Development of the conjugate addition/Nitro-Mannich reaction

A Thesis presented by
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Signed

Date
Abstract

This thesis describes the development of the conjugate addition/nitro-Mannich reaction and its use in the synthesis of useful molecules like pyrrolidin-2-ones and piperazin-2-ones. The introductory chapter of this thesis outlines the literature related to the nitro-Mannich reaction, describing the different existing methodologies for performing the reaction in diastereo- and enantioselective manner. The synthetic applications of the reaction are also described, especially its uses in the synthesis of biologically active natural products. Moreover, the syntheses and uses of two classes of compounds, pyrrolidin-2-ones and piperazin-2-ones are briefly discussed.

The results and discussion chapter starts by presenting the use of a one-pot conjugate addition/nitro-Mannich/lactamisation reaction in the synthesis of densely functionalised pyrrolidin-2-ones. The development of an asymmetric protocol, as well as some functionalisations of the pyrrolidinone core are also described. Our efforts to synthesise human neutrophil elastase inhibitor GW311616A using the developed methodology are then detailed.

The next part of the results and discussion chapter portrays the development of a conjugate addition/nitro-Mannich reaction of non-zinc nucleophiles to ethyl 3-nitroacrylate and β-nitrostyrene. The scope and limitations of the reaction were investigated using a variety of different nucleophiles including amines, thiols, phosphines, alcohols, enolates and nitriles.

Finally, our work towards synthesising the biologically active piperazin-2-one piperazirum, using the nitro-Mannich methodology is described. The diastereoselective synthesis and characterisation of a densely functionalised piperazin-2-one was accomplished.

A detailed description of the experimental details and analytical data for all novel compounds is described in the experimental section. Tables of coupling constants and X-ray crystallographic data are presented in the appendices section, followed by a list of literature references.
Acknowledgements

First of all I would like to thank my supervisor, Prof. Jim Anderson for giving me the opportunity to work in this very interesting subject and for his constant guidance and constructive criticism. I thank him for giving me valuable knowledge in chemistry during our weekly group meetings and our discussions.

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<td>Nu</td>
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<td>OMB</td>
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<td>Abbreviation</td>
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<td>OMP</td>
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1. Introduction

One of the ongoing and fundamental challenges in organic chemistry is the synthesis of complex molecules. The installation of useful functional groups in a short and concise fashion is important in accessing such molecules in an efficient manner. There is a constant need for reactions that install a lot of functionality, in short steps and with high selectivity. The work carried out in this thesis in developing such processes will be described in the next chapter, whereas this chapter will focus on describing the current literature in four areas related to our work. Those are the development of the nitro-Mannich reaction, the conjugate addition of nucleophiles to nitroalkenes, the synthetic applications of the nitro-Mannich reaction and the synthesis and applications of piperazinones and pyrrolidinones.

1.1 The nitro-Mannich reaction

1.1.1 Overview

The nitro-Mannich (or aza-Henry) reaction is a member of the family of synthetically useful carbon-carbon bond forming reactions, specifically the ones where an active C-H nucleophile is added to a C=X bond (Scheme 1). The other three members of this group are the aldol, the nitro-aldol and the Mannich reaction. The aldol reaction, the most thoroughly explored of the group, involves nucleophilic addition of an enolate to a carbonyl electrophile.\(^1\) Replacing the enolate nucleophile with a nitronate gives the nitro-Aldol (Henry) reaction,\(^2\) while replacing the carbonyl electrophile with an imine gives the Mannich reaction,\(^3\) both of which have been extensively researched. The last member of the family and the least explored one is the nitro-Mannich reaction, where a nitronate nucleophile adds to an imine electrophile. A brief review of the work in this field follows.
Louis Henry first reported the nitro-Mannich reaction in 1896 after first reporting the Henry reaction the previous year. Henry discovered that nitroalkanes could add to hemiaminals to form β-nitroamines (Scheme 2), however the exact conditions he used were not described. Presumably the hemiaminal loses a molecule of water to form an iminium ion, which is attacked by the nitronic acid tautomer of the nitroalkane. The process is repeated to give product 1.

\[
\begin{align*}
R^1\text{NO}_2 + R^1\text{N}\underbrace{\text{OH}}_{\text{Unknown conditions}} & \rightarrow R^2\text{N}^\text{NR}_2^R_1^2 \text{NO}_2 \\
\end{align*}
\]

Scheme 2. First reported nitro-Mannich reaction

A very limited number of publications on the nitro-Mannich reaction appeared over the next hundred years, most of them in the 1950s and those were of little scope and not stereoselective. However, some development was made in the methodology of the reaction. For example, the imine was either added to the reaction mixture or formed in situ by having an aldehyde and an amine as the reagents (Scheme 3). Both of these methods are still used today. It is noteworthy that Smiley was the first to use the nitro-Mannich reaction to make vicinal diamines by reducing the product nitroamines. The main use of the nitro-Mannich reaction today is for the synthesis of vicinal diamines.
A few decades later (1976), Jain and co-workers reported the formation of piperidinones 3 by reaction of nitroester 4 with aromatic aldehydes 5 and ammonium acetate (Scheme 4). The reaction gave piperidinones 3 in variable yields, as the anti diastereoisomers, but was only efficient using ammonia and not for other amines.

Scheme 3. Early developments of the nitro-Mannich reaction

Scheme 4. Synthesis of piperidinones via nitro-Mannich reaction

1.1.3 Non-catalytic nitro-Mannich reactions

The first diastereoselective nitro-Mannich reaction was reported by the Anderson group in 1998 (Scheme 5). Anderson and co-workers reported the 1,4-addition of nitronate ions 6, produced in situ from treatment of nitroalkanes 7 with n-BuLi, on N-PMB protected imines in the presence of a Brønsted acid, to yield anti-rich β-nitroamines 8 in excellent yields and diastereoselectivity. The products 8 were also subsequently reduced with SmI₂ and the PMB group cleaved on treatment with CAN to give vicinal diamines 9 (Scheme 5).

Scheme 5. The first diastereoselective nitro-Mannich reaction
Seven years later, the Anderson group showed that a silyl protected nitronate could also be used to perform the reaction instead of the free anion. Lewis acids were used to promote the addition of trimethylsilyl nitropropanate 10 to imines 11 to give β-nitroamines 12 (Scheme 6). Several Lewis acids were investigated, such as $\text{BF}_3\text{Et}_2\text{O}$, $\text{TiCl}_2(\text{OiPr})_2$ and lanthanide triflates and the best results were obtained using $\text{Sc(OTf)}_3$. Interestingly it was found that use of OMB (ortho-methoxybenzyl) instead of PMP (para-methoxyphenyl) and PMB (para-methoxybenzyl) protected imines greatly improved the yields and anti selectivity of the reaction. The authors proved this to be both a steric and an electronic effect.

Scheme 6. Nitro-Mannich reactions of silyl-nitronate 10

1.1.4 Non-catalytic enantioselective nitro-Mannich reactions

Only a small number of publications have reported examples of non-catalytic enantioselective nitro-Mannich reactions. These reactions required the presence of a chiral auxiliary in the imine, either on the imine nitrogen or on the part derived from the aldehyde. Petrini and co-workers reported the nitro-Mannich reaction of nitromethane with a variety of non-racemic chiral imines (Scheme 7). The imines were generated in situ from amidosulfones 13 and gave medium-good yields of β-nitroamines 14a and 14b with good diastereoselectivity. Although limited to nitromethane, this investigation showed that a nitro-Mannich reaction could be rendered stereoselective in the presence of a proximal chiral centre.

Scheme 7. Nitro-Mannich reaction in the presence of a chiral centre
The $N$-sulfinyl group, was successfully used by Garcia and co-workers as a chiral auxiliary. The authors reported the diastereoselective reaction of $N$-sulfinimines 15 with nitromethane and NaOH to yield enantiomerically pure $\beta$-nitroamines 16. When TBAF was used as the base, the reaction was much faster and the diastereoselectivity inverted (Scheme 8). The high selectivity with NaOH was explained by a cyclic transition state involving coordination of the sodium cation.

![Scheme 8](image)

**Scheme 8.** A diastereoselective nitro-Mannich reaction with $N$-sulfinimines

Similarly, Li and co-workers described the asymmetric nitro-Mannich reaction with chiral $N$-phosphonoyl imines 18 (Scheme 9). Even though only one example was reported, a good yield and enantioselectivity of product 19 was observed, while the chiral auxiliary could be later removed and recycled.

![Scheme 9](image)

**Scheme 9.** Asymmetric nitro-Mannich reaction with chiral $N$-phosphonoyl imines

### 1.1.5 Metal-catalysed nitro-Mannich reactions

The first metal-catalysed enantioselective nitro-Mannich reaction was reported by Shibasaki and co-workers in 1999. A Yb (III) complex, previously used in catalytic asymmetric Aldol reactions, was used to catalyse the addition of nitromethane to $N$-phosphinoyl imines 20 to give products 21 which were isolated in good yields and enantioselectivities (Scheme 10). The reactive complex contained Yb(OiPr)$_3$, KOtBu and ($R$)-binaphthol in a 1:1:3 ratio that formed the reactive mixed Lewis acid and Brønsted base catalyst. The authors argued that the phosphinoyl group on the imine was essential due to coordination to the metal centre. The reaction gave medium to
good yields and enantioselectivities, however was limited to nitromethane and aromatic imines and required 60 mol% of \( R \)-BINOL.

\[
\text{Ar-N}^+\text{Ph} + \text{CH}_3\text{NO}_2 \xrightarrow{\text{Yb(Ott)\text{KoBu/R-BINOL}}} \text{Ar-N}^+\text{Ph} \quad \text{Catalyst:} \quad \begin{array}{c}
\text{H-} \\
\text{O-Yb-O} \\
\text{H-}
\end{array}
\]

20, 49-93% 69-91% ee

\text{Scheme 10. The first metal-catalysed enantioselective nitro-Mannich reaction}

A few years later, in 2001, the same authors reported an alternative procedure using an aluminium catalyst (Scheme 11). The new catalyst was effective for a range of nitroalkanes and the reaction proceeded more rapidly, however the enantioselectivities of the products 22 were slightly lower.

\[
\text{Ar-N}^+\text{Ph} + \text{RCH}_2\text{NO}_2 \xrightarrow{\text{DCM, -40 °C, 48 h}} \begin{array}{c}
\text{Ar-N}^+\text{Ph} \\
\text{R = Me, Et, (CH}_2\text{)OPh}
\end{array}
\]

\[22, 68-98% 75-25:95.5 \text{dr} 60-75\% ee \quad \text{Catalyst:} \quad \begin{array}{c}
\text{[O-Al-O]^{2-}} \\
\text{Li^+}
\end{array}
\]

\text{Scheme 11. A metal-catalysed enantioselective nitro-Mannich reaction}

In the same year, Jørgensen and co-workers reported the enantioselective addition of silylnitronates 23 to PMP imine 24, derived from ethyl glyoxylate, in the presence of a Cu(II)-BOX catalyst (Scheme 12). The product \( \beta \)-nitroamines 25 were isolated in good yields and selectivities. The authors also reported the reduction of the ethyl analogue and subsequent reaction with thiophosgene to thioimidazolidinone 26, which helped to deduce the absolute stereochemistry by X-ray crystallography.

\[
\text{R-N}^+\text{OTMS} + \text{EtO}^+\text{C}=\text{N}\text{PMP} \xrightarrow{\text{Catalyst (20 mol%), THF, -100 °C, 1 h}} \begin{array}{c}
\text{HN-PMP} \\
\text{EtO}_2\text{C} \quad \text{R = Me, Et, Bn, Penty}
\end{array}
\]

\[25, 87-94% 90:10 \text{dr} 83-97\% ee \quad \text{R = Me, Et, Bn, Penty}
\]

\text{Scheme 12. An enantioselective nitro-Mannich reaction with silylnitronates}

Shortly after this publication, the same group also reported the enantioselective addition of nitroalkanes 27 to the same imine 24 in the presence of a different Cu(II)-
BOX catalyst (Scheme 13). The product β-nitro-α-amino esters 28 were obtained in good yields and excellent *dr* and *ee*, while the reactions were compatible with the presence of moisture and did not require the use of an inert atmosphere. However, this protocol only worked with glyoxylate imines as the ester oxygen and imine nitrogen provided a two-point binding site to the copper, which was essential in the catalysis mechanism.

Scheme 13. An enantioselective nitro-Mannich reaction catalysed by Cu(II)-BOX

A few years later, in 2005, the Anderson group reported a diastereoselective nitro-Mannich reaction from OMB protected imines 11. The reaction of 11 with either lithium nitropropanoate and acetic acid or trimethylsilyl nitropropanoate in the presence of a Lewis acid gave *anti*-rich β-nitroamines 12 in excellent yields and good diastereoselectivities (Scheme 14). The authors argued that the OMB protecting group was better than other groups due to chelation with the Lewis acid.

Scheme 14. A Lewis and Brønsted acid catalysed nitro-Mannich reaction

The Anderson group also reported a metal-catalysed enantioselective reaction as a continuation of the work reported before with trimethylsilyl nitropropanate 10. This reaction also used a 'Bu-BOX-Cu(II) catalyst with small loadings. The reaction worked well for a variety of alkyl, aryl and heterocyclic *N*-PMP imines 29 and gave good diastereo- and enantioselectivities and yields of products 30 (Scheme 15). In contrast to the previous work, the authors reported that PMP protected imines gave better enantioselectivities than OMB protected ones. This was attributed to the higher reactivity of the OMB imines, which gave a significant racemic background reaction.
The products 30 were reduced to diamines 31 with Sml₂ and then reacted with thiophosgene to give the corresponding thioimidazolidinones 32. In the same way as before, the presence of the heavy sulfur atom allowed for the assignment of the absolute stereochemistry of the products using X-ray crystallography.

Scheme 15. An enantioselective nitro-Mannich reaction catalysed by Cu(II)-BOX

In the same year, Jørgensen and co-workers reported an update of their methodology, using a cinchona alkaloid and a Ph-BOX-Cu(II) catalyst to affect a chiral nitro-Mannich reaction with secondary nitroalkane 33 and imine 24 (Scheme 16). The authors proposed that the cinchona catalyst was needed to deprotonate the nitroalkane and the Lewis acid to activate the imine, thereby forming a diastereomerically matched pair (Scheme 16). The reaction required a low catalyst loading and the product β-nitroamine 34, which contains two vicinal stereocentres, was isolated in good yield and excellent enantioselectivity.

Scheme 16. An enantioselective nitro-Mannich reaction by a dual activation catalyst

In 2007 Trost and co-workers used a binuclear zinc catalyst to give an asymmetric nitro-Mannich reaction between carbamate protected imines 35 and nitroalkanes 7 (Scheme 17). The reaction worked well with aryl, alkyl and even α,β-unsaturated imines to afford the desired products 36 in good yield and ee.
Andreas Kalogirou

University College London

Scheme 17. An enantioselective nitro-Mannich reaction by binuclear zinc catalyst

In the same year Shibasaki and co-workers reported the first asymmetric syn-selective nitro-Mannich reaction of \(N\)-Boc protected imines 37 with nitroalkanes 7, using a heterobimetallic catalyst complex comprised of a dinucleating Schiff base ligand and both \(\text{Cu}^{2+}\) and \(\text{Sm}^{3+}\) ions as well as a phenoxide ion (Scheme 18).\(^\text{26}\) The yields and stereoselectivities of products 38 were excellent, however the reaction did not proceed well with ortho-substituted aryl imines. The authors argued that the catalyst works by coordination of the nitro group to the samarium centre and the imine (via the Boc carbonyl) to the copper centre.

Scheme 18. The first asymmetric syn-selective nitro-Mannich reaction

More metal-catalysed nitro-Mannich reactions have been reported, however those follow similar protocols to the ones presented above. The next section will focus on the development of various organocatalytic protocols.

1.1.6 Organocatalytic nitro-Mannich reactions

Organocatalysis has been increasingly used in asymmetric synthesis,\(^\text{27}\) as it has some advantages over heavy metal catalysis. Organocatalysts tend to be cheaper, less toxic and more tolerant to air and moisture than metallic catalysts, while they often achieve high enantio- and diastereoselectivities. However, they do tend to require high loadings and long reaction times.

The first organocatalytic nitro-Mannich reaction appeared in 2004 by Takemoto and co-workers (Scheme 19).\(^\text{28}\) The authors reported that thiourea organocatalyst 39 affected the coupling of nitromethane with a range of \(N\)-phosphinoyl protected aryl
imines 20. The authors based their work on previous studies on the Michael addition of malonates to nitro olefins.29 They suggested that the thiourea moiety in the catalyst hydrogen-bonds to the nitro group of the nitroalkane, facilitating its deprotonation by the neighbouring tertiary amino group (Scheme 19). The reaction gave good yields but only moderate enantioselectivities of products 40 and was limited mainly to nitromethane and to aromatic imines.

![Scheme 19](image)

**Scheme 19.** The first organocatalytic nitro-Mannich reaction

Many other reports of thiourea-catalysed nitro-Mannich procedures appeared after Takemoto’s original report. The most impressive results were published by Wang and co-workers (Scheme 20).30 Thiourea catalyst 41 with two diamine units was used and the product β-nitroamines 42 were isolated in excellent yield and stereoselectivity.

![Scheme 20](image)

**Scheme 20.** Wang’s thiourea-catalysed nitro-Mannich

Cinchona alkaloids have been used as organocatalysts in the nitro-Mannich reaction. An interesting report by Palomo and co-workers used a quinine alkaloid as a chiral phase transfer catalyst to perform the reaction between N-Boc protected imines and nitroalkanes (Scheme 21).31 The imines were formed in situ from elimination of α-amido sulfones 43 under basic reaction conditions. The reaction was shown to tolerate a range of nitroalkanes 44 and enolisable imines, although lower yields and enantioselectivities were observed for secondary nitroalkanes. The product β-nitroamines 45 were converted into vicinal diamines, β-amino acids and allylic amines.
One other organocatalytic strategy used in the nitro-Mannich reaction is chiral proton catalysis, first reported by Johnston and co-workers in 2007. This report described the addition of nitroesters \( \text{46} \) to \( N \)-Boc protected imines \( \text{37} \) using an asymmetric bis(amidine) catalyst to give, after reduction, vicinal diamines \( \text{47} \) in good yields and selectivities (Scheme 22).

Soon after the previous report, the same group reported an expansion of their methodology using a similar catalyst with secondary nitroalkanes \( \text{48} \) (Scheme 23). The new methodology gave \( \text{syn-\( \alpha \)-amino-\( \beta \)-nitro esters 49} \) in slightly lower yields but excellent enantioselectivity.

An alternative chiral proton catalyst was reported by Rueping and Antonchick. Reaction of \( \alpha \)-imino ester \( \text{24} \) with various primary nitroalkanes \( \text{7} \) in the presence of a

Scheme 21. A Cinchona alkaloid organocatalysed nitro-Mannich reaction

Scheme 22. A stereoselective nitro-Mannich reaction by chiral proton catalysis

Scheme 23. The stereoselective synthesis of \( \text{syn-\( \alpha \)-amino-\( \beta \)-nitro esters 49} \)
phosphoric acid catalyst, gave $\beta$-nitroamines 50 in good yields and enantioselectivity but variable diastereoselectivities (Scheme 24).

![Scheme 24. A Brønsted acid catalysed nitro-Mannich reaction](image)

All the above-mentioned nitro-Mannich protocols have one common feature which is the origin of the nitronate anion. In most cases this anion originated from nitroalkanes or their derivatives (silyl nitronates). However, a limited number of nitroalkanes are commercially available or can be synthesised easily. A solution to this problem was provided by the use of nitroalkenes and formation of the reactive nitronate species by the conjugate addition of a suitable nucleophile, followed by a nitro-Mannich reaction in a tandem fashion. The use of nitroalkenes increases the variability and scope of the nitro-Mannich reaction. The conjugate addition/nitro-Mannich reaction of nitroalkenes with dialkylzincs and Superhydride® was investigated recently by the Anderson group and will be described in section 2.1. The literature of the conjugate additions to nitroalkenes will be reviewed in the following section.

1.2 Stereoselective 1,4-addition to nitroalkenes

Nitroalkenes are one of the most useful groups of synthetic building blocks. The presence of the highly electron withdrawing nitro group, controls their chemistry, making these olefins highly susceptible to 1,4-conjugate addition of nucleophiles, enabling the synthesis of more complex molecules. A range of nucleophiles could perform a conjugate addition on a nitroalkene in an enantioselective fashion including carbon, oxygen, nitrogen, sulfur and phosphorus nucleophiles.

1.2.1 Substrate/auxiliary controlled 1,4-Additions

The stereoselective Michael additions of various carbon nucleophiles using a chiral substrate or auxiliary control is initially presented. A large number of such reactions have been reported, so a few representative examples will be given in this section.
In 1996, Pätzel and co-workers reported the 1,4-addition of organometallic reagents to nitro-olefins 51 derived from (R)-2,3-isopropylidene glyceraldehyde (Scheme 25). The reactions gave mainly the anti adducts 52 in good diastereoselectivity.

\[ \text{Scheme 25. A diastereoselective Michael addition to glyceraldehydes 51} \]

Enders and co-workers described the use of chiral \( \alpha \)-silyl ketone 53 as a nucleophile in an enantioselective 1,4-addition reaction to nitroalkenes 54, for the synthesis of \( \alpha,\beta \)-disubstituted \( \gamma \)-nitro ketones 55. The ketone was first converted to a silyl enol ether and then reacted with the nitroalkene in the presence of SnCl\(_4\) as the Lewis acid (Scheme 26). The silyl group was then removed with TBAF to give the products 55 in excellent diastereo- and enantioselectivities.

\[ \text{Scheme 26. A diastereoselective Michael addition to chiral \( \alpha \)-silyl enol ethers} \]

The same group also reported the use of a chiral sugar auxiliary to afford the diastereo- and enantioselective Michael addition of enantiopure sulfonates 56 on nitroalkenes 57 (Scheme 27). The products 58 were isolated in high yields and selectivities and subsequently converted to sulfonates 59 and the absolute stereochemistry confirmed by X-ray crystallography.

\[ \text{Scheme 27. A diastereoselective Michael addition using a chiral sugar auxiliary} \]
Another auxiliary-controlled conjugate addition reaction was reported by d’Angelo and co-workers.\textsuperscript{43} Using chiral enamine 60 as the substrate, the 1,4-addition products 61a and 61b were isolated in good yields and selectivities (Scheme 28).

![Scheme 28. Michael addition of a chiral enamine](image)

**1.2.2 Metal-catalysed 1,4-Additions**

Seebach and co-workers first reported the use of diethylzinc as a nucleophile in the conjugate addition to nitroalkenes, in the presence of Lewis acids such as MgBr\textsubscript{2}, (Scheme 29).\textsuperscript{44} They also showed that this conjugate addition to aromatic nitroalkenes 54 could become enantioselective when carried out in the presence of a chiral Ti-TADDOLate complex, to give the product nitroalkanes 62 in high yield and enantiomeric excess. The reaction was however not catalytic as 1.2 equivalents of the metal complex was required.

![Scheme 29. The first metal-catalysed 1,4-addition](image)

In 1998 Sewald and Wendisch developed an asymmetric catalytic conjugate addition of diethyl zinc to nitroalkene 63 using phosphoramidite ligand 64, originally developed by Feringa (Scheme 30).\textsuperscript{45,46}The product 65 was obtained in quantitative yield and high enantioselectivity.

![Scheme 30. A copper phosphoramidite catalysed 1,4-addition of Et\textsubscript{2}Zn](image)
Later, Wendisch’s and Feringa’s groups both expanded this methodology to asymmetric conjugate additions of dialkylzincs to nitroacrylates using the same chiral ligand. The Alexakis group however, screened a whole range of phosphorus ligands and a variety of nitroalkenes \( \text{66} \) (Scheme 31). The reaction required only small catalyst loadings, while both enantiomers could be accessed from different catalysts.

\[
\begin{align*}
\text{Scheme 31. A more general copper phosphoramidite catalysed Michael addition}
\end{align*}
\]

Mampreian and Hoveyda reported the asymmetric Michael addition of dialkylzincs using a chiral dipeptide catalyst. The catalyst was chosen after a screening of different dipeptides, that showed that both chiral centres were necessary. A few different dialkylzinc reagents were investigated (mainly \( \text{Me}_2\text{Zn} \) and \( \text{Et}_2\text{Zn} \)). In addition, a number of alkyl and aryl substituted nitroalkenes \( \text{66} \) and the 1,4-addition products \( \text{68} \) were isolated in good yields and selectivities (Scheme 32).

\[
\begin{align*}
\text{Scheme 32. An asymmetric 1,4-addition of dialkylzincs}
\end{align*}
\]

Charette and co-workers demonstrated that Me-DuPHOS monoxide \( \text{69} \) was an effective ligand for copper in the asymmetric conjugate addition of diethylzinc on nitroalkenes (Scheme 33). A screening of solvents showed that \( \text{Et}_2\text{O} \) and toluene gave the best yields and selectivities. The nitroalkane products \( \text{70} \) were isolated in good yields and ee. Moreover, it was possible to reduce the amount of copper and catalyst used to 1.25 and 2.50 mol % respectively, by adding an additive (20 mol %). The best additive was found to be pivalamide. The authors stated that the additive coordinates to the copper, thereby favouring a monomeric instead of a polymeric ethylcopper species which is more active.
1.2.3 1,4-Additions of Oxygen nucleophiles

A large number of reports exist for the 1,4-addition of oxygen nucleophiles to nitroalkenes, however most of them were racemic. This section concentrates on some synthetically useful asymmetric reactions.

Enders and co-workers reported the conjugate addition of (-)-N-formylnorephedrine to nitroalkenes 66 (Scheme 34). This oxa-Michael reaction gave initially nitroethers 71, which were then converted to vicinal amino alcohols 72 in good yields and excellent ee. The chiral auxiliary was removed in a Na/NH\textsubscript{3} reduction step and recovered as (S)-N-formylamphetamine 73, while the absolute stereochemistry was confirmed by X-ray crystallography of 71.

Later, in 2003, Dixon and co-workers reported the oxa-Michael conjugate addition of the “chiral water” reagent 74. Nitroalkanes 75 were formed in good yields and ee and were converted to enantioenriched aminoalcohols 72 after hydrolysis of the THP group (Scheme 35).
An organocatalytic hydroxylation methodology was reported by Jørgensen and co-workers. The 1,4-addition of oxime 76 to nitroalkenes 66 catalysed by bifunctional thiourea-cinchona alkaloids, gave nitroalkanes 77 in good yields and ee (Scheme 36). It was shown that products 77 could be easily converted to nitroalcohols 78 or nitroamines 79 after the N-O bond was cleaved by reduction. Even though the reaction worked well for alkyl nitroalkenes, it failed for β-nitrostyrenes due to degradation of the products by retroaddition.

![Scheme 36. The first organocatalytic hydroxylation of nitroalkenes](image)

Very recently, Chen and co-workers described the enantioselective 1,4-addition of oxime 80 to trisubstituted β-nitroacrylates 81 to yield enantioenriched tertiary alcohols 82, using cinchona alkaloids as the chiral catalyst. The reaction had a wide scope and the products 82 were obtained in good yields and excellent enantioselectivities (Scheme 37). The S stereochemistry of the newly formed chiral centre was confirmed by X-ray crystallography, while cleavage of the N-O bond afforded aminoalcohol 83 in a good yield and without loss of ee. The authors found that thiourea catalysts were less enantioselective in this reaction, while they argued that the free OH group in the catalyst was involved in the mechanism as it hydrogenbonds to the nitroalkene activating it.

![Scheme 37. An organocatalytic 1,4-addition of oximes](image)
1.2.4 1,4-Additions of Nitrogen nucleophiles

As with oxygen nucleophiles, a large number of reports also exist for the 1,4-addition of nitrogen nucleophiles to nitroalkenes. The asymmetric aza-Michael additions were based on either chiral auxiliaries or the use of a chiral catalyst.

Enders and Wiedemann reported the stereoselective synthesis of vicinal diamines by the conjugate addition of a chiral equivalent of ammonia, ADMP $^{84}$. The product $\beta$-nitroamines $^{85}$ were isolated in good yields and selectivities. Subsequent reduction and Boc protection gave the protected diamines $^{86}$ in good overall yields and excellent ee (Scheme 38).

![Scheme 38](image)

**Scheme 38.** An auxiliary controlled aza-Michael addition

Another chiral auxiliary used in an asymmetric aza-Michael addition to nitroalkenes was chiral oxazolidinone $^{87}$ developed by Le Gall and co-workers (Scheme 39). $^{58}$ It was shown that the desired $\beta$-nitroamines $^{88}$ could be obtained in medium yields but high ee. Even though the scope of the reaction was limited, it was also possible to obtain the opposite enantiomers $^{89}$ by using S-oxazolidinone $^{90}$ as the nucleophile. Moreover, nitroamine $^{88}$ could be easily transformed to imidazolidinone $^{91}$, though the chiral auxiliary could not be recovered.

![Scheme 39](image)

**Scheme 39.** The aza-Michael addition of a chiral oxazolidinone

A diastereoselective-only example of the 1,4-addition of amines to nitroacrylates was reported by Ballini and co-workers in 2008. $^{59}$ The authors reported that one equivalent of amine reacted with one equivalent of nitroacrylate $^{92}$ at room
temperature in the absence of any solvent or catalyst (Scheme 40). Good yields of the product β-nitro-α-amino esters 93 were obtained, however in most cases with low diastereoselectivity.

Scheme 40. A diastereoselective conjugate addition of amines to nitroacrylates

Recently, two reports appeared of catalytic asymmetric aza-Michael reactions to nitroalkenes. Ooi and co-workers reported the use of a chiral Brønsted acid catalyst to afford the asymmetric 1,4-addition of 2,4-dimethoxyaniline to nitroalkenes 66 (Scheme 41).60 The product β-nitroamines 94 were isolated in excellent yields and ee.

Scheme 41. A chiral Brønsted acid catalysed 1,4-addition of amines

Maruoka and co-workers reported a catalytic asymmetric amination reaction of nitroalkenes using a chiral ammonium salt catalyst, under biphasic conditions.61 The reaction gave nitroamines 95 in good yields and ee (Scheme 42), with alkyl nitroalkenes giving lower ees (82-83% ee) than aromatic ones (91-95% ee). Catalyst loadings as low as 0.05 mol % were effective in most cases, however higher loadings (1 mol%) were needed for some “problematic” analogues. The absolute stereochemistry of the products was confirmed by conversion to the known diamine 96.
1.2.5 Miscellaneous 1,4-Additions

The conjugate additions of sulfur and phosphorus nucleophiles to nitroalkenes have also been widely reported. Focusing on sulfur nucleophiles, two publications stand out on the asymmetric additions of thiols to nitroalkenes, by Kobayashi and Connon, both using organocatalysis.

Kobayashi reported in 1981 the asymmetric conjugate addition of thioglycolic acid 97 to nitroalkenes 66 in the presence of a cinchona alkaloid catalyst (Scheme 43).\(^{62}\) The reaction had a limited scope and low enantioselectivity. Moreover, the \(ee\)s of all products 98 were not reported and the reaction was not catalytic as 1 equivalent of quinine was required. The authors argued that the ionic interaction between the carboxylic acid in 97 and the tertiary nitrogen in the catalyst was responsible for the asymmetric induction.

Recently, Connon reported the asymmetric 1,4-addition of alkane thiols 99 to \(\beta\)-nitrostyrenes 54, catalysed by a cinchona alkaloid-derived catalyst (Scheme 44).\(^{63}\) The product sulfides 100 were isolated in good yields and \(ee\) and the reaction showed good scope as it worked well for electron rich or deficient, as well as heterocyclic nitrostyrenes.
Organocatalysis was also used for the asymmetric conjugate additions of phosphorus nucleophiles. Melchiorre and co-workers first reported the asymmetric hydrophosphination of nitroalkenes 54, catalysed by a bifunctional cinchona alkaloid and thiourea organocatalysts (Scheme 45). This investigation was limited in scope and the observed ees were modest, however the authors showed that the phosphine products could be protected by forming borane complexes 101 and converted to aminophosphines like 102, which are potentially useful as chiral ligands. Moreover, the absolute stereochemistry of the products was confirmed by X-ray crystallography.

Scheme 45. The organocatalytic conjugate addition of phosphines to nitroalkenes

The 1,4-addition of phosphite 103 to nitroalkenes 66 using a chiral Brønsted base catalyst was reported by Terada and co-workers. The reaction gave enantioenriched phosphites 104 in good yields and ee, while low catalyst loadings were required (Scheme 46).

Scheme 46. The asymmetric Michael addition of phosphites
Recently, Rawal and co-workers reported a new diamine-based catalyst for the asymmetric 1,4-addition of phosphite $\text{103}$ to nitroalkenes $\text{66}$. The reaction was fast, with broad scope and gave excellent yields and $ee$s of the desired products $\text{104}$ (Scheme 47). The authors suggested that the squaramide catalyst works by hydrogen-bonding to the nitro group of the nitroalkene, which then obstructs one side of it to nucleophilic attack.

![Scheme 47. A squaramide catalysed 1,4-addition of phosphites](image)

1.2.6 Summary

Having briefly reviewed the literature of the asymmetric 1,4-additions to nitroalkenes, it is clear that the reaction is very general, as a wide variety of different nucleophiles have been shown to add to nitroalkenes. Moreover, a variety of asymmetric methods exist for performing these reactions to obtain enantioenriched $\alpha$-substituted nitroalkanes. This shows that there is great potential on using those 1,4-additions to provide the nitroalkane or nitronate partner of the nitro-Mannich reaction. By performing the 1,4-addition reaction asymmetrically, it would be expected that the nitro-Mannich reaction would also be rendered asymmetric, thereby offering control over the stereochemistry of three consecutive stereocentres.

The tandem conjugate addition/nitro-Mannich reaction of Superhydride® and dialkylzincs has been studied by the Anderson group and will also be described in this thesis. The conjugate addition/nitro-Mannich reaction of other nucleophiles, both carbon and heteroatom, the Michael additions of which were discussed above, will also be portrayed in this thesis. Our investigation expands into the synthesis of more diverse molecules using the nitro-Mannich reaction. It is therefore required to describe the reported synthetic applications of the nitro-Mannich reaction.
1.3 Synthetic applications of the nitro-Mannich reaction

As a C-C bond forming reaction, the nitro-Mannich reaction offers a wide variety of synthetic applications. The usability of the reaction lays in the fact that it allows the synthesis of β-nitroamines, compounds that have two adjacent nitrogen substituents in different oxidation states. The nitro group in particular, is extremely versatile, described by Seebach as a “chemical chameleon” as it can be transformed to other functional groups (Figure 1).\(^\text{67}\) A number of these modifications are described in the following section.

![Figure 1](image)

1.3.1 Functional group modifications-Nitro group reduction

The most widely used modification of the nitro group is its reduction to the corresponding amine. As it was seen in sections 1.1 and 1.2, the reduction of the nitro group frequently follows any reactions giving unstable nitroalkanes or β-nitroamines. The main reduction protocols reported were hydrogenation, hydride reduction and single electron transfer.

One example of a hydrogenation protocol, using Pd/C was reported by Palomo and co-workers.\(^\text{68}\) The authors reduced β-nitroamine 105 using only an atmospheric pressure of hydrogen at rt to give diamine 106 in excellent yield (Scheme 48).

![Scheme 48](image)

Hydride reduction is one of the most widely used methods for the reduction of nitro compounds. Usually, the combination of NaBH\(_4\) with a transition metal salt is used to form a more reactive metal boride species. Cobalt boride was used extensively by Johnston and co-workers for the reduction of nitroamines,\(^\text{32}\) while nickel boride was
used by Dixon, Melchiorre and others for the reduction of a variety of β-nitroamines. One example of a nickel boride reduction is reported by Shibasaki who reduced nitroamine 107 to diamine 108, fast and in excellent yield without any epimerisation (Scheme 49).

![Scheme 49. Nickel boride reduction of a nitro group](image)

Another method of nitro group reduction is the dissolving metal reduction or single electron transfer. Some methods used are the SmI₂ reduction reported by the Anderson group (Section 1.1.3, Scheme 5), the Zn/AcOH reduction developed by Feng and co-workers, the Al/Hg method used by the Anderson group and the In/Zn method reported by Ricci and co-workers. The latter method was used to reduce nitroamine 109 to diamine 110 in good yield and with no epimerisation. The method was tolerant to the presence of a phosphine oxide group which was not reduced (Scheme 50).

![Scheme 50. A dissolving metal reduction of the nitro group](image)

1.3.2 Functional group modifications-Nef reaction

After its discovery by Nef in 1894, the conversion of nitroalkanes to ketones has been extensively employed in synthesis. The original procedure included the treatment of nitro-compound 111 with a base, forming the nitronate anion 112, followed by acid that gave the protonated form 113 (Scheme 51). Addition of water gave 114 that decomposes by losing hyponitrous acid and water to give carbonyl compound 115. This method has been applied numerous times in synthesis and one example of it is the conversion of nitroalkane 116 to cyclohexanone 117 reported by Hwu and Gilbert.
The reaction can also be used in tandem syntheses such as that reported by Yoshikoshi and co-workers.\textsuperscript{74} The authors reported the Michael addition of enolate \textsuperscript{118} to nitroalkene \textsuperscript{119} to give nitronate \textsuperscript{120}, which after treatment with acid afforded diketones \textsuperscript{121} (Scheme 52).

\begin{align*}
\text{R}^1\text{R}^2\text{NO}_2 & \xrightarrow{\text{Base}} \text{R}^1\text{R}^2\text{N}^-\text{O}^- \xrightarrow{2\text{H}^+} \text{R}^1\text{R}^2\text{N}^+\text{O}^- \xrightarrow{\text{H}_2\text{O}} \text{R}^1\text{R}^2\text{NH}^+\text{OH}^- \xrightarrow{\text{R}^1\text{R}^2\text{OH}^+\text{OH}^-} \text{R}^1\text{R}^2\text{C}=\text{O} + \text{H}_2\text{O} + \text{H}^+ + \text{HNO} \\
\text{NO}_2 \xrightarrow{1) \text{KH}, \text{THF}} \text{TMS} \xrightarrow{2) 3.5\% \text{HCl}_{aq}} \text{TMS} \xrightarrow{\text{117}, 87\%} \text{TMS}
\end{align*}

\textbf{Scheme 51. Nef reaction by a base/acid treatment of nitroalkanes}

A variety of oxidative Nef reactions were also reported. Treatment of primary nitroalkanes \textsuperscript{122} with a buffered KMnO\textsubscript{4} solution (pH=11) can oxidise them to the respective carboxylic acids \textsuperscript{123} in good yields, as reported by Savilles-Stones and Lindell (Scheme 53).\textsuperscript{75} Oxone was also used in oxidative Nef reactions and was shown to not affect common protecting groups like TBS ethers, acetals and acetates. In the example shown below, nitroalkane \textsuperscript{124} could be transformed to ketone \textsuperscript{125} in good yield (Scheme 53).

\begin{align*}
\text{R}^1\text{R}^2\text{NO}_2 & \xrightarrow{\text{KMnO}_4, \text{KOH}, \text{K}_2\text{HPO}_4, \text{BuOH}, \text{rt}} \text{R}^1\text{R}^2\text{C}=\text{O} \xrightarrow{\text{R} = \text{alkyl, aryl}} \text{R}^1\text{R}^2\text{C}=\text{O} \xrightarrow{\text{1) NaOH, Na}_2\text{HPO}_4, 2) \text{Oxone, rt}} \text{R}^1\text{R}^2\text{CO} \xrightarrow{\text{123}, 96-99\%} \text{R}^1\text{R}^2\text{C}=\text{O} \xrightarrow{\text{125}, 87\%}
\end{align*}

\textbf{Scheme 53. Some oxidative Nef reactions}

Finally, a variety of reductive Nef reactions have also been reported, mostly using a single electron transfer methodology. One of the most frequently used procedures is the McMurry method that uses TiCl\textsubscript{3}.\textsuperscript{76} The method was used to convert nitroalkanes
to aldehydes and ketones and is thought to proceed via the intermediate oxime. The oxime is formed either by reduction of titanium nitronate or by reduction of ion to nitroso compound, followed by tautomerisation. The oxime is then reduced to imine, which is hydrolysed to carbonyl compound (Scheme 54).

**Scheme 54.** The mechanism of the TiCl₃ Nef reaction

### 1.3.3 Functional group modifications - Denitration

The nitro-group is not usually present in many natural molecules and pharmaceutical compounds, therefore methods for its removal (denitration) are very desirable. A very popular method is radical denitration using Bu₃SnH and an initiator that affects the replacement of the nitro group by a proton. An example of this method is the radical denitration of macrolide to developed by Ono and co-workers (Scheme 55).

**Scheme 55.** Radical denitration with Bu₃SnH

Another method of denitration is the elimination of HNO₂ from nitroalkanes where the nitro group is adjacent to an electron-withdrawing group by treatment with base. One example of this reaction is the reaction of β-nitroamines with DBU to give α,β-unsaturated esters in good yields, developed by Palomo and co-workers (Scheme 56).

**Scheme 56.** Ionic denitration with DBU
1.3.4 Synthesis of natural products

After the developments of the last two decades, the nitro-Mannich reaction has become an efficient and selective method to synthesise β-nitroamines.\(^7\) The development of the reaction along with the many functional group modifications that could be performed on these products, renders it very useful in the synthesis of complex molecules leading to pharmaceuticals or biologically active natural products.

The nitro-Mannich reaction was first used in synthesis by Shibasaki and co-workers in the synthesis of the pharmaceutical molecule ICI-199441 (137),\(^8\) which was found to be an opioid agonist.\(^9\) The first step in the synthesis was the nitro-Mannich reaction of N-phosphinoyl imine 138, catalysed by the metallic complex developed before,\(^1\) that gave β-nitroamine 139 in good yield and excellent \(ee\) (Scheme 57). A subsequent hydrogenation and reductive alkylation gave pyrrolidine 140, which could easily be converted to the desired compound 137 in an overall yield of 44%.

![Scheme 57. The synthesis of ICI-199441](image)

Bernardi and co-workers used the nitro-Mannich reaction to synthesise pseudo-C\(_2\)-symmetric triamines 141 which were precursors to HIV inhibitor A-74704 (142) (Scheme 58).\(^2\) Reaction of chiral imine 143 with silyl nitronate 144 in the presence of a Lewis acid gave, after reduction with nickel boride, triamine 141 in 66% yield but with a poor \(dr\).

![Scheme 58. The synthesis of HIV inhibitor 142 via a nitro-Mannich reaction](image)
Takemoto and co-workers later reported the synthesis of potential antiemetic CP-99994 (145), using a nitro-Mannich reaction as the first step. The synthesis started from the reaction of nitroalkane 146 with imine 147 in the presence of thiourea catalyst 39, which gave nitroamines 148a and 148b in good yield and ee, but medium dr (Scheme 59). Cyclisation then gave mainly trans-149 that was epimerised and reduced to cis-150. A further reductive amination step afforded the desired diamine 145 in a very efficient 48% overall yield.

Scheme 59. The synthesis of CP-99994

Dixon and co-workers recently published the synthesis of (-)-Nakadomarin A (151), a marine alkaloid that showed anticancer and antimicrobial activity. The key steps in the synthesis were the Michael addition of the ester enolate of 152 to nitroalkene 153 that gave nitroalkane 154 in medium yield and good dr, followed by a nitro-Mannich reaction with an in situ formed imine to give product 155 in good yield and excellent dr (Scheme 60). The two fragments 152 and 153 were synthesised in six and four steps respectively in 24% and 22% yields. Four further steps involving a radical denitration and an alkene methathesis reaction concluded the synthesis to give the natural product in 0.8% overall yield with the longest linear sequence being 12 steps.
Finally, Lu and co-workers reported the synthesis of oseltamivir (156), the active ingredient of the famous anti-influenza drug Tamiflu.\textsuperscript{87,88} The synthesis started from natural diethyl D-tartate 157 and involved an enantioselective nitro-Mannich reaction of imine 158 bearing a chiral sulfoxide protecting group with nitromethane. The nitro-Mannich reaction gave β-nitroamine 159 in good yield and \(dr\) (Scheme 61). The synthesis was completed with six further steps to give 156 in 21% overall yield.

\begin{center}
\textbf{Scheme 60. Dixon’s synthesis of (-)-Nakadomarin A}
\end{center}

\begin{center}
\textbf{Scheme 61. Lu’s synthesis of Oseltamivir}
\end{center}

1.4 Stereoselective synthesis of piperazinones

As can be observed from the previous section, a number of biologically interesting natural products and pharmaceuticals, like CP-99994 and Oseltamivir, contain vicinal diamines. The synthesis of vicinal diamines using a nitro-Mannich reaction and their use in the synthesis of a natural product is the subject of part of the research described in this thesis (section 2.6). This section will therefore discuss briefly the importance of 1,2-diamines and concentrate on piperazin-2-ones and the methods for their preparation.
1.4.1 Vicinal diamines

The 1,2-diamine motif is found in a variety of biologically active molecules, both natural and synthetic ones. Furthermore, this functional group has found numerous applications in asymmetric synthesis, as 1,2-diamines are often the source of chirality in many chiral catalysts, both metallic (as ligands) and organometallic ones. Some examples of biologically active diamines include biotin 160 (vitamin B<sub>7</sub>), Penicillin antibiotics 161 and the protein kinase inhibitor balanol 162 (Figure 2).<sup>89,90</sup>

![Figure 2. Some biologically active 1,2-diamines](image)

1.4.2 Biologically important piperazin-2-ones

A very useful group of compounds that contains the 1,2-diamine motif are piperazin-2-ones. The related piperazines, are found in a great number of drug molecules, specifically those with substitution only on the nitrogen atoms, due to the starting material being piperazine. Some examples include the antihistamine drug Cyclizine (163), the antidepressant Amoxapine (164) and the anti-ischemic agent Trimetazidine (165) (Figure 3).

![Figure 3. Drugs containing a piperazine moiety](image)

Even though piperazin-2-ones are not as widely prevalent as piperazines in drug molecules, they frequently exhibit biological activity and are the object of many medicinal chemistry studies. Some of these investigations will be presented in this section.

When investigating the synthesis of farnesyltransferase inhibitors, Williams and co-workers found that piperazinones 166 were effective targets (Figure 4).<sup>91</sup> The enzyme
farnesyltransferase is responsible for the activation of Ras protein, a small protein that directly affects tumor growth. This new class of inhibitors showed an inhibition of tumor growth in rats bearing H- or K-ras-dependent tumors.

More recently, Boger and co-workers investigated piperazinones 167 as inhibitors of the hemorrhagic fever arenavirus Lassa (LASV). After a screening of a large library of compounds, the authors identified the (−)-enantiomer of 167 as the most active, which after asymmetric synthesis was found to be (S)-167 (Figure 5).

Arora and co-workers investigated oligo-oxopiperazines as non-peptide mimetics of protein α-helixes. The authors used circular dichroism and NMR spectroscopy to conclude that oligooxopiperazine dimers 168 adopt conformations that resemble the peptide chain arrangement of an α-helix (Figure 6). Such scaffolds are very valuable tools in chemical biology.

Jankowski and co-workers investigated the use of cyclic oligopeptides as analogues of cyclosporine A, a known immunosuppressant drug. The authors reported that when
piperazinone 169 was used instead of a Phe-Phe dipeptide linkage, the synthesised peptides showed increased immunosuppressive activity (Figure 7).

![Figure 7](image)

1.4.3 Synthesis of piperazin-2-ones

As was seen in the previous section, piperazinones are useful compounds and are increasingly being used in drug design. Therefore, new methods to synthesise piperazinones are required. A few examples exist for the synthesis of multisubstituted piperazinones, that include formation of the ring system from condensation of 1,2-diamines with a suitable two-carbon synthon, by an intramolecular cyclisation from peptides and by an intramolecular [3+2] reaction of an azide.

Gonzalez-Muñiz and co-workers developed an intramolecular reductive amination of β-ketoesters 170 to prepare trisubstituted piperazin-2-ones 171 (Scheme 62).96 The desired piperazinones were obtained in good yields and selectivity while enamine 172 was proposed as the reaction intermediate. The reaction could be performed in one step by using H₂ (3 bar), Pd/C and a temperature of 45 °C, however better selectivities were observed from the two step protocol using NaBH₃CN (Scheme 62). According to this synthetic approach, different side chains could be incorporated in different positions of the piperazinone products by selecting the suitable dipeptide starting material.

![Scheme 62](image)

Scheme 62. Synthesis of piperazinones via an intramolecular reductive amination
Another synthetic route to piperazinones is by a [3+2] cycloaddition reaction developed by Gurjar and co-workers in their efforts towards the synthesis of serine protease inhibitors pseudotheonamide A₁ and A₂.⁹⁷ Starting from α-azidoacid 173 and aminoalcohol 174, the authors could access amide 175 in good yield, which could then undergo a dipolar cycloaddition reaction followed by elimination of N₂ to give piperazinone 176 (Scheme 63). Subsequent reduction with cyanoborohydride gave the final product as a mixture of the two diastereoisomers 177a and 177b, both of which were useful for the synthesis of the two natural products.

Hiemstra and co-workers reported the synthesis of 2,6-bridged piperazine-3-ones 178, starting from aminoacids.⁹⁸ Coupling of aminoacids 179 and 180 initially gave dipeptides 181 that after deprotection of the amine cyclised to piperazinediones 182, protected as carbamates (Scheme 64). Subsequent chemoselective reduction of the C₆ carbonyl to hydroxylactam 183 and treatment with TFA led to formation of acyliminium species 184 that was trapped by the nucleophilic R² group. The final products, 2,6-bridged piperazin-2-ones like 178 were isolated in good yields. It is noted that by adjusting the absolute configuration of 179, different diastereoisomers of the final product could be obtained.
Viso and co-workers reported the asymmetric synthesis of syn-diamines 185 in good yields as a single diastereoisomer using a chiral sulfoxide moiety. These diamines were used in a more recent publication in the synthesis of piperazin-2-ones. Subsequent treatment with α-chloroacetyl chloride and cyclisation gave piperazinones 186 in good yields (Scheme 65). Treatment with NaH led to elimination of the sulfinyl group to afford imines 187. The nucleophilic addition of a number of nucleophiles to imines 187 was then investigated. Variable yields and selectivities were observed with some nucleophiles favouring anti/syn diastereoisomer 188a (Et₂Zn, 78:22 dr) and some anti/anti diastereoisomer 188b (allylMgBr/CeCl₃, 0:100 dr). These diastereoselective alkylations showed that this method could be used to synthesise multi-functionalised piperazinones.

When investigating the absolute configuration of guadinomine C₂ 189 and related natural antibacterial agents, Sunazuka and co-workers developed an asymmetric synthesis for piperazin-2-one 190. Initially chiral diamine 191 was synthesised in.

**Scheme 64.** Synthesis of 2,6-bridged piperazine-3-ones

**Scheme 65.** Synthesis of piperazin-2-ones from vicinal diamines 185
eight steps from chiral oxazolidinone 192 in 38% overall yield. Subsequent coupling with optically active 2-bromopropionic acid, followed by deprotection of the nosyl group, gave piperazin-2-one 190 in good yield (Scheme 66). This study showed that the correct absolute configuration of 189 is the one shown below.

Scheme 66. Synthesis of piperazin-2-one 190 from vicinal diamine 191

1.5 Stereoselective syntheses of pyrrolidinones

Similar to piperazinones, pyrrolidinones are interesting synthetic targets due to their pharmacological properties and as precursors to other heterocycles. Many useful compounds contain the pyrrolidine-2-one moiety such as the dietary supplement pyroglutamic acid 193 and the nicotine metabolite cotinine 194 that is used as an antidepressant (Figure 8). Specifically, pyrrolidine compounds bearing a 1,2-diamine like 195 (Figure 8) have shown activity as proteasome and melanoma inhibitors.  

Figure 8. Biologically active pyrrolidinones

A variety of methods were reported in the literature for the synthesis of pyrrolidin-2-ones. A frequently used method is radical cyclisations, an example of which is the reaction of optically pure N-allyl-α-bromoacetamides 196 under tin-free conditions (Scheme 67). Wood and co-workers have reported the use of BEt3/H2O as the radical initiator. The reagent works by liberating an ethyl radical after reaction with molecular oxygen. The reaction gave good yields of 4-alkyl-pyrrolin-2-ones 197 via a 5-exo-trig radical cyclisation (Scheme 67).
Furthermore, [3+2] cycloaddition reactions have been used in the synthesis of pyrrolidin-2-ones. Woerpel and co-workers reported a stereoselective synthesis of pyrrolidinones via the [3+2] annulation of allylsilanes and chlorosulfonyl isocyanates (Scheme 68). Subsequent cleavage of the sulfinyl group gave pyrrolidinones in good yields and dr.

Lactamisation also provided useful routes to the pyrrolidin-2-one ring system. Mahboobi and co-workers reported the synthesis of nitroesters via an intermolecular Michael addition, starting from substituted acetate Michael donors and nitroalkenes. Subsequent reduction of the nitro group and cyclisation gave pyrrolidinones albeit in variable yields and dr (Scheme 69). This method was used for the synthesis of natural product Staurosporinone.

Recently, Hamada and co-workers reported the stereoselective synthesis of densely functionalised pyrrolidinones by a cascade reaction of enals with the both electrophilic and nucleophilic, fumaric acid amide esters (Scheme 70). A cascade aza-Michael/Michael reaction followed by epimerisation with K$_2$CO$_3$ and reduction with NaBH$_4$ gave pyrrolidinones in variable yields but good selectivities.
Perhaps more interesting is the synthesis of pyrrolidin-2-ones from ring expansion reactions of azetidin-2-ones. The reaction is driven by the release of strain of the four-membered ring, and has been frequently used in synthesis. An example is the diastereoselective electrophile-induced ring expansion of 4-isopropenylazetidin-2-ones towards 5-bromopyrrolidin-2-ones (Scheme 71). Treatment of 209 with bromine leads to electrophilic addition on the double bond to give bromonium cations 211, which then ring expand to give N-acyliminium cations 212. Subsequent nucleophilic addition of bromide affords pyrrolidonones 210 in good yield.

Another interesting method of making pyrrolidonones employs an intramolecular nucleophilic attack on a suitable electrophilic acceptor in the same molecule. Chatterjee and co-workers reported the stereoselective synthesis of 3-alkylidene pyrrolidonones 213 via a carbanion addition to acetylenes (Scheme 72). A more innovative synthesis of the related 1H-pyrrol-2(5H)ones 216, applying organometallic chemistry was developed by Murai and co-workers using a catalytic carbonylative [4+1] cycloaddition on a 1,3-conjugated system catalyzed by
Ru$_3$(CO)$_{12}$.\textsuperscript{111} In this synthesis, an $\alpha,\beta$-unsaturated imine 215 reacted with CO to give compounds 216 in good yield (Scheme 73).

\begin{center}
\begin{equation*}
\begin{array}{c}
\text{R}^1\text{C}N\text{Bu} \\
\text{R}^2
\end{array}
\end{equation*}
\end{center}

\begin{center}
\begin{equation*}
\text{Ru$_3$(CO)$_{12}$ (2 mol\%)} \\
\text{Toluene, 180 °C, 10 atm}
\end{equation*}
\end{center}

\begin{center}
\begin{equation*}
\begin{array}{c}
\text{O} \\
\text{R}^1 \\
\text{R}^2 \\
\text{N}^\text{Bu}
\end{array}
\end{equation*}
\end{center}

\begin{center}
\begin{equation*}
\begin{array}{c}
\text{Scheme 73. A carbonylative [4 + 1] cycloaddition}
\end{array}
\end{equation*}
\end{center}

An intriguing intramolecular oxo-Diels-Alder reaction has been developed by Murray and co-workers for the synthesis of multi-functionalised pyrrolidinones 217 (Scheme 74).\textsuperscript{112} The resulting pyrrolidinones 217 were isolated as the cis-fused isomers in good yields and as single diastereoisomers. However the synthesis suffers from the need to use NH-Boc protected $L$-amino acids as the source of chirality in the starting materials 218.

\begin{center}
\begin{equation*}
\begin{array}{c}
\text{COOEt} \\
\text{R}^1
\end{array}
\end{equation*}
\end{center}

\begin{center}
\begin{equation*}
\text{Toluene, reflux}
\end{equation*}
\end{center}

\begin{center}
\begin{equation*}
\begin{array}{c}
\text{218} \\
\text{217, 48-91%}
\end{array}
\end{equation*}
\end{center}

\begin{center}
\begin{equation*}
\text{Scheme 74. An intramolecular oxo-Diels-Alder reaction}
\end{equation*}
\end{center}

A novel route to pyrrolidinones via a tandem Heck-allylic substitution reaction was reported by Feringa and co-workers in 2003.\textsuperscript{113} Reacting amides 219 with bromides 220 gave pyrrolidinones 221 in medium yields. After optimisation it was found that Na$_2$CO$_3$ was the best base and that the use of $n$Bu$_4$NCl as a transfer reagent was required (Scheme 75). This method was also applied in the synthesis of piperidin-2-ones by the use of longer amides ($n=2$).

\begin{center}
\begin{equation*}
\begin{array}{c}
\text{O} \\
\text{R}^1, R^2, R^3 = \text{alkyl or aryl} \text{, } H, n = 1 \text{ or } 2
\end{array}
\end{equation*}
\end{center}

\begin{center}
\begin{equation*}
\begin{array}{c}
\text{Pd(OAc)$_2$ (5 mol\%), P(o-Tol)$_3$ (11 mol\%), Na$_2$CO$_3$ (2 equiv.), nBu$_4$NCl (2 equiv.), MeCN, 90 °C}
\end{array}
\end{equation*}
\end{center}

\begin{center}
\begin{equation*}
\begin{array}{c}
\text{219} \\
\text{220}
\end{array}
\end{equation*}
\end{center}

\begin{center}
\begin{equation*}
\begin{array}{c}
\text{221, 49-82%}
\end{array}
\end{equation*}
\end{center}

\begin{center}
\begin{equation*}
\text{Scheme 75. A tandem Heck-allylic substitution reaction}
\end{equation*}
\end{center}

Finally, a very recent and relevant synthesis of pyrrolidin-2-ones, is the one developed by Dixon and co-workers in 2009 that utilizes a nitro-Mannich reaction and a
lactamisation cascade.\textsuperscript{11} In this three-component synthesis, amine 222, aldehyde 223 and nitroalkane 224 (methyl 3-nitropropanoate) were heated in toluene leading to the in situ formation of an imine, that abstracted a proton from the nitroalkane to give ion pair 225. The anion was then added to the imine followed by cyclisation to give pyrrolidinones 226 (Scheme 76). The reaction was broad in scope and highly diastereoselective and was also extended to cyclic imines allowing the direct formation of polycyclic pyrrolidinone derivatives. This synthesis shows that the nitro-Mannich reaction can be used efficiently to make pyrrolidinones with variable substituents that could be of use as building blocks in synthesis.

\textbf{Scheme 76.} Synthesis of pyrrolidinones \textit{via} a nitro-Mannich reaction

As can be seen from the reported methods for synthesising pyrrolidinones, many of them are lengthy procedures, while others require starting materials that are expensive or hard to make. Moreover, while many syntheses are diastereoselective, only a few of them are enantioselective. Efficient syntheses of pyrrolidinones from simple starting materials, such as the last one presented (Scheme 76),\textsuperscript{11} would be very useful for the preparation of important pyrrolidinones and the formation of many analogues necessary for possible biological testing of drug candidates. One new method of synthesising pyrrolidin-2-ones is discussed in this thesis, using a tandem 1,4-addition/nitro-Mannich/lactamisation reaction (section 2.2).
2. Results and discussion

2.1 Previous work and methodology

Recently, the Anderson group has started to investigate the use of nitroalkenes as precursors for the nitro-Mannich reaction. The 1,4-addition of nucleophiles to nitroalkenes can create reactive nitronate species that can subsequently react with imines in the nitro-Mannich reaction. The use of hydride ions and dialkylzinc species as nucleophiles has been investigated.\(^{36,114}\)

As shown in Scheme 77, a variety of nitroalkenes 66 can undergo a one-pot reductive nitro-Mannich reaction when they are reduced with Superhydride® to form a nitronate ion. This can then react with OMB or PMP-imines in the presence of acetic acid. The acid is needed to activate the imine towards the reaction by making it more electrophilic. The $\beta$-nitroamines 227 were isolated in good yields and diastereoselectivities after being protected as the trifluoroacetamides 228. This protection was necessary as the $\beta$-nitroamines were unstable to purification, due to retroaddition.

It was postulated that the nitro-Mannich reaction proceeds via a Zimmerman-Traxler type transition state, which explains the observed anti relative stereochemistry of 227. Two possible transition states exist if we assume that the imine is fixed in the $E$ geometry (Scheme 77). Transition state A, leading to the syn isomer, suffers from an unfavourable 1,3-diaxial interaction between the axial CH$_2$R group and the imine protecting group P (OMB or PMP). Transition state B leads to the anti isomer and does not suffer from such an interaction, making it more favourable.

![Scheme 77. A one-pot reductive nitro-Mannich reaction](image-url)
Dialkylzinc reagents were also investigated. Diethylzinc was found to be a very effective reagent in the one pot 1,4-addition/nitro-Mannich reaction. The initial 1,4-addition of the ethyl group in the presence of Cu(OTf)$_2$ gave nitronate species 229 (Scheme 78). The nitronate then underwent a nitro-Mannich reaction giving, after protection with TFAA, highly-functionalised trifluoroacetamides 230a and 230b.\textsuperscript{35} Interestingly, different diastereoselectivity was observed with different solvents, with THF giving mainly syn/anti diastereoisomers and Et$_2$O giving syn/syn diastereoisomers (Scheme 78). The cause of this selectivity was suspected to be the difference in solubility of Zn(O$_2$CCF$_3$)$_2$ in the two solvents. In the case of THF, the reaction mixture was homogenous and the selectivity could be explained from a metal centred “Zimmerman-Traxler” type transition state. With Et$_2$O, the reaction was heterogenous and was suspected to react via acyclic transition state C. The reaction worked best with PMP protected imines and could also be performed asymmetrically using chiral phosphine ligands in the 1,4-addition step to give highly enantioenriched products.\textsuperscript{50,51}

\textbf{Scheme 78.} A 1,4-addition/nitro-Mannich reaction with diethylzinc

During this work, it was discovered that by using nitroacrylate 231 as the nitroalkene, the $\beta$-nitroamine produced from the nitro-Mannich reaction subsequently cyclised to give highly functionalised pyrrolidinones 232. When the reaction was attempted with PMP protected phenyl imine, the expected product 233 was isolated as a single diastereomer in 45% yield (Scheme 79).\textsuperscript{115}

\textbf{Scheme 79.} Synthesis of pyrrolidinones 232 from nitroacrylate 231
After optimisation it was found that the best conditions for the reaction were the use of THF as the solvent and the use of 1.10 equiv. of diethylzinc in the 1,4-addition step (found to be complete in 1.5 h). Also, the addition of excess imine (2.00 equiv.) and of 3.50 equiv. of TFA was found to be optimal, as well as a prolonged reaction time of 15 h. With all these improvements and the confirmation that the para-methoxyphenyl imine was the best for this reaction, the yield of phenyl substituted pyrrolidinone 233 reached 66% (Scheme 80).

\[
\begin{align*}
\text{E}1 \text{O} & \text{C} \text{H} \text{N} \text{O}2
\end{align*}
\]

1) Et\(_2\)Zn (1.10 equiv.), Cu(OTf)\(_2\) (5 mol%), -78 °C to rt, 1.5 h
2) Ph\(_{\text{PMP}}\) (2.00 eq.), THF, -78 °C, 20 min
3) TFA (3.5 eq.), THF, -78°C to rt, 15 h

Scheme 80. Optimised condition for the synthesis of 233

The reaction worked well with a variety of ortho, meta and para substituted aryl imines to give yields of 46-84% (Figure 9). The lowest yields were obtained for ortho-substituted aryl groups, presumably due to steric reasons. Single diastereoisomers were isolated in every case.

![Figure 9](image)

Alkyl analogues 234-238 were also made in yields of 38-69%, while the tBu analogue 237 was isolated in only 19% yield. Dimethylzinc was proven to work just as well as diethylzinc, to give pyrrolidinone 242 (Figure 10). Moreover, 239, 240 and 241 were the only heteroaryl analogues made in 64-70% yield, while no reaction occurred when 3-indole PMP protected imine was used. An initial effort to develop an asymmetric variant of the reaction was made using a phosphoramidite catalyst in the 1,4-addition step, which gave pyrrolidinone 233 in 52% ee, although the absolute stereochemistry was not determined.
Furthermore, some additional functionalisation of the pyrrolidinone core was attempted. The successful functionalisations include removal of the PMP group from pyrrolidinone 233, reduction of the nitro group to the corresponding amine and reduction of the amide group to an amine. However, some transformations were not so successful, such as the Nef reaction, which gave only 38% yield of pyrrolidinones 243a and 243b (Scheme 81).

Scheme 81. Functionalisations of pyrrolidinone 233

2.2 Proposed research

It was apparent that some further investigation of this reaction and of the functionalisation of the products was needed. The proposed research was to expand on the existing results and develop a more efficient asymmetric synthesis of these densely functionalised pyrrolidinones, in order to exploit its use in natural product synthesis.

The study would focus on functionalisation of the general structure 233 (Scheme 81) where the substituents can be varied. Variation of the R group derived from the
starting imine had been studied in some depth. However, some gaps remained such as the fact that no nitrogen containing heterocyclic imines had been used successfully. Various heterocyclic imines 248 can easily be accessed from the corresponding aldehydes 249 via a simple condensation with para-anisidine, in the presence of a suitable dehydrating agent (Scheme 82).

![Scheme 82. Synthesis of N-PMP imines](image)

The other variable that we wished to investigate was the type of nucleophile that could be used in this process. Previously only an ethyl nucleophile from diethylzinc had been used, however the presence of an ethyl group is rare in naturally occurring pyrrolidines and it is not versatile as it cannot be removed, modified or substituted. Some other diorganozinc reagents can be accessed using a combination of Zn(OMe)₂ and Grignard reagents, as reported by Charette.¹¹⁷ Perhaps more interesting would be the use of O and N nucleophiles like the ones mentioned in section 2.5. Successful use of these nucleophiles (NuH) and a suitable imine (250), would be beneficial as it would allow the preparation of a wider variety of pyrrolidinones 251 and allow for further functionalisation (Scheme 83).

Moreover, some further modifications of the pyrrolidinone core could be attempted. For example, a possible reaction with a Grignard reagent at the amide carbonyl could give 252, which after an ionic reduction with Et₃SiH/BF₃·OEt₂ could give the alkylated product 253 (Scheme 83).¹¹⁸

![Scheme 83. Synthesis and possible functionalisations of pyrrolidinones 251](image)

Compounds 253 still contain an acidic proton alpha to the nitro group that would give a reacting nitronate anion by deprotonation. This could then be reacted with electrophiles such as acrylates (Michael addition). Subsequent reduction of the nitro
group could lead to ring closure and yield interesting spiro fused heterocycles 254 (Scheme 84).

\[
\begin{align*}
\text{Nu} & \quad \text{base} & \quad \text{CH$_2$=CH$_2$, R$_1$} & \quad \text{[H]} & \quad \text{Ring closure} & \quad \text{spiro fused heterocycle} \\
253 & \quad & & \quad & \quad & \quad \quad 254
\end{align*}
\]

Scheme 84. Reaction of pyrrolidinones 253 with acrylates

Those are just a few of the possible transformations that could be studied and give rise to interesting heterocyclic structures. With the possible control of the absolute stereochemistry in the initial conjugate addition step, these structures could be made in enantiomerically pure form. The success of this methodology would be confirmed by the synthesis of one or more natural products.

2.3 Stereoselective synthesis of pyrrolidinones via Nitro-Mannich reaction

2.3.1 Synthesis of starting materials

With the methodology for the synthesis of pyrrolidinones already developed, we set out to expand the scope of this tandem synthesis. This required access to the non-commercially available starting material ethyl 3-nitroacrylate 231. An efficient synthesis of this material was required as a considerable quantity of it was needed for the study. Two possible routes to 231 have been used before (Scheme 85). In the first route, reaction of ethyl acrylate with ceric ammonium nitrate (CAN) and sodium nitrite gave nitroalcohol 255, which upon treatment with mesyl chloride and triethylamine gave the desired nitroacrylate 231 in 41% yield overall. In the second route, the same nitroalcohol could be obtained by reaction of ethyl glyoxylate with nitromethane in the presence of alumina, giving a total yield of 42% for 231.

\[
\begin{align*}
\text{EtO} & \quad \text{CH$_3$=CH$_2$, CH$_3$NO$_2$, 7.4 equiv., Al$_2$O$_3$, basic, 3 days, 62 \%} & \quad \text{1) CAN 3 equiv., NaNO$_2$ 3 equiv., CH$_3$CN, 24 h, 61 \%} & \quad \text{2) H$_2$O workup} & \quad \text{EtO} & \quad \text{MsCl 3 equiv., Et$_3$N 3 equiv. DCM, -25 \degree C, 30 min, 68 \%} & \quad \text{EtO} & \quad \text{EtO} & \quad \text{EtO} & \quad \text{EtO} & \quad \text{EtO}
\end{align*}
\]

Scheme 85. Synthesis of nitroacrylate 231
In this thesis, repeating the synthesis of nitroalcohol 255 from ethyl acrylate was attempted many times and it was found that the yield of the product was variable (32-45%) depending on the source of CAN used. It was found that using freshly dried and ground CAN gave a better yield 59-63%.

The synthesis of 255 from ethyl glyoxylate however, was more challenging. Use of neutral alumina, as in the literature procedure,120 gave a very low yield, whereas use of basic alumina and extension of the reaction time to 3 days gave a 62% yield of the nitroalcohol (Scheme 85). It was thought that a catalytic amount of base would also catalyse the reaction and indeed 10 mol % of Et3N gave 56% yield, while reducing the base to 2.00 mol % gave 44% yield after 24 h. The reaction of glyoxylate with basic alumina was our preferred method for the synthesis of nitroalcohol 255, as it required less quantities of reagents (ethyl acrylate method required 3 equiv. of CAN and NaNO2). Furthermore, it was much cleaner and easier to purify, as the starting materials were volatile, thus could be removed in vacuo, thereby avoiding chromatography. Subsequent dehydration by mesylation proceeded smoothly to give the desired nitroacrylate in 42% overall yield.

The final required reagents were the PMP protected imines, both heterocyclic and alkyl. The heterocyclic imines were synthesised via the condensation of the corresponding aldehyde with para-anisidine in a 1:1 ratio, in the presence of a dehydrating agent, usually basic Al2O3. The reaction was performed in DCM at room temperature and was usually completed within 15 h. The products were usually isolated as solids that were stable at -20 °C. The products were used without further purification when 1H NMR showed a purity of >95% and recrystalised otherwise (Table 1).

**Table 1. Synthesis of heterocyclic imines**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Imine</th>
<th>R</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>256</td>
<td>2-pyridyl</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>257</td>
<td>3-pyridyl</td>
<td>93</td>
</tr>
</tbody>
</table>
The synthesis of alkyl imines was more difficult than that of the heterocyclic ones because of their instability. Alkyl imines 267 and 268 required MgSO₄ as the dehydrating agent. With imine 266 the reaction should be performed at -78 °C and the imine was only stable for a few days at -5 °C (Table 2). This instability can be attributed to the tautomerisation of the imine to an enamine that could undergo side reactions.

**Table 2.** Synthesis of alkyl imines

<table>
<thead>
<tr>
<th>Entry</th>
<th>Imine</th>
<th>Method</th>
<th>R</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>266</td>
<td>Al₂O₃/rt</td>
<td>Methyl</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>266</td>
<td>Al₂O₃/-78 °C</td>
<td>Methyl</td>
<td>97</td>
</tr>
<tr>
<td>3</td>
<td>267</td>
<td>MgSO₄/rt</td>
<td>2,2-dimethoxyethyl</td>
<td>97</td>
</tr>
<tr>
<td>4</td>
<td>268</td>
<td>MgSO₄/rt</td>
<td>Cinnamyl</td>
<td>98</td>
</tr>
</tbody>
</table>

**2.3.2 Expansion of the reaction scope**

With ethyl 3-nitroacrylate 231 in hand, we continued towards the synthesis of pyrrolidinones using the conjugate addition/nitro-Mannich reaction. Using the
previously developed methodology, an expansion of the scope of the reaction, was attempted, in particular to the use of nitrogen containing heterocyclic imines and some alkyl imines.

The study of the reaction of N-containing imines started from imine 256 (Table 1). Reaction of this imine under the developed conditions gave the product pyrrolidinone 269 in 50% yield. As this yield was rather low, optimisation of the reaction was attempted. A number of modifications to the reaction conditions were attempted, such as altering the solvent, the equivalents of acid, the reaction time, the temperature and the protecting group (Table 3), however none of these led to any significant increase of the yield of 269.

**Table 3. Optimisation of the synthesis of pyrrolidinone 269**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction conditions</th>
<th>Yield of 269</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>As shown</td>
<td>50%</td>
</tr>
<tr>
<td>2</td>
<td>5.5 equiv. of TFA used</td>
<td>24%</td>
</tr>
<tr>
<td>3</td>
<td>Ether used as solvent, 48 h reaction time</td>
<td>32%</td>
</tr>
<tr>
<td>4</td>
<td>DCM used as solvent (steps 2 and 3)</td>
<td>32%</td>
</tr>
<tr>
<td>5</td>
<td>Step 3 left for 48 h</td>
<td>54%</td>
</tr>
<tr>
<td>6</td>
<td>Step 3: 5 Å molecular sieves added</td>
<td>21%</td>
</tr>
<tr>
<td>7</td>
<td>Step 3 left for 15 h at rt then 5 h reflux</td>
<td>45%</td>
</tr>
<tr>
<td>8</td>
<td>Triflic acid used instead of TFA</td>
<td>20%</td>
</tr>
<tr>
<td>9</td>
<td>Lewis acid Ti(O(^1)Pr(_4)) (_3) equiv.) instead of TFA</td>
<td>15%</td>
</tr>
<tr>
<td>10</td>
<td>OMP imine used instead of PMP</td>
<td>No product</td>
</tr>
</tbody>
</table>
The general reaction conditions shown above were then used in the synthesis of other heterocyclic pyrrolidinone analogues (Table 4). Imines 256, 257, 264 and 265 gave average yields (42-58 %) of pyrrolidinones 232 as single diastereoisomers, whereas the indole and pyrrole imines 258 and 261 gave no product. The failure of this reaction may be due to either the electron donating character of the pyrrole and indole rings or by possible side reactions that lead to degradation.

In light of this result, the reaction of both the N-methyl and the N-tosyl protected imines of pyrrole and indole was attempted. Not surprisingly, the N-Me protected imines 259 and 262 gave no product (by $^1$H NMR), while the N-tosyl protected ones gave a successful reaction. This result confirmed the previous hypothesis, as the presence of the Tosyl group removes electron density from the two heterocycles making imines 260 and 263 more electrophilic. In the case of imine 260, a 56% yield of pyrrolidinone 271 was isolated, while imine 263 gave only a poor yield of 33% of 272, isolated as a mixture of diastereomers ($dr$ 85:15).

**Table 4. Synthesis of heterocyclic substituted pyrrolidinones 232**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>R group</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>269</td>
<td>2-pyridyl</td>
<td>50%</td>
</tr>
<tr>
<td>2</td>
<td>270</td>
<td>3-pyridyl</td>
<td>42%</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>3-indolyl</td>
<td>No product</td>
</tr>
<tr>
<td>4</td>
<td>-</td>
<td>3-N-methylindolyl</td>
<td>No product</td>
</tr>
<tr>
<td>5</td>
<td>271</td>
<td>3-N-tosylindolyl</td>
<td>56%</td>
</tr>
<tr>
<td>6</td>
<td>-</td>
<td>2-pyrrolyl</td>
<td>No product</td>
</tr>
<tr>
<td>7</td>
<td>-</td>
<td>2-N-methylpyrrolyl</td>
<td>No product</td>
</tr>
<tr>
<td>8</td>
<td>272</td>
<td>2-N-tosylpyrolyl</td>
<td>33%</td>
</tr>
<tr>
<td>9</td>
<td>273</td>
<td>2-thiazolyl</td>
<td>58%</td>
</tr>
<tr>
<td>10</td>
<td>274</td>
<td>2-oxazolyl</td>
<td>53%</td>
</tr>
</tbody>
</table>
The use of alkyl imines for the synthesis of pyrrolidinones has been investigated before.\textsuperscript{116} It was found that secondary imines like isopropyl and cyclohexyl gave pyrrolidinones 235 and 236 in medium yield, while tertiary and primary imines were less successful (Figure 10, section 2.1). The reason for this poor result is postulated to be the instability of primary imines due to their tautomerisation to enamines.

For the same reason, when the reaction of imine 266 derived from acetaldehyde (section 2.3.1) was performed, only a complex mixture of products was observed. However, when imine 266 was synthesised at -78°C and used straight after without warming, pyrrolidinone 275 could be isolated in 40% yield as a single diastereoisomer (Scheme 86).

Scheme 86. Synthesis of pyrrolidinone 275

The usefulness of the developed methodology would be considerably increased if the group at the rings C\textsuperscript{5} position provided room for further functionalisation, as that would allow the synthesis of more complicated structures. One useful group to have at this position would be a formyl group. A possible alternative to installing a formyl group could be to have a masked aldehyde that would later be deprotected. Indeed, reaction of acetal-imine 267 was successful and yielded pyrrolidinone 276 in 63% yield (Scheme 87). Another useful functionality to have at the C\textsuperscript{5} position would be an alkene substituent, such as the one seen in compound 277. The presence of a double bond offers many derivatisation options, as an alkene could be transformed to a variety of other functional groups. However, from the reaction of cinnamaldehyde-derived imine 268 no pyrrolidinone could be isolated, as the crude reaction mixture contained only the 1,4-addition product of Et\textsubscript{2}Zn to 231 and degradation products.

Scheme 87. Attempts to synthesise pyrrolidinones 276 and 277
2.3.3 Use of other dialkylzinc reagents

In light of the success of diethylzinc, the use of other dialkylzinc reagents as nucleophiles for this 1,4-addition/nitro-Mannich reaction was then investigated. Dimethylzinc has already been shown to be as good a nucleophile as diethylzinc, however the use of diphenylzinc for the synthesis of pyrrolidinones was unsuccessful.\textsuperscript{119} As such, it was decided to reinvestigate the use of diphenylzinc. The 1,4-addition reaction of diphenylzinc to nitroacrylate 231 was found to be very slow. Increasing the equivalents of Ph\textsubscript{2}Zn to two or increasing the reaction time for this step to 4 days did not result in any improvement. Also, increasing the reaction time of the nitro-Mannich/lactamisation part of the reaction or using the stronger triflic acid instead of TFA was also not beneficial as the reaction gave a complicated mixture of products and none of the desired pyrrolidinone 278 (Scheme 88).

![Scheme 88. Attempt to synthesise pyrrolidinone 278](image)

In light of these results, it was decided to investigate doing the reaction stepwise and isolating the intermediate 1,4-addition product 279. It was therefore necessary to look at other ways of conducting the initial 1,4-addition reaction. The reaction of nitroacrylate 231 with diphenylzinc (1.1 equiv.) in the presence of Cu(OTf)\textsubscript{2} (5 mol %) gave nitroalkane 279 in 60\% yield. The 1,4-addition of the phenyl group was also attempted, where 1 equiv. of CuBr·SMe\textsubscript{2} was premixed with PhMgBr at -40 °C and then reacted with the nitroalkene, giving 48\% yield of 279.\textsuperscript{123} When the reaction of nitroacrylate 231 with PhMgBr was attempted at -78 °C, no 1,4-addition product was isolated but phenol was unexpectedly observed in the crude reaction mixture. This could be explained by the addition of the Grignard reagent to the nitro group, followed by elimination of phenol to form nitrosoalkene 280 (Scheme 89). This kind of reactivity has been reported in the first step of the mechanism of Bartoli’s indole synthesis.\textsuperscript{124}
Subsequently, deprotonation of nitroalkane $\text{279}$ with $^\text{nBuLi}$, followed by nitro-Mannich reaction with imine $\text{281}$ and lactamisation, gave $\text{278}$ in 51% yield (Scheme 90).

The use of an alternative dialkylzinc reagent, diisopropylzinc, was also investigated. The zinc reagent was synthesised from ZnBr$_2$ and $^1\text{PrMgCl}$, purified by distillation and used as a solution in hexane, after titration with I$_2$/LiCl.$^{125,126}$ Using imine $\text{281}$, the reaction worked well to give the expected pyrrolidinone $\text{282}$ in 51% yield (Scheme 91).

### 2.3.4 Superhydride$^\text{®}$ as a nucleophile

The 1,4-addition of Superhydride$^\text{®}$ to nitroalkenes and subsequent nitro-Mannich reaction has been reported.$^{36}$ Use of a hydride nucleophile to make pyrrolidinones would be useful, as the expected product $\text{283}$ would be unsubstituted in the C$_3$ position which opens up new possibilities for derivatisation, like for example enolate
alkylation (Scheme 92). Indeed the Superhydride® added to the nitroalkene in the predicted way, however no cyclisation product was observed. Heat should potentially energetically help the lactamisation to occur, though when the reaction was refluxed in THF after the nitro-Mannich reaction, only degradation products were isolated.

In all our investigations of 1,4-additions to nitroacrylate 231 (section 2.5.2), nucleophilic additions occurred 1,4 to the nitroalkene and not 1,4 to the acrylate. It was however desired to confirm that the hydride nucleophile adds 1,4 to the nitroalkene, so a deuteration experiment was performed. After 1,4-addition of Superhydride®, the mixture was quenched with AcOD, followed by aqueous workup. Indeed some deuteration (40%) was observed α to the nitro group (nitroester 284, Scheme 92) and no deuteration α to the ester group. It is possible though that the hydride added 1,4 to the acrylate and then a tautomerisation occurred that would give a nitronate (Route B), which on deuteration would give the same product 284 (Scheme 92). Therefore this experiment remains ambiguous, however we believe that this is not the reason of the failure to obtain pyrrolidinone 283. The percentage of deuteration was determined from the integration of the 1H NMR spectrum of the crude product.

From 1H NMR analysis of the crude reaction mixture it can be seen that the nitro-Mannich reaction is indeed occurring, but the initially formed β-nitroamine 285 does not cyclise. Based on the previous work on hydride conjugate addition/nitro-Mannich reactions (Scheme 77, section 2.1), it was assumed that the major product was anti-285 (Figure 11).36 It is surprising that cyclisation of β-nitroamine 285 does not occur even after heating, which could be explained by the rate of degradation of 285 by
retro-addition being faster than the rate of cyclisation. Heating (70 °C) has been used before to afford the cyclisation of similar β-nitroamines by Dixon and co-workers, who reported the synthesis of densely substituted pyrrolidinones 226 from nitroester 224 (Scheme 76, section 1.5).11

Compound 285, as well as diethylzinc adduct 286 (intermediate to pyrrolidinones 232), would react in the reactive conformations A and B, respectively. It is clear that conformation B has more steric hindrance around the ring because of the presence of the ethyl substituent. The Thorpe-Ingold effect states that increasing the substitution on a tetrahedral centre leads to enhancement of the intramolecular reactivity between parts of the remaining two substituents.127 Thereby, it is expected that conformation A of the less substituted nitroamine 285 would cyclise slower than conformation B of the more substituted 286.

![Conformations A and B](image)

**Figure 11**

**2.3.5 Tandem reaction**

A simplification to the tandem reaction would be to have the imine and nitroalkene in the same solution and add to this mixture diethylzinc, followed by TFA. In this reaction, it is desired for Et₂Zn to react preferentially with the nitroalkene and not the imine, something that is expected due to the more electrophilic nature of the nitroalkene. This tandem reaction was attempted for the synthesis of the parent pyrrolidinone 233. In this reaction, a solution of nitroalkene 231, imine 281 (2 equiv.) and Cu(OTf)₂ (5 mol %) in THF was cooled to -78 °C and Et₂Zn (1.1 equiv.) was added. After 10 min, the reaction was warmed to room temperature and when the nitroalkene was consumed (by TLC), TFA was added as usual and the same reaction conditions and workup were carried out according to the general procedure. The reaction gave the product 233 in 52% yield, as opposed to the originally obtained 67% yield with the one-pot sequential addition.
2.3.6 Relative stereochemistry

As previously described, the pyrrolidinones synthesised by the 1,4-addition/nitro-Mannich/lactamisation methodology described above were isolated mostly as single diastereoisomers, with the exception of pyrrolidinone 272 (85:15 dr). Previous work showed the relative stereochemistry of the pyrrolidinones in this reaction to be anti/anti in the ring structure of 269, using a combination of X-ray crystallography and ^1H NMR coupling constant data. The same stereochemistry also appeared in our work by the crystal structure of pyrrolidinone 269 (Figure 12) and later by that of trifluoroacetamide 287 derived from pyrrolidinone 241 (section 2.3.8).

![Figure 12. X-ray crystal structure of (±)-269](image)

As it was not possible to obtain X-ray crystal structures of all the analogues synthesised, the relative stereochemistry of the rest of the pyrrolidinones was assigned by comparison of their ^1H NMR coupling constants. In the 5-membered ring of 288 with a trans/trans relative stereochemistry it is expected that all substituents are in pseudo-equatorial positions (Figure 13). In previous work, couplings of 5.3-7.5 Hz were reported for J_HaHb (Figure 13) and 4.2-5.9 Hz for J_HbHc. In our analogues, couplings J_HaHb were found to be in the range of 4.6-8.0 Hz and couplings J_HbHc in the range of 3.4-6.3 Hz. Based on these results, it was assumed that the relative stereochemistry observed in the X-ray crystallographic data is also present in other analogues. A full table of coupling constants is presented in appendix 1.

Pyrrolidinone 272 is an exception as it was isolated as a mixture of two diastereoisomers, the major diastereoisomer having a J_HaHb of 2.4 Hz and a J_HbHc of 1.6 Hz as opposed to a J_HaHb of 7.4 Hz and a very small J_HbHc (≈ 0 Hz) for the minor diastereoisomer. In NOE studies of the major diastereoisomer, irradiation of the
\( \text{CHNO}_2 \) peak at \( \delta \) 4.94 ppm caused a 1.1% and 1.0% enhancement for the protons \( \text{CHN} \) and \( \text{CHCH}_2 \), respectively (Figure 13). Irradiation of the \( \text{CHNO}_2 \) peak of the minor diastereoisomer at \( \delta \) 5.33 ppm caused a 1.8% and 3.1% enhancement for the protons \( \text{CHN} \) and \( \text{CHCH}_2 \), respectively (Figure 13). The larger enhancement between the protons \( \text{CHCH}_2 \) and \( \text{CHNO}_2 \) indicates that those protons are closer in space in 272b than in 272a. Consequently, the major diastereoisomer is 272a bearing a trans/trans relative stereochemistry and the minor one cis/trans-272b. Furthermore, molecular modelling of these two structures using PCMODEL software, predicts for the trans/trans diastereoisomer the \( J_{\text{HabHb}} \) and \( J_{\text{HbHc}} \) values being 0.7 and 0.8 Hz respectively and for the cis/trans, 6.3 and 0.9 Hz. These values broadly agree with our experimental data. Deviation of up to 1.0 Hz in the calculated couplings constants is expected based on the error limit of the calculation. Moreover, contribution of other conformations to the experimental coupling constants, in particular the ring flipped conformation would also shift the observed value from the calculated one that corresponds to the lowest energy conformation only.

![Diagram](image_url)

**Figure 13**

### 2.3.7 Origin of diastereoselectivity

Previous work on the 1,4-addition of dialkylzinc reagents to nitroalkenes followed by a nitro-Mannich reaction has shown the syn/anti \( \beta \)-nitroamine to be the major product in homogenous solutions (section 2.1). Initial results of the reaction with nitroacrylate 231, where the reaction was quenched with aqueous \( \text{NaHCO}_3 \) after 5 min at rt and any uncyclised \( \beta \)-nitroamines were protected as trifluoroacetamides, showed that 4 products were isolated (Scheme 93). Those were the 1,4-addition product 289, pyrrolidinone 233 and the two trifluoroacetamides syn/anti-290 and syn/syn-290, with the syn/anti diastereoisomer being the major one. The two trifluoroacetamides were formed from TFA-protection of \( \beta \)-nitroamines syn/anti-286 and syn/syn-286. It was assumed that 289 originates from degradation of other \( \beta \)-nitroamine diastereoisomers of 286, as was previously observed during
trifluoroacetamide protection of other β-nitroamines of this type.\textsuperscript{35} The stereochemistry of 233 corresponds to the cyclisation of the major β-nitroamine diastereoisomer \textit{syn/anti-286}.

The stereochemistry of 233 corresponds to the cyclisation of the major β-nitroamine diastereoisomer \textit{syn/anti-286}.

\textbf{Scheme 93.} Initial studies of the nitro-Mannich reaction of nitroacrylate 231\textsuperscript{114}

Also in previous studies, the synthesis of 233 was repeated in \textit{d}\textsuperscript{8}-THF and analysed by \textit{1}H NMR in regular time intervals after warming the reaction mixture to ambient temperature.\textsuperscript{116} Initially only the \textit{syn/anti-286} and pyrrolidinone 233 were observed, with traces of other β-nitroamine diastereoisomers. The ratio of \textit{syn/anti-286} to 233 gradually decreased with time, suggesting that lactamisation is the slowest step in this sequence. It is known that the \textit{syn/anti-286} diastereoisomer is the kinetic product in conjugate additions of diethylzinc to nitroalkenes and subsequent nitro-Mannich reaction.\textsuperscript{35} It is also known that β-nitroamines are susceptible to retro- and re-addition.\textsuperscript{35} As any other isomers of pyrrolidinones 288 were rarely observed, it could be postulated that only \textit{syn/anti-286} cyclises to give the all equatorial product 233, presumably irreversibly. The transition state to the all equatorial product must be lower in energy than the transition state to other diastereoisomers. Other β-nitroamine diastereoisomers like the \textit{anti/anti} and \textit{syn/syn} have been isolated before in similar nitro-Mannich reactions, while an \textit{anti/syn} β-nitroamine was observed by \textit{1}H NMR but never isolated.\textsuperscript{114} These diastereoisomers have to equilibrate to \textit{syn/anti-286} before cyclisation (Scheme 94).

\textbf{Scheme 94.} Mechanism for the formation of 233 as a single diastereoisomer
This scenario is also supported by the results of Dixon and co-workers who reported the synthesis of densely substituted pyrrolidinones 226 from nitroester 224 (Scheme 95). In this work the authors suggested, based on some kinetic data, that the lactamisation step is also the rate determining in this related cascade reaction. However, a minor diastereoisomer of pyrrolidinones 226 is observed in many cases, something that is not surprising due to the harsher conditions (70 °C in toluene). The authors suggest that the origin of stereocontrol lies in the selective lactamisation of the diastereoisomer bearing all the substituents in pseudo-equatorial positions and not in the nitro-Mannich reaction which was reversible.

\[
\text{EtO} \quad \begin{array}{c}
\text{NO}_2 \\
224
\end{array} + R^1 \quad \begin{array}{c}
\text{\textit{O}} \\
\begin{array}{c}
\text{PhCOOH} \\
\text{PhMe, 70 °C, 4 h}
\end{array}
\end{array} + H_2N \quad \begin{array}{c}
\text{\textit{R}^2}
\end{array} \rightarrow \text{O} \quad \begin{array}{c}
\text{\textit{N}} \\
226
\text{\textit{R}^2}
\end{array}
\]

Scheme 95. Dixons’ synthesis of pyrrolidinones 226

2.3.8 Asymmetric methodology

The asymmetric 1,4-addition of diorganozinc reagents to nitroalkenes has been reported. In particular, the 1,4-addition of diethyl zinc to nitroalkene 291 has been reported to give up to 92% ee using a copper complex with a BINOL-based enantiopure phosphoramidite ligand as the catalyst. According to the authors, use of ligand 292 gave 1,4-addition product 293 of 77% ee while ligand 294 gave 92% (Scheme 96). Other ligands such as 69 have been used in asymmetric 1,4-addition reactions to other nitroalkenes (Scheme 33, section 1.2.2) and were also applied successfully in conjugate addition/nitro-Mannich reactions. However, we concentrated on phosphoramidite ligands as those were shown to be effective with nitroacrylates.

\[
\text{MeO} \quad \begin{array}{c}
\text{\textit{O}} \\
\text{\textit{NO}_2}
\end{array} \quad \text{EtZn (1.5 equiv.)} \quad \begin{array}{c}
\text{Cu(OTf)}_2 (2 \text{ mol}\%)
\text{Ligand (4 \text{ mol}\%)}
\end{array} \quad \text{MeO} \quad \begin{array}{c}
\text{\textit{O}} \\
\text{\textit{NO}_2}
\end{array}
\]

\[
\text{Me} \quad \begin{array}{c}
\text{\textit{O}} \\
\text{\textit{P}} \\
\text{\textit{N}} \\
\text{\textit{Ph}}
\end{array} \quad \text{Ph} \quad \text{Me} \quad \text{Me} \quad \text{Ph} \quad \text{Me}
\]

Scheme 96. The asymmetric conjugate addition of diethylzine to nitroacrylate 291
The asymmetric conjugate addition using ligand 292 and nitroacrylate 231, followed by a subsequent nitro-Mannich/cyclisation reaction with the imine 281, has been reported.\textsuperscript{119} This reaction gave the enantioenriched pyrrolidinone 233 in 52\% ee. In order to improve this result, the synthesis of ligand 294 and subsequent use as a catalyst for this reaction, was pursued. The synthesis was a 4 step procedure, starting from racemic BINOL (Scheme 97).\textsuperscript{130,131} In the last step of the synthesis, the authors separated the two diastereomers of the catalyst using chromatography. However, in our hands even after two chromatographic separations, it was only possible to obtain a sample of ligand 294 with 94\% de. Use of this ligand in the asymmetric conjugate addition on nitroacrylate 231 and subsequent nitro-Mannich reaction with imine 281 gave pyrrolidinone 233 in 73\% ee and 67\% yield. In light of this result, the synthesis of pure ligand 294 was carried out, starting from (S)-BINOL instead of racemic BINOL. The diastereomERICally pure ligand indeed gave an improved ee of 79\% and a yield of 72\%. During the HPLC resolution of pyrrolidinone 233, it was also observed that partial crystallisation from a solution of 233 in \emph{t}-PrOH led to an improved ee in the mother liquors. This indicates that the racemate of 233 is more crystalline than either of the single enantiomers, something that is common.\textsuperscript{132} As such, a recrystallisation of the product from \emph{t}-PrOH gave racemic crystals (18\% by mass) and a remainder solution of 99\% ee. Impressively, this meant that the enantiomerically pure pyrrolidinone 233 could now be isolated in 59\% yield overall and 99\% ee.

Scheme 97. Synthesis of phosphoramidite ligand 294

We were puzzled with the fact that a lower ee of pyrrolidinone 233 was obtained from our reaction than the one obtained by Sewald and co-workers for the 1,4-addition step. In particular, with ligand 292 the 1,4-addition step gave 77\% ee of 293 according to the literature,\textsuperscript{130} but only 52\% ee was obtained in our product 233.\textsuperscript{119} Similarly with ligand 294, from a reported 92\% ee of 293 in the 1,4-addition step, only 79\% ee of 233 was obtained in our one-pot reaction. It was postulated that this loss of enantioselectivity might be caused by the choice of nitroacrylate. Specifically we had been using the ethyl ester 231, whereas the literature work used the methyl
ester 291. It was assumed that the ethyl group is too far from the reaction centre to make a difference. Another possible reason could be that some degree of epimerisation at the C3 position of the final product 233 could be occurring under the acidic reaction conditions. To test the second hypothesis, an experiment was carried out, where a sample of pyrrolidinone 233 of 79% ee was subjected to the reaction conditions, in particular the presence of TFA overnight. However, no loss of enantioselectivity was observed, indicating that this was not the reason of the reduced ee.

To test the first hypothesis it was decided to synthesise two new nitroacrylates, 291 and 295 bearing a small and a large alkoxy-group, respectively (Scheme 98). Nitroacrylate 291 was made in a 3 step synthesis from glyoxylic acid. A condensation of glyoxylic acid with nitromethane gave 2-hydroxy-3-nitropropionic acid 296, followed by esterification with methanol to nitroalcohol 297 and dehydration to the desired nitroalkene 291 in a total yield of 50%. The synthesis of nitroacrylate 295 though was more challenging. Initially, a reported method was attempted to make nitroalcohol 298 starting from 4-butyl acrylate. However, this procedure in our hands, didn’t yield any of the desired product, probably because of the potential poor quality of reagent OsO₄ used (Scheme 98). In light of this, a different route to the nitroalkene 295 was then investigated, using the same procedure used before for the synthesis of nitroalkene 231. Surprisingly, when the reaction of 4-butyl acrylate with CAN and NaNO₂ was performed, no nitroalcohol 298 was observed in NMR. Instead the final nitroalkene 295 was detected, which was isolated in poor yield (10%).

![Scheme 98. Synthesis of nitroacrylates 291 and 295](image)

After the synthesis of the two new nitroalkenes, the one pot 1,4-addition/nitro-Mannich/lactamisation reactions with diethylzinc were attempted. As expected,
nitroalkene 291 reacted in a similar way to the ethyl ester 231 to give pyrrolidinone 233 in 66% yield. The reaction of nitroalkene 295 however was different; even though the 1,4-addition of diethylzinc occurred normally and some nitro-Mannich products were observed on $^1$H NMR, lactamisation did not occur and no pyrrolidinone 233 was isolated. Instead, only the uncyclised nitro-Mannich product was obtained. Heating the reaction mixture to reflux only led to degradation. In a separate experiment, the uncyclised nitro-Mannich products were isolated after protection as trifluoroacetamides 299 in 26% yield as a mixture of two diastereoisomers in 65:35 $dr$ (Scheme 99). The major diastereoisomer had a $J_{HaHb}$ value of 4.0 Hz and a $J_{HbHc}$ of 10.2 Hz, whereas the minor one had $J_{HaHb}$ value of 2.2 Hz and a $J_{HbHc}$ of 11.6 Hz. Comparison with the coupling constants previously reported for trifluoroacetamide 290 ($J_{HaHb} = 3.6$ Hz, $J_{HbHc} = 10.6$ Hz)\textsuperscript{114} showed that they were in agreement with the values of our major diastereoisomer. We can therefore tentatively conclude that our major diastereoisomer is syn/anti-299 and our minor one is syn/syn-299 (Scheme 99).

Scheme 99. Nitro-Mannich reaction of nitroacrylate 296

An asymmetric reaction of nitroalkene 291 was attempted using the same ligand 294 as before. The reaction was indeed better than that of nitroalkene 231, giving 89% $ee$ and 80% yield. This is very close to the reported value of 92% $ee$ for the asymmetric 1,4-addition of diethylzinc on the same substrate (Scheme 100).

Scheme 100. Asymmetric synthesis of 233
Lack of knowledge of the absolute stereochemistry of the 1,4-addition, prompted us to seek proof of the stereochemistry using X-ray crystallography. In order to accomplish this, it was necessary to synthesise pyrrolidinone 241 containing the heavy atom sulfur, in an asymmetric manner. Indeed, the desired pyrrolidinone was made in 89% ee, suggesting that the enantioselectivity remains independent of the imine used in the reaction. However, no suitable crystals could be obtained from 241. It was thought that the conversion of this pyrrolidinone to trifluoroacetamide 287, via reduction of the nitro functionality and TFA-protection, would make the compound more crystalline. This was achieved in good yields and without significant loss of ee and the final product could be recrystallised to 99% ee (Scheme 101).

Scheme 101. Asymmetric synthesis of 241 and conversion to trifluoroacetamide 287

Fortunately it was possible to obtain a crystal structure of trifluoroacetamide 287 and to determine its absolute stereochemistry (Figure 14), which was found to be (R,R,R). This requires that the asymmetric 1,4-addition step gives nitronate 300 with the chiral centre in the R configuration.

Figure 14. X-ray crystal structure of 287
2.3.9 Further functionalisation of the parent pyrrolidinone

2.3.9.1 Nef reaction

One of the targets of this project was to perform some functional group interconversions on the pyrrolidinone structure 233, something that will illustrate its usefulness as a synthetic scaffold.

One reaction that proved to be problematic in previous studies is the Nef reaction.\textsuperscript{119} Various methods of performing the Nef reaction exist in the literature, including the typical base/acid reaction,\textsuperscript{137} reductive methods,\textsuperscript{76} oxidative methods\textsuperscript{138,139} and others\textsuperscript{140} (section 1.3.2). The reaction that was performed previously in our system used CrCl\textsubscript{2} and gave a poor yield of the product 243a and its tautomer 243b (Scheme 102).\textsuperscript{140}

![Scheme 102. The Nef reaction of 233](image)

Many other methods were attempted in order to improve this result, but were unsuccessful. Treatment of pyrrolidinone 233 with a phosphate buffer at pH=13 in MeOH/H\textsubscript{2}O and oxone (1.00 equiv.), followed by a quench of aqueous 3 M HCl, gave decomposition.\textsuperscript{138} A similar result was obtained by a biphasic reaction with aqueous NaOH, DCM and Bu\textsubscript{4}N\textsuperscript{+}HSO\textsubscript{4}\textsuperscript{−} followed by addition of NaClO\textsubscript{2} (1.50 equiv.),\textsuperscript{139} as well as reaction with CAN (1.00 equiv.) and Et\textsubscript{3}N (7.00 equiv.) in MeCN/H\textsubscript{2}O at 60 \textdegree C.\textsuperscript{141} Reaction with NaHCO\textsubscript{3} in DCM/H\textsubscript{2}O/dioxane at 70\textdegree C,\textsuperscript{142} gave recovery of the starting material, as did reaction with DIPEA (2.00 equiv.) followed by H\textsubscript{2}SO\textsubscript{4} (10.0 equiv.). The same result was also obtained by reaction with LDA (1.05 equiv.), followed by H\textsubscript{2}SO\textsubscript{4} (10.0 equiv.) and reaction with DBU (5.00 equiv.) in MeCN at 60 \textdegree C,\textsuperscript{143} even though the later was reported to work well with secondary nitroalkenes. Simple treatment with NaOH (2.00 equiv.) in THF/H\textsubscript{2}O followed by H\textsubscript{2}SO\textsubscript{4} (10.0 equiv.) gave decomposition, while by using HCl 2 M (5.00 equiv.) instead, some starting material was also recovered. Reaction with \textsuperscript{t}BuONa (1.50 equiv.) led to decomposition. Treatment with Lewis acids such as SnCl\textsubscript{4} (2.00 equiv.) in DCM and
TiCl$_4$ (4.00 equiv.) at rt, followed by aqueous workup, led to recovery of the starting material. Reaction with NaNO$_2$ (15.0 equiv.) and AcOH (50.0 equiv.) in DMSO at room temperature,$^{144}$ gave decomposition as did reaction with TiCl$_3$ (4.00 equiv.) in THF.$^{76}$ When the TiCl$_3$ reaction was attempted in the presence of a buffered solution at pH=5, only recovered starting material was isolated.

Previous studies of the alkylations of pyrrolidinone 233 have shown an unexpected reactivity with bases.$^{119}$ Therefore, it was thought that a deuteration experiment might shed some light as to which protons on pyrrolidinone 233 are more acidic. Treatment with LDA (1.05 equiv.) at -78°C followed by addition of CD$_3$COOD (35 equiv.) and aqueous workup led to 14% deuteration at the 4 position only (Figure 15). This percentage was rather low and could be attributed to D/H exchange in the workup. Treatment with only CD$_3$COOD (150 equiv.) in CDCl$_3$, in an NMR tube gave no D-exchange even after two days and treatment with tBuONa (1.0 equiv.) and then CD$_3$COOD (35 equiv.) gave decomposition of the starting material. Finally, treatment with NaH (1.10 equiv.) in THF, followed by addition of CD$_3$COOD (7.1 equiv.) and no aqueous workup, gave 47% deuteration at the 4 position as well as 16% at the 5 and 22% at the 3 position (Figure 15). This indicates that, even though the acidity of the proton $\alpha$ to the nitro group is greater than the others, deprotonation still occurs on other positions when the pyrrolidinone is treated with base.

Due to the problems associated with attempted Nef reactions on pyrrolidinone 233, it was decided to study the reactivity of its reduction product, pyrrolidine 247, in the same reactions to give the ketone 301. Pyrrolidine 247 was obtained from a borane reduction of 233 (Scheme 81, section 2.1),$^{116}$ and lacking a carbonyl in the C$^2$ position might be less prone to degradation. Many methods were attempted for this modification, but the reactions were unsuccessful (Table 5).
### Table 5. Attempts of a Nef reaction of pyrrolidine 247

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents/Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EtONa (2 equiv.), EtOH, then H$_2$SO$_4$</td>
<td>Recovered sm</td>
</tr>
<tr>
<td>2</td>
<td>CrCl$_2$, MeOH/EtOAc, reflux</td>
<td>Degradation</td>
</tr>
<tr>
<td>3</td>
<td>TiCl$_3$, pH = 5 buffer, THF/H$_2$O, rt</td>
<td>Recovered sm</td>
</tr>
<tr>
<td>4</td>
<td>CAN, MeCN/H$_2$O, Et$_3$N, 60 °C</td>
<td>Recovered sm</td>
</tr>
<tr>
<td>5</td>
<td>DBU (2 equiv.), MeCN, rt, 13 days</td>
<td>Degradation</td>
</tr>
<tr>
<td>6</td>
<td>DBU (2 equiv.), MeCN, 60 °C, 3 days</td>
<td>Recovered sm</td>
</tr>
</tbody>
</table>

Moreover, it has been shown that nitro groups $\gamma$ to a carbonyl can eliminate HNO$_2$ on treatment with base to give an enone.$^{78}$ However, treatment with both DBU (5.00 equiv.) in MeCN at reflux and Et$_3$N (10.0 equiv.) in toluene at reflux, led to decomposition without any sign of the enone by NMR, while the use of fewer equivalents of amine and lower temperatures gave no reaction.

#### 2.3.9.2 Reactions of pyrrolidinone 233 with electrophiles

Further functionalisation of pyrrolidinone 233 $\alpha$ to the nitro group by reaction with electrophiles was pursued. Deprotonation at the C$^4$ position followed by Michael addition to ethyl acrylate was first attempted. When 233 reacted with DBU (1.50 equiv.) and ethyl acrylate (1.50 equiv.) in MeCN at room temperature,$^{145}$ the 1,4-addition product 302 was not isolated, but the unexpected elimination product 303 was obtained in 50% yield instead (Scheme 103). The unexpected 1$H$-pyrrol-2(5$H$)-one 303 was a crystalline solid and its structure was determined by X-ray crystallography (Scheme 103).
A tentative mechanism for the synthesis of this product is presented in Scheme 104. Presuming that a Michael addition first occurs to afford the expected product 302 that in the presence of base eliminates HNO$_2$ to give enone 304. DBU has been shown to affect ionic denitrations on nitroalkanes by elimination of HNO$_2$ (Scheme 56, section 1.3.3). Finally, an unexpected oxidation occurs at the C$^5$ position of 304, presumably from molecular oxygen, to give product 303. To our knowledge only one example of such an oxidation has been reported by Chauncey and Ninomiya. The authors observed product 305 whilst studying the biomimetic oxidation of nicotine (306) using metalloporphyrin catalysts and iodosobenzene as the oxidant (Scheme 104).

The similar reaction of pyrrolidinone 233 with DIPEA (2.00 equiv.) and ethyl acrylate (up to 10.0 equiv.) gave no product, while treatment with LDA (1.05 equiv.) in THF
at -78°C, followed by addition of ethyl acrylate (1.50-10.0 equiv.), gave a complex product mixture. Furthermore, reaction of 233 with LDA (1.20 equiv.) and the more electrophilic acrolein (5.00 equiv.) also gave a complicated reaction mixture.

It was also attempted to react pyrrolidine 247 with ethyl acrylate, hoping that the absence of a carbonyl in the molecule would make the addition product more stable. Deprotonation with NaH (1.10 equiv.), followed by reaction with ethyl acrylate (2.00 equiv.) in THF at rt, was slow. The starting material was consumed after 19 h and what appeared to be pyrrolidine 307 by 1H NMR was isolated in a crude form (Scheme 105). However, the product was found to be unstable to chromatography and to storage even at -5 °C. Among the degradation products was the starting pyrrolidine 247. In light of this instability, it was attempted to reduce the nitro group after the reaction and avoid isolating the unstable product 307. This unfortunately gave only a complicated mixture of degradation products and none of the expected 308 and 309.

Finally, it was attempted to methylate the C4 position of pyrrolidinone 233. First the pyrrolidinone was reacted with MeI (4.00 equiv.) and K2CO3 (4.00 equiv.) in acetone at reflux, however this led to decomposition of the starting material. Treatment of the pyrrolidinone with LDA (1.20 equiv.) in THF at -78 °C, followed by addition of MeI (3.50 equiv.) and stirring at room temperature, gave a mixture of products with only one being less polar that the starting material. The structure deduced from the spectroscopic analysis was that of compound 310 (Scheme 106), isolated in 21% yield. A possible mechanism for its formation involves first elimination of HNO2 and then methylation by MeI at the C3 position, to give product 310.
2.3.9.3 Denitration

A useful modification of pyrrolidinone 233 would be the complete removal of the nitro group (denitration). Such denitrations have been reported to occur via a radical method using Bu₃SnH and an initiator.⁷⁷ Heating a solution of 233 at 80°C in dry degassed toluene with Bu₃SnH (5.00 equiv.) and AIBN (1.00 equiv.), led to incomplete consumption of the starting material in 24 h. Use of ABCN as an initiator,¹⁴⁷ led to a faster reaction and a complete consumption of the starting material in 24 h, however it gave a complicated product mixture with very small amounts of possible denitrated product observed by ¹H NMR. There is some indication based on ¹H NMR for the presence of an oxime in the product mixture, however this has not been confirmed due to instability of the products. Consequently, another lengthier route to product 311 was investigated (Scheme 107). This route proved to be successful and most steps were high yielding. Moreover, it allowed to gain access to formamide 312 and isocyanide 313, which could be useful for the synthesis of other derivatives.

![Scheme 107. Four-step denitration sequence](image)

As isocyanides are versatile precursors to other functional groups, it was decided to investigate these. Use of bromine in methanol has been shown to give carbamates from isocyanides,¹⁴⁸ however simple stirring of 313 with Br₂/MeOH at rt gave dibromide 314 in 65% yield. These dibromides are the suspected intermediates to this transformation, so the formation of 314 is not unexpected. Refluxing the reaction mixture for 15 h gave the desired carbamate 315 in 42% yield (Scheme 108).
2.3.9.4 Modification of the C5 substituent, acetal hydrolysis

The synthesis of aldehyde 316 would be very useful as that would open the road to new functionalisations of the pyrrolidinone scaffold, which could lead to the synthesis of interesting molecules. After the successful synthesis of pyrrolidinone 276 it was attempted to hydrolyse the acetal group to obtain aldehyde 316. A number of methods were attempted, however so far it has not been possible to isolate 316 (Table 6).

Table 6. Attempts of acetal hydrolysis of 276

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents/Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Amberlyst-15, Acetone/H2O, rt and reflux(^{149})</td>
<td>Recovered sm</td>
</tr>
<tr>
<td>2</td>
<td>Acetone, HCl 2M (10.0 equiv.), rt</td>
<td>Recovered sm</td>
</tr>
<tr>
<td>3</td>
<td>DCM/ H2O, p-TSA, rt and reflux(^{150})</td>
<td>Recovered sm</td>
</tr>
<tr>
<td>4</td>
<td>MeOH, H2SO4 1M (2.50 equiv.), rt and reflux</td>
<td>Recovered sm</td>
</tr>
<tr>
<td>5</td>
<td>THF, H2SO4 1M (5.00 equiv.), reflux</td>
<td>Recovered sm</td>
</tr>
<tr>
<td>6</td>
<td>THF, H2SO4 2M (10.0 equiv.), reflux, 3 days</td>
<td>Recovered sm</td>
</tr>
<tr>
<td>7</td>
<td>DMSO, H2SO4 2M (10.0 equiv.), reflux</td>
<td>Degradation, trace of aldehyde</td>
</tr>
<tr>
<td>8</td>
<td>TiCl4, LiI, Et2O, rt</td>
<td>Rec. sm, trace of aldehyde</td>
</tr>
<tr>
<td>9</td>
<td>FeCl3/SiO2, CHCl3, rt(^{151})</td>
<td>Recovered sm</td>
</tr>
<tr>
<td>10</td>
<td>FeCl3/SiO2, CHCl3, formaldehyde, reflux(^{152})</td>
<td>Recovered sm</td>
</tr>
<tr>
<td>11</td>
<td>HCO2H neat</td>
<td>Recovered sm</td>
</tr>
</tbody>
</table>
The results show that acetal 276 was very inert to deprotection and when harsher conditions were used degradation occurred. A possible explanation for this seems to lie on the structure of 276. The presence of the nitro group β to the acetal in an anti-parallel arrangement should make it prone to elimination at strongly acidic conditions. Possible protonation of the nitro group might lead to the elimination shown in Scheme 109, giving enamine 317 that can then hydrolyse to aldehyde 318, which could degrade further.

Scheme 109. Degradation of acetal 276

In light of this poor result, a different way to access the desirable aldehyde 316 was sought. The Dondoni reaction is a known method to transform a thiazole group to an aldehyde group and has found various applications in synthesis. Since thiazole substituted pyrrolidinone 273 was previously synthesised, we investigated whether this could be a possible precursor to aldehyde 316. However, when thiazole 273 was subjected to the reaction conditions (Scheme 110), only a trace of aldehyde 316 (<10%) was seen in $^1$H NMR spectroscopy.

Scheme 110. Attempt of a Dondoni reaction

2.3.9.5 Modification of the C$^5$ substituent, synthesis of proline analogue 319.

A desirable modification would be to have a carboxylic acid substituent at the C$^5$ position of pyrrolidinone 232, as that will effectively be an analogue of proline, which would increase the potential for biological activity. Firstly, the oxidation of an
aromatic substituent at C⁵ to a carboxylic acid was studied. The oxidation of aromatic groups to carboxylic acids has been reported by Sharpless and co-workers.¹⁵⁶ The procedure uses a catalytic amount of RuCl₃ which forms the active oxidant RuO₄ in the presence of HIO₄ as the stoichiometric oxidant, in a biphasic solvent system (CCl₄/MeCN/H₂O).¹⁵⁷ However the reaction was not successful for pyrrolidinone 233 and led to decomposition. In another publication, Plietker showed that a furan group could be oxidized to a carboxylic acid using RuCl₃ and oxone, which was for them an unwanted side reaction in the ketohydroxylation of alkenes.¹⁵⁸ The same reaction conditions were used with the furan pyrrolidinone 240 (Scheme 111) but were ineffective, leading to recovery of the starting material.

Scheme 111. Synthesis of carboxylic acid 319 by oxidation of the C⁵ substituent

In light of this poor result, it was decided to look at obtaining carboxylic acid 319 from a simpler source, ester 242. Indeed, hydrolysis of this ester was successful in non basic conditions, using either the mild reagent Me₃SnOH¹⁵⁹ or simply refluxing in HCl/Acetone (Scheme 112).

Scheme 112. Synthesis of carboxylic acid 319 by ester hydrolysis of 242

Having synthesised carboxylic acid 319, we looked at the possibility of decarboxylation that would give access to new derivatives. We first looked at simply heating, to induce loss of CO₂. Whereas reflux in toluene gave recovered starting material, reflux with xylene at 140 °C led to degradation. The Hunsdiecker reaction was also investigated. In this reaction, a carboxylate salt 320 with a soft metal (Hg, Ag) is first formed and subsequent reaction with iodine gives iodide 321 bearing an O-I bond.¹⁶⁰ Under the influence of light or heat this decomposes to release CO₂ and
give radical 322, which then reacts with a radical iodide to give iodide 323 (Scheme 113). Two sets of conditions were tested, treatment with Pd(OAc)$_4$ and I$_2$ in CCl$_4$ under UV light,$^{160}$ and treatment with HgO and I$_2$ in Toluene, at reflux,$^{161}$ both with no success (Scheme 113).

![Scheme 113. Mechanism of the Hunsdiecker reaction](image)

Moreover, it was attempted to form the Barton ester of acid 324 and then affect a radical decarboxylation. Efforts to synthesise this ester either by formation of acid chloride 325 and then reaction with 2-mercaptopyridine N-oxide,$^{162}$ or by coupling with DCC or EDC in the presence of DMAP, failed to give the desired ester 324 (Scheme 114).

![Scheme 114. Attempts to synthesise Barton ester 324](image)

### 2.3.10 Conclusions

This chapter described further developments in the 1,4-addition/nitro-Mannich/lactamisation reaction sequence from nitroacrylate 231. Using the developed reaction conditions, the synthesis of 10 new analogues of pyrrolidinones 232, was accomplished (Scheme 115). The limitations of this methodology, in reactions with
heterocyclic and alkyl PMP-protected imines were investigated, as well as with the use of alternative dialkylzinc reagents Ph$_2$Zn and iPr$_2$Zn.

**Scheme 115. Synthesis of pyrrolidinones 232**

Furthermore, an enantioselective variant of this reaction was successfully developed, by utilising the reported method for asymmetric conjugate addition of dialkylzinc reagents to nitroalkenes as part of our one pot procedure. By synthesising phosphoramidite ligand 294 and using it as our chiral catalyst, a good enantioselectivity for pyrrolidinones 233 and 241 (89% ee, 99% ee after recrystallisation, Figure 16) was obtained. Furthermore, an X-ray crystal structure of 287 was successfully obtained, that showed us the absolute stereochemistry of pyrrolidinone 241 and therefore of the initial 1,4-addition product 300.

**Figure 16**

Finally, some functionalisations of selected pyrrolidinones were investigated. It has been possible to obtain isocyanate 313, deamination product 311 and proline analogue 319 (Figure 17), interconversions that prove the usability of the pyrrolidinone structure produced as a building block for the synthesis of useful molecules. Moreover, some unexpected products such as 310 and 303 were isolated (Figure 17), providing some knowledge on the reactivity of pyrrolidinones 232 and their tolerance to a variety of conditions and reagents.
2.3.11 Future work

The synthesis of pyrrolidinones 232 in an efficient one pot 3-step cascade was demonstrated. The pyrrolidinones produced were densely functionalised and diastereomically pure. Furthermore, a number of possible functional group interconversions in the pyrrolidinone core have been successful. This opens up the way for using our methodology in the synthesis of more complex molecules. A few molecules bearing the same stereochemistry around the pyrrolidine core have been identified. These include proteasome inhibitor 195, the dietary supplement pyroglutamic acid 193, nicotine metabolite cotinine 194 and the experimental human neutrophil elastase inhibitor 326 (Figure 18). The work towards the synthesis of 326 is presented in the following chapter 2.5.

Moreover, up to the present time the 1,4-addition/nitro-Mannich methodology has been limited to the use of dialkylzinc and hydride reagents in doing the conjugate addition step. However, a number of heteroatom nucleophiles are known to add to nitro-alkenes. Successfully using a non-zinc nucleophile and especially a heteroatom as part of our methodology, would greatly increase its versatility and applications in the synthesis of useful molecules. The reactions of nitroacrylate 231 and β-nitrostyrene with a variety of carbon, oxygen, nitrogen, sulphur and phosphorus nucleophiles, have been investigated and are presented in chapter 2.5.
2.4 Towards the synthesis of a human neutrophil elastase inhibitor (GW311616A)

2.4.1 Precedence and methodology

An important target of this project was to use the developed methodology to access a useful molecule, natural product or pharmaceutical. One such molecule is the human neutrophil elastase inhibitor 326. This pharmaceutical, was found to be active for the treatment of chronic bronchitis and is currently made from the precursor 327 (Scheme 116).\(^{165}\)

Research in GlaxoWellcome on identifying serine protease inhibitors, has discovered that 5,5-\textit{trans}-fused systems showed inhibitory activity. The systems studied were pyrrolidine-\textit{trans}-lactones\(^{166}\) and pyrrolidine-\textit{trans}-lactams,\(^{167}\) found to be active for several proteases such as chymotrypsin, thrombin, cathepsin G, trypsin, and human neutrophil elastase (HNE). The later, HNE is thought to be involved in respiratory diseases such as asthma and chronic bronchitis. Lactam 326 was found to have improved activity and bioavailability compared to previous studies.\(^{164}\)

This compound has been synthesised in an overall chemical yield of 1.3% in a 14 step synthesis.\(^{164}\) The authors first attempted a racemic synthesis, where key intermediate 328 could be accessed by synthesising first the disubstituted pyrrolidine ring and then using acyliminium chemistry to introduce the isopropyl group in a diastereoselective manner. The synthesis started from commercially available 2,4-diaminobutyric acid 329 that gave pyrrolidine 330 in five steps with 59% overall yield (Scheme 116). Pyrrolidine 330 could then lead to acyliminium cation 331 after treatment with a Lewis acid. Subsequent reaction with commercially available acetal 332 gave pyrrolidine 328, which in two more steps afforded the desirable 327 in 20% yield. The racemic synthesis had an overall yield of 12% over eight steps.

Two asymmetric syntheses were also developed starting from commercial \textit{R}-asparagine or \textit{R}-methionine. Enantiomerically pure 326, was synthesised in 7% overall yield from \textit{R}-asparagine in nine steps, while a yield of 5% over nine steps was obtained from \textit{R}-methionine (Scheme 116).
Pyrrolidinone 326 can easily be formed from precursor 333, which has an anti/anti stereochemistry around the pyrrolidinone ring. Assuming that the amine nitrogen is derived from reduction of the nitro group, then pyrrolidinone 334 can be a suitable precursor to 333. The pyrrolidine and pyrrolidinone rings are however trans-fused, something that would make it difficult to synthesise compound 333 starting from a pyrrolidinone like 334 (Scheme 117). Very few methods for making trans-fused octahydropentalenes exist, due to the ring strain in this system. Nonetheless, it was felt that we could overcome these problems by either of the two synthetic strategies described below.

Scheme 116. Synthesis of GW311616A (326)

The first synthetic strategy to synthesise the desired bicyclic pyrrolidinone 333, involved accessing protected aldehyde 335 through the nitro-Mannich methodology described in section 2.3. Phosphorane imine 336, could then be formed from the nitro group after a reduction and subsequent reaction with DEAD and Ph3P. Subsequent release of aldehyde 337 and aza-Wittig reaction should yield the desired compound 333 (Scheme 118). Intramolecular aza-Wittig reactions have previously been used to make strained five-membered rings. Moreover, Taylor and co-workers have reported Tandem oxidation processes to perform the oxidation of an alcohol and
subsequent Wittig reaction in one pot. Hence this could avoid the need to isolate aldehyde and make alcohol, derived from protected alcohol, also a good starting material for the aza-Wittig reaction (Scheme 118).

Scheme 118. Two possible routes to pyrrolidinone

Alternatively, the most obvious way to make pyrrolidinone, would be the simple intramolecular nucleophilic addition or substitution reaction of the free amine, derived from the nitro group, onto a carbon bearing a suitable leaving group (340) or a suitable electrophile on the C substituent (341). This could be either a tosylate, mesylate or simply an aldehyde (Figure 19). Moreover, an alkene like 342 could be used to perform a haloamination (after first reducing the nitro group) and the halogen subsequently removed with radical dehalogenation.

Figure 19. Possible precursors to 333

2.4.2 Investigation of the synthesis

Diisopropylzinc has already been shown to be successful in the synthesis of pyrrolidinone (Scheme 91, section 2.3.3). More intriguing would be the selection of a suitable imine that would give a useful functionality at the C position of our pyrrolidinone scaffold.

Initially, the synthesis of pyrrolidinones and was investigated, as those would be useful starting points for our investigation (Scheme 119). The imine required for
the synthesis of pyrrolidinone 343 exists only in the enamine form 345. Even though it is known that enamines do not react directly in the nitro-Mannich reaction, in this particular example, the α position to the nitrogen should still be electrophilic due to conjugation with the ester function. Unfortunately, nitro-Mannich experiments revealed that no isolation of any pyrrolidinone product from this reaction, which gave a complicated mixture of products.

Synthesis of pyrrolidinone 344 requires access to imine 346. The required aldehyde 347 was not commercially available though, so it was attempted to synthesise aldehyde 347 from a DIBAL reduction of commercially available ester 348 (Scheme 119). The DIBAL reduction gave a mixture of aldehydes 347 and 349. Disappointingly though, when the mixture of the two aldehydes was reacted with para-anisidine, the only product isolated from the reaction was imine 350. Nitro-Mannich reaction of imine 350 gave a complicated mixture of products (Scheme 119).

Scheme 119. Attempts to synthesise pyrrolidinones 343 and 344

In view of this failure to synthesise pyrrolidinones 343 and 344, a different route to aldehyde 341 via the protected alcohol 351 was investigated. To access the necessary imine 352, aldehyde 353 was synthesised in two steps from 1,3-propanediol (Scheme 120). It was however not possible to isolate imine 352, when 341 reacted with para-anisidine, in DCM, both with MgSO₄ at rt and with Al₂O₃ at -78 °C. Nevertheless, it was attempted to synthesise pyrrolidinone 355, by in situ forming imine 352 at -78 °C and maintaining the cold temperature while the solution of imine was transferred into the solution of the nitronate, derived from 231 and diethylzinc. With this method it was possible to isolate pyrrolidinone 355 in 25% yield. Disappointingly though, none of pyrrolidinone 351 was isolated from the reaction with diisopropylzinc. The instability of imine 352 and its poor reactivity as seen...
before for alkyl imines (section 2.3.2) is tentatively caused by its isomerisation to an
enamine that would not be reactive in the nitro-Mannich reaction and could
polymerise.

\[
\begin{align*}
\text{HO} & \xrightarrow{\text{NaH, BnBr, THF}} \text{HO} & \xrightarrow{\text{Bn, PCC, DCM}} \text{O} & \xrightarrow{\text{Bn, MgSO}_4} \text{O} & \xrightarrow{\text{p-anisidine}} \text{O} & \xrightarrow{\text{PMP, N}} & \text{O} & \xrightarrow{\text{Bn}} \\
\text{354, 29\%} & \text{353, 68\%} & \text{352} & \text{351} & \text{341} & \text{333} & \text{355, 25\% OBn} \\
\end{align*}
\]

**Scheme 120.** Use of imine 352 in the synthesis of pyrrolidinones

Some unsaturated imines were then examined as a way towards pyrrolidinones 341
and 342. Imine 356 was easy to synthesise (MgSO\(_4\), DCM, 0 °C, 1 h), but
unfortunately the nitro-Mannich reaction gave none of the desired pyrrolidinone 357
(Scheme 121). Instead, only 1,4-addition product, unreacted imine and degradation
products were isolated, presumably due to side reactions such as polymerisation.

On the other hand, imine 358 (derived from acrolein) could not be isolated. When
acrolein reacted with para-anisidine, in DCM, both with Al\(_2\)O\(_3\) at rt and with Al\(_2\)O\(_3\) at
-78 °C, only degradation products were observed using \(^1\)H NMR. Nevertheless, it was
possible that some of the imine is produced at -78 °C and degrades at higher
temperatures and/or workup (as seen above with imine 352). It was therefore
attempted to make pyrrolidinone 342 by synthesizing imine 358 in situ at -78 °C
(THF, molecular sieves) and transfer the solution of imine into the reaction mixture
while maintaining the cold temperature. This again was not successful.
Moreover, it was envisaged that protection of the double bond of acrolein or its conversion to a less reactive functionality, might facilitate the synthesis of a useful pyrrolidinone precursor. The reaction of acrolein with bromine was investigated. Acrolein reacted fast with 1.1 equiv. of bromine to give dibromide quantitatively. Unfortunately, the in situ formation of imine and nitro-Mannich reaction gave none of pyrrolidinone (Scheme 122).

Even though it would be preferable for the C\textsubscript{5} substituent on pyrrolidinone scaffold to be two-carbon atoms long, it was not possible to isolate any such pyrrolidinone in reasonable quantities. In light of that, the use of single carbon substituents was investigated, with the aim of extending the carbon chain by one carbon before cyclisation. Pyrrolidinones bearing a one-carbon C\textsubscript{5} substituent have been synthesised successfully before (section 2.3.2). The synthesis of pyrrolidinone using acetal imine was initially investigated (Scheme 123). The acetal protected pyrrolidinone was made successfully in 70\% yield.
However, to do any useful chemistry with pyrrolidinone 361, it was required to deprotect the acetal group to the free aldehyde. A similar deprotection was attempted before with pyrrolidinone 276 and was unsuccessful (section 2.3.9.4), so 361 was expected to also be hard to deprotect. In knowledge of this, a different deprotection route was investigated this time. First the PMP protecting group was removed to give 362 and then the nitro group was reduced and protected as a trifluoroacetamide, to give pyrrolidinone 363 in good yield (Scheme 124). It was then attempted to deprotect the acetal group in pyrrolidinone 363 by standard methods. Reaction with HCl/Acetone/reflux gave only a complicated mixture of products in which only traces of starting material were identified, as did reaction with TMSI (Scheme 124). This was similar to problems encountered earlier with a similar deprotection (section 2.3.9.4) and could be attributed to the trifluoroacetamide group being a good leaving group like the nitro group.

Scheme 124. Attempts of acetal hydrolysis

In light of these results, it was decided to avoid synthesising aldehyde 364 altogether and synthesise instead a protected primary alcohol 365, that could also potentially be chain extended to aldehyde 341 (Scheme 125). The synthesis of two such pyrrolidinones, 366 and 367 was investigated. Not surprisingly, the corresponding imines 368 and 369 were found to be unstable at room temperature, so were prepared at -78 °C and used in situ. The two pyrrolidinones 366 and 367 were isolated successfully, albeit in low yields, 13% and 31% respectively (Scheme 125).
In light of the low yields of compounds 366 and 367 (too low to be the first step in a linear synthesis), another route to pyrrolidinones of this type was investigated. This route involved the use of nitroalkene 370 as the starting material, instead of nitroacrylate 231 and use of a hydride nucleophile (Superhydride®) instead of diisopropylzinc. Nitroalkene 370 was synthesised from ketoester 371 in 29% yield over two steps (Scheme 126). To test if this was a better alternative to our current method it was first attempted to synthesise pyrrolidinone 282 and compare the results. Unfortunately, the yield of product 282 was lower than with the previous method (section 2.3.3) and the reaction slower, therefore this route was abandoned.

Finally, the synthesis of aldehyde 372 was investigated, starting from ester 373, which would require a selective reduction of the ester (Scheme 127). It is known that esters are easier to reduce than amides, as some reducing agents like borohydride salts have been reported to reduce ester groups, but do not reduce amides. However, pyrrolidinone 373 bears a lactam and an exocyclic ester group, which might reduce this difference in reactivity. Esters could be reduced to the corresponding alcohols using NaBH₄ in a refluxing methanol-THF mixture, while these conditions were
shown to be tolerant to the presence of a nitro group. Moreover, the reduction of esters to aldehydes using 1.00 equiv. of DIBAL has been reported, and has been widely used in synthesis, so it was felt that it could provide a selective reducing agent in our case too.

Ester 373 was successfully synthesised in 58% yield from imine 24. However, due to the high cost of diisopropylzinc compared to diethylzinc it was decided to perform reduction studies on the similar ethyl analogue 242, which was reported earlier.

![Scheme 127. Synthesis of ester 373](image)

Initially, reaction of ester 242 with DIBAL at -78 °C was attempted. When 1.00 equiv. of the reagent was used only starting material was observed after 1 h at -78 °C, as well as after warming to 0 °C. Using 2.00 equiv. of the reagent at -78 °C led to a complex mixture of products, from which only a small quantity of the starting material was observed. The reaction with sodium borohydride was then investigated. Refluxing a solution of ester 242 with NaBH₄ in MeOH/THF for 12 h, led to complete consumption of the starting material, however TLC and ^1^H-NMR analysis showed a complex mixture of products.

In light of the poor results in the selective reduction of ester 242, it was attempted to first hydrolyse to acid 319 (Scheme 112, section 2.3.9.5) and then investigate the selective reduction of the carboxylic acid group. The reduction of a carboxylic acid to an alcohol in mild conditions using BH₃·SMe₂ in THF, at rt has been reported, and was found to be tolerant of the presence of a nitro group. Moreover, it is known from previous work that BH₃·THF in refluxing THF is needed to reduce the amide of pyrrolidinone 233 to amine 247, which suggests that the acid group is more reactive than the lactam group towards reduction with this reagent (Scheme 128). When the reaction of acid 319 with 1.00 equiv. of BH₃·SMe₂ in THF, at rt was attempted, though, no product was observed after 4 h at rt. Switching to the more reactive BH₃·THF (1.00 equiv.) led to consumption of the starting material in 2 h, giving only
a complex mixture of products. Furthermore, when acid 319 was deprotonated with sodium hydride and then treated with DIBAL 2.00 equiv. at -78 °C, no product was observed. Rising the temperature to rt still gave an incomplete reaction after 24 h, while heating to 40 °C led to consumption of the starting material after 7 h. However, the only product isolated at this temperature was alcohol 374 in a low yield (Scheme 128).

**Scheme 128. Reduction of pyrrolidinones 233 and 319**

After the efforts of synthesising any useful intermediate to pyrrolidinone 333 were not successful, this investigation could not be continued due to time constraints and other lines of investigation.

### 2.4.3 Conclusions

This chapter described the work done towards the synthesis of bicyclic pyrrolidinone 333 starting from a suitable pyrrolidinone scaffold, accessed through our developed conjugate addition/nitro-Mannich/lactamisation method. Our initial efforts to synthesise a pyrrolidinone (340) bearing a two-carbon long substituent at C^5 position, did not give any satisfactory result. This failure was attributed to the poor reactivity of the corresponding imines in the nitro-Mannich reaction. Attempts to use an alternative route via a one carbon functional substituent at the same position, were also not promising. Although it was possible to synthesise acetal 361 in good yield, its deprotection to aldehyde 341 was not accomplished. Moreover, protected ethers 366 and 367 were isolated in low yields, therefore could not be used further in the synthesis sequence (Figure 20). Ester 373 was synthesised in good yield, however its selective reduction was not possible.

**Figure 20**
2.4.4 Future work

Our attempts to synthesise bicyclic pyrrolidinone 333, starting from a suitable monocyclic pyrrolidinone, have so far been unsuccessful. The poor results of this investigation are due to the poor reactivity of the alkyl imines investigated, as well as the vulnerability of the pyrrolidinone core towards any modifications to the C^5 substituent. A possible solution to these problems would be to use a suitable heterocyclic imine 375 to synthesise the initial pyrrolidinone scaffold 376. Pyrrolidinone 376 could then be transformed to the desirable aldehyde 341. Consequent reduction of the nitro group of 341 should lead to cyclisation to form the desired 333 (Scheme 129).

Scheme 129. Possible alternative route to 333

2.5 The 1,4-addition/nitro-Mannich reaction of non-zinc nucleophiles on β-nitrostyrene

2.5.1 Precedence and methodology

One of the targets of this project was to investigate the use of nucleophiles, other than dialkylzinc reagents or hydrides, in a 1,4-addition reaction on nitroacrylate 231 and consequently a nitro-Mannich/lactamisation reaction to afford new pyrrolidinones 377. Very few nitro-Mannich reactions exist in the literature, with a nitroalkane bearing a non-carbon group β- to the nitro group (Scheme 26, section 1.2.1). It was therefore desirable to investigate the reaction of nitroalkenes with heteroatom nucleophiles as well as more complex carbon nucleophiles, to give nitronates 378 that can then participate in the nitro-Mannich reaction (Scheme 130).
This methodology would yield highly functionalised structures like pyrrolidinones 377 and nitroamines 379, increasing the scope of the nitro-Mannich reaction. Furthermore, possible modification of the Nu group in the final products could enable further use of this reaction in the synthesis of complex molecules. From the large number of possible nucleophiles, we concentrated on a representative sample of carbon, oxygen, nitrogen, sulfur and phosphorus nucleophiles. The scope of nitroalkenes that could be used is also large, however this investigation was limited to the reactions of nitroacrylate 231 and β-nitrostyrene 380. Nitroacrylate 231 was chosen as it was already investigated in this thesis (section 2.2), while β-nitrostyrene 380 was chosen because it is commercially available and was widely used in previous studies.35

2.5.2 Investigation of 1,4-addition reactions to nitroacrylate 231

2.5.2.1 Carbon nucleophiles

We first concentrated on the reaction of nitroacrylate 231 with carbon nucleophiles. Nitroacrylate 231 could act as a Friedel-Crafts reagent for electron-rich aromatics such as indole.180 Simply stirring 231 with indole in DCM gave no reaction, but when the nitroalkene was activated by a mixture of CeCl₃/NaI/SiO₂, as it was reported, the 1,4-addition product 381 was isolated in good yield (Scheme 131).180 The same conditions were found to be effective for 1,3,5-trimethoxybenzene, giving nitroalkane 382.

![Scheme 130. Nitro-Mannich reaction with alternative nucleophiles](image)

**Scheme 130.** Nitro-Mannich reaction with alternative nucleophiles

**Scheme 131.** Reaction of nitroacrylate 231 with electron-rich aromatics
Some anionic nucleophiles were then investigated, beginning with malononitrile, diethyl malonate and Meldrum’s acid (Table 7). Disappointingly, most of those nucleophiles failed to give any desired 1,4-addition products 383, as under a variety of conditions only degradation products were observed, presumably due to polymerisation.

**Table 7.** Michael additions of carbon nucleophiles

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nucleophile, Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Meldrum’s acid, 2,6-Lutidine (10.0 mol %), THF</td>
<td>Degradation</td>
</tr>
<tr>
<td>2</td>
<td>Meldrum’s acid, Toluene, reflux</td>
<td>No reaction</td>
</tr>
<tr>
<td>3</td>
<td>Malononitrile, proton sponge (10.0 mol %), THF</td>
<td>Degradation</td>
</tr>
<tr>
<td>4</td>
<td>Malononitrile, NaH (1.00 equiv.), THF</td>
<td>Degradation</td>
</tr>
<tr>
<td>5</td>
<td>Malononitrile, Toluene, reflux</td>
<td>No reaction</td>
</tr>
<tr>
<td>6</td>
<td>Malononitrile, DMF, proline (20.0 mol %)(^{181})</td>
<td>Degradation</td>
</tr>
<tr>
<td>7</td>
<td>Diethyl malonate, Et(_3)N (20.0 mol %), MeOH(^{182})</td>
<td>Degradation</td>
</tr>
<tr>
<td>8</td>
<td>1,3-Cyclohexanedione, Et(_3)N (1.00 equiv.), MeOH, 0 °C(^{183})</td>
<td>384, 99%</td>
</tr>
</tbody>
</table>

In contrast to the poor results from the other carbon nucleophiles, the reaction of 1,3-cyclohexanedione according to the reported procedure for similar diketones was successful and the product 384 isolated in excellent yield (Scheme 132).\(^{183}\)

**Scheme 132.** Reaction of nitroacrylate 231 with 1,3-cyclohexanedione

In light of the poor results from malononitrile, the use of an alternative reagent was investigated. Dimethylsulfonium dicyanomethylide 385, can be synthesised easily from DMSO and malononitrile (Scheme 133)\(^{184}\) and has been reported to react as a
soft nucleophile instead of the harder malononitrile anion. Michael addition of ylide 386 on nitroacrylate 231, should give zwitterion 387, which after hydrolysis would afford nitroester 388. However, when the reaction with this reagent was attempted in MeOH at rt, only starting material was observed. Heating the mixture to reflux overnight though gave none of the desired product 388 but only the unexpected nitroether 389 from 1,4-addition of methanol on nitroacrylate 231 (Scheme 133).

Silyl enol ethers, have been reported to perform conjugate additions on nitroalkenes in the presence of a fluoride source. In light of this report, the reaction of 1-phenyl-1-trimethylsiloxeyethylene 390 with nitroacrylate 231 in the presence of TBAF in DCM at -45 °C was investigated. However, only acetophenone and unknown degradation products were isolated and none of the desired 1,4-addition product 391 was observed (Scheme 134).

2.5.2.2 Oxygen nucleophiles

The 1,4-additions of oxygen nucleophiles were then investigated. Initially, reaction of hydroxide anion with nitroacrylate 231 was attempted. Addition of a solution of nitroacrylate 231 in MeCN, to aqueous NaOH (0.10 M, 1.00 equiv.) cooled to 0 °C, mainly gave degradation products, with only 5% of the nitroalcohol 255 isolated. However, nitroalcohol 255 has been prepared previously by condensation of ethyl glyoxylate with nitromethane (62%, Scheme 85, section 2.3.1). It was thought that the
presence of a free hydroxyl group might interfere with the nitro-Mannich reaction, so it was attempted to protect the hydroxyl group. A few attempts were made to protect the hydroxyl group as a silyl ether 392, benzyl ether 393 and methyl ether 389 (Scheme 135). Reaction of nitroalcohol 255 with TMSCl (1.20 equiv.) and imidazole (2.50 equiv.),187 gave only a trace of 392 and 60% recovered starting material (Scheme 135). Reaction of nitroalcohol 255 with NaH (1.05 equiv.) and BnBr (2.00 equiv.) in THF, in the presence of 4\textsuperscript{t}BuN\textsuperscript{+}I\textsuperscript{-} (1.00 mol %),188 after refluxing overnight, gave a complicated mixture of products, among which was benzaldehyde as well as traces of starting nitroalcohol and benzyl bromide. The presence of benzaldehyde indicates that the benzylated product 393 presumably eliminates HNO\textsubscript{2} to give ethyl acrylate which is volatile and evaporates (Scheme 135). Treatment of nitroalcohol 255 with methyl triflate (up to 9.00 equiv.) and proton sponge (5.00 equiv.) in CHCl\textsubscript{3} gave only 7% of the methylated product 389 after 22 h at reflux. Treatment with TMSCHN\textsubscript{2} (3.00 equiv.) and fluoroboric acid (1.00 equiv.) in DCM, at rt, for 1 h gave nitroether 389 in 33% yield (Scheme 135).189

![Scheme 135. Attempts to protect nitroalcohol 255](image)

The enantioselective conjugate addition of oximes to trisubstituted β-nitroacrylates has been reported using a cinchona alkaloid as the chiral catalyst (Scheme 37, 1.2.3).56 Specifically, oxime 80 derived from anisaldehyde was reported to give nitroesters 82 in good yield and ee (Scheme 136). This prompted us to investigate the 1,4-addition of oxime 80 to nitroacrylate 231 that would give a “masked” hydroxyl group in products 394, which could be deprotected later in the synthesis. The deprotonation of oxime 80 with 4\textsuperscript{t}BuLi and subsequent reaction with nitroacrylate 231 in THF, at -78 °C and then at rt gave only degradation products and unreacted oxime 80, while simple reaction in toluene at rt with or without catalytic Et\textsubscript{3}N (10.0 mol%)
was also ineffective. Use of quinine as the catalyst, in toluene, at 5 °C, as reported, gave only degradation.

\[
\begin{align*}
\text{EtO} & \text{-} \text{\(\text{\(\text{NO}_2\)}\)} & + & \text{N} & \text{OH} \\
\text{231} & & & \text{80} & & \xrightarrow{\text{Conditions}} & \text{EtO} & \text{-} \text{\(\text{\(\text{NO}_2\)}\)} \\
& & & & & & \text{PMP} & \text{N} & \text{O} \\
& & & & & \text{394} \\
\end{align*}
\]

**Scheme 136.** Reaction of nitroacrylate 231 with oxime 80

The reaction of nitroacrylate 231 with alkoxides was then investigated. Addition of a solution of MeONa in MeOH (0.10 M) to a solution of nitroacrylate at rt, gave only degradation of the starting material (baseline on TLC). This result was attributed to base-catalysed polymerisation of the starting material and as such it was attempted to reverse the addition mode. This was indeed beneficial, as it led to formation of the 1,4-addition product 389 in 62% yield, after quenching with AcOH and workup (H₂O/DCM extraction). Performing the same reaction at -78 °C gave 389 in an improved 80% yield. Furthermore, when investigating the reaction with ylide 385 before (Scheme 132, section 2.5.2.1), product 389 was isolated in 63% yield. Nitroacrylate 231 was refluxed in MeOH overnight and after 24 h 389 was isolated in 85% yield (Table 8).

Moreover, it was thought that acidic conditions could also affect the conjugate addition reaction of alcohols, by activation of the nitroalkene through protonation of the nitro group. However, the 1,4-addition of MeOH in acidic conditions was found to be ineffective. In view of the success of 1,4-addition after refluxing with neat alcohol as the solvent, this method was used for the synthesis of other derivatives (Table 8). Reaction with phenol was unsuccessful even at 70 °C (melted).

**Table 8.** Michael additions of alcohols to nitroacrylate 231

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nucleophile</th>
<th>Result</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeONa/MeOH added to 231, rt</td>
<td>Degradation</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>231 added to MeONa/MeOH, rt</td>
<td>1,4-Addition</td>
<td>389</td>
<td>62%</td>
</tr>
</tbody>
</table>
2.5.2.3 Nitrogen nucleophiles

The 1,4-addition of nitrogen nucleophiles was subsequently investigated. The reactions were in most cases fast and without by-products, by simply mixing nitroacrylate 231 with the amine. With these conditions reactions with para-anisidine (1.80 equiv., 24 h), benzylamine (1.20 equiv., 1 h) and morpholine (1.10 equiv.) gave the desired products 397-399 in excellent yields (Table 9).

Table 9. Michael additions of amines to nitroacrylate 231

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nucleophile</th>
<th>Result</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>para-anisidine</td>
<td>1,4-Addition</td>
<td>397</td>
<td>98%</td>
</tr>
<tr>
<td>2</td>
<td>Morpholine</td>
<td>1,4-Addition</td>
<td>398</td>
<td>98%</td>
</tr>
<tr>
<td>3</td>
<td>Benzylamine</td>
<td>1,4-Addition</td>
<td>399</td>
<td>81%</td>
</tr>
</tbody>
</table>

Reaction with other amines however was less successful. Reaction with hydrazine hydrate (1.00 equiv.) in MeOH, at rt gave complete consumption of the starting material after 24 h, but no 1,4-addition product was observed by $^1$H NMR. The same result was observed with reaction with NH$_3$ (1.00 equiv., 0.5 M in THF) in THF at room temperature that led to complete degradation of the starting material in 5 min.
The conjugate addition of oxazolidin-2-ones to β-nitroalkenes after deprotonation with 1BuOK and 18-crown-6, in THF, at 0 °C, has been reported (Scheme 39, section 1.2.4).\(^{190}\) However, when this methodology was used with non-substituted oxazolidin-2-one at -78 °C, none of the desired 1,4-addition product \(400\) was observed, but only degradation of the starting material after 30 min of reaction (Scheme 137). Switching to a weaker catalytic base Et\(_3\)N (10.0 mol %), in THF at rt, gave a complex mixture of products. Use of a heterogenous base such as K\(_2\)CO\(_3\) (30.0 mol%) unfortunately gave the same result.

Scheme 137. Michael addition of oxazolidinone to nitroacrylate 231

Furthermore, the reaction of nitroacrylate 231 with 1H-benzotriazole 401 (1.10 equiv.), in DCM was attempted. In the absence of base at rt, no reaction occurred, but in the presence of Et\(_3\)N (10 mol%) the starting material was consumed after 48 h. The only isolated product however was not the desired 402, but the result of elimination of \(\text{HNO}_2\) 403, isolated in 47% yield (Scheme 138). This result is not unusual as elimination of \(\text{HNO}_2\) from nitroalkanes under basic or acidic conditions has been reported,\(^{191}\) while in this case this reaction is exacerbated by the presence of the acidic proton \(\alpha\) to the ester group.

Scheme 138. Michael addition of 1H-benzotriazole to nitroacrylate 231

In order to make more derivatives of 1,4-addition products, it was attempted to protect the free NH group of nitroamine 397. It would be useful to know how various protecting groups would affect the reactivity of these nitroamines later on in the nitro-Mannich reaction. Moreover, the \(\text{para}\)-methoxyphenyl group could be removed to give a number of different derivatives.\(^{116}\) Initially the protection of aniline 397 as a trifluoroacetamide was investigated, by reaction with TFAA (5.00 equiv.) and
pyridine (5.00 equiv.). From this reaction, though, only trifluoroacetamide 404 was isolated, indicating the elimination of the aniline. This was not unexpected as by forming a trifluoroacetamide, the aniline of 405 is turned into a good leaving group (Scheme 139). Protection with a silyl group was attempted but this was not effective even after using 12.0 equiv. of TMSCl, with Et$_3$N (1.00 equiv.) in DCM, at rt. Finally, it was attempted to methylate the nitrogen to give tertiary amine 406. Treatment with MeI (4.50 equiv.) in refluxing acetone gave no products after 20 h, but nitroamine 406 was successfully isolated (though in low yield) by a reductive amination reaction with paraformaldehyde (10.0 equiv.) and NaBH$_4$ (5.00 equiv.) in THF and TFA (Scheme 139).

![Scheme 139. Modifications of para-anisidine adduct 397](image_url)

2.5.2.4 Other nucleophiles

The conjugate addition of other nucleophiles to nitroacrylate 231 was also investigated. Reaction with 1-butanethiol (4.00 equiv.) and Et$_3$N (40 mol %), in THF, at rt, led to complete consumption of the nitroacrylate after 24 h. The only product isolated though, was not the desired 407 but 408 resulting from elimination of HNO$_2$ (Scheme 140). Repeating the same reaction in the absence of base, with 1-butanethiol (1.00 equiv.), in EtOH, at rt, was much faster (consumption of starting material in 10 min), but again failed to provide the desired product, as only a baseline spot was observed on TLC, indicating degradation presumably due to polymerisation.

The reaction with diphenylphosphine was then investigated. Simple addition of diphenylphosphine (1.10 equiv.) to a solution of 231 in THF, at rt, led to a complete consumption of the starting material in 20 min. It was not however possible to isolate any product, due to instability to purification. In light of this, it was considered that oxidation might be one reason for this instability, so it was decided to perform the reaction of nitroacrylate 231 with diphenylphosphine oxide. Reaction with diphenylphosphine oxide (1.10 equiv.) in THF, at rt, was slower than with
diphenylphosphine (completed in 17 h) and unfortunately the only product isolated was acrylate 409 and not 410 (Scheme 140).

Scheme 140. Michael additions of 1-butanelthiol and diphenylphosphine oxide to 231

2.5.3 Nitro-Mannich reactions of 1,4-addition products of nitroacrylate 231

2.5.3.1 One-pot reactions

After investigating the conjugate additions of a variety of nucleophiles on nitroacrylate 231, it was attempted to investigate whether a one-pot reaction would be effective. The conjugate addition to 231 in the presence of an imine and/or acid could yield either the nitro-Mannich product or the resulting lactamisation product.

Initially, a one-pot reaction of nitroacrylate 231 with para-anisidine and imine 281 was explored. Reaction of nitroacrylate 231 with para-anisidine (1.20 equiv.) and imine 281 (2.00 equiv.) in toluene, at rt led to complete consumption of the nitroacrylate in 48 h and isolation of a single product, nitroamine 397 in 86% yield and none of pyrrolidinone 410 (Scheme 141). Switching to DCM, using 1.10 equiv. of para-anisidine and refluxing the mixture led to consumption of the nitroacrylate in 4 h and isolation of the nitroamine 397 in quantitative yield, but none of the desired nitro-Mannich product was isolated.

Scheme 141. Attempt of a one-pot 1,4-addition/nitro-Mannich/lactamisation reaction
These results were attributed to two possible reasons. The first, is that the nitronate anion 411 (Scheme 142) formed from the initial 1,4-addition reaction, tautomerises to 397 under the reaction conditions faster than it reacts with the imine. However, it is known from kinetic studies that protonation of nitronates to the nitroalkane can be slow.\(^{194}\)

The second reason is that imine 281 is not reactive enough to participate in the nitro-Mannich reaction in the absence of acid, where it becomes protonated and hence more electrophilic. To test this hypothesis, the reaction of 231 with imine 281 (2.00 equiv.), para-anisidine (2.00 equiv.) and TFA (3.00 equiv.) in THF was investigated. The presence of acid is expected to protonate imine 281, thereby making it more electrophilic. This reaction though, gave none of pyrrolidinone 410 but only the 1,4-addition product 397 after 48 h in 93% yield (Scheme 142). Furthermore, the reaction with the more electrophilic N-tosyl imine 412 was also attempted. Nitroacrylate 231 was reacted with imine 412 (1.50 equiv.) and para-anisidine (1.20 equiv.), in THF, at rt, in the absence of acid. These conditions however, gave none of nitroamine 413 or pyrrolidinone 414, as only the starting materials and 1,4-addition product 397 were observed on TLC and \(^1\)H NMR (Scheme 142). These two experiments suggest that the poor reactivity of the imine was not the reason that pyrrolidinone 410 was not formed in these conditions.

Scheme 142. Attempt of a one-pot 1,4-addition/nitro-Mannich/lactamisation reaction

The tandem reaction of a few other nucleophiles was then investigated. Reaction of nitroacrylate 231 with morpholine (1.20 equiv.), imine 281 (1.50 equiv.) and TFA (2.00 equiv.) led after 24 h to consumption of the nitroacrylate, but only the 1,4-addition product of morpholine and unreacted imine 281 could be seen on TLC. A stepwise variant of the same reaction was also attempted. Nitroacrylate 231 and
morpholine (1.00 equiv.) were reacted first in THF, at rt (complete after 30 min, TLC) to give nitroamine 398. The mixture was then cooled to -78 °C and a solution of nBuLi (1.10 equiv.) was added, followed by a solution of imine and then TFA. The reaction gave only a complicated mixture of products, but none of the desired pyrrolidinone 415 (Scheme 143).

Scheme 143. Attempt of a one-pot 1,4-addition/nitro-Mannich/lactamisation reaction

Attention was also given to the reactions with nucleophiles, where previously it was not possible to isolate the 1,4-addition product, such as with phenol and 1-butanethiol, hoping that a possible reactive 1,4-addition product could be intercepted by an imine which could then undergo lactamisation. Reaction of nitroacrylate 231 with 1-butanethiol (1.20 equiv.), imine 281 (2.00 equiv.) and Et₃N (30.0 mol %) led after 24 h to a complicated mixture of products with no pyrrolidinone detected. Reaction with phenol (1.50 equiv.) and imine 281 (1.50 equiv.), in toluene, at rt, in the absence of acid was very slow, while increasing the equivalents of phenol to 2.50, gave after 3 days only nitroamine 397 in 73% yield and none of pyrrolidinone 416 (Scheme 144). This indicates that the imine is presumably hydrolysed by water over time and the more reactive para-anisidine produced then reacts with the nitroacrylate 231.

Scheme 144. Attempt of a one-pot 1,4-addition/nitro-Mannich/lactamisation reaction

The synthesis of pyrrolidinones 226 from refluxing nitroesters 224 with aldehydes 223, amines 222 and benzoic acid has been reported (Scheme 76, section 1.5). Inspired by this work, it was considered that refluxing a mixture of nitroacrylate 231, imine 281 and benzoic acid in methanol might lead to the in situ formation of addition product 417, which can potentially react with 281 and lactamise to the desired pyrrolidinone 418 (Scheme 145). However, when the reaction was performed with
1.50 equivalents of 281 and benzoic acid, only unreacted imine and the 1,4-addition product 389 were observed.

\[
\begin{align*}
224 & \quad \text{O}_2\text{N-CO}_2\text{Me} + \text{R}^{1-}\text{NH}_2 + \text{PhCOOH (1 equiv.)} \\
\text{Toluene, N}_2, 6 \text{ h}, 70^\circ \text{C} & \quad \rightarrow \quad \text{R}^2-\text{N=CH-CO}_2\text{Me} \quad \text{226}
\end{align*}
\]

**Scheme 145.** Attempt of a one-pot reaction inspired by Dixons’ methodology

### 2.5.3.2 Two-pot reactions

Due to the failure of the one-pot 1,4-addition/nitro-Mannich/lactamisation reaction, the two-pot procedure was investigated. In our general method, $^n$BuLi was used to deprotonate the nitroalkanes $\alpha$- to the nitro group to form nitronate 419, followed by the procedure previously developed for the synthesis of pyrrolidinones 232 (addition of a solution of imine 281 followed by TFA).\(^{116}\) This method has previously worked well for the synthesis of pyrrolidinone 279, where the one pot reaction with diphenylzinc was unsuccessful (Section 2.3.3).

Initially the reactions of nitroalkanes derived from the conjugate addition of carbon nucleophiles were investigated. Reaction of nitroalkanes 381 and 382 gave the highly functionalised pyrrolidinones 420 and 421 respectively, in moderate yields as single diastereoisomers (Scheme 146).

\[
\begin{align*}
\text{EtO}_2\text{C-N}=\text{N} & \quad (\text{R}=3\text{-indolyl}) \\
\text{O} & \quad (\text{R}=2,4,6\text{-trimethoxyphenyl})
\end{align*}
\]

**Scheme 146.** The nitro-Mannich/lactamisation reaction of adducts 420 and 421

In the reaction of nitroalkane 384, 2.10 equiv. of $^n$BuLi were used, to account for deprotonation of the hydroxyl group. Interestingly this reaction gave
octahydroquinoline 422, instead of the expected pyrrolidinone (Scheme 147). This result indicates that conjugate addition on the enone to form a six-membered ring is in this case preferential to lactamisation on the ethyl ester to form a five-membered ring.

![Scheme 147. Synthesis of octahydroquinoline 422 from nitroalkane 384](image)

The nitro-Mannich reaction of the rest of the nitroalkane adducts was then investigated using the same procedure. The results, however, were not encouraging as in most cases the reactions led to degradation and when it was possible to isolate the pyrrolidinone products, they were found to be unstable both to chromatography and to storage (Table 10).

**Table 10. Nitro-Mannich/lactamisation reactions of other Michael adducts**

<table>
<thead>
<tr>
<th>Entry</th>
<th>R group</th>
<th>[^{n}BuLi)/TFA (equiv.)</th>
<th>Product-Result/Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HO-</td>
<td>1.10/1.10(^a)</td>
<td>231, imine and degradation</td>
</tr>
<tr>
<td>2</td>
<td>HO-</td>
<td>2.10/2.20</td>
<td>231, imine and degradation</td>
</tr>
<tr>
<td>3</td>
<td>MeO-</td>
<td>1.10/2.50</td>
<td>Expected 423, 39(^b)</td>
</tr>
<tr>
<td>4</td>
<td>EtO-</td>
<td>1.10/2.50</td>
<td>Complicated</td>
</tr>
<tr>
<td>5</td>
<td>BnO-</td>
<td>1.10/2.50</td>
<td>Complicated</td>
</tr>
<tr>
<td>6</td>
<td>(p)-MeO-C(_6)H(_4)-NH-</td>
<td>1.05/2.10</td>
<td>231, imine and degradation</td>
</tr>
<tr>
<td>7</td>
<td>(p)-MeO-C(_6)H(_4)-NMe-</td>
<td>1.10/3.00</td>
<td>Complicated</td>
</tr>
<tr>
<td>8</td>
<td>Morpholine</td>
<td>1.10/2.20</td>
<td>Expected 424, 7(^b)</td>
</tr>
<tr>
<td>9</td>
<td>BnNH-</td>
<td>1.10/2.00</td>
<td>Imine and degradation</td>
</tr>
</tbody>
</table>

\(^a\)Reaction mixture was warmed to rt after the addition of \[^{n}BuLi\] and recooled before the addition of the imine.  
\(^b\)Product was found to be unstable.
It can be postulated that the desired pyrrolidinones are unstable due to the presence of an electron-rich group in the C\textsuperscript{3} position of the pyrrolidinone. This could induce the ring opening of the pyrrolidinone that could lead to further degradation (Scheme 148).

![Scheme 148. Degradation of pyrrolidinone 423](image)

**2.5.3.3 Relative stereochemistry**

Like the pyrrolidinones synthesised in sections 2.4 and 2.5, the pyrrolidinones obtained from our developed 2-pot procedure for non-zinc nucleophiles were isolated as single diastereoisomers. By comparison to the analogues synthesised before, the new analogues were tentatively assigned as bearing a \textit{trans/trans} relative stereochemistry around the pyrrolidinone ring. It was not possible to obtain an X-ray crystal structure of any of these analogues, however the relative stereochemistry was assigned by comparison of their \textsuperscript{1}H NMR coupling constants with the ones of previously synthesised pyrrolidinones. In our dialkylzinc methodology we reported couplings of 4.6-8.0 Hz for \(J_{HaHb}\) (Figure 21) and 3.4-6.3 Hz for \(J_{HbHc}\). In the new analogues we reported couplings of 6.0-9.5 Hz for \(J_{HaHb}\) and 5.7-7.9 Hz for \(J_{HbHc}\) (Figure 21). Most \(J_{HaHb}\) values agree with our previous values, with the exception of trimethoxyphenyl analogue 421 which has a high value of 9.5 Hz, while values for \(J_{HbHc}\) are found to be slightly higher than the previously reported ones. Maybe the very hindered nature of the 2,4,6-trimethoxyphenyl substituent warps the conformation of pyrrolidinone 421, but still leads to a coupling constant value within what could be expected for the depicted stereochemistry (Figure 21). Molecular modelling for the four pyrrolidinones below\textsuperscript{128} predicts the dihedral angles H-C-C-H between H\textsubscript{a} and H\textsubscript{b} and between H\textsubscript{b} and H\textsubscript{c} to be in the range 161-165\textdegree. This angle, according to the Karplus equation, corresponds to medium to high values for \(J_{HaHb}\) and \(J_{HbHc}\) as it was observed\textsuperscript{196}. 

\[\text{Molecular modelling for the four pyrrolidinones below,} \textsuperscript{128}\text{ predicts the dihedral angles H-C-C-H between H}_a \text{ and H}_b \text{ and between H}_b \text{ and H}_c \text{ to be in the range 161-165}^\circ. \text{ This angle, according to the Karplus equation, corresponds to medium to high values for} \ J_{HaHb} \text{ and} \ J_{HbHc} \text{ as it was observed.} \textsuperscript{196} \]
When investigating the nitro-Mannich reaction of 1,3-cyclohexadione adduct earlier (Scheme 147), piperidine 422 was isolated as a single diastereoisomer. The relative stereochemistry of this piperidine was unknown. As shown in Figure 22, the observed values of coupling constants $J_{HaHb}$ and $J_{HbHc}$ were 5.3 and 8.7 Hz respectively (Figure 22). NOE studies have shown that irradiation of the CHCOOEt (H_a) peak at $\delta$ 4.43 ppm caused a 3.17% and 0.57% enhancement for the protons H_b and H_c respectively (Figure 22). The medium value of $J_{HaHb}$ suggests that the H_a-H_b is cis, while the larger $J_{HaHb}$ suggests H_b-H_c are trans. The NOE values further support this hypothesis, as the very small enhancement of the peak of H_c excludes H_a and H_c being both axial, while the larger value for H_b suggests H_a and H_b have an axial-equatorial relationship. These data suggest a cis/trans relative stereochemistry and the most stable conformation to be the one shown below (Figure 22).

Molecular modelling was also used to confirm the relative stereochemistry of 422. All the possible diastereoisomers of 422 were modelled, in order to assess which one best fits the experimental data. After predicting the values of $J_{HaHb}$ and $J_{HbHc}$ and the distances of H_a-H_b and H_a-H_c (Table 11), it was concluded that the cis/trans stereochemistry is indeed the closest to the spectroscopic data. Deviation of 1.0 Hz in the calculated coupling constants is expected based on the error limit of the
calculation. However, the higher deviation observed in this case can be attributed to contribution of other conformations to the experimental coupling constants, in particular the ring flipped conformation that would have the ester group axial and the nitro and phenyl groups equatorial.

Table 11. Predicted values of couplings $J_{\text{HaHb}}$ and $J_{\text{HbHc}}$ and the distances of H$_a$-H$_b$ and H$_a$-H$_c$ for the four possible diastereoisomers of 422

<table>
<thead>
<tr>
<th>Compound:</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Rel. ster.</td>
<td>$J_{\text{HaHb}}$ (Hz)</td>
<td>$J_{\text{HbHc}}$ (Hz)</td>
<td>H$_a$-H$_b$ (Å)</td>
</tr>
<tr>
<td>trans/trans</td>
<td>11.8</td>
<td>10.6</td>
<td>3.09</td>
</tr>
<tr>
<td>cis/cis</td>
<td>3.9</td>
<td>2.0</td>
<td>2.41</td>
</tr>
<tr>
<td>trans/cis</td>
<td>12.1</td>
<td>3.4</td>
<td>3.08</td>
</tr>
<tr>
<td>cis/trans</td>
<td>4.5</td>
<td>10.6</td>
<td>3.06</td>
</tr>
</tbody>
</table>

2.5.3.4 Source of diastereoselectivity

In previous work (section 2.3.8) with 1,4-addition of dialkylzinc reagents on nitroacrylate 231 followed by a nitro-Mannich reaction, it has been possible to isolate the intermediate $\beta$-nitroamines by protection as trifluoroacetamides 290. However, in this work the intermediate $\beta$-nitroamines were not isolated, as they cyclised to give pyrrolidinones 377. Since the $^1$H NMR data support the trans/trans relative stereochemistry in the pyrrolidinone products, it can be postulated that only the syn/anti-425 cyclises to give pyrrolidinones 377, as it was observed before. It would be expected that the transition state 426 that gives the trans/trans pyrrolidinone would have the lowest energy, as it would have all the substituents in pseudo-equatorial positions, thereby minimizing 1,3-diaxial interactions (Scheme 149). Thereby it would be expected that all other $\beta$-nitroamine diastereoisomers equilibrate to syn/anti-425, which then cyclises (Scheme 149).
Similarly, for piperidine 422 we have observed a cis/trans relative stereochemistry, which originates from cyclisation of the syn/anti β-nitroamine 427 (Scheme 150). In this case, the cyclisation that would give the presumably lowest energy diastereoisomer (trans/trans), i.e. the one having all substituents in an equatorial type arrangement, does not occur. It would appear that the syn/anti-427 diastereoisomer was the major product from the reaction and only this product cyclises to piperidine 422, whereas any other β-nitroamine diastereoisomers slowly degrade by retroaddition. Cyclisation is probably the rate determining step, therefore only the predominant syn/anti diastereoisomer cyclises and the other diastereoisomers degrade by retro-addition.

Scheme 149. Mechanism of the formation of pyrrolidinones 377

2.5.4 Investigation of 1,4-addition reactions to β-nitrostyrene 380

2.5.4.1 Carbon nucleophiles

Continuing on with this work, it was then attempted to investigate the two-pot 1,4-addition/nitro-Mannich reaction to β-nitrostyrene 380 using the same range of nucleophiles. Initially, reactions with carbon nucleophiles were studied, that in most cases worked well to give the desired 1,4-addition products 428 in good yields (Table 12).
Table 12. Michael additions of carbon nucleophiles to $\beta$-nitrostyrene

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nucleophile</th>
<th>Product-Result</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Indole, CeCl$_3$, NaI, SiO$_2$</td>
<td>1,4-Addition, 429</td>
<td>92%</td>
</tr>
<tr>
<td>2</td>
<td>1,3,5-trimethoxybenzene, CeCl$_3$, NaI, SiO$_2$</td>
<td>1,4-Addition, 430</td>
<td>71%</td>
</tr>
<tr>
<td>3</td>
<td>Diethyl malonate, NaH, THF$^{182}$</td>
<td>1,4-Addition, 431</td>
<td>96%</td>
</tr>
<tr>
<td>4</td>
<td>Malononitrile, NaH, 15-crown-5, THF</td>
<td>No reaction</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>Malononitrile, DMF, proline$^{181}$</td>
<td>1,4-Addition, 432</td>
<td>89%</td>
</tr>
<tr>
<td>6</td>
<td>1,3-Cyclohexanediene, Et$_3$N, THF</td>
<td>Degradation</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>1,3-Cyclohexanediene, MeONa, MeOH$^{183}$</td>
<td>1,4-Addition, 433</td>
<td>34%</td>
</tr>
<tr>
<td>8</td>
<td>Meldrum’s acid, Et$_3$N, DCM$^{197}$</td>
<td>1,4-Addition, 434</td>
<td>96%</td>
</tr>
<tr>
<td>9</td>
<td>1-phenylvinyl trimethylsilyl ether, THF, -45°C, TBAF$^{186}$</td>
<td>No product</td>
<td>-</td>
</tr>
</tbody>
</table>

2.5.4.2 Oxygen nucleophiles

The formation of nitroalcohol 435 by conjugate addition of hydroxide to $\beta$-nitrostyrene was then investigated. When a solution of the nitroalkene in MeCN was added to an aqueous solution of NaOH (0.10 M, 1.00 equiv.) at 0°C, the starting material was consumed in 5 min. The only product observed however, was benzaldehyde, which could be produced by elimination of nitromethane in the basic reaction conditions (Scheme 151). It was possible to synthesise nitroalcohol 435 in 50% yield, by a simple condensation of benzaldehyde with nitromethane in the presence of Et$_3$N as reported for other nitroalcohols.$^{115}$
The conjugate addition of alcohols/alkoxides to β-nitrostyrene 380, was subsequently investigated. Even though this reaction is known,\textsuperscript{198} it was decided to briefly screen a few possible methods in order to find the most effective one. We started this investigation with an optimisation of the reaction of 380 with methanol (Table 13). Interestingly, refluxing 380 in alcohol did not affect the 1,4-addition reaction (only nitrostyrene remained after 24 h reflux in MeOH). Attempts of an acid catalysed (entries 2 and 3) conjugate addition of MeOH were also unsuccessful. Reaction with MeONa however, gave the desired product 436, the best result being from a modification of the reported procedure,\textsuperscript{198} by performing the reaction exclusively in MeOH, at rt.

\textbf{Table 13. Optimisation of the Michael addition of MeOH to β-nitrostyrene}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nucleophile</th>
<th>Product-Result</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeOH, reflux, 22 h</td>
<td>No reaction</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>MeOH, TFA (10.0 equiv.), 21 h</td>
<td>No reaction</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>MeOH, H\textsubscript{2}SO\textsubscript{4} (2.00 equiv.), 18 h</td>
<td>No reaction</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>MeONa, THF, 15-crown-5, 15 min</td>
<td>1,4-Addition</td>
<td>53%</td>
</tr>
<tr>
<td>5</td>
<td>MeONa, MeOH, Et\textsubscript{2}O, 15 min\textsuperscript{198}</td>
<td>1,4-Addition</td>
<td>62%</td>
</tr>
<tr>
<td>6</td>
<td>MeONa, MeOH, 15 min</td>
<td>1,4-Addition</td>
<td>73%</td>
</tr>
</tbody>
</table>

The optimised conditions were used with other alkoxides, using the alcohol of each alkoxide as the solvent (Table 14). This meant that with \textsuperscript{1}BuOH the mixture had to be warmed to about 30 °C to remain liquid, which led to a poor yield of 1,4-addition...
product. However, that could be improved if THF was used as a co-solvent (Table 14).

Table 14. Michael addition of alkoxides to \( \beta \)-nitrostyrene

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nucleophile(^a)</th>
<th>Product-Result</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EtONa, EtOH</td>
<td>1,4-Addition, 438</td>
<td>66%</td>
</tr>
<tr>
<td>2</td>
<td>BnONa, BnOH</td>
<td>1,4-Addition, 439</td>
<td>66%</td>
</tr>
<tr>
<td>3</td>
<td>(^i)PrONa, (^i)PrOH</td>
<td>1,4-Addition, 440</td>
<td>58%</td>
</tr>
<tr>
<td>4</td>
<td>(^t)BuONa, (^t)BuOH (30 °C)</td>
<td>1,4-Addition, 441</td>
<td>9%</td>
</tr>
<tr>
<td>5</td>
<td>(^t)BuONa, (^t)BuOH, DMF</td>
<td>Degradation(^b)</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>(^t)BuOK, THF, 18-crown-6</td>
<td>Degradation(^b)</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>(^t)BuONa (0.53 M in (^t)BuOH), THF(^c)</td>
<td>380 and Benzaldehyde</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>(^t)BuONa (0.53 M in (^t)BuOH), THF</td>
<td>1,4-Addition, 441</td>
<td>40%</td>
</tr>
</tbody>
</table>

\(^a\)Only 1.00 equiv. of alkoxide used in all cases. Reactions quenched with AcOH (6.00 equiv.). \(^b\)Only baseline spot observed on TLC. \(^c\)Reaction quenched with NH\(_4\)Cl.

In entry 7 (Table 15), although TLC indicated a complete consumption of starting material after quenching with NH\(_4\)Cl, only a trace of the desired 1,4-addition product 441 was observed, as well as a complicated mixture of degradation products, among which we could identify benzaldehyde and \( \beta \)-nitrostyrene. It is believed that nitroalkane 441 degrades to \( \beta \)-nitrostyrene by retro-1,4-addition upon workup (Scheme 152). The presence of benzaldehyde as the degradation product can be explained by elimination of 2-methylpropene and nitromethane (Scheme 152).

Scheme 152. Degradation of nitroalkane 441
2.5.4.3 Nitrogen nucleophiles

The conjugate addition of amines to β-nitrostyrene was then investigated (Table 15). The electron rich 2,4-dimethoxyaniline gave a good yield of 442 by just stirring a mixture of the aniline (1.20 equiv.) with the nitroalkene, in DCM, at rt, for 19 h. This method though, was not effective for less electron rich anilines. In particular, stirring a solution of aniline (1.00 equiv.) with β-nitrostyrene in DCM, at rt, gave no product, while refluxing the reaction mixture gave incomplete consumption of the starting material. The same result was observed with para-nitroaniline (1.20 equiv.). A different methodology, performing the reaction in water, worked well for the 1,4-addition of aniline (Table 15). The conjugate addition of para-nitroaniline was affected by deprotonation of the amine with nBuLi (1.00 equiv.) in THF, at -78 °C and subsequent addition of the nitroalkene, giving the 1,4-addition product 444 in medium yield.

Table 15. Michael addition of amines to β-nitrostyrene

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nucleophile</th>
<th>Product-Result</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2,4-dimethoxyaniline/DCM</td>
<td>1,4-Addition, 442</td>
<td>70%</td>
</tr>
<tr>
<td>2</td>
<td>Aniline/DCM</td>
<td>No reaction</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Aniline/H₂O¹⁹⁹</td>
<td>1,4-Addition, 443</td>
<td>67%</td>
</tr>
<tr>
<td>4</td>
<td>para-nitroaniline/DCM</td>
<td>No reaction</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>para-nitroaniline/BuLi/THF</td>
<td>1,4-Addition, 444</td>
<td>45%</td>
</tr>
<tr>
<td>6</td>
<td>Morpholine/DCM</td>
<td>1,4-Addition, 445</td>
<td>22%</td>
</tr>
<tr>
<td>7</td>
<td>Morpholine/DCM/Sm(OTf)₃ cat.²⁰⁰</td>
<td>1,4-Addition, 445</td>
<td>94%</td>
</tr>
<tr>
<td>8</td>
<td>NH₂NH₂.H₂O/MeOH</td>
<td>Degradation</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>NH₃/THF</td>
<td>Degradation</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>Benzotriazole/DCM²⁰¹</td>
<td>1,4-Addition, 446</td>
<td>83%</td>
</tr>
<tr>
<td>11</td>
<td>2-Oxazolidinone/THF/18-crown-6/BuOK⁵⁸</td>
<td>1,4-Addition, 447</td>
<td>90%</td>
</tr>
</tbody>
</table>
Reaction with morpholine (1.00 equiv.) in DCM, at rt, gave complete consumption of the nitroalkene in 24 h, but only a small yield of adduct 445 was isolated. Performing the reaction in the presence of Lewis acid Sm(OTf)_3 (0.200 mol%) led to a complete consumption of the nitroalkene in 24 h and isolation of adduct 445 in excellent yield (Table 16).^200^ Reaction of the nitroalkene with hydrazine (1.00 equiv.) in MeOH led to degradation, while reaction with a solution of NH_3 (5.00 equiv.) in THF gave no product after 5 h. Using a higher concentration of NH_3 by bubbling NH_3 gas through the solution for 5 min, led to degradation of the starting material after 1 h.

Reaction with benzotriazole (1.10 equiv.), in DCM, at rt, gave complete consumption of the nitroalkene in 19 h and isolation of adduct 446 in good yield. Reaction with oxazolidinone (1.00 equiv.), with tBuOK (1.00 equiv.) and 18-crown-6 (1.00 equiv.) in THF was over in 30 min and gave adduct 447 in excellent yield (Table 16).

2.5.4.4 Other nucleophiles

The conjugate addition of other nucleophiles to β-nitrostyrene was also investigated. Reaction with 1-butanol (1.00 equiv.) and Et_3N (5 mol %), in THF, at rt, led to complete consumption of 380 after 15 min and isolation of adduct 448 in excellent yield (Scheme 153). Using the same conditions, reaction with thiophenol gave adduct 449 in excellent yield after 15 min. Reaction with diphenyolphosphine oxide (1.00 equiv.) in THF, at rt, was slower as the starting material was consumed in 24 h, but 1,4-addition product 450 was isolated in good yield (Scheme 153). Moreover, to broaden the scope of our 1,4-addition products, sulfide 449 was oxidised to sulfone 451 using oxone (1.50 equiv.) in MeOH and H_2O (Scheme 153).

Scheme 153. Michael additions of other nucleophiles to β-nitrostyrene

2.5.5 Nitro-Mannich reactions of 1,4-addition products of β-nitrostyrene 380

With the 1,4-addition products 428 in hand, it was then attempted to perform the nitro-Mannich reaction from these. The procedure used was again deprotonation α- to the nitro group using tBuLi in THF at -78°C, followed by addition of imine 281 (2.00
equiv.) and trifluoroacetic acid (3.50 equiv.), stirring for 1 h at this temperature and then warming to room temperature over 5 min and quenching with a solution of NaHCO₃. The nitro-Mannich products 379 were unstable to purification and therefore were protected as trifluoroacetamides 452 with TFAA (3.00 equiv.) and pyridine (3.00 equiv.) in DCM, at rt (Scheme 154).

Scheme 154. The nitro-Mannich reaction of 1,4-addition products 428.

2.5.5.1 Adducts of carbon nucleophiles

Initially the nitro-Mannich reactions of the adducts of carbon nucleophiles were investigated. Reaction of the two aromatic substituted nitroalkanes 429 and 430, successfully gave the desired β-nitroamines 453 and 454, isolated in good conversions (63% and 84% respectively) and excellent dr (Scheme 155). After protection, the resulting trifluoroacetamides 455 and 456 were isolated in good yields (Scheme 155), as single diastereoisomers bearing an anti/anti stereochemistry (section 2.5.6.1).

Scheme 155. Synthesis of trifluoroacetamides 455 and 456

On the other hand, nitro-Mannich reaction of alkyl substituted nitroalkanes 431-434 was not successful and none of the desired trifluoroacetamides 457 could be isolated (Scheme 156). Reaction of malonate 431, as well as malononitrile adduct 432, gave only recovered starting material and unreacted imine. Cyclohexadione and Meldrum’s acid adducts 433 and 434, gave only a complicated mixture of degradation products.
It is noted that 2.00 equivalents of $^n$BuLi were used in those reactions as they all have another equally or more acidic proton than the one $\alpha$ to the nitro group.

Scheme 156. Nitro-Mannich reactions of other adducts of carbon nucleophiles

Due to the failure of the nitro-Mannich of the alkyl-substituted nitroalkanes above, it was attempted to use a different method to perform this reaction. It has recently been reported by Dixon, that by heating a mixture of a suitable nitroalkane, an amine and benzaldehyde with benzoic acid, in toluene, cyclisation occurs to give the desired piperidines.\textsuperscript{195} Thereby we envisioned that a nitro-Mannich reaction of nitroalkane 458 bearing a suitable electrophilic group, with an amine and benzaldehyde would give $\beta$-nitroamine 459, which under these reaction conditions should cyclise to form piperidinones 460 (Scheme 157). A similar reaction was observed before by the formation of piperidinone 422 from the nitro-Mannich reaction of cyclohexadione adduct 384 with imine 281 (section 2.5.3.2). The reactions of nitroalkanes 433 and 434 were investigated.

Starting from nitroether 433 and using the reported procedure,\textsuperscript{195} amines benzylatione and $^n$butylamine were tested, none of which gave the desirable product 461, but only degradation (Scheme 157). Starting from nitroalkane 434, three different amines were tested, para-anisidine, benzylatione and $^n$butylamine. Only the reaction with $^n$butylamine was successful and gave piperidinone 462 in 28% yield, resulting from a nitro-Mannich reaction, followed by loss of CO$_2$ and Me$_2$CO.
2.5.5.2 Adducts of oxygen nucleophiles

The nitro-Mannich reaction of nitroalcohol 435 was then investigated. Initial nitro-Mannich reaction, gave complete consumption of the starting nitroalcohol, to give what appeared by crude $^1$H NMR to be the desired $\beta$-nitroamine 463 in 26% conversion, as well as unreacted imine 281 (70%) and traces of other products. Submitting the crude product to TFA-protection, gave benzaldehyde (40%), $\beta$-nitrostyrene (7%), the trifluoroacetamide of para-anisidine 464 (53%) and small amounts of other unknown products. After purification by column chromatography (Hexane:Me$_2$CO 8:2), unknown product 465 was isolated as a white solid (mp = 145-146 °C). This product had a molecular parent ion of m/z 242 Da from CI$^+$ mass spectroscopy, with the high resolution mass supporting a molecular formula of C$_{15}$H$_{16}$NO$_2$. Two broad stretching bands in the IR spectrum at $\nu_{\text{max}}$ = 3410 and 3305 cm$^{-1}$ supported the presence of OH and NH functionalities, as well as a carbonyl group with $\nu_{\text{max}}$(C=O) = 1635 cm$^{-1}$. $^1$H and $^{13}$C NMR spectroscopy showed the presence of 10 aromatic protons, three aliphatic ones with a CHCH$_2$ structure and two exchangeable protons (OH and/or NH). The data were in agreement with that reported for amide 465, which was isolated in only 12% yield from our reaction (Scheme 158).
The mechanism of the formation of amide 465 was intriguing. The amide nitrogen cannot originate from \textit{para}-anisidine (present in imine 281), as that would require the difficult removal of the \textit{para}-methoxyphenyl group. We postulate it is more likely that the amide originates from the nitro group. This would require a reduction of the nitro group under the reaction conditions, which would require transfer of three hydrides to it from a reducing agent. Alternatively, this reduction could occur by single electron transfer, however that was not possible due to the absence of a suitable reagent in our conditions. In the speculative mechanism, nitroalcohol 435 can act as the reducing agent and transfer a hydride to the nitro group of another molecule of 435, which can be made more favourable by acylation of the nitro group’s oxygens by TFAA, reducing it eventually to amine 466, giving nitroketone 467 as the by-product. Amine 466 can then react with 467 to give the observed amide 465 (Scheme 159). We have no evidence to support this mechanism as none of nitroketone 467 was observed in the crude reaction mixture, however this might be due to degradation.

Scheme 159. Proposed mechanism for the formation of amide 465

To our knowledge, the reduction of nitro groups from alcohols has only been reported once and only in the presence of palladium catalysis.\(^{203}\) The reduction (transfer hydrogenation) of carbonyl groups from alcohols, is a lot more common and occurs in the presence of transition metals like Ruthenium,\(^ {204}\) trialkylaluminium compounds (Meerwein-Schmidt-Ponndorf-Verley reduction),\(^ {205}\) as well as enzymatic catalysis.\(^ {206}\) The transfer of hydride from nitroalcohols has not been observed before, however the transfer hydrogenation from benzyl alcohols in the presence of transition metals has been observed.\(^ {207}\) Various intermolecular redox reactions are widely known, such as the Cannizzaro reaction.\(^ {208}\)

The nitro-Mannich reactions of alcohol adducts 437, using the general methodology, were generally succesful and the desired \(\beta\)-nitroamines 468-471 were isolated in
good conversions and excellent diastereoselectivities (Scheme 160). After protection, the resulting trifluoroacetamides 472-475 were isolated in good yields as single diastereoisomers bearing again an anti/anti stereochemistry (section 2.5.6.2).

Scheme 160. Nitro-Mannich reactions of alcohol adducts to β-nitrostyrene

It is noted that in the case of tBuO-substituted nitroether 441 (Table 14, section 2.5.4.2), the nitro-Mannich reaction was very slow as mainly starting material was seen after 1 h at -78 °C. Extending the reaction time to 3 h at -78 °C led to complete consumption of the starting material, however only a trace of crude nitro-Mannich product was observed. Imine 281 (65% of the initial 2.00 equiv.), benzaldehyde (35% of the initial imine), β-nitrostyrene 380 (65% of the initial 441) and tBuOH (80% of the initial 441) were observed after workup. It is believed that nitroether 441 degrades to β-nitrostyrene and benzaldehyde in the same way observed during our efforts to synthesise 441 (section 2.5.4.2). However, this cannot be proven as in this case benzaldehyde is also forming from partial hydrolysis of the imine used.

Furthermore, it was attempted to perform the one pot 1,4-addition/nitro-Mannich reaction of methoxide to nitrostyrene. This would require the use of methanol as the solvent, as the 1,4-addition reaction of methoxide was found to be low yielding in other solvents. Methanol has not been used before as the solvent in the nitro-Mannich reaction, as it was incompatible to the previously used nucleophiles (dialkylzincs). Moreover, possible hydrogen-bonding of MeOH with the NH and NO2 groups might interfere with the 6-membered transition state proposed for the nitro-Mannich reaction (section 2.5.6), thereby altering the selectivity of the reaction.

Reaction of β-nitrostyrene with MeONa in MeOH, followed by addition of the imine and TFA as solutions in MeOH and TFA-protection of the resulting β-nitroamines
gave trifluoroacetamide 472 in 43% (Scheme 161). When imine 281 was present from the beginning as a mixture with the nitroalkene, trifluoroacetamide 472 was isolated in a yield of 49%, which is very close to the overall yield of the two-pot procedure (52%). This results show that the one-pot procedure in a solution of the alcohol, could potentially be used to substitute the two-step alkoxide conjugate addition/nitro-Mannich reaction protocol. A limitation of this one-pot procedure however, would be the melting point of the alcohol, as some heavier alcohols like benzyl alcohol would solidify at the initial temperature of the nitro-Mannich step (-78 °C).

Scheme 161. One-pot conjugate addition/nitro-Mannich reactions of β-nitrostyrene with MeONa

2.5.5.3 Adducts of nitrogen nucleophiles

The nitro-Mannich reactions of N-substituted nitroalkanes were not as successful as those of the O-substituted ones. Electron rich amines 442, 443 and 445 gave none of the desired trifluoroacetamides 452 (Scheme 162).

Scheme 162. Nitro-Mannich reactions of amine adducts to β-nitrostyrene

Nitro-Mannich reaction of 2,4-dimethoxyaniline adduct 442, gave none of the desired β-nitroamine 476, but instead an 88% conversion to β-nitrostyrene and 88% to 2,4-dimethoxyaniline and none of the initial 442 remained by 1H NMR. It is postulated that the formation of β-nitrostyrene from the nitro-Mannich step might be attributed to
elimination of the aniline under the acidic reaction conditions (Scheme 163). In light of this result, it was attempted to reduce the equivalents of trifluoroacetic acid used from 3.50 to 1.00 equiv., however this gave the same result. Since there was no advantage to using 3.50 equiv. of TFA, it was decided to use 1.00 equiv. for the rest of our investigation into nitrogen adducts.

Scheme 163. Nitro-Mannich reaction of 2,4-dimethoxyaniline adduct 442

Nitro-Mannich reaction of aniline 443, gave a 32% conversion to the crude β-nitroamine and 28% to β-nitrostyrene. Attempts to TFA-protect the product led to decomposition and only benzoaldehyde (from imine hydrolysis), and the trifluoroacetamides of aniline (53%) and para-anisidine (not isolated) were observed. Nitro-Mannich reaction of morpholine adduct 445 gave no desired β-nitroamine, but only starting material (43%) and β-nitrostyrene (24%).

In the case of para-nitroaniline as the substituent (444), the intermediate nitroamine 477 from the nitro-Mannich reaction was isolated in 65% conversion and a dr of 90:10 (Scheme 164). However, only a small yield of diastereomerically pure trifluoroacetamide 478 was isolated. This discrepancy between the conversion to nitroamine and yield of trifluoroacetamide indicated that a large amount of β-nitroamine 477 was degrading in the TFA-protection step. This degradation can be attributed tentatively to elimination of the trifluoroacetamide of any of the anilines in the basic reaction conditions. Attempts to synthesise trifluoroacetamide 478 in one pot from β-nitrostyrene were ineffective, as only a trace of the intermediate 477 was observed by $^1$H NMR.

Trifluoroacetamide products were also isolated from the reactions of oxazolidinone 447 and benzotriazole 446. In the case of 447 the intermediate nitroamine 479 was
isolated in modest conversion and \( dr \) and only a small yield of diastereomerically pure trifluoroacetamide 480 was isolated. With benzotriazole adduct 481, a small yield of trifluoroacetamide 482 was isolated, with a 79% yield of recovered starting material. The three products were assigned as having an \( anti/anti \) configuration (section 2.5.6.3).

![Scheme 164](image)

**Scheme 164.** Nitro-Mannich reactions of amine adducts to \( \beta \)-nitrostyrene

### 2.5.5.4 Adducts of other nucleophiles

Finally, the nitro-Mannich reaction of sulfur and phosphorus adducts was investigated. Reaction of \( \text{\textsuperscript{\#8}Bu} \)-butyl sulfide 448 gave unreacted sulfide (14%) and crude \( \beta \)-nitroamine 483 in a 73% conversion and \( dr \) of 45:55, while phenyl sulfide 449 gave unreacted sulfide (14%) and crude \( \beta \)-nitroamine 484 in 57% conversion and \( dr \) of 65:35. Subsequent TFA-protection, led to isolation of the desired trifluoroacetamides 485 and 486 in medium yields and almost unchanged \( dr \) (Scheme 165). The major products were assigned as the \( syn/anti \) diastereoisomers (see section 2.5.6.5).

![Scheme 165](image)

**Scheme 165.** Nitro-Mannich reactions of thiol adducts to \( \beta \)-nitrostyrene
Reactions of sulfone 451 and phosphine oxide 450 (Figure 23), were however less successful. Nitro-Mannich reaction of sulfone 451 gave only recovered starting material and unreacted imine, as did reaction of 450 (Figure 23). A reason for this lack of reactivity could be the possible deprotonation $\alpha$ to the phosphorus or sulfur atom, instead of $\alpha$ to the nitro group. The pka’s in DMSO are expected to be $\approx 25$ for the proton $\alpha$ to the phosphorus, $\approx 24$ for the one $\alpha$ to the sulfone, and $\approx 17$ for the one $\alpha$ to the nitro group, based on literature values of related compounds.\textsuperscript{209} Therefore it is unlikely that deprotonation would occur $\alpha$ to the phosphorus or sulfur atom. To our knowledge, there is only one example of a conjugate addition of a $\beta$-nitrophosphate\textsuperscript{210} and one for a $\beta$-nitrosulfone,\textsuperscript{211} and in both reports the conjugate addition occurred $\alpha$ to the nitro group. Moreover, the electron withdrawing phosphine oxide and sulfone groups would be expected to make the nitronate anion less nucleophilic, thereby unreactive in the nitro-Mannich reaction.

![Figure 23](image-url)

2.5.6 Relative stereochemistry

As previously described, the trifluoroacetamides synthesised by our two pot 1,4-addition/nitro-Mannich methodology, were isolated mostly as single diastereoisomers, with the exception of sulfides 485 and 486 (60:40 and 65:35 $dr$). To prove the relative stereochemistry, some trifluoroacetamides were crystallized and X-ray diffraction crystal structures were obtained. All crystal structures showed an anti/anti relative stereochemistry. However, it was not possible to obtain crystal structures for all analogues. Therefore, it was attempted to assign the relative stereochemistry for the rest of the trifluoroacetamides, by comparison of their $^1$H NMR coupling constants with the analogues where the stereochemistry was confirmed by X-ray crystallography. For this assignment we used the coupling constants between the 1,4-addition centre and the nitro group ($J_{HaHb}$) and between the nitro group and the amino centre ($J_{HbHc}$) of our derivatives 487 (Table 17).
Table 17. Table of coupling constants of synthesised β-nitroamines and trifluoroacetamides

<table>
<thead>
<tr>
<th>R²</th>
<th>R² = H</th>
<th>R² = TFA</th>
</tr>
</thead>
<tbody>
<tr>
<td>J_{HaHb} (Hz)</td>
<td>J_{HbHc} (Hz)</td>
<td>J_{HaHb} (Hz)</td>
</tr>
<tr>
<td>C</td>
<td>11.5-12.2</td>
<td>3.4</td>
</tr>
<tr>
<td>O</td>
<td>8.8-9.3</td>
<td>5.3-6.2</td>
</tr>
<tr>
<td>N</td>
<td>9.1</td>
<td>6.2</td>
</tr>
<tr>
<td>S</td>
<td>9.4-11.0&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3.5-5.3&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>The values for para-nitroaniline analogue are omitted.

<sup>b</sup>Values for the major diastereoisomer.

<sup>c</sup>All other trifluoroacetamides were isolated as single diastereoisomers.

As it can be seen in Table 17, although within each group of compounds the coupling constants generally fall within a narrow range (<2 Hz), there are significant differences between some groups, so it was decided to treat them separately. In previous work it had been proposed that β-nitroamines can exist in a chair conformation, due to hydrogen bonding between the NH proton and the nitro group (Figure 24). In this chair conformation, we expect the anti-β-nitroamines to have proton H₆ in an axial position and H₇ in an equatorial one. This means that the dihedral angle between them would be ≈60°, which should have a medium coupling constant according to Karplus equation, as it was indeed observed for J_{HbHc}.

After TFA-protection of the nitroamines, no intramolecular hydrogen bonding is possible (with the exception of aniline 478) and the molecule would have an open chain conformation. It is assumed however, that the molecule would have a conformation bearing the two electron withdrawing groups on opposite sites, in order to reduce the overall dipole moment (Figure 24). This would mean a dihedral angle of 180°, which would have a larger coupling constant for J_{HbHc}, which can be observed for all our analogues.
Figure 24. Explanation of the observed coupling constants

The assignment of the remaining centre (H_a-H_b) though was more intriguing. In the β-nitroamines (R^2 = H) it is expected that the molecule would reside in a conformation where the substituents of the exocyclic carbon and the endocyclic one would be staggered (Figure 25). Moreover, H_a is expected to occupy mostly the position antiperiplanar to H_b, in order to minimize any pseudo-diaxial interactions with the axial phenyl group (Figure 25). If the R group is electron withdrawing, it is expected that it would prefer to be antiperiplanar to the nitro group so as to minimize the dipole of the molecule. This would mean a dihedral angle of 180° between H_a and H_b, which would give a larger coupling constant for J_{H_aH_b}, as was observed for all our analogues.

After TFA-protection of the nitroamines, the molecule would have an open chain conformation, so again the Newman projections of the same two carbons must be considered. With the same reasoning as before, if the R group is electron withdrawing it is believed that the molecule would have a conformation bearing R antiperiplanar to the nitro group, so as to reduce the overall dipole (Figure 25). This would mean a dihedral angle of 180° between H_a and H_b, which would lead to a large coupling constant for J_{H_aH_b}. This was observed for most analogues with the exception of the two sulfides 485 and 486.

Figure 25. Explanation of the observed coupling constants

2.5.6.1 Carbon adducts

Trifluoroacetamides 455 and 456 were isolated from the 1,4-addition of carbon nucleophiles followed by a nitro-Mannich/TFA-protection reaction. Fortunately, it
was possible to obtain an X-ray crystal structure of trimethoxyphenyl analogue 456, which showed an \textit{anti/anti} relative stereochemistry (Figure 26).

![Figure 26. X-ray crystal structure of (±)-456](image)

With indole analogue 455, it was not possible to obtain a crystal structure as the compound was not crystalline, thus a comparison of the coupling constants \(J_{\text{HaHb}}\) and \(J_{\text{HbHc}}\) with those of trimethoxyphenyl analogue 456 was attempted. When examining the values for the two crude \(\beta\)-nitroamines 453 and 454, it was observed that for the trimethoxyphenyl adduct 454, \(J_{\text{HaHb}}\) was 12.2 Hz and \(J_{\text{HbHc}}\) could not be distinguished, whereas for indole adduct 453, \(J_{\text{HaHb}} = 11.5\) Hz and \(J_{\text{HbHc}} = 3.4\) Hz. As the values for \(J_{\text{HaHb}}\) are equally large, the two compounds are expected to have the same \textit{anti} relationship between \(H_a\) and \(H_b\) (Table 17). In light of the absence of data for \(J_{\text{HbHc}}\) though, the remaining \(H_b-H_c\) relative stereochemistry could not be determined.

The coupling constant data for the respective trifluoroacetamides were not as helpful, as for 456, \(J_{\text{HaHb}} = 11.5\) Hz and \(J_{\text{HbHc}} = 3.4\) Hz, while for 455, \(J_{\text{HaHb}} = 6.7\) Hz and \(J_{\text{HbHc}} = 9.2\) Hz were measured. It is not safe to draw any conclusions from the values of coupling constants of trifluoroacetamides 455 and 456, as those are the result of averaging the coupling constants of all the possible conformations, due to free rotation along the C-C bonds between our stereocentres.

In order to assign the \(H_b-H_c\) relative stereochemistry of indole 455, it was decided to perform another experiment. After the nitro-Mannich reaction of indole 429, the produced \(\beta\)-nitroamine 453 was subjected to reduction of the nitro group with Zn/HCl. The crude diamine then produced, was reacted with thiophosgene in
DCM/MeOH, to give imidazolidine-2-thione 488 as a single diastereoisomer (Scheme 166). The product was isolated in low yield, presumably due to degradation of part of the \( \beta \)-nitroamine 453 in the reduction conditions and other side reactions in the cyclisation step. The reaction conditions were not optimised due to time constrains, however some useful information could be obtained from derivative 488, which presumably comes from the major diastereoisomer of the initial nitroamine 453.

![Scheme 166. Synthesis of imidazolidine-2-thione 488](image)

NOE studies have shown that irradiation of the \( \text{H}_b \) peak at \( \delta \) 6.16 ppm caused a 3.95% enhancement of the peak of \( \text{H}_c \), but only 0.70% of \( \text{H}_a \) (Figure 27). The big value for \( \text{H}_c \) indicates that the relative stereochemistry between \( \text{H}_b \) and \( \text{H}_c \) in the imidazolidine-2-thione ring is \( \text{cis} \), which corresponds to an \textit{anti} configuration between the nitro group and the amine in \( \beta \)-nitroamine 453. The small value of \( \text{H}_a \) can be explained by a possible \textit{anti} conformation in the Newman projection between protons \( \text{H}_a \) and \( \text{H}_b \) (Figure 27). The \textit{anti} positioning of these two protons was also supported by the large value of the coupling constant between them of 10.3 Hz.

Furthermore, imidazolidine-2-thiones like 488 have been reported by the Anderson group as a means of protecting 1,2-diamines.\(^{14}\) In particular, imidazolidine-2-thione 489 which was isolated in enantiomerically pure form and characterised by X-ray crystallography, greatly resembles our derivative 488.\(^ {212}\) Therefore, it was possible to compare, at least for the stereochemistry of the imidazolidine ring, the coupling constants for the coupling \( \text{H}_b-\text{H}_c \) (\( J_{\text{HbHc}} \)). The value reported for 489 was 9.2 Hz which is very close to the one observed in 488 that was 8.7 Hz, further confirming the above conclusion.
As further proof, molecular modelling was used to predict the values of $J_{\text{HaHb}}$ and $J_{\text{HbHc}}$ for $\beta$-nitroamine 453, trifluoroacetamide 455 and imidazolidine-2-thione 488. The values were in agreement with our experimental data for both the $\beta$-nitroamine 453 and imidazolidine-2-thione 488 (Table 18). Based on these results, the relative stereochemistry of trifluoroacetamide 455 can be tentatively assigned as being anti/anti.

**Table 18.** Predicted and experimental values of coupling constants of 453, 455 and 488

<table>
<thead>
<tr>
<th>Compound</th>
<th>$J_{\text{observed (Hz)}}$</th>
<th>$J_{\text{predicted (Hz)}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$J_{\text{HaHb}}$</td>
<td>$J_{\text{HbHc}}$</td>
</tr>
<tr>
<td>453</td>
<td>11.5</td>
<td>3.4</td>
</tr>
<tr>
<td>455</td>
<td>6.7</td>
<td>9.2</td>
</tr>
<tr>
<td>488</td>
<td>10.3</td>
<td>8.7</td>
</tr>
</tbody>
</table>

When investigating the nitro-Mannich/cyclisation reaction of Meldrum’s acid adduct 433 with $n$-butylamine and benzaldehyde, piperidinone 462 was isolated (Section 2.5.5.1, Scheme 157). The observed coupling constant values of this compound were 11.3 and 8.6 Hz for $J_{\text{HaHb}}$ and $J_{\text{HbHc}}$ respectively (Figure 28). By comparison of the coupling constants with the very similar reported piperidinone 490, compound 462 can be tentatively assigned as having a trans/trans relative stereochemistry around the piperidinone ring (Figure 28).

NOE studies have shown that irradiation of the $\text{CHCH}_2$ peak (H$_c$) at $\delta$ 3.73 ppm caused a 0.37% enhancement for protons H$_b$ and 1.83% for proton H$_a$ (Figure 28). These values were in agreement with a trans/trans relative stereochemistry where the three protons H$_a$, H$_b$ and H$_c$ are in axial positions, therefore H$_a$ is close in space to H$_c$. 
Furthermore, molecular modelling of trans/trans-462 predicted the values of $J_{HaHb}$ and $J_{HbHc}$ to be 11.3 and 10.6 Hz respectively, values that are very close to our experimental data.\textsuperscript{128} The distances H$_a$-H$_c$ and H$_b$-H$_c$ were also calculated for trans/trans-462 and found to be 2.45 and 3.07 Å respectively, which agrees with our observed NOE values.

\begin{figure}
\centering
\includegraphics[width=0.8\textwidth]{Figure_28.png}
\caption{Figure 28}
\end{figure}

2.5.6.2 Oxygen adducts

From the nitro-Mannich reaction of oxygen adducts of $\beta$-nitrostyrene, trifluoroacetamides 472-475 were obtained. All the analogues of this series show a close range of coupling constants. For the intermediate $\beta$-nitroamines 468-471, a medium value of 5.3-6.2 Hz was observed for $J_{HbHc}$ and a larger value of 8.8-9.3 Hz for $J_{HaHb}$, as expected. For the trifluoroacetamide products the value for $J_{HaHb}$ decreased slightly to 6.7-8.5 Hz and that of $J_{HbHc}$ increased to 10.7-11.0 Hz. An X-ray crystal structure was obtained for methoxy-substituted analogue 472, which showed an anti/anti relative stereochemistry (Figure 29). Due to the close resemblance of the coupling constant values of all the analogues, they can all be comfortably assigned as the anti/anti diastereoisomers.

\begin{figure}
\centering
\includegraphics[width=0.8\textwidth]{Figure_29.png}
\caption{X-ray crystal structure of (±)-472}
\end{figure}
2.5.6.3 Nitrogen adducts

It was then attempted to assign the relative stereochemistry of trifluoroacetamides 478, 480 and 482, derived from nitrogen adducts to β-nitrostyrene. Unfortunately, some of the coupling constants of β-nitroamines 479 and 481 (appendix 1) could not be distinguished from the $^1$H NMR spectra. Although the values for 477 could be measured, this nitroamine has two NH protons, therefore it is unknown which one would hydrogen bond to the nitro group to give a chair conformation.

When looking at the coupling constant values for the three trifluoroacetamides, it can be seen that 480 and 482 have a large value for $J_{HaHb}$ (9.9-10.7 Hz), while $J_{HbHc}$ has a slightly smaller one (6.3-7.9 Hz). The coupling constant values for para-nitroamine analogue 477 were significantly different, which is explained below. An X-ray crystal structure was obtained for trifluoroacetamides 480 and 482, showing an anti/anti relative stereochemistry in both cases (Figure 30).

![Figure 30. X-ray crystal structures of (±)-480 and (±)-482](image-url)
To compare with our previous results, it was also attempted to synthesise an imidazolidine-2-thione derivative from oxazolidinone analogue 480, as was done in section 2.5.6.1. The desired imidazolidine-2-thione was synthesised as a mixture of diastereoisomers 491a and 491b with a $dr$ of 85:15, in 21% yield over 3 steps (Scheme 167). NOE studies have shown that irradiation of the H$_b$ peak of 491a at $\delta$ 5.78 ppm caused a 2.76% enhancement of the peak of H$_c$, but only 0.33% of H$_a$ (proton assignments like in Figure 27). The large NOE value between H$_b$ and H$_c$ indicates that the relative stereochemistry between H$_b$ and H$_c$ in the imidazolidine-2-thione ring is cis, which agrees with the observed anti relative stereochemistry between the nitro group and the amine in $\beta$-nitroamine 477. The smaller enhancement between H$_b$ and H$_a$ can be explained by a possible anti conformation in the Newman projection between protons H$_a$ and H$_b$, similar to the one seen previously (Figure 27).

The observed $J_{HbHc}$ value of 491a was 9.4 Hz, which is again close to the magnitude of that reported for 489 which was 9.2 Hz (Figure 27). This similarity supports the assignment of an anti relative stereochemistry between the NO$_2$ and NH groups in trifluoroacetamide 480, something that was proved by the X-ray structure obtained. For the minor diastereoisomer 491b, the $J_{HaHb}$ and $J_{HbHc}$ values observed were 10.0 and 9.8 Hz respectively. The value of $J_{HbHc}$ is almost identical to that of 491a, so it is fair to assume the same relative stereochemistry around the ring, but the opposite one at the remaining stereocentre. Thereby, it can be concluded that the major diastereoisomer of $\beta$-nitroamine 479 ($dr = 75:25$) is the anti/anti and the minor one the syn/anti.

Scheme 167. Synthesis of imidazolidine-2-thiones 491a and 491b

Furthermore, some molecular modelling data were collected on trifluoroacetamide 480 and imidazolidine-2-thione 491a in order to compare with the experimental values and assess the validity of the modelling data. For imidazolidine-2-thione 491a, both predicted coupling constants were in agreement with the experimental values.
(Table 19). For trifluoroacetamide 480, the predicted value for $J_{HaHb}$ was in agreement with the experimental one, however the experimental value for $J_{HbHc}$ was slightly lower, potentially due to limited contribution by gauche conformations.

**Table 19. Experimental and predicted coupling constants of 480 and 491a**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Coupling constant</th>
<th>$J$ observed (Hz)</th>
<th>$J$ predicted (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>480</td>
<td>$J_{HaHb}$</td>
<td>10.1</td>
<td>10.8</td>
</tr>
<tr>
<td>480</td>
<td>$J_{HbHc}$</td>
<td>7.9</td>
<td>10.8</td>
</tr>
<tr>
<td>491a</td>
<td>$J_{HaHb}$</td>
<td>10.7</td>
<td>10.7</td>
</tr>
<tr>
<td>491a</td>
<td>$J_{HbHc}$</td>
<td>9.4</td>
<td>7.8</td>
</tr>
</tbody>
</table>

For para-nitroaniline trifluoroacetamide 478, the observed values of coupling constants were significantly different from the other two analogues. A value of 3.1 Hz was observed for $J_{HaHb}$ and 10.8 Hz for $J_{HbHc}$. A possible explanation of this would be that trifluoroacetamide 478 still contains a proton capable of hydrogen bonding, so the molecule can form a chair structure like that seen before for other β-nitroamines. In this conformation $J_{HaHb}$ would be smaller than expected, while $J_{HbHc}$ would be larger (Figure 31).

![Figure 31](image_url)

This discrepancy was investigated by molecular modelling studies that predicted the values of $J_{HaHb}$ and $J_{HbHc}$ for the intermediate β-nitroamine 477 and trifluoroacetamide 478. A number of different conformations of β-nitroamine 477 were modelled, including ones where para-nitroaniline’s NH proton was hydrogen-bonded to the nitro group, para-anisidine’s NH proton was hydrogen-bonded to the nitro group, both the NH protons hydrogen bonded and finally no hydrogen-bonding. The closest agreement to the experimental value was from the model where no hydrogen bonding occurs, with an anti conformation over both C-C bonds considered. A number of
Andreas Kalogirou

Different conformations were also modelled for trifluoroacetamide 478. Those included para-nitroaniline’s NH proton hydrogen-bonding to the nitro group, para-nitroaniline’s NH proton hydrogen-bonding to the TFA group oxygen and no hydrogen-bonding. The closest agreement to the experimental value was interestingly from the model where para-nitroaniline’s NH proton hydrogen-bonded to the TFA group oxygen (Table 20).

Table 20. Predicted and experimental values of coupling constants of 477 and 478

<table>
<thead>
<tr>
<th>Compound</th>
<th>Coupling constant</th>
<th>J observed (Hz)</th>
<th>J predicted (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>477</td>
<td>$J_{HaHb}$</td>
<td>9.1</td>
<td>10.7</td>
</tr>
<tr>
<td>477</td>
<td>$J_{HbHc}$</td>
<td>6.2</td>
<td>10.6</td>
</tr>
<tr>
<td>478</td>
<td>$J_{HaHb}$</td>
<td>3.1</td>
<td>1.6</td>
</tr>
<tr>
<td>478</td>
<td>$J_{HbHc}$</td>
<td>10.8</td>
<td>10.8</td>
</tr>
</tbody>
</table>

2.5.6.4 Sulfur adducts

As reported earlier, the nitro-Mannich reaction/TFA-protection methodology gave poor dr’s for the two trifluoroacetamides derived from sulfides 485 and 486 (60:40 and 65:35 respectively). In order to assign the relative stereochemistry of both the major and the minor diastereoisomers, we looked at the coupling constants of initially formed β-nitroamines 483 and 484 (Table 21). The values of coupling constants though, showed only a small deviation (1.0-2.4 Hz) between the major and the minor diastereoisomers. When looking at the same values for trifluoroacetamides 485 and 486, it was observed that the values for $J_{HbHc}$ were almost identical in both cases between the two diastereoisomers, while they deviate slightly for $J_{HaHb}$.
Table 21. Experimental values of coupling constants of the major and minor diastereoisomers of 483-486.

<table>
<thead>
<tr>
<th></th>
<th>( J_{HaHb} ) (Hz)</th>
<th>( J_{HbHc} ) (Hz)</th>
<th>( J_{HaHb} ) (Hz)</th>
<th>( J_{HbHc} ) (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(^{a})Bu, major</td>
<td>11.0</td>
<td>3.5</td>
<td>6.2</td>
<td>10.4</td>
</tr>
<tr>
<td>(^{a})Bu, minor</td>
<td>8.6</td>
<td>5.9</td>
<td>4.6</td>
<td>10.4</td>
</tr>
<tr>
<td>Ph, major</td>
<td>9.4</td>
<td>5.1</td>
<td>5.1</td>
<td>9.8</td>
</tr>
<tr>
<td>Ph, minor</td>
<td>10.4</td>
<td>4.0</td>
<td>6.1</td>
<td>10.0</td>
</tr>
</tbody>
</table>

The observed values of \( J_{HbHc} \) for both diastereoisomers of \( \beta \)-nitroamines 483 and 484 (3.5-5.9 Hz) were in close agreement with those of other carbon, nitrogen and oxygen \( \beta \)-nitroamine derivatives (3.4-6.2 Hz, Table 17). Other similar nitroamines prepared in the past were assigned an anti relative stereochemistry between \( H_b - H_c \) based on \( J_{HbHc} \) values of 3.2-5.8 Hz,\(^{114}\) which agrees with our observed range (Figure 31). In light of this agreement and the fact that an intramolecular hydrogen-bonding chair conformation is assumed, that would fix the \( J_{HbHc} \) to medium values for an anti relation between the NO\(_2\) and NH groups, leads us to tentatively assign the relative stereochemistry between \( H_b \) and \( H_c \) as anti. Therefore the two diastereoisomers should be the anti/anti and the syn/anti.

![Figure 31. Comparison of \( J_{HbHc} \) values of anti-\( \beta \)-nitroamines](image)

Molecular modelling data were subsequently collected, in order to help assign the major diastereoisomer. All possible diastereoisomers were modelled and no
significant differences were observed in the values of $J_{HaHb}$ when modelling the lowest energy *anti* conformation of $H_a$ and $H_b$ in the Newman projection (Figure 25). It is unknown how much other rotational conformations contribute to the experimental coupling constant, thus it is very hard to draw any conclusion from this study.

The synthesis of the imidazolidine-2-thione derivatives for the two sulfides was also attempted (Scheme 168), as this has been shown before to be useful for the determination of relative stereochemistry (section 2.5.6.1). Reaction of $\beta$-nitroamine 483 ($dr$ 55:45) was successful in providing imidazolidine-2-thiones 492a and 492b with a $dr$ of 80:20 (Scheme 168) in 20% yield over 3 steps. Unfortunately, the desired product could not be isolated from the same reaction of phenylsulfide 449. The $J_{HaHb}$ and $J_{HbHc}$ values of the major diastereoisomer of 492 were 11.5 and 8.4 Hz respectively and for the minor they were 11.2 and 8.8 Hz respectively. Since these values are almost identical, it is very difficult to draw any conclusions of the relative stereochemistry for each diastereoisomer.

NOE studies for the major diastereoisomer of 492 showed that irradiation of the $H_b$ peak at $\delta$ 4.58 ppm caused a 4.73% enhancement of the peak of $H_c$ but only 0.41% of $H_a$. The large NOE value for $H_c$ indicates that the relative stereochemistry between $H_b$ and $H_c$ in the imidazolidine-2-thione ring is *cis*, which agrees with the observed *anti* relative stereochemistry between the nitro group and the amine in $\beta$-nitroamine 483. The small NOE value between $H_a$ and $H_b$, can be explained by a possible *anti* conformation in the Newman projection between protons $H_a$ and $H_b$, similar to the one seen previously (Figure 27). The *cis* relative stereochemistry between $H_b$ and $H_c$ in the imidazolidine-2-thione ring was also confirmed by the value for $J_{HbHc}$ in the imidazolidinone, which is in agreement to the one reported for 489 (9.2 Hz, Figure 27). The NOE study of the minor diastereoisomer was not possible due to overlapping of the peaks.

![Scheme 168. Synthesis of imidazolidine-2-thiones 492a and 492b](image-url)
It thereby remains uncertain, which is the relative stereochemistry between the SBu and NO₂ groups in β-nitroamines 483 and 484 and trifluoroacetamides 485 and 486. The possible relative stereochemistry of the major diastereoisomer would be suggested in the next section.

In conclusion, our data suggest that in most of our derivatives the nitro-Mannich reaction gives an anti/anti relative stereochemistry as the major diastereoisomer formed. All the coupling constant data are given in Appendix 1. In the next section the origins of this diastereoselectivity are discussed.

2.5.7 Source of diastereoselectivity

In the previous sections, it was demonstrated that the two-pot 1,4-addition/nitro-Mannich methodology, starting from β-nitrostyrene with non-zinc nucleophiles, showed relative stereocontrol in all three chiral centres formed to give the anti/anti diastereoisomers. In previous work with dialkylzinc reagents, the syn/anti trifluoroacetamides were the major products in homogenous solutions, while the syn/syn diastereoisomers were the major products in heterogenous solutions (section 2.1). In light of this, it was important to explain the observed anti/anti relative stereochemistry in this work and its difference with the previous results. Products 379 have two pairs of stereocentres that need to be considered, the relative stereochemistry between the nucleophile and the nitro group (C₁-C₂, Figure 32) and the one between the nitro group and the amine (C₂-C₃, Figure 32).

![Figure 32](image)

The origin of the C₁-C₂ relative stereochemistry is first examined. A number of general rules exist for the electrophilic attack α- to a stereocentre, taking under consideration steric and electronic parameters on the stereocentre. According to Houk’s outside-crowded model, when considering reactions of highly polarized double bonds, such as enolates and nitronates with electrophiles, the trajectory of the incoming electrophile is the one predicted by the Felkin-Ann model (angle of attack >90° to alkene). According to this model, in the reactive conformation of nitronate
the three groups on the adjacent stereocentre are positioned in such a way as the smaller group (S) is closer to the incoming electrophile, the medium one (M) closer to the double bond and the larger one (L) perpendicular to the double bond (Scheme 169). The electrophile would approach from an angle closer to the small group for steric reasons. This analysis correctly predicted the major syn-diastereoselectivity observed previously between C₁ and C₂ in the product β-nitroamines 230, in both addition protocols used in the previous work with dialkylzinc reagents (Scheme 169).³⁵

\[ \text{Scheme 169. Explanation of the C₁-C₂ syn relative stereochemistry reported for dialkylzinc additions to nitrostyrenes.}³⁵ \]

In light of this it was decided to use Houk’s model, described above, to explain the C₁-C₂ stereochemistry in the obtained trifluoroacetamides. This model ignores any stereoelectronic effects that could arise from polar substituents in the adjacent stereocentre. It can be assumed that the substituents in the two carbon adducts 455 and 456 are not polar for the model to be valid. To complete the interpretation, knowledge of the A-values of all groups considered was needed, in order to rank our substituents in the order of size. The reported values for a phenyl group is 2.8 Kcal/mol and for a proton 0.0 Kcal/mol.²¹⁴ However, no reported values for the 2,4,6-trimethoxyphenyl and 3-indoline groups exist, as well as for the BuS and PhS groups. In light of this, it was decided to predict the A-values required by calculating the energy difference of the cyclohexane ring bearing the substituent in question in equatorial or axial position, using molecular modelling.¹²⁸ The predicted values for MeS, PhS, Me, ³Pr and ³Bu groups were in good agreement with the reported values, while only the phenyl group deviated from the reported A-value (Chart 1). The deviation can be attributed to the fact that the reported values were recorded at rt, whereas the computer calculation assumes a temperature of zero Kelvin with no movement of atoms. Due to this deviation, the predicted A-values for Aromatic substituents were not expected to be accurate.
Chart 1. Comparison of calculated and reported\textsuperscript{214} A-values of chemical groups

Based on the molecular modelling results, the 2,4,6-trimethoxyphenyl and 3-indoline groups were found to be larger than the phenyl group, with A-values of 5.9 and 7.9 Kcal/mol respectively. These values are too large to be realistic, as A-values much larger than 5 Kcal/mol ('Bu group has 4.7 Kcal/mol) are not expected. However, it can be assumed that the A-values for the 2,4,6-trimethoxyphenyl and 3-indoline groups are indeed larger than the phenyl group.

Applying Houk’s model would require that the Ar group (2,4,6-trimethoxyphenyl or 3-indoline group) would occupy the \textit{anti} position to the incoming electrophile in the reactive conformation of nitronate 494, with the phenyl group being inside and the proton being in the crowded outside position (Scheme 170). The reaction will then proceed via the Newman projection shown in Scheme 170, which has an \textit{anti} stereochemistry between the Ar and NO\textsubscript{2} groups in \(\beta\)-nitroamines 495.

Scheme 170. Origin of the C\textsubscript{1}-C\textsubscript{2} relative stereochemistry when Ar is bigger than Ph

A different explanation however, is needed for the rest of our examples, as a variety of different heteroatoms are present in the adjacent stereocentre. Consequently, stereoelectronic effects that arise from the presence of polar substituents in the adjacent stereocentre of nitronate 496 are now important. Even though the Felkin-Ahn model predicts that the electronegative substituent would occupy the perpendicular
position in nucleophilic additions to double bonds,\textsuperscript{215} it is less clear what the reactive conformation is in electrophilic additions.\textsuperscript{216}

Some reports in the literature however, were helpful in understanding the stereoelectronic effects in the reaction of our nitronates. Very useful to the understanding of the model of electrophilic addition reactions to electron rich double bonds, was the report by Houk and co-workers on the stereoselective cycloadditions of nitrile oxides to chiral allyl ethers and alcohols.\textsuperscript{213} The authors reported a preference of alkoxy and hydroxyl groups to occupy the inside position, while other alkyl or aryl groups occupy the \textit{anti} position and the proton the remaining outside position (transition state A, Figure 33). The authors argue that the reason for the preference of the alkoxy group for the inside position is that during the attack of the electrophile, the \( \pi \) bond becomes electron deficient so electron-withdrawing groups would destabilize the transition state. If the alkoxy group is in the \textit{anti} position then the \( \sigma_{\text{CO}}^* \) overlaps with the \( \pi \) orbital of the alkene, withdrawing electron density from it. When C-O is inside however, this overlap is minimised, while overlap of electron donating \( \sigma_{\text{CH}} \) and \( \sigma_{\text{CR}} \) with the \( \pi \) bond is maximised thereby stabilizing the transition state. The authors also suggest that the second most favourable transition state would be B, where the alkoxy group is positioned outside and the proton inside. Transition state B is less favoured, as it places the OR group \textit{gauche} to the alkene’s H, something that would increase the sterical clash to the incoming electrophile.

![Figure 33](image_url)

**Figure 33.** Houk’s model of electrophilic additions to electron rich double bonds

Houk and co-workers argue that their inside alkoxy model can be used to explain other electrophilic additions to allyl ethers. When studying the osmylation of allylic ethers \textsuperscript{497}, Kishi and co-workers reported a good level of diastereoselectivity, that could not be explained by considering the steric factors only. The major diastereoisomers of the product diols \textsuperscript{498}, were the ones where the newly formed hydroxyl group was \textit{trans} to a pre-existing hydroxyl or ether group, suggesting an \textit{anti} attack of the reagent to the oxygen atom (Scheme 171).\textsuperscript{217,218} In a similar work Stork
and Kahn reported the hydroxylation of \( \alpha,\beta \)-unsaturated esters 499 by OsO\(_4\), to give diastereomerically pure 3,4-dihydroxy-\( \gamma \)-lactones 500.\(^{219}\) In this work, the authors suggest a different mechanism where the alkoxy group is in the outside position, which is the same as transition state B proposed by Houk (Figure 33). They argue that a favourable interaction exists between the \( \pi \) bond and the \( \gamma \)-oxygen’s lone pair because of the electron withdrawing character of the carbomethoxy functionality.

**Scheme 171.** Kishi’s and Stork’s electrophilic additions to electron rich double bonds

Furthermore, when studying the iodocyclisation of allylic alcohols 501, Chamberlin and co-workers reported a transition state for the electrophilic addition of iodine similar to Houk’s B model (Figure 33), which explains their high diastereoselectivity of lactones 502 produced (Scheme 172).\(^{220}\)

**Scheme 172.** Chamberlin’s electrophilic addition of iodine to double bonds

Based on the reported results, it can be assumed that one of the two models proposed by Houk (Figure 33) would be valid in our case, when we have an electronegative substituent (R) in the stereocentre adjacent to the nitronate 496. After a closer look into the two transition states (Scheme 173), it becomes apparent that transition state A would be destabilised by the repulsion of the nitro group with group R, as both of these groups are electron rich. Therefore, it would not be preferred for them to be close in space (Scheme 173). Such repulsion was not present in the above examples, as they lack an electron rich group on the double bond. Therefore, we can expect transition state B to be in operation when R is an electronegative substituent, with the Ph group, being larger than H, occupying the perpendicular position and the proton the inside position, giving rise to *anti-*379 \( \beta \)-nitroamines (Scheme 173).
The above reasoning correctly predicts the observed \textit{anti} relative stereochemistry between the groups $R$ and NO$_2$ in most of our derivatives. However, for the two sulfides 485 and 486 a very poor dr was observed (60:40 and 65:35 respectively), which shows that two competitive transition states are in operation that have a small energy difference. If sulfur is treated as an electronegative substituent, then transition state B would prevail where sulfur occupies the perpendicular position (Scheme 173). However, the reported value of electronegativity of sulfides is only 1.69, while that of the phenyl group is 3.64, which contradicts this hypothesis.$^{221}$ Moreover, the reported A-value for PhS is 1.1 Kcal/mol, while the predicted value for $^6$BuS is again 1.1 Kcal/mol (Chart 1). Both these values are smaller than the A-value of the Ph group (2.8 Kcal/mol).$^{214}$ Therefore, it is expected that the phenyl group would occupy the perpendicular position in the reactive conformation of 496 and both the transitions states A and B would be in operation (Scheme 173). A preference to transition state A would be expected, as the C-S bond is longer than the C-O or C-N ones and sulfur has less electron density (softer), thus it is expected to have less repulsion to the nitro group. Furthermore, transition state A is the one predicted by the Felkin-Ahn model, as it has the smallest group (H) closer to the incoming electrophile. Consequently, the major diastereoisomers of 503 in the two sulfide reactions can tentatively be assigned as the ones having a \textit{syn/anti} relative stereochemistry (Figure 34).

Having examined the origin of the C$_1$-C$_2$ relative stereochemistry, a plausible transition state model will now be formulated, in order to explain the origin of relative
stereochemistry across the C₂-C₃ stereocentres. The observed stereochemistry was in all of our examples *anti*, which implies a common mechanism. As was previously suggested for the conjugate addition/nitro-Mannich reactions of Superhydride® to nitroalkenes, it is postulated that the nitro-Mannich reaction proceeds via a Zimmerman-Traxler type transition state (Section 2.5.6). The most favoured transition state was the one leading to the *anti* isomer, as it avoids the 1,3-diaxial interactions between the axial R group and the PMP group, present in the transition state leading to the *anti* isomer (Scheme 174).

![Scheme 174. Origin of the C₂-C₃ relative stereochemistry](image)

Finally, the origin of the *trans/trans* relative stereochemistry in piperidinone 462 was investigated. The reaction was inspired from the work of Dixon and co-workers, who reported the synthesis of densely substituted pyrrolidinones by refluxing nitroesters with imines and benzoic acid (Scheme 76, section 1.5). The synthesis of piperidinones of this kind, starting from nitroesters, aldehydes and amines, has also been reported by the same group (Scheme 175). Piperidinones 504 were isolated mostly as single diastereoisomers bearing a *trans/trans* relative stereochemistry. The authors suggested two possible explanations to this, both supported by their experimental results. The first hypothesis was that the nitro-Mannich reaction was reversible and only one of the produced diastereoisomers cyclises preferentially in the irreversible lactamisation step, to give the most thermodynamically stable product. The second hypothesis was that two of the nitro-Mannich products cyclise and epimerization then occurs on the centre bearing the nitro group, leading to the most thermodynamically stable product. Likewise, in our experiment we can postulate either of these two hypotheses to be valid. No attempt to mechanistically investigate this reaction was made and no possible intermediates isolated, as this reaction was only performed to compare to our deprotonation/nitro-Mannich methodology.
2.5.8 Conclusions

This chapter described the investigation of the conjugate addition/nitro-Mannich reaction of non-zinc nucleophiles to nitroacrylate 231 and β-nitrostyrene 380. A variety of different nucleophiles were tested, including amines, thiols, phosphines, alcohols, enolates and nitriles. It was found that a two-pot procedure was more successful than a one-pot procedure. From nitroacrylate 231, the 1,4-addition products were isolated generally in good yields (81-99%) and then deprotonated with nBuLi and reacted with imine 281 and TFA. However, the success of this methodology was limited, as in most examples the pyrrolidinone products could not be isolated, while some of the isolated ones were found to be unstable. A few stable products were isolated, such as the highly functionalised pyrrolidinones 420 and 421 and octahydroquinoline 422 (Figure 35).

The conjugate addition of the same range of nucleophiles to β-nitrostyrene gave variable yields of 1,4-addition products 428 (45-97%). After deprotonation and nitro-Mannich reaction, the isolated β-nitroamines 379 were protected as trifluoroacetamides, as they were unstable to purification. The reaction of adducts of aromatic groups was successful and trifluoroacetamides 505 were isolated in medium yields as single diastereoisomers, whereas reactions of nucleophilic methylene adducts were mostly ineffective. Nitro-Mannich reactions of alcohol adducts gave good yields of trifluoroacetamides 506 and excellent diastereoselectivities. Reactions
of adducts of amines were mostly ineffective and only small yields of products were isolated in limited cases. Thiol adducts gave the desired trifluoroacetamides 507, albeit in medium yields and poor diastereoselectivities, while adducts of phosphines reacted poorly (Figure 36).

![Figure 36](image)

2.5.9 Future work

This chapter described the investigation of the 1,4-addition/nitro-Mannich reaction using non-zinc reagents. A comprehensive investigation was made into the conjugate addition of various reagents into nitroalkenes 231 and 380 and the feasibility of a nitro-Mannich reaction of the resulting nitroalkanes, however there is still plenty of work that could be carried out. Firstly, while this work was focused on the reactions of nitroalkenes 231 and 380, a wide variety of nitroalkenes exist, accessed easily from condensation of commercial aldehydes with nitromethane, followed by dehydration. Therefore, this study could be expanded to other nitroalkenes, especially trisubstituted ones 508 (Scheme 176). Such nitroalkenes were shown to react successfully in conjugate addition reactions (sections 1.2.3 and 1.2.4) and might offer a solution to some degradation issues encountered in this study, as they might be less prone to degradation by polymerisation due to steric reasons. Furthermore, this work focused on imine 281 and no other aromatic, heteroaromatic or alkyl imines were investigated. The investigation presented in this thesis offered the knowledge on which nucleophiles are more efficient in the reaction with \( \beta \)-nitrostyrene. The most effective nucleophiles were found to be electron-rich aromatics and alkoxides. Therefore, the investigation of the reactions of aromatic and alkoxy nucleophiles could be expanded to a combination of a variety of other nitroalkenes and imines, to give a wide range of possible products 509 (Scheme 176).
Furthermore, a variety of methods exist for performing asymmetric 1,4-additions to nitroalkenes using chiral catalysts (sections 1.2.3, 1.2.4 and 1.2.5). It would therefore be expected that if the conjugate addition to the nitroalkene was asymmetric, this would control the stereochemistry of all three newly formed stereocentres, giving rise to enantioenriched products. Alternatively, a chiral nucleophile could be used in the 1,4-addition reaction, something that should control the stereochemistry of the nitro-Mannich reaction. The chiral functionality could then potentially be removed to uncover highly functionalised enantioenriched products. Two promising examples of such reagents were reported, the “chiral water” reagent 74 developed by Dixon and co-workers and chiral oxazolidinone 87 developed by Le Gall and co-workers (Scheme 177).

Scheme 176. Possible conjugate addition/nitro-Mannich reactions

2.6 The synthesis of piperazirum via the nitro-Mannich methodology

2.6.1 Isolation

A number of biologically active piperazines exist. Many possess useful pharmaceutical properties, such as the HIV protease inhibitor indinavir 510 developed by Merck, as well as other experimental drugs.223 When studying the flowering plant Arum Palaestinum, Kim and co-workers isolated a new alkaloid compound from the “butanol fraction of the plants’ leaves which they named piperazirum.224 After structure elucidation through spectroscopic techniques (Mass spec., IR, 1H and 13C NMR), piperazirum was shown to be piperazinone 511 (Figure 37). Some studies of
the biological activity of this molecule showed that it exhibited inhibitory activity to a number of human cancer cell lines. Due to the activity of piperazirum as an anticancer agent and the presence of a 1,2-diamine functionality in the proposed structure 511, together with the absence of a synthetic route to such a simple looking small molecule, it was felt that the nitro-Mannich methodology previously developed in the Anderson group could be used in the synthesis of this molecule.

**Figure 37. Biologically active piperazines**

### 2.6.2 Strategy

A retrosynthetic analysis of 511, showed that the 1,2-diamine motif present could come from β-nitroamine 512 or 513, derived from a suitable nitro-Mannich reaction (Scheme 178). A simple condensation of diamine 514 or 515 with a suitable ketoacid derivative 516, should give enone 517 or 518. Further diastereoselective reduction and deprotection steps should provide 511. If the synthesis of β-nitroamine 512 or 513 was rendered asymmetric, then the enantiomerically pure form of 511 could be accessed. The natural compound was isolated as a single enantiomer, though the absolute stereochemistry has not been assigned by X-ray crystallography. Initially a racemic route was attempted with the hope that an asymmetric variant of the nitro-Mannich reaction could later be developed.

**Scheme 178. Retrosynthetic analysis of piperazine 511**
2.6.3 Synthesis

Initially, the synthesis of useful ketoacid 519 was investigated. Ketoester 520 was easily synthesised from a Grignard reaction of isobutyl magnesium chloride with diethyl oxalate in 94% yield (Scheme 179). Saponification of ketoester 520 with KOH then provided ketoacid 519 in excellent yield, while the respective acid chloride 521 could easily be prepared \textit{in situ} by treatment with oxalyl chloride (Scheme 179).

![Scheme 179. Synthesis of ketoester 520 and ketoacid 519](image)

With the ketoacid derivatives in hand, the synthesis of a suitable $\beta$-nitroamine was investigated. The synthesis of $\beta$-nitroamine 522 was attempted using nitroalkene 523 and imine 524 (Scheme 180). The 1,4-addition of Superhydride® on nitroalkenes and subsequent nitro-Mannich reaction has been reported by the Anderson group, to give \textit{anti} rich $\beta$-nitroamines 227 (scheme 77, section 2.1). Nitroalkene 523 was synthesised in one step from isobutyraldehyde and nitromethane (Scheme 180). Imine 524 was synthesised by the simple condensation of the same aldehyde and \textit{para}-anisidine with basic alumina, in DCM, at -78 °C, in 86% yield and used immediately to avoid degradation. The 1,4-addition of Superhydride® and subsequent nitro-Mannich reaction with imine 524 in THF gave $\beta$-nitroamine 522 in 64% conversion and 70:30 \textit{dr}. Using previously developed conditions to protect the amine \textit{in situ} using TFA-anhydride gave no trifluoroacetamide, but only nitroamine 525 was isolated as a single diastereoisomer in a low 15% yield. This result is not surprising as poor conversions and \textit{dr}, as well as resistance to TFA-protection were observed before with imines dissubstituted in the \textit{a} position, such as cyclohexyl imine.
The low yield of product 525 from the above reaction, as well as the fact that an electrophilic aromatic substitution reaction occurred instead of TFA-protection, meant that this product could not be used in our synthesis. However, as the conversion to intermediate β-nitroamine 522 was good, it was decided to avoid the TFA-protection step and reduce the nitroamine directly to 1,2-diamine 526. The isolation and reduction of β-nitroamines such as 522, suffers from the instability of these products due to retroaddition. However, it was found previously that it was possible to isolate β-nitroamines 230b by performing a column chromatography with no delay and gaining all possible data as fast as possible in cases where the products could not be TFA-protected (Scheme 78, section 2.1).\textsuperscript{35} Moreover, in previous studies samarium diiodide\textsuperscript{13} or aluminium amalgam\textsuperscript{37} were used to reduce β-nitroamines. Instead of these methods, a simpler method was attempted, the treatment of the β-nitroamine with Zn/HCl. After the nitro-Mannich reaction, the crude β-nitroamine product 522 was isolated by column chromatography and then immediately treated with Zn dust (10.0 equiv.) and 6 M aqueous HCl (20.0 equiv.) in EtOAc and EtOH, at rt for 2 h. The resulting diamine 526 was isolated in 50% overall yield as a single diastereoisomer (Scheme 181).

Scheme 180. Nitro-Mannich reaction from nitroalkene 523

Scheme 181. Synthesis of diamine 526
With diamine 526 in hand, the reaction with a suitable ketoacid derivative was investigated. The most reactive nitrogen was expected to be the primary amine. The most electrophilic carbonyl in ester 520 should be the ketone, as shown by reports on the reactivity of similar compounds. Therefore, the condensation of these two molecules should give 5,6-dihydropyrazin-2-one 527. The reaction under Dean-Stark conditions, after refluxing in toluene for 24 h in the presence of catalytic TsOH, gave only recovered starting materials. Simple heating of a 1,2-diamine with a ketoester in water at 50 °C was reported to give quinoxalinones 528 (Scheme 182). However, under these conditions, only a complicated mixture of products was isolated.

![Scheme 182. Attempt to synthesise 5,6-dihydropyrazin-2-one 527](image)

In light of this poor result, an alternative route to 511 via β-nitroamine 529 was investigated. For the synthesis of β-nitroamine 529, three possible methods were considered, starting from nitroalkenes 530 and 531 as well as from nitroalkane 532 (Scheme 183). Nitro-Mannich reaction of nitronate 533 with imine 534 should provide β-nitroamine 529. Nitronate 533 can be formed in three possible ways, from an addition of hydride to nitroalkene 530, addition of Me₂Zn to nitroalkene 531 or deprotonation of nitroalkane 532 (Scheme 183).

![Scheme 183. Possible routes to nitroamine 529](image)

The 1,4-addition/nitro-Mannich reaction of nitroalkene 530 with Superhydride® and imine 534 was initially investigated. Nitroalkene 530 was synthesised in three steps
from acetone and nitromethane, in low overall yield (Scheme 184). Imine 534 was synthesised by the simple condensation of isovaleraldehyde and para-anisidine with basic alumina, in DCM, at -78 °C, in 95% yield and used immediately to avoid degradation. The reductive nitro-Mannich reaction with imine 534 in THF gave β-nitroamine 529 in complete conversion and 85:15 dr and after TFA-protection trifluoroacetamide 535 in 78% yield and 95:5 dr. In previous work, improved anti-selectivity was observed when DCM was used as the solvent, therefore the reaction was repeated using DCM. Indeed, with DCM complete conversion to β-nitroamine 529 was observed with a dr of >95:5 and after TFA-protection, trifluoroacetamide 535 was isolated in 87% yield as a single diastereoisomer.

Scheme 184. Synthesis of nitroalkene 530 and trifluoroacetamide 535

After successfully obtaining trifluoroacetamide 535 in good yield, the synthesis of the corresponding diamine 538 was attempted. Transforming trifluoroacetamide 535 to 1,2-diamine 538 would require two further steps, specifically reduction with Zn/HCl to trifluoroacetamide 539 and then treatment with KOH to deprotect the trifluoroacetamide and release the amine 538, as has been previously reported (Scheme 185). Therefore, the direct reduction of β-nitroamine 529 to 1,2-diamine 538 was investigated, avoiding the two extra steps. After the nitro-Mannich reaction, the crude β-nitroamine 529 product was isolated by column chromatography and then immediately treated with Zn dust (10.0 equiv.) and 6 M aqueous HCl (20.0 equiv.) in EtOAc and EtOH, at rt for 2 h. The resulting diamine 538, was isolated in 85% overall yield as one diastereoisomer (Scheme 185).
In diamine 538 it would again be expected that the most reactive amine group would be that of the primary amine. To obtain a piperazinone of the desired geometry, a ketoacid derivative would be required, where the carboxylate carbonyl is more reactive than the ketone one. Two possible such compounds were considered, carboxylic acid 519 after activation by a coupling agent and acid chloride 521. Acid chloride 521 was prepared in situ by treatment of acid 519 with oxalyl chloride (2.00 equiv.) and catalytic DMF. Subsequent reaction with diamine 538 in the presence of pyridine (1.20 equiv.) and catalytic DMAP, over 24 h, according to previously reported reactions for similar ketoacids,\textsuperscript{227} gave only the bis-adduct 540 and none of the desired piperazinone 541. The reaction of carboxylic acid 519 though, with diamine 538, in the presence of EDC (1.50 equiv.) and 1-hydroxybenzotriazole (1.50 equiv.) at rt, gave the desired product 541 in good yield (Scheme 186).\textsuperscript{234} The assignment of the relative stereochemistry of 541 will be described in section 2.6.4.

Having successfully synthesised piperazinone 541, the reduction of the double bond was then required. Reduction of such enones has been reported using H\textsubscript{2} over Pd/C. The relative stereochemistry of 541 should render the hydrogenation
diastereoselective as the catalyst would be expected to approach the molecule from the less sterically hindered top face. Indeed, the hydrogenation in MeOH, at rt with only 1 atm of H₂ (balloon) afforded piperazinone 542 as a single diastereoisomer (Scheme 187). The assignment of relative stereochemistry of 542 will be described in section 2.6.4.

![Scheme 187. Hydrogenation of piperazinone 541](image)

The final step required to complete the synthesis of 511, was the deprotection of the PMP group in piperazinone 542. This deprotection can be affected using oxidation by CAN in MeCN/H₂O, at 0 °C.116 These conditions successfully affected the deprotection of 542 to give the desired piperazinone 511 in 41% yield (Scheme 188). Our compound 511 has the correct relative stereochemistry as proposed for the natural product (section 2.6.4). However, the ¹H NMR and ¹³C NMR data did not match the data given for the natural product. The details on structure elucidation of 511 will be described in the next section.

![Scheme 188. Deprotection of piperazinone 542](image)

2.6.4 Relative stereochemistry

The conjugate addition/nitro-Mannich reaction of Superhydride⁶ to nitroalkenes was reported to give anti-rich β-nitroamines 227 (Scheme 77, section 2.1).³⁶ Even thought this was the predicted relative stereochemistry for the β-nitroamines synthesised in this work, confirmation was needed. The β-nitroamines from this work (543) are expected, like before, to reside in a pseudo-chair conformation in solution (Scheme 189).¹¹⁵ The coupling constants expected between protons CHNO₂ and CHNH for anti-543 would therefore be expected to be of medium value. The values for β-
nitroamines 522 and 529 were 3.8 and 8.1 Hz respectively and are in agreement with the reported values for anti-β-nitroamines, which were in the range of 4.5-8.4 Hz.\textsuperscript{233} Moreover, the synthesis of imidazolidine-2-thione 544 from diamine 538 was attempted in order to further confirm the anti relative stereochemistry of the initial β-nitroamine 529. In the same way as before (section 2.5.6.1), reaction with thiophosgene gave imidazolidine-2-thione 544 in 42% yield as a single diastereoisomer (Scheme 189). NOE studies showed that irradiation of the CHNH peak at δ 3.70 ppm caused a 3.65% enhancement of the CHN peak, indicating a cis-relative stereochemistry between the two protons, which agrees with the observed anti relative stereochemistry between the nitro group and the amine in β-nitroamine 529 (Scheme 189). The observed coupling constant between the same two protons was 8.4 Hz, a value that is in agreement with the one reported for 489 which was 9.2 Hz (Figure 27, section 2.5.6.1), further corroborating our assignment.

The origin of the observed anti stereochemistry tentatively lies in the mechanism of the nitro-Mannich reaction, that is thought to proceed via a Zimmerman-Traxler type transition state (Section 2.5), as was previously suggested (Scheme 190).\textsuperscript{36}

The relative stereochemistry of 5,6-dihydropyrazin-2-one 541 was consequently examined. The relative stereochemistry of the C⁵-C⁶ stereocentres of 541 follows from the anti relative stereochemistry of acyclic diamine 538 which originated from the nitro-Mannich reaction. The double bond geometry was assigned by NOESY \textsuperscript{1}H NMR to have Z stereochemistry (Scheme 191). The reason for this stereochemistry
could be explained by the following mechanism (Scheme 191). Initial reaction of ketoacid 519 and diamine 538 should give ketoamide 545. Intramolecular nucleophilic addition of the secondary amine to the free carbonyl group would give 546, which after loss of water assisted by the nitrogen lone pair forms compound 547. The final deprotonation would occur in an antiperiplanar alignment to the C=N bond. There are two protons that can be eliminated, one giving the Z and the other the E isomer. Presumably the isopropyl group attached on the site of elimination in 547 would prefer to be on the top face as drawn, avoiding a destabilising interaction with the 1Pr and 1Bu groups on the underface. Elimination would give the observed Z isomer of enone 541.

Scheme 191. Origin of the relative stereochemistry of piperazinone 541

The hydrogenation of enone 541 was expected to preferentially afford piperazine 542. The expected cis/cis relative stereochemistry was indeed observed. NOE studies have shown that irradiation of the $H^3$ peak at $\delta$ 4.09 ppm caused a 0.17% enhancement of the $H^6$ peak and negligible enhancement of the $H^5$ peak. Irradiation of the $H^5$ peak at $\delta$ 3.37 ppm caused a 2.90% enhancement of the $H^6$ peak and a 0.07% enhancement of the $H^3$ peak. The NOE data suggests that protons $H^5$ and $H^6$ are close in space, confirming a cis relative stereochemistry. Moreover, the observed coupling constant between the same two protons was 3.3 Hz, a value that is typical between adjacent axial and equatorial protons in cyclohexane rings. The very small NOE between protons $H^3$ and $H^5$ indicates that these two protons could be in equatorial positions, therefore further apart than are protons $H^5$ and $H^6$, which would have an axial-equatorial relationship explaining the higher NOE in this case. Molecular modelling of piperazine 542 showed that indeed the conformation having the isopropyl group equatorial and the two isobutyl ones in axial positions was lower in energy than the
ring flipped conformation (Figure 38). The predicted values for the distances between the three protons $H^3$, $H^5$ and $H^6$ for the axial/axial/equatorial conformer of 542 were indeed in agreement with the magnitudes of our NOE data (Figure 38).

![Figure 38]

It was expected that the desired piperazinone 511 formed by deprotection of 542 would have the same cis/cis relative stereochemistry as the starting material, which is also the one assigned by the authors for the natural compound piperazirum. NOE studies have shown that irradiation of the $H^3$ peak at $\delta$ 3.40 ppm caused a 1.10% enhancement of the $H^5$ peak and 0.10% enhancement of the $H^6$ peak. There seems to be a change from the NOE data for PMP-protected 542 where proton $H^3$ was shown to be closer to $H^6$ than to $H^5$. This change could be attributed to a different conformation of piperazinone 511, as confirmed by molecular modelling (Figure 39). If equatorial/equatorial/axial-511 is now the prevalent conformation, then protons $H^3$ and $H^6$ have an axial-equatorial relationship, while $H^3$ and $H^5$ have an axial-axial one explaining the higher NOE in this case. The coupling constant of protons $H^3$ and $H^5$ could not be distinguished from the $^1$H NMR spectrum.

![Figure 39]

An X-ray crystal structure was obtained for the hydrochloride salt of piperazinone 511 (548), showing a cis/cis relative stereochemistry (Figure 40). The crystal structure shows that 511 had indeed the equatorial/equatorial/axial conformation, confirmed by the NOE data.
The novel alkaloid piperazirum, isolated from the flowering plant *Arum Palaestinum* by Kim and co-workers was characterised based on a combination of spectroscopic techniques. The compound was isolated as an amorphous white solid, which was judged by mass spectroscopy (ESI) to have a molecular formula of C$_{15}$H$_{30}$N$_2$O. IR spectroscopy revealed characteristic absorptions of the NH and C=O groups. $^1$H NMR spectroscopy in DMSO-$d_6$ identified the presence of two isobutyl groups in different environments, one isopropyl group, three protons in the region $\delta$ 3.4-3.6 ppm, as well as two broad signals at $\delta$ 8.45 and 9.45 ppm that were exchangeable with D$_2$O. Furthermore, $^{13}$C NMR showed the presence of fifteen carbon resonances whereas HSQC, HMBS and NOESY were used to completely assign the spectrum of piperazirum. The authors claimed that the observed NOE cross-peaks between protons $H^3$ and $H^5$, and $H^5$ and $H^6$ show that the three protons are on the same side of the piperazine ring, however no values for the observed NOEs were reported.

Comparison of the reported values of the $^1$H and $^{13}$C NMR resonances showed that these do not match the values for our synthesised compound. The authors obtained the $^{13}$C NMR in D$_2$O but in this case that was only possible for the HCl salt of 511 as the free amine was insoluble. However, the free amine was soluble in DMSO-$d_6$ and CDCl$_3$ so the $^{13}$C resonances were recorded in all those solvents (Table 22). The values of chemical shifts in the $^{13}$C NMR for the three ring protons ($C^3$, $C^5$ and $C^6$) were very close in all solvents, so a conclusion could not be drawn from those. However, a significant difference was observed for the chemical shifts of the methylene carbon atoms (CH$_2$), which were reported to have a difference of 15.4 ppm.
in chemical shift for *piperazirum*, but were much closer to each other in our synthesised molecule.

**Table 22.** $^{13}$C NMR chemical shifts of 511 and *piperazirum*

<table>
<thead>
<tr>
<th>Carbon</th>
<th>$\delta_C$ (ppm)</th>
<th>$\delta_C$ (ppm)</th>
<th>$\delta_C$ (ppm)</th>
<th>$\delta_C$ (ppm)</th>
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<td>DMSO-$d_6$</td>
<td>D$_2$O$^a$</td>
<td>D$_2$O$^b$</td>
</tr>
<tr>
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<td>172.5</td>
<td>169.9</td>
<td>175.7</td>
</tr>
<tr>
<td>C$^3$</td>
<td>56.9</td>
<td>56.4</td>
<td>54.9</td>
<td>53.6</td>
</tr>
<tr>
<td>C$^5$</td>
<td>53.3</td>
<td>53.2</td>
<td>53.9</td>
<td>59.7</td>
</tr>
<tr>
<td>C$^6$</td>
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<td>58.1</td>
<td>56.3</td>
<td>60.6</td>
</tr>
<tr>
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<td>41.5</td>
<td>38.8</td>
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<td>40.5</td>
<td>40.2</td>
<td>36.3</td>
<td>24.6</td>
</tr>
</tbody>
</table>

$^a$Data obtained for the HCl salt of 511. $^b$Reported data for *piperazirum*.

A significant difference was also observed in the $^1$H NMR spectra. The authors initially obtained the $^1$H NMR spectra in DMSO-$d_6$, however the full data they reported were in D$_2$O. The authors reported the presence of two broad signals at $\delta$ 8.45 and 9.45 ppm in DMSO-$d_6$ corresponding to NH protons. However, in our synthesised molecule only one broad peak was observed in the $^1$H NMR in DMSO-$d_6$ at $\delta$ 6.22 ppm.

After communication with the authors, it was unsuccessful to obtain a sample of the isolated natural compound or any of the spectra to compare to. In light of these results, it can be tentatively concluded that the reported structure for *piperazirum* was wrongly assigned.

**2.6.6 Synthesis of other analogues**

After the discovery that the biologically active *piperazirum* isolated from *Arum Palaestinum* did not have the relative stereochemistry claimed by the authors, it was attempted to investigate some other possible structures. As the mass spec and NMR data strongly suggested that the molecular formula and carbon connectivity of the
isolated compound was correctly assigned, it can only be assumed that the isolated molecule has a different relative stereochemistry from 511.

It was thought that access to some other isomers of 511 would be possible using the nitro-Mannich methodology. The syn selective nitro-Mannich reaction of dialkylzinc reagents with nitroalkenes has been reported by the Anderson group. This result was observed when Et₂O was used as the reaction solvent causing Zn(O₂CCF₃)₂ to precipitate from the solution, which was assumed to change the transition state to an acyclic one instead of cyclic. It was proved that syn-β-nitroamines 230b were the thermodynamic products in this reaction (Scheme 78, section 2.1). Therefore a possible route to syn-β-nitroamine 549 would be the conjugate addition of dimethylzinc to nitroalkene 531 in Et₂O and subsequent nitro-Mannich reaction with imine 534 (Scheme 192).

**Scheme 192.** Possible route to syn-β-nitroamine 549

Reduction of syn-β-nitroamine 549 and lactamisation with ketoacid 519 should give 5,6-dihydropyrazin-2-ones 550 and 551, that after hydrogenation and deprotection would yield the diastereoisomers 552 and 553 (Scheme 193).

**Scheme 193.** Possible route to piperazinones 552 and 553

Nitroalkene 531 was synthesised in two steps from acetaldehyde and nitromethane in 20% overall yield via nitroalcohol 554 (Scheme 194). However, brief attempts to access β-nitroamine 549 were unsuccessful. Reaction of nitroalkene 531 with dimethylzinc gave only a complicated mixture of products, with only a trace of the desired β-nitroamine 549 observed by ¹H NMR. This failure can be attributed to the possible instability of imine 534 in these reaction conditions, as no recovered imine or
para-anisidine were observed in the crude product mixture, suggesting possible polymerisation via initial tautomerisation to enamine.

$$\text{Me} + \text{Me}_2\text{NO}_2 \xrightarrow{\text{KF} (1.00 \text{ mol \%})} \text{PrOH, 0 °C, 15 h} \rightarrow \text{Me}_2\text{NO}_2 \xrightarrow{T\text{FAC} (1.05 \text{ equiv})} \text{Et}_2\text{N (2.10 equiv.)} \rightarrow \text{Me}_2\text{NO}_2$$

Scheme 19.4. Synthesis of nitroalkene 531

Finally, it was attempted to synthesise diastereoisomer 555 from the already formed piperazine 511, by epimerisation of the C3 stereocentre. Double deprotonation of 511 with nBuLi should give enolate 556, which after protonation could lead to a mixture of piperazinones 511 and 555 (Scheme 195). However, treatment of 511 with either nBuLi (2.00 equiv.) or LDA (2.00 equiv.), followed by protonation with water, gave only the starting material 511 and none of the trans/cis diastereoisomer 555.

To explain the above results some deuteration experiments were attempted. Treatment of 511 with either nBuLi (3.00 equiv.) at THF, at -78 °C to 0 °C or with NaH (5.00 equiv.) at rt, followed by a D2O quench, led only to deuteration of the amide proton. This result could be expected as initial deprotonation of the amide proton to give enolate 557 would make the proton H3 much less acidic, making a second deprotonation to 556 more difficult (Scheme 195).

Scheme 195. Epimerisation of piperazinone 511

In light of the failure of epimerisation under basic conditions, it was attempted to epimerize 511 by treatment with acid. Refluxing a solution of 511 in toluene with TsOH (5.00 mol %) for 12 h though, gave only recovered starting material as well as some degradation products.
2.6.7 Conclusions and future work

This section described the work done towards the synthesis of natural product piperazirum. The reported structure of piperazinone 511 was successfully synthesised using the conjugate addition/nitro-Mannich reaction of Superhydride® with nitroalkene 530 and imine 534. The desired compound was synthesised in five steps with a 25% overall yield, however the NMR data did not match those of the reported compound, suggesting a wrong assignment of the relative stereochemistry in the natural compound.

Initial attempts to synthesise any other diastereoisomers of 511, either by epimerisation of the C3 substituent in 511 or by synthesising piperazinones 552 and 553 via syn-β-nitroamine 549 were unsuccessful. This investigation was not continued due to time restrictions, however a more in-depth investigation of the reaction conditions could provide a route to these compounds.

A different route could also give access to piperazinone 555. Lactamisation of 1,2-diamine 538, formed earlier in this investigation with ethyl glyoxylate, should give 5,6-dihydropyrazin-2-one 558. Subsequent reaction of 558 with a suitable Grignard reagent such as iBuMgBr should lead to nucleophilic addition on the imine group at the C3 position. It would be expected that the addition of the reagent would occur from the least hindered upper side to give the desired piperazinone 555 (Scheme 196).

![Scheme 196. Possible route to piperazinone 555](image)

Furthermore, after the correct structure of piperazirum is identified, the assignment of the absolute stereochemistry and the development of an asymmetric synthesis would be required. A possible asymmetric synthesis of 511 could use organocatalysis to afford the conjugate addition of hydride and asymmetric nitro-Mannich reaction with imine 534. Thiourea organocatalysts have been used to affect the asymmetric nitro-Mannich reaction, giving high enantioselectivities and good yields.\(^{122}\)
3. Experimental

3.1 General experimental details

All non-aqueous chemistry, unless otherwise stated, was carried out in flame dried glassware, under an inert atmosphere (anhydrous \(\text{N}_2\)), using a Schlenk apparatus. Room temperature implies the temperature range of 20-25 °C. All reaction temperatures stated refer to the values of the external bath and not the reaction mixture. An ice-water bath was used for cooling at 0 °C, whereas cryogenic conditions (-78 °C and -25 °C) were accomplished using an acetone/dry-ice bath. Reagents were added into the reaction mixture fast (solution or liquid) and in one portion (solid), unless otherwise stated. Column chromatography was performed using Geduran® silica gel 60, 40-63 µm in the indicated solvent system. Thin layer chromatography (TLC) was used for monitoring both reactions and the progress of column chromatography and was performed on Polygram® SIL G/UV254 0.25 mm silica pre coated aluminium plates with fluorescent indicator, which were then visualised under UV light (254 nm) and a dip of basic potassium permanganate. Removal of solvents (in vacuo) was achieved using the house vacuum system and Büchi rotary evaporators. Pyrrolidinones 231 (racemic), 238, 240, 246 and 242 were made according to the reported procedure.\(^{119}\) Compounds 353,\(^{173}\) 370,\(^{175}\) 519,\(^{226}\) 520,\(^{225}\) 523,\(^{228}\) 530,\(^{232}\) and 531,\(^{189}\) were made according to the reported procedures. Imines 261 and 262 were provided by colleague Paul Koovits.\(^{122}\) Thiazole-2-carboxaldehyde,\(^{236}\) oxazole-2-carboxaldehyde,\(^{237}\) and (±)-3,3'-dimethyl-[1,1'-binaphthalene]-2,2'-diol,\(^{131}\) were made according to the reported procedures. Where the described compound is made by a literature procedure not used to make the specific compound before, this is referenced in the compound name.

3.2 Purification of solvents and reagents

Commercial solvents and reagents were used as supplied or purified in accordance to standard procedures.\(^{238}\) The dry solvents Diethyl Ether (Et\(_2\)O), Tetrahydrofuran (THF), Dichloromethane (DCM), Toluene and Hexane were obtained from a solvent tower, where degassed solvents were passed through two columns of activated alumina and a 7 micron filter under 4 bar pressure. All commercial reagents were used as supplied without further purification, unless otherwise stated. All amines, anilines, pyridines and phenols were distilled or recrystallised according to literature...
Benzaldehyde was distilled from calcium hydride under an atmosphere of nitrogen, and stored at 5 °C. Diethylzinc was purchased from Aldrich as a 1.0 M solution in hexanes and stored under nitrogen. Diisopropylzinc was synthesised according to a literature procedure, as a solution in hexane, titrated with I₂/LiCl, and stored under nitrogen at -20 °C. Diphenylzinc was purchased from Aldrich as a white solid and stored in an inert atmosphere box. Superhydride was purchased from Aldrich as a 1.0 M solution in THF and stored under nitrogen. Copper (II) triflate was stored in an inert atmosphere box and used immediately after being weighed out. All solutions of organolithium reagents were kept under a nitrogen atmosphere at 5 °C and standardised with Salicylaldehyde Phenylhydrazone. Activation of 4 Å molecular sieves was achieved by heating under high vacuum.

3.3 Characterisation

Melting points are uncorrected and were recorded on a Reichert Melting Point Apparatus. All ¹H and ¹³C NMR data were recorded using Bruker AVANCE III 400 MHz and Bruker AVANCE III 600 MHz machines at 400 and 600 MHz for ¹H and 100 and 125 MHz for ¹³C respectively. ¹⁹F NMR data were recorded on a Bruker AMX 300 MHz machine at 282 MHz. Samples were made as dilute solutions of CDCl₃ and spectra recorded at 298 K, unless otherwise stated. Data were manipulated directly using Bruker XwinNMR (version 2.6) or TopSpin (version 2.1). All chemical shifts (δ) are reported in parts per million (ppm), relative to residual solvent peaks δ = 7.26 for ¹H NMR and δ = 77.1 for ¹³C NMR. Multiplicities for ¹H coupled signals are denoted as s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet. Coupling constants (J) are reported in Hertz (Hz). ¹³C multiplicities were assigned using a DEPT sequence. Where appropriate, HMQC, COSY, HMBC, NOE experiments were carried out to aid assignment. Mass spectroscopy data were collected on Thermo Finnigan Mat900xp (EI/CI) VG-70se (FAB) and Waters LCT Premier XE (ES) instruments. Infrared data were collected using Perkin-Elmer 100 FTIR spectrometer as a thin film. Elemental analysis was performed on an Exeter Analytical Inc. EA440 horizontal load analyser. Optical rotations were obtained using a Perkin-Elmer 343 model polarimeter. X-ray crystallography was carried out using a AFC12 goniometer, equipped with an enhanced sensitivity (HG) Saturn724+ detector mounted at the window of an FR-E+ SuperBright molybdenum rotating anode generator with HF Varimax optics (100µm focus).
3.4 Experimental procedures

3.4.1 Stereoselective synthesis of pyrrolidinones via nitro-Mannich reaction

3.4.1.1 Preparation of imines, nitroalkenes and other starting materials

General Procedure A: Synthesis of PMP imines

To a solution of para-anisidine (1.0 mmol) in DCM (5 mL per mmol) was added basic Al₂O₃ (1.0 g per mmol) and the mixture stirred at rt for 5 min. Aldehyde (1.00 mmol) was then added and the mixture stirred for a further 15 h before being filtered through celite® and washed with DCM (5 mL per mmol). The filtrate was concentrated in vacuo to give crude imine.

(E)-N-benzylidene-4-methoxyaniline 281

Prepared by general procedure A. Benzaldehyde (3.00 mL, 30 mmol), para-anisidine (3.69 g, 30.0 mmol) and basic Al₂O₃ (30.0 g) afforded imine 281 (6.23 g, 95% pure by ¹H NMR, 98%), as a yellow solid which was used without further purification; mp. 71-72 °C (lit. 70-71 °C); ¹H NMR (600 MHz) δ 3.85 (3H, s, OCH₃), 6.95 (2H, app. d, J = 8.8, CH₃PMPC₃-H), 7.26 (2H, app. d, J = 8.8, CH₃PMPC₂-H), 7.48 (3H, m, CH Arom.), 7.91 (2H, m, CH Arom.), 8.50 (1H, s, N=CH). Data in agreement with that reported.²⁴⁰

(E)-4-methoxy-N-(thiophen-2-ylmethylene)aniline 558

Prepared by general procedure A. 2-Thiophene carboxaldehyde (2.80 mL, 30.0 mmol), para-anisidine (3.69 g, 30.0 mmol) and basic Al₂O₃ (30.0 g) afforded imine
558 (6.38 g, 98% pure by $^1$H NMR, 100%), as a yellow solid which was used without further purification; mp. 46-47 °C (lit. 47-48 °C); $^1$H NMR (600 MHz) δ 3.84 (3H, s, OCH$_3$), 6.93 (2H, app. d, $J = 8.8$, CH$_{PMPC3-H}$), 7.13 (1H, m, CH$_{thiophene}$), 7.24 (2H, app. d, $J = 8.8$, CH$_{PMPC2-H}$), 7.48 (2H, m, CH$_{thiophene}$), 9.96 (1H, s, N=CH). Data in agreement with that reported.$^{241}$

(E)-4-methoxy-N-(pyridin-2-ylmethylene)aniline 256

![E-4-methoxy-N-(pyridin-2-ylmethylene)aniline](image)

Prepared by general procedure A. 2-Pyridinecarboxaldehyde (0.950 mL, 10.0 mmol), para-anisidine (1.23 g, 10.0 mmol) and basic Al$_2$O$_3$ (10.0 g), afforded imine 256 (1.93 mg, 91%) as a white solid which was used without further purification; mp. 34-35 °C (36-37 °C); $^1$H NMR (600 MHz) δ 3.85 (3H, s, OCH$_3$), 6.96 (2H, app. d, $J = 8.8$, CH$_{PMPC3-H}$), 7.35 (3H, m, CH$_{PMPC2-H}$ and CH$_{pyridine}$), 7.80 (1H, m, CH$_{pyridine}$), 8.19 (1H, d, $J = 8.1$, CH$_{pyridine}$), 8.64 (1H, s, CHN), 8.71 (1H, m, CH$_{pyridine}$). Data in agreement with that reported.$^{242}$

(E)-2-methoxy-N-(pyridin-2-ylmethylene)aniline 559

![E-2-methoxy-N-(pyridin-2-ylmethylene)aniline](image)

To a solution of ortho-anisidine (1.13 mL, 10.0 mmol) in DCM (50 mL) were added dry molecular sieves 4 Å (10.0 g) and the mixture stirred at rt for 5 min. 2-Pyridinecarboxaldehyde (0.95 mL, 10.0 mmol) was then added and the mixture stirred for a further 6 h before being filtered through celite® and washed with DCM (50 mL). The filtrate was concentrated in vacuo to give crude imine 559 (1.93 mg, 80% pure by NMR, 91%), as a yellow solid which was used without further purification; $^1$H NMR (600 MHz) δ 3.92 (3H, s, OCH$_3$), 7.00 (2H, m, CH Arom.), 7.11 (1H, m, CH Arom.),
7.24 (1H, m, CH Arom.), 7.38 (1H, m, CH Arom.), 7.83 (1H, m, CH Arom.), 8.29 (1H, m, CH Arom.), 8.65 (1H, s, N=CH), 8.71 (1H, m, CH Arom.). Data in agreement with that reported.

(E)-4-methoxy-N-(pyridin-3-ylmethylene)aniline 257

Prepared by general procedure A. 3-Pyridinecarboxaldehyde (2.82 mL, 30.0 mmol), para-anisidine (3.69 g, 30.0 mmol) and basic Al₂O₃ (30.0 g) afforded crude imine 257 (5.87 g, 93%), recrystallised from Et₂O/Petrol (4.61 g, 73%) as a white solid; mp. 56-57 °C; ¹H NMR (600 MHz) δ 3.81 (3H, s, OCH₃), 6.97 (2H, app. d, J = 8.9, CHPMPC3-H), 7.28 (2H, app. d, J = 8.9, CHPMPC3-H), 7.41 (1H, m, CHpyridine), 8.28 (1H, m, CHpyridine), 8.54 (1H, s, N=CH), 8.69 (1H, m, CHpyridine), 9.0 (1H, m, CHpyridine). Data in agreement with that reported.

(E)-N-((1H-indol-3-yl)methylene)-4-methoxyaniline 258

Prepared by general procedure A. Indole-3-carboxaldehyde (1.45 g, 10.0 mmol), para-anisidine (1.23 g, 10.0 mmol) and basic Al₂O₃ (10.0 g) afforded imine 258 (2.38 g, 95%, lit. 98%) as a yellow solid which was used without further purification; mp. 116-118 °C (lit. 115-120 °C); ¹H NMR (600 MHz) δ 3.84 (3H, s, OCH₃), 6.93 (2H, app. d, J = 8.8, CHPMPC2-H), 7.40 (1H, m, CHindole), 7.62 (1H, s, N=CH), 8.51 (1H, m, CHindole), 8.68 (1H, br. s, NH), 8.71 (1H, s, CHindole). Data in agreement with that reported.
(E)-4-methoxy-N-((1-methyl-1H-indol-3-yl)methylene)aniline 259

To a solution of imine 258 (1.25 g, 5.00 mmol) in THF (15 mL), cooled to 0 °C was added NaH (151 mg, 6.00 mmol, 95%) and the mixture stirred for 15 min, then 1 h at rt. The mixture was then recooled to 0 °C and MeI (0.37 mL, 6.00 mmol) was added, the mixture warmed to rt and stirred for 30 min. Water (20 mL) was then added and the mixture extracted with DCM (3x20 mL), dried over MgSO₄ and evaporated in vacuo to afford imine 259 (1.23 g, 93%) as a yellow oil which was used without further purification; ¹H NMR (600 MHz) δ 3.82 (3H, s, NC₃H₃), 3.85 (3H, s, OC₃H₃), 6.95 (2H, app. d, J = 8.8, CH₃PMPC3-H), 7.25 (2H, app. d, J = 8.8, CH₃PMPC2-H), 7.31 (1H, m, CHindole), 7.36 (2H, m, CHindole), 7.49 (1H, m, CHindole), 8.50 (1H, m, CHindole), 8.65 (1H, s, N=C₃H). Data in agreement with that reported.²⁴⁶

1-Tosyl-1H-indole-3-carbaldehyde 560

A solution of indole-3-aldehyde (500 mg, 3.40 mmol) in DCM (7 mL) was cooled to 0 °C and then para-toluenesulfonyl chloride (730 mg, 3.80 mmol) was added followed by Et₃N (470 µL, 3.80 mmol) and the mixture left to warm to rt and stirred overnight until the starting aldehyde was consumed (TLC, 20 h). Saturated aqueous NaHCO₃ (10 mL) was then added, the layers separated and aqueous layer further extracted with DCM (2x10 mL), dried over MgSO₄ and evaporated in vacuo to give crude aldehyde 560. Purification by flash column chromatography (Hexane:DCM 1:1) gave aldehyde 560 (776 mg, 76%) as a yellow solid; mp. 141-143 °C (lit. 143-144 °C); Rf = 0.41 (Hexane:DCM 1:1); ¹H NMR (600 MHz) δ 2.38 (3H, s, ArC₃H₃), 7.29 (2H, d, J = 8.2, CHTsC3-H), 7.37 (1H, m, CHindole), 7.42 (2H, m, CHindole), 7.86 (2H, d, J = 8.4, CHTsC2-H), 7.96 (1H, d, J = 8.3, CHindole), 8.24 (1H, s, CHindoleC2-H), 8.26 (1H,
$d, J = 8.0, \text{CH}_{\text{indol}}$, 10.11 (1H, s, $O=CH$); $^{13}$C NMR (150 MHz) $\delta$ 21.8 (CH$_3$), 113.4 (CH Arom.), 122.5 (Cq Arom.), 122.7 (CH Arom.), 125.2 (CH Arom.), 126.3 (Cq Arom.), 126.4 (CH Arom.), 127.4 (CH Arom.), 130.5 (CH Arom.), 134.4 (Cq Arom.), 135.3 (Cq Arom.), 136.4 (CH Arom.), 146.4 (Cq Arom.), 185.7 (HC=O). Data in agreement with that reported.

$(E)$-4-methoxy-$N$-((1-tosyl-$1H$-indol-3-yl)methylene)aniline 260

\begin{center}
\includegraphics[width=0.2\textwidth]{image.png}
\end{center}

Prepared by general procedure A. Aldehyde 560 (4.61 g, 15.4 mmol), para-anisidine (1.90 g, 15.4 mmol) and basic Al$_2$O$_3$ (15.0 g) afforded imine 260 (5.40 g, 89%) as a brown solid which was used without further purification; mp. 90-92 °C; $^1$H NMR (600 MHz) $\delta$ 2.36 (3H, s, ArCH$_3$), 3.85 (3H, s, OC$_2$H$_3$), 6.95 (2H, d, $J = 9.0$, CH$_{\text{PMPC3-H}}$), 7.25 (4H, m, CH Arom.), 7.36 (2H, m, CH Arom.), 7.82 (2H, d, $J = 8.4$, CH Arom.), 7.98 (1H, s, CH Arom.), 8.00 (1H, m, CH Arom.), 8.54 (1H, m, CH Arom.), 8.63 (1H, s, N=CH). Data in agreement with that reported.

$(E)$-4-methoxy-$N$-((1-tosyl-$1H$-pyrrol-2-yl)methylene)aniline 263

\begin{center}
\includegraphics[width=0.2\textwidth]{image.png}
\end{center}

To a solution of imine 261 (380 mg, 1.90 mmol) in THF (10 mL) cooled to 0 °C was added NaH (46 mg, 1.9 mmol, 95%) and the mixture stirred for 15 min, then 30 min at rt. The mixture was then cooled to 0 °C and para-toluenesulfonyl chloride (362 mg, 1.90 mmol) was added, the mixture warmed to rt and stirred for 30 min. Water (20 mL) was then added and the mixture extracted with DCM (3x20 mL), dried over MgSO$_4$ and evaporated in vacuo to afford imine 263 (654 mg, 97%) as a yellow oil which was used without further purification; mp. 74-75 °C; IR $\nu_{\text{max}}$ (thin film) 2834 w
Andreas Kalogirou
University College London

(C-H), 1614 m (C=C), 1494 m, 1373 m, 1362 m, 1251 m, 1165 s, 1130 s, 1050 s, 813 s, 726 s, 671 s cm⁻¹; ¹H NMR (600 MHz) δ 2.38 (3H, s, ArCH₃), 3.83 (3H, s, OCH₃), 6.38 (1H, m, CH₇pyrrole), 6.92 (2H, app. d, J = 8.8, CHPMPC3-H), 7.10 (1H, m, CH₇pyrrole), 7.18 (2H, app. d, J = 8.8, CHPMPC2-H), 7.27 (2H, app. d, J = 8.3, CHtosylC₃-H), 7.46 (1H, m, CH₇pyrrole), 7.68 (2H, app. d, J = 8.3, CHtosylC₂-H), 8.89 (1H, s, N=C)

¹³C NMR (150 MHz) δ 21.6 (ArCH₃), 55.5 (OCH₃), 113.1 (C₇Arom.), 114.4 (C₇Arom.), 116.9 (C₇Arom.), 122.3 (C₇Arom.), 126.1 (C₇Arom.), 126.8 (C₇Arom.), 130.1 (C₇Arom.), 133.1 (Cq Arom.), 135.8 (Cq Arom.), 144.6 (Cq Arom.), 145.5 (Cq Arom.), 147.5 (N=CH), 158.4 (CqPMPC₃); m/z (ESI⁺) 355 (M+H⁺, 32%), 347 (24%), 199 (100%); HRMS: found 355.1111, C₁₉H₁₉N₂O₃S requires 355.1116; Anal. Cald. for C₁₉H₁₈N₂O₃S: C, 64.34, H, 5.12, N, 7.90. Found C, 64.17, H, 5.09, N, 7.85%.

(E)-4-methoxy-N-(thiazol-2-ylmethylene)aniline 264

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To a solution of para-anisidine (1.26 g, 10.0 mmol) in DCM (40 mL), was added anhydrous MgSO₄ (10.0 g) followed by thiazole-2-carboxaldehyde (1.16 g, 10.3 mmol) and the mixture was then stirred at rt for 2 h. The mixture was then filtered and evaporated in vacuo to give crude imine 264 (2.06 g, 92%) as a yellow solid which was recrystallised from Et₂O/hexane (1.11 g, 50%); mp. 64-66 °C; IR ν_max (thin film) 3008 w (C-H), 2961 w (C-H), 1615 s (C=C), 1504 s, 1410 m, 1291 s, 1247 s, 1237 s, 1166 s, 1028 s, 837 s, 785 s, 739 s cm⁻¹; ¹H NMR (600 MHz) δ 3.86 (3H, s, OCH₃), 6.96 (2H, d, J = 8.7, CHPMPC3-H), 7.35 (2H, d, J = 8.7, CHPMPC4-H), 7.48 (1H, d, J = 3.0, CH₃thiazoleC₅-H), 7.99 (1H, d, J = 3.0, CH₃thiazoleC₄-H), 8.73 (1H, s, N=CH); ¹³C NMR (150 MHz) δ 55.6 (OCH₃), 114.6 (CHPMPC₃), 122.0 (CH₃thiazoleC₄), 123.0 (CHPMPC₂), 142.7 (CqPMPC₁), 144.5 (CH₃thiazoleC₃), 150.6 (Cq₃thiazoleC₂), 159.5 (CqPMPC₄), 167.9 (HC=CH₃); m/z (ESI⁺) 219 (M + H, 100%), 218 (18%); HRMS: found 219.0596 C₁₁H₁₁N₂O₃S requires 219.0992; Anal. Cald. for C₁₁H₁₀N₂O₃S: C, 60.53, H, 4.92, N, 12.83. Found C, 60.59, H, 4.53, N, 12.70%.
(E)-4-methoxy-N-(oxazol-2-ylmethylene)aniline 265

To a solution of para-anisidine (492 mg, 4.00 mmol) in DCM (40 mL), was added anhydrous MgSO$_4$ (5.00 g) followed by oxazole-2-carboxaldehyde (400 mg, 4.11 mmol) and the mixture was then stirred at rt for 19 h. The mixture was then filtered and evaporated in vacuo to give crude imine 265 (1.22 g, 70% pure by $^1$H NMR, 85%), recrystallised from Et$_2$O/petrol (664 mg, 80%) as white needles which was used without further purification; mp. 92-93 °C; IR $\nu_{\text{max}}$ (thin film) 3119 w (C-H), 2954 w (C-H), 1628 m (C=C), 1591 m, 1540 m, 1507 s, 1493 s, 1294 s, 1031 m, 915 m cm$^{-1}$; $^1$H NMR (600 MHz) $\delta$ 3.86 (3H, s, OC$_3$H$_3$), 6.97 (2H, d, $J = 9.1$, CH$_{\text{PMPC3-H}}$), 7.37 (1H, s, CH$_{\text{oxazoleC4-H}}$), 7.39 (2H, d, $J = 9.1$, CH$_{\text{PMPC3-H}}$), 7.82 (1H, s, CH$_{\text{oxazoleC5-H}}$), 8.47 (1H, s, N=CH); $^{13}$C NMR (150 MHz) $\delta$ 55.5 (O$_3$C$_3$H$_3$), 114.6 (CH$_{\text{PMPC3}}$), 123.0 (CH$_{\text{PMPC2}}$), 129.4 (CH$_{\text{oxazoleC4}}$), 140.4 (CH$_{\text{oxazoleC5}}$), 142.4 (C$_q$PMPC1), 143.3 (C$_q$oxazoleC2), 159.8 (C$_q$PMPC4), 162.4 (N=C-H); m/z (ES$^+$) 202 (M$^+$, 75%), 187 (32%, M$^+$ - CH$_3$), 134 (62%, M$^+$ - oxazole), 98 (100%); HRMS: found 202.0732, C$_{11}$H$_{10}$N$_2$O$_2$ requires 202.0737; Anal. Cald. For C$_{11}$H$_{10}$N$_2$O$_2$: C, 65.34, H, 4.98, N, 13.85. Found C, 65.17, H, 4.88, N, 13.83%.

(E)-N-ethylidene-4-methoxyaniline 266

To a solution of para-anisidine (123 mg, 1.00 mmol) in DCM (5 mL), was added basic Al$_2$O$_3$ (1.00 g) and the mixture cooled to -78 °C. Acetaldehyde (67 $\mu$L, 1.2 mmol) was then added and the mixture stirred at this temperature for 1 h, then warmed to rt, filtered through celite® and evaporated in vacuo to give crude imine 266 (145 mg, 97%) as a colourless oil which was used immediately without further purification; IR $\nu_{\text{max}}$ (thin film) 2997 w (C-H), 1651 m (C=O), 1605 m, 1502 s, 1464 m, 1441 m, 1292 m, 1238 s, 1210 m, 1032 s, 819 s, 749 m, 714 m cm$^{-1}$; $^1$H NMR (600...
(E)-N-(2,2-dimethoxyethylidene)-4-methoxyaniline 267

Prepared according to the reported procedure. To a solution of para-anisidine (3.69 g, 30.0 mmol) in DCM (120 mL), was added anhydrous MgSO₄ (25.0 g) followed by 2,2-dimethoxyacetalddehyde (5.87 mL, 60% in H₂O, 39.0 mmol) and the mixture was stirred at rt for 2 h. The mixture was then filtered and evaporated in vacuo to give imine 267 (6.14 g, 98%, lit. 97%) as a colourless oil which was used without further purification; ¹H NMR (600 MHz) δ 3.48 (6H, s, OC₃H₃), 3.81 (3H, s, ArOC₃H₃), 4.89 (1H, d, J = 4.3, CH(OCH₃)₂), 6.89 (2H, app. d, J = 8.8, CH Arom.), 7.16 (2H, app. d, J = 8.8, CH Arom.), 7.74 (1H, d, J = 4.2, =CH). Data in agreement with that reported.

(E)-4-Methoxy-N-((E)-3-phenylallylidene)aniline 268

To a solution of para-anisidine (1.84 g, 15.0 mmol) in DCM (75 mL), was added anhydrous MgSO₄ (15.0 g) followed by cinnamaldehyde (1.90 mL, 15.0 mmol) and the mixture was stirred at rt for 2 h. The mixture was then filtered and evaporated in vacuo to give imine 268 (3.47 g, 98%) as a white solid which was used without further purification; mp. 117-118 °C (lit. 119-120 °C); ¹H NMR (600 MHz) δ 3.84 (3H, s, OCH₃), 6.94 (2H, app. d, J = 9.0, CH₃PMP3), 7.14 (2H, m, PhCH and
PhCH=CH), 7.23 (2H, app. d, J = 9.0, CH$_{PSMPC2}$), 7.36 (1H, m, CH Arom.), 7.41 (2H, m, CH Arom.), 7.55 (1H, m, CH Arom.), 8.81 (1H, s, N=CH). Data in agreement with that reported.

(E)-ethyl 3-nitroacrylate 231

![E-ethyl 3-nitroacrylate](image)

The compound was synthesised by a modification of the reported procedure.$^{121}$ In a 25 mL round bottom flask was added ethyl glyoxylate (4.08 g of a 50% solution in toluene, 20.0 mmol) followed by nitromethane (8 mL) and basic Al$_2$O$_3$ (4.00 g). The mixture was stirred at rt for 4 days before being filtered and concentrated in vacuo to give crude nitroalcohol 255 (1.99 g, 61% yield) as a yellow oil; R$_f$ 0.23 (Petrol:EtOAc 1:1) used without further purification. To a solution of crude nitroalcohol 255 (1.99 g, 12.2 mmol) in DCM (35 mL) at −25 °C was added methanesulfonyl chloride (2.83 mL, 36.6 mmol) followed by Et$_3$N (5.10 mL, 36.6 mmol) dropwise. The mixture was stirred at −25 °C until complete consumption of the nitroalcohol starting material (TLC, 20 min). The reaction mixture was then poured into ice (30 g) and the layers separated. The aqueous phase was extracted with DCM (2x20 mL) and the combined organics washed with saturated aqueous NaHCO$_3$ (20 mL), dried over MgSO$_4$ and concentrated in vacuo. Purification by flash column chromatography (Petrol:Et$_2$O 9:1) gave nitroacrylate 231 (1.28 g, 72%, 44% over two steps, lit. 77%) as a low melting yellow solid; mp. 36-37 °C (lit. 39-40 °C); R$_f$ 0.37 (Petrol:Et$_2$O 9:1); $^1$H NMR (600 MHz) δ 1.36 (3H, t, J = 7.1, CH$_3$), 4.34 (2H, q, J = 7.2, CH$_2$CH$_3$), 7.10 (1H, d, J = 13.5, =CHCO$_2$Et), 7.69 (1H, d, J = 13.5, =CHNO$_2$); $^{13}$C NMR (150 MHz) δ 14.1 (CH$_3$), 62.5 (CH$_2$), 127.8 (=CHCO), 149.0 (=CHNO$_2$), 162.8 (C=O). Data in agreement with that reported.$^{120}$

Also prepared by reaction of ethyl acrylate with CAN. To a stirred solution of ethyl acrylate (2.18 mL, 20.0 mmol) in MeCN (28 mL) at 0 °C were added CAN (32.8 g, 60.0 mmol) followed by NaNO$_2$ (4.14 g, 60.0 mmol) and the mixture was left to warm to rt and stirred for 24 h. Water (20 mL) was then added and the mixture extracted with EtOAc (3x20 mL), then the combined organics washed with saturated aqueous NaHCO$_3$ (10 mL) and brine (10 mL), dried over MgSO$_4$ and evaporated in
vacuo. Purification by flash column chromatography (Petrol:Et₂O 9:1) gave nitroacrylate 296 (1.99 g, 61%) as a yellow oil, identical to the one described above.

(E)-Methyl 3-nitroacrylate 291

The compound was synthesised in three steps according to the reported procedures starting from glyoxylic acid. In a 100 mL round bottom flask was added glyoxylic acid monohydrate (4.20 g, 45.5 mmol) and H₂O (50 mL) and the solution was neutralised by addition of aqueous NaOH 10% until pH = 9. Another 1 mL of the NaOH solution was then added followed by nitromethane (14.6 mL, 270 mmol) and the mixture stirred at rt for 22 h. A 3 M H₂SO₄ solution (100 mL) was then added and the mixture extracted with EtOAc (3x20 mL), dried over MgSO₄ and evaporated in vacuo to give 2-hydroxy-3-nitropropanoic acid (5.97 g, 97%) as a white solid; mp. 76-77 °C (lit. 76-77 °C), used without further purification. To a solution of the crude 2-hydroxy-3-nitropropanoic acid (5.97 g, 44.0 mmol) in MeOH (80 mL) was added concentrated H₂SO₄ (0.25 mL, 4.7 mmol) and the mixture was refluxed for 12 h, then neutralised with addition of saturated aqueous NaHCO₃, evaporated in vacuo to remove MeOH, then extracted with DCM (3 x 20 mL), dried over MgSO₄ and evaporated in vacuo to give crude methyl 2-hydroxy-3-nitropropanoate (6.00 g, 94%) as a colourless oil, used without further purification;¹³⁴ Rₚ 0.44 (Petrol:EtOAc 3:2); ¹H NMR (600 MHz) δ 3.30 (1H, d, J = 4.8, OCH), 3.91 (3H, s, OCH₃), 4.67 (1H, q, J = 4.3, CHCO), 4.79 (2H, dd, J = 3.9, 2.5, CH₂NO₂). To a solution of crude methyl 2-hydroxy-3-nitropropanoate (2.06 g, 13.8 mmol) in DCM (25 mL) at -25 °C was added methanesulfonyl chloride (3.20 mL, 41.4 mmol) followed by Et₃N (5.77 mL, 41.4 mmol) dropwise. The mixture was stirred at -25 °C until complete consumption of the nitroalcohol starting material (TLC, 20 min).¹²⁰ The reaction mixture was then poured into ice (30 g) and the layers separated. The aqueous phase was extracted with DCM (2x20 mL) and the combined organics washed with saturated aqueous NaHCO₃ (20 mL), dried over MgSO₄ and concentrated in vacuo. Purification by flash column chromatography (Petrol:Et₂O 9:1) gave nitroacrylate 291 (1.28 g, 72%, 44% over two steps, lit. 77%) as a low melting yellow solid; mp. 36-37 °C (lit. 34-35 °C); Rₚ 0.33
(Petrol:Et₂O 9:1); ¹H NMR (600 MHz) δ 3.89 (3H, s, OCH₃), 7.11 (1H, d, J = 13.5, =CHCO), 7.70 (1H, d, J = 13.5, =CHNO₂). Data in agreement with that reported.

(E)-tert-Butyl 3-nitroacrylate 296

![tert-Butyl 3-nitroacrylate](image)

To a stirred solution of tert-butyl acrylate (2.90 mL, 20.0 mmol) in MeCN (28 mL) at 0 °C were added CAN (32.8 g, 60.0 mmol) followed by NaNO₂ (4.14 g, 60.0 mmol) and the mixture was left to warm to rt and stirred for 24 h. Water (20 mL) was then added and the mixture extracted with EtOAc (3x20 mL), then the combined organics washed with saturated aqueous NaHCO₃ (10 mL) and brine (10 mL), dried over MgSO₄ and evaporated in vacuo. Purification by flash column chromatography (Petrol:Et₂O 9:1) gave nitroacrylate 296 (331 mg, 10%) as a yellow oil; Rₚ 0.68 (Petrol:Et₂O 9:1); ¹H NMR (600 MHz) δ 1.54 (9H, s, CH₃), 7.02 (1H, d, J = 13.4, =CHCO), 7.60 (1H, d, J = 13.4, =CHNO₂). Data in agreement with that reported.

((P)-Bis-3,3’-dimethyl-naphthaleno[1,2-f;2,1-d]-1,3-dioxa-2-phosphacycloheptan-2-yl)-(R,R)-bis(1-phenylethyl)amine 294

![((P)-Bis-3,3’-dimethyl-naphthaleno[1,2-f;2,1-d]-1,3-dioxa-2-phosphacycloheptan-2-yl)-(R,R)-bis(1-phenylethyl)amine](image)

Prepared according to the reported procedure. A solution of (+)-bis(R-1-phenylethyl)amine (530 µL, 2.32 mmol) and triethylamine (360 µL, 2.62 mmol) in toluene (2 mL) was added dropwise to a solution of phosphorus trichloride (200 µL, 2.32 mmol) in toluene (30 mL). The mixture was stirred at 70 °C for 6 h and allowed to cool to rt. Triethylamine (720 µL, 5.26 mmol) was then added dropwise and the reaction mixture cooled to -78 °C. A solution of (±)-3,3’-dimethyl-[1,1’-binaphthalene]-2,2’-diol (728 mg, 2.32 mmol) in a mixture of toluene (6 mL) and THF (2 mL) was added dropwise. The mixture was allowed to warm up to rt and stirred for 18 h. The mixture was evaporated in vacuo and the diastereomers separated.
and purified by flash column chromatography (Hexane:DCM 9:1). The desired product 294 was isolated as a white solid (853 mg, 32%, lit. 49%); mp. 117-119 °C (lit. 116-123 °C); Rf 0.32 (Hexane:DCM 9:1); 1H NMR (600 MHz) δ 1.70-195 (6H, br. s, CHCH₃), 2.44 (3H, s, ArCH₃), 2.76 (3H, s, ArCH₃), 4.59 (2H, br. s, CH), 7.00-7.14 (13H, m, CH Arom.), 7.37 (3H, m, CH Arom.), 7.83 (4H, m, CH Arom.). Data in agreement to the one reported.¹³⁰

3.4.1.2 Preparation of pyrrolidinones

**General procedure B for the asymmetric synthesis of pyrrolidinones 233 and 241.**

A suspension of Cu(OTf)₂ (8 mg, 22 µmol, 5 mol%) and BINOL derived catalyst 294 (15 mg, 27 µmol, 5 mol%) in Et₂O (3 mL) was stirred at rt for 1 h. The mixture was cooled to −78 °C and a solution of methyl nitroacrylate (76 mg, 0.58 mmol) in Et₂O (1 mL) was added, followed by diethylzinc (640 µL, 0.640 mmol of a 1 M sol. in hexanes, 1.1 equiv.) fast dropwise. The now orange mixture was stirred at this temperature for 10 min before being warmed to rt and stirred for a further 1.5 h. The mixture was re-cooled to −78 °C and the PMP-protected imine (1.16 mmol, 2.0 equiv.) in THF (2 mL) was added via cannula. The mixture was stirred for 20 min before TFA (156 µL, 2.03 mmol, 3.5 equiv.) in THF (0.5 mL) was added via cannula. The mixture was stirred at this temperature for a further 1 h before being warmed to rt and stirred for a further 16 h. Saturated aqueous NaHCO₃ (20 mL) and Et₂O (20 mL) were then added and the layers separated. The aqueous phase was extracted with Et₂O (3x20 mL) and the combined organics was washed with brine (20 mL), dried over MgSO₄ and concentrated in vacuo to leave crude pyrrolidinone.
(3R, 4R, 5S)-3-Ethyl-1-(4-methoxy-phenyl)-4-nitro-5-phenyl-pyrrolidin-2-one 233

Prepared by general procedure B. Nitroacrylate 291 (76 mg, 0.580 mmol), diethyl zinc (638 µL, 0.638 mmol), imine 281 (245 mg, 1.16 mmol) and TFA (155 µL, 2.03 mmol) afforded crude pyrrolidinone 233. Purification by flash column chromatography (Petrol:Me₂CO 4:1) gave pyrrolidinone 233 (157 mg, 80%) as a pale yellow solid; mp. 133-134 °C (lit. 134-136 °C); R_f 0.28 (Petrol:Me₂CO 4:1); ¹H NMR (600 MHz) δ 1.09 (3H, t, J = 7.5, CH₂CH₃), 1.83 (1H, ddq, J = 14.3, 8.2, 7.5, CH₂CH₃), 2.13 (1H, dqd, J = 14.3, 7.5, 4.8, CH₂CH₃), 3.32 (1H, ddd, J = 8.4, 6.8, 4.8, CHCH₂), 3.73 (3H, s, OCH₃), 4.81 (1H, dd, J = 6.8, 5.2, CHNO₂), 5.61 (1H, d, J = 5.3, CHPh), 6.79 (2H, app. d, J = 9.0, CHPMPC₃-H), 7.20-7.27 (4H, m, CH Arom.), 7.31-7.34 (3H, m, CH Arom.); HPLC (chiralcel AD 0.46 x 25 cm column, 90:10 hexane/IPA, 1 mL min-1) 35.8 min (major), 45.0 min (minor) measured 89% ee. Data in agreement to the one reported.¹¹⁵

Recrystallisation of the sample with IPA/hexane gave pyrrolidinone 233 (140 mg, 71% overall yield) as an identical pale yellow solid; [α]D -62.0 (c 0.98, CHCl₃, 20 °C); HPLC measured 99% ee.

(3R, 4R, 5R)-3-Ethyl-1-(4-methoxy-phenyl)-4-nitro-5-thiophen-2-yl-pyrrolidin-2-one 241

Prepared by general procedure B. Nitroacrylate 291 (76 mg, 0.580 mmol), diethyl zinc (638 µL, 0.638 mmol), imine 558 (245 mg, 1.16 mmol) and TFA (155 µL, 2.03 mmol) afforded crude pyrrolidinone 241. Purification by flash column chromatography (Petrol:EtOAc 4:1) gave pyrrolidinone 241 (149 mg, 74%) as a pale yellow solid; mp. 91-93 °C (lit. 90-92 °C); R_f 0.32 (Petrol:Me₂CO 4:1); ¹H NMR (400
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181 MHz) δ 1.12 (3H, t, J = 7.4, CH₂CH₃), 1.91 (1H, app. dquint, J = 15.0, 7.4, CH₂CH₃), 2.16 (1H, dqd, J = 14.2, 7.5, 5.2, CH₂CH₃), 3.29 (1H, ddd, J = 8.1, 6.8, 4.9, CHCH₂), 3.75 (3H, s, OCH₃), 4.94 (1H, dd, J = 6.4, 5.4, CHNO₂), 5.89 (1H, d, J = 5.1, NCH), 6.83 (2H, app. d, J = 8.8, CHPMPC₃-H), 6.91 (1H, dd, J = 4.0, 1.4, CHthiopheneC₃-H), 7.01 (1H, d, J = 2.8, CHthiopheneC₄H), 7.23 (2H, app. d, J = 9.2, CHPMPC₂-H), 7.27 (1H, d, J = 4.4, CHthiopheneC₅-H); [α]D -48.1 (c 1, CHCl₃, 20 °C); HPLC (chiralcel AD 0.46 x 25 cm column, 90:10 hexane/IPA, 1 mL min⁻¹) 38.8 min (major), 46.4 min (minor) measured 89% ee. Data in agreement to the one reported.¹¹⁶

**General procedure C for the synthesis of pyrrolidin-2-ones.**

To a solution of nitroacrylate 231 (0.69 mmol) in THF (3 mL), was added Cu(OTf)₂ (34.0 µmol, 5 mol%). The mixture was cooled to -78 °C and dialkylzinc (0.760 mmol, of a 1.0 M solution in hexanes, 1.1 equiv.) was added fast dropwise. The orange mixture was stirred at this temperature for 10 min before being warmed to rt and stirred for a further 1.5 h. The mixture was re-cooled to -78 °C and the corresponding imine (1.38 mmol, 2.0 equiv.) in THF (2 mL) was added via cannula. The mixture was stirred for 20 min before TFA (2.41 mmol, 3.5 equiv.) in THF (0.5 mL) was added via cannula. The mixture was stirred at this temperature for a further 1 h before being warmed to rt and stirred for a further 16 h. Saturated aqueous NaHCO₃ (20 mL) and Et₂O (20 mL) were then added and the layers separated. The aqueous phase was extracted with Et₂O (3x20 mL), and the combined organics washed with brine (20 mL), dried over MgSO₄, filtered and concentrated in vacuo to leave crude pyrrolidinone. The pyrrolidinone was then purified further by column chromatography.
(3S*, 4S*, 5S*)-3-ethyl-1-(4-methoxyphenyl)-4-nitro-5-(pyridin-2-yl)pyrrolidin-2-one 269

Prepared by general procedure C. Nitroacrylate 231 (100 mg, 0.690 mmol), diethylzinc (760 µL, 0.760 mmol), imine 256 (293 mg, 1.38 mmol) and TFA (180 µL, 2.41 mmol) afforded crude pyrrolidinone 269. Purification by flash column chromatography (Petrol:Me2CO 4:1) gave pyrrolidinone 269 (118 mg, 50%) as a white solid; mp. 115-117 °C; Rf 0.08 (Petrol:Me2CO 4:1); IR υmax (thin film) 3026 w (C-H), 2975 w (C-H), 1691 s (C=O), 1550 s (N=O), 1517 s, 1593 s, 1393 s, 1366 s (N-O), 1292 s, 1252 s, 1224 s, 1206 s, 1029 s, 755 s cm⁻¹; 1H NMR (600 MHz) δ 1.11 (3H, t, J = 7.3, CH₂CH₃), 1.89 (1H, ddq, J = 14.7, 9.0, 7.4, CH₂), 2.15 (1H, dqd, J = 14.3, 7.6, 4.8, CH₂), 3.27 (1H, ddd, J = 9.0, 5.8, 4.8, CHCH₂), 3.73 (3H, s, OCH₃), 5.26 (1H, dd, J = 5.8, 4.4, CHNO₂), 5.64 (1H, d, J = 4.4, CHN), 6.78 (2H, d, J = 9.1, CHPMPC3-H), 7.11 (1H, d, J = 7.8, CHpyridine), 7.14 (2H, d, J = 9.1, CHPMPC-H), 7.23 (1H, ddd, J = 7.5, 4.5, 0.7, CHpyridine), 7.60 (1H, td, J = 7.7, 1.7, CHpyridine), 8.63 (1H, m, CHpyridine); 13C NMR (150 MHz) δ 11.3 (CH₃), 23.6 (CH₂), 49.5 (CHCH₂), 55.5 (OCH₃), 67.2 (CHN), 87.9 (CHNO₂), 114.4 (CHPMPC3), 123.2 (CHPMPC2), 123.9 (CHpyridine), 126.0 (CHpyridine), 129.4 (C₃PMPC1), 137.1 (CHpyridine), 150.7 (CHpyridine), 155.8 (C₄pyridine), 158.1 (C₅PMPC4), 171.6 (C=O); m/z (Cl⁻) 342 (100%, M+H⁻); HRMS: found 342.1450, C₁₈H₂₀N₃O₄ requires 342.1448; Anal. Cald. For C₁₈H₁₉N₃O₄: C, 63.33, H, 5.61, N, 12.31. Found C, 63.04, H, 5.56, N, 12.11%.

(3S*, 4S*, 5R*)-3-ethyl-1-(4-methoxyphenyl)-4-nitro-5-(pyridin-3-yl)pyrrolidin-2-one 270

Prepared by general procedure C. Nitroacrylate 231 (100 mg, 0.690 mmol), diethylzinc (760 µL, 0.760 mmol), imine 257 (293 mg, 1.38 mmol) and TFA (180 µL,
2.41 mmol) afforded crude pyrrolidinone 270. Purification by flash column chromatography (Petrol:Me₂CO 4:1) gave pyrrolidinone 270 (99 mg, 42%) as a white solid; mp. 91-93 °C; Rᵣ 0.05 (Petrol:Me₂CO 4:1); IR 𝜈max (thin film) 2963 w (C-H), 1709 (C=O), 1550 s, 1511 s, 1362 s, 1252 s, 1184 m, 1035 m, 1025 m, 832 s, 712 s cm⁻¹; ¹H NMR (600 MHz) δ 1.11 (3H, t, J = 7.7, CH₂CH₃), 1.88 (1H, ddq, J = 14.4, 8.0, 4.9, CH₂), 2.15 (1H, dqd, J = 14.1, 7.5, 4.8, CH₂), 3.38 (1H, ddd, J = 8.0, 7.3, 4.7, CHCH₂), 3.74 (3H, s, OCH₃), 4.80 (1H, dd, J = 7.2, 5.7, CHNO₂), 5.65 (1H, d, J = 5.9, CHN), 6.80 (2H, d, J = 9.2, CHPMPC₃-H), 7.20 (2H, d, J = 9.2, CHPMPC₂-H), 7.28 (1H, dt, J = 7.9, 1.9, CH₃pyridine), 7.53 (1H, m, CH₃pyridine), 8.54 (1H, d, J = 2.1, CH₃pyridine), 8.57 (1H, dd, J = 4.8, 1.4, CH₃pyridine); ¹³C NMR (150 MHz) δ 10.7 (CH₃), 23.2 (CH₃), 48.8 (CHCH₂), 55.5 (OCH₃), 63.6 (NCH), 89.9 (CHNO₂), 114.6 (CHPMPC₃), 124.2 (CHPMPC₄), 125.3 (CH₃pyridine), 128.7 (C₉PMPC₁), 133.0 (C₉pyridine), 134.4 (CH₃pyridine), 148.8 (CH₃pyridine), 150.8 (CH₃pyridine), 158.0 (C₉PMPC₄), 170.7 (C=O); m/z (Cl⁻) 342 (100%, M+H⁺), 295 (10%); HRMS: found 342.1461, C₁₈H₂₀N₃O₄ requires 342.1458; Anal. Cald. For C₁₈H₁₉N₃O₄: C, 63.33, H, 5.61, N, 12.31. Found C, 63.36, H, 5.62, N, 12.24%.

(3S*, 4S*, 5R*)-3-ethyl-1-(4-methoxyphenyl)-4-nitro-5-(1-tosyl-1H-indol-3-yl)pyrrolidin-2-one 271

Prepared by general procedure C. Nitroacrylate 231 (100 mg, 0.690 mmol), diethylzinc (760 µL, 0.760 mmol), imine 260 (558 mg, 1.38 mmol) and TFA (180 µL, 2.41 mmol) afforded crude pyrrolidinone 271. Purification by flash column chromatography (Petrol:Me₂CO 4:1) gave pyrrolidinone 271 (206 mg, 56%) as a yellow solid; mp. 131-132 °C; Rᵣ 0.08 (Petrol:Me₂CO 4:1); IR 𝜈max (thin film) 3104 w (C-H), 2935 w (C-H), 1709 s (C=O), 1553 s (N=O), 1511 s, 1445 s, 1362 s (N-O), 1350 s, 1244 s, 1189 m, 1174 s, 1135 m, 1123 m, 1094 m, 1027 m, 977 m, 828 s, 816 m, 746 s, 706 m, 678 s cm⁻¹; ¹H NMR (600 MHz) δ 1.08 (3H, t, J = 7.4, CH₂CH₃), 1.82 (1H, ddq, J = 14.2, 8.5, 7.2, CH₂CH₃), 2.15 (1H, dqd, J = 14.2, 7.6, 4.8,
CH₂CH₃), 2.43 (3H, s, ArCH₃), 3.38 (1H, ddd, J = 8.5, 6.7, 4.8, CHCH₂), 3.76 (3H, s, OCH₃), 4.97 (1H, dd, J = 6.7, 5.2, CHNO₂), 5.83 (1H, d, J = 5.3, NCH), 6.76 (2H, d, J = 9.0, CH₃PMPC₃-H), 7.13 (2H, d, J = 8.4, CH₂tosylC3-H), 7.25 (2H, d, J = 9.0, CH₃PMPC₄-H), 7.29 (1H, m, CH_indole), 7.35 (1H, m, CH_indole), 7.46 (4H, m, CH_Arom.), 7.93 (1H, d, J = 8.4, CH_indoleC₆-H); ¹³C NMR (150 MHz) δ 11.1 (CH₂C₃H₃), 21.7 (ArCH₃), 23.6 (CH₂), 49.2 (CHCH₂), 55.5 (OCH₃), 59.5 (NCH), 88.2 (CHNO₂), 114.3 (CH₃PMPC₃), 114.4 (CH_indoleC₆), 118.3 (CqIndoleC3), 119.2 (CH_indoleC2), 124.2 (CH_indole), 124.8 (CHPMPC₂), 125.8 (CH_indole), 126.1 (CH_indole), 126.8 (CH₂tosylC₂), 127.5 (CqIndoleC₄), 129.3 (CqPMPC), 130.0 (CH₂tosylC₃), 134.5 (CqIndoleC₉), 135.7 (CqtosylC₁), 145.4 (CqtosylC₂), 157.8 (CqPMPC₄), 170.7 (C=O); m/z (ESI⁺) 534 (100%, M+H⁺), 445 (40%), 535 (30%); HRMS: found 534.1674, C₂₈H₂₇N₃O₆S requires 534.1699; Anal. Cald. For C₂₈H₂₆N₃O₆S: C, 63.03, H, 5.10, N, 7.87. Found C, 63.18, H, 5.48, N, 7.40%.

(3S*, 4S*, 5S*)-3-ethyl-1-(4-methoxyphenyl)-4-nitro-5-(1-tosyl-1H-pyrrol-2-yl)pyrrolidin-2-one 272

Prepared by general procedure C. Nitroacrylate 231 (100 mg, 0.690 mmol), diethylzinc (760 µL, 0.760 mmol), imine 263 (489 mg, 1.38 mmol) and TFA (180 µL, 2.41 mmol) afforded crude pyrrolidinone 272. Purification by flash column chromatography (Petrol:Me₂CO 4:1) gave pyrrolidinone 272 as an inseparable 85:15 mixture of diastereoisomers (110 mg, 33%), as a yellow solid; mp. 147-148 °C; Rₜ 0.18 (Petrol:Me₂CO 4:1); diastereoisomer ratio calculated by CH₃Et signal, δ major = 2.86, δ minor = 3.01; IR νmax (thin film) 3004 w (C-H), 2994 w (C-H), 1699 s (C=O), 1549 s (N=O), 1512 s, 1368 s (N=O), 1247 s, 1234 m, 1190 m, 1181 m, 1171 s, 1153 s, 1130 m, 1088 m, 1055 m, 1039 m, 832 s, 815 s, 736 s, 703 s, 671 s cm⁻¹; ¹H NMR (600 MHz, 60 °C) δ 1.13 (3H, t, J = 7.4, CH₂CH₃), 1.59 (1H, m, CH₂CH₃), 2.12 (1H, dqq, J = 14.8, 7.4, 4.8, CH₂CH₃), 2.50 (3H, s, ArCH₃), 2.86 (1H, ddd, J = 10.3, 4.7, 2.3, CHCH₂), 3.74 (3H, s, OCH₃), 4.94 (1H, t, J = 2.4, 1.6, CHNO₂), 6.02 (1H, s, NCH), 6.10 (1H, s, CH_pyroleC3-H), 6.22 (1H, t, J = 3.4, CH_pyroleC⁴-H), 6.58 (2H, d, J = 9.1, CHPMPC₃-H), 6.91 (2H, d, J = 9.2, CHPMPC₂-H), 7.38 (3H, m, CH_tosylC₃-H and
CH<sub>pyrroleC5-H</sub>), 7.63 (2H, d, J = 8.2, CH<sub>tosylC2-H</sub>); <sup>13</sup>C NMR (150 MHz) δ 12.0 (CH₂CH₃), 21.7 (ArCH₃), 25.5 (CH₂), 52.3 (CHCH₂), 55.3 (OCH₃), 59.4 (NCH), 86.4 (CHNO₂), 111.7 (CH<sub>pyrroleC3</sub>), 113.9 (CH<sub>PMPC3</sub>), 114.9 (CH<sub>pyrroleC4</sub>), 123.2 (CH<sub>PMPC2</sub>), 124.0 (CH<sub>pyrroleC5</sub>), 126.9 (CH<sub>tosylC2</sub>), 128.3 (C<sub>pyrroleC2</sub>), 129.8 (CH<sub>tosylC3</sub>), 130.5 (C<sub>PMPC1</sub>), 134.3 (C<sub>tosylC1</sub>), 145.9 (C<sub>tosylC4</sub>), 157.1 (C<sub>PMPC4</sub>), 171.6 (C=O); m/z (EI⁺) 483 (20%, M⁺), 281 (24%), 155 (22%, Ts⁺), 91 (100%, PhCH₂⁺); HRMS: found 483.1451, C<sub>24</sub>H<sub>25</sub>N<sub>3</sub>O<sub>6</sub>S requires 483.1464; Anal. Cald. For C<sub>24</sub>H<sub>25</sub>N<sub>3</sub>O<sub>6</sub>S: C, 55.32, H, 4.93, N, 12.10. Found C, 55.23, H, 4.89, N, 12.02%.

Minor diastereomer: <sup>1</sup>H NMR (600 MHz, 60 °C) δ 1.12 (3H, t, J = 7.4, CH<sub>2</sub>CH₃), 1.33 (1H, m, CH₂CH₃), 2.12 (1H, m, CH₂CH₃), 2.47 (3H, s, ArCH₃), 3.01 (1H, ddd, J = 9.6, 7.3, 4.6, CHCH₂), 3.74 (3H, s, OCH₃), 5.33 (1H, d, J = 7.4, CHNO₂), 5.73 (1H, s, NCH), 6.20 (1H, s, CH<sub>pyrroleC3-H</sub>), 6.27 (1H, t, J = 3.5, CH<sub>pyrroleC4-H</sub>), 6.61 (2H, d, J = 9.1, CH<sub>PMPC3-H</sub>), 6.98 (2H, d, J = 9.0, CH<sub>PMPC2-H</sub>), 7.32 (3H, m, CH<sub>tosylC3-H</sub> and CH<sub>pyrroleC5-H</sub>), 7.60 (2H, d, J = 8.2, CH<sub>tosylC2-H</sub>); <sup>13</sup>C NMR (150 MHz) δ 12.2 (CH₂CH₃), 18.9 (CH₂), 21.7 (ArCH₃), 45.8 (CHCH₂), 55.3 (OCH₃), 60.0 (NCH), 86.6 (CHNO₂), 112.0 (CH<sub>pyrroleC3</sub>), 113.9 (CH<sub>PMPC3</sub>), 114.6 (CH<sub>pyrroleC4</sub>), 123.2 (CH<sub>PMPC2</sub>), 124.4 (CH<sub>pyrroleC5</sub>), 126.7 (CH<sub>tosylC2</sub>), 129.6 (CH<sub>tosylC3</sub>), 171.0 (C=O), 4 carbons missing.

(3S*, 4S*, 5S*)-3-ethyl-1-(4-methoxyphenyl)-4-nitro-5-(thiazol-2-yl)pyrrolidin-2-one 273

Prepared by general procedure C. Nitroacrylate 231 (100 mg, 0.690 mmol), diethylzinc (760 µL, 0.760 mmol), imine 264 (301 mg, 1.38 mmol) and TFA (180 µL, 2.41 mmol) afforded crude pyrrolidinone 273. Purification by flash column chromatography (Petrol:EtOAc 7:3) gave pyrrolidinone 273 (139 mg, 58%) as a yellow solid; mp. 121-122 °C; R<sub>f</sub> 0.31 (Petrol:EtOAc 7:3); IR <i>υ</i> <sub>max</sub> (thin film) 2961 w (C-H), 1716 s (C=O), 1558 s (N=O), 1512 s, 1440 m, 1390 m, 1363 m (N-O), 1247 s, 1187 m, 1029 s, 832 s, 782 s, 752 s cm<sup>-1</sup>; <sup>1</sup>H NMR (600 MHz) δ 1.14 (3H, t, J = 7.1,
CH₂CH₃), 1.90 (1H, ddq, J = 14.3, 8.9, 7.1, CH₂CH₃), 2.15 (1H, dqd, J = 14.0, 7.6, 4.9, CH₂CH₃), 3.25 (1H, dt, J = 9.0, 5.0, CH₂CH₂), 3.78 (3H, s, OCH₃), 5.36 (1H, dd, J = 5.1, 3.8, CHNO₂), 6.02 (1H, d, J = 4.2, NCH), 6.87 (2H, d, J = 9.2, CHPMPC₃-H), 7.25 (2H, d, J = 9.2, CHPMPC₂-H), 7.31 (1H, d, J = 3.0, CH₃thiazoleC₅-H), 7.80 (2H, d, J = 3.4, CH₃thiazoleC₄-H); ¹³C NMR (150 MHz) δ 11.2 (CH₃), 23.7 (CH₂), 49.7 (CH₂CH₂), 55.5 (OCH₃), 63.3 (NCH), 87.4 (CHPMPC₂), 114.6 (CHPMPC₃), 121.0 (CH₃thiazoleC₅), 126.4 (CHPMPC₂), 128.7 (CqPMPC₃), 128.8 (CH₃thiazoleC₅), 128.9 (CqPMPC₄), 158.7 (CqPMPC₂), 165.7 (CqPMPC₄), 171.1 (C=O); m/z (EI⁺) 347 (100%, M⁺), 300 (55%, M⁺-HNO₂); HRMS: found 347.0940, C₁₆H₁₇N₃O₄S requires 347.0934; Anal. Cald. For C₁₆H₁₇N₃O₄S: C, 59.61, H, 5.21, N, 8.69. Found C, 59.52, H, 5.20, N, 8.61%.

(3S*, 4S*, 5S*)-3-ethyl-1-(4-methoxyphenyl)-4-nitro-5-(oxazol-2-yl)pyrrolidin-2-one 274

Prepared by general procedure C. Nitroacrylate 231 (100 mg, 0.690 mmol), diethylzinc (760 µL, 0.760 mmol), imine 265 (279 mg, 1.38 mmol) and TFA (180 µL, 2.41 mmol) afforded crude pyrrolidinone 274. Purification by flash column chromatography (Petrol:Me₂CO 4:1) gave pyrrolidinone 274 (121 mg, 53%) as a white solid; mp. 97-98 °C; Rₙ 0.15 (Petrol:Me₂CO 4:1); IR υmax (thin film) 2964 w (C-H), 1706 s (C=O), 1562 s (N=O), 1387 m (N-O), 1243 s, 1179 m, 1115 m, 1031 m, 834 s, 779 s cm⁻¹; ¹H NMR (600 MHz) δ 1.17 (3H, t, J = 7.5, CH₂CH₃), 1.96 (1H, ddq, J = 14.3, 8.7, 7.4, CH₂CH₂), 2.19 (1H, dqd, J = 14.3, 7.6, 4.9, CH₂CH₂), 3.25 (1H, ddd, J = 8.7, 5.7, 4.9, CHCH₂), 3.78 (3H, s, OCH₃), 5.28 (1H, dd, J = 5.6, 4.4, CHNO₂), 5.79 (1H, d, J = 4.4, NCH), 6.86 (2H, d, J = 9.0, CHPMPC₃-H), 7.11 (1H, s, CHoxazoleC₄-H), 7.19 (2H, d, J = 9.0, CHPMPC₂-H), 7.62 (1H, s, CHoxazoleC₅-H); ¹³C NMR (150 MHz) δ 11.1 (CH₂), 23.4 (CH₃), 49.2 (CHCH₂), 55.5 (OCH₃), 59.6 (NCH), 85.6 (CHNO₂), 114.6 (CHPMPC₃), 126.4 (CHPMPC₂), 128.2 (CHoxazoleC₄), 128.6 (CqPMPC₁), 140.5 (CHoxazoleC₅), 158.8 (CqPMPC₃), 159.3 (CqoxazoleC₂), 170.8 (C=O); m/z (EI⁺) 331 (100%, M⁺), 284 (72%, M⁺-HNO₂); HRMS: found 331.1155, C₁₆H₁₇N₃O₅S.
(3S*, 4S*, 5R*)-3-ethyl-1-(4-methoxyphenyl)-5-methyl-4-nitropyrrolidin-2-one

Prepared by general procedure C, with the exception that imine 266 was formed and used in situ. To a solution of acetaldehyde (77 μL, 1.38 mmol) in THF (5 mL) were added under Nitrogen dried 4Å molecular sieves (1.40 g) and the mixture cooled at -78 °C. A solution of para-anisidine (170 mg, 1.38 mmol) in THF (1 mL) was then added and the mixture stirred at this temperature for 1.5 h. The solution was then transferred into the reaction via cannula. Nitroacrylate 231 (100 mg, 0.69 mmol) diethylzinc (760 µL, 0.760 mmol), freshly prepared cold (-78 °C) solution of imine 266 (1.38 mmol) and TFA (180 μL, 2.41 mmol) afforded crude pyrrolidinone 275. Purification by flash column chromatography (Petrol:EtOAc 4:1) gave pyrrolidinone 275 (78 mg, 40%) as a colourless oil; Rf 0.22 (Petrol:EtOAc 4:1); IR νmax (thin film) 2967 w (C-H), 1702 s (C=O), 1554 s (N=O), 1513 s, 1368 m (N-O), 1248 s, 1033 m, 834 m cm⁻¹; ¹H NMR (600 MHz) δ 1.07 (3H, t, J = 7.4, CH₂C₃H₃), 1.35 (3H, d, J = 6.3, CHCH₃), 1.79 (1H, m, CH₂CH₃), 2.08 (1H, m, OCH₂CH₃), 3.26 (1H, ddd, J = 8.3, 7.3, 4.7, CHCH₂), 3.81 (3H, s, OCH₃), 4.49 (1H, app q, J = 6.2, NCHCH₃), 4.60 (1H, dd, J = 7.2, 5.7, CHNO₂), 6.93 (2H, app d, J = 8.9, CHPMPC₂-H); ¹³C NMR (125 MHz) δ 10.6 (CH₂CH₃), 19.3 (CHCH₃), 23.1 (CH₂CH₃), 48.5 (CHCH₂), 55.4 (OCH₃), 58.0 (CHCH₃), 89.3 (CHNO₂), 114.5 (CHPMPC₂), 126.6 (CHPMPC₂), 128.4 (CqPMPC₁), 158.4 (CqPMPC₄), 170.4 (C=O); m/z (EI⁺) 278 (5%, M⁺), 231 (21%), 148 (13%), 134 (24), 91 (100%); HRMS found 278.12631, C₁₄H₁₈N₂O₄ requires 278.12611; Anal. Cald. for C₁₄H₁₈N₂O₄: C, 60.42, H, 6.52, N, 10.07. Found C, 60.31, H, 6.61, N, 9.77%.
(2S*,3S*,4S*)-3-ethyl-5-(dimethoxymethyl)-1-(4-methoxyphenyl)-4-nitopyrrolidin-2-one 276

Prepared by general procedure C. Nitroacrylate 231 (100 mg, 0.690 mmol), diethylzinc (760 µL, 0.760 mmol), imine 267 (288 mg, 1.38 mmol) and TFA (180 µL, 2.41 mmol) afforded crude pyrrolidinone 276. Purification by flash column chromatography (Petrol:EtOAc 7:3) gave pyrrolidinone 276 (147 mg, 63%) as a white solid; mp. 112-113 °C; R<sub>f</sub> 0.41 (Petrol:EtOAc 7:3); IR <var>υ</var><sub>max</sub> (thin film) 2939 w (C-H), 1698 s, 1548 s (N=O), 1510 s, 1370 m (N-O), 1249 s, 1069 m, 1034 m, 834 m, 754 m cm<sup>-1</sup>; ¹H NMR (600 MHz) δ 1.14 (3H, t, <var>J</var> = 7.4, CH<sub>2</sub>C<sub>6</sub>H<sub>3</sub>), 1.81 (1H, ddq, <var>J</var> = 14.0, 9.7, 7.2, C<sub>6</sub>H<sub>2</sub>CH<sub>3</sub>), 2.09 (1H, dqd, <var>J</var> = 14.0, 7.4, 4.3, C<sub>6</sub>H<sub>2</sub>CH<sub>3</sub>), 2.97 (1H, dt, <var>J</var> = 9.8, 4.6, CH(CH<sub>3</sub>), 3.38 (3H, s, OCH<sub>3</sub>), 3.40 (3H, s, OCH<sub>3</sub>), 3.84 (3H, s, ArOCH<sub>3</sub>), 4.24 (1H, d, <var>J</var> = 2.4, CH(OCH<sub>3</sub>)), 4.76 (1H, dd, <var>J</var> = 3.2, 2.6, NCH), 5.07 (1H, dd, <var>J</var> = 4.9, 3.4, CHNO<sub>2</sub>), 6.97 (2H, d, <var>J</var> = 8.9, C<sub>6</sub>H<sub>2</sub>PMPC<sub>3</sub>-H), 7.30 (2H, d, <var>J</var> = 9.0, C<sub>6</sub>H<sub>2</sub>PMPC<sub>2</sub>-H); ¹³C NMR (150 MHz) δ 11.3 (CH<sub>2</sub>C<sub>6</sub>H<sub>3</sub>), 23.1 (CH<sub>2</sub>), 50.2 (CHCH<sub>2</sub>), 55.5 (OCH<sub>3</sub>), 56.9 (OCH<sub>3</sub>), 57.9 (OCH<sub>3</sub>), 64.3 (CHN), 82.1 (CHNO<sub>2</sub>), 102.3 (CH(OMe)<sub>2</sub>), 114.7 (CH<sub>PMPC</sub>), 126.2 (CH<sub>PMPC</sub>), 128.8 (C<sub>Q</sub><sub>PMPC</sub>), 158.3 (C<sub>q</sub><sub>PMPC</sub>), 171.7 (C=O); <var>m/z</var> (EI<sup>+</sup>) 338 (75%, M<sup>+</sup>), 217 (85%, M<sup>+</sup>-NO<sub>2</sub> -CH(OMe)<sub>2</sub>), 114 (100%); HRMS found 338.1472, C<sub>16</sub>H<sub>22</sub>N<sub>2</sub>O<sub>6</sub> requires 338.1470; Anal. Cald. for C<sub>16</sub>H<sub>22</sub>N<sub>2</sub>O<sub>6</sub>: C, 56.80, H, 6.55, N, 8.28. Found C, 56.70, H, 6.51, N, 8.11%.

(2S*,3S*,4R*)-<i>tert</i>-butyl 4-(2,2,2-trifluoro-N-(4-methoxyphenyl)acetamido)-2-ethyl-3-nitro-4-phenylbutanoate 299

To a solution of nitroacrylate 296 (222 mg, 1.28 mmol) in THF (5 mL), was added Cu(OTf)<sub>2</sub> (5 mol%, 23 mg) and the mixture cooled to -78 °C. A solution of Et<sub>2</sub>Zn
(1.32 mL, of a 1 M solution in hexanes, 1.32 mmol) was then added dropwise. The orange mixture was stirred at this temperature for 10 min and then at rt for 1.5 h. The mixture was then recooled to -78 °C and imine 281 (540 mg, 2.56 mmol) in THF (3 mL) was added via cannula. The mixture was stirred for 10 min before TFA (340 µL, 4.48 mmol) in THF (2 mL) was added dropwise. The mixture was stirred at this temperature for a further h, then warmed to rt and stirred for a further h. The mixture was then cooled to 0 °C and pyridine (0.51 mL, 6.4 mmol) followed by trifluoroacetic anhydride (0.89 mL, 6.4 mmol) were added. The mixture was then warmed to rt and stirred for a further 2 h. The mixture was then washed with 2 M aqueous HCl (3x10 mL) and brine (10 mL), dried over MgSO₄ and concentrated in vacuo to leave crude trifluoroacetamide 299. Purification by flash column chromatography (Petrol:DCM 4:6) gave trifluoroacetamide 299 (170 mg, 26%) as a colourless oil which was found to be a mixture of two diastereomers 65:35; diastereomer ratio calculated by CHET signal, δ major = 2.91, δ minor = 2.80; Rₚ 0.58 (Petrol:DCM 4:6); Major diastereomer: 1R νmax (thin film) 2976 w (C-H), 1727 m (C=O), 1698 s, 1558 m (N=O), 1510 m, 1206 s, 1034 m, 840 m, 734 m; 1H NMR (600 MHz) δ 1.09 (3H, t, J = 7.4, OC₃H₃), 1.49 (9H, s, C(CH₃)₃), 1.76 (1H, dqd, J = 12.7, 7.5, 5.3, CH₂CH₃), 1.98 (1H, m, CH₂CH₃), 2.91 (1H, ddd, J = 9.4, 5.2, 4.1, CHET), 3.81 (3H, s, OC₃H₃), 5.71 (1H, d, J = 10.2, CHPh), 5.86 (1H, dd, J = 10.2, 3.9, CHNO₂), 6.50-7.43 (7H, m, Arom. CH); 13C NMR (150 MHz) δ 11.7 (CH₂CH₃), 23.3 (CH₂), 27.8 (C(CH₃)₃), 48.3 (CHET), 55.4 (OCH₃), 65.1 (CHPh), 82.7 and 82.7 (C(CH₃)₃), 87.6 (CHNO₂), 113.4, 114.3, 128.7, 128.8, 129.4, 129.5, 130.6, 131.9, 133.1, 133.1, 133.8 (CH Arom.), 158.1 (q, J = 35.7, CF₃), 160.3 (C=OCF₃), 169.2 (OC=O); 19F NMR (282 MHz) δ -67.85 (3F, s, CF₃); m/z (CI⁺) 511 (M +1, 20%), 545 (100%, M +H⁻-tBu), 408 (43%, M -tBu-CO₂); HRMS: found 511.20545, C₂₅H₂₉F₃N₂O₆ requires 511.20560; Anal. Cald. For C₂₅H₃₀F₃N₂O₆: C, 58.82, H, 5.73, N, 5.49. Found C, 59.08, H, 6.06, N, 5.24%. Minor diastereoisomer: 1H NMR (600 MHz) δ 1.05 (3H, t, J = 7.4), 1.58 (9H, s, C(CH₃)₃), 1.63 (1H, dqd, J = 11.4, 7.1, 6.6, CH₂CH₃), 2.05 (1H, m, CH₂CH₃), 2.80 (1H, dt, J = 11.4, 2.2, CHET), 3.81 (3H, s, OCH₃), 5.52 (1H, dd, J = 11.6, 2.2, CHNO₂), 5.97 (1H, d, J = 8.7, CHPh), 6.50-7.43 (7H, m, Arom. CH); 13C NMR (150 MHz) δ 12.8 (CH₂CH₃), 18.9 (CH₂), 28.0 (C(CH₃)₃), 48.4 (CHET), 55.4 (OCH₃), 58.7 (CHPh), 82.7 and 82.7 (C(CH₃)₃), 86.8 (CHNO₂), 113.6, 113.9 (CH Arom.), 158.2 (q,
\[ J = 35.7, \text{CF}_3 \], \[ 160.1 \ (C=O\text{CF}_3) \], \[ 170.0 \ (O\text{C}=O) \], the rest of the \( ^{13} \text{C} \) peaks could not be distinguished between the two diastereomers; \(^{19} \text{F} \) NMR (282 MHz) \( \delta \ -67.36 \ (3\text{F}, \text{s, CF}_3) \).

\((3S^*, 4S^*, 5R^*)\)-3-isopropyl-1-(4-methoxyphenyl)-4-nitro-5-phenylpyrrolidin-2-one 282

Prepared by general procedure C. Nitroacrylate 231 (100 mg, 0.690 mmol), diisopropylzinc (0.760 mmol, of a 0.356 M solution in hexane, 1.1 equiv.), imine 281 (291 mg, 1.38 mmol) and TFA (180 µL, 2.41 mmol) afforded crude pyrrolidinone 282. Purification by flash column chromatography (Petrol:EtOAc 4:1) gave 282 (125 mg, 51\%) as a white solid; mp. 140-141 °C; R\(_f\) 0.50 (Petrol:EtOAc 4:1); IR \( \nu_{\text{max}} \) (thin film) 2961.6 w (C-H), 1707.7 m (C=O), 1556.8 m (N=O), 1513 s, 1369 w (N-O), 1249 m, 1032 w, 700 w cm\(^{-1}\); \(^1\)H NMR (600 MHz) \( \delta \) 1.07 (6H, dd, \( J = 8.3, 7.0, \text{CH}_3 \)), 2.55 (1H, m, \( \text{CH}(\text{CH}_3)_2 \)), 3.43 (1H, dd, \( J = 7.6, 4.5, \text{CHC}=\text{O} \)), 3.73 (3H, s, \( \text{OC}_3\text{H}_3 \)), 4.88 (1H, dd, \( J = 7.6, 5.9, \text{CHNO}_2 \)), 5.52 (1H, d, \( J = 5.9, \text{NCHPh} \)), 6.79 (2H, app d, \( J = 9.1, \text{CHPMPC}_3-\text{H} \)), 7.19 (2H, m, \( \text{CH Arom.} \)), 7.23 (2H, app d, \( J = 9.1, \text{CHPMPC}_2-\text{H} \)), 7.28-7.35 (3H, m, \( \text{CH Arom.} \)); \(^{13} \text{C} \) NMR (150 MHz) \( \delta \) 18.3 and 19.6 (\( \text{CH}_3 \)), 28.0 (\( \text{CH(CH}_3)_2 \)), 53.3 (\( \text{CHC}=\text{O} \)), 55.3 (\( \text{OCH}_3 \)), 65.9 (\( \text{NCHPh} \)), 88.4 (\( \text{CHNO}_2 \)), 114.1 (\( \text{CHPMPC}_3 \)), 125.0 (\( \text{CH Arom.} \)), 126.6 (\( \text{CH Arom.} \)), 129.1 (\( \text{CH Arom.} \)), 129.2 (\( \text{Cq Arom.} \)), 129.3 (\( \text{CH Arom.} \)), 137.2 (\( \text{Cq Arom.} \)), 157.5 (\( \text{CqPMPC}_4 \)), 170.5 (\( \text{C}=\text{O} \)); \( m/z \) (ESI\(^+\)) 355 (M+H\(^+\), 20\%), 308 (M\(^+\)-NO\(_2\), 100\%), 266 (M+H \(^+\)-NO\(_2\)-C\(_3\)H\(_7\), 30\%); HRMS: found 355.1647, C\(_{20}\)H\(_{23}\)N\(_2\)O\(_4\) requires 355.1658; Anal. Cald. For C\(_{20}\)H\(_{22}\)N\(_2\)O\(_4\): C, 67.78, H, 6.26, N, 7.90. Found C, 67.70, H, 6.22, N, 7.84\%.

Also prepared from the reaction of nitroalkene 370 with Superhydride\(^\circ\). To a solution of nitroalkene 370 (187 mg, 1.00 mmol) in THF (10 mL) was added Superhydride\(^\circ\) (1.05 mL, 1 M in THF, 1.05 mmol) and the suspension stirred at rt for 30 min. The mixture was then cooled to -78 °C and a solution of imine 281 (2.0 mmol) in THF (6 mL) was added, followed in 10 min by TFA (3.0 mmol) in THF (1 mL) dropwise.
The mixture was stirred at this temperature for 1 h and then warmed to rt and stirred for a further 24 h. Saturated aqueous NaHCO$_3$ (10 mL) was then added and the mixture extracted with Et$_2$O (3x10 mL), dried over MgSO$_4$ and evaporated in vacuo to give crude pyrrolidinone 282. Purification by flash column chromatography (Petrol:EtOAc 4:1) gave 282 (138 mg, 39%) as a white solid, same as the one reported above.

**Ethyl 3-nitro-2-phenylpropanoate 279**

![Structure of Ethyl 3-nitro-2-phenylpropanoate](structure.png)

To a solution of nitroacrylate 231 (100 mg, 0.690 mmol) in THF (3 mL), was added Cu(OTf)$_2$ (12 mg, 34 µmol, 5 mol%). The mixture was cooled to −78 °C and the diphenylzinc solution (0.760 mmol, 1.1 equiv.) was added fast dropwise. The orange mixture was stirred at this temperature for 10 min before being warmed to rt and stirred for a further 1.5 h. Saturated aqueous NH$_4$Cl (20 mL) and Et$_2$O (20 mL) was then added and the layers separated. The aqueous phase was extracted with Et$_2$O (3x20 mL), and the combined organics washed with brine (20 mL), dried over MgSO$_4$ and concentrated in vacuo to leave crude nitroalkane 279. Purification by flash column chromatography (Petrol:EtOAc 9:1) gave 279 (92 mg, 60%) as a colourless oil; R$_f$ 0.35 (Petrol:EtOAc 9:1); $^1$H NMR (600 MHz) δ 1.24 (3H, t, $J = 7.4$, CH$_2$C$_6$H$_3$), 4.17 (1H, m, OC$_2$H$_2$CH$_3$), 4.26 (1H, m, OCH$_2$CH$_3$), 4.44 (1H, dd, $J = 10.0$, 5.1, CHPh), 3.73 (3H, s, OC$_2$H$_3$), 4.56 (2H, dd, $J = 14.7$, 5.2, CH$_2$NO$_2$), 5.12 (1H, dd, $J = 14.6$, 10.0, CH$_2$NO$_2$), 7.30-7.38 (5H, m, CH Arom.). Data in agreement to the one reported.$^{175}$

Also prepared using a cuprate reagent according to the reported procedure.$^{253}$ To a mixture of CuBr·SMe$_2$ (205 mg, 1.00 mmol) in THF (2.5 mL) was added at -40 °C, PhMgBr (330 µL, 3 M in Et$_2$O, 1.00 mmol) and the mixture stirred for 30 min, then cooled to -78 °C and a solution of nitroalkene 231 (145 mg, 1.00 mmol) in THF (5 mL) was added dropwise. The mixture was stirred for 30 min, then warmed to rt and stirred until complete consumption of the nitroalkene (TLC, 3 h). Saturated aqueous NH$_4$Cl (20 mL) was then added and the mixture extracted with Et$_2$O (3x10 mL). The
combined organics were washed with saturated aqueous NaHCO$_3$ (10 mL) and brine (10 mL), dried over MgSO$_4$ and evaporated in vacuo to give crude nitroalkane 279. Purification by flash column chromatography (Petrol:Et$_2$O 9:1) gave 279 (108 mg, 48%) as a colourless oil same as the one reported above.

(3S*, 4S*, 5R*)-1-(4-methoxyphenyl)-4-nitro-3,5-diphenylpyrrolidin-2-one 278

A solution of nitroalkane 279 (121 mg, 0.540 mmol) in THF (3 mL), was cooled to -78 °C and a solution of nBuLi (320 µL, 0.540 mmol, 1.0 equiv., 1.7 M solution in hexanes) was added dropwise. The orange mixture was stirred at this temperature for 10 min before being warmed to rt and stirred for a further 30 min. The mixture was re-cooled to -78 °C and the PMP-protected imine (228 mg, 1.08 mmol, 2.0 equiv.) in THF (2 mL) was added via cannula. The mixture was stirred for 20 min before TFA (104 µL, 1.35 mmol, 2.5 equiv.) in THF (0.5 mL) was added via cannula. The mixture was stirred at this temperature for a further 1 h before being warmed to rt for 16 h. Saturated aqueous NaHCO$_3$ (20 mL) and Et$_2$O (20 mL) were then added and the layers separated. The aqueous phase was extracted with Et$_2$O (3x20 mL) and the combined organics were washed with brine (20 mL), dried over MgSO$_4$ and concentrate in vacuo to leave crude pyrrolidinone 278. Purification by flash column chromatography (Petrol:EtOAc 4:1) gave 278 (106 mg, 51%) as a white solid; mp. 136-137 °C; R$_f$ 0.24 (Petrol:EtOAc 4:1); IR $\nu$$_{max}$ (thin film) 1721 m(C=O), 1553 s(N=O), 1510 m, 1247 m, 1177 m, 1036 m, 847 m, 753 m, 714 s, 696 s cm$^{-1}$; $^1$H NMR (600 MHz) $\delta$ 3.73 (3H, s, OC$_3$H$_3$), 4.69 (1H, d, $J$ = 8.0, CHC=O), 5.15 (1H, dd, $J$ = 8.0, 6.3, CHNO$_2$), 5.68 (1H, d, $J$ = 6.2, NCH), 6.81 (2H, app d, $J$ = 6.2, CH Arom.), 7.23-7.45 (12H, m, CH Arom.); $^{13}$C NMR (150 MHz) $\delta$ 53.3 (CHC=O), 55.3 (OCH$_3$), 65.5 (NCH), 93.0 (CHNO$_2$), 114.2 (C$_3$PMPC3), 125.2 (CH Arom.), 126.9 (CH Arom.), 128.2 (CH Arom.), 128.5 (CH Arom.), 129.1 (Cq Arom.), 129.3 (CH Arom.), 129.4 (C$_3$PMPC2), 134.9 (C$_3$PMPC1), 157.7 (C$_3$PMPC4), 169.1 (C=O); $m/z$ (Cl$^+$) 389 (M+H$^+$, 6%), 342 (100%, M - NO$_2$); HRMS: found 389.15036, C$_{23}$H$_{21}$N$_2$O$_4$
requires 389.15013; Anal. Cald. For C_{23}H_{20}N_{2}O_{4}: C, 71.12, H, 5.19, N, 7.21. Found C, 70.91, H, 5.17, N, 7.15%.

3.4.1.3 Further functionalisation of pyrrolidonones

\((2R^*, 3S^*, 4R^*)-4\text{-Ethyl-1-(4-methoxy-phenyl)-3-nitro-2-phenyl-pyrrolidine} 247\)

Prepared by a modification of the reported procedure.\(^{119}\) To a solution of pyrrolidinone 233 (350 mg, 1.03 mmol) in THF (25 mL) at 0 °C was added BH\(_3\)·THF complex (3.61 mL, of a 1.0 M solution in THF, 3.61 mmol, 3.5 equiv.) dropwise. The mixture was stirred at 0 °C until no more effervescence was observed and then heated to reflux until the starting pyrrolidinone was consumed (TLC, 4.5 h). The mixture was cooled to rt and MeOH (50 mL) was added before being concentrated in vacuo to give crude pyrrolidine 247. Purification by flash column chromatography (Petrol:Me\(_2\)CO 4:1) gave pyrrolidine 247 (316 mg, 94%, lit. 79%) as a yellow solid; mp. 47-48 °C (50-52 °C); R\(_f\) 0.21 (Petrol:Me\(_2\)CO 4:1); \(^1\)H NMR (600 MHz) δ 0.97 (3H, t, \(J = 7.3\), CH\(_3\)), 1.58 (2H, m, CH\(_2\)CH\(_3\)), 2.85 (1H, m, CH\(_2\)Et), 3.67 (1H, dd, \(J = 9.1, 5.5\), NCH\(_2\)), 3.72 (3H, s, OCH\(_3\)), 3.85 (1H, dd, \(J = 9.1, 8.1\), NCH\(_2\)), 4.76 (1H, app. t, \(J = 5.2\), CHNO\(_2\)), 5.13 (1H, d, \(J = 4.7\), CHPh), 6.46-6.50 (2H, m, CH Arom.), 6.74-6.78 (2H, m, CH Arom.), 7.28-7.34 (5H, m, CH Arom.). Data in agreement to the one reported.\(^{116}\)

**General procedure D for the reduction of the nitro group**

To a solution of pyrrolidinone (0.29 mmol) in EtOAc/MeOH (2:1, 6 mL) at 0 °C, was added HCl (1.47 mL of an aqueous 6 M sol, 8.82 mmol, 30.0 equiv.). Zinc dust (1.15 g, 17.6 mmol, 60.0 equiv.) was added portionwise over 20 min. The mixture was then warmed to rt and stirred for a further 15 hr. Saturated aqueous NaHCO\(_3\) (30 mL) was added carefully, followed by EtOAc (20 mL). The layers were separated and the aqueous layer extracted with EtOAc (2x20 mL), and the combined organics washed
with saturated aqueous NaHCO$_3$ (20 mL), and brine (20 mL). The pH of the aqueous layer was tested and additional saturated aqueous NaHCO$_3$ was added as necessary to reach pH 9. The organics were dried over MgSO$_4$ and concentrated in vacuo to give the product diamine.

(3$R$, 4$R$, 5$R$)-4-amino-3-ethyl-1-(4-methoxyphenyl)-5-(thiophen-2-yl)pyrrolidin-2-one 561

Produced by general procedure D. Pyrrolidinone 241 (138 mg, 0.400 mmol, 89% ee), HCl (2.00 mL, 12.0 mmol, 30.0 equiv.) and zinc dust (1.57 g, 24.0 mmol, 60.0 equiv.) afforded crude amine 561. Purification by flash column chromatography (Petrol:Me$_2$CO 7:3) gave amine 561 as a yellow oil (113 mg, 89%); $R_f$ 0.25 (Petrol:Me$_2$CO 7:3); [α]$_D$ -22.2 (c 1, CHCl$_3$, 20 ºC); IR $\nu_{\text{max}}$ (thin film) 3363 br (N-H), 2962 w (C-H), 1687 s (C=O), 1509 s, 1367 m, 1295 m, 1244 s, 1029 m, 830 m, 699 m cm$^{-1}$; $^1$H NMR (600 MHz) $\delta$ 1.11 (3H, t, $J$ = 7.5, C$_H$$_3$), 1.82 (1H, m, C$_H$$_2$), 1.96 (1H, dqq, $J$ = 14.1, 7.6, 5.2, C$_H$$_2$), 2.17 (2H, br, NH$_2$), 2.38 (1H, ddd, $J$ = 9.4, 6.7, 5.1, CHEt), 3.32 (1H, dd, $J$ = 9.3, 7.2, CH$_2$NH$_2$), 3.70 (3H, s, OCH$_3$), 4.88 (1H, d, $J$ = 7.2, CHN), 6.76 (2H, app d, $J$ = 9.0, CH$_{\text{PMPC3-H}}$), 6.85 (1H, dd, $J$ = 5.1, 3.6, CH$_{\text{thiophene}}$), 6.95 (1H, dd, $J$ = 3.6, 1.3, CH$_{\text{thiophene}}$), 7.12 (2H, app d, $J$ = 8.9, CH$_{\text{PMPC2-H}}$), 7.18 (1H, d, $J$ = 5.0, CH$_{\text{thiophene}}$); $^{13}$C NMR (150 MHz) $\delta$ 11.0 (CH$_2$C$_H$$_3$), 51.2 (CHCH$_2$), 55.1 (OCH$_3$), 61.1 (CH$_2$NH$_2$), 67.1 (CHN), 113.7 (CH$_{\text{PMPC3}}$), 125.6 (CH$_{\text{PMPC2}}$), 125.8 (CH$_{\text{thiophene}}$), 126.6 (CH$_{\text{thiophene}}$), 126.8 (CH$_{\text{thiophene}}$), 130.0 (Cq Arom.), 142.4 (Cq Arom.), 157.2 (Cq$_{\text{PMPC4}}$), 173.9 (C=O); m/z (ESI$^+$) 317 (71%, M+H$^+$), 206 (100%); HRMS: found 317.1321, C$_{17}$H$_{21}$N$_2$O$_2$S requires 317.1324; Anal. Cald. For C$_{17}$H$_{20}$N$_2$O$_2$S: C, 64.53, H, 6.37, N, 8.85. Found C, 64.68, H, 6.56, N, 8.77%.
To a solution of amine 561 (127 mg, 0.410 mmol) in DCM (4 mL) at 0 °C, was added trifluoroacetic anhydride (280 µL, 2.05 mmol, 5 equiv.) followed by pyridine (160 µL, 2.05 mmol, 5 equiv.). The mixture was then warmed to rt and stirred for a further 2 h, then 2 M aqueous HCl (20 mL) and CH₂Cl₂ (20 mL) were added and the layers separated. The aqueous layer was extracted with CH₂Cl₂ (2x20 mL) and the combined organics washed with saturated aqueous NaHCO₃ (20 mL), dried over MgSO₄ and concentrated in vacuo to give crude trifluoroacetamide 287. Purification by flash column chromatography (Petrol:Me₂CO 7:3) gave trifluoroacetamide 287 (136 mg, 82%) as a white solid; mp. 139-140 °C; R_f 0.46 (Petrol:Me₂CO 7:3); HPLC (chiralcel AD 0.46 x 25 cm column, 90:10 hexane/IPA, 1 mL min⁻¹) 10.9 min (major), 20.4 min (minor) measured 87% ee; IR ν_max (thin film) 3257 br (N-H), 3089 w (C-H), 1720 m, 1672 s (C=O), 1515 m, 1254 m, 1212 m, 1168 s, 1030 m, 845 m, 693 s cm⁻¹; ¹H NMR (600 MHz) δ 0.96 (3H, t, J = 7.4, CH₃), 1.65 (1H, m, CH₂), 1.87 (1H, m, CH₂), 2.25 (1H, dt, J = 8.7, 5.5, CH₂Et), 3.74 (3H, s, OCH₃), 4.36 (1H, app dt, J = 8.7, 5.3, CH₂NHTFA), 5.18 (1H, d, J = 4.7, CHN), 6.81 (2H, app d, J = 8.9, CH₃PMPC₃-H), 6.85 (1H, m, CH₃thiophene), 6.89 (1H, m, CH₃thiophene), 7.15 (2H, app d, J = 8.9, CH₃PMPC₂-H), 7.19 (1H, d, J = 5.0 CH₃thiophene), 8.26 (1H, d, J = 8.7, CH₃PMPC₂-H); ¹³C NMR (150 MHz) δ 11.2 (CH₂C₂H), 23.7 (CH₂), 49.4 (CHCH₂), 55.3 (OCH₃), 56.9 (CHNHTFA), 65.0 (CHN), 114.1 (CH₃PMPC₃), 125.6 (CH₃PMPC₂), 115.7 (q, J₁C-F = 288, CF₃), 126.0 (CH₃thiophene), 126.5 (CH₃thiophene), 126.9 (CH₃thiophene), 129.2 (Cq Arom.), 141.3 (Cq Arom.), 157.0 (q, J₁C-F=288, CF₃C=O), 157.9 (CqPMPC₄), 173.6 (NC=O); ¹⁹F NMR (282 MHz) δ -76.0 (3F, s, CF₃); m/z (ESI⁺) 413 (100%, M+H⁺), 300 (30%, M⁺-NHTFA); HRMS: found 413.1139, C₁₉H₂₀F₃N₂O₃S requires 413.1147; Anal. Cald. For C₁₉H₁₉F₃N₂O₃S: C, 55.33, H, 4.64, N, 6.79. Found C, 55.24, H, 4.59, N, 6.69%.

Recrystallisation of the sample with Et₂O/hexane gave 287 (111 mg, 73% overall yield) as an identical white solid; [α]D +14.7 (c 1, CHCl₃, 20 °C); HPLC measured 99% ee.
To a solution of ethyl ester 242 (336 mg, 1.00 mmol) in acetone (11 mL) was added an aqueous solution of HCl (2 M, 10.0 mL, 20 equiv.) and the mixture was refluxed for 24 h. After the mixture was cooled, EtOAc (20 mL) was added and the layers separated. The aqueous layer was extracted with EtOAc (2x20 mL) and the combined organics extracted with saturated aqueous NaHCO₃ (2x10 mL). The combined aqueous extracts were then acidified to pH = 1 with addition of 2 M HCl and then extracted with EtOAc (3x20 mL), dried over MgSO₄ and concentrated in vacuo to give carboxylic acid 319 (265 mg, 86%) as a white solid; mp. 155-156 °C; Rf 0.34 (DCM:MeOH 9:1); IR νmax (thin film) 2967 w (C-H), 2463 m, 1739 m (C=O), 1634 m (C=O), 1248 s, 1222 m, 1203 m, 1183 m, 1020 m, 792 m cm⁻¹; ¹H NMR (600 MHz, CD₃OD) δ 1.13 (3H, t, J = 7.4, CH₂C₃H₃), 1.80 (1H, ddq, J = 14.2, 8.7, 7.4, CH₂CH₃), 2.00 (1H, dqd, J = 14.1, 7.4, 5.5, CH₂CH₃), 3.17 (1H, ddd, J = 8.9, 5.5, 3.7, CHCH₂), 3.79 (3H, s, OC₃H₃), 5.29 (1H, t, J = 3.3, CHNO₂), 5.34 (1H, d, J = 2.8, NCH), 6.95 (2H, app d, J = 8.9, CH₃PMPC₃-H), 7.36 (2H, app d, J = 8.9, CH₃PMPC₂-H); ¹³C NMR (150 MHz, CD₃OD) δ 11.5 (CH₃), 24.5 (CH₂), 51.0 (CHCH₂), 55.9 (OCH₃), 66.1 (NCH), 85.4 (CHNO₂), 115.3 (CH₃PMPC₃), 127.1 (CH₃PMPC₂), 130.9 (CqPMPC₁), 160.0 (CqPMPC₄), 171.4 (NC=O), 174.4 (OC=O); m/z (Cl⁺) 309 (100%, M+H⁺), 218 (40%, M⁺-CO₂-NO₂); HRMS: found 309.10666, C₁₄H₁₇N₂O₆ requires 309.10872; Anal. Cald. For C₁₄H₁₆N₂O₆: C, 54.54, H, 5.23, N, 9.09. Found C, 54.21, H, 5.19, N, 8.96%.

Also prepared by reaction of 242 with Me₃SnOH.¹⁵⁹ To a solution of ethyl ester 242 (161 mg, 0.48 mmol) in 1,2-dichloroethane (5 mL) was added Me₃SnOH (174 mg, 0.92 mmol) and the mixture was heated at reflux (80 °C) until complete consumption of the ethyl ester (TLC, 5 h). EtOAc (15 mL) was then added and the mixture washed with brine (10 mL), dried over MgSO₄ and evaporated in vacuo to give crude acid 319. Purification by flash column chromatography (DCM:MeOH 9:1) gave acid 319 (100 mg, 68%) identical to the one reported above.
To a solution of amine 246 (250 mg, 0.810 mmol) in formic acid (5 mL) at 0 °C was added dropwise acetic anhydride (810 µL, 8.06 mmol, 10 equiv.). The mixture was then stirred at rt for 2 h. Water (20 mL) was then added and the mixture extracted with DCM (3x20 mL). The combined organics were washed with saturated aqueous NaHCO₃ (2x20 mL) and brine (20 mL), dried over MgSO₄ and concentrated in vacuo to give crude formamide 312. Purification by flash column chromatography (Petrol:Me₂CO 7:3) gave formamide 312 (246 mg, 90%) as a white crystalline solid which was found to be a mixture of rotamers at a ratio of 80:20; rotamer ratio calculated by CHNH signal, δ major = 4.24, δ minor = 3.67; mp. 130-131 °C; Rf 0.16 (Petrol:Me₂CO 7:3); Major rotamer: IR νmax (thin film) 3239 br. (N-H), 3059 w (C-H), 2961 w (C-H), 1704 s (C=O), 1644 s (C=O), 1510 s, 1374 m, 1246 s, 1180 m, 1026 m, 834 m, 749 m, 737 m, 698 cm⁻¹; ¹H NMR (600 MHz) δ 1.03 (3H, t, J = 7.5, CH₂CH₃), 1.62 (1H, m, CH₂CH₃), 1.91 (1H, m, CH₂CH₃), 2.53 (1H, m, CHCH₂), 3.73 (3H, s, OCH₃), 4.24 (1H, dt, J = 7.8, 5.7, CHNH), 5.05 (1H, d, J = 4.9, NCH), 6.37 (1H, d, J = 8.4, NH), 6.75 (2H, app. d, J = 9.2, CHPMPC₃-H), 7.10-7.31 (7H, m, CH Arom.), 8.18 (1H, d, J = 1.2, O=CH); ¹³C NMR (150 MHz) δ 11.5 (CH₃), 23.4 (CH₂), 50.3 (CHCH₂), 55.3 (OCH₃), 68.4 (NCH), 114.0 (CHPMPC₃), 124.3 (CH Arom.), 126.7 (CH Arom.), 128.2 (CH Arom.), 128.9 (CH Arom.), 130.4 (Cq Arom.), 138.3 (Cq Arom.), 157.0 (CqPMPC₄), 160.9 (O=CH), 174.1 (C=O); m/z (CI⁺) 339 (M+H⁺, 30%), 294 (100%, M⁺ - NHCOH); HRMS: found 339.1699, C₂₀H₂₃N₂O₃ requires 339.1709.

Minor rotamer: ¹H NMR (600 MHz) δ 1.10 (3H, t, J = 7.4, CH₂CH₃), 1.62 (1H, m, CH₂CH₃), 1.91 (1H, m, CH₂CH₃), 2.53 (1H, m, CHCH₂), 3.67 (1H, m, CHNH), 3.71 (3H, s, OCH₃), 4.76 (1H, d, J = 7.7, NCH), 6.30 (1H, t, J = 10.8, NH), 6.75 (2H, app. d, J = 9.2, CHPMPC₃-H), 7.10-7.31 (7H, m, CH Arom.), 7.62 (1H, d, J = 11.5, O=CH); ¹³C NMR (150 MHz) δ 10.8 (CH₃), 21.6 (CH₂), 48.8 (CHCH₂), 55.3 (OCH₃), 60.9 (NCH), 68.4 (NCH), 113.9 (CHPMPC₃), 124.9 (CH Arom.), 127.0 (CH Arom.), 128.7
To a solution of formamide 312 (441 mg, 1.31 mmol) in THF (4 mL) at -78 °C, was added Et$_3$N (920 µL, 6.53 mmol, 5 equiv.) followed by a solution of POCl$_3$ (160 µL, 1.55 mmol, 1.18 equiv.) in THF (1 mL) dropwise. The mixture was then warmed to 0 °C and stirred for a further 1 h. Ice-water (20 mL) was then added and the mixture extracted with EtOAc (4x30 mL). The combined organics were washed with brine (20 mL), dried over MgSO$_4$ and concentrated in vacuo to give crude isocyanide 313.

Purification by flash column chromatography (Petrol:Me$_2$CO 4:1) gave isocyanide 313 (261 mg, 63%) as a white crystalline solid; mp. 168-169 °C; R$_f$ 0.26 (Petrol:Me$_2$CO 4:1); IR $\nu_{\text{max}}$ (thin film) 2970 w (C-H), 2141 m (C≡N), 1707 s, 1509 s, 1458 m, 1365 m, 1247 s, 1223 m, 1193 m, 1039 m, 830 s, 784 m, 742 s, 700 s cm$^{-1}$; $^1$H NMR (600 MHz) $\delta$ 1.16 (3H, t, $J = 7.5$, CH$_3$), 1.83 (1H, m, CH$_2$), 2.12 (1H, dddd, $J = 12.4$, 7.6, 4.7, CH$_2$), 2.92 (1H, dddd, $J = 9.4$, 7.9, 4.7, CHCH$_2$), 3.71 (3H, s, OC$_3$H$_3$), 3.79 (1H, dd, $J = 9.4$, 7.6, CHN≡C), 5.10 (1H, d, $J = 7.6$, CHPh), 6.77 (2H, app d, $J = 9.0$, CH$_{\text{PMPC3-H}}$), 7.15 (2H, app d, $J = 9.0$, CH$_{\text{PMPC2-H}}$), 7.22-7.35 (5H, m, CH Arom.); $^{13}$C NMR (150 MHz) $\delta$ 10.7 (CH$_2$CH$_3$), 22.5 (CH$_2$), 50.0 (CHCH$_2$), 55.2 (OCH$_3$), 59.9 (CHN≡C), 67.4 (CHPh), 114.0 (CH$_{\text{PMPC3}}$), 125.0 (CH$_{\text{PMPC2}}$), 126.8 (CH Arom.), 129.0 (CH Arom.), 129.2 (CH Arom.), 129.2 (C$q$ Arom.), 136.4 (C$q$ Arom.), 157.3 (C$q$$\text{PMPC4}$), 160.2 (-N≡C), 171.2 (C=O); $m/z$ (EI$^+$) 320 (M$^+$, 100%); HRMS: found 320.15222, C$_{20}$H$_{20}$N$_2$O$_2$ requires 320.15193; Anal. Cald. For C$_{20}$H$_{20}$N$_2$O$_2$: C, 74.98, H, 6.29, N, 8.74. Found C, 74.94, H, 6.27, N, 8.68%. 

(3S*,4S*,5R*)-3-ethyl-4-isocyano-1-(4-methoxyphenyl)-5-phenylpyrrolidin-2-one 313

![Structure of (3S*,4S*,5R*)-3-ethyl-4-isocyano-1-(4-methoxyphenyl)-5-phenylpyrrolidin-2-one 313](image-url)
(3S*, 5S*)-3-ethyl-1-(4-methoxyphenyl)-5-phenylpyrrolidin-2-one 311

To a solution of isocyanide 313 (56 mg, 0.18 mmol) in Toluene (1 mL) was added $^a$Bu$_3$SnH (100 µL, 0.320 mmol, 2 equiv.). The mixture was degassed with N$_2$ and then AIBN (6 mg, 0.04 mmol, 20 mol %) was added and the mixture refluxed for 3 h. The volatiles were then removed in vacuo to give crude pyrrolidine 311. Purification by flash column chromatography (Petrol:Et$_2$O 1:1) gave pyrrolidine 311 (45 mg, 87%) as a white solid; mp. 97-98 °C; R$f$ 0.19 (Petrol:Et$_2$O 1:1); IR $\nu$max (thin film) 2956 w (C-H), 1689 s (C=O), 1510 s, 1380 m, 1361 m, 1349 m, 1298 m, 1249 s, 1175 m, 1034 m, 829 s, 761 m, 699 s cm$^{-1}$; $^1$H NMR (600 MHz) δ 1.03 (3H, t, $J$ = 7.5, CH$_3$), 1.59 (1H, ddq, $J$ = 14.0, 9.2, 7.3, CH$_2$CH$_3$), 1.67 (1H, ddd, $J$ = 12.9, 10.5, 8.9, CHCH$_2$CH), 2.10 (1H, ddd, $J$ = 14.1, 7.5, 4.1, CH$_2$CH$_3$), 2.62 (1H, ddd, $J$ = 10.4, 9.0, 4.1, CHCH$_2$), 2.76 (1H, ddd, $J$ = 12.9, 8.8, 7.1, CHCH$_2$CH), 3.71 (3H, s, OCH$_3$), 5.10 (1H, dd, $J$ = 8.8, 7.1, CHPh), 6.75 (2H, app d, $J$ = 8.9, CH$_2$CH$_3$), 7.17-7.29 (7H, m, C$_H$ Arom.); $^{13}$C NMR (150 MHz) δ 11.5 (CH$_2$C$_H$3), 24.5 (CH$_2$CH$_3$), 36.2 (CHCH$_2$CH), 44.0 (CHEt), 55.2 (OCH$_3$), 62.2 (CHPh), 113.7 (CH$_2$PMPC3), 124.7 (CH$_2$PMPC2), 126.6 (CH Arom.), 127.6 (CH Arom.), 128.7 (CH Arom.), 130.9 (Cq$_{PMPC1}$), 141.4 (Cq$_{phenylC1}$), 156.7 (C$_q$PMPC4), 176.5 (C=O); m/z (EI$^+$) 295 (M$^+$, 100%); HRMS: found 295.15751, C$_{19}$H$_{21}$NO$_2$ requires 295.15667; Anal. Cald. For C$_{19}$H$_{21}$NO$_2$: C, 77.26, H, 7.17, N, 4.74. Found C, 77.19, H, 7.21, N, 4.79%.

((2$^R$*,3$^S$*,4$^S$*)-4-Ethyl-1-(4-methoxyphenyl)-5-oxo-2-phenylpyrrolidin-3-yl)carbonimidic dibromide 314$^{148}$

To a stirred solution of bromine (14 µL, 0.27 mmol) in MeOH (3 mL) was added a solution of isocyanide 313 (87 mg, 0.27 mmol) in MeOH (1 mL) at 0 °C over 30 min.
The mixture was stirred at this temperature for a further 30 min and then at rt until consumption of the starting isocyanide (TLC, 3.5 h). The mixture was then added to a stirred suspension of CaCO$_3$ (100 mg) in water (30 mL) and stirred for 2 h. The precipitate was filtered off and the filtrate extracted with DCM (3x10 mL), the combined organics then washed with H$_2$O (10 mL), dried over MgSO$_4$ and evaporated in vacuo to give crude pyrrolidinone 314. Purification by flash column chromatography (Petrol:EtOAc 4:1) gave pyrrolidinone 314 (85 mg, 65%) as a yellow solid; mp. 240 °C (decomposition); R$_f$ 0.42 (Petrol:EtOAc 4:1); IR $\nu_{\text{max}}$ (thin film) 2965 w (C-H), 2932 w (C-H), 1698 m (C=O), 1669 m, 1599 s, 1572 m, 1510 s, 1439 s, 1357 s, 1295 m, 1184 m, 1033 m, 831 m, 796 m, 751 m, 699 s cm$^{-1}$; $^1$H NMR (600 MHz) $\delta$ 1.08 (3H, t, $J = 7.5$, CH$_3$), 1.79 (1H, m, CH$_2$CH$_3$), 1.95 (1H, m, CH$_2$CH$_3$), 2.91 (1H, m, CHCH$_2$), 3.71 (3H, s, OC$_3$H$_3$), 3.96 (1H, dd, $J = 8.1$, 6.7, CHN=), 5.05 (1H, d, $J = 6.5$, PhCHN), 6.76 (2H, app d, $J = 8.7$, CH$_{\text{PMPC3-H}}$), 7.11-7.32 (7H, m, CH Arom.); $^{13}$C NMR (150 MHz) $\delta$ 11.0 (CH$_2$C$_3$H$_3$), 22.1 (C$_3$H$_2$CH$_3$), 49.4 (CHCH$_2$), 55.2 (OCH$_3$), 66.1 (CHPh), 75.9 (CHN=), 94.3 (=CBr$_2$), 113.9 (CH$_{\text{PMPC3}}$), 124.7 (CH Arom.), 126.9 (CH Arom.), 128.3 (CH Arom.), 129.0 (CH$_{\text{PMPC2}}$), 130.0 (Cq Arom.), 137.3 (Cq Arom.), 157.0 (C$_{\text{PMPC4}}$), 173.2 (C=O); m/z (Cl$^+$) 482 (M$^+$ Br$^{81}$Br$^{81}$, 52%), 480 (M$^+$ Br$^{79}$Br$^{81}$, 100%), 478 (M$^+$ Br$^{79}$Br$^{79}$, 51%), 436 (77%), 320 (M$^+$-Br$_2$, 47%), 294 (32); HRMS: found 477.98752, C$_{20}$H$_{20}$Br$_2$N$_2$O$_2$ requires 477.98860.

Methyl-((2R*,3S*,4S*)-4-ethyl-1-(4-methoxyphenyl)-5-oxo-2-phenylpyrrolidin-3-yl)carbamate 315

To a stirred solution of bromine (24 μL, 0.86 mmol) in MeOH (1 mL) was added a solution of isocyanide 313 (138 mg, 0.430 mmol) in MeOH (6 mL) and THF (2 mL) at 0 °C over 30 min. The mixture was warmed to rt, stirred until consumption of the starting isocyanide (TLC, 2 h) and then heated at reflux until the intermediate pyrrolidinone 314 was consumed (TLC, 15 h). The mixture was then added to a stirred suspension of CaCO$_3$ (100mg) in water (30 mL) and stirred for 2 h. The precipitate was filtered off and the filtrate extracted with DCM (3x10 mL), the
combined organics then washed with H₂O (10 mL), dried over MgSO₄ and evaporated \textit{in vacuo} to give crude pyrrolidinone 315. Purification by flash column chromatography (Petrol:EtOAc 1:1) gave pyrrolidinone 315 (66 mg, 42%) as a white solid; mp. 165-166 °C; R₇ 0.31 (Petrol:EtOAc 1:1); IR ν_max (thin film) 3317 br (N-H), 2933 w (C-H), 2939 w (C-H), 2877 w, 1731 s (C=O), 1658 s, 1509 s, 1449 m, 1372 s, 1244 s, 1183 s, 1172 s, 1030 m, 828 s, 700 m cm⁻¹; ¹H NMR (600 MHz, at 60 °C) δ 1.10 (3H, t, J = 7.6, C₃H₃), 1.72 (1H, m, C₃H₂CH₃), 1.97 (1H, m, CH₂CH₃), 2.59 (1H, m, CH₂CH₃), 3.67 (3H, s, O=COC₃H₃), 3.74 and 3.82 (3H, s, ArOC₃H₃), 3.96 (1H, m, CHNH), 4.92 (1H, m, NH), 5.00 (1H, m, C=Ph), 6.78 (2H, app d, J = 8.7, C₃H₂C₃H₂-CH₃), 7.20 - 7.35 (7H, m, CH Arom.); ¹³C NMR (150 MHz) δ 11.4 (CH₂C₃H₃), 23.0 (CH₂CH₃), 49.8 and 50.1 (CHCH₂), 52.4 (O=COCH₃), 55.3 and 56.3 (OCH₃), 58.9 (CHNH), 68.4 (CHPh), 111.4, 113.9, 124.2, 126.7, 126.8, 128.1, 128.8, 128.9 (CH Arom.), 130.6 (Cq Arom.), 138.5 (Cq Arom.), 156.2 (CqPMPC₄), 156.8 (O=O), 173.8 (CHC=O); m/z (ESI⁺) 369 (M+H⁺, 100%), 294 (M₊-CH₂CONH, 85%); HRMS: found 369.1799, C₂₁H₂₄N₂O₄ requires 369.1814.

Ethyl 3-(4-ethyl-2-hydroxy-1-(4-methoxyphenyl)-5-oxo-2-phenyl-2,5-dihydro-1H-pyrrol-3-yl)propanoate 303

To a solution of pyrrolidinone 233 (213 mg, 0.630 mmol) in wet MeCN (6 mL) at rt was added ethyl acrylate (103 µL, 0.950 mmol) followed by DBU (141 µL, 0.950 mmol). The mixture was then stirred at rt for 24 h, then evaporated \textit{in vacuo}. Purification by flash column chromatography (Petrol:Me₂CO 4:1) gave pyrrolidinone 303 (128 mg, 50%) as a white solid; mp. 99-100 °C; R₇ 0.19 (Petrol:Me₂CO 4:1); IR ν_max (thin film) 3318 br (O-H), 2967 w (C-H), 2939 w (C-H), 2877 w, 1731 s (C=O), 1658 s, 1509 s, 1449 m, 1372 s, 1244 s, 1183 s, 1172 s, 1030 m, 828 s, 700 m cm⁻¹; ¹H NMR (600 MHz) δ 1.16 (3H, t, J = 7.6, C₃H₂CH₃), 1.27 (3H, t, J = 7.1, OCH₂CH₃), 2.29 (1H, m, C₃H₂CH₂), 3.39 (2H, m, CH₂CH₃), 3.54 (3H, m, CCH₂CH₂ and CH₂CH₂CO), 3.71 (3H, s, OCH₃), 4.15 (2H, q, J = 7.3, OCH₂CH₃), 5.02 (1H, s, OH), 6.72 (2H, d, J = 9.2, CHPMPC₃-H), 7.20-7.32 (5H, m, CH Arom.), 7.39 (2H, m,
CH\textsubscript{PMPC2-H}); \textsuperscript{13}C NMR (150 MHz) δ 13.2 (CH\textsubscript{2}CH\textsubscript{3}), 14.1 (OCH\textsubscript{2}CH\textsubscript{3}), 17.2 (CCH\textsubscript{2}CH\textsubscript{3}), 20.3 (CH\textsubscript{2}CH\textsubscript{2}CO), 32.1 (CH\textsubscript{2}CH\textsubscript{2}CO), 55.2 (OCH\textsubscript{3}), 93.3 (CqOH), 113.7 (CH\textsubscript{PMPC1}), 126.1, 126.3, 128.2, 128.5 (Arom. C-H), 129.1 (CqPMPC1), 135.4 (=CqCO), 137.9 (Cqphenyl), 152.5 (=CqCH\textsubscript{2}), 157.1 (CqPMPC4), 169.7 (N\textsubscript{C}=O), 173.9 (EtO\textsubscript{C}=O); m/z (ESI-): 408 (M-H, 100%), 308 (40%, M-\textsubscript{C\textsubscript{5}H\textsubscript{8}O\textsubscript{2}}); HRMS: found 408.1796, C\textsubscript{24}H\textsubscript{26}NO\textsubscript{5} requires 408.1811; Anal. Cald. For C\textsubscript{24}H\textsubscript{26}NO\textsubscript{5}: C, 70.40, H, 6.65, N, 3.42. Found C, 70.08, H, 6.67, N, 3.42%.

3-Ethyl-1-(4-methoxyphenyl)-3-methyl-5-phenyl-1\textit{H}-pyrrol-2(3\textit{H})-one 310

[Chemical structure image]

A solution of \textsuperscript{1}Pr\textsubscript{2}NH (33 µL, 0.24 mmol) in THF (2 mL) was cooled to -78 °C and \textsuperscript{8}BuLi (12 µL, 2.10 M in hexanes, 0.24 mmol) was added. The mixture was then warmed to rt and stirred for 30 min. The mixture was recooled to -78 °C and a solution of pyrrolidinone 233 (70 mg, 0.20 mmol) in THF (2 mL) was added, the mixture stirred for 30 min before MeI (37 µL, 0.60 mmol) was added. The mixture was stirred for 10 min, then warmed to rt and stirred for a further 3 h. Saturated aqueous NaHCO\textsubscript{3} (10 mL) was then added and the mixture extracted with DCM (3x10 mL). The combined organics were washed with brine (10 mL), dried over MgSO\textsubscript{4} and concentrated in vacuo to give crude pyrrolone 310. Purification by flash column chromatography (Petrol:Me\textsubscript{2}CO 4:1) gave pyrrolone 310 (13 mg, 21%) as a yellow solid; mp. 71-73 °C; R\textsubscript{f} 0.42 (Petrol:Me\textsubscript{2}CO 4:1); IR \textit{v}\textsubscript{max} (thin film) 2964 w (C-H), 2930 w, 1718 s (C=O), 1511 s, 1248 s, 1177 w, 1032 w, 697 w cm\textsuperscript{-1}; \textsuperscript{1}H NMR (600 MHz) δ 0.91 (3H, t, J = 7.3, CH\textsubscript{2}C\textsubscript{H}\textsubscript{3}), 1.36 (3H, s, C\textsubscript{H}\textsubscript{3}), 1.70 (1H, dq, J = 14.9, 7.5, CH\textsubscript{2}CH\textsubscript{3}), 1.86 (1H, dq, J = 14.9, 8.4, CH\textsubscript{2}CH\textsubscript{3}), 3.78 (3H, s, OCH\textsubscript{3}), 5.47 (1H, s, =CH), 6.81 (2H, d, J = 9.0, CH\textsubscript{PMPC3-H}), 6.97 (2H, d, J = 9.0, CH\textsubscript{PMPC2-H}), 7.14 (2H, m, CH Arom.), 7.24 (3H, m, CH Arom.); \textsuperscript{13}C NMR (150 MHz) δ 9.2 (CH\textsubscript{2}C\textsubscript{H}\textsubscript{3}), 22.4 (C\textsubscript{CH\textsubscript{3}}), 31.0 (CH\textsubscript{2}CH\textsubscript{3}), 50.7 (Cq), 55.4 (OCH\textsubscript{3}), 113.9 (=CH), 114.0 (CH\textsubscript{PMPC3}), 127.6 (CH Arom.), 128.0 (CH Arom.), 128.1 (CH Arom.), 128.3 (CH Arom.), 128.7 (=C-Ph), 131.4 (CqPMPC1), 143.4 (Cqphenyl), 158.0 (CqPMPC4), 182.7 (C=O); m/z (EI+)}
307 (M⁺, 27%), 278 (100%, M⁺-Et); HRMS: found 307.1554, C₂₀H₂₁NO₂ requires 307.1567; Anal. Cald. For C₂₀H₂₁NO₂: C, 78.15, H, 6.89, N, 4.56. Found C, 77.68, H, 6.91, N, 4.53%.

3.4.2 Towards the synthesis of a human neutrophil elastase inhibitor (GW311616A)

3.4.2.1 Synthesis of starting materials

(E)-Methyl 3-((4-methoxyphenyl)amino)acrylate 345

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

3,3-Dimethoxypropanal 347 and (E)-3-methoxyacrylaldehyde 349

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

A 250 mL round bottom flask was charged with methyl 3,3-dimethoxypropionate (7.00 mL, 50.0 mmol) and dry hexane (100 mL). The mixture was then cooled to -78
\(^{\circ}\)C and a solution of DIBAL (51.5 mL, 51.5 mmol, 1 M in DCM) cooled to \(-78\) \(^{\circ}\)C was added dropwise via cannula. The mixture was stirred at this temperature for 1 h and then quenched by addition of MeOH (5 mL) and stirred for 15 min. Saturated Rochelle salt solution (100 mL) was then added and the mixture stirred for 1 h at rt. The aqueous phase was then separated and extracted with petrol (35 mL), dried over MgSO\(_4\) and concentrated \textit{in vacuo}. Purification by flash column chromatography (Petrol:DCM 2:8) gave an inseparable mixture of the two products \(\text{347} \) and \(\text{349} \) in the ratio of \(70:30\) (combined yield: 66\%) as a colourless liquid; \(R_f\) 0.53 (Petrol:DCM 2:8); 3,3-dimethoxypropanal \(\text{347} \) (major): \(^1\)H NMR (600 MHz) \(\delta\) 2.74 (2H, dd, \(J = 5.5, 2.2, \text{CH}_2\)), 3.39 (6H, s, OCH\(_3\)), 4.86 (1H, t, \(J = 5.3, \text{CH(OCH}_3)_2\)), 9.76 (1H, t, \(J = 2.2, \text{CHO}\)); \(^{13}\)C NMR (125 MHz) \(\delta\) 47.1 (C\(\text{H}_2\)), 53.7 (O\(\text{C}_\text{H}_3\)), 100.3 (C(\text{CH(OCH}_3)_2)), 199.5 (CHO). Data in agreement to that reported.\(^{256}\) (\(E\))-3-methoxyacrylaldehyde \(\text{349} \) (minor): \(^1\)H NMR (600 MHz) \(\delta\) 3.79 (3H, s, OCH\(_3\)), 5.62 (1H, dd, \(J = 12.7, 8.1, \text{OCCH}=\)), 7.42 (1H, d, \(J = 12.7, \text{MeOCH}=\)), 9.40 (1H, d, \(J = 8.1, \text{CHO}\)); \(^{13}\)C NMR (125 MHz) \(\delta\) 57.9 (CH\(_3\)), 109.6 (O=\text{CCH}), 171.1 (OCCH=), 191.2 (CHO). Data in agreement to that reported.\(^{256}\)

2,3-Dibromopropanal 359

![2,3-Dibromopropanal 359](image)

To a solution of acrolein (130 \(\mu\)L, 2.00 mmol) in dry DCM (10 mL) was added Br\(_2\) (110 \(\mu\)L, 2.20 mmol) at rt. The solution was instantly decolorized and the mixture was evaporated \textit{in vacuo} to give pure 2,3-dibromopropanal 359 (415 mg, 96\%) as a colourless oil; \(^1\)H NMR (600 MHz) \(\delta\) 3.73 (1H, dd, \(J = 10.6, 4.7, \text{CH}_2\)), 3.88 (1H, t, \(J = 10.5, \text{CH}_2\)), 4.54 (1H, ddd, \(J = 10.4, 4.5, 2.7, \text{CHBr}\)), 9.39 (1H, d, \(J = 2.7, \text{O=CH}\)); \(^{13}\)C NMR (150 MHz) \(\delta\) 26.8 (CH), 48.8 (CH\(_2\)), 189.0 (C=O). Data in agreement to the one reported.\(^{174}\)
(E)-4-methoxy-N-((E)-3-((4-methoxyphenyl)amino)allylidene)aniline 350

Prepared by general procedure A. The mixture of aldehydes 347 and 349 (11.5 mmol) in DCM (60 mL), para-anisidine (1.42 g, 11.5 mmol) and basic Al₂O₃ (11 g) afforded 350 (1.58 g, 97% based on para-anisidine) as a yellow solid which was used without further purification; mp. 122-123 °C (lit. 124 °C); \( \nu_{\text{max}} \) (thin film) 3199 w (N-H), 2952 w (C-H), 1629 s (C=O), 1594 s, 1574 s, 1502 w, 1594 s, 1574 s, 1502 w, 1305 s, 1279 s, 1246 s, 1233 s, 1156 s, 1031 m, 1007 m, 963 m, 830 s, 807 s cm\(^{-1}\); \(^1\)H NMR (600 MHz) \( \delta \) 3.81 (3H, s, OCH₃), 3.81 (3H, s, OCH₃), 5.27 (1H, dd, \( J = 7.4, 2.1 \), CH₂CH₃), 6.89 (4H, m, CH Arom.), 7.02-7.05 (4H, m, CH Arom.), 7.64 (1H, d, \( J = 6.1, =CH \)), 9.27 (1H, dd, \( J = 3.2, 2.1 \), N=CH), 11.72 (1H, br. s, NH); \(^13\)C NMR (150 MHz) \( \delta \) 55.5 (OCH₃), 97.0 (=CHC), 114.6 (CH Arom.), 114.9 (CH Arom.), 118.1 (CH Arom.), 119.2 (CH Arom.), 133.4 (Cq Arom.), 140.3 (Cq Arom.), 148.0 (=CHN), 156.1 (Cq Arom.), 156.6 (Cq Arom.), 189.1 (N=CH); \( m/z \) (EI\(^+\)) 282 (M\(^+\), 100%), 267 (33%); HRMS: found 282.13588, C\(_{17}\)H\(_{18}\)N\(_2\)O\(_2\) requires 282.13627.

(3-((trimethylsilyl)prop-2-yn-1-ylidene)aniline 356

To a solution of para-anisidine (123 mg, 1.00 mmol) in DCM (5 mL) was added dried MgSO\(_4\) (700 mg) and the mixture cooled to 0 °C. 3-((trimethylsilyl)-2-propynal (0.150 mL, 1.00 mmol) was then added and the mixture stirred for 5 min at this temperature and then warmed to rt and stirred for a further 1 h, then filtered through celite\(^\circledR\) and washed with DCM (10 mL) and concentrated in vacuo to give imine 356 (226 mg, 98%, lit. 56%) as a yellow oil which was used without further purification; \( R_f \) 0.47 (Petrol:EtOAc 9:1); \(^1\)H NMR (600 MHz) \( \delta \) 0.27 (9H, s, SiCH\(_3\)), 3.83 (3H, s, OCH\(_3\)), 6.90 (2H, app. d, \( J = 9.0, CH\(_{\text{PMPC3-H}}\)\)), 7.20 (2H, app. d, \( J = 9.0, CH\(_{\text{PMPC2-H}}\)\)), 7.72 (1H, s, CHO). Data in agreement with that reported.\(^{258}\)
3.4.2.2 Investigation of methodology

\((3S^*,4S^*,5R^*)-5-(2-(benzyloxy)ethyl)-3-ethyl-1-(4-methoxyphenyl)-4-nitropyrrlridin-2-one\) 355

![Chemical Structure](image)

Prepared by general procedure C, with the exception that imine 352 was formed and used *in situ*. To a solution of aldehyde 353 (226 mg, 1.38 mmol) in THF (5 mL) were added under Nitrogen dried 4Å molecular sieves (1.40 g) and the mixture cooled at -78 °C. A solution of para-anisidine (170 mg, 1.38 mmol) in THF (1 mL) was then added and the mixture stirred at this temperature for 1.5 h. The solution was then transferred into the reaction via cannula. Nitroalkene 231 (100 mg, 0.690 mmol), diethylzinc (760 µL, 0.760 mmol), freshly prepared cold (-78 °C) solution of above-formed imine (1.38 mmol) and TFA (183 µL, 2.41 mmol) afforded crude pyrrolidinone 355. Purification by flash column chromatography (Petrol:EtOAc 4:1) gave pyrrolidinone 355 (69 mg, 25%) as a colourless oil; Rf 0.23 (Petrol:EtOAc 4:1); IR \(\nu_{\text{max}}\) (thin film) 2934 w (C-H), 2967 w (C-H), 1702 s (C=O), 1554 s (N=O), 1511 s, 1455 w, 1366 m (N-O), 1296 w, 1248 s, 1180 w, 1098 m, 1030 m, 833 m, 740 m, \(699 m \text{ cm}^{-1}\); \(^1\)H NMR (600 MHz) \(\delta\) 1.06 (3H, t, \(J = 7.4\), CH\(_2\)C\(_6\)H\(_3\)), 1.76 (1H, m, CH\(_2\)CH\(_3\)), 1.76 (1H, m, CH\(_2\)CH\(_3\)), 2.03-2.13 (1H, m, CH\(_2\)CH\(_3\)), 2.03-2.13 (1H, m, CH\(_2\)CH\(_3\)), 3.12 (1H, m, CH\(_2\)C\(_6\)H\(_3\)), 3.43 (1H, m, OCH\(_2\)CH\(_3\)), 3.52 (1H, m, OCH\(_2\)CH\(_3\)), 3.80 (3H, s, OCH\(_3\)), 4.38 (1H, d, \(J = 11.8\), OCH\(_2\)Ph), 4.42 (1H, d, \(J = 11.8\), OCH\(_2\)Ph), 4.73 (1H, ddd, \(J = 9.2, 4.6, 3.2\), NCH\(_2\)CH\(_3\)), 5.13 (1H, dd, \(J = 6.0, 4.6, CHNO\(_2\)\)), 6.92 (2H, app d, \(J = 9.0, CH\text{PMPC3-4H}\)), 7.21 (2H, app d, \(J = 9.0, CH\text{PMPC2-4H}\)), 7.23-7.40 (5H, m, CH Arom.); \(^{13}\)C NMR (125 MHz) \(\delta\) 10.8 (CH\(_2\)CH\(_3\)), 23.5 (CH\(_2\)CH\(_3\)), 32.3 (CH\(_2\)CH\(_2\)C\(_6\)H\(_5\)), 49.5 (CHEt), 55.4 (OCH\(_3\)), 60.8 (CHCH\(_2\)CH\(_2\)), 65.9 (CH\(_2\)O), 73.4 (OCH\(_2\)Ph), 87.0 (CHNO\(_2\)), 114.5 (CH\text{PMPC3}), 126.3 (CH Arom.), 127.9 (CH Arom.), 128.4 (CH Arom.), 128.7 (Cq Arom.), 137.3 (Cq Arom.), 158.3 (Cq\text{PMPC4}), 170.9 (C=O); m/z (El\(^+\)) 398 (M\(^+\), 30%), 260 (M\(^+\)-Bn-HNO\(_2\), 10%), 217 (M\(^+\)-BnOCH\(_2\)CH\(_2\)-NO\(_2\), 10%), 188 (10%), 91 (C\(_6\)H\(_5\)CH\(_2\)+, 100%); HRMS found 398.18281, C\(_{22}\)H\(_{26}\)N\(_2\)O\(_5\) requires 398.18361.
(3S*,4S*,5S*)-5-(dimethoxymethyl)-3-isopropyl-1-(4-methoxyphenyl)-4-nitropyrrolidin-2-one 361

Prepared by general procedure C. Nitroalkene 231 (145 mg, 1.00 mmol), diisopropylzinc (3.09 mL, 0.356 M in hexane, 1.1 mmol), imine 267 (418 mg, 2.00 mmol) and TFA (270 µL, 3.50 mmol) afforded crude pyrrolidinone 361. Purification by flash column chromatography (Petrol:Me$_2$CO 4:1) gave pyrrolidinone 361 (248 mg, 70%) as a white solid; mp. 145-146 °C; R$_f$ 0.27 (Petrol:Me$_2$CO 4:1); IR $\nu_{\text{max}}$ (thin film) 2963 w (C-H), 2938 w (C-H), 2839 w (C-H), 1706 s (C=C), 1557 s, 1513 s, 1466 w, 1367 m, 1248 s, 1075 m, 1034 m, 836 w, 765 w cm$^{-1}$; $^1$H NMR (600 MHz) $\delta$ 1.06 (3H, d, $J$ = 7.0, CHC$_3$H$_3$), 1.13 (3H, d, $J$ = 7.0, CHC$_3$H$_3$), 2.46 (1H, m, CHCH(CH$_3$)$_2$), 3.03 (1H, dd, $J$ = 6.7, 4.8, CHCH(CH$_3$)$_2$), 3.33 (3H, s, OCH$_3$), 3.36 (3H, s, OCH$_3$), 3.82 (3H, s, OCH$_3$), 4.26 (1H, d, $J$ = 2.6, CHCH(O Me)$_2$), 4.68 (1H, dd, $J$ = 4.7, 2.6, CHCH(O Me)$_2$), 5.26 (1H, d, $J$ = 6.6, 4.8, CHNO$_2$), 6.95 (2H, app. d, $J$ = 8.9, CHP MPC3-H), 7.26 (2H, app. d, $J$ = 8.9, CHP MPC2-H); $^{13}$C NMR (125 MHz) $\delta$ 18.3 (CH$_3$), 19.6 (CH$_3$), 28.6 (CH(CH$_3$)$_2$), 54.0 (CHCH(CH$_3$)$_2$), 55.4 (OCH$_3$), 56.8 (OCH$_3$), 57.7 (OCH$_3$), 63.9 (CHCH(O Me)$_2$), 80.1 (CHNO$_2$), 102.6 (CH(O Me)$_2$), 114.6 (CHP MPC3), 126.3 (CHP MPC2), 128.8 (CqP MPC1), 158.4 (CqP MPC4), 170.8 (C=O); m/z (ES$^+$) 353 (M+H$^+$, 60%), 274 (M$^+$-NO$_2$-MeOH, 50%), 232 (M+H$^+$-NO$_2$-CH(O Me)$_2$, 100%); HRMS found 353.1706, C$_{17}$H$_{25}$N$_2$O$_6$ requires 353.1713; Anal. Cald. For C$_{17}$H$_{24}$N$_2$O$_6$: C, 57.94, H, 6.86, N, 7.95. Found C, 57.92, H, 6.86, N, 7.94%.

(3S*,4S*,5S*)-5-(dimethoxymethyl)-3-isopropyl-4-nitropyrrolidin-2-one 362

To a solution of pyrrolidinone 361 (107 mg, 0.300 mmol) in MeCN (4 mL) cooled to 0 °C was added a solution of CAN (658 mg, 1.20 mmol) in H$_2$O (4 mL) dropwise over 3 min. The solution turned from pale yellow to dark orange. The mixture was
stirred at this temperature for a further 2 h, over which the solution became light orange. Water (30 mL) was then added and the mixture extracted with EtOAc (3x20 mL), washed with saturated aqueous NaHCO₃ (40 mL), dried over MgSO₄ and evaporated in vacuo to give crude pyrrolidinone 362. Purification by flash column chromatography (Petrol:Me₂CO 7:3) gave pyrrolidinone 362 (61 mg, 83%) as a white solid; mp. 92-93 °C; Rf 0.33 (Petrol:Me₂CO 7:3); IR νmax (thin film) 3223 br (N-H), 2964 m (C-H), 1709 s (C=O), 1557 s (N=O), 1466 w, 1370 m (N=O), 1133 m, 1074 m cm⁻¹; ¹H NMR (600 MHz) δ 0.95 (3H, t, J = 7.0, CH₃), 1.03 (3H, t, J = 7.0, CH₃), 2.35 (1H, m, CH(CH₃)₂), 3.03 (1H, dd, J = 7.2, 4.4, CHCH=O), 4.28 (1H, d, J = 6.1, CH(OCH₃)₂), 4.91 (1H, dd, J = 7.2, 5.2, CHNO₂), 6.94 (1H, br. s, NH); ¹³C NMR (125 MHz) δ 18.0 (CH₃), 19.6 (CH₃), 27.5 (CH(CH₃)₂), 53.4 (CHCH=O), 55.2 (OCH₃), 55.4 (OCH₃), 57.8 (CHCHNH), 83.0 (CHNO₂), 104.3 (CH(OCH₃)₂), 173.7 (C=O); m/z (ES⁺) 247 (M+H⁺, 100%), 215 (M⁺-CH₃O, 30%), 168 (M⁺-CH₂OH-NO₂, 92%); HRMS found 247.12907, C₁₀H₁₉N₂O₅ requires 247.12940; Anal. Cald. For C₁₀H₁₈N₂O₅: C, 48.77, H, 7.37, N, 11.38. Found C, 48.38, H, 7.40, N, 11.20%.

\[ N-((2S*,3S*,4S*)-2-(dimethoxymethyl)-4-isopropyl-5-oxypyrrolidin-3-yl)-2,2,2-trifluoroacetamide \ 363 \]

Diamine 562 produced by general procedure D. Pyrrolidinone 362 (326 mg, 1.33 mmol), HCl (6.60 mL, 40.0 mmol, 30.0 equiv.) and zinc dust (5.20 g, 80.0 mmol, 60.0 equiv.) afforded crude diamine 562. To a solution of the crude diamine 562 (227 mg, 1.05 mmol) in DCM (10 mL) at 0 °C, was added trifluoroacetic anhydride (440 µL, 3.15 mmol, 3 equiv.) followed by pyridine (250 µL, 3.15 mmol, 3 equiv.). The mixture was then warmed to rt and stirred for a further 2 h. The mixture was then washed with aqueous 2 M HCl (2x20 mL), the combined organics washed with saturated aqueous NaHCO₃ (20 mL), dried over MgSO₄ and concentrated in vacuo to give crude trifluoroacetamide 363. Purification by flash column chromatography
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(Petrol:Me₂CO 7:3) gave trifluoroacetamide 363 (288 mg, 70%) as white needles; mp. 154-155 °C; Rf 0.27 (Petrol: Me₂CO 7:3); IR νmax (thin film) 3281 br (N-H), 3094 br (N-H), 2962 w (C-H), 2934 (C-H), 1696 s (C=O), 1560 w, 1467 w, 1374 w, 1254 w, 1185 s, 1159 s, 1073 m, 961 w, 722 w cm⁻¹; ¹H NMR (600 MHz) δ 0.99 (3H, d, J = 6.8, CH₃), 1.00 (3H, d, J = 6.9, CH₃), 2.27 (1H, m, CH₂), 2.48 (1H, m, O=CC₂H₃), 3.44 (3H, s, OCH₃), 3.49 (3H, s, OCH₃), 3.51 (1H, m, CH₂NHCOCF₃), 4.29 (1H, d, J = 6.1, CH(OMe)₂), 4.45 (1H, m, NHCH₂(OMe)₂), 5.96 (1H, br. s, NHCOCF₃), 6.87 (1H, m, NH=O); ¹³C NMR (150 MHz) δ 18.0 (CH₃), 20.1 (CH₃), 28.1 (CH₂), 48.8 (CH₂), 54.1 (O=CC₂H₃), 55.6 (O=CH₂), 56.5 (O=CH₂), 60.1 (CH₂), 107.4 (CH₂), 117.4 (q, J = 37.1 Hz, CF₃), 158.0 (q, J = 37.1 Hz, O=CC₂H₃), 177.7 (O=CH₂); ¹⁹F NMR (282 MHz) δ -76.56 (3F, s, CF₃); m/z (Cl⁺) 313 (M⁺H⁺, 42%), 281 (M⁺-CH₃O, 100%), 217 (56%); HRMS: found 313.13721, C₁₂H₂₀N₂O₄F₃ requires 313.13752; Anal. Cald. For C₁₂H₁₉N₂O₄F₃: C, 46.15, H, 6.13, N, 8.97. Found C, 46.21, H, 6.15, N, 8.95%.

(3S*,4S*,5S*)-5-(((tert-butyldimethylsilyloxy)methyl)-3-isopropyl-1-(4-methoxyphenyl)-4-nitopyrrolidin-2-one 366

Prepared by general procedure C, with the exception that imine 368 was formed and used in situ. To a solution of (tert-butyldimethylsiloxy)acetaldehyde (209 µL, 1.10 mmol) in THF (5 mL) were added under Nitrogen dried 4Å molecular sieves (1.10 g) and the mixture cooled at -78 °C. A solution of para-anisidine (135 mg, 1.10 mmol) in THF (1 mL) was added and the mixture stirred at this temperature for 1.5 h. The solution was then transferred into the reaction via cannula. Nitroalkene 231 (80 mg, 0.55 mmol), diisopropylzinc (1.74 mL, 0.356 M in hexane, 1.1 mmol), in situ prepared cold (-78 °C) solution of imine 368 (1.10 mmol) and TFA (140 µL, 1.93 mmol) afforded crude pyrrolidinone 366. Purification by flash column chromatography (Petrol:EtOAc 4:1) gave pyrrolidinone 366 (31 mg, 13%) as a white solid; mp. 112-113 °C; Rf 0.50 (Petrol:EtOAc 4:1); IR νmax (thin film) 2957 w (C-H), 2931 w, 2858 w, 1704 s (C=C), 1556 m (N=O), 1513 s (C=O), 1464 m, 1408 w, 1366
(3S*,4S*,5S*)-5-((benzyloxy)methyl)-3-isopropyl-1-(4-methoxyphenyl)-4-nitropyrrrolidon-2-one 367

Prepared by general procedure C, with the exception that imine 369 was formed and used in situ. To a solution of benzyloxyacetaldehyde (154 µL, 1.10 mmol) in THF (5 mL) were added under Nitrogen dried 4Å molecular sieves (1.10 g) and the mixture cooled at -78 °C. A solution of para-anisidine (135 mg, 1.10 mmol) in THF (1 mL) was then added and the mixture stirred at this temperature for 1.5 h. The solution was transferred into the reaction via cannula. Nitroalkene 231 (80 mg, 0.55 mmol), diisopropylzinc (1.74 mL, 0.356 M in hexane, 1.1 mmol), in situ prepared cold (-78 °C) solution of imine 369 (1.10 mmol) and TFA (140 µL, 1.93 mmol) afforded crude pyrrrolidonone 367. Purification by flash column chromatography (Petrol:EtOAc 4:1) gave pyrrrolidonone 367 (68 mg, 31%) as a colourless oil; Rf 0.32 (Petrol:EtOAc 4:1); IR v_max (thin film) 2961 w (C-H), 1702 s (C=C), 1555 s (N-O), 1512 s (C=O), 1465 w, 1459 w, 1404 w, 1369 m (N-O), 1298 w, 1248 s, 1106 m, 1035 m, 834 m, 742 m, 699 m cm⁻¹; ¹H NMR (600 MHz) δ 0.96 (3H, d, J = 7.0, CH(CH₃)₂), 1.06 (3H, d, J = 7.0, CH(CH₃)₂), 1.08 (3H, d, J = 7.0, CH(CH₃)₂), 2.49 (1H, m, CH(CH₃)₂), 3.36 (1H, dd, J = 7.9, 4.4, C=OCH), 3.68 (1H, dd, J = 11.3, 3.5, OCH₂), 3.75 (1H, dd, J = 11.3, 6.0, OCHNO₂), 6.92 (2H, app. d, J = 8.9, CH_PMPc3), 7.18 (2H, app. d, J = 8.9, CH_PMPc2); ¹³C NMR (125 MHz) δ -5.8 (SiCH₃), -5.8 (SiCH₃), 18.2 (CH(C₃H₃)₂), 19.6 (CH(CH₃)₂), 25.7 (C(CH₃)₃), 27.9 (CH(CH₃)₂), 52.3 (C=OCH), 55.3 (OCH), 59.5 (OCH₂), 63.3 (NCH), 81.1 (CHNO₂), 114.4 (CH_PMPc3), 126.8 (CH_PMPc2), 128.2 (CqPMPC1), 158.5 (CqPMPC4), 170.7 (C=O), 1 peak missing (C(CH₃)₃); m/z (ES⁺) 423 (M+H⁺, 75%), 376 (M⁺-NO₂, 100%); HRMS found 423.2315, C₂₁H₃₄N₂O₅Si requires 423.2315; Anal. Cald. For C₂₁H₃₄N₂O₅Si: C, 59.69, H, 8.11, N, 6.63. Found C, 59.68, H, 8.18, N, 6.57%.
CH(CH$_3$)$_2$, 2.47 (1H, m, CH(CH$_3$)$_2$), 3.30 (1H, dd, $J = 7.0$, 4.5, C=OCH$_3$), 3.48 (1H, dd, $J = 10.5$, 4.0, OCH$_2$CH), 3.63 (1H, dd, $J = 10.5$, 2.5, OCH$_2$CH), 3.81 (3H, s, OCH$_3$), 4.39 (1H, d, $J = 12.0$, OCH$_2$Ph), 4.45 (1H, m, NCH), 4.48 (1H, d, $J = 12.0$, OCH$_2$Ph), 5.20 (1H, dd, $J = 7.1$, 5.3, CHNO$_2$), 6.91 (2H, app. d, $J = 8.9$, CH Arom.); $^{13}$C NMR (125 MHz) δ 18.1 (CH(CH$_3$)$_2$), 19.7 (CH(CH$_3$)$_2$), 28.1 (CH(CH$_3$)$_2$), 52.6 (C=OCH$_3$), 55.5 (OCH$_3$), 62.2 (NCH), 66.3 (OCH$_2$CH), 73.4 (OCH$_2$Ph), 81.7 (CHNO$_2$), 114.6 (CH$_{PMPC3}$), 127.1 (CH Arom.), 127.6 (CH Arom.), 128.0 (CH Arom.), 128.3 (C$_q$PMPC), 128.4 (CH Arom.), 136.9 (C$_q$ Arom.), 156.6 (CQMPC$_4$), 170.8 (C=O); $m/z$ (ES$^+$) 399 (M+H$^+$, 55%), 352 (M$^+$-NO$_2$, 100%); HRMS found 399.1926, C$_{22}$H$_{27}$N$_2$O$_5$ requires 399.1920.

(2$^S*$,3$^S*$,4$^S*$)-Ethyl 4-isopropyl-1-(4-methoxyphenyl)-3-nitro-5-oxopyrrolidine-2-carboxylate 373

Prepared by general procedure C. Nitroalkene 231 (435 mg, 3.00 mmol), diisopropylzinc (9.27 mL, 0.356 M in hexane, 3.3 mmol), imine 24 (1.24 g, 6.00 mmol) and TFA (810 µL, 2.84 mmol) afforded crude pyrrolidinone 373. Purification by flash column chromatography (Petrol:EtOAc 4:1) gave pyrrolidinone 373 (245 mg, 23%) as a yellow solid; mp. 40–41 °C; Rf 0.38 (Petrol:EtOAc 4:1); IR $\nu_{max}$ (thin film) 2965 w (C-H), 1745 m (C=O), 1712 s (C=O), 1561 s (N=O), 1513 s, 1371 m (N-O), 1299 m, 1248 m, 1197 m, 1029 m, 833 m cm$^{-1}$; $^1$H NMR (600 MHz) δ 1.01 (3H, d, $J = 7.0$, CH(CH$_3$)$_2$), 1.14 (3H, d, $J = 7.0$, CH(CH$_3$)$_2$), 1.18 (3H, t, $J = 7.1$, CH$_2$CH$_3$), 2.45 (1H, m, CH(CH$_3$)$_2$), 3.14 (1H, t, $J = 4.9$, O=CCCH), 3.80 (1H, s, OCH$_3$), 4.18 (2H, m, CH$_2$CH$_3$), 5.05 (1H, dd, $J = 4.9$, 3.7, CHNO$_2$), 5.18 (1H, d, $J = 3.7$, NCH), 6.92 (2H, app. d, $J = 9.0$, CH$_{PMPC3}$), 7.31 (2H, app. d, $J = 9.0$, CH$_{PMPC2}$); $^{13}$C NMR (125 MHz) δ 13.9 (CH$_2$CH$_3$), 18.4 (CH(CH$_3$)$_2$), 20.0 (CH(CH$_3$)$_2$), 28.6 (CH(CH$_3$)$_2$), 53.9 (O=CCCH), 55.4 (OCH$_3$), 62.7 (OCH$_2$CH$_3$), 64.0 (NCH), 82.4 (CHNO$_2$), 114.4 (CH$_{PMPC3}$), 125.9 (CH$_{PMPC2}$), 129.2 (C$_q$PMPC), 158.5 (C$_q$PMPC), 168.3 (OC=O), 170.6 (NC=O); $m/z$ (EI$^+$) 350 (M$^+$, 100%), 303 (M$^+$-NO$_2$, 16%), 231 (M$^+$-NO$_2$-CO$_2$Et,
((2S*, 3S*, 4R*)-4-ethyl-1-(4-methoxyphenyl)-3-nitropyrrolidin-2-yl)methanol

To a solution of pyrrolidinone 373 (43 mg, 0.14 mmol) in THF (2 mL) cooled to 0 °C was added a NaH (3 mg, 0.14 mmol) and the suspension stirred for 10 min. Then a solution of DIBAL (0.28 mL, 1 M in THF, 0.28 mmol) was added and the mixture warmed to 40 °C. The mixture was stirred at this temperature until complete consumption of the starting material (7 h). Water (10 mL) was then added and the mixture extracted with EtOAc (3×10 mL), dried over MgSO₄ and evaporated in vacuo to give crude pyrrolidine 374. Purification by flash column chromatography (Petrol:EtOAc 8:2) gave pyrrolidine 374 (2 mg, 5%) as a colourless oil; Rᶠ 0.57 (Petrol: EtOAc 8:2); IR νₘₐₓ (thin film) 3434 br (O-H), 2963 w (C-H), 2931 w (C-H), 1550 m (N=O), 1512 (C=C), 1463 w, 1360 w (N-O), 1243 m, 1181 w, 1038 w, 818 w cm⁻¹; ¹H NMR (600 MHz) δ 1.02 (3H, t, J = 7.5, C₃H₃), 1.61 (1H, m, C₄H₂CH₃), 1.61 (1H, br. s, O-H), 1.78 (1H, m, CH₂CH₃), 2.82 (1H, m, CH₂Et), 3.30 (1H, dd, J = 7.5, 9.1, CH₂OH), 3.67 (1H, dd, J = 8.1, 9.1, CH₂OH), 3.77 (3H, s, OCH₃), 3.82 (1H, m, CH₂N), 4.99 (1H, dd, J = 5.4, 6.9, CHNO₂), 6.68 (2H, app d, J = 9.0, Arom. CH), 6.86 (2H, app d, J = 9.0, Arom. CH); ¹³C NMR (125 MHz) δ 12.0 (CH₃), 25.2 (CH₂), 44.6 (CH), 55.7 (CH), 55.8 (CH₂), 60.1 (CH₂), 65.3 (CH), 91.3 (CH), 114.9 (CH Arom.), 115.6 (CH Arom.), 140.3 (Cq Arom.), 152.9 (Cq Arom.); m/z (El⁺) 280 (M⁺, 15%), 203 (M⁺-NO₂-CH₂OH, 75%), 174 (M+H⁺-PMP, 68%), 84 (100%); HRMS found 280.14218, C₁₄H₂₀N₂O₄ requires 280.14176.
3.4.3 The 1,4-addition/nitro-Mannich reaction of non-zinc nucleophiles on β-nitrostyrene

3.4.3.1 1,4-Additions to nitroacrylate

**Ethyl 2-(1H-indol-3-yl)-3-nitropropanoate 381**

![Ethyl 2-(1H-indol-3-yl)-3-nitropropanoate](image)

To a preformed mixture of CeCl$_3$·NaI·SiO$_2$ (11:2.5:1, 339 mg) was added MeCN (4 mL) followed by indole (69 mg, 0.59 mmol) and nitroacrylate 231 (85 mg, 0.59 mmol). The mixture was stirred for 30 min and then the solvent removed *in vacuo* and the residue stirred for 24 h. The mixture was then filtered through celite® with Et$_2$O (30 mL) and evaporated *in vacuo*. Purification by flash column chromatography (Petrol:EtOAc 4:1) gave nitroalkane 381 (140 mg, 89%) as a yellow oil; $R_f$ 0.23 (Petrol:EtOAc 4:1); $^1$H NMR (600 MHz) δ 1.24 (3H, t, $J = 7.1$, CH$_3$), 4.20 (2H, m, OCH$_2$), 4.65 (1H, dd, $J = 14.5$, 5.0, CH$_2$NO$_2$), 4.76 (1H, dd, $J = 9.8$, 4.9, CHCH$_2$), 5.22 (1H, dd, $J = 14.4$, 9.9, CH$_2$NO$_2$), 7.12 (1H, app d, $J = 2.6$, CH Arom.), 7.19 (1H, m, CH Arom.), 7.26 (1H, m, CH Arom.), 7.39 (1H, app d, $J = 8.2$, CH Arom.), 8.34 (1H, br s, NH), in agreement with that reported.

**Ethyl 2-(2,4,6-trimethoxyphenyl)-3-nitropropanoate 382**

![Ethyl 2-(2,4,6-trimethoxyphenyl)-3-nitropropanoate](image)

To a preformed mixture of CeCl$_3$·NaI·SiO$_2$ (11:2.5:1, 289 mg) was added MeCN (3 mL) followed by 1,3,5-trimethoxybenzene (84 mg, 0.50 mmol) and nitroacrylate 231 (73 mg, 0.50 mmol). The mixture was stirred for 30 min, the solvent removed *in vacuo* and the residue stirred for 24 h, then filtered through celite® with Et$_2$O (30 mL) and evaporated *in vacuo*. Purification by flash column chromatography (Petrol:Et$_2$O...
1:1) gave nitroalkane 382 (140 mg, 89%) as white crystals, mp. 107-108 °C; Rf 0.27 (Petrol:Et₂O 1:1); IR υ max (thin film) 2952 w (C-H), 2843 w (C-H), 1732 s (C=O), 1609 s, 1594 s, 1554 s (N=O), 1500 m, 1459 m, 1420 m, 1378 m (N·O), 1344 w, 1329 w, 1226 m, 1203 s, 1119 s, 1058 w, 1029 m, 951 w, 815 m cm⁻¹; 1H NMR (600 MHz) δ 1.18 (3H, t, J = 7.1, CH₂CH₃), 3.79 (6H, s, OCH₃), 3.82 (3H, s, OCH₃), 4.10-4.21 (2H, m, OCH₂CH₃), 4.29 (1H, dd, J = 13.5, 5.2, CH₂NO₂), 5.05 (1H, dd, J = 8.8, 5.2, CH=C=O), 5.12 (1H, dd, J = 13.5, 8.8, CH₂NO₂), 6.12 (2H, s, CH Arom.); 13C NMR (150 MHz) δ 14.1 (CH₂CH₃), 38.0 (CH=C=O), 55.3 (OCH₃), 55.7 (OCH₃), 61.1 (OCH₂CH₃), 74.3 (CH₂NO₂), 90.6 (CH Arom.), 103.8 (Cq Arom.), 158.6 (Cq Arom.), 161.3 (Cq Arom.), 171.6 (C=O); m/z (CI⁺) 314 (M+H⁺, 73%), 267 (M+H⁺-NO₂, 100%), 240 (40%); HRMS: found 314.12450, C₁₄H₂₀NO₇ requires 314.12398.

Ethyl 3-nitro-2-(2,6-dioxocyclohexyl)propanoate 384

To a solution of 1,3-cyclohexadione (62 mg, 0.55 mmol) in MeOH (3 mL) was added triethylamine (77 µL, 0.55 mmol) at 0 °C, followed by a solution of nitroacrylate 231 (80 mg, 0.55 mmol) in MeOH (2 mL). The mixture was warmed to rt and stirred until complete consumption of the nitroacrylate (TLC, 2 h). A solution of HCl 0.5 M (10 mL) was then added and the mixture extracted with DCM (3x10 mL), dried over MgSO₄ and evaporated in vacuo. Purification by flash column chromatography (Petrol:Me₂CO 1:1) gave nitroalkane 384 (140 mg, 99%) as a white solid, mp. 91-92 °C; Rf 0.47 (Petrol:Me₂CO 1:1); IR υ max (thin film) 3420 w (O-H), 2981 w (C-H), 1710 s (C=O), 1584 s, 1557 s (N=O), 1382 s (N-O), 1282 m, 1248 m, 1192 m, 1031 m, 1012 m, 678 m cm⁻¹; 1H NMR (600 MHz) δ 1.23 (3H, m, CH₃), 2.01 (2H, m, CH₂CH₂CH₂), 2.52 (4H, m, CH₂CH₂C=O), 4.16 (2H, m, CH₃CH₂O), 4.36 (1H, m, CH₂NO₂), 4.72 (1H, m, CHCH₂NO₂), 5.02 (1H, dd, J = 13.7, 8.4, CH₂NO₂), 8.62 (1H, br s, O-H); 13C NMR (150 MHz) δ 13.9 (CH₂CH₃), 20.3 (CH₂CH₂CH₂), 32.5 (CH₂CH₂C=O), 37.5 (CHCH₂NO₂), 61.9 (OCH₂CH₃), 73.7 (CH₂NO₂), 110.1 (C=C-
OH), 171.8 (OC=O), 188.6 (CH\textsubscript{2}C=O); m/z (Cl\textsuperscript{+}) 178 (M+H\textsuperscript{+}, 30%), 211 (20%), 180 (27%), 165 (100%); HRMS: found 258.09712, C\textsubscript{11}H\textsubscript{16}NO\textsubscript{6} requires 258.09776.

### Ethyl 2-methoxy-3-nitropropanoate 389

![Ethyl 2-methoxy-3-nitropropanoate 389](image)

A solution of nitroacrylate 231 (80 mg, 0.55 mmol) in methanol (5 mL) was stirred at reflux until complete consumption of the starting material (24 h). The solvent was then evaporated in vacuo and flash column chromatography (Petrol:EtOAc 4:1) gave nitroalkane 389 (83 mg, 85%) as a colourless oil; R\textsubscript{f} 0.44 (Petrol:EtOAc 4:1); IR \( \nu_{\text{max}} \) (thin film) 2984 w (C-H), 1937 w (C-H), 1751 s (C=O), 1736 s (C=O) 1557 s (N=O), 1379 m (N-O), 1193 s, 1129 s, 1038 m, 1017 m cm\textsuperscript{-1}; \(^1\)H NMR (600 MHz) \( \delta \) 1.31 (3H, t, J = 7.2, CH\textsubscript{3}), 3.53 (3H, s, OCH\textsubscript{3}), 4.27 (2H, m, OCH\textsubscript{2}), 4.45 (1H, dd, J = 8.1, 3.5, CHOCH\textsubscript{3}), 4.65 (1H, dd, J = 13.9, 8.2, CH\textsubscript{2}NO\textsubscript{2}), 4.72 (1H, dd, J = 13.9, 3.6, CH\textsubscript{2}NO\textsubscript{2}); \(^{13}\)C NMR (150 MHz) \( \delta \) 14.0 (CH\textsubscript{2}CH\textsubscript{3}), 59.5 (OCH\textsubscript{3}), 62.1 (OCH\textsubscript{2}), 75.8 (CH\textsubscript{2}NO\textsubscript{2}), 76.6 (CHOCH\textsubscript{3}), 168.4 (C=O); m/z (EI\textsuperscript{+}) 178 (M\textsuperscript{+}, 100%); HRMS: found 178.07170, C\textsubscript{6}H\textsubscript{11}NO\textsubscript{5} requires 178.07155; Anal. Cald. For C\textsubscript{6}H\textsubscript{11}NO\textsubscript{5}: C, 40.68, H, 6.26, N, 7.91. Found C, 40.38, H, 6.29, N, 7.57%.

The product 389 was also isolated in low yield from the methylation of the respective nitroalcohol 255. A dry 50 mL round-bottom flask was charged with Proton-Sponge\textsuperscript{8} (1.86 g, 8.68 mmol), CHCl\textsubscript{3} (16 mL) and methyl trifluoromethanesulphonate (880 \( \mu \)L, 7.81 mmol) at rt. The nitroalcohol 255 (283 mg, 1.74 mmol) was then added under stirring and the mixture stirred at reflux overnight (22 h). Then saturated aqueous NH\textsubscript{3} (3 mL) was added and the mixture stirred for 2 h at rt. Water (10 mL) was the added and the mixture extracted with DCM (2x20 mL), washed with 2 M HCl (10 mL), dried over MgSO\textsubscript{4} and evaporated in vacuo. Purification by flash column chromatography (Petrol:EtOAc 4:1) gave nitroalkane 289 (21 mg, 7%) as a colourless oil, identical to the one described above.
**Ethyl 2-ethoxy-3-nitropropanoate 395**

![Chemical Structure](image1)

A solution of nitroacrylate 231 (100 mg, 0.69 mmol) in ethanol (7 mL) was stirred at reflux until complete consumption of the starting material (24 h). The solvent was then evaporated in vacuo and flash column chromatography (Petrol:Et<sub>2</sub>O 9:1) gave nitroalkane 395 (117 mg, 89%) as a colourless oil, R<sub>f</sub> 0.33 (Petrol:Et<sub>2</sub>O 9:1); IR <nu>max</nu> (thin film) 2923 w (C-H), 1753 m (C=O), 1736 m, 1559 s (N=O), 1379 m (N-O), 1200 m, 1130 m, 1052 m, 1019 m, 559 w m cm<sup>-1</sup>; <sup>1</sup>H NMR (600 MHz) δ 1.21 (3H, t, <i>J</i> = 7.1, OCH<sub>2</sub>C<sub>2</sub>H,), 1.31 (3H, t, <i>J</i> = 7.2, O=COCH<sub>2</sub>C<sub>2</sub>H,), 3.56 (1H, m, OC<sub>2</sub>H<sub>3</sub>), 3.84 (1H, m, OC<sub>2</sub>H<sub>3</sub>), 4.26 (2H, m, O=COC<sub>2</sub>H<sub>3</sub>), 4.57 (1H, dd, <i>J</i> = 3.5, 8.4, O=C-C<sub>2</sub>H-O), 4.64 (1H, dd, <i>J</i> = 8.5, 13.6, CH<sub>2</sub>NO<sub>2</sub>), 4.71 (1H, dd, <i>J</i> = 8.5, 13.5, CH<sub>2</sub>NO<sub>2</sub>); <sup>13</sup>C NMR (150 MHz) δ 14.1 (C<sub>2</sub>H<sub>3</sub>), 62.0 (O=COCH<sub>2</sub>C<sub>2</sub>H<sub>3</sub>), 75.1 (O=C-C<sub>2</sub>H-O), 76.1 (CH<sub>2</sub>NO<sub>2</sub>), 168.8 (C=O); no M+ peak on mass spec; Anal. Cald. For C<sub>7</sub>H<sub>13</sub>NO<sub>5</sub>: C, 43.98, H, 6.85, N, 7.33. Found C, 44.24, H, 6.86, N, 7.58%.

**Ethyl 2-(benzyloxy)-3-nitropropanoate 396**

![Chemical Structure](image2)

A solution of nitroacrylate 231 (73 mg, 0.50 mmol) in benzyl alcohol (1 mL) was stirred at 100 °C until complete consumption of the starting material (24 h). The solvent was then evaporated in vacuo and flash column chromatography (Petrol:DCM 1:1) gave nitroalkane 396 (79 mg, 62%) as a colourless oil; R<sub>f</sub> 0.46 (Petrol:DCM 1:1); IR <nu>max</nu> (thin film) 2922 s (C-H), 2852 m (C-H), 1745 m (C=O), 1559 m (N=O), 1456 m, 1378 m (N-O), 1274 w, 1203 m, 1131 m, 1020 m cm<sup>-1</sup>; <sup>1</sup>H NMR (600 MHz) δ 1.32 (3H, t, <i>J</i> = 7.1, CH<sub>2</sub>), 4.28 (2H, m, OCH<sub>2</sub>CH<sub>3</sub>), 4.60 (1H, d, <i>J</i> = 11.2, CH<sub>2</sub>Ph), 4.68 (3H, m, CH-O and CH<sub>2</sub>NO<sub>2</sub>), 4.87 (1H, d, <i>J</i> = 11.2, CH<sub>2</sub>Ph), 7.30-7.38 (5H, m, CH Arom.); <sup>13</sup>C NMR (150 MHz) δ 14.1 (CH<sub>3</sub>), 62.1 (OCH<sub>2</sub>CH<sub>3</sub>), 73.7 (CH<sub>2</sub>Ph), 74.2 (CH-O), 76.0 (CH<sub>2</sub>NO<sub>2</sub>), 128.3 (CH Arom.), 128.4 (CH Arom.), 128.5 (CH Arom.),
136.2 (Cq Arom.), 168.6 (C=O); m/z (Cl⁺) 254 (M+H⁺, 13%) (no HRMS), 181 (M+H⁺-COOEt, 100%).

**Ethyl 2-((4-methoxyphenyl)amino)-3-nitropropanoate 397**

To a stirred solution of nitroacrylate 231 (201 mg, 1.39 mmol) in DCM (14 mL) was added at rt para-anisidine (307 mg, 2.50 mmol) and the mixture was stirred until complete consumption of the nitroacrylate (TLC, 1 h). The mixture was then evaporated and purification by flash column chromatography (Petrol:EtOAc 4:1) gave nitroalkane 397 (364 mg, 98%) as an orange solid; mp. 74-75 °C, Rf 0.40 (Petrol:EtOAc 4:1); IR νmax (thin film) 3387 s (N-H), 3010 w (C-H), 2956 w (C-H), 2917 w (C-H), 2836 w (C-H), 1732 s (C=O), 1546 s (N=O), 1515 s, 1317 m (N-O), 1250 m, 1233 m, 1210 s, 1186 m, 1152 m, 1031 m, 829 m, 806 m cm⁻¹; ¹H NMR (600 MHz) δ 1.29 (3H, t, J = 7.1, CH₃), 3.75 (3H, s, OCH₃), 4.26 (1H, br. S, NH), 4.27 (2H, m, OCH₂), 4.55 (1H, t, J = 5.0, CHNH), 4.76 (1H, dd, J = 13.7, 4.8, CH₂NO₂), 4.82 (1H, dd, J = 13.7, 5.1, CH₂NO₂), 6.68 (2H, app d, J = 8.9, CHPMPC₃-H), 6.80 (2H, app d, J = 8.9, CHPMPC₂-H); ¹³C NMR (150 MHz) δ 14.0 (CH₂C₃H₃), 55.6 (OCH₃), 56.3 (CHNH), 62.5 (OCH₂), 75.8 (CH₂NO₂), 114.9 (CHPMPC₃), 115.9 (CHPMPC₂), 139.2 (CqPMPC₁), 153.6 (CqPMPC₄), 169.7 (C=O); m/z (EI⁺) 268 (M⁺, 20%), 149 (100%), 134 (46%); HRMS: found 268.10592, C₁₂H₁₆N₂O₅ requires 268.10686; Anal. Cald. For C₁₂H₁₆N₂O₅: C, 53.73, H, 6.01, N, 10.44. Found C, 53.74, H, 6.00, N, 10.15%.

**Ethyl 2-((4-methoxyphenyl)(methyl)amino)-3-nitropropanoate 406**

To a stirred solution of nitroalkane 397 (198 mg, 0.740 mmol) in THF (7 mL) was added at rt sodium borohydride (141 mg, 3.70 mmol) and paraformaldehyde (222 mg,
7.40 mmol). Trifluoroacetic acid (3.5 mL, 45 mmol) was then added dropwise over 1 h and the mixture stirred for another 1 h. A saturated aqueous solution of Na₂CO₃ was then added until pH = 11 and the mixture extracted with DCM (3x10 mL), dried over MgSO₄ and evaporated in vacuo. Purification by flash column chromatography (Petrol:EtOAc 4:1) gave nitroalkane 406 (78 mg, 37%) as an orange oil, R₇ 0.48 (Petrol:EtOAc 4:1); IR νmax (thin film) 2961 w (C-H), 1730 s (C=O), 1557 s (N=O), 1513 s, 1247 m, 1035 m, 825 w cm⁻¹; ¹H NMR (600 MHz) δ 1.24 (3H, t, J = 6.7, CH₂CH₃), 2.82 (3H, s, NC₃H₃), 4.21 (2H, m, OC₃H₂), 4.77 (1H, dd, J = 13.4, 8.8, CH₂NO₂), 4.92 (1H, dd, J = 13.4, 6.0, CH₂NO₂), 5.06 (1H, dd, J = 8.7, 6.0, NCH), 6.86 (4H, m, CH Arom.); ¹³C NMR (150 MHz) δ 14.2 (CH₂CH₃), 35.0 (NC₃H₃), 55.6 (OC₃H₃), 61.9 (OCH₂), 63.2 (NCH₂), 73.6 (CH₂NO₂), 114.5 (CHPMPC3), 117.9 (CHPMPC2), 143.1 (CqPMPC₁), 153.9 (CqPMPC₁), 168.8 (C=O); m/z (EI⁺) 282 (M⁺, 31%), 163 (100%, M⁺-NO₂-COOEt), 122 (25%); HRMS: found 282.12069, C₁₃H₁₈N₂O₅ requires 282.12102.

**Ethyl 2-morpholino-3-nitropropanoate 398**

![Chemical Structure](image)

To a stirred solution of nitroacrylate 231 (80 mg, 0.55 mmol) in wet DCM (5 mL) was added at rt morpholine (54 μL, 0.66 mmol) and the mixture was stirred at rt until complete consumption of the nitroacrylate (TLC, 30 min). The mixture was then evaporated and purification by flash column chromatography (Petrol:EtOAc 4:1) gave nitroalkane 398 (125 mg, 98%) as an orange oil, R₇ 0.33 (Petrol:EtOAc 4:1); IR νmax (thin film) 2965 w (C-H), 2858 w (C-H), 1729 s (C=O), 1557 s (N=O), 1383 w (N-O), 1187 w, 1116 m, 1023 w, 855 w cm⁻¹; ¹H NMR (600 MHz) δ 1.31 (3H, t, J = 7.2, CH₃), 2.50 (2H, m, CH₂N), 2.80 (2H, m, CH₂N), 3.62 (4H, m, CH₂CH₂O), 4.03 (1H, dd, J = 8.9, 6.4, CHCH₂), 4.23 (2H, m, OCH₂CH₃), 4.61 (1H, dd, J = 13.5, 9.0, CH₂NO₂), 4.67 (1H, dd, J = 13.6, 6.4, CH₂NO₂); ¹³C NMR (150 MHz) δ 14.3 (CH₂CH₃), 49.9 (CH₃N), 61.4 (OCH₂CH₃), 64.5 (CHN), 67.1 (CH₂CH₂O), 73.3 (CH₂NO₂), 168.1 (C=O); m/z (EI⁺) 232 (M⁺, 7%), 159 (M⁺-COOEt, 53%), 113 (M⁺-NO₂-COOEt, 100%); HRMS: found 232.10474, C₉H₁₈N₂O₃ requires 232.10537.
Ethyl 2-(benzylamino)-3-nitropropanoate 399

![Chemical Structure Image]

To a stirred solution of nitroacrylate 231 (80 mg, 0.55 mmol) in DCM (5 mL) was added at 0 °C benzylamine (72 μL, 0.66 mmol) and the mixture was stirred at this temperature until complete consumption of the nitroacrylate (TLC, 1 h). The mixture was then evaporated and purification by flash column chromatography (Petrol:EtOAc 4:1) gave nitroalkane 399 (112 mg, 81%) as an orange oil, Rf 0.59 (Petrol:EtOAc 4:1); IR υmax (thin film) 3340 br (N-H), 3030 w (C-H), 2982 w (C-H), 2931 w (C-H), 1735 s (C=O), 1557 s (N=O), 1379 m (N-O), 1196 m, 1020 m, 739 m, 699 m cm⁻¹; ¹H NMR (600 MHz) δ 1.31 (3H, t, J = 7.1, CH₃), 2.27 (1H, br s, NH), 3.81 (1H, d, J = 13.3, CH₂NH), 3.85 (1H, dd, J = 6.1, 5.0, CH₂CH₂), 3.96 (1H, d, J = 13.3, CH₂NH), 4.26 (2H, m, OCH₂), 4.63 (1H, dd, J = 13.5, 4.9, CH₂NO₂), 4.67 (1H, dd, J = 13.5, 6.0, CH₂NO₂), 7.28 (1H, m , CH Arom.), 7.31-7.36 (4H, m, CH Arom.); ¹³C NMR (150 MHz) δ 14.0 (CH₂CH₃), 52.0 (CH₂NH), 57.7 (CHCH₂), 62.0 (OCH₂), 76.7 (CH₂NO₂), 127.4 (CH Arom.), 128.2 (CH Arom.), 128.5 (CH Arom.), 138.8 (Cq Arom.), 170.8 (C=O); m/z (CI+) 253 (M+H⁺, 4%), 179 (9%), 133 (M⁺-NO₂-COOEt, 17%), 106 (PhCH=NH₂⁺, 20%), 91 (PhCH₃⁺, 100%); HRMS: found 253.11934, C₁₂H₁₇N₂O₄ requires 253.11883.

Ethyl 2-(1H-benzo[d][1,2,3]triazol-1-yl)acrylate 402

![Chemical Structure Image]

To a solution of nitroacrylate 231 (72 mg, 0.50 mmol) in DCM (5 mL) was added 1H-benzo[d][1,2,3]triazole (65 mg, 0.55 mmol) and the mixture was stirred at rt until complete consumption of the nitroacrylate (TLC, 2 days). The mixture was then evaporated in vacuo to give crude acrylate 402. Purification by flash column chromatography (Petrol:Et₂O 7:3) gave acrylate 402 (62 mg, 47%) as a colourless oil, Rf 0.38 (Petrol:Et₂O 7:3); IR υmax (thin film) 2984 w (C-H), 1729 s (C=C), 1635 m, 1455 m, 1378 m, 1276 m, 1240 m, 1178 s, 1074 m, 1055 m, 1018 m, 785 m, 747 s
cm$^{-1}$; $^1$H NMR (600 MHz) δ 1.32 (3H, t, $J = 7.2$, CH$_3$), 4.36 (2H, q, $J = 7.2$, OCH$_2$CH$_3$), 6.30 (1H, s, =CH$_2$), 6.74 (1H, s, =CH$_2$), 7.41 (1H, app. t, $J = 7.8$, CH Arom.), 7.44 (1H, app. d, $J = 8.4$, CH Arom.), 7.52 (1H, app. t, $J = 7.4$, CH Arom.), 8.10 (1H, d, $J = 8.3$, CH Arom.); $^{13}$C NMR (150 MHz) δ 14.0 (CCH$_3$), 62.5 (OCCH$_2$CH$_3$), 110.6 (CH Arom.), 120.1 (CH Arom.), 124.2 (CH Arom.), 125.2 (=CH$_2$), 128.2 (Cq Arom.), 133.1 (Cq Arom.), 134.4 (=C-N), 145.8 (Cq Arom.), 161.6 (C=O); m/z (Cl$^+$) 218 (M+H$^+$, 100%), 161 (26%), 133 (98%); HRMS: found 218.09295, C$_{11}$H$_{12}$N$_3$O$_2$ requires 218.09247; Anal. Cald. For C$_{11}$H$_{11}$N$_3$O$_2$: C, 60.82, H, 5.10, N, 19.34. Found C, 60.53, H, 5.21, N, 19.63%.

**Ethyl 2-(butylthio)acrylate 408**

To a stirred solution of nitroacrylate 231 (60 mg, 0.41 mmol) in THF (2 mL) was added at rt 1-butanethiol (180 µL, 1.24 mmol) and triethylamine (24 µL, 0.17 mmol) and the mixture was stirred overnight until complete consumption of the nitroalkene (TLC, 22 h). The mixture was then evaporated *in vacuo* and purifcation by flash column chromatography (Petrol: Et$_2$O 9:1) gave acrylate 408 (29 mg, 38%) as a colourless oil, which was found to be unstable and could not be completely characterised, R$_f$ 0.38 (Petrol:Et$_2$O 9:1); IR $\nu$$_{\text{max}}$ (thin film) 2959 m (C-H), 1719 s (C=C), 1583 m, 1465 m, 1385 m, 1277 m, 1248 s, 1117 s, 1025 m cm$^{-1}$; $^1$H NMR (600 MHz) δ 1.33 (3H, m, CCH$_3$), 1.47 (2H, m, CH$_2$CH$_2$CH$_3$), 1.66 (2H, m, CH$_2$CH$_2$CH$_3$), 2.72 (2H, m, SCH$_2$), 4.27 (2H, m, OCH$_2$CH$_3$), 5.40 (1H, s, =CH$_2$), 6.35 (1H, s, =CH$_2$); $^{13}$C NMR (150 MHz) δ 13.6 (CH$_3$), 14.1 (OCH$_2$CH$_3$), 22.2 (CH$_2$CH$_2$CH$_3$), 29.7 (SCH$_2$CH$_2$), 31.1 (SCH$_2$), 61.7 (OCH$_2$), 118.5 (=CH$_2$), 137.9 (=Cq), 164.6 (C=O); m/z (EI$^+$) 188 (M$^+$, 30%), 107 (100%); HRMS: found 188.08600, C$_9$H$_{16}$O$_2$S requires 188.08655.
Ethyl 2-(diphenylphosphoryl)acrylate 409

To a stirred solution of the nitroacrylate 231 (65 mg, 0.45 mmol) in dry THF (5 mL), was added at rt diphenylphosphine oxide (100 mg, 0.500 mmol) and the mixture was stirred at rt overnight, until complete consumption of the nitroacrylate (TLC, 16 h). After completion, the mixture was evaporated and purification by flash column chromatography gave acrylate 409 (75 mg, 56%) as a yellow oil, Rₚ 0.29 (Petrol:Me₂CO 3:2); IR νₘₐₓ (thin film) 3058 w (C-H), 2981 w (C-H), 1721 s (C=O), 1438 s, 1250 m, 1184 s, 1188 s, 1098 s, 1019 m, 728 s, 695 s cm⁻¹; ¹H NMR (600 MHz) δ 1.05 (3H, t, J = 7.1, CH₃), 4.10 (2H, q, J = 7.1, OC₂H₅), 6.30 (1H, dd, P-H J = 17.4, ²J = 1.4, =CH₂), 7.25 (1H, dd, P-H J = 33.6, ²J = 1.4, =CH₂), 7.40-7.60 (6H, m, CH Arom.), 7.85 (4H, m, CH Arom.); ¹³C NMR (150 MHz) δ 13.7 (CH₂C₅H₃), 61.4 (OCH₂CH₃), 128.4 (d, J = 12.6, CH Arom.), 131.2 (d, J = 108.6, Cq Arom.), 131.8 (d, J = 10.1, CH Arom.), 132.0 (d, J = 2.8, CH Arom.), 137.3 (d, J = 95.5, =Cq-P), 144.6 (d, J = 4.9, =CH₂), 164.3 (d, J = 14.1, C=O); ³¹P NMR (300 MHz) δ 26.0; m/z (ESI⁺) 301 (M+H⁺, 100%), 243 (55%), 215 (40%); HRMS: found 301.0996, C₁₇H₁₈O₃P requires 301.0994.

3.4.3.2 Nitro-Mannich reaction to nitroacrylate adducts

General procedure E for the synthesis of pyrrolidin-2-ones 232

A solution of nitroalkane (0.50 mmol) in THF (5 mL), was cooled to -78 °C and n-BuLi (0.55 mmol, of a 2.5 M solution in hexanes, 1.1 equiv.) was added dropwise. The orange mixture was stirred at this temperature for 10 min before the corresponding imine (0.75 mmol, 1.5 equiv.) in THF (2 mL) was added via cannula. The mixture was stirred for 20 min, before TFA (1.00 mmol, 2.0 equiv.) in THF (0.5 mL) was added via cannula. The mixture was stirred at this temperature for a further 1 h before being warmed to rt for 16 h. Saturated aqueous NaHCO₃ (20 mL) and Et₂O (20 mL) were then added and the layers separated. The aqueous phase was extracted with Et₂O (3x20 mL), and the combined organics washed with brine (20
mL), dried over MgSO₄ and concentrated *in vacuo* to leave crude pyrrolidinone. The pyrrolidinone was then purified further with column chromatography.

\((3S^*,4S^*,5R^*)-3-(1H-indol-3-yl)-1-(4-methoxyphenyl)-4-nitro-5-phenylpyrrolidin-2-one\) 420

Prepared by general procedure E. Nitroalkane 381 (153 mg, 0.620 mmol), ⁶BuLi (0.680 mmol), imine 281 (260 mg, 1.24 mmol) and TFA (1.54 mmol) afforded crude pyrrolidinone 420. Purification by flash column chromatography (Petrol:EtOAc 3:2) gave pyrrolidinone 420 (141 mg, 54%, 79% based on recovered starting material) as an orange solid; mp. 196-197 °C; R̂f 0.34 (Petrol:EtOAc 3:2); IR ν_max (thin film) 3329 br (N-H), 2960 w (C-H), 1701 s (C=O), 1555 s (N=O), 1512 s, 1364 m (N-O), 1250 m, 743 m cm⁻¹; ¹H NMR (600 MHz) δ 3.74 (1H, s, OC₃H₃), 4.92 (1H, d, J = 7.9, C₇HPhN), 5.27 (1H, dd, J = 7.8, 6.5, CHNO₂), 5.73 (1H, d, J = 6.3, CHC=O), 6.85 (3H, m, CH Arom.), 7.21 (2H, m, CH Arom.), 7.23-7.36 (7H, m, CH Arom.), 7.64 (1H, m, CH Arom.), 8.70 (1H, br s, NH); ¹³C NMR (150 MHz) δ 46.5 (CHC=O), 55.3 (OCH₃), 65.9 (CHPhN), 92.4 (CHNO₂), 108.5 (Cq Arom.), 112.0 (CH Arom.), 114.2 (CH Arom.), 118.1 (CH Arom.), 120.2 (CH Arom.), 122.5 (CH Arom.), 124.3 (CH Arom.), 125.4 (CH Arom.), 125.4 (Cq Arom.), 126.9 (CH Arom.), 129.2 (Cq Arom.), 129.3 (CH Arom.), 136.2 (Cq Arom.), 136.6 (Cq Arom.), 157.7 (Cq Arom.), 170.8 (C=O); m/z (EI⁺) 427 (M⁺, 20%), 380 (100%, M⁺-HNO₂), 351 (M+H⁺-Ph, 17%), 230 (10%), 210 (17%); HRMS: found 427.15312, C₁₈H₂₀N₅O₄ requires 427.15266.
(3S*,4S*,5R*)-1-(4-methoxyphenyl)-4-nitro-5-phenyl-3-(2,4,6-trimethoxyphenyl)pyrrolidin-2-one 421

Prepared by general procedure E. Nitroalkane 382 (126 mg, 0.400 mmol), nBuLi (0.40 mmol), imine 281 (170 mg, 0.800 mmol) and TFA (1.40 mmol) afforded crude pyrrolidinone 421. Purification by flash column chromatography (Petrol:Me₂CO 7:3) gave pyrrolidinone 421 (102 mg, 53%) as a white solid; mp. 96-97 °C; Rf 0.28 (Petrol:Me₂CO 7:3); IR υ max (thin film) 3003 w (C-H), 2940 w (C-H), 2839 w (C-H), 1713 s (C=O), 1611 s, 1595 s, 1553 s (N=O), 1512 s, 1457 m, 1595 s, 1553 s (N=O), 1249 s, 1205 s, 1152 s, 1118 s, 1033 m, 835 m, 817 m, 701 m cm⁻¹; ¹H NMR (600 MHz) δ 3.72 (3H, s, OC₃H₃), 3.77 (3H, br. s, OC₃H₃), 3.82 (3H, s, OC₃H₃), 3.95 (3H, br. s, OC₃H₃), 5.12 (1H, d, J = 9.5, CHC=O), 5.26 (1H, dd, J = 9.6, 7.5, CHNO₂), 5.70 (1H, d, J = 7.5, PhCHN), 6.18 (2H, m, CH Arom.), 6.78 (2H, app. d, J = 9.1, CHPMP₂-C₃-H), 7.24 (1H, app. d, J = 9.1, CHPMP₂-C₃-H), 7.26-7.32 (5H, m, CH Arom.); ¹³C NMR (150 MHz) δ 44.2 (CHC=O), 55.3, 55.4, 55.8 and 56.0 (OCH₃), 65.0 (PhCHN), 90.9 and 91.4 (CH Arom.), 92.2 (CHNO₂), 104.1 (Cq Arom.), 114.0 (CH Arom.), 125.0 (CH Arom.), 127.1 (CH Arom.), 128.9 (CH Arom.), 129.0 (CH Arom.), 129.7 (Cq Arom.), 137.4 (Cq Arom.), 157.1 (Cq Arom.), 158.6 (Cq Arom.), 159.7 (Cq Arom.), 161.6 (Cq Arom.), 170.0 (C=O); m/z (EI⁺) 479 (M+H⁺, 100%), 432 (M+H⁺-NO₂, 70%), 264 (30%); HRMS: found 479.1808, C₁₈H₁₄N₂O₄ requires 479.1818; Anal. Cald. For C₂₆H₂₇N₂O₇: C, 65.39, H, 5.78, N, 5.59%.

(2S*,3R*,4R*)-Ethyl 1-(4-methoxyphenyl)-3-nitro-5-oxo-2-phenyl-1,2,3,4,5,6,7,8-octahydroquinoline-4-carboxylate 422

Prepared by general procedure E. Nitroalkane 384 (36 mg, 0.14 mmol), nBuLi (0.28 mmol), imine 281 (59 mg, 0.28 mmol) and TFA (0.49 mmol) afforded crude
quinoline 422. Purification by flash column chromatography (Petrol:Me$_2$CO 7:3) gave quinoline 422 (24 mg, 38%) as a yellow oil; R$_f$ 0.17 (Petrol:Me$_2$CO 7:3); IR $\nu_{\text{max}}$ (thin film) 2932 w (C-H), 1730 m (C=O), 1557 s (N=O), 1508 s, 1396 m, 1247 s, 1181 s, 1027 m, 841 m, 733 m, 702 m cm$^{-1}$; $^1$H NMR (600 MHz) $\delta$ 1.28 (3H, t, $J=7.2$, CH$_2$CH$_3$), 1.92 (2H, m, CH$_2$CH$_2$CH$_3$), 2.22 (2H, m, CH$_2$CH$_2$C=), 2.40 (2H, m, CH$_2$C=O), 3.74 (3H, s, OCH$_3$), 4.22 (2H, m, CH$_3$C=O), 4.43 (1H, d, $J=5.3$, CHCOOEt), 5.19 (1H, dd, $J=8.7$, 5.3, CHNO$_2$), 5.24 (1H, d, $J=8.8$, CPh), 6.40-6.90 (4H, br, CH Arom.), 7.15 (2H, m, CH Arom.), 7.26 (3H, m, CH Arom.); $^{13}$C NMR (150 MHz) $\delta$ 14.0 (CH$_2$CH$_3$), 21.3 (CH$_2$CH$_2$CH$_2$), 28.9 (CH$_2$CH$_2$C=), 35.8 (CH$_2$C=O), 39.6 (CHCOOEt), 55.3 (OCH$_3$), 61.8 (OCH$_2$CH$_3$), 63.7 (CPh), 85.5 (CHNO$_2$), 104.2 (C=CC=O), 114.6 (CH$_{\text{PMPC3}}$ at 60$^\circ$C), 128.2 (CH Arom.), 28.9 (CH Arom.), 129.1 (CH Arom.), 130.1 (CH Arom., at 60$^\circ$C), 134.7 (Cq Arom.), 135.3 (Cq Arom.), 158.9 (Cq$_{\text{PMPC4}}$), 161.3 (Cq Arom.), 171.0 (OC=O), 193.8 (CH$_2$C=O); m/z (EI$^+$) 450 (M$^+$, 32%), 404 (M$^+$-NO$_2$, 86%), 330 (M$^+$-HNO$_2$-COOEt, 100%), 254 (M$^+$-NO$_2$-COOEt -Ph, 35%); HRMS: found 450.17902, C$_{25}$H$_{26}$N$_2$O$_6$ requires 450.17854.

(3S*,4R*,5R*)-3-methoxy-1-(4-methoxyphenyl)-4-nitro-5-phenylpyrrolidin-2-one 423

Prepared by general procedure E. Nitroalkane 389 (75 mg, 0.42 mmol), $^9$BuLi (0.460 mmol), imine 281 (134 mg, 0.640 mmol) and TFA (0.850 mmol) afforded crude pyrrolidinone 423. Purification by flash column chromatography (Petrol:EtOAc 7:3) gave pyrrolidinone 423 (60 mg, 42%) as an orange oil that was unstable (degradation was observed after 30 min at rt); R$_f$ 0.35 (Petrol:EtOAc 7:3); IR $\nu_{\text{max}}$ (thin film) 2958 w (C-H), 2925 w (C-H), 1713 s (C=O), 1555 s (N=O), 1511 s, 1367 m (N-O), 1248 m, 1106 m, 1030 m, 834 m, 700 m cm$^{-1}$; $^1$H NMR (600 MHz) $\delta$ 3.72 (1H, s, OCH$_3$), 3.75 (1H, s, OCH$_3$), 4.74 (1H, d, $J=6.0$, CHOMe), 5.02 (1H, t, $J=5.8$, CHNO$_2$), 5.48 (1H, d, $J=5.7$, CHN), 6.78 (2H, app d, $J=9.1$, CH$_{\text{PMPC3-h}}$), 7.20 (2H, app d, $J=9.1$, CH$_{\text{PMPC2-h}}$), 7.21-7.40 (5H, m, CH Arom.); $^{13}$C NMR (150 MHz) $\delta$ 37.2 (OCH$_3$), 3.75 (1H, s, OCH$_3$), 4.74 (1H, d, $J=6.0$, CHOMe), 5.02 (1H, t, $J=5.8$, CHNO$_2$), 5.48 (1H, d, $J=5.7$, CHN), 6.78 (2H, app d, $J=9.1$, CH$_{\text{PMPC3-h}}$), 7.20 (2H, app d, $J=9.1$, CH$_{\text{PMPC2-h}}$), 7.21-7.40 (5H, m, CH Arom.); $^{13}$C NMR (150 MHz) $\delta$ 55.3 (OCH$_3$), 59.6 (OCH$_3$), 64.1 (CHPhN), 81.2 (CHOMe), 91.1 (CHNO$_2$), 114.2 (CH$_{\text{PMPC3}}$), 125.3
(3S*,4R*,5R*)-1-(4-methoxyphenyl)-3-morpholino-4-nitro-5-phenylpyrrolidin-2-one 424

Prepared by general procedure E. Nitroalkane 398 (105 mg, 0.450 mmol), n-BuLi (0.500 mmol), imine 281 (143 mg, 0.680 mmol) and TFA (0.990 mmol) afforded crude pyrrolidinone 424. Purification by flash column chromatography (Petrol:EtOAc 3:2) gave pyrrolidinone 424 (118 mg, 50%) as an orange oil that was unstable (degradation was observed after 30 min at rt); Rf 0.31 (Petrol:EtOAc 3:2); IR νmax (thin film) 2961 w (C-H), 2853 w (C-H), 1709 m (C=O), 1557 m (N=O), 1512 s, 1249 s, 1115 m, 1031 w, 835 w cm⁻¹; ¹H NMR (600 MHz) δ 2.87 (4H, m, NC₅H₂), 3.73 (3H, s, OC₃H₃), 3.78 (4H, m, OCH₂), 4.46 (1H, d, J = 7.4, CHC=O), 5.10 (1H, dd, J = 7.4, 6.2, CHNO₂), 5.50 (1H, d, J = 6.2, CHPH₃), 6.79 (2H, app d, CH Arom.), 7.15-7.35 (7H, m, CH Arom.); ¹³C NMR (150 MHz) δ 49.3 (NCH₃), 55.3 (OCH₃), 64.2 (CH₃PHN), 66.8 (OCH₂), 70.4 (NCHC=O), 87.3 (CHNO₂), 114.2 (CH₃PMPC₃-H), 125.0 (CH Arom.), 126.6 (CH Arom.), 128.8 (Cq Arom.), 129.3 (CH Arom.), 129.4 (CH Arom.), 136.4 (Cq Arom.), 157.7 (Cq Arom.), 167.0 (C=O); m/z (EI⁺) 398 (M+H⁺, 7%), 310 (M⁺-C₄H₄NO, 11%), 266 (M⁺+H⁺- C₄H₄NO-NO₂, 18%), 227 (72%), 105 (100%); HRMS: found 398.17131, C₂₁H₂₄N₃O₅ requires 398.17160.
3.4.3.3 1,4-Additions to β-nitrostyrene

3-(2-nitro-1-phenylethyl)-1H-indole 429

\[
\begin{align*}
\text{NH} & \quad \text{NO}_2 \\
\end{align*}
\]

To a preformed mixture of CeCl₃·NaI·SiO₂ (11:2.5:1, 289 mg) was added MeCN (3 mL) followed by indole (59 mg, 0.50 mmol) and β-nitrostyrene (74 mg, 0.50 mmol). The mixture was stirred for 30 min, the solvent removed in vacuo and the residue stirred for 24 h. The mixture was then filtered through celite® with Et₂O (30 mL) and evaporated in vacuo. Purification by flash column chromatography (Petrol:EtOAc 4:1) gave nitroalkane 429 (123 mg, 92%) as a colourless oil, Rᵣ 0.43 (Petrol:EtOAc 4:1); ¹H NMR (600 MHz) δ 4.96 (1H, dd, J = 12.4, 8.4, CH₂NO₂), 5.09 (1H, dd, J = 12.4, 7.7, CH₂NO₂), 5.21 (1H, t, J = 8.1, CH), 7.04 (1H, d, J = 2.3, CH Arom.), 7.10 (1H, app. t, J = 7.5, CH Arom.), 7.22 (1H, app. t, J = 7.5, CH Arom.), 7.29 (1H, m, CH Arom.), 7.35 (5H, m, CH Arom.), 7.47 (1H, d, J = 7.9, CH Arom.), 8.09 (1H, br. s, NH); ¹³C NMR (150 MHz) δ 41.5 (CHCH₃), 79.5 (CH₂), 111.4 (CH₉indole), 114.4 (Cq₉indole), 118.9 (CH Arom.), 119.9 (CH Arom.), 121.6 (CH Arom.), 122.7 (CH Arom.), 126.0 (Cq Arom.), 127.5 (CH Arom.), 127.7 (CH Arom.), 128.9 (CH Arom.), 136.4 (Cq Arom.), 139.1 (Cq Arom.). Data in agreement with that reported.²⁶²

1,3,5-Trimethoxy-2-(2-nitro-1-phenylethyl)benzene 430

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

To a preformed mixture of CeCl₃·NaI·SiO₂ (11:2.5:1, 289 mg) was added MeCN (3 mL) followed by 1,3,5-trimethoxybenzene (84 mg, 0.50 mmol) and β-nitrostyrene (74 mg, 0.50 mmol). The mixture was stirred for 30 min, the solvent removed in vacuo and the residue stirred for 24 h. The mixture was then filtered through celite® with Et₂O (30 mL) and evaporated in vacuo. Purification by flash column chromatography (Petrol:EtOAc 4:1) gave nitroalkane 430 (113 mg, 71%) as a colourless oil, Rᵣ 0.43
(Petrol:EtOAc 4:1); $^1$H NMR (600 MHz) δ 3.80 (3H, s, OCH$_3$), 3.81 (6H, s, OCH$_3$), 5.14 (1H, dd, J = 12.8, 7.6, CH$_2$NO$_2$), 5.26 (1H, dd, J = 12.7, 8.1, CH$_2$NO$_2$), 5.51 (1H, t, J = 7.9, CH), 6.14 (2H, s, CH$_{trimethoxybenzene}$), 7.19 (1H, t, J = 7.3, CH Arom.), 7.27 (2H, t, J = 7.4, CH Arom.), 7.33 (2H, s, CH Arom.); $^{13}$C NMR (150 MHz) δ 38.5 (CH$_3$), 55.2 (OCH$_3$), 55.7 (OCH$_3$), 78.3 (CH$_2$), 91.0 (CH$_{trimethoxybenzene}$), 108.5 (Cq Arom.), 126.5 (CH Arom.), 127.5 (CH Arom.), 128.2 (CH Arom.), 140.4 (Cq$_{trimethoxybenzene}$), 158.9 (Cq-OMe), 160.5 (Cq-OMe). Data in agreement with that reported.$^{263}$

**Diethyl 2-(2-nitro-1-phenylethyl)malonate 431$^{182}$**

![Diethyl 2-(2-nitro-1-phenylethyl)malonate](image)

To a solution of diethylmalonate (0.15 mL, 1.0 mmol) in THF (3 mL) was added NaH (24 mg, 1.0 mmol, 95%) and the mixture stirred at rt for 15 min. A solution of β-nitrostyrene (74 mg, 0.50 mmol) in THF (2 mL) was then added and the mixture stirred at rt until complete consumption of the nitroalkene (TLC, 15 min). The mixture was then quenched with addition of saturated aqueous NH$_4$Cl (10 mL) and extracted with DCM (3x10 mL), the combined organics then washed with brine (10 mL), dried over MgSO$_4$ and evaporated *in vacuo* to give crude nitroalkane 431. Purification by flash column chromatography (Hexane:Et$_2$O 7:3) gave nitroalkane 431 (148 mg, 96%) as a colourless oil; R$_f$ 0.30 (Hexane:Et$_2$O 7:3); $^1$H NMR (600 MHz) δ 1.05 (3H, t, J = 7.1, CH$_3$), 1.27 (3H, t, J = 7.1, CH$_3$), 3.83 (1H, d, J = 9.4, CHC=O), 4.02 (2H, q, J = 7.2, OCH$_2$), 4.27 (3H, m, OCH$_2$ and PhCH), 4.85 (1H, dd, J = 13.1, 9.4, CH$_2$NO$_2$), 4.95 (1H, dd, J = 13.1, 4.8, CH$_2$NO$_2$), 7.23-7.34 (5H, m, CH Arom.); $^{13}$C NMR (150 MHz) δ 13.7 (CH$_3$), 14.0 (CH$_3$), 42.9 (CHPh), 54.9 (O=CCHC=O), 61.9 (OCH$_2$), 62.2 (OCH$_2$), 77.6 (CH$_2$NO$_2$), 128.0 (CH Arom.), 128.4 (CH Arom.), 128.9 (CH Arom.), 136.1 (Cq Arom.), 166.8 (C=O), 167.5 (C=O). Data in agreement with that reported.$^{264}$
2-(2-Nitro-1-phenylethyl)malononitrile 432

To a solution of L-Proline (11.5 mg, 10 mol %) in DMF (1 mL) was added malononitrile (66 mg, 1.0 mmol) followed by β-nitrostyrene (149 mg, 1.00 mmol) and the mixture was stirred at rt until complete consumption of the nitroalkene (TLC, 20 h). Water (10 mL) was then added and the mixture was extracted with Et₂O (3x10 mL), dried over MgSO₄ and evaporated in vacuo to give crude nitroalkane 432. Purification by flash column chromatography (DCM) gave nitroalkane 432 (192 mg, 89%) as a yellow oil; R_f 0.49 (DCM); ¹H NMR (600 MHz) δ 4.09 (1H, m, PhCH), 4.43 (1H, d, J = 6.0, NCCCN), 4.90 (1H, dd, J = 14.2, 6.2, CH₂NO₂), 4.97 (1H, dd, J = 14.3, 7.9, CH₂NO₂), 7.30-7.48 (5H, m, CH Arom.); ¹³C NMR (150 MHz) δ 27.6 (PhCH), 43.7 (NCCCN), 74.9 (CH₂NO₂), 110.3 (C=N), 110.4 (C=N), 127.7 (CH Arom.), 129.9 (CH Arom.), 130.4 (CH Arom.), 131.8 (Cq Arom.). Data in agreement with that reported. ¹⁸¹

3-Hydroxy-2-(2-nitro-1-phenylethyl)cyclohex-2-enone 433

To a solution of 1,3-cyclohexanedione (560 mg, 5.00 mmol) in methanol (1 mL) was added a solution of sodium (25 mg, 1.1 mmol) in methanol (2 mL) and the mixture stirred for 1 min at rt. The mixture was then cooled to 0 °C, a solution of β-nitrostyrene (745 mg, 5.00 mmol) in methanol (2 mL) was added and the mixture stirred at this temperature for 30 min, then at rt until complete consumption of the starting material (TLC, 5 h). The mixture was poured into ice-water, neutralised with 10% HCl, filtered and recrystallised from methanol to give pure nitroalkane 433 (440 mg, 34%, lit. 68%) as a white solid; mp. 142-143 °C (lit. 144-146 °C); R_f 0.35 (Petrol:Me₂CO 1:1); ¹H NMR (600 MHz) δ 1.86 (2H, m, CH₂), 2.37 (4H, m, CH₂), 5.08 (2H, m, CH₂NO₂), 5.19 (1H, m, CHPh), 7.19-7.34 (5H, m, CH Arom.), 9.91 (1H,
br. s, OH; $^{13}$C NMR (150 MHz) δ 20.4 (CH$_2$), 33.0 (CH$_2$), 35.2 (CH$_2$), 38.2 (CHPh), 77.3 (CH$_2$NO$_2$), 114.4 (Cq), 126.9 (CH Arom.), 127.8 (CH Arom.), 128.4 (CH Arom.), 138.8 (Cq Arom.), 139.7 (HO-Cq), 197.4 (C=O). Data in agreement with that reported.\(^{265}\)

**2,2-Dimethyl-5-(2-nitro-1-phenylethyl)-1,3-dioxane-4,6-dione 434\(^{197}\)**

![2,2-Dimethyl-5-(2-nitro-1-phenylethyl)-1,3-dioxane-4,6-dione](image)

To a solution of Meldrum’s acid (144 mg, 1.00 mmol) in DCM (7 mL) was added triethylamine (130 µL, 1.00 mmol) and the mixture stirred at rt for 30 min. β-nitrostyrene (149 mg, 1.00 mmol) was then added in one batch and the mixture stirred at rt until complete consumption of the starting material (TLC, 1 h). The mixture was acidified to pH = 2 with addition of 10% HCl, extracted with DCM (3x10 mL), dried over MgSO$_4$ and evaporated in vacuo to give pure nitroalkane 434 (280 mg, 96%, lit. 88%) as a white solid; mp. 92-94 °C (lit. 93-95 °C); $R_f$ 0.49 (DCM:MeOH 10:1); $^1$H NMR (600 MHz) δ 1.39 (3H, s, CH$_3$), 1.71 (3H, s, CH$_3$), 4.04 (1H, d, $J = 3.2$, O=CC=O), 4.64 (1H, m, CHPh), 5.02 (1H, dd, $J = 14.0$, 6.5, CH$_2$NO$_2$), 5.40 (1H, dd, $J = 14.0$, 9.0, CH$_2$NO$_2$), 7.30-7.35 (5H, m, CH Arom.); $^{13}$C NMR (150 MHz) δ 27.6 (CH$_3$), 28.1 (CH$_3$), 41.8 (O=CC=O), 48.5 (CHPh), 75.9 (CH$_2$NO$_2$), 105.9 (Cq), 128.8 (CH Arom.), 128.9 (CH Arom.), 129.2 (CH Arom.), 135.1 (Cq Arom.), 164.0 (C=O), 164.4 (C=O). Data in agreement with that reported.\(^{197}\)

**2-Nitro-1-phenylethanol 435\(^{115}\)**

![2-Nitro-1-phenylethanol](image)

In a 5 mL round bottom flask were added benzaldehyde (300 µL, 3.00 mmol), nitromethane (810 µL, 15.0 mmol) and triethylamine (1.46 mL, 10.5 mmol) and the
mixture stirred at rt overnight (20 h), then evaporated in vacuo to give crude nitroalcohol 435. Purification by flash column chromatography (Petrol:Et₂O 4:1) gave nitroalcohol 435 (247 mg, 50%) as a colourless oil; R_f 0.17 (Petrol:Et₂O 4:1); ¹H NMR (600 MHz) δ 2.90 (1H, br. s, OH), 4.52 (1H, dd, J = 13.3, 2.7, CH₂NO₂), 4.61 (1H, dd, J = 13.1, 9.6, CH₂NO₂), 5.47 (1H, d, J = 10.0, CHO), 7.35-7.45 (5H, m, CH Arom.). Data in agreement with that reported.²⁶⁶

(1-Methoxy-2-nitroethyl)benzene 436

A 1.5 M solution of MeONa in MeOH (670 µL, 1.00 mmol) was added at rt to a solution of β-nitrostyrene (149 mg, 1.00 mmol) in MeOH (10 mL). The mixture was stirred at rt until no nitroalkene was observed on TLC (15 min). Acetic acid (400 µL, 6.00 mmol) was then added and the mixture stirred for 5 min and then poured into water (20 mL). The mixture was extracted with DCM (3x10 mL), the combined organics washed with brine (10 mL), dried over MgSO₄ and evaporated in vacuo to give crude nitroalkane 436. Purification by flash column chromatography (Petrol:Et₂O 9:1) gave nitroalkane 436 (133 mg, 73%, lit. 60%)¹⁹⁸ as a colourless oil, R_f 0.63 (Petrol:Et₂O 9:1); ¹H NMR (600 MHz) δ 3.28 (3H, s, OCH₃), 4.41 (1H, dd, J = 12.8, 3.3, CH₂NO₂), 4.62 (1H, dd, J = 12.7, 10.1, CH₂NO₂), 4.97 (1H, dd, J = 10.2, 3.4, CHOHCH₃), 7.36-7.45 (5H, m, CH Arom.); ¹³C NMR (150 MHz) δ 57.1 (CH₃), 80.0 (CH), 80.4 (CH₂), 126.8 (CH Arom.), 129.0 (CH Arom.), 129.1 (CH Arom.), 135.9 (Cq Arom.). Data in agreement with that reported.¹⁹⁸

(1-Ethoxy-2-nitroethyl)benzene 438

A 1.5 M solution of EtONa in EtOH (670 µL, 1.00 mmol) was added at rt to a solution of β-nitrostyrene (149 mg, 1.00 mmol) in EtOH (10 mL). The mixture was
stirred at rt until no nitroalkene was observed on TLC (15 min). Acetic acid (400 µL, 6.00 mmol) was then added and the mixture stirred for 5 min and then poured into water (20 mL). The mixture was extracted with DCM (3x10 mL), the combined organics washed with brine (10 mL), dried over MgSO$_4$ and evaporated in vacuo to give crude nitroalkane 438. Purification by flash column chromatography (Petrol:Et$_2$O 9:1) gave nitroalkane 438 (129 mg, 66%, lit. 6%$^{198}$) as a colourless oil; R$_f$ 0.49 (Petrol:Et$_2$O 9:1); $^1$H NMR (600 MHz) δ 1.16 (3H, t, $J = 7.3$, CH$_3$), 3.39 (2H, m, OCH$_2$), 4.39 (1H, dd, $J = 12.8$, 3.4, CH$_2$NO$_2$), 4.61 (1H, dd, $J = 12.8$, 10.3, CH$_2$NO$_2$), 5.06 (1H, dd, $J = 10.0$, 3.3, CHO), 7.35-7.42 (5H, m, CH Arom.); $^{13}$C NMR (150 MHz) δ 14.9 (CH$_3$), 62.9 (OCH$_2$), 78.2 (CH), 80.5 (CH$_2$NO$_2$), 126.7 (CH Arom.), 128.9 (CH Arom.), 129.0 (CH Arom.), 136.7 (Cq Arom.). Data in agreement with that reported.$^{198}$

(1-(Benzyloxy)-2-nitroethyl)benzene 439

A 1.5 M solution of BnONa in BnOH (670 µL, 1.00 mmol) was added at rt to a solution of β-nitrostyrene (149 mg, 1.00 mmol) in BnOH (10 mL). The mixture was stirred at rt until no nitroalkene was observed on TLC (15 min). Acetic acid (400 µL, 6.00 mmol) was added and the mixture stirred for 5 min and then poured into water (20 mL). The mixture was extracted with DCM (3x10 mL), the combined organics washed with brine (10 mL), dried over MgSO$_4$ and evaporated in vacuo to give crude nitroalkane 439. Purification by flash column chromatography (Petrol:Et$_2$O 9:1) gave nitroalkane 439 (171 mg, 66%, lit. 30%$^{198}$) as a colourless oil; R$_f$ 0.39 (Petrol:Et$_2$O 9:1); $^1$H NMR (600 MHz) δ 4.34 (1H, d, $J = 11.6$, OCH$_2$), 4.42 (1H, dd, $J = 12.8$, 3.4, CH$_2$NO$_2$), 4.52 (1H, d, $J = 11.5$, OCH$_2$), 4.70 (1H, dd, $J = 12.8$, 10.1, CH$_2$NO$_2$), 5.16 (1H, dd, $J = 10.2$, 3.4, CHO), 7.23-7.41 (9H, m, CH Arom.); $^{13}$C NMR (150 MHz) δ 70.9 (OCH$_2$), 77.5 (CH), 80.3 (CH$_2$NO$_2$), 127.0 (CH Arom.), 127.9 (CH Arom.), 128.0 (CH Arom.), 128.4 (CH Arom.), 129.2 (CH Arom.), 129.2 (CH Arom.), 136.0 (Cq Arom.), 136.9 (Cq Arom.). Data in agreement with that reported.$^{198}$
(1-Isopropoxy-2-nitroethyl)benzene 440

\[
\begin{align*}
\text{O}^\text{Pr} & \\
& \text{NO}_2
\end{align*}
\]

A 0.5 M solution of \textsuperscript{1}PrONa in \textsuperscript{1}PrOH (2.00 mL, 1.00 mmol) was added at rt to a solution of \(\beta\)-nitrostyrene (149 mg, 1.00 mmol) in \textsuperscript{1}PrOH (8 mL). The mixture was stirred at rt until no nitroalkene was observed on TLC (10 min). Acetic acid (400 \(\mu\)L, 6.00 mmol) was then added and the mixture stirred for 5 min and then poured into water (20 mL). The mixture was extracted with DCM (3x10 mL), the combined organics washed with brine (10 mL), dried over MgSO\(_4\) and evaporated in vacuo to give crude nitroalkane 440. Purification by flash column chromatography (Petrol:Et\(_2\)O 9:1) gave nitroalkane 440 (121 mg, 58%) as a colourless oil; \(R_f\) 0.51 (Petrol:Et\(_2\)O 9:1); IR \(\nu_{\text{max}}\) (thin film) 2974 w (C-H), 1553 s (N=O), 1494 w, 1454 w, 1418 w, 1379 m (N-O), 1336 w, 1324 w, 1143 w, 1122 w, 1095 m, 1062 m, 1029 w, 976 m, 762 m, 717 m, 699 s cm\(^{-1}\); \textsuperscript{1}H NMR (600 MHz) \(\delta\) 1.07 (3H, d, \(J = 6.2\), C\(\text{H}_3\)), 1.13 (3H, d, \(J = 6.2\), C\(\text{H}_3\)), 3.56 (1H, sept, \(J = 6.1\), C\(\text{H}(\text{CH}_3)_2\)), 4.36 (1H, dd, \(J = 12.7\), 3.3, C\(\text{H}_2\text{NO}_2\)), 4.57 (1H, dd, \(J = 12.6\), 10.3, C\(\text{H}_2\text{NO}_2\)), 5.17 (1H, dd, \(J = 10.2\), 3.2, C\(\text{HOCCH}\)), 7.35 (1H, m, C\(\text{H Arom.}\)), 7.40 (4H, m, C\(\text{H Arom.}\)); \textsuperscript{13}C NMR (150 MHz) \(\delta\) 20.8 (C\(\text{H}_3\)), 23.2 (CH\(_3\)), 70.4 (CH\((\text{CH}_3)_2\)), 75.8 (OCH\(_2\text{CH}_2\)), 80.8 (CH\(_2\text{NO}_2\)), 126.7 (CH Arom.), 128.8 (CH Arom.), 128.9 (CH Arom.), 137.5 (Cq Arom.); m/z (CI\textsuperscript{+}) 210 (M+H\textsuperscript{+}, 6%), 162 (M\textsuperscript{+}-HNO\(_2\), 24%), 149 (M\textsuperscript{+}-CH\(_2\text{NO}_2\), 61%), 107 (PhCHO+H\textsuperscript{+}, 100%), 104 (PhCH=CH\(_2\)\textsuperscript{+}, 72%); HRMS: found 210.11276, C\(_{11}\)H\(_{16}\)NO\(_3\) requires 210.11302.

(1-(tert-Butoxy)-2-nitroethyl)benzene 441

\[
\begin{align*}
\text{O}^\text{Bu} & \\
& \text{NO}_2
\end{align*}
\]

A 0.53 M solution of \textsuperscript{1}BuONa in \textsuperscript{1}BuOH (1.90 mL, 1.00 mmol) was added at rt to a solution of \(\beta\)-nitrostyrene (149 mg, 1.00 mmol) in THF (10 mL) and the mixture turned yellow instantly. The mixture was stirred at this temperature for 5 min and then acetic acid (4.00 \(\mu\)L, 6.00 mmol) was added, the mixture stirred for 5 min and then poured into water (20 mL). The mixture was extracted with DCM (3x10 mL), the combined organics washed with brine (10 mL), dried over MgSO\(_4\) and evaporated in vacuo to give crude nitroalkane 441. Purification by flash column chromatography (Petrol:Et\(_2\)O 9:1) gave nitroalkane 441 (150 mg, 63%) as a colourless oil; \(R_f\) 0.58 (Petrol:Et\(_2\)O 9:1); IR \(\nu_{\text{max}}\) (thin film) 2974 w (C-H), 1553 s (N=O), 1494 w, 1454 w, 1418 w, 1379 m (N-O), 1336 w, 1324 w, 1143 w, 1122 w, 1095 m, 1062 m, 1029 w, 976 m, 762 m, 717 m, 699 s cm\(^{-1}\); \textsuperscript{1}H NMR (600 MHz) \(\delta\) 1.07 (3H, d, \(J = 6.2\), C\(\text{H}_3\)), 1.13 (3H, d, \(J = 6.2\), C\(\text{H}_3\)), 3.56 (1H, sept, \(J = 6.1\), C\(\text{H}(\text{CH}_3)_2\)), 4.36 (1H, dd, \(J = 12.7\), 3.3, C\(\text{H}_2\text{NO}_2\)), 4.57 (1H, dd, \(J = 12.6\), 10.3, C\(\text{H}_2\text{NO}_2\)), 5.17 (1H, dd, \(J = 10.2\), 3.2, C\(\text{HOCCH}\)), 7.35 (1H, m, C\(\text{H Arom.}\)), 7.40 (4H, m, C\(\text{H Arom.}\)); \textsuperscript{13}C NMR (150 MHz) \(\delta\) 20.8 (C\(\text{H}_3\)), 23.2 (CH\(_3\)), 70.4 (CH\((\text{CH}_3)_2\)), 75.8 (OCH\(_2\text{CH}_2\)), 80.8 (CH\(_2\text{NO}_2\)), 126.7 (CH Arom.), 128.8 (CH Arom.), 128.9 (CH Arom.), 137.5 (Cq Arom.); m/z (CI\textsuperscript{+}) 210 (M+H\textsuperscript{+}, 6%), 162 (M\textsuperscript{+}-HNO\(_2\), 27%), 149 (M\textsuperscript{+}-CH\(_2\text{NO}_2\), 61%), 107 (PhCHO+H\textsuperscript{+}, 100%), 104 (PhCH=CH\(_2\)\textsuperscript{+}, 72%); HRMS: found 210.11264, C\(_{11}\)H\(_{16}\)NO\(_3\) requires 210.11273.
vacuo to give crude nitroalkane 441. Purification by flash column chromatography (Petrol:Et₂O 9:1) gave nitroalkane 441 (89 mg, 40%) as a white solid, mp. 45-46 °C; Rₐ 0.57 (Petrol:Et₂O 9:1); IR νₘₐₓ (thin film) 2977 w (C-H), 1555 s (N=O), 1455 w, 1379 m (N-O), 1190 m, 1092 m, 1066 m, 965 w, 722 w, 701 m cm⁻¹; ¹H NMR (600 MHz) δ 1.10 (9H, s, C₃H₃), 4.32 (1H, dd, J = 12.0, 3.3, CH₂NO₂), 4.49 (1H, dd, J = 12.0, 10.2, CH₂NO₂), 5.27 (1H, dd, J = 10.1, 3.2, OCH), 7.31-7.41 (5H, m, CH Arom.); ¹³C NMR (150 MHz) δ 28.3 (C₃H₃), 72.0 (OCH), 75.5 (Cq), 81.9 (CH₂NO₂), 126.2 (CH Arom.), 128.3 (CH Arom.), 128.7 (CH Arom.), 140.2 (Cq Arom.); m/z (Cl⁺) 224 (M+H⁺, 6%), 163 (M+H⁺-CH₃NO₂, 65%), 150 (M+H⁺-tBuOH, 26%), 107 (PhCHO+H⁺, 100%); HRMS: found 224.12912, C₁₂H₁₈N₂O₃ requires 224.12867; Anal. Cald. For C₁₂H₁₇NO₃: C, 64.55, H, 7.67, N, 6.27. Found C, 64.76, H, 7.79, N, 6.07%.

2,4-Dimethoxy-N-(2-nitro-1-phenylethyl)aniline 442

![2,4-Dimethoxy-N-(2-nitro-1-phenylethyl)aniline](image)

To a solution of β-nitrostyrene (149 mg, 1.00 mmol) in dry DCM (5 mL) was added 2,3-dimethoxyaniline (184 mg, 1.20 mmol) at rt and the mixture was stirred overnight until no more nitroalkene was observed (TLC, 19 h). The mixture was then evaporated in vacuo and purification by flash column chromatography (Petrol:EtOAc 4:1) gave the aniline 442 (212 mg, 70%) as a yellow oil; Rₐ 0.38 (Petrol:EtOAc 4:1); ¹H NMR (600 MHz) δ 3.72 (3H, s, OC₃H₃), 3.85 (3H, s, OC₃H₃), 4.66 (1H, br. s, NH), 4.70 (1H, dd, J = 12.3, 5.5, CH₂NO₂), 4.73 (1H, dd, J = 12.2, 8.3, CH₂NO₂), 5.13 (1H, dd, J = 8.0, 5.9, PhCHβ), 6.31 (1H, dd, J = 8.8, 2.6, CH Arom.), 6.45 (2H, d, J = 2.5, CH Arom.), 7.32 (1H, m, CH Arom.), 7.39 (4H, m, CH Arom.); ¹³C NMR (150 MHz) δ 55.6 (OCH₃), 55.6 (OCH₃), 57.2 (OCH₃), 80.1 (CH₂), 99.2 (CHCH₂), 103.5 (CH Arom.), 111.9 (CH Arom.), 126.5 (CH Arom.), 128.5 (CH Arom.), 129.2 (CH Arom.), 129.6 (Cq Arom.), 138.1 (Cq Arom.), 148.3 (Cq Arom.), 152.8 (Cq Arom.). Data in agreement with that reported.⁶⁰
In a 10 mL round-bottom flask was added β-nitrostyrene (149 mg, 1.00 mmol), aniline (110 µL, 1.20 mmol) and H₂O (4 mL) and the mixture was stirred vigorously for 2 h. The mixture was then extracted with DCM (3×10 mL), dried over MgSO₄ and evaporated in vacuo. Purification by flash column chromatography (Petrol:Et₂O 9:1) gave nitroalkane **443** (163 mg, 67%) as a yellow oil, Rₚ 0.28 (Petrol:Et₂O 9:1); ¹H NMR (600 MHz) δ 4.44 (1H, d, J = 6.6, NH), 4.73 (2H, d, J = 6.7, CH₂), 5.21 (1H, q, J = 6.9, CH), 6.65 (2H, d, J = 8.0, CH Arom.), 6.78 (1H, t, J = 7.4, CH Arom.), 7.18 (2H, t, J = 7.9, CH Arom.), 7.36 (1H, m, CH Arom.), 7.42 (4H, m, CH Arom.); ¹³C NMR (150 MHz) δ 56.5 (CH), 79.9 (CH₂), 113.8 (CH Arom.), 118.8 (CH Arom.), 126.4 (CH Arom.), 128.6 (CH Arom.), 129.2 (CH Arom.), 129.3 (CH Arom.), 137.6 (Cq Arom.), 145.6 (Cq Arom.). Data in agreement to that reported.

**4-Nitro-N-(2-nitro-1-phenylethyl)aniline 444**

To a solution of para-nitroaniline (138 mg, 1.00 mmol) in dry THF (10 mL) cooled at -78 ºC, was added nBuLi (400 µL, 2.5 M in hexane, 1.00 mmol) and the mixture stirred for 10 min, before a solution of β-nitrostyrene (149 mg, 1.00 mmol) in dry THF (2 mL) was added dropwise. The mixture was stirred at this temperature for 10 min and then let to warm to rt and stirred until complete consumption of the starting nitroalkene (TLC, 1.5 h). Saturated aqueous NaHCO₃ solution (10 mL) was then added and the mixture extracted with DCM (3×10 mL), dried over MgSO₄ and evaporated in vacuo. Purification by flash column chromatography (Petrol:EtOAc 4:1) gave nitroalkane **444** (129 mg, 45%) as a yellow oil; Rₚ 0.21 (Petrol:EtOAc 4:1); IR νmax (thin film) 3365 br (N-H), 3065 w (C-H), 2922 w (C-H), 1596 s (C=C), 1551 s (N=O), 1503 m, 1476 m, 1378 w (N-O), 1302 s, 1277 s, 1184 m, 1110 s, 833 m, 752 m, 698 s cm⁻¹; ¹H NMR (600 MHz) δ 4.79 (2H, m, CH₂NO₂), 5.28 (1H, m, CHNH)
5.40 (1H, d, J = 6.5, NH), 6.59 (2H, app. d, J = 8.9, CH<sub>a</sub>), 7.36-7.44 (5H, m, CH Arom.), 8.05 (2H, app. d, J = 8.9, CH<sub>a</sub>); 13<sup>C</sup> NMR (150 MHz) δ 56.0 (CH<sub>N</sub>), 79.6 (CH<sub>2</sub>NO<sub>2</sub>), 112.5 (CH<sub>a</sub>), 126.2 (CH<sub>a</sub>), 126.2 (CH Arom.), 129.2 (CH Arom.), 129.2 (CH Arom.), 129.6 (CH Arom.), 135.9 (C<sub>a</sub>), 139.3 (C<sub>q</sub> Arom.), 151.0 (C<sub>a</sub>); m/z (EI+) 287 (M<sup>+</sup>, 25%), 227 (85%), 181 (17%), 138 (24%), 104 (100%); HRMS: found 287.09031, C<sub>14</sub>H<sub>13</sub>N<sub>3</sub>O<sub>4</sub> requires 287.09005.

**N-(2-Nitro-1-phenylethyl)morpholine 445**

![Morpholine](image)

To a solution of β-nitrostyrene (149 mg, 1.00 mmol) in DCM (5 mL) was added morpholine (87 μL, 1.0 mmol) followed by Sm(OTf)<sub>3</sub> (1 mg, 0.2 mol%) and the mixture was stirred at rt overnight until the nitroalkene was consumed (TLC, 24 h). DCM (10 mL) was then added, the mixture washed with H<sub>2</sub>O (10 mL) and brine (10 mL), dried over MgSO<sub>4</sub> and evaporated in vacuo to give nitroalkane 445 (222 mg, 94%) as a red oil, used without further purification; R<sub>f</sub> 0.46 (Petrol:EtOAc 4:1); 1<sup>H</sup> NMR (600 MHz) δ 2.36 (2H, m, NC<sub>H</sub>), 2.52 (2H, m, NCH), 3.64 (4H, m, OCH<sub>2</sub>), 4.34 (1H, dd, J = 9.5, 5.8, CH), 4.57 (1H, dd, J = 12.3, 5.8, CH<sub>2</sub>NO<sub>2</sub>), 4.99 (1H, dd, J = 12.3, 9.5, CH<sub>2</sub>NO<sub>2</sub>), 7.20 (2H, m, CH Arom.), 7.37 (3H, m, CH Arom.); 13<sup>C</sup> NMR (150 MHz) δ 49.8 (NCH<sub>2</sub>), 66.9 (OCH<sub>2</sub>), 66.9 (CH), 79.6 (CH<sub>2</sub>NO<sub>2</sub>), 128.3 (CH Arom.), 128.6 (CH Arom.), 129.3 (CH Arom.), 133.6 (C<sub>q</sub> Arom.). Data in agreement to that reported.

**1-(2-nitro-1-phenylethyl)-1H-benzo[d][1,2,3]triazole 446**

![Triaazole](image)

To a solution of β-nitrostyrene 380 (74 mg, 0.50 mmol) in DCM (5 mL) was added 1H-benzo[d][1,2,3]triazole (65 mg, 0.55 mmol) followed by Et<sub>3</sub>N (6 μL, 10 mol%)
and the mixture was stirred at rt until complete consumption of the nitroalkene (TLC, 19 h). The mixture was then evaporated in vacuo to give crude nitroalkane 446. Purification by flash column chromatography (Petrol:Et₂O 7:3) gave nitroalkane 446 (111 mg, 83%) as a colourless oil, Rₚ 0.45 (Petrol:Et₂O 7:3); ¹H NMR (600 MHz) δ 5.16 (1H, dd, J = 14.8, 4.8, CH₂NO₂), 5.95 (1H, dd, J = 14.6, 9.8, CH₂NO₂), 6.60 (1H, dd, J = 9.8, 4.8, CHN), 7.36 (2H, m, CH Arom.), 7.43 (3H, m, CH Arom.), 8.07 (1H, d, J = 8.4, CH Arom.); ¹³C NMR (150 MHz) δ 59.7 (CHN), 76.5 (CH₂NO₂), 109.3 (CH Arom.), 120.1 (CH Arom.), 124.5 (CH Arom.), 126.8 (CH Arom.), 128.0 (CH Arom.), 129.5 (CH Arom.), 129.7 (CH Arom.), 132.6 (C₉triazole), 133.9 (C₉triazole), 146.1 (Cq Arom.). Data in agreement with that reported.

3-(2-Nitro-1-phenylethyl)oxazolidin-2-one 447¹⁹⁰

To a mixture of 2-oxazolidinone (87 mg, 1 mmol), ¹BuOK (112 mg, 1 mmol) and 18-crown-6 (264 mg, 1.00 mmol) was added dry THF (5 mL) and the mixture was stirred at rt for 1 h. The mixture was then cooled to -78 °C and a solution of β-nitrostyrene (149 mg, 1.00 mmol) in THF (5 mL) was added and the mixture stirred at this temperature until complete consumption of the starting material (TLC, 30 min). A saturated aqueous solution of NH₄Cl (20 mL) was then added and the mixture warmed to rt and extracted with Et₂O (3x20 mL), dried over MgSO₄ and evaporated in vacuo. Purification by flash column chromatography (Petrol:Me₂CO 7:3) gave nitroalkane 447 (213 mg, 90%) as a colourless oil, Rₚ 0.50 (Petrol:Me₂CO 3:2); IR νₘₐₓ (thin film) 2976 w (C-H), 2925 w (C-H), 1740 s (C=O), 1553 s (N=O), 1482 w, 1419 m, 1380 m (N-O), 1248 m, 1111 w, 1076 w, 1047 w, 761 m, 733 s cm⁻¹; ¹H NMR (600 MHz) δ 3.36 (1H, dt, J = 8.0, 8.8, NCH₂), 3.61 (1H, m, NCH₂), 4.29 (2H, m, OCH₂), 4.86 (1H, dd, J = 5.4, 13.0, CH₂NO₂), 5.28 (1H, dd, J = 10.3, 13.0, CH₂NO₂), 5.58 (1H, dd, J = 5.4, 10.3, CHN), 7.31-7.35 (2H, m, CH Arom.), 7.37-7.43 (3H, m, CH Arom.); ¹³C NMR (150 MHz) δ 42.0 (CH₂N), 55.7 (CHN), 62.2 (OCH₂), 74.5 (CH₂NO₂), 127.3 (CH Arom.), 129.3 (CH Arom.), 133.6 (Cq Arom.), 157.6 (C=O), one CH peak missing; m/z (Cl⁺) 237 (M+H⁺, 100%), 176 (M⁺-CH₃NO₂,
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67%); HRMS: found 237.08724, C$_{11}$H$_{13}$N$_{2}$O$_{4}$ requires 237.08753; Anal. Cald. For C$_{11}$H$_{13}$N$_{2}$O$_{4}$: C, 55.93, H, 5.12, N, 11.86. Found C, 56.19, H, 5.23, N, 11.60%.

Butyl(2-nitro-1-phenylethyl)sulfane 448$^{261}$

To a stirred solution of β-nitrostyrene (74 mg, 0.50 mmol) in ethanol (1 mL) was added 1-butanethiol (53 μL, 0.50 mmol) at rt followed by Et$_3$N (4 μL, 5 mol%) when the mixture was instantly decolorized and after 5 min of stirring the mixture was evaporated to give pure nitroalkane 448 (114 mg, 95%) as a colourless oil, used without further purification; R$_f$ 0.63 (Petrol:Et$_2$O 9:1); IR $\nu_{\text{max}}$ (thin film) 2959 w (C-H), 2930 w, 2873 w. 1555 (N=O), 1455 w, 1376 m (N-O), 747 w, 699 m cm$^{-1}$; $^1$H NMR (600 MHz) δ 0.87 (3H, t, $J = 7.4$, C$_{3}$H$_{3}$), 1.35 (2H, m, C$_{2}$H$_{2}$CH$_{3}$), 1.53 (2H, qui., $J = 7.6$, CH$_{2}$), 2.45 (2H, t, $J = 7.4$, SCH$_{2}$), 4.56 (1H, t, $J = 7.9$, SCH), 4.76 (2H, d, $J = 7.8$, CH$_{2}$NO$_{2}$), 7.30-7.38 (5H, m, CH Arom.); $^{13}$C NMR (150 MHz) δ 13.5 (CH$_{3}$), 21.8 (CH$_{2}$CH$_{3}$), 31.1 (CH$_{2}$), 31.3 (CH$_{2}$), 46.5 (CHS), 79.3 (CH$_{2}$NO$_{2}$), 127.6 (CH Arom.), 128.4 (CH Arom.), 129.0 (CH Arom.), 137.4 (Cq Arom.); m/z (CI$^+$) 240 (M+H$^+$, 100%), 193 (M$^-$-NO$_{2}$, 56%), 179 (69%), 150 (M$^-$-BuS, 67%); HRMS: found 240.10582, C$_{12}$H$_{18}$NO$_{2}$S requires 240.10617; Anal. Cald. For C$_{12}$H$_{17}$NO$_{2}$S: C, 60.22, H, 7.16, N, 5.85. Found C, 60.32, H, 7.21, N, 5.92%.

(2-Nitro-1-phenylethyl)(phenyl)sulfane 449$^{261}$

To a stirred solution of β-nitrostyrene (74 mg, 0.50 mmol) in ethanol (2 mL) was added thiophenol (51 μL, 0.50 mmol) at rt, followed by Et$_3$N (4 μL, 5 mol%). The mixture was instantly decolourised and after 5 min of stirring the mixture was evaporated to give pure nitroalkane 449 (125 mg, 97%) as a colourless oil, used without further purification; R$_f$ 0.67 (Petrol:Et$_2$O 9:1); $^1$H NMR (600 MHz) δ 4.73
(1H, dd, J = 12.8, 6.0, SCH), 4.86 (1H, m, CH₂NO₂), 4.91 (1H, m, CH₂NO₂), 7.27-7.44 (10H, m, CH Arom.); ¹³C NMR (150 MHz) δ 49.7 (SJCH), 78.4 (C₂H), 127.6 (CH Arom.), 128.5 (CH Arom.), 128.7 (CH Arom.), 128.9 (CH Arom.), 129.3 (CH Arom.), 131.7 (Cq Arom.), 133.7 (CH Arom.), 136.2 (Cq Arom.). Data in agreement with that reported.²⁶⁹

(2-Nitro-1-(phenylsulfonyl)ethyl)benzene 451²⁷⁰

To a solution of thioether 449 (259 mg, 1.00 mmol) in MeOH (5 mL), cooled to 0 °C, was added Oxone® (923 mg, 1.50 mmol) in H₂O (10 mL) and the resulting suspension was stirred for 1 h, then left to warm to rt and stirred overnight (22 h). After completion H₂O (10 mL) was added and the mixture extracted with DCM (3x10 mL). The combined organics were then washed with brine (10 mL), dried over MgSO₄ and evaporated in vacuo to give pure sulfone 451 (301 mg, 97%) as a white solid used without further purification, mp. 180-181 °C; Rf 0.49 (Petrol:Et₂O 4:1); IR νmax (thin film) 3068 w (C-H), 3009 w (C-H), 2956 w (C-H), 1553 s (N=O), 1496 w, 1447 m, 1417 m, 1374 m (N-O), 1360 w, 1298 s, 1280 m, 1143 s, 1080 m, 852 w, 760 m, 727 s, 700 s, 688 s cm⁻¹; ¹H NMR (600 MHz) δ 4.99 (1H, dd, J = 10.1, 4.7, CH₂SO₂), 5.10 (1H, dd, J = 14.0, 10.0, CH₂NO₂), 5.37 (1H, dd, J = 14.0, 4.6, CH₂NO₂), 7.14 (2H, m, CH Arom.), 7.29 (2H, m, CH Arom.), 7.36 (1H, m, CH Arom.), 7.45 (2H, m, CH Arom.), 7.52 (2H, m, CH Arom.), 7.63 (1H, m, CH Arom.); ¹³C NMR (150 MHz) δ 67.9 (CHSO₂), 72.7 (CH₂NO₂), 128.7 (Cq Arom.), 129.0 (CH Arom.), 129.1 (CH Arom.), 129.4 (CH Arom.), 130.0 (CH Arom.), 134.5 (CH Arom.), 135.8 (Cq Arom.); m/z (CI⁻) 292 (M⁻, 30%), 251 (11%), 186 (13%), 150 (100%); HRMS: found 292.06466, C₁₄H₁₃NO₄S requires 292.06435; Anal. Cald. For C₁₄H₁₃NO₄S: C, 57.72, H, 4.50, N, 4.81. Found C, 57.71, H, 4.40, N, 4.72%.
(2-Nitro-1-phenylethyl)diphenylphosphine oxide 450\textsuperscript{271}

![Structural formula of compound](image)

To a solution of \(\beta\)-nitrostyrene 380 (74 mg, 0.50 mmol) in THF (2 mL) at rt was added diphenylphosphine oxide (101 mg, 0.50 mmol) followed by Et\(_3\)N (4 \(\mu\)L, 5 mol \%) and the mixture was stirred at rt until the nitroalkene was consumed (TLC, 24 h). After completion, the mixture was evaporated to give crude phosphine oxide 450. Purification by flash column chromatography (Petrol:Me\(_2\)CO 1:1) gave phosphine oxide 450 (157 mg, 89%, lit. 86%) as a white solid, mp. 206-207\(^\circ\)C (lit. 208-209\(^\circ\)C); \(R_f\) 0.61 (Petrol:Me\(_2\)CO 1:1); \(^1\)H NMR (600 MHz) \(\delta\) 4.42 (1H, m, \(\text{CH}\)), 4.76 (1H, m, \(\text{CH}_2\text{NO}_2\)), 5.12 (1H, m, \(\text{CH}_2\text{NO}_2\)), 7.21-7.28 (7H, m, \(\text{CH}\) Arom.), 7.39-7.44 (3H, m, \(\text{CH}\) Arom.), 7.62 (3H, m, \(\text{CH}\) Arom.), 7.99 (2H, m, \(\text{CH}\) Arom.); \(^{13}\)C NMR (150 MHz) \(\delta\) 45.8 (d, \(J=64.0\), \(\text{CH}\)), 72.7 (d, \(J=5.9\), \(\text{CH}_2\text{NO}_2\)), 128.2 (d, \(J=2.5\), \(\text{CH}\) Arom.), 128.3 (d, \(J=12.3\), \(\text{CH}\) Arom.), 128.7 (d, \(J=1.7\), \(\text{CH}\) Arom.), 129.3 (d, \(J=11.6\), \(\text{CH}\) Arom.), 129.4 (d, \(J=5.1\), \(\text{CH}\) Arom.), 129.6 (d, \(J=8.6\), Cq Arom.), 130.3 (Cq Arom.), 130.9 (d, \(J=9.2\), \(\text{CH}\) Arom.), 131.1 (d, \(J=8.8\), \(\text{CH}\) Arom.), 131.6 (d, \(J=5.6\), Cq Arom.), 132.0 (d, \(J=2.8\), \(\text{CH}\) Arom.), 132.7 (d, \(J=2.8\), \(\text{CH}\) Arom.). Data in agreement to that reported.\textsuperscript{271}

3.4.3.4 Nitro-Mannich reaction to \(\beta\)-nitrostyrene adducts

**General procedure F for the synthesis of \(\beta\)-nitroamides 452**

A solution of nitroalkane (0.500 mmol) in THF (5 mL), was cooled to -78 \(^\circ\)C and \(^9\)BuLi (0.550 mmol, of a 2.5 M solution in hexanes, 1.1 equiv.) was added dropwise. The orange mixture was stirred at this temperature for 10 min, before the corresponding imine (1.00 mmol, 2.0 equiv.) in THF (2 mL) was added via cannula. The mixture was stirred for 10 min before a 1:1 vol. mixture of TFA:THF (TFA 1.75 mmol, 3.5 equiv.) was added dropwise. The mixture was stirred at this temperature for a further 1 h, then warmed to rt over 5 min and quenched with saturated aqueous NaHCO\(_3\) (10 mL) extracted with Et\(_2\)O (3x10 mL), dried over MgSO\(_4\) and concentrated \textit{in vacuo} to give crude \(\beta\)-nitroamine. A sample was taken for \(^1\)H NMR
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analysis and the rest of the crude product was dissolved in DCM (6 mL), cooled to -78 °C and then pyridine (140 µL, 1.50 mmol) and trifluoroacetic anhydride (240 µL, 1.50 mmol) were added. The mixture was then warmed to rt and stirred for a further 3 h. The mixture was then washed with aqueous HCl 2 M (3x10 mL) and brine (10 mL), dried over MgSO₄ and concentrated in vacuo to leave crude trifluoroacetamide, which was purified further with flash column chromatography.

\[ N-((1R^*,2S^*,3R^*)-3-(1H-indol-3-yl)-2-nitro-1,3-diphenylpropyl)-2,2,2-trifluoro-N-(4-methoxyphenyl)acetamide 455 \]

Prepared by general procedure F. Nitroalkane 429 (123 mg, 0.460 mmol), \(^{9}\)BuLi (184 µL, 2.5 M, 0.460 mmol), imine 281 (194 mg, 0.920 mmol) and TFA (123 µL, 1.61 mmol) afforded after TFA-protection crude trifluoroacetamide 455. Purification by flash column chromatography (Petrol:Et₂O 1:1) gave trifluoroacetamide 455 (133 mg, 50%) as a colourless oil; \( \text{R} \text{f} \) 0.34 (Petrol:Et₂O 1:1); IR \( \nu_{\text{max}} \) (thin film) 3420 w (N-H), 3063 w, 3034 w, 2927 w, 2840 w (C-H), 1691 s (C=O), 1606 w, 1555 s (N=O), 1510 w, 1497 m, 1456 m, 1414 w, 1367 w (N-O), 1301 w, 1255 m, 1206 s, 1180 s, 1157 s, 1112 w, 1033 m, 840 m, 756 m, 734 s, 699 s cm\(^{-1}\); \(^1\)H NMR (600 MHz) \( \delta \) 3.74 (3H, s, OC\(_3\)H₃), 4.91 (1H, d, \( J = 6.7 \), PhCHCq), 5.92 (1H, dd, \( J = 8.9, 2.8 \), CH Arom.), 6.25 (1H, d, \( J = 9.2 \), CHNC=O), 6.40 (1H, dd, \( J = 6.6, 9.2 \), CHNO₂), 6.49 (1H, dd, \( J = 8.8, 3.0 \), CH Arom.), 6.63 (1H, dd, \( J = 8.8, 3.0 \), CH Arom.), 6.79 (1H, dd, \( J = 8.7, 2.7 \), CH Arom.), 6.92 (2H, dd, \( J = 8.2, 1.1 \), CH Arom.), 7.01-7.34 (9H, m, CH Arom.), 7.41 (3H, m, CH Arom.), 6.92 (1H, d, \( J = 2.5 \), CH Arom.), 8.25 (1H, br. s, NH); \(^{13}\)C NMR (150 MHz) \( \delta \) 43.9 (PhCH), 55.3 (OCH₃), 62.8 (CHNC=O), 89.1 (CHNO₂), 111.2 (CH Arom.), 113.4 (CH Arom.), 113.6 (CH Arom.), 114.7 (Cq Arom.), 116.1 (q, \( J = 289.0, \) CF₃), 118.8, 120.0, 122.3, 122.6, 127.7, 128.4, 128.6, 128.7, 129.3, 129.6, 131.1 and 132.5 (CH Arom.), 126.4, 126.9, 132.8, 136.0 and 138.3 (Cq Arom.), 158.3 (q, \( J = 35.5, \) C=O), 160.1 (Cq Arom); \(^{19}\)F NMR (282 MHz) \( \delta \) -67.60 (3F, s, CF₃); \( m/z \)
(EI) 573 (M⁺, 27%), 308 (M⁺-NO₂-PMP-NH-TFA, 100%), 206 (PhCH⁺-(Indole), 32%); HRMS: found 573.18730, C₃₂H₂₆F₃N₃O₄ requires 573.18699.

2,2,2-Trifluoro-Ν-(4-methoxyphenyl)-Ν-((1R*,2S*,3R*)-2-nitro-1,3-diphenyl-3-(2,4,6-trimethoxyphenyl)propyl)acetamide 456

Prepared by general procedure F. Nitroalkane 430 (113 mg, 0.360 mmol), nBuLi (144 µL, 2.5 M, 0.360 mmol), imine 281 (150 mg, 0.720 mmol) and TFA (96 µL, 1.26 mmol) afforded after TFA-protection crude trifluoroacetamide 456. Purification by flash column chromatography (Petrol:Et₂O 4:1) gave trifluoroacetamide 456 (185 mg, 83%) as a white solid, mp. 185-186 °C; Rf 0.13 (Petrol:Et₂O 4:1); IR υmax (thin film) 3031 w (C-H), 2939 w (C-H), 2841 w (C-H), 1696 s (C=O), 1605 s, 1590 s, 1550 s (N=O), 1510 s, 1495 m, 1455 s, 1418 w, 1365 w (N-O), 1254 w, 1203 s, 1180 s, 1150 s, 1122 s, 1059 m, 1035 m, 952 w, 814 m, 735 s, 699 s cm⁻¹; ¹H NMR (600 MHz) δ 3.30 (3H, br. s, OC₃H₃), 3.72 (3H, s, OC₃H₃), 3.77 (3H, s, OC₃H₃), 4.05 (3H, br. s, OC₃H₃), 5.14 (1H, d, J = 11.5, PhCHAr), 5.70-6.20 (2H, br. s, CH Arom.), 5.78 (1H, d, J = 6.8, CHNC=O), 6.01 (1H, dd, J = 9.0, 2.9, CH Arom.), 6.35 (1H, dd, J = 9.0, 3.1, CH Arom.), 6.73 (2H, d, J = 7.6, CH Arom.), 6.76 (1H, dd, J = 8.8, 2.9, CH Arom.), 7.01 (2H, app. t, J = 7.6, CH Arom.), 7.04 (1H, m, CH Arom.), 7.13 (1H, dd, J = 11.5, 6.8, CHNO₂), 7.15-7.19 (4H, m, CH Arom.), 7.46 (2H, app. d, J = 7.6, CH Arom.); ¹³C NMR (150 MHz) δ 41.2 (PhCHCHNO₂), 55.3 (OCH₃), 65.2 (CHNC=O), 87.0 (CHNO₂), 90.0 (CH Arom.), 107.3 (Cq Arom.), 112.9 (CH Arom.), 113.4 (CH Arom.), 116.1 (CF₃, q, J = 288.7), 126.7 and 127.4 (CH Arom.), 127.7 (Cq Arom.), 127.9, 128.2, 128.3 and 131.6 (CH Arom.), 131.6 (Cq Arom.), 131.7 and 132.7 (CH Arom.), 140.1 (Cq Arom.), 157.5 (O=CCF₃, q, J = 35.6), 159.5 and 160.6 (Cq Arom.); ¹⁹F NMR (282 MHz) δ -67.74 (3F, s, CF₃); m/z (ES⁺) 647 (M+Na⁺, 20%), 625 (M+H⁺, 15%), 578 (M⁺-NO₂, 15%), 457 (25%), 378 (15%), 359 (M⁺-NO₂-PMP-NH-TFA, 70%), 257 ((OMe)₃C₆H₃CH⁺Ph, 100%); HRMS: found 647.2003,
C\textsubscript{33}H\textsubscript{31}F\textsubscript{3}N\textsubscript{2}O\textsubscript{7}Na requires 647.1981; Anal. Cald. For C\textsubscript{22}H\textsubscript{26}N\textsubscript{2}O\textsubscript{5}: C, 63.46, H, 5.00, N, 4.48. Found C, 63.36, H, 4.96, N, 4.44%.

(4S*,5S*,6R*)-1-butyl-5-nitro-4,6-diphenylpiperidin-2-one 462\textsuperscript{195}

\begin{center}
\includegraphics[width=0.2\textwidth]{piperidinone.png}
\end{center}

In a 10 mL round bottom flask were added nitroalkane 433 (147 mg, 0.50 mmol), benzoic acid (92 mg, 0.75 mmol) and toluene (3 mL). Nitrogen was bubbled through the mixture for 10 min and then \textsuperscript{5}butyl amine (74 μL, 0.75 mmol) and benzaldehyde (76 μL, 0.75 mmol) were added. The reaction was heated to 70 °C in a sealed vessel and monitored by TLC. After 20 h the mixture was evaporated \textit{in vacuo} and dissolved in DCM (20 mL), then washed with aqueous HCl 2 M (3x10 mL), dried over MgSO\textsubscript{4} and concentrated \textit{in vacuo}. Purification by flash column chromatography (Petrol:EtOAc 4:1) gave piperidinone 462 (50 mg, 28%) as a white solid; mp. 210-211 °C; R\textsubscript{f} 0.29 (Petrol:EtOAc 4:1); IR \(\nu_{\text{max}}\) (thin film) 2984 w (C-H), 1729 s (C=C), 1635 m, 1455 m, 1378 m (N-O), 1276 m, 1240 m, 1178 s, 1074 m, 1055 m, 1018 m, 785 m, 747 s cm\textsuperscript{-1}; \textsuperscript{1}H NMR (600 MHz) \(\delta\) 0.86 (3H, t, \(J = 7.4\), CH\textsubscript{3}), 1.24 (2H, m, CH\textsubscript{2}CH\textsubscript{3}), 1.50 (2H, m, CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}), 2.54 (1H, m, NCH\textsubscript{2}), 2.82 (1H, dd, \(J = 13.2\), 17.4, O=CC\textsubscript{H}2), 2.90 (1H, dd, \(J = 4.8\), 17.4, O=CC\textsubscript{H}2), 3.73 (1H, ddd, \(J = 13.2\), 11.3, 4.8, CH\textsubscript{2}CHPh), 3.96 (1H, ddd, \(J = 13.7\), 9.7, 6.4, NCH\textsubscript{2}), 4.99 (1H, dd, \(J = 8.5\), 11.3, CHNO\textsubscript{2}), 5.05 (1H, d, \(J = 8.6\), NCHPh), 7.17-7.40 (10H, m, CH Arom.); \textsuperscript{13}C NMR (150 MHz) \(\delta\) 13.7 (CH\textsubscript{3}), 20.0 (CH\textsubscript{2}CH\textsubscript{3}), 28.7 (CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}), 37.6 (O=CC\textsubscript{H}2), 43.1 (CH\textsubscript{2}CHPh), 44.0 (NCH\textsubscript{2}), 64.3 (NCHPh), 94.7 (CHNO\textsubscript{2}), 126.9 (CH Arom.), 126.9 (CH Arom.), 128.5 (CH Arom.), 129.2 (CH Arom.), 129.4 (CH Arom.), 129.5 (CH Arom.), 136.6 (Cq Arom.), 136.7 (Cq Arom.), 168.2 (C=O); \(m/z\) (Cl\textsuperscript{+}) 353 (M+H\textsuperscript{+}, 100%), 306 (M\textsuperscript{-}-NO\textsubscript{2}, 50%), 216 (37%); HRMS: found 353.1863, C\textsubscript{21}H\textsubscript{24}N\textsubscript{2}O\textsubscript{3} requires 353.1865; Anal. Cald. For C\textsubscript{21}H\textsubscript{24}N\textsubscript{2}O\textsubscript{3}: C, 71.57, H, 6.86, N, 7.95. Found C, 71.27, H, 6.84, N, 7.79%. 

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N-(2-Hydroxy-2-phenylethyl)benzamide 465

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\begin{array}{c}
\text{O} \\
\text{H} \\
\text{N} \\
\text{O}
\end{array}
\]

Prepared by general procedure F. Nitroalcohol 435 (115 mg, 0.690 mmol), nBuLi (552 µL, 2.5 M, 1.38 mmol), imine 281 (291 mg, 1.38 mmol) and TFA (184 µL, 2.41 mmol) afforded after TFA-protection crude amide 465. Purification by flash column chromatography (Petrol:DCM 2:8) gave amide 465 (20 mg, 12%) as a white solid; mp. 145-146 °C (lit. 143-145 °C); Rf 0.45 (Petrol:DCM 2:8); IR \( \nu \text{max} \) (thin film) 3410 br (N-H or O-H), 3305 (N-H or O-H), 3061 w (C-H), 2933 w (C-H), 1635 s (C=O), 1618 s, 1545 s, 1061 s, 693 s cm\(^{-1}\); \(^1\)H NMR (600 MHz) δ 3.40 (1H, br, O-H), 3.53 (1H, ddd, \( J = 5.0, 7.9, 14.1, CH_2 \)), 3.94 (1H, ddd, \( J = 3.4, 7.1, 14.1, CH_2 \)), 4.98 (1H, dd, \( J = 3.3, 7.8, OCH_2OH \)), 6.64 (1H, br, NH), 7.27-7.60 (8H, m, C-H Arom.), 7.77 (2H, m, C-H Arom.); \(^13\)C NMR (150 MHz) δ 47.8 (C-H), 73.8 (OCH_2CH_3), 125.8 (CH Arom.), 127.0 (CH Arom.), 128.0 (CH Arom.), 128.6 (CH Arom.), 128.6 (CH Arom.), 131.7 (CH Arom.), 134.0 (Cq Arom.), 141.7 (Cq Arom.), 167.3 (C=O); \( m/z \) (CI\(^+\)) 242 (M+H\(^+\), 10%), 224 (M-OH\(^-\), 100%), 105 (31%); HRMS: found 242.11844, C\(_{15}\)H\(_{15}\)NO\(_2\) requires 242.11810. Data in agreement to the one reported.\(^{202}\)

2,2,2-Trifluoro-N-((1R\(^*\),2R\(^*\),3S\(^*\))-3-methoxy-2-nitro-1,3-diphenylpropyl)-N-(4-methoxyphenyl)acetamide 472

\[
\begin{array}{c}
\text{O} \\
\text{CF}_3 \\
\text{N} \\
\text{O} \\
\text{Me} \\
\text{O} \\
\text{NO}_2
\end{array}
\]

Prepared by general procedure F. Nitroalkane 436 (44 mg, 0.24 mmol), nBuLi (96 µL, 2.5 M, 0.24 mmol), imine 281 (101 mg, 0.480 mmol) and TFA (64 µL, 0.840 mmol) afforded after TFA-protection crude trifluoroacetamide 472. Purification by flash column chromatography (Petrol:Et\(_2\)O 4:1) gave trifluoroacetamide 472 (83 mg, 71%) as a white solid; mp. 69-70 °C; Rf 0.32 (Petrol:Et\(_2\)O 4:1); IR \( \nu \text{max} \) (thin film) 2937 w (C-H), 2837 w (C-H), 1692 s (C=O), 1557 s (N=O), 1509 s, 1457 w, 1254 m, 1203 s, 1182 s, 1151 s, 1096 m, 1026 m, 842 m, 754 m, 733 m, 699 s, 659 m cm\(^{-1}\); \(^1\)H NMR
(600 MHz) δ 3.24 (3H, s, CHOCH₃), 3.82 (3H, s, OCH₃), 5.06 (1H, d, J = 8.4, CHOCH₃), 5.38 (1H, dd, J = 10.9, 8.5, CHNO₂), 6.01 (1H, dd, J = 8.8, 2.6, CH Arom.), 6.54 (1H, dd, J = 8.8, 3.0, CH Arom.), 6.89 (1H, d, J = 11.0, CHN), 6.92 (2H, m, CH Arom.), 7.00 (1H, dd, J = 8.7, 3.0, CH Arom.), 7.16 (2H, app t, J = 7.7, CH Arom.), 7.25 (1H, m, CH Arom.), 7.36-7.44 (5H, m, CH Arom.), 7.73 (1H, dd, J = 8.8, 2.6, CH Arom.); ¹³C NMR (150 MHz) δ 55.4 (OCH₃), 57.0 (CHOCH₃), 61.7 (CHN), 84.7 (CHOCH₃), 89.5 (CHNO₂), 113.5 (CH Arom.), 113.6 (CH Arom.), 116.6 (q, J = 290.1, CF₃), 126.8 (Cq Arom.), 127.7 (CH Arom.), 128.4 (CH Arom.), 128.7 (CH Arom.), 129.3 (CH Arom.), 129.5 (CH Arom.), 131.4 (CH Arom.), 132.9 (Cq Arom.), 133.5 (CH Arom.), 135.6 (CH Arom.), 157.9 (q, J = 35.7, C=OCF₃), 160.1 (Cq Arom.); ¹⁹F NMR (282 MHz) δ -67.82 (3F, s, CF₃); m/z (EI⁺) 488 (M⁺, 5%), 219 (PMPNHTFA⁺, 8%), 149 (14%), 121 (PhCH-OMe⁺, 100%); HRMS: found 488.15642, C₂₂H₂₆N₂O₅ requires 488.15535; Anal. Cald. For C₂₂H₂₆N₂O₅: C, 61.47, H, 4.75, N, 5.74. Found C, 61.60, H, 5.05, N, 5.63%.

**N-((1R*,2R*,3S*)-3-ethoxy-2-nitro-1,3-diphenylpropyl)-2,2,2-trifluoro-N-(4-methoxyphenyl)acetamide 473**

Prepared by general procedure F. Nitroalkane 438 (110 mg, 0.560 mmol), ⁹BuLi (224 µL, 2.5 M, 0.560 mmol) imine 281 (236 mg, 1.12 mmol) and TFA (150 µL, 1.96 mmol) afforded after TFA-protection crude trifluoroacetamide 473. Purification by flash column chromatography (Petrol:Et₂O 4:1) gave trifluoroacetamide 473 (219 mg, 78%) as a yellow oil; Rₚ 0.36 (Petrol:Et₂O 4:1); IR ν_max (thin film) 2977 w (C-H), 1694 s (C=O), 1608 w, 1556 s (N=O), 1510 s, 1457 m, 1370 w (N-O), 1300 m, 1254 m, 1203 s, 1182 s, 1152 s, 1092 m, 1075 m, 1032 m, 912 w, 876 w, 843 m, 783 m, 755 m, 733 s, 699 s cm⁻¹; ¹H NMR (600 MHz) δ 1.17 (3H, t, J = 7.1, CH₃), 3.40 (2H, m, OCH₂CH₃), 3.82 (3H, s, OCH₃), 5.13 (1H, d, J = 8.4, CHO), 5.38 (1H, dd, J = 10.9, 8.5, CHNO₂), 6.01 (1H, dd, J = 9.1, 2.4, CH Arom.), 6.55 (1H, dd, J = 8.9, 3.1, CH Arom.), 6.83 (1H, d, J = 10.9, CHN), 6.92 (2H, m, CH Arom.), 7.00 (1H, dd, J = 8.8, 3.0, CH Arom.), 7.16 (2H, m, CH Arom.), 7.25 (2H, m, CH Arom.), 7.38 (5H, m,
\( \text{CH Arom.}, 7.74 \) (1H, dd, \( J = 8.7, 2.5, \text{CH Arom.} \); \(^{13}\text{C NMR (150 MHz) \( \delta \) 14.6 (CH\(_3\)), 55.4 (OCH\(_3\)), 61.7 (CHN), 65.2 (OCH\(_2\)CH\(_3\)), 83.2 (CHO), 89.9 (CHNO\(_2\)), 113.5 (CH Arom.), 113.6 (CH Arom.), 116.4 (q, \( J = 288.5, \text{CF}_3\)), 126.8 (Cq Arom.), 127.6 (CH Arom.), 128.4 (CH Arom.), 128.7 (CH Arom.), 129.2 (CH Arom.), 129.3 (CH Arom.), 131.7 (CH Arom.), 133.4 (Cq Arom.), 133.5 (CH Arom.), 136.4 (Cq Arom.), 157.7 (q, \( J = 35.0, C=O\)), 160.2 (Cq Arom.); \(^{19}\text{F NMR (282 MHz) \( \delta \) -67.31 (3F, s, CF\(_3\)); \( m/z \) (CI\(^+\)) 502 (M\(^+\), 27%), 410 (M\(^+\)-EtOH-NO\(_2\), 24%), 135 (100%); HRMS: found 502.17064, \( C_{26}H_{25}F_3N_2O_5 \) requires 502.17101.

\( N-((1R^*,2R^*,3S^*)-3-(benzyloxy)-2-nitro-1,3-diphenylpropyl)-2,2,2-trifluoro-N-(4-methoxyphenyl)acetamide 474 \)

\[
\begin{align*}
\text{O} & \equiv \text{CF}_3 \\
\text{N} & \equiv \text{O} \\
\text{Me} & \equiv \text{OCCH}_3 \\
\text{NO}_2 & \equiv \text{CH}_2 \\
\text{Ph} & \equiv \text{C}_6\text{H}_{4} \\
\text{Ph} & \equiv \text{C}_6\text{H}_{4} \\
\text{Ph} & \equiv \text{C}_6\text{H}_{4} \\
\text{Ph} & \equiv \text{C}_6\text{H}_{4}
\end{align*}
\]

Prepared by general procedure F. Nitroalkane \( 439 \) (160 mg, 0.620 mmol), \(^6\text{BuLi (248 \( \mu\)L, 2.5 M, 0.620 mmol), imine \( 281 \) (262 mg, 1.24 mmol) and TFA (166 \( \mu\)L, 2.17 mmol) afforded after TFA-protection crude trifluoroacetamide \( 474 \). Purification by flash column chromatography (Petrol:Et\(_2\)O 9:1) gave trifluoroacetamide \( 474 \) (224 mg, 64%) as a yellow oil; \( R_f \) 0.26 (Petrol:Et\(_2\)O 9:1); IR \( \nu_{\max} \) (thin film) 3035 w (C-H), 1696 s (C-O), 1557 s (N=O), 1510 s, 1456 w, 1348 w (N-O), 1300 w, 1254 m, 1206 s, 1183 s, 1169 s, 1156 s, 1069 w, 1029 w, 912 w, 842 w, 756 w, 734 m, 700 s cm\(^{-1}\); \(^1\text{H NMR (600 MHz) \( \delta \) 3.78 (3H, s, OCCH}_3\), 4.33 (1H, d, \( J = 10.9, \text{CH}_2\)), 4.53 (1H, d, \( J = 10.9, \text{CH}_2\)), 5.22 (1H, d, \( J = 6.7, \text{CHO}\)), 5.50 (1H, dd, \( J = 11.0, 6.8, \text{CHNO}_2\)), 5.96 (1H, dd, \( J = 8.8, 2.5, \text{Arom. CH}\)), 6.50 (1H, dd, \( J = 8.8, 3.0, \text{CH Arom.}\)), 6.70 (1H, d, \( J = 11.0, \text{CHN}\)), 6.82 (1H, dd, \( J = 8.8, 3.0, \text{CH Arom.}\)), 6.94 (2H, d, \( J = 7.4, \text{CH Arom.}\)), 7.17 (2H, m, \text{CH Arom.}), 7.25 (2H, m, \text{CH Arom.}), 7.30 (5H, m, \text{CH Arom.}), 7.47 (3H, m, \text{CH Arom.}), 7.52 (2H, m, \text{CH Arom.}); \(^{13}\text{C NMR (150 MHz) \( \delta \) 55.3 (OCH}_3\), 61.0 (CHN), 71.5 (CH\(_2\)), 81.7 (CHO), 90.0 (CHNO\(_2\)), 113.3 and 113.6 (CH Arom.), 116.1 (q, \( J = 288.7, \text{CF}_3\)), 126.4 (Cq Arom.), 127.9, 128.2, 128.4, 128.7, 128.9, 129.0, 129.3, 129.6, 131.4 and 133.2 (CH Arom.), 133.4, 135.4 and 136.3 (Cq Arom.), 157.8 (q, \( J = 35.2, C=O\)), 160.1 (Cq Arom.); \(^{19}\text{F NMR (282 MHz) \( \delta \) -67.31 (3F, s, CF\(_3\))}}

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δ -67.47 (3F, s, CF₃); m/z (CI⁺) 564 (M⁺, 100%), 410 (M⁺-BnOH-NO₂, 57%), 197 (28%); HRMS: found 564.18742, C₃₁H₂₇F₃N₂O₅ requires 564.18666.

2,2,2-Trifluoro-N-((1R*,2R*,3S*)-3-isoproxy-2-nitro-1,3-diphenylpropyl)-N-(4-methoxyphenyl)acetamide 475

Prepared by general procedure F. Nitroalkane 440 (95 mg, 0.45 mmol), nBuLi (180 µL, 2.5 M, 0.450 mmol), imine 281 (190 mg, 0.900 mmol) and TFA (121 µL, 1.58 mmol) afforded after TFA-protection crude trifluoroacetamide 475. Purification by flash column chromatography (Petrol:Et₂O 4:1) gave trifluoroacetamide 475 (186 mg, 80%) as a yellow oil; Rₚ 0.36 (Petrol:Et₂O 4:1); IR νmax (thin film) 2976 w (C-H), 1695 s (C=O), 1556 s (N=O), 1510 w, 1373 w (N-O), 1300 w, 1254 m, 1203 s, 1168 s, 1153 s, 1120 m, 1090 m, 1067 m, 1034 m, 911 w, 843 m, 757 m, 733 m, 700 s cm⁻¹; ¹H NMR (600 MHz) δ 1.16 (6H, d, J = 6.2, CH₃), 3.53 (2H, m, OCH(CH₃)₂), 3.83 (3H, s, OCH₃), 5.24 (1H, d, J = 7.7, CHO), 5.43 (1H, dd, J = 10.7, 7.7, CHNO₂), 6.07 (1H, d, J = 8.7, CH Arom.), 6.58 (1H, dd, J = 8.9, 3.0, CH Arom.), 6.75 (1H, d, J = 10.8, CHN), 6.95 (2H, m, CH Arom.), 6.99 (1H, dd, J = 8.8, 3.0, CH Arom.), 7.17 (2H, m, CH Arom.), 7.26 (2H, m, CH Arom.), 7.38 (5H, m, CH Arom.), 7.70 (1H, m, CH Arom.), ¹³C NMR (150 MHz) δ 19.6 (CH₃), 23.0 (CHCH₃), 55.4 (OCH₃), 61.1 (PhCHO), 69.3 (OCH(CH₃)₂), 80.2 (CHN), 90.4 (CHNO₂), 113.5 (CH Arom.), 113.6 (CH Arom.), 116.3 (q, J = 288.7, CF₃), 126.8 (Cq Arom.), 127.6 (CH Arom.), 128.4 (CH Arom.), 128.8 (CH Arom.), 129.1 (CH Arom.), 129.3 (CH Arom.), 131.7 (CH Arom.), 133.5 (CH Arom.), 133.7 (Cq Arom.), 136.5 (Cq Arom.), 157.5 (q, J = 35.4, C=O), 160.2 (Cq Arom.); ¹⁹F NMR (282 MHz) δ -67.24 (3F, s, CF₃); m/z (CI⁺) 516 (M⁺, 32%), 410 (M⁺-IPA-NO₂, 100%), 308 (24%); HRMS: found 516.18577, C₂₇H₂₇F₃N₂O₅ requires 516.18666.
2,2,2-Trifluoro-N-(4-methoxyphenyl)-N-((1R*,2S*,3S*)-2-nitro-3-((4-nitrophenyl)amino)-1,3-diphenylpropyl)acetamide 478

Prepared by general procedure F. Nitroalkane 444 (114 mg, 0.400 mmol), \(^9\)BuLi (160 µL, 2.5 M, 0.400 mmol), imine 281 (169 mg, 0.800 mmol) and TFA (31 µL, 0.400 mmol) afforded after TFA-protection crude trifluoroacetamide 478. Purification by flash column chromatography (Petrol:Me\(_2\)CO 4:1) gave trifluoroacetamide 478 (40 mg, 17%) as a yellow solid; mp. 141-142 °C, R\(_f\) 0.30 (Petrol:Me\(_2\)CO 4:1); IR \(\nu_{max}\) (thin film) 3332 w (N-H), 1693 m (C=O), 1595 m, 1558 m (N=O), 1510 m, 1287 s, 1258 s, 1209 s, 1180 s, 1160 s, 1038 m, 838 s, 754 m, 733 m, 698 s cm\(^{-1}\); \(^1\)H NMR (600 MHz) \(\delta\) 3.77 (3H, s, OC\(_3\)H\(_3\)), 5.33 (1H, dd, \(J\) = 9.4, 3.1, C\(_6\)HNO\(_2\)), 5.75 (1H, dd, \(J\) = 10.8, 3.1, C\(_6\)HNO\(_2\)), 5.97 (1H, app d, \(J\) = 8.8, C\(_6\)H Arom.), 6.18 (1H, d, \(J\) = 9.4, NH), 6.34 (1H, app d, \(J\) = 8.8, C\(_6\)H Arom.), 6.37 (1H, d, \(J\) = 10.8, CHNC=O), 6.54 (1H, dd, \(J\) = 8.8, 3.0, C\(_6\)H Arom.), 6.67 (1H, app d, \(J\) = 9.1, C\(_6\)H Arom.), 6.72 (1H, dd, \(J\) = 8.8, 3.1, C\(_6\)H Arom.), 7.00 (2H, m, C\(_6\)H Arom.), 7.24 (2H, app t, \(J\) = 7.3, C\(_6\)H Arom.), 7.33 (1H, app t, \(J\) = 7.5, C\(_6\)H Arom.), 7.40-7.48 (5H, m, C\(_6\)H Arom.), 8.09 (2H, app d, \(J\) = 9.1, C\(_6\)H Arom.); \(^{13}\)C NMR (150 MHz) \(\delta\) 55.5 (O\(_3\)CH), 60.4 (CHNC=O), 90.0 (CHNO\(_2\)), 112.5 (C\(_8\)H Arom.), 113.4 (C\(_8\)H Arom.), 113.7 (C\(_8\)H Arom.), 116.0 (q, \(J\) = 288.3, CF\(_3\)), 126.3, 127.0, 128.7, 128.9, 129.6, 129.8, 130.1 and 132.5 (C\(_8\)H Arom.), 133.2 (C\(_7\)Arom.), 135.0 (C\(_6\)Arom.), 139.6 (C\(_6\)Arom.), 150.8 (C\(_5\)Arom.), 158.8 (q, \(J\) = 35.8, C=OCH\(_3\)), 160.4 (C\(_7\)Arom.); \(^{19}\)F NMR (282 MHz) \(\delta\) -67.41 (3F, s, CF\(_3\)); m/z (EI) 593 (M-H\(^+\), 75%), 547 (M-HNO\(_2^+\), 100%); HRMS: found 593.1653, C\(_{30}\)H\(_{24}\)F\(_3\)N\(_4\)O\(_6\) requires 593.1648; Anal. Cald. For C\(_{30}\)H\(_{25}\)F\(_3\)N\(_4\)O\(_6\): C, 60.61, H, 4.24, N, 9.42. Found C, 60.33, H, 4.21, N, 9.39%.
\(N-((1R^*,2R^*,3S^*)-3-(1H\text{-benzo}[d][1,2,3]triazol-1-yl)-2-nitro-1,3-diphenylpropyl)-2,2,2\text{-trifluoro-}N-(4\text{-methoxyphenyl})\text{acetamide} 482\)

Prepared by general procedure F. Nitroalkane 446 (111 mg, 0.410 mmol), \(^{6}\)BuLi (164 \(\mu\)L, 2.5 M, 0.410 mmol), imine 281 (173 mg, 0.820 mmol) and TFA (110 \(\mu\)L, 1.44 mmol) afforded after TFA-protection crude trifluoroacetamide 482. Purification by flash column chromatography (Petrol:Et\(_2\)O 9:1) gave trifluoroacetamide 482 (23 mg, 10\%, 47\% based on recovered starting material) as a colourless oil; \(R_f\) 0.13 (Petrol:Et\(_2\)O 9:1); IR \(\nu_{\text{max}}\) (thin film) 2958 w (C-H), 2926, 2856, 1694 s (C=O), 1557 s (N=O), 1510 s, 1455 m, 1409 w, 1366 w (N-O), 1300 m, 1254 m, 1207 s, 1180 s, 1163 s, 1036 m, 841 m, 744 s, 734 s, 701 s cm\(^{-1}\); \(^1\)H NMR (600 MHz) \(\delta\) 3.74 (3H, s, O\(\text{CH}_3\)), 5.87 (1H, d, \(J = 6.3\), C\(\text{HNC}=\text{O}\)), 6.02 (1H, dd, \(J = 8.8, 2.4\), CH Arom.), 6.08 (1H, d, \(J = 10.7\), NCH), 6.39 (1H, dd, \(J = 8.8, 2.9\), CH Arom.), 6.75 (2H, d, \(J = 7.7\), CH Arom.), 6.80 (1H, dd, \(J = 8.8, 2.9\), CH Arom.), 7.16 (3H, m, CH Arom.), 7.32 (1H, m, CHNO\(_2\)), 7.39 (7H, m, CH Arom.), 7.52 (2H, s, CH Arom.), 8.01 (1H, d, \(J = 8.3\), CH Arom.); \(^{13}\)C NMR (150 MHz) \(\delta\) 55.3 (O\(\text{CH}_3\)), 63.0 (O=C\(\text{NCH}\)), 63.9 (NCH), 86.0 (CHNO\(_2\)), 109.1 (CH Arom.), 113.2 (CH Arom.), 113.8 (CH Arom.), 115.9 (q, \(J = 288.6\), CF\(_3\)), 120.2 (CH Arom.), 124.4 (CH Arom.), 126.9 (CH Arom.), 127.2 (Cq Arom.), 127.9 (CH Arom.), 128.4 (CH Arom.), 129.0 (CH Arom.), 129.2 (CH Arom.), 129.6 (CH Arom.), 129.8 (Cq Arom.), 129.9 (CH Arom.), 130.2 (CH Arom.), 131.4 (CH Arom.), 131.7 (CH Arom.), 132.2 (Cq Arom.), 132.6 (CH Arom.), 132.5 (Cq Arom.), 145.8 (Cq Arom.), 158.2 (q, \(J = 35.9\), O=CCF\(_3\)), 159.9 (Cq Arom); \(^{19}\)F NMR (282 MHz) \(\delta\) -67.86 (3F, s, CF\(_3\)); \(m/z\) (EI\(^+\)) 575 (M\(^+\), 18\%), 410 (M\(^+\)-C\(_6\)H\(_4\)N\(_3\)-HNO\(_2\), 25\%), 357 (M\(^+\)-PMP-N-TFA, 100\%), 282 (39\%), 180 (65\%); HRMS: found 575.17786, C\(_{30}\)H\(_{24}\)F\(_3\)N\(_3\)O\(_4\) requires 575.17749.
2,2,2-trifluoro-N-(4-methoxyphenyl)-N-((1R*,2R*,3S*)-2-nitro-3-(2-oxooxazolidin-3-yl)-1,3-diphenylpropyl)acetamide 480

Prepared by general procedure F. Nitroalkane 447 (134 mg, 0.570 mmol), n-BuLi (248 µL, 2.5 M, 0.620 mmol), imine 281 (240 mg, 1.14 mmol) and TFA (153 µL, 2.00 mmol) afforded after TFA-protection crude trifluoroacetamide 480. Purification by flash column chromatography (Petrol:EtOAc 4:1) gave trifluoroacetamide 480 (101 mg, 33%) as a white solid; mp. 202-203 °C; Rf 0.21 (Petrol:EtOAc 4:1); IR υmax (thin film) 2926 w (C-H), 1748 s (C=O), 1695 s (C=C), 1557 s (N=O), 1511 s, 1412 m, 1376 w (N-O), 1301 w, 1252 s, 1207 s, 1181 s, 1034 m, 911 w, 842 w, 760 w, 734 m, 703 m cm⁻¹; 1H NMR (600 MHz, 60 °C) δ 3.22 (1H, dt, J = 8.2, 7.3, NCH₂), 3.78 (3H, s, OCH₃), 3.82 (1H, ddd, J = 12.2, 8.3, 3.9, NCH₂), 4.25 (1H, ddd, J = 12.8, 9.1, 4.0, OCH₂), 4.32 (1H, dt, J = 9.5, 8.6, OCH₂), 5.56 (1H, d, J = 10.3, CH₂NCH), 5.77 (1H, d, J = 7.8, O=CNCH), 6.55 (1H, dd, J = 9.9, 7.9, CHNO₂), 6.66 (1H, dd, J = 8.9, 2.8, CH Arom.), 6.71 (1H, m, CH Arom.), 6.80 (1H, dd, J = 8.9, 2.9, CH Arom.), 7.04 (2H, app. d, J = 7.6, CH Arom.), 7.09 (1H, app. d, J = 8.1, CH Arom.), 7.21 (2H, app. t, J = 7.7, CH Arom.), 7.31 (1H, m, CH Arom.), 7.37 (5H, m, CH Arom.); 13C NMR (150 MHz) δ 42.5 (NCH₂), 55.4 (OCH₂), 59.1 (CHNCH₂), 62.4 (OCH₂), 67.2 (CHNCOF₃), 85.8 (CHNO₂), 113.4 (CH Arom.), 114.4 (CH Arom.), 116.0 (q, J = 288.9, CF₃), 128.3 (CH Arom.), 128.5 (CH Arom.), 128.5 (Cq Arom), 129.1 (CH Arom.), 129.5 (CH Arom.), 129.8 (CH Arom.), 130.3 (CH Arom.), 131.5 (CH Arom.), 131.7 (Cq Arom), 131.9 (CH Arom.), 132.5 (Arom Cq), 158.2 (OC=O), 158.6 (q, J = 35.9, O=CCF₃), 160.1 (Cq Arom); 19F NMR (282 MHz) δ -67.63 (3F, s, CF₃); m/z (ESI⁺) 544 (M+H⁺, 55%), 497 (M⁺-NO₂, 100%), 325 (M⁺-PMPNTFA, 40%), 308 (PhCHN(TFA)PMP, 40%); HRMS: found 544.1682, C₂₇H₂₅F₃N₅O₆ requires 544.1695; Anal. Cald. For C₂₇H₂₅F₃N₅O₆: C, 59.67, H, 4.45, N, 7.73. Found C, 59.43, H, 4.51, N, 7.44%.
**N-((1R*,2R*)-3-(butylthio)-2-nitro-1,3-diphenylylpropyl)-2,2,2-trifluoro-N-(4-methoxyphenyl)acetamide 485**

Prepared by general procedure F. Nitroalkane 448 (92 mg, 0.39 mmol), t-BuLi (156 µL, 2.5 M, 0.390 mmol), imine 281 (163 mg, 0.780 mmol) and TFA (105 µL, 1.37 mmol) afforded after TFA-protection crude trifluoroacetamide 485. Purification by flash column chromatography (Petrol:Et₂O 9:1) gave trifluoroacetamide 485 (118 mg, 56%) as a yellow oil, R₇ 0.44 (Petrol:Et₂O 9:1); diastereoisomer ratio (60:40) calculated by CH₃S signal, δ major = 4.49, δ minor = 4.44; IR νmax (thin film) 2960 w (C-H), 1697 s (C=O), 1557 s (N=O), 1510 s (C=C), 1456 w, 1364 w (N-O), 1301 w, 1255 m, 1208 s, 1165 s, 1035 w, 840 w, 734 w, 700 m cm⁻¹; ¹H NMR (600 MHz) δ 0.86 (3H, t, J = 7.4, CH₃), 1.31-1.57 (4H, m, CH₂), 2.32 (2H, t, J = 7.4, SCH₂), 3.82 (3H, s, OCH₃), 4.49 (1H, d, J = 6.2, PhCHₛ), 5.64 (1H, dd, J = 10.4, 6.2, CHNO₂), 6.04 (1H, dd, J = 8.8, 2.7, CH Arom.), 6.40 (1H, d, J = 10.3, PhCHₙN), 6.56 (1H, dd, J = 8.8, 2.9, CH Arom.), 6.93-7.44 (10H, m, CH Arom.); ¹³C NMR (150 MHz) δ 13.5 (CH₃), 21.8, 30.5, 31.7 (CH₂), 49.5 (PhCHₛ), 55.4 (OCH₃), 62.0 (PhCHₙN), 89.8 (CHNO₂), 113.7, 113.8 (CH Arom.), 116.4 (q, J = 288.4, CF₃), 126.7 (C₉ Arom.), 128.1, 128.5, 128.7, 128.8, 129.3, 129.6, 131.2, 132.9 (CH Arom.), 133.0, 136.0, 137.4 (C₉ Arom.), 158.3 (q, J = 35.6, O=CCF₃), 160.2 (C₉ Arom.); ¹⁹F NMR (282 MHz) δ -67.71 (3F, s, CF₃); m/z (EI⁺) 547 (M+H⁺, 4%), 500 (M⁺-NO₂, 52%), 457 (M⁺-BuS, 100%), 193 (38%); HRMS: found 547.18784, C₂₈H₃₀F₃N₂O₄S requires 547.18833; Anal. Cald. For C₂₈H₂₉F₃N₂O₄S: C, 61.53, H, 5.35, N, 5.13. Found C, 61.14, H, 5.48, N, 5.33%.

Minor diastereomer: ¹H NMR (600 MHz) δ 0.84 (3H, t, J = 7.4, CH₃), 1.31-1.57 (4H, m, CH₂), 2.45 (2H, td, J = 7.1, 2.5, SCH₂), 3.82 (3H, s, OCH₃), 4.44 (1H, d, J = 4.6, PhCHₛ), 5.59 (1H, br. d, J = 9.6, PhCHₙN), 6.24 (1H, dd, J = 10.4, 4.6, CHNO₂), 6.63 (1H, d, J = 8.6, CH Arom.), 6.74 (1H, dd, J = 8.8, 2.9, CH Arom.), 6.83 (1H, dd, J = 8.8, 3.0, CH Arom.), 6.93-7.44 (9H, m, CH Arom.); ¹³C NMR (150 MHz) δ 13.5 (CH₃), 22.0, 31.0, 32.4 (CH₂), 49.9 (PhCHₛ), 55.4 (OCH₃), 67.9 (PhCHₙN), 92.4 (CHNO₂), 113.3, 114.6 (CH Arom.), 116.2 (q, J = 288.4, CF₃), 128.5, 128.7, 129.3,
129.6, 130.6, 130.7 (CH Arom.), 133.5 (Cq Arom.), 158.3 (q, \( J = 35.6 \), O=CCF₃), 160.1 (Cq Arom.), 6 CH and 3 Cq peaks missing; \(^{19}\)F NMR (282 MHz) \( \delta -67.73 \) (3F, s, CF₃).

**2,2,2-Trifluoro-N-(4-methoxyphenyl)-N-((1R*,2R*)-2-nitro-1,3-diphenyl-3-(phenylthio)propyl)acetamide 486**

![Chemical structure](image)

Prepared by general procedure F. Nitroalkane \( 449 \) (125 mg, 0.480 mmol), \(^{6}\)BuLi (192 \( \mu \)L, 2.5 M, 0.480 mmol), imine \( 281 \) (203 mg, 0.920 mmol) and TFA (129 \( \mu \)L, 1.68 mmol) afforded after TFA-protection crude trifluoroacetamide \( 486 \). Purification by flash column chromatography (Petrol:Et₂O 4:1) gave trifluoroacetamide \( 486 \) (129 mg, 47%) as an orange solid, mp. 51-52°C; \( R_f \) 0.25 (Petrol:Et₂O 9:1); diastereoisomer ratio (65:35) calculated by CHS signal, \( \delta \) major = 4.76, \( \delta \) minor = 4.70; IR \( \nu_{max} \) (thin film) 3063 w (C-CH), 3032 w, 2964 w, 2935 w, 2840 w, 1695 s (C=O), 1557 s (N=O), 1509 s (C=C), 1301 w, 1254 m, 1208 s, 1180 s, 1166 s, 1033 m, 840 m, 733 m, 699 s cm\(^{-1}\); \(^1\)H NMR (600 MHz) \( \delta 3.79 \) (3H, s, OC\(_3\)H\(_3\)), 4.76 (1H, d, \( J = 5.1 \), PhCHS), 5.69 (1H, d, \( J = 9.8 \), PhCHN), 6.35 (1H, dd, \( J = 9.8 \), 5.1, CHNO\(_2\)), 6.65-7.40 (19H, m, Arom. CH); \(^{13}\)C NMR (150 MHz) \( \delta 54.0 \) (PhCHS), 55.4 (OCH\(_3\)), 67.9 (PhCHN), 92.2 (CHNO\(_2\)), 113.4 and 114.5 (CH Arom.), 116.1 (q, \( J = 288.6 \) and 288.3, CF\(_3\)), 126.7 (Cq Arom.), 127.7, 128.0, 128.5, 128.7, 128.8, 128.9, 129.2, 129.4, 129.5, 129.7, 129.8, 130.5, 130.8, 130.9, 131.2, 132.9 and 134.2 (CH Arom.), 132.0, 133.1, 133.8, 135.5, 135.6 and 137.0 (Cq Arom.), 158.4 (q, \( J = 35.6 \) and 35.8, O=CCF\(_3\)), 160.1 (Cq Arom.); \(^{19}\)F NMR (282 MHz) \( \delta -67.84 \) (3F, s, CF\(_3\)); \( m/z \) (EI\(^{+}\)) 566 (M\(^+\), 10%), 457 (M\(^+\)-PhS, 38%), 308 (64%), 301 (M\(^+\)-NO\(_2\)-PMP-NH-TFA, 100%), 199 (44%); HRMS: found 566.14870, C\(_{30}\)H\(_{25}\)F\(_3\)N\(_2\)O\(_4\)S requires 566.14816.

Minor diastereomer: \(^1\)H NMR (600 MHz) \( \delta 3.80 \) (3H, s, OCH\(_3\)), 4.70 (1H, d, \( J = 6.1 \), PhCHS), 5.79 (1H, dd, \( J = 10.0 \), 6.0, CHNO\(_2\)), 6.01 (1H, dd, \( J = 8.8 \), 2.0, CH Arom.), 6.43 (1H, d, \( J = 10.0 \), PhCHN), 6.53 (1H, dd, \( J = 8.8 \), 2.9, CH Arom.), 6.65-7.40 (17H, m, CH Arom.); \(^{13}\)C NMR (150 MHz) \( \delta 52.9 \) (PhCHS), 55.4 (OCH\(_3\)), 62.0
(PhCHN), 88.8 (CHNO₂), 113.7 and 113.8 (CH Arom.), 116.3 (q, J = 288.6 and 288.3, CF₃), 158.4 (q, J = 35.6 and 35.8, O=CCF₃), 160.2 (Cq Arom.), the rest of the ¹³C peaks could not be distinguished between the two diastereomers; ¹⁹F NMR (282 MHz) δ -67.58 (3F, s, CF₃).

**General procedure G for the synthesis of 2-thioxoimidazolidines**

A solution of nitroalkane (1.00 mmol) in THF (10 mL), was cooled to -78 °C and "BuLi (1.10 mmol, of a 2.5 M solution in hexanes) was added dropwise. The orange mixture was stirred at this temperature for 10 min before the corresponding imine (2.00 mmol) in THF (4 mL) was added via cannula. The mixture was stirred for 10 min before a 1:1 mixture of TFA:THF (3.50 mmol TFA) was added dropwise. The mixture was stirred at this temperature for a further 1 h, then warmed to rt over 5 min and quenched with saturated aqueous NaHCO₃ (10 mL) extracted with Et₂O (3x10 mL), dried over MgSO₄ and concentrated in vacuo to leave crude β-nitroamine. A sample was taken for ¹H NMR analysis and the rest of the crude product was dissolved in EtOH (30 mL) and EtOAc (30 mL) and then an aqueous solution of 6 M HCl (10 mL, 60 mmol) was added followed by Zn dust (1.96 g, 30 mmol) in 3 portions over 1 h. The mixture was stirred vigorously for 1 h and then the solvents were removed in vacuo. The residue was neutralised with saturated aqueous Na₂CO₃ and extracted with EtOAc (3x20 mL), washed with brine (10 mL), dried over MgSO₄ and concentrated in vacuo to leave crude diamine. The diamine was purified further with column chromatography to remove by-product para-anisidine and was then reacted with thiophosgene without further purification. The diamine (0.25 mmol) was dissolved in DCM (7 mL) and MeOH (3 mL) and saturated aqueous NaHCO₃ (1 mL) and H₂O (1 mL) were added. The mixture was stirred for 5 min at rt and then CSCl₂ (29 µL, 0.37 mmol) was added and the mixture stirred for 24 h. Water (10 mL) was then added and the mixture extracted with DCM (3x10 mL), dried over MgSO₄ and evaporated in vacuo to give crude 2-thioxoimidazolidine that was purified by flash column chromatography.
(4S*,5R*)-O-methyl 5-((R*)-(1H-indol-3-yl)(phenyl)methyl)-3-(4-methoxyphenyl)-4-phenyl-2-thioxoimidazolidine-1-carbothioate 488

Prepared by general procedure G. Nitroalkane 429 (222 mg, 0.830 mmol), nBuLi (0.913 mmol), imine 281 (350 mg, 1.66 mmol) and TFA (220 µL, 2.91 mmol) afforded after reduction and column chromatography (Petrol:EtOAc 1:1, Rf 0.29) the crude diamine (296 mg, 80%). Subsequent reaction of the diamine (0.66 mmol) with CSCl₂ (90 µL, 0.99 mmol) gave crude 2-thioxoimidazolidine 488. Purification by flash column chromatography (Petrol:EtOAc 7:3) gave 2-thioxoimidazolidine 488 (31 mg, 7%) as a brown oil, Rf 0.77 (Petrol:EtOAc 1:1); IR υmax (thin film) 3338 br (N-H), 3058 w (C-H), 1512 s (C=O), 1556 s (C=C), 1450 m, 1338 m, 1322 m, 1289 m, 1245 s, 1030 m, 831 m, 742 m, 700 m cm⁻¹; ¹H NMR (600 MHz) δ 3.69 (3H, s, OCH₃), 3.70 (3H, s, OCH₃), 4.34 (1H, d, J = 10.4, PhCHAr), 5.45 (1H, d, J = 8.7, NCNPh), 6.16 (1H, dd, J = 8.7, 10.3, NCH), 6.74 (2H, m, CH Arom.), 6.88 (8H, m, CH Arom.), 7.05 (6H, m, CH Arom.), 2.24 (3H, m, CH Arom.), 8.02 (1H, s, NH); ¹³C NMR (150 MHz) δ 44.2 (PhCHAr), 55.2 (ArOCH₃), 58.9 (OCH₃), 67.1 (NCH), 69.6 (NCHPh), 110.8 and 114.0 (CH Arom.), 115.8 (Cq Arom.), 119.0, 119.3, 121.8, 122.1 (CH Arom.), 126.4 (Cq Arom.), 126.8, 127.7, 127.7, 128.0, 128.4, 128.7 and 130.5 (CH Arom.), 131.5, 133.7, 135.8 and 139.7 (Cq Arom.), 158.4 (CqPMPc1), 182.2 (NC=S), 194.4 (OC=S); m/z (CI⁻) 563 (M⁻, 22%), 504 (16%), 297 (100%); HRMS: found 563.16883, C₃₃H₂₉N₃O₂S₂ requires 563.17012.
3-((S*)-((4R*,5S*)-1-(4-methoxyphenyl)-5-phenyl-2-thioximidazolidin-4-yl)(phenyl)methyl)oxazolidin-2-one 491a and 3-((R*)-((4R*,5S*)-1-(4-methoxyphenyl)-5-phenyl-2-thioximidazolidin-4-yl)(phenyl)methyl)oxazolidin-2-one 491b

Prepared by general procedure G. Nitroalkane 447 (213 mg, 0.900 mmol), tBuLi (0.990 mmol), imine 281 (380 mg, 1.80 mmol) and TFA (241 µL, 3.15 mmol) afforded after reduction and column chromatography (Et2O, Rf 0.27) crude diamine (106 mg, 28%). Subsequent reaction of the diamine (0.25 mmol) with CSCl2 (29 µL, 0.37 mmol) gave crude 2-thioxoimidazolidines 491a and 491b. Purification by flash column chromatography (Petrol:Et2O 1:1) gave 2-thioxoimidazolidines 491a and 491b (87 mg, 21%) as a white solid, isolated as a mixture of diastereomers, mp. 141-142 °C; Rf 0.51 (Et2O); diastereoisomer ratio (85:15) calculated by the NC2H2 signal, δ major = 3.02, δ minor = 3.25; IR νmax (thin film) 3277 br. (N-H), 2923 w (C-H), 1739 s (C=S), 1513 s (C=C), 1446 m, 1246 s, 1034 w, 705 m cm⁻¹; 1H NMR (600 MHz) δ 2.05 (1H, ddd, J = 9.5, 8.3, 5.9, NC2H2), 3.02 (1H, dt, J = 9.5, 8.0, NC2H2), 3.67 (1H, d, J = 10.7, O=CNCH), 3.72 (3H, s, OCH3), 3.92 (1H, dt, J = 9.4, 8.0, OCH2), 4.02 (1H, ddd, J = 9.5, 8.6, 5.8, OCH2), 5.40 (1H, br. s, NH), 5.46 (1H, d, J = 9.4, NCHPh), 5.78 (1H, dd, J = 10.0, 9.5, CHNH), 6.77 (2H, app. d, J = 8.9, CHPmPC3-H), 7.21 (2H, app. d, J = 8.9, CHPmPC2-H), 7.25-7.40 (10H, m, CH Arom.); 13C NMR (150 MHz) δ 45.2 (NCH2), 55.3 (OCH3), 58.9 (NHCH), 61.1 (O=CNCH), 62.0 (OCH2), 70.4 (NCHPh), 114.0 (CHPmPC3), 128.0, 128.2, 128.4, 128.6, 129.1, 129.5 and 129.5 (CH Arom.), 131.2, 135.5, 136.5, 157.2 and 158.4 (Cq Arom.), 183.4 (C=Q); m/z (EI⁺) 459 (M⁺, 49%), 386 (M⁺-IPA-NO2, 30%), 372 (M⁺-oxazolidone, 50%), 297 (38%), 283 (M⁺-PhCH(C3H4NO2), 100%); HRMS: found 459.16088, C26H25N3O3S requires 459.16111.

Minor diastereomer: 1H NMR (600 MHz) δ 2.42 (1H, m, NCH2), 3.25 (1H, m, NCH2), 3.67 (3H, s, OCH3), 3.75 (1H, m, OCH2), 3.85 (1H, m, OCH2), 4.13 (1H, d, J = 10.0, O=CNCH), 5.40 (1H, d, J = 9.8, NCHPh), 5.56 (1H, m, CHNH), 6.73 (2H, app. d, J = 8.9, CHPmPC3-H), 7.02 (2H, app. d, J = 8.9, CHPmPC2-H), 7.25-7.40 (10H, m,

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CH Arom.), NH peak missing; $^{13}$C NMR (150 MHz) $\delta$ 44.1 (NCH$_2$), 55.3 (OCH$_3$), 60.3 (NHCH), 61.1 (NCHPh), 61.7 (OCH$_2$), 114.1 (CH$_{\text{PMPC3}}$), 127.3 and 128.1 (CH Arom.), the rest of the aromatic region could not be distinguished.

$(4S^*,5S^*)$-4-((S*)-(butylthio)(phenyl)methyl)-1-(4-methoxyphenyl)-5-phenylimidazolidine-2-thione 492a and $(4S^*,5S^*)$-4-((R*)-(butylthio)(phenyl)methyl)-1-(4-methoxyphenyl)-5-phenylimidazolidine-2-thione 492b

Prepared by general procedure G. Nitroalkane 448 (235 mg, 0.980 mmol), $^n$BuLi (1.08 mmol), imine 281 (414 mg, 1.96 mmol) and TFA (262 µL, 3.43 mmol) afforded after reduction and column chromatography (Petrol:Et$_2$O 1:1, Rf 0.31) crude diamine (182 mg, 44%). Subsequent reaction of the diamine (0.43 mmol) with CSCl$_2$ (49 µL, 0.65 mmol) gave crude 2-thioxoimidazolidine 492. Purification by flash column chromatography (Petrol:Et$_2$O 1:1) gave 2-thioxoimidazolidine 492 (89 mg, 20%) as a white solid, isolated as a mixture of diastereomers, mp. 183-184 °C; Rf 0.54 (Petrol:Et$_2$O 1:1); diastereoisomer ratio (80:20) calculated by the NCH$_2$Ph signal, $\delta$ major = 3.14, $\delta$ minor = 3.44; IR $\nu_{\text{max}}$ (thin film) 3386 br. (N-H), 2955 w (C-H), 1609 w, 1511 s, 1445 s, 1241 s, 1174 m, 1027 m, 735 m, 697 s cm$^{-1}$; $^1$H NMR (600 MHz) $\delta$ 0.68 (3H, t, $J = 7.0$, C$_3$H$_3$), 1.04 (4H, m, C$_2$H$_2$), 1.83 (1H, m, SCH$_2$), 1.95 (1H, m, SCH$_2$), 3.14 (1H, d, $J = 11.5$, CH$_3$), 3.72 (3H, s, OCH$_3$), 4.58 (1H, ddd, $J = 11.5$, 8.4, 1.1, CHN), 5.31 (1H, d, $J = 8.4$, NCHPh), 5.40 (1H, br. s, NH), 6.77 (2H, m, CH Arom.), 7.17 (2H, m, CH Arom.), 7.23-7.38 (10H, m, CH Arom.); $^{13}$C NMR (150 MHz) $\delta$ 13.4 (CH$_3$), 21.6 (CH$_2$), 30.4 (CH$_2$), 30.6 (CH$_2$), 49.1 (CHS), 55.2 (OCH$_3$), 62.8 (NHCH), 71.2 (NCHPh), 113.9 (CH$_{\text{PMPC3-H1}}$), 127.6, 128.3, 128.3, 128.3, 128.4, 128.9 and 129.0 (CH Arom.), 131.6, 134.2 and 138.8 (Cq Arom.), 158.3 (Cq$_{\text{PMPC4}}$), 183.4 (C=S); $m/z$ (EI) 461 (M, 5%), 451 (30%), 437 (24%); HRMS: found 461.1765, C$_2$H$_{29}$N$_2$OS$_2$ requires 461.1721; Anal. Cald. For C$_{27}$H$_{30}$N$_2$OS$_2$: C, 70.09, H, 6.54, N, 6.05. Found C, 69.97, H, 6.54, N, 5.97%.

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Minor diastereomer: $^1$H NMR (600 MHz) δ 0.81 (3H, t, $J = 7.4$, CH$_3$), 1.27 (2H, m, CH$_2$), 1.38 (2H, m, CH$_2$), 2.28 (2H, m, SCH$_2$), 3.44 (1H, d, $J = 11.2$, CHS), 3.69 (3H, s, OCH$_3$), 4.85 (1H, d, $J = 8.8$, NCHPh), 4.91 (1H, ddd, $J = 11.2$, 8.8, 0.9, CHNH), 6.70 (1H, br. s, NH), 6.70 (2H, m, CH Arom.), 7.10 (2H, m, CH Arom.), 7.23-7.38 (10H, m, CH Arom.); $^{13}$C NMR (150 MHz) δ 13.5 (CH$_3$), 21.9 (CH$_2$), 30.1 (CH$_2$), 31.2 (CH$_2$), 49.7 (CHS), 55.2 (OCH$_3$), 61.4 (NHCH), 70.6 (NCHPh), 113.8 ($CH_{PMPC3-H}$), 127.6 and 128.8 (CH Arom.), 131.5, 134.2 and 138.3 (Cq Arom.), 158.3 (Cq$_{PMPC_4}$), 183.1 (C=S), the rest of the aromatic region could not be distinguished.

3.4.4 Piperazirum synthesis

3.4.4.1 Synthesis of starting materials

(E)-4-Methoxy-N-(3-methylbutyldiene)aniline 534

To a solution of para-anisidine (123 mg, 1.00 mmol) in DCM (5 mL), was added basic alumina (1.00 g) and the mixture cooled to -78 °C. Isovaleraldehyde (107 µL, 1.00 mmol) was then added and the mixture stirred at this temperature for 1 h, then warmed to rt, filtered and evaporated in vacuo to give crude imine 534 (182 mg, 95%) as a colourless oil used immediately without further purification; $^1$H NMR (600 MHz) δ 1.02 (6H, d, $J = 6.7$, CH$_3$), 2.04 (1H, sept, $J = 6.7$, CH(CH$_3$)$_2$), 2.34 (2H, dd, $J = 7.0$, 5.4, CH$_2$), 3.80 (1H, s, OCH$_3$), 6.87 (2H, app. d, $J = 8.9$, CH$_{PMPC3-H}$), 7.02 (2H, app. d, $J = 8.9$, CH$_{PMPC2-H}$), 7.86 (1H, t, $J = 5.4$, N=CH); $^{13}$C NMR (150 MHz) δ 22.0 (CH$_3$), 24.8 (CH$_3$), 77.7 (Cq), 80.8 (CH$_2$), 170.5 (C=O). Data in agreement to that reported.$^{272}$
(E)-4-Methoxy-N-(2-methylpropylidene)aniline 524

To a solution of para-anisidine (246 mg, 2.00 mmol) in DCM (10 mL), was added basic alumina (2.00 g) and the mixture cooled to -78 °C. Isobutyraldehyde (182 µL, 2.00 mmol) was added and the mixture stirred at this temperature for 1 h, then warmed to rt, filtered and evaporated in vacuo to give crude imine 524 (343 mg, 89% pure by 1H NMR, 86%) as a colourless oil which was used without further purification; IR $\nu_{\max}$ (thin film) 2962 w (C-H), 2869 w, 1649 m (C=C), 1503 s, 1464 m, 1441 m, 1291 m, 1211 m, 1179 m, 1105 m, 1034 m, 823 m, 759 m cm$^{-1}$; 1H NMR (600 MHz) $\delta$ 1.18 (3H, d, $J$ = 6.9, CH$_3$), 2.62 (1H, m, CH(CH$_3$)$_2$), 3.80 (3H, s, OCH$_3$), 6.87 (2H, app. d, $J$ = 8.8, Arom. CH), 7.02 (2H, app. d, $J$ = 8.8, Arom. CH), 7.73 (1H, d, $J$ = 4.9, =CH); 13C NMR (150 MHz) $\delta$ 19.2 (CH$_3$), 34.7 (CH), 55.4 (OCH$_3$), 114.1 (CH Arom.), 121.7 (CH Arom.), 145.3 (Cq Arom.), 157.7 (Cq Arom.), 169.4 (=CH); $m/z$ (EI$^+$) 177 (M$^+$, 100%), 162 (M$^+$-Me, 53%); HRMS: found 177.11441 C$_{11}$H$_{15}$NO requires 177.11482.

3.4.4.2 Investigation of the synthesis

General procedure H for the synthesis of trifluoroacetamides 525 and 535.

Prepared by modification of the reported method. To a solution of nitroalkene (1.00 mmol) in DCM (6 mL) was added Superhydride® (1.10 mmol) and the suspension stirred at rt for 15 min. The mixture was then cooled to -78 °C and freshly prepared imine (2.00 mmol) in DCM (6 mL) was added. The reaction was stirred for 10 min before the addition of TFA (3.00 mmol) in DCM (2 mL) dropwise. The mixture was stirred at this temperature for 1 h and then quenched with brine (10 mL) at -78 °C and extracted with Et$_2$O (3x10 mL). The combined organics were dried over MgSO$_4$ and evaporated in vacuo to give crude β-nitroamine. A sample was taken for 1H-NMR analysis and the rest of the crude product was dissolved in DCM (5 mL), cooled to 0 °C and trifluoroacetic anhydride (550 µL, 4.00 mmol) and then pyridine (320 µL, 4.00 mmol) were added dropwise. The mixture was then warmed to rt and stirred for
30 min. The mixture was then washed with 2 M aqueous HCl (3x10 mL) and brine (10 mL), dried over MgSO₄ and concentrated in vacuo to give crude trifluoroacetamide that was further purified by flash column chromatography.

\[
1-(2-((3R^*,4S^*)-2,6-Dimethyl-4-nitroheptan-3-yl)amino)-5-methoxyphenyl)-2,2,2-trifluoroethanone 525
\]

Prepared by general method H. Nitroalkene 523 (115 mg, 1.00 mmol), Superhydride® (1.10 mL, 1 M in THF, 1.10 mmol), freshly prepared imine 524 (345 mg, 2.00 mmol) and TFA (230 µL, 3.00 mmol) gave crude β-nitroamine 522. Reaction with trifluoroacetic anhydride (550 µL, 4.00 mmol) and pyridine (320 µL, 4.00 mmol) for 1 h gave crude trifluoroacetamide 525. Purification by flash column chromatography (Petrol:Et₂O 9:1) gave trifluoroacetamide 525 (60 mg, 15%) as an orange solid; mp. 99-100 °C; R₇ 0.61 (Petrol:Et₂O 9:1); IR \(\nu_{\text{max}}\) (thin film) 3310 br (N-H), 2964 w (C-H), 1652 m (C=O), 1582 m, 1552 m (C=C), 1525 s (N-O), 1468 m, 1421 w, 1372 m (N-O), 1265 m, 1233 m, 1193 m (C-F), 1148 s (C-F), 1117 m, 1045 m cm⁻¹; \(^1\)H NMR (600 MHz) δ 0.89 (3H, d, \(J=6.7\), CH₃), 0.90 (3H, d, \(J=6.3\), CH₃), 0.91 (3H, d, \(J=6.6\), CH₃), 1.04 (3H, d, \(J=6.8\), CH₃), 1.44 (1H, m, CH₂), 1.51 (1H, m, CH₂CH₃), 2.09 (1H, ddd, \(J=14.6, 11.7, 3.5\), CH₂), 3.78 (3H, s, OCH₃), 4.10 (1H, ddd, \(J=10.5, 7.9, 4.6\), CHNH), 4.72 (1H, ddd, \(J=11.7, 7.9, 2.4\), CHNO₂), 6.92 (1H, app. d, \(J=9.4\), CH Arom.), 7.20 (2H, m, CH Arom.), 8.70 (1H, d, \(J=10.4\), NH); \(^{13}\)C NMR (150 MHz) δ 16.3 (CH₃), 20.0 (CH₃), 20.9 (CH₃), 23.3 (CH₃), 25.1 (CH(CH₃)₂), 30.5 (CH(CH₃)₂), 38.4 (CH₂), 55.7 (OCH₃), 60.5 (CHNH), 88.2 (CHNO₂), 110.3 (Cq Arom.), 112.5 (q, \(J=4.6\), CH Arom.), 114.0 (CH Arom.), 116.3 (CH Arom.), 117.2 (q, \(J=291.0\), CF₃), 128.4 (CH Arom.), 149.4 (Cq Arom.), 150.1 (Cq Arom.), 180.3 (q, \(J=33.3\), C=O); \(^{19}\)F NMR (282 MHz) δ -69.40 (3F, s, CF₃); m/z (EI⁺) 390 (M⁺, 15%), 301 (25%), 274 (100%), 258 (36%); HRMS: found 390.175746, \(\text{C}_{18}\text{H}_{25}\text{F}_3\text{N}_2\text{O}_4\) requires 390.17609; Anal. Cald. For \(\text{C}_{18}\text{H}_{25}\text{F}_3\text{N}_2\text{O}_4\): C, 55.38, H, 6.45, N, 7.18. Found C, 55.43, H, 6.51, N, 6.93%.
Prepared by general procedure H. Nitroalkene 530 (101 mg, 1.00 mmol), Superhydride® (1.10 mL, 1 M in THF, 1.1 mmol), freshly prepared imine 534 (282 mg, 2.0 mmol) and TFA (230 µL, 3.00 mmol) gave crude β-nitroamine 529. Subsequent reaction with trifluoroacetic anhydride (550 µL, 4.00 mmol) and pyridine (320 µL, 4.00 mmol) gave crude trifluoroacetamide 535. Purification by flash column chromatography (Toluene) gave trifluoroacetamide 535 (340 mg, 87%) as a colourless oil; Rf 0.61 (Toluene); IR νmax (thin film) 2963 w (C–H), 1694 s (C=C), 1549 s (N=O), 1511 s, 1466 m, 1367 w (N–O), 1300 m, 1255 m, 1204 s, 1185 s, 1150 s, 1113 m, 1032 m, 829 m, 757 m, 735 m cm⁻¹; ¹H NMR (600 MHz) δ 0.89 (3H, t, J = 6.8, CH₃), 1.04 (3H, t, J = 6.4, CH₃), 1.09 (3H, t, J = 6.5, CH₃), 1.14 (3H, t, J = 6.9, CH₃), 1.47 (2H, br. s, CH₂), 1.69 (1H, m, CH(CH₃)₂), 2.35 (1H, m, CH(CH₃)₂), 3.85 (3H, s, OCH₃), 4.41 (1H, br. s, CH(NO₂)), 5.31 (1H, br. s, CHN), 6.93 (2H, app. d, J = 9.2, CH Arom.), 6.98 (2H, m, CH Arom.), 7.06 (2H, m, CH Arom.); ¹³C NMR (150 MHz) δ 17.3 (CH₃), 19.9 (CH₃), 21.3 (CH₃), 23.3 (CH₃), 24.8 (CH), 29.1 (CH), 36.1 (CH₂), 54.3 (CHN), 55.5 (OCH₃), 94.1 (CHNO₂), 114.3 (CH Arom.), 114.4 (CH Arom.), 116.2 (q, CF₃, J = 288.5), 125.8 (Cq Arom.), 130.4 (CH Arom.), 131.8 (CH Arom.), 158.5 (q, C=O, J = 35.6), 160.4 (Cq Arom.); ¹⁹F NMR (282 MHz) δ -67.94 (3F, s, CF₃); m/z (Cl⁻) 391 (M+H⁻, 23%), 349 (15%), 288 (100%); HRMS: found 391.18488, C₁₈H₂₆F₃N₂O₄ requires 391.18447; Anal. Cald. For C₁₈H₂₆F₃N₂O₄: C, 55.38, H, 6.45, N, 7.18. Found C, 55.31, H, 6.47, N, 7.06%.

**General procedure I for the synthesis of diamines 526 and 538.**

Crude β-nitroamines 522 and 529 were prepared by general procedure H, purified quickly by flash column chromatography and reduced immediately. To a solution of β-nitroamine in EtOH (20 mL) and EtOAc (20 mL) was added an aqueous solution of 6 M HCl (6.60 mL, 40.0 mmol), followed by Zn dust (1.30 g, 20.0 mmol) in 3
portions over 1 h. The mixture was stirred vigorously for 1 h before the solvents were removed in vacuo. The residue was neutralised with saturated aqueous Na₂CO₃ and extracted with EtOAc (3x20 mL), washed with brine (10 mL), dried over MgSO₄ and concentrated in vacuo to leave the crude diamine that was further purified by flash column chromatography.

\[ (3R^*,4S^*)-N3-(4-Methoxyphenyl)-2,6-dimethylheptane-3,4-diamine \text{526} \]

Prepared by general procedure I. Nitroalkene \text{523} (230 mg, 2.00 mmol), Superhydride® (2.20 mmol), imine \text{524} (708 mg, 4.00 mmol) and TFA (460 µL, 6.00 mmol) gave crude \( \beta \)-nitroamine \text{522}, that was purified quickly by column chromatography (Petrol:Et₂O 4:1). A sample was taken for \(^1\)H-NMR analysis. Subsequent reaction with 6 M HCl (6.60 mL, 40.0 mmol) and Zn dust (1.30 g, 20.0 mmol) gave crude diamine \text{526}. Purification by flash column chromatography (DCM:MeOH 20:1) gave diamine \text{526} (248 mg, 50%) as a white solid; mp. 86-87 °C; \( R_f \) 0.29 (DCM:MeOH 20:1); IR \( \nu_{\text{max}} \) (thin film) 3374 br (N-H), 2954 m (C-H), 1509 s (C=C), 1465 m, 1230 s, 1178 m, 1039 m, 815 m cm\(^{-1}\); \(^1\)H NMR (600 MHz) \( \delta \) 0.91 (12H, m, CH₃), 1.21 (2H, m, CH₂), 1.81 (2H, m, CH(CH₃)₂), 1.81 (2H, m, NH₂), 2.93 (1H, m, CH(NH)₂), 3.05 (1H, m, CH(NH)), 3.15 (1H, br. S, NH), 3.72 (3H, s, OCH₃), 6.62 (2H, app. d, \( J = 8.7 \), CH Arom.), 6.73 (2H, app. d, \( J = 8.5 \), CH Arom.); \(^{13}\)C NMR (150 MHz) \( \delta \) 19.1 (CH₃), 20.6 (CH₃), 21.2 (CH₃), 24.3 (CH₃), 24.6 (CH(CH₃)₂), 31.3 (CH(CH₃)₂), 41.5 (CH₂), 50.9 (CH(NH)₂), 55.7 (OCH₃), 65.6 (CH(NH)), 113.9 (CH Arom.), 114.8 (CH Arom.), 144.2 (Cq Arom.), 151.3 (Cq Arom.); m/z (EI⁺) 264 (M⁺, 6%), 178 (100%); HRMS: found 264.219570, C₁₆H₂₈N₂O requires 264.21962.
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(3S*,4R*)-N-4-(4-Methoxyphenyl)-2,6-dimethylheptane-3,4-diamine 538

Prepared by general procedure I. Nitroalkene 530 (202 mg, 2.00 mmol), Superhydride® (2.20 mmol), imine 534 (4.00 mmol) and TFA (6.00 mmol) gave crude β-nitroamine 529, that was purified quickly by column chromatography (Petrol:Et₂O 4:1). A sample was taken for ¹H-NMR analysis. Subsequent reaction with 6 M HCl (6.60 mL, 40.0 mmol) and Zn dust (1.30 g, 20.0 mmol) gave crude diamine 538. Purification by flash column chromatography (DCM:MeOH 10:1) gave diamine 538 (452 mg, 85%) as a brown oil; R<sub>f</sub> 0.50 (DCM:MeOH 10:1); IR <var>υ</var> <sub>max</sub> (thin film) 3374 br (N-H), 2955 w (C-H), 1618 w, 1508 s (C=C), 1465 m, 1441 w, 1385 w, 1366 w, 1292 w, 1238 s, 1179 w, 1154 w, 1038 m, 816 m, 752 s cm⁻¹; ¹H NMR (600 MHz) δ 0.90 (3H, d, <var>J</var> = 6.5, C<sub>6</sub>H<sub>3</sub>), 0.92 (3H, d, <var>J</var> = 6.7, CH₃), 0.99 (6H, d, <var>J</var> = 6.6, CH₃), 1.21 (1H, m, CH₂), 1.35 (1H, m, CH₂), 1.59 (1H, m, CH(CH₃)₂), 1.80 (1H, m, CH(CH₃)₂), 2.53 (1H, dd, <var>J</var> = 9.1, 2.7, CHNH₂), 3.52 (1H, m, CH₂), 3.73 (3H, s, OCH₃), 6.57 (2H, app. d, <var>J</var> = 8.9, Arom. CH), 6.76 (2H, app. d, <var>J</var> = 8.9, Arom. CH); ¹³C NMR (150 MHz) δ 19.6 (CH₃), 20.6 (CH₃), 21.7 (CH₃), 24.1 (CH₃), 24.7 (CH(CH₃)₂), 31.4 (CH(CH₃)₂), 37.2 (CH₂), 52.9 (CHNH), 55.8 (OCH₃), 59.1 (CHNH₂), 114.4 (CH Arom.), 115.0 (CH Arom.), 142.3 (Cq Arom.), 151.6 (Cq Arom.); m/z (EI⁺) 264 (M⁺, 5%), 192 (M⁺-NH-CH₂(CH₃)₂, 100%); HRMS: found 264.22013, C₁₆H₂₈N₂O requires 264.21962.

(4R*,5S*)-4-Isobutyl-5-isopropyl-1-(4-methoxyphenyl)imidazolidine-2-thione 544

Diamine 538 (130 mg, 0.490 mmol) was dissolved in DCM (14 mL) and MeOH (7 mL) and saturated aqueous NaHCO₃ (2.40 mL) and H₂O (2.40 mL) were added, stirred for 5 min at rt and then CSCl₂ (55 µL, 0.74 mmol) was added and the mixture stirred for 24 h. Water (20 mL) was then added and the mixture extracted with DCM.
(3x20 mL), dried over MgSO₄ and evaporated in vacuo to give crude 2-thioxoimidazolidine 544. Purification by flash column chromatography (Petrol:EtOAc 4:1) gave 2-thioxoimidazolidine 544 (130 mg, 42%) as a white solid; mp. 123-124 °C; Rₙ 0.53 (Petrol:EtOAc 4:1); IR νₘₐₓ (thin film) 3200 br (N-H), 2955 m (C-H), 1612 w, 1515 s (C=O), 1485 s (C=C), 1253 s, 1225 m, 1172 m, 1033 m, 840 m, 808 m cm⁻¹; ¹H NMR (600 MHz) δ 0.77 (3H, d, J = 6.6, CH₃), 0.79 (3H, d, J = 6.6, CH₃), 0.96 (3H, d, J = 6.8, CH₃), 1.05 (3H, d, J = 6.6, CH₃), 1.35 (1H, m, CH₂CH(CH₃)₂), 1.44 (1H, m, CH₂), 1.49 (1H, m, CH₂), 1.96 (1H, m, CHCH(CH₃)₂), 3.70 (1H, dd, J = 8.4, 5.4, CHNH), 3.82 (3H, s, OC₃H₃), 4.31 (1H, dt, J = 7.9, 5.9, NCH₂CH₂), 6.36 (1H, br. s, NH), 6.92 (2H, app. d, J = 8.9, CH₃PMPC3-H), 7.22 (2H, app. d, J = 8.9, CH₃PMPC2-H); ¹³C NMR (150 MHz) δ 19.1 (C₃H₃), 20.6 (C₃H₃), 21.2 (CH₃), 24.3 (CH₃), 24.6 (CH(CH₃)₂), 31.3 (CH(CH₃)₂), 41.5 (CH₂), 50.9 (CHNH₂), 55.7 (OCH₃), 65.6 (CHNH), 113.9 (CH Arom.), 114.8 (CH Arom.), 144.2 (Cq Arom.), 151.3 (Cq Arom.); m/z (EI⁺) 264 (M⁺, 6%), 178 (100%); HRMS: found 264.219570, C₁₇H₂₆N₂O₅ requires 264.21962; Anal. Cald. For C₁₇H₂₆N₂O₅: C, 66.62, H, 8.55, N, 9.14. Found C, 66.30, H, 8.60, N, 9.93%.

N-((3R*,4S*)-2,6-dimethyl-3-(4-methyl-2-oxopentanamido)heptan-4-yl)-N-(4-methoxyphenyl)-4-methyl-2-oxopentanamide 540

To a solution of ketoacid 519 (130 mg, 1.00 mmol) in DCM (2 mL) was added oxalyl chloride (2.00 equiv., 170 µL) and DMF (two drops) and the mixture stirred at rt for 1 h. The solvent and excess oxalyl chloride were then removed in vacuo and a solution of diamine 538 (188 mg, 0.710 mmol) in DCM (5 mL) was added, followed by pyridine (1.20 equiv., 97 µL) and DMAP (5 mg). The solution was stirred for 24 h. Water (20 mL) was then added and the mixture extracted with DCM (3x20 mL), dried over MgSO₄ and evaporated in vacuo to give crude di-amide 540. Purification by flash column chromatography (Petrol:Et₂O 4:1) gave di-amide 540 (111 mg, 32%) as a colourless oil; Rₙ 0.23 (Petrol:Et₂O 4:1); IR νₘₐₓ (thin film) 3352 br (N-H), 2958 m
(C-H), 1714 m (C=O), 1684 m (C=O), 1649 s (C=O), 1510 s, 1467 m, 1368 m, 1297 m, 1251 m, 1171 m, 1147 m, 1074 m, 1035 m, 831 m cm$^{-1}$; $^1$H NMR (600 MHz) δ 0.71 (3H, d, $J = 6.6$, $CH_3$), 0.72 (3H, d, $J = 6.7$, $CH_3$), 0.90-1.00 (18H, m, $CH_3$), 1.05 (2H, m, CHCH$_2$CH), 1.73 (1H, m, $CH(CH_3)_2$), 1.97 (1H, m, $CH(CH_3)_2$), 2.12 (2H, m, $CH(CH_3)_2$), 2.33 (2H, m, $CH_2$), 2.72 (2H, m, $CH_2$), 3.78 (3H, s, OCH$_3$), 3.87 (1H, m, $CH_2$), 4.83 (1H, br. s, $CH_2$NAr), 6.77 (1H, br. d, $J = 10.9$, $NCOH$), 6.83 (2H, app. d, $J = 8.7$, $CH_2PMPC3-H$), 7.03 (2H, app. d, $J = 8.7$, $CH_2PMPC2-H$); $^{13}$C NMR (150 MHz) δ 16.7 ($CH_3$), 20.2 ($CH_3$), 21.8 ($CH_3$), 22.1 ($CH_3$), 22.4 ($CH_3$), 22.5 ($CH_3$), 23.2 ($CH_3$), 23.6 ($CH_3$), 24.5 (CH), 24.8 (CH), 29.2 (CH$_2$CHNAr), 36.4 (CHCH$_2$CH), 45.2 ($CH_2CO$), 49.1 ($CH_2CO$), 55.4 ($OCH_3$), 55.8 ($CHNHCO$), 114.5 (CH Arom.), 127.3 (Cq Arom.), 131.1 (CH Arom.), 159.8 (ArNCO=O), 160.2 (Cq Arom.), 169.3 (NHC=O), 198.6 ($CH_2C=O$), 200.2 ($CH_2C=O$); m/z (Cl$^+$) 489 (M+H$^+$, 60%), 471 (M+H$^+$-H$_2$O, 61%), 359 (40%), 93 (100%); HRMS: found 489.33410, C$_{28}$H$_{45}$N$_2$O$_5$ requires 489.33230.

(5S*,6R*,Z)-5-Isobutyl-6-isopropyl-4-(4-methoxyphenyl)-3-(2-methylpropylidene)piperazin-2-one 541$^{234}$

To a solution of diamine 538 (61 mg, 0.23 mmol) in THF (5 mL) was added at rt N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (EDC, 67 mg, 0.35 mmol) and 1-hydroxybenzotriazole hydrate (47 mg, 0.35 mmol) followed by a solution of ketoacid 519 (30 mg, 0.23 mmol) in DCM (5 mL). The mixture was stirred at rt for 24 h, then diluted with DCM (20 mL) and washed with brine (10 mL). The combined organics were then dried over MgSO$_4$ and evaporated in vacuo. Purification by flash column chromatography (Petrol:EtOAc 7:3) gave piperazinone 541 (57 mg, 69%) as a brown solid; mp. 152-153 °C; R$_f$ 0.30 (Petrol:EtOAc 7:3); IR $\nu_{max}$ (thin film) 3209 br (N-H), 2956 w (C-H), 1671 s (C=C), 1622 s, 1499 s, 1464 m, 1442 m, 1409 m, 1384 m, 1366 m, 1331 m, 1283 m, 1241 s, 1180 m, 1153 m, 1037 m, 826 s, 767 m cm$^{-1}$; $^1$H NMR (600 MHz) δ 0.68 (3H, d, $J = 6.6$, $CH_3$), 0.79 (3H, d, $J = 6.6$, $CH_3$), 0.79 (3H, d, $J = 6.6$, $CH_3$).
(3R*,5S*,6R*)-3,5-diisobutyl-6-isopropyl-4-(4-methoxyphenyl)piperazin-2-one

To a solution of piperazinone 541 (170 mg, 0.470 mmol) in MeOH (10 mL) was added at rt palladium on carbon (50 mg, 10% by weight, 0.047 mmol) and the mixture was flushed with hydrogen, then stirred under a hydrogen atmosphere (balloon). After the piperazinone starting material was consumed (TLC, 4 h) the mixture was filtered through celite® and washed with DCM (20 mL) and evaporated in vacuo to give crude piperazinone 542. Purification by flash column chromatography (Petrol:Me2CO 4:1) gave the product (170 mg, 100%) as a colourless oil; Rf 0.50 (Petrol:Me2CO 4:1); IR νmax (thin film) 3207 br (N-H), 2954 m (C-H), 1658 s (C=O), 1505 (C=C), 1465 m, 1367 m, 1242 s, 1180 m, 1039 m, 827 m, 788 m, 733 m cm⁻¹; 1H NMR (600 MHz) δ 0.70 (3H, d, J = 6.5, CH3), 0.77 (3H, d, J = 6.7, CH3), 0.90 (3H, d, J = 6.7, CH3), 0.97 (3H, d, J = 6.5, CH3), 0.98 (3H, d, J = 6.8, CH3), 1.03 (3H, d, J = 6.5, CH3), 1.03 (1H, m, CHCHCH2), 1.55 (1H, m, CHCHCH2), 1.55 (1H, m, O=CHCH2), 1.55 (1H, m, CHCH(CH3)2), 1.84 (1H, m, O=CHCH2), 1.92 (1H, m, O=CHCH2CH(CH3)2), 2.06 (1H, m, CHCHCH2CH(CH3)2), 3.18 (1H, dd, J = 10.0, 3.5, NHCH), 3.37 (1H,
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dt, \( J = 12.4, 3.1, \text{NHCHCHN} \), 3.77 (3H, s, OCH\(_3\)), 4.09 (1H, dd, \( J = 9.9, 4.5, O=\text{CCH} \)), 6.02 (1H, br. S, NH), 6.80 (2H, app. d, \( J = 8.9, \text{CH Arom.} \)), 6.91 (2H, app. d, \( J = 8.9, \text{CH Arom.} \)); \(^{13}\text{C NMR (150 MHz)} \delta 18.0 (\text{CCH}_3), 19.5 (\text{CH}_3), 21.5 (\text{CH}_3), 21.6 (\text{CH}_3), 23.3 (\text{CH}_3), 23.4 (\text{CHCHCH}_2\text{CH(CH}_3)_2), 23.7 (\text{CH}_3), 24.7 (O=\text{CCHCH}_2\text{CH(CH}_3)_2), 29.2 (\text{NHCHCH(CH}_3)_2), 34.7 (\text{CCH}_2\text{CHCH}), 44.0 (\text{O=CCHCH}_2\text{CH(CH}_3)_2), 29.2 (\text{NHCHCH(CH}_3)_2), 34.7 (\text{CCH}_2\text{CHCH}), 44.0 (\text{CH}_2\text{CHC}=\text{O}), 55.4 (\text{OCH}_3), 57.2 (\text{NCHCH}=\text{O}), 58.4 (\text{NCHCH}), 58.5 (\text{NHCH}), 114.5 (\text{CCH Arom.}), 122.6 (\text{CH Arom.}), 146.2 (\text{Cq Arom.}), 154.3 (\text{Cq Arom.}), 173.9 (\text{C}=\text{O}); m/z (El) 360 (M\(^+\), 15%), 303 (18%), 192 (100%); HRMS: found 360.27742, \text{C}_{22}\text{H}_{36}\text{N}_2\text{O}_2 \text{requires 360.27713.}

\((3R^*, 5S^*, 6R^*)\)-3,5-diisobutyl-6-isopropylpiperazin-2-one 511\(^{116}\)

![](image)

To a solution of piperazinone 542 (320 mg, 0.880 mmol) in MeCN (10 mL) cooled to 0 °C was added a solution of CAN (2.08 g, 3.52 mmol) in H\(_2\)O (10 mL) dropwise over 3 min. The solution turned from pale yellow to dark orange. The mixture was stirred at this temperature for a further 2 h, over which the solution became light orange. Water (30 mL) was then added and the mixture extracted with EtOAc (3x20 mL), washed with saturated aqueous NaHCO\(_3\) (40 mL), dried over MgSO\(_4\) and evaporated in vacuo to give crude pyrrolidinone 511. Purification by flash column chromatography (Petrol:Me\(_2\)CO 3:2) gave pyrrolidinone 511 (91 mg, 41%) as a brown oil; \( R_f \) 0.53 (Petrol:Me\(_2\)CO 3:2); IR \( \nu_{\text{max}} \) (thin film) 3209 w (N-H), 2955 (C-H), 1658 s (C=O), 1467 m, 1367 m, 1165 w, 918 w, 722 w cm\(^{-1}\); \(^1\text{H NMR (600 MHz)} \delta 0.87-0.99 (18H, m, \text{CCH}_3), 1.30 (2H, m, \text{CCH}_2\text{C}_3\text{H}), 1.40 (1H, m, \text{C}_3\text{HCH}_2), 1.65 (1H, m, \text{C}_5\text{HCHCH}_2\text{CH(CH}_3)_2), 1.74 (1H, m, \text{C}_3\text{HCHCH}_2\text{CH(CH}_3)_2), 1.90 (1H, m, \text{C}_6\text{H(CH}_3)_2), 1.90 (1H, m, \text{C}_5\text{HCH}_2), 3.07 (1H, m, \text{C}_6\text{H}), 3.15 (1H, ddd, \( J = 8.5, 5.8, 4.3, \text{C}_5\text{H} \)), 3.40 (1H, dd, \( J = 10.2, 3.4, \text{C}_3\text{H} \)), 6.22 (1H, br. s, N\(^1\)H), N\(^4\)H peak missing; \(^{13}\text{C NMR (125 MHz)} \delta 17.1 (\text{CH}_3), 20.0 (\text{CH}_3), 21.6 (\text{CH}_3), 22.4 (\text{CH}_3), 23.1 (\text{CH}_3), 23.7 (\text{CH}_3), 24.4 (\text{CH}), 24.8 (\text{CH}), 27.9 (\text{C}_6\text{HCH} \text{H}), 40.5 (\text{C}_5\text{HCH}_2), 41.1 (\text{C}_3\text{HCH}_2), 53.3 (\text{C}_5\text{H}), 56.9 (\text{C}_3\text{H}), 59.4 (\text{C}_6\text{H}), 174.3 (\text{C}=\text{O}); m/z (El) 254 (M\(^+\), 30%), 197 (22%), 169 (43%), 154 (31%); HRMS found 254.23550, \text{C}_{15}\text{H}_{36}\text{N}_2\text{O} \text{requires 254.23527.}
4. Appendixes

4.1 Appendix 1 – Table of coupling constants for pyrrolidinones

The coupling constants of all the pyrrolidinones synthesised during our study are presented in the following table. Coupling $J_{\text{HaHb}}$ refers to the coupling constant between protons $H_a$ and $H_b$ (Figure 41) and $J_{\text{HbHc}}$ between protons $H_b$ and $H_c$. The notation $J_{\text{HaHb}}$ refers to the coupling seen in the signal of proton $H_a$ and $J_{\text{HbHa}}$ to that of proton $H_b$. The constants presented are not averaged.

![Figure 41](image_url)

**Table 23.** Coupling constants of synthesised pyrrolidinones.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Structure</th>
<th>$J_{\text{HaHb}}$</th>
<th>$J_{\text{HbHa}}$</th>
<th>$J_{\text{HbHc}}$</th>
<th>$J_{\text{HcHb}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image_url" alt="Structure 1" /></td>
<td>5.8</td>
<td>5.8</td>
<td>4.4</td>
<td>4.4</td>
</tr>
<tr>
<td>2</td>
<td><img src="image_url" alt="Structure 2" /></td>
<td>7.3</td>
<td>7.2</td>
<td>5.7</td>
<td>5.9</td>
</tr>
<tr>
<td>3</td>
<td><img src="image_url" alt="Structure 3" /></td>
<td>6.7</td>
<td>6.7</td>
<td>5.2</td>
<td>5.3</td>
</tr>
<tr>
<td>4</td>
<td><img src="image_url" alt="Structure 4" /></td>
<td>4.7</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td><img src="image_url" alt="Structure 5" /></td>
<td>5.0</td>
<td>5.1</td>
<td>3.8</td>
<td>4.2</td>
</tr>
<tr>
<td></td>
<td>Structure</td>
<td>5.7</td>
<td>5.6</td>
<td>4.4</td>
<td>4.4</td>
</tr>
<tr>
<td>---</td>
<td>-----------</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>7</td>
<td><img src="image.png" alt="Structure" /></td>
<td>7.3</td>
<td>7.2</td>
<td>5.7</td>
<td>6.2</td>
</tr>
<tr>
<td>8</td>
<td><img src="image.png" alt="Structure" /></td>
<td>4.6</td>
<td>4.9</td>
<td>3.4</td>
<td>3.2</td>
</tr>
<tr>
<td>9</td>
<td><img src="image.png" alt="Structure" /></td>
<td>7.6</td>
<td>7.6</td>
<td>5.9</td>
<td>5.9</td>
</tr>
<tr>
<td>10</td>
<td><img src="image.png" alt="Structure" /></td>
<td>8.0</td>
<td>8.0</td>
<td>6.3</td>
<td>6.2</td>
</tr>
<tr>
<td>11</td>
<td><img src="image.png" alt="Structure" /></td>
<td>-a</td>
<td>6.0</td>
<td>4.6</td>
<td>4.6</td>
</tr>
<tr>
<td>12</td>
<td><img src="image.png" alt="Structure" /></td>
<td>6.7</td>
<td>6.6</td>
<td>4.8</td>
<td>4.7</td>
</tr>
<tr>
<td>13</td>
<td><img src="image.png" alt="Structure" /></td>
<td>7.9</td>
<td>7.9</td>
<td>6.0</td>
<td>-a</td>
</tr>
<tr>
<td>14</td>
<td><img src="image.png" alt="Structure" /></td>
<td>7.0</td>
<td>7.1</td>
<td>5.3</td>
<td>-a</td>
</tr>
<tr>
<td>15</td>
<td><img src="image.png" alt="Structure" /></td>
<td>4.9</td>
<td>4.9</td>
<td>3.7</td>
<td>3.7</td>
</tr>
</tbody>
</table>

*aCould not be distinguished.*
4.2 Appendix 2 – Table of coupling constants for β-nitroamines 379 and trifluoroacetamides 452

The values of coupling constants of all the crude β-nitroamines 379 from the nitro-Mannich reaction of β-nitrostyrene adducts and the trifluoroacetamides 452 derived after protection with TFAA and pyridine are presented in the following table. Coupling $J_{HaHb}$ refers to the coupling constant between protons $H_a$ and $H_b$ (Figure 42) and $J_{HbHc}$ between protons $H_b$ and $H_c$. The notation $J_{HaHb}$ refers to the coupling seen in the signal of proton $H_a$ and $J_{HbHb}$ to that of proton $H_b$. The constants presented are not averaged.

![Figure 42: Protons referring to coupling constants in the $^{1}$H NMR spectra.](image)

Table 24. Coupling constants for C-substituted crude β-nitroamines.

<table>
<thead>
<tr>
<th>R group</th>
<th>$J_{HaHb}$</th>
<th>$J_{HbHa}$</th>
<th>$J_{HbHc}$</th>
<th>$J_{HcHb}$</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-indoline</td>
<td>11.5</td>
<td>11.5</td>
<td>3.4</td>
<td>a</td>
<td>95:5</td>
</tr>
<tr>
<td>1,3,5-trimethoxybenzyl</td>
<td>12.2</td>
<td>a</td>
<td>a</td>
<td>a</td>
<td>&gt;95:5</td>
</tr>
</tbody>
</table>

Table 25. Coupling constants for C-substituted trifluoroacetamides.

<table>
<thead>
<tr>
<th>R group</th>
<th>$J_{HaHe}$</th>
<th>$J_{HeHa}$</th>
<th>$J_{HeHf}$</th>
<th>$J_{HfHe}$</th>
<th>Stereochemistry</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-indoline</td>
<td>2.8</td>
<td>a</td>
<td>a</td>
<td>a</td>
<td>anti, anti</td>
</tr>
<tr>
<td>1,3,5-trimethoxybenzyl</td>
<td>11.5</td>
<td>11.5</td>
<td>6.8</td>
<td>6.8</td>
<td>anti, anti</td>
</tr>
</tbody>
</table>

Table 26. Coupling constants for alkoxy-substituted crude β-nitroamines.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R group</th>
<th>$J_{HaHb}$</th>
<th>$J_{HbHa}$</th>
<th>$J_{HbHc}$</th>
<th>$J_{HcHb}$</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeO-</td>
<td>9.2</td>
<td>9.2</td>
<td>5.3</td>
<td>5.4</td>
<td>90:10</td>
</tr>
<tr>
<td>2</td>
<td>EtO-</td>
<td>9.2</td>
<td>9.3</td>
<td>5.8</td>
<td>5.8</td>
<td>&gt;95:5</td>
</tr>
<tr>
<td>3</td>
<td>BnO-</td>
<td>9.1</td>
<td>9.2</td>
<td>5.3</td>
<td>5.3</td>
<td>90:10</td>
</tr>
<tr>
<td>4</td>
<td>'PrO-</td>
<td>8.8</td>
<td>8.8</td>
<td>6.2</td>
<td>6.0</td>
<td>&gt;95:5</td>
</tr>
</tbody>
</table>
### Table 27. Coupling constants for alkoxy-substituted trifluoroacetamides.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R group</th>
<th>$J_{HdHe}$</th>
<th>$J_{HeHd}$</th>
<th>$J_{HeHf}$</th>
<th>$J_{HfHe}$</th>
<th>Stereochemistry</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeO-</td>
<td>8.4</td>
<td>8.5</td>
<td>10.9</td>
<td>11.0</td>
<td>anti, anti</td>
</tr>
<tr>
<td>2</td>
<td>EtO-</td>
<td>8.4</td>
<td>8.5</td>
<td>10.9</td>
<td>10.9</td>
<td>anti, anti</td>
</tr>
<tr>
<td>3</td>
<td>BnO-</td>
<td>6.7</td>
<td>6.8</td>
<td>11.0</td>
<td>11.0</td>
<td>anti, anti</td>
</tr>
<tr>
<td>4</td>
<td>'PrO-</td>
<td>7.7</td>
<td>7.7</td>
<td>10.7</td>
<td>10.8</td>
<td>anti, anti</td>
</tr>
</tbody>
</table>

### Table 28. Coupling constants for N-substituted crude β-nitroamines.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R group</th>
<th>$J_{HaHb}$</th>
<th>$J_{HbHa}$</th>
<th>$J_{HbHc}$</th>
<th>$J_{HcHb}$</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>p-NO$_2$C$_6$H$_4$NH-</td>
<td>-$^a$</td>
<td>9.1</td>
<td>6.2</td>
<td>6.3</td>
<td>90:10</td>
</tr>
<tr>
<td>2</td>
<td>1H-benzotriazol-1-yl</td>
<td>-$^a$</td>
<td>-$^a$</td>
<td>-$^a$</td>
<td>-$^a$</td>
<td>&gt;95:5</td>
</tr>
<tr>
<td>3</td>
<td>Oxazolidin-2-one</td>
<td>-$^a$</td>
<td>-$^a$</td>
<td>-$^a$</td>
<td>-$^a$</td>
<td>75:25</td>
</tr>
</tbody>
</table>

### Table 29. Coupling constants for N-substituted trifluoroacetamides.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R group</th>
<th>$J_{HdHe}$</th>
<th>$J_{HeHd}$</th>
<th>$J_{HeHf}$</th>
<th>$J_{HfHe}$</th>
<th>Stereochemistry</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>p-NO$_2$C$_6$H$_4$NH-</td>
<td>3.1</td>
<td>3.1</td>
<td>10.8</td>
<td>10.8</td>
<td>anti, anti</td>
</tr>
<tr>
<td>2</td>
<td>1H-benzotriazol-1-yl</td>
<td>10.7</td>
<td>-$^a$</td>
<td>-$^a$</td>
<td>6.3</td>
<td>anti, anti</td>
</tr>
<tr>
<td>3</td>
<td>Oxazolidin-2-one</td>
<td>10.3</td>
<td>9.9</td>
<td>7.9</td>
<td>7.8</td>
<td>anti, anti</td>
</tr>
</tbody>
</table>

### Table 30. Coupling constants for S-substituted crude β-nitroamines.

<table>
<thead>
<tr>
<th>R group</th>
<th>$J_{HaHb}$</th>
<th>$J_{HbHa}$</th>
<th>$J_{HbHc}$</th>
<th>$J_{HcHb}$</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>nBuS-</td>
<td>11.0</td>
<td>11.0</td>
<td>3.5</td>
<td>-$^a$</td>
<td>60:40</td>
</tr>
<tr>
<td>PhS-</td>
<td>9.5</td>
<td>9.4</td>
<td>5.3</td>
<td>-$^a$</td>
<td>65:35</td>
</tr>
</tbody>
</table>

### Table 31. Coupling constants for S-substituted trifluoroacetamides.

<table>
<thead>
<tr>
<th>R group</th>
<th>$J_{HdHe}$</th>
<th>$J_{HeHd}$</th>
<th>$J_{HeHf}$</th>
<th>$J_{HfHe}$</th>
<th>Stereochemistry</th>
</tr>
</thead>
<tbody>
<tr>
<td>nBuS-</td>
<td>6.2</td>
<td>6.2</td>
<td>10.4</td>
<td>10.3</td>
<td>anti, anti</td>
</tr>
<tr>
<td>PhS-</td>
<td>5.1</td>
<td>5.1</td>
<td>9.8</td>
<td>9.8</td>
<td>anti, anti</td>
</tr>
</tbody>
</table>
4.3 Appendix 3 – Crystallography data

(3S*, 4S*, 5S*)-3-ethyl-1-(4-methoxyphenyl)-4-nitro-5-(pyridin-2-yl)pyrrolidin-2-one 269

Table 32. Crystal data and structure refinement at 100(2) K.

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>C_{18}H_{19}N_{3}O_{4}</td>
</tr>
<tr>
<td>Formula weight</td>
<td>341.36</td>
</tr>
<tr>
<td>Wavelength</td>
<td>1.54187 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P21/c</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>a = 12.6533(8) Å, (\alpha = 90^\circ)</td>
</tr>
<tr>
<td></td>
<td>b = 15.8418(2) Å, (\beta = 105.971(8)^\circ)</td>
</tr>
<tr>
<td></td>
<td>c = 8.85870(10) Å, (\gamma = 90^\circ)</td>
</tr>
<tr>
<td>Volume</td>
<td>1707.19(11) Å³</td>
</tr>
<tr>
<td>Z</td>
<td>4</td>
</tr>
<tr>
<td>Density (calculated)</td>
<td>1.328 Mg / m³</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>0.789 mm⁻¹</td>
</tr>
<tr>
<td>(F(000))</td>
<td>720</td>
</tr>
<tr>
<td>Crystal</td>
<td>Plate; Colourless</td>
</tr>
<tr>
<td>Crystal size</td>
<td>0.07 \times 0.01 \times 0.01 mm³</td>
</tr>
<tr>
<td>(\theta) range for data collection</td>
<td>6.67 – 66.44°</td>
</tr>
<tr>
<td>Index ranges</td>
<td>(-11 \leq h \leq 15, -18 \leq k \leq 18, -10 \leq l \leq 10)</td>
</tr>
<tr>
<td>Reflections collected</td>
<td>11691</td>
</tr>
</tbody>
</table>
Independent reflections 2947 \[ R_{int} = 0.0855 \]
Completeness to \( \theta = 66.44^\circ \) 98.1 %
Absorption correction Semi–empirical from equivalents
Max. and min. transmission 0.9922 and 0.9469
Refinement method Full-matrix least-squares on \( F^2 \)
Data / restraints / parameters 2947 / 0 / 229
Goodness-of-fit on \( F^2 \) 1.062
Final \( R \) indices \([F^2 > 2\sigma(F^2)]\) \( R_I = 0.0739, wR_2 = 0.2028 \)
\( R \) indices (all data) \( R_I = 0.0900, wR_2 = 0.2354 \)
Extinction coefficient 0.0068(15)
Largest diff. peak and hole 0.362 and \(-0.337 \) eÅ\(^{-3}\)
Diffractometer type Rigaku Saturn724+ area detector (\( \omega \) scans to fill asymmetric unit sphere)
Cell determination CrystalClear-SM Expert 2.0 r7 (Rigaku 2011)

\[ \text{N-}((2R, 3R, 4R)-4\text{-ethyl-1-(4-methoxyphenyl)-5-oxo-2-(thiophen-2-yl)pyrrolidin-3-yl)-2,2,2-trifluoroacetamide 287} \]

**Table 33.** Crystal data and structure refinement at 100(2) K.

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>C(<em>{19})H(</em>{19})F(_3)N(_2)O(_3)S</td>
</tr>
<tr>
<td>Formula weight</td>
<td>412.42</td>
</tr>
</tbody>
</table>
Wavelength                          1.54187 Å
Crystal system                     Orthorhombic
Space group                        P212121
Unit cell dimensions               
  a = 8.33990(10) Å               \(\alpha = 90^\circ\)
  b = 10.16140(10) Å              \(\beta = 90^\circ\)
  c = 22.2832(15) Å              \(\gamma = 90^\circ\)
Volume                             1888.39(13) Å³
Z                                   4
Density (calculated)               1.451 Mg / m³
Absorption coefficient             2.000 mm⁻¹
F(000)                             856
Crystal                             Cut Block; Colourless
Crystal size                       0.26 × 0.22 × 0.16 mm³
\(\theta\) range for data collection 6.63 – 66.37°
Index ranges                       \(-7 \leq h \leq 9, -12 \leq k \leq 10, -24 \leq l \leq 26\)
Reflections collected              7566
Independent reflections            3114 [Rint = 0.0329]
Completeness to \(\theta = 66.37^\circ\) 97.2 %
Absorption correction              Semi-empirical from equivalents
Max. and min. transmission         0.7402 and 0.6244
Refinement method                  Full-matrix least-squares on \(F^2\)
Data / restraints / parameters      3114 / 0 / 255
Goodness-of-fit on F2              1.058
Final R indices \([F^2 > 2\sigma(F^2)]\) R1 = 0.0248, wR2 = 0.0635
R indices (all data)               R1 = 0.0253, wR2 = 0.0637
Absolute structure parameter       0.011(13)
Largest diff. peak and hole         0.161 and –0.173 e Å⁻³
Diffractometer type                Rigaku Saturn724+ area detector (\(\omega\) scans to fill asymmetric unit sphere)
Cell determination                CrystalClear-SM Expert 2.0 r7 (Rigaku 2011)
Ethyl 3-(4-ethyl-2-hydroxy-1-(4-methoxyphenyl)-5-oxo-2-phenyl-2,5-dihydro-1H-pyrrol-3-yl)propanoate 303

Table 34. Crystal data and structure refinement at 120(2) K.

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>C_{24}H_{27}NO_5</td>
</tr>
<tr>
<td>Formula weight</td>
<td>409.47</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71075 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Triclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P-1</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>a = 9.9597(6) Å, b = 10.7744(6) Å, c = 11.8214(8) Å</td>
</tr>
<tr>
<td></td>
<td>α = 66.695(5)°, β = 87.864(6)°, γ = 62.888(4)°</td>
</tr>
<tr>
<td>Volume</td>
<td>1021.04(11) Å^3</td>
</tr>
<tr>
<td>Z</td>
<td>2</td>
</tr>
<tr>
<td>Density (calculated)</td>
<td>1.332 Mg / m^3</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>0.093 mm^{-1}</td>
</tr>
<tr>
<td>F(000)</td>
<td>436</td>
</tr>
<tr>
<td>Crystal</td>
<td>Prism; Colourless</td>
</tr>
<tr>
<td>Crystal size</td>
<td>0.20 × 0.20 × 0.20 mm^3</td>
</tr>
<tr>
<td>θ range for data collection</td>
<td>3.26 − 27.46°</td>
</tr>
<tr>
<td>Index ranges</td>
<td>−12 ≤ h ≤ 12, −13 ≤ k ≤ 13, −15 ≤ l ≤ 15</td>
</tr>
<tr>
<td>Reflections collected</td>
<td>10380</td>
</tr>
<tr>
<td>Independent reflections</td>
<td>4598 [R_{int} = 0.0234]</td>
</tr>
<tr>
<td>Completeness to θ = 27.46°</td>
<td>98.5 %</td>
</tr>
<tr>
<td>Absorption correction</td>
<td>Semi–empirical from equivalents</td>
</tr>
</tbody>
</table>
Max. and min. transmission: 0.9816 and 0.9816
Refinement method: Full-matrix least-squares on $F^2$
Data / restraints / parameters: 4598 / 0 / 275
Goodness-of-fit on $F^2$: 1.107
Final $R$ indices [$F^2 > 2\sigma(F^2)$]: $R1 = 0.0350$, $wR2 = 0.0834$
$R$ indices (all data): $R1 = 0.0551$, $wR2 = 0.1051$
Largest diff. peak and hole: 0.364 and −0.239 e Å$^{-3}$
Diffractometer type: Rigaku Saturn724+ area detector ($\omega$ scans to fill asymmetric unit sphere)
Cell determination: CrystalClear-SM Expert 2.0 r7 (Rigaku 2011)

**2,2,2-Trifluoro-N-(4-methoxyphenyl)-N-((1R\*,2S\*,3R\*)-2-nitro-1,3-diphenyl-3-(2,4,6-trimethoxyphenyl)propyl)acetamide 456**

![Chemical structure image]

**Table 35.** Crystal data and structure refinement at 120(2) K.

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>C$<em>{33}$H$</em>{31}$F$_3$N$_2$O$_7$</td>
</tr>
<tr>
<td>Formula weight</td>
<td>624.60</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Triclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>$P\bar{1}$</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>$a = 11.9846(6)$ Å, $\alpha = 63.816(5)^{\circ}$</td>
</tr>
<tr>
<td></td>
<td>$b = 12.2669(4)$ Å, $\beta = 64.578(5)^{\circ}$</td>
</tr>
<tr>
<td></td>
<td>$c = 12.7033(8)$ Å, $\gamma = 80.069(6)^{\circ}$</td>
</tr>
<tr>
<td>Volume</td>
<td>1513.31(13) Å$^3$</td>
</tr>
</tbody>
</table>
\[ Z \]

Density (calculated) \( 1.371 \, \text{Mg} / \text{m}^3 \)

Absorption coefficient \( 0.108 \, \text{mm}^{-1} \)

\[ F(000) \]

652

Crystal Prism; Colourless

Crystal size \( 0.25 \times 0.21 \times 0.10 \, \text{mm}^3 \)

\( \theta \) range for data collection \( 3.19 - 25.03^\circ \)

Index ranges \(-14 \leq h \leq 14, -13 \leq k \leq 14, -15 \leq l \leq 15 \)

Reflections collected 17291

Independent reflections 5343 [\( R_{int} = 0.0320 \)]

Completeness to \( \theta = 25.03^\circ \) 99.8 %

Absorption correction Semi–empirical from equivalents

Max. and min. transmission 0.9892 and 0.9734

Refinement method Full-matrix least-squares on \( F^2 \)

Data / restraints / parameters 5343 / 0 / 411

Goodness-of-fit on \( F^2 \) 1.085

Final \( R \) indices \([ F^2 > 2\sigma(F^2) ] \) \( RI = 0.0606, \, wR2 = 0.1772 \)

\( R \) indices (all data) \( RI = 0.0933, \, wR2 = 0.2630 \)

Extinction coefficient 0.042(8)

Largest diff. peak and hole 0.453 and \(-0.435 \, \text{e} \, \text{Å}^{-3} \)

Diffractometer type \( \text{Rigaku R-Axis Spider} \) including curved Fujifilm image plate and a graphite monochromated sealed tube Mo generator.

Cell determination CrystalClear-SM Expert 2.0 r7 (Rigaku 2011)
### Table 36. Crystal data and structure refinement at 100(2) K.

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>$C_{25.50}H_{23.50}Cl_{1.50}F_3N_2O_5$</td>
</tr>
<tr>
<td>Formula weight</td>
<td>548.14</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71075 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Triclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>$P\bar{1}$</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>$a = 11.7772(3)$ Å, $\alpha = 69.247(5)^\circ$</td>
</tr>
<tr>
<td></td>
<td>$b = 14.4495(4)$ Å, $\beta = 77.347(6)^\circ$</td>
</tr>
<tr>
<td></td>
<td>$c = 17.3239(12)$ Å, $\gamma = 66.473(5)^\circ$</td>
</tr>
<tr>
<td>Volume</td>
<td>2517.3(2) Å$^3$</td>
</tr>
<tr>
<td>$Z$</td>
<td>4</td>
</tr>
<tr>
<td>Density (calculated)</td>
<td>1.446 Mg / m$^3$</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>0.267 mm$^{-1}$</td>
</tr>
<tr>
<td>$F(000)$</td>
<td>1132</td>
</tr>
<tr>
<td>Crystal</td>
<td>Block; Colourless</td>
</tr>
<tr>
<td>Crystal size</td>
<td>$0.07 \times 0.05 \times 0.03$ mm$^3$</td>
</tr>
<tr>
<td>$\theta$ range for data collection</td>
<td>$3.02 – 27.48^\circ$</td>
</tr>
<tr>
<td>Index ranges</td>
<td>$-12 \leq h \leq 15, -17 \leq k \leq 18, -22 \leq l \leq 22$</td>
</tr>
<tr>
<td>Reflections collected</td>
<td>34108</td>
</tr>
<tr>
<td>Independent reflections</td>
<td>11500 [$R_{int} = 0.0491$]</td>
</tr>
<tr>
<td>Completeness to $\theta = 27.48^\circ$</td>
<td>99.5 %</td>
</tr>
<tr>
<td>Absorption correction</td>
<td>Semi–empirical from equivalents</td>
</tr>
</tbody>
</table>
Max. and min. transmission 0.9920 and 0.9815
Refinement method Full-matrix least-squares on $F^2$
Data / restraints / parameters 11500 / 0 / 671
Goodness-of-fit on $F^2$ 1.068
Final $R$ indices [$F^2 > 2\sigma(F^2)$] $R1 = 0.0442$, $wR2 = 0.0992$
$R$ indices (all data) $R1 = 0.0712$, $wR2 = 0.1120$
Largest diff. peak and hole 0.359 and −0.607 e Å$^{-3}$
Diffractometer type Rigaku AFC12 goniometer equipped with an enhanced sensitivity (HG) Saturn724+ detector mounted at the window of an FR-E+ SuperBright molybdenum rotating anode generator with HF Varimax optics (100µm focus)
Cell determination CrystalClear-SM Expert 2.0 r7 (Rigaku 2011)

$N$-((1$R^*$,2$R^*$,3$S^*$)-3-(1$H$-benzo[d][1,2,3]triazol-1-yl)-2-nitro-1,3-diphenylpropyl)-2,2,2-trifluoro-$N$-(4-methoxyphenyl)acetamide 482

Table 37. Crystal data and structure refinement at 100(2) K.

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>$C_{30}H_{24}F_3N_5O_4$</td>
</tr>
<tr>
<td>Formula weight</td>
<td>575.54</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71075 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>$P2_1/c$</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>$a = 16.6181(15)$ Å</td>
</tr>
</tbody>
</table>
b = 14.1560(13) Å  \quad  \beta = 93.776(7)°  

c = 11.7132(10) Å  \quad  \gamma = 90°  

Volume  
2749.5(4) Å³  

Z  
4  

Density (calculated)  
1.390 Mg / m³  

Absorption coefficient  
0.108 mm⁻¹  

F(000)  
1192  

Crystal  
Platelet; Colourless  

Crystal size  
0.04 × 0.04 × 0.01 mm³  

θ range for data collection  
3.13 – 25.03°  

Index ranges  
−19 ≤ h ≤ 18, −16 ≤ k ≤ 16, −13 ≤ l ≤ 12  

Reflections collected  
15500  

Independent reflections  
4823 \left[ R_{int} = 0.1439 \right]  

Completeness to θ = 25.03°  
99.7 %  

Absorption correction  
Semi–empirical from equivalents  

Max. and min. transmission  
0.9989 and 0.9957  

Refinement method  
Full-matrix least-squares on F²  

Data / restraints / parameters  
4823 / 0 / 380  

Goodness-of-fit on F²  
0.989  

Final R indices [F² > 2σ(F²)]  
R1 = 0.0820, wR2 = 0.1534  

R indices (all data)  
R1 = 0.1994, wR2 = 0.1961  

Largest diff. peak and hole  
0.300 and −0.258 e Å⁻³  

Diffractometer type  
Rigaku AFC12 goniometer equipped with an enhanced sensitivity (HG) Saturn724+ detector mounted at the window of an FR-E+ SuperBright molybdenum rotating anode generator with HF Varimax optics (100µm focus)  

Cell determination  
CrystalClear-SM Expert 2.0 r7 (Rigaku 2011)
2,2,2-trifluoro-N-(4-methoxyphenyl)-N-(2-nitro-3-(2-oxooxazolidin-3-yl)-1,3-diphenylpropyl)acetamide 480

Table 38. Crystal data and structure refinement at 100(2) K.

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>C_{27}H_{24}F_{3}N_{3}O_{6}</td>
</tr>
<tr>
<td>Formula weight</td>
<td>543.49</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71075 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P21/n</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>a = 9.1677(14) Å</td>
</tr>
<tr>
<td></td>
<td>b = 9.7544(14) Å</td>
</tr>
<tr>
<td></td>
<td>c = 28.121(5) Å</td>
</tr>
<tr>
<td></td>
<td>α = 90°</td>
</tr>
<tr>
<td></td>
<td>β = 97.894(7)°</td>
</tr>
<tr>
<td></td>
<td>γ = 90°</td>
</tr>
<tr>
<td>Volume</td>
<td>2490.9(7) Å³</td>
</tr>
<tr>
<td>Z</td>
<td>4</td>
</tr>
<tr>
<td>Density (calculated)</td>
<td>1.449 Mg \text{ / m}^3</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>0.118 mm(^{-1})</td>
</tr>
<tr>
<td>(F(000))</td>
<td>1128</td>
</tr>
<tr>
<td>Crystal</td>
<td>Plate; Colourless</td>
</tr>
<tr>
<td>Crystal size</td>
<td>0.03 \times 0.03 \times 0.01 \text{ mm}³</td>
</tr>
<tr>
<td>(θ) range for data collection</td>
<td>3.03 – 25.03°</td>
</tr>
<tr>
<td>Index ranges</td>
<td>(-10 \leq h \leq 10, -11 \leq k \leq 10, -25 \leq l \leq 33)</td>
</tr>
<tr>
<td>Reflections collected</td>
<td>11836</td>
</tr>
<tr>
<td>Independent reflections</td>
<td>4246 ([R_{int} = 0.2162])</td>
</tr>
<tr>
<td>Completeness to (θ = 25.03°)</td>
<td>96.6%</td>
</tr>
</tbody>
</table>
Absorption correction  
Semi-empirical from equivalents

Max. and min. transmission  
0.9988 and 0.9965

Refinement method  
Full-matrix least-squares on $F^2$

Data / restraints / parameters  
4246 / 0 / 354

Goodness-of-fit on $F^2$  
0.967

Final $R$ indices [$F^2 > 2\sigma(F^2)$]  
$R1 = 0.0991$, $wR2 = 0.1774$

$R$ indices (all data)  
$R1 = 0.2528$, $wR2 = 0.2418$

Extinction coefficient  
0.0055(18)

Largest diff. peak and hole  
0.342 and −0.341 e Å$^{-3}$

Diffractometer type  
Rigaku AFC12 goniometer equipped with an enhanced sensitivity (HG) Saturn724+ detector mounted at the window of an FR-E+ SuperBright molybdenum rotating anode generator with HF Varimax optics (100µm focus)

Cell determination  
CrystalClear-SM Expert 2.0 r7 (Rigaku 2011)

(2$S^*$,3$R^*$,6$R^*$)-2,6-diiisobutyl-3-isopropyl-5-oxopiperazin-1-ium chloride 548

Table 39. Crystal data and structure refinement at 100(2) K.

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>C$<em>{13}$H$</em>{31}$ClN$_2$O</td>
</tr>
<tr>
<td>Formula weight</td>
<td>290.87</td>
</tr>
<tr>
<td>Temperature</td>
<td>100(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71075 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>$P2_1/c$</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>$a = 12.6231(15)$ Å</td>
</tr>
<tr>
<td></td>
<td>$\alpha = 90^\circ$</td>
</tr>
</tbody>
</table>
Volume 1938.9(4) Å³

Density (calculated) 0.996 Mg / m³

Absorption coefficient 0.194 mm⁻¹

$F(000)$ 640

Crystal Blade; Colourless

Crystal size $0.22 \times 0.03 \times 0.01$ mm³

$\theta$ range for data collection 3.23 – 27.48°

Index ranges $-16 \leq h \leq 16$, $0 \leq k \leq 8$, $0 \leq l \leq 30$

Reflections collected 4443

Independent reflections 4443 [$R_{int} = 0.0000$]

Completeness to $\theta = 27.48°$ 99.9 %

Absorption correction Semi–empirical from equivalents

Max. and min. transmission 0.9981 and 0.9585

Refinement method Full-matrix least-squares on $F^2$

Data / restraints / parameters 4443 / 0 / 178

Goodness-of-fit on $F^2$ 1.045

Final $R$ indices [$F^2 > 2 \sigma(F^2)$] $R1 = 0.0726$, $wR2 = 0.1803$

$R$ indices (all data) $R1 = 0.1159$, $wR2 = 0.1966$

Largest diff. peak and hole 0.416 and −0.249 e Å⁻³

Diffractometer type Rigaku AFC12 goniometer equipped with an enhanced sensitivity (HG) Saturn724+ detector mounted at the window of an FR-E+ SuperBright molybdenum rotating anode generator with HF Varimax optics (100µm focus)

Cell determination CrystalClear-SM Expert 2.0 r11 (Rigaku 2011)
5. References


114. Mills, M. PhD Thesis, University College London, **2010**.

115. Stepney, G. PhD Thesis, University of Nottingham, **2008**.


