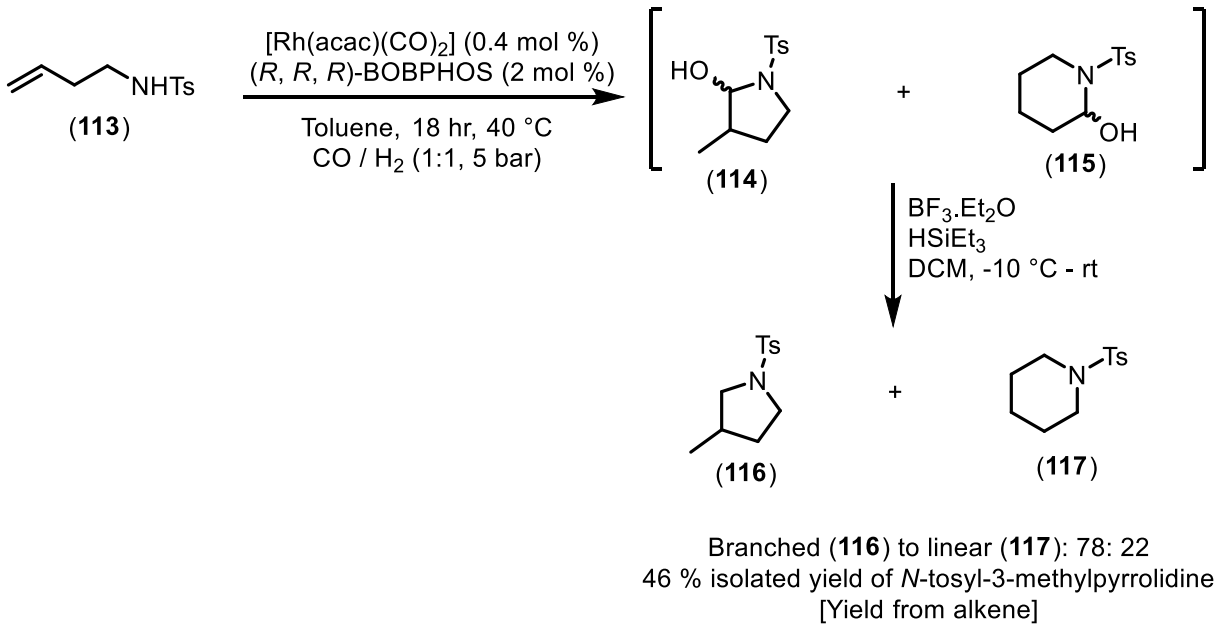
An alkene substrate was required in order to form small enantio-enriched 3-methyl-5-membered nitrogen heterocycles. Previously, a tosyl-protecting group had been established as the best choice for this methodology and was again chosen here. A benzoyl carbamate protecting group was briefly investigated but, as is discussed in chapter 2, was found to deprotect under the reaction conditions for the reduction of the hemi-aminal to pyrrolidine. The first substrate was prepared according to known literature procedures, Scheme 118.[89]



Scheme 118: Synthetic route to N-(but-3-en-1-yl)-4-methylbenzenesulfonamide

Hydroformylation of the substrate was carried out using the conditions previously used for the *N*-(pent-4-en-1-yl)-4-methylbenzenesulfonamide and again complete conversion of the alkene starting material was observed. As expected, no aldehydes were observed in the crude NMR mixture but only the hemi-aminals. The diastereomers and conformers remained and since it was difficult to assign peaks from the crude, attempts were made to isolate these intermediates. Again, elimination of water was observed on the column, despite treating the silica with triethyl amine prior to loading in an attempt to neutralise the acidity, but some samples of the linear and branched hemiaminal were recovered.

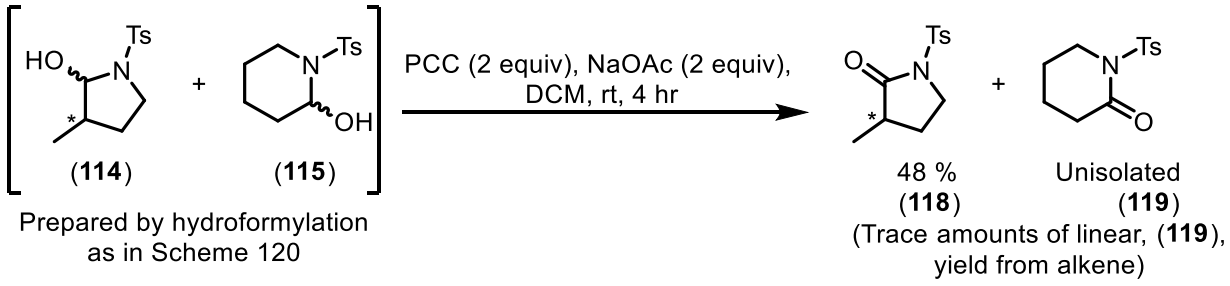
Since these compounds were so reactive that isolation was proving difficult, following literature procedures for similar compounds, a one-pot reduction of the hemi-aminal was attempted at the end of the hydroformylation-cyclisation reaction, Scheme 119.[66]



Scheme 119: Hydroformylation and reduction

This proceeded smoothly and after a work-up had been performed on the reaction, an accurate measurement of the conversion and the branched to linear ratio could be determined. A clean sample of both the *N*-tosyl-3-methylpyrrolidine and *N*-tosylpiperidine were recovered after purification by column chromatography. Since the regioselectivity is determined by the formation of the branched aldehyde over the linear, the terms branched and linear here apply to describing the ratio of the pyrrolidine and piperidine rings respectively.

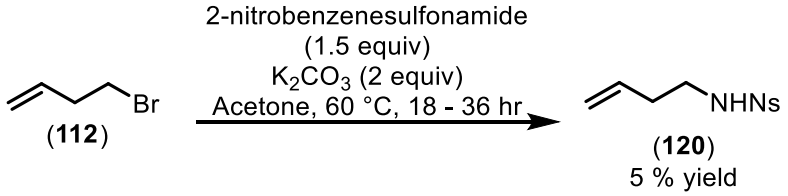
In addition, oxidising the hemi-aminals to the corresponding pyrrolidinones and lactams was investigated, Scheme 120. The conditions here again were based on literature precedent and the reaction proceeded as expected.[66] Isolation of the compounds, as indicated in the literature, proved to be more complex for the pyrrolidinones than for the pyrrolidines owing to the difficulty of removing PCC from the reaction mixture.



Scheme 120: Oxidation conditions for crude hydroformylation reaction mixture.

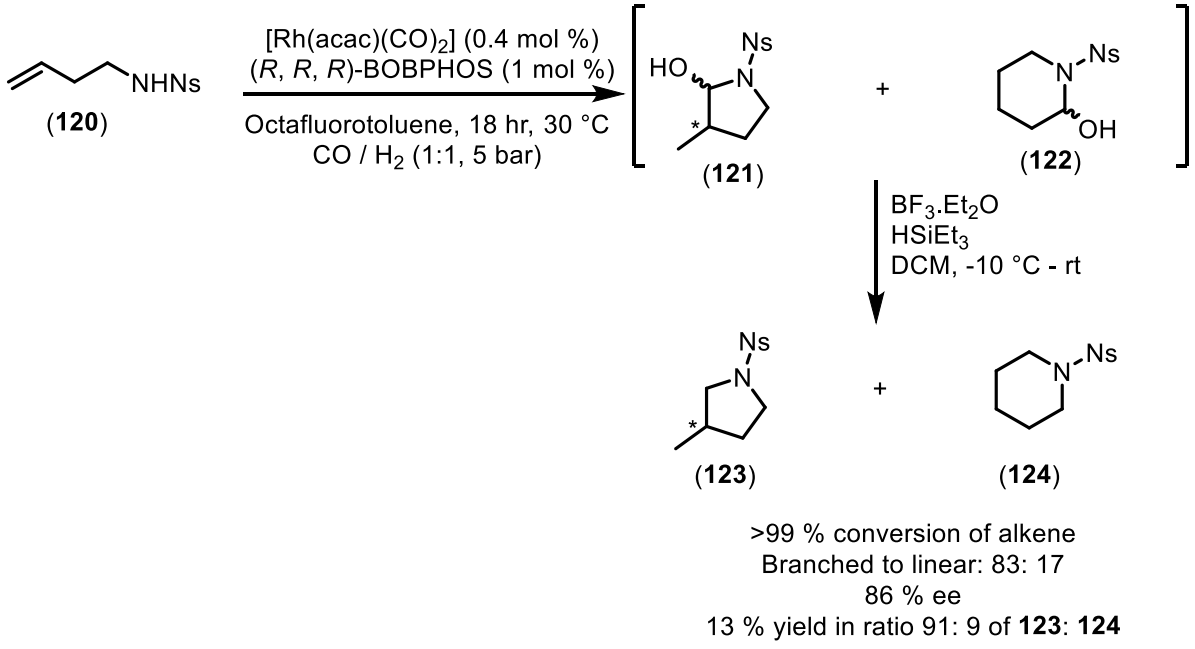
A nosyl protecting group was also investigated since it is known to be easier to deprotect than the tosylate protecting group. Initial attempts to synthesise the substrate using the previous route that

had synthesised the tosyl protected substrate was found to give approximately 15 % conversion of the 4-bromo-1-butene starting material and of the 15 % conversion, 10 % was to the double alkylated product whilst 5 % was to the desired target material, Scheme 121.



Scheme 121: Initial synthesis of N-(but-3-en-1-yl)-2-nitrobenzenesulfonamide

Enough material was obtained to carry out a hydroformylation-cyclisation reaction and this gave full conversion of the alkene to the desired hemi-aminal product which was then reduced *in-situ* to give the protected 3-methylpyrrolidine, Scheme 122. Similar regioselectivity to the tosyl protecting group was observed and in this case the reduced products could be analysed by chiral HPLC. Again, owing to the low formation of branched product when using triphenylphosphine to prepare a racemic sample of *N*-nosyl-3-methylpyrrolidine, the HPLC method was developed by using opposite enantiomers of compound (**123**) prepared by using opposite enantiomers of BOBPHOS.



Scheme 122: Hydroformylation-cyclisation reaction of N(but-3-en-1-yl)-2-nitrobenzenesulfonamide

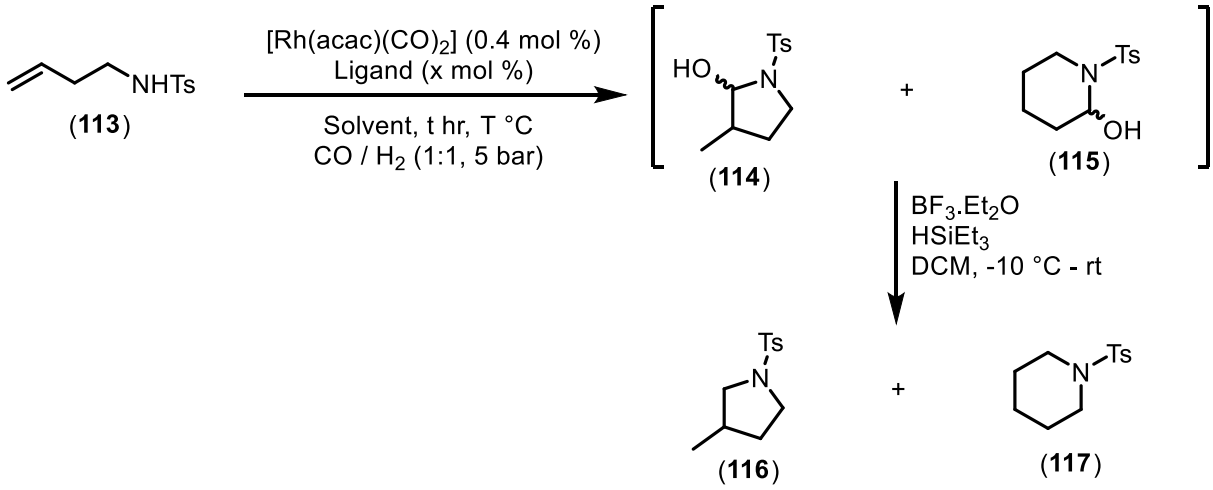
Development of a Synthetically Useful Method for Protected 3-Methylpyrrolidine

Optimisation

As mentioned in the previous section analysing the hydroformylation reaction by ^{1}H NMR after the pressure had been released from the autoclave proved difficult due to the overlapping peaks and mixtures of diastereomers as well as regioisomers. Due to this, to obtain reliable results on the

conversion of the alkene starting material and the regioselectivity of the reaction it was necessary to reduce the hydroformylation-cyclisation mixture and then carry out measurement of the conversion of alkene and the branched to linear ratio by ^{1}H NMR. Utilising the tosyl protecting group, since this had been shown to give full conversion to the hemi-aminal and be stable to reducing conditions afterwards, the optimisation of the hydroformylation conditions was carried out.

First, different ligands were analysed. Rh/ triphenylphosphine is often used in hydroformylation reactions at more forcing conditions than the temperature and pressure used for Rh/ BOBPHOS, which is highly reactive under mild conditions. Rh/ triphenylphosphine normally gives a modest to good linear regioselectivity, though this is dependent on the substrate. A rhodium catalyst derived from triphenylphosphine was used for the hydroformylation of *N*-(3-buten-1-yl)-4-methylsulfonamide and as predicted gave predominantly the linear product with a small amount of racemic branched product. From here the conditions were investigated as in the table below, Table 3.



[a] Syngas pressure at 20 bar. [b] Conversion determined by amount of alkene compared to amount of A and B in ^{1}H NMR after reduction. [c] Obtained by chiral HPLC on AD-H column of 3-methylpyrrolidinone. [d] Performed on 3 mmol scale. [e] HPLC performed on samples prepared in a separate hydroformylation to the mixture that was reduced. [f] Purification performed by recrystallisation.

Ligand	Ligand Loading (mol %)	Solvent	Temp. (° C)	Time (hr)	Conversion (%)[b]	Isolated yield of (116)	Branched: Linear	ee[c]
PPh_3 [a] (20 bar syngas)	2.0	Toluene	50	6	> 99 %	4 %	14: 86	5
(*S*, *S*)-Ph-BPE	1.0	Toluene	40	18	n.d.	n.d.	32: 68	n.d.
(*R*, *R*, *R*)-Bobphos	0.5	Toluene	40	18	> 99	n.d.	60: 40	n.d.
(*R*, *R*, *R*)-Bobphos	1.0	Toluene	40	18	> 99	54 %	70: 30	79 [e]
(*R*, *R*, *R*)-Bobphos	2.0	Toluene	40	18	> 99	69 % [d]	81: 19	79[c, e]
(*R*, *R*, *R*)-Bobphos	2.0	Octafluoro-toluene	40	18	> 99	n.d.	85: 15	89
(*R*, *R*, *R*)-Bobphos	2.0	Toluene	20	18	54	n.d.	78: 22	n.d.
(*R*, *R*, *R*)-Bobphos	2.0	Octafluoro-toluene	30	18	> 99	n.d.	89: 11	85
(*R*, *R*, *R*)-Bobphos	1.0	Octafluoro-toluene	30	18	> 99	49 % [f]	87: 13	n.d.

Table 3: Optimisation of hydroformylation-cyclisation reaction for N-tosyl-3-methylpyrrolidine

As discussed previously, Ph-BPE is a privileged ligand over a variety of reactions and is commonly used in hydroformylation reactions for introducing enantioselectivity for substrates which have an inherent preference for forming the branched regioisomer. Investigations using a rhodium catalyst derived from Ph-BPE with this substrate led to the linear product predominating, entry 2. This control experiment therefore successfully establishes the unique nature of the Rh/ BOBPHOS catalyst to

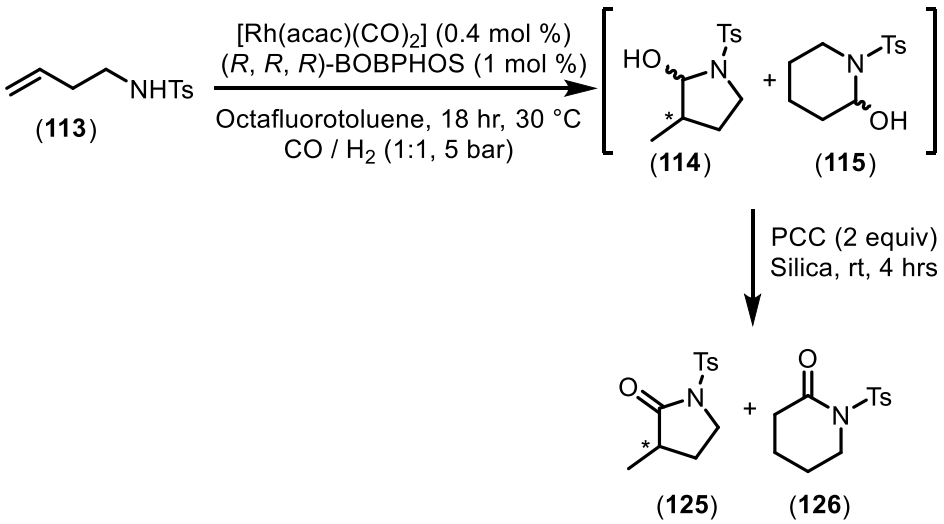
deliver branched products from unbiased alkenes and that this substrate shows a stronger tendency for linear products using other catalysts.

Next attention was turned to the ligand loading of the reaction. Previously in the group conditions identified for the synthesis of the nemonoxacin intermediate had found an optimum ligand to rhodium precursor ratio of 2 mol % to 0.4 mol % for the highest branched regioselectivity, yet here it was found that the ligand loading could be dropped to 1 mol % with minor losses of regioselectivity. Dropping the ligand loading further to 0.5 mol % lead to large losses of regioselectivity, suspected as a result of the unselective rhodium complexes arising from the uncomplexed rhodium precursor catalysing the hydroformylation reaction. A 69 % yield of compounds (**116**) and (**117**) in the ratio 90:10 could be isolated by column chromatography, entry 5.

The temperature could be moderately lowered from 40 °C to 30 °C which improved the regio- and enantioselectivity without loss of activity. Dropping the temperature further to 20 °C lowered the activity too much and so inhibited conversion, leading to incomplete reaction after 18 hours.

Next the solvent was changed from toluene to octafluorotoluene. A previous group member had investigated the use of fluorinated solvents with Rh/ BOBPHOS catalysts and found they favourably affected the regioselectivity.[90] Investigations by chemists were prompted by an interest owing to a *Science* publication in 1966 that discussed the superior use of fluorocarbons as oxygen storage for the submersion of intact mice and cats.[91] Fluorocarbons were found to be suitable for the solvation of oxygen and carbon dioxide, thus chemists looking to use gases in their homogeneous reactions were curious to use fluorinated solvents to see if this may improve the solubility of the gases. It is difficult to ascertain if this is the effect that octafluorotoluene is having in this AHF, but it is certain that it improves the branched regioselectivity.

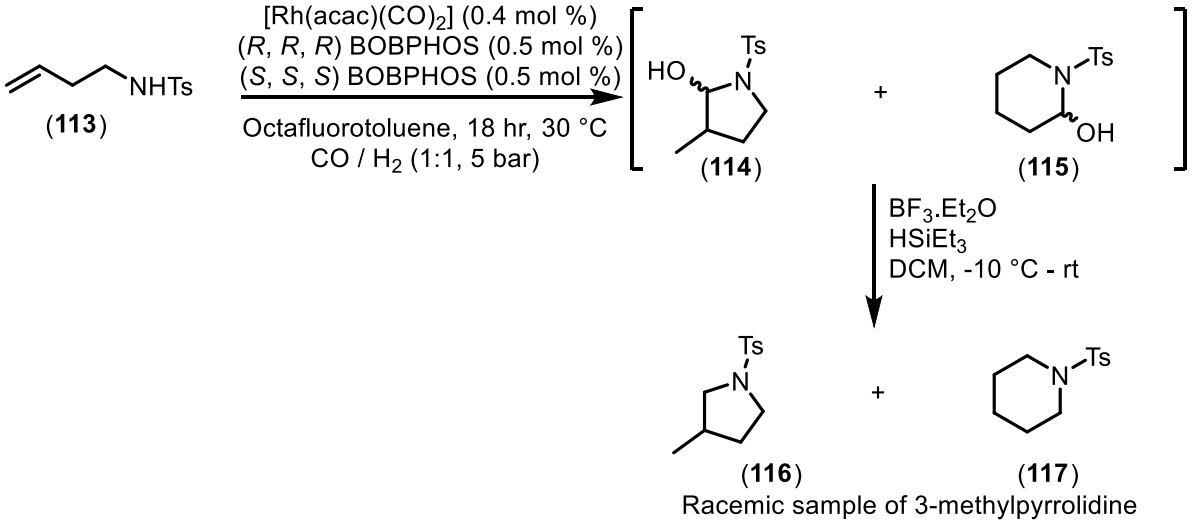
For reasons outlined below, the measurement of the enantioselectivity of the reaction was not carried out on the *N*-tosyl-3-methylpyrrolidine product but instead on the *N*-tosyl-3-methylpyrrolidinone product, obtained by oxidation of the hydroformylation-cyclisation reaction mixture, as depicted in the scheme below, Scheme 123.



Scheme 123: Hydroformylation-cyclisation followed by one-pot oxidation

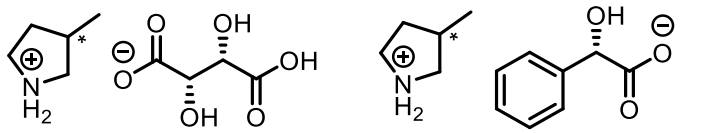
Measuring the Enantioselectivity of the Reaction

As noted in Table 3, Rh/ PPh_3 delivered a very low yield of racemic, branched product. It was expected that these hydroformylation conditions would produce a higher ratio of the linear product since triphenyl phosphine is known to be an unselective ligand and it was predicted that the substrate would have an electronic bias for forming the linear hemi-aminal. This preference was so strong however that it meant that isolation of racemic 3-methylpyrrolidinone was inefficient. A switch in catalyst was undertaken and whilst racemic BOBPHOS was not available, mixing the separate enantiomers in equal amounts should lead to the formation of equal amounts of each enantioselective catalyst, which in turn will generate equal amounts of each enantiomer, thereby giving approximately a racemate within the reaction mixture, Scheme 124. This was later confirmed by comparison with the reaction mixture from Rh/ PPh_3.



Scheme 124: Synthesis of racemic sample of 3-methylpyrrolidine

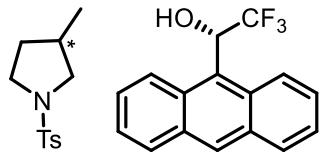
Thorough attempts to separate the enantiomers of *N*-tosyl-3-methylpyrrolidine by chiral HPLC gave no baseline separation for the racemate, hence attempts were made to deprotect the amine and then form a chiral salt, Figure 5. Deprotection of the tosyl group was not facile, as discussed in a later section. However, on the material that could be isolated, it was found that none of the chiral salts tested gave adequate peak splitting in either the ^{1}H NMR or ^{13}C NMR spectrum in order to measure an accurate enantioselectivity.



(**127**) (*L*)-Tartaric acid (**128**) (*S*)-(+)-Mandelic acid

Figure 5: Chiral salts of 3-methylpyrrolidine

Instead, an investigation into the use of a chiral solvating agent was undertaken. Chiral solvating agents (CSAs) interact with a substrate through non-covalent interactions, as opposed to chiral derivatizing agents (CDAs) which react with the substrate to form a covalent bond.[92] Both CSAs and CDAs are normally enantiomerically pure, this means that when they interact with a substrate that is a mixture of enantiomers, diastereomers are formed. The diastereomer ratio can then be measured directly from ^{1}H or ^{13}C NMR. For some compounds, CSAs and CDAs have been used to assign the absolute stereochemistry of the molecule. Here in this instance, the only interest was in obtaining a measurement of the diastereomeric ratio. The CSAs used often vary greatly depending upon the substrate that is being tested. On this occasion, the chiral solvating agent chosen was (*S*)-1-(anthracen-9-yl)-2,2,2-trifluoroethan-1-ol and was tried at different concentrations, Figure 6.



(**116**) (**129**)

(*S*)-1-(anthracen-9-yl)-2,2,2-trifluoroethan-1-ol

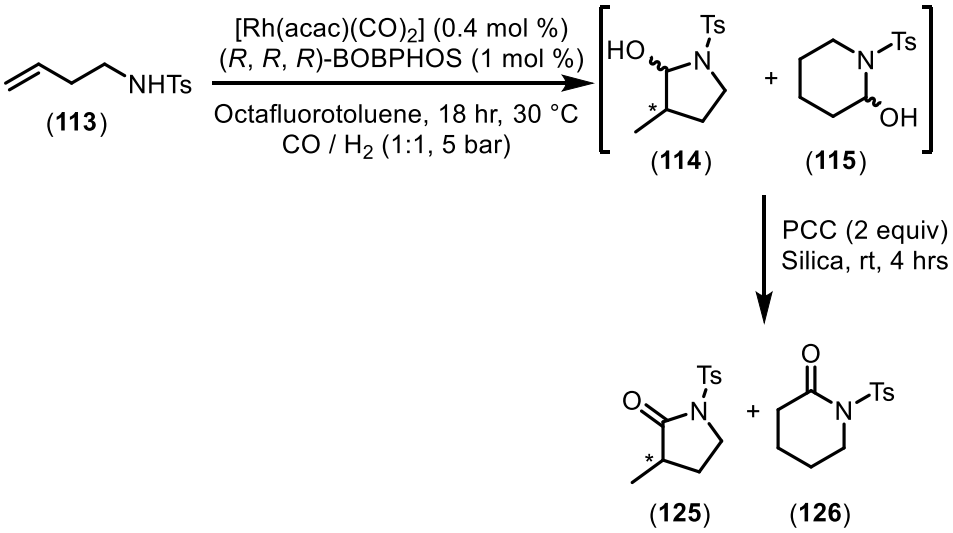
Figure 6: CSA and N-tosyl-3-methylpyrrolidine

Unfortunately, the same occurrence as with the chiral salts was observed and inadequate peak splitting in the ^{1}H NMR spectrum meant no accurate measurement could be made. Whilst originally an increase in the concentration of the CSA caused an increase in peak splitting, this eventually reached a maximum and no further increase in the concentration allowed for any further peak splitting. Changing deuterated solvents for the NMR had some effect on the peak shift but did not increase the peak separation between the diastereomers. Three different solvents, deuterated

chloroform, deuterated DCM and deuterated methanol were tested at the ratio of 10:1 of CSA, (**129**): *N*-tosyl-3-methylpyrrolidine, (**116**) but insufficient peak splitting was observed.

It was considered that the formation of 3-methylpyrrolidine using a chiral protecting group would give a mixture of diastereomers when hydroformylated and then reduced. Since these were diastereomers, separate peaks would be visible in the ^{1}H NMR or ^{13}C NMR in order to measure the enantioselectivity of the reaction. Since investigations of the chiral sulfinamide protecting group were being studied for the piperidine this was also attempted here. However, on carrying out the hydroformylation-cyclisation followed by one-pot reduction it was found that the peaks were not adequately separated to form accurate conclusions about the enantioselectivity, and that matters were complicated by the loss of the protecting group in the reduction step, leading to multiple products visible in the crude NMR. Hence this methodology could not be used to determine the enantioselectivity of the hydroformylation step.

A literature search showed that there was greater precedent for successful chiral HPLC separation of *N*-tosylpyrrolidinones rather than *N*-tosylpyrrolidines, and these would be accessible from the crude hydroformylation mixture by oxidising at the end of the reaction as opposed to reducing. Precedent for this had been established by Zhang et al. in their paper on interrupted hydroaminomethylation.[66] This paper implied that the ee obtained from the reduced product was near-identical to that obtained from the oxidised product. The conditions used initially were the same as they had quoted but were eventually optimised to those stated below, Scheme 125.



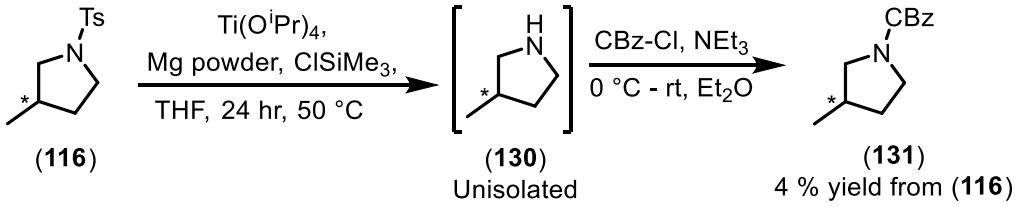
Scheme 125: Hydroformylation-cyclisation followed by one-pot oxidation

Following purification by preparative TLC, the racemate of 3-methylpyrrolidinone was successfully analysed by chiral HPLC and measurement of the enantioselectivity of the AHF reaction could be undertaken.

Deprotection:

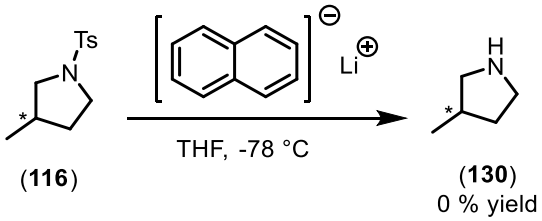
Since the conditions required for the removal of the nosyl protecting group are altogether milder than those required for the removal of the tosyl group, this was considered first for the synthesis of free 3-methylpyrrolidine. Prior to carrying out the deprotection, the separation of the corresponding nosyl protected compounds must be undertaken. This proved challenging: separation by column chromatography proved unfeasible due to the low solubility of the substrates in the highly unpolar solvents that are typically required for good separation between molecules of similar size and properties. This led to no movement of the compound on the column if these solvents were used, if a more polar solvent system was used then insufficient separation was obtained. As such, recrystallisation was considered to be the best way forward yet despite trying various solvents and solvent mixtures, no recrystallisation conditions were selective for *N*-nosyl-3-methylpyrrolidine. Hence finding a selective method for isolation of *N*-tosyl-3-methylpyrrolidine and then deprotection of this compound was attempted next.

It was found that the *N*-tosyl-3-methylpyrrolidine could be separated from the *N*-tosylpiperidine by either column chromatography or recrystallisation. It is known that harsh conditions are required for the removal of the tosyl protecting group, but in an attempt to avoid those the first set of reaction conditions tested were complex, but altogether milder than some of the more standard conditions used, Scheme 126. Published in 2011, the authors hypothesised that the tosyl group was removed by reaction with a low-valent titanium compound to leave the amine and corresponding hydrocarbon, which in this case would be toluene.[93]



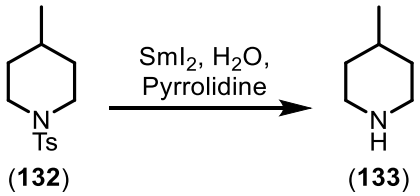
Scheme 126: Attempted deprotection with a low-valent titanium compound

Owing to the volatility of the 3-methylpyrrolidine product, after work up the reaction crude of the deprotection was carried through to the next step without purification. The isolation and purification was then carried out for the benzyl carbamate protected 3-methylpyrrolidine. Whilst this deprotection had partially worked, the yield was poor and so other literature methods were investigated. The next used an in-situ generated lithium naphthalide ion in THF to carry out the tosyl deprotection by a radical mechanism, Scheme 127. Despite giving the appropriate colour changes which indicated that the lithium naphthalide ion had been formed correctly, no free 3-methylpyrrolidine was observed in the crude NMR.



Scheme 127: Attempted deprotection with lithium naphthalide ion

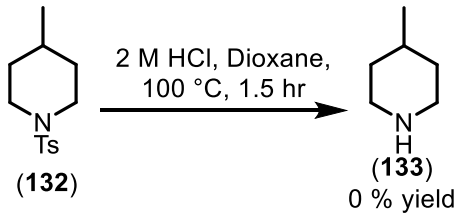
After that, the use of samarium iodide was investigated. Samarium iodide was reported as an instantaneous and fairly mild remover of the tosyl protecting group. However, further investigations have found that the source of the samarium iodide greatly affects the reactivity and reproducibility. Sources of samarium iodide that are freshly prepared in the lab are commonly held to be more active than those obtained from commercial sources. First, since it was readily available, a commercially available source of SmI_2 as a solution in THF was used in various equivalences before switching to a freshly prepared solution from samarium metal and iodine in accordance with the recommendations on the differing activity of these sources. The time and temperature were also varied but no synthetically useful conversions could be obtained from either source. In order to use the enantiomerically enriched material formed through the AHF reaction more efficiently, a commercially available piperidine was tosyl protected by a standard literature procedure and then used for tosyl deprotection studies. The different results are tabulated below, Table 4.



Entry	SmI_2 Source	Conditions	Conversion
1	Commercial	SmI_2 (6 equiv), rt, 5 min	5 %
2	Commercial	SmI_2 (12 equiv), rt, 18 hr	16 %
3	Lab made	SmI_2 (3 equiv), rt, 18 hr	22 %
4	Lab made	SmI_2 (3 equiv), 30 °C, 60 hr	>1 %

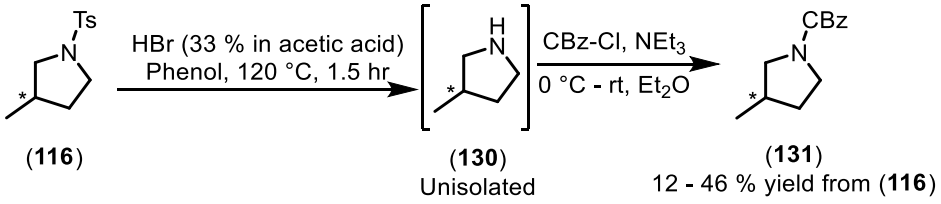
Table 4: Investigation into tosyl deprotection with samarium iodide

2 M HCl in dioxane was found to give no conversion to the free amine, Scheme 128.



Scheme 128: Attempted deprotection with hydrochloric acid

Finally, the use of HBr (33 % in acetic acid) and phenol was attempted and gave the highest isolated yield of *N*-CBz-3-methylpyrrolidine, Scheme 129. Using HBr (33 % in acetic acid) without the phenol counterpart gave no conversion.



Scheme 129: Deprotection with hydrobromic acid

Unfortunately, this yield and repeatability was not high enough for practical purposes yet no improved method could be identified.

Determination of Absolute Stereochemistry:

Column chromatography was predominantly used to isolate the *N*-tosyl-3-methylpyrrolidine made using Rh/ BOBPHOS in 46 – 69 % yield. However, after studying a range of conditions, it was also possible to obtain pure *N*-tosyl-3-methylpyrrolidine by recrystallisation. This was carried out multiple times to obtain a 49 % yield. On another occasion the recrystallisation yielded 26 % of crystals that were good enough for single crystal X-ray diffraction structure determination. This was carried out by Prof. Alex Slawin of the University of St Andrews. This showed that within the crystal structure, there were two distinct molecules of *N*-tosyl-3-methylpyrrolidine, both with (*S*) stereocentres at the 3-methyl position of the pyrrolidine ring, Figure 7.

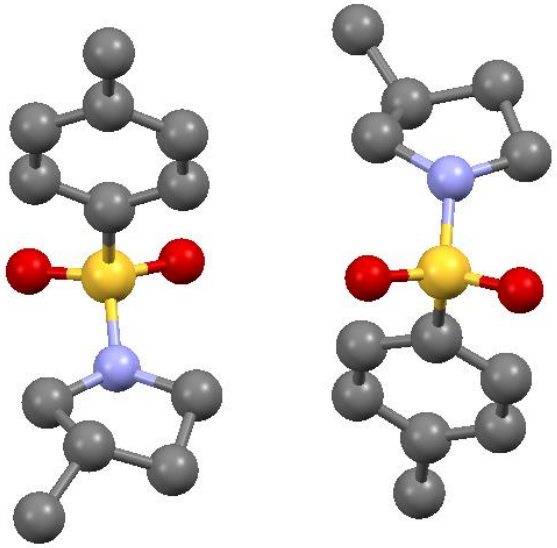
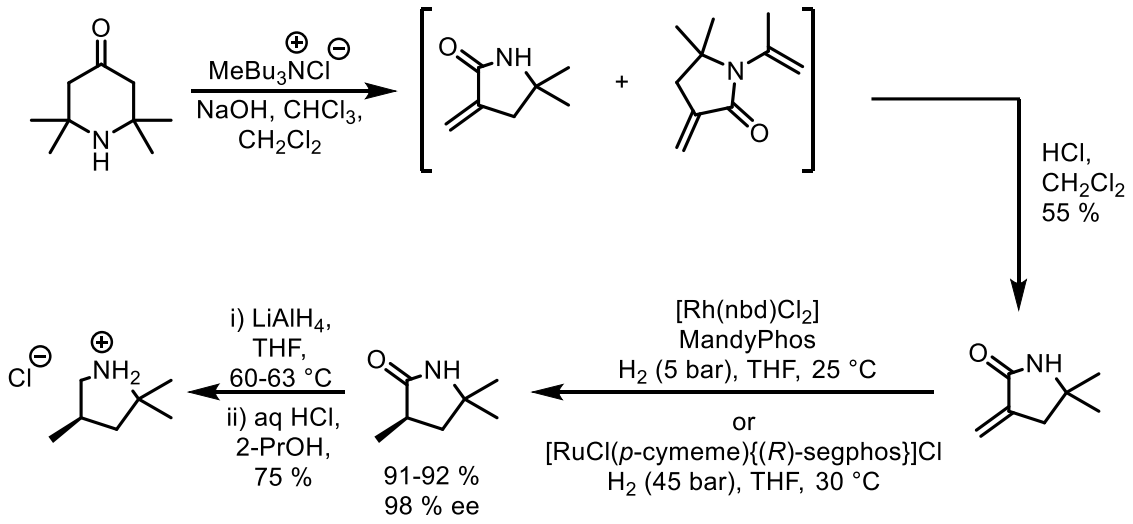


Figure 7: Single crystal X-Ray crystal structure of recrystallised sample of N-tosyl-(S)-3-methylpyrrolidine, hydrogen atoms not shown.

The Flack parameter is used to indicate the accuracy of the determination of absolute stereochemistry, for this crystal it was reported as 0.01(3) which is well below the accepted upper limit of 0.08.[94] The assignment of (*S*) is consistent with the induction of enantioselectivity for simple terminal alkenes using (*S*, *S*, *S*)-BOBPHOS in the hydroformylation reaction.

Elexacaftor Component:

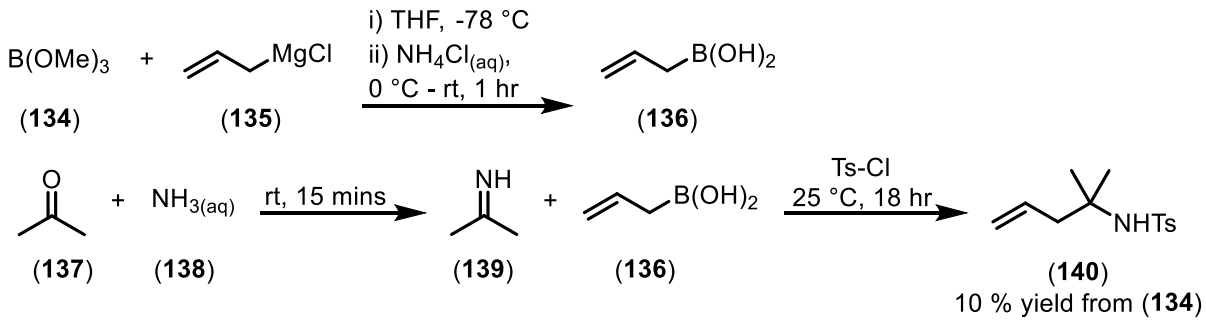
A new drug known as elexacaftor was released to the market in 2019. This drug was approved for the treatment of cystic fibrosis and is combined with other molecules in the dosage to form multiple active components. Elexacaftor contains a 3, 5, 5-trimethylpyrrolidine component and the synthetic route to this component from the patent is depicted below, Scheme 130.[95]



Scheme 130: Patent preparation of Elexacaftor intermediate component.[95]

As can be seen, the route starts from a relatively complex starting material and contains multiple steps. Whilst the stereocentre is set through asymmetric catalysis, the use of lithium aluminium hydride is not ideal. It was considered that by using the AHF-cyclisation methodology it would be possible to set the stereocentre and carry out the cyclisation in one step.

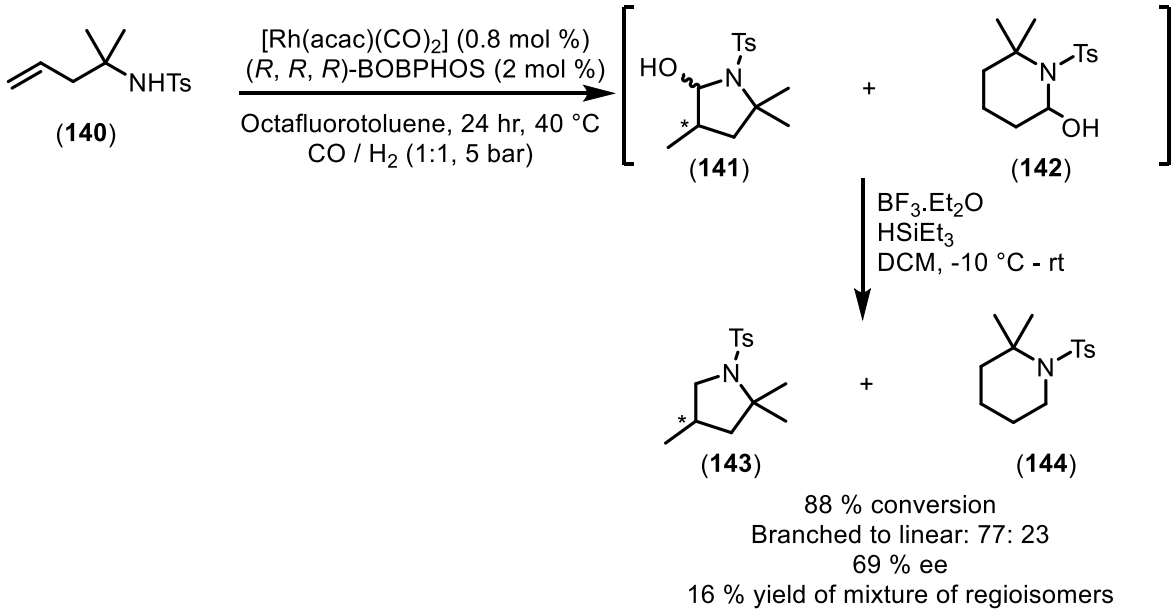
In order to attempt this first the gem-dimethyl substituted alkene starting material must be synthesised. This was done by a multi-component Petasis reaction from commercially available starting materials. The boronic ester was synthesised first from methylboronate and allyl magnesium chloride, and then hydrolysed to give the allylic boronic acid. This was then added to a solution of imine that had been formed in-situ, before the crude reaction mixture then underwent direct protection with a tosyl group to give the starting substrate after purification, Scheme 131.



Scheme 131: Synthesis of gem dimethyl substituted starting substrate.

Issues with this synthesis included ensuring that the solvent for the formation of the boronic ester was especially dry, as well as the low formation of imine under various conditions and ammonia sources was observed. Unfortunately the yield was low, although this is calculated from the fundamental trimethoxy boronate starting material. Enough material was obtained to carry out the AHF.

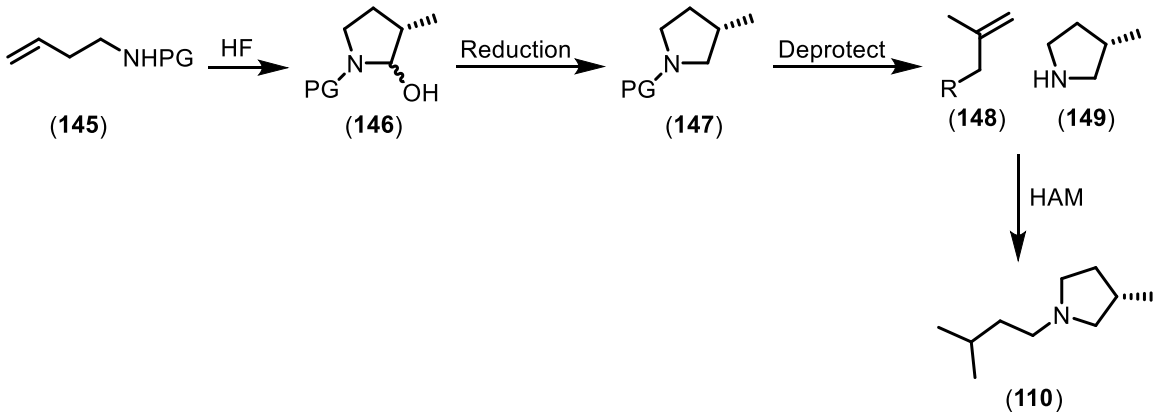
The substrate was then tested under the optimised reaction conditions but unfortunately incomplete conversion was obtained. The reaction was left for longer at a higher temperature, yet after 24 hours at 40 °C with double the normal catalyst loading, starting material was still present and hence the substrate was deemed to be too bulky to efficiently interact with the catalyst, Scheme 132. A 69 % ee was also obtained for this process, further demonstrating the deleterious effect of the gem-dimethyl group on the substrate to catalyst interaction.



Scheme 132: Hydroformylation-cyclisation and reduction of gem dimethyl substituted substrate.

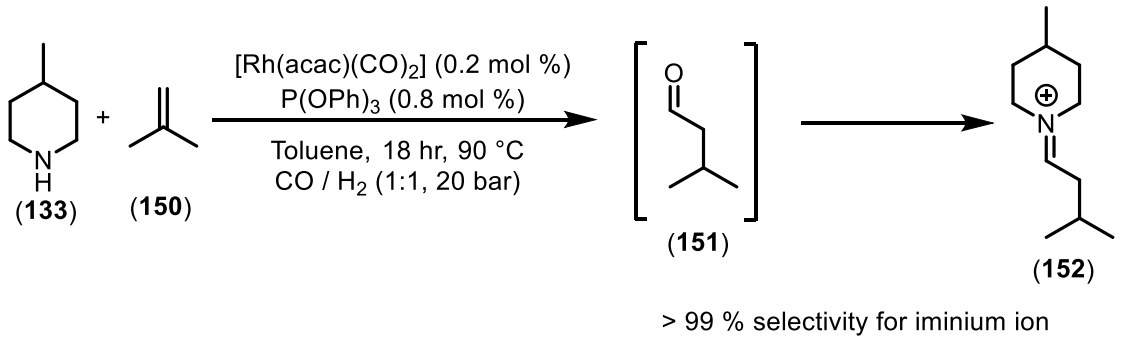
Hydroaminomethylation for Ant Venom Natural Product

Previously isolated in 1995 were a series of ant venom natural products.[96] Though there have been attempts since then to synthesise these compounds, one efficient and novel way would be to use the hydroformylation-cyclisation for the pyrrolidine moiety, followed by a hydroaminomethylation (HAM) to add on the alkyl chain. The proposed route is shown below, Scheme 133.



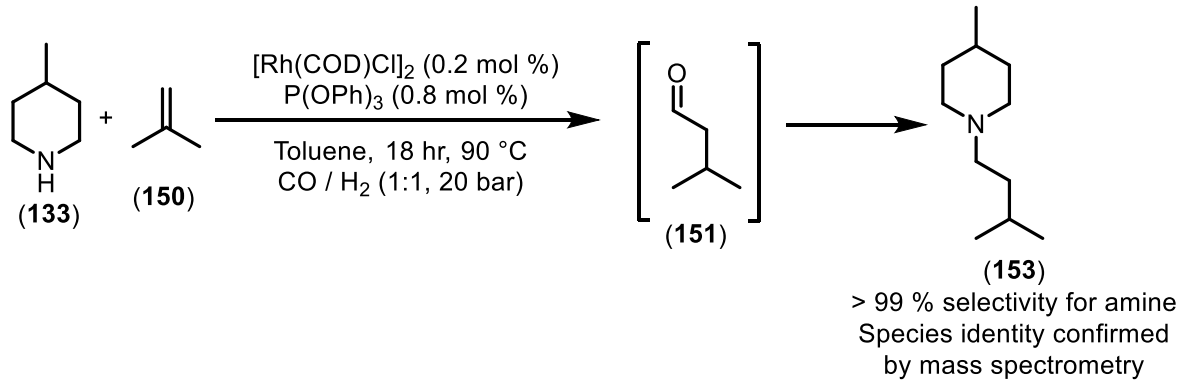
Scheme 133: Proposed route to ant venom component.

Since isobutene is a gas at room temperature, it had to be diffused into the solvent, toluene, at a low temperature and used in the reaction in excess as a stock solution. Next the hydroaminomethylation reaction was optimised using commercially available 4-methylpiperidine as the amine counterpart instead of the 3-methylpyrrolidine. Using the conditions shown below, Scheme 134, incomplete hydrogenation of the enamine was observed at the end of the reaction.



Scheme 134: Hydroaminomethylation of 4-methylpiperidine with isobutene

Switching to a different rhodium metal precursor which is considered more efficient for hydrogenation gave the desired product, Scheme 135. However, due to multiple conformers existing from the inversion of not only the piperidine ring but also the nitrogen lone pair, as well as conformers arising from the rotation of the alkyl chain, large peak broadening in the NMR spectrum was observed and made it difficult to analyse. This phenomenon has been reported previously but makes it difficult to accurately determine and quantify the outcome of the reaction.[97] As such, a combination of ^{1}H and ^{13}C NMR were used to determine unique environments for the iminium ion, enamine and aldehyde products. Analysis was carried out on the HCl salts owing to the volatility of the product.



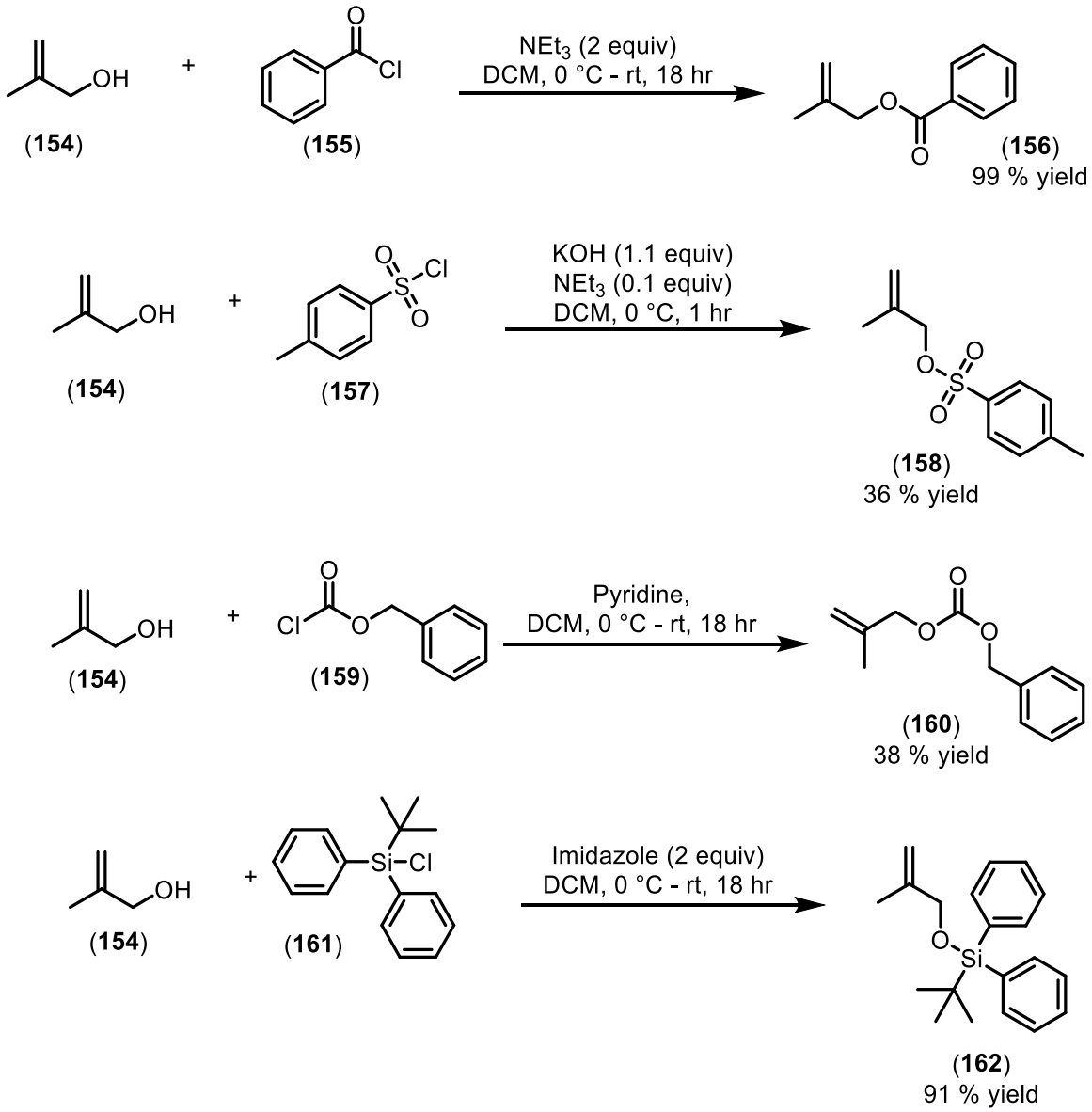
Scheme 135: Adapted conditions for hydroaminomethylation of 4-methylpiperidine with isobutene

From here it was investigated as to whether a pyrrolidine ring as the amine counterpart might limit some of the configuration fluxes. The reaction was carried out under the same conditions, however no substantial difference in the NMR spectra was observed. Low temperature NMR can be useful in reducing the conformational possibilities of fluxional molecules to fewer or even one conformation,

in this instance lowering the temperature seemed to have a worsening effect on the ^{1}H NMR peak shape. However, increasing the temperature to 35 °C provided a better spectrum of the pyrrolidine sample.

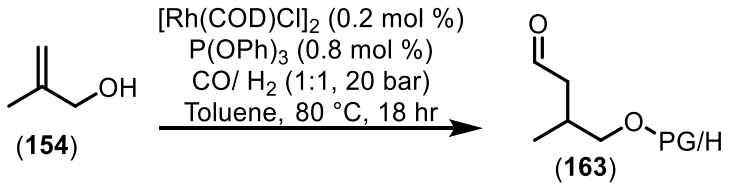
From these experiments it was determined that high conversions from isobutene and a saturated cyclic amine to a tertiary amine through a hydroaminomethylation reaction is possible. The *N*-tosyl-3-methylpyrrolidine can be isolated in good yields by column chromatography or by recrystallisation, yet a high yielding procedure for the deprotection to the free amine has not yet been achieved. This is the final stage needed for carrying out the synthesis of the ant venom component, the natural product Leptothoracine.

Of interest was the development of an asymmetric HAM and investigations began by using 2-methylprop-2-en-3-ol. On carrying out the hydroformylation of this substrate, the reaction underwent complete conversion to give the cyclised hemi-acetal as the product in a mixture of diastereomers. Near-complete regioselectivity for the linear product was observed on account of the high energy barrier for the formation of a quaternary carbon centre arising from the branched. It was considered that having an equilibrium between the hemi-acetal, enamine, iminium ion and amine product would make the reaction mixture difficult to analyse. Furthermore, the lack of any chromophore meant that measurement of the enantioselectivity by HPLC using UV detection would not be possible. Finally, whilst the oxygen of the alcohol would potentially offer a coordinating group that may help to establish enantioselectivity, increasing the difference in size between the two sides of the alkene would be beneficial to selectivity. For these reasons, a protecting group on the alcohol was considered. The following groups were chosen and the protections carried out according to literature procedures, Scheme 136.



Scheme 136: Conditions for the synthesis of protected alcohols.

Next, the hydroformylation reaction of these compounds was carried out to ensure that no coordination to the catalyst, resulting in catalyst inhibition, or loss of protecting group occurred under the standard reaction conditions. The resulting aldehydes were then reduced to the corresponding alcohols in a one-pot procedure before analysis by ^{1}H NMR and then purification by column chromatography. As can be seen from Table 5, the benzoyl carbamate, entry 4, and the tosyl protecting group, entry 3, were unstable to this sequence of reactions, whilst the benzoate protecting group, entry 2, appeared to reversibly bind to the catalyst and cause catalyst inhibition, thus slowing the reaction down and giving incomplete conversion. As a result, the silyl protecting group, entry 5, was chosen for screening conditions for the HAM reaction.



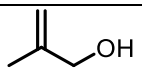
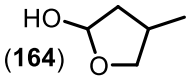
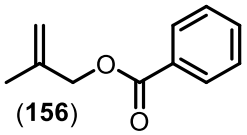
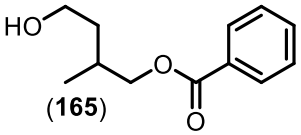
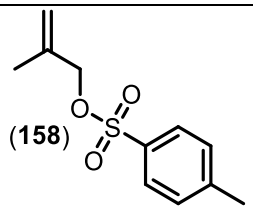
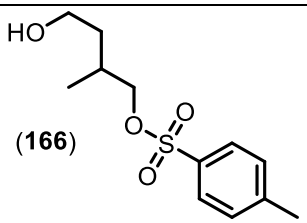
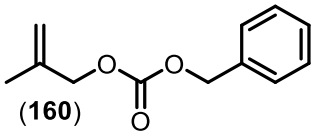
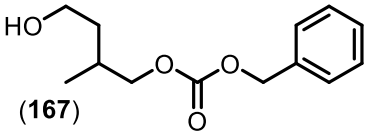
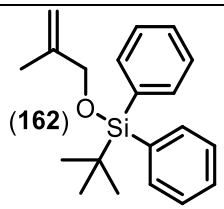
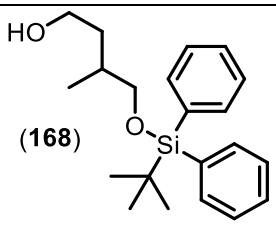
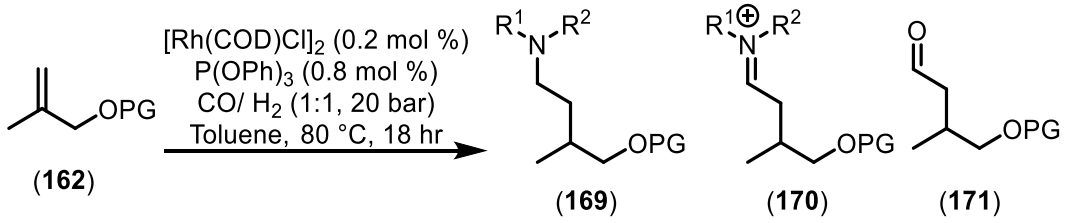
Entry	Starting Substrate	Conversion	Reduced Compound	Isolated Yield
1	 (154)	> 99 %	N/A.  (164) Hemi-acetal diastereomers in ratio 1.3:1.	N/A
2	 (156)	50 %	 (165)	30 %
3	 (158)	> 99 %	 (166)	N/D Loss of OTs.
4	 (160)	38 %	 (167)	N/D Loss of CBz.
5	 (162)	> 99 %	 (168)	55 %

Table 5: Investigation into alcohol protecting group for hydroformylation reaction

Next, a selection of amines were initially screened in a rhodium catalysed HAM of the protected alcohol, Table 6. In line with literature precedent, addition of the amine and the additional steps in the catalytic cycle meant that incomplete conversion was observed in all cases, whilst aryl-alkyl amines did not undergo reductive amination to give the amine product, entry 4. 4-methylpiperidine is closest to the target amine of 3-methylpyrrolidine for the natural product and hence this was chosen as the amine counterpart for optimisation of the reaction conditions.

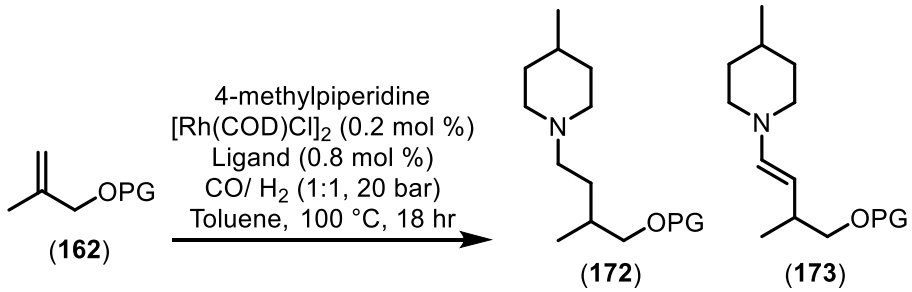


PG = *tert*-butyldiphenylsilyl

Entry	Amine Component	162 (%)	169 (%)	170 (%)	171 (%)
1	Tetrahydroquinoline	62	0	0	38
2	Morpholine	14	86	0	0
3	4-methylpiperidine	77	23	0	0
4	N-methyl-aniline	1	0	0	99

Table 6: Investigation into amine for hydroaminomethylation of protected alcohol

The optimisation began by screening different electronic properties of three different monodentate phosphine ligands, Table 7.

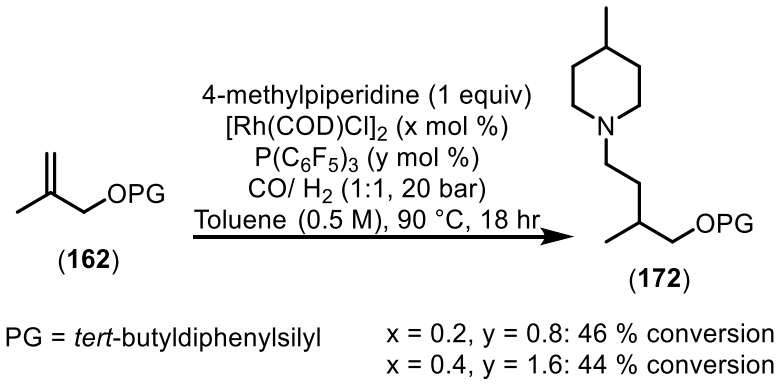


PG = *tert*-butyldiphenylsilyl

Entry	Ligand	162 (%)	172 (%)	173 (%)
1	$P(OPh)_3$	63	37	0
2	PPh_3	0	47	53
3	$P(C_6F_5)$	54	46	0

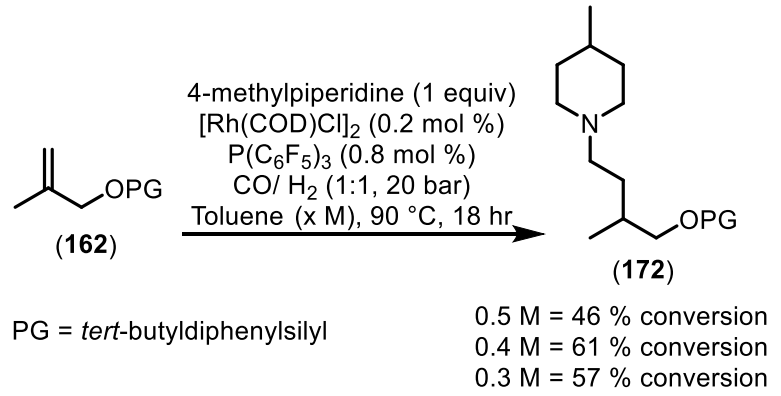
Table 7: Ligand investigation for hydroaminomethylation reaction

From here it was decided to use tris(pentafluorophenyl)phosphine as the ligand since this gave both the greatest amount of conversion and the greatest selectivity to the desired amine. Triphenylphosphite is commonly used for these reactions but is unstable and easily hydrolysed. Within the course of these studies a reaction with clean triphenylphosphite gave full conversion in 18 hours, whereas a degraded sample of ligand gave only 23 % conversion in 18 hours. Next, doubling the catalyst loading was investigated, Scheme 137.



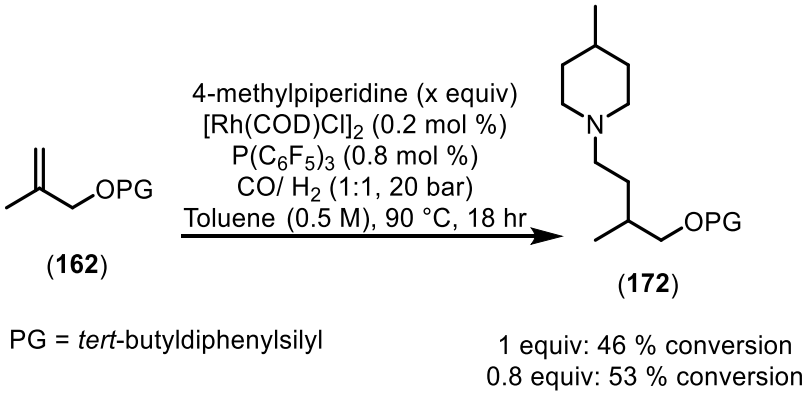
Scheme 137: Optimisation of catalyst loading

This showed no particular increase in conversion, hence the lower catalyst loading was kept and an investigation into the concentration of the reaction was undertaken, Scheme 138.



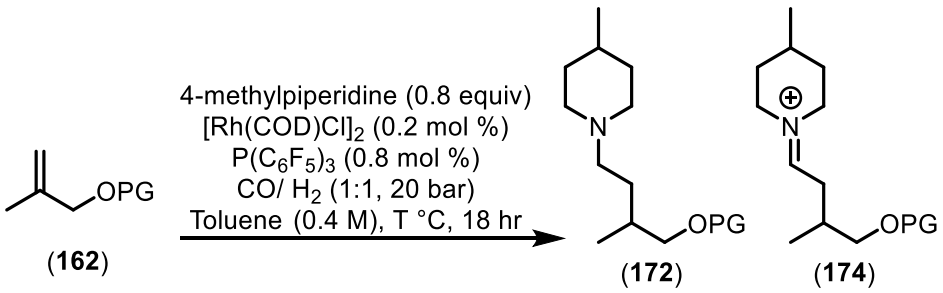
Scheme 138: Optimisation of concentration

The decrease from 0.5 M to 0.4 M provided a noticeable increase in conversion, whilst a further decrease from 0.4 M to 0.3 M was negligible. At the same time, the effect of the amine equivalence was examined, Scheme 139.



Scheme 139: Optimisation of amine equivalence

This showed a slight increase in the conversion, and hence both this and the concentration of the reaction were taken into consideration when investigating the temperature, Table 8.



PG = *tert*-butyldiphenylsilyl

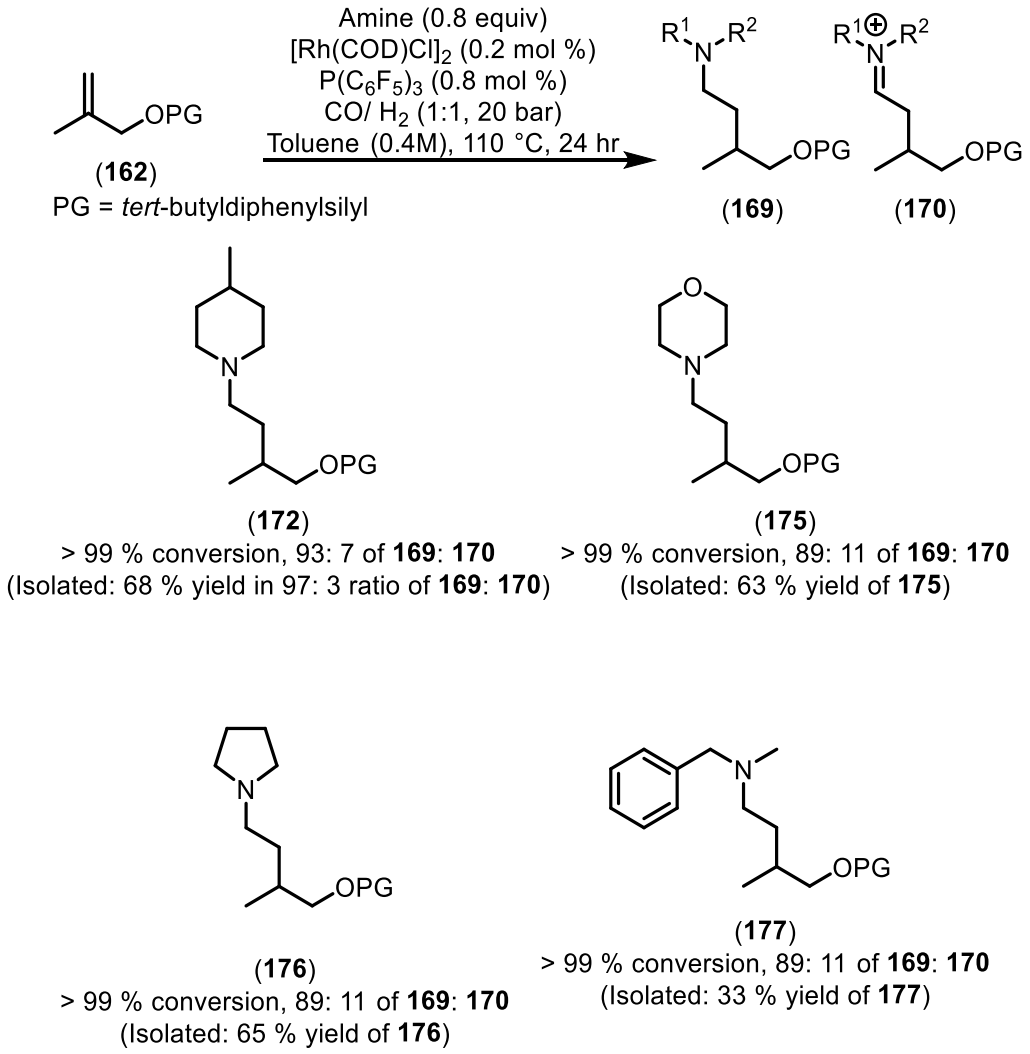
Entry	Temperature	162 (%)	172 (%)	174 (%)
1	90 °C	39	61	0
2	100 °C	16	84	0
3	110 °C	0	90	10
4	120 °C	0	91	9

Table 8: Temperature optimisation for hydroaminomethylation reaction

The increase in temperature to 110 °C showed full conversion of the alkene for the hydroformylation and subsequent reductive amination, however there was incomplete hydrogenation of the iminium ion intermediate, Table 8, entry 3. Further increasing the temperature to 120 °C showed no difference in this result. The reaction time was increased from 18 hours to 24 hours at 110 °C. However, this again showed only minor improvements, with a reduction from 10 % imine to 7 % imine. Increasing the ratio of hydrogen to carbon monoxide from 1:1 at 20 bar to 3:1 at 40 bar made only a further incremental difference in the amount of iminium ion observed, with 5 % still present in the reaction mixture.

It was considered that the water produced from the reductive amination may be degrading the catalyst before it can complete the full HAM reaction to give only an amine product. With this in mind, a water spiking experiment was carried out whereby 1 equivalent of water was added into the reaction mixture at the same time as the amine and alkene. This again showed no alteration to the reaction profile, hence it was determined that this does not seem to be the cause of the problem.

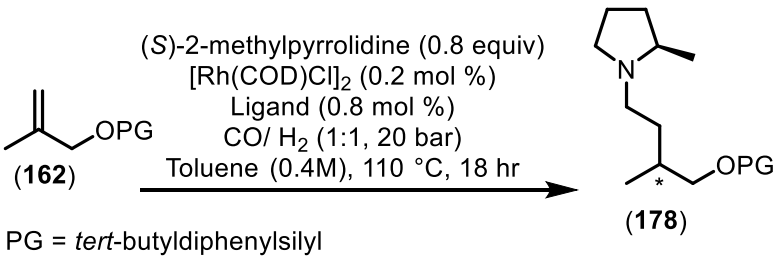
As such, differentiation of the amine substrate was then investigated under the best conditions to give the following results, Scheme 140.



Scheme 140: Testing of optimised reaction conditions with different amines

Thus the methodology was sufficient for carrying out the hydroaminomethylation of a bulky protected alcohol with high conversion and selectivity, giving good yields of the desired amine product.

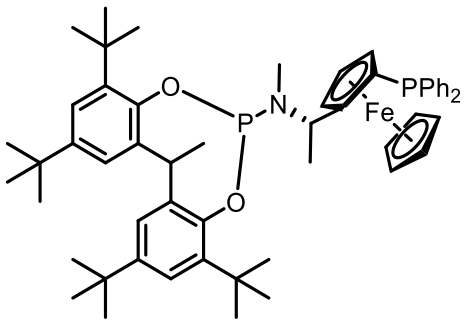
The interest in developing this reaction was for the particular application to the synthesis of an ant venom component, compound (**110**). For this to be achieved, the reaction must go with control over the enantioselectivity and this requires a chiral ligand. To facilitate measurement of the enantiomeric excess of the reaction, an enantiopure amine was used so that the product would give diastereomers and the diastereomeric ratio could be measured directly on the crude reaction mixture by NMR. Any reaction would be formally diastereoselective but since the stereocentre is set before the carbon-nitrogen bond formation, it was expected that any diastereoselectivity would arise purely from the catalyst. Since it is commercially available and similar in size and electronics to the target amine, (*S*)-2-methylpyrrolidine was chosen and investigated under the previous conditions, Table 9.



PG = *tert*-butyldiphenylsilyl

Entry	Ligand	Conversion and d.r.
1	$P(C_6F_5)_3$	> 99 % conversion, 85 % amine, 15 % imine; dr = 51:49
2	(*S*, *S*)-Ph-BPE	> 99 % conversion, 93 % amine, 7 % imine; dr = 48:52
3	(*S*, *S*, *S*)-BOBPHOS	> 99 % conversion, 91 % amine, 9 % imine; dr = 51:49
4	Bidentate Ligand (**179**)	> 99 % conversion, mix of at least 4 products: amine, imine, aldehyde and unknown, dr of amine = 54:46

Table 9: Ligand investigation for asymmetric hydroaminomethylation reaction

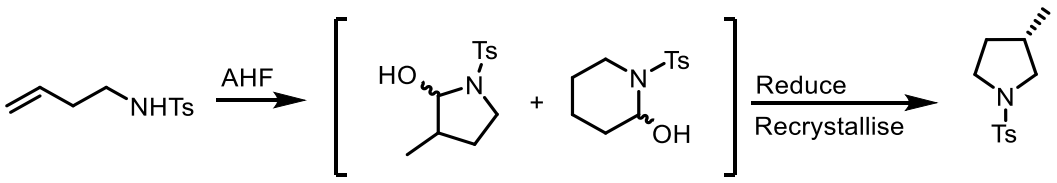


(**179**)

No ligand showed any significant enantiomeric induction and due to time constraints the investigation ended here.

Summary

Within this chapter a novel method for the synthesis of 3-methylpyrrolidine has been disclosed. Through AHF-cyclisation followed by a one-pot reduction and then recrystallisation, *N*-tosyl-3-methylpyrrolidine could be obtained as a pure compound in 49 % yield, Scheme 141. The determination of the absolute stereochemistry was carried out by single crystal X-ray diffraction and an indication of the enantiopurity by comparing the optical rotation to a literature reference of known enantiomeric excess.



Scheme 141: Summary of synthetic steps to N-tosyl-3-methylpyrrolidine

The intention for this molecule was for it then to be used to form the natural product Leptothoracine by a HAM reaction with isobutene. Of interest as well was another ant venom component and preliminary studies into the HAM of a protected alcohol were conducted. High selectivity for the amine product was achieved when using alkyl-alkyl secondary amines yet attempts to introduce enantioselectivity through chiral ligands did not give any promising results.

Summary

In chapter one, the summarisation of the current literature identified that there were many studies on the use of linear regioselective hydroformylation cyclisation for the synthesis of complex products, but that there was no general hydroformylation-cyclisation method that delivered chiral saturated nitrogen heterocycles with high regioselectivity and enantioselectivity from terminal alkenes. The exception to this was work from the Clarke group on the synthesis of one chiral piperidine intermediate for the drug nemonoxacin.[69]

The work in chapter two, Figure 8, has expanded upon this to highlight the importance of the right choice of protecting group for obtaining a stable hemi-aminal intermediate, a sulfonamide group, as well as demonstrating the potential for expanding the substrate scope to substituted alkenes. The synthesis of a chiral starting material proved more complex than initially anticipated but on completion the hydroformylation-cyclisation was found to proceed with high regioselectivity when the enantiomer of ligand was matched to the enantiomer of substrate. Expansion of known literature reactions on the hemi-aminal intermediate did not yield successful results.

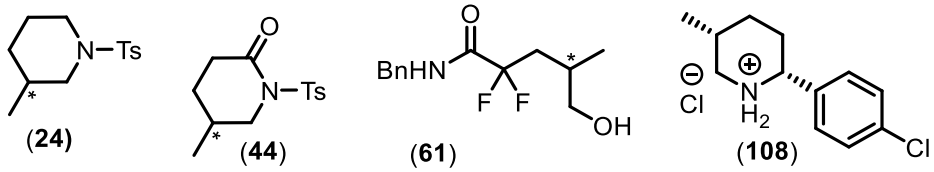
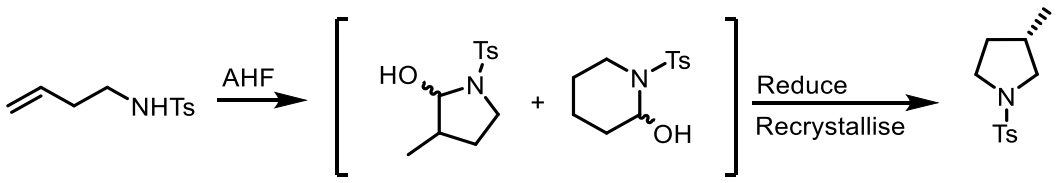


Figure 8: Selected compounds from chapter 2.

In chapter three this methodology was applied to the synthesis of chiral pyrrolidines. The current most concise synthesis to chiral *N*-tosyl-3-methylpyrrolidine from readily available starting materials is disclosed, Scheme 142. Purification by either silica column chromatography or recrystallisation led to isolation of the desired compound in good yields. The absolute stereochemistry of this molecule was determined through single crystal X-ray diffraction and comparison of the optical rotation with literature values, confirming that the enantiomer of the product matched the enantiomer of the ligand of BOBPHOS used. Synthesis of an intermediate for the drug elexacaftor highlighted a limitation of this methodology, since the increased steric hindrance of a gem dimethyl group lowered the conversion, regioselectivity and enantioselectivity. The preliminary investigations into the HAM of 1,1-disubstituted alkenes found that after optimisation high selectivity for the amine could be obtained using tri(pentafluoro)phenylphosphine as the ligand. Early reactions with the use of bidentate ligands for the purpose of introducing asymmetry showed no promising results.



Scheme 142: Synthetic steps for the synthesis of N-tosyl-3-methylpyrrolidine.

Thus the work in this thesis has expanded the knowledge of unbiased alkenes that can be used with the Rh/ BOBPHOS catalysts to access the major product as the branched regioisomer. Furthermore, in most cases, only one stereocentre was introduced and no functional groups or directing groups were used: the enantioselectivity arises only from the catalyst. It has been found that whilst various functional groups are well tolerated by the hydroformylation step, steric hindrance can be detrimental to the regio and enantioselectivity.

Chapter 4: Experimental:

General Procedures:

All reactions carried out in air-sensitive conditions were conducted under an inert atmosphere of nitrogen or argon using standard Schlenk techniques. Dry solvents were obtained from an SPS solvent purification still. 1:1 CO / H_2 'syngas' was acquired from a 200 bar cylinder, supplied from BOC (made to order). Hydrogen gas was acquired from a 200 bar cylinder, supplied from BOC. All chemicals were purchased from either Sigma-Aldrich, Alfa Aesar, fluorochem, Acros-UK, Apollo Scientific or TCI and used without further purification. Reactions that were carried out at room temperature refer to 18 – 22 °C. Heated reactions were conducted in an oil bath, either paraffin or silicon oil, and a contact thermometer was used. Removal of solvent was conducted via a Heidolph Laborota 4000 or a BÜCHI 461 rotatory evaporator. Analytical thin layer chromatography (TLC) was performed on pre-coated aluminium plates (Kieselgel 60 F254 silica) before analysing under ultraviolet light (254 nm). TLC plates were stained with 1 % aqueous potassium permanganate solution and gently heated with a heat gun. All SiO_2 column chromatography was performed with Kieselgel 60 silica.

All spectra were obtained at room temperature. ^{1}H, ^{13}C nuclear magnetic resonance (NMR) spectra were obtained from a Bruker Avance 300 (300 MHz, ^{1}H and 75 MHz, ^{13}C), a Bruker Avance II 400 (400 MHz, ^{1}H and 100 MHz, ^{13}C), or a Bruker Ultrashield 500 (500 MHz, ^{1}H and 126 MHz, ^{13}C) spectrometer. All chemical shifts are quoted in parts per million (ppm) relative to the residual solvent as the internal standard. All coupling constants, *J*, are quoted in Hz and reported to the nearest 0.1 Hz. Multiplicities are indicated by: s (singlet), d (doublet), t (triplet); q (quartet), hept (heptet), m (multiplet) or a combination of these abbreviations.

Infrared spectroscopy was recorded using a MIRacle^{TM} single reflection horizontal ATR accessory from Pike (ZnSe single crystal) to analyse solid compounds (neat).

Mass spectrometry data was obtained from the University of St Andrews Mass Spectrometry facility, using electrospray ionisation (ESI), or electron impact (EI). High resolution ESI was carried out on a Micromass LCT spectrometer.

Asymmetric Hydroformylation:

Standard procedure for asymmetric hydroformylation/ -cyclisation:

[Rh(acac)$(CO)_2$] (0.4 mol %) and (*R*, *R*, *R*) – BOBPHOS (1 mol %) were added to a microwave vial, which was then sealed and purged (3 x vacuum / N_2). Dry toluene or octafluorotolene was added, the septum pierced with 2 needles, and the vial sealed in a similarly purged autoclave which was then flushed with syngas before being pressurised with syngas (10 bar, CO: H_2 1:1). The autoclave was heated (50 °C, 1 hour) and stirred to preactivate the catalyst. The autoclave was then cooled to room temperature and

depressurised before a solution of the alkene substrate (1 equiv) in dry solvent was injected to the vial. The autoclave was then pressurised again with syngas (5 bar) and heated and stirred overnight (30 °C). The autoclave was then cooled to room temperature and the pressure released. Analysis of the crude reaction mixture was carried out by ^{1}H NMR.

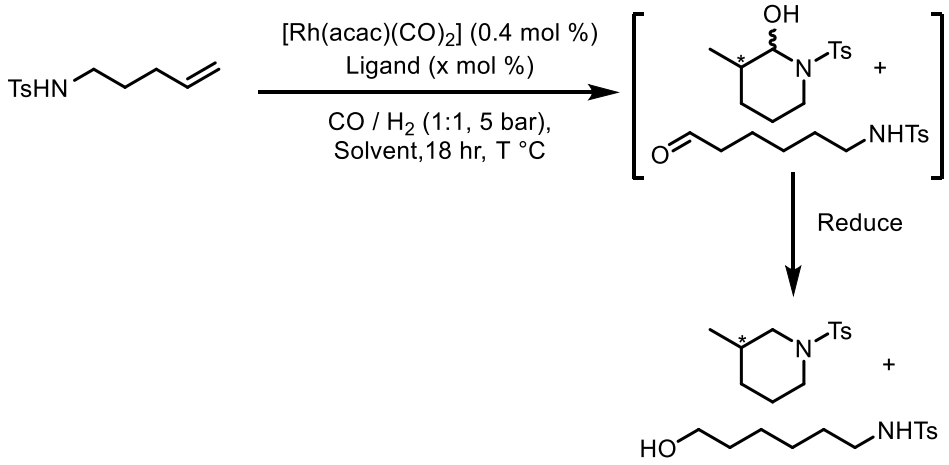
Reduction with Triethylsilane and Boron trifluoride diethyletherate:

To the microwave vial containing the crude AHF reaction mixture (1 equiv) in solvent was added DCM (2 mL) and the solution cooled (-15 °C). Triethylsilane (3 equiv) and boron trifluoride diethyletherate (3 equiv) were added and the solution stirred at -15 °C (15 mins) before warming to room temperature (30 mins). 1M HCl (2.5 mL) was added and the layers separated. The aqueous layer was extracted with DCM (3 x 2.5 mL) and the combined organic layers washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated in vacuo.

Reduction with Sodium Borohydride:

To a 15 mL RBF was added crude AHF reaction mixture (1 equiv) in solvent. Ethanol (2 mL) and sodium borohydride (0.5 equiv) were added and the solution stirred (rt, 2 hours). DCM (5 mL), water (5 mL) and 1M HCl (aq, 5 mL) were added. The layers were separated and the aqueous layer extracted with DCM (2 x 5 mL) before the combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo.

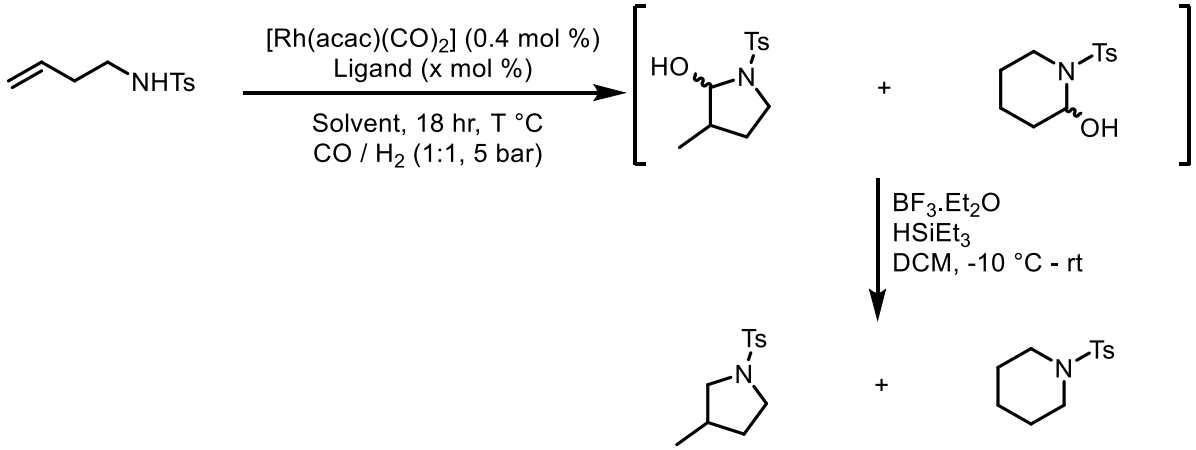
Piperidine Optimisation – Full table:



Entry[a]	Ligand	Solvent	Temperature / °C	Conversion	Branched: linear	ee[b]
1	(*R*, *R*, *R*)-BOBPHOS (0.5 mol %)	Toluene	40	95 %[c]	76:24	37 %
2	(*R*, *R*, *R*)-BOBPHOS (1.0 mol %)	Toluene	40	> 99 %	80:20	53 %
3	(*R*, *R*, *R*)-BOBPHOS (1.5 mol %)	Toluene	40	> 99 %	80:20	53 %
4	(*R*, *R*, *R*)-BOBPHOS (2.0 mol %)	Toluene	40	> 99 %	83:17	64 %
5	Ph-BPE (1.0 mol %)	Toluene	40	61 %[c]	54: 46	13 %
6	PPh_3 (1.0 mol %)	Toluene	40	37 %[c]	55: 45	N/A
7	(*R*, *R*, *R*)-BOBPHOS (1.0 mol %)	Toluene	30	95 %	77:23	85 %
8	(*R*, *R*, *R*)-BOBPHOS (1.0 mol %)	Octafluorotoluene	30	> 99 %	88: 12	84 %
9	(*R*, *R*, *R*)-BOBPHOS (1.0 mol %)	Heptane	30	95 %	87: 13	45 %
10	(*R*, *R*, *R*)-BOBPHOS (1.0 mol %)	Hexafluorobenzene	30	90 %	89:11	56 %
11	(*R*, *R*, *R*)-BOBPHOS (2.0 mol %)	Octafluorotoluene	30	> 99 %	86: 14	88 %
12	(*R*, *R*, *R*)-BOBPHOS (1.0 mol %)	Octafluorotoluene	40	> 99 %	89: 11	72 %
13	(*R*, *R*, *R*)-BOBPHOS (1.0 mol %)	Octafluorotoluene	20 (24 hr)	98 %	92: 8	85 %

[a]Standard reaction conditions: substrate (0.50 mmol), $[Rh(acac)(CO)_2]$ = 0.4 mol %, L = 1.0 mol %. Measurements made by ^1H NMR after one-pot reduction with $HSiEt_3$ (3 equiv, 1.5 mmol) and BF_3Et_2O (3 equiv, 1.5 mmol) in DCM (-15 °C, 15 mins). See SI for details. [b] Enantioselectivity measured by chiral HPLC. [c] Unknown impurity present, predicted to be isomerised starting material.

Pyrrolidine Optimisation – Full table:

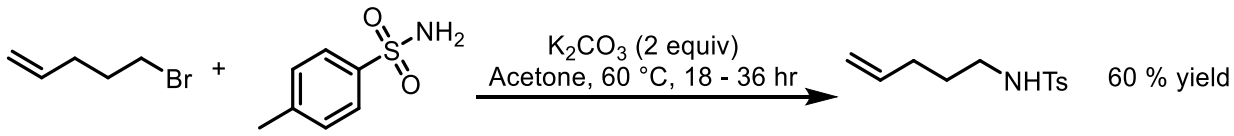


Ligand	Ligand Loading (mol %)	Solvent	Temperature (° C)	Time (hours)	% Alkene[a]	Isolated yield of A.	Branch: Linear[b]	e.e.[c]
(*R*, *R*, *R*)-Bobphos	0.5	Toluene	40	18	1 % >	n.d.	60: 40	n.d.
(*R*, *R*, *R*)-Bobphos	1.0	Toluene	40	18	1 % >	54 %	70: 30	79 [d]
(*R*, *R*, *R*)-Bobphos	2.0	Octafluoro-toluene	40	18	1 % >	n.d.	85: 15	89
(*R*, *R*, *R*)-Bobphos	2.0	Toluene	20	18	46	n.d.	78: 22	n.d.
(*R*, *R*, *R*)-Bobphos	2.0	Octafluoro-toluene	30	18	1 % >	n.d.	89: 11	85
(*R*, *R*, *R*)-Bobphos	1.0	Octafluoro-toluene	30	18	1 % >	49 % [e]	87: 13	n.d.
(*S*, *S*)-Ph-BPE	1.0	Toluene	40	18	n.d.	n.d.	32: 68	n.d.

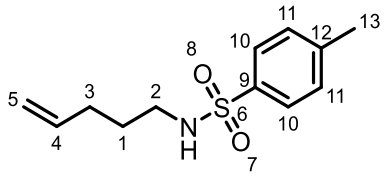
[a] Alkene percentage determined by amount of alkene compared to amount of A and B in ^{1}H NMR after reduction.
[b] Ratio A to B after reduction.
[c] Obtained by chiral HPLC on AD-H column of 3-methylpyrrolidinone.
[d] HPLC performed on samples prepared in a separate hydroformylation to the mixture that was reduced.
[e] Purification performed by recrystallisation.

Chapter 2 Experimental:

Substrate Synthesis:



Acetone (40 mL), 5-bromo-1-pentene (1.8 mL, 7.5 mmol, 1 equiv), *p*-toluenesulfonamide (2.57 g, 15 mmol, 1 equiv) and potassium carbonate (3.12g, 22.5 mmol, 1.5 equiv) were heated overnight (60 °C, 18 hr). The orange suspension was then filtered through a plug of celite and washed with ethyl acetate before concentrating in vacuo. The crude orange solid was then purified by silica column chromatography, hexane: diethyl ether (80:20) to give the product as a yellow oil, (1.077 g, 4.5 mmol, 60 % yield). Data matches the literature: *Org. Lett.*, 2011, 16, 3666-3669.

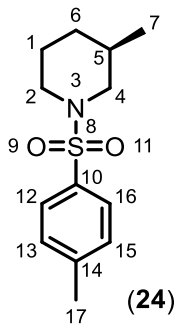


(**20**)

^{1}H NMR δ(400 MHz, $CDCl_3$): 7.76 (2H, d, J = 8.3, 2 x Ar-CH, 10), 7.27 (2H, d, J = 8.3, 2 x Ar-CH, 11), 5.66 (1H, ddt, J = 16.9, 10.2, 6.8, CH, 4), 5.47 (1H, t, J = 6.0, N-*H*), 4.90 (2H, m, CH_2, 5), 2.89 (2H, q, J = 6.8, CH_2, 2), 2.38 (3H, s, CH_3, 13), 2.00 (2H, q app, J = 7.1, CH_2, 3), 1.57 – 1.51 (2H, m, CH_2, 1).

^{13}C NMR δ(126 MHz, $CDCl_3$): 143.3 (1 x C, s, 9), 137.3 (1 x CH, s, 4), 137.0 (1 x C, s, 12), 129.7 (2 x CH, s, 10), 127.1 (2 x CH, s, 11), 115.4 (1 x CH_2, s, 5), 42.6 (1 x CH_2, s, 2), 30.6 (1 x CH_2, s, 3), 28.6 (1 x CH_2, s, 1), 21.5 (1 x CH_3, s, 13).

Asymmetric HF-Cyclisation:



(**24**)

The standard AHF procedure was followed with 1.0 mmol of alkene. The crude AHF reaction mixture was reduced with triethylsilane and boron trifluoride diethyletherate as detailed in the general procedures. After this the conversion and branched to linear ratio were measured by ^{1}H NMR: > 99 %

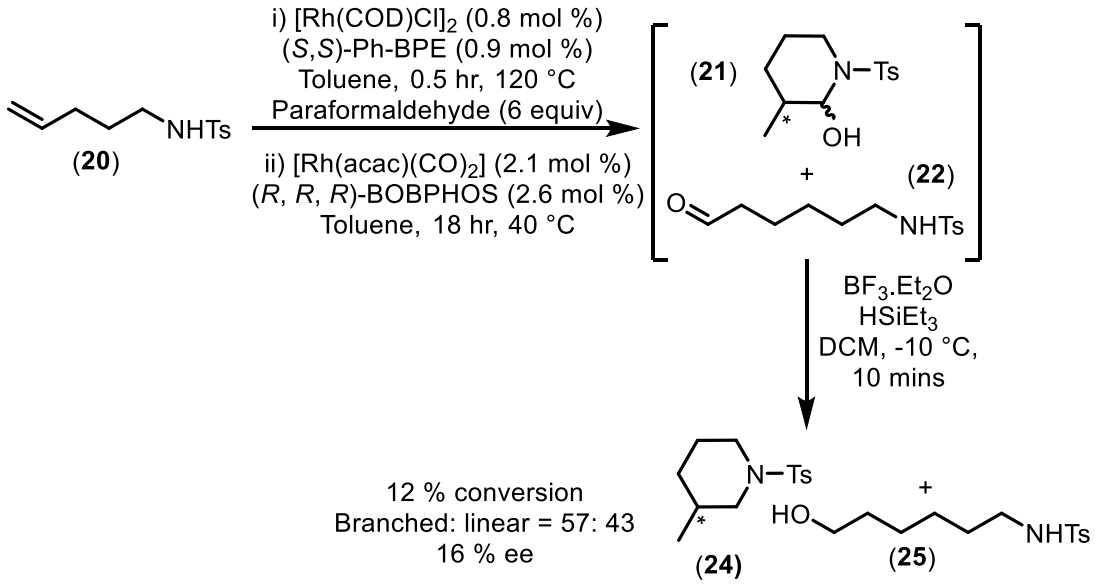
conversion and 88:12 branched to linear ratio were recorded in this example. Purified by silica column chromatography, hexane: diethyl ether: DCM (6:1:1), to give a pale yellow oil as an inseparable mixture of 3-methyl-1-tosyl-piperidine (branched) and *N*-(7-hydroxylheptyl)-4-methylbenzenesulfonamide (linear) in the ratio 88:12, (0.091 g, 0.36 mmol, 36 % yield from alkene). Enantioselectivity measured by HPLC, Chiracel AS-H column, hexane: IPA (90:10), 0.5 mL min^{-1}, 254-210 nm, t_R (minor): 50.8 min, t_R (major): 62.8 min. 84 % ee. Assignments made with the assistance of 2D NMR: HMBC and HSQC. Data matches the literature: *J. Am. Chem. Soc.*, 2010, 132 (26), 8880–8881.

The above procedure was repeated with 1.5 mmol of alkene to give a yield of 46 % of a mixture of the branched and linear products in the ratio 81:19.

^{1}H NMR δ(400 MHz, $CDCl_3$): 7.63 (2H, d, J = 8.2, Ar, 12 + 16), 7.32 (2H, d, J = 8.2, Ar, 13 + 15), 3.71 – 3.55 (2H, m, 2 x H of CH_2, 4a + 2a), 2.43 (3H, s, CH_3, 17), 2.19 (1H, td, J = 11.4, 2.7, 1H of CH_2, 2b), 1.86 (1H, t app, J = 10.7, 1H of CH_2, 4b), 1.80 – 1.54 (4H, m, CH_2 + CH + 1H of CH_2, 1 + 5 + 6a), 0.87 (3H, d, J = 6.5, CH_3, 7), 0.84 – 0.76 (1H, m, 1H of CH_2, 6b).

^{13}C NMR δ(126 MHz, $CDCl_3$): 143.4 (1 x C, s, 10), 133.4 (1 x C, s, 14), 129.7 (2 x CH, s, 13 + 15), 127.8 (2 x CH, s, 12 + 16), 53.4 (1 x CH_2, s, 4), 46.6 (1 x CH_2, s, 2), 32.2 (1 x CH_2, s, 6), 30.8 (1 x CH, s, 5), 24.8 (1 x CH_2, 1), 21.7 (1 x CH_3, s, 17), 19.1 (1 x CH_3, s, 7).

Asymmetric Transfer HF:

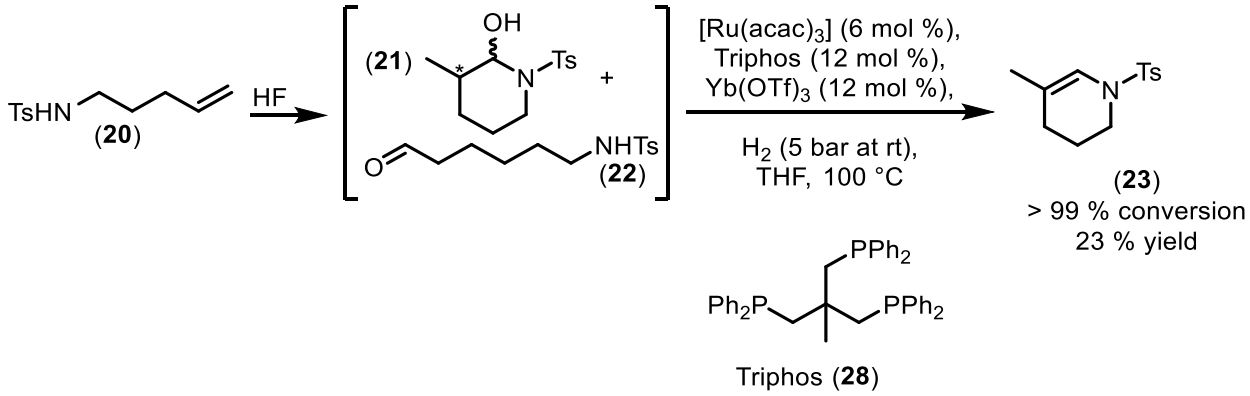


Procedure from *Adv. Syn. Catal.*, 2019, 361, 4334.

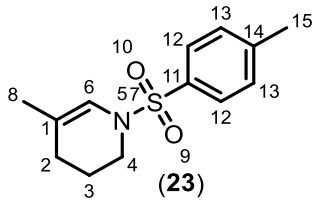
To an 8 mL pressure vial was added paraformaldehyde (90 mg, 3.0 mmol, 6 equiv), a stirrer bar and a small vial containing a flea stirrer bar. This was sealed with a septum and purged (3 x vacuum / N_2)

before the addition of the catalyst stock solutions outside the small vial. Catalyst stock solution 1: $[Rh(acac)(CO)_2]$ (2.7 mg, 0.0105 mmol, 2.1 mol %) and (*R*, *R*, *R*)-BOBPHOS (8.5 mg, 0.013 mmol, 2.6 mol %) in toluene (1 mL). Catalyst stock solution 2: $[Rh(COD)_2Cl]$ (2.0 mg, 0.004 mmol, 0.8 mol %) and (*S*, *S*)-Ph-BPE (2.3 mg, 0.0045 mmol, 0.9 mol %) in toluene (1 mL). A solution of alkene (0.120 g, 0.5 mmol, 1 equiv) in toluene (1 mL) was added inside the small vial. The septum was exchanged for a lid and the vial heated at 120 °C (30 mins). The solution turned orange then brown. The vial was then cooled (30 mins) before stirring at 40 °C (30 mins). The vial was then inverted several times and stirred at 40 °C overnight (18 hr). The vial was then cooled to room temperature and the brown solution taken onto the standard reduction procedure. The conversion, regioselectivity and enantioselectivity were measured on the reduced reaction mixture as described previously.

Catalytic Reduction of Hemi-aminal Reaction Mixture from AHF Reaction:



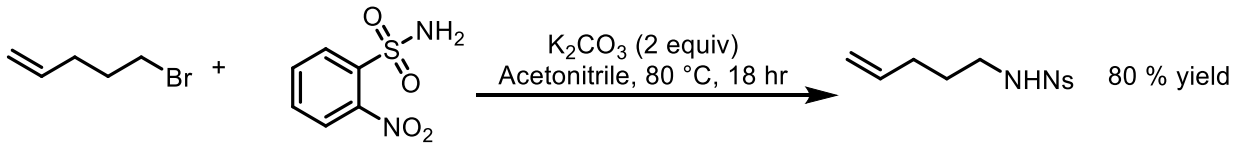
To an oven dried autoclave liner was added $[Ru(acac)_3]$ (24 mg, 0.06 mmol, 6 mol %), triphos (75 mg, 0.12 mmol, 12 mol %) and $Yb(OTf)_3$ (74 mg, 0.12 mmol, 12 mol %). The liner was sealed in an autoclave and the autoclave purged (3 x vacuum / N_2) before the addition of THF between the liner and the autoclave then the hemi-aminal substrate (reaction mixture from hydroformylation, **2.3** + **2.4**, approximately 0.269 g, 1.0 mmol, 1 equiv) was added in anhydrous THF (4 mL). The autoclave was sealed and flushed with hydrogen (x 3) before pressurising with hydrogen (5 bar) and heating (100 C, 40 hr). The autoclave was then cooled to room temperature (water bath, 40 mins) then the pressure released. The red solution was diluted with ethyl acetate (5 mL), filtered through a silica plug and concentrated in vacuo. Analysis by ^1H NMR shows only enamine present in the sample. The product was a yellow oil (0.0569 g, 0.23 mmol, 23 % yield).



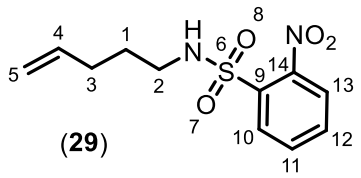
^{1}H NMR δ (400 MHz, $CDCl_3$): 7.68 – 7.61 (2H, m, Ar, 13), 7.29 (2H, d, J = 8.0, Ar, 12), 6.44 – 6.39 (1H, m, CH, 6), 3.33 – 3.26 (2H, m, CH_2, 4), 2.41 (3H, s, CH_3, 15), 1.81 (2H, t, J = 6.3, CH_2, 2), 1.65 – 1.56 (2H, m, CH_2, 3).

^{13}C NMR δ (126 MHz, $CDCl_3$): 143.5 (1 x C, s, 11), 135.3 (1 x C, s, 14), 129.8 (2 x CH, s, 12), 127.2 (2 x CH, s, 13), 119.6 (1 x CH, s, 6), 117.7 (1 x C, s, 1), 43.5 (1 x CH_2, s, 4), 26.5 (1 x CH_2, s, 3), 21.7 (1 x CH_3, s, 15), 21.1 (1 x CH_3, s, 8), 21.0 (1 x CH_s, s, 2).

Substrate Synthesis:



Acetonitrile, 5-bromo-1-pentene (0.6 mL, 5 mmol, 1 equiv), 2-nitrobenzenesulfonamide (1.52 g, 7.5 mmol, 1.5 equiv) and potassium carbonate (1.38g, 10 mmol, 2 equiv) were heated overnight (80 °C, 18 hr). The orange suspension was then filtered through a plug of celite and washed with ethyl acetate before concentrating in vacuo. The crude orange solid was then purified by silica column chromatography, hexane: diethyl ether (80:20) followed by a DCM flush to give the product as a yellow oil (1.025 g, 4.0 mmol, 80 % yield). Data matches the literature: *Tetrahedron*, 2003, 59, 46, 9239-9247.

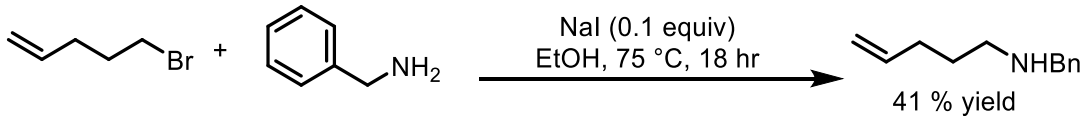


(**29**)

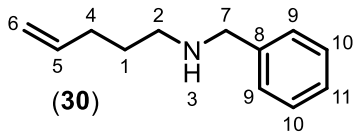
^{1}H NMR δ(400 MHz, $CDCl_3$): 8.17 – 8.10 (1H, m, Ar-CH, 13), 7.90 – 7.83 (1H, m, Ar-CH), 7.79 – 7.71 (2H, m, Ar-CH), 5.71 (1H, ddt, J = 16.9, 10.2, 6.7, CH, 4), 5.29 (1H, t, J = 5.7, N-*H*), 5.05 – 4.92 (2H, m, CH_2, 5), 3.17 – 3.06 (2H, m, CH_2, 2), 2.13 – 2.05 (2H, m, CH_2, 3), 1.66 – 1.58 (2H, m, CH_2, 1).

^{13}C NMR δ(126 MHz, $CDCl_3$): 148.0 (1 x C, s, 9), 137.0 (1 x CH, s, 4), 133.8 (1 x CH, s, Ar), 132.9 (1 x CH, s, Ar), 131.0 (1 x CH, s, Ar), 125.4 (1 x CH, s, Ar), 115.7 (1 x CH_2, s, 5), 43.2 (1 x CH_2, s, 2), 30.5 (1 x CH_2, s, 3), 28.6 (1 x CH_2, s, 1).

Substrate Synthesis:



To an oven dried microwave vial was added sodium iodide (30 mg, 0.2 mmol, 0.1 equiv), ethanol (5 mL), benzylamine (1.08 mL, 10 mmol, 5 equiv) and 5-bromo-1-pentene (0.24 mL, 2.0 mmol, 1 equiv). The vial was sealed and the solution heated overnight (75 °C, 18 hr). The solution was then concentrated in vacuo. DCM (5 mL) was added and a white solid precipitated. The suspension was filtered and the filtrate concentrated in vacuo to yield an orange oil. This was purified by distillation (90 °C, 1.5 mbar) to give the product as a colourless oil (0.145 g, 0.82 mmol, 41 % yield). Data matches the literature: *Beilstein J. Org. Chem.*, 2015, 11, 622–627.

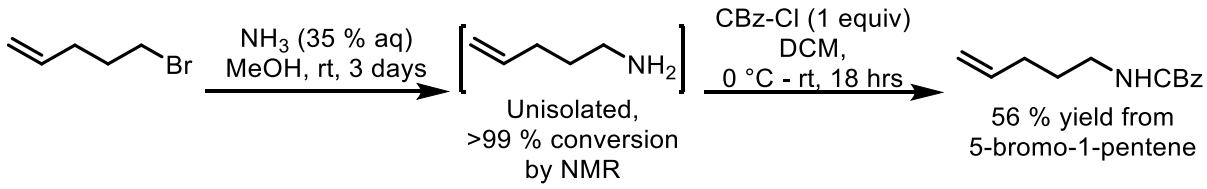


(**30**)

^{1}H NMR δ(400 MHz, $CDCl_3$): 7.47 – 7.22 (5H, m, Ar, 9-11), 5.86 (1H, ddt, J = 16.9, 10.1, 6.7, CH, 5), 5.15 – 4.93 (2H, m, CH_2, 6), 3.83 (2H, s, CH_2, 7), 2.69 (2H, t, J=7.2, CH_2, 2), 2.21 – 2.08 (2H, m, CH_2, 4), 1.71 – 1.61 (2H, m, CH_2, 1), 1.46 (1H, s, N-H, 3).

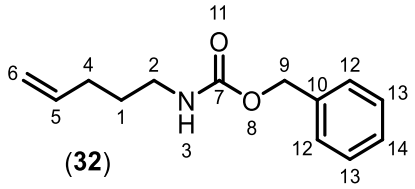
^{13}C NMR δ(126 MHz, $CDCl_3$): 140.4 (1 x C, s, 8), 138.6 (1 x CH, s, 5), 128.5 (2 x CH, s, Ar), 128.2 (2 x CH, s, Ar), 127.0 (1 x CH, s, 11), 114.8 (1 x CH_2, s, 6), 54.1 (1 x CH_2, s, 7), 48.9 (1 x CH_2, s, 2), 31.6 (1 x CH_2, s, 4), 29.3 (1 x CH_2, s, 1).

Substrate Synthesis:



To a 15 mL RBF was added methanol (1 mL), ammonia solution (35 % aqueous, 2.2 mL, 55 mmol, 11 equiv) and 5-bromo-1-pentene (0.59 mL, 5 mmol, 1 equiv). The colourless solution was stirred (rt, 3 days) before taking onto the next reaction with no further purification or isolation.

The solution of crude amine was diluted into DCM (7.5 mL) and cooled to 0 °C. Triethylamine (0.77 mL, 5.5 mmol, 1.1 equiv) and benzyl chlorocarbamate (0.79 mL, 5.5 mmol, 1.1 equiv) were added and the solution warmed to room temperature over 3 hours. The suspension was filtered and sat. NaHCO3 (aq, 5 mL) was added. The biphasic solution was stirred (rt, 45 mins) and then the layers separated. The organic layer was washed with water, dried over Na_2SO_4, filtered and concentrated in vacuo to give a colourless solid (0.614 g, 2.8 mmol, 56 % yield). Data matches the literature: *J. Am. Chem. Soc.* 2006, 128, 13, 4246–4247.

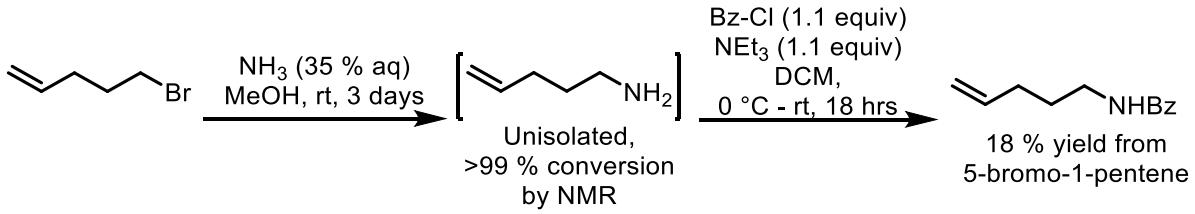


(**32**)

^{1}H NMR δ(400 MHz, $CDCl_3$): 7.41 – 7.27 (5H, m, 5 x Ar-CH, 12-14), 5.85 – 5.74 (1H, m, CH, 5), 5.23 – 4.88 (4H, m, 2 x CH_2, 6 + 9), 4.74 (1H, br s, N-H, 3), 3.28 – 3.19 (2H, m, CH_2, 2), 2.12 – 2.01 (2H, m, CH_2, 4), 1.65 – 1.57 (2H, m, CH_2, 1).

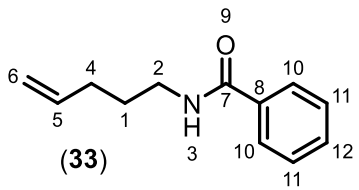
^{13}C NMR δ(126 MHz, $CDCl_3$): 156.5 (1 x C, s, 7), 137.8 (1 x CH, s, 5 or Ar), 136.7 (1 x C, s, 10), 128.6 (2 x CH, s, Ar), 128.1 (2 x CH, Ar), 115.3 (1 x CH_2, s, 6), 66.6 (1 x CH_2, s, 9), 40.6 (1 x CH_2, s, 2), 30.9 (1 x CH_2, s, 4), 29.1 (1 x CH_2, s, 1). CH of alkene not visible or under aryl CH signal.

Substrate Synthesis:



To a 15 mL RBF was added methanol (1 mL), ammonia solution (35 % aqueous, 2.2 mL, 55 mmol, 11 equiv) and 5-bromo-1-pentene (0.59 mL, 5 mmol, 1 equiv). The colourless solution was stirred (rt, 3 days) before taking onto the next reaction with no further purification or isolation.

To a 15 mL RBF was added crude pent-4-en-1-amine (0.426g, 5.0 mmol, 1 equiv) in DCM (2 mL) and triethylamine (0.77 mL, 5.5 mmol, 1.1 equiv). The solution was cooled to 0 °C before the addition of benzoyl chloride (0.64 mL, 5.5 mmol, 1.1 equiv). The solution was stirred at 0 °C before warming to room temperature (3 hr). sat $NaHCO_3$ (aq, 5 mL) was added and a solid precipitated. The biphasic solution was stirred (rt, 1 hr). Water (5 mL) and DCM (5 mL were added. The layers were separated and the aqueous layer was extracted with DCM (2 x 5 mL) before the combined organic layers were washed with water (5 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. Purified by aluminium oxide column chromatography, Hex: EtOAc (75: 25 to 50:50); (0.170 g, 0.9 mmol, 18 % yield). Data matches the literature: *Org. Lett.*, 2013, 15, 9, 2314-2317.

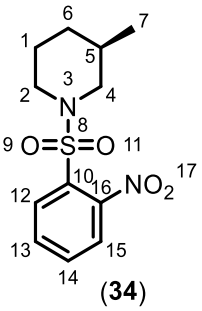


(**33**)

^{1}H NMR δ(400 MHz, $CDCl_3$): 7.75 (2H, dd, J = 8.3, 1.4, Ar, 10), 7.55 – 7.37 (3H, m, Ar, 11), 6.23 (1H, s, N-H, 3), 5.84 (1H, ddt, J = 16.9, 10.2, 6.7, CH, 5), 5.15 – 4.95 (2H, m, CH_2, 6), 3.60 – 3.35 (2H, m, CH_2, 2), 2.24 – 2.06 (2H, m, CH_2, 4), 1.84 – 1.62 (2H, m, CH_2, 1).

^{13}C NMR δ(126 MHz, $CDCl_3$): 167.5 (1 x C, s, 7), 137.9 (1 x CH, s, 5), 134.8 (1 x C, s, 8), 131.4 (1 x CH, s, 12), 128.6 (2 x CH, s, 10), 126.8 (2 x CH, s, 11), 115.4 (1 x CH_2, s, 6), 39.7 (1 x CH_2, s, 2), 31.3 (1 x CH_2, s, 4), 28.8 (1 x CH_2, s, 1).

Asymmetric HF-Cyclisation:



(**34**)

Table 2, entry 2: The standard AHF procedure was followed with 1.0 mmol of alkene. The crude AHF reaction mixture was reduced with triethylsilane and boron trifluoride diethyletherate as detailed in the general procedures. After this the conversion and branched to linear ratio were measured by ^{1}H NMR: > 99 % conversion and 85:15 branched to linear ratio were recorded in this example. Purified by silica column chromatography, hexane: diethyl ether: DCM (6:1:1) to give the product as a single regioisomer and as a pale yellow oil, (0.063 g, 0.22 mmol, 22 % yield from alkene). Enantioselectivity measured by HPLC, Chiracel AS-H column, hexane: IPA (90:10), 0.5 mL min^{-1}, 254-210 nm, t_R (minor): 59.4 min, t_R (major): 63.1 min. 90 % ee. Assignments made with the assistance of 2D NMR: HSQC and HMBC.

^{1}H NMR δ(400 MHz, $CDCl_3$): 8.01 – 7.93 (1H, m, Ar), 7.72 – 7.63 (2H, m, Ar), 7.63 – 7.55 (1H, m, Ar), 3.78 – 3.64 (2H, m, CH_2, 2), 2.70 (1H, td, J = 12.1, 2.8, 1H of CH_2, 4a), 2.37 (1H, dd, J = 12.1, 10.5, 1H of CH_2, 4b), 1.83 – 1.52 (4H, m, 2 x CH_2, 1 + 6), 1.05 – 0.93 (1H, m, CH, 5), 0.90 (3H, d, J = 6.6, CH_3, 7).

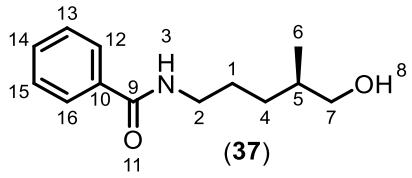
^{13}C NMR δ(126 MHz, $CDCl_3$): 148.5 (1 x C, s, 10), 133.5 (1 x CH, s, Ar), 132.1 (1 x C, s, 16), 131.5 (1 x CH, s, Ar), 131.0 (1 x CH, s, Ar), 124.1 (1 x CH, s, Ar), 53.0 (1 x CH_2, s, 4), 46.4 (1 x CH_2, s, 2), 32.3 (1 x CH_2, s, 6), 31.0 (1 x CH, s, 5), 25.1 (1 x CH_2, s, 1), 19.0 (1 x CH_3, s, 7).

IR (neat, cm^{-1}): 1541, 1371, 1344, 1171 and 1157.

Mass Spec: M + Na: 307.0715 m/z, $C_{12}H_{16}N_2O_4SNa$ requires 307.0723.

$[\alpha]^{D}_{20}$ = - 5.85 (c = 0.94, CH_2Cl_2)

Asymmetric HF:



(**37**)

Table 2, entry 5: The standard AHF procedure was followed with 0.5 mmol of alkene. The crude AHF reaction mixture was reduced with sodium borohydride as detailed in the general procedures. After this the conversion and branched to linear ratio were measured by ^{1}H NMR: 98 % conversion and 72:28 branched to linear ratio were recorded in this example. Purified by aluminium oxide column chromatography with DCM and NEt_3 (1 %) followed by DCM: MeOH (9:1) flush to give an inseparable mix of the branched and linear alcohols as a pale yellow oil (0.032 g, 0.145 mmol, 29 % yield from alkene). Enantioselectivity measured by HPLC, Chiracel column AD-H, Hexane: IPA (90:10), 0.8 mLmin^{-1}, 254-230 nm, t_R (major): 24.4 min, t_R (minor): 25.3 min. 75 % ee. Assignments made with the assistance of 2D NMR: HSQC and HMBC.

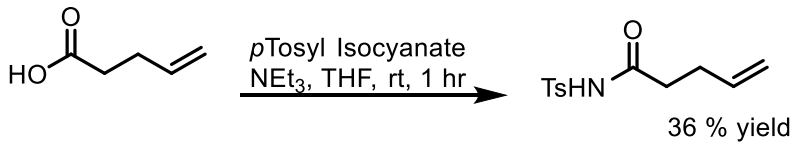
^{1}H NMR δ(400 MHz, $CDCl_3$): 7.92 – 7.14 (5H, m, Ar, 12-16), 3.43 – 3.36 (4H, m, 2 x CH_2, 2 + 7), 1.75 – 1.37 (5H, m, 2 x CH_2 + CH, 1 + 4 + 5), 0.86 (3H, d, J=6.6, CH_3, 6).

^{13}C NMR δ(126 MHz, $CDCl_3$): 167.9 (1 x C, s, 9), 134.7 (1 x C, s, 10), 131.3 (1 x CH, s, 14), 128.4 (2 x CH, 13 + 15), 127.0 (2 x CH, s, 12 + 16), 67.6 (1 x CH_2, 7), 40.2 (1 x CH_2, s, 2), 35.2 (1 x CH, s, 5), 30.3 (1 x CH_2, s, 4), 26.8 (1 x CH_2, s, 1), 16.7 (1 x CH_3, s, 6).

IR (neat, cm^{-1}): 3312, 2930, 1636, 1543 and 1310.

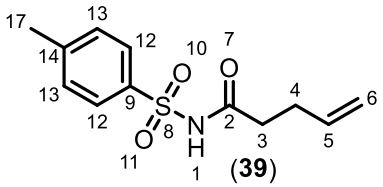
Mass Spec: M + Na: 244.1304 m/z, $C_{13}H_{19}NO_2Na^+$ requires 244.1308.

Substrate Synthesis:



To a flame dried Schlenk was added anhydrous THF (10 mL), 4-pentenoic acid (1 mL, 10 mmol, 1 equiv) and *p*-tosyl isocyanate (1.5 mL, 10 mmol, 1 equiv). The solution was stirred under inert conditions (10 mins) before opening to air and dropwise addition of triethyl amine (1.4 mL, 10 mmol, 1 equiv). CO_2 gas evolved and the solution was stirred (rt, 45 mins) before being quenched with 1M HCl (10 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL) before the combined organic fractions were dried over Na_2SO_4, filtered and concentrated in vacuo. Purified by silica column chromatography, Hex:

EtOAc (7:3) to give the product as a colourless, crystalline solid (0.912 g, 3.6 mmol, 36 % yield). Data matches the literature: *Chem. Eur. J.*, 2014, 20, 6, 1539-1546.

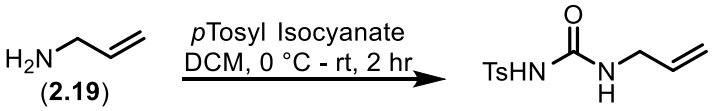


(**39**)

^{1}H NMR δ(400 MHz, $CDCl_3$): 7.94 (2H, d, J = 8.2, Ar, 12), 7.34 (2H, d, J = 8.2, Ar, 13), 5.71 (1H, ddt, J = 16.7, 10.4, 6.3, CH, 5), 4.98 (2H, m, CH_2, 6), 2.44 (3H, s, CH_3, 17), 2.41 – 2.22 (4H, m, 2 x CH_2, 3 + 4).

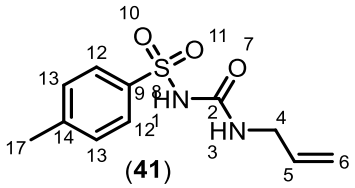
^{13}C NMR δ(126 MHz, $CDCl_3$): 170.5 (1 x C, s, 2), 145.3 (1 x C, s, 9), 135.9 (1 x CH, s, 5), 135.6 (1 x C, s, 14), 129.8 (2 x CH, s, 12), 128.5 (2 x CH, s, 13), 116.3 (1 x CH_2, s, 6), 35.5 (1 x CH_2, s, 3), 28.2 (1 x CH_2, s, 4), 21.8 (1 x CH_3, s, 17).

Substrate Synthesis:



(**2.20**)
63 % yield

To a flame dried Schlenk was added dry DCM (12 mL) and allyl amine (0.45 mL, 5.99 mmol, 1.0 equiv). This colourless solution was cooled to 0 C before the addition of p-tosylisocyanate (0.93 mL, 6.12 mmol, 1.02 equiv). The solution was stirred at 0 C (10 min) before warming to room temperature (1.5 hr). The white suspension was concentrated in vacuo to yield a fluffy white solid. This was suspended in ethyl acetate (20 mL) before washing with water (10 mL). The aqueous layer was extracted with ethyl acetate (2 x 12 mL) before the combined organic layers were dried over MgSO4, filtered and concentrated in vacuo to give the product as a white solid (0.966 g, 3.8 mmol, 63 % yield). Data matches the literature: *Angew. Chem. Int. Ed.*, 2011, 50 (20), 4680 – 4683.

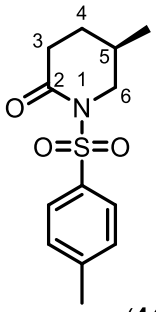


(**41**)

^{1}H NMR δ(400 MHz, $CDCl_3$): 7.78 (2H, d, J = 8.4, Ar, 12 + 16), 7.33 (2H, d, J = 8.1, Ar, 13 + 15), 6.66 (1H, s, NH, 3), 5.78 (1H, ddt, J = 17.3, 10.7, 5.5, CH, 5), 5.20 – 5.05 (2H, m, CH_2, 6), 3.91 – 3.73 (2H, m, CH_2, 4), 2.45 (3H, s, CH_3, 17).

^{13}C NMR δ(101 MHz, $CDCl_3$): 133.5 (1 x CH, s, 5), 130.2 (2 x CH, s, 13 + 15), 127.1 (2 x CH, s, 12 + 16), 116.7 (1 x CH_2, s, 6), 42.8 (1 x CH_2, s, 4), 21.8 (1 x CH_3, s, 17).

Asymmetric HF-Cyclisation:



(**44**)

The standard AHF procedure was followed with 0.5 mmol of alkene. The crude AHF reaction mixture was reduced with triethylsilane and boron trifluoride diethyletherate as detailed in the general procedures. After this the conversion and branched to linear selectivity were measured by ^{1}H NMR: > 99 % conversion and 93:7 branched to linear ratio were recorded in this example. Purified by silica column chromatography, hexane: ethyl acetate (7:3) to give the product as one regioisomer and as a colourless, crystalline solid, (0.037 g, 0.14 mmol, 28 % yield from alkene). Enantioselectivity measured by HPLC, Chiracel AD-H, hexane: IPA (80:20), 1 mLmin^{-1}, 254 – 230 nm, t_R (major): 16.6 min, t_R (minor): 19.6 min. 89 % ee. Assignments made with the assistance of 2D NMR: HSQC and HMBC.

^{1}H NMR δ(400 MHz, $CDCl_3$): 7.90 (2H, d, J = 8.2, Ar, 12 + 16), 7.31 (2H, d, J = 8.2, Ar, 13 + 15), 4.14 (1H, ddd, J = 12.0, 4.7, 1.8, 1H of CH_2, 4a), 3.33 – 3.20 (1H, m, 1H of CH_2, 4b), 2.52 – 2.33 (2H, m, CH_2, 1), 2.07 – 1.97 (1H, m, CH, 5), 1.87-1.84 (1H, m, 1H of CH_2, 6a), 1.46 – 1.38 (1H, m, 1H of CH_2, 6b), 1.08 (3H, d, J = 6.6, CH_3, 7).

^{13}C NMR δ(126 MHz, $CDCl_3$): 170.3 (1 x C, s, 2), 144.9 (1 x C, s, 10), 136.1 (1 x C, s, 14), 129.4 (2 x CH, s, 13 + 15), 128.9 (2 x CH, s, 12 + 16), 53.1 (1 x CH_2, s, 4), 33.4 (1 x CH_2, s, 1), 29.5 (1 x CH, s, 5), 28.6 (1 x CH_2, s, 6), 21.8 (1 x CH_3, s, 17), 18.6 (1 x CH_3, s, 7).

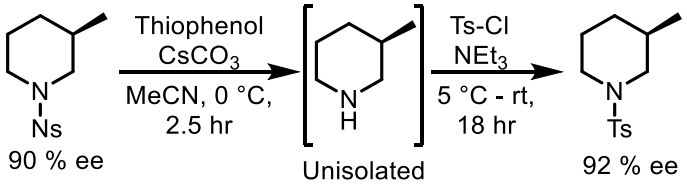
IR (neat, cm^{-1}): 1684, 1350, 1171, 818 and 664.

Mass spec: M + Na = 290.0815 m/z, $C_{13}H_{17}NO_3SNa^+$ requires 290.0821.

Melting point: 135 – 138 °C.

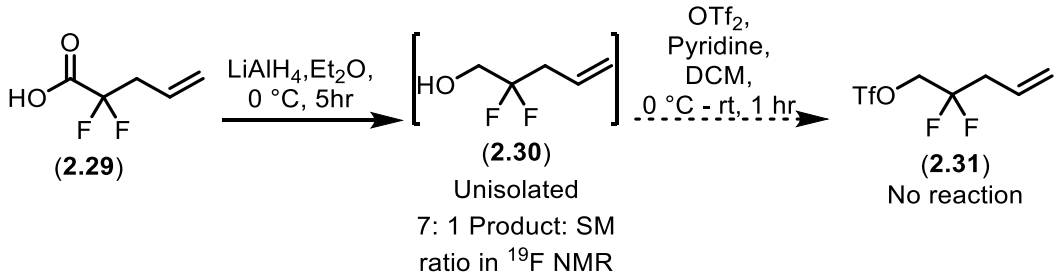
$[\alpha]^D_{20}$: +52.5 (c = 1.0, MeOH)

Deprotection of *N*-nosyl-3-methylpiperidine and Reprotection:



To a 25 mL RBF was added *N*-nosyl-3-methylpiperidine (64 mg, 0.23 mmol, 1 equiv) and thiophenol (0.04 mL, 0.35 mmol, 1.5 equiv) in acetonitrile (5 mL). Cesium carbonate (91 mg, 0.28 mmol, 1.2 equiv) was added and the solution stirred at 0 °C (2.5 hr). The suspension was filtered to remove cesium carbonate and then triethyl amine (0.03 mL, 0.23 mmol, 1 equiv) and tosyl chloride (40 mg, 0.21 mmol, 0.9 equiv) were added. The solution was stored at 5 °C overnight. The suspension was then filtered and diluted into ethyl acetate (5 mL) and saturated $NaHCO_3$ (aq., 5 mL). This biphasic solution was stirred (rt, 1 hr) before the layers were separated and the organic layer washed with water (5 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. NMR data and HPLC methods are listed previously in this document.

Substrate Synthesis:

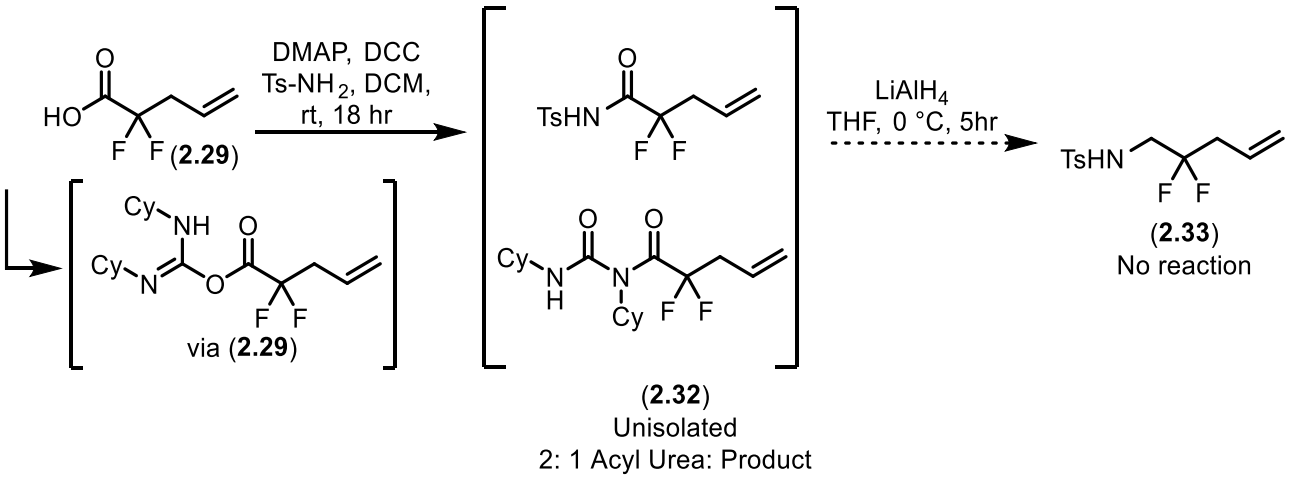


To a flame dried Schlenk was added dry diethyl ether (50 mL) and cooled to 0 C. 2,2-difluoro-4-pentenoic acid (1.6 mL, 14.7 mmol, 1 equiv) was added before dropwise addition of lithium aluminium hydride (1M in THF, 1.8 mL, 44.1 mmol, 3 equiv) at 0 C. The solution was stirred (0 C, 2 hr) then at room temperature (3 hr). The solution was cooled (0 C, 10 mins) and water (2 mL) was added dropwise to quench before 15 % w/v aq. NaOH solution (1.6 mL) and more water (5 mL) were added. The suspension was stirred (rt, 1 hr) before filtering through a celite plug. The filter cake was washed with water and the layers separated. The organic layer was dried over $MgSO_4$ and filtered. The crude was taken onto the next reaction without further purification. Analysis by ^{19}F NMR showed product and starting material at a ratio of 7:1.

To a flame dried Schlenk was added the crude alcohol (1.795 g, 14.7 mmol, 1 equiv) in diethyl ether (50 mL) and cooled to 0 °C before the addition of pyridine (1.3 mL, 16.17 mmol, 1.1 equiv). A solution of trifluoromethanesulfonic anhydride (2.7 mL, 16.17 mmol, 1.1 equiv) in DCM (5 mL) was added dropwise at 0 °C before the solution was warmed to room temperature (30 mins). The solution was

placed in an ice bath and water (5 mL) was added. The layers were separated and the organic layer washed with water (15 mL) and brine (15 mL) before drying over $MgSO_4$, filtering and analysis by ^{19}F NMR. No peak relating to the desired product was observed.

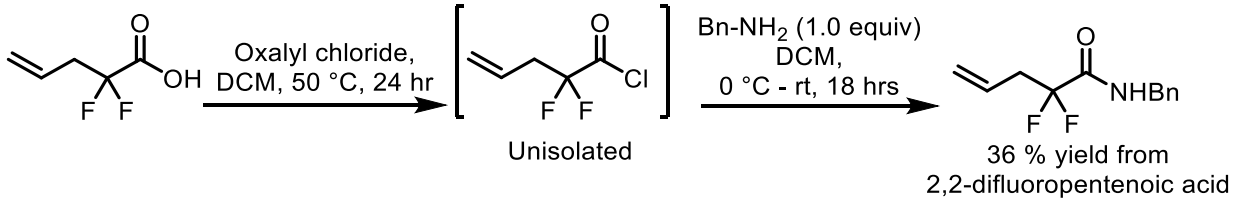
Substrate Synthesis:



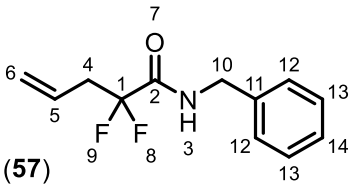
To a 50 mL RBF was added *p*-tosylsulfonamide (0.634 g, 3.7 mmol, 1 equiv), dimethylaminopyridine (0.678 g, 5.55 mmol, 1.5 equiv). 2,2-difluoro-4-pentenoic acid (0.41 mL, 3.7 mmol, 1 equiv) and DCM (7.5 mL). The suspension was stirred until solvated (2 mins) and then dicyclohexylcarbodiimide (1.14 g, 5.5 mmol, 1.5 equiv) was added. The orange solution was then stirred overnight (rt, 18 hr). 4 M HCl (3 mL) was added to the white suspension to quench. The layers were separated and the aqueous layer was extracted with DCM (3 x 5 mL). The combined organic portions were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. Analysis by ^1H NMR and ^{19}F NMR showed a 2:1 mixture of acyl urea and product, the crude reaction was taken onto the next step without purification.

To a flame dried Schlenk was added the crude amide reaction mixture (1.07 g, 3.7 mmol, 1 equiv), anhydrous THF (7.5 mL) and cooled to 0 C before dropwise addition of lithium aluminium hydride (1 M in THF, 0.31 mL, 7.4 mmol, 2 equiv). The white suspension was stirred at 0 C (1 hr) then at room temperature (3 hr). The solution was cooled to 0 C and water (2 mL) was added to quench, followed by 10 % w/v aq. NaOH solution (5 mL) and more water (5 mL). The slurry was stirred (rt, 1 hr) before the layers were separated and the aqueous layer extracted with diethyl ether (3 x 5 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. Analysis by ^1H NMR and ^{19}F NMR showed no conversion to the desired product.

Substrate Synthesis:



To an oven dried microwave vial was added 2,2-difluoropent-4-enoic acid (0.34 mL, 3.0 mmol, 1 equiv) and oxalyl chloride (1.3 mL, 9.0 mmol, 3 equiv) as a 2M solution in DCM. The vial was sealed and heated (50 °C, 24 hr). CAUTION: Pressure build up. The vial was then cooled to room temperature and the solution injected into an RBF containing benzylamine (0.56 mL, 5.14 mmol, 1.2 equiv) and DCM (5 mL) at 0 °C. The solution was stirred at 0 °C (1 hr) then warmed to room temperature overnight. The sample was further diluted into DCM (10 mL) and washed with saturated $NaHCO_3$ (3 x 5 mL). The layers were separated and the organic layer dried over Na_2SO_4, filtered and concentrated in vacuo. Purified by silica column chromatography, Hexane: DCM (1:1 through to 0:1) to give the target compound as a yellow oil (0.243 g, 1.08 mmol, 36 % yield over the two steps).


(**57**)

^{1}H NMR δ(400 MHz, $CDCl_3$): 7.43 – 7.25 (5H, m, Ar, 12-14), 5.76 (1H, ddt, J = 17.3, 10.2, 7.2, CH, 5), 5.36 – 5.21 (2H, m, CH_2, 6), 4.51 (2H, d, J = 5.9, CH_2, 10), 2.92 (2H, tdt, J = 16.8, 7.2, 1.2, CH_2, 4).

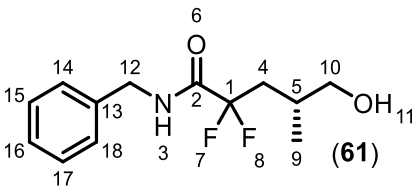
^{13}C NMR δ(126 MHz, $CDCl_3$): 163.9 (1 x C, s, 2), 136.9 (1 x C, s, 11), 129.0 (2 x CH, s, 13), 128.1 (1 x CH, s, 14), 128.0 (2 x CH, s, 12), 127.4 (CH, t, J = 5.5, 5), 122.0 (1 x CH_2, s, 6), 117.3 (1 x CF_2, t, J = 253.4, 1), 43.6 (1 x CH_2, s, 10), 38.6 (1 x CH_2, t, J = 24.0, 4).

^{19}F{^{1}H} NMR: δ(377 MHz, $CDCl_3$): -106.0 (s).

IR (neat, cm^{-1}): 1682, 1541, 1454, 1429 and 696.

Mass spec: M + H = 226.1038 m/z, $C_{12}H_{14}F_2NO^+$ requires 226.1038 and M + Na = 248.0855 m/z, $C_{12}H_{13}F_2NONa^+$ requires 248.0847.

Asymmetric HF:


(**61**)

The standard AHF procedure was followed with 0.5 mmol of alkene. The crude AHF reaction mixture was reduced with sodium borohydride as detailed in the general procedures. After this the conversion and branched to linear ratio were measured by ^{1}H NMR: > 99 % conversion and 90:10 branched to linear ratio were recorded in this example. Purified by silica column chromatography, DCM: NEt_3 (2 %) to give the product as an inseparable mixture of branched and linear alcohols, a pale yellow oil (0.046 g, 0.18 mmol, 36 % yield from alkene). Enantioselectivity measured by HPLC, Chiracel AD-H, hexane: IPA (90-10), 0.5 mL min^{-1}, 254-230 nm, t_R (minor): 32.2 min, t_R (major): 35.1 min. 80 % ee. Assignments made with the assistance of 2D NMR: HSQC and HMBC.

^{1}H NMR δ(400 MHz, $CDCl_3$): 7.48 – 7.22 (5H, m, Ar, 14-18), 4.51 (2H, d, J = 5.8, CH_2, 12), 3.59 – 3.41 (2H, m, CH_2, 10), 2.50 – 2.27 (1H, m, 1H of CH_2, 4a), 2.08 – 1.87 (2H, m, 1H of CH_2 + CH, 4b + 5), 1.04 (3H, d, J = 6.5, CH_3, 9).

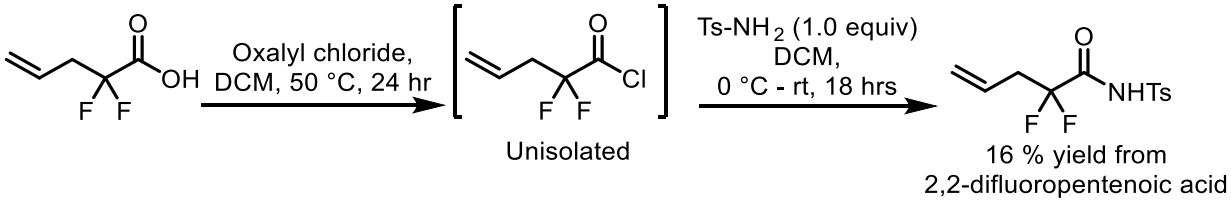
^{13}C NMR δ(126 MHz, $CDCl_3$): 164.6 (1 x C, s, 2), 136.8 (1 x C, s, 13), 129.1 (2 x CH, s, 14 + 18), 128.2 (1 x CH, 16), 128.0 (2 x CH, s, 15 + 17), 118.6 (1 x CF_2, t, J = 252.6, 1), 67.3 (1 x CH_2, s, 10), 43.7 (1 x CH_2, s, 12), 36.7 (1 x CH_2, t, J = 22.6, 4), 30.45 (1 x CH, t, J = 3.0, 5), 17.66 (1 x CH_3, s, 9).

^{19}F{^{1}H} NMR δ(377 MHz, $CDCl_3$): -102.0 (d, J=257.1), -105.0 (d, J=257.1).

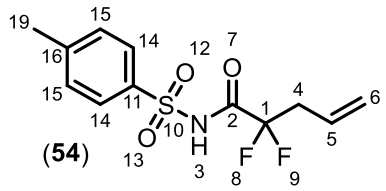
IR (neat, cm^{-1}): 1680, 1543, 1188, 1030, and 696.

Mass spec: M = 258.1294 m/z, $C_{13}H_{18}F_2NO_2^+$ requires 258.1300.

Substrate Synthesis:



To an oven dried microwave vial was added 2,2-difluoropent-4-enoic acid (0.34 mL, 3.0 mmol, 1 equiv) and oxalyl chloride (1.3 mL, 9.0 mmol, 3 equiv) as a 2M solution in DCM. The vial was sealed and heated (50 °C, 24 hr). CAUTION: Pressure build up. The vial was then cooled to room temperature and the solution injected into an RBF containing tosylamide (0.514g, 3.0 mmol, 1 equiv) and DCM (5 mL) at 0 °C. The solution was stirred at 0 °C (1 hr) then warmed to room temperature overnight. Saturated $NaHCO_3$ (5 mL) and EtOAc (5 mL) were added and the solution stirred (room temperature, 1 hr). The layers were separated and the organic layer dried over Na_2SO_4, filtered and concentrated in vacuo. Purified by silica column chromatography, Hexane: DCM (1:1 through to 0:1) to give the target compound as a white, crystalline solid (0.139 g, 0.48 mmol, 16 % yield over the two steps).



(**54**)

^{1}H NMR δ(400 MHz, $CDCl_3$): 8.80 (1H, s, NH, 3), 7.97 (2H, d, J = 8.3, Ar, 14 + 18), 7.37 (2H, d, J = 8.3, Ar, 15 + 17), 5.60 (1H, ddt, J = 17.4, 10.2, 7.2, CH, 5), 5.24 – 5.07 (2H, m, CH_2, 6), 2.78 (2H, td, J = 16.7, 7.2, CH_2, 4), 2.46 (3H, s, CH_3, 19).

^{13}C NMR δ(126 MHz, $CDCl_3$): 161.3 (1 x C, t, J = 32.0, 2), 146.1 (1 x C, s, 11), 134.3 (1 x C, s, 16), 129.9 (2 x CH, s, 14 + 18), 128.8 (2 x CH, s, 15 + 17), 125.8 (1 x CH, t, J = 5.3, 5), 122.9 (1 x CH_2, s, 6), 116.2 (1 x CF_2, t, J = 225.2, 1) 38.0 (1 x CH_2, t, J = 23.3, 4), 21.8 (1 x CH_3, s, 19).

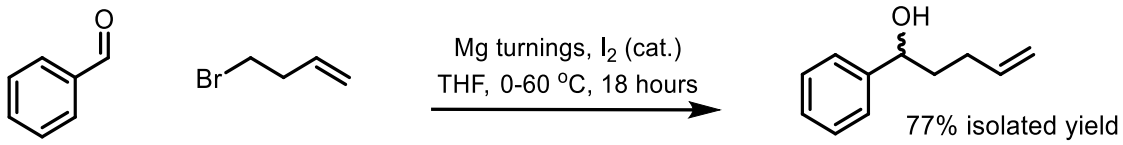
^{19}F{^{1}H} NMR: δ(377 MHz, $CDCl_3$): -105.4 (s).

IR (neat, cm^{-1}): 1742, 1447, 1350, 1169 and 1086.

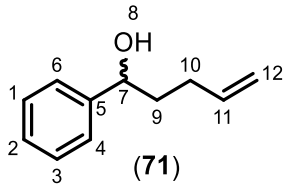
Mass spec: M + Na = 312.0466 m/z, $C_{12}H_{13}F_2NO_3SNa^+$ requires 312.0476.

Melting point: 113 – 116 °C

Substrate Synthesis:



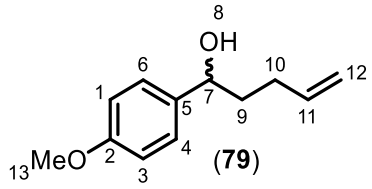
To a small crystal of iodine in anhydrous THF was added magnesium turnings (170 mg, 7.0 mmol, 3.5 equiv). The resulting suspension was stirred at 0 °C before the addition of 4-bromo-1-butene (0.71 mL, 7.0 mmol, 3.5 equiv). The suspension was then stirred until a clear solution observed (0 °C, 1 hr). Benzaldehyde (0.22 mL, 2.0 mmol, 1 equiv) in anhydrous THF was then added slowly at 0 °C and stirred (0.5 hr) before the temperature was increased to 65 °C and the reaction heated overnight. The resulting orange solution was cooled to 0 °C before quenching with sat. NH_4Cl, filtered and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with brine and dried over Na_2SO_4 before being filtered and concentrated in vacuo. The resulting orange oil was purified by silica column chromatography, hexane: ethyl acetate (7:3) to give the product as a colourless oil (0.249 g, 1.54 mmol, 77 % yield). Enantioselectivity measured by chiral HPLC, Chiralpak AS-H, 250 x 4.6 mm, hexane: IPA (98: 2), 0.5 mL/ min, 254 – 230 nm, t_R (minor): 22.7 min, t_R (major): 24.7 min. Data matches the literature: *Green Chem.,* 2017, 19, 670 – 674.



(**71**)

^{1}H NMR δ(500 MHz, $CDCl_3$): 7.50 – 7.26 (5H, m, Ar, 1-4 + 6), 5.91 – 5.83 (1H, m, CH, 11), 5.11 – 4.99 (2H, m, CH_2, 12), 4.69 (1H, t, J = 6.6, CH, 7), 2.22 – 2.08 (2H, m, CH_2, 9), 1.99 – 1.73 (2H, m, CH_2, 10).

^{13}C NMR δ(126 MHz, $CDCl_3$): 138.3 (1 x CH, s, 2), 138.2 (1 x C, s, 5), 128.5 (2 x CH, 4 + 6), 127.6 (1 x CH, s, 11), 126.0 (2 x CH, s, 1 + 3), 115.0 (1 x CH_2, s, 12), 74.0 (1 x CH, s, 7), 38.1 (1 x CH_2, s, 9), 30.1 (1 x CH_2, s, 10).



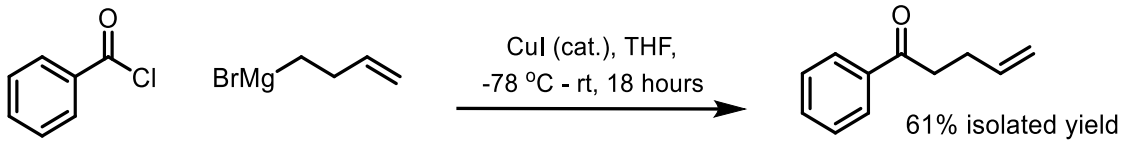
(**79**)

Compound was purified by silica column chromatography, hexane: ethyl acetate (4:1) to give the product as a yellow oil (1.461 g, 7.6 mmol, 76 % yield). Data matches the literature: *J. Org. Chem.,* 2018, 83 (15), 7694 - 7713.

^{1}H NMR δ(500 MHz, $CDCl_3$): 7.34 – 7.22 (2H, m, Ar, 1 + 3), 6.97 – 6.83 (2H, m, Ar, 4 + 6), 5.90 – 5.81 (1H, m, CH, 11), 5.15 – 4.94 (2H, m, CH_2, 12), 4.71 – 4.56 (1H, m, CH, 7), 3.81 (3H, s, CH_3, 13), 2.20 – 2.03 (2H, m, CH_2, 9), 1.97 – 1.72 (2H, m, CH_2, 10).

^{13}C NMR δ(126 MHz, $CDCl_3$): 159.0 (1 x C, s, 2), 138.3 (1 x CH, s, 11), 136.8 (1 x C, s, 5), 127.2 (2 x CH, s, 1 + 3), 114.9 (1 x CH_2, s, 12), 113.8 (2 x CH, s, 4 + 6), 73.6 (1 x CH, s, 7), 55.3 (1 x CH_3, s, 13), 38.0 (1 x CH_2, s, 9), 30.2 (1 x CH_2, s, 10).

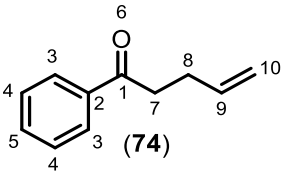
Substrate Synthesis:



Compound prepared as according to literature: *J. Am. Chem. Soc.,* 2006, 128 (11), 3748 - 3759.

To magnesium turnings (248 mg, 10.2 mmol, 1.02 equiv) in anhydrous THF was added 4-bromo-1-butene (1 mL, 10.2 mmol, 1.02 equiv) at room temperature and this was stirred until a clear solution obtained (1 hr). The Grignard reagent was then added dropwise to a solution of copper iodide (93 mg, 0.5 mmol, 5 mol %) and benzoyl chloride (1.2 mL, 10 mmol, 1 equiv) in anhydrous THF at -78 °C. The

solution was then warmed to room temperature overnight. The pale yellow solution was concentrated in vacuo before the addition of DCM and 1M HCl. The layers were then separated and the aqueous layer extracted with DCM. The combined organic layers were washed with sat. $NaHCO_3$ and dried over $MgSO_4$, filtered and concentrated in vacuo before purification by silica column chromatography.

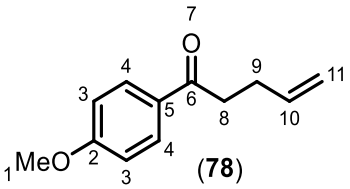


(**74**)

Purified by silica column chromatography, hexane: ethyl acetate (40:1) to give the product as a colourless oil (0.979 g, 6.1 mmol, 61 % yield). Data matches the literature: *J. Am. Chem. Soc.,* 2006, 128 (11), 3748 - 3759.

^{1}H NMR δ(500 MHz, $CDCl_3$): 7.94 (2H, d, J = 7.2, Ar, 3), 7.59 – 7.37 (3H, m, Ar, 4,5), 5.89 (1H, ddt, J = 18.4, 9.5, 6.7, CH, 9), 5.10 – 4.99 (2H, m, CH_2, 10), 3.12 – 2.98 (2H, m, CH_2, 7), 2.48 (2H, q, J = 6.4, CH_2, 8).

^{13}C NMR δ(126 MHz, $CDCl_3$): 199.4 (1 x C, s, 1), 137.3 (1 x CH, s, 5), 136.9 (1 x C, s, 2), 133.0 (1 x CH, s, 9), 128.6 (2 x CH, s, 3), 128.0 (2 x CH, s, 4), 115.3 (1 x CH_2, s, 10), 37.7 (1 x CH_2, s, 7), 28.2 (1 x CH_2, s, 8).



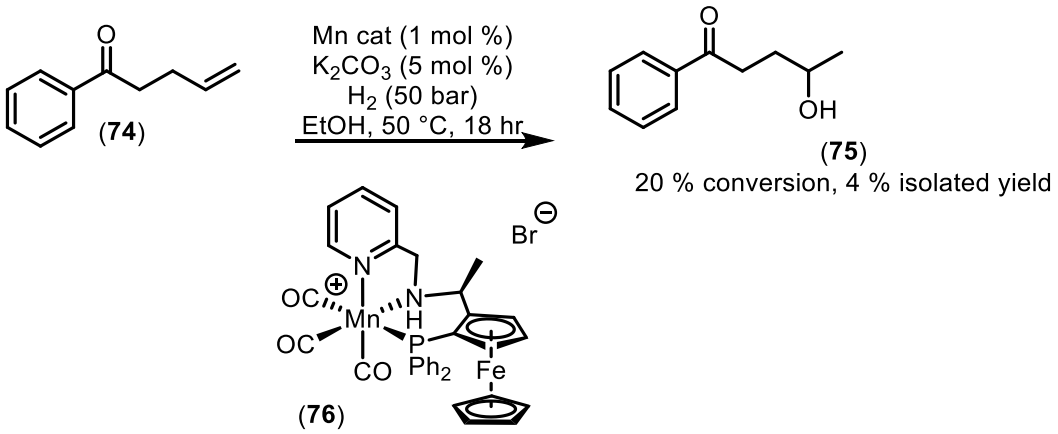
(**78**)

Purified by silica column chromatography, hexane: ethyl acetate (9:1) to give the product as a yellow oil (0.970 g, 5.1 mmol, 51 % yield). Data matches the literature: *Chem. Commun.,* 2012, 83, 5889 – 5891.

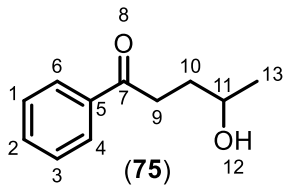
^{1}H NMR δ(500 MHz, $CDCl_3$): 8.06 – 7.86 (2H, m, Ar, 4), 7.03 – 6.83 (2H, m, Ar, 3), 5.90 (1H, ddt, J = 16.8, 10.2, 6.5, CH, 10), 5.19 – 4.91 (2H, m, CH_2, 11), 3.87 (3H, s, CH_3, 1), 3.13 – 2.89 (2H, m, CH_2, 8), 2.56 – 2.38 (2H, m, CH_2, 9).

^{13}C NMR δ(126 MHz, $CDCl_3$): 198.1 (1 x C, s, 6), 163.4 (1 x C, s, 2), 137.5 (1 x CH, s, 10), 130.3 (2 x CH, s, 4), 115.2 (1 x CH_2, s, 11), 113.7 (2 x CH, s, 3), 55.5 (1 x CH_3, s, 1), 37.4 (1 x CH_2, s, 8), 28.4 (1 x CH_2, s, 9).

Asymmetric Hydrogenation:



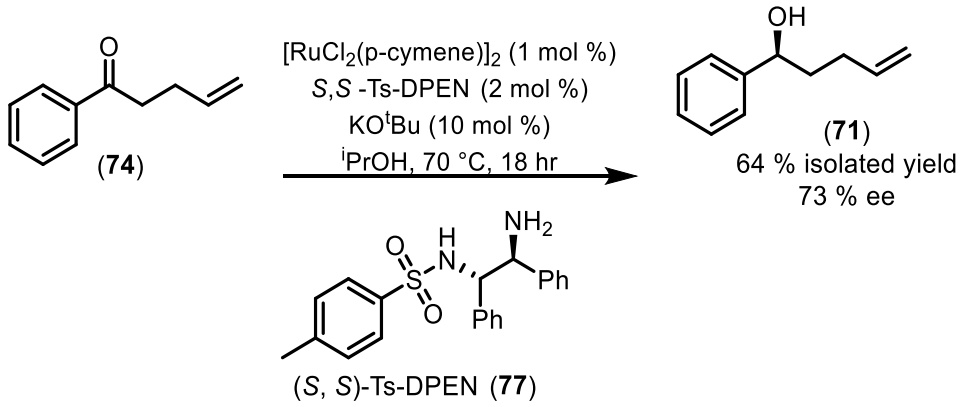
Procedure developed in house. Dry ethanol was degassed under argon (1.5 hr) before the addition of the alkene substrate (81 mg, 0.5 mmol, 1 equiv). An autoclave was charged with the manganese catalyst (3.6 mg, 0.005 mmol, 1 mol %) and potassium carbonate (3.5 mg, 0.025 mmol, 5 mol %) and purged. The solution containing the substrate was injected and the autoclave pressurised to 50 bar with dihydrogen gas. The autoclave was heated overnight (50 °C). The autoclave was then cooled to room temperature and the pressure released before the solvent was removed in vacuo to leave a brown oil. The oil was solvated in ethyl acetate (5 mL) and washed with brine (5 mL) before the layers were separated and the organic layer dried over $MgSO_4$, filtered and concentrated in vacuo. The crude reaction mixture was purified by silica column chromatography, hexane: ethyl acetate (19: 1) to recover starting material and a sample of the unexpected product as a colourless oil (0.0036 g, 0.02 mmol, 4 % yield overall, 20 % yield from converted material). Data matches the literature: *Adv. Syn. Catal.*, 2020, 362 (2), 337 – 343.



^{1}H NMR δ(500 MHz, $CDCl_3$): 7.99 (2H, d, J = 7.4, Ar, 4 + 6), 7.58 (1H, t, J = 7.4, Ar, 2), 7.48 (2H, t, J = 7.7, Ar, 1 + 3), 4.17 (1H, dqd, J = 9.9, 6.6, 3.5, CH, 11), 3.29 – 3.14 (2H, m, CH_2, 9), 2.28 (1H, dtd, J = 14.8, 7.5, 3.4, 1H of CH_2, 10a), 2.09 – 1.99 (1H, m, 1H of CH_2, 10b), 1.59 (3H, d, J = 6.6, CH_3, 13).

^{13}C NMR δ(126 MHz, $CDCl_3$): 133.3 (1 x CH, s, 2), 128.8 (2 x CH, s, 1 + 3), 128.2 (2 x CH, s, 4 + 6), 58.6 (1 x CH, s, 11), 35.7 (1 x CH_2, s, 9), 34.4 (1 x CH_2, s, 10), 25.8 (1 x CH_3, s, 13). Quarternary carbon signals for 5 and 7 were too weak to assign.

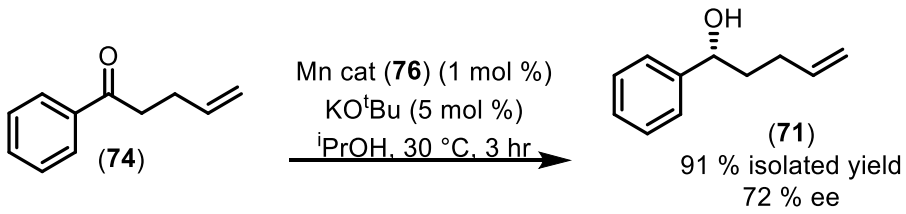
Asymmetric Transfer Hydrogenation:



Compound prepared according to literature procedure: *Catal. Sci. Technol.,* 2019, 9, 6047 - 6058

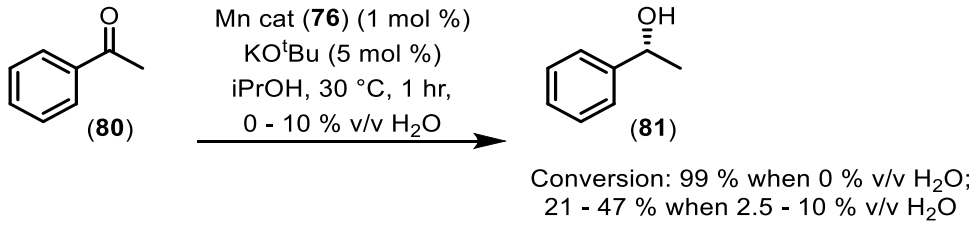
The alkene substrate (801 mg, 5 mmol, 1 equiv) was solvated in dry isopropanol and degassed under argon (40 mins). $[RuCl_2(p\text{-cymeme})]_2$ (37 mg, 0.05 mmol, 1 mol %) and (*S*, *S*) – Ts – DPEN (37 mg, 0.1 mmol, 2 mol %) were suspended in dry isopropanol and the orange suspension heated to 70 °C under argon (25 mins). Potassium *tert* – butoxide (56 mg, 0.5 mmol, 10 mol %) and the alkene substrate solution were added to the preactivated, orange catalyst solution turning the solution briefly purple on addition of the base, and this was stirred at room temperature overnight. The orange solution was neutralised with 1M HCl and concentrated in vacuo. The orange residue was diluted with ethyl acetate and washed with brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The orange oil was purified by silica column chromatography, hexane: ethyl acetate (19:1 gradient to 1:1).

Asymmetric Transfer Hydrogenation:



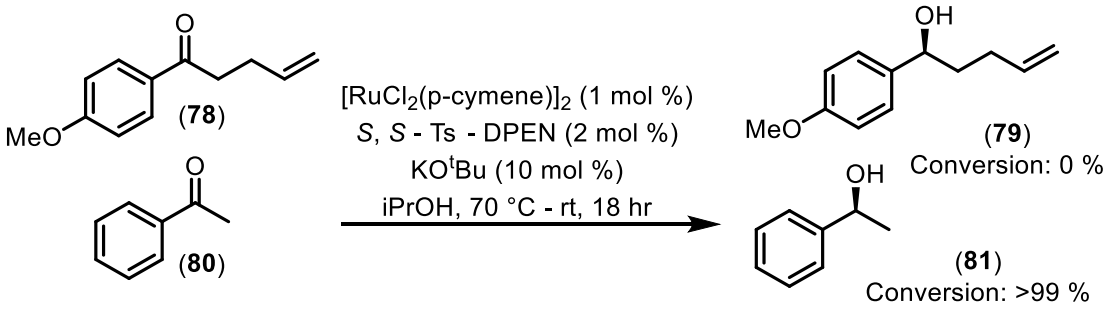
A solution of alkene substrate (273 mg, 1.7 mmol, 1 equiv) in dry isopropanol was degassed under nitrogen (30 mins). The manganese catalyst (12 mg, 0.017 mmol, 1 mol %) was added to a separate Schlenk and purged before the addition of the alkene substrate in dry isopropanol. Potassium *tert*-butoxide (0.085 mmol, 1M in *t*BuOH, 5 mol %) was added and the orange solution stirred at 30 °C (3 hours). The solution was then concentrated in vacuo and the orange oil purified by silica column chromatography hexane: ethyl acetate (19:1 gradient to 15:5).

Asymmetric Transfer Hydrogenation with Water Spiking:



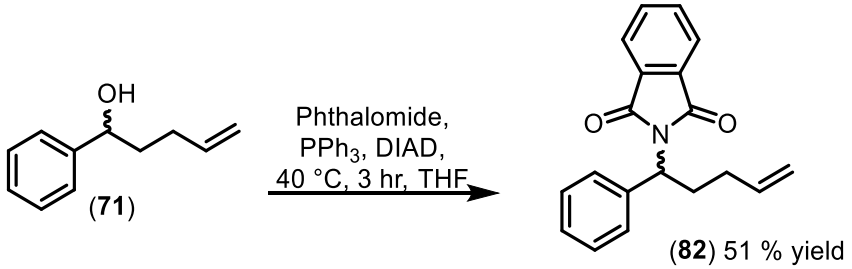
To a flame dried Schlenk was added acetophenone (60 mg, 0.5 mmol, 1 equiv) and dry isopropanol (5 – x mL) and the solution degassed under nitrogen (30 mins). The manganese catalyst (2 mg, 0.005 mmol, 1 mol %) and potassium *tert*-butoxide (0.025 mmol, 1M in ^{t}BuOH, 5 mol %) were added followed by the addition of water (x mL, 2.5 – 10 % v/v) and the orange solutions stirred at 30 °C (1 hr). Conversion measured by ^{1}H NMR.

Asymmetric Transfer Hydrogenation Cross-Over Experiment:



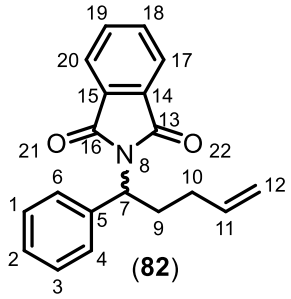
To a flame dried Schlenk was added [RuCl$_2$(*p*-cymene)]$_2$ (6 mg, 0.01 mmol, 1 mol %) and *S*, *S*- Ts- DPEN (7 mg, 0.02 mmol, 2 mol %) and dry isopropanol. The catalyst was then preactivated (40 mins, 70 °C). To a separate flame dried Schlenk was added acetophenone (60 mg, 0.5 mmol, 0.5 equiv) and 1-(4-methoxyphenyl)pent-4-en-1-one (95 mg, 0.5 mmol, 0.5 equiv) and dry isopropanol. This solution was then degassed under nitrogen (40 mins). The substrate solution was then added to the orange catalyst solution, followed by potassium *tert*-butoxide (0.1 mmol, 1M in ^{t}BuOH, 10 mol %) and the reaction stirred overnight at room temperature. Conversion measured by ^{1}H NMR.

Mitsunobu Reaction:



Compound prepared according to adapted literature procedure: *J. Org. Chem.,* 2013, 78 (8), 3783 – 3801.

Phthalimide (103mg, 0.7 mmol, 1.4 equiv) and triphenyl phosphine (184 mg, 0.7 mmol, 1.4 equiv) were stirred in THF until dissolved before the addition of the alcohol substrate (96 mg, 0.5 mmol, 1 equiv) and dropwise addition of diisopropylazodicarboxylate (0.14 mL, 0.7 mmol, 1.4 equiv). The yellow solution was then heated (40 °C, 3 hours). The solvent was then removed in vacuo and the yellow oil purified by silica column chromatography, hexane: ethyl acetate (20: 1).



(**82**)

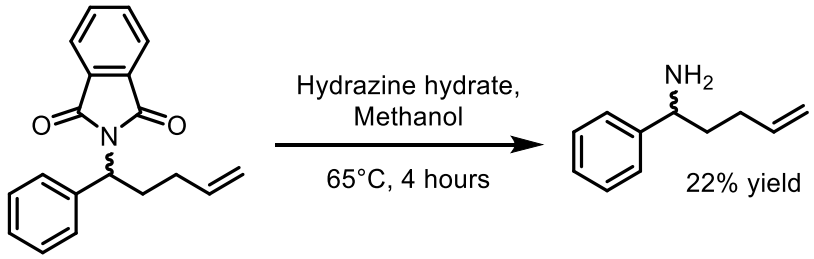
Compound has previously been reported and data is in agreement with the literature values: *J. Org. Chem.,* 2013, 78 (8), 3783 – 3801.

Yellow oil, (0.371 g, 1.27 mmol, 51 % yield).

^{1}H NMR δ(500 MHz, $CDCl_3$): 7.84 – 7.66 (4H, m, Ar, 17 - 20), 7.62 – 7.54 (2H, m, Ar, 4 + 6), 7.35 (3H, m, Ar, 1-3), 5.89 – 5.81 (1H, m, CH, 11), 5.39 (1H, dd, J = 9.7, 6.7, CH, 7), 5.05 – 4.96 (2H, m, CH_2, 12), 2.78 – 2.71 (1H, m, 1H of CH_2, 9a), 2.45 – 2.38 (1H, m, 1H of CH_2, 9b), 2.16 – 2.11 (2H, m, CH_2, 10).

^{13}C NMR: δ(126 MHz, $CDCl_3$): 168.4 (2 x C, s, 13 + 16), 139.6 (1 x C, s, 5), 137.2 (1 x CH, s, 11), 134.0 (2 x CH, s, 17 + 20), 131.9 (2 x C, s, 14 + 15), 128.6 (2 x CH, s, 18 + 19), 128.2 (2 x CH, s, 4 + 6), 127.9 (1 x CH, s, 2), 123.2 (2 x CH, s, 1 +3), 115.7 (1 x CH_2, s, 12), 54.5 (1 x CH, s, 7), 31.2 (1 x CH_2, s, 9), 30.2 (1 x CH_2, s, 10).

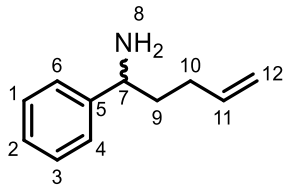
Phthalimide Deprotection:



Compound prepared according to literature procedure: *J. Org. Chem.,* 2013, 78 (8), 3783 - 3801

The phthalimide substrate (277 mg, 1.0 mmol, 1 equiv) was dissolved in methanol and hydrazine hydrate (100 µL of 50 – 60 % solution, 1.5 mmol, 1.5 equiv) added. The solution was refluxed (65 °C, 4 hours). The reaction was quenched with 1M HCl and filtered to remove a white solid. The residue was diluted with water and the aqueous layer extracted with diethyl ether. The aqueous layer was then

neutralised with solid NaOH to pH 11 and extracted with DCM. The organic layer was washed with brine then dried over Na_2SO_4, filtered and concentrated in vacuo.



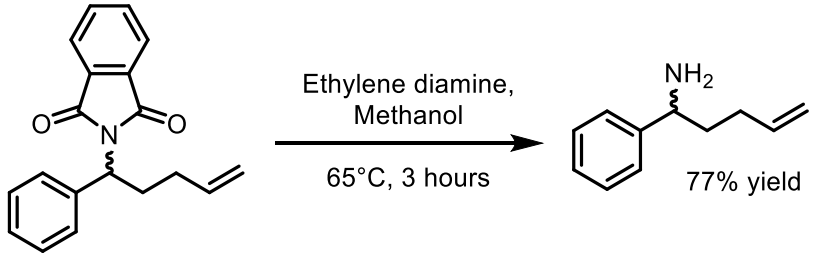
Compound has previously been reported and our data is in agreement with the literature values: *J. Org. Chem.,* 2013, 78 (8), 3783 - 3801.

Yellow solid (0.035 g, 0.22 mmol, 22 % yield).

^{1}H NMR δ(500 MHz, $CDCl_3$): 7.40 – 7.24 (5H, m, Ar, 1-4 + 6), 5.94 – 5.68 (1H, m, CH, 11), 5.08 – 4.96 (2H, m, CH_2, 12), 3.94 (1H, t, J = 7.0, CH, 7), 2.19 – 1.97 (2H, m, CH_2, 9), 1.90 – 1.73 (2H, m, CH_2, 10).

^{13}C NMR δ(126 MHz, $CDCl_3$): 145.7 (1 x C, s, 5), 138.2 (1 x CH, s, 11), 128.6 (2 x CH, s, 4 + 6), 127.1 (1 x CH, s, 2), 126.5 (2 x CH, s, 1 + 3), 114.9 (1 x CH_2, s, 12), 55.7 (1 x CH, s, 7), 38.3 (1 x CH_2, s, 9), 30.7 (1 x CH_2, s, 10).

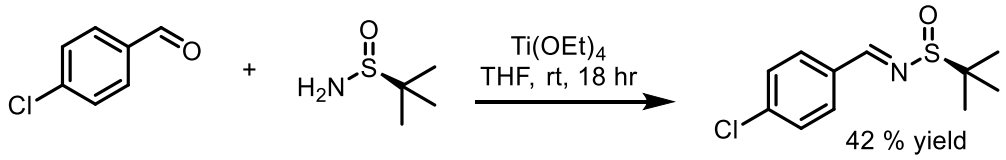
Phthalimide Deprotection:



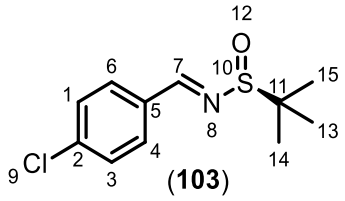
Compound prepared according to literature procedure: *J. Am. Chem. Soc.,* 2015, 137 (7), 2480 - 2483

The phthalimide substrate (156 mg, 0.53 mmol, 1 equiv) was dissolved in methanol and ethylene diamine (0.4 mL, 5.3 mmol, 10 equiv) added. The solution was then refluxed (65 °C, 3 hours). The solvent was removed in vacuo before purification by silica plug, flushed with DCM: MeOH: NEt_3 (20: 1: 0.1). Yellow solid (0.049 g, 0.41 mmol, 77 % yield)

Imine Synthesis:



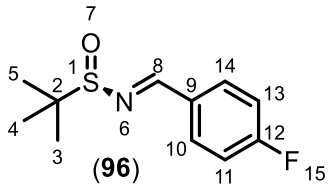
To a flame dried Schlenk was added 4-chlorobenzaldehyde (0.77 g, 5.5 mmol, 1.1 equiv) and titanium ethoxide (2.1 mL, 10.0 mmol, 2 equiv) in anhydrous THF (7.5 mL). A solution of (*S*)-^{t}butanesulfinamide (0.66 g, 5.0 mmol, 1 equiv) and anhydrous THF (2.5 mL) was added and the solution stirred overnight (room temperature, 18 hr). The solution was poured into a stirred solution of brine (10 mL) and a white precipitate formed. The suspension was filtered over a celite plug and the filtercake washed with ethyl acetate (2 x 10 mL). The layers were separated and the organic layer dried over Na_2SO_4, filtered and concentrated in vacuo. Purified by silica column chromatography, petroleum ether: diethyl ether (8:2). Colourless, crystalline solid (2.1 mmol, 0.512 g, 42 % yield). Data matches the literature: *Org. Lett.*, 2005, 7, 8, 1481–1484.



(**103**)

^{1}H NMR δ(400 MHz, $CDCl_3$): 8.52 (1H, s, CH, 7), 7.76 (2H, d, J = 8.5, Ar, 1 + 3), 7.42 (2H, d, J = 8.5, Ar, 4 + 6), 1.24 (9H, s, 3 x CH_3, 13-15)

^{13}C NMR δ(126 MHz, $CDCl_3$): 161.4 (1 x CH, s, 7), 138.6 (1 x C, s, 2), 132.5 (1 x C, s, 5), 130.5 (2 x CH, s, 1 + 3), 129.3 (2 x CH, s, 4 + 6), 57.9 (1 x C, s, 11), 22.7 (3 x CH_3, s, 13-15).



(**96**)

^{1}H NMR δ(500 MHz, $CDCl_3$): 8.47 (1H, s, CH, 8) 7.83 – 7.75 (2H, m, Ar, 11 + 13), 7.07 (2H, t, J = 8.6, Ar, 10 + 14), 1.18 (9H, s, 3 x CH_3, 3 - 5).

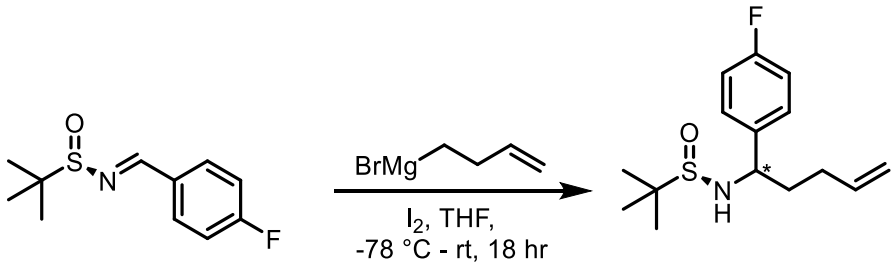
^{13}C NMR δ(126 MHz, $CDCl_3$): 166.2 (1 x C, s, 12), 164.2 (1 x C, s, 9), 161.3 (1 x CH, s, 8), 131.5 (2 x CH, d, J = 9.1, 11 + 13), 116.2 (2 x CH, d, J = 22.1, 10 + 14), 57.6 (1 x C, s, 2), 22.5 (3 x CH_3, s, 3-5).

Mass spec: M + Na = 250.0665 m/z, $C_{11}H_{14}ONFSNa^{+}$ requires 250.0672.

IR (neat, cm^{-1}): 2984, 2953, 1601, 1582, 1504, 1223, 1150, 1082.

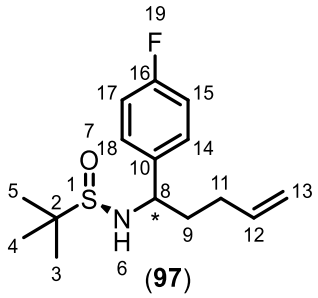
Melting point: 40 – 42 °C

Grignard Addition To Imine:



Compound prepared according to literature procedure: *Org. Biomol. Chem.,* 2005, 3, 2109-2113

Magnesium turnings (204 mg, 8.4 mmol, 2.2 equiv), iodine (catalytic amount) were suspended in dry THF before the dropwise addition of 4-bromo-1-butene (0.8 mL, 7.6 mmol, 2 equiv). This was stirred at room temperature (1 hr) before transferring to a second Schlenk to remove excess magnesium, and cooled to – 78 °C. The imine (0.863 g, 3.8 mmol, 1 equiv) in dry THF was added in 4 aliquots at this temperature before allowing to warm to room temperature overnight. The reaction was quenched with saturated, aqueous ammonium chloride and the aqueous layer extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The crude was then purified by silica column chromatography, hexane: ethyl acetate (85:15) to give the product as a colourless solid in separate diastereomers.



(**97**)

Major diastereomer:

Colourless, crystalline solid.

Melting point: 92 – 94 °C

^{1}H NMR δ(500 MHz, $CDCl_3$): 7.33 – 7.24 (2H, m, Ar, 15 + 17), 7.05 – 6.98 (2H, m, Ar, 14 + 18), 5.71 (1H, m, CH, 12), 4.99 – 4.94 (2H, m, CH_2, 13), 4.92 (1H, t, J = 1.3, NH, 6), 4.36 (1H, ddd, J = 8.0, 5.9, 2.5, CH, 8), 3.38 (1H, d, J = 4.0, 1H of CH_2, 9a), 2.27 – 2.05 (1H, m, 1H of CH_2, 9b), 2.01 – 1.85 (1H, m, 1H of CH_2, 11a), 1.78 (1H, d, J = 8.4, 1H of CH_2, 11b), 1.21 (9H, s, 3 x CH_3, 3 - 5).

^{13}C NMR δ(126 MHz, $CDCl_3$): 163.2 (1 x C, s, 16), 161.3 (1 x C, s, 10), 137.5 (1 x CH, s, 12), 129.4 (2 x CH, d, J = 8.0, 15 + 17), 115.5 (2 x CH, d, J = 21.4, 14 + 18), 115.3 (1 x CH_2, s, 13), 58.1 (1 x CH, s, 8), 55.8 (1 x C, s, 2), 35.8 (1 x CH_2, s, 9), 29.9 (1 x CH_2, s, 11), 22.6 (3 x CH_3, s, 3 - 5).

Mass spec: M + Na = 306.1219 m/z, $C_{15}H_{22}FNOSNa^+$ requires 306.1298.

IR (cm^{-1}): 3210, 2953, 2920, 1641, 1603, 1508, 1219, 1053.

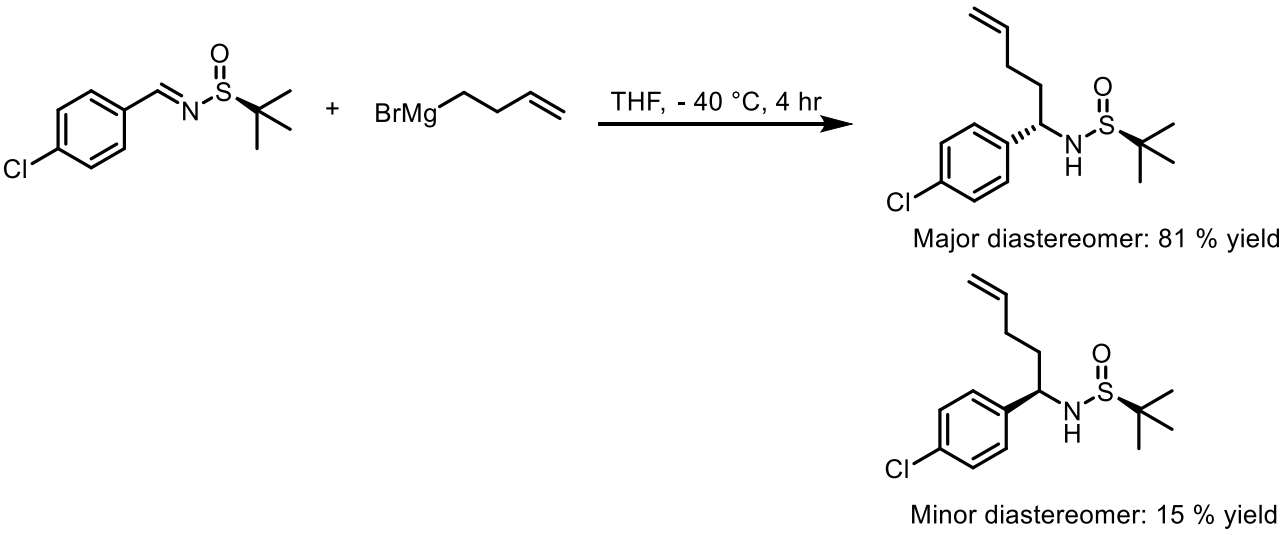
$[\alpha]^D$ = +108.5 (c = 1, $CHCl_3$).

Minor diastereomer:

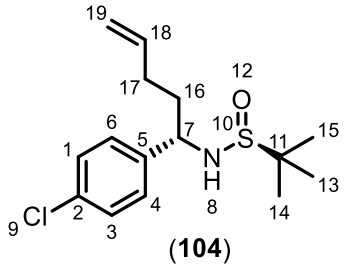
Colourless, crystalline solid.

^1H NMR δ(500 MHz, $CDCl_3$): 7.37 – 7.21 (2H, m, Ar, 15 + 17), 7.13 – 6.95 (2H, m, Ar, 14 + 18), 5.87 – 5.68 (1H, m, CH, 12), 5.11 – 4.92 (2H, m, CH_2, 13), 4.41 (1H, ddd, J = 8.0, 6.0, 2.3, CH, 8), 3.46 (1H, m, 1H of CH_2, 9a), 2.14 – 1.78 (3H, m, 1H of CH_2 + CH_2, 9b + 11), 1.19 (9H, s, 3 x CH_3, 3 - 5).

^{13}C NMR δ(126 MHz, $CDCl_3$): 163.2 (1 x C, s, 16), 161.3 (1 x C, s, 10), 137.3 (1 x CH, s, 12), 129.3 (1 x CH, s, 15 or 17), 129.3 (1 x CH, s, 15 or 17), 115.7 (1 x CH_2, s, 13), 115.5 (1 x CH, s, 14 or 18), 115.3 (1 x CH, s, 14 or 18), 58.0 (1 x CH, s, 8), 55.5 (1 x C, s, 2), 37.8 (1 x CH_2, s, 9), 30.1 (1 x CH_2, s, 11), 22.5 (3 x CH_3, s, 3 - 5).



To a flame dried Schlenk containing magnesium turnings (0.160 g, 6.6 mmol, 2.5 equiv) was added anhydrous THF (5 mL) and a solution of 4-bromo-1-butene (0.61 mL, 6.0 mmol, 2.3 equiv) in anhydrous THF (2 mL). This was stirred at room temperature (1 hr) and then the suspension was cooled to – 40 °C and a solution of imine (0.638 g, 2.6 mmol, 1 equiv) in anhydrous THF (3 mL) was added. Stirred at – 40 °C (4 hr). Saturated ammonium chloride (5 mL) was added and the layers separated. The aqueous layer was extracted with ethyl acetate (3 x 5 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. Purified by silica column chromatography, petroleum ether: ethyl acetate: triethylamine (1:1:0.1). Major diastereomer: 2.1 mmol, 0.632 g, 81 % yield, minor: 0.39 mmol, 0.117 g, 15 % yield. The assignment of the major and minor are based on discussion of the selectivity of the Grignard addition to *t*-butylsulfinimines as reported in the literature: *J. Am. Chem. Soc.*, 1997, 119, 9913–9914.



(**104**)

^{1}H NMR δ(400 MHz, $CDCl_3$): 7.30 (2H, d, J = 8.5, Ar, 1 + 3), 7.22 (2H, d, J = 8.5, Ar, 4 + 6), 5.85 – 5.67 (1H, m, CH, 18), 5.09 – 4.91 (2H, m, CH_2, 19), 4.45 – 4.33 (1H, m, CH, 7), 2.11 – 1.75 (4H, m, 2 x CH_2, 16 + 17), 1.16 (9H, s, 3 x CH_3, 13-15).

^{13}C NMR δ(126 MHz, $CDCl_3$): 140.8 (1 x C, s, 2), 137.5 (1 x CH, s, 18), 133.8 (1 x C, s, 5), 129.1 (2 x CH, s, 1 + 3), 128.7 (2 x CH, s, 4 + 6), 115.5 (1 x CH_2, s, 19), 58.3 (1 x CH, s, 7), 56.0 (1 x C, s, 11), 35.8 (1 x CH_2, s, 16), 29.9 (1 x CH_2, 17), 22.7 (3 x CH_3, s, 13-15).

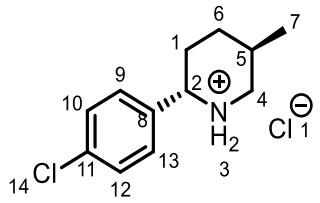
IR (neat, cm^{-1}): 1090, 1053, 1012, 916 and 829.

Mass spec: M + Na = 322.0992 m/z, $C_{15}H_{22}ClNOSNa^{+}$ requires 322.1003.

Melting point: 108- 110 °C

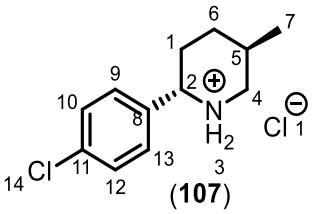
$[\alpha]^{D}_{20}$ = + 33.2 (c = 1.4, CH_2Cl_2)

Asymmetric HF:



The standard AHF procedure was followed with 0.5 mmol of alkene. After the reaction, the crude reaction mixture was checked by ^{1}H NMR to observe > 99 % conversion. To the microwave vial containing the crude AHF reaction mixture (1 equiv) in solvent was added DCM (2 mL) and the solution cooled (-15 °C). Triethylsilane (3 equiv) and boron trifluoride diethyletherate (3 equiv) were added and the solution stirred at -15 °C (15 mins) before warming to room temperature (30 mins). 1M HCl (aq) was added and the solution stirred (rt, 1 hr). The layers were separated and the organic layer returned to the reaction flask. 2M HCl in diethyl ether (2 equiv) was added and the solution stirred (rt, 30 mins). At the end of the reaction time the solution was removed by cannula and the residue dried under vacuum and analysed by ^{1}H NMR to measure the branched to linear ratio and the diastereomeric ratio on the crude oil. When (*R*, *R*, *R*)-BOBPHOS was used as the ligand, the branched to linear ratio was

90:10 and the diastereomeric ratio was found to be 85:15; when (*S*, *S*, *S*)-BOBPHOS was used as the ligand the branched to linear ratio was 69:31 and the diastereomeric ratio was found to be 80:20. Data matches the literature: *J. Am. Chem. Soc.*, 2019, 141, 4815 – 4819. Assignments made with the assistance of 2D NMR: HSQC and HMBC.

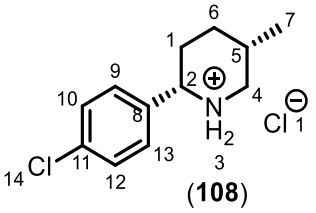


(**107**)

(0.09 mmol, 0.022 g, 18 % of both diastereomers in the ratio 85:15). The major diastereoisomer is drawn, from (*R*, *R*, *R*)-BOBPHOS as ligand.

^{1}H NMR δ(400 MHz, CD_3OD): 7.46 – 7.05 (4H, m, Ar, 9, 10, 12, 13), 4.05 (1H, dd, J=9.3, 5.8, 2), 3.14 (2H, d, J=6.1, CH_2, 4), 1.96 – 1.63 (2H, m, CH_2, 1) 1.45 – 0.87 (3H, m, CH + CH_2, 5+ 6) 0.69 (3H, d, J=6.7, CH_3, 7).

^{13}C NMR δ(126 MHz, CD_3OD): 137.1 (1 x C, s, 11), 136.1 (1 x C, s, 8), 130.4 (2 x CH, s, 10 + 12), 130.2 (2 x CH, s, 9 + 13), 67.7 (1 x CH_2, s, 4), 56.5 (1 x CH, s, 2), 36.4 (1 x CH, s, 4), 32.9 (1 x CH_2, s, 1), 30.36 (1 x CH_2, s, 6), 16.92 (1 x CH3, s, 7).



(**108**)

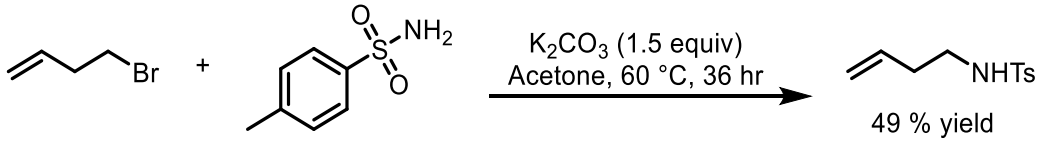
(0.099 g, 0.4 mmol, 80 % yield of both diastereomers in 69: 31 ratio and the linear product). The major diastereoisomer is drawn, from (*S*, *S*, *S*)-BOBPHOS as ligand.

^{1}H NMR δ(400 MHz, CD_3OD): 7.65 – 7.35 (4H, m, Ar, 9, 10, 12, 13), 4.39 – 4.14 (1H, m, CH, 2), 3.44 – 3.35 (1H, m, 1H of CH_2, 4a), 2.87 (1H, t, J = 12.3, 1H of CH_2, 4b), 2.17 – 1.86 (2H, m, CH + 1H of CH_2, 5 + 6a), 1.69 – 1.29 (1H, m, 1H of CH_2, 6b), 1.08 (3H, d, J = 6.4, CH_3).

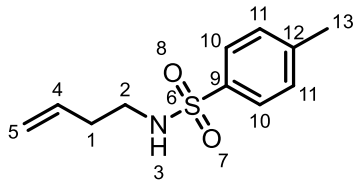
^{13}C NMR δ(126 MHz, CD_3OD): 137.0 (1 x C, s, 11), 136.1 (1 x C, s, 8), 130.4 (2 x CH, s, 10 + 12), 130.2 (2 x CH, s, 9 + 13), 56.1 (1 x CH, s, 2), 52.3 (1 x CH_2, s, 4), 32.5 (1 x CH_2, s, 6), 29.5 (1 x CH, s, 5), 18.8 (1 x CH_3, s, 7). The ^{13}C signal relating to carbon 1 could not be identified and is presumed to overlap with another signal.

Chapter 3 Experimental:

Substrate Synthesis:



To a 100 mL RBF was added *p*-toluenesulfonamide (1.712 g, 10 mmol, 1 equiv), potassium carbonate (2.073g, 15 mmol, 1.5 equiv), acetone (30 mL) and 4-bromo-1-butene (1.0 mL, 10 mmol, 1 equiv). The suspension was heated (60 °C, 36 hr). The orange suspension was then filtered through a plug of celite and washed with ethyl acetate before concentrating in vacuo. The crude orange solid was then purified by silica column chromatography, hexane: ethyl acetate (85:15:0.1) to give the target compound as a yellow oil (4.9 mmol, 1.104 g, 49 % yield). Data matches the literature: *J. Org. Chem.*, 2016, 81 (3), 849 – 859.

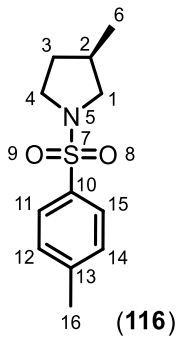


(**113**)

^{1}H NMR δ(500 MHz, $CDCl_3$): 7.77 – 7.70 (2H, m, Ar, 10), 7.32 – 7.25 (2H, m, Ar, 11), 5.62 (1H, ddt, J = 17.3, 10.6, 6.8, CH, 4), 5.10 – 4.95 (2H, m, CH_2, 5), 2.98 (2H, q app, J = 6.8, CH_2, 2), 2.40 (3H, s, CH_3, 13), 2.21 – 2.15 (2H, m, CH_2, 1).

^{13}C NMR δ(126 MHz, $CDCl_3$): 143.4 (1 x C, s, 9), 136.9 (1 x C, s, 12), 134.3 (1 x CH, s, 4), 129.7 (2 x CH, s, 11), 127.1 (2 x CH, s, 10), 117.2 (1 x CH_2, s, 5), 42.2 (1 x CH_2, s, 2), 33.6 (1 x CH_2, s, 1), 21.5 (1 x CH_3, s, 13).

Asymmetric HF:



(**116**)

The standard AHF procedure was followed with 1.0 mmol of alkene. The crude AHF reaction mixture was reduced with triethylsilane and boron trifluoride diethyletherate as detailed in the general procedures. After this the conversion and branched to linear selectivity were measured by ^{1}H NMR: > 99 % conversion and 87:13 branched to linear ratio were recorded in this example. Purified by silica column chromatography, hexane: diethyl ether: ammonia (8:2:0.025) to give the product as one regioisomer and as a colourless, crystalline solid (0.46 mmol, 0.110 g, 46 % yield from alkene). Data matches the literature: *Chem. Commun.*, 2013, 49, 4352 - 4354.

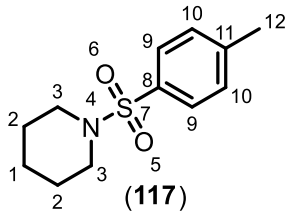
The above procedure was repeated with 1.0 mmol of alkene. 3-methyl-*N*-tosylpyrrolidine was recrystallised from the reaction mixture multiple times with Petroleum ether: Ethanol (5: 0.5) to give the target compound in 49 % yield.

The above procedure was repeated with 1.0 mmol of alkene and (*S*, *S*, *S*)-BOBPHOS as the enantiomer of the ligand. 3-methyl-*N*-tosylpyrrolidine was recrystallised from the reaction mixture with Hexane: Ethanol (5: 0.5) to give the target compound in 23 % yield. The optical rotation was measured as $[\alpha]^{D}_{20}$ = -12.72 (c = 0.66, CH_2Cl_2) and confirms the absolute configuration as *S* as recorded in the literature: *Org. Lett.*, 2015, 17, 2370–2373.

^{1}H NMR δ(500 MHz, $CDCl_3$): 7.75 – 7.68 (2H, m, Ar, 11 + 15), 7.32 (2H, d, J = 7.9, Ar, 12 + 14), 3.42 (1H, dd, J = 9.7, 7.2, 1H of CH_2, 1a), 3.41 – 3.27 (1H, m, 1H of CH_2, 4a), 3.21 (1H, ddd, J = 9.7, 8.2, 7.2, 1H of CH_2, 4b), 2.74 (1H, dd, J = 9.7, 7.8, 1H of CH_2, 1b), 2.43 (3H, s, CH_3, 16), 2.20 – 2.02 (1H, m, CH, 2), 1.98 – 1.82 (1H, m, 1H of CH_2, 3a), 1.35 (1H, dq app, J = 12.2, 8.2, 1H of CH_2, 3b), 0.91 (3H, d, J = 6.7, CH_3, 6).

^{13}C NMR δ(126 MHz, $CDCl_3$): 143.3 (1 x C, s, 10), 134.0 (1 x C, s, 13), 129.6 (2 x CH, s, 12 + 14), 127.5 (2 x CH, s, 11 + 15), 54.8 (1 x CH_2, s, 1), 47.6 (1 x CH_2, s, 4), 33.3 (1 x CH, s, 2), 33.3 (1 x CH_2, s, 3), 21.6 (1 x CH_3, s, 16), 17.7 (1 x CH_3, s, 6).

Melting point: 93 – 96 °C (recrystallised sample).



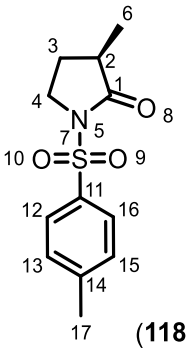
(**117**)

Compound has previously been reported and this data is in agreement with the literature values: *Org. Lett.,* 2015, 17 (10), 2370 – 2373. Colourless solid (0.036g, 0.15 mmol, 10 % yield).

^{1}H NMR δ(500 MHz, $CDCl_3$): 7.65 (2H, d, J = 8.2, Ar, 9), 7.34 (2H, d, J = 8.2, Ar, 10), 3.06 – 2.90 (4H, m, 2 x CH_2, 3), 2.45 (3H, s, 1 x CH_3, 12), 1.65 (4H, dd app, J = 10.7, 5.1, 2 x CH_2, 2), 1.42 (2H, m, 1 x CH_2, 1).

^{13}C NMR δ(126 MHz, $CDCl_3$): 143.4 (1 x C, s, 8), 133.1 (1 x C, s, 11), 129.6 (2 x CH, s, 10), 127.7 (2 x CH, s, 9), 47.0 (2 x CH_2, s, 3), 25.2 (2 x CH_2, s, 2), 23.5 (1 x CH_2, s, 1), 21.6 (1 x CH_3, s, 12).

Asymmetric HF and Oxidation of Crude Reaction Mixture:



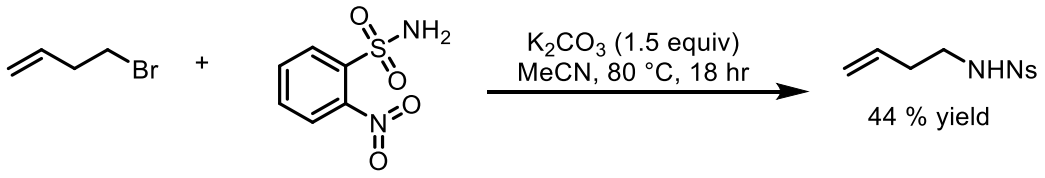
(**118**)

The standard AHF procedure was followed with 1.0 mmol of alkene. The crude AHF mixture was transferred to a glass vial and sodium acetate (0.164 g, 2.0 mmol, 2 equiv), DCM (2 mL) and pyridinium chlorochromate (0.474 g, 2.0 mmol, 2 equiv) were added. The vial was sealed with a septum and the resulting orange suspension was stirred (room temperature, 4 hours) before being filtered and the solvent removed in vacuo. The orange residue was purified by silica column chromatography, hexane: diethyl ether (1:1) to give the product as a the major regioisomer with traces, less than 10 %, of the linear, and as a white, crystalline solid (0.48 mmol, 0.122 g, 48 % yield). Enantioselectivity was measured by chiral HPLC, Chiracel AD-H, hexane: IPA (80:20), 1 $mLmin^{-1}$, 254-210 m, t_R (minor): 9.4 min, t_R (major): 10.2 min. 85 % ee. Data matches the literature: *Org. Lett.*, 2009, 11, 15, 3458–3461.

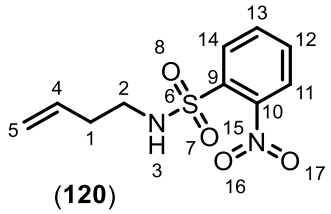
^{1}H NMR δ(500 MHz, $CDCl_3$): 7.97 – 7.85 (2H, m, Ar-CH, 12 + 16), 7.30 (2H, d, J = 8.0, Ar-CH, 13 + 15), 3.92 (1H, ddd, J = 9.9, 8.6, 2.5, 1H of CH_2, 4a), 3.66 (1H, td, J = 9.9, 6.9, 1H of CH_2, 4b), 2.40 (4H, m, CH and CH_3, 2 + 17), 2.28 – 2.20 (1H, m, 1H of CH_2, 3a), 1.86 – 1.81 (1H, m, 1H of CH_2, 3b), 1.11 (3H, d, J = 7.1, CH_3, 6).

^{13}C NMR: δ(126 MHz, $CDCl_3$): 175.9 (1 x C, s, 1), 145.2 (1 x C, s, 11), 135.1 (1 x C, s, 14), 129.7 (2 x CH, s, 13 + 15), 128.0 (2 x CH, s, 12 + 16), 45.3 (1 x CH_2, s, 4), 38.2 (1 x CH, s, 2), 27.1 (1 x CH_2, s, 3), 21.7 (1 x CH_3, s, 17), 15.0 (1 x CH_3, s, 6).

Substrate Synthesis:



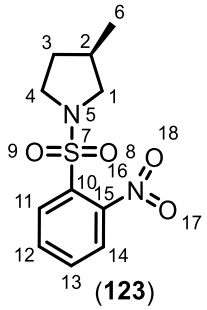
To a 100 mL RBF was added potassium carbonate (1.38 g, 10.0 mmol, 2 equiv), 2-nitrobenzenesulfonamide (1.52 g, 7.5 mmol, 1.5 equiv), acetonitrile (40 mL) and 4-bromo-1-butene (0.5 mL, 5 mmol, 1 equiv). The suspension was heated (80 °C, 18 hr). The brown suspension was then cooled to room temperature, filtered and the filtercake washed with ethyl acetate before concentrating in vacuo. The crude orange solid was then purified by silica column chromatography, hexane: diethyl ether (80: 20) to give the target compound as a yellow oil (2.2 mmol, 0.572 g, 44 % yield). Data matches the literature: *Angew. Chem. Int. Ed.*, 2008, 48 (1), 104 – 109.


(**120**)

^{1}H NMR δ(500 MHz, $CDCl_3$): 8.15 – 8.08 (1H, m, Ar, 11), 7.87 – 7.81 (1H, m, Ar, 13), 7.78 – 7.70 (2H, m, Ar, 12 + 14), 5.64 (1H, ddt, J = 17.1, 10.4, 6.8, CH, 4), 5.37 (1H, t, J = 5.7, NH, 3), 5.07 – 4.98 (2H, m, CH_2, 5), 3.17 (2H, q app, J = 6.8, CH_2, 1), 2.31 – 2.21 (2H, m, CH_2, 2).

^{13}C NMR δ(126 MHz, $CDCl_3$): 148.0 (1 x C, s, 10), 133.9 (1 x CH, s, 4), 133.8 (1 x CH, s, 11), 133.6 (1 x C, s, 9), 133.0 (1 x CH, s, 13), 131.0 (1 x CH, s, 14), 125.4 (1 x CH, s, 12), 118.3 (1 x CH_2, s, 5), 42.9 (1 x CH_2, 2), 33.7 (1 x CH_2, s, 1).

Asymmetric HF:


(**123**)

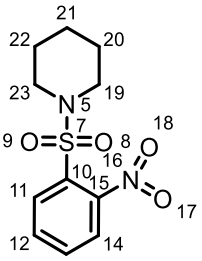
Purified by silica column chromatography, hexane: diethyl ether: DCM (6:1:1) to give the product as a yellow oil (0.0364 g, 0.13 mmol, 13 % yield) of N-nosyl-3-methylpyrrolidine in ratio 91:9 pyrrolidine to piperidine, plus a second fraction (0.0174 g, 0.06 mmol, 6 % yield), ratio 73: 27 of pyrrolidine to

piperidine. Enantioselectivity measured by HPLC, Chiracel AS-H column, hexane: IPA (90:10), 0.5 mL min^{-1}, 254-210 nm, t_R (minor): 97.3 min, t_R (major): 104.2 min. 86 % ee. Assignments made with the assistance of 2D NMR: HSQC and HMBC.

Data matches the literature: *J. Org. Chem.*, 2021, 86 (23), 17380–17394.

^{1}H NMR δ(500 MHz, $CDCl_3$): 8.05 – 7.91 (1H, m, Ar, 14), 7.73 – 7.64 (2H, m, Ar, 11 + 13), 7.63 – 7.56 (1H, s, Ar, 12), 3.64 – 3.48 (2H, m, 2 x 1H of CH_2, 1a + 4a), 3.44 – 3.34 (1H, m, 1H of CH_2, 4b), 2.98 – 2.89 (1H, m, 1H of CH_2, 1b), 2.38 - 2.22 (1H, m, CH, 2), 2.07 – 2.01 (1H, m, 1H of CH_2, 3a), 1.57 – 1.50 (1H, m, 1H of CH_2, 3b), 1.03 (3H, d, J = 6.6, CH_3, 6).

^{13}C NMR δ(126 MHz, $CDCl_3$): 135.7 (1 x C, s, 10), 133.5 (1 x CH, s, 11), 132.3 (1 x C, s, 15), 131.6 (1 x CH, s, 13), 130.8 (1 x CH, s, 14), 124.0 (1 x CH, s, 12), 54.8 (1 x CH_2, s, 1), 47.8 (1 x CH_2, s, 4), 33.9 (1 x CH, s, 2), 33.7 (1 x CH_2, s, 3), 17.5 (1 x CH_3, s, 6).



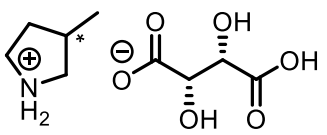
(**124**)

Data matches the literature: *Tet. Lett.*, 2016, 57 (11), 1232 – 1235.

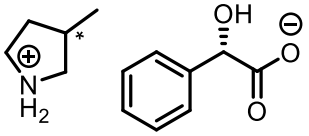
^{1}H NMR δ(500 MHz, $CDCl_3$): 8.05 – 7.91 (1H, m, Ar, 14), 7.73 – 7.64 (2H, m, Ar, 11 + 13), 7.63 – 7.56 (1H, s, Ar, 12), 3.29 – 3.19 (4H, m, 2 x CH_2, 19 + 23), 1.66 – 1.62 (4H, m, 2 x CH_2, 20 + 22), 1.58 – 1.49 (2H, m, 1 x CH_2, 21).

^{13}C NMR δ(126 MHz, $CDCl_3$): 133.6 (1 x CH, s, 11), 131.8 (1 x C, s, 15), 131.5 (1 x CH, s, 13), 131.0 (1 x CH, s, 14), 124.1 (1 x CH, s, 12), 46.9 (2 x CH_2, s, 19 + 23), 25.5 (2 x CH_2, s, 20 + 22), 23.7 (1 x CH_2, s, 21).

Chiral Salt Formation:



(**127**) (*L*)-Tartaric acid

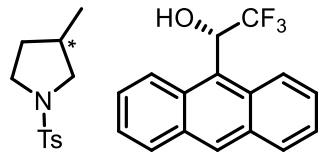


(**128**) (*S*)-(+)-Mandelic acid

After the appropriate deprotection procedure, the acid (1 equiv) was added to the organic solution containing the free 3-methylpyrrolidine and the solution stirred (rt, 5 mins). The solution was then

concentrated in vacuo, the resulting oily precipitate washed with hexane (2 mL) and then concentrated again to give a salt which was analysed by ^{1}H NMR in deuterated methanol. Insufficient peak separation was observed for measurement of a diastereomeric ratio by NMR.

Chiral Solvating Agent Investigation:



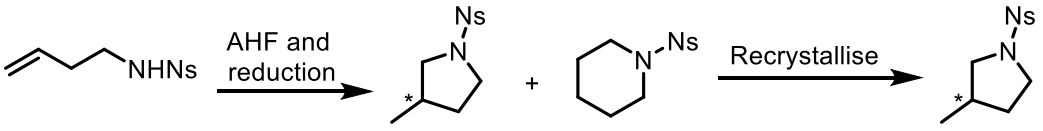
(**116**) (**129**)

(*S*)-1-(anthracen-9-yl)-2,2,2-trifluoroethan-1-ol

NMR Solvent	Ratio of CSA: *N*-Tosyl-3-methylpyrrolidine
$CDCl_3$	3:1
$CDCl_3$	5:1
$CDCl_3$	10:1
d^2-DCM	10:1
d^4- MeOD	10:1

To a sample vial containing *N*-tosyl-3-methylpyrrolidine was added the appropriate amount of chiral solvating agent and the solids dissolved in the appropriate deuterated solvent and then analysed by ^{1}H NMR. Insufficient peak separation was observed in order to measure a diastereomeric ratio.

Recrystallisation Procedure:

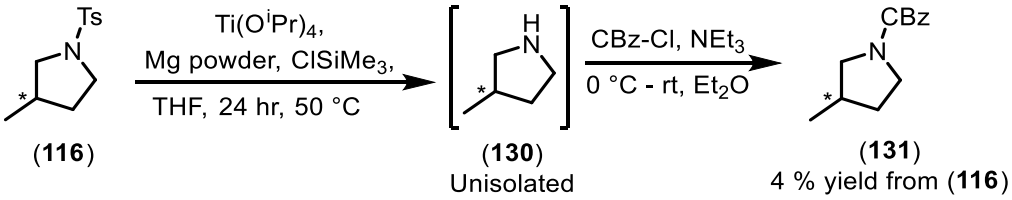


>99 % conversion of alkene
Branch to linear: 83: 17

To a 25 mL RBF was added the crude reduction reaction mixture (0.168 g, mmol, 1 equiv) and then the appropriate solvent (2 mL) was added. The solution was stirred at room temperature (1 hr) and if no solvation occurred then the sample was heated to reflux. If the sample was soluble at room temperature, then the solution was cooled to 5 °C and observed after 1 hr.

Solvent	Relative Polarity	Mass/ Volume	Reflux (T °C)	Room Temperature (1 hr)	5 ° C (1 hr)	Selective for / against 3-MP?
Cyclohexane	0.006	0.168 g / 2 mL	Yes (81 °C)	No	No	No
Toluene	0.099	0.168 g / 2 mL	Presume Yes	Yes	Partially	No
Diethyl ether	0.117	0.168 g / 2 mL	No (34 °C)	No	No	No
Dioxane	0.164	0.168 g / 2 mL	Presume Yes	Yes	Yes	No
THF	0.207	0.168 g / 2 mL	Presume Yes	Yes	Yes	No
Ethyl Acetate	0.228	0.168 g / 2 mL	Presume Yes	Yes	Yes	No

Deprotection Procedure:

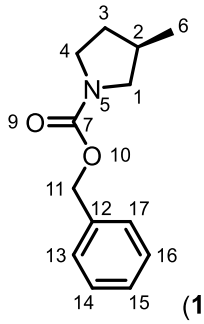


(**116**) (**130**) Unisolated (**131**) 4 % yield from (**116**)

To an oven dried microwave vial was added *N*-tosyl-3-methylpyrrolidine (0.060 g, 0.25 mmol, 1 equiv) and magnesium powder (0.030 g, 1.25 mmol, 5 equiv). The vial was sealed and purged (3 x vacuum / N_2) before the addition of anhydrous THF (1.25 mL), titanium isopropoxide (76 µL, 0.25 mmol, 1 equiv) and chlorotrimethylsilane (47 µL, 0.38 mmol, 1.5 equiv). The reaction was heated (50 °C, 24 hr) before cooling to room temperature (30 mins). 3 M NaOH (0.1 mL) was added, followed by diethyl ether (2 mL), sodium fluoride (0.3 g) and celite (0.3 g). The reaction was filtered and diluted with diethyl ether (1 mL). The filtrate was washed with 3 M NaOH (2 x 2 mL) and the organic layer dried over Na_2SO_4 and filtered.

To a 50 mL RBF was added 3-methylpyrrolidine (0.021 g, 0.25 mmol, 1 equiv) in diethyl ether (6 mL) and then triethylamine (0.1 mL, 0.325 mmol, 1.3 equiv). The solution was cooled to 0 °C before the addition of benzyl chloroformate (35 µL, 0.25 mmol, 1 equiv) dropwise at 0 °C. The solution was stirred (0 °C, 1 hr) before warming to room temperature (1 hr). The reaction was then quenched with 1 M

HCl (2.5 mL) and the layers separated. The organic layer was washed with 1 M HCl (2.5 mL), water (2.5 mL) and brine (2.5 mL) before drying over Na_2SO_4, filtering and concentrating in vacuo. The reaction was purified by silica column chromatography, hexane: ethyl acetate: NH_3 (9: 1: 0.01) to give the product as a colourless oil (0.0021 g, 0.009 mmol, 4 % yield).



(**131**)

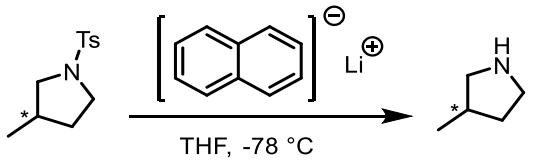
No splitting patterns were observed in the room temperature ^{1}H NMR spectra due to multiple conformational possibilities and hydrogen bonding, as detailed in this publication: *J. Org. Chem.,* 1996, 61, 8402-8406.

^{1}H NMR δ(500 MHz, $CDCl_3$): 7.46 – 6.97 (5H, m, Ar, 13 - 17), 3.41 – 3.23 (3H, m, 1H of CH_2 + CH_2, 4a + 1), 3.13 – 3.04 (2H, m, CH_2, 11), 2.75 – 2.66 (1H, m, 1H of CH_2, 4b), 2.41 – 2.34 (1H, m, CH, 2), 2.19 – 2.10 (1H, m, 1H of CH_2, 3a), 1.61 – 1.5 (1H, m, 1H of CH_2, 3b), 1.14 – 1.06 (3H, m, CH_3, 6).

^{13}C NMR δ(126 MHz, $CDCl_3$): 130.7 (2 x CH, Ar, 13 + 17), 130.3 (1 x CH, Ar, 15), 129.7 (2 x CH, Ar, 14 + 16), 53.2 (1 x CH_2, s, 4), 47.0 (1 x CH_2, s, 1), 46.2 (1 x CH_2, s, 11), 34.1 (1 x CH, s, 2), 33.4 (1 x CH_2, s, 3), 17.4 (1 x CH_3, s, 6). The signals for quaternary carbons 7 and 12 were too weak to be assigned.

Data matches the literature: *Angew. Chem. Int. Ed.*, 2021, 60 (26), 14360-14364

Deprotection Procedure:



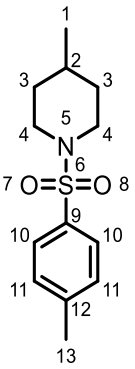
(**116**) (**130**)
0 % yield

Lithium Naphthalamide solution:

Lithium (39.7 mg, 5 mmol, 1 equiv) was washed with ethanol, then hexane then placed in a flame dried Schlenk and dried (3 x vacuum/ N_2). Naphthalene (0.640 g, 5 mmol, 1 equiv) and anhydrous THF (5 mL) were added before stirring at room temperature (1 hr).

To a flame dried Schlenk was added *N*-tosyl-3-methylpyrrolidine (60 mg, 0.25 mmol, 1 equiv) and anhydrous THF (2 mL). The solution was cooled (-78 °C) before the dropwise addition of the reducing agent (0.75 mL, 0.75 mmol, 3 equiv) until the green colour persisted. The solution was stirred (-78 °C, 15 mins) before warming to room temperature (15 mins). The amber solution was then quenched with 0.1 M NaOH (3 mL) and the layers separated. The aqueous layer was extracted with diethyl ether (3 mL) and the combined organic layers added to a 50 mL RBF. (*S*)-(+)-mandelic acid (38 mg, 0.25 mmol) was added and the solution stirred (rt, 30 mins). The solvent was then removed in vacuo and the oil residue washed with petroleum ether, causing precipitation. The precipitate was dried under vacuum then analysed by ^{1}H NMR. No conversion to the free amine was observed.

Tosyl Protection Procedure:



(**132**)

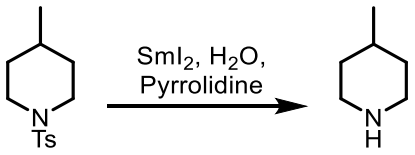
To a 50 mL RBF was added DCM (20 mL) and 4-methylpiperidine (1.8 mL, 15 mmol, 1 equiv), triethylamine (6.3 mL, 45 mmol, 3 equiv) and 4-methylbenzenesulfonyl chloride (2.86 g, 15 mmol, 1 equiv). On addition of the sulfonyl chloride a gas was given off and a white solid precipitated. The suspension was stored at 5 °C overnight (18 hr). The suspension was filtered and then ethyl acetate (10 mL) and sat. $NaHCO_3$ (10 mL) were added. The biphasic solution was stirred (rt, 1 hr) before the layers were separated and the organic layer was washed with 1 M HCl (10 mL) and then water (10 mL) before concentrating in vacuo to give the product as an orange solid (3.097 g, 12.2 mmol, 81 % yield).

Data matches the literature: *J. Am. Chem. Soc.*, 2016, 138 (35), 11132–11135

^{1}H NMR δ(500 MHz, $CDCl_3$): 7.63 (2H, d, J = 8.2, Ar, 10), 7.31 (2H, d, J = 8.2, Ar, 11), 3.73 (2H, d, J = 11.3, 2 x 1H of CH_2, 4a), 2.43 (3H, s, CH_3, 13), 2.21 (2H, t, J = 11.3, 2 x 1H of CH_2, 4b), 1.69 – 1.61 (2H, m, 2 x 1H of CH_2, 3a), 1.34 – 1.23 (3H, m, CH + 2 x 1H of CH_2, 2 + 3b), 0.90 (3H, d, J = 5.4, CH_3, 1).

^{13}C NMR δ(126 MHz, $CDCl_3$): 143.4 (1 x C, s, 9), 133.4 (1 x C, s, 12), 129.7 (2 x CH, s, 11), 127.9 (2 x CH, s, 10), 46.7 (2 x CH_2, s, 4), 33.5 (2 x CH_2, s, 3), 30.3 (1 x CH, s, 2), 21.7 (1 x CH_3, s, 1 or 13), 21.6 (1 x CH_3, s, 1 or 13).

Deprotection Procedure:



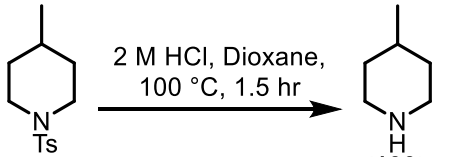
(**132**) (**133**)

To a flame dried Schlenk was added samarium iodide (0.1 M in THF, 5.3 mL, 1.2 mmol, 6 equiv), *N*-tosyl-4-methylpiperidine (0.051 g, 0.2 mmol, 1 equiv), water (65 µL, 3.6 mmol, 18 equiv) and pyrrolidine (0.2 mL, 2.4 mmol, 12 equiv). The blue solution gave a white precipitate and turned colourless on addition of the pyrrolidine. Potassium carbonate solution (10 % w/v, 4 mL) was added and the suspension filtered. The layers were separated and the aqueous layer extracted with diethyl ether (2 x 5 mL) before the combined organic layers were dried over $MgSO_4$, filtered and (*S*)-(+)-mandelic acid (0.030 g, 0.2 mmol, 1 equiv) added before concentrating in vacuo. The resulting oil was washed with hexane and then concentrated in vauo to give a colourless solid which was analysed by ^{1}H NMR to measure the conversion.

Preparation of Samarium Iodide:

A flame dried Schlenk was purged (3 x vacuum/ argon) before the addition of samarium powder (0.165 g, 1.1 mmol, 2.0 equiv) and a second purge cycle (3 x vacuum/ argon) took place. This powder was stirred (rt, 24 hr, 700 rpm). Anhydrous THF (4 mL) was added followed by a solution of iodine (0.14 g, 0.55 mmol, 1 equiv) in anhydrous THF (1.5 mL). The solution was heated overnight (60 °C, 18 hr). The blue solution was removed from the heat and allowed to stand at room temperature (2 hr) before use.

Deprotection Procedure:

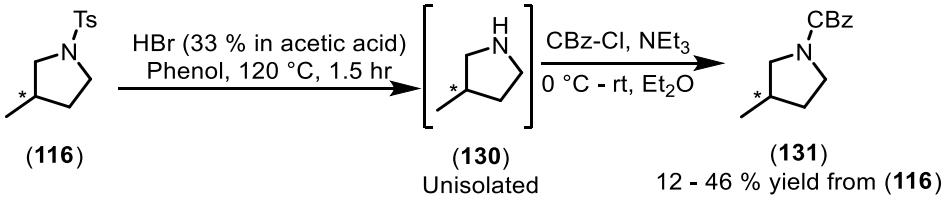


(**132**) (**133**)
0 % yield

N-tosyl-4-methylpiperidine (0.125 g, 0.5 mmol, 1 equiv), 1,4-dioxane (2 mL) and 2 M HCl (2 mL) were heated at reflux (100 °C, 1.5 hr). The colourless solution was cooled to room temperature (20 mins) before 2 M NaOH (5 mL) was added. Diethyl ether (5 mL) was added and the layers separated. The aqueous layer was extracted with diethyl ether (5 mL) before the combined organic layers were dried

over $MgSO_4$, filtered and then acidified with 2M HCl in diethyl ether. The solution was concentrated in vacuo and analysed by ^1H NMR but only starting material was recovered.

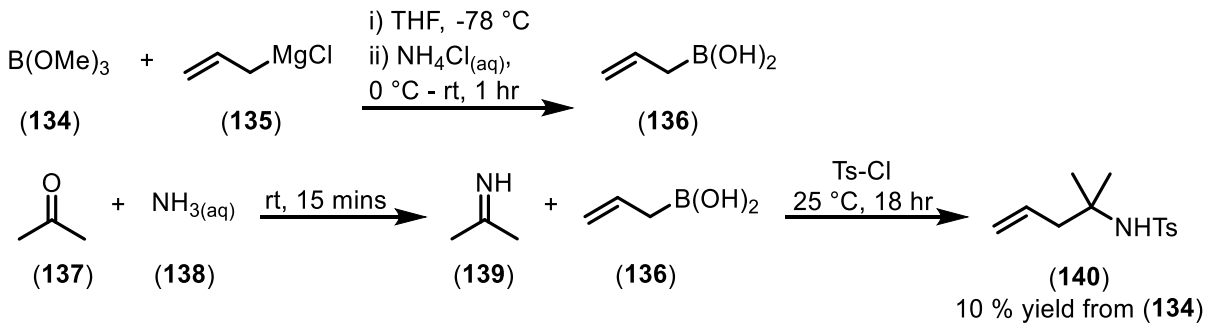
Deprotection Procedure:



To a 25 mL RBF was added *N*=tosyl-3-methylpyrrolidine (0.060 g, 0.25 mmol, 1 equiv), phenol (0.25 g) and HBr (33 % in acetic acid, 2.25 mL). The solution was heated to reflux (120 C, 2 hr) then cooled to room temperature and diluted into diethyl ether (5 mL) before the addition of NaOH (30 % w/v) until pH > 12. The layers were separated and the aqueous layer extracted with diethyl ether (2 x 2.5 mL). The combined organic layers were dried over $MgSO_4$, filtered and taken onto the next reaction without further purification or isolation.

To a 50 mL RBF was added 3-methylpyrrolidine (0.021 g, 0.25 mmol, 1 equiv) in diethyl ether (10 mL) and triethylamine (0.05 mL, 0.325 mmol, 1.3 equiv) before cooling to 0 °C. Benzyl chloroformate (35 µL, 0.25 mmol, 1 equiv) was added at 0 °C and the reaction stirred (0 °C, 1 hr) before warming to room temperature (1 hr). 1 M HCl (2.5 mL) was added and the layers separated. The organic layer was washed with water (2.5 mL), brine (2.5 mL) and dried over $MgSO_4$, filtered and concentrated in vacuo. The data for this compound is listed elsewhere within this document.

Elexacaftor Component Substrate Synthesis:

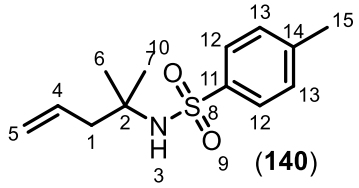


To a flame dried Schlenk was added anhydrous THF (10 mL) and cooled to -78 °C. Simultaneously, slowly and separately a solution of allylmagnesium chloride (5 mL, 10.5 mL, 1 equiv) in anhydrous THF (10 mL) and a solution of trimethyl borate (1.2 mL, 10.5 mmol, 1 equiv) in anhydrous THF (20 mL) were added. The grey suspension was stirred at -78 °C (3 hr) then warmed to 0 °C and 2M HCl (10 mL) added. The solution was stirred at 0 °C (5 mins) then warmed to room temperature (1 hr). The layers were

separated and the aqueous layer extracted with diethyl ether: DCM (5:1, 2 x 6 mL). The combined organic layers were dried over $MgSO_4$, filtered and taken onto the next step without further isolation or purification.

To a 100 mL RBF was added acetone (1.25 mL, 17 mmol, 1.6 equiv) and ammonia solution (2.2 mL, 55 mmol, 5.2 equiv) and stirred at 25 °C for 15 mins. A solution of allyl boronic acid (10.5 mmol, 1 equiv) in THF (40 mL) was added and the suspension stirred overnight (25 °C, 18 hr). The solution was acidified with 6M HCl to pH 1 and the layers separated. The aqueous layer was extracted with DCM (3 x 2.5 mL) and then basified to pH > 9 with sat. KOH. The aqueous layer was extracted with ethyl acetate (3 x 5 mL), dried over KOH, filtered and taken onto the next step without further isolation or purification.

To a 25 mL RBF was added crude amine (, 5.0 mmol, 1 equiv) in ethyl acetate (15 mL) and cooled to 0 °C. Triethyl amine (1.4 mL, 10 mmol, 2 equiv) and tosyl chloride (1.049 g, 5.5 mmol, 1.1 equiv) and the solution warmed to room temperature overnight (18 hr). The suspension was filtered, saturated $NaHCO_3$ (5 mL) was added and the biphasic solution stirred (room temperature, 1 hr). The layers were separated and the organic layer washed with water (5 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. Purified by silica column chromatography, petroleum ether: diethyl ether (9:1) followed by a DCM flush. The compound was obtained as a colourless, crystalline solid (0.275 g, 1.05 mmol, 10 % yield) over 3 steps from the trimethyl borate.



(**140**)

^{1}H NMR δ(400 MHz, $CDCl_3$): 7.77 (2H, d, J = 8.3, Ar, 12), 7.30 – 7.23 (2H, m, Ar, 13), 5.75 (1H, ddt, J = 17.6, 10.2, 7.4, CH, 4), 5.19 – 5.03 (2H, m, CH_2, 5), 4.74 (1H, s, NH, 3), 2.41 (3H, s, CH_3, 15), 2.24 (2H, d, J = 7.4, CH_2, 1), 1.17 (6H, s, 2 x CH_3, 6 + 7).

^{13}C NMR δ(126 MHz, $CDCl_3$): 143.0 (1 x C, s, 11), 140.7 (1 x C, s, 14), 133.2 (1 x CH, s, 4), 129.6 (2 x CH, s, 12), 127.1 (2 x CH, s, 13), 119.8 (1 x CH_2, s, 5), 56.5 (1 x C, s, 2), 47.6 (1 x CH_2, s, 1), 27.5 (2 x CH_3, s, 6 + 7), 21.6 (1 x CH_3, s, 15).

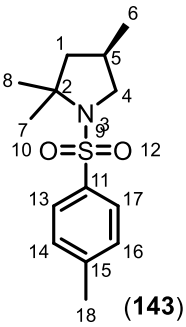
IR (neat, cm^{-1}): 1177, 1150, 1090, 993 and 924.

Mass spec: M + Na: 276.1019 m/z, $C_{13}H_{19}NO_2SNa^+$ requires 276.1029.

Melting point: 100 – 102 °C

Elexacaftor Component Asymmetric HF:

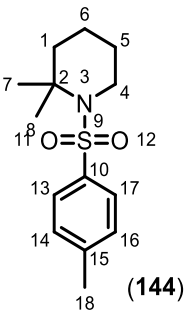
The standard AHF procedure was followed with the following deviations: a higher catalyst loading of 0.8 mol % [Rh(acac)$(CO)_2$] and 2.0 mol % (*R*, *R*, *R*)-BOBPHOS; an extended reaction time of 24 hr and a higher temperature of 40 °C. The crude AHF reaction mixture was reduced with triethylsilane and boron trifluoride diethyletherate as detailed in the general procedures. After this the conversion and branched to linear ratio were measured by ^{1}H NMR: 88 % conversion and 77:23 branched to linear ratio were recorded in this example. Purified by silica column chromatography, hexane: diethyl ether (99:1 to 97.5: 2.5), the product was a white solid and an inseparable mixture of branched and linear (0.0108 g, 0.04 mmol, 16 % yield). Enantioselectivity measured by HPLC, Chiracel AD-H, hexane: IPA (97: 3), 0.5 mL min^{-1}, 254- 220 nm, t_R (minor): 62.7, t_R (major): 77.4. 69 % ee.



(**143**)

^{1}H NMR δ(400 MHz, $CDCl_3$): 7.76 – 7.70 (2H, m, Ar, 13 + 17), 7.31 – 7.25 (2H, m, Ar, 14 + 16), 3.61 (1H, m, 1H of CH_2, 4a), 2.75 (1H, dd, J = 10.1, 9.2, 1H of CH_2, 4b), 2.41 (3H, s, 18), 2.36 – 2.20 (1H, m, CH, 5), 1.87 (1H, dd, J = 11.7, 5.8, 1H of CH_2, 1a), 1.67 – 1.52 (3H, m, CH_3, 7 or 8), 1.50 – 1.35 (4H, m, 1H of CH_2 + CH_3, 1b + 7 or 8), 0.96 (3H, d, J = 6.5, CH_3, 6).

^{13}C NMR δ(126 MHz, $CDCl_3$): 142.6 (1 x C, s, 11), 138.7 (1 x C, s, 15), 129.5 (2 x CH, s, 14 + 16), 127.3 (2 x CH, s, 13 + 17), 66.0 (1 x C, s, 2), 56.2 (1 x CH_2, s, 4), 51.5 (1 x CH_2, s, 1), 30.5 (1 x CH, s, 5), 29.2 (1 x CH_3, s, 7 or 8), 28.7 (1 x CH_3, s, 7 or 8), 21.6 (1 x CH_3, s, 18), 17.1 (1 x CH_3, s, 6).



(**144**)

^{1}H NMR δ(400 MHz, $CDCl_3$): 7.70-7.68 (2H, m, Ar, 13 + 17), 7.28-7.27 (2H, m, Ar, 14 + 16), 3.52-3.49 (2H, m, 4), 1.63-1.56 (4H, m, 2 x CH_2, 5 + 6), 1.47-1.37 (2H, m, CH_2, 1), 1.28 (6H, s, 2 x CH_3, 7 + 8).

^{13}C NMR δ(126 MHz, $CDCl_3$): 142.6 (1 x C, s, 11), 138.7 (1 x C, s, 15), 129.5 (2 x CH, s, 14 + 16), 127.3 (2 x CH, s, 13 + 17), 58.0 (1 x C, s, 2), 43.8 (1 x CH_2, s, 4), 41.5 (1 x CH_2, s, 1), 26.3 (1 x CH_2, s, 5), 26.3 (2 x CH_3, s, 7 + 8), 21.6 (1 x CH_3, s, 18) 20.7 (1 x CH_2, s, 6).

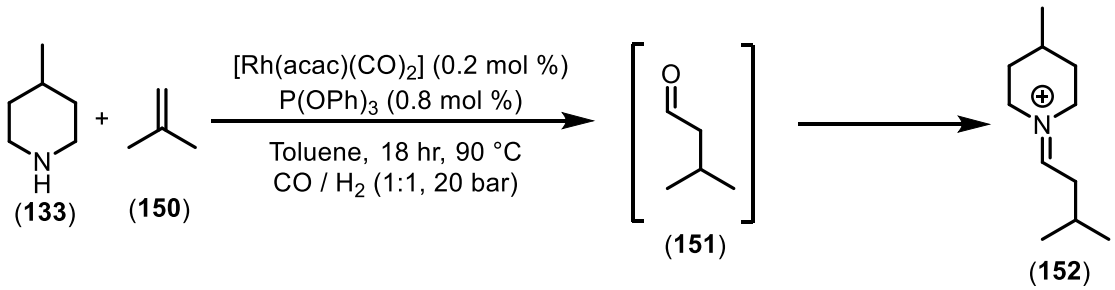
IR (neat, cm^{-1}): (Mix of regioisomers) 1327, 1150, 1092, 588 and 550.

Mass spec (Mix of regioisomers): M + Na: 290.1180 m/z, $C_{14}H_{21}NO_2SNa^+$ requires 290.1185.

Isobutene Stock Solution:

To an oven dried Schlenk was added toluene (5 mL) and this was cooled in a dry ice bath. A needle connected to the isobutene gas canister was inserted into the toluene, a syringe with a balloon attached was inserted into the Schlenk septum and then the Schlenk closed to nitrogen. The isobutene gas canister was then opened and the isobutene condensed into the Schlenk. This was monitored via the increase in liquid volume, rate of bubbling and also the pressure of the balloon. The gas canister was then sealed and the needle removed. More toluene (3 x 5 mL) was added in aliquots until the solution was stable enough to withdraw an NMR sample at room temperature. The Schlenk was then left sealed with a septum and parafilm and stored at – 70 °C. An ^{1}H NMR shows a ratio of isobutene: toluene at 2.95: 1.

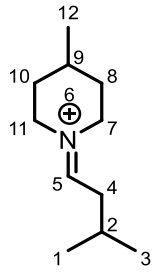
Hydroaminomethylation Reaction:



> 99 % selectivity for iminium ion

To an oven dried microwave vial was added [Rh(acac)$(CO)_2$] (1 mg, 0.004 mmol, 0.2 mol %) and the vial purged (3 x vacuum / N_2) before the addition of triphenylphosphite (5 mg, 0.016 mmol, 0.8 mol %) and dry toluene (1 mL). The solution was stirred (rt, 2 mins) before the addition of isobutene in toluene (0.36 mL, 3.0 mmol, 1.5 equiv) and a solution of amine (0.24 mL, 2.0 mmol, 1 equiv), 1-methylnaphthalene (28 µL, 0.2 mmol, 0.1 equiv) in dry toluene (1 mL). The vial was sealed and the seal pierced with two needles before placing in a similarly purged autoclave. The autoclave was flushed with syngas (x 3), pressurised with syngas (20 bar) and heated overnight (90 °C, 18 hr). The autoclave was cooled to room temperature (water bath, 30 mins) and the pressure released. The sample was analysed by 1H NMR before the addition of 1 M HCl (5 mL) and diethyl ether (5 mL). The layers were

separated and the aqueous layer basified to pH > 12 with 1 M NaOH. The aqueous layers were extracted with ethyl acetate (3 x 5 mL), dried over $MgSO_4$, filtered and concentrated in vacuo.

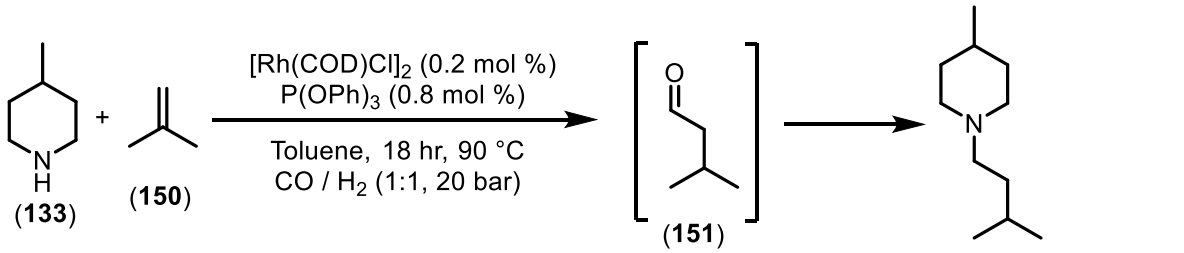


(**152**)

^{1}H NMR δ(500 MHz, $CDCl_3$): 8.01 (1H, s, CH, 5), 4.42 – 4.31 (1H, m, 1H of CH_2, 4a), 3.58 (1H, dd, J = 13.2, 2.2, 1H of CH_2, 7a or 11a), 3.14 – 3.00 (2H, m, 2 x 1H of CH_2, 7b or 11b + 7a or 11a), 2.68 – 2.52 (2H, m, 2 x 1H of CH_2, 4b + 7b or 11b), 1.75 – 1.49 (3H, m, CH + 2 x 1H of CH_2, 2 + 8a + 10a), 1.19 – 1.03 (2H, m, 2 x 1H of CH_2, 8b + 10b), 1.02 – 0.77 (10H, m, CH + 3 x CH_3, 1 + 3 + 9 + 12) .

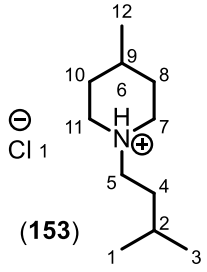
^{13}C NMR δ(126 MHz, $CDCl_3$): 161.0 (1 x CH, s, 5), 46.4 (1 x CH_2, s, 7 or 11), 43.9 (1 x CH_2, s, 7 or 11), 40.2 (1 x CH_2, s, 4), 34.8 (1 x CH_2, s, 8 or 10), 31.5 (1 x CH, s, 2), 30.6 (1 x CH_2, s, 8 or 10), 22.4 (1 x CH, s, 9), 21.9 (2 x CH_3, s, 1 + 3), 21.4 (1 x CH_3, 12).

Hydroaminomethylation Reaction:



> 99 % selectivity for amine
Species identity confirmed
by mass spectrometry

The same procedure as above was used but with $[Rh(COD)Cl]_2$ (2 mg, 0.004 mmol, 0.2 mol %) in place of $[Rh(acac)(CO)_2]$.



(**153**)

Due to ring inversion, nitrogen lone pair inversion and isopentane chain rotation, no peak splitting could be seen in the ^{1}H NMR. This is discussed further in this paper: *J. Org. Chem.*, 1998, 63, 3310

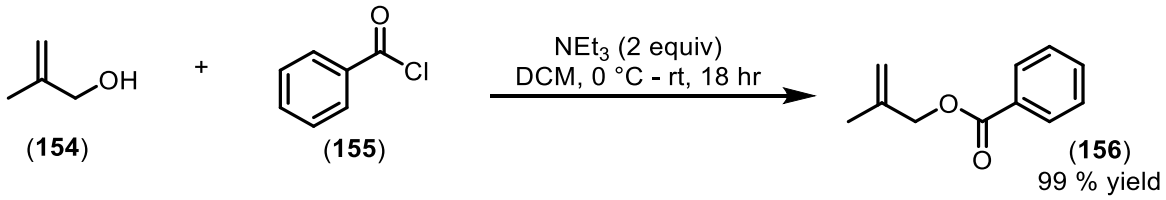
^{1}H NMR δ(400 MHz, CD_3OD): 3.64 – 3.48 (1H, m), 3.35 (2H, dd, J = 18.8, 5.7), 3.12 (1H, br s), 3.00 (3H, br s), 1.90 (3H, d, J = 12.7), 1.58 (1H, s), 1.53 – 1.34 (3H, m), 1.12 (1H, br s), 1.09 – 0.94 (8H, m).

^{13}C NMR δ(126 MHz, CD_3OD): 57.2 (1 x CH_2, s), 54.3 (1 x CH_2, s), 45.3 (2 x CH_2, s), 32.5 (1 x CH_2, s), 31.7 (1 x CH_2, s), 29.9 (2 x CH_3, s), 27.5 (1 x CH, s), 22.7 (1 x CH, s), 21.8 (1 x CH_3, s).

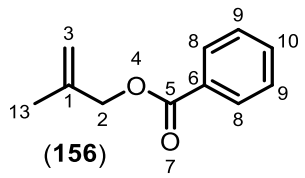
IR (neat, cm^{-1}): 2957, 2932, 2468, 1443 and 583.

Mass spec: M = 170.1898 m/z, $C_{11}H_{24}N^+$ requires 170.1903.

Substrate Synthesis:



To a 50 mL RBF was added 2-methylprop-2-en-1-ol (1.0 mL, 10 mmol, 1 equiv), triethylamine (2.8 mL, 20 mmol, 2 equiv) and DCM (17 mL). The colourless solution was cooled to 0 °C before the addition of benzoyl chloride (1.2 mL, 10 mmol, 1 equiv). The yellow solution was stirred and warmed to room temperature overnight (18 hr). The suspension was diluted into ethyl acetate (10 mL) then washed with 1 M HCl (aq., 10 mL), saturated $NaHCO_3$ (aq., 10 mL) and brine (10 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. This gave the product as a colourless oil (1.7 g, 9.9 mmol, 99 % yield). Data matches the literature: *Org. Lett.*, 2003, 5 (18), 3213 – 3216.



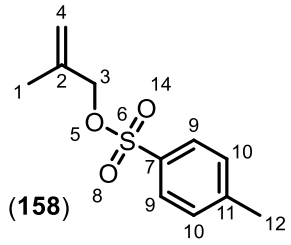
^{1}H NMR δ(400 MHz, $CDCl_3$): 8.08 (2H, dd, J = 8.4, 1.3, Ar, 8), 7.55 (1H, t, J = 7.6, Ar, 10), 7.44 (2H, t, J = 7.6, Ar, 9), 5.08 (1H, s, 1H of CH_2, 3a), 4.98 (1H, s, 1H of CH_2, 3b), 4.75 (2H, s, CH_2, 2), 1.84 (3H, s, CH_3, 13).

^{13}C NMR δ(126 MHz, $CDCl_3$): 166.3 (1 x C, s, 5), 140.0 (1 x C, s, 6), 133.0 (1 x CH, s, 10), 130.2 (1 x C, s, 1), 129.7 (2 x CH, s, 8), 128.4 (2 x CH, s, 9), 113.0 (1 x CH_2, s, 3), 68.2 (1 x CH_2, s, 2), 19.7 (1 x CH_3, s, 13).

Substrate Synthesis:

(**154**) (**157**) (**158**)
36 % yield

To a 50 mL RBF was added tosyl chloride (1.049 g, 5.5 mmol, 1.1 equiv), potassium hydroxide (0.309 g, 5.5 mmol, 1.1 equiv) and DCM (10 mL). The solution was cooled to 0 °C before the addition of triethylamine (0.05 mL, 5 mmol, 0.1 equiv) and 2-methylprop-2-en-1-ol (0.42 mL, 5.0 mmol, 1 equiv). The suspension was stirred at 0 °C (1 hr) then filtered and the filtrate washed with water (7.5 mL). The aqueous layer was extracted with ethyl acetate (7.5 mL) before the combined organic layers were washed with brine (7.5 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude reaction mixture was purified by silica column chromatography, hexane: ethyl acetate (92.5: 7.5) to give the product as a colourless oil (0.42 g, 1.8 mmol, 36 % yield). Data matches the literature: *Tetrahedron*, 1999, 55(8), 2183-2192

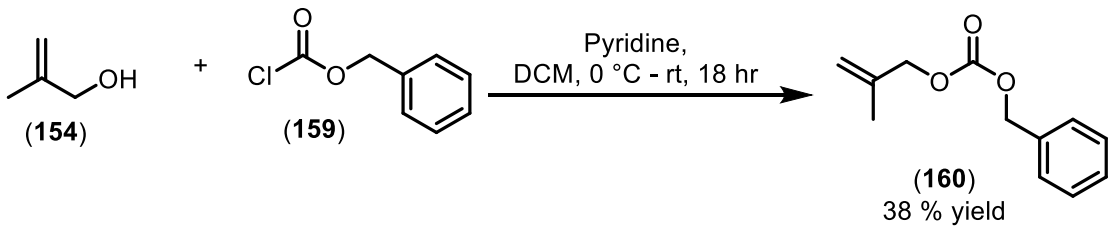


(**158**)

^{1}H NMR δ(400 MHz, $CDCl_3$): 7.77 (2H, m, Ar, 9), 7.33 (2H, d, J = 8.0, Ar, 10), 4.96 (1H, s, 1H of CH_2, 4a), 4.92 (1H, s, 1H of CH_2, 4b), 4.41 (2H, s, CH_2, 3), 2.43 (3H, s, CH_3, 12), 1.67 (3H, s, CH_3, 1).

^{13}C NMR δ(101 MHz, $CDCl_3$): 144.9 (1 x C, s, 7), 138.0 (1 x C, s, 11), 129.9 (2 x CH, s, 10), 127.9 (2 x CH, s, 9), 115.7 (1 x CH_2, s, 4), 73.8 (1 x CH_2, s, 3), 21.6 (1 x CH_3, s, 12), 19.1 (1 x CH_3, s, 1).

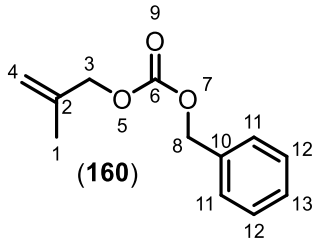
Substrate Synthesis:



(**154**) (**159**) (**160**)
38 % yield

To a 50 mL RBF was added DCM (13 mL), 2-methylprop-2-en-1-ol (0.42 mL, 5.0 mmol, 1 equiv) and benzyl chloroformate (1.0 mL, 7.0 mmol, 1.4 equiv). The colourless solution was cooled to 0 °C and

pyridine (0.57 mL, 7.0 mmol, 1.4 equiv) was added dropwise. The colourless solution was warmed to room temperature overnight (18 hr). DCM (3 mL) was added and the colourless solution washed with 1 M HCl (2 x 5 mL) then saturated $NaHCO_3$ (aq., 3 x 3 mL) before the organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The crude reaction mixture was purified by silica column chromatography, petroleum ether: diethyl ether (95: 5) to give the product as a colourless oil (0.39 g, 1.9 mmol, 38 % yield). Data matches the literature: *Eur. JOC*, 2011, 2011 (32), 6519-6526.

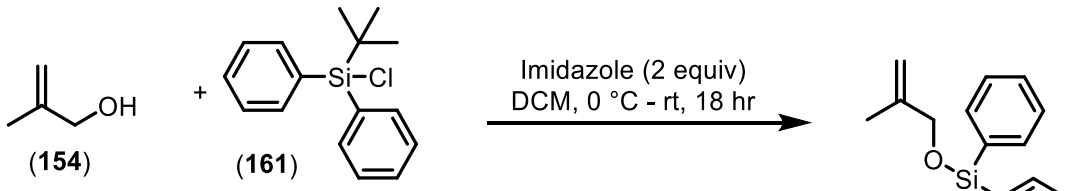


(**160**)

^{1}H NMR δ(400 MHz, $CDCl_3$): 7.42 – 7.35 (5H, m, Ar, 11 – 13), 5.19 (2H, s, CH_2, 8), 5.04 (1H, s, 1H of CH_2, 4a), 4.97 (1H, s, 1H of CH_2, 4b), 4.58 (2H, s, CH_2, 3), 1.79 (3H, s, CH_3, 1).

^{13}C NMR δ(126 MHz, $CDCl_3$): 155.1 (1 x C, s, 6), 139.4 (1 x C, s, 10), 135.3 (1 x C, s, 2), 128.6 (2 x CH, s, 11), 128.6 (1 x CH, s, 13), 128.4 (2 x CH, s, 12), 113.6 (1 x CH_2, s, 4), 71.2 (1 x CH_2, s, 8), 69.7 (1 x CH_2, s, 3), 19.37 (1 x CH_3, s, 1).

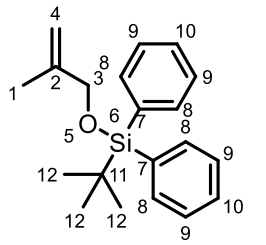
Substrate Synthesis:



(**154**) (**161**) (**162**)
91 % yield

To a 50 mL RBF was added imidazole (2.723 g, 40 mmol, 2.0 equiv) and DCM (28 mL) followed by 2-methylprop-2-en-1-ol (1.7 mL, 20.0 mmol, 1 equiv). The colourless solution was cooled to 0 °C before the dropwise addition of chloro^{t}butyldiphenylsilane (7.7 mL, 30 mmol, 1.5 equiv). A precipitate formed and the suspension was stirred at 0 °C before warming to room temperature overnight (18 hr). Water (12 mL) was added to quench the reaction and the layers separated. The aqueous layer was extracted with DCM (3 x 20 mL) before the combined organic layers were washed with brine (3 x 20 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude reaction mixture was purified by silica

column chromatography, hexane: diethyl ether (10:1) to give the product as a colourless oil (5.64 g, 18. 2 mmol, 91 % yield). Data matches the literature: *J. Am. Chem. Soc.*, 2014, 136 (45), 15913–15916



(**162**)

^{1}H NMR δ(400 MHz, $CDCl_3$): 7.77-7.75 (4H, m, Ar, 8,), 7.49-7.41 (6H, m, Ar, 9 + 10), 5.20 (1H, s, 1H of CH_2, 4a), 4.92 (1H, s, 1H of CH_2, 4b), 4.14 (2H, s, CH_2, 2H), 1.74 (3H, s, CH_3, 1), 1.14 (9H, s, 3 x CH_3, 12).

^{13}C NMR δ(126 MHz, $CDCl_3$): 144.3 (2 x C, s, 7), 135.6 (1 x C, s, 2), 133.8 (4 x CH, s, 8), 129.7 (2 x CH, s, 10), 127.7 (4 x CH, s, 9), 109.2 (1 x CH_2, 4), 67.3 (1 x CH_2, s, 3), 26.9 (3 x CH_3, s, 12), 19.4 (1 x C, s, 14), 19.1 (1 x CH_3, s, 1).

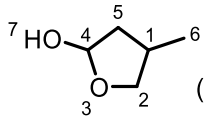
General Procedure for the Hydroformylation of 1,1-Disubstituted Alkenes:

To a flame dried Schlenk was added $[Rh(COD)Cl]_2$ (0. 2 mol %) and the Schlenk purged (3 x vacuum / N_2) and then triphenylphosphite (0.8 mol %) and dry toluene (2 mL) were added. This was stirred (rt, 5 mins) before injecting into a sealed, purged microwave vial. The vial was pierced with x 2 needles, placed in a similarly purged autoclave and the autoclave flushed with syngas. The autoclave was then pressurised with syngas (CO: H_2 = 1:1, 10 bar) and heated (50 °C, 40 mins) before cooling to room temperature (water bath, 20 mins) and the pressure released. A solution of the appropriate alcohol in toluene (1 mL) was injected and the autoclave pressurised with syngas (20 bar) and heated overnight (80 C, 18 hr). The autoclave was then cooled to room temperature and the pressure released. An aliquot of the reaction mixture was analysed by ^{1}H NMR to measure the conversion and selectivity before carrying out a reduction of the aldehyde to the alcohol.

General Procedure for the Reduction of Aldehydes:

To the microwave vial containing the crude HF reaction mixture was added sodium borohydride (0.5 equiv) and ethanol (2 mL). The solution was then stirred (rt, 2 hr) before 1 M HCl (5 mL), water (5 mL) and DCM (5 mL) were added. The layers were separated and the aqueous layer extracted with DCM (2 x 5 mL) before the combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo.

Hydroformylation:



(**164**)

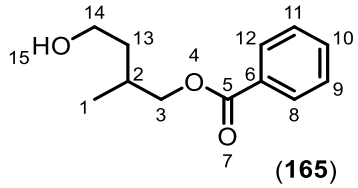
From 2-methylprop-2-en-1-ol. Purified by silica column chromatography, hexane: ethyl acetate (8:2). Product is a mixture of diastereomers in the ratio 1.3: 1 and a colourless oil (0.0197 g, 0.19 mmol, 19 % yield). Data matches the literature: *J. Am. Chem. Soc.*, 2006, 126 (34), 10682 – 10691.

^{1}H NMR δ(400 MHz, $CDCl_3$): 5.41 (2H, t, J = 5.0, CH, 4 + 4'), 4.02 (1H, td, J = 7.8, 5.0, 2a), 3.93 (1H, m, 2a'), 3.39 (2H, dq, J = 15.3, 7.8, 2 x 1H of CH_2, 2b + 2b'), 2.53 – 2.40 (1H, m, CH, 1), 2.30 - 2.20 (2H, m, 1H of CH_2 + CH, 5a' + 1'), 2.05 – 1.95 (1H, m, 1H of CH_2, 5a), 1.57 (1H, ddt, J = 13.9, 8.8, 5.0, 1H of CH_2, 5b), 1.51 – 1.39 (1H, m, 1H of CH_2, 5b'), 1.03 (6H, dd, J = 6.7, 2.9, 2 x CH_3, 6 + 6').

Both diastereomers and conformers are visible in ^{13}C NMR, reported as aggregation.

^{13}C NMR δ(126 MHz, $CDCl_3$): 101.5, 101.2, 101.1, 100.8 (1 x CH, s, 4 + 4'), 74.3, 74.2 (1 x CH_2, s, 2), 73.7, 73.6 (1 x CH_2, s, 2'), 41.2, 41.2, (1 x CH_2, s, 5'), 40.9, 40.8 (1 x CH_2, s, 5), 32.9 (1 x CH, s, 1'), 31.5 (1 x CH, s, 1), 18.3, 18.3 (1 x CH_3, s, 6'), 17.6, 17.5 (1 x CH_3, s, 6).

Hydroformylation:



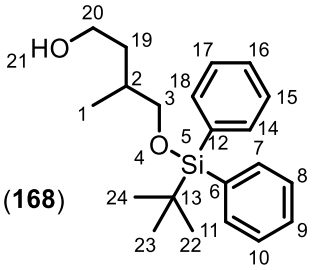
(**165**)

From 2-methylallyl benzoate. Purified by silica column chromatography, hexane: ethyl acetate (9:1) to give the product as a colourless oil (0.063 g, 0.3 mmol, 30 % yield). Data matches the literature: *Tet. Lett.*, 2003, 44 (18), 3663-3665

^{1}H NMR δ(400 MHz, $CDCl_3$): 8.08 – 7.98 (2H, m, Ar, 8 + 12), 7.59 – 7.49 (1H, m, Ar, 10), 7.47 – 7.39 (2H, m, Ar, 9 + 11), 4.27 – 4.12 (2H, m, CH_2, 3), 3.80 – 3.61 (2H, m, CH_2, 14), 2.81 (1H, br s, OH, 15) 2.18 – 2.06 (1H, m, CH, 2), 1.81 – 1.72 (1H, m, 1H of CH_2, 13a), 1.59 – 1.46 (1H, m, 1H of CH_2, 13b), 1.05 (3H, d, J = 6.8, CH_3, 1).

^{13}C NMR δ(126 MHz, $CDCl_3$): 166.8 (1 x C, s, 5), 133.0 (1 x CH, s, 10), 130.3 (1 x C, s, 6), 129.6 (2 x CH, s, 8 + 12), 128.4 (2 x CH, s, 9 + 11), 69.7 (CH_2, s, 3), 60.6 (CH_2, s, 14), 36.3 (CH_2, s, 13), 29.7 (CH, s, 2), 17.1 (CH_3, s, 1).

Hydroformylation:

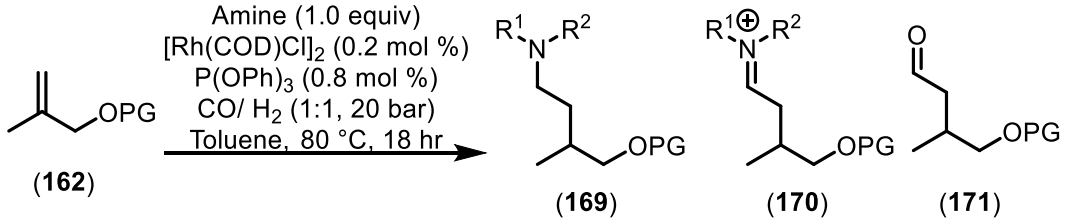


From *tert*-butyl((2-methylallyl)oxy)diphenylsilane. Purified by silica plug with DCM as eluent, product is a colourless oil (0.188 g, 0.55 mmol, 55 % yield). Data matches the literature: *J. Am. Chem. Soc.*, 2018, 140 (15), 4977 – 4981.

^{1}H NMR δ(500 MHz, $CDCl_3$): 7.78 – 7.72 (4H, m, Ar, 7, 11, 14, 18), 7.50 – 7.40 (6H, m, Ar, 8-10 + 15-17), 3.8 – 3.66 (2H, m, CH_2, 20), 3.59 (2H, m, CH_2, 3), 1.94 – 1.69 (3H, m, CH + 1H of CH_2, 2 + 19a), 1.60 – 1.53 (1H, m, 1H of CH_2, 19b), 1.15 (9H, d, J = 8.6, 3 x CH_3, 22-23), 0.96 (3H, d, J = 6.8, CH_3, 1).

^{13}C NMR δ(126 MHz, $CDCl_3$): 135.7 (4 x CH, s, 7, 11, 14, 18), 133.6 (2 x C, s, 6 + 12), 129.9 (2 x CH, 9 + 16), 127.8 (4 x CH, s, 8, 10, 15, 17), 69.3 (1 x CH_2, s, 3), 61.1 (1 x CH_2, s, 20), 37.3 (1 x CH_2, s, 19), 33.3 (1 x CH, s, 2), 27.0 (3 x CH_3, s, 22 - 24), 19.3 (1 x C, s, 13), 17.3 (1 x CH_3, s, 1).

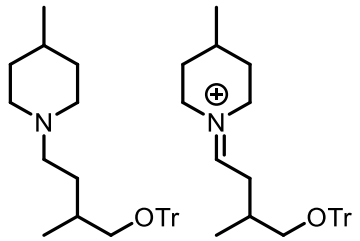
General Procedure for the Hydroaminomethylation of 1,1-Disubstituted Alkenes:



PG = *tert*-butyldiphenylsilyl

To a flame dried Schlenk was added $[Rh(COD)Cl]_2$ (0. 2 mol %) and the Schlenk purged (3 x vacuum / N_2) and then triphenylphosphite (0.8 mol %) and dry toluene were added. This was stirred (rt, 5 mins) before injecting into a sealed, purged microwave vial. The vial was pierced with x 2 needles, placed in a similarly purged autoclave and the autoclave flushed with syngas. The autoclave was then pressurised with syngas (CO: H_2 = 1:1, 10 bar) and heated (50 °C, 40 mins) before cooling to room temperature (water bath, 20 mins) and the pressure released. A solution of the appropriate alcohol and amine in toluene was injected and the autoclave pressurised with syngas (20 bar) and heated overnight (18 hr). The autoclave was then cooled to room temperature and the pressure released. An aliquot of the reaction mixture was concentrated in vacuo then analysed by ^{1}H NMR to measure the conversion and selectivity before carrying out purification by silica column chromatography.

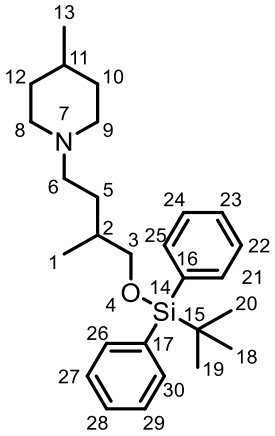
Hydroaminomethylation:



(**172**) (**170**)

> 99 % conversion, 93: 7 of **169**: **170**

68 % yield in 97: 3 ratio of **169**: **170**



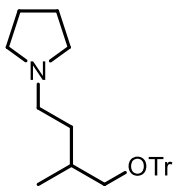
^{1}H NMR δ(500 MHz, $CDCl_3$): 7.69 (4H, d, J = 7.1, Ar, 21, 25, 26, 30), 7.52 – 7.30 (6H, m, Ar, 22-24 + 27-29), 3.66 - 3.55 (2H, m, CH_2, 3), 2.95 – 2.79 (2H, m, CH_2, 8 or 9), 2.47 - 2.33 (2H, m, CH_2, 6), 1.98 - 1.92 (2H, m, CH_2, 8 or 9), 1.82 – 1.43 (4H, m, CH + 1H of CH_2 + CH_2, 2 + 5a + 10 or 12), 1.40 – 1.21 (4H, m, CH + 1H of CH_2 + CH_2, 11 + 5b + 10 or 12), 1.09 (9H, s, 3 x CH_3), 0.93 (6H, m, 2 x CH_3, 1 + 13).

^{13}C NMR δ(126 MHz, $CDCl_3$): 135.7 (4 x CH, s, 21, 25, 26, 30), 134.1 (2 x C, s, 16, 17), 129.6 (2 x CH, s, 23, 28), 127.7 (4 x CH, s, 22, 24, 27, 29), 69.0 (1 x CH_2, s, 3), 57.2 (2 x CH_2, 8, 9), 54.1 (1 x CH_2, s, 6), 34.7 (1 x CH, s, 2), 34.3 (1 x CH_2, s, 5), 30.9 (1 x CH, s, 11), 30.4 (2 x CH_2, s, 10, 12), 27.0 (3 x CH_3, s, 18 – 20), 22.0 (1 x CH_3, s, 13), 19.4 (1 x C, s, 15), 17.1 (1 x CH_3, s, 1).

IR (neat, cm^{-1}): 2951, 1427, 1111, 700 and 503.

Mass spec: M+H = 424.3021 m/z, $C_{27}H_{42}NOSi^{+}$ requires 424.3030.

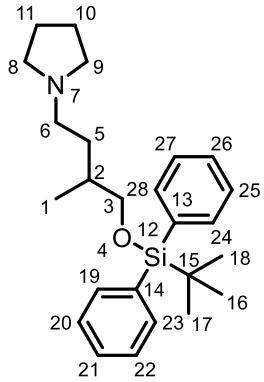
Hydroaminomethylation:



(**176**)

> 99 % conversion, 89: 11 of **169**: **170**

65 % yield of **176**



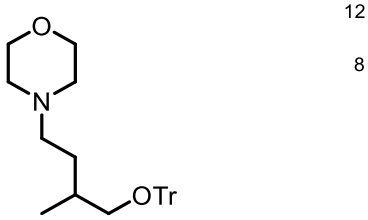
^{1}H NMR δ(500 MHz, $CDCl_3$): 7.69-7.66 (4H, m, Ar, 19, 23, 24, 28), 7.45 – 7.32 (6H, m, Ar, 20 – 22 + 25 – 27), 3.54 – 3.45 (2H, m, CH_2, 3), 2.51 – 2.33 (6H, m, CH_2 + 2 x CH_2, 6 + 8, 9), 1.80 – 1.65 (6H, m, CH + 1H of CH_2 + 2 x CH_2, 2 + 5a + 10, 11), 1.39 – 1.30 (1H, m, 1H of CH_2, 5b), 1.06 (9H, s, 3 x CH_3, 16 - 18), 0.94 (3H, d, J = 6.6, CH_3, 1).

^{13}C NMR δ(126 MHz, $CDCl_3$): 135.7 (4 x CH, s, 19, 23, 24, 28), 134.0 (2 x C, s, 13 + 14), 129.5 (2 x CH, 21 + 26), 127.6 (4 x CH, 20, 22, 25, 27), 69.0 (1 x CH_2, s, 3), 54.6 (1 x CH_2, 6), 54.3 (2 x CH_2, s, 8 + 9), 34.5 (1 x CH, s, 2), 32.3 (1 x CH_2, s, 5), 26.9 (3 x CH_3, s, 16 – 18), 23.4 (2 x CH_2, s, 10 – 11), 19.3 (1 x C, s, 15), 17.0 (1 x CH_3, s, 1).

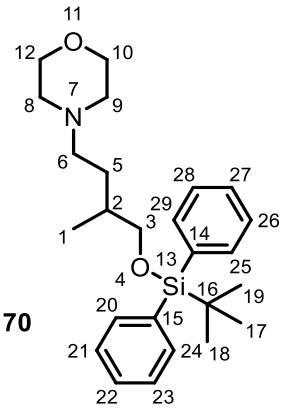
IR (neat, cm^{-1}): 2929, 1427, 1109, 700 and 503.

Mass spec: M+H = 396.2706 m/z, $C_{25}H_{38}NOSi^+$ requires 396.2717.

Hydroaminomethylation:



(**175**)
> 99 % conversion, 89: 11 of **169**: **170**
63 % yield of **175**



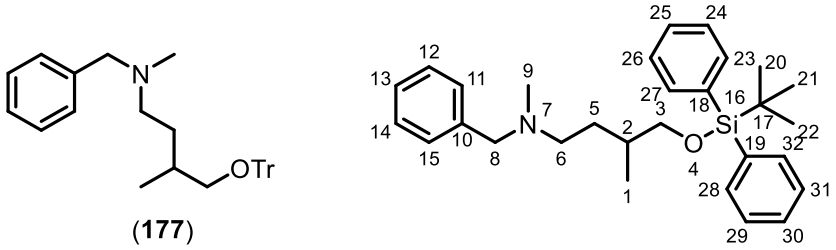
^{1}H NMR δ(500 MHz, $CDCl_3$): 7.71 – 7.65 (4H, m, Ar, 20, 24, 25, 29), 7.47 – 7.34 (6H, m, Ar, 21-23 + 26 - 28), 3.72 – 3.70 (4H, m, 2 x CH_2, 10 + 12), 3.54 – 3.47 (2H, m, CH_2, 3), 2.41 (4H, br s, 2 x CH_2, 8 + 9), 2.38 – 2.29 (2H, m, CH_2, 6), 1.79 – 1.61 (2H, m, CH + 1H of CH_2, 2 + 5a), 1.36 – 1.23 (1H, m, 1H of CH_2, 5b), 1.07 (9H, s, 3 x CH_3, 17-19), 0.95 (3H, d, J = 6.6, CH_3, 1).

^{13}C NMR δ(126 MHz, $CDCl_3$): 135.7 (4 x CH, s, 20, 24, 25, 29), 134.0 (2 x C, s, 14 + 15), 129.6 (2 x CH, s, 22 + 27), 127.8 (4 x CH, s, 21, 23, 26, 28), 68.9 (1 x CH_2, s, 3), 67.1 (2 x CH_2, s, 10 + 12), 57.1 (1 x CH_2, s, 6), 53.9 (2 x CH_2, s, 8 + 9), 34.3 (1 x CH, s, 2), 30.1 (1 x CH_2, s, 5), 27.0 (3 x CH_3, s, 17 – 19), 19.4 (1 x C, s, 16), 17.1 (1 x CH_3, s, 1).

IR (neat, cm^{-1}): 2856, 1427, 1111, 700 and 503.

Mass spec: M+H = 412.2657 m/z, $C_{25}H_{38}NO_2Si^+$ requires 412.2666.

Hydroaminomethylation:



(**177**)
> 99 % conversion, 89: 11 of **169**: **170**
33 % yield of **177**

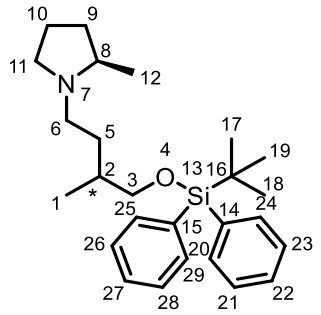
^{1}H NMR δ(500 MHz, $CDCl_3$): 7.71 – 7.63 (4H, m, Ar, 23, 27, 28, 32), 7.46 – 7.35 (6H, Ar, 24 – 26 + 29 – 31), 7.30 (3H, Ar, d, J = 4.4, 12 – 14), 7.28 – 7.21 (2H, Ar, m, 11 + 15), 3.55 – 3.39 (4H, m, 2 x CH_2, 3 + 8), 2.39 (2H, t, J = 7.3, 1 x CH_2, 6), 2.17 (3H, s, 1 x CH_3, 9), 1.79 – 1.71 (2H, m, CH + 1H of CH_2, 2 + 5a), 1.37 – 1.25 (1H, m, 1H of CH_2, 5b), 1.06 (9H, s, 3 x CH_3, 20 – 22), 0.91 (3H, d, J = 6.5, 1 x CH_3, 1).

^{13}C NMR δ(126 MHz, $CDCl_3$): 139.4 (1 x C, s, 10), 135.8 (4 x CH, s, 23, 27, 28, 32), 134.2 (2 x C, s, 19 + 18), 129.6 (2 x CH, 25 + 30), 129.2 (2 x CH, s, 11 + 15), 128.3 (2 x CH, s, 12 + 14), 127.7 (4 x CH, s, 24, 26, 29, 31), 127.0 (1 x CH, s, 13), 69.0 (1 x CH_2, s, 3), 62.4 (1 x CH_2, s, 8), 55.5 (1 x CH_2, s, 6), 42.3 (1 x CH_3, s, 9), 34.2 (1 x CH, s, 2), 30.8 (1 x CH_2, s, 5), 27.0 (3 x CH_3, s, 20 - 22), 19.5 (1 x C, s, 17), 17.1 (1 x CH_3, s, 1).

IR (neat, cm^{-1}): 2856, 1427, 1111, 698 and 503.

Mass spec: M+H = 446.2859 m/z, $C_{29}H_{40}NOSi^{+}$ requires 446.2874.

Hydroaminomethylation:



(**178**)

^{1}H NMR δ(500 MHz, $CDCl_3$): 7.68 – 7.66 (4H, m, Ar, 20, 24, 25, 29), 7.47 – 7.33 (6H, m, Ar, 21 – 23 + 26 – 28), 3.57 – 3.42 (2H, m, CH_2, 3), 3.21 – 3.15 (1H, m, 1H of CH_2, 11a), 2.89 – 2.79 (1H, m, 1H of CH_2, 6a), 2.28 (1H, br s, CH, 8), 2.15 – 1.85 (3H, m, 3 x 1H of CH_2, 5a + 6b + 11b), 1.85 – 1.54 (4H, m, CH + 1H of CH_2 + CH_2, 2 + 9a + 10), 1.54 – 1.30 (2H, m, 2 x 1H of CH_2, 5b + 9), 1.10 (3H, d, J = 6.0, CH_3, 12), 1.05 (9H, s, 3 x CH_3, 17 - 19), 0.98 – 0.91 (3H, m, CH_3, 1).

Diastereomer 1:

^{13}C NMR δ(126 MHz, $CDCl_3$): 135.8 (4 x CH, s, 20, 24, 25, 29), 134.1 (2 x C, s, 14 + 15), 129.6 (2 x CH, s, 22 + 27), 127.7 (4 x CH, s, 21, 23, 26, 28), 68.8 (1 x CH_2, s, 3), 60.5 (1 x CH, s, 8), 53.9 (1 x CH_2, s, 11), 52.4 (1 x CH_2, s, 6), 34.7 (1 x CH, s, 2), 32.7 (1 x CH_2, s, 9), 32.4 (1 x CH_2, s, 5), 27.0 (3 x CH_3, s, 17 – 19), 21.7 (1 x CH_2, s, 10), 19.4 (1 x C, s, 16), 18.8 (1 x CH_3, s, 12), 17.3 (1 x CH_3, s, 1).

Diastereomer 2:

^{13}C NMR δ(126 MHz, $CDCl_3$): 135.8 (4 x CH, s, 20, 24, 25, 29), 134.1 (2 x C, s, 14 + 15), 129.6 (2 x CH, s, 22 + 27), 127.7 (4 x CH, s, 21, 23, 26, 28), 69.2 (1 x CH_2, s, 3), 60.5 (1 x CH, s, 8), 53.9 (1 x CH_2, s, 11), 52.1 (1 x CH_2, s, 6), 34.5 (1 x CH, s, 2), 32.7 (1 x CH_2, s, 9), 32.3 (1 x CH_2, s, 5), 27.0 (3 x CH_3, s, 17 – 19), 21.7 (1 x CH_2, s, 10), 19.4 (1 x C, s, 16), 18.9 (1 x CH_3, s, 12), 16.9 (1 x CH_3, s, 1)

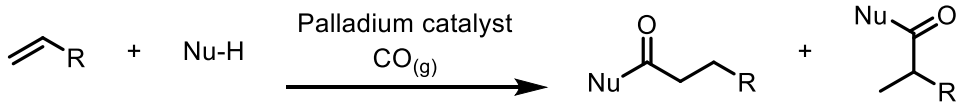
IR (neat, cm^{-1}): 2856, 1427, 1111, 698 and 503.

Mass spec: M+H = 410.2863 m/z, $C_{26}H_{40}NOSi^+$ requires 410.2874.

Appendix 1: Palladium Carbonylations

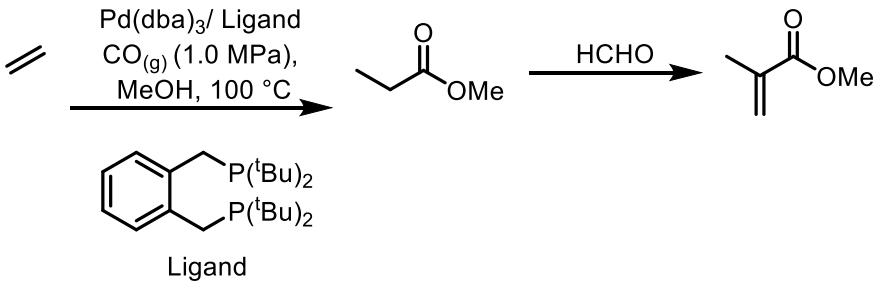
Introduction and Brief Summarisation of Current Literature

Palladium-catalysed carbonylations are the reaction of an alkene and appropriate nucleophile in the presence of a palladium catalyst and carbon monoxide gas to give the carbonyl derivative. Many suitable components can be used as substrates but to affect the regioselectivity of the reaction the electronics of the substrate as well as the electronics and sterics of the ligand must be considered. In addition, the last step of the reaction mechanism is the attack of the nucleophile into the Pd-C=O bond to release the final product. As a result, the nucleophile can vary but must be sterically undemanding and active to attacking the carbon of carbonyl bonds, whilst not being so nucleophilic as to inhibit the catalytic cycle, Scheme 143.



Scheme 143: Palladium-catalysed carbonylation of an alkene with a general nucleophile

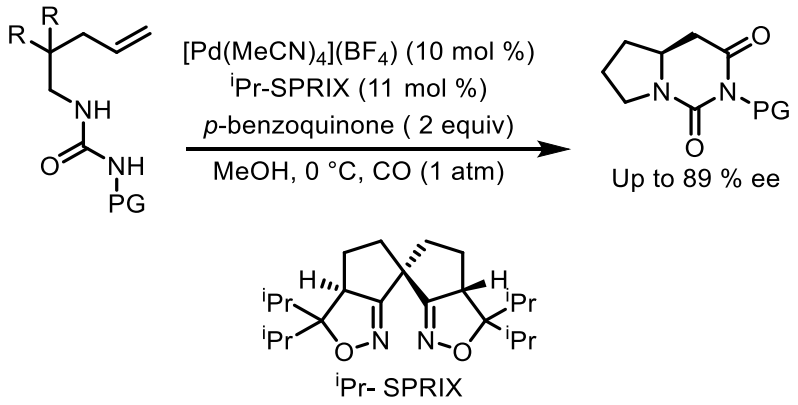
Since the use of carbon monoxide gas requires special consideration on account of the toxicity, this reaction is more commonly found in industry than in academia. One of the most prominent examples is the synthesis of methyl propionate, a precursor to an important plastic monomer methyl methacrylate, through a palladium-catalysed carbonylation reaction of ethylene in the presence of methanol, Scheme 144. The key to achieving such high activity is the use of the ligand, 1,2-bis(di-tert-butylphosphinomethyl)benzene.[100] The recovery and recyclability of the catalyst as well as the simplicity of the reaction conditions and atom efficiency make the reaction very attractive for production of this plastic monomer on an industrial scale.



Scheme 144: Industrial process for the synthesis of methyl methacrylate using a palladium-catalysed carbonylation for the first step.[100]

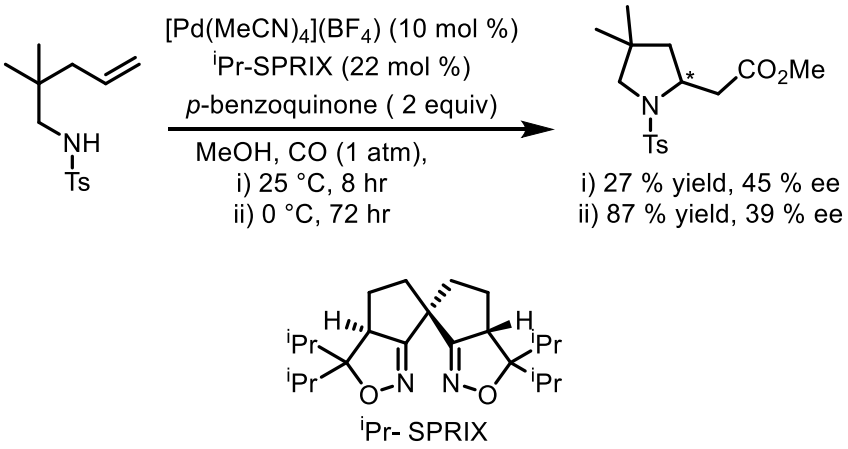
In this appendix, the attempted synthesis of chiral nitrogen heterocycles through a palladium-catalysed carbonylation reaction is described. One of the first examples of this is from 2009 when a

palladium catalyst with a spiro bis(isooxazoline) ligand was used for the synthesis of a series of chiral nitrogen heterocycles, Scheme 145.[101]



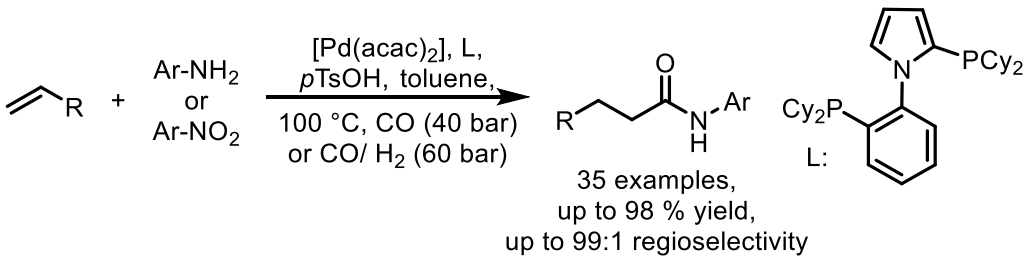
Scheme 145: Palladium-catalysed carbonylation using a spiro bis(isooxazoline) ligand.[101]

This reaction struggles with activity: a high loading of the palladium catalyst and long reaction times are required to achieve acceptable conversions. Furthermore, the spiro bis(isooxazoline) ligand is not easily derivatised for creating analogues, nor is it commercially available, and only induces low to good enantioselectivity. Within this publication was one example of the use of this reaction to synthesise a chiral substituted pyrrolidine, although this was subject to the inefficient reaction conditions stated prior, Scheme 146.



Scheme 146: Synthesis of a chiral pyrrolidine using a spiro bis(isooxazoline) catalyst.[101]

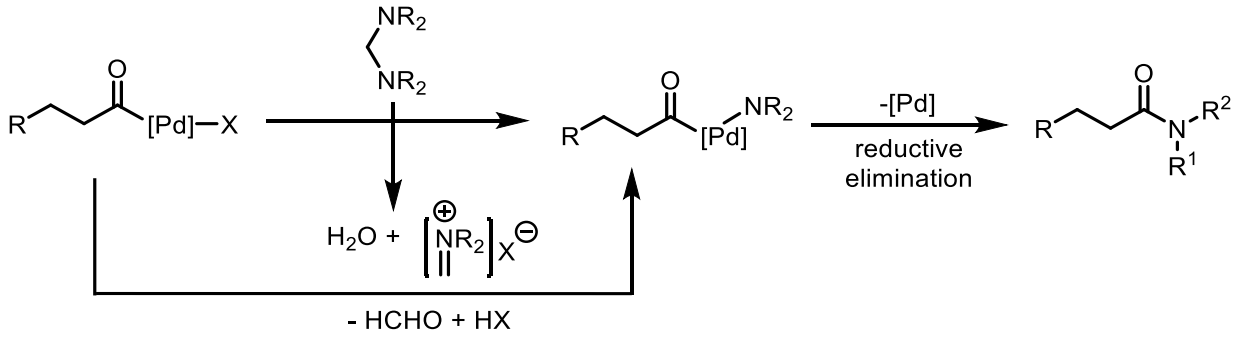
In 2013, the Beller group published an efficient synthetic route for the synthesis of linear amides through a palladium-catalysed carbonylation reaction.[102] This reaction demonstrated excellent regioselectivity and high yields over 35 different substrates, Scheme 147. Aryl nitro compounds could also be used, although these required a mixture of carbon monoxide and hydrogen gas at 60 bars of pressure.



Scheme 147: Synthesis of linear amides by palladium-catalysed carbonylation reactions.[102]

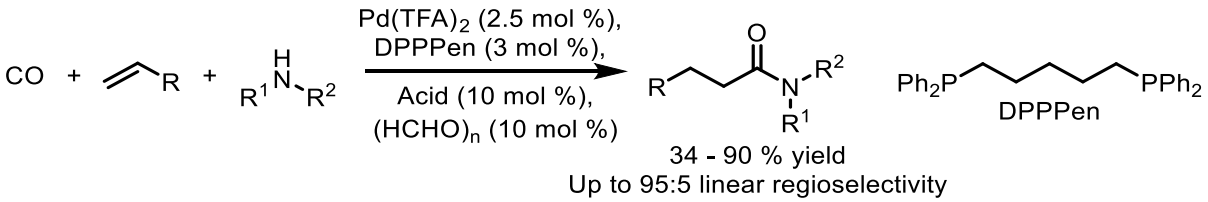
The bidentate ligand that was synthesised by the group is key to achieving the high regioselectivity: a selection of commercially available bidentate ligands showed a low selectivity for the desired product and monodentate ligands showed only trace conversion. The presence of the *para*-toluenesulfonic acid was also required for any conversion to occur and was speculated to be due to it's role in forming the catalytically active palladium hydride species. Furthermore, it was noted that no other metal precursors gave any conversion.

Beller's work was limited to aryl amines, but in 2015 Huang and co-workers found a route to working with aliphatic amines in the palladium-catalysed carbonylation by masking their basicity.[103] The authors hypothesised that the basicity of the aliphatic amine substrates prohibited the formation of the palladium hydride species that is needed for the start of the catalytic cycle, and that by masking the amines as aminals, which have a lower basicity, would allow the formation of the palladium hydride species, Scheme 148.



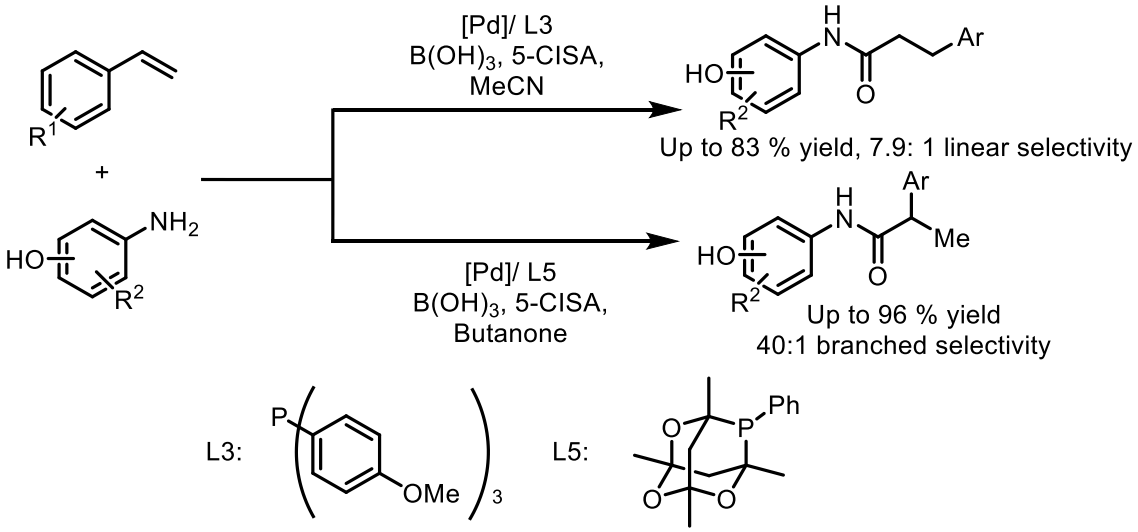
Scheme 148: Hypothesis for approach to disguising the basicity of aliphatic amines.[103]

The reaction conditions were carefully optimised, with the main problem thought to be the potential for an off-cycle reaction of formamide which would trap the nitrogen nucleophile. Fortunately, this was never observed, and the optimised conditions were established, Scheme 149.



Scheme 149: Synthesis of linear amides using aliphatic amines.[103]

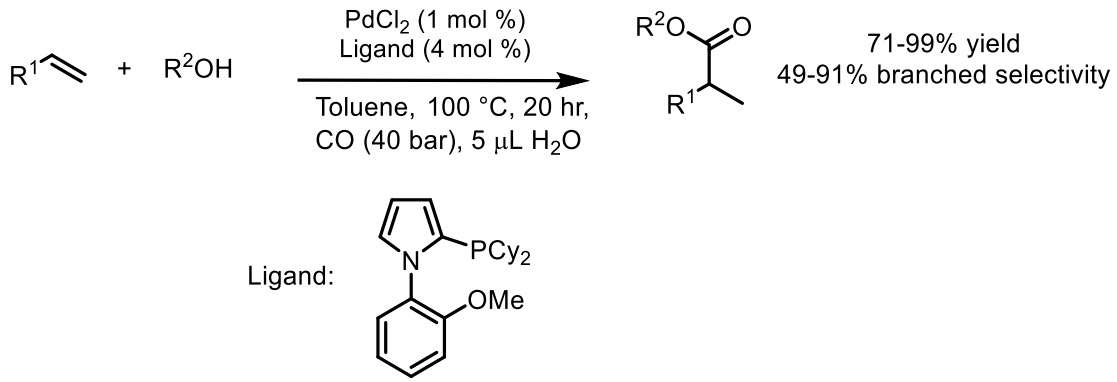
A regiodivergent catalytic system published by Alper and co-workers in 2016 used different ligands to control the selectivity over the substrate and synthesise either the linear regioisomer or the branched, Scheme 150.[104]



Scheme 150: Regiodivergent catalysis for the synthesis of aryl amides.[104]

The reaction was tolerant to a wide range of functional groups, although those with steric hindrance at the alkene, such as β-methyl styrene, produced no branched amide. Again, only aryl amines and aryl alkenes were used in this reaction. Furthermore, the presence of urea was noted which indicates a competitive off-cycle process.

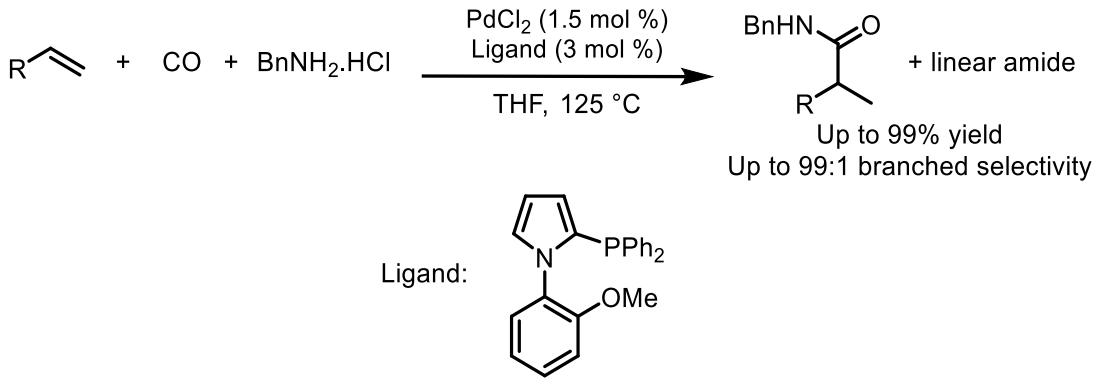
Beller and co-workers published a prominent work in 2016 with a catalytic system that consistently favoured the branched regioisomer, Scheme 151.[105] This was a break-through in affecting the regioselectivity of the alkoxycarbonylation of alkenes and required a specialised ligand that was synthesised in house. The ligand motif was based off of the bidentate ligand previously reported for high linear regioselectivity of amines.[102] Here it was found that the ligand needed to be monodentate and that the electronic effects of the methoxy group increased the preference for the branched regioisomer but in particular when in the ortho position, since this increases the steric preference for the branched isomer.



Scheme 151: First example of general conditions for achieving branched regioselectivity.[105]

Computational work was carried out to understand which step determined the regioselectivity. There were two steps in the catalytic cycle which could be key: the insertion of the palladium hydride bond into the carbon-carbon double bond or carbon monoxide coordination to the allyl complex and subsequent carbon monoxide insertion or carbonylation. For the insertion of the palladium hydride bond, it was calculated that the intermediate $[L_2Pd(isopropyl)]^+$ for the branched isomer was far more stable than the intermediate $[L_2Pd(propyl)]^+$ that related to the linear isomer, to such an extent that the expected regioselectivity would be approximately 96:4 in favour of the branched regioisomer, much higher than the experimentally observed regioselectivity of 75:25. Therefore this could not be the step that determined the regioselectivity. For the step concerning carbon monoxide coordination, the intermediate $[L_2Pd(CO)(isopropyl)]^+$ was calculated to be more stable than $[L_2Pd(CO)(propyl)]^+$ by an appropriate amount that reflects the experimentally observed regioselectivity, thus indicating that this is the step that determines the regioselectivity.

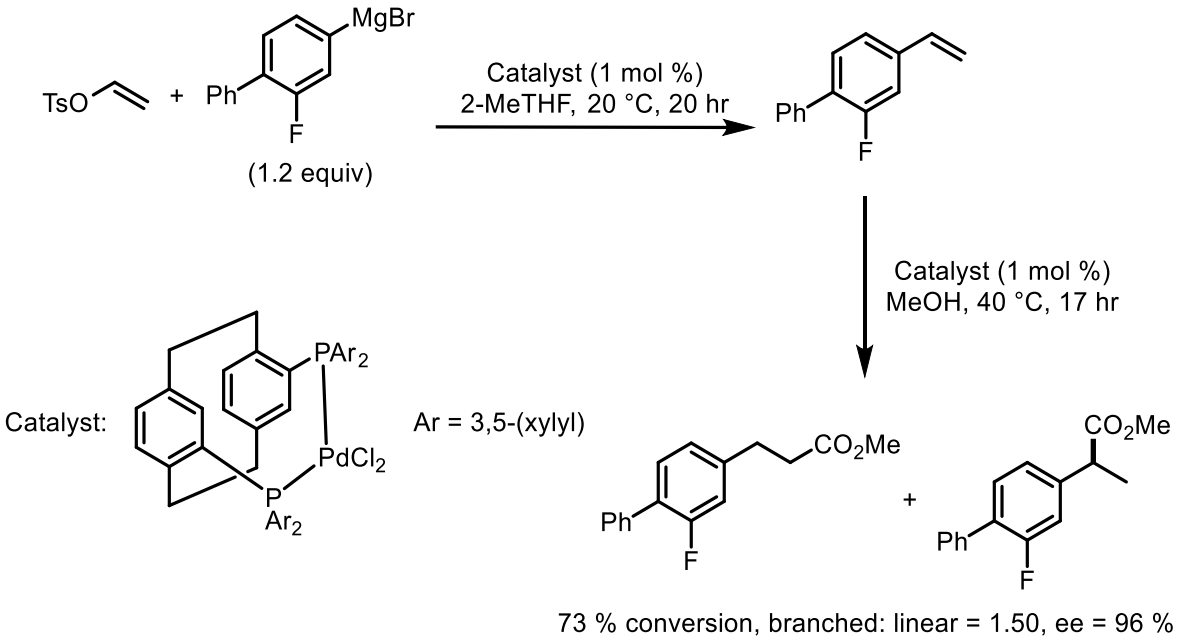
This work was followed up on by Beller and co-workers by applying a very similar catalytic system to the synthesis of amides through branched selective palladium-catalysed carbonylation reactions.[106] As mentioned previously, the use of aliphatic amines in this reaction is difficult because their increased basicity hinders the formation of the catalytically active palladium hydride complex. Rather than mask the basicity, here the authors attempted to use acid additives to form the palladium hydride complex and adjust the pH of the reaction. Unfortunately, the use of hydrochloride salts, Bronsted acids and Lewis acids gave no positive results. The solution to this problem came by adding the amine component as the hydrochloride salt itself, Scheme 152.



Scheme 152: Conditions for the reliable synthesis of branched selectivity, racemic amides.[106]

Primary, secondary and aromatic amines underwent conversion with good yields and regioselectivity, whilst a range of amino acid derivatives were also synthesised with no racemisation of the pre-existing stereocentre.

These previous papers have made excellent progress on addressing the issue of reliable branched regioselectivity, but none of these recent developments have addressed the issue of low enantioselectivity. Within the Clarke group there have been two distinct efforts at exploring ligands that will induce enantioselectivity. The first focussed on the synthesis of a drug, Flurbiprofen, through a palladium-catalysed cross coupling, followed by a palladium-catalysed carbonylation reaction, Scheme 153.[107]

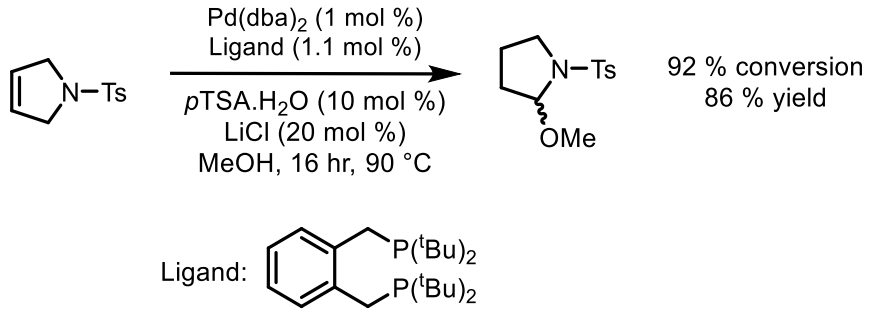


Scheme 153: Synthesis of the drug Flurbiprofen through a cross-coupling then carbonylation reaction.[107]

The bidentate phanephos ligands were the only ones to induce a reasonable amount of enantioselectivity, whilst the xylylphanephos ligand was the only one to give reasonable

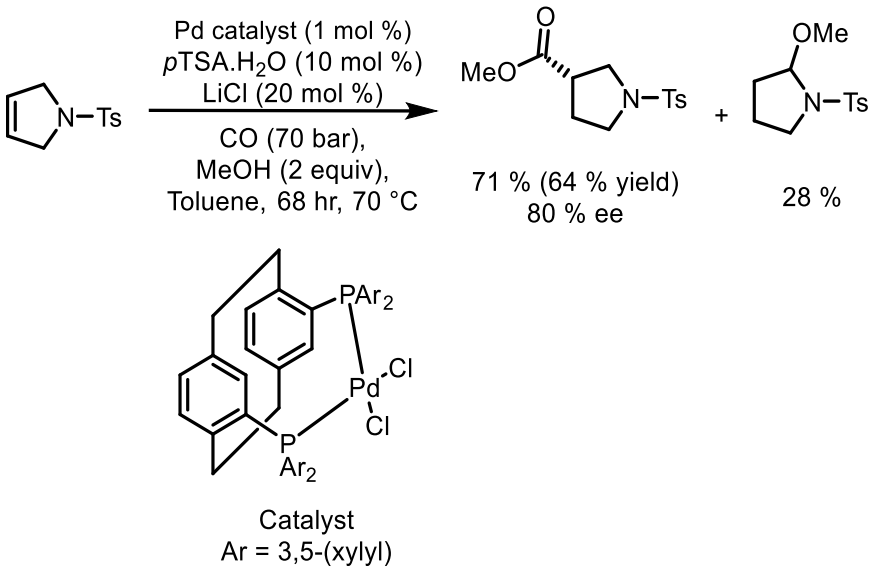
regioselectivity and enantioselectivity. For this reaction, only the (*S*)-enantiomer of the catalyst gave high ee and conversion albeit with low regioselectivity. The extra addition of ligand for the second step was required to improve the yield.

Other work from the group investigated the hydroxy-, methoxy- and amino-carbonylation of *N*-tosyl-3-pyrroline.[108] This found that there was a competing pathway between isomerisation and carbonylative pathways which needed to be controlled. Initial testing found that when subjecting the pyrroline starting material to the reaction conditions, no desired product was formed. When subjecting the starting material to the same conditions but in the absence of carbon monoxide gas, the isomerisation-addition product is formed in high yields, Scheme 154. This indicated that the isomerisation-addition pathway was the main one and was being inhibited by the carbon monoxide gas.



Scheme 154: Competing isomerisation-addition reaction under palladium-catalysed carbonylation reaction conditions.[108]

In order to synthesise the desired methoxy-carbonylated product, changes to the reaction system had to be made. These included the use of a less bulky catalyst, although these are normally held to be less reactive, higher carbon monoxide pressure and lower concentrations of methanol. Thus this allowed the desired product to be to be synthesised with high conversions and good chemo and enantioselectivity, Scheme 155. The reaction was then extended to hydroxy- and amino-carbonylations, with amino-carbonylations proving the most challenging.

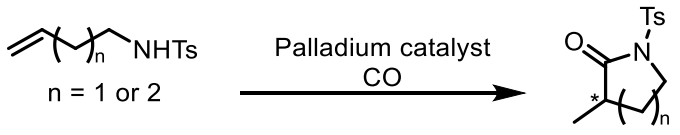


Scheme 155: Finalised conditions for the methoxy-carbonylation of N-tosyl-3-pyrroline.[108]

Building on this work, the aim of this project was to explore the use branched selective palladium-catalysed carbonylation reactions for the synthesis of enantioenriched, substituted pyrrolidinones and piperidinones.

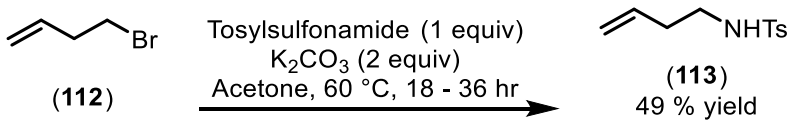
Ligand Investigation with *N*-(3-buten-1-yl)-4-methylbenzenesulfonamide:

As mentioned in the previous section, the use of palladium catalysed carbonylation reactions of alkenes has been underused in organic chemistry owing to the practical issues with the use of carbon monoxide gas and pressure vessels as well as difficulties in reliably obtaining high regioselectivity. Research investigations into this area are not extensive but are ongoing, although there are no catalysts that have been reported to be both highly enantioselective and regioselective yet. Thus, with the previous precedent in the Clarke group as mentioned, investigation of the asymmetric synthesis of 3-methylpyrrolidinone and 3-methylpiperidinone through palladium-catalysed carbonylation reactions was of interest, Scheme 156.



Scheme 156: Generic scheme for palladium carbonylation reaction

Initial investigations began by screening a range of catalysts with the previously used substrate, *N*-(3-buten-1-yl)-4-methylbenzenesulfonamide. The synthesis of this substrate, Scheme 157, was mentioned previously in chapter three on the hydroformylation-cyclisation reaction for pyrrolidines.

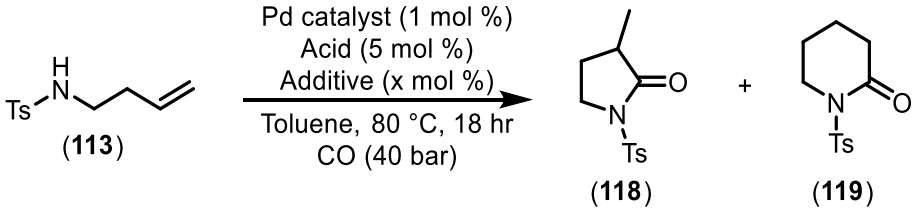


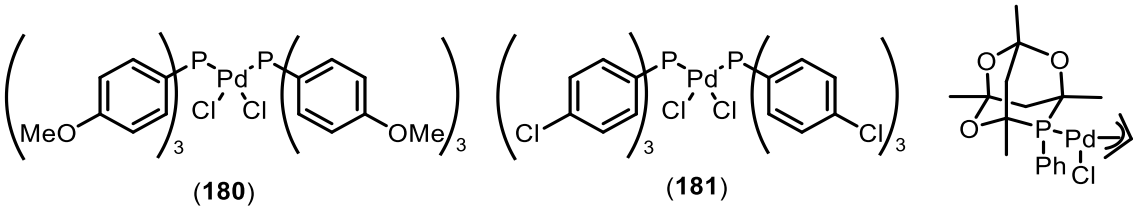
Scheme 157: Synthesis of N-(but-3-en-1-yl)-4-methylbenzenesulfonamide

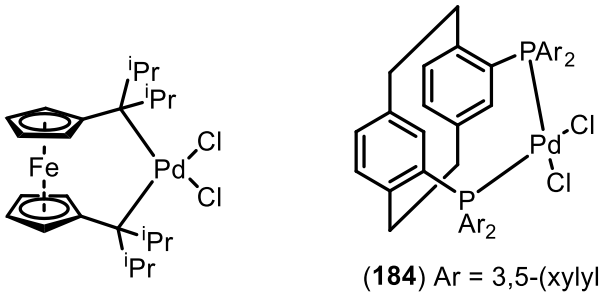
Initial testing took place with the palladium cage catalyst, (**182**), and found that approximately 20 % conversion of the alkene to 5 and 6 membered lactams was achieved after 18 hours, Table 10, entry 1. To attempt to improve this, investigations were first carried out into the acid source and found that it had a considerable effect on the conversion of the reaction. Sulfonic acids and TFA were found to give the greatest conversions whilst oxalic acid prohibited any conversion occurring. Control experiments proved that the acid is necessary for any conversion to occur.

Since no great improvements to the conversion had been observed by altering the acid source, other catalysts were investigated. On changing the catalyst, it was found that simple monodentate phosphine ligands in general gave higher conversions of alkene to the desired carbonylated products, with no chemoselectivity issues observed. In addition, the monodentate ligands also showed good regioselectivity for the branched product, 3-methylpyrrolidinone. Altering the electronic effects of the ligands was carried out by testing catalyst (**180**), Table 10, entry 7 against catalyst (**181**), Table 10, entry 8. This established that electron withdrawing groups on the aryl groups of the phosphine ligand gave a higher branched regioselectivity compared to phosphines with electron donating groups.

On moving on to bidentate ligands it was found that addition of TFA as the acid source gave no conversion. Using *p*TSA.H_2O with xylylphanephos catalysts gave conversions similar to the catalysts using simple phosphine monodentate ligands, however here the regioselectivity was now reversed to predominantly favour the linear isomer. Furthermore, using a ligand that contained electron withdrawing groups, Table 10, entry 11, was no longer found to increase the regioselectivity for the branched isomer but instead decreased it, and the catalyst showed decreased activity with approximately 86 % alkene starting material remaining after the 18 hour reaction time.







Entry	Acid	Catalyst & Additive	Branched to Linear	Conversion (%)	ee
1	*p*TsOH.H_2O	Palladium cage catalyst (**182**)	>99:1	20	Rac
2	MsOH	Palladium cage catalyst (**182**)	>99:1	14	Rac
3	TFA	Palladium cage catalyst (**182**)	>99:1	28	Rac
4	Oxalic acid	Palladium cage catalyst (**182**)	/	< 1	Rac
5	No acid	Palladium cage catalyst (**182**)	/	< 1	Rac
6	*p*TsOH.H_2O (20 mol %)	Palladium cage catalyst (**182**)	>99:1	15	Rac
7	TFA	$PdCl_2(P(p\text{-}OMePh)_3)_2$ (**180**)	66: 34	92	Rac
8	TFA	$PdCl_2(P(p\text{-}ClPh)_3)_2$ (**181**)	70: 30	92	Rac
9	TFA	Xylylphanephos (**184**)	N.D.	< 1	N.D.
10	*p*TsOH.H_2O	Xylylphanephos (**184**)	27: 73	> 99	N.D.
11	*p*TsOH.H_2O	F24-phanephos (**185**)	21: 79	14	N.D.
12	*p*TsOH.H_2O	(Dippf)$PdCl_2$ (**183**)	N.D.	< 1	Rac

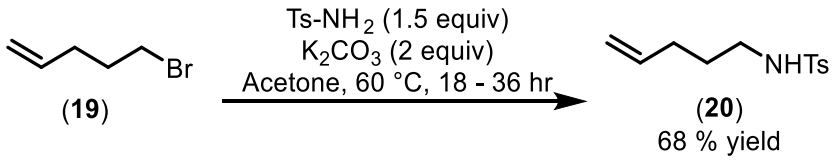
Table 10: Investigations into the synthesis of 3-methylpyrrolidinone through palladium-catalysed carbonylations

As a general trend with this substrate, simple phosphine monodentate ligands gave good conversions from the alkene to carbonylated products and showed moderate regioselectivity for the branched product, whilst bidentate ligands gave variable conversions and had higher selectivity for the linear product. Using monodentate ligands to induce enantioselectivity is particularly difficult, however bidentate ligands do not show adequate regioselectivity for the branched product in order to be able to achieve reasonable product yields of the 3-methylpyrrolidinone product. As a result of this, a change in substrate was undertaken.

Conditions Investigation with *N*-(4-penten-1-yl)-4-methylbenzenesulfonamide:

It was hypothesised that increasing the carbon chain of the starting material by one CH_2 unit would form the *N*-tosyl-3-methyl-2-piperidone product on cyclisation, and that the formation of the 7-membered heterocycle would be thermodynamically prohibited. Thus this would overcome the problem of regioselectivity when using bidentate ligands and allow for high regioselectivity for the branched product with enantioselectivity.

The substrate was synthesised as mentioned in chapter two, Scheme 158.



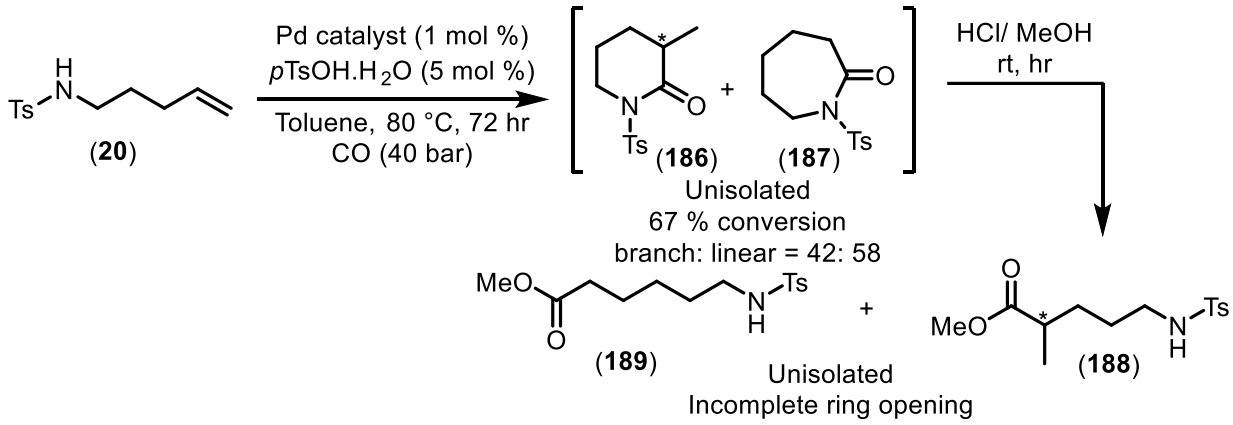
Scheme 158: Synthesis of N-(pent-4-en-1-yl)-4-methylbenzenesulfonamide

The xylylphanephos catalyst was chosen for the initial reaction and the reaction conditions identified in the previous section were used, Table 11 entry 1. Disappointingly, the conversion was much slower and after 18 hours only 23 % of the reaction mixture corresponded to 6 and 7 membered lactams as observed by NMR. Leaving the reaction for 72 hours, entry 2, gave higher levels of conversion, proving that it was slow turnover rates rather than inhibition of the catalyst that was causing the decreased activity.

The use of lithium chloride as an additive, previously shown in the literature to be of benefit to palladium carbonylation reactions, here showed no positive effect, Table 11 entry 3. Increasing the catalyst loading from 1 mol %, entry 2, to 2 mol %, entry 6, showed no difference in the regioselectivity, whilst the catalyst loading could also be dropped to 0.5 mol %, entry 5, without any effect on the on the regioselectivity or the conversion when measured over 72 hours. The measured enantiomeric excess of the *N*-tosyl-3-methylpiperidinone was only moderate, and the isolation process laborious.

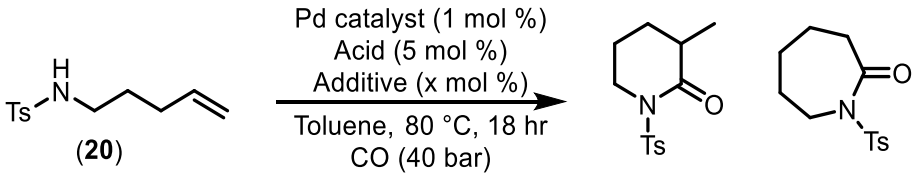
Copper acetate was considered as an additive since it might serve as a co-catalyst for the palladium, or as an activator for the nitrogen nucleophile.[109] Unfortunately, here it inhibited conversion even when the reaction time was extended to 72 hours, Table 11, entry 7.

As a different approach to isolating the products and measuring the conversion, regioselectivity and enantioselectivity, deliberately ring-opening the products after the carbon monoxide gas had been released from the autoclave was considered. This was attempted by adding hydrogen chloride and methanol, however the NMR showed incomplete conversion to the ring opened products and hence it was not optimised further or taken forward, Scheme 159.

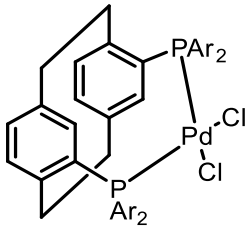


Scheme 159: Attempted ring opening of palladium carbonylation reaction products.

Taking into account the long conversion times, the unfavourable regioselectivity, moderate enantioselectivity and also the difficulties encountered in purification and analysis, this project was not pursued further.



(**184**) Ar = 3,5-(xylyl)



Entry	Acid	Additive	Branched to Linear	Conversion (%)	ee
1	*p*TsOH.H_2O	N/A	27: 73	23	/
2	*p*TsOH.H_2O	72 hr	51: 49	79	44[a]
3	*p*TsOH.H_2O	LiCl (5 mol %)	50:50	18	/
4	Methanesulfonic acid	N/A	N/D – too little presence of linear.	3	/
5	*p*TsOH.H_2O	72 hr, S enantiomer of catalyst, 0.5 mol % Pd cat	38: 62	> 99	48
6	*p*TsOH.H_2O	72 hr, 2 mol % Pd cat	27:73	> 99	/
7	*p*TsOH.H_2O	72 hr, Copper (II) Acetate (2.5 mol %)	53: 47	13	/

[a] Measured on a different sample.

Table 11: Investigations into the synthesis of 3-methylpiperidinone through palladium-catalysed carbonylation reactions

Summary:

The initial aim of this project was to form chiral pyrrolidinones and piperidinones through palladium-catalysed carbonylation reactions. The initial investigations with *N*-(but-3-en-1-yl)-4-methylbenzenesulfonamide found that simple, monodentate phosphine ligands were the most active catalysts and had excellent regioselectivity for the branched 3-methylpyrrolidine products. These were not enantioselective however, and there is minimal literature precedent for inducing enantioselectivity with monodentate ligands. The bidentate ligands tested showed overwhelming preference for the linear product, and so synthesis of the 3-methylpyrrolidine would be inefficient.

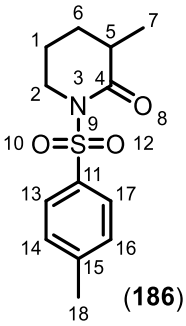
Using *N*-(pent-4-en-1-yl)-4-methylbenzenesulfonamide it was hypothesised that the 7-membered lactam would be thermodynamically unfavourable to form. Unfortunately, this was not the case and whilst the regioselectivity had a higher proportion of branched isomer than when *N*-(but-3-en-1-yl)-4-methylbenzenesulfonamide was used as the substrate, there was still a high proportion of the linear regioisomer present. This, combined with the moderate enantioselectivity present in the 3-methylpiperidinone, meant that this project was not pursued further.

Experimental:

General Procedure for Palladium Carbonylation:

To a flame dried Schlenk was added the alkene substrate (1 equiv), toluene (2 mL) and any liquid additive. To an oven dried microwave vial was added palladium catalyst (1 mol %) and any solid additive. The vial was sealed, pierced with x2 needles and placed in an autoclave. The autoclave was purged (3 x vacuum / N_2) before the addition of alkene in toluene. The autoclave was flushed with carbon monoxide (x 3), pressurised with carbon monoxide (40 bar) and heated overnight (80 °C, 18 hr). The autoclave was cooled to room temperature (water bath, 30 mins) and the pressure released. The sample diluted into ethyl acetate (5 mL) and washed with sat. $NaHCO_3$ (5 mL). The layers were separated, and the organic layer washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated in vacuo before analysis by ^1H NMR.

The procedure for the synthesis of starting materials and the corresponding data for these compounds are reported elsewhere in the experimental.



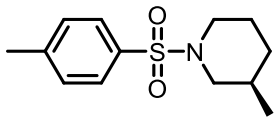
(**186**)

From a palladium-catalysed carbonylation reaction. Purified by silica column chromatography, hexane: diethyl ether: DCM (3:1:1). 10 % yield, yellow oil with trace impurities. Data matches the literature: *Org. Lett.*, 2009, 11 (15), 3458–3461.

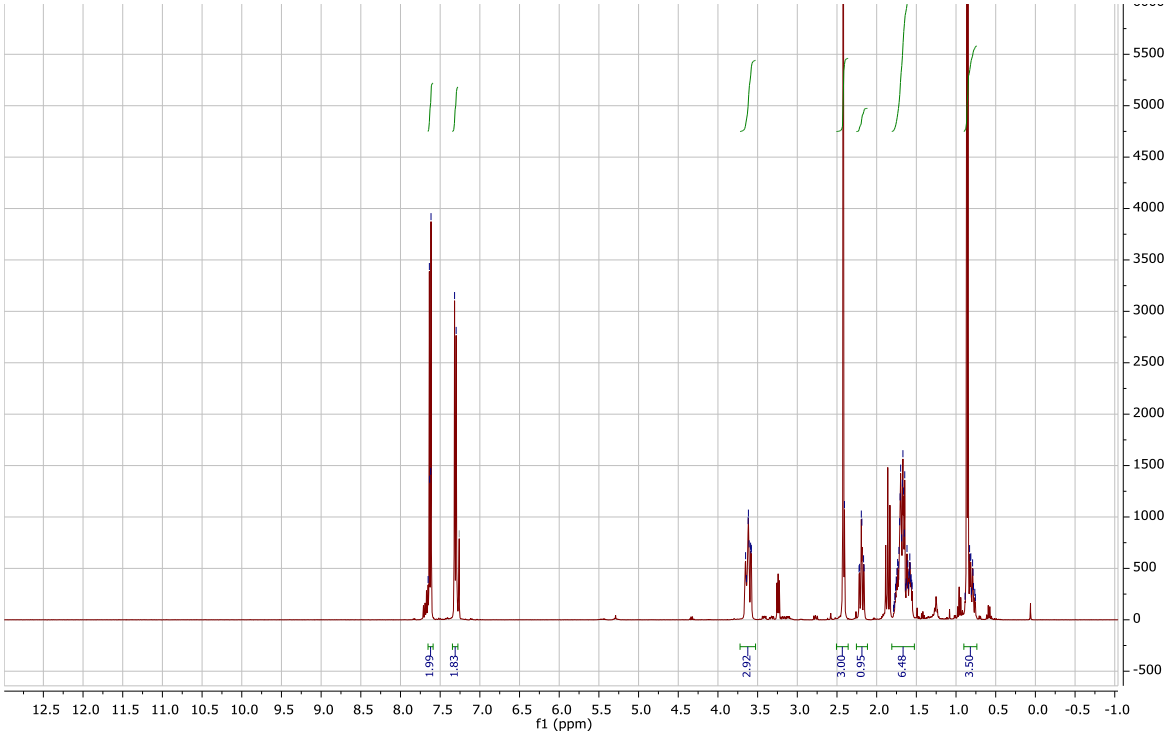
^{1}H NMR δ(500 MHz, $CDCl_3$): 7.89 (2H, d, J = 8.3, Ar, 13 + 17), 7.30 (2H, d, J = 8.3, Ar, 14 + 16), 4.01 – 3.84 (2H, m, CH_2, 2), 2.45 – 2.39 (4H, m, CH + CH_3, 5 + 18), 2.02 – 1.92 (2H, m, 2 x 1H of CH_2, 1a + 6a), 1.92 – 1.66 (1H, m, 1H of CH_2, 6b), 1.52 – 1.40 (1H, m, 1H of CH_2, 1b), 1.14 (3H, d, J = 7.0, CH_3, 7).

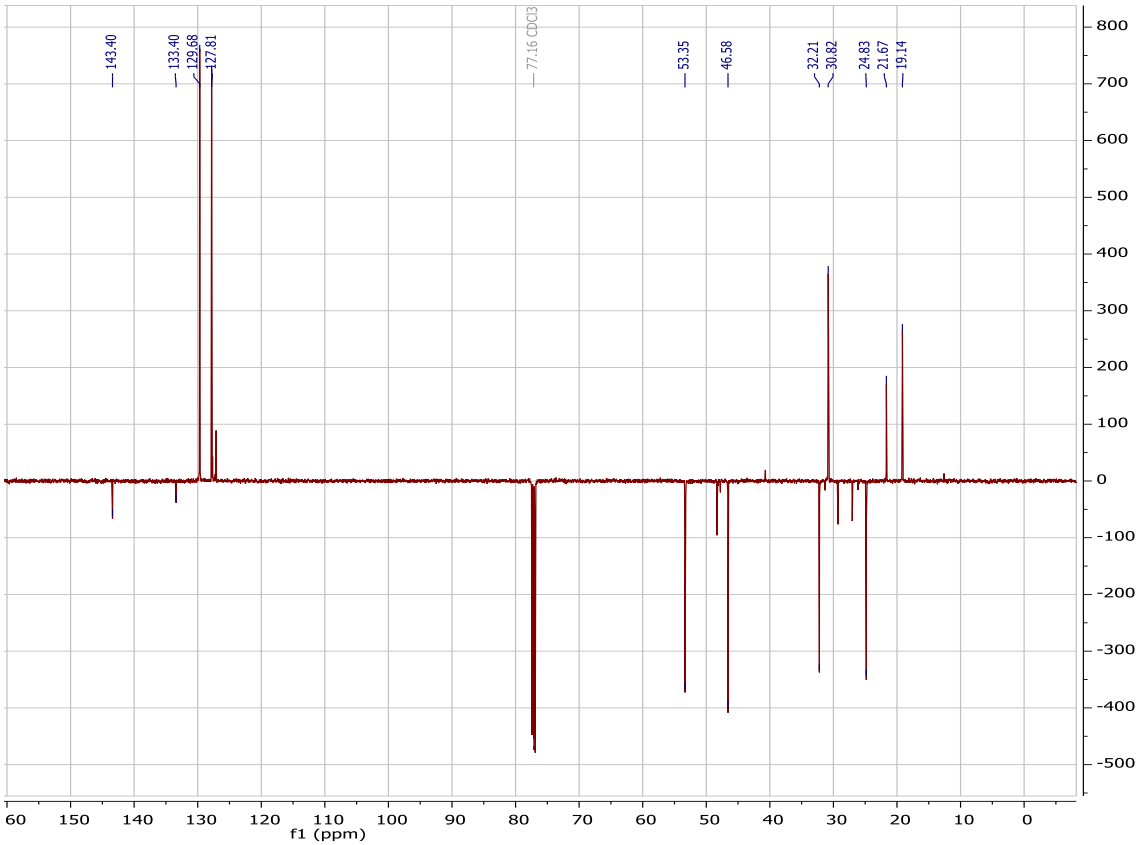
^{13}C NMR δ(126 MHz, $CDCl_3$): 173.9 (1 x C, s, 4), 144.7 (1 x C, s, 11), 136.4 (1 x C, s, 15), 129.5 (2 x CH, s, 14 + 16), 128.7 (2 x CH, s, 13 + 17), 46.9 (1 x CH_2, s, 2), 38.8 (1 x CH, s, 5), 28.6 (1 x CH_2, s, 1), 22.6 (1 x CH_2, s, 6), 21.8 (1 x CH_3, s, 18), 16.5 (1 x CH_3, s, 7).

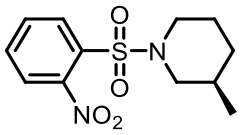
Appendix 2:



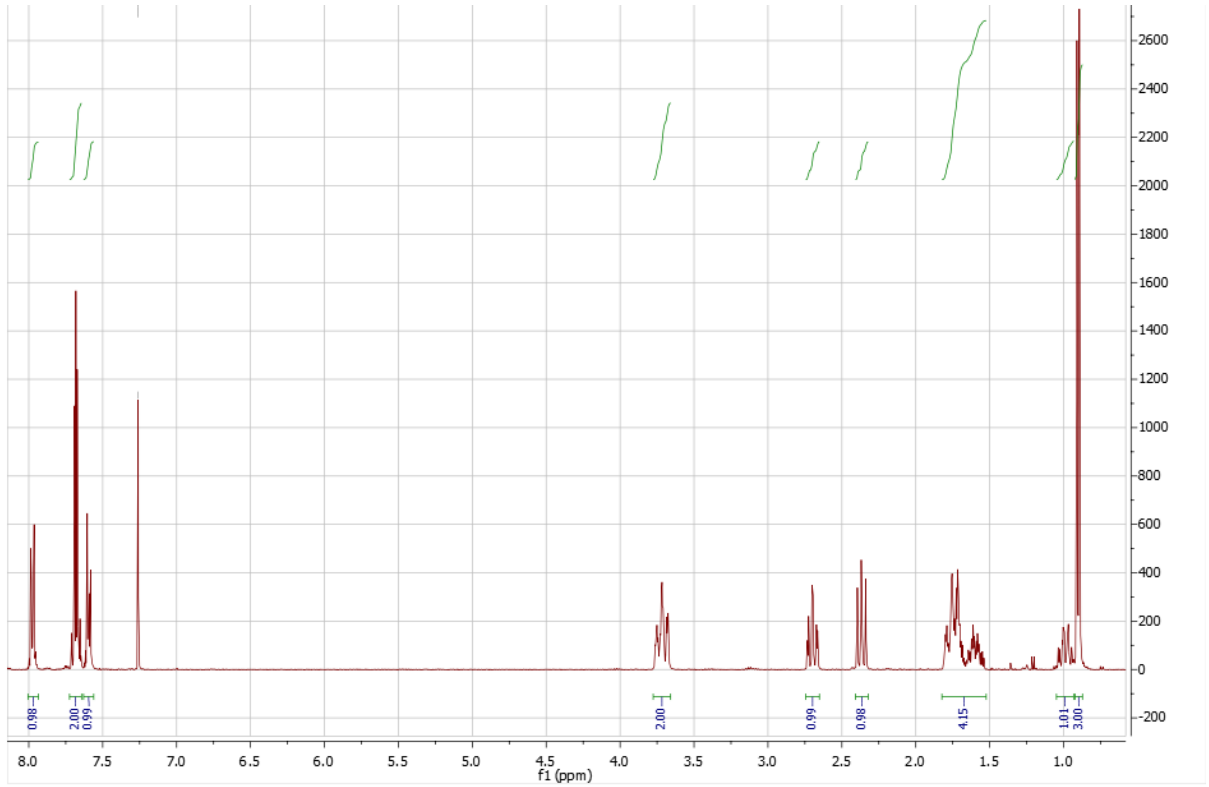
(**24**)

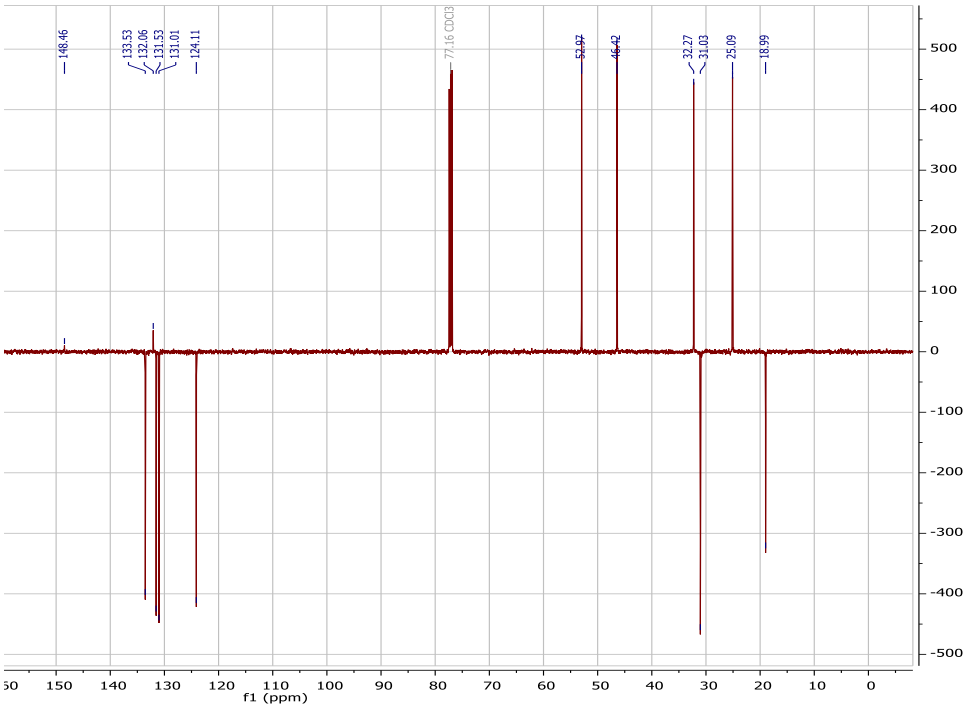


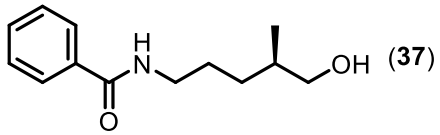



O
S
N
O
NO2

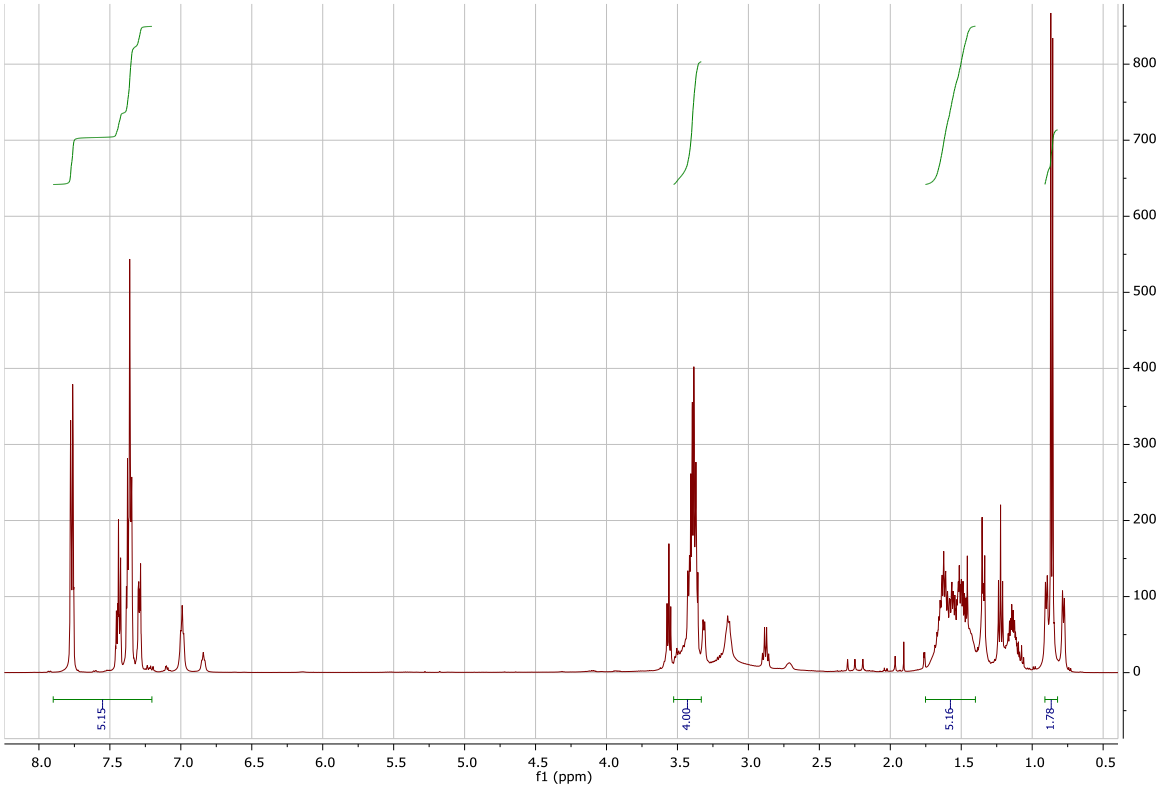
(**34**)

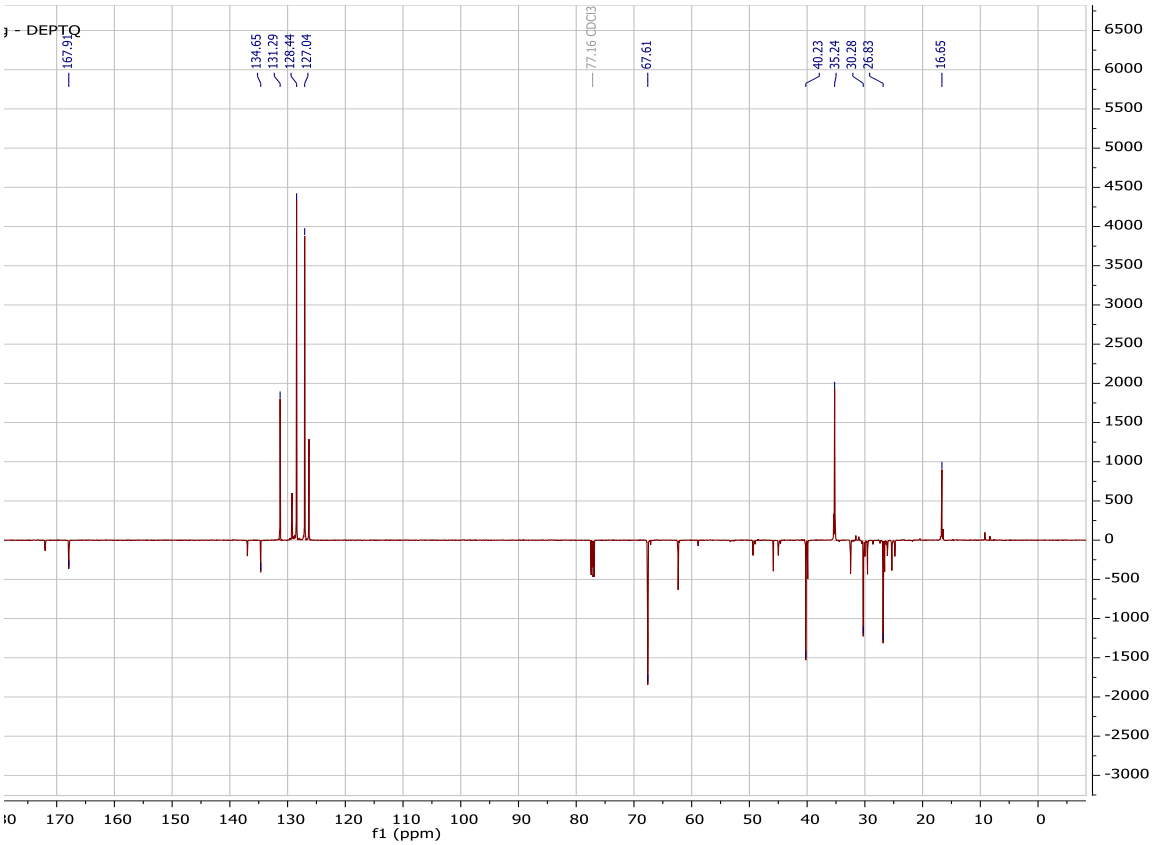

0.98
2.00
0.99
2.00
0.99
0.98
4.15
1.01
3.00
f1 (ppm)

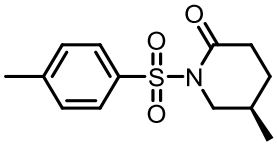

148.46
133.53
132.06
131.53
131.01
124.11
77.16 CDCl3
52.97
46.42
32.27
31.03
25.09
18.99
f1 (ppm)


H
N
O
OH

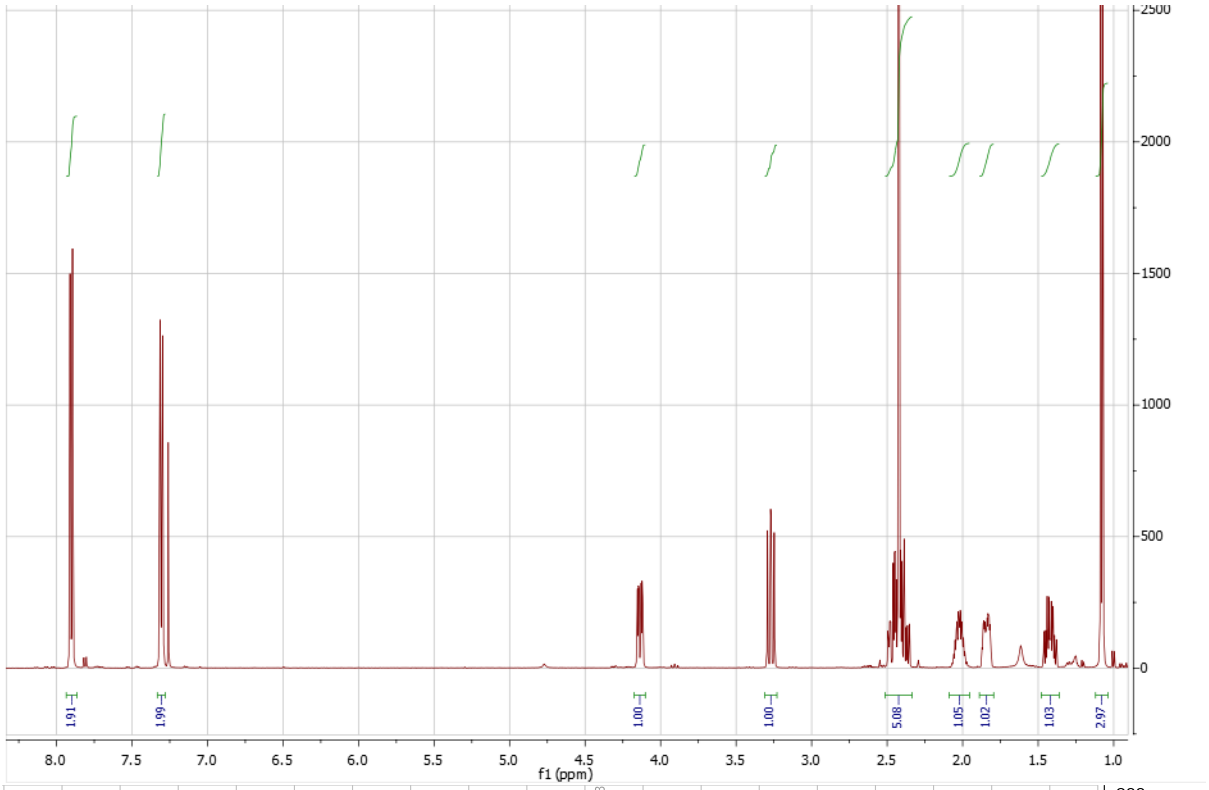
(37)

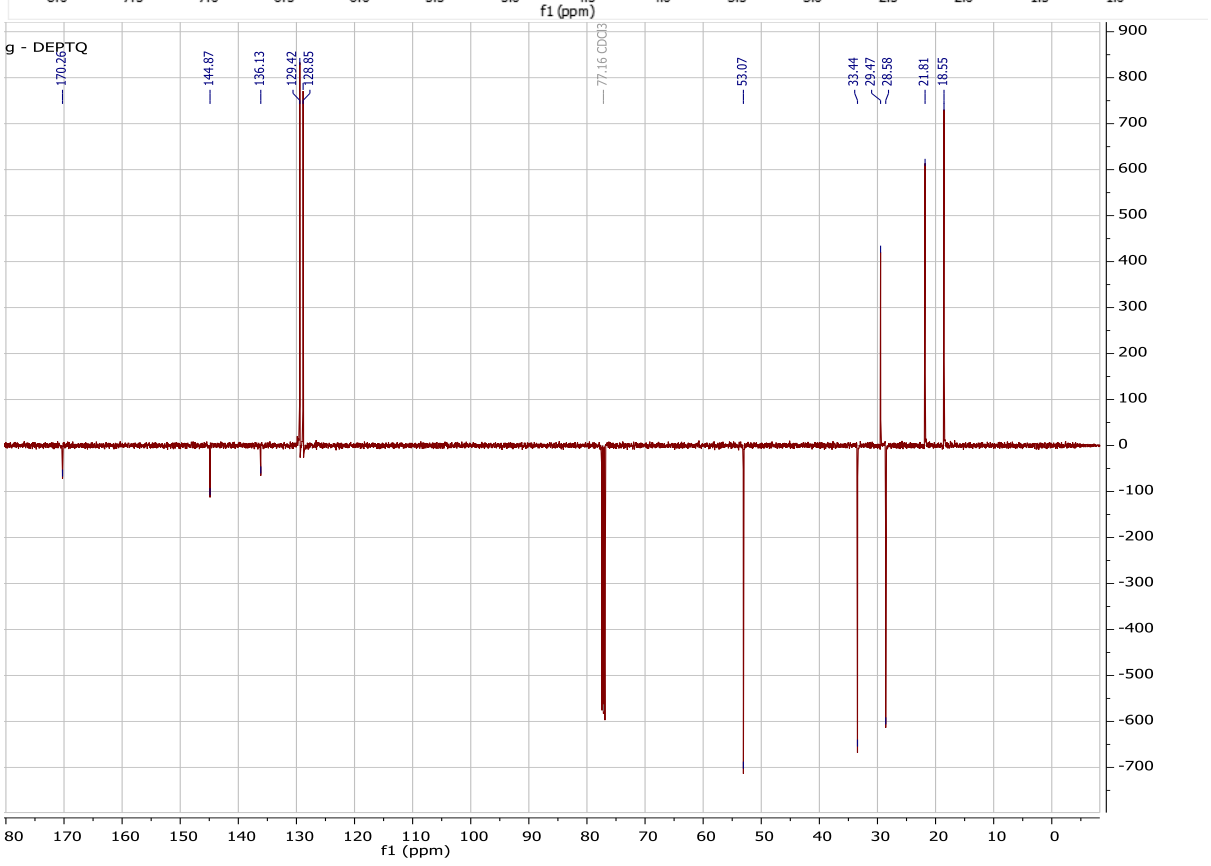

5.15
4.00
5.16
1.78
f1 (ppm)

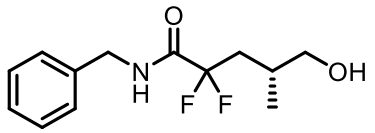

- DEPTQ
167.91
134.65
131.29
128.44
127.04
77.16 CDCl3
67.61
40.23
35.24
30.28
26.83
16.65
f1 (ppm)



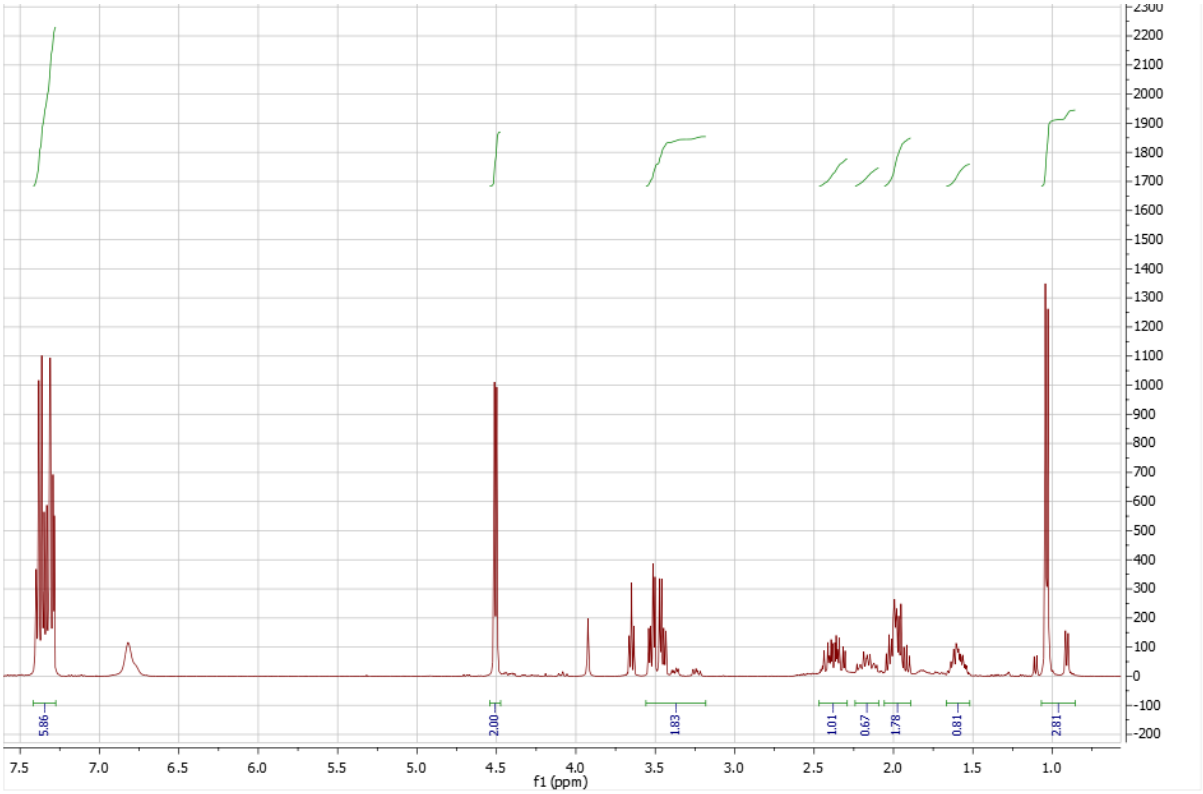
(**44**)

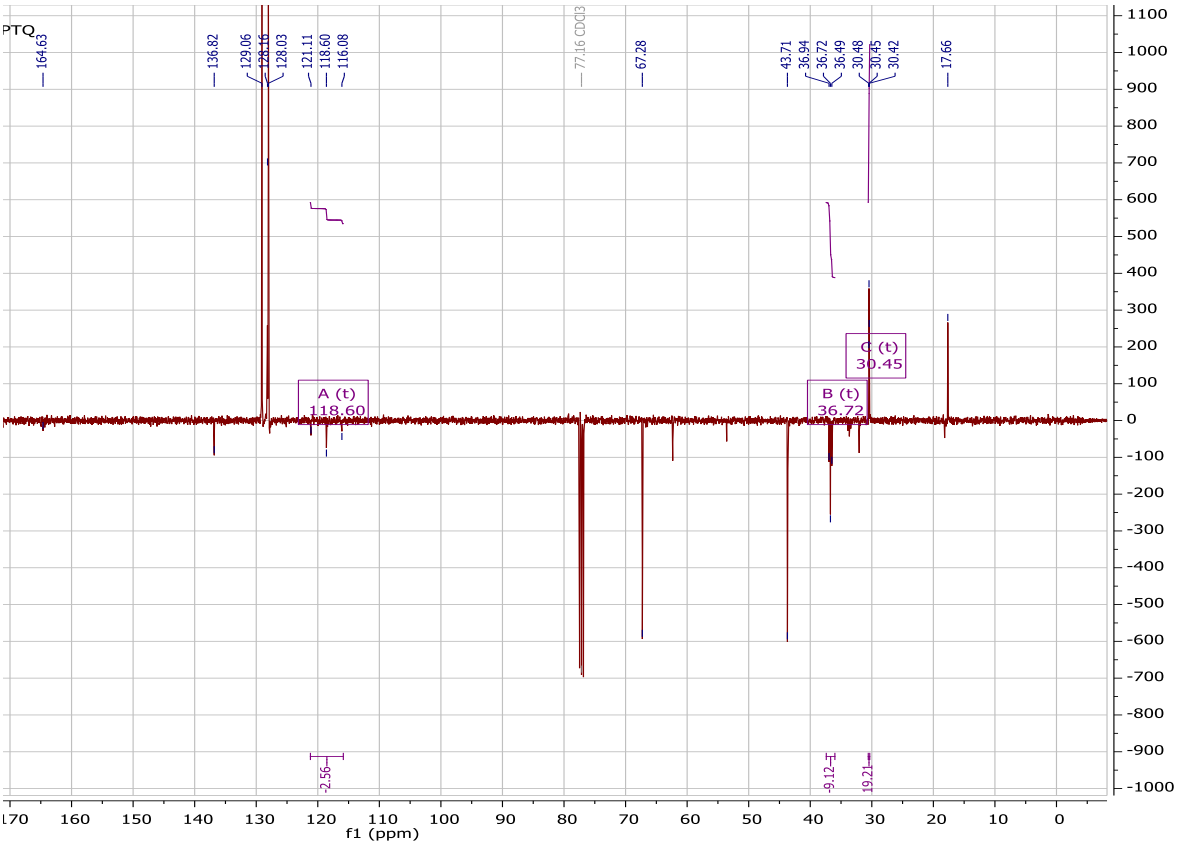

1.91
1.99
1.00
1.00
5.08
1.05
1.02
1.03
2.97
f1 (ppm)

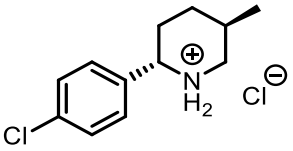

g - DEPTQ
170.26
144.87
136.13
129.42
128.85
77.16 CDCl3
53.07
33.44
29.47
28.58
21.81
18.55
f1 (ppm)


O
N
H
F
F
OH

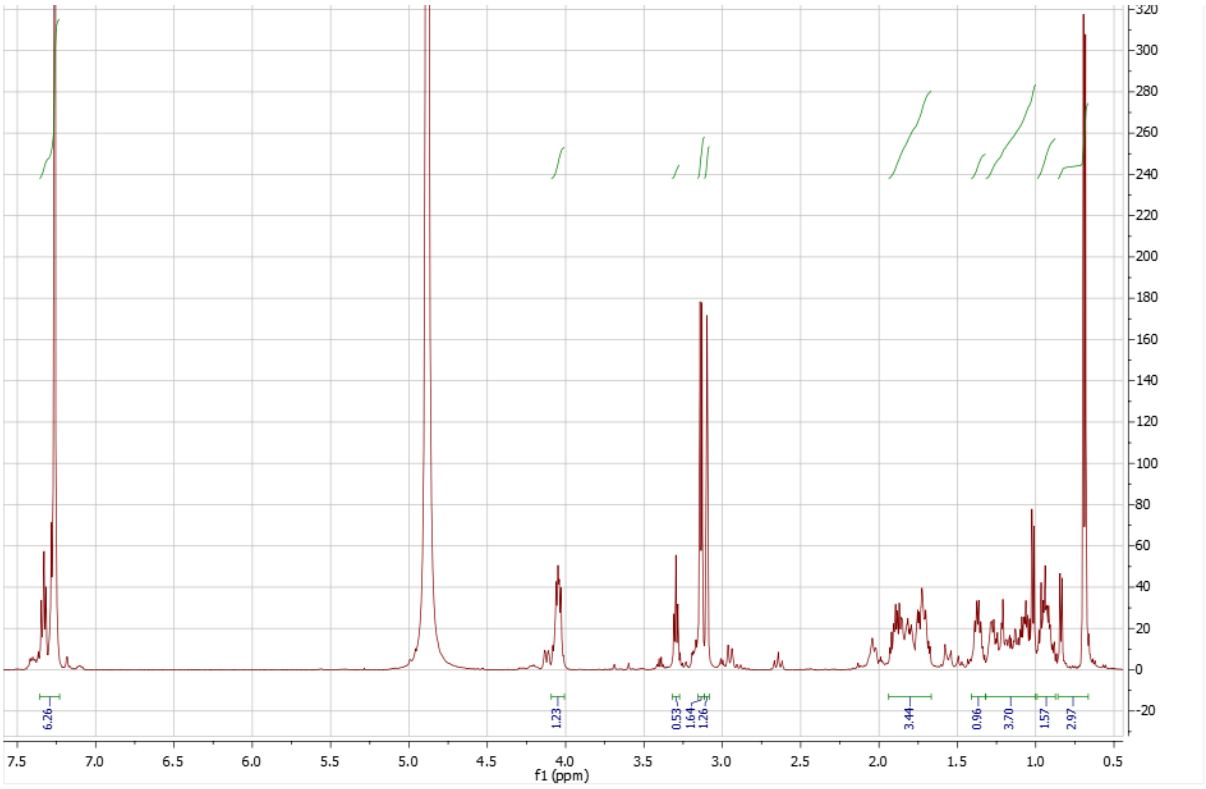
(**61**)

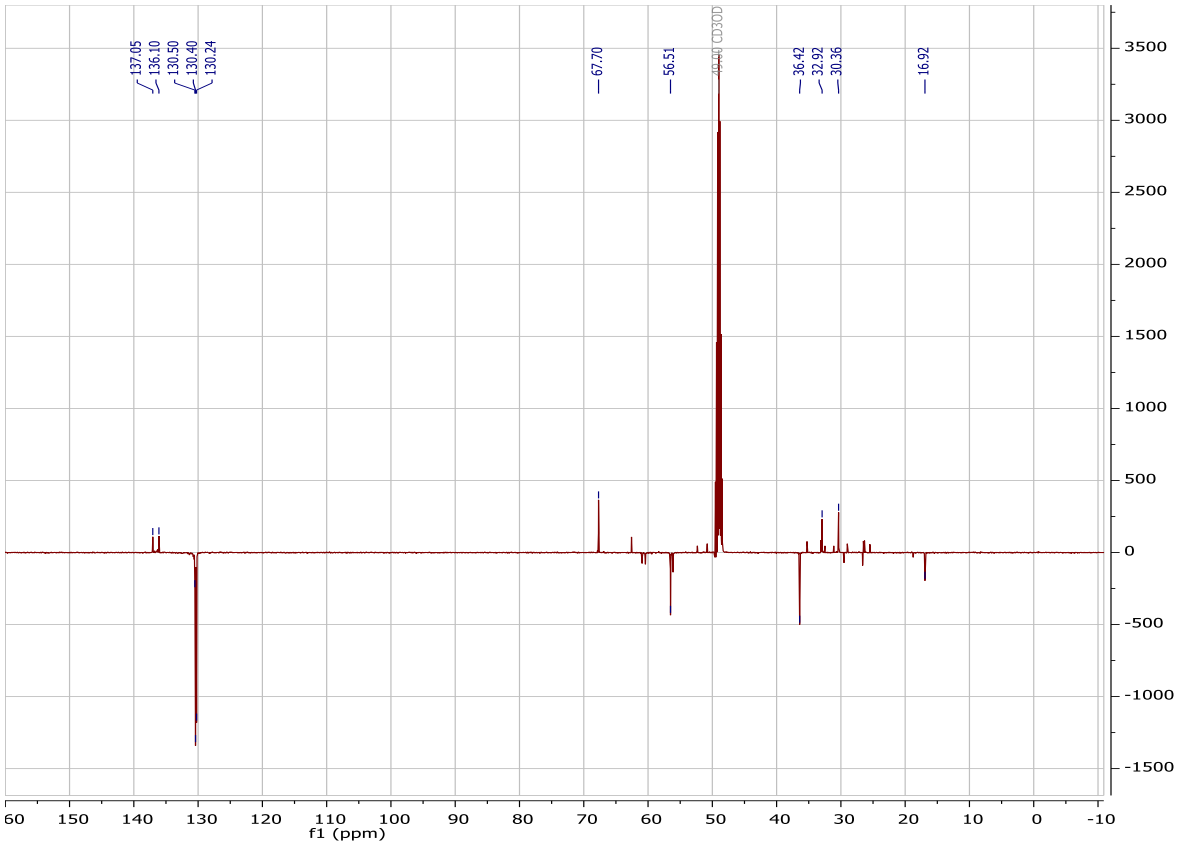

5.86
2.00
1.83
1.01
0.67
1.78
0.81
2.81
f1 (ppm)

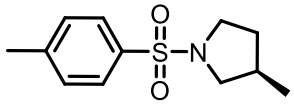

PTQ
164.63
136.82
129.06
128.16
128.03
121.11
118.60
116.08
77.16 CDCl3
67.28
43.71
36.94
36.72
36.49
30.48
30.45
30.42
17.66
A (t)
118.60
B (t)
36.72
C (t)
30.45
2.56
9.12
19.21
f1 (ppm)


Cl
N
H2
Cl

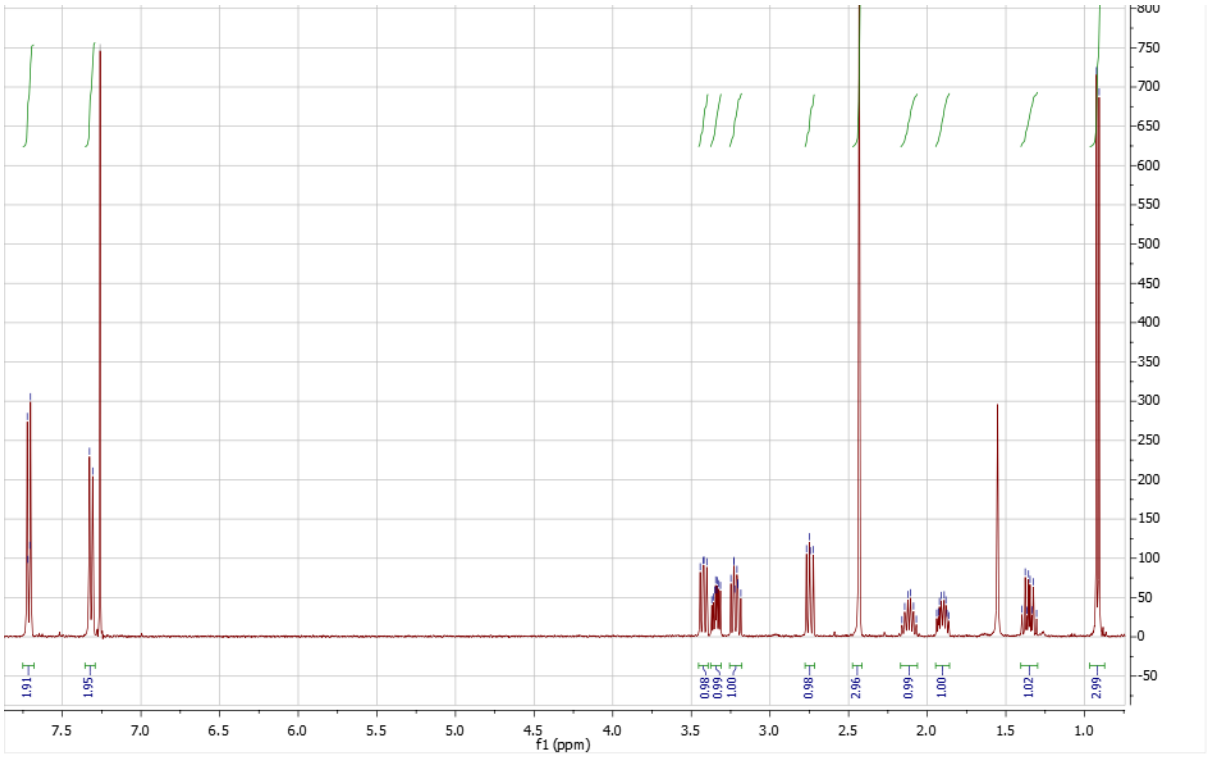
(**107**)

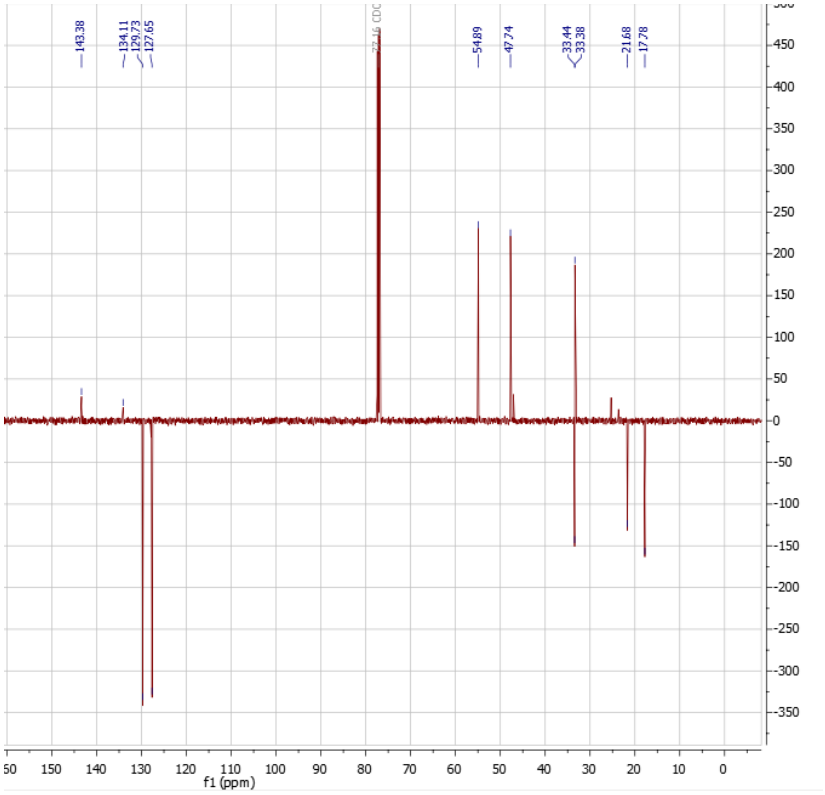

6.26
1.23
0.53
1.64
1.26
3.44
0.96
3.70
1.57
2.97
f1 (ppm)

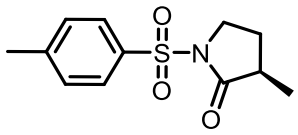

137.05
136.10
130.50
130.40
130.24
67.70
56.51
49.00 CD3OD
36.42
32.92
30.36
16.92
f1 (ppm)



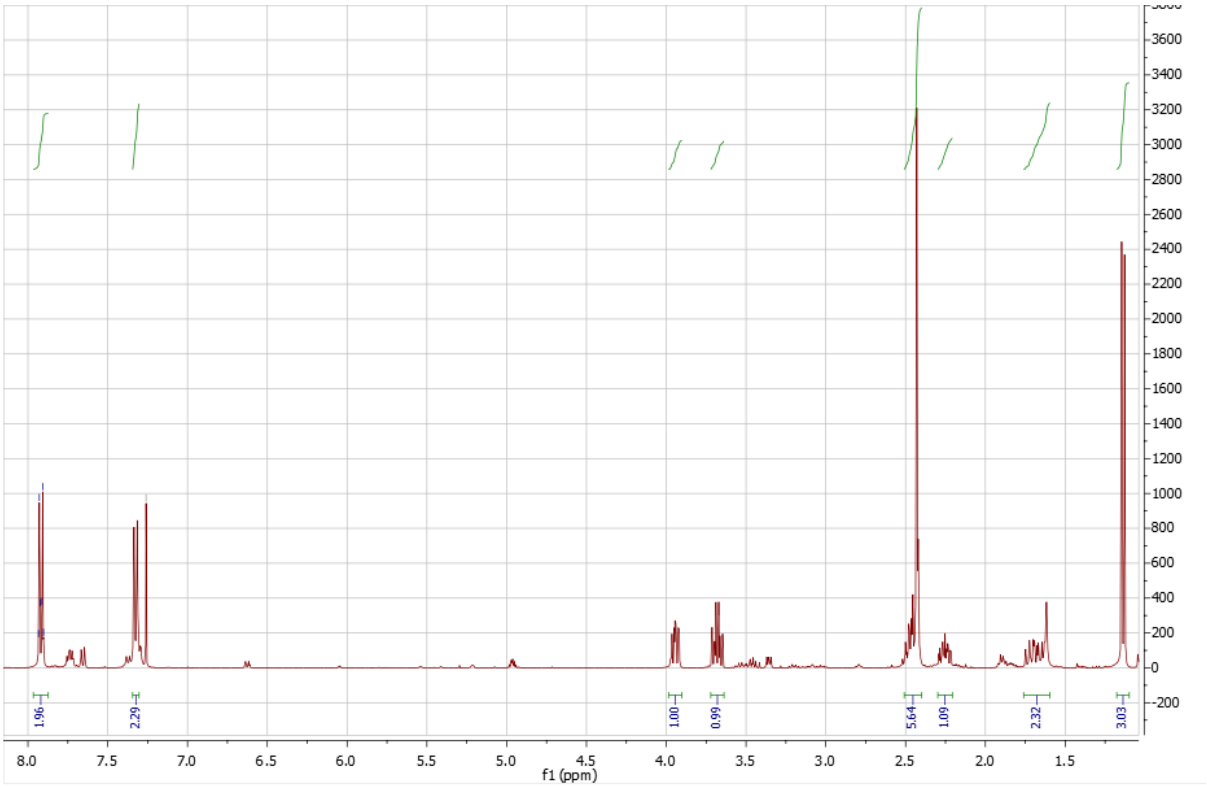
(**116**)

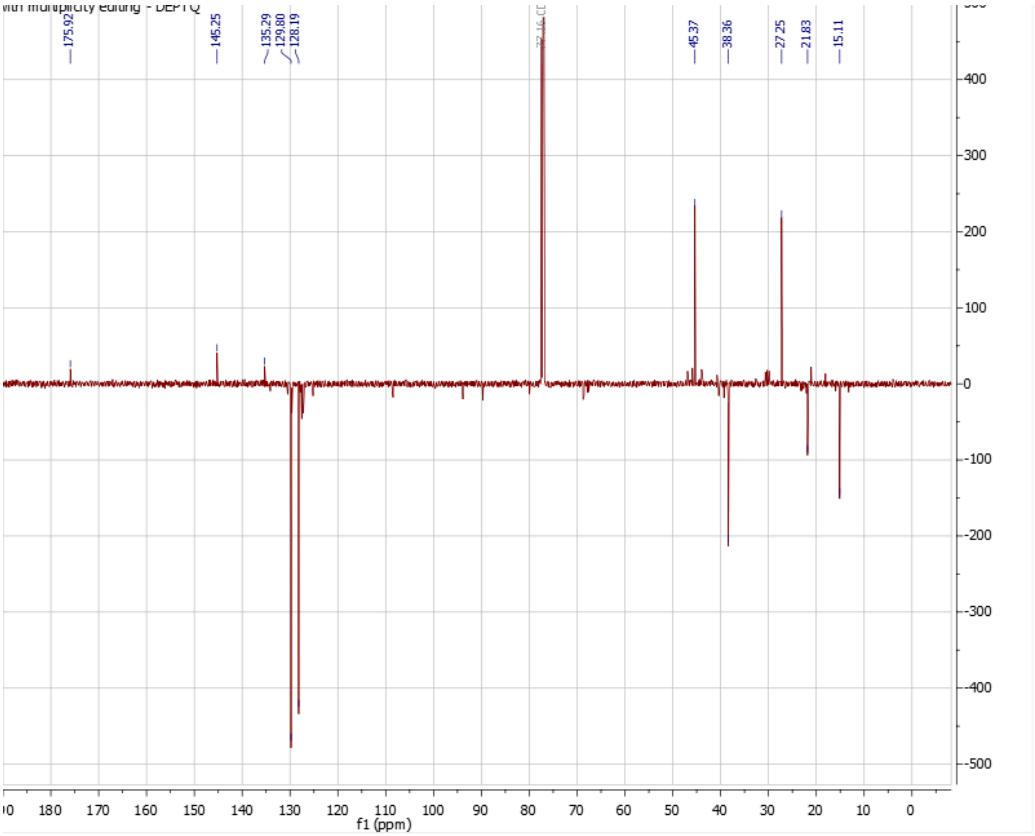

1.91
1.95
0.98
0.99
1.00
0.98
2.96
0.99
1.00
1.02
2.99
f1 (ppm)

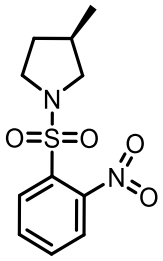

143.38
134.11
129.73
127.65
77.16 CDC
54.89
47.74
33.44
33.38
21.68
17.78
f1 (ppm)



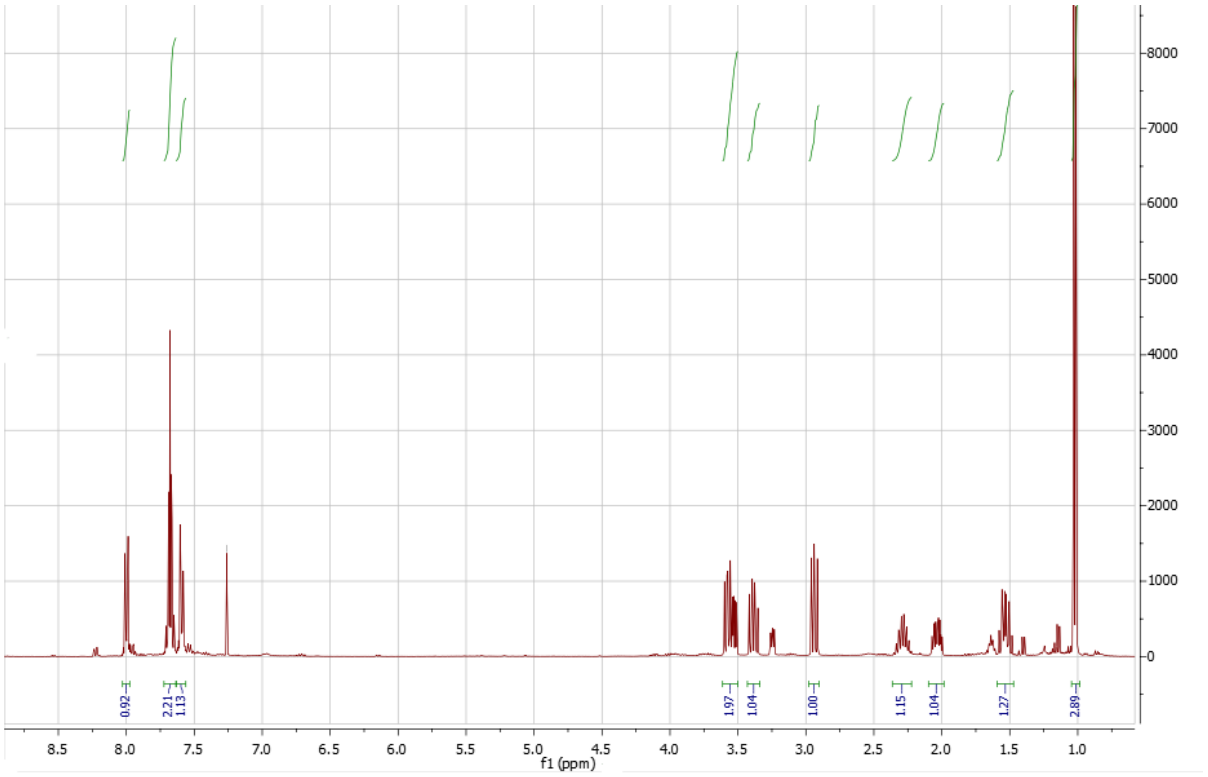
(**118**)

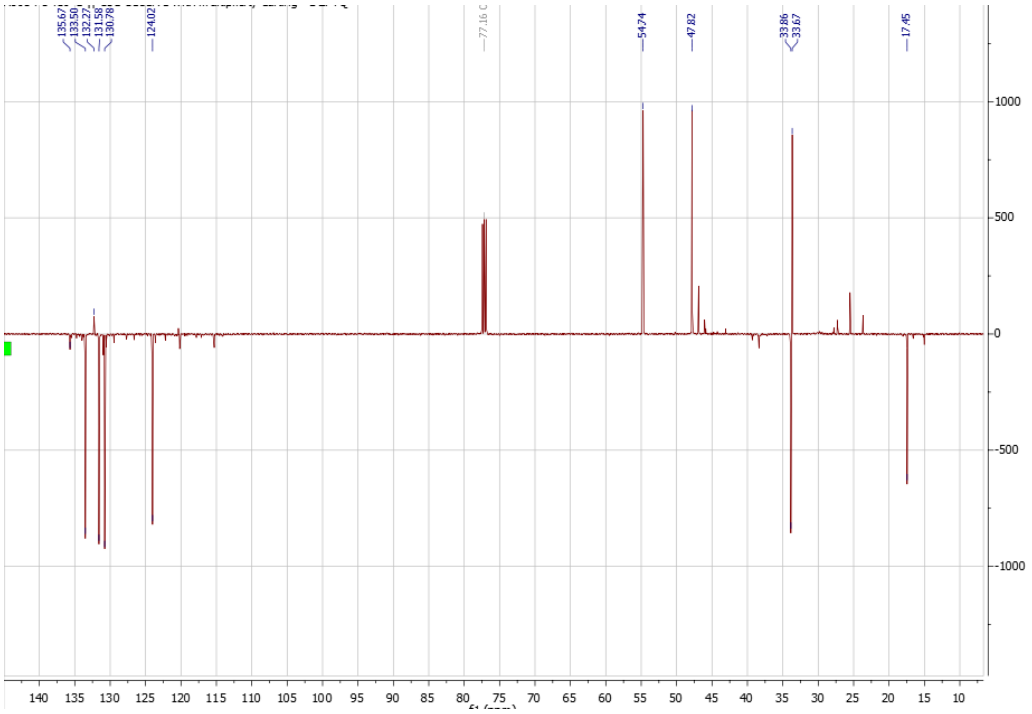

1.96
2.29
1.00
0.99
5.64
1.09
2.32
3.03
f1 (ppm)


175.92
145.25
135.29
129.80
128.19
45.37
38.36
27.25
21.83
15.11
f1 (ppm)



(**123**)


8000
7000
6000
5000
4000
3000
2000
1000
0
0.92
2.21
1.13
1.97
1.04
1.00
1.15
1.04
1.27
2.89
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)


135.67
133.50
132.27
131.58
130.78
124.02
77.16
54.74
47.82
33.86
33.67
17.45
1000
500
0
-500
-1000
140
135
130
125
120
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10

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