Development of an Enantioselective Reductive Nitro-Mannich Reaction using Thiourea Catalysis

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I, Paul John Koovits confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signed ..................................................

Date ..................................................
Abstract

The introductory chapter of this thesis describes in detail the chemistry of the nitro-Mannich reaction from its inception to the current “state of the art”. Additionally, the products of the nitro-Mannich reaction and their uses in synthesis are also discussed. The final section of the introduction deals with the use of thiourea organocatalysis and its application in synthetic transformations using imines or nitroalkenes as electrophiles.

The results and discussion initially focuses on the development of a racemic reductive nitro-Mannich reaction. It has been found that when using Superhydride™ as a hydride source, a variety of nitroalkenes underwent selective reduction. The corresponding nitronates formed then underwent an in situ nitro-Mannich reaction upon addition of an N-para-methoxy phenyl (PMP) protected imine and trifluoroacetic acid to form β-nitroamines in excellent conversion (>90%) and high diastereoselectivities (75:25 to >95:5 dr). These products were then protected by reaction with trifluoroacetic anhydride and pyridine, to enable isolation of the products as trifluoroacetamides in good to excellent yields (58-87%) and diastereoselectivity (>90:10 dr). The second part details the development of an enantioselective variant using thiourea organocatalysis. It was discovered that the desired reductive nitro-Mannich reaction could be promoted with excellent levels of stereocontrol using a Hantzsch ester as the hydride source and a simple thiourea catalyst derived from L-valine. The reaction worked well for a variety of different nitroalkenes and N-PMP protected imines using toluene as a solvent at -20 °C. The resultant products could be isolated after protection as trifluoroacetamides in moderate to excellent yields (32-84%), high diastereoselectivity (>90:10 dr) and good to excellent enantioselectivity (73-99% ee). The final part of this chapter discusses progress towards the synthesis of 1,2-diamine containing natural product Eudistomidin B, using a reductive nitro-Mannich reaction as the key step.
The conclusions of the research and potential future work are also presented along with analytical data. Detailed preparative methods for all compounds synthesised in this research are also described. Finally an appendix section is included, which contains a list of abbreviations, a table of coupling constants and a comprehensive list of references.
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So with that there’s just one thing left to do (the pint of ice cold cava). Oh and there’s the small matter of a viva as well.

Cheers everyone
# Table of contents

## Chapter 1. Introduction

1.1 The nitro-Mannich reaction ............................. 9
   1.1.1 Overview .......................................................... 9
   1.1.2 Discovery and developments pre-1998 ......................... 10
   1.1.3 Non-catalytic coupling ............................................ 11
   1.1.4 Metal catalysed reactions ......................................... 13
   1.1.5 Organocatalytic nitro-Mannich reactions .......................... 19
   1.1.6 Miscellaneous nitro-Mannich reactions ......................... 24
   1.1.7 Conjugate addition/nitro-Mannich reactions .................. 26

1.2 Synthetic utility of nitro-Mannich products .................. 31
   1.2.1 Overview .......................................................... 31
   1.2.2 Nitro reduction .................................................... 31
   1.2.3 Nef reaction ....................................................... 34
   1.2.4 Peptide synthesis via umpolung reactivity ...................... 36
   1.2.5 Radical and ionic denitration ..................................... 37

1.3 Thiourea organocatalysis ........................................ 39
   1.3.1 Overview .......................................................... 39
   1.3.2 Background and early research ................................... 40
   1.3.3 Thiourea catalysed additions to imine electrophiles ........... 42
   1.3.4 Thiourea catalysed additions to nitroalkene electrophiles ... 47
   1.3.5 Thiourea catalysed additions to other electrophiles .......... 54

1.4 Proposed research .................................................. 58
   1.4.1 Overview and limitations of the nitro-Mannich reaction ..... 58
   1.4.2 Chosen strategy ................................................... 58
   1.4.3 Precedent for a racemic reductive nitro-Mannich reaction .... 59
   1.4.4 Precedent for an asymmetric reductive nitro-Mannich reaction 61

## Chapter 2. Results and discussion ............................... 63
2.1 The racemic reductive nitro-Mannich reaction ..................64
  2.1.1 Initial investigations ..................................................64
  2.1.2 Scope of reductive nitro-Mannich reaction ..................70
  2.1.3 Assignment and origin of relative stereochemistry .........81
  2.1.4 Concluding paragraph ..................................................84
2.2 Tandem asymmetric reductive nitro-Mannich reaction .........86
  2.2.1 Initial investigations ..................................................86
  2.2.2 Catalyst screen for the tandem reductive nitro-Mannich reaction .................................................94
  2.2.3 Optimisation of reaction with selected catalyst ............97
  2.2.4 Investigation of the reaction scope .........................99
  2.2.5 Determination and origin of absolute stereochemistry ....105
  2.2.6 Forming three contiguous stereocentres .....................114
  2.2.7 Reaction with ketimines to form quaternary centres .......120
  2.2.8 Concluding paragraph ..................................................123
2.3 Towards the total synthesis of Eudistomidin B ...............125
  2.3.1 Introduction and retrosynthesis ....................................125
  2.3.2 Forward synthesis route .............................................128

Chapter 3. Conclusions and future studies ......................134
3.1 Conclusions .................................................................135
3.2 Future studies ...............................................................137
  3.2.1 Asymmetric reductive nitro-Mannich reaction .................137
  3.2.2 Asymmetric reductive nitro-Mannich reaction of ketimines ..139
  3.2.3 Reductive nitro-Mannich reaction to form three stereocentres ....140
  3.2.4 Tandem nitro-Mannich reactions with different nucleophiles ....141
  3.2.5 Total synthesis of Eudistomidin B ......................................141

Chapter 4. Experimental ..................................................143
4.1 General experimental ......................................................144
  4.1.1 General experimental details ........................................144
  4.1.2 Purification of reagents ...............................................145
4.2 Synthetic procedures ......................................................146
  4.2.1 Procedures for preparation of nitroalkenes ...................146
  4.2.2 Procedures for preparation of imines .............................151
4.2.3 Preparation of catalysts ................................................................. 156
4.2.4 Preparation of β-nitroamines and β-nitrotrifluoroacetamides .......... 172
4.2.5 Miscellaneous compounds and total synthesis intermediates .......... 204

Chapter 5. Appendices ....................................................................... 217

5.1 Abbreviations .................................................................................. 218
5.2 Table of coupling constants for β-nitroamines ................................. 222
5.3 References .......................................................................................... 226
Chapter 1. Introduction
1.1 The nitro-Mannich reaction

1.1.1 Overview

The formation of new carbon-carbon bonds represents some of the most fundamental reactions available to synthetic chemists. The addition of an active C-H nucleophile to a C=X π bond represents a simple and atom efficient carbon-carbon bond forming reaction. Within this widely utilised family of reactions are the famous aldol reaction, and its aza-equivalents: the Mannich, Henry (or aza-aldol) and the nitro-Mannich (or aza-Henry) reactions (Figure 1).

![Reaction Mechanisms (aldol, nitroaldol, Mannich and nitro-Mannich reactions)](image)

**Figure 1.** The aldol, nitroaldol, Mannich and nitro-Mannich reactions

Whilst the enolate-based aldol and Mannich reactions have been extensively studied, the nitro-Mannich and Henry reactions, which react via a nitronate species, have been much less well researched. The β-nitroamine products possess two nitrogens in different oxidation states which allows for complete chemoselectivity in subsequent transformations. Despite the high potential of the nitro-Mannich reaction products, the reaction had received little attention up until 1998 when the Anderson group published the first efficient diastereoselective procedure. Since that seminal publication, there has been much more research performed in this field. This has led to the discovery of several protocols utilising organometallic and organocatalysts to deliver both the common *anti* and the rarer *syn* diastereomers with high levels of enantioselectivity. There have been several small reviews on the nitro-Mannich...
reaction. As such, the remainder of this section will discuss a brief history of the nitro-Mannich reaction and will try to focus on some of the more pivotal publications in greater detail.

1.1.2 Discovery and developments pre-1998

The first nitro-Mannich (or aza-Henry) reaction was reported in 1896 by Henry. It was disclosed that a variety of nitroalkanes would add to hemiaminal 1 to form β-nitroamines (Scheme 1). The exact conditions were never reported but it is assumed that loss of a water molecule from the hemiaminal to give an iminium ion followed by attack from the nitronate occurs. Very similar results to this were reported a few years later by Mousset using nitroisobutane and hemiaminal 1 but the exact conditions were once more not reported.

![Scheme 1](image)

Scheme 1. The first reported nitro-Mannich reaction

The next major development came in the mid-20th century when Senkus and Johnson simultaneously published more detailed accounts of the nitro-Mannich reaction (Scheme 2). Senkus was able to report moderate to good conversion to β-nitroamine products 7 when using hemiaminals 6, formed from primary amines. Johnson described a similar protocol using hemiaminals 8 formed from secondary amines and formaldehyde.
Another notable report of a nitro-Mannich reaction prior to 1998 was the publication of the first nitro-Mannich reaction using pre-formed imine 10 with nitroethane or nitromethane in refluxing ethanol by the group of Hurd. However, these reactions only proceeded with moderate yields and the authors did not comment on the diastereoselectivity (Scheme 3).  

As well as the reactions described thus far there were some other examples of early nitro-Mannich reactions pre-1998 but they are less noteworthy in regards to this work.  

1.1.3 Non-catalytic coupling

It was over 100 years from the nitro-Mannich reaction’s discovery to the development of the first acyclic diastereoselective nitro-Mannich reaction by the Anderson group in 1998.  

The authors reported that the direct addition of lithium nitronates, formed from nitroethane 13, to para-methoxy benzyl (PMB) protected imines 14 in the presence of acetic acid gave the desired β-nitroamines 15 diastereomERICally enriched as the anti diastereomer (Scheme 4). The acetic acid was required in the reaction to
activate the imine. Without activation using a Brønsted acid there is no reaction observed.

**Scheme 4.** First acyclic diastereoselective nitro-Mannich reaction

The β-nitroamine products 15 were unstable to standard purification techniques and as such had to be reduced to vicinal diamines using samarium diiodide to calculate an isolated yield. This instability of β-nitroamines is a recurrent problem with the nitro-Mannich reaction, especially if there is no electron withdrawing group on the amine. The products frequently have to be immediately reacted to prevent degradation of the β-nitroamine via a retro nitro-Mannich reaction.

One year later, Petrini et al. reported the base assisted reaction between α-amidoalkyl sulfones 17 and sodium methanenitronate (Scheme 5). It was proposed that the excess of the sodium methanenitronate species (formed from nitromethane and sodium hydride) can eliminate phenyl sulfinic acid from α-amidoalkyl sulfone 17 and form an acyl imine species in situ. This imine can then react with the remainder of the sodium methanenitronate via a nitro-Mannich reaction to form β-nitroamines 18 in high yields.

**Scheme 5.** Base-assisted nitro-Mannich reaction of α-amidoalkyl sulfones

The Anderson group have also reported another diastereoselective non-catalytic nitro-Mannich reaction using Lewis acids. Using BF₃·OEt₂ or Ti(O′Pr)₂Cl₂ as a Lewis acid to activate PMB-imines 19, the nitro-Mannich reaction could be promoted when added to pre-formed lithium nitronate 21 (Scheme 6). The reaction gave good
conversions but the scope was not explored as the authors were seeking to develop a catalytic method which was later achieved using silyl nitronates (see section 1.1.4).

![Scheme 6](image)

**Scheme 6.** Lewis acid promoted nitro-Mannich reaction

There have also been several chiral auxiliary controlled nitro-Mannich reactions reported.\(^{13}\) Ruano and Cid *et al.* reported the first auxiliary controlled nitro-Mannich reaction in 2005 (Scheme 7).\(^{14}\) Using para-tolylsulfinyl imines 23, desired \(\beta\)-nitroamines 24 were synthesised in moderate to good yields and with good to excellent diastereoselectivity. The authors were also able to promote the reaction using TBAF (tetrabutylammonium fluoride) instead of sodium hydroxide, however the diastereoselectivity was significantly lower.

![Scheme 7](image)

**Scheme 7.** Chiral auxiliary controlled nitro-Mannich reaction

### 1.1.4 Metal catalysed reactions

Shibasaki and co-workers reported the first catalytic enantioselective nitro-Mannich reaction in 1999 using phosphonate protected imines 25, nitromethane and chiral Yb/K/BINAP catalyst 26, which acted as both a Lewis acid and Brønsted base (Scheme 8).\(^{15}\) The main drawbacks of the reaction were the long reaction times and that the catalyst could only promote the nitro-Mannich reaction with nitromethane.
An improved catalytic system was later published by the Shibasaki group that overcame the limitations of the previous work to become the first diastereoselective and enantioselective nitro-Mannich reaction (Scheme 9). Although some of the limitations of the previous publication have been dealt with, the new catalyst system was unable to furnish the products with as high a level of enantioselectivity as those with simpler nitroalkane precursors.

In between the two reports by Shibasaki et al. the Anderson group published a nitro-Mannich reaction of silyl nitronate with para-methoxy phenyl (PMP) imines promoted by a catalytic quantity of Sc(OTf)₃ (Scheme 10). The reactions had initially been attempted with PMB-imines, as used in previous work, but the diastereoselectivity was poor. Altering the protecting group to PMP gave much better diastereomeric ratios. The scope of the reaction was reported in greater detail in 2004 when Cu(OTf)₂ and Ti(OiPr)₄ were also shown to be effective catalysts for the reaction and an ortho-methoxy benzyl (OMB) group was used as the protecting group.
Jørgensen et al. reported the first asymmetric nitro-Mannich reaction of silyl-nitronates 33 with PMP-α-imino esters 34 to give optically active β-nitro-α-amino esters 36 using a chiral copper catalyst (Scheme 11). The products were formed with high enantio- and diastereoselectivity when reactions were performed at -100 °C but the scope of the reaction was limited to imino esters.

Scheme 11. First asymmetric nitro-Mannich reaction using silyl-nitronates

The same group also published an alternative strategy using simple nitroalkanes 11 instead of silyl-nitronates (Scheme 12). This reaction required the use of an organic base to deprotonate the nitroalkane as well as chiral copper catalyst 37. Unlike the reaction depicted in scheme 11, the reaction temperatures used were much easier to achieve although the reaction times were also much longer. Later, the group of Hyeon immobilized this catalyst onto a silica support to create a recyclable catalyst system. Although successful, the new catalyst was less selective and upon recycling the levels of stereoselectivity further decreased.
In 2005, encouraged by their own research, and the publication by Jørgensen et al., the Anderson group reported the catalytic enantioselective nitro-Mannich reaction of silyl-nitronate with PMP-protected imines giving anti β-nitroamines in good yields and selectivity (Scheme 13). The authors used a chiral tBu-BOX ligand and copper (II) metal as the Lewis acid catalyst.

In the following year, Palomo and co-workers reported an enantioselective nitro-Mannich reaction using zinc (II) catalysis. The authors used (-)-N-methylephedrine (NME) as the chiral ligand and a tertiary amine as base to produce the desired products in good yield and enantioselectivity. However, the reaction used large amounts of ligand (45 mol%) and nitromethane was used as solvent. The groups of Qian and Trost have also published Zn catalysed nitro-Mannich reactions. These reactions use a dinuclear zinc complex and are significantly more efficient, requiring 5 and 2 equivalents of nitromethane respectively.
So far only anti selective reactions have been discussed; the development of a syn-selective metal catalysed nitro-Mannich reaction was not published until 2007. Shibasaki’s group reported the use of heterobimetallic Cu/Sm/Schiff base complex with Schiff base 44 as the catalyst in a syn-selective nitro-Mannich reaction (Scheme 15, 1st generation). The reaction achieved excellent selectivity, was high yielding and works well for a large range of substrates. The 4-t-Bu-phenol additive was crucial for the very high enantioselectivity (80 vs. 94% ee in screening). It was proposed to be involved as a ligand and not as a simple proton source as the use of hindered 2,6-(t-Bu)2-phenol had no beneficial effect on enantioselectivity. The only limitation of the catalyst system was that imines with alkyl groups such as n-pentyl or iso-butyl gave poor enantioselectivity. More recently, a much more detailed report of this syn-selective nitro-Mannich reaction complete with ESI-MS analysis of the catalyst structure has been disclosed.
As a result of this report it was discovered that 4-MeO-phenol and Sm$_3$O(O$i$Pr)$_{13}$ gave the best enantioselectivity and allowed catalyst loadings as low as 1 mol% for some reactions. The new catalyst system also overcame the previous limitations and an expanded scope for the reaction was shown (Scheme 15, 2$^{nd}$ generation). However, the reaction is still limited by the large excess of nitroalkane 11 (10 equiv.) required. A possible transition state was also proposed to explain the unusual syn-selectivity through cooperative dual activation of the nitroalkane by Sm and the imine by Cu. Of the plausible transition states (Figure 2), TS-1 has less unfavourable steric clashes and as such is favoured over TS-2.

**Figure 2.** Proposed transition states for syn-selective nitro-Mannich reaction

In 2008, Feng et al. reported the first enantioselective nitro-Mannich reaction of ketimines 46 (Scheme 16). Using a combination of copper (I) triflate and $N,N'$-dioxide ligand 47 in phenyl ethyl ether the authors were able to react nitromethane with a variety ketimines in moderate to good yields and high levels of enantioselectivity. Unfortunately, the rate of reaction was very slow, taking 10 days to reach acceptable yields and used approximately 20 equivalents of nitromethane.

**Scheme 16.** First enantioselective nitro-Mannich reaction of ketimines

Although there have been other reports of metal-catalysed nitro-Mannich protocols, the reactions currently described in this section represent the state-of-the-art for this
particular aspect of nitro-Mannich chemistry and as such the remainder of this section shall discuss the use of non-metallic catalytic systems.

1.1.5 Organocatalytic nitro-Mannich reactions

Despite the first enantioselective organocatalysed reactions having been described in the early 1970s,\textsuperscript{27} the field of organocatalysis lay dormant for almost 30 years after. Since the late 1990s however, thanks to the seminal publications by a few research groups,\textsuperscript{28} the field has exploded with research and nowadays many reactions can be performed asymmetrically using organocatalysis. The nitro-Mannich reaction is no exception and has been shown to proceed asymmetrically using a variety of organocatalysts. The first organocatalytic nitro-Mannich reaction was reported by Takemoto \textit{et al.} in 2004.\textsuperscript{29} Using thiourea catalyst 49, good yields and moderate to good enantioselectivities could be achieved for the nitro-Mannich reaction between nitromethane and a variety of phosphinoylimines 25 (Scheme 17).

![Scheme 17. First organocatalytic nitro-Mannich reaction](image)

More details on this organocatalysed reaction were published by the Takemoto group two years later.\textsuperscript{30} This paper described how the enantioselectivities of the reaction could be greatly improved by using $N$-Boc-imines 41 and lowering the temperature to -20 °C.
It was also showed that under these conditions the reaction could be performed with various other nitroalkanes 11 to give desired products 51 with moderate to high diastereoselectivity and excellent enantioselectivity. The authors also proposed a mechanism with TS-3 as the transition state. In TS-3, both the imine and the nitroalkane are activated by the thiourea group and the acidic Me₂NH⁺ group. Almost simultaneous to the original Takemoto publication in 2004, Johnston et al. disclosed the use of Brønsted acid catalysis to promote the nitro-Mannich reaction. Using the triflate salt of chiral bisamidine (BAM) 52 the authors were able to promote the reaction of N-Boc imines 41 bearing electron withdrawing groups with nitromethane or nitroethane as solvent to give desired β-nitroamines 51 in moderate to good yields and in some cases excellent enantioselectivity (Scheme 19).

Recently, Johnston’s group have reported a greatly improved procedure using a combination of BAM ligand 53 and triflic acid (Scheme 20). It was observed that
the use of the mono-triflate salt of BAM 53 gave a great a drastic improvement in the rate of reaction when using nitroethane (complete reaction 24 h with 1.5 equiv. EtNO₂) in comparison to the mono-triflate salt of 52 (<5 % conversion in 24 h) used in the previous work (Scheme 19). This is reasoned to be due to the increased basicity of 53 resulting from the pyrrolidine groups in the 4-position of the quinolones. Interestingly, the ratio of triflic acid to BAM 53 was found to be crucial and a ratio of 3:2 was found to be the optimum mixture.

Scheme 20. Improved Brønsted acid catalysed nitro-Mannich reaction

In 2005, Jacobsen et al.³³ described a stereoselective nitro-Mannich reaction of nitroalkanes 11 to a variety of N-Boc Imines 41 using thiourea catalyst 54 and an external organic base (Scheme 21). The reaction gave the desired products in high yields with good diastereoselectivity and excellent enantioselectivity in most cases.

Scheme 21. Thiourea catalysed nitro-Mannich reaction

Shortly after, the groups of Palomo and Herrera independently reported the first phase-transfer catalysed asymmetric nitro-Mannich reactions (Scheme 22).³⁴ Their
procedures were very similar and only differed in the choice of inorganic base. Palomo’s group also tested nitroethane in the reaction to produce diastereomeric products with modest to excellent selectivity.

Palomo:  
\[
\text{Palomo:} \quad \begin{array}{c}
\text{HN}^\cdot \text{Boc} \\
\text{R}_1^\cdot \text{Ts}
\end{array} + \quad \begin{array}{c}
\text{R}_2^\cdot \text{NO}_2 \\
5.0 \text{ equiv.}
\end{array} \xrightarrow{12 \text{ mol}\% \text{ 56} \quad 1.3 \text{ equiv. CsOH.H}_2\text{O}} \quad \begin{array}{c}
\text{Boc}^\cdot \text{NH} \\
\text{R}_1^\cdot \text{R}_2^\cdot \text{NO}_2
\end{array} \quad \begin{array}{c}
72-88\% \text{ yield} \\
3-13:1 \text{ dr} \\
78-98\% \text{ ee}
\end{array}
\]

Toluene, -50 °C, 44 h

Hererra:  
\[
\text{Hererra:} \quad \begin{array}{c}
\text{HN}^\cdot \text{Boc} \\
\text{R}_1^\cdot \text{Ts}
\end{array} + \quad \begin{array}{c}
\text{MeNO}_2 \\
5.0 \text{ equiv.}
\end{array} \xrightarrow{10 \text{ mol}\% \text{ 56} \quad 5.0 \text{ equiv. KOH}} \quad \begin{array}{c}
\text{Boc}^\cdot \text{NH} \\
\text{R} \cdot \text{NO}_2
\end{array} \quad \begin{array}{c}
70-98\% \text{ yield} \\
75-98\% \text{ ee}
\end{array}
\]

Toluene, -45 °C, 40-64 h

\[\text{R}_1 = \text{Ar, } 1^\circ \text{ alkyl, } 2^\circ \text{ alkyl} \]
\[\text{R}_2 = \text{H, Me}\]

\[\text{Scheme 22. Phase-transfer catalysed nitro-Mannich reactions}\]

Palomo et al. later published a more detailed report of their phase-transfer system, complete with experimental and theoretical studies.\(^{35}\) After extensive computational calculations the group proposed that the nitro group, rather than the imine, H-bonds to the OH group of the catalyst (bond B in Figure 3). An intramolecular H-bond in the catalyst was also observed between this oxygen and a C-H bond on the quinoline ring (bond A). From this they computed a variety of possible transition states and found that when the imine is attacked from the Si face (TS-4) the resulting transition state had the lowest possible energy (Figure 3), predicting the observed stereochemistry. In TS-4, the Boc-amide of the imine is tightly bound to the catalyst by three H-bonds (C, D and E) and both the tert-butyl and phenyl groups of the imine are placed in non-sterically demanding positions. The authors suggest that contrastingly when the nitronate attacks from the Re face (TS-5), giving the opposite enantiomer, the tert-butyl group is pointed towards the bicycle of the catalyst. This may explain the increase in energy for this transition state.
In 2008, C. Wang et al. reported the most selective organocatalytic nitro-Mannich reaction to date.\textsuperscript{36} Using thiourea 58 with two chiral diamine groups, exceptional diastereoselectivity and enantioselectivity was obtained for the reaction between N-Boc imines 41 and nitroalkanes 11 (Scheme 23). Unfortunately, despite the excellent stereoselectivity the reaction requires 5 equivalents of nitroalkane 11 to obtain good yields within the reported reaction time.

Scheme 23. Highly \textit{anti} selective thiourea catalysed nitro-Mannich reaction

In 2011, W. Wang reported the first organocatalysed nitro-Mannich reaction of ketimines.\textsuperscript{37} Using only 1 mol\% of cinchona-alkaloid derived thiourea 60, the authors were able to couple a variety of nitroalkanes to trifluoromethyl ketimines 59 in excellent yields and enantioselectivity albeit moderate diastereoselectivity (Scheme 24). Unfortunately, the scope of the reaction could not be extended beyond trifluoromethyl ketimines and when simple methyl ketimines were used no reaction was observed.
1.1.6 Miscellaneous nitro-Mannich reactions

So far this introduction has dealt exclusively with “classical” nitro-Mannich reactions. Recently however, there have been reports of less conventional reactions such as oxidative nitro-Mannich reactions and nitro-Mannich reactions of isoquinolines. This chapter will briefly examine some of these exciting new approaches to the β-nitroamine framework.

Scheme 25. Cross-dehydrogenative coupling reaction and tertiary amines and nitroalkanes

In 2005, Li et al. reported an oxidative nitro-Mannich reaction using a copper catalyst and tert-butylhydroperoxide (TBHP) as an oxidant. This so-called cross-dehydrogenative coupling (CDC) reaction was able to couple nitromethane and nitroethane with a variety of amines bearing α sp³ C-H bonds in varying yields (Scheme 25). The authors were unsure about the reaction mechanism but proposed that intermediates such as 64, 65 and 66 are most likely to be involved.
Li’s group have since reported some improvements to their procedure enabling the amount of nitroalkane to be lowered to two equivalents,\textsuperscript{39} and the use of molecular oxygen instead of the explosive tert-butylhydroperoxide.\textsuperscript{40} The group of Klussmann have performed detailed mechanistic work on both the TBHP and molecular oxygen reactions and have proposed the following mechanisms (Figure 4).\textsuperscript{41}

![Figure 4. Mechanisms for CDC reaction when using A) O\textsubscript{2} and B) TBHP as oxidants](image)

The groups of Todd,\textsuperscript{42} Liang,\textsuperscript{43} and Stephensen,\textsuperscript{44} have also reported CDC reactions using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), hypervalent iodine species PhI(OAc)\textsubscript{2} and an Ir visible light photoredox catalyst respectively. However, as yet no group have been able to develop an enantioselective CDC reaction so the utility of this reaction is still somewhat limited.

![Scheme 26. Nitro-Mannich reaction of activated isoquinolines](image)

Another non-classical reaction reported in the literature is the nitro-Mannich reaction of isoquinolines. Yadav \textit{et al.} published a three-component synthesis of nitromethyl...
derivatives of 1,2-dihydroisoquinolines. The authors were able to couple a variety of isoquinolines to nitromethane to give the desired 1,2-dihydroisoquinolines in good yield. The authors proposed the reaction proceeded with initial activation of the isoquinoline to give Zwitter ion which then underwent a nitro-Mannich reaction with the aci form of nitromethane.

1.1.7 Conjugate addition/nitro-Mannich reactions

In addition to the standard deprotonation strategy to form the reactive nitronate species of the nitro-Mannich reaction, there have also been a number of reports where a conjugate addition to a nitroalkene has led to the formation of the nitronate species which has then undergone an in situ nitro-Mannich. The first example of such a reaction came in 1978 when Walser et al. unexpectedly observed a nitro-Mannich reaction whilst investigating pharmacologically active benzodiazepines.

![Scheme 27. Unexpected reductive nitro-Mannich reaction](image)

The authors were attempting to reduce nitroalkene with sodium borohydride but instead observed an instantaneous nitro-Mannich reaction to give β-nitroamine in an 81% yield (Scheme 27). The structure was also confirmed by single crystal X-ray analysis.

![Scheme 28. First reported [3+2] cycloaddition nitro-Mannich reaction](image)

In 1985, the group of Padwa reported the [3+2] cycloadditions of chiral azomethine ylides with a variety of dipolarophiles including nitroalkene. The authors
used AgF to form the azomethine ylides from $\alpha$-cyanoaminosilanes 79, giving desired 3-nitropyrrrolidines 82 in low to moderate yields and diastereoselectivity (Scheme 28). Although, [3+2] cycloadditions often proceed in a concerted manner, the majority of [3+2] cycloadditions involving nitroalkenes have been shown to progress in a stepwise manner.\textsuperscript{48} This is due to the high electrophilicity of the $\pi$-deficient nitroalkene, and as such these [3+2] cycloadditions with azomethine ylides can be thought of as nitro-Mannich reactions.

**Scheme 29.** Enantioselective catalytic [3+2] cycloaddition nitro-Mannich reaction

Since this publication there have been a number of asymmetric [3+2] cycloaddition nitro-Mannich reactions.\textsuperscript{49} Hou has reported the broadest reaction scope using a chiral ferrocene ligand and copper catalyst.\textsuperscript{49c} Amazingly, a simple change in the electronics of the aryl groups of the phosphine of the catalyst resulted in a switch in the endo/exo selectivity allowing the authors to synthesise both isomers (Scheme 29).

**Scheme 30.** Morita-Bayliss-Hilman type nitro-Mannich reaction

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*University College London*
In 2009, a report by Xu et al. detailed the use of Takemoto’s catalyst 54 in a Morita-Baylis-Hillman (MBH) type nitro-Mannich reaction. The authors were able to react nitrostyrene 89 with a range of N-tosylated imines 90 to produce the desired β-nitroamines 91 possessing a γ-methylene (Scheme 30). Interestingly, when simple β-nitrostyrene 84a was used instead of nitroalkene 89, no reaction was observed. The authors believe this suggests that an intramolecular deprotonation is required to eliminate the catalyst from intermediate 93 and produce the product (Scheme 31).

Scheme 31. Proposed mechanism of MBH type nitro-Mannich reaction

In 2010, the group of Xu reported the enantioselective synthesis of piperidines 99 using a nitro-Michael/nitro-Mannich/cyclisation sequence. The authors utilised two organocatalysts (pyrrolidine 97 and thiourea 98) in an one-pot reaction to promote the desired reaction in moderate to good yields, excellent enantioselectivity and as single diastereomers (Scheme 32). The authors did not discuss the mechanism of the reaction nor did they disclose which if any of the intermediates are isolated after chromatography. Therefore we can only speculate as to whether nitronate 100 formed by the nitro-Michael reacts immediately or if it exists in an equilibrium with nitroalkane 101. There have been a number of reports of similar reactions since using just one organocatalyst, however these reactions proceed in a stepwise manner requiring addition of an external base after the nitro-Michael reaction. As such the nitro-Mannich reaction is activated by the standard means of deprotonation and shall not be further discussed in this section.
More recently the Anderson group have examined the addition of organometallic reagents to nitroalkenes and their subsequent nitro-Mannich reactions.\textsuperscript{53} Using Hoveyda’s (102) and Charette’s (103) catalysts for dialkyl zinc additions to nitroalkenes,\textsuperscript{54} the authors were able to form nitro-Mannich products with excellent diastereo- and enantioselectivity when reacted with \textit{N}-PMP imines 30 in the presence of trifluoroacetic acid (Scheme 33).

**Scheme 32.** An one-pot nitro-Michael/nitro-Mannich/cyclisation to piperidines

**Scheme 33.** One-pot dialkyl zinc addition/nitro-Mannich reaction of nitroalkenes
The authors observed a remarkable dependency of diastereoselectivity on solvent selection. Weak Lewis base solvents such as diethyl ether and toluene gave syn,syn nitro-Mannich products 105a whereas more coordinating solvents such as tetrahydrofuran favoured syn,anti diastereomer 105b. This was proposed to be caused by the different solubilities of Zn(O₂CCF₃)₂ formed in the reaction. In toluene and diethyl ether, the zinc (II) trifluoroacetate precipitated out of solution whereas in tetrahydrofuran the salt remained in the solution. The authors suggest that the reaction may proceed by two mechanisms, one where the zinc salt is involved in a closed transition state and another where no zinc is present and hence a mechanism via an open transition state operates. In toluene or diethyl ether there is no zinc to participate so the reaction proceeds via transition state TS-6, whilst in tetrahydrofuran the zinc acts as a chelating metal in transition state TS-7 (Figure 5).

![Figure 5. Proposed transition states leading to syn and anti nitro-Mannich products](image)

The Anderson group have also expanded this methodology by using ethyl (E)-3-nitroacrylate as the nitroalkene to form nitro-Mannich products which cyclise to give pyrrolidinones.⁵⁵
1.2 Synthetic utility of nitro-Mannich products

1.2.1 Overview

The products of the nitro-Mannich reaction, $\beta$-nitroamines, contain two nitrogens in differing oxidation states allowing for complete chemoselectivity in subsequent transformations. This synthetic versatility gives $\beta$-nitroamines great potential for their application in synthesis. This chapter will briefly discuss some of the possible transformations of $\beta$-nitroamines and showcase their potential application as key intermediates in the total synthesis of some complex natural products and pharmaceuticals, some examples of which are shown in figure 6.

![Diagram showing transformations of β-nitroamines](image)

Figure 6. Examples of the synthetic utility of $\beta$-nitroamines

1.2.2 Nitro reduction

Probably the most useful transformation of the nitro-Mannich products is the reduction of the nitro group to give vicinal diamines. In addition to the fact that the reaction is more atom economical than the other transformations shown in figure 6,
there are also a limited number of ways of synthesising 1,2-diamines efficiently.\textsuperscript{56} Vicinal diamines are important structural motifs and have many applications in a variety of natural products, pharmaceuticals and catalysis (Figure 7). As such, efficient syntheses to produce 1,2-diamines are highly desirable.

The reduction of aromatic nitro groups has been well documented in the literature and these reactions have been performed on industrial scale as they provide the most important method for the synthesis of anilines. The reduction of aliphatic nitro groups however, possesses different challenges.\textsuperscript{57} The reactions are frequently more sluggish than their aromatic counterparts and are often complicated by unwanted side-products. Despite these challenges, there are a variety of methods known to reduce aliphatic nitro compounds, including $\beta$-nitroamines which also often have a tendency to undergo retro-addition. This section will now discuss some of the previously used methods to achieve this.

The first nitro reduction of $\beta$-nitroamines was performed by Duden \textit{et al.} using stannous chloride in hydrochloric acid.\textsuperscript{10a} The reduction was performed as the product from the nitro-Mannich was too unstable. However, the yield of the reaction (26\%) was poor. Other early conditions used to reduce $\beta$-nitroamines include the use of aluminium amalgam,\textsuperscript{10b} and high pressure hydrogenation with Raney nickel.\textsuperscript{8} In recent years much milder and better yielding reactions have been developed. In 1993, Sturges’s group reported the rapid and mild reduction of $\beta$-nitroamines \textsuperscript{106}, formed via Michael addition of amines to nitroalkenes, using the single electron transfer reducing agent samarium (II) iodide (Scheme 34).\textsuperscript{58} This was the first report of a reduction of unstable $\beta$-nitroamines that could tolerate a range of substrates, giving the desired diamines in good yields. This SmI$_2$ reduction was then later utilised by the Anderson,\textsuperscript{5} and Shibasaki groups to form vicinal diamines.\textsuperscript{15,16}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure7.png}
\caption{Examples of importance of vicinal diamines}
\end{figure}
Jørgensen et al. reduced nitro-Mannich product 108 via catalytic hydrogenation with Raney nickel at atmospheric pressure over two days in good yield. These conditions are distinctly milder than those previously reported (34 bar) by Senkus and Johnson for the reduction of nitro-Mannich products in 1946.\(^8\)

Another commonly used protocol for the reduction of nitro-Mannich products uses zinc powder in an acidic media. This method was first used for \(\beta\)-nitroamines in Shibasaki’s synthesis of CP-99994, giving the desired diamine in 85% yield (Scheme 36).\(^5^9\) There have since been a variety of other nitro reductions using Zn including many in hydrochloric acid solutions such as those reported by Feng,\(^2^6\) and Anderson.\(^5^3\)

Another popular reagent for the reduction of \(\beta\)-nitroamines is nickel boride. This is typically formed \textit{in situ} from NiCl\(_2\)•6H\(_2\)O and NaBH\(_4\). Bernardi and Ricci first demonstrated its use in the reduction of \(\beta\)-nitroamines during their synthesis of HIV protease inhibitors. It has since been applied by the groups of Shibasaki,\(^2^4\) and
Takemoto (Scheme 37)\(^{\text{30}}\) to effect nitro reductions in excellent yields. Johnston et al. have also used CoCl\(_2\) in place of NiCl\(_2\) in similar reductions.\(^{\text{60}}\)

\[
\begin{align*}
\text{Ph} & \quad \text{NHBoc} & \quad \text{NO}_2 \\
1 \text{ equiv. NiCl}_2 & 6\text{H}_2\text{O} & 12 \text{ equiv. NaBH}_4 \\
\text{MeOH, 0 }^\circ\text{C, 1 h} & \quad & \text{95% yield}  \\
\text{Ph} & \quad \text{NHBoc} & \quad \text{NH}_2 \\
\end{align*}
\]

\[
\begin{array}{c}
\text{112} \\
90\% \text{ ee}
\end{array}
\]

Scheme 37. Nickel boride reduction of nitro-Mannich product

An alternative reduction protocol that has been frequently used is aluminium amalgam reductions. This method has been shown to be particular successful for sensitive substrates by the Anderson group.\(^{\text{61}}\)

\[
\begin{align*}
\text{R}^1 & \text{ Ph, Furyl, } \text{Ph} \\
\text{R}^2 & \text{ OMB, PMB, PMP, allyl, (CH}_2\text{)OTBS}
\end{align*}
\]

Scheme 38. Aluminium amalgam reduction of \(\beta\)-nitroamines

It was found that the aluminium amalgam gently reduced the nitro-Mannich products \textbf{114} to stable hydroxylamines \textbf{115}. Further reduction using LiAlH\(_4\) or Pd/C hydrogenation could then give desired diamines \textbf{116} in excellent yields (Scheme 38).

\subsection*{1.2.3 Nef reaction}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Figure8.png}
\caption{Examples of important \(\alpha\)-amino carbonyl containing compounds}
\end{figure}

The Nef reaction is the direct conversion of a nitro group to a carbonyl group.\(^{\text{62}}\) In particular, a nitro-Mannich/Nef reaction route has the potential to provide an efficient route to highly enantioselective un-natural \(\alpha\)-amino acids. In addition, the Nef
reaction of β-nitroamines could furnish α-amino ketones, which are found in several important medicines and biologically active natural products (Figure 8). The first examples of Nef reactions on β-nitroamines 117 were reported in 1998 by Mioskowski et al. using sodium nitrite and acetic acid in DMSO. Subsequent removal of the chiral auxiliary gave desired α-amino acids 119 in variable yields. Since this publication many other groups have also applied this methodology and showed a negligible loss of enantioselectivity during the transformation. There have also been reports of Nef reactions to give α-amino acids using potassium permanganate, and ozone.

Scheme 39. Nef reaction of β-nitroamines to give α-amino acids

There have been few reported Nef reactions of nitro-Mannich products to give α-amino ketones. The first was reported by Ruano and Cid et al. using potassium permanganate. The authors initially attempted the Nef reaction using sulfinyl-β-nitroamines 120 but all conditions tested failed to give the desired products. However, when converted to sulfonyl-β-nitroamines 121 the desired Nef reaction could be performed in high yields (Scheme 40).

Scheme 40. Nef reaction using KMnO₄ to give α-amino ketones

Ellman’s group have also reported a Nef reaction to give an α-amino ketone but instead using ozone. This reaction was performed to confirm the absolute stereochemistry of the nitro-Mannich product and only proceeded with a moderate yield (51%) (Scheme 41).
1.2.4 Peptide synthesis via umpolung reactivity

In 2010, the group of Johnston reported an innovative new method for the synthesis of amide and peptide bonds. The authors hypothesised that α-bromo nitroalkane could provide the correct oxidation state for a coupling with an amine to give α-amino nitroalkane. Subsequent hydrolysis with water via a Nef-like reaction could then form amide (Scheme 42). When attempting such a reaction, after 10 days a trace amount of desired product and also some de-brominated nitroalkane were observed.

From this observation it was thought that the reaction may be proceeding through an umpolung reaction with an N-bromo amine and nitronate pair, formed via bromonium transfer. The authors consequently examined the action of an electrophilic halogen source, N-iodosuccinimide (NIS), in the reaction and observed substantial amounts of desired product. After optimisation of the reaction conditions the authors were able to form a variety of different amides using this methodology. They subsequently turned their attention to nitro-Mannich products in order to synthesise a range of different peptides in moderate to good yields and crucially without any loss of stereoselectivity (Scheme 43).
1.2.5 Radical and ionic denitration

Although not the most atom efficient use of a nitro-Mannich reaction, the radical elimination of the nitro group from nitro-Mannich products has been utilised numerous times in the total synthesis of a variety of important products. Despite this poor atom economy this transformation still has a place in modern organic chemistry due to the need for highly stereoselective syntheses of amines.

Scheme 43. Aryl glycine couplings to a range of amino acids

Scheme 44. Dixon’s total synthesis of (−)-Nakodomarin A featuring a radical denitration

Radical denitration with Bu₃SnH and AIBN has been the most commonly applied form of elimination of the nitro group from β-nitroamines. There have been a series of total syntheses that have utilised this strategy,⁶⁹ some of which used the nitro-Mannich reaction to form the starting materials.⁷⁰ The most recent example of such a transformation is in Dixon’s total synthesis of Nakodomarin A.⁷⁰c–f The authors first formed 6-membered lactam 134 via a nitro-Mannich/lactamisation cascade...
reaction. Afterwards the nitro group was removed under standard conditions using Bu$_3$SnH and AIBN to form intermediate 135. With this in hand the authors could complete the synthesis of (-)-Nakodomarin A in three more steps.

\[
\begin{array}{c}
\text{NHBoc} \\
\begin{array}{c}
\text{R'} \\
\text{CO$_2$Et}
\end{array}
\end{array}
\begin{array}{c}
\rightarrow \\
3 \text{ equiv. DBU} \\
\text{CH$_2$Cl$_2$, rt, 4 h}
\end{array}
\begin{array}{c}
\text{NHBoc} \\
\begin{array}{c}
\text{R'} \\
\text{CO$_2$Et}
\end{array}
\end{array}
\]

\[92.96\% \text{ ee}\]

\[R' = \text{PhCH$_2$CH$_2$, } \text{^3} \text{Bu, Et, } ^7 \text{Hex}\]

**Scheme 45.** Ionic denitration of nitro-Mannich products

Ionic denitration requires an acidic $\beta$-hydrogen in order to eliminate the NO$_2$ group and results in the formation of a double bond. Palomo et al. have successfully performed this reaction on a variety of nitro-Mannich products 136 using DBU as base. This process represented a new entry to the synthesis of enantiopure vinylogous amino acids.
1.3 Thiourea organocatalysis

1.3.1 Overview

Lewis acids have long been regarded as a crucial element of the synthetic chemists’ toolbox and have a longstanding use as catalysts to activate electrophiles. Far-reaching research in ligand design and Lewis acid catalysis has resulted in a huge array of chiral catalysts that can selectivity control many reactions.\(^7\) However, such catalytic systems have their limitations: Firstly, several metals are known to be toxic, and as such their use in industries such as the pharmaceutical industry would ideally be avoided. Secondly, many commonly used Lewis acid metals possess strong oxophilicity or are moisture sensitive limiting their practical use. Thirdly, many metals used in catalysis, particularly rare earth metals, are very expensive limiting their use in large scale processes. Finally, there is a limited supply of many metals and their use is not sustainable long term. Organocatalysis has emerged as an alternative method over the past decade with the potential to supersede traditional metal catalysis in many areas. Thioureas have been shown to be excellent catalysts to activate electrophilic components, particular in reactions that can undergo general acid catalysis. In this sense they offer a complimentary approach to Lewis acid catalysis and the recent field of chiral Brønsted acid catalysis.\(^7\) Thioureas offer many potential advantages over Lewis acid catalysts in that they are potentially significantly cheaper than many commonly used metals, they may be less toxic than many heavy metal catalysts and their use may be more sustainable in the long term. However, there are also limitations and currently most thiourea catalysed reactions require large catalyst loadings (typically 5-10 mol%). Presumably this is due to a weak activation of the electrophiles compared to Lewis acids. There have been several reviews of thiourea organocatalysis in recent years.\(^7\) Due to the large size of the research in this field, it would be impossible to cover every development in this introduction. Therefore, this section will attempt to introduce thiourea organocatalysts through the early research which has led to their widespread use and highlight some of the key possible transformations in particular those involving additions to imines and nitroalkenes.
1.3.2 Background and early research

Although thioureas have been one of a number of organocatalysts at the forefront of asymmetric catalysis for around a decade the basis for their use was first reported much earlier. In 1984, Hine et al. showed a variety of phenols could catalyse the addition of secondary amines to glycidyl phenyl ether. They were able to show that a rigid biphenylenediol catalyst was able to promote the reaction significantly faster than standard phenols (Scheme 46). If the reaction was solely promoted by acidity then to achieve such a rate of reaction, diol 151 would be expected to be 600 times more acidic than its actual pK\textsubscript{a}. The authors proposed that the enhanced catalytic activity was the result of simultaneous donation of the two H-bonds. Later, a 1:1 solid-state structure of the catalyst and substrate gave support to this model. Then in 1990, Kelly and co-workers reported a similar catalyst capable of promoting Diels-Alder reactions.

\begin{center}
\begin{tabular}{|c|c|c|}
\hline
Catalyst & pK\textsubscript{a} & K\textsubscript{cat} \\
\hline
phenol & 9.98 & 1.0 \\
m-nitrophenol & 8.40 & 2.4 \\
p-nitrophenol & 7.15 & 2.8 \\
140 & 8.00 & 12.5 \\
\hline
\end{tabular}
\end{center}

*Scheme 46. Biphenylenediol catalysed ring-opening of epoxide*

The next advance came towards the end of the same decade when Etter et al. reported co-crystallised structures of N-N'-diarylureas with a variety of Lewis basic functional groups such as nitros, ethers, ketones and sulfoxides. Each implicated the donation of two H-bonds from the urea molecule to the Lewis base.

In 1994, Curran and co-workers reported a urea catalysed allylation of cyclic \(\alpha\)-sulfinyl radicals with allyltributylstannane (Scheme 47, A). In the following year the same authors reported a Claisen rearrangement of allyl vinyl ethers 144 also catalysed by urea 142 (Scheme 47, B).
Despite these early reports of H-bonding catalysts, researchers in the field of asymmetric catalysis failed to see the potential of such molecules as asymmetric catalysts. It wasn’t until a serendipitous discovery from the Jacobsen group was reported that the field began to flourish. Jacobsen et al. were screening a variety of ligand and metal combinations for asymmetric Strecker reactions when it was observed that the reaction using thiourea 147 as a ligand proceeded with greater enantioselectivity in the absence of a metal.\(^\text{80}\)

At low temperatures the authors were able to add cyanide into a variety of allyl protected imines 146 in good to excellent yields and enantioselectivity (Scheme 48).
This report showed three important factors which would lead to significant interest in the field of organocatalysis. Firstly, that diaryl(thio)ureas are not essential for high catalytic activity; that the ability of (thio)ureas to catalyse organic transformations via H-bond is a general phenomenon; and that (thio)ureas containing chiral substituents are capable of transferring their chirality to the products of a reaction.

The final milestone, which really accelerated the field, was Takemoto’s discovery of the relatively simple bifunctional thiourea catalyst 49 for the nitro-Michael reaction (Scheme 49).81 The authors were able to add dialkyl malonates 149 to a variety of nitroalkenes 84 in good yields and with high to excellent levels of enantiocontrol.

\[
\begin{align*}
\text{R}^1 & = \text{Ph, (MeO)}_2\text{C}_6\text{H}_4, \text{FC}_6\text{H}_4, \text{Thienyl, 'Bu} \\
\text{R}^2 & = \text{Et, 'Pr}
\end{align*}
\]

**Scheme 49.** Asymmetric nitro-Michael addition of malonates to nitroalkenes

### 1.3.3 Thiourea catalysed additions to imine electrophiles

\[
\begin{align*}
\text{R}^1 & = \text{Ph, MeOC}_6\text{H}_4, \text{Furyl, F}_2\text{C}_6\text{H}_4, \text{NCC}_6\text{H}_4, \text{XCO}_2\text{H}_4, \text{'Bu, Adamantyl, Cy} \\
\text{X} & = \text{Cl, Br}
\end{align*}
\]

**Scheme 50.** Improved conditions for asymmetric Strecker reaction with simpler catalyst

Jacobsen’s Strecker reaction was the first example of an enantioselective thiourea catalysed reaction of imines,80 and consequently it was also that group that published the majority of the early research in the field. Further to their original paper, the
authors reported an extended scope of the reaction in 2000,\(^8^2\) and a reaction of ketimines to form quaternary centres.\(^8^3\) More recently, a much simpler catalyst structure and detailed mechanistic investigation has been reported by the same group (Scheme 50).\(^8^4\) In order to minimise any exposure to toxic hydrogen cyanide, the authors used a combination of TMSCN and methanol to form HCN \textit{in-situ}. Interestingly, large differences were observed in the stereoselectivity of the reaction with different amide substituents on the catalyst. It was noted that dimethyl amide 154 gave only 14\% ee, whereas amido thiourea derivative 153 gave the desired product in 98\% ee. Intrigued by this large difference and an interest in the mechanism the authors undertook an experimental and theoretical investigation into the origin of the enantioselectivity of the reaction.\(^8^4\) The computational studies were able to calculate several possible transition states for the reaction and the lowest energies for the transition states depicted in figure 9, explaining the observed levels of enantioselectivity.

\textbf{Figure 9.} Calculated transition states for the thiourea catalysed Strecker reaction

In addition to the Strecker reaction the Jacobsen group have reported a number of other thiourea catalysed additions to imines. In 2002, the first thiourea controlled Mannich reaction was reported using silyl ketal acetal 155 and \(N\)-Boc protected imines 41 (Scheme 51).\(^8^5\) Using thiourea 156 the authors were able to form a variety of \(\beta\)-amino esters 157 in excellent yield and enantioselectivity. The Jacobsen group have also applied a similar catalyst structure in the synthesis of chiral \(\alpha\)-amino phosphonic acids.\(^8^6\)
In 2006, Dixon et al. disclosed a chiral addition of malonates $\text{158}$ into $N$-Boc and $N$-CBz imines $\text{159}$ catalysed by thiourea $\text{160}$ containing a Cinchona alkaloid skeleton. High yields and enantioselectivities were obtained for the reaction, and formation of quaternary centres with high levels of selectivity was also possible when using methyl cyclopentanone-2-carboxylate $\text{162}$ (Scheme 52). The authors were also able to de-carboxylate these Mannich products without observing racemisation. The groups of Deng, and Takemoto also reported similar reactions shortly after this publication.

Scheme 51. Thiourea catalysed Mannich reaction of $N$-Boc imines

In the same year, Deng’s group reported a thiourea catalysed asymmetric Friedel-Crafts reaction with imines. Using cinchona-alkaloid thiourea $\text{165}$ the
authors were able to add indoles 164 to N-tosyl protected imines 90 to give desired products 166 (Scheme 53).

Scheme 53. Thiourea catalysed Friedel-Crafts reaction of indoles with imines

In 2007, Takemoto’s group reported a Petasis-type reaction using 1,2-amino alcohol containing thiourea 168. The authors had hoped that by activating quinolines 166 via acylation with phenylchloroformate they would be able to promote the desired reaction as shown in TS-12. Using this activation strategy the authors were able to form desired products 169 using a variety of vinylboronic acids 167 in dichloromethane (Scheme 54). Interestingly, water and sodium bicarbonate were crucial additives required in order to obtain high enantioselectivities and good yields.

Scheme 54. Thiourea catalysed Petasis-type reaction of vinylboronic acids

Another Mannich reaction was reported in 2009 by Smith’s group using a new rationally designed thiourea organocatalyst. Inspired by their earlier research on
parallel-turn linkers in un-natural foldamers, the authors synthesised conformationally well-defined yet flexible thiourea catalyst 193.

![Chemical structure image]

**Scheme 55.** Mannich reaction catalysed by conformationally well-defined thiourea

The authors then examined the Mannich reaction with silyl enolate 192 and found the catalyst to be highly enantioselective and high yielding (Scheme 55). To confirm the catalyst’s efficiency over catalysts not bearing the intra-molecular hydrogen bonding network, a competition experiment between catalysts 170 (known to generate (S)-157) and 171 (known to generate (R)-157) was initiated. It was found that when 1 mol% of each catalyst was used, Mannich product (S)-157 was obtained in a 97% yield and with 93% ee (Scheme 56). This indicates that the intramolecular hydrogen bonding network of 170 has created a significantly more reactive catalyst for the reaction.

![Chemical structure images]

**Scheme 56.** Competition experiment for thiourea catalysed Mannich reaction
Huang and Lu’s groups reported a Mannich reaction of fluorinated malonates 172 and N-Boc imines 41. Attempts to use thioureas based on cinchona alkaloids such as those used by Dixon et al. (Scheme 52) failed to give the desired products in high enantio- and diastereoselectivity. However, the authors found that thioureas based on amino acid tryptophan such as 173 could catalyse the reaction to give desired Mannich products 274 with excellent enantioselectivity (Scheme 57).193

![Scheme 57. Asymmetric Mannich reaction of fluorinated ketoesters](image)

1.3.4 Thiourea catalysed additions to nitroalkene electrophiles

Along with Jacobsen’s early work on thiourea catalysed Strecker reactions, Takemoto’s work on the additions of malonates to nitroalkenes greatly increased the interest in the field of thiourea organocatalysis.

![Scheme 58. Expanded scope of thiourea catalysed nitro-Michael reactions](image)

Further to their initial 2003 report, the group disclosed a report two years later with an improved substrate scope as well as experimental investigations into the mechanism.
of the reaction (Scheme 58). The authors were able to show that the reaction could form quaternary centres with high enantioselectivity, albeit with variable diastereoselectivity, as well as tolerate a variety of cyclic malonates. Kinetic studies showed that the reaction was first-order in nitroalkene, malonate and catalyst. Takemoto’s group suggested a transition step similar to TS-14 where the nitroalkene H-bonds to the thiourea moiety (Figure 10). However, computational studies by Pápai et al. suggest that the mechanism involves bonding of the malonate to the thiourea, rather than the nitroalkene, as depicted in TS-15. The R enantiomer is proposed to be preferred over the S enantiomer in both mechanisms as this positions the substrates in a staggered conformation along the forming C-C bonds, thus minimising any steric interactions.

**Figure 10.** Possible transition states for thiourea catalysed nitro-Michael reaction

Since Takemoto’s group published the first thiourea catalysed addition of malonates to nitroalkenes there have been a variety of other thiourea catalysts used to perform similar reactions such as those based on binaphthene scaffolds, Cinchona alkaloids, and those bearing multiple hydrogen bonding donors.

**Scheme 59.** Thiourea catalysed Friedel-Crafts reaction of indoles with nitroalkenes
In 2005, Ricci et al. reported an asymmetric Friedel-Crafts alkylation reaction of indoles 177 with nitroalkenes 84. Using thiourea catalyst 178 the authors were able to obtain the desired products 179 in good enantioselectivity and moderate to high yields (Scheme 59).  

**Scheme 60.** Improved Friedel-Crafts reaction using a quinolinium containing thiourea

More recently, the group of Seidel have improved this reaction using a rationally designed quinolinium containing thiourea. The new catalyst greatly enhances the rate of reaction with the majority of reactions reaching completion within 24 h using only 5 mol% of catalyst 180 (Scheme 60). The increased reactivity is attributed to the intramolecular H-bond between the sulfur and quinolinium species increasing the H-bond acidity of the catalyst.

**(A) Wang’s methodology**

**(B) Ellman’s methodology**

**Scheme 61.** (thio)urea catalysed additions of thioacetic acid to nitroalkenes
In 2006, Wang et al. applied Takemoto’s catalyst 49 in the enantioselective addition of thioacetic acid to nitroalkenes 84. Although, the reaction was high yielding the enantioselectivity was only moderate (Scheme 61, A), presumably due to competitive background reactions and retro-addition. In 2009, Ellman’s group reported an improved procedure using urea catalyst 183 which resulted in significantly higher enantioselectivities albeit with lower yields and significantly longer reaction times (Scheme 61, B). The low temperature of -78 °C was required to prevent the background racemic reaction occurring.

Also in 2006, Scheidt’s group reported a direct acylation of nitroalkenes promoted by a thiourea/flouride anion combination. Using a mixture of triethylsilyl thiozolium carbinol 184, tetramethylammonium fluoride and thiourea 186 desired β-nitro ketones 187 could be formed in good yields (Scheme 62). Without the addition of the thiourea the reaction yields were approximately half of those obtained with the dual activation strategy. An asymmetric reaction was also attempted using cinchona-alkaloid derived thiourea 165 which gave β-nitro ketone 189 in a 67% yield and in 74% ee (Scheme 62). However, no catalytic variant has been reported since.
In the same year List’s group disclosed an asymmetric transfer hydrogenation of nitroalkenes.\textsuperscript{102} Using thiourea \textsuperscript{191} and Hantzsch ester \textsuperscript{190} as an NADPH mimic, the authors could efficiently reduce a variety of $\alpha$-alkyl-$\beta$-nitrostyrenes \textsuperscript{185} with high degrees of stereocontrol (Scheme 63). The authors have since extended their methodology to include $\beta$-nitroacrylates,\textsuperscript{103} and a number of similar reports have appeared, although these fail to match the results of the original procedure.\textsuperscript{104}

\begin{equation}
\begin{array}{c}
\text{R}^1 = \text{Ph, MeC}_9\text{H}_4, \text{NCC}_9\text{H}_4, \text{ClC}_9\text{H}_4, \\
\text{FC}_9\text{H}_4, \text{Naph, Furyl, }^t\text{Bu, Et} \\
\text{R}^2 = \text{Me, Et, }^t\text{Pr}
\end{array}
\end{equation}

Scheme 63. Thiourea catalysed reduction of nitroalkenes

Jørgensen \textit{et al.} reported an enantioselective hydroxylation of nitroalkenes using oxime \textsuperscript{193} as a “masked” water molecule.\textsuperscript{105} Using thiourea catalyst \textsuperscript{165} the authors were able to form a variety of $\beta$-nitro oximes \textsuperscript{194} in good yields and high enantioselectivity (Scheme 64), which could be simply reduced to give $\beta$-nitroalcohols \textsuperscript{195} or 1,2-aminoalcohols \textsuperscript{196}.
In 2009, the group of Barbas III published an anti selective asymmetric nitro-Michael reaction using thiourea 198. Using (tert-butyldimethylsilyloxy)acetaldehyde 197 as the nucleophile the authors could react a variety of nitroalkenes to form desired products 199 in good yields and with excellent stereoselectivity (Scheme 65). Using standard proline catalysis the reaction favours the syn diastereomer due to acyclic synclinal transition state TS-17 where the more stable E enamine is the reactive species. However, using catalysts with primary amines such as thiourea 198 the reaction forms the anti diastereomer as it is proposed that the Z enamine is the reactive species in transition state TS-18 (Figure 11).

In 2010, Jørgensen’s group, inspired by the use of imines as ammonia equivalents in Buchwald-Hartwig couplings, developed a thiourea catalysed aza-nitro-Michael reaction. Using thiourea 201 the authors were able to add ketimines 200 into a variety of nitroalkenes 84 with good levels of enantioselectivity and high yields. The protecting group could be easily removed from products 202 under acidic aqueous conditions to give amine hydrochloride salt 203 (Scheme 66).
Scheme 66. Thiourea catalysed aza-nitro-Michael reaction of imines

Interestingly, the authors observed an inversion of stereochemistry when using molecular sieves prompting them to hypothesise the possible involvement of water in the transition state of the reaction (Figure 12). In the absence of water the highlighted C-H bond sits in the same plane as the C=S bond resulting in blocking of the bottom face by the large tert-butyl group as shown in transition state TS-20 resulting in formation of the R enantiomer.

Figure 12. Proposed transition states for aza-nitro-Michael reaction

In the presence of water, a bridging interaction between water, the carbonyl and thiocarbonyl could give intriguing transition state TS-19, which increases rigidity in the catalyst, leading to the observed S enantiomer of 202. The authors referenced water induced conformational changes in peptide-like structures as support for their proposed transition state.109

In 2011, Shao’s group disclosed a highly enantioselective one-pot synthesis of spirocyclopentaneoxindoles 206 using thiourea 205.110 Using a combination of
oxindoles 204, nitroalkenes 84, TMSCI and then tetrabutylammonium fluoride (TBAF) the authors could form complex spirocycle products 206 containing three stereocentres in high yields and excellent stereoselectivity (Scheme 67).

Scheme 67. One-pot synthesis of spirocyclopentaneoxindoles using thiourea catalysis

The reaction proceeds via a nitro-Michael reaction to give 207, which is then turned into silyl-nitronate 208 which undergoes an intra-molecular silyl nitronate-olefin cycloaddition to form 209. Upon addition of TBAF, isoxazolidine 209 fragments to form desired spirocycle 206 (Scheme 68).

Scheme 68. Mechanism of spirocyclopentaneoxindole formation

1.3.5 Thiourea catalysed additions to other electrophiles

As well as imines and nitroalkenes, a number of reports of thiourea catalysed reactions such as additions to various Michael acceptors, 1,2 additions to carbonyls, anion recognition, kinetic resolutions and desymmetrisation reactions have been reported. Due to the large amount of research performed in this area, this section will only briefly detail some representative examples that are deemed noteworthy due
to their high levels of stereocontrol and complexity or the use of novel innovative catalysts.

\[
\begin{align*}
\text{R}^1 & = \text{Ph, MeOC}_6\text{H}_{14}, \text{F}_3\text{CC}_6\text{H}_{14}, \text{XC}_6\text{H}_{14}, \text{Cl}_2\text{C}_6\text{H}_5, \\
& \quad \text{O}_2\text{NC}_6\text{H}_{14}, \text{NCC}_6\text{H}_{14}, \text{Naph, Furyl, H, Me, CF}_3 \\
\text{R}^2 & = \text{Ph, XC}_6\text{H}_{14}, \text{Naph, Me, Et} \\
X & = \text{F, Cl, Br}
\end{align*}
\]

**Scheme 69.** Thiourea catalysed conjugate addition of \(\gamma\)-substituted butenolides

Recently, the groups of Huang, Tan and Jiang have reported a highly enantio- and diastereoselective vinylogous conjugate addition of \(\gamma\)-substituted butenolides \(210\) (Scheme 69).\(^{111}\) Using only 1 mol\% of thiourea \(212\) the authors were able to form desired products \(213\) with excellent levels of stereo- and chemoselectivity. The authors also performed some density functional theory (DFT) calculations to calculate the transition state for the enantiodetermining step. It was found that for the lowest energy transition state a crucial non-classical C-H⋯O hydrogen bond between the \(\alpha\)-H of the pyrrolium moiety and the oxazolidinone C=O bond was present (Figure 13).

**Figure 13.** Proposed transition state for conjugate addition of \(\gamma\)-substituted butenolides

In 2010, Deng and co-workers reported an asymmetric vinylogous aldol reaction of siloxy furan \(215\) using thiourea containing chiral salt \(216\) giving rise to desired products \(217\) in excellent yields and stereoselectivity (Scheme 70).\(^{112}\) The authors had recently determined the structure of chiral salt \(216\) by X-ray crystallography. They envisaged a possible catalytic cycle, whereby the Hydrogen-bonded carboxylate
could react with siloxy furan 215 to form the 2-furoxy anion and trimethylsilylester. This anion could then undergo the desired reaction under catalyst control.

\[
\begin{align*}
\text{R}^1 & = \text{Ph, MeC}_2\text{H}_4, \text{MeOC}_2\text{H}_4, \text{XC}_2\text{H}_4, \text{F}_3\text{CC}_2\text{H}_4, \text{Naph}, \text{Furyl, Thieryl, } ^6\text{Hex, Cy, } ^\beta\text{-Styrenyl} \\
X & = \text{F, Cl, Br}
\end{align*}
\]

**Scheme 70.** Asymmetric vinylogous aldol reaction of siloxy furans using a chiral salt

There have also been a number of reports detailing the use of thioureas as anion abstractors to generate highly reactive cationic intermediates.\(^{113}\) One such example was reported by Jacobsen *et al.* in 2010 detailing thiourea catalysed polycyclisations.\(^{114}\) Using thiourea 219 the authors were able to perform a bicyclisation of hydroxylactams 218 to form tetracycles 220 in good yield and with excellent enantioselectivity (Scheme 71).

**Scheme 71.** Enantioselective thiourea-catalysed cationic polycyclisation

It was proposed that there was a cation-\(\pi\) interaction between the large arene ring and the cationic \(N\)-acyliminium species giving rise to high levels of stereocontrol. This
was supported by a decrease in enantioselectivity when using smaller polyarenes which correlated strongly with the polarisability and quadropole moments of the arenes.

\[ \text{Scheme 72. } \text{Enantioselective dynamic kinetic resolution using thiourea catalysis} \]

In 2005, Berkessel’s group disclosed the first example of a thiourea-based dynamic kinetic resolution of azlactones, as a means to produce enantioenriched un-natural amino acids. Using thiourea and allyl alcohol, a range of racemic azlactones could be converted into \( N \)-benzyolamino acid allyl esters in high enantiomeric excess (Scheme 72).

\[ \text{Scheme 73. Catalytic enantioselective desymmetrisation of meso-diamines} \]

A final use of thiourea catalysts has been in desymmetrisation reactions. Seidel et al. reported the use of thiourea in the desymmetrisation of meso-diamines (Scheme 73). When combined with 4-dimethylaminopyridine, thiourea and benzoic anhydride form a chiral ion pair which can control the enantiospecificity of the subsequent amide formation. The same strategy has also been applied to the kinetic resolution of amines.
1.4 Proposed research

1.4.1 Overview and limitations of the nitro-Mannich reaction

As has been shown in the previous sections, the nitro-Mannich reaction is a powerful carbon-carbon bond forming reaction. The products obtained from the reaction are also particularly useful as they contain two nitrogen groups in distinct oxidation states allowing for complete chemoselectivity in subsequent reactions. However, despite the advances observed in the chemistry of the nitro-Mannich reaction over the past thirteen years, some problems still exist (Scheme 74, A).

- The scope of the reaction with respect to the nitroalkane substrate has still not been fully explored with the majority of reports only examining common commercially available nitroalkanes such as nitromethane, nitroethane and nitropropane.
- Nitroalkanes are often used in a large excess (typically 5 to 10 equivalents) or long reaction times are required due to slow rates of reaction.
- Formation of the reactive nitronate species requires either an extra synthetic step, to form a more stable nitronate as in the case of silyl-nitronates; the addition of an external base to deprotonate the nitroalkane, which reduces the atom efficiency of the reaction; or the use of a much more complex bifunctional catalyst containing basic and acidic functionalities, which are often much more expensive to buy or synthesise.
- The majority of current syntheses use N-Boc protected imines which are inherently moisture sensitive, often requiring the addition of molecular sieves.
- The nitro-Mannich reaction has limited reactivity with ketimines rendering it difficult to produce products possessing a quaternary centre.

1.4.2 Chosen strategy

We hoped to overcome some of, if not all of these problems by applying a reductive strategy, whereby addition of a hydride nucleophile to a nitroalkene should form the reactive nitronate species which can then undergo an in situ nitro-Mannich reaction with an imine (Scheme 74, B).
Using such a strategy would enable the use of more complex nitroalkene starting materials, many of which are commercially available or can be readily accessed via an Henry condensation reaction. The synthesis of complex nitroalkanes, required for the standard nitro-Mannich reaction, would most likely originate from the corresponding nitroalkene. Hence the one-pot reductive strategy is more a more efficient route to \( \beta \)-nitroamines. In addition, such a strategy has the potential to build three contiguous stereocentres enabling rapid formation of complex molecular architectures. Forming the reactive nitronate species via addition of a hydride nucleophile rather than via deprotonation may also result in a significantly faster rate of reaction and therefore require less equivalents of the nitro-partner than in “standard” procedures. Such a rapid formation of the nitronate may also lead to better reactivity with ketimines.

### 1.4.3 Precedent for a racemic reductive nitro-Mannich reaction

There is some literature precedent for a racemic reductive nitro-Mannich reaction, as was detailed in section 1.1.7, scheme 27. An unexpected intramolecular nitro-Mannich reaction has been observed previously upon addition of sodium borohydride to a nitroalkene compound containing an imine.\(^{46}\)
Additionally, the Anderson group have recently reported a conjugate addition/nitro-Mannich reaction. In these systems the reactive nitronate species is accessed via addition of dialkyl zinc, in a similar fashion to our proposed hydride addition, before an \textit{in situ} nitro-Mannich reaction with an imine ensues (section 1.1.7, Scheme 33). Both of these reactions are summarised in scheme 75.

\begin{center}
\begin{tikzpicture}
\node[draw,rectangle] (a) {\textbf{a) Unexpected reductive nitro-Mannich reaction}};
\node[draw,rectangle, below=of a] (b) {\textbf{b) Conjugate addition/nitro-Mannich reaction}};
\node[draw,rectangle, below=of b] (c) {\textbf{Scheme 75. Literature precedent for a general reductive nitro-Mannich reaction}};
\end{tikzpicture}
\end{center}

\begin{center}
\begin{tikzpicture}
\node[draw,rectangle] (a) {R'\text{CH} \equiv \text{NO}_2 \rightarrow \text{HNO}_2 \rightarrow \text{N}^+\text{OMB}};
\node[draw,rectangle, below=of a] (b) {\text{OMB} \rightarrow \text{R}^1\text{CH} \equiv \text{NO}_2 \rightarrow \text{HNO}_2 \rightarrow \text{N}^+\text{OMB}};
\node[draw,rectangle, below=of b] (c) {\textbf{Scheme 76. Previous work on the reductive nitro-Mannich reaction}};
\end{tikzpicture}
\end{center}

Preliminary work in the Anderson group by G. Stepney began to examine the potential of a general reductive nitro-Mannich reaction. It was found that by using a reductant with a precise hydride stoichiometry, such as \textit{Superhydride}^{TM} (lithium triethylborohydride), a selective conjugate reduction of nitroalkenes \textbf{84} could be performed. Subsequent cooling to \(-78\,^{\circ}\text{C}\) and addition of \textit{ortho}-methoxybenzyl (OMB) imine \textbf{230} followed by acetic acid formed desired \(\beta\)-nitroamines \textbf{231}.

However, the reaction was only successful when using aliphatic nitroamines. No reactivity was observed with nitrostyrenes and the scope of the reaction with respect to different imines was never fully explored (Scheme 76).
1.4.4 Precedent for an asymmetric reductive nitro-Mannich reaction

Further to this there are several reports that suggested potential for an asymmetric variant of a reductive nitro-Mannich reaction. One such method would be to use thiourea organocatalysis which has been previously shown to catalyse both reductions of nitroalkenes (see section 1.3.4, Scheme 63) and nitro-Mannich reactions (section 1.1.5).

![Scheme 77. Literature precedent for an asymmetric reductive nitro-Mannich reaction](image)

Given the similarities of the catalysts it is reasonable to assume that a reaction performing both transformations should be possible. However, there may be some compatibility issues with regards to the reduction which may favour reduction of the imine over the nitroalkene.

![Scheme 78. Copper hydride asymmetric reduction of nitroalkenes](image)

If such a strategy was unsuccessful, it may also be possible to perform the reaction using copper hydride chemistry. Carreira et al. have reported the asymmetric reduction of nitroalkenes 185 using chiral phosphine ligand 233 and a mixture of...
phenylsilane and polymethylhydrosiloxane (PMHS) as the hydride source (Scheme 78). The authors later reported two improved procedures, one using an alternative more air stable copper source, the second allowing reduction of an isomeric mixture of nitroalkenes. Presumably, such a reaction would form a silyl nitronate species. Given that the Anderson and Jørgensen groups have both reported copper catalysed nitro-Mannich reactions of silyl nitronates, combining these two methodologies seems plausible (Scheme 79). In addition to this, for the other members of the nitro-Mannich reaction family; enantioselective reductive aldol, and Mannich reactions have been previously reported. A racemic reductive Henry reaction has also been disclosed using copper hydride.

![Scheme 79. Proposed copper catalysed reductive nitro-Mannich reaction](image-url)
Chapter 2. Results and discussion
2.1 The racemic reductive nitro-Mannich reaction

2.1.1 Initial investigations

As was stated in section 1.4.3, a previous member of the group had conducted investigations into a racemic reductive nitro-Mannich.\(^{118}\) It was discovered that using Superhydride\(^\text{TM}\) as a reductant followed by addition of an \(N\)-OMB imine and acetic acid at -78 °C would form the desired products. However, the reaction was only successful for aliphatic nitroalkenes with no conversion to the desired product observed when using \(\beta\)-nitrostyrene. Consequently, initial investigations were aimed at solving this problem. The previous researcher, G. Stepney, had performed some additional experiments aiming to identify the cause of the intolerance of nitrostyrenes. Scheme 80 shows the reactions using cyclohexyl nitroalkene 84b (A) and \(\beta\)-nitrostyrene 84a (B). Full reduction of the nitrostyrene occurred suggesting that the nitro-Mannich reaction was unable to proceed.

\[\text{Scheme 80: Comparing aliphatic and aromatic nitroalkenes under reaction conditions}\]

Subsequently, G. Stepney examined the ability of nitroalkane 234 to undergo a standard nitro-Mannich reaction by deprotonation with \(^{6}\)BuLi. This was successful, achieving greater than 90% conversion to desired \(\beta\)-nitroamine 231aa with a 95:5 diastereomeric ratio (Scheme 81).
Paul J. Koovits

Scheme 81. Standard deprotonation nitro-Mannich reaction of nitroalkane 234

The success of this reaction suggested that the presence of triethylborane may be responsible for the lack of reactivity of nitrostyrene 84a in the reductive nitro-Mannich reaction. However, further experiments performed by G. Stepney proved inconclusive as it was found that allyl protected imine 146a could promote the desired reductive nitro-Mannich reaction albeit with a lower yield than via a standard deprotonation strategy (Scheme 82).

A)

Scheme 82. Comparing reductive and deprotonation strategy for n-allyl imine 146a

These experiments pointed to there being a combination of factors preventing a successful reaction occurring when using N-OMB imine 230a with nitroalkene 84a.

In addition to the work on the reductive nitro-Mannich reaction other recent work in the Anderson group has examined a conjugate addition/nitro-Mannich reaction using diethyl zinc (see section 1.1.7, Scheme 33) which used N-PMP imines 30.
This reaction was successful when using nitrostyrenes, although the nitronate formed from such a reaction would be different to the nitronate arising from hydride addition, this seemed like a good place to start our new investigations (Scheme 83). It should be noted that trifluoroacetic acid was used to activate the less basic N-PMP imine (compared to the use of acetic acid with more basic N-OMB imine 230).

With this knowledge in hand, the reductive nitro-Mannich reaction was first performed on β-nitrostyrene 84a using N-PMP protected imine 30a. Pleasingly the reaction proceeded to give desired β-nitroamine 237aa in high diastereoselectivity (dr - 95:5) and quantitative conversion (Scheme 84). Although this was a pleasing result it did not help to explain the poor reactivity of N-OMB imine 230a. To further probe this reaction and explain why the reaction with N-OMB imine 230a and β-nitrostyrene 84a did not work more experiments were performed. Surprisingly, the reaction between β-nitrostyrene 84a, N-OMB protected imine 230a and trifluoroacetic acid was successful (Scheme 85).
Interestingly, it was observed that the resultant nitronate \(238a\) from the reduction of \(84a\) with Superhydride™ was insoluble in the reaction solvent. It could even be isolated as a white solid. However, when TFA was added to this heterogeneous mixture the nitronate species dissolves, but with acetic acid the precipitate remains. The analogous aliphatic nitronate \(238b\) was much more soluble in the reaction solvent and the reaction mixtures became completely homogenous on addition of TFA or acetic acid (Figure 14).

![Figure 14. Solubilities of nitronates upon addition of acid](image)

A final experiment using aliphatic nitroalkene \(84b\) and \(N\)-PMP imine \(30a\) with acetic acid gave the desired product with 50% conversion as a single diastereomer (Scheme 86).

The difference in conversion between \(N\)-PMP imine \(30a\) and \(N\)-OMB imine \(230a\) may be due to the reduced basicity of the \(N\)-PMP imine \(30a\) slowing the rate of protonation with AcOH. In summation, the evidence described above seems to suggest that in order for the reductive nitro-Mannich reaction to proceed with good
conversion, the nitrate must dissolve upon addition of an acid. Trifluoroacetic acid probably works well as not only is it strongly acidic (pKₐ = -1) but the trifluoro group helps to solubilise the precipitates. The choice of imine is also evidently important as when using N-allyl imine 146a some desired nitro-Mannich product was observed even when using acetic acid (Scheme 82). It is possible that the acid first protonates the imine and it is the solubilising effect of this protonated iminium species on the nitronate that is crucial. This could again explain the crucial role of trifluoroacetic acid as when protonating an imine this would form an iminium species with a highly solubilising trifluoroacetate counter ion.

![Acidic conditions](image1)

**Scheme 87.** Degradation of nitro-Mannich products via retro-addition

As with many nitro-Mannich reactions the products were unstable to purification by standard chromatographic methods (silica, neutral and basic alumina) and also only bench stable for a short while, with retro-addition products observed after approximately 24 hours. This reverse reaction could be acid promoted as well as occurring under neutral or basic conditions (Scheme 87). Theoretically, loss of diastereoselectivity could also be observed under strongly basic conditions due to epimerisation. In order to prevent the retro-addition and isolate the desired nitro-Mannich products, additional derivatisation of the amino functionality was required. Previous work in the Anderson group has used various reduction conditions to form 1,2-diamines, however these are also often unstable and require further derivatisation to make bench stable. A protection of the β-nitroamine would be a more preferable strategy. Fortunately, G. Stepney was able to show that N-OMB β-nitroamines 231 could be protected as trifluoroacetamides 232 using trifluoroacetic anhydride and Hunig’s base (Scheme 88). Other standard nitrogen protecting
group strategies such as employing Boc, tosyl or acetyl groups failed to form the desired products.\textsuperscript{125}

\begin{equation}
\begin{align*}
\text{Cy} & \quad \text{NO}_2 \\
\text{HN} & \quad \text{ OMIB} \\
\text{Cy} & \quad \text{Ph} \\
\text{NO}_2 & \quad \text{OMIB} \\
\end{align*}
\end{equation}

\begin{equation}
\begin{align*}
\text{F}_3\text{C} & \quad \text{N} \\
\text{OMIB} & \quad \text{Ph} \\
\text{Cy} & \quad \text{Ph} \\
\text{NO}_2 & \quad \text{Ph} \\
\end{align*}
\end{equation}

\textbf{Scheme 88.} Trifluoroacetate protection of N-OMIB nitro-Mannich product

Pleasingly, a similar protection could be performed on N-PMP $\beta$-nitroamine \textbf{237aa} giving trifluoroacetamide \textbf{239aa} in an 82\% yield in high diastereomeric purity (Scheme 89). Using only 2.5 equivalents of anhydride and base did not lead to full conversion to the desired trifluoroacetamide and some retro-addition was observed. However, a large excess (5 equivalents) of anhydride and base allowed the formation of the desired trifluoroacetamide before retro-addition could take place. Pyridine was used instead of Hunig’s base to avoid formation of an unexpected by-product that had been observed during previous work.\textsuperscript{118}

\begin{equation}
\begin{align*}
\text{Ph} & \quad \text{NO}_2 \\
\text{HN} & \quad \text{ PMP} \\
\text{Ph} & \quad \text{NO}_2 \\
\text{Ph} & \quad \text{PMP} \\
\end{align*}
\end{equation}

\begin{equation}
\begin{align*}
\text{F}_3\text{C} & \quad \text{N} \\
\text{PMP} & \quad \text{Ph} \\
\text{Ph} & \quad \text{PMP} \\
\text{NO}_2 & \quad \text{Ph} \\
\end{align*}
\end{equation}

\textbf{Scheme 89.} Trifluoroacetate protection of N-PMP nitro-Mannich products

The conditions for the reductive nitro-Mannich reaction were then optimised (Table 1). It was discovered that the amount of imine could be reduced to 1.1 equivalents without having a detrimental effect on the reaction conversion and this also slightly increased the diastereoselectivity (Table 1, entry 2).
Table 1. Optimisation of reductive nitro-Mannich reaction with N-PMP-imines

<table>
<thead>
<tr>
<th>Entry</th>
<th>N° equiv. imine</th>
<th>Acid (N° equiv.)</th>
<th>Solvent</th>
<th>Reaction temp. and time</th>
<th>% Conv.</th>
<th>dr²</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.0</td>
<td>TFA (3.5)</td>
<td>THF</td>
<td>-78 °C 1 h, rt 1 h</td>
<td>&gt;95</td>
<td>95:5</td>
</tr>
<tr>
<td>2</td>
<td>1.1</td>
<td>TFA (2.5)</td>
<td>THF</td>
<td>-78 °C 1 h, rt 1 h</td>
<td>&gt;95</td>
<td>&gt;95:5</td>
</tr>
<tr>
<td>3</td>
<td>1.1</td>
<td>TFA (2.5)</td>
<td>DCM</td>
<td>-78 °C 1 h, rt 1 h</td>
<td>&gt;95</td>
<td>&gt;95:5</td>
</tr>
<tr>
<td>4</td>
<td>1.1</td>
<td>TFA (2.5)</td>
<td>Et₂O</td>
<td>-78 °C 1 h, rt 1 h</td>
<td>&gt;95</td>
<td>&gt;95:5</td>
</tr>
<tr>
<td>5</td>
<td>1.1</td>
<td>TFA (2.0)</td>
<td>THF</td>
<td>-78 °C 1 h, rt 1 h</td>
<td>&gt;95</td>
<td>90:10</td>
</tr>
<tr>
<td>6</td>
<td>1.1</td>
<td>TFA (1.0)</td>
<td>THF</td>
<td>-78 °C 1 h, rt 1 h</td>
<td>80</td>
<td>90:10</td>
</tr>
<tr>
<td>7</td>
<td>1.1</td>
<td>AcOH (2.5)</td>
<td>THF</td>
<td>-78 °C 1 h, rt 1 h</td>
<td>&lt;5</td>
<td>n/a</td>
</tr>
<tr>
<td>8</td>
<td>1.1</td>
<td>TFA (2.5)</td>
<td>THF</td>
<td>-78 °C 1 h, rt 5 min</td>
<td>&gt;95</td>
<td>&gt;95:5</td>
</tr>
</tbody>
</table>

¹ % Conv. to 124a calculated from ¹H NMR. ² dr of crude 124a calculated from ¹H NMR.

Varying the solvent had no significant effect on the reaction. Altering the equivalents of acid had a slightly negative effect on the reaction (Table 1, entries 5-6) and the use of acetic acid did not effectively promote the reaction. It was found that the reaction was complete after stirring for 5 min at room temperature, therefore these conditions were used in further experiments (Table 1, entry 8).

2.1.2 Scope of reductive nitro-Mannich reaction

With the reaction optimised to an acceptable standard the scope of the reaction with respect to the nitroalkene was ready to be tested. A variety of nitroalkenes were then synthesised using three different methods. Nitroalkenes 84a-j could be synthesised using any of the three methods, and as such the method used was chosen based on their state at room temperature and pressure. Solids were typically formed using method A as the product nitroalkene precipitated upon addition to 8 M HCl, allowing simple isolation of the desired nitroalkene. Whereas, nitroalkenes which existed as
oils were prepared using method B which typically gave greater yields compared to method A.

\[ \text{Method A: } \quad \text{R}^1\text{C}=\text{O} + \text{MeNO}_2 \xrightarrow{(i) 1 \text{ M NaOH, MeOH}} \text{R}^1\text{C}=\text{HO}_2 \xrightarrow{(ii) 8 \text{ M HCl, 1 h}} \]

\[ \text{Method B: } \quad \text{R}^1\text{C}=\text{O} + \text{MeNO}_2 \xrightarrow{(i) \text{Et}_3\text{N}} \text{R}^1\text{C}=\text{HO}_2 \]

\[ \text{Method C: } \quad \text{R}^1\text{C}=\text{O} + \text{MeNO}_2 \xrightarrow{\text{NH}_2\text{OAc, reflux}} \]

Pyridyl nitroalkene 84k could only be formed using method B albeit in moderate yield (40%). Pyridyl nitroalkene 84k had a tendency to degrade at room temperature, presumably due to polymerisation, but could be stored at -20 °C for several weeks and re-purified by rapid column chromatography if required. The unprotected N-H Pyrrole nitroalkene 84l could not be formed under any of the conditions tested and instead formed a black tar, presumably due to polymerisation. As such, N-Me pyrrole nitroalkene 84m was synthesised using method C. Methods A and B produced little to no product for this reaction, the reasons for this failure are unclear but it is plausible that the aldehyde is too electron rich to undergo the initial Henry reaction. N-tosylated pyrrole nitroalkene 84n was synthesised using method B without any difficulties.

\[ \text{Scheme 90. Synthesis of nitroalkenes} \]
### Table 2. Reaction scope with respect to nitroalkenes

<table>
<thead>
<tr>
<th>Entry</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Nitroalkene</th>
<th>Yield&lt;sup&gt;a&lt;/sup&gt;</th>
<th>dr&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Final product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Phenyl</td>
<td>84a</td>
<td>82</td>
<td>&gt;95:5</td>
<td>239aa</td>
</tr>
<tr>
<td>2</td>
<td>Cyclohexyl</td>
<td>84b</td>
<td>82</td>
<td>90:10</td>
<td>239ba</td>
</tr>
<tr>
<td>3</td>
<td>&quot;Pentyl</td>
<td>84c</td>
<td>78</td>
<td>95:5</td>
<td>239ca</td>
</tr>
<tr>
<td>4</td>
<td>2-Furyl</td>
<td>84d</td>
<td>79</td>
<td>&gt;95:5</td>
<td>239da</td>
</tr>
<tr>
<td>4</td>
<td>2-Tolyl</td>
<td>84e</td>
<td>72</td>
<td>95:5</td>
<td>239ea</td>
</tr>
<tr>
<td>5</td>
<td>4-Tolyl</td>
<td>84f</td>
<td>75</td>
<td>&gt;95:5</td>
<td>239fa</td>
</tr>
<tr>
<td>6</td>
<td>2-MeO-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>84g</td>
<td>79</td>
<td>95:5</td>
<td>239ga</td>
</tr>
<tr>
<td>7</td>
<td>4-MeO-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>84h</td>
<td>86</td>
<td>&gt;95:5</td>
<td>239ha</td>
</tr>
<tr>
<td>8</td>
<td>2- F&lt;sub&gt;3&lt;/sub&gt;C-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>84i</td>
<td>79</td>
<td>&gt;95:5</td>
<td>239ia</td>
</tr>
</tbody>
</table>

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Paul J. Koovits

University College London
With a large number of nitroalkenes now in hand the scope of the reaction was examined (Table 2). The reaction worked well with aliphatic nitroalkenes giving excellent yields and diastereoselectivities (Table 2, entries 2-3). The use of electron rich and electron deficient aromatics had no major effects on the reaction (Table 2, entries 4-9) and the nitro-Mannich reaction also proceeded well using N-heterocycles (Table 2, entry 10). When employing N-methyl-pyrrole nitroalkene 84m, although the desired nitro-Mannich product was formed, trifluoroacetylation resulted in an additional electrophilic addition of a trifluoroacetyl group at the 2-position of the pyrrole ring to give 240ma (Table 2, entry 11). Attempts to prevent this formation by using less equivalents of trifluoroacetic anhydride resulted in a mixture of products. However, using N-tosylated pyrrole 84n allowed the formation of the desired product in good yield without any Friedel-Crafts acylation product forming (Table 2, entry 12). Unlike the unprotected β-nitroamines 237, all of the trifluoroacetylated products 239 were stable for several months at room temperature apart from 2-pyridyl product 239k which interestingly changed from a yellow to black oil when left to stand for several days. Examination of the 1H NMR showed epimerisation had occurred at the α-position to the nitro group, and a new dr of 55:45 was observed in favour of the syn isomer. No retro-nitro-Mannich products were observed. This is interesting as epimerisation of trifluoroacetylated products 239 has not been observed before. Although based on pKₐ values pyridine should not readily
deprotonate a nitroalkane (~5 vs. ~10), the epimerisation may be facilitated by an intramolecular deprotonation of the α-nitro proton by the pyridine nitrogen in the 2-position (Figure 15). Such a deprotonation may be significantly more rapid than an intermolecular deprotonation.

**Figure 15.** Possible epimerisation mechanism

With the scope of the reaction with respect to nitroalkenes examined, attention was turned towards varying the imine substituents. However, initial investigations with different imines proved problematic (Table 3).

**Table 3.** Reductive nitro-Mannich reaction with different imines

<table>
<thead>
<tr>
<th>Entry</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Imine</th>
<th>% Conv.&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Crude dr&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Phenyl</td>
<td>30a</td>
<td>&gt;95</td>
<td>&gt;95:5</td>
<td>237aa</td>
</tr>
<tr>
<td>2</td>
<td>2-Furyl</td>
<td>30b</td>
<td>&gt;95</td>
<td>65:35</td>
<td>237ab</td>
</tr>
<tr>
<td>3</td>
<td>4-MeO-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>30e</td>
<td>&gt;95</td>
<td>85:15</td>
<td>237ae</td>
</tr>
</tbody>
</table>

<sup>a</sup> % Conv. to 237 calculated from <sup>1</sup>H NMR. <sup>b</sup> dr of crude 237 calculated from <sup>1</sup>H NMR.

Imines substituted with electron-rich aromatics did not undergo the reaction with the same high levels of diastereoselectivity as the standard phenyl substituted imine 30a. Imine 30b, possessing a furyl substituent, was fully converted to desired product.
237ab but with low diastereoselectivity (65:35 \textit{dr}, entry 2). The \textit{para}-methoxyphenyl substituted product 237ae was produced with greater selectivity (85:15 \textit{dr}, entry 3) but this was still lower than previous examples.

Table 4. Optimisation with an electron rich imine

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid (N° equiv.)</th>
<th>Solvent</th>
<th>Reaction temp. and time</th>
<th>% Conv. \textsuperscript{b}</th>
<th>\textit{dr} \textsuperscript{c}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TFA (2.5)</td>
<td>THF</td>
<td>-78 °C 1 h</td>
<td>&gt;95</td>
<td>65:35</td>
</tr>
<tr>
<td>2</td>
<td>TFA (2.5)</td>
<td>THF</td>
<td>-100 °C 1 h</td>
<td>&gt;95</td>
<td>65:35</td>
</tr>
<tr>
<td>3</td>
<td>TFA (1.2)</td>
<td>THF</td>
<td>-78 °C 1 h</td>
<td>&gt;95</td>
<td>75:25</td>
</tr>
<tr>
<td>4</td>
<td>AcOH (1.2)</td>
<td>THF</td>
<td>-78 °C 1 h</td>
<td>&lt;5</td>
<td>n/a</td>
</tr>
<tr>
<td>5</td>
<td>AcOH (1.2)</td>
<td>THF</td>
<td>-78 °C 1 h, rt 1 h</td>
<td>&lt;5</td>
<td>n/a</td>
</tr>
<tr>
<td>6</td>
<td>BrCH\textsubscript{2}CO\textsubscript{2}H (1.2)</td>
<td>THF</td>
<td>-78 °C 1 h</td>
<td>40</td>
<td>65:35</td>
</tr>
<tr>
<td>7</td>
<td>BrCH\textsubscript{2}CO\textsubscript{2}H (1.2)</td>
<td>THF</td>
<td>-78 °C 1 h, rt 1 h</td>
<td>80</td>
<td>70:30</td>
</tr>
<tr>
<td>8</td>
<td>Cl\textsubscript{2}CHCO\textsubscript{2}H (1.2)</td>
<td>THF</td>
<td>-78 °C 1 h</td>
<td>&gt;95</td>
<td>80:20</td>
</tr>
<tr>
<td>9</td>
<td>Cl\textsubscript{3}C\textsubscript{2}O\textsubscript{2}H (1.2)</td>
<td>THF</td>
<td>-78 °C 1 h</td>
<td>&gt;95</td>
<td>80:20</td>
</tr>
<tr>
<td>10</td>
<td>TFA\textsuperscript{a} (1.2)</td>
<td>THF</td>
<td>-78 °C 1 h</td>
<td>&gt;95</td>
<td>80:20</td>
</tr>
<tr>
<td>11</td>
<td>Me\textsubscript{3}SO\textsubscript{3}H (1.2)</td>
<td>THF</td>
<td>-78 °C 1 h</td>
<td>50</td>
<td>80:20</td>
</tr>
<tr>
<td>12</td>
<td>TfOH (1.2)</td>
<td>THF</td>
<td>-78 °C 1 h</td>
<td>&gt;95</td>
<td>80:20</td>
</tr>
<tr>
<td>13</td>
<td>TfOH (1.2)</td>
<td>CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>-78 °C 1 h</td>
<td>&gt;95</td>
<td>80:20</td>
</tr>
<tr>
<td>14</td>
<td>TFA\textsuperscript{a} (1.2)</td>
<td>CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>-78 °C 1 h</td>
<td>&gt;95</td>
<td>90:10</td>
</tr>
<tr>
<td>15</td>
<td>TFA\textsuperscript{a} (1.2)</td>
<td>Et\textsubscript{2}O</td>
<td>-78 °C 1 h</td>
<td>&gt;95</td>
<td>65:35</td>
</tr>
<tr>
<td>16</td>
<td>TFA\textsuperscript{a} (1.2)</td>
<td>Toluene</td>
<td>-78 °C 1 h</td>
<td>&gt;95</td>
<td>85:15</td>
</tr>
</tbody>
</table>

\textsuperscript{a} TFA was added to rxn. as a neat solution (normally added in 1 mL solvent). \textsuperscript{b} \% Conv. to 237 calculated from \textsuperscript{1}H NMR. \textsuperscript{c} \textit{dr} of crude 237 calculated from \textsuperscript{1}H NMR.

It was hoped that this poor selectivity could be improved upon by further reducing the temperature or by using a weaker acid. A range of different conditions to attempt to optimise the reaction using electron rich imines were then investigated, as shown in table 4. Reducing the temperature to -100 °C failed to have any effect on the reaction.
Reducing the equivalents of acid to 1.2 had a slightly positive outcome on the diastereoselectivity of the reaction (1.2 equivalents were used so as to also protonate the excess imine and the remaining Superhydride\textsuperscript{TM} in the reaction) as can be seen in Table 4, entry 3. Various acids were tested in the reaction with pK\textsubscript{a} values varying from 4.76 to -14. Acetic acid (pK\textsubscript{a} = 4.76) and bromoacetic acid (pK\textsubscript{a} = 2.86) failed to promote the reaction at -78 °C. Acetic acid also failed to promote the reaction after 1 h at room temperature whereas bromoacetic acid caused some reaction at room temperature but could not achieve an improvement in diastereoselectivity. Dichloroacetic acid (pK\textsubscript{a} = 1.29), and trichloroacetic acid (pK\textsubscript{a} = 0.65) were able to promote the reaction at -78 °C and trichloroacetic acid was able to give a slightly improved diastereoselectivity (Table 4, entry 9). This diastereoselectivity could also be achieved using TFA (pK\textsubscript{a} = -0.25) as a neat solution (Table 4, entry 10). Presumably this is because a smaller volume of solution is charged to the reaction and this causes less of a temperature increase to the reaction. Charging the acid neat was more difficult with trichloroacetic acid as it is quite a sticky solid at room temperature. Methanesulfonic acid (pK\textsubscript{a} = -2.6) also gave a small improvement to the selectivity but was unable to promote the reaction sufficiently to obtain more than a moderate conversion to β-nitroamine 237\textsuperscript{ab}. Triflic acid (pK\textsubscript{a} = -14) gave the best diastereoselectivity (Table 4, entry 12) so this acid along with trifluoroacetic acid were used in an additional solvent screen. In dichloromethane the \( dr \) was greatly improved when using trifluoroacetic acid (Table 4, entry 14) but not when using triflic acid (Table 4, entry 13). The reaction in diethyl ether was poorly diastereoselective (Table 4, entry 15) but in toluene the reaction was also reasonably selective (Table 4, entry 16). The reaction seems to be best in non-coordinating solvents such as dichloromethane and toluene. It is possible that tetrahydrofuran and diethyl ether interfere with the transition state resulting in a less selective reaction.

With new optimised conditions for electron rich imines in hand, the reaction and the scope with respect to a variety of imines could be investigated. A number of imines were synthesised from their corresponding aldehydes using basic alumina as a desiccant (Scheme 91). All of these imines, apart from alkyl chain imines 30i-j, were crystalline and could be stored at -18 °C indefinitely. Cyclohexyl imine 30j would solidify in the freezer at -18 °C and as such could be stored for several months.
without significant degradation. The "pentyl imine 30i rapidly decomposed at room temperature, presumably by enamine formation and subsequent oligomerisation, and consequently was used immediately and had to be prepared at -78 °C.

Scheme 91. Synthesis of imines

With a range of imines in hand the scope of the reaction was then examined (Table 5). The reaction worked well for both electron rich and electron deficient aryl imines (Table 5, entries 1, 3, 4 and 6). For more sterically demanding aryl imines with ortho substituents (Table 5, entries 2, 5, 7) the diastereoselectivity was slightly reduced but still very respectable, and these diastereomers could often be separated by column chromatography resulting in diastereomerically pure products (Table 5, entry 7). The reaction also worked well with straight chain alkyl imine 30i (Table 5, entry 7) but was poorly diastereoselective with the bulkier cyclohexyl imine 30j (Table 5, entry 9). The product from imine 30j did not undergo trifluoroacetamide protection even with a 5 times excess of trifluoroacetic anhydride and pyridine. Fortunately, it was stable enough to purify by chromatography to give 237aj as a single diastereomer in a 58% yield. Despite the reactions being performed using dichloromethane as a solvent there was still some tetrahydrofuran present in the reaction as the Superhydride™ is only available as a 1 M solution in tetrahydrofuran.
Table 5. Reaction scope of reductive nitro-Mannich reaction with respect to imine

<table>
<thead>
<tr>
<th>Entry</th>
<th>$R^2$</th>
<th>Imine</th>
<th>Yield</th>
<th>$dr$</th>
<th>Final product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2-Furyl</td>
<td>30b</td>
<td>83</td>
<td>90:10</td>
<td>239ab</td>
</tr>
<tr>
<td>2</td>
<td>2-MeO-C$_6$H$_4$</td>
<td>30c</td>
<td>87</td>
<td>90:10</td>
<td>239ac</td>
</tr>
<tr>
<td>3</td>
<td>3-MeO-C$_6$H$_4$</td>
<td>30d</td>
<td>86</td>
<td>&gt;95:5</td>
<td>239ad</td>
</tr>
<tr>
<td>4</td>
<td>4-MeO-C$_6$H$_4$</td>
<td>30e</td>
<td>80</td>
<td>&gt;95:5</td>
<td>239ae</td>
</tr>
<tr>
<td>5</td>
<td>2- F$_3$C-C$_6$H$_4$</td>
<td>30f</td>
<td>76</td>
<td>95:5</td>
<td>239af</td>
</tr>
<tr>
<td>6</td>
<td>4-F$_3$C-C$_6$H$_4$</td>
<td>30g</td>
<td>78</td>
<td>&gt;95:5</td>
<td>239ag</td>
</tr>
<tr>
<td>7</td>
<td>2-Tolyl</td>
<td>30h</td>
<td>72</td>
<td>&gt;95:5</td>
<td>239ah</td>
</tr>
<tr>
<td>No.</td>
<td>Functional Group</td>
<td>Product</td>
<td>Yield (%)</td>
<td>Diastereomeric Ratio</td>
<td>Isolated Yield of 239</td>
</tr>
<tr>
<td>-----</td>
<td>----------------</td>
<td>---------</td>
<td>-----------</td>
<td>----------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>8</td>
<td>&quot;Pentyl</td>
<td>30i</td>
<td>84</td>
<td>&gt;95:5</td>
<td>239ai</td>
</tr>
<tr>
<td>9</td>
<td>Cyclohexyl</td>
<td>30j</td>
<td>58</td>
<td>&gt;95:5 (75:25)</td>
<td>237aj</td>
</tr>
<tr>
<td>10</td>
<td>2-Pyridyl</td>
<td>30k</td>
<td>60</td>
<td>&gt;95:5 (75:25)</td>
<td>239ak</td>
</tr>
<tr>
<td>11</td>
<td>3-Pyridyl</td>
<td>30l</td>
<td>80</td>
<td>&gt;95:5</td>
<td>239al</td>
</tr>
<tr>
<td>12</td>
<td>2-Pyrrole</td>
<td>30m</td>
<td>15&lt;sup&gt;c&lt;/sup&gt;</td>
<td>50:50&lt;sup&gt;d&lt;/sup&gt;</td>
<td>237am</td>
</tr>
<tr>
<td>13</td>
<td>N-Me-2-Pyrole</td>
<td>30n</td>
<td>75&lt;sup&gt;c&lt;/sup&gt;</td>
<td>57:43&lt;sup&gt;d&lt;/sup&gt;</td>
<td>237an</td>
</tr>
<tr>
<td>14</td>
<td>N-Ts-2-Pyrole</td>
<td>30o</td>
<td>74</td>
<td>&gt;95:5</td>
<td>239ao</td>
</tr>
<tr>
<td>15</td>
<td>3-Indole</td>
<td>30p</td>
<td>80&lt;sup&gt;c&lt;/sup&gt;</td>
<td>50:50&lt;sup&gt;d&lt;/sup&gt;</td>
<td>237ap</td>
</tr>
<tr>
<td>16</td>
<td>N-Ts-3-Indole</td>
<td>30q</td>
<td>64</td>
<td>&gt;95:5 (90:10)</td>
<td>239aq</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated yield of 239. <sup>b</sup> DR of isolated 239 calculated from 1H NMR, DR of crude product given in parentheses if this differed from purified product. <sup>c</sup> Conv. to 237 calculated from 1H NMR. <sup>d</sup> DR of crude 237 calculated from 1H NMR.

It was thought that by removing the tetrahydrofuran in vacuo from the reaction after the reduction had been performed, the diastereoselectivity may be further increased. This reaction was performed using nitroalkene 84a and imine 30j but unfortunately did not improve the selectivity any further. Nitrogen containing heterocycles were also examined, 2-Pyridyl-N-PMP-imine 30k was subjected to the standard reductive
nitro-Mannich conditions giving a high conversion (>95%) but unfortunately the diastereoselectivity of the reaction was only 75:25 (Table 5, entry 10). However, 3-pyridyl analogue 30l worked very well giving essentially a single diastereomer in 80% yield (Table 5, entry 11). Pyrrole containing imines 30m and 30n were poorly selective and N-H-pyrrole imine 30m also gave a low conversion (Table 5, entries 12-13). This is presumably due to the electron rich nature of these imines. Protecting the pyrrole with an electron withdrawing group, such as a tosyl group, resulted in a much more reactive and stereoselective nitro-Mannich reaction (Table 5, entry 14). A similar reactivity pattern was observed with the indole imines 30p and 30q, again a tosyl group was required to obtain good diastereoselectivity (Table 5, entries 15-16).

Table 6. Reductive nitro-Mannich reaction at room temperature

<table>
<thead>
<tr>
<th>Entry</th>
<th>R1</th>
<th>Imine</th>
<th>Rxn. time</th>
<th>% Conv.</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Phenyl</td>
<td>30a</td>
<td>5 min</td>
<td>&gt;95</td>
<td>90:10</td>
</tr>
<tr>
<td>2</td>
<td>Phenyl</td>
<td>30a</td>
<td>3.5 h</td>
<td>&gt;95</td>
<td>85:15</td>
</tr>
<tr>
<td>3a</td>
<td>Phenyl</td>
<td>30a</td>
<td>5 min</td>
<td>66</td>
<td>85:15</td>
</tr>
<tr>
<td>4</td>
<td>2-Furyl</td>
<td>30b</td>
<td>5 min</td>
<td>&gt;95</td>
<td>85:15</td>
</tr>
<tr>
<td>5</td>
<td>2-Tolyl</td>
<td>30h</td>
<td>5 min</td>
<td>&gt;95</td>
<td>80:20</td>
</tr>
</tbody>
</table>

*Reaction performed in THF. % Conv. to 237 by 1H NMR. dr of crude 237 calculated from 1H NMR.

As the change of solvent from tetrahydrofuran to dichloromethane had shown such a good improvement in selectivity, the reaction was attempted at room temperature to see if any preferential selectivity would still exist. Remarkably even at room temperature the reaction in dichloromethane showed good diastereoselectivity, albeit not as impressive as when the reaction was performed at low temperature (Table 6, entry 1). Additionally, when left to stir at room temperature for long periods of time, the diastereoselectivity of the reaction also remained high (Table 6, entry 2). In tetrahydrofuran however, the reaction is not as efficient or selective (Table 6, entry 3), even when stirred for longer periods of time the conversion to the desired product...
did not improve. Presumably in tetrahydrofuran at room temperature the rate of quenching of the nitronate is more competitive with the nitro-Mannich reaction than in dichloromethane, although the reasons for this are unclear. The reaction also showed good diastereoselectivity with electron rich 2-furyl imine 30b (Table 6, entry 4), greater even than the selectivity obtained using tetrahydrofuran at -78 °C (Table 4, entry 3). Using more sterically demanding imines with \textit{ortho} substituents slightly reduced the diastereoselectivity (Table 4, entry 5).

### 2.1.3 Assignment and origin of relative stereochemistry

So far all of the examples of the nitro-Mannich reaction in this research have depicted the major diastereomer as the \textit{anti}-product. These assignments are based on the $^1$H NMR coupling constants of the unprotected $\beta$-nitroamine products 237. This method of assignment was based on the prior work by Seebach \textit{et al.} from their seminal work on the Henry reaction.\textsuperscript{126} There, the authors proposed that the $\beta$-nitroalcohol products would preferentially exist in a H-bonded \textit{pseudo} chair conformation. In such a conformation, the coupling constants could be compared to those observed in cyclohexane structures to identify axial-axial or axial-equatorial couplings. It was assumed that $\beta$-nitroamines 237 would adopt a similar conformation and the same strategy could be applied to assign the diastereomers with the axial-axial coupling larger than the axial-equatorial coupling (Figure 16, full tables of coupling constants can be found in appendix 5.2). This method of analysis has since been supported by the solving of the crystal structures of several trifluoroacetamides using single crystal X-ray crystallography.\textsuperscript{118,127}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure16.png}
\caption{Assignment of relative stereochemistry}
\end{figure}

Although this method of assignment provided coupling constants within similar ranges for the majority of examples, further suggesting its suitability for determining the relative stereochemistry, there were some cases where the coupling constants were not conclusive. This was common with $\beta$-nitroamines derived from more hindered \textit{ortho}-substituted imines 30c, 30f and 30h; as well as cyclohexyl imine 30j.
and 2-pyridyl imine 30k. In the case of cyclohexyl imine derived β-nitroamine 237aj, a larger coupling constant (7.8 Hz) was observed for the major diastereomer, suggesting the syn diastereomer. Whereas the minor diastereomer had a smaller coupling constant (4.8 Hz), suggesting formation of the anti diastereomer. In similar work within the Anderson group, another analogue closely resembling 237aj also possessed coupling constants differing from those expected for the protons in the α-positions of the amino and nitro functionalities. The crystal structure of this analogue has since been solved, thus confirming the preference for the anti diastereomer (Figure 17). So for this reason, we tentatively assign β-nitroamine 237aj as the anti diastereomer.

![Figure 17. Single X-ray crystal structure of similar analogue](image)

With regards to the other β-nitroamines with inconclusive coupling constants, it is thought that the ortho-substituents may interfere with a cyclic conformation resulting in less characteristic J-values. The 2-pyridyl substituted β-nitroamine 237ak may be doing something similar as interestingly 3-pyridyl substituted β-nitroamine 237an has coupling constants within the expected ranges. For these reasons, β-nitroamines 237ca, 237fa, 237ha, and 237ak are somewhat tentatively assigned as anti diastereomers.

Previous reports have observed that the syn diastereomer is the thermodynamic product. This is also suggested when examining the cyclic intramolecular H-bonded structures shown in figure 16 as this diastereomer places all of the larger substituents
into the *pseudo* equatorial positions. Therefore it suggests that the nitro-Mannich reaction is under kinetic control and that the *anti* diastereomer should be formed by the lowest energy transition state. It is proposed that the preference for the *anti* diastereomer originates from a cyclic transition state as depicted in figure 18. As the imine is locked in an *E* configuration, both the PMP group and the R₂ substituent are forced into *pseudo* axial positions in order for a successful H-bonding network to form.

![Figure 18. Proposed origin of diastereoselectivity](image)

The substituent on the nitro-partner can then either adopt a *pseudo* equatorial (TS-23) or a *pseudo* axial (TS-24) position. The most favoured position to adopt is the *pseudo* equatorial position as this would avoid any unfavourable 1,3-diaxial interactions. Because of this desire to minimise diaxial strain we believe the *anti* diastereomer is formed preferentially.

![Figure 19. Acyclic transition states for the nitro-Mannich reaction](image)

An alternative reaction pathway could proceed via an acyclic transition state (Figure 19). However, both of the possible acyclic transition states suffer from steric clashes and it seems unlikely that the reaction proceeds via such a transition state due to the high level of diastereoselectivity observed. These proposed transition states may also offer some insight into the cause of some interesting and anomalous results obtained during the course of this research. Firstly, the higher diastereoselectivities obtained when using non-coordinating solvents such as dichloromethane and toluene instead of tetrahydrofuran and diethyl ether. It is proposed that ethereal solvents such as
tetrahydrofuran and diethyl ether may interfere with the hydrogen bonding make-up of the transition state. Several solvent molecules could break up the intramolecular H-bonding structure and hence favour an acyclic pathway which may be less selective (Figure 20).

![Possible effect of coordinating solvents on nitro-Mannich reaction](image)

**Figure 20.** Possible effect of coordinating solvents on nitro-Mannich reaction

A second example can be found in the poor diastereoselectivity of the reaction when using cyclohexyl imine 30j when only a 75:25 ratio was observed. It was earlier suggested that the coupling constants observed for β-nitroamine 237aj were not indicative of a cyclic conformation. This could mean that the cyclic transition state is also not of a low energy and as such the reaction proceeds *via* an acyclic pathway. As to reasons for such a difference in energy, as yet we are unable to suggest why the cyclohexyl group would not favour a cyclic structure.

### 2.1.4 Concluding paragraph

In this first section, the development of a racemic reductive nitro-Mannich reaction has been described. Continuing from preliminary studies performed in the Anderson group, this research has overcome the initial limitation of the reductive nitro-Mannich reaction where β-nitrostyrenes were not tolerated. This was achieved by using *N*-PMP protected imines 30a in place of *N*-OMB protected imines 230; and the use of a stronger Brønsted acid, namely trifluoroacetic acid in place of acetic acid. The reaction worked well with a variety of nitroalkenes however upon examining a range of electron rich imines in the reaction the diastereoselectivity was significantly reduced. It was discovered that by using non-coordinating solvents such as dichloromethane the diastereoselectivity could be greatly increased and a variety of different imines could be employed in the reaction to give the desired β-nitroamines 237 in high conversion and excellent diastereoselectivity. The β-nitroamine products 237 were unstable to standard purification techniques and as such were protected as trifluoroacetamides 239 to enable their isolation in good yields (58-87% yield) and
diastereoselectivity (up to >95:5 \(dr\)) enriched in the \textit{anti}-form. The high levels of diastereoselectivity are thought to originate from a cyclic transition state.
2.2 Tandem asymmetric reductive nitro-Mannich reaction

2.2.1 Initial investigations

After successfully developing a racemic reductive nitro-Mannich reaction, attention was turned towards an enantioselective variant. As described in section 1.4, it was proposed that thiourea organocatalysis may offer an effective method to achieve such an aim. Initially it was decided to synthesise thiourea organocatalysts 54 and 191 which have been successfully used by the groups of Jacobsen,33 and List,102 in nitro-Mannich reactions and reductions of nitroalkenes respectively. Jacobsen’s catalyst was initially synthesised as described in the original publication (Scheme 92). However, in our hands the final two steps proved problematic and suffered from irreproducible yields.

This was presumably due to the poor selectivity for the reaction of diamine 245 with isothiocyanate 244, which could form a bis-urea compound; as well as difficulty in purifying resultant amine 246 which gave variable yields after chromatography.
Performing these last two reactions in one-pot rather than purifying also had no positive effect on the reproducibility of the reaction. To circumvent these problems it was attempted to mono-acetylate diaminocyclohexane. This was successfully performed by first synthesising benzoimidazole, which has been previously synthesised using an in situ formed Pinner salt of acetonitrile under dry conditions, or more conveniently by simply refluxing trimethyl orthoacetate in hexafluoroisopropanol (HFIP). Benzoimidazole can then be simply hydrolysed to give the desired mono-acetylated diamine (Scheme 93).

Scheme 93. Alternative synthesis of Jacobsen’s thiourea organocatalyst

The synthesis of List’s thiourea catalyst proved less problematic with the only low yielding step being the coupling of diethylamine with the Boc-protected amino acid forming amide in 47% yield (Scheme 94). Boc-deprotection proceeded in good yield in neat TFA to give amine which was then reacted with thiophosgene to give isothiocyanate. Isothiocyanate was then used without further purification to give final thiourea by stirring with chiral diamine in an overall yield of 34% for the 4 linear steps. Diamine could itself be formed simply by the condensation of diaminocyclohexane with diketone.
With these two catalysts synthesised, attention was turned towards the reductive nitro-Mannich reaction. Whereas List’s thiourea 191 has been previously shown to catalyse the reduction of nitroalkenes by Hantzsch esters, Jacobsen’s catalyst 54 had not previously been examined in such a reaction. It seemed prudent to examine its potential before commencing more complicated two-step reactions. The reduction of β-nitrostyrene 84a using Jacobsen’s catalyst 54 was investigated using Hantzsch esters 254 and 255. Pleasingly, 70% reduction after 3 h occurred using tert-buty1 Hantzsch ester 254, increasing to 90% conversion after 16 h. Interestingly, less than 10% conversion was observed when using 255 as the hydride source (Scheme 95). This large discrepancy is difficult to explain at first glance as there is minimal difference in electronics between the two species and the tert-butyl group seems too far away to be inducing a steric effect.

**Scheme 94.** Synthesis of List’s thiourea catalyst

**Scheme 95.** Reduction of β-nitrostyrene using Jacobsen’s catalyst
Intrigued by this difference in reactivity, a thorough search of the literature was performed to discover if this is a general trend or a rare phenomenon. Surprisingly, only one other report, from the Macmillan group, described such a difference in the reactivity of these two hydride sources. Eventually the authors were able to shed some light upon the cause of the difference in reactivity when the crystal structures of the two Hantzsch esters were solved by X-ray crystallography. It was revealed that exists in a puckered conformation which results in two different C-H bond lengths and one C-H bond sitting in the same plane as the π-orbitals, presumably due to the steric effect of the t-Bu groups. In this conformation, the π-orbitals can donate into the C-H σ*-orbital weakening it and greatly increasing its reactivity towards electrophiles. Conversely, Hantzsch ester was planar and the two C-H bonds were of equal length (Figure 21).

![Figure 21. Crystal structures of Hantzsch esters](image)

With this knowledge in hand, the reductive nitro-Mannich reaction was attempted using the tert-butyl Hantzsch ester 254. Due to its use in most thiourea-catalysed nitro-Mannich reactions, N-Boc imine 41a was utilised as the imine electrophile. Initial attempts to perform the reaction in tandem were thwarted as perhaps unsurprisingly, the N-Boc imine was reduced in preference over β-nitrostyrene 84a when using either catalyst (Scheme 96).
Subsequently, a two-step, one-pot reaction was attempted. The reduction was left overnight to ensure complete conversion before N-Boc imine 41a was added. No desired product was observed; instead the imine was hydrolysed. This is a common occurrence with N-Boc imines so 4 Å powdered molecular sieves were added to the reaction to prevent this degradation. Again no nitro-Mannich product was observed upon addition of the N-Boc imine 41a.

This was not unexpected as nitroalkane 234 needs to be deprotonated for the nitro-Mannich reaction to occur. Although nitronate 258 should be initially formed from the reduction of β-nitrostyrene, due to the large difference in acidity it would be protonated by pyridinium species 259. This equilibrium is likely to favour nitroalkane 234 and pyridine 260 and hence no nitro-Mannich reaction occurs (Scheme 98).

Scheme 96. Attempted tandem reductive nitro-Mannich reaction with N-Boc imine 41a

Scheme 97. Two-step one-pot reaction with N-Boc imines

Scheme 98. Equilibrium between nitroalkane and nitronate
To overcome this, an equivalent of Hunig’s base (Pr₂NEt) was added to the reaction after complete reduction. Once more no desired reaction was observed with either catalyst (Scheme 99).

![Scheme 99](image)

Scheme 99. Two-step one-pot reaction with added base

This lack of reactivity was confusing as these conditions were close to mimicking those used by Jacobsen’s group in their nitro-Mannich reactions with catalyst 54. Essentially the only differences between these reactions that could prevent formation of desired product 257 was the presence of pyridine 260.

![Scheme 100](image)

Scheme 100. Attempted nitro-Mannich reaction of nitroalkane 234

To check that it indeed was pyridine 260 that was hindering the reaction, a simple nitro-Mannich reaction using Jacobsen’s exact conditions was performed. Interestingly no reaction was observed even after several days at room temperature (Scheme 100). This result brought into question the purity of our reagents and so one of the reactions from Jacobsen’s original publication using nitroethane 261 was repeated so that the suitability of our materials could be evaluated. Pleasingly, the reaction proceeded in a similar fashion to how it was reported in the literature, although the enantioselectivity was not determined (Scheme 101). Satisfied that the starting materials were of adequate purity, it was thought that simply nitroalkane 234 and N-Boc imine 41a do not undergo a nitro-Mannich reaction with Jacobsen’s catalyst; however the reasons for this are unknown.
Scheme 101. Repeat of literature reaction using Jacobsen’s catalyst

After these results, attention was focused on N-PMP imine 30 with which excellent results for the racemic reaction had already been achieved. As such, a tandem reaction with equimolar amounts of β-nitrostyrene 84a, N-PMP imine 30a, Hantzsch ester 254 and 10 mol% Jacobsen’s catalyst 54 was investigated (Table 7).

Table 7. Initial investigations into asymmetric reaction with N-PMP imine 30a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Rxn. time</th>
<th>% Conv. a to 239aa</th>
<th>% Conv. a to 234</th>
<th>% Conv. a to 263</th>
<th>Yield b of 239aa</th>
<th>dr of 239aa</th>
<th>% ee c of 239aa</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2 h</td>
<td>60</td>
<td>10</td>
<td>5</td>
<td>29</td>
<td>95:5</td>
<td>58</td>
</tr>
<tr>
<td>2</td>
<td>9 h</td>
<td>70</td>
<td>30</td>
<td>5</td>
<td>45</td>
<td>95:5</td>
<td>52</td>
</tr>
<tr>
<td>3</td>
<td>22 h</td>
<td>60</td>
<td>40</td>
<td>10</td>
<td>23</td>
<td>95:5</td>
<td>44</td>
</tr>
<tr>
<td>4 d</td>
<td>2 h</td>
<td>45</td>
<td>10</td>
<td>10</td>
<td>26</td>
<td>95:5</td>
<td>56</td>
</tr>
<tr>
<td>5 e</td>
<td>2 h</td>
<td>75</td>
<td>15</td>
<td>&lt;5</td>
<td>60</td>
<td>95:5</td>
<td>54</td>
</tr>
<tr>
<td>6 f</td>
<td>2 h</td>
<td>90</td>
<td>35</td>
<td>5</td>
<td>77</td>
<td>95:5</td>
<td>50</td>
</tr>
</tbody>
</table>

a Calculated from 1H NMR before trifluoroacetamide protection, based on limiting reagent. b Isolated yield of 239aa. c Determined by chiral HPLC. d Reaction performed with 2.0 equiv. 30a. e Reaction performed with 2.0 equiv. 84a. f Reaction performed with 2.0 equiv. 84a and 2.0 equiv. 254.

Gratifyingly, a positive result was obtained immediately and desired nitro-Mannich product 239aa was isolated in a 29% yield, with a dr of 95:5 and a respectable 58% ee after 2 h at room temperature (Table 7, entry 1). Extended reaction times initially led to increased yields up until 9 h, at which point complete consumption of
β-nitrostyrene 84a was observed, and the product was isolated in a 45% yield and a slightly reduced 52% ee (Table 7, entry 2). After that point, the reaction yield decreased (23% after 22 h) and the enantioselectivity was reduced further to 44% ee (Table 7, entry 3). Before initiating a catalyst screen, a quick optimisation of the reagent stoichiometry was performed in an attempt to improve the reaction yields. It was observed that increasing the equivalents of N-PMP imine 30a had no noticeable effect on the reaction (Table 7, entry 4). However increasing the equivalents of β-nitrostyrene 84a did have a positive effect and the isolated yield was increased to 60% after 2 h (Table 7, entry 5). Increasing the equivalents of Hantzsch ester 254 further increased the isolated yield to give 87% 239aa albeit in a slightly reduced 50% ee (Table 7, entry 6). In addition to the desired product, a small amount of reduced imine was observed in each case (5-20%) and this was also decreased when using an excess of nitroalkene.

As can be seen from scheme 102, the reaction is more complicated than it may first appear. After initial reduction of β-nitrostyrene 84a, nitronate anion 258 can either undergo a catalyst controlled nitro-Mannich reaction with imine 30a or simply be protonated by pyridinium 259 to give nitroalkane 234. Of these two processes, the nitro-Mannich reaction is reversible whereas the protonation is irreversible and hence as the reaction progresses the product can be funnelled to nitroalkane 234 reducing the reaction yield. In addition to this, reduction of imine 30a to give amine 264 adds another complication to the reaction. However, despite these problems it was felt that the reaction conditions were promising enough to conduct a large catalyst screen for the reaction.
2.2.2 Catalyst screen for the tandem reductive nitro-Mannich reaction

Using the optimised reaction conditions (Table 7, entry 6) a variety of catalysts were examined in the reductive nitro-Mannich reaction (Table 8). Firstly, two commercially available thioureas 49 and 160 were examined in the reaction but no reaction was observed with either (Table 8, entries 2-3). In fact, less than 5% reduction of β-nitrostyrene 84a was detected. It may be that the basic functionality present in these catalysts is preventing reduction from occurring as List’s group also saw no reduction of nitroalkenes when similar thioureas were examined. Subsequently, catalyst 265 bearing an extra H-bond donor on the amide was examined as it was felt that this may help stabilise the transition state of the reaction. This theory proved false as the enantioselectivity of the reaction with this catalyst was poor giving 239aa in only 12% ee with a 60% conversion (Table 8, entry 4). List’s thiourea catalyst 191 was also examined and pleasingly delivered 239aa in an excellent 86% ee albeit with a greatly reduced reaction yield of 25% (Table 8, entry 5). Interestingly, near complete reduction of β-nitrostyrene 84a had occurred so it appears that this catalyst does not promote the nitro-Mannich reaction as well as 54. This result, prompted alteration of the group attached to the diaminocyclohexane moiety. Due to the ease of formation of mono-tosylated diaminocyclohexanes, catalyst 266 could be quickly synthesised in an analogous route to Jacobsen’s catalyst (Scheme 93) and was as such investigated in the reductive nitro-Mannich reaction (Table 8, entry 6). Pleasingly, thiourea 266 supplied desired product 239aa in a moderate 48% yield but more importantly with an excellent level of stereocontrol (>95:5 dr, 90% ee). The moderate yield was simply due a slower relative rate of reaction than when using catalyst 54 and hence the yield could be increased by prolonging the reaction time to 5 h to give 239aa in a 72% yield with a dr of >95:5 and in a slightly reduced 88% ee (Table 8, entry 7). Afterwards, the electronics of the sulfonamide were altered to measure the effect on the reaction. As such catalysts 267 and 268 were synthesised and examined in the reaction (Table 8, entries 8-9). Essentially no difference in enantioselectivity was observed with these catalysts but significant differences could be observed in the relative rates of reaction and the more electron withdrawn sulfonyl group provided the fastest rate of reaction.
Table 8. Catalyst screen for asymmetric tandem reductive nitro-Mannich reaction

![Chemical structure of catalysts](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>% Conv.</th>
<th>% Conv.</th>
<th>Yield</th>
<th>dr</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>to 239</td>
<td>a to 263</td>
<td>of 239</td>
<td>of 239</td>
<td>of 239</td>
</tr>
<tr>
<td>1</td>
<td><img src="image" alt="Catalyst 1" /></td>
<td>54</td>
<td>90</td>
<td>5</td>
<td>77</td>
<td>95:5</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="Catalyst 2" /></td>
<td>49</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="Catalyst 3" /></td>
<td>160</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="Catalyst 4" /></td>
<td>265</td>
<td>60</td>
<td>15</td>
<td>47</td>
<td>95:5</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="Catalyst 5" /></td>
<td>191</td>
<td>30</td>
<td>5</td>
<td>25</td>
<td>&gt;95:5</td>
</tr>
<tr>
<td>6</td>
<td><img src="image" alt="Catalyst 6" /></td>
<td>266</td>
<td>55</td>
<td>10</td>
<td>48</td>
<td>&gt;95:5</td>
</tr>
</tbody>
</table>
Conscious of the possibility that only one side of the catalyst may be influencing the enantioselectivity of the reaction, catalyst 270, which does not contain the amino acid

<p>| | | | | | |</p>
<table>
<thead>
<tr>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>266</td>
<td>80</td>
<td>10</td>
<td>72</td>
<td>&gt;95:5</td>
</tr>
<tr>
<td>8</td>
<td>267</td>
<td>80</td>
<td>10</td>
<td>67</td>
<td>&gt;95:5</td>
</tr>
<tr>
<td>9</td>
<td>268</td>
<td>55</td>
<td>15</td>
<td>45</td>
<td>&gt;95:5</td>
</tr>
<tr>
<td>10</td>
<td>269</td>
<td>50</td>
<td>25</td>
<td>37</td>
<td>&gt;95:5</td>
</tr>
<tr>
<td>11</td>
<td>270</td>
<td>60</td>
<td>40</td>
<td>36</td>
<td>95:5</td>
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<td>12</td>
<td>271</td>
<td>90</td>
<td>5</td>
<td>72</td>
<td>&gt;95:5</td>
</tr>
<tr>
<td>13</td>
<td>272</td>
<td>90</td>
<td>5</td>
<td>75</td>
<td>90:10</td>
</tr>
</tbody>
</table>

* Calculated from $^1$H NMR before trifluoroacetamide protection, based on limiting reagent.  
  Isolated yield of 239aa.  
  Determined by chiral HPLC.  
  Reaction time of 5 h.
derived side-chain; and mismatched catalyst 269 were synthesised. Mismatched catalyst 269 formed the same enantiomer as 266 but in lower yield and enantiopurity (37% yield, 76% ee). The reaction was also much less selective, forming significantly more reduced imine 263 than previous reactions (Table 8, entry 10). Curiously, catalyst 270 formed the opposite enantiomer (-64% ee) and also produced a lot more reduced imine 263 than other reactions (Table 8, entry 11). These two results suggested that the diaminocyclohexane moiety was not responsible for the high levels of enantioselectivity. In addition to finding the part of the catalyst responsible for the high stereoselectivity, producing a cheaper catalyst seemed a valuable aim. Mindful of the high price of un-natural amino acid L-tert-leucine, which was the starting material in our catalyst synthesis, the use of natural amino acid L-valine was investigated and catalyst 271 was synthesised. Pleasingly, no noticeable difference in stereoselectivity was observed when using this catalyst and additionally the relative rate of reaction (based on the rate of formation of desired product 239aa after 2 h) was significantly enhanced compared to catalyst 266, yielding 72% of 239aa with a dr of >95:5 and in 90% ee (Table 8, entry 12). Combining the concepts of these last few experiments, simple catalyst 272 was prepared and remarkably desired product 239aa was formed in a 75% yield and in 90% ee with only a slight reduction in the dr of 90:10 (Table 8, entry 13). It was thought that the small drop in the diastereoselectivity was more than compensated for by the simplicity of catalyst 272 and could be easily overcome with some further optimisation. Hence, catalyst 272 was the chosen catalyst from the screen.

2.2.3 Optimisation of reaction with selected catalyst

With catalyst 272 chosen, further optimisation of the reaction to improve the diastereoselectivity was carried out. Initially, solvents were examined to confirm that toluene was the ideal choice (Table 9). Dichloromethane gave essentially identical results to toluene although slightly more reduced imine 263 was observed (Table 9, entry 2). Diethyl ether also gave a good yield but the enantioselectivity of the reaction was greatly reduced to 16% ee (Table 9, entry 3). Interestingly, the reaction in tetrahydrofuran was very selective (94% ee) but the reaction yield after 2 hours was only 13% suggesting a significantly slower rate of reaction (Table 9, entry 4). Finally, acetonitrile was investigated but no desired product was observed (Table 9,
entry 5). Presumably more polar solvents disrupt the H-bonding between the thiourea and substrates preventing any desired reaction.

Table 9. Solvent screen for asymmetric reductive nitro-Mannich reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Yield(^a) of 239aa</th>
<th>(dr)^b of 239aa</th>
<th>% ee(^c) of 239aa</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Toluene</td>
<td>75</td>
<td>90:10</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>CH(_2)Cl(_2)</td>
<td>70</td>
<td>90:10</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>Et(_2)O</td>
<td>70</td>
<td>90:10</td>
<td>16</td>
</tr>
<tr>
<td>4</td>
<td>THF</td>
<td>13</td>
<td>90:10</td>
<td>94</td>
</tr>
<tr>
<td>5</td>
<td>MeCN</td>
<td>&lt;5</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
</tbody>
</table>

\(^a\)Isolated yield of 239aa. \(^b\)Calculated from \(^1\)H NMR. \(^c\)Determined by chiral HPLC.

After confirming toluene as the ideal solvent the effects of the reaction time and temperature were investigated (Table 10). Initially the reaction was monitored by \(^1\)H NMR and it was observed that the reaction had reached completion after only 30 minutes. When the reaction was then subjected to the protection conditions after this time, 239aa could be isolated with a slightly increased 94% ee (Table 10, entry 2).

As had been observed with Jacobsen’s catalyst (Table 7), extended reaction times led to erosion of enantioselectivity presumably via retro-addition and the uncatalysed background nitro-Mannich reaction. In an attempt to limit or prevent this retro-addition reaction the temperature of the reaction was lowered. At 0 °C, the reaction reached completion after 6 h and 239aa could be isolated in 95% ee and as a single diastereomer (Table 10, entry 3). Further decreasing the temperature gave further slight improvements giving 239aa in 97% ee after 14 h at -10 °C and in 98% ee after 20 h at -20 °C (Table 10, entries 4-5). It was felt that although further decreasing the temperature may lead to higher enantioselectivity, reaction times greater than one day would be undesirable so -20 °C was selected as the chosen...
temperature to investigate the full reaction scope. Finally, the reaction was left at -20 °C over several days to confirm that no erosion of enantioselectivity would be observed at this temperature and after 3 days at -20 °C 239aa could still be isolated in 98% ee (Table 10, entry 6).

Table 10. Investigating the effect of reaction time and temperature

<table>
<thead>
<tr>
<th>Entry</th>
<th>Rxn. time(^a)</th>
<th>Temp.</th>
<th>Yield(^b) of 239aa</th>
<th>(dr)^c of 239aa</th>
<th>% ee(^d) of 239aa</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2 h</td>
<td>rt</td>
<td>75</td>
<td>90:10</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>30 min</td>
<td>rt</td>
<td>74</td>
<td>90:10</td>
<td>94</td>
</tr>
<tr>
<td>3</td>
<td>6 h</td>
<td>0 °C</td>
<td>70</td>
<td>&gt;95:5</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>14 h</td>
<td>-10 °C</td>
<td>78</td>
<td>&gt;95:5</td>
<td>97</td>
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<td>5</td>
<td>20 h</td>
<td>-20 °C</td>
<td>81</td>
<td>&gt;95:5</td>
<td>98</td>
</tr>
<tr>
<td>6</td>
<td>72 h</td>
<td>-20 °C</td>
<td>83</td>
<td>&gt;95:5</td>
<td>98</td>
</tr>
</tbody>
</table>

\(^a\) Reaction time for part (i). \(^b\) Isolated yield of 239aa. \(^c\) Calculated from \(^1\)H NMR. \(^d\) Determined by chiral HPLC.

2.2.4 Investigation of the reaction scope

With optimised conditions for the reaction with catalyst 272 in hand, the scope of the reaction with respect to imines was investigated (Table 11). The reaction worked well for a variety of aromatic and heteroaromatic imines, furyl imine 30b gave the desired product in a 77% yield, in 97% ee and as a 90:10 mixture of diastereomers (Table 11, entry 2). The reaction also worked well with electron rich aromatic groups producing the products in near enantiopurity (Table 11, entries 3-4). Electron deficient aromatics were less consistent as when the imine was substituted with a trifluoromethyl group in the ortho position, 239af was formed in an 80:20 diastereomeric ratio.
Table 11. Scope of asymmetric reductive nitro-Mannich reaction with respect to imine

<table>
<thead>
<tr>
<th>Entry</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Yield&lt;sup&gt;a&lt;/sup&gt;</th>
<th>dr&lt;sup&gt;b&lt;/sup&gt;</th>
<th>ee&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Final product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Phenyl</td>
<td>81</td>
<td>&gt;95:5</td>
<td>98</td>
<td>239aa</td>
</tr>
<tr>
<td>2</td>
<td>2-Furyl</td>
<td>77</td>
<td>90:10</td>
<td>97</td>
<td>239ab</td>
</tr>
<tr>
<td>3</td>
<td>2-MeO-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>83</td>
<td>&gt;95:5</td>
<td>99</td>
<td>239ac</td>
</tr>
<tr>
<td>4</td>
<td>4-MeO-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>75</td>
<td>&gt;95:5</td>
<td>97</td>
<td>239ae</td>
</tr>
<tr>
<td>5</td>
<td>2-F&lt;sub&gt;3&lt;/sub&gt;C-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>66</td>
<td>&gt;95:5</td>
<td>80</td>
<td>239af</td>
</tr>
<tr>
<td>6</td>
<td>4-F&lt;sub&gt;3&lt;/sub&gt;C-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>74</td>
<td>90:10</td>
<td>94</td>
<td>239ag</td>
</tr>
<tr>
<td>7</td>
<td>2-Tolyl</td>
<td>75</td>
<td>&gt;95:5</td>
<td>90</td>
<td>239ah</td>
</tr>
</tbody>
</table>
These could be separated by column chromatography to yield 66% of the anti diastereomer in an 80% ee (Table 11, entry 5). The para substituted analogue 239ag however was formed in a 74% yield as a 90:10 dr and in 94% ee (Table 11, entry 6) suggesting that the lower diastereo- and enantioselectivity observed with ortho-CF₃ analogue 239af is not due to electronic effects. The result obtained using ortho-tolyl substituted imine 30h suggested that sterics may be responsible for the low stereoselectivity as 239ah was also formed as a diastereomeric mixture (85:15 dr) but with an improved enantiopurity of 90% ee (Table 11, entry 7). That the trifluoromethyl group (A-value – 2.1)¹³³ is slightly larger than a methyl group (A-value – 1.7)¹³³ is supportive of such a steric effect. The ortho-bromo substituted analogue 239ar also formed as a mixture of diastereomers (80:20 dr) and in 92% ee (Table 11, entry 8). Interestingly, as these three ortho-substituted analogues were only formed with moderate diastereoselectivity, it enabled isolation and determination of the enantiopurity of the minor syn diastereomers. In each case the syn diastereomers were found to be considerably less enantioenriched compared to their anti counterparts (Table 11, entries 5,7 and 8). This suggests that the syn
diastereomers are being formed via an alternative reaction mechanism to the anti diastereomers. Pleasingly, 2-pyridyl analogue 239ak was also formed with excellent levels of stereocontrol (>95:5 dr, 96% ee) and in 76% yield (Table 11, entry 9). The high diastereoselectivity of this example was particularly encouraging as in the previously described racemic synthesis this analogue was formed as a 75:25 mixture of diastereomers (see section 2.1.2, Table 5). Finally, alkyl imines 30i and 30j were examined in the reaction. Unfortunately, due to the instability of n-pentyl substituted imine 30i the desired product was only formed with a low yield of 31% (Table 11, entry 10). However, it was discovered that by conducting the reaction at room temperature, the reaction could be completed before significant degradation of imine 30i occurred to form 239ai in a 59% yield and in 73% ee (Table 11, entry 11). As of yet, it is unknown as to why n-pentyl substituted imine 30i gives 239ai with only moderate enantioenrichment. Cyclohexyl imine 30j was also examined in the reaction, and as previously noted in the racemic reaction (see section 2.1.2, Table 5), the reaction was poorly diastereoselective (65:35 dr) and trifluoroacetamide protection could not be performed (Table 11, entry 12).

Scheme 103. Attempts to form stable analogue of 237aj

Unfortunately, although 237aj could be isolated by column chromatography as a single diastereomer, degradation was observed whilst analysing the product by chiral HPLC, preventing measurement of the enantiopurity. Several methods were attempted to synthesise a more stable product from the nitro-Mannich reaction using
cyclohexyl imine 30j, but no success was achieved (Scheme 103). Reduction of β-nitroamine 237aj using zinc dust and hydrochloric acid gave a complex mixture of products that could not be separated by chromatography. Attempted reduction to hydroxylamine 274 using an aluminium amalgam appeared to succeed but the product was unstable in air and rapidly degraded. Finally, deprotection of the para-methoxy phenyl group using ceric ammonium nitrate (CAN) followed by N-Boc protection also gave a complicated mixture of products.\textsuperscript{134}

The scope of the reaction with respect to nitroalkenes was also examined (Table 12). Initially, alkyl substituted nitroalkenes 84b and 84c were investigated and pleasingly, desired products 239ba and 239ca were formed in excellent yields (75% and 71% respectively), and with excellent levels of stereocontrol (>95:5 dr, 95% ee and 97% ee respectively) for both analogues (Table 12, entries 1-2). Electron rich nitroalkenes however, were less successful. As the electron donating ability of the substituent increases, much longer reaction times were required to complete the reaction. This is best exemplified with furyl nitroalkene 84d where the reaction took 10 days to reach completion (Table 12, entry 5). Additionally the reaction yield was also greatly reduced in these examples as the reduction of N-PMP imine 30a became more competitive. Despite these poor yields, the diastereo- and enantioselectivity of these reactions remained excellent (Table 12, entries 3-5). Nitroalkenes bearing electron withdrawing substituents worked well in the reaction giving the desired products in excellent yields and with excellent diastereo- and enantiocontrol (Table 12, entries 6-7). Pyridyl analogue 84k was also successful in the reaction forming 239ka in a 68% yield with a >95:5 dr and in 98% ee (Table 12, entry 8). Overall, the reaction exhibited excellent stereocontrol with all nitroalkenes tested, presumably the substituents are too far away from the reacting centre to have an effect on the enantioselectivity of the reaction. The slow reactions with a number of electron rich nitroalkenes suggested that the rate limiting step of the reaction is the reduction of the nitroalkene.
Table 12. Scope of asymmetric reductive nitro-Mannich reaction with respect to nitroalkene

![Chemical structures](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Rxn. time</th>
<th>Yield&lt;sup&gt;a&lt;/sup&gt;</th>
<th>dr&lt;sup&gt;b&lt;/sup&gt;</th>
<th>ee&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Final product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cyclohexyl</td>
<td>20 h</td>
<td>75</td>
<td>&gt;95:5</td>
<td>95</td>
<td>239ba</td>
</tr>
<tr>
<td>2</td>
<td>'Pentyl</td>
<td>20 h</td>
<td>71</td>
<td>&gt;95:5</td>
<td>97</td>
<td>239ca</td>
</tr>
<tr>
<td>3</td>
<td>2-Tolyl</td>
<td>48 h</td>
<td>70</td>
<td>&gt;95:5</td>
<td>98</td>
<td>239ea</td>
</tr>
<tr>
<td>4</td>
<td>2-MeO-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>72 h</td>
<td>64</td>
<td>&gt;95:5</td>
<td>98</td>
<td>239ga</td>
</tr>
<tr>
<td>5</td>
<td>2-Furyl</td>
<td>240 h</td>
<td>32</td>
<td>&gt;95:5</td>
<td>95</td>
<td>239da</td>
</tr>
<tr>
<td>6</td>
<td>2-F&lt;sub&gt;3&lt;/sub&gt;C-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>20 h</td>
<td>73</td>
<td>&gt;95:5</td>
<td>95</td>
<td>239ia</td>
</tr>
<tr>
<td>7</td>
<td>2-Br-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>20 h</td>
<td>79</td>
<td>&gt;95:5</td>
<td>98</td>
<td>239oa</td>
</tr>
<tr>
<td>8</td>
<td>2-Pyridyl</td>
<td>28 h</td>
<td>68</td>
<td>&gt;95:5</td>
<td>98</td>
<td>239ka</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated % yield of 239.  
<sup>b</sup> dr of isolated 239 calculated from 'H NMR.  
<sup>c</sup> % ee of isolated 239 determined by chiral HPLC.
2.2.5 Determination and origin of absolute stereochemistry

Initially, it was attempted to determine the absolute stereochemistry by single X-ray crystallography. Unfortunately, attempts to form suitable crystals of \( \beta \)-nitrotrifluoroacetamides containing heavy atoms such as bromo-substituted analogues 239oa and 239ar were unsuccessful. Although crystals could be grown, they formed as extremely thin needles. Suitable crystals also could not be grown with reduced product 276oa either (Scheme 104).

Eventually it was discovered that the para-methoxy phenyl protecting group could be cleaved from \( \beta \)-nitroamine 239aa and an in-situ Boc protection could be performed to produce literature compound 257 in a 39\% yield from imine 30a. The optical rotation of this product matched the literature value, giving some evidence that product 239aa from the reductive nitro-Mannich reaction has the 1R,2S stereochemistry. The other \( \beta \)-nitrotrifluoroacetamides synthesised (Table 11 and table 12) have been assigned the same stereochemistry by analogy.

Scheme 104. Attempts to grow crystals for X-ray crystallography

Scheme 105. Confirmation of absolute stereochemistry through comparison
This assignment of the absolute stereochemistry is not definitive however, as the original literature assignment of 257 was also determined by analogy based on the assignment of 262 which could also be formed by a nitro-Mannich reaction.\(^{31,36}\) The assignment of 262 as 1\(R\),2\(S\) was based on comparison with literature compound (1\(R\),2\(S\))-1,2-diamino-1-phenylpropane 277 which itself was synthesised from (1\(R\),1\(S\))-\(L\)-(-)-Norephedrine 278 (Scheme 106).\(^{135}\)

\[\text{Scheme 106. Literature assignment of 257 based on comparison to 262}\]

With the absolute stereochemistry now tentatively assigned, thoughts were turned towards the mechanism of the reaction and the enantiodetermining step. Firstly reduction of the nitroalkene occurs. Presumably, the amide group of the catalyst directs the attack of the hydride from the top face, as drawn in TS-25 (Scheme 107), although this is inconsequential in this example. This is based on List’s work where a similar amide containing catalyst 191 directs the face of the hydride’s attack in a similar fashion (see section 1.3.4).\(^{102}\) The results from optimising the stoichiometry of the reaction, where the rate of reaction was insensitive to an excess of imine, and increasing rate of reaction with increasing stoichiometry of nitroalkene and Hantzsch ester were observed (see section 2.2.1); as well as a slower rate of reaction with more electron rich nitroalkenes, (Table 12) suggest that the reduction is the rate limiting step. It is thought that after reduction, the nitronate must react with an imine almost instantaneously as no reduced nitroalkene 234 is typically observed until complete consumption of imine 30 has occurred. Presumably, due to the greater basicity of \(N\)-PMP imine 30 and the large size of the pyridinium species, rapid displacement occurs and six-membered transition state TS-27 is formed suggesting that \(k_{\text{disp.}} \gg k_{\text{taut.}}\). This then collapses to give \(anti\) diastereomer 239 with the (1\(R\), 2\(S\)) stereochemistry (Scheme 107).
It is thought that the enantioselectivity of this reaction is determined in the six-membered transition state **TS-27**. Before discussing this, it is important to consider the lowest energy conformation of the catalyst as this is likely to be similar to the conformation during the enantiodetermining step. Jacobsen’s thiourea **153**, used in asymmetric Strecker reactions, possesses a similar structure to catalyst **272** and extensive experimental and theoretical calculations have been performed on this catalyst (Figure 22).

![Scheme 107. Proposed reaction mechanism for the tandem reductive nitro-Mannich reaction](image)

**Figure 22.** Comparison between **272** and catalyst for Strecker reaction

In these computational calculations, **153** exists with the highlighted C-H bond in the same plane as the C=S bond. This is presumably to minimise steric interactions.
between the large sulfur atom and the amide or tert-butyl group. If we assume that catalyst 272 will adopt a similar conformation for the same reasons, then one of two likely transition states should be favoured (Figure 23).

![Figure 23. Two possible reaction transition states](image1)

In TS-28, the thiourea H-bonds to the nitronate species and the iminium species is H-bonded to the amide. Conversely, this could be the opposite way round as in TS-29, as imines are known to be stronger H-bond acceptors than nitro groups. Although this is indeed a possible scenario it is thought to be less likely because several previous computational studies have found that the lower energy transition state involves the thiourea binding to the anionic (nucleophilic) reaction partner. Additional support is given to TS-28 from Jacobsen’s work on the asymmetric Strecker reaction as the authors calculate lower energy transition states when the imine is H-bonded to the amide, as shown in TS-28, rather than the thiourea moiety of the catalyst (see Figure 9, section 1.3.3). This information was combined with the suggested transition states for the racemic reaction to give proposed enantiodetermining conformations in figure 24.

![Figure 24. Proposed transition states for enantioselective reductive nitro-Mannich reaction](image2)

In TS-29 the catalyst is in its lowest energy conformation (with the highlighted C-H bond in the same plane as the C=S bond), this allows the amide moiety of the catalyst to hydrogen-bond to the imine in a pseudo equatorial position stabilising the transition state. In TS-30 in order for the amide moiety to H-bond in a pseudo
equatorial fashion, the large iso-propyl group has to be in the same plane as the large sulfur atom which is unfavourable. Another possible transition state would involve the amide moiety H-bonding to the imine in a pseudo axial position. In such a transition state **TS-32** looks of lower energy than **TS-31** as the C-H bond is in the same plane as the C=S bond (Figure 25). However, as the H-bond is in a pseudo axial position to R² it is anticipated that there would be a steric penalty compared to **TS-29** and as such **TS-32** is likely to be of higher energy.

With a transition state model for the formation of the anti diastereomer proposed, attention was turned towards proposing a cause for the poor enantioselectivity observed in the syn diastereomers which were formed in some examples. When N-PMP imine 30 was substituted in the ortho position with a CF₃, Me or Br. group the reactions were only moderately diastereoselective and the enantioselectivity was poor for the syn diastereomer (Table 11, entries 5, 7 and 8). This low enantioselectivity suggests that the syn diastereomer is formed via an alternative transition state. In keeping with the proposed transition states for the racemic reaction, the syn diastereomer could be formed by a cyclic transition state where all substituents are in pseudo axial positions (see section 2.1.3). Due to the unfavourable steric interactions in such a transition state this seems unlikely so an acyclic transition state may be in operation. In such a transition state it would be very difficult for the amide moiety of the catalyst to also H-bond to the imine, preventing the catalyst from implementing high levels of stereocontrol for the syn diastereomer (Figure 26).
Table 13 shows the calculated hydrogen bond basicities for a variety of hydrogen bond acceptors (HBA). Using this information, combined with the proposed transition state, we can begin to explain some of the observed differences in enantioselectivity of the reaction with different catalysts. Additionally, these ideas can be used to suggest new catalysts to synthesise to probe the mechanism further.

Table 13. Hydrogen-bond basicities of several small molecules

<table>
<thead>
<tr>
<th>Entry</th>
<th>HBA</th>
<th>$-\Delta H^\circ$ (KJmol$^{-1}$)$^a$</th>
<th>$pK_{HB}$$^b$</th>
<th>$\beta_2^H$$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$N,N$-dimethylacetamide</td>
<td>29.2</td>
<td>2.44$^{137}$</td>
<td>0.76$^{137}$</td>
</tr>
<tr>
<td>2</td>
<td>$N,N$-dimethylbenzenesulfonamide</td>
<td>18.1</td>
<td>1.19$^{138}$</td>
<td>0.49$^{138}$</td>
</tr>
<tr>
<td>3</td>
<td>$N,N$-dimethylthioacetamide</td>
<td>20.0</td>
<td>1.32$^{139}$</td>
<td>0.52$^{139}$</td>
</tr>
<tr>
<td>4</td>
<td>Methyl acetate</td>
<td>20.8</td>
<td>1.00$^{140}$</td>
<td>0.45$^{141}$</td>
</tr>
<tr>
<td>5</td>
<td>1,1,3,3-tetramethylurea</td>
<td>28.6</td>
<td>2.44$^{137}$</td>
<td>0.76$^{137}$</td>
</tr>
<tr>
<td>6</td>
<td>1,1,3,3-tetramethylthiourea</td>
<td>-</td>
<td>1.35$^{139}$</td>
<td>0.53$^{139}$</td>
</tr>
</tbody>
</table>

$^a$ Enthalpy of H-bond with 4-fluorophenol in CCl$_4$. $^b$ Data taken from H-bond with 4-fluorophenol in CCl$_4$, $pK_{HB} = \log_{10}(K_{HB})$. $^c$ $\beta_2^H = (pK_{HB} + 1.1)/4.636$.

During the catalyst screen a large difference between the enantioselectivity achieved with catalyst 54 (Table 14, entry 1) and catalyst 266 (Table 14, entry 2) was observed. Since it is now known that the diaminocyclohexane moiety is not responsible for the high enantioselectivity, it suggests that the acetyl group on catalyst 54 was responsible for the low stereoselectivity. Amides are typically stronger HBAs (Table 13, entry 1) than sulfonamides (Table 13, entry 2) so its plausible that with catalyst 54 the acetyl group on the diaminocyclohexane can form a H-bonded transition state that is competitive with the proposed transition state TS-35 (Figure 27). The sulfonamide must form a weaker H-bond so is not as competitive and hence the enantioselectivity is higher. That catalyst 270 (Table 14, entry 3) forms the opposite enantiomer gives
some credence to this idea as it suggests that when the diaminocyclohexane is the only chiral group on the catalyst, a transition state similar to $\text{TS-38}$ is in operation.

![TS-35](image1.png) \quad ![TS-36](image2.png) \quad ![TS-37](image3.png) \quad ![TS-38](image4.png)

**Figure 27.** Competitive and uncompetitive transition states with catalysts 54 and 266

To further probe the mechanism of this reaction some more catalyst structures were synthesised and examined in the reductive nitro-Mannich reaction, these along with selected examples from the earlier catalyst screen are shown in table 14. Although, no reaction rates were measured absolutely, it is thought that the reduction of the nitroalkene is the rate limiting step of the reductive nitro-Mannich reaction. As such the amount of $\beta$-nitrostyrene 84a consumed in each example can be used as crude indicator of the rate of reaction for each catalyst. Although, this data should not be extrapolated too far, it should be sufficient to identify the more active catalyst. The first new catalyst synthesised was thiourea 279 where the bis-trifluoromethylbenzene group was substituted for a phenyl ring (Table 14, entry 5), as expected no difference in the stereoselectivity was observed but the relative rate of reaction was slightly reduced as indicated by comparing the amount of reduction of $\beta$-nitrostyrene 84a with thiourea 272 (Table 14, entry 4).
Table 14. Further probing of the reaction mechanism with different catalysts

![Reaction Mechanism Diagram]

Table: | Entry | Catalyst | % Conv.\(^a\) of 84a | % Conv.\(^b\) to 239 | Yield\(^c\) of 239 | dr\(^d\) of 239 | % ee\(^d\) of 239 |
<table>
<thead>
<tr>
<th></th>
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<td>54</td>
<td>75</td>
<td>90</td>
<td>77</td>
<td>95:5</td>
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<tr>
<td>2</td>
<td><img src="image2" alt="Catalyst 2" /></td>
<td>266</td>
<td>40</td>
<td>55</td>
<td>48</td>
<td>&gt;95:5</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3" alt="Catalyst 3" /></td>
<td>270</td>
<td>55</td>
<td>60</td>
<td>36</td>
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<td>272</td>
<td>85</td>
<td>90</td>
<td>75</td>
<td>90:10</td>
</tr>
<tr>
<td>5</td>
<td><img src="image5" alt="Catalyst 5" /></td>
<td>279</td>
<td>60</td>
<td>95</td>
<td>72</td>
<td>90:10</td>
</tr>
<tr>
<td>6</td>
<td><img src="image6" alt="Catalyst 6" /></td>
<td>280</td>
<td>50</td>
<td>70</td>
<td>62</td>
<td>90:10</td>
</tr>
<tr>
<td>7</td>
<td><img src="image7" alt="Catalyst 7" /></td>
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<td>90</td>
<td>95</td>
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</tr>
<tr>
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<td><img src="image8" alt="Catalyst 8" /></td>
<td>282</td>
<td>45</td>
<td>70</td>
<td>53</td>
<td>90:10</td>
</tr>
</tbody>
</table>

\(^a\) Calculated from \(^1\)H NMR. As reduction of nitroalkene 84 is rate limiting step, this value can be thought of as a crude indicator of the rate of reaction. \(^b\) Calculated from \(^1\)H NMR before trifluoroacetamide protection. \(^c\) Isolated yield of 239aa. \(^d\) Determined by chiral HPLC.
The slower relative rate of reaction in this case is not surprising as phenyl thiourea 279 should be a weaker H-bond donor than 272 bearing a bis-trifluoromethylbenzene group. Next, tert-butyl substituted catalyst 280 was tested in the reaction. A slight increase in the enantioselectivity of the reaction was noticed with 239aa isolated in 94% ee (Table 14, entry 6) compared to iso-propyl substituted catalyst 272 (Table 14, entry 4) suggesting that the bulkier tert-butyl group results in a more selective reaction. However, the relative rate of reaction with this catalyst was slower than the reaction with catalyst 272. This could explain the higher enantioselectivity as less retro-addition may have occurred, as when the reaction with catalyst 272 was stopped after 30 min desired product 239aa was also formed in 94% ee (Table 10, entry 2, see section 2.2.3). Urea catalyst 281 was also investigated and also delivered 239aa in 90% ee (Table 14, entry 7). This result suggests that the thio(urea) moiety of the catalyst is acting as a H-bond donor rather than a H-bond acceptor. Unexpectedly, the relative rate of reaction using urea 281 was also very similar to that observed with thiourea 272. Finally, it was thought that a good way to probe the idea of a key H-bond between the amide of the catalyst and the iminium species would be to make either a thioamide or ester containing catalyst as both these functional groups are weaker HBAs (compare entries 1,3 and 4, table 13) than dimethylamide and should result in weaker binding and hence a lower enantioselectivity for the reaction. It was attempted to synthesise thioamide catalyst 283 using Lawesson’s reagent, but unfortunately, no desired product was obtained from the reaction (Scheme 108). As a result, the reductive nitro-Mannich reaction using methyl ester catalyst 282, which was synthesised from the commercially available L-valine methyl ester, was performed. Interestingly, the reaction formed 239aa in excellent enantiopurity (92% ee) albeit in only a moderate yield of 53% (Table 14, entry 8). This result was also unexpected as the methyl ester of 282 should not be able to form as strong a H-bond with the iminium species as the dimethylamide moiety (Table 13, entries 1 and 4). This final result suggests that the enantiodetermining step is more complex than previously thought.
2.2.6 Forming three contiguous stereocentres

One of the possibilities that prompted the examination of a reductive nitro-Mannich reaction was the potential to synthesise molecules with three contiguous stereocentres by using \( \alpha \)-substituted-\( \beta \)-nitrostyrenes as the starting nitroalkene. A few preliminary experiments towards this aim have been performed and this section will briefly discuss these results. Nitroalkene 286 was synthesised from \( \alpha \)-methylstyrene by nitration in acetic anhydride followed by elimination to give 286 in 44\% yield over two steps. This method was chosen as Henry reactions of ketones are typically low yielding.\(^{142}\)

With nitroalkene 286 in hand the reductive nitro-Mannich reaction was examined using two equivalents of nitroalkene 286 and two equivalents of Hantzsch ester 254 and 10 mol\% thiourea 272 as catalyst. The reaction was monitored by \(^1\)H NMR with small aliquots taken from the reaction at three different intervals (Table 15). It was immediately noticed that the reduction of nitroalkene 286 was significantly slower than with \( \beta \)-nitrostyrene 84a as only 10\% conversion to the desired product was observed after 30 min. With 84a, complete conversion to the desired product had occurred by this point. Although, the reaction had only reached 10\% conversion after 30 min the \( dr \) of the reaction could be determined and it was observed that \( \text{syn,anti} \) diastereomer 287b was favoured (Table 15, entry 1). Interestingly, as the reaction was left to stir for longer the diastereoselectivity of the reaction altered to favour \( \text{syn,syn} \) diastereomer 287a in a 65:5:30:0 ratio after 2h 30 min with 30\% conversion (Table 15, entry 2). After stirring overnight, 287a was favoured with a \( dr \) of 95:0:5:0 and 60\% conversion (Table 15, entry 3). Unlike, the \( \text{anti} \) nitro-Mannich products
which have been synthesised for most of this research syn,syn product 287a was stable to chromatography and could be isolated in 37% yield and 84% ee.

**Table 15.** Preliminary investigations into reaction forming 3 stereocentres

<table>
<thead>
<tr>
<th>Entry</th>
<th>Rxn. time</th>
<th>% Conv&lt;sup&gt;a&lt;/sup&gt; to 287</th>
<th>% Conv&lt;sup&gt;a&lt;/sup&gt; to 264</th>
<th>dr&lt;sup&gt;b&lt;/sup&gt; (a:b:c:d)</th>
<th>% Yield&lt;sup&gt;c&lt;/sup&gt;</th>
<th>% ee&lt;sup&gt;d&lt;/sup&gt;</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>30 min</td>
<td>10</td>
<td>10</td>
<td>10 : 80 : 10 : 0</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>2</td>
<td>2 h 30</td>
<td>30</td>
<td>35</td>
<td>65 : 5 : 30 : 0</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>3</td>
<td>17 h</td>
<td>55</td>
<td>45</td>
<td>95 : 0 : 5 : 0</td>
<td>37</td>
<td>84</td>
</tr>
</tbody>
</table>

<sup>a</sup> Calculated from <sup>1</sup>H NMR.  
<sup>b</sup> dr of crude reaction mixture, calculated from <sup>1</sup>H NMR.  
<sup>d</sup> Yield of isolated 287.  
<sup>c</sup> % ee of isolated 287, determined by chiral HPLC.

It should be pointed out that this level of enantioselectivity is very impressive considering the simplicity of the catalyst and that List’s catalyst achieves a 94% ee for the reduction of the same nitroalkene, albeit at higher temperature (Scheme 110).  

**Scheme 110.** Reduction of nitroalkene 286 using List’s thiourea
In addition to the high enantioselectivity several other interesting observations were made during this experiment. Firstly, the poor reactivity of nitroalkene 286 towards reduction can be explained by a steric argument. When nitroalkene 286 exists in its fully conjugated conformation 286a, there is an unfavourable steric interaction between the methyl and the nitro group. Because of this clash, nitroalkene 286 is more likely to adopt conformation 286b wherein the nitro group is not in conjugation with the styrene and hence the nitroalkene is a weaker electrophile (Figure 28). Such a problem does not exist in $\beta$-nitrostyrene 84a where the $\alpha$-substituent is a small hydrogen atom.

![Figure 28. Explanation for poor reactivity of $\alpha$-methyl-$\beta$-nitrostyrene](image)

The observed stereochemistry of the reaction is also of great interest. The absolute stereochemistry was based on comparison of the $[\alpha]_D$ of 287a with that previously observed when 287a was synthesised by the Anderson group.\(^5\) Additionally, nitroalkane 288, obtained from reduction of nitroalkene 286 using thiourea 272, matched the value obtained with List’s catalyst revealing the (S) stereochemistry. The nitro-Mannich reaction that follows the reduction is then under substrate control rather than catalyst control as the stereochemistry of the desired product is the opposite (287b 1S, 2R, 3S) to what has been previously seen using catalyst 272 (1R, 2S, see section 2.2.5). The observed initial diastereoselectivity can be explained by the proposed transition states in figure 29. In transition state TS-39 steric interactions are minimised resulting in the lowest energy and hence resulting in the observed syn,anti stereochemistry. When attempting to react the nitronate and imine under catalyst control (i.e. cyclic transition states TS-40 or TS-41) unfavourable steric clashes exist (Figure 29). Of even greater interest than the reaction being under substrate control, is the changing diastereoselectivity over time.
Figure 29. Transition state for initial observed stereochemistry

This suggests initial formation of kinetic syn,anti product 287b which then converts to the thermodynamic syn,syn product 287a. The idea that syn,syn product 287a is the thermodynamic product becomes more clear when the $\beta$-nitroamines are drawn as H-bonded cyclic structures (Figure 30). In 287a all of the substituents are in pseudo equatorial positions whereas in 287b one substituent has to sit in a pseudo axial position creating unfavourable steric interactions.

Figure 30. Chair conformation structures of 287a and 287b

It is proposed that the conversion from the kinetic to thermodynamic product occurs via a retro-addition/nitro-Mannich reaction sequence rather than by deprotonation, as catalyst 272 is already known to catalyse the retro-addition. In order to gain a better insight into this reaction it was compared to the conjugate addition/nitro-Mannich reactions using dialkyl zinca described by Anderson’s group (see Scheme 111 for example). In this work the choice of solvent used would either favour syn,syn diastereomer 290a (when diethyl ether, toluene or dichloromethane were used as
solvent), or syn,anti diastereomer 290b (when tetrahydrofuran, dimethoxyethane or acetone). The authors attributed this difference to the role of zinc (II) trifluoroacetate which was precipitated during the reaction in diethyl ether, leading to a proposed open transition state. In tetrahydrofuran the reaction remained homogenous, suggesting the proposed closed transition state (Scheme 111).

![Scheme 111. Conjugate addition/nitro-Mannich reaction using diethyl zinc](image)

Intrigued by this research and keen to see if any similarities can be found between the mechanisms of the conjugate addition/nitro-Mannich reaction and the thiourea catalysed reductive nitro-Mannich reaction, some extra experiments were performed to examine the role of the zinc species in these reactions. Using the same conditions as the authors, a repeat of the reaction in tetrahydrofuran was performed but the products of the reaction were monitored using $^1$H NMR. The reaction was sampled at regular intervals and produced some interesting results (Table 16). Although, the reaction favours syn,anti diastereomer 290b initially (Table 16, entry 1), very quickly the reaction favours syn,syn diastereomer 290a (Table 16, entries 2-6). These results are in close agreement to what was obtained using thiourea catalyst 272 in the reductive nitro-Mannich reaction (albeit with a methyl substituent, A-value = 1.7, rather than the similarly sized ethyl group, A-value = 1.75)$^{133}$. This suggests that the zinc species (or possibly the copper (II) triflate) is catalysing the retro-addition in a similar fashion to thiourea 272.
Table 16. Conjugate addition/nitro-Mannich reaction with diethyl zinc in THF

<table>
<thead>
<tr>
<th>Entry</th>
<th>Time at rt</th>
<th>% Conv. (^a)</th>
<th>(dr) (a:b:c:d) (^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5 min</td>
<td>77</td>
<td>15:80:5:0</td>
</tr>
<tr>
<td>2</td>
<td>30 min</td>
<td>76</td>
<td>40:20:20:0</td>
</tr>
<tr>
<td>3</td>
<td>1 h</td>
<td>83</td>
<td>70:10:20:0</td>
</tr>
<tr>
<td>4</td>
<td>2 h</td>
<td>88</td>
<td>65:10:25:0</td>
</tr>
<tr>
<td>5</td>
<td>4 h 30 min</td>
<td>89</td>
<td>70:5:25:0</td>
</tr>
<tr>
<td>6</td>
<td>24 h</td>
<td>88</td>
<td>70:5:25:0</td>
</tr>
</tbody>
</table>

\(^a\) % Conv. to 290 by \(^1\)H NMR. \(^b\) \(dr\) of crude 290 calculated from \(^1\)H NMR.

To further support this idea a nitro-Mannich reaction using nitroalkane 289 was examined to ensure that the interconversion between diastereomers is a catalysed process (Table 17). As can be seen, although the reaction is gradually moving towards favouring syn,syn diastereomer 290a, the rate at which this is occurring is significantly slower than that observed in the presence of the zinc species or with thiourea 272.
Table 17. Effects of reaction time on nitro-Mannich reaction of nitroalkane 291

<table>
<thead>
<tr>
<th>Entry</th>
<th>Time at rt</th>
<th>% Conv.</th>
<th>dr (a:b:c:d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5 min</td>
<td>55</td>
<td>5:90:5:0</td>
</tr>
<tr>
<td>2</td>
<td>30 min</td>
<td>55</td>
<td>10:85:5:0</td>
</tr>
<tr>
<td>3</td>
<td>1 h</td>
<td>51</td>
<td>10:85:5:0</td>
</tr>
<tr>
<td>4</td>
<td>2 h</td>
<td>50</td>
<td>15:75:10:0</td>
</tr>
<tr>
<td>5</td>
<td>4 h 30 min</td>
<td>45</td>
<td>25:65:10:0</td>
</tr>
</tbody>
</table>

\(^a\) % Conv. of 290 by \(^1\)H NMR. \(^b\) dr of crude 290 calculated from \(^1\)H NMR.

2.2.7 Reaction with ketimines to form quaternary centres

Currently, there have been no reports of a general asymmetric nitro-Mannich reaction with ketimines so the ability of the thiourea catalysed reductive nitro-Mannich reaction to form quaternary centres has also been briefly investigated. Using N-PMP protected ketimine 291 the reaction was attempted initially at room temperature. After 1 h at this temperature 60% conversion to the desired product was observed with a dr of 75:25 (Table 18, entry 1). After an additional hour at this temperature the conversion to the desired product had reduced slightly to 50% conversion and the dr had also reduced to 70:30 (Table 18, entry 2). The reducing amount of product is likely to be due to a more competitive retro-addition reaction as the \(\beta\)-nitroamine product 292 is less stable with a quaternary centre. By reducing the reaction temperature to \(-20^\circ\)C better conversion and diastereoselectivity could be obtained with approximately 76% of imine 291 converted to desired product 292 with a dr of 95:5 after 20 h (Table 18, entry 4). It appears at this point there exists a dynamic equilibrium between the forward and reverse reaction as the conversion remained constant over the next 4 h (Table 18, entry 5).
Table 18. Reductive nitro-Mannich reaction with ketimines

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>% Conv.²</th>
<th>dr分解²</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>rt</td>
<td>1</td>
<td>60</td>
<td>75:25</td>
</tr>
<tr>
<td>2</td>
<td>rt</td>
<td>2</td>
<td>50</td>
<td>70:30</td>
</tr>
<tr>
<td>3</td>
<td>-20</td>
<td>16</td>
<td>68</td>
<td>95:5</td>
</tr>
<tr>
<td>4</td>
<td>-20</td>
<td>20</td>
<td>76</td>
<td>95:5</td>
</tr>
<tr>
<td>5</td>
<td>-20</td>
<td>24</td>
<td>76</td>
<td>95:5</td>
</tr>
</tbody>
</table>

² % Conv. to 292 by 1H NMR. ²dr of crude 292 calculated from 1H NMR.

The β-nitroamine product 292 is tentatively assigned as anti since the kinetic product from nitro-Mannich reactions is typically the anti diastereomer. It is assumed that the absolute stereochemistry is 2R,3S as shown based on the previous work with aldmines (see section 2.2.5). As with the reductive nitro-Mannich reaction with aldmines, β-nitroamine product 292 was unstable to chromatography. Unfortunately, 292 could not be protected as a trifluoroacetamide using the standard conditions (Scheme 112) meaning that the level of enantiopurity could not be determined. In addition to trifluoroacetamide protection a number of other strategies were also attempted but were unsuccessful including triflate protection; acetate protection, via ketene formation; formylation using acetic formic anhydride; and attempted removal of the PMP group using ceric ammonium nitrate (CAN), followed by Boc protection. Instead only degradation of β-nitroamine 292 was observed (Scheme 112).
Scheme 112. Attempted protection of β-nitroamine 292

After the failed attempts to protect 292, an in situ reduction was attempted (Scheme 113). Unfortunately, once more no desired reduced product was isolated with either a complex mixture of products obtained or degradation of β-nitroamine 292 by retro-addition observed. One of the problems with the reduction methods is that they are all in different solvents to the reaction solvent choice for the reductive nitro-Mannich reaction (toluene).

Scheme 113. Attempted reduction of β-nitroamine 292

It could be imagined that when conducting a solvent swap, β-nitroamine 292 is already undergoing degradation. To check this, a small aliquot was removed from a
solution of 292 after a solvent swap from toluene to tetrahydrofuran. Indeed, significant degradation had occurred making it difficult to ascertain whether the reduction conditions had caused degradation in previous reactions. It may be possible to perform a reduction without altering the reaction solvent but due to time constraints such reactions have not been attempted.

2.2.8 Concluding paragraph

In this section, the development of an enantioselective tandem reductive nitro-Mannich reaction of nitroalkenes using thiourea organocatalysis has been described. This was achieved using Hantzsch ester 254 as the hydride source, N-PMP protected imines 30, and thiourea 272 as a simple organocatalyst. The reaction formed the desired β-nitroamines which after protection as trifluoroacetamides 239 could be isolated in moderate to high yields (32-83% yield) excellent diastereoselectivities (typically >90:10 dr) and good to excellent enantioselectivity (73-99% ee) in the majority of cases. The reaction was uniformly diastereo- and enantioselective when the nitroalkene was altered however; the rate of reaction was greatly altered when using more electron rich nitroalkenes leading to lower yields due to competitive reduction of imine 30a. Various heterocyclic, electron rich and electron deficient aromatic imines all gave excellent results but when using more sterically hindered ortho-tolyl or ortho-trifluoromethyl substituted imines lower stereoselectivity was observed (80:20 crude dr, 80-90% ee). Alkyl imines such as the "pentyl substituted imine 30i were poorly enantioselective in the reaction however the cause of this is currently unknown. It is proposed that the high enantioselectivity of the reaction is the result of a cyclic transition state which is stabilised by multiple cooperative H-bonding interactions between the substrates and thiourea catalyst 272, however this transition state is currently only speculative. The ability of the reaction to promote the reductive nitro-Mannich reaction with α-methyl-β-nitrostyrene 286 has also been investigated and the desired β-nitroamine bearing three contiguous stereocentres was isolated in a 32% yield as a single diastereomer (syn,anti) and in 84% ee. The reaction initially formed syn,syn diastereomer 287b but over time converted to the syn,anti diastereomer 287a which is believed to be the thermodynamic product. Some comparisons with this result and the results obtained in the similar conjugate addition/nitro-Mannich reactions of nitroalkenes with dialkyl
zincs were also drawn. Finally, the ability of thiourea 272 to promote the reaction with ketimine 291 was examined. Although, from $^1$H NMR data, desired $\beta$-nitroamine 292, bearing a quaternary centre, appears to have been synthesised it is too unstable to isolate and currently all attempts to protect or reduce 292 have failed.
2.3 Towards the total synthesis of Eudistomidin B

2.3.1 Introduction and retrosynthesis

Eudistomidin B is a member of a family of alkaloids and was first isolated in 1990 by Kobayashi and co-workers from the Okinawan marine tunicate *Eudistoma glaucus*.\(^{143}\) It was found to display some interesting biological activities including potent cytotoxicity against murine leukaemia cells L1210 (3.4 µg/mL) and L5178Y (3.1 µg/mL). In addition Eudistomidin B also activated rabbit heart muscle actomyosin ATPase by 93% at 3x10\(^{-5}\) M. Eudistomidin B is comprised of a tetrahydro β-carboline with a bromine atom substituted in the 5-position. It also features a vicinal diamine and as such could potentially be accessed by a nitro-Mannich reaction.

![Figure 31. Original reported and revised structure of Eudistomidin B](image)

The first enantioselective total synthesis of Eudistomidin B was reported in 2009 by Takayama with an overall yield of 0.12% over 20 steps but the NMR data of the natural and synthesised material contained several differences prompting the authors to question the proposed structure of Eudistomidin B.\(^{144}\) In 2010, Kobayashi *et al.* proposed a new structure for Eudistomidin B (Figure 31) and completed the first total synthesis in an overall yield of 9% over 5 steps starting from chiral amino acid 298 and 5-bromotryptamine 297 (Scheme 114). In that synthesis, the only low yielding step was the Bischler-Napieralski reaction of 299 which gave ketimine 300 in 12% yield. Additionally, neither of the starting materials are particularly cheap.
Scheme 114. First total synthesis of Eudistomidin B

An alternative synthesis of Eudistomidin B could be to use a reductive nitro-Mannich reaction as proposed in scheme 115. Eudistomidin B could be accessed by mono-methylation of each of the amines of diamine 302, which itself could be obtained from a reduction of β-nitroamine 303. This β-nitroamine could be derived from a reductive nitro-Mannich reaction between imine 304 and β-nitrostyrene 84a. Imine 304 should be easily formed by a Bischler-Napieralski reaction of formamide 305 with POCl₃, and formamide 305 could be simply synthesised from 5-bromotryptamine 297. Using known chemistry from the literature 5-bromotryptamine 297 could be readily sourced from 5-bromoindole 308. But since 5-bromotryptamine 297 could be sourced commercially, the synthesis was started from this point.
One observation that stands out amongst this synthetic scheme is that β-nitroamine 303 has a *syn* relationship. This is the opposite diastereoselectivity to what has been observed in the reductive nitro-Mannich reaction with *N*-PMP protected imines. However, there is a key difference between *N*-PMP protected imines and imine 304. Whereas *N*-PMP imines exist in the *E* conformation, imine 304 is locked in the *Z* conformation. It is proposed that this should result in a *syn* selective reaction rather than an *anti* selective reaction, as when locked in a *Z* conformation the substituents should be forced into *pseudo* equatorial positions (Figure 32). If this transition state is correct then catalyst 272 based on natural *L*-valine should provide the product with the desired absolute chemistry.
2.3.2 Forward synthesis route

The first stage of the proposed synthesis was the formylation of 5-bromotryptamine 297 to give formamide 305. This could be simply achieved by refluxing in ethylformate overnight to give formamide 305 in a quantitative yield. The second step was the synthesis of imine 304. Although imine 304 is not known in the literature, its non-brominated analogue is and so the literature synthesis of this was followed.\(^\text{146}\) The literature procedure described addition of the formamide as a solid in one portion to a solution of neat POCl\(_3\) at 3 °C. As this procedure reported an exotherm of 60 °C it was decided to add formamide 305 portionwise. After 2 h at 3 °C imine 304 was formed and could be filtered to give the acid salt of 304 in excellent purity in 85% yield. However, upon attempting to isolate the free base of imine 304 variable yields were obtained (20-80%).

As this reaction was only attempted a few times the cause of this variability has yet to be discovered. It was also found that imine 304 was quite unstable and could not be stored for more than 3 days at -20 °C before significant degradation had occurred. The acid salt of imine 304 was slightly more stable but also underwent degradation after one week at -20 °C. With imine 304 in hand the reductive nitro-Mannich reaction could be attempted. Initially the racemic reaction using Superhydride\(^\text{TM}\) was performed and pleasingly, after addition of trifluoroacetic acid desired β-nitroamine 303 was observed in a 80:20 dr and with 70% conversion. Crucially the coupling constants, of the protons in the α-position to the amino and nitro group, of the major
(\(J = 8.3\) Hz) and minor (\(J = 4.9\) Hz) diastereomers seem to suggest preferential formation of the syn diastereomer. Trifluoroacetamide protection was also successful to give 309 in a 23% yield. However, the product was slightly unstable and degraded before full data could be collected.

Scheme 117. Racemic reductive nitro-Mannich reaction with imine 304

Despite this, it was felt that an alternative protection strategy or rapid reduction could overcome this stability issue so examination of the asymmetric variant was performed. The reaction with thiourea catalyst 272 however, failed to give the desired product instead an unknown compound was formed. As imine 304 was insoluble in toluene it was thought that this may have prevented the reaction from succeeding and as such it was then attempted to perform the reaction in dichloromethane. Imine 304 was also found to be insoluble in dichloromethane but the reaction was continued regardless.

Scheme 118. A) Unexpected reaction with imine 304 and B) Literature reaction
It was observed that upon addition of nitroalkene 84a to a suspension of imine 304 the reaction became homogenous suggesting a possible reaction. This reaction was then left to age for 4 h upon which precipitation of the unknown product occurred and was isolated in a 68% yield based upon limiting reagent β-nitrostyrene 84a reacting with imine 304 in a 1:2 molar ratio.

Scheme 119. Proposed mechanism of formation of 310

From examining the $^1$H NMR and mass spectra it was proposed that the unknown product formed was 310 (Scheme 118, A). A literature search revealed a similar structure has been formed by the same reaction of an imine 311 and nitroalkene 84a previously by simply stirring in ethanol to give 312 in an 85% yield, although no data was given for this compound (Scheme 118, B). The proposed mechanism for the formation of 310 is shown in scheme 119.

Scheme 120. Attempts to synthesise N-Boc protected imine 314
It was assumed that the cause of this reaction was the use of extremely electron rich imine 304. It was hoped that by placing an electron withdrawing protecting group on the indole ring this undesired reaction could be suppressed. Initially, it was attempted to form N-Boc protected imine 314. Formylated tryptamine 305 could be selectively protected by gently heating with di-tert-butyl carbonate in tetrahydrofuran to form N-Boc protected product 313. Unfortunately, attempts to form imine 314 failed instead forming imine 304 after unsurprisingly Boc deprotection occurred due to the acidic conditions. Attempts to N-Boc protect this imine also failed and only degradation was observed (Scheme 120).

\[
\text{Scheme 121. Attempted tosylation of imine 304}
\]

It was next attempted to form N-tosylated imine 315. Initial efforts to achieve this directly from imine 304 failed despite literature precedent that described the same reactions on an un-brominated analogue (Scheme 121).\(^{148}\) After this failed it was attempted to first synthesise cyclisation precursor 319.

\[
\text{Scheme 122. Synthesis of tosylated formyl tryptamine 319}
\]
This could be achieved, albeit in a circuitous fashion from 5-bromotryptamine (Scheme 122). First, 5-bromotryptamine 297 was Boc protected to give 316 which was then selectively tosylated to give orthogonally protected 317. The Boc group could then be removed under acidic conditions and formylated in ethyl formate to give 319 in a 94% yield over 4 steps. With formamide 319 in hand the Bischler-Napieralski reaction was attempted (Table 19).

**Table 19.** Examination of various reaction conditions for Bischler-Napieralski reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Reaction conditions</th>
<th>Yielda of 315</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>neat</td>
<td>10 equiv. POCl₃, rt, 16 h</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>toluene</td>
<td>10 equiv. POCl₃, 110 °C, 16 h</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>acetonitrile</td>
<td>10 equiv. POCl₃, 82 °C, 16 h</td>
<td>15</td>
</tr>
<tr>
<td>4</td>
<td>propionitrile</td>
<td>10 equiv. POCl₃, 98 °C, 16 h</td>
<td>7</td>
</tr>
<tr>
<td>5</td>
<td>degassed acetonitrile</td>
<td>10 equiv. POCl₃, 82 °C, 16 h</td>
<td>15-45</td>
</tr>
<tr>
<td>6</td>
<td>dichloromethane</td>
<td>1.2 equiv. 2-Cl-pyridine, 1.1 equiv. Tf₂O, -78 °C 5 min, 140 °C 30 min MW</td>
<td>0</td>
</tr>
</tbody>
</table>

Reactions performed on 50 mg scale. a isolated yield of 315.

Attempts to perform the desired reaction in neat POCl₃ failed to give the desired reaction (Table 19, entry 1) as did the reaction in toluene at reflux (Table 19, entry 2). Some desired product was observed when acetonitrile was used as solvent and 315 was isolated in 15% yield (Table 19, entry 3). Using higher boiling propionitrile as the solvent however, gave a lower reaction yield of 7% (Table 19, entry 4). Although its identity could not be confirmed it was suspected that one of the by-products from the reaction was from oxidation of 315 to form the fully aromatised β-carboline ring. For this reason it was attempted to degas the acetonitrile and pleasingly desired product 315 was obtained in a moderate 45% yield (Table 19, entry 5). However, upon increasing the scale of the reaction to 100 mg only a 15% yield was obtained.
Unfortunately, due to time constraints the cause of this variability in yield could not be determined. Finally, the reaction was attempted using the conditions developed by Movassaghi et al. but no desired product was observed (Table 19, entry 6).[^149]

[Scheme 123. Asymmetric reductive nitro-Mannich reaction of imine 315]

With a small amount of N-tosylated imine 315 in hand, the asymmetric reductive nitro-Mannich reaction was attempted at room temperature using thiourea organocatalyst 272 (Scheme 123). Unlike with unprotected imine 304 the desired reductive nitro-Mannich reaction proceeded in good conversion (>95%) with a \(dr\) of 75:25. Unfortunately, the coupling constants of both diastereomers differed substantially from the expected values and as such it was not possible to identify whether the \(syn\) or \(anti\) diastereomer was formed. Pleasingly, \(\beta\)-nitroamine 320 could be protected as trifluoroacetamide 321 and the major diastereomer was isolated in a 55% yield. Regrettably, the product was only obtained in 16% \(ee\). Performing the reaction at lower temperature (-20 °C) over 20 h did improve the enantioselectivity forming 321 in 48% \(ee\), a similar level of diastereoselectivity, and in 33% yield. The difference in yield is thought to originate from experimental error due to the small scale the reactions are performed on rather than a difference in the reactivity at these temperatures. The increase in the enantioselectivity to 48% \(ee\) does suggest that the reaction could be optimised. The cause of the poor enantioselectivity compared to \(N\)-PMP imines is currently unknown but it is suspected that imine 315 is likely to have a different basicity to \(N\)-PMP imines 30 and hence may not bind to the catalyst as strongly. Another possible cause could be that the nitro-Mannich reaction does not proceed \(via\) a cyclic transition state. The coupling constants of \(\beta\)-nitroamine 320 are not indicative of a H-bonded cyclic conformation so it is plausible that a cyclic transition state does not occur as well.
Chapter 3. Conclusions and future studies
3.1 Conclusions

This doctoral thesis has successfully developed both a racemic and an asymmetric reductive nitro-Mannich reaction. The racemic variant was a continuation of previous work established in the group and it was found that the limitations of this research, namely an inability for the reaction to proceed with $\beta$-nitrostyrenes, could be overcome by using a stronger Brønsted acid (trifluoroacetic acid) and an alternative imine ($N$-PMP protected). With these changes a variety of $\beta$-nitroamines could be formed with conversion (>90%) and high diastereoselectivities (75:25 to >95:5 dr) by the one-pot Superhydride™ reduction/nitro-Mannich sequence of nitroalkenes. It was also discovered that when using electron rich aromatic imines the diastereoselectivity of the reaction was poor. This problem was overcome by switching the solvent to a non-coordinating solvent such as dichloromethane. The $\beta$-nitroamines were protected by reaction with trifluoroacetic anhydride and pyridine, due to their instability towards purification, enabling isolation of the products as trifluoroacetamides in good to excellent yields (58-87%) and diastereoselectivity (>90:10 dr).

The enantioselective reductive nitro-Mannich reaction of nitroalkenes was achieved using thiourea organocatalysis. It was discovered that the desired reaction could be promoted in tandem using a Hantzsch ester as the hydride source, thiourea catalyst and $N$-PMP protected imine. After a careful catalyst screen, it was discovered that a very simple and economic catalyst could promote the reaction with exquisite levels of stereocontrol after one day at -20 °C. The reaction was then examined with a variety of different substrates and was found to work well in almost all examples. Once more, after protection as trifluoroacetamides, the resultant products could be isolated in moderate to excellent yields (32-84%), high diastereoselectivity (>90:10 dr) and good to excellent enantioselectivity (73-99% ee). Observations from these experiments have led to the proposal that the reduction is the rate determining step of the reaction and a H-bond stabilised six-membered transition state has been proposed as the enantiodetermining step. Additionally, a preliminary investigation into the ability of the catalyst to promote a reductive nitro-Mannich reaction using...
α-methyl-β-nitrostyrene was examined to give the desired product containing three contiguous stereo centres as a single diastereomer in low yield (32%) and in 85% ee. The potential of the thiourea to catalyse a reductive nitro-Mannich reaction with ketimines was also explored. Although this reaction was successful, forming the desired product containing a quaternary centre in 95:5 dr and 80% conversion, it could not be isolated and the enantioselectivity was not calculated. These preliminary experiments should pave the way for further studies in this area.

The final research of the thesis focussed on progress towards the synthesis of 1,2-diamine containing natural product Eudistomidin B, using a nitro-Mannich reaction as the key step. Using an unprotected N-H-indole containing pre-cursor an unexpected by-product was formed instead of the nitro-Mannich product. However it was later discovered that the desired tandem reductive nitro-Mannich would succeed when using a N-tosyl protected analogue to form the desired product in a 33% yield and 48% ee as a single diastereomer after purification. The synthesis was halted at this point due to time constraints but significant optimisation will be required to make this a viable route to Eudistomidin B.
3.2 Future studies

3.2.1 Asymmetric reductive nitro-Mannich reaction

Although, the reaction using simple catalyst 272 generally formed the desired products with excellent stereoselectivity and in good yields there were some limitations with the reaction. In particular, the reaction yield was poor when using more electron rich nitroalkenes due to a combination of a slow rate of reduction and competitive reduction of the N-PMP protected imine. To overcome these problems a more reactive hydride source may be required as simply increasing the reactivity of the catalyst is likely to result in an increased amount of the retro-nitro-Mannich reaction. A hydride source with only one electron withdrawing group should achieve this as You’s group have shown such dihydropyridines are typically stronger hydride donors.\textsuperscript{150}

<table>
<thead>
<tr>
<th>current procedure</th>
<th>possible improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image.png" alt="Chemical structure" /></td>
<td><img src="image.png" alt="Chemical structure" /></td>
</tr>
</tbody>
</table>

**Figure 33.** Possible improvements to enantioselective reductive nitro-Mannich reaction

This could also eventually lead to catalytic use of a dihydropyridine,\textsuperscript{151} which would be valuable as Hantzsch ester 254 is not an atom economical reagent. Additionally a different imine-protecting group or a more selective thiourea organocatalyst would be required too as simply increasing the reactivity of the hydride source would not prevent competitive reduction of the imine. An alternative protecting group such as benzyl should result in an imine less active towards reduction as well as being easier to remove in subsequent synthesis steps. Another limitation of the reaction is the
poor reactivity with alkyl substituted imines. This is a difficult problem to fix as the majority of alkyl substituted imines exist in both the imine and enamine form and as such can either undergo oligomerisation, as in the case of N-PMP protected imines, or remain unreactive to nucleophilic attack by existing solely in the enamine form. A possible solution is to form the imine in situ so that only a small concentration of imine exists at any one point. Such a method has been previously utilised by Palomo et al. with a variety of N-Boc protected imines (see section 1.1.5, Scheme 22). Whether such a method could be applied in the reductive nitro-Mannich reaction is unclear as N-Boc imines were previously shown to undergo reduction in these conditions (see section 2.2.1, Scheme 96). Unfortunately, such a method could not be employed with N-PMP imines as their rate of formation is too rapid.

In addition to improving the reaction, a detailed investigation into the mechanism of the reaction should be initiated. In section 2.2.5 the synthesis of alternative catalyst structures to probe the mechanism of the enantiodetermining step were touched upon. Another catalyst structure which should help to educate about the mechanism would be thioamide catalyst 283 whose synthesis was attempted using Lawesson’s reagent directly from 272 (Scheme 124). This was only attempted once however, and appears straightforward enough. Synthesis of 283 could provide useful evidence as to whether a H-bond interaction exists between the iminium species and the (thio)amide moiety of the catalyst as this bond should be weaker with catalyst 283 and hence result in lower enantioselectivity. Although, methyl ester catalyst 282 has already been synthesised and suggests this interaction is not as important as first thought (see section 2.2.5, Table 14), for the sake of completeness and to provide further evidence synthesising thioamide catalyst 283 seems like a worthwhile pursuit.

Given the unexpected result with methyl ester catalyst 282 and the simplicity of catalyst 272 it seems sensible to examine the possibility that this nitro-Mannich reaction is catalysed by more than one thiourea unit. To examine this possibility, the order of the reaction with respect to the catalyst would need to be determined.
However, this would only provide information about the rate determining step, which is believed to be the reduction step, and would not necessarily inform about the enantiodetermining step. Another, series of experiments could set out to uncover relationships between the enantiopurity of the catalyst and the enantiopurity of the resultant product. Any deviations from linearity would suggest that the catalyst is a heterodimeric species in the enantiodetermining step and may help to explain the high levels of enantioselectivity.\textsuperscript{152} Computational studies may offer the best solution to determining the mechanism of the enantio-determining step and there have been several theoretical studies performed on thiourea catalysts, including some with similar structures to the catalyst used in the reductive nitro-Mannich reaction.\textsuperscript{84}

3.2.2 Asymmetric reductive nitro-Mannich reaction of ketimines

The enantioselective reductive nitro-Mannich reaction with ketimines has shown some promise as the desired $\beta$-nitroamine is formed but cannot be isolated. \textit{In situ} reduction may offer a solution but currently, either complex mixtures or degradation products have been isolated. One of the problems of the reaction is due to the large number of components in the reaction complicating the spectra. An idea that could make identification of products easier could be to use nitroethylene 324 as the nitroalkene rather than $\beta$-nitrostyrene (Scheme 125, A).

\begin{center}
\textbf{A) Reductive nitro-Mannich reaction using low boiling nitroethylene}
\end{center}

\begin{center}
\begin{align*}
\text{NO}_2^- + \quad \begin{array}{c}
\text{Ph} \\
\text{Me}
\end{array}
\xrightarrow{2 \text{ equiv. } 324}
\xrightarrow{2.0 \text{ equiv. } 254}
\xrightarrow{\text{Toluene, } -20 \text{ °C, } 20 \text{ h}}
\text{Me} \xrightarrow{[\text{H}] \text{ conditions}}
\end{align*}
\end{center}

\begin{center}
\begin{align*}
\text{MeHN-PMP} \quad \begin{array}{c}
\text{Ph} \\
\text{NH}_2
\end{array}
\xrightarrow{292}
\xrightarrow{325}
\xrightarrow{\text{bp } \sim 20 \text{ °C}}
\end{align*}
\end{center}

\begin{center}
\textbf{B) Reductive nitro-Mannich reaction using 4-hydroxy phenyl protected imine}
\end{center}

\begin{center}
\begin{align*}
\text{PhNO}_2^- + \quad \begin{array}{c}
\text{Ph} \\
\text{Me}
\end{array}
\xrightarrow{2 \text{ equiv. } 84a}
\xrightarrow{2.0 \text{ equiv. } 254}
\xrightarrow{\text{Toluene, } -20 \text{ °C, } 20 \text{ h}}
\xrightarrow{\text{TF}_2\text{O, pyridine}}
\text{MeHN-Ph}
\end{align*}
\end{center}

\begin{center}
\begin{align*}
\text{Ph} \xrightarrow{326}
\xrightarrow{327}
\xrightarrow{\text{NH}_2}
\end{align*}
\end{center}

\textbf{Scheme 125.} Possible solutions to the instability of $\beta$-nitroamines with a quaternary centre
The unreacted nitroethylene or its reduction products could then be removed from the reaction under vacuum as both are low boiling (nitroethylene bp ~ 99 °C, ethylamine bp ~ 20 °C). Nitroethylene may also be more reactive than β-nitrostyrene enabling complete conversion of imine 291 to occur before the retro-addition is competitive. Another possible solution to the poor stability could be to use a hydroxy imine such as 326. This could then be protected after the nitro-Mannich reaction to form a more stable β-nitroamine such as 327 which may be stable to purification (Scheme 125, B). However, ketimine 326 may be very insoluble in a solvent such as toluene so the feasibility of such a reaction is unknown.

3.2.3 Reductive nitro-Mannich reaction to form three stereocentres

The preliminary result into the potential to build β-nitroamines with three contiguous stereocentres using the reductive nitro-Mannich reaction showed good promise forming the desired product in a 32% yield, as a single diastereomer and in 84% ee. The reaction is limited by similar problems to the reductive nitro-Mannich reactions with electron rich nitroalkenes in that the rate of reaction is slow and that competitive reduction of N-PMP imine 291 occurs. A more selective reduction of nitroalkenes is required and further catalyst screening would need to be performed to achieve this. Another reaction that could be examined which should result in a more selective reduction of the nitroalkene over the imine would be the reductive nitro-Mannich reaction of substituted nitroacrylates such as 328. These should then also cyclise to form enantiomerically enriched pyrrolidinones (Scheme 126). The Anderson group have previously synthesised such compounds using the conjugate addition/nitro-Mannich reaction with diethyl zinc, and List’s group have performed asymmetric reductions of nitroacrylates, so there is good literature precedence for such a reaction.

Scheme 126. Reductive nitro-Mannich reaction of nitroacrylates
3.2.4 Tandem nitro-Mannich reactions with different nucleophiles

As was discussed in the introduction (see section 1.3.4) thiourea organocatalysis has been used to promote the addition of a variety of nucleophiles to nitroalkenes. It would be of great interest to investigate the possibility of performing some of these additions in tandem with a nitro-Mannich reaction. Scheme 127 shows some of the possible transformations.

![Scheme 127. Other possible thiourea catalysed tandem nitro-Mannich reactions](image)

3.2.5 Total synthesis of Eudistomidin B

The total synthesis of Eudistomidin B was halted after poor enantioselectivity for the nitro-Mannich reaction was observed. It is thought that the cause of this may be the basicity of imine 315 which is likely to be different to N-PMP protected imines 30 used in the earlier research. It is likely that further catalyst screening will be required to overcome this low enantioselectivity. One alternative may be to attempt the reductive nitro-Mannich reaction on β-carboline 330 as this should have similar basicity to the N-PMP imines. However, as to whether the nitro-Mannich reaction would be able to break the aromaticity of such a system is unclear.
If a catalyst screen was to be performed, due to the poor reproducibility of the Bischler-Napieralski reaction to synthesise imine 315 it may be better to develop the initial reductive nitro-Mannich methodology on 3,4-dihydroisoquinolines 333 as these should hopefully react in a similar manner but can be synthesised much more readily (Scheme 129).\textsuperscript{153} Such a reaction would also be of use to the synthetic community as currently, no diastereoselective nitro-Mannich reactions to form $\beta$-nitroamines such as 334 are known. Additionally, only a single enantioselective nitro-Mannich reaction of 3,4-dihydroisoquinolines has been reported.\textsuperscript{154}

**Scheme 129.** Reductive nitro-Mannich reaction of 3,4-dihydroisoquinolines
Chapter 4. Experimental
4.1 General experimental

4.1.1 General experimental details

Unless specified otherwise for all non-aqueous chemistry, glassware was flame-dried under an inert (N\textsubscript{2} or Ar) atmosphere. Cryogenic conditions (-78 °C) were achieved using solid carbon dioxide/acetone baths. Temperatures of -100 °C were achieved using a liquid N\textsubscript{2}/toluene bath and reaction temperatures of -20 °C were achieved using a NESLAB CB-80 Cryobath. Temperatures of 0 °C were obtained by means of an ice bath. Room temperature indicates temperatures in the range of 20-25 °C.

For the purposes of thin layer chromatography (tlc), Merck silica-aluminium plates were used, with \textit{uv} light (254 nm) and potassium permanganate used for visualisation. For column chromatography, Apollo Scientific ZEOprep 60 or Merck Geduran® Si 60 silica gel was used. Removal of solvents (\textit{in vacuo}) was achieved using a Vacuubrand diaphragm pump or house vacuum and Büchi rotary evaporators.

All NMR data was collected using a Bruker AMX 300 MHz, Bruker AVANCE III 400 MHz, Bruker AVANCE 500 MHz or Bruker AVANCE III 600 MHz. Data was manipulated directly using Bruker XwinNMR (version 2.6) or TopSpin (version 2.1). Reference values for residual solvents were taken as δ = 7.27 (CDCl\textsubscript{3}) and 2.51 ppm (DMSO-\textit{d}6) for \textsuperscript{1}H NMR; δ = 77.16 ppm (CDCl\textsubscript{3}) for \textsuperscript{13}C NMR. Multiplicities for coupled signals were denoted as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br. = broad, apt. = apparent and dd = double doublet \textit{etc.} Coupling constants (\textit{J}) are given in Hz and are uncorrected. Where appropriate, COSY, DEPT, HMBC, HMQC and NOE experiments were carried out to aid assignment.

Mass spectroscopy data was collected on a Thermo Finnigan Mat900xp (EI/CI) VG-70se (FAB) and Waters LCT Premier XE (ES) instruments. Infrared data was collected using a Perkin-Elmer 1600 FTIR machine as a thin film unless otherwise stated. Elemental analysis was performed on an Exeter Analytical Inc. EA440 horizontal load analyser. Melting points are uncorrected and were recorded on a Stuart Scientific SMP3 system. Optical rotations were obtained using a Jasco DIP370 digital polarimeter and are reported in deg cm\textsuperscript{-2} g\textsuperscript{-1}. Chiral HPLC was performed using either a Chiralcel AD 25 cm analytical column or an OD-H 15 cm analytical column.
Samples were dissolved in solutions of MeCN/PrOH/hexane (5:15:80) to concentrations of 2.5 mg/mL.

4.1.2 Purification of reagents

All solvents and reagents were used as supplied or purified using standard techniques, unless alternatively specified herein. All solutions of organo-lithium reagents were standardised with diphenyl acetic acid. Activation of molecular sieves was achieved by flame-drying under high vacuum.

*Cyclohexane carboxaldehyde* was distilled from calcium hydride powder under reduced pressure and stored in a darkened refrigerator.

(R,R)-1,2-Diaminocyclohexane mono-(-)-tartrate was resolved from (±)-trans-1,2-diaminocyclohexane using L-(-)-tartaric acid according to literature procedure.

*Dichloromethane* was obtained from a solvent tower, where degassed dichloromethane was passed through two columns of alumina and a 7 micron filter under 4 bar pressure.

*Diethyl ether* was obtained from a solvent tower, where degassed diethyl ether was passed through two columns of alumina and a 7 micron filter under 4 bar pressure.

*Hexanal* was distilled from calcium hydride powder and stored in a darkened refrigerator.

*β-Nitrostyrene* was recrystallised from diethyl ether and stored in a darkened freezer. (E)-2-(2-Nitrovinyl)pyridine was stored in a darkened refrigerator and passed through a short column of silica prior to use.

2-Pyridine carboxaldehyde was distilled and stored in a darkened refrigerator.

*Tetrahydrofuran* was obtained from a solvent tower, where degassed tetrahydrofuran was passed through two columns of alumina and a 7 micron filter under 4 bar pressure.

*Toluene* was obtained from a solvent tower, where degassed toluene was passed through two columns of alumina and a 7 micron filter under 4 bar pressure.
4.2 Synthetic procedures

4.2.1 Procedures for preparation of nitroalkenes

General procedure A: 1.0 M NaOH (2.5 mL per mmol) was added to a solution of MeNO₂ (2.5 equiv.) and carbonyl compound (limiting reagent) in MeOH (7.5 mL per mmol) at 0 °C (CAUTION: EXOTHERM!). After a 10 min stir, ice water (2.0 mL per mmol) was added and the mixture charged to a dropping funnel. The mixture was then added dropwise to 8.0 M HCl (2.0 mL per mmol) over 30 min at 0 °C (CAUTION: EXOTHERM!). The reaction was stirred for 1 h after which time the product was collected by filtration if precipitation had occurred. If precipitation did not occur, the mixture was extracted with CH₂Cl₂ (3 x 5.0 mL per mmol) and the combined organic phases were dried (MgSO₄) and the solvent removed in vacuo to leave crude nitroalkene.

General procedure B: Carbonyl compound (limiting reagent), MeNO₂ (5.0 equiv.) and Et₃N (0.35 equiv.) were stirred overnight under N₂ at rt. Once reaction complete, as judged by tlc analysis, the excess MeNO₂ and Et₃N were removed in vacuo. Crude nitroalcohol was then dissolved in CH₂Cl₂ (10 mL per mmol) and cooled to 0 °C. To this solution was then added dropwise MsCl (1.2 equiv.) and the solution was stirred for 5 min. A solution of iPr₂NEt (2.5 equiv.) in CH₂Cl₂ (2.0 mL per mmol) was then added via cannula over a period of 10 min. When the reaction was judged complete by tlc analysis (typically 1 h), it was returned to room temperature. The reaction was then washed with water (2 x 3.0 mL per mmol), 2.0 M HCl (2 x 3.0 mL per mmol), dried (MgSO₄) and concentrated in vacuo to leave crude nitroalkene.
**General procedure C:** To a mixture of ammonium acetate (1.0 equiv.) and MeNO₂ (4.0 mL per mmol) was added carbonyl compound (limiting reagent) and the mixture was heated to reflux (105 °C). Once the reaction was judged complete by tlc analysis the reaction was cooled to rt and the excess solvent was removed *in vacuo*. The crude residue was then re-dissolved in CH₂Cl₂ (10.0 mL per mmol) and washed with sat. aq. NaHCO₃ (3.0 mL per mmol). The organic phase was then dried (MgSO₄) and the excess solvent removed *in vacuo* to leave crude nitroalkene.

**Prepared by General procedure B.** Cyclohexanecarboxaldehyde (26.7 mmol) afforded after purification by column chromatography (8% Et₂O/pet. ether) 84b (3.39 g, 21.8 mmol, 82% yield) as a pale yellow oil which solidified in the freezer; ¹H NMR (600 MHz, CDCl₃) δ 1.15-1.26 (3H, m, Cy), 1.26-1.37 (2H, m, Cy), 1.67-1.74 (1H, m, Cy), 1.74-1.85 (4H, m, Cy), 2.21-2.30 (1H, m, Cy), 6.93 (1H, dd, J = 13.4, 1.3, HC=C), 7.22 (1H, dd, J = 13.5, 7.2, HC=C). ¹H NMR data are consistent with literature data.¹⁵⁷

**Prepared by General procedure B.** n-Hexanal (10.0 mmol) afforded after purification by column chromatography (2.5% Et₂O/pet. ether) 84c (874 mg, 6.1 mmol, 61% yield) as a pale yellow oil; ¹H NMR (600 MHz, CDCl₃) δ 0.90 (3H, t, J = 7.0, CH₃), 1.26-1.38 (4H, m, (CH₂)₂), 1.47-1.56 (2H, m, nPrCH₂), 2.27 (2H, qd, J = 7.4, 1.5, nBuCH₂), 6.98 (1H, dt, J = 13.4, 1.5, nPnCH), 7.28 (1H, dt, J = 13.6, 7.5, CHNO₂). ¹H NMR data are consistent with literature data.¹⁵⁷
**Prepared by General procedure A.** 2-Furancarboxaldehyde (14.0 mmol) afforded 84d (1.21 g, 8.7 mmol, 62% yield) as a yellow solid; mp 72-74 °C (Lit.\(^{158}\) 74-75 °C); \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 6.58 (1H, dd, \(J = 3.5, 1.8\), ArH), 6.89 (1H, d, \(J = 3.4\), ArH), 7.52 (1H, d, \(J = 13.2\), ArCH), 7.59 (1H, d, \(J = 1.3\), ArH), 7.77 (1H, d, \(J = 13.2\), CHNO\(_2\)). \(^1\)H NMR data are consistent with literature data.\(^{158}\)

\[
(E)-1\text{-methyl-2-(2-nitrovinyl)benzene 84e}
\]

\[
\begin{array}{c}
\text{NO}_2 \\
\end{array}
\]

**Prepared by General procedure A.** ortho-Tolualdehyde (25.0 mmol) afforded crude 84e which did not crystallise and was purified by column chromatography (5% EtOAc/pet. ether) to give 84e (3.42 g, 21.0 mmol, 84% yield) as a yellow oil which solidified in the freezer; IR \(\nu_{\text{max}}\) 3109 (C-H), 1630 (C=C), 1511 (N-O), 1337 (N-O), 1219, 963, 762 cm\(^{-1}\); \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 2.49 (3H, s, CH\(_3\)), 7.24-7.26 (1H, m, ArH), 7.28 (1H, d, \(J = 8.3\), ArH), 7.36-7.41 (1H, m, ArH), 7.49-7.54 (2H, m, ArH, ArCH), 8.31 (1H, d, \(J = 13.6\), CHNO\(_2\)); \(^{13}\)C NMR (151 MHz, CDCl\(_3\)) \(\delta\) 20.1 (CH\(_3\)), 126.9 (CH), 127.5 (CH), 129.0 (C), 131.5 (CH), 132.1 (CH), 136.9 (CH), 137.7 (CH), 139.4 (C); \(m/z\) (EI) 163 (36, M); HRMS C\(_9\)H\(_9\)NO\(_2\) calcd. 163.0633, found 163.0628.

\[
(E)-1\text{-Methoxy-4-(2-nitrovinyl)benzene 84h}
\]

\[
\begin{array}{c}
\text{O} \\
\text{NO}_2 \\
\end{array}
\]

**Prepared by General procedure A.** 4-Methoxybenzaldehyde (22.0 mmol) afforded 84h (2.09 g, 11.7 mmol, 53% yield) as a yellow solid; mp 79-81 °C (Lit.\(^{159}\) 83-85 °C); \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 3.87 (3H, s, CH\(_3\)), 6.95 (2H, dm, \(J = 8.8\). ArH), 7.47-7.54 (3H, m, ArH, ArCH), 7.98 (1H, d, \(J = 13.6\), CHNO\(_2\)). \(^1\)H NMR data are consistent with literature data.\(^{159}\)

\[
(E)-1\text{-[(2-nitrovinyl)-2-(trifluoromethyl)benzene 84i}
\]

\[
\begin{array}{c}
\text{F}_3\text{C} \\
\text{NO}_2 \\
\end{array}
\]

**Prepared by General procedure A.** 2-(Trifluoromethyl)benzaldehyde (17.0 mmol) afforded 84i (2.32 g, 10.7 mmol, 63% yield) as a yellow solid; mp 54-56 °C; IR \(\nu_{\text{max}}\) 3108 (C-H), 1643 (C=C), 1516 (N-O), 1345 (N-O), 1311 (C-F), 1157, 1106 cm\(^{-1}\); \(^1\)H
NMR (600 MHz, CDCl$_3$) $\delta$ 7.50 (1H, d, $J = 13.6$, HC=C), 7.58-7.69 (3H, m, ArH, HC=C), 7.79 (1H, dd, $J = 7.3$, 0.9, ArH); 8.38 (1H, dd, $J = 13.6$, 1.7, ArH); $^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 123.7 (1C, q, $J = 274.0$, CF$_3$), 127.0 (1C, q, $J = 5.5$, ArH), 128.6 (CH), 128.7 (1C, m, Ar), 130.6 (1C, q, $J = 30.8$, ArCF$_3$), 131.5 (CH), 132.6 (CH), 134.9 (1C, q, $J = 2.2$, CH), 139.9 (CH); m/z (EI) 217 (17, M), 170 (50, M–HNO$_2$); HRMS C$_9$H$_6$F$_3$NO$_2$ calcd. 217.0351, found 217.0343.

(E)-2-(2-Nitrovinyl)pyridine 84k

Prepared by General procedure B. N-Methyl-pyrrole-2-carboxaldehyde (15.0 mmol) afforded crude 84k as a black solid which was purified by column chromatography (40% Et$_2$O/pet. ether) to give 84k (900 mg, 6.0 mmol, 40% yield) as a yellow solid; mp 61-62 °C; IR $\nu_{max}$ 3121 (C–H), 3056 (C–H), 1638 (C=C), 1569, 1506 (N-O), 1345 (N-O), 963, 785 cm$^{-1}$; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.38 (1H, dd, $J = 7.6$, 4.8, ArH), 7.48 (1H, d, $J = 7.7$, ArH), 7.79 (1H, td, $J = 7.7$, 1.9, ArH), 7.92 (1H, d, $J = 13.2$, ArCH), 8.02 (1H, d, $J = 13.2$, CHNO$_2$), 8.69 (1H, d, $J = 4.1$, ArH); $^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 125.8 (ArH), 126.5 (ArH), 137.3 (CH), 137.3 (CH), 140.9 (CH), 149.5 (Ar), 150.8 (ArH); m/z (EI) 150 (15, M), 104 (59, M–NO$_2$); HRMS C$_7$H$_6$N$_2$O$_2$ calcd. 150.0429, found 150.0427.

(E)-1-Methyl-2-(2-nitrovinyl)-1H-pyrrole 84m

Prepared by General procedure C. N-Methyl-pyrrole-2-carboxaldehyde (10.0 mmol) afforded crude 84m as a black solid which was purified by chromatography (10% EtOAc/pet. ether) to give 84m (1.30 g, 8.5 mmol, 85% yield) as an orange solid; mp 92-95 °C; IR $\nu_{max}$ 3133 (C–H), 3093 (C–H), 1609 (C=C), 1528 (N-O), 1489, 1471, 1307 (N-O), 1273, 1245, 1071, 959, 817 cm$^{-1}$; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 3.77 (3H, s, CH$_3$), 6.27 (1H, dd, $J = 4.0$, 2.5, ArH), 6.80 (1H, dd, $J = 4.1$, 1.3, ArH), 6.92-6.97 (1H, m, ArH), 7.46 (1H, d, $J = 13.2$, CHNO$_2$), 7.99 (1H, d, $J = 13.2$, ArCH); $^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 34.9 (NCH$_3$), 111.2 (ArH), 116.3 (ArH), 125.0 (Ar), 127.6 (ArH), 130.8 (ArCH), 131.8 (CHNO$_2$); m/z (EI) 152 (54, M); HRMS C$_7$H$_6$N$_2$O$_2$ calcd. 152.0586, found 152.0581.
**Prepared by General procedure B.** 

N-Tosyl-pyrrole-2-carboxaldehyde (5.0 mmol) afforded crude **84n** as a black oil which was purified by chromatography (20% EtOAc/pet. ether) to give **84n** (2.48 g, 8.5 mmol, 85% yield) as an orange solid; mp 139-140 °C; IR $\nu_{\text{max}}$ 3119 (C-H), 1622 (C=C), 1505 (N-O), 1373 (N-O), 1323 (S=O), 1175, 1152, 666 cm$^{-1}$; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 2.42 (3H, s, Me), 6.40 (1H, t, $J$ = 3.5, ArH), 6.82 (1H, d, $J$ = 2.4, ArH), 7.33 (2H, d, $J$ = 8.3, ArH), 7.36 (1H, d, $J$ = 13.6, ArCH), 7.56-7.66 (1H, m, ArH), 7.74 (2H, d, $J$ = 8.5, ArH), 8.50 (1H, d, $J$ = 13.6, CHNO$_2$); $^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 21.8 (CH$_3$), 113.5 (ArH), 118.7 (ArH), 125.7 (Ar), 127.1 (CH), 127.2 (ArH), 128.5 (CH), 130.6 (ArH), 135.2 (Ar), 135.7 (CH), 146.3 (Ar); $m/z$ (El) 292 (4, M), 249 (9), 155 (43), 91 (100); HRMS C$_{13}$H$_{12}$N$_2$O$_4$S calcd. 292.0512, found 292.0529.

**Prepared according to a modified literature procedure.** To a pre-cooled solution of acetic anhydride (32.0 mL, 340.0 mmol) at -20 °C was added dropwise a solution of 70% nitric acid in water (2.8 mL, 44.0 mmol). The mixture was then allowed to warm to rt (CAUTION – temperature rises rapidly above 0 °C) and then cooled back to -20 °C. To this colourless solution was then added dropwise $\alpha$-methylstyrene (2.6 mL, 20.0 mmol) keeping the reaction temperature below -15 °C. The reaction was then stirred between -10 and -20 °C for 15 min or until reaction complete as monitored by tlc. Ice/water (15 g) was then added and the mixture was allowed to warm to rt and stirred for 15 min. The pale pink solution was then diluted with sat. brine (5 mL) and extracted with Et$_2$O (3 x 15 mL). The combined organics were then washed with sat. aq. NaHCO$_3$ 5 x 100 mL) and with sat. brine (25 mL) and dried (MgSO$_4$). The excess solvent was removed in vacuo to give crude $\beta$-nitroacetate (3.75 g, 16.8 mmol, 84% yield) which was re-dissolved in CHCl$_3$ (25 mL) before Et$_3$N (12.5 mL, 90.0 mmol) was added and the reaction was stirred for 12 h at rt
until reaction judged complete by tlc analysis. The reaction was then diluted with more CHCl₃ (25 mL) and washed with 2.0 M HCl (2 x 50 mL) and sat. brine (25 mL). The resultant organic phase was then dried (MgSO₄) and the excess solvent removed to afford, after purification by column chromatography (1% Et₂O/pet. ether), **286** (1.42 g, 8.7 mmol, 44% yield) as a yellow oil which solidified in the freezer; ¹H NMR (600 MHz, CDCl₃) δ 2.65 (3H, s, CH₃), 7.31 (1H, s, ArH), 7.42-7.49 (5H, m, ArH); ¹H NMR data are consistent with literature data.⁵⁴a

### 4.2.2 Procedures for preparation of imines

![Chemical structure of imine](image)

**General procedure D:** To a mixture of basic alumina (1.0 g per mmol) and amine (limiting reagent) in CH₂Cl₂ (5.0 mL per mmol) under N₂ at rt was added carbonyl compound (1.0 equiv.). The mixture was stirred until reaction complete (typically less than 30 min) as monitored by ¹H NMR. Filtration through celite® and removal of solvents *in vacuo* afforded crude imine.

![Chemical structure of imine](image)

**General procedure E:** To a mixture of basic alumina (1.0 g per mmol) amine (limiting reagent) in CH₂Cl₂ (5.0 mL per mmol) under N₂ at -78 °C was added carbonyl compound (1.0 equiv.). The mixture was stirred at -78 °C for 1 h and then warmed in an ice bath for 5 min before allowing the reaction to warm to rt over 5 min. Filtration through celite® and removal of solvents *in vacuo* afforded crude imine which was used without further purification.

![Chemical structure of imine](image)

**General procedure F:** To a flask containing rigorously flame-dried 4Å molecular sieves (1.0 g per mmol) in Et₂O (5.0 mL per mmol) under N₂ at rt was added amine (limiting reagent). After 5 min, carbonyl compound (1.0 equiv.) was added and the mixture was stirred until reaction complete (typically 16 h) as monitored by ¹H NMR. Filtration through celite® and removal of solvents *in vacuo* afforded crude imine.
**Prepared by General procedure D.** Benzaldehyde (10.0 mmol) afforded crude 30a as a pale yellow solid. Recrystallisation in EtOAc/pet. ether gave 30a (1.52 g, 7.2 mmol, 72% yield) as off-white flakes; mp 68-69 °C (Lit. 66-68 °C); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 3.84 (3H, s, OCH\(_3\)), 6.94 (2H, dm, \(J = 9.1\), ArH), 7.24 (2H, dm, \(J = 9.1\), ArH), 7.43-7.50 (3H, m, ArH), 7.85-7.92 (2H, m, ArH), 8.49 (1H, s, H\(\text{C}=\text{N}\)). \(^1\)H NMR data are consistent with literature data.\(^{160}\)

\((E)-4\)-**Methoxy-N-(4-methoxybenzylidene)aniline 30e**

**Prepared by General procedure D.** 4-Methoxybenzaldehyde (10.0 mmol) afforded crude 30e as a yellow/orange solid. Recrystallisation in EtOAc/pet. ether gave 30e (2.03 g, 8.4 mmol, 84% yield) as a pale yellow solid; mp 136-138 °C (Lit. 137-139 °C); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 3.83 (3H, s, OCH\(_3\)), 3.87 (3H, s, OCH\(_3\)), 6.92 (2H, dm, \(J = 9.1\), ArH), 6.98 (2H, dm, \(J = 8.8\), ArH), 7.21 (2H, dm, \(J = 9.1\), ArH), 7.83 (2H, dm, \(J = 8.8\), ArH), 8.41 (1H, s, H\(\text{C}=\text{N}\)). \(^1\)H NMR data are consistent with literature data.\(^{162}\)

\((E)-4\)-**Methoxy-N-(2-(trifluoromethyl)benzylidene)aniline 30g**

**Prepared by General procedure D.** 2-(Trifluoromethyl)benzaldehyde (15.0 mmol) afforded crude 30g as a yellow solid. Recrystallisation in EtOAc/pet. ether gave 30g (2.38 g, 8.5 mmol, 57% yield) as yellow flakes; mp 54-56 °C; IR \(\nu_{\text{max}}\) 2959 (C-H), 1622 (C=\(\text{N}\)), 1574, 1502, 1311, 1166, 1105 cm\(^{-1}\); \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 3.85 (3H, s, OCH\(_3\)), 6.96 (2H, dm, \(J = 9.0\), ArH), 7.25-7.30 (2H, m, ArH), 7.55 (1H, t, \(J = 7.5\), ArH), 7.65 (1H, t, \(J = 7.6\), ArH), 7.73 (1H, d, \(J = 7.9\), ArH), 8.44 (1H, d, \(J = 7.9\), ArH), 8.83-8.86 (1H, m, N=CH\(_2\)); \(^{13}\)C NMR (151 MHz, CDCl\(_3\)) \(\delta\) 55.6 (CH\(_3\)), 114.6...
(ArH), 122.7 (ArH) 124.4 (1C, q, J = 275.1, CF₃), 125.8 (1C, q, J = 5.5, ArH), 128.3 (ArH), 129.5 (1C, q, J = 31.9, ArCF₃), 130.4 (ArH), 132.2 (Ar), 144.5 (C=N), 154.2 (ArH), 158.9 (ArO); m/z (EI) 279 (100, M); HRMS C₁₅H₁₂F₃NO calcd. 279.0871, found 279.0866.

(E)-N-Hexylidene-4-methoxyaniline 30i

Prepared by General procedure E. α-Hexanal (0.55 mmol) afforded crude 30i (115 mg, 0.56 mmol, quantitative yield) as a colourless oil which was used without further purification; IR νmax 1621 (C=N), 1505, 1249, 1165, 1127 cm⁻¹; ¹H NMR (400 MHz, CD₆D₆) δ 0.85 (3H, t, J = 7.0, CH₃), 1.18-1.28 (4H, m, CH₂), 1.50 (2H, m, CH₂), 2.28 (2H, m, CH₂), 3.33 (3H, s, OCH₃), 6.78 (2H, d, J = 8.9, ArH), 7.08 (2H, d, J = 8.9, ArH), 7.63 (1H, t, J = 7.7, HC=N); ¹³C NMR (100 MHz, CD₆D₆) δ 14.0 (CH₃), 22.8 (CH₂), 25.6 (CH₂), 31.6 (CH₂), 36.4 (CH₂), 54.8 (CH₂), 114.4 (ArH), 115.2 (ArH), 121.9 (Ar), 145.5 (C=N), 163.4 (ArO); compound unstable to mass spec. analysis. ¹H NMR data are consistent with literature data.¹⁷

(E)-4-Methoxy-N-(pyridin-2-ylmethylene)aniline 30k

Prepared by General procedure D. 2-Pyridinecarboxaldehyde (15.0 mmol) afforded crude 30k as a yellow/orange solid. Recrystallisation in EtOAc/pet. ether gave 30k (1.24 g, 5.8 mmol, 39% yield) as a pale yellow solid; mp 40-42 ºC (Lit.¹⁶³ 36-37 ºC); ¹H NMR (400 MHz, CDCl₃) δ 3.87 (3H, s, OCH₃), 6.98 (2H, dm, J = 9.0, ArH), 7.32-7.41 (3H, m, ArH), 7.78-7.86 (1H, m, ArH), 8.21 (1H, dt, J = 8.0, 1.0, ArH), 8.66 (1H, m, N=CH), 8.68-8.76 (1H, m, ArH). ¹H NMR data are consistent with literature data.¹⁶³
Prepared by General procedure D. 3-Pyridinecarboxaldehyde (5.0 mmol) afforded crude 30l as a yellow/orange solid. Recrystallisation in Et₂O/pet. ether gave 30l (2.30 g, 10.8 mmol, 72% yield) as a pale yellow solid; mp 63-65 °C; IR \( \nu_{\text{max}} \) 3140 (C-H), 2942 (C-H), 2835 (C-H), 1613 (C=N), 1504, 1365, 1246, 1174, 670 cm\(^{-1}\); \(^1\)H NMR (600 MHz, CDCl\(_3\)) \( \delta \) 3.84 (3H, s, OCH\(_3\)), 6.92-6.97 (2H, m, ArH), 7.23-7.29 (2H, m, ArH), 7.39 (1H, dd, \( J = 7.9, 4.7, \) ArH), 8.27 (1H, m, ArH), 8.49-8.53 (1H, m, ArH), 8.67 (1H, dd, \( J = 4.7, 1.5 \)), 8.99 (1H, s); \(^13\)C NMR (151 MHz, CDCl\(_3\)) \( \delta \) 55.6 (CH\(_3\)), 114.6 (ArH), 122.5 (ArH), 123.9 (ArH), 132.2 (Ar), 134.8 (ArH), 144.3 (Ar), 150.9 (ArH), 151.8 (ArH), 155.0 (CH=N), 158.9 (ArO); m/z (EI) 212 (100, M); HRMS C\(_{13}\)H\(_{12}\)N\(_2\)O calcd. 212.0950, found 212.0951.

\((E)-N-((1H-Pyrrol-2-yl)methylene)-4-methoxyaniline\) 30m

Prepared by General procedure D. Pyrrole-2-carboxaldehyde (10.5 mmol) afforded crude 30m (2.40 g) as a yellow/orange solid. Recrystallisation in 50% Et₂O/pet. ether (12.5 mL per gram) gave 30m (1.43 g, 7.2 mmol, 68% yield) as a pale yellow solid; mp 82-84 °C; IR \( \nu_{\text{max}} \) 3205 (C-H), 2963 (C-H), 2835 (C-H), 1616 (C=N), 1502, 1410, 1239, 1203, 1132, 1029, 830 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 3.82 (3H, s, OCH\(_3\)), 6.30 (1H, dd, \( J = 3.8, 2.8, \) ArH), 6.64 (1H, dd, \( J = 3.5, 1.3 \), ArH), 6.91 (2H, dm, \( J = 8.8, \) ArH), 6.94-6.97 (1H, m, ArH), 7.17 (2H, dm, \( J = 8.8, \) ArH), 8.26 (1H, s, \( \text{HC}=\text{N} \)); \(^13\)C NMR (151 MHz, CDCl\(_3\)) \( \delta \) 55.6 (CH\(_3\)), 110.4 (ArH), 114.6 (ArH), 116.2 (ArH), 122.1 (ArH), 123.1 (ArH), 131.0 (Ar), 144.9 (Ar), 148.5 (CH=N), 157.9 (ArO); m/z (EI) 200 (100, M); HRMS C\(_{12}\)H\(_{12}\)N\(_2\)O calcd. 200.0950, found 200.0939.

\((E)-4\text{-Methoxy-}N-((1\text{-methyl-1\text{-H-pyrrol-2-yl)methylene})aniline}\) 30n

Prepared by General procedure D. \(N\)-Methyl-pyrrole-2-carboxaldehyde (5.0 mmol) afforded crude 30n as a yellow/orange solid. Recrystallisation in EtOAc/pet. ether gave 30n (685 mg, 3.2 mmol, 64% yield) as a pale yellow solid; mp 58-59 °C; IR \( \nu_{\text{max}} \) 2944 (C-H), 2835 (C-H), 1622 (C=N), 1504, 1426, 1244 cm\(^{-1}\); \(^1\)H NMR (600 MHz, CDCl\(_3\)) \( \delta \) 3.82 (3H, s, OCH\(_3\)), 4.05 (3H, s, NCH\(_3\)), 6.18-6.23 (1H, m, ArH), 6.30 (1H, d, \( J = 3.8, \) ArH), 6.44 (1H, dd, \( J = 3.5, 1.3 \), ArH), 6.91 (2H, dm, \( J = 8.8, \) ArH), 6.94-6.97 (1H, m, ArH), 7.17 (2H, dm, \( J = 8.8, \) ArH), 8.26 (1H, s, \( \text{HC}=\text{N} \)); \(^13\)C NMR (151 MHz, CDCl\(_3\)) \( \delta \) 55.6 (CH\(_3\)), 110.4 (ArH), 114.6 (ArH), 116.2 (ArH), 122.1 (ArH), 123.1 (ArH), 131.0 (Ar), 144.9 (Ar), 148.5 (CH=N), 157.9 (ArO); m/z (EI) 200 (100, M); HRMS C\(_{12}\)H\(_{12}\)N\(_2\)O calcd. 200.0950, found 200.0939.
6.65 (1H, dd, J = 3.9, 1.8, ArH), 6.78 (1H, t, J = 2.3, ArH), 6.91 (2H, dm, J = 8.8, ArH), 7.13 (2H, dm, J = 8.8, ArH), 8.30 (1H, s, H=CN); \(^{13}\)C NMR (151 MHz, CDCl\(_3\)) \(\delta\) 37.0 (NCH\(_3\)), 55.6 (OCH\(_3\)), 108.7 (ArH), 114.5 (ArH), 118.0 (ArH), 121.9 (ArH), 128.8 (ArH), 130.6 (ArH); m/z (EI) 214 (100, M); HRMS C\(_{13}\)H\(_{14}\)N\(_2\)O calcd. 214.1106, found 214.1109.

\((E\)-4-Methoxy-N-((1-tosyl-1H-pyrrol-2-yl)methylene)aniline 30k\)

Prepared by General procedure D. N-Tosyl-pyrrole-2-carboxaldehyde (10.0 mmol) afforded crude 30k (3.30 g) as a yellow solid. Recrystallisation in EtOAc/pet. ether gave 30k (2.62 g, 7.4 mmol, 74% yield) as a pale yellow solid; mp 76-79 °C; IR \(\nu_{\text{max}}\) 2994 (C-H), 2834 (C-H), 1614 (C=N), 1373 (S=O), 1130 (S=O), 726, 671 cm\(^{-1}\); \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 2.38 (3H, s, ArCH\(_3\)), 3.84 (3H, s, OCH\(_3\)), 6.38 (1H, t, J = 3.6, ArH), 6.93 (2H, dm, J = 8.9, ArH), 7.10 (1H, dd, J = 3.7, 1.2, ArH), 7.18 (2H, dm, J = 8.9, ArH), 7.27 (2H, d, J = 7.9, ArH), 7.46 (1H, dd, J = 3.2, 1.7, ArH), 7.68 (2H, dm, J = 8.5, ArH), 8.89 (1H, s, N=CH\(_2\)); \(^{13}\)C NMR (151 MHz, CDCl\(_3\)) \(\delta\) 21.8 (CH\(_3\)), 55.6 (OCH\(_3\)), 113.3 (ArH), 114.5 (ArH), 117.1 (ArH), 122.5 (ArH), 126.2 (ArH), 126.9 (ArH), 130.3 (ArH), 133.2 (Ar), 135.9 (Ar), 144.8 (Ar), 145.7 (Ar), 147.7 (CH=NN), 158.5 (ArO); m/z (ESI\(^{\pm}\)) 355 (27, M\(^{+}\)+H), 199 (100, M-Ts); HRMS C\(_{19}\)H\(_{18}\)N\(_2\)O\(_3\)S\(^{+}\) calcd. 355.1116, found 355.1111.

\((E\)-4-Methoxy-N-((1-tosyl-1H-indol-3-yl)methylene)aniline 30q\)

Prepared by General procedure A. N-Tosyl-indole-3-carboxaldehyde (5.0 mmol) afforded crude 30q (1.80 g) as a yellow solid. Recrystallisation in EtOAc/pet. ether gave 30q (1.40 g, 3.5 mmol, 74% yield) as an off-white solid; mp 92-95 °C; IR \(\nu_{\text{max}}\) 2836 (C-H), 1616 (C=O), 1505, 1365 (S=O), 1167 (S=O), 1126, 795, 672 cm\(^{-1}\); \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 2.35 (3H, s, ArCH\(_3\)), 3.84 (3H, s, OCH\(_3\)), 6.94 (2H, dm, J = 9.0, ArH), 7.22-7.26 (4H, m, ArH), 7.33-7.36 (1H, m, ArH), 7.37-7.41 (1H, m,
ArH), 7.81 (2H, dm, J = 8.3, ArH), 7.97 (1H, s, ArH), 8.52 (1H, dm, J = 7.8), 8.62 (1H, s, N=CH); \(^{13}\)C NMR (151 MHz, CDCl\(_3\)) \(\delta\) 21.7 (ArCH\(_3\)), 55.6 (OCH\(_3\)), 113.4 (ArH), 114.5 (ArH), 121.2 (Ar), 122.2 (ArH), 123.4 (ArH), 125.9 (ArH), 127.1 (ArH), 128.0 (ArH), 129.7 (ArH), 130.7 (ArH), 131.4 (ArH), 132.4 (ArH), 134.9 (Ar), 135.7 (Ar), 145.4 (Ar), 145.6 (HC=N), 151.4 (ArH), 158.3 (ArO); m/z 404 (100, M); HRMS C\(_{23}\)H\(_{20}\)N\(_2\)O\(_3\)S calcd. 404.1195, found 404.1188.

**\((E)\)-tert-Butyl benzylidene carbamate 41a**

Prepared according to literature procedure.\(^{164}\) Benzaldehyde (10.0 mmol) gave 41a (1.63 g, 7.9 mmol, 79% yield) as a colourless oil; \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 1.59 (9H, s, C(C\(_3\)H\(_3\)))\(_3\)), 7.47 (2H, t, J = 7.7, ArH), 7.57 (1H, t, J = 7.5, ArH), 7.92 (2H, d, J = 8.1, ArH), 8.88 (1H, s, HC=N). \(^1\)H NMR data are consistent with literature data.\(^{164}\)

**\((E)\)-4-Methoxy-N-(1-phenylethylidene)aniline 291**

Prepared according to General procedure F. Acetophenone (10.0 mmol) gave crude 291 as an orange solid. Recrystallisation in 5% EtOAc/pet. ether (15 mL per gram) afforded 291 (1.49 g, 6.6 mmol, 66% yield) as a pale yellow solid; mp 83-85 °C (Lit.\(^{165}\) 84-85 °C); \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 2.26 (3H, s, N=CC\(_3\)H), 3.82 (3H, s, OC\(_3\)H), 6.76 (2H, dm, J = 4.5, ArH), 6.92 (2H, dm, J = 8.8, ArH), 7.42-7.47 (3H, m, ArH), 7.95-7.98 (2H, m, ArH). \(^1\)H NMR data are consistent with literature data.\(^{165}\)

### 4.2.3 Preparation of catalysts

**General Procedure G:** A solution of cold (ice bath, 0 °C) TFA (10 mL per mmol) was added to a pre-cooled flask (ice bath, 0 °C) containing N-Boc-amine (limiting reagent) and stirred for 2 h. The excess solvent was then removed in vacuo and the concentrated residue was cooled to 0 °C. To this residue was added 2.0 M NaOH (20
mL per mmol) and 5% MeOH/CH₂Cl₂ (30 mL per mmol) and the mixture was stirred for 15 min. The biphasic mixture was then separated and the aqueous layer was re-extracted with more 5% MeOH/CH₂Cl₂ (2 x 30 mL per mmol). The combined organics were dried (Na₂SO₄) and the excess solvent was removed in vacuo to give amine.

General Procedure H: Modification of literature procedure.³³ A solution of amine (limiting reagent) in CH₂Cl₂ (10 mL per mmol) and sat. aq. NaHCO₃ (10 mL per mmol) was cooled to 3 °C (ice bath) and stirred for 15 min. Stirring was then stopped and thiophosgene (1.5 equiv.) was syringed directly into the organic layer. The mixture was then vigorously stirred for 1 h at 3 °C. The reaction was extracted with CH₂Cl₂ (2 x 10 mL per mmol), dried (MgSO₄) and the excess solvent removed to give pure product.

General Procedure I: Modification of literature procedure.¹³² To a solution of (R,R)-diaminocyclohexane L-tartrate (1.5 equiv.) in 2.0 M NaOH (2.0 mL per mmol) was added Et₃N (2.0 equiv.) and CH₂Cl₂ (15 mL per mmol). The mixture was cooled to 0 °C and a solution of sulfonyl chloride (limiting reagent) in CH₂Cl₂ (11 mL per mmol) was added dropwise over 30 min. After complete addition the reaction was allowed to warm to rt and stirred for 16 h. The reaction was then extracted with 2.0 M HCl (3 x 5 mL per mmol). The combined aqueous extracts were basified to ~ pH 9 with NaOH pellets to give a cloudy white mixture which was then extracted with CH₂Cl₂ (3 x 5 mL per mmol). The combined organics were then dried (MgSO₄) and the excess solvent removed in vacuo to give pure product.
General Procedure J: To a solution of isothiocyanate (limiting reagent) in CH₂Cl₂ (5 mL per mmol) at room temperature was added amine (1.2 equiv.) and the reaction was stirred at rt for 3 days or until reaction complete, as judged by tlc analysis. The excess solvent was then removed in vacuo to give the crude product. 

General Procedure K: To a solution of iso(thio)cyanate (limiting reagent) in CH₂Cl₂ (5 mL per mmol) at room temperature was added amine (1.2 equiv.) and the reaction was stirred at rt for 3 days or until reaction complete, as judged by tlc analysis. The excess solvent was then removed in vacuo to give the crude product. 

(S)-2-((tert-Butoxycarbonyl)amino)-3,3-dimethylbutanoic acid 241

Prepared according to literature procedure.\textsuperscript{166} L-tert-leucine (40.0 mmol) gave 241 (7.40 g, 32.0 mmol, 80% yield) as a white solid; mp 108-110 °C (Lit.\textsuperscript{166} 122-123 °C); \textsuperscript{1}H NMR (600 MHz, CDCl₃) δ 1.02 (9H, s, C(CH₃)₃), 1.44 (9H, s, C(CH₃)₃), 4.12 (1H, d, J = 9.6, CHᵗBu), 5.09 (1H, d, J = 9.2, NH); \textsuperscript{1}H NMR\textsubscript{Rot} δ 3.89 (1H, br. s), 5.86 (1H, br. s). \textsuperscript{1}H NMR data are consistent with literature data.\textsuperscript{166} 

(S)-tert-butyl (1-(dimethylamino)-3,3-dimethyl-1-oxobutan-2-yl)carbamate 242

Prepared according to literature procedure.\textsuperscript{167} N-Boc-L-tert-leucine 241 (2.0 mmol) gave 242 (410 mg, 1.6 mmol, 80% yield) as a colourless oil; \textsuperscript{1}H NMR (600 MHz, CDCl₃) δ 0.97 (9H, s, C(CH₃)₃), 1.42 (9H, s, C(CH₃)₃), 2.96 (3H, s, N(CH₃)₂), 3.13 (3H, s, N(CH₃)₂), 4.52 (1H, d, J = 9.8, CHᵗBu), 5.34 (1H, d, J = 9.8, NH). \textsuperscript{1}H NMR data are consistent with literature data.\textsuperscript{167}
(S)-2-Amino-N,N,3,3-tetramethylbutanamide 243

Prepared by General procedure G. Boc-protected amine 242 (2.09 mmol) gave 243 (248 mg, 1.57 mmol, 75% yield) as a colourless oil; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.85 (9H, s, C(CH$_3$)$_3$), 2.84 (3H, s, N(CH$_3$)$_2$), 2.97 (3H, s, N(CH$_3$)$_2$), 3.42 (1H, s, CH$t^t$Bu); $^1$H NMR data are consistent with literature data. $^{167}$(S)-2-Isothiocyanato-N,N,3,3-tetramethylbutanamide 244

Prepared by General procedure H. Amine 243 (1.57 mmol) gave 244 (342 mg, 1.72 mmol, quantitative yield) as a colourless oil; IR $\nu_{max}$ 2970 (C-H), 2037 (N=C=S), 1641 (C=O), 1496, 1473, 1398, 1137 cm$^{-1}$; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 1.09 (9H, s, C(CH$_3$)$_3$), 3.01 (3H, s, N(CH$_3$)$_2$), 3.08 (3H, s, N(CH$_3$)$_2$), 4.27 (1H, s, CH$t^t$Bu); $^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 26.6 (C(CH$_3$)$_3$), 36.5 (N(CH$_3$)$_2$), 37.7 (CMe$_3$), 38.4 (N(CH$_3$)$_2$), 64.2 (CH$t^t$Bu), 135.6 (N=C=S), 166.5 (C=O); m/z (CI) 201 (72, M+H), 144 (100, M+H-tBu); HRMS C$_9$H$_{16}$N$_2$OS calcd. 201.1062, found 201.1053.

(3aR,7aR)-2-Methyl-3a,4,5,6,7,7a-hexahydro-1H-benzo[d]imidazole 247

Prepared according to literature procedure.$^{129}$ Trimethyl orthoacetate (0.90 mmol) gave 247 (151 mg, 1.09 mmol, quantitative yield) as a colourless solid which was used in the next step without further purification; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 1.24-1.36 (2H, m, Cy), 1.41-1.53 (2H, m, Cy), 1.81-1.91 (2H, m, Cy), 2.10 (3H, s, CH$_3$), 2.17 (2H, br. d, $J = 12.0$, Cy), 3.20-3.28 (2H, m, Cy); $^1$H NMR data are consistent with literature data.$^{129}$
N-((1R,2R)-2-Aminocyclohexyl)acetamide 248

\[
\begin{align*}
\text{H}_2\text{O}/\text{EtOH} & \xrightarrow{\text{reflux, 16 h}} \\
\end{align*}
\]

Prepared according to literature procedure.\textsuperscript{128} Benzoimidazole 247 (0.90 mmol) gave 248 (133 mg, 0.85 mmol, 95% yield) as a colourless solid which was used in the next step without further purification. \textsuperscript{1H NMR (400 MHz, CDCl\textsubscript{3})} δ 1.02-1.36 (4H, m, Cy), 1.63-1.74 (2H, m, Cy), 1.88-1.97 (2H, m, Cy), 1.98 (3H, s, CH\textsubscript{3}), 2.36 (1H, td, \textit{J} = 10.4, 4.0, CH\textsubscript{N}H\textsubscript{2}), 3.41-3.53 (1H, m, CH\textsubscript{N}HCO); \textsuperscript{1H NMR data} are consistent with literature data.\textsuperscript{128}

(S)-2-(3-((1R,2R)-2-Acetamidocyclohexyl)thioureido)-N,N,3,3-tetramethylbutanamide 54

Prepared according to literature procedure (21-60% yield),\textsuperscript{33} or by General procedure J. Isothiocyanate 244 (0.80 mmol) gave crude 54 (295 mg) which was purified by recrystallisation (EtOAc/pet. ether) to give 54 (206 mg, 0.58 mmol, 72% yield) as a white solid; mp 208-209 °C; [\alpha]\textsubscript{D}\textsuperscript{25} = +58.7 ° (c = 1.00, acetone); \textsuperscript{1H NMR (400 MHz, CDCl\textsubscript{3})} δ 1.04 (9H, s, C(C\textsubscript{6}H\textsubscript{3})), 1.22-1.40 (4H, m, Cy), 1.75-1.82 (2H, m, Cy), 1.98 (3H, s, COCH\textsubscript{3}), 2.11 (1H, br. d, \textit{J} = 9.5, Cy), 2.21 (1H, br. d, \textit{J} = 12.5, Cy), 2.97 (3H, s, NCH\textsubscript{3}), 3.28 (3H, s, NCH\textsubscript{3}), 3.57-3.67 (1H, m, CHN), 4.28-4.42 (1H, m, CHN), 5.57 (1H, d, \textit{J} = 9.5, CH\textsubscript{Bu}), 6.62-6.76 (1H, br. s, NH), 6.93 (1H, d, \textit{J} = 9.0, NH), 7.04 (1H, d, \textit{J} = 7.8, NH). \textsuperscript{1H NMR data} are consistent with literature data.\textsuperscript{33}

(S)-tert-Butyl (1-(diethylamino)-3,3-dimethyl-1-oxobutan-2-yl)carbamate 249

Prepared according to literature procedure.\textsuperscript{102} N-Boc-L-tert-leucine 241 (3.00 mmol) gave, after purification by column chromatography (15% EtOAc/pet. ether), 249 (387 mg, 1.35 mmol, 45% yield) as a colourless oil; \textsuperscript{1H NMR (600 MHz, CDCl\textsubscript{3})} δ
1.02 \( (9H, s, C(CH_3)_3) \), 1.44 \( (9H, s, C(CH_3)_3) \), 4.12 \( (1H, d, J = 9.6, CH^jBu) \), 5.09 \( (1H, d, J = 9.2, NH) \); \(^1\text{H NMR}_{\text{Rot}} \delta 3.89 \( (1H, \text{br. s}) \), 5.86 \( (1H, \text{br. s}) \). \(^1\text{H NMR} \) data are consistent with literature data.\(^{102}\)

\((S)-2\text{-Amino}-N,N\text{-diethyl}-3,3\text{-dimethylbutanamide} 250\)

\[
\begin{align*}
\text{Et}_3\text{N} & \quad \text{O} \\
& \quad \text{NH}_2
\end{align*}
\]

Prepared by General procedure G. Boc-protected amine 249 \((0.47 \text{ mmol})\) gave 250 \((75 \text{ mg}, 0.40 \text{ mmol, 86\% yield})\) as a colourless oil; \(^1\text{H NMR} \) \( (400 \text{ MHz}, CDCl_3) \) \( \delta 0.99 \( (9H, s, C(CH_3)_3) \), 1.13 \( (3H, t, J = 7.2, CH_2CH_3) \), 1.20 \( (3H, t, J = 7.2, CH_2CH_3) \), 3.09 \( (1H, \text{m, CH}_2\text{Me}) \), 3.20 \( (1H, \text{m, CH}_2\text{Me}) \), 3.39 \( (1H, s, CH^jBu) \), 3.59 \( (1H, \text{m, CH}_2\text{Me}) \), 3.70 \( (1H, \text{m, CH}_2\text{Me}) \); \(^1\text{H NMR} \) data are consistent with literature data.\(^{102}\)

\((S)-N,N\text{-Diethyl-2-isothiocyanato-3,3-dimethylbutanamide} 251\)

\[
\begin{align*}
\text{Et}_3\text{N} & \quad \text{O} \\
& \quad \text{S}
\end{align*}
\]

Prepared by General procedure H. Amine 250 \((0.40 \text{ mmol})\) gave 251 \((97 \text{ mg}, 0.42 \text{ mmol, quantitative yield})\) as a colourless oil; \(^1\text{H NMR} \) \( (500 \text{ MHz}, CDCl_3) \) \( \delta 1.11 \( (9H, s, C(CH_3)_3) \), 1.15 \( (3H, t, J = 7.1, CH_2CH_3) \), 1.20 \( (3H, t, J = 7.3, CH_2CH_3) \), 3.18 \( (1H, \text{dq, J = 14.2, 7.3, CH}_2\text{CH}_3) \), 3.27 \( (1H, \text{dq, J = 14.5, 7.3, CH}_2\text{CH}_3) \), 3.44 \( (1H, \text{dq, J = 14.8, 6.9, CH}_2\text{CH}_3) \), 3.62-3.79 \( (1H, \text{m, CH}_2\text{CH}_3) \); \(^1\text{H NMR} \) data are consistent with literature data.\(^{102}\)

\((1R,2R)-2-(2,5\text{-Dimethyl-1H-pyrrol-1-yl})\text{cyclohexanamine} 252\)

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{NH}_2 \\
& \quad \text{AcOH, MeOH, 50 °C} \\
& \quad \text{H}_2\text{N} \quad \text{N}
\end{align*}
\]

Prepared according to literature procedure.\(^{168}\) \((1R,2R)-1,2\text{-Diaminocyclohexane} \) \((2.19 \text{ mmol})\) afforded, after purification by column chromatography \( (5\% \text{ MeOH/CH}_2\text{Cl}_2) \), 252 \((310 \text{ mg}, 1.61 \text{ mmol, 74\% yield})\) as a yellow oil; \(^1\text{H NMR} \) \( (600 \text{ MHz}, CDCl_3) \) \( \delta 1.16-1.25 \( (1H, m, Cy) \), 1.31-1.42 \( (2H, m, Cy) \), 1.75-1.82 \( (1H, m, Cy) \), 1.82-1.96 \( (3H, m, Cy) \), 2.01-2.09 \( (1H, m, Cy) \), 2.23 \( (3H, s, ArCH_3) \), 2.36 \( (3H, s, \text{ar}) \).
ArCH₃), 3.26 (1H, td, J = 10.6, 4.0, CyHN), 3.60 (1H, apt. td, J = 11.1, 4.6, CyHN), 5.76 (2H, d, J = 19.2, NH₂); ¹H NMR data are consistent with literature data.¹⁶⁸

(S)-2-((1R,2R)-2-(2,5-Dimethyl-1H-pyrrol-1-yl)cyclohexyl)thioureido)-N,N-diethyl-3,3-dimethylbutanamide 191

Prepared according to literature procedure.¹⁰² Isothiocyanate 251 (0.40 mmol) gave, after purification by column chromatography (10% EtOAc/pet. ether), 191 (117 mg, 0.28 mmol, 70 % yield) as a pink solid; mp 99-101 °C; [α]D²⁵ = -26.2 ° (c = 1.025, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 0.96 (9H, s, C(C₃H₃)), 1.10 (3H, t, J = 7.1, CH₂C₃H₃), 1.19-1.23 (1H, m, Cy), 1.26 (3H, t, J = 7.1, CH₂CH₃), 1.34-1.51 (2H, m, Cy), 1.79-2.00 (4H, m, Cy), 2.22 (3H, br. s, ArCH₃), 2.35 (3H, br. s, ArCH₃), 2.53 (1H, br. d, J = 12.6, Cy), 3.07 (1H, dq, J = 13.7, 7.0, CH₂Me), 3.33 (1H, dq, J = 14.7, 7.1, CH₂Me), 3.58-3.72 (2H, m, CH₂Me), 3.76-3.87 (1H, m, Cy), 4.29-4.46 (1H, m, Cy), 5.43 (1H, br. s, CHᵀBu), 5.64 (1H, br. s, NH), 5.71 (2H, s, ArH), 6.28 (1H, br. d, J = 9.5, NH). ¹H NMR data are consistent with literature data.¹⁰²

(S)-tert-Butyl (3,3-dimethyl-1-(methylamino)-1-oxobutan-2-yl)carbamate

Prepared according to literature procedure.¹⁶⁹ N-Boc-L-tert-leucine 241 (1.50 mmol) gave the title compound (302 mg, 1.24 mmol, 82% yield) as a white solid which was used without further purification; ¹H NMR (400 MHz, CDCl₃) δ 1.00 (9H, s, C(CH₃)₃), 1.44 (9H, s, C(CH₃)₃), 2.81 (3H, d, J = 4.8, NHCH₃), 3.86 (1H, d, J = 9.6, CHᵀBu), 5.35 (1H, br. d, J = 9.5, NHboc), 6.17 (1H, br. s, NHMe). ¹H NMR data are consistent with literature data.¹⁶⁹

(S)-2-Amino-N,3,3-trimethylbutanamide
Prepared by General procedure G. (S)- tert-Butyl (3,3-dimethyl-1-(methylamino)-1-oxobutan-2-yl)carbamate (2.09 mmol) gave the title compound (248 mg, 1.57 mmol, 75% yield) as a colourless oil; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.99 (9H, s, C(CH$_3$)$_3$), 2.82 (3H, d, $J = 4.9$, NHCH$_3$), 3.10 (1H, s, CH$^t$Bu), 7.28 (2H, br. s, NH$_2$); $^1$H NMR data are consistent with literature data.\(^{170}\)

(S)-2- Isothiocyanato-N,3,3-trimethylbutanamide

Prepared by General procedure H. (S)- Amino-N,3,3-trimethylbutanamide (2.15 mmol) gave the title compound (384 mg, 2.06 mmol, 96% yield) as a colourless oil; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.09 (9H, s, C(CH$_3$)$_3$), 2.89 (3H, d, $J = 4.8$, NHCH$_3$), 4.07 (1H, s, CH$^t$Bu), 6.08 (1H, s, NH); $^1$H NMR data are consistent with literature data.\(^{169}\)

(S)-2-(3-((1R,2R)-2-acetamidocyclohexyl)thioureido)-N,3,3-trimethylbutanamide

Prepared using same procedure as for 54.\(^{33}\) (S)- Isothiocyanato-N,3,3-trimethylbutanamide (0.70 mmol) gave crude 265 (209 mg) which was purified by column chromatography to give 265 (150 mg, 0.44 mmol, 63% yield) as a white solid; mp 149-150 °C; $[\alpha]_D^{25} = +35.0$ ° (c = 0.995, CHCl$_3$); IR $\nu_{max}$ 3282, 2934 (C-H), 1644 (C=O), 1531 (N-H), 1321 (S=O), 1156 (S=O), 664 cm$^{-1}$; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 1.04 (9H, s, C(CH$_3$)$_3$), 1.21-1.42 (4H, m, Cy), 1.80 (2H, br. d, $J = 5.3$, Cy), 1.94 (3H, s, COCH$_3$), 2.01-2.07 (1H, m, Cy), 2.13-2.21 (1H, m, Cy), 2.78 (3H, d, $J = 4.9$, NHCH$_3$), 3.48-3.71 (1H, m, CH), 4.45 (1H, br. s, CH), 4.75 (1H, br. s, CH$^t$Bu), 6.19 (1H, br. s, NH), 6.87 (1H, br. s, NH), 7.47 (2H, br. s, NH); $^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 23.4 (C(CH$_3$)$_3$), 24.9 (CH$_2$), 25.0 (CH$_2$), 26.2 (CH$_3$), 27.0 (C(CH$_3$)$_3$), 32.6 (2C, br, CH$_2$), 34.5 (CMe$_3$), 56.3 (2C, br, CHN), 66.3 (CH$^t$Bu), 171.8 (2C, C=O), 183.9 (C=S); $m/z$ (ESI$^+$) 365 (96, M+Na), 312 (100, M-NMe$_2$); HRMS C$_{15}$H$_{27}$N$_3$O$_2$SNa$^+$ calcd. 365.1987, found 365.1998.
N-((1R,2R)-2-aminocyclohexyl)-4-methylbenzenesulfonamide

![Chemical structure]

**Prepared by General procedure I.** (1R,2R)-1,2-Diaminocyclohexane L-tartrate (34.1 mmol) gave the title compound (5.18 g, 19.3 mmol, 85% yield) as a white solid; mp 97-99 °C (Lit.\(^\text{171}\) 108-110 °C); \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta 1.01-1.23\) (4H, m, Cy), \(1.54-1.67\) (2H, m, Cy), \(1.74-1.84\) (1H, m, Cy), \(1.88-1.95\) (1H, m, Cy), \(2.36\) (1H, apt. td, \(J = 10.4, 4.0\), Cy), \(2.42\) (3H, s, CH\(_3\)), \(2.63\) (1H, apt. td, \(J = 10.3, 4.2\), Cy), \(7.29\) (2H, d, \(J = 7.9\), ArH), \(7.77\) (2H, dm, \(J = 8.3\), ArH). \(^1\)H NMR data are consistent with literature data.\(^\text{132}\)

N-((1R,2R)-2-aminocyclohexyl)-4-nitrobenzenesulfonamide

![Chemical structure]

**Prepared by General procedure I.** (1R,2R)-1,2-Diaminocyclohexane L-tartrate (5.68 mmol) gave the title compound (860 mg, 2.87 mmol, 76% yield) as a yellow solid; mp 159-161 °C (Lit.\(^\text{172}\) 177.5-178 °C); \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta 1.05-1.27\) (4H, m, Cy), \(1.59-1.70\) (2H, m, Cy), \(1.86-1.96\) (2H, m, Cy), \(2.40\) (1H, apt. td, \(J = 10.5, 4.0\), Cy), \(2.70\) (1H, apt. td, \(J = 10.4, 4.1\), Cy), \(8.10\) (2H, dm, \(J = 8.8\), ArH), \(8.36\) (2H, dm, \(J = 8.8\), ArH). \(^1\)H NMR data are consistent with literature data.\(^\text{172}\)

N-((1R,2R)-2-aminocyclohexyl)-4-methoxybenzenesulfonamide

![Chemical structure]

**Prepared by General procedure I.** (1R,2R)-1,2-Diaminocyclohexane L-tartrate (5.68 mmol) gave the title compound (859 mg, 3.02 mmol, 80% yield) as a white solid; mp 90-92 °C (Lit.\(^\text{173}\) 96-98 °C); \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta 1.01-1.25\) (4H, m, Cy), \(1.56-1.67\) (2H, m, Cy), \(1.78-1.86\) (1H, m, Cy), \(1.88-1.94\) (1H, m Cy), \(2.30-2.37\) (1H, m, Cy), \(2.60\) (1H, m, Cy), \(3.87\) (3H, s, OCH\(_3\)), \(6.97\) (2H, dm, \(J = 8.8\), ArH), \(7.82\) (2H, dm, \(J = 8.8\), ArH). \(^1\)H NMR data are consistent with literature data.\(^\text{173}\)
Prepared by General procedure J. Isothiocyanate 244 (0.80 mmol) afforded, after purification by column chromatography (5% MeOH/CHCl₃), 266 (362 mg, 0.77 mmol, 96% yield) as a white solid; mp 84-86 ºC; [α]D²⁵ = +63.8 º (c = 1.015, CHCl₃); IR νmax 3311, 2934 (C-H), 1622 (C=O), 1528, 1318 (S=O), 1156 (S=O), 1091, 661 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 1.02 (9H, s, C(CH₃)₃), 1.05-1.16 (2H, m, Cy), 1.21-1.35 (2H, m, Cy), 1.56-1.70 (2H, m, Cy), 1.97 (1H, apt. d, J = 11.9, Cy), 2.07 (1H, apt. d, J = 11.7, Cy), 2.41 (3H, s, CH₃), 2.84-2.93 (1H, m, Cy), 2.98 (3H, s, N(CH₃)₂), 3.28 (3H, s, N(CH₃)₂), 4.21-4.34 (1H, m, Cy), 5.69 (1H, br. d, J = 9.2, CH₃Bu), 6.11 (1H, br. d, J = 7.0, NH), 6.63-6.82 (2H, br. m, NH), 7.22-7.29 (2H, m, ArH), 7.69 (2H, d, J = 8.1, ArH); ¹³C NMR (151 MHz, CDCl₃) δ 21.7 (ArC(CH₃)), 24.5 (CH₂), 24.7 (CH₂), 26.8 (C(CH₃)₃), 33.0 (CH₂), 34.0 (CH₂), 35.9 (NCH₃), 36.6 (CMes), 38.9 (NCH₃), 56.8 (CH), 59.0 (CH), 59.8 (CH), 127.1 (ArH), 129.7 (ArH), 138.4 (Ar), 143.1 (Ar), 172.2 (C=O), 183.8 (C=S); m/z (ESI⁺) 491 (100, M+Na), 424 (54, M–Me₂N); HRMS C₂₂H₃₆N₄O₅S₂Na⁺ calcd. 491.2127, found 491.2119.

Prepared by General procedure J. Isothiocyanate 244 (0.82 mmol) gave crude 267 (423 mg) which was purified by column chromatography (5% MeOH/CHCl₃) to give 267 (403 mg, 0.81 mmol, 99% yield) as a yellow solid; mp 197-199 ºC; [α]D²⁵ = +72.5 º (c = 1.00, CHCl₃); IR νmax 3336, 3067, 2937 (C-H), 2865 (C-H), 1641 (C=O), 1529 (N-O), 1349, 1307, 1159 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 1.02 (9H, s, C(CH₃)₃), 1.09-1.17 (2H, m Cy), 1.20-1.35 (2H, m, Cy), 1.62 (1H, br. d, J = 13.4, Cy), 1.68 (1H, br. d, J = 13.4, Cy), 1.90 (1H, br. d, J = 13.4, Cy), 2.08 (1H, br. d, J =
12.4, C), 2.98-3.04 (1H, m, C), 3.06 (3H, s, N(CH$_3$)$_2$), 3.28 (3H, s, N(CH$_3$)$_2$), 4.28-4.37 (1H, m, C), 5.68 (1H, br. d, J = 8.7, CH$_3$Bu), 6.31 (1H, br. s, NH), 6.88 (1H, br. d, J = 9.2, NH), 7.61 (1H, br. s, NH), 8.04 (2H, d, J = 8.8, ArH), 8.32 (2H, d, J = 9.2, ArH); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 24.4 (CH$_2$), 24.7 (CH$_2$), 26.8 (CH$_3$), 32.8 (CH$_2$), 34.1 (CH$_2$), 36.0 (NCH$_3$), 36.7 (CMe$_3$), 38.9 (NCH$_3$), 56.6 (CH), 59.3 (CH), 60.0 (CH), 124.4 (ArH), 128.2 (ArH), 147.8 (Ar), 149.8 (Ar), 172.4 (C=O), 183.7 (C=S); m/z (ESI$^+$) 522 (79, M+Na), 455 (100, M-Me$_2$N); HRMS C$_{21}$H$_{33}$N$_2$O$_5$S$_2$Na$^+$ calcd. 522.1821, found 522.1813.

(S)-2-(3-((1R,2R)-2-(4-Methoxyphenylsulfonamido)cyclohexyl)thioureido)-N$_2$N,3,3-tetramethylbutanamide 268

Prepared by General procedure J. Isothiocyanate 244 (0.63 mmol) gave, after purification by column chromatography (2.5% MeOH, 47.5% EtOAc, 50% CH$_2$Cl$_2$), 268 (273 mg, 0.56 mmol, 90% yield) as an off-white solid; mp 98-100 °C; [$\alpha$]$_D^25$ = +73.6 ° (c = 0.990, CHCl$_3$); IR $\nu_{max}$ 3315 (C-H), 2938 (C=O), 1620 (C=O), 1531, 1319 (S=O), 1258 (C=S), 1154 (S=O), 731 cm$^{-1}$; $^{1}$H NMR (400 MHz, CDCl$_3$) δ 1.01 (9H, s, C(CH$_3$)$_3$), 1.04-1.13 (2H, m, C), 1.18-1.38 (2H, m, C), 1.63 (2H, t, J = 11.7, C), 1.95-2.13 (2H, m, C), 2.71-2.82 (1H, m, C), 2.85 (3H, s, N(CH$_3$)$_2$), 3.27 (3H, s, N(CH$_3$)$_2$), 3.85 (3H, s, OCH$_3$), 4.25-4.38 (1H, m, C), 5.76 (1H, d, J = 9.5, CH$_3$Bu), 6.73 (1H, d, J = 8.0, NH), 6.90 (2H, dm, J = 9.0, ArH), 7.05 (2H, d, J = 9.3, NH), 7.64 (2H, d, J = 8.8, ArH); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 24.5 (CH$_2$), 24.8 (CH$_2$), 26.8 (C(CH$_3$)$_3$), 33.0 (CH$_2$), 34.0 (CH$_2$), 35.8 (NCH$_3$), 36.6 (CMe$_3$), 38.9 (NCH$_3$), 55.8 (OCH$_3$), 56.8 (CH), 59.0 (CH), 59.9 (CH), 114.2 (ArH), 129.2 (ArH), 132.6 (Ar), 162.7 (ArO), 172.2 (C=O), 183.8 (C=S); m/z (ESI$^+$) 507 (88, M+Na), 440 (100, M-Me$_2$N); HRMS C$_{21}$H$_{30}$N$_2$O$_5$S$_2$Na$^+$ calcd. 507.2076, found 507.2066.

(S)-N$_2$N,3,3-Tetramethyl-2-(3-((1S,2S)-2-(4-methylphenylsulfonamido)cyclohexyl)thioureido)butanamide 269
Prepared by General procedure J. Isothiocyanate 244 (0.68 mmol) gave crude 269 (445 mg) which was purified by column chromatography (2.5% MeOH, 47.5% EtOAc, 50% CH2Cl2) to give 269 (273 mg, 0.58 mmol, 86% yield) as an off-white solid; mp 181-183 °C; [α]D25 = -75.7 ° (c = 1.01, CHCl3); IR νmax 3353, 3088 (C-H), 2935 (C=CH), 1622 (C=O), 1539, 1326 (S=O), 1160 (S=O), 1074, 900, 666 cm⁻¹; 1H NMR (600 MHz, CDCl3) δ 0.90-1.09 (2H, m, Cy), 1.04 (9H, m, C(CH3)3), 1.14-1.33 (2H, m, Cy), 1.54-1.70 (2H, m, Cy), 1.80-1.97 (2H, m, Cy), 2.41 (3H, s, ArCH3), 2.85-2.95 (4H, m, N(CH3)2), 3.26 (3H, s, N(CH3)2), 4.27 (1H, br. s, Cy), 5.60 (1H, br. s, CH’Bu), 6.27-6.45 (1H, m, NH), 6.47-6.64 (1H, m, NH), 6.91-7.07 (1H, m, NH), 7.22-7.29 (2H, m, ArH), 7.73 (2H, d, J = 8.3, ArH); 13C NMR (151 MHz, CDCl3) δ 21.7 (ArCH3), 24.6 (CH2), 24.8 (CH2), 26.9 (C(CH3)3), 32.7 (CH2), 33.9 (CH2), 35.9 (NCH3), 36.1 (CMe3) 38.8 (NCH3), 56.3 (CH), 59.8 (CH), 60.2 (CH), 127.1 (ArH), 129.6 (ArH), 138.6 (Ar), 142.9 (Ar), 173.0 (C=O), 183.9 (C=S); m/z (Cl) 469 (4, M+H), 435 (100, M-H2O); HRMS C22H36N4O3S2H⁺ calcd. 469.2305, found 469.2305.

N-((1R,2R)-2-(3-(3,5-bis(trifluoromethyl)phenylthioureido)cyclohexyl)-4-methylbenzenesulfonamide 270

Prepared by General procedure K. Isothiocyanate 244 (1.00 mmol) gave, after recrystallisation (CH2Cl2/pet. ether), 270 (384 mg, 0.71 mmol, 71% yield) as a white solid; mp 180-182 °C; [α]D25 = +37.0 ° (c = 1.03, CHCl3); IR νmax 3353, 3088 (C-H), 2935 (C-H), 2862 (C-H), 1538, 1387, 1305 (S=O), 1270 (C-F), 1113 (S=O) cm⁻¹; 1H NMR (600 MHz, CDCl3) δ 1.13-1.23 (1H, m, Cy), 1.23-1.36 (3H, m, Cy), 1.64 (1H, apt. d, J = 13.4, Cy), 1.68-1.79 (2H, m, Cy), 2.13-2.22 (1H, m, Cy), 2.36 (3H, s, CH3), 3.23 (1H, apt. td, J = 11.1, 4.0, Cy), 4.37 (1H, br. s, Cy), 6.28 (1H, br. s, NH), 6.88 (1H, d, J = 8.1, NH), 7.20-7.30 (2H, m, ArH), 7.57 (1H, s, ArH), 7.73 (2H, d, J = 8.3, ArH), 7.91 (2H, s, ArH), 8.48 (1H, br. s, NH); 13C NMR (151 MHz, CDCl3) δ 21.5 (ArCH3), 24.5 (CH2), 24.6 (CH2), 32.1 (CH2), 33.6 (CH2), 57.4 (CH), 59.0 (CH), 118.7 (m, ArH), 123.0 (2C, q, J = 272.9, CF3), 123.7 (ArH), 126.7 (ArH), 129.9 (ArH), 132.0 (2C, q, J = 33.0, ArCF3), 138.1 (Ar), 139.6 (Ar), 143.9 (Ar), 181.4
(S)-tert-Butyl (1-(dimethylamino)-3-methyl-1-oxobutan-2-yl)carbamate

Prepared according to literature procedure. N-Boc-L-valine (19.2 mmol) gave the title compound (4.60 g, 18.2 mmol, 95% yield). mp 54-55 °C; ¹H NMR (600 MHz, CDCl₃) δ 0.89 (3H, d, J = 6.8, CH(C₃H₃)₂), 0.94 (3H, d, J = 6.8, CH(CH₃)₂), 1.42 (9H, s, C(C₃H₃)₃), 1.87-1.97 (1H, m, CHMe₂), 2.96 (3H, s, N(C₃H₃)₂), 3.10 (3H, s, N(C₃H₃)₂), 4.46 (1H, dd, J = 9.2, 6.0, CH²Pr), 5.37 (1H, d, J = 8.7, NH). ¹H NMR data are consistent with literature data.

(S)-2-Amino-N,N,N,3-trimethylbutanamide

Prepared by General procedure G. (S)-tert-Butyl (1-(dimethylamino)-3-methyl-1-oxobutan-2-yl)carbamate (6.05 mmol) gave the title compound (820 mg, 5.70 mmol, 94% yield) as a white solid; mp 30-32 °C; ¹H NMR (600 MHz, CDCl₃) δ 0.91 (2H, d, J = 6.8, CH(CH₃)₂), 0.96 (2H, d, J = 7.0, CH(CH₃)₂), 1.70 (2H, br. s, NH₂), 1.85(1H, apt. oct, J = 6.6, CHMe₂), 2.97 (3H, s, N(CH₃)₂), 3.03 (3H, s, N(CH₃)₂), 3.50 (1H, d, J = 5.3, CH²Pr). ¹H NMR data are consistent with literature data.

(S)-2-Isothiocyanato-N,N,3-trimethylbutanamide

Prepared by General procedure H. (S)-2-Amino-N,N,3-trimethylbutanamide (0.63 mmol) gave the title compound (107 mg, 0.58 mmol, 92% yield) as a colourless oil; IR νmax 2967 (C-H), 2067 (N=C=S), 1655, 1495, 1400 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.03 (3H, d, J = 6.8, CH(CH₃)₂), 1.06 (3H, d, J = 6.5, CH(CH₃)₂), 2.18-2.30 (1H, m, CHMe₂), 3.00 (3H, s, N(CH₃)₂), 3.06 (3H, s, N(CH₃)₂), 4.26 (1H, d, J = 5.8, CH²Pr); ¹³C NMR (151 MHz, CDCl₃) δ 17.8 (CH₃), 20.0 (CH₃), 32.2 (CH), 36.5
Paul J. Koovits

University College London

(NCH₃), 37.4 (NCH₃), 63.6 (CH), 136.6 (N=C=S), 166.9 (C=O); m/z (Cl) 187 (75, M+H); HRMS C₉H₁₄N₂OSH⁺ calcd. 187.0897, found 187.0950.

(S)-N,N,3-Trimethyl-2-(3-((1R,2R)-2-(4-methylphenylsulfonamido)cyclohexyl)thioureido)butanamide 271

Prepared by General procedure J. (S)-2-Isothiocyanato-N,N,3-trimethylbutanamide (0.40 mmol) gave, after purification by column chromatography (2.5% MeOH, 47.5% EtOAc, 50% CH₂Cl₂), 271 (157 mg, 0.35 mmol, 86% yield) as an off-white solid; mp 75-77 °C; [α]D²⁵ = +39.8 ° (c = 1.015, CHCl₃); IR νmax 3303 (C-H), 2934 (C-H), 1625 (C=O), 1540, 1324 (S=O), 1159 (S=O/C=S), 1091 (C=S), 915, 730 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 0.91 (3H, dd, J = 6.8, 0.9, CH(CMe₂)₂), 0.99 (3H, d, J = 6.8, CH(CH₃)₂), 1.02-1.16 (2H, m, Cy), 1.02-1.16 (2H, m, Cy), 1.56-1.70 (2H, m, Cy), 1.75-1.82 (1H, m, Cy), 1.95-2.09 (2H, m, Cy, CHMe₂), 2.38 (3H, s, ArCH₃), 2.86-2.93 (4H, m, Cy, N(CH₂)₂), 3.32 (3H, s, N(CH₂)₂), 4.31 (1H, m, Cy), 5.40-5.63 (1H, m, CH₂Pr), 6.72-7.03 (2H, br. m, NH), 7.20 (2H, d, J = 7.3, ArH), 7.52-7.63 (1H, br. m, NH), 7.65 (2H, d, J = 7.9, ArH); ¹³C NMR (151 MHz, CDCl₃) δ 18.6 (C(CH₃)₂), 18.9 (C(CH₃)₂), 21.7 (ArCH₃), 24.4 (CH₂), 24.8 (CH₂), 33.0 (CH₂), 33.0 (CHMe₂), 33.8 (CH₂), 36.0 (NCH₃), 38.5 (NCH₃), 56.2 (CH), 58.9 (CH), 59.8 (CH), 126.9 (ArH), 129.5 (ArH), 138.5 (Ar), 143.1 (Ar), 173.1 (C=O), 183.7 (C=S); m/z (ESI⁺) 477 (57, M+Na), 410 (100, M-Me₂N); HRMS C₂₁H₃₄N₄O₃S₂Na⁺ calcd. 477.1970, found 477.1961.

1-Isothiocyanato-3,5-bis(trifluoromethyl)benzene

Prepared by General procedure H. 3,5-Bis(trifluoromethyl)aniline (21.8 mmol) gave the title compound (5.33 g, 19.7 mmol, 90% yield) as a pale yellow oil; ¹H NMR (600 MHz, CDCl₃) δ 7.64 (2H, s, ArH), 7.76 (1H, s, ArH). ¹H NMR data are consistent with literature data.¹⁷₅
(S)-2-(3-(3,5-Bis(trifluoromethyl)phenyl)thioureido)-N,N,3-trimethylbutanamide 272

Prepared by General procedure K. 1-Isothiocyanato-3,5-bis(trifluoromethyl)benzene (5.18 mmol) gave crude 272 (2.03 g) which was recrystallised (40% TBME/pet. ether) to give 272 (1.62 g, 3.90 mmol, 75% yield) as a white solid; mp 135-136 °C; [α]D25 = -45.9 ° (c = 1.015, CHCl3); IR νmax 3200 (C-H), 2971 (C-H), 1609 (C=O), 1534, 1380, 1272, 1164, 1111 cm⁻¹; ¹H NMR (600 MHz, CDCl3) δ 1.05 (3H, d, J = 6.8, CH(CH₃)₂), 1.10 (3H, d, J = 6.8, CH(CH₃)₂), 2.06 (1H, apt. oct, J = 7.0, CH(CH₃)₂), 3.05 (3H, s, N(CH₃)₂), 3.39 (3H, s, N(CH₃)₂), 5.34 (1H, apt. t, J = 8.2, CHPr), 7.51 (1H, s, ArH), 8.04 (2H, s, ArH), 8.30 (1H, d, J = 7.7, NH), 9.43 (1H, br. s, ArNH); ¹³C NMR (151 MHz, CDCl3) δ 19.1 (C(CH₃)₂), 19.2 (C(CH₃)₂), 32.0 (CMc₂), 36.3 (NCH₃), 38.5 (NCH₃), 59.3 (CHPr), 117.6 (1C, m, ArH), 122.6 (2C, m, ArH), 123.3 (2C, q, J = 272.9, CF₃), 131.5 (2C, q, J = 34.1, ArCF₃), 140.7 (Ar), 174.6 (C=O), 181.5 (C=S); m/z (CI) 416 (18, M+H), 396 (34, M-F), 371 (100, M–Me₂N); HRMS C₁₅H₁₉F₆N₅O₂H⁺ calcd. 416.12313, found 416.12264.

(S)-N,N,3-Trimethyl-2-(3-phenylthioureido)butanamide 279

Prepared by General procedure K. Phenyl isothiocyanate (0.67 mmol) gave, after purification by column chromatography (20% EtOAc/CH₂Cl₂), 279 (139 mg, 0.50 mmol, 74% yield) as a white solid; mp 133-135 °C; [α]D25 = +39.2 ° (c = 1.06, CHCl₃); IR νmax 3311 (C-H), 2965 (C-H), 1628 (C=O), 1596, 1538, 1495, 1308 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 0.94 (3H, d, J = 6.8, CH(CH₃)₂), 1.00 (3H, d, J = 6.8, CH(CH₃)₂), 2.04 (1H, apt. oct, J = 6.8, CHMe₂), 2.94 (3H, s, N(CH₃)₂), 3.23 (3H, s, N(CH₃)₂), 5.51 (1H, apt. t, J = 7.8, CHPr), 7.18 (1H, br. s, NH) 7.22-7.26 (1H, m, ArH), 7.29 (2H, d, J = 7.7, ArH), 7.36-7.43 (2H, m, ArH), 8.17 (1H, br. m, NH); ¹³C NMR (151 MHz, CDCl₃) δ 18.4 (C(CH₃)₂), 19.4 (C(CH₃)₂), 32.2 (CHMe₂), 35.9 (NCH₃), 37.9 (NCH₃), 59.6 (CHPr), 125.0 (ArH), 126.9 (ArH), 129.9 (ArH), 136.7
Paul J. Koovits

171.4 (C=O), 180.9 (C=S); m/z (EI) 279 (5, M), 234 (100, M-Me₂NH₂); HRMS C₁₄H₂₁N₃O₈ calcd. 279.1405, found 279.1396.

(S)-2-(3-(3,5-Bis(trifluoromethyl)phenyl)thioureo)-N,N,3,3-tetramethylbutanamide 280

Prepared by General procedure K. 1-Isothiocyanato-3,5-bis(trifluoromethyl)benzene (0.52 mmol) gave, after purification by column chromatography (5% MeOH/CH₂Cl₂), 280 (178 mg, 0.41 mmol, 80% yield) as a white solid; mp 112-114 oC; [α]D₂₅ = -32.4 ° (c = 1.01, CHCl₃); IR νmax 3328 (C-H), 2968 (C-H), 1615 (C=O), 1533, 1474, 1385, 1176, 1132 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 1.12 (9H, s, C(CH₃)₃), 2.96 (3H, s, N(CH₃)₂), 3.34 (3H, s, N(CH₃)₂), 5.66 (1H, d, J = 9.2, CHtBu), 7.55 (1H, s, ArH), 7.79 (1H, d, J = 9.0, NH), 7.90 (2H, s, ArH), 9.11 (1H, s, NH); ¹³C NMR (151 MHz, CDCl₃) δ 27.2 (C(CH₃)₃), 36.0 (CMe₃), 36.2 (NCH₃), 39.0 (NCH₃), 60.8 (CHtBu), 118.2 (1C, dq, J = 3.3, 3.3, ArH), 123.2 (2C, q, J = 279.2, CF₃), 123.7 (2C, m, ArH), 131.7 (2C, q, J = 34.1, ArCF₃), 140.2 (Ar), 173.8 (C=O), 181.8 (C=S); m/z (CI) 430 (45, M+H), 410 (63, M-F), 385 (67, M-NMe₂); HRMS C₁₇H₂₁F₆N₃OS⁺ calcd. 430.1388, found 430.1383.

(S)-2-(3-(3,5-Bis(trifluoromethyl)phenyl)ureido)-N,N,3-trimethylbutanamide 281

Prepared by General procedure K. 3,5-Bis(trifluoromethyl)phenyl isocyanate (0.42 mmol) afforded, after recrystallisation (25% TBME/pet. ether), 281 (90 mg, 0.23 mmol, 54% yield) as a white solid; mp 162-164 oC; [α]D₂₅ = -25.7 ° (c = 1.02, CHCl₃); IR νmax 3343, 3116, 2968 (C-H), 1704 (C=O), 1611, 1287, 1117 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 1.05 (6H, dd, J = 6.8, 2.3, CH(CH₃)₂), 1.96-2.05 (1H, m, CHMe₂), 3.12 (3H, s, N(CH₃)₂), 3.32 (3H, s, N(CH₃)₂), 4.75 (1H, apt. t, J = 8.2, CHtPr), 6.84 (1H, d, J = 9.0, NH), 7.34 (1H, s, ArH), 7.72 (2H, s, ArH), 8.53 (1H, s, ArH), 9.11 (1H, s, NH); ¹³C NMR (151 MHz, CDCl₃) δ 27.2 (C(CH₃)₃), 36.0 (CMe₃), 36.2 (NCH₃), 39.0 (NCH₃), 60.8 (CHtBu), 118.2 (1C, dq, J = 3.3, 3.3, ArH), 123.2 (2C, q, J = 279.2, CF₃), 123.7 (2C, m, ArH), 131.7 (2C, q, J = 34.1, ArCF₃), 140.2 (Ar), 173.8 (C=O), 181.8 (C=S); m/z (CI) 430 (45, M+H), 410 (63, M-F), 385 (67, M-NMe₂); HRMS C₁₇H₂₁F₆N₃OS⁺ calcd. 430.1388, found 430.1383.

University College London 171
Paul J. Koovits

University College London

172

$^1$H NMR (151 MHz, CDCl$_3$) $\delta$ 18.4 (C(CH$_3$)$_2$), 19.6 (C(CH$_3$)$_2$), 31.6 (CHMe$_2$), 36.3 (NCH$_3$), 38.2 (NCH$_3$), 54.9 (CHPr), 115.1 (1C, m, ArH), 117.9 (2C, m, ArH), 123.4 (2C, q, $J$ = 272.9, CF$_3$), 131.8 (2C, q, $J$ = 33.0, ArCF$_3$), 141.1 (ArN), 155.3 (C=O), 174.9 (C=O); $m/z$ (CI) 400 (23, M+H), 380 (100, M-F), 355 (22, M-NMe$_2$), 327 (96, M-Me$_2$NCO); HRMS C$_{16}$H$_9$F$_6$N$_2$O$_2$H$^+$ calcd. 400.1460, found 400.1442.

(S)-Methyl 2-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)-3-methylbutanoate 282

To a mixture of 1-Isothiocyanato-3,5-bis(trifluoromethyl)benzene (406 mg, 1.50 mmol) and L-valine methyl ester hydrochloride (335 mg, 2.00 mmol) in CH$_2$Cl$_2$ (20 mL) was added Et$_3$N (210 $\mu$L, 1.50 mmol) and the reaction was stirred at room temperature until reaction complete as judged by tlc analysis (ca. 24 h). The excess solvent was then removed to give crude 282 which was purified by column chromatography (25% EtOAc/pet. ether) to give 282 (450 mg, 1.12 mmol, 75% yield) as a colourless oil; $[\alpha]_D^{25}$ = +17.1$^o$ (c = 1.005, CHCl$_3$); IR $\nu$$_{max}$ 3309, 2968 (C-H), 1716 (C=O), 1535, 1473, 1383, 1278, 1177, 1132; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 0.98 (3H, d, $J$ = 7.0, CH(C$_3$H$_3$)$_2$), 1.02 (3H, d, $J$ = 7.0, CH(CH$_3$)$_2$), 2.25-2.35 (1H, m, CHMe$_2$), 3.80 (3H, s, OCH$_3$), 5.17 (1H, br. s, CHPr), 7.34 (1H, d, $J$ = 8.8, NH), 7.63 (1H, s, ArH), 7.94 (2H, s, ArH), 8.81 (1H, s, NH); $^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 18.7 (C(CH$_3$)$_2$), 19.0 (C(CH$_3$)$_2$), 31.3 (CHMe$_2$), 52.9 (OCH$_3$), 62.9 (CHPr), 119.0 (1C, m, ArH), 122.9 (2C, q, $J$ = 273.1, CF$_3$), 123.4 (2C, m, ArH), 132.5 (2C, q, $J$ = 31.3, ArCF$_3$), 139.3 (Ar), 174.4 (C=O), 181.5 (C=S); $m/z$ (CI) 403 (100, M+H); HRMS C$_{15}$H$_{16}$F$_6$N$_2$O$_2$SH$^+$ calcd. 403.0915, found 403.0904.

4.2.4 Preparation of $\beta$-nitroamines and $\beta$-nitrotrifluoroacetamides

$^{(i)}$LiHBEt$_3$

$^{(ii)}$PMP

$^{(iii)}$TFA

General Procedure L: To a solution of nitroalkene 84 (limiting reagent) in THF (6 mL per mmol) was added Superhydride$^{TM}$ (1.1 equiv., 1.0 M in THF).
suspension was then stirred for 30 min at rt before cooling to –78 °C over 30 min. A solution of imine 30 (1.1 equiv.) in THF (6 mL per mmol) was added via cannula and the mixture stirred at -78 °C for 10 min. A solution of TFA (2.5 equiv.) in THF (2 mL per mmol) was then added by cannula and the reaction stirred for 1 h at –78 °C. The reaction was then quenched with sat. aq. NH₄Cl (10 mL per mmol) and diluted with Et₂O (20 mL per mmol). The organic phase was washed with sat. brine (10 mL per mmol) and dried (MgSO₄). The excess solvents were then removed in vacuo to afford crude β-nitroamine. Crude β-nitroamine was re-dissolved in CH₂Cl₂ (5 mL per mmol) and trifluoroacetic anhydride (5.0 equiv.), followed by pyridine (5.0 equiv.) were added at rt and the solution was stirred at rt for 2 h. After this time, 2.0 M HCl (10 mL per mmol) was added and the aqueous phase was extracted with CH₂Cl₂ (2 x 5 mL per mmol) and the combined organic phases were washed with sat. aq. NaHCO₃ (10 mL per mmol) and sat. brine (10 mL per mmol). The organic phase was then dried (MgSO₄) and the excess solvents were removed in vacuo to afford crude β-nitrotrifluoroacetamide.

**General Procedure M:** To a solution of nitroalkene 84 (limiting reagent) in CH₂Cl₂ (6 mL per mmol) was added Superhydride™ (1.1 equiv., 1.0 M in THF). The suspension was then stirred for 30 min at rt before cooling to –78 °C over 30 min. A solution of imine 30 (1.1 equiv.) in CH₂Cl₂ (6 mL per mmol) was then added via cannula and the mixture stirred at -78 °C for 10 min. A solution of TFA (1.2 equiv.) was added and the reaction was stirred for 1 h at –78 °C. The reaction was then quenched with sat. aq. NH₄Cl (10 mL per mmol) and diluted with Et₂O (20 mL per mmol). The organic phase was washed with sat. brine (10 mL per mmol) and dried (MgSO₄). The excess solvents were then removed in vacuo to afford crude β-nitroamine. Crude β-nitroamine was re-dissolved in CH₂Cl₂ (5 mL per mmol) and trifluoroacetic anhydride (5.0 equiv.), followed by pyridine (5.0 equiv.) were added at rt and the solution was stirred at rt for 2 h. After this time, 2.0 M HCl (10 mL per mmol) was added and the aqueous phase was extracted with CH₂Cl₂ (2 x 5 mL per mmol) and the combined organic phases were washed with sat. aq. NaHCO₃ (10 mL per mmol) and sat. brine (10 mL per mmol). The organic phase was then dried (MgSO₄) and the excess solvents were removed in vacuo to afford crude β-nitrotrifluoroacetamide.
General Procedure N: For catalyst screening. To a flask containing N-PMP-phenyl imine 30a (0.20 mmol), β-nitrostyrene 84a (0.40 mmol), Hantzsch ester 254 (0.40 mmol) and catalyst (0.02 mmol) was added toluene (1.5 mL) and the reaction was stirred at room temperature for 2 h. After this time, a small aliquot (10 μL) was removed and analysed by $^1$H NMR spectroscopy to measure reaction progress. Then trifluoroacetic anhydride (1.0 mmol), followed by pyridine (1.0 mmol) were added at -20 °C and the solution was allowed to warm to rt and stirred for 2 h. After this time, 2.0 M HCl (10 mL) was added and the aqueous phase was extracted with CH$_2$Cl$_2$ (2 x 5 mL) and the combined organic phases were washed with sat. aq. NaHCO$_3$ 10 mL) and sat. brine (10 mL). The organic phase was then dried (MgSO$_4$) and the excess solvents were removed in vacuo to afford crude β-nitrotrifluoroacetamide.

General Procedure O: For asymmetric reactions at -20 °C. To a mixture containing imine (limiting reagent), nitroalkene (2.0 equiv.) and Hantzsch ester 254 (2.0 equiv.) in toluene (1.5 mL per mmol) cooled to -20 °C (Cryobath) was added a solution of catalyst (0.1 equiv., 0.2 M in toluene) and the reaction was stirred until reaction complete as monitored by $^1$H NMR. Once reaction complete, trifluoroacetic anhydride (5.0 equiv.), followed by pyridine (5.0 equiv.) were added at -20 °C and the solution was allowed to warm to rt and stirred for 2 h. After this time, 2.0 M HCl (10.0 mL per mmol) was added and the aqueous phase was extracted with CH$_2$Cl$_2$ (2 x 20 mL per mmol) and the combined organic phases were washed with sat. aq. NaHCO$_3$ (10 mL per mmol) and sat. brine (10 mL per mmol). The organic phase was then dried (MgSO$_4$) and the excess solvents were removed in vacuo to afford crude β-nitrotrifluoroacetamide.

2,2,2-Trifluoro-N-(4-methoxyphenyl)-N-((1R,2S)-2-nitro-1,3-diphenylpropyl)acetamide 239aa
When prepared by general procedure L. Nitroalkene 84a (0.50 mmol) afforded, after purification by column chromatography (10% EtOAc/pet. ether), 239aa (188 mg, 0.41 mmol, 82% yield) as a yellow solid; mp 128-131 °C; IR \( \nu_{\text{max}} \) 2936 (C-H), 1699 (C=O), 1557 (N-O), 1511, 1254, 1209, 1169 cm\(^{-1}\); \(^1\)H NMR (600 MHz, CDCl\(_3\)) \( \delta \) 3.47 (1H, dd, \( J = 14.4, 10.8 \), PhCH\(_2\)), 3.56 (1H, dd, \( J = 14.4, 3.0 \), PhCH\(_2\)), 3.83 (3H, s, OCH\(_3\)), 5.61 (1H, br. s, CHNO\(_2\)), 6.06 (1H, br. s, CHN), 6.39 (1H, br. s, ArH), 6.72 (1H, dd, \( J = 8.4, 2.4 \), ArH), 6.93 (1H, dd, \( J = 8.4, 2.4 \), ArH), 7.04 (1H, br. d, \( J = 7.8 \), ArH), 7.12 (2H, d, \( J = 7.2 \), ArH), 7.22-7.27 (3H, m, ArH), 7.29-7.38 (5H, m, ArH); \(^{19}\)F NMR (300 MHz, CDCl\(_3\)) \( \delta \) -67.8 (3F, s, CF\(_3\)); \(^{13}\)C NMR (151 MHz, CDCl\(_3\)) \( \delta \) 38.4 (PhCH\(_2\)), 55.7 (OCH\(_3\)), 65.2 (PhCHN), 89.8 (CHNO\(_2\)), 114.1 (ArH), 114.5 (ArH), 116.3 (1C, q, \( J = 286.5 \), CF\(_3\)), 128.0 (ArH), 128.7 (ArH), 128.9 (ArH), 129.2 (ArH), 129.4 (ArH), 129.9 (ArH), 130.2 (ArH) 132.2 (ArH), 133.2 (Ar), 134.6 (Ar), 158.3 (1C, q, \( J = 36.0 \), C=O), 160.1 (ArO); m/z (EI) 458 (17, M), 219 (96, M+H–C\(_15\)H\(_{14}\)NO\(_2\)), 114.1 (ArH), 114.5 (ArH), 116.3 (1C, q, \( J = 286.5 \), CF\(_3\)), 128.0 (ArH), 128.7 (ArH), 128.9 (ArH), 129.2 (ArH), 129.4 (ArH), 129.9 (ArH), 130.2 (ArH) 132.2 (ArH), 133.2 (Ar), 134.6 (Ar), 158.3 (1C, q, \( J = 36.0 \), C=O), 160.1 (ArO); m/z (EI) 458 (17, M), 219 (96, M+H–C\(_15\)H\(_{14}\)NO\(_2\)), HRMS C\(_{24}\)H\(_{21}\)F\(_3\)N\(_2\)O\(_4\) calcd. 458.1448, found 458.1456; anal. calcd. for C\(_{24}\)H\(_{21}\)F\(_3\)N\(_2\)O\(_4\) C, 62.88; H, 4.62; N, 6.11. Found. C, 62.47; H, 4.49; N, 6.06%.

When prepared by general procedure O. Imine 30a (0.200 mmol) afforded, after purification by column chromatography (10% Me\(_2\)CO/pet. ether and 50% CH\(_2\)Cl\(_2\)/pet. ether), 239aa (74 mg, 0.162 mmol, 81% yield) as a yellow foamy solid; HPLC analysis (Chiralcel AD, hexane/iso-propanol 95:5, flow rate = 1 mL/min, \( \lambda = 254 \) nm): retention time \( t_\text{r} \) (major) = 7.8 min, \( t_\text{r} \) (minor) = 10.6 min, shows 98% ee; mp 70-72 °C; \([\alpha]_D^{25} = -61.5^\circ \) (c = 1.01, CHCl\(_3\)).

\[ N-((1R,2S)-3-Cyclohexyl-2-nitro-1-phenylpropyl)-2,2,2-trifluoro-N-(4-methoxyphenyl)acetamide \ 239ba \]

When prepared by general procedure L. Nitroalkene 84b (0.50 mmol) afforded, after purification by column chromatography (4% Me\(_2\)CO/pet. ether), 239ba (405 mg, 0.87 mmol, 87% yield) as a white solid; mp 164-167 °C; IR \( \nu_{\text{max}} \) 2927 (C-H), 1701 (C=O), 1555 (N-O), 1511, 1256, 1209, 1156 cm\(^{-1}\); \(^1\)H NMR (600 MHz, CDCl\(_3\)) \( \delta \) 1.01 (1H, apt. qd, \( J = 12.0, 3.0 \), Cy), 1.08 (1H, apt qd, \( J = 12.0, 3.0 \), Cy), 1.25 (4H, m, Cy), 1.70 (3H, m, Cy), 1.80 (1H, br. d, \( J = 13.2 \), Cy), 1.90 (1H, m, CyCH\(_2\)), 2.09
Paul J. Koovits

(1H, br. d, J = 12.0, Cy), 2.28 (1H, m, CyCH₂), 3.82 (3H, s, OCH₃), 5.45 (1H, br. s, CHNO₂), 6.03 (1H, br. s, CHN), 6.24 (1H, br. s, ArH), 6.66 (1H, br. d, J = 10.2, ArH), 6.89 (1H, dd, J = 9.0, 3.0, ArH), 6.96 (1H, br. d, J = 7.8, ArH), 7.06 (2H, d, J = 7.8, ArH), 7.24 (2H, t, J = 7.8, ArH), 7.31 (1H, t, J = 7.8, ArH); ¹⁹F NMR (300 MHz, CDCl₃) δ -67.6 (3F, s, CF₃); ¹³C NMR (151 MHz, CDCl₃) δ 26.0 (CH₂), 26.2 (CH₂), 26.3 (CH₂), 31.9 (CH₂), 34.1 (CH₂), 34.5 (CH), 39.5 (CyCH₂), 55.6 (OCH₃), 64.3 (CHN), 85.6 (CHNO₂), 113.9 (ArH), 114.3 (ArH), 116.3 (1C, q, J = 288.7, CF₃), 127.6 (br., Ar) 128.8 (ArH), 129.3 (ArH), 129.7 (ArH), 130.2 (ArH), 132.5 (br., ArH), 133.4 (Ar), 158.0 (1C, q, J = 35.9, C=O), 160.47 (ArO); m/z (EI) 464 (38, M); HRMS C₂₄H₂₇F₃N₂O₄ calcd. 464.1917, found 464.1905; anal. calcd. for C₂₄H₂₇F₃N₂O₄: C, 62.06; H, 5.86; N, 6.03; found C, 61.89; H, 5.84; N, 5.97%.

When prepared by general procedure O. Imine 30a (0.200 mmol) afforded, after purification by column chromatography (4% Me₂CO/pet. ether and 40% CH₂Cl₂/pet. ether), 239aa (70 mg, 0.150 mmol, 75% yield) as a yellow foam; HPLC analysis (Chiralcel AD, hexane/iso-propanol 95:5, flow rate = 1 mL/min, λ = 254 nm): retention time tᵣ (major) = 4.8 min, tᵣ (minor) = 6.2 min, shows 95% ee; mp 56-57 °C; [α]D²⁵ = -38.7 ° (c = 1.00, CHCl₃).

2,2,2-Trifluoro-N-(4-methoxyphenyl)-N-((1R,2S)-2-nitro-1-phenyloctyl) acetamide 239ca

When prepared by general procedure L. Nitroalkene 84c (0.50 mmol) afforded, after purification by column chromatography (7.5% Me₂CO/pet. ether), 239ca (184 mg, 0.41 mmol, 82% yield) as a yellow oil; IR νₘₚₓₙₙ 2931 (C-H), 1698 (C=O), 1554 (N-O), 1510, 1254, 1206, 1180, 1152 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 0.91 (3H, t, J = 6.6, CH₃CH₂), 1.30-1.50 (8H, m, Me(CH₂)₃CH₂), 2.14 (1H, m, "PnCH₂), 2.26 (1H, m, "PnCH₂), 3.80 (3H, s, OCH₃), 5.30 (1H, br. s, CHNO₂), 6.03 (1H, br. s, CHN), 6.27 (1H, br. s, ArH), 6.66 (1H, d, J = 9.0, ArH), 6.88 (1H, dd, J = 9.0, 3.0, ArH), 6.92 (1H, d, J = 8.4, ArH), 7.07 (2H, d, J = 7.8, ArH), 7.24 (2H, d, J = 7.8, ArH), 7.31 (1H, t, J = 7.2, ArH); ¹⁹F NMR (300 MHz, CDCl₃) δ-67.51 (3F, s, CF₃); ¹³C NMR (151 MHz, CDCl₃) δ 14.1 (CH₃CH₂), 22.6 (MeCH₂), 25.9 (CH₂), 28.6
(CH₂), 31.6 (CH₂), 32.0 (CH₂), 55.6 (OCH₃), 64.3 (CHN), 88.0 (CHNO₂), 114.0 (ArH), 114.3 (ArH), 116.3 (1C, q, J = 289.3, CF₃), 127.7 (Ar), 128.8 (ArH), 129.2 (ArH), 129.7 (ArH), 130.1 (ArH), 132.4 (ArH), 133.5 (Ar), 158.0 (1C, q, J = 34.4, C=O), 160.5 (ArO); m/z 452 (32, M); HRMS C₂₃H₂₇F₃N₂O₄ calcd. 452.19174, found 452.19160. **When prepared by general procedure O.** Imine 30a (0.200 mmol) afforded, after purification by column chromatography (7.5% Me₂CO/pet. ether and 40% CH₂Cl₂/pet. ether), 239ca (64 mg, 0.142 mmol, 71% yield) as a yellow oil; HPLC analysis (Chiralcel AD, hexane/iso-propanol 99:1, flow rate = 1 mL/min, λ = 254 nm): retention time t₁ (major) = 7.9 min, tᵢ (minor) = 9.3 min, shows 97% ee; [α]ₐ° = -12.9° (c = 0.96, CHCl₃).

**2,2,2-Trifluoro-N-((1S*,2R*)-3-(furan-2-yl)-2-nitro-1-phenylpropyl)-N-(4-methoxyphenyl)acetamide 239da**

**When prepared by general procedure L.** Nitroalkene 84d (70 mg, 0.50 mmol) afforded after purification by column chromatography (10% EtOAc/pet. ether) β-nitrotrifluoroacetamide 239da (176 mg, 0.39 mmol, 79% yield) as a yellow solid; mp 118-121 °C; IR νmax 2939 (C-H), 1699 (C=O), 1558 (N-O), 1511, 1255, 1208, 1182, 1156 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 3.57 (1H, dd, J = 16.2, 3.6, PhCH₂), 3.63 (1H, dd, J = 16.2, 10.2, PhCH₂), 3.83 (3H, s, OCH₃), 5.24, (1H, br. t, J = 10.2, CHNO₂), 6.17 (1H, d, J = 7.8, ArH), 6.21 (1H, d, J = 3.0, ArH), 6.32 (1H, br. s, CHN), 6.34 (1H, dd, J = 3.0, 1.8, ArH), 6.64 (1H, dd, J = 9.0, 3.0, ArH), 6.97 (1H, dd, J = 8.4, 2.4, ArH), 7.04 (2H, d, J = 7.2, ArH), 7.15 (1H, dd, J = 8.4, 2.4, ArH), 7.24 (2H, t, J = 7.8, ArH), 7.33 (1H, m, ArH), 7.44 (1H, d, J = 1.2, ArH); ¹⁹F NMR (300 MHz, CDCl₃) δ -67.5 (3F, s, CF₃); ¹³C NMR (151 MHz, CDCl₃) δ 31.2 (PhCH₂), 55.6 (OCH₃), 62.8 (CHN), 86.6 (CHNO₂), 108.9 (ArH), 110.9 (ArH), 114.1 (ArH), 114.2 (ArH), 116.3 (1C, q, J = 288.4, CF₃), 127.8 (Ar), 128.8 (ArH), 129.3 (ArH), 129.9 (ArH), 130.4 (ArH), 132.7 (Ar), 132.9 (ArH), 142.9 (ArH), 148.2 (Ar), 158.3 (1C, q, J = 36.2, C=O), 160.6 (ArO); m/z (CI) 449 (3, M+H), 402 (88, M–NO₂); HRMS C₂₂H₁₀F₃N₂O₄⁺ calcd. 449.1324, found 449.1310; anal. calcd. for C₂₂H₁₀F₃N₂O₄: C, 58.93; H, 4.27; N, 6.25; found C, 58.74; H, 4.21; N, 6.20. **When**
prepared by general procedure O. Imine 30a (0.200 mmol) afforded, after purification by column chromatography (4% Me₂CO/pet. ether and 40% CH₂Cl₂/pet. ether), 239da (29 mg, 0.064 mmol, 32% yield) as a yellow foam; HPLC analysis (Chiralcel AD, hexane/iso-propanol 95:5, flow rate = 1 mL/min, λ = 254 nm): retention time t₁ (major) = 8.8 min, t₂ (minor) = 14.8 min, shows 95% ee; [α]₂⁵ = -66.2° (c = 0.75, CHCl₃).

2,2,2-Trifluoro-N-(4-methoxyphenyl)-N-((1S,2R)-2-nitro-1-phenyl-3-(o-tolyl)propyl)acetamide 239ea

When prepared by general procedure L. Nitroalkene 84e (82 mg, 0.50 mmol) afforded after purification by column chromatography (10% Me₂CO/pet. ether) β-nitrotrifluoroacetamide 239ea (170 mg, 0.36 mmol, 72% yield) as an off-white solid; mp 143-145 °C; IR νmax 2937 (C-H), 1699 (C=O), 1558 (N-O), 1511, 1254, 1210, 1168 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 2.41 (3H, s, ArCH₃), 3.54 (2H, m, ArCH₂), 3.84 (3H, s, OCH₃), 5.82 (2H, m, CHNO₂CHN), 6.57 (1H, br. s, ArH), 6.77 (1H, d, J = 7.2, ArH), 6.89 (1H, dd, J = 8.4, 2.4, ArH), 6.98 (1H, d, J = 8.4, ArH), 7.14-7.21 (6H, m, ArH), 7.27 (2H, t, J = 7.8, ArH), 7.34 (1H, m, ArH); ¹⁹F NMR (300 MHz, CDCl₃) δ -67.8 (3F, s, CF₃); ¹³C NMR (151 MHz, CDCl₃) δ 19.7 (ArCH₃), 35.5 (ArCH₂), 55.7 (OCH₃), 67.3 (CHN), 88.4 (CHNO₂), 114.1 (ArH), 114.7 (ArH), 116.3 (1C, q, J = 288.7, CF₃), 126.7 (ArH), 128.0 (ArH), 129.0 (ArH), 129.3 (ArH), 129.5 (ArH), 129.8 (ArH), 130.3 (ArH), 131.0 (ArH), 131.6 (ArH), 132.6 (Ar), 133.4 (Ar), 136.6 (Ar), 158.1 (1C, q, J = 35.6, C=O), 160.5 (ArO); m/z (EI) 472 (4, M), 219 (77, M+H-C₆H₄NO₂); HRMS C₂₅H₂₃F₃N₂O₄ calcd. 472.1604, found 472.1606; anal. calcd. for C₂₅H₂₃F₃N₂O₄: C, 63.55; H, 4.91; N, 5.93; found C, 63.26; H, 4.81; N, 5.86. When prepared by general procedure O. Imine 30a (0.200 mmol) afforded, after purification by column chromatography (4% Me₂CO/pet. ether and 40% CH₂Cl₂/pet. ether), 239ea (66 mg, 0.140 mmol, 70% yield) as a yellow foamy solid; mp 52-54 °C; HPLC analysis (Chiralcel AD, hexane/iso-propanol 99:1, flow rate = 1 mL/min, λ = 254 nm): retention time t₁,
When prepared by general procedure L. Nitroalkene 84f (82 mg, 0.50 mmol) afforded after purification by column chromatography (10% Me₂CO/pet. ether) \( \beta \)-nitrotrifluoroacetamide 239fa (176 mg, 0.37 mmol, 75% yield) as a yellow solid; mp 92-96 °C; IR \( \nu_{\text{max}} \) 2932 (C-H), 1699 (C=O), 1557 (N-O), 1511, 1255, 1209, 1168 cm⁻¹; \(^1\)H NMR (600 MHz, CDCl₃) δ 2.33 (3H, s, ArCH₃), 3.43 (1H, dd, \( J = 14.4 \), 10.8, PhCH₂), 3.51 (1H, dd, \( J = 14.4 \), 3.0, PhCH₂), 3.83 (3H, s, OCH₃), 5.57 (1H, br. s, CHNO₂), 6.06 (1H, br. s, CHN), 6.38 (1H, br. s, ArH), 6.71 (1H, dd, \( J = 8.4 \), 2.4, ArH), 6.93 (1H, dd, \( J = 9.0 \), 3.0, ArH), 7.05 (1H, d, \( J = 8.4 \), ArH), 7.10-7.13 (4H, m, ArH), 7.15 (2H, d, \( J = 7.8 \), ArH), 7.25 (2H, t, \( J = 7.8 \), ArH), 7.33 (1H, m, ArH); \(^1\)F NMR (300 MHz, CDCl₃) δ -67.6 (3F, s, CF₃); \(^{13}\)C NMR (151 MHz, CDCl₃) δ 21.2 (ArCH₃), 38.0 (ArCH₂), 55.6 (OCH₃), 65.2 (CHN), 89.8 (CHNO₂), 114.1 (ArH), 114.5 (ArH), 116.3 (1C, q, \( J = 289.0 \), CF₃), 128.0 (Ar), 128.6 (ArH), 128.9 (ArH), 129.4 (ArH), 129.7 (ArH), 129.9 (ArH), 130.2 (ArH) 131.5 (Ar), 132.2 (ArH), 133.2 (Ar), 137.7 (Ar), 158.1 (1C, q, \( J = 35.9 \), C=O), 160.5 (ArO); m/z (El) 472 (3, M), 219 (40, M+H-C₁₆H₁₆NO₂); HRMS C₂₅H₂₃F₃N₂O₄ calcd. 472.1604, found 472.1606; anal. calcd. for C₂₅H₂₃F₃N₂O₄: C, 63.55; H, 4.91; N, 5.93; found C, 63.24; H, 4.92; N, 5.80.

When prepared by general procedure L. Nitroalkene 84g (0.50 mmol) afforded, after purification by column chromatography (10% EtOAc/pet. ether), 239ga (192
mg, 0.39 mmol, 79% yield) as a yellow solid; mp 146-150 °C; IR $\nu_{\text{max}}$ 2938 (C-H), 1698 (C=O), 1556 (N-O) 1513 (C=C), 1496, 1248, 1208, 1155 (N-O) cm$^{-1}$; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 3.31 (1H, dd, $J = 14.4, 12.0$, ArCH$_2$), 3.78 (1H, dd, $J = 14.4, 3$, ArCH$_2$), 3.82 (3H, s, OCH$_3$), 4.00 (3H, s, OCH$_3$), 5.54 (1H, br. t, $J = 9.6$, CHNO$_2$), 6.08 (1H, br. d, $J = 7.2$, CHN), 6.52 (1H, br. d, $J = 8.4$, ArH), 6.57 (1H, dd, $J = 8.4, 2.4$, ArH), 6.89 (1H, td, $J = 7.8, 0.6$, ArH), 6.93 (1H, d, $J = 7.8$, ArH), 6.96 (1H, dd, $J = 8.4, 2.4$, ArH), 6.99 (2H, d, $J = 7.2$, ArH), 7.03 (1H, dd, $J = 7.8, 1.8$, ArH), 7.19 (2H, t, $J = 8.4$, ArH), 7.26-7.30 (2H, m, ArH), 7.53 (1H, d, $J = 7.2$, ArH); $^{19}$F NMR (300 MHz, CDCl$_3$) $\delta$ -67.42 (3F, s, CF$_3$); $^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 34.2 (ArCH$_2$), 55.5 (OCH$_3$), 55.6 (OCH$_3$), 62.9 (CHN), 87.1 (CHNO$_2$), 110.4 (ArH), 113.6 (ArH), 114.0 (ArH), 116.4 (1C, q, $J = 287.6$, CF$_3$), 121.4 (ArH), 122.7 (Ar), 127.0 (Ar), 128.7 (ArH), 129.4 (ArH), 129.5 (ArH), 129.6 (ArH), 130.7 (ArH), 131.2 (ArH), 132.9 (Ar), 133.1 (ArH), 157.1 (ArO), 158.1 (1C, q, $J = 35.6$, C=O), 160.4 (ArO); m/z (EI) 488 (5, M); HRMS C$_{25}$H$_{23}$F$_3$N$_2$O$_5$ calcd. 488.1554, found 488.1540; anal. calcd. for C$_{25}$H$_{23}$F$_3$N$_2$O$_5$: C, 61.47; H, 4.75; N, 5.74%.

When prepared by general procedure O. Imine 30a (0.200 mmol) afforded, after purification by column chromatography (4% Me$_2$CO/pet. ether and 40% CH$_2$Cl$_2$/pet. ether), 239ga (63 mg, 0.129 mmol, 64% yield) as a yellow foam; HPLC analysis (Chiralcel AD, hexane/iso-propanol 90:10, flow rate = 1 mL/min, $\lambda = 254$ nm): retention time $t_r$ (major) = 7.3 min, $t_r$ (minor) = 15.6 min, shows 98% ee; $[\alpha]_D^{25} = -64.3^\circ$ (c = 0.98, CHCl$_3$).

2,2,2-Trifluoro-N-(4-methoxyphenyl)-N-((1R*,2S*)-3-(4-methoxyphenyl)-2-nitro-1-phenylpropyl)acetamide 239ha

When prepared by general procedure L. Nitroalkene 84h (80 mg, 0.50 mmol) afforded after purification by column chromatography (10% EtOAc/pet. ether) $\beta$-nitrotirifluoroacetamide 239ha (211 mg, 0.43 mmol, 86% yield) as a brown oil; IR $\nu_{\text{max}}$ 2935 (C-H), 2840 (C-H), 1697 (C=O), 1556 (N-O), 1510, 1301, 1250, 1207, 1179, 1155 cm$^{-1}$; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 3.43 (1H, dd, $J = 14.4, 10.8$, ArCH$_2$), 3.53 (1H, dd, $J = 14.4, 3.0$, ArCH$_2$), 3.77 (3H, s, OCH$_3$), 3.80 (3H, s,
OCH₃), 5.59 (1H, br. s, CHNO₂), 6.09 (1H, br. s, CHN), 6.40 (1H, br. s, ArH), 6.72 (1H, dd, J = 9.0, 2.4, ArH), 6.88 (2H, dm, J = 8.4, ArH), 6.93 (1H, dd, J = 8.4, 3.0 ArH), 7.08 (1H, d, J = 7.8, ArH), 7.13 (2H, d, J = 7.2, ArH), 7.16 (2H, dm, J = 9.0, ArH), 7.24 (2H, t, J = 7.8, ArH), 7.32 (1H, t, J = 7.8, ArH); ¹⁹F NMR (300 MHz, CDCl₃) δ -67.6 (3F, s, CF₃); ¹³C NMR (151 MHz, CDCl₃) δ 37.6 (ArCH₂), 55.3 (OCH₃), 55.6 (OCH₃), 65.2 (CHN), 90.0 (CHNO₂), 114.1 (ArH), 114.6 (ArH), 116.4 (1C, q, J = 288.7, CF₃), 126.5 (Ar), 128.0 (Ar), 128.9 (ArH), 129.4 (ArH), 129.8 (ArH), 130.2 (ArH), 132.2 (ArH) 133.3 (Ar), 158.1 (1C, q, J = 35.5, C=O), 159.3 (ArO), 160.6 (ArO); m/z (EI) 488 (46, M); HRMS C₂₅H₂₃F₃N₂O₅ calcd. 488.1554, found 488.1550.

2,2,2-Trifluoro-N-(4-methoxyphenyl)-N-(1S,2R)-2-nitro-1-phenyl-3-(2-(trifluoromethyl)phenyl)propyl)acetamide 239ia

When prepared by general procedure L. Nitroalkene 84i (109 mg, 0.50 mmol) afforded after purification by column chromatography (10% Me₂CO/pet. ether) β-nitrotrifluoroacetamide 239ia (209 mg, 0.40 mmol, 79% yield) as an off-white solid; mp 108-112 °C; IR νmax 2939 (C-H), 1698 (C=O), 1558 (N-O), 1511, 1315, 1209, 1180, 1110 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 3.65 (1H, dd, J = 14.4, 12.0, ArCH₂), 3.82 (3H, s, OCH₃), 3.85 (1H, dd, J = 15.0, 3.0, ArCH₂), 5.74 (1H, br. s, CHNO₂), 5.17 (1H, br. s, CHN), 6.33 (1H, br. s, ArH), 6.65 (1H, d, J = 6.6, ArH), 6.92 (1H, dd, J = 9.0, 3.0, ArH), 7.10 (2H, d, J = 7.2, ArH), 7.15 (1H, d, J = 7.8, ArH), 7.24 (2H, t, J = 7.8, ArH), 7.29-7.33 (2H, m, ArH), 7.42 (1H, t, J = 7.8 ArH), 7.51 (1H, t, J = 7.8, ArH), 7.71 (1H, d, J = 7.8, ArH); ¹⁹F NMR (300 MHz, CDCl₃) δ -59.5 (3F, s, ArCF₃), -67.7 (3F, s, CF₃); ¹³C NMR (151 MHz, CDCl₃) δ 35.1 (ArCH₂), 55.6 (OCH₃), 65.8 (CHN), 88.5 (CHNO₂), 113.9 (ArH), 114.5 (ArH), 116.3 (1C, q, J = 288.7, F₃CC=O), 124.6 (1C, q, J = 273.9, F₃CAr), 126.7 (1C, q, J = 5.7, ArH), 128.3 (ArH), 128.7 (1C, q, J = 30.0, ArCF₃), 128.9 (ArH), 129.8 (ArH), 130.4 (ArH), 131.8 (ArH), 132.1 (ArH), 132.7 (Ar) 132.8 (ArH), 132.9 (Ar), 158.4 (1C, q, J = 36.2, C=O), 160.5 (ArO); m/z (EI) 526 (27, M), 262 (100, M-C₉H₇N₂O₄); HRMS C₂₅H₂₀F₆N₂O₄ calcd. 526.1322, found 526.1335; anal. calcd. for C₂₅H₂₀F₆N₂O₄: C,
When prepared by general procedure O. Imine 30a (0.200 mmol) afforded, after purification by column chromatography (4% Me₂CO/pet. ether and 40% CH₂Cl₂/pet. ether), 239ia (77 mg, 0.146 mmol, 73% yield) as a yellow solid; HPLC analysis (Chiralcel AD, hexane/iso-propanol 90:10, flow rate = 1 mL/min, λ = 254 nm): retention time t_r (major) = 5.2 min, t_r (minor) = 9.6 min, shows 95% ee; mp 109-111 °C; [α]D^25 = -69.0° (c = 1.00, CHCl₃).

2,2,2-Trifluoro-N-(4-methoxyphenyl)-N-((1S*,2R*)-2-nitro-1-phenyl-3-(4-(trifluoromethyl)phenyl)propyl)acetamide 239ja

When prepared by general procedure L. Nitroalkene 84j (109 mg, 0.50 mmol) afforded after purification by column chromatography (10% Me₂CO/pet. ether) β-nitrotrifluoroacetamide 239ja (213 mg, 0.41 mmol, 81% yield) as a yellow oil; IR \(\nu_{\text{max}}\) 2939 (C-H), 1697 (C=O), 1557 (N-O), 1510, 1254, 1209, 1157, 1111 cm⁻¹; \(^1\)H NMR (600 MHz, CDCl₃) δ 3.54 (1H, dd, J = 14.4, 11.4, ArCH₂), 3.60 (1H, dd, J = 14.4, 3.0, ArCH₂), 3.83 (3H, s, OCH₃), 5.69 (1H, br. s, CHN), 6.48 (1H, br. s, ArH), 6.75 (1H, dd, J = 8.4, 1.8, ArH), 6.92 (1H, dd, J = 8.4, 2.4, ArH), 7.00 (1H, d, J = 7.8, ArH), 7.13 (2H, d, J = 7.8, ArH), 7.26 (2H, t, J = 7.8, ArH), 7.34 (1H, t, J = 7.2, ArH), 7.37 (2H, d, J = 7.8 ArH), 7.61 (2H, d, J = 7.8, ArH); \(^{19}\)F NMR (300 MHz, CDCl₃) δ -63.1 (3F, s, ArCF₃), -67.7 (3F, s, CF₃); \(^{13}\)C NMR (151 MHz, CDCl₃) δ 38.0 (ArCH₂), 55.6 (OCH₃), 66.0 (CHN), 89.6 (CHNO₂), 114.2 (ArH), 114.7 (ArH), 116.3 (1C, q, J = 289.0, F₂CC=O), 124.1 (1C, q, J = 271.8, F₂C(C), 126.2 (1C, q, J = 4.5, ArH), 128.2 (br., Ar), 129.1 (ArH), 129.2 (ArH), 129.3 (ArH), 130.0 (ArH), 130.1 (ArH), 130.4 (1C, q, J = 33.2, ArCF₃), 131.9 (ArH), 133.0 (Ar), 138.6 (Ar), 158.3 (1C, q, J = 35.9, C=O), 160.6 (ArO); m/z (EI) 526 (7, M), 261 (100, M-C₉H₈N₂O₄); HRMS C₂₅H₂₆F₆N₂O₄ calcd. 526.1322, found 526.1317; anal. calcd. for C₂₅H₂₆F₆N₂O₄: C, 57.04; H, 3.83; N, 5.32; found C, 56.99; H, 3.75; N, 5.25.
When prepared by general procedure L. Nitroalkene \textbf{84k} (75 mg, 0.50 mmol) afforded after purification by column chromatography (20\% EtOAc/pet. ether) \( \beta \)-nitro trifluoroacetamide \textbf{239ka} (149 mg, 0.32 mmol, 65\% yield) as a yellow oil; IR \( \nu_{\text{max}} \) 2935 (C-H), 1696 (C=O), 1555 (N-O), 1255, 1206, 1180, 1152 cm\(^{-1}\); \(^1\)H NMR (600 MHz, CDCl\(_3\)) \( \delta \) 3.66 (1H, dd, \( J = 15.0, 10.5, \text{PhCH}_2 \)), 3.72 (1H, dd, \( J = 15.0, 3.5, \text{PhCH}_2 \)), 3.82 (3H, s, OCH\(_3\)), 5.94 (1H, apt. td, \( J = 11.0, 3.5, \text{CHNO}_2 \)), 6.13 (1H, d, \( J = 7.0, \text{ArH} \)), 6.50 (1H, d, \( J = 11.5, \text{CHN} \)), 6.60 (1H, dd, \( J = 8.5, 3.0, \text{ArH} \)), 7.01 (1H, dd, \( J = 9.0, 3.0, \text{ArH} \)), 7.04 (2H, d, \( J = 7.5, \text{ArH} \)), 7.15 (1H, d, \( J = 7.5, \text{ArH} \)), 7.20-7.23 (3H, m, \text{ArH}), 7.30 (1H, m, \text{ArH}), 7.52 (1H, dd, \( J = 8.5, 2.5, \text{ArH} \)), 7.63 (1H, td, \( J = 7.5, 2.0, \text{ArH} \)), 8.65 (1H, m, \text{ArH}); \(^{19}\)F NMR (300 MHz, CDCl\(_3\)) \( \delta \) -67.3 (s, CF\(_3\)); \(^{13}\)C NMR (151 MHz, CDCl\(_3\)) \( \delta \) 40.3 (\text{ArCH}_2), 55.6 (OCH\(_3\)), 62.5 (CHN), 87.8 (\text{CHNO}_2), 114.0 (\text{ArH}), 114.1 (\text{ArH}), 116.4 (1C, q, \( J = 288.4, \text{CF}_3 \)), 122.8 (\text{ArH}), 123.8 (\text{ArH}), 126.6 (Ar), 128.7 (\text{ArH}), 129.5 (\text{ArH}), 129.7 (\text{ArH}), 131.0 (\text{ArH}), 132.6 (Ar), 133.0 (\text{ArH}), 137.1 (\text{ArH}), 150.2 (\text{ArH}), 155.1 (Ar), 158.3 (1C, q, \( J = 36.2, \text{C=O} \)), 160.5 (\text{ArO}); \text{m/z} (\text{ESI}^+) 560 (86, M+H), 413 (48, M-\text{NO}_2); HRMS C\(_{23}\)H\(_{20}\)F\(_3\)N\(_3\)O\(_4\)H\(^+\) calcd. 460.1484, found 460.1494. 

When prepared by general procedure O. Imine \textbf{30a} (0.20 mmol) afforded, after purification by column chromatography (4\% Me\(_2\)CO/pet. ether and 40\% CH\(_2\)Cl\(_2\)/pet. ether), \textbf{239ka} (62 mg, 0.135 mmol, 68\% yield) as a pink solid; HPLC analysis (Chiralcel AD, hexane/\textit{iso}-propanol 80:20, flow rate = 1 mL/min, \( \lambda = 254 \) nm): retention time \( t_r \) (major) = 6.9 min, \( t_r \) (minor) = 12.9 min, shows 98\% ee; mp 100-102 °C; \([\alpha]_D^{25} = -25.6 ^\circ \) (c = 1.01, CHCl\(_3\)).
2,2,2-Trifluoro-N-(4-methoxyphenyl)-N-((1S*,2R*)-3-(1-methyl-5-(2,2,2-trifluoro acetyl)-1H-pyrrol-2-yl)-2-nitro-1-phenylpropyl)acetamide 240ma

When prepared by general procedure L. Nitroalkene 84m (76 mg, 0.50 mmol) afforded after purification by column chromatography (50% CH₂Cl₂/pet. ether) β-nitrotrifluoroacetamide 240ma (175 mg, 0.32 mmol, 63% yield) as a yellow foam; IR υ max 2963 (C-H), 1686 (C=O), 1672 (C=O), 1560 (N-O), 1511, 1210, 1181, 1147 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 3.48 (1H, d, J = 16.0, ArCH₂), 3.68 (1H, dd, J = 16.0, 11.0, ArCH₂), 3.83 (3H, s, OCH₃), 3.98 (3H, s, NCH₃), 5.8 (2H, br. s, CHN, CHNO₂), 6.25 (1H, d, J = 4.4, ArH), 6.54 (1H, br. s, ArH), 6.78 (1H, dd, J = 8.7, 2.3, ArH), 6.84 (1H, d, J = 8.5, ArH), 6.88 (1H, dd, J = 8.7, 2.6, ArH), 7.15 (2H, d, J = 7.6, ArH), 7.20 (1H, dd, J = 4.0, 1.9, ArH), 7.29 (2H, t, J = 7.7, ArH), 7.37 (1H, t, J = 7.4, ArH); ¹⁹F NMR (300 MHz, CDCl₃), δ -71.6 (3F, s, CF₃), -67.7 (3F, s, CF₃); m/z (ESI⁺), 558 (18, M+H), 511 (32, M-NO₂); ¹³C NMR (151 MHz, CDCl₃) δ 29.2 (ArCH₂), 33.7 (CH₃), 55.7 (OCH₃), 66.8 (CHN), 87.0 (CHNO₂), 110.9 (ArH), 114.2 (ArH), 114.9 (ArH), 116.2 (1C, q, J = 288.7, CF₃), 117.1 (1C, q, J = 290.8, CF₃), 124.0 (1C, q, J = 3.9, ArH), 125.9 (Ar), 128.3 (Ar), 129.2 (ArH), 129.4 (ArH), 130.1 (ArH), 130.2 (ArH), 131.5 (ArH), 132.6 (Ar), 158.5 (1C, q, J = 36.2, C=O), 160.7 (ArO), 170.1 (1C, q, J = 34.7, C=O); m/z (ESI⁺) 558 (8, M+H), 511 (32, M-NO₂); HRMS C₂₈H₂₁F₆N₃O₅H⁺ calcd. 558.1464, found 558.1451.

2,2,2-Trifluoro-N-(4-methoxyphenyl)-N-((1S*,2R*)-2-nitro-1-phenyl-3-(1-tosyl-1 H-pyrrol-2-yl)propyl)acetamide 239na

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University College London
When prepared by general procedure L. Nitroalkene 84n (113 mg, 0.39 mmol) afforded after purification by column chromatography (50% CH₂Cl₂/pet. ether) β-nitrotrifluoroacetamide 239na (173 mg, 0.29 mmol, 74% yield) as a yellow foam; IR $\nu_{max}$ 2968 (C-H), 1698 (C=O), 1558 (N-O), 1512, 1366, 1208, 1180, 1153 cm⁻¹; $^1$H NMR (600 MHz, CDCl$_3$) δ 2.41 (3H, s, ArCH$_3$), 3.60 (1H, dd, $J = 15.8, 11.2, \text{ArCH}_2$), 3.80 (3H, s, OCH$_3$), 5.62 (1H, apt. td, $J = 11.0, 2.5, \text{CHNO}_2$), 6.07-6.13 (2H, m, ArH), 6.22 (1H, t, $J = 3.4, \text{ArH}$), 6.34 (1H, d, $J = 9.9, \text{CHN}$), 6.54 (1H, dd, $J = 8.8, 2.8, \text{ArH}$), 6.93-6.98 (3H, m, ArH), 7.17 (2H, t, $J = 7.8, \text{ArH}$), 7.24-7.28 (1H, m, ArH), 7.31 (2H, d, $J = 8.2, \text{ArH}$), 7.34 (1H, dd, $J = 3.3, 1.6, \text{ArH}$), 7.60 (1H, d, $J = 7.7, \text{ArH}$), 7.63 (2H, d, $J = 8.4, \text{ArH}$); $^{19}$F NMR (300 MHz, CDCl$_3$), δ -67.38 (3F, s, C$_F$₃); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 21.8 (ArCH$_3$), 30.8 (ArCH$_2$), 55.6 (OCH$_3$), 63.9 (CHN), 88.2 (CHNO$_2$), 112.6 (ArH), 113.8 (ArH), 114.2 (ArH), 116.4 (ArH), 116.4 (1C, q, $J = 288.9, \text{CF}_3$), 124.1 (ArH), 126.5 (ArH), 127.2 (Ar), 127.3 (Ar), 128.7 (ArH), 129.6 (ArH), 129.7 (ArH), 130.5 (ArH), 131.0 (ArH), 132.4 (Ar), 132.7 (ArH), 135.8 (Ar), 145.7 (Ar), 158.4 (1C, q, $J = 35.6, \text{C}=\text{O}$), 160.3 (ArO); m/z (ESI⁺) 624 (56, M+Na), 555 (100, M-NO$_2$); HRMS C$_{29}$H$_{26}$F$_3$N$_3$O$_6$SNa$^+$ calcd. 624.1384, found 624.1392.

$\text{N-}((\text{1R,2S})-\text{3-(2-Bromophenyl)-2-nitro-1-phenylpropyl})\text{-2,2,2-trifluoro-N-(4-methoxyphenyl)acetamide 239oa}$

Prepared by general procedure O. Nitroalkene 84o (6.00 mmol) afforded, after purification by column chromatography (10% Me$_2$CO/pet. ether and 40% CH$_2$Cl$_2$/pet. ether), 239oa (1.27 g, 2.36 mmol, 79% yield, 98% ee) as a white solid; HPLC analysis (Chiralcel AD, hexane/iso-propanol 95:5, flow rate = 1 mL/min, $\lambda = 254$ nm): retention time $t_r$ (major) = 8.0 min, $t_r$ (minor) = 16.1 min, shows 98% ee; which after recrystallisation (iso-propanol) gave enantiopure 239oa (990 mg, 1.84 mmol, 61% yield) as a white solid; HPLC analysis (Chiralcel AD, hexane/iso-propanol 95:5, flow rate = 1 mL/min, $\lambda = 254$ nm): retention time $t_r$ (major) = 8.0 min, $t_r$ (minor) = 16.1 min, shows >99% ee; mp 128-130 °C; $[\alpha]_{D}^{25} = -114.7$ (c = 0.97, CHCl$_3$, after recrystallisation (iso-propanol) to >99% ee); $^1$H NMR (600 MHz, CDCl$_3$) δ 3.59 (1H,
dd, J = 14.3, 11.5, ArCH₂, 3.78 (1H, dd, J = 14.3, 3.8, ArCH₂), 3.81 (3H, s, OCH₃), 
5.74 (1H, br. t, J = 10.0, CHNO₂), 6.25 (1H, br. s, ArH), 6.31 (1H, br. s, CHN), 6.62 
(1H, dd, J = 8.7, 2.6, ArH), 6.91 (1H, dd, J = 8.8, 2.9, ArH), 7.06 (2H, d, J = 7.5, 
ArH), 7.15-7.20 (2H, m, ArH), 7.22 (2H, t, J = 7.7, ArH), 7.24-7.28 (1H, m, ArH), 
7.28-7.32 (1H, m, ArH), 7.41 (1H, br. d, J = 7.9, ArH), 7.61 (1H, dd, J = 8.1, 1.1, 
ArH). ¹H NMR data are consistent with literature data.¹²

2,2,2-Trifluoro-N-((1R,2R)-1-(furan-2-yl)-2-nitro-3-phenylpropyl)-N-(4-methoxy 
phenyl)acetamide 239ab

When prepared by general procedure M. Nitroalkene 84a (75 mg, 0.50 mmol) 
afforded after purification by column chromatography (10% Me₂CO/pet. ether) 
β-nitrotrifluoroacetamide 239ab (186 mg, 0.42 mmol, 83% yield) as a yellow solid; 
mp 120-123 °C; IR vₘₐₓ 2937 (C-H), 1698 (C=O), 1557 (N-O), 1509, 1253, 1207, 
1180, 1152 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 3.41 (1H, dd, J = 14.4, 10.8, PhC 
H₂), 3.49 (1H, dd, J = 15.0, 3.6, PhCH₂), 3.83 (3H, s, OCH₃), 5.35 (1H, apt. td, J = 
11.4, 3.6, CHNO₂), 6.27, (2H, dd, J = 0.6, ArH), 6.33 (1H, d, J = 10.8, CHN), 6.47 
(1H, d, J = 8.4, ArH), 6.75 (1H, dd, J = 9.0, 2.4, ArH), 6.96 (1H, dd, J = 8.4, 6.0, 
ArH), 7.20 (3H, d, J = 7.2, ArH), 7.29-7.37 (4H, m, ArH); ¹⁹F NMR (300 MHz, 
CDCl₃) δ -67.7 (3F, s, CF₃); ¹³C NMR (151 MHz, CDCl₃) δ 37.8 (PhCH₂), 55.6 
(OCH₃), 58.0 (CHN), 88.6 (CHNO₂), 111.0 (ArH), 111.9 (ArH), 114.2 (ArH), 114.7 
(ArH), 116.2 (1C, q, J = 288.7, CF₃), 127.9 (Ar), 128.1 (ArH), 128.7 (ArH), 129.2 
(ArH), 130.0 (ArH), 131.1 (ArH), 134.3 (Ar), 143.4 (ArH), 146.2 (Ar), 158.0 (1C, q, J 
= 36.2, C=O), 160.6 (ArO); m/z (CI) 449 (24, M+H), 402 (97, M-NO₂); HRMS 
C₂₂H₁₉F₃N₂O₅⁺ calcd. 449.1324, found 449.1313; anal. calcd. for C₂₂H₁₉F₃N₂O₅: C, 
58.93; H, 4.27; N, 6.25; found C, 59.07; H, 4.20; N, 6.21. When prepared by 
general procedure O. Imine 30b (0.200 mmol) afforded, after purification by 
column chromatography (4% Me₂CO/pet. ether and 40% CH₂Cl₂/pet. ether), 239ab 
(69 mg, 0.154 mmol, 77% yield) as an orange foamy solid; HPLC analysis (Chiralcel 
AD, hexane/iso-propanol 97.5:2.5, flow rate = 1 mL/min, λ = 254 nm): retention time
t_r (major) = 11.6 min, t_r (minor) = 17.5 min, shows 97% ee; mp 53-54 °C; [α]_D^{25} = -104.3 ° (c = 1.04, CHCl_3).

**2,2,2-Trifluoro-N-(4-methoxyphenyl)-N-((1S,2R)-1-(2-methoxyphenyl)-2-nitro-3-phenylpropyl)acetamide 239ac**

When prepared by general procedure M. Nitroalkene 84a (75 mg, 0.50 mmol) afforded after purification by column chromatography (10% Me_2CO/pet. ether) β-nitrotrifluoroacetamide 239ac (212 mg, 0.43 mmol, 87% yield) as a yellow solid; mp 136-140 °C; IR ν_max 2940 (C-H), 1698 (C=O), 1510, 1495, 1298, 1252, 1206, 1180, 1152 cm⁻¹; H NMR (600 MHz, CDCl_3) δ 3.50-3.57 (2H, m, PhCH_2), 3.77 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 5.48 (1H, m, CHNO_2), 6.20 (1H, d, J = 7.8, ArH), 6.59 (1H, dd, J = 8.8, 2.8, ArH), 6.70 (1H, t, J = 7.5 ArH), 6.79 (1H, br. d, J = 11.0, CHN), 6.83 (1H, br. d, J = 6.2, ArH), 6.86 (1H, d, J = 8.2, ArH), 6.92 (1H, dd, J = 8.7, 2.9, ArH), 7.08 (1H, dd, J = 8.6, 2.1, ArH), 7.23-7.28 (3H, m, ArH), 7.30 (1H, m, ArH), 7.36 (2H, t, J = 7.6, ArH); ^19F NMR (300 MHz, CDCl_3) δ -67.5 (3F, s, CF_3); ^13C NMR (151 MHz, CDCl_3) δ 38.4 (PhCH_2), 55.6 (OCH_3), 57.3 (CHN), 89.2 (CHNO_2), 110.9 (ArH), 113.7 (ArH), 114.1 (ArH), 116.5 (1C, q, J = 288.9, CF_3), 120.4 (ArH), 121.3 (Ar), 127.3 (Ar), 127.9 (ArH), 128.7 (ArH), 129.2 (ArH), 130.1 (ArH), 130.8 (ArH), 132.2 (ArH), 135.0 (Ar), 157.9 (1C, q, J = 35.5, C=O), 157.9 (ArO), 160.3 (ArO); m/z (EI) 488 (8, M), 224 (100, M-C_9H_7F_3N_2O_3); HRMS C_{25}H_{23}F_3N_2O_5 calcd. 488.1554, found 488.1543; anal. calcd. for C_{25}H_{23}F_3N_2O_5: C, 61.47; H, 4.75; N, 5.74; found C, 61.28; H, 4.57; N, 5.70.

When prepared by general procedure O. Imine 30c (0.200 mmol) afforded, after purification by column chromatography (4% Me_2CO/pet. ether and 40% CH_2Cl_2/pet. ether), 239ac (81 mg, 0.166 mmol, 83% yield) as a yellow foamy solid; HPLC analysis (Chiralcel AD, hexane/iso-propanol 97.5:2.5, flow rate = 1 mL/min, λ = 254 nm): retention time t_r (minor) = 12.2 min, t_r (major) = 15.3 min, shows 99% ee; mp 49-51 °C; [α]_D^{25} = -69.1 ° (c = 1.03, CHCl_3).
When prepared by general procedure M. Nitroalkene 84a (75 mg, 0.50 mmol) afforded after purification by column chromatography (10% Me₂CO/pet. ether) β-nitrotrifluoroacetamide 239ad (210 mg, 0.43 mmol, 86% yield) as a yellow solid; mp 130-134 °C; IR ν max 2938 (C-H), 1697 (C=O), 1557 (N-O), 1510, 1254, 1207, 1180, 1154 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 3.48 (1H, dd, J = 14.4, 11.4, PhCH₂), 3.59 (1H, dd, J = 15.0, 3.0, PhCH₂), 3.68 (3H, s, OCH₃), 3.81 (3H, s, OCH₃), 5.62 (1H, br. s, CHNO₂), 6.07 (1H, br. s, CHN), 6.48 (1H, br. s, ArH), 6.70 (2H, br. s, ArH), 6.74 (1H, dd, J = 9.0, 2.4, ArH), 6.87 (1H, dd, J = 7.8, 1.8 ArH), 6.94 (1H, dd, J = 9.0, 3.0, ArH), 7.09 (1H, br. d, J = 7.8 ArH), 7.15 (1H, t, J = 7.8, ArH), 7.26 (2H, d, J = 7.2, ArH), 7.31 (1H, t, J = 7.2, ArH), 7.36 (2H, t, J = 7.2, ArH); ¹⁹F NMR (300 MHz, CDCl₃) δ -67.5 (3F, s, CF₃); ¹³C NMR (151 MHz, CDCl₃) δ 38.4 (PhCH₂), 55.3 (OCH₃), 55.6 (OCH₃), 65.2 (CHN), 89.8 (CHNO₂), 114.1 (ArH), 114.6 (ArH), 114.7 (ArH), 115.6 (ArH), 116.4 (1C, q, J = 289.0, CF₃), 121.6 (ArH), 128.1 (ArH), 128.8 (ArH), 129.2 (ArH), 129.9 (ArH), 130.2 (ArH), 132.2 (ArH), 134.5 (Ar), 134.6 (Ar), 158.2 (1C, q, J = 35.9, C=O), 159.8 (ArO), 160.6 (ArO); m/z (EI) 488 (5, M); HRMS C₂₅H₂₃F₃N₂O₅ calcd. 488.1554, found 488.1558; anal. calcd. for C₂₅H₂₃F₃N₂O₅: C, 61.47; H, 4.75; N, 5.74; found C, 61.40; H, 4.67; N, 5.72.

When prepared by general procedure M. Nitroalkene 84a (75 mg, 0.50 mmol) afforded after purification by column chromatography (10% Me₂CO/pet. ether)
$\beta$-nitrotrifluoroacetamide 239ae (195 mg, 0.40 mmol, 80% yield) as a brown oil; IR $\nu_{\text{max}}$ 2939 (C-H), 1695 (C=O), 1555 (N-O), 1512, 1252, 1209, 1183, 1152 cm$^{-1}$; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 3.48 (1H, dd, $J = 14.6, 10.9$, ArCH$_2$), 3.80 (3H, s, OCH$_3$), 3.86 (3H, s, OCH$_3$), 5.59 (1H, br. t, $J = 9.5$, CHNO$_2$), 6.01 (1H, br. s, CHN), 6.47 (1H, br. d, $J = 7.2$, ArH), 6.70-6.80 (3H, m, ArH), 6.95 (1H, dd, $J = 8.7, 2.8$, ArH), 7.00-7.10 (3H, m, ArH), 7.20-7.30 (2H, m, ArH), 7.30-7.40 (3H, m, ArH); $^{19}$F NMR (300 MHz, CDCl$_3$) $\delta$ -67.6 (3F, s, CF$_3$); $^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 38.3 (PhCH$_2$), 55.4 (OCH$_3$), 55.7 (OCH$_3$), 64.9 (CHN), 90.1 (CHNO$_2$), 114.1 (ArH), 114.2 (ArH), 114.6 (ArH), 116.3 (1C, q, $J = 291.4$, CF$_3$), 125.0 (Ar), 128.0 (ArH), 128.7 (ArH), 129.2 (ArH), 130.2 (ArH), 130.7 (ArH) 132.3 (ArH), 134.7 (Ar), 158.1 (1C, q, $J = 34.7$, C=O), 160.5 (2C, ArO); m/z (EI) 488 (4, M), 441 (3, M - NO$_2$H); HRMS C$_{25}$H$_{23}$F$_3$N$_2$O$_5$ calcd. 488.1554, found 488.1557; anal. calcd. for C$_{25}$H$_{23}$F$_3$N$_2$O$_5$: C, 61.47; H, 4.75; N, 5.74; found C, 61.40; H, 4.68; N, 5.70. When prepared by general procedure O. Imine 30e (0.20 mmol) afforded, after purification by column chromatography (10% EtOAc/pet. ether and 50% CH$_2$Cl$_2$/pet. ether), 239ae (73 mg, 0.150 mmol, 75% yield) as a yellow solid; HPLC analysis (Chiralcel AD, hexane/iso-propanol 90:10, flow rate = 1 mL/min, $\lambda$ = 254 nm): retention time $t_r$ (major) = 8.6 min, $t_r$ (minor) = 15.4 min, shows 97% ee; mp 59-61 $^\circ$C; [$\alpha$]$_D$ = -58.7 $^\circ$ (c = 0.87, CHCl$_3$).

2,2,2-Trifluoro-N-(4-methoxyphenyl)-N-((1S,2R)-2-nitro-3-phenyl-1-(2-(trifluoromethyl)phenyl)propyl)acetamide 239af

When prepared by general procedure M. Nitroalkene 84a (75 mg, 0.50 mmol) afforded after purification by column chromatography (7.5% EtOAc/pet. ether) $\beta$-nitrotrifluoroacetamide 239af (201 mg, 0.38 mmol, 76% yield) as a yellow sticky solid; mp 126-128 $^\circ$C; IR $\nu_{\text{max}}$ 2939 (C-H), 1704 (C=O), 1557 (N-O), 1511, 1312, 1209, 1181, 1154, 1121 cm$^{-1}$; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 3.53 (1H, dd, $J = 15.0, 3.0$, PhCH$_2$), 3.64 (1H, dd, $J = 15.0, 11.4$, PhCH$_2$), 3.80 (3H, s, O CH$_3$), 5.40 (1H, apt. td, $J = 11.4, 3.0$, CHNO$_2$), 6.04 (1H, dd, $J = 9.0, 1.8$, ArH), 6.51 (1H, dd, $J = 9.0, 3.0$, ArH), 6.68 (1H, d, $J = 5.4$, ArH), 6.98 (1H, dd, $J = 8.4, 3.0$, ArH), 7.06 (1H,
d, J = 10.9, CHN), 7.14-7.19 (2H, m, ArH), 7.23-7.26 (2H, m, ArH), 7.32 (1H, t, J = 7.2, ArH), 7.35-7.41 (3H, m, ArH), 7.74 (1H, d, J = 7.8, ArH); 19F NMR (300 MHz, CDCl3) δ -67.7 (3F, s, CF3), -60.2 (3F, s, ArCF3); 13C NMR (151 MHz, CDCl3) δ 38.3 (PhCD2), 55.6 (OCH3), 57.1 (CHN), 89.9 (CHNO2), 114.0 (ArH), 114.4 (ArH), 116.3 (1C, q, J = 288.7, F3CC=O), 127.0 (1C, q, J = 274.4, F3CAr), 126.4 (Ar), 127.0 (1C, q, J = 5.7, ArH), 128.1 (ArH), 128.7 (ArH), 129.3 (ArH), 129.8 (ArH), 130.2 (Ar), 130.3 (1C, q, J = 30.7, ArCF3), 130.4 (ArH), 131.3 (ArH), 133.0 (ArH), 134.7 (Ar), 157.9 (1C, q, J = 35.9, C=O), 160.6 (ArO); m/z (EI) 526 (7, M), 261 (100, M-C9H3NO2); HRMS C25H30F6N2O4 calcd. 526.1322, found 526.1327; anal. calcd. for C25H20F6N2O4: C, 57.04; H, 3.83; N, 5.32; found C, 56.79; H, 3.69; N, 5.30. When prepared by general procedure O. Imine 30f (0.200 mmol) afforded, after purification by column chromatography (10-20% EtOAc/pet. ether and 40-50% CH2Cl2/pet. ether), major diastereomer 239af (70 mg, 0.133 mmol, 67% yield) as a white solid; HPLC analysis (Chiralcel AD, hexane/iso-propanol 97.5:2.5, flow rate = 1 mL/min, λ = 254 nm): retention time tR (major) = 9.0 min, tR (minor) = 11.0 min, shows 80% ee; mp 128-130 °C; [α]D25 = -28.2° (c = 1.06, CHCl3).

2,2,2-Trifluoro-N-(4-methoxyphenyl)-N-((1S,2S)-2-nitro-3-phenyl-1-(2-(trifluoro methyl)phenyl)propyl)acetamide 239af syn

When prepared by general procedure O. Imine 30f (0.200 mmol) afforded, after purification by column chromatography (10-20% EtOAc/pet. ether and 40-50% CH2Cl2/pet. ether), minor diastereomer 239af syn (16 mg, 0.030 mmol, 15% yield) as a white solid; HPLC analysis (Chiralcel OD-H 15 cm, hexane/iso-propanol 95:5, flow rate = 1 mL/min, λ = 254 nm): retention time tR (major) = 7.8 min, tR (minor) = 9.0 min, shows 8% ee; mp 150-152 °C; IR νmax 1706 (C=O), 1561 (N-O), 1511 (N-O), 1313 (N-O), 1207, 1156, 1120 cm⁻¹; 1H NMR (600 MHz, CDCl3) δ 2.60 (1H, dd, J = 15.1, 2.4, PhCH2), 3.26 (1H, dd, J = 15.0, 11.4, PhCH2), 3.81 (3H, s, OCH3), 5.63 (1H, br. s, CHNO2), 6.27 (1H, br. d, J = 6.6, CHN), 6.61 (1H, dd, J = 8.8, 2.8, ArH), 6.74 (1H, br. s, ArH), 6.80 (1H, br. s, ArH), 6.90 (1H, dd, J = 8.7, 2.8, ArH), 6.97-7.02 (2H, m, ArH), 7.19-7.29 (3H, m, ArH), 7.38 (1H, t, J = 7.6, ArH), 7.42 (1H, d, J
When prepared by general procedure M. Nitroalkene 84a (75 mg, 0.50 mmol) afforded after purification by column chromatography (10% Me₂CO/pet. ether and then neat Toluene) β-nitrotrifluoroacetamide 239ag (204 mg, 0.39 mmol, 78% yield) as a yellow solid; mp 122-126 °C; IR νmax 2941 (C-H), 1700 (C=O), 1557 (N-O), 1510, 1325, 1211, 1165, 1119 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 3.60 (1H, dd, J = 14.4, 11.4, PhCH₂), 3.62 (1H, dd, J = 14.4, 2.4, PhCH₂), 3.82 (3H, s, OCH₃), 5.70 (1H, br. s, CHNO₂), 6.11 (1H, br. s, CHN), 6.49 (1H, br. s, ArH), 6.78 (1H, d, J = 6.6, ArH), 6.97 (1H, dd, J = 8.4, 2.4, ArH), 7.08 (1H, br. d, J = 7.2, ArH), 7.26 (2H, d, J = 7.2, ArH), 7.29-7.34 (3H, m, ArH), 7.37 (2H, t, J = 7.2, ArH), 7.55 (2H, d, J = 7.8 ArH); ¹⁹F NMR (300 MHz, CDCl₃) δ -63.3 (3F, s, ArCF₂), -67.7 (3F, s, CF₃); ¹³C NMR (151 MHz, CDCl₃) δ 38.3 (PhCH₂), 55.6 (OCH₃), 65.0 (CHN), 89.7 (CHNO₂), 114.4 (ArH), 114.8 (ArH), 116.3 (1C, q, J = 289.0, F₃C), 123.8 (1C, q, J = 272.9, F₃CAr), 125.9 (1C, q, J = 3.6, ArH), 127.9 (Ar), 128.2 (ArH), 128.7 (ArH), 129.3 (ArH), 129.9 (ArH), 130.2 (ArH), 131.9 (ArH), 131.9 (1C, q, J = 32.6, ArCF₃), 134.3 (Ar), 137.2 (Ar), 158.4 (1C, q, J = 35.9, C=O), 160.8 (ArO); m/z (EI) 526 (100, M), 261 (100, M-C₉H₈N₂O₄); HRMS C₂₅H₂₉F₆N₂O₄ calcd. 526.1322, found 526.1319; anal. calcd. for C₂₅H₂₉F₆N₂O₄: C, 57.04; H, 3.83; N, 5.32; found C, 57.02; H, 3.76; N, 5.32. When prepared by general procedure O. Imine 30g (0.200 mmol) afforded, after purification by column chromatography (10% EtOAc/pet. ether and 40%
CH₂Cl₂/pet. ether), **239ag** (78 mg, 0.148 mmol, 74% yield) as a yellow foamy solid; HPLC analysis (Chiralcel AD, hexane/iso-propanol 97.5:2.5, flow rate = 1 mL/min, λ = 254 nm): retention time t₁ (major) = 8.2 min, t₂ (minor) = 10.9 min, shows 94% ee; mp 48-50 °C; [α]₀^25 = -55.7 ° (c = 0.91, CHCl₃).

![image](https://example.com/239ah.png)

When prepared by general procedure M. Nitroalkene **84a** (75 mg, 0.50 mmol) afforded after purification by column chromatography (10% EtOAc/pet. ether and then neat Toluene) β-nitrotrifluoroacetamide **239ah** (169 mg, 0.36 mmol, 72% yield) as an off-white solid; mp 143-145 °C; IR νₘₐₓ 2938 (C-H), 1696 (C=O), 1556 (N-O), 1510, 1255, 1207, 1180, 1154 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 2.36 (3H, s, ArCH₃), 3.56 (2H, m, PhCH₂), 3.81 (3H, s, OCH₃), 5.47 (1H, br. s, CHNO₂), 6.13 (1H, br. s, ArH), 6.59 (1H, dd, J = 8.4, 2.4, ArH), 6.66 (2H, br. s, CHN, ArH), 6.89 (1H, t, J = 7.2, ArH), 6.93 (1H, dd, J = 8.4, 3.0, ArH), 7.07 (1H, d, J = 7.8, ArH), 7.15-7.20 (2H, m, ArH), 7.25 (2H, d, J = 7.8, ArH), 7.32 (1H, t, J = 7.2, ArH), 7.37 (2H, t, J = 7.2, ArH); ¹³F NMR (300 MHz, CDCl₃) δ -67.2 (3F, s, CF₃); ¹³C NMR (151 MHz, CDCl₃) δ 19.8 (ArCH₃), 38.4 (PhCH₂), 55.6 (OCH₃), 59.2 (CHN), 89.7 (CHNO₂), 113.9 (ArH), 114.6 (ArH), 116.5 (1C, q, J = 290.5, CF₃), 125.9 (ArH), 127.0 (Ar), 128.0 (ArH), 128.2 (ArH), 128.7 (ArH), 129.2 (ArH), 129.5 (ArH), 130.0 (ArH), 131.0 (Ar), 131.2 (ArH), 132.8 (ArH), 134.8 (Ar), 138.1 (Ar), 158.2 (1C, q, J = 34.1, C=O), 160.5 (ArO); m/z (EI) 472 (14, M), 426 (8, M-NO₂); HRMS C₂₃H₂₃F₃N₂O₄ calcd. 472.1604, found 472.1607; anal. calcd. for C₂₃H₂₃F₃N₂O₄: C, 63.55; H, 4.91; N, 5.93; found C, 63.26; H, 4.82; N, 5.86. When prepared by general procedure O. Imine **30h** (0.200 mmol) afforded, after purification by column chromatography (10% EtOAc/pet. ether and 50% CH₂Cl₂/pet. ether), major diastereomer **239ah** (71 mg, 0.150 mmol, 75% yield) as a yellow foamy solid; HPLC analysis (Chiralcel AD, hexane/iso-propanol 99:1, flow rate = 1 mL/min, λ = 254 nm): retention time t₁ (major) = 10.5 min, t₂ (minor) = 14.6 min, shows 90% ee; mp 60-61 °C; [α]₀^25 = -67.2 ° (c = 0.69, CHCl₃).
When prepared by general procedure O. Imine 30h (0.200 mmol) afforded, after purification by column chromatography (10% EtOAc/pet. ether and 50% CH₂Cl₂/pet. ether), minor diastereomer 239ah syn (11 mg, 0.023 mmol, 12% yield) as an off-white solid; HPLC analysis (Chiralcel AD, hexane/iso-propanol 99:1, flow rate = 1 mL/min, λ = 254 nm): retention time t₁ (major) = 12.7 min, tᵣ (minor) = 16.0 min, shows 34% ee; mp 123-124 °C; IR νmax 2925 (C-H), 1700 (C=O), 1557 (N-O), 1511, 1254, 1206, 1156 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 2.44 (3H, s, ArC₃H₃), 2.84 (1H, dd, J = 14.9, 2.3, PhC₂H₂), 3.13 (1H, dd, J = 14.8, 11.2, PhC₂H₂), 3.80 (3H, s, OCH₃), 5.53 (1H, br. t, J = 10.2, CHNO₂), 6.13 (1H, br. d, J = 6.2, CHN), 6.55 (1H, br. s, ArH), 6.59 (1H, dd, J = 8.8, 2.9, ArH), 6.65 (1H, br. d, J = 9.2, ArH), 6.90 (1H, dd, J = 8.8, 2.9, ArH), 6.97-7.06 (3H, m, ArH), 7.21-7.28 (4H, m, ArH), 7.28-7.32 (1H, m, ArH), 7.36 (1H, d, J = 7.5, ArH); ¹⁹F NMR (300 MHz, CDCl₃) δ -67.5; ¹³C NMR (151 MHz, CDCl₃) δ 20.2 (ArCH₃), 37.4 (PhCH₂), 55.5 (OCH₃), 59.8 (CHN), 90.5 (CHNO₂), 113.8 (ArH), 114.0 (ArH), 116.2 (1C, q, J = 289.1), 126.2 (ArH), 127.0 (Ar), 127.8 (ArH), 128.7 (ArH), 128.8 (ArH), 129.1 (ArH), 129.5 (ArH), 131.2 (ArH), 131.3 (Ar), 131.7 (ArH), 132.9 (ArH), 134.8 (Ar), 138.6 (Ar), 157.5 (1C, q, J = 35.8, C=O), 160.3 (ArO); m/z (ESI⁺) 495 (17, M+Na), 473 (3, M+H), 426 (30, M-NO₂); HRMS C₂₅H₂₃F₃N₂O₄Na⁺ calcd. 495.1508, found 495.1489.

When prepared by general procedure M. Nitroalkene 84a (75 mg, 0.50 mmol) afforded after purification by column chromatography (10% Me₂CO/pet. ether) β-nitrotrifluoroacetamide 239ai (190 mg, 0.41 mmol, 84% yield) as a yellow oil; IR
$\nu_{\text{max}}$ 2931 (C-H), 2861 (C-H), 1701 (C=O), 1556 (N-O), 1511, 1255, 1209, 1183, 1157 cm$^{-1}$; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 0.89 (3H, t, $J = 7.0$, $CH_3CH_2$), 1.20-1.35 (4H, m, Me(CH$_2$)$_2$), 1.40-1.50 (3H, m, CH$_2$), 1.65 (1H, br. s, $^3$BuCH$_2$), 3.30-3.40 (2H, m, PhCH$_2$), 3.88 (3H, s, OCH$_3$), 4.87 (1H, br s, CHNO$_2$), 4.97 (1H, br. s, CHN), 6.96-7.01 (2H, m, ArH), 7.14 (2H, d, $J = 7.0$, ArH), 7.19 (2H, d, $J = 7.0$, ArH), 7.26-7.29 (1H, m, ArH), 7.30-7.33 (2H, m, ArH); $^{19}$F NMR (300 MHz, CDCl$_3$) $\delta$ -67.4 (s, CF$_3$); $^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 14.1 (CH$_3$), 22.5 (MeCH$_2$), 26.1 (EtCH$_2$), 31.3 (CH$_2$), 37.8 (CH$_2$), 55.7 (OCH$_3$), 61.1 (CHN), 91.5 (CHNO$_2$), 114.7 (ArH), 114.9 (ArH), 116.3 (1C, q, $J = 288.4$, CF$_3$), 127.6 (Ar), 127.9 (ArH), 128.6 (ArH), 129.2 (ArH), 130.3 (ArH), 131.1 (ArH), 134.7 (Ar), 158.7 (1C, q, $J = 36.2$, C=O), 160.6 (ArO); $m/z$ (EI) 452 (84, M), 406 (13, M-NO$_2$); HRMS C$_{23}$H$_{27}$F$_3$N$_2$O$_4$ calcd. 452.1917, found 452.1921. When prepared enantioenriched.

To a mixture containing imine 30i (0.200 mmol), nitroalkene 84a (0.400 mmol) and Hantzsch ester 254 (0.400 mmol) in toluene (1.5 mL) at room temperature was added a solution of catalyst 272 (0.020 mmol, 0.2 M in toluene) and the reaction was stirred until reaction complete as monitored by $^1$H NMR (1 h). Once reaction complete, trifluoroacetic anhydride (1.0 mmol), followed by pyridine (1.0 mmol) were added and the solution was stirred for 2 h at rt. After this time, 2.0 M HCl (10 mL) was added and the aqueous phase was extracted with CH$_2$Cl$_2$ (2 x 5 mL). The combined organic phases were then washed with sat. aq. NaHCO$_3$ (10 mL) and sat. brine (10 mL). The organic phase was then dried (MgSO$_4$) and the excess solvents were removed in vacuo to afford crude $\beta$-nitrotrifluoroacetamide 239ai which was purified by column chromatography (4% Me$_2$CO/pet. ether and 40% CH$_2$Cl$_2$/pet. ether) to give 239ai (53 mg, 0.117 mmol, 59% yield) as a yellow oil; HPLC analysis (Chiracel AD, hexane/iso-propanol 99:1, flow rate = 1 mL/min, $\lambda = 254$ nm): retention time $t_r$ (major) = 10.2 min, $t_r$ (minor) = 15.9 min, shows 73% ee; $[\alpha]_D^{25} = -39.5^0$ (c = 1.10, CHCl$_3$).
To a solution of nitroalkene 84a (75 mg, 0.50 mmol) in CH$_2$Cl$_2$ (3 mL) was added Superhydride$^\text{TM}$ (0.55 mmol, 1.0 M in THF). The suspension was then stirred for 30 min at rt before cooling to −78 °C over 30 min. A solution of imine 30 (0.55 mmol) in CH$_2$Cl$_2$ (3 mL) was then added via cannula and the mixture stirred at −78 °C for 10 min. A solution of TFA (0.60 mmol) was added and the reaction was stirred for 1 h at −78 °C. The reaction was then quenched with sat. aq. NH$_4$Cl 5 mL) and diluted with EtO (10 mL). The organic phase was washed with sat. brine (5 mL) and dried (MgSO$_4$). The excess solvents were then removed in vacuo to afford crude $\beta$-nitroamine 237aj which was purified by column chromatography (10% EtOAc/pet. ether) to first elute $\beta$-nitrotrifluoroacetamide 237aj major (anti) (107 mg, 0.29 mmol, 58% yield) as a yellow oil; IR $\nu_{\text{max}}$ 3405 (N-H), 2927 (C-H), 2853 (C-H), 1545 (N-O), 1509, 1234 cm$^{-1}$; $^1$H NMR (600 MHz, CDCl$_3$) δ 1.00–1.20 (2H, m, Cy), 1.20–1.30 (3H, m, Cy), 1.50–1.60 (1H, m, Cy), 1.60 (1H, br. d, $J = 9.0$, Cy), 1.67 (1H, br. d, $J = 13.2$, Cy), 1.73 (1H, br. d, $J = 10.2$, Cy), 1.78 (1H br. d, $J = 13.2$, Cy), 1.85 (1H, br. d, $J = 12.6$, Cy), 3.26–3.32 (2H, m, PhCH$_2$), 3.41 (1H, d, $J = 10.2$, N-H), 3.80 (3H, s, OCH$_3$), 3.82 (1H, m, CyC$_2$H$_2$), 4.81 (1H, ddd, $J = 9.4$, 7.8, 4.8, CHNO$_2$), 6.61–6.64 (2H, m, ArH), 6.77–6.80 (2H, m, ArH), 7.13 (2H, d, $J = 7.2$, ArH), 7.22–7.25 (1H, m, ArH), 7.28 (2H, t, $J = 7.2$, ArH); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 26.0 (CH$_2$), 26.2 (CH$_2$), 26.3 (CH$_2$), 26.9 (CH$_2$), 31.2 (CH$_2$), 36.6 (PhCH$_2$), 40.6 (CH), 55.9 (OCH$_3$), 62.1 (CHN), 91.7 (CHNO$_2$), 114.5 (ArH), 115.2 (ArH), 127.4 (ArH), 128.8 (ArH), 128.9 (ArH), 136.3(Ar), 142.0 (Ar), 152.6 (ArO); m/z (El) 368 (8, M), 239 (52), 218 (100); HRMS C$_{22}$H$_{28}$N$_2$O$_3$ calcd. 368.2094, found 368.2089; and then elute 237aj minor (syn) (55 mg, 0.15 mmol, 30% yield) as a yellow oil; IR $\nu_{\text{max}}$ 3395 (N-H), 2925 (C-H), 2853 (C-H), 1547 (N-O), 1510, 1232 cm$^{-1}$; $^1$H NMR (600 MHz, CDCl$_3$) δ 1.00–1.30 (5H, m, Cy), 1.50–1.60 (1H, m, Cy), 1.68 (1H, br. d, $J = 12.0$, Cy), 1.76 (2H, br. d, $J = 12.8$, Cy), 1.86 (2H, br. s, Cy), 3.16 (1H, dd, $J =$
14.4, 8.4, PhCH₂), 3.40 (1H, dd, J = 14.0, 8.0, PhCH₂), 3.51 (1H, m, CHN), 3.78 (3H, s, OCH₃), 3.91 (1H, d, NH), 5.08 (1H, ddd, J = 9.1, 5.5, 4.9, CHNO₂), 6.56-6.61 (2H, m, ArH), 6.77-6.81 (2H, m, ArH), 7.11-7.13 (2H, m, ArH), 7.27-7.33 (3H, m, ArH); ¹³C NMR (151 MHz, CDCl₃) δ 26.0 (CH₂), 26.1 (CH₂), 26.2 (CH₂), 29.2 (CH₂), 30.7 (CH₂), 37.6 (PhCH₂), 41.6 (CH), 55.8 (OCH₃), 60.8 (CHN), 91.0 (CHNO₂), 114.1 (ArH), 115.0 (ArH), 127.4 (ArH), 128.8 (ArH), 128.9 (ArH), 135.7 (Ar), 142.5 (Ar), 152.2 (ArO); m/z (EI) 368 (33, M), 239 (23), 218 (47); HRMS C₂₂H₂₈N₂O₃ calcd. 368.2094, found 368.2086.

2,2,2-Trifluoro-N-(4-methoxyphenyl)-N-((1R,2R)-2-nitro-3-phenyl-1-(pyridin-2-yl)propyl)acetamide 239ak

When prepared by general procedure M. Nitroalkene 84a (75 mg, 0.50 mmol) afforded after purification by column chromatography (20% EtOAc/pet. ether) β-nitrotrifluoroacetamide 239ak (138 mg, 0.30 mmol, 60% yield) as an off-white solid; mp 109-112 °C; IR νmax 2919 (C-H), 1698 (C=O), 1555 (N-O), 1510, 1253, 1207, 1182, 1152 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 3.41 (1H, dd, J = 14.4, 10.8, PhCH₂), 3.60 (1H, dd, J = 14.4, 3.0, PhCH₂), 3.80 (3H, s, OCH₃), 5.63 (1H, apt. td, J = 10.8, 3.0, CHNO₂), 6.08 (1H, d, J = 7.2, ArH), 6.59 (2H, d, J = 10.8, CHN, ArH), 6.94 (1H, d, J = 7.2, ArH), 7.19-7.24 (4H, m, ArH), 7.28-7.32 (1H, m, ArH), 7.35 (2H, t, J = 6.6, ArH), 7.48 (1H, d, J = 7.8, ArH), 7.71 (1H, td, J = 7.8, 1.8, ArH), 8.31 (1H, d, J = 4.8 ArH); ¹⁹F NMR (300 MHz, CDCl₃) δ -67.3 (3F, s, CF₃); ¹³C NMR (151 MHz, CDCl₃) δ 38.1 (PhCH₂), 55.6 (OCH₃), 62.6 (CHN), 87.4 (CHNO₂), 114.1 (ArH), 114.5 (ArH), 116.4 (1C, q, J = 289.0, F₃C), 124.1 (ArH), 124.6 (ArH), 127.1 (ArH), 128.0 (ArH), 128.8 (ArH), 129.1 (ArH), 130.3 (ArH), 131.6 (ArH), 134.6 (Ar), 137.4 (Ar), 149.1 (ArH), 153.7 (Ar), 158.4 (1C, q, J = 35.9, C=O), 160.5 (ArO); m/z (ESI⁺) 460 (100, M+H), 413 (95, M-NO₂); HRMS C₂₃H₂₉F₃N₃O₃H⁺ calcd. 460.1491, found 460.1484; anal. calcd. for C₂₃H₂₉F₃N₃O₃: C, 60.13; H, 4.39; N, 9.15; found C, 60.19; H, 4.30; N, 9.14. When prepared by general procedure O. Imine 30k (0.200 mmol) afforded, after purification by column chromatography (40% EtOAc/pet. ether and 25% Me₂CO/pet. ether), 239ak (70 mg, 0.152 mmol, 76%
yield) as a white solid; HPLC analysis (Chiralcel AD, hexane/iso-propanol 90:10, flow rate = 1 mL/min, λ = 254 nm): retention time $t_r$ (major) = 10.4 min, $t_r$ (minor) = 18.3 min, shows 96% ee; mp 94-95 °C; $[\alpha]_D^{25} = -55.5^\circ$ (c = 0.99, CHCl$_3$).

**2,2,2-Trifluoro-N-(4-methoxyphenyl)-N-((1S*,2R*)-2-nitro-3-phenyl-1-(pyridin-3-yl)propyl)acetamide 239al**

When prepared by general procedure M. Nitroalkene 84a (75 mg, 0.50 mmol) afforded after purification by column chromatography (30% EtOAc/pet. ether) β-nitrotrifluoroacetamide 239al (183 mg, 0.40 mmol, 80% yield) as an off-white solid; mp 147-150 °C; IR υ$_{max}$ 3032 (C-H), 2970 (C-H), 1700 (C=O), 1557 (N-O), 1511, 1255, 1211, 1182, 1168 cm$^{-1}$; $^1$H NMR (600 MHz, CDCl$_3$) δ 3.47 (1H, dd, $J = 14.5, 11.1$, PhCH$_2$), 3.55 (1H, dd, $J = 14.5, 3.0$, PhCH$_2$), 3.83 (3H, s, OCH$_3$), 5.68 (1H, br. s, CHNO$_2$), 5.95 (1H, br. s, CHN), 6.53 (1H, br. s, ArH), 6.79 (1H, dd, $J = 8.8, 2.6$, ArH), 6.95 (1H, dd, $J = 8.7, 2.8$, ArH), 7.03 (1H, d, $J = 7.1$, ArH), 7.20-7.24 (3H, m, ArH), 7.31 (1H, m, ArH), 7.36 (2H, m, ArH), 7.53 (1H, d, $J = 7.0$, ArH), 8.34 (1H, d, $J = 1.8$, ArH), 8.59 (1H, dd, $J = 4.8, 1.2$, ArH); $^{19}$F NMR (300 MHz, CDCl$_3$) δ -67.8 (3F, s, CF$_3$); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 38.2 (PhCH$_2$), 55.7 (OCH$_3$), 63.9 (CHN), 89.5 (CHNO$_2$), 114.6 (ArH), 115.0 (ArH), 116.1 (1C, q, $J = 289.0$, CF$_3$), 123.7 (ArH), 128.0 (Ar), 128.2 (ArH), 128.7 (ArH), 129.1 (Ar), 129.3 (ArH), 130.2 (ArH), 131.8 (ArH), 134.1 (Ar), 136.7 (ArH), 150.6 (ArH), 151.2 (ArH), 158.3 (1C, q, $J = 36.2$, C=O), 160.8 (ArO); m/z (EI) 459 (15, M), 413 (7, M-NO$_2$); HRMS C$_{23}$H$_{20}$N$_3$F$_3$O$_4$ calcd. 459.1400, found 459.1408; anal. calcd. for C$_{23}$H$_{20}$F$_3$N$_3$O$_4$: C, 60.13; H, 4.39; N, 9.15; found C, 59.80; H, 4.33; N, 9.06.
2,2,2-Trifluoro-N-(4-methoxyphenyl)-N-((1R*,2R*)-2-nitro-3-phenyl-1-(1-tosyl-1
H-pyrrol-2-yl)propyl)acetamide 239ao

When prepared by general procedure M. Nitroalkene 84a (75 mg, 0.50 mmol) afforded after purification by column chromatography (10% EtOAc/pet. ether) β-nitrotrifluoroacetamide 239ao (225 mg, 0.374 mmol, 75% yield) as a yellow solid; mp 192-196 °C; IR νmax 2938 (C-H), 1702 (C=O), 1557 (N-O), 1511, 1370, 1179, 1154 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 2.47 (3H, s, ArCH₃), 3.34 (1H, dd, J = 14.4, 10.8, PhCH₂), 3.40 (1H, dd, J = 15.0, 4.2, PhCH₂), 3.80 (3H, s, OCH₃), 4.96 (1H, apt. td, J = 10.8, 4.2, CHNO₂), 5.74 (1H, dd, J = 3.6, 1.2, ArH), 5.97 (1H, t, J = 3.6, ArH), 6.51 (1H, dd, J = 8.9, 2.2, ArH), 6.64 (1H, dd, J = 8.9, 2.9, ArH), 6.72 (1H, d, J = 11.0, CHN), 6.90 (1H, dd, J = 8.6, 2.9, ArH), 7.02 (1H, dd, J = 8.6, 2.6, ArH), 7.14 (2H, d, J = 7.0, ArH), 7.27-7.35 (3H, m, ArH), 7.40-7.43 (3H, m, ArH), 7.86 (2H, d, J = 8.4, ArH); ¹⁹F NMR (300 MHz, CDCl₃) δ -68.0 (3F, s, CF₃); ¹³C NMR (151 MHz, CDCl₃) δ 21.9 (ArCH₃), 38.0 (PhCH₂), 54.8 (CHN), 55.6 (OCH₃), 90.0 (CHNO₂), 111.0 (ArH), 113.8 (ArH), 114.4 (ArH), 116.3 (1C, q, J = 288.6, CF₃), 117.9 (ArH), 124.5 (Ar), 124.7 (ArH), 127.7 (ArH), 127.7 (ArH), 128.0 (ArH), 128.6 (ArH), 129.2 (ArH), 129.7 (ArH), 130.4 (ArH), 134.7 (Ar), 134.8 (Ar), 146.1 (Ar), 158.2 (1C, q, J = 36.2, C=O), 160.4 (ArO); m/z (CI) 602 (4, M+H), 555 (6, M-NO₂), 383 (100, M-C₆H₄F₃NO₂); HRMS C₂⁹H₂₆N₃F₃O₆SH⁺ calcd. 602.1573, found 602.1586; anal. calcd. for C₂⁹H₂₆N₃F₃O₆S: C, 57.90; H, 4.36; N, 6.98; found C, 57.82; H, 4.28; N, 6.95.
When prepared by general procedure M. Nitroalkene 84a (75 mg, 0.50 mmol) afforded after purification by column chromatography (10% EtOAc/pet. ether) β-nitrotrifluoroacetamide 239aq (208 mg, 0.32 mmol, 64% yield) as an off-white solid; mp 90–95 °C; IR ν max 2934 (C–H), 1698 (C=O), 1557 (N–O), 1511, 1448, 1371, 1210 1171 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 2.31 (3H, s, ArCH₃), 3.51 (1H, dd, J = 14.5, 11.5, PhCH₂), 3.61 (1H, dd, J = 14.6, 2.8, PhCH₂), 3.84 (3H, s, OCH₃), 5.33 (1H, br. s, CHNO₂), 6.09 (1H, br. s, CHN), 6.54 (1H, d, J = 7.3, ArH), 6.68 (1H, br. s, ArH), 6.97 (1H, dd, J = 8.6, 2.2, ArH), 7.13-7.22 (4H, m, ArH), 7.24 (2H, d, J = 7.2, ArH), 7.28-7.40 (5H, m, ArH), 7.51 (1H, br. s, ArH), 7.57 (2H, d, J = 8.3, ArH), 7.95 (1H, d, J = 8.3, ArH); ¹⁹F NMR (300 MHz, CDCl₃) δ -67.61 (3F, s, CF₃); ¹³C NMR (151 MHz, CDCl₃) δ 21.7 (ArCH₃), 38.0 (PhCH₂), 54.9 (CHN), 55.7 (OCH₃), 89.8 (CHNO₂), 114.0 (ArH), 114.2 (ArH), 114.7 (ArH), 114.8 (Ar), 116.2 (1C, q, J = 288.5, CF₃), 119.3 (ArH), 124.4 (ArH), 125.9 (ArH), 126.6 (ArH), 127.0 (ArH), 128.2 (ArH), 128.6 (ArH), 129.2 (Ar), 129.3 (ArH), 129.8 (ArH), 130.1 (ArH), 132.0 (ArH), 134.2 (Ar), 134.3 (Ar), 134.6 (Ar), 145.6 (Ar), 158.5 (1C, q, J = 36.2, C=O), 160.7 (ArO); m/z (ESI⁺), 674 (21, M+Na), 605 (16, M–NO₂); HRMS C₃₃H₂₈F₃N₃O₆SNa⁺ calcd. 674.1549, found 674.1558.

N-((1R,2S)-1-(2-Bromophenyl)-2-nitro-3-phenylpropyl)-2,2,2-trifluoro-N-(4-methoxyphenyl)acetamide 239ar

Prepared by general procedure O. Imine 30r (0.200 mmol) afforded, after purification by column chromatography (10% EtOAc/pet. ether and 50% CH₂Cl₂/pet.
ether), major diastereomer 239ar (75 mg, 0.140 mmol, 70% yield) as a white solid; HPLC analysis (Chiralcel AD, hexane/iso-propanol 97.5:2.5, flow rate = 1 mL/min, λ = 254 nm): retention time \( t_r \) (major) = 12.6 min, \( t_r \) (minor) = 15.7 min, shows 92% ee; mp 158-160 °C; \([\alpha]_D^{25} = -61.4^\circ \) (c = 1.04, CHCl\(_3\)); IR \( \nu_{max} \) 2935 (C-H), 1702 (C=O), 1556 (N-O), 1510, 1256, 1208, 1181 cm\(^{-1}\); \(^1\)H NMR (600 MHz, CDCl\(_3\)) \( \delta \) 3.55 (1H, dd, \( J = 14.7, 2.8, \) PhCH\(_2\)), 3.60 (1H, dd, \( J = 15.2, 10.7, \) PhCH\(_2\)), 3.80 (3H, s, OCH\(_3\)), 5.48 (1H, apt. td, \( J = 10.7, 3.4, \) CHNO\(_2\)), 6.27 (1H, br. d, \( J = 8.3, \) ArH), 6.58 (1H, dd, \( J = 8.8, 2.7, \) ArH), 6.80 (1H, br. d, \( J = 11.1, \) CHN), 6.83 (1H, br. d, \( J = 7.7, \) ArH), 6.92 (1H, dd, \( J = 8.8, 2.9, \) ArH), 7.02 (1H, t, \( J = 7.6, \) ArH), 7.05 (1H, dd, \( J = 8.7, 1.7, \) ArH), 7.15 (1H, td, \( J = 7.5, 1.1, \) ArH), 7.25 (2H, d, \( J = 7.2, \) ArH), 7.32 (1H, t, \( J = 7.3, \) ArH), 7.37 (2H, t, \( J = 7.3, \) ArH), 7.62 (1H, d, \( J = 8.1, \) ArH); \(^1^9\)F NMR (300 MHz, CDCl\(_3\)) \( \delta \) -67.6; \(^{13}\)C NMR (151 MHz, CDCl\(_3\)) \( \delta \) 38.2 (PhCH\(_2\)), 55.6 (OCH\(_3\)), 62.2 (CHN), 89.7 (CHNO\(_2\)), 113.9 (ArH), 114.5 (ArH), 116.4 (1C, q, \( J = 288.5, \) CF\(_3\)), 126.1 (Ar), 127.2 (Ar), 127.4 (ArH), 128.1 (ArH), 128.7 (ArH), 129.3 (ArH), 129.8 (ArH), 130.1 (ArH), 131.0 (ArH), 132.3 (ArH), 132.4 (Ar), 133.8 (ArH), 134.7 (Ar), 157.9 (1C, q, \( J = 35.8, \) C=O), 160.5 (ArO); \( m/z \) (Cl) 538 (17, \(^{81}\)M), 536 (17, \(^{79}\)M), 492 (26, \(^{81}\)N-NO\(_2\)), 490 (25, \(^{79}\)N-NO\(_2\)); HRMS C\(_{24}H_{29}BrF_3N_2O_4\) calcd. 536.0559, found 536.0554.

\( \)N-((1\(R\),2\(R\))-1-(2-Bromophenyl)-2-nitro-3-phenylpropyl)-2,2,2-trifluoro-N-(4-methoxyphenyl)acetamide 239ar \( \)syn

\[ \begin{align*}
\text{O} & \quad \text{F}\text{c}_3 \text{C} \quad \text{N} \quad \text{O} \\
\text{O}_2 \text{Ar} \quad \text{Br}
\end{align*} \]

Prepared by general procedure O. Imine 30r (0.200 mmol) afforded, after purification by column chromatography (10% EtOAc/pet. ether and 50% CH\(_2\)Cl\(_2\)/pet. ether), minor diastereomer 239ar \( \)syn (10 mg, 0.019 mmol, 9% yield) as a white solid; HPLC analysis (Chiralcel AD, hexane/iso-propanol 90:10, flow rate = 1 mL/min, λ = 254 nm): retention time \( t_r \) (major) = 11.3 min, \( t_r \) (minor) = 17.4 min, shows 10% ee; mp 134-135 °C; IR \( \nu_{max} \) 2843 (C-H), 1706 (C=O), 1559 (N-O), 1511, 1206, 1183 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 2.79 (1H, br. d, \( J = 13.6, \) PhCH\(_2\)), 3.26 (1H, dd, \( J = 14.8, 11.3, \) PhCH\(_2\)), 3.83 (3H, s, OCH\(_3\)), 5.84 (1H, br. t, \( J = 9.8, \) CHNO\(_2\)), 6.56 (2H, br. d, \( J = 8.3, \) CHN, ArH), 6.72 (1H, dd, \( J = 8.8, 3.0, \) ArH), 6.87
(1H, dd, J = 8.8, 3.0, ArH), 7.02-7.09 (2H, m, ArH), 7.10-7.28 (7H, m, ArH), 7.71 (1H, d, J = 7.5, ArH); $^{19}$F NMR (300 MHz, CDCl$_3$) δ -67.7; $^{13}$C NMR (151 MHz, CDCl$_3$) δ 37.3 (PhCH$_2$), 55.6 (OCH$_3$), 65.2 (CHN), 89.9 (CHNO$_2$), 113.9 (ArH), 114.5 (ArH), 116.1 (1C, q, J = 289.1, CF$_3$), 126.4 (Ar), 127.8 (ArH), 128.0 (ArH), 128.6 (ArH), 129.1 (ArH), 130.5 (ArH), 131.0 (ArH), 131.1 (ArH), 131.6 (ArH), 133.3 (Ar), 134.1 (ArH), 134.7 (Ar), 157.5 (1C, q, J = 35.8, C=O), 160.3 (OCH$_3$); m/z (ESI$^+$) 539 (5, $^{81}$M+H), 537 (6, $^{79}$M+H), 492 (100, $^{81}$M-NO$_2$), 490 (98, $^{79}$M-NO$_2$); HRMS C$_{24}$H$_{20}$BrF$_3$N$_2$O$_4$ calcd. 537.0637, found 537.0631.

**tert-Butyl ((1R,2S)-2-nitro-1,3-diphenylpropyl)carbamate 257**

![Chemical structure](image)

To a mixture containing imine 30a (84 mg, 0.40 mmol), nitroalkene 84a (120 mg, 0.80 mmol) and Hantzsch ester 254 (248 mg, 0.80 mmol) in toluene (3 mL) cooled to -20 °C (Cryobath) was added a solution of catalyst 272 (200 μL, 0.04 mmol, 0.2 M in toluene) and the reaction was stirred for 20 h. The excess solvent was removed in vacuo and the crude β-nitroamine was dissolved in MeCN (8 mL) and added to a pre-cooled solution of ceric ammonium nitrate (1.10 g, 2.00 mmol) in water (8 mL) at 0 °C. The reaction was stirred for 1 h at this temperature to give a black mixture and then di-tert-butyl dicarbonate (611 mg, 2.80 mmol) and 4-dimethylpyridine (5 mg, 0.04 mmol) were added and the reaction was allowed to warm to rt and stirred for 16 h. The excess solvent was then removed in vacuo and the resultant residue was diluted with EtOAc (40 mL). This mixture was then washed with sat. aq. NaHCO$_3$ 2 x 20 mL), dried (MgSO$_4$) and the excess solvent was removed in vacuo to give crude 257 which was purified by column chromatography (20% EtOAc/pet. ether) to give 257 (56 mg, 0.16 mmol, 39% yield) as a white solid; HPLC analysis (Chiralcel AD, hexane/iso-propanol 90:10, flow rate = 1 mL/min, $\lambda$ = 254 nm): retention time $t_1$ (major) = 11.0 min, $t_2$ (minor) = 12.7 min, shows 94% ee; mp 179-180 °C; $[\alpha]_D^{25}$ = -46.0 ° (c = 0.90, CHCl$_3$); $^1$H NMR (600 MHz, CDCl$_3$) δ 1.47 (9H, s, C(C$_3$H$_7$)$_3$), 3.18 (1H, dd, J = 14.8, 3.52, PhCH$_2$), 3.32 (1H, dd, J = 14.6, 10.56, PhCH$_2$), 5.13 (1H, br. s, CHNO$_2$), 5.26 (2H, br. s, NH, CHN), 7.16 (2H, d, J = 6.8, ArH), 7.23-7.33 (5H, m, ArH), 7.36-7.43 (3H, m, ArH); $^1$H NMR data are consistent with literature data.
4-Methoxy-N-((1R,2R,3S)-2-nitro-1,3-diphenylbutyl)aniline 287a

![Chemical structure of 4-Methoxy-N-((1R,2R,3S)-2-nitro-1,3-diphenylbutyl)aniline 287a]

To a solution of β-nitro-α-methylstyrene 286 (64 mg, 0.400 mmol) in toluene (2 mL) at rt was added Hantzsch ester 254 (124 mg, 0.400 mmol) and N-PMP phenyl imine 30a (42 mg, 0.200 mmol) and the reaction was stirred at rt for 5 min after which a solution of thiourea 272 (0.2 M in toluene, 100 μL, 0.020 mmol) was added and the reaction was stirred at rt for 16 h. The excess solvent was removed in vacuo to give crude product which was then purified by column chromatography (10% Me₂CO/pet. ether, then 10% EtOAc/pet. ether) to give 287a (28 mg, 0.074 mmol, 37% yield) as a white foam; HPLC analysis (Chiralcel AD, hexane/iso-propanol 99:1, flow rate = 1 mL/min, λ = 254 nm): retention time t₁ (major) = 12.4 min, tᵢ (minor) = 14.2 min, shows 84% ee; [α]₀° = +9.2° (c = 0.68, CH₂Cl₂); ¹H NMR syn,syn (600 MHz, CDCl₃) δ 1.37 (3H, d, J = 7.0, CH₃), 3.67 (3H, s, OCH₃), 3.87 (1H, dq, J = 10.9, 6.8, PhCHMe), 4.25 (1H, dd, J = 10.4, 3.6, CHN), 4.88 (1H, dd, J = 10.9, 3.8, CHNO₂), 5.10 (1H, d, J = 10.5, NH), 6.29-6.34 (2H, m, ArH), 6.62-6.66 (2H, m, ArH), 7.06-7.09 (2H, m, ArH), 7.19-7.22 (1H, m, ArH), 7.23-7.29 (4H, m, ArH), 7.29-7.35 (3H, m, ArH); ¹H NMR data consistent with literature data. Minor diastereomers unstable to purification but partially visible from ¹H NMR data; ¹H NMR syn,anti (600 MHz, CDCl₃) δ 3.60 (1H, apt. t, J = 7.0, PhCHMe), 4.18 (1H, d, J = 9.0, NH), 4.83 (1H, dd, J = 8.7, 6.6), 6.51-6.55 (2H, m, ArH) other peaks not visible; ¹H NMR anti,syn (600 MHz, CDCl₃) δ 3.43 (1H, dq, J = 10.0, 7.0, PhCHMe) 4.08 (1H, d, J = 8.3, NH), 4.64 (1H, dd, J = 7.9, 4.9) other peaks not visible.

2,2,2-trifluoro-N-(4-methoxyphenyl)-N-((1S,2R,3S)-2-nitro-1,3-diphenylbutyl)acetamide

![Chemical structure of 2,2,2-trifluoro-N-(4-methoxyphenyl)-N-((1S,2R,3S)-2-nitro-1,3-diphenylbutyl)acetamide]
To confirm stereochemistry of 287b a solution of crude reaction mixture of 287 (after 30 min reaction time) diastereomerically enriched with syn,syn 287b in toluene (2 mL) at 0 °C was added trifluoroacetic anhydride (0.40 mmol) and iPr3Net (0.40 mmol) and the reaction was allowed to warm to rt and stirred for 1 h. After this time, 2.0 M HCl (10 mL) was added and the aqueous phase was extracted with CH2Cl2 (2 x 5 mL) and the combined organic phases were washed with sat. aq. NaHCO3 10 mL) and sat. brine (10 mL). The organic phase was then dried (MgSO4) and the excess solvents were removed in vacuo to afford crude β-nitrotrifluoroacetamide; 1H NMR syn,anti (600 MHz, CDCl3) δ 1.61 (3H, d, J = 7.2, C2H3), 3.66 (1H, qd, J = 7.9, 4.5, CHMe), 3.80 (3H, s, OMe), 5.68 (1H, dd, J = 10.8, 4.3, CHNO2), 6.19 (1H, d, J = 10.6 CHN), 6.22-6.28 (1H, m, ArH) remaining peaks could not be distinguished; 13H NMR data are consistent with literature data.53

4-Methoxy-N-((2R,3S)-3-nitro-2,4-diphenylbutan-2-yl)aniline 292

\[
\begin{align*}
\text{Me} & \quad \text{H} \quad \text{N} \\
\text{NO}_2 & \quad \text{O} \\
\end{align*}
\]

To a mixture containing imine 291 (0.20 mmol), nitroalkene 84a (0.40 mmol) and Hantzsch ester 254 (0.40 mmol) in toluene (1.5 mL) cooled to -20 °C (Cryobath) was added a solution of catalyst 272 (0.02 mmol, 0.2 M in toluene) and the reaction was stirred at this temperature. After a set time (16-24 h) the excess solvent was removed in vacuo to give crude product 292 which was analysed by 1H NMR. 1H NMRMAJOR (400 MHz, CDCl3) δ 2.94 (1H, dd, J = 15.1, 2.8, PhCH2), 3.45 (1H, dd, J = 15.1, 11.8, PhCH2), 3.73 (3H, s, OCH3), 4.80 (1H, dd, J = 12.0, 2.8, CHNO2), 6.45-6.50 (2H, m, ArH), 6.66-6.71 (2H, m, ArH) other signals could not be determined; 1H NMRMINOR (600 MHz, CDCl3) δ 4.84 (1H, dd, J = 13.7, 8.1, CHNO2), 6.28-6.33 (2H, m, ArH), 6.56-6.60 (2H, m, ArH) other signals could not be determined.
4.2.5 Miscellaneous compounds and total synthesis intermediates

**(2-Nitroethyl)benzene 234**

![Chemical structure of (2-Nitroethyl)benzene 234](image)

Superhydride™ (500 μL, 0.50 mmol, 1.0 M, in THF) was added to a yellow solution of β-nitrostyrene (75 mg, 0.50 mmol) in THF (3 mL) at 0 °C. After 30 min, 1.0 M HCl (2 mL) was added and the mixture was stirred vigorously for 15 min. The mixture was then extracted with Et$_2$O (2 x 10 mL) and the combined organics were washed with sat. brine (5 mL), dried (MgSO$_4$) and the excess solvent was removed *in vacuo* to leave crude **234** as a yellow oil. Purification by flash chromatography (5% EtOAc/pet. ether) afforded **234** (72 mg, 0.48 mmol, 95%) as a colourless oil; $^1$H NMR (CDCl$_3$) δ 3.36 (2H, t, $J = 7.4$, C$_2$H$_2$Ar), 4.63 (2H, t, $J = 7.4$, C$_2$H$_2$NO$_2$), 7.24 (2H, m, ArH), 7.32 (3H, m, ArH). $^1$H NMR data are consistent with literature data.

**Diethyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate 255**

Prepared according to literature procedure.$^{177}$ Ammonium acetate (20.0 mmol) gave crude **255** (2.30 g) as a yellow solid which was recrystallised (EtOH, 10 mL/g) to give **255** (1.53 g, 6.0 mmol, 60% yield) as a pale yellow solid; mp 188-190 °C (Lit.$^{178}$ 183-185 °C); $^1$H NMR (400 MHz, CDCl$_3$) δ 1.30 (6H, t, $J = 7.1$, CH$_2$CH$_3$), 2.20 (6H, s, CH$_3$), 3.28 (2H, s, CH$_2$), 4.18 (4H, q, $J = 7.1$, CH$_2$CH$_3$), 5.11 (1H, br. s, NH); $^1$H NMR data are consistent with literature data.

**Di-tert-butyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate 254**

![Chemical structure of Di-tert-butyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate 254](image)

To a mixture of ammonium acetate (6.17 g, 80.0 mmol) in EtOH (60 mL) was added tert-butylacetocacetate (6.5 mL, 40.0 mmol), formaldehyde (35 wt% in water, 1.6 mL, 20 mmol) and para-toluenesulfonic acid monohydrate (0.76 g, 4.0 mmol). The colourless mixture was heated at reflux (80 °C) for 1 h to give a yellow solution
which was then allowed to cool to rt. After 5 min, water (50 mL) was added and a precipitate was formed upon cooling. The reaction was then cooled to 0 °C and filtered to give 254 (4.76 g, 15.4 mmol, 77% yield) as a pale yellow solid; mp 127-129 °C; IR νmax 2978 (C-H), 1718 (C=O), 1369, 1267, 1157 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 1.47 (18H, s, C(CH₃)₃), 2.14 (6H, s, CH₃), 3.17 (2H, s, CH₂), 5.00 (1H, br. s, NH); ¹³C NMR (151 MHz, CDCl₃) δ 19.4 (C(CH₃)₃), 25.5 (C(H₂)), 28.5 (C(CH₃)₃), 79.5 (CMe₃), 101.0 (CMe), 143.8 (CCO), 167.7 (C=O); m/z (CI) 309 (20, M), 308 (100, M-H); HRMS C₁₇H₂₇NO₄ calcd. 309.1940, found 309.1927.

Di-tert-butyl 2,6-dimethylpyridine-3,5-dicarboxylate 260

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{N} & \quad \text{N}
\end{align*}
\]

Formed as a by-product from general procedures N and O as a yellow solid; mp 88-90 °C (Lit. 179 108-110 °C) ¹H NMR (600 MHz, CDCl₃) δ 1.60 (18H, s, C(CH₃)₃), 2.80 (6H, s, CH₃), 8.52 (1H, s, ArH); ¹H NMR data are consistent with literature data. ¹H NMR data are consistent with literature data.

N-Benzyl-4-methoxyaniline 264

\[
\begin{align*}
\text{O} \\
\text{N} & \quad \text{Ar}
\end{align*}
\]

Formed as a by-product from general procedures N and O as a brown solid; mp 49-51 °C (Lit. 180 50 °C); ¹H NMR (600 MHz, CDCl₃) δ 3.72 (3H, s, OC₃H₃), 4.24 (2H, s, PhCH₂N), 6.52-6.60 (2H, m, ArH), 6.77-6.75 (2H, m, ArH), 7.22-7.35 (5H, m, ArH). ¹H NMR data are consistent with literature data.

N-((1R,2S)-3-(2-Bromophenyl)-1-((4-methoxyphenyl)amino)-1-phenylpropan-2-yl)-2,2,2-trifluoroacetamide 276oa

\[
\begin{align*}
\text{Br} & \quad \text{O} \\
\text{F₃C} & \quad \text{HN} \quad \text{Ar} \\
\text{O} & \quad \text{NH} \quad \text{Ar}
\end{align*}
\]

Prepared using a modified literature procedure. To a solution of β-nitrotrifluoroacetamide 239oa (0.80 g, 1.5 mmol) in EtOH (60 mL) and EtOAc (45
mL) pre-cooled to 0 °C was added 6.0 M HCl (62.5 mL, 375.0 mmol). To this white suspension was added portionwise Zn dust (7.35 g, 112.5 mmol) [CAUTION – gas evolution] over 30 min. The reaction was then allowed to warm to rt and stirred for 2 h 30, after which time water (120 mL) was added. The organics were then removed in vacuo and the resultant aqueous mixture was extracted with EtOAc (250 mL, then 50 mL). The combined organics were then washed with sat. aq. NaHCO₃ (2 x 100 mL) and with sat. brine (25 mL). The resultant organic phase was then dried (Na₂SO₄) and the excess solvent removed to give a pink oil. This residue was redissolved in EtOH (60 mL) and EtOAc (40 mL) and 6.0 M HCl (5 mL, 30.0 mmol) was added and the mixture was stirred at rt for 1 h. The organics were then removed in vacuo and the resultant residue was diluted with EtOAc (100 mL) and water (50 mL). The bi-phasic mixture was separated and the organic phase was washed with aqueous sat. aq. NaHCO₃ (100 mL), dried (Na₂SO₄) and the excess solvent was removed in vacuo to afford 1,2-diamine 276oa (0.73 g, 1.4 mmol, 96% yield) as a pink solid; mp 112-113 °C; [α]D²⁵ = -34.7 ° (c = 0.945, CHCl₃); ¹H NMR (600 MHz, CDCl₃) δ 2.82 (1H, dd, J = 13.9, 11.1, ArC₂H₂), 3.14 (1H, dd, J = 14.0, 3.7, ArC₂H₂), 3.69 (3H, s, OC₃H₃), 4.32 (1H, br. s, NH₂PMP), 4.69 (1H, d, J = 3.6, PhCHN), 4.74 (1H, m, CH₂CHN), 6.35 (1H, d, J = 8.8, NHCO), 6.54 (2H, d, J = 9.0, ArH), 6.70 (2H, d, J = 8.8, ArH), 7.07-7.12 (2H, m, ArH), 7.19-7.23 (1H, m, ArH), 7.31-7.35 (1H, m, ArH), 7.38-7.42 (4H, m, ArH), 7.49-7.53 (1H, m, ArH). ¹H NMR data are consistent with literature data.¹²⁷

(S)-(1-Nitropropan-2-yl)benzene 288

To a solution of β-nitro-α-methylstyrene 286 (0.200 mmol) in toluene (0.5 mL) at rt was added Hantzsch ester 254 (62 mg, 0.200 mmol) and the reaction was stirred at rt for 5min after which a solution of thiourea 272 (0.2 M in toluene, 100 μL, 0.020 mmol) was added and the reaction was stirred at rt until complete as judged from ¹H NMR data (ca. 72 h). The excess solvent was then removed in vacuo to give the crude product which was purified by column chromatography (1-2% Et₂O/pet. ether) to give 288 (26 mg, 0.157 mmol, 79% yield) as a colourless oil; [α]D²⁵ = -48.7 ° (c = 0.855, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 1.41 (3H, d, J = 7.0, CH₃), 3.61-3.71
(1H, m, PhCH), 4.51 (1H, dd, J = 11.8, 8.2, CH2NO2), 4.58 (1H, dd, J = 12.0, 7.0, CH2NO2), 7.23-7.33 (3H, m, ArH), 7.34-7.40 (2H, m, ArH). 1H NMR data are consistent with literature data.119

N-(2-(5-Bromo-1H-indol-3-yl)ethyl)formamide 305

![Chemical structure of N-(2-(5-Bromo-1H-indol-3-yl)ethyl)formamide 305]

Prepared using a modified literature procedure.182 A mixture of 5-Bromotryptamine (570 mg, 2.39 mmol) in ethylformate (20 mL) was heated at reflux (56 °C) for 16 h and then cooled to rt. The excess solvent was then removed in vacuo to give crude 305 (645 mg, quantitative yield) as an off-white solid; mp 128-131 °C; 1H NMR (600 MHz, DMSO-d6) δ 2.81 (2H, t, J = 7.2, ArCH2), 3.35 (2H, apt. q, J = 6.6, CH2NH), 7.17 (1H, dd, J = 8.6, 1.8, ArH), 7.23 (1H, d, J = 1.9, ArH), 7.31 (1H, d, J = 8.7, ArH), 7.71 (1H, d, J = 1.7, ArH), 8.02 (1H, s ArH), 8.08 (1H, br. s, NH), 11.07 (1H, s, HCO); 1H NMRROTAMER δ 7.22 (1H, d, J = 2.1), 7.74 (1H, d, J = 1.5), 7.80 (1H, d, J = 11.9) other peaks not visible; 13C NMR (151 MHz, DMSO-d6) δ 24.9 (CH2), 38.0 (CH2), 111.0 (Ar), 111.6 (Ar), 113.4 (ArH), 120.6 (ArH), 123.4 (ArH), 124.6 (ArH), 129.1 (Ar), 134.9 (Ar), 161.1 (O=CH); 13C NMRROTAMER (151 MHz, DMSO-d6) δ 26.9 (CH2), 41.8 (CH2), 111.1 (Ar), 111.2 (Ar), 113.4 (ArH), 120.7 (ArH), 123.4 (ArH), 124.9 (ArH), 129.1 (Ar), 134.9 (Ar), 164.5 (O=CH); m/z (EI) 268 (14, 81M), 266 (14, 79M), 223 (86, 88M-NCOH), 221 (87, 79M-NCOH), 210 (96, 81M-NC2OH4), 208 (100, 79M-NC2OH4); HRMS C11H11BrN2O calcd. 266.0055, found 266.0050.

6-Bromo-4,9-dihydro-3H-pyrido[3,4-b]indol-2-ium chloride 304

![Chemical structure of 6-Bromo-4,9-dihydro-3H-pyrido[3,4-b]indol-2-ium chloride 304]

Prepared using a modified literature procedure.146 To a pre-cooled solution of POCl3 (700 μL, 7.50 mmol) at 3 °C (ice-bath) was added portionwise over 30 min formamide 305 (200 mg, 0.75 mmol). After approximately 30 min at this temperature a thick yellow suspension formed which would no longer stir. To this mixture was added Et2O (2 mL) and the reaction was left to warm to rt and stirred for 2 h or until reaction complete as judged by tlc analysis. The yellow suspension was then filtered and washed with more Et2O to give acid salt of 304 (182 mg, 0.64
mmol, 85% yield) as a yellow HCl salt; \(^1\)H NMR (600 MHz, DMSO-\(d_6\)) \(\delta 3.25\) (2H, t, \(J = 9.1\), ArCH\(_2\)), \(3.98\) (2H, q, \(J = 9.0\), CH\(_2\)N), \(7.54\) (1H, dd, \(J = 8.8\), 1.7, ArH), \(7.57\) (1H, dd, \(J = 8.8\), 0.6, ArH), \(7.98\)–\(8.18\) (1H, m, ArH), \(9.08\) (1H, s, N=CH), \(12.48\) (1H, s, NH), \(12.75\) (1H, br. s, NH); \(^1\)H NMR (151 MHz, DMSO-\(d_6\)) \(\delta 18.4\) (CH\(_2\)), \(41.7\) (CH\(_2\)), \(113.8\) (Ar), \(115.7\) (ArH), \(122.8\) (Ar), \(124.2\) (ArH), \(125.3\) (Ar), \(126.1\) (Ar), \(130.9\) (ArH), \(139.4\) (Ar), \(155.9\) (HC=N).

6-Bromo-4,9-dihydro-3H-pyrido[3,4-b]indole 304

Prepared using a modified literature procedure.\(^{146}\) The acid salt of 304 (182 mg, 0.64 mmol) was stirred vigorously in water (10 mL) until dissolved. The aqueous solution was then washed with Et\(_2\)O (10 mL) and basified with aqueous ammonia (30 wt%) to pH 10, giving a cloudy white mixture. This was then extracted with more Et\(_2\)O (3 x 10 mL), dried (Na\(_2\)SO\(_4\)) and filtered to give desired product 304 (149 mg, 0.60 mmol, 80% yield) as a yellow foam; IR \(\nu_{\text{max}}\) 2924 (C-H), 1726 (C=N), 1596, 1549, 1438, 1380, 1358, 1172 cm\(^{-1}\); \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta 2.86\) (2H, t, \(J = 8.7\), ArCH\(_2\)), \(3.94\) (2H, t, \(J = 7.9\), CH\(_2\)N), \(7.24\) (1H, d, \(J = 8.8\), ArH), \(7.35\) (1H, dd, \(J = 8.7\), 1.3, ArH), \(7.72\) (1H, s, ArH), \(8.37\) (1H, br. s, N=CH), \(8.51\) (1H, br. s, NH); too unstable to get clean carbon; \(m/z\) (El) 250 (65, \(^{81}\)M), 249 (100, \(^{81}\)M-H), 248 (88, \(^{79}\)M), 247 (94, \(^{79}\)M-H); HRMS C\(_{11}\)H\(_9\)BrN\(_2\) calcd. 247.9950, found 247.9938.

6-Bromo-1-(1-nitro-2-phenylethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole 303

To a solution of \(\beta\)-nitrostyrene 84a (30 mg, 0.20 mmol) in CH\(_2\)Cl\(_2\) (1.5 mL) was added Superhydride\(^{\text{TM}}\) (220 \(\mu\)L, 0.22 mmol, 1.0 M in THF). The suspension was then stirred for 30 min at rt before cooling to -78 °C over 30 min. A solution of imine 304 (44 mg, 0.18 mmol) in CH\(_2\)Cl\(_2\) (3 mL) was added via cannula and the mixture stirred at -78 °C for 10 min. A solution of TFA (20 \(\mu\)L, 0.24 mmol) was added and the reaction was stirred for 1 h at -78 °C. The reaction was then quenched with sat. aq. NH\(_4\)Cl 10 mL) and diluted with Et\(_2\)O (20 mL). The organic phase was washed with
sat. brine (10 mL) and dried (MgSO₄). Solvents were removed in vacuo to afford crude β-nitroamine 303 as a yellow oil; ¹H NMR_{MAJOR(SYN)} (600 MHz, CDCl₃) δ 2.68-2.78 (2H, m, CH₂), 3.07-3.14 (1H, m, CH₂), 3.24-3.30 (1H, m, CH₂), 3.41 (1H, dd, J = 14.8, 10.1, PhCH₂), 3.57 (1H, dd, J = 14.6, 3.3, PhCH₂), 4.55 (1H, d, J = 8.3, CHN), 4.89-4.94 (1H, ddd, J = 10.2, 8.4, 3.0, CHNO₂), 7.16 (2H, d, J = 8.5, ArH), 7.23-7.25 (2H, m, ArH), 7.27-7.35 (3H, m, ArH), 7.62 (1H, s, ArH), 7.75 (1H, br. s, NH); ¹H NMR_{MINOR(ANTI)} (600 MHz, CDCl₃) δ 2.89-2.95 (1H, m, CH₂), 3.90 - 3.99 (1H, m, CH₂), 4.64 (1H, d, J = 4.9, CHN), 4.98-5.03 (1H, m, CHNO₂) other signals could not be determined.

1-(6-Bromo-1-(1-nitro-2-phenylethyl)-3,4-dihydro-1H-pyrido[3,4-b]indol-2(9H)-yl)-2,2,2-trifluoroethanone 309

Crude β-nitroamine 303 was re-dissolved in CH₂Cl₂ (5 mL), cooled to 0 °C and then trifluoroacetic anhydride (140 µL, 1.00 mmol) followed by pyridine (80 µL, 1.00 mmol) were added at rt and the solution was stirred at rt for 2 h. After this time, 2.0 M HCl (10 mL) was added and the aqueous phase was extracted with CH₂Cl₂ (2 x 5 mL). The combined organic phases were washed with sat. aq. NaHCO₃ 10 mL) and sat. brine (10 mL). The organic phase was then dried (MgSO₄) and the solvents were removed in vacuo to afford crude β-nitrotrifluoroacetamide which was purified by column chromatography (10-40% EtOAc/pet. ether) to give major diastereomer 309 (23 mg, 0.05 mmol, 23% yield) as a colourless oil which degraded at room temperature before full data could be obtained. ¹H NMR_{MAJOR(SYN)} (600 MHz, CDCl₃) δ 2.88 (1H, dd, J = 15.8, 4.0, CH₂), 2.97 (1H, ddd, J = 16.8, 12.2, 5.9, CH₂), 3.23 (1H, dd, J = 14.7, 4.3, CH₂), 3.47 (1H, dd, J = 14.7, 10.2, CH₂), 3.52 (1H, ddd, J = 15.1, 11.9, 4.3, CH₂), 4.30 (1H, dd, J = 15.0, 5.4, CH₂), 5.08 (1H, apt. td, J = 9.7, 4.4, CHNO₂), 6.35 (1H, d, J = 9.6, CHN), 7.15 (2H, d, J = 7.2, ArH), 7.20 (1H, d, J = 9.2, ArH), 7.28-7.37 (4H, m, ArH), 7.60 (1H, d, J = 1.5, ArH), 7.86 (1H, br. s, NH); ¹H NMR_{MINOR(ANTI)} (600 MHz, CDCl₃) δ 5.21 (1H, ddd, J = 10.7, 6.2, 4.1, CHNO₂), 6.28 (1H, d, J = 6.4, CHN) other signals could not be determined.
To a mixture of imine 304 (25 mg, 0.100 mmol) in CH₂Cl₂ (1 mL) was added β-nitrostyrene 84a (15 mg, 0.100 mmol) to give a yellow solution. The reaction was stirred at rt for 4 h until precipitation occurred. The reaction mixture was then filtered to give 310 (22 mg, 0.034 mmol, 68% yield) as a yellow solid; mp 192-194 °C; IR νmax 3379 (N-H), 1547 (N-O), 1445, 1374, 1312, 1225, 1112 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 2.37 (1H, td, J = 11.4, 3.4, CH₂), 2.55 (1H, br. d, J = 15.1, CH₂), 2.69-2.81 (2H, m, CH₂), 2.81-2.90 (1H, m, CH₂), 2.91-3.01 (2H, m, CH₂), 3.19 (1H, td, J = 12.2, 4.0, CH₂), 4.01 (1H, d, J = 10.0, CHN), 4.91 (1H, d, J = 10.4, CHN), 5.08 (1H, s, NCHN), 5.16 (1H, apt. t, J = 10.1, CHNO₂), 7.15 (1H, d, J = 8.5, ArH), 7.24-7.27 (4H, m, ArH), 7.28-7.32 (1H, m, ArH), 7.34-7.44 (3H, m, ArH), 7.62 (2H, dd, J = 6.6, 1.3, ArH), 7.64 (1H, s, NH), 8.18 (1H, s, NH); ¹³C NMR (151 MHz, CDCl₃) δ 21.4 (CH₂), 21.8 (CH₂), 40.4 (CH₂), 47.9 (CH₂), 58.4 (CHN), 71.9 (CHN), 79.0 (NCHN), 90.2 (CHNO₂), 110.1 (Ar), 112.3 (Ar), 112.8 (ArH), 112.9 (ArH), 113.1 (Ar), 113.2 (Ar), 121.4 (ArH), 121.4 (ArH), 125.3 (ArH), 125.6 (ArH), 128.3 (Ar), 128.7 (Ar), 129.4 (ArH), 131.3 (Ar), 131.4 (Ar), 135.0 (Ar), 135.1 (Ar), 136.7 (Ar); m/z (ESI) 648 (26, ⁸¹M-H), 646 (45, ⁷⁹M-H), 644 (27, ⁷⁹M-H); HRMS C₃₀H₂₄Br₂N₂O₂ calcd. 644.0297, found 644.0315.

**tert-Butyl 5-bromo-3-(2-formamidoethyl)-1H-indole-1-carboxylate 313**

Prepared using a modified literature procedure.¹⁸³ To a solution of formamide 305 (500 mg, 1.87 mmol) in THF (10 mL) was added 4-dimethylpyridine (23 mg, 0.19 mmol) and di-tert-butyl dicarbonate (490 mg, 2.25 mmol). The solution was heated
to 40 °C and stirred for 16 h. The excess solvent was then removed in vacuo to give crude 313 which was purified by column chromatography (2.5% MeOH/CH$_2$Cl$_2$) to give 313 (561 mg, 1.53 mmol, 82% yield) as a white solid; mp 130-133 °C; IR $\nu_{\text{max}}$ 3322 (C-H), 2980 (C-H), 1665, 1451, 1379, 1257, 1157 cm$^{-1}$; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 1.66 (9H, s, C(CH$_3$)$_3$), 2.91 (2H, t, $J = 6.9$, ArCH$_2$), 3.63 (2H, apt. q, $J = 6.7$, CH$_2$NH), 5.59 (1H, br. s, NH), 7.42 (2H, dd, $J = 8.8$, 1.9, ArH), 7.65 (1H, d, $J = 1.7$, ArH), 8.02 (1H, br, ArH), 8.18 (1H, s, H C=O); $^1$H NMR$_{\text{ROTAMER}}$ 2.88 (2H, t, $J = 7.0$, ArCH$_2$), 3.56 (2H, apt. q, $J = 6.6$, CH$_2$NH), 7.60 (1H, d, $J = 1.9$, ArH), 7.97 (1H, d, $J = 11.9$, H C=O); $^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 25.1 (Ar C H$_2$), 28.3 (C(CH$_3$)$_3$), 37.7 (CH$_2$), 84.3 (CMe$_3$), 116.1 (Ar), 116.7 (Ar), 117.0 (ArH), 121.7 (ArH), 124.6 (ArH), 127.6 (ArH), 132.0 (Ar), 134.4 (1C, br, Ar), 149.4 (C=O), 161.3 (HC=O); $^{13}$C NMR$_{\text{ROTAMER}}$ (151 MHz, CDCl$_3$) $\delta$ 27.3 (Ar C H$_2$), 28.3 (C(CH$_3$)$_3$), 41.2 (CH$_2$), 84.5 (CMe$_3$), 115.6 (Ar), 116.2 (Ar), 117.1 (ArH), 121.4 (ArH), 125.0 (ArH), 127.7 (ArH), 131.6 (Ar), 149.3 (C=O), 164.5 (HC=O); $m/z$ (EI) 368 (5, 81M), 366 (5, 79M), 267 (16, 81M-Boc), 265 (17, 79M–Boc); HRMS C$_{16}$H$_{19}$BrN$_2$O$_3$ calcd. 366.0579, found 366.0570.

**tert-Butyl (2-(5-bromo-1H-indol-3-yl)ethyl)carbamate 316**

To a solution of 5-bromotryptamine (430 mg, 1.80 mmol) in Me$_2$CO/water (1:1, 30 mL) was added K$_2$CO$_3$ (500 mg, 3.60 mmol) and di-tert-butyl dicarbonate (420 mg, 1.93 mmol) and the mixture was stirred for 16 h at rt. The excess solvent was removed in vacuo and the resultant residue was extracted with EtOAc (40 mL), dried (MgSO$_4$) and the excess organics were removed in vacuo to give crude 316 (632 mg, quantitative yield) as a colourless oil which was used without further purification; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 1.46 (9H, s, C(CH$_3$)$_3$), 2.87 (2H, t, $J = 6.8$, ArCH$_2$), 3.41 (2H, br. q, $J = 6.2$, CH$_2$NH), 4.76 (1H, br. s, NHCO), 6.95 (1H, s, ArH), 7.20 (1H, d, $J = 8.1$, ArH), 7.24 (1H, dd, $J = 8.3$, 1.9, ArH), 7.70 (1H, s, ArH), 8.78 (1H, br. s, NH); $^1$H NMR data are consistent with literature data.$^{184}$
tert-Butyl (2-(5-bromo-1-tosyl-1H-indol-3-yl)ethyl)carbamate 317

Prepared using a modified literature procedure.\textsuperscript{185} To a solution of 316 (150 mg, 0.44 mmol) in THF (5 mL) was added \textit{para}-toluenesulfonyl chloride (95 mg, 0.50 mmol) and potassium tert-butoxide (100 mg, 0.88 mmol) and the suspension was stirred for 16 h at rt. Water (5 mL) was then added and the excess organics were removed \textit{in vacuo}. Sat. aq. NaHCO\textsubscript{3} 5 mL was added and the reaction was extracted with EtOAc (2 x 10 mL), dried (MgSO\textsubscript{4}) and the excess solvent removed to give 317 (223 mg, 0.45 mmol, quantitative yield) as a yellow oil; IR $\upsilon_{\text{max}}$ 3354 (N-H), 2977 (C-H), 2930 (C-H), 1702, 1512, 1442, 1366, 1169 cm\textsuperscript{-1}; $^1$H NMR (600 MHz, CDCl\textsubscript{3}) $\delta$ 1.45 (9H, s, C(CH\textsubscript{3})\textsubscript{3}), 2.34 (3H, s, ArCH\textsubscript{3}), 2.81 (2H, t, $J$ = 6.6, ArCH\textsubscript{2}), 3.38 (2H, apt. q, $J$ = 6.1, CH\textsubscript{2}NH), 4.58 (1H, br. s, N\textsubscript{H}), 7.19-7.24 (2H, m, ArH), 7.37 (1H, s, ArH), 7.40 (1H, dd, $J$ = 8.8, 1.8, ArH), 7.60 (1H, d, $J$ = 1.7, ArH), 7.71 (2H, d, $J$ = 8.5, ArH), 7.84 (1H, d, $J$ = 8.8, ArH); $^{13}$C NMR (151 MHz, CDCl\textsubscript{3}) $\delta$ 21.7 (ArCH\textsubscript{3}), 25.6 (CH\textsubscript{2}), 28.5 (C(CH\textsubscript{3}))\textsubscript{3}, 40.2 (CH\textsubscript{2}), 79.7 (CMe\textsubscript{3}), 115.3 (ArH), 116.9 (Ar), 119.6 (Ar), 122.4 (ArH), 124.8 (ArH), 126.9 (ArH), 127.8 (ArH), 130.1 (ArH), 132.7 (Ar), 134.1 (Ar), 134.9 (Ar), 145.3 (Ar), 155.9 (C=O); m/z (EI) 494 (3, $^{81}$M), 492 (3, $^{79}$M), 377 (13, $^{81}$M–NH\textsubscript{2}Boc), 375 (13, $^{79}$M–NH\textsubscript{2}Boc); HRMS C\textsubscript{22}H\textsubscript{25}BrN\textsubscript{2}O\textsubscript{4}S calcd. 492.0718, found 492.0727.

2-(5-Bromo-1-tosyl-1H-indol-3-yl)ethanamine 318

Pre-cooled (ice bath, 0 °C) TFA (10 mL) was added to a cooled flask (ice bath, 0 °C) containing 317 (195 mg, 0.365 mmol). The resultant yellow solution which was stirred at 0 °C for 2 h to give a red solution. The excess solvent was then removed \textit{in vacuo} and the concentrated residue was cooled to 0 °C. To this was added 2.0 M
NaOH (20 mL) and 5% MeOH/CH₂Cl₂ (30 mL) and the mixture was stirred for 15 min. The biphasic mixture was then separated and the aqueous phase was re-extracted with more CH₂Cl₂ (2 x 10 mL). The combined organics were dried (Na₂SO₄) and excess solvent removed to give 318 (146 mg, 0.372 mmol, 94% yield) as a yellow oil; IR ʋₘₐₓ 2924 (C-H), 1711, 1442, 1370, 1171 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 2.35 (3H, s, CH₃), 2.76 (2H, t, J = 6.6, ArCH₂), 2.99 (2H, t, J = 6.8, CH₂), 7.22 (2H, d, J = 7.9, ArH), 7.38 (1H, s, ArH), 7.41 (1H, dd, J = 8.7, 1.9, ArH), 7.62 (1H, d, J = 1.7, ArH), 7.73 (2H, d, J = 8.5, ArH), 7.86 (1H, d, J = 8.8, ArH); ¹³C NMR (151 MHz, CDCl₃) δ 21.7 (CH₃), 29.2 (CH₂), 41.5 (CH₂), 115.4 (ArH), 116.8 (Ar), 120.1 (Ar), 122.4 (ArH), 124.7 (ArH), 126.8 (ArH), 127.7 (ArH), 130.1 (ArH), 132.8 (Ar), 134.2 (Ar), 135.0 (Ar), 145.3 (Ar); m/z (EI) 394 (14, ¹⁸¹M), 392 (14, ⁷⁹M), 365 (34, ¹⁸¹M−NH₂CH₂), 363 (32, ⁷⁹M−NH₂CH₂); HRMS C₁₇H₁₇BrN₂O₂S calcd. 392.0194, found 392.0182.

**N-(2-(5-Bromo-1-tosyl-1H-indol-3-yl)ethyl)formamide 319**

![Chemical structure of 319](image)

A mixture of tryptamine 318 (1.25 g, 3.18 mmol) in ethylformate (50 mL) was heated at reflux (56 °C) for 2 h, or until reaction complete as judged by tlc analysis, and then cooled to rt. The excess solvent was then removed in vacuo to give crude 319 (1.39 g, quantitative yield) as an off-white solid; mp 119–121 °C; IR ʋₘₐₓ 3256, 3044, 2871 (C-H), 1740, 1651 (C=O), 1442, 1372, 1293, 1164 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 2.35 (3H, s, CH₃), 2.87 (1H, t, J = 6.9, ArCH₂), 3.59 (1H, apt. q, J = 6.7, CH₂NH), 5.57 (1H, br. s, NH), 7.24 (2H, d, J = 7.9, ArH), 7.39-7.44 (2H, m, ArH), 7.62 (1H, d, J = 1.9, ArH), 7.71-7.74 (2H, m, ArH), 7.86 (1H, d, J = 8.7, ArH), 8.17 (1H, s, HC=O); ¹H NMR_/ROTAMER_ (600 MHz, CDCl₃) δ 2.85 (2H, t, J = 6.6, ArCH₂), 3.50 (2H, apt. q, J = 6.7, CH₂NH), 7.57 (1H, d, J = 1.7, ArH), 7.88-7.92 (1H, m, ArH) remaining signals could not be determined; ¹³C NMR (151 MHz, CDCl₃) δ 21.7 (CH₃), 25.1 (CH₂), 37.6 (CH₂), 115.4 (ArH), 117.0 (Ar), 118.9 (Ar), 122.3 (ArH), 124.8 (ArH), 126.9 (ArH), 128.0 (ArH), 130.1 (ArH), 132.4 (Ar), 134.1 (Ar), 134.9 (Ar), 145.5 (Ar), 161.3 (O=CH); ¹³C NMR_/ROTAMER_ (151 MHz, CDCl₃) δ 27.3 (CH₂).
To a flame-dried schlenk flask was added formamide 319 (40 mg, 0.095 mmol) and the flask was placed under vacuum and evacuated/backfilled with nitrogen three times. To this was then added acetonitrile (degassed freeze/pump/thaw three times, 2 mL). To this solution POCl₃ (90 μL, 0.950 mmol) was added dropwise over 5 min. After complete addition the reaction was submerged in an oil bath pre-heated to 85 °C. The reaction was stirred for 16 h at reflux and then allowed to cool to rt. The excess solvent was removed and the residue was partitioned in EtOAc (20 mL) and 2 M NaOH (10 mL). The bi-phasic mixture was separated and the organic was dried (Na₂SO₄) and the excess solvent removed to give crude 315 which was purified by column chromatography (80% EtOAc/pet. ether) to give 315 (17 mg, 0.042 mmol, 44% yield) as a yellow oil; IR νₓ (C-H), 1726, 1596, 1549, 1438, 1380, 1358, 1172 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 2.35 (3H, s, CH₃), 2.73 (2H, apt. t, J = 8.8, ArCH₂), 3.86 (2H, apt. td, J = 8.8, 2.1, CH₂N), 7.21 (2H, d, J = 8.3, ArH), 7.53 (1H, dd, J = 8.9, 1.8, ArH), 7.61 (1H, d, J = 1.7, ArH), 7.65 (2H, d, J = 8.5, ArH), 8.07 (1H, d, J = 8.8, ArH), 8.99 (1H, s, N=CH); ¹³C NMR (151 MHz, CDCl₃) δ 18.7 (CH₂), 21.7 (CH₃), 47.3 (CH₂), 116.7 (ArH), 117.8 (Ar), 123.1 (ArH), 124.6 (Ar), 126.7 (ArH), 129.6 (Ar), 129.7 (Ar), 130.1 (ArH), 130.3 (ArH), 134.6 (Ar), 135.6 (Ar), 145.6 (Ar), 150.9 (N=CH); m/z (ESI⁺) 405 (98, ⁸¹M+H), 403 (100, ⁷⁹M+H), 250 (38, ⁸¹M+H-Ts), 248 (40, ⁷⁹M+H-Ts); HRMS C₁₈H₁₅BrN₂O₂SH⁺ calcd. 403.0116, found 403.0110.
To a flask containing imine 315 (17 mg, 0.042 mmol) in toluene (0.5 mL) was added β-nitrostyrene 84a (12 mg, 0.080 mmol) and Hantzsch ester 254 (25 mg, 0.080 mmol) and the mixture was cooled to -20 °C. A solution of catalyst 272 (45 μL, 0.008 mmol, 0.184 M in toluene) was then added and the reaction was stirred at room temperature for 24 h. After this time, a small aliquot (10 μL) was removed and analysed by $^1$H NMR to measure reaction progress; $^1$H NMRMAJOR (400 MHz, CDCl$_3$) δ 2.34 (3H, s, ArC$_H$$_3$), 3.47 (1H, dd, $J$ = 14.6, 9.5, PhC$_H$$_2$), 5.31-5.37 (1H, m, CHN), 5.92 (1H, ddd, $J$ = 9.5, 4.0, 3.0, CHNO$_2$) remaining signals could not be determined; $^1$H NMRMINOR (400 MHz, CDCl$_3$) δ 3.75 (1H, dd, $J$ = 14.3, 10.5, PhC$_H$$_2$), 5.60 (1H, apt. dt, $J$ = 10.5, 4.8, CHNO$_2$) remaining signals could not be determined.

1-(6-Bromo-1-((S)-1-nitro-2-phenylethyl)-9-tosyl-2,3,4-dihydro-1H-pyrido[3,4-b]indol-2(9H)-yl)-2,2,2-trifluoroethanone 321

To the reaction flask containing crude 320 was added trifluoroacetic anhydride (28 μL, 0.200 mmol), followed by Pr$_2$NEt (33 μL, 0.200 mmol) were added and the solution was stirred at rt for 1 h. After this time, 2.0 M HCl (2 mL) was added and the aqueous phase was extracted with Et$_2$O (2 x 5 mL) and the combined organic phases were washed with sat. aq. NaHCO$_3$ (5 mL) and sat. brine (5 mL). The organic phase was then dried (MgSO$_4$) and the solvents were removed in vacuo to afford crude β-nitrotrifluoroacetamide 321 which was purified by chromatography (20% Me$_2$CO/pet. ether then 20% EtOAc/pet. ether) to give major diastereomer 321 (9 mg,
0.014 mmol, 33% yield) as a colourless oil; HPLC analysis (Chiralcel AD, hexane/iso-propanol 90:10, flow rate = 1 mL/min, λ = 254 nm): retention time \( t_r \) (major) = 18.7 min, \( t_r \) (minor) = 32.5 min, shows 48% ee; IR \( \nu \) max 2924 (C-H), 1697 (C=O), 1557 (N-O), 1441, 1368 (N-O), 1207, 1170 cm\(^{-1}\); \( ^1\)H NMR MAJOR (600 MHz, CDCl\(_3\)) \( \delta \) 2.32 (3H, s, ArC\(_\text{H}_3\)), 2.77-2.89 (2H, m, CH\(_2\)), 2.91 (1H, dd, \( J = 14.7, 2.4\), PhCH\(_2\)), 3.55 (1H, dd, \( J = 14.5, 11.9\), PhCH\(_2\)), 3.88 (1H, ddd, \( J = 15.6, 11.3, 4.9\), CH\(_2\)N), 4.31 (1H, apt. dd, \( J = 14.8, 6.1\), CH\(_2\)N), 5.86 (1H, ddd, \( J = 11.9, 5.3, 2.6\), C\(_\text{H}_2\)N), 7.07 (1H, d, \( J = 5.3\), CHN), 7.12 (2H, d, \( J = 7.2\), ArH), 7.18-2.28 (4H, m, ArH), 7.49 (1H, d, \( J = 1.9\), ArH), 7.51-7.55 (2H, m, ArH), 7.61-7.65 (2H, m, ArH), 8.13 (1H, d, \( J = 8.8\), ArH); \( ^{13}\)C NMR (151 MHz, CDCl\(_3\)) \( \delta \) 21.5 (CH\(_2\)), 21.8 (ArCH\(_3\)), 35.9 (PhCH\(_2\)), 40.5 (CH\(_2\)N), 52.0 (CHN), 90.7 (CH\(_\text{NO}_2\)), 116.3 (1C, q, \( J = 287.8\), CF\(_3\)), 117.7 (ArH), 118.6 (Ar), 120.7 (Ar), 122.0 (ArH), 127.0 (ArH), 127.6 (ArH), 128.8 (ArH), 129.1 (ArH), 129.4 (ArH), 129.5 (Ar), 130.3 (ArH), 131.0 (Ar), 133.1 (Ar), 135.5 (Ar), 136.2 (Ar), 146.2 (Ar), 157.5 (1C, q, \( J = 287.8\), C=O); m/z (EI) 651 (7, \( ^{81}\)M), 649 (7, \( ^{79}\)M), 605 (8, \( ^{81}\)M-NO\(_2\)), 603 (8, \( ^{79}\)M-NO\(_2\)), 501 (92, \( ^{81}\)M-NO\(_2\)CHCH\(_2\)Ph), 499 (88, \( ^{79}\)M-NO\(_2\)CHCH\(_2\)Ph); HRMS C\(_{28}\)H\(_{23}\)BrF\(_3\)N\(_3\)O\(_5\)S calcd. 649.0494, found 649.0519.
Chapter 5. Appendices
5.1 Abbreviations

δ  chemical shift
Å  Angstrom
Ac acetyl
AIBN azobisisobutyronitrile
anal. analysis
aq. aqueous
Ar aryl
atm atmosphere
BAM bisamidine
BINAP 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn benzyl
Boc tert-butyl carbonyl
BOX 3-[(E)-2-butenoyl]-1,3-oxazolidin-2-one
bp boiling point
Bt benzotriazyl
iBu iso-butyl
nBu n-butyl
tBu tert-butyl
C celcius
c.a. approximately
calcd. calculated
CAN ceric ammonium nitrate
Cat catalyst
Cbz carboxybenzyl
CDC cross-dehydrogenative coupling
CI chemical ionisation
conv. conversion
CPME cyclopentylmethyl ether
Cy  cyclohexyl

d  day

DBU  1,8-diazabicycloundec-7-ene

DCC  N,N’-dicyclohexylcarbodiimide

DCM  CH2Cl2

DDQ  2,3-dichloro-5,6-dicyanobenzoquinone

DIPEA  diisopropylethylamine

DMAP  N,N-4-dimethylanlimopyridine

DME  dimethoxyethane

DMF  dimethylformamide

DMSO  dimethylsulfoxide

\( dr \)  diastereomeric ratio

E+  electrophile

EDC  1-ethyl-3-(3-dimethylanlimopropyl)carbodiimide

ee  enantiomeric excess

EI  electron impact

ESI  electrospray ionisation

Et  ethyl

equiv.  equivalents of

FAB  fast atom bombardment

Fu  furyl

g  gram

h  hour

HBA  hydrogen bond acceptor

H-bond  hydrogen bond

HBTU  \( N,N,N',N'\)-tetramethyl-\( O-(1H\)-benzotriazol-1-yl)uronium

hexafluorophosphate

Hex  hexyl

HFIP  1,1,1,3,3,3-hexafluoro-2-propanol

HIV  human immunodeficiency virus

HOMO  highest occupied molecular orbital

HPLC  high performance liquid chromatography

HRMS  high resolution mass spectrometry
Hz  hertz
IR  infrared spectroscopy
J  coupling constant
J  joule
kcal  kilocalorie
LA  Lewis acid
Lit.  literature
LUMO  lowest unoccupied molecular orbital
m  meta
M  mole per litre
MBH  Morita-Bayliss-Hilman
mCPBA  meta-chloroperoxybenzoic acid
Me  methyl
mg  milligram
MHz  megahertz
min  minute
mL  millilitre
mmol  millimole
mol%  mole percentage
mp  melting point
MS  molecular sieves
Ms  mesyl chloride
Naph  naphthyl
NIS  N-iodosuccinimide
NME  (-)-N-methylephedrine
NMR  nuclear magnetic resonance
Nu  nucleophile
o  ortho
OMB  ortho-methoxybenzyl
p  para
pet.  petroleum
PG  protecting group
Ph  phenyl
PMB  *para*-methoxybenzyl
PMHS  polymethylhydrosiloxane
PMP  *para*-methoxyphenyl
\textsuperscript{a}Pn  \textit{n}-pentyl
ppm  parts per million
\textsuperscript{i}Pr  \textit{iso}-propyl
\textsuperscript{n}Pr  \textit{n}-propyl
\textit{p}-TSA  \textit{para}-toluenesulfonic acid monohydrate
Py  pyridyl
Pyr  pyrrole
Ra-Ni  Raney\textregistered  Nickel
Rf  retention factor
rt  room temperature
rxn.  reaction
sat.  saturated
Temp.  temperature
TBAF  tetra-\textit{n}-butylammonium fluoride
TBAT  tetra-\textit{n}-butylammonium triphenylsilyl difluorosilicate
TBDMS  tert-butyldimethylsilyl
TBHP  tert-butylhydroperoxide
TBME  tert-butylmethyl ether
TEA  triethylamine
TFA  trifluoroacetic acid
Tf  trifluoromethanesulfonyl
TfOH  trifluoromethanesulfonic acid
THF  tetrahydrofuran
tlc  thin layer chromatography
TMS  trimethylsilyl
Tol  \textit{para}-tolyl
TOF  time of flight
Ts  \textit{para}-toluenesulfonyl
TS  transition state
uv  ultraviolet
5.2 Table of coupling constants for $\beta$-nitroamines

As depicted in figure 34, it is thought that the $\beta$-nitroamines exist in a pseudo chair conformation allowing the assignment of the relative stereochemistry based on the coupling constant between the protons in the $\alpha$-position of the amino and nitro groups.

![Figure 34. Assignment of relative stereochemistry](image)

The following table lists the structure and the $^1$H NMR coupling constants of several $\beta$-nitroamines synthesised. The relative diastereochemistry was then assigned based on the $J_{a\gamma}$-value. Typically, the anti diastereomer had a coupling constant of approximately 5.5 Hz whereas the $J_{a\gamma}$-value for the syn diastereomer was greater than 7.0 Hz. Coupling constants were taken as an average of the two $J$-values except where only one was visible in the crude $^1$H NMR spectra. For some $\beta$-nitroamines the $J_{a\gamma}$-value could not be determined due to overlapping signals and hence these are not in the table. However these $\beta$-nitroamines have been tentatively assigned as anti diasteromers based on the results from other analogues.
Table 20. Coupling constants for β-nitroamines for assignment of relative stereochemistry

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<tr>
<th>Entry</th>
<th>β-Nitroamine</th>
<th>$J_a$</th>
<th>$J_b$</th>
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<tr>
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</table>
Paul J. Koovits

<table>
<thead>
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<th></th>
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<th>J-values</th>
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*J*-values are given as an average of two values unless only one could be determined.
5.3 References


Denmark, S. E.; Marcin, L. R. J. Org. Chem. 1993, 58, 3850.


Kotke, M.; Schreiner, P. R. Synthesis 2007, 779.


