The Development of Nitro-Mannich/ Hydroamination Cascades for the Synthesis of Substituted *N*-Heterocycles

A thesis submitted in partial fulfilment of the requirement for the degree of Doctor of Philosophy (D.Phil.)

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To Mum, Dad, Sarah and Lauren

Table of Contents

Abstract

The Development of Nitro-Mannich/Hydroamination Cascades for the Synthesis of Substituted *N*-Heterocycles

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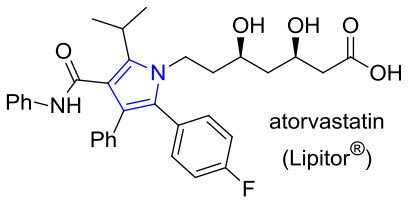
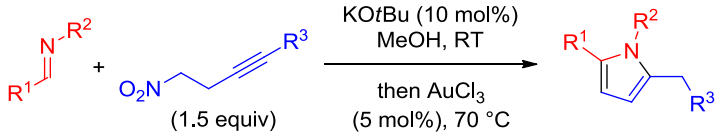
This thesis describes the development of nitro-Mannich/hydroamination cascade reactions for the synthesis of *N*-heterocycles, which are important motifs found in a variety of biologically active natural products and pharmaceuticals, such as atorvastatin (Lipitor®).

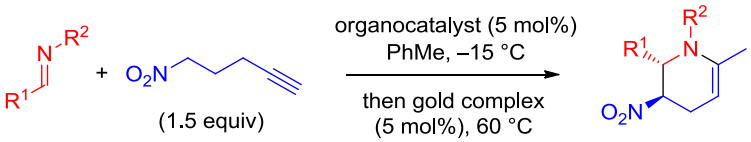


Chapter 2 outlines the development of an efficient synthesis of 2,5-disubstituted pyrroles using a nitro-Mannich/hydroamination cascade. Starting from easily prepared *N*-protected imines and nitroalkyne substrates, a compatible combination of KO*t*Bu (10 mol%) and $AuCl_3$ (5 mol%) was used to afford the desired pyrrole products, after an alkene isomerisation/HNO_2 elimination reaction sequence.

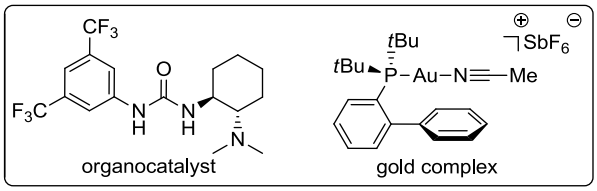


22 examples, 21-86% yield

Chapter 3 describes the extension of this methodology to the diastereo- and enantioselective synthesis of 1,2,3,4-tetrahydropyridine derivatives using a nitroalkyne substrate with an extended carbon chain. The sequential addition of a bifunctional Brønsted base/H-bond donor organocatalyst and a gold complex was found to facilitate the desired cascade reaction affording substituted 1,2,3,4-tetrahydropyridine products.

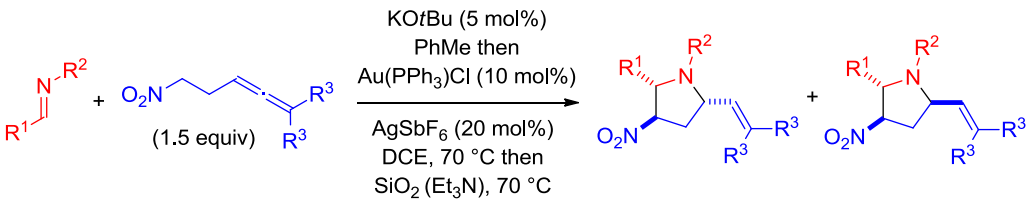


20 examples,15-72% yield
dr 85:15-97:3, 15-96% ee



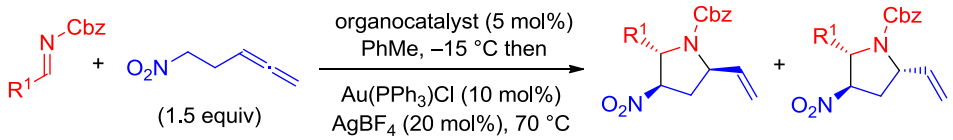
We then established that highly substituted pyrrolidine compounds could be prepared by replacing the nitroalkyne substrate with a nitroallene substrate (Chapter 4). The combination of KO*t*Bu (5 mol%) and a gold catalyst derived from $Au(PPh_3)Cl$

(10 mol%) and $AgSbF_6$ (20 mol%) was found to give an efficient diastereoselective synthesis of pyrrolidine derivatives after an additional nitro group epimerisation step.

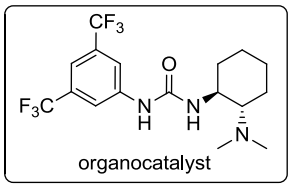


19 examples, 24-81% yield, dr 53:47-95:5

In addition, the nitro-Mannich/hydroamination cascade using nitroallene substrates was developed into an enantioselective variant using the previously employed bifunctional Brønsted base/H-bond donor organocatalyst. This afforded enantioenriched pyrrolidine derivatives.



13 examples, 36-67% yield, dr 76:24-87:13, 85-96% ee



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I declare that thesis has been written by me, that it is the record of work carried out by me and that it has not been submitted in any previous application for a higher degree at this or any other university or institute of learning. Any work done in collaboration with a research colleague has been fully acknowledged and referenced within the text.

I was admitted as a probationary research student in October 2009 and as a candidate for the degree of Doctor of Philosophy in October 2010; the higher study for which this is a record was carried out in the University of Oxford between 2009 and 2013.

David M. Barber

Date Signature of candidate

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Firstly, I would like the thank Darren for giving me the opportunity to conduct a D.Phil in his research group. Thank you for your enthusiasm, optimism and helpful comments during the last three and a half years. During my time in Oxford I have been able to work on a number of exciting projects alongside some truly outstanding chemists, for this I am especially grateful.

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Thanks to Hilary, Hannah and Matt for their friendship during my D.Phil. Exeter would not have been the same without you guys. Also, massive thanks to the 'Spanish Mafia' and everyone that I had the pleasure to play hockey with in Oxford, Hawks and Exeter.

Special thanks to the chemistry guru's that are Dr. Jakubec and Dr. Núñez. Without your knowledge, time and dedication this thesis would not have been possible. Thank you to all of your hard work in the laboratory and in the preparation of this thesis. I will never forget the phrase, "all of these are suggestions… but this is wrong".

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Abbreviations

°C	degrees Celsius
Å	Ångström
µL	microlitre
Ac	acetyl
acac	acetylacetone
AcOH	acetic acid
Ad	adamantyl
AIBN	azobisisobutyronitrile
aq.	aqueous
Ar	aromatic group, not phenyl
BEMP	2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine
BINOL	1,1´-binaphtalene-2,2´-diol
BMS	borane dimethylsulfide
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
BOX	bis(oxazoline)
br	broad
Bu	butyl
Bz	benzoyl
c	concentration
CAN	ceric ammonium nitrate
cat.	catalyst
Cbz	carboxybenzyl
cm	centimetre
cod	1,5-cyclooctadiene
coe	cyclooctene
COSY	correlation spectroscopy
Cp	cyclopentadienyl
Cy	cyclohexyl
d	doublet/deuterium
DBU	1,8-diazabicycloundec-7-ene

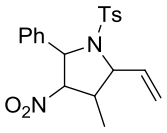
DCD	Dewar-Chatt-Duncanson model
DCE	1,2-dichloroethane
DEIPS	diethylisopropylsilyl
DEPT	distortionless enhancement by polarisation transfer
DFT	density functional theory
DIPEA	*N*,*N*-diisopropylethylamine
DMA	dimethylacetamide
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DPP	diphenylphosphate
dr	diastereomeric ratio
E	electrophile
ee	enantiomeric excess
equiv	equivalents
ESI	electrospray ionisation
Et	ethyl
EtOAc	ethyl acetate
FI	field ionisation
Fmoc	9-fluorenylmethyloxycarbonyl
g	gram
h	hour(s)
HBMC	heteronuclear multiple-bond correlation experiment
Hept	heptyl
Hex	hexyl
HMPT	tris(dimethylamino) phosphine
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
HRMS	high-resolution mass spectrometry
HSQC	heteronuclear single-quantum coherence experiment
Hz	hertz
i	*iso*
IR	infrared
K	degrees Kelvin
Kcal	kilocalorie

LUMO	lowest unoccupied molecular orbital
[M]	metal complex
M	molar
m	multiplet
m	*meta*
mM	millimolar
m/z	mass-to-charge ratio
max	maximum
Me	methyl
MeOH	methanol
Mes	mesityl
mg	milligram
MHz	megahertz
min	minute(s)
mL	millilitre
mmol	millimole
mol	mole
MOM	methoxymethyl
MS	low-resolution mass spectrometry
Ms	methanesulfonyl
N	nitrogen
n	straight chain
nm	nanometre
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
NOE(SY)	nuclear Overhauser effect
Ns	*para*-nitrobenzenesulfonyl
Nu	nucleophile
o	*ortho*
Oct	octyl
p	*para*
PE	petroleum ether
Pent	pentyl
PG	protecting group

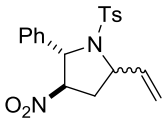
Ph	phenyl
PMB	*para*-methoxybenzyl
PMP	*para*-methoxyphenyl
ppm	parts per million
Pr	propyl
PS	polymer supported
q	quartet
qu	quintet
R	generic substituent
rac	racemic
R_f	retardation factor
RT	room temperature
s	singlet
s	*sec*
t	triplet
t/*tert*	tertiary
TBAF	tetra-*n*-butylammonium fluoride
TBS	*tert*-butyldimethylsilyl
Temp	temperature
Tf	triflate
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography
TMG	1,1,3,3-tetramethylguanidine
TMS	trimethylsilyl
t_R	retention time (HPLC)
Troc	2,2,2-trichlorethoxycarbonyl
Ts	*para*-toluenesulfonyl
UV	ultraviolet
W	watt
VT	variable temperature

Stereochemistry

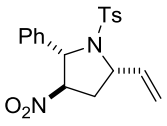
Stereochemistry is drawn in accordance with the conventions proposed by Maehr.[*] Normal bond thickness is to indicate racemic compounds, enantioenriched compounds or a mixture of compounds where the relative or absolute configuration is unknown (**a**). A wavey bond is used to indicate a mixture of diastereomers or enantiomers with known relative or absolute configurations (**b**). Solid and hashed lines are used to indicate the relative configuration of diastereopure or diastereoenriched racemic compounds (**c**). Solid and hashed wedges are used to indicate the absolute configuration of enantiopure or enantioenriched compounds (**d**).



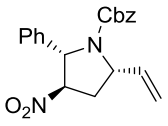
a
racemic, enantioenriched
or mixture of compounds
with unknown configurations



b
a wavey bond represents
a mixture of diastereomers
with known configurations



c
racemic diastereopure or
diastereoenriched compound with
known relative configuration



d
enantiopure or enantioenriched
compound with known
absolute configuration

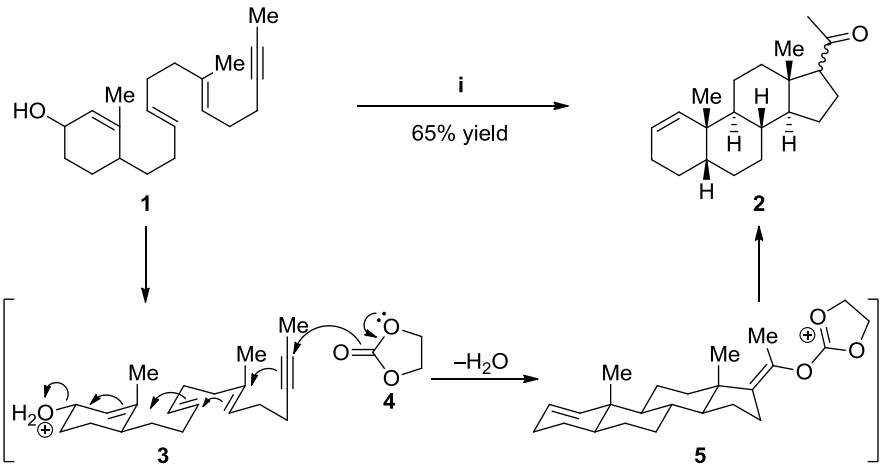
[*] H. Maehr, *J. Chem. Educ*. **1985**, *62*, 114.

Chapter 1: Introduction

1.1 Cascade Reactions

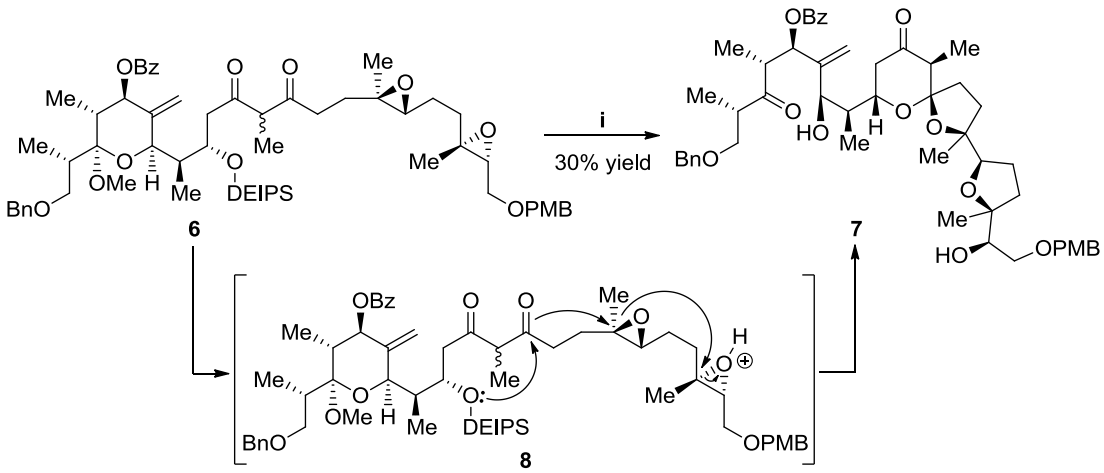
During the last century, huge advancements in the field of synthetic organic chemistry have been made, with molecules of ever increasing complexity being synthesised in laboratories all over the world.[1] Although chemists can now prepare almost any molecule they choose, the impact that organic chemistry has on the environment needs to be considered as the conservation of resources becomes of paramount importance.[2] One method of increasing resource efficiency that has attracted significant attention from the synthetic community in the last few decades is that of cascade reactions.[3] These multi-step and often multi-component reaction sequences provide a powerful method to increase the level of molecular complexity, whilst also significantly improving the efficiency of the process when compared to their step-wise counterparts. By avoiding the isolation of intermediate compounds, cascade reactions also reduce the time and labour required for a specific process.

One classic example of a cascade reaction is the polyene cyclisation cascade reported by Johnson and co-workers in 1973 (Scheme 1).[4] TFA and ethylene carbonate (**4**) initiate a four bond forming cascade reaction of polyene **1**, proceeding via intermediates **3** and **5**, resulting in the formation of complex polycycle **2** in 65% yield. This process is very selective, with only one out of a possible 64 diastereomers being formed. Another example of a complex cascade reaction is the polyether cyclisation cascade. In this cascade reaction, a nucleophilic addition to an epoxide initiates a series of epoxide opening reactions that results in the formation of several 5-, 6- or 7-membered oxygen containing heterocycles.



Scheme 1. Johnson's polyene cyclisation cascade reaction. Reagents and conditions: i) TFA, CH_3CHF_2, –30 °C.

In the example reported by Paterson and co-workers (Scheme 2),[5] both tetrahydropyran and tetrahydrofuran motifs are created in an acid catalysed polyether cyclisation cascade. The configuration of the epoxides in compound **6** governs the configuration of the cyclised product **7**, allowing access to different configurations of **7** depending on the precise structure of the starting material employed.



Scheme 2. Paterson's polyether cyclisation cascade reaction. Reagents and conditions: i) 0.5 M HCl, THF, 25 °C, 2.5 h.

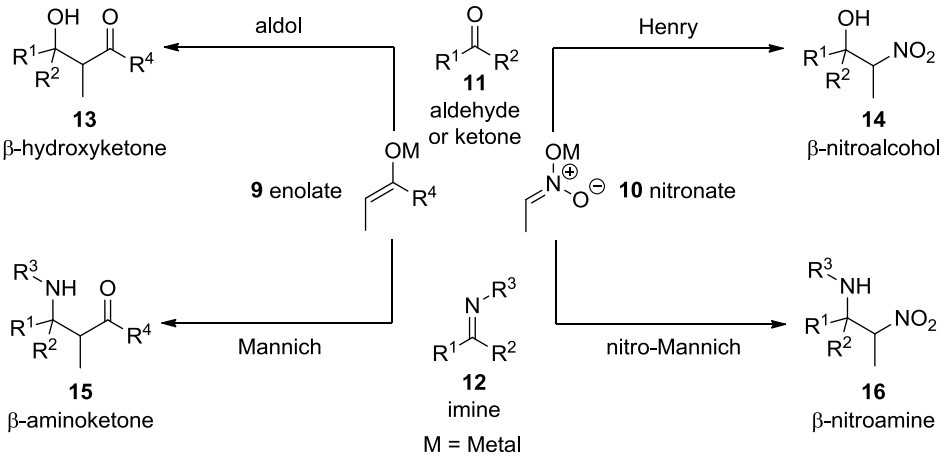
Due to the structural complexity that can be rapidly introduced into a molecular structure using cascade reactions, we envisaged that we could develop a series of general and resourceful cascade reactions by combining the highly selective and

atom efficient nitro-Mannich and hydroamination reactions. Previous reports from several groups, have highlighted the nitro-Mannich reaction as a powerful method for carbon-carbon bond formation, allowing the preparation of important intermediate compounds and target molecules using a wide range of metal catalysts and organocatalysts. It has also been shown to be compatible in a variety of cascade reaction methodologies, with the Dixon group making a significant contribution to this field.[6,7] In recent years, hydroamination has become a valuable method for the synthesis of important carbon-nitrogen bonds from readily available starting materials. Hydroamination reactions are completely atom efficient and there are a large number of metal complexes that can catalyse these reactions. With the Dixon group also reporting cascade reactions incorporating hydroamination reactions,[8] we envisaged that an appropriate catalyst combination will enable us to combine the benefits of these two reactions, creating a new class of simple and practical cascade reactions.

1.2 The Nitro-Mannich Reaction

1.2.1 Importance of the Nitro-Mannich Reaction

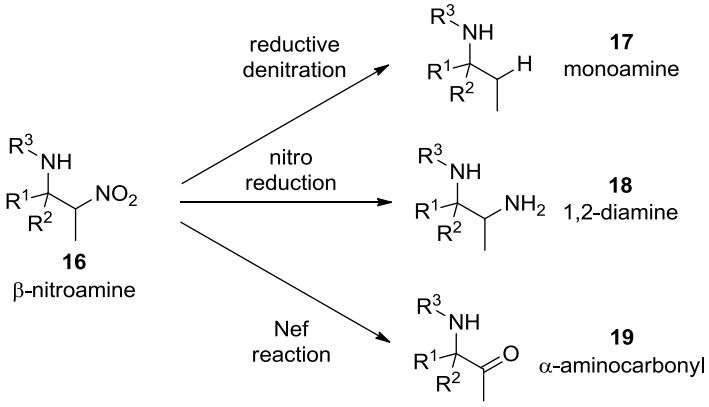
The nitro-Mannich (or aza-Henry) reaction is the nucleophilic addition of a nitroalkane (or the corresponding nitronate anion **10**) to an imine **12**, resulting in the formation of a β-nitroamine **16** (Scheme 3).[9] With the reaction involving the addition of an acidic carbon nucleophile to a carbon-heteroatom double bond, the nitro-Mannich reaction is related to some of the most fundamental carbon-carbon bond forming reactions in organic chemistry, including the aldol,[10] Henry (nitro-aldol)[11] and Mannich[12] reactions (Scheme 3).



Scheme 3. Summary of enolate and nitronate nucleophilic additions to imines and aldehydes/ketones.[9]

Although extensive research has been conducted into the aforementioned reactions, the nitro-Mannich reaction has been studied to a far lesser extent even though it has been known for well over 100 years.[13] Significant attention only started to develop after the report of Anderson and co-workers[14] at the turn of the century, and has since resulted in a wide range of novel methodologies. The interest into the nitro-Mannich reaction stems from the synthetic utility of the β-nitroamine products (Scheme 4). They can be further manipulated by various methods, including reductive removal of the nitro group allowing access to monoamines **17**, reduction of the nitro group

affords 1,2-diamines **18** and conversion of the nitro group into a carbonyl functionality furnishes α-aminocarbonyl compounds **19**.



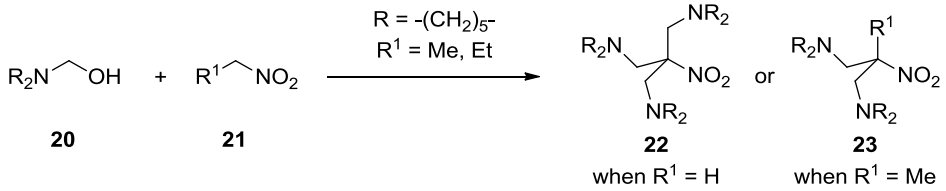
Scheme 4. Selected examples of the synthetic utility of β-nitroamines synthesised via nitro-Mannich reactions.

With such synthetic potential possessed by the products, it was only a matter of time before synthetic chemists developed the initial non-stereoselective and uncatalysed examples into highly stereoselective variants. With these advancements, the nitro-Mannich reaction has become a powerful method for the stereoselective synthesis of chiral building blocks as well as complex target synthesis. This has recently resulted in an excellent and comprehensive review by Anderson and Noble.[9] In this introduction we will discuss the nitro-Mannich reaction of aldimines and nitroalkanes, except in some examples where reactions involving ester substituted nitroalkanes and conjugated nitroalkenes will also be discussed. For further examples of the nitro-Mannich reactions, including the reaction of ketimines, see reference 9.

1.2.2 Early Examples of the Nitro-Mannich Reaction

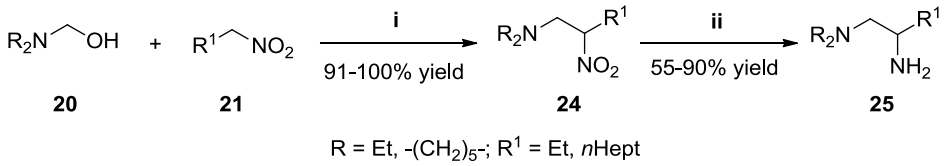
The first nitro-Mannich reaction was reported by Henry in 1896.[13] In this report, Henry described the addition of nitroalkanes **21** to an imine derived from hemiaminal **20** (Scheme 5). Elimination of water from **20** forms the imine in situ, which then reacts with the nitronate ion of **21** to form a β-nitroamine that can subsequently react

further forming adducts **22** or **23**. Although this is the first report of the nitro-Mannich reaction, no yields of the products **22** and **23** were given.



Scheme 5. Henry's first report of the nitro-Mannich reaction.

After Henry's seminal report, Mousset[15] and Duden[16] made contributions to the field by studying the addition of branched nitroalkanes to hemiaminals using the same procedures reported by Henry. An example of nitro group reduction to an amine using $SnCl_2$ and HCl was also disclosed by Duden and co-workers, thus representing the first use of the nitro-Mannich reaction to prepare polyamines. The next report did not appear until 1931, when Cerf de Mauny[17] conducted a thorough study of Henry's original work using hemiaminals **20** (Scheme 6).

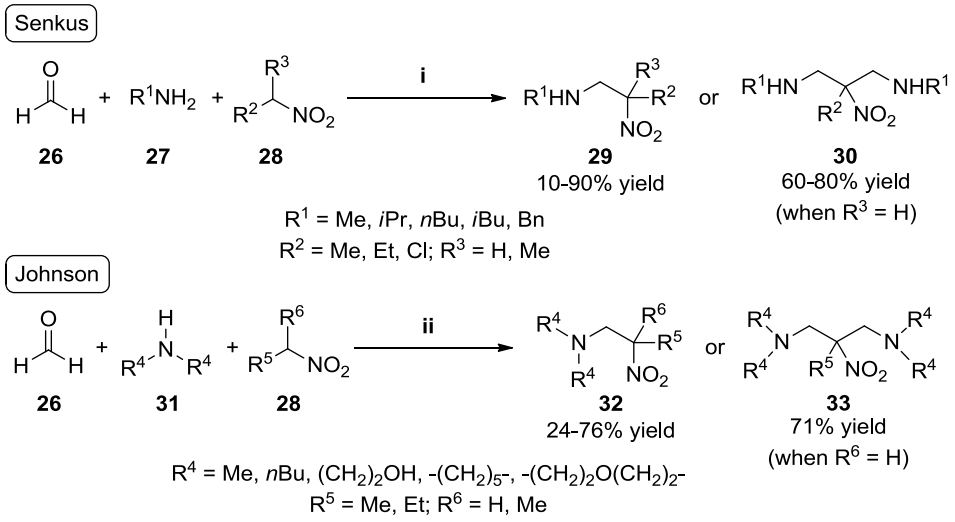


Scheme 6. Cerf de Mauny's nitro-Mannich reaction of hemiaminals **20** and nitro group reduction using aluminium amalgam. Reagents and conditions: i) 33% aq. solution of **21**, 0 °C - RT, 8-22 h; ii) Al/Hg, Et_2O, 0 °C.

The scope of the reaction was extended to higher order nitroalkanes affording β-nitroamines **24** in excellent yields. More detailed experimental procedures were described as well as an improved protocol for nitro group reduction using aluminium amalgam.

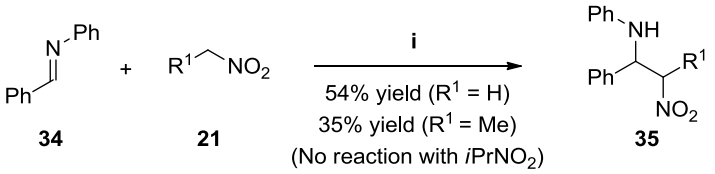
The next contributions appeared in 1946, when Senkus and Johnson independently reported their studies into the nitro-Mannich reaction (Scheme 7). Senkus and co-

workers[18] illustrated that nitroalkanes **28** could react with formaldehyde (**26**) and substituted primary amines **27** in the presence of Na_2SO_4 to afford a variety of substituted β-nitroamines **29** in moderate to good yields. When using primary nitroalkane substrates, double addition of the nitroalkane to the imine was observed, but this could be avoided by employing secondary nitroalkanes. The study reported by Johnson and co-workers[19] also employed formaldehyde (**26**), but this was used in conjunction with a selection of secondary amines **31**, furnishing the corresponding β-nitroamines **32** in moderate to good yields. Both authors also reduced the nitro group to an amine functionality using Raney Nickel.



Scheme 7. The nitro-Mannich reactions reported by Senkus and Johnson. Reagents and conditions: i) Na_2SO_4, RT; ii) NaCl, RT.

Up until this point, all of the nitro-Mannich methodologies reported had used imines that were formed in situ from an aldehyde and an amine. In 1950, Hurd and Strong[20] reported the first nitro-Mannich reaction using a preformed imine (Scheme 8). Exposing imine **34** to nitroalkanes **21** in refluxing ethanol afforded substituted β-nitroamines **35** in moderate yields. The moderate yields obtained when using the preformed imine **34** could possibly be attributed to a competing decomposition pathway of imine **34** or product **35**.

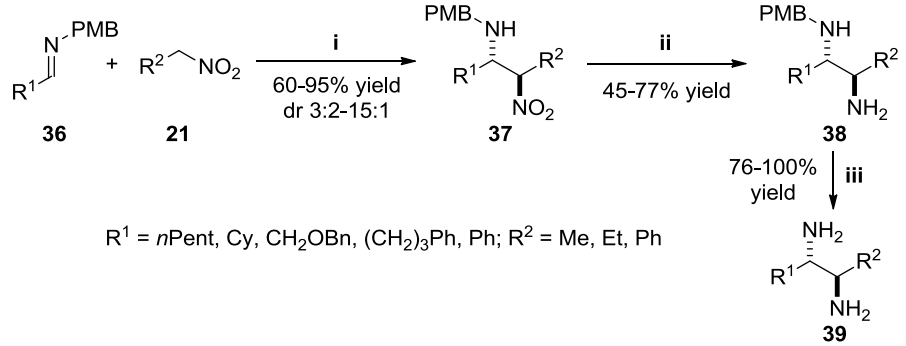


Scheme 8. The first nitro-Mannich reactions using preformed imines. Reagents and conditions: i) EtOH, reflux.

These early nitro-Mannich methodologies have been used by a number of groups for the synthesis of a variety of heterocyclic products,[21] conjugated nitroalkenes (via elimination of the amino group)[22] and dinitroamines.[19,23]

1.2.3 Non-Enantioselective Nitro-Mannich Reactions

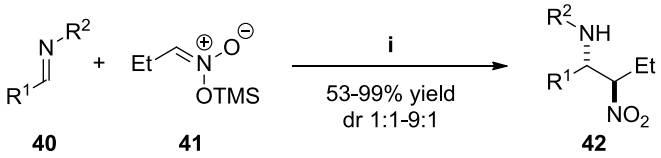
Although the nitro-Mannich reaction enables access to synthetically useful β-nitroamine motifs, the lack of selectivity in their synthesis remained a significant problem. Interest in the field started to increase considerably after Anderson and co-workers reported the first diastereoselective acyclic nitro-Mannich reaction (Scheme 9).[14] Nitroalkanes **21** and *n*BuLi were combined at –78 °C in THF to give the corresponding nitronate ions. A selection of *N*-PMB imines **36** were then added to the reaction mixture and after quenching with acetic acid, the β-nitroamine products **37** were afforded in good yields with moderate to good diastereoselectivities.



Scheme 9. Anderson's diastereoselective nitro-Mannich reaction using *n*BuLi and AcOH. Reagents and conditions: i) *n*BuLi, THF, –78 °C then *N*-PMB imine **36** then AcOH, –78 °C to 0 °C; ii) SmI_2, THF/MeOH; iii) CAN, MeCN/H_2O.

The authors then converted the β-nitroamines into unprotected 1,2-diamines **39** via a two step procedure. Firstly, the nitro group was reduced to amines **38** using samarium iodide, followed by PMB removal in the presence of CAN. The same group later reported improvements to this methodology and expanded these preliminary results in further publications.[24]

In 2000, Anderson and co-workers reported the racemic nitro-Mannich reaction of TMS-protected nitronate **41** with *N*-PMB or *N*-PMP imines **40** catalysed by $Sc(OTf)_3$ (Scheme 10).[25] The authors first attempted the nitro-Mannich reaction using lithium-nitronates, however no product was formed using these conditions. As a result, TMS-protected nitronate **41** was used in conjunction with $Sc(OTf)_3$ (4 mol%) to afford β-nitroamine products **42** in moderate to excellent yields for a range of alkyl and aryl *N*-PMB and *N*-PMP protected imines.

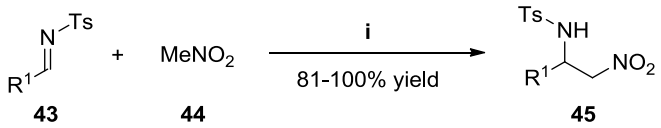


40 **41** **42**

R^1 = Ph, Cy, *n*Pent, $(CH_2)_4Ph$, 2-furyl; R^2 = PMP, PMB

Scheme 10. Anderson's $Sc(OTf)_3$ catalysed nitro-Mannich reaction using TMS-protected nitronates **41**. Reagents and conditions: i) $Sc(OTf)_3$ (4 mol%), MeCN, 0 °C.

Following Anderson's report, Qian and co-workers described the $Yb(OiPr)_3$ catalysed nitro-Mannich reaction of *N*-sulfonyl imines **43** and nitromethane (**44**) (Scheme 11).[26]



43 **44** **45**

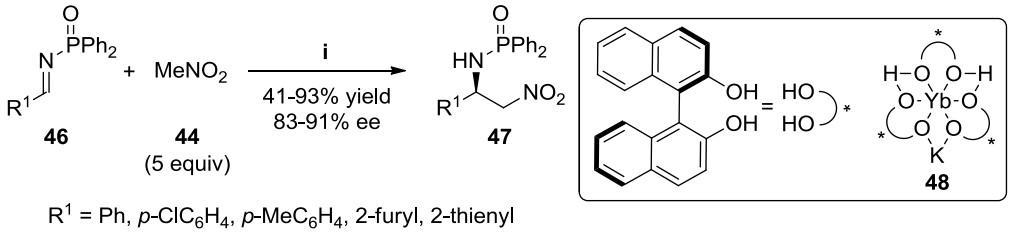
R^1 = Ph, *p*-MeC_6H_4, *o*-$MeOC_6H_4$, *p*-$MeOC_6H_4$
p-ClC_6H_4, *p*-$NO_2C_6H_4$,

Scheme 11. Qian's $Yb(OiPr)_3$ catalysed nitro-Mannich reaction. Reagents and conditions: i) $Yb(OiPr)_3$ (5 mol%), THF, RT, 5 h.

Using mild reactions conditions, the β-nitroamines **45** bearing electron-rich and electron-poor aryl substituents were furnished in excellent yields after short reaction times.

1.2.4 Direct Metal Catalysed Enantioselective Nitro-Mannich Reactions

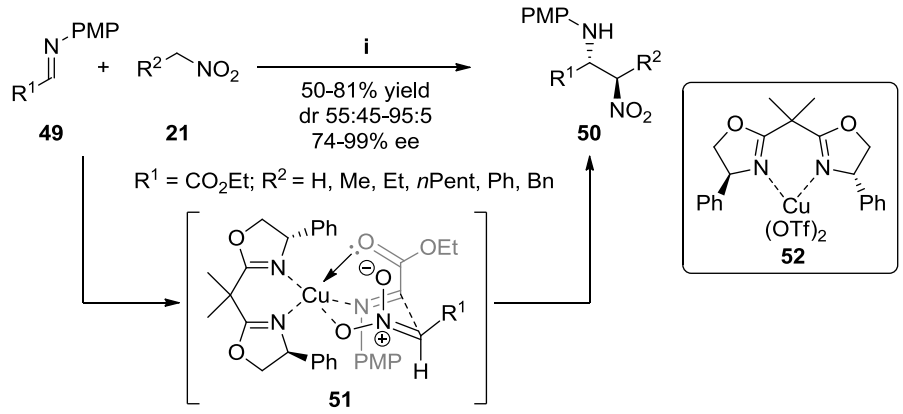
The first enantioselective metal catalysed nitro-Mannich reaction was reported by Shibasaki and co-workers in 1999 (Scheme 12).[27] The authors used the binaphthol ligated Yb/K heterobimetallic complex **48** to induce enantiocontrol in the reaction, furnishing β-nitroamines **47** in moderate to good yields with good enantioselectivities. However, nitromethane (**44**) was the only nitroalkane that could be used with the heterobimetallic complex **48** and the reactions were very slow (2.5-7 days) even when using a relatively high catalyst loading of 20 mol%.



R^1 = Ph, *p*-ClC_6H_4, *p*-MeC_6H_4, 2-furyl, 2-thienyl

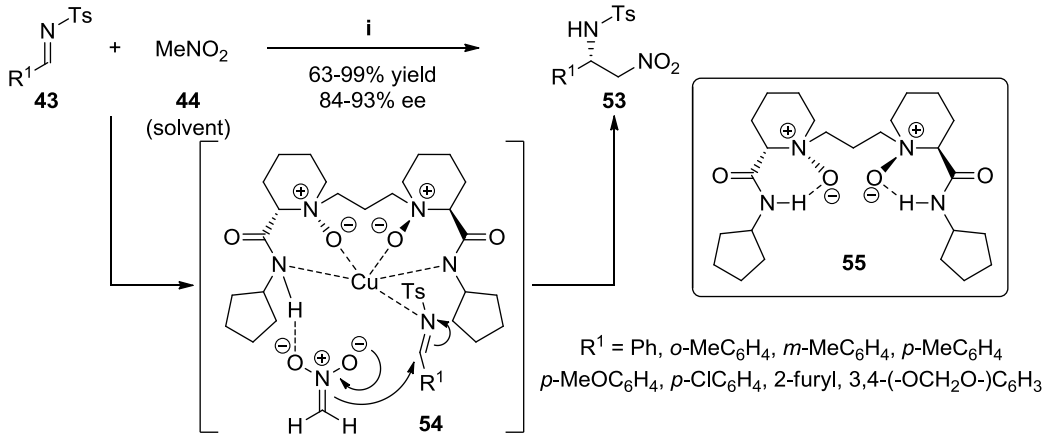
Scheme 12. Shibasaki's enantioselective nitro-Mannich reaction of *N*-phosphinoyl imines **46** and nitromethane (**44**). Reagents and conditions: i) complex **48** (20 mol%), PhMe/THF, –20 °C, 2.5-7 days.

Building on the work of Shibasaki, Jørgensen and co-workers reported the asymmetric nitro-Mannich reaction of nitroalkanes **21** and *N*-PMP-α-iminoesters **49** (Scheme 13).[28] Catalysed by Cu(II)-BOX **52** and Et_3N, the reaction afforded β-nitro-α-aminoesters **50** in good yields with excellent enantiocontrol (up to 99% ee). The reaction tolerates a selection of nitroalkanes but is limited exclusively to *N*-PMP-α-iminoesters. The authors propose that the reaction proceeds via the chair-like transition structure **51**, where both *N*-PMP-α-iminoester **49** and the nitronate anion bind to the Cu(II)-BOX complex **52**.



Scheme 13. Jorgensen's enantioselective nitro-Mannich reaction using Cu(II)-BOX **52** and Et_3N. Reagents and conditions: i) Cu(II)-BOX **52** (20 mol%), Et_3N (20 mol%), CH_2Cl_2, 0 °C or RT.

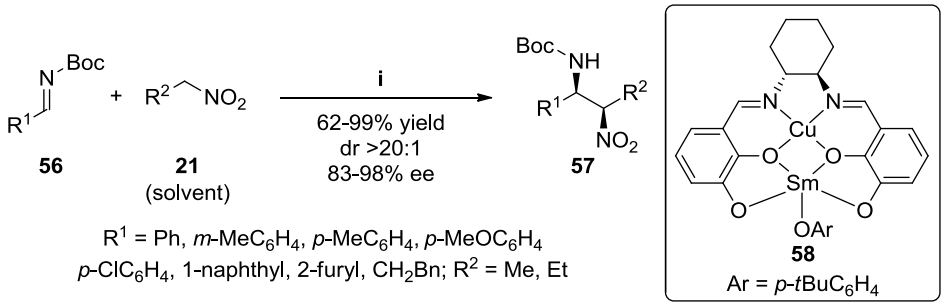
In 2007, Feng and co-workers reported that CuOTf used in conjunction with the chiral *N*-oxide ligand **55** and DIPEA is an efficient catalytic system for the enantioselective nitro-Mannich reaction of nitromethane (**44**) with *N*-sulfonyl imines **43** (Scheme 14).[29] Combining all of the reagents in THF at –40 °C resulted in the formation of β-nitroamines **53** in excellent yields (up to 99%) and good enantioselectivities for a variety of substituted aryls groups. The postulated intermediate complex **54** is similar to transition structure **51** proposed by Jørgensen and co-workers, where the ligated copper species binds to the *N*-sulfonyl imine **43**.



Scheme 14. Feng's enantioselective copper catalysed nitro-Mannich reaction using chiral *N*-oxide ligand **55**. Reagents and conditions: i) CuOTf (20 mol%), ligand **55** (20 mol%), DIPEA (5 mol%), THF, –45 °C, 4 Å molecular sieves, 22-87 h.

A hydrogen bonding interaction is also proposed to exist between the amide NH and the nitronate species.

Around the same time as the report of Feng, Shibasaki and co-workers reported one of the most successful enantioselective nitro-Mannich reactions, catalysed by the Cu/Sm heterobimetallic complex **58** (Scheme 15).[30] Combining *N*-Boc protected imines **56** and nitroalkanes **21** resulted in moderate to excellent yields and good to excellent enantioselectivities of the products. Interestingly, the nitro-Mannich reaction catalysed by complex **58** affords *syn*-β-nitroamines **57**, whereas most other enantioselective methodologies favour *anti*-β-nitroamines.



Scheme 15. Shibasaki's Cu/Sm heterobimetallic complex **58** for enantioselective nitro-Mannich reactions. Reagents and conditions: i) complex **58** (2.5-10 mol%), THF, –40 °C, 23-72 h.

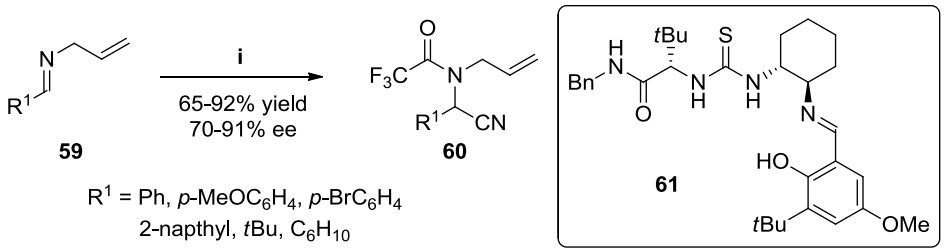
The authors later reported an improved version of the protocol using complex **58** and proposed a mechanistic rational to account for the observed *syn* diastereoselectivity.[31]

1.2.5 Organocatalysed Enantioselective Nitro-Mannich Reactions

Since the inception of organocatalysis, numerous accounts of organocatalysed enantioselective nitro-Mannich reactions have been reported.[9] These include examples using Brønsted base catalysts, Brønsted acid catalysts, bifunctional Brønsted base/H-bond donor catalysts and phase-transfer catalysts. This introduction will focus on the major developments made in enantioselective nitro-Mannich reactions using bifunctional Brønsted base/H-bond donor and Brønsted acid organocatalysts because these examples are directly related to the work presented in this thesis.

1.2.5.1 Bifunctional Brønsted Base/H-Bond Donor Organocatalysis

Over the last decade, the use of small chiral molecule H-bond donors has emerged as a powerful method for enantioselective synthesis.[32] These low molecular weight entities containing structural frameworks with distinct H-bond donor motifs can catalyse a wide range of carbon-carbon and carbon-heteroatom bond-forming reactions, occurring via H-bond donor activation of the reaction partners as well as through organisation of their spatial arrangement. This area of organic chemistry received limited attention until the seminal work of Jacobsen and Sigman,[33] in which they reported a highly enantioselective Strecker reaction using the H-bond donor organocatalyst **61** (Scheme 16).



Scheme 16. Jacobsen's thiourea organocatalyst for asymmetric Strecker reactions. Reagents and conditions: i) HCN, catalyst **61** (2 mol%), PhMe, −78 °C, 24 h then TFAA.

Building on the work of Jacobsen, it was recognised that H-bond donor motifs could be linked via a chiral scaffold to Brønsted basic moieties, creating a new class of bifunctional organocatalysts (Figure 1). The incorporation of these two functionalities would allow the simultaneous activation of the nucleophile (via deprotonation by the Brønsted base) and electrophile (via H-bond donation), thus allowing the development of novel enantioselective reactions through new activation modes.

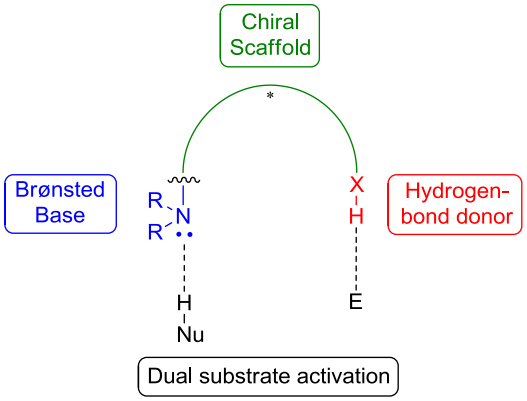


Figure 1. Concept of bifunctional Brønsted base/H-bond donor organocatalysis.

Based on this concept, Takemoto and co-workers reported the first bifunctional Brønsted base/H-bond donor thiourea organocatalyst **62** (Figure 2) in 2003.[34] This organocatalyst, based on the 1,2-*trans*-cyclohexanediamine scaffold, imparted high levels of enantiocontrol in the Michael addition of dimethylmalonate to a variety of nitrostyrenes. After this seminal report, numerous contributions to the field occurred with the development of bifunctional organocatalysts derived from the readily available cinchona alkaloid scaffold. Deng and co-workers first reported that the quinidine-derived bifunctional organocatalyst **63** was a proficient catalyst for Michael addition reactions.[35] In this organocatalytic system, the H-bonding interaction arising from the quinoline alcohol is thought to be crucial for achieving high enantioselectivities.

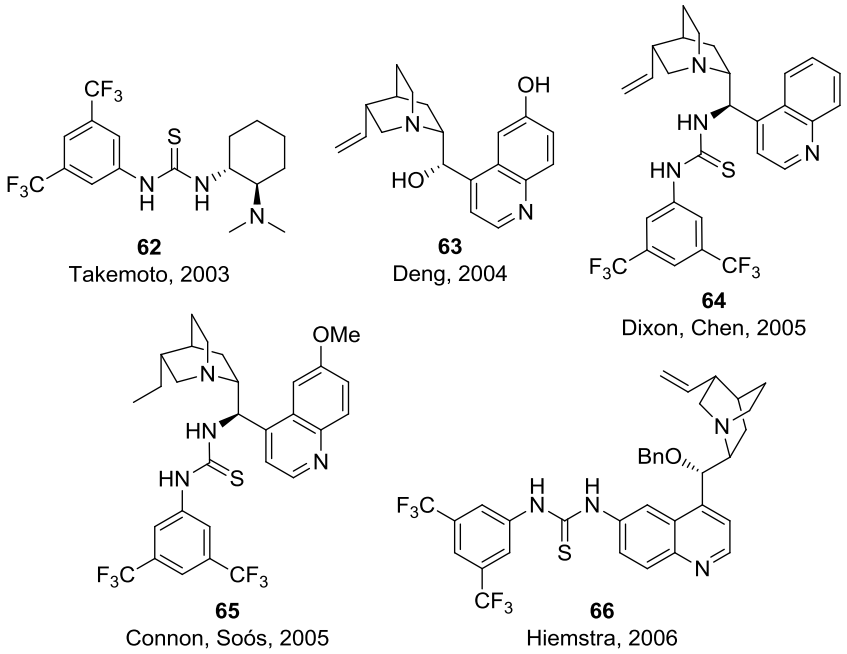
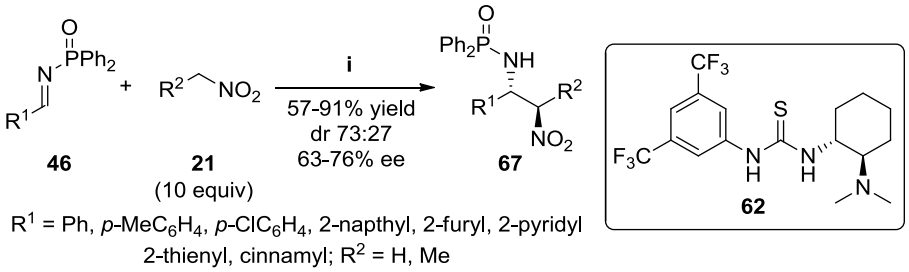


Figure 2. Selection of pioneering bifunctional Brønsted base/H-bond donor organocatalysts.

Shortly after this disclosure, the groups of Dixon,[36] Chen,[37] Connon[38] and Soós[39] found that bifunctional thioureas **64** and **65**, also derived from the cinchona alkaloids, were very effective catalysts in Michael addition reactions. Hiemstra and co-workers also contributed to the field, demonstrating that bifunctional thiourea **66** was able to impart high levels of enantiocontrol in the nitro-aldol (Henry) reaction.[40] Bifunctional thiourea **66** differs structurally from bifunctional thioureas **64** and **65**, as the thiourea moiety is attached to the quinoline ring of the cinchona scaffold instead of the central stereocentre. Since these seminal reports, numerous other bifunctional organocatalyst systems have been described, further expanding the range of reactions that can be conducted using bifunctional (thio)urea organocatalysis.[32]

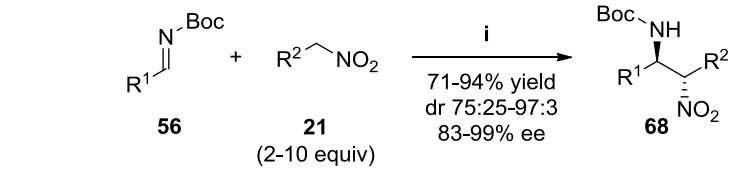
1.2.5.2 Bifunctional Brønsted Base/H-bond Donor (Thio)urea Organocatalytic Nitro-Mannich Reactions

The rise to prominence of bifunctional Brønsted base/H-bond donor (thio)urea organocatalysis has been accompanied by several reports of bifunctional organocatalytic nitro-Mannich reactions. The first asymmetric organocatalysed nitro-Mannich reaction was reported by Takemoto and co-workers using bifunctional organocatalyst **62** (Scheme 17).[41] This investigation focused on the addition of nitromethane to *N*-phosphinoyl protected imines **46** bearing aryl substituents, affording the desired β-nitroamines **67** in good yields but with moderate enantioselectivities. One example using nitroethane was also described, with moderate diastereoselectivity being obtained in favour of the *anti*-diastereomer (dr 73:27).



Scheme 17. Takemoto's first asymmetric organocatalytic nitro-Mannich reaction using bifunctional thiourea **62**. Reagents and conditions: i) catalyst **62** (10 mol%), CH_2Cl_2, RT.

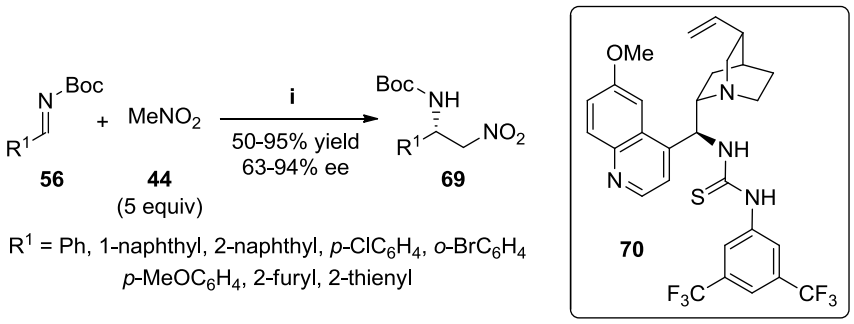
Takemoto further examined the nitro-Mannich reaction using bifunctional thiourea **62**, substituting the previously used *N*-phosphinoyl imines for *N*-Boc protected imines **56** (Scheme 18).[42] Modification of the protecting group in conjunction with a reduction of the reaction temperature led to the formation of β-nitroamines **68** with greatly improved enantioselectivities. The scope of the nitro-Mannich reaction was broadened with a range of functionalised linear nitroalkanes being submitted to the optimal conditions, furnishing the products with excellent diastereocontrol.



R^1 = Ph, *p*-$CF_3C_6H_4$, *p*-MeC_6H_4, *p*-$MeOC_6H_4$, 1-naphthyl, 2-naphthyl, 2-furyl, 3-pyridyl 2-thienyl; R^2 = H, Me, *n*Bu, Bn, CH_2OBn, $(CH_2)_2OBn$, $(CH_2)_3OBn$, $(CH_2)_2OH$, $(CH_2)_2OTf$

Scheme 18. Improvement of Takemoto's nitro-Mannich reaction using *N*-Boc imines. Reagents and conditions: i) catalyst **62** (10 mol%), CH_2Cl_2, –20 °C.

In 2006, Ricci and co-workers reported an asymmetric nitro-Mannich reaction catalysed by the quinine-derived thiourea **70** (Scheme 19).[43] This example employed *N*-Boc aryl imines **56** with nitromethane (**44**), furnishing the β-nitroamine products **69** in good yields with good enantiocontrol. However, relatively high catalyst loadings of thiourea **70** (20 mol%) were required to allow completion of the reaction in a suitable timeframe. Another drawback was that only reactions using nitromethane were investigated in this report. Schaus and co-workers also reported a similar protocol using a cinchona alkaloid derived bifunctional organocatalyst and *N*-protected imines.[44]

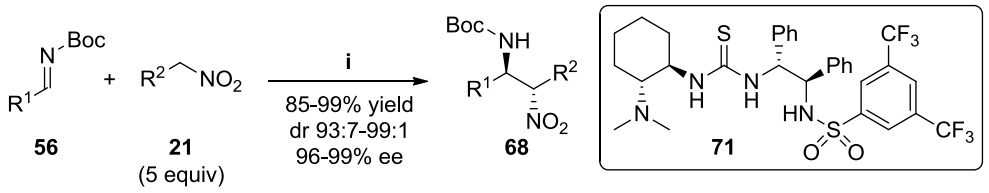


R^1 = Ph, 1-naphthyl, 2-naphthyl, *p*-ClC_6H_4, *o*-BrC_6H_4 *p*-$MeOC_6H_4$, 2-furyl, 2-thienyl

Scheme 19. Ricci's quinine-derived thiourea catalysed nitro-Mannich reaction. Reagents and conditions: a) catalyst **70** (20 mol%), PhMe, –40 °C or –24 °C.

In 2008, Wang and co-workers reported the highly enantioselective nitro-Mannich reaction of *N*-Boc imines **56** and nitroalkanes **21** using the sulfonamide containing bifunctional thiourea **71** (Scheme 20).[45] This protocol is one of the most efficient nitro-Mannich reactions in the literature, with exceptional yields and

stereoselectivities being obtained in the majority of examples described. The reaction tolerates the typically used aryl substituted *N*-Boc imines, but the system also gives an excellent result when using alkyl substituted *N*-Boc imines, further demonstrating the superiority of the bifunctional thiourea **71** in the nitro-Mannich reaction compared to other bifunctional systems.

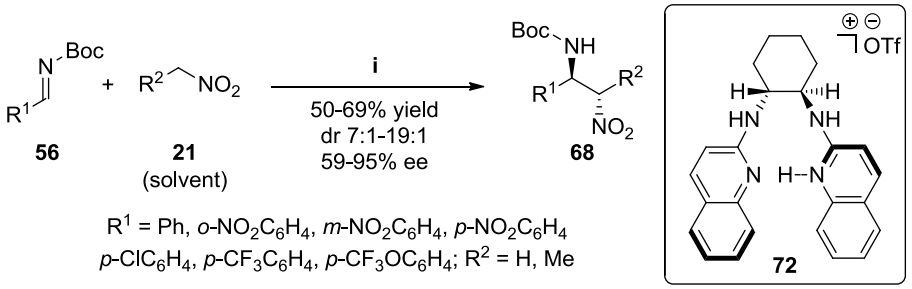


R^1 = Ph, *p*-MeC_6H_4, *o*-$MeOC_6H_4$, *p*-$MeOC_6H_4$, *o*-ClC_6H_4, *p*-ClC_6H_4, *p*-FC_6H_4, *p*-$CF_3C_6H_4$, 1-naphthyl 2-naphthyl, 2-furyl, 3-pyridyl, *i*Bu; R^2 = H, Me, Et, Bn

Scheme 20. Wang's bifunctional thiourea catalysed nitro-Mannich reaction. Reagents and conditions: i) catalyst **71** (10 mol%), MeCN, 4 Å molecular sieves, –20 °C, 10-15 h.

1.2.5.3 Brønsted Acid Organocatalysed Nitro-Mannich Reactions

Soon after Takemoto reported the first asymmetric nitro-Mannich reaction, Johnston and co-workers described the highly diastereo- and enantioselective nitro-Mannich reaction catalysed by chiral bis-amidine salt **72** (Scheme 21).[46] Although high diastereo- and enantioselectivities were obtained using this method, the reactions were very slow (5 days) even with the nitroalkanes being used as the reaction solvent. Johnston and co-workers conducted further studies into the nitro-Mannich reaction by modifying their original chiral bis-amidine scaffold.

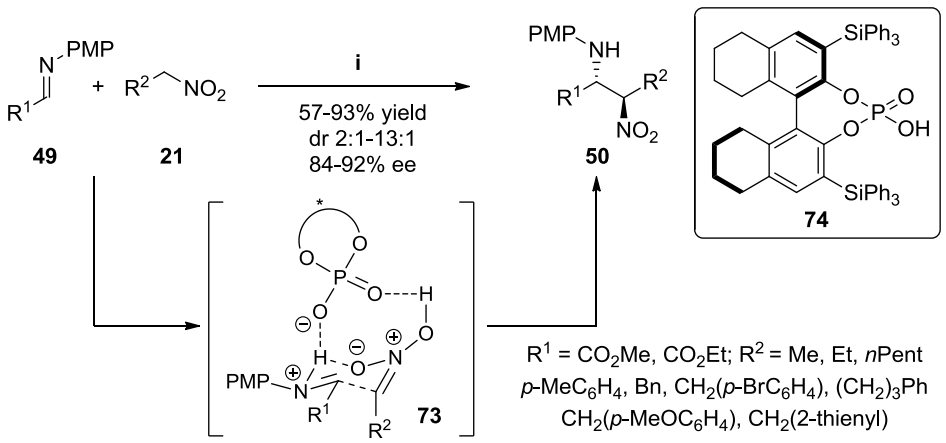


R^1 = Ph, *o*-$NO_2C_6H_4$, *m*-$NO_2C_6H_4$, *p*-$NO_2C_6H_4$ *p*-ClC_6H_4, *p*-$CF_3C_6H_4$, *p*-$CF_3OC_6H_4$; R^2 = H, Me

Scheme 21. Johnston's chiral bis-amidine **72** for diastereo- and enantioselective nitro-Mannich reactions. Reagents and conditions: i) catalyst **72** (10 mol%), –20 °C, [**21**] 0.25 M, 5 days.

This has resulted in a number of new and improved protocols for the nitro-Mannich reaction.[47]

In 2008, Rueping and Antonchick reported the BINOL-derived phosphoric acid catalysed nitro-Mannich reaction of *N*-PMP-α-iminoesters **49** and nitroalkanes **21** (Scheme 22).[48] The Brønsted acid catalyst **74** was found to impart high levels of enantiocontrol for a range of substituted nitroalkanes to furnish β-nitro-α-aminoesters **50** in moderate to good yields. Unfortunately, the reaction only tolerates *N*-PMP-α-iminoesters **49** and a large excess of the nitroalkane (10 equiv) is required for the reaction to reach completion in an adequate timeframe. Enantiocontrol in the reaction is postulated to arise from transition structure **73**. The phosphoric acid is proposed to activate both the imine and nitroalkane reaction partners by protonation, the phosphate salt then chelates the resulting iminium ion and nitronate species in a chair like configuration.



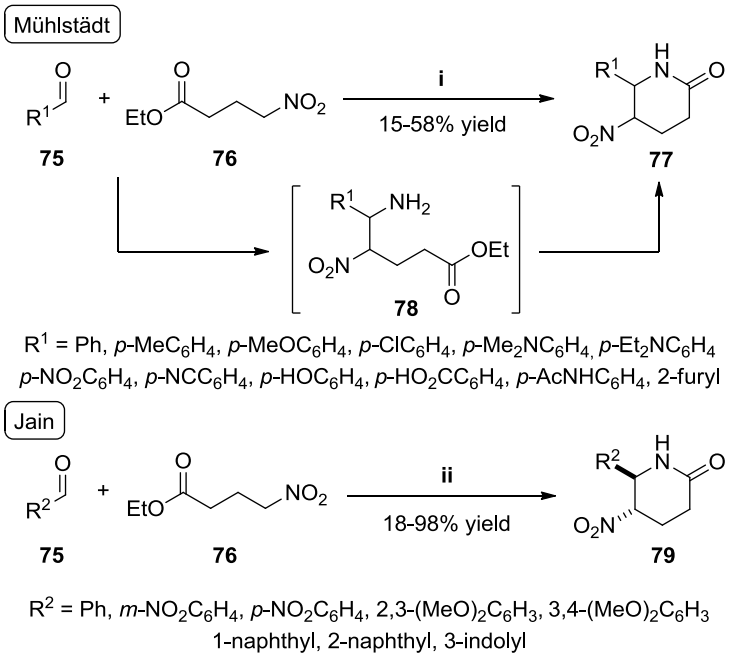
Scheme 22. Rueping's BINOL phosphoric acid catalysed nitro-Mannich reaction. Reagents and conditions: i) catalyst **74** (10 mol%), benzene, 30 °C, 12-166 h.

1.2.6 Cascade Reactions Involving Nitro-Mannich Reactions

As discussed earlier in this introduction, the increasing need for new and resource efficient reaction processes is essential to reduce the impact that synthetic chemistry has on the environment. With the recent advancements made in the nitro-Mannich reaction, synthetic chemists became interested in combining these new methods with other reactions to develop novel cascade reaction methodologies. Two of the most frequently used will be discussed in this introduction, nitro-Mannich/lactamisation cascades and [3+2] cycloaddition reactions.

1.2.6.1 Nitro-Mannich/Lactamisation Cascades

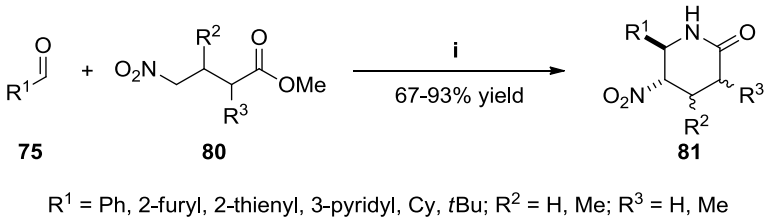
The first nitro-Mannich/lactamisation cascade reactions were reported independently in the 1970s by Mühlstädt[49] and Jain.[50] Building on their previous studies into nitro-Mannich reactions using nitroester substrates,[51] Mühlstädt investigated the reaction between nitroesters **76**, substituted aldehydes **75** and ammonium acetate (Scheme 23). Interestingly, in refluxing acetic acid, piperidinones **77** were obtained in moderate yields instead of the expected β-nitroamines. The piperidinone products presumably form via an initial nitro-Mannich reaction that furnishes intermediate **78**. A subsequent lactamisation reaction then affords the piperidinone products **77** bearing a range of substituted aromatic groups. This report represents the first example of a nitro-Mannich/lactamisation cascade but there is no mention of the configuration of the products in the manuscript. Jain also developed a nitro-Mannich/lactamisation cascade to piperidinone motifs using a combination of aryl aldehydes, ammonium acetate and nitroester **76** (Scheme 23). An improved substrate scope was presented with aldehydes bearing heteroaromatic substituents undergoing the cascade reaction as well as an improvement in the isolated yields of the products.



Scheme 23. Mühlstädt's and Jain's nitro-Mannich/lactamisation cascades to piperidinones **77** and **79**. Reagents and conditions: i) NH_4OAc, AcOH, reflux; ii) NH_4OAc, EtOH, reflux.

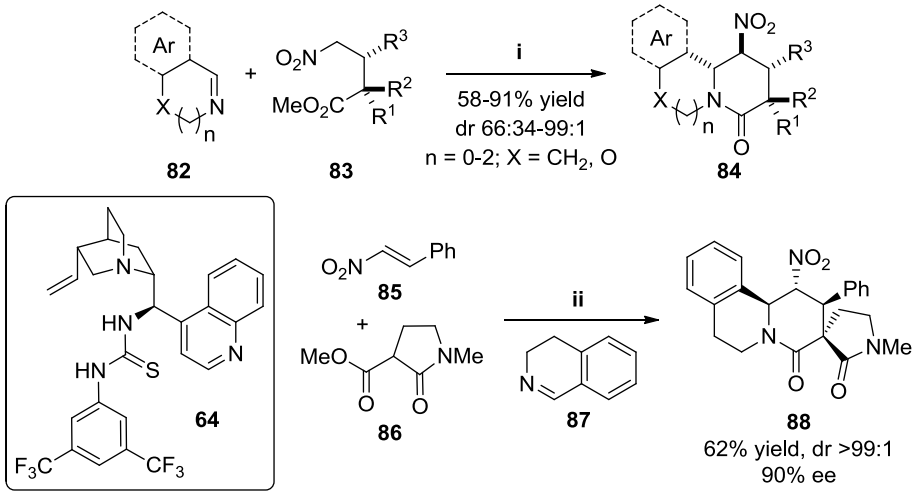
Also, the configuration of the piperidinone products was determined to be *trans* by ^1H NMR analysis. The diastereoselectivity observed in this reaction is attributed to the formation of the most thermodynamically stable *trans*-isomer, possibly by a kinetically controlled cyclisation reaction or a post cyclisation epimerisation of the nitro group.

It was not until 1993, when Desai and co-workers reported an expansion of the methodology by using substituted nitroester substrates **80** (Scheme 24).[52] Extra substituents were added to the piperidinone motif **81** with good to excellent yields being obtained.



Scheme 24. Desai's nitro-Mannich/lactamisation cascade using substituted nitroesters **80**. Reagents and conditions: i) NH_4OAc, EtOH, reflux.

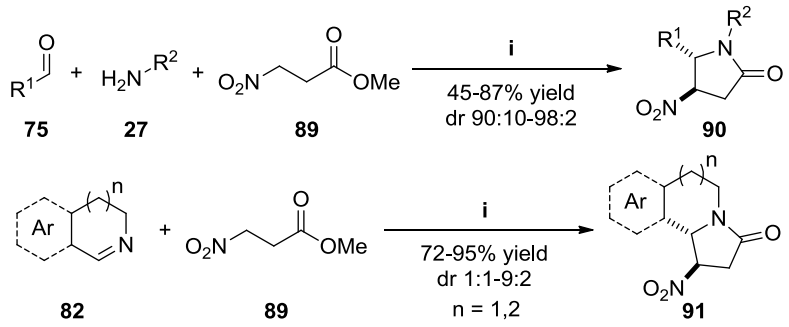
In 2008, Dixon and co-workers reported a highly diastereoselective nitro-Mannich/lactamisation cascade using preformed cyclic imines **82** and trisubstituted nitroester substrates **83** (Scheme 25).[6a] The authors reported that heating the starting materials at 70 °C in water resulted in the formation of numerous complex polycyclic products **84** in good yields with excellent diastereocontrol over two contiguous stereocentres. The methodology was found to tolerate 5-, 6- and 7-memebered cyclic imines, however the diastereoselectivities observed using the 5-membered cyclic imines were considerably lower than the other examples. A highly diastereoselective one-pot variant of this cascade reaction was also demonstrated to be possible, by first incorporating an enantioselective organocatalytic Michael addition reaction of nitrostyrene (**85**) and pro-nucleophile **86** using cinchonine-derived thiourea **64**. The resulting Michael addition/nitro-Mannich/lactamisation cascade afforded complex polycycle **88** as a single diastereomer in 90% ee. Further expansion of the cascade reaction incorporating acyclic imines has recently been reported.[6b]



Scheme 25. Dixon's nitro-Mannich/lactamisation cascade of cyclic imines **82** and nitroesters **83**. Reagents and conditions: i) H_2O, 70 °C, 6-240 h; ii) catalyst **64** (10 mol%), THF, –20 °C, 14 days then cyclic imine **87**, THF:H_2O (1:4), 70 °C, 48 h.

Dixon and co-workers later described a nitro-Mannich/lactamisation cascade to pyrrolidinone derivatives by combining methyl 3-nitropropanoate (**89**) with

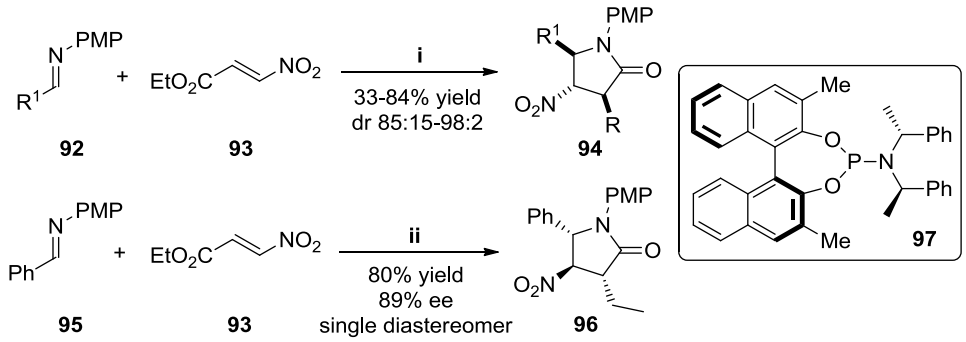
substituted imines formed in situ from the corresponding aldehydes and amines (Scheme 26).[7] In contrast to their previous studies,[6] no product formation was observed when using H_2O as the reaction solvent, with the best results for the cascade reaction being obtained using toluene with one equivalent of benzoic acid. The cascade reaction tolerated a wide variety of aldehydes and amines forming substituted pyrrolidinones **90** in good yields with excellent diastereoselectivities. Cyclic imines were also employed, but the diastereocontrol in the cascade reaction was reduced in these examples.



R^1 = *i*Pr, *n*Pent, 3-cyclohexenyl, *p*-$NO_2C_6H_4$, *p*-ClC_6H_4, *o*-$MeOC_6H_4$, *m*-$MeOC_6H_4$ *p*-$MeOC_6H_4$, 2-furyl, 3-furyl, 2-pyridyl, 2-thienyl
R^2 = *i*Pr, *n*Bu, Bn, allyl, CH_2-2-naphthyl, $(CH_2)_2$-3-indolyl, $(CH_2)_2$-*m*-$MeOC_6H_4$, $(CH_2)_2$-1-cyclohexenyl, CH_2CO_2Et, $(CH_2)_3Cl$, $(CH_2)_5OH$, $(CH_2)_2CH(OEt)_2$

Scheme 26. Dixon's nitro-Mannich/lactamisation cascade to substituted pyrrolidinones **90** and **91**. Reagents and conditions: i) benzoic acid, PhMe, 70 °C, N_2.

Very recently, Anderson and co-workers reported a three component Michael addition/nitro-Mannich/lactamisation cascade to prepare 1,3,5-trisubstituted pyrrolidinones **94** (Scheme 27).[53] The reaction proceeds via a Michael addition of an organozinc species to conjugated nitroalkene **93**, to give an intermediate nitronate which then undergoes a nitro-Mannich reaction with *N*-PMP imine **92**. The subsequent lactamisation reaction furnishes the pyrrolidinone products **94** with excellent diastereocontrol.



R^1 = Ph, *p*-MeC_6H_4, *p*-$NO_2C_6H_4$, *p*-$CF_3C_6H_4$, *p*-$MeOC_6H_4$, *p*-ClC_6H_4, *m*-MeC_6H_4, *o*-$MeOC_6H_4$ *o*-MeC_6H_4, *o*-BrC_6H_4, 3,5-$Cl_2C_6H_3$, 2-Br-4-FC_6H_4, 2-furyl, 3-furyl, 2-pyridyl, 3-pyridyl, 2-thienyl *N*-tosyl-3-indolyl, *N*-tosyl-2-pyrrolyl, Me, *n*Pent, *i*Pr, Cy, CO_2Et, $CH(OMe)_2$; R = Me, Et, *i*Pr, Ph

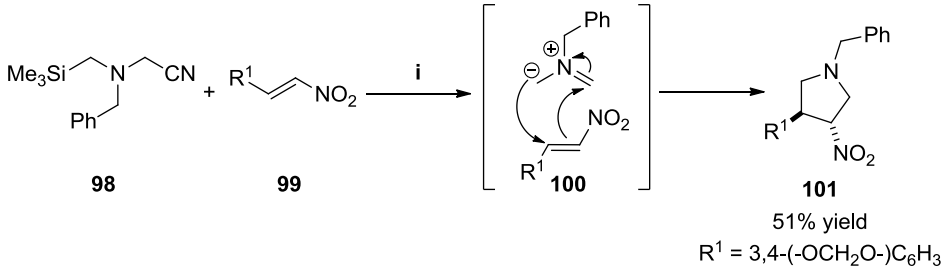
Scheme 27. Anderson's Michael addition/nitro-Mannich/lactamisation cascade to 1,3,5-trisubstituted pyrrolidinones **94**. Reagents and conditions: i) ZnR_2, CuOTf (2 mol%), THF, –78 °C - RT then imine **92**, TFA, –78 °C - RT; ii) $ZnEt_2$, CuOTf (2 mol%), ligand **97** (4 mol%), Et_2O, –78 °C - RT, 1.5 h then imine **95**, TFA, –78 °C - RT, 16 h.

This cascade has a very broad scope, tolerating a considerable number of different substituents on the imine as well as alkyl and aryl groups on the organozinc nucleophile. An example using a cyclic imine was described but the diastereoselectivity of the cascade was significantly reduced (dr 5:1). Additionally, the authors illustrated that the cascade can be carried out in an enantioselective fashion by conducting the initial Michael addition reaction in the presence of phosphoramidite ligand **97**. The enantioenriched pyrrolidinone **96** was afforded as a single diastereomer in 89% ee.

1.2.6.2 [3+2] Cycloaddition Reactions

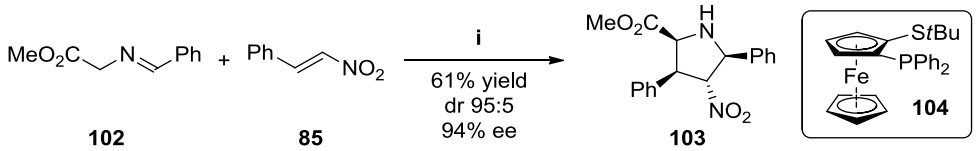
[3+2] Cycloaddition reactions of azomethine ylides with nitroalkenes present a powerful method for the preparation of 3-nitropyrrolidines. Because nitroalkenes are very π-deficient Michael acceptors, the [3+2] cycloaddition reaction can actually be considered as a conjugate addition/nitro-Mannich cascade reaction, rather than a concerted reaction, as supported by studies carried out by Cossío and co-workers.[54]

The first [3+2] cycloaddition of an azomethine ylide with a nitroalkene was reported in 1983 by Padwa and Chen (Scheme 28).[55] This silver fluoride catalysed reaction of α-cyanoaminosilane **98** and nitroalkene **99** resulted in the highly diastereo- and regioselective synthesis of pyrrolidine **101**. This report inspired several groups to explore this reaction further, leading to highly enantioselective variants using metal catalysis and organocatalysis.



Scheme 28. Padwa's silver catalysed [3+2] cycloaddition of α-cyanoaminosilane **98** and nitroalkene **99**. Reagents and conditions: i) AgF, MeCN, 25 °C, 10 h.

The first enantioselective [3+2] cycloaddition using a nitroalkene substrate was reported in 2005 by Carretero and co-workers (Scheme 29).[56] This report described the [3+2] cycloaddition of methyl *N*-benzylideneglycine (**102**) with a variety of Michael acceptors using a catalyst derived from $[Cu(MeCN)_4]ClO_4$ and ferrocene ligand **104**. There was one example of the reaction using nitrostyrene (**85**), affording the pyrrolidine product **103** in moderate yield with excellent enantioselectivity and *exo*-selectivity.

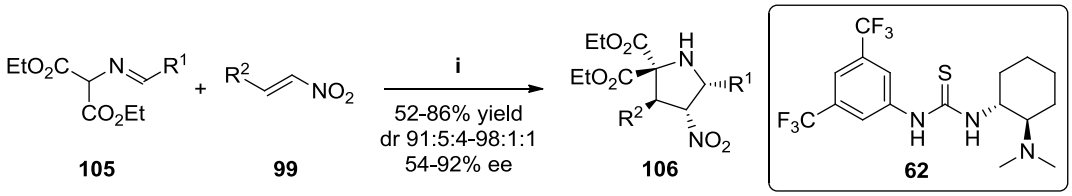


Scheme 29. Carretero's enantioselective [3+2] cycloaddition of methyl *N*-benzylideneglycine (**102**) and nitrostyrene (**85**). Reagents and conditions: i) ligand **104** (3 mol%), $[Cu(MeCN)_4]ClO_4$ (3 mol%), Et_3N (18 mol%), THF, –10 °C.

In 2006, Hou and co-workers reported a more comprehensive study of the [3+2] cycloaddition using nitroalkene substrates.[57] Further substrate scope was reported

along with improvements in the enantioselectivity of the reaction by using a different ferrocene containing ligand. The *exo* and *endo* products could both be obtained with excellent enantiocontrol, by judicious choice of the ferrocene ligand.

In 2008, similar organocatalysed enantioselective [3+2] cycloaddition reactions of azomethine ylides and nitroalkenes were reported by the groups of Chen,[58] Zhang[59] and Takemoto.[60] In the example presented by Takemoto and co-workers (Scheme 30), thiourea **62** was found to efficiently catalyse the Michael addition of malonate imines **105** to nitroalkenes **99**. However, the addition of 2,2,2-trifluoroethanol was required to allow the ring closing nitro-Mannich reaction to occur, affording the desired substituted pyrrolidines **106** in moderate to good yields and excellent diastereoselectivities. The level of enantiocontrol varied depending on the nature of the aryl substituent on the imine, with electron-withdrawing groups being required to obtain high enantioselectivities.



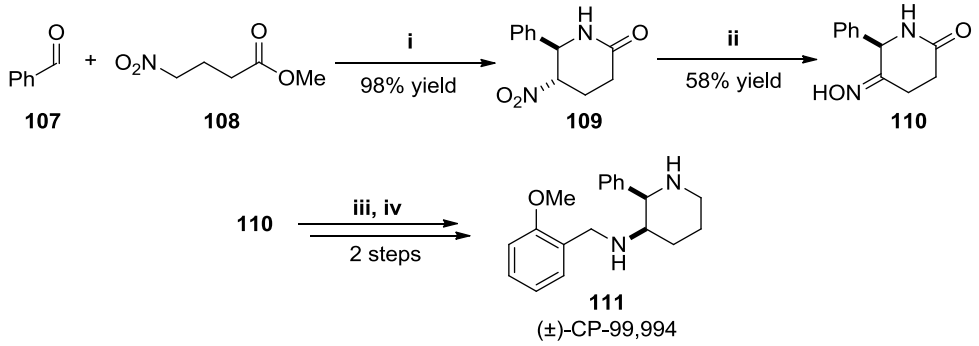
R^1 = Ph, *p*-MeC_6H_4, *p*-ClC_6H_4, *p*-$CF_3C_6H_4$
R^2 = Ph, *o*-ClC_6H_4, *m*-ClC_6H_4, *p*-ClC_6H_4, *p*-$MeOC_6H_4$, 1-napthyl, 2-thienyl

Scheme 30. Takemoto's organocatalysed [3+2] cycloaddition of malonate imines **105** and nitroalkenes **99**. Reagents and conditions: i) catalyst **62** (10 mol%), PhMe, 0 °C, 9 h then 2,2,2-trifluoroethanol, 0 °C, 36 h.

1.2.7 The Nitro-Mannich Reaction in Target Synthesis

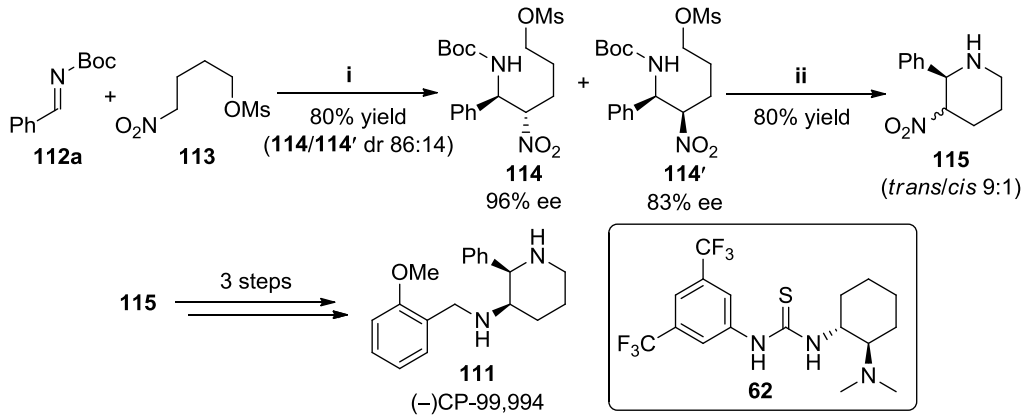
Due to the versatility of the nitro-Mannich reaction and its ability to provide a variety of complex synthetic building blocks in high enantiomeric excess, it has unsurprisingly been applied to the synthesis of several natural products and biologically active molecules.

In 1993, Desai and co-workers reported a short racemic synthesis of the neurokinin 1 (NK_1) antagonist CP-99,994 using a nitro-Mannich/lactamisation cascade as the key step (Scheme 31).[52] Firstly, a nitro-Mannich/lactamisation cascade reaction using benzaldehyde, ammonium acetate and nitroester **108** afforded *trans*-piperidinone **109**. Conversion of the nitro group to oxime **110** via a Nef reaction followed by a stereoselective reduction enabled the *cis*-configuration of CP-99,994 to be formed.



Scheme 31. Desai's synthesis of (±)-CP-99,994 (**111**). Reagents and conditions: i) NH_4OAc, EtOH, reflux; ii) KO*t*Bu, ozone, −78 °C, Me_2S then $NH_2OH{\cdot}HCl$; iii) Raney Ni, H_2 then *o*-anisaldehyde, $NaBH_3CN$, 4 Å molecular sieves; iv) BMS, THF, reflux then Et_2O-HCl.

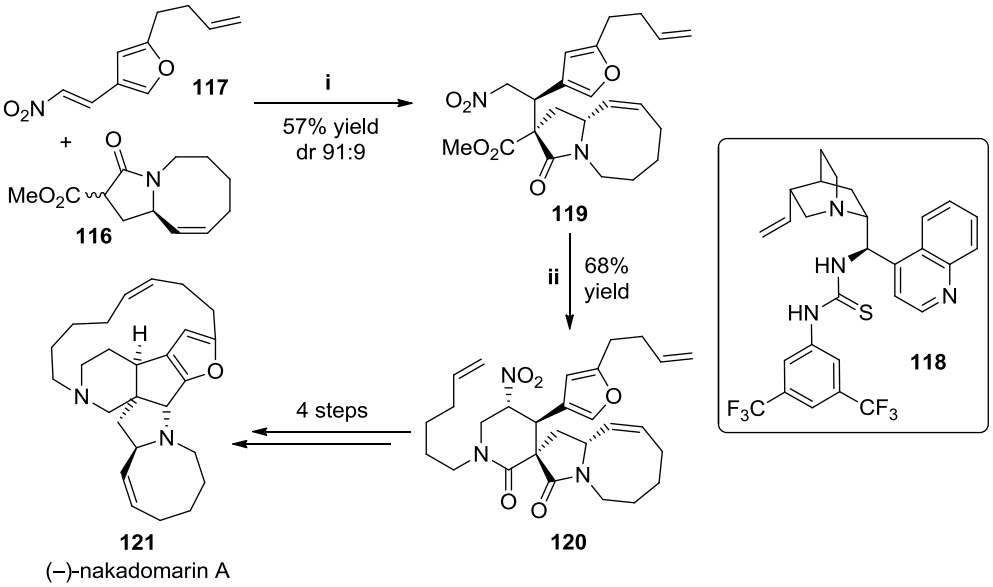
In 2006, Takemoto developed a highly enantioselective synthesis of (–)-CP-99,994 (**111**) via an organocatalysed nitro-Mannich reaction of *N*-Boc imine **112a** and nitroalkane **113** (Scheme 32).[42] Using bifunctional thiourea **62** as the organocatalyst, the synthesis of β-nitroamines **114** and **114′** was achieved in 80% combined yield as a 86:14 mixture of diastereomers with 96% ee being obtained for the major *anti*-diastereomer **114**.



Scheme 32. Takemoto's enantioselective synthesis of (–)-CP-99,994 (**111**) using thiourea **62**. Reagents and conditions: i) catalyst **62** (10 mol%), CH_2Cl_2, –20 °C, 72 h; ii) TFA, CH_2Cl_2, 20 °C, 3 h then aq. K_2CO_3 work up.

Removal of the *N*-Boc protecting group using TFA facilitated ring closure to form piperidine **115** in 80% yield, which was then converted into (–)-CP-99,994 (**111**) in 3 steps including nitro group epimerisation to give the desired *cis* configuration.

In 2009, Dixon demonstrated the power of the nitro-Mannich/lactamisation cascade reaction by utilising it in the synthesis of the complex alkaloid (–)-nakadomarin A (**121**) (Scheme 33).[61] Firstly, the diastereoselective union of pro-nucleophile **116** and nitroalkene **117** catalysed by urea **118**, resulted in the formation of nitroester **119**. In the presence of an imine derived from formaldehyde and hex-5-enamine, a nitro-Mannich/lactamisation cascade occurred to afford the decorated piperidinone **120** in 68% yield as a single diastereomer after purification. From the complex intermediate **120**, the total synthesis of (–)-nakadomarin A (**121**) was completed in four steps. More recently, the Dixon group has elegantly used nitro-Mannich/lactamisation cascades in two further total syntheses of (–)-nakadomarin A[62] and the total synthesis of (+)-manzamine A.[63]



Scheme 33. Dixon's total synthesis of (–)-nakadomarin A using a nitro-Mannich/lactamisation cascade. Reagents and conditions: i) catalyst **118** (15 mol%), toluene, 30 °C, 8 days; ii) formaldehyde, hex-5-enamine, MeOH, reflux, 5 h.

Johnston and co-workers have also used the nitro-Mannich reaction as a key reaction in the synthesis of a number of complex targets. These include a formal synthesis of (+)-chaenorhine[64] and a total synthesis of the potent p53/MDM2 inhibitor (–)-nutlin-3.[65]

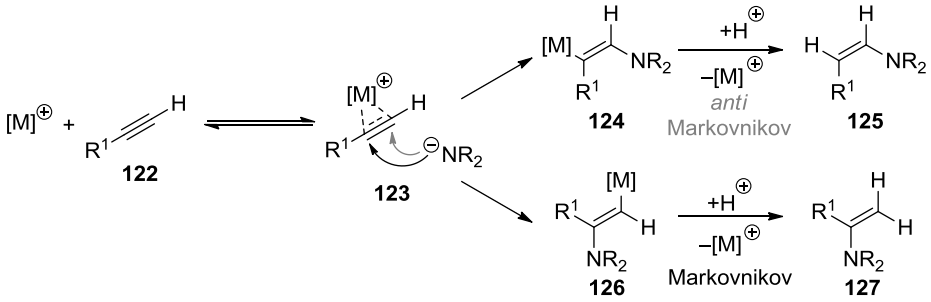
1.3 Hydroamination Reactions

1.3.1 Importance of Hydroamination Reactions

The addition of heteroatom nucleophiles to unsaturated carbon-carbon bonds has become a valuable synthetic method for the creation of carbon-heteroatom bonds. Due to the importance of amine, enamine and imine containing motifs in bulk chemicals and biologically active compounds, particular attention has been given to hydroamination reactions (addition of nitrogen nucleophiles to unsaturated carbon-carbon bonds).[66]

Hydroamination reactions are atom-efficient processes that generally use readily available and cheap starting materials, therefore a general catalytic strategy has been highly sought after.[67] Also, direct catalytic hydroamination strategies would have significant benefits over more classical methods to prepare amine containing compounds, including the reduction in the number of synthetic steps required.[68] However, hydroamination reactions pose some tough challenges for catalysis. Strong electron repulsion of the nitrogen atom lone pair and the electron rich carbon-carbon multiple bond, coupled with hydroamination reactions being entropically disfavoured (particularly the intermolecular version),[69] results in a large reaction barrier. Regioselectivity issues also hamper the synthetic utility of the resulting products, with Markovnikov addition of the amine being the most common outcome over the less favoured *anti*-Markovnikov addition (Scheme 34).

Due to the synthetic challenges that are associated with hydroamination reactions, the synthetic community has shown ever increasing interest in this field, particularly during the last decade.



Scheme 34. General scheme of a transition-metal catalysed alkyne hydroamination reaction showing the possible Markovnikov and *anti*-Markovnikov addition of the amine.

As a result, there are now numerous catalysts that can be utilised in the hydroamination of alkene, allene and alkyne substrates, including various metal based heterogeneous catalysts, early-transition metal complexes (e.g. titanium and zirconium), late-transition metal complexes (e.g. ruthenium and palladium), lanthanide and actinide complexes (e.g. samarium and lanthanium), as well as Brønsted acids and bases.[70] Due to the breadth of the field, this introduction will focus on the developments made in alkyne hydroamination reactions using late-transition metal complexes and gold complexes because of their relevance to the work presented in this thesis.

1.3.2 Transition Metal Activation of Alkynes

The alkyne functionality consists of two carbon atoms that are joined together by a triple bond (Figure 3). The two carbon atoms each have one sp hybridised orbital to form a σ-bond, whilst the remaining p-orbitals of the carbon atoms overlap to form two π-bonds. With the alkyne triple bond being very electron-rich, alkynes undergo a variety of electrophilic addition reactions. However, alkynes can also be activated towards nucleophilic addition by their interaction with a variety of metal complexes. The bonding interaction of a metal and a ligand in an organometallic complex is most simply described using the Dewar-Chatt-Duncanson (DCD) model.[71]

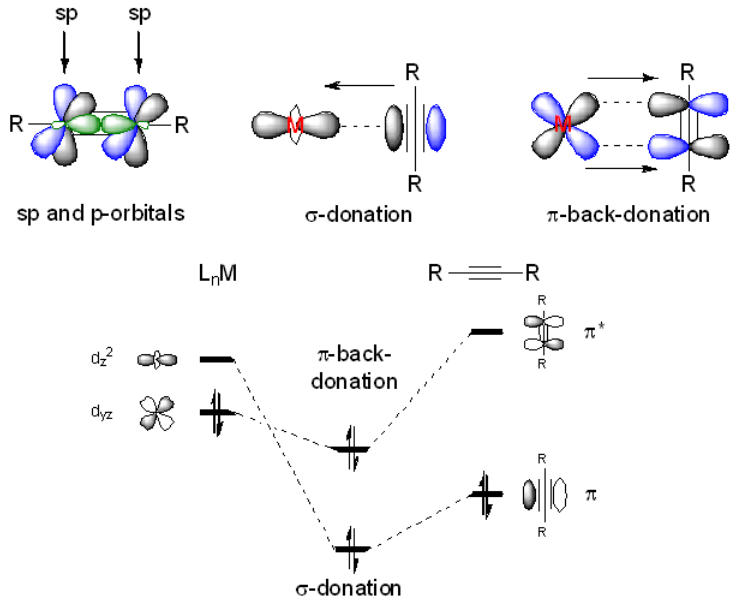


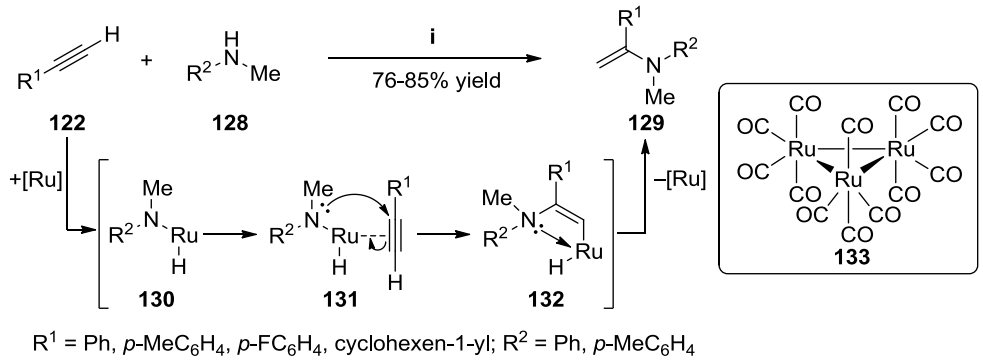
Figure 3. Orbital overlap in an alkyne and the Dewar-Chatt-Duncanson model showing σ-donation and π-back-donation interactions of an alkyne with a transition metal.

Essentially the DCD model has two key principles to describe the bonding in an organometallic complex: ligand to metal σ-donation and metal to ligand π-back-donation. When the ligand in question is an alkyne, the model can be described more accurately (Figure 3). Firstly, σ-donation arises from the donation of electrons from a filled π-orbital of the alkyne into an empty d-orbital of the transition metal. Secondly, π-back-donation arises from the donation of electrons from a filled metal d-orbital into the π* *anti*-bonding orbital of the alkyne. Overall, these interactions result in the removal of electron density from the alkyne into the d-orbitals of the transition metal, thus making the alkyne more susceptible to nucleophilic attack.

1.3.3 Late-Transition Metal Catalysed Alkyne Hydroamination Reactions[a]

1.3.3.1 Intermolecular Hydroamination Reactions

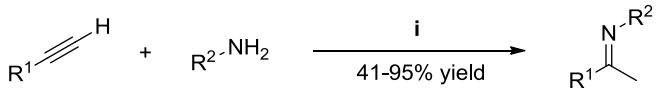
An early example of a ruthenium catalysed intermolecular alkyne hydroamination was reported by Uchimaru in 1999 (Scheme 35).[72] Ruthenium complex **133** was found to catalyse the Markovnikov addition of amines **128** to terminal alkynes **122** when heated to 75 °C, affording substituted enamine products **129** in good yields. Although the alkyne tolerated aryl and alkyl substituents, the reaction only gave good yields when using amines **128**, with the reaction of aniline and phenylacetylene giving less than 5% yield of the corresponding enamine. Based on this result, the reaction was proposed to proceed via ruthenium insertion into the nitrogen-hydrogen bond. Species **130** then binds to the alkyne, activating it towards the attack of the amine lone pair. Finally, protodemetallation furnishes enamine **129** and the ruthenium complex **133**.



Scheme 35. Uchimaru's ruthenium catalysed hydroamination of terminal alkynes **122** with amines **128**. Reagents and conditions: i) complex **133** (5 mol%), 75 °C, 18 h.

Around the same time as the report by Uchimaru, Wakatsuki and co-workers reported that the combination of complex **133** and a strong acid (e.g. HBF_4) catalysed the intermolecular addition of substituted amines **27** to terminal alkynes **122** furnishing the Markovnikov imine products **134** (Scheme 36).[73]

[a] In this section 'late-transition metal' refers to all late-transition metals except gold.



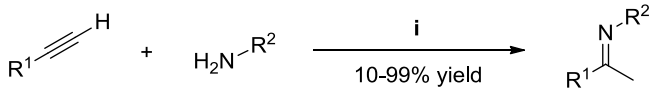
122 **27** **134**

R^1 = Ph, *n*Hex, CH_2OMe; R^2 = Ph, *p*-$MeOC_6H_4$, *p*-ClC_6H_4, *p*-$MeCOC_6H_4$

Scheme 36. Wakatsuki's intermolecular alkyne hydroamination using substituted amines **27**. Reagents and conditions: i) complex **133** (0.1-1 mol%), NH_4PF_6 or HBF_4, 100 °C, 3-12 h.

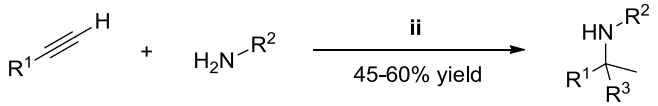
The authors reported that their catalytic system significantly improved the results with substrates that gave very poor yields using Uchimaru's conditions. The reaction could also be conducted without any solvent and an inert atmosphere was not required. However, aliphatic substituted alkynes were considerably less reactive than those bearing aryl substituents.

In 2001, Beller and co-workers reported the first intermolecular alkyne hydroamination using a rhodium complex (Scheme 37).[74] The reaction involved the addition of substituted amines **27** to alkynes bearing one substituent. The reaction proceeded smoothly at RT, affording the corresponding Markovnikov imine products **134** in up to 99% yield. The synthetic utility of this hydroamination reaction was also demonstrated with the development of a one-pot amine synthesis.



122 **27** **134**

R^1 = *n*Hex, Ph; R^2 = Ph, *o*-MeC_6H_4, *p*-MeC_6H_4, *p*-$MeCOC_6H_4$, *m*-FC_6H_4, *p*-ClC_6H_4



122 **27** **135**

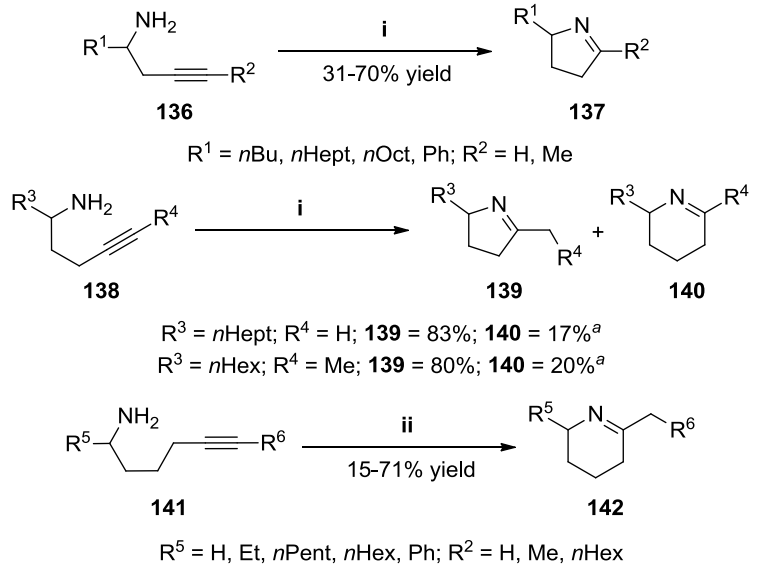
R^1 = *n*Bu, *n*Hex; R^2 = Ph, *p*-MeC_6H_4; R^3 = Me, *n*Bu, Ph

Scheme 37. Beller's rhodium catalysed intermolecular hydroamination of alkynes. Reagents and conditions: i) $[Rh(cod)_2]BF_4$ (1-2.5 mol%), PCy_3 (3-7.5 mol%), PhMe, RT, 20-44 h; ii) $[Rh(cod)_2]BF_4$ (1.5 mol%), PCy_3 (4.5 mol%), PhMe, RT, 20 h then R^3Li.

Because the imine products **134** are formed without the elimination of H_2O, the authors envisaged that an organometallic reagent could be added to the imine after the initial hydroamination reaction has reached completion. Accordingly, a range of organolithium reagents were added to the reaction mixture after the hydroamination reaction and the desired amines **135** were afforded in moderate yields. This provides a useful and resource efficient method for the synthesis of substituted amines.

1.3.3.2 Intramolecular Hydroamination Reactions

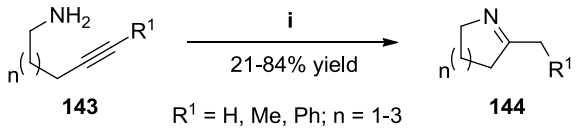
In 1991, Utimoto and co-workers reported an intramolecular hydroamination reaction catalysed by a palladium complex (Scheme 38).[75] In this report, the cyclisation mode of amino tethered alkynes with varying carbon chain lengths was studied. The aminoalkynes **136** were found to react exclusively via a *5-endo-dig* cyclisation, affording cyclic imines **137** in moderate to good yields after an *exo/endo* isomerisation reaction.



Scheme 38. Utimoto's palladium catalysed intramolecular hydroamination reaction. Reagents and conditions: i) $PdCl_2(MeCN)_2$ (2.5 mol%), $MeCN/H_2O$, reflux, 5-10 h; ii) $PdCl_2(MeCN)_2$ (2.5 mol%), MeCN or EtCN, reflux, 20 h. [a] Yields were determined by ^1H NMR analysis.

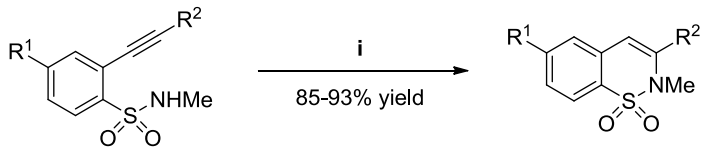
The hydroamination of aminoalkynes **138** resulted in a mixture of 5-membered imines **139** and 6-membered imines **140**, with the reaction favouring the 5-membered ring product. The cyclisation of aminoalkynes **141** only proceeded via a *6-exo-dig* mechanism to afford 6-membered imines **142** in moderate yields. The reaction tolerated a range of alkyl substituents on the alkyne terminus and in the α-position of the amine. Two aryl substituted derivatives were also described.

In 2001, Mitsudo and co-workers reported their investigations into ruthenium catalysed intramolecular hydroamination reactions of amine tethered alkynes **143** (Scheme 39).[76] The cyclisation was *exo* selective, affording 5-, 6- and 7-membered heterocycles **144** after an *exo/endo* isomerisation reaction, resulting in the formation of an imine. The intramolecular hydroamination of aminoalkynes **143** has also been studied using rhodium[77] and copper complexes.[78]



Scheme 39. Mitsudo's intramolecular hydroamination of amine tethered alkynes **143**. Reagents and conditions: i) complex **133** (2.5 mol%), dimethoxyethane, 110-140 °C, 4 h.

In 2007, Pal and co-workers disclosed that $AgSbF_6$ was an efficient catalyst in the intramolecular hydroamination of alkynyl sulfonamides **145** (Scheme 40).[79] The hydroamination reaction proceeded exclusively through a *6-endo-dig* mechanism, affording the desired products **146** in excellent yields for a range of alkyl and aryl substituted alkyne substrates. During the optimisation study of the cyclisation reaction, silver salts were found to significantly reduce the time of the hydroamination reaction compared to the same reaction using copper salts, even with increased temperatures.



145 **146**

R^1 = F, Me; R^2 = *n*Pent, *n*Hex, $(CH_2)_3Cl$, $(CH_2)_2Ph$, $(CH_2)_3CN$, $(CH_2)_3OH$

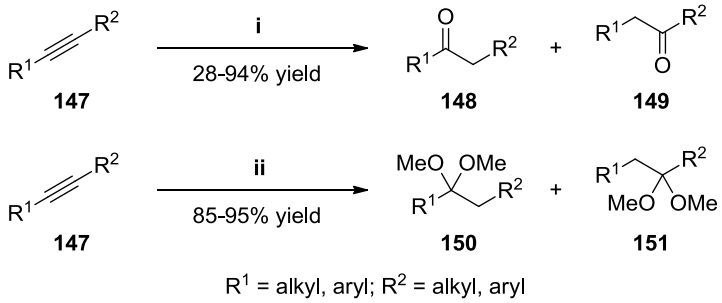
Scheme 40. Pal's silver catalysed intramolecular alkyne hydroamination of alkynyl sulfonamides **145**. Reagents and conditions: i) $AgSbF_6$ (15 mol%), Et_3N (3 equiv), EtOH, 80 °C, 5 min.

1.3.4 Gold Catalysed Alkyne Hydroamination Reactions

1.3.4.1 Early Examples of Gold Catalysis

Catalytic reactions conducted with gold complexes have seen a dramatic rise to prominence over the last decade, with an ever increasing myriad of new reactions being reported that use the mild and efficient catalytic properties associated with gold complexes.[80]

The first reports of reactions using gold catalysis were made by Thomas and co-workers in the 1970s. In these reports, the authors described their findings into the gold catalysed addition of H_2O to unactivated alkenes[81] and alkynes.[82] In 1985, Hutchings reported that supported gold(III) catalysts efficiently facilitated the hydrochlorination of ethyne, affording vinyl chloride.[83] This disclosure demonstrated that gold catalysis could have a dramatic effect on organic chemistry in general, as well as large scale industrial processes, as gold(III) complexes could replace the highly toxic mercury(II) complexes that were previously used in the hydrochlorination of ethyne. After this report, the interest in gold catalysis started to gain momentum, with the seminal work of Utimoto and co-workers into gold catalysed alkyne hydroamination[84] and hydroalkoxylation[85] reactions (Scheme 41) demonstrating the utility of homogeneous gold catalysis.



Scheme 41. Utimoto's hydroalkoxylation of alkynes using $Na[AuCl_4]$. Reagents and conditions: i) $Na[AuCl_4]$ (2 mol%), $MeOH/H_2O$ (10:1), reflux, 1-10 h; ii) $Na[AuCl_4]$ (2 mol%), MeOH, reflux, 1-10 h.

However, it was not until 1998, when Teles and co-workers reported the hydroalkoxylation of unactivated alkynes using a gold(I) phosphine complex,[86] that the field of gold catalysis started to gain mainstream interest from the synthetic community.[80]

1.3.4.2 Characteristics of Gold Catalysts

Gold complexes exhibit various properties that govern their interesting catalytic activity. Originally, Lewis defined an acid as a chemical entity that is capable of accepting a pair of electrons.[87] Some years later, Pearson described the concept of *hard* and *soft* (Lewis) acids and bases (HSAB) in a series of publications.[88] He defined a *hard* Lewis acid as a chemical entity that has a small ionic or atomic radius, resulting in a highly charged and weakly polarisable species. In contrast, a *soft* Lewis acid has a large ionic or atomic radius, resulting in a lowly charged and strongly polarisable species. Based on this definition, gold(I) and gold(III) complexes are termed as *soft* Lewis acids along with many other late-transition metal cations (Figure 4). Using these concepts, the reactivity profiles of many metal cations can be accurately predicted.

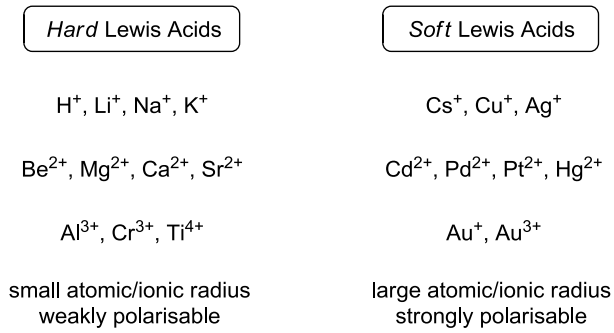


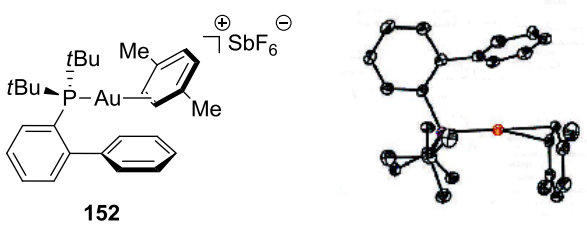
Figure 4. Examples of *hard* and *soft* Lewis Acids.

The electronic configuration of elemental gold also provides valuable insight into its chemical reactivity. As with the other transition metals present in the sixth period of the periodic table, gold displays "relativistic effects".[89,90] The term "relativistic effects" relates to the behaviour that is caused when the electrons in an atom are travelling at very high velocity (close to the speed of light). This typically occurs in elements that have large atomic radii and high atomic masses. By modifying the Schrödinger equation the relativistic effects can be considered, resulting in a more realistic description of the electron orbitals in an element. Regarding the electron orbitals of gold, the relativistic effects cause two main changes in the orbital structure, which have a profound effect on its reactivity.

1. Contraction of the 6s and 6p orbitals: This causes the bond strength between the metal centre and a ligand to increase. It also results in the greater Lewis acidity of cationic gold(I) complexes compared to other group 11 transition metals. Additionally, the electronegativity of gold is exceptionally high (2.5), with it being more electronegative than carbon (2.4).[91] As a result, a C-Au bond essentially has no significant dipole moment.
2. Expansion of the 5d orbitals: This causes the electron cloud in gold to increase in size, leading to a reduction in the electron-electron repulsions. A

consequence of this effect is that the first ionisation energy of gold is very high (9.22 eV).[92]

The above effects result in the high π-acidity exhibited by gold complexes. This is the ability of gold to interact with π-electron clouds, predominantly in alkyne functionalities but also in alkenes and allenes. These interactions are now well known and have been proven by single crystal X-ray diffraction analysis of several gold complexes. Complex **152** is just one example showing the bond between the gold atom and the π-electron species (Figure 5).[93]



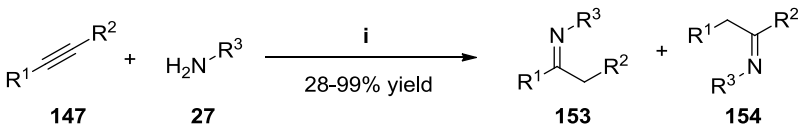
152

Figure 5. Ortep plot (shown at 50% probability) of the cationic part of complex **152**. The hydrogen atoms have been omitted for clarity.[93]

Toste and Shapiro used density functional theory (DFT) calculations to determine the bonding interactions in gold(I) alkyne complexes.[94] They determined that the π-to-metal σ-donation interaction is 56.6 Kcal/mol and this is accompanied by a metal-to-π* back donation interaction of 13.3 Kcal/mol. The value of the π-to-metal σ-donation was the largest value for the gold alkyne complex when compared to similar copper and silver complexes, demonstrating the superior Lewis acidity of gold complexes compared to other Lewis acidic metals.

1.3.4.3 Gold Catalysed Intermolecular Alkyne Hydroamination Reactions

The first intermolecular gold catalysed alkyne hydroamination reaction was reported in 2003 by Tanaka and co-workers (Scheme 42).[95] The Markovnikov addition of amines **27** to a variety of aryl and alkyl substituted alkynes **147** occurred to afford imines **153** after tautomerisation of the resulting enamine. The reactions occurred smoothly at 70 °C in the presence of $Au(PPh_3)Me$ and the acidic activating agent $H_3PW_{12}O_{40}$. The catalyst loadings reported were very low, with as little as 0.01 mol% of $Au(PPh_3)Me$ and 0.05 mol% of $H_3PW_{12}O_{40}$ being able to result in good yields of imine **153**. Although the reaction was highly regioselective towards imine **153**, there were four examples where the formation of imine **154** was observed.



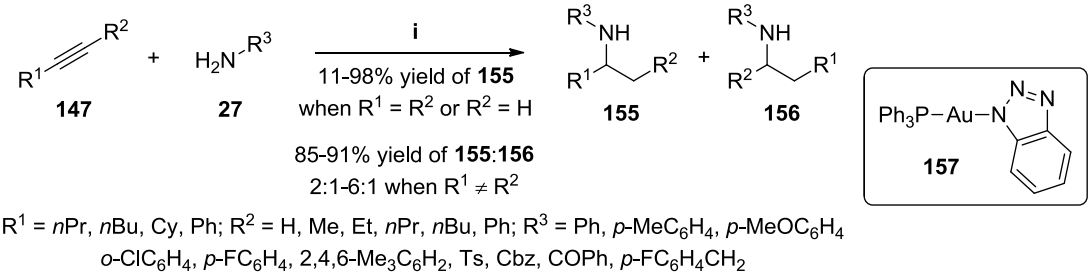
147 **27** **153** **154**

R^1 = *n*Pr, *n*Hex, Ph, *p*-FC_6H_4, *p*-BrC_6H_4, *p*-$MeOC_6H_4$; R^2 = H, Me *n*Pr, *n*Hex
R^3 = Ph, *p*-BrC_6H_4, *p*-NCC_6H_4, *p*-$NO_2C_6H_4$, 2,4,6-$Me_3C_6H_2$, *p*-$MeOC_6H_4$, C_6H_5NH

Scheme 42. Tanaka's gold catalysed intramolecular hydroamination of amines **27** to alkynes **147**. Reagents and conditions: i) $Au(PPh_3)Me$ (0.01-0.5 mol%), $H_3PW_{12}O_{40}$ (0.05-1 mol%), 70 °C, 0.25-24 h.

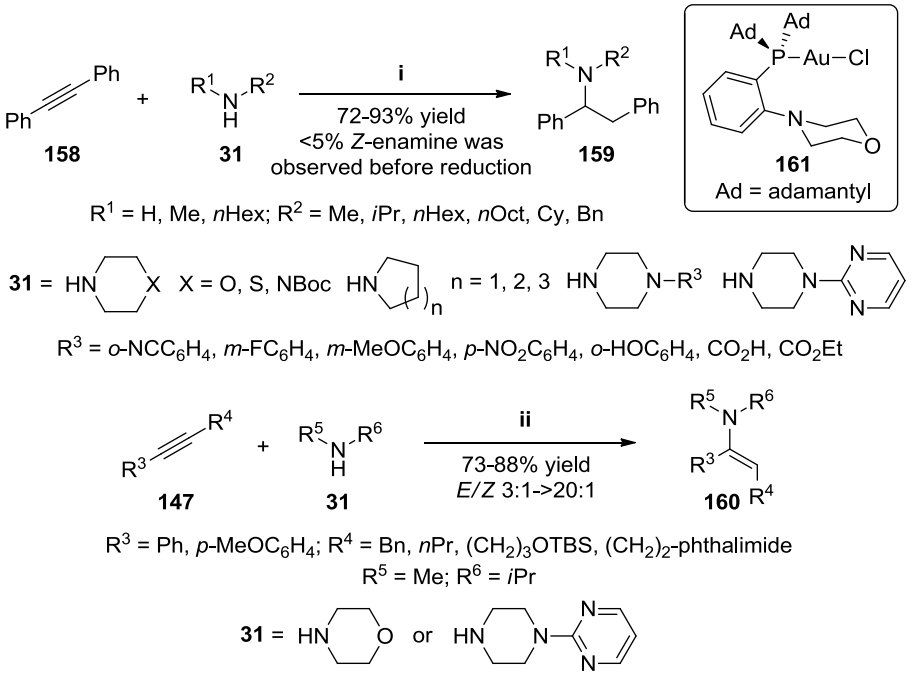
Since the seminal work of Tanaka, new and improved methods for intermolecular gold catalysed alkyne hydroaminations have been reported. In 2009, Shi and co-workers reported a new class of gold(I) catalysts for the intermolecular hydroamination of alkynes (Scheme 43).[96] Gold(I) complex **157**, containing a benzotriazole ligand, used in conjunction with $H_3PW_{12}O_{40}$ was found to give superior isolated yields of amines **155** (after in situ reduction of the corresponding imine) compared to previous reports. The reaction was highly regioselective, with the Markovnikov products **155** being formed exclusively when R^2 = H in alkyne **147**. When the alkynes were unsymmetrical ($R^1 \neq R^2$), mixtures of amines **155** and **156**

were afforded in good yields with moderate regioselectivities (2:1-6:1). An improved substrate scope was also presented, with a range of amines being tolerated, along with examples of sulfonamides, carbamates and amides being appropriate substrates for the reaction.



Scheme 43. Shi's intermolecular alkyne hydroamination using gold complex **157**. Reagents and conditions: i) complex **157** (0.1-10 mol%), $H_3PW_{12}O_{40}$ (0.2-10 mol%), PhMe, 80 °C then BH_3·THF, *o*-phthalic acid, –20 °C - RT over 2 h.

In 2010, Stradiotto and Hesp reported the intermolecular hydroamination of substituted alkynes with aliphatic amines using gold complex **161** with $Ag[B(C_6F_5)_4]$ (Scheme 44).[97]

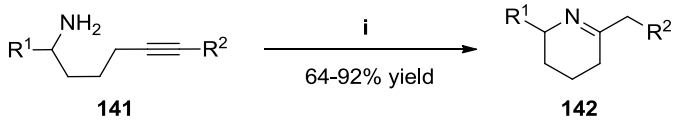


Scheme 44. Stradiotto's gold catalysed intermolecular alkyne hydroamination using gold complex **161**. Reagents and conditions: i) complex **161** (2.5 mol%), $Ag[B(C_6F_5)_4]$ (2.5 mol%), PhMe, 110 °C then $NaBH(OAc)_3$, AcOH and CH_2Cl_2 or $LiAlH_4$ and Et_2O; ii) complex **161** (5 mol%), $Ag[B(C_6F_5)_4]$ (5 mol%), PhMe, 110 °C, 16 h.

When using the symmetrical alkyne **158**, a wide variety of cyclic and acyclic aliphatic amines efficiently reacted to afford the desired amine products **159** in good to excellent yields, after in situ reduction of the obtained enamine. In all of these cases, less than 5% of the *Z*-enamine was observed before the in situ reduction reaction. The authors then studied the intermolecular hydroamination of non-symmetric alkynes **147**. In these examples, no in situ reduction was conducted, allowing the enamine products **160** to be isolated. The reaction was generally found to be highly regioselective towards the *E*-enamine, however some examples only showed moderate selectivity.

1.3.4.4 Gold Catalysed Intramolecular Alkyne Hydroamination Reactions

The first gold catalysed intramolecular hydroamination reaction was reported by Utimoto and co-workers in 1987 (Scheme 45).[84] Building on the work of Thomas and Hutchings,[82,83] Utimoto found that $Na[AuCl_4]$ is a suitable catalyst for the intramolecular hydroamination of substituted aminoalkynes **141**. The reactions proceeded via a selective *6-exo-dig* cyclisation followed by an alkene isomerisation reaction to afford cyclic imines **142** in good yields. When conducting the reaction in refluxing acetonitrile, the reaction was usually complete with in 1-2 h, where-as the reaction needed extended times (12 h) when conducted at room temperature.



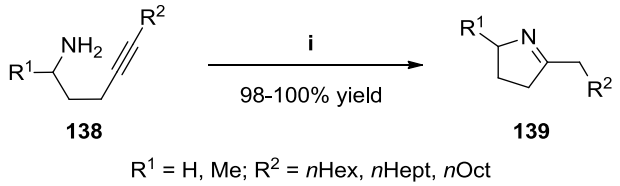
141 **142**

R^1 = H, Me, *n*Hex, $(CH_2)_{10}CH_3$; R^2 = H, Et, *n*Pent, *n*Hex, $(CH_2)_2CH{=}CH_2$, Ph

Scheme 45. Utimoto's gold catalysed intramolecular alkyne hydroamination to 6-membered cyclic imines **142**. Reagents and conditions: i) $Na[AuCl_4]$ (5 mol%), MeCN, reflux.

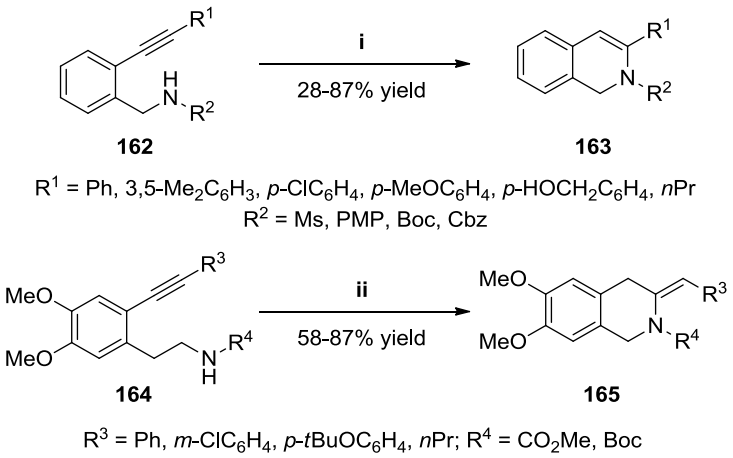
Utimoto and Fukuda later conducted a study into the gold catalysed hydroamination of aminoalkynes **138** (Scheme 46).[98] Using the same conditions as in their earlier

report into 6-membered ring systems enabled the highly efficient synthesis of 5-membered cyclic imines **139** in excellent yields. However, the scope of the reaction was very limited, with only examples featuring straight chained aliphatic substituents being reported. Several reports of gold catalysed intramolecular alkyne hydroamination reactions followed the seminal work of Utimoto. But significant advancements were not made in this reaction until relatively recently.



Scheme 46. Utimoto's gold catalysed intramolecular alkyne hydroamination to 5-membered imines **139**. Reagents and conditions: i) $Na[AuCl_4]$ (5 mol%), MeCN, reflux.

In 2008, Takemoto and co-workers reported their investigations into the synthesis of hydroisoquinolines via *6-endo-dig* and *6-exo-dig* alkyne hydroamination reactions (Scheme 47).[99] The phenyl linked aminoalkynes **162** were found to undergo a *6-endo-dig* cyclisation when exposed to a catalytic combination of $Au(PPh_3)Cl$ and $AgNTf_2$, affording 1,2-dihydroisoquinolines **163**. A variety of nitrogen protecting groups was tolerated, including the sterically demanding *N*-Boc and *N*-Cbz groups. A range of substituted phenyl groups and an alkyl chain were also accommodated on the terminus of the alkyne. The intramolecular cyclisation of phenyl linked aminoalkynes **164** bearing an extended carbon chained was then studied. Using the same catalytic system, the aminoalkynes **164** efficiently cyclised via a *6-exo-dig* hydroamination reaction, furnishing 1,2,3,4-tetrahydroisoquinolines **165** containing an *exo*-alkene. Good yields were obtained in this reaction for aryl and alkyl substituted alkynes and carbamate protected amines.



162 **163**

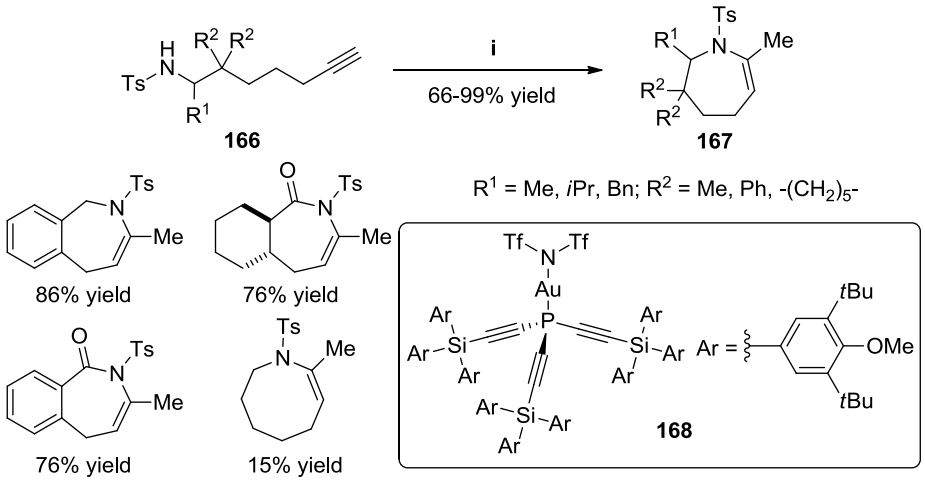
R^1 = Ph, 3,5-$Me_2C_6H_3$, *p*-ClC_6H_4, *p*-$MeOC_6H_4$, *p*-$HOCH_2C_6H_4$, *n*Pr
R^2 = Ms, PMP, Boc, Cbz

164 **165**

R^3 = Ph, *m*-ClC_6H_4, *p*-*t*$BuOC_6H_4$, *n*Pr; R^4 = CO_2Me, Boc

Scheme 47. Takemoto's synthesis of 1,2-dihydroisoquinolines **163** via *6-endo-dig* hydroamination and 1,2,3,4-tetrahydroisoquinolines **165** via *6-exo-dig* alkyne hydroamination reactions. Reagents and conditions: i) $Au(PPh_3)Cl$ (1 mol%), $AgNTf_2$ (1 mol%), EtOH (5 equiv), DCE, RT, 0.5-7 h; ii) $Au(PPh_3)Cl$ (3 mol%), $AgNTf_2$ (3 mol%), EtOH (5 equiv), DCE, RT, 5-48 h.

In 2011, Sawamura and co-workers described the gold catalysed *7-exo-dig* hydroamination of sulfonamide protected aminoalkynes **166** to afford protected azepanes **167** after *exo/endo* isomerisation (Scheme 48).[100] Sawamura demonstrated that gold complex **168** containing a bulky phosphine alkynyl ligand gave superior yields in *7-exo-dig* hydroamination compared to other more commonly used gold complexes.



166 **167**

R^1 = Me, *i*Pr, Bn; R^2 = Me, Ph, -$(CH_2)_5$-

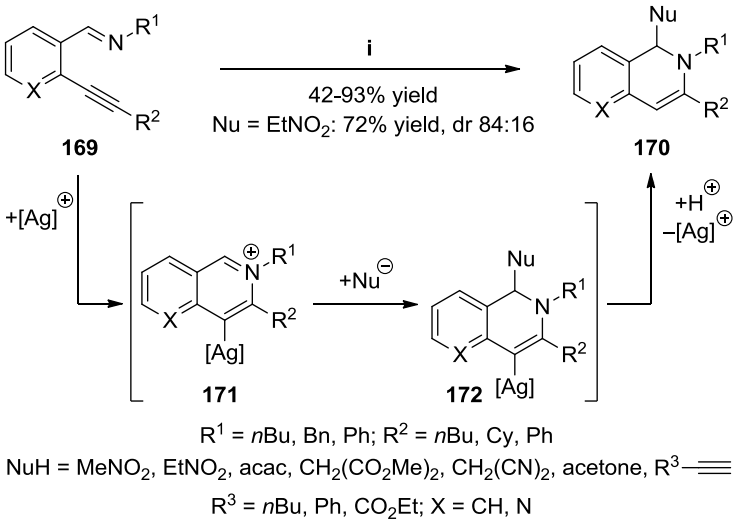
168

Scheme 48. Sawamura's gold catalysed *7-exo-dig* hydroamination to azepane structures. Reagents and conditions: i) complex **168** (2.5-5 mol%), DCE, 80 °C, 4-48 h.

A range of alkyl and aryl substituents on the aminoalkyne starting materials were tolerated, as well as phenyl and cyclohexyl scaffolds. One example of a particularly challenging *8-exo-dig* cyclisation was also disclosed, affording the azocane product in a modest 15% yield, but no examples of cyclisation using substituted alkynes were described.

1.3.5 Cascade Reactions Involving Alkyne Hydroamination Reactions

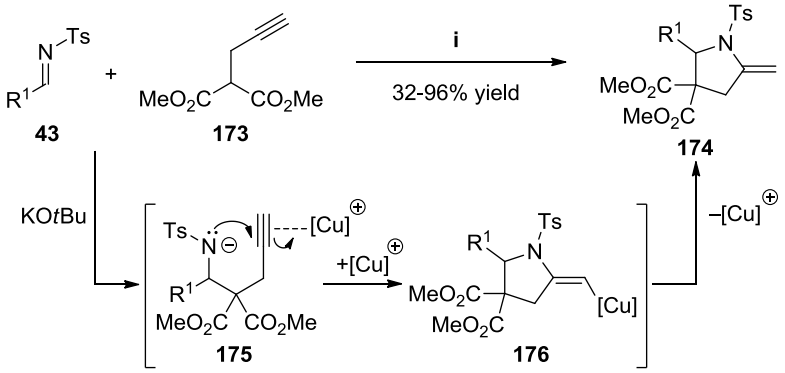
Due to the high utility and atom economy of hydroamination reactions, their incorporation into cascade reactions was seen as very attractive. In 2005, Asao and co-workers reported a silver catalysed hydroamination/nucleophile addition cascade to prepare 1,2-dihydroisoquinolines **170** (Scheme 49).[101] Starting from the imine tethered alkynes **169**, featuring a linking phenyl scaffold, a silver triflate catalysed cyclisation afforded the iminium ion intermediate **171**. Addition of a nucleophilic species to the iminium ion furnished the desired 1,2-dihydroisoquinoline products **170** after a subsequent protodemellation.



Scheme 49. Asao's silver catalysed hydroamination/nucleophile addition cascade to 1,2-dihydroisoquinolines **170**. Reagents and conditions: i) NuH, AgOTf (3 mol%), DCE, 60-80 °C, 6 h.

The range of nucleophiles tolerated in this reaction cascade was particularly impressive, with nitroalkanes, malonates and terminal alkynes all being appropriate nucleophiles, thus leading to the efficient synthesis of structurally diverse dihydroisoquinolines. One example using nitroethane resulted in 72% yield and good diastereoselectivity (dr 84:16).

In 2009, Dixon and co-workers described a Mannich/hydroamination cascade of *N*-sulfonyl imines **43** and propargylated malonate **173** for the synthesis of pyrrolidines **174** (Scheme 50).[8] Using a compatible combination of KO*t*Bu and CuOTf·$^1/_2C_6H_6$, an initial Mannich reaction between imine **43** and malonate **173** gave intermediate **175** which then underwent a *5-exo-dig* cyclisation to afford a range of aryl substituted pyrrolidines in moderate to excellent yields.



R^1 = Ph, *o*-MeC_6H_4, *m*-MeC_6H_4, *p*-MeC_6H_4, *o*-$MeOC_6H_4$, *p*-$MeOC_6H_4$, *o*-FC_6H_4, *p*-NCC_6H_4
o-ClC_6H_4, *m*-ClC_6H_4, *p*-ClC_6H_4, *p*-$NO_2C_6H_4$, *o*-BrC_6H_4, *p*-BrC_6H_4, 2-furyl, 3-pyridyl, *n*Pr

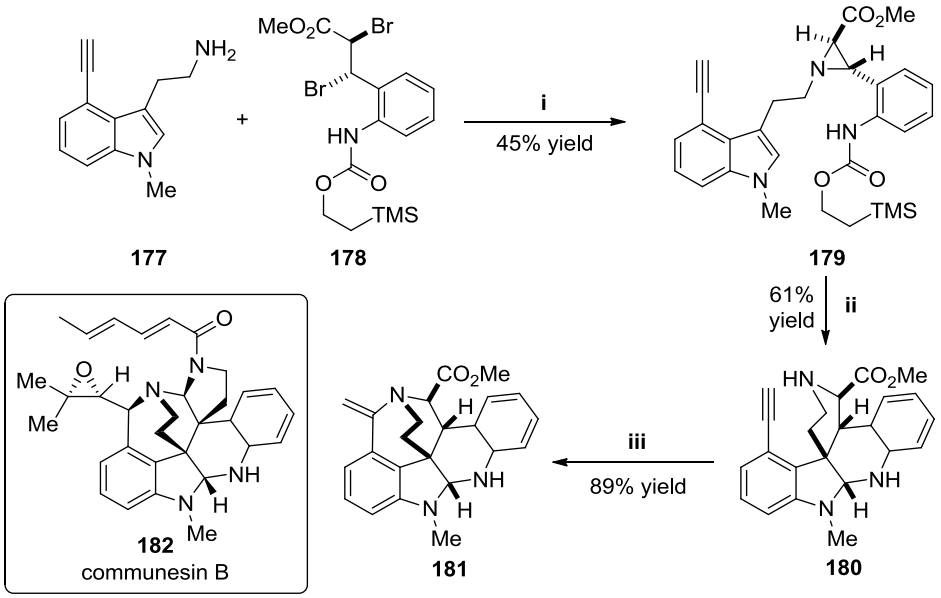
Scheme 50. Dixon's Mannich/hydroamination cascade to substituted pyrrolidines **174**. Reagents and conditions: i) KO*t*Bu (10 mol%), CuOTf·$^1/_2C_6H_6$ (5 mol%), PPh_3 (15 mol%), MeOH, RT, 10-48 h.

A selection of electron-rich and electron-poor aryl substituted imines efficiently underwent the cascade reaction giving good yields of **174**, whereas an *n*Pr substituted imine resulted in a reduction of the isolated yield (32%). No examples using substituted alkynes were reported. Examples of cascade reactions involving gold

catalysed alkyne hydroamination reactions will be discussed in the introduction of Chapter 3.

1.3.6 Alkyne Hydroamination Reactions in Target Synthesis

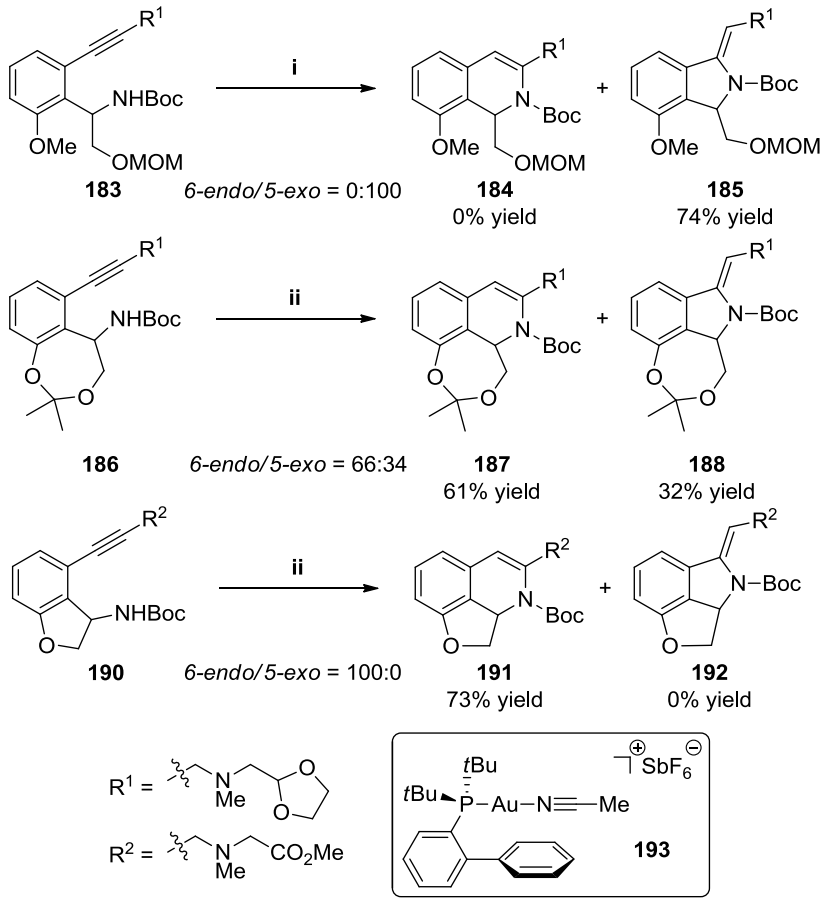
In 2006, Funk and Crawley utilised a gold catalysed alkyne hydroamination reaction to install a complex 7-membered bicyclic motif in the core of communesin B (**182**) (Scheme 51).[102] Using a TBAF deprotection/aziridine ring opening/Diels-Alder cyclisation strategy, compound **179** was converted into the hydroamination precursor **180** in 61% yield. A catalytic system derived from $Au(PPh_3)Cl$ and AgOTf then activated the alkyne functionality towards a *7-exo-dig* cyclisation to afford the complex bicycle **181** in 89% yield.



Scheme 51. Synthesis of the communesin family core structure via a gold catalysed intramolecular alkyne hydroamination reaction. Reagents and conditions: i) Cs_2CO_3, MeCN, 0 °C then RT, 16 h; ii) TBAF, THF, RT, 4 h; iii) $Au(PPh_3)Cl$ (1 mol%), AgOTf (1 mol%), CH_2Cl_2, 40 °C, 12 h.

Very recently, Ohno and co-workers reported the use of a gold catalysed *6-endo-dig* alkyne hydroamination to synthesise the 1,2-dihydroisoquinoline motif found in the core of (–)-quinocarcin (**200**).[103] Knowing that only a selective *6-endo-dig*

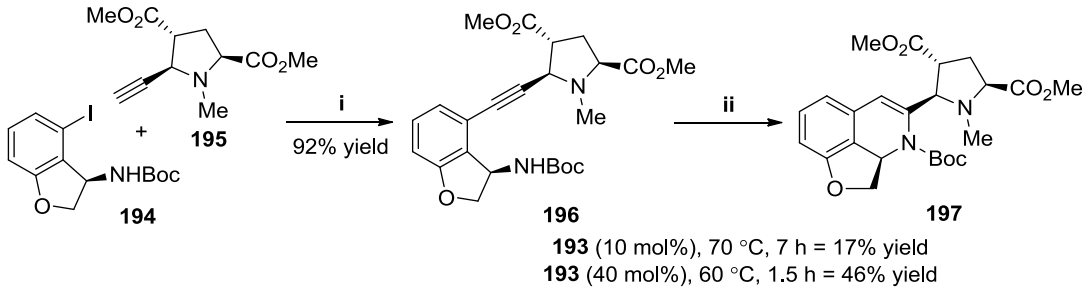
cyclisation would afford the desired 1,2-dihydroisoquinoline, the authors prepared a range of model precursors to study the outcome of the gold catalysed hydroamination reaction (Scheme 52). Substrate **183**, containing a branched *N*-Boc amine side chain, was the first to be tested in the hydroamination reaction. Unfortunately, only the *5-exo-dig* cyclisation product **185** was observed after treatment of substrate **183** with complex **193** in DCE for 12 hours. The cyclisation of substrate **186**, containing a cyclic 7-membered acetal motif, gave improved results with the *6-endo-dig* cyclisation now being favoured over the *5-exo-dig* cyclisation (*6-endo/5-exo* 66:34).



Scheme 52. Ohno's model systems to study the selectivity of the gold catalysed intramolecular alkyne hydroamination reaction. Reagents and conditions: i) complex **193** (5 mol%), DCE, 20 °C, 12 h; ii) complex **193** (5 mol%), DCE, 45 °C, 16 h.

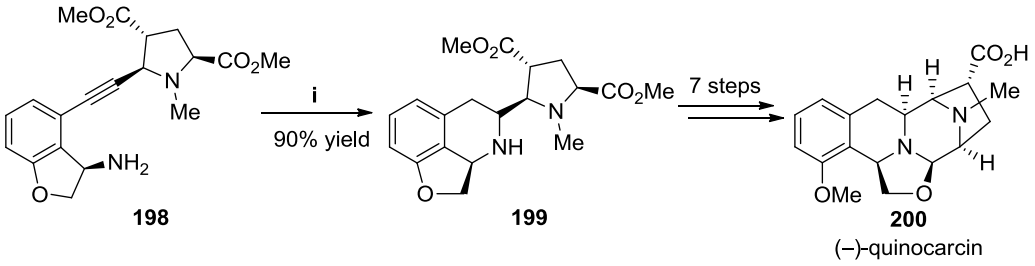
Further modification of the cyclic motif in the starting substrate showed that the cyclic 5-membered ether substrate **190** resulted in excellent *6-endo-dig* selectivity,

with none of the *5-exo* product **192** being observed and the *6-endo* product **191** being isolated in 73% yield. The change in cyclisation selectivity is presumably caused by the increasing bond angle that is accompanied by the introduction of the rigid cyclic side chains. The cyclic 5-membered ether motif **194** was then synthesised and converted into hydroamination substrate **196** via a Sonogashira coupling with alkyne **195** (Scheme 53). The hydroamination substrate **196** was then exposed to the previously optimised conditions. Although the cyclisation reaction was *6-endo-dig* selective, the isolated yield of the cyclised product was only 17%. Increasing the loading of complex **193** to 40 mol% did improve the yield of **197**, but only to 46%.



Scheme 53. Synthesis of hydroamination precursor **196** and initial cyclisation study. Reagents and conditions: i) $Pd(PPh_3)_4$ (15 mol%), $CuSO_4$ (7.5 mol%), sodium ascorbate (30 mol%), DMF/Et_3N (3:2), 80 °C, 4 h; ii) complex **193**, DCE.

Due to the disappointing result in the cyclisation of the *N*-Boc protected precursor **196**, the *N*-Boc protecting group was removed using TFA and the cyclisation was conducted using amine **198** (Scheme 54).



Scheme 54. Ohno's synthesis of (–)-quinocarcin (**200**) using a gold catalysed intramolecular alkyne hydroamination. Reagents and conditions: i) complex **193** (20 mol%), DCE, 45 °C, 1 h then $NaBH_3CN$, MeOH, 1 M HCl, 0 °C.

The hydroamination reaction was still highly *6-endo-dig* selective, affording 1,2,3,4-tetrahydroisoquinoline **199** in a dramatically increased 90% yield after heating at 45 °C for 1 h followed by in situ reduction of the enamine using $NaBH_3CN$. A further 7 synthetic steps then furnished (−)-quinocarcin (**200**).

1.4 Aims of this Thesis

The aim of this thesis was to develop a range of novel cascade reactions that would allow access to a variety of *N*-heterocyclic compounds. To accomplish this, we were going to create cascade reactions that combined a nitro-Mannich reaction with a hydroamination reaction. Simple modifications of the reaction partners would then govern the *N*-heterocycle afforded by the cascade sequence, allowing structurally diverse heterocycles to be prepared.

The following chapters detail the results obtained from our investigations into the synthesis of *N*-heterocycles using nitro-Mannich/hydroamination cascades.

1. Synthesis of 2,5-disubstituted pyrroles via a base and gold catalysed hydroamination cascade.
2. Enantioselective synthesis of substituted 1,2,3,4-tetrahydropyridines using bifunctional organocatalysis and gold catalysis.
3. Diastereo- and enantioselective synthesis of substituted pyrrolidine derivatives using nitro-Mannich/hydroamination cascades.

Chapter 2: Synthesis of Disubstituted Pyrroles via a One-Pot Nitro-Mannich/Hydroamination Cascade

2.1 Introduction

2.1.1 Pyrrole Containing Compounds

Molecules containing the pyrrole heterocycle are recognised to be an important class of biologically relevant compounds due to the attractive properties that they exhibit.[104] Not only is pyrrole found in a myriad of natural products and pharmaceuticals such as (–)-rhazinicine (**202**), atorvastatin (Lipitor®) (**204**) and the axially chiral (–)-marinopyrrole A (**201**) (Figure 6), but also in the porphyrin tetrapyrrole structural motif that constitutes a vital fragment of heme and chlorophyll, making this *N*-heterocycle essential for life.[105] More recently, pyrrole containing molecules have also found extensive use in materials science.[106]

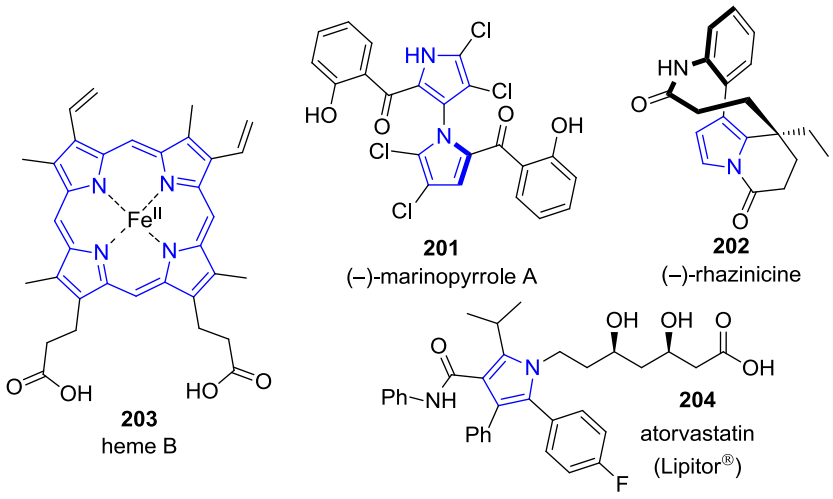
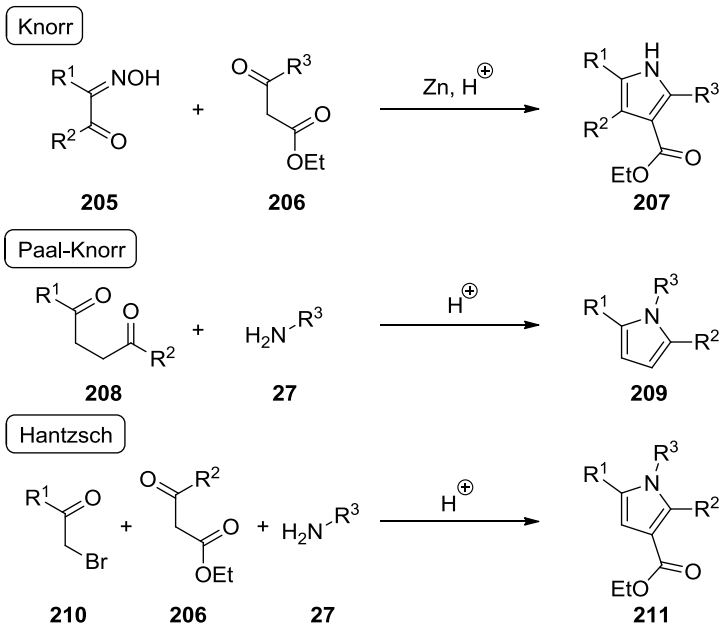


Figure 6. Biologically relevant molecules containing the pyrrole structural motif.

Due to its importance, developing new methods to synthesise the pyrrole motif continues to be of significant interest to the synthetic community. Since the seminal work of Knorr,[107] Paal[108] and Hantzsch[109] (Scheme 55), increasingly elegant methods

to access the pyrrole motif continue to be reported and subsequently utilised in target synthesis, resulting in a number of excellent reviews of the field.[110]



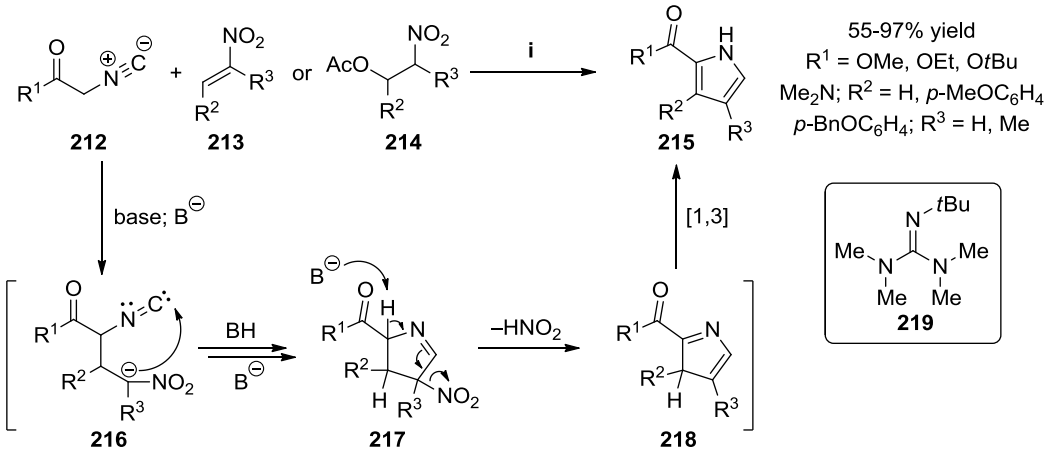
Scheme 55. The Knorr, Paal-Knorr and Hantzsch pyrrole syntheses.

In this introduction to pyrrole synthesis, the most relevant examples relating to our proposed nitro-Mannich/hydroamination cascade methodology will be discussed. This will focus on pyrrole syntheses that use conjugated nitroalkene, nitroalkane or alkyne containing starting materials.

2.1.2 Examples of Pyrrole Synthesis using Nitroalkenes

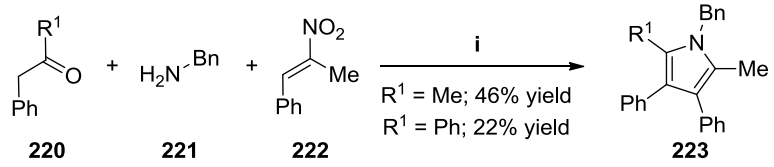
In 1985, Barton and Zard reported a mild and efficient organic base catalysed pyrrole synthesis using isocyanoacetates **212** and nitroalkenes **213** or β-nitroacetate precursors **214** (Scheme 56).[111] In the presence of guanidine **219**, the authors propose that the isocyanoacetate **212** undergoes a Michael addition to nitroalkene **213**, affording intermediate **216**. Cyclisation of the acidic carbon to the isocyano group followed by base catalysed nitrous acid elimination ($-HNO_2$) then results in **218** and a subsequent [1,3] sigmatropic shift furnishes the 2,3,4-trisubstituted pyrrole **215** in

good to excellent yields with a variety of aryl and alkyl substituents. The pyrroles synthesised via this method are particularly useful as they are important precursors to porphyrin ring systems.



Scheme 56. Barton and Zard's pyrrole synthesis using isocyanoacetates **212** and nitroalkenes **213**/β-nitroacetates **214**. Reagents and conditions: i) guanidine **219**, THF/*i*PrOH (1:1), RT-50 °C.

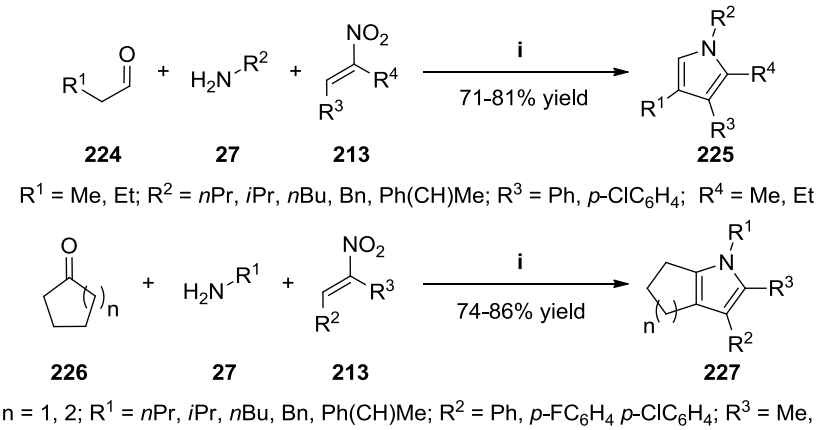
Before the article of Barton and Zard, Meyer reported that pyrroles could be accessed via a three-component cascade reaction of nitroalkene **222**, amine **221** and ketones **220** (Scheme 57).[112] With only two examples synthesised in moderate yields and no mechanistic rationale, this report was not very comprehensive. However, this disclosure demonstrated that the concept of pyrrole synthesis using nitroalkenes, amines and ketones was valid, allowing other researchers to further develop the concept.



Scheme 57. Meyer's pyrrole synthesis using nitroalkenes, amines and ketones. Reagents and conditions: i) EtOH, reflux, 8-15 h.

Ranu and Hajra expanded Meyer's report 20 years later, conducting the reaction in the solid phase using alumina under microwave irradiation (Scheme 58).[113] The

scope of the reaction was also significantly expanded with substituted aldehydes being tolerated as well as alkyl and aryl substituents on the nitroalkene reaction partner. Cyclic ketones could also be employed to furnish pyrroles bearing cyclic substituents in good yields.

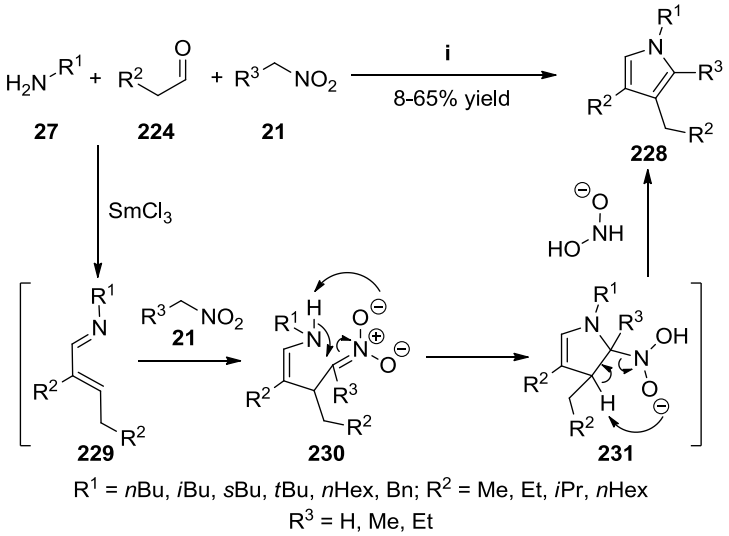


Scheme 58. Ranu and Hajra's solid phase synthesis of substituted pyrroles using nitroalkenes **213** and aldehydes **224** or cyclic ketones **226**. Reagents and conditions: i) Al_2O_3, microwave irradiation 120 W, 13 min.

2.1.3 Examples of Pyrrole Synthesis using Nitroalkanes

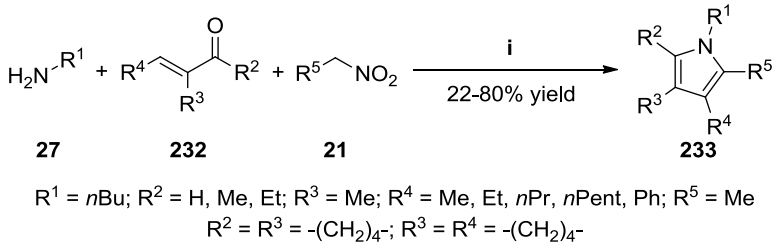
A samarium chloride catalysed three-component coupling of aldehydes, amines and nitroalkanes to afford substituted pyrroles **228** was disclosed by Ishii and co-workers in 1998 (Scheme 59).[114] The key step in this cascade reaction is the samarium catalysed condensation of aldehyde **224** and amine **27** to form the α,β-unsaturated imine **229**. Michael addition of nitroalkane **21** to imine **229** followed by successive intramolecular cyclisation and elimination furnishes the substituted pyrroles **228**. Although the cascade combines three simple and readily available starting materials, the yields obtained are relatively low and the substrate scope is limited exclusively to alkyl substituents. In the same manuscript, Ishii and co-workers also reported that a related three-component coupling of α,β-unsaturated enones **232**, amines **27** and

nitroalkanes **21** resulted in the formation of pentasubstituted pyrroles **233** without the need for an additional catalyst (Scheme 60).



Scheme 59. Ishii's samarium catalysed three-component pyrrole synthesis. Reagents and conditions: i) $SmCl_3$ (5 mol%), THF, 60 °C, 15 h.

One possible explanation for the reaction proceeding without the samarium catalyst is that the initially formed imine (derived from amine **27** and enone **232**) is stabilised due to conjugation with the alkene. This reaction affords the pentasubstituted pyrroles **233** in higher yields than the previously reported synthesis using aldehydes.

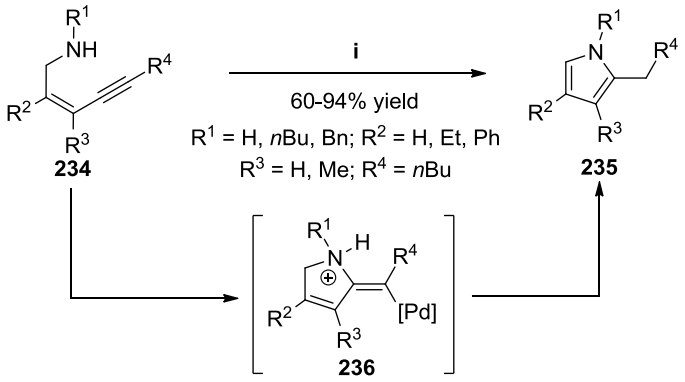


Scheme 60. Ishii's three-component pyrrole synthesis using enones, amines and nitroalkanes. Reagents and conditions: i) THF, 60 °C, 15 h.

Building on Ishii's work, Ranu and co-workers expanded the three-component pyrrole synthesis by conducting it under microwave irradiation using reagents supported on silica gel.[115] Using this method, the authors showed that the isolated yields and scope of the reaction could be improved.

2.1.4 Examples of Pyrrole Synthesis Using Alkyne Hydroamination Reactions

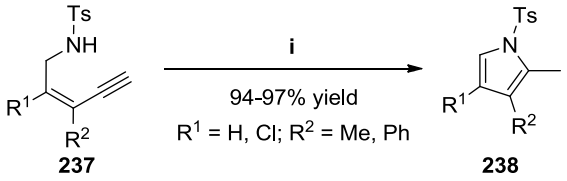
In 2001, Gabriele and Salerno reported a palladium catalysed intramolecular hydroamination reaction of enynamines **234** to afford substituted pyrroles **235** (Scheme 61).[116]



Scheme 61. Gabriele and Salerno's pyrrole synthesis using a palladium catalysed enynamine hydroamination. Reagents and conditions: i) $PdCl_2$ (10 mol%), KCl (20 mol%), DMA, 25-100 °C, 4-6 h.

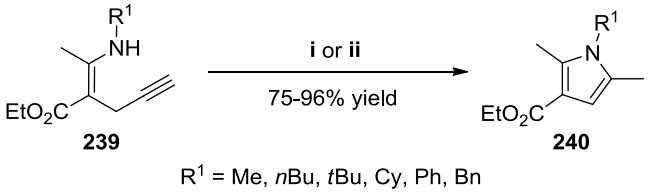
The palladium catalyst activates the alkyne to facilitate nucleophilic attack of the pendant amine forming intermediate **236**. Protodemetallation and aromatisation then furnished a range of pyrroles with alkyl and aryl substituents in good to excellent yields. Additional studies into the conversion of enynamines to pyrrole derivatives showed that copper complexes were equally efficient as palladium complexes at catalysing this process. Improvements in the scope of the reaction were later documented.[117]

During their studies into gold catalysed aza-Claisen-type rearrangements, Istrate and Gagosz reported that substituted *N*-sulfonyl enynamines **237** could be rapidly cyclised to pyrroles **238** at RT using $Au(PPh_3)NTf_2$ (Scheme 62).[118] This reaction uses very mild conditions and affords the pyrrole products in excellent yields after a *5-exo-dig* cyclisation.



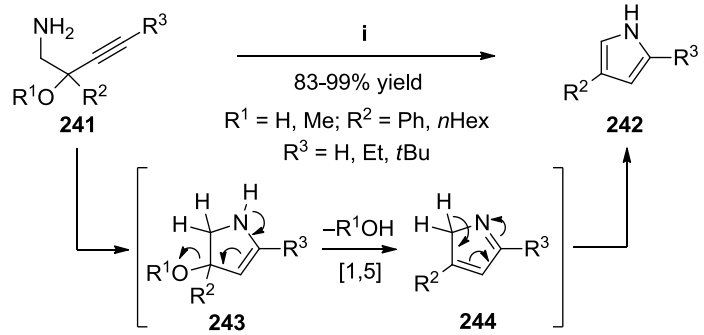
Scheme 62. Istrate and Gagosz's pyrrole synthesis using gold catalysis. Reagents and conditions: i) $Au(PPh_3)NTf_2$ (1 mol%), CH_2Cl_2, RT, 5 min.

In 2004, Dovey and co-workers cyclised substituted propargyl enamines **239** to pyrroles **240** in the presence of $AgNO_3$ (Scheme 63).[119] Following activation of the alkyne by the silver salt, a *5-exo-dig* cyclisation occurs to furnish pyrroles **240**. Alkyl and aryl groups could be substituted onto the nitrogen atom, however no other substituents were varied in this study.



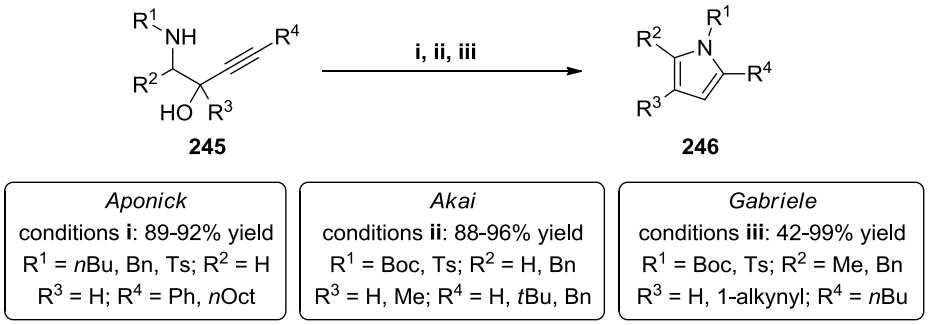
Scheme 63. Dovey's silver nitrate catalysed pyrrole synthesis. Reagents and conditions: i) $AgNO_3$ (20 mol%), MeCN, RT, 16-20 h; ii) $AgNO_3$ (20 mol%), MeCN, MW, 1 min.

In 1981, Utimoto and co-workers described the synthesis of 3,5-disubstituted pyrroles **242** from aminoalkynes **241** via a hydroamination/elimination process (Scheme 64).[120]



Scheme 64. Utimoto's hydroamination/elimination pyrrole synthesis using a palladium catalyst. Reagents and conditions: i) $PdCl_2$ (1-10 mol%), MeCN, reflux.

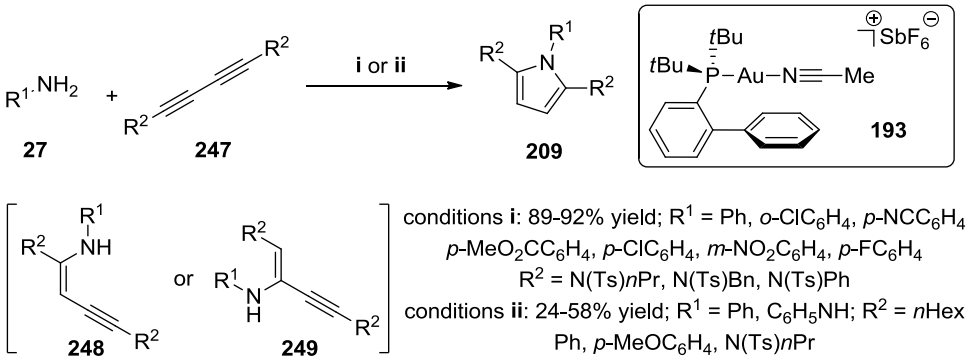
Using a palladium catalyst, Utimoto found that after an initial intramolecular *5-endo-dig* cyclisation of the amine onto the alkyne, the hydroxy or methoxy group present in the 3-position could eliminate from intermediate **243** without the need for a strong base. [1,5] Sigmatropic shift then afforded the pyrrole products in good to excellent yields but with a limited substrate scope. This hydroamination/elimination reaction of aminoalkynes did not receive further attention from the synthetic community until 2009, when it was revisited by the groups of Aponick[121] and Akai[122] who both used gold complexes to efficiently catalyse the reaction under mild conditions, affording pyrroles **246** in excellent yields (Scheme 65). More recently, Gabriele and co-workers demonstrated that $CuCl_2$ could also catalyse this reaction.[123] However, increased reaction times and temperatures (24 h, 80-100 °C) were required to afford the substituted pyrroles in goods yields.



Scheme 65. Gold and copper catalysed hydroamination/elimination reactions for the synthesis of substituted pyrroles **246**. Reagents and conditions: i) Au[P(*t*Bu)$_2$(*o*-biphenyl)]Cl (2 mol%), AgOTf (2 mol%), THF, 4 Å molecular sieves, 0 °C, 10-50 min; ii) Au(PPh$_3$)Cl (0.5 mol%), AgOTf (0.5 mol%), PhMe, RT, 1-9 h; iii) $CuCl_2$ (2-5 mol%), MeOH, 80-100 °C, 1-24 h.

In 2010, Skrydstrup and co-workers reported the synthesis of 2,5-disubstituted pyrroles **209** using a gold catalysed dihydroamination strategy (Scheme 66).[124] Their findings showed that the success of the reaction depended on the regioselective addition of amine **27** to diyne **247** forming intermediate **248**, which allowed a subsequent *5-endo-dig* hydroamination to afford pyrroles **209**. Formation of the

isomeric intermediate **249** led to none of the desired pyrrole product. The authors found that electron rich diynes would cyclise to the pyrrole products in the presence of $Au(PPh_3)NTf_2$ and mild heating. In contrast, deactivated diynes required much harsher conditions to achieve cyclisation, with toluene at 80 °C used in conjunction with complex **193** required for the reaction to proceed to acceptable conversions (56-63% conversion).



Scheme 66. Skrydstrup's dihydroamination pyrrole synthesis using amines **27** and diynes **247**. Reagents and conditions: i) $Au(PPh_3)NTf_2$ (1 mol%), CH_2Cl_2, 30 °C, 30 min; ii) complex **193** (5 mol%), PhMe, 80 °C, 24 h.

Although all of the presented pyrrole syntheses using alkyne hydroamination reactions are efficient and high yielding, they all use relatively complex starting materials that require a number of synthetic steps to prepare or are derived from expensive commercially available starting materials. This reduces the overall versatility and resourcefulness of these methodologies. In addition, the high number of synthetic steps required makes library generation using the discussed methods laborious and time consuming.

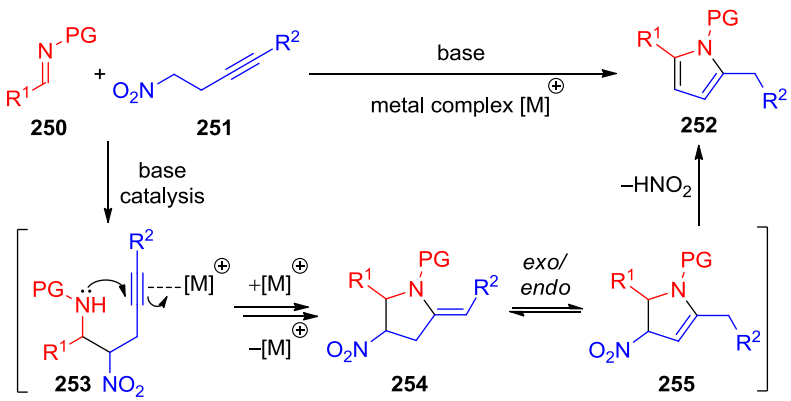
2.2 Project Aims

Due to the importance of the pyrrole heterocyclic motif the development of a new and efficient one-pot cascade methodology to access substituted pyrroles would be an attractive tool for the organic chemistry community. Building on the recent

literature (Introduction, Chapter 2), we postulated that a pyrrole synthesis using a nitro-Mannich/hydroamination cascade of *N*-protected imines and nitroalkyne substrates would be viable when using an appropriate catalyst combination. This newly developed methodology could then be utilised to prepare a range of valuable synthetic intermediates for target synthesis or biological evaluation using starting materials that are easily prepared and relatively cheap.

2.3 Our Concept

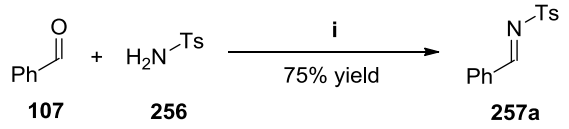
In our proposed concept (Scheme 67), it was envisaged that a suitable *N*-protected imine **250** would undergo a nitro-Mannich reaction with nitroalkyne **251** under base catalysis. This would lead to the formation of β-nitroamine **253** where the resulting amine and alkyne functionalities were poised to react in a *5-exo-dig* intramolecular hydroamination reaction, when the alkyne was activated by an appropriate metal complex. Subsequent protodemetallation of the metal complex would then furnish pyrrolidine **254**. Under the proposed reaction conditions, we further postulated that *exo*/*endo* alkene isomerisation could occur, in turn facilitating elimination of nitrous acid (HNO_2, reminiscent of the Barton-Zard pyrrole synthesis)[111] to afford 2,5-disubstituted pyrrole **252**.



Scheme 67. Proposed one-pot nitro-Mannich/hydroamination cascade for the synthesis of 2,5-disubstituted pyrroles.

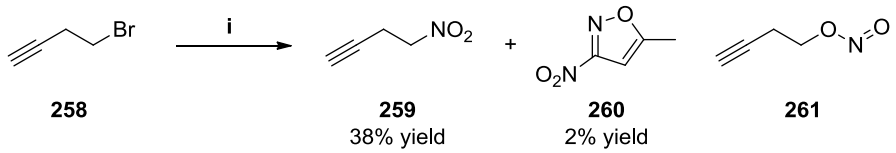
2.4 Synthesis of Starting Materials and Proof of Principle Study

In our initial proof of principle studies, we determined that the main obstacle would be finding a metal complex to facilitate the ring closing hydroamination reaction. To investigate this reaction, we wanted to conduct a step-wise study that required the preparation of a suitably protected β-nitroamine from an imine and the corresponding nitroalkyne substrate. Accordingly, *N*-sulfonyl imine **257a** was selected as a suitable imine for our initial studies and it was easily synthesised on gram scale from benzaldehyde (**107**) and *p*-toluenesulfonamide (**256**) in the presence of tetraethylorthosilicate. After a straightforward purification of the crude product by trituration with Et_2O, *N*-sulfonyl imine **257a** was afforded in 75% yield (Scheme 68).[125]



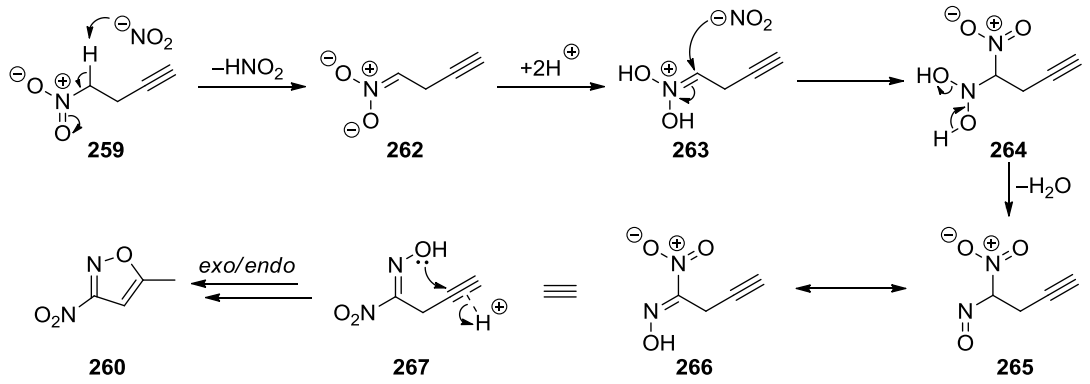
Scheme 68. Synthesis of *N*-sulfonyl imine **257a**. Reagents and conditions: i) tetraethyl-orthosilicate, neat, 170 °C, 3 h.

The nitroalkyne substrate **259** was easily prepared in a moderate 38% yield by treating the commercially available 4-bromobut-1-yne (**258**) with $NaNO_2$ in DMSO at RT (Scheme 69).[126] The moderate yield obtained using this procedure can be attributed to the competing formation of nitrite **261**, however this compound was never isolated.



Scheme 69. Synthesis of nitroalkyne **259** and isolation of isoxazole by-product **260**. Reagents and conditions: i) $NaNO_2$, DMSO, RT, 2 h.

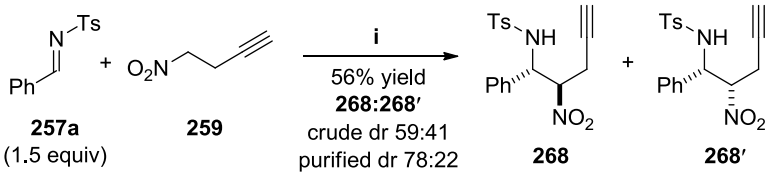
Interestingly, under the reaction conditions employed isoxazole **260** was identified as a by-product of the reaction, being isolated in 2% yield. We suggest that isoxazole **260** is formed by the following mechanism that is reminiscent of a Nef reaction (Scheme 70).[127] Firstly, the excess $NaNO_2$ deprotonates nitroalkyne **259** to form nitronate **262** and HNO_2. The HNO_2 then protonates the oxygen atoms of the nitronate group and $NaNO_2$ adds into the resulting iminium ion species **263** to furnish nitroalkyne **264**. Elimination of water gives *trans*-oxime **266** which then undergoes an acid catalysed *5-exo-dig* cyclisation followed by *exo/endo* alkene isomerisation to afford isoxazole **260**.[128]



Scheme 70. Plausible mechanistic rationale for the formation of isoxazole **260**.

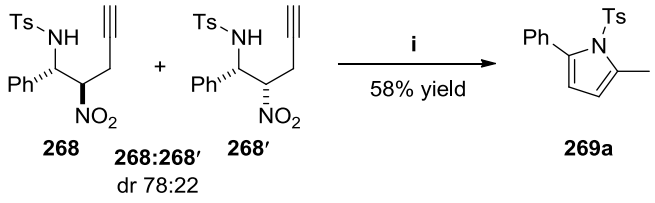
Attempts to replace $NaNO_2$ with $AgNO_2$[129] in the synthesis of nitroalkyne **259** were explored, but none of the desired product was isolated. The most likely explanation for this is that the $AgNO_2$ activates the alkyne functionality resulting in the degradation of either the starting material or product.[130]

With the desired starting materials in hand, *N*-sulfonyl imine **257a** and nitroalkyne **259** were reacted together in the presence of catalytic KO*t*Bu to afford an inseparable mixture of β-nitroamines **268** and **268′** in 56% combined yield and 78:22 dr in favour of the *anti*-diastereomer **268** (Scheme 71).



Scheme 71. Synthesis of β-nitroamines **268** and **268′**. Reagents and conditions: i) KO*t*Bu (5 mol%), THF, RT, 24 h.

The isolated mixture of β-nitroamines **268** and **268′** (dr 78:22) was then subjected to a range of alkynophilic metal complexes to determine if an intramolecular hydroamination reaction to pyrrole **269a** would occur. Gratifyingly, when β-nitroamines **268** and **268′** were exposed to $AuCl_3$ (5 mol%) in THF for 24 hours, the expected cyclisation reaction did occur. Furthermore, the *exo/endo* isomerisation and HNO_2 elimination pathway also proceeded to afford pyrrole **269a** in 58% yield (Scheme 72).



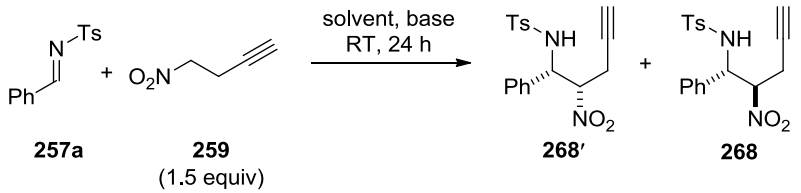
Scheme 72. Proof of principle for a gold catalysed intramolecular alkyne hydroamination of β-nitroamines **268** and **268′**. Reagents and conditions: i) $AuCl_3$ (5 mol%), THF, RT, 24 h.

2.5 Optimisation of the Nitro-Mannich Reaction

With proof of principle obtained, it was decided to optimise each individual step of the cascade reaction before we attempted to develop a one-pot procedure. Firstly, the nitro-Mannich reaction between *N*-sulfonyl imine **257a** and nitroalkyne **259** was further investigated by screening a variety of solvents and bases (Table 1). It was generally observed that increasing the polarity of the solvent improved the yield of β-nitroamines **268** and **268′** when KO*t*Bu was used as the base (Table 1, entries 1-5). The highest isolated yield was obtained when methanol was used as the reaction

solvent, affording β-nitroamines **268′** and **268** in 90% yield and 83:17 dr in favour of the *syn*-diastereomer **268′** (Table 1, entry 5). With methanol identified as the solvent of choice for the nitro-Mannich reaction, several organic bases were also screened to evaluate their efficiency (Table 1, entries 6-9). The nature of the base was found to give moderate variations in the yield (73-93%) and diastereoselectivity (dr 73:27-86:14) of the nitro-Mannich reaction. However, none of the results using the organic bases (Et_3N, DBU, TMG and BEMP) significantly improved on the yield obtained using KO*t*Bu.

Table 1. Optimisation studies in the nitro-Mannich reaction of *N*-sulfonyl imine **257a** and nitroalkyne **259**.



257a **259** (1.5 equiv) **268′** **268**

entry	solvent	base (10 mol%)	dr[a] (**268′**:**268**)	yield[b] (%)
1	THF	KO*t*Bu	52:48	35
2	PhMe	KO*t*Bu	54:46	47
3	CH_2Cl_2	KO*t*Bu	63:37	63
4	MeCN	KO*t*Bu	77:23	75
5	MeOH	KO*t*Bu	83:17	90
6	MeOH	Et_3N	73:27	93
7	MeOH	DBU	82:18	73
8	MeOH	TMG	82:18	78
9	MeOH	BEMP	86:14	84
10[c]	MeOH	—	64:36	56
11[d]	MeOH	—	—	—

[a] Determined by ^{1}H NMR analysis of the crude reaction mixture. [b] Combined yield of both diastereomers. [c] Reaction time of 9 days. [d] Reaction conducted at 70 °C.

Surprisingly, a control reaction showed that the nitro-Mannich reaction proceeded smoothly without any base (Table 1, entry 10). However, the reaction was very slow, affording β-nitroamines **268′** and **268** in 56% yield and 64:36 dr after 9 days at RT. In light of this result, we conducted another control reaction in the absence of any base, but with an elevated temperature in an attempt to increase the reaction rate (Table 1, entry 11). From this reaction no product was isolated after heating at 70 °C for 24 hours. This result was probably due to the retro nitro-Mannich reaction being favoured when the reaction temperature was increased.[24a]

To determine the relative configurations of β-nitroamines **268** and **268′**, we obtained a single crystal of β-nitroamine **268′** suitable for X-ray diffraction analysis. When using methanol as the reaction solvent in the nitro-Mannich reaction (Table 1, entry 4), β-nitroamine **268′** precipitated out of solution, allowing it to be isolated by filtration (dr 95:5). This compound was then recrystallised from CH_2Cl_2 (slow evaporation of CH_2Cl_2) and the resulting X-ray diffraction data confirmed that the relative configuration of β-nitroamine **268′** was *syn* (Figure 7).

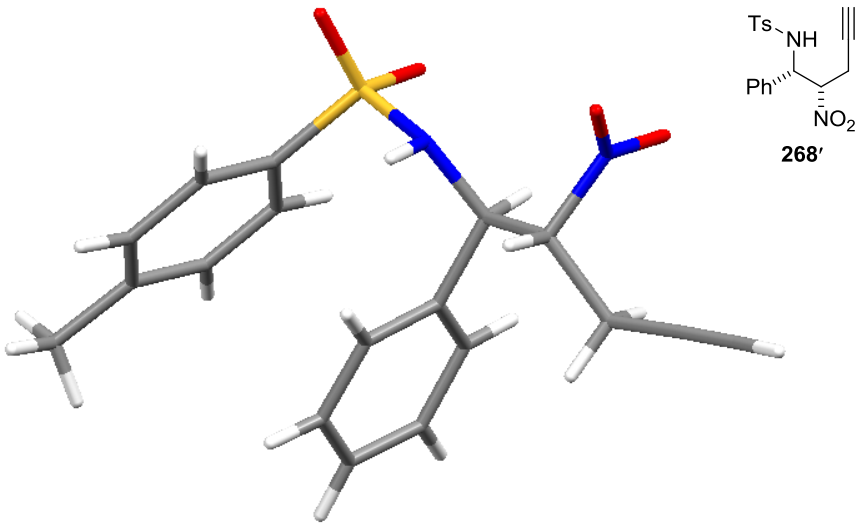
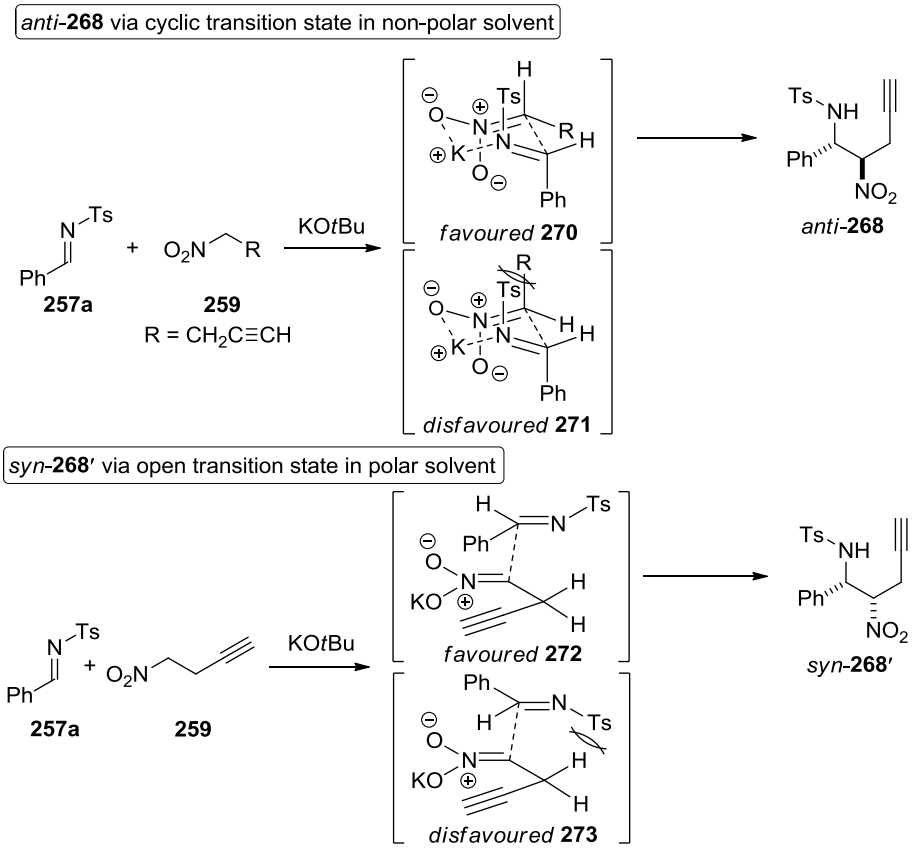


Figure 7. X-Ray diffraction representation of *syn*-β-nitroamine **268′**.

During the nitro-Mannich optimisation studies, it was observed that as the solvent polarity increased, the diastereoselectivity towards the *syn*-diastereomer **268′** also increased. This suggests that there are two different reaction mechanisms occurring which are dependent on the polarity of the reaction solvent. Using a model similar to that proposed by Anderson and co-workers,[131] we propose that the Zimmerman-Traxler[132] like chair transition state **270** of the *anti*-diastereomer **268** becomes more disfavoured as the solvent polarity increases (Scheme 73).



Scheme 73. Proposed origin of *anti*- and *syn*-diastereoselectivity in the nitro-Mannich reaction of *N*-sulfonyl imine **257a** and nitroalkyne **259**.[131]

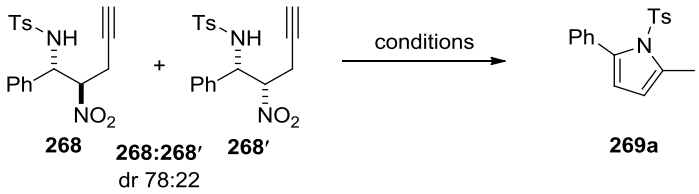
This is due to disruption of the chelating potassium interactions by the polar solvent. As the solvent polarity continues to increase, the disruption of the potassium interactions also increase, allowing the open transition state **272** to be in operation. The *syn* selectivity can be explained by this mechanism, by assuming that the most favoured transition state **272** will minimise the unfavoured steric interaction between

the *N*-sulfonyl protecting group and the nitronate alkyl chain substituent. This can correctly account for the formation of *syn*-β-nitroamine **268′**. The above rationale for the diastereoselectivity matches our experimental data as the highest *syn* selectivity was witnessed when conducting the nitro-Mannich reaction in the polar protic solvent methanol.

2.6 Optimisation of the Hydroamination Reaction

With our initial proof of principle in the hydroamination reaction obtained by treating β-nitroamines **268** and **268′** with $AuCl_3$ in THF (Scheme 72), other reaction conditions were screened in an attempt to further optimise the cyclisation (Table 2). Pleasingly, using $AuCl_3$ in toluene at RT slightly increased the yield of pyrrole **269a** to 68% (Table 2, entry 1). Using gold(I) complexes in conjunction with AgOTf resulted in the formation of the desired pyrrole **269a**, however the previously obtained yield of 68% was not improved upon (Table 2, entries 2 and 3). In contrast, the employment of the Lewis acidic $CuOTf\cdot{}^{1}/_{2}PhMe$, did afford pyrrole **269a** in 29% yield, but only after heating the reaction mixture to 110 °C for 24 hours (Table 2, entry 4). The reduction in reaction rate observed using copper complexes is in line with previously reported results obtained in a similar hydroamination reaction.[123] This difference in reactivity using copper complexes and gold complexes is presumably caused by the differing electron pair acceptance of the alkyne π-bonding electrons into the empty electron orbitals of the copper and gold complexes. Whereas gold complexes exhibit relativistic contraction of the 6s and 6p orbitals (resulting in a relatively low energy LUMO and improved electron pair acceptance), copper complexes do not exhibit such strong relativistic effects and therefore the LUMO is at a much higher energy (resulting in decreased electron pair acceptance).[90]

Table 2. Optimisation of the hydroamination reaction of β-nitroamines **268** and **268′**.

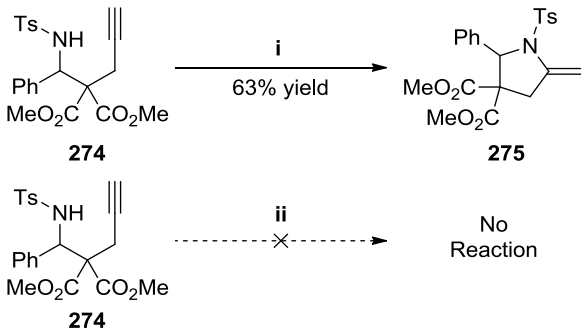


entry	solvent	metal complex (5 mol%)	temp (°C)	time (h)	yield (%)
1	PhMe	$AuCl_3$	RT	24	68
2[a]	PhMe	$Au(PPh_3)Cl$	RT	24	48
3[a]	PhMe	Au[P(*t*Bu)$_2$(*o*-biphenyl)]Cl	RT	24	59
4	PhMe	CuOTf·$^1/_2$PhMe	110	24	29
5	CH_2Cl_2	$AuCl_3$	RT	24	32
6	MeCN	$AuCl_3$	RT	24	64
7	MeOH	$AuCl_3$	RT	24	41
8	MeOH	$AuCl_3$	70	36	58
9[b]	MeOH	$AuCl_3$	70	36	87

[a] With AgOTf (5 mol%). [b] With KO*t*Bu (10 mol%).

The use of CH_2Cl_2 and acetonitrile as the reaction solvents did not improve the yield of the hydroamination reaction when used in conjunction with $AuCl_3$ (Table 2, entries 5 and 6). With a successful KO*t*Bu catalysed nitro-Mannich reaction proceeding smoothly in methanol and with the main goal being to develop a one-pot cascade reaction, we ideally wanted the hydroamination reaction to proceed under the same conditions. Pleasingly, conducting the reaction in methanol using $AuCl_3$ (5 mol%) afforded pyrrole **269a** in 41% yield after 24 hours at RT (Table 2, entry 7), validating that a one-pot cascade could be conducted in methanol. Increasing the reaction temperature to 70 °C (reaction conducted in a microwave vial) improved the yield of **269a** to 58% after a reaction time of 36 hours (Table 2, entry 8). Increasing the reaction temperature enabled β-nitroamines **268** and **268′** to dissolve in the

methanol reaction solvent, aiding the hydroamination reaction. To our delight, addition of KO*t*Bu (10 mol%) to the reaction mixture further enhanced the yield of pyrrole **269a** to 87% after 36 hours at 70 °C (Table 2, entry 9). The significant increase in yield by adding KO*t*Bu to the reaction mixture could be explained by the interaction of the base with the *N*-sulfonamide protecting group. The base (*t*BuOH pK_a in DMSO = 32.2)[133] could fully or partially deprotonate the sulfonamide NH (benzenesulfonamide pK_a in DMSO = 16.1),[134] increasing the sulfonamide's nucleophilicity towards the alkyne and thus enhancing the hydroamination reaction. Previously reported results from the Dixon group[8] also support the hypothesis of sulfonamide deprotonation favouring the hydroamination reaction (Scheme 74). In the case of sulfonamide **274**, it was shown that hydroamination to pyrrolidine **275** would only occur in the presence of both KO*t*Bu and CuOTf·$^1/_2C_6H_6$. When sulfonamide **274** was exposed to only CuOTf·$^1/_2C_6H_6$, no reaction occurred.



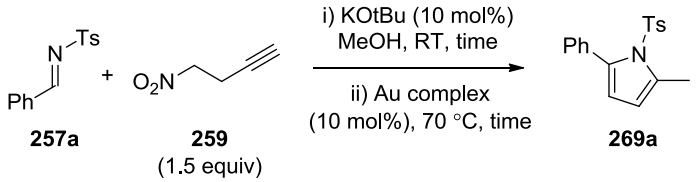
Scheme 74. Hydroamination reaction mechanism study of sulfonamide **274**. Reagents and conditions: i) KO*t*Bu (10 mol%), CuOTf·$^1/_2C_6H_6$ (5 mol%), PPh_3 (15 mol%), MeOH, RT, 2 h; ii) CuOTf·$^1/_2C_6H_6$ (5 mol%), PPh_3 (15 mol%), MeOH, RT, 7 h.

2.7 Optimisation of the One-Pot Nitro-Mannich/Hydroamination Cascade

With high yields obtained in both the nitro-Mannich and hydroamination reactions, developing a one-pot procedure became our main focus. In our initial studies, KO*t*Bu and $AuCl_3$ were added simultaneously to *N*-sulfonyl imine **257a** and nitroalkyne **259**. Pleasingly, pyrrole **269a** was obtained when using stoichiometric amounts of KO*t*Bu,

but unfortunately only low yields of pyrrole **269a** were obtained using this method possibly due to decomposition of the starting materials (Table 3, entries 1-3).

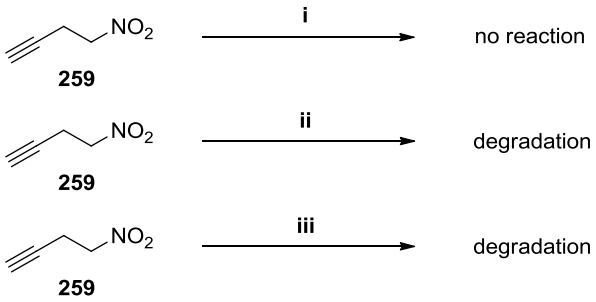
Table 3. Optimisation of the one-pot nitro-Mannich/hydroamination cascade reaction.



entry	KO*t*Bu	Au complex (10 mol%)	(i) time (h)	(ii) time (h)	yield (%)
1[a]	0.5 equiv	$AuCl_3$	24	—	0
2[a]	1.0 equiv	$AuCl_3$	1	—	26
3[a]	1.5 equiv	$AuCl_3$	2	—	21
4	10 mol%	$AuCl_3$	4	4	51
5	10 mol%	$AuCl_3$	4	36	81
6[b]	10 mol%	$AuCl_3$	4	36	48
7[b,c]	10 mol%	Au[P(*t*Bu)$_2$(*o*-biphenyl)]Cl	4	36	48
8[c]	10 mol%	Au[P(*t*Bu)$_2$(*o*-biphenyl)]Cl	4	36	57
9[d]	—	$AuCl_3$	4	36	41
10	10 mol%	—	4	36	0
11[e]	10 mol%	$AuCl_3$	4	36	78

[a] Simultaneous addition of base and gold catalysts. [b] MeCN used as solvent. [c] With AgOTf (10 mol %). [d] Et_3N used as base (10 mol %). [e] $AuCl_3$ (5 mol %).

In an attempt to understand why the yield of pyrrole **269a** had been so poor when using a simultaneous addition procedure, a series of control experiments to test the stability of nitroalkyne **259** towards base and gold catalysts were conducted (Scheme 75). Nitroalkyne **259** was found to be stable to KO*t*Bu in methanol at RT. In contrast, nitroalkyne **259** was found to degrade when exposed to either $AuCl_3$ (5 mol%) or a mixture of KO*t*Bu (10 mol%) and $AuCl_3$ (5 mol%) in methanol at RT.



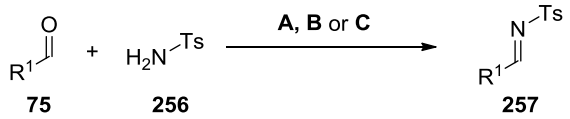
Scheme 75. Control experiments investigating the stability of nitroalkyne **259**. Reagents and conditions: i) KO*t*Bu (10 mol%), MeOH, RT, 24 h; ii) $AuCl_3$ (5 mol%), MeOH, RT, 24 h; iii) KO*t*Bu (10 mol%), $AuCl_3$ (5 mol%), MeOH, RT, 24 h.

As a result, sequential addition of KO*t*Bu and $AuCl_3$ catalysts was implemented in an attempt to improve the yield of the cascade. Gratifyingly, addition of KO*t*Bu (10 mol%) to *N*-sulfonyl imine **257a** and nitroalkyne **259** in methanol at RT, followed by addition of $AuCl_3$ (10 mol%) with heating at 70 °C, dramatically improved the reaction, with pyrrole **269a** being afforded in 81% yield. Reducing the $AuCl_3$ loading to 5 mol% was found to have no major detrimental effect on the cascade reaction, with pyrrole **269a** being isolated in 78% yield (Table 3, entry 11).

2.8 Scope of Nitro-Mannich/Hydroamination Cascade for the Synthesis of Substituted Pyrroles

With a good yield of pyrrole **269a** obtained using *N*-sulfonyl imine **257a**, the scope of the nitro-Mannich/hydroamination cascade was probed with respect to the substituent on the imine. Initially, a range of substituted aromatic *N*-sulfonyl imines were readily synthesised from a series of commercially available aldehydes using literature procedures (Table 4). *N*-Sulfonyl imines **257a**, **257b**, **257g-j**, **257o**, **257p** and **257r** were synthesised in one step and in 35-91% yield by condensation of the relevant aldehyde and *p*-toluenesulfonamide (**256**) in the presence of tetraethylorthosilicate at 170 °C.[125]

Table 4. Synthesis of *N*-sulfonyl protected imines **257**.



75 **256** **257**

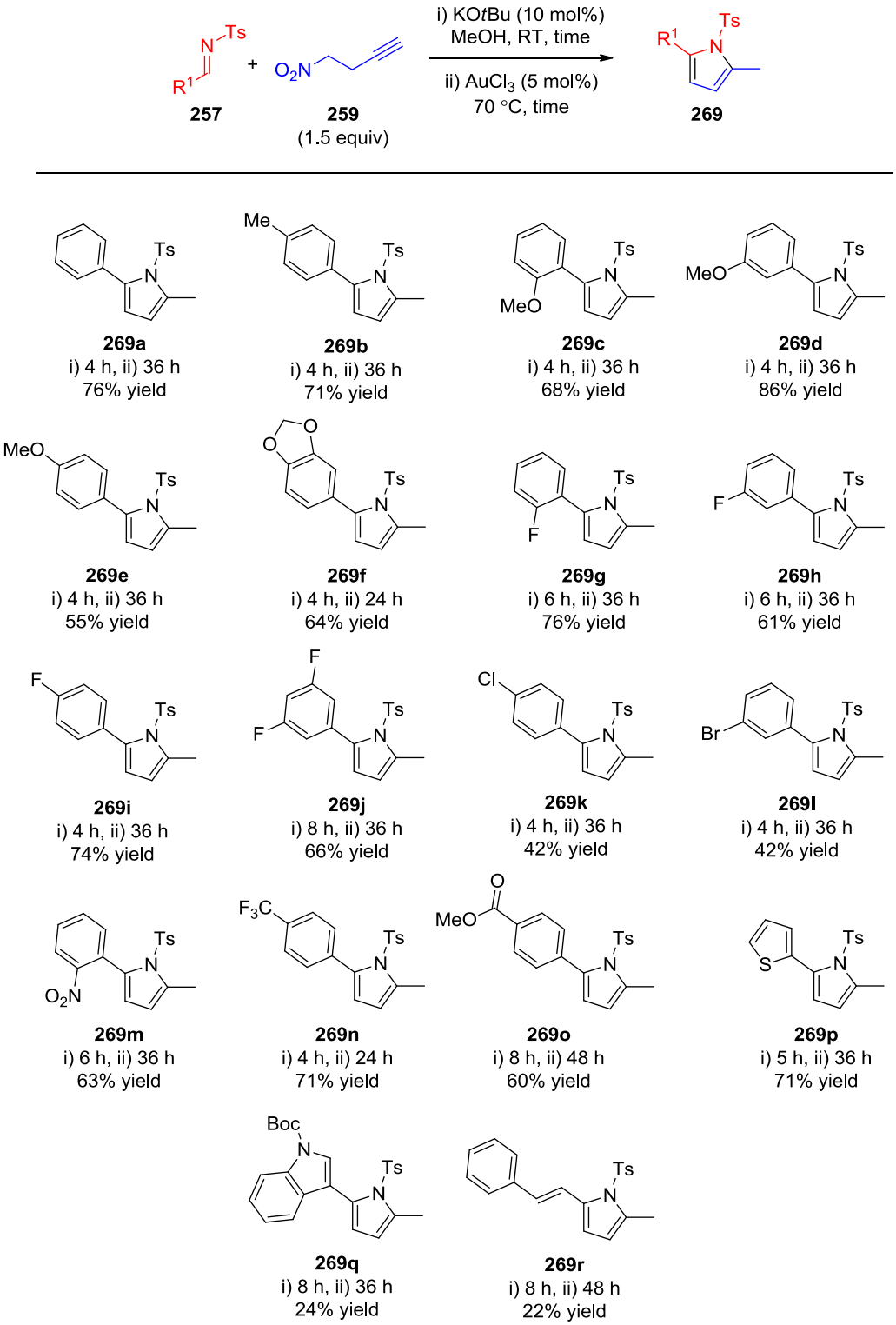
Method A: $Si(OEt)_4$, neat, 170 °C, 3 h
Method B: $TiCl_4$, Et_3N, CH_2Cl_2, 0 °C, 30 min
Method C: i) $C_6H_5SO_2Na$ (**276**), H_2O/formic acid (1:1) RT, 12 h then ii) sat. aq. $NaHCO_3$, CH_2Cl_2, RT, 2 h

entry	R^1	method	product	yield (%)
1	Ph	A	**257a**	75
2	*p*-MeC_6H_4	A	**257b**	86
3	*o*-$MeOC_6H_4$	B	**257c**	39
4	*m*-$MeOC_6H_4$	B	**257d**	10
5	*p*-$MeOC_6H_4$	B	**257e**	31
6	3,4-(-OCH_2O-)C_6H_3	C	**257f**	36
7	*o*-FC_6H_4	A	**257g**	71
8	*m*-FC_6H_4	A	**257h**	35
9	*p*-FC_6H_4	A	**257i**	57
10	3,5-$F_2C_6H_3$	A	**257j**	77
11	*p*-ClC_6H_4	B	**257k**	39
12	*m*-BrC_6H_4	C	**257l**	28
13	*o*-$NO_2C_6H_4$	B	**257m**	25
14	*p*-$F_3CC_6H_4$	C	**257n**	55
15	*p*-$MeO_2CC_6H_4$	A	**257o**	47
16	2-thienyl	A	**257p**	80
17	*N*-Boc 3-indolyl	B	**257q**	48
18	(*E*)PhCH=CH	A	**257r**	91
19	*i*Pr	C	**257s**	77

N-Sulfonyl imines **257c-e**, **257k**, **257m** and **257q** were synthesised in one step and in 10-39% yield from the corresponding aldehydes and *p*-toluenesulfonamide (**256**) using $TiCl_4$.[135] Lastly, *N*-sulfonyl imines **257f**, **257l**, **257n** and **257s** were synthesised by condensation of the appropriate aldehyde with *p*-toluenesulfonamide (**256**) and benzenesulfinic acid sodium salt (**276**), followed by elimination using saturated aq. $NaHCO_3$ and CH_2Cl_2.[136]

With *N*-sulfonyl imines **257a-s** in hand, they were individually subjected to the optimised nitro-Mannich/hydroamination cascade conditions (Scheme 76). Pleasingly, *N*-sulfonyl imines bearing electron-rich aryl substituents were all found to tolerate the cascade conditions, furnishing pyrroles **269c-e** in 55-86% yields. In addition, the piperonal-derived *N*-sulfonyl imine **257f** also yielded the corresponding pyrrole **269f**. A range of halogen substituted aryl imines were easily tolerated in moderate to good yields. Aryl groups bearing a fluorine substituent resulted in good yields of the pyrrole products **269g-j** (61-76%) whereas the chlorine and bromine substituted pyrroles **269k** and **269l** were both afforded in moderate yields of 42%. *N*-Sulfonyl imines bearing electron-poor aryl groups with nitro, trifluoromethyl and carboxylate functionalities were then tested in the cascade reaction and pleasingly, they all furnished the desired pyrroles **269m-o** in good yields (60-71%). The heteroaromatic 2-thienyl imine **257p** was easily tolerated with 71% yield being obtained for pyrrole **269p**. However, the *N*-Boc 3-indolyl substituted imine **257q** afforded pyrrole **269q** in only 24% yield. An *N*-sulfonyl imine **257r** derived from cinnamaldehyde also furnished the desired pyrrole, albeit in only 22% yield. The cascade reaction was also attempted using aliphatic imine **257s**, however this led to only a complex mixture of unidentified compounds when exposed to our optimal

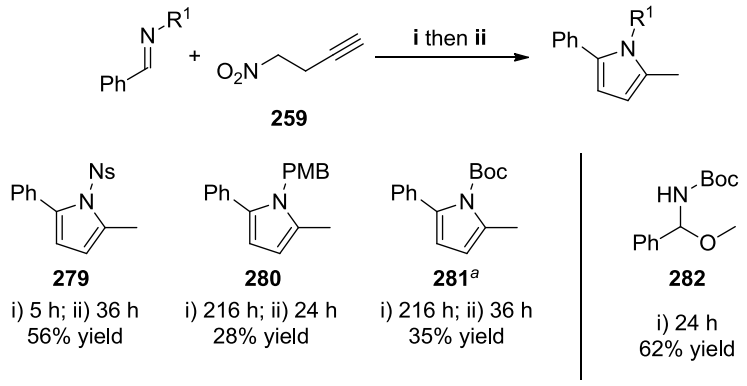
conditions. This observation is most likely due to the reduced stability of *N*-sulfonyl imine **257s** under our optimised conditions.



Scheme 76. Scope of the nitro-Mannich/hydroamination cascade to 2,5-disubstituted pyrroles **269**.

2.9 Variation of Imine *N*-Protecting Group

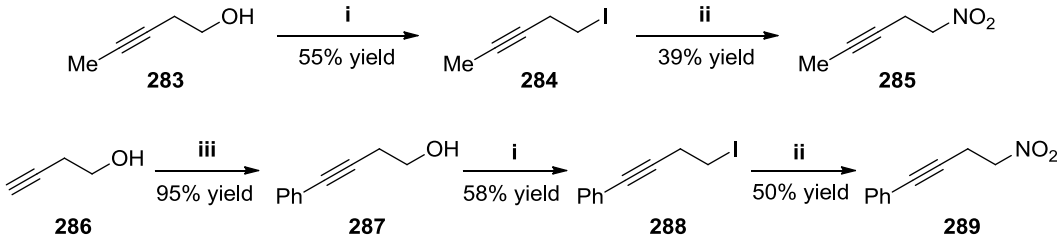
With the scope of the reaction explored using *N*-sulfonyl imines, we then investigated how the protecting group on the nitrogen atom affected the cascade reaction. Hence, *N*-nosyl imine **277**,[125] *N*-PMB imine **278**[137] and *N*-Boc imine **112a**[138] were synthesised using known procedures and then subjected to our nitro-Mannich/hydroamination cascade conditions (Scheme 77). The *N*-nosyl imine **277** afforded pyrrole **279** in 56% yield, similar to the yield obtained using *N*-sulfonyl imine **257a**. When *N*-PMB imine **278** was employed in the cascade reaction, it was witnessed that the base catalysed nitro-Mannich reaction was very slow, with the reaction not progressing to full conversion after 216 h. The slow reaction rate observed is presumably due to the reduced electrophilicity of the *N*-PMB protected imine employed.[139] In spite of the slow nitro-Mannich reaction, the addition of $AuCl_3$ (5 mol%) still led to the formation of the desired pyrrole **280** in 28% yield. Using *N*-Boc imine **112a** in conjunction with our optimised conditions only afforded amine **282** in 62% yield after the nitro-Mannich step. As a result, the solvent for the cascade reaction was changed to acetonitrile to prevent the reaction pathway leading to amine **282**. This modification enabled *N*-Boc pyrrole **281** to be furnished in 35% yield.



Scheme 77. Variation of imine *N*-protecting group. Reagents and conditions: i) KO*t*Bu (10 mol%), MeOH, RT, 5-216 h; ii) $AuCl_3$ (5 mol%), 70 °C, 24-36 h. [a] MeCN used as solvent.

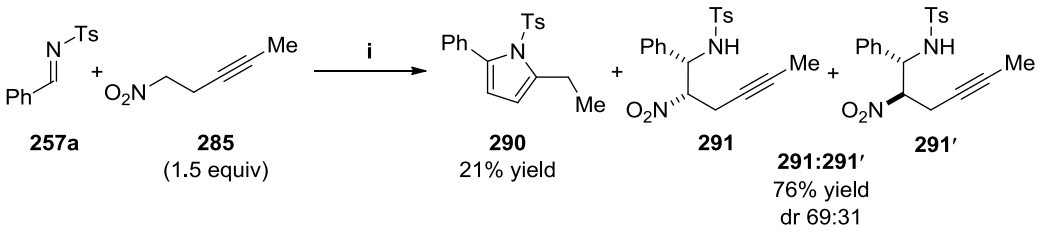
2.10 Extension of Methodology to Substituted Nitroalkyne Substrates

To further extend the scope of the developed methodology, we wanted to investigate whether the cascade reaction would proceed when using nitroalkyne substrates bearing a substituent on the alkyne terminus. Accordingly, the methyl and phenyl substituted nitroalkynes **285** and **289** were prepared (Scheme 78). Conversion of the commercially available pent-3-yn-1-ol (**283**) to iodoalkyne **284** was accomplished via an Appel reaction[140] using PPh_3 and iodine, treatment with $NaNO_2$ then furnished nitroalkyne **285**. The phenyl substituted nitroalkyne substrate **289** was synthesised in a similar fashion after a Sonogashira coupling[141] had installed the phenyl ring in compound **287**.



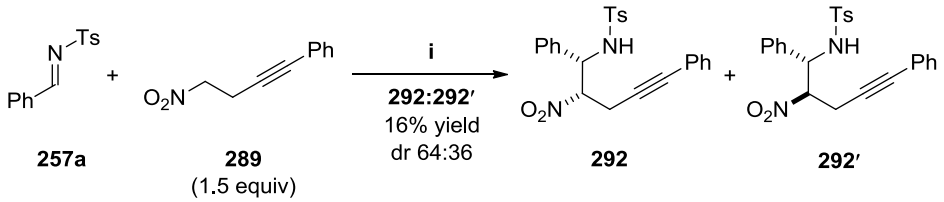
Scheme 78. Synthesis of substituted nitroalkynes **285** and **289**. Reagents and conditions: i) PPh_3, I_2, imidazole, CH_2Cl_2, RT, 3 h; ii) $NaNO_2$, DMSO, RT, 2 h; iii) iodobenzene, $Pd(PPh_3)_2Cl_2$ (3 mol%), CuI (6 mol%), piperidine, PhMe, 30 °C, 3 h.

With the substituted nitroalkyne substrates **285** and **289** in hand, we exposed them to our previously optimised conditions. Unfortunately, no product formation was witnessed in either example when using $AuCl_3$. However, we were able to recover the corresponding β-nitroamine intermediates from the reaction mixtures, demonstrating that the nitro-Mannich reaction still progressed when the alkyne terminus was bearing a substituent. In light of this result, we screened other gold sources in an attempt to achieve reactivity in this hydroamination reaction. Pleasingly, $Au(PPh_3)Cl$ used in conjunction with AgOTf was found to catalyse the hydroamination reaction using nitroalkyne **285** (Scheme 79).



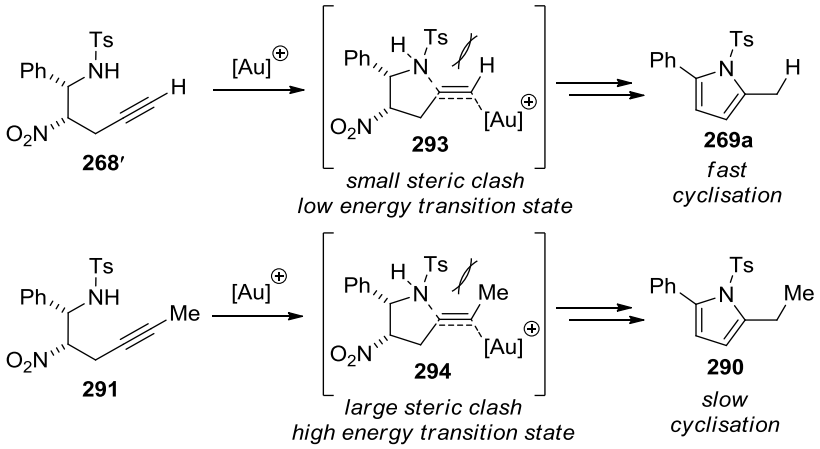
Scheme 79. Cyclisation of methyl-substituted nitroalkyne **285**. Reagents and conditions: i) KO*t*Bu (10 mol%), MeOH, RT 6 h then Au(PPh_3)Cl (5 mol%), AgOTf (5 mol%), 70 °C, 72 h.

However, the reaction was relatively slow, only affording pyrrole **290** in 21% yield after heating at 70 °C for 72 hours. β-Nitroamine intermediates **291** and **291′** were also successfully recovered from the reaction mixture in 74% yield and 69:31 dr. Conducting the hydroamination reaction at 90 °C did not improve the efficiency of the reaction. We then investigated the cyclisation of the phenyl substituted nitroalkyne substrate **289** (Scheme 80). Unfortunately, the hydroamination reaction did not occur using Au(PPh_3)Cl and AgOTf at 70 °C for 72 hours, only the β-nitroamines **292** and **292′** were isolated from the reaction mixture in 16% yield and 64:36 dr.



Scheme 80. Attempted cyclisation of phenyl-substituted nitroalkyne **289**. Reagents and conditions: i) KO*t*Bu (10 mol%), MeOH, RT 6 h then Au(PPh_3)Cl (5 mol%), AgOTf (5 mol%), 70 °C, 72 h.

We propose that the poor yield of pyrrole **290** obtained from the cascade reaction with nitroalkyne **285** is caused by 1,3 allylic strain arising in the transition state of the hydroamination reaction (Scheme 81). Firstly, *anti* addition of the nucleophile (sulfonamide NH) and $AuCl_3$ across the alkyne[142] results in the sulfonamide group and the alkyne substituent occupying the 1,3-allylic positions.



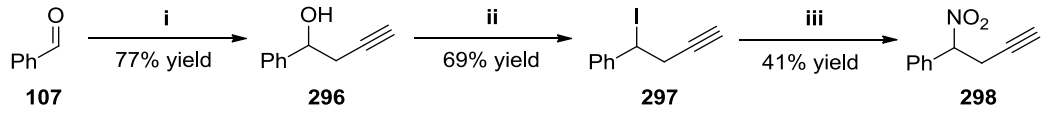
Scheme 81. Proposed mechanistic rationale for an unfavoured hydroamination reaction using internal alkyne substrates.

In the case of the terminal alkyne transition state **293**, the sulfonamide group and the proton of the alkyne are close in space but the steric clash is minimal. In the methyl substituted transition state **294**, the sulfonamide and the methyl group occupy the same positions as transition state **293**. However, the increased size of the methyl group creates a strong steric interaction making transition state **294** higher in energy. Increasing the size of the alkyne substituent (e.g. phenyl group) causes an even greater steric interaction, effectively demonstrating why no cyclisation occurred when the alkyne was bearing a phenyl substituent. Similar explanations for gold catalysed carbocyclisation reactions using alkynes have previously been proposed by Toste and co-workers.[142]

2.11 Extension to α-Substituted Nitroalkyne Substrates

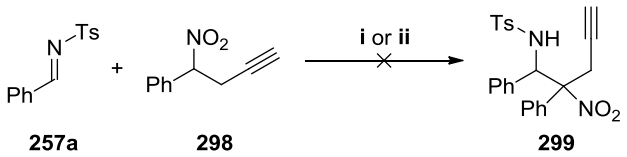
With the substituted alkyne substrates **285** and **289** giving varying results, we decided to synthesise nitroalkyne substrates carrying substituents in the α-position and test them in our nitro-Mannich/hydroamination cascade (Scheme 82). Accordingly, alkyne **296** was prepared in 77% yield from benzaldehyde (**107**) and propargyl bromide (**295**) using zinc-copper couple.[143] Alkyne **296** was then

converted to iodoalkyne **297** in 69% yield and subsequent treatment with $NaNO_2$ furnished nitroalkyne **298** in 41% yield after 2 hours at RT.



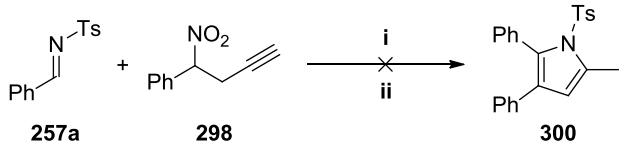
Scheme 82. Synthesis of α-substituted nitroalkyne **298**. Reagents and conditions: i) propargyl bromide (**295**), Zn-Cu couple, THF, 65 °C, 1 h; ii) PPh_3, I_2, imidazole, CH_2Cl_2, RT, 3 h; iii) $NaNO_2$, DMSO, RT, 2 h.

The prepared α-substituted nitroalkyne **298** was then exposed to the nitro-Mannich reaction conditions (Scheme 83). Using either 10 mol% or 1 equivalent of KO*t*Bu in methanol at RT did not result in any conversion to β-nitroamine **299**, with only the starting *N*-sulfonyl imine **257a** and nitroalkyne **298** being present in the crude reaction mixture.



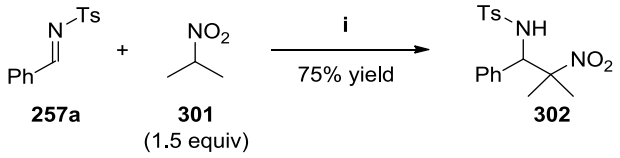
Scheme 83. Attempted nitro-Mannich reaction using the α-substituted nitroalkyne **298**. Reagent and conditions: i) KO*t*Bu (10 mol%), MeOH, RT, 24 h; ii) KO*t*Bu (1.0 equiv), MeOH, RT, 96 h.

We then investigated if a mixture of KO*t*Bu and $AuCl_3$ could facilitate the cascade reaction to directly afford pyrrole **300** (Scheme 84). However, this proved unsuccessful with only the starting materials being recovered even after heating at 70 °C for 72 hours.



Scheme 84. Attempted nitro-Mannich/hydroamination cascade using the α-substituted nitroalkyne **298**. Reagent and conditions: i) KO*t*Bu (10 mol%), $AuCl_3$ (5 mol%), MeOH, RT, 24 h; ii) KO*t*Bu (10 mol%), $AuCl_3$ (5 mol%), MeOH, 70 °C, 72 h.

To ascertain why nitroalkyne **298** showed no reactivity towards *N*-sulfonyl imine **257a**, we conducted a control experiment using *N*-sulfonyl imine **257a** (Scheme 85). Under our base catalysed nitro-Mannich conditions, the sterically hindered 2-nitropropane (**301**) was found to be an active substrate for the nitro-Mannich reaction, furnishing β-nitroamine **302** in good yield.



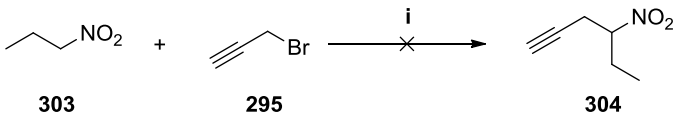
257a **301** (1.5 equiv) **302**

Scheme 85. Control experiment using 2-nitropropane (**301**) in the nitro-Mannich reaction. Reagents and conditions: i) KO*t*Bu (10 mol%), MeOH, RT, 24 h.

Due to this result, we propose that the lack of reactivity displayed by nitroalkyne **298** in the nitro-Mannich reaction is either because of increased steric hindrance from the α-phenyl substituent, or reduced nucleophilicity of the nitronate anion. To further test these proposals, various attempts were made to synthesise α-alkyl-substituted nitroalkynes. Initially we attempted to substitute the phenyl group for a straight-chained aliphatic substituent using the previously employed zinc-copper couple method. However, these conditions proved unsuccessful and as a result we looked for other ways to prepare the α-alkyl-substituted nitroalkyne substrates.

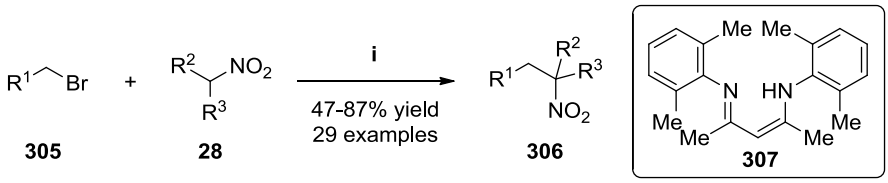
An inherent problem of nitroalkane alkylation is that they predominantly undergo alkylation on the oxygen atom and not the α-carbon atom. This results in the formation of the corresponding carbonyl compound from the starting haloalkane.[144] Seebach and co-workers reported that formation of a nitronate dianion can overcome this problem, so we attempted the direct α-alkylation of nitropropane (**303**) using the reported conditions.[145] Accordingly, 2 equivalents of *n*BuLi were added to nitropropane at –90 °C and then propargyl bromide (**295**) was added as the

quenching electrophile (Scheme 86). Unfortunately none of the desired nitroalkyne **304** was isolated from the crude reaction mixture.



Scheme 86. Attempted α-alkylation of nitropropane (**303**) using Seebach's procedure. Reagent and conditions: i) *n*BuLi, THF/HMPT (5:1), –90 °C then propargyl bromide (**295**), HCl in THF.

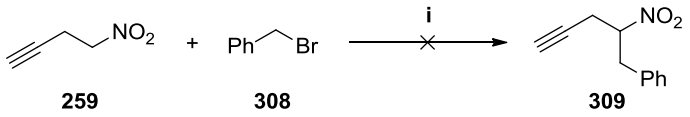
Recently, Watson and co-workers reported an elegant solution to this inherent reactivity problem of nitroalkanes by describing a method to α-alkylate nitroalkanes with substituted benzyl bromides (Scheme 87).[146] Using a ligated copper catalyst, they were able to successfully alkylate a wide variety of nitroalkanes with substituted benzyl bromides **305**.



R^1 = Ph, *o*-MeC_6H_4, *m*-MeC_6H_4, *p*-*t*BuC_6H_4, *m*-$MeOC_6H_4$, *p*-$MeOC_6H_4$, *p*-NCC_6H_4, *p*-FC_6H_4
p-ClC_6H_4, 2,5-$Cl_2C_6H_3$, *m*-BrC_6H_4, *p*-BrC_6H_4, *p*-$MeO_2CC_6H_4$, *p*-$F_3CC_6H_4$, *p*-$NO_2C_6H_4$
2-naphthyl, 2-pyridyl, 2-thienyl; R^2 = H, *n*Pent, *i*Pr, $(CH_2)_3OAc$ $(CH_2)_2CO_2Me$
$CH_2CH{=}CH_2$; R^3 = H, Me; $R^2 = R^3$ = $-(CH_2)_5-$

Scheme 87. Watson's copper catalysed α-alkylation of nitro containing compounds. Reagents and conditions: i) CuBr (20 mol%), ligand **307** (25 mol%), NaO*t*Bu, hexane, 60 °C, 6-24 h.

Due to its simplicity and broad substrate scope, we subjected nitroalkyne **259** to the reported reaction conditions to try and install a benzyl substituent in the α-position (Scheme 88).



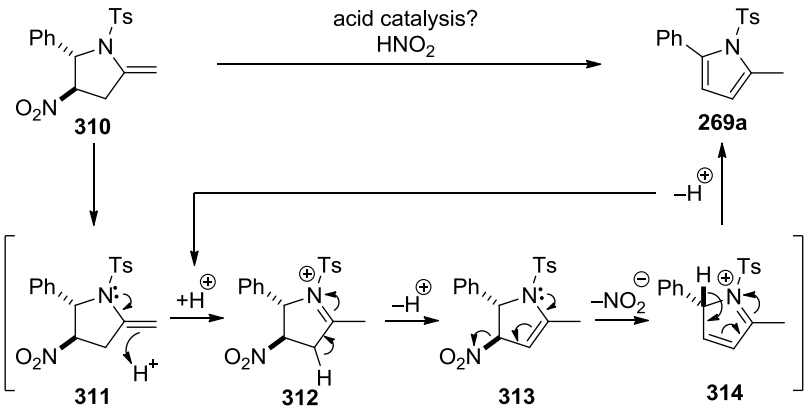
Scheme 88. Attempted α-alkylation of nitroalkyne **259** with benzyl bromide (**308**). Reagents and conditions: i) CuBr (20 mol%), ligand **307** (25 mol%), NaO*t*Bu, hexane, 60 °C, 24 h.

However, only a complex mixture of compounds was obtained possibly due to degradation of the starting nitroalkyne **259** under the reaction conditions employed. Subsequent efforts to separate the mixture via column chromatography did not afford any of the desired product.

Due to the difficulties encountered in the preparation of aliphatic α-substituted nitroalkyne substrates, no further investigations were conducted into the nitro-Mannich/hydroamination cascade of these substrates.

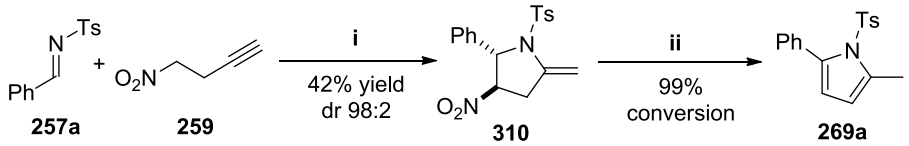
2.12 Investigation into the Mechanistic Pathway

During the course of our studies we had postulated that the nitro-Mannich/hydroamination cascade proceeded via pyrrolidine **310**, with pyrrole **269a** being formed by an *exo/endo* alkene isomerisation and HNO_2 elimination pathway. To test this hypothesis, we wanted to either isolate pyrrolidine **310** or intercept it by in situ reduction of the alkene using an appropriate reagent. To accomplish the isolation of pyrrolidine **310**, we proposed a mechanistic rationale for the occurrence of the *exo/endo* isomerisation and subsequent HNO_2 elimination (Scheme 89). Under acidic conditions, isomerisation of pyrrolidine **310** to enamide **313** could occur.[8,147]



Scheme 89. Proposed acid catalysed *exo/endo* alkene isomerisation and HNO_2 elimination to pyrrole **269a**.

Electron pair donation by the nitrogen atom would then allow the elimination of the $–NO_2$, with the resulting intermediate **314** isomerising to afford pyrrole **269a**. Although the nitro-Mannich reaction is initially conducted in the presence of KO*t*Bu (10 mol%), the Lewis acidic $AuCl_3$ (5 mol%) is added to the reaction mixture and our proposed reaction pathway eliminates HNO_2, thus making an acid catalysed *exo/endo* alkene isomerisation entirely plausible. Therefore, to test our hypothesis, the cascade reaction was conducted using 0.5 equivalents of KO*t*Bu in the initial nitro-Mannich reaction (Scheme 90).

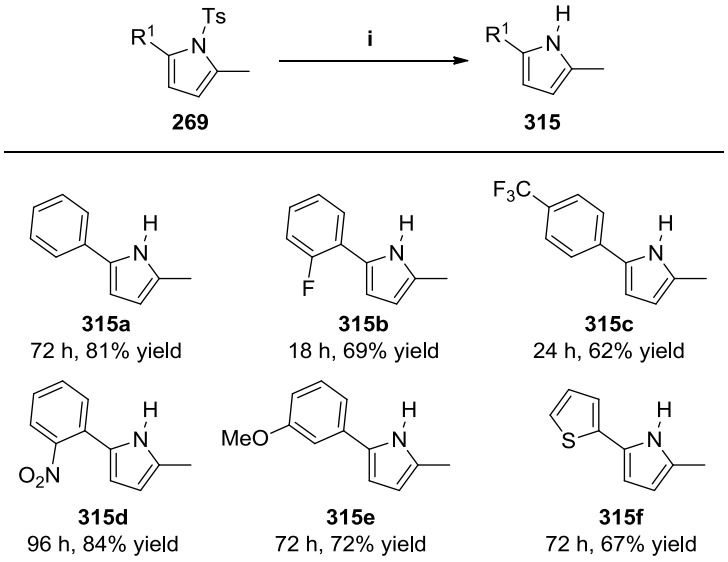


Scheme 90. Synthesis of pyrrolidine **310** and transformation into pyrrole **269a**. Reagents and conditions: i) KO*t*Bu (0.5 equiv), MeOH, RT, 4 h then $AuCl_3$ (5 mol%), 70 °C, 2 h; ii) 1 M HCl work up.

$AuCl_3$ (5 mol%) was then added in line with the general procedure and to our delight, pyrrolidine **310** was isolated in 42% yield after heating at 70 °C for 2 hours following purification by flash column chromatography on silica gel. The isolated pyrrolidine **310** was then washed with a 1 M solution of HCl and extracted with EtOAc to give quantitative conversion to pyrrole **269a**. This experimental evidence strongly supports our hypothesis of an acid catalysed isomerisation and subsequent HNO_2 elimination reaction pathway. Also, as none of the *endo*-alkene product was observed by ^1H NMR, we suggest that the HNO_2 elimination occurs almost instantaneously after the *exo/endo* alkene isomerisation reaction.

2.13 Deprotection of Synthesised Pyrroles

To show that the synthesised pyrroles are synthetically useful, we wanted to demonstrate that the sulfonamide protecting group could be removed to afford the corresponding NH pyrroles. Sulfonamide protecting groups are known to be very robust and therefore harsh conditions are often required to facilitate their removal.[148] Pleasingly, using KOH (3.5 equiv) in methanol and heating at 80 °C[149] enabled the removal of the sulfonamide group to yield the deprotected pyrrole **315a** in 50% yield. Increasing the amount of KOH (7.0 equiv) raised the yield of pyrrole **315a** to 81% after 72 hours (Scheme 91).



Scheme 91. Deprotection of the pyrrole sulfonyl protecting group. Reagents and conditions: i) KOH, MeOH, 80 °C.

Using these optimised conditions, we were able to deprotect a range of pyrroles with varying substituents on the aromatic ring with good yields achieved in all cases (62-84%).

2.14 Summary and Conclusion

In summary, we have developed an efficient one-pot procedure to synthesise 2,5-disubstituted pyrroles using a nitro-Mannich/hydroamination cascade. The cascade reaction unites easily prepared *N*-sulfonyl imines and nitroalkyne **259** using a compatible combination of KO*t*Bu and $AuCl_3$ to afford the pyrrole products in good yields (22-86%). Extension of the methodology to substituted nitroalkyne substrates was also conducted. Mechanistic investigations have shown that after the gold catalysed hydroamination reaction, an acid catalysed *exo/endo* alkene isomerisation reaction is followed by a nitro group elimination to yield the desired pyrrole products.

Chapter 3: Enantioselective Synthesis of Tetrahydropyridines via a One-Pot Nitro-Mannich/Hydroamination Cascade

3.1 Introduction

3.1.1 Combining Organocatalysis with Transition Metal Catalysis[b]

With the emergence of organocatalysis as a powerful method for the synthesis of highly enantioenriched molecules,[32] several groups proposed that combining organocatalysis with transition metal catalysis could lead to a wealth of unprecedented transformations that would not be possible using the catalysts individually. Since Córdova and Ibrahem first reported combining organocatalysis and transition metal catalysis in the intermolecular α-allylic alkylation of aldehydes,[150] the vast potential of this research area has been realised by a number of groups, including the Dixon group,[151] leading to the rapid growth of this emerging field.[152]

Due to the multitude of catalyst combinations and activation modes, reactions that combine different catalysts are classified depending on how they perform a certain reaction sequence. This classification has three types: cooperative catalysis, synergistic catalysis and sequential (relay) catalysis (Figure 8).[152c] In cooperative catalysis, both of the catalysts work cooperatively together in the same catalytic cycle. In synergistic catalysis, the catalysts both simultaneously activate the reaction partners in catalytic cycles that are united. In sequential (relay) catalysis, the catalysts

[b] In this introduction 'transition metal' catalysis refers to all transition metals except gold.

both work in completely independent catalytic cycles to accomplish the desired transformation. For example, **Cat1** could combine starting materials **A** and **B** to give an intermediate compound (**int**). Addition of **Cat2** would then covert **int** into the desired product (**pro**).

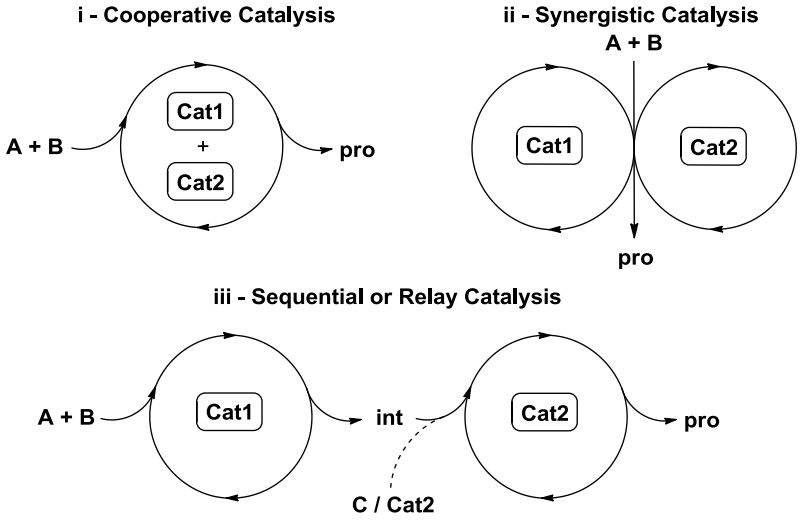


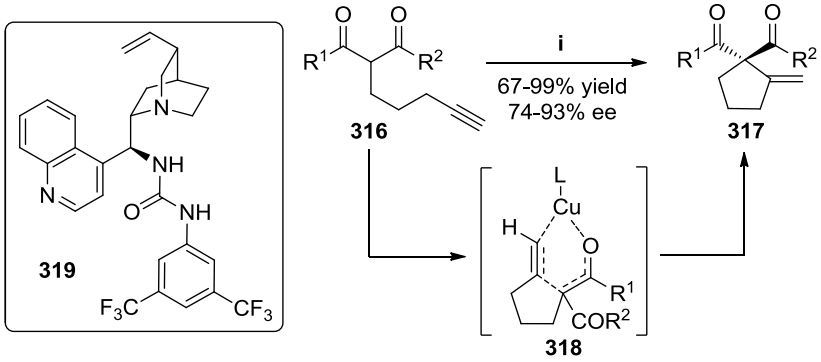
Figure 8. Schematic diagram depicting cooperative, synergistic and sequential (relay) catalysis.[152c]

3.1.2 Combining H-Bond Donor Organocatalysis and Transition Metal Catalysis

Although there is now an abundance of reactions combining organocatalysis with transition metal catalysis,[152] this short introduction will focus only on examples that combine H-bond donor organocatalysis and transition metal catalysis.

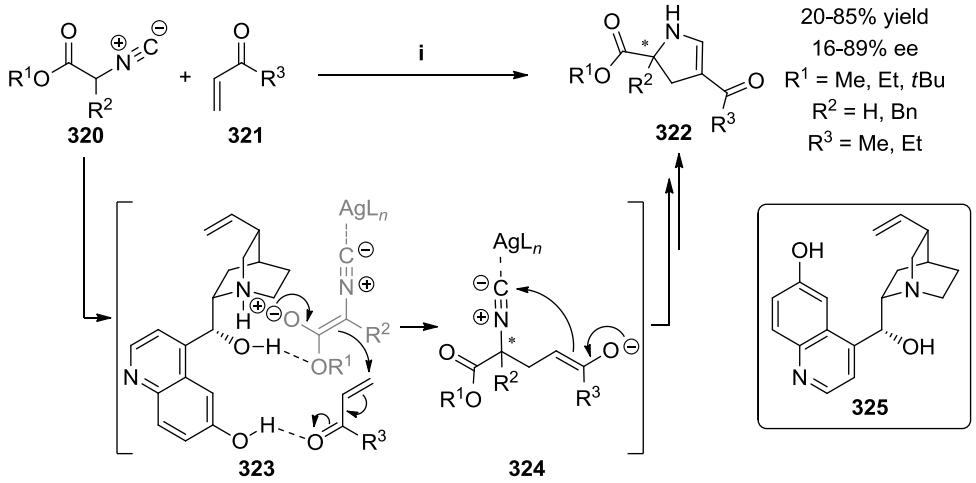
In 2009, Dixon and co-workers reported an enantioselective carbocyclisation reaction of alkyne tethered β-keto-esters **316** using a cooperative catalytic system of cinchonidine-derived urea **319** and CuOTf·½C_6H_6 (Scheme 92).[153] The reaction was proposed to proceed via the copper enolate species **318** that is ligated by urea **319**, imparting enantiocontrol in the process. This resulted in highly enantioenriched cyclopentane products **317** in good to excellent yields for a number of aryl and alkyl substituted dicarbonyl starting substrates **316**. A β-keto-amide substrate was also

found to be compatible with the reaction conditions maintaining the good enantiocontrol observed in the other examples.



Scheme 92. Dixon's cooperative Brønsted base/Lewis acid catalysed enantioselective carbocyclisation reaction. Reagents and conditions: i) catalyst **319** (20 mol%), $CuOTf{\cdot}\frac{1}{2}C_6H_6$ (5 mol%), CH_2Cl_2, RT, 1-10 days.

Escolano and co-workers reported a formal [3+2] cycloaddition of isocyanoacetates **320** and α,β-unsaturated ketones **321** to prepare enantioenriched dihydropyrroles **322** using cooperative cupreine (**325**) and $AgNO_3$ catalysis (Scheme 93).[154]

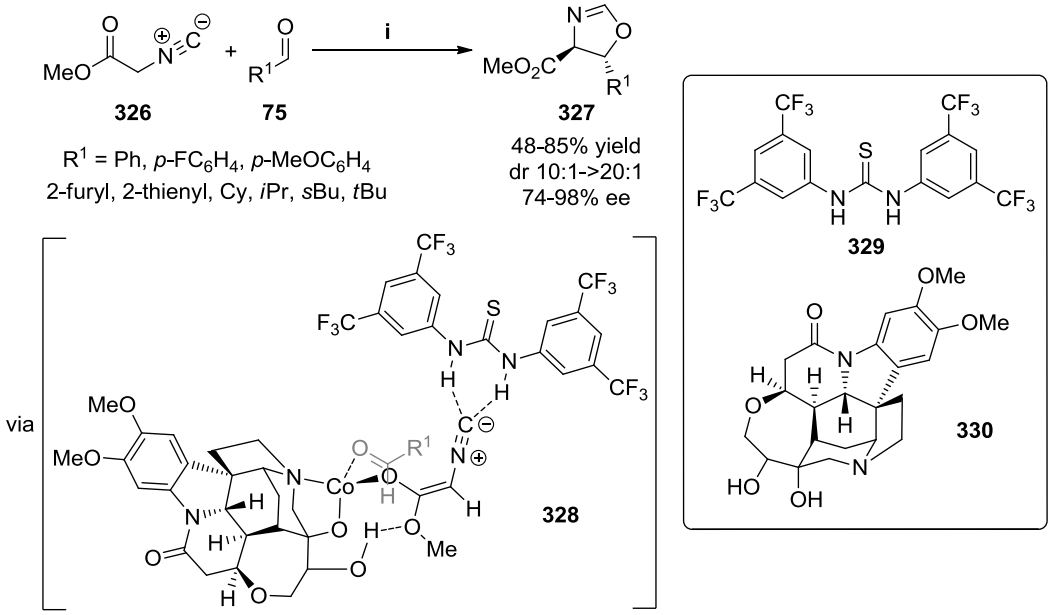


Scheme 93. Escolano's cooperative cupreine (**325**)/$AgNO_3$ catalysed asymmetric formal [3+2] cycloaddition of isocyanoacetates and α,β-unsaturated ketones. Reagents and conditions: i) catalyst **325** (10 mol%), $AgNO_3$ (5 mol%), CH_2Cl_2, RT, 14 h.

The authors proposed that the enantioselectivity of the reaction arises from complex **323**, where the bifunctional organocatalyst **325** activates the isocyanoacetate and

α,β-unsaturated ketone substrates via H-bonding interactions, to afford dihydropyrroles **322** in modest to good yields and enantioselectivities. Presumably, the role of the $AgNO_3$ is to complex the isocyanide making the α-proton more acidic than the non complexed isocyanoacetate **320**. Therefore, the basic quinuclidine moiety present in organocatalyst **325** is then able to deprotonate the α-position leading to the formation of intermediate **323**.

In 2011, Oh and Kim reported an asymmetric aldol reaction of α-isocyanoacetate **326** under the control of a chiral cobalt complex and the achiral thiourea **329** (Scheme 94).[155]



Scheme 94. Oh and Kim's isocyanoacetate aldol reaction using cooperative catalysis. Reagents and conditions: i) CoI_2/**330** (10 mol%), thiourea **329** (20 mol%), DBU (20 mol%), THF/1,4-dioxane (4:1), 23 °C, 18 h.

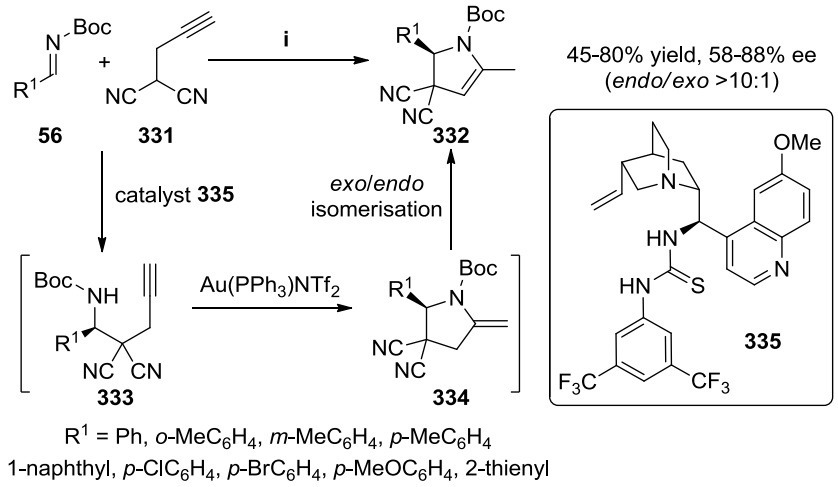
In this cooperatively catalysed reaction the authors state that achiral thiourea **329** complexes the isocyanide moiety of **326** while the cobalt catalyst, featuring the complex ligand **330** derived from brucine, binds the acetate and aldehyde groups as depicted in the proposed intermediate **328**. The resulting reaction was found to be general for a range of aromatic and aliphatic aldehydes affording substituted

oxazolines **327** in good yields with good to excellent diastereo- and enantioselectivities.

3.1.3 Combining H-Bond Donor Organocatalysis and Gold Catalysis

After the discovery of a multitude of new methodologies by combining H-bond donor organocatalysis and transition metal catalysis, the field naturally progressed to unite the emerging field of homogeneous gold catalysis. Gold catalysis had seen a dramatic rise to prominence during the last decade, with numerous reports of new and unprecedented transformations.[80] Owing to the novel reactions that can be performed using gold catalysis and the high enantioselectivities that can be obtained using H-bond donor organocatalysis, the potential of combining the two catalytic systems seemed very attractive.

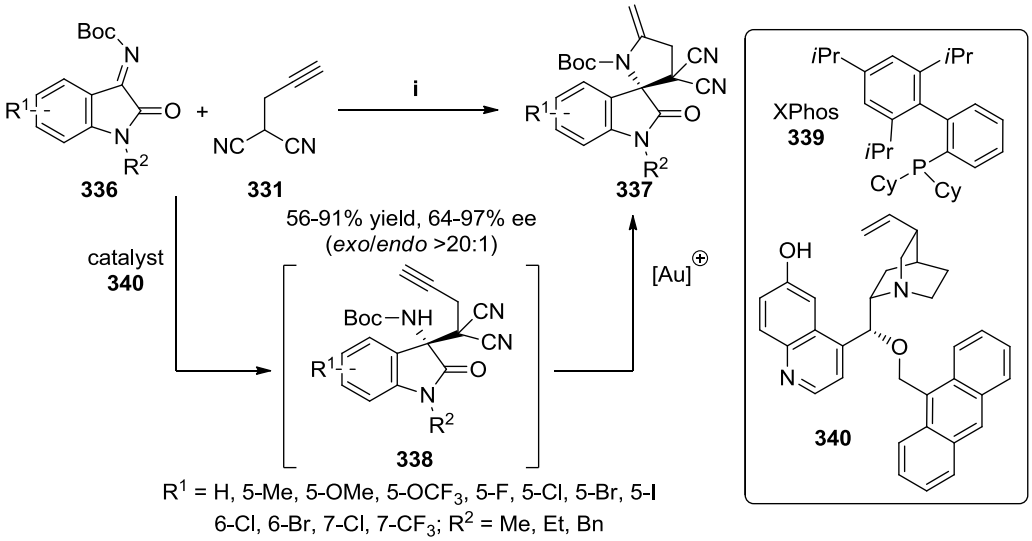
The first example that combined H-bond donor organocatalysis with gold catalysis was described by Jørgensen and co-workers in 2010 (Scheme 95).[147] The authors reported the use of quinidine-derived thiourea **335** and $Au(PPh_3)NTf_2$ in a sequential Mannich/hydroamination cascade of *N*-Boc imines **56** and alkyne substrate **331**.



Scheme 95. Jørgensen's Mannich/hydroamination cascade to enantioenriched dihydropyrroles **332** using sequential bifunctional organocatalysis and gold catalysis. Reagents and conditions: i) catalyst **335** (1 mol%), $CHCl_3$, –60 °C then *p*-TsOH (10 mol%), $Au(PPh_3)NTf_2$ (5 mol%), RT.

In the first step, thiourea **335** was employed to catalyse the Mannich reaction, affording the enantioenriched adducts **333** when using a catalyst loading of only 1 mol%. The gold complex was then added to facilitate the hydroamination reaction furnishing dihydropyrroles **332**. The addition of *p*-TsOH to the reaction mixture before the addition of $Au(PPh_3)NTf_2$ was crucial to achieve high yields of the dihydropyrroles **332**. The authors suggested that the acid additive is required to protonate the basic quinuclidine and quinoline moieties present in thiourea **335**, thus preventing the deactivation of the gold catalyst by its chelation with these basic functionalities. Although this report represented an important development in the field, it also highlighted that the inherent problem of catalyst deactivation could limit this combination of catalysts to sequential protocols.

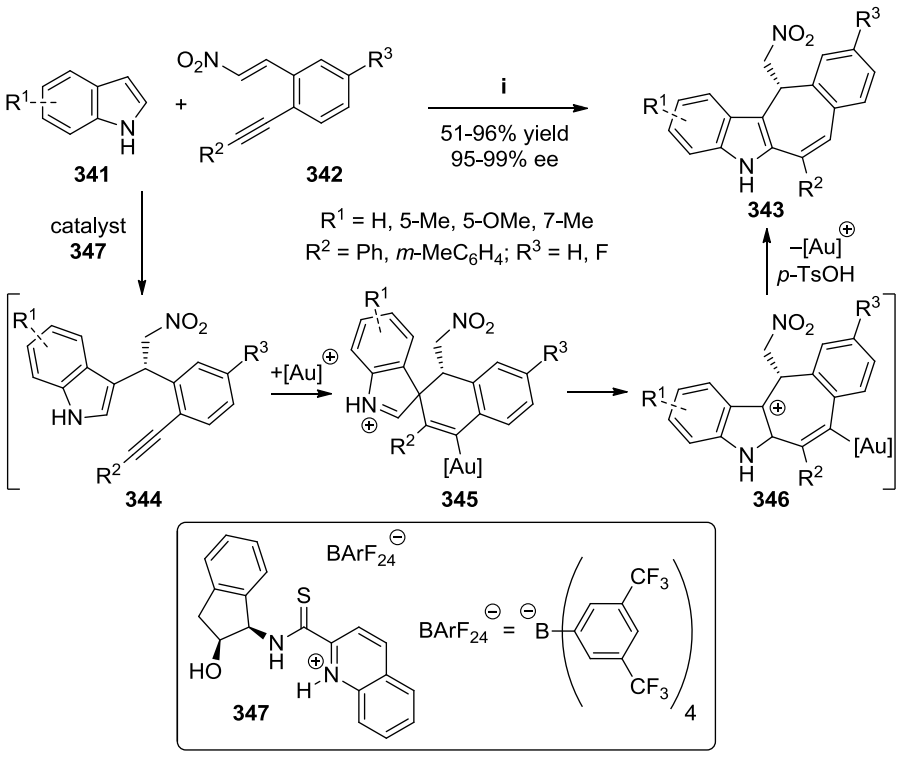
Building on the work of Jørgensen, Jiang and Liu very recently described an enantioselective Mannich/hydroamination cascade to spirooxindole derivatives using sequential bifunctional organocatalysis and gold catalysis (Scheme 96).[156]



Scheme 96. Jiang and Liu's Mannich/hydroamination cascade of spirooxindoles **336** with propargylated malononitrile **331** using sequential bifunctional organocatalysis and gold catalysis. Reagents and conditions: i) catalyst **340** (5 mol%), PhMe, –70 °C, 24 h then $BF_3{\cdot}Et_2O$ (20 mol%), RT, 30 min then $Au(XPhos)NTf_2$ (10 mol%), RT, 6-24 h.

In this report, the aryl derived *N*-Boc imines previously employed by Jørgensen were substituted by *N*-Boc spirooxindole imines **336** which were united with propargylated malononitrile **331** under the control of the bifunctional organocatalyst **340**. The resulting intermediate **338** was then exposed to Au(XPhos)NTf_2 after the addition of $BF_3{\cdot}Et_2O$ (20 mol%) to afford the spirooxindole products **337** in good yields with excellent enantiocontrol (up to 97% ee). In addition, minimal alkene isomerisation was witnessed; all of the furnished products contained predominantly the *exo*-alkene (*exo/endo* >20:1).

In 2011, Enders and co-workers reported an enantioselective synthesis of complex indole-derived tetracycles **343** using H-bond donor catalysis and gold catalysis (Scheme 97).[157]



Scheme 97. Enders's enantioselective synthesis of tetracyclic indole derivatives using sequential organo- and gold catalysis. Reagents and conditions: i) catalyst **347** (10 mol%), $CHCl_3$, –30 °C, 16-48 h then *p*-TsOH (0.75 equiv), Au(PPh_3)NTf_2 (10 mol%), RT to reflux, 15-67 h.

In the first step of the reaction cascade, an organocatalysed Michael addition of indole **341** and nitroalkene **342** furnished intermediate **344**. A subsequent $Au(PPh_3)NTf_2$ catalysed Friedel-Crafts reaction then formed spirocyclic intermediate **345** which underwent ring expansion and protodemetallation to afford tetracycles **343** in good yields with excellent enantioselectivities (95-99% ee). Addition of an acid to the reaction mixture with the gold catalyst was again demonstrated to be of paramount importance to achieve the desired outcome from the reaction. However, the authors stated that the addition of *p*-TsOH could allow propagation of the reaction by increasing the rate of protodemetallation, rather than preventing the chelation of organocatalyst **347** to the gold complex.

Due to the considerable interest that combining organocatalysis and gold catalysis has gained from the synthetic community, Enders and Loh recently published an excellent review that comprehensively examines this expanding area.[158]

3.1.4 Tetrahydropyridine Heterocycles

Tetrahydropyridines are a class of nitrogen-containing heterocycles that are structurally related to the unsaturated pyridine (**348**) and the saturated piperidine (**352**) heterocycles (Figure 9). Tetrahydropyridines **349-351** contain one unsaturated double bond that can occupy different positions within the ring structure, thus affecting its properties and synthetic utility.

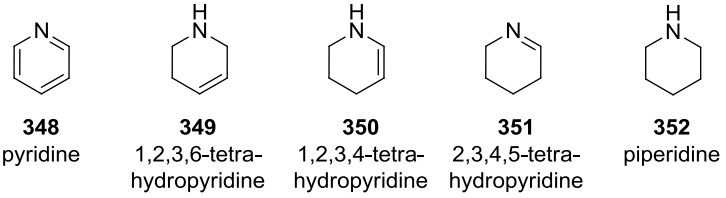
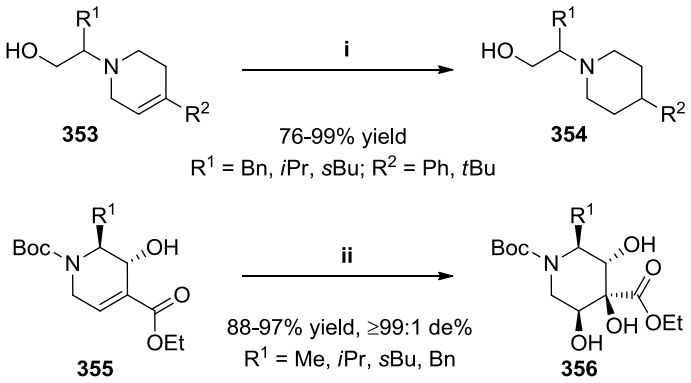


Figure 9. Comparison of pyridine, tetrahydropyridines and piperidine heterocycles.

Since tetrahydropyridine motifs are present in a number of compounds that exhibit an interesting range of biological activities, they have become attractive targets for organic chemists.[159] Tetrahydropyridines are also valuable intermediates for target synthesis because they can be easily converted into more elaborate structures by a range of methods. For example, the corresponding piperidine **354** can be accessed via reduction of the unsaturated double bond present in **353**,[160] or a dihydroxylation reaction can afford densely functionalised piperidine motifs **356** from tetrahydropyridine **355** (Scheme 98).[161]



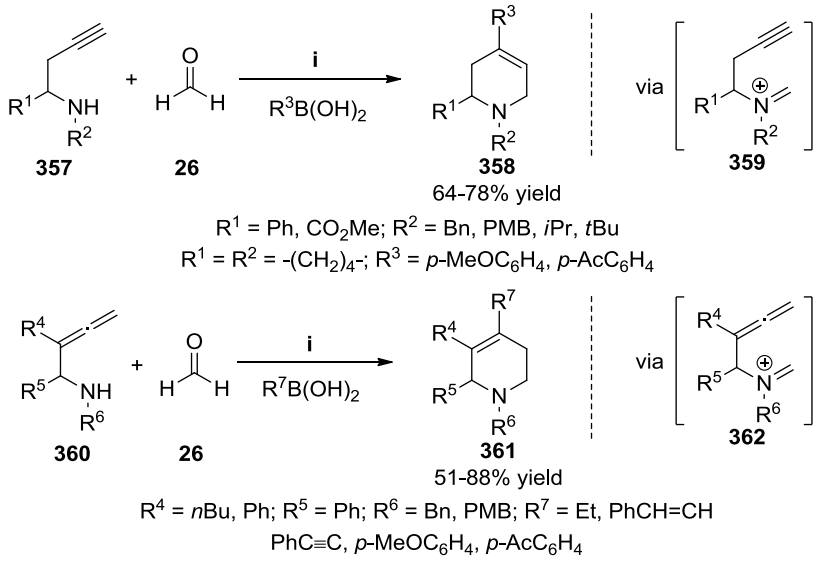
Scheme 98. Synthetic elaboration of tetrahydropyridines **353** and **355**. Reagents and conditions: i) Pd/C (10 mol%), H_2, MeOH; ii) OsO_4 (5% solution in PhMe), NMO (50% aq. solution), acetone-H_2O (4:1), RT, 36-43 h.

3.1.5 Previous Examples of Tetrahydropyridine Synthesis

Due to their versatility, many research groups have developed elegant methodologies that allow access to tetrahydropyridine derivatives. Because of the high number of reports on this topic, only some relevant examples will be highlighted in this introduction.

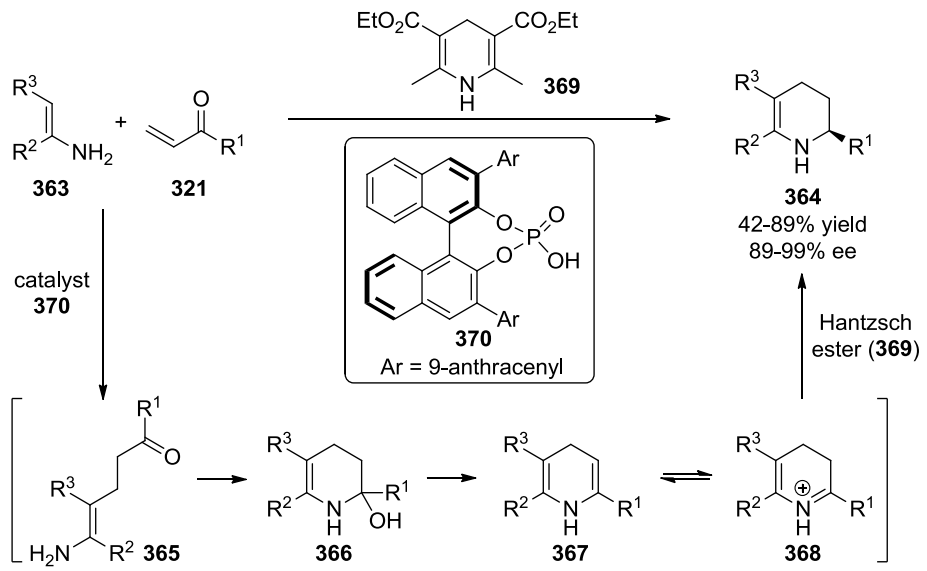
In 2008, Tsukamoto and Kondo reported the synthesis of 1,4-disubstituted 1,2,3,6-tetrahydropyridines via a palladium catalysed iminium ion cyclisation of aminoalkynes and aminoallenes (Scheme 99).[162] Firstly, the authors demonstrated that aminoalkynes **357** could react with formaldehyde (**26**) and substituted boronic

acids to form substituted 1,2,3,6-tetrahydropyridines **358** in the presence of a palladium catalyst. After the initial formation of iminium ion **359**, the palladium catalyst then facilitates the cyclisation reaction and a subsequent transmetallation with the boronic acid furnishes 1,2,3,6-tetrahydropyridines **358** in good yields. An extension of the methodology using aminoallenes **360** under the same conditions also afforded 1,2,3,6-tetrahydropyridines **361** possessing different substitution patterns.



Scheme 99. Tsukamoto and Kondo's 1,2,3,6-tetrahydropyridine synthesis using a palladium catalysed cyclisation. Reagents and conditions: i) $Pd(PPh_3)_4$ (2 mol%) or $PdCp(\eta^3\text{-}C_3H_5)$ (3 mol%) and $PPh(Cy)_2$ (12 mol%), THF, 50 °C.

An organocatalytic approach to tetrahydropyridines was developed by Antonchick and Rueping in 2008 (Scheme 100).[163] The authors combined enones and substituted enamines under the control of a BINOL phosphoric acid to provide an enantioselective synthesis of 1,2,3,4-tetrahydropyridines **364**. In the catalytic cycle, exposure of enone **321** to enamine **363** and the acid catalyst **370** propagates a Michael addition/cyclisation/elimination reaction sequence to afford dihydropyridine **367**.



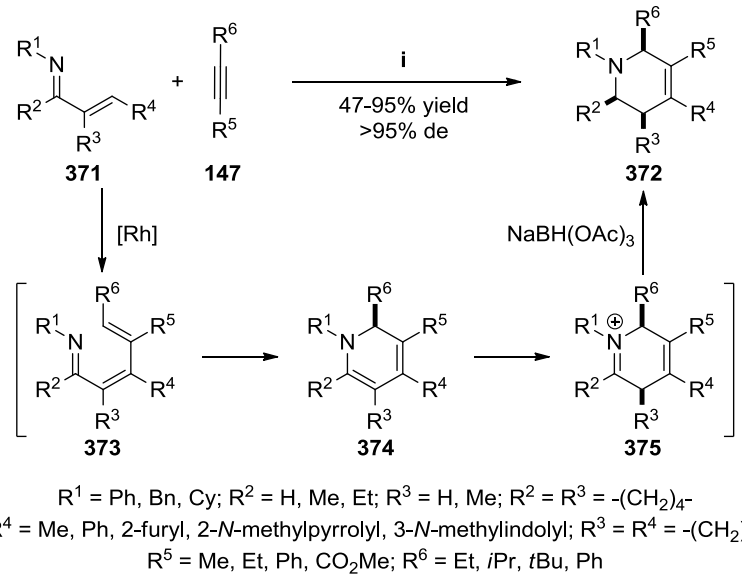
R^1 = Ph, *p*-MeC_6H_4, *p*-$MeOC_6H_4$, *p*-BrC_6H_4, *p*-$F_3CC_6H_4$, 2,4-$F_2C_6H_3$, *p*-MeC_6H_4, 3,4-(-OCH_2O-)C_6H_3
5-methyl-2-thienyl, *n*Pent; R^2 = Me; R^3 = CN, $COCH_3$, CO_2Me; $R^2 = R^3$ = -$(CH_2)_3CO$-

Scheme 100. Antonchick and Rueping's enantioselective 1,2,3,4-tetrahydropyridine synthesis using BINOL phosphoric acid catalysis. Reagents and conditions: i) catalyst **370** (5 mol%), Hantzsch ester (**369**), 50 °C, $CHCl_3$ or benzene.

Reversible formation of iminium ion **368** then allows transfer hydrogenation by the Hantzsch ester (**369**) to occur, furnishing a range of aryl and alkyl substituted tetrahydropyridines **364** with excellent enantioselectivities. Several electron withdrawing groups were also tolerated on the enamine **363** and enone **321** starting materials, making this a resourceful method to synthesise enantioenriched 1,2,3,4-tetrahydropyridine scaffolds.

Recently, Bergman and Ellman developed a highly diastereoselective synthesis of 1,2,3,6-tetrahydropyridines using a C-H activation/cyclisation/reduction cascade (Scheme 101).[164] In the presence of a rhodium complex, the reaction proceeds via the activation of the β-C-H bond of the α,β-unsaturated imine **371**, which then undergoes addition to an alkyne **147**. Subsequent electrocyclisation of azatriene **373** affords 1,2-dihydropyridine **374**, which is then reduced with $NaBH(OAc)_3$ and AcOH to furnish tetrahydropyridines **372**. Using this method 1,2,3,6-

tetrahydropyridines substituted in all six positions and with three stereocentres can be synthesised with excellent diastereocontrol. Single crystal X-ray diffraction showed that the major diastereomer contained an all *cis*-configuration.



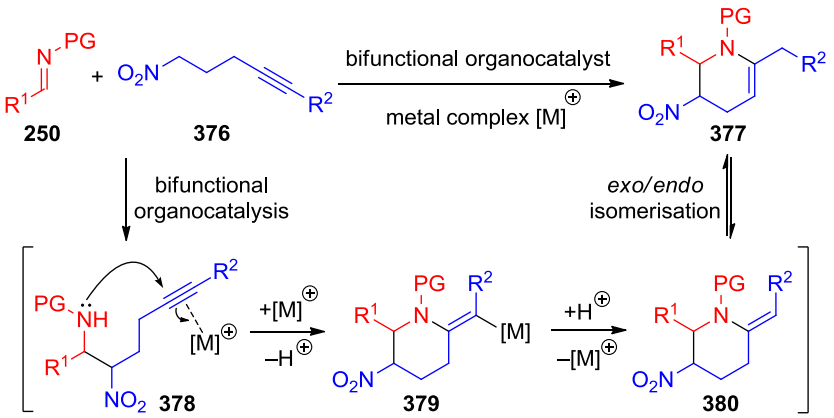
Scheme 101. Bergman and Ellman's synthesis of fully substituted 1,2,3,6-tetrahydropyridines via a C-H activation/cyclisation/reduction reaction cascade. Reagents and conditions: i) $[Rh(coe)_2Cl]_2$ (1-2.5 mol%), *p*-$Me_2NC_6H_4P(Et)_2$ (2-5 mol%), PhMe, 80 °C, 2 h then $NaBH(OAc)_3$, PhMe, EtOH/AcOH, 0 °C to RT overnight.

3.2 Project Aims

After the development of a nitro-Mannich/hydroamination cascade to 2,5-disubstituted pyrroles (Chapter 2),[165] we wanted to apply this methodology to the synthesis of enantioenriched 1,2,3,4-tetrahydropyridine derivatives by modification of the nitroalkyne reaction partner. Building on the seminal work of Dixon[8] and Jørgensen[147] on one-pot Mannich/hydroamination cascades, we postulated that we could combine bifunctional Brønsted base/H-bond donor organocatalysis and gold catalysis to enable an efficient enantioselective cascade to the desired products. With tetrahydropyridine compounds being important biologically active compounds as well as fundamental synthetic precursors, the development of a new methodology for these targets would be of great benefit to the synthetic community.

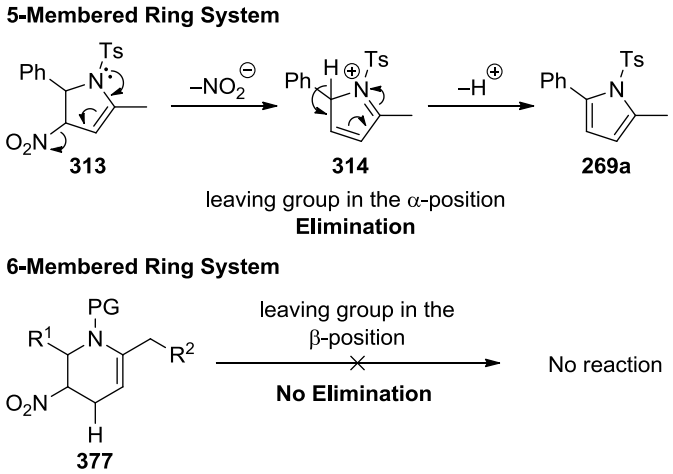
3.3 Concept of Enantioselective Tetrahydropyridine Synthesis

We recognised that replacing nitroalkyne **269** (Chapter 2) with the one-carbon homologue **376** would allow access to 1,2,3,4-tetrahydropyridine scaffolds **377** using a combination of bifunctional organo- and metal catalysis (Scheme 102).



Scheme 102. Proposed synthesis of enantioenriched 1,2,3,4-tetrahydropyridine derivatives using a one-pot nitro-Mannich/hydroamination cascade.

Following a similar reaction pathway to our previous study on 5-membered ring systems (Scheme 67, Chapter 2), an appropriately protected imine **250** would undergo a nitro-Mannich reaction with nitroalkyne **376** in the presence of a suitable Brønsted base/H-bond donor bifunctional organocatalyst.

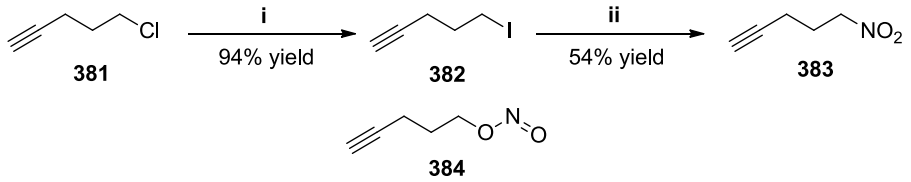


Scheme 103. Comparison of nitro group elimination pathways in 5- and 6-membered ring systems.

Intramolecular *6-exo-dig* cyclisation of the resulting β-nitroamine **378** under the control of a metal catalyst would then furnish piperidine **380**, with *exo/endo* alkene isomerisation affording 1,2,3,4-tetrahydropyridine **377**. In contrast to our previous study, we were confident that the nitro group would not be eliminated in the 6-membered ring system as there is no obvious driving force for this elimination reaction.[166] We also proposed that the nitro group cannot be eliminated because it no longer occupies the α-position next to the alkene functionality (Scheme 103).

3.4 Synthesis of Starting Materials and Proof of Principle Study

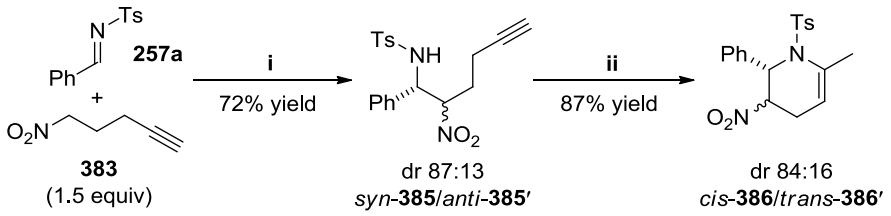
To obtain proof of principle for our proposed cascade reaction, we conducted a step-wise study to test if we could successfully synthesise the desired tetrahydropyridine motif using our proposed method. Firstly, nitroalkyne **383** was synthesised on gram scale in two steps starting from the commercially available 5-chloropent-1-yne (**381**) (Scheme 104). A Finkelstein reaction[167] using NaI afforded iodoalkyne **382** which was then converted to nitroalkyne **383** by treatment with $NaNO_2$ in DMSO at RT.[126] As with the synthesis of nitroalkyne **259** (Scheme 69, Chapter 2), the low yield of nitroalkyne **383** can be attributed to competing formation of the corresponding nitrite ester **384**.



Scheme 104. Synthesis of nitroalkyne **383**. Reagent and conditions: i) NaI, acetone, reflux, 20 h; ii) $NaNO_2$, DMSO, RT, 2 h.

With nitroalkyne **383** in hand, it was combined with *N*-sulfonyl imine **257a** in a KO*t*Bu catalysed nitro-Mannich, affording β-nitroamines **385** and **385′** as an inseparable mixture in 72% combined yield and 83:17 dr after 24 hours at RT

(Scheme 105). With β-nitroamines **385** and **385′** in hand, our attention turned to finding a metal complex that would facilitate the intramolecular hydroamination reaction. Due to our previous success using gold complexes in the synthesis of pyrroles (Chapter 2), we attempted the cyclisation reaction using $AuCl_3$ (5 mol%) and $Au(PPh_3)Cl$ (5 mol%).



Scheme 105. Hydroamination proof of principle study using β-nitroamines **385** and **385′**. Reagents and conditions: i) KO*t*Bu (5 mol%), MeOH, RT, 24 h; ii) $Au(PPh_3)Cl$ (5 mol%), AgOTf (5 mol%), PhMe, 75 °C, 2 h.

Unfortunately, no cyclised product was formed in either of these reactions, even after extensive heating and prolonged reactions times. This prompted us to explore a catalytic system using an activated gold(I) complex. Pleasingly, heating β-nitroamines **385** and **385′** to 75 °C in toluene with $Au(PPh_3)Cl$ (5 mol%) and AgOTf (5 mol%), furnished tetrahydropyridines **386** and **386′** as an inseparable mixture in 87% combined yield and 84:16 dr after 2 hours.

3.5 Optimisation of the Enantioselective Organocatalytic Nitro-Mannich Reaction

With proof of concept acquired for the synthesis of the racemic tetrahydropyridine **386**, we turned our attention to developing an enantioselective nitro-Mannich/hydroamination cascade. Using the nitro-Mannich reaction between *N*-sulfonyl imine **257a** and nitroalkyne **383** as an example, we screened a variety of known Brønsted base/H-bond donor bifunctional organocatalysts (Figure 10) to

assess the level of enantioinduction that could be achieved in the synthesis of β-nitroamines **385** and **385′** (Scheme 106).

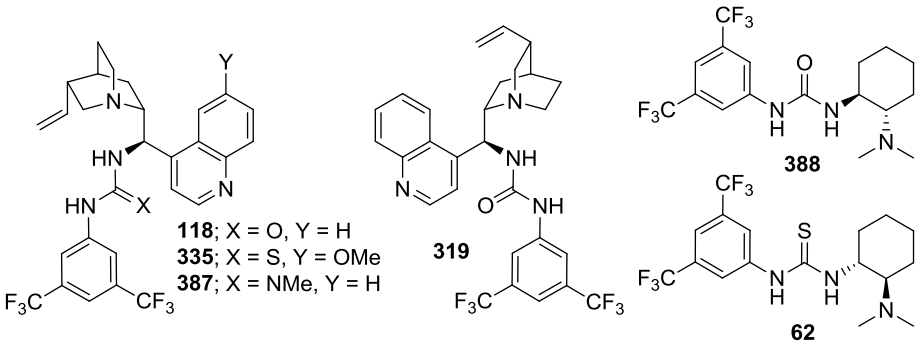
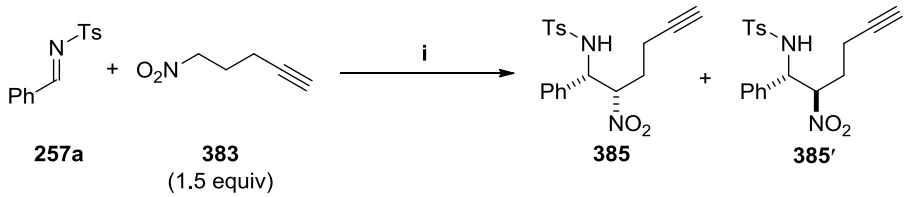


Figure 10. Brønsted base/H-bond donor bifunctional organocatalysts screened in the nitro-Mannich reaction using nitroalkyne **383**.

Using cinchonine-derived urea **118**, β-nitroamines **385** and **385′** were afforded in a combined 86% combined yield after stirring in toluene at RT for 72 hours. The reaction was found to show good diastereoselectivity towards the *syn*-diastereomer **385**, as was previously observed using KO*t*Bu (Scheme 105). However, the urea catalyst **118** and the *pseudo*-enantiomer **319** did not impart any major enantiocontrol on the reaction. As a result, we changed the *N*-protecting group of the imine to a Boc group. Pleasingly, a significant increase in enantioselectivity was achieved using *N*-Boc imine **112a** and urea **118**, affording β-nitroamines **389** and **389′** in 84% combined yield with 71% ee for the major diastereomer **389′** (Table 5, entry 1).

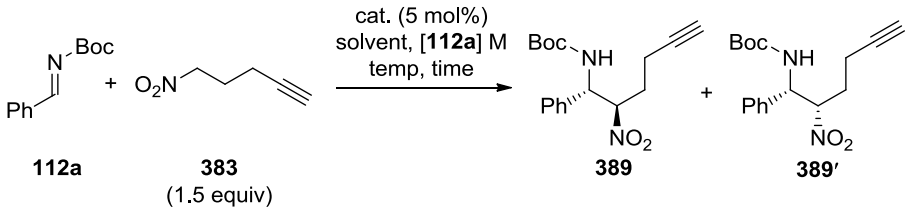


catalyst **118**: 86% yield, 91:9 dr, *major: syn*-**385** 3% ee; *minor: anti*-**385′** 25% ee
catalyst **319**: 80% yield, 95:5 dr, *major: syn*-**385** 2% ee; *minor: anti*-**385′** 16% ee

Scheme 106. Initial catalyst screen in the enantioselective nitro-Mannich reaction of *N*-sulfonyl imine **257a** and nitroalkyne **383**. Reagents and conditions: i) catalyst (5 mol%), PhMe, [**257a**] 0.1 M, RT, 72 h. The absolute configurations of **385** and **385′** were not determined, therefore only the relative configuration is shown.

The large increase in enantioselectivity using *N*-Boc imine **112a** is in line with previously reported results and is presumably due to the increased binding of urea **118** to the carbamate protecting group.[42] With good enantioselectivity achieved in the synthesis of β-nitroamines **389** and **389′** using urea **118**, we then screened various conditions and organocatalysts in an attempt to increase our initial 71% ee.

Table 5. Bifunctional organocatalyst optimisation studies in the nitro-Mannich reaction of *N*-Boc imine **112a** and nitroalkyne **383**.



entry	solvent	cat.	temp (°C)	time (h)	[**112a**] M	yield[a] (%)	dr[b] **389**:**389′**	ee[b] **389**/**389′** (%)
1	PhMe	**118**	RT	48	0.1	84	66:34	71/68[c]
2	MeCN	**118**	RT	48	0.1	60	78:22	70/61[c]
3	Et_2O	**118**	RT	48	0.1	67	65:35	70/56[c]
4	CH_2Cl_2	**118**	RT	48	0.1	61	70:30	62/56[c]
5	PhMe	**335**	RT	48	0.1	75	67:33	66/42[c]
6	PhMe	**387**	RT	48	0.1	32	66:34	31/35[c]
7	PhMe	**319**	RT	48	0.1	85	65:35	60/63
8	PhMe	**388**	RT	24	0.1	89	66:34	69/67
9	PhMe	**388**	3	24	0.1	63	74:26	85/76
10	PhMe	**388**	–15	24	0.1	46	81:19	82/80
11	PhMe	**388**	–15	24	0.5	87	87:13	92/82
12	PhMe	**62**	–15	24	0.5	56	82:18	91/68[c]

[a] Combined yield of inseparable β-nitroamines **389** and **389′**. [b] Determined by HPLC analysis of the purified product. [c] Opposite (2*R*,3*S*) and (2*R*,3*R*) enantiomers obtained.

To begin with, a solvent screen was conducted using urea **118**. Acetonitrile and diethylether both provided β-nitroamines **389** and **389′** with 70% ee for the major diastereomer, but with slightly reduced combined yields when compared to the reaction conducted in toluene (Table 5, entries 2 and 3). The use of dichloromethane led to a decrease in enantioselectivity of the major diastereomer **389**, with 62% ee being obtained. Due to these results, toluene was selected as the solvent of choice for further optimisation. We then studied the effect that the bifunctional organocatalyst structure had on the diastereo- and enantioselectivity of the reaction. The quinidine-derived thiourea **335** and the cinchonine-derived urea **319**, both afforded β-nitroamines **389** and **389′** in good yields, but with minor reductions in the enantiopurity of the major diastereomer **389** (Table 5, entries 5 and 7). Urea **388** pleasingly afforded β-nitroamines **389** and **389′** in an improved 89% yield after a reduced reaction time of 24 hours, while also retaining the previously observed enantioselectivity for **389** (Table 5, entry 8). Due to the improved yield and reduced reaction time, additional studies were conducted using urea **388**. Reduction of the reaction temperature to 3 °C resulted in improvements in the diastereoselectivity (dr 74:26) and enantioselectivity of **389** (85% ee; Table 5, entry 9). Further decrease of the temperature to −15 °C led to an increase in the diastereoselectivity (dr 81:19) and retention of the enantioselectivity of β-nitroamine **389** (82% ee), however the reaction was significantly slower with only 46% combined yield being obtained after 24 hours (Table 5, entry 10). In an effort to increase the reaction rate, the reaction mixture was concentrated to 0.5 M with respect to *N*-Boc imine **112a**. Gratifyingly, not only did the yield of **389** and **389′** increase to 87%, the diastereo- and enantioselectivities were also significantly enhanced (dr 87:13, 92% ee; Table 5, entry 11). Excellent enantiocontrol was also witnessed when using thiourea **62** but

the yield of β-nitroamines **389** and **389′** was reduced to 56% after 24 hours (Table 5, entry 12). In light of these results, urea **388** was identified as the best organocatalyst to use in our one-pot optimisation studies.

3.6 Bifunctional (Thio)urea Organocatalyst Mode of Action

Interestingly, using urea **388** and thiourea **62** in the nitro-Mannich reaction of *N*-Boc imine **112a** and nitroalkyne **383** both afforded β-nitroamines **389** and **389′** in similar diastereoselectivities with essentially the same enantioselectivity (Table 5, entries 11 and 12). Based on the isolated yields of β-nitroamines **389** and **389′**, the only difference in these reactions was that the reaction using thiourea **62** (56% yield after 24 hours) was slower than the reaction using urea **388** (87% yield after 24 hours). This result contradicts the instinctive outcome that the more acidic thiourea functionality should exhibit increased activity in the reaction through improved H-bond donation.[168] Similar observations have been reported by Hynes[169] and Kyle[170] in Michael addition reactions when using the bifunctional cinchona-derived urea **118** and thiourea **64** organocatalysts. They suggest that a possible explanation for these observations is that the urea functionality shows increased H-bond acceptor character than the corresponding thiourea. This facilitates the formation of an intramolecular H-bonding interaction between the urea oxygen atom and an electron poor hydrogen atom in the *o*-position on the adjacent phenyl ring (Figure 11).[171]

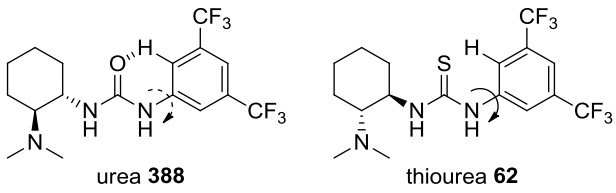
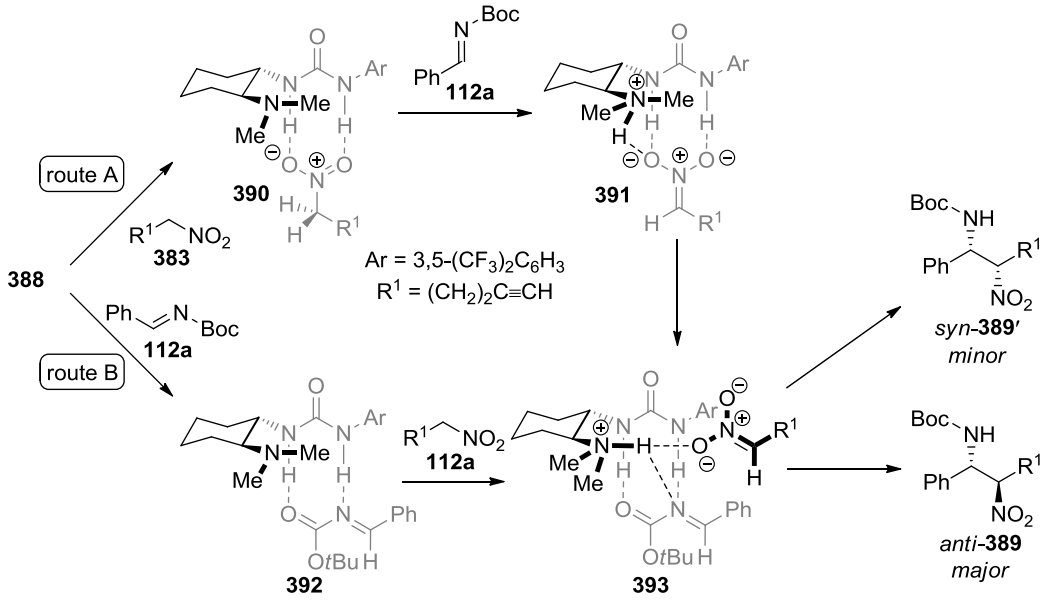


Figure 11. Effect of H-bonding interaction on catalyst conformation.

As a result, there is reduced rotation of the phenyl substituent which increases the conjugation of the π-system, thus making the urea moiety more acidic. In contrast, the thiourea functionality exhibits increased rotation of the phenyl substituent and hence less conjugation of the π-system, resulting in reduced catalyst activity.[169,170] Although the model described in Figure 11 can be a possible rationale for the observed changes in activity, urea **388** and thiourea **62** cannot be considered as conformationally rigid structures in solution. Extensive DFT modelling studies of Takemoto's thiourea **62** catalyst conducted by Pápai and Soós[172] and a related study into cinchona-derived thioureas[173] have demonstrated that other low energy conformations are readily accessible. Another important consideration reported by Soós and co-workers[174] is that these bifunctional (thio)urea systems can often form dimeric structures through intermolecular H-bonding interactions. This can have a dramatic effect on the expected catalytic activity depending on how the organocatalyst exists and performs while in solution. A report by Song[175] elegantly demonstrates the explanation of Soós, where decreasing the concentration of the organocatalyst increases the enantioselectivity observed in the reaction products. This effect was attributed to the catalyst existing in its monomer form as the catalyst concentration decreased.

To account for the high stereoselectivity observed in the nitro-Mannich reaction of *N*-Boc imine **112a** and nitroalkyne **383**, Takemoto proposed that the reactions proceed via ternary complex **393**, where *N*-Boc imine **112a** and the nitronate anion of **383** coordinate to organocatalyst **388** by H-bonding interactions (Scheme 107).[42] Two possible routes to generate ternary complex **393** were proposed. In route A, urea **388** activates nitroalkyne **383** by H-bonding interactions and subsequent intra- or intermolecular deprotonation by the basic tertiary amine forms complex **391**.



Scheme 107. Proposed reaction mechanism of the enantioselective nitro-Mannich reaction using bifunctional organocatalyst **388**.[42]

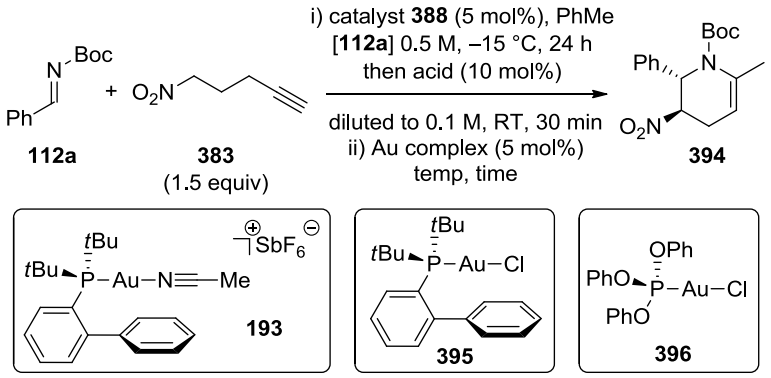
It is envisaged that imine **112a** then coordinates to the urea moiety in place of the nitronate anion to produce ternary complex **393**. In route B, the urea first coordinates imine **112a** and then nitroalkyne **383** is deprotonated to form ternary complex **393**. From ternary complex **393** the major *anti*-diastereomer **389** would be the predominant product, with another competing mechanism accounting for the formation of the minor *syn*-diastereomer **389′**. However the mechanism of the reaction proceeds, it is evident that either activation of imine **112a** by the urea moiety and/or deprotonation of nitroalkyne **383** by the tertiary amine must occur in order to obtain the resulting β-nitroamine **389** with high enantiocontrol.

3.7 Optimisation of the One-Pot Nitro-Mannich/Hydroamination Cascade

With the highly enantioselective synthesis of β-nitroamine **389** achieved using bifunctional organocatalyst **388**, our interest turned to developing a one-pot procedure to access the desired 1,2,3,4-tetrahydropyridine motifs. Our previous study had demonstrated that gold complexes can efficiently catalyse intramolecular

hydroamination reactions with substrates containing nitro groups (Chapter 2). However, gold complexes are known to be incompatible with Brønsted base/H-bond donor bifunctional organocatalysts because of the high affinity that basic nitrogen atoms have for gold complexes.[147] To overcome this problem, we adopted a sequential cascade approach whereby a Brønsted acid was added to the reaction mixture before the gold complex in order to quench the basic nitrogen atom present in the bifunctional organocatalyst **388**. Our preliminary studies used 4-nitrophenol (10 mol%) as the quenching additive in conjunction with complex **193**[176] (5 mol%) introduced by Echavarren and co-workers (Table 6, entry 1). We changed the gold complex at this stage as using $Au(PPh_3)Cl$ in conjunction with AgOTf had previously been shown to result in diminished yields of tetrahydropyridine **394**. Pleasingly, tetrahydropyridine **394** was afforded as a 85:15 mixture of diastereomers with 88% ee for the major diastereomer after 8 hours at 60 °C, albeit in a low yield of 11%. A screen of acids identified diphenylphosphate (DPP, 10 mol%) as the optimum quenching acid for this cascade reaction, affording tetrahydropyridine **394** in 65% yield, with excellent diastereo- and enantiocontrol (dr 94:6, 93% ee) after 6 hours at 60 °C (Table 6, entry 3). Changing the gold complex counterion from SbF_6^- to OTf^- in situ, resulted in a reduction of the reaction efficiency, with **394** being isolated in 50% yield (Table 6, entry 5). Decreasing the reaction temperature to RT and 40 °C resulted in slightly impaired yields and longer reaction times (Table 6, entries 7 and 8). Increasing the reaction temperature to 100 °C led to a shorter reaction time but the diastereoselectivity of the cascade was reduced (dr 91:9) when compared to the reaction cascade carried out at 60 °C (Table 6, entry 9).

Table 6. One-pot optimisation studies between *N*-Boc imine **112a** and nitroalkyne **383** using organocatalysis and gold catalysis.



entry	acid (10 mol%)	Au complex (5 mol%)	(ii) temp (°C)	(ii) time (h)	dr[a]	yield (%)	dr[b]	ee[b] (%)
1	4-nitrophenol	**193**	60	8	84:16	11	85:15	88
2	benzoic acid	**193**	60	8	90:10	9	99:1	92
3	DPP	**193**	60	6	94:6	65	99:1	93
4	*p*-TsOH	**193**	60	3	95:5	53	99:1	93
5	DPP	**395**[c]	60	8	94:6	50	98:2	92
6	DPP	**396**[d]	60	3	92:8	33	99:1	92
7	DPP	**193**	RT	24	95:5	55	99:1	92
8	DPP	**193**	40	8	95:5	58	99:1	91
9	DPP	**193**	100	6	91:9	55	95:5	91
10[e]	DPP	—	60	24	—	—	—	—
11[e]	—	**193**	60	24	—	—	—	—

[a] Determined by ^{1}H NMR analysis of the crude reaction mixture. [b] Determined by HPLC analysis of the purified product. [c] With AgOTf (10 mol%). [d] With $AgSbF_6$ (10 mol%). [e] No reaction observed.

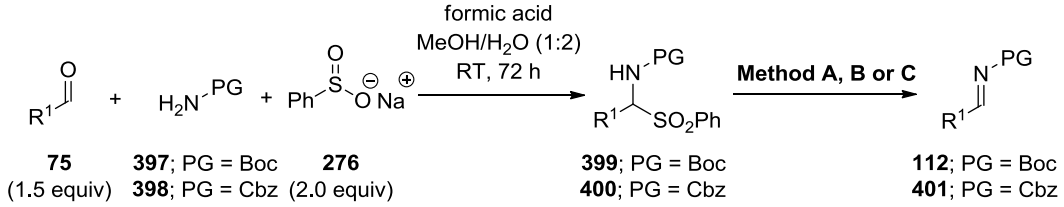
A control experiment conducted using only complex **193** (5 mol%) without the presence of an acidic additive revealed that no cyclisation occurred even after heating at 60 °C for 24 hours (Table 6, entry 11), highlighting the critical role of the

acid in protonation of the amine prior to the addition of the gold complex. Finally, no cyclisation occurred when using only DPP (10 mol%), thus confirming the need for the gold complex in the hydroamination reaction (Table 11, entry 10).

3.8 Scope of the Nitro-Mannich/Hydroamination Cascade

With optimal conditions identified, we set about exploring the scope of the enantioselective nitro-Mannich/hydroamination cascade. Accordingly, a range of substituted aryl *N*-Boc imines were prepared using a known two-step procedure.[138] Firstly, condensation of the appropriate aryl aldehyde **75** with *tert*-butyl carbamate (**397**) or benzyl carbamate (**398**) and benzenesulfinic acid sodium salt (**276**) in the presence of formic acid, afforded amidosulfones **399** and **400** in 17-82% yield after a simple filtration/trituration purification procedure (Table 7). Each of these reactions was conducted on multi-gram scale and the products could easily be stored at room temperature for a significant period of time (over 12 months) without any degradation being observed by ^{1}H NMR analysis. To synthesise the imine products, the corresponding amidosulfones were treated with K_2CO_3 and Na_2SO_4 in refluxing THF for 15 hours, furnishing the *N*-Boc imines **112a-g** and **112i-o** in 83-97% yield. Imines **112h** and **401a-d** were synthesised by treating the corresponding amidosulfones with a 1.4 M aq. solution of K_2CO_3 in CH_2Cl_2.[177] The cyclohexyl substituted imine **401p** was synthesised by elimination of amidosulfone **399p** with Cs_2CO_3 in CH_2Cl_2.[178] The prepared *N*-Boc and *N*-Cbz imines are known to be sensitive to moisture. Therefore, they were used in the nitro-Mannich/hydroamination cascade as they were obtained from the reaction, without further purification.

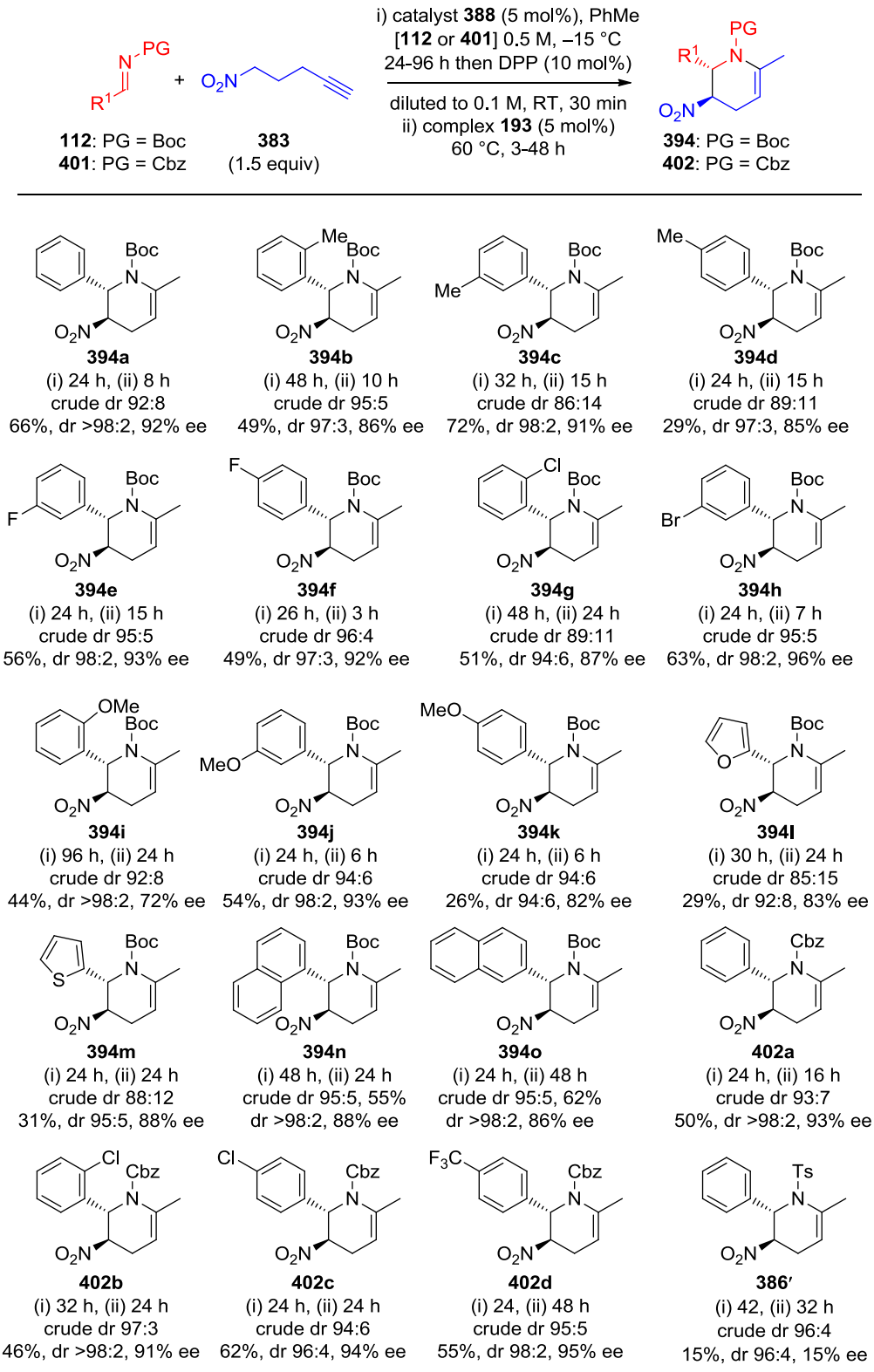
Table 7. Synthesis of amidosulfones and *N*-carbamate protected imines.



entry	R^1	PG	amido-sulfone	yield (%)	method	imine	yield (%)
1	Ph	Boc	**399a**	78	A	**112a**	96
2	*o*-MeC_6H_4	Boc	**399b**	33	A	**112b**	96
3	*m*-MeC_6H_4	Boc	**399c**	75	A	**112c**	94
4	*p*-MeC_6H_4	Boc	**399d**	73	A	**112d**	95
5	*m*-FC_6H_4	Boc	**399e**	82	A	**112e**	92
6	*p*-FC_6H_4	Boc	**399f**	60	A	**112f**	97
7	*o*-ClC_6H_4	Boc	**399g**	75	A	**112g**	89
8	*m*-BrC_6H_4	Boc	**399h**	71	B	**112h**	97
9	*o*-$MeOC_6H_4$	Boc	**399i**	66	A	**112i**	92
10	*m*-$MeOC_6H_4$	Boc	**399j**	70	A	**112j**	84
11[a]	*p*-$MeOC_6H_4$	Boc	**399k**	79	A	**112k**	94
12	2-furyl	Boc	**399l**	34	A	**112l**	84
13	2-thienyl	Boc	**399m**	27	A	**112m**	83
14	1-naphthyl	Boc	**399n**	48	A	**112n**	90
15	2-naphthyl	Boc	**399o**	17	A	**112o**	91
16	Cy	Boc	**399p**	81	C	**112p**	90
17	Ph	Cbz	**400a**	57	B	**401a**	96
18[b]	*o*-ClC_6H_4	Cbz	**400b**	–	B	**401b**	97
19[b]	*p*-ClC_6H_4	Cbz	**400c**	–	B	**401c**	98
20[b]	*p*-$F_3CC_6H_4$	Cbz	**400d**	–	B	**401d**	94

[a] Reaction time of 10 hours. [b] Prepared by Dr. L. Tillman. **Method A**: K_2CO_3, Na_2SO_4, THF, reflux, 15 h; **Method B**: 1.4 M aq. K_2CO_3, CH_2Cl_2, RT, 2 h; **Method C**: Cs_2CO_3, CH_2Cl_2, RT, 12 h.

With a wide array of carbamate protected imines in hand, we subjected them to the optimised nitro-Mannich/hydroamination conditions. Pleasingly, the cascade reaction was found to tolerate a range of aryl substituted *N*-Boc imines, affording the tetrahydropyridine products in good yields with good to excellent diastereo- and enantioselectivities (Scheme 108). The methyl substituted aryl *N*-Boc imines **112b-d** afforded the corresponding 1,2,3,4-tetrahydropyridines **394b-d** in low to good yields and good enantioselectivities (29-72%, 85-91% ee). Electron-poor aryl groups bearing halogens in the *ortho*-, *meta*- and *para*-positions were all found to be suitable substrates for the cascade reaction, furnishing the desired products **394e-h** in good yields and high enantioselectivities (49-63% yield, 87-96% ee). The electron-rich methoxy substituted aryl *N*-Boc imines all gave the desired tetrahydropyridines **394i-k**, however the enantioselectivity obtained when the methoxy group was in the *ortho*-position was considerably lower than the previous results (72% ee). The heteroaromatic 2-furyl and 2-thienyl substituents gave results that were comparable to other electron-rich methoxy aryl substituents, with low yields being obtained (29-31%) and slight reductions in enantioselectivities (83-88%). The 1- and 2-naphthyl derived *N*-Boc imines gave rise to the corresponding tetrahydropyridines in good yields (55-62%) and enantioselectivities (86-88%). When using the cyclohexyl substituted *N*-Boc imine **112p** a complex mixture of compounds inseparable via flash column chromatography was obtained. This could have been caused by the retro nitro-Mannich being favoured over the hydroamination reaction at 60 °C. Alteration of the *N*-protecting group was also possible with several *N*-Cbz imines easily tolerating the reaction conditions, furnishing the equivalent tetrahydropyridines **402a-d** in good yields with excellent enantiocontrol (46-62% yield, 91-95% ee).



Scheme 108. Scope of the enantioselective nitro-Mannich/hydroamination cascade.

Generally, good diastereoselectivities were observed in all of the crude reaction mixtures from the nitro-Mannich/hydroamination cascade, with the lowest results

being obtained with *meta*-methyl **394c** (86:14) and 2-furyl **394l** (85:15). From all of the results obtained it can be seen that the enantioselectivities are highest when the aromatic ring is substituted in the *meta*-position by an electron-withdrawing group. In contrast, the reaction yields are at their lowest when the aromatic ring is substituted in the *para*-position (**394d** and **394k**) or when there is a strong electron-donating group present on the aryl ring. The cascade reaction was also attempted using the previously employed *N*-sulfonyl imine **257a**. However, the product **386′** was obtained in poor yield and enantioselectivity. The low enantioselectivity observed is in line with our earlier studies into enantioselective nitro-Mannich reactions using *N*-sulfonyl imine **257a**. Conversely the low yield of tetrahydropyridine **386′** was not expected but we postulate that the product may not be stable to the acidic reaction conditions, leading to decomposition of the product during the cascade reaction.

3.9 Determination of the Absolute Configuration

To determine the absolute configuration of the synthesised tetrahydropyridines, we decided to use single crystal X-ray diffraction analysis of a crystalline tetrahydropyridine. Accordingly, the *ortho*-chloro substituted tetrahydropyridine **394g** was crystallised from methanol by slow evaporation of the solvent. After filtration, good quality crystals of **394g** were obtained in >98% ee. Single crystal X-ray diffraction data determined that the aryl and nitro substituents occupied the *pseudo*-axial positions of the tetrahydropyridine ring, with the absolute configuration being confirmed as (2*S*,3*R*). All other tetrahydropyridine structures were assigned by analogy to the crystal structure of tetrahydropyridine **394g**. The β-nitroamines diastereomers *anti*-**389** and *syn*-**389′** were also assigned by analogy to this crystal structure.

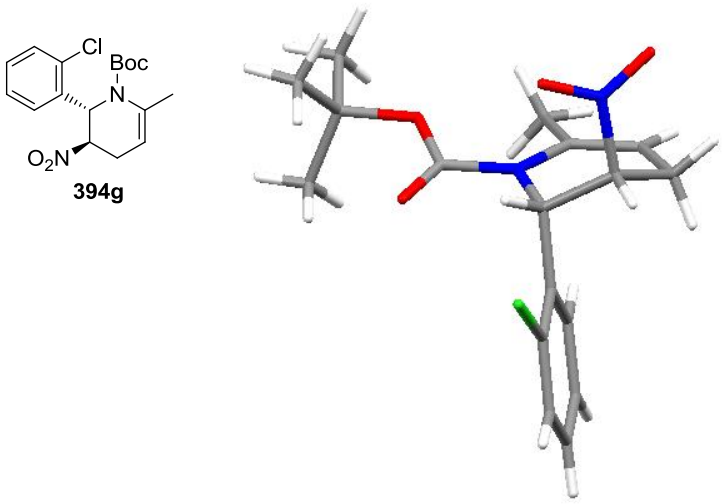
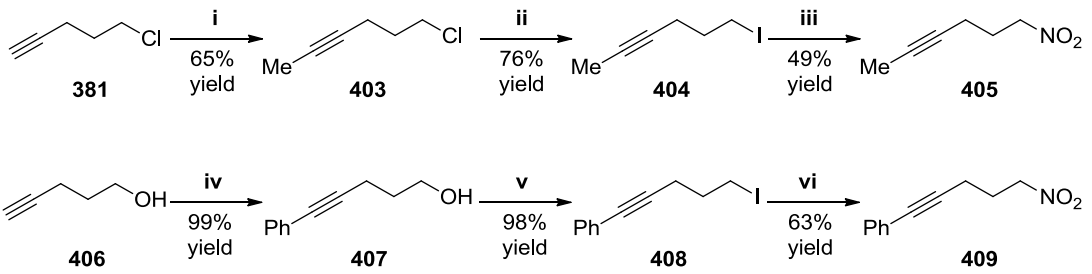


Figure 12. X-Ray diffraction representation of tetrahydropyridine **394g**.

3.10 Extension of Methodology to Substituted Nitroalkyne Substrates

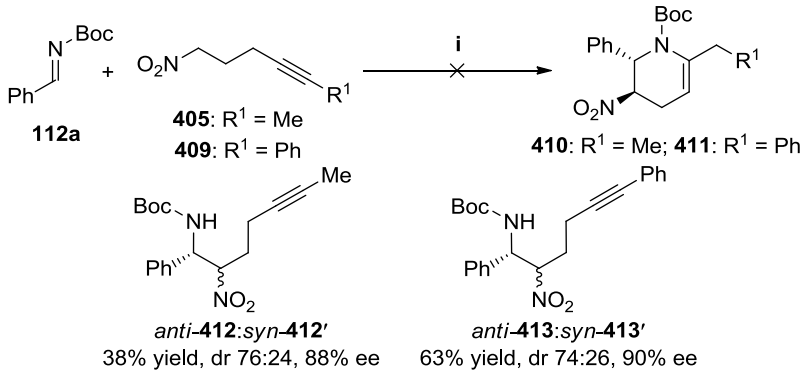
In an effort to extend this methodology, we attempted the challenging cyclisation of nitroalkyne substrates bearing substituents on the alkyne terminus. Firstly, the synthesis of the substituted nitroalkynes was undertaken (Scheme 109). The methyl substituted nitroalkyne **405** was synthesised starting from 5-chloropent-1-yne (**381**). Alkylation using *n*BuLi and iodomethane followed by halogen exchange via a Finkelstein reaction[167] afforded iodoalkyne **404** in 76% yield.



Scheme 109. Synthesis of substituted nitroalkynes **405** and **409**. Reagents and conditions: i) *n*BuLi, THF, 0 °C, 1 h then MeI, 0 °C to RT over 30 min; ii) NaI, acetone, reflux, 16 h; iii) $NaNO_2$, DMSO, RT, 3 h; iv) iodobenzene, piperidine, CuI (6 mol%), $Pd(PPh_3)_2Cl_2$ (3 mol%), PhMe, 30 °C, 2 h; v) I_2, PPh_3, imidazole, CH_2Cl_2, RT, 3 h; vi) $NaNO_2$, DMSO, RT, 2 h.

Nitroalkyne **405** was then afforded in 49% yield after iodoalkyne **404** was treated with $NaNO_2$ in DMSO at RT for 2 hours.[126] The phenyl substituted nitroalkyne **409** was synthesised from pent-4-yn-1-ol (**406**) via a Sonogashira coupling[141] with iodobenzene, affording alkyne **407** in 99% yield. Conversion of alcohol **407** into iodoalkyne **408** was accomplished via an Appel reaction[140] using iodine and PPh_3 followed by displacement of the iodide with $NaNO_2$ to furnish nitroalkyne **409** in 63% yield.

With adequate quantities of nitroalkyne substrates **405** and **409** in hand, they were both reacted with *N*-Boc imine **112a** using the optimal nitro-Mannich/hydroamination conditions previously determined (Scheme 110). The nitro-Mannich reaction proceeded smoothly under the control of urea **388**, but unfortunately no cyclisation was witnessed when heating at 60 °C using either nitroalkyne **405** or **409**.

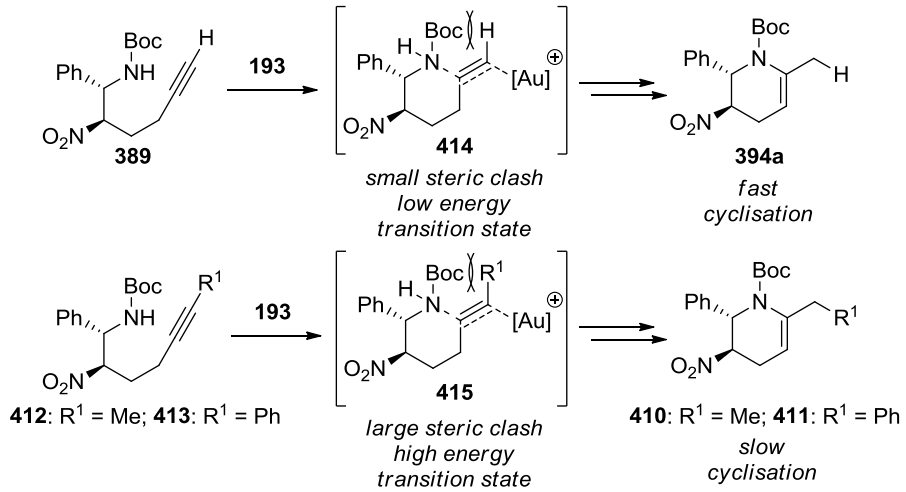


Scheme 110. Nitro-Mannich/hydroamination cascade using substituted nitroalkynes **405** and **409**. Reagents and conditions: i) catalyst **388** (5 mol%), PhMe, [**112a**] 0.5 M, –15 °C, 24 h then DPP (10 mol%), diluted to 0.1 M, RT, 30 min then catalyst **388** (5 mol%), 100 °C, 72 h.

Increasing the temperature of the hydroamination reaction to 100 °C for 72 hours did not facilitate the cyclisation reaction either, with the corresponding β-nitroamine intermediates **412** and **412′** (38%, dr 76:24, 88% ee) and **413** and **413′** (63%,

dr 74:26, 90% ee) being recovered from the reaction mixtures in moderate yields and good enantioselectivities.

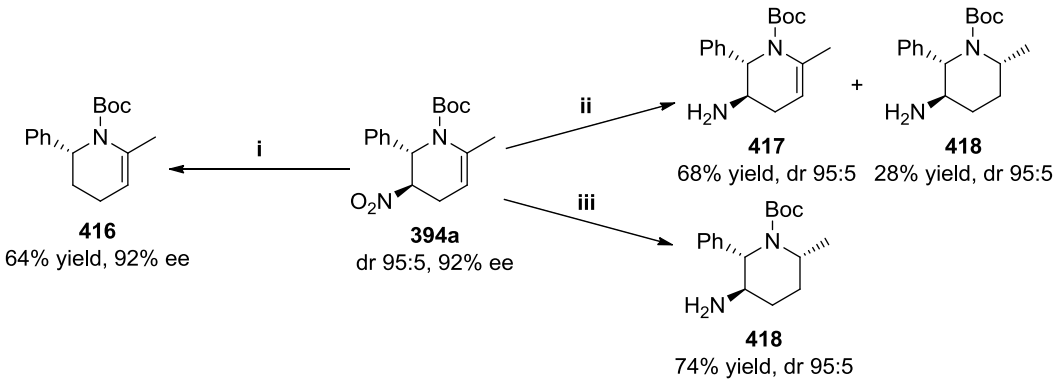
We proposed that the cyclisation of the internal alkyne substrates does not proceed due to 1,3-allylic strain arising in the transition state between the bulky *N*-Boc protecting group and the substituent on the alkyne terminus (Scheme 111). This hypothesis is in-line with our previous study on 5-membered ring systems and is supported by similar observations in metal catalysed carbocyclisation reactions using substituted alkynes.[142]



Scheme 111. Proposed 1,3-allylic strain arising in the hydroamination reaction transition state.

3.11 Synthetic Elaboration of Tetrahydropyridine 394a

To illustrate that the synthesised tetrahydropyridines are useful intermediates for target synthesis, compound **394a** was further elaborated using a variety of methods (Scheme 112). Reductive removal of the nitro group proceeded smoothly using Bu_3SnH and AIBN[179] in toluene at 110 °C to furnish tetrahydropyridine **416** in 64% yield without racemisation of the stereogenic centre.



Scheme 112. Synthetic elaboration of tetrahydropyridine **394a**. Reagents and conditions: i) Bu_3SnH, AIBN, PhMe, 110 °C, 3 h; ii) $NiCl_2{\cdot}6H_2O$, $NaBH_4$, MeOH, 0 °C, 20 min; iii) $NiCl_2{\cdot}6H_2O$, $NaBH_4$, MeOH, RT, 5 h.

Reduction of the nitro group using nickel boride (prepared in situ from $NiCl_2$ and $NaBH_4$) afforded amine **417** in 68% yield with retention of the diastereoselectivity (dr 95:5). The fully reduced piperidine **418** was also isolated from the reaction mixture in 28% yield with excellent diastereoselectivity (dr 95:5). Shibasaki and co-workers have reported that nitro group reduction using nickel boride does not lead to epimerisation at the nitro group stereocentre.[31] Therefore, the configuration of amine **417** was assigned by analogy to the X-ray crystal structure of tetrahydropyridine **394g**. Increasing the equivalents of nickel boride and conducting the reaction at room temperature allowed the exhaustive reduction of both the nitro and enamide functionalities, affording piperidine **418** in 74% yield and 95:5 dr. The configuration of piperidine **418** was confirmed by NOE analysis with a strong interaction being observed between the protons on the axial phenyl and methyl groups (Figure 13). The high diastereoselectivity observed in the formation of piperidine **418** can be rationalised by the steric interactions imparted by the *N*-Boc protecting group. To minimise the 1,3-allylic strain with the *N*-Boc group, the C6-methyl group naturally occupies the axial position in piperidine **418**.[180]

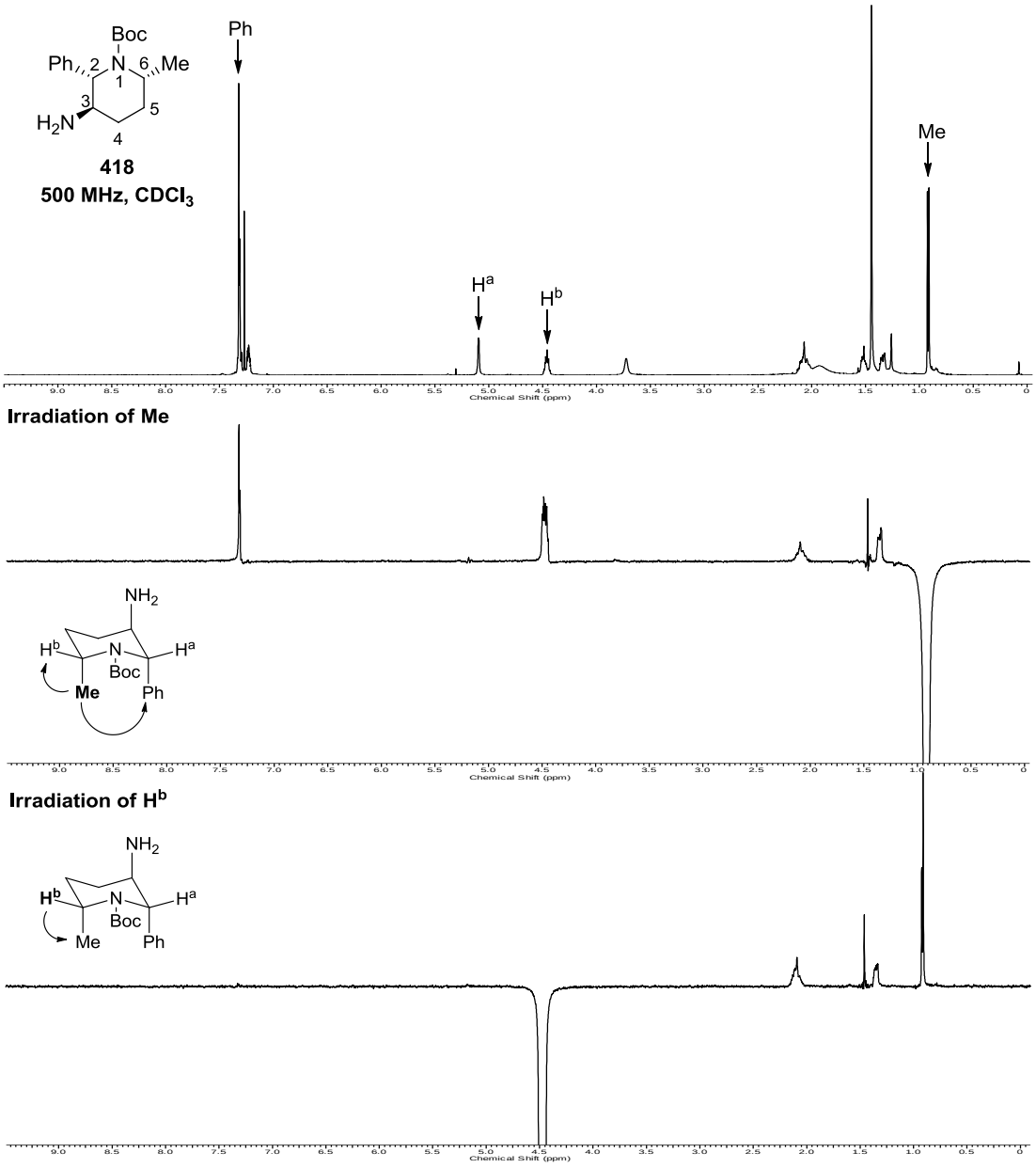
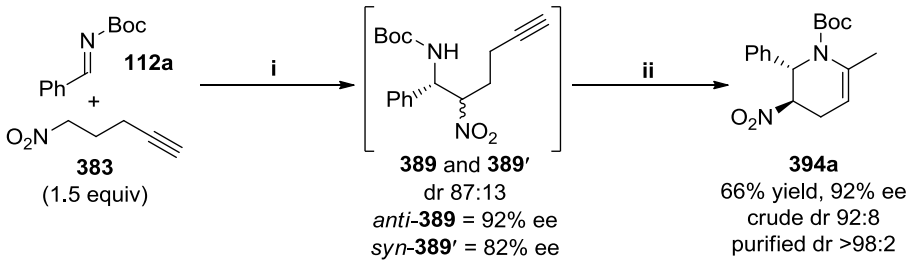


Figure 13. NOE interaction between the axial phenyl and methyl groups proving the C2-C6 *cis*-stereochemistry.

3.12 Investigation into the Mechanistic Pathway

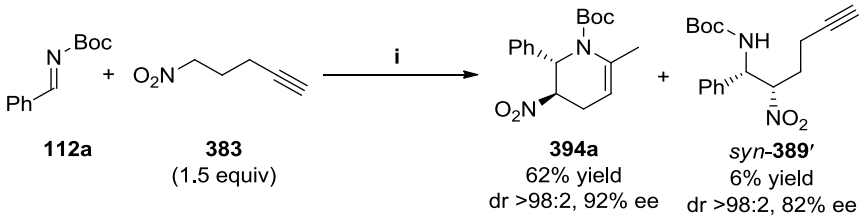
During this investigation, we had observed an enhancement of the diastereomeric ratio of the products as the reaction cascade progressed (Scheme 113). For example, in the case of the synthesis of tetrahydropyridine **394a**, β-nitroamines **389** and **389′** exhibited a diastereomeric ratio of 87:13 in favour of the *anti*-diastereomer **389**. Upon treatment with DPP (10 mol%) and complex **193** at 60 °C for 8 hours, the

diastereomeric ratio of tetrahydropyridine **394a** increased to 92:8. This diastereomeric ratio was further enhanced to >98:2, after purification by flash column chromatography on silica gel.



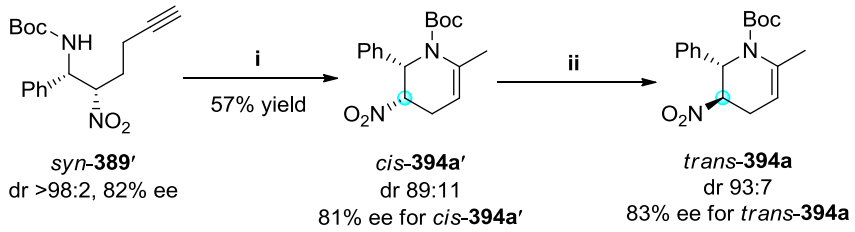
Scheme 113. Observed diastereomeric enrichment during the cascade reaction. Reagents and conditions: i) catalyst **388** (5 mol%), PhMe, [**112a**] 0.5 M, –15 °C, 24 h then DPP (10 mol%), diluted to 0.1 M with PhMe, RT, 30 min; ii) complex **193** (5 mol%), 60 °C, 8 h.

These observations demonstrate that a kinetic resolution of the *anti*-diastereomer **389** is occurring as the cascade reaction progresses. This kinetic resolution favours the cyclisation of the major *anti*-diastereomer **389**over the minor *syn*-diastereomer **389′**, thus giving an increase in the diastereomeric ratio of tetrahydropyridine **394a**.[181] To investigate the kinetic resolution further, we wanted to conduct the hydroamination reaction using only the *syn*-diastereomer **389′**. As the β-nitroamines **389** and **389′** could not be separated by flash column chromatography on silica gel, we exploited the kinetic resolution of the hydroamination reaction to isolate *syn*-diastereomer **389′** (Scheme 114).



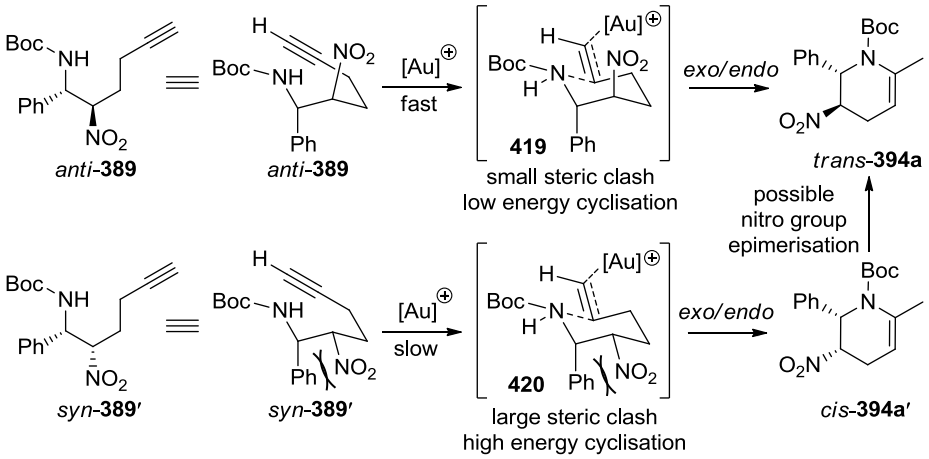
Scheme 114. Isolation of *syn*-β-nitroamine **389′**. Reagents and conditions: i) catalyst **388** (5 mol%), PhMe, [**112a**] 0.5 M, –15 °C, 24 h then DPP (10 mol%), diluted to 0.1 M with PhMe, RT, 30 min then complex **193** (5 mol%), 60 °C, 8 h.

From the nitro-Mannich/hydroamination cascade of *N*-Boc imine **112a** and nitroalkyne **383**, we were able to recover unreacted *syn*-β-nitroamine **389′** as a single diastereomer in 6% yield with 82% ee. β-Nitroamine **389′** was then subjected to the hydroamination conditions at the elevated temperature of 100 °C. Pleasingly, *cis*-tetrahydropyridine **394a′** was afforded in 57% yield, 89:11 dr and 81% ee (Scheme 115). We then studied the stability of *cis*-tetrahydropyridine **394a′** using HPLC analysis on a chiral stationary phase. Regular analysis showed that epimerisation of *cis*-**394a′** into *trans*-**394a** occurred smoothly over 12 days affording the *trans*-diastereomer **394a** in 93:7 dr and 83% ee.



Scheme 115. Synthesis and epimerisation study of *cis*-tetrahydropyridine **394a′**. Reagents and conditions: i) complex **193** (5 mol%), PhMe, 100 °C, 24 h; ii) Standing in EtOH, RT, 12 days.

To account for the observed kinetic resolution in the hydroamination reaction, we propose that the transition state of the *syn*-diastereomer **389′** is higher in energy than the corresponding transition state of the *anti*-diastereomer **389**, based on the steric interactions of the phenyl and nitro substituents (Scheme 116). In the case of the *anti*-β-nitroamine **389**, a relatively small steric clash occurs between the phenyl and nitro groups in transition state **419**, thus providing a low energy transition state and a relatively fast hydroamination reaction. In the case of the *syn*-β-nitroamine **389′**, a relatively large steric clash exists between the phenyl and nitro substituents in the C2 and C3 positions of transition state **420**, thus providing a high energy transition state and a relatively slow cyclisation.



Scheme 116. Proposed rational for diastereomeric enhancement during the nitro-Mannich/hydroamination cascade.

Even with this kinetic resolution occurring during the hydroamination reaction, small quantities of *cis*-**394a′** were still observed in the ^{1}H NMR spectrum of the crude reaction mixture, but the amount of *cis*-**394a′** present was reduced further after the purification procedure. This is most likely caused by separation of the diastereomers by flash column chromatography on silica gel. Another possibility to explain the enhancement of the diastereomeric ratio is that *cis*-**394a′** epimerises into the more thermodynamically stable *trans*-**394a** during the purification procedure. However, if this was occurring in this example we would expect the enantioenrichment of *trans*-tetrahydropyridine **394a** (92% ee) to be lower than that of the *anti*-β-nitroamine intermediate **389** (92% ee).

3.13 Summary and Conclusion

In summary, we have developed an efficient one-pot enantioselective nitro-Mannich/hydroamination cascade reaction to substituted 1,2,3,4-tetrahydropyridine motifs using readily available *N*-Boc and *N*-Cbz imines and a nitroalkyne substrate. Proceeding with a combination of Brønsted base/H-bond donor bifunctional organocatalysis and gold catalysis, the sequential cascade reaction affords the tetrahydropyridine products in moderate to good yields (26-72%) with good to excellent enantio- (72-96% ee) and diastereoselectivities (dr 85:15-97:3). The synthetic utility of the tetrahydropyridine products was demonstrated by the high stereoselective reduction of the amine and enamide functionalities to afford piperidine building blocks that could be used for biological evaluation and target synthesis.

Chapter 4: Diastereo- and Enantioselective Synthesis of Substituted Pyrrolidines via a Nitro-Mannich/Hydroamination Cascade

The work presented in this chapter was conducted in collaboration with Dr. Andrej Ďuriš. All of the results from this collaboration have been included in this chapter for completeness. All compounds that were independently prepared and characterised by Dr. A. Ďuriš are referenced within the text.

4.1 Introduction

4.1.1 Pyrrolidine Containing Compounds

Pyrrolidine heterocycles are prevalent structures found in a myriad of biologically active molecules and natural products (Figure 14).[104] With pyrrolidine heterocycles being such an important structural unit, research into the synthesis of pyrrolidine derivatives is ever expanding. Some of the most well known approaches to prepare substituted pyrrolidines include [3+2] cycloadditions,[182] iminium ion cyclisations[183] and various metal catalysed reactions.[184]

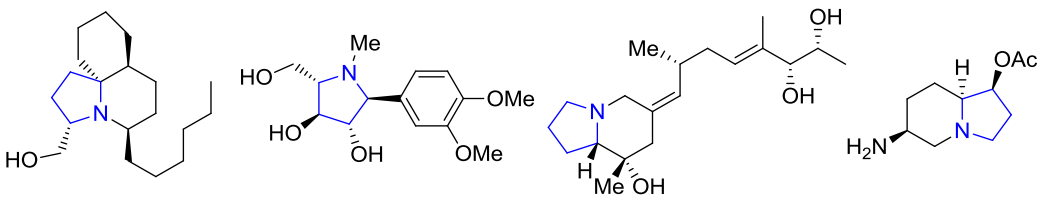


Figure 14. Selection of biologically active natural products containing pyrrolidine heterocycles.

Due to the considerable interest into pyrrolidines from the synthetic community, the development of a nitro-Mannich/hydroamination cascade allowing the efficient preparation of novel pyrrolidine derivatives with new substitution patterns would be of significant value. This methodology would enable new libraries of compounds to be synthesised, which in turn could be used for complex target synthesis.

4.1.2 The Allene Functionality

With two new cascade reactions developed using gold catalysed alkyne hydroaminations, we rationalised that modifying the π-electrophile could allow us to prepare new chemical entities using our nitro-Mannich/hydroamination cascade methodology. Accordingly, the allene functionality was selected as an appropriate substitute for the alkyne functionality due to its high affinity for transition metal complexes.[185] The first allene containing compounds were described by Burton and Pechmann in 1887,[186] but the structure of the allene motif was only determined in 1954.[187] An allene consists of three carbon atoms that are joined by two consecutive double bonds (Figure 15). The central carbon atom is sp hybridised whilst the two terminal carbon atoms, connected to the central carbon, are sp^2 hybridised. Due to the orbital overlap that is required to form this functionality, allenes containing different substituents on each terminus are chiral because there is no mirror plane present in the molecule.

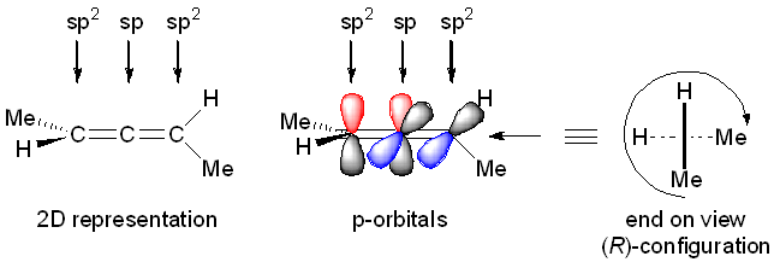
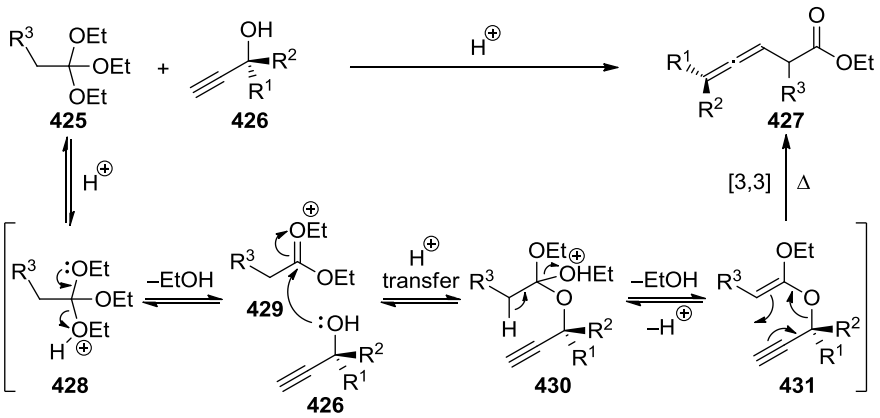


Figure 15. Different representations of the allene functional group, demonstrating p-orbital overlap and chirality.

Allene containing compounds have attracted significant attention from synthetic organic chemists as important intermediates because of the reactions that they can undergo when using transition metal catalysis.[185] This introduction will focus on the most relevant examples of allene synthesis and gold catalysed intramolecular allene hydroamination reactions to form pyrrolidine heterocycles.

4.1.3 Synthesis of Allene Containing Compounds

The significant interest into allenes as essential intermediates has been accompanied by numerous reports on their preparation. These include nucleophilic substitution of alkynyl substrates using organometallic reagents, 1,2-elimination of alkenyl substrates, [2,3] and [3,3] sigmatropic rearrangements and the Crabbé homologation of alkynes.[185] Among these methods, the orthoester Johnson-Claisen rearrangement ([3,3] sigmatropic rearrangement) has become a versatile method to synthesise allene substrates.[188] This reaction has been utilised during this work, with the rearrangement of propargyl alcohols **426** and triethyl orthoesters **425** affording allene esters **427** (Scheme 117).[189] Proceeding in the presence of an acid catalyst (typically propionic acid), the orthoester substrate eliminates a molecule of ethanol to form the reactive oxonium ion **429**.

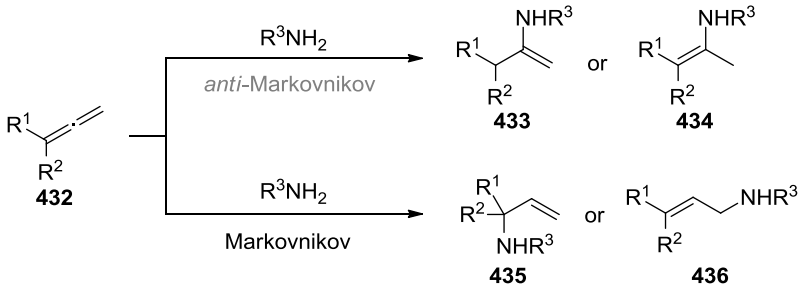


Scheme 117. Synthesis of allenes via an orthoester Johnson-Claisen rearrangement.

Nucleophilic addition of the hydroxy group followed by proton transfer and elimination of another ethanol molecule results in the formation of intermediate **431**. A [3,3] sigmatropic rearrangement then furnishes the desired allene product **427**. This method has proven to be very useful, combining cheap and readily available starting materials to produce allene substrates on large scale.

4.1.4 Allene Hydroamination Reactions

With alkyne hydroamination being a powerful method for carbon-nitrogen bond formation, synthetic chemists naturally became interested in the transformations that could be accomplished using other π-systems such as allenes. However, the intermolecular hydroamination of allenes posed some challenging problems with respect to the reactivity and regioselectivity of the reactions (Scheme 118).[190]



Scheme 118. Intermolecular allene hydroamination showing Markovnikov and *anti*-Markovnikov addition.

Although there have recently been significant advancements in the field of intermolecular allene hydroamination,[191] it is not as developed as the corresponding intramolecular reaction due to the regioselectivity issues previously mentioned. Additionally, as intramolecular allene hydroamination reactions enable the preparation of biologically important *N*-heterocyclic motifs, considerable attention has been paid to their development.

4.1.5 Interaction of Gold Complexes with Allenes

Whereas gold complexes typically activate alkynes and alkenes via η^2 bonding modes, allene substrates can also be activated by a number of η^1 bonding modes. These include the η^1 allylic cation **439**, carbene **440** and bend **441** (Figure 16).[192] Widenhoefer and co-workers have shown that gold complexes can form η^2 complexes with allenes in the form of complexes with general structures **437** and **438**. Out of these two complexes, complex **437** is most favoured because the steric interactions between the gold complex and the allene substituents are minimised.

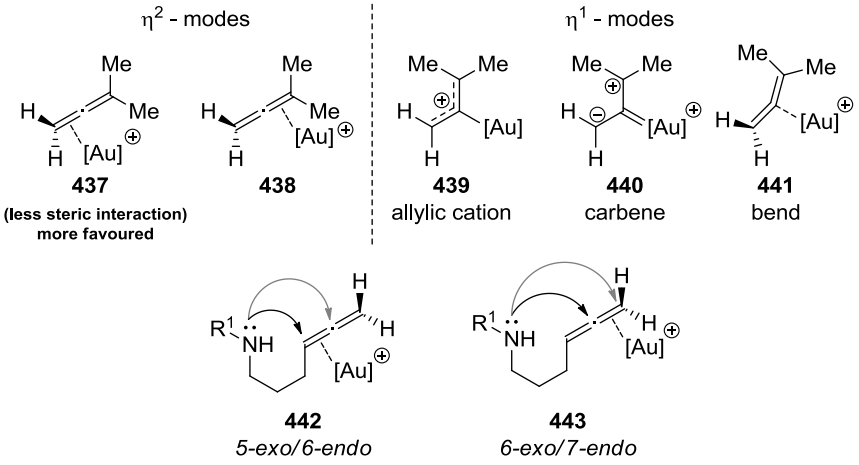
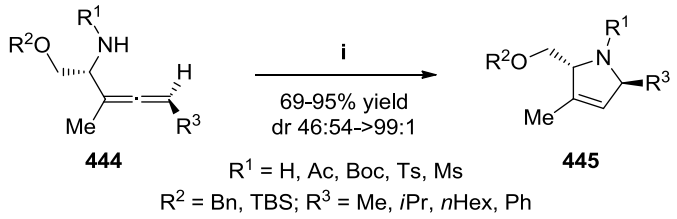


Figure 16. Possible bonding modes and cyclisation modes of allenes activated by gold complexes.

Taking this into account and applying it to intramolecular hydroamination reactions, aminoallene **443** should be the most stable gold complex, however binding of the gold complex at this site would lead to a *6-exo* or *7-endo* cyclisation (Figure 16). These cyclisation modes are more disfavoured than the *5-exo* or *6-endo* cyclisations available to aminoallene **442**. This demonstrates how the kinetics of ring-closure can govern the selectivity of intramolecular allene hydroamination reactions.

4.1.6 Intramolecular Gold Catalysed Allene Hydroamination Reactions

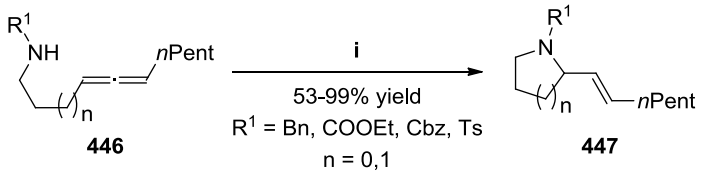
With the advent of intermolecular allene hydroamination reactions, synthetic organic chemists acknowledged that intramolecular allene hydroamination reactions could provide a powerful method to synthesise *N*-heterocyclic motifs. In 2004, Morita and Krause reported the $AuCl_3$ catalysed *5-endo-trig* cyclisation of enantioenriched aminoallenes **444** to afford dihydropyrroles **445** (Scheme 119).[193] The reaction was found to be highly regio- and diastereoselective depending on the nitrogen protecting group, with chirality transfer occurring during the hydroamination reaction. However, the enantioenrichment of the products was not determined. The reaction was relatively quick for the aminoallenes bearing an *N*-protecting group, with only 30 minutes being required for the reaction to reach completion. In contrast, a free aminoallene substrate required 5 days to react completely. One major limitation of this methodology is the 6 step synthesis of the starting enantiopure aminoallenes **444**, making this procedure unattractive for library synthesis.



Scheme 119. Krause's intramolecular *5-endo-trig* allene hydroamination. Reagents and conditions: i) $AuCl_3$ (2 mol%), CH_2Cl_2 or THF, RT, 30 min or 5 days.

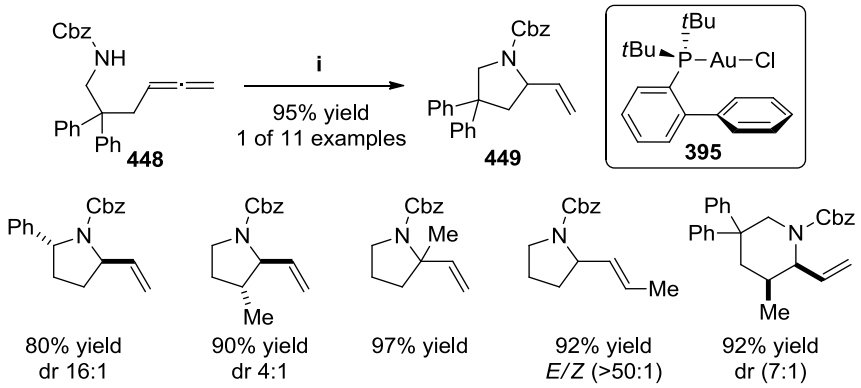
In 2006, Yamamoto and co-workers described the *5-exo-trig* hydroamination of aminoallenes **446** to furnish 2-vinylpyrrolidines **447** (Scheme 120).[194] Using AuCl, $AuCl_3$ or $AuBr_3$ in THF at room temperature, pyrrolidines **447** were obtained in good to excellent yields when the nitrogen atom was bearing a protecting group. Piperidine motifs could also be prepared via this method by extension of the carbon chain in the allene starting material, but the reactions required higher catalyst loadings (5 mol%)

and increased reaction times (24 hours). One example using an enantioenriched aminoallene was presented (96% ee), with chirality transfer occurring to furnish the corresponding enantioenriched pyrrolidine in 94% ee. It should be noted that the products **447** are obtained solely as the *trans*-isomer.



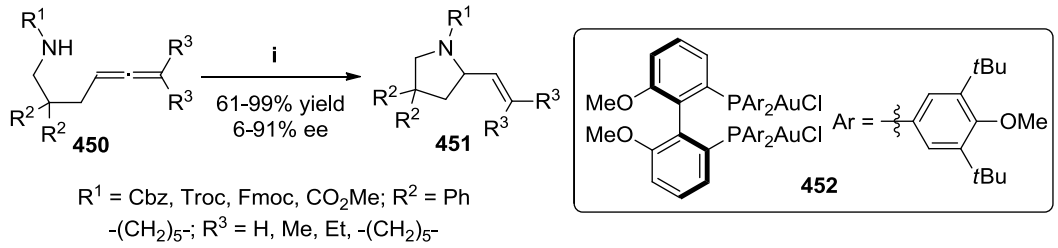
Scheme 120. Yamamoto's intramolecular *5-exo-trig* allene hydroamination. Reagents and conditions: i) AuCl (1-5 mol%) or $AuCl_3$ (1 mol%) or $AuBr_3$ (1 mol%), THF, RT, 3-24 h.

Similar to the work of Yamamoto, Widenhoefer and co-workers reported the intramolecular *5-exo-trig* hydroamination of *N*-Cbz protected aminoallenes (Scheme 121).[195] Using gold complex **395** (5 mol%) in conjunction with AgOTf (5 mol%) under mild conditions allowed smooth cyclisation to furnish 2-vinylpyrrolidines in excellent yields with diastereoselectivities up to 16:1. Widenhoefer also demonstrated a vastly expanded substrate scope compared to the work of Yamamoto and co-workers, with substituents being tolerated in the 2, 3 and 4 positions of the pyrrolidine ring as well as on the allene. The preparation of 6-membered rings was also possible using this method.



Scheme 121. Widenhoefer's intramolecular allene hydroamination of *N*-Cbz protected aminoallenes. Reagents and conditions: i) complex **395** (5 mol%), AgOTf (5 mol%), dioxane, 25 °C, 5-180 min or 22 h.

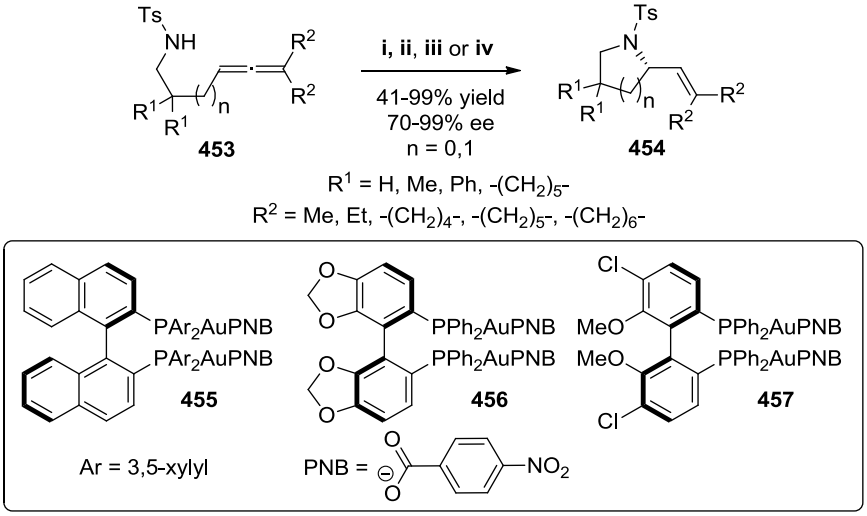
Building on their non-enantioselective allene hydroamination reaction, Widenhoefer and co-workers developed an enantioselective allene hydroamination reaction of racemic aminoallenes **450** to afford enantioenriched 2-vinylpyrrolidines **451** (Scheme 122).[196] The employment of the axially chiral gold complex **452** (2.5 mol%) with $AgClO_4$ (5 mol%) gave good yields and enantioselectivities in the hydroamination reaction with a range of nitrogen protecting groups and substituents present in the aminoallene starting materials. The hydroamination reaction also proceeded under very mild conditions, with –40 °C being suitable to obtain the desired cyclised products after 24 hours.



Scheme 122. Widenhoefer's enantioselective intramolecular *5-exo-trig* allene hydroamination. Reagents and conditions: i) complex **452** (2.5 mol%), $AgClO_4$ (5 mol%), *m*-xylene, –40 °C or –20 °C or RT, 24-48 h.

Higher enantioselectivities were achieved by Toste and co-workers in the *5-exo-trig* hydroamination of sulfonamide protected aminoallenes **453**.[197] Similar to Widenhoefer, Toste used gold catalysts featuring axially chiral phosphine ligands to attain excellent enantioselectivities (up to 99% ee) in the 2-vinylpyrrolidine products **454** (Scheme 123). The counterion of the gold complex was demonstrated to be crucial to achieve high levels of enantiocontrol, with benzoate motifs being identified as the best counterions for the reaction after an extensive optimisation study. Piperidine rings were also accessed with high yields and enantioselectivities for a range of substituted aminoallenes **453**. Although the enantioselectivities obtained in this report are exceptional, no rationales for the enantiocontrol or the vital role of the

para-nitrobenzoate counterion were disclosed. Another drawback of the presented allene hydroamination methodologies is that the majority of substrates contain a *geminally* disubstituted carbon atom, aiding the cyclisation reaction through the Thorpe-Ingold effect.[198] This disubstitution limits the complexity and the utility of the products that can be formed from these reactions.



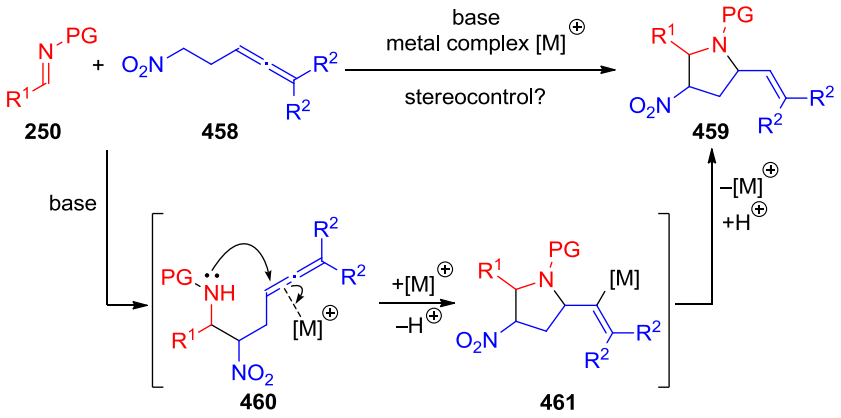
Scheme 123. Toste's enantioselective intramolecular allene hydroamination. Reagents and conditions: i) complex **455** (3 mol%), DCE, RT; ii) complex **455** (5 mol%), $MeNO_2$, 50 °C; iii) complex **456** (5 mol%), $MeNO_2$, 50 °C; iv) complex **457** (5 mol%), $MeNO_2$, 50 °C.

4.2 Project Aims

With previous success achieved in nitro-Mannich/hydroamination cascade reactions using nitroalkyne substrates, we wanted to develop a new methodology for the synthesis of pyrrolidine derivatives using nitroallene substrates. By incorporating an intramolecular allene hydroamination into our cascade reaction, a new stereogenic centre would be created affording pyrrolidine products with new substitution patterns. The resulting alkene functionality would also provide a valuable handle for further synthetic manipulation, allowing new molecular architectures to be prepared using our nitro-Mannich/hydroamination cascade methodology.

4.3 Concept of Nitro-Mannich/Hydroamination Cascade Using Nitroallenes

With the saturated pyrrolidine heterocycle being unattainable using our nitroalkyne substrates, we postulated that substituting the alkyne for an allene could allow us access to the desired pyrrolidine motifs. In our proposed concept (Scheme 124), nitroallene **458** would react with a protected imine **250** under base catalysis. The resulting β-nitroamine **460** would then be poised to cyclise via a *5-exo-trig* hydroamination reaction when a metal complex activated the allene moiety.



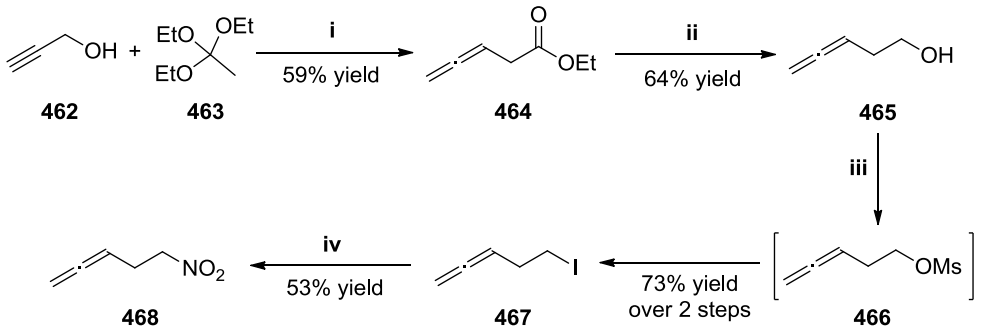
Scheme 124. Concept of pyrrolidine synthesis using a nitro-Mannich/hydroamination cascade.

Protodemetallation would then afford the desired pyrrolidine **459** and allow the catalytic cycle to continue as the metal species is released back into the reaction mixture. Based on literature reports of metal catalysed allene hydroamination reactions,[196,197] we expected that the ensuing alkene present in pyrrolidine product **459** would be stable and no isomerisation would take place. Consequently, no elimination of the nitro group would occur and therefore the three stereocentres created in the cascade reaction would be retained.

4.4 Diastereoselective Nitro-Mannich/Hydroamination Cascades to Substituted Pyrrolidines

4.4.1 Synthesis of Starting Materials and Proof of Principle Study

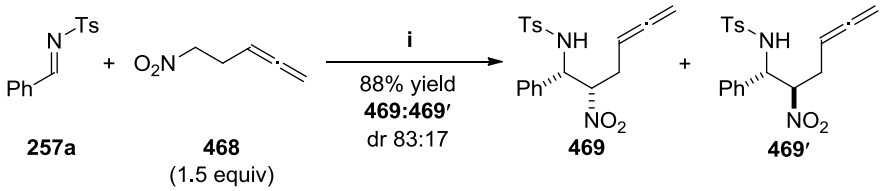
To gain proof of principle for our proposed pyrrolidine synthesis, we wanted to prepare an appropriately protected β-nitroamine possessing an allene side chain and cyclise it using a gold complex. Firstly, we developed a robust and scalable route to prepare nitroallene **468** on gram scale by treating iodoallene **467** with $NaNO_2$ (Scheme 125). Starting from propargyl alcohol (**462**) and triethyl orthoacetate (**463**), allene **464** was afforded in 59% yield via a propionic acid catalysed Johnson-Claisen rearrangement.[189] Reduction of the ester using $LiAlH_4$ followed by mesylation of the alcohol and displacement with NaI furnished iodoallene **467**. Finally, nitration of the iodide with $NaNO_2$ in DMSO afforded nitroallene **468** in 53% yield.[126] Although 5-synthetic steps are required to prepare nitroallene **468**, the whole route needs only one purification procedure. This is conducted after the last step, with the final nitroallene **468** being purified by flash column chromatography on silica gel.



Scheme 125. Synthesis of nitroallene **468**. Reagents and conditions: i) propionic acid (3.5 mol%), 150 °C, 3 h; ii) $LiAlH_4$, THF, 0 °C to RT, 1 h; iii) MsCl, Et_3N, CH_2Cl_2, –30 °C to –10 °C, 1.5 h then NaI, acetone, reflux, 12 h; iv) $NaNO_2$, DMSO, RT, 1.5 h.

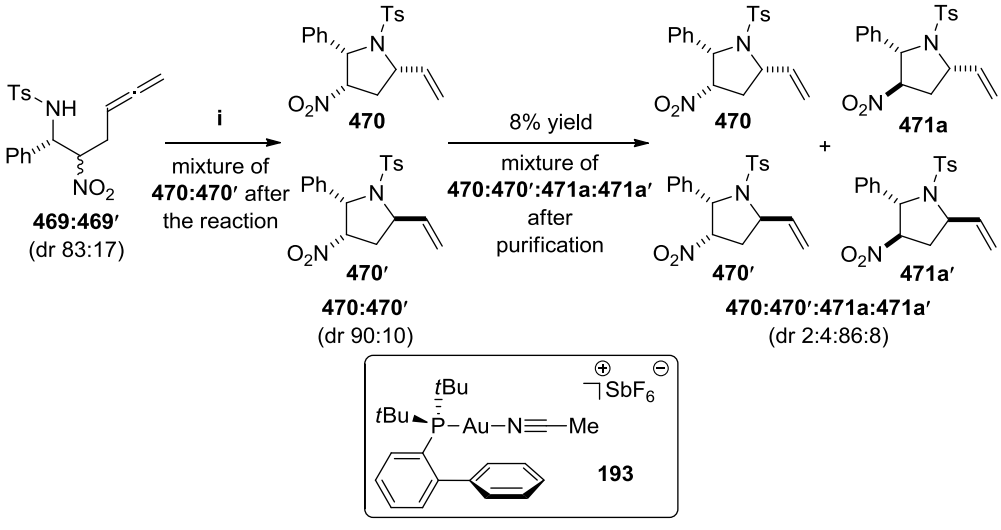
With a substantial quantity of nitroallene **468** in hand, we selected *N*-sulfonyl imine **257a** (Chapters 2 and 3) for use in our proof of principle study. Hence, imine **257a** and nitroallene **468** were reacted together in the presence of PS-BEMP (10 mol%) to

afford β-nitroamines **469** and **469′** in 88% combined yield and 83:17 dr in favour of the *syn*-diastereomer **469** (Scheme 126). The isolated β-nitroamine mixture was then reacted with complex **193** (5 mol%) in toluene at 100 °C for 16 hours (Scheme 127). Pleasingly, partial conversion to pyrrolidines **470** and **470′** was observed with good diastereoselectivity (**470:470′** dr 90:10) being obtained in the crude reaction mixture.



Scheme 126. Synthesis of β-nitroamines **469** and **469′** using *N*-sulfonyl imine **257a** and nitroallene **468**. Reagents and conditions: i) PS-BEMP (10 mol%), PhMe, RT, 22 h.[c]

Upon purification by flash column chromatography on silica gel, epimerisation of the nitro group stereocentre occurred to afford a mixture of **470**:**470′**:**471a**:**471a′** in 8% yield (dr 2:4:86:8). Although the yield of the hydroamination reaction was poor, it did provide step-wise proof of principle for this nitro-Mannich/hydroamination cascade.



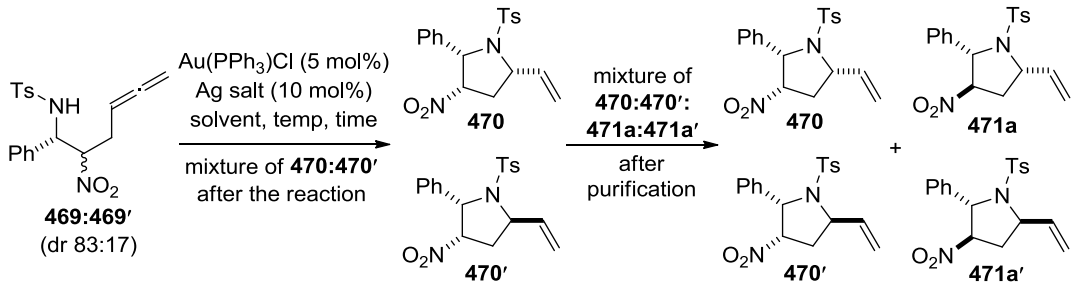
Scheme 127. Intramolecular hydroamination proof of principle for the synthesis of pyrrolidines. Reagents and conditions: i) complex **193** (5 mol%), PhMe, 100 °C, 16 h.

[c] Compounds **469** and **469′** were independently prepared and characterised by Dr. A. Ďuriš.

4.4.2 Optimisation of the Allene Hydroamination Reaction

With proof of principle obtained, the hydroamination reaction was further investigated by varying solvent, temperature and the catalyst combination (Table 8). Changing the catalytic system to $Au(PPh_3)Cl$ (5 mol%) and AgOTf (5 mol%) improved the efficiency of the hydroamination reaction with the products being isolated in 35% yield (Table 8, entry 1). Increasing the loading of AgOTf (10 mol%) also led to an enhancement of the chemical yield, with 52% of the desired products being isolated after flash column chromatography on silica gel (Table 8, entry 2).

Table 8. Optimisation study of the intramolecular hydroamination reaction using β-nitroamines **469** and **469′**.



entry	solvent	Ag salt (10 mol%)	temp (°C)	time (h)	dr[a] **470**:**470′**	yield[b] (%)	dr[c] **470**:**470′**:**471a**:**471a′**
1[d]	PhMe	AgOTf	100	16	52:48	35	32:28:22:18
2	PhMe	AgOTf	100	16	57:43	52	34:24:21:21
3	PhMe	AgOTf	70	34	63:37	64	52:33:8:7
4	PhMe	$AgBF_4$	70	14	83:17	52	63:14:15:8
5	DCE	AgOTf	70	4	80:20	81	63:17:15:2
6	DCE	$AgBF_4$	70	4	86:14	81	66:9:22:3
7	DCE	$AgSbF_6$	70	6	92:8	53	55:5:37:3
8[e]	DCE	$AgSbF_6$	70	2	92:8	71	72:8:19:1

[a] Determined by ^1H NMR analysis of the crude reaction mixture. [b] Isolated yield of **470**:**470′**:**471a**:**471a′** mixture (via nitro group epimerisation) after purification by flash column chromatography on silica gel. [c] Determined by ^1H NMR analysis of the purified mixture. [d] With AgOTf (5 mol%). [e] With DPP (10 mol%).

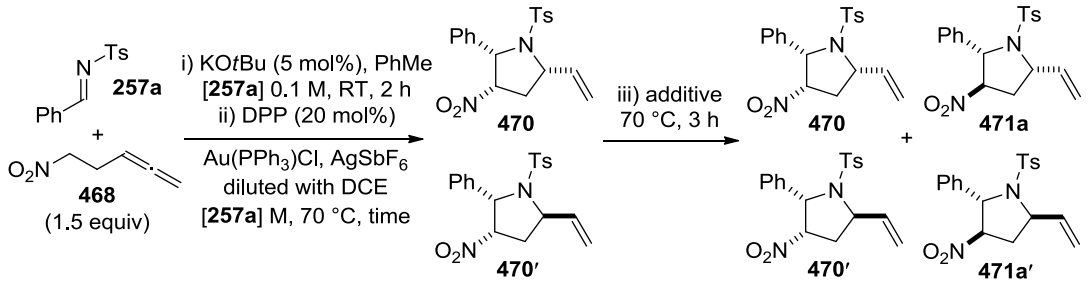
The improvement in the reaction efficiency observed when increasing the AgOTf loading would suggest that the "silver effect" is operating in this reaction, with the dual activation of the substrate by both the gold and silver complexes.[199] The presence of the "silver effect" was confirmed when a control reaction using only AgOTf (5 mol%) in PhMe at 100 °C resulted in no cyclisation to pyrrolidines **470** and **470′**. Lowering the temperature of the reaction to 70 °C resulted in an improvement of the yield to 64% and the diastereoselectivity (crude dr 63:37) after an extended reaction time (34 h; Table 8, entry 3). Changing the solvent to DCE significantly reduced the time of the reaction and also gave increases in yield and diastereoselectivity (81% yield, crude dr 80:20; Table 8, entry 5). Replacing AgOTf with $AgSbF_6$ reduced the yield of product to 53%, but the crude diastereoselectivity was increased (dr 92:8; Table 8, entry 7). Because of the number of diastereomers that could be formed in the reaction, an increase in the diastereoselectivity of the reaction was preferred over a slight increase in the isolated yield. However, addition of DPP (10 mol%) to the reaction mixture improved the yield to 71% whilst retaining the excellent diastereoselectivity present in the reaction mixture (crude dr 92:8; Table 8, entry 8). The presence of DPP in the reaction mixture could enhance the yield by aiding the protodemetallation of the gold complex after the cyclisation has occurred. The results obtained in this optimisation study suggest that the cyclisation of *syn*-β-nitroamine **469** results in the formation of pyrrolidines **470** and **470′** in the crude reaction mixture. As pyrrolidines **471a** and **471a′** are not observed in the crude reaction mixture, we postulate that the *anti*-β-nitroamine **469′** does not cyclise under our conditions, or a pre-cyclisation epimerisation of the nitro group occurs to allow the cyclisation reaction to take place, affording pyrrolidines **470** and **470′**.

4.4.3 Optimisation of the Diastereoselective One-Pot Cascade

With good yield and diastereoselectivity achieved in the hydroamination reaction, we wanted to develop a one-pot cascade reaction by combining these conditions with a KO*t*Bu catalysed nitro-Mannich reaction, because of our success in previous cascade reactions using this base (Chapter 2). One problem that we faced was that the nitro-Mannich reaction did not proceed when using DCE as the solvent. Because of this, we conducted the nitro-Mannich reaction in PhMe and then added DCE along with the gold and silver complexes. On our first attempt, KO*t*Bu (5 mol%) combined with $Au(PPh_3)Cl$ (5 mol%) and $AgSbF_6$ (10 mol%) furnished the pyrrolidine products in 49% yield after 7 hours at 70 °C (Table 9, entry 1). Raising the $Au(PPh_3)Cl$ (10 mol%) and $AgSbF_6$ (20 mol%) loadings and altering the solvent system to DCE/PhMe (3:1, 0.025 M) improved the yield to 83% with good crude diastereoselectivity (dr 94:6; Table 9, entry 4).

We next investigated incorporating a full epimerisation step into the reaction sequence to overcome the changing diastereoselectivity (via nitro group epimerisation) during the purification procedure. As we had witnessed epimerisation of the nitro group during the purification on silica gel, we postulated that adding silica gel directly to the reaction mixture after the cyclisation had finished, could allow complete epimerisation of the nitro group. Unfortunately, a complex mixture of diastereomers was isolated after the reaction mixture had been stirred in silica gel at 70 °C for 3 hours (Table 9, entry 5). As acidic silica gel had not afforded complete epimerisation, we thought that using a base may result in a smooth epimerisation step.

Table 9. One-pot nitro-Mannich/hydroamination cascade optimisation studies of *N*-sulfonyl imine **257a** and nitroallene **468**.



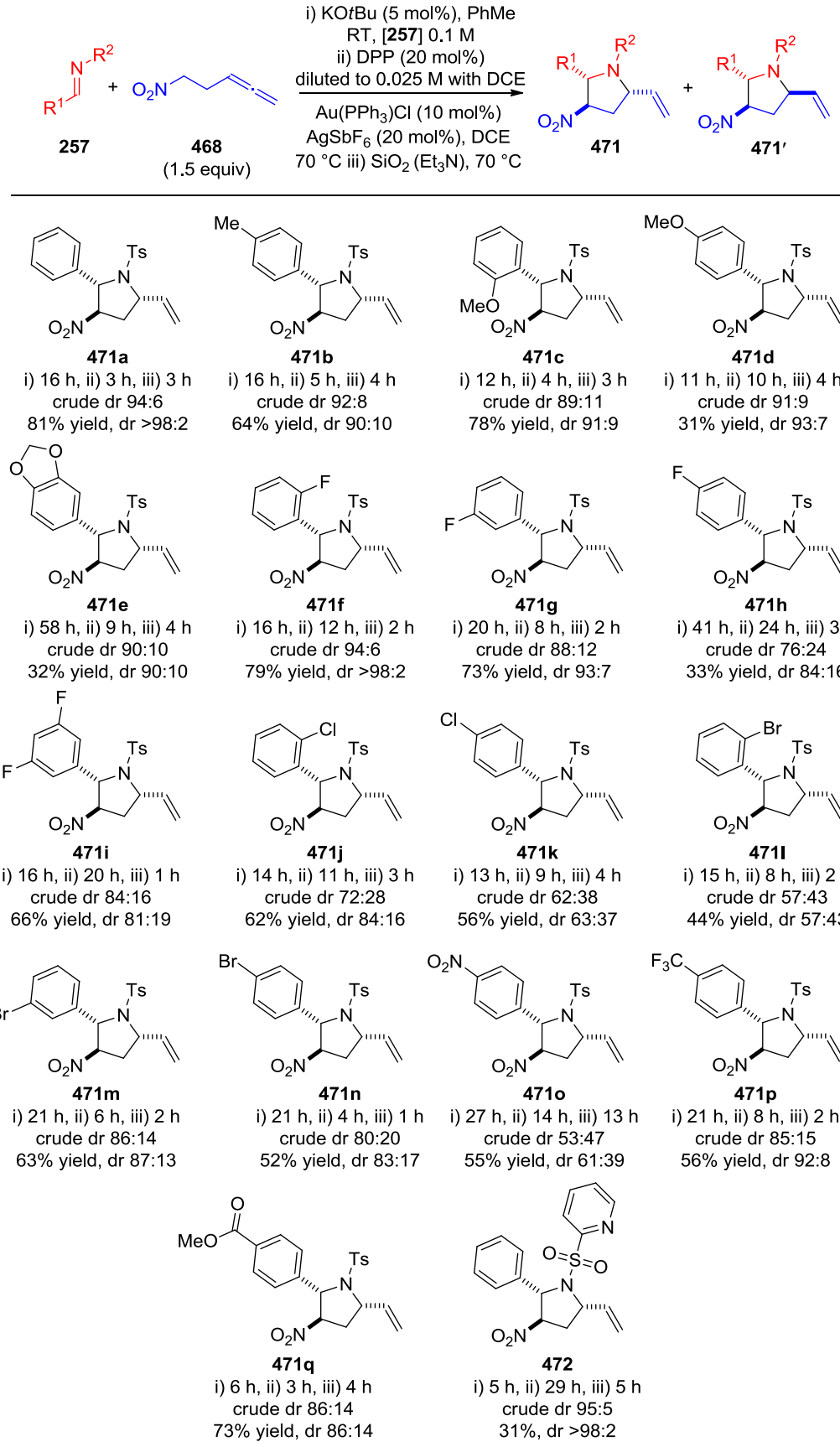
entry[a]	solvent (ii)	$Au(PPh_3)Cl$ (mol%)	$AgSbF_6$ (mol%)	(ii) time (h)	additive (iii)	dr[b]	yield[c] (%)	dr[d] **470:470′ :471a:471a′**
1	DCE[e]	5	10	7	–	90:10[f]	49	66:14:13:7
2	DCE[e]	7.5	15	5	–	91:9[f]	59	68:16:12:4
3	DCE[e]	10	20	2	–	94:6[f]	73	78:1:15:6
4	DCE[g]	10	20	2	–	94:6[f]	83	83:6:10:1
5	DCE[g]	10	20	2	SiO_2	–	78	36:27:35:2
6	DCE[g]	10	20	2	Et_3N	75:25[h]	76	0:0:77:23
7	DCE[g]	10	20	2	SiO_2 (Et_3N)	98:2[h]	83	0:0:98:2

[a] All reactions were performed using the same conditions for step (i) in all entries. [b] Determined by ^1H NMR analysis of the crude reaction mixture. [c] Isolated yield of **470:470′:471a:471a′** mixture after purification by flash column chromatography on silica gel. [d] Determined by ^1H NMR analysis of the purified mixture. [e] Diluted to 0.05 M. [f] **470:470′** obtained. [g] Diluted to 0.025 M. [h] **471a:471a′** obtained.

Pleasingly, addition of Et_3N (1.0 equiv) to the reaction mixture after cyclisation did indeed improve the epimerisation, furnishing only a mixture of pyrrolidines **471a** and **471a′** after purification, but the diastereomeric ratio of the products had been reduced (dr 75:25). Building on this result, we attempted the epimerisation using silica gel treated with Et_3N as the additive and, to our delight, pyrrolidines **471a** and **471a′** were furnished in 83% yield with excellent control of the diastereoselectivity (dr 98:2).

4.4.4 Scope of the Diastereoselective Cascade to Substituted Pyrrolidines

With optimised conditions identified using *N*-sulfonyl protected imine **257a**, we wanted to examine the scope of the reaction with respect to the aromatic substituent on the imine reaction partner. Using the previously prepared *N*-sulfonyl imines and some newly synthesised examples using the same experimental procedure (Table 4, Chapter 2),[125] the scope of the cascade reaction was investigated (Scheme 128). The cascade reaction tolerated both electron-rich and electron-poor aryl substituents. The imines containing electron-rich substituents afforded the pyrrolidine products **471c-471e** with moderate to good yields (31-78%) and good diastereoselectivities (dr 89:11-91:9). Fluorine, chlorine and bromine substituents in the *ortho*-, *meta*- and *para*-positions were all found to be compatible with the cascade reaction, but in some cases the diastereoselectivities of the reactions were only moderate (dr 62:38-94:6). The electron-poor aryls bearing nitro, trifluoromethyl and methyl carboxylate groups were also found to tolerate the nitro-Mannich/hydroamination cascade with pyrrolidines **471p** and **471q** being afforded with good diastereoselectivities. In contrast, the *para*-NO_2 substituted pyrrolidine **471o** was furnished with almost no diastereoselectivity (dr 53:47). Variation of the *N*-protecting group was also attempted but using *N*-Boc imine **112a**, *N*-PMB imine **278** and *N*-nosyl imine **277** (Scheme 77, Chapter 2) afforded none of the desired pyrrolidines. However, the *N*-pyridine-2-sulfonyl protected imine was compatible with the reaction conditions, furnishing pyrrolidine **472** in a modest 31% yield, but with excellent diastereoselectivity (dr 92:8). Overall, the cascade reaction gave lower yields when the aryl group contained an electron-donating group in the *p*-position, possibly due to reduced reactivity of the corresponding *N*-sulfonyl imine in the nitro-Mannich step, although the diastereoselectivity obtained in these cases was not greatly affected.



Scheme 128. Scope of the nitro-Mannich/hydroamination cascade reaction. (Only the major diastereomers **471** are depicted in the Scheme).

Aromatic groups bearing electron-withdrawing chlorine or bromine substituents resulted in only moderate diastereoselectivities of the pyrrolidine products.

4.4.5 Determination of the Relative Configurations

With the possibility of the major product being any of four diastereomers, it was imperative to accurately determine the relative configuration of as many observable diastereomers as possible. The most conclusive method for the determination of the relative configuration is single crystal X-ray diffraction analysis. As pyrrolidine **471a** had been obtained with excellent diastereoselectivity, we recrystallised this compound by slow evaporation of CH_2Cl_2. The single crystal X-ray diffraction data of pyrrolidine **471a** showed that the C2-C3 substituents exhibited a *trans* relationship while the C2-C5 substituents had a *cis* relationship (Figure 17).

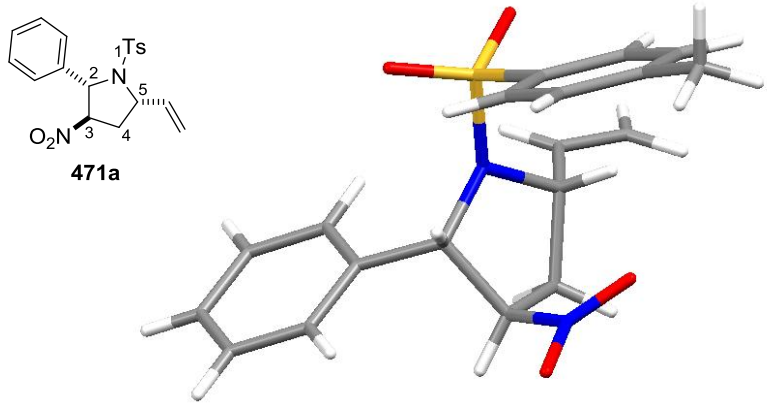


Figure 17. X-ray crystal structure representation of pyrrolidine **471a**.

Using the X-ray crystal structure of pyrrolidine **471a** as a basis, we were now able to assign the configurations of the other observable diastereomers using NOE analysis and by comparison of the ^{1}H NMR coupling constants. As we could not separate any of the minor pyrrolidine diastereomers **471′** from the major diastereomers **471** using flash column chromatography, we conducted NOE analysis on a mixture of *para*-chloro diastereomers **471k** and **471k′** because the sample showed adequate

resolution of the appropriate ^{1}H NMR signals while containing a significant proportion of the minor isomer **471k′** (Figure 18). From this NOE analysis it was observed that a strong interaction existed between the protons in the C2 and C5 positions in major diastereomer **471k**, clearly confirming the *cis* relationship between them.

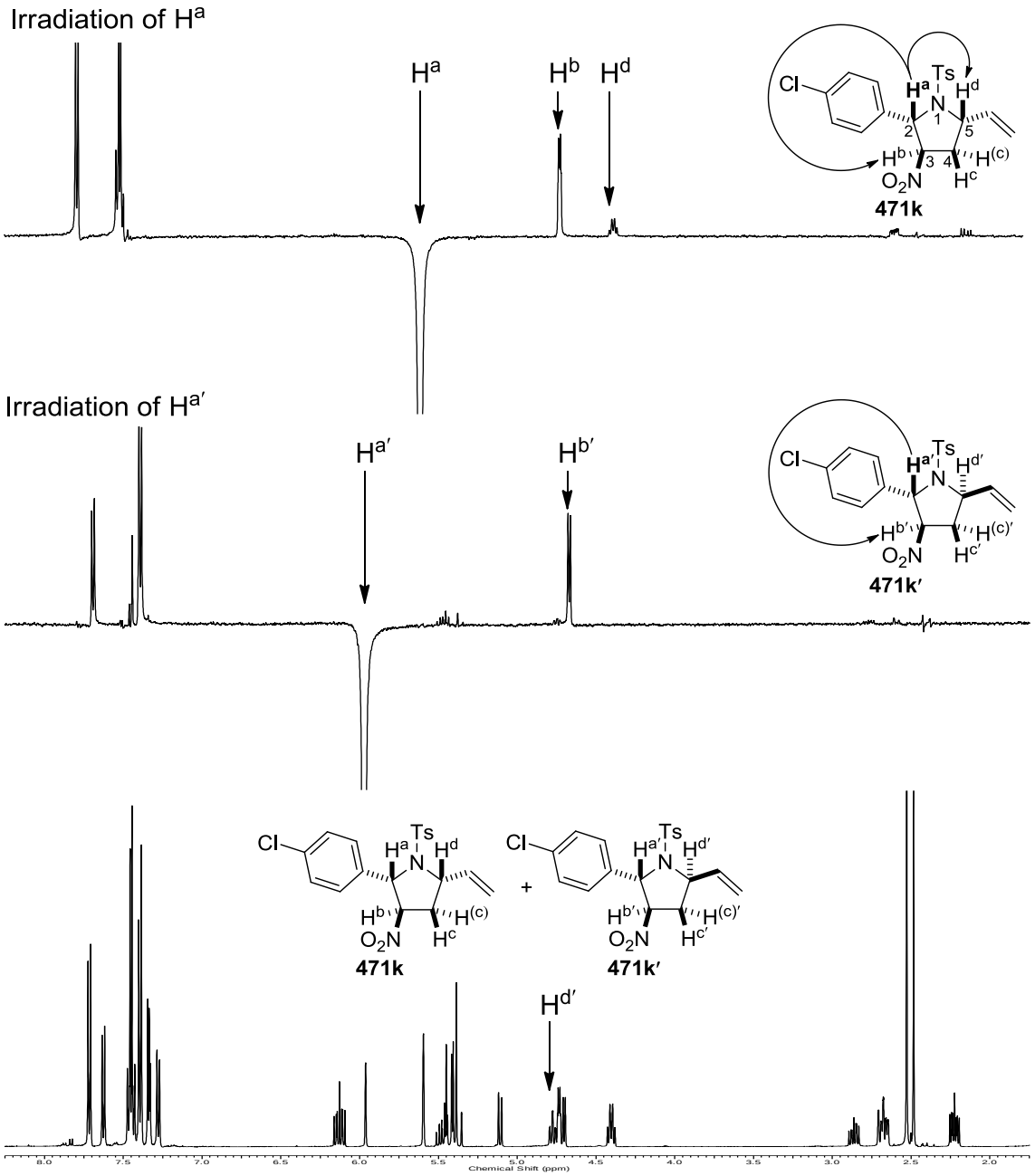
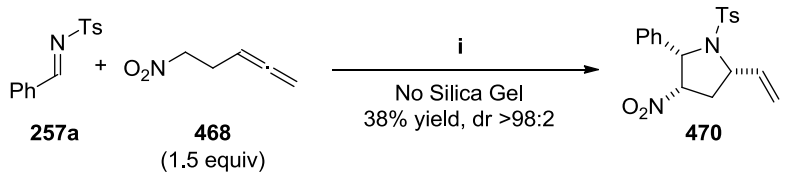


Figure 18. NOE analysis of *para*-chloro diastereomers **471k** and **471k′**.

In contrast, the minor diastereomer **471k′** only showed a very weak NOE interaction between these protons, demonstrating that this diastereomer has a C2-C5 *trans* relationship.

Although we could clearly determine the C2-C5 configuration, the C2-C3 configuration still remained unclear. During our previous studies we had proposed that nitro group epimerisation was occurring during purification of the pyrrolidines on silica gel, resulting in an inseparable mixture of 4 diastereomers. As our optimised conditions gave excellent diastereoselectivity in certain examples (pyrrolidine **471a**, dr 98:2), we postulated that if silica gel was facilitating the nitro group epimerisation, then if no silica gel was added to the reaction mixture we would be able to obtain the all *cis*-diastereomer **470** (Scheme 129).



Scheme 129. Synthesis of *cis*-pyrrolidine **470** using *N*-sulfonyl imine **257a** and nitroallene **468**. Reagents and conditions: i) KO*t*Bu (5 mol%), PhMe, [**257a**] 0.1 M, RT, 18 h then diluted to 0.025 M with DCE, DPP (20 mol%), $Au(PPh_3)Cl$ (10 mol%), $AgSbF_6$ (20 mol%), 70 °C, 4 h. Purified by filtration through celite® and recrystallisation from CH_2Cl_2/Et_2O.

To our delight, we conducted the reaction using our optimised conditions and then purified the crude product by filtration through a plug of celite® followed by recrystallisation to afford *cis*-pyrrolidine **470** in 38% yield with excellent diastereocontrol (dr >98:2). Similarly, we were able to confirm the C2-C5 *cis* configuration of pyrrolidine **470** by NOE analysis with the protons in the C2 and C5 positions showing a through space interaction (Figure 19).

Our attention then turned to assigning the relative configuration of the C2 and C3 positions. The X-ray crystal structure of pyrrolidine **471a** had shown that a *trans*

relationship was present between these positions. Also, the corresponding ^{1}H NMR of pyrrolidine **471a** displayed the benzylic proton at the C2 position as a singlet, showing that there is only a very small coupling between the protons at the C2 and C3 positions ($^{3}J_{H,H} \approx 90°$).[200] In comparison, the benzylic proton in *cis*-pyrrolidine **470** appears as a doublet (J = 9.0 Hz).

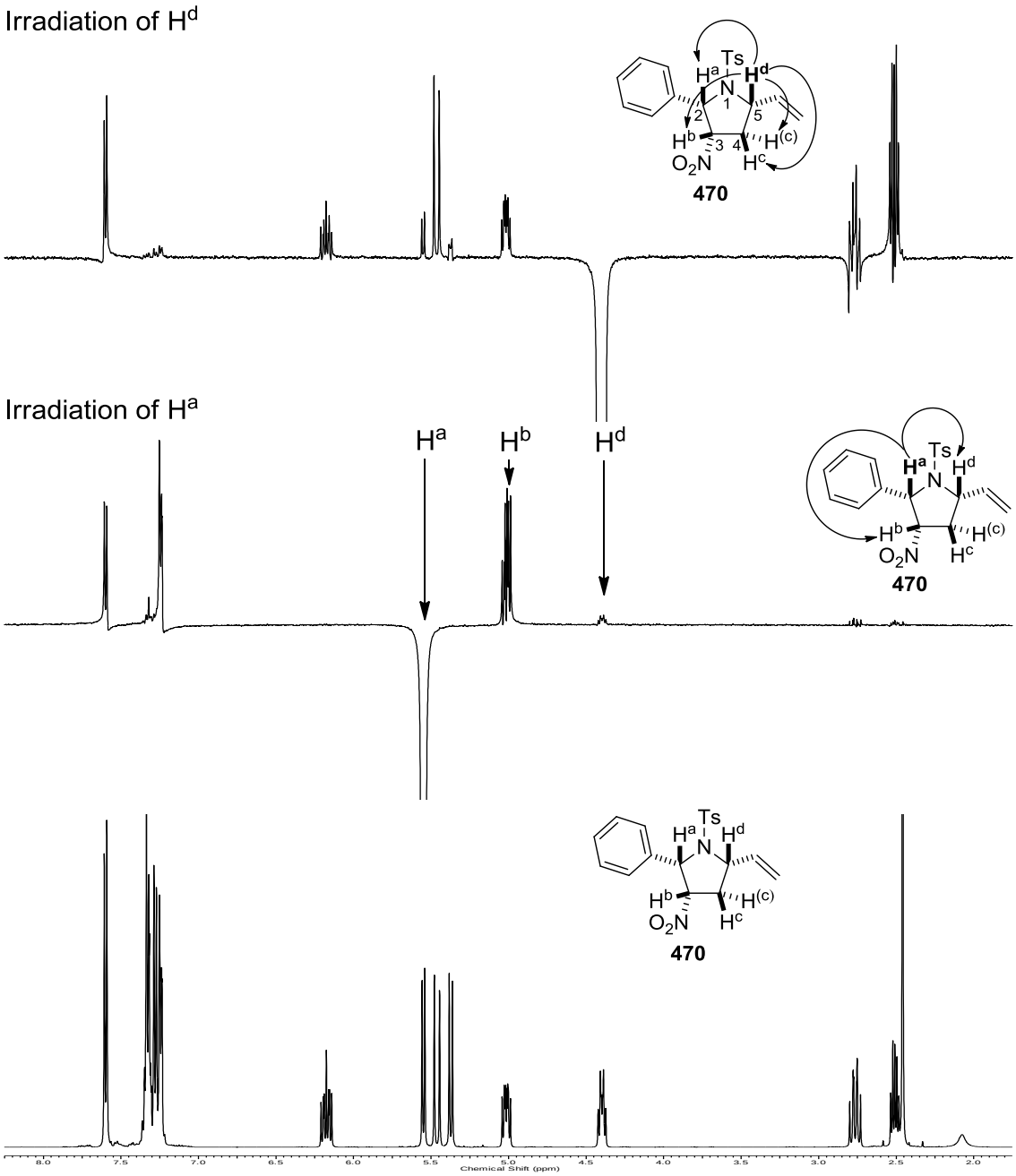
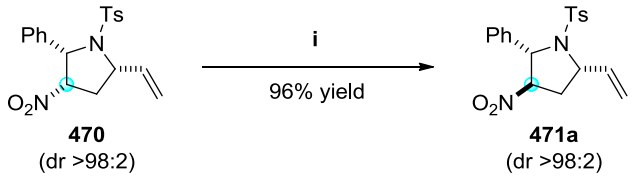


Figure 19. NOE analysis of *cis*-pyrrolidine **470**.

This coupling constant is indicative of a *cis* relationship between the C2-C3 positions when comparing it to similar compounds reported in the literature.[201]

In a further experiment to confirm the silica gel (treated with Et_3N) epimerisation of the nitro group, we exposed the isolated *cis*-pyrrolidine **470** to silica gel (treated with Et_3N) in DCE/PhMe (3:1) at 70 °C for 3 hours (Scheme 130). Pleasingly, the epimerisation proceeded smoothly to furnish pyrrolidine **471a** in 96% yield and >98:2 dr, thus demonstrating that *cis*-pyrrolidine **470** is converted to pyrrolidine **471a** when exposed to silica gel (treated with Et_3N) after the hydroamination reaction.



470
(dr >98:2)

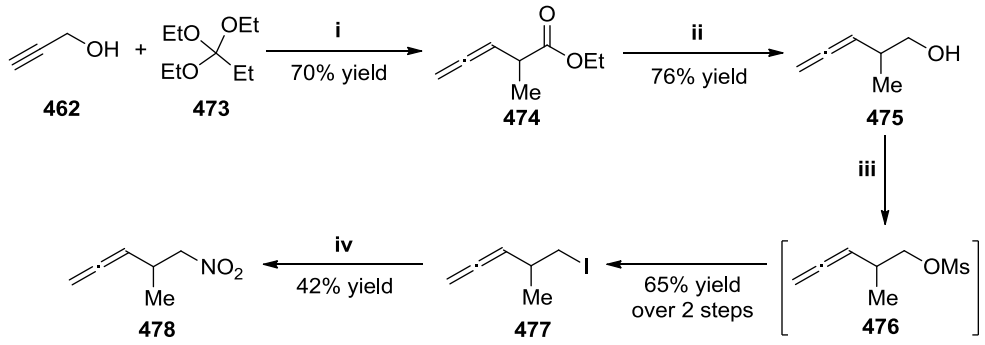
471a
(dr >98:2)

Scheme 130. Epimerisation of *cis*-pyrrolidine **470** into pyrrolidine **471a** using silica gel (treated with Et_3N). Reagents and conditions: i) SiO_2 (treated with Et_3N), DCE/PhMe (3:1), 70 °C, 3 h.

Although we had been able to determine the relative configuration of three of the pyrrolidine diastereomers, we had not been able to isolate the fourth diastereomer to confirm its relative configuration. However, a process of elimination identifies this diastereomer as pyrrolidine **470′**.

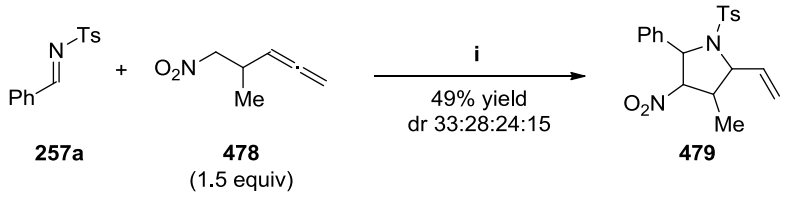
4.4.6 Extension of the Methodology to Substituted Nitroallene Substrates

To extend the scope of the diastereoselective pyrrolidine synthesis, we sought to investigate the effect that substituted nitroallene substrates had on the cascade reaction. Using our procedure for the synthesis of nitroallene **468** as a basis, nitroallene **478** bearing a methyl substituent in the β-position to the nitro group was prepared (Scheme 131).



Scheme 131. Synthesis of methyl substituted nitroallene **478**. Reagents and conditions: i) propionic acid (10 mol%), 150 °C, 11 h; ii) $LiAlH_4$, THF, 0 °C to RT, 1 h; iii) MsCl, Et_3N, CH_2Cl_2, −30 °C to −10 °C, 1.5 h then NaI, acetone, reflux, 12 h; iv) $NaNO_2$, DMSO, RT, 1.5 h.[d]

As with the synthesis of nitroallene **468**, none of the intermediate compounds required any purification except the final nitroallene **478** substrate, which was purified by flash column chromatography on silica gel at the end of the synthetic sequence. The use of nitroallene **478** was potentially very interesting, as a successful cascade reaction using this substrate would furnish a fully substituted pyrrolidine derivative. Gratifyingly, we found that under the optimised cascade conditions, nitroallene **478** did react as expected with imine **257a** to furnish the desired pentasubstituted pyrrolidine **479** in 49% yield (Scheme 132).



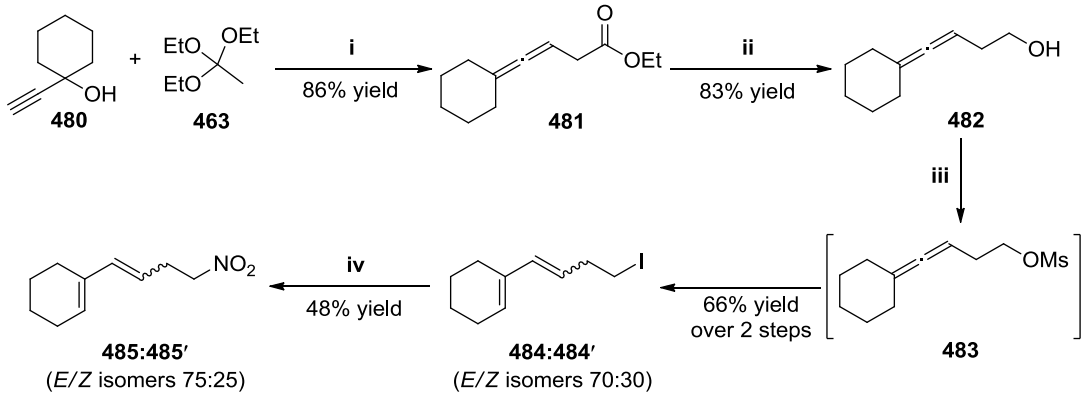
Scheme 132. Synthesis of fully substituted pyrrolidine **479** using nitroallene **478**. Reagents and conditions: i) KO*t*Bu (5 mol%), PhMe, [**257a**] 0.1 M, RT, 48 h then diluted to 0.025 M with DCE, DPP (20 mol%), $Au(PPh_3)Cl$ (10 mol%), $AgSbF_6$ (20 mol%), 70 °C, 7 h then SiO_2 (treated with Et_3N), 70 °C, 3 h.

However, the diastereoselectivity of the reaction was poor, with an inseparable mixture of four unassigned diastereomers (dr 33:28:24:15) being obtained after

[d] All compounds shown in Scheme 131 were independently prepared and characterised by Dr. A. Ďuriš.

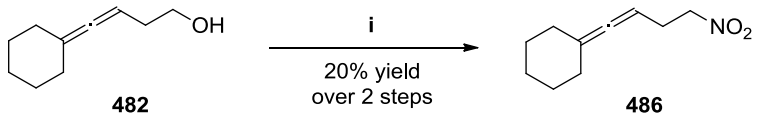
purification by flash column chromatography on silica gel. Due to the complexity of the ^{1}H NMR spectra of the purified product, no assignment of the relative configurations could be made by NOE analysis.

Building on this result, we wanted to further the scope of our methodology to accommodate substrates bearing substituents on the allene functionality. We therefore attempted the synthesis of the cyclohexyl substituted nitroallene **486** (Scheme 134) via the previously used pathway. When we implemented the mesylation and iodide substitution protocol, we found that under the conditions of the iodide substitution reaction, isomerisation for the allene occurred resulting in the formation of iododienes **484** and **484′** as an inseparable mixture of *E/Z* isomers (70:30). In an effort to separate the *E* and *Z* isomers to allow for individual characterisation, the mixture of iododienes **484** and **484′** was converted to nitrodienes **485** and **485′** in 48% yield using $NaNO_2$ in DMSO. However, we once again found that the mixture of isomers could not be separated by flash column chromatography on silica gel (Scheme 133). As a result, nitrodienes **485** and **485′** were furnished as an inseparable mixture of *E/Z* isomers (75:25).



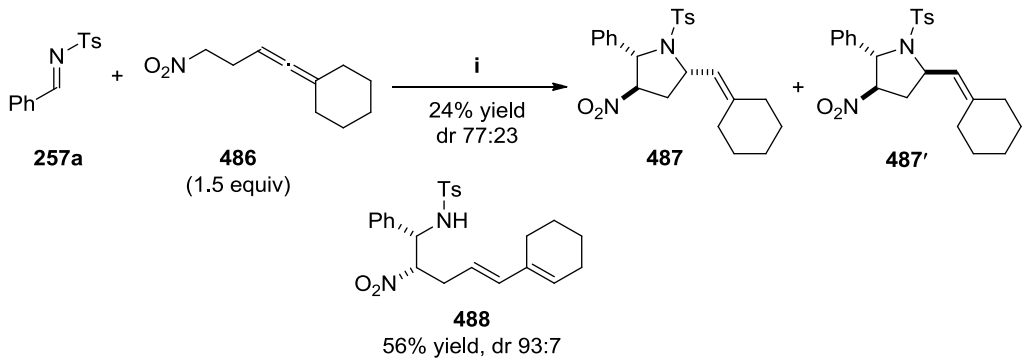
Scheme 133. Attempted synthesis of the cyclohexyl substituted nitroallene **486**. Reagents and conditions: i) propionic acid (3.5 mol%), 150 °C, 3 h; ii) $LiAlH_4$, THF, 0 °C to RT, 1 h; iii) MsCl, Et_3N, CH_2Cl_2, –30 °C to –10 °C, 1 h then NaI, acetone, reflux, 12 h; iv) $NaNO_2$, DMSO, RT, 1.5 h.

To circumvent the isomerisation of the allene moiety during the iodide substitution reaction, alcohol **482** was converted to mesylallene **483**, which was then directly converted to nitroallene **486** in 20% yield using $NaNO_2$ (Scheme 134). It is known that alkyl sulfonate compounds (e.g. mesyl and tosyl) give significantly lower yields than the corresponding alkyl halides (bromide and iodide) when they are reacted with $NaNO_2$.[202] Nevertheless, we wanted to test the substrate's performance in the cascade reaction, so a yield of only 20% was acceptable in this instance.



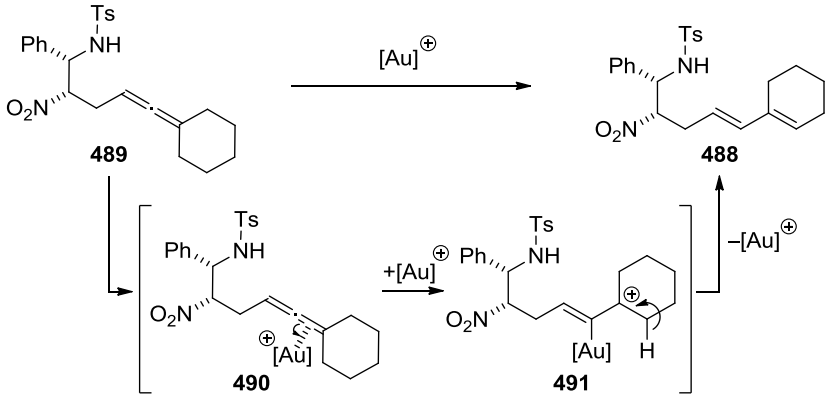
Scheme 134. Synthesis of the cyclohexyl substituted nitroallene **486**. Reagents and conditions: i) MsCl, Et_3N, CH_2Cl_2, –30 °C to –10 °C, 1.5 h then $NaNO_2$, DMSO, RT, 48 h.

With the cyclohexyl substituted nitroallene **486** in hand, the nitro-Mannich/hydroamination cascade reaction was undertaken (Scheme 135). Nitroallene **486** was found to be compatible with the optimal reaction conditions, but the cascade reaction furnished a mixture of pyrrolidines **487** and **487′** in only 24% yield with moderate diastereoselectivity (dr 77:23) in favour of the C2-C5 *cis*-diastereomer **487**.



Scheme 135. Nitro-Mannich/hydroamination cascade using cyclohexyl substituted nitroallene **486**. Reagents and conditions: i) KO*t*Bu (5 mol%), PhMe, [**257a**] 0.1 M, RT, 6 h then DPP (20 mol%), diluted to 0.025 M with DCE, $Au(PPh_3)Cl$ (10 mol%), $AgSbF_6$ (20 mol%), 70 °C, 72 h then SiO_2 treated with Et_3N, 70 °C, 2 h.

The low yield of **487** and **487′** was explained by the isolation of *E*-β-nitroamine **488** in 56% yield and 93:7 dr. The presence of *E*-β-nitroamine **488** shows that the yield of pyrrolidines **487** and **487′** is reduced because of a competing gold/silver catalysed allene isomerisation reaction (Scheme 136).[203] For the formation of the *E*-β-nitroamine **488** to occur, we propose that the gold complex co-ordinates to the allene moiety resulting in the stabilised tertiary carbocation **491**. Elimination of H^+ and protodemetallation of the gold complex affords *E*-β-nitroamine **488**. We propose that *E*-β-nitroamine **488** cannot undergo the hydroamination reaction using our conditions, therefore halting the reaction. This isomerisation reaction is a very important limiting factor of this methodology and further work to find a catalytic system that favours the hydroamination over the isomerisation would be a valuable contribution.

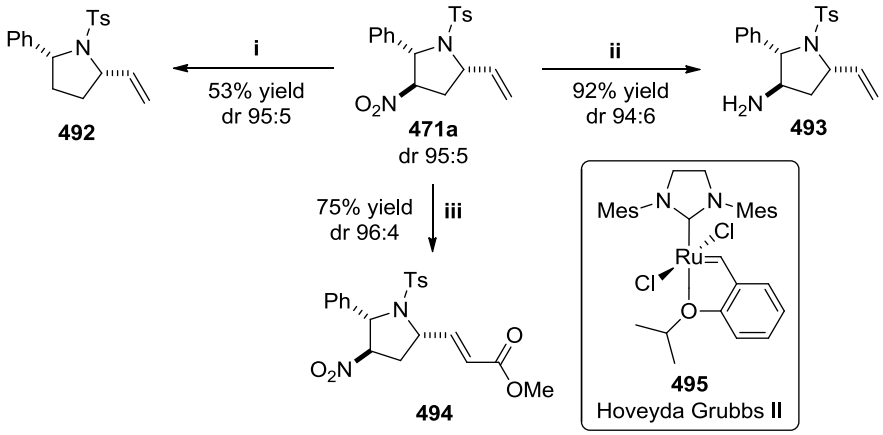


Scheme 136. Proposed gold catalysed allene isomerisation of β-nitroamine **489** to *E*-β-nitroamine **488**.

4.4.7 Synthetic Elaboration of Pyrrolidine 471a

To show that the obtained pyrrolidine products are valuable synthetic intermediates, pyrrolidine **471a** was further derivatised by a variety of methods (Scheme 137). Removal of the nitro group using AIBN and Bu_3SnH,[179] furnished disubstituted pyrrolidine **492** in 53% yield and with no degradation of the diastereoselectivity after

heating at 110 °C for 3 hours. A mixture of zinc powder and acetic acid smoothly reduced the nitro group at room temperature to afford amine **493** in 88% yield after 48 hours.[42] The diastereoselectivity of the reduction reaction was also very good, with amine **493** (dr 94:6) being obtained with essentially the same ratio of diastereomers as pyrrolidine **471a** (dr 95:5). We also undertook the functionalisation of the alkene moiety by means of a cross metathesis reaction. Using methyl acrylate and Hoveyda Grubbs 2nd generation catalyst **495**[204] resulted in the formation of ester **494** in 74% yield after heating at 40 °C in CH_2Cl_2 for 24 hours.



Scheme 137. Derivatisation of pyrrolidine **471a**. Reagents and conditions: i) Bu_3SnH, AIBN (5 mol%), PhMe, 110 °C, 3 h; ii) Zn powder, acetic acid, THF, RT, 24 h; iii) Hoveyda Grubbs II **495** (5 mol%), methyl acrylate, CH_2Cl_2, 40 °C, 24 h.

4.5 Enantioselective Nitro-Mannich/Hydroamination Cascades to Substituted Pyrrolidines

4.5.1 Optimisation of the Enantioselective Nitro-Mannich Reaction

Having developed an efficient diastereoselective synthesis of pyrrolidine derivatives using our nitro-Mannich/hydroamination cascade, we wanted to use a combination of organocatalysis and gold catalysis to allow for the highly enantioselective preparation of substituted pyrrolidines.

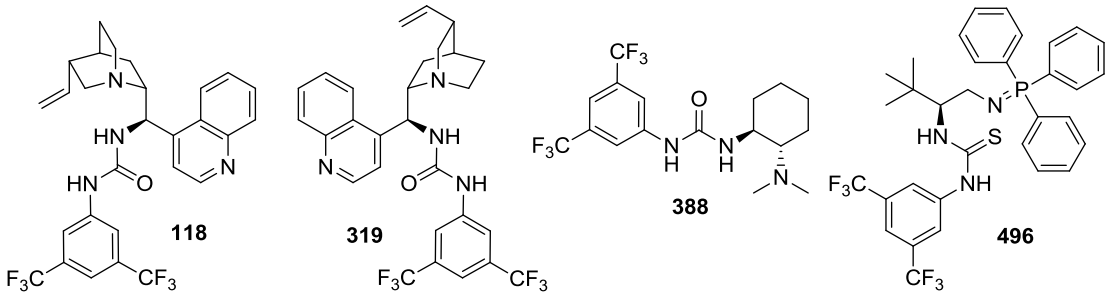
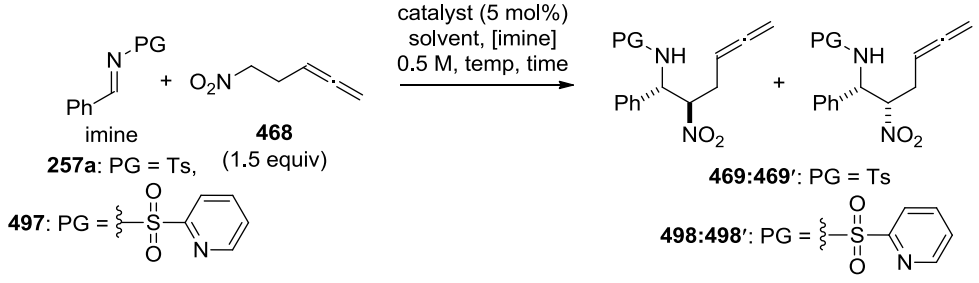


Figure 20. Organocatalysts used in preliminary enantioinduction screen in the nitro-Mannich reaction using nitroallene **468**.

Using organocatalysts **118**, **319**, **388** and **496** (Figure 20), we initially investigated the level of enantioinduction obtained when using *N*-sulfonyl imine **257a** (Table 10) in conjunction with the optimised conditions for the enantioselective nitro-Mannich reaction of *N*-Boc imine **112a** and nitroalkyne **383** (0.5 M, –15 °C; Table 5, Chapter 3). The results obtained were very similar to our previous study, with the highest enantioinduction of 30% ee being achieved using catalyst **388**. In an effort to increase the enantioselectivity when employing an *N*-sulfonyl protected imine, we selected imine **497**, containing an *N*-pyridine-2-sulfonyl protecting group for the remaining optimisation studies. This protecting group is reported to give higher enantioselectivities than the corresponding tosyl protecting group in bifunctional Brønsted base/H-bond donor organocatalysed reactions by increased H-bonding interactions of the (thio)urea with the basic nitrogen of the pyridine ring.[205] Using

urea catalyst **118** in the nitro-Mannich reaction of imine **497** with nitroallene **468** afforded the β-nitroamines **498′** and **498** in 74% yield, but with modest diastereo- and enantioselectivities (dr 61:39, 28% ee; Table 10, entry 4). The *pseudo*-enantiomer **319** provided a decrease in the enantioselectivity to 16% ee (Table 10, entry 5), whilst urea **388** gave almost no enantioinduction in the reaction (4% ee; Table 10, entry 6).

Table 10. Optimisation of *N*-sulfonyl imine protecting group in the organocatalytic nitro-Mannich reaction of nitroallene **468**.

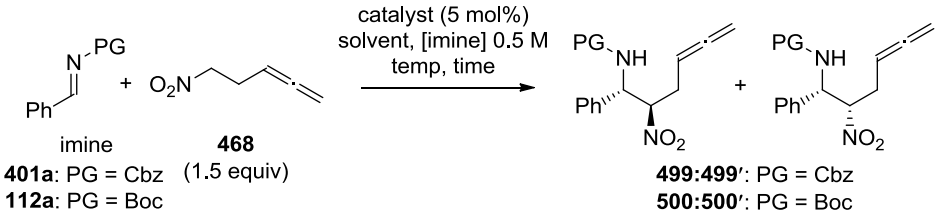


entry	imine	catalyst	solvent	temp (°C)	time (h)	product	yield (%)	dr[a] *anti/syn*	ee[a] (%) *anti/syn*
1	**257a**	**118**	PhMe	–15	48	**469:469′**	80	55:45	7/61
2	**257a**	**319**	PhMe	–15	48	**469:469′**	92	52:48	7/56
3	**257a**	**388**	PhMe	–15	48	**469:469′**	81	58:42	30/46
4[b]	**497**	**118**	CH_2Cl_2	RT	24	**498:498′**	73	39:61	28/11
5[b]	**497**	**319**	CH_2Cl_2	RT	24	**498:498′**	75	38:62	16/12[c]
6[b]	**497**	**388**	CH_2Cl_2	RT	24	**498:498′**	74	30:70	4/14[c]
7[b]	**497**	**496**	CH_2Cl_2	RT	24	**498:498′**	86	60:40	21/1
8	**497**	**118**	CH_2Cl_2	–15	24	**498:498′**	59	53:47	41/31
9	**497**	**496**	CH_2Cl_2	–15	24	**498:498′**	65	66:34	39/4

[a] Determined by HPLC analysis of the purified product. [b] Reaction conducted with [imine] 0.1 M. [c] Opposite enantiomers obtained. The absolute configurations of β-nitroamines **469**, **469′**, **498** and **498′** were not determined, only the relative configuration is shown.

The highly basic bifunctional thiourea iminophosphorane catalyst **496**, introduced by our group,[206] improved the isolated yield of the reaction to 86% as well as altering the diastereoselectivity to favour the *anti*-diastereomer **498** (dr 60:40, 21% ee; Table 10, entry 7). Because of the promising results obtained using urea **118** and bifunctional iminophosphorane **496**, they were further investigated by employing the previously optimised conditions (0.5 M, –15 °C; Table 5, Chapter 3). Unfortunately the enantioselectivities were only increased to 41% ee and 39% ee respectively. As a result, we decided to change the *N*-protecting group to a Cbz group as this had yielded high enantioselectivities in our earlier studies on tetrahydropyridine systems.

Table 11. Optimisation of the diastereo- and enantioselectivity in the organocatalytic nitro-Mannich reaction of nitroallene **468**.[e]



entry	imine	catalyst	temp (°C)	time (h)	product	yield (%)	dr[a] *anti/syn*	ee[a] (%) *anti/syn*
1	**401a**	**118**	RT	20	**499:499′**	59	65:35	55/33[b]
2	**401a**	**388**	RT	15	**499:499′**	77	75:25	86/75
3	**401a**	**118**	–15	72	**499:499′**	57	79:21	51/37[b]
4	**401a**	**319**	–15	72	**499:499′**	59	82:18	58/55
5	**401a**	**388**	–15	44	**499:499′**	77	87:13	91/77
6	**112a**	**388**	–15	24	**500:500′**	38	82:18	88/84

[a] Determined by HPLC analysis of the purified product. [b] Opposite enantiomers obtained.

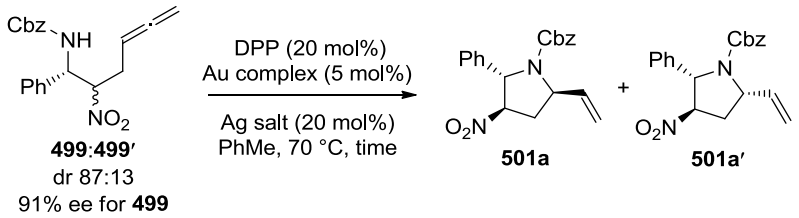
[e] Compounds **499**, **499′**, **500** and **500′** were independently prepared and characterised by Dr. A. Ďuriš.

After a concise optimisation study investigating the organocatalyst, temperature and reaction mixture concentration (Table 11), we found that the use of catalyst **388** (5 mol%), −15 °C and [imine] 0.5 M resulted in the best diastereo- and enantioselectivity (dr 87:13, 91% ee) as well as the best isolated yield (77%; Table 11, entry 5). *N*-Boc imine **112a** also gave good diastereo- and enantioselectivity (dr 82:18, 88% ee) but with a significantly reduced yield of 38%. As a result, the cyclisation studies were conducted on the *N*-Cbz containing β-nitroamines **499** and **499′**.

4.5.2 Optimisation of the Allene Hydroamination Reaction

With the optimised gold and silver complexes from the diastereoselective pyrrolidine synthesis, we were able to successfully cyclise β-nitroamines **499** and **499′** (dr 87:13, 91% ee for the major diastereomer) to afford *N*-Cbz pyrrolidine **501a** in 61% yield and 81:19 crude dr with retention of the enantioselectivity observed in the β-nitroamine **499** (91% ee; Table 12, entry 1). Interestingly, we discovered that the hydroamination reaction proceeded smoothly without using DCE as the reaction solvent. Changing the silver salt to AgOTf and $AgNTf_2$ gave minor increases in the diastereoselectivity of the hydroamination reaction whilst maintaining good yields of pyrrolidine **501a** (Table 12, entries 2 and 3).

Table 12. Cyclisation optimisation of *N*-Cbz β-nitroamines **499** and **499′**.



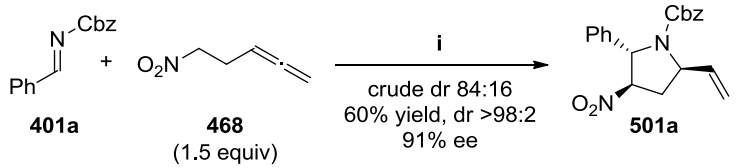
entry	Au complex (5 mol%)	Ag salt (20 mol%)	time (h)	yield[a] (%)	dr[b] **501a:501a′**	ee[c] (%)
1	$Au(PPh_3)Cl$	$AgSbF_6$	2	61	81:19	91
2	$Au(PPh_3)Cl$	AgOTf	2	58	83:17	91
3	$Au(PPh_3)Cl$	$AgNTf_2$	2	65	82:18	91
4	$Au(PPh_3)Cl$	$AgBF_4$	2	69	89:11	91
5	$Au[(PhO)_3P]Cl$	$AgBF_4$	4	54	80:20	91
6	$Au(PtBu_3)Cl$	$AgBF_4$	3	50	83:17	91

[a] Isolated yield of single diastereomer **501a** after purification by flash column chromatography on silica gel. [b] Determined by ^1H NMR analysis of the crude reaction mixture. [c] Determined by HPLC analysis of the purified product; ee of the major diastereomer **501a** is shown, ee of the minor diastereomer **501a′** was not determined.

Employment of $AgBF_4$ not only gave an improved yield of pyrrolidine **501a** (69%), but the diastereoselectivity of the crude reaction mixture was also improved to 89:11 dr (Table 12, entry 4). Changing the phosphine ligand led to reduced yields of pyrrolidine **501a** and erosion of the diastereoselectivity (Table 12, entries 5 and 6).

4.5.3 One-pot Enantioselective Cascade Development and Scope of Reaction

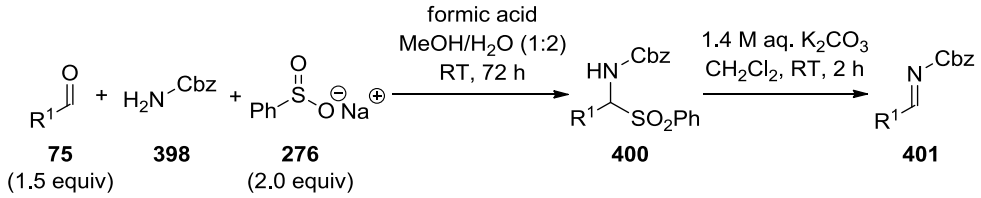
With both the nitro-Mannich and hydroamination reactions independently optimised, we were confident that combining these two reactions in a sequential cascade procedure would allow for a highly enantioselective pyrrolidine synthesis. Pleasingly, the sequential procedure was successful, affording pyrrolidine **501a** in 60% yield and 91% ee as a single diastereomer after purification by (Scheme 138).



Scheme 138. One-pot cascade reaction to enantioenriched pyrrolidine **501a**. Reagents and conditions: i) catalyst **388** (5 mol%), PhMe, −15 °C, [**401a**] 0.5 M, 40 h then DPP (20 mol%), diluted to 0.1 M with PhMe, $Au(PPh_3)Cl$ (5 mol%), $AgBF_4$ (20 mol%), 70 °C, 3 h.

To determine the breadth of this one-pot enantioselective pyrrolidine cascade, we prepared a range of substituted *N*-Cbz imines. Firstly, the *N*-Cbz amidosulfones **400** were synthesised on multi-gram scale from benzyl carbamate (**398**), benzene sulfinic acid sodium salt (**276**) and the corresponding aldehydes **75** (Table 13). After stirring at room temperature for 72 hours, a filtration and trituration provided the amidosulfones **400** in 11-77% yields.[138] The amidosulfones **400** were then treated with 1.4 M aq. solution of K_2CO_3 in CH_2Cl_2 at RT for 2 hours to afford the corresponding *N*-Cbz imines **401** in 86-98% yields.[177]

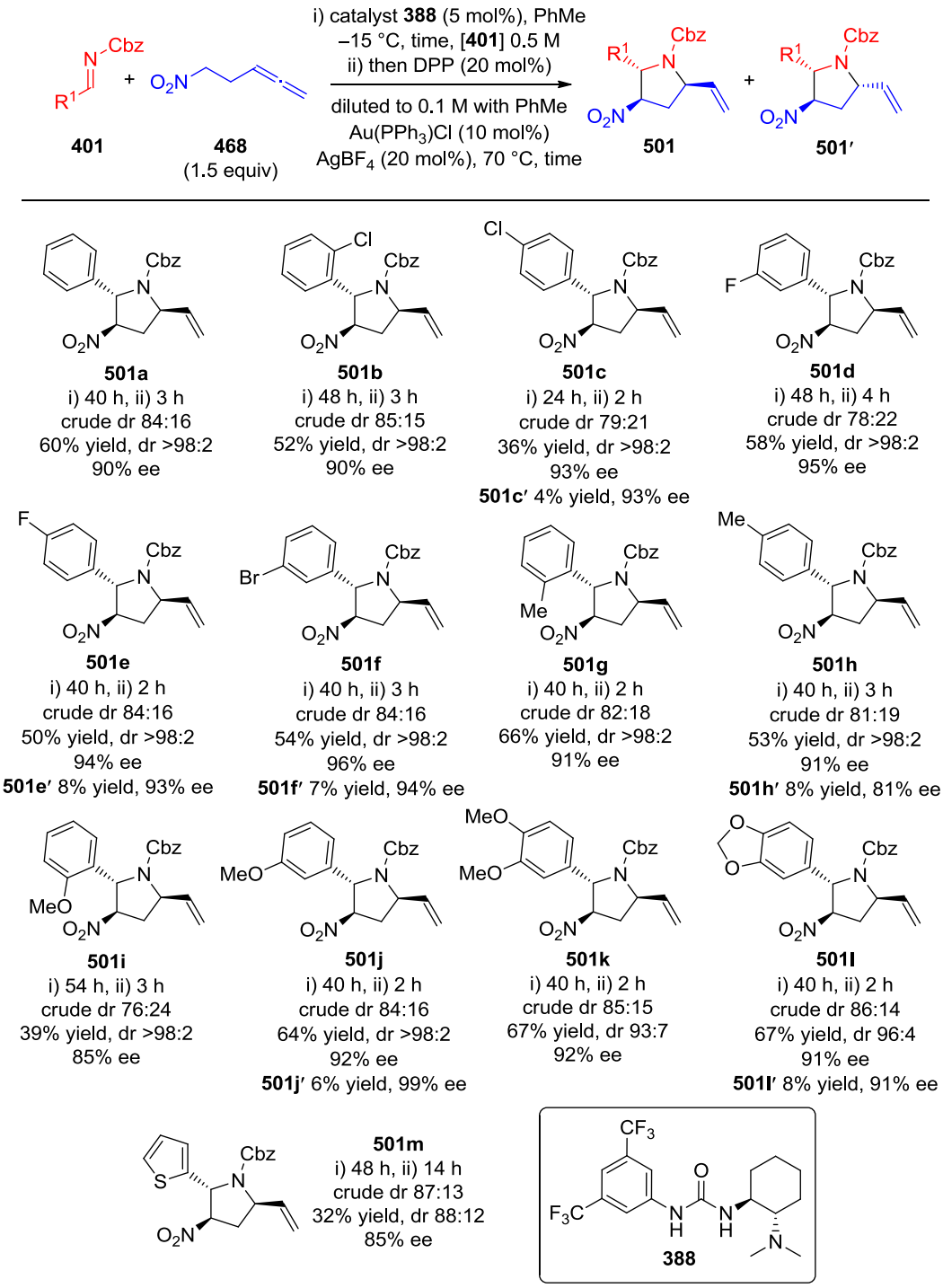
Table 13. Synthesis of amidosulfones **400** and *N*-Cbz imines **401**.[f]



entry	R^1	amidosulfone **400**	yield (%)	imine **401**	yield (%)
1	Ph	**400a**	57	**401a**	96
2	*o*-ClC_6H_4	**400b**	44	**401b**	97
3	*p*-ClC_6H_4	**400c**	—	**401c**	98
4	*m*-FC_6H_4	**400e**	54	**401e**	91
5	*p*-FC_6H_4	**400f**	65	**401f**	95
6	*m*-BrC_6H_4	**400g**	50	**401g**	94
7	*o*-MeC_6H_4	**400h**	40	**401h**	87
8	*p*-MeC_6H_4	**400i**	40	**401i**	95
9	*o*-$MeOC_6H_4$	**400j**	77	**401j**	76
10	*m*-$MeOC_6H_4$	**400k**	41	**401k**	96
11	3,4-$(MeO)_2C_6H_3$	**400l**	23	**401l**	86
12	3,4-(-OCH_2O-)C_6H_3	**400m**	38	**401m**	88
13	2-thienyl	**400n**	11	**401n**	93

The substituted *N*-Cbz imines **401** were then exposed to our optimised nitro-Mannich/hydroamination conditions (Scheme 139). Pleasingly, the cascade reaction was shown to tolerate variations in the substituents present on the aromatic ring of the *N*-Cbz imines. The electron-poor halogen (fluoro, chloro and bromo) substituted aryl groups all afforded the desired enantioenriched pyrrolidines **501b-501f** in moderate to good yields (36-58%). The diastereoselectivity observed in the crude reaction mixtures were generally good (dr 78:22-85:15), with the major isomer being isolated as a single diastereomer after purification with excellent enantioselectivities being observed in all of the examples (90-96% ee).

[f] All *N*-Cbz imines **401** were independently prepared and characterised by Dr. A. Ďuriš.



Scheme 139. Scope of the enantioselective nitro-Mannich/hydroamination cascade for the enantioselective synthesis of pyrrolidines **501**. (Only the major diastereomers **501** are depicted in the scheme).

In the preparation of compounds **501c**, **501e** and **501f**, the minor isomers were also isolated after purification by column chromatography on silica gel in excellent enantioselectivities (93-94% ee). The electron-rich methoxy substituted aryl groups

were also found to be suitable *N*-Cbz imines for the cascade reaction. The *ortho*-methoxy substituted aryl pyrrolidine **501i** did suffer from a diminished yield and enantioenrichment (39% yield, 85% ee), but all of the other pyrrolidines bearing methoxy groups were afforded with good yields (64-67%) and enantioselectivities (91-92% ee). The minor diastereomers **501j′** and **501l′** were also isolated from these reactions, with pyrrolidine **501j′** exhibiting 99% ee. The electron-rich 2-thienyl substituted pyrrolidine **501m** was pleasingly furnished by the cascade reaction, although it was obtained in only 32% yield and 85% ee.

4.5.4 Determination of Rotamers

Analysis of the ^{1}H NMR spectra of the major pyrrolidine diastereomers **501** suggested that the compounds were rotameric in deuterated methanol. Typically, rotameric molecules (equilibrating species) are distinguished from diastereomers (nonequilibrating species) by the use of techniques such as variable-temperature (VT) NMR spectroscopy,[207] solvent switching[208] or by adding a complexing agent.[209] In an effort to prove that pyrrolidines **501** were indeed mixtures of rotamers and not diastereomers, we attempted to use VT NMR analysis. However, this technique proved unsuccessful as the ^{1}H and ^{13}C NMR signals did not coalesce when heated to 100 °C in d_6-DMSO.

Recently, Ley and co-workers described a 1D selective exchange NOE technique to distinguish between rotamers and diastereomers.[210] This technique is similar to a normal NOE experiment, but instead of a through-space interaction responding in the opposite phase to the initial irradiation, the response of isomers that are under chemical exchange appear in the same phase. To use this technique, we dissolved pyrrolidine **501h** in deuterated benzene to resolve the rotamer signals and then

irradiated the protons at the C2 and C5 positions (Figure 21). As figure 21 shows, the corresponding rotamer peaks responded in the same phase as the initial pulse, confirming that the signals are under chemical exchange and are therefore rotamers, not diastereomers.

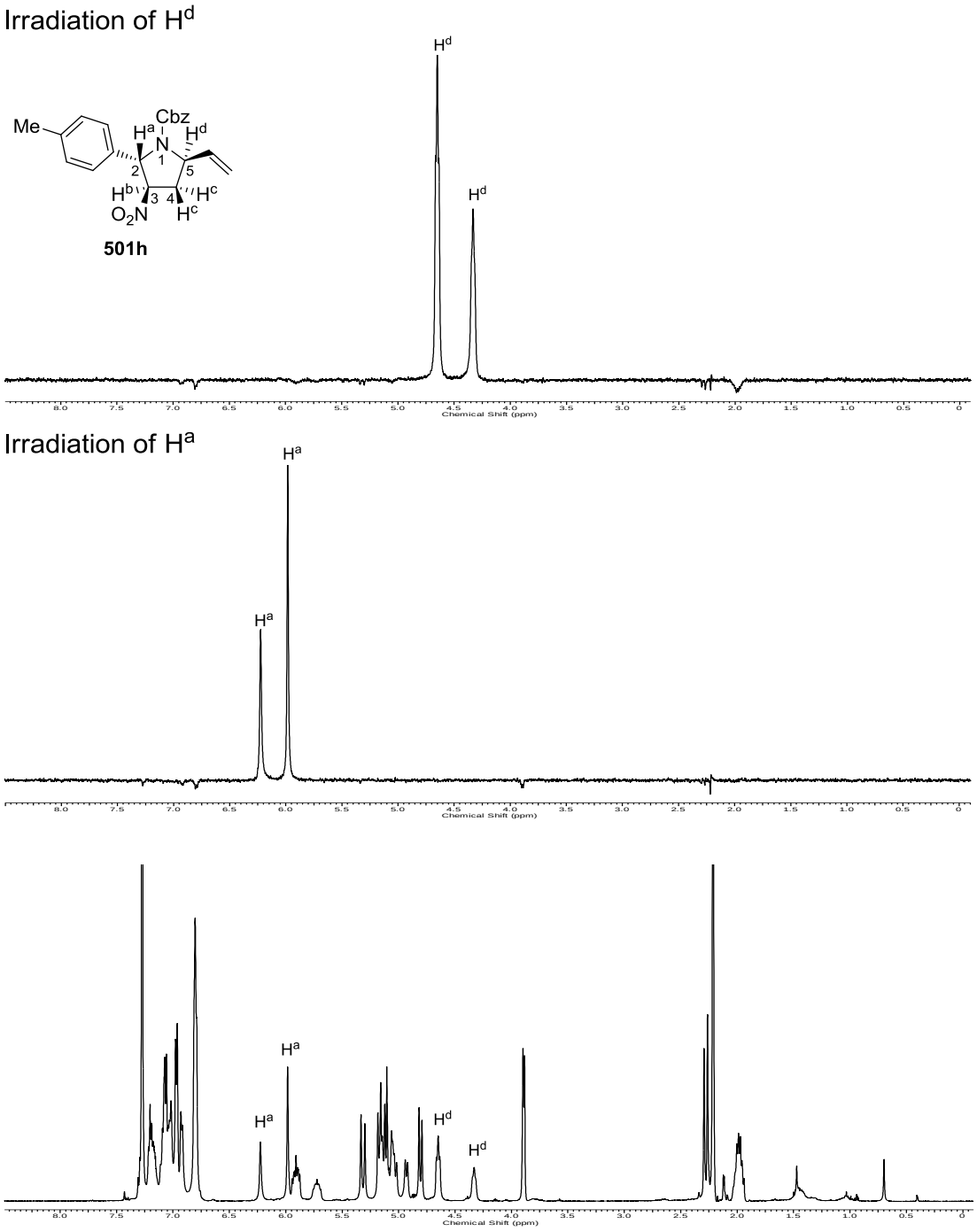


Figure 21. 1D gradient NOE experiment spectra for pyrrolidine **501h** in deuterated benzene at 25 °C.

4.5.5 Determination of the Absolute and Relative Configurations

To prove the absolute configuration of the synthesised pyrrolidines, we obtained a single crystal of pyrrolidine **501k** for X-ray diffraction analysis by crystallisation from $CHCl_3$. The X-ray diffraction data showed that pyrrolidine **501k** contained a (2*S*,3*R*,5*R*) configuration (Figure 22). All the other major pyrrolidine diastereomers **501** were assigned by analogy to this X-ray crystal structure.

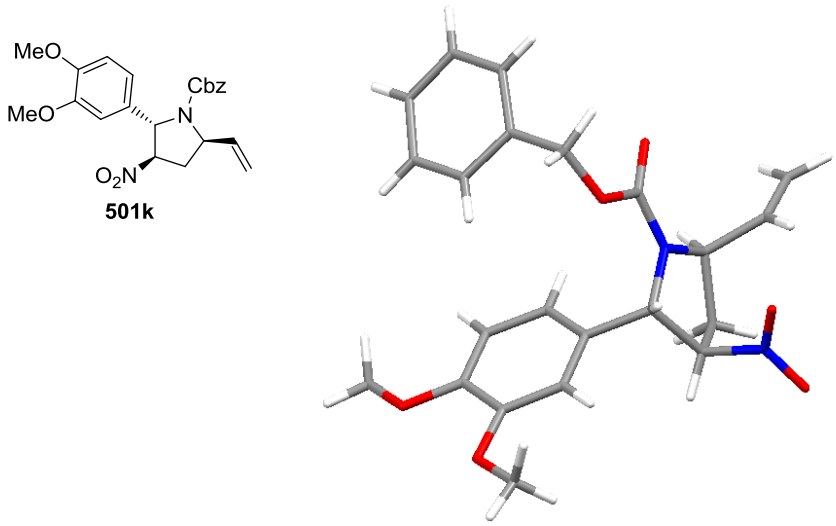


Figure 22. X-Ray crystal structure representation of pyrrolidine **501k**.

In an attempt to determine the relative configuration of the minor pyrrolidine diastereomers **501′**, we conducted NOESY experiments on the minor diastereomer **501h′**. In the case of the minor diastereomer **501h′** (Figure 23), an interaction between the C2 (H^a) and C5 (H^d) protons is observed, providing strong evidence for a C2-C5 *cis* configuration. The C2-C3 configuration of both **501h** and **501h′** could not be determined by NOESY analysis as both the *cis* and *trans* configurations can allow the protons to show an interaction. As a result, the configuration at the C2-C3 positions was assigned as *trans* because the proton in the C2 position showed such a small coupling constant with the proton in the C3 ($^3J_{H,H} \approx 90°$) position that the C2 signal appeared as a broad singlet.[200]

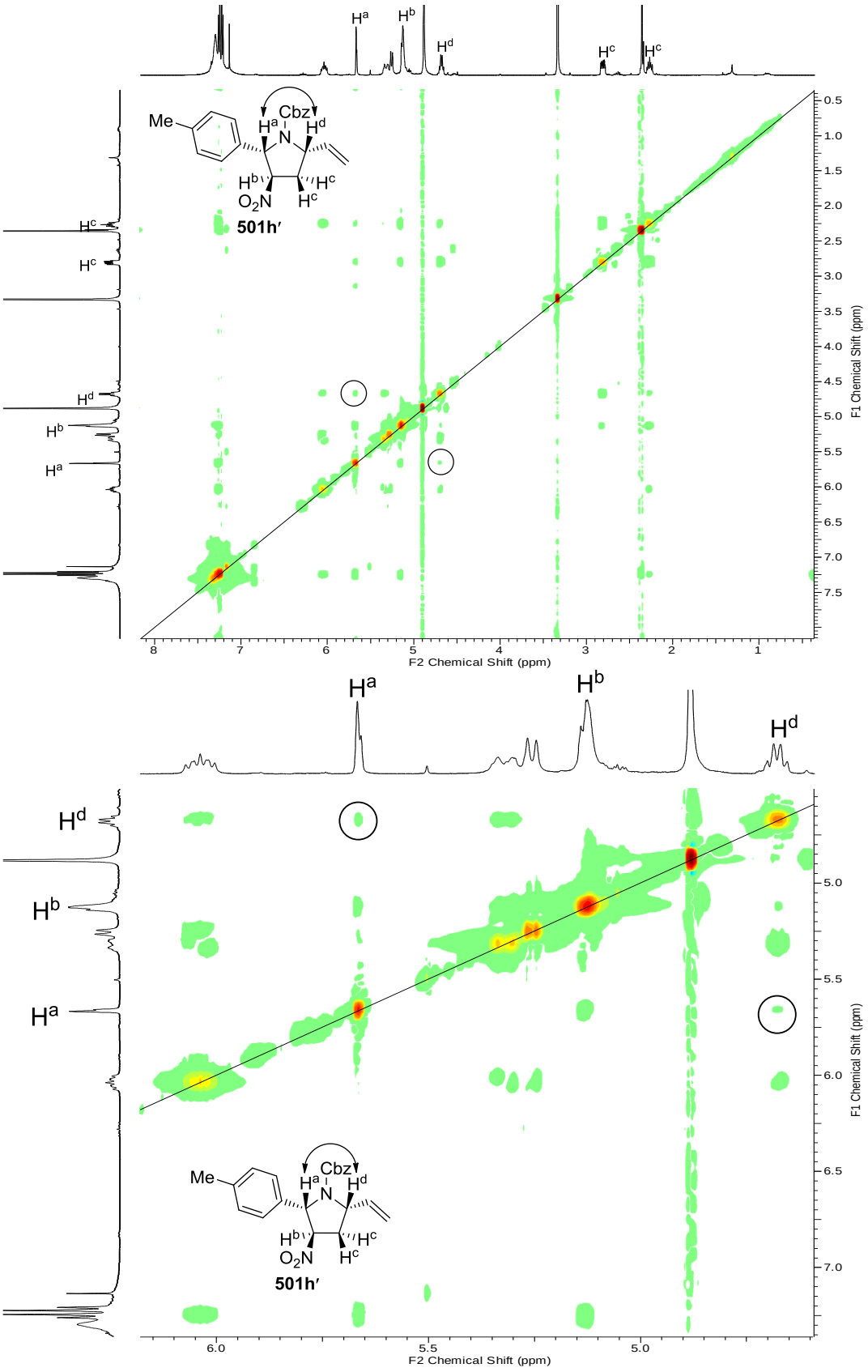


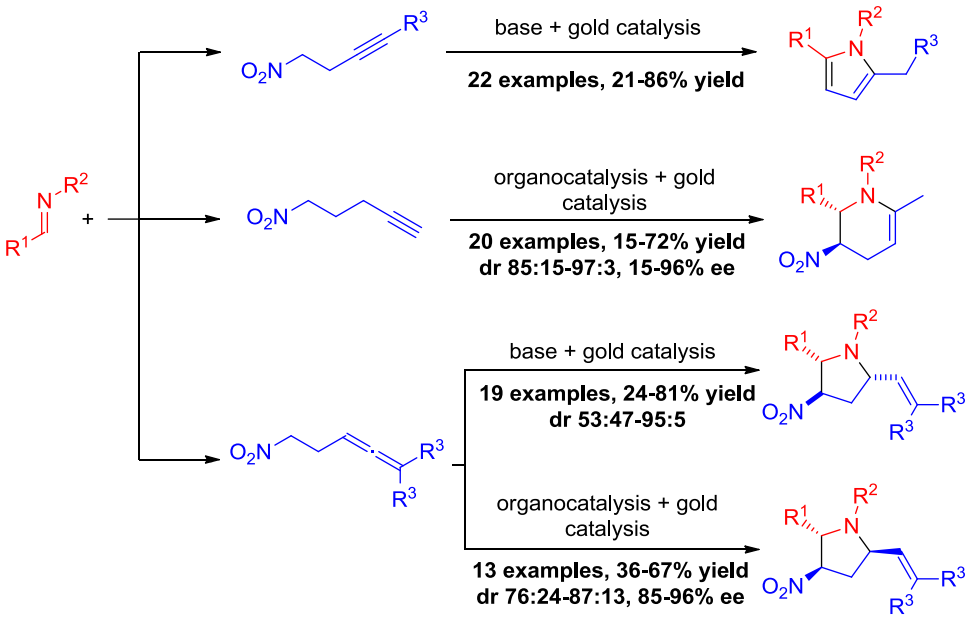
Figure 23. NOESY analysis of minor pyrrolidine diastereomer **501h′**.

4.6 Summary and Conclusion

In summary, we have developed a diastereoselective and enantioselective synthesis of substituted pyrrolidines using a nitro-Mannich/hydroamination cascade methodology. Firstly, a highly diastereoselective preparation of pyrrolidine derivatives was discovered using *N*-sulfonyl imines and nitroallene substrates. Using a sequential combination of KO*t*Bu and $Au(PPh_3)Cl$ with $AgSbF_6$ followed by the addition of silica gel (treated with Et_3N) enabled the efficient synthesis of sulfonamide protected pyrrolidines **471** in modest to good yields (31-81%) with modest to excellent diastereoselectivities (up to dr 95:5). Single crystal X-ray diffraction analysis of pyrrolidine **471a** proved the relative configuration of the major diastereomers **471** and NOE experiments confirmed the relative configuration of the minor diastereomers **471′**. The synthetic utility of the products was demonstrated by converting the pyrrolidine products into useful intermediates. This nitro-Mannich/hydroamination cascade was then extended to an enantioselective cascade by sequential addition of catalyst **388** and $Au(PPh_3)Cl$ with $AgBF_4$ using *N*-Cbz protected imines affording pyrrolidines **501** in moderate to good yields (32-67%) with excellent enantioselectivities (85-96% ee). The absolute configuration of the major diastereomers **501** was proven using single crystal X-ray diffraction analysis of pyrrolidine **501k** and the configuration of the minor diastereomers **501′** was assigned by NOESY analysis of **501h′**. These methodologies will allow new highly substituted pyrrolidine based architectures to be prepared for library generation and target synthesis.

Thesis Summary and Future Work

During the course of our investigations, we have shown that a range of substituted pyrroles **269**, tetrahydropyridines **396** and pyrrolidines **471**/**501** can be prepared using the nitro-Mannich/hydroamination cascade methodologies that we have developed (Scheme 140). The product obtained from the cascade reaction is dependent on the structure of the nitroalkyne (pyrrole, tetrahydropyridine) or nitroallene (pyrrolidine) reaction partner used in the cascade reaction. All of these nitro substrates can be easily synthesised on gram scale from commercially available starting materials, as are the *N*-sulfonyl, *N*-Boc or *N*-Cbz imines that are also used as starting materials. The nitro-Mannich/hydroamination cascade reactions are efficient and easy to perform, utilising commercially available gold complexes and silver salts in catalytic quantities. Also, the enantioselective cascades employ bifunctional organocatalysts that can be straightforwardly prepared from commercially available starting materials.



Scheme 140. Summary of the nitro-Mannich/hydroamination cascades described in this thesis.

Due to the efficiency of these cascade reactions and the diversity of the products prepared, we envisage that this methodology should find use in rapid compound library synthesis as well as complex target synthesis.

In order to expand the potential and versatility of this project, future work on the development of nitro-Mannich/hydroamination cascade reactions that can accommodate aliphatic substituents on the protected imine reaction partner, as well as incorporating non-terminal nitroalkyne substrates should be conducted. Applying this cascade methodology to the synthesis of an appropriately selected natural product will also be an interesting challenge to further the utility of this methodology.

Chapter 5: Experimental

5.1 General Experimental

5.1.1 General Techniques

All non-aqueous reactions were conducted using oven-dried glassware under a positive pressure of dry nitrogen and were magnetically stirred unless otherwise stated. Yields refer to spectroscopically pure compounds, unless otherwise stated.

5.1.2 Solvents and Reagents

Concentration under reduced pressure was performed by rotary evaporation at 40 °C at the appropriate pressure. Reagents used were obtained from commercial suppliers or purified according to standard procedures. Petroleum ether (PE) refers to distilled light petroleum of fraction 30 - 40 °C. Anhydrous toluene, tetrahydrofuran, dichloromethane, diethyl ether and acetonitrile were dried by filtration through activated alumina (powder ~150 mesh, pore size 58 Å, basic) columns. Anhydrous methanol was dried by distillation over magnesium iodide. Dimethyl sulfoxide was used as supplied. Deuterated solvents were used as supplied.

5.1.3 Chromatography

Reactions were monitored by thin layer chromatography (TLC) using Merck silica gel 60 F_{254} plates and visualised by fluorescence quenching under UV light. In addition, TLC plates were stained with aq. basic potassium permanganate solution or vanillin solution as appropriate. Flash column chromatography was carried out on VWR 60 silica gel (40 - 63 μm) using technical grade solvents that were used as supplied. Enantiomeric excesses were determined using high performance liquid chromatography (HPLC) performed on an Agilent Technologies 1260 Infinity series

machine (column and solvent conditions are reported with the appropriate compound).

5.1.4 Spectroscopy

All ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Spectrospin spectrometer operating at 400 MHz or 500 MHz (^{1}H acquisitions) and 100 MHz or 125 MHz (^{13}C acquisitions). Chemical shifts (δ) are reported in ppm with the solvent resonance as the internal standard (e.g. Chloroform δ 7.27 ppm for ^{1}H and 77.0 ppm for ^{13}C). Coupling constants (*J*) are reported in hertz (Hz) and are rounded to the nearest 0.5 decimal places. Data are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, qu = quintet, m = multiplet, br = broad, coupling constants *J*/Hz (where appropriate), integration and assignment. DEPT 135, two-dimensional (COSY, HSQC and HMBC) and NOE/NOESY NMR spectroscopy were used to assist in the assignment of the signals in the ^{1}H and ^{13}C NMR spectra. The multiplets in the ^{1}H NMR spectra are reported as they are observed, not taking into account the theoretical NMR multiplicity. Low resolution mass spectra (electrospray ionisation, ESI) were recorded on a Waters LCT Premier XE Micromass spectrometer or an Agilent Technologies 6120 Quadrupole LC/MS spectrometer. High resolution mass spectra (ESI) were recorded on a Bruker Daltonics Micro TOF spectrometer. High resolution mass spectra (field ionisation, FI) were recorded on a Bruker FT-ICR Apex III spectrometer. Infrared spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer as a thin film deposited onto a sodium chloride plate or diamante ATR module. Only selected maximum absorbances are reported. Melting points were recorded on a Leica Galen III Hot-stage melting point apparatus and microscope and are reported uncorrected. Optical rotations were recorded using a Perkin-Elmer 341 polarimeter; $[\alpha]_D^T$ values are reported in 10^{-1} deg cm^2 g^{-1}, concentrations (c) are

quoted in g/100 mL, D refers to the D-line of sodium (589 nm), temperatures (T) are given in degrees Celsius (°C). (+) and (–) compound number prefixes indicate the sign of the optical rotation.

5.1.5 Naming of Compounds

All compound names were generated using ACD Labs 12.0 following IUPAC nomenclature.

5.1.6 X-Ray Crystallographic Data

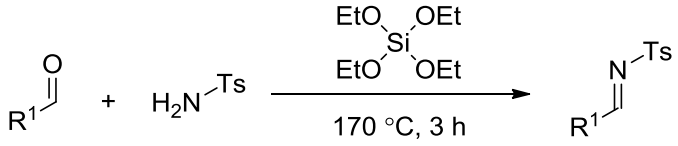
Single crystal X-ray diffraction data were collected at 150 °K[211] using an Enraf-Nonius KCCD diffractometer or an Oxford Diffraction SuperNova diffractometer.[212] The crystal structures of compounds **268′**, **394g** and **471a** were solved with SIR92[213] and refined with CRYSTALS[214] including the Flack x parameter (where appropriate)[215] under the guidance of Dr. A. L. Thompson of the University of Oxford Chemical Crystallography department. The crystal structure of compound **501k** was solved by Dr. A. L. Thompson. Crystallographic data is provided in the appendices.

5.2 Experimental Section for Chapter 2

5.2.1 Reagents and Synthesis of Starting Materials

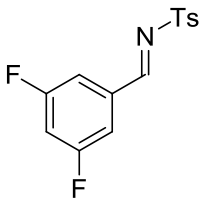
All commercially available reagents were used as received unless otherwise stated. *N*-Sulfonyl imines **257a**,[125] **257b**,[125] **257c-e**,[135] **257f**,[136] **257g-j**,[125] **257k**,[135] **257l**,[136] **257m**,[135] **257n**,[136] **257o**,[125] **257p**,[125] **257q**,[135] **257r**,[125] and **257s**[136] were all prepared according to literature procedures. *N*-Nosyl imine **277**,[125] *N*-PMB imine **278**[137] and *N*-Boc imine **112a**[138] were prepared according to literature procedures. The following alkyne substrates were prepared according to literature procedures: iodopent-2-yne (**284**),[216] 4-phenylbut-3-yn-1-ol (**287**),[217] (4-iodobut-1-yn-1-yl)benzene (**288**)[216] and (1-iodobut-3-yn-1-yl)benzene (**297**).[143] Compound **307** was prepared according to a literature procedure.[147] The data for compounds **282**[218] and **302**[219] were in accordance to those reported in the literature.

General Procedure A: Synthesis of *N*-sulfonyl imines



To a mixture of the corresponding aldehyde (1.1 equiv) and *p*-toluenesulfonamide (**256**) (1.0 equiv) at RT in a flask equipped with a Dean-Stark trap was added tetraethylorthosilicate (1.1 equiv). The reaction mixture was heated to 170 °C for 3 h and then allowed to cool to RT. The resulting solid was purified by trituration with Et_2O to afford the desired *N*-sulfonyl imine.

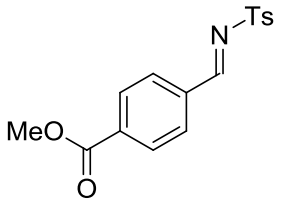
Synthesis and characterisation of *N*-[(*E*)-(3,5-difluorophenyl)methylene]-4-methylbenzenesulfonamide (257j)



257j

Prepared according to general procedure A. 3,5-Difluorobenzaldehyde (780 mg, 5.50 mmol, 0.52 mL) was reacted with *p*-toluenesulfonamide (**256**) (856 mg, 5.00 mmol) to afford compound **257j** (1.13 g, 77%) as a white solid, after purification by trituration with Et_2O. **Melting Point**: 131 - 134 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 8.95 (s, 1H, C**H**=N), 7.90 (d, *J* = 8.5 Hz, 2H, Ar**H**), 7.49 - 7.43 (m, 2H, Ar**H**), 7.38 (d, *J* = 8.5 Hz, 2H, Ar**H**), 7.07 (tt, *J* = 8.5, 2.5 Hz, 1H, Ar**H**), 2.46 (s, 3H, ArC**H$_3$**); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 167.4 (t, *J* = 3.0 Hz, **C**H=N), 163.1 (dd, *J* = 251.5, 12.0 Hz, 2 × Ar**C**F), 145.1 (Ar**C**), 135.3 (t, *J* = 9.0 Hz, Ar**C**), 134.3 (Ar**C**), 129.9 (2 × Ar**C**H), 128.2 (2 × Ar**C**H), 113.6 (dd, *J* = 19.0, 7.0 Hz, 2 × Ar**C**H), 110.0 (t, *J* = 25.5 Hz, Ar**C**H), 21.6 (Ar**C**H_3); **^{19}F NMR** (376.5 MHz, $CDCl_3$): –107.1 (2 × Ar**F**); **IR** (film/cm^{-1}): ν_{max} 3078, 1621, 1584, 1440, 1316, 1183, 1123, 1089, 868, 808, 710; **MS** (ESI): *m/z* 296.1 [$(M + H)^+$]; **HRMS** (ESI): exact mass calculated for $C_{15}H_{15}F_2NNaO_3S$ [$(M + Na + MeOH)^+$], 350.0633; found 350.0637.

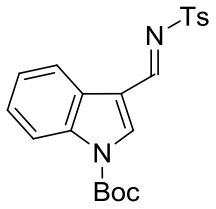
Synthesis and characterisation of methyl 4-[(*E*)-{[(4-methylphenyl)sulfonyl] imino}methyl]benzoate (257o)



257o

Prepared according to general procedure A. Methyl 4-formylbenzoate (411 mg, 2.50 mmol) was reacted with *p*-toluenesulfonamide (**256**) (389 mg, 2.27 mmol) to afford compound **257o** (339 mg, 47%) as a white solid, after purification by trituration with Et_2O. **Melting Point**: 183 - 185 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 9.07 (s, 1H, C**H**=N), 8.17 - 8.10 (m, 2H, Ar**H**), 8.03 - 7.96 (m, 2H, Ar**H**), 7.93 - 7.87 (m, 2H, Ar**H**), 7.36 (d, *J* = 8.0 Hz, 2H, Ar**H**), 3.95 (s, 3H, $CO_2C\mathbf{H_3}$), 2.45 (s, 3H, $ArC\mathbf{H_3}$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 168.8 (**C**H=N), 165.8 (**C**=O), 144.9 (Ar**C**), 135.8 (Ar**C**), 135.3 (Ar**C**), 134.5 (Ar**C**), 131.0 (2 × Ar**C**H), 130.1 (2 × Ar**C**H), 129.9 (2 × Ar**C**H), 128.2 (2 × Ar**C**H), 52.6 ($CO_2\mathbf{C}H_3$), 21.6 ($Ar\mathbf{C}H_3$); **IR** (film/cm^{-1}): ν_{max} 1717, 1603, 1566, 1323, 1282, 1160, 1109, 1088, 783, 765; **MS** (ESI): *m/z* 318.1 [$(M + H)^+$]; **HRMS** (FI): exact mass calculated for $C_{16}H_{15}NO_4S$ [M], 317.0722; found 317.0722.

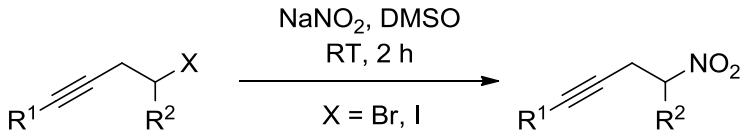
Synthesis and characterisation of *tert*-butyl 3-[(*E*)-{[(4-methylphenyl)sulfonyl] imino}methyl]-1*H*-indole-1-carboxylate (257q)



257q

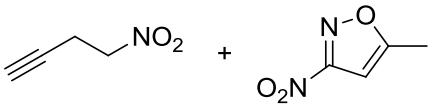
To a stirred solution of *tert*-butyl 3-formyl-1*H*-indole-1-carboxylate (809 mg, 3.00 mmol), *p*-toluenesulfonamide (**256**) (514 mg, 3.00 mmol) and Et_3N (1.21 g, 12.0 mmol, 1.66 mL) in CH_2Cl_2 (24 mL) at 0 °C was added $TiCl_4$ (1.50 mL, 1.0 M solution in CH_2Cl_2). The resulting mixture was stirred at 0 °C for 30 min. The reaction mixture was filtered through a pad of celite® washing with CH_2Cl_2 and the resulting filtrate was concentrated under reduced pressure. The residual solid was refluxed in Et_2O (100 mL) for 5 min and the insoluble material was removed by filtration (×2). The resulting filtrate was concentrated under reduced pressure to afford a solid, which was purified by trituration with Et_2O to afford compound **257q** (578 mg, 48%) as a pale yellow solid. **Melting Point**: 147 - 149 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 9.16 (s, 1H, C**H**=N), 8.30 (d, *J* = 8.0 Hz, 1H, Ar**H**), 8.29 (s, 1H, Ar**H**), 8.15 (d, *J* = 8.5 Hz, 1H, Ar**H**), 7.95 - 7.89 (m, 2H, Ar**H**), 7.45 - 7.39 (m, 1H, Ar**H**), 7.38 - 7.31 (m, 3H, Ar**H**), 2.43 (s, 3H, ArC**H$_3$**), 1.71 (s, 9H, C(C**H$_3$**)$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 163.3 (**C**=N), 148.3 (**C**=O), 144.1 (Ar**C**), 137.6 (Ar**C**H), 136.2 (Ar**C**), 135.9 (Ar**C**), 129.7 (2 × Ar**C**H), 127.8 (2 × Ar**C**H), 126.3 (Ar**C**H), 126.2 (Ar**C**), 124.6 (Ar**C**H), 122.8 (Ar**C**H), 116.4 (Ar**C**), 115.2 (ArCH), 86.0 (**C**(CH$_3$)$_3$), 28.0 (C(**C**H$_3$)$_3$), 21.6 (Ar**C**H$_3$); **IR** (film/cm^{-1}): ν_{max} 2981, 1749, 1596, 1576, 1452, 1367, 1327, 1275, 1235, 1152, 1088, 823, 770; **MS** (ESI): *m/z* 339.2 [(M + H)$^+$]; No meaningful HRMS data was obtained for this compound.

General Procedure B: Synthesis of nitroalkynes



To a stirred solution of the corresponding haloalkyne (1.0 equiv) in DMSO (1 mL/mmol of haloalkyne) at RT was added $NaNO_2$ (2.0 equiv) behind a blast shield and the resulting mixture was stirred at RT for 2 h. The reaction mixture was diluted with ice water (4 mL/mmol) and extracted with Et_2O (3 × 4 mL/mmol). The combined organic extracts were washed with ice water (4 mL/mmol), dried over Na_2SO_4, filtered and concentrated under reduced pressure (water bath <20 °C). The resulting residue was purified by flash column chromatography on silica gel to afford the desired nitroalkyne.

Synthesis and characterisation of 4-nitrobut-1-yne (259) and 5-methyl-3-nitro-1,2-oxazole (260)



259 **260**

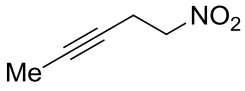
Prepared according to general procedure B. 4-Bromobut-1-yne (**258**) (3.85 g, 29.0 mmol) was reacted with $NaNO_2$ (4.00 g, 58.0 mmol) to afford compound **259** (1.10 g, 38%) as a colourless oil and compound **260** (79 mg, 2%) as a pale yellow solid, after purification by flash column chromatography on silica gel eluting with PE/Et_2O (19:1) → (9:1).

Nitroalkyne 259: TLC: R_f = 0.21 (PE/Et_2O 19:1, $KMnO_4$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 4.48 (t, *J* = 7.0 Hz, 2H, $CH_2C\mathbf{H_2}NO_2$), 2.88 (td, *J* = 7.0, 2.5 Hz, 2H, $C\mathbf{H_2}CH_2NO_2$), 2.09 (t, *J* = 2.5 Hz, 1H, **H**C≡C); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C

77.6 (**C**≡C), 73.0 (CH_2**C**H_2NO_2), 71.6 (C≡**C**), 17.3 (**C**$H_2CH_2NO_2$); **IR** (film/cm^{-1}): ν_{max} 3309, 2254, 1731, 1560, 1470, 1378, 1096; **HRMS** (FI): exact mass calculated for $C_4H_5NO_2$ [M], 99.0320; found 99.0321.

Isoxazole 260: TLC: R_f = 0.24 (PE/Et_2O 4:1, $KMnO_4$); **Melting Point:** 75 - 78 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 6.62 - 6.59 (m, 1H, Ar**H**), 2.59 - 2.56 (m, 3H, ArC**H$_3$**); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 174.8 (Ar**C**), 157.3 (**C**=N), 97.5 (Ar**C**H), 13.0 (Ar**C**H_3). The data was in accordance with that reported in the lilterature.[220]

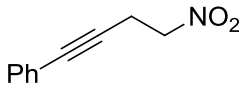
Synthesis and characterisation of 5-nitropent-2-yne (285)



285

Prepared according to general procedure B. 5-Iodopent-2-yne (**284**) (1.07 g, 5.50 mmol) was reacted with $NaNO_2$ (759 mg, 11.0 mmol) to afford compound **285** (245 mg, 39%) as a pale yellow oil, after purification by flash column chromatography on silica gel eluting with PE/Et_2O (19:1). **TLC**: R_f = 0.26 (PE/Et_2O 19:1, $KMnO_4$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 4.46 (t, *J* = 7.0 Hz, 2H, CH_2C**H$_2$**NO_2), 2.85 (tq, *J* = 7.0, 2.5 Hz, 2H, C**H$_2$**CH_2NO_2), 1.78 (t, *J* = 2.5 Hz, 3H, **H$_3$**CC≡C); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 79.1 (C≡**C**), 73.8 (CH_2**C**H_2NO_2), 72.4 (**C**≡C), 17.7 (**C**$H_2CH_2NO_2$), 3.3 (H_3**C**C≡C); **IR** (film/cm^{-1}): ν_{max} 2924, 2240, 1558, 1430, 1380, 1338, 1200, 861; **HRMS** (FI): exact mass calculated for $C_5H_7NO_2$ [M], 113.0477; found 113.0475.

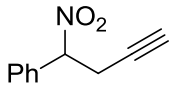
Synthesis and characterisation of (4-nitrobut-1-yn-1-yl)benzene (289)



289

Prepared according to general procedure B. (4-Iodobut-1-yn-1-yl)benzene (**288**) (700 mg, 2.70 mmol) was reacted with $NaNO_2$ (373 mg, 5.40 mmol) to afford compound **289** (238 mg, 50%) as a pale yellow oil, after purification by flash column chromatography on silica gel eluting with PE/Et_2O (19:1). **TLC**: R_f = 0.18 (PE/Et_2O 19:1, UV, $KMnO_4$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.43 - 7.37 (m, 2H, Ar**H**), 7.35 - 7.28 (m, 3H, Ar**H**), 4.60 (t, *J* = 7.0 Hz, 2H, $CH_2C\mathbf{H_2}NO_2$), 3.15 (t, *J* = 7.0 Hz, 2H, $C\mathbf{H_2}CH_2NO_2$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 131.7 (2 × Ar**C**H), 128.8 (Ar**C**H), 128.3 (2 × Ar**C**H), 127.9 (Ar**C**), 83.4 (**C**≡C), 82.7 (C≡**C**), 73.3 ($CH_2\mathbf{C}H_2NO_2$), 18.3 ($\mathbf{C}H_2CH_2NO_2$); **IR** (film/cm^{-1}): ν_{max} 3034, 2921, 1596, 1557, 1490, 1481, 1428, 1377, 1339, 824, 758, 693; **HRMS** (FI): exact mass calculated for $C_{10}H_9NO_2$ [M], 175.0633; found 175.0634.

Synthesis and characterisation of (1-nitrobut-3-yn-1-yl)benzene (298)



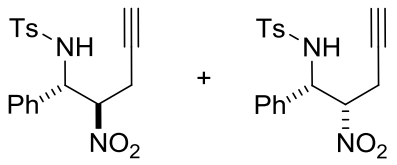
298

Prepared according to general procedure B. (1-Iodobut-3-yn-1-yl)benzene (**297**) (512 mg, 2.00 mmol) was reacted with $NaNO_2$ (276 mg, 4.00 mmol) to afford compound **298** (142 mg, 41%) as a pale yellow oil, after purification by flash column chromatography on silica gel eluting with PE/Et_2O (19:1). **TLC**: R_f = 0.26 (PE/Et_2O 19:1, UV, $KMnO_4$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.50 - 7.40 (m, 5H, Ar**H**), 5.63 (dd, *J* = 9.0, 6.0 Hz, 1H, C**H**NO_2), 3.40 (ddd, *J* = 17.0, 9.0, 3.0 Hz, 1H, C**H**H′), 2.97

(ddd, *J* = 17.0, 6.0, 3.0 Hz, 1H, CH**H′**), 2.09 (t, *J* = 3.0 Hz, 1H, C≡C**H**); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 133.1 (Ar**C**), 130.3 (ArC**H**), 129.1 (2 × ArC**H**), 127.4 (2 × ArC**H**), 89.1 (**C**$CHNO_2$), 77.6 (**C**≡CH), 71.9 (C≡**C**H), 24.0 (**C**H_2); **IR** (film/cm^{-1}): ν_{max} 3230, 3067, 1607, 1556, 1498, 1471, 1455, 1407, 1367, 1267, 1081, 950, 905, 850, 770, 719; **HRMS** (FI): exact mass calculated for $C_{10}H_9NO_2$ [M], 175.0633; found 175.0639.

5.2.2 Synthesis and Characterisation of β-Nitroamines 268 and 268′

Synthesis and characterisation of *rac*-4-methyl-*N*-[(1*S*,2*R*)-2-nitro-1-phenylpent-4-yn-1-yl]benzenesulfonamide (268) and *rac*-4-methyl-*N*-[(1*S*,2*S*)-2-nitro-1-phenylpent-4-yn-1-yl]benzenesulfonamide (268′)

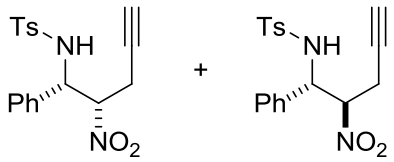


268 **268′**

To a stirred solution of nitroalkyne **259** (297 mg, 3.00 mmol) and *N*-sulfonyl imine **257a** (1.17 g, 4.50 mmol) in THF (15.0 mL) at RT was added KO*t*Bu (33 mg, 0.30 mmol, 10 mol%) and the mixture was stirred at RT for 24 h. The reaction was quenched with aq. 1 M HCl (20 mL) and then extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with H_2O (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford a brown oil (dr 59:41). Purification by flash column chromatography on silica gel eluting with PE/EtOAc (4:1) afforded a mixture of diastereomers **268** and **268′** (605 mg, 56%, dr 78:22) as a pale yellow solid. Further purification by trituration with Et_2O afforded a mixture of diastereomers **268** and **268′** (dr 88:12). Only the ^{1}H and ^{13}C NMR signals corresponding to the major diastereomer **268** are reported, all other characterisation data is for the mixture of diastereomers **268** and **268′** (dr 88:12). **TLC**: R_f = 0.33 (PE/EtOAc 4:1, UV, vanillin); **Melting Point**: 121 - 124 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.54 (d, *J* = 8.0 Hz, 2H, Ar**H**), 7.25 - 7.09 (m, 5H, Ar**H**), 6.93 (d, *J* = 7.5 Hz, 2H, Ar**H**), 5.84 (d, *J* = 9.0 Hz, 1H, N**H**), 4.89 - 4.79 (m, 2H, C**H**NH and C**H**NO_2), 2.95 - 2.90 (m, 2H, C**HH′**), 2.36 (s, 3H, ArC**H_3**), 2.18 (t, *J* = 2.5 Hz, 1H, C≡C**H**); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 143.9 (Ar**C**), 136.5 (Ar**C**), 133.9 (Ar**C**), 129.6 (2 × Ar**C**H), 129.0 (Ar**C**H), 128.9 (2 × Ar**C**H), 127.1 (2 × Ar**C**H), 126.7 (2 ×

Ar**C**H), 88.9 (C**H**NO_2), 77.2 (**C**≡CH), 72.9 (C≡**C**H), 58.7 (**C**HNH), 21.5 (Ar**C**H_3), 20.7 (**C**H_2); **IR** (film/cm^{-1}): ν_{max} 3287, 1559, 1458, 1370, 1324, 1161, 1090, 813, 703, 667; **MS** (ESI): *m/z* 381.1 [$(M + Na)^+$]; **HRMS** (ESI): exact mass calculated for $C_{18}H_{18}N_2NaO_4S$ [$(M + Na)^+$], 381.0879; found 381.0873.

Synthesis and characterisation of *rac*-4-methyl-*N*-[(1*S*,2*S*)-2-nitro-1-phenylpent-4-yn-1-yl]benzenesulfonamide (268′) and *rac*-4-methyl-*N*-[(1*S*,2*R*)-2-nitro-1-phenylpent-4-yn-1-yl]benzenesulfonamide (268)



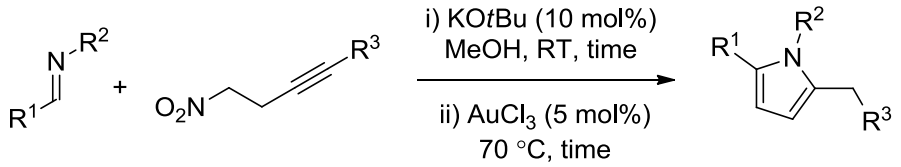
268′ **268**

To a stirred solution of nitroalkyne **259** (21 mg, 0.210 mmol) and *N*-sulfonyl imine **257a** (36 mg, 0.140 mmol) in MeOH (1.5 mL) at RT was added KO*t*Bu (1.6 mg, 0.014 mmol, 10 mol%) and the mixture was stirred at RT for 24 h. The resulting white precipitate was filtered off and dried to afford compound **268′** (18 mg, 36%, dr 95:5) as a white solid. The mother liquor was concentrated under reduced pressure to afford a pale yellow solid (dr 75:25). Purification by flash column chromatography on silica gel eluting with PE/EtOAc (4:1) afforded a mixture of diastereomers **268′** and **268** (27 mg, 54%, dr 75:25) as an off-white solid (90% combined yield). All characterisation data reported corresponds to the major diastereomer **268′** (dr 95:5). **TLC**: R_f = 0.33 (PE/EtOAc 4:1, UV, vanillin); **Melting Point**: 166 - 169 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.56 - 7.50 (m, 2H, Ar**H**), 7.25 - 7.18 (m, 3H, Ar**H**), 7.11 (d, *J* = 8.0 Hz, 2H, Ar**H**), 7.03 - 6.98 (m, 2H, Ar**H**), 5.65 (d, *J* = 10.0 Hz, 1H, N**H**), 4.93 (dd, *J* = 10.0, 6.0 Hz, 1H, C**H**NH), 4.88 - 4.82 (m, 1H, C**H**NO_2), 2.93 (ddd, *J* = 17.5, 9.0, 2.5 Hz, 1H, C**H**H′), 2.67 (ddd, *J* = 17.5, 5.5, 2.5 Hz, 1H, CH**H′**), 2.34 (s, 3H, ArC**H$_3$**), 2.15 (t, *J* = 2.5 Hz, 1H, C≡C**H**); **^{13}C NMR** (125 MHz, $CDCl_3$):

δ_C 143.7 (Ar**C**), 136.9 (Ar**C**), 134.8 (Ar**C**), 129.4 (2 × Ar**C**H), 129.1 (2 × Ar**C**H), 128.8 (Ar**C**H), 127.0 (2 × Ar**C**H), 126.3 (2 × Ar**C**H), 89.9 (**C**HNO$_2$), 76.4 (**C**≡CH), 73.1 (C≡**C**H), 58.5 (**C**HNH), 21.5 (**C**H$_2$), 21.5 (Ar**C**H$_3$); **IR** (film/cm^{-1}): ν_{max} 3281, 2923, 1561, 1457, 1371, 1325, 1162, 1090, 904, 813, 703; **MS** (ESI): *m/z* 381.1 [(M + Na)$^+$]; **HRMS** (ESI): exact mass calculated for $C_{18}H_{18}N_2NaO_4S$ [(M + Na)$^+$], 381.0879; found 381.0883. The relative configuration of diastereomer **268′** was determined to be *syn* by single crystal X-Ray diffraction data after crystallisation by slow evaporation of CH_2Cl_2. The *anti*-diastereomer **268** was assigned by analogy to the X-ray crystal structure of *syn*-**268′**.

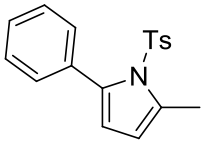
5.2.3 Synthesis and Characterisation of 2,5-Disubstituted Pyrroles

General Procedure C: Nitro-Mannich/hydroamination cascade to 2,5-disubtituted pyrroles



To a stirred solution of the corresponding imine (0.40 mmol, 1.0 equiv) and the corresponding nitroalkyne (0.60 mmol, 1.5 equiv) in freshly distilled MeOH (3.2 mL) at RT in a microwave vial equipped with a rubber septum, was added KO*t*Bu (4.5 mg, 0.04 mmol, 10 mol%). The resulting mixture was stirred at RT for the indicated time. $AuCl_3$ (6.1 mg, 0.02 mmol, 5 mol%) was added and the reaction mixture was sealed in a microwave vial, purged with nitrogen (×2), protected from light and heated to 70 °C for the indicated time. The reaction mixture was cooled to RT and concentrated under a stream of nitrogen. The resulting residue was purified by flash column chromatography on silica gel to afford the desired pyrrole.

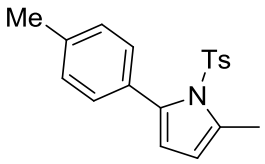
Synthesis and characterisation of 2-methyl-1-[(4-methylphenyl)sulfonyl]-5-phenyl-1*H*-pyrrole (269a)



269a

Prepared according to general procedure C. *N*-Sulfonyl imine **257a** (104 mg, 0.40 mmol) was reacted with nitroalkyne **259** (60 mg, 0.60 mmol) for 4 h (step i) and 36 h (step ii) to afford compound **269a** (95 mg, 76%) as a white solid, after purification by flash column chromatography on silica gel eluting with PE/EtOAc (19:1). **TLC**: R_f = 0.28 (PE/EtOAc 19:1, UV, vanillin); **Melting Point**: 115 - 118 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.38 - 7.29 (m, 7H, Ar**H**), 7.17 (d, *J* = 8.0 Hz, 2H, Ar**H**), 6.07 (d, *J* = 3.0 Hz, 1H, pyrrolyl **H**), 6.03 - 5.98 (m, 1H, pyrrolyl **H**), 2.54 (s, 3H, pyrrolyl C**H$_3$**), 2.38 (s, 3H, ArC**H$_3$**); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 144.3 (Ar**C**), 137.6 (Ar**C**), 136.4 (Ar**C**), 134.3 (Ar**C**), 133.2 (Ar**C**), 130.6 (2 × Ar**C**H), 129.4 (2 × Ar**C**H), 127.7 (Ar**C**H), 127.2 (2 × Ar**C**H), 126.4 (2 × Ar**C**H), 115.3 (pyrrolyl **C**H), 113.5 (pyrrolyl **C**H), 21.5 (Ar**C**H_3), 16.1 (pyrrolyl **C**H_3); **IR** (film/cm^{-1}): ν_{max} 2930, 1596, 1484, 1444, 1369, 1173, 1120, 809, 763; **MS** (ESI): *m/z* 334.1 [(M + Na)$^+$]; **HRMS** (ESI): exact mass calculated for $C_{18}H_{17}NNaO_2S$ [(M + Na)$^+$], 334.0872; found 334.0874.

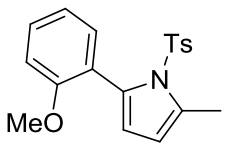
Synthesis and characterisation of 2-methyl-5-(4-methylphenyl)-1-[(4-methyl phenyl)sulfonyl]-1*H*-pyrrole (269b)



269b

Prepared according to general procedure C. *N*-Sulfonyl imine **257b** (109 mg, 0.40 mmol) was reacted with nitroalkyne **259** (60 mg, 0.60 mmol) for 4 h (step i) and 36 h (step ii) to afford compound **269b** (79 mg, 61%) as a white solid, after flash column chromatography on silica gel eluting with PE/EtOAc (19:1). **TLC**: R_f = 0.42 (PE/EtOAc 19:1, UV, vanillin); **Melting Point**: 100 - 103 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.35 - 7.30 (m, 2H, Ar**H**), 7.25 - 7.21 (m, 2H, Ar**H**), 7.20 - 7.12 (m, 4H, Ar**H**), 6.03 (d, *J* = 3.0 Hz, 1H, pyrrolyl **H**), 6.01 - 5.97 (m, 1H, pyrrolyl **H**), 2.53 - 2.50 (m, 3H, pyrrolyl C**H$_3$**), 2.40 (s, 3H, ArC**H$_3$**), 2.38 (s, 3H, ArC**H$_3$**); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 144.2 (Ar**C**), 137.8 (Ar**C**), 137.6 (Ar**C**), 136.5 Ar**C**), 134.1 (Ar**C**), 130.4 (2 × Ar**C**H), 130.4 (Ar**C**), 129.4 (2 × Ar**C**H), 128.0 (2 × Ar**C**H), 126.4 (2 × Ar**C**H), 115.0 (pyrrolyl **C**H), 113.5 (pyrrolyl **C**H), 21.6 (Ar**C**H$_3$), 21.3 (Ar**C**H$_3$), 16.1 (pyrrolyl **C**H$_3$); **IR** (film/cm^{-1}): ν_{max} 2926, 1596, 1494, 1369, 1248, 1174, 1118, 816, 705; **MS** (ESI): *m/z* 326.1 [(M + H)$^+$]; **HRMS** (ESI): exact mass calculated for $C_{19}H_{20}NO_2S$ [(M + H)$^+$], 326.1209; found 326.1201.

Synthesis and characterisation of 2-(2-methoxyphenyl)-5-methyl-1-[(4-methyl phenyl)sulfonyl]-1*H*-pyrrole (269c)

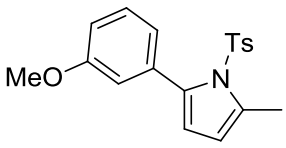


269c

Prepared according to general procedure C. *N*-Sulfonyl imine **257c** (116 mg, 0.40 mmol) was reacted with nitroalkyne **259** (60 mg, 0.60 mmol) for 4 h (step i) and

36 h (step ii) to afford compound **269c** (93 mg, 68%) as a white solid, after purification by flash column chromatography on silica gel eluting with PE/EtOAc (19:1). **TLC**: R_f = 0.18 (PE/EtOAc 19:1, UV, vanillin); **Melting Point**: 125 - 127 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.42 (d, *J* = 8.5 Hz, 2H, Ar**H**), 7.40 - 7.34 (m, 1H, Ar**H**), 7.21 (d, *J* = 8.5 Hz, 2H, Ar**H**), 7.14 (dd, *J* = 7.5, 2.0 Hz, 1H, Ar**H**), 6.97 - 6.92 (m, 1H, Ar**H**), 6.89 (d, *J* = 8.5 Hz, 1H, Ar**H**), 6.09 - 6.06 (m, 1H, pyrrolyl **H**), 6.06 - 6.03 (m, 1H, pyrrolyl **H**), 3.75 (s, 3H, ArOC**H$_3$**), 2.45 (s, 3H, pyrrolyl C**H$_3$**), 2.40 (s, 3H, ArC**H$_3$**); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 158.6 (Ar**C**), 144.0 (Ar**C**), 137.2 (Ar**C**), 133.2 (Ar**C**), 133.1 (Ar**C**), 131.9 (Ar**C**H), 129.8 (Ar**C**H), 129.4 (2 × Ar**C**H), 126.5 (2 × Ar**C**H), 122.9 (Ar**C**), 119.5 (Ar**C**H), 114.1 (pyrrolyl **C**H), 112.8 (pyrrolyl **C**H), 110.2 (Ar**C**H), 55.3 (ArO**C**H_3), 21.5 (Ar**C**H_3), 15.7 (pyrrolyl **C**H_3); **IR** (film/cm^{-1}): ν_{max} 2931, 1597, 1483, 1368, 1254, 1175, 1116, 1027, 792, 755; **MS** (ESI): *m/z* 364.1 [(M + Na)$^+$]; **HRMS** (ESI): exact mass calculated for $C_{19}H_{20}NO_3S$ [(M + H)$^+$], 342.1158; found 342.1158.

Synthesis and characterisation of 2-(3-methoxyphenyl)-5-methyl-1-[(4-methyl phenyl)sulfonyl]-1*H*-pyrrole (269d)

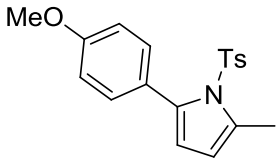


269d

Prepared according to general procedure C. *N*-Sulfonyl imine **257d** (116 mg, 0.40 mmol) was reacted with nitroalkyne **259** (60 mg, 0.60 mmol) for 4 h (step i) and 36 h (step ii) to afford compound **269d** (118 mg, 86%) as a white solid, after purification by flash column chromatography on silica gel eluting with PE/EtOAc (19:1). **TLC**: R_f = 0.23 (PE/EtOAc 19:1, UV, vanillin); **Melting Point**: 112 - 114 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.34 (d, *J* = 8.5 Hz, 2H, Ar**H**), 7.24 (t, *J* = 8.0 Hz,

1H, Ar**H**), 7.17 (d, *J* = 8.5 Hz, 2H, Ar**H**), 6.95 - 6.84 (m, 3H, Ar**H**), 6.09 - 6.04 (m, 1H, pyrrolyl **H**), 6.02 - 5.96 (m, 1H, pyrrolyl **H**), 3.81 (s, 3H, ArOC**H$_3$**), 2.53 (s, 3H, pyrrolyl C**H$_3$**), 2.38 (s, 3H, ArC**H$_3$**); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 158.4 (Ar**C**), 144.3 (Ar**C**), 137.4 (Ar**C**), 136.3 (Ar**C**), 134.4 (Ar**C**), 134.4 (Ar**C**), 129.4 (2 × Ar**C**H), 128.1 (Ar**C**H), 126.5 (2 × Ar**C**H), 123.1 (Ar**C**H), 116.0 (Ar**C**H), 115.2 (pyrrolyl **C**H), 113.6 (Ar**C**H), 113.4 (pyrrolyl **C**H), 55.2 (ArO**C**H$_3$), 21.5 (Ar**C**H$_3$), 16.1 (pyrrolyl **C**H$_3$); **IR** (film/cm^{-1}): ν_{max} 2932, 1594, 1482, 1369, 1219, 1174, 1118, 1044, 785; **MS** (ESI): *m/z* 364.1 [(M + Na)$^+$]; **HRMS** (ESI): exact mass calculated for $C_{19}H_{19}NNaO_3S$ [(M + Na)$^+$], 364.0978; found 364.0985.

Synthesis and characterisation of 2-(4-methoxyphenyl)-5-methyl-1-[(4-methyl phenyl)sulfonyl]-1*H*-pyrrole (269e)

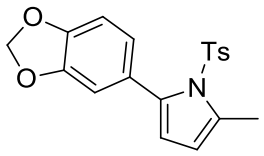


269e

Prepared according to general procedure C. *N*-Sulfonyl imine **257e** (116 mg, 0.40 mmol) was reacted with nitroalkyne **259** (60 mg, 0.60 mmol) for 4 h (step i) and 36 h (step ii) to afford compound **269e** (75 mg, 55%) as a white solid, after purification by flash column chromatography on silica gel eluting with PE/EtOAc (19:1). **TLC**: R_f = 0.23 (PE/EtOAc 19:1, UV, vanillin); **Melting Point**: 114 - 117 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.30 (d, *J* = 8.5 Hz, 2H, Ar**H**), 7.24 - 7.20 (m, 2H, Ar**H**), 7.17 (d, *J* = 8.5 Hz, 2H, Ar**H**), 6.88 - 6.84 (m, 2H, Ar**H**), 6.01 - 5.97 (m, 2H, pyrrolyl **H**), 3.85 (s, 3H, ArOC**H$_3$**), 2.52 (s, 3H, pyrrolyl C**H$_3$**), 2.38 (s, 3H, ArC**H$_3$**); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 159.3 (Ar**C**), 144.2 (Ar**C**), 137.3 (Ar**C**), 136.6 (Ar**C**), 133.9 (Ar**C**), 131.9 (2 × Ar**C**H), 129.4 (2 × Ar**C**H), 126.5 (2 × Ar**C**H), 125.6 (Ar**C**), 114.7 (pyrrolyl **C**H), 113.3 (pyrrolyl **C**H), 112.6 (2 × Ar**C**H), 55.2

(ArO**C**H_3), 21.6 (Ar**C**H_3), 16.2 (pyrrolyl **C**H_3); **IR** (film/cm^{-1}): ν_{max} 2930, 1613, 1368, 1287, 1205, 1175, 1119, 1032, 832; **MS** (ESI): *m/z* 364.1 [$(M + Na)^+$]; **HRMS** (ESI): exact mass calculated for $C_{19}H_{20}NO_3S$ [$(M + H)^+$], 342.1158; found 342.1158.

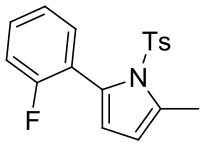
Synthesis and characterisation of 2-(1,3-benzodioxol-5-yl)-5-methyl-1-[(4-methylphenyl)sulfonyl]-1*H*-pyrrole (269f)



269f

Prepared according to general procedure C. *N*-Sulfonyl imine **257f** (121 mg, 0.40 mmol) was reacted with nitroalkyne **259** (60 mg, 0.60 mmol) for 4 h (step i) and 24 h (step ii) to afford compound **269f** (91 mg, 64%) as a white solid, after purification by flash column chromatography on silica gel eluting with PE/EtOAc (19:1). **TLC**: R_f = 0.18 (PE/EtOAc 19:1, UV, vanillin); **Melting Point**: 134 - 136 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.38 - 7.32 (m, 2H, Ar**H**), 7.21 - 7.16 (m, 2H, Ar**H**), 6.82 (d, *J* = 1.5 Hz, 1H, Ar**H**), 6.76 (d, *J* = 8.0 Hz, 1H, Ar**H**), 6.74 (dd, *J* = 8.0, 1.5 Hz, 1H, Ar**H**), 6.02 - 5.99 (m, 3H, pyrrolyl **H** and OC**H$_2$**O), 5.98 - 5.95 (m, 1H, pyrrolyl **H**), 2.52 - 2.49 (m, 3H, pyrrolyl C**H$_3$**), 2.38 (s, 3H, ArC**H$_3$**); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 147.4 (Ar**C**), 146.6 (Ar**C**), 144.3 (Ar**C**), 137.1 (Ar**C**), 136.5 (Ar**C**), 134.1 (Ar**C**), 129.4 (2 × Ar**C**H), 127.0 (Ar**C**), 126.5 (2 × Ar**C**H), 124.2 (Ar**C**H), 115.0 (pyrrolyl **C**H), 113.3 (pyrrolyl **C**H), 111.5 (Ar**C**H), 107.2 (Ar**C**H), 101.2 (O**C**H_2O), 21.6 (Ar**C**H_3), 16.1 (pyrrolyl **C**H_3); **IR** (film/cm^{-1}): ν_{max} 2891, 1596, 1478, 1368, 1223, 1175, 1106, 1038, 935, 816, 706; **MS** (ESI): *m/z* 378.1 [$(M + Na)^+$]; **HRMS** (ESI): exact mass calculated for $C_{19}H_{17}NNaO_4S$ [$(M + Na)^+$], 378.0770; found 378.0771.

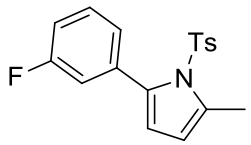
Synthesis and characterisation of 2-(2-fluorophenyl)-5-methyl-1-[(4-methyl phenyl)sulfonyl]-1*H*-pyrrole (269g)



269g

Prepared according to general procedure C. *N*-Sulfonyl imine **257g** (111 mg, 0.40 mmol) was reacted with nitroalkyne **259** (60 mg, 0.60 mmol) for 6 h (step i) and 36 h (step ii) to afford compound **269g** (100 mg, 76%) as a white solid, after purification by flash column chromatography on silica gel eluting with PE/EtOAc (19:1). **TLC**: R_f = 0.24 (PE/EtOAc 19:1, UV, vanillin); **Melting Point**: 105 - 108 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.41 - 7.36 (m, 2H, Ar**H**), 7.35 - 7.30 (m, 1H, Ar**H**), 7.24 (td, *J* = 7.5, 2.0 Hz, 1H, Ar**H**), 7.19 (d, *J* = 8.0 Hz, 2H, Ar**H**), 7.11 (td, *J* = 7.5, 1.0 Hz, 1H, Ar**H**), 7.08 - 7.02 (m, 1H, Ar**H**), 6.12 (d, *J* = 3.0 Hz, 1H, pyrrolyl **H**), 6.03 (m, 1H, pyrrolyl **H**), 2.45 - 2.42 (m, 3H, pyrrolyl C**H$_3$**), 2.36 (s, 3H, ArC**H$_3$**); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 160.8 (d, *J* = 247.5 Hz, Ar**C**F), 144.5 (Ar**C**), 136.5 (Ar**C**), 134.1 (Ar**C**), 132.5 (d, *J* = 2.5 Hz, Ar**C**H), 130.1 (Ar**C**), 130.0 (d, *J* = 8.0 Hz, Ar**C**H), 129.6 (2 × Ar**C**H), 126.4 (Ar**C**H), 123.0 (d, *J* = 3.0 Hz, Ar**C**H), 121.6 (d, *J* = 16.0 Hz, Ar**C**), 115.8 (pyrrolyl **C**H), 115.0 (d, *J* = 21.5 Hz, Ar**C**H), 113.2 (pyrrolyl **C**H), 21.5 (Ar**C**H_3), 15.6 (pyrrolyl **C**H_3); **IR** (film/cm^{-1}): ν_{max} 2930, 1597, 1535, 1480, 1450, 1370, 1250, 1218, 1175, 1125, 814, 760, 706; **MS** (ESI): *m/z* 352.1 [(M + Na)$^+$]; **HRMS** (ESI): exact mass calculated for $C_{18}H_{16}FNNaO_2S$ [(M + Na)$^+$], 352.0778; found 352.0787.

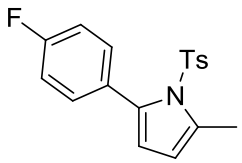
Synthesis and characterisation of 2-(3-fluorophenyl)-5-methyl-1-[(4-methyl phenyl)sulfonyl]-1*H*-pyrrole (269h)



269h

Prepared according to general procedure C. *N*-Sulfonyl imine **257h** (111 mg, 0.40 mmol) was reacted with nitroalkyne **259** (60 mg, 0.60 mmol) for 6 h (step i) and 36 h (step ii) to afford compound **269h** (80 mg, 61%) as a pale pink solid, after purification by flash column chromatography on silica gel eluting with PE/EtOAc (19:1). **TLC**: R_f = 0.38 (PE/EtOAc 19:1, UV, vanillin); **Melting Point**: 135 - 138 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.37 - 7.32 (m, 2H, Ar**H**), 7.31 - 7.28 (m, 1H, Ar**H**), 7.20 (d, *J* = 8.0 Hz, 2H, Ar**H**), 7.15 (dt, *J* = 7.5, 1.0 Hz, 1H, Ar**H**), 7.08 - 7.00 (m, 2H, Ar**H**), 6.09 (d, *J* = 3.0 Hz, 1H, pyrrolyl **H**), 6.03 - 5.99 (m, 1H, pyrrolyl **H**), 2.54 - 2.50 (m, 3H, pyrrolyl C**H$_3$**), 2.39 (s, 3H, ArC**H$_3$**); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 161.8 (d, *J* = 245.5 Hz, Ar**C**F), 144.6 (Ar**C**), 136.2 (Ar**C**), 135.2 (d, *J* = 9.0 Hz, Ar**C**), 134.9 (Ar**C**), 129.5 (2 × Ar**C**H), 128.6 (d, *J* = 9.0 Hz, Ar**C**H), 126.4 (2 × Ar**C**H), 126.4 (d, *J* = 3.0 Hz, Ar**C**H), 117.3 (d, *J* = 22.5 Hz, Ar**C**H), 115.8 (pyrrolyl **C**H), 114.6 (d, *J* = 21.0 Hz, Ar**C**H), 113.6 (pyrrolyl **C**H), 21.6 (Ar**C**H_3), 16.0 (pyrrolyl **C**H_3); **IR** (film/cm^{-1}): ν_{max} 1589, 1474, 1436, 1370, 1173, 1117, 785, 680; **MS** (ESI): *m/z* 352.1 [(M + Na)$^+$]; **HRMS** (ESI): exact mass calculated for $C_{18}H_{16}FNNaO_2S$ [(M + Na)$^+$], 352.0778; found 352.0787.

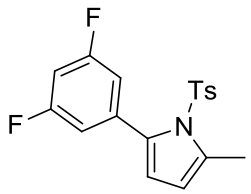
Synthesis and characterisation of 2-(4-fluorophenyl)-5-methyl-1-[(4-methyl phenyl)sulfonyl]-1*H*-pyrrole (269i)



269i

Prepared according to general procedure C. *N*-Sulfonyl imine **257i** (111 mg, 0.40 mmol) was reacted with nitroalkyne **259** (60 mg, 0.60 mmol) for 4 h (step i) and 36 h (step ii) to afford compound **269i** (97 mg, 74%) as a white solid, after purification by flash column chromatography on silica gel eluting with PE/EtOAc (19:1). **TLC**: R_f = 0.23 (PE/EtOAc 19:1, UV, vanillin); **Melting Point**: 126 - 129 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.32 - 7.24 (m, 4H, Ar**H**), 7.20 - 7.16 (m, 2H, Ar**H**), 7.04 - 6.97 (m, 2H, Ar**H**), 6.03 (d, *J* = 3.0 Hz, 1H, pyrrolyl **H**), 6.01 - 5.98 (m, 1H, pyrrolyl **H**), 2.52 (d, *J* = 1.0 Hz, 3H, pyrrolyl C**H$_3$**), 2.38 (s, 3H, ArC**H$_3$**); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 162.5 (d, *J* = 247.5 Hz, Ar**C**F), 144.4 (Ar**C**), 136.4 (Ar**C**), 136.3 (Ar**C**), 134.4 (Ar**C**), 132.3 (d, *J* = 8.0 Hz, 2 × Ar**C**H), 129.5 (2 × Ar**C**H), 129.2 (d, *J* = 3.0 Hz, Ar**C**), 126.4 (2 × Ar**C**H), 115.3 (pyrrolyl **C**H), 114.2 (d, *J* = 21.5 Hz, 2 × Ar**C**H), 113.4 (pyrrolyl **C**H), 21.5 (Ar**C**H_3), 16.0 (pyrrolyl **C**H_3); **IR** (film/cm^{-1}): ν_{max} 2929, 1535, 1493, 1369, 1222, 1174, 1119, 837, 812, 705; **MS** (ESI): *m/z* 330.1 [$(M + H)^+$]; **HRMS** (ESI): exact mass calculated for $C_{18}H_{17}FNO_2S$ [$(M + H)^+$], 330.0959; found 330.0954.

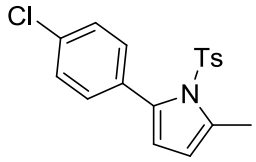
Synthesis and characterisation of 2-(3,5-difluorophenyl)-5-methyl-1-[(4-methyl phenyl)sulfonyl]-1*H*-pyrrole (269j)



269j

Prepared according to general procedure C. *N*-Sulfonyl imine **257j** (119 mg, 0.40 mmol) was reacted with nitroalkyne **259** (60 mg, 0.60 mmol) for 8 h (step i) and 36 h (step ii) to afford compound **269j** (91 mg, 66%) as a white solid, after purification by flash column chromatography on silica gel eluting with PE/EtOAc (19:1). **TLC**: R_f = 0.38 (PE/EtOAc 19:1, UV, vanillin); **Melting Point**: 167 - 169 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.35 (d, *J* = 8.5 Hz, 2H, Ar**H**), 7.22 (d, *J* = 8.5 Hz, 2H, Ar**H**), 6.90 - 6.83 (m, 2H, Ar**H**), 6.79 (tt, *J* = 9.0, 2.5 Hz, 1H, Ar**H**), 6.11 (d, *J* = 3.5 Hz, 1H, pyrrolyl **H**), 6.03 - 5.97 (m, 1H, pyrrolyl **H**), 2.51 (s, 3H, pyrrolyl C**H$_3$**), 2.40 (s, 3H, ArC**H$_3$**); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 161.9 (dd, *J* = 247.5, 13.5 Hz, 2 × Ar**C**F), 144.8 (Ar**C**), 136.2 (Ar**C**), 136.1 (Ar**C**), 135.5 (Ar**C**), 135.2 (t, *J* = 2.5 Hz, Ar**C**), 129.6 (2 × Ar**C**H), 126.4 (2 × Ar**C**H), 116.4 (pyrrolyl **C**H), 113.7 (pyrrolyl **C**H), 113.4 (dd, *J* = 18.5, 7.0 Hz, 2 × Ar**C**H), 103.1 (t, *J* = 25.0 Hz, Ar**C**H), 21.6 (Ar**C**H_3), 15.9 (pyrrolyl **C**H_3); **IR** (film/cm^{-1}): ν_{max} 1623, 1594, 1432, 1369, 1186, 1169, 1119, 984, 872, 848, 810, 714; **MS** (ESI): *m/z* 348.1 [$(M + H)^+$]; **HRMS** (ESI): exact mass calculated for $C_{18}H_{16}F_2NO_2S$ [$(M + H)^+$], 348.0864; found 348.0858.

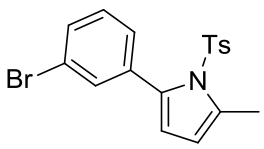
Synthesis and characterisation of 2-(4-chlorophenyl)-5-methyl-1-[(4-methyl phenyl)sulfonyl]-1*H*-pyrrole (269k)



269k

Prepared according to general procedure C. *N*-Sulfonyl imine **257k** (118 mg, 0.40 mmol) was reacted with nitroalkyne **259** (60 mg, 0.60 mmol) for 4 h (step i) and 36 h (step ii) to afford compound **269k** (58 mg, 42%) as a white solid, after purification by flash column chromatography on silica gel eluting with PE/EtOAc (19:1). **TLC**: R_f = 0.31 (PE/EtOAc 19:1, UV, vanillin); **Melting Point**: 122 - 125 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.36 - 7.31 (m, 4H, Ar**H**), 7.28 (d, *J* = 8.5 Hz, 2H, Ar**H**), 7.21 (d, *J* = 8.0 Hz, 2H, Ar**H**), 6.08 (d, *J* = 3.5 Hz, 1H, pyrrolyl **H**), 6.05 - 6.01 (m, 1H, pyrrolyl **H**), 2.55 (s, 3H, pyrrolyl C**H$_3$**), 2.41 (s, 3H, ArC**H$_3$**); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 144.5 (Ar**C**), 136.3 (Ar**C**), 136.3 (Ar**C**), 134.8 (Ar**C**), 133.8 (Ar**C**), 131.7 (Ar**C**), 131.7 (2 × Ar**C**H), 129.5 (2 × Ar**C**H), 127.5 (2 × Ar**C**H), 126.4 (2 × Ar**C**H), 115.7 (pyrrolyl **C**H), 113.6 (pyrrolyl **C**H), 21.6 (Ar**C**H_3), 16.0 (pyrrolyl **C**H_3); **IR** (film/cm^{-1}): ν_{max} 2929, 1597, 1494, 1369, 1174, 1119, 1093, 1015, 830, 811, 662; **MS** (ESI): *m/z* 346.1 [$(M + H)^+$]; **HRMS** (ESI): exact mass calculated for $C_{18}H_{17}ClNO_2S$ [$(M + H)^+$], 346.0663 and 348.0634; found 346.0661 and 348.0634.

Synthesis and characterisation of 2-(3-bromophenyl)-5-methyl-1-[(4-methyl phenyl)sulfonyl]-1*H*-pyrrole (269l)

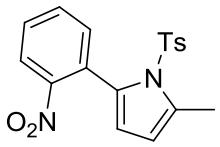


269l

Prepared according to general procedure C. *N*-Sulfonyl imine **257l** (135 mg, 0.40 mmol) was reacted with nitroalkyne **259** (60 mg, 0.60 mmol) for 4 h (step i) and

36 h (step ii) to afford compound **269l** (66 mg, 42%) as a white solid, after purification by flash column chromatography on silica gel eluting with PE/EtOAc (19:1). **TLC**: R_f = 0.31 (PE/EtOAc 19:1, UV, vanillin); **Melting Point**: 117 - 119 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.46 (d, *J* = 8.0 Hz, 1H, Ar**H**), 7.36 - 7.28 (m, 4H, Ar**H**), 7.24 - 7.17 (m, 3H, Ar**H**), 6.07 (d, *J* = 3.5 Hz, 1H, pyrrolyl **H**), 6.03 - 5.98 (m, 1H, pyrrolyl **H**), 2.53 (s, 3H, pyrrolyl C**H$_3$**), 2.40 (s, 3H, ArC**H$_3$**); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 144.6 (Ar**C**), 136.2 (Ar**C**), 135.7 (Ar**C**), 135.1 (Ar**C**), 134.9 (Ar**C**), 133.0 (Ar**C**H), 130.6 (Ar**C**H), 129.5 (2 × Ar**C**H), 129.5 (Ar**C**H), 128.6 (Ar**C**H), 126.4 (2 × Ar**C**H), 121.1 (Ar**C**), 115.7 (pyrrolyl **C**H), 113.4 (pyrrolyl **C**H), 21.6 (Ar**C**H$_3$), 16.0 (pyrrolyl **C**H$_3$); **IR** (film/cm^{-1}): ν_{max} 2929, 1597, 1494, 1370, 1188, 1174, 1121, 784, 670; **MS** (ESI): *m/z* 390.06 [(M + H)$^+$]; **HRMS** (ESI): exact mass calculated for $C_{18}H_{17}BrNO_2S$ [(M + H)$^+$], 390.0158 and 392.0138; found 390.0157 and 392.0133.

Synthesis and characterisation 2-methyl-1-[(4-methylphenyl)sulfonyl]-5-(2-nitrophenyl)-1*H*-pyrrole (269m)

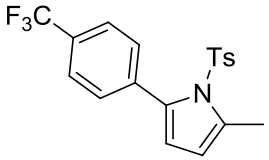


269m

Prepared according to general procedure C. *N*-Sulfonyl imine **257m** (122 mg, 0.40 mmol) was reacted with nitroalkyne **259** (60 mg, 0.60 mmol) for 6 h (step i) and 36 h (step ii) to afford compound **269m** (90 mg, 63%) as a yellow solid, after purification by flash column chromatography on silica gel eluting with PE/EtOAc (19:1). **TLC**: R_f = 0.12 (PE/EtOAc 19:1, UV, vanillin); **Melting Point**: 129 - 132 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 8.11 - 8.05 (m, 1H, Ar**H**), 7.61 - 7.48 (m, 2H, Ar**H**), 7.39 (d, *J* = 8.5 Hz, 2H, Ar**H**), 7.35 - 7.29 (m, 1H, Ar**H**), 7.22 (d, *J* = 8.5 Hz,

2H, Ar**H**), 6.11 (d, *J* = 3.0 Hz, 1H, pyrrolyl **H**), 6.08 - 6.04 (m, 1H, pyrrolyl **H**), 2.45 (s, 3H, pyrrolyl C**H$_3$**), 2.39 (s, 3H, ArC**H$_3$**); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 149.2 (Ar**C**), 144.7 (Ar**C**), 136.4 (Ar**C**), 134.1 (Ar**C**), 133.5 (Ar**C**H), 132.0 (Ar**C**H), 131.3 (Ar**C**), 129.7 (2 × Ar**C**H), 129.1 (Ar**C**H), 128.4 (Ar**C**), 126.6 (2 × Ar**C**H), 124.1 (Ar**C**H), 114.8 (pyrrolyl **C**H), 113.1 (pyrrolyl **C**H), 21.5 (Ar**C**H$_3$), 15.4 (pyrrolyl **C**H$_3$); **IR** (film/cm^{-1}): ν_{max} 2929, 1596, 1527, 1348, 1174, 1126, 854, 789, 753; **MS** (ESI): *m/z* 379.1 [(M + Na)$^+$]; **HRMS** (ESI): exact mass calculated for $C_{18}H_{16}N_2NaO_4S$ [(M + Na)$^+$], 379.0723; found 379.0726.

Synthesis and characterisation of 2-methyl-1-[(4-methylphenyl) sulfonyl]-5-[4-(trifluoromethyl)phenyl]-1*H*-pyrrole (269n)

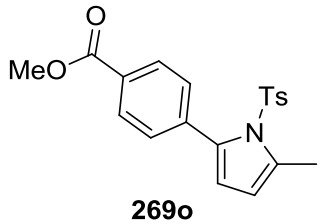


269n

Prepared according to general procedure C. *N*-Sulfonyl imine **257n** (131 mg, 0.40 mmol) was reacted with nitroalkyne **259** (60 mg, 0.60 mmol) for 4 h (step i) and 24 h (step ii) to afford compound **269n** (108 mg, 71%) as a white solid, after purification by flash column chromatography on silica gel eluting with PE/EtOAc (19:1). **TLC**: R_f = 0.30 (PE/EtOAc 19:1, UV, vanillin); **Melting Point**: 111 - 113 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.59 (d, *J* = 8.0 Hz, 2H, Ar**H**), 7.46 (d, *J* = 8.0 Hz, 2H, Ar**H**), 7.33 - 7.28 (m, 2H, Ar**H**), 7.19 (d, *J* = 8.0 Hz, 2H, Ar**H**), 6.12 (d, *J* = 3.5 Hz, 1H, pyrrolyl **H**), 6.05 - 6.01 (m, 1H, pyrrolyl **H**), 2.52 (d, *J* = 1.0 Hz, 3H, pyrrolyl C**H$_3$**), 2.39 (s, 3H, ArC**H$_3$**); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 144.7 (Ar**C**), 136.9 (Ar**C**), 136.2 (Ar**C**), 136.1 (Ar**C**), 135.4 (Ar**C**), 130.5 (2 × Ar**C**H), 129.6 (2 × Ar**C**H), 129.6 (q, *J* = 32.5 Hz, Ar**C**), 126.3 (2 × Ar**C**H), 124.2 (q, *J* = 272.0 Hz, Ar**C**F$_3$), 124.2 (q, *J* = 4.0 Hz, 2 × Ar**C**H), 116.6 (pyrrolyl **C**H), 113.9 (pyrrolyl **C**H),

21.6 (Ar**C**H_3), 16.0 (pyrrolyl **C**H_3); **IR** (film/cm^{-1}): ν_{max} 2932, 1618, 1371, 1326, 1174, 1123, 1072, 843, 811; **MS** (ESI): *m/z* 402.1 [$(M + Na)^+$]; **HRMS** (ESI): exact mass calculated for $C_{19}H_{16}F_3NNaO_2S$ [$(M + Na)^+$], 402.0746; found 402.0747.

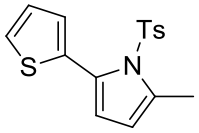
Synthesis and characterisation of methyl 4-{5-methyl-1-[(4-methylphenyl) sulfonyl]-1*H*-pyrrol-2-yl}benzoate (269o)



269o

Prepared according to general procedure C, adding THF (3.0 mL) as a co-solvent at the start of step ii. *N*-Sulfonyl imine **257o** (127 mg, 0.40 mmol) was reacted with nitroalkyne **259** (60 mg, 0.60 mmol) for 8 h (step i) and 48 h (step ii) to afford compound **269o** (89 mg, 60%) as an off-white solid, after flash column chromatography on silica gel eluting with PE/EtOAc (19:1). **TLC**: R_f = 0.16 (PE/EtOAc 19:1, UV, vanillin); **Melting Point**: 115 - 117 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 8.03 - 7.98 (m, 2H, Ar**H**), 7.45 - 7.40 (m, 2H, Ar**H**), 7.33 - 7.28 (m, 2H, Ar**H**), 7.21 - 7.15 (m, 2H, Ar**H**), 6.12 (d, *J* = 3.5 Hz, 1H, pyrrolyl **H**), 6.04 - 6.00 (m, 1H, pyrrolyl **H**), 3.94 (s, 3H, $CO_2C\mathbf{H_3}$), 2.51 (d, *J* = 1.0 Hz, 3H, pyrrolyl C$\mathbf{H_3}$), 2.38 (s, 3H, ArC$\mathbf{H_3}$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 166.9 (**C**=O), 144.6 (Ar**C**), 137.8 (Ar**C**), 136.7 (Ar**C**), 136.0 (Ar**C**), 135.5 (Ar**C**), 130.2 (2 × Ar**C**H), 129.5 (2 × Ar**C**H), 129.1 (Ar**C**), 128.5 (2 × Ar**C**H), 126.3 (2 × Ar**C**H), 116.5 (pyrrolyl **C**H), 114.0 (pyrrolyl **C**H), 52.1 ($CO_2\mathbf{C}H_3$), 21.5 (Ar**C**H_3), 16.0 (pyrrolyl **C**H_3); **IR** (film/cm^{-1}): ν_{max} 2952, 1721, 1609, 1436, 1370, 1227, 1175, 1114, 812, 773, 703; **MS** (ESI): *m/z* 392.1 [$(M + Na)^+$]; **HRMS** (ESI): exact mass calculated for $C_{20}H_{19}NNaO_4S$ [$(M + Na)^+$], 392.0927; found 392.0938.

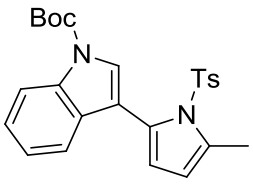
Synthesis and characterisation of 2-methyl-1-[(4-methylphenyl)sulfonyl]-5-(2-thienyl)-1*H*-pyrrole (269p)



269p

Prepared according to general procedure C. *N*-Sulfonyl imine **257p** (106 mg, 0.40 mmol) was reacted with nitroalkyne **259** (60 mg, 0.60 mmol) for 5 h (step i) and 36 h (step ii) to afford compound **269p** (90 mg, 71%) as a white solid, after purification by flash column chromatography on silica gel eluting with PE/EtOAc (19:1). **TLC**: R_f = 0.28 (PE/EtOAc 19:1, UV, vanillin); **Melting Point**: 71 - 74 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.37 (d, *J* = 8.5 Hz, 2H, Ar**H**), 7.32 - 7.28 (m, 1H, thienyl **H**), 7.18 (d, *J* = 8.5 Hz, 2H, Ar**H**), 7.10 - 7.06 (m, 1H, thienyl **H**), 7.04 - 6.99 (m, 1H, thienyl **H**), 6.18 (d, *J* = 3.5 Hz, 1H, pyrrolyl **H**), 6.03 - 5.99 (m, 1H, pyrrolyl **H**), 2.56 (s, 3H, pyrrolyl C**H$_3$**), 2.38 (s, 3H, ArC**H$_3$**); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 144.4 (Ar**C**), 136.5 (Ar**C**), 135.1 (Ar**C**), 133.1 (Ar**C**), 130.0 (thienyl **C**H), 129.5 (2 × Ar**C**H), 128.3 (Ar**C**), 126.6 (2 × Ar**C**H), 126.4 (thienyl **C**H), 126.4 (thienyl **C**H), 116.7 (pyrrolyl **C**H), 112.8 (pyrrolyl **C**H), 21.5 (Ar**C**H_3), 16.2 (pyrrolyl **C**H_3); **IR** (film/cm^{-1}): ν_{max} 2927, 1596, 1370, 1218, 1174, 1117, 843, 811, 704; **MS** (ESI): *m/z* 340.1 [$(M + Na)^+$]; **HRMS** (ESI): exact mass calculated for $C_{16}H_{16}NO_2S_2$ [$(M + H)^+$], 318.0617; found 318.0620.

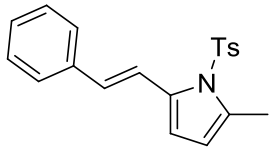
Synthesis and characterisation of *tert*-butyl 3-{5-methyl-1-[(4-methylphenyl) sulfonyl]-1*H*-pyrrol-2-yl}-1*H*-indole-1-carboxylate (269q)



269q

Prepared according to general procedure C. *N*-Sulfonyl imine **257q** (159 mg, 0.40 mmol) was reacted with nitroalkyne **259** (60 mg, 0.60 mmol) for 8 h (step i) and 36 h (step ii) to afford compound **269q** (43 mg, 24%) as a pale yellow oil, after purification by flash column chromatography on silica gel eluting with PE/EtOAc (19:1). **TLC**: R_f = 0.35 (PE/EtOAc 19:1, UV, vanillin); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 8.12 (d, *J* = 8.0 Hz, 1H, Ar**H**), 7.54 (s, 1H, indolyl **H**), 7.33 - 7.23 (m, 4H, Ar**H**), 7.17 - 7.11 (m, 1H, Ar**H**), 7.04 (d, *J* = 8.0 Hz, 2H, Ar**H**), 6.17 (d, *J* = 3.5 Hz, 1H, pyrrolyl **H**), 6.07 - 6.03 (m, 1H, pyrrolyl **H**), 2.56 (d, *J* = 1.0 Hz, 3H, pyrrolyl C**H$_3$**), 2.29 (s, 3H, ArC**H$_3$**), 1.69 (s, 9H, C(C**H$_3$**)$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 149.7 (**C**=O), 144.3 (Ar**C**), 136.4 (Ar**C**), 134.5 (Ar**C**), 134.5 (Ar**C**), 131.2 (Ar**C**), 129.4 (2 × Ar**C**H), 127.6 (Ar**C**), 126.5 (2 × Ar**C**H), 126.3 (Ar**C**H), 124.3 (Ar**C**H), 122.6 (Ar**C**H), 122.1 (Ar**C**), 120.2 (Ar**C**H), 115.9 (pyrrolyl **C**H), 114.9 (Ar**C**H), 113.2 (pyrrolyl **C**H), 83.8 (**C**(CH$_3$)$_3$), 28.2 (C(**C**H$_3$)$_3$), 21.5 (Ar**C**H$_3$), 16.1 (pyrrolyl **C**H$_3$); **IR** (film/cm^{-1}): ν_{max} 2979, 1735, 1597, 1452, 1371, 1308, 1282, 1237, 1174, 1108, 1060, 748, 704; **MS** (ESI): *m/z* 473.2 [(M + Na)$^+$]; **HRMS** (ESI): exact mass calculated for $C_{25}H_{26}N_2NaO_4S$ [(M + Na)$^+$], 473.1505; found 473.1512.

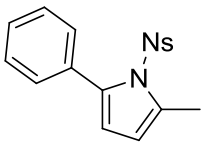
Synthesis and characterisation of 2-methyl-1-[(4-methylphenyl)sulfonyl]-5-[(*E*)-2-phenylethenyl]-1*H*-pyrrole (269r)



269r

Prepared according to general procedure C. *N*-Sulfonyl imine **257r** (114 mg, 0.40 mmol) was reacted with nitroalkyne **259** (60 mg, 0.60 mmol) for 8 h (step i) for 48 h (step ii) to afford compound **269r** (30 mg, 22%) as a pale brown oil, after purification by flash column chromatography on silica gel eluting with PE/EtOAc (19:1). **TLC**: 0.41 (PE/EtOAc 19:1, UV, vanillin); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.69 (d, *J* = 16.0 Hz, 1H, C**H**=CH), 7.62 (d, *J* = 8.5 Hz, 2H, Ar**H**), 7.51 - 7.45 (m, 2H, Ar**H**), 7.36 (t, *J* = 7.5 Hz, 2H, Ar**H**), 7.29 - 7.21 (m, 3H, Ar**H**), 6.77 (d, *J* = 16.0 Hz, 1H, CH=C**H**), 6.42 (d, *J* = 3.0 Hz, 1H, pyrrolyl **H**), 6.00 - 5.94 (m, 1H, pyrrolyl **H**), 2.48 (s, 3H, pyrrolyl C**H$_3$**), 2.37 (s, 3H, ArC**H$_3$**); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 144.6 (Ar**C**), 137.4 (Ar**C**), 136.8 (Ar**C**), 135.6 (Ar**C**), 134.0 (Ar**C**), 129.8 (2 × Ar**C**H), 128.7 (2 × Ar**C**H), 128.6 (Ar**C**H), 127.5 (**C**H=CH), 126.4 (4 × Ar**C**H), 119.0 (CH=**C**H), 113.5 (pyrrolyl **C**H), 111.0 (pyrrolyl **C**H), 21.6 (Ar**C**H$_3$), 15.9 (pyrrolyl **C**H$_3$); **IR** (film/cm^{-1}): ν_{max} 2927, 1597, 1493, 1365, 1193, 1169, 1116, 959, 812, 749, 693; **MS** (ESI): *m/z* 338.2 [(M + H)$^+$]; **HRMS** (ESI): exact mass calculated for $C_{20}H_{20}NO_2S$ [(M + H)$^+$], 338.1209; found 338.1210.

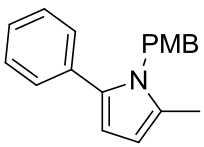
Synthesis and characterisation of 2-methyl-1-[(4-nitrophenyl)sulfonyl]-5-phenyl-1*H*-pyrrole (279)



279

Prepared according to general procedure C. *N*-Nosyl imine **277** (116 mg, 0.40 mmol) was reacted with nitroalkyne **259** (60 mg, 0.60 mmol) for 5 h (step i) and 36 h (step ii) to afford, compound **279** (76 mg, 56%) as a pale yellow solid, after purification by flash column chromatography on silica gel eluting with PE/EtOAc (19:1). **TLC**: R_f = 0.27 (PE/EtOAc 19:1, UV, vanillin); **Melting Point**: 130 - 133 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 8.25 - 8.18 (m, 2H, Ar**H**), 7.59 - 7.51 (m, 2H, Ar**H**), 7.39 - 7.32 (m, 3H, Ar**H**), 7.30 - 7.25 (m, 2H, Ar**H**), 6.11 (d, *J* = 3.5 Hz, 1H, pyrrolyl **H**), 6.09 - 6.05 (m, 1H, pyrrolyl **H**), 2.56 (s, 3H, pyrrolyl C**H$_3$**); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 150.3 (Ar**C**), 144.2 (Ar**C**), 137.8 (Ar**C**), 134.7 (Ar**C**), 132.3 (Ar**C**), 130.5 (2 × Ar**C**H), 128.2 (Ar**C**H), 127.8 (2 × Ar**C**H), 127.5 (2 × Ar**C**H), 124.0 (2 × Ar**C**H), 116.2 (pyrrolyl **C**H), 114.8 (pyrrolyl **C**H), 16.2 (pyrrolyl **C**H$_3$); **IR** (film/cm^{-1}): ν_{max} 3106, 1532, 1402, 1376, 1311, 1183, 1118, 855, 764, 743; **MS** (ESI): *m/z* 365.1 [(M + Na)$^+$]; **HRMS** (ESI): exact mass calculated for $C_{17}H_{14}N_2NaO_4S$ [(M + Na)$^+$], 365.0566; found 365.0568.

Synthesis and characterisation of 1-(4-methoxybenzyl)-2-methyl-5-phenyl-1*H*-pyrrole (280)

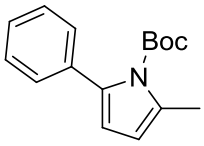


280

Prepared according to general procedure C. *N*-PMB imine **278** (90 mg, 0.40 mmol) was reacted with nitroalkyne **259** (60 mg, 0.60 mmol) for 216 h (step i) and 24 h

(step ii) to afford compound **280** (31 mg, 28%) as a white solid, after purification by flash column chromatography on silica gel eluting with PE/EtOAc (98:2). **TLC**: R_f = 0.28 (PE/EtOAc 98:2, UV, vanillin); **Melting Point**: 88 - 91 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.34 - 7.21 (m, 5H, Ar**H**), 6.90 - 6.82 (m, 4H, Ar**H**), 6.24 (d, *J* = 3.5 Hz, 1H, pyrrolyl **H**), 6.05 (dd, *J* = 3.5, 0.5 Hz, 1H, pyrrolyl **H**), 5.09 (s, 2H, ArC**H$_2$**), 3.80 (s, 3H, ArOC**H$_3$**), 2.17 (s, 3H, pyrrolyl C**H$_3$**); **^{13}C NMR** (100 MHz, $CDCl_3$) 158.5 (Ar**C**), 134.5 (Ar**C**), 133.8 (Ar**C**), 131.0 (Ar**C**), 130.4 (Ar**C**), 128.6 (2 × Ar**C**H), 128.3 (2 × Ar**C**H), 126.8 (2 × Ar**C**H), 126.6 (Ar**C**H), 114.1 (2 × Ar**C**H), 107.9 (pyrrolyl **C**H), 107.1 (pyrrolyl **C**H), 55.2 (ArO**C**H$_3$), 47.1 (Ar**C**H$_2$), 12.6 (pyrrolyl **C**H$_3$); **IR** (film/cm^{-1}): ν_{max} 2933, 1613, 1512, 1444, 1401, 1292, 1248, 1174, 1033, 819, 751, 700; **MS** (ESI): *m/z* 276.1 [(M – H)$^-$]; **HRMS** (FI): exact mass calculated for $C_{19}H_{19}NO$ [M], 277.1467; found 277.1472.

Synthesis and characterisation of *tert*-butyl 2-methyl-5-phenyl-1*H*-pyrrole-1-carboxylate (281)

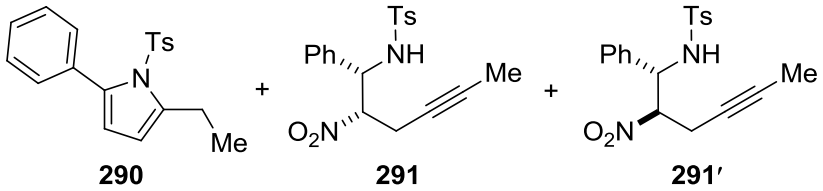


281

Prepared according to general procedure C, replacing MeOH with MeCN (3.2 mL). *N*-Boc imine **112a** (82 mg, 0.40 mmol) was reacted with nitroalkyne **259** (60 mg, 0.60 mmol) for 216 h (step i) and 36 h (step ii) to afford compound **281** (23 mg, 35%) as a colourless oil, after purification by flash column chromatography on silica gel eluting with PE/Et_2O (98:2). **TLC**: R_f = 0.30 (PE/Et_2O 98:2, UV, vanillin); **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.37 - 7.32 (m, 2H, Ar**H**), 7.31 - 7.25 (m, 3H, Ar**H**), 6.08 (d, *J* = 3.0 Hz, 1H, pyrrolyl **H**), 5.98 - 5.94 (m, 1H, pyrrolyl **H**), 2.47 - 2.45 (m, 3H, pyrrolyl C**H$_3$**), 1.27 (s, 9H, C(C**H$_3$**)$_3$); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C

150.2 (**C**=O), 135.4 (Ar**C**), 134.8 (Ar**C**), 133.1 (Ar**C**), 128.1 (2 × Ar**C**H), 127.7 (2 × Ar**C**H), 126.6 (Ar**C**H), 112.1 (pyrrolyl **C**H), 110.3 (pyrrolyl **C**H), 83.3 (**C**$(CH_3)_3$), 27.3 (C(**C**$H_3)_3$), 15.3 (pyrrolyl **C**H_3); **IR** (film/cm^{-1}): ν_{max} 2980, 1742, 1368, 1312, 1147, 1085, 848, 787, 758; **MS** (ESI): *m/z* 280.1 $[(M + Na)^+]$; **HRMS** (ESI): exact mass calculated for $C_{16}H_{19}NNaO_2$ $[(M + Na)^+]$, 280.1308; found 280.1307.

Synthesis and characterisation of 2-ethyl-1-[(4-methylphenyl)sulfonyl]-5-phenyl-1*H*-pyrrole (290), *rac*-4-methyl-*N*-[(1*S*,2*S*)-2-nitro-1-phenylhex-4-yn-1-yl]benzenesulfonamide (291) and *rac*-4-methyl-*N*-[(1*S*,2*R*)-2-nitro-1-phenylhex-4-yn-1-yl]benzenesulfonamide (291′)



290 **291** **291′**

Prepared according to general procedure C, replacing $AuCl_3$ with Au(PPh_3)Cl (9.9 mg, 0.02 mmol) and AgOTf (5.2 mg, 0.02 mmol). *N*-Sulfonyl imine **257a** (104 mg, 0.40 mmol) was reacted with nitroalkyne **285** (68 mg, 0.60 mmol) for 6 h (step i) and 72 h (step ii) to afford compound **290** (27 mg, 21%) as a colourless oil, after purification by flash column chromatography on silica gel eluting with PE/EtOAc (19:1). Further elution of the silica gel column with PE/EtOAc (4:1) afforded a mixture of diastereomers **291** and **291′** (111 mg, 74%, dr 69:31) as an off-white solid.

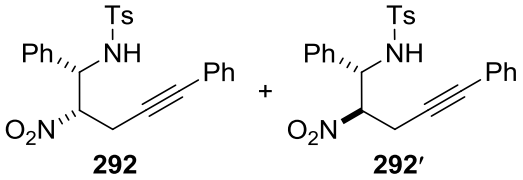
Pyrrole 290: TLC: R_f = 0.33 (PE/EtOAc 19:1, UV, vanillin); **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.36 - 7.28 (m, 7H, Ar**H**), 7.16 (d, *J* = 8.0 Hz, 2H, Ar**H**), 6.10 (d, *J* = 3.0 Hz, 1H, pyrrolyl **H**), 6.07 - 6.04 (m, 1H, pyrrolyl **H**), 2.97 (qd, *J* = 7.5, 1.0 Hz, 2H, C**H$_2$**CH_3), 2.37 (s, 3H, ArC**H$_3$**), 1.31 (t, *J* = 7.5 Hz, 3H, CH_2C**H$_3$**); **^{13}C NMR** (125

MHz, $CDCl_3$): δ_C 144.2 (Ar**C**), 141.1 (Ar**C**), 138.0 (Ar**C**), 136.4 (Ar**C**), 133.3 (Ar**C**), 130.5 (2 × Ar**C**H), 129.4 (2 × Ar**C**H), 127.7 (Ar**C**H), 127.2 (2 × Ar**C**H), 126.4 (2 × Ar**C**H), 115.5 (pyrrolyl **C**H) 111.7 (pyrrolyl **C**H), 22.8 (**C**H_2CH_3), 21.5 (Ar**C**H_3), 13.5 (CH_2**C**H_3); **IR** (film/cm^{-1}): ν_{max} 3292, 1598, 1360, 1176, 1097, 981, 904, 815, 767, 663; **MS** (ESI): *m/z* 348.1 [$(M + Na)^+$]; **HRMS** (ESI): exact mass calculated for $C_{19}H_{19}NNaO_2S$ [$(M + Na)^+$], 348.1029; found 348.1029.

Diastereomers 291 and 291′: All characterisation data reported corresponds to the mixture of diastereomers **291** and **291′** (dr 69:31). **TLC**: R_f = 0.31 (PE/EtOAc 4:1, UV, $KMnO_4$); **Melting Point**: 136 - 138 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.57 - 7.40 (m, Ar**H**, 2H *major* and 2H *minor*), 7.23 - 7.05 (m, Ar**H**, 5H *major* and 5H *minor*), 7.04 - 6.98 (m, 2H, Ar**H**, *major*), 6.96 - 6.91 (m, 2H, Ar**H**, *minor*), 6.15 (d, *J* = 10.0 Hz, 1H, N**H**, *major*), 5.99 (d, *J* = 9.5 Hz, 1H, N**H**, *minor*), 4.92 - 4.74 (m, C**H**NH and C**H**NO_2, 2H *major* and 2H *minor*), 2.88 - 2.71 (m, C**HH′**, 1H *major* and 2H *minor*), 2.49 - 2.37 (m, 1H, CH**H′**, *major*), 2.35 (s, 3H, ArC**H$_3$**, *minor*) 2.32 (s, 3H, ArC**H$_3$**, *major*), 1.78 (t, *J* = 2.5 Hz, 3H, C≡CC**H$_3$**, *minor*), 1.72 (t, *J* = 2.5 Hz, 3H, C≡CC**H$_3$**, *major*); **^{13}C NMR** (100 MHz, $CDCl_3$, assignment is made where possible): δ_C 143.7 (Ar**C**), 143.5 (Ar**C**), 136.8 (Ar**C**), 136.6 (Ar**C**), 134.9 (Ar**C**), 134.2 (Ar**C**), 129.5 (2 × Ar**C**H, *minor*), 129.3 (2 × Ar**C**H, *major*), 129.0 (2 × Ar**C**H, *major*), 128.8 (Ar**C**H), 128.6 (2 × Ar**C**H, *minor*), 127.0 (2 × Ar**C**H, *minor*), 127.0 (2 × Ar**C**H, *major*), 126.8 (2 × Ar**C**H, *minor*), 126.5 (2 × Ar**C**H, *major*), 90.4 (C**H**NO_2, *major*), 89.4 (C**H**NO_2, *minor*), 80.6 (**C**≡C), 80.4 (**C**≡C), 71.8 (C≡**C**), 71.2 (C≡**C**), 59.0 (**C**HNH, *major*), 58.7 (**C**HNH, *minor*), 21.9 (**C**H_2, *major*), 21.4 (Ar**C**H_3, *minor*), 21.4 (Ar**C**H_3, *major*), 21.0 (**C**H_2, *minor*), 3.5 (C≡C**C**H_3, *minor*), 3.4 (C≡C**C**H_3, *major*); **IR** (film/cm^{-1}): ν_{max} 3252, 2979, 1563, 1459, 1321, 1162, 1090,

907, 851, 731, 705, 670; **MS** (ESI): *m/z* 395.1 [(M + Na)$^+$]; **HRMS** (ESI): exact mass calculated for $C_{19}H_{20}N_2NaO_4S$ [(M + Na)$^+$], 395.1036; found 395.1034. The relative configurations of diastereomers **291** and **291′** were assigned by analogy to the X-ray crystal structure of *syn*-**268′**.

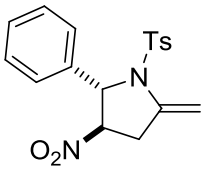
Synthesis and characterisation of 4-methyl-*N*-[(1*S*,2*S*)-2-nitro-1,5-diphenylpent-4-yn-1-yl]benzenesulfonamide (292) and 4-methyl-*N*-[(1*S*,2*R*)-2-nitro-1,5-diphenylpent-4-yn-1-yl]benzenesulfonamide (292′)



Prepared according to general procedure C, replacing $AuCl_3$ with $Au(PPh_3)Cl$ (9.9 mg, 0.02 mmol) and AgOTf (5.2 mg, 0.02 mmol). *N*-Sulfonyl imine **257a** (104 mg, 0.40 mmol) was reacted with nitroalkyne **289** (105 mg, 0.60 mmol) for 6 h (step i) and 72 h (step ii) to afford a mixture of diastereomers **292** and **292′** (27 mg, 16%, dr 64:36) as a pale yellow solid, after purification by flash column chromatography on silica gel eluting with PE/EtOAc (4:1). All characterisation data reported corresponds to the mixture of diastereomers **292** and **292′** (dr 64:36). **TLC**: R_f = 0.32 (PE/EtOAc 4:1, UV, $KMnO_4$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.95 - 7.84 (m, 2H, Ar**H**, *minor*), 7.61 - 7.50 (m, Ar**H**, 2H *major* and 2H *minor*), 7.48 - 7.41 (m, 2H, Ar**H**, *minor*), 7.40 - 7.13 (m, Ar**H**, 8H *major* and 4H *minor*), 7.12 - 7.01 (m, Ar**H**, 4H *major* and 4H *minor*), 6.09 - 5.96 (m, N**H**, 1H *major* and 1H *minor*), 5.04 - 4.86 (m, C**H**NH and C**H**NO_2, 2H *major* and 2H *minor*), 3.09 (dd, *J* = 17.5, 8.5 Hz, 1H, C**H**H′, *major*), 3.04 - 2.96 (m, 2H, C**HH′**, *minor*), 2.82 (dd, *J* = 17.5, 5.0 Hz, 1H, CH**H′**, *major*), 2.32 (s, 3H, ArC**H$_3$**, *major*) 2.31 (s, 3H, ArC**H$_3$**, *minor*); **^{13}C NMR** (100 MHz, $CDCl_3$, unassigned mixture of diastereomers): δ_C 143.5 (Ar**C**), 143.4

(Ar**C**), 136.9 (Ar**C**), 136.8 (Ar**C**), 136.1 (Ar**C**), 135.2 (Ar**C**), 134.8 (Ar**C**), 133.5 (Ar**C**), 131.7 (Ar**C**H), 129.4 (Ar**C**H), 129.3 (Ar**C**H), 129.0 (Ar**C**H), 128.9 (Ar**C**H), 128.7 (Ar**C**H), 128.7 (Ar**C**H), 128.5 (Ar**C**H), 128.2 (Ar**C**H), 127.9 (Ar**C**H), 127.0 (Ar**C**H), 127.0 (Ar**C**H), 126.5 (Ar**C**H), 126.5 (Ar**C**H), 91.1 (**C**HNO_2), 90.0 (**C**HNO_2), 84.8 (**C**≡C), 81.5 (**C**≡C), 59.5 (**C**HNH), 58.8 (**C**HNH), 33.7 (**C**H_2), 22.5 (**C**H_2), 21.4 (Ar**C**H_3), 21.4 (Ar**C**H_3); **IR** (film/cm^{-1}): ν_{max} 3236, 2923, 1686, 1556, 1445, 1326, 1162, 1091, 909, 812, 759, 731, 702; **MS** (ESI): *m/z* 457.1 [$(M + Na)^+$]; **HRMS** (ESI): exact mass calculated for $C_{24}H_{22}N_2NaO_4S$ [$(M + Na)^+$], 457.1192; found 457.1196. The relative configurations of diastereomers **292** and **292′** were assigned by analogy to the X-ray crystal structure of *syn*-**268′**.

Synthesis and characterisation of *rac*-(2*S*,3*R*)-5-methylidene-1-[(4-methyl phenyl)sulfonyl]-3-nitro-2-phenylpyrrolidine (310)



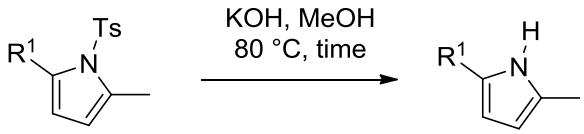
310

Prepared according to general procedure C, using KO*t*Bu (0.5 equiv). *N*-Sulfonyl imine **257a** (104 mg, 0.40 mmol) was reacted with nitroalkyne **259** (60 mg, 0.60 mmol) for 6 h (step i) and 2 h (step ii) to afford compound **310** (60 mg, 42%, dr >98:2) as a pale red solid after purification by flash column chromatography on silica gel eluting with PE/EtOAc (19:1). **TLC**: R_f = 0.61 (PE/EtOAc 4:1, UV, $KMnO_4$); **Melting Point**: 78 - 81 °C; **^{1}H NMR** (500 MHz, C_6D_6): δ_H 7.77 (d, *J* = 8.5 Hz, 2H, Ar**H**), 7.24 - 7.20 (m, 2H, Ar**H**), 7.09 - 6.96 (m, 3H, Ar**H**), 6.77 (d, *J* = 8.5 Hz, 2H, Ar**H**), 6.04 (s, 1H, C**H**N), 5.42 - 5.39 (m, 1H, C=C**H**H′), 4.19 - 4.16 (m, 1H, C=CH**H′**), 3.76 (d, *J* = 6.5 Hz, 1H, C**H**NO_2), 2.48 (dt, *J* = 17.5, 1.5 Hz, 1H, C**H**H′),

2.20 - 2.08 (ddt, *J* = 17.5, 6.5, 2.5 Hz, 1H, CH**H′**), 1.81 (s, 3H, ArC**H**$_3$); **^{13}C NMR** (125 MHz, C_6D_6): δ_C 144.7 (Ar**C**), 141.2 (Ar**C**), 139.2 (**C**=CH_2), 136.0 (Ar**C**), 130.0 (2 × Ar**C**H), 129.6 (2 × Ar**C**H), 128.9 (Ar**C**H), 128.7 (2 × Ar**C**H), 126.2 (2 × Ar**C**H), 91.1 (C=**C**H_2), 87.6 (**C**HNO_2), 71.2 (**C**HN), 34.5 (**C**H_2), 21.5 (Ar**C**H_3); **IR** (film/cm^{-1}): ν_{max} 3286, 2924, 1597, 1556, 1454, 1367, 1188, 1167, 1119, 1090, 813, 763, 701; **MS** (ESI): *m/z* 334.1 [(M – HNO_2 + Na)$^+$]; **HRMS** (ESI): exact mass calculated for $C_{18}H_{17}NNaO_2S$ [(M – HNO_2 + Na)$^+$], 334.0872; found 344.0872. The relative configuration of pyrrolidine **310** was determined by comparison of the ^{1}H NMR spectrum to that of pyrrolidine **471a** (Chapter 4).

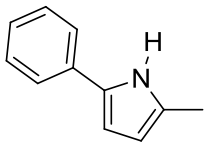
5.2.4 Synthesis and Characterisation of Deprotected Pyrroles

General procedure D: Deprotection of pyrroles



To a stirred mixture of the corresponding pyrrole (1.0 equiv) in MeOH (1 mL/0.1 mmol of pyrrole) at RT in a microwave vial was added powdered KOH (7.0 equiv). The resulting mixture was heated to 80 °C for the indicated time. The reaction mixture was cooled to RT and concentrated under a stream of nitrogen. The resulting residue was purified by flash column chromatography on silica gel to afford the corresponding deprotected pyrrole.

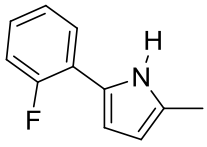
Synthesis and characterisation of 2-methyl-5-phenyl-1*H*-pyrrole (315a)



315a

Prepared according to general procedure D. Pyrrole **269a** (62 mg, 0.20 mmol) was reacted with KOH (39 mg, 1.40 mmol) for 72 h to afford compound **315a** (26 mg, 81%) as a white solid, after purification by flash column chromatography on silica gel eluting with PE/Et_2O (19:1). **TLC**: R_f = 0.26 (PE/Et_2O 19:1, UV, vanillin); **Melting Point**: 91 - 94 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 8.11 (br s, 1H, N**H**), 7.46 - 7.42 (m, 2H, Ar**H**), 7.38 - 7.32 (m, 2H, Ar**H**), 7.20 - 7.14 (m, 1H, Ar**H**), 6.41 (t, *J* = 3.0 Hz, 1H, pyrrolyl **H**), 5.98 - 5.95 (m, 1H, pyrrolyl **H**), 2.35 (s, 3H, pyrrolyl C**H$_3$**); **MS** (ESI): *m/z* 156.1 [$(M - H)^-$]; **HRMS** (ESI): exact mass calculated for $C_{11}H_{10}N$ [$(M - H)^-$], 156.0819; found 156.0820. The data was in accordance with that reported in the literature.[221]

Synthesis and characterisation of 2-(2-fluorophenyl)-5-methyl-1*H*-pyrrole (315b)

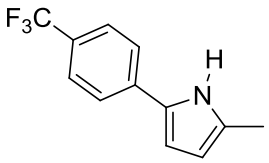


315b

Prepared according to general procedure D. Pyrrole **269g** (66 mg, 0.20 mmol) was reacted with KOH (79 mg, 1.40 mmol) for 18 h to afford compound **315b** (24 mg, 69%) as a white solid, after purification by flash column chromatography on silica gel eluting with PE/EtOAc (19:1). **TLC**: R_f = 0.38 (PE/EtOAc 19:1, UV, vanillin); **Melting point**: 104 - 107 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 8.70 (br s, 1H, N**H**), 7.64 - 7.55 (m, 1H, Ar**H**), 7.18 - 7.06 (m, 3H, Ar**H**), 6.56 (t, *J* = 3.0 Hz, 1H, pyrrolyl

H), 6.02 - 5.97 (m, 1H, pyrrolyl **H**), 2.36 (s, 3H, pyrrolyl C**H$_3$**); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 158.2 (d, *J* = 243.0 Hz, Ar**C**F), 129.4 (d, *J* = 3.0 Hz, Ar**C**), 126.3 (d, *J* = 8.5 Hz, Ar**C**H), 126.1 (d, *J* = 5.0 Hz, Ar**C**H), 125.4 (d, *J* = 2.0 Hz, Ar**C**H), 124.6 (d, *J* = 3.0 Hz, Ar**C**H), 120.4 (d, *J* = 11.5 Hz, Ar**C**), 116.1 (d, *J* = 23.0 Hz, Ar**C**H), 107.9 (d, *J* = 2.0 Hz, pyrrolyl **C**H), 107.4 (pyrrolyl **C**H), 13.2 (pyrrolyl **C**H$_3$); **^{19}F NMR** (470.5 MHz, $CDCl_3$): δ_F –119.4 (Ar**F**); **IR** (film/cm^{-1}): ν_{max} 2933, 2835, 1662, 1512, 1444, 1292, 1248, 1174, 1033, 819, 751, 700; **MS** (ESI): *m/z* 174.1 [(M –H)$^-$]. No meaningful HRMS data was obtained for this compound.

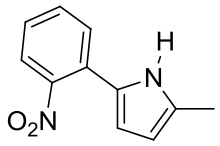
Synthesis and characterisation of 2-methyl-5-[4-(trifluoromethyl)phenyl]-1*H*-pyrrole (315c)



315c

Prepared according to general procedure D. Pyrrole **269n** (51 mg, 0.135 mmol) was reacted with KOH (53 mg, 0.945 mmol) for 24 h to afford compound **315c** (19 mg, 62%) as a white solid, after purification by flash column chromatography on silica gel eluting with PE/EtOAc (19:1). **TLC**: R_f = 0.30 (PE/EtOAc 19:1, UV, vanillin); **Melting Point**: 127 - 130 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 8.19 (br s, 1H, N**H**), 7.58 (d, *J* = 8.0 Hz, 2H, Ar**H**), 7.50 (d, *J* = 8.0 Hz, 2H, Ar**H**), 6.52 (t, *J* = 3.0 Hz, 1H, pyrrolyl **H**), 6.02 - 5.99 (m, 1H, pyrrolyl **H**), 2.37 (s, 3H, pyrrolyl C**H$_3$**); **^{19}F NMR** (376.5 MHz, $CDCl_3$): δ_F –62.3 (ArC**F$_3$**); **IR** (film/cm^{-1}): ν_{max} 3400, 1615, 1528, 1479, 1431, 1327, 1161, 1109, 1076, 777; **MS** (ESI): *m/z* 224.1 [(M – H)$^-$]. The data was in accordance with that reported in the literature.[221]

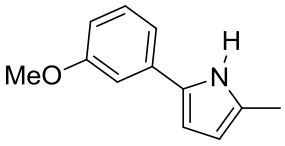
Synthesis and characterisation of 2-methyl-5-(2-nitrophenyl)-1*H*-pyrrole (315d)



315d

Prepared according to general procedure D. Pyrrole **269m** (36 mg, 0.10 mmol) was reacted with KOH (39 mg, 0.70 mmol) for 96 h to afford compound **315d** (17 mg, 84%) as a yellow solid, after purification by flash column chromatography on silica gel eluting with PE/EtOAc (19:1). **TLC**: R_f = 0.17 (PE/EtOAc 19:1, UV, vanillin); **Melting Point**: 51 - 54 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 8.64 (br s, 1H, N**H**), 7.72 - 7.68 (m, 1H, Ar**H**), 7.62 - 7.58 (m, 1H, Ar**H**), 7.56 - 7.50 (m, 1H, Ar**H**), 7.33 - 7.28 (m, 1H, Ar**H**), 6.40 (t, *J* = 3.0 Hz, 1H, pyrrolyl **H**), 6.02 - 5.98 (m, 1H, pyrrolyl **H**), 2.34 (s, 3H, pyrrolyl C**H$_3$**); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 132.3 (Ar**C**H), 131.0 (Ar**C**), 130.2 (Ar**C**H), 127.0 (Ar**C**), 126.3 (Ar**C**H), 124.9 (Ar**C**), 124.5 (Ar**C**H), 111.7 (pyrrolyl **C**H), 108.3 (pyrrolyl **C**H), 13.2 (pyrrolyl **C**H$_3$); **MS** (ESI): *m/z* 201.1 [(M – H)$^-$]. The data was in accordance with that reported in the literature.[222]

Synthesis and characterisation of 2-(3-methoxyphenyl)-5-methyl-1*H*-pyrrole (315e)

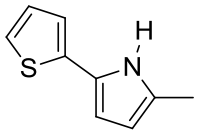


315e

Prepared according to general procedure D. Pyrrole **269d** (68 mg, 0.20 mmol) was reacted with KOH (79 mg, 1.40 mmol) for 72 h to afford compound **315e** (27 mg, 72%) as a white solid, after purification by flash column chromatography on silica gel eluting with PE/Et_2O (19:1). **TLC**: R_f = 0.10 (PE/Et_2O 19:1, UV, vanillin);

Melting Point: 54 - 57 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 8.17 (br s, 1H, N**H**), 7.27 (t, *J* = 8.0 Hz, 1H, Ar**H**), 7.06 - 7.00 (m, 1H, Ar**H**), 7.00 - 6.96 (m, 1H, Ar**H**), 6.77 - 6.70 (m, 1H, Ar**H**), 6.42 (t, *J* = 3.0 Hz, 1H, pyrrolyl **H**), 5.99 - 5.93 (m, 1H, pyrrolyl **H**), 3.85 (s, 3H, ArOC**H$_3$**), 2.35 (s, 3H, pyrrolyl C**H$_3$**); **^{13}C NMR** (100 MHz, CDCl3): δ_C 160.0 (Ar**C**), 134.3 (Ar**C**), 130.6 (Ar**C**), 129.8 (Ar**C**H), 129.1 (Ar**C**), 115.9 (Ar**C**H), 111.0 (Ar**C**H), 109.2 (Ar**C**H), 107.9 (pyrrolyl **C**H), 106.4 (pyrrolyl **C**H), 55.2 (ArO**C**H_3), 13.1 (pyrrolyl **C**H_3); **IR** (film/cm^{-1}): ν_{max} 3384, 2938, 1609, 1511, 1487, 1466, 1237, 1206, 1173, 1039, 830, 768, 689; **MS** (ESI): *m/z* 186.1 [(M – H)$^-$]; **HRMS** (ESI): exact mass calculated for $C_{12}H_{12}NO$ [(M – H)$^-$], 186.0924; found 186.0926.

Synthesis and characterisation of 2-methyl-5-(2-thienyl)-1*H*-pyrrole (315f)



315f

Prepared according to general procedure D. Pyrrole **269p** (32 mg, 0.10 mmol) was reacted with KOH (39 mg, 0.70 mmol) for 72 h to afford compound **315f** (11 mg, 67%) as a pale orange oil, after purification by flash column chromatography on silica gel eluting with PE/Et_2O (19:1). **TLC**: R_f = 0.15 (PE/Et_2O 19:1, UV, vanillin); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.11 (dd, *J* = 5.0, 1.5 Hz, 1H, thienyl **H**), 7.02 - 6.98 (m, 1H, thienyl **H**), 6.97 (dd, *J* = 3.5, 1.5 Hz, 1H, thienyl **H**), 6.29 (t, *J* = 3.0 Hz, 1H, pyrrolyl **H**), 5.94 - 5.90 (m, 1H, pyrrolyl **H**), 2.32 (s, 3H, pyrrolyl C**H$_3$**); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_H 128.7 (Ar**C**), 127.5 (thienyl **C**H), 122.0 (thienyl **C**H), 120.0 (thienyl **C**H), 119.3 (Ar**C**), 113.5 (Ar**C**), 107.8 (pyrrolyl **C**H), 106.9 (pyrrolyl **C**H), 13.1 (pyrrolyl **C**H_3); **IR** (film/cm^{-1}): ν_{max} 3403, 1536, 1366, 1173, 770, 695;

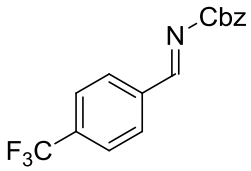
MS (ESI): *m/z* 162.0 [$(M - H)^-$]. No meaningful HRMS data was obtained for this compound.

5.3 Experimental Section for Chapter 3

5.3.1 Reagents and Synthesis of Starting Materials

All commercially available reagents were used as received unless otherwise stated. Amidosulfones **399a-p** and **400a** were prepared according to a literature procedure.[138] Amidosulfones **400b-d** were prepared by Dr. A. L. Tillman according to a literature procedure.[138] *N*-Boc imines **112a-g**,[138] **112h**,[177] **112i-o**,[138] **112p**[178] and *N*-Cbz imines **401a**[138] and **401b-d**[177] were prepared according to literature procedures starting from the corresponding amidosulfones **399a-p** and **400a-d**. Synthesis and characterisation data for the novel *N*-Cbz imine **401d** is reported. The following alkyne substrates were prepared according to literature procedures: 5-iodopent-1-yne (**382**),[223] 5-chloro-1-pentyne (**403**),[62a] 6-iodohex-2-yne (**404**),[223] 5-phenylpent-4-yn-1-ol (**407**)[217] and (5-iodopent-1-yn-1-yl)benzene (**408**).[216] Catalysts **118** and **335** were prepared by other members of the Dixon group according to a literature procedure.[39] Catalyst **319** was prepared by Dr. A. F. Kyle according to a literature procedure.[62a] Catalysts **388** and **62** were prepared according to a literature procedure.[222]

Synthesis and characterisation of benzyl {(*E*)-[4-(trifluoromethyl)phenyl] methylene}carbamate (401d)

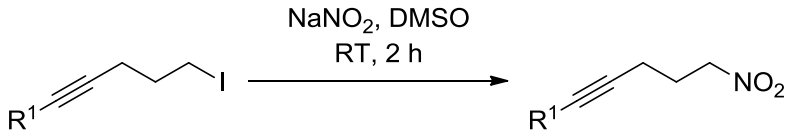


401d

To a stirred suspension of *N*-Cbz amidosulfone **400d** (674 mg, 1.50 mmol) in CH_2Cl_2 (24 mL) at RT was added K_2CO_3 (24 mL, 1.4 M solution in H_2O). The resulting biphasic mixture was vigorously stirred at RT for 4 h. The organic layer was decanted and the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The

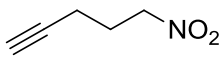
combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford compound **401d** (432 mg, 94%) as a white solid. The product was used in the next step without further purification. **Melting Point**: 39 - 40 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 8.94 (s, 1H, C**H**=N), 8.06 - 8.01 (m, 2H, Ar**H**), 7.78 - 7.72 (m, 2H, Ar**H**), 7.50 - 7.45 (m, 2H, Ar**H**), 7.44 - 7.35 (m, 3H, Ar**H**), 5.35 (s, 2H, C**H**$_2$CO$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 169.1 (**C**H=N), 163.1 (**C**=O), 136.8 (Ar**C**), 135.0 (Ar**C**), 134.8 (q, *J* = 32.5 Hz, Ar**C**), 130.4 (Ar**C**), 130.3 (2 × Ar**C**H), 128.6 (2 × Ar**C**H), 128.6 (2 × Ar**C**H), 125.8 (q, *J* = 3.5 Hz, 2 × Ar**C**H), 123.5 (q, *J* = 272.5 Hz, Ar**C**F$_3$), 69.1 (**C**H$_2$CO$_2$); **IR** (film/cm^{-1}): ν_{max} 1699, 1632, 1324, 1261, 1205, 1168, 1117, 1064, 835, 755, 694; **MS** (ESI): *m/z* 362.1 [(M + Na + MeOH)$^+$]; **HRMS** (ESI): exact mass calculated for $C_{17}H_{16}F_3NNaO_3$ [(M + Na + MeOH)$^+$], 362.0974; found 362.0964.

General Procedure E: Synthesis of nitroalkynes



To a stirred solution of $NaNO_2$ (1.2 equiv) in DMSO (1 mL/mmol of iodoalkyne) maintained at RT with a water bath was added a solution of the corresponding iodoalkyne (1.0 equiv) in DMSO (1 mL/10 mmol) behind a blast shield and the resulting mixture was stirred at RT for 2 h. The reaction mixture was diluted with ice water (1 mL/mmol) and extracted with Et_2O (6 × 1 mL/mmol). The combined organic extracts were washed with ice water (1 mL/mmol), dried over Na_2SO_4, filtered and concentrated under reduced pressure (water bath <20 °C). The resulting residue was purified by flash column chromatography on silica gel to afford the desired nitroalkyne.

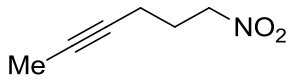
Synthesis and characterisation of 5-nitropent-1-yne (383)



383

Prepared according to general procedure E. 5-Iodopent-1-yne **(382**) (18.0 g, 93.0 mmol) was reacted with $NaNO_2$ (7.70 g, 112.0 mmol) to afford compound **383** (5.68 g, 54%) as a pale yellow oil, after purification by flash column chromatography on silica gel eluting with PE/Et_2O (19:1). **TLC**: R_f = 0.22 (PE/Et_2O 19:1, $KMnO_4$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 4.55 (t, *J* = 7.0 Hz, 2H, C**H$_2$**NO_2), 2.39 (td, *J* = 7.0, 2.5 Hz, 2H, C**H$_2$**$CH_2CH_2NO_2$), 2.23 (qu, *J* = 7.0 Hz, 2H, C**H$_2$**CH_2NO_2), 2.05 (t, *J* = 2.5 Hz, 1H, **H**C≡C); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 81.2 (HC≡**C**), 73.7 (**C**H_2NO_2), 70.4 (H**C**≡C), 25.7 (**C**$H_2CH_2NO_2$), 15.5 (**C**$H_2CH_2CH_2NO_2$); **IR** (film/cm^{-1}): ν_{max} 3296, 2946, 2120, 1556, 1435, 1384, 1357, 1186, 651; **HRMS** (FI): exact mass calculated for $C_5H_7NO_2$ [M], 113.0477; found 113.0478.

Synthesis and characterisation of 6-nitrohex-2-yne (405)

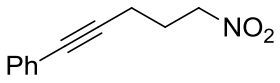


405

Prepared according to general procedure E. 6-Iodohex-2-yne (**404**) (1.87 g, 9.0 mmol) was reacted with $NaNO_2$ (745 mg, 10.8 mmol) to afford compound **405** (564 mg, 49%) as a pale yellow oil, after purification by flash column chromatography on silica gel eluting with PE/Et_2O (19:1). **TLC**: R_f = 0.44 (PE/Et_2O 19:1, $KMnO_4$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 4.52 (t, *J* = 7.0 Hz, 2H, C**H$_2$**NO_2), 2.34 - 2.26 (m, 2H, C**H$_2$**$CH_2CH_2NO_2$), 2.22 - 2.11 (m, 2H, C**H$_2$**CH_2NO_2), 1.78 (t, *J* = 2.5 Hz, 3H, C**H$_3$**); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 77.8 (**C**≡C), 76.0 (C≡**C**), 74.1 (**C**H_2NO_2), 26.4 (**C**$H_2CH_2NO_2$), 15.9 (**C**$H_2CH_2CH_2NO_2$), 3.4 (**C**H_3); **IR** (film/cm^{-1}):

ν_{max} 2922, 1550, 1434, 1381, 1355; **HRMS** (FI): exact mass calculated for $C_6H_9NO_2$ [M], 127.0633; found 127.0633.

Synthesis and characterisation of (5-nitropent-1-yn-1-yl)benzene (409)

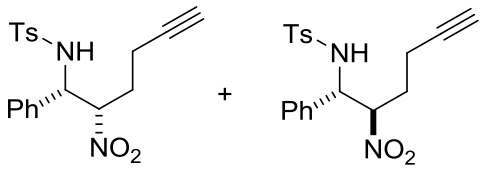


409

Prepared according to general procedure E. (5-Iodopent-1-yn-1-yl)benzene (**408**) (3.52 g, 13.0 mmol) was reacted with $NaNO_2$ (1.08 g, 15.6 mmol) to afford compound **409** (1.55 g, 63%) as a pale yellow oil, after purification by flash column chromatography on silica gel eluting with PE/EtOAc (19:1). **TLC**: R_f = 0.30 (PE/EtOAc 19:1, UV, $KMnO_4$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.44 - 7.37 (m, 2H, Ar**H**), 7.34 - 7.28 (m, 3H, Ar**H**), 4.60 (t, *J* = 7.0 Hz, 2H, C**H$_2$**NO_2), 2.61 (t, *J* = 7.0 Hz, 2H, C**H$_2$**$CH_2CH_2NO_2$), 2.31 (qu, *J* = 7.0 Hz, 2H, C**H$_2$**CH_2NO_2); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 131.6 (2 × Ar**C**H), 128.3 (2 × Ar**C**H), 128.1 (Ar**C**H), 123.1 (Ar**C**), 86.6 (**C**≡C), 82.5 (C≡**C**), 74.0 (**C**H_2NO_2), 26.1 (**C**$H_2CH_2CH_2NO_2$), 16.6 (**C**$H_2CH_2NO_2$); **IR** (film/cm^{-1}): ν_{max} 1548, 1432, 1381, 1355, 756, 691; **HRMS** (FI): exact mass calculated for $C_{11}H_{11}NO_2$ [M], 189.0790; found 189.0785.

5.3.2 Synthesis of Characterisation of Tetrahydropyridines 386 and 386′

Synthesis and characterisation of *rac*-4-methyl-*N*-[(1*S*,2*S*)-(2-nitro-1-phenylhex-5-yn-1-yl)benzenesulfonamide (385) and *rac*-4-methyl-*N*-[(1*S*,2*R*)-(2-nitro-1-phenylhex-5-yn-1-yl)benzenesulfonamide (385′)



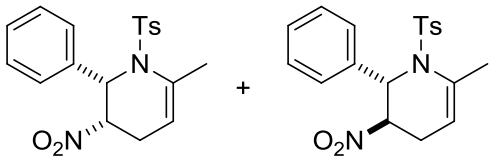
385 **385′**

To a stirred solution of *N*-sulfonyl imine **257a** (51.9 mg, 0.20 mmol) and nitroalkyne **383** (33.9 mg, 0.30 mmol) in MeOH (2.0 mL) at RT was added KO*t*Bu (2.3 mg, 0.02 mmol, 10 mol%). The reaction mixture was stirred at RT for 48 h. The resulting white precipitate was filtered off and dried to afford compound **385** (16 mg, 17%, dr 98:2) as a white solid. The mother liquor was concentrated under reduced pressure to afford a pale yellow solid. Purification by flash column chromatography on silica gel eluting with PE/EtOAc (4:1) afforded a mixture of diastereomers **385** and **385′** (51 mg, 55%, dr 87:13; 72% combined yield) as a white solid. All characterisation data reported corresponds to the major diastereomer **385** (dr 98:2).**TLC**: R_f = 0.36 (PE/EtOAc 4:1, UV, vanillin); **Melting Point**: 158 - 161 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.51 (d, *J* = 8.5 Hz, 2H, Ar**H**), 7.23 - 7.12 (m, 3H, Ar**H**), 7.07 (d, *J* = 8.5 Hz, 2H, Ar**H**), 7.01 - 6.94 (m, 2H, Ar**H**), 5.98 (d, *J* = 10.0 Hz, 1H, N**H**), 4.98 (ddd, *J* = 9.0, 6.5, 5.0 Hz, 1H, C**H**NO_2), 4.84 (dd, *J* = 10.0, 6.5 Hz, 1H, C**H**NH), 2.42 - 2.31 (m, 4H, CHH′C**H**H′C≡C and Ar$C\mathbf{H_3}$), 2.31 - 2.16 (m, 2H, C**H**H′CH**H′**C≡C), 2.04 (t, *J* = 2.5 Hz, 1H, C≡C**H**), 2.02 - 1.91 (m, 1H, CH**H′**CHH′C≡C); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 143.5 (Ar**C**), 136.9 (Ar**C**), 135.1 (Ar**C**), 129.3 (2 × Ar**C**H), 128.9 (2 × Ar**C**H), 128.5 (Ar**C**H), 126.9 (2 × Ar**C**H), 126.3 (2 × Ar**C**H), 90.6 (**C**HNO_2), 80.7 (**C**≡CH), 70.6 (C≡**C**H), 58.8 (**C**HNH), 29.7 (**C**H_2CH_2C≡C), 21.4 (Ar**C**H_3), 15.0

(CH_2**C**H_2C≡C); **IR** (film/cm^{-1}): ν_{max} 3293, 2922, 1553, 1457, 1435, 1328, 1159, 1089, 1069, 909, 813, 731; **MS** (ESI): *m/z* 395.1 [$(M + Na)^+$]; **HRMS** (ESI): exact mass calculated for $C_{18}H_{18}N_2NaO_4S$ [$(M + Na)^+$], 381.0879; found 381.0883. The relative configurations of diastereomers **385** and **385′** were assigned by analogy to the X-ray crystal structure of *syn*-**268′** (Chapter 2).

Enantioselective synthesis of diastereomers 385 and 385′: Diastereomers **385** and **385′** were synthesised on a 0.10 mmol scale in an analogous manner to the described procedure by replacing KO*t*Bu with catalyst **118** (5 mol%) and stirring at RT for 72 h. The reaction mixture was directly purified by flash column chromatography on silica gel eluting with PE/EtOAc (4:1) to afford a mixture of diastereomers **385** and **385′** (32 mg, 86%) as a white solid. The dr and ee were determined by HPLC analysis using a Chiralpak OD column [hexane/*i*PrOH 90:10, flow rate 1.0 mL/min, λ = 210 nm]; dr 91:9; ***MAJOR:*** t_R major = 16.81 min, t_R minor = 21.61 min (3% ee), ***MINOR:*** t_R minor = 15.50 min, t_R major = 19.27 min (25% ee). The absolute configurations of diastereomers **385** and **385′** were not determined, only the relative configuration is known. All other data was in agreement with that of the corresponding racemic diastereomers **385** and **385′**.

Synthesis and characterisation of *rac*-(2*S*,3*S*)-6-methyl-1-[(4-methylphenyl) sulfonyl]-3-nitro-2-phenyl-1,2,3,4-tetrahydropyridine (386) and *rac*-(2*S*,3*R*)-6-methyl-1-[(4-methylphenyl)sulfonyl]-3-nitro-2-phenyl-1,2,3,4-tetrahydropyridine (386′)



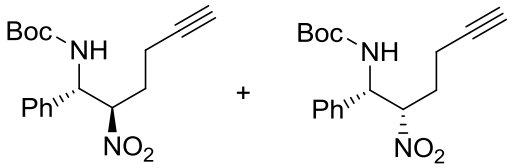
386 **386′**

To a stirred solution of diastereomers **385** and **385′** (37.2 mg, 0.10 mmol, dr 87:13) in PhMe (1.0 mL) at RT was added $Au(PPh_3)Cl$ (2.5 mg, 5.0 μmol) and AgOTf (2.6 mg, 0.01 mmol). The resulting mixture was stirred at 75 °C for 2 h. The reaction mixture was cooled to RT and then directly purified by flash column chromatography on silica gel eluting with PE/EtOAc (9:1) to afford a mixture of diastereomers **386** and **386′** (32 mg, 87%, dr 84:16) as an off-white solid. Only the ^{1}H and ^{13}C NMR signals corresponding to the major diastereomer **386** are reported, all other characterisation data is for the mixture of diastereomers **386** and **386′**. **TLC**: R_f = 0.21 (PE/EtOAc 9:1, UV, $KMnO_4$); **Melting Point**: 116 - 118 °C; **^{1}H NMR** (400 MHz, CD_3OD): δ_H 7.72 (d, *J* = 8.0 Hz, 2H, Ar**H**), 7.41 (d, *J* = 8.0 Hz, 2H, Ar**H**), 7.34 - 7.24 (m, 3H, Ar**H**), 7.14 - 7.06 (m, 2H, Ar**H**), 6.05 (d, *J* = 5.0 Hz, 1H, C**H**N), 5.12 - 5.05 (m, 1H, C=C**H**), 4.45 - 4.35 (m, 1H, C**H**NO_2), 2.43 (s, 3H, Ar**C**H_3), 2.41 - 2.33 (m, 2H, **C**H_2), 2.24 (s, 3H, CH=CC**H$_3$**) **^{13}C NMR** (100 MHz, CD_3OD): δ_C 146.3 (Ar**C**), 137.8 (Ar**C**), 136.1 (Ar**C**), 135.3 (CH=**C**CH_3), 131.4 (2 × ArC**H**), 130.0 (Ar**C**H), 129.9 (2 × ArC**H**), 128.4 (2 × ArC**H**), 128.4 (2 × ArC**H**), 110.3 (C=**C**H), 81.4 (**C**HNO_2), 60.9 (**C**HN), 23.7 (CH_2), 23.1 (CH=C**C**H_3), 21.6 (Ar**C**H_3); **IR** (film/cm^{-1}): ν_{max} 2927, 1554, 1457, 1333, 1222, 1163, 1090, 814, 703; **MS** (ESI): *m/z* 371.0 [$(M - H)^-$]; **HRMS** (ESI): exact mass calculated for $C_{19}H_{20}N_2NaO_4S$ [$(M + Na)^+$], 395.1036; found 395.1034. The relative configurations

of diastereomers **386** and **386′** were assigned by analogy to the X-ray crystal structure of tetrahydropyridine **394g**.

5.3.3 Synthesis and Characterisation of β-Nitroamines 389 and 389′

Synthesis and characterisation of *tert*-butyl [(1*S*,2*R*)-2-nitro-1-phenylhex-5-yn-1-yl]carbamate (389) and *tert*-butyl [(1*S*,2*S*)-2-nitro-1-phenylhex-5-yn-1-yl]carbamate (389′)

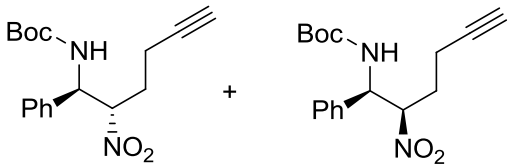


389 **389′**

To a stirred solution of nitroalkyne **383** (16.9 mg, 0.15 mmol) and *N*-Boc imine **112a** (20.5 mg, 0.10 mmol) in PhMe at –15 °C was added catalyst **388** (2.0 mg, 5.0 μmol, 5 mol%). The resulting solution was stirred at –15 °C for 24 h. The reaction mixture was directly purified by flash column chromatography on silica gel eluting with PE/EtOAc (9:1) to afford a mixture of diastereomers **389** and **389′** (28 mg, 87%). The dr and ee were determined by HPLC analysis using a Chiralpak AD-H column [hexane/*i*PrOH 90:10, flow rate 1.0 mL/min, λ = 210 nm]; dr 87:13; ***MAJOR:*** t_R major = 13.41 min, t_R minor = 16.40 min (92% ee), ***MINOR:*** t_R major = 14.64 min, t_R minor = 18.39 min (82% ee). Only the ^{1}H and ^{13}C NMR signals corresponding to the major diastereomer **389** are reported, all other characterisation data is for the mixture of diastereomers **389** and **389′**. **TLC**: R_f = 0.29 (PE/EtOAc 9:1, UV, $KMnO_4$); **Melting Point**: 113 - 116 °C; $\mathbf{[\alpha]_D^{25}}$ = +35.2 (c = 1.00, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.42 - 7.31 (m, 3H, Ar**H**), 7.28 - 7.22 (m, 2H, Ar**H**), 5.21 (br s, 2H, N**H** and C**H**N), 5.12 - 4.93 (m, 1H, C**H**NO_2), 2.42 - 2.14 (m, 3H, C**H**H′C**HH′**C≡CH), 2.08 - 1.97 (m, 2H, CH**H′**CHH′C≡C**H**), 1.44 (s, 9H, C(C**H$_3$**)$_3$);

^{13}C NMR (125 MHz, $CDCl_3$): δ_C 154.8 (**C**=O), 136.3 (Ar**C**), 129.1 (2 × Ar**C**H), 128.8 (Ar**C**H), 126.8 (2 × Ar**C**H), 89.6 (**C**HNO_2), 81.2 (**C**≡CH), 80.7 (**C**$(CH_3)_3$), 70.4 (C≡**C**H), 56.9 (**C**HN), 28.6 (**C**H_2CH_2C≡CH) 28.2 (C(**C**$H_3)_3$), 15.4 (**C**H_2C≡CH); **IR** (film/cm^{-1}): ν_{max} 3299, 2979, 1702, 1553, 1497, 1368, 1248, 1165, 1047; **MS** (ESI): *m/z* 341.1 [(M + Na)$^+$]; **HRMS** (ESI): exact mass calculated for $C_{17}H_{22}N_2NaO_4$ [(M + Na)$^+$], 341.1472; found 341.1474. The absolute configurations of diastereomers **389** and **389′** were assigned by analogy to the X-ray crystal structure of tetrahydropyridine **394g**.

Synthesis and characterisation of *tert*-butyl [(1*R*,2*S*)-2-nitro-1-phenylhex-5-yn-1-yl]carbamate (389a) and *tert*-butyl [(1*R*,2*R*)-2-nitro-1-phenylhex-5-yn-1-yl]carbamate (389a′)

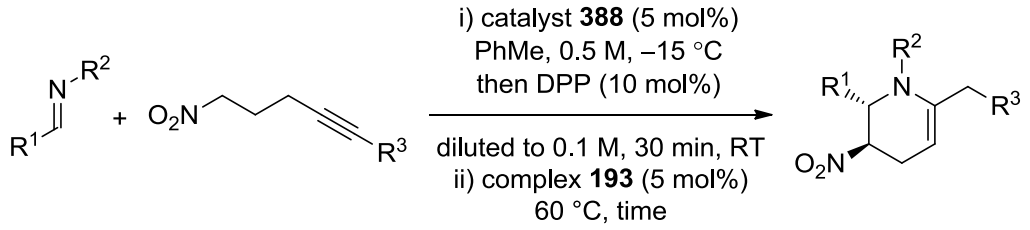


389a **389a′**

The opposite enantiomers **389a** and **389a′** were synthesised in an analogous manner to diastereomers **389** and **389′** using (*R*,*R*) catalyst **388**. The reaction mixture was directly purified by flash column chromatography on silica gel eluting with PE/EtOAc (9:1) to afford a mixture of diastereomers **389a** and **389a′** (26 mg, 83%) as a white solid. The dr and ee were determined by HPLC analysis using a Chiralpak AD-H column [hexane/*i*PrOH 90:10, flow rate 1.0 mL/min, λ = 210 nm]; dr 86:14; ***MAJOR:*** t_R minor = 13.33 min, t_R major = 15.99 min (93% ee), ***MINOR:*** t_R minor = 14.53 min, t_R major = 18.19 min (81% ee); **Melting Point**: 115 - 118 °C; **$[\alpha]_D^{25}$** = –37.7 (c = 1.00, $CHCl_3$). All other data was in agreement with that of diastereomers **389** and **389′**.

5.3.4 Synthesis and Characterisation of Substituted Tetrahydropyridines

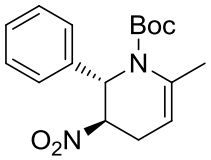
General Procedure F: Nitro-Mannich/hydroamination cascade to substituted 1,2,3,4-tetrahydropyridines



To a mixture of the corresponding imine (0.40 mmol, 1.0 equiv) and the corresponding nitroalkyne (0.60 mmol, 1.5 equiv) in PhMe (0.8 mL) at –15 °C in a sealable vial was added catalyst **388** (8.0 mg, 0.02 mmol, 5 mol%). The resulting mixture was stirred at –15 °C for the indicated time. Diphenylphosphate (10.1 mg, 0.04 mmol, 10 mol%) was added, the reaction mixture was diluted with PhMe (3.2 mL) and the resulting solution was stirred for 30 min at RT. Complex **193** (15.4 mg, 0.02 mmol, 5 mol%) was added and the resulting mixture was stirred at 60 °C for the indicated time. The reaction mixture was cooled to RT and then directly purified by flash column chromatography on silica gel to afford the desired tetrahydropyridines.

General procedure for racemic tetrahydropyridine synthesis: Racemic samples were prepared in an analogous manner to general procedure F, by replacing catalyst **388** with PS-BEMP (~2.2 mmol/g, 5 mol%) and stirring at RT for 6-24 h. The PS-BEMP was removed by filtration, washing with CH_2Cl_2 (3.0 mL) and the filtrate was concentrated under a stream of nitrogen. The residue was dissolved in PhMe (4.0 mL), complex **193** (15.4 mg, 0.02 mmol, 5 mol%) was added and the resulting mixture was stirred at 80 °C for 8-24 h. Direct purification on silica gel afforded the desired racemic tetrahydropyridines.

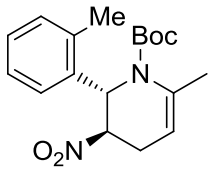
Synthesis and characterisation of *tert*-butyl (2*S*,3*R*)-6-methyl-3-nitro-2-phenyl-3,4-dihydropyridine-1(2*H*)-carboxylate (394a)



394a

Prepared according to general procedure F. *N*-Boc imine **112a** (82.1 mg, 0.40 mmol) was reacted with nitroalkyne **383** (67.9 mg, 0.60 mmol) for 24 h (step i) and 8 h (step ii) to afford compound **394a** (84 mg, 66%, dr >98:2) as a colourless oil, after purification by flash column chromatography on silica gel eluting with PE/Et_2O (9:1). On standing the product crystallised as a white solid. The ee was determined by HPLC analysis using a Chiralpak AD-H column [hexane/*i*PrOH 90:10, flow rate 1.0 mL/min, λ = 230 nm]; ***MAJOR:*** t_R major = 7.54 min, t_R minor = 20.02 min (92% ee); ***MINOR:*** t_R major = 4.08 min, t_R minor = 4.51 min (86% ee). **TLC**: R_f = 0.29 (PE/Et_2O 9:1, UV, $KMnO_4$); **Melting Point**: 80 - 83 °C; $\mathbf{[\alpha]_D^{25}}$ = +108.1 (c = 1.00, MeOH); **^{1}H NMR** (400 MHz, CD_3OD): δ_H 7.42 - 7.33 (m, 2H, Ar**H**), 7.33 - 7.25 (m, 3H, Ar**H**), 6.23 (br s, 1H, C**H**N), 5.39 - 5.33 (m, 1H, C**H**NO_2), 4.82 - 4.77 (m, 1H, C=C**H**), 2.85 - 2.75 (m, 1H, C**H**H′), 2.21 - 2.07 (m, 4H, CH=CC**H$_3$** and CH**H**′), 1.45 (s, 9H, C(C**H$_3$**)$_3$); **^{13}C NMR** (100 MHz, CD_3OD): δ_C 155.3 (**C**=O), 138.6 (Ar**C**), 135.6 (**C**=CH), 130.1 (2 × Ar**C**H), 129.0 (Ar**C**H), 126.8 (2 × Ar**C**H), 108.2 (C=**C**H), 83.5 (**C**HNO_2), 83.0 (**C**$(CH_3)_3$), 59.5 (**C**HN), 28.5 (C(**C**$H_3)_3$), 24.1 (**C**H_2), 23.0 (CH=C**C**H_3); **IR** (film/cm^{-1}): ν_{max} 2977, 1702, 1668, 1547, 1388, 1368, 1331, 1256, 1161, 1103, 751, 698; **MS** (ESI): *m/z* 341.2 [(M + Na)$^+$]; **HRMS** (ESI): exact mass calculated for $C_{17}H_{22}N_2NaO_4$ [(M + Na)$^+$], 341.1472; found 341.1455.

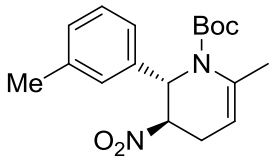
Synthesis and characterisation of *tert*-butyl (2*S*,3*R*)-6-methyl-2-(2-methyl phenyl)-3-nitro-3,4-dihydropyridine-1(2*H*)-carboxylate (394b)



394b

Prepared according to general procedure F. *N*-Boc imine **112b** (87.6 mg, 0.40 mmol) was reacted with nitroalkyne **383** (67.9 mg, 0.60 mmol) for 48 h (step i) and 10 h (step ii) to afford compound **394b** (65 mg, 49%, dr 97:3) as a colourless oil, after purification by flash column chromatography on silica gel eluting with PE/Et_2O (19:1). On standing the product crystallised as a white solid. The ee was determined by HPLC analysis using a Chiralpak AS-H column [hexane/*i*PrOH 99:1, flow rate 1.0 mL/min, λ = 230 nm]; ***MAJOR:*** t_R minor = 6.28 min, t_R major = 7.70 min (86% ee). **TLC**: R_f = 0.41 (PE/Et_2O 19:1, UV, $KMnO_4$); **Melting Point**: 94 - 97 °C; $\mathbf{[\alpha]_D^{25}}$ = –85.3 (c = 1.00, MeOH); **^{1}H NMR** (400 MHz, CD_3OD): δ_H 7.25 - 7.14 (m, 4H, Ar**H**), 6.35 - 6.31 (m, 1H, C**H**N), 4.97 - 4.92 (m, 1H, C**H**NO_2), 4.91 - 4.85 (m, 1H, C=C**H**), 2.89 - 2.78 (m, 1H, C**H**H′), 2.47 (s, 3H, ArC**H$_3$**), 2.27 - 2.14 (m, 4H, CH=CC**H$_3$** and CH**H′**), 1.37 (s, 9H, C(C**H$_3$**)$_3$); **^{13}C NMR** (100 MHz, CD_3OD): δ_C 154.9 (**C**=O), 138.1 (Ar**C**), 136.9 (Ar**C**), 136.0 (**C**=CH), 132.2 (Ar**C**H), 129.3 (Ar**C**H), 127.8 (Ar**C**H), 126.4 (Ar**C**H), 106.5 (C=**C**H), 82.9 (**C**$(CH_3)_3$), 82.1 (**C**HNO_2), 57.6 (**C**HN), 28.5 (C(**C**$H_3)_3$), 23.5 (**C**H_2), 23.3 (CH=C**C**H_3), 19.3 (Ar**C**H_3); **IR** (film/cm^{-1}): ν_{max} 2977, 1716, 1664, 1548, 1366, 1328, 1278, 1254, 1161, 1114, 1091, 756; **MS** (ESI): *m/z* 355.2 [(M + Na)$^+$]; **HRMS** (ESI): exact mass calculated for $C_{18}H_{24}N_2NaO_4$ [(M + Na)$^+$], 355.1628; found 355.1622.

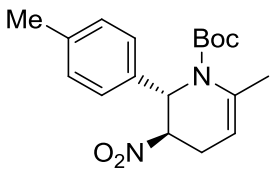
Synthesis and characterisation of *tert*-butyl (2*S*,3*R*)-6-methyl-2-(3-methyl phenyl)-3-nitro-3,4-dihydropyridine-1(2*H*)-carboxylate (394c)



394c

Prepared according to general procedure F. *N*-Boc imine **112c** (87.6 mg, 0.40 mmol) was reacted with nitroalkyne **383** (67.9 mg, 0.60 mmol) for 32 h (step i) and 15 h (step ii) to afford compound **394c** (96 mg, 72%, dr 98:2) as a white solid, after purification by flash column chromatography on silica gel eluting with PE/Et_2O (19:1). The ee was determined by HPLC analysis using a Chiralpak AD-H column [hexane/*i*PrOH 95:5, flow rate 1.0 mL/min, λ = 230 nm]; ***MAJOR:*** t_R major = 8.83 min, t_R minor = 18.17 min (91% ee), ***MINOR:*** t_R major = 4.12 min, t_R minor = 4.54 min (88% ee). **TLC**: R_f = 0.29 (PE/Et_2O 19:1, UV, $KMnO_4$); **Melting Point**: 61 - 64 °C; $\mathbf{[\alpha]_D^{25}}$ = +104.5 (c = 1.00, MeOH); **^{1}H NMR** (400 MHz, CD_3OD): δ_H 7.24 (t, *J* = 7.5 Hz, 1H, Ar**H**), 7.13 - 7.03 (m, 3H, Ar**H**), 6.18 (br s, 1H, C**H**N), 5.36 - 5.30 (m, 1H, C**H**NO_2), 4.82 - 4.75 (m, 1H, C=C**H**), 2.83 - 2.72 (m, 1H, C**H**H′), 2.33 (s, 3H, ArC$\mathbf{H_3}$), 2.19 - 2.07 (m, 4H, CH=CC$\mathbf{H_3}$ and CH**H′**), 1.45 (m, 9H, C(C$\mathbf{H_3}$)$_3$); **^{13}C NMR** (100 MHz, CD_3OD): δ_C 155.3 (**C**=O), 139.9 (Ar**C**), 138.6 (Ar**C**), 135.6 (**C**=CH), 130.0 (Ar**C**H), 129.6 (Ar**C**H), 127.4 (Ar**C**H), 123.8 (Ar**C**H), 108.3 (C=**C**H), 83.6 (**C**HNO_2), 83.0 (**C**$(CH_3)_3$), 59.5 (**C**HN), 28.5 (C(**C**$H_3)_3$), 24.1 (**C**H_2), 23.0 (CH=C**C**H_3), 21.7 (Ar**C**H_3); **IR** (film/cm^{-1}): ν_{max} 2977, 1703, 1668, 1548, 1387, 1367, 1334, 1255, 1558, 1106, 1084, 772; **MS** (ESI): *m/z* 355.2 [(M + Na)$^+$]; **HRMS** (ESI): exact mass calculated for $C_{18}H_{24}N_2NaO_4$ [(M + Na)$^+$], 355.1628; found 355.1629.

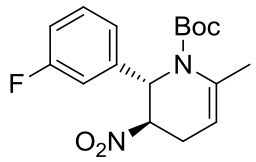
Synthesis and characterisation of *tert*-butyl (2*S*,3*R*)-6-methyl-2-(4-methyl phenyl)-3-nitro-3,4-dihydropyridine-1(2*H*)-carboxylate (394d)



394d

Prepared according to general procedure F. *N*-Boc imine **112d** (87.6 mg, 0.40 mmol) was reacted with nitroalkyne **383** (67.9 mg, 0.60 mmol) for 24 h (step i) and 15 h (step ii) to afford compound **394d** (38 mg, 29%) as a colourless oil, after purification by flash column chromatography on silica gel eluting with PE/Et_2O (19:1). The dr and ee were determined by HPLC analysis using a Chiralpak AD-H column [hexane/*i*PrOH 95:5, flow rate 1.0 mL/min, λ = 230 nm]; dr = 97:3, ***MAJOR:*** t_R major = 10.41 min, t_R minor = 18.24 min (85% ee), ***MINOR:*** t_R major = 4.57 min, t_R minor = 4.97 min (88% ee). **TLC**: R_f = 0.23 (PE/Et_2O 19:1, UV, $KMnO_4$); $[\alpha]_D^{25}$ = +93.8 (c = 1.00, MeOH); **^{1}H NMR** (400 MHz, CD_3OD): δ_H 7.21 - 7.14 (m, 4H, Ar**H**), 6.19 - 6.16 (m, 1H, C**H**N), 5.36 - 5.30 (m, 1H, C**H**NO_2), 4.82 - 4.76 (m, 1H, C=C**H**), 2.83 - 2.73 (m, 1H, C**H**H′), 2.32 (s, 3H, ArC**H**$_3$), 2.18 - 2.08 (m, 4H, CH=CC**H**$_3$ and CH**H′**), 1.45 (s, 9H, C(C**H**$_3$)$_3$); **^{13}C NMR** (100 MHz, CD_3OD): δ_C 155.3 (**C**=O), 138.9 (Ar**C**), 135.6 (**C**=CH or Ar**C**), 135.6 (**C**=CH or Ar**C**), 130.6 (2 × Ar**C**H), 126.7 (2 × Ar**C**H), 108.3 (C=**C**H), 83.6 (**C**HNO_2), 83.0 (**C**$(CH_3)_3$), 59.3 (**C**HN), 28.5 (C(**C**$H_3)_3$), 24.2 (**C**H_2), 23.0 (CH=C**C**H_3), 21.2 (Ar**C**H_3); **IR** (film/cm^{-1}): ν_{max} 2977, 1703, 1668, 1548, 1515, 1388, 1367, 1334, 1256, 1162, 1086, 818, 771; **MS** (ESI): *m/z* 355.2 [$(M + Na)^+$]; **HRMS** (ESI): exact mass calculated for $C_{18}H_{24}N_2NaO_4$ [$(M + Na)^+$], 355.1628; found 355.1622.

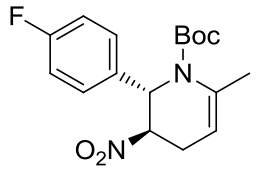
Synthesis and characterisation of *tert*-butyl (2*S*,3*R*)-2-(3-fluorophenyl)-6-methyl-3-nitro-3,4-dihydropyridine-1(2*H*)-carboxylate (394e)



394e

Prepared according to general procedure F. *N*-Boc imine **112e** (89.2 mg, 0.40 mmol) was reacted with nitroalkyne **383** (67.9 mg, 0.60 mmol) for 24 h (step i) and 15 h (step ii) to afford compound **394e** (75 mg, 56%, dr 98:2) as a pale yellow oil, after purification by flash column chromatography on silica gel eluting with PE/Et_2O (9:1). The ee was determined by HPLC analysis using a Chiralpak AD-H column [hexane/*i*PrOH 90:10, flow rate 1.0 mL/min, λ = 230 nm]; ***MAJOR:*** t_R major = 7.13 min, t_R minor = 16.48 min (93% ee), ***MINOR:*** t_R major = 4.20 min, t_R minor = 4.59 min (90% ee). **TLC**: R_f = 0.23 (PE/Et_2O 9:1, UV, $KMnO_4$); $\mathbf{[\alpha]_D^{25}}$ = +82.1 (c = 1.00, MeOH); **^{1}H NMR** (400 MHz, CD_3OD): δ_H 7.44 - 7.36 (m, 1H, Ar**H**), 7.17 - 7.10 (m, 1H, Ar**H**), 7.08 - 7.00 (m, 2H, Ar**H**), 6.24 (br s, 1H, C**H**N), 5.42 - 5.36 (m, 1H, C**H**NO_2), 4.84 - 4.79 (m, 1H, C=C**H**), 2.89 - 2.76 (m, 1H, C**H**H′), 2.22 - 2.09 (m, 4H, CH=CC**H$_3$** and CH**H**′), 1.46 (s, 9H, C(C**H$_3$**)$_3$); **^{13}C NMR** (100 MHz, CD_3OD): δ_C 164.7 (d, *J* = 245.0 Hz, Ar**C**F), 155.1 (**C**=O), 141.6 (d, *J* = 7.0 Hz, Ar**C**), 135.5 (**C**=CH), 132.0 (d, *J* = 9.0 Hz, Ar**C**H), 122.7 (d, *J* = 2.5 Hz, Ar**C**H), 115.8 (d, *J* = 21.0 Hz, Ar**C**H), 113.9 (d, *J* = 23.0 Hz, Ar**C**H), 108.2 (C=**C**H), 83.3 (**C**$(CH_3)_3$), 83.1 (**C**HNO_2), 59.0 (**C**HN), 28.5 (C(**C**H_3)$_3$), 24.1 (**C**H_2), 23.0 (CH=C**C**H_3); **^{19}F NMR** (376.5 MHz, CD_3OD): δ_F –114.0 (Ar**F**); **IR** (film/cm^{-1}): ν_{max} 2977, 2930, 1704, 1668, 1551, 1389, 1369, 1336, 1300, 1256, 1164, 1108, 784; **MS** (ESI): *m/z* 359.1 [(M + Na)$^+$]; **HRMS** (ESI): exact mass calculated for $C_{17}H_{21}FN_2NaO_4$ [(M + Na)$^+$], 359.1378; found 359.1374.

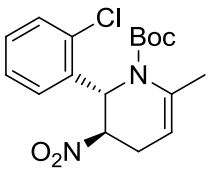
Synthesis and characterisation of *tert*-butyl (2*S*,3*R*)-2-(4-fluorophenyl)-6-methyl-3-nitro-3,4-dihydropyridine-1(2*H*)-carboxylate (394f)



394f

Prepared according to general procedure F. *N*-Boc imine **112f** (89.2 mg, 0.40 mmol) was reacted with nitroalkyne **383** (67.9 mg, 0.60 mmol) for 26 h (step i) and 3 h (step ii) to afford compound **394f** (65 mg, 49%, dr 97:3) as a colourless oil, after purification by flash column chromatography on silica gel eluting with PE/Et_2O (9:1). The ee was determined by HPLC analysis using a Chiralpak AD-H column [hexane/*i*PrOH 90:10, flow rate 1.0 mL/min, λ = 230 nm]; ***MAJOR:*** t_R major = 7.60 min, t_R minor = 20.58 min (92% ee), ***MINOR:*** t_R major = 4.17 min, t_R minor = 4.49 min (90% ee). **TLC**: R_f = 0.25 (PE/Et_2O 9:1, UV, $KMnO_4$); $\mathbf{[\alpha]_D^{25}}$ = +91.1 (c = 1.00, MeOH); **^{1}H NMR** (400 MHz, CD_3OD): δ_H 7.36 - 7.27 (m, 2H, Ar**H**), 7.11 (t, *J* = 8.5 Hz, 2H, Ar**H**), 6.21 (br s, 1H, C**H**N), 5.38 - 5.31 (m, 1H, C**H**NO_2), 4.81 (br s, 1H, C=C**H**), 2.87 - 2.76 (m, 1H, C**H**H′), 2.20 - 2.09 (m, 4H, CH=CC**H$_3$** and CH**H′**), 1.46 (s, 9H, C(C**H$_3$**)$_3$); **^{13}C NMR** (100 MHz, CD_3OD): δ_C 163.8 (d, *J* = 245.5 Hz, Ar**C**F), 155.2 (**C**=O), 135.5 (**C**=CH), 134.6 (d, *J* = 3.0 Hz, Ar**C**), 128.9 (d, *J* = 8.0 Hz, 2 × Ar**C**H), 116.8 (d, *J* = 22.5 Hz, 2 × Ar**C**H), 108.2 (C=**C**H), 83.3 (**C**HNO_2), 83.2 (**C**$(CH_3)_3$), 58.9 (**C**HN), 28.5 (C(**C**H_3)$_3$), 24.1 (**C**H_2), 23.0 (CH=C**C**H_3); **^{19}F NMR** (376.5 MHz, CD_3OD): δ_F –116.7 (Ar**F**); **IR** (film/cm^{-1}): ν_{max} 2978, 1703, 1668, 1549, 1510, 1387, 1368, 1335, 1228, 1160, 1108, 834; **MS** (ESI): *m/z* 359.1 [(M + Na)$^+$]; **HRMS** (ESI): exact mass calculated for $C_{17}H_{21}FN_2NaO_4$ [(M + Na)$^+$], 359.1378; found 359.1376.

Synthesis and characterisation of *tert*-butyl (2*S*,3*R*)-2-(2-chlorophenyl)-6-methyl-3-nitro-3,4-dihydropyridine-1(2*H*)-carboxylate (394g)

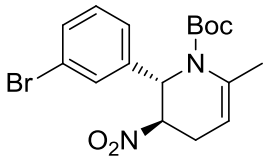


394g

Prepared according to general procedure F. *N*-Boc imine **112g** (95.9 mg, 0.40 mmol) was reacted with nitroalkyne **383** (67.9 mg, 0.60 mmol) for 48 h (step i) and 28 h (step ii) to afford compound **394g** (72 mg, 51%, dr 94:6) as a pale yellow oil, after purification by flash column chromatography on silica gel eluting with PE/Et_2O (19:1). On standing the product crystallised as an off-white solid. The ee was determined by HPLC analysis using a Chiralpak AD-H column [hexane/*i*PrOH 99:1, flow rate 1.0 mL/min, λ = 230 nm]; ***MAJOR:*** t_R minor = 6.74 min, t_R major = 7.18 min (87% ee). **TLC**: R_f = 0.25 (PE/Et_2O 19:1, UV, $KMnO_4$); **Melting Point**: 94 - 96 °C; $\mathbf{[\alpha]_D^{25}}$ = –62.3 (c = 1.00, MeOH); **^{1}H NMR** (400 MHz, CD_3OD): δ_H 7.50 - 7.45 (m, 1H, Ar**H**), 7.38 - 7.28 (m, 3H, Ar**H**), 6.55 - 6.52 (m, 1H, C**H**N), 5.14 - 5.09 (m, 1H, C**H**NO_2), 4.90 - 4.82 (m, 1H, C=C**H** superimposed by residual solvent), 2.93 - 2.82 (m, 1H, C**H**H′), 2.29 - 2.25 (m, 3H, CH=CC$\mathbf{H_3}$), 2.19 - 2.08 (m, 1H, CH**H′**), 1.39 (s, 9H, C(C$\mathbf{H_3}$)$_3$); **^{13}C NMR** (100 MHz, CD_3OD): δ_C 154.6 (**C**=O), 136.9 (Ar**C**), 136.6 (**C**=CH), 133.0 (Ar**C**), 131.2 (Ar**C**H), 131.0 (Ar**C**H), 129.0 (Ar**C**H), 128.5 (Ar**C**H), 106.0 (C=**C**H), 83.2 (**C**$(CH_3)_3$), 81.0 (**C**HNO_2), 57.7 (**C**HN), 28.5 (C(**C**$H_3)_3$), 23.7 (**C**H_2), 23.2 (CH=C**C**H_3); **IR** (film/cm^{-1}): ν_{max} 2977, 1719, 1664, 1548, 1391, 1367, 1328, 1297, 1160, 1103, 754; **MS** (ESI): *m/z* 375.1 and 377.1 [(M + Na)$^+$]; **HRMS** (ESI): exact mass calculated for $C_{17}H_{21}ClN_2NaO_4$ [(M + Na)$^+$], 375.1082 and 377.1054; found 375.1082 and 377.1059. The absolute configuration of tetrahydropyridine **394g** was determined to be (2*S*,3*R*) by single crystal X-ray

diffraction analysis after crystallisation by slow evaporation of MeOH. All other tetrahydropyridine structures were assigned by analogy.

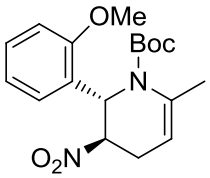
Synthesis and characterisation of *tert*-butyl (2*S*,3*R*)-2-(3-bromophenyl)-6-methyl-3-nitro-3,4-dihydropyridine-1(2*H*)-carboxylate (394h)



394h

Prepared according to general procedure F. *N*-Boc imine **112h** (113.6 mg, 0.40 mmol) was reacted with nitroalkyne **383** (67.9 mg, 0.60 mmol) for 24 h (step i) and 7 h (step ii) to afford compound **394h** (100 mg, 63%, dr 98:2) as a colourless oil, after purification by flash column chromatography on silica gel eluting with PE/Et_2O (9:1). The ee was determined by HPLC analysis using a Chiralpak AD-H column [hexane/*i*PrOH 90:10, flow rate 1.0 mL/min, λ = 230 nm]; ***MAJOR:*** t_R major = 7.31 min, t_R minor = 12.40 min (96% ee); ***MINOR:*** t_R major = 4.28 min, t_R minor = 4.60 min (93% ee). **TLC**: R_f = 0.24 (PE/Et_2O 9:1, UV, $KMnO_4$); $\mathbf{[\alpha]_D^{25}}$ = +92.0 (c = 1.00, MeOH); **^{1}H NMR** (400 MHz, CD_3OD): δ_H 7.48 - 7.40 (m, 2H, Ar**H**), 7.31 - 7.23 (m, 2H, Ar**H**), 6.24 - 6.18 (m, 1H, C**H**N), 5.39 - 5.31 (m, 1H, C**H**NO_2), 4.83 - 4.76 (m, 1H, C=C**H**), 2.87 - 2.76 (m, 1H, C**H**H′), 2.19 - 2.07 (m, 4H, CH=CC**H$_3$** and CH**H′**), 1.46 (s, 9H, C(C**H$_3$**)$_3$); **^{13}C NMR** (100 MHz, CD_3OD): δ_C 155.1 (**C**=O), 141.2 (Ar**C**), 135.4 (**C**=CH), 132.1 (Ar**C**H), 131.9 (Ar**C**H), 130.0 (Ar**C**H), 125.8 (Ar**C**H), 123.9 (Ar**C**), 108.2 (C=**C**H), 83.3 (**C**$(CH_3)_3$), 83.0 (**C**HNO_2), 58.9 (**C**HN), 28.5 (C(**C**$H_3)_3$), 24.1 (**C**H_2), 23.0 (CH=C**C**H_3); **IR** (film/cm^{-1}): ν_{max} 2977, 1704, 1668, 1550, 1386, 1368, 1336, 1162, 1108, 766; **MS** (ESI): *m/z* 419.1 and 421.0 [(M + Na)$^+$]; **HRMS** (ESI): exact mass calculated for $C_{17}H_{21}BrN_2NaO_4$ [(M + Na)$^+$], 419.0577 and 421.0557; found 419.0579 and 421.0558.

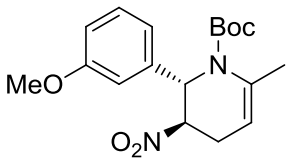
Synthesis and characterisation of *tert*-butyl (2*S*,3*R*)-2-(2-methoxyphenyl)-6-methyl-3-nitro-3,4-dihydropyridine-1(2*H*)-carboxylate (394i)



394i

Prepared according to general procedure F. *N*-Boc imine **112i** (94.1 mg, 0.40 mmol) was reacted with nitroalkyne **383** (67.9 mg, 0.60 mmol) for 96 h (step i) and 24 h (step ii) to afford compound **394i** (61 mg, 44%, dr >98:2) as a white solid, after purification by flash column chromatography on silica gel eluting with PE/Et_2O (9:1). The ee was determined by HPLC analysis using a Chiralpak AD-H column [hexane/*i*PrOH 99:1, flow rate 1.0 mL/min, λ = 230 nm]; ***MAJOR:*** t_R major = 8.62 min, t_R minor = 10.29 min (72% ee). **TLC**: R_f = 0.21 (PE/Et_2O 9:1, UV, $KMnO_4$); **Melting Point**: 101 - 103 °C; **$[\alpha]_D^{25}$** = +16.3 (c = 1.00, MeOH); **^{1}H NMR** (400 MHz, $(CD_3)_2CO$): δ_H 7.36 - 7.29 (m, 1H, Ar**H**), 7.12 - 7.04 (m, 2H, Ar**H**), 6.94 (td, *J* = 7.5, 1.0 Hz, 1H, Ar**H**), 6.49 - 6.44 (m, 1H, C**H**N), 5.30 - 5.25 (m, 1H, C**H**NO_2), 4.80 - 4.75 (m, 1H, C=C**H**), 3.93 (s, 3H, ArOC**H_3**), 2.83 - 2.73 (m, 1H, C**H**H′), 2.27 - 2.21 (m, 3H, CH=C**H_3**), 2.10 - 1.99 (m, 1H, CH**H′**), 1.40 (s, 9H, C(C**H_3**)$_3$); **^{13}C NMR** (100 MHz, $(CD_3)CO$): δ_C 157.3 (Ar**C**), 154.4 (**C**=O), 136.3 (**C**=CH), 130.6 (Ar**C**H), 127.7 (Ar**C**H), 126.8 (Ar**C**H), 122.0 (Ar**C**H), 112.3 (Ar**C**H), 106.1 (C=**C**H), 82.2 (**C**$(CH_3)_3$), 81.4 (**C**HNO_2), 56.6 (**C**HN), 55.8 (ArO**C**H_3), 28.8 (C(**C**$H_3)_3$), 24.5 (**C**H_2), 23.8 (CH=C**C**H_3); **IR** (film/cm^{-1}): ν_{max} 2972, 1717, 1549, 1488, 1390, 1370, 1328, 1279, 1241, 1160, 1113, 1084, 757; **MS** (ESI): *m/z* 371.1 [(M + Na)$^+$]; **HRMS** (ESI): exact mass calculated for $C_{18}H_{24}N_2NaO_5$ [(M + Na)$^+$], 371.1577; found 371.1586.

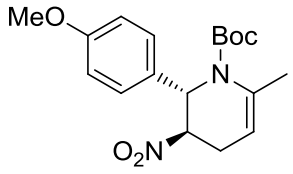
Synthesis and characterisation of *tert*-butyl (2*S*,3*R*)-2-(3-methoxyphenyl)-6-methyl-3-nitro-3,4-dihydropyridine-1(2*H*)-carboxylate (394j)



394j

Prepared according to general procedure F. *N*-Boc imine **112j** (94.1 mg, 0.40 mmol) was reacted with nitroalkyne **383** (67.9 mg, 0.60 mmol) for 24 h (step i) and 6 h (step ii) to afford compound **394j** (75 mg, 54%, dr 98:2) as a white solid, after purification by flash column chromatography on silica gel eluting with PE/Et_2O (9:1). The ee was determined by HPLC analysis using a Chiralpak AD-H column [hexane/*i*PrOH 90:10, flow rate 1.0 mL/min, λ = 230 nm]; ***MAJOR:*** t_R major = 9.73 min, t_R minor = 14.69 min (93% ee), ***MINOR:*** t_R major = 4.59 min, t_R minor = 4.86 min (84% ee). **TLC**: R_f = 0.18 (PE/Et_2O 9:1, UV, $KMnO_4$); **Melting Point**: 71 - 73 °C; $\mathbf{[\alpha]_D^{25}}$ = +107.6 (c = 1.00, MeOH); **^{1}H NMR** (400 MHz, CD_3OD): δ_H 7.29 (t, *J* = 8.0 Hz, 1H, Ar**H**), 6.89 - 6.79 (m, 3H, Ar**H**), 6.20 (br s, 1H, C**H**N), 5.38 - 5.32 (m, 1H, C**H**NO_2), 4.83 - 4.77 (m, 1H, C=C**H**), 3.78 (s, 3H, OC$\mathbf{H_3}$), 2.84 - 2.74 (m, 1H, C**H**H′), 2.20 - 2.10 (m, 4H, CH=CC$\mathbf{H_3}$ and CH**H**′), 1.46 (s, 9H, C(C$\mathbf{H_3}$)$_3$); **^{13}C NMR** (100 MHz, CD_3OD): δ_C 161.7 (Ar**C**), 155.3 (**C**=O), 140.2 (Ar**C**), 135.6 (**C**=CH), 131.2 (Ar**C**H), 118.9 (Ar**C**H), 114.1 (Ar**C**H), 112.8 (Ar**C**H), 108.3 (C=**C**H), 83.5 (**C**HNO_2), 83.1 (**C**$(CH_3)_3$), 59.4 (**C**HN), 55.8 (ArO**C**H_3), 28.5 (C(**C**$H_3)_3$), 24.2 (**C**H_2), 23.0 (CH=C**C**H_3); **IR** (film/cm^{-1}): ν_{max} 2976, 1705, 1668, 1550, 1389, 1369, 1338, 1254, 1162, 1107, 774; **MS** (ESI): *m/z* 371.1 [(M + Na)$^+$]; **HRMS** (ESI): exact mass calculated for $C_{18}H_{24}N_2NaO_5$ [(M + Na)$^+$], 371.1577; found 371.1583.

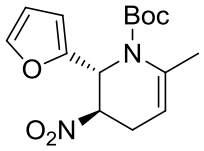
Synthesis and characterisation of *tert*-butyl (2*S*,3*R*)-2-(4-methoxyphenyl)-6-methyl-3-nitro-3,4-dihydropyridine-1(2*H*)-carboxylate (394k)



394k

Prepared according to general procedure F. *N*-Boc imine **112k** (94.1 mg, 0.40 mmol) was reacted with nitroalkyne **383** (67.9 mg, 0.60 mmol) for 24 h (step i) and 6 h (step ii) to afford compound **394k** (36 mg, 26%) as a colourless oil, after purification by flash column chromatography on silica gel eluting with PE/Et_2O (9:1). The dr and ee was determined by HPLC analysis using a Chiralpak AD-H column [hexane/*i*PrOH 90:10, flow rate 1.0 mL/min, λ = 230 nm]; dr 94:6, ***MAJOR:*** t_R major = 9.34 min, t_R minor = 20.13 min (82% ee), ***MINOR:*** t_R major = 5.02 min, t_R minor = 5.32 min (82% ee). **TLC**: R_f = 0.11 (PE/Et_2O 9:1, UV, $KMnO_4$); $\mathbf{[\alpha]_D^{25}}$ = +74.8 (c = 1.00, MeOH); **^{1}H NMR** (400 MHz, CD_3OD): δ_H 7.22 - 7.18 (m, 2H, Ar**H**), 6.94 - 6.90 (m, 2H, Ar**H**), 6.17 - 6.14 (m, 1H, C**H**N), 5.33 - 5.28 (m, 1H, C**H**NO_2), 4.83 - 4.79 (m, 1H, C=C**H**), 3.78 (s, 3H, OC**H**$_3$), 2.83 - 2.73 (m, 1H, C**H**H′), 2.21 - 2.11 (m, 4H, CH=CC**H**$_3$ and CH**H′**), 1.45 (s, 9H, C(C**H**$_3$)$_3$); **^{13}C NMR** (100 MHz, CD_3OD): δ_C 160.8 (Ar**C**), 155.3 (**C**=O), 135.5 (**C**=CH), 130.4 (Ar**C**), 128.0 (2 × Ar**C**H), 115.4 (2 × Ar**C**H), 108.4 (C=**C**H), 83.6 (**C**HNO_2), 83.0 (**C**(CH_3)$_3$), 59.1 (**C**HN), 55.9 (ArO**C**H_3), 28.5 (C(**C**H_3)$_3$), 24.1 (**C**H_2), 23.0 (CH=C**C**H_3); **IR** (film/cm^{-1}): ν_{max} 2976, 1703, 1669, 1548, 1514, 1389, 1368, 1335, 1282, 1250, 1162, 1086, 1033, 830; **MS** (ESI): *m/z* 371.1 [(M + Na)$^+$]; **HRMS** (ESI): exact mass calculated for $C_{18}H_{24}N_2NaO_5$ [(M + Na)$^+$], 371.1577; found 371.1576.

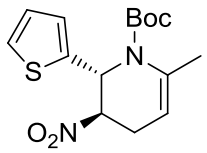
Synthesis and characterisation of *tert*-butyl (2*R*,3*R*)-2-(2-furyl)-6-methyl-3-nitro-3,4-dihydropyridine-1(2*H*)-carboxylate (394l)



394l

Prepared according to general procedure F. *N*-Boc imine **112l** (78.1 mg, 0.40 mmol) was reacted with nitroalkyne **383** (67.9 mg, 0.60 mmol) for 30 h (step i) and 24 h (step ii) to afford compound **394l** (36 mg, 29%, dr 92:8) as a white solid, after purification by flash column chromatography on silica gel eluting with PE/Et_2O (9:1). The ee was determined by HPLC analysis using a Chiralpak AD-H column [hexane/*i*PrOH 90:10, flow rate 1.0 mL/min, λ = 230 nm]; ***MAJOR:*** t_R major = 6.22 min, t_R minor = 6.87 min (83% ee), ***MINOR:*** t_R major = 4.47 min, t_R minor = 5.00 min (81% ee). **TLC**: R_f = 0.30 (PE/Et_2O 9:1, UV, $KMnO_4$); **Melting Point**: 68 - 70 °C; $\mathbf{[\alpha]_D^{25}}$ = +89.9 (c = 1.00, MeOH); $^{\mathbf{1}}$**H NMR** (400 MHz, CD_3OD): δ_H 7.50 - 7.46 (m, 1H, furyl **H**), 6.39 (dd, *J* = 3.5, 2.0 Hz, 1H, furyl **H**), 6.28 - 6.25 (m, 1H, furyl **H**), 6.25 - 6.22 (m, 1H, C**H**N), 5.37 - 5.32 (m, 1H, C**H**NO_2), 4.91 - 4.86 (m, 1H, C=C**H**), 2.88 - 2.79 (m, 1H, C**H**H′), 2.41 - 2.30 (m, 1H, CH**H′**), 2.11 - 2.06 (m, 3H, CH=CC$\mathbf{H_3}$), 1.48 (s, 9H, C(C$\mathbf{H_3}$)$_3$); $^{\mathbf{13}}$**C NMR** (100 MHz, CD_3OD): δ_C 154.8 (**C**=O), 151.5 (furyl **C**), 143.9 (furyl **C**H), 135.1 (**C**=CH), 111.8 (furyl **C**H), 109.0 (C=**C**H), 108.3 (furyl **C**H), 83.3 (**C**$(CH_3)_3$), 82.0 (**C**HNO_2), 54.9 (**C**HN), 28.5 (C(**C**$H_3)_3$), 24.9 (**C**H_2), 22.7 (CH=C**C**H_3); **IR** (film/cm^{-1}): ν_{max} 2978, 1703, 1671, 1551, 1370, 1338, 1256, 1164, 1090, 1012, 739; **MS** (ESI): *m/z* 331.1 [$(M + Na)^+$]; **HRMS** (ESI): exact mass calculated for $C_{15}H_{20}N_2NaO_5$ [$(M + Na)^+$], 331.1264; found 331.1275.

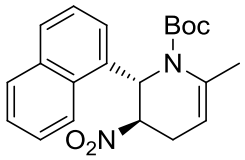
Synthesis and characterisation of *tert*-butyl (2*R*,3*R*)-6-methyl-3-nitro-2-(2-thienyl)-3,4-dihydropyridine-1(2*H*)-carboxylate (394m)



394m

Prepared according to general procedure F. *N*-Boc imine **112m** (84.5 mg, 0.40 mmol) was reacted with nitroalkyne **383** (67.9 mg, 0.60 mmol) for 24 h (step i) and 24 h (step ii) to afford compound **394m** (41 mg, 31%, dr 95:5) as a pale yellow oil, after purification by flash column chromatography on silica gel eluting with PE/Et_2O (9:1). The ee was determined by HPLC analysis using a Chiralpak AD-H column [hexane/*i*PrOH 95:5, flow rate 1.0 mL/min, λ = 230 nm]; ***MAJOR:*** t_R major = 10.16 min, t_R minor = 23.69 min (88% ee), ***MINOR:*** t_R major = 5.18 min, t_R minor = 6.39 min (88% ee). **TLC**: R_f = 0.28 (PE/Et_2O 9:1, UV, $KMnO_4$); $\mathbf{[\alpha]_D^{25}}$ = +54.1 (c = 1.00, MeOH); **^{1}H NMR** (400 MHz, CD_3OD): δ_H 7.33 (dd, *J* = 5.0, 1.0 Hz, 1H, thienyl **H**), 7.07 - 7.03 (m, 1H, thienyl **H**), 6.99 (dd, *J* = 5.0, 3.5 Hz, 1H, thienyl **H**), 6.41 - 6.37 (m, 1H, C**H**N), 5.37 - 5.32 (m, 1H, C**H**NO_2), 4.92 - 4.88 (m, 1H, C=C**H**), 2.90 - 2.81 (m, 1H, C**H**H′), 2.52 - 2.42 (m, 1H, CH**H′**), 2.10 - 2.07 (m, 3H, CH=CC$\mathbf{H_3}$), 1.48 (s, 9H, C(C$\mathbf{H_3}$)$_3$); **^{13}C NMR** (100 MHz, CD_3OD): δ_C 154.8 (**C**=O), 142.3 (thienyl **C**), 135.2 (**C**=CH), 128.1 (thienyl **C**H), 126.2 (thienyl **C**H), 126.0 (thienyl **C**H), 109.3 (C=**C**H), 83.5 (**C**HNO_2), 83.3 (**C**$(CH_3)_3$), 56.4 (**C**HN), 28.5 (C(**C**$H_3)_3$), 24.6 (**C**H_2), 22.8 (CH=C**C**H_3); **IR** (film/cm^{-1}): ν_{max} 2977, 1702, 1669, 1550, 1368, 1335, 1256, 1161, 1089, 768, 704; **MS** (ESI): *m/z* 347.1 [$(M + Na)^+$]; **HRMS** (ESI): exact mass calculated for $C_{15}H_{20}N_2NaO_4S$ [$(M + Na)^+$], 347.1036; found 347.1035.

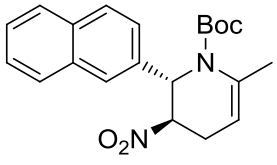
Synthesis and characterisation of *tert*-butyl (2*S*,3*R*)-6-methyl-2-(1-naphthyl)-3-nitro-3,4-dihydropyridine-1(2*H*)-carboxylate (394n)



394n

Prepared according to general procedure F. *N*-Boc imine **112n** (102.1 mg, 0.40 mmol) was reacted with nitroalkyne **383** (67.9 mg, 0.60 mmol) for 48 h (step i) and 24 h (step ii) to afford compound **394n** (81 mg, 55%, dr >98:2) as a colourless oil, after purification by flash column chromatography on silica gel eluting with PE/Et_2O (19:1). On standing the product crystallised into a white solid. The ee was determined by HPLC analysis using a Chiralpak AD-H column [hexane/*i*PrOH 98:2, flow rate 1.0 mL/min, λ = 230 nm]; ***MAJOR:*** t_R major = 7.74 min, t_R minor = 9.57 min (88% ee). **TLC**: R_f = 0.25 (PE/Et_2O 19:1, UV, $KMnO_4$); **Melting Point**: 127 - 130 °C; $\mathbf{[\alpha]_D^{25}}$ = –96.1 (c = 1.00, $(CH_3)_2CO$); **^{1}H NMR** (400 MHz, $(CD_3)_2CO$): δ_H 8.25 (d, *J* = 8.5 Hz, 1H, Ar**H**), 7.97 (d, *J* = 8.0 Hz, 1H, Ar**H**), 7.89 (d, *J* = 8.0 Hz, 1H, Ar**H**), 7.68 - 7.62 (m, 1H, Ar**H**), 7.58 - 7.52 (m, 1H, Ar**H**), 7.50 - 7.40 (m, 2H, Ar**H**), 7.02 (br s, 1H, C**H**N), 5.29 - 5.25 (m, 1H, C**H**NO_2), 4.87 - 4.83 (m, 1H, C=C**H**), 2.85 - 2.75 (m, 1H, C**H**H′), 2.30 - 2.27 (m, 3H, CH=CC$\mathbf{H_3}$), 2.14 - 2.04 (m, 1H, CH**H**′), 1.29 (s, 9H, C(C$\mathbf{H_3}$)$_3$); **^{13}C NMR** (100 MHz, CD_3OD): δ_C 154.4 (**C**=O), 136.7 (Ar**C**), 135.5 (**C**=CH), 134.8 (Ar**C**), 131.1 (Ar**C**), 130.7 (Ar**C**H), 130.3 (Ar**C**H), 128.5 (Ar**C**H), 127.4 (Ar**C**H), 126.9 (Ar**C**H), 124.7 (Ar**C**H), 123.4 (Ar**C**H), 105.7 (C=**C**H), 82.6 (**C**HNO_2), 82.5 (**C**$(CH_3)_3$), 57.3 (**C**HN), 28.7 (C(**C**$H_3)_3$), 23.9 (C=C**C**H_3 and **C**H_2); **IR** (film/cm^{-1}): ν_{max} 2964, 1693, 1655, 1546, 1367, 1313, 1259, 1157, 1086, 1015, 800, 772; **MS** (ESI): *m/z* 391.2 [(M + Na)$^+$]; **HRMS** (ESI): exact mass calculated for $C_{21}H_{24}N_2NaO_4$ [(M + Na)$^+$], 391.1628; found 391.1629.

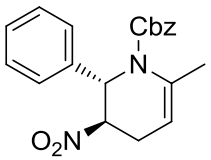
Synthesis and characterisation of *tert*-butyl (2*S*,3*R*)-6-methyl-2-(2-naphthyl)-3-nitro-3,4-dihydropyridine-1(2*H*)-carboxylate (394o)



394o

Prepared according to general procedure F. *N*-Boc imine **112o** (102.1 mg, 0.40 mmol) was reacted with nitroalkyne **383** (67.9 mg, 0.60 mmol) for 24 h (step i) and 48 h (step ii) to afford compound **394o** (91 mg, 62%, dr >98:2) as a pale yellow oil, after purification by flash column chromatography on silica gel eluting with PE/Et_2O (9:1). The ee was determined by HPLC analysis using a Chiralpak AD-H column [hexane/*i*PrOH 95:5, flow rate 1.0 mL/min, λ = 230 nm]; ***MAJOR:*** t_R major = 14.28 min, t_R minor = 28.78 min (86% ee), ***MINOR:*** t_R major = 5.88 min, t_R minor = 6.39 min (84% ee). **TLC**: R_f = 0.21 (PE/Et_2O 9:1, UV, $KMnO_4$); $\mathbf{[\alpha]_D^{25}}$ = +107.4 (c = 1.00, MeOH); **^{1}H NMR** (400 MHz, CD_3OD): δ_H 7.84 - 7.72 (m, 3H, Ar**H**), 7.65 (s, 1H, Ar**H**), 7.46 - 7.32 (m, 3H, Ar**H**), 6.33 (br s, 1H, C**H**N), 5.43 - 5.37 (m, 1H, C**H**NO_2), 4.76 - 4.70 (m, 1H, C=C**H**), 2.79 - 2.68 (m, 1H, C**H**H′), 2.18 (s, 3H, CH=CC**H$_3$**), 2.11 - 2.00 (m, 1H, CH**H**′), 1.40 (s, 9H, C(C**H$_3$**)$_3$); **^{13}C NMR** (100 MHz, CD_3OD): δ_C 155.3 (**C**=O), 135.9 (Ar**C**), 135.6 (**C**=CH), 134.9 (Ar**C**), 134.4 (Ar**C**), 129.9 (Ar**C**H), 129.1 (Ar**C**H), 128.8 (Ar**C**H), 127.7 (Ar**C**H), 127.5 (Ar**C**H), 125.8 (Ar**C**H), 124.6 (Ar**C**H), 108.4 (C=**C**H), 83.5 (**C**HNO_2), 83.1 (**C**$(CH_3)_3$), 59.6 (**C**HN), 28.5 (C(**C**H_3)$_3$), 24.2 (**C**H_2), 23.0 (CH=C**C**H_3); **IR** (film/cm^{-1}): ν_{max} 2976, 1702, 1667, 1548, 1388, 1368, 1335, 1253, 1158, 1106, 1048, 772; **MS** (ESI): *m/z* 391.1 [(M + Na)$^+$]; **HRMS** (ESI): exact mass calculated for $C_{21}H_{24}N_2NaO_4$ [(M + Na)$^+$], 391.1628; found 391.1629.

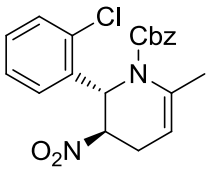
Synthesis and characterisation of benzyl (2*S*,3*R*)-6-methyl-3-nitro-2-phenyl-3,4-dihydropyridine-1(2*H*)-carboxylate (402a)



402a

Prepared according to general procedure F. *N*-Cbz imine **401a** (95.7 mg, 0.40 mmol) was reacted with nitroalkyne **383** (67.9 mg, 0.60 mmol) for 24 h (step i) and 16 h (step ii) to afford compound **402a** (70 mg, 50%, dr >98:2) as a colourless oil, after purification by flash column chromatography on silica gel eluting with PE/Et_2O (9:1). The ee was determined by HPLC analysis using a Chiralpak AD-H column [hexane/*i*PrOH 90:10, flow rate 1.0 mL/min, λ = 230 nm]; ***MAJOR:*** t_R major = 24.89 min, t_R minor = 52.11 min (93% ee), ***MINOR:*** t_R major = 8.74 min, t_R minor = 10.49 min (92% ee). **TLC**: R_f = 0.10 (PE/Et_2O 9:1, UV, $KMnO_4$); $\mathbf{[\alpha]_D^{25}}$ = +99.7 (c = 1.00, MeOH); **^{1}H NMR** (400 MHz, CD_3OD): δ_H 7.39 - 7.22 (m, 10H, Ar**H**), 6.31 (br s, 1H, C**H**N), 5.37 - 5.30 (m, 1H, C**H**NO_2), 5.17 (d, *J* = 12.5 Hz, 1H, C**H**H′CO_2), 5.10 (d, *J* = 12.5 Hz, 1H, CH**H′**CO_2), 4.81 (br s, 1H, C=C**H**), 2.85 - 2.74 (m, 1H, C**H**H′$CHNO_2$), 2.20 - 2.06 (m, 4H, CH=CC$\mathbf{H_3}$ and CH**H′**$CHNO_2$); **^{13}C NMR** (100 MHz, CD_3OD): δ_C 156.1 (**C**=O), 138.3 (Ar**C**), 137.4 (Ar**C**), 135.4 (**C**=CH), 130.1 (2 × Ar**C**H), 129.7 (2 × Ar**C**H), 129.4 (Ar**C**H), 129.1 (2 × Ar**C**H), 129.1 (Ar**C**H), 126.8 (2 × Ar**C**H), 108.5 (C=**C**H), 83.3 (**C**HNO_2), 69.2 (**C**H_2CO_2), 59.5 (**C**HN), 24.1 (**C**H_2CHNO_2), 22.9 (CH=C**C**H_3); **IR** (film/cm^{-1}): ν_{max} 1712, 1669, 1547, 1397, 1323, 1269, 1141, 1090, 740, 697; **MS** (ESI): *m/z* 375.1 [$(M + Na)^+$]; **HRMS** (ESI): exact mass calculated for $C_{20}H_{20}N_2NaO_4$ [$(M + Na)^+$], 375.1315; found 375.1318.

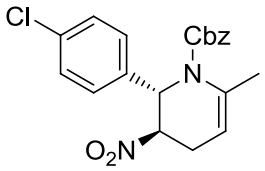
Synthesis and characterisation of benzyl (2*S*,3*R*)-2-(2-chlorophenyl)-6-methyl-3-nitro-3,4-dihydropyridine-1(2*H*)-carboxylate (402b)



402b

Prepared according to general procedure F. *N*-Cbz imine **401b** (109.5 mg, 0.40 mmol) was reacted with nitroalkyne **383** (67.9 mg, 0.60 mmol) for 32 h (step i) and 24 h (step ii) to afford compound **402b** (71 mg, 46%, dr >98:2) as a colourless oil, after purification by flash column chromatography on silica gel eluting with PE/Et_2O (8:1). The ee was determined by HPLC analysis using a Chiralpak IA column [hexane/*i*PrOH 90:10, flow rate 1.0 mL/min, λ = 230 nm]; t_R minor = 9.85 min, t_R major = 10.58 min (91% ee). **TLC**: R_f = 0.28 (PE/Et_2O 8:1, UV, $KMnO_4$); **$[\alpha]_D^{25}$** = –48.6 (c = 1.00, MeOH); **^{1}H NMR** (400 MHz, CD_3OD): δ_H 7.46 - 7.40 (m, 1H, Ar**H**), 7.34 - 7.24 (m, 6H, Ar**H**), 7.22 - 7.16 (m, 2H, Ar**H**), 6.61 (t, *J* = 2.0 Hz, 1H, C**H**N), 5.15 - 5.08 (m, 2H, C**H**NO_2 and C**H**H′CO_2), 5.07 - 5.04 (d, *J* = 12.5 Hz, 1H, CH**H′**CO_2), 4.89 - 4.84 (m, 1H, C=C**H**), 2.92 - 2.80 (m, 1H, C**H**H′$CHNO_2$), 2.28 - 2.24 (m, 3H, CH=CC**H$_3$**), 2.16 - 2.06 (m, 1H, CH**H′**$CHNO_2$); **^{13}C NMR** (100 MHz, CD_3OD): δ_C 155.5 (**C**=O), 137.2 (Ar**C**), 136.4 (**C**=CH), 133.0 (Ar**C**), 131.4 (Ar**C**), 131.1 (Ar**C**H), 129.6 (2 × Ar**C**H), 129.3 (2 × Ar**C**H), 129.0 (Ar**C**H), 128.9 (2 × Ar**C**H), 128.4 (Ar**C**H), 106.5 (C=**C**H), 80.8 (C**H**NO_2), 69.2 (**C**H_2CO_2), 57.7 (**C**HN), 23.6 (**C**H_2CHNO_2), 23.2 (CH=C**C**H_3); **IR** (film/cm^{-1}): ν_{max} 2929, 1724, 1667, 1548, 1396, 1323, 1294, 1266, 1230, 1087, 1052, 752; **MS** (ESI): *m/z* 409.1 and 411.1 [(M + Na)$^+$]; **HRMS** (ESI): exact mass calculated for $C_{20}H_{19}ClN_2NaO_4$ [(M + Na)$^+$], 409.0926 and 411.0898; found 409.0917 and 411.0904.

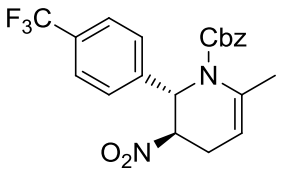
Synthesis and characterisation of benzyl (2*S*,3*R*)-2-(4-chlorophenyl)-6-methyl-3-nitro-3,4-dihydropyridine-1(2*H*)-carboxylate (402c)



402c

Prepared according to general procedure F. *N*-Cbz imine **401c** (109.5 mg, 0.40 mmol) was reacted with nitroalkyne **383** (67.9 mg, 0.60 mmol) for 24 h (step i) and 24 h (step ii) to afford compound **402c** (95 mg, 62%, dr 96:4) as a colourless oil, after purification by flash column chromatography on silica gel eluting with PE/Et_2O (6:1). The ee was determined by HPLC analysis using a Chiralpak AD-H column [hexane/*i*PrOH 90:10, flow rate 1.0 mL/min, λ = 230 nm]; ***MAJOR:*** t_R major = 25.93 min, t_R minor = 39.29 min (94% ee), ***MINOR:*** t_R major = 9.21 min, t_R minor = 10.57 min (87% ee). **TLC**: R_f = 0.25 (PE/Et_2O 6:1, UV, $KMnO_4$); $\mathbf{[\alpha]_D^{25}}$ = +88.3 (c = 1.00, MeOH); **^{1}H NMR** (400 MHz, CD_3OD): δ_H 7.37 - 7.21 (m, 9H, Ar**H**), 6.30 - 6.27 (m, 1H, C**H**N), 5.34 - 5.29 (m, 1H, C**H**NO_2), 5.17 (d, *J* = 12.5 Hz, 1H, C**H**H′CO_2) 5.11 (d, *J* = 12.5 Hz, 1H, CH**H′**CO_2), 4.84 - 4.79 (m, 1H, C=C**H**), 2.86 - 2.76 (m, 1H, C**H**H′$CHNO_2$), 2.18 - 2.07 (m, 4H, CH=CC$\mathbf{H_3}$ and CH**H′**$CHNO_2$); **^{13}C NMR** (100 MHz, CD_3OD): δ_C 156.0 (**C**=O), 137.4 (Ar**C**), 137.1 (Ar**C**), 135.3 (**C**=CH), 134.9 (Ar**C**), 130.2 (2 × Ar**C**H), 129.7 (2 × Ar**C**H), 129.4 (Ar**C**H), 129.2 (2 × Ar**C**H), 128.6 (2 × Ar**C**H), 108.4 (C=**C**H), 83.0 (**C**$CHNO_2$), 69.3 (**C**H_2CO_2), 58.9 (**C**HN), 24.0 (**C**H_2CHNO_2), 22.9 (CH=C**C**H_3); **IR** (film/cm^{-1}): ν_{max} 2974, 1716, 1669, 1548, 1493, 1392, 1324, 1285, 1227, 1192, 1090, 764, 697; **MS** (ESI): *m/z* 409.1 and 411.1 [(M + Na)$^+$]; **HRMS** (ESI): exact mass calculated for $C_{20}H_{19}ClN_2NaO_4$ [(M + Na)$^+$], 409.0926 and 411.0898; found 409.0917 and 411.0901.

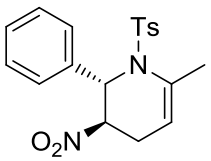
Synthesis and characterisation of benzyl (2*S*,3*R*)-6-methyl-3-nitro-2-[4-(trifluoromethyl)phenyl]-3,4-dihydropyridine-1(2*H*)-carboxylate (402d)



402d

Prepared according to general procedure F. *N*-Cbz imine **401d** (122.9 mg, 0.40 mmol) was reacted with nitroalkyne **383** (67.9 mg, 0.60 mmol) for 24 h (step i) and 28 h (step ii) to afford compound **402d** (93 mg, 55%, dr 98:2) as a colourless oil, after purification by flash column chromatography on silica gel eluting with PE/Et_2O (4:1). The ee was determined by HPLC analysis using a Chiralpak AD-H column [hexane/*i*PrOH 90:10, flow rate 1.0 mL/min, λ = 230 nm]; ***MAJOR:*** t_R major = 16.36 min, t_R minor = 29.80 min (95% ee), ***MINOR:*** t_R major = 7.44 min, t_R minor = 8.05 min (93% ee). **TLC**: R_f = 0.33 (PE/Et_2O 4:1, UV, $KMnO_4$); $\mathbf{[\alpha]_D^{25}}$ = +86.2 (c = 1.00, MeOH); **^{1}H NMR** (400 MHz, CD_3OD): δ_H 7.66 (d, *J* = 8.0 Hz, 2H, Ar**H**), 7.47 (d, *J* = 8.0 Hz, 2H, Ar**H**), 7.29 (s, 5H, Ar**H**), 6.39 (br s, 1H, C**H**N), 5.44 - 5.38 (m, 1H, C**H**NO_2), 5.18 (d, *J* = 12.5 Hz, 1H, C**H**H′CO_2) 5.12 (d, *J* = 12.5 Hz, 1H, CH**H′**CO_2), 4.83 (br s, 1H, C=C**H**), 2.89 - 2.79 (m, 1H, C**H**H′$CHNO_2$), 2.19 (s, 3H, CH=CC**H$_3$**), 2.16 - 2.06 (m, 1H, CH**H′**$CHNO_2$); **^{13}C NMR** (100 MHz, CD_3OD): δ_C 156.0 (**C**=O), 142.8 (Ar**C**), 137.3 (Ar**C**), 135.4 (**C**=CH), 131.2 (q, *J* = 33.0 Hz, Ar**C**), 129.7 (2 × Ar**C**H), 129.4 (Ar**C**H), 129.2 (2 × Ar**C**H), 127.7 (2 × Ar**C**H), 127.0 (q, *J* = 4.0 Hz, 2 × Ar**C**H), 125.6 (q, *J* = 271.0 Hz, Ar**C**F_3), 108.4 (C=**C**H), 82.9 (**C**HNO_2), 69.3 (**C**H_2CO_2), 59.2 (**C**HN), 24.1 (**C**H_2CHNO_2), 22.8 (CH=C**C**H_3); **^{19}F NMR** (376.5 MHz, CD_3OD): δ_F –64.0 (ArC**F$_3$**); **IR** (film/cm^{-1}): ν_{max} 2972, 1716, 1669, 1551, 1395, 1322, 1272, 1167, 1117, 1069, 767; **MS** (ESI): *m/z* 443.1 [$(M + Na)^+$]; **HRMS** (ESI): exact mass calculated for $C_{21}H_{19}F_3N_2NaO_4$ [$(M + Na)^+$], 443.1189; found 443.1186.

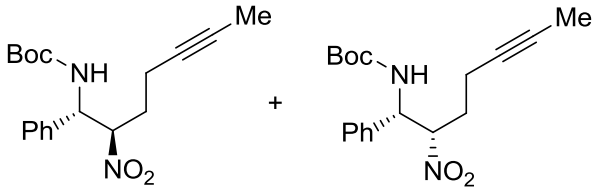
Synthesis and characterisation of (2*S*,3*R*)-6-methyl-1-[(4-methylphenyl) sulfonyl]-3-nitro-2-phenyl-1,2,3,4-tetrahydropyridine (386′)



386′

Prepared according to general procedure F. *N*-Sulfonyl imine **257a** (103.7 mg, 0.40 mmol) was reacted with nitroalkyne **383** (67.9 mg, 0.60 mmol) for 42 h (step i) and 32 h (step ii) to afford compound **386′** (23 mg, 15%, dr 96:4) as an off-white solid, after purification by flash column chromatography on silica gel eluting with PE/Et_2O (4:1). The ee was determined by HPLC analysis using a Chiralpak AD-H column [hexane/*i*PrOH 90:10, flow rate 1.0 mL/min, λ = 230 nm]; ***MAJOR:*** t_R major = 21.09 min, t_R minor = 35.92 min (17% ee), ***MINOR:*** t_R major = 11.20 min, t_R minor = 15.23 min (16% ee). **TLC**: R_f = 0.18 (PE/Et_2O 4: 1, UV, $KMnO_4$); **Melting Point**: 111 - 113 °C; $[\alpha]_D^{25}$ = +11.2 (c = 1.00, MeOH); **^{1}H NMR** (400 MHz, CD_3OD): δ_H 7.59 (d, *J* = 8.5 Hz, 2H, Ar**H**), 7.41 - 7.27 (m, 7H, Ar**H**), 6.41 (d, *J* = 2.5 Hz, 1H, C**H**N), 5.30 - 5.24 (m, 1H, C**H**NO_2), 4.88 - 4.83 (m, 1H, C=C**H**), 2.70 - 2.59 (m, 1H, C**H**H′), 2.41 (s, 3H, ArC**H$_3$**), 2.12 - 1.99 (m, 4H, CH**H′** and CH=CC**H$_3$**); **^{13}C NMR** (100 MHz, CD_3OD): δ_C 145.8 (Ar**C**), 140.0 (Ar**C**), 139.1 (Ar**C**), 134.9 (**C**=CH), 130.9 (2 × Ar**C**H), 130.2 (2 × Ar**C**H), 129.4 (Ar**C**H), 128.6 (2 × Ar**C**H), 127.3 (2 × Ar**C**H), 107.3 (C=**C**H), 83.9 (**C**HNO_2), 62.0 (**C**HN), 23.5 (**C**H_2), 22.3 (CH=C**C**H_3), 21.6 (Ar**C**H_3); **IR** (film/cm^{-1}): ν_{max} 2925, 1598, 1551, 1451, 1340, 1162, 1097, 1056, 943, 804, 718; **MS** (ESI): *m/z* 395.1 [$(M + Na)^+$]; **HRMS** (ESI): exact mass calculated for $C_{19}H_{20}N_2NaO_4S$ [$(M + Na)^+$], 395.1036; found 395.1031.

Synthesis and characterisation of *tert*-butyl [(1*S*,2*R*)-2-nitro-1-phenylhept-5-yn-1-yl]carbamate (412) and *tert*-butyl [(1*S*,2*S*)-2-nitro-1-phenylhept-5-yn-1-yl]carbamate (412′)

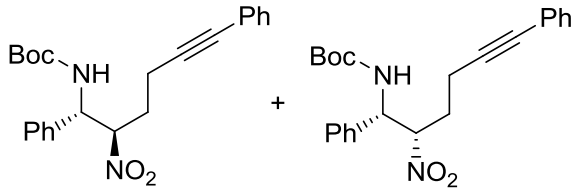


412 **412′**

Prepared according to general procedure F. *N*-Boc imine **112a** (82.1 mg, 0.40 mmol) was reacted with nitroalkyne **405** (76.3 mg, 0.60 mmol) for 72 h (step i) and 72 h at 100 °C(step ii) to afford a mixture of diastereomers **412** and **412′** (68 mg, 51%) as an off-white solid, after purification by flash column chromatography on silica gel eluting with PE/EtOAc (9:1). The dr and ee were determined by HPLC analysis using a Chiralpak OD-H column [hexane/*i*PrOH 98:2, flow rate 1.0 mL/min, λ = 210 nm]; dr 73:27; ***MAJOR:*** t_R minor = 14.41 min, t_R major = 16.94 min (93% ee), ***MINOR:*** t_R major = 8.49 min, t_R minor = 10.15 min (74% ee). **TLC**: R_f = 0.34 (PE/EtOAc 9:1, UV, $KMnO_4$); **Melting Point**: 118 - 120 °C; $\mathbf{[\alpha]_D^{25}}$ = +23.5 (c = 1.00, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.42 - 7.29 (m, Ar**H**, 3H *major* and 3H *minor*), 7.29 - 7.14 (m, Ar**H**, 2H *major* and 2H *minor*), 5.72 (d, *J* = 9.5 Hz, 1H, N**H**, *minor*), 5.39 - 5.26 (m, 1H, N**H**, *major*), 5.25 - 5.15 (m, C**H**N, 1H *major* and 1H *minor*), 5.12 - 4.92 (m, C**H**NO_2, 1H *major* and 1H *minor*), 2.37 - 2.04 (m, C**H**H′CHNO_2, 1H *major* and 1H *minor*; C**HH′**C≡C, 2H *major* and 2H *minor*), 2.02 - 1.88 (m, CH**H′**CHNO_2, 1H *major* and 1H *minor*), 1.80 - 1.72 (m, C$\mathbf{H_3}$, 3H *major* and 3H *minor*), 1.43 (s, C(C$\mathbf{H_3}$)$_3$, 9H *major* and 9H *minor*); **^{13}C NMR** (100 MHz, $CDCl_3$, unassigned mixture of diastereomers): δ_C 154.8 (**C**=O), 137.4 (Ar**C**), 136.4 (Ar**C**), 129.0 (Ar**C**H), 128.9 (Ar**C**H), 128.7 (Ar**C**H), 128.4 (Ar**C**H), 126.7 (Ar**C**H), 126.2 (Ar**C**H), 90.7 (**C**HNO_2), 89.8 (**C**HNO_2), 80.5 (**C**(CH_3)$_3$), 77.7 (**C**≡C), 77.2

(**C**≡C), 76.0 (C≡**C**), 75.7 (C≡**C**), 57.0 (**C**HN), 56.9 (**C**HN), 30.3 (**C**H_2CHNO_2), 28.9 (**C**H_2CHNO_2), 28.2 (C(**C**H_3)$_3$), 15.7 (**C**H_2C≡C), 15.5 (**C**H_2C≡C), 3.4 (**C**H_3); **IR** (film/cm^{-1}): ν_{max} 2978, 1700, 1551, 1496, 1455, 1367, 1246, 1162, 1047, 755, 700; **MS** (ESI): *m/z* 355.2 [$(M + Na)^+$]; **HRMS** (ESI): exact mass calculated for $C_{18}H_{24}N_2NaO_4$ [$(M + Na)^+$], 355.1628; found 355.1617. The absolute configurations of diastereomers **412** and **412′** were assigned by analogy to diastereomers **389** and **389′** and the X-ray crystal structure of tetrahydropyridine **394g**.

Synthesis and characterisation of *tert*-butyl [(1*S*,2*R*)-2-nitro-1,6-diphenylhex-5-yn-1-yl]carbamate (413) and *tert*-butyl [(1*S*,2*S*)-2-nitro-1,6-diphenylhex-5-yn-1-yl]carbamate (413′)



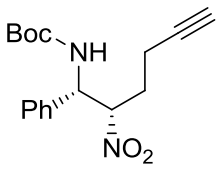
413 **413′**

Prepared according to general procedure F. *N*-Boc imine **112a** (82.1 mg, 0.40 mmol) was reacted with nitroalkyne **409** (113.5 mg, 0.60 mmol) for 32 h (step i) and 72 h at 100 °C (step ii) to afford a mixture of diastereomers **413** and **413′** (99 mg, 63%, dr 74:26) as a pale yellow oil, after purification by flash column chromatography on silica gel eluting with PE/EtOAc (9:1). The ee was determined by HPLC analysis using a Chiralpak AD-H column [hexane/*i*PrOH 95:5, flow rate 1.0 mL/min, λ = 230 nm]; ***MAJOR***: t_R minor = 28.76 min, t_R major = 44.81 min (90% ee); ***MINOR***: t_R major = 20.13 min, t_R minor = 39.16 min (85% ee). **TLC**: R_f = 0.36 (PE/EtOAc 9:1, UV, $KMnO_4$); **$[\alpha]_D^{25}$** = +16.7 (c = 2.00, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.48 - 7.21 (m, Ar**H**, 10H *major* and 10H *minor*), 5.75 (d, *J* = 9.5 Hz, 1H, N**H**, *minor*) 5.38 - 5.22 (m, N**H**, 1H *major*; C**H**N, 1H *major* and 1H *minor*), 5.12 (br s, C**H**NO_2, 1H *major* and 1H *minor*), 2.67 - 2.30 (m, C**H$_2$**C≡C and C**H**H'CHNO_2, 3H

major and 3H *minor*), 2.17 - 2.00 (m, CH**H'**$CHNO_2$, 1H *major* and 1H *minor*), 1.45 (s, C(CH_3)$_3$, 9H *major* and 9H *minor*); **^{13}C NMR** (100 MHz, $CDCl_3$, unassigned mixture of diastereomers): δ_C 154.8 (**C**=O), 137.2 (Ar**C**), 136.3 (Ar**C**), 131.5 (2 × Ar**C**), 129.1 (2 × Ar**C**H), 129.0 (2 × Ar**C**H), 128.7 (Ar**C**), 128.4 (Ar**C**), 128.2 (2 × Ar**C**H), 128.2 (2 × Ar**C**H), 128.0 (2 × Ar**C**H), 128.0 (2 × Ar**C**H), 126.7 (Ar**C**H), 126.3 (Ar**C**H), 123.1 (Ar**C**H), 123.0 (Ar**C**H), 90.7 (**C**$CHNO_2$), 89.8 (**C**$CHNO_2$), 86.6 (**C**≡C), 86.2 (**C**≡C), 82.5 (C≡**C**), 82.4 (C≡**C**), 80.6 (**C**(CH_3)$_3$), 57.0 (**C**HN), 30.0 (**C**H_2CHNO_2), 28.6 (**C**H_2CHNO_2), 28.2 (C(**C**H_3)$_3$), 16.4 (**C**H_2C≡C), 16.2 (**C**H_2C≡C); **IR** (film/cm^{-1}): ν_{max} 2978, 1700, 1552, 1491, 1367, 1246, 1161, 910, 756, 732, 692; **MS** (ESI): *m/z* 417.2 [(M + Na)$^+$]; **HRMS** (ESI): exact mass calculated for $C_{23}H_{26}N_2NaO_4$ [(M + Na)$^+$], 417.1785; found 417.1775. The absolute configurations of diastereomers **413** and **413′** were assigned by analogy to diastereomers **389** and **389′** and the X-ray crystal structure of tetrahydropyridine **394g**.

5.3.5 Synthesis and Characterisation of *cis*-Terahydropyridine 394a′

Synthesis and characterisation of *tert*-butyl [(1*S*,2*S*)-2-nitro-1-phenylhex-5-yn-1-yl]carbamate (389′)

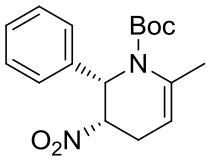


389′

Compound **389′** was obtained as a white solid (7.2 mg, 6%, dr >98:2) after purification by flash column chromatography on silica gel eluting with PE/Et_2O (4:1) from the synthesis of compound **394a**. The ee was determined by HPLC analysis using a Chiralpak AD-H column [hexane/*i*PrOH 90:10, flow rate 1.0 mL/min, λ =

210 nm]; t_R major = 16.84 min, t_R minor = 20.18 min (82% ee). **TLC**: R_f = 0.24 (PE/Et_2O 4:1, UV, $KMnO_4$); **Melting Point**: 85 - 88 °C; $\mathbf{[\alpha]_D^{25}}$ = –2.7 (c = 0.50, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.41 - 7.30 (m, 3H, Ar**H**), 7.26 (d, *J* = 7.5 Hz, 2H, Ar**H**), 5.73 - 5.59 (m, 1H, N**H**), 5.21 (br s, 1H, C**H**N), 5.10 (br s, 1H, C**H**NO_2), 2.44 - 2.19 (m, 3H, C**HH′**$CHNO_2$ and C**H**H′C≡CH), 2.09 - 1.93 (m, 2H, C≡C**H** and CH**H′**C≡CH), 1.44 (s, 9H, C(C$\mathbf{H_3}$)$_3$); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 155.0 (**C**=O), 137.2 (Ar**C**), 129.1 (2 × Ar**C**H), 128.5 (Ar**C**H), 126.2 (2 × Ar**C**H), 90.4 (**C**HNO_2), 80.9 (**C**≡CH), 80.5 (**C**$(CH_3)_3$), 70.6 (C≡**C**H), 55.5 (**C**HN), 29.7 (**C**H_2CHNO_2), 28.2 (C(**C**$H_3)_3$), 15.2 (**C**H_2C≡CH); **IR** (film/cm^{-1}): ν_{max} 3298, 2919, 1682, 1547, 1366, 1255, 1162, 708, 639; **MS** (ESI): *m/z* 341.15 [$(M + Na)^+$]; **HRMS** (ESI): exact mass calculated for $C_{17}H_{22}N_2NaO_4$ [$(M + Na)^+$], 341.1472; found 341.1459.

Synthesis and characterisation of *tert*-butyl (2*S*,3*S*)-6-methyl-3-nitro-2-phenyl-3,4-dihydropyridine-1(2*H*)-carboxylate (394a′)



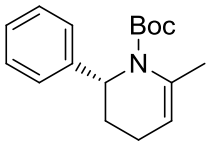
394a′

To a stirred solution of compound **389′** (5.6 mg, 17.5 µmol) in PhMe (1.0 mL) in a sealable vial at RT was added complex **193** (0.7 mg, 0.875 µmol, 5 mol%). The resulting solution was heated to 100 °C for 24 h. The reaction mixture was cooled to RT and directly purified by flash column chromatography on silica gel eluting with PE/Et_2O (9:1) to afford diastereomers **394a′** and **394a** (3.2 mg, 57%, dr 89:11) as a colourless oil. Only the ^{1}H and ^{13}C NMR signals corresponding to the major diastereomer **394a′** are reported, all other characterisation data is for the mixture of

diastereomers **394a′** and **394a**. The ee was determined by HPLC analysis using a Chiralpak AD-H column [hexane/*i*PrOH 90:10, flow rate 1.0 mL/min, λ = 230 nm]; ***MAJOR:*** t_R major = 4.16 min, t_R minor = 4.63 min (81% ee); ***MINOR:*** t_R major = 7.76 min, t_R minor = 21.35 min (86% ee). **TLC**: R_f = 0.32 (PE/Et_2O 9:1, UV, $KMnO_4$); $[\alpha]_D^{25}$ = –5.2 (c = 0.25, EtOH); **^{1}H NMR** (400 MHz, CD_3OD): δ_H 7.32 - 7.25 (m, 3H, Ar**H**), 7.16 - 7.09 (m, 2H, Ar**H**), 6.07 (d, *J* = 5.0 Hz, 1H, C**H**N), 5.12 - 5.02 (m, 1H, C**H**NO_2), 4.90 - 4.85 (m, 1H, C=C**H**), 2.55 - 2.47 (m, 2H, C$\mathbf{H_2}$), 2.23 (s, 3H, CH=CC$\mathbf{H_3}$), 1.42 (s, 9H, C(C$\mathbf{H_3}$)$_3$); **^{13}C NMR** (100 MHz, CD_3OD): δ_C 154.5 (**C**=O), 137.4 (Ar**C**), 136.7 (**C**=CH), 129.7 (2 × Ar**C**H), 129.6 (Ar**C**H), 128.3 (2 × Ar**C**H), 106.6 (C=**C**H), 83.4 (**C**$(CH_3)_3$), 82.7 (**C**HNO_2), 59.6 (**C**HN), 28.5 (C(**C**$H_3)_3$), 24.1 (**C**H_2), 23.2 (CH=C**C**H_3); **IR** (film/cm^{-1}): ν_{max} 2924, 1719, 1663, 1553, 1457, 1369, 1338, 1281, 1259, 1163, 750, 668; **MS** (ESI): *m/z* 341.1 [(M + Na)$^+$]; **HRMS** (ESI): exact mass calculated for $C_{17}H_{22}N_2NaO_4$ [(M + Na)$^+$], 341.1472; found 341.1466.

5.3.6 Synthetic Elaboration of Tetrahydropyridine 394a

Synthesis and characterisation of *tert*-butyl (2*R*)-6-methyl-2-phenyl-3,4-dihydro pyridine-1(2*H*)-carboxylate (416)

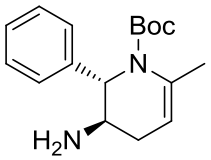


416

To a solution of compound **394a** (31.8 mg, 0.10 mmol) in PhMe (2.5 mL) in a microwave vial at RT was added AIBN (3.3 mg, 0.02 mmol, 5 mol%) and Bu_3SnH (146 mg, 0.50 mmol, 135 μL). The resulting mixture was degassed and flushed with nitrogen several times (×5), then rapidly heated to 110 °C and stirred for 3 h. The

reaction mixture was allowed to cool to RT and then directly purified by flash column chromatography on silica gel eluting with PE (100%) → PE/Et_2O (98:2) to afford compound **416** (17 mg, 64%) as a colourless oil. On standing the product crystallised as a white solid. The ee was determined by HPLC analysis using a Chiralpak AD-H column [hexane/*i*PrOH 99:1, flow rate 1.0 mL/min, λ = 230 nm]; t_R major = 4.46 min, t_R minor = 6.09 min (92% ee). **TLC**: R_f = 0.21 (PE/Et_2O 98:2, UV, $KMnO_4$); **Melting Point**: 66 - 68 °C; **$[\alpha]_D^{25}$** = +172.6 (c = 0.50, MeOH); **^{1}H NMR** (500 MHz, CD_3OD): δ_H 7.33 - 7.26 (m, 2H, Ar**H**), 7.24 - 7.18 (m, 3H, Ar**H**), 5.48 (t, *J* = 4.0 Hz, 1H, C**H**N), 4.84 - 4.81 (m, 1H, C=C**H**), 2.30 - 2.23 (m, 1H, C**H**H′CHN), 2.16 (d, *J* = 1.0 Hz, 3H, CH=CC**H$_3$**), 2.06 - 1.97 (m, 1H, CH**H′**CHN), 1.96 - 1.88 (m, 1H, C**H**H′CH=C), 1.79 - 1.69 (m, 1H, CH**H′**CH=C), 1.44 (s, 9H, C(C**H$_3$**)$_3$); **^{13}C NMR** (125 MHz, CD_3OD): δ_C 155.8 (**C**=O), 142.5 (Ar**C**), 135.2 (**C**=CH), 129.5 (2 × Ar**C**H), 127.7 (Ar**C**H), 126.9 (2 × Ar**C**H), 112.8 (C=**C**H), 82.2 (**C**$(CH_3)_3$), 57.6 (**C**HN), 28.7 (C(**C**$H_3)_3$), 28.4 (**C**H_2CHN), 23.6 (CH=C**C**H_3), 20.4 (**C**H_2CH=C); **IR** (film/cm^{-1}): ν_{max} 2975, 1695, 1661, 1387, 1367, 1352, 1333, 1169, 1101, 1073, 700; **MS** (ESI): *m/z* 296.2 [$(M + Na)^+$]; **HRMS** (ESI): exact mass calculated for $C_{17}H_{23}NNaO_2$ [$(M + Na)^+$], 296.1621; found 296.1629. The absolute configuration of compound **416** was assigned by analogy to the X-ray crystal structure of compound **394g**.

Synthesis and characterisation of *tert*-butyl (2*S*,3*R*)-3-amino-6-methyl-2-phenyl-3,4-dihydropyridine-1(2*H*)-carboxylate (417)

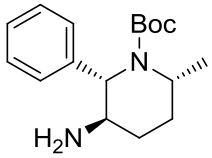


417

To a stirred solution of compound **394a** (31.8 mg, 0.10 mmol) in MeOH (1.0 mL) at 0 °C was added $NiCl_2{\cdot}6H_2O$ (23.8 mg, 0.10 mmol) and $NaBH_4$ (18.9 mg, 0.50 mmol) [CAUTION: Hydrogen Gas Release]. The resulting black suspension was stirred at 0 °C for 20 min. The reaction was quenched with sat. aq. NH_4Cl (5 mL), diluted with H_2O (5 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with H_2O (5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the crude product (dr >95:5). Purification by flash column chromatography on silica gel eluting with CH_2Cl_2/MeOH (98:2) → CH_2Cl_2/MeOH (19:1) afforded compound **417** (20 mg, 68%, dr >95:5) as a pale yellow oil. Further elution with CH_2Cl_2/MeOH (9:1) afforded compound **418** (8 mg, 28%, dr >95:5) as a colourless oil. **TLC**: R_f = 0.15 (CH_2Cl_2/MeOH 95:5, UV, $KMnO_4$); $\mathbf{[\alpha]_D^{25}}$ = +91.8 (c = 0.50, MeOH); **^{1}H NMR** (500 MHz, CD_3OD): δ_H 7.35 - 7.29 (m, 2H, Ar**H**), 7.26 - 7.18 (m, 3H, Ar**H**), 5.27 (d, *J* = 3.0 Hz, 1H, C**H**N), 4.74 - 4.70 (m, 1H, C=C**H**), 3.46 - 3.40 (m, 1H, C**H**NH_2), 2.27 - 2.23 (m, 3H, CH=CC$\mathbf{H_3}$), 1.99 - 1.90 (m, 1H, C**H**H′), 1.86 - 1.78 (m, 1H, CH**H′**), 1.43 (s, 9H, C(C$\mathbf{H_3}$)$_3$); **^{13}C NMR** (125 MHz, CD_3OD): δ_C 156.2 (**C**=O), 141.8 (Ar**C**), 135.2 (**C**=CH), 129.7 (2 × Ar**C**H), 128.2 (Ar**C**H), 126.7 (2 × Ar**C**H), 108.2 (C=**C**H), 82.6 (**C**$(CH_3)_3$), 64.5 (**C**HN), 50.1 (**C**HNH_2), 28.6 (C(**C**$H_3)_3$), 28.2 (**C**H_2), 23.5 (CH=C**C**H_3); **IR** (film/cm^{-1}): ν_{max} 2976, 2930, 1701, 1661, 1390, 1367, 1336, 1162, 1096, 668; **MS** (ESI): *m/z* 289.2 [$(M + H)^+$]; **HRMS** (ESI): exact mass calculated for $C_{17}H_{25}N_2O_2$ [$(M + H)^+$], 289.1911; found 289.1908.

The absolute configuration of compound **417** was assigned by analogy to the X-ray crystal structure of tetrahydropyridine **394g**.

Synthesis and characterisation of *tert*-butyl (2*S*,3*R*,6*R*)-3-amino-6-methyl-2-phenylpiperidine-1-carboxylate (418)



418

To a stirred solution of compound **394a** (31.8 mg, 0.10 mmol) in MeOH (1.0 mL) at 0 °C was added $NiCl_2{\cdot}6H_2O$ (47.5 mg, 0.20 mmol) and $NaBH_4$ (37.8 mg, 1.0 mmol) [CAUTION: Hydrogen Gas Release]. The resulting black suspension was stirred at 0 °C for 5 min and then warmed to RT and stirred for 3 h. An extra portion of $NaBH_4$ (18.9 mg, 0.50 mmol) was added and stirring continued at RT for 1 h. The reaction was quenched with sat. aq. NH_4Cl (10 mL), diluted with H_2O (10 mL) and then extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with H_2O (5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield the crude product (dr >95:5). Purification by flash column chromatography eluting with CH_2Cl_2/MeOH (9:1) afforded compound **418** (22 mg, 74%, dr >95:5) as a colourless oil. **TLC**: R_f = 0.28 (CH_2Cl_2/MeOH 9:1, UV, $KMnO_4$); $[\alpha]_D^{25}$ = +52.8 (c = 0.25, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.34 - 7.29 (m, 4H, Ar**H**), 7.25 - 7.20 (m, 1H, Ar**H**), 5.09 (br d, *J* = 2.5 Hz, 1H, C**H**N), 4.50 - 4.42 (m, 1H, NC**H**CH_3), 3.72 (br s, 1H, C**H**NH_2), 2.15 - 2.00 (m, 2H, C**H**H′$CHNH_2$ and C**H**H′CHH′$CHNH_2$), 1.56 - 1.48 (m, 1H, CH**H′**$CHNH_2$), 1.45 (s, 9H, C(C**H$_3$**)$_3$), 1.38 - 1.31 (m, 1H, CH**H′**CHH′$CHNH_2$), 0.92 (d, *J* = 7.0 Hz, 3H, C**H$_3$**); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 156.5 (**C**=O), 142.2 (Ar**C**), 128.1 (2 × Ar**C**H), 126.7 (2 ×

Ar**C**H), 126.6 (Ar**C**H), 79.8 (**C**$(CH_3)_3$), 60.9 (**C**HN), 47.2 (N**C**HCH_3), 46.3 (**C**HNH_2), 28.4 (C(C**H$_3$**)$_3$), 24.5 (**C**H_2), 23.6 (1C, **C**H_2), 21.5 (NCH**C**H_3); **IR** (film/cm^{-1}): ν_{max} 2972, 2932, 1681, 1403, 1365, 1255, 1171, 717, 698; **MS** (ESI): *m/z* 291.2 [$(M + H)^+$]; **HRMS** (ESI): exact mass calculated for $C_{17}H_{27}N_2O_2$ [$(M + H)^+$], 291.2067; found 291.2066. The absolute configuration of compound **418** was assigned by analogy to the X-ray crystal structure of compound **394g** and by NOE analysis.

5.4 Experimental Section for Chapter 4

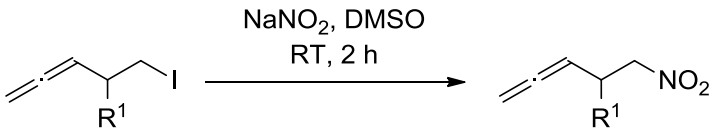
5.4.1 Reagents and Synthesis of Starting Materials

The work presented in this chapter was conducted in collaboration with Dr. Andrej Ďuriš during a research stay at the University of Oxford. All of the compounds from this collaboration have been included in this chapter for completeness. Compounds prepared and characterised by Dr. A. Ďuriš are referenced within the text.

All commercially available reagents were used as received unless otherwise stated. The synthesis of *N*-Sulfonyl imines **257a-o** was previously described in Chapter 2. *N*-Sulfonyl imines **257t-w** (starting materials for pyrrolidines **471j**, **471l**, **471n** and **471o** respectively) were prepared by Dr. A. Ďuriš according to a literature procedure.[125] *N*-Sulfonyl 2-pyridyl imine **497** was prepared according to a literature procedure.[125] Amidosulfones **400e-n** were prepared according to a literature procedure.[138] *N*-Cbz imines **401a-n**[177] were prepared by Dr. A. Ďuriš according to a literature procedure starting from the corresponding amidosulfones **400a-n**. Synthesis and characterisation data for the novel amidosulfones and *N*-Cbz imines is reported. The following allene substrates were prepared according to literature procedures: ethyl penta-3,4-dienoate (**464**),[225] penta-3,4-dien-1-ol (**465**),[225] 5-iodopenta-1,2-diene (**467**),[226] ethyl 4-cyclohexylidenebut-3-enoate (**481**)[227] and 4-cyclohexylidenebut-3-en-1-ol (**482**).[227] The following allene substrates were prepared by Dr. A. Ďuriš according to literature procedures: ethyl 2-methylpenta-3,4-dienoate (**474**),[225] 2-methylpenta-3,4-dien-1-ol (**475**)[225] and 5-iodo-4-methylpenta-1,2-diene (**477**).[226] Catalyst **118** was prepared by Dr. M. G. Núñez according to a literature procedure.[39] Catalyst **319** was prepared by Dr. A. F. Kyle according to a

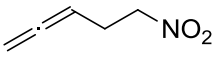
literature procedure.[62a] Catalyst **388** was prepared according to a literature procedure.[224] Catalyst **496** was prepared by Dr. M. G. Núñez and A. J. M. Farley.

General Procedure G: Synthesis of nitroallenes



To a stirred solution of $NaNO_2$ (1.2 equiv) in DMSO (1 mL/mmol of iodoallene) maintained at RT with a water bath was added a solution of the corresponding iodoallene (1.0 equiv) in DMSO (1 mL/1.5 mmol) behind a blast shield and the resulting mixture was stirred at RT for 1.5 h. The reaction mixture was diluted with ice water (1.25 mL/mmol) and extracted with Et_2O (6 × 1.25 mL/mmol). The combined organic extracts were washed with ice water (1.25 mL/mmol), dried over Na_2SO_4, filtered and concentrated under reduced pressure (water bath <20 °C). The resulting residue was purified by flash column chromatography on silica gel to afford the desired nitroallene.

Synthesis and characterisation of 5-nitropenta-1,2-diene (468)

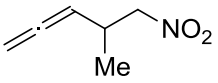


468

Prepared according to general procedure G. 5-iodopenta-1,2-diene (**467**) (12.4 g, 63.7 mmol) was reacted with $NaNO_2$ (5.28 g, 76.4 mmol) to afford compound **468** (3.85 g, 53%) as a colourless oil, after purification by flash column chromatography on silica gel eluting with PE/Et_2O (19:1). **TLC**: R_f = 0.38 (PE/Et_2O 19:1, $KMnO_4$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 5.15 (qu, *J* = 6.5 Hz, 1H, CH_2=C=C**H**), 4.81 (dt, *J* = 6.5, 3.5 Hz, 2H, C**H$_2$**=C=CH), 4.47 (t, *J* = 7.0 Hz, 2H, CH_2C**H$_2$**NO_2), 2.74 - 2.64 (m, 2H, C**H$_2$**CH_2NO_2); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 208.6 (CH_2=**C**=CH), 85.0

(CH_2=C=**C**H), 77.1 (**C**H_2=C=CH), 74.2 (CH_2**C**H_2NO_2), 25.5 (**C**$H_2CH_2NO_2$); **IR** (film/cm^{-1}): ν_{max} 2923, 1957, 1548, 1429, 1379, 1194, 1067, 851; No meaningful HRMS data was obtained for this compound.

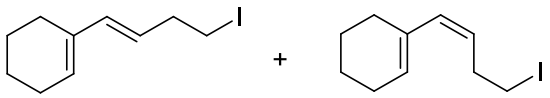
Synthesis and characterisation of 4-methyl-5-nitropenta-1,2-diene (478)



478

Prepared according to general procedure G. 5-iodo-4-methylpenta-1,2-diene **(477**) (1.30 g, 6.24 mmol) was reacted with $NaNO_2$ (517 mg, 7.45 mmol) to afford compound **478** (335 mg, 42%) as a colourless oil, after purification by flash column chromatography on silica gel eluting with PE/Et_2O (19:1). **TLC**: R_f = 0.63 (PE/Et_2O 19:1, $KMnO_4$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 5.14 (q, *J* = 6.5 Hz, 1H, (CH_2=C=C**H**), 4.87 - 4.79 (m, 2H, C**H$_2$**=C=CH), 4.39 (dd, *J* = 12.0, 7.0 Hz, 1H, C**H**H'NO_2), 4.26 (dd, *J* = 12.0, 7.0 Hz, 1H, CH**H**'NO_2), 3.11 - 2.97 (m, 1H, C**H**CH_3), 1.15 (d, *J* = 7.0 Hz, 3H, CHC**H$_3$**); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 207.5 (CH_2=**C**=CH), 91.2 (CH_2=C=**C**H), 80.5 (**C**H_2NO_2), 77.8 (**C**H_2=C=CH), 31.6 (**C**HCH_3), 17.5 (CH**C**H_3); **IR** (film/cm^{-1}): ν_{max} 2974, 1956, 1547, 1457, 1431, 1379, 1218, 854; **HRMS** (ESI): exact mass calculated for $C_6H_9NO_2$ [M], 127.0633; found 127.0646. Compound **478** was prepared and characterised by Dr. A. Ďuriš.

Synthesis and characterisation of 1-[(1*E*)-4-iodobut-1-en-1-yl]cyclohexene (484) and 1-[(1*Z*)-4-iodobut-1-en-1-yl]cyclohexene (484′)

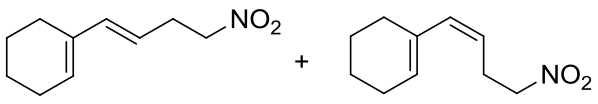


484 **484′**

To a stirred solution of 4-cyclohexylidenebut-3-en-1-ol (**482**) (3.30 g, 25.0 mmol) and Et_3N (3.54 g, 35.0 mmol, 4.85 mL) in CH_2Cl_2 (45 mL) at –30 °C was added

MsCl (2.87 g, 25.0 mmol, 1.94 mL). The resulting mixture was stirred at –10 °C for 1 h. The reaction was quenched with sat. aq. $NaHCO_3$ (30 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the crude mesylate as a yellow oil. The crude mesylate was dissolved in acetone (100 mL) at RT and NaI (9.37, 62.5 mmol) was added. The resulting mixture was heated to reflux for 20 h. The reaction mixture was allowed to cool to RT and was then diluted with Et_2O (100 mL). The organic phase was washed with sat. aq. Na_2SO_3 (100 mL), brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography on silica gel eluting with PE (100%) afforded a mixture of isomers **484** and **484′** (4.31 g, 66%, *E/Z* 70:30) as a pale yellow oil. **TLC**: R_f = 0.59 (PE 100%, $KMnO_4$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 6.10 (d, *J* = 15.5 Hz, 1H, C**H**=CHCH$_2$, *E-isomer*), 5.94 - 5.84 (m, 1H, C**H**=CHCH$_2$, *Z-isomer*), 5.72 (br s, 1H, C=C**H**, *E-isomer*), 5.65 (br s, 1H, C=C**H**, *Z-isomer*), 5.47 (dt, *J* = 15.5, 7.0 Hz, 1H, CH=C**H**CH$_2$, *E-isomer*), 5.21 (dt, *J* = 11.5, 7.5 Hz, 1H, CH=C**H**CH$_2$, *Z-isomer*), 3.17 (t, *J* = 7.5 Hz, C**H$_2$**I, 2H *E-isomer* and 2H *Z-isomer*), 2.84 (q, *J* = 7.5 Hz, 2H, CH=CHC**H$_2$**, *Z-isomer*), 2.65 (q, *J* = 7.0 Hz, 1H, CH=CHC**H$_2$**, *E-isomer*), 2.21 - 2.03 (m, cyclohexenyl **H**, 4H *E-isomer* and 4H *Z-isomer*), 1.77 - 1.50 (m, cyclohexenyl **H**, 4H *E-isomer* and 4H *Z-isomer*). The major isomer **484** was assigned as the *E-isomer* due to the presence of the characteristic *trans* ^{1}H coupling constant (*J* = 15.5 Hz). The purified iododienes **484** and **484′** were then converted to nitrodienes **485** and **485′** for full characterisation.

Synthesis and characterisation of 1-[(1*E*)-4-nitrobut-1-en-1-yl]cyclohexene (485) and 1-[(1*Z*)-4-nitrobut-1-en-1-yl]cyclohexene (485′)

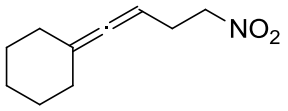


485 **485′**

Prepared according to general procedure G. Iododienes **484** and **484′** (4.19 g, 16.0 mmol) was reacted with $NaNO_2$ (1.32 g, 19.2 mmol) to afford a mixture of isomers **485** and **485′** (1.37 mg, 48%, *E/Z* 75:25) as a pale yellow oil, after purification by flash column chromatography on silica gel eluting with PE/Et_2O (19:1). **TLC**: R_f = 0.39 (PE/Et_2O 19:1, $KMnO_4$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 6.14 (d, *J* = 15.5 Hz, 1H, C**H**=CHCH_2, *E-isomer*), 5.93 (d, *J* = 11.5 Hz, 1H, C**H**=CHCH_2, *Z-isomer*), 5.72 (br s, 1H, C=C**H**, *E-isomer*), 5.64 (br s, 1H, C=C**H**, *Z-isomer*), 5.42 (dt, *J* = 15.5, 7.0 Hz, 1H, CH=C**H**CH_2, *E-isomer*), 5.19 (dt, *J* = 11.5, 7.5 Hz, 1H, CH=C**H**CH_2, *Z-isomer*), 4.42 (t, *J* = 7.0 Hz, 2H, C**H$_2$**NO_2, *E-isomer*), 4.40 (t, *J* = 7.5 Hz, 2H, C**H$_2$**NO_2, *Z-isomer*), 2.97 (q, *J* = 7.5 Hz, 2H, CH=CHC**H$_2$**, *Z-isomer*), 2.78 (q, *J* = 7.0 Hz, 2H, CH=CHC**H$_2$**, *E-isomer*), 2.17 - 2.01 (m, 8H, cyclohexenyl **H**, 4H *E-isomer* and 4H *Z-isomer*), 1.77 - 1.48 (m, 8H, cyclohexenyl **H**, 4H *E-isomer* and 4H *Z-isomer*); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 137.6 (**C**H=CHCH_2, *E-isomer*), 135.9 (**C**H=CHCH_2, *Z-isomer*), 134.9 (**C**=CH, *E-isomer*), 134.6 (**C**=CH, *Z-isomer*), 129.9 (C=**C**H, *E-isomer*), 128.6 (C=**C**H, *Z-isomer*), 121.0 (CH=**C**HCH_2, *Z-isomer*), 118.3 (CH=**C**HCH_2, *E-isomer*), 75.5 (**C**H_2NO_2, *Z-isomer*), 75.3 (**C**H_2NO_2, *E-isomer*), 30.7 (CH=CH**C**H_2, *E-isomer*), 28.7 (cyclohexenyl C**H$_2$**, *Z-isomer*), 26.9 (CH=CH**C**H_2, *Z-isomer*), 25.7 (cyclohexenyl C**H$_2$**, *E-isomer*), 25.5 (cyclohexenyl C**H$_2$**, *Z-isomer*), 24.4 (cyclohexenyl C**H$_2$**, *E-isomer*), 22.7 (cyclohexenyl C**H$_2$**, *Z-isomer*), 22.4 (cyclohexenyl C**H$_2$**, *E-isomer*), 22.3 (cyclohexenyl C**H$_2$**, *E-isomer*), 21.9 (cyclohexenyl C**H$_2$**, *Z-isomer*); **IR** (film/cm^{-1}):

ν_{max} 2927, 2859, 1548, 1433, 1378, 1336, 1185, 966; **HRMS** (ESI): exact mass calculated for $C_{10}H_{15}NO_2$ [M], 181.1103; found 181.1104. The major isomer **485** was assigned as the *E-isomer* due to the presence of the characteristic *trans* ^{1}H coupling constant (J = 15.5 Hz).

Synthesis and characterisation of (4-nitrobut-1-en-1-ylidene)cyclohexane (486)



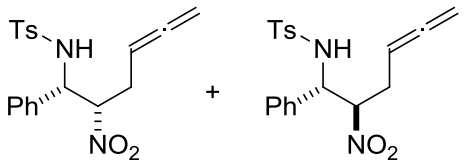
486

To a stirred solution of 4-cyclohexylidenebut-3-en-1-ol (**482**) (2.28 g, 15.0 mmol) and Et_3N (2.13 g, 21.0 mmol, 2.92 mL) in CH_2Cl_2 (25 mL) at –30 °C was added MsCl (1.72 g, 15.0 mmol, 1.16 mL). The resulting mixture was stirred at –10 °C for 1 h. The reaction was quenched with sat. aq. $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield the crude mesylate as a yellow oil. The crude mesylate was added drop wise to a stirred solution of $NaNO_2$ (1.24 g, 18.0 mmol) in DMSO (15 mL) at RT maintained using a water bath and the resulting mixture was stirred at RT for 48 h. The reaction mixture was diluted with ice water (20 mL) and extracted with Et_2O (6 × 30 mL). The combined organic extracts were washed with ice water (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography on silica gel eluting with PE/Et_2O (98:2) afforded compound **486** (531 mg, 20%) as a pale yellow oil. **TLC**: R_f = 0.22 (PE/Et_2O 98:2, $KMnO_4$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 5.04 - 4.96 (m, 1H, C=C=C**H**), 4.45 (t, J = 6.5 Hz, 2H, $CH_2C\mathbf{H_2}NO_2$), 2.69 - 2.61 (m, 2H, $C\mathbf{H_2}CH_2NO_2$), 2.12 - 2.04 (m, 4H, 2 × cyclohexyl C$\mathbf{H_2}$), 1.64 - 1.45 (m, 6H, 3 × cyclohexyl C$\mathbf{H_2}$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 198.5 (C=**C**=CH), 105.4

(**C**=C=CH), 83.5 (C=C=**C**H), 74.4 (CH_2**C**H_2NO_2), 31.3 (2 × cyclohexyl **C**H_2), 27.2 (2 × cyclohexyl **C**H_2), 26.5 (**C**$H_2CH_2NO_2$), 25.9 (cyclohexyl **C**H_2); **IR** (film/cm^{-1}): ν_{max} 2927, 2854, 1551, 1433, 1375, 1341, 853, 768; **HRMS** (ESI): exact mass calculated for $C_{10}H_{15}NO_2$ [M], 181.1103; found 181.1108.

5.4.2 Synthesis and Characterisation of β-Nitroamines 469 and 469′

Synthesis and characterisation of *rac*-4-methyl-*N*-[(1*S*,2*S*)-2-nitro-1-phenylhexa-4,5-dien-1-yl]benzenesulfonamide (469) and *rac*-4-methyl-*N*-[(1*S*,2*R*)-2-nitro-1-phenylhexa-4,5-dien-1-yl]benzenesulfonamide (469′)



469 **469′**

To a stirred mixture of *N*-sulfonyl imine **257a** (764 mg, 2.94 mmol) and nitroallene **468** (500 mg, 4.42 mmol) in PhMe (29 mL) at RT was added PS-BEMP (155 mg, 0.294 mmol, ~2.2 mmol/g, 10 mol%). The resulting mixture was stirred at RT for 22 h. The reaction mixture was concentrated under a stream of nitrogen and the resulting solid was purified by flash column chromatography on silica gel eluting with PE/EtOAc (6:1) to afford a mixture of diastereomers **469** and **469′** (963 mg, 88%, dr 83:17) as an off-white solid. **TLC**: R_f = 0.19 (PE/EtOAc 6:1, UV, $KMnO_4$); **Melting Point**: 126 - 129 °C; **Major diastereomer 469:** ^{1}**H NMR** (400 MHz, $CDCl_3$): δ_H 7.54 - 7.47 (m, *J* = 8.0 Hz, 2H, Ar**H**), 7.22 - 7.03 (m, 5H, Ar**H**), 7.02 - 6.96 (m, 2H, Ar**H**), 6.26 (d, *J* = 10.0 Hz, 1H, N**H**), 5.09 - 4.92 (m, 1H, C**H**=C=CH_2), 4.90 - 4.68 (m, 4H, C**H**N, C**H**NO_2 and CH=C=C**H**$_2$), 2.67 - 2.54 (m, 1H, C**H**H′), 2.37 - 2.25 (m, 4H, ArC**H**$_3$ and CH**H′**); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ_C 209.2 (CH=**C**=CH_2), 143.4 (Ar**C**), 136.8 (Ar**C**), 135.1 (Ar**C**), 129.3 (2 × Ar**C**H), 128.9

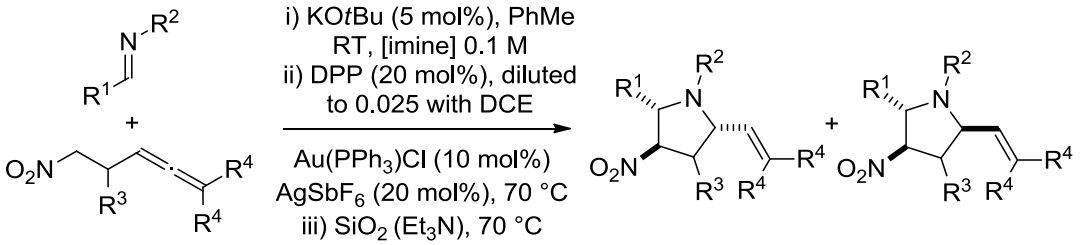
(2 × Ar**C**H), 128.5 (Ar**C**H), 126.9 (2 × Ar**C**H), 126.5 (2 × Ar**C**H), 91.3 (**C**HNO$_2$), 83.7 (**C**H=C=CH$_2$), 76.8 (CH=C=**C**H$_2$), 59.2 (**C**HN), 30.0 (**C**H$_2$), 21.4 (Ar**C**H$_3$); **Minor diastereomer 469′:** ^{1}**H NMR** (400 MHz, CDCl$_3$, observable peaks): δ_H 7.85 (d, *J* = 8.5 Hz, 2H, Ar**H**), 7.31 (d, *J* = 8.5 Hz, 2H, Ar**H**), 6.95 - 6.90 (m, 2H, Ar**H**), 6.06 (d, *J* = 9.5 Hz, 1H, N**H**), 5.08 - 4.99 (m, 1H, C**H**=C=CH$_2$), 2.82 - 2.68 (m, 2H, C**HH′**), 2.33 (s, 3H, ArC**H$_3$**); ^{13}**C NMR** (100 MHz, CDCl$_3$, observable peaks): 209.1 (CH=**C**=CH$_2$), 143.7 (Ar**C**), 136.5 (Ar**C**), 134.7 (Ar**C**), 129.5 (2 × Ar**C**H), 128.7 (2 × Ar**C**H), 128.6 (Ar**C**H), 127.0 (2 × Ar**C**H), 126.8 (2 × Ar**C**H), 90.6 (**C**HNO$_2$), 84.2 (**C**H=C=CH$_2$), 77.2 (CH=C=**C**H$_2$), 59.4 (**C**HN), 28.9 (**C**H$_2$), 21.4 (Ar**C**H$_3$); **IR** (film/cm^{-1}): ν_{max} 3265, 2923, 1956, 1598, 1554, 1457, 1370, 1327, 1307, 1158, 1089, 910, 850, 813, 771; **MS** (ESI): *m/z* 395.1 [(M + Na)$^+$]; **HRMS** (ESI): exact mass calculated for $C_{19}H_{20}N_2NaO_4S$ [(M + Na)$^+$], 395.1036; found 395.1031. The relative configurations of diastereomers **469** and **469′** were assigned by analogy to the single crystal X-ray structure of *syn*-**268′**.

Enantioselective synthesis of diastereomers 469′ and 469: Enantioenriched diastereomers **469′** and **469** were synthesised on a 0.10 mmol scale in an analogous manner to the described procedure by replacing KO*t*Bu with catalyst **118** (5 mol%) and stirring at RT for 48 h. Purification by flash column chromatography on silica gel eluting with PE/EtOAc (6:1) afforded a mixture of diastereomers **469′** and **469** (30 mg, 80%, dr 55:45) as a pale yellow solid. The ee was determined by HPLC analysis using a Chiralpak AD column [hexane/*i*PrOH 80:20, flow rate 1.0 mL/min, λ = 210 nm]; ***MAJOR:*** t_R major = 9.71 min, t_R minor = 10.73 min (7% ee), ***MINOR:*** t_R minor = 12.05 min, t_R major = 20.75 min (61% ee). $\mathbf{[\alpha]_D^{23}}$ = +5.3 (c = 2.81, CHCl$_3$); **Melting Point:** 95 - 98 °C. All other data was in agreement with that of the

corresponding racemic diastereomers **469** and **469′**. The absolute configurations of diastereomers **469** and **469′** were not determined. Enantioenriched compounds **469′** and **469** were prepared and characterised by Dr. A. Ďuriš.

5.4.3 Synthesis and Characterisation of Substituted Pyrrolidines

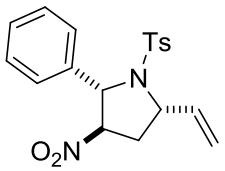
General Procedure H: Diastereoselective nitro-Mannich/hydroamination cascade to substituted pyrrolidines



To a stirred mixture of the corresponding imine (0.20 mmol, 1.0 equiv) and the corresponding nitroallene (0.30 mmol, 1.5 equiv) in PhMe (2.0 mL) at RT in a sealable vial was added KO*t*Bu (1.1 mg, 0.01 mmol, 5 mol%). The resulting mixture was stirred at RT for the indicated time. The reaction mixture was diluted with DCE (6.0 mL), then diphenylphosphate (10.0 mg, 0.04 mmol, 20 mol%), $Au(PPh_3)Cl$ (9.9 mg, 0.02 mmol, 10 mol%) and $AgSbF_6$ (13.7 mg, 0.04 mmol, 20 mol%) were added. The resulting mixture was heated to 70 °C for the indicated time. Silica gel treated with Et_3N (150 mg) was added and the resulting mixture was stirred at 70 °C for the indicated time. The reaction mixture was concentrated under a stream of nitrogen and the residue was purified by flash column chromatography on silica gel to afford the desired pyrrolidine.

The compounds reported in this section (5.4.3) were prepared by Dr. A. Ďuriš and characterised by D. M. Barber unless otherwise stated.

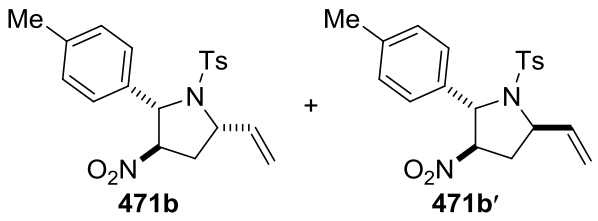
Synthesis and characterisation of *rac*-(2*S*,3*R*,5*S*)-1-[(4-methylphenyl) sulfonyl]-3-nitro-2-phenyl-5-vinylpyrrolidine (471a)



471a

Prepared according to general procedure H. *N*-Sulfonyl imine **257a** (51.9 mg, 0.20 mmol) was reacted with nitroallene **468** (33.9 mg, 0.30 mmol) for 16 h (step i), 3 h (step ii) and 3 h (step iii) to afford compound **471a** (60 mg, 81%, dr >98:2) as a white solid, after purification by flash column chromatography on silica gel eluting with PE/EtOAc (5:1). **TLC**: R_f = 0.45 (PE/EtOAc 5:1, UV, $KMnO_4$); **Melting Point**: 160 - 161 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.66 (d, *J* = 8.5 Hz, 2H, Ar**H**), 7.49 - 7.29 (m, 7H, Ar**H**), 6.10 (ddd, *J* = 17.0, 10.0, 7.5 Hz, 1H, C**H**=CH_2), 5.60 (s, 1H, C**H**N), 5.38 (d, *J* = 17.0 Hz, 1H, CH=CH_{cis}**H**$_{trans}$), 5.33 (d, *J* = 10.0 Hz, 1H, CH=C**H**$_{cis}$$H_{trans}$), 4.75 - 4.69 (m, 1H, C**H**NO_2), 4.40 - 4.31 (m, 1H, NC**H**CH=CH_2), 2.66 - 2.56 (m, 1H, C**H**H′), 2.46 (s, 3H, ArC**H$_3$**) 2.24 - 2.12 (m, 1H, CH**H′**); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 144.2 (Ar**C**), 138.9 (Ar**C**), 137.4 (**C**H=CH_2), 134.1 (Ar**C**), 129.6 (2 × Ar**C**H), 128.9 (2 × Ar**C**H), 128.4 (Ar**C**H), 127.8 (2 × Ar**C**H), 126.1 (2 × Ar**C**H), 117.9 (CH=**C**H_2), 90.1 (**C**HNO_2), 68.9 (**C**HN), 62.1 (N**C**HCH=CH_2), 34.9 (**C**H_2), 21.6 (Ar**C**H_3); **IR** (film/cm^{-1}): ν_{max} 2918, 1549, 1344, 1313, 1162, 1129, 1096, 1024, 1011, 917, 814, 701; **MS** (ESI): *m/z* 395.1 [(M + Na)$^+$]; **HRMS** (ESI): exact mass calculated for $C_{19}H_{20}N_2NaO_4S$ [(M + Na)$^+$], 395.1036; found 395.1029. The relative configuration of pyrrolidine **471a** was determined by single crystal X-ray diffraction analysis. All other pyrrolidines **471** were assigned by analogy.

Synthesis and characterisation of *rac*-(2*S*,3*R*,5*S*)-2-(4-methylphenyl)-1-[(4-methylphenyl)sulfonyl]-3-nitro-5-vinylpyrrolidine (471b) and *rac*-(2*S*,3*R*,5*R*)-2-(4-methylphenyl)-1-[(4-methylphenyl)sulfonyl]-3-nitro-5-vinylpyrrolidine (471b′)

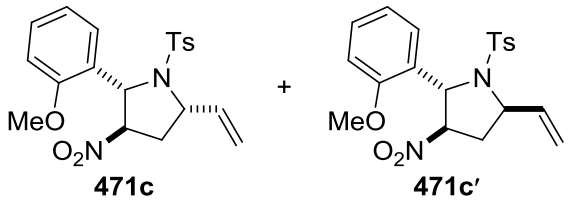


471b + **471b′**

Prepared according to general procedure H. *N*-Sulfonyl imine **257b** (54.7 mg, 0.20 mmol) was reacted with nitroallene **468** (33.9 mg, 0.30 mmol) for 16 h (step i), 5 h (step ii) and 4 h (step iii) to afford a mixture of diastereomers **471b** and **471b′** (50 mg, 64%, dr 90:10) as a pale yellow solid, after purification by flash column chromatography on silica gel eluting with PE/EtOAc (6:1). **TLC**: R_f = 0.39 (PE/EtOAc 6:1, UV, $KMnO_4$); **Melting Point**: 151 - 153 °C; **Major diastereomer 471b:** **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.66 (d, *J* = 8.0 Hz, 2H, Ar**H**), 7.33 (t, *J* = 8.5 Hz, 4H, Ar**H**), 7.21 (d, *J* = 8.0 Hz, 2H, Ar**H**), 6.09 (ddd, *J* = 17.0, 10.0, 7.5 Hz, 1H, C**H**=CH_2), 5.55 (s, 1H, C**H**N), 5.37 (d, *J* = 17.0 Hz, 1H, CH=CH_{cis}**H_{trans}**), 5.32 (d, *J* = 10.0 Hz, 1H, CH=C**H_{cis}**H_{trans}), 4.74 - 4.64 (m, 1H, C**H**NO_2), 4.40 - 4.30 (m, 1H, NC**H**CH=CH_2), 2.64 - 2.54 (m, 1H, C**H**H′), 2.46 (s, 3H, ArC**H_3**), 2.37 (s, 3H, ArC**H_3**), 2.17 (ddd, *J* = 14.5, 9.5, 6.0 Hz, 1H, CH**H′**); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 144.1 (Ar**C**), 138.2 (Ar**C**), 137.5 (**C**H=CH_2), 136.0 (Ar**C**), 134.1 (Ar**C**), 129.6 (4 × Ar**C**H), 127.8 (2 × Ar**C**H), 126.0 (2 × Ar**C**H), 117.8 (CH=**C**H_2), 90.1 (**C**HNO_2), 68.8 (**C**HN), 62.1 (N**C**HCH=CH_2), 34.9 (**C**H_2), 21.6 (Ar**C**H_3), 21.0 (Ar**C**H_3); **Minor diastereomer 471b′:** **^{1}H NMR** (400 MHz, $CDCl_3$, observable peaks): δ_H 7.56 (d, *J* = 8.0 Hz, 2H, Ar**H**), 7.16 (d, *J* = 8.0 Hz, 2H, Ar**H**), 5.90 (s, 1H, C**H**N), 5.50 - 5.41 (m, 1H, C**H**=CH_2), 5.03 (d, *J* = 10.0 Hz, 1H, CH=C**H_{cis}**H_{trans}), 2.83 (ddd, *J* = 15.5, 9.0, 7.0 Hz, 1H, C**H**H′), 2.41 (s, 3H, ArC**H_3**); **^{13}C NMR** (100 MHz, $CDCl_3$, observable

peaks): δ_C 136.5 (**C**H=CH_2), 129.1 (Ar**C**H), 127.7 (Ar**C**H), 126.0 (Ar**C**H), 90.4 (**C**HNO_2), 68.2 (**C**HN), 62.4 (N**C**HCH=CH_2); **IR** (film/cm^{-1}): ν_{max} 2922, 1546, 1513, 1351, 1163, 1096, 1028, 1013, 916, 817, 806, 664; **MS** (ESI): *m/z* 409.1 $[(M + Na)^+]$; **HRMS** (ESI): exact mass calculated for $C_{20}H_{22}N_2NaO_4S$ $[(M + Na)^+]$, 409.1192; found 409.1186.

Synthesis and characterisation of *rac*-(2*S*,3*R*,5*S*)-2-(2-methoxyphenyl)-1-[(4-methylphenyl)sulfonyl]-3-nitro-5-vinylpyrrolidine (471c) and *rac*-(2*S*,3*R*,5*R*)-2-(2-methoxyphenyl)-1-[(4-methylphenyl)sulfonyl]-3-nitro-5-vinylpyrrolidine (471c′)

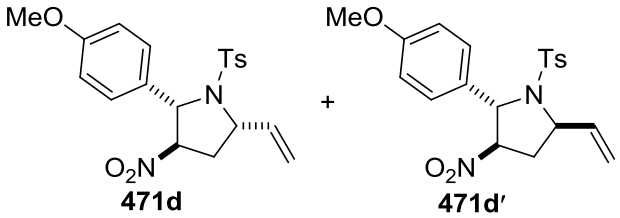


471c **471c′**

Prepared according to general procedure H. *N*-Sulfonyl imine **257c** (57.9 mg, 0.20 mmol) was reacted with nitroallene **468** (33.9 mg, 0.30 mmol) for 12 h (step i), 4 h (step ii) and 3 h (step iii) to afford a mixture of diastereomers **471c** and **471c′** (63 mg, 78%, dr 91:9) as a pale yellow solid, after purification by flash column chromatography on silica gel eluting with PE/EtOAc (6:1). **TLC**: R_f = 0.27 (PE/EtOAc 6:1, UV, $KMnO_4$); **Melting Point**: 156 - 158 °C; **Major diastereomer 471c: ^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.74 (d, *J* = 8.0 Hz, 2H, Ar**H**), 7.64 - 7.59 (m, 1H, Ar**H**), 7.39 - 7.28 (m, 3H, Ar**H**), 7.03 (t, *J* = 7.5 Hz, 1H, Ar**H**), 6.89 (d, *J* = 8.5 Hz, 1H, Ar**H**), 6.14 (ddd, *J* = 17.5, 10.0, 8.0 Hz, 1H, C**H**=CH_2), 5.77 (s, 1H, C**H**N), 5.33 (d, *J* = 17.5 Hz, 1H, CH=CH_{cis}**H**$_{trans}$), 5.31 (d, *J* = 10.0 Hz, 2H, CH=C**H**$_{cis}$H$_{trans}$), 4.73 (d, *J* = 6.0 Hz, 1H, C**H**NO_2), 4.30 - 4.21 (m, 1H, NC**H**CH=CH_2), 3.86 (s, 3H, ArOC**H$_3$**), 2.52 - 2.39 (m, 4H, ArC**H$_3$** and C**H**H′), 2.20 - 2.09 (m, 1H, CH**H′**); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 155.5 (Ar**C**), 144.0 (Ar**C**),

137.6 (**C**H=CH_2), 134.0 (Ar**C**), 129.5 (2 × Ar**C**H), 129.5 (Ar**C**H), 128.0 (2 × Ar**C**H), 127.4 (Ar**C**H), 127.0 (Ar**C**), 120.7 (Ar**C**H), 117.6 (CH=**C**H_2), 110.2 (Ar**C**H), 88.3 (**C**HNO_2), 64.8 (**C**HN), 62.2 (N**C**HCH=CH_2), 55.3 (ArO**C**H_3), 36.0 (**C**H_2), 21.6 (Ar**C**H_3); **Minor diastereomer 471c′: ^{1}H NMR** (400 MHz, $CDCl_3$, observable peaks): δ_H 7.48 (d, *J* = 7.5 Hz, 1H, Ar**H**), 7.23 (d, *J* = 8.0 Hz, 2H, Ar**H**), 6.84 (d, *J* = 8.0 Hz, 1H, Ar**H**), 5.04 - 4.98 (m, 1H, CH=C**H**H′), 3.80 (s, 3H, ArOC**H$_3$**), 2.75 (ddd, *J* = 15.5, 9.0, 7.0 Hz, 1H, C**H**H′); **^{13}C NMR** (100 MHz, $CDCl_3$, observable peaks): δ_C 143.1 (Ar**C**), 136.3 (**C**H=CH_2), 129.0 (Ar**C**H), 127.7 (Ar**C**H), 120.9 (Ar**C**H), 118.5 (CH=**C**H_2), 110.3 (Ar**C**H), 88.2 (**C**HNO_2), 64.6 (**C**HN), 62.6 (N**C**HCH=CH_2), 55.2 (ArO**C**H_3), 36.2 (**C**H_2), 21.5 (Ar**C**H_3); **IR** (film/cm^{-1}): ν_{max} 2919, 1552, 1370, 1343, 1286, 1250, 1156, 1091, 1027, 1003, 814, 756, 663; **MS** (ESI): *m/z* 425.1 [(M + Na)$^+$]; **HRMS** (ESI): exact mass calculated for $C_{20}H_{22}N_2NaO_5S$ [(M + Na)$^+$], 425.1142; found 425.1138.

Synthesis of characterisation of *rac*-(2*S*,3*R*,5*S*)-2-(4-methoxyphenyl)-1-[(4-methylphenyl)sulfonyl]-3-nitro-5-vinylpyrrolidine (471d) and *rac*-(2*S*,3*R*,5*R*)-2-(4-methoxyphenyl)-1-[(4-methylphenyl)sulfonyl]-3-nitro-5-vinylpyrrolidine (471d ′)

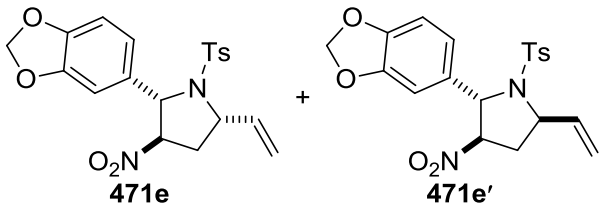


471d **471d′**

Prepared according to general procedure H. *N*-Sulfonyl imine **257e** (57.9 mg, 0.20 mmol) was reacted with nitroallene **468** (33.9 mg, 0.30 mmol) for 11 h (step i), 10 h (step ii) and 4 h (step iii) to afford a mixture of diastereomers **471d** and **471d′** (25 mg, 31%, dr 93:7) as an off-white solid, after purification by flash column chromatography on silica gel eluting with PE/EtOAc (4:1). **TLC**: R_f = 0.43

(PE/EtOAc 4:1, UV, $KMnO_4$); **Melting Point**: 129 - 132 °C; **Major diastereomer 471d:** ^{1}**H NMR** (400 MHz, $CDCl_3$): δ_H 7.65 (d, *J* = 8.0 Hz, 2H, Ar**H**), 7.36 (d, *J* = 8.5 Hz, 2H, Ar**H**), 7.31 (d, *J* = 8.0 Hz, 2H, Ar**H**), 6.92 (d, *J* = 8.5 Hz, 2H, Ar**H**), 6.08 (ddd, *J* = 17.0, 10.0, 7.5 Hz, 1H, C**H**=CH_2), 5.52 (s, 1H, C**H**N), 5.37 (d, *J* = 17.0 Hz, 1H, CH=CH_{cis}**H**$_{\boldsymbol{trans}}$), 5.31 (d, *J* = 10.0 Hz, 1H, CH=C**H**$_{\boldsymbol{cis}}$$H_{trans}$), 4.72 - 4.64 (m, 1H, C**H**NO_2), 4.40 - 4.31 (m, 1H, NC**H**CH=CH_2), 3.83 (s, 3H, ArOC**H$_3$**), 2.64 - 2.55 (m, 1H, C**H**H′), 2.46 (s, 3H, ArC**H$_3$**), 2.18 (ddd, *J* = 14.5, 9.0, 6.0 Hz, 1H, CH**H′**); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ_C 159.6 (Ar**C**), 144.1 (Ar**C**), 137.5 (**C**H=CH_2), 134.2 (Ar**C**), 130.9 (Ar**C**), 129.6 (2 × Ar**C**H), 127.8 (2 × Ar**C**H), 127.4 (2 × Ar**C**H), 117.8 (CH=**C**H_2), 114.3 (2 × Ar**C**H), 90.2 (**C**HNO_2), 68.5 (**C**HN), 62.0 (N**C**HCH=CH_2), 55.4 (ArO**C**H_3), 34.9 (**C**H_2), 21.6 (Ar**C**H_3); **Minor diastereomer 471d′:** ^{1}**H NMR** (400 MHz, $CDCl_3$, observable peaks): δ_H 7.54 (d, *J* = 8.0 Hz, 2H, Ar**H**), 7.25 - 7.16 (m, 4H, Ar**H**), 6.87 (d, *J* = 8.5 Hz, 2H, Ar**H**), 5.87 (s, 1H, C**H**N), 5.05 (d, *J* = 10.0 Hz, 1H, CH=C**H**$_{\boldsymbol{cis}}$$H_{trans}$), 2.84 (ddd, *J* = 15.5, 8.5, 7.0 Hz, 1H, C**H**H′), 2.41 (s, 3H, ArC**H$_3$**); **IR** (film/cm^{-1}): ν_{max} 2921, 1550, 1511, 1339, 1249, 1161, 1087, 1020, 1005, 839, 815, 665; **MS** (ESI): *m/z* 425.2 [$(M + Na)^+$]; **HRMS** (ESI): exact mass calculated for $C_{20}H_{22}N_2NaO_5S$ [$(M + Na)^+$], 425.1142; found 425.1139.

Synthesis and characterisation of *rac*-(2*S*,3*R*,5*S*)-2-(1,3-benzodioxol-5-yl)-1-[(4-methylphenyl)sulfonyl]-3-nitro-5-vinylpyrrolidine (471e) and *rac*-(2*S*,3*R*,5*R*)-2-(1,3-benzodioxol-5-yl)-1-[(4-methylphenyl)sulfonyl]-3-nitro-5-vinylpyrrolidine (471e′)

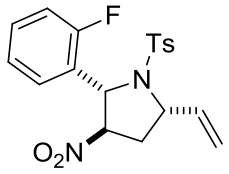


471e **471e′**

Prepared according to general procedure H. *N*-Sulfonyl imine **257f** (30.3 mg, 0.10 mmol) was reacted with nitroallene **468** (17.0 mg, 0.15 mmol) for 58 h (step i), 9 h (step ii) and 4 h (step iii) to afford a mixture of diastereomers **471e** and **471e′** (14 mg, 32%, dr 90:10) as an off-white solid, after purification by flash column chromatography on silica gel eluting with PE/EtOAc (3:1). **TLC**: R_f = 0.47 (PE/EtOAc 3:1, UV, $KMnO_4$); **Melting Point**: 142 - 144 °C; **Major diastereomer 471e:** ^{1}**H NMR** (500 MHz, $CDCl_3$): δ_H 7.70 - 7.62 (m, 2H, Ar**H**), 7.32 (d, *J* = 8.0 Hz, 2H, Ar**H**), 6.94 - 6.88 (m, 2H, Ar**H**), 6.85 - 6.78 (m, 1H, Ar**H**), 6.08 (ddd, *J* = 17.5, 10.0, 7.5 Hz, 1H, C**H**=CH_2), 6.02 - 5.97 (m, 2H, OC**H$_2$**O), 5.45 (s, 1H, C**H**N), 5.37 (d, *J* = 17.5 Hz, 1H, CH=CH_{cis}**H$_{trans}$**), 5.33 (d, *J* = 10.0 Hz, 1H, CH=C**H$_{cis}$**H_{trans}), 4.69 - 4.64 (m, 1H, C**H**NO_2), 4.37 - 4.28 (m, 1H, NC**H**CH=CH_2), 2.62 - 2.53 (m, 1H, C**H**H′), 2.48 - 2.44 (m, 3H, ArC**H$_3$**), 2.19 (ddd, *J* = 15.0, 9.0, 6.0 Hz, 1H, CH**H′**); ^{13}**C NMR** (125 MHz, $CDCl_3$): δ_C 148.3 (Ar**C**), 147.7 (Ar**C**), 144.2 (Ar**C**), 137.4 (**C**H=CH_2), 134.0 (Ar**C**), 132.9 (Ar**C**), 129.7 (2 × Ar**C**H), 127.8 (2 × Ar**C**H), 119.7 (Ar**C**H), 117.9 (CH=**C**H_2), 108.5 (Ar**C**H), 106.6 (Ar**C**H), 101.4 (O**C**H_2O), 90.2 (**C**HNO_2), 68.7 (**C**HN), 62.0 (N**C**HCH=CH_2), 34.9 (**C**H_2), 21.6 (Ar**C**H_3); **Minor diastereomer 471e′:** ^{1}**H NMR** (500 MHz, $CDCl_3$, observable peaks): δ_H 7.59 - 7.53 (m, 2H, Ar**H**), 7.21 (d, *J* = 8.0 Hz, 2H, Ar**H**), 5.81 (s, 1H, C**H**N), 5.04 (d, *J* = 10.0 Hz, 1H, CH=C**H$_{cis}$**H_{trans}), 2.84 (ddd, *J* = 16.0, 9.5, 7.5 Hz, 1H, C**H**H′), 2.41 (s, 3H,

Ar**C**$\mathbf{H_3}$); ^{13}**C NMR** (125 MHz, $CDCl_3$, observable peaks): δ_C 147.7 (Ar**C**), 143.4 (Ar**C**), 138.1 (Ar**C**), 136.4 (**C**H=CH_2), 132.4 (Ar**C**), 129.1 (2 × Ar**C**H), 127.7 (2 × Ar**C**H), 119.9 (Ar**C**H), 118.5 (CH=**C**H_2), 108.3 (Ar**C**H), 106.5 (Ar**C**H), 102.1 (O**C**H_2O), 90.4 (**C**HNO_2), 68.0 (**C**HN), 62.6 (N**C**HCH=CH_2), 35.3 (**C**H_2), 21.5 (Ar**C**H_3); **IR** (film/cm^{-1}): ν_{max} 2887, 1548, 1487, 1348, 1231, 1162, 1098, 1028, 1013, 915, 819; **MS** (ESI): *m/z* 439.1 [$(M + Na)^+$]; **HRMS** (ESI): exact mass calculated for $C_{20}H_{20}N_2NaO_6S$ [$(M + Na)^+$], 439.0934; found 439.0926.

Synthesis and characterisation of *rac*-(2*S*,3*R*,5*S*)-2-(2-fluorophenyl)-1-[(4-methylphenyl)sulfonyl]-3-nitro-5-vinylpyrrolidine (471f)

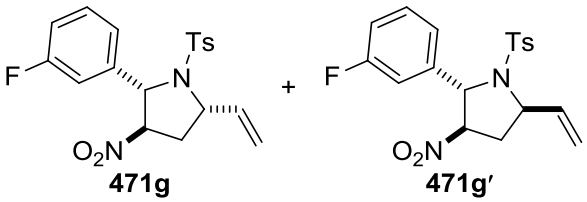


471f

Prepared according to general procedure H. *N*-Sulfonyl imine **257g** (55.5 mg, 0.20 mmol) was reacted with nitroallene **468** (33.9 mg, 0.30 mmol) for 16 h (step i), 12 h (step ii) and 2 h (step iii) to afford compound **471f** (62 mg, 79%, dr >98:2) as an off-white solid, after purification by flash column chromatography on silica gel eluting with PE/EtOAc (5:1). **TLC**: R_f = 0.39 (PE/EtOAc 5:1, UV, $KMnO_4$); **Melting Point**: 118 - 120 °C; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ_H 7.71 (d, *J* = 8.0 Hz, 2H, Ar**H**), 7.64 (t, *J* = 7.5 Hz, 1H, Ar**H**), 7.39 - 7.31 (m, 3H, Ar**H**), 7.23 (t, *J* = 7.5 Hz, 1H, Ar**H**), 7.14 - 7.05 (m, 1H, Ar**H**), 6.13 (ddd, *J* = 17.0, 10.0, 7.5 Hz, 1H, C**H**=CH_2), 5.79 (s, 1H, C**H**N), 5.36 (d, *J* = 17.0 Hz, 1H, CH=$CH_{cis}\mathbf{H}_{\boldsymbol{trans}}$), 5.34 (d, *J* = 10.0 Hz, 1H, CH=C$\mathbf{H}_{\boldsymbol{cis}}H_{trans}$), 4.76 (d, *J* = 6.0 Hz, 1H, C**H**NO_2), 4.31 - 4.20 (m, 1H, NC**H**CH=CH_2), 2.65 - 2.53 (m, 1H, C**H**H′), 2.47 (s, 3H, Ar$\mathbf{CH_3}$), 2.25 - 2.13 (m, 1H, CH**H′**); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ_C 159.3 (d, *J* = 247.0 Hz, Ar**C**F), 144.3

(Ar**C**), 137.2 (**C**H=CH_2), 133.5 (Ar**C**), 130.3 (d, *J* = 9.0 Hz, Ar**C**H), 129.7 (2 × Ar**C**H), 128.3 (d, *J* = 3.0 Hz, Ar**C**H), 127.9 (2 × Ar**C**H), 126.2 (d, *J* = 12.0 Hz, Ar**C**), 124.6 (d, *J* = 3.0 Hz, Ar**C**H), 118.0 (CH=**C**H_2), 115.6 (d, *J* = 21.0 Hz, Ar**C**H), 88.2 (**C**HNO_2), 63.6 (d, *J* = 2.5 Hz, **C**HN), 62.0 (N**C**HCH=CH_2), 35.6 (**C**H_2), 21.6 (Ar**C**H_3); **^{19}F NMR** (376.5 MHz, $CDCl_3$): δ_F –116.6 (Ar**F**); **IR** (film/cm^{-1}): ν_{max} 2922, 1552, 1485, 1368, 1345, 1159, 1090, 1027, 1021, 816, 766, 666; **MS** (ESI): *m/z* 413.0 [$(M + Na)^+$]; **HRMS** (ESI): exact mass calculated for $C_{19}H_{19}FN_2NaO_4S$ [$(M + Na)^+$], 413.0942; found 413.0938.

Synthesis and characterisation of *rac*-(2*S*,3*R*,5*S*)-2-(3-fluorophenyl)-1-[(4-methylphenyl)sulfonyl]-3-nitro-5-vinylpyrrolidine (471g) and *rac*-(2*S*,3*R*,5*R*)-2-(3-fluorophenyl)-1-[(4-methylphenyl)sulfonyl]-3-nitro-5-vinylpyrrolidine (471g′)

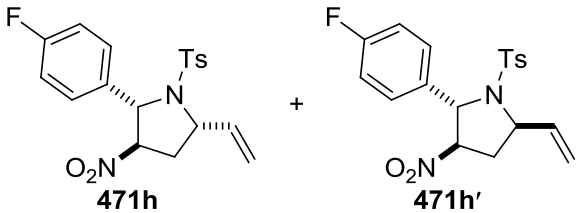


471g **471g′**

Prepared according to general procedure H. *N*-Sulfonyl imine **257h** (55.5 mg, 0.20 mmol) was reacted with nitroallene **468** (33.9 mg, 0.30 mmol) for 20 h (step i), 8 h (step ii) and 2 h (step iii) to afford a mixture of diastereomers **471g** and **471g′** (57 mg, 73%, dr 93:7) as a white solid, after purification by flash column chromatography on silica gel eluting with PE/EtOAc (5:1). **TLC**: R_f = 0.42 (PE/EtOAc 5:1, UV, $KMnO_4$); **Melting Point**: 166 - 167 °C; **Major diastereomer 471g: ^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.66 (d, *J* = 8.0 Hz, 2H, Ar**H**), 7.43 - 7.30 (m, 3H, Ar**H**), 7.29 - 7.13 (m, 2H, Ar**H**), 7.09 - 6.98 (m, 1H, Ar**H**), 6.08 (ddd, *J* = 17.5, 10.0, 7.5 Hz, 1H, C**H**=CH_2), 5.57 (s, 1H, C**H**N), 5.38 (d, *J* = 17.5 Hz, 1H, CH=CH_{cis}**H**$_{trans}$), 5.34 (d, *J* = 10.0 Hz, 1H, CH=C**H**$_{cis}$$H_{trans}$), 4.76 - 4.63 (m, 1H, C**H**NO_2), 4.39 - 4.27 (m, 1H, NC**H**CH=CH_2), 2.69 - 2.55 (m, 1H, C**H**H′), 2.46 (s,

3H, ArC**H$_3$**), 2.17 (ddd, *J* = 14.5, 9.0, 6.0 Hz, 1H, CH**H′**); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 163.0 (d, *J* = 247.5 Hz, Ar**C**F), 144.4 (Ar**C**), 141.6 (d, *J* = 6.5 Hz, Ar**C**), 137.1 (**C**H=CH$_2$), 133.7 (Ar**C**), 130.6 (d, *J* = 9.0 Hz, Ar**C**H), 129.7 (2 × Ar**C**H), 127.8 (2 × Ar**C**H), 121.8 (d, *J* = 3.0 Hz, Ar**C**H), 118.1 (CH=**C**H$_2$), 115.4 (d, *J* = 21.5 Hz, Ar**C**H), 113.4 (d, *J* = 23.0 Hz, Ar**C**H), 89.8 (**C**HNO$_2$), 68.3 (d, *J* = 1.5 Hz, **C**HN), 62.1 (N**C**HCH=CH$_2$), 34.9 (**C**H$_2$), 21.6 (Ar**C**H$_3$); **^{19}F NMR** (376.5 MHz, $CDCl_3$): δ_F –111.3 (Ar**F**); **Minor diastereomer 471g′: ^{1}H NMR** (400 MHz, $CDCl_3$, observable peaks): δ_H 7.58 (d, *J* = 8.0 Hz, 2H, Ar**H**), 5.94 (s, 1H, C**H**N), 5.04 (d, *J* = 9.5 Hz, 1H, C**H**NO$_2$), 2.88 - 2.75 (m, 1H, C**H**H′), 2.42 (s, 3H, ArC**H$_3$**); **^{13}C NMR** (100 MHz, $CDCl_3$, observable peaks): δ_C 143.6 (Ar**C**), 141.2 (Ar**C**), 137.9 (Ar**C**), 136.1 (**C**H=CH$_2$), 129.2 (2 × Ar**C**H), 127.6 (2 × Ar**C**H), 118.7 (CH=**C**H$_2$), 113.2 (d, *J* = 23.0 Hz, Ar**C**H), 90.0 (**C**HNO$_2$), 67.6 (**C**HN), 62.5 (N**C**HCH=CH$_2$), 35.3 (**C**H$_2$), 21.5 (Ar**C**H$_3$); **^{19}F NMR** (376.5 MHz, $CDCl_3$): δ_F –111.4 (Ar**F**); **IR** (film/cm^{-1}): ν_{max} 1543, 1369, 1342, 1164, 1119, 1090, 1029, 1013, 916, 816, 786, 698, 665; **MS** (ESI): *m/z* 413.1 [(M + Na)$^+$]; **HRMS** (ESI): exact mass calculated for $C_{19}H_{19}FN_2NaO_4S$ [(M + Na)$^+$], 413.0942; found 413.0939.

Synthesis and characterisation of *rac*-(2*S*,3*R*,5*S*)-2-(4-fluorophenyl)-1-[(4-methylphenyl)sulfonyl]-3-nitro-5-vinylpyrrolidine (471h) and *rac*-(2*S*,3*R*,5*R*)-2-(4-fluorophenyl)-1-[(4-methylphenyl)sulfonyl]-3-nitro-5-vinylpyrrolidine (471h′)



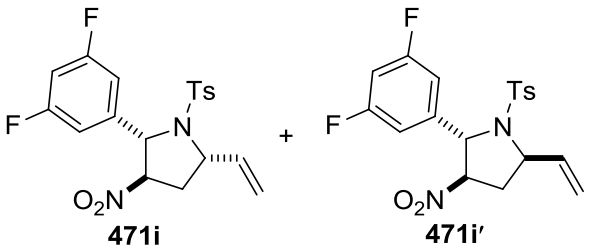
471h **471h′**

Prepared according to general procedure H. *N*-Sulfonyl imine **257i** (55.5 mg, 0.20 mmol) was reacted with nitroallene **468** (33.9 mg, 0.30 mmol) for 41 h (step i), 24 h (step ii) and 3 h (step iii) to afford a mixture of diastereomers **471h** and **471h′**

(26 mg, 33%, dr 84:16) as an off-white solid, after purification by flash column chromatography on silica gel eluting with PE/EtOAc (5:1). **TLC**: R_f = 0.35 (PE/EtOAc 5:1, UV, $KMnO_4$); **Melting Point:** 132 - 134 °C; **Major diastereomer 471h:** ^{1}**H NMR** (500 MHz, $CDCl_3$): δ_H 7.68 - 7.63 (m, 2H, Ar**H**), 7.47 - 7.40 (m, 2H, Ar**H**), 7.36 - 7.28 (m, 2H, Ar**H**), 7.12 - 7.02 (m, 2H, Ar**H**), 6.07 (ddd, *J* = 17.5, 10.5, 7.5 Hz, 1H, C**H**=CH_2), 5.54 (s, 1H, C**H**N), 5.37 (d, *J* = 17.5 Hz, 1H, CH=CH_{cis}**H**$_{\boldsymbol{trans}}$), 5.33 (d, *J* = 10.5 Hz, 1H, CH=C**H**$_{\boldsymbol{cis}}$$H_{trans}$), 4.70 - 4.66 (m, 1H, C**H**NO_2), 4.39 - 4.32 (m, 1H, NC**H**CH=CH_2), 2.66 - 2.57 (m, 1H, C**H**H′), 2.46 (s, 3H, ArC**H$_3$**), 2.18 (ddd, *J* = 15.0, 9.0, 6.0 Hz, 1H, CH**H′**); ^{13}**C NMR** (125 MHz, $CDCl_3$): δ_C 162.6 (d, *J* = 248.0 Hz, Ar**C**F), 144.4 (Ar**C**), 137.3 (**C**H=CH_2), 134.7 (d, *J* = 3.0 Hz, Ar**C**), 133.9 (Ar**C**), 129.7 (2 × Ar**C**H), 127.9 (d, *J* = 7.5 Hz, 2 × Ar**C**H), 127.8 (2 × Ar**C**H), 118.0 (CH=**C**H_2), 115.9 (d, *J* = 22.0 Hz, 2 × Ar**C**H), 90.0 (**C**HNO_2), 68.3 (**C**HN), 62.0 (N**C**HCH=CH_2), 34.9 (**C**H_2), 21.6 (Ar**C**H_3); ^{19}**F NMR** (470.5 MHz, $CDCl_3$): δ_F –113.5 (Ar**F**); **Minor diastereomer 471h′:** ^{1}**H NMR** (500 MHz, $CDCl_3$, observable peaks): δ_H 7.58 - 7.53 (m, 2H, Ar**H**), 7.31 - 7.28 (m, 2H, Ar**H**), 7.23 - 7.19 (m, 2H, Ar**H**), 5.91 (s, 1H, C**H**N), 5.47 - 5.40 (m, 1H, C**H**=CH_2), 5.05 (d, *J* = 10.0 Hz, 1H, CH=C**H**$_{\boldsymbol{cis}}$$H_{trans}$), 4.74 - 4.70 (m, 1H, NC**H**CH=CH_2), 4.66 - 4.63 (m, 1H, C**H**NO_2), 2.82 (ddd, *J* = 16.0, 9.5, 7.0 Hz, 1H, C**H**H′), 2.42 (m, 3H, ArC**H$_3$**); ^{13}**C NMR** (125 MHz, $CDCl_3$, observable peaks): δ_C 143.6 (Ar**C**), 138.0 (Ar**C**), 136.2 (**C**H=CH_2), 134.5 (d, *J* = 3.0 Hz, Ar**C**), 129.2 (2 × Ar**C**H), 127.9 (d, *J* = 8.5 Hz, 2 × Ar**C**H), 127.7 (2 × Ar**C**H), 118.7 (CH=**C**H_2), 116.0 (d, *J* = 22.0 Hz, 2 × Ar**C**H), 90.2 (**C**HNO_2), 67.6 (**C**HN), 62.5 (N**C**HCH=CH_2), 35.3 (**C**H_2), 21.5 (Ar**C**H_3); ^{19}**F NMR** (470.5 MHz, $CDCl_3$): δ_F –113.4 (Ar**F**); **IR** (film/cm^{-1}): ν_{max} 2923, 1605, 1553, 1509, 1349, 1225, 1163, 1095, 1027, 1012, 843, 814, 668; **MS**

(ESI): *m/z* 413.1 [(M + Na)$^+$]; **HRMS** (ESI): exact mass calculated for $C_{19}H_{19}FN_2NaO_4S$ [(M + Na)$^+$], 413.0942; found 413.0941.

Synthesis and characterisation of *rac*-(2*S*,3*R*,5*S*)-2-(3,5-difluorophenyl)-1-[(4-methylphenyl)sulfonyl]-3-nitro-5-vinylpyrrolidine (471i) and *rac*-(2*S*,3*R*,5*R*)-2-(3,5-difluorophenyl)-1-[(4-methylphenyl)sulfonyl]-3-nitro-5-vinylpyrrolidine (471i′)

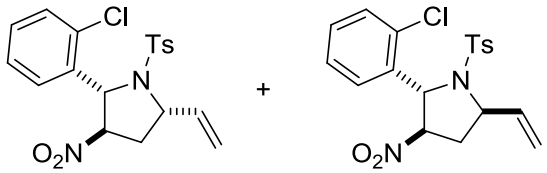


471i **471i′**

Prepared according to general procedure H. *N*-Sulfonyl imine **257j** (59.1 mg, 0.20 mmol) was reacted with nitroallene **468** (33.9 mg, 0.30 mmol) for 16 h (step i), 20 h (step ii) and 1 h (step iii) to afford a mixture of diastereomers **471i** and **471i′** (54 mg, 66%, dr 81:19) as a white solid, after purification by flash column chromatography on silica gel eluting with PE/EtOAc (6:1). **TLC**: R_f = 0.41 (PE/EtOAc 6:1, UV, $KMnO_4$); **Melting Point**: 157 - 160 °C; **Major diastereomer 471i: ^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.67 (d, *J* = 8.0 Hz, 2H, Ar**H**), 7.35 (d, *J* = 8.0 Hz, 2H, Ar**H**), 7.06 - 6.97 (m, 2H, Ar**H**), 6.83 - 6.73 (m, 1H, Ar**H**), 6.07 (ddd, *J* = 17.0, 10.0, 7.5 Hz, 1H, C**H**=CH_2), 5.57 (s, 1H, C**H**N), 5.37 (d, *J* = 17.0 Hz, 1H, CH=CH_{cis}**H**$_{trans}$), 5.35 (d, *J* = 10.0 Hz, 1H, CH=C**H**$_{cis}$H$_{trans}$), 4.75 - 4.62 (m, 1H, C**H**NO_2), 4.34 - 4.25 (m, 1H, NC**H**CH=CH_2), 2.69 - 2.57 (m, 1H, C**H**H′), 2.47 (s, 3H, ArC**H**$_3$), 2.16 (ddd, *J* = 15.0, 9.0, 6.0 Hz, 1H, CH**H′**); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ_C 163.2 (dd, *J* = 250.0, 13.0 Hz, 2 × Ar**C**F), 144.6 (Ar**C**), 143.1 (t, *J* = 8.5 Hz, Ar**C**), 136.9 (**C**H=CH_2), 133.4 (Ar**C**), 129.8 (2 × Ar**C**H), 127.8 (2 × Ar**C**H), 118.3 (CH=**C**H_2), 109.4 (dd, *J* = 19.0, 8.0 Hz, 2 × Ar**C**H), 104.0 (t, *J* = 25.0 Hz, Ar**C**H), 89.5 (**C**HNO_2), 67.9 (t, *J* = 2.5 Hz, **C**HN), 62.1 (N**C**HCH=CH_2), 34.9 (**C**H_2),

21.6 (Ar**C**CH_3); **^{19}F NMR** (376.5 MHz, $CDCl_3$): δ_F –107.5 (2 × Ar**F**); **Minor diastereomer 471i′: ^{1}H NMR** (400 MHz, $CDCl_3$, observable peaks): δ_H 7.60 (d, *J* = 8.0 Hz, 2H, Ar**H**), 7.24 (d, *J* = 8.0 Hz, 2H, Ar**H**), 6.92 - 6.85 (m, 2H, Ar**H**), 5.91 (s, 1H, C**H**N), 5.07 - 5.02 (m, 1H, CH=C**H**H′), 4.75 - 4.62 (m, 2H, NC**H**CH=CH_2 and C**H**NO_2), 2.80 (ddd, *J* = 15.5, 9.0, 7.0 Hz, 1H, C**H**H′), 2.42 (s, 3H, ArC**H$_3$**); **^{13}C NMR** (100 MHz, $CDCl_3$, observable peaks): δ_C 143.8 (Ar**C**), 142.8 (Ar**C**), 137.7 (Ar**C**), 135.7 (**C**H=CH_2), 129.2 (2 × Ar**C**H), 127.7 (2 × Ar**C**H), 119.0 (CH=**C**H_2), 103.9 (t, *J* = 25.5 Hz, Ar**C**H), 89.7 (C**H**NO_2), 67.2 (t, *J* = 2.5 Hz, **C**HN), 62.6 (N**C**HCH=CH_2), 35.2 (**C**H_2), 21.5 (Ar**C**H_3); **IR** (film/cm^{-1}): ν_{max} 1598, 1551, 1346, 1166, 1116, 1011, 997, 918, 816, 666, 652; **MS** (ESI): *m/z* 431.0 [(M + Na)$^+$]; **HRMS** (ESI): exact mass calculated for $C_{19}H_{18}F_2N_2NaO_4S$ [(M + Na)$^+$], 431.0848; found 431.0850.

Synthesis and characterisation of *rac*-(2*S*,3*R*,5*S*)-2-(2-chlorophenyl)-1-[(4-methylphenyl)sulfonyl]-3-nitro-5-vinylpyrrolidine (471j) and *rac*-(2*S*,3*R*,5*R*)-2-(2-chlorophenyl)-1-[(4-methylphenyl)sulfonyl]-3-nitro-5-vinylpyrrolidine (471j′)

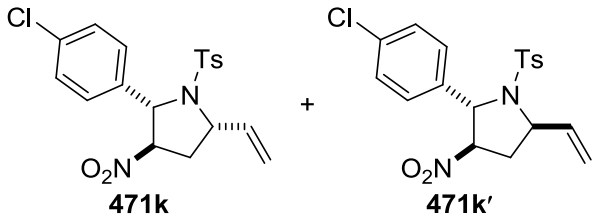


471j **471j′**

Prepared according to general procedure H. *N*-Sulfonyl imine **257t** (58.8 mg, 0.20 mmol) was reacted with nitroallene **468** (33.9 mg, 0.30 mmol) for 14 h (step i), 11 h (step ii) and 3 h (step iii) to afford a mixture of diastereomers **471j** and **471j′** (51 mg, 62%, dr 84:16) as a white solid, after purification by flash column chromatography on silica gel eluting with PE/EtOAc (5:1). **TLC**: R_f = 0.24 (PE/EtOAc 5:1, UV, $KMnO_4$); **Melting Point**: 109 - 110 °C; **Major diastereomer 471j: ^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.78 - 7.70 (m, 3H, Ar**H**), 7.45 - 7.25 (m, 5H,

Ar**H**), 6.19 (ddd, *J* = 17.5, 10.0, 7.5 Hz, 1H, C**H**=CH_2), 5.87 (s, 1H, C**H**N), 5.36 (d, *J* = 10.0 Hz, 1H, CH=C$\mathbf{H}_{\boldsymbol{cis}}H_{trans}$), 5.35 (d, *J* = 17.5 Hz, 1H, CH=$CH_{cis}\mathbf{H}_{\boldsymbol{trans}}$), 4.74 - 4.68 (m, 1H, C**H**NO_2), 4.23 - 4.13 (m, 1H, NC**H**CH=CH_2), 2.58 - 2.50 (m, 1H, C**H**H′), 2.48 (s, 3H, ArC$\mathbf{H_3}$), 2.19 (ddd, *J* = 14.5, 11.0, 6.0 Hz, 1H, CH**H′**); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 144.4 (Ar**C**), 137.2 (**C**H=CH_2), 136.4 (Ar**C**), 133.3 (Ar**C**), 131.9 (Ar**C**), 129.9 (Ar**C**H), 129.7 (3 × Ar**C**H), 128.3 (Ar**C**H), 128.1 (2 × Ar**C**H), 127.4 (Ar**C**H), 118.0 (CH=**C**H_2), 88.0 (**C**HNO_2), 66.2 (**C**HN), 62.3 (N**C**HCH=CH_2), 35.9 (**C**H_2), 21.7 (Ar**C**H_3); **Minor diastereomer 471j′: ^{1}H NMR** (500 MHz, $CDCl_3$, observable peaks): δ_H 7.66 - 7.52 (m, 2H, Ar**H**), 6.29 (s, 1H, C**H**N), 5.32 (dd, *J* = 17.0, 1.0 Hz, 1H, CH=$CH_{cis}\mathbf{H}_{\boldsymbol{trans}}$), 5.25 - 5.15 (m, 1H, C**H**=CH_2), 5.00 (dd, *J* = 10.0, 1.0 Hz, 1H, CH=C$\mathbf{H}_{\boldsymbol{cis}}H_{trans}$), 4.85 - 4.78 (m, 1H, NC**H**CH=CH_2), 2.77 (ddd, *J* = 15.5, 9.5, 7.0, Hz, 1H, C**H**H′), 2.44 (s, 3H, ArC$\mathbf{H_3}$); **^{13}C NMR** (125 MHz, $CDCl_3$, observable peaks): δ_C 143.6 (Ar**C**), 138.2 (Ar**C**), 136.3 (Ar**C**), 135.7 (**C**H=CH_2), 131.4 (Ar**C**), 130.0 (Ar**C**H), 129.2 (2 × Ar**C**H), 127.9 (2 × Ar**C**H), 127.5 (Ar**C**H),119.3 (CH=**C**H_2), 88.2 (**C**HNO_2), 65.6 (**C**HN), 62.8 (N**C**HCH=CH_2), 35.7 (**C**H_2), 21.6 (Ar**C**H_3); **IR** (film/cm^{-1}): ν_{max} 2923, 1598, 1553, 1444, 1353, 1163, 1095, 1027, 1013, 930, 815, 758, 669; **MS** (ESI): *m/z* 429.1 [(M + Na)$^+$]; **HRMS** (ESI): exact mass calculated for $C_{19}H_{19}ClN_2NaO_4S$ [(M + Na)$^+$], 429.0646; found 429.0634.

Synthesis and characterisation of *rac*-(2*S*,3*R*,5*S*)-2-(4-chlorophenyl)-1-[(4-methylphenyl)sulfonyl]-3-nitro-5-vinylpyrrolidine (471k) and *rac*-(2*S*,3*R*,5*R*)-2-(4-chlorophenyl)-1-[(4-methylphenyl)sulfonyl]-3-nitro-5-vinylpyrrolidine (471k′)

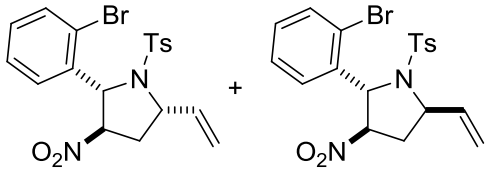


471k **471k′**

Prepared according to general procedure H. *N*-Sulfonyl imine **257k** (58.8 mg, 0.20 mmol) was reacted with nitroallene **468** (33.9 mg, 0.30 mmol) for 13 h (step i), 9 h (step ii) and 4 h (step iii) to afford a mixture of diastereomers **471k** and **471k′** (45 mg, 56%, dr 63:37) as an off-white solid, after purification by flash column chromatography on silica gel eluting with PE/EtOAc (3:1). **TLC**: R_f = 0.36 (PE/EtOAc 3:1, UV, $KMnO_4$); **Melting Point**: 126 - 127 °C; **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of diastereomers): δ_H 7.65 (d, *J* = 8.0 Hz, 2H, Ar**H**, *major*), 7.56 (d, *J* = 8.0 Hz, 2H, Ar**H**, *minor*), 7.44 - 7.30 (m, Ar**H**, 6H *major* and 2H *minor*), 7.29 - 7.25 (m, 2H, Ar**H**, *minor*), 7.22 (d, *J* = 8.0 Hz, 2H, Ar**H**, *minor*), 6.07 (ddd, *J* = 17.0, 10.0, 7.5 Hz, 1H, C**H**=CH_2, *major*), 5.90 (s, 1H, C**H**N, *minor*), 5.53 (s, 1H, C**H**N, *major*), 5.47 - 5.27 (m, CH=C$\mathbf{H}_{cis}\mathbf{H}_{trans}$, 2H *major*; C**H**=$CH_{cis}\mathbf{H}_{trans}$, 2H *minor*), 5.04 (d, *J* = 9.5 Hz, 1H, CH=C$\mathbf{H}_{cis}H_{trans}$, *minor*), 4.76 - 4.61 (m, 3H, C**H**NO_2, 1H *major* and 1H *minor*; NC**H**CH=CH_2, 1H *minor*), 4.38 - 4.29 (m, 1H, NC**H**CH=CH_2, *major*), 2.86 - 2.74 (m, 1H, C**H**H′, *minor*), 2.67 - 2.55 (m, 2H, CH**H′**, 1H *major* and 1H *minor*), 2.46 (s, 3H, ArC$\mathbf{H}_3$, *major*), 2.42 (s, 3H, ArC$\mathbf{H}_3$, *minor*), 2.21 - 2.11 (m, 1H, C**H**H', *major*); **^{13}C NMR** (100 MHz, $CDCl_3$, mixture of diastereomers): δ_C 144.4 (Ar**C**), 143.6 (Ar**C**), 138.0 (Ar**C**), 137.5 (Ar**C**), 137.2 (**C**H=CH_2, *major*), 137.2 (Ar**C**), 136.0 (**C**H=CH_2, *minor*), 134.4 (Ar**C**), 134.3 (Ar**C**), 133.8 (Ar**C**), 129.7 (2 × Ar**C**H, *major*), 129.2 (4 × Ar**C**H, *minor*), 129.1 (2 × Ar**C**H, *major*), 127.8

(2 × Ar**C**H, *major*), 127.7 (2 × Ar**C**H, *minor*), 127.6 (2 × Ar**C**H, *major*), 127.5 (2 × Ar**C**H, *minor*), 118.8 (CH=**C**H_2, *minor*), 118.1 (CH=**C**H_2, *major*), 90.1 (**C**HNO_2, *minor*), 89.8 (**C**HNO_2, *major*), 68.3 (**C**HN, *major*), 67.6 (**C**HN, *minor*), 62.5 (N**C**HCH=CH_2, *minor*), 62.0 (N**C**HCH=CH_2, *major*), 35.2 (**C**H_2, *minor*), 34.9 (**C**H_2, *major*), 21.6 (Ar**C**H_3, *major*), 21.5 (Ar**C**H_3, *minor*); **IR** (film/cm^{-1}): ν_{max} 2922, 1551, 1488, 1365, 1344, 1161, 1092, 1027, 1009, 927, 868, 812, 731, 666; **MS** (ESI): *m/z* 429.0 [$(M + Na)^+$]; **HRMS** (ESI): exact mass calculated for $C_{19}H_{19}ClN_2NaO_4S$ [$(M + Na)^+$], 429.0646; found 429.0645.

Synthesis and characterisation of *rac*-(2*S*,3*R*,5*S*)-2-(2-bromophenyl)-1-[(4-methylphenyl)sulfonyl]-3-nitro-5-vinylpyrrolidine (471l) and *rac*-(2*S*,3*R*,5*R*)-2-(2-bromophenyl)-1-[(4-methylphenyl)sulfonyl]-3-nitro-5-vinylpyrrolidine (471l)

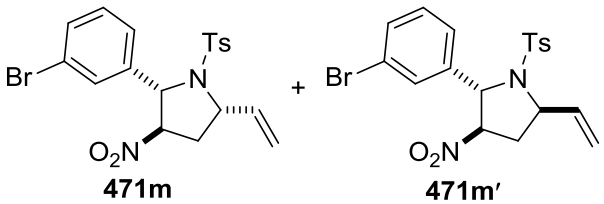


471l **471l′**

Prepared according to general procedure H. *N*-Sulfonyl imine **257u** (33.8 mg, 0.10 mmol) was reacted with nitroallene **468** (17.0 mg, 0.15 mmol) for 15 h (step i), 8 h (step ii) and 2 h (step iii) to afford a mixture of diastereomers **471l** and **471l′** (20 mg, 44%, dr 57:43) as a pale yellow solid, after purification by flash column chromatography on silica gel eluting with PE/EtOAc (6:1). **TLC**: R_f = 0.23 (PE/EtOAc 6:1, UV, $KMnO_4$); **Melting Point**: 122 - 124 °C; **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of diastereomers): δ_H 7.81 - 7.69 (m, Ar**H**, 2H *major* and 3H *minor*), 7.65 - 7.55 (m, Ar**H**, 1H *major* and 2H *minor*), 7.46 - 7.35 (m, Ar**H**, 3H *major* and 1H *minor*), 7.33 - 7.19 (m, Ar**H**, 2H *major* and 2H *minor*), 6.27 - 6.14 (m, C**H**=CH_2, 1H *major* and C**H**N, 1H *minor*), 5.83 (s, 1H, C**H**N, *major*), 5.40 - 5.27 (m, CH=C**HH'**, 2H *major* and CH=CH_{cis}**H**$_{trans}$, 1H *minor*), 5.24 - 5.11 (m, 1H, C**H**=CH_2,

minor), 4.99 (d, *J* = 10.0 Hz, 1H, CH=C**H**$_{\textit{cis}}$H$_{\textit{trans}}$, *minor*), 4.84 (t, *J* = 9.5 Hz, 1H, NC**H**CH=CH$_2$, *minor*), 4.75 - 4.67 (m, C**H**NO$_2$, 1H *major* and 1H *minor*), 4.21 - 4.09 (m, 1H, NC**H**CH=CH$_2$, *major*), 2.79 (ddd, *J* = 15.5, 9.5, 7.0 Hz, 1H, C**H**H', *minor*), 2.57 - 2.46 (m, ArC**H$_3$**, 3H *major*, C**H**H', 1H *major* and CH**H'**, 1H *minor*), 2.44 (s, 3H, ArC**H$_3$**, *minor*), 2.21 (ddd, *J* = 15.0, 11.0, 6.5 Hz, 1H, CH**H'**, *major*); **^{13}C NMR** (100 MHz, $CDCl_3$, unassigned mixture of diastereomers): δ_C 144.4 (Ar**C**), 143.6 (Ar**C**), 138.1 (Ar**C**), 137.9 (Ar**C**), 137.8 (Ar**C**), 137.7 (Ar**C**), 137.1 (**C**H=CH$_2$), 135.6 (**C**H=CH$_2$), 133.3 (Ar**C**H), 133.3 (Ar**C**H), 133.2 (Ar**C**H), 130.0 (Ar**C**H), 129.9 (Ar**C**H), 129.7 (Ar**C**H), 129.2 (Ar**C**H), 128.6 (Ar**C**H), 128.2 (Ar**C**H), 128.1 (Ar**C**H), 128.0 (Ar**C**H), 127.9 (Ar**C**H), 122.0 (Ar**C**), 121.3 (Ar**C**), 119.3 (CH=**C**H$_2$), 118.1 (CH=**C**H$_2$), 88.4 (**C**HNO$_2$), 88.1 (**C**HNO$_2$), 68.0 (**C**HN), 67.4 (**C**HN), 63.0 (N**C**HCH=CH$_2$), 62.4 (N**C**HCH=CH$_2$), 36.1 (**C**H$_2$), 35.7 (**C**H$_2$), 21.7 (Ar**C**H$_3$), 21.6 (Ar**C**H$_3$); **IR** (film/cm^{-1}): ν_{max} 2916, 1548, 1463, 1439, 1366, 1348, 1158, 1095, 1014, 935, 817, 751, 668; **MS** (ESI): *m/z* 472.9 [(M + Na)$^+$]; **HRMS** (ESI): exact mass calculated for $C_{19}H_{19}BrN_2NaO_4S$ [(M + Na)$^+$], 473.0141; found 473.0141.

Synthesis and characterisation of *rac*-(2*S*,3*R*,5*S*)-2-(3-bromophenyl)-1-[(4-methylphenyl)sulfonyl]-3-nitro-5-vinylpyrrolidine (471m) and *rac*-(2*S*,3*R*,5*R*)-2-(3-bromophenyl)-1-[(4-methylphenyl)sulfonyl]-3-nitro-5-vinylpyrrolidine (471m′)

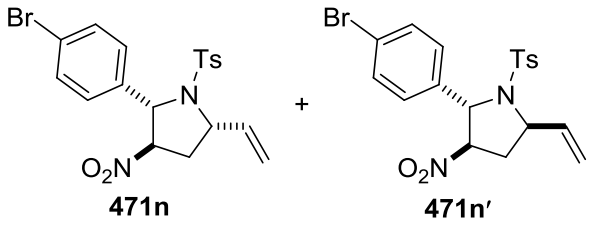


471m **471m′**

Prepared according to general procedure H. *N*-Sulfonyl imine **257l** (67.6 mg, 0.20 mmol) was reacted with nitroallene **468** (33.9 mg, 0.30 mmol) for 21 h (step i),

6 h (step ii) and 2 h (step iii) to afford a mixture of diastereomers **471m** and **471m′** (57 mg, 63%, dr 87:13) as an off-white solid, after purification by flash column chromatography on silica gel eluting with PE/EtOAc (7:1). **TLC**: R_f = 0.30 (PE/EtOAc 7:1, UV, $KMnO_4$); **Melting Point**: 146 - 148 °C; **Major diastereomer 471m:** ^{1}**H NMR** (400 MHz, $CDCl_3$): δ_H 7.65 (d, *J* = 8.5 Hz, 2H, Ar**H**), 7.57 - 7.51 (m, 1H, Ar**H**), 7.50 - 7.37 (m, 2H, Ar**H**), 7.36 - 7.24 (m, 3H, Ar**H**), 6.07 (ddd, *J* = 17.5, 10.0, 7.5 Hz, 1H, C**H**=CH_2), 5.54 (s, 1H, C**H**N), 5.39 (d, *J* = 17.5 Hz, 1H, CH=CH_{cis}**H**$_{trans}$), 5.35 (d, *J* = 10.0 Hz, 1H, CH=C**H**$_{cis}$$H_{trans}$), 4.70 - 4.66 (m, 1H, C**H**NO_2), 4.40 - 4.31 (m, 1H, NC**H**CH=CH_2), 2.70 - 2.57 (m, 1H, C**H**H′), 2.46 (s, 3H, ArC**H$_3$**), 2.17 (ddd, *J* = 15.0, 9.5, 6.0 Hz, 1H, CH**H′**); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ_C 144.4 (Ar**C**), 141.1 (Ar**C**), 137.1 (**C**H=CH_2), 133.8 (Ar**C**), 131.6 (Ar**C**H), 130.5 (Ar**C**H), 129.7 (2 × Ar**C**H), 129.2 (Ar**C**H), 127.8 (2 × Ar**C**H), 124.9 (Ar**C**H), 123.1 (Ar**C**), 118.2 (CH=**C**H_2), 89.8 (**C**HNO_2), 68.1 (**C**HN), 62.1 (N**C**HCH=CH_2), 34.9 (**C**H_2), 21.6 (Ar**C**H_3); **Minor diastereomer 471m′:** ^{1}**H NMR** (400 MHz, $CDCl_3$, observable peaks): δ_H 7.21 (d, *J* = 8.0 Hz, 2H, Ar**H**), 5.89 (s, 1H, C**H**N), 5.52 - 5.43 (m, 1H, C**H**=CH_2), 5.08 (d, *J* = 10.0 Hz, 1H, CH=C**H**H'), 4.75 - 4.71 (m, 1H, NC**H**CH=CH_2), 4.66 - 4.62 (m, 1H, C**H**NO_2), 2.82 (ddd, *J* = 15.5, 9.0, 7.0 Hz, 1H, C**H**H′), 2.42 (s, 3H, ArC**H$_3$**); ^{13}**C NMR** (100 MHz, $CDCl_3$, observable peaks): δ_C 136.3 (**C**H=CH_2), 129.1 (Ar**C**H), 127.5 (Ar**C**H), 125.1 (Ar**C**H), 118.6 (CH=**C**H_2), 90.0 (**C**HNO_2), 67.4 (**C**HN), 62.6 (N**C**HCH=CH_2), 35.3 (**C**H_2), 21.5 (Ar**C**H_3); **IR** (film/cm^{-1}): ν_{max} 3065, 2919, 1548, 1422, 1366, 1340, 1312, 1159, 1091, 1014, 988, 922, 813, 782; **MS** (ESI): *m/z* 473.0 [$(M + Na)^+$]; **HRMS** (ESI): exact mass calculated for $C_{19}H_{19}BrN_2NaO_4S$ [$(M + Na)^+$], 473.0141; found 473.0137.

Synthesis and characterisation of *rac*-(2*S*,3*R*,5*S*)-2-(4-bromophenyl)-1-[(4-methylphenyl)sulfonyl]-3-nitro-5-vinylpyrrolidine (471n) and *rac*-(2*S*,3*R*,5*R*)-2-(4-bromophenyl)-1-[(4-methylphenyl)sulfonyl]-3-nitro-5-vinylpyrrolidine (471n′)

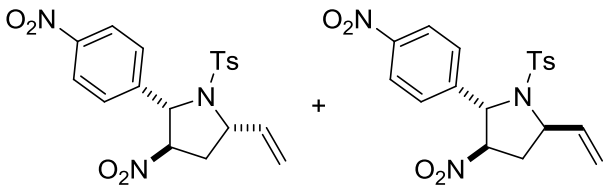


471n **471n′**

Prepared according to general procedure H. *N*-Sulfonyl imine **257v** (67.6 mg, 0.20 mmol) was reacted with nitroallene **468** (33.9 mg, 0.30 mmol) for 21 h (step i), 4 h (step ii) and 1 h (step iii) to afford a mixture of diastereomers **471n** and **471n′** (47 mg, 52%, dr 83:17) as an off-white solid, after purification by flash column chromatography on silica gel eluting with PE/EtOAc (5:1). **TLC**: R_f = 0.36 (PE/EtOAc 5:1, UV, $KMnO_4$); **Melting Point**: 132 - 135 °C; **Major diastereomer 471n: ^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.65 (d, *J* = 8.0 Hz, 2H, Ar**H**), 7.53 (d, *J* = 8.5 Hz, 2H, Ar**H**), 7.38 - 7.30 (m, 4H, Ar**H**), 6.06 (ddd, *J* = 17.5, 10.0, 7.5 Hz, 1H, C**H**=CH_2), 5.51 (s, 1H, C**H**N), 5.37 (d, *J* = 17.5 Hz, 1H, CH=CH_{cis}**H*$_{trans}$**), 5.33 (d, *J* = 10.5 Hz, 1H, CH=C**H*$_{cis}$**H_{trans}), 4.70 - 4.61 (m, 1H, C**H**NO_2), 4.38 - 4.29 (m, 1H, NC**H**$CH=CH_2$), 2.67 - 2.56 (m, 1H, C**H**H'), 2.47 (s, 3H, ArC**H$_3$**), 2.16 (ddd, *J* = 15.0, 9.0, 6.0 Hz, 1H, CH**H'**); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 144.4 (Ar**C**), 138.0 (Ar**C**), 137.2 (**C**H=CH_2), 133.7 (Ar**C**), 132.1 (2 × ArCH), 129.7 (2 × Ar**C**H), 127.9 (2 × Ar**C**H), 127.8 (2 × Ar**C**H), 122.5 (Ar**C**), 118.1 (CH=**C**H_2), 89.8 (**C**HNO_2), 68.3 (**C**HN), 62.0 (N**C**HCH=CH_2), 34.9 (**C**H_2), 21.6 (Ar**C**H_3); **Minor diastereomer 471n′: ^{1}H NMR** (400 MHz, $CDCl_3$, observable peaks): δ_H 7.49 (d, *J* = 8.0 Hz, 2H, Ar**H**), 7.21 (d, *J* = 8.0 Hz, 4H, Ar**H**), 5.88 (s, 1H, C**H**N), 5.47 - 5.40 (m, 1H, CH=CH_{cis}**H*$_{trans}$**), 5.05 (d, *J* = 9.5 Hz, 1H, CH=C**H*$_{cis}$**H_{trans}), 4.75 - 4.60 (m, 2H, NC**H**$CH=CH_2$ and C**H**NO_2), 2.85 - 2.74 (m, 1H, C**H**H'), 2.42 (s, 3H, ArC**H$_3$**);

^{13}C NMR (100 MHz, $CDCl_3$, observable peaks): δ_C 143.6 (Ar**C**), 136.0 (**C**H=CH_2), 129.2 (2 × Ar**C**H), 127.8 (2 × Ar**C**H), 127.6 (2 × Ar**C**H), 118.8 (CH=**C**H_2), 90.0 (**C**HNO_2), 67.6 (**C**HN), 62.5 (N**C**HCH=CH_2), 35.2 (**C**H_2), 21.5 (Ar**C**H_3); **IR** (film/cm^{-1}): ν_{max} 2924, 1553, 1485, 1366, 1342, 1161, 1094, 1006, 809, 719, 707, 664; **MS** (ESI): *m/z* 473.0 [$(M + Na)^+$]; **HRMS** (ESI): exact mass calculated for $C_{19}H_{19}BrN_2NaO_4S$ [$(M + Na)^+$], 473.0141; found 473.0134.

Synthesis and characterisation of *rac*-(2*S*,3*R*,5*S*)-1-[(4-methylphenyl)sulfonyl]-3-nitro-2-(4-nitrophenyl)-5-vinylpyrrolidine (471o) and *rac*-(2*S*,3*R*,5*R*)-1-[(4-methylphenyl)sulfonyl]-3-nitro-2-(4-nitrophenyl)-5-vinylpyrrolidine (471o′)

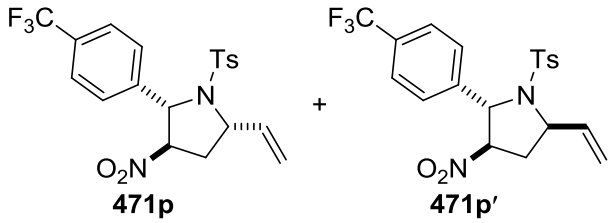


471o **471o′**

Prepared according to general procedure H. *N*-Sulfonyl imine **257w** (60.9 mg, 0.20 mmol) was reacted with nitroallene **468** (33.9 mg, 0.30 mmol) for 27 h (step i), 14 h (step ii) and 13 h (step iii) to afford a mixture of diastereomers **471o** and **471o′** (46 mg, 55%, dr 61:39) as a pale yellow solid, after purification by flash column chromatography on silica gel eluting with PE/EtOAc (3:1). **TLC**: R_f = 0.41 (PE/EtOAc 3:1, UV, $KMnO_4$); **Melting Point**: 146 - 148 °C; **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of diastereomers): δ_H 8.32 - 8.20 (m, Ar**H**, 2H *major* and 2H *minor*), 7.73 - 7.64 (m, 4H, Ar**H**, *major*), 7.61 (d, *J* = 8.0 Hz, 2H, Ar**H**, *minor*), 7.58 (d, *J* = 8.5 Hz, 2H, Ar**H**, *minor*), 7.36 (d, *J* = 8.0 Hz, 2H, Ar**H**, *major*), 7.24 (d, *J* = 8.0 Hz, 2H, Ar**H**, *minor*), 6.15 - 6.02 (m, C**H**=CH_2, 1H *major* and C**H**N, 1H *minor*), 5.63 (s, 1H, C**H**N, *major*), 5.38 (d, *J* = 17.0 Hz, 1H, CH=CH_{cis}**H**$_{trans}$, *major*), 5.37 (d, *J* = 10.0 Hz, 1H, CH=C**H**$_{cis}$$H_{trans}$, *major*), 5.34 - 5.28 (m, 2H, C**H**=C**H**H', *minor*), 5.07 - 5.02 (m, 1H, CH=CH**H'**, *minor*), 4.82 - 4.75 (m, 1H, NC**H**CH=CH_2, *minor*), 4.74 -

4.64 (m, C**H**NO_2, 1H *major* and 1H *minor*), 4.38 - 4.28 (m, 1H, NC**H**CH=CH_2, *major*), 2.80 (ddd, *J* = 15.5, 9.0, 7.0 Hz, 1H, C**H**H', *minor*), 2.71 - 2.59 (m, C**HH'**, 1H *major* and 1H *minor*), 2.48 (s, 3H, ArC$\mathbf{H_3}$, *major*), 2.43 (s, 3H, ArC$\mathbf{H_3}$, *minor*), 2.23 - 2.13 (m, 1H, CH**H'**, *major*); **^{13}C NMR** (100 MHz, $CDCl_3$, mixture of diastereomers): δ_C 147.9 (Ar**C**), 147.8 (Ar**C**), 146.0 (Ar**C**), 146.0 (Ar**C**), 144.8 (Ar**C**), 144.0 (Ar**C**), 137.7 (Ar**C**), 136.8 (**C**H=CH_2, *major*), 135.4 (**C**H=CH_2, *minor*), 133.3 (Ar**C**), 129.9 (2 × Ar**C**H, *major*), 129.3 (2 × Ar**C**H, *minor*), 127.8 (2 × Ar**C**H, *major*), 127.7 (2 × Ar**C**H, *major*), 127.3 (2 × Ar**C**H, *minor*), 127.1 (2 × Ar**C**H, *minor*), 124.3 (2 × Ar**C**H, *minor*), 124.2 (2 × Ar**C**H, *major*), 119.4 (CH=**C**H_2, *minor*), 118.4 (CH=**C**H_2, *major*), 89.7 (**C**HNO_2, *minor*), 89.4 (**C**HNO_2, *major*), 68.1 (**C**HN, *major*), 67.3 (**C**HN, *minor*), 62.6 (N**C**HCH=CH_2, *minor*), 62.1 (N**C**HCH=CH_2, *major*), 35.2 (**C**H_2, *minor*), 35.0 (**C**H_2, *major*), 21.6 (Ar**C**H_3, *major*), 21.5 (Ar**C**H_3, *minor*); **IR** (film/cm^{-1}): ν_{max} 2923, 1597, 1554, 1372, 1339, 1157, 1097, 1004, 908, 818, 727, 708, 671; **MS** (ESI): *m/z* 440.0 [$(M + Na)^+$]; **HRMS** (ESI): exact mass calculated for $C_{19}H_{19}N_3NaO_6S$ [$(M + Na)^+$], 440.0887; found 440.0889.

Synthesis and characterisation of *rac*-(2*S*,3*R*,5*S*)-1-[(4-methylphenyl) sulfonyl]-3-nitro-2-[4-(trifluoromethyl)phenyl]-5-vinylpyrrolidine (471p) and *rac*-(2*S*,3*R*,5*R*)-1-[(4-methylphenyl)sulfonyl]-3-nitro-2-[4-(trifluoromethyl)phenyl]-5-vinylpyrrolidine (471p′)

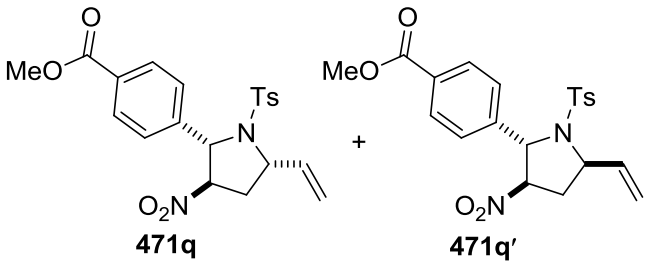


471p **471p′**

Prepared according to general procedure H. *N*-Sulfonyl imine **257n** (65.5 mg, 0.20 mmol) was reacted with nitroallene **468** (33.9 mg, 0.30 mmol) for 21 h (step i),

8 h (step ii) and 2 h (step iii) to afford a mixture of diastereomers **471p** and **471p′** (45 mg, 56%, dr 92:8) as a white solid, after purification by flash column chromatography on silica gel eluting with PE/EtOAc (5:1). **TLC**: R_f = 0.38 (PE/EtOAc 5:1, UV, $KMnO_4$); **Melting Point**: 145 - 147 °C; **Major diastereomer 471p:** ^{1}**H NMR** (400 MHz, $CDCl_3$): δ_H 7.71 - 7.63 (m, 4H, Ar**H**), 7.60 (d, *J* = 8.0 Hz, 2H, Ar**H**), 7.34 (d, *J* = 8.0 Hz, 2H, Ar**H**), 6.09 (ddd, *J* = 17.0, 10.0, 7.5 Hz, 1H, C**H**=CH_2), 5.61 (s, 1H, C**H**N), 5.38 (d, *J* = 17.5 Hz, 1H, CH=CH_{cis}**H**$_{trans}$), 5.35 (d, *J* = 10.0 Hz, 1H, CH=**C**$_{cis}$$H_{trans}$), 4.73 - 4.67 (m, 1H, C**H**NO_2), 4.40 - 4.31 (m, 1H, NC**H**CH=CH_2), 2.67 - 2.58 (m, 1H, C**H**H′), 2.47 (s, 3H, ArC**H$_3$**), 2.17 (ddd, *J* = 15.0, 9.0, 6.0 Hz, 1H, CH**H′**); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ_C 144.6 (Ar**C**), 142.9 (Ar**C**), 137.1 (**C**H=CH_2), 133.6 (Ar**C**), 130.7 (q, *J* = 33.0 Hz, Ar**C**), 129.8 (2 × Ar**C**H), 127.8 (2 × Ar**C**H), 126.7 (2 × Ar**C**H), 126.4 (q, *J* = 251.5 Hz, Ar**C**F_3), 126.0 (q, *J* = 4.0 Hz, 2 × Ar**C**H), 118.2 (CH=**C**H_2), 89.7 (**C**HNO_2), 68.3 (**C**HN), 62.1 (N**C**HCH=CH_2), 34.9 (**C**H_2), 21.6 (Ar**C**H_3); ^{19}**F NMR** (376.5 MHz, $CDCl_3$): δ_F –62.6 (ArC**F$_3$**); **Minor diastereomer 471p′:** ^{1}**H NMR** (400 MHz, $CDCl_3$, observable peaks): δ_H 7.57 (d, *J* = 8.0 Hz, 2H, Ar**H**), 7.47 (d, *J* = 8.0 Hz, 2H, Ar**H**), 7.21 (d, *J* = 8.0 Hz, 2H, Ar**H**), 5.99 (s, 1H, C**H**N), 5.06 (d, *J* = 10.0 Hz, 1H, CH=C**H**$_{cis}$$H_{trans}$), 4.80 - 4.73 (m, 1H, NC**H**CH=CH_2), 2.81 (ddd, *J* = 15.5, 9.0, 7.0 Hz, C**H**H′), 2.41 (s, 3H, ArC**H$_3$**); ^{13}**C NMR** (100 MHz, $CDCl_3$, observable peaks): δ_C 135.9 (**C**H=CH_2), 129.2 (Ar**C**H), 126.6 (Ar**C**H), 35.2 (**C**H_2), 21.5 (Ar**C**H_3); ^{19}**F NMR** (376.5 MHz, $CDCl_3$): δ_F –62.7 (ArC**F$_3$**); **IR** (film/cm^{-1}): ν_{max} 1554, 1416, 1344, 1324, 1160, 1115, 1066, 1006, 930, 845, 813, 665; **MS** (ESI): *m/z* 463.1 [$(M + Na)^+$]; **HRMS** (ESI): exact mass calculated for $C_{20}H_{19}F_3N_2NaO_4S$ [$(M + Na)^+$], 463.0910; found 463.0905.

Synthesis and characterisation of *rac*-methyl 4-{(2*S*,3*R*,5*S*)-1-[(4-methylphenyl)sulfonyl]-3-nitro-5-vinylpyrrolidin-2-yl}benzoate (471q) and *rac*-methyl 4-{(2*S*,3*R*,5*R*)-1-[(4-methylphenyl)sulfonyl]-3-nitro-5-vinylpyrrolidin-2-yl}benzoate (471q′)

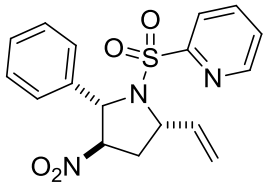


471q **471q′**

Prepared according to general procedure H. *N*-Sulfonyl imine **257o** (31.7 mg, 0.10 mmol) was reacted with nitroallene **468** (17.0 mg, 0.15 mmol) for 6 h (step i), 3 h (step ii) and 4 h (step iii) to afford a mixture of diastereomers **471q** and **471q′** (32 mg, 73%, dr 86:14) as an off-white solid, after purification by flash column chromatography on silica gel eluting with PE/EtOAc (5:1). **TLC**: R_f = 0.27 (PE/EtOAc 5:1, UV, $KMnO_4$); **Melting Point**: 183 - 185 °C (decomp); **Major diastereomer 471q:** **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 8.07 (d, *J* = 8.0 Hz, 2H, Ar**H**), 7.66 (d, *J* = 8.0 Hz, 2H, Ar**H**), 7.55 (d, *J* = 8.0 Hz, 2H, Ar**H**), 7.33 (d, *J* = 8.0 Hz, 2H, Ar**H**), 6.09 (ddd, *J* = 17.0, 10.0, 7.5 Hz, 1H, C**H**=CH_2), 5.63 (s, 1H, C**H**N), 5.38 (d, *J* = 17.0 Hz, 1H, CH=CH_{cis}**H_{trans}**), 5.34 (d, *J* = 10.0 Hz, 1H, CH=C**H_{cis}**H_{trans}), 4.72 - 4.68 (m, 1H, C**H**NO_2), 4.39 - 4.29 (m, 1H, NC**H**CH=CH_2), 3.94 (s, 3H, CO_2C**H_3**), 2.68 - 2.56 (m, 1H, C**H**H′), 2.46 (s, 3H, Ar**C**H_3), 2.16 (ddd, *J* = 15.0, 9.0, 6.0 Hz, 1H, CH**H′**); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 166.4 (**C**=O), 144.5 (Ar**C**), 143.8 (Ar**C**), 137.1 (**C**H=CH_2), 133.8 (Ar**C**), 130.3 (Ar**C**),130.3 (2 × Ar**C**H), 129.8 (2 × Ar**C**H), 127.8 (2 × Ar**C**H), 126.2 (2 × Ar**C**H), 118.2 (CH=**C**H_2), 89.7 (**C**HNO_2), 68.6 (**C**HN), 62.1 (N**C**HCH=CH_2), 52.3 (CO_2**C**H_3), 35.0 (**C**H_2), 21.6 (Ar**C**H_3); **Minor diastereomer 471q′:** **^{1}H NMR** (400 MHz, $CDCl_3$, observable peaks): δ_H 8.04 (d, *J* = 8.0 Hz, 2H, Ar**H**), 7.59 (d, *J* = 8.0 Hz, 2H, Ar**H**), 7.43 (d, *J* = 8.0 Hz, 2H, Ar**H**), 7.21 (d, *J* = 8.0 Hz, 2H, Ar**H**), 6.00 (s, 1H, C**H**N), 5.04 (d, *J* = 10.0 Hz, 1H,

CH=C**H**$_{cis}$H$_{trans}$), 4.79 - 4.63 (m, 2H, NC**H**CH=CH_2 and C**H**NO_2), 2.81 (ddd, *J* = 15.5, 9.0, 7.0 Hz, 1H, C**H**H′), 2.41 (s, 3H, Ar**C**H_3); **^{13}C NMR** (100 MHz, $CDCl_3$, observable peaks): δ_C 130.3 (2 × Ar**C**H), 129.2 (2 × Ar**C**H), 127.7 (2 × Ar**C**H), 126.1 (2 × Ar**C**H), 90.0 (**C**HNO_2), 62.6 (N**C**HCH=CH_2), 21.5 (Ar**C**H_3); **IR** (film/ cm^{-1}): ν_{max} 2923, 1722, 1546, 1367, 1344, 1275, 1183, 1160, 1104, 1014, 819, 669; **MS** (ESI): *m/z* 453.1 [(M + Na)$^+$]; **HRMS** (ESI): exact mass calculated for $C_{21}H_{22}N_2NaO_6S$ [(M + Na)$^+$], 453.1091; found 453.1079.

Synthesis and characterisation of *rac*- 2-{[(2*S*,3*R*,5*S*)-5-ethenyl-3-nitro-2-phenylpyrrolidin-1-yl]sulfonyl}pyridine (472)

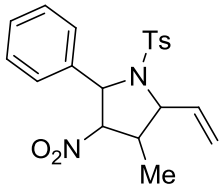


472

Prepared according to general procedure H. *N*-pyridine-2-sulfonyl imine **497** (24.6 mg, 0.10 mmol) was reacted with nitroallene **468** (17.0 mg, 0.15 mmol) for 5 h (step i), 29 h (step ii) and 5 h (step iii) to afford compound **472** (11 mg, 31%, dr >98:2) as a pale yellow solid, after purification by flash column chromatography on silica gel eluting with PE/Et_2O (1:1). **TLC**: R_f = 0.38 (PE/Et_2O 1:1, UV, $KMnO_4$); **Melting Point**: 102 - 103 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 8.70 (d, *J* = 4.5 Hz, 1H, Ar**H**), 7.99 - 7.88 (m, 2H, Ar**H**), 7.59 - 7.50 (m, 3H, Ar**H**), 7.45 - 7.31 (m, 3H, Ar**H**), 6.22 (ddd, *J* = 17.5, 10.5, 7.0 Hz, 1H, C**H**=CH_2), 5.99 (s, 1H, C**H**N), 5.37 (d, *J* = 17.5 Hz, 1H, CH=CH$_{cis}$**H$_{trans}$**), 5.33 (d, *J* = 10.5 Hz, 1H, CH=C**H**$_{cis}$H$_{trans}$), 4.79 - 4.74 (m, 1H, C**H**NO_2), 4.73 - 4.64 (m, 1H, NC**H**CH=CH_2), 2.83 - 2.75 (m, 1H, C**H**H′), 2.19 (ddd, *J* = 15.0, 9.0, 6.0 Hz, 1H, CH**H′**); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 156.1 (Ar**C**), 150.1 (Ar**C**H), 139.1 (Ar**C**), 137.9 (Ar**C**H), 137.8 (**C**H=CH_2), 128.9

(2 × Ar**C**H), 128.3 (Ar**C**H), 127.1 (Ar**C**H), 126.0 (2 × Ar**C**H), 123.1 (Ar**C**H), 117.7 (CH=**C**H_2), 90.5 (**C**HNO_2), 69.6 (**C**HN), 62.9 (N**C**HCH=CH_2), 34.2 (**C**H_2); **IR** (film/cm^{-1}): ν_{max} 1546, 1427, 1346, 1172, 1115, 1019, 926, 762, 701; **MS** (ESI): *m/z* 382.1 [$(M + Na)^+$]; **HRMS** (ESI): exact mass calculated for $C_{17}H_{17}N_3NaO_4S$ [$(M + Na)^+$], 382.0832; found 382.0827.

Synthesis and characterisation of *rac*-3-methyl-1-[(4-methylphenyl)sulfonyl]-4-nitro-5-phenyl-2-vinylpyrrolidine (479)

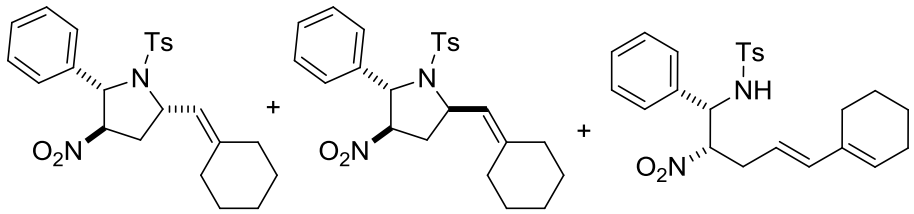


479

Prepared according to general procedure H. *N*-Sulfonyl imine **257a** (51.9 mg, 0.20 mmol) was reacted with nitroallene **478** (38.1 mg, 0.30 mmol) for 48 h (step i), 7 h (step ii) and 3 h (step iii) to afford a mixture of diastereomers **479^{I}**, **479^{II}**, **479^{III}** and **479^{IV}** (33 mg, 49%, dr 33:28:24:15) as an off-white solid, after purification by flash column chromatography on silica gel eluting with PE/EtOAc (4:1). **TLC**: R_f = 0.25 (PE/EtOAc 4:1, UV, $KMnO_4$); **Melting Point**: 85 - 88 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.68 (d, *J* = 8.5 Hz, 2H, Ar**H**, **479^{I}**), 7.56 (d, *J* = 8.0 Hz, 2H, Ar**H**, **479^{IV}**), 7.52 (d, *J* = 8.5 Hz, 2H, Ar**H**, **479^{III}**), 7.45 - 7.15 (m, Ar**H**, 7H **479^{I}**, 7H **479^{II}**, 7H **479^{III}** and 7H **479^{IV}**), 7.09 (d, *J* = 8.0 Hz, 2H, Ar**H**, **479^{II}**), 6.00 (ddd, *J* = 17.0, 10.0, 8.5 Hz, 1H, C**H**=CH_2, **479^{I}**), 5.94 - 5.83 (m, C**H**=CH_2, 1H **479^{II}** and 1H **479^{III}**), 5.78 (ddd, *J* = 17.0, 10.0, 8.5 Hz, 1H, C**H**=CH_2, **479^{IV}**), 5.62 (d, *J* = 5.0 Hz, 1H, C**H**N, **479^{II}**), 5.54 (d, *J* = 9.0 Hz, 1H, C**H**N, **479^{III}**), 5.47 - 5.26 (m, C**H**N, 1H **479^{I}** and 1H **479^{IV}**; CH=C**H$_2$**, 2H **479^{I}**, 2H **479^{II}**, 2H **479^{III}** and 2H **479^{IV}**), 4.74 (d, *J* = 6.0 Hz, 1H, C**H**NO_2, **479^{I}**), 4.69 - 4.54 (m, C**H**NO_2, 1H **479^{II}**, 1H **479^{III}** and 1H **479^{IV}**;

NC**H**CH=CH_2, 1H **479^{IV}**), 3.94 (t, *J* = 8.5 Hz, 1H, NC**H**CH=CH_2, **479^{II}**), 3.84 - 3.69 (m, NC**H**CH=CH_2, 1H **479^{I}** and 1H **479^{III}**), 2.90 - 2.77 (m, 1H, C**H**CH_3, **479^{III}**), 2.76 - 2.59 (m, C**H**CH_3, 1H **479^{II}** and 1H **479^{IV}**), 2.46 (s, 3H, ArC**H$_3$**, **479^{I}**), 2.45 - 2.39 (m, ArC**H$_3$**, 3H **479^{III}** and 3H **479^{IV}**; C**H**CH_3, 1H **479^{I}**), 2.37 (s, 3H, ArC**H$_3$**, **479^{II}**), 1.18 (d, *J* = 7.0 Hz, 3H, CHC**H$_3$**, **479^{II}**), 1.03 (d, *J* = 6.5 Hz, 3H, CHC**H$_3$**, **479^{III}**), 0.98 (d, *J* = 7.0 Hz, 3H, CHC**H$_3$**, **479^{IV}**), 0.89 (d, *J* = 7.0 Hz, 3H, CHC**H$_3$**, **479^{I}**); **^{13}C NMR** (100 MHz, $CDCl_3$, assignment was made where possible): δ_C 144.0 (Ar**C**), 144.0 (Ar**C**), 143.9 (Ar**C**), 143.0 (Ar**C**), 139.4 (Ar**C**), 138.2 (Ar**C**), 137.5 (Ar**C**), 136.8 (**C**H=CH_2, **479^{I}**), 135.6 (**C**H=CH_2, **479^{II}** or **479^{III}**), 135.5 (Ar**C**), 135.4 (**C**H=CH_2, **479^{II}** or **479^{III}**), 135.1 (Ar**C**), 135.0 (Ar**C**), 134.4 (Ar**C**), 133.3 (**C**H=CH_2, **479^{IV}**), 129.6 (Ar**C**H), 129.5 (Ar**C**H), 129.4 (Ar**C**H), 129.1 (Ar**C**H), 129.0 (Ar**C**H), 128.9 (Ar**C**H), 128.8 (Ar**C**H), 128.5 (Ar**C**H), 128.4 (Ar**C**H), 128.3 (Ar**C**H), 128.1 (Ar**C**H), 127.7 (Ar**C**H), 127.6 (Ar**C**H), 127.5 (Ar**C**H), 127.4 (Ar**C**H), 127.3 (Ar**C**H), 126.7 (Ar**C**H), 126.1 (Ar**C**H), 120.0 (CH=**C**H_2), 119.7 (CH=**C**H_2), 119.1 (CH=**C**H_2), 119.0 (CH=**C**H_2), 96.9 (**C**HNO_2, **479^{II}**), 96.7 (**C**HNO_2, **479^{IV}**), 94.2 (**C**HNO_2, **479^{I}**), 90.1 (**C**HNO_2, **479^{III}**), 70.6 (N**C**HCH=CH_2, **479^{II}**), 68.2 (N**C**HCH=CH_2, **479^{I}**), 68.0 (**C**HN, **479^{I}** or *B*), 67.8 (**C**HN, **479^{I}** or **479^{II}**), 67.3 (N**C**HCH=CH_2, **479^{III}**), 67.0 (**C**HN, **479^{IV}**), 65.5 (N**C**HCH=CH_2, **479^{IV}**), 64.0 (**C**HN, **479^{III}**), 45.5 (**C**HCH_3, **479^{II}**), 42.4 (**C**HCH_3, **479^{IV}**), 41.0 (**C**HCH_3, **479^{I}**), 39.6 (**C**HCH_3, **479^{III}**), 21.6 (Ar**C**H_3), 21.5 (Ar**C**H_3), 21.5 (Ar**C**H_3), 21.4 (Ar**C**H_3), 15.4 (CH**C**H_3, **479^{II}**), 13.3 (CH**C**H_3, **479^{III}**), 12.5 (CH**C**H_3, **479^{III}**), 10.2 (CH**C**H_3, **479^{IV}**); **IR** (film/cm^{-1}): ν_{max} 3065, 3033, 2974, 2923, 1599, 1552, 1455, 1348, 1306, 1158, 1092, 1044, 932, 814, 735, 700, 665; **MS** (ESI): *m/z* 409.1 [(M + Na)$^+$]; **HRMS** (ESI): exact mass calculated for $C_{20}H_{22}N_2NaO_4S$ [(M + Na)$^+$], 409.1192; found 409.1187.

Synthesis and characterisation of *rac*-(2*S*,3*R*,5*S*)-5-(cyclohexylidenemethyl)-1-[(4-methylphenyl)sulfonyl]-3-nitro-2-phenylpyrrolidine (487), *rac*-(2*S*,3*R*,5*R*)-5-(cyclohexylidenemethyl)-1-[(4-methylphenyl)sulfonyl]-3-nitro-2-phenylpyrrolidine (487′) and *rac*-*N*-[(1*S*,2*S*,4*E*)-5-(cyclohex-1-en-1-yl)-2-nitro-1-phenylpent-4-en-1-yl]-4-methylbenzenesulfonamide (488)



487 **487′** **488**

Prepared according to general procedure H. *N*-Sulfonyl imine **257a** (51.9 mg, 0.20 mmol) was reacted with nitroallene **486** (54.4 mg, 0.30 mmol) for 6 h (step i), 72 h (step ii) and 2 h (step iii) to afford a mixture of diastereomers **487** and **487′** (21 mg, 24%, dr 77:23) as a white solid and compound **488** (49 mg, 56%, dr 93:7) as a pale yellow solid, after purification by flash column chromatography on silica gel eluting with PE/EtOAc (6:1).

Diastereomers 487 and 487′: TLC: R_f = 0.36 (PE/EtOAc 6:1, UV, $KMnO_4$); **Melting Point**: 119 - 122 °C; **^{1}H NMR** (500 MHz, $CDCl_3$, mixture of diastereomers): δ_H 7.68 - 7.63 (m, 2H, Ar**H**, *minor*), 7.62 - 7.56 (m, 2H, Ar**H**, *major*), 7.48 - 7.37 (m, Ar**H**, 4H *major* and 4H *minor*), 7.36 - 7.25 (m, Ar**H**, 3H *major* and 1H *minor*), 7.23 (d, *J* = 8.0 Hz, 2H, Ar**H**, *minor*), 6.00 (s, 1H, C**H**N, *minor*), 5.65 (s, 1H, C**H**N, *major*), 5.26 (d, *J* = 9.0 Hz, 1H, C**H**=C, *major*), 5.11 - 5.07 (m, 1H, NC**H**CH=C, *minor*) 4.77 - 4.65 (m, C**H**NO_2, 1H *major* and 1H *minor*; NC**H**CH=C, 1H *major*), 4.51 (d, *J* = 10.0 Hz, C**H**=C, *minor*), 2.78 (ddd, *J* = 15.5, 9.5, 7.0 Hz, 1H, C**H**H′, *minor*), 2.55 (dd, *J* = 15.0, 6.5 Hz, 1H, C**H**H′, *major*), 2.51 - 2.45 (m, 1H, CH**H′**, *minor*), 2.44 (s, 3H, ArC**H$_3$**, *major*), 2.42 (s, 3H, ArC**H$_3$**, *minor*), 2.35 - 2.25 (m, cyclohexyl **H**, 1H *major* and 2H *minor*), 2.24 - 2.09 (m, 3H, cyclohexyl **H**, *major*), 2.05 (ddd, *J* = 15.0, 10.0, 6.0 Hz, 1H, CH**H′**, *major*), 1.87 -

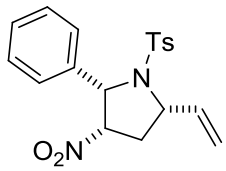
1.45 (m, cyclohexyl **H**, 6H *major* and 8H *minor*); **^{13}C NMR** (125 MHz, $CDCl_3$, mixture of diastereomers): δ_C 143.9 (Ar**C**), 143.8 (Ar**C**), 143.8 (CH=**C**), 143.1 (CH=**C**), 139.3 (Ar**C**), 139.2 (Ar**C**), 139.0 (Ar**C**), 135.1 (Ar**C**), 129.4 (2 × Ar**C**H, *major*), 129.0 (2 × Ar**C**H, *minor*), 128.9 (2 × Ar**C**H, *minor*), 128.9 (2 × Ar**C**H, *major*), 128.3 (Ar**C**H, *major*), 128.2 (Ar**C**H, *minor*), 127.7 (2 × Ar**C**H, *major*), 127.5 (2 × Ar**C**H, *minor*), 126.2 (2 × Ar**C**H, *major*), 125.8 (2 × Ar**C**H, *minor*), 120.8 (**C**H=C, *major*), 119.8 (**C**H=C, *minor*), 90.6 (**C**HNO_2, minor), 90.2 (**C**HNO_2, *major*), 68.5 (**C**HN, *major*), 68.0 (**C**HN, *minor*), 57.1 (N**C**HCH=C, *major*), 56.1 (N**C**HCH=C, *minor*), 37.0 (cyclohexyl **C**H_2, *major*), 36.7 (cyclohexyl **C**H_2, *minor*), 36.0 (**C**H_2, *major*), 35.9 (**C**H_2, *minor*), 29.3 (cyclohexyl **C**H_2, *major*), 28.7 (cyclohexyl **C**H_2, *minor*), 28.2 (cyclohexyl **C**H_2, *major*), 27.6 (cyclohexyl **C**H_2, *major*), 27.3 (cyclohexyl **C**H_2, *minor*), 26.6 (cyclohexyl **C**H_2, *major*), 26.5 (cyclohexyl **C**H_2, *minor*), 21.6 (Ar**C**H_3, *major*), 21.5 (Ar**C**H_3, *minor*); **IR** (film/cm^{-1}): ν_{max} 2929, 2854, 1599, 1552, 1495, 1449, 1351, 1159, 1093, 1011, 814, 702, 670; **MS** (ESI): *m/z* 441.2 $[(M + Na)^+]$; **HRMS** (ESI): exact mass calculated for $C_{24}H_{28}N_2NaO_4S$ $[(M + Na)^+]$, 463.1662; found 463.1685.

β-Nitroamine 488: TLC: R_f = 0.13 (PE/EtOAc 6:1, UV, $KMnO_4$); **Melting Point**: 147 - 150 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.51 (d, *J* = 8.5 Hz, 2H, Ar**H**), 7.23 - 7.03 (m, 5H, Ar**H**), 7.02 - 6.96 (m, 2H, Ar**H**), 6.17 (d, *J* = 10.0 Hz, 1H, N**H**), 6.01 (d, *J* = 15.5 Hz, 1H, C**H**=$CHCH_2$), 5.66 (br s, 1H, C=C**H**), 5.33 - 5.19 (m, 1H, CH=C**H**CH_2), 4.89 - 4.78 (m, 1H, C**H**N), 4.76 - 4.66 (m, 1H, C**H**NO_2), 2.73 - 2.60 (m, 1H, C**H**H′), 2.44 - 2.27 (m, 4H, CH**H′** and Ar$C\mathbf{H_3}$), 2.14 - 1.93 (m, 4H, cyclohexenyl **H**), 1.70 - 1.46 (m, 4H, cyclohexenyl **H**); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 143.3 (Ar**C**), 138.6 (**C**H=$CHCH_2$), 136.9 (Ar**C**), 135.3 (Ar**C**), 134.8

(**C**=CH), 130.2 (C=**C**H), 129.3 (2 × Ar**C**H), 128.9 (2 × Ar**C**H), 128.4 (Ar**C**H), 126.9 (2 × Ar**C**H), 126.6 (2 × Ar**C**H), 116.8 (CH=**C**HCH$_2$), 92.2 (C**H**NO$_2$), 59.3 (**C**HN), 34.7 (**C**H$_2$), 25.7 (cyclohexenyl **C**H$_2$), 24.3 (cyclohexenyl **C**H$_2$), 22.3 (cyclohexenyl **C**H$_2$), 22.2 (cyclohexenyl **C**H$_2$), 21.4 (Ar**C**H$_3$); **IR** (film/cm^{-1}): ν_{max} 2927, 1555, 1436, 1333, 1161, 1091, 967, 901, 813, 703; **MS** (ESI): *m/z* 439.1 [(M – H)$^-$]; **HRMS** (ESI): exact mass calculated for $C_{24}H_{28}N_2NaO_4S$ [(M + Na)$^+$], 463.1662; found 463.1665. The relative configuration of compound **488** was assigned by analogy to the X-ray crystal structure of *syn*-**268′**.

Compounds **487**, **487′** and **488** were prepared and characterised by D. M. Barber.

Synthesis and characterisation of *rac*-(2*S*,3*S*,5*S*)-1-[(4-methylphenyl) sulfonyl]-3-nitro-2-phenyl-5-vinylpyrrolidine (470)



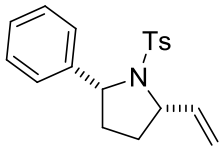
470

To a stirred mixture of *N*-sulfonyl imine **257a** (51.9 mg, 0.20 mmol) and nitroallene **468** (33.9 mg, 0.30 mmol) in PhMe (2.0 mL) at RT in a sealable vial was added KO*t*Bu (1.1 mg, 0.010 mmol). The resulting mixture was stirred at RT for the 18 h. The reaction mixture was diluted with DCE (6.0 mL), then diphenylphosphate (10.0 mg, 0.04 mmol), Au(PPh$_3$)Cl (9.9 mg, 0.02 mmol) and AgSbF$_6$ (13.7 mg, 0.04 mmol) were added and the resulting mixture was heated to 70 °C for 4 h. The reaction mixture was filtered through a plug of celite and the filtrate was concentrated under a stream of nitrogen. The resulting solid was purified by recrystallisation from CH$_2$Cl$_2$/Et$_2$O to afford compound **470** (28 mg, 38%, dr >98:2) as a pale brown solid. **TLC**: R_f = 0.24 (PE/EtOAc 6:1, UV, KMnO4); **Melting**

Point: 172 - 174 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.55 (d, *J* = 8.5 Hz, 2H, Ar**H**), 7.34 - 7.16 (m, 7H, Ar**H**), 6.12 (ddd, *J* = 17.0, 10.0, 7.5 Hz, 1H, C**H**=CH_2), 5.50 (d, *J* = 8.5 Hz, 1H, C**H**N), 5.41 (d, *J* = 17.0 Hz, 1H, CH=CH_{cis}**H**$_{\boldsymbol{trans}}$), 5.32 (d, *J* = 10.0 Hz, 1H, CH=C**H**$_{\boldsymbol{cis}}$$H_{trans}$), 4.96 (ddd, *J* = 11.5, 8.5, 6.5 Hz, 1H, C**H**NO_2), 4.40 - 4.30 (m, 1H, N**C**HCH=CH_2), 2.78 - 2.65 (m, 1H, C**H**H′), 2.51 - 2.37 (m, 4H, ArC**H$_3$** and CH**H′**); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 144.1 (Ar**C**), 136.8 (**C**H=CH_2), 135.3 (Ar**C**), 134.8 (Ar**C**), 129.6 (2 × Ar**C**H), 128.9 (Ar**C**H), 128.4 (2 × Ar**C**H), 127.7 (2 × Ar**C**H), 127.5 (2 × Ar**C**H), 118.4 (CH=**C**H_2), 84.3 (**C**HNO_2), 64.9 (**C**HN), 60.5 (N**C**HCH=CH_2), 33.0 (**C**H_2), 21.5 (Ar**C**H_3); **IR** (film/cm^{-1}): ν_{max} 2919, 1598, 1549, 1375, 1347, 1309, 1163, 1090, 1008, 971, 927, 814, 707, 662; **MS** (ESI): *m/z* 395.0 [$(M + Na)^+$]; **HRMS** (ESI): exact mass calculated for $C_{19}H_{20}N_2NaO_4S$ [$(M + Na)^+$], 395.1036; found 395.1034. The relative configuration of compound **470** was assigned by analogy to the X-ray crystal structure of pyrrolidine **471a** and by NOE analysis.

5.4.4 Synthetic Elaboration of Pyrrolidine 471a

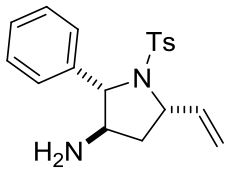
Synthesis and characterisation of *rac*-(2*R*,5*S*)-1-[(4-methylphenyl)sulfonyl]-2-phenyl-5-vinylpyrrolidine (492)



492

To a solution of compound **471a** (37.2 mg, 0.10 mmol) in PhMe (2.5 mL) in a microwave vial at RT was added AIBN (3.3 mg, 0.02 mmol) and Bu_3SnH (146 mg, 0.50 mmol, 135 μL). The resulting mixture was degassed and flushed with nitrogen several times (×5), heated to 120 °C and stirred for 2.5 h. The reaction mixture was allowed to cool to RT and then directly purified by flash column chromatography on silica gel eluting with PE/EtOAc (9:1) to afford compound **492** (17 mg, 53%, dr 96:4) as a colourless oil. On standing the product crystallised as a white solid. **TLC**: R_f = 0.29 (PE/EtOAc 9:1, UV, $KMnO_4$); **Melting Point**: 69 - 71 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.65 (d, *J* = 8.0 Hz, 2H, Ar**H**), 7.38 - 7.21 (m, 7H, Ar**H**), 6.02 (ddd, *J* = 17.0, 10.5, 6.5 Hz, 1H, C**H**=CH_2), 5.35 (dt, *J* = 17.5, 1.0 Hz, 1H, CH=CH_{cis}**H*$_{trans}$**), 5.21 (dt, *J* = 10.5, 1.0 Hz, 1H, CH=C**H*$_{cis}$**H_{trans}), 4.86 - 4.79 (m, 1H, C**H**N), 4.38 - 4.31 (m, 1H, NC**H**CH=CH_2), 2.43 (s, 3H, ArC**H$_3$**), 2.04 - 1.95 (m, 1H, ArCHC**H**H′CHH′), 1.92 - 1.72 (m, 3H, ArCHCH**H′**C**HH′**); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 143.2 (Ar**C**), 142.4 (Ar**C**), 139.0 (**C**H=CH_2), 135.5 (Ar**C**), 129.4 (2 × Ar**C**H), 128.2 (2 × Ar**C**H), 127.7 (2 × Ar**C**H), 127.1 (Ar**C**H), 126.5 (2 × Ar**C**H), 116.1 (CH=**C**H_2), 64.9 (**C**HN), 63.6 (N**C**HCH=CH_2), 34.5 (ArCH**C**H_2CH_2), 30.9 (ArCHCH_2**C**H_2), 21.5 (Ar**C**H_3); **IR** (film/cm^{-1}): ν_{max} 2982, 1599, 1494, 1450, 1402, 1160, 1093, 986, 784; **MS** (ESI): *m/z* 350.1 [$(M + Na)^+$]; **HRMS** (ESI): exact mass calculated for $C_{19}H_{21}NNaO_2S$ [$(M + Na)^+$], 350.1185; found 350.1171.

Synthesis and characterisation of *rac*-(2*S*,3*R*,5*S*)-1-[(4-methylphenyl)sulfonyl]-2-phenyl-5-vinylpyrrolidin-3-amine (493)

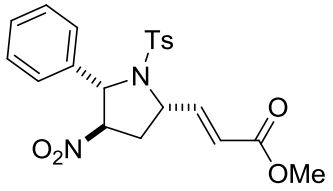


493

To a stirred solution of compound **471a** (37.2 mg, 0.10 mmol) in THF (1.0 mL) at RT was added zinc powder (157 mg, 2.40 mmol) and acetic acid (0.3 mL). The resulting mixture was stirred at RT for 36 h. The reaction was quenched with sat. aq. $NaHCO_3$ (30 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with CH_2Cl_2/MeOH (97:3) to afford compound **493** (30 mg, 88%, dr 94:6) as an off-white solid. **TLC**: R_f = 0.28 (CH_2Cl_2/MeOH 97:3, UV, $KMnO_4$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.63 - 7.56 (m, 2H, Ar**H**), 7.37 - 7.20 (m, 7H, Ar**H**), 6.02 (ddd, *J* = 17.0, 10.5, 6.5 Hz, 1H, C**H**=CH_2), 5.38 (dt, *J* = 17.0, 1.0 Hz, 1H, CH=CH_{cis}**H*$_{trans}$**), 5.23 (dt, *J* = 10.5, 1.0 Hz, 1H, CH=C**H*$_{cis}$**H_{trans}), 4.61 - 4.50 (m, 1H, C**H**NH_2), 4.38 (d, *J* = 5.0 Hz, 1H, C**H**N), 3.44 - 3.34 (m, 1H, NC**H**CH=CH_2), 2.40 (s, 3H, ArC**H$_3$**), 2.25 (br s, 2H, N**H$_2$**), 2.06 - 1.95 (m, 1H, C**H**H′), 1.83 - 1.72 (m, 1H, CH**H′**); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 143.4 (Ar**C**), 139.9 (Ar**C**), 138.7 (**C**H=CH_2), 135.3 (Ar**C**), 129.4 (2 × Ar**C**H), 128.4 (2 × Ar**C**H), 127.7 (2 × Ar**C**H), 127.6 (Ar**C**H), 126.8 (2 × Ar**C**H), 116.3 (CH=**C**H_2), 72.8 (**C**HNH_2), 61.1 (**C**HN), 59.3 (N**C**HCH=CH_2), 38.5 (**C**H_2), 21.5 (Ar**C**H_3); **IR** (film/cm^{-1}): ν_{max} 3375, 3063, 3030, 2926, 1598, 1494, 1451, 1342, 1156, 1092, 1004, 921; **MS** (ESI): *m/z* 343.2 [$(M + H)^+$]; **HRMS** (ESI): exact mass calculated for $C_{19}H_{23}N_2O_2S$ [$(M + H)^+$], 343.1475; found 343.1472. The

relative configuration of compound **493** was assigned by analogy to the X-ray crystal structure of pyrrolidine **471a**.

Synthesis and characterisation of *rac*-methyl (2*E*)-3-{(2*S*,4*R*,5*S*)-1-[(4-methylphenyl)sulfonyl]-4-nitro-5-phenylpyrrolidin-2-yl}acrylate (494)



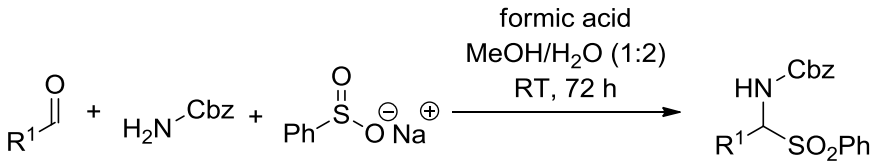
494

To a stirred solution of compound **471a** (37.2 mg, 0.10 mmol) in CH_2Cl_2 (1.0 mL) at RT in a sealable vial was added methyl arcylate (34.4 mg, 0.40 mmol, 36.0 uL) and Hoveyda Grubbs II (**495**) catalyst (3.2 mg, 5.0 μmol, 5 mol%). The resulting mixture was heated to 45 °C for 24 h. The reaction mixture was allowed to cool to RT and then directly purified by flash column chromatography on silica gel eluting with PE/EtOAc (4:1) to afford compound **494** (32 mg, 74%, dr 97:3) as a white solid. **TLC**: R_f = 0.18 (PE/EtOAc 4:1, UV, $KMnO_4$); **Melting Point**: 177 - 179 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.63 (d, *J* = 8.0 Hz, 2H, Ar**H**), 7.49 - 7.29 (m, 7H, Ar**H**), 7.08 (dd, *J* = 15.5, 7.5 Hz, 1H, C**H**=CHCO$_2$), 6.12 (d, *J* = 15.5 Hz, 1H, CH=C**H**CO$_2$), 5.58 (s, 1H, C**H**N), 4.73 (d, *J* = 5.5 Hz, 1H, C**H**NO$_2$), 4.54 - 4.44 (m, 1H, NC**H**CH=CH), 3.81 (s, 3H, CO$_2$C**H$_3$**), 2.73 - 2.59 (m, 1H, C**H**H′), 2.46 (s, 3H, ArC**H$_3$**), 2.24 - 2.12 (m, 1H, CH**H′**); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 166.0 (**C**=O), 145.9 (**C**H=CHCO$_2$), 144.6 (Ar**C**), 138.3 (Ar**C**), 133.5 (Ar**C**), 129.8 (2 × Ar**C**H), 129.1 (2 × Ar**C**H), 128.6 (Ar**C**H), 127.7 (2 × Ar**C**H), 126.0 (2 × Ar**C**H), 123.4 (CH=**C**HCO$_2$), 89.9 (**C**HNO$_2$), 69.1 (**C**HN), 60.3 (N**C**HCH=CH), 51.9 (CO$_2$**C**H$_3$), 34.5 (**C**H$_2$), 21.6 (Ar**C**H$_3$); **IR** (film/cm^{-1}): ν_{max} 3034, 2952, 1706, 1495, 1355, 1333, 1112, 1096, 1012, 825, 737, 672; **MS** (ESI): *m/z* 453.1 [(M + Na)$^+$]; **HRMS** (ESI):

exact mass calculated for $C_{21}H_{22}N_2NaO_6S$ [$(M + Na)^+$], 453.1091; found 453.1086. The relative configuration of compound **494** was assigned by analogy to the X-ray crystal structure of pyrrolidine **471a**.

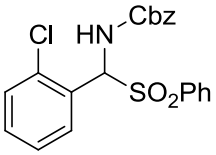
5.4.5 Synthesis and Characterisation of Amidosulfones 400

General Procedure I: Synthesis of amidosulfones



To a stirred mixture of the corresponding aldehyde (37.5 mmol, 1.5 equiv), benzyl carbamate (**398**) (3.78 g, 25.0 mmol, 1.0 equiv) and benzenesulfinic acid sodium salt (**276**) (8.26 g, 50.0 mmol, 2.0 equiv) in a mixture of H_2O/MeOH (2:1, 75 mL) at RT was added formic acid (1.9 mL). The reaction mixture was stirred at RT for 72 h and the resulting precipitate was filtered off washing with water. The filtered solid was purified by trituration with Et_2O to afford the desired amidosulfone. Synthesis and characterisation data for the novel amidosulfones is reported.

Synthesis and characterisation of benzyl [(2-chlorophenyl)(phenylsulfonyl) methyl]carbamate (400b)

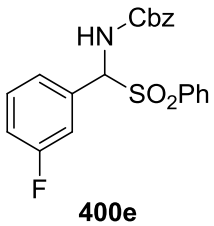


400b

Prepared according to general procedure I. 2-Chlorobenzaldehyde (5.27 g, 37.5 mmol, 4.22 mL) was reacted with benzyl carbamate (**398**) (3.78 g, 25.0 mmol) and benzenesulfinic acid sodium salt (**276**) (8.26 g, 50.0 mmol) to afford compound **400b** (4.59 g, 44%) as a white solid, after purification by trituration with Et_2O. **Melting Point**: 145 - 147 °C; **^{1}H NMR** (400 MHz, DMSO-d_6): δ_H 9.34 (d, *J* = 10.5 Hz, 1H, N**H**), 8.07 - 7.89 (m, 1H, Ar**H**), 7.87 - 7.71 (m, 3H, Ar**H**), 7.69 - 7.15 (m, 10H, Ar**H**), 6.59 (d, *J* = 10.5 Hz, 1H, C**H**NH), 4.95 (d, *J* = 12.5 Hz, C**H**H′), 4.88 (d,

J = 12.5 Hz, 1H, CH**H′**); **^{13}C NMR** (100 MHz, DMSO-d_6) δ_C 155.4 (**C**=O), 136.5 (Ar**C**), 136.2 (Ar**C**), 134.5 (Ar**C**H), 134.1 (Ar**C**), 131.4 (Ar**C**H), 130.9 (Ar**C**H), 129.4 (2 × Ar**C**H), 129.3 (Ar**C**H), 128.9 (2 × Ar**C**H), 128.7 (Ar**C**), 128.4 (2 × Ar**C**H), 128.1 (Ar**C**H), 127.9 (2 × Ar**C**H), 127.5 (Ar**C**H), 70.9 (**C**HNH), 66.4 (Ar**C**H_2); **IR** (film/cm^{-1}): ν_{max} 3345, 1725, 1527, 1327, 1306, 1273, 1233, 1137, 1080, 1044, 1002, 759, 733; **MS** (ESI): *m/z* 438.1 and 440.0 [$(M + Na)^+$]; **HRMS** (ESI): exact mass calculated for $C_{21}H_{18}ClNNaO_4S$ [$(M + Na)^+$], 438.0537 and 440.0509; found 438.0527 and 440.0507.

Synthesis and characterisation of benzyl [(3-fluorophenyl)(phenylsulfonyl) methyl]carbamate (400e)

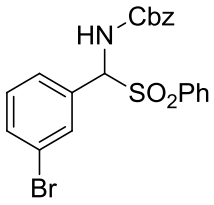


400e

Prepared according to general procedure I. 3-Fluorobenzaldehyde (4.65 g, 37.5 mmol, 3.98 mL) was reacted with benzyl carbamate (**398**) (3.78 g, 25.0 mmol) and benzenesulfinic acid sodium salt (**276**) (8.26 g, 50.0 mmol) to afford compound **400e** (5.35 g, 54%) as a white solid, after purification by trituration with Et_2O. **Melting Point**: 161 - 163 °C; **^{1}H NMR** (400 MHz, DMSO-d_6): δ_H 9.18 (d, *J* = 10.5 Hz, 1H, N**H**), 7.84 (d, *J* = 7.5 Hz, 2H, Ar**H**), 7.80 - 7.70 (m, 1H, Ar**H**), 7.67 - 7.53 (m, 3H, Ar**H**), 7.53 - 7.23 (m, 6H, Ar**H**), 7.19 (d, *J* = 7.0 Hz, 2H, Ar**H**), 6.22 (d, *J* = 10.5 Hz, 1H, C**H**NH), 4.90 (d, *J* = 12.5 Hz, 1H, C**H**H′), 4.85 (d, *J* = 12.5 Hz, 1H, CH**H′**); **^{13}C NMR** (100 MHz, DMSO-d_6) δ_C 161.8 (d, *J* = 243.5 Hz, Ar**C**F), 155.1 (**C**=O), 136.4 (Ar**C**), 136.3 (Ar**C**), 134.3 (Ar**C**H), 132.8 (d, *J* = 8.0 Hz, Ar**C**), 130.1 (d, *J* = 9.0 Hz, Ar**C**H), 129.2 (2 × Ar**C**H), 129.1 (2 × Ar**C**H), 128.4 (2 × Ar**C**H),

128.0 (Ar**C**H), 127.8 (2 × Ar**C**H), 126.1 (d, *J* = 1.5 Hz, Ar**C**H), 116.5 (d, *J* = 23.0 Hz, Ar**C**H), 116.4 (d, *J* = 21.0 Hz, Ar**C**H), 74.1 (**C**HNH), 66.2 (Ar**C**H_2); **^{19}F NMR** (376.5 MHz, DMSO-d_6) δ_F –112.9 (ArC**F**); **IR** (film/cm^{-1}): ν_{max} 3347, 3065, 1730, 1518, 1489, 1445, 1309, 1251, 1231, 1144, 1082, 995, 772, 717; **MS** (ESI): *m/z* 422.1 [(M + Na)$^+$]; **HRMS** (ESI): exact mass calculated for $C_{21}H_{18}FNNaO_4S$ [(M + Na)$^+$], 422.0833; found 422.0831.

Synthesis and characterisation of benzyl [(3-bromophenyl)(phenylsulfonyl) methyl]carbamate (400g)

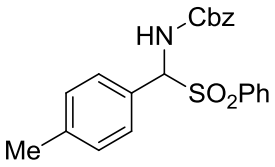


400g

Prepared according to general procedure I. 3-Bromobenzaldehyde (6.94 g, 37.5 mmol, 4.37 mL) was reacted with benzyl carbamate (**398**) (3.78 g, 25.0 mmol) and benzenesulfinic acid sodium salt (**276**) (8.26 g, 50.0 mmol) to afford compound **400g** (5.74 g, 50%) as a white solid, after purification by trituration with Et_2O. **Melting Point**: 163 - 164 °C; **^{1}H NMR** (400 MHz, DMSO-d_6): δ_H 9.19 (d, *J* = 10.5 Hz, 1H, N**H**), 7.94 (s, 1H, Ar**H**), 7.86 (d, *J* = 8.0 Hz, 2H, Ar**H**), 7.76 (t, *J* = 7.5 Hz, 1H, Ar**H**), 7.70 - 7.54 (m, 4H, Ar**H**), 7.41 - 7.26 (m, 4H, Ar**H**), 7.23 - 7.14 (m, 2H, Ar**H**), 6.21 (d, *J* = 10.5 Hz, 1H, C**H**NH), 4.89 (d, *J* = 12.5 Hz, 1H, C**H**H′), 4.83 (d, *J* = 12.5 Hz, 1H, CH**H′**); **^{13}C NMR** (100 MHz, DMSO-d_6) δ_C 155.2 (**C**=O), 136.4 (Ar**C**), 136.3 (Ar**C**), 134.4 (Ar**C**H), 132.8 (Ar**C**), 132.3 (Ar**C**H), 132.3 (Ar**C**H), 130.3 (Ar**C**H), 129.2 (2 × Ar**C**H), 129.2 (2 × Ar**C**H), 129.0 (Ar**C**H), 128.4 (2 × Ar**C**H), 128.0 (Ar**C**H), 127.7 (2 × Ar**C**H), 121.5 (Ar**C**), 74.0 (**C**HNH), 66.2 (Ar**C**H_2); **IR** (film/cm^{-1}): ν_{max} 3335, 1699, 1526, 1333, 1309, 1246, 1144, 1081,

1059, 732, 689; **MS** (ESI): *m/z* 482.0 and 484.0 [(M + Na)$^+$]; **HRMS** (ESI): exact mass calculated for $C_{21}H_{18}BrNNaO_4S$ [(M + Na)$^+$], 482.0032 and 484.0012; found 482.0035 and 484.0014.

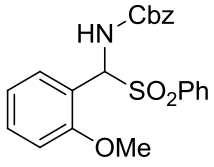
Synthesis and characterisation of benzyl [(4-methylphenyl)(phenylsulfonyl) methyl]carbamate (400i)



400i

Prepared according to general procedure I. *p*-Tolylaldehyde (4.54 g, 37.5 mmol, 4.42 mL) was reacted with benzyl carbamate (**398**) (3.78 g, 25.0 mmol) and benzenesulfinic acid sodium salt (**276**) (8.26 g, 50.0 mmol) to afford compound **400i** (3.94 g, 40%) as a white solid, after purification by trituration with Et_2O. **Melting Point**: 168 - 170 °C; **^{1}H NMR** (400 MHz, DMSO-d_6): δ_H 9.12 (d, *J* = 10.5 Hz, 1H, N**H**), 7.92 - 7.77 (m, 2H, Ar**H**), 7.74 (t, *J* = 7.5 Hz, 1H, Ar**H**), 7.58 (t, *J* = 7.5 Hz, 2H, Ar**H**), 7.50 (d, *J* = 8.0 Hz, 2H, Ar**H**), 7.43 - 7.26 (m, 3H, Ar**H**), 7.26 - 7.09 (m, 4H, Ar**H**), 6.04 (d, *J* = 10.5 Hz, 1H, C**H**NH), 4.88 (d, *J* = 12.5 Hz, 1H, C**H**H′), 4.83 (d, *J* = 12.5 Hz, 1H, CH**H′**), 2.31 (s, 3H, ArC**H$_3$**); **^{13}C NMR** (100 MHz, DMSO-d_6) δ_C 155.3 (**C**=O), 139.0 (Ar**C**), 136.8 (Ar**C**), 136.4 (Ar**C**), 134.1 (Ar**C**H), 129.8 (Ar**C**), 129.6 (2 × Ar**C**H), 129.1 (2 × Ar**C**H), 129.1 (2 × Ar**C**H), 128.8 (2 × Ar**C**H), 128.4 (2 × Ar**C**H), 128.0 (Ar**C**H), 127.7 (2 × Ar**C**H), 74.8 (**C**HNH), 66.1 (Ar**C**H$_2$), 20.9 (Ar**C**H$_3$); **IR** (film/cm^{-1}): ν_{max} 3333, 1728, 1522, 1446, 1302, 1230, 1136, 1078, 1042, 1004, 772, 720; **MS** (ESI): *m/z* 254.1 [(M – PhSO$_2$H + H)$^+$]; **HRMS** (FI): exact mass calculated for $C_{16}H_{15}NO_2$ [M – PhSO$_2$H], 253.1103; found 253.1135.

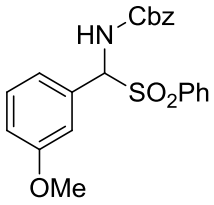
Synthesis and characterisation of benzyl [(2-methoxyphenyl)(phenylsulfonyl) methyl]carbamate 400j



400j

Prepared according to general procedure I. 2-Anisaldehyde (5.11 g, 37.5 mmol, 4.53 mL) was reacted with benzyl carbamate (**398**) (3.78 g, 25.0 mmol) and benzenesulfinic acid sodium salt (**276**) (8.26 g, 50.0 mmol) to afford compound **400j** (7.92 g, 77%) as a white solid, after purification by trituration with Et_2O. **Melting Point**: 153 - 154 °C; **^{1}H NMR** (400 MHz, DMSO-d_6): δ_H 9.09 (d, *J* = 10.5 Hz, 1H, N**H**), 7.80 - 7.61 (m, 4H, Ar**H**), 7.60 - 7.50 (m, 2H, Ar**H**), 7.42 - 7.20 (m, 6H, Ar**H**), 7.00 (t, *J* = 7.5 Hz, 1H, Ar**H**), 6.92 (d, *J* = 8.5 Hz, 1H, Ar**H**), 6.52 (d, *J* = 11.0 Hz, 1H, C**H**NH), 4.97 (d, *J* = 12.5 Hz, 1H, C**H**H′), 4.92 (d, *J* = 12.5 Hz, 1H, CH**H′**), 3.56 (s, 3H, ArOC**H$_3$**); **^{13}C NMR** (100 MHz, DMSO-d_6) δ_C 156.7 (Ar**C**), 155.6 (**C**=O), 137.1 (Ar**C**), 136.4 (Ar**C**), 134.1 (Ar**C**H), 131.1 (Ar**C**H), 129.8 (Ar**C**H), 129.0 (2 × Ar**C**H), 128.9 (2 × Ar**C**H), 128.5 (2 × Ar**C**H), 128.1 (Ar**C**H), 127.9 (2 × Ar**C**H), 120.5 (Ar**C**H), 119.1 (Ar**C**), 111.0 (Ar**C**H), 68.2 (**C**HNH), 66.3 (Ar**C**H_2), 55.7 (ArO**C**H_3); **IR** (film/cm^{-1}): ν_{max} 3334, 1716, 1528, 1492, 1338, 1310, 1284, 1238, 1139, 1043, 1026, 1005, 751; **MS** (ESI): *m/z* 270.1 [(M – $PhSO_2H$ + H)$^+$]; **HRMS** (FI): exact mass calculated for $C_{16}H_{15}NO_3$ [M – $PhSO_2H$], 269.1052; found 269.1011.

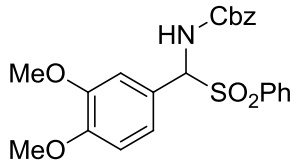
Synthesis and characterisation of benzyl [(3-methoxyphenyl)(phenylsulfonyl) methyl]carbamate (400k)



400k

Prepared according to general procedure I. 3-Anisaldehyde (5.11 g, 37.5 mmol, 4.57 mL) was reacted with benzyl carbamate (**398**) (3.78 g, 25.0 mmol) and benzenesulfinic acid sodium salt (**276**) (8.26 g, 50.0 mmol) to afford compound **400k** (4.22 g, 41%) as a white solid, after purification by trituration with Et_2O. **Melting Point**: 129 - 131 °C; **^{1}H NMR** (400 MHz, DMSO-d_6): δ_H 9.14 (d, *J* = 10.5 Hz, 1H, N**H**), 7.82 (d, *J* = 7.5 Hz, 2H, Ar**H**), 7.74 (t, *J* = 7.5 Hz, 1H, Ar**H**), 7.58 (t, *J* = 7.5 Hz, 2H, Ar**H**), 7.42 - 7.11 (m, 8H, Ar**H**), 7.01 - 6.93 (m, 1H, Ar**H**), 6.07 (d, *J* = 10.5 Hz, 1H, C**H**NH), 4.90 (d, *J* = 12.5 Hz, 1H, C**H**H′), 4.85 (d, *J* = 12.5 Hz, 1H, CH**H′**), 3.72 (s, 3H, ArOC**H$_3$**); **^{13}C NMR** (100 MHz, DMSO-d_6) δ_C 159.0 (Ar**C**), 155.3 (**C**=O), 136.7 (Ar**C**), 136.3 (Ar**C**), 134.2 (Ar**C**H), 131.6 (Ar**C**), 129.2 (3 × Ar**C**H), 129.1 (2 × Ar**C**H), 128.4 (2 × Ar**C**H), 128.0 (Ar**C**H), 127.8 (2 × Ar**C**H), 122.1 (Ar**C**H), 115.3 (Ar**C**H), 115.0 (Ar**C**H), 75.0 (**C**HNH), 66.1 (Ar**C**H_2), 55.3 (ArO**C**H_3); **IR** (film/cm^{-1}): ν_{max} 3343, 1723, 1515, 1489, 1455, 1303, 1247, 1228, 1138, 1053, 1041, 1004, 769, 738, 718; **MS** (ESI): *m/z* 434.0 [(M + Na)$^+$]; **HRMS** (ESI): exact mass calculated for $C_{22}H_{21}NNaO_5S$ [(M + Na)$^+$], 434.1033; found 434.1028.

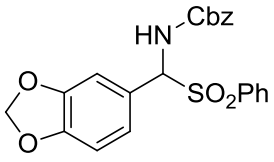
Synthesis and characterisation of benzyl [(3,4-dimethoxyphenyl)(phenyl sulfonyl)methyl]carbamate (400l)



400l

Prepared according to general procedure I. 3 4-Dimethoxybenzaldehyde (6.23 g, 37.5 mmol) was reacted with benzyl carbamate (**398**) (3.78 g, 25.0 mmol) and benzenesulfinic acid sodium salt (**276**) (8.26 g, 50.0 mmol) to afford compound **400l** (2.50 g, 23%) as a white solid, after purification by trituration with Et_2O. **Melting Point**: 154 - 155 °C; **^{1}H NMR** (400 MHz, DMSO-d_6): δ_H 9.09 (d, *J* = 10.5 Hz, 1H, N**H**), 7.79 (d, *J* = 8.0 Hz, 2H, Ar**H**), 7.73 (t, *J* = 7.5 Hz, 1H, Ar**H**), 7.58 (t, *J* = 7.5 Hz, 2H, Ar**H**), 7.41 - 7.15 (m, 6H, Ar**H**), 7.12 (d, *J* = 8.5 Hz, 1H, Ar**H**), 6.94 (d, *J* = 8.5 Hz, 1H, Ar**H**), 6.01 (d, *J* = 10.5 Hz, 1H, C**H**NH), 4.91 (d, *J* = 12.5 Hz, 1H, ArC**H**H′), 4.87 (d, *J* = 12.5 Hz, 1H, ArCH**H′**), 3.76 (s, 3H, ArOC**H$_3$**), 3.69 (s, 3H, ArOC**H$_3$**); **^{13}C NMR** (100 MHz, DMSO-d_6) δ_C 155.3 (**C**=O), 149.7 (Ar**C**), 148.3 (Ar**C**), 136.8 (Ar**C**), 136.4 (Ar**C**), 134.1 (Ar**C**H), 129.2 (2 × Ar**C**H), 129.0 (2 × Ar**C**H), 128.4 (2 × Ar**C**H), 128.0 (Ar**C**H), 127.8 (2 × Ar**C**H), 122.7 (Ar**C**H), 122.2 (Ar**C**), 113.0 (Ar**C**H), 111.1 (Ar**C**H), 75.1 (**C**HNH), 66.1 (Ar**C**H_2), 55.6 (ArO**C**H_3), 55.5 (ArO**C**H_3); **IR** (film/cm^{-1}): ν_{max} 1702, 1593, 1445, 1309, 1266, 1235, 1214, 1148, 1026, 910, 871, 773, 697; **MS** (ESI): *m/z* 354.1 [(M – $PhSO_2H$ + Na + MeOH)$^+$]. No meaningful HRMS data was obtained for this compound.

Synthesis and characterisation of benzyl [1,3-benzodioxol-5-yl(phenylsulfonyl) methyl]carbamate (400m)

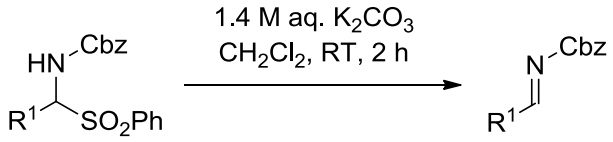


400m

Prepared according to general procedure I. Piperonal (5.63 g, 37.5 mmol) was reacted with benzyl carbamate (**398**) (3.78 g, 25.0 mmol) and benzenesulfinic acid sodium salt (**276**) (8.26 g, 50.0 mmol) to afford compound **400m** (4.01 g, 38%) as a white solid, after purification by trituration with Et_2O. **Melting Point**: 177 - 178 °C; **^{1}H NMR** (400 MHz, DMSO-d_6): δ_H 9.06 (d, *J* = 10.5 Hz, 1H, N**H**), 7.83 (d, *J* = 8.0 Hz, 2H, Ar**H**), 7.74 (t, *J* = 7.5 Hz, 1H, Ar**H**), 7.59 (t, *J* = 7.5 Hz, 2H, Ar**H**), 7.40 - 7.25 (m, 4H, Ar**H**), 7.22 - 7.15 (m, 2H, Ar**H**), 7.08 (d, *J* = 8.0 Hz, 1H, Ar**H**), 6.92 (d, *J* = 8.0 Hz, 1H, Ar**H**), 6.10 - 5.98 (m, 3H, OC**H$_2$**O and C**H**NH), 4.88 (d, *J* = 12.5 Hz, 1H, C**H**H′), 4.84 (d, *J* = 12.5 Hz, 1H, CH**H′**); **^{13}C NMR** (100 MHz, DMSO-d_6) δ_C 155.2 (**C**=O), 148.2 (Ar**C**), 147.2 (Ar**C**), 136.8 (Ar**C**), 136.3 (Ar**C**), 134.1 (Ar**C**H), 129.1 (2 × Ar**C**H), 129.1 (2 × Ar**C**H), 128.4 (2 × Ar**C**H), 128.0 (Ar**C**H), 127.8 (2 × Ar**C**H), 124.2 (Ar**C**H), 123.7 (Ar**C**), 109.7 (Ar**C**H), 107.9 (Ar**C**H), 101.4 (O**C**H_2O), 74.6 (**C**HNH), 66.1 (Ar**C**H_2); **IR** (film/cm^{-1}): ν_{max} 3331, 1727, 1524, 1505, 1490, 1445, 1314, 1303, 1271, 1234, 1138, 1037, 922, 685; **MS** (ESI): *m/z* 284.1 [(M – $PhSO_2H$ + H)$^+$]. No meaningful HRMS data was obtained for this compound.

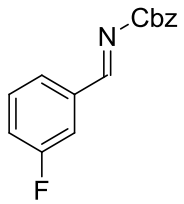
5.4.6 Synthesis and Characterisation of *N*-Cbz Imines 401

General Procedure J: Synthesis of *N*-Cbz imines



To a stirred mixture of the corresponding amidosulfone (1.09 mmol) in CH_2Cl_2 (10 mL) at RT was added K_2CO_3 (1.4 M aq. solution, 10 mL). The resulting biphasic mixture was vigorously stirred at RT for 2 h. The organic layer was decanted and then the resulting aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the desired *N*-Cbz imine, which was used in the next step without further purification. Synthesis and characterisation data for the novel *N*-Cbz imines is reported. *N*-Cbz imines **401** were prepared and characterised by Dr. A. Ďuriš.

Synthesis and characterisation of benzyl [(*E*)-(3-fluorophenyl)methylidene] carbamate (401e)

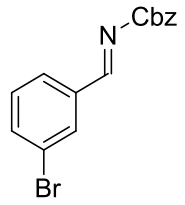


401e

Prepared according to general procedure J. Compound **400e** (434 mg, 1.09 mmol) was reacted with K_2CO_3 (1.4 M aq. solution in H_2O, 10 mL) in CH_2Cl_2 (10 mL) to afford compound **401e** (253 mg, 91%) as a white solid. **Melting Point**: 34 - 35 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 8.89 (s, 1H, C**H**=N), 7.71 - 7.63 (m, 2H, Ar**H**), 7.52

- 7.33 (m, 6H, Ar**H**), 7.32 - 7.24 (m, 1H, Ar**H**), 5.33 (s, 2H, ArC**H$_2$**); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 169.5 (d, *J* = 3.0 Hz, C**H**=N), 163.3 (**C**=O), 162.9 (d, *J* = 248.5 Hz, Ar**C**F), 136.0 (d, *J* = 7.0 Hz, Ar**C**), 135.1 (Ar**C**), 130.6 (d, *J* = 8.0 Hz, Ar**C**H), 128.6 (2 × Ar**C**H), 128.6 (3 × Ar**C**H), 126.7 (d, *J* = 2.5 Hz, Ar**C**H), 120.8 (d, *J* = 21.5 Hz, Ar**C**H), 115.8 (d, *J* = 22.5 Hz, Ar**C**H), 69.0 (Ar**C**H_2); **^{19}F NMR** (376.5 MHz, DMSO-d_6) δ_F –111.5 (ArC**F**); **IR** (film/cm^{-1}): ν_{max} 1708, 1624, 1579, 1489, 1362, 1217, 1139, 892, 849, 797, 750; **MS** (ESI): *m/z* 312.1 [(M + MeOH + Na)$^+$]; **HRMS** (ESI): exact mass calculated for $C_{16}H_{16}FNNaO_3$ [(M + MeOH + Na)$^+$], 312.1006; found 312.1003.

Synthesis and characterisation of benzyl [(*E*)-(3-bromophenyl)methylidene] carbamate (401g)

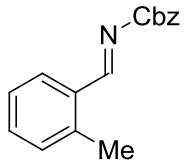


401g

Prepared according to general procedure J. Compound **400g** (500 mg, 1.09 mmol) was reacted with K_2CO_3 (1.4 M aq. solution in H_2O, 10 mL) in CH_2Cl_2 (10 mL) to afford compound **401g** (324 mg, 94%) as a white solid. **Melting Point**: 63 - 64 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 8.86 (s, 1H, C**H**=N), 8.11 (t, *J* = 1.5 Hz, 1H, Ar**H**), 7.82 (d, *J* = 8.0 Hz, 1H, Ar**H**), 7.74 - 7.67 (m, 1H, Ar**H**), 7.51 - 7.44 (m, 2H, Ar**H**), 7.44 - 7.31 (m, 4H, Ar**H**), 5.33 (s, 2H, ArC**H$_2$**); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 169.4 (**C**H=N), 163.2 (**C**=O), 136.6 (Ar**C**H), 135.7 (Ar**C**), 135.1 (Ar**C**), 132.5 (Ar**C**H), 130.4 (Ar**C**H), 129.2 (Ar**C**H), 128.6 (2 × ArCH), 128.6 (3 × Ar**C**H), 123.2 (Ar**C**), 69.1 (Ar**C**H_2); **IR** (film/cm^{-1}): ν_{max} 3061, 1709, 1618, 1555, 1359, 1246, 1199, 1159, 958, 834, 796, 748; **MS** (ESI): *m/z* 372.0 and 374.0 [(M + MeOH +

Na)$^+$]; **HRMS** (ESI): exact mass calculated for $C_{16}H_{16}BrNNaO_3$ [(M + MeOH + Na)$^+$], 372.0206 and 374.0186; found 372.0200 and 374.0179.

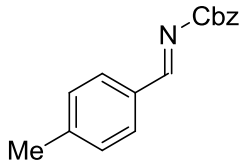
Synthesis and characterisation of benzyl [(*E*)-(2-methylphenyl)methylidene] carbamate (401h)



401h

Prepared according to general procedure J. Compound **400h** (429 mg, 1.09 mmol) was reacted with K_2CO_3 (1.4 M aq. solution in H_2O, 10 mL) in CH_2Cl_2 (10 mL) to afford compound **401h** (268 mg, 87%) as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 9.29 (s, 1H, C**H**=N), 8.09 (d, *J* = 8.0 Hz, 1H, Ar**H**), 7.52 - 7.33 (m, 6H, Ar**H**), 7.30 (d, *J* = 7.5 Hz, 1H, Ar**H**), 7.29 - 7.21 (m, 2H, Ar**H**), 5.34 (s, 2H, ArC**H$_2$**), 2.60 (s, 3H, ArC**H$_3$**); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 169.7 (**C**H=N), 164.0 (**C**=O), 141.2 (Ar**C**), 135.4 (Ar**C**), 133.5 (Ar**C**H), 131.8 (Ar**C**), 131.3 (Ar**C**H), 129.1 (Ar**C**H), 128.6 (2 × Ar**C**H), 128.5 (2 × Ar**C**H), 128.5 (Ar**C**H), 126.4 (Ar**C**H), 68.8 (Ar**C**H$_2$), 19.3 (Ar**C**H$_3$); **IR** (film/cm^{-1}): ν_{max} 3033, 1709, 1619, 1597, 1455, 1379, 1248, 1194, 1013, 911, 752, 696; **MS** (ESI): *m/z* 308.1 [(M + MeOH + Na)$^+$]; **HRMS** (ESI): exact mass calculated for $C_{17}H_{19}NNaO_3$ [(M + MeOH + Na)$^+$], 308.1257; found 308.1246.

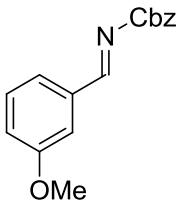
Synthesis and characterisation of benzyl [(*E*)-(4-methylphenyl)methylidene] carbamate (401i)



401i

Prepared according to general procedure J. Compound **400i** (429 mg, 1.09 mmol) was reacted with K_2CO_3 (1.4 M aq. solution in H_2O, 10 mL) in CH_2Cl_2 (10 mL) to afford compound **401i** (261 mg, 95%) as a white solid. **Melting Point**: 40 - 41 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 8.95 (s, 1H, C**H**=N), 7.83 (d, *J* = 8.0 Hz, 2H, Ar**H**), 7.50 - 7.44 (m, 2H, Ar**H**), 7.43 - 7.33 (m, 3H, Ar**H**), 7.29 (d, *J* = 8.0 Hz, 2H, Ar**H**), 5.32 (s, 2H, ArC**H$_2$**), 2.44 (s, 3H, ArC**H$_3$**); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 171.5 (**C**H=N), 163.8 (**C**=O), 145.1 (Ar**C**), 135.4 (Ar**C**), 131.3 (Ar**C**), 130.6 (2 × Ar**C**H), 129.7 (2 × Ar**C**H), 128.6 (2 × Ar**C**H), 128.6 (2 × Ar**C**H), 128.5 (Ar**C**H), 68.8 (Ar**C**H$_2$), 21.9 (Ar**C**H$_3$); **IR** (film/cm^{-1}): ν_{max} 3032, 1703, 1603, 1567, 1377, 1256, 1195, 1018, 934, 912, 823, 748, 696; **MS** (ESI): *m/z* 308.1 [(M + MeOH + Na)$^+$]; **HRMS** (ESI): exact mass calculated for $C_{17}H_{19}NNaO_3$ [(M + MeOH + Na)$^+$], 308.1257; found 308.1253.

Synthesis and characterisation of benzyl [(*E*)-(3-methoxyphenyl)methylidene] carbamate (401k)

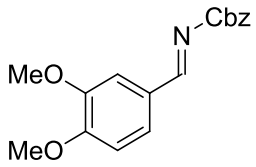


401k

Prepared according to general procedure J. Compound **400k** (447 mg, 1.09 mmol) was reacted with K_2CO_3 (1.4 M aq. solution in H_2O, 10 mL) in CH_2Cl_2 (10 mL) to

afford compound **401k** (281 mg, 96%) as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 8.93 (s, 1H, C**H**=N), 7.52 (s, 1H, Ar**H**), 7.50 - 7.28 (m, 7H, Ar**H**), 7.18 - 7.11 (m, 1H, Ar**H**), 5.33 (s, 2H, ArC**H$_2$**), 3.86 (s, 3H, ArOC**H$_3$**); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 171.3 (**C**H=N), 163.6 (**C**=O), 160.0 (Ar**C**), 135.3 (Ar**C**), 135.2 (Ar**C**), 129.9 (Ar**C**H), 128.6 (4 × Ar**C**H), 128.5 (Ar**C**H), 124.5 (Ar**C**H), 121.3 (Ar**C**H), 112.3 (Ar**C**H), 68.9 (Ar**C**H_2), 55.5 (ArO**C**H_3); **IR** (film/cm^{-1}): ν_{max} 2959, 1715, 1623, 1582, 1456, 1267, 1216, 1189, 1166, 1153, 1037, 734, 683; **MS** (ESI): *m/z* 324.1 [(M + MeOH + Na)$^+$]; **HRMS** (ESI): exact mass calculated for $C_{17}H_{19}NNaO_4$ [(M + MeOH + Na)$^+$], 324.1206; found 324.1201.

Synthesis and characterisation of benzyl [(*E*)-(3,4-dimethoxyphenyl) methylidene]carbamate (401l)

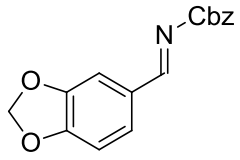


401l

Prepared according to general procedure J. Compound **400l** (479 mg, 1.09 mmol) was reacted with K_2CO_3 (1.4 M aq. solution in H_2O, 10 mL) in CH_2Cl_2 (10 mL) to afford compound **401l** (278 mg, 86%) as a white solid. **Melting Point**: 67 - 69 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 8.94 (s, 1H, C**H**=N), 7.60 (d, *J* = 1.5 Hz, 1H, Ar**H**), 7.50 - 7.44 (m, 2H, Ar**H**), 7.43 - 7.31 (m, 4H, Ar**H**), 6.93 (d, *J* = 8.0 Hz, 1H, Ar**H**), 5.32 (s, 2H, ArC**H$_2$**), 3.96 (s, 3H, ArOC**H$_3$**), 3.94 (s, 3H, ArOC**H$_3$**); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 171.7 (**C**H=N), 163.8 (**C**=O), 154.4 (Ar**C**), 149.5 (Ar**C**), 135.5 (Ar**C**), 128.6 (2 × Ar**C**H), 128.5 (2 × Ar**C**H), 128.4 (Ar**C**H), 128.1 (Ar**C**H), 127.0 (Ar**C**), 110.4 (Ar**C**H), 109.4 (Ar**C**H), 68.8 (Ar**C**H_2), 56.1 (ArO**C**H_3), 56.0 (ArO**C**H_3); **IR** (film/cm^{-1}): ν_{max} 2932, 1704, 1571, 1508, 1457, 1271, 1241, 1216,

1182, 1141, 1018, 871, 814, 737; **MS** (ESI): *m/z* 354.1 [(M + MeOH + Na)$^+$]; **HRMS** (ESI): exact mass calculated for $C_{18}H_{21}NNaO_5$ [(M + MeOH + Na)$^+$], 354.1312; found 354.1302.

Synthesis and characterisation of benzyl [(*E*)-1,3-benzodioxol-5-ylmethylidene] carbamate (400m)

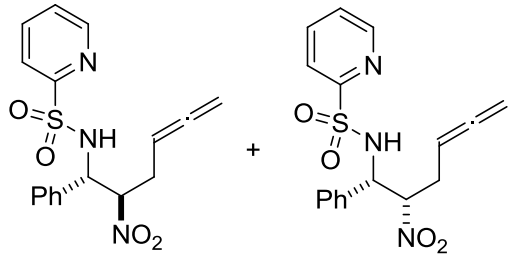


401m

Prepared according to general procedure J. Compound **400m** (462 mg, 1.09 mmol) was reacted with K_2CO_3 (1.4 M aq. solution in H_2O, 10 mL) in CH_2Cl_2 (10 mL) to afford compound **401m** (270 mg, 88%) as a white solid. **Melting Point**: 70 - 71 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 8.88 (s, 1H, C**H**=N), 7.52 (s, 1H, Ar**H**), 7.49 - 7.42 (m, 2H, Ar**H**), 7.42 - 7.29 (m, 4H, Ar**H**), 6.89 (d, *J* = 8.0 Hz, 1H, Ar**H**), 6.06 (s, 2H, OC**H$_2$**O), 5.31 (s, 2H, ArC**H$_2$**); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 171.1 (**C**H=N), 163.7 (**C**=O), 152.9 (Ar**C**), 148.6 (Ar**C**), 135.4 (Ar**C**), 129.4 (Ar**C**H), 128.6 (Ar**C**), 128.5 (2 × Ar**C**H), 128.5 (2 × Ar**C**H), 128.4 (Ar**C**H), 108.4 (Ar**C**H), 107.5 (Ar**C**H), 102.0 (O**C**H$_2$O), 68.8 (Ar**C**H$_2$); **IR** (film/cm^{-1}): ν_{max} 2915, 1699, 1589, 1502, 1447, 1256, 1217, 1189, 1103, 1037, 925, 903, 819, 695; **MS** (ESI): *m/z* 338.1 [(M + MeOH + Na)$^+$]; **HRMS** (ESI): exact mass calculated for $C_{17}H_{17}NNaO_5$ [(M + MeOH + Na)$^+$], 338.0999; found 338.0996.

5.4.7 Synthesis and Characterisation of β-Nitroamines Intermediates

Synthesis and characterisation of *rac*-*N*-[(1*S*,2*R*)-2-nitro-1-phenylhexa-4,5-dien-1-yl]pyridine-2-sulfonamide (498) and *rac*-*N*-[(1*S*,2*S*)-2-nitro-1-phenylhexa-4,5-dien-1-yl]pyridine-2-sulfonamide (498′)



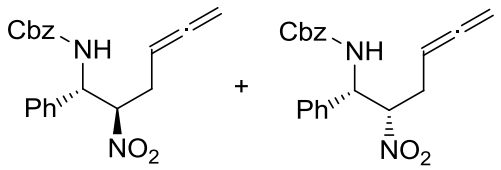
498 **498′**

To a stirred solution of *N*-pyridine-2-sulfonyl imine **497** (24.6 mg, 0.10 mmol) and nitroallene **468** (16.9 mg, 0.15 mmol) in CH_2Cl_2 (1.0 mL) at RT was added KO*t*Bu (1.2 mg, 0.01 mmol, 10 mol%). The resulting mixture was stirred at RT for 24 h and then directly purified by flash column chromatography on silica gel eluting with PE/EtOAc (2:1) to afford a mixture of diastereomers **498** and **498′** (17 mg, 48%, dr 32:68) as a pale yellow solid. **TLC**: R_f = 0.22 (PE/EtOAc 2:1, UV, $KMnO_4$); **Melting Point**: 138 - 140 °C; **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of diastereomers): δ_H 8.51 - 8.45 (m, 1H, Ar**H**, *major*), 8.43 - 8.38 (m, 1H, Ar**H**, *minor*), 7.79 (d, *J* = 8.0 Hz, 1H, Ar**H**, *minor*), 7.77 - 7.68 (m, Ar**H**, 1H *major* and 1H *minor*), 7.66 (td, *J* = 7.5, 1.5 Hz, 1H, Ar**H**, *major*), 7.38 - 7.25 (m, Ar**H**, 1H *major* and 1H *minor*), 7.20 - 7.07 (m, Ar**H**, 3H *major* and 3H *minor*), 7.04 - 6.94 (m, Ar**H**, 2H *major* and 2H *minor*), 6.49 (d, *J* = 10.0 Hz, 1H, N**H**, *major*), 6.18 (d, *J* = 9.0 Hz, 1H, N**H**, *minor*), 5.15 - 4.90 (m, C**H**N, 1H *major* and 1H *minor*; C**H**NO_2, 1H *minor*, C**H**=CH_2, 1H *major* and 1H *minor*), 4.88 - 4.71 (m, C**H**NO_2, 1H *major*; CH=C**H$_2$**, 2H *major* and 2H *minor*), 2.91 - 2.62 (m, C**HH′**, 1H *major* and 2H *minor*), 2.54 - 2.40 (m, 1H, CH**H′**, *major*); **^{13}C NMR** (100 MHz, $CDCl_3$, unassigned mixture of diastereomers): δ_C 209.2 (CH=**C**=CH_2), 209.2 (CH=**C**=CH_2), 157.0 (Ar**C**), 156.9

(Ar**C**), 149.8 (2 × Ar**C**H), 137.7 (Ar**C**H), 137.6 (Ar**C**H), 134.8 (Ar**C**), 134.5 (Ar**C**), 128.8 (2 × Ar**C**H), 128.6 (Ar**C**H), 128.6 (2 × Ar**C**H), 128.5 (Ar**C**H), 127.1 (2 × Ar**C**H), 126.8 (2 × Ar**C**H), 126.5 (Ar**C**H), 126.4 (Ar**C**H), 122.0 (Ar**C**H), 121.8 (Ar**C**H), 91.0 (**C**HNO_2), 90.4 (**C**HNO_2), 84.1 (**C**H=C=CH_2), 83.6 (**C**H=C=CH_2), 76.8 (CH=C=**C**H_2), 76.7 (CH=C=**C**H_2), 59.8 (**C**HN), 59.6 (**C**HN), 30.2 (**C**H_2), 29.5 (**C**H_2); **IR** (film/cm^{-1}): ν_{max} 3261, 2923, 1957, 1555, 1457, 1428, 1336, 1177, 1120, 851, 769, 738; **MS** (ESI): *m/z* 382.1 [$(M + Na)^+$]; **HRMS** (ESI): exact mass calculated for $C_{17}H_{17}N_3NaO_4S$ [$(M + Na)^+$], 382.0832; found 382.0833. The relative configurations of diastereomers **498** and **498′** were assigned by analogy to the single crystal X-ray structure of *syn*-**268′**.

Enantioselective synthesis of diastereomers 498 and 498′: Diastereomers **498** and **498′** were synthesised on a 0.10 mmol scale in an analogous manner to the described procedure by replacing KO*t*Bu with catalyst **496** (5 mol%) and stirring at RT for 24 h. The reaction mixture was directly purified by flash column chromatography on silica gel eluting with PE/EtOAc (2:1) to afford diastereomers **498** and **498′** (31 mg, 86%) as a pale yellow solid. The dr and ee were determined by HPLC analysis using a Chiralpak IA column [hexane/*i*PrOH 85:15, flow rate 1.0 mL/min, λ = 210 nm]; dr 60:40; ***MAJOR:*** t_R major = 25.88 min, t_R minor = 27.29 min (21% ee), ***MINOR:*** t_R minor = 20.06 min, t_R major = 31.42 min (1% ee). $\mathbf{[\alpha]_D^{23}}$ = –1.7 (c = 2.1, $CHCl_3$); **Melting Point:** 129 - 132 °C. All other data was in agreement with that of the corresponding racemic diastereomers **498** and **498′**. The absolute configurations of diastereomers **498** and **498′** were not determined, only the relative configuration is shown.

Synthesis and characterisation of benzyl [(1*S*,2*R*)-2-nitro-1-phenylhexa-4,5-dien-1-yl]carbamate (499) and benzyl [(1*S*,2*S*)-2-nitro-1-phenylhexa-4,5-dien-1-yl]carbamate (499′)

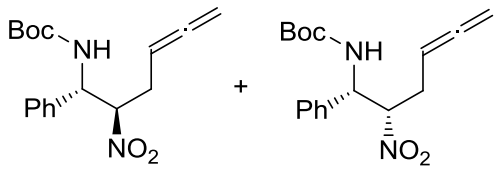


499 **499′**

To a stirred solution of *N*-Cbz imine **401a** (47.9 mg, 0.20 mmol) and nitroallene **468** (33.9 mg, 0.30 mmol) in PhMe (0.4 mL) at –15 °C was added catalyst **388** (4.0 mg, 0.01 mmol, 5 mol%). The resulting mixture was stirred at –15 °C for 44 h and then directly purified by flash column chromatography on silica gel eluting with PE/Et_2O (2:1) to afford a mixture of diastereomers **499** and **499′** (54 mg, 77%) as an off-white solid. The dr and ee were determined by HPLC analysis using a Chiralpak AD column [hexane/*i*PrOH 90:10, flow rate 1.0 mL/min, λ = 210 nm]; dr 87:13; ***MAJOR:*** t_R major = 23.18 min, t_R minor = 36.25 min (91% ee), ***MINOR:*** t_R major = 33.79 min, t_R minor = 43.80 min (77% ee). **TLC**: R_f = 0.30 (PE/Et_2O 2:1, UV, $KMnO_4$); **Melting Point**: 83 - 86 °C; $[\alpha]_D^{23}$ = +5.5 (c = 2.38, $CHCl_3$); **Major diastereomer 499:** ^{1}**H NMR** (500 MHz, $CDCl_3$): δ_H 7.43 - 7.28 (m, 8H, Ar**H**), 7.26 - 7.14 (m, 2H, Ar**H**), 5.65 (d, *J* = 8.0 Hz, 1H, N**H**), 5.34 - 5.22 (m, 1H, C**H**NH), 5.17 - 5.01 (m, 3H, ArC$\mathbf{H_2}$ and C**H**=C=CH_2), 4.99 - 4.87 (m, 1H, C**H**NO_2), 4.85 - 4.71 (m, 2H, CH=C=C$\mathbf{H_2}$), 2.78 - 2.64 (m, 1H, C**H**H′), 2.57 - 2.45 (m, 1H, CH**H′**); ^{13}**C NMR** (125 MHz, $CDCl_3$): δ_C 209.1 (CH=**C**=CH_2), 155.5 (**C**=O), 135.8 (Ar**C**), 135.7 (Ar**C**), 129.1 (2 × Ar**C**H), 129.0 (Ar**C**H), 128.6 (2 × Ar**C**H), 128.3 (Ar**C**H), 128.2 (2 × Ar**C**H), 126.8 (2 × Ar**C**H), 89.9 (**C**HNO_2), 84.3 (**C**H=C=CH_2), 77.0 (CH=C=**C**H_2), 67.4 (Ar**C**H_2), 57.0 (**C**HNH), 28.6 (**C**H_2); **Minor diastereomer 499′:** ^{1}**H NMR** (500 MHz, $CDCl_3$, observable peaks): δ_H 6.01 (d, *J* = 9.5 Hz, 1H, N**H**), all other signals

are superimposed by the signals corresponding to the major diastereomer **499**; **^{13}C NMR** (125 MHz, $CDCl_3$, observable peaks): δ_C 209.3 (CH=**C**=CH_2), 155.7 (**C**=O), 135.8 (Ar**C**), 129.1 (Ar**C**H), 128.6 (Ar**C**H), 127.9 (Ar**C**H), 90.0 (**C**$CHNO_2$), 83.8 (**C**H=C=CH_2), 76.9 (CH=C=**C**H_2), 67.4 (Ar**C**H_2), 56.0 (**C**HNH), 29.7 (**C**H_2); **IR** (film/cm^{-1}): ν_{max} 3369, 2953, 1960, 1690, 1531, 1496, 1452, 1373, 1285, 1250, 1226, 1030, 1004; **MS** (ESI): *m/z* 375.2 [(M + Na)$^+$]; **HRMS** (ESI): exact mass calculated for $C_{20}H_{20}N_2NaO_4$ [(M + Na)$^+$], 375.1315; found 375.1304. The absolute configurations of diastereomers **499** and **499′** were assigned by analogy to the single crystal X-ray structure of compound **501k**. Compounds **499** and **499′** were prepared and characterised by Dr. A. Ďuriš.

Synthesis and characterisation of *tert*-butyl [(1*S*,2*R*)-2-nitro-1-phenylhexa-4,5-dien-1-yl]carbamate (500) and *tert*-butyl [(1*S*,2*S*)-2-nitro-1-phenylhexa-4,5-dien-1-yl]carbamate (500′)



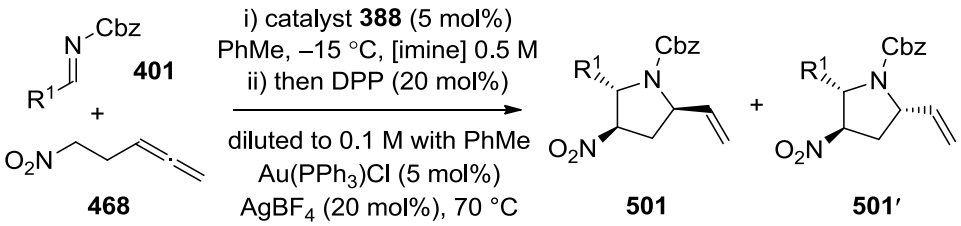
500 **500′**

To a stirred solution of *N*-Boc imine **112a** (20.5 mg, 0.10 mmol) and nitroallene **468** (16.9 mg, 0.15 mmol) in PhMe (0.2 mL) at –15 °C was added catalyst **388** (2.0 mg, 5 μmol, 5 mol%). The resulting mixture was stirred at –15 °C for 24 h and then directly purified by flash column chromatography on silica gel eluting with PE/EtOAc (9:1) to afford a mixture of diastereomers **500** and **500′** (12 mg, 38%) as a white solid. The dr and ee were determined by HPLC analysis using a Chiralpak AD-H column [hexane/*i*PrOH 95:5, flow rate 1.0 mL/min, λ = 220 nm]; dr 82:18; ***MAJOR:*** t_R major = 19.20 min, t_R minor = 28.01 min (88% ee), ***MINOR:*** t_R major = 25.69 min, t_R minor = 28.99 min (84% ee). **TLC**: R_f = 0.29 (PE/EtOAc 9:1, UV,

$KMnO_4$); **Melting Point**: 74 - 76 °C; $[\alpha]_D^{23}$ = +11.3 (c = 0.59, $CHCl_3$); **Major diastereomer 500:** ^{1}**H NMR** (500 MHz, $CDCl_3$): δ_H 7.43 - 7.30 (m, 3H, Ar**H**), 7.29 - 7.17 (m, 2H, Ar**H**), 5.29 (d, *J* = 8.5 Hz, 1H, N**H**), 5.20 (br s, 1H, C**H**N), 5.08 (qu, *J* = 6.5 Hz, 1H, C**H**=C=CH_2), 4.91 (br s, 1H, C**H**NO_2), 4.79 (dt, *J* = 6.5, 3.0 Hz, 2H, CH=C=C**H$_2$**), 2.81 - 2.62 (m, 1H, C**H**H′), 2.58 - 2.43 (m, 1H, CH**H′**), 1.44 (m, 9H, C(C**H$_3$**)$_3$); ^{13}**C NMR** (125 MHz, $CDCl_3$): δ_C 209.1 (CH=**C**=CH_2), 154.8 (**C**=O), 136.1 (Ar**C**), 129.0 (2 × Ar**C**H), 128.8 (2 × Ar**C**H), 126.9 (Ar**C**H), 90.2 (**C**HNO_2), 84.5 (**C**H=C=CH_2), 80.6 (**C**$(CH_3)_3$), 76.9 (CH=C=**C**H_2), 56.6 (**C**HN), 28.7 (**C**H_2), 28.2 (C(**C**$H_3)_3$); **Minor diastereomer 500′:** ^{1}**H NMR** (500 MHz, $CDCl_3$, observable peaks): δ_H 5.78 - 5.62 (m, 1H, N**H**), 1.46 (s, 9H, C(C**H$_3$**)$_3$), all other signals are superimposed by the signals corresponding to the major diastereomer **500**; ^{13}**C NMR** (125 MHz, $CDCl_3$, observable peaks): δ_C 209.3 (CH=**C**=CH_2), 137.3 (Ar**C**), 128.5 (Ar**C**H), 126.2 (Ar**C**H), 91.2 (**C**HNO_2), 84.0 (**C**H=C=CH_2), 76.8 (CH=C=**C**H_2), 55.5 (**C**HN), 30.2 (**C**H_2), 28.2 (C(**C**$H_3)_3$); **IR** (film/cm^{-1}): ν_{max} 3376, 2979, 2928, 1683, 1533, 1520, 1368, 1252, 1166, 852, 703; **MS** (ESI): *m/z* 341.1 [(M + Na)$^+$]; **HRMS** (ESI): exact mass calculated for $C_{17}H_{22}N_2NaO_4$ [(M + Na)$^+$], 341.1472; found 341.1461. The absolute configurations of diastereomers **500** and **500′** were assigned by analogy to the single crystal X-ray structure of compound **501k**. Compounds **500** and **500′** were prepared and characterised by Dr. A. Ďuriš.

5.4.8 Synthesis and Characterisation of Substituted Pyrrolidines 501

General Procedure K: Enantioselective nitro-Mannich/hydroamination cascade to substituted pyrrolidines

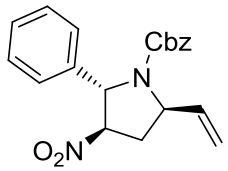


To a stirred mixture of the corresponding *N*-Cbz imine **401** (0.20 mmol, 1.0 equiv) and nitroallene **468** (0.30 mmol, 1.5 equiv) in PhMe (0.4 mL) at –15 °C in a sealed vial was added catalyst **388** (4.0 mg, 0.01 mmol, 5 mol%). The resulting mixture was stirred at –15 °C for the indicated time. The reaction mixture was diluted with PhMe (1.6 mL), then diphenylphosphate (10.0 mg, 0.04 mmol, 20 mol%), $Au(PPh_3)Cl$ (4.9 mg, 0.01 mmol, 5 mol%) and $AgBF_4$ (8.0 mg, 0.04 mmol, 20 mol%) were added and the resulting mixture was heated to 70 °C for the indicated time. The reaction mixture was cooled to RT and concentrated under a stream of nitrogen. The residue was purified by flash column chromatography on silica gel to afford the desired enantioenriched pyrrolidine **501**.

General procedure for racemic pyrrolidine synthesis: Racemic samples of pyrrolidines **501** and **501′** were prepared using the general procedure H.

The compounds reported in this section (5.4.8) were prepared by Dr. A. Ďuriš, purified by D. M. Barber and characterised by D. M. Barber unless otherwise stated.

Synthesis and characterisation of benzyl (2*S*,3*R*,5*R*)-5-ethenyl-3-nitro-2-phenylpyrrolidine-1-carboxylate (501a)

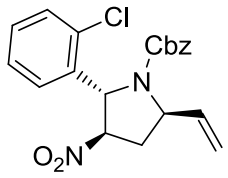


501a

Prepared according to general procedure K. *N*-Cbz imine **401a** (47.9 mg, 0.20 mmol) was reacted with nitroallene **468** (33.9 mg, 0.30 mmol) for 40 h (step i) and 3 h (step ii) to afford compound **501a** (42 mg, 60%, dr >98:2) as a colourless oil, after purification by flash column chromatography on silica gel eluting with PE/Et_2O (2:1). The ee was determined by HPLC analysis using a Chiralpak IA column [hexane/*i*PrOH 85:15, flow rate 1.0 mL/min, λ = 220 nm]; t_R major = 9.75 min, t_R minor = 21.73 min (90% ee). **TLC**: R_f = 0.37 (PE/Et_2O 2:1, UV, $KMnO_4$); $\mathbf{[\alpha]_D^{23}}$ = −28.5 (c = 0.47, $CHCl_3$); **^{1}H NMR** (500 MHz, CD_3OD, 60:40 mixture of rotamers): δ_H 7.44 - 7.05 (m, 9H, Ar**H**), 6.80 (d, *J* = 7.5 Hz, 1H, Ar**H**), 5.94 (s, 0.4H, C**H**N), 5.93 (s, 0.6H, C**H**N), 5.82 - 5.70 (m, 1H, C**H**=CH_2), 5.15 (d, *J* = 17.0 Hz, 0.6H, CH=CH_{cis}**H**$_{trans}$), 5.12 - 4.98 (m, 3H, ArC**H$_2$** and CH=C**H$_2$**), 4.92 - 4.77 (m, 2.4H, C**H**NO_2, ArC**H$_2$** and NC**H**CH=CH_2, superimposed by residual solvent), 2.88 - 2.78 (m, 1H, C**H**H′), 2.65 (dt, *J* = 15.5, 1.5 Hz, 1H, CH**H′**); **^{13}C NMR** (125 MHz, CD_3OD, mixture of rotamers): δ_C 156.2 (**C**=O), 155.8 (**C**=O), 141.4 (Ar**C**), 140.4 (Ar**C**), 139.3 (**C**H=CH_2), 138.4 (**C**H=CH_2), 137.8 (Ar**C**), 137.6 (Ar**C**), 130.3 (Ar**C**H), 130.2 (Ar**C**H), 129.6 (Ar**C**H), 129.4 (Ar**C**H), 129.3 (Ar**C**H), 129.3 (Ar**C**H), 129.2 (Ar**C**H), 128.9 (Ar**C**H), 128.6 (Ar**C**H), 126.9 (Ar**C**H), 116.2 (CH=**C**H_2), 116.1 (CH=**C**H_2), 91.3 (**C**HNO_2), 90.6 (**C**HNO_2), 68.7 (Ar**C**H_2), 68.3 (Ar**C**H_2), 66.7 (**C**HN), 66.6 (**C**HN), 61.4 (N**C**HCH=CH_2), 61.1 (N**C**HCH=CH_2), 35.4 (**C**H_2), 34.5 (**C**H_2); **IR** (film/cm^{-1}): ν_{max} 3033, 1705, 1552, 1453, 1406, 1347, 1215, 1120, 1020,

751, 699; **MS** (ESI): *m/z* 375.1 [(M + Na)$^+$]; **HRMS** (ESI): exact mass calculated for $C_{20}H_{20}N_2NaO_4$ [(M + Na)$^+$], 375.1315; found 375.1307.

Synthesis and characterisation of benzyl (2*S*,3*R*,5*R*)-2-(2-chlorophenyl)-5-ethenyl-3-nitropyrrolidine-1-carboxylate (501b)

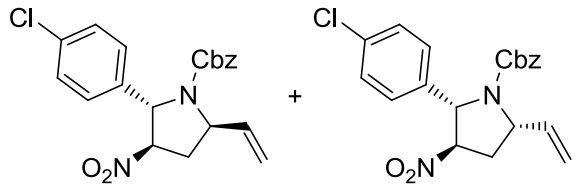


501b

Prepared according to general procedure K. *N*-Cbz imine **401b** (54.7 mg, 0.20 mmol) was reacted with nitroallene **468** (33.9 mg, 0.30 mmol) for 48 h (step i) and 3 h (step ii) to afford compound **501b** (40 mg, 52%, dr >98:2) as a colourless oil, after purification by flash column chromatography on silica gel eluting with PE/Et_2O (2:1). The ee was determined by HPLC analysis using a Chiralpak IA column [hexane/*i*PrOH 85:15, flow rate 1.0 mL/min, λ = 220 nm]; t_R major = 9.34 min, t_R minor = 18.29 min (90% ee). **TLC**: R_f = 0.25 (PE/Et_2O 2:1, UV. $KMnO_4$); $[\alpha]_D^{23}$ = – 21.5 (c = 1.40, $CHCl_3$); **^{1}H NMR** (500 MHz, CD_3OD, 39:17:30:14 mixture of rotamers): δ_H 7.49 - 7.42 (m, 1H, Ar**H**), 7.37 - 7.08 (m, 7H, Ar**H**,), 6.86 (d, *J* = 7.0 Hz, 1H, Ar**H**), 6.33 (s, 0.4H, C**H**N), 6.32 (s, 0.2H, C**H**N), 6.30 (s, 0.3H, C**H**N), 6.29 (s, 0.1H, C**H**N), 5.81 - 5.70 (m, 1H, C**H**=CH_2), 5.16 (d, *J* = 17.5 Hz, 0.6H, CH=CH$_{cis}$**H**$_{trans}$), 5.12 - 4.99 (m, 3H, CH=C**H$_2$** and ArC**H$_2$**), 4.90 - 4.80 (m, 2.4H, C**H**NO_2, ArC**H$_2$** and NC**H**CH=CH_2, superimposed by residual solvent), 2.83 - 2.72 (m, 1H, C**H**H′), 2.69 - 2.60 (m, 1H, CH**H′**); **^{13}C NMR** (125 MHz, CD_3OD, mixture of rotamers): δ_C 155.9 (**C**=O), 155.4 (**C**=O), 138.9 (**C**H=CH_2), 138.1 (Ar**C**), 138.0 (**C**H=CH_2), 137.7 (Ar**C**), 137.5 (Ar**C**), 137.1 (Ar**C**), 133.6 (Ar**C**), 133.3 (Ar**C**), 131.3 (Ar**C**H), 131.3 (Ar**C**H), 130.9 (Ar**C**H), 130.8 (Ar**C**H), 129.6 (Ar**C**H), 129.4

(Ar**C**H), 129.4 (Ar**C**H), 129.4 (Ar**C**H), 129.0 (Ar**C**H), 129.0 (Ar**C**H), 128.8 (Ar**C**H), 128.6 (Ar**C**H), 127.7 (Ar**C**H), 127.6 (Ar**C**H), 116.4 (CH=**C**H_2), 89.8 (**C**HNO_2), 89.0 (**C**HNO_2), 68.8 (Ar**C**H_2), 68.4 (Ar**C**H_2), 64.1 (**C**HN), 64.0 (**C**HN), 63.7 (**C**HN), 63.7 (**C**HN), 61.3 (N**C**HCH=CH_2), 61.1 (N**C**HCH=CH_2), 35.9 (**C**H_2), 35.9 (**C**H_2), 34.8 (**C**H_2), 34.8 (**C**H_2); **IR** (film/cm^{-1}): ν_{max} 2953, 1704, 1549, 1444, 1402, 1348, 1213, 1114, 1048, 925, 752; **MS** (ESI): *m/z* 409.l and 411.0 [$(M + Na)^+$]; **HRMS** (ESI): exact mass calculated for $C_{20}H_{19}ClN_2NaO_4$ [$(M + Na)^+$], 409.0926 and 411.0898; found 409.0919 and 411.0892.

Synthesis and characterisation of benzyl (2*S*,3*R*,5*R*)-2-(4-chlorophenyl)-5-ethenyl-3-nitropyrrolidine-1-carboxylate (501c) and benzyl (2*S*,3*R*,5*S*)-2-(4-chlorophenyl)-5-ethenyl-3-nitropyrrolidine-1-carboxylate (501c′)



501c **501c′**

Prepared according to general procedure K. *N*-Cbz imine **401c** (54.7 mg, 0.20 mmol) was reacted with nitroallene **468** (33.9 mg, 0.30 mmol) for 24 h (step i) and 2 h (step ii) to afford diastereomer **501c** (28 mg, 36%, dr >98:2) as a colourless oil and diastereomer **501c′** (3.1 mg, 4%) as a colourless oil after purification by flash column chromatography on silica gel eluting with PE/Et_2O (4:1).

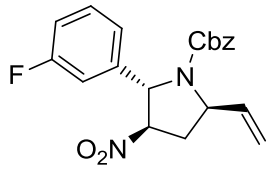
Major diastereomer 501c: The ee was determined by HPLC analysis using a Chiralpak IA column [hexane/*i*PrOH 80:20, flow rate 1.0 mL/min, λ = 230 nm]; t_R major = 8.84 min, t_R minor = 25.16 min (93% ee). **TLC**: R_f = 0.15 (PE/Et_2O 4:1, UV, $KMnO_4$); $[\alpha]_D^{23}$ = −16.0 (c = 0.78, $CHCl_3$); **^{1}H NMR** (500 MHz, CD_3OD, 60:40 mixture of rotamers): δ_H 7.41 - 7.11 (m, 8H, Ar**H**), 6.84 (d, *J* = 7.5 Hz, 1H, Ar**H**),

5.92 (s, 0.4H, C**H**N), 5.90 (s, 0.6H, C**H**N), 5.75 (ddd, *J* = 17.0, 10.5, 6.0 Hz, 1H, C**H**=CH_2), 5.14 (d, *J* = 17.5 Hz, 0.6H, CH=CH_{cis}**H**$_{trans}$), 5.11 - 4.98 (m, 3H, ArC**H$_2$** and CH=C**H$_2$**), 4.84 - 4.72 (m, 2.4H, C**H**NO_2, ArC**H$_2$** and NC**H**CH=CH_2, superimposed by residual solvent), 2.82 (ddd, *J* = 15.5, 9.0, 7.0 Hz, 1H, C**H**H′), 2.66 (d, *J* = 15.5 Hz, 1H, CH**H′**); **^{13}C NMR** (125 MHz, CD_3OD, mixture of rotamers): δ_C 156.1 (**C**=O), 155.6 (**C**=O), 140.2 (Ar**C**), 139.3 (Ar**C**), 139.1 (**C**H=CH_2), 138.2 (**C**H=CH_2), 137.7 (Ar**C**), 137.5 (Ar**C**), 135.0 (Ar**C**), 134.9 (Ar**C**), 130.3 (Ar**C**H), 130.2 (Ar**C**H), 129.6 (Ar**C**H), 129.4 (Ar**C**H), 129.3 (Ar**C**H), 129.1 (Ar**C**H), 128.9 (Ar**C**H), 128.7 (Ar**C**H), 116.2 (CH=**C**H_2), 116.2 (CH=**C**H_2), 91.3 ($CHNO_2$), 90.6 ($CHNO_2$), 68.7 (Ar**C**H_2), 68.4 (Ar**C**H_2), 66.1 (**C**HN), 66.0 (**C**HN), 61.3 (N**C**HCH=CH_2), 61.1 (N**C**HCH=CH_2), 35.5 (CH_2), 34.5 (CH_2); **IR** (film/cm^{-1}): ν_{max} 2970, 1704, 1551, 1492, 1405, 1349, 1216, 1120, 1091, 1014, 731; **MS** (ESI): *m/z* 409.0 and 411.0 [$(M + Na)^+$]; **HRMS** (ESI): exact mass calculated for $C_{20}H_{19}ClN_2NaO_4$ [$(M + Na)^+$], 409.0926 and 411.0898; found 409.0912 and 411.0895.

Minor diastereomer 501c′: The ee was determined by HPLC analysis using a Chiralpak IA column [hexane/*i*PrOH 80:20, flow rate 1.0 mL/min, λ = 230 nm]; t_R major = 9.81 min, t_R minor = 15.10 min (93% ee). **TLC**: R_f = 0.25 (PE/Et_2O (4:1, UV, $KMnO_4$); **$[\alpha]_D^{23}$** = −5.6 (c = 0.25, $CHCl_3$); **^{1}H NMR** (500 MHz, CD_3OD, mixture of rotamers): δ_H 7.42 - 7.02 (m, 9H, Ar**H**), 6.02 (ddd, *J* = 17.0, 10.0, 7.0 Hz, 1H, C**H**=CH_2), 5.66 (s, 1H, C**H**N), 5.37 - 5.20 (m, 2H, CH=C**H$_2$**), 5.18 - 5.01 (m, 2H, ArC**H$_2$**), 4.92 - 4.78 (m, 1H, C**H**NO_2, superimposed by residual solvent), 4.70 - 4.61 (m, 1H, NC**H**CH=CH_2), 2.80 (ddd, *J* = 15.0, 7.5, 1.5 Hz, 1H, C**H**H′), 2.27 (dd, *J* = 15.0, 9.0 Hz, 1H, CH**H′**); **^{13}C NMR** (125 MHz, CD_3OD, mixture of rotamers): δ_C 157.1 (br s, **C**=O), 139.1 (br s, Ar**C**), 138.7 (br s, **C**H=CH_2), 137.8 (Ar**C**), 135.1

(Ar**C**), 130.1 (Ar**C**H), 129.6 (Ar**C**H), 129.2 (Ar**C**H), 129.1 (Ar**C**H), 128.8 (br s, Ar**C**H), 118.2 (CH=**C**H_2), 90.7 (br s, **C**HNO_2), 68.7 (br s, Ar**C**H_2), 67.8 (br s, **C**HN), 61.4 (N**C**HCH=CH_2), 36.1 (br s, **C**H_2); **IR** (film/cm^{-1}): ν_{max} 2927, 1704, 1544, 1492, 1402, 1349, 1091, 1014, 983, 751; **MS** (ESI): *m/z* 409.1 and 411.0 [$(M + Na)^+$]; **HRMS** (ESI): exact mass calculated for $C_{20}H_{19}ClN_2NaO_4$ [$(M + Na)^+$], 409.0926 and 411.0898; found 409.0919 and 411.0892. The ^{1}H NMR of diastereomer **501c′** showed that another compound was present in a ratio of 95:5. From the data collected we were not able to confidently determine the structure of this compound; therefore no assignment has been made.

Synthesis and characterisation of benzyl (2*S*,3*R*,5*R*)-5-ethenyl-2-(3-fluoro phenyl)-3-nitropyrrolidine-1-carboxylate (501d)

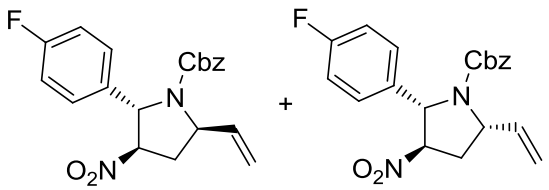


501d

Prepared according to general procedure K. *N*-Cbz imine **401e** (51.5 mg, 0.20 mmol) was reacted with nitroallene **468** (33.9 mg, 0.30 mmol) for 48 h (step i) and 4 h (step ii) to afford compound **501d** (43 mg, 58%, dr >98:2) as a colourless oil, after purification by flash column chromatography on silica gel eluting with PE/Et_2O (4:1). The ee was determined by HPLC analysis using a Chiralpak IA column [hexane/*i*PrOH 85:15, flow rate 1.0 mL/min, λ = 220 nm]; t_R major = 10.32 min, t_R minor = 24.36 min (95% ee). **TLC**: R_f = 0.16 (PE/Et_2O 4:1, UV, $KMnO_4$); $\mathbf{[\alpha]_D^{23}}$ = −28.1 (c = 0.60, $CHCl_3$); **^{1}H NMR** (400 MHz, CD_3OD, mixture of rotamers): δ_H 7.47 - 6.91 (m, 8H, Ar**H**), 6.85 (d, *J* = 7.0 Hz, 1H, Ar**H**), 5.94 (br s, 1H, C**H**N), 5.83 - 5.66 (m, 1H, C**H**=CH_2), 5.22 - 4.96 (m, 3H, CH=C**H$_2$** and ArC**H$_2$**), 4.93 - 4.74 (m,

3H, C**H**NO_2, ArC**H$_2$** and NC**H**CH=CH_2, superimposed by residual solvent), 2.90 - 2.74 (m, 1H, C**H**H′), 2.66 (d, *J* = 15.5 Hz, 1H, CH**H′**); **^{13}C NMR** (125 MHz, CD_3OD, mixture of rotamers): δ_C 164.8 (d, *J* = 246.0 Hz, Ar**C**F), 156.1 (**C**=O), 155.6 (**C**=O), 144.3 (d, *J* = 6.5 Hz, Ar**C**), 144.3 (d, *J* = 6.5 Hz, Ar**C**), 139.1 (**C**H=CH_2), 138.2 (**C**H=CH_2), 137.7 (Ar**C**), 137.5 (Ar**C**), 132.2 (d, *J* = 7.5 Hz, Ar**C**H), 132.1 (d, *J* = 7.5 Hz, Ar**C**H), 129.6 (Ar**C**H), 129.4 (Ar**C**H) 129.4 (Ar**C**H), 129.3 (Ar**C**H), 129.1 (Ar**C**H), 128.8 (Ar**C**H), 122.8 (d, *J* = 3.0 Hz, Ar**C**H), 122.8 (d, *J* = 3.0 Hz, Ar**C**H), 116.3 (CH=**C**H_2), 116.2 (CH=**C**H_2), 116.1 (d, *J* = 22.0 Hz, Ar**C**H), 116.0 (d, *J* = 22.0 Hz, Ar**C**H), 114.0 (d, *J* = 23.0 Hz, Ar**C**H), 114.0 (d, *J* = 23.0 Hz, Ar**C**H), 91.3 (**C**HNO_2), 90.6 (**C**HNO_2), 68.8 (Ar**C**H_2), 68.4 (Ar**C**H_2), 66.2 (**C**HN), 66.2 (**C**HN), 66.0 (**C**HN), 66.0 (**C**HN), 61.4 (N**C**HCH=CH_2), 61.1 (N**C**HCH=CH_2), 35.6 (**C**H_2), 35.5 (**C**H_2), 34.6 (**C**H_2), 34.5 (**C**H_2); **^{19}F NMR** (376.5 MHz, CD_3OD, mixture of rotamers): δ_F –113.8, –114.1; **IR** (film/cm^{-1}): ν_{max} 2982, 1704, 1593, 1549, 1489, 1450, 1405, 1348, 1115; **MS** (ESI): *m/z* 393.1 [(M + Na)$^+$]; **HRMS** (ESI): exact mass calculated for $C_{20}H_{19}FN_2NaO_4$ [(M + Na)$^+$], 393.1221; found 393.1215.

Synthesis and characterisation of benzyl (2*S*,3*R*,5*R*)-5-ethenyl-2-(4-fluorophenyl)-3-nitropyrrolidine-1-carboxylate (501e) and benzyl (2*S*,3*R*,5*S*)-5-ethenyl-2-(4-fluorophenyl)-3-nitropyrrolidine-1-carboxylate (501e′)



501e **501e′**

Prepared according to general procedure K. *N*-Cbz imine **401f** (51.5 mg, 0.20 mmol) was reacted with nitroallene **468** (33.9 mg, 0.30 mmol) for 40 h (step i) and 2 h (step ii) to afford diastereomer **501e** (37 mg, 50%, dr >98:2) as a colourless oil and

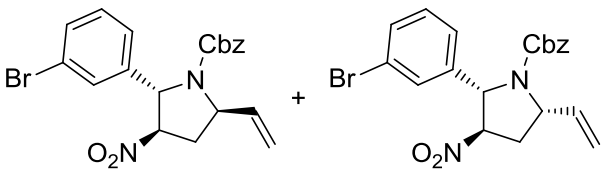
diastereomer **501e′** (5.8 mg, 8%) as a colourless oil, after purification by flash column chromatography on silica gel eluting with PE/Et_2O (4:1) → PE/Et_2O (2:1).

Major diastereomer 501e: The ee was determined by HPLC analysis using a Chiralpak IA column [hexane/*i*PrOH 85:15, flow rate 1.0 mL/min, λ = 220 nm]; t_R major = 10.23 min, t_R minor = 30.29 min (94% ee). **TLC**: R_f = 0.23 (PE/Et_2O 2:1, UV, $KMnO_4$); $[\alpha]_D^{23}$ = −29.0 (c = 0.96, $CHCl_3$); **^{1}H NMR** (500 MHz, CD_3OD, 60:40 mixture of rotamers): δ_H 7.40 - 7.00 (m, 8H, Ar**H**), 6.85 (d, *J* = 7.5 Hz, 1H, Ar**H**), 5.93 (s, 0.4H, C**H**N), 5.91 (s, 0.6H, C**H**N), 5.81 - 5.69 (m, 1H, C**H**=CH_2), 5.14 (d, *J* = 17.0 Hz, 0.6H, CH=CH_{cis}**H_{trans}**), 5.10 - 4.98 (m, 2.4H, CH=C**H_2** and ArC**H_2**), 4.88 - 4.75 (m, 3H, C**H**NO_2, ArC**H_2** and NC**H**CH=CH_2, superimposed by residual solvent), 2.88 - 2.77 (m, 1H, C**H**H′), 2.66 (d, *J* = 15.0 Hz, 1H, CH**H′**); **^{13}C NMR** (125 MHz, CD_3OD, mixture of rotamers): δ_C 164.0 (d, *J* = 245.0 Hz, Ar**C**F), 156.1 (**C**=O), 155.6 (**C**=O), 139.2 (**C**H=CH_2), 138.3 (**C**H=CH_2), 137.7 (Ar**C**), 137.6 (Ar**C**), 137.4 (d, *J* = 3.0 Hz, Ar**C**), 136.4 (d, *J* = 3.0 Hz, Ar**C**), 129.6 (Ar**C**H), 129.4 (Ar**C**H), 129.4 (d, *J* = 7.5 Hz, Ar**C**H), 129.0 (Ar**C**H), 128.9 (d, *J* = 7.5 Hz, Ar**C**H), 128.8 (Ar**C**H), 116.9 (d, *J* = 22.0 Hz, Ar**C**H), 116.8 (d, *J* = 22.0 Hz, Ar**C**H), 116.2 (CH=**C**H_2), 116.1 (CH=**C**H_2), 91.4 (**C**HNO_2), 90.7 (**C**HNO_2), 68.7 (Ar**C**H_2), 68.3 (Ar**C**H_2), 66.1 (**C**HN), 65.9 (**C**HN), 61.3 (N**C**HCH=CH_2), 61.0 (N**C**HCH=CH_2), 35.5 (**C**H_2), 34.5 (**C**H_2); **^{19}F NMR** (470.5 MHz, CD_3OD, mixture of rotamers): δ_F –116.6 (Ar**F**), –116.5 (Ar**F**); **IR** (film/cm^{-1}): ν_{max} 2917, 2849, 1703, 1552, 1509, 1456, 1404, 1349, 1223, 1118, 1017, 810; **MS** (ESI): *m/z* 393.1 [$(M + Na)^+$]; **HRMS** (ESI): exact mass calculated for $C_{20}H_{19}FN_2NaO_4$ [$(M + Na)^+$], 393.1221; found 393.1213.

Minor diastereomer 501e′: The ee was determined by HPLC analysis using a Chiralpak IA column [hexane/*i*PrOH 85:15, flow rate 1.0 mL/min, λ = 220 nm]; t_R

major = 11.30 min, t_R minor = 17.04 min (93% ee). **TLC**: R_f = 0.16 (PE/Et_2O 4:1, UV, $KMnO_4$); $[\alpha]_D^{23}$ = −16.7 (c = 0.37, $CHCl_3$); **^{1}H NMR** (500 MHz, CD_3OD, mixture of rotamers): δ_H 7.50 - 6.99 (m, 9H, Ar**H**), 6.03 (ddd, *J* = 17.0, 10.0, 7.0 Hz, 1H, C**H**=CH_2), 5.67 (s, 1H, C**H**N), 5.38 - 5.19 (m, 2H, CH=C**H$_2$**), 5.18 - 5.01 (m, 3H, C**H**NO_2 and ArC**H$_2$**), 4.71 - 4.61 (m, 1H, NC**H**CH=CH_2), 2.85 - 2.76 (m, 1H, C**H**H′), 2.28 (ddd, *J* = 15.0, 9.0, 6.0 Hz, 1H, CH**H′**); **^{13}C NMR** (125 MHz, CD_3OD, mixture of rotamers): δ_C 164.1 (d, *J* = 245.0 Hz, Ar**C**F), 157.2 (**C**=O), 138.8 (br s, **C**H=CH_2), 137.8 (Ar**C**), 136.2 (br d, *J* = 3.0 Hz, Ar**C**), 129.6 (Ar**C**H), 129.4 (d, *J* = 8.0 Hz, Ar**C**H), 129.2 (Ar**C**H), 128.8 (br s, Ar**C**H), 118.1 (CH=**C**H_2), 116.7 (d, *J* = 22.0 Hz, Ar**C**H), 91.2 (br s, **C**HNO_2), 68.6 (br s, Ar**C**H_2), 67.8 (br s, **C**HN), 61.4 (N**C**HCH=CH_2), 36.1 (br s, **C**H_2); **^{19}F NMR** (470.5 MHz, CD_3OD): δ_F −116.6 (Ar**F**); **IR** (film/cm^{-1}): ν_{max} 2922, 1705, 1551, 1509, 1402, 1349, 1315, 1226, 1158, 1120, 984, 929, 839; **MS** (ESI): *m/z* 393.1 [(M + Na)$^+$]; **HRMS** (ESI): exact mass calculated for $C_{20}H_{19}FN_2NaO_4$ [(M + Na)$^+$], 393.1221; found 393.1221. The ^{1}H NMR of diastereomer **501e′** showed that another compound was present in a ratio of 97:3. From the data collected we were not able to confidently determine the structure of this compound; therefore no assignment has been made.

Synthesis and characterisation of benzyl (2*S*,3*R*,5*R*)-2-(3-bromophenyl)-5-ethenyl-3-nitropyrrolidine-1-carboxylate (501f) and benzyl (2*S*,3*R*,5*S*)-2-(3-bromophenyl)-5-ethenyl-3-nitropyrrolidine-1-carboxylate (501f′)



501f **501f′**

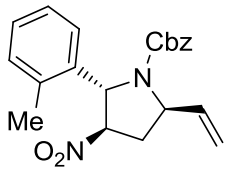
Prepared according to general procedure K. *N*-Cbz imine **401g** (63.6 mg, 0.20 mmol) was reacted with nitroallene **468** (33.9 mg, 0.30 mmol) for 40 h (step i) and 3 h

(step ii) to afford diastereomer **501f** (47 mg, 54%, dr >98:2) as a colourless oil and diastereomer **501f′** (5.8 mg, 7%) as a colourless oil, after purification by flash column chromatography on silica gel eluting with PE/Et_2O (4:1).

Major diastereomer 501f: The ee was determined by HPLC analysis using a Chiralpak IA column [hexane/*i*PrOH 85:15, flow rate 1.0 mL/min, λ = 220 nm]; t_R major = 10.52 min, t_R minor = 21.99 min (96% ee). **TLC**: R_f = 0.13 (PE/Et_2O 4:1, UV, $KMnO_4$); **$[\alpha]_D^{23}$** = −17.1 (c = 1.23, $CHCl_3$); **^{1}H NMR** (500 MHz, CD_3OD, 58:42 mixture of rotamers): δ_H 7.52 - 7.42 (m, 1.4H, Ar**H**), 7.40 (s, 0.6H, Ar**H**), 7.37 - 7.11 (m, 6H, Ar**H**), 6.84 (d, *J* = 7.0 Hz, 1H, Ar**H**), 5.94 - 5.85 (m, 1H, C**H**N), 5.80 - 5.68 (m, 1H, C**H**=CH_2), 5.15 (d, *J* = 17.5 Hz, 0.6H, CH=CH_{cis}**H_{trans}**), 5.10 - 4.98 (m, 3H, CH=C**H_2** and ArC**H_2**), 4.91 - 4.76 (m, 2.4H, C**H**NO_2, ArC**H_2** and NC**H**CH=CH_2, superimposed by residual solvent), 2.86 - 2.77 (m, 1H, C**H**H′), 2.66 (dd, *J* = 15.0, 5.0 Hz, 1H, CH**H′**); **^{13}C NMR** (125 MHz, CD_3OD, mixture of rotamers): δ_C 156.0 (**C**=O), 155.5 (**C**=O), 144.0 (Ar**C**), 143.1 (Ar**C**), 139.0 (**C**H=CH_2), 138.1 (**C**H=CH_2), 137.7 (Ar**C**), 137.4 (Ar**C**), 132.5 (Ar**C**H), 132.4 (Ar**C**H), 132.1 (Ar**C**H), 132.0 (Ar**C**H), 130.2 (Ar**C**H), 130.1 (Ar**C**H), 129.6 (Ar**C**H), 129.5 (Ar**C**H), 129.3 (Ar**C**H), 129.3 (Ar**C**H), 129.1 (Ar**C**H), 128.7 (Ar**C**H), 125.8 (Ar**C**H), 125.7 (Ar**C**H), 124.2 (Ar**C**), 124.1 (Ar**C**), 116.3 (CH=**C**H_2), 116.2 (CH=**C**H_2), 91.3 (**C**HNO_2), 90.6 (**C**HNO_2), 68.7 (Ar**C**H_2), 68.4 (Ar**C**H_2), 66.1 (**C**HN), 66.1 (**C**HN), 65.9 (**C**HN), 65.9 (**C**HN), 61.4 (N**C**HCH=CH_2), 61.1 (N**C**HCH=CH_2), 35.5 (**C**H_2), 35.5 (**C**H_2), 34.6 (**C**H_2), 34.5 (**C**H_2); **IR** (film/cm^{-1}): ν_{max} 2953, 1703, 1549, 1403, 1349, 1212, 1119, 925, 772; **MS** (ESI): *m/z* 453.0 and 455.0 [$(M + Na)^+$]; **HRMS** (ESI): exact mass calculated for $C_{20}H_{19}BrN_2NaO_4$ [$(M + Na)^+$], 453.0420 and 455.0401; found 453.0415 and 455.0398.

Minor diastereomer 501f′: The ee was determined by HPLC analysis using a Chiralpak IA column [hexane/*i*PrOH 85:15, flow rate 1.0 mL/min, λ = 220 nm]; t_R major = 11.79 min, t_R minor = 13.81 min (94% ee). **TLC**: R_f = 0.20 (PE/Et_2O 4:1, UV, $KMnO_4$); **$[\alpha]_D^{23}$** = −2.7 (c = 0.58, $CHCl_3$); **^{1}H NMR** (500 MHz, CD_3OD, mixture of rotamers): δ_H 7.59 - 7.47 (m, 2H, Ar**H**), 7.41 - 6.99 (m, 7H, Ar**H**), 6.01 (ddd, *J* = 17.0, 10.0, 7.0 Hz, 1H, C**H**=CH_2), 5.68 (s, 1H, C**H**N), 5.39 - 5.22 (m, 2H, CH=C**H$_2$**), 5.20 - 5.01 (m, 3H, C**H**NO_2 and ArC**H$_2$**), 4.72 - 4.64 (m, 1H, NC**H**CH=CH_2), 2.88 - 2.79 (m, 1H, C**H**H′), 2.28 (ddd, *J* = 15.0, 8.5, 6.5 Hz, 1H, CH**H′**); **^{13}C NMR** (125 MHz, CD_3OD, mixture of rotamers): δ_C 157.1 (br s, **C**=O), 142.9 (br s, Ar**C**), 138.6 (br s, **C**H=CH_2), 137.7 (Ar**C**), 132.4 (Ar**C**H), 131.9 (Ar**C**H), 130.6 (Ar**C**H), 129.6 (Ar**C**H), 129.2 (Ar**C**H), 128.8 (br s, Ar**C**H), 126.2 (Ar**C**H), 124.0(Ar**C**), 118.3 (CH=**C**H_2), 91.0 (br s, **C**HNO_2), 68.7 (br s, Ar**C**H_2), 67.7 (br s, **C**HN), 61.3 (N**C**HCH=CH_2), 36.1 (br s, **C**H_2); **IR** (film/cm^{-1}): ν_{max} 2919, 1703, 1550, 1400, 1349, 1309, 1201, 1117, 1071, 928, 774; **MS** (ESI): *m/z* 453.0 and 455.0 [$(M + Na)^+$]; **HRMS** (ESI): exact mass calculated for $C_{20}H_{19}BrN_2NaO_4$ [$(M + Na)^+$], 453.0420 and 455.0401; found 453.0402 and 455.0385. The ^{1}H NMR of diastereomer **501f′** showed that another compound was present in a ratio of 97:3. From the data collected we were not able to confidently determine the structure of this compound; therefore no assignment has been made.

Synthesis and characterisation of benzyl (2*S*,3*R*,5*R*)-5-ethenyl-2-(2-methyl phenyl)-3-nitropyrrolidine-1-carboxylate (501g)

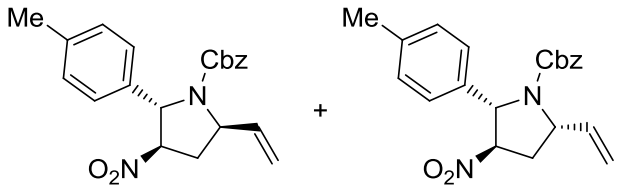


501g

Prepared according to general procedure K. *N*-Cbz imine **401h** (50.7 mg, 0.20 mmol) was reacted with nitroallene **468** (33.9 mg, 0.30 mmol) for 40 h (step i) and 2 h (step ii) to afford compound **501g** (48 mg, 66%, dr >98:2) as a colourless oil, after purification by flash column chromatography on silica gel eluting with PE/EtOAc (9:1). The ee was determined by HPLC analysis using a Chiralpak IA column [hexane/*i*PrOH 80:20, flow rate 1.0 mL/min, λ = 220 nm]; t_R major = 7.33 min, t_R minor = 13.18 min (91% ee). **TLC**: R_f = 0.23 (PE/EtOAc 9:1, UV, $KMnO_4$); $[\alpha]_D^{23}$ = −54.2 (c = 0.90, $CHCl_3$); **^{1}H NMR** (500 MHz, CD_3OD, 64:36 mixture of rotamers): δ_H 7.38 - 7.27 (m, 2H, Ar**H**), 7.26 - 7.07 (m, 5H, Ar**H**), 7.07 - 6.98 (d, *J* = 8.0 Hz, 1H, Ar**H**), 6.74 (d, *J* = 7.5 Hz, 1H, Ar**H**), 6.15 (s, 0.4H, C**H**N), 6.13 (s, 0.6H, C**H**N), 5.83 - 5.70 (m, 1H, C**H**=CH_2), 5.15 (d, *J* = 17.5 Hz, 0.6H, CH=CH_{cis}**H**$_{trans}$), 5.11 - 4.99 (m, 2H, CH=C**H$_2$** and ArC**H$_2$**), 4.96 (d, *J* = 12.5 Hz, 0.6H, ArC**H$_2$**), 4.89 - 4.71 (m, 2.4H, C**H**NO_2, NC**H** and ArC**H$_2$**, superimposed by residual solvent), 2.88 - 2.65 (m, 2H, C**H$_2$**), 2.43 (s, 1.2H, ArC**H$_3$**), 2.34 (s, 1.8H, ArC**H$_3$**); **^{13}C NMR** (125 MHz, CD_3OD, mixture of rotamers): δ_C 156.0 (**C**=O), 155.6 (**C**=O), 139.5 (Ar**C**), 139.3 (**C**H=CH_2), 138.4 (**C**H=CH_2), 138.3 (Ar**C**), 137.8 (Ar**C**), 137.5 (Ar**C**), 136.6 (Ar**C**), 136.4 (Ar**C**), 132.2 (Ar**C**H), 129.6 (Ar**C**H), 129.4 (Ar**C**H), 129.3 (Ar**C**H), 129.3 (Ar**C**H), 129.2 (Ar**C**H), 128.9 (Ar**C**H), 128.4 (Ar**C**H), 128.0 (Ar**C**H), 127.7 (Ar**C**H), 125.4 (Ar**C**H), 125.2 (Ar**C**H), 116.1 (CH=**C**H_2), 116.0 (CH=**C**H_2), 90.5 (**C**HNO_2), 89.7 (**C**HNO_2), 68.7 (Ar**C**H_2), 68.3 (Ar**C**H_2), 64.1 (**C**HN), 63.7 (**C**HN), 61.4

(N**C**HCH=CH_2), 61.1 (N**C**HCH=CH_2), 35.1 (**C**H_2), 34.1 (**C**H_2), 19.6 (Ar**C**H_3); **IR** (film/cm^{-1}): ν_{max} 2953, 1703, 1549, 1403, 1345, 1219, 1122, 1102, 920, 752, 698; **MS** (ESI): *m/z* 389.1 [$(M + Na)^+$]; **HRMS** (ESI): exact mass calculated for $C_{21}H_{22}N_2NaO_4$ [$(M + Na)^+$], 389.1472; found 389.1465.

Synthesis and characterisation of benzyl (2*S*,3*R*,5*R*)-5-ethenyl-2-(4-methylphenyl)-3-nitropyrrolidine-1-carboxylate (501h) and benzyl (2*S*,3*R*,5*S*)-5-ethenyl-2-(4-methylphenyl)-3-nitropyrrolidine-1-carboxylate (501h′)



501h **501h′**

Prepared according to general procedure K. *N*-Cbz imine **401i** (50.7 mg, 0.20 mmol) was reacted with nitroallene **468** (33.9 mg, 0.30 mmol) for 40 h (step i) and 3 h (step ii) to afford diastereomer **501h** (39 mg, 53%, dr >98:2) as a colourless oil and diastereomer **501h′** (6.1 mg, 8%) as a colourless oil after purification by flash column chromatography on silica gel eluting with PE/Et_2O (4:1).

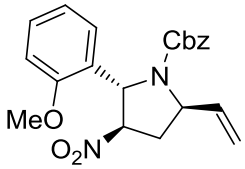
Major diastereomer 501h: The ee was determined by HPLC analysis using a Chiralpak IA column [hexane/*i*PrOH 85:15, flow rate 1.0 mL/min, λ = 230 nm]; t_R major = 9.49 min, t_R minor = 22.11 min (91% ee). **TLC**: R_f = 0.23 (PE/Et_2O 4:1, UV, $KMnO_4$); $[\alpha]_D^{23}$ = −18.6 (c = 0.96, $CHCl_3$); **^{1}H NMR** (500 MHz, CD_3OD, 63:37 mixture of rotamers): δ_H 7.38 - 7.25 (m, 2.2H, Ar**H**), 7.21 - 7.04 (m, 5.8H, Ar**H**), 6.80 (d, *J* = 7.5 Hz, 1H, Ar**H**, 1H), 5.90 (s, 0.4H, C**H**N), 5.88 (s, 0.6H, C**H**N), 5.80 - 5.69 (m, 1H, C**H**=CH_2), 5.14 (d, *J* = 17.5 Hz, 0.6H, CH=CH_{cis}C$\mathbf{H}_{trans}$), 5.09 - 4.98 (m, 3H, ArC$\mathbf{H_2}$ and CH=C$\mathbf{H_2}$), 4.88 - 4.73 (m, 2.4H, C**H**NO_2, ArC$\mathbf{H_2}$ and NC**H**CH=CH_2, superimposed by residual solvent), 2.85 - 2.74 (m, 1H, C**H**H′), 2.66 -

2.59 (m, 1H, CH**H′**), 2.35 (s, 1.8H, ArC**H$_3$**), 2.31 (s, 1.2H, ArC**H$_3$**); **^{13}C NMR** (125 MHz, CD_3OD, mixture of rotamers): δ_C 156.1 (**C**=O), 155.8 (**C**=O), 139.3 (**C**H=CH_2), 139.2 (Ar**C**), 139.1 (Ar**C**), 138.4 (**C**H=CH_2), 138.4 (Ar**C**), 137.8 (Ar**C**), 137.6 (Ar**C**), 137.4 (Ar**C**), 130.9 (Ar**C**H), 130.7 (Ar**C**H), 129.6 (Ar**C**H), 129.3 (Ar**C**H), 128.9 (Ar**C**H), 128.9 (Ar**C**H), 128.6 (Ar**C**H), 126.8 (Ar**C**H), 116.2 (CH=**C**H_2), 116.1 (CH=**C**H_2), 91.6 (**C**HNO_2), 90.9 (**C**HNO_2), 68.6 (Ar**C**H_2), 68.2 (Ar**C**H_2), 66.6 (**C**HN), 66.4 (**C**HN), 61.3 (N**C**HCH=CH_2), 61.1 (N**C**HCH=CH_2), 35.5 (**C**H_2), 34.5 (**C**H_2), 21.3 (Ar**C**H_3), 21.2 (Ar**C**H_3); **IR** (film/cm^{-1}): ν_{max} 2985, 1703, 1550, 1444, 1403, 1347, 1211, 1118, 1019, 921; **MS** (ESI): *m/z* 389.1 [(M + Na)$^+$]; **HRMS** (ESI): exact mass calculated for $C_{21}H_{22}N_2NaO_4$ [(M + Na)$^+$], 389.1472; found 389.1468.

Minor diastereomer 501h′: The ee was determined by HPLC analysis using a Chiralpak IA column [hexane/*i*PrOH 85:15, flow rate 1.0 mL/min, λ = 230 nm]; t_R major = 10.91 min, t_R minor = 13.31 min (81% ee). **TLC**: R_f = 0.31 (PE/Et_2O 4:1, UV. $KMnO_4$); **$[\alpha]_D^{23}$** = −1.4 (c = 0.49, $CHCl_3$); **^{1}H NMR** (500 MHz, CD_3OD, 65:35 mixture of rotamers): δ_H 7.45 - 7.03 (m, 9H, Ar**H**), 6.02 (ddd, *J* = 17.0, 10.0, 7.5 Hz, 1H, C**H**=CH_2), 5.65 (s, 0.7H, C**H**N), 5.64 (s, 0.3H, C**H**N), 5.37 - 5.19 (m, 2H, CH=C**H$_2$**), 5.15 - 5.05 (m, 3H, ArC**H$_2$** and C**H**NO_2), 4.70 - 4.62 (m, 1H, NC**H**CH=CH_2), 2.83 - 2.75 (m, 1H, C**H**H′), 2.34 (s, 3H, ArC**H$_3$**), 2.25 (ddd, *J* = 14.5, 9.0, 6.0 Hz, 1H, CH**H′**); **^{13}C NMR** (125 MHz, CD_3OD, mixture of rotamers) δ_C 157.2 (br s, **C**=O), 139.3 (Ar**C**), 138.9 (br s, **C**H=CH_2), 137.9 (Ar**C**), 137.1 (br s, Ar**C**), 130.6 (Ar**C**H), 129.6 (Ar**C**H), 129.2 (Ar**C**H), 128.7 (br s, Ar**C**H), 127.2 (Ar**C**H), 118.1 (CH=**C**H_2), 91.5 (br s, **C**HNO_2), 68.6 (br s, Ar**C**H_2), 68.3 (br s, **C**HN), 61.4 (N**C**HCH=CH_2), 36.1 (br s, **C**H_2), 21.2 (Ar**C**H_3); **IR** (film/cm^{-1}): ν_{max} 2924, 1704, 1544, 1514, 1401, 1349, 1183, 1110, 983; **MS** (ESI): *m/z* 389.1 [(M +

Na)$^+$]; **HRMS** (ESI): exact mass calculated for $C_{21}H_{22}N_2NaO_4$ [(M + Na)$^+$], 389.1472; found 389.1469. The ^{1}H NMR of diastereomer **501h′** showed that another compound was present in a ratio of 94:6. From the data collected we were not able to confidently determine the structure of this compound; therefore no assignment has been made.

Synthesis and characterisation of benzyl (2*S*,3*R*,5*R*)-5-ethenyl-2-(2-methoxyphenyl)-3-nitropyrrolidine-1-carboxylate (501i)

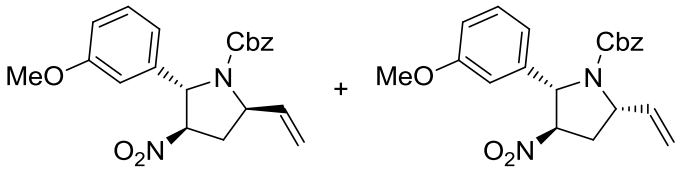


501i

Prepared according to general procedure K. *N*-Cbz imine **401j** (53.9 mg, 0.20 mmol) was reacted with nitroallene **468** (33.9 mg, 0.30 mmol) for 54 h (step i) and 3 h (step ii) to afford compound **501i** (30 mg, 39%, dr >98:2) as a colourless oil, after purification by flash column chromatography on silica gel eluting with PE/EtOAc (6:1). The ee was determined by HPLC analysis using a Chiralpak IA column [hexane/*i*PrOH 80:20, flow rate 1.0 mL/min, λ = 220 nm]; t_R major = 9.61 min, t_R minor = 15.99 min (85% ee). **TLC**: R_f = 0.39 (PE/EtOAc 5:1, UV, $KMnO_4$); $[\alpha]_D^{23}$ = −11.7 (c = 1.56, $CHCl_3$); **^{1}H NMR** (500 MHz, CD_3OD, 59:41 mixture of rotamers): δ_H 7.38 - 7.24 (m, 3.2H, Ar**H**), 7.22 - 7.10 (m, 1.8H, Ar**H**), 7.05 - 6.88 (m, 3H, Ar**H**), 6.86 (d, *J* = 7.5 Hz, 1H, Ar**H**), 6.18 (s, 0.6H, C**H**N), 6.16 (s, 0.4H, C**H**N), 5.82 - 5.70 (m, 1H, C**H**=CH_2), 5.16 (d, *J* = 17.0 Hz, 0.6H, CH=CH_{cis}**H**$_{trans}$), 5.11 - 4.98 (m, 3H, CH=C**H$_2$** and ArC**H$_2$**), 4.91 - 4.81 (m, 0.4H, ArC**H$_2$**, superimposed by residual solvent), 4.80 - 4.71 (m, 2H, C**H**NO_2 and NC**H**CH=CH_2), 3.86 (s, 1.2H, ArOC**H$_3$**), 3.82 (s, 1.8H, ArOC**H$_3$**), 2.80 - 2.67 (m, 1H, C**H**H′), 2.61 - 2.52 (m, 1H, CH**H′**);

^{13}C NMR (125 MHz, CD_3OD, mixture of rotamers): δ_C 157.8 (Ar**C**), 157.6 (Ar**C**), 156.1 (**C**=O), 155.8 (**C**=O), 139.4 (**C**H=CH_2), 138.5 (**C**H=CH_2), 137.8 (Ar**C**), 137.7 (Ar**C**), 130.6 (Ar**C**H), 130.6 (Ar**C**H), 129.6 (Ar**C**), 129.4 (Ar**C**H), 129.3 (Ar**C**H), 129.3 (Ar**C**H), 128.9 (Ar**C**H), 128.5 (Ar**C**H), 126.7 (Ar**C**H), 126.5 (Ar**C**H), 122.1 (Ar**C**H), 121.8 (Ar**C**H), 116.3 (CH=**C**H_2), 116.2 (CH=**C**H_2), 112.2 (Ar**C**H), 112.1 (Ar**C**H), 90.1 (**C**HNO_2), 89.3 (**C**HNO_2), 68.7 (Ar**C**H_2), 68.2 (Ar**C**H_2), 62.2 (**C**HN), 61.8 (**C**HN), 61.3 (N**C**HCH=CH_2), 61.1 (N**C**HCH=CH_2), 56.2 (ArO**C**H_3), 56.2 (ArO**C**H_3), 36.3 (**C**H_2), 35.3 (**C**H_2); **IR** (film/cm^{-1}): ν_{max} 2958, 1706, 1551, 1491, 1405, 1345, 1243, 1122, 1025, 755; **MS** (ESI): *m/z* 405.1 [(M + Na)$^+$]; **HRMS** (ESI): exact mass calculated for $C_{21}H_{22}N_2NaO_5$ [(M + Na)$^+$], 405.1421; found 405.1410.

Synthesis and characterisation of benzyl (2*S*,3*R*,5*R*)-5-ethenyl-2-(3-methoxyphenyl)-3-nitropyrrolidine-1-carboxylate (501j) and benzyl (2*S*,3*R*,5*S*)-5-ethenyl-2-(3-methoxyphenyl)-3-nitropyrrolidine-1-carboxylate (501j′)



501j **501j′**

Prepared according to general procedure K. *N*-Cbz imine **401k** (53.9 mg, 0.20 mmol) was reacted with nitroallene **468** (33.9 mg, 0.30 mmol) for 40 h (step i) and 2 h (step ii) to afford diastereomer **501j** (49 mg, 64%, dr >98:2) as a colourless oil and diastereomer **501j′** (4.6 mg, 6%) as a colourless oil after purification by flash column chromatography on silica gel eluting with PE/Et_2O (4:1) → PE/Et_2O (2:1).

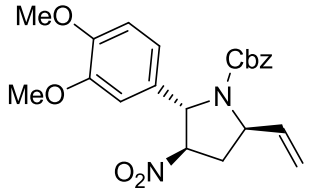
Major diastereomer 501j: The ee was determined by HPLC analysis using a Chiralpak IA column [hexane/*i*PrOH 80:20, flow rate 1.0 mL/min, λ = 220 nm]; t_R major = 10.08 min, t_R minor = 19.48 min (92% ee). **TLC**: R_f = 0.23 (PE/Et_2O 2:1,

UV, $KMnO_4$); **$[\alpha]_D^{23}$** = –21.9 (c = 1.12, $CHCl_3$); **^{1}H NMR** (500 MHz, CD_3OD, 61:39 mixture of rotamers): δ_H 7.37 - 7.23 (m, 3H, Ar**H**), 7.22 - 7.07 (m, 1.8H, Ar**H**), 6.92 - 6.77 (m, 3.6H, Ar**H**), 6.73 (s, 0.6H, Ar**H**), 5.91 (s, 0.4H, C**H**N) 5.89 (s, 0.6H, C**H**N), 5.79 - 5.69 (m, 1H, C**H**=CH_2), 5.14 (d, *J* = 17.5 Hz, 0.6H, CH=CH_{cis}**H_{trans}**), 5.10 - 4.96 (m, 2.4H, CH=C**H_2** and ArC**H_2**), 4.85 - 4.73 (m, 3H, C**H**NO_2, ArC**H_2** and NC**H**CH=CH_2, superimposed by residual solvent), 3.75 (s, 1.2H, ArOC**H_3**), 3.73 (s, 1.8H, ArOC**H_3**), 2.87 - 2.74 (m, 1H, C**H**H′), 2.67 - 2.59 (m, 1H, CH**H′**); **^{13}C NMR** (125 MHz, CD_3OD, mixture of rotamers): δ_C 161.9 (Ar**C**), 161.8 (Ar**C**), 156.1 (**C**=O), 155.8 (**C**=O), 143.0 (Ar**C**), 142.0 (Ar**C**), 139.3 (**C**H=CH_2), 138.3 (**C**H=CH_2), 137.8 (Ar**C**), 137.6 (Ar**C**), 131.5 (Ar**C**H), 131.3 (Ar**C**H), 129.6 (Ar**C**H), 129.4 (Ar**C**H), 129.3 (Ar**C**H), 128.9 (Ar**C**H), 128.6 (Ar**C**H), 118.8 (Ar**C**H), 116.2 (CH=**C**H_2), 116.1 (CH=**C**H_2), 114.7 (Ar**C**H), 114.5 (Ar**C**H), 112.6 (Ar**C**H), 112.6 (Ar**C**H), 91.6 (**C**HNO_2), 90.9 (**C**HNO_2), 68.6 (Ar**C**H_2), 68.3 (Ar**C**H_2), 66.7 (**C**HN), 66.5 (**C**HN), 61.4 (N**C**HCH=CH_2), 61.1 (N**C**HCH=CH_2), 55.9 (ArO**C**H_3), 35.6 (**C**H_2), 34.6 (**C**H_2); **IR** (film/cm^{-1}): ν_{max} 2957, 1704, 1602, 1551, 1491, 1404, 1349, 1263, 1118, 1048, 777; **MS** (ESI): *m/z* 405.1 [$(M + Na)^+$]; **HRMS** (ESI): exact mass calculated for $C_{21}H_{22}N_2NaO_5$ [$(M + Na)^+$], 405.1421; found 405.1415.

Minor diastereomer 501j′: The ee was determined by HPLC analysis using a Chiralpak AS-H column [hexane/*i*PrOH 80:20, flow rate 1.0 mL/min, λ = 220 nm]; t_R minor = 12.30 min, t_R major = 14.12 min (99% ee). **TLC**: R_f = 0.19 (PE/EtOAc 4:1, UV, $KMnO_4$); **$[\alpha]_D^{23}$** = –3.8 (c = 0.26, $CHCl_3$); **^{1}H NMR** (500 MHz, CD_3OD, 69:31 mixture of rotamers): δ_H 7.43 - 7.04 (m, 6H, Ar**H**), 6.93 (d, *J* = 8.0 Hz, 1H, Ar**H**), 6.91 - 6.85 (m, 2H, Ar**H**), 6.11 - 5.97 (m, 1H, C**H**=CH_2), 5.67 (s, 0.3H, C**H**N), 5.66 (s, 0.7H, C**H**N), 5.40 - 5.20 (m, 2H, CH=C**H_2**), 5.18 - 5.06 (m, 3H, ArC**H_2** and C**H**NO_2), 4.70 - 4.62 (m, 1H, NC**H**CH=CH_2), 3.76 (s, 3H, ArOC**H_3**), 2.85 - 2.74 (m,

1H, C**H**H′), 2.31 - 2.21 (m, 1H, CH**H′**); **^{13}C NMR** (125 MHz, CD_3OD, mixture of rotamers): δ_C 161.8 (Ar**C**), 157.2 (br s, **C**=O), 141.8 (br s, Ar**C**), 138.2 (br s, **C**H=CH_2), 137.9 (Ar**C**), 131.2 (Ar**C**H), 129.6 (Ar**C**H), 129.2 (Ar**C**H), 128.8 (br s, Ar**C**H), 119.3 (Ar**C**H), 118.1 (CH=**C**H_2), 114.8 (Ar**C**H), 112.9 (Ar**C**H), 91.4 (br s, **C**HNO_2), 68.6 (br s, Ar**C**H_2), 68.3 (br s, **C**HN), 61.3 (NC**H**CH=CH_2), 55.9 (ArO**C**H_3), 36.1 (br s, **C**H_2); **IR** (film/cm^{-1}): ν_{max} 2917, 1706, 1602, 1546, 1402, 1350, 1313, 1286, 1262, 1114, 1048, 984, 747; **MS** (ESI): *m/z* 405.1 [$(M + Na)^+$]; **HRMS** (ESI): exact mass calculated for $C_{21}H_{22}N_2NaO_5$ [$(M + Na)^+$], 405.1421; found 405.1421. The ^{1}H NMR of diastereomer **501j′** showed that another compound was present in a ratio of 94:6. From the data collected we were not able to confidently determine the structure of this compound; therefore no assignment has been made.

Synthesis and characterisation of benzyl (2*S*,3*R*,5*R*)-2-(3,4-dimethoxyphenyl)-5-ethenyl-3-nitropyrrolidine-1-carboxylate (501k)

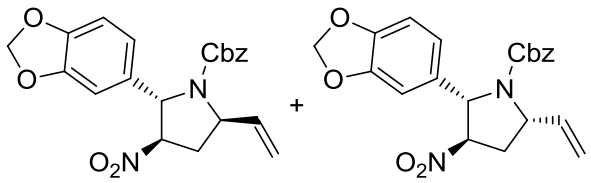


501k

Prepared according to general procedure K. *N*-Cbz imine **401l** (59.9 mg, 0.20 mmol) was reacted with nitroallene **468** (33.9 mg, 0.30 mmol) for 40 h (step i) and 2 h (step ii) to afford compound **501k** (55 mg, 67%, dr 93:7) as a colourless oil, after purification by flash column chromatography on silica gel eluting with PE/Et_2O (1:1). The ee was determined by HPLC analysis using a Chiralpak IA column [hexane/*i*PrOH 80:20, flow rate 1.0 mL/min, λ = 220 nm]; ***MAJOR:*** t_R major = 11.70 min, t_R minor = 28.58 min (92% ee); ***MINOR:*** t_R major = 13.15 min, t_R minor

= 15.65 min (87% ee). Only the ^{1}H and ^{13}C NMR signals corresponding to diastereomer **501k** are reported. All other characterisation data corresponds to the mixture of diastereomers (dr 93:7). **TLC**: R_f = 0.16 (PE/Et_2O 1:1, UV, $KMnO_4$); **$[\alpha]_D^{23}$** = −32.0 (c = 0.99, $CHCl_3$); **^{1}H NMR** (500 MHz, CD_2Cl_2, mixture of rotamers): δ_H 7.40 - 7.27 (m, 2H, Ar**H**), 7.26 - 7.11 (m, 2H, Ar**H**), 6.91 - 6.79 (m, 2H, Ar**H**), 6.76 - 6.68 (m, 1.4H, Ar**H**), 6.65 (br s, 0.6H, Ar**H**), 5.92 - 5.74 (m, 2H, C**H**N and C**H**=CH_2), 5.20 (d, *J* = 17.5 Hz, 0.6H, CH=CH_{cis}**H_{trans}**), 5.15 - 5.00 (m, 3H, CH=C**H_2** and ArC**H_2**), 4.94 - 4.73 (m, 1.4H, ArC**H_2** and NC**H**CH=CH_2), 4.69 - 4.58 (m, 1H, C**H**NO_2), 3.90 - 3.76 (m, 6H, 2 × ArOC**H_3**), 2.85 - 2.73 (m, 1H, C**H**H′), 2.72 - 2.61 (m, 1H, CH**H′**); **^{13}C NMR** (125 MHz, CD_2Cl_2, mixture of rotamers): δ_C 154.4 (**C**=O), 154.3 (**C**=O), 150.2 (Ar**C**), 149.6 (Ar**C**), 138.4 (**C**H=CH_2), 137.8 (**C**H=CH_2), 137.1 (Ar**C**), 136.9 (Ar**C**), 132.8 (Ar**C**), 132.1 (Ar**C**), 128.9 (Ar**C**H), 128.6 (Ar**C**H), 128.5 (Ar**C**H), 128.2 (Ar**C**H), 128.0 (Ar**C**H), 127.9 (Ar**C**H), 117.7 (Ar**C**H), 117.7 (Ar**C**H), 116.1 (CH=**C**H_2), 116.0 (CH=**C**H_2), 112.3 (Ar**C**H), 109.5 (Ar**C**H), 91.2 (**C**HNO_2), 90.3 (**C**HNO_2), 67.7 (Ar**C**H_2), 67.4 (Ar**C**H_2), 65.5 (**C**HN), 65.4 (**C**HN), 60.4 (N**C**HCH=CH_2), 60.1 (N**C**HCH=CH_2), 56.4 (ArO**C**H_3), 56.4 (ArO**C**H_3), 35.0 (**C**H_2), 34.0 (**C**H_2); **IR** (film/cm^{-1}): ν_{max} 2957, 1701, 1549, 1515, 1453, 1402, 1346, 1259, 1238, 1140, 1116, 1024, 955, 923, 767; **MS** (ESI): *m/z* 435.1 [$(M + Na)^+$]; **HRMS** (ESI): exact mass calculated for $C_{22}H_{24}N_2NaO_6$ [$(M + Na)^+$], 435.1527; found 435.1506. The absolute configuration of pyrrolidine **501k** was determined to be (2*S*,3*R*,5*R*) by single crystal X-ray diffraction analysis after crystallisation by slow evaporation of MeOH. All other pyrrolidine structures were assigned by analogy.

Synthesis and characterisation of benzyl (2*S*,3*R*,5*R*)-2-(1,3-benzodioxol-5-yl)-5-ethenyl-3-nitropyrrolidine-1-carboxylate (501l) and benzyl (2*S*,3*R*,5*S*)-2-(1,3-benzodioxol-5-yl)-5-ethenyl-3-nitropyrrolidine-1-carboxylate (501l′)



501l **501l′**

Prepared according to general procedure K. *N*-Cbz imine **401m** (56.7 mg, 0.20 mmol) was reacted with nitroallene **468** (33.9 mg, 0.30 mmol) for 40 h (step i) and 2 h (step ii) to afford diastereomer **501l** (53 mg, 67%, dr 96:4) as a colourless oil and diastereomer **501l′** (6.7 mg, 8%) as a colourless oil, after purification by flash column chromatography on silica gel eluting with PE/Et_2O (2:1).

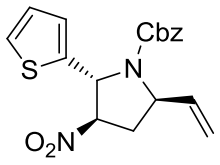
Major diastereomer 501l: The ee was determined by HPLC analysis using a Chiralpak IA column [hexane/*i*PrOH 80:20, flow rate 1.0 mL/min, λ = 220 nm]; ***MAJOR:*** t_R major = 13.19 min, t_R minor = 32.32 min (91% ee); ***MINOR:*** t_R major = 12.46 min, t_R minor = 20.41 min (90% ee). Only the ^1H and ^{13}C NMR signals corresponding to diastereomer **501l** are reported. All other characterisation data corresponds to the mixture of diastereomers (dr 96:4). **TLC**: R_f = 0.26 (PE/Et_2O 2:1, UV, $KMnO_4$); $[\alpha]_D^{23}$ = −21.1 (c = 0.96, $CHCl_3$); **^{1}H NMR** (400 MHz, CD_3OD, 65:35 mixture of rotamers): δ_H 7.39 - 7.09 (m, 4H, Ar**H**), 6.94 - 6.61 (m, 4H, Ar**H**), 5.94 (s, 1.2H, OC**H$_2$**O), 5.92 (s, 0.8H, OC**H$_2$**O), 5.83 (s, 0.4H, C**H**N), 5.81 (s, 0.6H, C**H**N), 5.79 - 5.65 (m, 1H, C**H**=CH_2), 5.20 - 4.94 (m, 3H, CH=C**H$_2$** and ArC**H$_2$**), 4.92 - 4.70 (m, 3H, C**H**NO_2, ArC**H$_2$** and NC**H**CH=CH_2, superimposed by residual solvent), 2.89 - 2.73 (m, 1H, C**H**H′), 2.61 (d, *J* = 15.0 Hz, 1H, CH**H′**); **^{13}C NMR** (100 MHz, CD_3OD, mixture of rotamers): δ_C 156.0 (**C**=O), 155.7 (**C**=O), 149.9 (Ar**C**), 149.8 (Ar**C**), 149.0 (Ar**C**), 149.0 (Ar**C**), 139.2 (**C**H=CH_2), 138.4 (**C**H=CH_2), 137.7 (Ar**C**),

137.6 (Ar**C**), 135.3 (Ar**C**), 134.4 (Ar**C**), 129.6 (Ar**C**H), 129.3 (Ar**C**H), 129.3 (Ar**C**H), 129.0 (Ar**C**H), 128.7 (Ar**C**H), 120.2 (Ar**C**H), 116.2 (CH=**C**H_2), 116.1 (CH=**C**H_2), 109.7 (Ar**C**H), 109.6 (Ar**C**H), 107.3 (Ar**C**H), 102.8 (O**C**H_2O), 91.6 (**C**HNO_2), 90.9 (**C**HNO_2), 68.6 (Ar**C**H_2), 68.2 (Ar**C**H_2), 66.5 (**C**HN), 66.4 (**C**HN), 61.3 (N**C**HCH=CH_2), 61.0 (N**C**HCH=CH_2), 35.5 (**C**H_2), 34.5 (**C**H_2); **IR** (film/cm^{-1}): ν_{max} 2898, 1703, 1548, 1503, 1489, 1445, 1404, 1348, 1310, 1239, 1124, 1038, 928; **MS** (ESI): *m/z* 419.1 [$(M + Na)^+$]; **HRMS** (ESI): exact mass calculated for $C_{21}H_{20}N_2NaO_6$ [$(M + Na)^+$], 419.1214; found 419.1206.

Minor diastereomer 501l′: The ee was determined by HPLC analysis using a Chiralpak IA column [hexane/*i*PrOH 80:20, flow rate 1.0 mL/min, λ = 220 nm]; t_R major = 14.55 min, t_R minor = 17.23 min (91% ee). **TLC**: R_f = 0.43 (PE/Et_2O 2:1, UV, $KMnO_4$); **[α]$_D^{23}$** = −5.5 (c = 0.63, $CHCl_3$); **^{1}H NMR** (500 MHz, CD_3OD, 60:40 mixture of rotamers): δ_H 7.49 - 7.04 (m, 5H, Ar**H**), 6.89 - 6.79 (m, 3H, Ar**H**), 6.04 (ddd, *J* = 17.0, 10.0, 7.0 Hz, 1H, C**H**=CH_2), 5.98 (s, 2H, OC**H$_2$**O), 5.61 (s, 0.6H, C**H**N), 5.60 (s, 0.4H, C**H**N), 5.39 - 5.21 (m, 2H, CH=C**H$_2$**), 5.19 - 5.03 (m, 3H, C**H**NO_2 and ArC**H$_2$**), 4.70 - 4.62 (m, 1H, NC**H**CH=CH_2), 2.85 - 2.75 (m, 1H, C**H**H′), 2.36 - 2.25 (m, 1H, CH**H′**); **^{13}C NMR** (125 MHz, CD_3OD, mixture of rotamers): δ_C 157.2 br s, **C**=O), 149.8 (Ar**C**), 149.1 (Ar**C**), 138.8 (br s, **C**H=CH_2), 137.8 (Ar**C**), 134.1 (br s, Ar**C**), 129.6 (Ar**C**H), 129.2 (Ar**C**H), 128.8 (Ar**C**H), 120.7 (Ar**C**H), 118.1 (CH=**C**H_2), 109.4 (Ar**C**H), 107.7 (Ar**C**H), 102.9 (O**C**H_2O), 91.4 (br s, C**H**NO_2), 68.6 (br s, Ar**C**H_2), 68.2 (br s, **C**HN), 61.3 (N**C**HCH=CH_2), 36.0 (br s, **C**H_2); **IR** (film/cm^{-1}): ν_{max} 2898, 1704, 1545, 1504, 1490, 1445, 1402, 1348, 1240, 1038, 929; **MS** (ESI): *m/z* 419.1 [$(M + Na)^+$]; **HRMS** (ESI): exact mass calculated for $C_{21}H_{20}N_2NaO_6$ [$(M + Na)^+$], 419.1214; found 419.1204. The ^{1}H NMR of diastereomer **501l′** showed that another compound was present in a ratio of 92:8.

From the data collected we were not able to confidently determine the structure of this compound; therefore no assignment has been made.

Synthesis and characterisation of benzyl (2*R*,3*R*,5*R*)-5-ethenyl-3-nitro-2-(thiophen-2-yl)pyrrolidine-1-carboxylate (501m)



501m

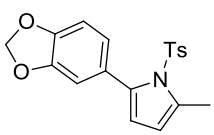
Prepared according to general procedure K. *N*-Cbz imine **401n** (49.1 mg, 0.20 mmol) was reacted with nitroallene **468** (33.9 mg, 0.30 mmol) for 48 h (step i) and 14 h (step ii) to afford compound **501m** (23 mg, 32%, dr 88:12) as a colourless oil, after purification by flash column chromatography on silica gel eluting with PE/Et_2O (2:1). The ee was determined by HPLC analysis using a Chiralpak IA column [hexane/*i*PrOH 85:15, flow rate 1.0 mL/min, λ = 220 nm]; ***MAJOR:*** t_R major = 11.22 min, t_R minor = 31.73 min (85% ee); ***MINOR:*** t_R major = 11.98 min, t_R minor = 18.94 min (86% ee). Only the ^1H and ^{13}C NMR signals corresponding to diastereomer **501m** are reported. All other characterisation data corresponds to the mixture of diastereomers (dr 88:12). **TLC**: R_f = 0.36 (PE/Et_2O 2:1, UV, $KMnO_4$); **$[\alpha]_D^{23}$** = −41.0 (c = 1.21, $CHCl_3$); **^{1}H NMR** (500 MHz, CD_3OD, mixture of rotamers): δ_H 7.44 - 7.12 (m, 5H, Ar**H**), 7.10 - 6.89 (m, 3H, Ar**H**), 6.18 (br s, 1H, C**H**N), 5.77 - 5.63 (m, 1H, C**H**=CH_2), 5.19 - 4.90 (m, 5H, CH=C**H$_2$**, C**H**NO_2 and ArC**H$_2$**), 4.75 - 4.67 (m, 1H, NC**H**CH=CH_2), 3.06 - 2.91 (m, 1H, C**H**H′), 2.75 - 2.64 (m, 1H, CH**H′**); **^{13}C NMR** (125 MHz, CD_3OD, mixture of rotamers): δ_C 156.1 (**C**=O), 155.6 (**C**=O), 144.5 (Ar**C**), 143.8 (Ar**C**), 139.1 (**C**=CH_2), 138.2 (**C**=CH_2), 137.7 (Ar**C**), 137.6 (Ar**C**), 129.6 (Ar**C**H), 129.5 (Ar**C**H), 129.3 (Ar**C**H), 129.1

(Ar**C**H), 129.0 (Ar**C**H), 128.7 (Ar**C**H), 128.6 (Ar**C**H), 128.5 (Ar**C**H), 128.4 (Ar**C**H), 126.4 (Ar**C**H), 126.2 (Ar**C**H), 126.2 (Ar**C**H), 116.3 (CH=**C**H_2), 116.2 (CH=**C**H_2), 91.2 (**C**HNO_2), 90.4 (**C**HNO_2), 68.7 (Ar**C**H_2), 68.5 (Ar**C**H_2), 62.6 (**C**HN), 62.4 (**C**HN), 60.7 (N**C**HCH=CH_2), 60.5 (N**C**HCH=CH_2), 36.2 (**C**H_2), 35.0 (**C**H_2); **IR** (film/cm^{-1}): ν_{max} 2954, 1703, 1549, 1441, 1401, 1344, 1216, 1116, 1016, 989, 923, 697; **MS** (ESI): *m/z* 381.1 [$(M + Na)^+$]; **HRMS** (ESI): exact mass calculated for $C_{18}H_{18}N_2NaO_4S$ [$(M + Na)^+$], 381.0879; found 381.0865.

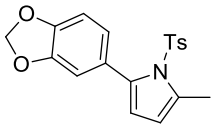
Chapter 6: Appendices

6.1 ^{1}H NMR, ^{13}C NMR and HPLC Data

6.1.1 ^{1}H and ^{13}C NMR Spectra of Pyrrole 269f

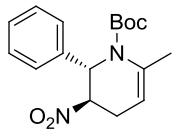


269f
500 MHz, $CDCl_3$



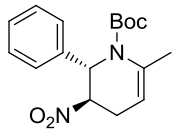
269f
125 MHz, $CDCl_3$

6.1.2 ^{1}H and ^{13}C NMR Spectra of Tetrahydropyridine 394a



394a

400 MHz, CD_3OD

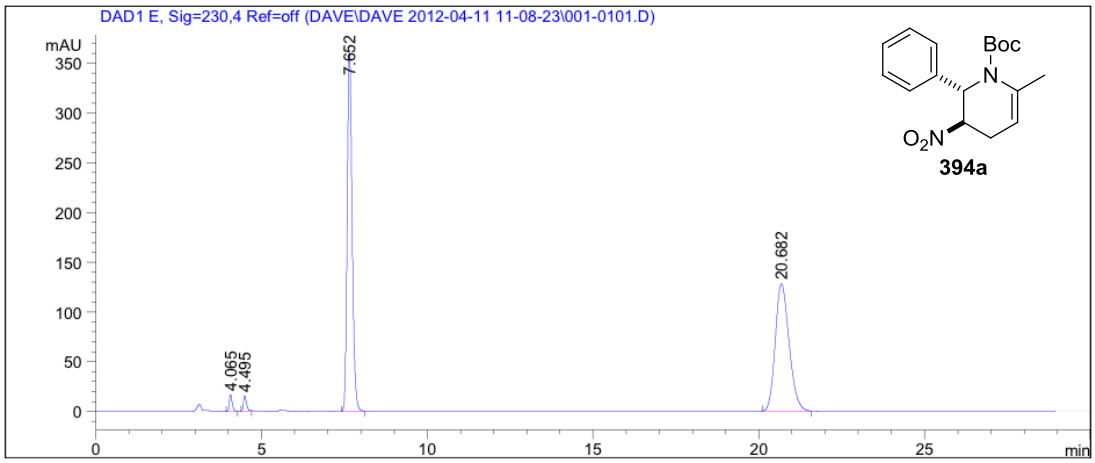


394a

100 MHz, CD_3OD

6.1.3 HPLC Data for Tetrahydropyridine 394a

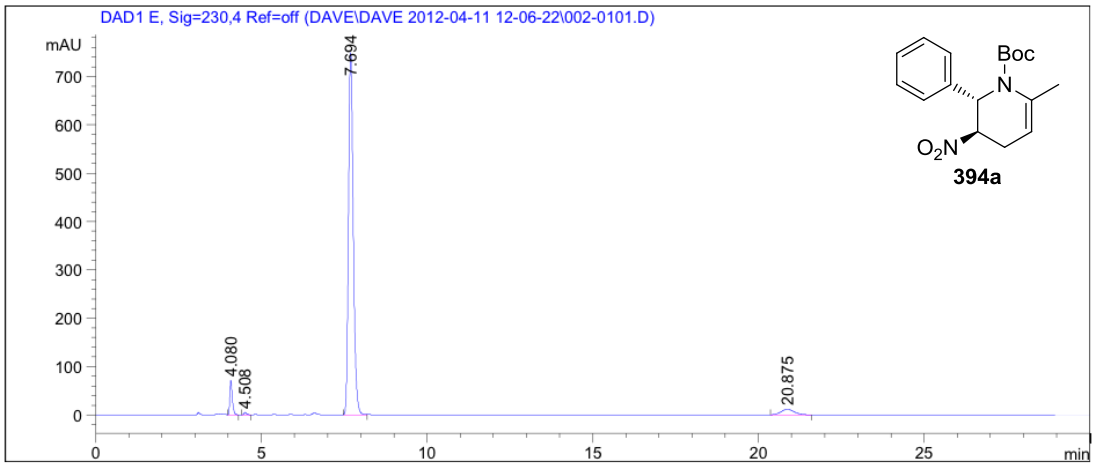
Racemic



Signal 5: DAD1 E, Sig=230,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.065	VB	0.0906	99.80546	16.72771	1.3034
2	4.495	BB	0.0956	99.11555	15.70270	1.2943
3	7.652	BB	0.1587	3732.52588	360.63116	48.7429
4	20.682	BB	0.4481	3726.12793	128.18375	48.6594

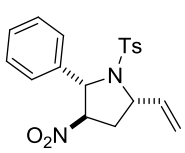
Enantioenriched



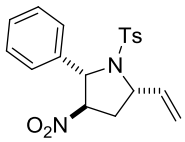
Signal 5: DAD1 E, Sig=230,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.080	VB	0.0792	372.42911	71.00246	4.5354
2	4.508	BB	0.0865	26.90599	4.72364	0.3277
3	7.694	BB	0.1538	7498.73633	749.24884	91.3194
4	20.875	BB	0.4298	313.47955	11.15772	3.8175

6.1.4 ^{1}H and ^{13}C NMR spectra of Pyrrolidine 471a

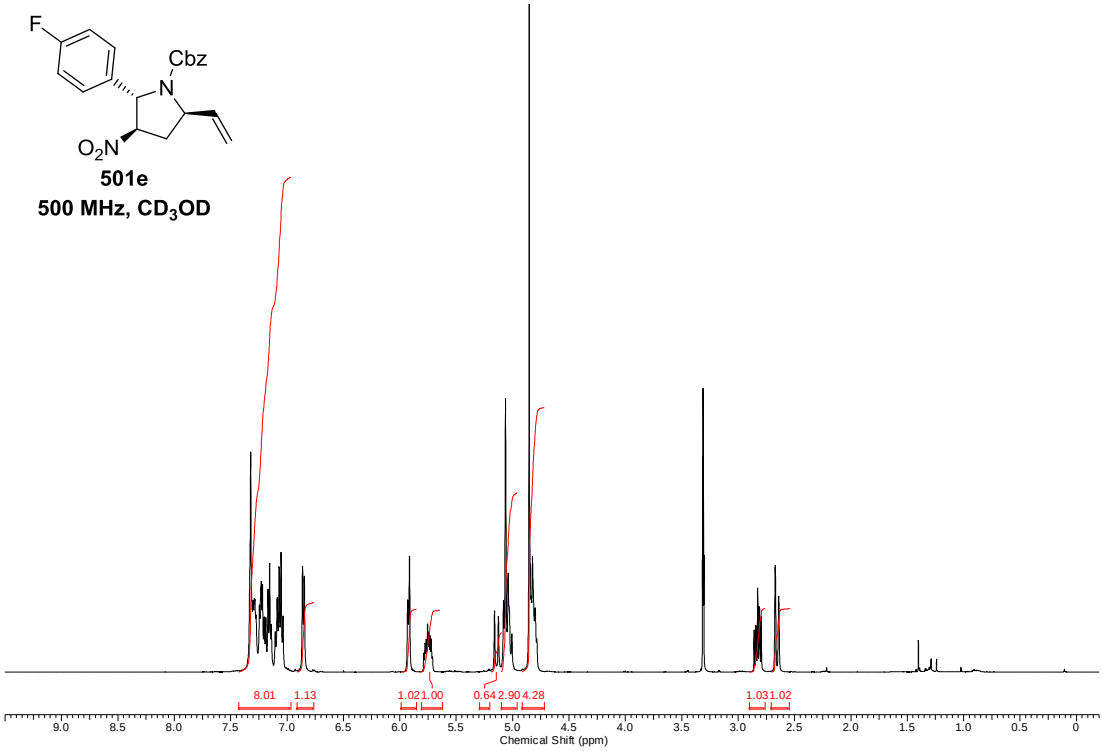


471a
400 MHz, $CDCl_3$

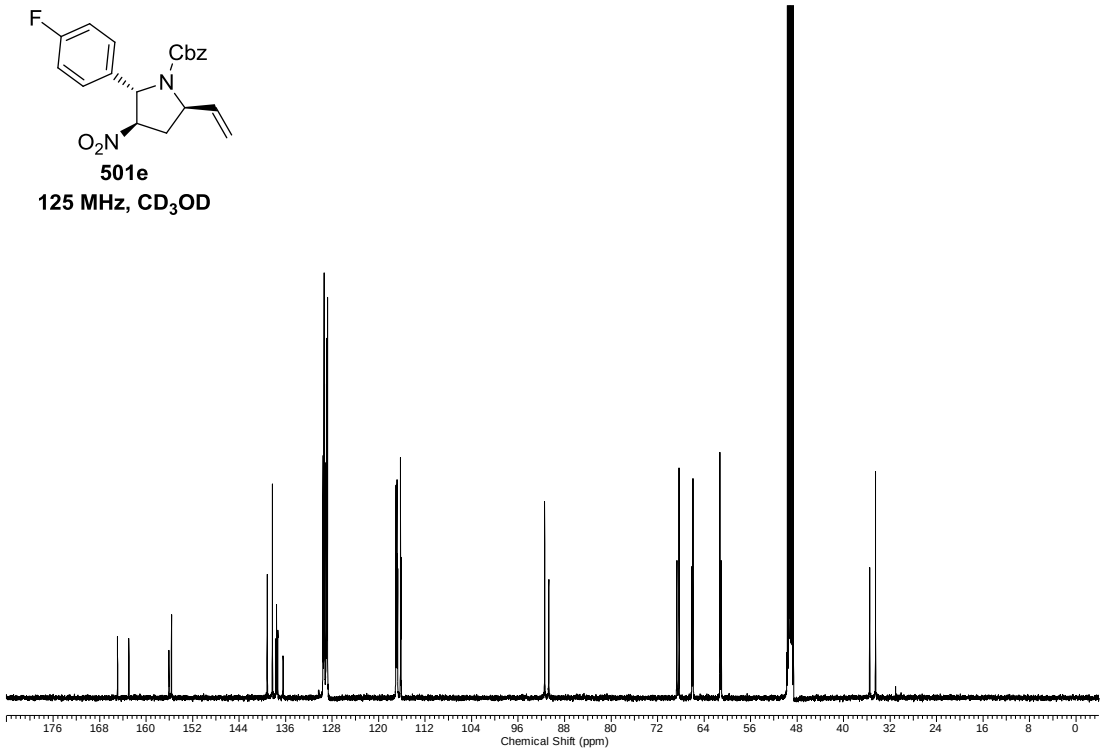


471a
100 MHz, $CDCl_3$

6.1.5 ^{1}H and ^{13}C NMR spectra of Pyrrolidine 501e



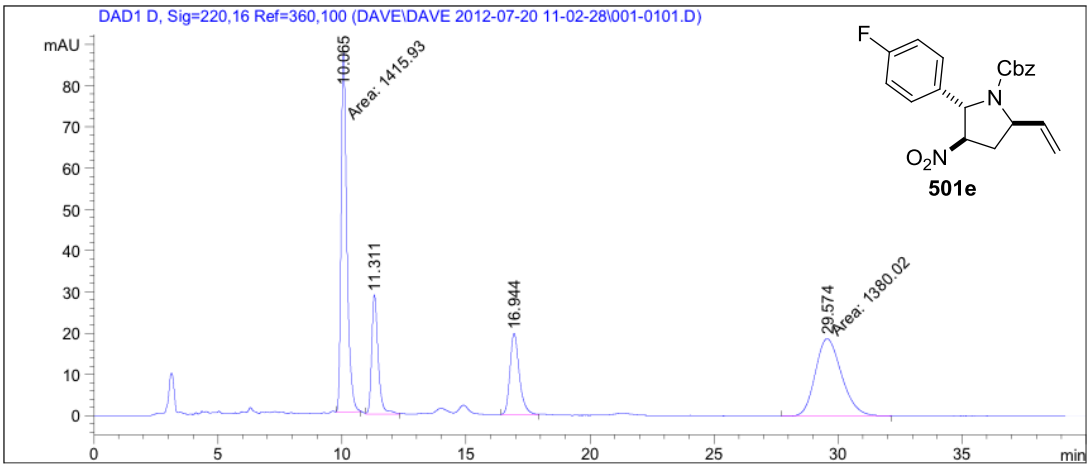
501e
500 MHz, CD_3OD



501e
125 MHz, CD_3OD

6.1.6 HPLC Data for Pyrrolidine 501e

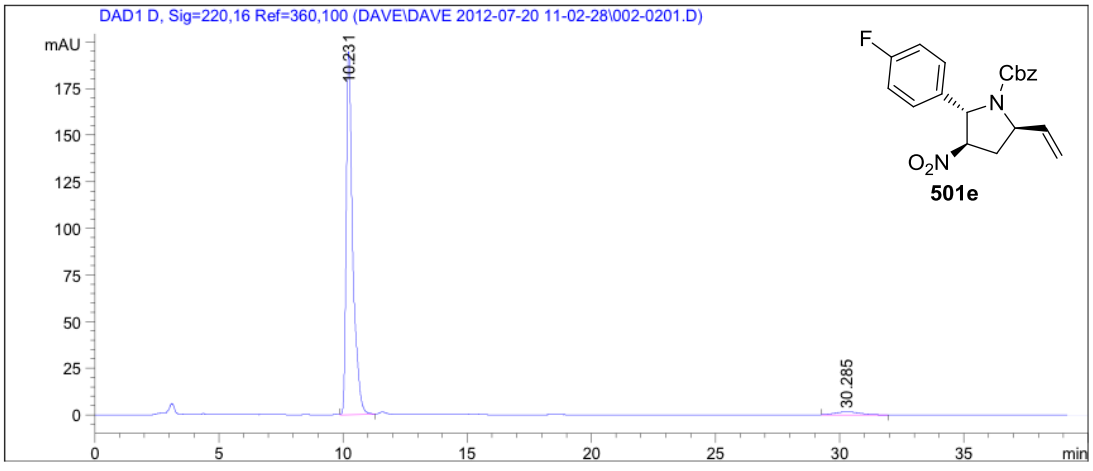
Racemic (Mixture of diastereomers)



Signal 4: DAD1 D, Sig=220,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.065	MM	0.2704	1415.92798	87.27438	36.8758
2	11.311	VB	0.2740	526.10162	28.95518	13.7016
3	16.944	BB	0.3984	517.67731	19.71409	13.4822
4	29.574	MM	1.2275	1380.01599	18.73773	35.9405

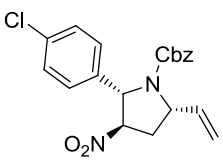
Enantioenriched (Single Diastereomer)



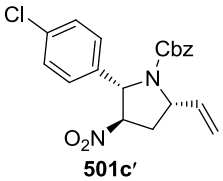
Signal 4: DAD1 D, Sig=220,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.231	VV	0.2714	3560.83301	194.67354	97.0314
2	30.285	BB	0.8032	108.94203	1.62288	2.9686

6.1.7 ^{1}H and ^{13}C NMR Spectra of Pyrrolidine 501c′



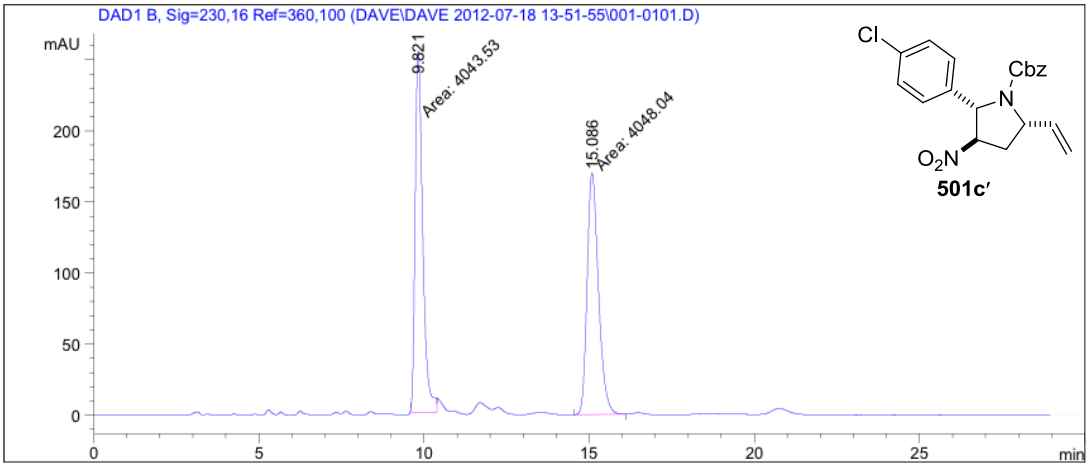
501c′
500 MHz, CD_3OD



501c′
125 MHz, CD_3OD

6.1.8 HPLC Data for Pyrrolidine 501c′

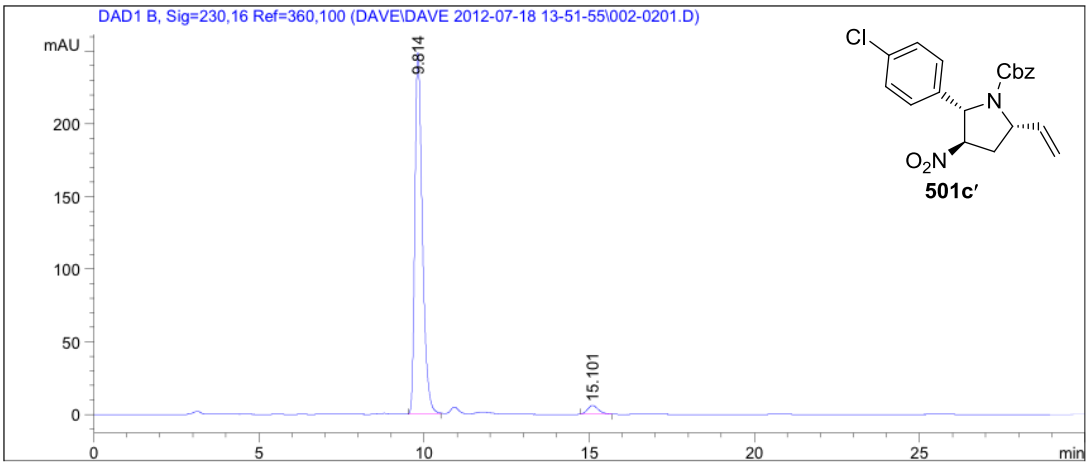
Racemic



Signal 2: DAD1 B, Sig=230,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.821	MM	0.2653	4043.52686	254.02005	49.9721
2	15.086	MM	0.3972	4048.04077	169.87854	50.0279

Enantioenriched

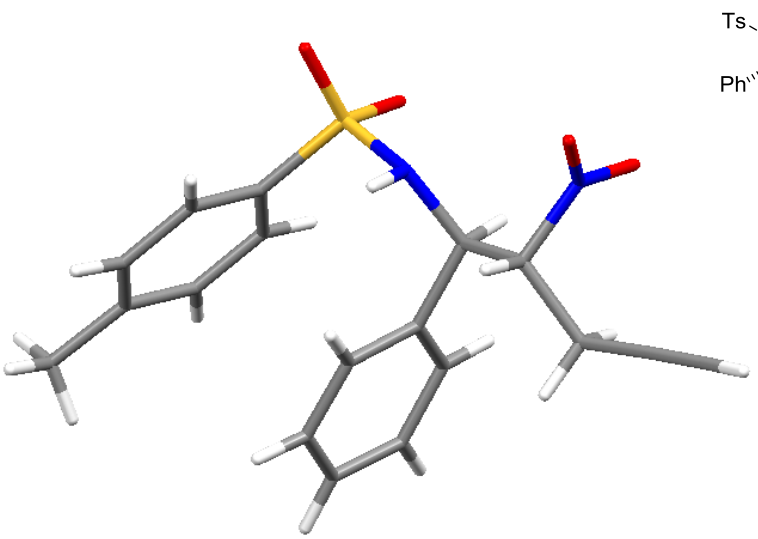


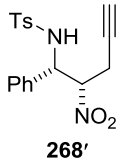
Signal 2: DAD1 B, Sig=230,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.814	BB	0.2400	3927.59497	249.01569	96.5408
2	15.101	BB	0.3533	140.73303	6.00870	3.4592

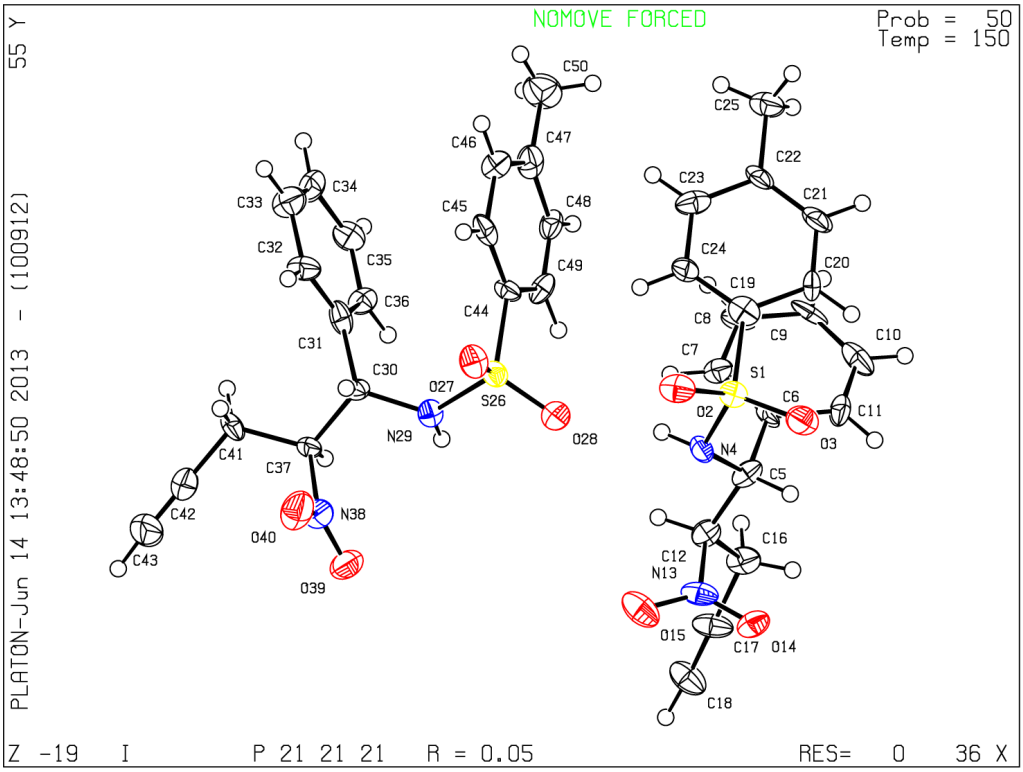
6.2 X-Ray Diffraction Data

6.2.1 X-Ray Diffraction Data for β-Nitroamine 268′





268′



Experimental details

Crystal data	
Chemical formula	$C_{18}H_{18}N_2O_4S$
M_r	358.42
Crystal system, space group	Orthorhombic, $P2_12_12_1$
Temperature (K)	150

a, *b*, *c* (Å)	7.2116 (1), 19.5826 (4), 24.5613 (5)
V (Å^3)	3468.59 (11)
Z	8
Radiation type	Mo *K*α
μ (mm^{-1})	0.21
Crystal size (mm)	0.70 × 0.20 × 0.20
Data collection	
Diffractometer	Nonius KappaCCD diffractometer
Absorption correction	Multi-scan *DENZO*/*SCALEPACK* (Otwinowski & Minor, 1997)
T_{min}, T_{max}	0.96, 0.96
No. of measured, independent and observed [$I > 2.0\sigma(I)$] reflections	7581, 4392, 2967
R_{int}	0.032
$(\sin \theta/\lambda)_{max}$ (Å^{-1})	0.649
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.045, 0.135, 0.97
No. of reflections	4392
No. of parameters	151
No. of restraints	0
H-atom treatment	H-atom parameters constrained
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.58, −0.56

Selected geometric parameters (Å, º)

S1—O2	1.450 (5)	S26—O27	1.412 (6)
S1—O3	1.450 (6)	S26—O28	1.430 (5)
S1—N4	1.638 (6)	S26—N29	1.614 (6)
S1—C19	1.743 (6)	S26—C44	1.776 (6)
N4—C5	1.484 (8)	N29—C30	1.461 (8)
C5—C6	1.523 (8)	C30—C31	1.508 (8)
C5—C12	1.521 (10)	C30—C37	1.554 (9)
C6—C7	1.381 (9)	C31—C32	1.359 (9)
C6—C11	1.419 (7)	C31—C36	1.397 (9)
C7—C8	1.397 (8)	C32—C33	1.377 (10)
C8—C9	1.377 (11)	C33—C34	1.405 (11)
C9—C10	1.357 (11)	C34—C35	1.392 (10)
C10—C11	1.400 (10)	C35—C36	1.374 (9)
C12—N13	1.509 (8)	C37—N38	1.525 (7)
C12—C16	1.553 (9)	C37—C41	1.501 (9)
N13—O14	1.208 (8)	N38—O39	1.208 (7)
N13—O15	1.221 (8)	N38—O40	1.245 (8)
C16—C17	1.466 (10)	C41—C42	1.465 (10)
C17—C18	1.187 (10)	C42—C43	1.150 (12)
C19—C20	1.411 (9)	C44—C45	1.366 (10)
C19—C24	1.386 (10)	C44—C49	1.405 (9)
C20—C21	1.380 (9)	C45—C46	1.398 (9)
C21—C22	1.379 (10)	C46—C47	1.403 (10)
C22—C23	1.393 (10)	C47—C48	1.389 (10)

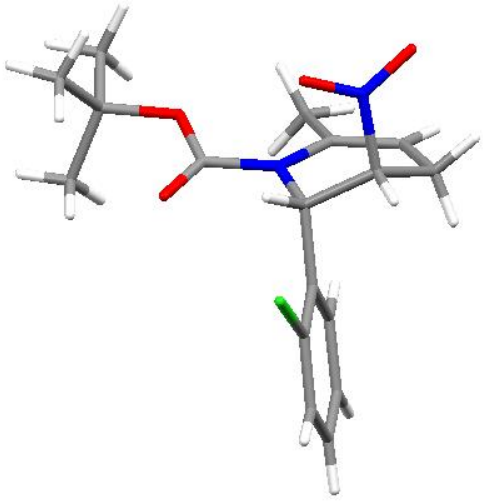
C22—C25	1.501 (8)	C47—C50	1.507 (10)
C23—C24	1.398 (9)	C48—C49	1.367 (9)
O2—S1—O3	119.5 (4)	O27—S26—O28	121.5 (4)
O2—S1—N4	104.1 (3)	O27—S26—N29	107.7 (3)
O3—S1—N4	107.7 (3)	O28—S26—N29	104.7 (3)
O2—S1—C19	107.1 (3)	O27—S26—C44	107.6 (3)
O3—S1—C19	108.5 (3)	O28—S26—C44	106.8 (3)
N4—S1—C19	109.8 (3)	N29—S26—C44	108.0 (3)
S1—N4—C5	119.9 (5)	S26—N29—C30	122.4 (4)
N4—C5—C6	115.2 (5)	N29—C30—C31	115.6 (5)
N4—C5—C12	105.2 (6)	N29—C30—C37	107.7 (5)
C6—C5—C12	111.6 (6)	C31—C30—C37	110.8 (5)
C5—C6—C7	121.4 (5)	C30—C31—C32	121.9 (6)
C5—C6—C11	118.5 (6)	C30—C31—C36	120.4 (6)
C7—C6—C11	120.1 (6)	C32—C31—C36	117.7 (6)
C6—C7—C8	119.4 (7)	C31—C32—C33	123.1 (7)
C7—C8—C9	121.0 (7)	C32—C33—C34	118.2 (7)
C8—C9—C10	119.5 (6)	C33—C34—C35	120.1 (7)
C9—C10—C11	122.1 (6)	C34—C35—C36	119.0 (7)
C6—C11—C10	117.7 (6)	C31—C36—C35	121.8 (7)
C5—C12—N13	108.7 (6)	C30—C37—N38	106.5 (5)
C5—C12—C16	111.8 (6)	C30—C37—C41	111.9 (5)
N13—C12—C16	108.8 (5)	N38—C37—C41	108.7 (5)
C12—N13—O14	117.3 (6)	C37—N38—O39	118.4 (6)
C12—N13—O15	117.9 (6)	C37—N38—O40	116.6 (6)
O14—N13—O15	124.8 (6)	O39—N38—O40	125.0 (6)
C12—C16—C17	113.5 (6)	C37—C41—C42	113.6 (6)
C16—C17—C18	178.7 (8)	C41—C42—C43	176.6 (10)
S1—C19—C20	121.0 (6)	S26—C44—C45	120.1 (5)
S1—C19—C24	119.8 (5)	S26—C44—C49	118.1 (5)
C20—C19—C24	119.1 (6)	C45—C44—C49	121.8 (6)
C19—C20—C21	118.8 (6)	C44—C45—C46	119.1 (7)
C20—C21—C22	123.1 (6)	C45—C46—C47	120.1 (7)
C21—C22—C23	117.7 (6)	C46—C47—C48	118.9 (6)
C21—C22—C25	122.4 (6)	C46—C47—C50	119.4 (7)
C23—C22—C25	119.8 (7)	C48—C47—C50	121.7 (7)
C22—C23—C24	120.8 (7)	C47—C48—C49	121.6 (7)
C23—C24—C19	120.5 (7)	C44—C49—C48	118.4 (6)

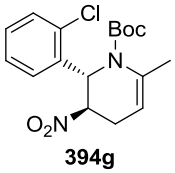
Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N4—H41···O28	0.88	2.07	2.917 (10)	163 (1)
N29—H291···O2^{i}	0.87	2.10	2.915 (10)	157 (1)

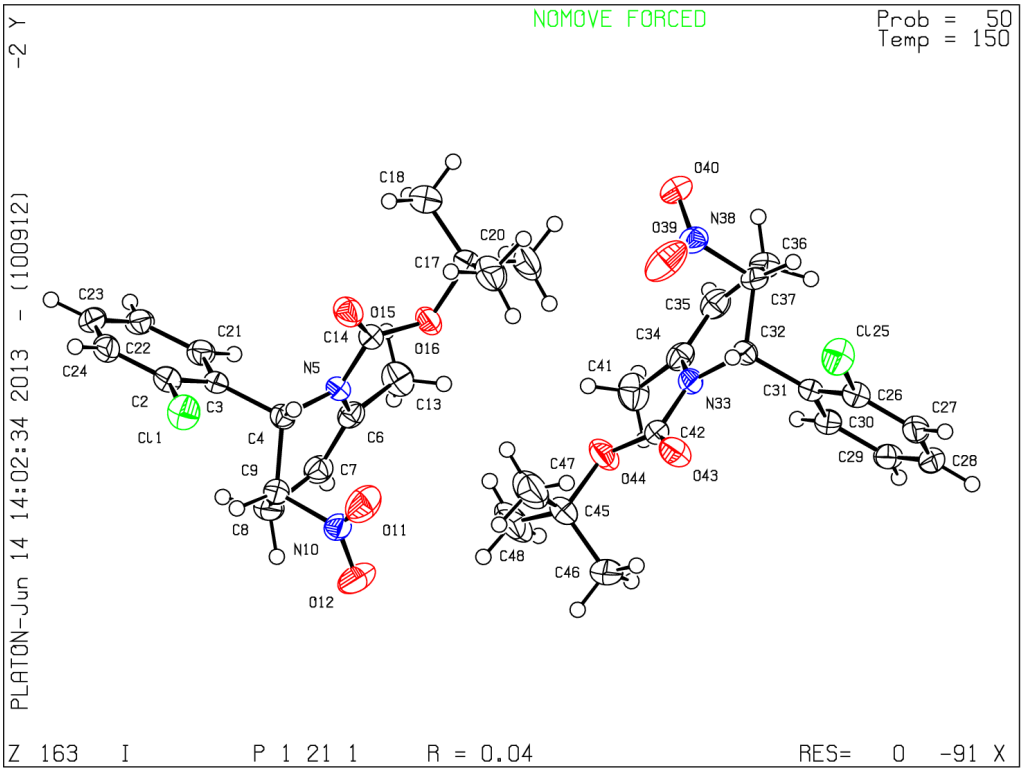
Symmetry code: (i) *x*–1, *y*, *z*.

6.2.2 X-Ray Diffraction Data for Tetrahydropyridine 394g





394g



Experimental details

Crystal data	
Chemical formula	$C_{17}H_{21}ClN_2O_4$
M_r	352.82
Crystal system, space group	Monoclinic, $P2_1$
Temperature (K)	150
a, *b*, *c* (Å)	14.9959 (2), 7.1013 (1), 18.0983 (4)
β (°)	113.6819 (7)
V (Å^3)	1765.00 (5)

Z	4
Radiation type	Mo $K\alpha$
μ (mm^{-1})	0.24
Crystal size (mm)	0.70 × 0.40 × 0.30
Data collection	
Diffractometer	Nonius KappaCCD diffractometer
Absorption correction	Multi-scan *DENZO*/*SCALEPACK* (Otwinowski & Minor, 1997)
T_{min}, T_{max}	0.78, 0.93
No. of measured, independent and observed [$I > 2.0\sigma(I)$] reflections	36469, 8017, 6403
R_{int}	0.047
$(\sin \theta/\lambda)_{max}$ ($Å^{-1}$)	0.649
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.038, 0.093, 0.91
No. of reflections	8017
No. of parameters	146
No. of restraints	1
H-atom treatment	H-atom parameters constrained
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e $Å^{-3}$)	0.27, −0.32
Absolute structure	Flack (1983), 3679 Friedel-pairs
Flack parameter	0.00 (5)

Selected geometric parameters (Å, º)

Cl1—C2	1.746 (2)	Cl25—C26	1.742 (2)
C2—C3	1.390 (3)	C26—C27	1.386 (3)
C2—C24	1.385 (3)	C26—C31	1.394 (3)
C3—C4	1.518 (3)	C27—C28	1.382 (4)
C3—C21	1.398 (3)	C28—C29	1.383 (3)
C4—N5	1.475 (3)	C29—C30	1.391 (3)
C4—C9	1.530 (3)	C30—C31	1.393 (3)
N5—C6	1.424 (3)	C31—C32	1.518 (3)
N5—C14	1.393 (3)	C32—N33	1.476 (2)
C6—C7	1.342 (3)	C32—C37	1.528 (3)
C6—C13	1.502 (3)	N33—C34	1.429 (3)
C7—C8	1.489 (3)	N33—C42	1.395 (3)
C8—C9	1.503 (4)	C34—C35	1.338 (3)
C9—N10	1.530 (3)	C34—C41	1.503 (3)
N10—O11	1.215 (3)	C35—C36	1.490 (3)
N10—O12	1.219 (3)	C36—C37	1.499 (4)
C14—O15	1.208 (3)	C37—N38	1.533 (3)
C14—O16	1.321 (2)	N38—O39	1.225 (3)
O16—C17	1.485 (3)	N38—O40	1.209 (3)
C17—C18	1.513 (4)	C42—O43	1.209 (3)
C17—C19	1.517 (4)	C42—O44	1.323 (3)
C17—C20	1.508 (4)	O44—C45	1.488 (3)
C21—C22	1.389 (3)	C45—C46	1.506 (4)
C22—C23	1.383 (4)	C45—C47	1.513 (5)

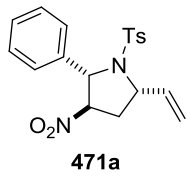
C23—C24	1.382 (4)	C45—C48	1.516 (4)
Cl1—C2—C3	119.93 (17)	Cl25—C26—C27	117.63 (18)
Cl1—C2—C24	117.70 (19)	Cl25—C26—C31	119.88 (17)
C3—C2—C24	122.3 (2)	C27—C26—C31	122.5 (2)
C2—C3—C4	120.99 (19)	C26—C27—C28	119.1 (2)
C2—C3—C21	117.2 (2)	C27—C28—C29	120.0 (2)
C4—C3—C21	121.81 (19)	C28—C29—C30	120.1 (2)
C3—C4—N5	113.61 (17)	C29—C30—C31	121.3 (2)
C3—C4—C9	110.12 (16)	C26—C31—C30	117.02 (19)
N5—C4—C9	110.16 (17)	C26—C31—C32	120.85 (19)
C4—N5—C6	119.17 (17)	C30—C31—C32	122.12 (18)
C4—N5—C14	112.51 (17)	C31—C32—N33	112.88 (16)
C6—N5—C14	128.29 (18)	C31—C32—C37	110.51 (16)
N5—C6—C7	120.1 (2)	N33—C32—C37	110.82 (17)
N5—C6—C13	120.1 (2)	C32—N33—C34	119.07 (17)
C7—C6—C13	119.7 (2)	C32—N33—C42	112.14 (17)
C6—C7—C8	124.9 (2)	C34—N33—C42	128.76 (18)
C7—C8—C9	110.35 (19)	N33—C34—C35	119.8 (2)
C4—C9—C8	112.33 (18)	N33—C34—C41	120.4 (2)
C4—C9—N10	108.86 (18)	C35—C34—C41	119.6 (2)
C8—C9—N10	110.57 (19)	C34—C35—C36	125.3 (2)
C9—N10—O11	118.4 (2)	C35—C36—C37	110.49 (19)
C9—N10—O12	117.8 (2)	C32—C37—C36	112.46 (19)
O11—N10—O12	123.7 (2)	C32—C37—N38	108.81 (18)
N5—C14—O15	121.40 (19)	C36—C37—N38	110.44 (19)
N5—C14—O16	112.80 (19)	C37—N38—O39	117.7 (2)
O15—C14—O16	125.8 (2)	C37—N38—O40	118.8 (2)
C14—O16—C17	120.62 (18)	O39—N38—O40	123.4 (2)
O16—C17—C18	109.92 (19)	N33—C42—O43	121.33 (19)
O16—C17—C19	110.0 (2)	N33—C42—O44	113.22 (19)
C18—C17—C19	111.7 (2)	O43—C42—O44	125.4 (2)
O16—C17—C20	102.17 (19)	C42—O44—C45	120.33 (19)
C18—C17—C20	111.3 (2)	O44—C45—C46	110.4 (2)
C19—C17—C20	111.4 (2)	O44—C45—C47	109.8 (2)
C3—C21—C22	121.1 (2)	C46—C45—C47	111.9 (3)
C21—C22—C23	120.0 (2)	O44—C45—C48	101.8 (2)
C22—C23—C24	120.1 (2)	C46—C45—C48	109.9 (3)
C2—C24—C23	119.3 (2)	C47—C45—C48	112.7 (3)

Hydrogen-bond geometry (Å, º)

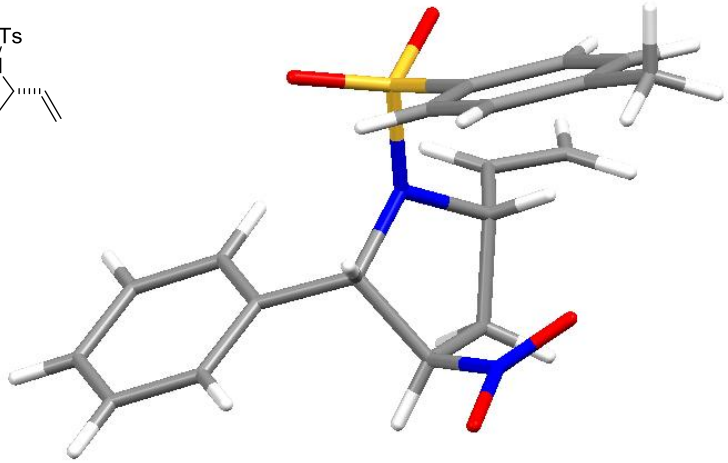
D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C7—H71···O11^{i}	0.95	2.58	3.514 (4)	166 (1)
C20—H201···O40	0.98	2.58	3.419 (4)	145 (1)
C23—H231···O15^{ii}	0.94	2.56	3.233 (4)	129 (1)
C28—H281···O43^{iii}	0.94	2.46	3.160 (4)	131 (1)
C35—H351···O39^{i}	0.95	2.53	3.483 (4)	173 (1)

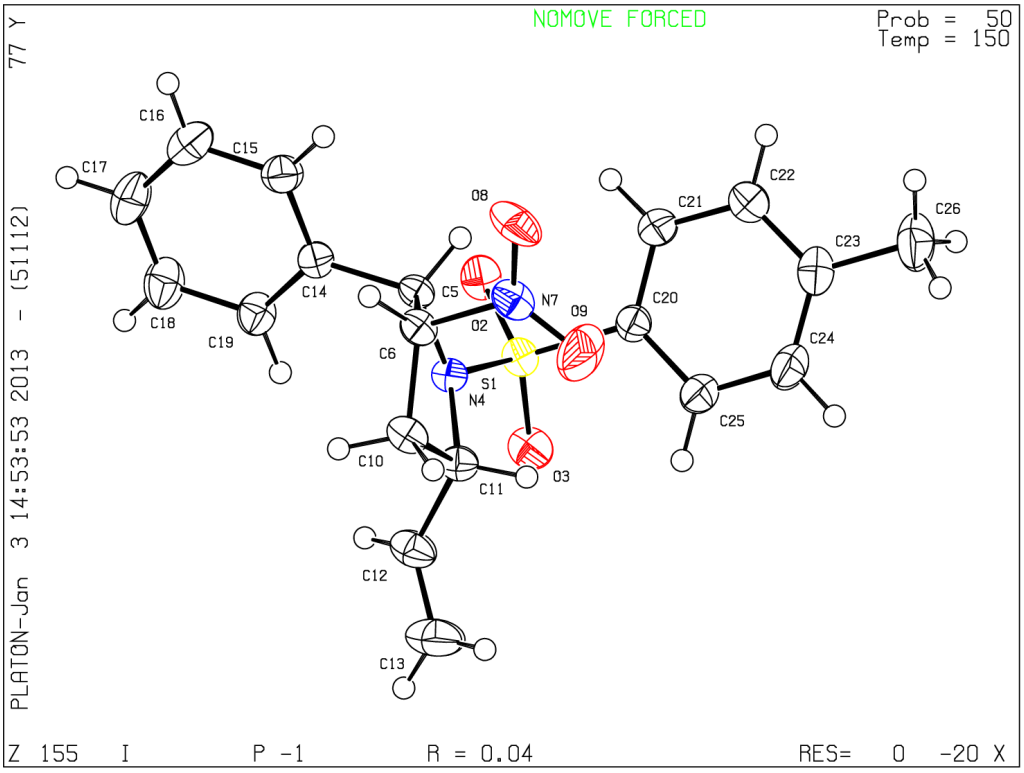
Symmetry codes: (i) *x*, *y*−1, *z*; (ii) −*x*+2, *y*−1/2, −*z*+1; (iii) −*x*, *y*−1/2, −*z*.

6.2.3 X-Ray Diffraction Data for Pyrrolidine 471a



471a





Experimental details

Crystal data	
Chemical formula	$C_{19}H_{20}N_2O_4S$
M_r	372.44
Crystal system, space group	Triclinic, *P*1
Temperature (K)	150
a, *b*, *c* (Å)	7.4965 (2), 10.6303 (2), 11.6630 (3)
α, β, γ (°)	100.5307 (9), 94.2654 (9), 96.0409 (10)

V (Å^3)	904.52 (4)
Z	2
Radiation type	Mo $K\alpha$
μ (mm^{-1})	0.21
Crystal size (mm)	0.60 × 0.40 × 0.40
Data collection	
Diffractometer	Nonius KappaCCD diffractometer
Absorption correction	Multi-scan *DENZO*/*SCALEPACK* (Otwinowski & Minor, 1997)
T_{min}, T_{max}	0.71, 0.92
No. of measured, independent and observed [$I > 2.0\sigma(I)$] reflections	14483, 4113, 3495
R_{int}	0.020
(sin θ/λ)$_{max}$ (Å^{-1})	0.649
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.044, 0.120, 0.93
No. of reflections	4112
No. of parameters	235
No. of restraints	0
H-atom treatment	H-atom parameters constrained
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.42, −0.45

Selected geometric parameters (Å, º)

S1—O2	1.4348 (13)	C12—C13	1.314 (3)
S1—O3	1.4364 (13)	C14—C15	1.394 (2)
S1—N4	1.6309 (13)	C14—C19	1.390 (2)
S1—C20	1.7591 (17)	C15—C16	1.389 (3)
N4—C5	1.4780 (19)	C16—C17	1.392 (3)
N4—C11	1.486 (2)	C17—C18	1.378 (3)
C5—C6	1.547 (2)	C18—C19	1.390 (3)
C5—C14	1.521 (2)	C20—C21	1.388 (2)
C6—N7	1.511 (2)	C20—C25	1.391 (2)
C6—C10	1.516 (2)	C21—C22	1.391 (3)
N7—O8	1.213 (2)	C22—C23	1.390 (3)
N7—O9	1.206 (2)	C23—C24	1.395 (3)
C10—C11	1.539 (2)	C23—C26	1.513 (3)
C11—C12	1.506 (2)	C24—C25	1.391 (3)
O2—S1—O3	120.16 (8)	N4—C11—C12	112.53 (14)
O2—S1—N4	106.13 (7)	C11—C12—C13	123.4 (2)
O3—S1—N4	105.90 (7)	C5—C14—C15	118.18 (15)
O2—S1—C20	107.83 (8)	C5—C14—C19	122.41 (15)
O3—S1—C20	107.45 (8)	C15—C14—C19	119.39 (16)
N4—S1—C20	109.01 (7)	C14—C15—C16	119.86 (18)
S1—N4—C5	118.39 (10)	C15—C16—C17	120.48 (19)
S1—N4—C11	120.26 (11)	C16—C17—C18	119.58 (18)
C5—N4—C11	113.44 (12)	C17—C18—C19	120.31 (19)
N4—C5—C6	103.38 (12)	C18—C19—C14	120.37 (18)
N4—C5—C14	113.25 (12)	S1—C20—C21	120.19 (13)

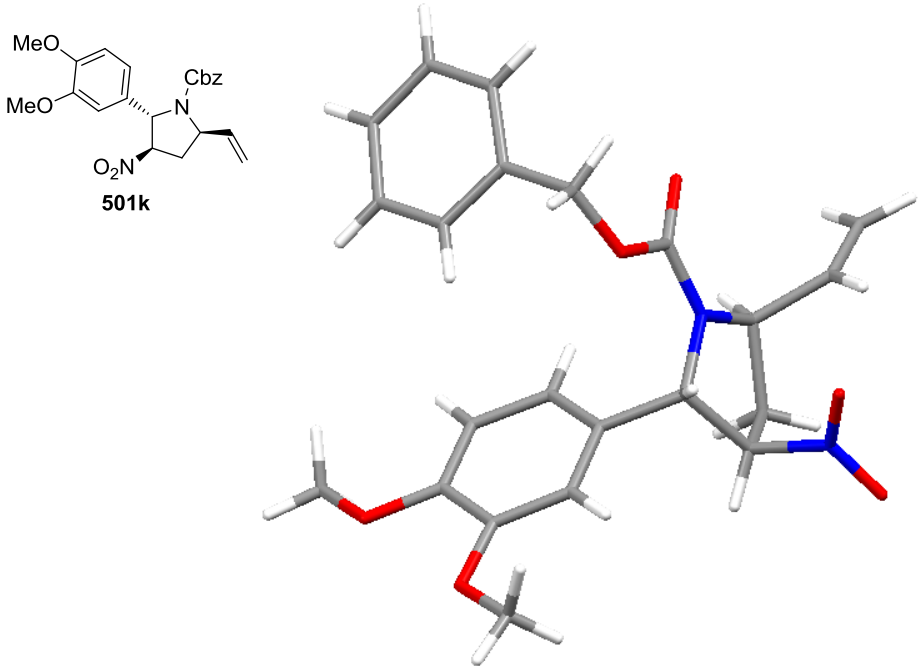
C6—C5—C14	109.97 (13)	S1—C20—C25	119.34 (14)
C5—C6—N7	108.78 (13)	C21—C20—C25	120.45 (17)
C5—C6—C10	104.25 (12)	C20—C21—C22	119.46 (17)
N7—C6—C10	112.04 (14)	C21—C22—C23	121.14 (18)
C6—N7—O8	116.62 (16)	C22—C23—C24	118.50 (17)
C6—N7—O9	119.42 (15)	C22—C23—C26	120.3 (2)
O8—N7—O9	123.96 (17)	C24—C23—C26	121.17 (19)
C6—C10—C11	106.01 (13)	C23—C24—C25	121.14 (18)
C10—C11—N4	101.98 (13)	C20—C25—C24	119.27 (18)
C10—C11—C12	112.06 (14)		

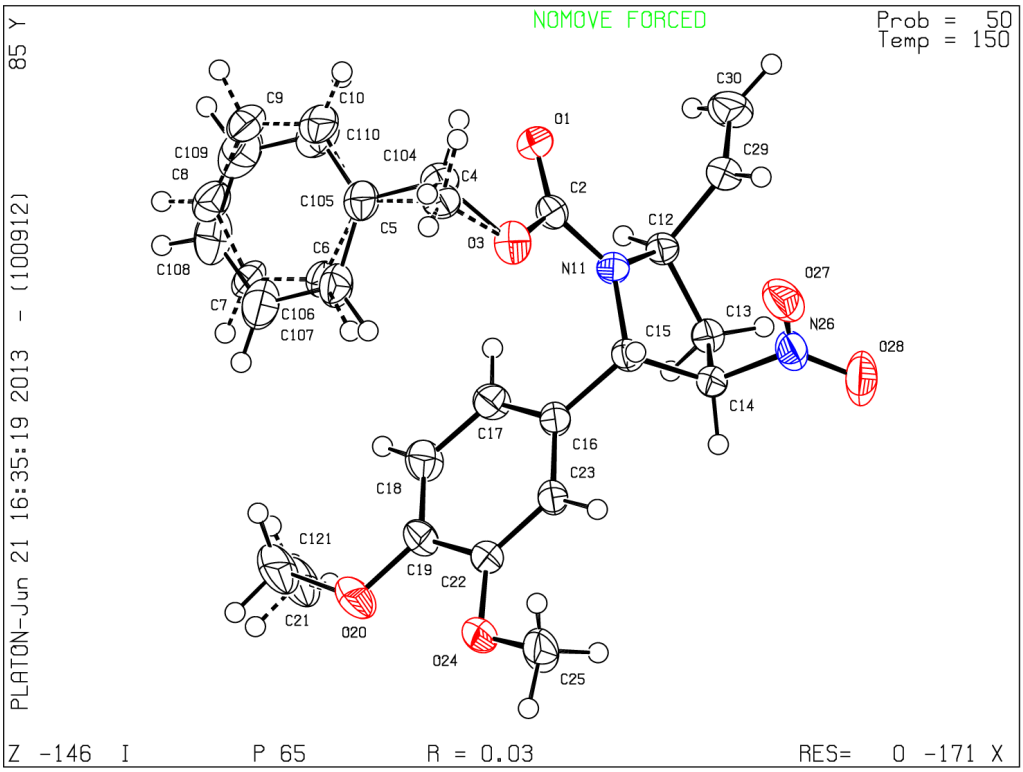
Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C5—H51···O8^{i}	0.98	2.37	3.235 (3)	148 (1)
C10—H101···O3^{ii}	0.99	2.54	3.408 (3)	147 (1)
C18—H181···O3^{iii}	0.95	2.60	3.301 (3)	131 (1)

Symmetry codes: (i) −*x*+2, −*y*, −*z*+1; (ii) *x*+1, *y*, *z*; (iii) −*x*+1, −*y*, −*z*.

6.2.4 X-Ray Diffraction Data for Pyrrolidine 501k





Experimental details

Crystal data	
Chemical formula	$C_{22}H_{24}N_2O_6$
M_r	412.44
Crystal system, space group	Hexagonal, $P6_5$
Temperature (K)	150
a, c (Å)	9.8241 (1), 37.0024 (7)
V (Å^3)	3092.76 (7)
Z	6
Radiation type	Cu $K\alpha$
μ (mm^{-1})	0.81
Crystal size (mm)	0.16 × 0.08 × 0.02
Data collection	
Diffractometer	Oxford Diffraction SuperNova diffractometer
Absorption correction	Multi-scan CrysAlis, (Oxford Diffraction, 2002)
T_{min}, T_{max}	0.84, 0.98
No. of measured, independent and observed [$I > 2.0\sigma(I)$] reflections	42763, 4199, 4020
R_{int}	0.029
(sin θ/λ)$_{max}$ (Å^{-1})	0.630
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.027, 0.066, 1.02
No. of reflections	4186
No. of parameters	325
No. of restraints	301
H-atom treatment	H-atom parameters constrained
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.13, −0.17
Absolute structure	Flack (1983), 1998 Friedel-pairs
Flack parameter	0.04 (11)

Selected geometric parameters (Å, º)

O1—C2	1.2143 (15)	C16—C23	1.3973 (16)
C2—O3	1.3525 (15)	C17—C18	1.3967 (18)
C2—N11	1.3504 (16)	C18—C19	1.380 (2)
O3—C4	1.365 (8)	C19—O20	1.3706 (14)
O3—C104	1.539 (8)	C19—C22	1.4109 (19)
C4—C5	1.511 (5)	O20—C21	1.389 (15)
C5—C6	1.403 (4)	O20—C121	1.466 (7)
C5—C10	1.376 (4)	C22—C23	1.3860 (17)
C6—C7	1.363 (4)	C22—O24	1.3675 (15)
C7—C8	1.370 (4)	O24—C25	1.425 (2)
C8—C9	1.384 (4)	N26—O27	1.2230 (18)
C9—C10	1.363 (4)	N26—O28	1.2253 (17)
N11—C12	1.4747 (14)	C29—C30	1.3121 (19)
N11—C15	1.4641 (15)	C104—C105	1.501 (5)
C12—C13	1.5369 (17)	C105—C106	1.378 (4)

C12—C29	1.5067 (16)	C105—C110	1.402 (4)
C13—C14	1.5265 (18)	C106—C107	1.421 (4)
C14—C15	1.5241 (18)	C107—C108	1.384 (4)
C14—N26	1.5206 (17)	C108—C109	1.367 (4)
C15—C16	1.5235 (15)	C109—C110	1.414 (4)
C16—C17	1.3784 (17)		
O1—C2—O3	124.26 (12)	C15—C16—C23	117.99 (10)
O1—C2—N11	124.47 (11)	C17—C16—C23	119.36 (11)
O3—C2—N11	111.26 (10)	C16—C17—C18	120.53 (12)
C2—O3—C4	119.6 (3)	C17—C18—C19	120.41 (12)
C2—O3—C104	110.4 (3)	C18—C19—O20	124.72 (13)
O3—C4—C5	116.5 (5)	C18—C19—C22	119.41 (11)
C4—C5—C6	120.33 (6)	O20—C19—C22	115.85 (12)
C4—C5—C10	120.16 (6)	C19—O20—C21	113.4 (8)
C6—C5—C10	118.85 (6)	C19—O20—C121	115.6 (3)
C5—C6—C7	120.42 (6)	C19—C22—C23	119.60 (11)
C6—C7—C8	119.28 (6)	C19—C22—O24	115.98 (11)
C7—C8—C9	121.03 (6)	C23—C22—O24	124.41 (12)
C8—C9—C10	119.44 (6)	C16—C23—C22	120.64 (12)
C5—C10—C9	120.50 (6)	C22—O24—C25	115.79 (10)
C2—N11—C12	120.44 (10)	C14—N26—O27	119.92 (12)
C2—N11—C15	124.68 (10)	C14—N26—O28	115.63 (14)
C12—N11—C15	114.36 (9)	O27—N26—O28	124.44 (13)
N11—C12—C13	102.09 (9)	C12—C29—C30	123.36 (13)
N11—C12—C29	112.64 (10)	O3—C104—C105	107.2 (4)
C13—C12—C29	113.79 (10)	C104—C105—C106	120.56 (6)
C12—C13—C14	105.08 (10)	C104—C105—C110	120.45 (6)
C13—C14—C15	104.26 (10)	C106—C105—C110	118.74 (6)
C13—C14—N26	109.44 (10)	C105—C106—C107	120.35 (6)
C15—C14—N26	112.02 (12)	C106—C107—C108	119.37 (6)
C14—C15—N11	101.94 (9)	C107—C108—C109	121.05 (6)
C14—C15—C16	110.71 (10)	C108—C109—C110	119.37 (6)
N11—C15—C16	113.53 (9)	C109—C110—C105	120.40 (6)
C15—C16—C17	122.64 (10)		

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C10—H101···C21^{i}	0.94	2.60	3.423 (6)	146 (1)
C21—H211···O3^{ii}	0.96	2.56	3.211 (6)	125 (1)
C121—H211···O3^{ii}	1.01	2.56	3.322 (6)	132 (2)
C23—H231···O1^{iii}	0.95	2.36	3.235 (6)	153 (1)
C104—H1042···O27^{iv}	0.99	2.56	3.540 (6)	169 (1)

Symmetry codes: (i) *y*+1, −*x*+*y*, *z*+1/6; (ii) *x*−1, *y*−1, *z*; (iii) *x*−*y*, *x*, *z*−1/6; (iv) *y*, −*x*+*y*, *z*+1/6.

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