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Approaches to Amino Acid Building Blocks via Catalytic Asymmetric Reduction

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A dissertation submission for the degree of Doctor of Philosophy

Aug 2022

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Declaration

This dissertation records the work carried out between October 2018 and July 2022 in the department of Chemistry, Sheffield, and all work is original except where acknowledged by referencing. No part of this work has been submitted for any other qualification at this or any other institution.

Publications

Current applications of kinetic resolution in the asymmetric synthesis of substituted pyrrolidines. S. S. Berry, S. Jones, *Org. Biomol. Chem.*, 2021, **19**, 10493-10515.

Acknowledgments

Firstly, I would like to thank my supervisor Prof. Simon Jones his guidance and for this valuable opportunity.

I am extremely grateful for the continued help and support from Dr Dan Cox from RedBrick molecular. Many thanks to the residents of E27 in particular past Jones group members, Dr Jenna Spencer-Briggs, Dr Joe Ferner, and Dr Haneesh Gangotra, and past and current Coldham group members, Dr Anthony Choi, Jennifer Yeo, and Beth Ritchie for their moral support and for keeping lab life interesting.

Lastly, I would like to thank my Mum, Dad, and Terri for all their encouragement throughout my PhD, and for listening to me talk about my chemistry even when they have no clue what I was taking about.

Abbreviations

Ac	Acetyl
Ala	Alanine
Aq.	Aqueous
Ar	Aryl
atm	Atmosphere
BINAP	2,2’-Bis(diphenylphosphino)-1,1’-binaphthyl
BINAPINE	4,4’-Di-*tert*-butyl-4,4’,5,5’-tetrahydro-3,3’-bi-3H-dinaphtho[2,1-c:1’,2’-e]phosphenpin
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
Bu	Butyl
Cat.	Catalyst
Cbz	Benzyloxycarbonyl
COD	1,5-Cyclooctadiene
Cy	Cyclohexyl
DABCO	1,4-Diazabicyclo[2.2.2]octane
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	N,N’-Dicyclohexylcarbodiimide
DCE	1,2-Dichloroethane
DCM	Dichloromethane
de	Diastereomeric excess
DECL	DNA encoded chemical libraries
$(DHQD)_2PHAL$	Hydroquinidine 1,4-phthalazinediyl diether
DIBAL-H	Diisobutylaluminium hydride
DIPEA	Diisopropyl ethyl amine
DKR	Dynamic kinetic resolution
DMA	Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
dr	Diastereomeric ratio
EA	Ethyl acetate
ee	Enantiomeric excess
er	Enantiomeric ratio
eq	Equivalent

Et	Ethyl
FBDD	Fragment based drug design
Gly	Glycine
h	Hour(s)
HPLC	High performance liquid chromatography
HTS	High throughput screening
LiHMDS	Lithium bis(trimethylsilyl)amide
i-Pr	*iso*-Propyl
IR	Infrared
LRMS	Low resolution mass spectroscopy
Me	Methyl
MOM	Methoxymethyl
Mpt	Melting point
MS	Molecular sieves
MW	Microwave
nbd	Norbornadiene
NMP	*N*-Methyl-2-pyrrolidone
NMR	Nuclear magnetic resonance
PAM	Phenylalanine aminomutase
PE	Petroleum ether
Ph	Phenyl
Piv	Pivaloyl
PKR	Parallel kinetic resolution
PMP	*para*-Methoxyphenyl
Py	Pyridyl
Red-Al	Sodium bis(2-methoxyethoxy)aluminum hydride
rt	Room temperature
SM	Starting material
STAB	Sodium triacetoxyborohydride
TangPhos	1,1'-Di-*tert*-butyl-(2,2')-diphospholane
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide
TBDPS	*tert*-Butyldiphenylsilyl
t-Bu	*tert*-Butyl
TEA	Triethylamine
TFA	Trifluoroacetic acid

TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
tol	Toluene
Tosic acid/*p*-TsOH	*p*-Toluenesulfonic acid
Ts	Tosyl
Turbo Grignard	Isopropyl magnesium chloride lithium chloride complex

Abstract

Work previously conducted within the Jones group on the asymmetric reduction of ketimines and β-enamino esters employed trichlorosilane and an imidazole based organocatalyst (*S*)-**49**. This methodology was investigated in relation to imines and enamine based on amino acids. Firstly, naturally available amino acids, glycine and valine, were investigated as *N*-substituents to synthesise α-methylbenzyl substituted amino acids. By-product formation limited the use of glycine. A poor yield of 11% for the major diastereoisomer was obtained during the trichlorosilane mediated reduction of the valine ketimine with a good diastereoselectivity of 85:15 dr. Due to time limitation brought on by Covid-19 safety procedures, these substrates were not investigated further.

Constrained amino acids based on 2,5-disubstituted pyrrolidines and 2,3-disubstituted piperidines were investigated in a trichlorosilane mediated reduction and a hydrogenation using a H-cube® flow reactor, respectively. Excellent diastereoselectivities of up to 98:2 dr and >99:1 dr were obtained for each method. Difficulties with the determination of the enantioselectivities of the pyrrolidines prevented further optimisation of the reaction and investigation into a kinetic resolution. Hydrogenation using the H-cube® was expanded to 2,3-disubstituted pyrrolidines and azepines, obtaining excellent diastereoselectivities of >99:1 dr.

Amino acid analogues, β-amino phosphonates, were reduced in a trichlorosilane mediated reduction. These compounds were found reduce significantly faster than their carbon counterparts, giving an uncontrollable background reaction. This was investigated and some self-catalysis was occurring but not to the extent that it would be the only factor encouraging the fast reduction without a catalyst.

1 Introduction

1.1 Fragment based drug design

Drug discovery typically follows the same path (Figure 1).[1] A target, generally a protein, is selected and a library of molecules is screened for beneficial interactions between the target and the molecule. Once a hit compound has been identified, modification and optimization of its properties is conducted before it enters drug development. One common method for hit identification is high throughput screening (HTS) whereby a large collection of drug-like molecules is rapidly screened for hit compounds. These molecules generally follow Lipinski's rule of 5, wherein each molecule has a molecular weight less than 500 da, contains 5 or less hydrogen bond donors, 10 or less hydrogen bond acceptors, and a log *P* less than 5.[2] An alternative method is fragment-based drug design (FBDD).

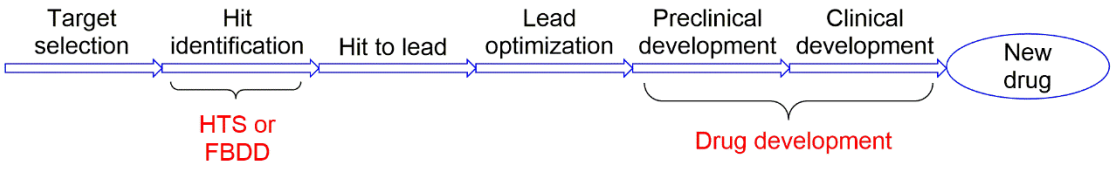


Figure 1: Drug discovery methodology

In the past 25 years, FBDD has become increasingly important as a methodology for the development of new pharmaceuticals.[3,4] Over 30 drugs have entered clinical trials by way of this method with 8 having been approved for use (Figure 2). Unlike HTS, the starting molecules are often not based on pre-existing drug molecules. Fragments generally follow a rule of 3, wherein the molecule has a molecular weight <300 da, contains 3 or less hydrogen bond donors, and a log *P* less than 3. Starting from small molecules has several advantages over starting with significantly larger drug-like molecules. Principally, it is easier to synthesise and maintain a library of small fragments allowing this chemistry to be applied within smaller companies and academia. Current libraries of small fragments are significantly smaller compared to those used in HTS of drug-like molecules, consisting of only a few thousand fragments.

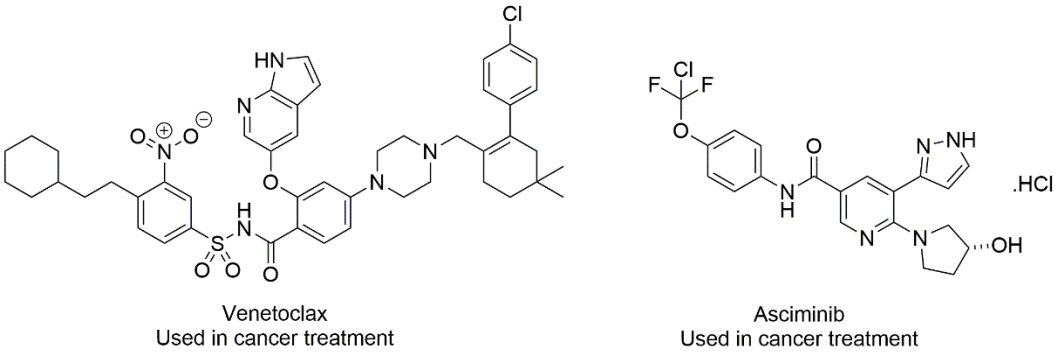


Figure 2: Drugs approved for used created through FBDD

DNA encoded chemical libraries (DECLs) are an example of a chemical library used to screen small molecules.[5] Each small molecule is tagged with a chain of DNA, effectively acting as a barcode (Figure 3). The library is screened against an immobilized target protein, hit compounds bind to the target and any unbound compounds are removed by washing. The binding is reversed, hit compound removed, and the DNA sequenced to determine which small molecule is the hit compound. This methodology is simple and makes for easy identification of hit compounds. Each small molecule requires an attachment point to be tagged by DNA, typically this is done through amide couplings.

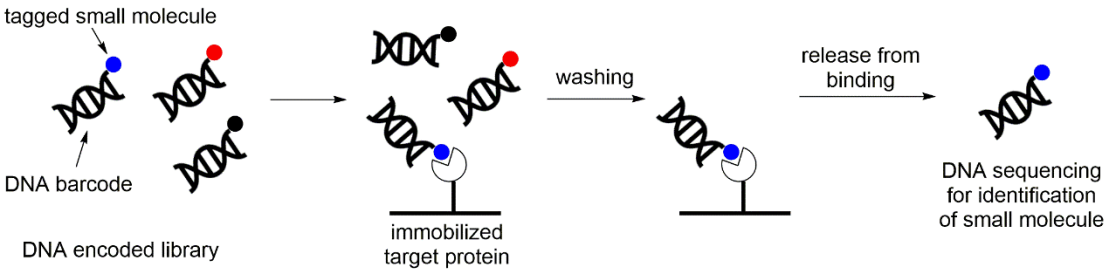


Figure 3: Process of a DNA encoded library

Multifunctional building blocks are important for both DECLs and FBDD as they have multiple points to expand and optimise the compound as well as potential attachment points for DNA tagging. Amino acids are particularly useful in this regard as even the most basic molecules contain two attachment points.

1.2 Amino acids

1.2.1 Importance and applications of amino acids

Amino acids can take many forms, the most common found in living organisms being α-amino acids, 500 of which are known to occur naturally.[6] Only 20 of this large selection are classified as standard amino acids due to being encoded in DNA. These important building blocks are the main constituent of proteins, used as frameworks within natural products, and are frequently used in drug discovery. The pharmaceutical applications of amino acids are vast (Figure 4).[7–9]

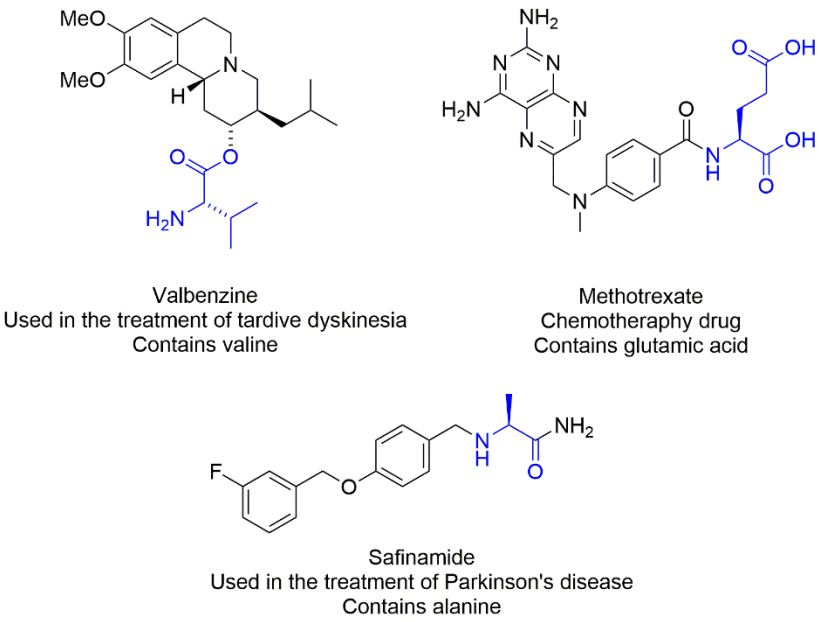


Figure 4: Pharmaceuticals containing standard amino acids

The β-amino acids are a less common class of amino acids than the α-form.[10] β-Alanine is the most common and, unlike its α-counterpart, it is non-chiral. It is a constituent of two antioxidants found within the brain, anserine and carnosine, and is a key component of vitamin B_5 (Figure 5).[11] β-Amino acids are commonly found in bacteria; β-lysine and β-arginine are constituents of the antibiotics Streptothricin F and Blasticidin S, respectively, both produced by *Streptomyces* bacteria.[12–14]

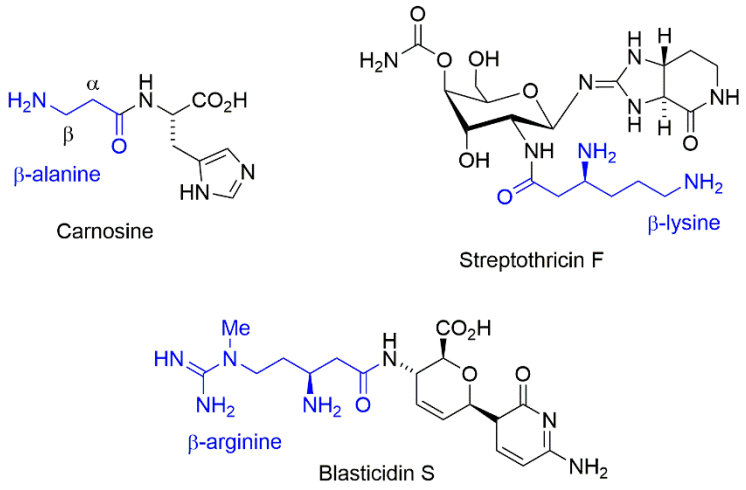


Figure 5: Naturally available β-amino acids

There are different classes of β-amino acids, dependent on where the stereogenic centre lies within the molecule. The convention, first used by Seebach, follows that β^2-amino acids have a stereogenic centre at the α-carbon and β^3-amino acids at the β-carbon (Figure 6).[15]

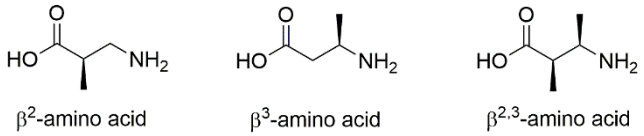


Figure 6: Seebach convention for naming β-amino acids

In biology, only the L-isomer of α-amino acids is biologically active, with most exceptions occurring in bacteria and fungi. D-Serine is the only common D-isomer present in mammals due to its role in neurotransmission.[16] For this reason, enantioenrichment of these species is vital for biological activity and significant in the synthesis of unnatural amino acids. Furthermore, only a limited number of chiral β-amino acids are naturally available. This is a consequence of how they are synthesised biologically, often being formed from their α-amino acid counterparts. Many non-standard and unnatural amino acids are used in pharmaceuticals (Figure 7).[7,17] Artificial amino acids expand on the diversity already available from natural amino acids.

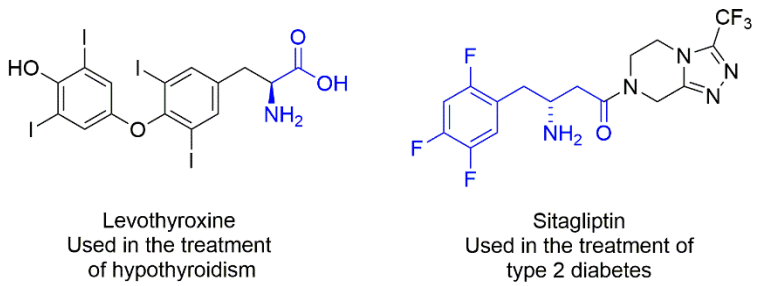
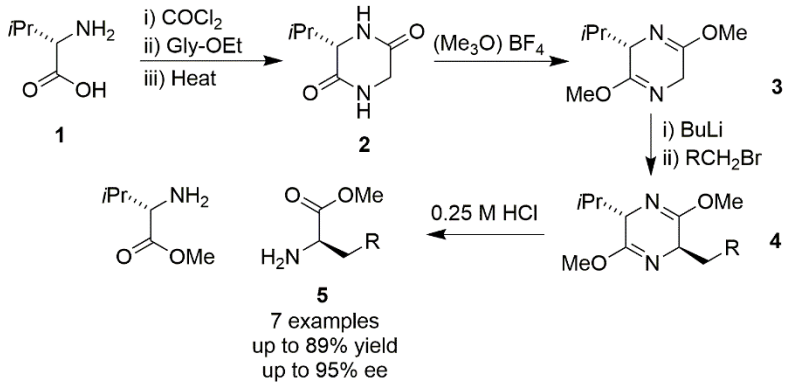


Figure 7: Pharmaceuticals containing unnatural amino acids

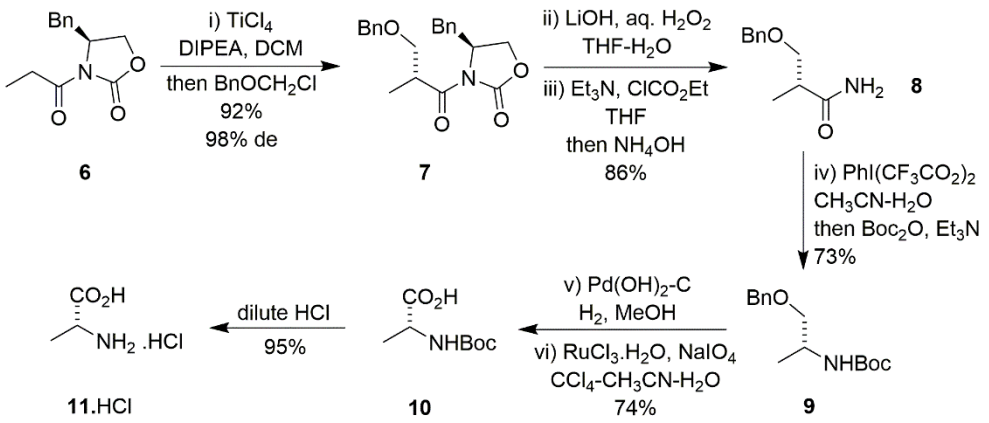
1.2.2 Synthesis of α-amino acids

One popular method for the synthesis of α-amino acids involves the use of chiral auxiliaries. The Schöllkopf method employs L-valine **1**, a naturally available amino acid, as a chiral template (Scheme 1).[18,19] After formation of the pyrazine ring **3**, the glycine moiety is deprotonated and alkylated. Hydrolysis affords the amino acid **5** in high yields up to 89% and excellent enantiomeric excesses of up to 95% ee.



Scheme 1: Schöllkopf method for the synthesis of amino acids

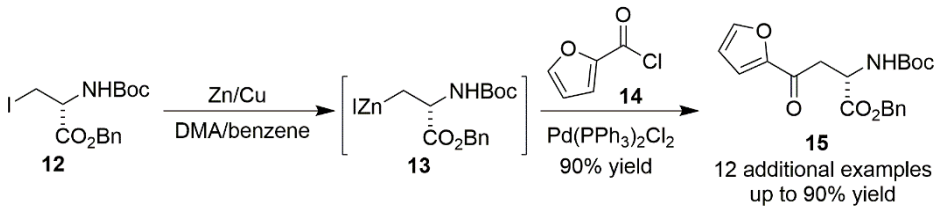
In 2002, Ghosh *et al*. reported using an oxazolidinone chiral auxiliary (Scheme 2).[20] D-Alanine **11** was obtained in an excellent 95% yield with good enantioselectivity, determined by comparison of the optical rotation of Boc-D-Ala-OMe, $[\alpha]_D$ +45.2 (*c* 1.75, MeOH), to a commercially available sample.



Scheme 2: Application of an oxazolidinone chiral auxiliary in amino acid synthesis

The main issue with the use of chiral auxiliaries is the multistep syntheses involved. For the two given examples, 7 steps are required, inevitably leading to a low overall yield. D-Alanine formed using the oxazolidinone chiral auxiliary was obtained in a 35% yield over the 7 steps. Additionally, this is exceptionally time-consuming and labour-intensive, both in general application of the method and the initial optimization of each step.

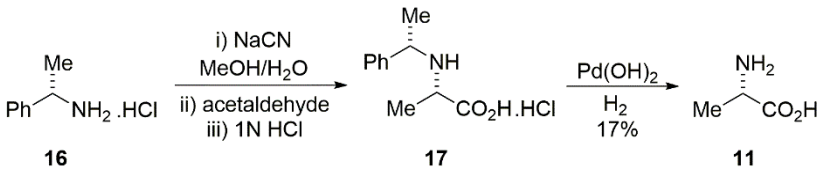
Another commonly used method is the modification of naturally available amino acids via cross-coupling reactions.[21] This approach retains the pre-existing stereogenic centre from the starting amino acid. In 1992, Jackson *et al*. reported using an organozinc reagent synthesised from serine via iodo-alanine **12** (Scheme 3).[22] Good yields of up to 90% were obtained in this 3 step synthesis with complete retention of enantiomeric purity.



Scheme 3: Modification of iodo-alanine

One important, long-established route to α-amino acids has been via the Strecker synthesis. First identified in 1850, the addition of hydrogen cyanide to an imine, formed from an aldehyde and ammonia, followed by the addition of aqueous acid produces racemic amino acids.[23] In

1963, the first asymmetric variant of the reaction was conducted by Harada employing the use of (*S*)-(−)-α-methylbenzylamine **16** as a chiral auxiliary (Scheme 4).[24] A good enantioselectivity of 90% ee was achieved when synthesising L-alanine, however, a poor yield of 17% was obtained.



Scheme 4: The first asymmetric variant of Strecker amino acid synthesis

Various organocatalysts have been applied to the Strecker synthesis.[25] These catalysts not only avoid the use of chiral auxiliaries but also avoid the use of toxic, often expensive metals. In 1996, Lipton *et al*. reported the use of cyclic dipeptide **18** (Figure 8).[26] High yields of up to 97% and poor to excellent enantioselectivities between 10-99% ee were obtained. In 2009, Jacobsen *et al*. reported the use of organocatalyst **19** which obtained excellent yields up to 99% and enantioselectivities up to 99% ee.[27] This catalyst had the advantage of being compatible with aqueous cyanide salts which are a considerably safer source of cyanide than was traditionally used.

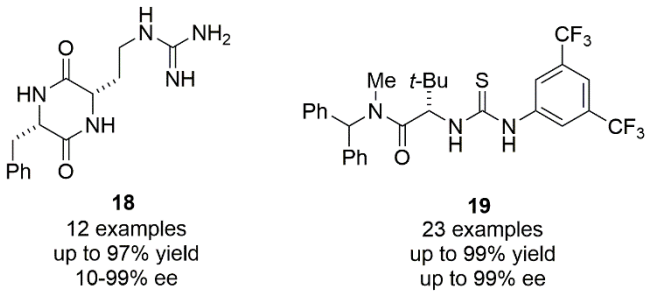
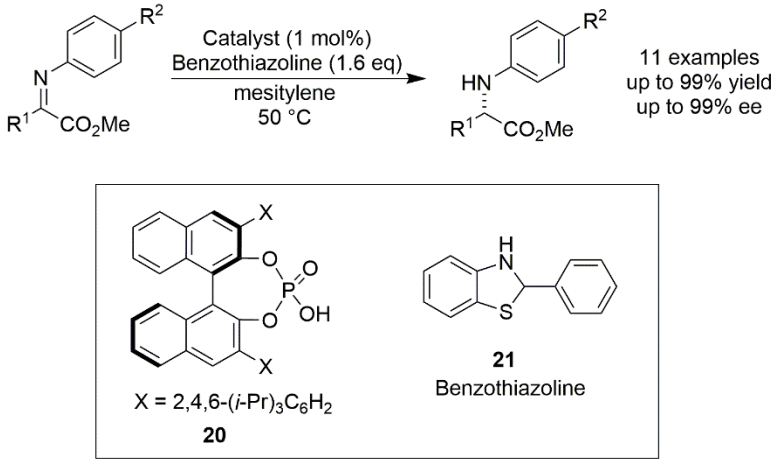


Figure 8: Examples of organocatalysts used in the Strecker synthesis

An important route to α-amino acids is via the reduction of their imino ester counterparts. Various synthesises have used this method, often employing expensive metal catalysts and high pressure.[28–30] Transfer hydrogenations catalysed using organocatalysts have been investigated. Akiyama *et al*. employed benzothiazoline **21** as a reducing agent in the reduction

of a series of imino esters (Scheme 5).[31] Chiral phosphoric acid organocatalyst **20** was utilised in the reaction, obtaining excellent yields of up to 99% and excellent enantioselectivities of up to 99% ee.



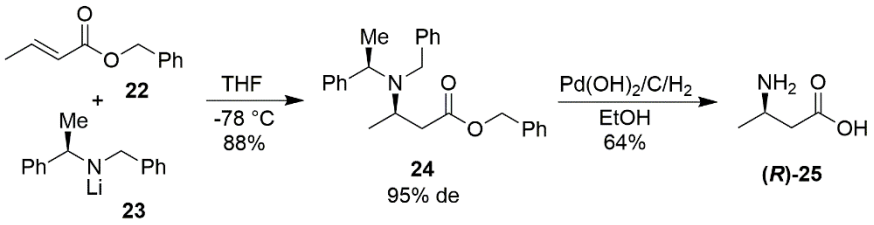
Scheme 5: Transfer hydrogenation of imino esters using benzothiazoline as a reducing agent

There is large diversity in the routes available to α-amino acids, with the routes shown being only a small selection.[32,33]

1.2.3 Synthesis of β^3-amino acids

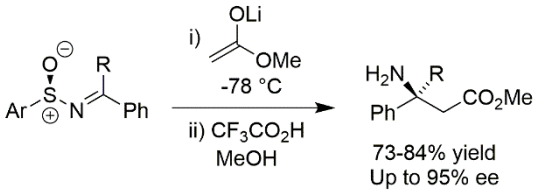
Synthesis of β^3-amino acids is important for peptide-based drug design, having been shown to increase the stability of peptides. Enzymes within the body have a high specificity for α-amino peptide bonds, therefore, peptides containing β-amino acids are not as easily hydrolysed.[10,34]

There are an extensive number of routes to β-amino acids.[10] A few key methods are detailed here. In 1991, Davies *et al*. employed the conjugate addition of a lithium amide derived from a chiral amine to α,β-unsaturated esters (Scheme 6).[35] An excellent diastereomeric excess of >99% de was exhibited. After removal of the stereodirecting group, (*R*)-β-amino butanoic acid **25** was produced in a moderate 56% yield over the two steps. This remains a popular approach with the same group publishing a number of reviews on the method.[36,37]



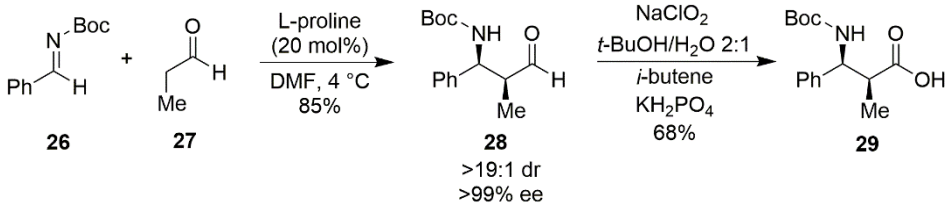
Scheme 6: Michael addition of a lithium amide to α,β-unsaturated esters

Another common synthetic method is via the Mannich reaction. Initially, difficulties involving the poor electrophilicity of the imine and α-deprotonation forming the enamine led to poor results.[38] Solutions to this problem often involved the application of performed enolates paired with a chiral auxiliary to impart selectivity. Reddy *et al*. used a sulfoxide chiral template and obtained excellent enantioselectivities of up to 95% ee and good yields up to 84% (Scheme 7).[39]



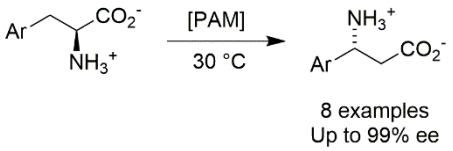
Scheme 7: Use of a sulfoxide chiral template in a Mannich type reaction

Chiral organocatalysts have been applied to this strategy. In 2007, Córdova *et al*. reported the use of L-proline as the catalyst, forming β-amino aldehydes in good selectivities, >19:1 dr and up to 99% ee, and good yields up to 85% (Scheme 8).[40] A Pinnick oxidation was employed, obtaining the Boc protected β[2,3]-amino acid **29** in a moderate 68% yield.



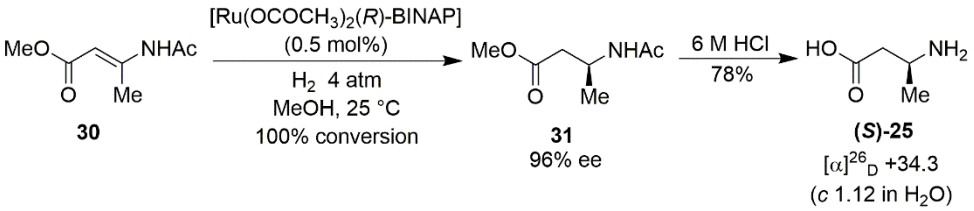
Scheme 8: Organocatalytic route to β-amino acids via the Mannich reaction

Biologically, β-amino acids are often formed from their α-amino counterparts. The enzyme phenylalanine aminomutase (PAM) can perform this conversion. In 2007, Walker *et al*. reported its use and obtained excellent enantioselectivities of up to 99% ee from crude samples (Scheme 9).[41] No yields were reported.



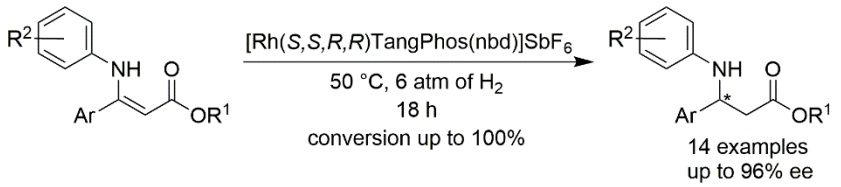
Scheme 9: Biosynthesis of β-amino acids from α-amino acids using a PAM catalyst

One of the more promising routes is via the reduction of enamino esters. In 1991, Noyori *et al*. reported the ruthenium(II) catalysed hydrogenation of β-enamido esters (Scheme 10).[42] Excellent conversions of >99% were obtained with excellent enantioselectivities of up to 96% ee. Treatment with acid afforded the β-amino acid **(*S*)-25** in a good 78% yield.



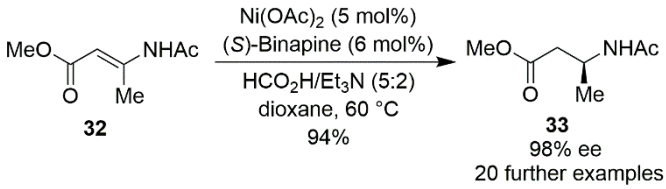
Scheme 10: Ruthenium catalysed hydrogenation of β-enamido esters

In 2005, Zhang *et al*. employed a rhodium catalyst in the hydrogenation of β-enamino esters (Scheme 11).[43] Excellent conversions up to 100% and excellent enantioselectivities of up to 96% ee were obtained. The absolute stereochemistry of the products were not reported. Methods using metal catalysis such as rhodium, ruthenium, and indium are popular.[44] However, use of these expensive metal catalysts coupled with high pressures make these procedures costly.



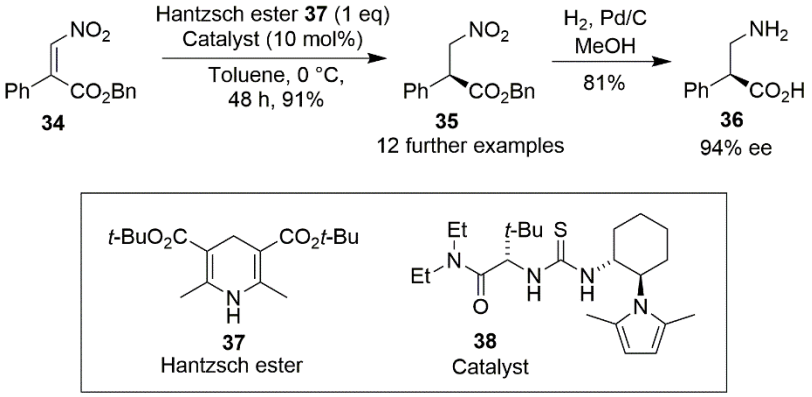
Scheme 11: Hydrogenation of β-enamino esters using a rhodium catalyst

Methods involving transfer hydrogenations avoid the use of high pressures. In 2014, Zhou *et al*. reported a nickel catalysed transfer hydrogenation of β-enamido esters (Scheme 12).[45] Excellent yields up to 99% and excellent enantioselectivities of up to 99% ee were obtained. Ni catalysts are cheaper than Rh and Ru catalysts, however, the chiral ligand used in this reaction is costly.



Scheme 12: Nickel catalysed transfer hydrogenation of β-enamido esters

Use of Hantzsch ester **37** with organocatalyst **38** was reported by List *et al*. in 2008 (Scheme 13).[46] Moderate to excellent yields (61-97%) were obtained with excellent enantioselectivities of up to 95% ee after protecting group removal and reduction of the nitro group.



Scheme 13: Reduction of β-nitroacrylates using a Hantzsch ester as the reducing agent

Reduction of enamino esters is an important synthetic strategy which remains popular. An alternative to the use of expensive metal catalysts or reducing agents such as the Hantzsch ester is trichlorosilane.

1.3 Trichlorosilane

1.3.1 Ketimine reduction

Primarily used in the synthesis of ultrapure silicon, trichlorosilane ($HSiCl_3$) is a cheap, widely available, reducing agent. Aldehydes, ketones, and ketimines were among the first substrates reduced using trichlorosilane.[47,48] Mild conditions were typically used making it an attractive option. A Lewis base, such as dimethylformamide (DMF), is required to activate trichlorosilane (Figure 9). When using an achiral base such as DMF, both the base and the substrate coordinate to the silicon of trichlorosilane. The six-coordinate silicon complex can now act as a reducing agent.

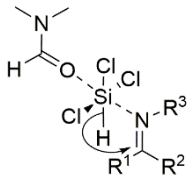
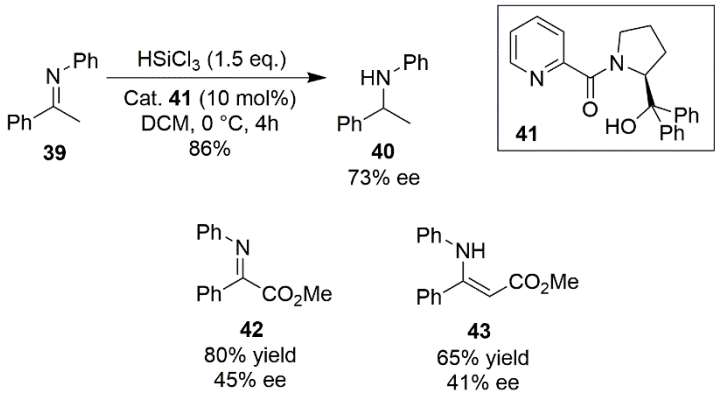


Figure 9: General trichlorosilane action

Employing a chiral Lewis base gives the potential for stereoselective reductions. In 2006, Matsumura *et al*. reported the first enantioselective hydrosilylation of aromatic ketimines using the L-proline based organocatalyst **41** (Scheme 14).[49] Good yields up to 90% with good enantioselectivities of up to 80% ee were obtained. Of the 9 examples, only 2 substrates gave poor selectivities of less than 50% ee, the α-imino ester **42** and β-enamino ester **43** substrates. They proposed that the catalyst coordinates to trichlorosilane via the pyridine nitrogen and the amide oxygen, forming the required six coordinate silicon centre (Figure 10). The substrate was then proposed to hydrogen bond to the catalyst via the alcohol, with steric clashes

between the *N*-phenyl group of the substrate and the diphenyl group of the catalyst dictating direction of binding. Selective hydride insertion can then occur.



Scheme 14: Enantioselective hydrosilylation of ketimines

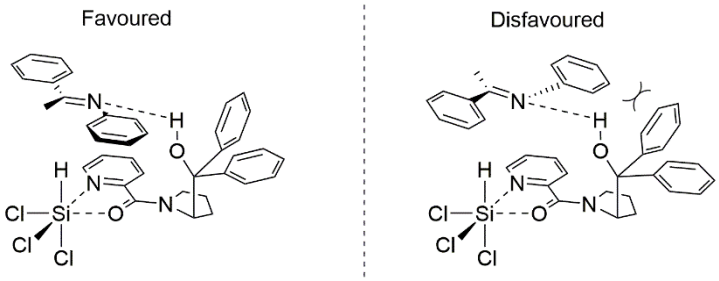


Figure 10: Matsumura's proposed transition state model for selectivity

Since the first enantioselective trichlorosilane mediated reduction of ketimines, many catalysts have been developed (Figure 11). Sun *et al*. developed *S*-chiral sulfinamide organocatalysts **44** and **47** based on L-proline and L-valine, respectively.[50,51] Both exhibited excellent yields and excellent enantioselectivities, however, **47** required a significantly higher catalyst loading. Benaglia *et al*. reported the use of a series of chiral picolinamide catalysts such as **45** which exhibited excellent yields with excellent enantioselectivites.[52] Itoh *et al*. developed a simple L-proline based catalyst **46** which produced excellent yields with good selectivities.[53] More recently, Zhu *et al*. reported a series of axially chiral biscarboline-based sulfones such as **48** which exhibited excellent yields with excellent enantioselectivies.[54] Numerous other catalyst classes have been employed and this is just a small variety of those available.[55–61]

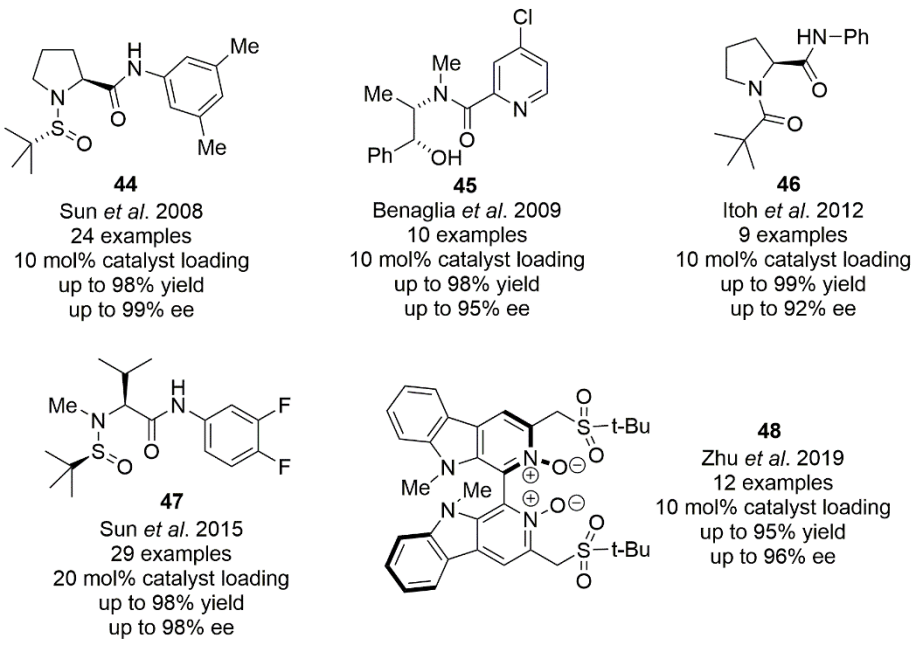


Figure 11: Examples of organocatalysts employed in trichlorosilane mediated ketimine reductions

Research conducted by the Jones group led to the development of the L-proline derived imidazole catalyst **(*S*)-49** (Figure 12).[62] A low catalyst loading of 1 mol% was required to achieve moderate to excellent yields between 41-96% with good selectivities up to 87% ee. This is significantly lower than the catalyst loading required for the catalysts previously described. NMR and IR spectroscopic experiments inverted Matsumura's model of action for the catalyst, with the protonated imidazole nitrogen bonding to the substrate (Figure 13).[63]

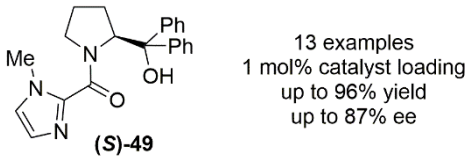


Figure 12: Proline derived imidazole organocatalyst

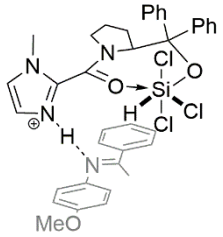


*Figure 13: Model of action involving catalyst (S)-**49***

Beyond ketimine reduction, non-traditional substrate classes have been investigated (Figure 14). Nakajima *et al*. reported the synthesis of 4H-1,3-oxazines **50** in good yields with good selectivities.[64] In 2010, Zhang *et al*. achieved excellent yields with excellent selectivities for both benzoxazinones **51** (R^1=O) and quinoxalinones **51** (R^1=NH).[65] In the following years, they reported the synthesis of 4-substituted-4,5-dihydro-1H-[1,5]benzodiazepine-2(3H)-ones **52** and γ-amino esters **53** in similarly excellent yields and enantioselectivities.[66,67] 2,3-Disubstituted indolines **54** were obtained in good yields with good selectivities by Sun *et al*. in 2014.[68] More recently, Nakajima *et al*. reported an enantioselective conjugate reduction affording saturated ketones **55** in excellent yields with excellent enantioselectivies.[69]

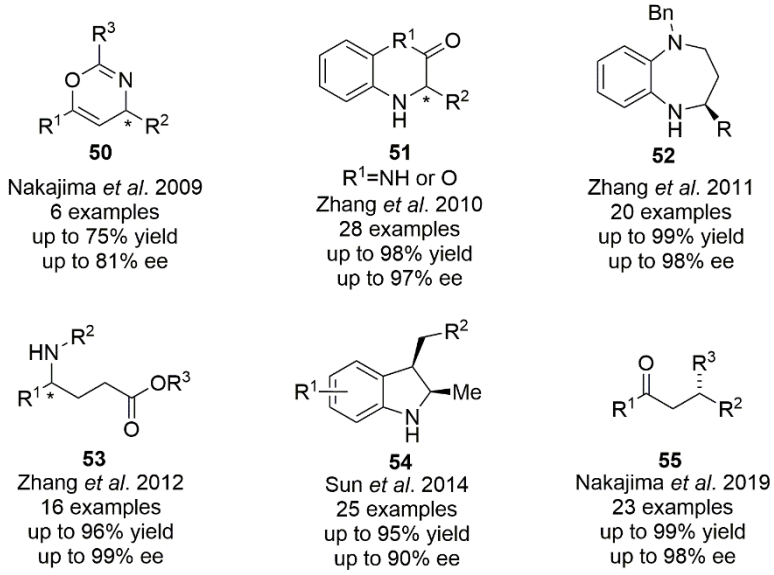
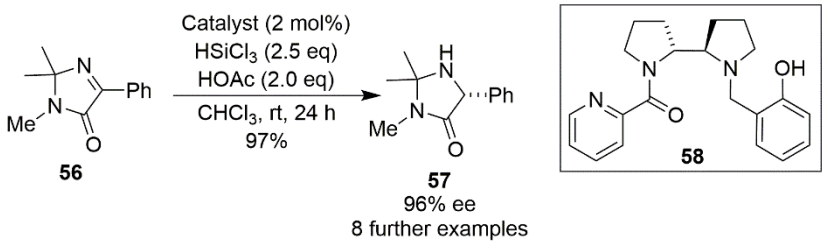
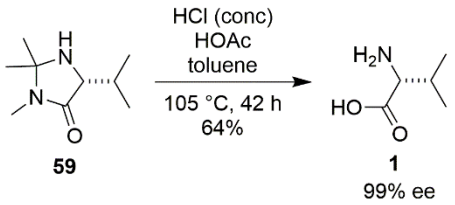


Figure 14: Various substrates synthesised via trichlorosilane reduction

Recently, Kirsch *et al*. reduced a series of imidazolinones employing a 2,2'-bispyrrolidine based catalyst **58** (Scheme 15).[70] Excellent yields of up to 99% with excellent selectivities of 96% ee were obtained across 9 examples. An acid additive, such as acetic acid, was found to be key for the reproducibility of this reaction. α-Amino acids can be liberated from imidazolidinones under strongly acidic conditions (Scheme 16). They produced D-valine **1** in a moderate 64% yield with excellent enantioselectivity of 99% ee.



Scheme 15: Trichlorosilane mediated reduction of imidazolinones

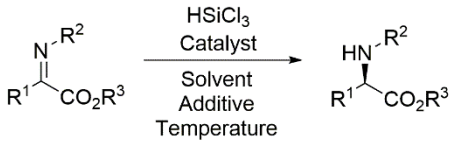


*Scheme 16: Synthesis of D-valine from an imidazolidinone **59***

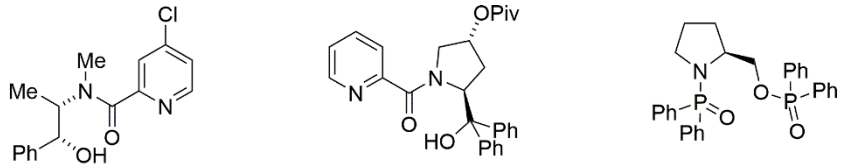
An easier route to α-amino acids is via the trichlorosilane reduction of their imino ester counterpart.

1.3.2 α-Imino ester and β-enamino ester reduction

The first attempt of the reduction of an α-imino ester was conducted by Matsumura in 2006 with very little success.[49] In 2009, Benaglia *et al*. achieved a moderate improvement in enantioselectivity, an increase from 45% ee to 71% ee, with a quantitative yield employing chiral picolinamide catalyst **45** (Scheme 17, Figure 15).[71] Later, the same group employed L-proline based phosphinate catalyst **61** further improving the enantioselectivity to 81% ee.[72] In 2010, Zhang *et al*. was the first to reduce a series of α-imino esters to great success.[73] An L-proline derived organocatalyst **60** similar to Matsumura's achieved excellent yields of up to 97% with good enantioselectivities of up to 93% ee. Pentanoic acid was used as an additive, however, no explanation was given in this paper as to the reasoning behind this.



Scheme 17: General scheme of the trichlorosilane mediated reduction of α-imino esters



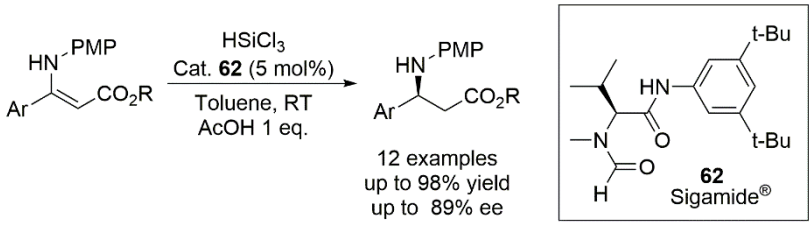
45
Benaglia *et al*. 2009
1 example
10 mol% catalyst loading
No additive
quant. yield
71% ee

60
Zhang *et al*. 2010
10 examples
10 mol% catalyst loading
pentanoic acid additive
up to 97% yield
up to 93% ee

61
Benaglia *et al*. 2011
1 example
10 mol% catalyst loading
No additive
99% yield
81% ee

Figure 15: Catalysts employed in the reduction of α-imino esters

There are a very limited number of examples of trichlorosilane mediated reductions of α-imino esters. By contrast, the reduction of β-enamino esters is significantly more common. In 2008, Malkov *et al*. reported the first procedure employing the L-valine based organocatalyst Sigamide® **62** (Scheme 18).[74] They obtained a range of yields from a moderate 63% to an excellent 98% with moderate to good selectivities of 59-89% ee. They noted that traces of HCl present in commercial trichlorosilane could be beneficial to the reaction, promoting enamine-imine tautomerization. Attempts to buffer the reaction led to the addition of 1 equivalent of AcOH, enhancing the yield from 78% to 98% but slightly lowering the enantioselectivity from 92% ee to 89% ee. After recrystallization, the β^3-amino ester could be obtained in excellent selectivities of up to 99.9% ee.



Scheme 18: General scheme for the reduction of β-enamino esters forming β^3-amino esters

There have been numerous reports of the synthesis of β^3-amino esters with a variety of catalysts (Figure 16). In 2008, Zhang *et al*. employed L-proline based organocatalyst **63**.[75] Higher catalyst loadings were required compared to the use of Sigamide®, however, across the 25 examples, overall higher yields between 82-97% were obtained with excellent selectivities of up to 96% ee. In 2011, Benaglia *et al*. reported the use of L-proline based phosphinate catalyst **61**, achieving excellent yields with good enantioselectivies.[72] In the same year, Sun *et al*. obtained excellent yields and enantioselectivities employing sulfinamide catalyst **64**.[76] After testing a number of Brønsted acids, water (1 eq.) was chosen as an additive, affording higher yields and selectivities. The following year, Jones *et al*. employed the L-proline derived imidazole catalyst **(*S*)-49** with benzoic acid as an additive, obtaining good yields with good enantioselectivities.[77] In 2013, Zhang *et al*. developed a picolinamide derived catalyst **65** which offered a slight improvement in the yields and enantioselectivities obtained compared to their previous catalyst **63**.[78]

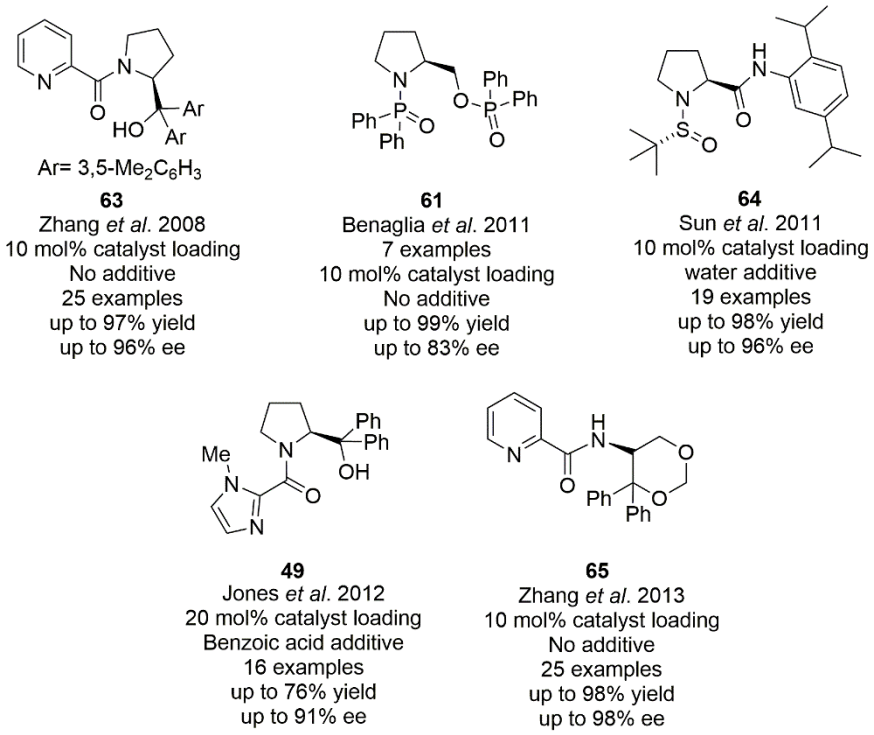
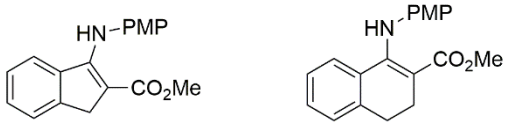


Figure 16: Catalysts used in the reduction of β-enamino esters

Both catalysts used by Zhang *et al*. were applied to the reduction β-enamino esters based on 2-substituted indanones **66** and tetralones **67** (Figure 17).[75,78] L-Proline based catalyst **63** obtained good yields of up to 93% with excellent diastereoselectivities of >99:1 dr, however, poor enantioselectivities were obtained of 28% ee and 54% ee for the indanone and tetralone substrates, respectively. The picolinamide derived catalyst **65** achieved better yields of up to 98% with excellent diastereoselectivities of >99:1 dr with a significant improvement in enantioselectivities obtaining 95% ee and 92% ee for **66** and **67**, respectively.

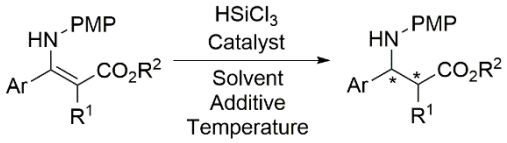


66 **67**

Figure 17: Cyclic substrates reduced by Zhang et al.

β[2,3]-Amino esters can also be accessed via trichlorosilane reduction of their enamino ester counterparts (Scheme 19). Numerous investigations into β[2,3]-amino ester synthesis have been conducted (Figure 18). Malkov *et al*. produced a series of alkyl and aryl α-substituted amino esters **68** using Sigamide® as the catalyst.[74] They obtained good yields with good enantioselectivities and excellent diastereoselectivities. In 2011, Zhang *et al*. employed a catalyst similar to picolinamide derived catalyst **65** to synthesise α-acetoxy-β-amino esters **69** obtaining excellent yields with excellent enantio- and diastereoselectivities.[79] It was noted that the reaction proceeded sluggishly in dry solvents leading to the same reasoning as Malkov that traces of water promote imine-enamine tautomerization. The same group synthesised a series of α-acetamido-β-amino esters **71**.[80] Picolinamide derived catalyst **65** obtained excellent yields with excellent enantioselectivities for the *syn*-isomers, however, the diastereoselectivity was lower than obtained for the previous substrate. More recently, they synthesised a series of α-mercapto-β-acylamido esters **72** using a different L-proline derived catalyst similar to **60**, obtaining excellent yields with excellent diastereoselectivities and good enantioselectivities.[81] In 2012, Sun *et al*. synthesised a series of α-fluoro-β-enamino esters **70**

using a sulfinamide catalyst containing an indanol moiety.[82] They obtained excellent yields with excellent diastereoselectivities and good enantioselectivities.



Scheme 19: General scheme for the reduction of β-enamino esters producing β[2,3]-amino esters

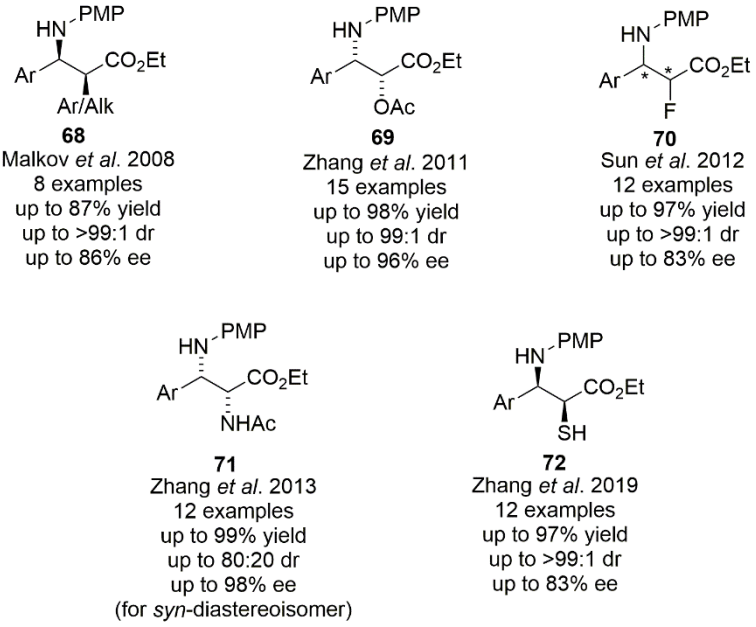
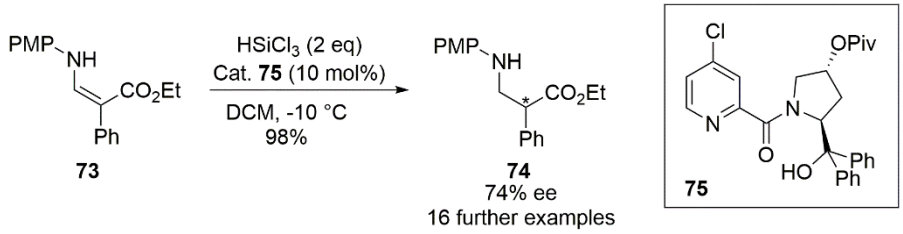


Figure 18: β[2,3]-Amino ester substrates synthesised via trichlorosilane reduction

In 2014, Zhang *et al*. reported the first and only synthesis of β[2]-amino acids via trichlorosilane reduction (Scheme 20).[83] L-Proline derived catalyst **75** obtained excellent yields of up to 99% with poor to good enantioselectivities between 19-77% ee across the 17 examples.

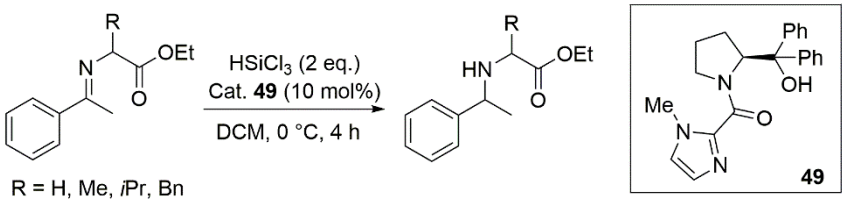


Scheme 20: Trichlorosilane reduction of a α-aryl-β-enamino ester forming a β[2]-amino ester

1.4 Aims

Previous work conducted within the Jones group, employing the L-proline derived imidazole organocatalyst **49** in the reductions of ketimines and β-enamino esters, will be expanded to various amino ester-based structures.

1. Initial work will focus on the synthesis and reduction of ketimines based on naturally available amino acids (Scheme 21). The aim is to expand the diversity of N-substituents available during the ketimine reductions with readily available amino acids such as glycine. This will add important functional handles creating new small molecular building blocks.



Scheme 21: Trichlorosilane mediated reduction of α-methyl benzyl substituted amino acids

2. Investigations into viable constrained amino acids will be conducted (Figure 19). Current examples of contained amino acids used in trichlorosilane reductions are limited to the indanone and tetralone substrates, **66** and **67**, respectively. Further diversification in this area would provide access new multifunctional building blocks.

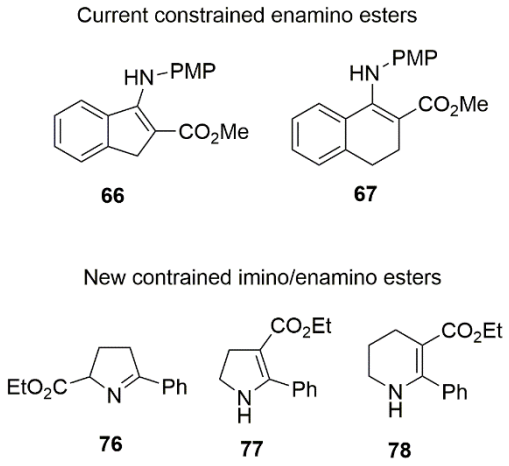
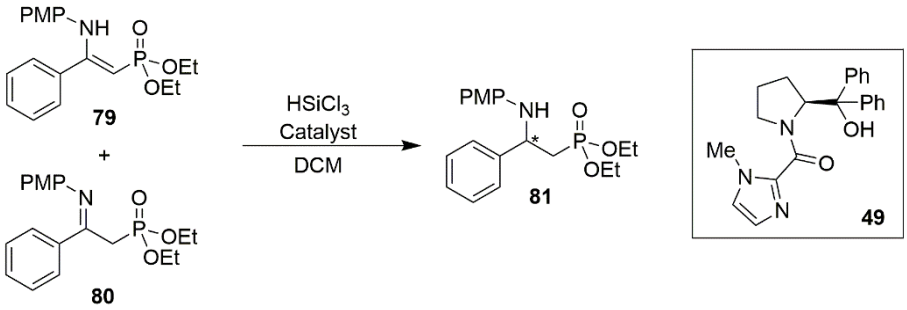


Figure 19: Current and potential imino/enamino esters for trichlorosilane mediated reductions

3. A structural analogue of amino acids, aminophosphonic acids, will be examined (Scheme 22). β-Enamino phosphonates will be synthesised and their trichlorosilane meditated reduction will be evaluated.



Scheme 22: Trichlorosilane mediated reduction of β-enamino phosphonates

2 Results and discussion

2.1 α-Methyl benzyl substituted amino acids

2.1.1 Background

Amines of low molecular weight are frequently used in fragment-based drug design (Figure 20).[4,84–86] A screening library was developed by Wijtmans *et al*. containing a series of chiral amines based on cyclobutanes such as *cis*-cyclobutane **82** and *trans*-cyclobutane **83** with the aim to investigate 3D-chemical space.[84] D-Arrigo *et al*. employed FBDD in the synthesis of new compounds aiming to prevent or treat Alzheimer's disease.[85] Poly-phenol **84** was synthesised from 4 fragments including an amine. A similar method was employed by Liao *et al*. using an inden-1-amine fragment based on Rasagiline for the development of new drugs, such as **85**, for the treatment of Parkinson's disease.[86]

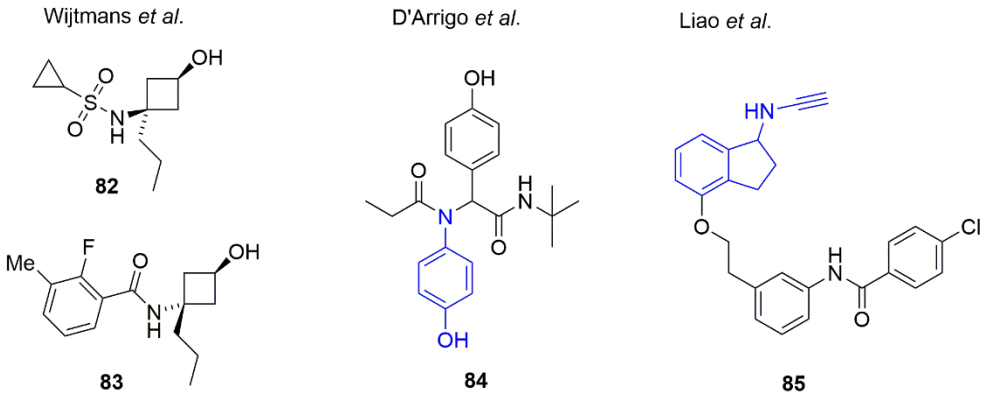


Figure 20: Examples of amine fragments used in FBDD

With chiral amines being a popular building block, easy routes to synthesise these molecules are important. Ketimines are a popular substrate for asymmetric trichlorosilane mediated reductions providing easy access to chiral amines. Generally, the nitrogen substituents are aryl groups, with the most common being phenyl, *p*-methoxyphenyl, and *p*-bromophenyl (Figure 21).[49,55,62] There have been a limited number of alternative substituents reported. In 2008, Sun *et al*. reported the trichlorosilane mediated reduction of *N*-alkyl ketimines.[50] Excellent yields of up to 98% with excellent enantioselectivities of up to 99% ee were obtained across the 24 examples.

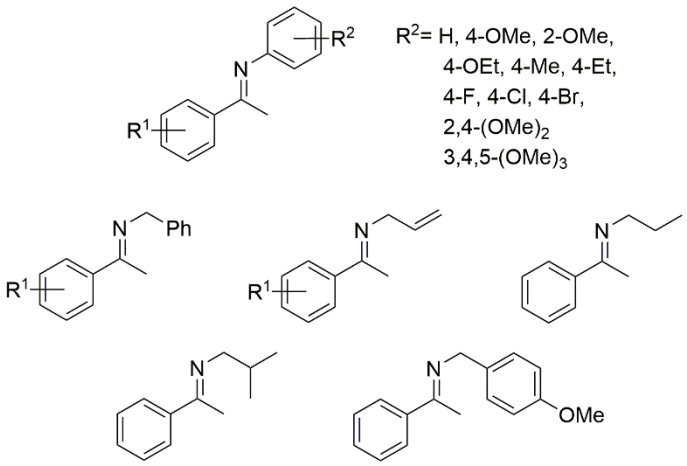
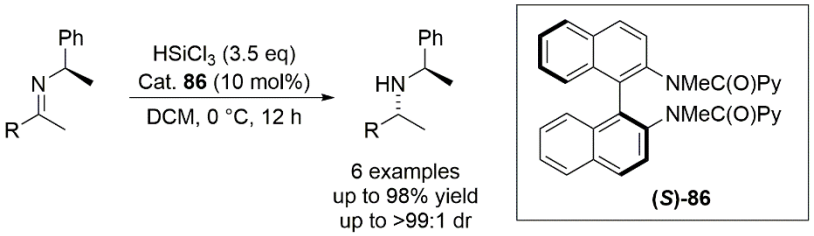


Figure 21: N-aryl and N-alkyl ketimine substrates used in trichlorosilane mediated reductions

Further to the common *N*-substituents, Benaglia *et al*. reported the use of a chiral template with organocatalyst (*S*)-**86** in the hydrosilylation of ketimines (Scheme 23).[71] Excellent yields of up to 98% were obtained with excellent diastereoselectivities of up to >99:1 dr. Use of the opposite enantiomer of catalyst (*R*)-**86** during the reduction of the ketimine (R=Ph) obtained a significantly lower diastereoselectivity of 80:20 dr. This highlights the importance of matching the catalyst to the chiral template to obtain complete stereocontrol of the reaction.

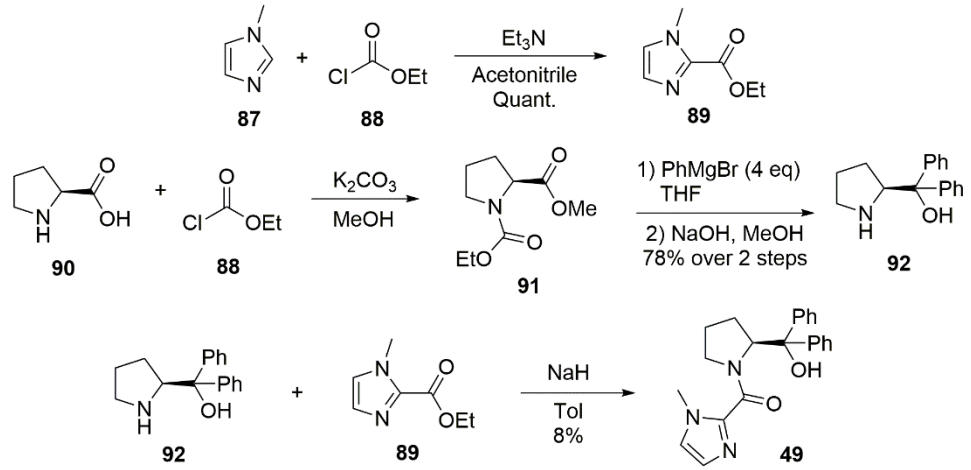


Scheme 23: Hydrosilylation of ketimines reported by Guizzetti et al.

Current *N*-substituents lack functional handles, apart from *p*-bromophenyl which can be used in cross-coupling reactions to build on the small molecule. With this current limitation on ketimine reductions, expanding the range to include amino acid-based molecules holds significant potential. This opens the door to amide coupling reactions which are key for the development of DNA encoded libraries.[87] The aim of this project is to expand the range of *N*-substituents by employing naturally available α-amino acids.

2.1.2 Catalyst synthesis

The imidazole base catalyst (*S*)-**49** developed within the Jones groups was synthesised via a known method (Scheme 24).[62] Imidazole **89** was synthesised from 1-methyl-imidazole and ethyl chloroformate in a quantitative yield and was used directly in the next step without further purification. (*S*)-Prolinol (*S*)-**92** was synthesised in three steps from L-proline in a good 78% yield and was used directly in the next step without further purification. (*R*)-Prolinol (*R*)-**92** was synthesised via the same procedure from D-proline in a good 78% yield across the three steps.

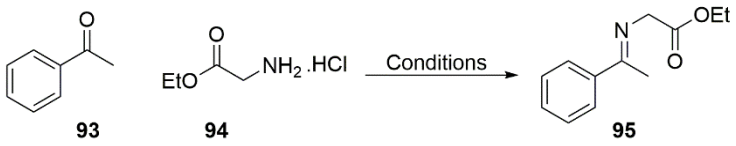


*Scheme 24: Synthesis of imidazole catalyst (S)-**49***

Deprotonation of (*S*)-prolinol (*S*)-**92** using 2 equivalents of sodium hydride followed by addition of imidazole **89** afforded the desired catalyst (*S*)-**49** in a poor 8% yield. Previous work performed in the Jones group afforded the crude product as a solid allowing for recrystallizations to be performed in order to purify the catalyst. Unfortunately, in this case, a black oil was obtained therefore column chromatography followed by repeated recrystallizations was needed to obtain the product as clean product. The opposite enantiomer suffered from the same issue and catalyst (*R*)-**49** was obtained in a poor 11% yield. A significant scale-up of this reaction was performed by Dan Cox at RedBrick Molecular who kindly donated some of imidazole catalyst (*S*)-**49** for future trichlorosilane reactions.

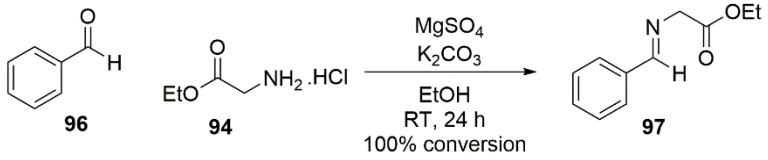
2.1.3 Trichlorosilane reduction of glycine derivatives

Glycine, the simplest naturally available α-amino acid, was chosen as the first substrate. Glycine ethyl ester hydrochloride **94** was initially used in the ketimine formation with acetophenone (Scheme 25). The standard conditions used previously in the Jones group for the formation of ketimines were trialled.[62] Without the use of a base to neutralise the hydrochloride salt, none of the desired product was formed, and it was assumed that the amine was not available to react (Table 1, entries 1 and 2). Different bases were trialled in the reaction with varying numbers of equivalents of each base. Although magnesium sulfate was employed to remove water, only trace amounts of the product were observed in the ^{1}H NMR spectra (Table 1, entries 3 to 12). Increasing the equivalences of the bases and the amine salt **94** failed to improve the reaction, giving only traces of product in the ^{1}H NMR spectra. In addition, stirring the hydrochloride salt with base to produce the free amine failed to improve the outcome of the reaction (Table 1, entries 7 to 12).



*Scheme 25: Synthesis of glycine ketimine **95***

In order to confirm that the amine was being produced, glycine hydrochloride salt **94** was reacted with benzaldehyde under the previously used conditions (Scheme 26). The aldimine **97** was produced in 100% conversion suggesting that the lower electrophilicity of the ketone is the cause of the slow reaction. Addition of *p*-TsOH to catalyse the ketimine formation reaction had little to no effect on the formation of product, with only traces of product being observed in the ^{1}H NMR spectrum (Table 1, entries 2, 10 and 11).



Scheme 26: Aldimine test reaction

*Table 1: Reaction conditions for the synthesis of glycine ketimine **95**[a]*

Entry	Additives	Temp/ °C	Eq. glycine HCl salt	Eq. Base	Ratio **93**:**95**[i]
1	$MgSO_4$	RT	1	-	1:0
2	$MgSO_4$, *p*-TsOH	RT	1	-	1:0
3	$MgSO_4$, K_2CO_3	RT	1	1	1:<0.05
4	$MgSO_4$, K_2CO_3	RT	1	0.25	1:<0.05
5	$MgSO_4$, K_2CO_3	RT	1	0.50	1:<0.05
6	$MgSO_4$, K_2CO_3	RT	1	0.75	1:<0.05
7[b]	$MgSO_4$, K_2CO_3	RT	2	2	1:<0.05
8[b]	$MgSO_4$, NEt_3	RT	2	2	1:<0.05
9[b]	$MgSO_4$, DIPEA	RT	2	2	1:<0.05
10[b,c]	$MgSO_4$, DIPEA, *p*-TsOH	RT	2	2	1:<0.05
11[b,c]	$MgSO_4$, DIPEA, *p*-TsOH	RT	3	3	1:<0.05
12[b]	$MgSO_4$, DIPEA	RT	2	1.8	1:<0.05
13[c,d,e,f,g]	DIPEA, *p*-TsOH	Reflux	2	2	1:2
14[c,d,e,f,h]	DIPEA, *p*-TsOH	Reflux	3	3	1:5.3

[a]1 mmol of acetophenone dissolved in 20 mL of ethanol and stirred for 24 h with glycine ethyl ester hydrochloride and additives. [b]Stirred base with glycine ethyl ester hydrochloride for 30 min before addition to acetophenone. [c]Stirred *p*-TsOH with acetophenone before addition of glycine ethyl ester hydrochloride. [d]Toluene (25 mL) under Dean-Stark conditions. [e]Slow addition of base over 2-3 h. [f]By-products formed. [g]Stirred for 4 h. [h]Stirred for 3.5 h. [i]As determined by ^{1}H NMR spectrum.

Changing the water removal technique to azeotropic removal of water under Dean-Stark conditions afforded a higher conversion of the starting materials to ketimine product **95** was observed in the ^{1}H NMR spectrum, however, there were two observed by-products in the

reaction (Table 1, entry 13, Figure 22). One of the by-products, acyclic imine **98** was generated as a single geometric isomer and was potentially formed through an aldol condensation reaction between the desired product **95** and acetophenone. None of the aldol condensation product between two molecules of acetophenone was observed and therefore the ketimine formation towards acyclic imine **98** is likely to have occurred first rather than the aldol condensation. Cyclic imine **99** was afforded as a mixture of diastereoisomers with a 55:45 dr. The cyclic imine **99** potentially forms from aldol product **98** through deprotonation of the α-C of the amino acid moiety followed by intramolecular 1,4-addition to the α,β-unsaturated imine. The assignment of the by-products is supported by ^{1}H, ^{13}C NMR and mass spectroscopy.

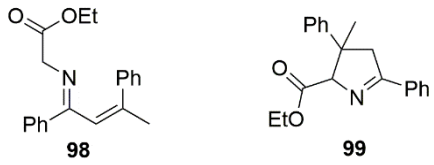
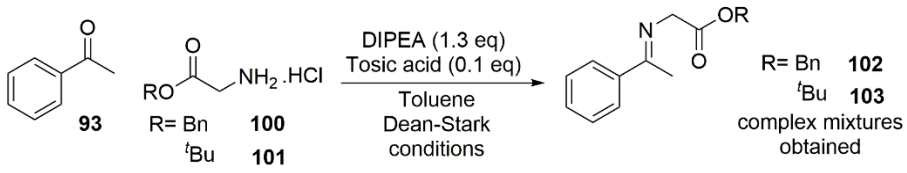


*Figure 22: By-products from the synthesis of glycine ketimine **95***

Glycine ethyl ester has a lower boiling point than that of toluene, so under Dean-Stark conditions this probably boils off leaving an excess of acetophenone in the reaction. This would promote the formation of the acyclic imine **98** as its synthesis requires 2 equivalents of acetophenone. Shorter reaction times with higher equivalents of both the glycine salt **94** and base improved the ratio of remaining acetophenone to ketimine **95** to 1:5.3 (Table 1, entry 14). Dropwise addition of the base ensured gradual formation of the amine and therefore reduced the amount of glycine ethyl ester boiling off into the Dean-Stark trap. Multiple attempts at purification via flash column chromatography using silica gel, alumina, or Florisil failed to separate imine **95** from acetophenone. Degradation of the imine during purification was a major issue with the mass returns from the columns being poor.

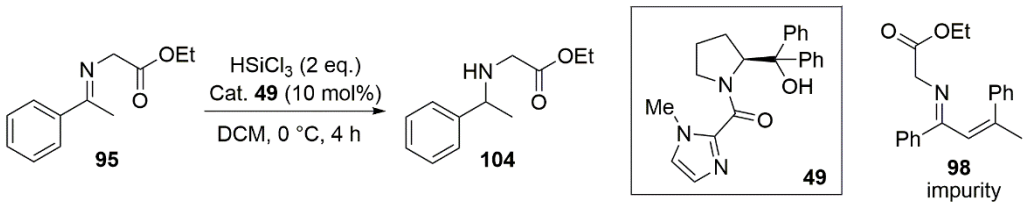
Changing the ester could potentially diminish the formation of the by-products by increasing the boiling point of the amine (Scheme 27). Two different esters were trialled, benzyl and *tert*-butyl. Use of the benzyl ester **100** afforded a complex mixture from the ^{1}H NMR spectrum with

both evidence of the desired benzyl ester ketimine **102** and the benzyl derivatives of the by-products being present. These were not isolated. Use of the *tert*-butyl ester **101** afforded a cleaner crude mixture as noted from the ^{1}H NMR spectrum in comparison to the benzyl ester **100**, however, *tert*-butyl ester derivatives of the by-products could be observed. Despite the remaining acetophenone and the acyclic and cyclic by-products, the ethyl ester ketimine **95** was chosen for the subsequent reductions due to it providing the cleanest crude reaction mixtures as evidenced by ^{1}H NMR spectrum.



Scheme 27: Synthesis of alternative glycine protected ketimines

Due to the difficulties with purification, the unpurified ethyl ester imine **95** was reduced using trichlorosilane with imidazole-based catalyst (*S*)-**49** (Scheme 28). Upon purification via flash column chromatography, the amine **104** was obtained as a mixture with acyclic by-product **98** that was retained from the ketimine formation step. Unfortunately, both compounds have the same R_f values making separation of these compounds via column chromatography impossible.



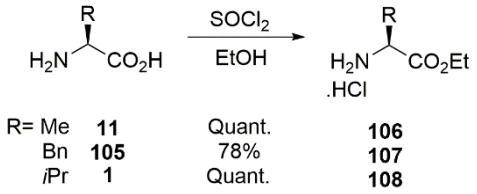
*Scheme 28: Trichlorosilane reduction of glycine ketimine **95***

Since it was not possible to obtain either clean ketimine **95** during the ketimine formation or pure glycine amine **104** from the reduction, different amino acids were trialled.

2.1.4 Trichlorosilane reduction involving chiral amino acids

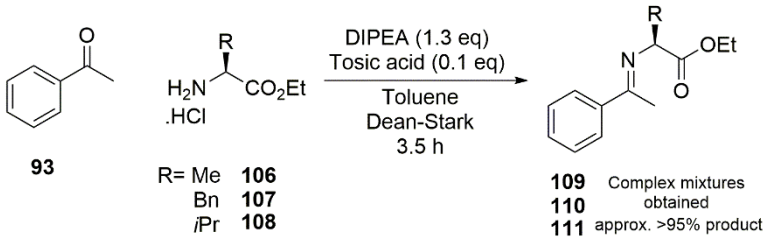
Naturally available amino acids, with the exception of glycine, are chiral molecules. Using these during the reduction of ketimines derived from them could lead to a cooperative effect between the compound and the catalyst (*S*)-**49**. This would work in a similar way to the work undertaken by Benaglia *et al*. with methyl-benzyl ketimines.[71]

L-Alanine, L-valine and L-phenylalanine were selected as test substrates. Each amino acid was esterified using ethanol with thionyl chloride affording the ethyl ester hydrochloride salts in good to excellent yields of 78% to quantitative (Scheme 29).



Scheme 29: Formation of amino ester hydrochloride salts

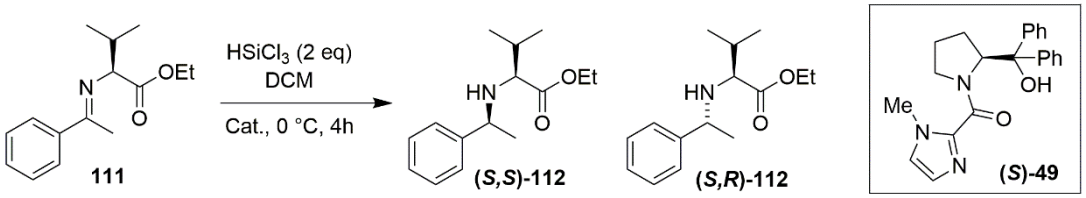
In the ketimine formation reactions under Dean-Stark conditions, no evidence of by-products like those observed with glycine, were observed (Scheme 30). The crude product isolated from the formation of L-Valine ketimine **111** contained the least impurities and remaining starting materials as evidenced by ^{1}H NMR spectra compared to the L-alanine **109** and L-phenylalanine **110** ketimines, so therefore this was used directly in the next step without further purification.



Scheme 30: Synthesis of amino acid based ketimines

The yields reported are the isolated yields given over two steps, the ketimine formation and the reduction. Initially, L-valine ketimine **111** was reduced using trichlorosilane with DMF as

an achiral catalyst (Scheme 31, Table 2, entry 1). Poor yields of 20% were obtained with poor diastereoselectivities of 60:40 dr. When using catalyst (*S*)-**49**, good diastereoselectivities of 15:85 dr were obtained, however, a poor yield of 11% was obtained for the major diastereoisomer (Table 2, entry 2). The stereochemistry of the major isomer was assigned to be (*S*,*S*)-**112** by tentative analogy to the previous work conducted in the Jones group using the same catalyst on simpler ketimines.[62] Due to the use of a chiral ketimine in this example, this assignment is not definitive and further analysis is required to confirm the absolute stereochemistry of the products. When changing the catalyst to its opposite enantiomer catalyst (*R*)-**49**, the diastereoselectivity observed was a moderate 70:30 dr, with the opposite diastereoisomer (*S*,*R*)-**112** being obtained as the major, as expected. The diastereoselectivity was lower for catalyst (*R*)-**49** than that obtained with (*S*)-**49** suggesting that (*S*)-**49** interacts more favourably with the L-valine ketimine substrate.



*Scheme 31: Trichlorosilane mediated reduction of L-valine ketimine **111***

*Table 2: Results of the catalysed trichlorosilane reduction of L-valine ketimine **111**[a]*

Entry	Catalyst	dr (*S*,*R*):(*S*,*S*)[b]	Yield/%[c]
1	DMF	60:40	20
2	(*S*)-**49**	15:85	11[d]
3	(*R*)-**49**	70:30	4[e]

[a]Reactions were conducted using 1 mmol of ketimine **111**, 2 eq of $HSiCl_3$, 10 mol% of catalyst (*S*)-**49**, in 1 mL of dry DCM at 0 °C under argon. [b]As determined by ^1H NMR spectrum of the crude product. [c]Isolated yield of **112** over both the ketimine formation and reduction steps. [d]Yield of major diastereoisomer. [e]Yield of minor diastereoisomer.

Further optimisation of this reaction was not attempted as it was at this stage that lockdown due to Covid-19 occurred. Once work resumed in the lab, other projects were focused on initially due to lack of time in the lab and significant progress was being made in other projects.

2.1.5 Conclusion and future work

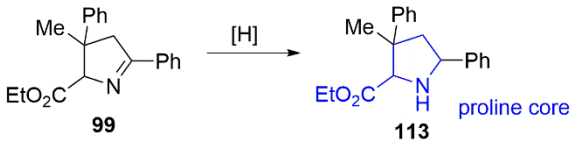
During the ketimine formation with glycine two by-products were made, aldol addition product **98** and cyclic imine **99**. Purification issues due to degradation of the ketimine during flash column chromatography made isolation of clean ketimine **95** difficult and therefore was used directly in the next step without further purification. Unfortunately, the trichlorosilane mediated reduction of the glycine ketimine resulted in a mixture of the desired amine **104** and the aldol addition by-product **98** carried forward from the previous step as both these compounds have the same R_f. Use of glycine was halted as the problems were deemed too major.

Chiral amino acids held significantly more potential than glycine given the potential for cooperative effects between the chiral ketimine and the catalyst (*S*)-**49**. An L-valine derived ketimine was determined as the best amino acid to employ as it provided the cleanest crude ketimine. The reduction of valine ketimine **111** afforded a good diastereoselectivity of 15:85 dr with the major diastereoisomer predicted to be the (*S*,*S*)-**112** isomer obtained in a poor 20% yield. A lower diastereoselectivity was observed when using catalyst (*R*)-**49** compared to catalyst (*S*)-**49** suggesting that catalyst (*S*)-**49** interacts more favourably with ketimine **111** than catalyst (*R*)-**49**. With this project being side-lined due to Covid-19 lockdown, further work is needed to optimise the valine ketimine reduction to increase the diastereoselectivity and increase the poor 20% yield of the major diastereoisomer.

2.2 Cyclic α-amino-acids based on 2,5-disubstituted pyrrolidines

2.2.1 Background

The cyclic imine **99**, afforded as a by-product during the imine formation of acetophenone with glycine ethyl ester, could potentially be reduced (Scheme 32). This leads to a multi-substituted cyclic amino ester with a proline core.



*Scheme 32: Reduction of cyclic imine **99***

Cyclic amino acids based on proline hold significant interest in synthesis, medicine, and biology. Due to being conformationally constrained in comparison to their acyclic counterparts, they can be installed into proteins to investigate structure-activity relationships within simple protein chains by being exchanged with an acyclic counterpart.[88,89] Mignani *et al*., employed proline derivatives in non-peptide mimics for a sequence of octreotide, a drug used in cancer treatment (Figure 23).[88]

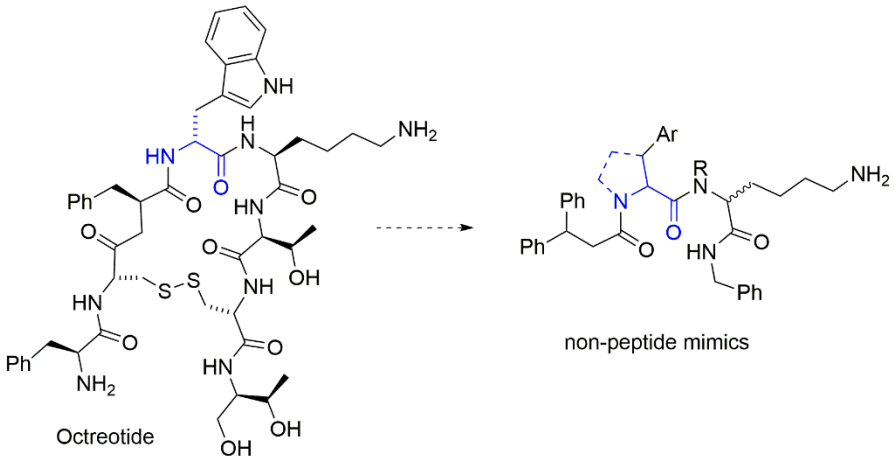
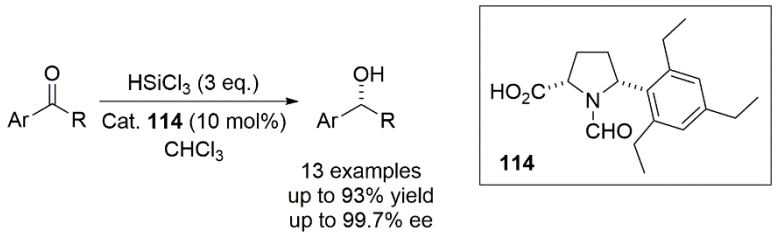


Figure 23: Octreotide with non-peptide mimics synthesised by Mignani et al.

Proline is used extensively in synthesis, notably as a catalyst in a range of reactions.[90] In 2006, Matsumura *et al*. employed 5-substituted proline **114** as an organocatalyst in the asymmetric

trichlorosilane mediated reduction of ketones (Scheme 33).[91] They obtained good yields of up to 93% with excellent enantioselectivities of up to 99.7% ee.



Scheme 33: Trichlorosilane mediated reduction of ketones employing a proline derived catalyst

Various pharmaceuticals contain substituted proline core units (Figure 24). Lincomycin is an antibiotic which contains a 4-substituted proline.[92] Due to its toxicity, it is often only used in patients who are allergic to penicillin or in cases of antibiotic resistant bacteria. Another example is the cholecystokinin antagonist (+)-RP 66083 which contains a 5-substituted proline.[93,94]

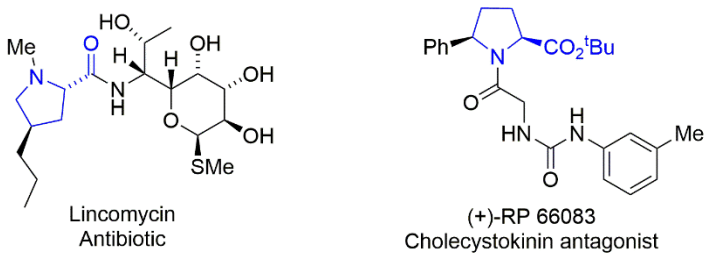
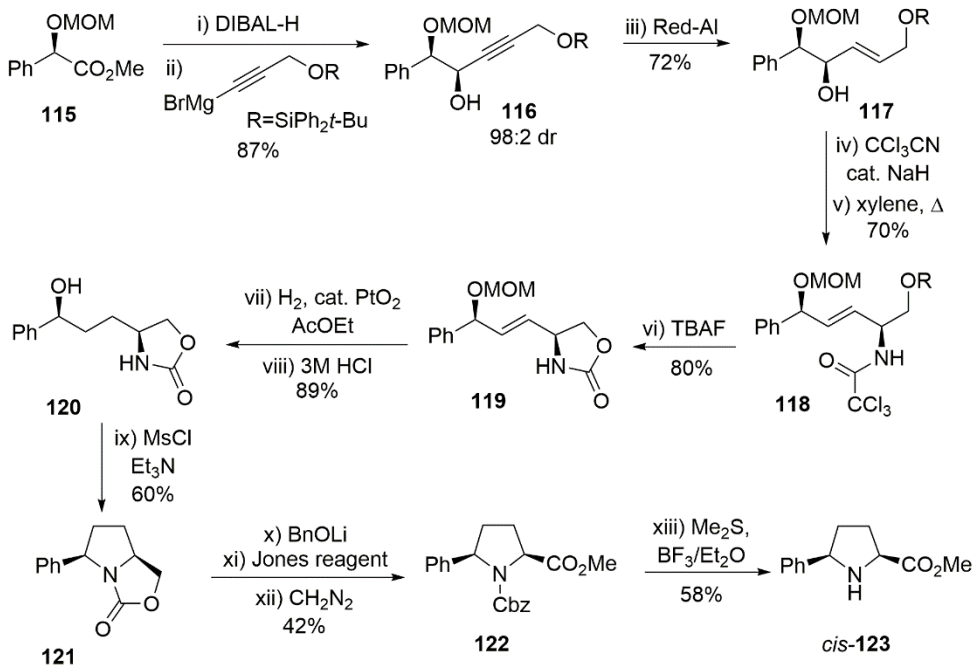


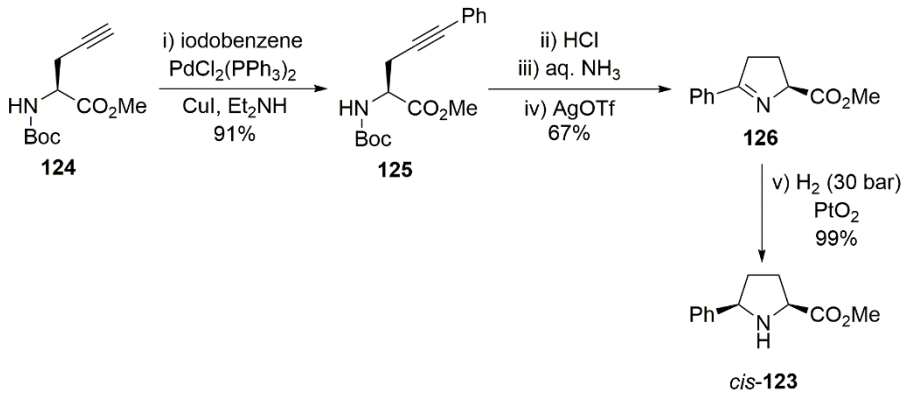
Figure 24: Pharmaceuticals containing proline based amino acids

Numerous investigations into the synthesis of the proline moiety within (+)-RP 66083 have been conducted. In 1998, Larchevêque *et al*. reported the first enantioselective synthesis of *cis*-2,5-substituted pyrrolidine **123** (Scheme 34).[95] They employed an Overmann rearrangement as the key step, affording diol **118** as a single diastereoisomer in a good 70% yield. Overall, the method used 13 steps and obtained pyrrolidine **123** in a 5% yield.



*Scheme 34: First enantioselective synthesis of cis-pyrrolidine **123***

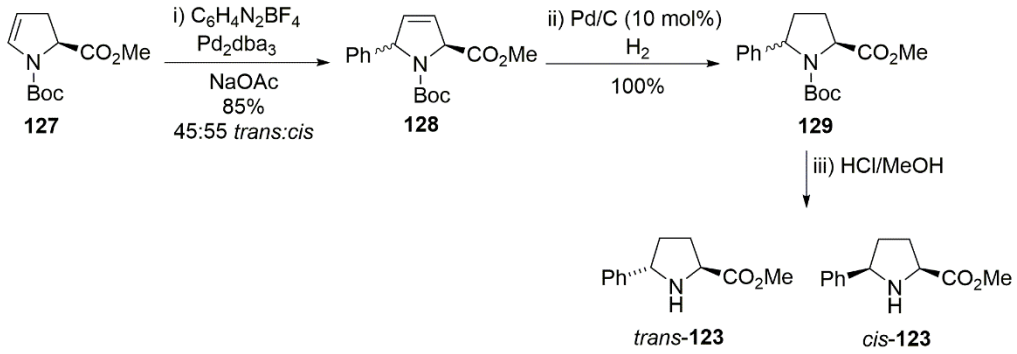
In 2005, Rutjes *et al*. reported the synthesis of pyrrolidine **123** via silver catalysed cyclisation of alkynylamines (Scheme 35).[96] This method required significantly fewer steps than the previous method and afforded the pyrrolidine **123** in a good 60% yield over the 4 steps. A key intermediate in the synthetic route was cyclic imine **126** which was afforded in a good 67% yield with complete retention of stereochemistry.



*Scheme 35: Synthesis of pyrrolidine **123** reported by Rutjes et al.*

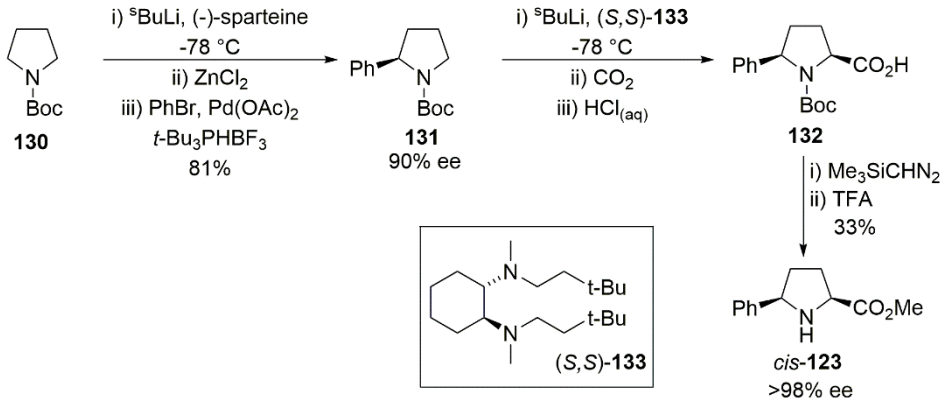
In 2003, Correia *et al*. synthesised pyrrolidine **123** via a Heck arylation (Scheme 36).[94] Dehydroproline**128** was obtained in a good 85% yield, however, a poor diastereoselectivity of

45:55 dr was observed and the isomers were found to be inseparable at this stage. After hydrogenation of the alkene and deprotection of the pyrrolidine nitrogen, the separated diastereoisomers were obtained in moderate yields of 30% and 31% for *trans* and *cis* isomers, respectively. Over the 3 reported steps, the *cis*-disubstituted pyrrolidine **123** was obtained in a moderate 26% overall yield, however, it should be noted that the cyclic enamine starting material **127** is costly so is unlikely to be the starting point for synthesis.



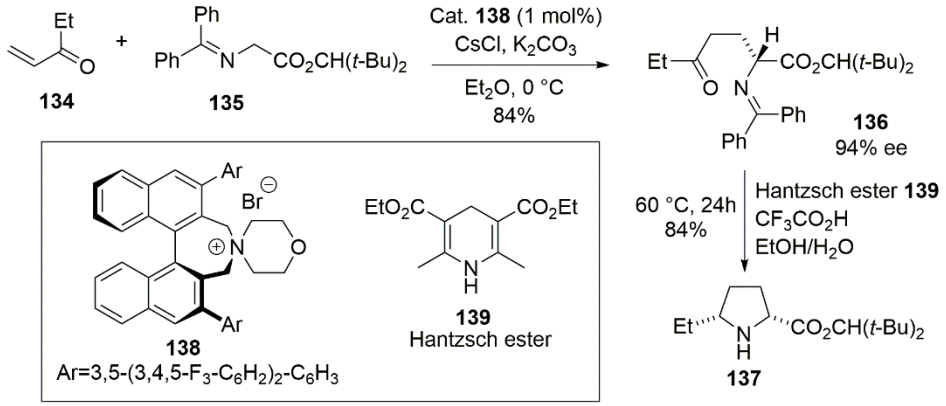
*Scheme 36: Synthesis of both cis and trans pyrrolidine **123** via Heck arylation*

In 2008, O'Brien *et al*. reported the asymmetric deprotonation of *N*-Boc pyrrolidine **130** as a route to synthesise pyrrolidine **123** (Scheme 37).[97] *N*-Boc pyrrolidine is a significantly cheaper starting material than that used by Correia *et al*. making this route more affordable. The monosubstituted pyrrolidine **131** was obtained in a good yield of 80% with a good enantioselectivity of 90% ee. *cis*-Pyrrolidine **123** was obtained in a moderate 27% yield over the 4 steps with excellent enantioselectivity of >98% ee. They also synthesised *trans*-pyrrolidine **123** from monosubstituted pyrrolidine **131** by switching the chiral amine employed in the second deprotonation from (*S,S*)-diamine **133** to (−)-sparteine. The *trans*-pyrrolidine was obtained in a similar yield of 22% over the 4 steps with no report of the enantioselectivity of the final product.



*Scheme 37: Synthesis of pyrrolidine **123** via asymmetric deprotonation of N-Boc pyrrolidine*

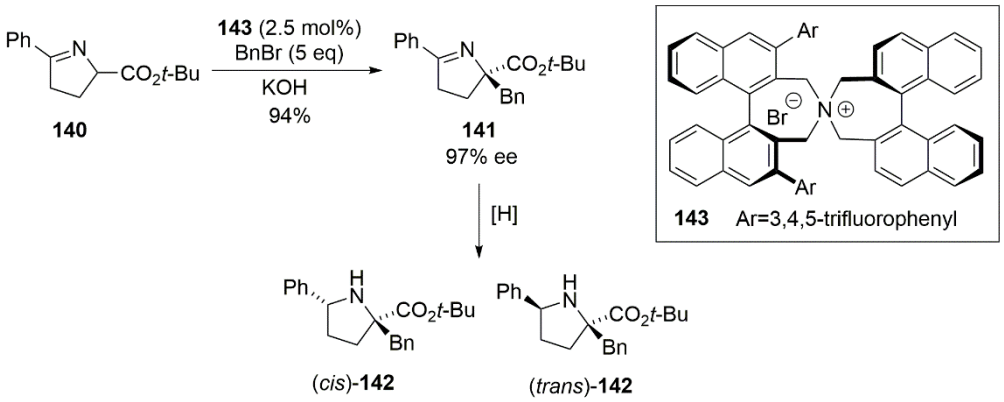
Other routes have been employed to the synthesis of pyrrolidine **123** and similar 5-subsititued prolines.[90,98,99] Maruoka *et al*. developed a one-pot method for the synthesis of pyrrolidine **137** via an enantioselective Michael addition and reductive amination (Scheme 38).[100] They obtained a good yield of 84% with good enantioselectivity of 94% ee for conjugate addition product **136**, and subsequent reductive amination occurred stereospecifically, affording pyrrolidine **137** in a good 84% yield. No further examples of pyrrolidines were synthesised via this method.



*Scheme 38: Synthesis of pyrrolidine **137** via enantioselective Michael addition and reductive amination*

Additional functionalisation at the 2-position has been investigated. A series of 2-alkylprolines were synthesised by Park *et al*. in 2013 by selectively alkylating cyclic imines in the presence of phase-transfer catalyst **143** (Scheme 39).[101] They obtained excellent yields of up to 98%

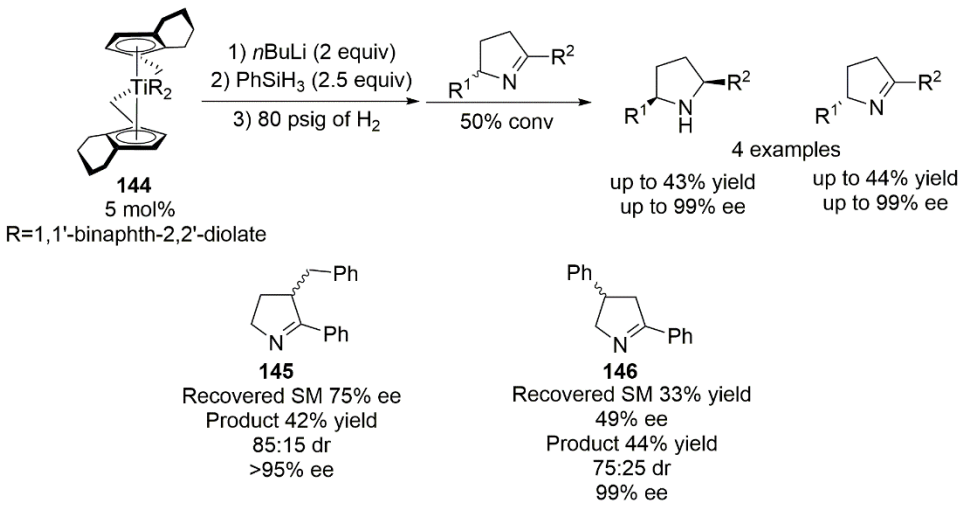
with excellent enantioselectivities of up to 98% ee across the 7 examples. Attempts to reduce 2-alkylproline **141** (R=PhCH$_2$) via different methods failed to occur with signifcant diastereoselectivity. Employing Pt/C with H_2 afforded more of the *cis*-isomer **142** (77% yield) than the *trans*-isomer **142** (19% yield), whereas employing sodium cyanoborohydride with acetic acid afforded more of the *trans*-isomer **142** (50% yield) than the *cis*-isomer **142** (22% yield). Other reports of functionalisation at this position have been published, employing similar methods of alkylation.[102,103]



Scheme 39: Alkylation of 5-phenyl-prolines

One method that has not been investigated towards proline derivatives is conducting a kinetic resolution while performing reduction of the cyclic imine. Kinetic resolutions have been used extensively in the synthesis of substituted pyrrolidines, using enzymatic processes for simpler substrates and cycloaddition and annulation reactions for more densely populated pyrrolidines.[104] A small series of disubstituted pyrrolidines have been synthesised by Büchwald *et al*. via reduction using phenylsilane and titanocene catalyst **144** (Scheme 40).[105,106] They obtained excellent yields and enantioselectivities of up to 99% ee across four 2,5-disubstituted pyrrolidines for both the pyrrolidine products and the recovered starting materials. They were limited to alkyl and aryl substituents. Attempts to make the 2,3- and 2,4-disustituted pyrrolidines from imines **145** and **146**, respectively, were not as successful, obtaining mixtures of diastereoisomers during the reaction. The major diastereomers were still obtained in good enantioselectivities of up to 99% ee however, the enantioselectivities for the

recovered starting imines were considerably lower than that obtained for the 2,5-disubstituted pyrrolidines.

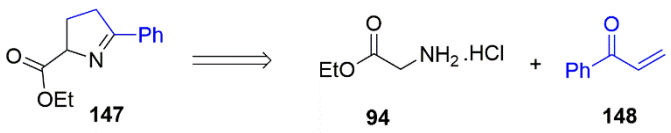


*Scheme 40: Reduction of cyclic imines using phenylsilane and titanocene catalyst **144***

Previous methods to access proline derivatives via the endocyclic imine install one stereogenic centre before either a nonselective or diastereoselective reduction. Herein lies the attempts to asymmetrically reduce cyclic imines using trichlorosilane and the imidazole based organocatalyst (*S*)-**49**.

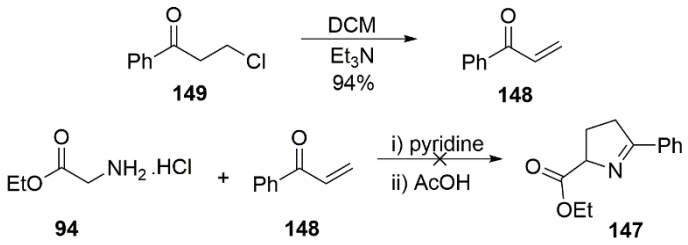
2.2.2 Cyclic imine synthesis

For this work, the cyclic imine **147** could be synthesised from glycine ethyl ester hydrochloride and enone **148** (Scheme 41). Michael addition of glycine ethyl ester, deprotonated at the α-carbon, to the enone **148** followed by intramolecular cyclisation could lead to the formation of cyclic imine **147**.



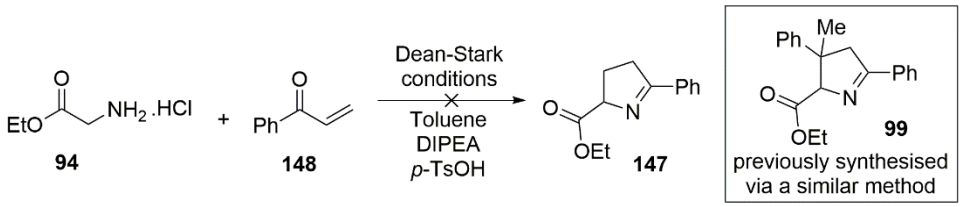
*Scheme 41: Retrosynthesis of cyclic imine **147***

Enone **148** was synthesised from 3-chloropropiophenone **149** in a good 94% yield (Scheme 42). Enone **148** and glycine salt **94** were then refluxed in pyridine following the first step of the procedure used by Opatz *et al*. in the synthesis of pyrroles from chalcones and glycine salt **94**.[107] A complex crude ^{1}H NMR spectrum was obtained and none of the desired product was afforded after flash column chromatography.



*Scheme 42: Unsuccessful synthesis of cyclic imine **147***

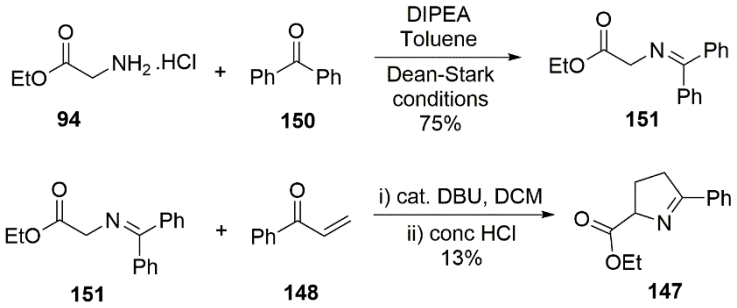
During the imine formation of acetophenone with glycine ethyl ester, the cyclic by-product **99** was obtained, therefore the synthesis of the similar cyclic imine **147** was attempted under the same conditions (Scheme 43). Enone **148**, glycine salt **94** and *p*-TsOH were dissolved in toluene and heated under Dean-Stark conditions. DIPEA was added dropwise over three hours due to both the base and the glycine ethyl ester having lower boiling points than that of toluene. The crude ^{1}H NMR spectrum showed a complex mixture, and no product was detected via this method.



*Scheme 43: Unsuccessful synthesis of cyclic imine **147***

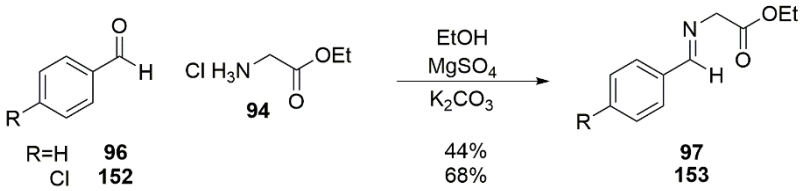
Alternative methods involve the protection of the glycine by forming an imine.[103] Benzophenone was reacted with glycine salt **94** under Dean-Stark conditions with dropwise addition of DIPEA, obtaining glycine ketimine **151** in a 75% yield (Scheme 44). Glycine ketimine **151** was deprotonated using catalytic amounts of DBU, reacted with enone **148** and

deprotected using concentrated hydrochloric acid, allowing for intramolecular imine formation/cyclisation. This method afforded the cyclic imine **147** in a poor 13% yield.



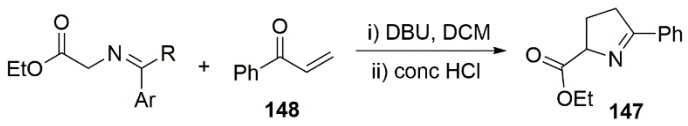
*Scheme 44: Synthesis of cyclic imine **147***

Different imine protecting groups were next tested. The aldimines were synthesised by stirring their respective aldehydes with glycine salt **94**, potassium carbonate, and magnesium sulfate in ethanol at RT overnight (Scheme 45). Aldimines **97** and **153** were obtained in moderately good yields of 44% and 68%, respectively.



Scheme 45: Synthesis of aldimines

Use of the 4-chlorophenyl aldimine **153** afforded the highest yield of 17% compared to the 13% yield of the benzophenone ketimine **151** and 7% yield of phenyl aldimine **97** (Scheme 46, Table 3, entries 1-3). Despite the increase being relatively small, 4-chlorophenyl aldimine **153** was chosen for future reactions, both due to the increase in yield and the ease of synthesis of the aldimine compared to the ketimine.



*Scheme 46: Synthesis of cyclic imine **147** using different protecting groups*

Table 3: Alternative glycine protecting groups[a]

Entry	R	Ar	Yield/%[b]
1	Ph	Ph	13
2	H	Ph	7
3	H	4-ClC_6H_4	17

[a]Reactions conducted with 1.1 mmol of enone **148** and 1 mmol of imine in 2 mL DCM with 0.1 eq of DBU and 0.3 eq of conc. HCl. [b]Isolated yield of **147**

Due to the poor mass return during column chromatography, the method of purification was investigated further. Different solid phases were trialled. Silica, triethylamine deactivated silica, alumina, and florisil were selected, however, very little variation in the yield and mass return was observed for the same test reaction.

To determine the cause of the poor yields, ^{1}H NMR spectroscopy experiments were conducted. The aim was to record conversion against a mesitylene internal standard while performing the reaction. Under the standard conditions, a good conversion of 69% after working up the reaction was obtained which upon purification gave a poor 21% yield of imine **147**. This would suggest that one of the main issues is with the purification, however, attempts to improve this failed to increase the yields. With the conversion not reaching 100%, the progress of the reaction at different timepoints was investigated. During ^{1}H NMR analysis of the reaction at t=0 min, it was observed that very little of enone **148** was present in the ^{1}H NMR spectra, which was unexpected. After testing the sample of enone **148**, it was found that enone **148** was rapidly degrading, even when stored in the freezer under argon for as little as 24 h. It was likely that enone **148** was undergoing polymerisation and upon repeating the initial internal standard reaction with freshly synthesised enone **148**, the conversion improved to 95% with the yield also improving to 34%.

Due to the instability of the enone, a one-pot method was proposed (Scheme 47). This would require an elimination, Michael addition, protecting group deprotection, and intramolecular imine formation/cyclisation to occur in one-pot through the subsequent addition of different reagents.

*Scheme 47: One-pot method for synthesis of cyclic imine **147***

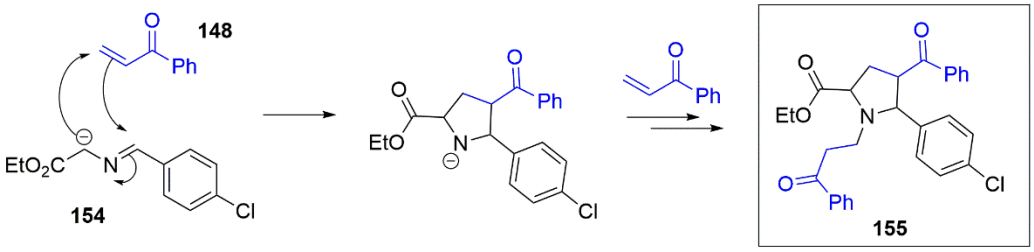
A base screen was conducted to identify any base that would work for both the elimination and the Michael addition (Table 4). At this stage, the steps were performed separately as they had been done previously. The elimination (step 1) was initially tested with DBU, the base previously used as a catalyst for the Michael addition (step 2), however after 4 h no product was formed (Table 4, entry 1). Additionally, when triethylamine was used, an excellent 98% yield could be obtained for step 1, however in step 2 no product was formed (Table 4, entry 2). Pyridine, DIPEA, and benzimidazole afforded no product in step 2 therefore were not tested in step 1 (Table 4, entries 4, 6, and 10). Caesium carbonate obtained a good conversion of 86% in step 1 after significantly longer reaction times than with triethylamine, 18 h compared to 1 h (Table 4, entry 3). In step 2, very little product formed after 4.5 h. This could be due to the poor solubility of caesium carbonate in DCM. In step 1, DABCO obtained a good conversion of 91% in shorter reaction times compared to caesium carbonate of 3 h compared to 18 h, however, in step 2 negligible amounts of product were observed in the ^{1}H NMR spectrum (Table 4, entry 5). Potassium *tert*-butoxide and imidazole both afforded product in step 2 as evidenced by ^{1}H NMR spectrum, however, due to the poor quality of enone **148** used in these test reactions, only approximate conversions could be calculated (Table 4, entries 7 and 8). When both these bases were tested in step 1, only potassium *tert*-butoxide afforded a good conversion, 86% after only 2 h. From this result, potassium *tert*-butoxide was selected as the base for the one-pot method.

*Table 4: Base screen for one-pot synthesis of cyclic imine **147***

		Step 1[a]		Step 2[b]		
Entry	Base	Conversion/%[c]	Time/h	Conversion/%[c]	Time/h	By-product formed
1	DBU	0	4	95	4.5	No
2	Et_3N	(98%)[d]	1	0	4.5	No
3	$CsCO_3$	86	18	<5	4.5	Yes
4	Pyridine	-	-	0	4.5	No
5	DABCO	91	3	<5	3.5	Yes
6	DIPEA	-	-	0	4.5	Yes
7	*t*-BuOK	86	2	>80[e]	3	Yes
8	Imidazole	<5	4	>80[e]	3.5	Yes
9	1,2,4-triazole	-	-	<5[e]	3	No
10	Benzimidazole	-	-	0[e]	4.5	No

[a]1 mmol of 3-chloropropiophenone in 1 mL of DCM at RT with 1.2 eq of base. [b]1.1 mmol of enone **148** (prepared from 3-chloropropiophenone directly before use) and 1 mmol of imine **153** dissolved in 1 mL of DCM at RT with 0.1 eq of base. Step 3 conducted directly after step 2 to provide the cyclic imine **147**, by addition of 1 mL 1M HCl with stirring for 1 h. [c]As determined by ^{1}H NMR spectrum. [d]Yield of **148**. [e]Enone prepared before reaction was of poor conversion.

A pyrrolidine by-product **155** was formed during step 2 when using caesium carbonate, DABCO, DIPEA, potassium *tert*-butoxide or imidazole as the base (Scheme 48). The *N*-protected pyrrolidine is made up from two molecules of enone **148** and one molecule of aldimine **153**. This assignment was confirmed by ^{1}H and ^{13}C NMR spectra through comparison to the methyl ester equivalent of pyrrolidine **155** reported by Fukuzawa *et al*.[108] Its formation could potentially occur via a cycloaddition reaction between enone **148** and anion **154**.



*Scheme 48: Proposed formation of by-product **155***

In 2019, Mayr *et al*. reported the nucleophilic reactivities of Schiff base derivatives of amino acids, including the glycine aldimine **153** used in the synthesis of cyclic imine **147** (Figure 25).[109] In this report, phenyl imine anion **156** was found to be 1.4 times more reactive towards a quinone methide than 4-chloro phenyl imine anion **154**. Different aldimines were tested in the one-pot method, including a 4-methoxy phenyl variant with the theory that adding a more electron donating group to the phenyl substituent would increase the reactivity of the imine anion and improve the yield. However, this was not found to be the case, with the phenyl imine **97** affording the highest yield of 34%, with no pyrrolidine by-product obtained (Table 5, entry 3). Both substituted phenyl rings afforded inseparable mixtures of the cyclic imines and their respective by-products. The yields of isolated pure product were significantly lower at 23% and 18% for the 4-chloro and 4-methoxy substituents, respectively (Table 5, entries 1 and 2). Including material from impure fractions as well, the yields were still very low at 28% and 25%, respectively.

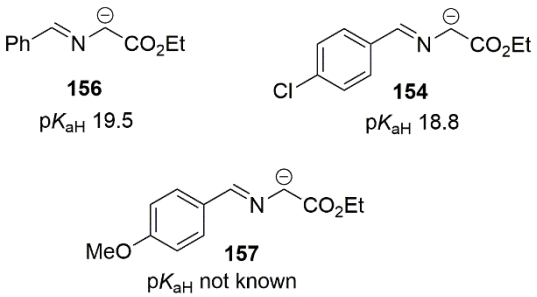


Figure 25: Nucleophiles derived from glycine and benzaldehydes

*Table 5: Alternative aldimines used in the one-pot method for the synthesis of cyclic imine **147**[a]*

Entry	Ar	R	Yield/%[b]	Potential yield/%[c]
1	4-ClC_6H_4	H	23	28
2	4-$MeOC_6H_4$	H	18	25
3	Ph	H	34	-

[a]Reactions conducted on 1 mmol scale with 1 eq imine, 1.5 eq of 3-chloropropiophenone, 1.7 eq of KO^{t}Bu at RT. Total reaction time 24 h. [b]Isolated yield of **147**. [c]Mixed fractions of cyclic imine **147** and the respective by-products obtained. The yield is corrected to include the product contained in the mixed fraction.

The phenyl aldimine **97** was selected for the one-pot method with potassium *tert*-butoxide as the base. Optimization of this reaction started with varying the reaction solvents (Table 6). DCM provided the highest yield of 34% however, 1,4-dioxane also provided a similar yield of 33% (Table 6, entries 2 and 5).

Table 6: Optimization of one-pot method, changing the solvent[a]

Entry	Solvent	Yield/%[b]
1	THF	25
2	1,4-dioxane	33
3	$CHCl_3$	14
4	Toluene	12
5	DCM	34

[a]Reactions conducted using 1 mmol of imine **97** with 1.5 eq of 3-chloropropoiphenone, 1.7 eq of *t*-BuOK, in 4 mL of solvent at RT. [b]Isolated yield of **147**.

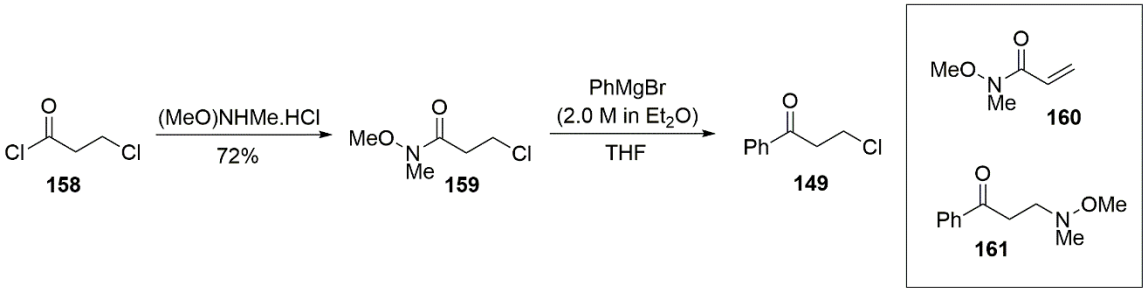
The equivalents of 3-chloropropiophenone were next varied, with the equivalents of potassium *tert*-butoxide remaining as 0.2 equivalents in the second step (Table 7). A very small difference in the yield of cyclic imine **147** was observed when using 1.2 equivalents of 3-chloropropiophenone in comparison to 1.5 equivalents, 36% compared to 34% (Table 7, entries 2 and 3). Within error, these yields were identical, therefore the equivalents of 3-chloropropiophenone has very little effect on the outcome of this reaction.

Table 7: Optimization of one-pot method, changing the equivalents of 3-chloropropiopheone[a]

Entry	Eq of 3-chloropropiophenone	Yield/%[b]
1	1	35
2	1.2	36
3	1.5	34

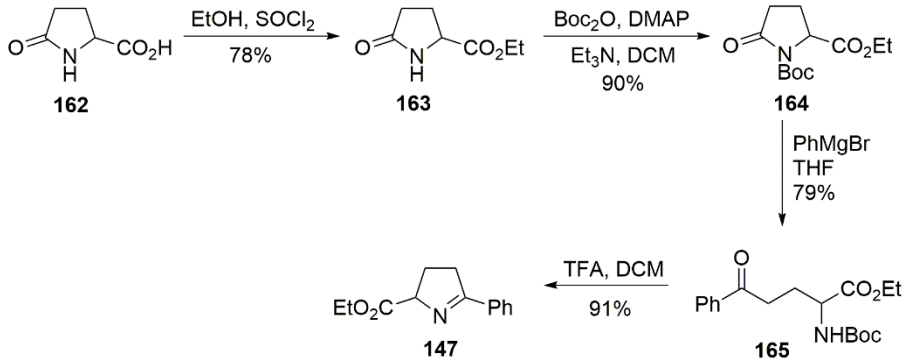
[a]Reactions conducted using 1 mmol of imine **97** in 4 mL of DCM at rt. Eq of *t*-BuOH was 0.2 eq + eq of 3-chloropropiophenone. [b]Isolated yield of **147**.

For this route to be viable for examination of substrate scope at a later stage, a method to synthesise 3-chloropropiophenone needed to be developed. It was important that this route could be easily modified to allow for substate scope expansion later. Grignard addition to a Weinreb amide was investigated (Scheme 49). The Weinreb amide was synthesised from acid chloride **158** in a good 72% yield. The Grignard addition reaction was attempted using commercially available phenylmagnesium bromide. Significant quantities of starting material were recovered from the reaction and very little of the desired product obtained, giving a very poor 2% yield of 3-chloropropiophenone after 2 h at 0 °C. A by-product in the form of eliminated Weinreb amine **160** was observed in a 1:1 ratio with the desired product as calculated from ^{1}H NMR spectrum. Reaction times above 6 h provided amine **161** as an additional by-product and gave eliminated Weinreb amide **160** as the major product. Lower temperatures were attempted but the ratio of desired product to amide **160** remained the same at 1:1. The elimination to amide **160** was unavoidable with the Grignard acting as a base deprotonating α- to the carbonyl. The amine formed from Grignard addition to the Weinreb amide was then able to add to the enone **148** via a 1,4-addition.



Scheme 49: Attempted synthesis of 3-chloropropiophenone

With the simplest route to 3-chloroproiphenone providing a mixture of products, an alternative synthetic route to the cyclic imine was tested (Scheme 50). (±)-Pyroglutamic acid **162** was esterified using ethanol and a catalytic amount of thionyl chloride in a good 78% yield. Amine **163** was Boc protected using Boc_2O with catalytic DMAP in a good 90% yield. Both these steps were performed on a scale of tens of grams demonstrating scalability of the reaction. Ring opening of the lactam **164** via addition of commercially available phenylmagnesium bromide achieved a good 79% yield of ketone **165**. In comparison, synthesis of the Grignard from bromobenzene was also conducted and a good 68% yield was obtained for the ketone **165**. Deprotection of the amine with trifluoroacetic acid afforded cyclic imine **147** in a good 91% yield. The imine was clean enough to be used directly in the next step without further purification. When samples of the cyclic imine were purified by flash column chromatography, good yields of 72% were obtained. This would suggest that very little of the cyclic imine is degrading on the column.



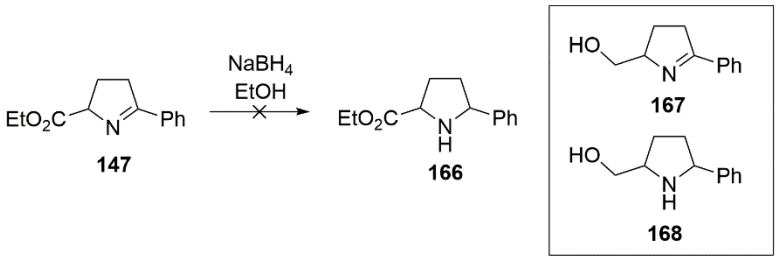
*Scheme 50: Alternative synthetic route to cyclic imine **147***

The new method from (±)-pyroglutamic acid is significantly better than the one-pot method and so this method was used exclusively going forward.

2.2.3 Trichlorosilane reduction

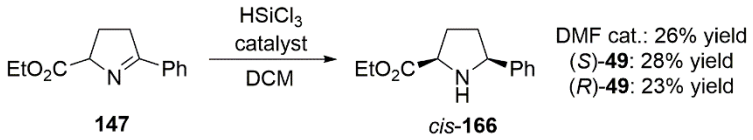
During the reduction of cyclic imine **147** using sodium borohydride, the ester functional group was reduced, affording a mixture of imino alcohol **167** and amino alcohol **168** (Scheme 51).

None of the desired product was obtained. The presence of imino alcohol **167** and the lack of amino ester **166** would suggest that the ester is being reduced first under these reaction conditions. The sole aim of this reaction was to obtain a racemic mixture of pyrrolidine **166** for analysis. An alternative route to this is to use trichlorosilane in the presence of an achiral catalyst such as DMF.



*Scheme 51: Sodium borohydride reduction of cyclic imine **147***

The trichlorosilane mediated reduction of cyclic imine **147** was attempted using three different catalysts: DMF and imidazole-based catalyst (*S*)-**49** and (*R*)-**49** (Scheme 52). The crude ^{1}H NMR spectra for these reactions were slightly different, suggesting different products were being obtained. Column chromatography on the crude samples gave the desired product as the *cis*-isomer in low yields even when the pyrrolidine *cis*-**166** had not been present in the crude spectrum. (For in depth confirmation of stereochemistry, see page 70).



*Scheme 52: Trichlorosilane reduction of cyclic imine **147***

Previous work conducted in the Jones group investigating the reaction mechanism of the trichlorosilane mediated reduction of ketimines identified that the reduced amine forms complex **169** with additional trichlorosilane (Figure 26).[63] The reaction with the cyclic imine is likely to form a similar complex after the reduction. With the more rigid structure of the proline moiety, a more stable complex is likely to form wherein coordination to the oxygen carbonyl of the ester can occur obtaining complex **170**. These complexes decompose upon work up,

however, since pyrrolidine complex **170** is more stable, it is harder to break apart. Changing the work-up procedure gave more consistent results. Rather than just neutralising the reaction and separating, neutralisation had to be repeated until the mixture remained at pH 7 after five-ten minutes of stirring.

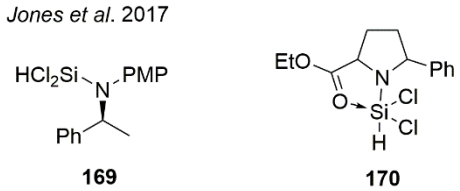


*Figure 26: Trichlorosilane intermediate **169** during ketimine reduction and postulated intermediate **170** during cyclic imine reduction*

With the work-up issues resolved, investigations into the diastereoselectivity of the trichlorosilane mediated reduction could be conducted (Table 8). When using DMF as an achiral catalyst, a good diastereoselectivity of 88:12 dr (*cis*:*trans*) was obtained with a poor 26% yield for the major isomer whereas the imidazole-based catalyst (*S*)-**49** gave a lower diastereoselectivity of 75:25 dr with a poor 28% yield for the major isomer (Table 8, entries 1 and 2). Two conversion studies, one at 0 °C with 10 mol% of imidazole catalyst (*S*)-**49** and the other at −18 °C with 5 mol% of imidazole catalyst (*S*)-**49**, were conducted wherein aliquots were removed from the reaction at regular intervals, mini-work ups performed and crude ^{1}H NMR spectra recorded to determine the conversion and diastereoselectivity. At 0 °C, the reaction was complete between 30 and 60 minutes with a moderate diastereoselectivity of 80:20 dr recorded at 15 min (Table 8, entries 3-5). At −18 °C, the reaction was complete between 60 and 120 minutes, with an excellent diastereoselectivity of 98:2 dr recorded at 15 min (Table 8, entries 6-9). Looking at the results obtained so far it was clear that the higher the percentage conversion of the starting material to the desired product, the lower the diastereomeric ratio would be of the final product. As the starting imine **147** is racemic, interactions between each of the isomers and the chiral catalyst (*S*)-**49** will be different whereby the one of the imine enantiomers will preferentially match with the catalyst and be

reduced first in a diastereoselective manner. As the reaction progresses, the other enantiomer will start to be reduced, which in turn reduces the diastereoselectivity of the reaction. A further reaction was conducted using 1 mol% of (*S*)-**49** at −18°C (Table 8, entry 10). At 15 minutes, an excellent diastereoselectivity of 98:2 dr was observed at 50% conversion.

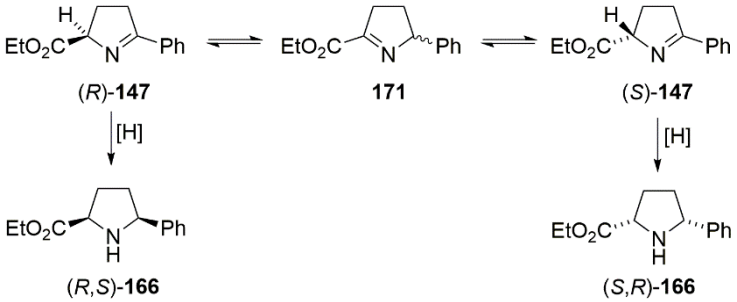
*Table 8: Initial optimisation Trichlorosilane reduction of cyclic imine **147**[a]*

Entry	Catalyst (mol%)	Time/min	Temperature/°C	dr[c]	ee[d]	Conversion/%[c]
1	DMF (20)	240	0	88:12		100
2	(*S*)-**49** (10)	240	0	75:25		100
3[b]	(*S*)-**49** (10)	15	0	80:20		75
4[b]	(*S*)-**49** (10)	30	0	75:25		89
5[b]	(*S*)-**49** (10)	60	0	75:25		100
6[b]	(*S*)-**49** (5)	15	−18	98:2	(88%)	68
7[b]	(*S*)-**49** (5)	30	−18	84:16		82
8[b]	(*S*)-**49** (5)	60	−18	80:20		89
9[b]	(*S*)-**49** (5)	120	−18	77:23		100
10[b]	(*S*)-**49** (1)	15	−18	98:2	(64%)	50

[a]Reactions were performed on 1 mmol scale, imine **147** (1 eq), $HSiCl_3$ (2 eq) in DCM (2 mL). [b]Rate study, 0.1 mL aliquots removed from the reaction pot at the required time. [c]Determined via ^1H NMR spectroscopy. [d]Determined via chiral HPLC however contaminates made analysis difficult.

Chiral HPLC analysis was attempted for several the clean *cis*-isomer samples. Unfortunately, the results were inconsistent with each other due to poor quality HPLC traces being obtained which also contained impurity peaks which overlapped with the isomer peaks. Approximations of the enantiomeric excesses were calculated from the HLPC trace for two of the samples. At −18 °C with 5 mol% of (*S*)-**49** the enantioselectivity for the *cis*-pyrrolidine **166** was approximately 88% ee whereas with 1 mol% of (*S*)-**49** the enantioselectivity was lower at 64% ee. For the result using 5 mol% of (*S*)-**49**, the enantioselectivity was higher than would be expected for a kinetic resolution process as the conversion was significantly higher than 50%. The acidic conditions under which the reaction takes place could allow for epimerisation

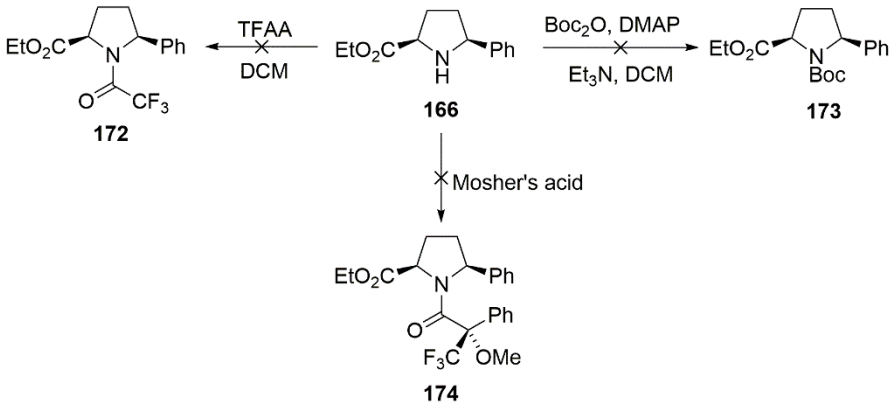
of the α-carbon within the molecule (Scheme 53). If this is the case, then a dynamic kinetic resolution could potentially be taking place. In order to investigate the potential for DKR, the current problems with the chiral HPLC analysis needed to be resolved.



*Scheme 53: Proposed dynamic kinetic resolution process involved in the reduction of cyclic imine **147***

Attempts to improve the HPLC analysis proved unsuccessful. Firstly, the UV-vis spectrum of the product was recorded to find the maximum absorbance to ensure the UV detector attached to the chiral HLPC was set to the best wavelength. Unfortunately, no improvement in the quality of the HPLC traces was observed.

Derivatisation of the pyrrolidine was also attempted (Scheme 54). Synthesis of the trifluoroacetamide **172** failed to provide any of the desired product, providing a complex mixture of compounds by ^{1}H NMR analysis of the crude product. Boc protection of pyrrolidine **173** gave inconsistent results across five different samples, wherein samples contained contaminates in the HLPC trace that were not observable in the ^{1}H NMR spectrum.



*Scheme 54: Derivatisation of pyrrolidine **166***

Next, different NMR spectroscopy techniques were evaluated. First, salting pyrrolidine **166** with various chiral acids to produce observable diastereoisomers within the ^{1}H NMR spectrum was attempted. The acids used were L-tartaric acid, mandelic acid, and camphorsulfonic acid (CSA). Unfortunately, none of these had the desired effect. Next, synthesis of the Mosher amide **174** was undertaken. None of the desired product was obtained, returning only recovered starting material after the reaction.

Lastly, two samples of racemic *cis*-pyrrolidine **166** were sent away for analysis by Onyx Scientific in the hopes that HPLC conditions could potentially be found. HPLC chromatograms received from the company had four peaks in each of the spectra (overlay in appendix, pg 244). This was unexpected as they should only have had two peaks as it was a clean sample of a single diastereoisomer by ^{1}H NMR spectra.

With many of the options for analysis of the enantioselectivity exhausted, more focus was placed on the diastereoselective reaction and establishing if the dr could be increased at higher conversions/yields (Table 9). Increasing the concentration of the reaction caused the reduction to be complete in under 15 minutes, giving a moderate 80:20 dr with a moderate 50% yield for the major *cis*-isomer of pyrrolidine **166** (Table 9, entry 1). Lowering the concentration led to no reaction being observed in a 15-minute timeframe (Table 9, entry 2). Lowering the temperature to −40 °C and increasing the reaction time to 30 minutes had the same outcome (Table 9, entry 3). Alternative solvents used previously in the trichlorosilane reduction of ketimines were also investigated (Table 9, entries 4 and 5). Ethyl acetate provided a very high conversion of 81% after 15 minutes with a good diastereoselectivity of 90:10 dr, obtaining the *cis*-pyrrolidine **166** in a moderate 41% yield. The yield of the recovered starting material, the cyclic imine **147**, was a poor 7% with a poor 24% ee. Chloroform produced the *cis*-pyrrolidine **166** a higher diastereoselectivity of 93:7 dr at a significantly lower conversion of 41%. The yield was lower which was to be expected from the lower conversion. A higher yield of 30% was obtained for the recovered cyclic imine **147** with a moderate enantioselectivity of 54% ee. Increasing the catalyst loading to 10 mol% increased the

conversion to 75% but this caused a decrease in the diastereoselectivity to 83:17 dr and the *cis*-pyrrolidine **166** was obtained in a poor 23% yield (Table 9, entry 6). The starting material was recovered in a poor 8% yield but with excellent enantioselectivity of 96% ee. This high enantioselectivity would suggest a kinetic resolution process is occurring here.

*Table 9: Continued optimisation of the trichlorosilane mediated reduction of cyclic imine **147**[a]*

Entry	Solvent	dr[f]	Conversion/%[f]	Yield/%[g]	Recovered **147** yield/%[g] (%ee)[h]
1[b]	DCM	80:20	100	50	
2[c]	DCM		0		
3[d]	DCM		0		
4	EtOAc	90:10	81	41	7 (24)
5	$CHCl_3$	93:7	41	12	30 (54)
6[e]	DCM	83:17	75	23	8 (96)

[a]Reactions were performed on a 1 mmol scale, imine **147** (1 mmol), catalyst (*S*)-**49** (5 mol%), −18 °C, 15 min, solvent (2 mL). [b]Solvent (1 mL). [c]Solvent (10 mL). [d]−40 °C, 30 min. [e]Catalyst (*S*)-**49** (10 mol%). [f]Determined via ^{1}H NMR spectroscopy. [g]Isolated yield after flash column chromatography. [h]Determined from chiral HPLC.

From the results of the enantioselectivities for the recovered starting imine **147**, there is the possibility to conduct a kinetic resolution. However, without the accurate results for the enantioselectivity of the product pyrrolidine **166** it is very difficult to make conclusive arguments as to whether it is operating via a standard kinetic resolution or via a dynamic kinetic resolution. The initial results obtaining high diastereoselectivities of 98:2 dr at moderate 68% conversion with an approximate 88% ee for the product pyrrolidine **166** would suggest a DKR process over a KR process.

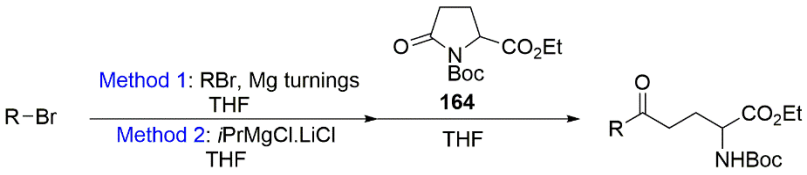
2.2.4 Substrate scope

To investigate the scope of the diastereoselective reduction, a series of cyclic imines were synthesised from (±)-pyroglutamic acid. The first step is the Grignard addition reaction to protected (±)-pyroglutamate **164** (Scheme 55, Table 10). Two different methods were utilised

whereby the first method (method 1) involved the synthesis of the Grignard reagents from their respective aryl bromides using magnesium and direct heating or iodine to initiate the reaction. The Grignard reagent was added to a solution of the pyroglutamate **164**. This method worked well for *para*-substituted phenyl examples, achieving poor to moderate yields between 18% and 55% (Table 10, entries 1-5). *meta*-Substituted phenyls proved more difficult with the nitro and nitrile aryl bromides failing to initiate during the formation of the Grignard (Table 10, entries 7 and 8). *meta*-Bromo phenyl **180** was afforded in a moderate 24% yield via this method (Table 10, entry 6). *ortho*-Substituted phenyls, bromo, nitrile and fluoro, caused Boc deprotection of the starting material affording a complex mixture of products as evidenced by ^{1}H NMR spectrum of the crude products (Table 10, entries 9, 10, and 13). No Boc deprotection was observed for any other substrates, suggesting that interactions with the closer *ortho*-substitution encourages Boc deprotection over Grignard addition. However, a surprising result was obtained with the *ortho*-methylphenyl **185** derivative, which was isolated in a poor 14% yield (Table 10, entry 11). Cyclohexane and pyridine substrates **188** and **189** were tolerated, giving yields of 45% and 15%, respectively (Table 10, entries 14 and 15). An attempt to synthesise the thiophene **190** was unsuccessful due to failure in initiating the Grignard reagent synthesis (Table 10, entry 16).

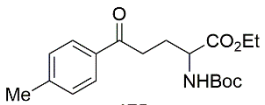
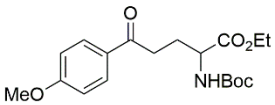
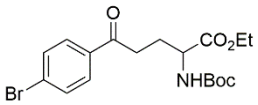
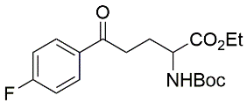
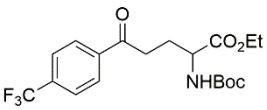
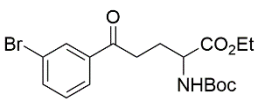
The second method investigated (method 2) involved the use of Turbo Grignard (isopropyl magnesium chloride lithium chloride complex) to synthesise the required Grignard reagent. This method was milder than the traditional method used to synthesis Grignard reagents and was found to significantly improve the yield of *meta*-bromo substate **180** from 24% to 41% (Table 10, entry 6). The change in how the required Grignard reagent is made decreases the degree to which Wurtz coupling of the aryl bromides occurs. This is of particular importance with dibromobenzene as this can polymerize during the synthesis of the Grignard reagent, resulting in poor yield of the desired products. In addition, the *meta*-nitrile substrate **182** which failed to be synthesised via method 1 was synthesised in a moderate 48% yield via method 2 (Table 10, entry 8). Unfortunately, the synthesis of *meta*-nitro substrate **181** was unsuccessful

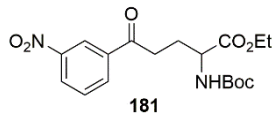
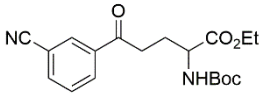
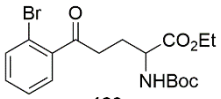
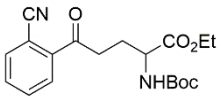
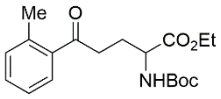
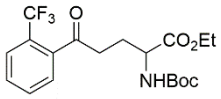
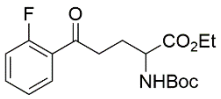
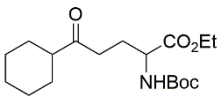
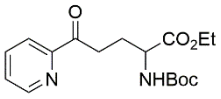
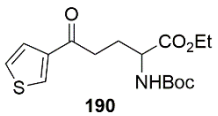
via both methods (Table 10, entry 7). Furthermore, *ortho*-substituted phenyl groups containing bromo and nitrile substituents failed to give the desired products as well, returning only starting materials (Table 10, entries 9 and 10). However, *ortho*-trifluoromethyl substrate **186** was synthesised in a poor 25% yield with no evidence of Boc deprotection via this method (Table 10, entry 12).



*Scheme 55: Grignard addition to lactam **164***

Table 10: Grignard addition products

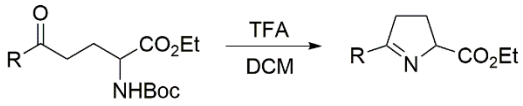
Entry	Product	Method 1 yield/%[a]	Method 2 yield/%[b]
1	 **175**	55	-
2	 **176**	48	-
3	 **177**	28	-
4	 **178**	48	-
5	 **179**	18	-
6	 **180**	24	41

7	 **181**	0	0
8	 **182**	0	48
9	 **183**	0	0
10	 **184**	0	0
11	 **185**	14	-
12	 **186**	-	25
13	 **187**	0	-
14	 **188**	45	-
15	 **189**	15	-
16	 **190**	0	-

[a]Reaction performed on a 5 mmol scale, lactam **164** (5 mmol), aryl bromide (7.5 mmol), magnesium turnings (7.5 mmol), in THF (6 mL), overnight at rt. Isolated yield. [b]Reaction performed on a 5 mmol scale, lactam **164** (5 mmol), aryl bromide (5 mmol), turbo Grignard (1.3 M in THF, 5 mmol), in THF (10 mL), overnight at rt. Isolated yield.

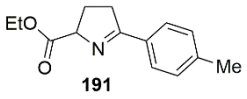
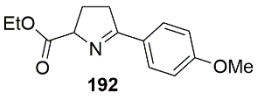
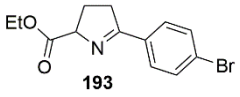
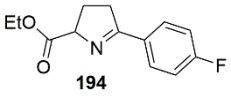
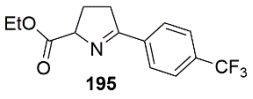
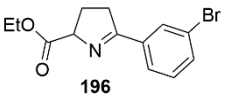
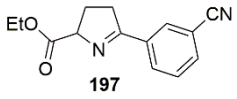
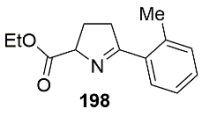
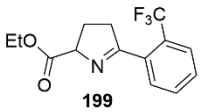
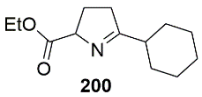
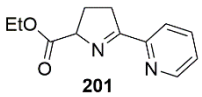
Deprotection of the amine using trifluoroacetic acid was the conducted on the Grignard addition products, allowing for ring closure upon neutralisation of the reaction (Scheme 56,

Table 11). Moderate to good yields of up to 93% were obtained across the 11 examples. These compounds were found to be relatively clean directly from the reaction and so purification was not necessary for most substrates. *para*-Bromophenyl imine **193** and pyridyl imine **201** were obtained in poor 28% and 26% yields, respectively, after purification via flash column chromatography on silica gel (Table 11, entry 3 and 11).



Scheme 56: Boc deprotection of Grignard addition products

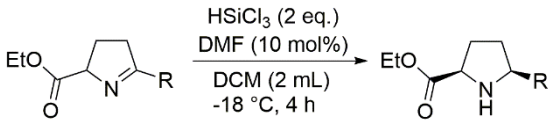
Table 11: Synthesis of cyclic imines[a]

Entry	Product	Yield/%	Entry	Product	Yield/%
1	 **191**	77	2	 **192**	76
3	 **193**	28[b]	4	 **194**	64
5	 **195**	83	6	 **196**	74
7	 **197**	93	8	 **198**	68
9	 **199**	73	10	 **200**	45
11	 **201**	26[b]			

[a]Reactions were performed with Grignard addition products (1 eq.), TFA (38 eq.) in DCM (5-20 mL) at rt for 3 h before neutralisation and stirring for a further 2 h. [b]Purified via flash column chromatography.

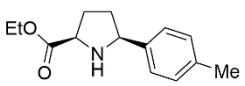
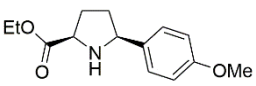
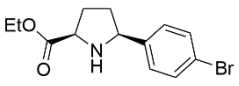
The trichlorosilane mediated reduction was conducted using DMF as a catalyst at −18 °C for 4 h (Scheme 57, Table 12). Conducting the reaction under these conditions should have allowed the reaction to go to complete conversion, allowing for the *cis*-isomers of the

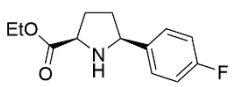
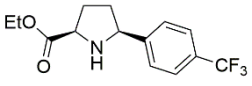
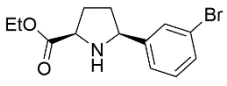
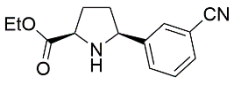
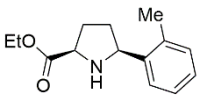
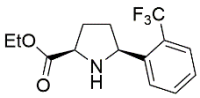
pyrrolidines to be obtained for future attempts of chiral HPLC analysis. *para*-Substituted examples achieved moderate to excellent diastereoselectivities, with the best results being obtained for *para*-methoxy **203** and *para*-fluoro **205** both of which failed to go to complete conversion within the reaction time (Table 12, entries 1-5). The lowest diastereoselectivity was observed for *para*-bromo **204** achieving a poor 62:38 dr at 100% conversion, however, the *cis*-isomer was isolated in a moderate 38% yield. Excellent diastereoselectivities of 96:4 dr were obtained for the *meta*-substituted examples even at full conversion (Table 12, entries 6 and 7). Increased steric interactions between the *meta*-substituted compounds and the trichlorosilane/DMF complex compared to the *para*-substituted compounds may be attributed to the improvement of diastereoselectivity at high conversions. Unfortunately, the *cis*-isomer of *meta*-bromo **207** was obtained in a poor 8% yield, whereas *meta*-nitrile **208** was obtained in a good 61% yield. *ortho*-Substituted examples were obtained in excellent diastereoselectivities of 96:4 dr however the conversion was significantly lower than that of the *meta*-substituted examples (Table 12, entries 8 and 9).



Scheme 57: Trichlorosilane mediated reduction of cyclic imines

Table 12: Results of the trichlorosilane mediated reduction of cyclic imines[a]

Entry	Product	dr[b]	Conversion/%[b]	Yield/%[c]
1	 **202**	90:10	100	33
2	 **203**	94:6	50	8
3	 **204**	62:38	100	38

4	 **205**	96:4	72	31
5	 **206**	88:12	100	29
6	 **207**	96:4	100	8
7	 **208**	96:4	100	61
8	 **209**	96:4	50	17
9	 **210**	96:4	40	9

[a]Reactions performed on a 0.5 mmol scale, imine (0.5 mmol), $HSiCl_3$ (1 mmol), DMF (0.05 mmol), DCM (1 mL), −18 °C for 4 h. [b]Deteremined by ^1H NMR spectroscopy. [c]Isolated yield of the major *cis*-isomer.

To confirm the structure of the major diastereoisomer obtained for each of the pyrrolidines required a closer inspection of the ^1H NMR spectra (Figure 27, Table 13). Both isomers of pyrrolidine **166** have been reported in the literature and the major isomer isolated was confirmed to be the *cis* by comparison to the literature data.[110] The difference in the peak shift of the proton labelled H^A was smallest for the *cis*-isomer compared to the *trans*-isomer in every example. Larger differences were observed for the proton labelled H^B especially for the *para*- and *ortho*-trifluoromethyl, *meta*-nitrile, and *ortho*-methyl where the difference for the *trans*-isomer is smaller than that of the *cis*-isomer. With the significantly larger differences observed for proton H^B compared to proton H^A in all cases, the results for proton H^A were used solely to determine the major isomers, wherein all compounds were predicted to be the *cis*-isomer. While this analysis has its flaws, the preference for the *cis*-isomer can be supported by predicting the mechanism to be operating with the attack of the hydride coming from the opposite face of the molecule to the ester moiety.

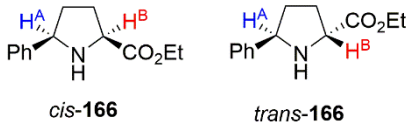


*Figure 27: Proton numbering for pyrrolidine **166***

Table 13: Isomer comparison table for pyrrolidines

Isomer	H^A (ppm)	H^B (ppm)
cis-**166**	3.94	4.14
trans-**166**	4.07	4.39

Entry		Δδ[a] (X-3.94)	Δδ (X-4.07)	Δδ (X-4.14)	Δδ (X-4.39)
1	4-Me	0.00	-0.13	0.06	-0.19
2	4-OMe	-0.03	-0.16	0.03	-0.22
3	4-Br	-0.01	-0.14	0.05	-0.20
4	4-F	-0.01	-0.14	0.07	-0.18
5	4-CF_3	0.03	-0.10	0.17	-0.08
6	3-Br	0.00	-0.13	0.06	-0.19
7	3-CN	0.03	-0.10	0.16	-0.09
8	2-Me	0.00	-0.13	0.31	0.06
9	2-CF_3	0.03	-0.10	0.53	0.28

[a]Whereby X is the peak shift of the respective proton within each of the pyrrolidines.

2.2.5 Conclusion and future work

Two different routes to the cyclic imines were investigated. The first route, proceeded via the elimination of 3-chloropropiophenone, Michael addition reaction, deprotection of the amine, and ring closure gave the cyclic imine **147** in a moderate 36% during a one-pot method. Despite optimization attempts, this route was not viable, giving only moderate yields and with no easy routes for derivatisation as shown by the attempted Grignard addition to Weinreb amide **159**, an alternative method was required. Route two utilised (±)-pyroglutamic acid which

was converted to the ethyl ester and Boc protected on a large scale. Grignard addition to lactam **164** could be achieved in a good yield of 79%, followed by Boc deprotection and ring closure afforded the cyclic imine in a good 91% yield. This method was successfully applied to 10 further examples, with the main issue being the Grignard addition step, however some of the more difficult substrates could be made by using Turbo Grignard. Most *ortho*-substrates resulted in Boc deprotection and complex mixtures after the Grignard addition.

The trichlorosilane mediated reduction was conducted on cyclic imine **147**. Attempts to determine the enantioselectivity of the reaction ultimately failed due to a combination of poor HPLC traces being obtained from the chiral HPLC, failure to find a suitable derivative for analysis and the lack of reproducibility. Applying classic NMR spectroscopy techniques via salting with chiral acids and synthesis of the Mosher's amide did not provide any significant results. For any future work on this method to be viable, a method to determine the enantioselectivity needs to be found and be able to produce reliable results.

On a positive note, the diastereoselectivity of this reaction is excellent at moderate conversions. Given how high the conversion is, there is the potential for a DKR to be conducted, however, without data for the enantioselectivities this was not able to be investigated at this stage. The *meta*-substituted examples gave excellent diastereomeric ratios of 96:4 dr at complete conversion. Unfortunately, the yields for many of the trichlorosilane reductions are poor to moderate. Ultimately, this route to proline-based molecules is not viable with these current results.

2.3 Cyclic β-amino acids based on 2,3-disubstiuted piperidines

2.3.1 Background

Piperidines are versatile molecular building blocks and are frequently found in natural products and pharmaceuticals (Figure 28).[111–115] In fact, during an analysis of U.S. FDA approved drugs, they were found to be the most frequently used nitrogen heterocycle.[116] Installing a carboxylic acid onto the molecule allows constrained amino acids such as pipecolic acid and nipecotic acid to be obtained. Avacopan, a C5a receptor antagonist, is derived from nipecotic acid, containing a *cis*-2,3-disubstituted piperidine core unit.

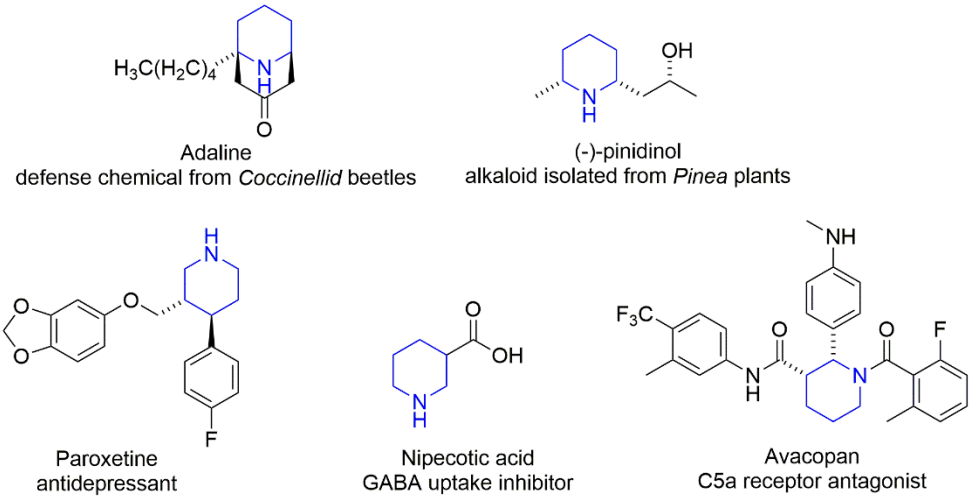


Figure 28: Various piperidine containing natural products and pharmaceuticals

Functional handles and the small, constrained structure make them an ideal target for exploration into 3D-chemical space. In 2020, O' Brien and co-workers developed a fragment library aiming to investigate new 3D-chemical space (Figure 29).[117] The selected molecules were based on piperidines and pyrrolidines and achieved a high degree of shape diversity and high proportion of sp^3 carbons.

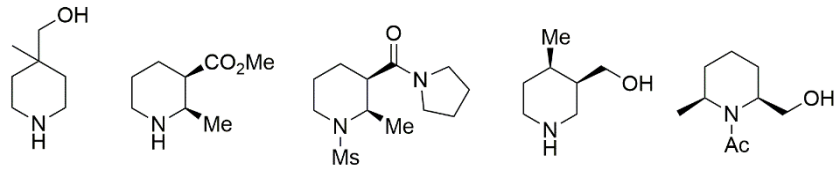
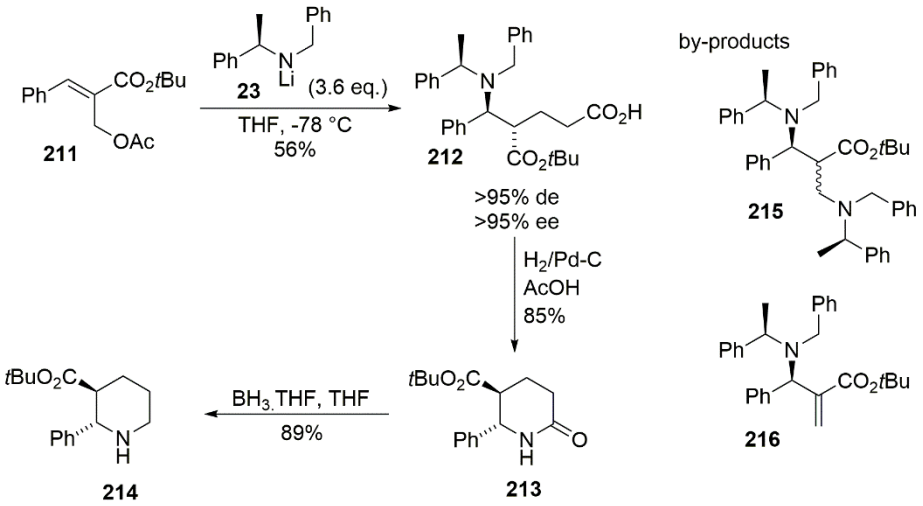


Figure 29: Selected piperidines synthesised by O' Brien and co-workers

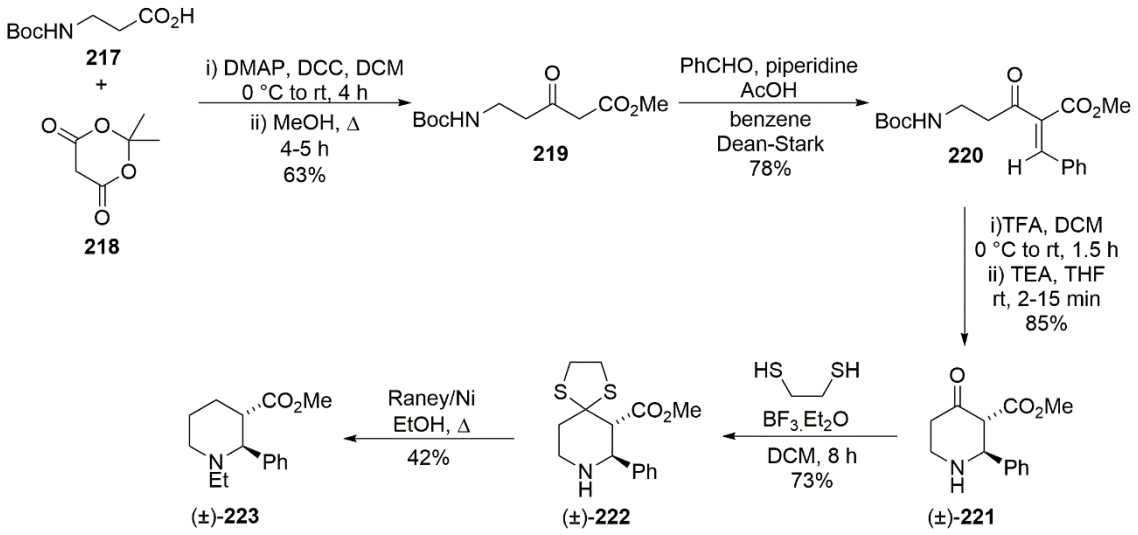
There are numerous ways to synthesise piperidines; the current most popular routes operate via intramolecular S_N2 displacement of a suitable leaving group by a nitrogen nucleophile, ring expansion reactions, ring closing metathesis, and aza-Michael reactions.[118–120] There is a very limited number of selective routes to 2,3-disubstituted piperidines furnished with an acid, ester or amide functional group. A stereoselective synthesis of *trans*-2,3-disubstituted piperidines was investigated by Garrido *et al* in 2008 (Scheme 58).[121] The key step involved a domino Ireland-Claisen rearrangement and Michael addition using a chiral lithium amide, affording δ-amino acid (4*S*,5*S*)-**212** in a good 56% yield with excellent diastereoselectivity and enantioselectivity of >95% de and >95% ee, respectively. Another diastereoisomer, δ-amino acid (4*R*,5*S*)-**212**, was also detected however no further information on yields or enantioselectivity of this compound was given. A scale up of this step was performed on 5 g of material, obtaining a moderate 45% yield. Numerous by-products were observed during this reaction, obtaining two isomers of diamine **215** and β-amino ester **216** in an overall 29% yield. Removal of the chiral protecting group and formation of the lactam afforded piperdin-2-one **213** in a good 85% yield. *trans*-2,3-Piperidine **214** was obtained after reduction of the lactam with borane in a good 89% yield.



Scheme 58: Ireland-Claisen rearrangement and Michael addition method used by Garrido et al.

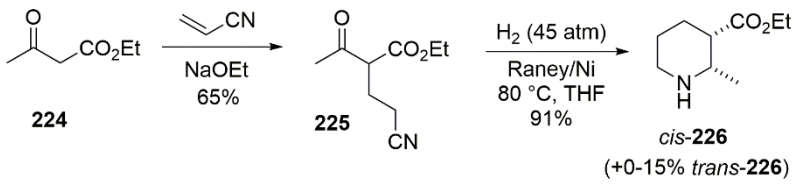
Bhat *et al*. developed a method to *trans*-2,3-disubstituted piperidines via TFA or $BF_3.Et_2O$ mediated Boc deprotection and intramolecular aza-Michael addition (Scheme 59).[122]

Piperidin-4-one (±)-**221** was obtained in a good 85% yield as a single diastereoisomer using a TFA/TEA one-pot method. A further 9 examples were synthesised, achieving good yields up to 88%. An alternative method for this step was also investigated, employing $BF_3.Et_2O$ in a cascade reaction. Across 6 examples good yields of up to 85% were obtained including piperidin-4-one (±)-**221** in a 64% yield. 2,3-Disubstituted piperidine **223** was synthesised by treatment of piperidone **221** with 1,2-ethanedithiol followed by reduction using Raney nickel.



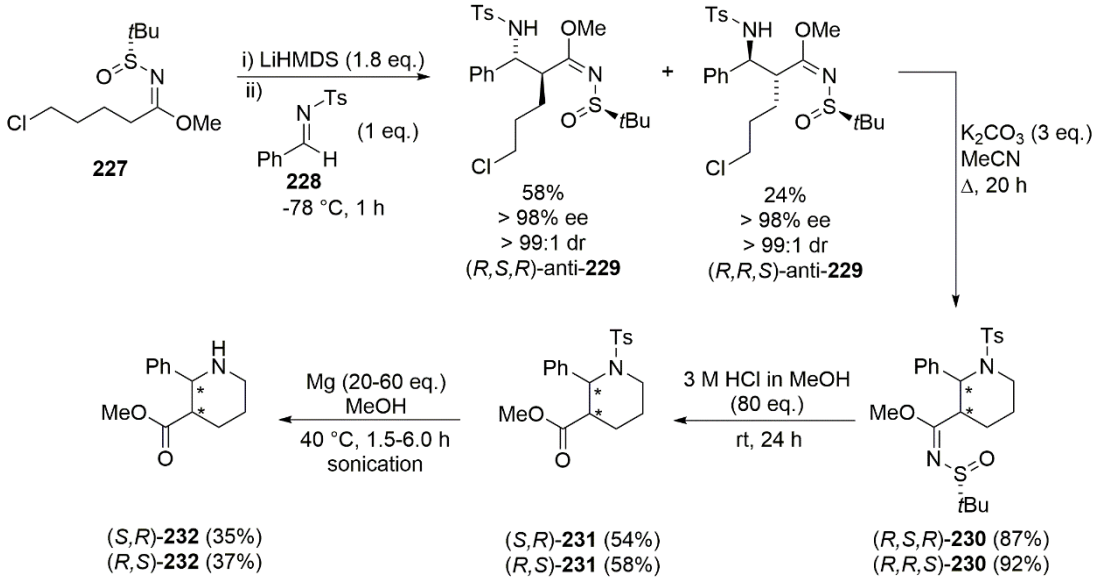
Scheme 59: One-pot Boc deprotection intramolecular aza-Michael addition cascade reaction

One of the simplest routes to *cis*-disubstituted piperidines is via a Michael addition reaction between acrylonitrile and β-keto ester **224** followed by reduction of the nitrile (Scheme 60).[123] Bols *et al.* used this method to synthesise piperidine **226** in a moderate 59% yield over two steps. Unfortunately, the diastereoselectivity of the reaction was variable, ranging from 100:0 to 85:15 dr depending on the scale of the reaction. Boc protection of the pyrrolidine **226** allowed for easy separation of the diastereoisomers.



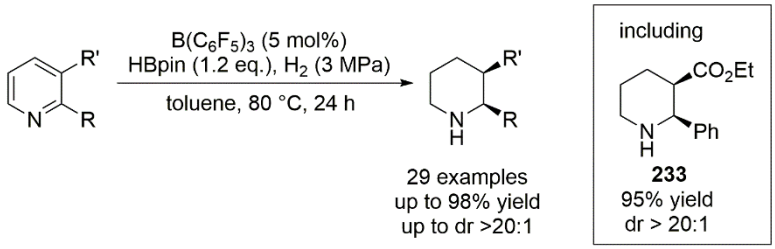
*Scheme 60: Michael addition and reduction method to synthesise 2,3-disubstituted piperidine **226***

In 2015, Mangelinckx *et al*. performed an asymmetric addition reaction between *N*-sulfinyl imidate **227** and aldimine **228** aiming to synthesise *cis*-2,3-disubsituted piperidines (Scheme 61).[124] They obtained a mixture of two separable diastereoisomers in a 72:28 dr, and after separation by column chromatography both were obtained in excellent enantioselectivities with moderate yields. Subsequent intramolecular S_N2 displacement of the chloride, piperidines (*R,S,R*)-**230** and (*R,R,S*)-**230** were obtained in good yields up to 92%. Removal of the sulfinyl chiral template and tosyl protecting group afforded amino ester **232** in moderate yields.



Scheme 61: Application of chiral auxiliaries in the synthesis of 2,3-disubstituted piperidines developed by Mangelinckx et al

One of the most common routes to piperidines is via the reduction of their respective pyridines. This well-established method was expanded to 2,3-disubstituted piperidines by Du *et al.* in 2016.[125,126] While this body of work focuses on 2,5-disubstituted piperidines, they were able to achieve a moderate yield of 44% with a poor 67:33 dr (*cis*:*trans*) for 2,3-disubstituted piperidine **233**. In 2021, Wang *et al*. improved on this methodology, achieving an excellent 95% yield and >20:1 dr during a borane catalysed hydrogenation of pyridines (Scheme 62).

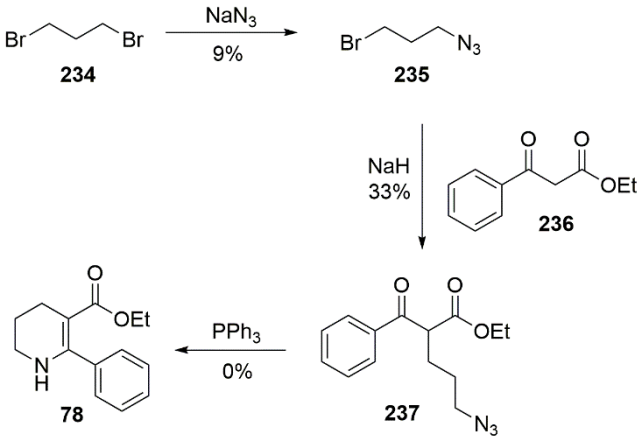


Scheme 62: Synthesis of 2,3-disubstituted piperidines via reduction of pyridines

The aim of this chapter is to develop a novel route to 2,3-disubstituted piperidines via the reduction of endocyclic enamino esters. These esters will be synthesised by alkylation of β-keto esters followed by protecting group deprotection and ring closure. Various reduction methods will be investigated, and the substrate scope of the hydrogenation will be analysed.

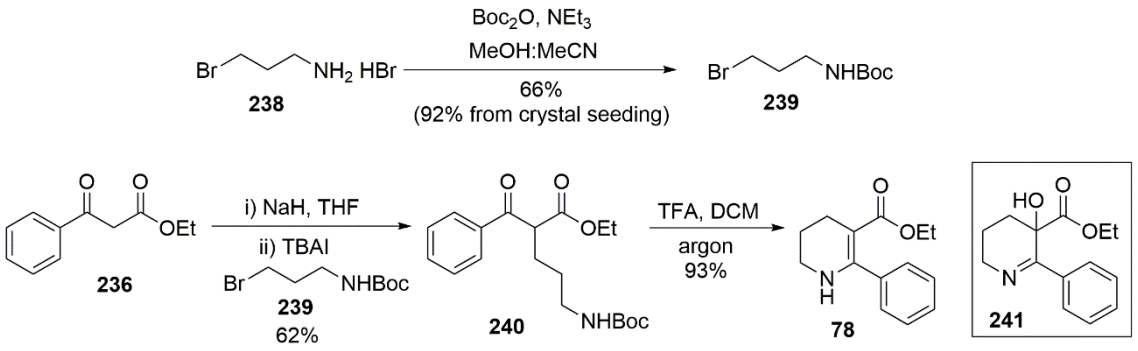
2.3.2 Synthesis and reduction of piperidine based β-enamino esters

Initial work to synthesise β-enamino ester **78** was conducted by master's student Sophie Jedrzejczak.[127] The aim of her project was to form azide **235** from dibromide **234**, perform an alkylation with β-keto ester **236**, and then reduce the azide via a Staudinger reduction to furnish β-enamino ester **78** (Scheme 63). Unfortunately, low yields were obtained for both the azide **235** and alkylation product **237** and the final step in this route failed to provide any of the desired product **78**. Following on from her work, a different route was investigated.



*Scheme 63: Initial route to β-enamino ester **78** developed by S.Jedrzejczak*

The alternative method was to Boc protect 3-bromopropylamine forming bromide **239**, perform an alkylation between bromide **239** and β-ketoester **236**, and finally do a Boc deprotection in a similar fashion to the pyrrolidines synthesised in the previous chapter (Scheme 64). The Boc protection step worked well, obtaining a good 66% yield.[128] After obtaining the first batch of this compound, the purification was made simpler by crystal seeding using previous batches, greatly improving the yield to 92%.



*Scheme 64: Boc protecting group method to synthesise β-enamino ester **78***

Alkylation of β-ketoester **236** with bromide **239** required significant optimisation due to the intrinsic problems with having an acidic proton on the Boc protected amine and needing to prevent dialkylation of the β-ketoester (Table 14). Initial attempts using sodium ethoxide (NaOEt) as the base afforded an 18% yield of the desired alkylated product **240** (Table 14, entry 1). When decreasing the equivalents of bromide **239** and increasing the equivalents of the base, to allow for complete deprotonation of both bromide **239** and β-keto ester **236**, no product was obtained (Table 14, entries 2 and 3). Switching the base to sodium hydride initially showed no improvement when used on its own (Table 14, entry 4). Fortunately, the addition of 1 equivalent of tetrabutylammonium iodide (TBAI) greatly improved the yield of the desired alkylated product **240** up to 62% when 1.5 equivalents of NaH were used (Table 14, entry 6). In typical alkylation reactions, TBAI would be used catalytically. Lowering the equivalents of TBAI to a catalytic amount (0.1 eq.) while increasing the base (2 eq.) and slightly increasing bromide **239** (0.7 eq.) greatly decreased the yield to 14% (Table 14, entry 7). From the results obtained so far, it can be seen that TBAI was only truly effective when used in excess with

respect to bromide **239** suggesting that even with formation of a more reactive species, the alkyl iodide, this reaction is still very slow. Use of TBAI with sodium ethoxide afforded no product (Table 14, entry 8). Formation of the more reactive iodide from bromide **239** improved this reaction but only when NaH was used as a base. The addition rate of bromide **239** was probed by adding a bromide **239**/THF solution dropwise over 5 h via syringe pump (Table 14, entry 9). Unfortunately, this led to none of the desired product being obtained indicating the rate at which bromide **239** was added was an important factor in the reaction.

*Table 14: Optimisation of alkylation of β-ketoester **236** by bromide **239**[a]*

Entry	Base	Eq. Base	Eq. bromide **239**	Yield/%
1[b]	NaOEt	1.8	1.2	18
2[b]	NaOEt	2.3	0.6	0
3[b]	NaOEt	2.8	0.9	0
4[c]	NaH	1	0.6	0
5[c,d]	NaH	1.2	0.6	58
6[c,d]	NaH	1.5	0.6	62
7[c,e]	NaH	2.0	0.7	14
8[b,d]	NaOEt	1.8	1.2	0
9[c,d,f]	NaH	1.5	0.6	0
10[c,d,g]	NaH	1.5	0.9	61
11[c,d,g]	NaH	1.5	1.0	53

[a]Reactions conducted on 2.60 mmol scale, β-ketoester **236** stirred with based for 30 min before addition of bromide **239**, 20 h, 55 °C. Isolated yield of **240**. [b]NaOEt 21% wt in EtOH, [c]NaH 60% wt dispersion in mineral oil, in dry THF. [d]tetrabutylammonium iodide (TBAI) additive, 1 eq. [e]TBAI additive, 0.1 eq. [f] Slow addition of bromide **239** in THF via syringe pump over 5 h. [g]5.20 mmol scale.

A scale-up of the alkylation reaction was performed whilst continuing to test the effect of changing the number of equivalents of bromide **239** (Table 14, entries 10 and 11). The yield of the desired alkylation product **240** was the same when 0.9 equivalents were used when compared to using 0.6 equivalents on a smaller scale, 61% compared to 62%, respectively. When switching to 1.0 equivalent of bromide **239**, the yield decreased slightly to 53%. As the

equivalences of NaH were not increased in this case, the enolate was likely to have deprotonated the amine **239** and without enough base to reform the enolate, no further alkylation could occur. In no cases was the dialkylated product observed or isolated.

The Boc deprotection of alkylation product **240** worked well with enamine **78** being produced relatively cleanly directly out of the reaction. During recrystallisation attempts, imino alcohol **241** was obtained rather than the desired enamino ester **78** in a 37% yield. This product was confirmed by single crystal X-ray crystallography (Figure 30). It was postulated that enamino ester **78** was oxidizing on exposure to air and so any attempts at purification while exposing the sample to air increased the amount of imino alcohol **241** present. The heat used during recrystallisation accelerated this process and preferentially encouraged crystallisation of the imino alcohol. Fortunately, the enamino ester was formed relatively cleanly during the Boc deprotection and its purity was improved by performing the reaction under argon. After this result, the enamine was used directly in the next step without further purification.

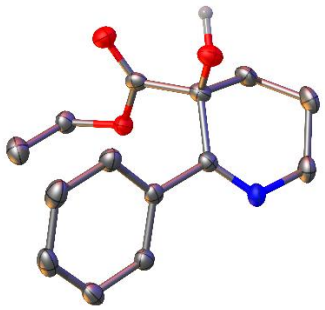
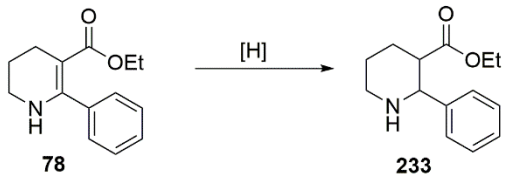


*Figure 30: Single crystal X-ray structure of imino alcohol **241***

The enamino ester **78** was used directly in various reductions (Scheme 65, Table 15). When sodium borohydride was employed, the reaction occurred very sluggishly, obtaining a 22% yield and recovering mainly starting material after 22 h (Table 15, entry 1). Common reducing agents for β-enamino esters, lithium borohydride and sodium triacetoxyborohydride (STAB), failed to produce any of the desired product, only recovering the starting material (Table 15, entry 2 and 3).



*Scheme 65: Reduction of enamino ester **78***

*Table 15: Optimisation of the reduction of enamino ester **78**[a]*

Entry	time / (hrs)	reagent [H]	Yield / (%)[d]	dr[e]
1	22	$NaBH_4$ (1 eq)	22	94:6
2	22	$LiBH_4$ (1 eq)	NR	-
3	24	STAB (1 eq)	NR	-
4[b]	10	$HSiCl_3$ (4 eq), DMF (0.5 eq), $PhCO_2H$ (0.1 eq)	NR	-
5	22	$HSiCl_3$ (4 eq), DMF (0.5 eq), $PhCO_2H$ (0.1 eq)	NR	-
6	48	Mg turnings (4 eq), MeOH	NR	-
7	24	Hantzsch ester **139** (1.1 eq), phenylphosphinic acid	NR	-
8	22	H_2, 10% wt Pd/C	53	60:40
9[c]	-	H_2, 5% wt Pd/C CatCart®	89	96:4

[a]Enamino ester **78** (0.5 mmol), 25 °C, [b]0 °C, [c]ThalesNano H-cube reaction®, **78** (0.25 mmol), 30 bar, 35 °C, 1 mL/min flow rate, reaction mixture cycles through three times, [d]Isolated yield of **233** [e]Determined by ^{1}H NMR spectroscopy

The cyclic β-enamino ester **78** was significantly less reactive towards reductions than the linear β-enamino esters reduced previously by the group.[77] In those cases, the reaction with 4 equivalents of trichlorosilane, an acid additive (benzoic acid, 0.1 eq.), and 20 mol% of the imidazole based organocatalyst (*S*)-**49** fully reduced linear β-enamino esters in 10 h. Under similar conditions, with the catalyst being changed to DMF in an achiral variant of the reaction, the reduction of cyclic β-enamino ester **78** was unsuccessful with only starting material being

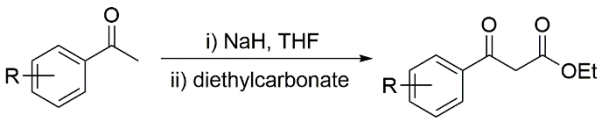
recovered (Table 15, entries 4 and 5). Even when increasing the temperature to rt and lengthening the reaction time to 22 h, none of the desired product was observed.

Attempts with other common reducing agents, magnesium or Hantzsch ester **139**, also afforded no desired product. Finally, using a hydrogen balloon with a 10% wt Pd/C catalyst afforded the desired product in a moderate 53% yield with a poor 60:40 dr of *cis:trans* diastereoisomers. Switching to use the safer H-cube flow reactor and increasing the temperature and pressure to 35 °C and 30 bar respectively afforded the product in a good 89% yield and excellent 96:4 dr. The *cis*-isomer was confirmed to be the major diastereoisomer by comparison to the literature values and further confirmed by X-ray crystallography (see pg 88 and 89).[125]

Unfortunately, due to employing a catalyst cartridge (CatCart®) for the hydrogenation using the H-cube, there was no options for conducting this reduction enantioselectivity. The potential for a chiral CatCart was investigated but none were commercially available and would have to be specially requested knowing exactly what ligand would work.

2.3.3 Substrate Scope

Having now explored the initial synthetic route to the parent 2,3-disubstituted piperidine **23**, it was now necessary to expand the substrate scope. First, a series of β-keto esters were synthesised via a Claisen condensation reaction (Scheme 66, Table 16). The yields were variable, ranging from a poor yield of 16% for *ortho*-bromo substituted phenyl β-keto ester **253**, to a good 75% yield for thiophene β-keto ester **254**.



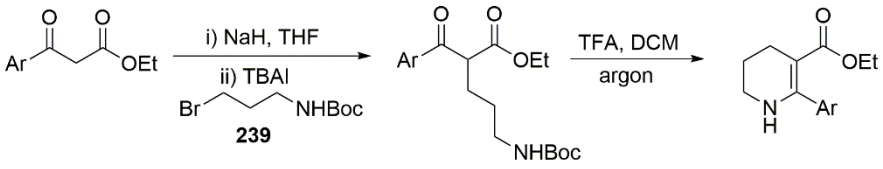
Scheme 66: Claisen condensation of various acetophenones

Table 16: Claisen condensation products[a]

Entry	R group	Compound number	Yield/%
1	*p*-Me	**242**	58
2	*p*-OMe	**243**	68
3	*p*-Ph	**244**	66
4	*p*-Br	**245**	43
5	*p*-Cl	**246**	60
6	*p*-F	**247**	63
7	*p*-CF_3	**248**	66
8	*m*-OMe	**249**	24
9	*m*-Br	**250**	62
10	*m*-F	**251**	67
11	*o*-OMe	**252**	68
12	*o*-Br	**253**	16
13	Thiothen-2-yl	**254**	75

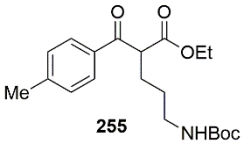
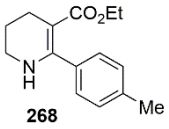
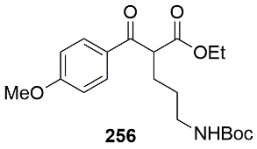
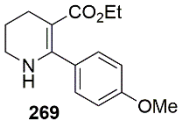
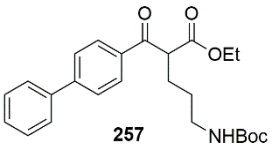
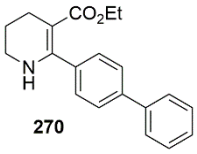
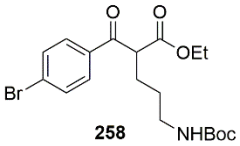
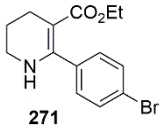
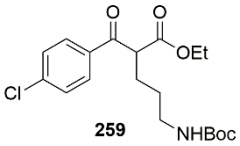
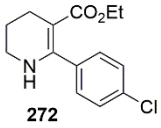
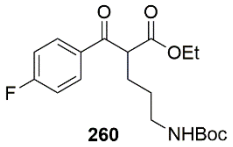
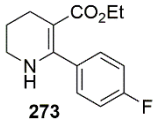
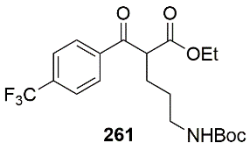
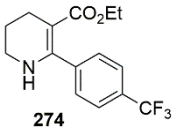
[a]All reactions were conducted on 10 mmol scale, 1 eq of acetophenone, 1.5 eq. of NaH (60% dispersion in mineral oil), 2 eq. of diethyl carbonate, THF (12 mL), reflux until the reaction was complete as indicated by TLC. Isolated yields of products.

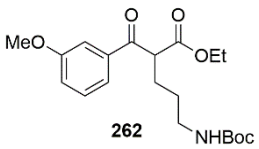
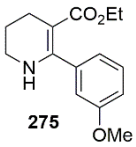
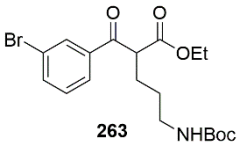
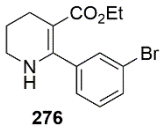
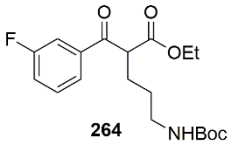
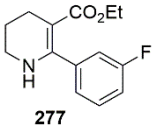
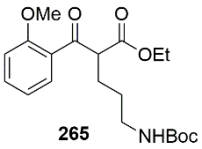
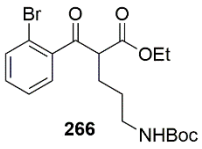
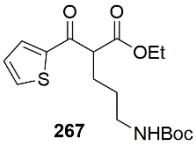
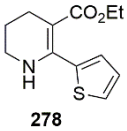
With β-keto esters in hand, the alkylation with bromide **239** was conducted (Scheme 67, Table 17). Moderate to good yields of up to 72% were obtained for *para*-substituted examples **255** to **261** (Table 17, entries 1-7) with lower yields of up to 51% being obtained for *meta*-substituted examples **262** to **264** (Table 17, entries 8-10). Unfortunately, the alkylation of *ortho*-substituted examples **265** and **266** (Table 17, entries 11 and 12) failed to produce any of the desired product, giving a complex mixture of unknown products. *ortho*-Substitution potentially created steric hinderance, partially blocking the approach of bromide **239** towards the enolate, preventing the desired alkylation and resulting in none of the desired product being obtained. Finally, alkylation of the thiophene β-keto ester **269** occurred in a good yield of 87% (Table 17, entry 13).



Scheme 67: Alkylation and Boc deprotection steps to syntheses cyclic enamines

Table 17: Alkylated and enamine products

Entry	Alkylated product[a]	Yield/%	Enamine product[c]	Yield/%
1	 **255**	52	 **268**	69[d]
2	 **256**	72	 **269**	83
3[b]	 **257**	27	 **270**	63
4	 **258**	41	 **271**	91
5	 **259**	32	 **272**	71
6	 **260**	36	 **273**	86
7	 **261**	23	 **274**	83

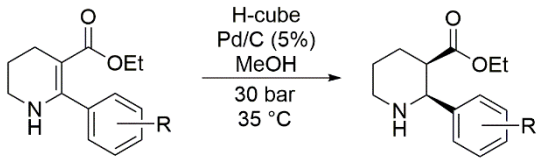
8	 **262**	51	 **275**	80[d]
9	 **263**	22	 **276**	86
10	 **264**	19	 **277**	88
11	 **265**	No prod.	N.A	-
12	 **266**	No prod.	N.A	-
13	 **267**	87	 **278**	65[d]

[a]Reaction conducted on a 2 mmol scale, 1 eq. of β-keto ester, 1 eq. of bromide **239**, 1.5 eq. of NaH (60% dispersion in mineral oil), 1 eq TBAI, THF (6 mL), 55 °C, overnight. Isolated yields. [b]Conducted on 1 mmol scale. [c]1 eq. of alkylation product, 10 eq. of TFA. [d]Significant amounts of imino alcohol present.

The TFA mediated deprotection of the amine occurred in good yields of 68-91% and provided products clean enough to be used directly in the next step without further purification. This lessened the risk of oxidation of the enamine to the imino alcohol provided that the hydrogenation was performed in less than an hour after isolation of the enamine. Keeping the enamines under an inert atmosphere was vital to the success of a number of these substrates. *meta*-Methoxy substituted enamine **275** and thiophene enamine **278** oxidised to their respected imino-alcohols significantly faster than observed with other substrates. A mixture of compounds was observed by ^{1}H and ^{13}C NMR spectroscopy, with key signals in the ^{13}C NMR spectrum at around 94.0 ppm for the *C*=C enamine and 164.0 ppm for the *C*=N imine. Both

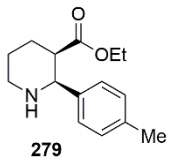
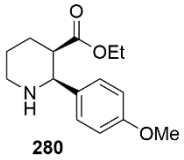
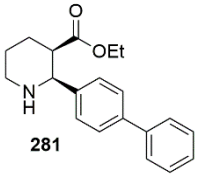
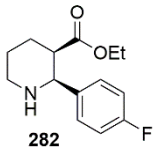
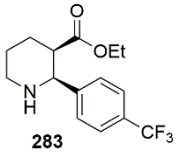
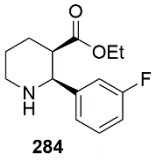
these key signals were observed in the ^{13}C NMR spectrum (15 min collection) less than an hour after isolation of *m*-methoxy enamine **275** and thiophene enamine **278**. In contrast, for the *p*-methoxy enamine **269** only the enamine signal was observed in the ^{13}C NMR spectrum (1.5 h collection) despite this spectrum being recorded hours after isolation of the product.

The substrate scope for the hydrogenation was tested under the optimised conditions used previously for the phenyl enamine **233** (Scheme 68, Table 18). *para*-Substituted examples **279** to **283** were obtained in good to excellent yields between 76% to 95% in excellent diastereoselectivities up to >99:1 dr (Table 18, entries 1-5). Electron donating and electron withdrawing groups were well tolerated. Even the bulky bi-phenyl substrate **281** achieved a good 76% yield with an excellent diastereoselectivity of 96:4 dr. *meta*-Fluoro substituted piperidine **284** was obtained in an excellent 95% yield with a similarly excellent diastereoselectivity of >99:1 dr. Unfortunately, *p*-methyl piperidine **279** showed evidence of the reduced imino alcohol in the ^{1}H NMR spectrum, attributing to about 5% of the sample. The piperidine and the piperdin-3-ol were found to be inseparable. The oxidation of the enamine to the imino alcohol before the hydrogenation, although slow for this substrate, still occurred. After this result, samples were prepared in argon purged vials and dissolved in anhydrous, degassed methanol. With these improvements, for all further *para*- examples and *m*-fluoro substrate **284**, none of the reduced imino alcohol was observed in the ^{1}H NMR spectrum.



Scheme 68:Substrate scope of the hydrogenation of piperidine based enamino esters

Table 18: Results from the hydrogenation of enamino esters[a]

Entry	Product	Yield/%	dr
1	 **279**	95	>99:1
2	 **280**	77	98:2
3	 **281**	76	96:4
4	 **282**	91	>99:1
5	 **283**	92	>99:1
6	 **284**	95	>99:1

[a]All reactions conducted on 0.25 mmol scale, 5% wt Pd/C CatCart®, 0.05 M solutions in MeOH cycled through Thalesnano H-Cube flow reaction three times, 1.0 mL/min flow rate. All samples of enamine stored under argon until use. Isolated yields of the piperidine products.

The most extreme case of the oxidation of the enamine to the imino alcohol before hydrogenation, as previously stated, was that of the *m*-methoxy enamine **275**. This led to an inseparable mixture of piperidine **285** and piperidin-3-ol **286** after hydrogenation (Figure 31). On a positive note, both of these compounds were obtained in excellent diastereoselectivities of >99:1 dr. The relative stereochemistry of piperindin-3-ol **286** was not determined as it could not be separated from piperidine **285**.

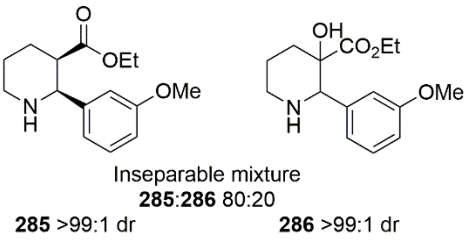
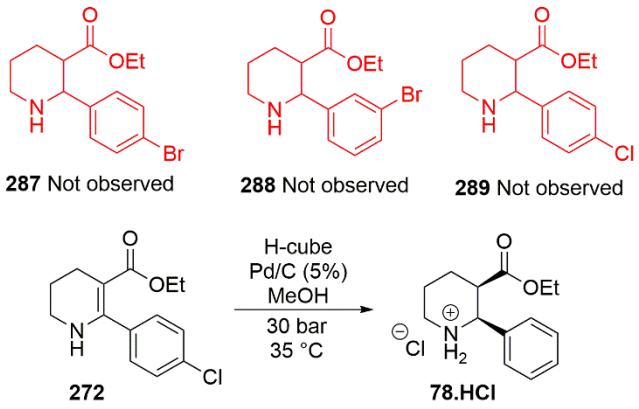


*Figure 31: Product mixture from the hydrogenation of enamino ester **275***

Attempts to hydrogenate halogen containing enamines *p*-bromide **271**, *m*-bromide **276**, and *p*-chloride **272** led to dehalogenation of the compounds as well as reduction of the enamine (Scheme 69). This was confirmed by attaining a single crystal X-ray structure of the product from the hydrogenation of *p*-chloride enamine **272** (Figure 32). The product was identified as the hydrochloride salt of piperidine **78**. From this, it can be assumed that the products from the hydrogenation of bromide enamines **271** and **276** are the hydrobromide salt of piperidine **78**. The relative stereochemistry of the piperidine **78**.HCl was confirmed to be the *cis*-isomer from the X-ray structure.



Scheme 69: Dehydrogenation of bromo- and chloro-substituted β-enamino esters

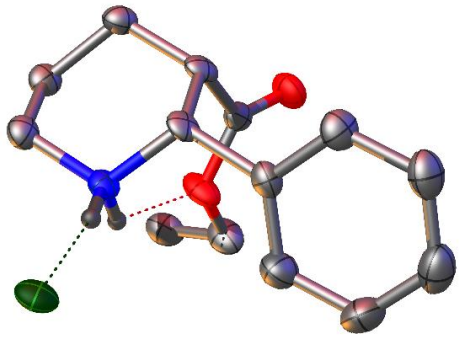


*Figure 32: Single crystal X-ray structure of **78**.HCl*

Confirmation of the *cis*-isomer assignment to all other piperidines was corroborated by comparison of the ^{1}H NMR spectral data (Figure 33, Table 19). Firstly, in the literature the proton α to the nitrogen (labelled H^{A}) in piperidine **78** is reported as a multiplet at 3.23-3.39 ppm for the *cis*-isomer and as a multiplet at 3.13-3.23 ppm for the *trans*-isomer.[125] The proton β to the nitrogen (labelled H^{B}) is reported as a multiplet at 2.56-3.04 ppm where the peaks overlap for both isomers (the integral of this multiplet was equal to 3H and so was made up of H^{B} and two other protons on the piperidine ring). No peak was observed at 3.13-3.23 ppm for piperidine **78** synthesised via this hydrogenation. Instead, the key peaks were cleanly observed at 3.36 ppm as a ddt for proton H^{A} and at 2.82 ppm as a ddd for proton H^{B}. Comparing the peak shift, coupling, and coupling constants, very little variation was observed in the data indicating that the *cis*-isomer predominates during this reaction.

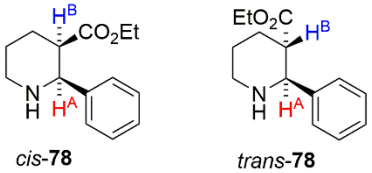


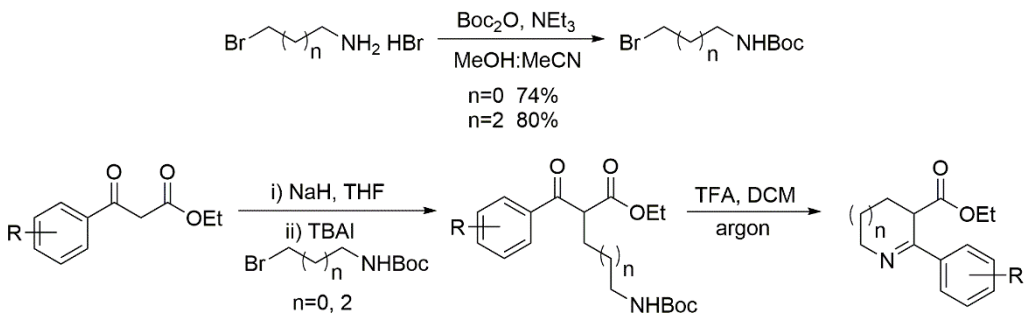
*Figure 33: Proton numbering for piperidine **78***

*Table 19: Comparison of cis-**78** isomer ^{1}H NMR data with alternative substrates*

Isomer	H^A/ppm (*J*/Hz)	H^B/ppm (*J*/Hz)
cis-**78**	ddt, 3.36 (13.2, 4.3, 2.1)	ddd, 2.82 (13.2, 12.1, 3.1)

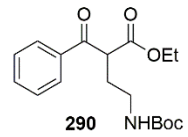
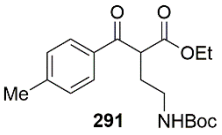
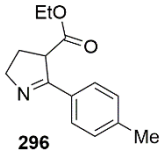
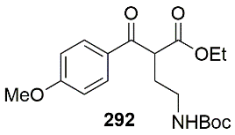
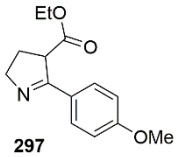
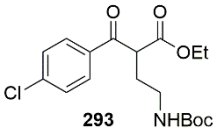
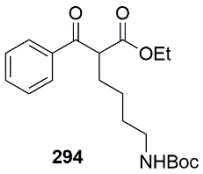
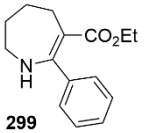
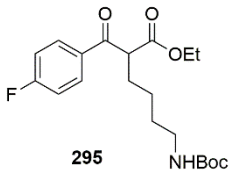
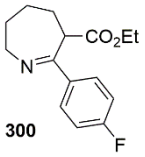
Entry	R group	Δδ (**X**-3.36)	Δ*J* (**X**-**XX**)	Δδ (**X**-2.82)	Δ*J* (**X**-**XX**)
1	4-Me	0.00	-0.1, 0.0, 0.0	-0.01	-0.1, 0.0, 0.0
2	4-OMe	-0.01	0.0, -0.1, 0.0	-0.01	0.0, 0.0, -0.1
3	4-Ph	0.03	-0.1, 0.0, 0.0	0.03	-0.1, 0.3, -0.1
4	4-F	0.00	0.0, 0.1, 0.0	0.00	0.0, 0.3, 0.0
5	4-CF_3	0.01	0.0, 0.1, 0.0	0.01	0.0, 0.4, 0.1
6	3-F	0.00	0.0, 0.1, 0.0	0.00	0.0, 0.3, 0.0
7	3-OMe	-0.01	-0.1, 0.0, 0.0	-0.01	-0.1, 0.0, -0.1

Beyond just piperidines, there was the potential for different heterocycles to be accessed via this method. Pyrrolidines and azepines could be prepared using different bromides (Scheme 70). *N*-Boc-2-Bromo-ethylamine and *N*-Boc-4-bromo-butylamine were synthesised from their respective hydrobromide salts in good yields of 74% and 80%, respectively.



Scheme 70: Synthesis of imino esters based on pyrrolidines and azepines

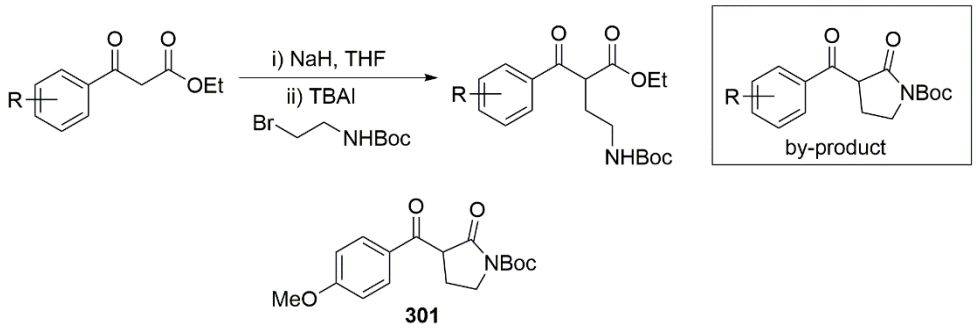
Table 20: Further alkylation and imino ester products based on pyrrolidines and azepines

Entry	Alkylated product[a]	Yield/%	Imino ester[b]	Yield/%
1	 **290**	Not isolated	NA	
2	 **291**	29	 **296**	75
3	 **292**	20	 **297**	93
4	 **293**	Not isolated	 **298**	-
5	 **294**	22	 **299**	73
6	 **295**	29	 **300**	73

[a]Reaction conducted on a 2 mmol scale, 1.0 eq. of β-keto ester, 1.0 eq. of bromide, 1.5 eq. of NaH (60% dispersion in mineral oil), THF (6 mL), 55 °C, overnight. Isolated yields of alkylated products. [b]Reactions conducted using 1 eq. of alkylated product, 10 eq. of TFA

Alkylation of various β-keto esters with these bromides was attempted (Table 20). When employing the ethyl bromide, a lactam by-product was observed, often in up to a 1:1 ratio with the desired product (Scheme 71). Lactam by-product **301** from the alkylation of *p*-methoxy β-keto ester **243** was isolated and confirmed to be the product by ^{1}H NMR, ^{13}C NMR and mass spectroscopy. It likely forms when the amine is deprotonated after alkylation allowing for intramolecular amide formation. These lactams frequently had either the same R_F or very

similar R_F to the desired products making purification difficult for this set of compounds. Fortunately, the *p*-methoxy alkylation product **292** and the *p*-methyl alkylation product **291** could be separated, however, the yields were low, providing 29% and 20% yields respectively. Isolation of phenyl alkylation product **290** and *p*-chloro alkylation product **293** was not achieved.



Scheme 71: By-product formation during the alkylation of β-keto esters with N-Boc-2-bromoethylamine

When employing the butyl bromide, the yields for the alkylation were similarly low. Phenyl alkylation product **294** and *p*-fluoro alkylation product **295** were obtained in a low 22% and 29% yields, respectively. No by-products were observed in this reaction and a significant amount of starting material was isolated after the reaction. This would suggest that the reaction with the butyl bromide progresses slower than with the ethyl or propyl bromides.

Interestingly, the products after the Boc deprotection employing TFA were identified as the imine tautomer rather than the enamine tautomer that was obtained from the six membered analogues. This was confirmed by ^{13}C NMR spectroscopy with the loss of the key enamine C=C peak around 95 ppm, gaining the key imine peak at around 170 ppm. Looking at these molecules, there was nothing obvious that would be causing this difference. Both the imine and enamine have a double bond in the ring adding strain to the ring. On first principles, the enamine is the thermodynamically more stable tautomer and so would be assumed to be favoured, which is only true for the six-membered ring. Molecular modelling of the tautomers of all three ring sizes was conducted using Avogadro (MMFF94) aiming to find the energies of

each compound (Figure 34). The energies for the enamines were lower than that of the imines in every case with the largest difference in energy being observed for the 6-membered ring. With the five-membered ring, the energy difference was very small <1.5 kJ/mol.

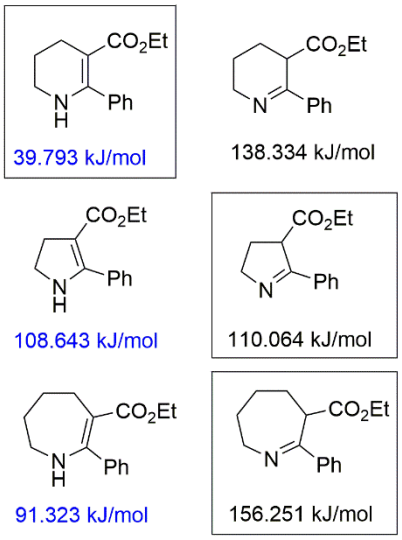
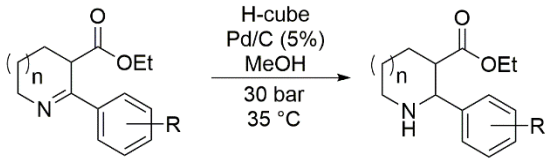


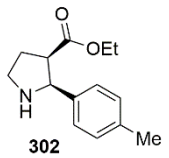
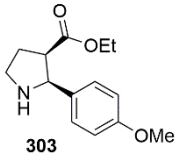
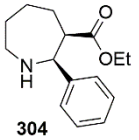
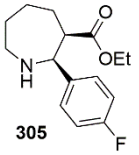
Figure 34: Molecular modelling of enamines and imines

The hydrogenation was conducted using the optimised conditions used for the primary piperidine substrate **78** (Scheme 72, Table 21). Unfortunately, the pyrrolidine imines, 4-methyl **296** and 4-methoxy **297**, failed to fully reduce despite being cycled through the machine three times affording a 22:78 ratio and 17:83 ratio of starting imine to amine, respectively. The pyrrolidines were obtained in good diastereoselectivities and were confirmed to be the *cis*-isomer by comparison to literature values of similar compounds (see pages 93/94). Azepine amines **304** and **305** were obtained in good yields of 69% and 70%, respectively in excellent diastereoselectivities. These were assumed to be the *cis*-isomer by analogy to the previous piperidine and pyrrolidine substrates synthesised.



Scheme 72: Hydrogenation of imino esters based on pyrrolidines and azepines

Table 21: Results of the hydrogenation of imino esters based on pyrrolidines and azepines[a]

Entry	Product	Yield/%	dr
1	 **302**	79[b]	>99:1
2	 **303**	76[c]	>99:1
3	 **304**	69	>99:1
4	 **305**	70	>99:1

[a]All reactions conducted on 0.125 mmol scale, 5% wt Pd/C CatCart®, 0.05 M solutions in MeOH cycled through Thalesnano H-Cube flow reaction three times, 1.0 mL/min flow rate. All samples of enamine stored under argon until use. Isolated yields of products. [b]Mixture of starting material and product (22:78), [c]Mixture of starting material and product (17:83).

Comparison of the literature chemical shifts and coupling constants for a similar pyrrolidine (methyl ester **306**) was conducted (Figure 306, Table 22).[129] The peaks for the *cis*- and *trans*-isomers were very close together so nothing could be determined from this information, however, the coupling constants were significantly closer to that of the *cis*-isomer. This was the case for both pyrrolidines and so the major diastereoisomer was assumed to be the *cis*-isomer.

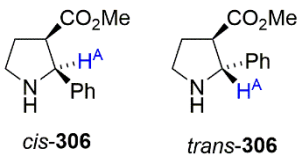
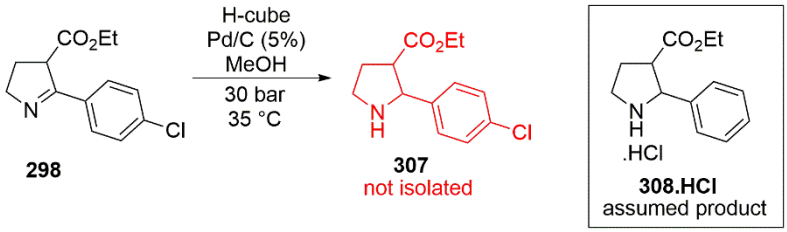


*Figure 35: proton numbering for pyrrolidine **306***

Table 22: Comparison of literature chemical shifts and coupling constants to synthesised pyrrolidines

	Isomer	*cis*-**306** H^A/ppm (*J*/Hz)		*trans*-**306** H^A/ppm (*J*/Hz)	
		d 4.34 (7.6)		d 4.37 (7.1)	
Entry	R group	Δδ (**X**-4.34)	Δ*J* (**X**-7.6)	Δδ (**X**-4.37)	Δ*J* (**X**-7.1)
1	4-Me	0.01	0.3	-0.02	0.8
2	4-OMe	0.02	0.0	-0.01	0.5

Despite being unable to separate the lactam by-product from *p*-chloro alkylated product **293**, the Boc deprotection was conducted and the mixture of products was taken on to the hydrogenation (Scheme 73). A complex mixture of products was obtained after the hydrogenation. None of the desired *p*-chloro pyrrolidine **307** was observed, with dehalogenation confirmed by mass spectroscopy. As with the piperidines, the major product was assumed to be the hydrochloride salt of piperidine **308**.HCl. This confirms that the dehalogenation process will occur with any of the ring sizes, not just the six-membered heterocycles.



*Scheme 73: Hydrogenation of chloro-substituted imine **298***

2.3.4 Conclusion and future work

Enamine **78** and its analogues were easily synthesised from β-keto esters via an alkylation reaction with bromide **239** and a Boc deprotection. Clean enamine was obtained from the deprotection reaction when the reaction is conducted under argon to prevent oxidisation of the enamine to an imino alcohol. Enamine **78** was found to be significantly less reactive than its

acyclic enamino ester counterparts and so harsher reduction conditions were employed. The hydrogenation employing the H-cube flow reactor with 5% wt Pd/C CatCart® afforded good to excellent yields of the *cis*-diastereoisomer exclusively for a small series of piperidines. Moving on from this work, there is potential for enantioselective variants of this hydrogenation if a suitable catalyst system for the H-cube can be devised.

Oxidation of the enamine to the imino alcohol was found to occur readily with the *meta*-methoxy piperidine **275** resulting in an inseparable mixture of piperidine **285** and piperidin-3-ol **286** being obtained. Hydrogenation of bromide and chloride substituted enamines resulted in dehalogenation of the compound as well as reduction of the enamine. The resulting products were found to be the hydrobromide or hydrochloride salts and this was supported by single crystal X-ray crystallography.

Expansion of the substrate scope to pyrrolidines and azepines was also achieved. Alkylation towards the pyrrolidines unfortunately provided a lactam by-product which in many cases was inseparable from the desired product. Further optimization to potentially prevent formation of the lactam would make this a more viable route towards 2,3-disubstituted pyrrolidines. During the synthesis of the pyrrolidines and azepines, the cyclised imine was formed rather than the enamine after the Boc deprotection. In addition, it was found that the hydrogenation of the pyrrolidine imines performed at a slower rate when compared to the piperidine enamines, failing to go to full conversion after the reaction mixture was cycled through the H-cube reactor three times. However, the azepines were obtained in good yields and excellent diastereoselectivities.

From the diverse structures generated, method holds significant potential for future work. With larger groups such as the biphenyl piperidine **281** achieving a good yield and excellent diastereoselectivity further functionalisation of the aryl group is an option. The use of arylbromide containing alkylation addition products could allow for further derivatisation, such as via palladium cross-coupling reactions, which would be an easy way to increase the substrate scope of the reaction while avoiding the dehalogenation problems.

2.4 β-Aminophosphonic acids

2.4.1 Background

Aminophosphonic acids are structural analogues of amino acids, where the carboxylic acid group of the amino acid is replaced by a phosphonic acid group within the molecule.[130] Ciliatine was the first naturally identified aminophosphonic acid, discovered originally in the membranes of cells from sheep, and later identified in a wide variety of plants and insects (Figure 36).[131] It is the structural analogue of β-alanine. Interestingly, only β- and γ-aminophosphonic acids have been found to exist within living organisms with α-aminophosphonic acids only being available synthetically.[132]

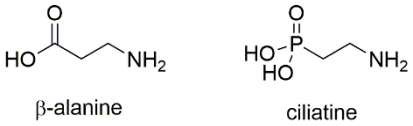


Figure 36: β-Alanine and the aminophosphonic acid analogue ciliatine

The existence of aminophosphonic acids within living systems has been known for some time, however, their roles and activities are poorly understood. In some instances, they have been known to replace amino acids within peptide chains. This ability to act as competitive inhibitors has led to interest in their use in pharmaceuticals and agriculture (Figure 37).[133–135] The tetrahedral geometry of the phosphonic acid group lends itself to inhibit enzyme catalysed processes by mimicking unstable tetrahedral intermediates.[135] Due to the specificity of enzymes, enantioenrichment of these species at the α- or β-carbon within the molecule is likely to increase their activity, however, all examples shown are racemic with the exception of human renin inhibitor **309**.

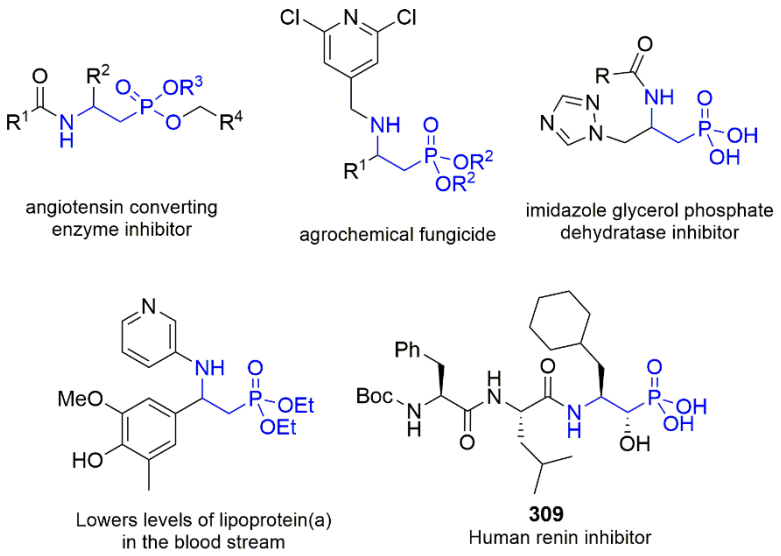
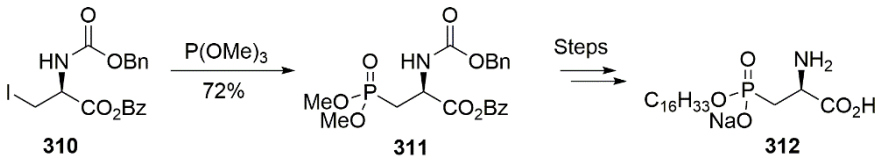


Figure 37: Pharmaceuticals and agrochemicals containing β-aminophosphonates and β-aminophosphonic acids

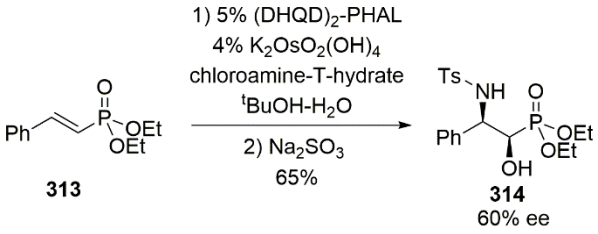
With a wide variety of applications and a very limited number of naturally available β-aminophosphonic acids, synthetic routes to these species are vital. There are a number of routes available, however very few are selective.[134] The Michaelis-Arbuzov reaction is a well-known reaction for the formation of C-P bonds. Brachwitz *et al*. employed this as the key step in the synthesis of alkylphospho-L-serine analogues as a new class of antineoplastic agents (Scheme 74).[136] They reported a good yield of 72% for phosphonate **311** from iodo-serine analogue **310**, synthesised from L-serine. The stereogenic centre from L-serine should not be compromised throughout the synthesis, however, no optical rotations or enantioselectivities were reported after any of the steps in the synthesis of aminophosphonate **312**.



Scheme 74: Michaelis-Arbuzov reaction employed in the synthesis of alkylphospho-L-serine analogues

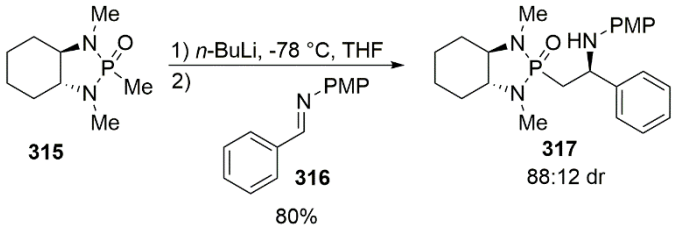
Sharpless asymmetric aminohydroxylation is one route to aminophosphonic acids of a similar structure to that of the human renin inhibitor **309**. In 1998, Sisti *et al*. synthesised a series of

β-amino-α-hydroxyphosphonates using this method in good yields of up to 75% with good enantioselectivities of up to 92% ee for the *syn*-diastereoisomer (Scheme 75).[137] The enantioselectivity could be improved via recrystallisation. In the case of β-amino-α-hydroxyphosphonate **314**, the selectivity increased from 60% ee to 92% ee. There was no evidence of the α-amino-β-hydroxy regioisomer or the *anti*-diastereoisomer.



Scheme 75: Sharpless asymmetric aminohydroxylation of α,β-unsaturated phosphonates

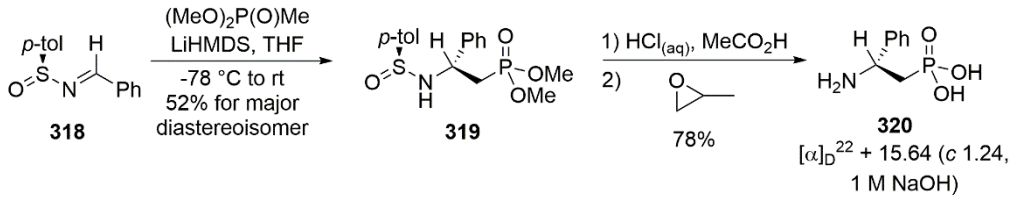
Asymmetric routes to α-nonfunctionalized aminophosphonic acids are rare, with one of the more popular methods involving chiral auxiliaries. In 1993, Hanessian *et al*. reported one of the first asymmetric syntheses of β-aminophosphonic acids via the addition of aryl imines to methyl bicyclic phosphonamides (Scheme 76).[138] They obtained good yields of up to 80% with good diastereoselectivities (up to 88:12 dr). Acid hydrolysis of the phosphonamide product **317** and subsequent esterification with methanol gave the phosphonate derivative in a quantitative yield.



Scheme 76: Addition of aryl imines to methyl bicyclic phosphonamide

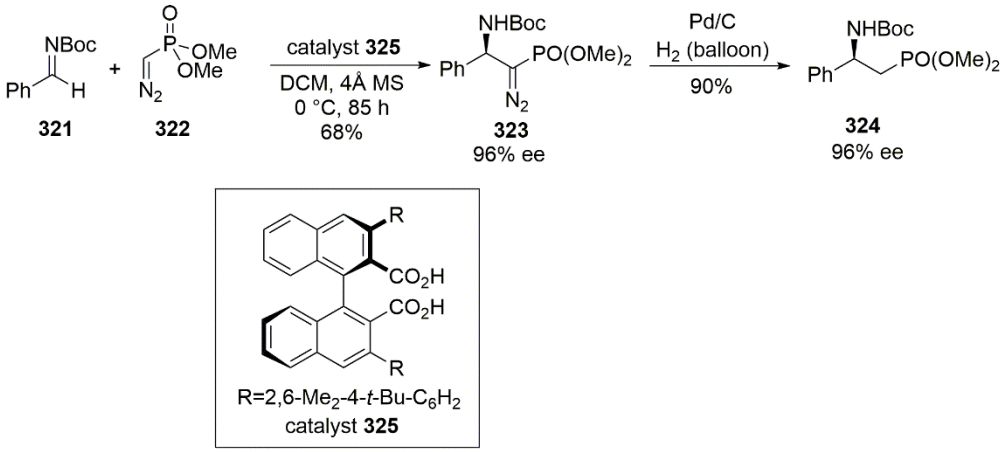
In 1996, Mikolajczyk *et al*. reported the addition of α-phosphonate carbanions to enantiopure sulfinimines (Scheme 77).[139] Phosphonate **319** was produced as a mixture of diastereoisomers (10.3:1 dr) which were isolated by flash chromatography with the major diastereoisomer being obtained in a moderate 52% yield. β-Aminophosphonic acid **320** was

obtained in a good yield after refluxing the diester **319** in acid followed by a workup involving the addition of methyloxirane.



Scheme 77: Addition of α-phosphonate carbanions to sulfinimines

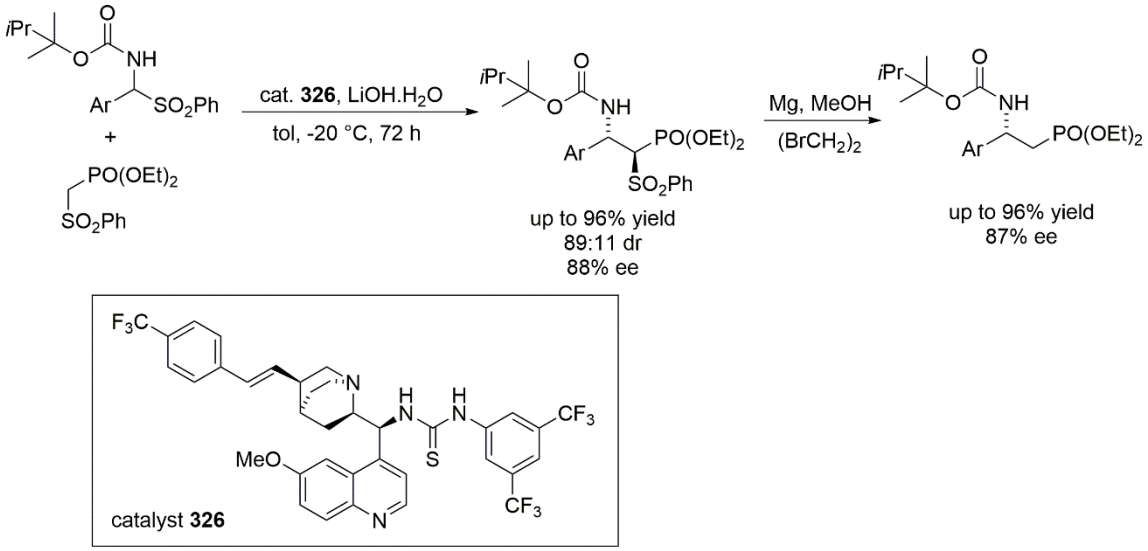
Mannich reactions are another popular route to chiral aminophosphonates. In 2007, Maruoka *et al.* developed an asymmetric Mannich between *N*-Boc-imines and azo phosphonates employing axially chiral organocatalyst **325** (Scheme 78).[140] They obtained moderate to good yields of 40-89% and good to excellent enantioselectivities of 92-96% ee across 6 examples for the Mannich adducts. Azo compound **323** was exposed to hydrogenation conditions affording aminophosphonate **324** in a good 90% yield with no loss of enantioselectivity.



Scheme 78: Asymmetric Mannich reaction of N-Boc imines and azo compounds

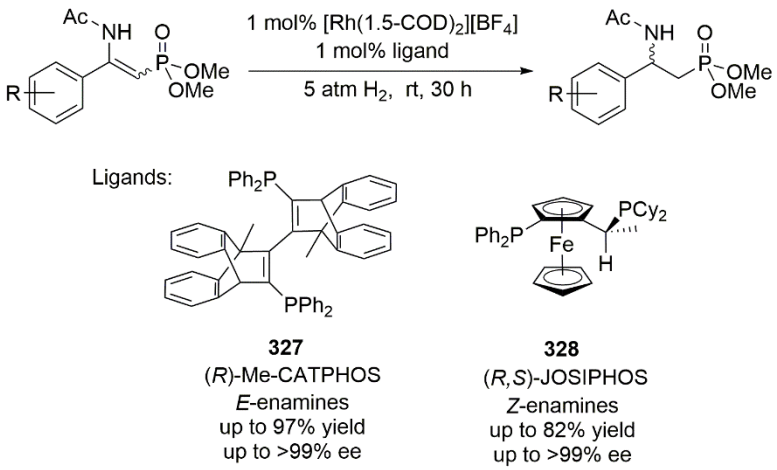
More recently, Peng *et al*. developed a similar method reacting *N*-protected α-sulfones with β-benzene sulfonyl phosphonates employing chiral cinchona catalyst **326** (Scheme 79).[141] During the key asymmetric Mannich reaction step, they obtained excellent yields of up to 96% with good diastereoselectivities up to 89:11 dr and good enantioselectivities up to 88% ee.

Removal of the sulfone using magnesium/MeOH occurred in equally excellent yields of up to 96% with very little change in enantioselectivity.



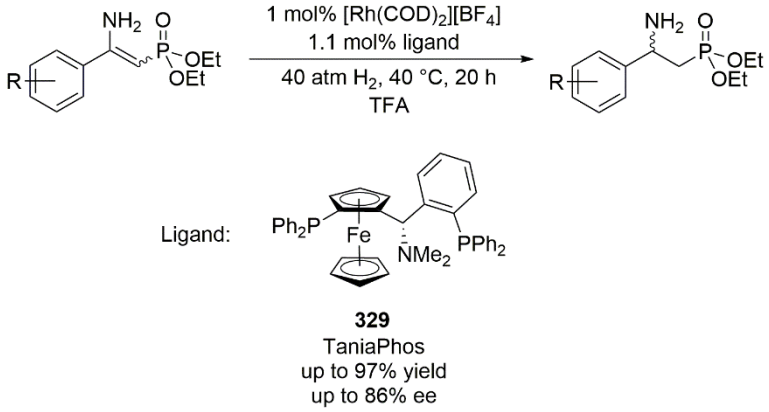
Scheme 79: Asymmetric Mannich reaction with N-protected sulfones and sulfonyl phosphonates

The main issue with these methods is the additional steps required to remove chiral auxiliaries or unwanted functional groups after the key asymmetric step. Similar to β-amino acids, reduction of the β-enamino phosphonate counterparts with the use of metal catalysis is a popular route to avoid this. In 2009, Doherty *et al*. employed rhodium catalysts in the enantioselective hydrogenation of a series of (*E*)- and (*Z*)-enamino phosphonates (Scheme 80).[142] Different ligands were required depending on the *E*/*Z* isomer to obtain selectivity, an observation reported the previous year by Börner *et al*. on a significantly smaller number of substrates.[143] (*R*)-Me-CATPHOS **327** was used to reduce *E*-enamino phosphonates and obtained excellent yields of up to 97% with excellent enantioselectivities of >99% ee. (*R,S*)-JOSIPHOS **328** was employed in the *Z*-enamino phosphonate reductions, obtaining slightly lower yields of up to 82% but retaining excellent enantioselectivities of >99% ee.



Scheme 80: Hydrogenation of β-enamino phosphonates

More recently, Zhang *et al*. reported the asymmetric hydrogenation of a series of unprotected β-enamino phosphonates with a rhodium catalyst and the chiral ligand TaniaPhos **329** (Scheme 81).[144] Excellent yields of up to 97% with good enantioselectivities of up to 86% ee were obtained. Unlike previous reports, the *E/Z* isomer ratios were not mentioned, therefore it was unknown which isomer or ratio of isomers were being reduced.

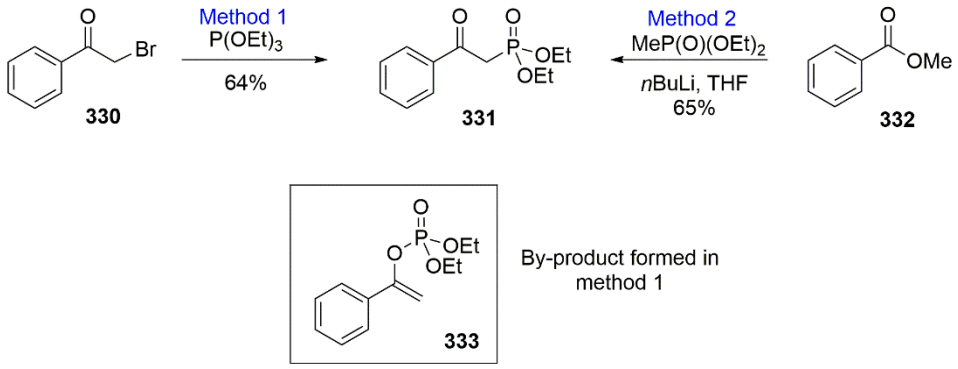


Scheme 81: Hydrogenation of unprotected β-enamino phosphonates

To date, no transfer hydrogenations or non-metal catalysed asymmetric reductions of β-enamino phosphonates have been reported. Herein lies the attempts at the asymmetric trichlorosilane mediated reduction of β-enamino phosphonates.

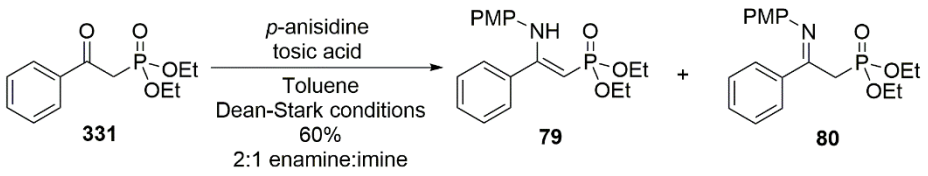
2.4.2 Trichlorosilane reduction of β-enamino phosphonates

β-Ketophosphonate **331** was synthesised via two routes (Scheme 82). The Michaelis-Arbuzov reaction was employed in method 1, reacting triethylphosphite with 2-bromoacetophenone affording β-ketophosphonate **331** in a moderate yield of 64%. During this method, phosphoenol **333** was obtained as a major by-product as a result of the Perkow reaction. In method 2, lithiated diethyl methyl phosphonate was reacted with methyl benzoate affording β-ketophosphonate **331** in a similar yield of 65%. Going forward, method 1 was employed due to the similar yields obtained from the two methods. Method 1 also utilised cheap starting materials and was synthetically easier to carry out.



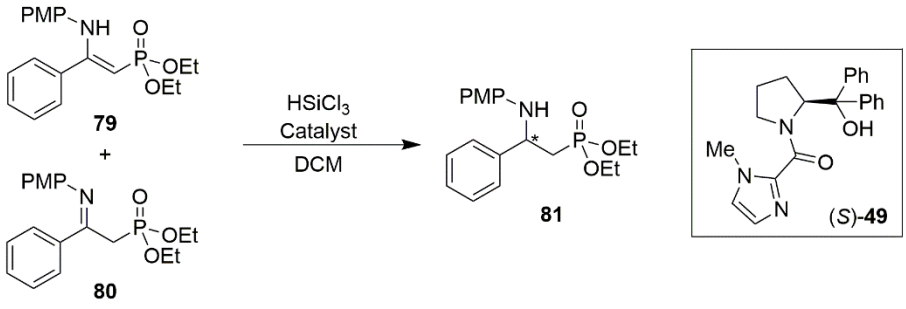
*Scheme 82: Synthesis of β-ketophosphonate **331***

Initial attempts at synthesising β-enamino phosphonate **79** via the same route employed previously in the Jones group in the synthesis of β-enamino esters, using tosic acid as a catalyst, in ethanol, and heating at reflux overnight, failed to form the desired product, returning only starting materials.[77] Following a procedure conducted by Deb *et al*., performing the reaction with azeotropic removal of water via Dean-Stark apparatus, an enamine/imine mixture (**79**:**80**) was obtained in a 2:1 ratio with a moderate yield of 60% (Scheme 83).[145] Obtaining a mixture was unusual in comparison to the carbon analogues (enamino esters) where only the enamine is obtained.



*Scheme 83: Synthesis of enamine/imine mixture of phosphonates **79**:**80***

Initially, the standard conditions for the trichlorosilane mediated reduction of the carbon analogues with imidazole-based catalyst (*S*)-**49** were employed (Scheme 84).[77] Unlike the previous work, no acid additives such as benzoic acid, were used at this stage. After 18 h, the reaction was found to have gone to complete conversion both with and without the use of catalyst (*S*)-**49** (Table 23, entries 1 and 3). The reduction occurring without the use of a designated catalyst, such as (*S*)-**49** will be referred to as the background reaction. In order for this to be a viable method, and to have this reaction occur enantioselectively, the background reaction needed to be minimal compared to the catalysed variant of the reduction. The Lewis basic phosphonate moiety within the molecule can potentially coordinate to and activate the trichlorosilane, catalysing the reduction resulting in a significant background reaction. After observing that the reaction was complete after only 30 minutes with fewer equivalents of trichlorosilane, both with and without catalyst, (Table 23, entries 4 and 5), the concentration of the reaction was decreased 10-fold, however, the conversion for the background reaction was still high at 76% (Table 23, entry 6).



*Scheme 84: Trichlorosilane mediated reduction of β-enamino phosphonate **79***

*Table 23: Reaction conditions for the trichlorosilane mediated reduction of β-enamino phosphonate **79**[a]*

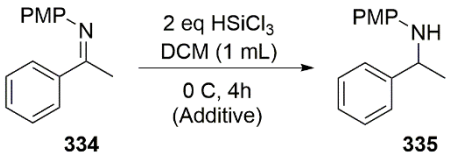
Entry	Catalyst	Solvent volume/mL	Temperature/°C	Time/h	Conversion/%[d]
1[b]	Y	0.2	0	18	100
2[b]	Y (DMF)	0.2	0	3	100
3[b]	N	0.2	0	18	100
4	Y	0.2	0	0.5	100
5	N	0.2	0	0.5	100
6	N	2.0	0	4	76
7	N	2.0	-78	4	37
8	N	2.0	-78	4	52
9	Y	2.0	-78	4	43
10[c]	N	2.0	-78	4	30
11[c]	N	2.0	-78	4	37
12[c]	Y	2.0	-78	4	30
13[c]	Y	2.0	-78	4	28
14[c]	Y	2.0	0	1	30
15[c]	N	2.0	0	1	44
16[c]	Y	2.0	0	4	46
17[c]	N	2.0	0	4	62
18[c]	Y	4.0	0	1	9
19[c]	N	4.0	0	1	6

[a]All reactions performed using 0.1 mmol of β-enamino phosphonate **79** in dry DCM. [b]4 eq. of $HSiCl_3$. [c]0.5 M solution of $HSiCl_3$ in dry DCM used. [d]As determined by ^1H NMR spectroscopy.

While conducting the reactions at -78 °C, it was observed that the reproducibility of the reaction was poor (Table 23, entries 7 and 8). Due to the small quantities of trichlorosilane being employed, practical errors in the amount added to the reaction via syringe were high. As a result, a 0.5 M trichlorosilane stock solution was employed to decrease the impact of this error.

This improved the reproducibility of the reaction, however, the conversion for both the catalysed and background reactions remained similar (Table 23, entries 10 to 19).

After many attempts at optimization of this reaction, sufficient difference between the catalysed and background reactions was not obtained. Due to the Lewis basic nature of the phosphonate moiety, investigations into autocatalysis were conducted. Ketimine **334** was subjected to standard trichlorosilane reduction conditions reported previously in the Jones group with and without phosphonate additives (Scheme 85).[62] The additives were used at 10 mol% to determine catalytic activity. The imine/enamine phosphonate **79**/**80** mixture exhibited a moderate increase in conversion by comparison to the background reaction, from 18% to 33% (Table 24, entries 1 and 2). The increase is relatively small which suggests that, although the imine/enamine phosphonate is catalysing the reaction, the effect is very small. A similar conversion was observed upon the addition of the amino phosphonate **81** to the reduction of ketimine **334** indicating that the Lewis basicity of the phosphonate, and its ability to catalyse the reaction, is not affected by the neighbouring nitrogen moiety. Therefore, the autocatalysis is not accelerated during the reduction of the imino/enamino phosphonate to the aminophosphonate by the increasing conversion to the aminophosphonate.



*Scheme 85: Trichlorosilane mediated reduction of imine **334** investigating autocatalysis*

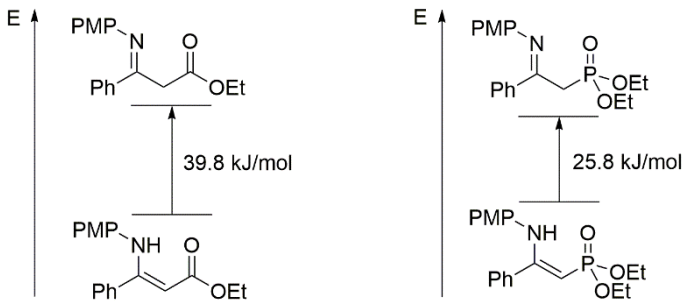
*Table 24: Additives tested for the catalysis of the trichlorosilane mediated reduction of imine **334**[a]*

Entry	Additive	Conversion/%[b]
1	No additive	18
2	**79**/**80**	33
3	**81**	31

[a]All reactions performed using 1 mmol of imine **334** with 10 mol% of additive in dry DCM (1 mL) at 0 °C for 4 h. [b]As determined by ^{1}H NMR spectroscopy.

As previously mentioned, the phosphonate existing as an enamine/imine mixture is unusual in comparison to the carbon analogues. Previous work on the carbon analogues proposed that the imine form is reduced.[77] However, as the enamine form was the more stable tautomer, additives, such as acetic acid, were used to encourage formation of the imine.[74] With the phosphonate already partially existing in the imine form, the requirement for additives to encourage tautomerisation before reduction is no longer essential to the reaction. To attempt to find out why the enamine/imine phosphonate mixture forms rather than just the enamine, molecular modelling was conducted.

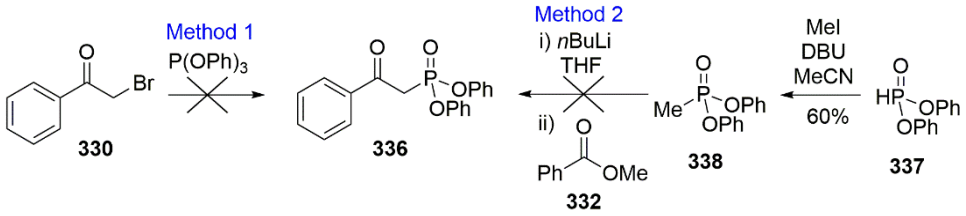
Simple DFT calculations were performed to obtain the relative energy difference between the imine and enamine tautomers for both the phosphonates and the carbon analogues (Scheme 86). A moderately smaller energy difference was observed for the phosphonates, 25.8 kJ/mol compared to 39.8 kJ/mol for their carbon analogues. From this data, it can be postulated that the smaller energy difference results in more of the imine being present in the reduction of the phosphonate, supported by the imine/enamine mixtures that were afforded experimentally. However, without information regarding the equilibrium or transition state energies, how quickly these species interchange is unknown.



Scheme 86: DFT (B3LYP) calculation results for the comparison of enamine and imine energies

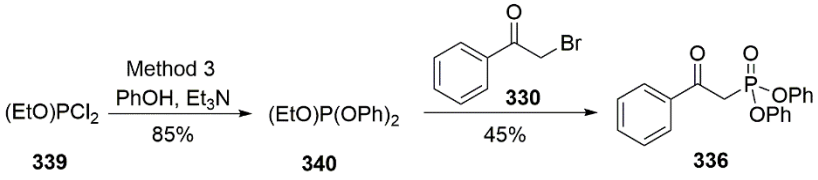
Alternative phosphonates with reduced Lewis basicity of the phosphonate moiety were investigated next. The aim of this was to slow down the autocatalysis and potentially afford different ratios of the enamine to the imine. Initially, the previous methods used to make β-ketophosphonate **331** were applied towards the synthesis of the new β-ketophosphonate **336**,

based on the Ando Wittig reagent (Scheme 87). The first method attempted was method 1 via the Michaelis-Arbuzov reaction, however, this was unsuccessful, generating none of the desired product. This was most likely due to the reaction requiring an S_NAr reaction to remove one of the phenyl groups on triphenyl phosphite which was highly unlikely to occur. Switching to an alternative method, method 2, diphenyl methyl phosphonate **338** was synthesised from diphenylphosphite in a moderate yield of 60%. However, the reaction of lithiated phosphonate **338** with methyl benzoate afforded none of the desired product.



*Scheme 87: Failed syntheses of β-ketophosphonate **336***

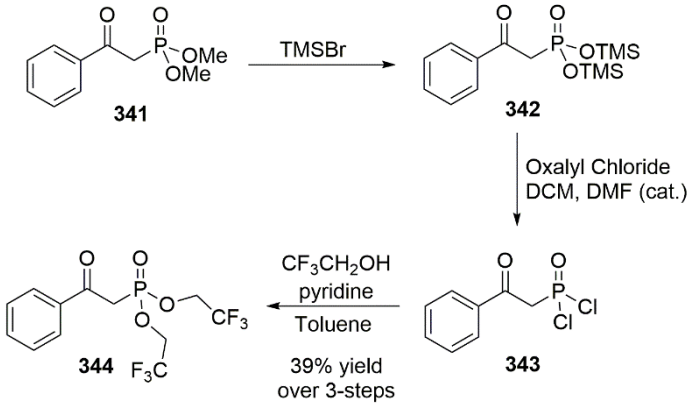
Adapting the Michaelis-Arbuzov reaction was initially attempted, a mixed phosphite **340** was synthesised from ethyl dichlorophosphite in a good yield of 85% (Scheme 88). Due to product instability, ethyl diphenylphosphite **340** was then reacted directly with 2-bromoacetophenone affording β-ketophosphonate **336** in a moderate yield of 45%.



*Scheme 88: Synthesis of β-ketophosphonate **336***

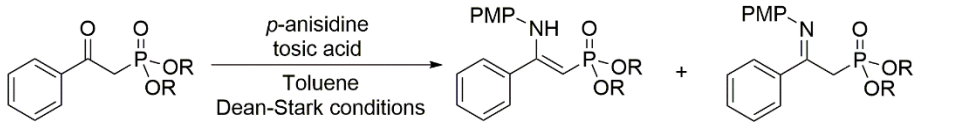
Another reagent synthesised was trifluoroethyl β-ketophosphonate **344**, which was based on the Still-Gennari Wittig reagents, and was synthesised via an adapted procedure reported by Molnár *et al*. (Scheme 89).[146] β-Ketophosphonate **341** was synthesised via the Michaelis-Arbuzov reaction using trimethylphosphite in a moderate 50% yield. Silylation of **341** with bromotrimethylsilane afforded **342** in a good 86% yield which was used directly in a chlorination reaction with oxalyl chloride, affording dichloride **343** in a quantitative yield which

was used without further purification. Formation of the final phosphonate **344** was achieved in a moderate 45% yield after reacting the dichloride **343** with trifluoroethanol in pyridine. Overall, the *bis*-trifluoroethyl phosphonate **344** was obtained in a moderate 39% yield over the three steps.



*Scheme 89: Synthesis of β-ketophosphonate **344***

Following the previous procedure, β-enamino/imino phosphonate **345**/**346** was obtained in a moderate yield of 43% with a 7:1 ratio of enamine:imine (Scheme 90). The trifluoroethyl phosphonate **347**/**348** was obtained in a 9:1 ratio of enamine:imine, however, due to difficulties with purification, a pure **347**/**348** mixture was not obtained. This substrate was not used in future reactions due to the impurities. Both substrates had a higher ratio of enamine to imine in comparison to the initial ethyl substrate **79**/**80**.

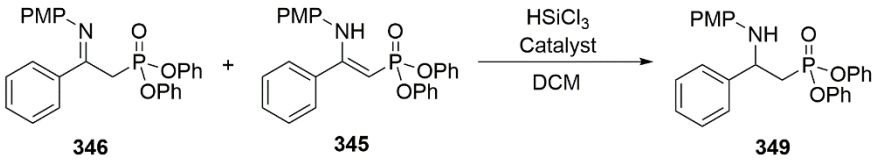


R= Ph, 43% yield, 7:1 ratio of enamine **345**:imine **346**
R= CH_2CF_3, 32% yield (contaminated),
9:1 ratio of enamine **347**:imine **348**

Scheme 90: Synthesis of β-enamino phosphonates

Subjecting phenyl phosphonate mixture **345**/**346** to the previously optimised conditions for the ethyl phosphonate **79**/**80** afforded none of the desired aminophosphophonate **349** (Scheme 91, Table 25, entries 1 and 2). This supports the hypothesis that the more imine that is present,

the faster the reaction will occur as the ethyl substrate **79**/**80** was afforded in a 46% and 62% conversion with and without catalyst (*S*)-**49**, respectively, under the same conditions. The reaction conditions used for the carbon analogues were also tested, including the use of benzoic acid as an additive, which led to 100% conversion after 10 h (Table 25, entry 3).



*Scheme 91: Trichlorosilane mediated reduction of β-enamine phosphonate **345***

*Table 25: Reaction conditions for the trichlorosilane mediated reduction of β-enamino phosphonate **345**[a]*

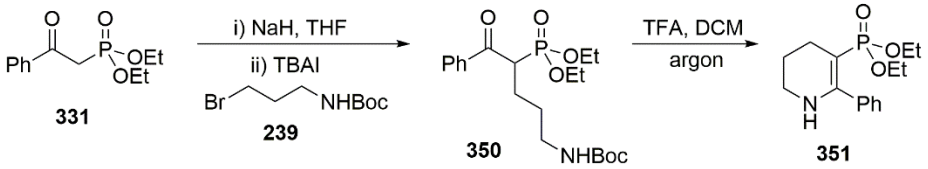
Entry	$HSiCl_3$ eq.	Catalyst	Solvent volume/mL	Time/h	Conversion/%[c]
1	2	Y	2.0	4	0
2	2	N	2.0	4	0
3[b]	4	Y	0.2	10	100
4[b]	4	Y	0.4	4	<5
5[b]	4	N	0.4	4	25
6	4	Y	0.2	4	100
7	4	N	0.2	4	55
8	2	Y	0.2	4	29
9	2	N	0.2	4	71

[a]0.1 mmol of β-enamino phosphonate **345** in dry DCM, 10 mol% of catalyst, 0 °C. 0.5 M solution of $HSiCl_3$ in dry DCM used. [b]$PhCO_2H$ additive used. [c]As determined by ^1H NMR spectroscopy.

Time and concentration were both decreased, and this resulted in the catalysed reaction not proceeding, however, the reaction with no catalyst went to a 25% conversion (Table 25, entries 4 and 5). This result is unexpected as the catalysed reaction should always go to a greater conversion than the uncatalysed due the background reaction operating in both versions. Despite optimization attempts, sufficient difference in the catalysed and background reaction

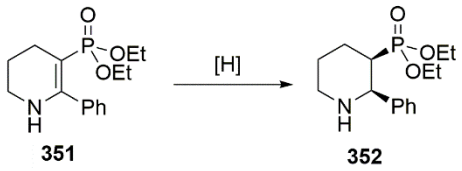
was not obtained. Furthermore, the reproducibility of the reaction was poor, regardless of the use of a trichlorosilane stock solution which improved reproducibility for the previous substrate (Table 25, entries 6-9).

With the poor reproducibility and lack of control of the background reaction, attempts to synthesise simple aminophosphonates such as ethylphosphonate **81** and phenylphosphonate **349** in an enantioselective fashion were halted. Instead, the success of the diastereoselective hydrogenation making 2,3-disubstituted piperidines demonstrated in the previous section was proposed as an approach towards amino phosphonates (Scheme 92). Switching a β-ketoester for β-ketophosphonate **331** in the alkylation reaction with bromide **239** afforded alkylation product **350**. Unfortunately, the alkylation product **350** could not be fully separated from the starting β-ketophosphonate **331** and so some of the starting material was present in the deprotection step. Under the same conditions used previously for the Boc deprotection afforded mostly enamino phosphonate **351** however, the alkylation product failed to fully Boc deprotect under the reaction conditions. None of the imino phosphonate was present in this mixture as indicated by ^{13}C NMR spectroscopy unlike the acyclic variant.



Scheme 92: Synthesis of piperidine based enamino phosphonate

The crude mixture of enamino phosphonate **351** was trialled in two different reductions (Scheme 93). First, hydrogenation using the H-cube flow reactor with 5% wt Pd/C CatCart® obtained the desired amino phosphonate in a good 87% yield as the *cis*-isomer exclusively. This was confirmed by comparison of the ^{1}H NMR peak shift and coupling constants to the piperidines obtained by the same method (Figure 38, Table 26). There was a slight difference in the peak shift of H^{A} however there was very little variation in the coupling constants for either proton.



*Scheme 93: Reduction of piperidine phosphonate **351***

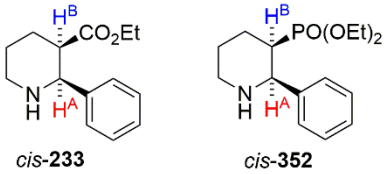


Figure 38: Proton labelling of piperidines for table 26

*Table 26: Comparison of 1H shift and J values for piperidine **233** and phosphonate piperidine **352***

	H^A/ppm (*J*/Hz)		H^B/ppm (*J*/Hz)	
	ddt, 3.36 (13.2, 4.3, 2.1)		ddd, 2.82 (13.2, 12.1, 3.1)	
Entry	Δδ (**X**-3.36)	Δ*J* (**X**-**XX**)	Δδ (**X**-2.82)	Δ*J* (**X**-**XX**)
1	0.08	0.3, -0.1, -0.1	0.02	0.3, 0.0, 0.3

An attempt to reduce enamino phosphonate **351** (0.1 mmol) using trichlorosilane (4 eq.) with imidazole catalyst (*S*)-**49** (20 mol%) was conducted in DCM (0.2 mL). Unfortunately, none of the desired product was obtained, returning only starting material. Under the same conditions, the reductions both the acyclic ethyl phosphonate **79** and phenyl phosphonate **345** went to complete conversion. The lower reactivity of the cyclic phosphonate **351** is in line with the observation made previously for the cyclic ester **78** wherein the cyclic ester was significantly less reactive than its acyclic counterpart. The cyclic enamino phosphonate **351** exists only as the enamine rather than as a mixture of enamine:imine as seen for the acyclic phosphonates, therefore this substrate will require additives to assist in the tautomerization to the imine to

allow for reduction using trichlorosilane. Further work on the viability of the trichlorosilane mediated reduction is required.

2.1.4 Conclusion and future work

Three different β-ketophosphonates were successfully synthesised via different routes in moderate to good yields. These were used to synthesise enamino phosphonates in moderate yields, however, differing mixtures of the enamino:imino phosphonates were obtained depending on the phosphonate moiety. The ethyl and phenyl phosphonates were assessed in a trichlorosilane mediated reduction. Regrettably, a significant difference between the catalysed and background reactions could not be obtained, despite optimization attempts. Although minor autocatalysis was observed, the main problem lied with the enamine/imine phosphonate mixtures, where the imine was being rapidly reduced.

The synthesis of piperidine based phosphonate **352** was successful when the enamine **351** was reduced employing the H-cube flow reactor, affording the desired phosphonate in a good 87% yield as the *cis*-isomer exclusively. Unfortunately, the enamine **351** failed to be reduced using trichlorosilane and the imidazole catalyst (*S*)-**49**. Further work could be done in this area to optimise the alkylation of the β-ketophosphonate **331** and to further investigate the reduction of the enamino phosphonate.

3 Conclusion and future work

Various molecular building blocks based on amino acids, accessed via reduction methods, have been investigated. Simple amines were synthesised from naturally available amino acids, such as glycine and valine, were synthesised, however, several problems were encountered during this substrate class (Figure 39). The major problem was the synthesis of ketimine intermediates that were difficult to purify and when glycine was used, led to unavoidable by-products **98** and **99** being formed. Upon reduction of the crude product mixture, although the desired amine product **104** had formed, it could not be separated from the by-product **98**. Encouragingly, the use of valine prevented formation of the by-products. The trichlorosilane mediated reduction of the valine ketimine afforded the desired product in a good 85:15 dr when using (*S*)-**49** as the catalyst. Unfortunately, a poor yield of 20% for the major (*S*,*S*)-isomer was obtained.

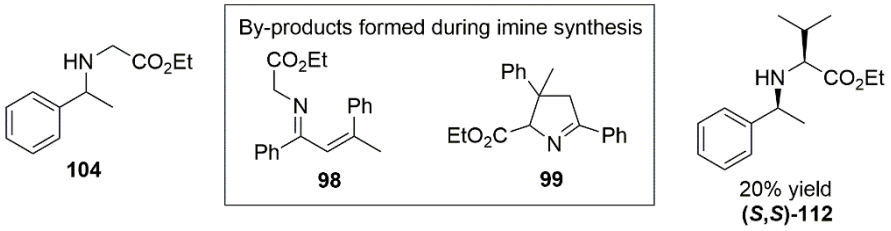
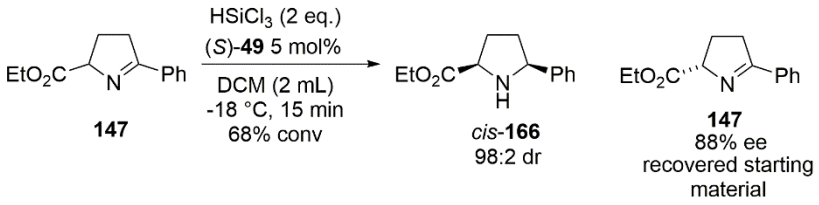


Figure 39: Substrates investigated for the synthesis of α-methyl benzyl substituted amino acids

With many poor results being obtained from this substrate class, and a limited time available in the lab due to COVID-19 safety protocols, this project was side-lined for a focus on substrates delivering results. Further investigations into the interactions between the catalyst and the valine ketimine during the reduction is required. Optimisation and improvement of the overall poor yields is solely needed.

Of the two different routes investigated to synthesise the cyclic imines based on 2,3-disubstituted pyrrolidines, the method from (±)-pyroglutamic acid provided the highest yields of up to 91% for the Boc deprotection step. Reduction of the phenyl imine **147** was conducted with trichlorosilane and the imidazole catalyst (*S*)-**49** and after 15 min at -18 °C, excellent diastereoselectivities of 98:2 dr could be obtained. Difficulties in analysis of the

enantioselectivity ultimately resulted in no results of the enantioselectivity of the product, however, some results obtained for the recovered starting material would suggest that a kinetic resolution would be viable if the analysis of the product could be resolved (Scheme 94). For the substrate scope, changing the method employed during the Grignard addition step from the used of magnesium turnings to Turbo Grignard increased the yields for some substrates and allowed access to *m*-CN Grignard addition product **182**. Unfortunately, with the poor current yields of the trichlorosilane mediated reductions, this route to 5-substituted prolines is not viable.



*Scheme 94: Results suggesting a potential kinetic resolution of cyclic imine **147***

Synthesis of 2,3-disubstituted piperidines via alkylation, Boc deprotection, and hydrogenation using a H-cube® flow reactor obtained good results, achieving excellent diastereoselectivities of up to >99:1 dr for the reduction step across 8 examples (Figure 40). Oxidation of the enamine to the imino alcohol was observed and was particularly prevalent with *meta*-methoxy phenyl **275** resulting in an inseparable mixture of piperidine **285** and piperidinol **286**. Unfortunately, bromo and chloro compounds underwent dehalogenation during the reduction affording piperidine **79** as its hydrobromide and hydrochloride salts, respectively. Pyrrolidines and azepines could also be accessed via this method however, significantly lower yields were obtained for the alkylation steps. Optimization of this step for these heterocyclics is needed for this route to be viable. Use of the H-cube®, while is a safe way to perform hydrogenations, is significantly limited by the scale and which catalysts can be employed. There is the potential for an enantioselective reduction if a catalyst system can be devised.

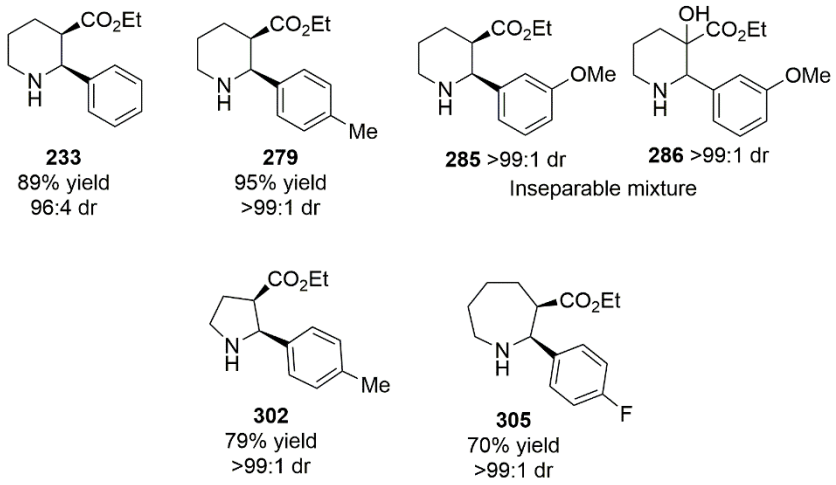


Figure 40: Examples of substrates synthesised using the H-cube flow reactor

Various β-enamino phosphonates were synthesised and reduced using trichlorosilane. Unlike their carbon counterparts, they were found to exist as a mixture of the enamine and imine and rapidly reduced even without the presence of a catalyst. Optimisation of the reaction failed to limit the background reaction and so an enantioselective version of this reaction was unobtainable using this reduction/catalyst system. The variant based of 2,3-disubstituted piperidines failed to be reduced using trichlorosilane under the same conditions as its acyclic counterparts, however, the hydrogenation using the H-cube® flow reactor did obtain the desired product in an excellent diastereoselectivity of >99:1 dr and a good 87% yield. Further work on the piperidine based enamino phosphonates is needed to further develop the method.

4. Experimental

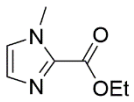
4.1 Experimental details

Unless otherwise stated, all commercial reagents were used as supplied. All non-aqueous reactions were conducted in flame-dried glassware. Anhydrous solvents were obtained from the University of Sheffield Chemistry department Grubbs solvent system. Anhydrous methanol was obtained from Fisher-Scientific and was degassed with argon before use. All reactions requiring heating were performed in a heating mantle unless otherwise stated. Thin layer chromatography was carried out on alumina backed silica TLC plates (VWR chemicals silica gel 60 μm) and visualized using UV light, potassium permanganate, phosphomolybdic acid (PMA), ninhydrin, or 2,4-dinitrophenolhydrazine (2,4-DNP) staining agents. Solid phases used for column chromatography were silica gel (40-63 μm particle size), aluminium oxide (Brockmann grade), or florisil (60-100 mesh) and were supplied by VWR chemicals. Automated column chromatography was performed on a CombiFlash® instrument using RediSep Rf Gold® silica gel disposable flash column cartridges. Hydrogenations performed under pressure were conducted using a ThalesNano® H-cube flow reactor with a 5% wt Pd/C Cat.Cart®.

Melting point determinations were made using a Galenkamp MFB-595 electrothermal melting point apparatus and were recorded uncorrected. Infra-red absorption spectra were recorded as neat liquid compounds as thin films on NaCl plates or using an attenuated total reflectance (ATR) module on a Perkin-Elmer 100 FT-IR instrument. Optical rotation measurements were obtained using a Bellingham and Stanley ADP 220 polarimeter at 20 °C. ^{1}H, ^{13}C, ^{19}F and ^{31}P NMR spectra were recorded at 400, 101, 376 and 162 MHz respectively on a Bruker Avance DPX 400 instrument. ^{1}H NMR assignments given as s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. Coupling constants, *J*, are given in Hz. Chiral high-pressure liquid chromatography was carried out on a Gilson analytical system with UV detection on a Shimadzu SPD-10A detector set at 254 nm unless otherwise stated. High-resolution mass spectrometry (HRMS) spectra were recorded on an Agilent Q-TOF instrument.

4.2 Compound synthesis and characterisation

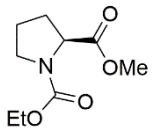
Ethyl-1-methylimidazole-2-carboxylate 89[62]



A solution of 1-methylimidazole (7.9 mL, 100 mmol) and triethylamine (25.0 mL, 180 mmol) in dry acetonitrile (50 mL) was cooled to −30 °C under a nitrogen atmosphere. A solution of ethyl chloroformate (15.3 mL, 160 mmol) in acetonitrile was added dropwise maintaining the temperature below 5 °C. The reaction was slowly warmed to room temperature and stirred overnight. The white precipitate was filtered, and the filtrate was concentrated under reduced pressure. The residue was dissolved in water (200 mL) and extracted using DCM (3 × 90 mL). The combined organic phases were washed using brine (100 mL), dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure affording the crude product as a yellow oil (16.18 g, 100%) which was used directly in the next step without further purification. A small amount was purified via column chromatography (ethyl acetate) affording a pale-yellow solid allowing for characterization; mpt. 40-42 °C (lit.[62] 41-43 °C); ν_{max}/cm^{-1} (thin film) 3406, 3110, 2983, 1710; δ_H (400 MHz, $CDCl_3$) 1.41 (3H, t, *J* 7.1, C*H*$_3$CH$_2$), 4.00 (3H, s, NC*H*$_3$), 4.39 (2H, q, *J* 7.1, C*H*$_2$O), 7.02 (1H, s, ArC*H*), 7.12 (1H, s, ArC*H*).

Data are in accordance with the literature.

(*S*)-*N*-Ethylcarbonylproline methyl ester (*S*)-91[62]



L-Proline (11.5 g, 100 mmol) was dissolved in methanol (200 mL) with potassium carbonate (13.8 g, 100 mmol) and cooled to 0 °C. Ethyl chloroformate (20.9 mL, 220 mmol) was added dropwise after which the mixture was warmed to room temperature and stirred overnight. The

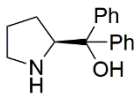
solvent was removed under reduced pressure and the resulting residue was redissolved in water (100 mL). The mixture was extracted using chloroform (3 × 100 mL) and the combined organic phases were washed with brine (100 mL), dried ($MgSO_4$) and filtered. The solvent was removed under reduced pressure affording the desired product as a colourless oil (25.4 g, 100%) which was used directly in the next step without further purification; $[\alpha]_D$ −56.0 (*c* 1.00 in EtOH, lit.[147] −70 *c* 1.00 in EtOH); ν_{max}/cm^{-1} (thin film) 2983, 2883, 1749, 1701; δ_H (400 MHz, $CDCl_3$, 50:50 mixture of rotamers) 1.20 (3H, t, *J* 7.1, C*H*$_3$CH$_2$, rotamer A), 1.27 (3H, t, *J* 7.2, C*H*$_3$CH$_2$, rotamer B), 1.85-2.30 (8H, m, C*H*$_2$), 3.39-3.63 (4H, m, C*H*$_2$N), 3.72 (3H, s, C*H*$_3$O, rotamer A), 3.74 (3H, s, C*H*$_3$O, rotamer B), 4.03-4.23 (4H, m, C*H*$_2$O), 4.30 (1H, dd, *J* 8.6, 3.8, NC*H*, rotamer A), 4.37 (1H, dd, *J* 8.4, 3.4, NC*H*, rotamer B).

Data are in accordance with the literature.

(*R*)-*N*-Ethylcarbonylproline methyl ester (*R*)-**91**[62,147] was synthesised via the same procedure from D-proline (5.76 g, 50 mmol) and used directly in the next step (9.90 g, 98%); $[\alpha]_D$ +65.0 (*c* 1.00 in EtOH, lit.[147] −70.0 for (*S*)-enantiomer, *c* 1.00 in EtOH); ν_{max}/cm^{-1} (thin film) 2983, 2957, 1749, 1703; δ_H (400 MHz, $CDCl_3$, 50:50 mixture of rotamers) 1.21 (3H, t, *J* 7.1, C*H*$_3$CH$_2$O, rotamer A), 1.28 (3H, t, *J* 7.1, C*H*$_3$CH$_2$O, rotamer B), 1.84-2.35 (8H, m, C*H*$_2$), 3.39-3.64 (4H, m, C*H*$_2$N), 3.73 (3H, s, C*H*$_3$O, rotamer A), 3.75 (3H, s, C*H*$_3$O, rotamer B), 4.04-4.24 (4H, m, C*H*$_2$O), 4.31 (1H, dd, *J* 3.6, 8.7, NC*H*, rotamer A), 4.38 (1H, dd, *J* 3.6, 8.7, NC*H*, rotamer B).

Data are in accordance with the literature.

(*S*)-α,α-Diphenylprolinol (*S*)-92[62,148]



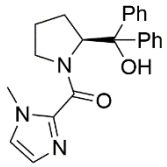
Magnesium turnings (8.60 g, 354 mmol) and iodine (1 crystal) in dry THF (80 mL) were introduced to a flame dried 3-necked round bottom flask under a nitrogen atmosphere. Bromobenzene (18.5 mL, 177 mmol) was dissolved in THF (80 mL) and 8 mL of this solution was added and the reaction was initiated by direct heating. The remainder of the bromobenzene/THF solution was added dropwise maintaining reflux and the reaction was heated at reflux for a further 30 min. After cooling to 0 °C, (*S*)-*N*-ethylcarbonylproline methyl ester (11.88 g, 59 mmol) in THF (20 mL) was added dropwise and the reaction was stirred overnight at room temperature. After cooling to 0 °C, aq. saturated ammonium chloride (30 mL) was added, and the mixture was stirred for 30 min. The white precipitate was filtered off and the filtrate was concentrated under reduced pressure. The residue was redissolved in DCM (300 mL), washed using brine (150 mL), dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was dissolved in methanol (170 mL), KOH (33.10 g, 590 mmol) added, and the reaction was heated at reflux overnight. After cooling to room temperature, the solvent was removed under reduced pressure. The residue was dissolved in water (170 mL) and extracted using DCM (4 × 100 mL). The combined organic phases were washed using brine (150 mL), dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure affording the crude product as a brown oil (11.67 g, 78%), which was used directly in the next step without further purification; $[\alpha]_D$ −37 (*c* 2.00 in MeOH, lit.[148] −59, *c* 2.00 in MeOH); ν_{max}/cm^{-1} (thin film, NaCl plates) 3353, 3059, 3026, 2970, 2872; δ_H (400 MHz, $CDCl_3$) 1.56-1.86 (4H, m, C*H*$_2$), 2.94-3.08 (2H, m, C*H*$_2$N), 4.29 (2H, t, *J* 7.6, NC*H*), 7.12-7.43 (10H, m, ArC*H*).

Data are in accordance with the literature.

(*R*)-α,α-Diphenylprolinol (*R*)-**92**[148] was synthesised via the same procedure from (*R*)-*N*-ethylcarbonylproline methyl ester (9.50 g, 47 mmol) and used directly in the next step (9.52 g, 80%); $[\alpha]_D$ +43 (*c* 2.00 in MeOH, lit.[148] +59, *c* 2.00 in MeOH); ν_{max}/cm^{-1} (thin film, NaCl plates) 3353, 3084, 3058, 3026, 2969, 2871, 1598; δ_H (400 MHz, $CDCl_3$) 1.56-1.80 (4H, m, C*H*$_2$), 2.94-3.08 (2H, m, C*H*$_2$N), 4.29 (1H, t, *J* 7.6, NC*H*), 7.14-7.42 (10H, m, ArC*H*).

Data are in accordance with the literature.

(2*S*)-[2-(Hydroxydiphenylmethyl)pyrrolindine-1-yl](1-methyl-1H-imidazol-2-yl)methanone (*S*)-49[62]



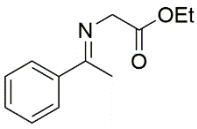
Sodium hydride (60% dispersion in mineral oil, 2.17 g, 54 mmol) was washed using petroleum ether (3 × 10 mL) in a flame dried flask under a N_2 atmosphere before being dissolved in toluene (10 mL). (*S*)-α,α-Diphenylprolinol (6.80 g, 27 mmol) in toluene (20 mL) was added slowly and the mixture was stirred for 30 min. Ethyl-1-methylimindazole-2-carboxylate (5.00 g, 32 mmol) in toluene (5 mL) was then added dropwise and the reaction was stirred at 70 °C for 46 h. After cooling to room temperature, the reaction was quenched using water (30 mL). The mixture was extracted using DCM (4 × 100 mL) and the combined organic phases were washed using brine (100 mL), dried ($MgSO_4$), and filtered. The solvent was removed under reduced pressure affording a thick brown oil which was purified via flash column chromatography on silica gel (70:30, ethyl acetate:petroleum ether). The resulting yellow/orange solid was recrystallized from ethyl acetate affording the pure product as white crystals (0.75 g, 8%); Mpt 148-150 °C (lit.[62], 143-145 °C); $[\alpha]_D$ −135 (*c* 0.6 in $CHCl_3$, lit.,[62] −88 *c* 0.5 in $CHCl_3$); ν_{max}/cm^{-1} (thin film) 3407 (OH), 1613, 1458; δ_H (500 MHz, 101.7 °C, d^6-DMSO), 1.68 – 1.85 (2H, m, C*H*$_2$), 1.94 – 2.00 (1H, m, CH*H*), 2.07 – 2.15 (1H, m, CH*H*), 2.98 (3H, s, NC*H*$_3$), 3.47 – 3.53 (1H, m, NC*H*$_2$), 3.90 – 3.96 (1H, m, NC*H*$_2$), 5.85 (1H, s, NC*H*), 6.17 (1H, bs, O*H*), 6.86 – 6.88 (1H, m, ArC*H*), 6.98 – 7.00 (1H, m, ArC*H*), 7.05 – 7.09 (3H, m, ArC*H*), 7.13 – 7.19 (2H, m, ArC*H*), 7.22 – 7.26 (1H, m, ArC*H*), 7.31 – 7.36 (2H, m, ArC*H*), 7.45 – 7.48 (2H, m, ArC*H*).

Data are in accordance with the literature.

(2*R*)-[2-(Hydroxydiphenylmethyl)pyrrolindine-1-yl](1-methyl-1H-imidazol-2-yl)methanone (*R*)-**49**[62] was obtained via the same procedure as a white solid (0.79 g, 11%); Mpt 140-142 °C; $[\alpha]_D$ +127 (*c* 0.6 in $CHCl_3$, lit.,[62] −88 *c* 0.5 in $CHCl_3$ for other enantiomer); δ_H (500 MHz, 101.7 °C, d^6-DMSO), 1.68 – 1.85 (2H, m, CH_2), 1.94 – 2.00 (1H, m, CH*H*), 2.07 – 2.15 (1H, m, CH*H*), 2.98 (3H, s, NCH_3), 3.47 – 3.53 (1H, m, NCH_2), 3.91 – 3.96 (1H, m, NCH_2), 5.85 (1H, s, NC*H*), 6.17 (1H, bs, O*H*), 6.86 – 6.88 (1H, m, ArC*H*), 6.97 – 6.99 (1H, m, ArC*H*), 7.05 – 7.09 (3H, m, ArC*H*), 7.13 – 7.19 (2H, m, ArC*H*), 7.22 – 7.26 (1H, m, ArC*H*), 7.31 – 7.36 (2H, m, ArC*H*), 7.46 – 7.48 (2H, m, ArC*H*).

Data are in accordance with the literature.

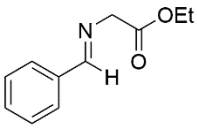
N-(1-Phenylethylidene)-ethyl ester glycine 95



Acetophenone (0.58 mL, 5 mmol) and *p*-toluenesulfonic acid (0.09 g, 0.5 mmol) was dissolved in dry toluene (30 mL) in a 100 mL round bottom flask with Dean-Stark apparatus attached. After stirring for 15 min, glycine ethyl ester hydrochloride (1.40 g, 10 mmol) was added in one portion. The reaction was heated under Dean-Stark conditions. DIPEA (1.74 mL, 2 mmol) was added dropwise via syringe pump (0.87 mL/h). Once addition was complete, the reaction was heated for a further 1.5 h. After cooling to rt., reaction mixture was washed with water (20 mL), dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure affording the crude product as a yellow oil (0.97 g, 95%); δ_H (400 MHz, $CDCl_3$, 1:2 ratio of acetophenone to ketimine) 1.33 (3H, t, *J* 7.1, CH_3), 2.28 (3H, t, *J* 0.9, CH_3), 4.27 (2H, q, *J* 7.1, OCH_2), 4.37 (2H, d, *J* 0.9, NCH_2), 7.35-7.44 (3H, m, ArC*H*), 7.82-7.88 (2H, m, ArC*H*).

Selected data from crude ^{1}H NMR spectrum.

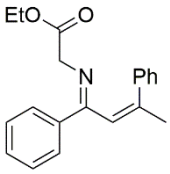
N-(Phenylmethylene)-ethyl ester glycine 97[149]



Benzaldehyde (0.50 mL, 5.0 mmol), potassium carbonate (0.69 g, 5.0 mmol), and anhydrous magnesium sulfate (approx. 0.5 g) were stirred in ethanol (10 mL). Glycine ethyl ester hydrochloride (0.70 g, 5.0 mmol) was added, and the reaction was stirred at rt overnight. The reaction was vacuum filtered, and the solvent removed under reduced pressure affording the product as a pale-yellow oil (0.54 g, 56%) which was used directly in the next step without further purification: δ_H (400 MHz, $CDCl_3$) 1.31 (3H, t, *J* 7.1, C*H*$_3$), 4.25 (2H, q, *J* 7.1, OC*H*$_2$), 4.41 (2H, d, *J* 1.0, NC*H*$_2$), 7.39-7.47 (3H, m, ArC*H*), 7.79 (2H, dd, *J* 7.6, 1.7, ArC*H*), 8.30 (1H, s, C*H*N).

Selected data from crude ^{1}H NMR spectrum. Data are in accordance with the literature.

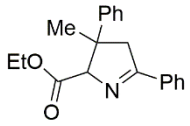
N-(1,3-Diphenyl-2-buten-1-ylidene)-ethyl ester glycine 98



Acetophenone (0.12 mL, 1.0 mmol) and *p*-toluenesulfonic acid (0.02 g, 0.1 mmol) was dissolved in dry toluene (25 mL) in a 50 mL round bottom flask with Dean-Stark apparatus attached. After stirring for 15 min, glycine ethyl ester hydrochloride (0.28 g, 2.0 mmol) was added in one portion. The reaction was heated under Dean-Stark conditions. Diisopropylethyl amine (0.35 mL, 2.0 mmol) was added dropwise via syringe pump (0.17 mL/h). Once addition was complete, the reaction was heated for a further 2 h. After cooling to rt., reaction mixture was washed with water (20 mL), dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure. Purification via flash column chromatography on silica gel (20:80, ethyl

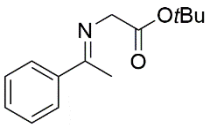
acetate:petroleum ether) afforded the named product as a yellow oil (30 mg, 20%); δ_H (400 MHz, $CDCl_3$) 1.32 (3H, t, *J* 7.1, C*H*$_3$), 1.96 (3H, d, *J* 1.0, C*H*$_3$), 4.26 (2H, q, *J* 7.1, OC*H*$_2$), 4.44 (2H, d, *J* 0.7, NC*H*$_2$), 6.47 (1H, d, *J* 1.0, C=C*H*), 7.35-7.49 (6H, m, ArC*H*), 7.54-7.62 (2H, m, ArC*H*), 7.89-7.97 (2H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 14.3 (*C*H$_3$), 18.1 (*C*H$_3$), 55.2 (*C*H$_2$), 60.9 (O*C*H$_2$), 121.5 (H*C*=C), 125.8 (2 × Ar*C*H), 128.0 (2 × Ar*C*H), 128.3 (Ar*C*H), 128.4 (2 × Ar*C*H), 128.6 (2 × Ar*C*H), 130.5 (Ar*C*H), 138.5 (HC=*C*), 140.8 (Ar*C*), 142.3 (Ar*C*), 169.7 (*C*=N), 170.7 (*C*=O); *m*/*z* (ESI$^+$) 308.2 [100%, (M+H)$^+$].

4-Hydro-3,5-diphenyl-3-methyl-2H-pyrrole-2-carboxylic acid ethyl ester 99



Obtained via the same procedure as *N*-(1,3-diphenyl-2-buten-1-ylidene)-ethyl ester glycine **98**. Purification via flash column chromatography on silica gel (20:80, ethyl acetate:petroleum ether) afforded the named product as a yellow oil (20 mg, 13%); δ_H (400 MHz, $CDCl_3$, 55:45 dr) 0.88 (1.35H, t, *J* 7.1, minor, C*H*$_3$), 1.32 (1.65H, t, *J* 7.1, major, C*H*$_3$), 1.50 (1.65H, s, major, C*H*$_3$), 1.61 (1.35H, s, minor, C*H*$_3$), 3.15 (0.45H, d, *J* 16.3, minor, C*H*H), 3.33 (0.55H, dd, *J* 17.0, 1.7, major, C*H*H), 3.50 (0.55H, dd, *J* 17.0, 1.7, major, C*H*H), 3.66-3.75 (0.45H, m, minor, C*H*H), 3.78-3.88 (0.90H, m, minor, OC*H*$_2$), 4.29 (1.10H, qd, *J* 7.1, 2.9, major, OC*H*$_2$), 5.03 (0.45H, d, *J* 0.9, minor, NC*H*), 5.19 (0.55H, t, *J* 1.7, major, NC*H*), 7.18-7.56 (8H, m, ArC*H*), 7.92-8.04 (2H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 13.7 (*C*H$_3$), 14.4 (*C*H$_3$), 24.5 (*C*H$_3$), 30.5 (*C*H$_3$), 48.1 (*C*H$_2$), 49.5 (*C*), 50.8 (*C*), 52.0 (*C*H$_2$), 60.6 (O*C*H$_2$), 60.9 (O*C*H$_2$), 83.5 (N*C*H), 85.2 (N*C*H), 126.0 (Ar*C*H), 126.4 (Ar*C*H), 126.5 (ArC*H*), 126.6 (Ar*C*H), 128.0 (Ar*C*H), 128.3 (Ar*C*H), 128.5 (Ar*C*H), 128.6 (2 × Ar*C*H), 131.1 (Ar*C*), 131.2 (Ar*C*), 170.4 (*C*=N), 171.1 (*C*=N), 174.5 (*C*=O), 176.7 (*C*=O); *m*/*z* (ESI$^+$) 308.2 [100%, (M+H)$^+$].

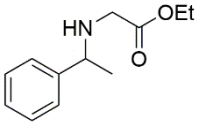
N-(1-Phenylethylidene)-*tert*-butyl ester glycine 103[150]



Acetophenone (0.12 mL, 1.0 mmol) and *p*-toluenesulfonic acid (0.02 g, 0.1 mmol) was dissolved in dry toluene (25 mL) in a 50 mL round bottom flask with Dean-Stark apparatus attached. After stirring for 15 min, glycine *t*-butyl ester hydrochloride (0.50 g, 3.0 mmol) was added in one portion. The reaction was heated under Dean-Stark conditions. Diisopropyl ethyl amine (0.52 mL, 3 mmol) was added dropwise via syringe pump (0.26 mL/h). Once addition was complete, the reaction was heated for a further 1.5 h. After cooling to rt., reaction mixture was washed with water (20 mL), dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure affording the crude product as a yellow oil (0.21 g, 90%); δ_H (400 MHz, $CDCl_3$) 1.52 [9H, s, C(C*H*$_3$)$_3$], 1.96 (3H, s, C*H*$_3$), 4.35 (2H, s, C*H*$_2$), 7.06-7.66 (3H, m, ArC*H*), 7.90-7.96 (2H, m, ArC*H*).

Selected data from crude ^{1}H NMR spectrum. Data are in accordance with the literature.

N-(1-Phenylethyl)-ethyl ester glycine 104[151]

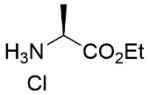


N-(Phenylmethylene)-ethyl ester glycine (0.21 g, 1.0 mmol) and (*S*)-**49** (36 mg, 0.1 mmol) were dissolved in dry DCM (1 mL) under argon and cooled to 0 °C. Trichlorosilane (0.20 mL, 2.0 mmol) was added dropwise. The reaction was stirred at 0 °C for 4 h. Aq. 1 M HCl (1 mL) was added and the mixture was warmed to rt. The mixture was neutralised using aq. 1 M NaOH and the layers were separated. The aqueous layer was extracted using DCM (3 × 10 mL). The combined organic layers were washed using brine (20 mL), dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. Purification via flash column

chromatography on silica gel (20:80 ethyl acetate:petroleum ether) afforded the desired product contaminated with aldol product **98** as a yellow oil (0.04 g, 19%); δ_H (400 MHz, $CDCl_3$) 1.23 (3H, t, *J* 7.2, C*H*$_3$), 1.80 (3H, d, *J* 6.9, C*H*$_3$), 3.60 (1H, q, *J* 6.9, NC*H*), 4.16 (2H, q, *J* 7.2, OC*H*$_2$), 7.19-7.34 (5H, m, ArC*H*).

Selected data from contaminated ^{1}H NMR spectrum. Data are in accordance with the literature.

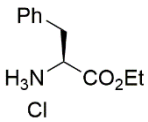
L-Alanine ethyl ester hydrochloride 106[152]



L-Alanine (1.34 g, 15 mmol) was suspended in absolute ethanol (15 mL) and cooled to −5 °C. Thionyl chloride (3.8 mL, 53 mmol) was added dropwise over 20 min. The reaction was warmed slowly to reflux and stirred for 4 h. After cooling to room temperature, the reaction was concentrated under reduced pressure affording the desired product as a white crystalline solid (2.35 g, 100%) which was used directly in the next step without further purification; Mpt. 70-72 °C (lit.[153] 76 °C); $[\alpha]_D^{25}$ +4.0 (*c* 2.5 in H_2O, lit.[153] +3.1, *c* 2.5 in H_2O); δ_H (400 MHz, *d*^{6}-DMSO) 1.24 (3H, t, *J* 7.1, C*H*$_3$), 1.41 (3H, d, *J* 7.2, C*H*$_3$), 4.16-4.24 (3H, m, OC*H*$_2$ and NC*H*), 8.56 (3H, bs, N*H*$_3$).

Data are in accordance with the literature.

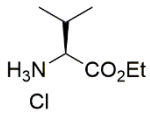
L-Phenylalanine ethyl ester hydrochloride 107[154]



L-Phenylalanine (1.65 g, 10 mmol) was suspended in absolute ethanol (10 mL) and the mixture cooled to -5 °C. Thionyl chloride (2.45 mL, 34 mmol) was added dropwise. The reaction was stirred and heated at reflux for 4 h. After cooling to room temperature, the solvent was removed under reduced pressure affording the product as a white solid (1.79 g, 78%) which was used directly in the next step without further purification; Mpt 138-140 °C (lit.[155] 150-151 °C); $[\alpha]_D^{25}$ −3.8 (*c* 4.00 in H_2O, lit.[155] −7.7, *c* 4.00 in H_2O); δ_H (400 MHz, d^6-DMSO) 1.08 (3H, t, *J* 7.1, CH_3), 3.06 (1H, dd, *J* 13.9, 7.9, C*H*H), 3.22 (1H, dd, *J* 13.9, 5.7, C*H*H), 4.05-4.13 (2H, m, OCH_2), 4.20-4.25 (1H, m, C*H*), 7.24-7.36 (5H, m, ArC*H*), 8.71 (3H, bs, NH_3).

Data are in accordance with the literature.

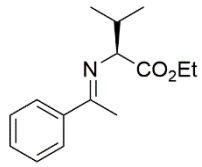
L-Valine ethyl ester hydrochloride 108[156]



L-Valine (1.17 g, 10 mmol) was suspended in ethanol (10 mL) and cooled to -5 °C. Thionyl chloride (2.47 mL, 34 mmol) was added dropwise over 10 min. The reaction was slowly warmed to reflux and stirred for 4 h. After cooling to room temperature, the reaction was concentrated under reduced pressure affording the product as a pale yellow solid (1.18 g, 65%) which was used directly in the next step without further purification; Mpt 96-98 °C (lit.[153] 102-104 °C); $[\alpha]_D^{25}$ +8.5 (*c* 2 in H_2O, lit.[153] +6.7, *c* 2 in H_2O); δ_H (400 MHz, d^6-DMSO) 0.95 (3H, d, *J* 6.9, CH_3), 0.99 (3H, d, *J* 6.9, CH_3), 1.25 (3H, t, *J* 7.1, CH_3), 2.18 (1H, heptet of doublets, *J* 6.9, 4.6, C*H*), 3.85 (1H, d, *J* 4.6, NC*H*), 4.16-4.30 (2H, m, OCH_2), 8.53 (3H, bs, NH_3).

Data are in accordance with the literature.

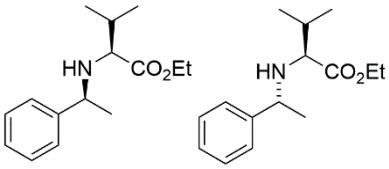
N-(1-Phenylethylidene)-L-valine ethyl ester 111[157]



Acetophenone (0.35 mL, 3.0 mmol), L-valine ethyl ester hydrochloride (0.71 g, 3.9 mmol), and *p*-toluene sulfonic acid (0.05 g, 0.3 mmol) were dissolved in dry toluene (40 mL) and heated at reflux under Dean-Stark conditions. Diisopropylethyl amine (0.68 mL, 3.9 mmol) was added dropwise at a rate of 0.25 mL/h via syringe pump. After addition was complete, the reaction was stirred for a further 3 h. Once cooled to rt, water (20 mL) was added, layers separated, and the aqueous layer washed with toluene (30 mL). The combined organic layers were dried ($MgSO_4$), filtered, and solvent removed under reduced pressure affording the product as a yellow oil (0.69 g, 90%) which was used directly in the next step without further purification; δ_H (400 MHz, $CDCl_3$) 1.03 [6H, t, *J* 6.8, CH(C*H*$_3$)$_2$], 1.30 (3H, t, *J* 7.1, C*H*$_3$), 2.28 (3H, s, C*H*$_3$), 2.41-2.54 (1H, m, C*H*), 4.06 (1H, d, *J* 6.8 NC*H*), 4.22 (2H, qd, *J* 7.1, 0.9, OC*H*$_2$), 7.26-7.44 (3H, m, ArC*H*), 7.80-7.91 (2H, m, ArC*H*).

Data are in accordance with the literature.

N-(1-Phenylethyl)-L-valine ethyl ester 112[157]

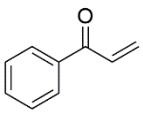


N-(1-Phenylethylene)-L-valine ethyl ester (2.97 g, 12 mmol) was dissolved in dry DCM (12 mL) with DMF under a nitrogen atmosphere and cooled to 0 °C. Trichlorosilane (2.4 mL, 24 mmol) was added dropwise and then stirred at 0 °C for 4 h. The reaction was diluted with DCM (15 mL), transferred to a dropping funnel and added dropwise to an ice/water slurry (20 mL)

with vigorous stirring. The mixture was neutralised using solid sodium carbonate and filtered through celite. The layers were separated, and the aqueous layer extracted using DCM (3 × 40 mL). The combined organic layers were washed using saturated brine (60 mL), dried (Na_2SO_4), filtered, and the solvent removed under reduced pressure. The orange oil was redissolved in Et_2O (60 mL) and washed with aq. 1 M HCl (3 × 30 mL). The combined aqueous layers were neutralised using solid sodium carbonate and extracted using DCM (3 × 30 mL). The combined organic layers were washed using brine (60 mL), dried (Na_2SO_4), filtered, and solvent removed under reduced pressure. Purification by column chromatography on silica gel (5:95 ethyl acetate:hexane) affording the major diastereoisomer (*S*,*R*)-**112** as a colourless oil (23 mg, 8%); δ_H (400 MHz, $CDCl_3$) 0.89 (3H, d, *J* 6.8, C*H*$_3$), 0.93 (3H, d, *J* 6.8, C*H*$_3$), 1.29 (3H, t, *J* 7.1, C*H*$_3$), 1.35 (3H, d, *J* 6.5, C*H*$_3$), 1.74 (1H, bs, N*H*), 1.79-1.91 (1H, m, C*H*), 2.77 (1H, d, *J* 6.1, NC*H*), 3.65 (1H, q, *J* 6.5, NC*H*), 4.21 (2H, q, *J* 7.1, OC*H*$_2$), 7.19-7.40 (5H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 14.5 (*C*H$_3$), 18.5 (*C*H$_3$), 19.5 (*C*H$_3$), 25.7 (*C*H$_3$), 31.5 (*C*H), 56.8 (N*C*H), 60.3 (O*C*H$_2$), 64.7 (N*C*H), 126.9 (Ar*C*H), 127.1 (2 × Ar*C*H), 128.3 (2 × Ar*C*H), 145.3 (Ar*C*), 175.9 (*C*=O); and the minor diastereoisomer (*S*,*S*)-**112** as a colourless oil (67 mg, 22%); δ_H (400 MHz, $CDCl_3$) 0.96 (3H, d, *J* 6.8, C*H*$_3$), 0.97 (3H, d, *J* 6.8, C*H*$_3$), 1.23 (3H, t, *J* 7.1, C*H*$_3$), 1.34 (3H, d, *J* 6.5, C*H*$_3$), 1.64 (1H, bs, N*H*), 1.78-1.99 (1H, m, C*H*), 3.08 (1H, d, *J* 6.1, NC*H*), 3.71 (1H, q, *J* 6.5, NC*H*), 3.98-4.14 (2H, m, OC*H*$_2$), 7.15-7.43 (5H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 14.3 (*C*H$_3$), 18,8 (*C*H$_3$), 19.1 (*C*H$_3$), 22.7 (*C*H$_3$), 31.8 (*C*H), 57.0 (N*C*H), 60.3 (O*C*H$_2$), 65.0 (N*C*H), 126.8 (2 × Ar*C*H), 127.0 (Ar*C*H), 128.3 (2 × Ar*C*H), 145.9 (Ar*C*), 175.3 (*C*=O).

Data are in accordance with the literature.

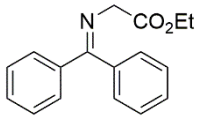
1-Phenyl-2-propen-1-one 148[158]



3-Chloropropiophenone (1.69 g, 10 mmol) was dissolved in DCM (20 mL). Triethylamine (1.5 mL, 11 mmol) was added dropwise over 10 min. The reaction was stirred at rt for 3 h. Water (20 mL) was added and then extracted using DCM (2 × 20 mL). The combined organic layers were washed using brine (30 mL), dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure affording the product as a colourless oil (1.24 g, 94%) which was used directly in the next step without further purification; δ_H (400 MHz, $CDCl_3$) 5.95 (1H, dd, *J* 10.6, 1.6, CH*H*), 6.46 (1H, dd, *J* 17.1, 1.6, C*H*H), 7.18 (1H, dd, *J* 17.1, 10.6, C*H*), 7.49 (2H, t, *J* 7.5, ArC*H*), 7.59 (1H, t, *J* 7.5, ArC*H*), 7.95-7.96 (2H, m, ArC*H*).

Data are in accordance with the literature.

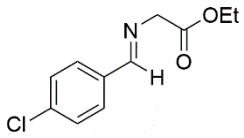
N-(Diphenylmethylene)glycine ethyl ester 151[159]



Benzophenone (1.82 g, 10 mmol) was dissolved in dry toluene (40 mL). Glycine ethyl ester hydrochloride (1.40 g, 10 mmol) was added, and the reaction heated under Dean-Stark conditions. Diethyl isopropyl amine (2.10 mL, 12 mmol) was added dropwise via syringe pump (0.7 mL/h). After addition was complete, the reaction was heated for a further 2 h. After cooling to rt, water (30 mL) was added. The layers were separated, and the aqueous layer extracted with toluene (2 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and solvent removed under reduced pressure affording the product as a yellow oil (2.01 g, 75%) which was used directly in the next step without further purification: δ_H (400 MHz, $CDCl_3$) 1.30 (3H, t, *J* 7.1, CH_3), 4.14-4.29 (4H, m, OCH_2 and NCH_2), 7.32-7.79 (10H, m, ArC*H*).

Selected data from crude ^{1}H NMR spectrum. Data are in accordance with the literature.

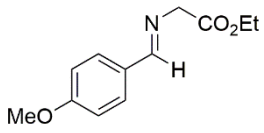
N-[(4-Chlorophenyl)methylene]-glycine ethyl ester 153[159]



4-Chlorobenzaldehyde (2.81 g, 20 mmol) was dissolved in ethanol (40 mL) and glycine ethyl ester hydrochloride (2.79 g, 20 mmol), potassium carbonate (2.79 g, 20 mmol) and magnesium sulfate (approx. 5.0 g) were added. The reaction was stirred overnight at rt. After filtration, the solvent was removed under reduced pressure. The residue was redissolved in DCM (60 mL) and water (60 mL) added. The layers were separated, and the aqueous layer extracted using DCM (3 × 30 mL). The combined organic layers were washed with brine (40 mL), dried (Na_2SO_4), filtered, and the solvent removed under reduced pressure affording the crude product as a pale-yellow oil (2.53 g, 56%) which was used directly in the next step without further purification; δ_H (400 MHz, $CDCl_3$) 1.32 (3H, t, *J* 7.1, C*H*$_3$), 4.26 (2H, q, *J* 7.1, OC*H*$_2$), 4.41 (2H, s, NC*H*$_2$), 7.41 (2H, d, *J* 8.5, ArC*H*), 7.74 (2H, d, *J* 8.5, ArC*H*), 8.27 (1H, s, C*H*N).

Selected data from crude ^{1}H NMR spectrum. Data are in accordance with the literature.

N-[(4-Methoxyphenyl)methylene]-glycine ethyl ester[159]

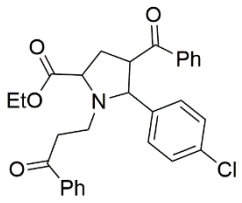


4-Methoxybenzaldehyde (1.22 mL, 10 mmol) was dissolved in ethanol (20 mL). Glycine ethyl ester hydrochloride (1.40 g, 10 mmol), potassium carbonate (1.38 g, 10 mmol), and anhydrous magnesium sulfate (approx. 1.50 g) were added and the resulting mixture was stirred at rt overnight. The reaction was vacuum filtered, and the solvent removed under reduced pressure. The white residue was dissolved in DCM (60 mL) and washed with water (60 mL),

brine (30 mL), dried ($MgSO_4$), filtered, and solvent was removed under reduced pressure affording the product as a pale-yellow oil (1.03 g, 47%) which was used directly in the next step without further purification: δ_H (400 MHz, $CDCl_3$) 1.32 (3H, t, *J* 7.1, C*H*$_3$), 3.86 (3H, s, OC*H*$_3$), 4.25 (2H, q, *J* 7.1, OC*H*$_2$), 4.38 (2H, d, *J* 0.9, NC*H*$_2$), 6.95 [2H, (AX)$_2$, ArC*H*], 7.74 [2H, (AX)$_2$, ArC*H*], 8.23 (1H, s, C*H*N).

Selected data from crude ^{1}H NMR spectrum. Data are in accordance with the literature.

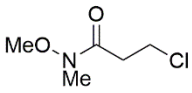
4-Benzoyl-5-(4-chlorophenyl)-1-(3-oxo-3-phenylpropyl)-proline ethyl ester 155



1-Phenyl-2-propen-1-one (0.20 g, 1.5 mmol) and *N*-[(4-chlorophenyl)methylene]-glycine ethyl ester (0.23 g, 1.0 mmol) were dissolved in DCM (2 mL). DABCO (0.01 g, 0.1 mmol) added, and the reaction was stirred for 2 h. More DABCO (0.09 g, 0.9 mmol) was added, and the reaction was stirred for a further 1.5 h. Aq. 1 M HCl (2 mL) was added, and the mixture was stirred for 30 min. After neutralisation using solid sodium carbonate, the layers were separated, and the aqueous layer was extracted using DCM (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure. Purification via flash column chromatography on silica gel (20:80, ethyl acetate:hexane) afforded the product as a yellow oil (30 mg, 6%); δ_H (400 MHz, $CDCl_3$) 1.36 (3H, t, *J* 7.1, C*H*$_3$), 2.20-2.36 (1H, m, C*H*H), 2.74-2.95 (2H, m, C*H*$_2$), 3.02 (1H, dt, *J* 14.2, 6.7, C*H*H), 3.22 (2H, t, *J* 7.0, C*H*$_2$), 3.77 (1H, dd, *J* 10.2, 6.7, C*H*), 4.20-4.48 (4H, m, OC*H*$_2$ and NC*H*), 6.82-6.96 [2H, (AX)$_2$, ArC*H*], 6.96-7.06 [2H, (AX)$_2$, ArC*H*], 7.32-7.43 (4H, m, ArC*H*), 7.43-7.58 (2H, m, ArC*H*), 7.58-7.78 (4H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 14.3 (*C*H$_3$), 31.3 (*C*H$_2$), 37.6 (*C*H$_2$), 49.1 (*C*H$_2$), 50.5 (*C*H), 61.0 (O*C*H$_2$), 65.8 (N*C*H), 65.8 (N*C*H), 127.8 (2 × Ar*C*H), 127.9 (2 × Ar*C*H), 128.2 (2 × Ar*C*H), 128.47 (2 × Ar*C*H), 128.49 (2 × Ar*C*H), 129.6

(2 × Ar*C*H), 133.0 (Ar*C*), 133.0 (2 × Ar*C*H), 136.6 (Ar*C*), 137.4 (Ar*C*), 139.5 (Ar*C*), 173.6 (*C*=O), 197.4 (*C*=O), 199.0 (*C*=O); *m*/*z* (ESI$^+$) 490 [100%, (M+H)$^+$], 451 (2) 370 (2).

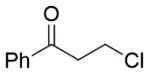
3-Chloro-*N*-methoxy-*N*-methyl-propanamide 159[160]



Potassium carbonate (4.19 g, 30.0 mmol) was dissolved in water (45 mL) under nitrogen. *N*,*O*-Dimethylhydroxyamine hydrochloride (2.19 g, 22.5 mmol) in diethyl ether (45 mL) was added and the mixture was cooled to 0 °C. 3-Chloropropanoyl chloride (1.40 mL, 15.0 mmol) was added dropwise. The reaction was slowly warmed to rt and stirred overnight. The layers were separated, and the aqueous layer was extracted using diethyl ether (3 × 20 mL). The combined organic layers were washed using brine (60 mL), dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure affording the desired product as a colourless oil (1.63 g, 72%) which was used directly in the next step without further purification; δ_H (400 MHz, $CDCl_3$) 2.94 (2H, t, *J* 6.8, CH_2), 3.22 (3H, s, NCH_3), 3.72 (3H, s, OCH_3), 3.82 (2H, t, *J* 6.8, CH_2).

Data are in accordance with the literature.

3-Chloropropiophenone 149[161]

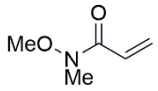


3-Chloro-*N*-methoxy-*N*-methyl-propanamide (0.152 g, 1.0 mmol) was dissolved in dry THF (1 mL) under argon and cooled to 0 °C. Phenylmagnesium bromide (2.5 M in diethyl ether, 0.40 mL, 1.0 mmol) was added dropwise. The reaction was stirred at 0 °C for 2 h and then quenched using aq. ammonium chloride (1 mL). The layers were separated, and the aqueous layer was extracted using ethyl acetate (3 × 5 mL). The combined organic layers were washed

with brine (10 mL), dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure. Purification via flash column chromatography on silica gel (20:80, ethyl acetate:hexane) afforded the desired product as a pale-yellow oil (5 mg, 3%); δ_H (400 MHz, $CDCl_3$) 3.49 (2H, t, *J* 6.8, CH_2), 3.96 (2H, t, *J* 6.8, CH_2), 7.46-7.57 (2H, m, ArC*H*), 7.58-7.69 (1H, m, ArC*H*), 7.95-8.03 (2H, m, ArC*H*).

Data are in accordance with the literature.

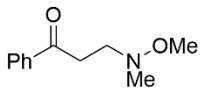
N-Methoxy-*N*-methylacrylamide 160[162]



Obtained via same procedure as 3-chloropropiophenone **149**. Purification via flash column chromatography on silica gel (20:80, ethyl acetate:hexane) afforded the desired product as a pale-yellow oil (4 mg, 3%); δ_H (400 MHz, $CDCl_3$) 3.28 (3H, s, NCH_3), 3.72 (3H, s, OCH_3), 5.78 (1H, dd, *J* 10.4, 2.0, C*H*), 6.45 (1H, dd, *J* 17.1, 2.0, C*H*), 6.75 (1H, dd, *J* 17.1, 10.4, C*H*).

Data are in accordance with the literature.

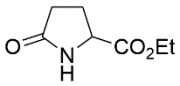
3-(Methoxymethylamino)-1-phenyl-1-propanone 161[163]



Obtained via same procedure as 3-chloropropiophenone **149** with a change in reaction time to 6 h. Crude product was obtained as a yellow oil (0.17 g) and was not purified or used in further reactions; δ_H (400 MHz, $CDCl_3$) 2.62 (3H, s, NCH_3), 3.06-3.14 (2H, m, CH_2), 3.24-3.33 (2H, m, CH_2), 3.53 (3H, s, OCH_3), 7.40-7.67 (3H, m, ArC*H*), 7.93-8.04 (2H, m, ArC*H*).

Selected data from crude ^{1}H NMR spectrum. Data are in accordance with the literature.

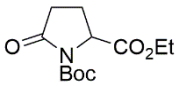
(±)-5-Oxo-proline ethyl ester 163[164]



Thionyl chloride (2.2 mL, 31 mmol) was added dropwise to a stirred suspension of DL-pyroglutamic acid (25.0 g, 194 mmol) in ethanol (100 mL). The reaction was stirred overnight. Solvent removed in vacuo. The residue was redissolved in DCM (200 mL) and washed with aq. saturated $NaHCO_3$ (200 mL). Aqueous layer was extracted using DCM (3 × 100 mL). Combined organic layers were washed with brine (100 mL), dried (Na_2SO_4), filtered and the solvent removed under reduced pressure affording the product as a white solid (23.9 g, 78%) which was used directly in the next step without further purification: Mpt 54-58 °C (lit.[164], 54 °C); ν_{max}/cm^{-1} (thin film, KBr plates) 3247 (NH), 1739, 1699; δ_H (400 MHz, $CDCl_3$) 1.32 (3H, t, *J* 7.1, C*H*$_3$), 2.09-2.63 (4H, m, C*H*$_2$), 4.21-4.30 (3H, m, C*H* and OC*H*$_2$), 6.00 (1H, s, N*H*); δ_C (101 MHz, $CDCl_3$) 14.2 (*C*H$_3$), 24.8, (*C*H$_2$), 29.2 (*C*H$_2$), 55.4 (NCH), 61.7 (O*C*H$_2$), 172.0 (*C*=O), 177.9 (*C*=O); *m/z* (ESI^+) 158.0816 [100%, $(M+H)^+$, $C_7H_{13}NO_3$ requires 158.0812].

Data are in accordance with the literature.

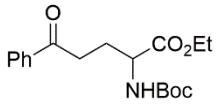
(±)-1-*tert*-Butyl-2-ethyl-5-oxopyrrolidine-1,2-dicarboxylate 164



Di-*tert*-butyl-dicarbonate (8.29 g, 38 mmol) was dissolved in DCM (40 mL) with DMAP (0.20 g, 1.6 mmol) and triethylamine (4.50 mL, 32 mmol). 5-Oxo-proline ethyl ester (5.00 g, 32 mmol) in DCM (15 mL) was gradually added and the reaction was stirred overnight. The mixture was washed with brine (250 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure. Purification by dry column chromatography on silica gel (75:25 ethyl acetate:hexane) afforded the product as a yellow oil (7.39 g, 90%); ν_{max}/cm^{-1} (thin film, KBr plates) 2982, 2937, 1793, 1747, 1717; δ_H (400 MHz, $CDCl_3$) 1.30 (3H, t, *J* 7.1, C*H*$_3$), 1.50 [9H,

s, (C*H*$_3$)$_3$], 1.98-2.10 (1H, m, C*H*H), 2.26-2.40 (1H, m, C*H*H), 2.49 (1H, ddd, *J* 17.5, 9.4, 3.5, C*H*H), 2.64 (1H, dt, *J* 17.5, 9.8, C*H*H), 4.24 (2H, q, *J* 7.1, OC*H*$_2$), 4.60 (1H, dd, *J* 9.4, 2.9, NC*H*); δ_C (101 MHz, $CDCl_3$) 14.2 (*C*H$_3$), 21.5 (*C*H$_2$), 27.9 [(*C*H$_3$)$_3$], 31.2 (*C*H$_2$), 59.0 (NCH), 61.7 [*C*(CH$_3$)$_3$], 83.5 (O*C*H$_2$), 149.3 (*C*=O), 171.3 (*C*=O), 173.4 (*C*=O); *m*/*z* (ESI$^+$) 280.1168 [100%, (M+Na)$^+$ $C_{12}H_{19}NO_5Na$ requires 280.1179].

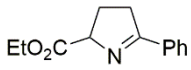
(±)-α-{[(1,1-Dimethylethoxy)carbonyl]amino}-δ-oxo-benzenepentanoic acid ethyl ester 165



1-*tert*-Butyl-2-ethyl-5-oxopyrrolidine-1,2-dicarboxylate (1.87 g, 7.3 mmol) was dissolved in dry THF (5 mmol) and cooled to −10 °C under argon. Phenyl magnesium bromide (11.0 mL, 11.0 mmol, 1 M in THF) was added dropwise. The reaction was warmed to room temperature and stirred overnight and then quenched using saturated aq. ammonium chloride (8 mL). The layers were separated, and the aqueous layer extracted using diethyl ether (3 × 20 mL). The combined organic layers washed using brine (30 mL), dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure. Purification via flash column chromatography on silica gel (20:80 ethyl acetate:hexane) afforded the product as a colourless oil (1.93 g, 79%); δ_H (400 MHz, $CDCl_3$) 1.29 (3H, t *J* 7.0, C*H*$_3$), 1.44 [9H, s, C(C*H*$_3$)$_3$], 2.11 (1H, td, *J* 14.3, 8.4, C*H*H), 2.25-2.41 (1H, m, C*H*H), 2.99-3.23 (2H, m, C*H*$_2$), 4.32 (2H, q, *J* 7.0, OC*H*$_2$), 4.38 (1H, s, C*H*), 5.19 (1H, d, *J* 6.8, N*H*), 7.48 (2H, t, *J* 7.3, ArC*H*), 7.59 (1H, t, *J* 7.3, ArC*H*), 7.97 (2H, d, *J* 7.3, ArC*H*).

Due to product instability, this was then used directly in the next step without further characterisation. Selected data from impure ^{1}H NMR spectrum.

(±)-3,4-Dihydro-5-phenyl-2*H*-pyrrole-2-carboxylic acid ethyl ester 147[164]



From 1-phenyl-2-propen-1-one:

1-Phenyl-2-propen-1-one (0.20 g, 1.5 mmol) and *N*-(diphenylmethylene) glycine ethyl ester (0.48 g, 1.8 mmol) were dissolved in dry DCM (1.5 mL) under argon and cooled to 0 °C. DBU (0.02 mL, 0.15 mmol) was added, the reaction was warmed up to rt and stirred for 4 h. 12 M HCl (0.01 mL, 0.45 mmol) was added, and the reaction stirred overnight. 1 M aq HCl (2 mL) was added, and the reaction stirred for 30 min. The organic layer was separated, and the aqueous layer extracted using DCM (3 × 10 mL). The combined organic layers were washed using brine (10 mL), dried ($MgSO_4$), filtered, and the solvent removed under reduced pressure. Purification by column chromatography on Florisil (1:99 to 20:80, ethyl acetate:hexane) afforded the product as a pale-yellow oil (0.10 g, 31%); δ_H (400 MHz, $CDCl_3$) 1.33 (3H, t, *J* 7.1, C*H*$_3$), 2.20-2.30 (1H, m, CH*H*), 2.32-2.41 (1H, m, CH*H*), 3.00 (1H, dddd, *J* 16.9, 9.8, 7.0, 1.7, CH*H*), 3.18 (1H, dddd, *J* 16.9, 9.9, 5.5, 2.1, CH*H*), 4.26 (2H, q, *J* 7.1, OC*H*$_2$), 4.89-4.94 (1H, m, NC*H*), 7.40-7.49 (3H, m, ArC*H*), 7.88-7.92 (2H, m, ArC*H*).

One-pot method from 3-chloropropiophenone:

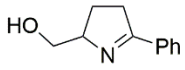
3-Chloropropiophenone (0.20 g, 1.2 mmol) was dissolved in DCM (3 mL) and potassium *tert*-butoxide (0.16 g, 1.4 mmol) was gradually added. Stirred for 20 min. *N*-(Phenylmethylene)-glycine ethyl ester (0.19 g, 1.0 mmol) in DCM (1 mL) was added dropwise and the reaction was stirred overnight. Aq. 1 M HCl was added until the reaction was pH 1 and then stirred for a further 3 h. The reaction was neutralised using aq. saturated $NaHCO_3$. The layers were separated and the aqueous layer extracted using DCM (3 × 10 mL). The combined organic layers were washed using brine (20 mL), dried (Na_2SO_4), filtered and the solvent was removed under reduced pressure. Purification by flash column chromatography on silica gel (20:80 ethyl acetate:hexane) afforded the product as a yellow oil (0.08 g, 36%).

From α-[{(-1,1-dimethylethoxy)carbonyl]amino}-δ-oxo-benzenepentanoic acid ethyl ester:

α-[{(-1,1-Dimethylethoxy)carbonyl]amino}-δ-oxo-benzenepentanoic acid ethyl ester (1.22 g, 3.6 mmol) was dissolved in DCM (10 mL) and cooled to 0 °C. Trifluoroacetic acid (10.7 mL, 140 mmol) was added dropwise over 15 mins, the reaction warmed to rt, and stirred for 2.5 h. An ice/water slurry (20 mL) was added, and the mixture neutralised using solid $NaHCO_3$. After stirring at rt for 1.5 h, the layers were separated, and the aqueous layer extracted using DCM (4 × 20 mL). The combined organic layers were washed using brine (40 mL), dried (Na_2SO_4), filtered and solvent removed under reduced pressure affording the product as a yellow oil (0.71 g, 91%) which was used directly in the next step without further purification.

Data are in accordance with the literature.

(±)-3,4-dihydro-5-phenyl-2H-pyrrole-2-methanol 167[165]

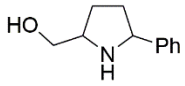


3,4-Dihydro-5-phenyl-2H-pyrrole-2-carboxylic acid ethyl ester (0.217 g, 1.0 mmol) was dissolved in ethanol (4 mL). Sodium borohydride (0.057 g, 1.5 mmol) slowly added, and the reaction was stirred overnight at room temperature. The reaction was quenched using aq. 1 M HCl (0.1 mL) and diluted with DCM (10 mL) and water (10 mL). The layers were separated, and the aqueous layer extracted using DCM (3 × 5 mL). Combined organic layers were washed using brine (10 mL), dried (Na_2SO_4), filtered, and solvent removed under reduced pressure. Purification by flash column chromatography on silica gel (5:95 to 10:90, MeOH:DCM) afforded the product as a white oil (10 mg, 6%); δ_H (400 MHz, $CDCl_3$) 1.76-1.92 (1H, m, C*H*), 2.10-2.22 (1H, m, C*H*), 2.46 (1H, s, O*H*), 2.94 (1H, dddd, *J* 17.2, 9.8, 7.8, 2.2, CH_2), 3.09 (1H, dddd, *J* 17.2, 10.3, 4.5, 2.2, CH_2), 3.66 (1H, dd, *J* 11.2, 6.0, C*H*), 4.04 (1H, dd, *J* 11.2, 4.0, C*H*), 4.35-4.44 (1H, m, C*H*), 7.38-7.51 (3H, m, ArC*H*), 7.78-7.88 (2H, m, ArC*H*);

δ_C (101 MHz, $CDCl_3$) 24.5 (*C*H_2), 35.6 (*C*H_2), 66.1 (*C*H_2OH), 74.7 (N*C*H), 127.9 (Ar*C*H), 128.5 (2 × Ar*C*H), 130.8 (2 × Ar*C*H), 134.1 (Ar*C*), 174.6 (*C*=N).

Data are in accordance with the literature.

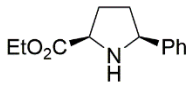
(±)-*cis*-3,4-Dihydro-5-phenyl-2H-pyrrole-2-methanol 168[166]



Obtained via same procedure as 3,4-dihydro-5-phenyl-2H-pyrrole-2-methanol. Purification by flash column chromatography on silica gel (5:95 to 10:90 MeOH:DCM) afforded the product as a colourless oil (50 mg, 28%); δ_H (400 MHz, $CDCl_3$) 1.68-2.10 (3H, m, C*H*$_2$), 2.10-2.34 (1H, m, C*H*H), 3.21-3.73 (3H, m, C*H*H and C*H*), 3.82 (1H, bs, N*H*), 4.16-4.32 (1H, m, C*H*), 7.20-7.45 (5H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 27.5 (*C*H_2), 34.0 (*C*H_2), 59.0 (*C*H), 63.6 (*C*H), 68.7 (O*C*H_2), 126.7 (2 × Ar*C*H), 127.3 (Ar*C*H), 128.4 (2 × Ar*C*H), 142.8 (Ar*C*).

Data are in accordance with the literature.

(±)-*cis*-5-Phenyl-proline ethyl ester 166[110]

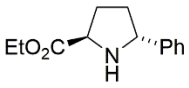


3,4-Dihydro-5-phenyl-2H-pyrrole-2-carboxylic acid ethyl ester (0.217 g, 1.0 mmol) and (*S*)-**49** (0.018 g, 0.05 mmol) were dissolved in DCM (2 mL) under argon and cooled to −18 °C. Trichlorosilane (0.20 mL, 2.0 mmol) was added dropwise, and the reaction was stirred for 15 min. Aq. 1 M HCl (2 mL) was added, and the reaction was warmed to rt. Aq. 1 M NaOH was added until neutral pH was maintained after 5 min of stirring. The layers were separated, and the aqueous layer was extracted using DCM (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), filtered and solvent was removed under reduced

pressure. Purification via flash column chromatography on silica gel (20:80 to 40:60 ethyl acetate:hexane) afforded the product as a pale-yellow oil (0.04 g, 18%); δ_H (400 MHz, $CDCl_3$) 1.33 (3H, t, *J* 7.1, C*H*$_3$), 1.62-1.95 (1H, m, C*H*H), 2.04-2.32 (3H, m, C*H*H), 2.44 (1H, bs, N*H*), 3.94 (1H, dd, *J* 8.6, 4.7, C*H*^{A}), 4.15-4.30 (3H, m, OC*H*$_2$ and C*H*^{B}), 7.20-7.41 (3H, m, ArC*H*), 7.47 (2H, d, *J* 7.2, ArC*H*).

Data are in accordance with the literature.

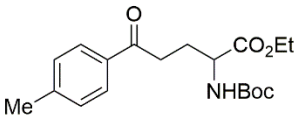
(±)-*trans*-5-Phenyl-proline ethyl ester 166[110]



3,4-Dihydro-5-phenyl-2H-pyrrole-2-carboxylic acid ethyl ester (0.217 g, 1.0 mmol) and DMF (0.02 mL, 0.2 mmol) were dissolved in DCM (2 mL) under argon and cooled to 0 °C. Trichlorosilane (0.20 mL, 2.0 mmol) was added dropwise, and the reaction was stirred for 4 h at 0 °C. Aq. 1 M HCl (2 mL) was added, and the reaction was warmed to rt. Aq. 1 M NaOH was added until neutral pH was maintained after 5 min of stirring. The layers were separated, and the aqueous layer was extracted using DCM (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), filtered and solvent was removed under reduced pressure. Purification via flash column chromatography on silica gel (20:80 to 40:60 ethyl acetate:hexane) afforded the product as a pale-yellow oil (5 mg, 1%); δ_H (400 MHz, $CDCl_3$) 1.32 (3H, t, *J* 7.1, C*H*$_3$), 1.80 (1H, dq, *J* 12.2, 8.7, C*H*H), 2.01 (1H, dddd, *J* 12.6, 8.7, 7.9, 5.9, C*H*H), 2.17-2.29 (1H, m, C*H*H), 2.40 (1H, dtd, *J* 12.6, 8.7, 4.0, C*H*H), 4.07 (1H, dd, *J* 8.7, 5.9, C*H*^{A}), 4.24 (2H, q, *J* 7.1, OC*H*$_2$), 4.39 (1H, dd, *J* 8.7, 6.7, C*H*^{B}), 7.18-7.47 (5H, m, ArC*H*).

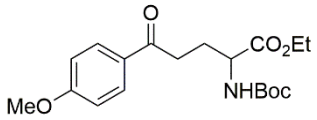
Data are in accordance with the literature.

(±)-α-[{(-1,1-Dimethylethoxy)carbonyl]amino}-4-methyl-δ-oxo-benzenepentanoic acid ethyl ester 175



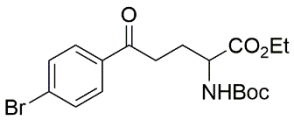
Mg turnings (0.18 g, 7.5 mmol) were stirred under a N_2 atmosphere. Dry THF (1 mL) followed by 0.5 mL of 4-bromotoluene (1.28 g, 7.5 mmol) were added and the reaction initiated by direct heating. The remining 4-bromotoluene was dissolved in dry THF (5 mL) and added dropwise maintaining reflux. Once addition was complete, the reaction was heated at reflux for 1 h. The reaction was cooled to 0 °C and 1-*tert*-butyl-2-ethyl-5-oxopyrrolidine-1,2-dicarboxylate (1.29 g, 5.0 mmol) in dry THF (1.5 mL) added dropwise then warmed to rt and stirred overnight. The reaction was quenched by addition of saturated aq. ammonium chloride (8 mL) and stirred for 10 min. The layers were separated and the aqueous layer was extracted using DCM (3 × 20 mL). The combined organic layers were washed using brine (30 mL), dried (Na_2SO_4), filtered, and solvent removed under reduced pressure. Purification via flash column chromatography on silica gel (15:85 ethyl acetate:hexane) afforded the product as a pale-yellow oil (0.96 g, 55%); ν_{max}/cm^{-1} (thin film, KBr plates) 3364 (NH), 2977, 2921, 1714, 1686, 1609, 1510, 1367, 1167; δ_H (400 MHz, $CDCl_3$) 1.29 (3H, t, *J* 7.1, C*H*$_3$), 1.44 [9H, s, (C*H*$_3$)$_3$], 2.09 (1H, dd, *J* 15.0, 6.5, C*H*$_2$), 2.26-2.36 (1H, m, C*H*$_2$), 2.43 (3H, s, C*H*$_3$), 2.98-3.18 (2H, m, C*H*$_2$), 4.22 (2H, q, *J* 7.1, OC*H*$_2$), 4.38 (1H, dd, *J* 12.9, 8.0, NC*H*), 5.20 (1H, d, *J* 8.0, N*H*), 7.24-7.30 (2H, m, ArC*H*), 7.87 (2H, d, *J* 8.3, ArC*H*); δ_C (101 MHz, $CDCl_3$) 14.2 (*C*H$_3$), 21.7 (*C*H$_3$), 27.1 [O*C*H$_2$ or O*C*(CH$_3$)$_3$], 28.3 [(*C*H$_3$)$_3$], 34.5 [O*C*H$_2$ or O*C*(CH$_3$)$_3$], 53.2 (N*C*H), 61.5 (*C*H$_2$), 128.2 (2 × Ar*C*H), 129.4 (2 × Ar*C*H), 134.2 (Ar*C*), 144.0 (Ar*C*), 155.5 (*C*=O), 172.5 (*C*=O), 198.6 (*C*=O); *m*/*z* (ESI$^+$) 372.1779 [100%, (M+Na)$^+$, $C_{19}H_{27}NO_5Na$ requires 372.1781].

(±)-α-[{(-1,1-Dimethylethoxy)carbonyl]amino}-4-methoxy-δ-oxo-benzenepentanoic acid ethyl ester 176



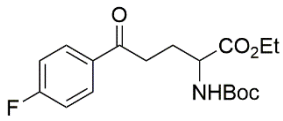
Magnesium turnings (0.18 g, 7.5 mmol) were stirred in dry THF (1.5 mL) under nitrogen. 0.1 mL of 4-bromoanisole (0.94 mL, 7.5 mmol) was added and the reaction activated by direct heating. The remaining 4-bromoanisole was dissolved in dry THF (5 mL) and the mixture was added dropwise maintaining the reaction at reflux. Once addition was complete, the mixture was heated at reflux for 1 h. This was then cooled to 0 °C and 1-*tert*-butyl-2-ethyl-5-oxopyrrolidine-1,2-dicarboxylate (1.29 g, 5.0 mmol) in dry THF (1.5 mL) was added dropwise. After warming to rt and stirring overnight, aq. saturated ammonium chloride (8 mL) was added and stirred for 20 mins. The layers were separated, and the aqueous layer extracted using DCM (3 × 25 mL). The combined organic layers were washed using brine (40 mL), dried (Na_2SO_4), filtered and solvent removed under reduced pressure. Purification by flash column chromatography on silica gel (15:85 to 30:70 ethyl acetate:hexane) afforded the product as a pale yellow oil (0.52 g, 28%); ν_{max}/cm^{-1} (thin film, KBr plates) 3362 (NH), 2978, 1713, 1678, 1601, 1512, 1368; δ_H (400 MHz, $CDCl_3$) 1.29 (3H, t, *J* 7.1, C*H*$_3$),1.44 [9H, s, (C*H*$_3$)$_3$], 2.02-2.15 (1H, m, C*H*H), 2.25-2.36 (1H, m, C*H*H), 2.96-3.17 (2H, m, C*H*$_2$), 3.89 (3H, s, OC*H*$_3$), 4.22 (2H, q, *J* 7.1, OC*H*$_2$), 4.37 (1H, dd, *J* 12.8, 7.7, NC*H*), 5.20 (1H, d, *J* 8.0, N*H*), 6.95 (2H, d, *J* 8.9, ArC*H*), 7.95 (2H, d, *J* 8.9, ArC*H*); δ_C (101 MHz, $CDCl_3$) 14.2 (*C*H$_3$), 27.2 (*C*H$_2$), 28.3 [O*C*(CH$_3$)$_3$], 34.2 (*C*H$_2$), 53.2 (N*C*H), 55.5 (O*C*H$_3$), 61.5 (O*C*H$_2$), 113.7 (2 × Ar*C*H), 129.7 (Ar*C*), 130.31 (2 × Ar*C*H), 155.5 (Ar*C*O), 163.5 (*C*=O), 172.5 (*C*=O), 197.5 (*C*=O); *m/z* (ESI$^+$) 388.1736 [100%, (M+Na)$^+$, $C_{19}H_{27}NO_6Na$ requires 388.1731].

(±)-α-[{(-1,1-Dimethylethoxy)carbonyl]amino}-4-bromo-δ-oxo-benzenepentanoic acid ethyl ester 177



Magnesium turnings (0.18 g, 7.5 mmol) were stirred in dry THF (1 mL) under a nitrogen atmosphere. 0.4 mL of a 1,4-dibromobenzene (1.18 g, 7.5 mmol)/ dry THF (2 mL) solution was added. Iodine (1 crystal) added, and the reaction activated through direct heating. The remaining 1,4-dibromobenzene/THF solution was added dropwise maintaining reflux. Once addition was complete, the reaction was heated at reflux for a further 1 h. After cooling to 0 °C, 1-t*ert*-butyl-2-ethyl-5-oxopyrrolidine-1,2-dicarboxylate (1.29 g, 5.0 mmol) was dissolved in dry THF (5 mL) and added dropwise. This was warmed to rt and stirred overnight. Aq. saturated ammonium chloride (8 mL) was added, the mixture was stirred for 10 min, the layers separated, and the aqueous layer extracted using DCM (3 × 50 mL). The combined organic layers were washed using brine (40 mL), dried (Na_2SO_4), filtered and solvent removed under reduced pressure. Purification via flash column chromatography on silica gel (20:80 ethyl acetate: hexane) afforded the product as a colourless oil (0.57 g, 28%); ν_{max}/cm^{-1} (thin film, KBr plates) 3364 (NH), 2979, 1742, 1711, 1691, 1395, 1368, 1166; δ_H (400 MHz, $CDCl_3$) 1.28 (3H, t, *J* 7.1, C*H*$_3$), 1.43 [9H, s, (C*H*$_3$)$_3$], 1.99-2.16 (1H, m, C*H*H), 2.32 (1H, td, *J* 14.3, 8.4, CH*H*), 2.96-3.22 (2H, m, C*H*$_2$), 4.21 (2H, q, *J* 7.1, OC*H*$_2$), 4.31-4.43 (1H, m, NC*H*), 5.20 (1H, d, *J* 7.1, N*H*), 7.45-7.97 (4H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 14.2 (*C*H$_3$), 27.0 (*C*H$_2$), 28.3 [(*C*H$_3$)$_3$C], 34.6 (*C*H$_2$), 53.0 (N*C*H), 61.5 [O*C*(CH$_3$)$_3$], 61.6 (O*C*H$_2$), 128.4 (Ar*C*), 129.6 (2 × Ar*C*H), 131.9 (2 × Ar*C*H), 135.4 (Ar*C*), 155.5 (*C*=O), 172.4 (*C*=O), 197.9 (*C*=O); *m*/*z* (ESI$^+$) 436.0748 [100%, (M+Na)$^+$ $C_{18}H_{24}{}^{79}BrNO_5Na$ requires 436.0730], 438.0730 [100%, (M$^+$Na)$^+$ $C_{18}H_{24}{}^{81}BrNO_5Na$ requires 438.0712].

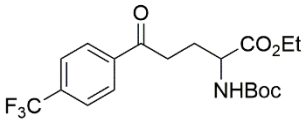
(±)-α-[{(1,1-Dimethylethoxy)carbonyl]amino}-4-fluoro-δ-oxo-benzenepentanoic acid ethyl ester 178



Magnesium turnings (0.182 g, 7.5 mmol) in dry THF (1 mL) were stirred under nitrogen. 0.1 mL of 1-bromo-4-fluorobenzene (0.83 mL, 7.5 mmol) was added and the reaction initiated by direct heating. The remaining 1-bromo-4-fluorobenzene was dissolved in dry THF (2 mL) and added dropwise maintaining reflux. Once addition was complete, the reaction was heated at reflux for 2 h. After cooling to 0 °C, 1-*tert*-butyl-2-ethyl-5-oxopyrrolidine-1,2-dicarboxylate (1.29 g, 5.0 mmol) in dry THF (5 mL) was added dropwise, the reaction warmed rt, and stirred overnight. The reaction was cooled to 0 °C and quenched using aq. saturated ammonium chloride (8 mL). The layers were separated, and the aqueous layer extracted using diethyl ether (3 × 40 mL). The combined organic layers were washed using brine (40 mL), dried (Na_2SO_4), filtered, and solvent removed under reduced pressure. Purification via flash column chromatography on silica gel (20:80 to 30:70 ethyl acetate:hexane) afforded the product as a colourless oil (0.79 g, 48%); δ_H (400 MHz, $CDCl_3$) 1.29 (3H, t, *J* 7.1, C*H*$_3$), 1.43 [9H, s, C(C*H*$_3$)$_3$], 2.00-2.15 (1H, m, C*H*H), 2.25-2.41 (1H, m, C*H*H), 2.98-3.19 (2H, m, C*H*H), 4.22 (2H, q, *J* 7.1, OC*H*$_2$), 4.38 (1H, dd, *J* 12.9, 8.0, C*H*), 5.19 (1H, d, *J* 7.6, N*H*), 7.15 (2H, t, *J* 8.6, ArC*H*), 7.95-8.06 (2H, m, ArC*H*).

Due to product instability, this was then used directly in the next step without further characterisation. Selected data from impure ^{1}H NMR spectrum.

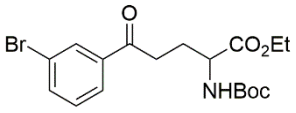
(±)-α-[{(1,1-Dimethylethoxy)carbonyl]amino}-4-(1,1,1-trifluoromethyl)-δ-oxo-benzenepentanoic acid ethyl ester 179



Magnesium turnings (0.182 g, 7.5 mmol) were stirred under a nitrogen atmosphere. Dry THF (1 mL) followed by 0.2 mL of 4-bromobenzotrifluoride (1.05 mL, 7.5 mmol) added and the reaction initiated by direct heating. The remaining 4-bromobenzotrifluoride was dissolved in dry THF (3 mL) and added dropwise maintaining reflux. Once addition was complete, the reaction was heated at reflux for 2 h. After cooling to 0 °C, 1-*tert*-butyl-2-ethyl-5-oxopyrrolidine-1,2-dicarboxylate (1.29 g, 5.0 mmol) in dry THF (5 mL) was added dropwise, then warmed to rt and stirred overnight. The reaction was cooled to 0 °C and aq. saturated ammonium chloride (8 mL) added. The layers were separated, and the aqueous layer extracted using diethyl ether (3 × 30 mL). The combined organic layers were washed with brine (30 mL), dried (Na_2SO_4), filtered, and solvent was removed under reduced pressure. Purification via flash column chromatography on silica gel (30:70, ethyl acetate:hexane) afforded the product as a colourless oil (0.37 g, 18%); δ_H (400 MHz, $CDCl_3$) 1.29 (3H, t, *J* 7.1, C*H*$_3$), 1.42 [9H, s, C(C*H*$_3$)$_3$], 2.02-2.16 (1H, m, C*H*H), 2.29-2.42 (1H, m, C*H*H), 3.02-3.25 (2H, m, C*H*H), 4.23 (2H, qd, *J* 7.1, 1.3, OC*H*$_2$), 4.34-4.44 (1H, m, C*H*), 5.20 (1H, d, *J* 8.3, N*H*), 7.49-8.10 (4H, m, ArC*H*).

Due to product instability, this was then used directly in the next step without further characterisation. Selected data from impure ^{1}H NMR spectrum.

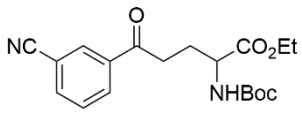
(±)-α-{[(1,1-Dimethylethoxy)carbonyl]amino}-δ-oxo-(3-bromo)benzenepentanoic acid ethyl ester 180



Isopropylmagnesium chloride lithium chloride solution (4.2 mL, 5.5 mmol, 1.3 M solution in THF) was cooled to −5 °C under argon. 1,3-Dibromobenzene (0.60 mL, 5.0 mmol) was dissolved in dry THF (5 mL) and added dropwise. Once addition was complete, the reaction was stirred at 0 °C for 2 h. In a separate flask, 1-*tert*-butyl-2-ethyl-5-oxopyrrolidine-1,2-dicarboxylate (1.29 g, 5.0 mmol) was dissolved in dry THF (5 mL) and cooled to 0 °C under argon. The freshly prepared Grignard reagent was added dropwise via syringe, and the reaction was stirred for 30 min before warming to rt and stirring overnight. After cooling to 0 °C, aq. saturated ammonium chloride (8 mL) was added, the layers separated, and the aqueous layer extracted using diethyl ether (3 × 40 mL). The combined organic layers were washed using brine (30 mL), dried (Na_2SO_4), filtered, and solvent removed under reduced pressure. Purification via flash column chromatography on silica gel (20:80 ethyl acetate:hexane) afforded the product as a colourless oil (0.85 g, 41%); δ_H (400 MHz, $CDCl_3$) 1.30 (3H, t, *J* 7.1, C*H*$_3$), 1.44 [9H, s, C(C*H*$_3$)$_3$], 2.01-2.14 (1H, m, C*H*H), 2.27-2.39 (1H, m, C*H*H), 3.03-3.12 (2H, m, C*H*H), 4.23 (2H, qd, *J* 7.1, 0.9, OC*H*$_2$), 4.38 (1H, d, *J* 4.7, NC*H*), 5.18 (1H, d, *J* 7.5, N*H*), 7.36 (1H, t, *J* 7.9, ArC*H*), 7.68-7.72 (1H, m, ArC*H*), 7.86-7.91 (1H, m, ArC*H*), 8.09 (1H, t, *J* 1.8, ArC*H*).

Due to product instability, this was then used directly in the next step without further characterisation. Selected data from impure ^{1}H NMR spectrum.

(±)-α-{[(1,1-Dimethylethoxy)carbonyl]amino}-δ-oxo-(3-cyano)benzenepentanoic acid ethyl ester 182

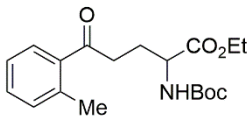


Isopropylmagnesium chloride lithium chloride solution (4.2 mL, 5.5 mmol, 1.3 M solution in THF) was cooled to 0 °C under argon. 3-Bromobenzonitrile (0.91 g, 5.0 mmol) was dissolved in dry THF (5 mL) and added dropwise. Once addition was complete, the reaction was stirred

at 0 °C for 2 h. In a separate flask, 1-*tert*-butyl-2-ethyl-5-oxopyrrolidine-1,2-dicarboxylate (1.29 g, 5.0 mmol) was dissolved in dry THF (5 mL) and cooled to 0 °C under argon. The freshly prepared Grignard reagent was added dropwise via syringe, and the reaction was stirred for 30 min before warming to rt and stirring overnight. After cooling to 0 °C, aq. saturated ammonium chloride (8 mL) was added, the layers separated, and the aqueous layer was extracted using diethyl ether (3 × 20 mL). The combined organic layers were washed using brine (30 mL), dried (Na_2SO_4), filtered, and solvent removed under reduced pressure. Purification via flash column chromatography on silica gel (40:60 ethyl acetate:hexane) afforded the product as a white solid (0.86 g, 48%); Mpt 110-113 °C; δ_H (400 MHz, $CDCl_3$) 1.31 (3H, t, *J* 7.1, C*H*$_3$), 1.43 [9H, s, C(C*H*$_3$)$_3$], 2.01-2.16 (1H, m, C*H*H), 2.38 (1H, ddd, *J* 13.3, 9.8, 6.8, C*H*H), 3.06-3.17 (2H, m, C*H*$_2$), 4.24 (2H, qd, *J* 7.1, 1.8, OC*H*$_2$), 4.40 (1H, dd, *J* 12.8, 8.0, NC*H*), 5.18 (1H, d, *J* 8.0, N*H*), 7.63 (1H, t, *J* 7.8, ArC*H*), 7.87 (1H, d, *J* 7.8, ArC*H*), 8.19 (1H, d, *J* 7.8, ArC*H*), 8.25 (1H, s, ArC*H*).

Due to product instability, this was then used directly in the next step without further characterisation. Selected data from impure ^{1}H NMR spectrum.

(±)-α-[{(1,1-Dimethylethoxy)carbonyl]amino}-2-methyl-δ-oxo-benzenepentanoic acid ethyl ester 185

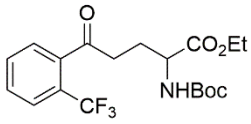


Magnesium turnings (0.182 g, 7.5 mmol) were stirred under a nitrogen atmosphere. Dry THF (1 mL) followed by 0.1 mL of 2-bromotoluene (0.90 mL, 7.5 mmol) added and the reaction initiated by direct heating. The remaining 2-bromotoluene was dissolved in dry THF (2 mL) and added dropwise maintaining reflux. Once addition was complete, the reaction was heated at reflux for 1.5 h. After cooling to 0 °C, 1-*tert*-butyl-2-ethyl-5-oxopyrrolidine-1,2-dicarboxylate (1.29 g, 5.0 mmol) in dry THF (5 mL) was added dropwise, then warmed to rt and stirred

overnight. The reaction was cooled to 0 °C and aq. saturated ammonium chloride (8 mL) added. The layers were separated, and the aqueous layer was extracted using diethyl ether (3 × 40 mL). The combined organic layers were washed with brine (40 mL), dried (Na_2SO_4), filtered, and solvent removed in vacuo. Purification via flash column chromatography on silica gel (20:80, ethyl acetate:hexane) afforded the product as a colourless oil (0.24 g, 14%); δ_H (400 MHz, $CDCl_3$) 1.30 (3H, t, *J* 7.2, C*H*$_3$), 1.44 [9H, s, C(C*H*$_3$)$_3$)], 2.01-2.18 (1H, m, C*H*H), 2.22-2.38 (1H, m, C*H*H), 2.52 (3H, s, ArC*H*$_3$), 2.99-3.08 (2H, m, C*H*H), 4.23 (2H, q, *J* 7.2, OC*H*$_2$), 4.32-4.42 (1H, m, NC*H*), 5.16 (1H, d, *J* 8.0, N*H*), 7.21-7.31 (2H, m, ArC*H*), 7.40 (1H, t, *J* 7.3, ArC*H*), 7.66 (1H, d, *J* 7.3, ArC*H*).

Due to product instability, this was then used directly in the next step without further characterisation. Selected data from impure ^{1}H NMR spectrum.

(±)-α-[{(1,1-Dimethylethoxy)carbonyl]amino}-2-(1,1,1-trifluoromethyl)-δ-oxo-benzenepentanoic acid ethyl ester 186

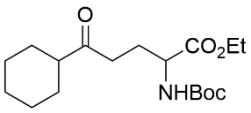


Isopropylmagnesium chloride lithium chloride solution (4.2 mL, 5.5 mmol, 1.3 M solution in THF) was cooled to −10 °C under argon. 2-Bromobenzotrifluoride (0.60 mL, 5.0 mmol) was dissolved in dry THF (5 mL) and added dropwise. Once addition was complete, the reaction was stirred at 0 °C for 2 h. In a separate flask, 1-*tert*-butyl-2-ethyl-5-oxopyrrolidine-1,2-dicarboxylate (1.29 g, 5.0 mmol) was dissolved in dry THF (5 mL) and cooled to 0 °C under argon. The freshly prepared Grignard reagent was added dropwise via syringe, and the reaction was stirred for 30 min before warming to rt and stirring overnight. After cooling to 0 °C, aq. saturated ammonium chloride (8 mL) was added, the layers separated, and the aqueous layer was extracted using diethyl ether (3 × 40 mL). The combined organic layers were washed

using brine (40 mL), dried (Na_2SO_4), filtered, and solvent removed under reduced pressure. Purification via flash column chromatography on silica gel (20:80 ethyl acetate:hexane) afforded the product as a colourless oil (0.51 g, 25%); δ_H (400 MHz, $CDCl_3$) 1.31 (3H, t, *J* 7.1, C*H*$_3$), 1.46 [9H, s, C(C*H*$_3$)$_3$)], 1.99-2.14 (1H, m, C*H*H), 2.28-2.38 (1H, m, C*H*H), 2.87-3.10 (2H, m, C*H*$_2$), 4.24 (2H, q, *J* 7.1, OC*H*$_2$), 4.30-4.44 (1H, m, NC*H*), 5.16 (1H, d, *J* 7.2, N*H*), 7.48 (1H, d, *J* 7.4, ArC*H*), 7.52-7.67 (2H, m, ArC*H*), 7.73 (1H, d, *J* 7.4, ArC*H*).

Due to product instability, this was then used directly in the next step without further characterisation. Selected data from impure ^{1}H NMR spectrum.

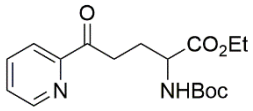
(±)-α-[{(1,1-Dimethylethoxy)carbonyl]amino}-δ-oxo-cyclohexanepentanoic acid ethyl ester 188



Magnesium turnings (0.182 g, 7.5 mmol) in dry THF (1 mL) were stirred under nitrogen. 0.5 mL of bromocyclohexane (1.22 g, 7.5 mmol) was added and the reaction activated by direct heating. The remaining bromocyclohexane was dissolved in dry THF (2 mL) and added dropwise. Once addition was complete, the reaction was heated at reflux for 1.5 h then cooled to 0 °C. 1-*tert*-Butyl-2-ethyl-5-oxopyrrolidine-1,2-dicarboxylate (1.29 g, 5.0 mmol) in dry THF (5 mL) was added dropwise. The reaction was warmed to rt, stirred overnight, quenched using aq. saturated ammonium chloride (8 mL) and stirred for 10 min. DCM (20 mL) added and the layers separated. The aqueous layer was extracted using DCM (3 × 20 mL). The combined organic layers were washed using brine (40 mL), dried (Na_2SO_4), filtered and solvent removed under reduced pressure. Purification via flash column chromatography on silica gel (15:85 to 40:60 ethyl acetate:hexane) afforded the product as a colourless oil (0.29 g, 17%); δ_H (400 MHz, $CDCl_3$) 1.30 (3H, t, *J* 7.2, C*H*$_3$), 1.46 [9H, s, C(C*H*$_3$)$_3$], 2.28-2.39 (2H, m, C*H*$_2$), 2.45-2.68 (2H, m, C*H*$_2$), 4.21 (2H, q, *J* 7.2, OC*H*$_2$), 5.07 (1H, d, *J* 7.8, NC*H*).

Due to product instability, this was then used directly in the next step without further characterisation. Selected data from impure ^{1}H NMR spectrum.

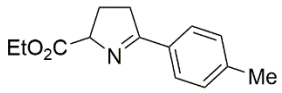
(±)-α-{[(1,1-Dimethylethoxy)carbonyl]amino}-δ-oxo-(2-pyridyl)pentanoic acid ethyl ester 189



Magnesium turnings (0.18 g, 7.5 mmol) were stirred in dry THF (1 mL) under a nitrogen atmosphere. 0.2 mL of 2-bromopyridine (1.19 g, 7.5 mmol) was added and the reaction was initiated by direct heating. The remaining 2-bromopyridine was dissolved in dry THF (2 mL) and added dropwise maintaining reflux. Once addition was complete, the reaction was heated at reflux for a further 1.5 h. After cooling to 0 °C, 1-*tert*-butyl-2-ethyl-5-oxopyrrolidine-1,2-dicarboxylate (1.29 g, 5.0 mmol) in dry THF (5 mL) was added dropwise. The reaction was warmed to rt and stirred overnight, then cooled to 0 °C and quenched by addition of aq. saturated ammonium chloride (8 mL). After stirring for 30 min, the layers were separated, and the aqueous layer extracted using diethyl ether (3 × 15 mL). The combined organic layers were washed using brine (20 mL), dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure. Purification via flash column chromatography on silica gel (20: 80 to 40:60 ethyl acetate:hexane) afforded the product as a yellow oil (0.25 g, 15%); δ_H (400 MHz, $CDCl_3$) 1.30 (3H, t, *J* 7.1, C*H*$_3$), 1.46 [9H, s, C(C*H*$_3$)$_3$], 2.03-2.16 (1H, m, C*H*H), 2.26-2.36 (1H, m, C*H*H), 3.25-3.48 (2H, m, C*H*$_2$), 4.21 (2H, q, *J* 7.1, OC*H*$_2$), 4.31-4.60 (1H, m, NC*H*), 5.26 (1H, d, *J* 7.6, N*H*), 7.35 (1H, dd, *J* 6.5, 5.0, ArC*H*), 7.79-7.93 (2H, m, ArC*H*), 8.05 (1H, d, *J* 7.8, ArC*H*).

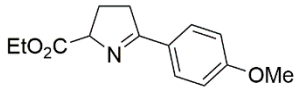
Due to product instability, this was then used directly in the next step without further characterisation. Selected data from impure ^{1}H NMR spectrum.

(±)-3,4-Dihydro-5-(4-methylphenyl)-2H-pyrrole-2-carboxylic acid ethyl ester 191



α-[{(-1,1-Dimethylethoxy)carbonyl]amino}-4-methyl-δ-oxo-benzenepentanoic acid ethyl ester (0.96 g, 2.7 mmol) was dissolved in DCM (20 mL) and cooled to 0 °C. Trifluoroacetic acid (8.0 mL, 104 mmol) was added dropwise. The reaction was warmed to rt and stirred for 2 h. An ice/water slurry (50 mL) was added and then solid $NaHCO_3$ added until neutral pH followed by stirring for a further 1 h. The layers were separated, and the aqueous layer extracted using DCM (3 × 20 mL). The combined organic layers were washed using brine (30 mL), dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure affording the product as a yellow oil (0.36 g, 57%), which was used directly in the next step. A small quantity was purified via flash column chromatography on silica gel (20:80 to 30:70 ethyl acetate:hexane) afforded the product as a yellow oil; ν_{max}/cm^{-1} (thin film, KBr plates) 2980, 1737, 1611; δ_H (400 MHz, $CDCl_3$) 1.33 (3H, t, *J* 7.1, C*H*$_3$), 2.18-2.43 (2H, m, C*H*$_2$), 2.40 (3H, s, C*H*$_3$), 2.98 (1H, dddd, *J* 16.9, 9.8, 7.0, 1.8, C*H*H), 3.16 (1H, dddd, *J* 16.9, 9.9, 5.5, 1.8, CH*H*), 4.26 (2H, q, *J* 7.1, OC*H*$_2$), 4.90 (1H, ddt, *J* 8.5, 6.6, 1.8, C*H*), 7.23 (2H, d, *J* 8.1, ArC*H*), 7.79 (2H, d, *J* 8.1, ArC*H*); δ_C (101 MHz, $CDCl_3$) 14.3 (*C*H$_3$), 21.5 (*C*H$_3$), 26.5 (*C*H$_2$), 35.4 (*C*H$_2$), 61.1 (O*C*H$_2$), 74.5 (N*C*H), 128.1 (2 × Ar*C*H), 129.2 (2 × Ar*C*H), 131.1 (Ar*C*), 141.3 (Ar*C*), 173.1 (*C*=N), 176.0 (*C*=O); *m/z* (ESI$^+$) 232.1342 [100%, $(M+H)^+$, $C_{14}H_{18}NO_2$ requires 232.1332].

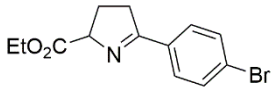
(±)-3,4-Dihydro-5-(4-methoxyphenyl)-2H-pyrrole-2-carboxylic acid ethyl ester 192



α-[{(-1,1-Dimethylethoxy)carbonyl]amino}-4-methoxy-δ-oxo-benzenepentanoic acid ethyl ester (0.85 g, 2.3 mmol) was dissolved in DCM (20 mL) and cooled to 0 °C. Trifluoroacetic acid (6.24 mL, 82 mmol) added dropwise. The reaction was warmed to rt and stirred for 1.5 h.

An ice/water slurry (50 mL) added and solid $NaHCO_3$ added until neutral pH. After stirring for 1 h, the layers were separated, and the aqueous layer extracted using DCM (3 × 20 mL). The combined organic layers were washed using brine (30 mL), dried (Na_2SO_4), filtered, and the solvent removed under reduced pressure affording the product as an orange oil (0.50 g, 88%) which was used directly in the next step without further purification. A small quantity was purified by flash column chromatography on silica gel (20:80 ethyl acetate:hexane) for characterisation affording the product as a yellow oil; ν_{max}/cm^{-1} (thin film, KBr plates) 2982, 1735, 1607, 1515; δ_H (400 MHz, $CDCl_3$) 1.32 (3H, t, *J* 7.1, C*H*$_3$), 2.22 (1H, ddt, *J* 13.1, 9.9, 6.6. C*H*H), 2.29-2.40 (1H, m, CH*H*), 2.96 (1H, dddd, *J* 17.0, 9.9, 6.6, 1.8, C*H*H), 3.14 (1H, dddd, *J* 17.0, 9.9, 5.5, 1.8, CH*H*), 3.86 (3H, s, OC*H*$_3$), 4.25 (2H, q, *J* 7.1, OC*H*$_2$), 4.88 (1H, ddt, *J* 8.4, 6.5, 1.8, NC*H*), 6.93 (2H, d, *J* 8.8, ArC*H*), 7.85 (2H, d, *J* 8.8, ArC*H*); δ_C (101 MHz, $CDCl_3$) 14.3 (*C*H$_3$), 26.5 (*C*H$_2$), 35.3 (*C*H$_2$), 55.4 (N*C*H), 61.1 (O*C*H$_2$), 74.4 (O*C*H$_3$), 113.7 (2 × Ar*C*H), 126.6 (Ar*C*), 129.8 (2 × Ar*C*H), 161.8 (Ar*C*O), 173.2 (*C*=N), 175.4 (*C*=O); *m/z* (ESI$^+$) 248.1292 [100%, $(M+H)^+$ $C_{14}H_{18}NO_3$ requires 248.1281].

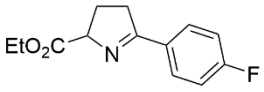
(±)-3,4-Dihydro-5-(4-bromophenyl)-2H-pyrrole-2-carboxylic acid ethyl ester 193



α-[{(-1,1-Dimethylethoxy)carbonyl]amino}-4-bromo-δ-oxo-benzenepentanoic acid ethyl ester (0.52 g, 1.3 mmol) was dissolved in DCM (15 mL) and cooled to 0 °C. Trifluoroacetic acid (3.5 mL, 45 mmol) was added dropwise. Once addition was complete, the reaction was warmed to rt and stirred for 3 h. An ice/water slurry (20 mL) was added, and the reaction neutralised using solid $NaHCO_3$. After stirring at rt for 1.5 h, the layers were separated, and the aqueous layer extracted using DCM (3 × 20 mL). The combined organic layers were washed using brine (30 mL), dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure affording the product as a colourless oil (0.30 g, 78%) which was used directly in the next step without further purification. A small quantity was purified by flash

column chromatography on silica gel (20% ethyl acetate: hexane) for characterisation affording the product as a colourless oil; ν_{max}/cm^{-1} (thin film, KBr plates) 2981, 1737, 1615, 1590; δ_H (400 MHz, $CDCl_3$) 1.33 (3H, t, *J* 7.1, C*H*$_3$), 2.26 (1H, ddt, *J* 13.2, 9.9, 6.7, C*H*H), 2.38 (1H, dddd, *J* 13.2, 9.7, 8.7, 5.4, C*H*H), 2.97 (1H, dddd, *J* 17.0, 9.9, 5.4, 1.9, C*H*H), 3.14 (1H, dddd, *J* 17.0, 9.7, 6.7, 1.9), 4.26 (2H, q, *J* 7.1, OC*H*$_2$), 4.9 (1H, ddt, *J* 8.7, 6.7, 1.9, NC*H*), 7.56 (2H, d, *J* 8.5, ArC*H*), 7.76 (2H, d, *J* 8.5, ArC*H*); δ_C (101 MHz, $CDCl_3$) 14.2 (*C*H$_3$), 26.5 (*C*H$_2$), 35.4 (*C*H$_2$), 61.2 (O*C*H$_2$), 74.7 (N*C*H), 125.6 (Ar*C*), 129.6 (2 × Ar*C*H), 131.7 (2 × Ar*C*H), 132.7 (Ar*C*), 172.8 (*C*=N), 175.1 (*C*=O); *m/z* (ESI$^+$) 296.0294 [100%, $(M+H)^+$ $C_{13}H_{15}{}^{79}BrNO_2$ requires 296.0281], 298.0275 [100%, $(M+H)^+$ $C_{13}H_{15}{}^{81}BrNO_2$ requires 298.0261].

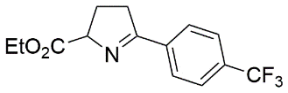
(±)-3,4-Dihydro-5-(4-fluorophenyl)-2H-pyrrole-2-carboxylic acid ethyl ester 194



α-[{(-1,1-Dimethylethoxy)carbonyl]amino}-δ-oxo-4-fluoro-benzenepentanoic acid ethyl ester (0.69 g, 2.0 mmol) was dissolved in DCM (8 mL) and cooled to 0 °C. Trifluoroacetic acid (5.7 mL, 74 mmol) was added dropwise. The reaction was warmed to rt and stirred for 2 h. An ice/water slurry (30 mL) was added followed by solid $NaHCO_3$ until neutral pH was obtained. The reaction was stirred for 1.5 h. The layers were separated, and the aqueous layer extracted using DCM (3 × 10 mL). The combined organic layers were washed using brine (20 mL), dried (Na_2SO_4), filtered and the solvent was removed under reduced pressure. Purification via flash column chromatography on silica gel (20:80 ethyl acetate:hexane) afforded the product as a colourless oil (0.30 g, 64%); ν_{max}/cm^{-1} (thin film, KBr plates) 3453, 3073, 2983, 1737, 1618, 1602, 1511; δ_H (400 MHz, $CDCl_3$) 1.32 (3H, t, *J* 7.1, C*H*$_3$), 2.25 (1H, ddt, *J* 13.2, 9.9, 6.8, C*H*H), 2.36 (1H, dddd, *J* 13.2, 9.8, 8.8, 5.4, C*H*H), 2.97 (1H, dddd, *J* 17.0, 9.8, 6.8, 1.9, C*H*H), 3.14 (1H, dddd, *J* 17.0, 9.9, 5.4, 1.9), 4.25 (2H, q, *J* 7.1, OC*H*$_2$), 4.85-4.94 (1H, m, NC*H*), 7.04-7.15 (2H, m, ArC*H*), 7.82-7.95 (2H, m, ArC*H*); δ_C (101 MHz, ^{4}*d*-MeOD) 13.1 (*C*H$_3$), 26.2 (*C*H$_2$), 35.2 (*C*H$_2$), 60.9 (O*C*H$_2$), 74.0 (N*C*H), 115.2 (d, $J_{C\text{-}F}$ 22.0, 2 × Ar*C*H), 129.8 (d, $J_{C\text{-}F}$ 3.0, Ar*C*), 130.3

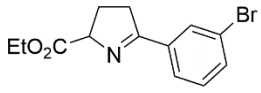
(d, $J_{C\text{-}F}$ 9.0, 2 × Ar*C*H), 164.7 (d, $J_{C\text{-}F}$ 250.5, Ar*C*F), 173.0 (*C*=N), 176.7 (*C*=O); δ_F (376 MHz, $CDCl_3$) -109.2 (ArC*F*);*m*/*z* (ESI$^+$) 236.1090 [100%, $(M+H)^+$ $C_{13}H_{15}FNO_2$ requires 236.1081].

(±)-3,4-Dihydro-5-[4-(1,1,1-trifluoromethyl)phenyl]-2H-pyrrole-2-carboxylic acid ethyl ester 195



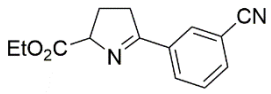
α-[{(1,1-Dimethylethoxy)carbonyl]amino}-4-(1,1,1-trifluoromethyl)-δ-oxo-benzenepentanoic acid ethyl ester (0.371 g, 0.92 mmol) was dissolved in DCM (3 mL) and cooled to 0 °C. Trifluoroacetic acid (2.67 mL, 35 mmol) was added dropwise and, once addition was complete, the reaction was warmed to rt and stirred for 2 h. An ice/water slurry (20 mL) was added. The reaction was neutralised using solid $NaHCO_3$ and stirred for a further 1.5 h. The layers were separated, and the aqueous layer extracted using DCM (3 × 20 mL). The combined organic layers were washed using brine (30 mL), dried (Na_2SO_4), filtered, and solvent removed under reduced pressure. Purification via flash column chromatography on silica gel (30:70 ethyl acetate:hexane) afforded the product as a yellow oil (0.19 g, 72%); ν_{max}/cm^{-1} (ATR, thin film) 2925, 1732, 1619; δ_H (400 MHz, $CDCl_3$) 1.33 (3H, t, *J* 7.1, C*H*$_3$), 2.29 (1H, ddt, *J* 13.3, 10.0, 6.8, C*H*H), 2.41 (1H, dddd, *J* 13.3, 9.8, 8.7, 5.4, C*H*H), 3.02 (1H, dddd, *J* 17.1, 9.8, 6.8, 2.0, C*H*H), 3.19 (1H, dddd, *J* 17.1, 10.0, 5.4, 2.0), 4.27 (2H, q, *J* 7.1, OC*H*$_2$), 4.95 (1H, ddt, *J* 8.7, 6.8, 2.0, NC*H*), 7.69 (2H, d, *J* 8.2, ArC*H*), 8.01 (2H, d, *J* 8.2, ArC*H*); δ_C (101 MHz, $CDCl_3$) 14.2 (*C*H$_3$), 26.4 (*C*H$_2$), 35.5 (*C*H$_2$), 61.3 (O*C*H$_2$), 74.9 (NC*H*), 123.9 (q, $J_{C\text{-}F}$ 272.5, *C*F$_3$), 125.4 (q, $J_{C\text{-}F}$ 3.5, 2 × Ar*C*H), 128.4 (2 × Ar*C*H), 132.5 (q, $J_{C\text{-}F}$ 32.5, Ar*C*CF$_3$), 137.0 (Ar*C*), 172.6 (*C*=N), 174.9 (*C*=O); δ_F (376 MHz, $CDCl_3$) -62.9 (C*F*$_3$); *m*/*z* (ESI$^+$) 286.1062 [100%, $(M+H)^+$ $C_{14}H_{15}F_3NO_2$ requires 286.1049].

(±)-3,4-Dihydro-5-(3-bromophenyl)-2H-pyrrole-2-carboxylic acid ethyl ester 196



α-[{(1,1-Dimethylethoxy)carbonyl]amino}-3-bromo-δ-oxo-benzenepentanoic acid ethyl ester (0.49 g, 1.2 mmol) was dissolved in DCM (10 mL) and cooled to 0 °C. Trifluoroacetic acid (3.3 mL, 43 mmol) was added dropwise. Once addition was complete, the reaction was warmed to rt and stirred for 2.5 h. An ice/water slurry (10 mL) was added. The reaction was neutralised using solid $NaHCO_3$ and stirred for a further 1.5 h. The layers were separated, and the aqueous layer extracted using DCM (3 × 20 mL). The combined organic layers were washed using brine (20 mL), dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure. Purification via flash column chromatography on silica gel (20:80 ethyl acetate:hexane) afforded the product as a colourless oil (0.27 g, 76%); ν_{max}/cm^{-1} (thin film, KBr plates) 2980, 1736, 1615, 1561; δ_H (400 MHz, $CDCl_3$) 1.33 (3H, t, *J* 7.1, C*H*$_3$), 2.26 (1H, ddt, *J* 13.1, 9.9, 6.9, C*H*H), 2.38 (1H, dddd, *J* 13.2, 9.8, 8.7, 5.4, C*H*H), 2.97 (1H, dddd, *J* 17.0, 9.8, 6.9, 2.0, C*H*H), 3.14 (1H, dddd, *J* 17.0, 9.9, 5.4, 2.0), 4.26 (2H, q, *J* 7.1, OC*H*$_2$), 4.91 (1H, ddt, *J* 8.7, 6.9, 2.0, NC*H*), 7.30 (1H, t, *J* 7.9, ArC*H*), 7.55-7.62 (1H, m, ArC*H*), 7.76-7.83 (1H, m, ArC*H*), 8.03-8.12 (1H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 14.2 (*C*H$_3$), 26.4 (*C*H$_2$), 35.4 (*C*H$_2$), 61.3 (O*C*H$_2$), 74.6 (N*C*H), 122.7 (Ar*C*), 126.7 (Ar*C*H), 130.0 (Ar*C*H), 131.0 (Ar*C*H), 133.9 (Ar*C*H), 135.7 (Ar*C*), 172.7 (*C*=N), 174.9 (*C*=O); *m*/*z* (ESI$^+$) 296.0295 [100%, $(M^+H)^+$ $C_{13}H_{15}{}^{79}BrNO_2$ requires 296.0281].

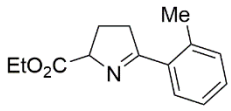
(±)-3,4-Dihydro-5-(3-cyanophenyl)-2H-pyrrole-2-carboxylic acid ethyl ester 197



α-[{(1,1-Dimethylethoxy)carbonyl]amino}-3-cyano-δ-oxo-benzenepentanoic acid ethyl ester (70 mg, 0.20 mmol) was dissolved in DCM (2 mL) and cooled to 0 °C. Trifluoroacetic acid

(0.56 mL, 7.4 mmol) was added dropwise. Once addition was complete, the reaction was warmed to rt and stirred for 2 h. An ice/water slurry (10 mL) was added. The reaction was neutralised using solid $NaHCO_3$ and stirred for 1.5 h. The layers were separated, and the aqueous layer extracted using DCM (3 × 15 mL). The combined organic layers were washed using brine (20 mL), dried (Na_2SO_4), filtered and solvent removed under reduced pressure. Purification via flash column chromatography on silica gel (40:60 ethyl acetate:hexane) afforded the product as a colourless oil (28 mg, 58%); ν_{max}/cm^{-1} (ATR, thin film) 2982, 2231, 1732, 1618; δ_H (400 MHz, $CDCl_3$) 1.33 (3H, t, *J* 7.1, C*H*$_3$), 2.29 (1H, ddt, *J* 13.3, 10.0, 6.7, C*H*H), 2.41 (1H, dddd, *J* 13.3, 9.8, 8.7, 5.4, C*H*H), 2.99 (1H, dddd, *J* 17.1, 9.8, 6.7, 2.0, C*H*H), 3.16 (1H, dddd, *J* 17.1, 10.0, 5.4, 2.0, C*H*H), 4.26 (2H, q, *J* 7.1, OC*H*$_2$), 4.94 (1H, ddt, *J* 8.7, 6.7, 2.0, NC*H*), 7.55 (1H, t, *J* 7.8, ArC*H*), 7.74 (1H, dt, *J* 7.8, ArC*H*), 8.12 (1H, dt, *J* 7.8, 1.4, ArC*H*), 8.18 (1H, t, *J* 1.4, ArC*H*); δ_C (101 MHz, $CDCl_3$) 14.2 (*C*H$_3$), 26.4 (*C*H$_2$), 35.4 (*C*H$_2$), 61.4 (O*C*H$_2$), 74.8 (N*C*H), 112.8 (*C*N), 118.3 (Ar*C*), 129.4 (Ar*C*H), 131.4 (Ar*C*H), 132.1 (Ar*C*H), 134.0 (Ar*C*H), 135.0 (Ar*C*), 172.5 (*C*=N), 174.1 (*C*=O); *m*/*z* (ESI$^+$) 243.1134 [100%, $(M+H)^+$ $C_{14}H_{15}N_2O_2$ requires 243.1128].

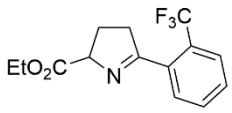
(±)-3,4-Dihydro-5-(2-methylphenyl)-2H-pyrrole-2-carboxylic acid ethyl ester 198



α-[{(1,1-Dimethylethoxy)carbonyl]amino}-2-methyl-δ-oxo-benzenepentanoic acid ethyl ester (0.213 g, 0.6 mmol) was dissolved in DCM (3 mL) and cooled to 0°C. Trifluoroacetic acid (1.8 mL, 23 mmol) was added dropwise. Once addition was complete, the reaction was warmed to rt and stirred for 2 h. An ice/water slurry (20 mL) was added, and the reaction neutralised using solid $NaHCO_3$. The reaction was stirred for 1.5 h. The layers were separated, and the aqueous layer extracted using DCM (3 × 10 mL). The combined organic layers were washed using brine (20 mL), dried (Na_2SO_4), filtered and the solvent was removed under

reduced pressure. Purification via flash column chromatography on silica gel (20:80 ethyl acetate:hexane) afforded the product as a yellow oil (51 mg, 37%); ν_{max}/cm^{-1} (thin film, KBr plates) 3453, 3061, 2980, 1736, 1613; δ_H (400 MHz, $CDCl_3$) 1.33 (3H, t, *J* 7.1, C*H*$_3$), 2.21 (1H, ddt, *J* 13.1, 9.6, 6.4, C*H*H), 2.29-2.40 (1H, m, C*H*H), 2.55 (3H, s, C*H*$_3$), 2.94-3.17 (2H, m, C*H*H), 4.26 (2H, q, *J* 7.1, OC*H*$_2$), 4.97 (1H, ddt, *J* 8.2, 6.4, 1.8, NC*H*), 7.19-7.36 (3H, m, ArC*H*), 7.46 (1H, dd, *J* 7.6, 1.2, ArC*H*); δ_C (101 MHz, $CDCl_3$) 14.2 (*C*H$_3$), 21.4 (*C*H$_3$), 26.5 (*C*H$_2$), 38.9 (*C*H$_2$), 61.1 (O*C*H$_2$), 75.1 (N*C*H), 125.6 (Ar*C*H), 128.9 (Ar*C*H), 129.5 (Ar*C*H), 131.3 (Ar*C*H), 134.3 (Ar*C*), 137.5 (Ar*C*), 173.1 (*C*=N), 178.1 (*C*=O); *m/z* (ESI$^+$) 232.1340 [100%, $(M+H)^+$ $C_{14}H_{18}NO_2$ requires 232.1332].

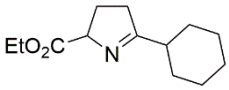
(±)-3,4-Dihydro-5-[2-(1,1,1-trifluoromethyl)phenyl]-2H-pyrrole-2-carboxylic acid ethyl ester 199



α-[{(1,1-Dimethylethoxy)carbonyl]amino}-2-(1,1,1-trifluoromethyl)-δ-oxo-benzenepentanoic acid ethyl ester (0.51 g, 1.3 mmol) was dissolved in DCM (6 mL) and cooled to 0 °C. Trifluoroacetic acid (3.7 mL, 48 mmol) was added dropwise. After warming to rt, the reaction was stirred for 2 h. An ice/water slurry (20 mL) was added, and the mixture neutralised using solid sodium hydrogen carbonate. The layers were separated, and the aqueous layer extracted using DCM (3 × 20 mL). The combined organic layers were washed with brine (30 mL), dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure. Purification via flash column chromatography on silica gel (30:70, ethyl acetate:hexane) afforded the product as a pale-pink oil (0.27 g, 72%); ν_{max}/cm^{-1} (ATR, thin film) 2985, 1735; δ_H (400 MHz, $CDCl_3$) 1.34 (3H, t, *J* 7.1, C*H*$_3$), 2.25-2.46 (2H, m, C*H*H), 2.90-3.13 (2H, m, C*H*H), 4.27 (2H, q, *J* 7.1, OC*H*$_2$), 4.93 (1H, ddt, *J* 8.5, 6.4, 2.0, NC*H*), 7.48-7.53 (2H, m, ArC*H*), 7.56-7.63 (1H, m, ArC*H*), 7.69-7.75 (1H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 14.2 (*C*H$_3$), 27.0 (*C*H$_2$),

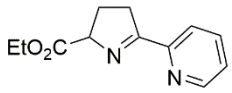
40.3 (q, $J_{C\text{-}F}$ 2.5, *C*H_2), 61.2 (O*C*H_2), 75.1 (N*C*H), 124.0 (q, $J_{C\text{-}F}$ 274.0, *C*F_3), 126.3 (q, $J_{C\text{-}F}$ 5.0, Ar*C*H), 129.2 (Ar*C*H), 129.4 (Ar*C*H), 131.8 (Ar*C*H), 135.3 (Ar*C*), 172.3 (*C*=N), 177.4 (*C*=O); δ_F (376 MHz, $CDCl_3$) -58.3; *m*/*z* (ESI$^+$) 286.1058 [100%, $(M+H)^+$, $C_{14}H_{15}NO_2F_3$ requires 286.1049].

(±)-3,4-Dihydro-5-cyclohexyl-2H-pyrrole-2-carboxylic acid ethyl ester 200



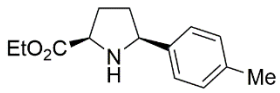
α-[{(-1,1-Dimethylethoxy)carbonyl]amino}-δ-oxo-cyclohexyl-pentanoic acid ethyl ester (0.29 g, 0.8 mmol) was dissolved in DCM (10 mL) and cooled to 0 °C. Trifluoroacetic acid (2.3 mL, 30 mmol) was added dropwise. The reaction was warmed to rt and stirred for 3 h. An ice/water slurry (20 mL) was added followed by addition of solid $NaHCO_3$ until neutralised, then stirred at rt for 2 h. The layers were separated, and the aqueous layer was extracted using DCM (3 × 10 mL). The combined organic layers were washed using brine (30 mL), dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure. Purification via flash column chromatography on silica gel (20:80 to 30:70 ethyl acetate:hexane) afforded the product as a pale-yellow oil (0.08 g, 45%); ν_{max}/cm^{-1} (thin film, KBr plates) 2979, 2929, 2854, 1739, 1634; δ_H (400 MHz, $CDCl_3$) 1.14-1.41 (5H, m, C*H*H), 1.26 (3H, t, *J* 7.1, C*H*$_3$), 1.59-1.91 (5H, m, C*H*H), 1.99 (1H, ddt, *J* 13.2, 9.8, 6.5, C*H*H), 2.07-2.18 (1H, m, C*H*H), 2.35-2.54 (2H, m, C*H*H), 2.65 (1H, dddd, *J* 17.5, 9.9, 5.4, 1.9, C*H*H), 4.17 (2H, q, *J* 7.1, OC*H*$_2$), 4.62 (1H, t, *J* 7.5, NC*H*); δ_C (101 MHz, $CDCl_3$) 14.2 (*C*H_3), 25.9 (*C*H_2), 26.0 (*C*H_2), 26.1 (*C*H_2), 30.3 (*C*H_2), 30.4 (*C*H_2), 35.3 (*C*H_2), 42.5 (*C*H), 60.9 (O*C*H_2), 73.7 (N*C*H), 173.2 (C=N), 185.6 (C=O); *m*/*z* (ESI$^+$) 224.1651 [100%, $(M+H)^+$ $C_{13}H_{22}NO_2$ requires 224.1645].

(±)-3,4-Dihydro-5-(2-pyridyl)-2H-pyrrole-2-carboxylic acid ethyl ester 201



α-[{(1,1-Dimethylethoxy)carbonyl]amino}-δ-oxo-2-pyridyl-pentanoic acid ethyl ester (0.25 g, 0.7 mmol) was dissolved in DCM (3 mL) and cooled to 0 °C. Trifluoroacetic acid (2.2 mL, 28 mmol) was added dropwise. Once addition was complete, the reaction was warmed to rt stirred for 2 h. An ice/water slurry (10 mL) was added followed by addition of solid $NaHCO_3$ until neutralised and left to stir for 1 h. The layers were separated, and the aqueous layer was extracted using DCM (3 × 10 mL). The combined organic layers were washed using brine (20 mL), dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure. Purification via flash column chromatography on silica gel (75:25 ethyl acetate:hexane) afforded the product as a pale-yellow oil (39 mg, 26%); ν_{max}/cm^{-1} (thin film, KBr plates) 2981, 1736, 1620, 1586, 1567; δ_H (400 MHz, $CDCl_3$) 1.33 (3H, t, *J* 7.1, C*H*$_3$), 2.24 (1H, dddd, *J* 13.2, 10.0, 6.9, 6.9, C*H*H), 2.39 (1H, dddd, *J* 13.2, 9.6, 8.8, 5.2, C*H*H), 3.09-3.22 (1H, m, C*H*H), 3.35 (1H, dddd, *J* 18.0, 10.0, 5.2, 2.3, C*H*H), 4.27 (2H, q, *J* 7.1, OC*H*$_2$), 4.97 (1H, ddt, *J* 8.8, 6.9, 2.3, NC*H*), 7.36 (1H, ddd, *J* 7.7, 4.9, 1.0, ArC*H*), 7.77 (1H, td, *J* 7.7, 1.7, ArC*H*), 8.23 (1H, d, *J* 7.7, Ar*C*H), 8.64-8.68 (1H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 14.3 (*C*H$_3$), 26.4 (*C*H$_2$), 35.5 (*C*H$_2$), 61.2 (O*C*H$_2$), 75.1 (N*C*H), 122.5 (Ar*C*H), 125.2 (Ar*C*H), 136.4 (Ar*C*H), 149.1 (Ar*C*H), 152.6 (Ar*C*), 172.8 (C=N), 177.9 (C=O); *m*/*z* (ESI$^+$) 219.1137 [100%, $(M+H)^+$ $C_{12}H_{15}N_2O_2$ requires 219.1128].

(±)-*cis*-5-(4-Methylphenyl)-proline ethyl ester 202[110]

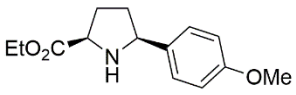


3,4-Dihydro-5-(4-methylphenyl)-2H-pyrrole-2-carboxylic acid ethyl ester (0.116 g, 0.50 mmol) was dissolved in dry DCM (1 mL) under argon and cooled to −18 °C. Trichlorosilane (0.10 mL,

1.00 mmol) was added dropwise. The reaction was stirred for 4 h. Aq. 1 M HCl (1 mL) was added followed by addition of aq. 1 M NaOH until neutral pH was maintained after 5 min of stirring. The layers were separated, and the aqueous layer was extracted using DCM (3 × 15 mL). The combined organic layers were washed using brine (20 mL), dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure. Purification via flash column chromatography on silica gel (30:70 ethyl acetate;hexane) afforded the product as a pale-yellow oil (38 mg, 33%); δ_H (400 MHz, $CDCl_3$, >99:1 dr) 1.33 (3H, t, *J* 7.1, C*H*$_3$), 1.65-1.79 (1H, m, C*H*H), 2.08-2.32 (3H, m, C*H*H), 2.36 (3H, s, C*H*$_3$), 2.44 (1H, bs, N*H*), 3.94 (1H, dd, *J* 8.7, 4.7, NC*H*^{A}), 4.16-4.30 (3H, m, OC*H*$_2$ and NC*H*^{B}), 7.17 (2H, d, *J* 7.8, ArC*H*), 7.36 (2H, d, *J* 7.8, ArC*H*); δ_C (101 MHz, $CDCl_3$) 14.3 (*C*H$_3$), 21.1 (*C*H$_3$), 30.8 (*C*H$_2$), 34.1 (*C*H$_2$), 60.2 (N*C*H), 61.2 (O*C*H$_2$), 63.5 (N*C*H), 126.8 (2 × Ar*C*H), 129.2 (2 × Ar*C*H), 137.0 (Ar*C*), 139.9 (Ar*C*), 175.1 (*C*=O).

Data are in accordance with the literature.

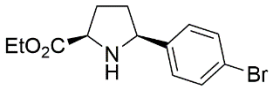
(±)-*cis*-5-(4-Methoxyphenyl)-proline ethyl ester 203



3,4-Dihydro-5-(4-methoxyphenyl)-2H-pyrrole-2-carboxylic acid ethyl ester (0.124 g, 0.50 mmol) was dissolved in dry DCM (1 mL) with DMF (0.01 mL, 0.05 mmol) under argon and cooled to −18 °C. Trichlorosilane (0.1 mL, 1.00 mmol) was added dropwise and the reaction was stirred at −18 °C for 4 h. Aq. 1 M HCl (1 mL) was added and the mixture was warmed to rt. Aq. 1 M NaOH was added until neutral pH was maintained after 5 min of stirring. The layers were separated, and the aqueous layer was extracted using DCM (3 × 15 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure. Purification via flash column chromatography on silica gel (40:60 ethyl acetate:hexane) afforded the product as a colourless oil (10 mg, 8%); ν_{max}/cm^{-1}

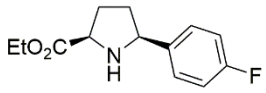
(thin film, KBr plates); δ_H (400 MHz, $CDCl_3$) 1.33 (3H, t, *J* 7.1, C*H*$_3$), 1.71 (1H, ddd, *J* 9.6, 7.7, 4.8, C*H*H), 2.02 (1H, bs, N*H*), 2.08-2.28 (3H, m, C*H*H), 3.82 (3H, s, OC*H*$_3$), 3.91 (1H, dd, *J* 8.9, 4.8, NC*H*^{A}), 4.17 (1H, dd, *J* 9.5, 5.8, NC*H*^{B}), 4.25 (2H, q, *J* 7.1, OC*H*$_2$), 6.88-6.92 (2H, m, ArC*H*), 7.37-7.41 (2H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 14.3 (*C*H$_3$), 30.8 (*C*H$_2$), 34.2 (*C*H$_2$), 55.3 (O*C*H$_3$), 60.1 (N*C*H), 61.1 (O*C*H$_2$), 63.2 (N*C*H), 113.7 (2 × Ar*C*H), 127.9 (2 × Ar*C*H), 135.3 (Ar*C*), 158.8 (Ar*C*), 175.3 (*C*=O); *m*/*z* (ESI$^+$) 250.1449 [100%, $(M+H)^+$, $C_{14}H_{20}NO_3$ requires 250.1438].

(±)-*cis*-5-(4-Bromophenyl)-proline ethyl ester 204



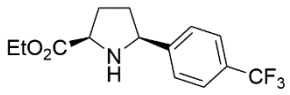
3,4-Dihydro-5-(4-bromophenyl)-2H-pyrrole-2-carboxylic acid ethyl ester (0.102 g, 0.34 mmol) was dissolved in dry DCM (1 mL) with DMF (0.01 mL, 0.034 mmol) under argon and cooled to −18 °C. Trichlorosilane (0.07 mL, 0.68 mmol) was added dropwise and the reaction was stirred at −18 °C for 4 h. Aq. 1 M HCl (1 mL) was added and the mixture was warmed to rt. Aq. 1 M NaOH was added until neutral pH was maintained after 5 min of stirring. The layers were separated, and the aqueous layer was extracted using DCM (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure. Purification via flash column chromatography on silica gel (40:60, ethyl acetate:hexane) afforded the product as a colourless oil (39 mg, 38%); ν_{max}/cm^{-1} (thin film, KBr plates) 3376, 2978, 2941, 2908, 2873, 1732, ;δ_H (400 MHz, $CDCl_3$) 1.32 (3H, t, *J* 7.1, C*H*$_3$), 1.61-1.80 (1H, m, C*H*H), 2.05-2.30 (4H, m, C*H*H and N*H*), 3.93 (1H, dd, *J* 8.6, 4.8, NC*H*^{A}), 4.16-4.29 (3H, m, OC*H*$_2$ and NC*H*^{B}), 7.33-7.38 (2H, m, ArC*H*), 7.44-7.49 (2H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 14.3 (*C*H$_3$), 30.5 (*C*H$_2$), 34.4 (*C*H$_2$), 60.1 (*C*H), 61.1 (O*C*H$_2$), 62.9 (*C*H), 120.9 (Ar*C*), 128.5 (2 × Ar*C*H), 131.5 (2 × Ar*C*H), 142.7 (Ar*C*), 175.2 (*C*=O); *m*/*z* (ESI$^+$) 298.0447 [100%, $(M+H)^+$, $C_{13}H_{17}{}^{79}BrNO_2$ requires 298.0437].

(±)-*cis*-5-(4-Fluorophenyl)-proline ethyl ester 205



3,4-Dihydro-5-(4-fluorophenyl)-2H-pyrrole-2-carboxylic acid ethyl ester (0.118 g, 0.50 mmol) was dissolved in dry DCM (1 mL) with DMF (0.01 mL, 0.05 mmol) under argon and cooled to −18 °C. Trichlorosilane (0.1 mL, 1.00 mmol) was added dropwise and the reaction was stirred at −18 °C for 4 h. Aq. 1 M HCl (1 mL) was added and the mixture was warmed to rt. Aq. 1 M NaOH was added until neutral pH was maintained after 5 min of stirring. The layers were separated, and the aqueous layer was extracted using DCM (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure. Purification via flash column chromatography on silica gel (40:60, ethyl acetate:hexane) afforded the product as a colourless oil (37 mg, 31%); v_{max}/cm^{-1} (thin film, KBr plates) 3364, 2979, 1729, 1609; δ_H (400 MHz, $CDCl_3$) 1.32 (3H, t, *J* 7.1, C*H*$_3$), 1.63-1.76 (1H, m, C*H*H), 2.07-2.35 (3H, m, C*H*H), 3.93 (1H, dd, *J* 8.7, 4.7, NC*H*^{A}), 4.21 (1H, dd, *J* 9.2, 5.8, NC*H*^{B}), 4.25 (2H, q, *J* 7.1, OC*H*$_2$), 6.98-7.08 (2H, m, ArC*H*), 7.39-7.48 (2H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 14.3 (*C*H$_3$), 30.6 (*C*H$_2$), 34.4 (*C*H$_2$), 60.1 (NCH), 61.01 (O*C*H$_2$), 62.9 (N*C*H), 115.2 (d, $J_{C\text{-}F}$ 21.0, 2 × Ar*C*H), 128.3 (d, $J_{C\text{-}F}$ 8.0, 2 × ArC*H*), 139.2 (d, $J_{C\text{-}F}$ 3.0, Ar*C*), 162.0 (d, $J_{C\text{-}F}$ 245.0, Ar*C*F), 175.3 (*C*=O); δ_F (376 MHz, $CDCl_3$) -115.9 (ArC*F*); *m*/*z* (ESI^+) 238.1247 [100%, $(M+H)^+$ $C_{13}H_{17}FNO_2$ requires 238.1238].

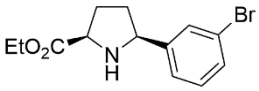
(±)-*cis*-5-[4-(1,1,1-Trifluoromethyl)phenyl]-proline ethyl ester 206



3,4-Dihydro-5-[4-(1,1,1-trifluoromethyl)phenyl]-2H-pyrrole-2-carboxylic acid ethyl ester (0.143 g, 0.50 mmol) was dissolved in dry DCM (1 mL) with DMF (0.01 mL, 0.05 mmol) under argon and cooled to −18 °C. Trichlorosilane (0.1 mL, 1.00 mmol) was added dropwise and the

reaction was stirred at −18 °C for 4 h. Aq. 1 M HCl (1 mL) was added and the mixture was warmed to rt. Aq. 1 M NaOH was added until neutral pH was maintained after 5 min of stirring. The layers were separated, and the aqueous layer was extracted using DCM (3 × 15 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure. Purification via flash column chromatography on silica gel (30:70 ethyl acetate:hexane) afforded the product as a colourless oil (41 mg, 29%); ν_{max}/cm^{-1} (ATR, thin film) 3419 (NH), 2984, 1730, 1619; δ_H (400 MHz, $CDCl_3$) 1.33 (3H, t, *J* 7.1, C*H*$_3$), 1.67-1.79 (1H, m, C*H*H), 2.07-2.19 (1H, m, C*H*H), 2.23 (2H, tdd, *J* 9.7, 8.4, 5.8, C*H*H), 3.97 (1H, dd, *J* 8.4, 5.2, NC*H*^{A}), 4.25 (2H, q, *J* 7.1, OC*H*$_2$), 4.31 (1H, dd, *J* 9.1, 5.8, NC*H*^{B}), 7.60 (4H, s, ArC*H*); δ_C (101 MHz, $CDCl_3$) 14.3 (*C*H$_3$), 30.4 (*C*H$_2$), 34.5 (*C*H$_2$), 60.1 (N*C*H), 61.1 (O*C*H$_2$), 62.9 (N*C*H), 125.4 (q, $J_{C\text{-}F}$ 3.7, 2 × Ar*C*H), 125.6 (Ar*C*), 127.1 (2 × Ar*C*H), 147.9 (Ar*C*), 175.1 (*C*=O); δ_F (376 MHz, $CDCl_3$) -62.4; *m*/*z* (ESI$^+$) 288.1212 [100%, $(M+H)^+$, $C_{14}H_{17}NO_2F_3$ requires 288.1211].

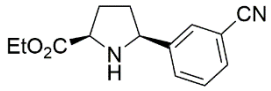
(±)-*cis*-5-(3-Bromophenyl)-proline ethyl ester 207



3,4-Dihydro-5-(3-bromophenyl)-2H-pyrrole-2-carboxylic acid ethyl ester (0.148 g, 0.50 mmol) was dissolved in dry DCM (1 mL) with DMF (0.02 mL, 0.10 mmol) under argon and cooled to −18 °C. Trichlorosilane (0.10 mL, 1.00 mmol) was added dropwise and the reaction was stirred at −18 °C for 4 h. Aq. 1 M HCl (1 mL) was added and the mixture was warmed to rt. Aq. 1 M NaOH was added until neutral pH was maintained after 5 min of stirring. The layers were separated, and the aqueous layer was extracted using DCM (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure. Purification via flash column chromatography on silica gel (20:80 ethyl acetate:hexane) afforded the product as a colourless oil (12 mg, 8%); ν_{max}/cm^{-1}

(thin film, KBr plates) 3371, 2978, 1730; δ_H (400 MHz, $CDCl_3$) 1.33 (3H, t, *J* 7.1, C*H*$_3$), 1.71 (1H, tdd, *J* 10.0, 8.9, 6.4, C*H*H), 2.04-2.28 (3H, m, C*H*H), 2.34 (1H, s, N*H*), 3.93 (1H, dd *J* 8.3, 5.2, NC*H*^{A}), 4.16-4.30 (3H, m, OC*H*$_2$ and NC*H*^{B}), 7.21 (1H, t, *J* 7.8, ArC*H*), 7.35-7.44 (2H, m, ArC*H*), 7.63 (1H, t, *J* 1.7, ArC*H*); δ_C (101 MHz, $CDCl_3$) 14.3 (*C*H$_3$), 30.3 (*C*H$_2$), 34.3 (*C*H$_2$), 60.1 (*C*H), 61.1 (O*C*H$_2$), 62.9 (*C*H), 122.6 (Ar*C*), 125.4 (Ar*C*H), 129.9 (ArC*H*), 130.0 (Ar*C*H), 130.2 (Ar*C*H), 146.3 (Ar*C*), 175.0 (*C*=O); *m*/*z* (ESI$^+$) 298.0439 [100%, $(M+H)^+$, $C_{13}H_{17}{}^{79}BrNO_2$ requires 298.0437].

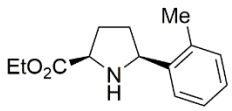
(±)-*cis*-5-(3-Cyanophenyl)-proline ethyl ester 208



3,4-Dihydro-5-(3-cyanophenyl)-2H-pyrrole-2-carboxylic acid ethyl ester (0.121 g, 0.50 mmol) was dissolved in dry DCM (1 mL) with DMF (0.01 mL, 0.05 mmol) under argon and cooled to −18 °C. Trichlorosilane (0.1 mL, 1.00 mmol) was added dropwise and the reaction was stirred at −18 °C for 4 h. Aq. 1 M HCl (1 mL) was added and the mixture was warmed to rt. Aq. 1 M NaOH was added until neutral pH was maintained after 5 minutes of stirring. The layers were separated, and the aqueous layer was extracted using DCM (3 × 15 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure. Purification via flash column chromatography on silica gel (40:60 ethyl acetate:hexane) afforded the product as a white solid (75 mg, 61%); Mpt 60-62 °C; ν_{max}/cm^{-1} (thin film, KBr plates) 3428, 3368, 2992, 2976, 2829, 2228, 1735; δ_H (400 MHz, $CDCl_3$) 1.34 (3H, t, *J* 7.1, C*H*$_3$), 1.72 (1H, qdd, *J* 9.9, 7.6, 4.1, C*H*H), 2.10-2.29 (3H, m, C*H*H), 3.98 (1H, dd, *J* 8.4, 5.4, NC*H*^{A}), 4.21-4.35 (3H, m, OC*H*$_2$ and NC*H*^{B}), 7.45 (1H, t, *J* 7.7, ArC*H*), 7.56 (1H, dt, *J* 7.7, 1.3, ArC*H*), 7.75 (1H, d, *J* 7.7, ArC*H*), 7.80 (1H, s, ArC*H*); δ_C (101 MHz, $CDCl_3$) 14.3 (*C*H$_3$), 30.2 (*C*H$_2$), 34.5 (*C*H$_2$), 60.0 (N*C*H), 61.2 (O*C*H$_2$), 62.5 (N*C*H), 112.4 (Ar*C*),

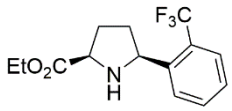
119.0 (Ar*C*H), 130.6 (Ar*C*H), 130.8 (Ar*C*H), 131.4 (Ar*C*H), 145.7 (*C*≡N), 174.9 (*C*=O); *m/z* (ESI$^+$) 245.1291 [100%, (M+H)$^+$ $C_{14}H_{17}N_2O_2$ requires 245.1285].

(±)-*cis*-5-(2-Methylphenyl)-proline ethyl ester 209



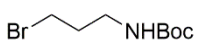
3,4-Dihydro-5-(2-methylphenyl)-2H-pyrrole-2-carboxylic acid ethyl ester (0.071 g, 0.31 mmol) was dissolved in dry DCM (0.5 mL) with DMF (0.01 mL, 0.03 mmol) under argon and cooled to −18 °C. Trichlorosilane (0.06 mL, 0.61 mmol) was added dropwise, and the reaction was stirred at −18 °C for 4 h. Aq. 1 M HCl (1 mL) was added and the mixture was warmed to rt. Aq. 1 M NaOH was added until neutral pH was maintained after 5 min of stirring. The layers were separated, and the aqueous layer was extracted using DCM (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure. Purification via flash column chromatography on silica gel (25:75 ethyl acetate:hexane) afforded the product as a pale-yellow oil (17 mg, 17%); ν_{max}/cm^{-1} (thin film) 3419 (NH), 2979, 2873, 1730, 1641; δ_H (400 MHz, $CDCl_3$) 1.34 (3H, t, *J* 7.1, C*H*$_3$), 1.61-1.77 (1H, m, C*H*H), 2.05-2.32 (4H, m, C*H*H and N*H*), 2.40 (3H, s, C*H*$_3$), 3.94 (1H, dd, *J* 8.6, 5.9, NC*H*^{A}), 4.26 (2H, q, *J* 7.1, OC*H*$_2$), 4.45 (1H, dd, *J* 8.6, 5.9, NC*H*^{B}), 7.12-7.24 (2H, m, ArC*H*), 7.20-7.30 (1H, m, ArC*H*), 7.64-7.71 (1H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 14.3 (*C*H$_3$), 19.5 (*C*H$_3$), 30.5 (*C*H$_2$), 32.9 (*C*H$_2$), 59.4 (*C*H), 60.1 (*C*H), 61.0 (O*C*H$_2$), 125.3 (Ar*C*H), 126.3 (Ar*C*H), 126.8 (Ar*C*H), 130.2 (Ar*C*H), 135.6 (Ar*C*), 141.6 (Ar*C*), 175.2 (*C*=O); *m/z* (ESI) 234.1494 [100%, (M+H)$^+$, $C_{14}H_{20}NO_2$ requires 234.1489].

(±)-*cis*-5-[2-(1,1,1-Trifluoromethyl)phenyl]-proline ethyl ester 210



3,4-Dihydro-5-[4-(1,1,1-trifluoromethyl)phenyl]-2H-pyrrole-2-carboxylic acid ethyl ester (0.143 g, 0.50 mmol) was dissolved in dry DCM (1 mL) with DMF (0.01 mL, 0.05 mmol) under argon and cooled to −18 °C. Trichlorosilane (0.1 mL, 1.00 mmol) was added dropwise and the reaction was stirred at −18 °C for 4 h. Aq. 1M HCl (1 mL) was added and the mixture was warmed to rt. Aq. 1 M NaOH was added until neutral pH was maintained after 5 min of stirring. The layers were separated, and the aqueous layer was extracted using DCM (3 × 15 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure. Purification via flash column chromatography on silica gel (30:70 ethyl acetate:hexane) afforded the product as a colourless oil (16 mg, 9%); ν_{max}/cm^{-1} (ATR, thin film) 2983, 1732; δ_H (400 MHz, $CDCl_3$) 1.34 (3H, t, *J* 7.1, C*H*$_3$), 1.64-1.79 (1H, m, C*H*H), 1.91 (1H, bs, N*H*), 2.12-2.30 (3H, m, C*H*H), 3.99 (1H, dd, *J* 8.1, 5.6, NC*H*^{A}), 4.27 (2H, q, *J* 7.1, OC*H*$_2$), 4.61-4.74 (1H, m, NC*H*^{B}), 7.34 (1H, t, *J* 7.7, ArC*H*), 7.52-7.66 (2H, m, ArC*H*), 8.14 (1H, d, *J* 7.7, ArC*H*); δ_C (101 MHz, $CDCl_3$) 14.3 (*C*H$_3$), 30.2 (*C*H$_2$), 35.2 (*C*H$_2$), 58.1 (N*C*H), 59.8 (N*C*H), 60.9 (O*C*H$_2$), 124.6 (q, $J_{C\text{-}F}$ 274.0, Ar*C*), 125.3 (q, $J_{C\text{-}F}$ 6.0, ArC*H*), 126.8 (Ar*C*H), 128.4 (Ar*C*H), 132.3 (Ar*C*H), 143.7 (Ar*C*), 175.1 (*C*=O); δ_F (376 MHz, $CDCl_3$) -58.3 (C*F*$_3$); *m/z* (ESI$^+$) 288.1213 [100%, $(M+H)^+$, $C_{14}H_{17}NO_2F_3$ requires 288.1206].

N-Boc-3-Bromopropylamine 239[167]

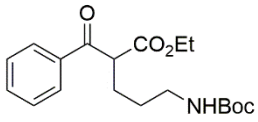


Di-*tert*-butyl dicarbonate (8.51 g, 39.0 mmol) was dissolved in methanol/acetonitrile (1:1, 25 mL) with triethylamine (10.8 mL, 81.0 mmol) and the solution was cooled to 0 °C. 3-Bromopropylamine hydrobromide (5.00 g, 23.0 mmol) in methanol/acetonitrile (1:1, 25 mL) was added dropwise to the cooled solution over 20 min. After warming to rt., the reaction was

stirred for 2 h and then concentrated in vacuo. The residue redissolved in ethyl acetate (50 mL), washed with water (4 × 50 mL), brine (50 mL), dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. Purification via dry column chromatography on silica gel (20:80, ethyl acetate:hexane) afforded the product as a white solid (3.61 g, 66%); Mpt 37-39 °C (lit., 38-40 °C); δ_H (400 MHz, $CDCl_3$) 1.45 [9H, s, C(C*H*$_3$)$_3$]. 2.05 (2H, p, *J* 6.5, C*H*$_2$), 3.27 (2H, t, *J* 6.5, C*H*$_2$), 3.45 (2H, t, *J* 6.5, C*H*$_2$).

Data are in accordance with the literature.

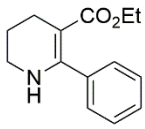
α-{[[(1,1-Dimethylethoxy)carbonyl]amino]propyl}-β-oxo-benzenepropanoic acid ethyl ester 240



Sodium hydride (60% dispersion in mineral oil, 0.31 g, 7.8 mmol) was washed with hexane (3 × 1 mL) under nitrogen and suspended in dry THF (4 mL). Ethyl benzoylacetate (1.00 g, 5.2 mmol) in dry THF (4 mL) was added dropwise over 5 min. The reaction was heated at 35 °C for 30 min. *N*-Boc-3-Bromopropylamine (1.11 g, 7.8 mmol) in dry THF (6 mL) was added dropwise followed by tetrabutylammonium iodide (1.92 g, 5.2 mmol) in one portion. The reaction was heated at 50 °C for 22 h. After cooling to 0 °C, aq. saturated ammonium chloride (2 mL) was added. The layers were separated, and the aqueous layer extracted using ethyl acetate (3 × 30 mL). The combined organic layers were washed using brine (50 mL), dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure. Purification via flash column chromatography on silica gel (25:75, ethyl acetate:hexane) afforded the product as a yellow oil (0.99 g, 55%); ν_{max}/cm^{-1} (thin film) 3387 (NH), 2978, 2935, 1734, 1684; δ_H (400 MHz, $CDCl_3$) 1.16 (2H, t, *J* 7.1, C*H*$_3$), 1.42 [9H, s, C(C*H*$_3$)$_3$], 1.50-1.61 (2H, m, C*H*$_2$), 1.97-2.08 (2H, m, C*H*$_2$), 3.15 (2H, q, *J* 6.3, C*H*$_2$), 4.14 (2H, q, *J* 7.1, OC*H*$_2$), 4.33 (1H, t, *J* 7.2, C*H*), 4.67 (1H, bs, N*H*), 7.43-7.52 (2H, m, ArC*H*). 7.54-7.63 (1H, m, ArC*H*), 7.95-8.02 (2H, m, ArC*H*); δ_C (101

MHz, $CDCl_3$) 14.0 (*C*H_3), 26.0 (*C*H_2), 27.9 (*C*H_2), 28.4 [C(CH_3)], 40.1 (*C*H_2), 53.7 (*C*H), 61.4 (*C*H_2), 128.6 (2 × Ar*C*H), 128.8 (2 × Ar*C*H), 133.6 (Ar*C*H), 136.2 (Ar*C*), 156.0 (*C*=O), 169.8 (*C*=O), 195.0 (*C*=O); *m/z* (ESI) 372.1784 [100%, $(M+H)^+$, $C_{19}H_{28}NO_5$ requires 372.1781].

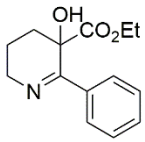
1,4,5,6-Tetrahydro-2-phenyl-4H-pyrridyl-3-carboxylic acid ethyl ester 78



α-{[[(1,1-Dimethylethoxy)carbonyl]amino]propyl}-β-oxo-benzenepropanoic acid ethyl ester (0.99 g, 2.8 mmol) was dissolved in DCM (25 mL) under argon and cooled to 0 °C. Trifluoroacetic acid (2.1 mL, 28.0 mmol) was added dropwise. The reaction was warmed to rt. and stirred for 2.5 h. An ice/water slurry (20 mL) was added, and the mixture was neutralised to pH 7 using solid sodium hydrogen carbonate. After stirring for 1.5 h, the layers were separated, and the aqueous layer was extracted using DCM (3 × 30 mL). The combined organic layers were washed with brine (30 mL), dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure. The product was afforded as a pale-yellow solid (0.59 g, 91%) which was used directly in the next step without further purification; mpt. 94-96 °C; δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, *J* 7.1, C*H*$_3$), 1.89 (2H, t, *J* 6.4, C*H*H), 1.91 (2H, t, *J* 6.4, C*H*H), 2.55 (2H, t, *J* 6.4, C*H*$_2$), 3.30-3.38 (2H, m, C*H*$_2$), 3.87 (2H, q, *J* 7.1, OC*H*$_2$), 4.04-4.10 (1H, m, N*H*), 7.29-7.39 (5H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 13.9 (*C*H_3), 21.7 (*C*H_2), 23.2 (*C*H_2), 42.1 (*C*H_2), 58.7 (O*C*H_2), 127.9 (2 × Ar*C*H), 127.2 (2 × Ar*C*H), 128.2 (Ar*C*H), 140.2 (Ar*C*), 154.2 (N*C*=C), 168.8 (*C*=O); *m/z* (ESI^+) 323.13 [100%, $(M+H)^+$].

Selected data from crude ^{1}H and ^{13}C NMR spectra.

5,6-Dihydro-2-phenyl-3-pyrridinol-3-carboxylic acid ethyl ester 241



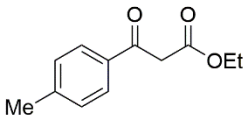
Obtained the product after attempted recrystallisation (hexane:DCM) of 1,4,5,6-tetrahydro-2-phenyl-4H-pyrridyl-3-carboxylic acid ethyl ester as yellow needle shaped crystals (0.084 g, 37%); mpt. 80-82 °C; ν_{max}/cm^{-1} (ATR) 3066, 2975, 2846, 1743, 1636; δ_H (400 MHz, $CDCl_3$) 0.93 (3H, t, *J* 7.1, C*H*$_3$), 1.79-1.79 (1H, m, C*H*H), 1.95-2.09 (3H, m, C*H*H), 3.69-3.83 (2H, m, C*H*H and O*H*), 3.97-4.23 (3H, m, C*H*H and OC*H*$_2$), 7.29-7.38 (3H, m, ArC*H*), 7.66-7.73 (2H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 13.6 (*C*H$_3$), 17.7 (*C*H$_2$), 34.0 (*C*H$_2$), 50.0 (*C*H$_2$), 62.5 (O*C*H$_2$), 71.3 (O*C*), 127.1 (2 × Ar*C*H), 128.1 (2 × Ar*C*H), 129.2 (Ar*C*H), 138.9 (Ar*C*), 162.1 (*C*=N), 175.6 (*C*=O); *m*/*z* (ESI$^+$) 248.1287 [100%, (M+H$^+$), $C_{14}H_{18}NO_3$ requires 248.1281].

(±)-*cis*-Ethyl-2-phenylpiperidine-3-carboxylate 233[125]

1,4,5,6-Tetrahydro-2-phenyl-4H-pyrridyl-3-carboxylic acid ethyl ester (0.231 g, 1.00 mmol) was dissolved in methanol (20 mL). Hydrogenation was performed employing the H-Cube® reactor (30 bar, 35 °C, 1 mL/min) with 5% Pd/C CatCart®. The reaction mixture was cycled through three times. The solvent was removed under reduced pressure. Purification via small scale column chromatology on silica gel (3:97 methanol:DCM) afforded the product as a pale-yellow oil (0.19 g, 81%); δ_H (400 MHz, $CDCl_3$, dr 98:2) 0.97 (3H, t, *J* 7.2, C*H*$_3$), 1.47-1.57 (1H, m, C*H*H), 1.79-2.02 (2H, m, C*H*H), 2.13-2.23 (2H, m, C*H*H and N*H*), 2.82 (1H, ddd, *J* 13.2, 12.1, 3.1, C*H*^{B}), 2.94-3.01 (1H, m, C*H*H), 3.36 (1H, ddt, *J* 13.2, 4.3, 2.1, C*H*^{A}), 3.84-3.96 (2H, m, OC*H*$_2$), 3.97 (1H, d, *J* 3.5, C*H*), 7.19-7.25 (1H, m, ArC*H*), 7.29-7.34 (4H, m, ArC*H*).

Data are in accordance with the literature.

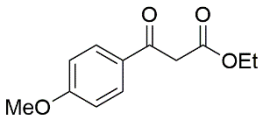
Ethyl (4-methylbenzoyl)acetate 242[168]



Sodium hydride (60% dispersion in mineral oil, 0.60 g, 15.0 mmol) was washed with hexane (3 × 1 mL) under N_2 and then suspended in dry THF (12 mL). 4'-Methylacetophenone (1.34 mL, 10.0 mmol) was added dropwise, and the mixture heated at 35 °C for 40 min. Diethyl carbonate (2.40 mL, 20.0 mmol) was added dropwise and the reaction was heated at reflux for 3 h. After cooling to rt., an ice/water slurry (20 mL) was added and then stirred for 10 min. The layers were separated, and the aqueous layer extracted using diethyl ether (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure. Purification via flash column chromatography on silica gel (5:95, ethyl acetate:hexane) afforded the product as a pale-yellow oil (1.37 g, 58%); δ_H (400 MHz, $CDCl_3$, 20% *enol* tautomer) 1.28 (2.40H, t, *J* 7.1, *keto* CH_3), 1.35 (0.60H, t, *J* 7.1, *enol* CH_3), 2.41 (2.40H, s, *enol* CH_3), 2.44 (0.60H, s, *keto* CH_3), 3.98 (1.60H, s, *keto* CH_2), 4.23 (1.60H, q, *J* 7.1, *keto* OCH_2), 4.28 (0.40H, q, *J* 7.1, *enol* OCH_2), 5.65 (0.20H, s, *enol* C*H*), 7.24 (0.40H, d, *J* 8.1, *enol* ArC*H*), 7.29 (1.60H, d, *J* 7.3, *keto* ArC*H*), 7.66-7.73 (0.40H, m, *enol* ArC*H*), 7.83-7.90 (1.60H, m, *keto* ArC*H*), 12.60 (0.20H, s, *enol* O*H*).

Data are in accordance with the literature.

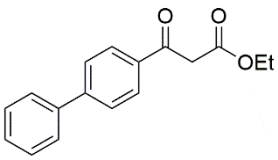
Ethyl (4-methoxybenzoyl)acetate 243[169,170]



Sodium hydride (60% dispersion in mineral oil, 0.60 g, 15.0 mmol) was washed with hexane (3 × 1 mL) under nitrogen and then suspended in dry THF (6 mL). 4-Methoxyacetophenone (1.50 g, 10.0 mmol) in dry THF (4 mL) was added dropwise and the mixture was heated at 35 °C for 40 min. Diethyl carbonate (2.40 mL, 20.0 mmol) was added dropwise and the reaction was heated at reflux for 3.5 h. After cooling to rt., water (4 mL) was added, and the mixture concentrated in vacuo. After diluting with water (20 mL), the solution was extracted using ethyl acetate (4 × 10 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure. Purification via flash column chromatography on silica gel (15:85 ethyl acetate:hexane) affording the product as a pale yellow oil (1.69 g, 68%); δ_H (400 MHz, $CDCl_3$, 9% *enol* tautomer) 1.27 (2.73H, t, *J* 7.1, *keto* C*H*$_3$), 1.35 (0.27H, t, *J* 7.1, *enol* C*H*$_3$), 3.87 (0.27H, s, *enol* OC*H*$_3$), 3.89 (2.73H, s, *keto* OC*H*$_3$), 3.96 (1.82H, s, *keto* C*H*$_2$), 4.23 (1.82H, q, *J* 7.1, *keto* OC*H*$_2$), 4.28 (0.18H, q, *J* 7.1, *enol* OC*H*$_2$), 5.60 (0.09H, s, *enol* C*H*), 6.90-7.00 (2H, m, *keto* and *enol* ArC*H*), 7.74-7.76 (0.18H, m, *enol* ArC*H*), 7.93-7.96 (1.82H, m *keto* ArC*H*), 12.65 (0.09H, s, *enol* O*H*).

Data are in accordance with the literature.

Ethyl (4-phenylbenzoyl)acetate 244[171]

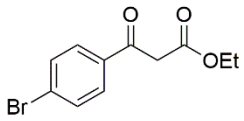


Sodium hydride (60% dispersion in mineral oil, 0.30 g, 7.5 mmol) was washed with hexane (3 × 1 mL) under nitrogen and then suspended in dry THF (4 mL). 4-Acetylbiphenyl (0.98 g, 5.0 mmol) was dissolved in dry THF (6 mL) and added dropwise. Once addition was complete, the mixture was heated at 35 °C for 30 min. Diethyl carbonate (1.20 mL, 10.0 mmol) was added dropwise and the reaction was heated at reflux for 3.5 h. After cooling to rt., aq. saturated ammonium chloride (4 mL) was added. The layers were separated, and the aqueous

layer was extracted using ethyl acetate (3 × 15 mL). The combined organic layers were washed using brine (20 mL), dried ($MgSO_4$), filtered, and solvent removed under reduced pressure. Purification via recrystallisation from hexane/DCM afforded the product as a pale-yellow solid (0.88 g, 66%); mpt 72-74 °C (lit.,[171] 76° C); δ_H (400 MHz, $CDCl_3$, 15% *enol* tautomer) 1.30 (2.55H, t, *J* 7.2, *keto* CH_3), 1.38 (0.45H, t, *J* 7.2, *enol* CH_3), 4.05 (1.70H, s, *keto* CH_2), 4.26 (1.70H, q, *J* 7.2, *keto* OCH_2), 4.32 (0.30H, q, *J* 7.2, *enol* OCH_2), 5.74 (0.15H, s, *enol* C*H*), 7.40-7.56 (3H, m, ArC*H*), 7.62-7.70 (2.30H, m, ArC*H*), 7.73 (1.70H, d, *J* 8.4, *keto* ArC*H*), 7.88 (0.30H, d, *J* 8.6, *enol* ArC*H*), 8.05 (1.70H, d, *J* 8.4, *keto* ArC*H*), 12.63 (0.15H, s, *enol* O*H*).

Data are in accordance with the literature.

Ethyl (4-bromobenzoyl)acetate 245[169]

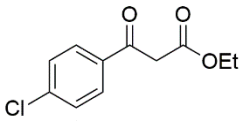


Sodium hydride (60% dispersion in mineral oil, 0.60 g, 15.0 mmol) was washed with hexane (3 × 1 mL) under nitrogen and then suspended in dry THF (6 mL). 4'-Bromoacetophenone (1.99 g, 10.0 mmol) was dissolved in dry THF (6 mL) and added dropwise. Once addition was complete, the mixture was heated at 35 °C for 30 min. Diethyl carbonate (2.40 mL, 20 mmol) was added dropwise and the reaction was heated at reflux for 3.5 h. After cooling to rt., water (6 mL) was added. The layers were separated, and the aqueous layer was extracted using ethyl acetate (3 × 30 mL). The combined organic layers were washed using brine (50 mL), dried ($MgSO_4$), filtered, and solvent removed under reduced pressure. Purification via flash column chromatography on silica gel (5:95 ethyl acetate:hexane) afforded the product as a pale-yellow oil (1.29 g, 43%); δ_H (400 MHz, $CDCl_3$, 32% *enol* tautomer) 1.27 (2.04H, t, *J* 7.1, *keto* CH_3), 1.35 (0.96H, t, *J* 7.1, *enol* CH_3), 3.97 (1.36H, s, *keto* CH_2), 4.22 (1.36H, q, *J* 7.1, *keto* OCH_2), 4.28 (0.64H, q, *J* 7.1, *enol* OCH_2), 5.65 (0.32H, s, *enol* C*H*), 7.52-7.60 (0.64H, m,

enol ArC*H*), 7.60-7.69 (2H, m, *enol* and *keto* ArC*H*), 7.78-7.86 (1.36H, m, *keto* ArC*H*), 12.58 (0.32H, s, *enol* O*H*).

Data are in accordance with the literature.

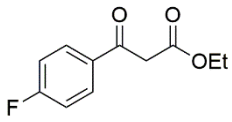
Ethyl (4-chlorobenzoyl)acetate 246[172]



Sodium hydride (60% dispersion in mineral oil, 0.60 g, 15.0 mmol) was washed with hexane (3 × 1 mL) under nitrogen and then suspended in dry THF (8 mL). 4'-Chloroacetophenone (1.55 g, 10.0 mmol) was dissolved in dry THF (2 mL) and added dropwise. Once addition was complete, the mixture was heated at 35 °C for 30 min. Diethyl carbonate (2.40 mL, 20 mmol) was added dropwise and the reaction was heated at reflux for 3.5 h. After cooling to rt., saturated aq. ammonium chloride (8 mL) was added. The layers were separated, and the aqueous layer was extracted using ethyl acetate (3 × 30 mL). The combined organic layers were washed using brine (40 mL), dried ($MgSO_4$), filtered, and solvent removed under reduced pressure. Purification via flash column chromatography on silica gel (5:95 ethyl acetate:hexane) afforded the product as a yellow oil (1.35 g, 60%); δ_H (400 MHz, $CDCl_3$, 20% *enol* tautomer) 1.27 (2.40H, t, *J* 7.2, *keto* CH_3), 1.35 (0.60H, t, *J* 7.1, *enol* CH_3), 3.98 (1.60H, s, *keto* CH_2), 4.23 (1.60H, q, *J* 7.2, *keto* OCH_2), 4.29 (0.40H, q, *J* 7.1, *enol* OCH_2), 5.65 (0.20H, s, *enol* C*H*), 7.37-7.44 (0.40H, m, *enol* ArC*H*), 7.44-7.51 (1.60H, m, *keto* ArC*H*), 7.69-7.76 (0.40H, m, *enol* ArC*H*), 7.87-7.95 (1.60H, m, *keto* ArC*H*), 12.59 (0.20H, s, *enol* OH).

Data are in accordance with the literature.

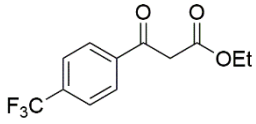
Ethyl (4-fluorobenzoyl)acetate 247[173]



Sodium hydride (60% dispersion in mineral oil, 0.60 g, 15.0 mmol) was washed with hexane (3 × 1 mL) under nitrogen and then suspended in dry THF (8 mL). 4'-Fluoroacetophenone (1.38 g, 10.0 mmol) was dissolved in dry THF (2 mL) and added dropwise. Once addition was complete, the mixture was heated at 35 °C for 30 min. Diethyl carbonate (2.40 mL, 20 mmol) was added dropwise and the reaction was heated at reflux for 3 h. After cooling to rt., saturated aq. ammonium chloride (8 mL) was added. The layers were separated, and the aqueous layer was extracted using diethyl ether (3 × 40 mL). The combined organic layers were washed using brine (50 mL), dried ($MgSO_4$), filtered, and solvent removed under reduced pressure. Purification via flash column chromatography on silica gel (10:90 ethyl acetate:hexane) afforded the product as a pale-yellow oil (1.32 g, 63%); δ_H (400 MHz, $CDCl_3$, 15% *enol* tautomer) 1.27 (2.55H, t, *J* 7.1, *keto* CH_3), 1.35 (0.45H, t, *J* 7.2, *enol* CH_3), 3.98 (1.70H, s, *keto* CH_2), 4.23 (1.70H, q, *J* 7.1, *keto* OCH_2), 4.28 (0.30H, q, *J* 7.2, *enol* CH_2), 5.62 (0.15H, s, *enol* C*H*), 7.07-7.21 (2H, m, ArC*H*), 7.79 (0.30H, dd, *J* 9.0, 5.3, *enol* ArC*H*), 7.96-8.04 (1.70H, m, *keto* ArC*H*), 12.63 (0.15H, s, *enol* O*H*); δ_F (376 MHz, $CDCl_3$) -108.5 (*enol*), -103.9 (*keto*).

Data are in accordance with the literature.

Ethyl 4-(1,1,1-trifluoromethyl)benzoylacetate 248[174]

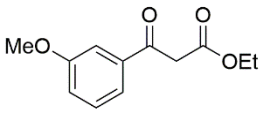


Sodium hydride (60% dispersion in mineral oil, 0.60 g, 15.0 mmol) was washed with hexane (3 × 1 mL) under nitrogen and then suspended in dry THF (6 mL). 4'-(1,1,1-Trifluoromethyl)acetophenone (1.88 g, 10.0 mmol) was dissolved in dry THF (4 mL) and added

dropwise. Once addition was complete, the mixture was heated at 35 °C for 30 min. Diethyl carbonate (2.40 mL, 20 mmol) was added dropwise and the reaction was heated at reflux for 3 h. After cooling to rt., saturated aq. ammonium chloride (8 mL) was added. The layers were separated, and the aqueous layer was extracted using diethyl ether (3 × 50 mL). The combined organic layers were washed using brine (50 mL), dried ($MgSO_4$), filtered, and solvent removed under reduced pressure. Purification via flash column chromatography on silica gel (10:90 ethyl acetate:hexane) afforded the product as a pale-yellow oil (1.73 g, 66%); δ_H (400 MHz, $CDCl_3$, 36% *enol* tautomer) 1.28 (1.92H, t, *J* 7.2, *keto* CH_3), 1.37 (1.08H, t, *J* 7.2, *enol* CH_3), 4.04 (1.28H, s, *keto* CH_2), 4.25 (1.28H, q, *J* 7.1, *keto* OCH_2), 4.31 (0.72H, q, *J* 7.2, *enol* OCH_2), 5.74 (0.36H, s, *enol* C*H*), 7.67-7.74 (0.72H, m, *enol* ArC*H*), 7.75-7.82 (1.28H, m, *keto* ArC*H*), 7.87-7.94 (0.72H, m, *enol* ArC*H*), 8.05-8.12 (1.28H, m, *keto* ArC*H*), 12.59 (0.36H, s, *enol* O*H*); δ_F (376 MHz, $CDCl_3$) -63.2 (*keto*), -63.0 (*enol*).

Data are in accordance with the literature.

Ethyl (3-methoxybenzoyl)acetate 249[175]

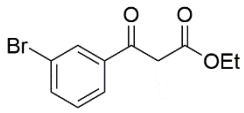


Sodium hydride (60% dispersion in mineral oil, 0.60 g, 15 mmol) was washed using hexane (3 × 1 mL) under nitrogen and then suspended in dry THF (8 mL). 3'-Methoxyacetophenone (1.50 g, 10 mmol) was dissolved in dry THF (2 mL) and added dropwise. The mixture was stirred at 35 °C for 40 min. Diethyl carbonate (2.40 mL, 20 mmol) was added dropwise and the reaction was heated at reflux for 3 h. After cooling to rt., aq. saturated ammonium chloride (8 mL) was added, the mixture diluted with water (10 mL) and the layers were separated. The aqueous layer was extracted using diethyl ether (3 × 30 mL). The combined organic layers were washed using brine (40 mL), dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. Purification via flash column chromatography on silica gel (15:85 ethyl

acetate:hexane) afforded the product as a pale-yellow oil (1.56 g, 62%); ν_{max}/cm^{-1} (thin film, ATR) 2980, 2939, 1736, 1684; δ_H (400 MHz, $CDCl_3$, 15% *enol* tautomer) 1.28 (2.55H, t, *J* 7.1, *keto* CH_3), 1.35 (0.45H, t, *J* 7.1, *enol* CH_3), 3.86 (0.45H, s, *enol* OCH_3), 3.87 (2.55H, s, *keto* OCH_3), 3.99 (1.70H, s, *keto* CH_2), 4.22 (1.70H, q, *J* 7.1, *keto* OCH_2), 4.29 (0.30H, q, *J* 7.1, *enol* OCH_2), 5.67 (0.15H, s, *enol* C*H*), 7.16 (0.85H, ddd, *J* 8.0, 2.6, 1.0, *keto* ArC*H*), 7.31-7.37 (0.45H, m, *enol* ArC*H*), 7.40 (0.85H, t, *J* 8.0, *keto* ArC*H*), 7.47-7.56 (1.85H, m, *keto* and *enol* ArC*H*), 12.59 (0.15H, s, *enol* OH).

Data are in accordance with the literature.

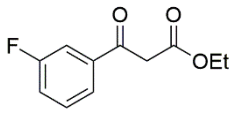
Ethyl (3-bromobenzoyl)acetate 250[176]



Sodium hydride (60% dispersion in mineral oil, 0.60 g, 15.0 mmol) was washed using hexane (3 × 1 mL) under nitrogen and then suspended in dry THF (10 mL). 3'-Bromoacetophenone (1.32 mL, 10.0 mmol) was added dropwise, and the mixture was heated at 35 °C for 30 min. Diethyl carbonate (2.40 mL, 20.0 mmol) was added dropwise and the reaction was heated at reflux for 3 h. After cooling to rt., water (8 mL) was added, and the layers separated. The aqueous layer was extracted using diethyl ether (3 × 30 mL). The combined organic layers were washed using brine (40 mL), dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure. Purification via flash column chromatography on silica gel (10:90 ethyl acetate:hexane) afforded the product as a pale-yellow oil (0.72 g, 24%); δ_H (400 MHz, $CDCl_3$, 34% *enol* tautomer) 1.28 (1.98H, t, *J* 7.1, *keto* CH_3), 1.36 (1.02H, t, *J* 7.1, *enol* CH_3), 3.98 (1.32H, s, *keto* CH_2), 4.18-4.34 (2.00H, m, OCH_2), 5.67 (0.34H, s, *enol* C*H*), 7.31 (0.34H, t, *J* 7.8, *enol* ArC*H*), 7.39 (0.66H, t, *J* 7.8, *keto* ArC*H*), 7.57-7.64 (0.34H, m, *enol* ArC*H*), 7.67-7.78 (1H, m, ArC*H*), 7.88 (0.66H, dt, *J* 7.8, 1.4, *keto* ArC*H*), 7.94 (0.34H, d, *J* 1.9, *enol* ArCH), 8.07-8.13 (0.66H, m, *keto* ArC*H*), 12.56 (0.34H, s, *enol* O*H*).

Data are in accordance with the literature.

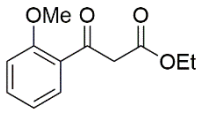
Ethyl (3-fluorobenzoyl)acetate 251[177]



Sodium hydride (60% dispersion in mineral oil, 0.60 g, 15.0 mmol) was washed with hexane (3 × 1 mL) under nitrogen and then suspended in dry THF (8 mL). 3'-Fluoroacetophenone (1.38 g, 10.0 mmol) was dissolved in dry THF (2 mL) and added dropwise. Once addition was complete, the mixture was heated at 35 °C for 30 min. Diethyl carbonate (2.40 mL, 20 mmol) was added dropwise and the reaction was heated at reflux for 3.5 h. After cooling to rt., saturated aq. ammonium chloride (8 mL) was added. The layers were separated, and the aqueous layer was extracted using diethyl ether (3 × 40 mL). The combined organic layers were washed using brine (30 mL), dried ($MgSO_4$), filtered, and solvent removed under reduced pressure. Purification via flash column chromatography on silica gel (10:90 ethyl acetate:hexane) afforded the product as a pale-yellow oil (1.40 g, 67%); δ_H (400 MHz, $CDCl_3$, 26% *enol* tautomer) 1.27 (2.22H, t, *J* 7.2, *keto* CH_3), 1.35 (0.78H, t, *J* 7.1, *enol* CH_3), 3.99 (1.48H, s, *keto* CH_2), 4.23 (1.48H, q, *J* 7.2, *keto* OCH_2), 4.30 (0.52H, q, *J* 7.1, *enol* OCH_2), 5.67 (0.26H, s, *enol* C*H*), 7.17 (0.26H, tdd, *J* 8.2, 2.6, 1.0, *enol* ArC*H*), 7.31 (0.74H, tdd, *J* 8.2, 2.6, 1.0, *keto* ArC*H*), 7.36-7.43 (0.26H, m, *enol* ArC*H*), 7.43-7.53 (1H, m, ArC*H*), 7.56 (0.26H, ddd, *J* 7.8, 1.7, 1.0, *enol* ArC*H*), 7.65 (0.74H, ddd, *J* 9.4, 2.6, 1.5, *keto* ArC*H*), 7.74 (0.74H, ddd, *J* 7.8, 1.5, 1.0, *keto* ArC*H*), 12.57 (0.26H, s, *enol* O*H*); δ_F (376 MHz, $CDCl_3$) -111.4 (*keto*), 112.4 (*enol*).

Data are in accordance with the literature.

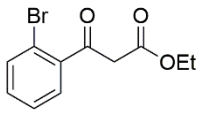
Ethyl (2-methoxybenzoyl)acetate 252[177]



Sodium hydride (60% dispersion in mineral oil, 0.60 g, 15.0 mmol) was washed with hexane (3 × 1 mL) under nitrogen and then suspended in dry THF (6 mL). 2'-methoxyacetophenone (1.50 g, 10.0 mmol) was dissolved in dry THF (4 mL) and added dropwise. Once addition was complete, the mixture was heated at 35 °C for 30 min. Diethyl carbonate (2.40 mL, 20 mmol) was added dropwise and the reaction was heated at reflux for 3.5 h. After cooling to rt., saturated aq. ammonium chloride (8 mL) was added. The layers were separated, and the aqueous layer was extracted using diethyl ether (3 × 40 mL). The combined organic layers were washed using brine (30 mL), dried ($MgSO_4$), filtered, and solvent removed under reduced pressure. Purification via flash column chromatography on silica gel (10:90 ethyl acetate:hexane) afforded the product as a pale-yellow oil (1.52 g, 68%); δ_H (400 MHz, $CDCl_3$, 8% *enol* tautomer) 1.25 (2.76H, t, *J* 7.2, *keto* CH_3), 1.36 (0.24H, t, *J* 7.2, *enol* CH_3), 3.92 (2.76H, s, *keto* OCH_3), 3.93 (0.24H, s, *enol* CH_3), 3.99 (1.84H, s, *keto* CH_2), 4.20 (1.84H, q, *J* 7.2, *keto* OCH_2), 4.28 (0.16H, q, *J* 7.2, *enol* OCH_2), 6.04 (0.08H, s, *enol* C*H*), 6.98-7.10 (2H, m, ArC*H*), 7.41-7.45 (0.08H, m, *enol* ArC*H*), 7.53 (0.92H, ddd, *J* 8.4, 7.3, 1.8, *keto* ArC*H*), 7.88-7.91 (1H, m, ArC*H*), 12.72 (0.08H, s, *enol* O*H*).

Data are in accordance with the literature.

Ethyl (2-bromobenzoyl)acetate 253[176]

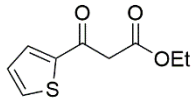


Sodium hydride (60% dispersion in mineral oil, 0.60 g, 15.0 mmol) was washed using hexane (3 × 1 mL) under nitrogen and the suspended in dry THF (10 mL). 2'-Bromoacetophenone

(1.35 mL, 10.0 mmol) was added dropwise, and the mixture was heated at 35 °C for 30 min. Diethyl carbonate (2.40 mL, 20.0 mmol) was added dropwise and the reaction was heated at reflux for 3 h. After cooling to rt., water (8 mL) was added, and the layers separated. The aqueous layer was extracted using diethyl ether (3 × 50 mL). the combined organic layers were washed using brine (100 mL), dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. Purification via flash column chromatography on silica gel (10:90 ethyl acetate:hexane) afforded the product as a pale yellow oil (0.47 g, 16%); δ_H (400 MHz, $CDCl_3$, 36% *enol* tautomer) 1.26 (1.98H, t, *J* 7.1, *keto* C*H*$_3$), 1.36 (1.08H, t, *J* 7.1, *enol* C*H*$_3$), 4.04 (1.28H, s, *keto* C*H*$_2$), 4.21 (1.28H, q, *J* 7.1, *keto* OC*H*$_2$), 4.30 (0.72H, q, *J* 7.1, *enol* OC*H*$_2$), 5.47 (0.36H, s, *enol* C*H*), 7.25-7.45 (2.34H, m, *keto* and *enol* ArC*H*), 7.49-7.56 (1.08H, m, *enol*, ArC*H*), 7.65 (0.64H, dt, *J* 7.9, 1.3, *keto* ArC*H*), 12.45 (0.32H, s, *enol* O*H*).

Data are in accordance with the literature.

Ethyl-3-oxo-3-(thiophen-3-yl)propanoate 254[178]

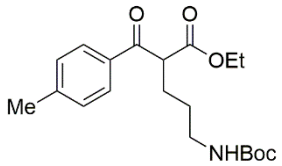


Sodium hydride (60% dispersion in mineral oil, 0.60 g, 15 mmol) was washed using hexane (3 × 1 mL) under nitrogen and then suspended in dry THF (8 mL). 2-Acetylthiophene (1.10 g, 10 mmol) in dry THF (2 mL) was added dropwise and the mixture was heated at 35 °C for 30 min. Diethyl carbonate (2.40 mL, 20 mmol) was added dropwise and the reaction was heated at reflux for 3 h. After cooling to rt., saturated aq. ammonium chloride (8 mL) was added, diluted using water (20 mL), and the layers were separated. The aqueous layer was extracted using diethyl ether (3 × 30 mL). The combined organic layers were washed with brine (40 mL), dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. Purification via flash column chromatography on silica gel (20:80 ethyl acetate:hexane) afforded the product as a brown oil (1.48 g, 75%); δ_H (400 MHz, $CDCl_3$, 4% *enol* tautomer)

1.23 (2.88H, t, *J* 7.1, *keto* C*H*$_3$), 1.30 (0.12H, t, *J* 7.1, *enol* C*H*$_3$), 3.90 (1.92H, s, *keto* C*H*$_2$), 4.18 (1.92H, q, *J* 7.1, *keto* OC*H*$_2$), 5.54 (0.04H, s, *enol* C*H*), 7.12 (0.96H, m, *keto* ArC*H*), 7.70 (1.92H, ddd, *J* 17.9, 4.4, 1.1, *keto* ArC*H*), 12.49 (0.04H, s, *enol* O*H*).

The data are in accordance with the literature.

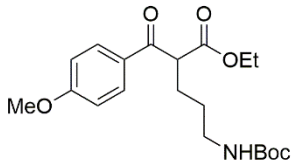
α-{[[(1,1-dimethylethoxy)carbonyl]amino]propyl}-β-oxo-4'-methyl-benzenepentanoic acid ethyl ester 255



Sodium hydride (60% dispersion in mineral oil, 0.120 g, 3.0 mmol) was washed using hexane (3 × 1 mL) under nitrogen and then suspended in dry THF (1 mL). Ethyl(4-methylbenzoyl)acetate (0.469 g, 2.0 mmol) in dry THF (2 mL) was added dropwise and the mixture was then stirred at 35 °C for 40 min. *N*-Boc-3-Bromopropylamine (0.571 g, 2.4 mmol) was dissolved in dry THF (3 mL) and added dropwise. Tetrabutylammonium iodide (0.739 g, 2.0 mmol) was added in one portion and the reaction was heated at 55 °C for 20 h. After cooling to rt., aqueous saturated ammonium chloride (2 mL) was added, and the mixture was diluted with water (10 mL). The layers were separated, and the aqueous layers was extracted using diethyl ether (3 × 15 mL). the combined organic layers were washed using brine (30 mL), dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure. Purification via flash column chromatography on silica gel (20:80 to 30:70 ethyl acetate:hexane) afforded the product as a pale-yellow oil (0.38 g, 52%); ν_{max}/cm^{-1} (thin film, ATR) 3385, 2977, 2933, 1733, 1683, 1607; δ_H (400 MHz, $CDCl_3$) 1.18 (3H, t, *J* 7.1, C*H*$_3$), 1.43 [9H, s, C(C*H*$_3$)$_3$], 1.55 (2H, p, *J* 7.1, C*H*$_2$), 2.02 (2H, ddd, *J* 9.9, 8.3, 6.3, C*H*$_2$), 2.42 (3H, s, C*H*$_3$), 3.15 (2H, q, *J* 7.1, OC*H*$_2$), 4.31 (1H, t, *J* 7.1, C*H*), 4.65 (1H, s, N*H*), 7.28 (2H, d, *J* 8.4, ArC*H*), 7.86-7.93 (2H, m, ArC*H*); δ_C (100 MHz, $CDCl_3$) 14.0 (*C*H$_3$), 21.7 (*C*H$_3$), 26.1 (*C*H$_2$), 27.9 (*C*H$_2$), 28.4 [C(*C*H$_3$)$_3$],

40.1 [*C*(CH_3)$_3$], 53.6 (*C*H), 61.4 (O*C*H_2), 128.8 (Ar*C*H), 129.5 (Ar*C*H), 133.7 (Ar*C*), 144 (Ar*C*), 156.0 (*C*=O), 170.0 (*C*=O), 194.6 (*C*=O); *m*/*z* (ESI$^+$) 386.1938 [100%, (M+Na)$^+$, $C_{20}H_{29}NO_5Na$ requires 386.1938].

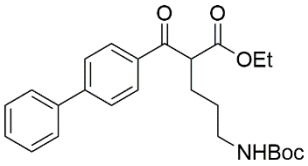
α-{[[(1,1-dimethylethoxy)carbonyl]amino]propyl}-β-oxo-4'-methoxy-benzenepropanoic acid ethyl ester 256



Sodium hydride (60% dispersion in mineral oil, 0.120 g, 3.0 mmol) was washed using hexane (3 × 1 mL) under nitrogen and then suspended in dry THF (1 mL). Ethyl(4-methoxybenzoyl) acetate (0.500 g, 2.0 mmol) in dry THF (2 mL) was added dropwise and the mixture was heated at 35 °C for 30 min. *N*-Boc-3-Bromopropylamine (0.571 g, 2.4 mmol) in dry THF (3 mL) was added dropwise followed by tetrabutylammonium iodide (0.739 g, 2.0 mmol) in one portion. The reaction was heated a 55 °C overnight. After cooling to rt., the reaction was quenched via the addition of aqueous saturated ammonium chloride (3 mL). The layers were separated, and the aqueous layer was extracted using diethyl ether (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure. Purification via flash column chromatography on silica gel (30:70 ethyl acetate:hexane) afforded the product as a pale yellow oil (0.55 g, 72%); ν_{max}/cm^{-1} (thin film, ATR) 3386, 2977, 2933, 1736, 1702, 1682, 1600; δ_H (400 MHz, $CDCl_3$) 1.19 (3H, t, *J* 7.1, C*H*$_3$), 1.44 [9H, s, C(C*H*$_3$)$_3$], 1.49-1.62 (2H, m, C*H*$_2$), 2.03 (2H, ddd, *J* 14.7, 8.4, 4.3, C*H*$_2$), 3.11-3.20 (2H, m, C*H*$_2$), 3.89 (3H, s, OC*H*$_3$), 4.15 (2H, q, *J* 7.1, OC*H*$_2$), 4.29 (1H, t, *J* 7.1, C*H*), 4.63 (1H, s, N*H*), 6.93-7.00 (2H, m, ArC*H*), 7.94-8.03 (2H, m, ArC*H*); δ_C (100 MHz, $CDCl_3$) 14.0 (*C*H$_3$), 26.1 (*C*H$_2$), 27.9 (*C*H$_2$), 28.4 [C(*C*H$_3$)$_3$], 40.1 [*C*(CH$_3$)$_3$], 53.4 (*C*H), 55.5 (OCH$_3$), 61.4 (O*C*H$_2$), 114.0 (Ar*C*H), 129.2 (Ar*C*), 131.0 (Ar*C*H), 156.0 (Ar*C*O), 163.9 (*C*=O)

170.0 (*C*=O), 193.4 (*C*=O); *m*/*z* (ESI$^+$) 402.1901 [100%, (M+Na)$^+$, $C_{20}H_{29}NO_6Na$ requires 402.1887].

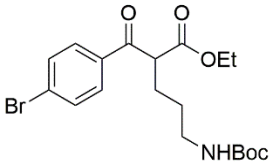
α-{[[(1,1-Dimethylethoxy)carbonyl]amino]propyl}-β-oxo-4'-phenyl-benzenepropanoic acid ethyl ester 257



Sodium hydride (60% dispersion in mineral oil, 0.120 g, 3.0 mmol) was washed with hexane (3 × 1 mL) under nitrogen and then suspended in dry THF (1 mL). Ethyl (4-phenylbenzoyl) acetate (0.537 g, 2.0 mmol) was dissolved in dry THF (2 mL) and added dropwise. The mixture was heated at 35 °C for 30 min. *N*-Boc-3-Bromopropylamine (0.619 g, 2.6 mmol) in dry THF (3 mL) was added dropwise and the reaction was then heated at 60 °C for 20 h. After cooling to rt., aq. saturated ammonium chloride (2 mL) was added, the mixture was diluted with water (10 mL), and the layers were separated. The aqueous layer was extracted using ethyl acetate (3 × 20 mL). The combined organic layers were washed using brine (20 mL), dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure. Purification using Combi Flash (silica gel, ethyl acetate:hexane gradient) afforded the product as a pale-yellow oil (0.231 g, 27%); ν_{max}/cm^{-1} (thin film, ATR) 3388, 2976, 2934, 1732, 1682, 1603; δ_H (400 MHz, $CDCl_3$) 1.21 (3H, t, *J* 7.1, C*H*$_3$), 1.45 [9H, s, C(C*H*$_3$)$_3$], 1.60 (2H, p, *J* 7.2, C*H*$_2$), 2.02-2.13 (2H, m, C*H*$_2$), 3.19 (2H, q, *J* 6.2, C*H*$_2$), 4.19 (2H, q, *J* 7.1, OC*H*$_2$), 4.39 (1H, t, *J* 7.2, C*H*), 4.63 (1H, s, N*H*), 7.39-7.47 (1H, m, ArC*H*), 7.47-7.55 (2H, m, ArC*H*), 7.61-7.69 (2H, m, ArC*H*), 7.69-7.76 (2H, m, ArC*H*), 8.05-8.13 (2H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 14.0 (*C*H$_3$), 26.1 (*C*H$_2$), 27.9 (*C*H$_2$), 28.4 [C(*C*H$_3$)$_3$], 40.1 (*C*H$_2$), 53.7 (*C*H), 60.4 [*C*(CH$_3$)$_3$], 61.5 (OCH$_2$), 127.3 (2 × Ar*C*H), 127.4 (2 × Ar*C*H), 128.4 (Ar*C*H), 129.0 (2 × Ar*C*H), 129.3 (2 × Ar*C*H), 134.8 (Ar*C*), 139.7 (Ar*C*),

146.3 (Ar*C*), 156.0 (*C*=O), 169.9 (*C*=O), 194.6 (*C*=O); *m*/*z* (ESI$^+$) 448.2103 [100%, (M+Na)$^+$, $C_{25}H_{31}NO_5Na$ requires 448.2094].

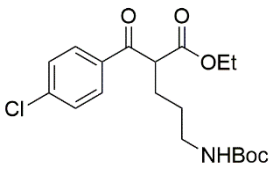
α-{[[(1,1-dimethylethoxy)carbonyl]amino]propyl}-β-oxo-4'-bromo-benzenepropanoic acid ethyl ester 258



Sodium hydride (60% dispersion in mineral oil, 0.120 g, 3.0 mmol) was washed with hexane (3 × 1 mL) under nitrogen and then suspended in dry THF (1 mL). Ethyl(4-bromobenzoyl)acetate (0.598 g, 2.0 mmol) was dissolved in dry THF (2 mL) and added dropwise. The mixture was heated at 35 °C for 30 min. *N*-Boc-3-Bromopropylamine (0.571 g, 2.4 mmol) in dry THF (3 mL) was added dropwise and the reaction was then heated at 60 °C for 20 h. After cooling to rt., aq. saturated ammonium chloride (2 mL) was added, the mixture was diluted with water (10 mL), and the layers were separated. The aqueous layer was extracted using diethyl ether (3 × 15 mL). The combined organic layers were washed using brine (20 mL), dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure. Purification via flash column chromatography on silica gel (20:80 ethyl acetate:hexane) afforded the product as a yellow oil (0.35 g, 41%); ν_{max}/cm^{-1} (thin film, ATR) 3385 (NH), 2977, 2934, 1736, 1688, 1585; δ_H (400 MHz, $CDCl_3$) 1.18 (3H, td, *J* 7.1, 1.4, C*H*$_3$), 1.44 [9H, s, C(C*H*$_3$)$_3$], 1.55 (2H, p, *J* 7.3, C*H*$_2$), 1.97-2.08 (2H, m, C*H*$_2$), 3.16 (2H, q, *J* 6.6, C*H*$_2$), 4.15 (2H, q, *J* 7.1, OC*H*$_2$), 4.29 (1H, t, *J* 7.1, C*H*), 4.64 (1H, s, N*H*), 7.59-7.68 (2H, m, ArC*H*), 7.86 (2H, dd, *J* 8.5, 1.6, ArC*H*); δ_C (101 MHz, $CDCl_3$) 14.0 (*C*H$_3$), 25.9 (*C*H$_2$), 27.9 (*C*H$_2$), 28.4 [C(*C*H$_3$)$_3$], 40.0 [*C*(CH$_3$)$_3$], 53.7 (*C*H), 61.6 (O*C*H$_2$), 128.9 (Ar*C*), 130.1 (2 × Ar*C*H), 132.1 (2 × Ar*C*H), 134.9 (Ar*C*), 156.0 (*C*=O), 169.5 (*C*=O), 194.0 (*C*=O); *m*/*z* (ESI$^+$) 452.0883 [100%, (M Na$^+$),

$C_{19}H_{26}NO_5Na^{81}Br$ requires 452.0866], 450.0897 [99%, (M Na^+), $C_{19}H_{26}NO_5Na^{79}Br$ requires 450.0887].

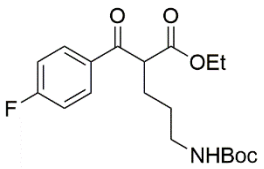
α-{[[(1,1-Dimethylethoxy)carbonyl]amino]propyl}-β-oxo-4'-chloro-benzenepropanoic acid ethyl ester 259



Sodium hydride (60% dispersion in mineral oil, 0.120 g, 3.0 mmol) was washed using hexane (3 × 1 mL) under nitrogen and the suspended in dry THF (1 mL). Ethyl(4-chlorobenzoyl)acetate (0.453 g, 2.0 mmol) in dry THF (2 mL) was added dropwise and the reaction mixture was heated at 35 °C for 30 min. *N*-Boc-3-Bromopropylamine (0.571 g, 2.4 mmol) in dry THF (3 mL) was added dropwise followed by tetrabutylammonium iodide (0.739 g, 2.0 mmol) in one portion. The reaction was heated a 60 °C overnight. After cooling to rt., the reaction was quenched via the addition of aq. saturated ammonium chloride (2 mL) and diluted with water (10 mL). The layers were separated, and the aqueous layer was extracted using diethyl ether (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure. Purification using Combi Flash (silica gel, ethyl acetate:hexane as eluent) afforded the product as a pale-yellow oil (0.247 g, 32%); ν_{max}/cm^{-1} (thin film, ATR) 3363, 2977, 2934, 1733, 1685; δ_H (400 MHz, $CDCl_3$) 1.18 (3H, t, *J* 7.1, C*H*$_3$), 1.43 [9H, s, C(C*H*$_3$)$_3$], 1.55 (2H, p, *J* 7.2, C*H*$_2$), 1.97-2.08 (2H, m, C*H*$_2$), 3.16 (2H, q, *J* 6.7, C*H*$_2$), 4.14 (2H, q, *J* 7.1, OC*H*$_2$), 4.29 (1H, t, *J* 7.1, C*H*), 4.64 (1H, s, N*H*), 7.42-7.50 (2H, m, ArC*H*), 7.90-7.98 (2H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 14.0 (*C*H$_3$), 25.9 (*C*H$_2$), 27.8 (*C*H$_2$), 28.4 [C(*C*H$_3$)$_3$], 40.0 (*C*H$_2$), 53.7 (*C*H), 60.4 [*C*(CH$_3$)$_3$], 61.6 (O*C*H$_2$), 129.1 (2 × Ar*C*H), 130.0 (2 × Ar*C*H), 134.5 (Ar*C*), 140.1 (Ar*C*), 156.0 (*C*=O), 169.6 (*C*=O), 193.8 (*C*=O);

m/z (ESI$^+$) 406.1392 [100%, $(M+Na)^+$, $C_{19}H_{26}NO_5Na^{35}Cl$ requires 406.1392], 408.1376 [32, $(M+Na)^+$, $C_{19}H_{26}NO_5Na^{37}Cl$ requires 408.1362].

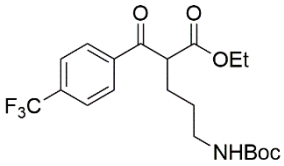
α-{[[(1,1-Dimethylethoxy)carbonyl]amino]propyl}-β-oxo-4'-fluoro-benzenepropanoic acid ethyl ester 260



Sodium hydride (60% dispersion in mineral oil, 0.120 g, 3.0 mmol) was washed using hexane (3 × 1 mL) under nitrogen and the suspended in dry THF (1 mL). Ethyl(4-fluorobenzoyl)acetate (0.420 g, 2.0 mmol) in dry THF (2 mL) was added dropwise and the reaction mixture was heated at 35 °C for 30 min. *N*-Boc-3-Bromopropylamine (0.571 g, 2.4 mmol) in dry THF (3 mL) was added dropwise followed by tetrabutylammonium iodide (0.739 g, 2.0 mmol) in one portion. The reaction was heated a 60 °C overnight. After cooling to rt., the reaction was quenched via the addition of aq. saturated ammonium chloride (2 mL) and diluted with water (10 mL). The layers were separated, and the aqueous layer was extracted using ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure. Purification using Combi Flash (silica gel, ethyl acetate:hexane as eluent) afforded the product as a pale-yellow oil (0.267 g, 36%); ν_{max}/cm^{-1} (thin film, ATR) 3386, 2978, 2934, 1734, 1684, 1598, 1507; δ_H (400 MHz, $CDCl_3$) 1.19 (3H, t, *J* 7.1, C*H*$_3$), 1.44 [9H, s, C(C*H*$_3$)$_3$], 1.56 (2H, p, *J* 7.2, C*H*$_2$), 1.99-2.09 (2H, m, C*H*$_2$), 3.13-3.22 (2H, m, C*H*$_2$), 4.16 (2H, q, *J* 7.1, OC*H*$_2$), 4.31 (1H, t, *J* 7.2, C*H*), 4.26 (1H, s, N*H*), 7.17 (2H, t, *J* 8.6, ArC*H*), 8.05 (2H, dd, *J* 8.6, 5.4, ArC*H*); δ_C (101 MHz, $CDCl_3$) 14.0 (*C*H$_3$), 25.9 (*C*H$_2$), 27.9 (*C*H$_2$), 28.4 [C(*C*H$_3$)$_3$], 40.0 (*C*H$_2$), 53.7 (*C*H), 61.6 (O*C*H$_2$), 116.0 (d, $J_{C\text{-}F}$ 22.0, 2 × Ar*C*H), 131.4 (d, $J_{C\text{-}F}$ 9.5, 2 × Ar*C*H), 132.6 (d, $J_{C\text{-}F}$ 3.0, ArC), 156.0 (*C*=O), 166.0

(d, $J_{C\text{-}F}$ 256.0, Ar*C*F), 169.7 (*C*=O), 193.4 (*C*=O); δ_F (376 MHz, $CDCl_3$) -104.2; *m*/*z* (ESI^+) 390.1691 [100%, $(M+Na)^+$, $C_{19}H_{26}NO_5FNa$ requires 390.1687].

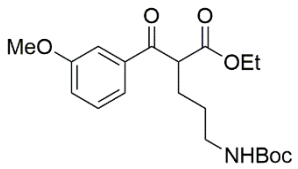
α-{[[(1,1-Dimethylethoxy)carbonyl]amino]propyl}-β-oxo-4'-(1,1,1-trifluoromethyl)-benzenepropanoic acid ethyl ester 261



Sodium hydride (60% dispersion in mineral oil, 0.120 g, 3.0 mmol) was washed using hexane (3 × 1 mL) under nitrogen and the suspended in dry THF (1 mL). Ethyl[4-(1,1,1-trifluoromethyl)benzoyl]acetate (0.520 g, 2.0 mmol) in dry THF (2 mL) was added dropwise and the reaction mixture was heated at 35 °C for 30 min. *N*-Boc-3-Bromopropylamine (0.571 g, 2.4 mmol) in dry THF (3 mL) was added dropwise followed by tetrabutylammonium iodide (0.739 g, 2.0 mmol) in one portion. The reaction was heated a 60 °C overnight. After cooling to rt., the reaction was quenched via the addition of aq. saturated ammonium chloride (2 mL) and diluted with water (10 mL). The layers were separated, and the aqueous layer was extracted using ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure. Purification using Combi Flash (silica gel, ethyl acetate:hexane as eluent) afforded the product as a pale-yellow oil (0.192 g, 23%); ν_{max}/cm^{-1} (thin film, ATR) 3385, 2978, 2935, 1736, 1691, 1512; δ_H (400 MHz, $CDCl_3$) 1.19 (3H, t, *J* 7.2, C*H*$_3$), 1.44 [9H, s, C(C*H*$_3$)$_3$], 1.57 (2H, p, *J* 7.6, C*H*$_2$), 2.00-2.11 (2H, m, C*H*$_2$), 3.13-3.23 (2H, m, C*H*$_2$), 4.16 (2H, q, *J* 7.2, OC*H*$_2$), 4.36 (1H, t, *J* 7.3, C*H*), 4.62 (1H, s, N*H*), 7.77 (2H, d, *J* 8.4, ArC*H*), 8.11 (2H, d, *J* 8.4, ArC*H*); δ_C (101 MHz, $CDCl_3$) 14.0 (*C*H$_3$), 25.8 (*C*H$_2$), 27.8 (*C*H$_2$), 28.4 [C(*C*H$_3$)$_3$], 39.9 (*C*H$_2$), 53.9 (*C*H), 61.7 (O*C*H$_2$), 123.5 (q, $J_{C\text{-}F}$ 272.5, *C*F$_3$), 125.9 (q, $J_{C\text{-}F}$ 4.0, 2 × Ar*C*H), 128.9 (2 × Ar*C*H), 134.6 (Ar*C*), 156.0

(*C*=O), 169.4 (*C*=O), 194.2 (*C*=O); δ_F (376 MHz, $CDCl_3$) -63.2; *m/z* (ESI$^+$) 440.1668 [100%, $(M+Na)^+$, $C_{20}H_{26}NO_5F_3Na$ requires 440.1655].

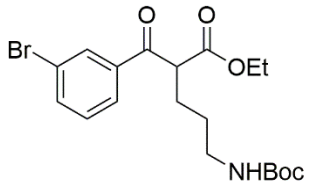
α-{[[(1,1-dimethylethoxy)carbonyl]amino]propyl}-β-oxo-3'-methoxy-benzenepropanoic acid ethyl ester 262



Sodium hydride (60% dispersion in mineral oil, 0.120 g, 3.0 mmol) was washed using hexane (3 × 1 mL) under nitrogen and then suspended in dry THF (1 mL). Ethyl(3-methoxybenzoyl) acetate (0.500 g, 2.0 mmol) in dry THF (2 mL) was added dropwise and the mixture was heated at 35 °C for 30 min. *N*-Boc-3-Bromopropylamine (0.571 g, 2.4 mmol) in dry THF (3 mL) was added dropwise followed by tetrabutylammonium iodide (0.739 g, 2.0 mmol) in one portion. The reaction was heated a 55 °C overnight. After cooling to rt., the reaction was quenched via the addition of aq. saturated ammonium chloride (3 mL). The layers were separated, and the aqueous layer was extracted using diethyl ether (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure. Purification using Combi Flash (silica gel, ethyl acetate:hexane as eluent) afforded the product as a colourless oil (0.39 g, 51%); ν_{max}/cm^{-1} (thin film, ATR) 3388 2976, 2935, 1733, 1687, 1597, 1582; δ_H (400 MHz, $CDCl_3$) 1.19 (3H, t, *J* 7.1, C*H*$_3$), 1.44 [9H, s, C(C*H*$_3$)$_3$], 1.56 (2H, p, *J* 6.8, C*H*$_2$), 1.98-2.09 (2H, m, C*H*$_2$), 3.17 (2H, q, *J* 6.8, C*H*$_2$), 4.16 (2H, q, *J* 7.1, OC*H*$_2$), 4.32 (1H, t, *J* 7.1, C*H*), 4.63 (1H, s, N*H*), 7.15 (1H, dd, *J* 8.3, 2.3, ArC*H*), 7.40 (1H, t, *J* 7.8, ArC*H*), 7.52 (1H, t, *J* 2.3, ArC*H*), 7.58 (1H, dd, *J* 7.8, 1.4, ArC*H*); δ_C (101 MHz, $CDCl_3$) 14.0 (*C*H$_3$), 26.1 (*C*H$_2$), 27.9 (*C*H$_2$), 28.4 [C(*C*H$_3$)$_3$], 40.1 (*C*H$_2$), 53.8 (OCH$_3$), 55.5 (OCH$_3$), 60.4 [*C*(CH$_3$)], 61.5 (OCH$_2$), 112.7 (Ar*C*H), 120.3 (Ar*C*H),

121.2 (Ar*C*H), 129.7 (Ar*C*H), 137.5 (Ar*C*), 156.0 (Ar*C*), 160.0 (*C*=O), 170.0 (*C*=O), 194.9 (*C*=O); *m*/*z* (ESI$^+$) 402.1902 [100%, (M+Na$^+$), $C_{20}H_{29}NO_6Na$ requires 402.1887].

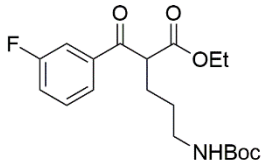
α-{[[(1,1-Dimethylethoxy)carbonyl]amino]propyl}-β-oxo-3'-bromo-benzenepropanoic acid ethyl ester 263



Sodium hydride (60% dispersion in mineral oil, 0.120 g, 3.0 mmol) was washed with hexane (3 × 1 mL) under nitrogen and then suspended in dry THF (1 mL). Ethyl(3-bromobenzoyl)acetate (0.598 g, 2.0 mmol) dissolved in dry THF (2 mL) was added dropwise. The mixture was heated at 35 °C for 30 min. *N*-Boc-3-Bromopropylamine (0.571 g, 2.4 mmol) in dry THF (3 mL) was added dropwise, tetrabutylammonium iodide (0.739 g, 2.0 mmol) was added in one portion, and then the reaction was heated at 60 °C for 20 h. After cooling to rt., aq. saturated ammonium chloride (2 mL) was added, diluted with water (10 mL), and the layers were separated. The aqueous layers were extracted using diethyl ether (3 × 15 mL). The combined organic layers were washed using brine (20 mL), dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure. Purification via flash column chromatography on silica gel (20:80 to 30:70 ethyl acetate:hexane) afforded the product as a yellow oil (0.19 g, 22%); ν_{max}/cm^{-1} (thin film, ATR) 3386, 2977, 2933, 1733, 1688; δ_H (400 MHz, $CDCl_3$) 1.19 (3H, t, *J* 7.1, C*H*$_3$), 1.44 [9H, s, C(C*H*$_3$)$_3$], 1.50-1.63 (2H, m, C*H*$_2$), 1.98-2.06 (2H, m, C*H*$_2$), 3.17 (2H, q, *J* 6.7, C*H*$_2$), 4.08-4.22 (2H, m, OC*H*$_2$), 4.28 (1H, t, *J* 7.2, C*H*), 4.63 (1H, s, N*H*), 7.37 (1H, t, *J* 7.9, ArC*H*), 7.69-7.76 (1H, m, ArC*H*), 7.92 (1H, dt, *J* 7.9, 1.5, ArC*H*), 8.13 (1H, t, *J* 1.5, ArC*H*); δ_C (101 MHz, $CDCl_3$) 14.0 (*C*H$_3$), 25.9 (*C*H$_2$), 27.8 (*C*H$_2$), 28.4 [C(*C*H$_3$)$_3$], 40.0 [*C*(CH$_3$)$_3$], 53.8 (*C*H), 61.6 (O*C*H$_2$), 123.2 (Ar*C*), 127.1 (Ar*C*H), 130.3 (Ar*C*H), 131.6 (Ar*C*H), 136.4 (Ar*C*H), 137.9 (Ar*C*), 155.9 (*C*=O), 169.4 (*C*=O), 193.7 (*C*=O); *m*/*z* (ESI$^+$) 450.0906

[100%, (M+Na^+), $C_{19}H_{26}NO_5Na^{79}Br$ requires 450.0887], 452.0887 [100%, (M+Na^+), $C_{19}H_{26}NO_5Na^{81}Br$ requires 452.0866].

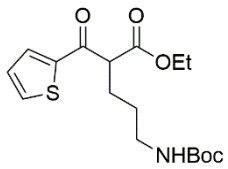
α-{[[(1,1-Dimethylethoxy)carbonyl]amino]propyl}-β-oxo-3'-fluoro-benzenepropanoic acid ethyl ester 264



Sodium hydride (60% dispersion in mineral oil, 0.120 g, 3.0 mmol) was washed using hexane (3 × 1 mL) under nitrogen and the suspended in dry THF (1 mL). Ethyl(3-fluorobenzoyl)acetate (0.420 g, 2.0 mmol) in dry THF (2 mL) was added dropwise and the reaction mixture was heated at 35 °C for 30 min. *N*-Boc-3-Bromopropylamine (0.571 g, 2.4 mmol) in dry THF (3 mL) was added dropwise followed by tetrabutylammonium iodide (0.739 g, 2.0 mmol) in one portion. The reaction was heated a 60 °C overnight. After cooling to rt., the reaction was quenched via the addition of aq. saturated ammonium chloride (2 mL) and diluted with water (10 mL). The layers were separated, and the aqueous layer was extracted using ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure. Purification using Combi Flash (silica gel, ethyl acetate:hexane as eluent) affording the product as a pale-yellow oil (0.14 g, 19%); ν_{max}/cm^{-1} (thin film, ATR) 3386, 2978, 2935, 1734, 1690, 1589, 1514; δ_H (400 MHz, $CDCl_3$) 1.19 (3H, t, *J* 7.1, C*H*$_3$), 1.45 [9H, s, C(C*H*$_3$)$_3$], 1.57 (2H, p, *J* 6.8, C*H*$_2$), 1.99-2.09 (2H, m, C*H*$_2$), 3.18 (2H, q, *J* 6.8, C*H*$_2$), 4.12-4.22 (2H, m, OC*H*$_2$), 4.30 (1H, t, *J* 7.2, C*H*), 4.61 (1H, s, N*H*), 7.31 (1H, tdd, *J* 8.2, 2.6, 1.0, ArC*H*), 7.48 (1H, td, *J* 8.2, 5.5, ArC*H*), 7.65-7.73 (1H, m, ArC*H*), 7.79 (1H, dt, *J* 7.8, 1.0, ArC*H*); δ_C (101 MHz, $CDCl_3$) 14.0 (*C*H$_3$), 25.9 (*C*H$_2$), 27.9 (*C*H$_2$), 28.4 [C(*C*H$_3$)$_3$], 40.0 (*C*H$_2$), 53.9 (*C*H), 61.6 (O*C*H$_2$), 115.4 (d, $J_{C\text{-}F}$ 22.5, Ar*C*H), 120.7 (d, $J_{C\text{-}F}$ 21.5, Ar*C*H), 124.3 (d, $J_{C\text{-}F}$ 3.0, Ar*C*H), 130.5 (d, $J_{C\text{-}F}$ 7.5, Ar*C*H), 138.3 (d, $J_{C\text{-}F}$ 6.5,

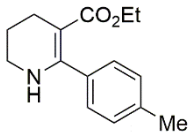
Ar*C*), 156.0 (*C*=O), 162.9 (d, $J_{C\text{-}F}$ 248.5, Ar*C*F), 169.5 (*C*=O), 193.8 (*C*=O); δ_F (376 MHz, $CDCl_3$) -111.3; *m/z* (ESI$^+$) 390.1696 [100%, $(M+Na)^+$, $C_{19}H_{26}NO_5FNa$ requires 390.1687].

α-{[[(1,1-Dimethylethoxy)carbonyl]amino]propyl}-β-oxo-thiothen-2-yl-propanoic acid ethyl ester 267



Sodium hydride (60% dispersion in mineral oil, 0.120 g, 3.0 mmol) was washed using hexane (3 × 1 mL) under nitrogen and then suspended in dry THF (1 mL). Ethyl-3-oxo-3-(thiophen-3-yl)propanoate (0.396 g, 2.0 mmol) in dry THF (2 mL) was added dropwise and the mixture was heated at 35 °C for 30 min. *N*-Boc-3-Bromopropylamine (0.571 g, 2.4 mmol) in dry THF (3 mL) was added dropwise followed by tetrabutylammonium iodide (0.739 g, 2.0 mmol) in one portion. The reaction was heated a 55 °C overnight. After cooling to rt., the reaction was quenched via the addition of aq. saturated ammonium chloride (3 mL). The layers were separated, and the aqueous layer was extracted using diethyl ether (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure. Purification using Combi Flash (silica gel, ethyl acetate:hexane as eluent) afforded the product as a yellow oil (0.62 g, 87%); ν_{max}/cm^{-1} (thin film, ATR) 3385, 2976, 2933, 1733, 1693, 1662; δ_H (400 MHz, $CDCl_3$) 1.21 (3H, t, *J* 7.1, C*H*$_3$), 1.44 [9H, s, C(C*H*$_3$)$_3$], 1.56 (2H, p, *J* 7.2, C*H*$_2$), 2.05 (2H, dt, *J* 9.9, 7.2, C*H*$_2$), 3.17 (2H, q, *J* 6.6, C*H*$_2$), 4.12-4.23 (3H, m, OC*H*$_2$ and C*H*), 4.62 (1H, s, N*H*), 7.16 (1H, dd, 4.9, 3.9, ArC*H*), 7.71 (dd, *J* 4.9, 1.1, ArC*H*), 7.84 (d, *J* 3.9, 1.1, ArC*H*); δ_C (101 MHz, $CDCl_3$) 14.0 (*C*H$_3$), 26.1 (*C*H$_2$), 27.8 (*C*H$_2$), 28.4 [C(*C*H$_3$)$_3$], 40.0 (*C*H$_2$), 53.4 [*C*(CH$_3$)$_3$], 54.9 (*C*H), 61.6 (O*C*H$_2$), 128.4 (Ar*C*H), 133.1 (Ar*C*H), 134.9 (Ar*C*H), 143.5 (Ar*C*), 156.0 (*C*=O), 169.4 (*C*=O), 187.6 (*C*=O); *m/z* (ESI$^+$) 378.1346 [100%, $(M+Na^+)$, $C_{17}H_{25}NO_5NaS$ requires 378.1357].

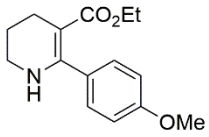
1,4,5,6-Tetrahydro-2-(4'-methyl)phenyl-4H-pyrridyl-3-carboxylic acid ethyl ester 268



α-{[[(1,1-Dimethylethoxy)carbonyl]amino]propyl}-β-oxo-4'-methyl-benzenepropanoic acid ethyl ester (0.350 g, 1.0 mmol) was dissolved in DCM (5 mL) under argon and cooled to 0 °C. Trifluoroacetic acid (0.74 mL, 10.0 mmol) was added dropwise, the reaction was warmed to rt., and stirred for 2.5 h. An ice/water slurry (10 mL) was added, and the mixture was neutralised using solid sodium hydrogen carbonate. After stirring for 2 h, the layers were separated, and the aqueous layer was extracted using DCM (3 × 10 mL). The combined organic layers were washed using brine (20 mL), dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure affording the product as an off-white solid (0.17 g, 69%) which was used directly in the next step without further purification; mpt. 78-80 °C; ν_{max}/cm^{-1} (ATR) 3384, 2949, 2853, 1737, 1666, 1632, 1562; δ_H (400 MHz, $CDCl_3$) 0.94 (3H, t, *J* 7.1, C*H*$_3$), 1.89 (2H, p, *J* 6.3, C*H*$_2$), 2.38 (3H, s, C*H*$_3$), 2.54 (2H, t, *J* 6.3, C*H*$_2$), 3.28-3.36 (2H, m, C*H*$_2$), 3.90 (2H, q, *J* 7.1, OC*H*$_2$), 4.05 (1H, s, N*H*), 7.13-7.23 (4H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 14.0 (*C*H$_3$), 21.3 (*C*H$_3$), 21.8 (*C*H$_2$), 23.2 (*C*H$_2$), 42.1 (*C*H$_2$), 58.7 (O*C*H$_2$), 94.4 (*C*=C), 127.8 (2 × Ar*C*H), 128.6 (2 × Ar*C*H), 137.2 (Ar*C*), 138.0 (Ar*C*), 154.4 (N*C*=C), 168.8 (*C*=O); *m/z* (ESI$^+$) 246.1494 [100%, $(M+H)^+$, $C_{15}H_{20}NO_2$ requires 246.1489].

Selected data from crude ^{1}H and ^{13}C NMR spectra.

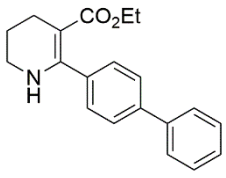
1,4,5,6-Tetrahydro-2-(4'-methoxy)phenyl-4H-pyrridyl-3-carboxylic acid ethyl ester 269



α-{[[(1,1-Dimethylethoxy)carbonyl]amino]propyl}-β-oxo-4'-methoxy-benzenepropanoic acid ethyl ester (0.42 g, 1.1 mmol) was dissolved in DCM (5 mL) under argon and cooled to 0 °C. Trifluoroacetic acid (0.85 mL, 11.1 mmol) was added dropwise. The reaction was warmed to rt. and stirred for 2.5 h. An ice/water slurry (10 mL) was added, and the mixture was neutralised using solid sodium hydrogen carbonate. After stirring for 1.5 h, the layers were separated, and the aqueous layer was extracted using DCM (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure. The product was afforded as a pale-yellow solid (0.24 g, 83%) which was used directly in the next step without further purification. A small quantity was purified by flash column chromatography on silica gel (50:50 ethyl acetate:hexane) for characterisation; mpt. 80-82 °C; ν_{max}/cm^{-1} (ATR) 3348, 2977, 2947, 2838, 1626, 1607, 1588; δ_H (400 MHz, $CDCl_3$) 0.96 (3H, t, *J* 7.1, C*H*$_3$), 1.88 (2H, qd, *J* 6.3, 3.7, C*H*$_2$), 2.54 (2H, t, *J* 6.3, C*H*$_2$), 3.28-3.36 (2H, m, C*H*$_2$), 3.84 (3H, s, OC*H*$_3$), 3.91 (2H, q, *J* 7.1, OC*H*$_2$), 4.03-4.14 (1H, m, N*H*), 6.84-6.92 (2H, m, ArC*H*), 7.21-7.29 (2H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 14.1 (*C*H$_3$), 21.9 (*C*H$_2$), 23.3 (*C*H$_2$), 42.2 (*C*H$_2$), 55.3 (O*C*H$_3$), 58.7 (O*C*H$_2$), 94.5 (*C*=C), 113.3 (2 × Ar*C*H), 129.3 (2 × Ar*C*H), 132.4 (Ar*C*), 154.1 (Ar*C*O), 159.7 (N*C*=C), 168.9 (*C*=O); *m/z* (ESI$^+$) 262.1445 [100%, $(M+H)^+$, $C_{15}H_{20}NO_3$ requires 262.1438].

Selected data from crude ^{1}H and ^{13}C NMR spectra.

1,4,5,6-Tetrahydro-2-(4'-phenyl)phenyl-4H-pyrridyl-3-carboxylic acid ethyl ester 270

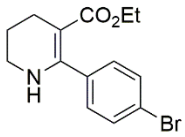


α-{[[(1,1-Dimethylethoxy)carbonyl]amino]propyl}-β-oxo-4'-phenyl -benzenepropanoic acid ethyl ester (0.231 g, 0.54 mmol) was dissolved in DCM (5 mL) under argon and cooled to 0 °C. Trifluoroacetic acid (0.46 mL, 5.43 mmol) was added dropwise. The reaction was warmed to

rt. and stirred for 2.5 h. An ice/water slurry (10 mL) was added, and the mixture was neutralised using solid sodium hydrogen carbonate. After stirring for 1.5 h, the layers were separated, and the aqueous layer was extracted using DCM (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure. The product was afforded as a pale-yellow solid (0.10 g, 63%) which was used directly in the next step without further purification; mpt. 99-101 °C; δ_H (400 MHz, $CDCl_3$) 0.92 (3H, t, *J* 7.1, C*H*$_3$), 1.92 (2H, p, *J* 6.3, C*H*$_2$), 2.57 (2H, t, *J* 6.4, C*H*$_2$), 3.31-3.40 (2H, m, C*H*$_2$), 3.91 (2H, q, *J* 7.1, OC*H*$_2$), 4.06-4.17 (1H, m, N*H*), 7.33-7.42 (3H, m, ArC*H*), 7.47 (2H, t, *J* 7.6, ArC*H*), 7.56-7.66 (4H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 14.0 (*C*H$_3$), 21.7 (*C*H$_2$), 23.2 (*C*H$_2$), 42.2 (*C*H$_2$), 58.8 (O*C*H$_2$), 94.8 (*C*=C), 126.6 (2 × Ar*C*H), 127.1 (2 × Ar*C*H), 127.4 (Ar*C*H), 128.5 (2 × Ar*C*H), 128.8 (2 × Ar*C*H), 139.2 (Ar*C*), 140.8 (Ar*C*), 141.1 (Ar*C*), 154.0 (N*C*=C), 168.8 (*C*=O); *m/z* (ESI$^+$) 308.1659 [100%, $(M+H)^+$, $C_{20}H_{22}NO_2$ requires 308.1645].

Selected data from crude ^{1}H and ^{13}C NMR spectra.

1,4,5,6-Tetrahydro-2-(4'-bromo)phenyl-4H-pyrridyl-3-carboxylic acid ethyl ester 271

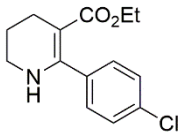


α-{[[(1,1-Dimethylethoxy)carbonyl]amino]propyl}-β-oxo-4'-bromo-benzenepropanoic acid ethyl ester (0.32 g, 0.75 mmol) was dissolved in DCM (4 mL) under argon and cooled to 0 °C. Trifluoracetic acid (0.57 mL, 7.50 mmol) was added dropwise. Once addition was complete, the reaction warmed to rt. and stirred for 2.5 h. An ice/water slurry (10 mL) was added, and the mixture neutralised using solid sodium hydrogen carbonate. After stirring for 2 h, the layers were separated, and the aqueous layer was extracted using DCM (3 × 10 mL). The combined organic layers were washed using brine (20 mL), dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure affording the product as a pale-yellow solid (0.28 g, 91%)

which was used directly in the next step without further purification; mpt. 103-104 °C; δ_H (400 MHz, $CDCl_3$) 0.96 (3H, t, *J* 7.1, C*H*$_3$), 1.89 (2H, p, *J* 6.3, C*H*$_2$), 2.53 (2H, t, *J* 6.3, C*H*$_2$), 3.29-3.37 (2H, m, C*H*$_2$), 3.90 (2H, q, *J* 7.1, OC*H*$_2$), 7.15 (2H, m, ArC*H*), 7.46-7.52 (2H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 14.0 (*C*H$_3$), 21.6 (*C*H$_2$), 23.1 (*C*H$_2$), 42.1 (*C*H$_2$), 58.9 (O*C*H$_2$), 129.7 (2 × Ar*C*H), 131.1 (2 × Ar*C*H), 139.0 (Ar*C*), 153.0 (Ar*C*); *m*/*z* (ESI$^+$) 310.0449 [100%, $(M+H)^+$, $C_{14}H_{17}NO_2{}^{79}Br$ requires 310.0437].

Selected peaks from crude ^{1}H and ^{13}C NMR spectra. Quaternary carbons not observable in the ^{13}C NMR spectra due to running a short collection time because of the oxidation process observed with this compound class.

1,4,5,6-Tetrahydro-2-(4'-chloro)phenyl-4H-pyrridyl-3-carboxylic acid ethyl ester 272

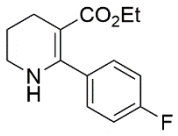


α-{[[(1,1-Dimethylethoxy)carbonyl]amino]propyl}-β-oxo-4'-chloro-benzenepropanoic acid ethyl ester (0.25 g, 0.64 mmol) was dissolved in DCM (5 mL) under argon and cooled to 0 °C. Trifluoracetic acid (0.49 mL, 6.40 mmol) was added dropwise. Once addition was complete, the reaction warmed to rt. and stirred for 2.5 h. An ice/water slurry (10 mL) was added, and the mixture neutralised using solid sodium hydrogen carbonate. After stirring for 1.5 h, the layers were separated, and the aqueous layer was extracted using DCM (3 × 10 mL). The combined organic layers were washed using brine (15 mL), dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure affording the product as a pale-yellow solid (0.12 g, 71%) which was used directly in the next step without further purification; mpt: 101-103 °C; δ_H (400 MHz, $CDCl_3$) 0.95 (3H, t, *J* 7.2, C*H*$_2$), 1.89 (2H, p, *J* 6.3, C*H*$_2$), 2.53 (2H, t, *J* 6.3, C*H*$_2$), 3.28-3.36 (2H, m, C*H*$_2$), 3.89 (2H, q, *J* 7.2, OC*H*$_2$), 4.04 (1H, s, N*H*), 7.21-7.30 (2H, m, ArC*H*), 7.30-7.36 (2H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 14.0 (*C*H$_3$), 21.6 (*C*H$_2$), 23.1 (*C*H$_2$),

42.1 (*C*H_2), 58.8 (O*C*H_2), 95.1 (*C*=C), 128.1 (2 × Ar*C*H), 129.4 (2 × Ar*C*H), 134.1 (Ar*C*), 138.6 (Ar*C*), 153.0 (N*C*=C), 168.5 (*C*=O); *m*/*z* (ESI$^+$) 266.0946 [100%, (M+H)$^+$, $C_{14}H_{17}NO_2{}^{35}Cl$ requires 266.0942].

Selected peaks from crude ^{1}H and ^{13}C NMR spectra.

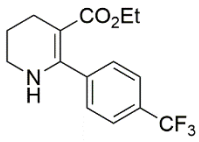
1,4,5,6-Tetrahydro-2-(4'-fluoro)phenyl-4H-pyrridyl-3-carboxylic acid ethyl ester 273



α-{[[(1,1-Dimethylethoxy)carbonyl]amino]propyl}-β-oxo-4'-fluoro-benzenepropanoic acid ethyl ester (0.169 g, 0.46 mmol) was dissolved in DCM (5 mL) under argon and cooled to 0 °C. Trifluoracetic acid (0.39 mL, 4.60 mmol) was added dropwise. Once addition was complete, the reaction warmed to rt. and stirred for 2.5 h. An ice/water slurry (10 mL) was added, and the mixture neutralised using solid sodium hydrogen carbonate. After stirring for 1.5 h, the layers were separated, and the aqueous layer was extracted using DCM (3 × 10 mL). The combined organic layers were washed using brine (10 mL), dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure affording the product as a pale-yellow solid (0.10 g, 86%) which was used directly in the next step without further purification; mpt. 98-100 °C; δ_H (400 MHz, $CDCl_3$) 0.94 (3H, t, *J* 7.1, C*H*$_3$), 1.84-1.94 (2H, m, C*H*$_2$), 2.54 (2H, t, *J* 6.4, C*H*$_2$), 3.29-3.37 (2H, m, C*H*$_2$), 3.89 (2H, q, *J* 7.1, OC*H*$_2$), 4.03 (1H, s, N*H*), 7.00-7.09 (2H, m, ArC*H*), 7.24-7.32 (2H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 14.0 (*C*H_3), 21.7 (*C*H_2), 23.1 (*C*H_2), 42.1 (*C*H_2), 58.8 (O*C*H_2), 114.8 (d, $J_{C\text{-}F}$ 22.0, 2 × Ar*C*H), 129.8 (d, $J_{C\text{-}F}$ 8.0, 2 × Ar*C*H), 153.2 (N*C*=C), 168.6 (*C*=O); δ_F (376 MHz, $CDCl_3$) -113.6; *m*/*z* (ESI$^+$) 250.1247 [100%, (M+H)$^+$, $C_{14}H_{17}NO_2F$ requires 250.1238].

Selected peaks from crude ^{1}H, ^{13}C and ^{19}F NMR spectra. Most quaternary carbons not observable in the ^{13}C NMR spectra due to running a short collection time because of the oxidation process observed with this compound class.

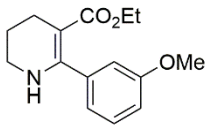
1,4,5,6-Tetrahydro-2-[4'-(1,1,1-trifluoromethyl)]phenyl-4H-pyrridyl-3-carboxylic acid ethyl ester 274



α-{[[(1,1-Dimethylethoxy)carbonyl]amino]propyl}-β-oxo-4'-(1,1,1-trifluoromethyl)-benzenepropanoic acid ethyl ester (0.154 g, 0.37 mmol) was dissolved in DCM (4 mL) under argon and cooled to 0 °C. Trifluoracetic acid (0.31 mL, 3.69 mmol) was added dropwise. Once addition was complete, the reaction warmed to rt. and stirred for 2.5 h. An ice/water slurry (10 mL) was added, and the mixture neutralised using solid sodium hydrogen carbonate. After stirring for 2 h, the layers were separated, and the aqueous layer was extracted using DCM (3 × 10 mL). The combined organic layers were washed using brine (10 mL), dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure affording the product as a pale-yellow solid (0.09 g, 83%) which was used directly in the next step without further purification; mpt. 95-97 °C; δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 7.2, C*H*$_3$), 1.92 (2H, p, *J* 6.3, C*H*$_2$), 2.55 (2H, t, *J* 6.3, C*H*$_2$), 3.31-3.39 (2H, m, C*H*$_2$), 3.87 (2H, q, *J* 7.2, OC*H*$_2$), 4.03 (1H, t, *J* 3.2, N*H*), 7.43 (2H, d, *J* 8.2, ArC*H*), 7.62 (2H, d, *J* 8.2, ArC*H*); δ_C (101 MHz, $CDCl_3$) 13.8 (*C*H$_3$), 21.5 (*C*H$_2$), 22.9 (*C*H$_2$), 42.1 (*C*H$_2$), 58.9 (O*C*H$_2$), 95.5 (*C*=C), 124.9 (2 × Ar*C*H), 128.4 (2 × Ar*C*H), 143.8 (N*C*=C), 152.7 (*C*=O); *m/z* (ESI$^+$) 300.1213 [100%, $(M+H)^+$, $C_{15}H_{17}NO_2F_3$ requires 300.1206].

Selected peaks from crude ^{1}H and ^{13}C NMR spectra. Some quaternary carbons not observable in the ^{13}C NMR spectra due to running a short collection time because of the oxidation process observed with this compound class.

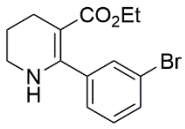
1,4,5,6-Tetrahydro-2-(3'-methoxy)phenyl-4H-pyrridyl-3-carboxylic acid ethyl ester 275



α-{[[(1,1-Dimethylethoxy)carbonyl]amino]propyl}-β-oxo-3'-methoxy-benzenepropanoic acid ethyl ester (0.253 g, 0.67 mmol) was dissolved in DCM (4 mL) under argon and cooled to 0 °C. Trifluoroacetic acid (0.51 mL, 6.7 mmol) was added dropwise. Once addition was complete, the reaction was warmed to rt. and stirred for 2.5 h. An ice/water slurry (10 mL) was added. The mixture was neutralised using solid sodium hydrogen carbonate and then stirred for 1.5 h. The layers were separated, and the aqueous layers were extracted using DCM (3 × 10 mL). The combined organic layers were washed using brine (20 mL), dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure affording the product as a pale-yellow solid (0.14 g, 80%) which was used directly in the next step without further purification; mpt. 102-104 °C; δ_H (400 MHz, $CDCl_3$) 0.90 (3H, t, *J* 7.2, C*H*$_3$), 2.54 (2H, t, *J* 6.4, C*H*$_2$), 3.28-3.36 (2H, m, C*H*$_2$), 3.81 (3H, s, OC*H*$_3$), 3.87 (2H, q, *J* 7.2, OC*H*$_2$), 6.86-6.93 (2H, m, ArC*H*), 7.18-7.31 (2H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 13.9 (*C*H$_3$), 21.7 (*C*H$_2$), 23.1 (*C*H$_2$), 42.1 (*C*H$_2$), 55.3 (O*C*H$_3$), 58.7 (O*C*H$_2$), 94.5 (*C*=C), 113.3 (Ar*C*H), 114.0 (Ar*C*H), 120.4 (Ar*C*H), 128.9 (Ar*C*H), 141.6 (Ar*C*), 154.0 (Ar*C*), 159.2 (N*C*=C), 168.8 (*C*=O); *m/z* (ESI$^+$) 262.1439 [100%, $(M+H)^+$, $C_{15}H_{20}NO_3$ requires 262.1438].

Selected peaks from crude ^{1}H and ^{13}C NMR spectra.

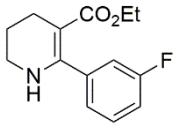
1,4,5,6-Tetrahydro-2-(3'-bromo)phenyl-4H-pyrridyl-3-carboxylic acid ethyl ester 276



α-{[[(1,1-Dimethylethoxy)carbonyl]amino]propyl}-β-oxo-3'-bromo-benzenepropanoic acid ethyl ester (0.162 g, 0.38 mmol) was dissolved in DCM (4 mL) under argon and cooled to 0 °C. TFA (0.29 mL, 3.80 mmol) was added dropwise. After addition was complete, the reaction was warmed to rt. and stirred for 2.5 h. An ice/water slurry (10 mL) was added, the mixture neutralised using solid sodium hydrogen carbonate, and the mixture stirred for 1.5 h. The layers were separated, and the aqueous layer was extracted using DCM (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure affording the product as a yellow solid (0.10 g, 86%) which was used directly in the next step without further purification; mpt. 84-86 °C; δ_H (400 MHz, $CDCl_3$) 0.92 (3H, t, *J* 7.1, C*H*$_3$), 1.89 (2H, p, *J* 6.2, C*H*$_2$), 2.54 (2H, t, *J* 6.3, C*H*$_2$), 3.29-3.37 (2H, m, C*H*$_2$), 3.89 (2H, q, *J* 7.1, OC*H*$_2$), 4.02 (1H, bs, N*H*), 7.20-7.27 (2H, m, ArC*H*), 7.45-7.52 (2H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 13.9 (*C*H$_3$), 21.6 (*C*H$_2$), 23.0 (*C*H$_2$), 42.1 (*C*H$_2$), 58.9 (O*C*H$_2$), 95.4 (*C*=C), 121.7 (Ar*C*), 126.7 (Ar*C*H), 129.4 (Ar*C*H), 131.1 (Ar*C*H), 131.2 (Ar*C*H), 142.1 (Ar*C*), 152.4 (N*C*=C), 168.4 (*C*=O); *m/z* (ESI$^+$) 310.0449 [100%, $(M+H)^+$, $C_{14}H_{17}NO_2{}^{79}Br$ requires 310.0437].

Selected peaks from crude ^{1}H and ^{13}C NMR spectra.

1,4,5,6-Tetrahydro-2-(3'-fluoro)phenyl-4H-pyrridyl-3-carboxylic acid ethyl ester 277

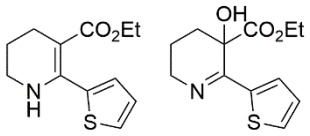


α-{[[(1,1-Dimethylethoxy)carbonyl]amino]propyl}-β-oxo-3'-fluoro-benzenepropanoic acid ethyl ester (0.121 g, 0.33 mmol) was dissolved in DCM (5 mL) under argon and cooled to 0 °C.

Trifluoracetic acid (0.25 mL, 3.29 mmol) was added dropwise. Once addition was complete, the reaction warmed to rt. and stirred for 2.5 h. An ice/water slurry (10 mL) was added, and the mixture neutralised using solid sodium hydrogen carbonate. After stirring for 1.5 h, the layers were separated, and the aqueous layer was extracted using DCM (3 × 10 mL). The combined organic layers were washed using brine (10 mL), dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure affording the product as a pale-yellow solid (0.072 g, 88%) which was used directly in the next step without further purification; mpt. 94-96 °C; δ_H (400 MHz, $CDCl_3$) 0.92 (3H, t, *J* 7.2, C*H*$_3$), 1.90 (2H, qd, *J* 6.4, 3.9, C*H*$_2$), 2.54 (2H, t, *J* 6.4, C*H*$_2$), 3.29-3.37 (2H, m, C*H*$_2$), 3.89 (2H, q, *J* 7.2, OC*H*$_2$), 4.04 (1H, s, N*H*), 6.99-7.12 (3H, m, ArC*H*), 7.27-7.37 (1H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 13.9 (*C*H$_3$), 21.6 (*C*H$_2$), 23.0 (*C*H$_2$), 42.1 (*C*H$_2$), 58.8 (O*C*H$_2$), 114.9 (Ar*C*H), 115.4 (Ar*C*H), 123.8 (Ar*C*H), 129.4 (d, $J_{C\text{-}F}$ 8.0, Ar*C*H); δ_F (376 MHz, $CDCl_3$) -113.8; *m/z* (ESI$^+$) 250.1244 [100%, $(M+H)^+$, $C_{14}H_{17}NO_2F$ requires 250.1238].

Selected peaks from crude ^{1}H, ^{13}C and ^{19}F NMR spectra. Most quaternary carbons not observable in the ^{13}C NMR spectra due to running a short collection time because of the oxidation process observed with this compound class.

1,4,5,6-Tetrahydro-2-(thiothen-2-yl)-4H-pyrridyl-3-carboxylic acid ethyl ester 278 (a) and 5,6-dihydro-2-(thiothen-2-yl)-3-pyrridinol-3-carboxylic acid ethyl ester (b)

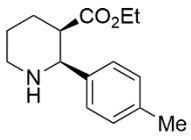


α-{[[(1,1-Dimethylethoxy)carbonyl]amino]propyl}-β-oxo-thiothen-2-yl-propanoic acid ethyl ester (0.270 g, 0.76 mmol) was dissolved in DCM (5 mL) under argon and cooled to 0 °C. Trifluoracetic acid (0.65 mL, 7.60 mmol) was added dropwise. Once addition was complete, the reaction warmed to rt. and stirred for 2.5 h. An ice/water slurry (10 mL) was added, and

the mixture neutralised using solid sodium hydrogen carbonate. After stirring for 1.5 h, the layers were separated, and the aqueous layer was extracted using DCM (3 × 15 mL). The combined organic layers were washed using brine (15 mL), dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure affording the product as an orange oil (0.12 g, 65%) which was used directly in the next step without further purification; δ_H (400 MHz, $CDCl_3$, **a**:**b** 45:55) 1.00 (1.35H, t, *J* 7.1, **a** C*H*$_3$), 1.20 (1.65H, t, *J* 7.1, **b** C*H*$_3$), 1.60-1.74 (0.55H, m, **b** C*H*H), 2.53 (0.90H, t, *J* 6.4, **a** C*H*$_2$), 3.26-3.34 (0.90H, m, **a** C*H*$_2$), 3.95 (0.90H, q, *J* 7.1, **a** OC*H*$_2$), 4.16 (1.10H, q, *J* 7.1, **b** OC*H*$_2$), 6.93-7.10 (1.45H, m, ArC*H*), 7.24-7.36 (1.55H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 97.6 (**a**, *C*=C), 156.6 (**b**, *C*=N), 168.7 (**a**, *C*=O), 172.1 (**b**, *C*=O); *m*/*z* (ESI$^+$, **a**) 238.0905 [100%, $(M+H)^+$, $C_{12}H_{16}NO_2S$ requires 238.0896]; *m*/*z* (ESI$^+$, **b**) 254.0856 [100%, $(M+H)^+$, $C_{12}H_{16}NO_3S$ requires 254.0845].

Selected peaks from crude ^{1}H and ^{13}C NMR spectra.

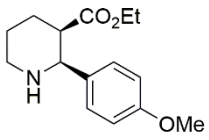
(±)-*cis*-Ethyl 2-(4'-methyl)phenylpiperidine-3-carboxylate 279



1,4,5,6-Tetrahydro-2-(4'-methyl)-phenyl-4H-pyrridyl-3-carboxylic acid ethyl ester (61 mg, 0.25 mmol) was dissolved in methanol (5 mL). Hydrogenation was performed employing the H-Cube® reactor (30 bar, 35 °C) with 5% Pd/C CatCart®. The reaction mixture was cycled through three times. The solvent was removed under reduced pressure. Purification via small scale column chromatography on silica gel (5:95 methanol:DCM) afforded the product as a pale -yellow oil (59 mg, 95%); ν_{max}/cm^{-1} (thin film, ATR) 2978, 2931, 2855, 1718, 1515; δ_H (400 MHz, $CDCl_3$, >99:1 dr *cis*:*trans*) 1.00 (3H, t, *J* 7.1, C*H*$_3$), 1.46-1.55 (1H, m, C*H*H), 1.78-2.01 (2H, m, C*H*$_2$), 2.13-2.21 (1H, m, C*H*), 2.23 (1H, bs, N*H*), 2.32 (3H, s, C*H*$_3$), 2.81 (1H, dd, *J* 13.1, 12.1, 3.1, C*H*^{B}), 2.95 (1H, dt, *J* 6.2, 3.0, C*H*), 3.36 (1H, ddt, *J* 13.1, 4.3, 2.1, C*H*^{A}), 3.86-

4.00 (3H, m, OCH_2 and CH), 7.11 (2H, d, J 8.1, ArCH), 7.20 (2H, d, J 8.1, ArCH); δ_C (101 MHz, $CDCl_3$) 14.0 (*C*H_3), 21.0 (*C*H), 21.1 (*C*H_2), 27.9 (*C*H_2), 44.5 (*C*H), 47.1 (*C*H_2), 59.7 (O*C*H_2), 60.9 (*C*H), 125.9 (2 × Ar*C*H), 128.8 (2 × Ar*C*H), 136.1 (Ar*C*), 139.3 (Ar*C*), 173.7 (*C*=O); *m*/*z* (ESI^+) 248.1653 [100%, $(M+H)^+$, $C_{15}H_{22}NO_2$ requires 248.1645].

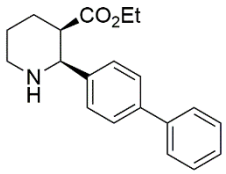
(±)-*cis*-Ethyl 2-(4'-methoxy)phenylpiperidine-3-carboxylate 280[125]



1,4,5,6-Tetrahydro-2-(4'-methoxy)-phenyl-4H-pyrridyl-3-carboxylic acid ethyl ester (65 mg, 0.25 mmol) was dissolved in methanol (5 mL). Hydrogenation was performed employing the H-Cube® reactor (30 bar, 35 °C) with 5% Pd/C CatCart®. The reaction mixture was cycled through three times. The solvent was removed under reduced pressure. Purification via small scale column chromatology on silica gel (5:95 methanol:DCM) afforded the product as a pale-yellow oil (48 mg, 64%); v_{max}/cm^{-1} (thin film, ATR) 2934, 2855, 1717, 1612, 1583, 1513; δ_H (400 MHz, $CDCl_3$, dr 98:2) 1.02 (3H, t, J 7.1, CH_3), 1.44-1.56 (1H, m, CHH), 1.78-2.01 (2H, m, CH_2), 2.04 (1H, bs, NH), 2.17 (1H, dt, J 13.0, 2.5, CH), 2.82 (1H, ddd, J 13.2, 12.1, 3.0, CH^B), 2.94 (1H, dt, J 6.0, 3.1, CH), 3.35 (1H, ddt, J 13.2, 4.2, 2.1, CH^A), 3.80 (3H, s, OCH_3), 3.80-4.01 (3H, m, OCH_2 and CH), 6.91-6.89 [2H, $(AX)_2$, ArCH], 7.20-7.28 [2H, $(AX)_2$, ArCH]; δ_C (101 MHz, $CDCl_3$) 14.0 (*C*H_3), 22.0 (*C*H_2), 27.8 (*C*H_2), 44.5 (*C*H), 47.1 (*C*H_2), 55.2 (O*C*H_3), 59.7 (O*C*H_2), 60.7 (N*C*H), 113.4 (2 × Ar*C*H), 127.1 (2 × Ar*C*H), 134.6 (Ar*C*), 158.3 (Ar*C*O), 173.7 (*C*=O); *m*/*z* (ESI^+) 264.1600 [100%, $(M+H)^+$, $C_{15}H_{22}NO_3$ requires 264.1594].

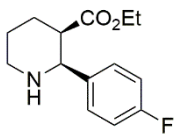
Data are in accordance with the literature.

(±)-*cis*-Ethyl 2-(4'-phenyl)phenylpiperidine-3-carboxylate 281



1,4,5,6-Tetrahydro-2-(4'-phenyl)-phenyl-4H-pyrridyl-3-carboxylic acid ethyl ester (76.8 mg, 0.25 mmol) was dissolved in methanol (5 mL). Hydrogenation was performed employing the H-Cube® reactor (30 bar, 35 °C) with 5% Pd/C CatCart®. The reaction mixture was cycled through three times. The solvent was removed under reduced pressure. Purification via small scale column chromatology on silica gel (5:95 methanol:DCM) afforded the product as a pale-yellow oil (59 mg, 76%); ν_{max}/cm^{-1} (thin film, ATR) 3029, 2934, 2856, 1717; δ_H (400 MHz, $CDCl_3$, dr 96:4) 1.00 (3H, t, *J* 7.1, C*H*$_3$), 1.51-1.60 (1H, m, C*H*H), 1.81-2.06 (2H, m, C*H*$_2$), 2.15-2.26 (2H, m, C*H* and N*H*), 2.85 (1H, ddd, *J* 13.1, 12.4, 3.0, C*H*^{B}), 2.99-3.06 (1H, m, C*H*H), 3.36 (1H, ddt, *J* 13.1, 4.3, 2.1, C*H*^{A}), 3.94 (2H, q, *J* 7.1, OC*H*$_2$), 4.04 (1H, d, *J* 3.3, C*H*), 7.30-7.49 (5H, m, ArC*H*), 7.53-7.64 (4H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 14.0 (*C*H$_3$), 22.1 (*C*H$_2$), 27.8 (*C*H$_2$), 44.4 (*C*H), 47.1 (*C*H$_2$), 59.8 (O*C*H$_2$), 60.9 (*C*H), 126.5 (2 × Ar*C*H), 126.8 (2 × Ar*C*H), 127.0 (2 × Ar*C*H), 127.1 (Ar*C*H), 128.7 (2 × Ar*C*H), 139.5 (Ar*C*), 140.9 (Ar*C*), 141.3 (Ar*C*), 173.6 (*C*=O); *m/z* (ESI$^+$) 310.1809 [100%, $(M+H)^+$, $C_{20}H_{24}NO_2$ requires 310.1802].

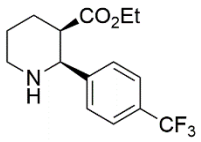
(±)-*cis*-Ethyl 2-(4'-fluoro)phenylpiperidine-3-carboxylate 282



1,4,5,6-Tetrahydro-2-(4'-fluoro)-phenyl-4H-pyrridyl-3-carboxylic acid ethyl ester (62.0 mg, 0.25 mmol) was dissolved in methanol (5 mL). Hydrogenation was performed employing the H-Cube® reactor (30 bar, 35 °C) with 5% Pd/C CatCart®. The reaction mixture was cycled through three times. The solvent was removed under reduced pressure. Purification via small

scale column chromatology on silica gel (5:95 methanol:DCM) afforded the product as a pale-yellow oil (57 mg, 91%); ν_{max}/cm^{-1} (thin film, ATR) 3318, 2935, 2856, 1718, 1606, 1509; δ_H (400 MHz, $CDCl_3$, dr >99:1) 1.02 (3H, t, *J* 7.2, C*H*$_3$), 1.48-1.58 (1H, m, C*H*H), 1.76-2.02 (2H, m, C*H*H), 2.13-2.24 (1H, m, C*H*H), 2.37 (1H, bs, N*H*), 2.82 (1H, ddd, *J* 13.2, 12.4, 3.1, C*H*^{B}), 2.92-2.99 (1H, m, C*H*H), 3.36 (1H, ddt, *J* 13.2, 4.2, 2.1, C*H*^{A}), 3.87-3.99 (3H, m, OC*H*$_2$ and C*H*), 6.96-7.05 (2H, m, ArC*H*), 7.26-7.34 (2H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 14.0 (*C*H$_3$), 21.9 (*C*H$_2$), 27.7 (*C*H$_2$), 44.4 (*C*H), 47.0 (*C*H$_2$), 59.9 (*C*H$_2$), 60.5 (*C*H), 114.9 (d, $J_{C\text{-}F}$ 21.0, Ar*C*H), 127.6 (d, $J_{C\text{-}F}$ 8.0, Ar*C*H), 137.9 (d, $J_{C\text{-}F}$ 2.5, Ar*C*), 161.7 (d, $J_{C\text{-}F}$ 244.5, Ar*C*F), 173.4 (*C*=O); δ_F (376 MHz, $CDCl_3$) -116.5; *m*/*z* (ESI$^+$) 252.1407 [100%, (M+H)$^+$, $C_{14}H_{19}NO_2F$ requires 252.1394].

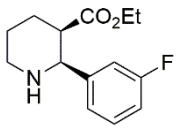
(±)-*cis*-Ethyl 2-[4'-(1,1,1-trifluoromethyl)]phenylpiperidine-3-carboxylate 283



1,4,5,6-Tetrahydro-2-(4'-fluoro)-phenyl-4H-pyrridyl-3-carboxylic acid ethyl ester (74.8 mg, 0.25 mmol) was dissolved in methanol (5 mL). Hydrogenation was performed employing the H-Cube® reactor (30 bar, 35 °C) with 5% Pd/C CatCart®. The reaction mixture was cycled through three times. The solvent was removed under reduced pressure. Purification via small scale column chromatology on silica gel (5:95 methanol:DCM) afforded the product as a pale-yellow oil (69.1 mg, 92%); ν_{max}/cm^{-1} (thin film, ATR) 2936, 2858, 1720, 1619; δ_H (400 MHz, $CDCl_3$, dr >99:1) 1.00 (3H, t, *J* 7.2, C*H*$_3$), 1.56 (1H, dt *J* 13.3, 3.2, C*H*H), 1.76-1.90 (1H, m, C*H*H), 1.92-2.06 (2H, m, C*H*H and N*H*), 2.17-2.28 (1H, m, C*H*H), 2.83 (1H, td, *J* 13.2, 12.4, 3.2, C*H*^{B}), 3.01 (1H, dt, *J* 5.6, 2.9, C*H*H), 3.37 (1H, ddt, *J* 13.2, 4.3, 2.1, C*H*^{A}), 3.92 (2H, qd, *J* 7.2, 5.3, OC*H*$_2$), 4.03 (1H, d, *J* 3.2, C*H*H), 7.46 (2H, d, *J* 7.3, ArC*H*), 7.58 (2H, d, *J* 7.3, ArC*H*); δ_C (101 MHz, $CDCl_3$) 13.9 (*C*H$_3$), 22.0 (*C*H$_2$), 27.9 (*C*H$_2$), 44.2 (*C*H), 47.0 (*C*H$_2$), 60.0 (*C*H$_2$), 60.8 (*C*H), 125.0 (q, $J_{C\text{-}F}$ 3.5, 2 × Ar*C*H), 126.4 (2 × Ar*C*H), 127.7 (q, $J_{C\text{-}F}$ 279.5, *C*F$_3$), 146.4

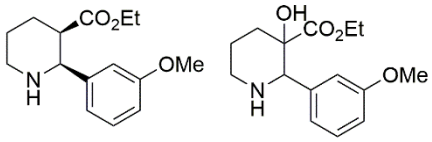
(Ar*C*), 173.2 (*C*=O); δ_F (376 MHz, $CDCl_3$) -62.4; *m/z* (ESI$^+$) 302.1371 [100%, $(M+H)^+$, $C_{15}H_{19}NO_2F_3$ requires 302.1362].

(±)-cis-Ethyl 2-(3'-fluoro)phenylpiperidine-3-carboxylate 284



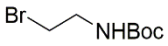
1,4,5,6-Tetrahydro-2-(4'-fluoro)-phenyl-4H-pyrridyl-3-carboxylic acid ethyl ester (62.0 mg, 0.25 mmol) was dissolved in methanol (5 mL). Hydrogenation was performed employing the H-Cube® reactor (30 bar, 35 °C) with 5% Pd/C CatCart®. The reaction mixture was cycled through three times. The solvent was removed under reduced pressure. Purification via small scale column chromatology on silica gel (5:95 methanol:DCM) afforded the product as a pale-yellow oil (59 mg, 95%); ν_{max}/cm^{-1} (thin film, ATR) 2935, 2857, 1719, 1615, 1589; δ_H (400 MHz, $CDCl_3$, dr >99:1) 1.02 (3H, t, *J* 7.2, C*H*$_3$), 1.50-1.59 (1H, m, C*H*H), 1.76-1.92 (1H, m, C*H*H), 1.96 (1H, tdd, *J* 13.3, 5.1, 3.9, C*H*H), 2.14-2.32 (2H, m, C*H*H and N*H*), 2.82 (1H, ddd, *J* 13.2, 12.4, 3.1, C*H*^{B}), 2.95-3.02 (1H, m, C*H*H), 3.36 (1H, ddt, *J* 13.2, 4.4, 2.1, C*H*^{A}), 3.90-4.00 (3H, m, OC*H*$_2$ and C*H*), 6.92 (1H, td, *J* 8.4, 2.4, ArC*H*), 7.03-7.14 (2H, m, ArC*H*), 7.23-7.33 (1H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 14.0 (*C*H$_3$), 22.0 (*C*H$_2$), 27.8 (*C*H$_2$), 44.2 (*C*H), 47.0 (*C*H$_2$), 59.9 (O*C*H$_2$), 60.6 (*C*H), 113.2 (d, $J_{C\text{-}F}$ 22.5, Ar*C*H), 113.6 (d, $J_{C\text{-}F}$ 21.5, Ar*C*H), 121.6 (d, $J_{C\text{-}F}$ 3.0, Ar*C*H), 129.5 (d, $J_{C\text{-}F}$ 8.0, Ar*C*H), 144.9 (d, $J_{C\text{-}F}$ 7.0, Ar*C*), 162.8 (d, $J_{C\text{-}F}$ 245.0, Ar*C*F), 173.3 (*C*=O); δ_F (376 MHz, $CDCl_3$) -113.6; *m/z* (ESI$^+$) 252.1405 [100%, $(M+H)^+$, $C_{14}H_{19}NO_2F$ requires 252.1394].

(±)-*cis*-Ethyl 2-(3-methoxy)phenylpiperidine-3-carboxylate 285 (a) and Ethyl 2-(3-methoxy)phenylpiperidine-3-carboxylate 286 (b)



1,4,5,6-Tetrahydro-2-(3'-methoxy)-phenyl-4H-pyrridyl-3-carboxylic acid ethyl ester (43 mg, 0.16 mmol) was dissolved in methanol (3 mL). Hydrogenation was performed employing the H-Cube® reactor (30 bar, 35 °C) with a 5% Pd/C CatCart®. The reaction mixture was cycled through three times. The solvent was removed under reduced pressure. Purification via small scale column chromatography on silica gel (5:95 methanol:DCM) afforded a pale-yellow oil as a mixture of inseparable products (40 mg, 94%); ν_{max}/cm^{-1} (thin film, ATR) 3323, 2935, 2856, 1712, 1602, 1584; δ_H (400 MHz, $CDCl_3$, 80:20 **a:b**, **285** dr >99:1 and **286** dr >99:1) 1.01 (2.40H, t, *J* 7.2, **a** C*H*$_3$), 1.21 (0.60H, t, *J* 7.2, **b** C*H*$_3$) 1.52 (0.80H, dt, *J* 12.7, 2.4, **a** C*H*H), 1.79-2.00 (2.20H, m, C*H*H), 2.06 (0.80H, bs, **a** N*H*) 2.12-2.26 (1.00H, m, C*H*H), 2.76-2.87 (1.00H, m, **a** C*H*^{B} and **b** C*H*H), 2.96-2.99 (0.80H, m, **a** C*H*H), 3.24-3.41 (1.00H, m, C*H*H), 3.73 (0.20H, s, **b** C*H*), 3.80 (0.60H, s, **b** OC*H*$_3$), 3.81 (2.40H, s, **a** OC*H*$_3$), 3.88-3.98 (2.40H, m, **a** OC*H*$_2$ and C*H*), 4.08-4.22 (0.40H, m, **b** OC*H*$_2$), 6.74-7.86 (1.00H, m, ArC*H*), 6.87-6.94 (2.00H, m, ArC*H*), 7.18-7.27 (1.00H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 14.0 (**a**, *C*H$_3$), 14.1 (**b**, *C*H$_3$), 22.1 (**a**, *C*H$_2$), 24.5 (**b**, *C*H$_2$), 27.9 (**a**, *C*H$_2$), 35.5 (**b**, *C*H$_2$), 44.4 (**a**, *C*H), 46.6 (**b**, *C*H$_2$), 47.1 (**a**, *C*H$_2$), 55.2 (O*C*H$_3$), 59.8 (**a**, O*C*H$_2$), 61.2 (**a**, *C*H), 61.6 (**b**, O*C*H$_2$), 69.3 (**b**, *C*H), 74.5 (**b**, O*C*), 111.7 (**a**, Ar*C*H), 112.4 (**a**, Ar*C*H), 113.3 (**b**, Ar*C*H), 113.3 (**b**, Ar*C*H), 118.4 (**a**, ArCH), 119.8 (**b**, Ar*C*H), 129.0 (**a**, Ar*C*H), 129.1 (**b**, Ar*C*H), 140.4 (**b**, Ar*C*), 144.1 (**a**, Ar*C*), 159.4 (**b**, Ar*C*), 159.5 (**a**, Ar*C*), 173.57 (**a**, *C*=O), 173.60 (**b**, *C*=O); *m*/*z* (ESI$^+$, **285**) 264.1604 [100%, $(M+H)^+$, $C_{15}H_{22}NO_3$ requires 264.1594]; *m*/*z* (ESI$^+$, **286**) 280.1555 [100%, $(M+H)^+$, $C_{15}H_{22}NO_4$ requires 280.1543].

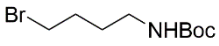
N-Boc-2-Bromoethylamine[179]



Di-*tert*-butyl dicarbonate (14.90 g, 68.3 mmol) was dissolved in methanol/acetonitrile (1:1, 50 mL) with triethylamine (22.7 mL, 171 mmol). 2-Bromoethylamine hydrobromide (10.00 g, 48.8 mmol) in methanol/acetonitrile (1:1, 30 mL) was added dropwise to the solution over 45 min. The reaction was stirred overnight and then concentrated in vacuo. The residue was redissolved in ethyl acetate (50 mL), washed with water (4 × 70 mL) and brine (70 mL), the dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. Purification via dry column chromatography on silica gel (15:75, ethyl acetate:hexane) afforded the product as a colourless liquid (8.04 g, 74%): δ_H (400 MHz, $CDCl_3$) 1.47 [9H, s, C(CH_3)$_3$], 3.41-3.59 (4H, m, CH_2), 4.99 (1H, s, N*H*).

Data are in accordance with the literature.

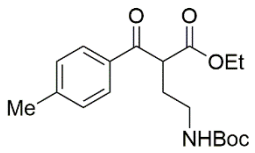
N-Boc-4-Bromobutan-1-amine[180]



Di-*tert*-butyl dicarbonate (6.00 g, 27.5 mmol) was dissolved in methanol/acetonitrile (1:1, 20 mL) with triethylamine (9.8 mL, 73.9 mmol) and the solution was cooled to 0 °C. 3-Bromopropylamine hydrobromide (4.92 g, 21.1 mmol) in methanol/acetonitrile (1:1, 50 mL) was added dropwise to the cooled solution over 20 min. After warming to rt., the reaction was stirred for overnight and then concentrated in vacuo. The residue redissolved in ethyl acetate (50 mL), washed with water (4 × 50 mL) and brine (50 mL), the dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. Purification via dry column chromatography on silica gel (15:85, ethyl acetate:hexane) afforded the product as a colourless oil (4.25 g, 80%); δ_H (400 MHz, $CDCl_3$) 1.46 [9H, s, C(CH_3)$_3$], 1.60-1.72 (2H, m, CH_2), 1.82-1.97 (2H, m, CH_2), 3.18 (2H, q, *J* 6.8, CH_2), 3.45 (2H, t, *J* 6.8, CH_2), 4.56 (1H, bs, N*H*).

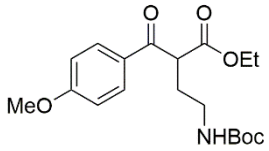
Data are in accordance with the literature.

α-{[[(1,1-Dimethylethoxy)carbonyl]amino]ethyl}-β-oxo-4'-methyl-benzenepropanoic acid ethyl ester 291



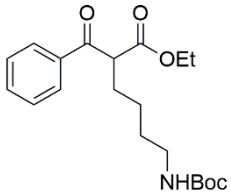
Sodium hydride (60% dispersion in mineral oil, 0.120 g, 3.0 mmol) was washed using hexane (3 × 1 mL) under nitrogen and then suspended in dry THF (1 mL). Ethyl(4-methylbenzoyl) acetate (0.469 g, 2.0 mmol) in dry THF (2 mL) was added dropwise and the mixture was heated at 35 °C for 30 min. *N*-Boc-2-Bromoethylamine (0.538 g, 2.4 mmol) in dry THF (3 mL) was added dropwise followed by tetrabutylammonium iodide (0.739 g, 2.0 mmol) in one portion. The reaction was heated a 55 °C overnight. After cooling to rt., the reaction was quenched via the addition of aq. saturated ammonium chloride (2 mL). The layers were separated, and the aqueous layer was extracted using diethyl ether (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure. Purification using Combi Flash (silica gel, ethyl acetate:hexane as eluent) afforded the product as a white solid (0.205 g, 29%); ν_{max}/cm^{-1} (ATR) 3321, 2984, 2947, 1732, 1676, 1608, 1528; δ_H (400 MHz, $CDCl_3$) 1.19 (3H, t, *J* 7.1, C*H*$_3$), 1.42 [9H, s, C(C*H*$_3$)$_3$], 2.16-2.27 (2H, m, C*H*$_2$), 2.44 (3H, s, C*H*$_3$), 3.16-3.32 (2H, m, C*H*$_2$), 4.11-4.19 (2H, m, OC*H*$_2$), 4.39 (1H, t, *J* 7.0, C*H*), 4.64 (1H, s, N*H*), 7.29 (2H, d, *J* 8.3, ArC*H*), 7.87-7.94 (2H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 14.0 (*C*H$_3$), 21.7 (*C*H$_3$), 28.3 [C(*C*H$_3$)$_3$], 29.2 (*C*H$_2$), 38.8 (*C*H$_2$), 51.7 (*C*H), 61.5 (O*C*H$_2$), 128.9 (2 × Ar*C*H), 129.5 (2 × Ar*C*H), 133.5 (Ar*C*), 144.6 (Ar*C*), 155.9 (*C*=O), 169.9 (*C*=O), 194.5 (*C*=O); *m*/*z* (ESI$^+$) 372.1788 [100%, (M+Na)$^+$, $C_{19}H_{27}NO_5Na$ requires 372.1781].

α-{[[(1,1-Dimethylethoxy)carbonyl]amino]ethyl}-β-oxo-4'-methoxy-benzenepropanoic acid ethyl ester 292



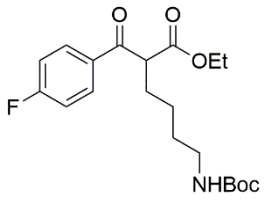
Sodium hydride (60% dispersion in mineral oil, 0.120 g, 3.0 mmol) was washed using hexane (3 × 1 mL) under nitrogen and then suspended in dry THF (1 mL). Ethyl(4-methoxybenzoyl) acetate (0.500 g, 2.0 mmol) in dry THF (2 mL) was added dropwise and the mixture was heated at 35 °C for 30 min. *N*-Boc-2-Bromoethylamine (0.538 g, 2.4 mmol) in dry THF (3 mL) was added dropwise followed by tetrabutylammonium iodide (0.739 g, 2.0 mmol) in one portion. The reaction was heated a 55 °C overnight. After cooling to rt., the reaction was quenched via the addition of aq. saturated ammonium chloride (2 mL). The layers were separated, and the aqueous layer was extracted using diethyl ether (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure. Purification using Combi Flash (silica gel, ethyl acetate:hexane as eluent) afforded the product as a white solid (0.15 g, 20%); mpt. 60-62 °C; ν_{max}/cm^{-1} (thin film, ATR) 3384, 2977, 2935, 1732, 1709, 1709, 1676, 1599, 1575, 1511; δ_H (400 MHz, $CDCl_3$) 1.20 (3H, t, *J* 7.1, C*H*$_3$), 1.42 [9H, s, C(C*H*$_3$)$_3$], 2.22 (2H, q, *J* 7.5, C*H*$_2$), 3.16-3.24 (2H, m, C*H*$_2$), 3.90 (3H, s, OC*H*$_3$), 4.17 (2H, q, *J* 7.1, OC*H*$_2$), 4.37 (1H, t, *J* 6.9, C*H*), 4.64 (1H, s, N*H*), 6.96 (2H, s, *J* 8.6, ArC*H*), 8.00 (2H, d, *J* 8.6, ArC*H*); δ_C (101 MHz, $CDCl_3$) 14.0 (*C*H$_3$), 28.4 [C(*C*H$_3$)$_3$], 29.2 (*C*H$_2$), 38.9 (*C*H$_2$), 51.5 (*C*H), 55.5 (O*C*H$_3$), 60.4 [*C*(CH$_3$)$_3$], 61.5 (O*C*H$_2$), 113.9 (2 × Ar*C*H), 129.0 (Ar*C*), 131.1 (2 × Ar*C*H), 155.9 (Ar*C*O), 163.9 (*C*=O), 170.0 (*C*=O), 193.3 (*C*=O); *m*/*z* (ESI$^+$) 388.1736 [100%, (M+Na$^+$), $C_{19}H_{27}NO_6Na$ requires 388.1731].

α-{[[(1,1-Dimethylethoxy)carbonyl]amino]butyl}-β-oxo-benzenepropanoic acid ethyl ester 294



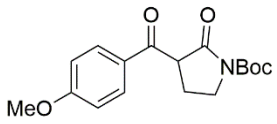
Sodium hydride (60% dispersion in mineral oil, 0.120 g, 3.0 mmol) was washed using hexane (3 × 1 mL) under nitrogen and then suspended in dry THF (1 mL). Ethyl benzoylacetate (0.384 g, 2.0 mmol) in dry THF (2 mL) was added dropwise and the mixture was heated at 35 °C for 30 min. *N*-Boc-4-Bromobutylamine (0.605 g, 2.4 mmol) in dry THF (3 mL) was added dropwise followed by tetrabutylammonium iodide (0.739 g, 2.0 mmol) in one portion. The reaction was heated a 60 °C overnight. After cooling to rt., the reaction was quenched via the addition of aq. saturated ammonium chloride (2 mL). The layers were separated, and the aqueous layer was extracted using ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure. Purification using Combi Flash (silica gel, ethyl acetate:hexane as eluent) afforded the product as a colourless oil (0.163 g, 22%); ν_{max}/cm^{-1} (thin film, ATR) 3385, 2976, 2932, 2865, 1733, 1684, 1514; δ_H (400 MHz, $CDCl_3$) 1.18 (3H, t, *J* 7.2, C*H*$_3$), 1.35-1.45 (2H, m, C*H*$_2$), 1.44 [9H, s, C(C*H*$_3$)$_3$], 1.48-1.58 (2H, m, C*H*$_2$), 1.97-2.08 (2H, m, C*H*$_2$), 3.12 (2H, q, *J* 6.7, C*H*$_2$), 4.16 (2H, q, *J* 7.2, OC*H*$_2$), 4.30 (1H, t, *J* 7.2, C*H*), 4.56 (1H, s, N*H*), 7.45-7.54 (2H, m, ArC*H*), 7.56-7.64 (1H, m, ArC*H*), 7.96-8.03 (2H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 14.0 (*C*H$_3$), 24.8 (*C*H$_2$), 28.4 [C(*C*H$_3$)$_3$], 28.5 (*C*H$_2$), 29.9 (*C*H$_2$), 40.2 (*C*H$_2$), 54.2 (*C*H), 61.4 (O*C*H$_2$), 79.1 [*C*(CH$_3$)$_3$], 128.6 (2 × Ar*C*H), 128.8 (2 × Ar*C*H), 133.5 (Ar*C*H), 136.2 (Ar*C*), 156.0 (*C*=O), 169.9 (*C*=O), 195.1 (*C*=O); *m*/*z* (ESI$^+$) 386.1941 [100%, (M+Na)$^+$, $C_{20}H_{29}NO_5Na$ requires 386.1938].

α-{[[(1,1-Dimethylethoxy)carbonyl]amino]butyl}-β-oxo-4-fluoro-benzenepropanoic acid ethyl ester 295



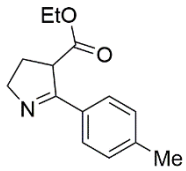
Sodium hydride (60% dispersion in mineral oil, 0.120 g, 3.0 mmol) was washed using hexane (3 × 1 mL) under nitrogen and then suspended in dry THF (1 mL). Ethyl (4-fluorobenzoyl)acetate (0.420 g, 2.0 mmol) in dry THF (2 mL) was added dropwise and the mixture was heated at 35 °C for 30 min. *N*-Boc-4-Bromobutylamine (0.605 g, 2.4 mmol) in dry THF (3 mL) was added dropwise followed by tetrabutylammonium iodide (0.739 g, 2.0 mmol) in one portion. The reaction was heated a 60 °C overnight. After cooling to rt., the reaction was quenched via the addition of aq. saturated ammonium chloride (2 mL). The layers were separated, and the aqueous layer was extracted using ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure. Purification using Combi Flash (silica gel, ethyl acetate:hexane as eluent) afforded the product as a pale-yellow oil (0.22 g, 29%); ν_{max}/cm^{-1} (thin film, ATR) 3387, 2978, 2934, 1734, 1686, 1598. 1508; δ_H (400 MHz, $CDCl_3$) 1.19 (3H, t, *J* 7.2, C*H*$_3$), 1.34-1.44 (2H, m, C*H*$_2$), 1.45 [9H, s, C(C*H*$_3$)$_3$], 1.48-1.58 (2H, m, C*H*$_2$), 1.99-2.09 (2H, m, C*H*$_2$), 3.13 (2H, q, *J* 6.6, C*H*$_2$), 4.16 (2H, q, *J* 7.2, OC*H*$_2$), 4.25 (1H, t, *J* 7.2, C*H*), 4.55 (1H, s, N*H*), 7.12-7.22 (2H, m, ArC*H*), 7.99-8.09 (2H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 14.0 (*C*H$_3$), 24.8 (*C*H$_2$), 28.4 [C(*C*H$_3$)$_3$], 28.5 (*C*H$_2$), 29.9 (*C*H$_2$), 40.2 (*C*H$_2$), 54.2 (*C*H), 61.5 (O*C*H$_2$), 115.9 (d, $J_{C\text{-}F}$ 22.0, 2 × Ar*C*H), 131.3 (d, $J_{C\text{-}F}$ 9.0, 2 × Ar*C*H), 132.6 (Ar*C*), 155.9 (*C*=O), 166.0 (d, $J_{C\text{-}F}$ 256.5, Ar*C*F), 169.7 (*C*=O), 193.4 (*C*=O); δ_F (376 MHz, $CDCl_3$) -104.3 (Ar*F*); *m*/*z* (ESI^+) 404.1850 [100%, $(M+Na)^+$, $C_{20}H_{28}NO_5FNa$ requires 404.1844].

1-(1,1-Dimethylethyl)-3-(4'-methoxybenzoyl)-2-oxo-1-pyrrolidinedicarboxylate 301



Obtained via same procedure as α-{[[(1,1-dimethylethoxy)carbonyl]amino]ethyl}-β-oxo-4'-methoxy-benzenepropanoic acid ethyl ester. Purification using Combi Flash® (silica gel, ethyl acetate:hexane as eluent) afforded the by-product as a yellow oil (0.14 g, 21%); ν_{max}/cm^{-1} (thin film, ATR) 2978, 2934, 1779, 1741, 1715, 1668, 1599, 1575, 1511; δ_H (400 MHz, $CDCl_3$) 1.53 [9H, s, C(C*H*$_3$)$_3$], 2.14-2.28 (1H, m, C*H*H), 2.61 (1H, ddt, *J* 13.1, 8.3, 5.0, C*H*H), 3.76-3.85 (1H, m, C*H*H), 3.89 (3H, s, OC*H*$_3$), 3.91-4.02 (1H, m, C*H*H), 4.54 (1H, dd, *J* 8.9, 5.1, C*H*), 6.98 (2H, d, *J* 9.0, ArC*H*), 8.09 (2H, d, *J* 9.0, ArC*H*); δ_C (101 MHz, $CDCl_3$) 21.1 (*C*H$_2$), 28.0 [C(*C*H$_3$)$_3$], 45.4 (*C*H$_2$), 52.0 (*C*H), 55.7 (O*C*H$_3$), 83.3 [*C*(CH$_3$)$_3$], 118.9 (2 × Ar*C*H), 128.8 (Ar*C*), 132.1 (2 × Ar*C*H), 150.1 (Ar*C*), 164.1 (*C*=O), 169.6 (*C*=O), 192.7 (*C*=O); *m*/*z* (ESI$^+$) 342.1327 [100%, (M+Na)$^+$, $C_{17}H_{21}NO_5Na$ requires 342.1312].

3,4,5-Trihydro-2-(4-methyl)phenyl-3H-pyrrole-3-carboxylic acid ethyl ester 296

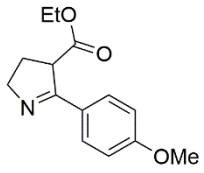


α-{[[(1,1-Dimethylethoxy)carbonyl]amino]ethyl}-β-oxo-4'-methyl-benzenepropanoic acid ethyl ester (0.093 g, 0.27 mmol) was dissolved in DCM (5 mL) under argon and cooled to 0 °C. Trifluoracetic acid (0.20 mL, 2.68 mmol) was added dropwise. Once addition was complete, the reaction warmed to rt. and stirred for 2.5 h. An ice/water slurry (10 mL) was added, and the mixture neutralised using solid sodium hydrogen carbonate. After stirring for 1.5 h, the layers were separated, and the aqueous layer was extracted using DCM (3 × 10 mL). The combined organic layers were washed using brine (10 mL), dried (Na_2SO_4), filtered, and the

solvent was removed under reduced pressure affording the product as a pale-yellow oil (0.047 g, 75%) which was used directly in the next step without further purification; δ_H (400 MHz, $CDCl_3$) 1.18 (3H, t, *J* 7.2, C*H*$_3$), 2.30-2.38 (2H, m, C*H*$_2$), 2.39 (3H, s, C*H*$_3$), 4.05-4.23 (5H, m, OC*H*$_2$, C*H*, and C*H*$_2$), 7.22, 92H, d, *J* 7.9, ArC*H*), 7.75-7.81 (2H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 14.0 (*C*H$_3$), 21.4 (*C*H$_3$), 29.4 (*C*H$_2$), 53.6 (*C*H), 61.0 (*C*H$_2$), 61.1 (*C*H$_2$), 127.9 (2 × Ar*C*H), 129.2 (2 × Ar*C*H), 130.7 (Ar*C*), 140.9 (Ar*C*), 169.1 (*C*=N), 172.4 (*C*=O); *m*/*z* (ESI$^+$) 232.1343 [100%, $(M+H)^+$, $C_{14}H_{18}NO_2$ requires 232.1332].

Selected data from crude ^{1}H and ^{13}C NMR spectra.

3,4,5-Trihydro-2-(4-methoxy)phenyl-3H-pyrrole-3-carboxylic acid ethyl ester 297

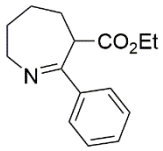


α-{[[(1,1-Dimethylethoxy)carbonyl]amino]ethyl}-β-oxo-4'-methoxy-benzenepropanoic acid ethyl ester (0.125 g, 0.34 mmol) was dissolved in DCM (5 mL) under argon and cooled to 0 °C. Trifluoracetic acid (0.26 mL, 3.42 mmol) was added dropwise. Once addition was complete, the reaction warmed to rt. and stirred for 2.5 h. An ice/water slurry (10 mL) was added, and the mixture neutralised using solid sodium hydrogen carbonate. After stirring for 1.5 h, the layers were separated, and the aqueous layer was extracted using DCM (3 × 10 mL). The combined organic layers were washed using brine (10 mL), dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure affording the product as a pale-yellow oil (0.076 g, 93%) which was used directly in the next step without further purification; δ_H (400 MHz, $CDCl_3$) 1.18 (3H, t, *J* 7.2, C*H*$_3$), 2.35 (2H, q, *J* 7.2, C*H*H), 3.36 (3H, s, OC*H*$_3$), 4.07-4.22 (5H, m, OC*H*$_2$, C*H*$_2$ and C*H*), 6.89-6.96 (2H, m, ArC*H*), 7.82-7.88 (2H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 14.1 (*C*H$_3$), 29.4 (*C*H$_2$), 53.6 (*C*H), 55.3 (O*C*H$_3$), 61.0 (O*C*H$_2$), 61.1 (N*C*H$_2$),

113.8 (2 × Ar*C*H), 126.2 (Ar*C*), 129.6 (2 × Ar*C*H), 161.5 (Ar*C*O), 168.5 (*C*=N), 172.4 (*C*=O); *m*/*z* (ESI$^+$) 248.1283 [100%, (M+H)$^+$, $C_{14}H_{18}NO_3$ requires 248.1281].

Selected peaks from crude ^{1}H and ^{13}C NMR spectra.

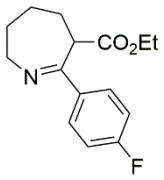
3,4,5,6,7-Pentahydro-2-phenyl-1H-azapine-3-carboxylic acid ethyl ester 299



α-{[[(1,1-Dimethylethoxy)carbonyl]amino]butyl}-β-oxo-benzenepropanoic acid ethyl ester (0.089g, 0.24 mmol) was dissolved in DCM (3 mL) under argon and cooled to 0 °C. Trifluoracetic acid (0.21 mL, 2.47 mmol) was added dropwise. Once addition was complete, the reaction warmed to rt. and stirred for 2.5 h. An ice/water slurry (5 mL) was added, and the mixture neutralised using solid sodium hydrogen carbonate. After stirring for 1.5 h, the layers were separated, and the aqueous layer was extracted using DCM (3 × 5 mL). The combined organic layers were washed using brine (10 mL), dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure affording the product as a pale-yellow oil (0.043 g, 73%) which was used directly in the next step without further purification; δ_H (400 MHz, $CDCl_3$) 1.18 (3H, t, *J* 7.2, C*H*$_3$), 1.36-1.57 (4H, m, C*H*$_2$), 1.98-2.09 (2H, m, C*H*$_2$), 2.71 (2H, t, *J* 6.9, C*H*$_2$), 4.16 (2H, qd, *J* 7.2, 1.2, OC*H*$_2$), 4.31 (1H, t, *J* 7.1, C*H*), 7.46-7.54 (2H, m, ArC*H*), 7.56-7.65 (1H, m, ArC*H*), 7.97-8.04 (2H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 14.0 (*C*H$_3$), 24.9 (*C*H$_2$), 28.7 (*C*H$_2$), 33.4 (*C*H$_2$), 41.8 (*C*H$_2$), 54.3 (*C*H), 61.4 (O*C*H$_2$), 128.6 (2 × Ar*C*H), 128.8 (2 × Ar*C*H), 133.5 (Ar*C*H), 136.3 (Ar*C*), 170.0 (*C*=O), 195.2 (*C*=N); *m*/*z* (ESI$^+$) 246.1496 [100%, (M+H)$^+$, $C_{15}H_{20}NO_2$ requires 246.1489].

Selected data from crude ^{1}H and ^{13}C NMR spectra.

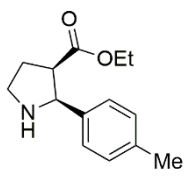
3,4,5,6,7-Pentahydro-2-(4-fluoro)phenyl-1H-azapine-3-carboxylic acid ethyl ester 300



α-{[[(1,1-Dimethylethoxy)carbonyl]amino]butyl}-β-oxo-(4-fluoro)benzenepropanoic acid ethyl ester (0.172 g, 0.45 mmol) was dissolved in DCM (5 mL) under argon and cooled to 0 °C. Trifluoracetic acid (0.35 mL, 4.51 mmol) was added dropwise. Once addition was complete, the reaction warmed to rt. and stirred for 2.5 h. An ice/water slurry (5 mL) was added, and the mixture neutralised using solid sodium hydrogen carbonate. After stirring for 1.5 h, the layers were separated, and the aqueous layer was extracted using DCM (3 × 5 mL). The combined organic layers were washed using brine (10 mL), dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure affording the product as a pale-yellow oil (0.086 g, 73%) which was used directly in the next step without further purification; δ_H (400 MHz, $CDCl_3$) 1.18 (3H, t, *J* 7.1, C*H*$_3$), 1.40-1.50 (2H, m, C*H*$_2$), 1.67 (2H, p, *J* 7.4, C*H*$_2$), 1.97-2.08 (2H, m, C*H*$_2$), 2.86 (2H, t, *J* 7.4, C*H*$_2$), 4.16 (2H, q, *J* 7.1, OC*H*$_2$), 4.28 (1H, t, *J* 7.4, C*H*), 7.12-7.21 (2H, m, ArC*H*), 8.00-8.08 (2H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 14.0 (*C*H$_3$), 24.6 (*C*H$_2$), 28.4 (*C*H$_2$), 30.4 (*C*H$_2$), 40.7 (*C*H$_2$), 54.1 (*C*H), 61.6 (O*C*H$_2$), 116.0 (d, $J_{C\text{-}F}$ 22.0, 2 × Ar*C*H), 117.4 (Ar*C*), 131.4 (d, $J_{C\text{-}F}$ 9.5, 2 × Ar*C*H), 167.3 (Ar*C*F), 169.8 (*C*=N), 193.4 (*C*=O); *m*/*z* (ESI$^+$) 264.1401 [100%, (M+H)$^+$, $C_{15}H_{19}NO_2F$ requires 264.1394].

Selected data from crude ^{1}H and ^{13}C NMR spectra.

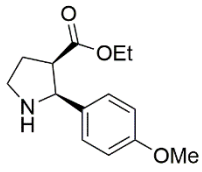
(±)-*cis*-Ethyl 2-(4'-methyl)phenylpyrrolidine-3-carboxylate 302



3,4,5-Trihydro-2-(4'-methyl)-phenyl-2H-pyrrole-3-carboxylic acid ethyl ester (57.8 mg, 0.25 mmol) was dissolved in methanol (5 mL). Hydrogenation was performed employing the H-Cube® reactor (30 bar, 35 °C, 1 mL/min) with 5% Pd/C CatCart®. The reaction mixture was cycled through three times. The solvent was removed under reduced pressure. Purification via small scale column chromatology on silica gel (5:95 methanol:DCM) afforded the product as a colourless oil (46.0 mg, 79%); ν_{max}/cm^{-1} (thin film, ATR) 2977, 2925, 2870, 1726, 1697; δ_H (400 MHz, $CDCl_3$, dr >99:1, 78:22 inseparable mixture of product:recovered starting material) 0.87 (3H, t, *J* 7.1, C*H*$_3$), 2.06-2.32 (3H, m, C*H* and N*H*), 2.33 (3H, s, C*H*$_3$), 3.04 (1H, dt, *J* 11.0, 8.3, C*H*H), 3.27 (1H, td, *J* 8.3, 5.0, C*H*H), 3.44 (1H, ddd, *J* 11.0, 8.5, 3.7, C*H*H), 3.62-3.83 (2H, m, OC*H*$_2$), 4.36 (1H, d, *J* 7.6, C*H*^{A}), 7.08-7.15 [2H, (AX)$_2$, ArC*H*], 7.17-7.21 [2H, (AX)$_2$, ArC*H*]; δ_C (101 MHz, $CDCl_3$) 13.7 (*C*H$_3$), 21.1 (*C*H$_3$), 29.8 (*C*H$_2$), 46.6 (*C*H$_2$), 49.5 (*C*H), 60.1 (O*C*H$_2$), 66.2 (*C*H), 126.7 (2 × Ar*C*H), 128.8 (2 × Ar*C*H), 136.2 (Ar*C*), 136.8 (Ar*C*), 174.1 (*C*=O); *m*/*z* (ESI$^+$) 234.1497 [100%, $(M+H)^+$, $C_{14}H_{20}NO_2$ requires 234.1489].

Selected peaks for the desired product in the ^{1}H and ^{13}C NMR spectrum.

(±)-*cis*-Ethyl 2-(4'-methoxy)phenylpyrrolidine-3-carboxylate 303

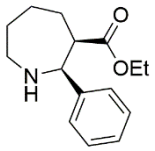


3,4,5-Trihydro-2-(4'-methoxy)-phenyl-2H-pyrrole-3-carboxylic acid ethyl ester (22.0 mg, 0.09 mmol) was dissolved in methanol (2 mL). Hydrogenation was performed employing the H-Cube® reactor (30 bar, 35 °C, 1 mL/min) with 5% Pd/C CatCart®. The reaction mixture was cycled through three times. The solvent was removed under reduced pressure. Purification via small scale column chromatology on silica gel (5:95 methanol:DCM) afforded the product as a colourless oil (17 mg, 76%); ν_{max}/cm^{-1} (thin film, ATR) 2936, 1724, 1611, 1512; δ_H (400 MHz, $CDCl_3$, dr >99:1, 83:17 inseparable mixture of product:recovered starting material)

0.90 (3H, t, *J* 7.2, C*H*$_3$), 1.19 (0.6H, t, *J* 7.1, *trans* C*H*$_3$), 1.96 (1H, bs, N*H*), 2.08-2.19 (1H, m, C*H*H), 2.20-2.30 (1H, m, C*H*H), 3.02 (1H, dt, *J* 11.1, 8.3, C*H*H), 3.25 (1H, td, *J* 7.9, 5.1, C*H*), 3.44 (1H, ddd, *J* 11.0, 8.4, 3.5, C*H*H), 3.65-3.88 (2H, m, OC*H*$_2$), 3.80 (3H, s, OC*H*$_3$), 4.35 (1H, d, *J* 7.9, C*H*^{A}), 6.81-6.89 [2H, (AX)$_2$, ArC*H*], 7.19-7.28 [2H, (AX)$_2$, ArC*H*]; δ_C (101 MHz, $CDCl_3$) 13.8 (*C*H$_3$), 29.8 (*C*H$_2$), 46.6 (*C*H$_2$), 49.5 (*C*H), 55.3 (*C*H), 60.1 (*C*H$_2$), 65.9 (O*C*H$_2$), 113.5 (2 × Ar*C*H), 127.9 (2 × Ar*C*H), 131.5 (Ar*C*), 158.8 (Ar*C*O), 174.2 (*C*=O); *m*/*z* (ESI$^+$) 250.1446 [100%, $(M+H)^+$, $C_{14}H_{20}NO_3$ requires 250.1438].

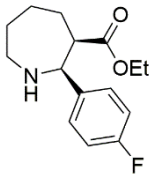
Selected peaks for the desired product in the ^{1}H and ^{13}C NMR spectrum.

(±)-*cis*-2,3,4,5,6,7-Hexahydro-2-phenyl-1H-azepine-3-carboxylic acid ethyl ester 304



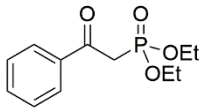
3,4,5,6,7-Pentahydro-2-phenyl-1H-azapine-3-carboxylic acid ethyl ester (30.7 mg, 0.125 mmol) was dissolved in methanol (2.5 mL). Hydrogenation was performed employing the H-Cube® reactor (30 bar, 35 °C, 1 mL/min) with 5% Pd/C CatCart®. The reaction mixture was cycled through three times. The solvent was removed under reduced pressure. Purification via small scale column chromatology on silica gel (5:95 methanol:DCM) afforded the product as a colourless oil (21.3 mg, 69%); ν_{max}/cm^{-1} (thin film, ATR) 2935, 2861, 1724; δ_H (400 MHz, $CDCl_3$, dr >99:1) 1.18-1.46 (8H, m, C*H*$_3$, 5 × C*H*H), 1.54-.68 (1H, m, C*H*H), 2.39-2.46 (2H, m, N*H*, C*H*), 2.60 (1H, t, *J* 7.0, C*H*H), 2.70-2.80 (1H, m, C*H*H), 4.17 (2H, qd, *J* 7.1, 1.2, OC*H*$_2$), 4.79 (1H, d, *J* 7.7, C*H*), 7.25-7.41 (5H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 14.2 (*C*H$_3$), 24.4 (*C*H$_2$), 29.2 (*C*H$_2$), 32.9 (*C*H$_2$), 41.6 (*C*H$_2$), 53.1 (*C*H), 60.6 (O*C*H$_2$), 75.2 (N*C*H), 126.4 (2 × Ar*C*H), 127.9 (Ar*C*H), 128.5 (2 × Ar*C*H), 142.2 (Ar*C*), 175.2 (*C*=O); *m*/*z* (ESI$^+$) 248.1641 [100%, $(M+H)^+$, $C_{15}H_{22}NO_2$ requires 248.1651].

(±)-*cis*-2,3,4,5,6,7-Hexahydro-2-(4'-fluoro)phenyl-1H-azapine-3-carboxylic acid ethyl ester 305



3,4,5,6,7-Pentahydro-2-phenyl-1H-azapine-3-carboxylic acid ethyl ester (65.8 mg, 0.25 mmol) was dissolved in methanol (5 mL). Hydrogenation was performed employing the H-Cube® reactor (30 bar, 35 °C, 1 mL/min) with 5% Pd/C CatCart®. The reaction mixture was cycled through three times. The solvent was removed under reduced pressure. Purification via small scale column chromatology on silica gel (5:95 methanol:DCM) afforded the product as a colourless oil (46.2 mg, 70%); v_{max}/cm^{-1} (thin film, ATR) 2935, 2857, 1719, 1615, 1589; δ_H (400 MHz, $CDCl_3$, dr >99:1) 1.16 (3H, t, *J* 7.1, C*H*$_3$), 1.31-1.53 (3H, m, C*H*H), 2.68-2.78 (3H, m, C*H*H), 2.68-2.78 (1H, m, C*H*), 2.92 (2H, td, *J* 7.2, 2.6, C*H*H), 4.09 (2H, q, *J* 7.1, OC*H*$_2$), 4.67 (1H, bs, N*H*), 4.86 (1H, d, *J* 6.6, C*H*), 6.99-7.09 (2H, m, ArC*H*), 7.27-7.35 (2H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 14.0 (*C*H$_3$), 23.9 (*C*H$_2$), 27.4 (*C*H$_2$), 28.3 (*C*H$_2$), 39.7 (*C*H$_2$), 52.8 (*C*H), 60.9 (O*C*H$_2$), 73.6 (*C*H), 115.2 (d, $J_{C\text{-}F}$ 21.5, 2 × Ar*C*H), 127.9 (d, $J_{C\text{-}F}$ 8.0, 2 × Ar*C*H), 137.7 (d, $J_{C\text{-}F}$ 3.0, 2 × Ar*C*H), 162.3 (d, $J_{C\text{-}F}$ 245.5, Ar*C*), 174.8 (*C*=O); δ_F (376 MHz, $CDCl_3$) -114.5; *m/z* (ESI$^+$) 266.1559 [100%, $(M+H)^+$, $C_{15}H_{21}NO_2F$ requires 266.1551].

Diethyl 2-oxo-2-phenylethylphosphonate 331[181]



Method 1

2-Bromoacetophenone (0.995 g, 5.0 mmol) and triethylphosphite (0.86 mL, 5.0 mmol) were mixed and heated at reflux for 6 h. After cooling to room temperature, the crude orange oil

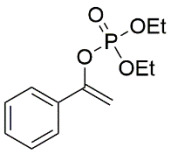
was purified by flash column chromatography on silica gel (30:70 to 70:30 ethyl acetate:petroleum ether) affording the product as a pale-yellow oil (0.89 g, 64%).

Method 2

^{n}Butyl lithium (2.5 M in THF, 0.48 mL, 1.2 mmol) was added slowly in a solution of diethyl methylphosphonate (0.20 mL, 1.4 mmol) in dry THF (4 mL) at −78 °C under argon. After stirring for 50 min, methyl benzoate (0.08 mL, 0.6 mmol) in dry THF (4 mL) was added dropwise. The reaction was stirred for 2 h at −78 °C. Following the addition of aq. saturated ammonium chloride (15 mL), the reaction was warmed to room temperature and stirred for 20 min. Water (20 mL) and DCM (20 mL) were added and the mixture acidified to pH 4 using aqueous 1 M HCl (0.5 mL). The mixture was extracted using DCM (2 ×15 mL), the combined organic layers dried ($MgSO_4$), filtered, and the solvent removed under reduced pressure. Purification by flash column chromatography on silica gel (50:50 DCM:ethyl acetate) afforded the product as a pale-yellow oil (0.11 g, 65%); δ_H (400 MHz, $CDCl_3$) 1.30 (6H, t, *J* 7.1, CH_2CH_3), 3.65 (2H, d, *J* 22.7, CH_2P), 4.11-4.20 (4H, m, OCH_2CH_3), 7.50 (2H, t, *J* 7.4, Ar-*H*), 7.61 (1H, t, *J* 7.4, ArC*H*), 8.03 (2H, d, *J* 7.4, ArC*H*); δ_P (162 MHz, $CDCl_3$) 19.9.

Data are in accordance with the literature.

Diethyl (1-phenylvinyl) phosphate 333[182]

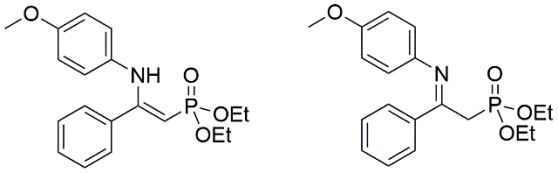


2-Bromoacetophenone (0.995 g, 5.0 mmol) and triethylphosphite (0.86 mL, 5.0 mmol) were mixed and heated at reflux for 6 h under a nitrogen atmosphere. The reaction was cooled to rt and purified via flash column chromatography on silica gel (30:70 to 70:30 ethyl acetate:petroleum ether) affording the product as a yellow oil (0.23 g, 18%); δ_H (400 MHz,

$CDCl_3$) 1.36 (6H, td, *J* 7.1, 1.1, C*H*$_3$), 4.21-4.27 (4H, m, OC*H*$_2$), 5.25 (1H, dd, *J* 2.8, 2.1, C*H*H), 5.31 (1H, t, *J* 2.8, C*H*H), 7.31-7.43 (3H, m, ArC*H*), 7.57-7.64 (2H, m, ArC*H*).

Data are in accordance with the literature.

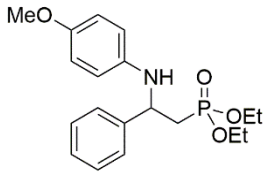
{2-[(4-Methoxyphenyl)amino]-2-phenylethenyl}-diethyl ester phosphonic acid 79 and {2-[(4-methoxyphenyl)imino]-2-phenylethyl}-diethyl ester phosphonic acid 80[145]



Diethyl 2-oxo-2-phenylethylphosphonate (0.50 g, 1.8 mmol), *p*-anisidine (0.27 g, 2.2 mmol), and *p*-toluenesulfonic acid monohydrate (17 mg, 0.1 mmol) were dissolved in dry toluene (40 mL) under nitrogen. The reaction was heated under Dean-Stark conditions for 18 h. After cooling to room temperature, the solvent was removed under reduced pressure. Purification by flash column chromatography on silica gel pre-treated with triethylamine (50:50, ethyl acetate:petroleum ether) afforded the product mixture (0.78 g, 60%,); v_{max}/cm^{-1} (thin film, ATR) 3260, 2982, 2835, 1608, 1573, 1511; δ_H (400 MHz, $CDCl_3$, 66:34 enamine:imine) 1.15 (2.04H, t, *J* 7.1, CH_2CH_3, imine), 1.38 (3.96H, t, *J* 7.1, CH_2CH_3, enamine), 3.44 (0.68H, d, *J* 23.3, PC*H*$_2$, imine), 3.71 (1.98H, s, OC*H*$_3$, enamine), 3.74-3.96 (2.38H, m, imine), 4.08-4.18 (2.64H, m, OC*H*$_2$, enamine), 4.28 (0.66H, d, *J* 12.4, PC*H*, enamine), 6.62 (2.64H, $[AX]_2$, ArC*H,* enamine), 6.93 (1.36H, $[AX]_2$, ArC*H*, imine), 7.16-8.00 (5H, m, ArC*H*), 9.16 (0.64H, s, N*H*, enamine); δ_P (162 MHz, $CDCl_3$) 21.6 (imine), 24.2 (enamine).

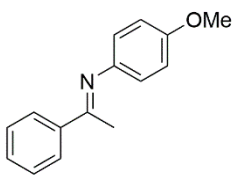
Data are in accordance with the literature.

{2-[(4-Methoxyphenyl)amino]-2-phenylethyl}-diethyl ester phosphonic acid 81



{2-[(4-Methoxyphenyl)amino]-2-phenylethenyl}-diethyl ester phosphonic acid (0.10 g, 0.2 mmol) was dissolved in dry DCM (0.4 mL) under argon and cooled to 0 °C. Trichlorosilane (0.04 mL, 0.4 mmol) was added dropwise. After warming to rt, the reaction was stirred for 2 h. The reaction was diluted with DCM (5 mL) and quenched by addition of 1M aq NaOH (3 mL). The layers were separated, and the aqueous layer extracted using DCM (3 × 10 mL). The combined organic layers were washed using brine (30 mL), dried (Na_2SO_4), filtered, and solvent removed under reduced pressure. Purification via flash column chromatography on silica gel (40:60 to 70:30, ethyl acetate:hexane) afforded the product as a pale-yellow solid (0.04 g, 60%); mpt. 68-70 °C; v_{max}/cm^{-1} (thin film) 3326 (NH), 2983, 2906, 1510; δ_H (400 MHz, $CDCl_3$) 1.27 (6H, td, *J* 7.1, 2.4, C*H*$_3$), 2.19-2.39 (2H, m, C*H*$_2$P), 3.71 (3H, s, OC*H*$_3$), 3.97-4.19 (4H, m, OC*H*$_2$), 4.59-4.70 (1H, m, NC*H*), 6.47-6.56 [2H, (AX)$_2$, ArC*H*], 6.65-6.74 [2H, (AX)$_2$, ArC*H*], 7.23-7.29 (1H, m, ArC*H*), 7.34 (2H, t, *J* 7.6, ArC*H*), 7.40-7.45 (2H, m, ArC*H*); δ_C (100 MHz, $CDCl_3$) 16.4 (*C*H$_3$), 34.9 (d, $J_{C\text{-}P}$ 136.5, PCH$_2$), 54.7 (NCH), 55.7 (OCH$_3$), 61.8 (d, $J_{C\text{-}P}$ 6.5, OC*H*$_2$), 62.1 (d, $J_{C\text{-}P}$ 6.5, OCH$_2$), 114.6 (2 × Ar*C*H), 115.3 (2 × Ar*C*H), 126.2 (2 × Ar*C*H), 127.4 (Ar*C*H), 128.8 (2 × Ar*C*H), 140.9 (Ar*C*), 143.5 (Ar*C*), 152.3 (Ar*C*); δ_P (162 MHz, $CDCl_3$) 27.8 [*P*(O)(OEt)$_2$]; *m/z* (ESI$^+$) 364.1673 [100%, (M+H$^+$), $C_{19}H_{27}NO_4P$ requires 364.1672].

[1-Phenylethylidene]-(4-methoxyphenyl)-amine 334[62]



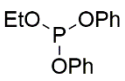
p-Anisidine (0.50 g, 4.0 mmol) was dissolved in dry toluene (15 mL) with 4Å molecular sieves (approx. 1.0 g) under nitrogen. Acetophenone (0.47 mL, 4.0 mmol) was added, and the reaction was stirred for 22 h. The reaction was filtered, and the solvent was removed under reduced pressure. Purification via recrystallisation from 60-80 petroleum ether afforded the product as an orange solid (0.42 g, 48%); mpt. 82-84 °C (lit.[62], 86 °C); ν_{max}/cm^{-1} (ATR) 2996, 2954, 2835, 1615, 1501; δ_H (400 MHz, $CDCl_3$) 2.31 (3H, s, C*H*$_3$), 3.85 (3H, s, C*H*$_3$), 6.82 (2H, d, *J* 8.4, ArC*H*), 6.90-6.99 (2H, m, ArC*H*), 7.43-7.58 (3H, m, ArC*H*), 7.98-8.06 (2H, m, ArC*H*).

Data are in accordance with the literature.

Diphenyl methyl phosphonate 337[183]

Diphenyl phosphite (0.76 mL, 4.0 mmol) and DBU (0.66 mL, 4.4 mmol) were dissolved in dry acetonitrile (8 mL) under a nitrogen atmosphere. After cooling to 0 °C, methyl iodide (0.27 mL, 4.4 mmol) was added dropwise. The reaction was stirred at 0 °C for 2 h then warmed to room temperature and stirred for a further 30 min. The solvent and excess MeI were removed under reduced pressure. Purification via flash column chromatography on silica gel (ethyl acaetate:hexane 40:60) as eluent afforded the pure product as a pale-yellow oil (0.59 g, 60%); δ_H (400 MHz, $CDCl_3$) 1.81 (3H, d, *J* 17.7, PC*H*$_3$), 7.17-7.24 (6H, m, ArC*H*), 7.32-7.38 (4H, m, ArC*H*); δ_P (162 MHz, $CDCl_3$) 23.9.

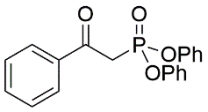
Ethyl diphenylphosphite 340[184]



Phenol (0.73 g, 7.8 mmol) was dissolved in toluene (7 mL) with triethylamine (1.1 mL, 8.2 mmol) under nitrogen and cooled to 0 °C. Ethyl dichlorophosphite (0.5 mL, 4 mmol) was dissolved in diethyl ether (3 mL) and slowly added. The reaction was stirred at 0 °C for 30 min before being warmed to room temperature and stirred for a further 3 h. The salt was filtered off and washed with toluene (20 mL). The organic phase was passed through a pad of basic alumina and the solvent was removed under reduced pressure affording the crude product as a colourless thin oil (0.86 g, 85%) which was used directly in the next step without further purification due to product instability; δ_H (400 MHz, $CDCl_3$) 1.39 (3H, t, *J* 7.1, CH_2CH_3), 4.24-4.31 (2H, m, OCH_2), 7.14-7.38 (10H, m, ArC*H*); δ_P (162 MHz, $CDCl_3$) 128.9.

Selected data from crude ^{1}H NMR spectra. Data are in accordance with the literature.

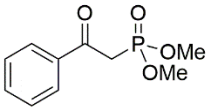
Diphenyl 2-oxo-2-phenylethyl phosphonate 336[185]



2-Bromoacetophenone (1.79 g, 9.0 mmol) and ethyl diphenylphosphite (2.39 g, 9.0 mmol) were mixed then heated at reflux under nitrogen for 4 h. After cooling to room temperature, the crude brown oil was purified by flash column chromatography on silica gel (30:70, ethyl aceate:hexane) affording the product as a pale yellow solid (2.51 g, 78%); Mpt 68-70 °C; δ_H (400 MHz, $CDCl_3$) 3.96 (2H, d, *J* 22.8, PCH_2, 7.16-7.21 (6H, m, ArC*H*), 7.30-7.35 (4H, m, ArC*H*), 7.52 (2H, t, *J* 7.7, ArC*H*), 7.64 (1H, t, *J* 7.4, ArC*H*), 8.07 (2H, d, *J* 7.3, ArC*H*); δ_P (162 MHz, $CDCl_3$) 13.04.

Reported as an oil within the literature. All other data are in accordance with the literature.

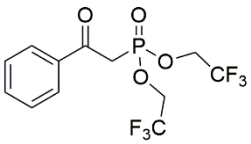
Dimethyl 2-oxo-2-phenylethylphosphonate 341[181]



2-Bromoacetophenone (1.00 g, 5 mmol) and trimethylphosphite (0.59 mL, 5mmol) were mixed and heated at reflux for 4 h. After cooling to room temperature, the crude yellow oil was purified by flash column chromatography on silica gel with ethyl acetate: petroleum ether (gradient from 75% EA in PE to 100% EA) affording the product as a pale-yellow oil (0.58 g, 50%); δ_H (400 MHz, $CDCl_3$) 3.66 (2H, d, *J* 22.6, PC*H*$_2$), 3.79 (6H, d, *J* 11.2, OC*H*$_3$), 7.50 (2H, t, *J* 7.5, ArC*H*), 7.61 (1H, t, *J* 7.5, ArC*H*), 8.02 (2H, d, *J* 7.5, ArC*H*); δ_P ($CDCl_3$, 162 MHz) 22.8.

Data are in accordance with the literature.

(2-Oxo-2-phenylethyl)-bis(2,2,2-trifluoroethyl) ester phosphonic acid 344[186]

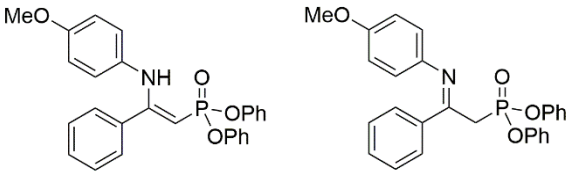


Trimethylsilyl bromide (0.87 mL, 6.6 mmol) was added dropwise to dimethyl 2-oxo-2-phenylethylphosphonate (0.50 g, 2.2 mmol) under nitrogen. The mixture was stirred for 1.5 h at rt and then concentrated under reduced pressure. The resulting yellow oil was dissolved in dry DCM (3 mL) with DMF (1 drop) and cooled to 0 °C under nitrogen. Oxalyl chloride (0.5 mL, 5.9 mmol) was added dropwise, the reaction was warmed to room temperature and stirred for 1 h. The solvent was removed under reduced pressure affording a yellow solid which was redissolved toluene (6 mL). This mixture was added to 2,2,2-trifluoroethanol (0.27 mL, 3.8 mmol) in pyridine (5 mL). The reaction was heated at 50 °C for 1.5 h. After cooling to room temperature, the reaction was quenched with aq. saturated $NaHCO_3$ (60 mL) and extracted with toluene (3 × 20 mL). The combined organic layers were washed with water (30 mL), aq.

saturated $NaHCO_3$ (30 mL), and brine (2 × 50 mL), then dried ($MgSO_4$), filtered, and the solvent removed under reduced pressure affording the crude product as a yellow oil (0.31 g, 39%); ν_{max}/cm^{-1} (thin film) 3064, 2975, 1684 (C=O), 1598, 1582; δ_H (400 MHz, $CDCl_3$) 3.86 (2H, d, *J* 21.2, PC*H*$_2$), 4.44-4.60 (4H, m, C*H*$_2$CF$_3$), 7.53 (2H, t, *J* 7.5, ArC*H*), 7.67 (1H, t, *J* 7.5, ArC*H*), 7.97 (2H, d, *J* 7.5, ArC*H*); δ_P (162 MHz, $CDCl_3$) 24.8.

Data are in accordance with the literature.

{2-[(4-Methoxyphenyl)amino]-2-phenylethenyl}-diphenyl ester phosphonic acid 345 and {2-[(4-methoxyphenyl)imino]-2-phenylethyl}-diphenyl ester phosphonic acid 346

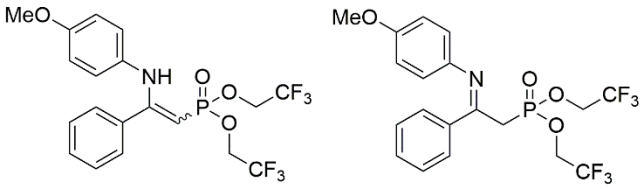


Diphenyl 2-oxo-2-phenylethyl phosphonate (0.20 g, 0.60 mmol), *p*-anisidine (0.09 g, 0.70 mmol) and *p*-toluenesulfonic acid monohydrate (5 mg, 0.03 mmol) were dissolved in dry toluene (30 mL). The reaction was heated under Dean-Stark conditions for 2 days. After cooling to room temperature, the solvent was removed under reduced pressure. Purification via flash column chromatography on silica gel (20:80, ethyl acetate:hexane) afforded the product mixture (0.12 g, 43%); ν_{max}/cm^{-1} (thin film) 3274, 3062, 3042, 2955, 2934, 2908, 2835, 1607, 1588, 1571, 1512; δ_H (400 MHz, $CDCl_3$, 88:12 *enamine*:*imine*) 3.71 (2.64H, s, *enamine* OC*H*$_3$), 3.79 (0.24H, d, *J* 23.4, *imine* PC*H*$_2$), 3.85 (0.36H, s, *imine* OC*H*$_3$), 4.38 (0.88H, d, *J* 13.7, *enamine* PC*H*), 6.52-6.63 (4H, m, ArC*H*), 6.87-7.63 (14.88H, m, ArC*H*), 8.03-8.07 (0.12H, m, *imine* ArC*H*); δ_C (100 MHz, $CDCl_3$) 55.3 (O*C*H$_3$), 79.3 (d, $J_{C\text{-}P}$ 193.0, P*C*H), 113.8 (Ar*C*H), 114.5 (Ar*C*H), 120.3 (d, $J_{C\text{-}P}$ 5.0, Ar*C*H), 120.6 (Ar*C*H), 120.8 (d, $J_{C\text{-}P}$ 4.5, ArCH), 124.4 (Ar*C*H), 124.9 (Ar*C*H), 128.3 (d, $J_{C\text{-}P}$ 8.0, Ar*C*H), 129.4 (Ar*C*H), 129.5 (Ar*C*H), 129.7 (Ar*C*H), 133.9 (Ar*C*), 136.8 (Ar*C*), 137.0 (Ar*C*), 150.7 (Ar*C*), 155.7 (Ar*C*), 163.4 (Ar*C*), 176.9 (N*C*=C);

δ_P (162 MHz, $CDCl_3$) *imine* 14.2 , *enamine* 17.9; *m/z* (EI) 458.1522 [100%, $(M+H)^+$, $C_{27}H_{24}NO_4P$ requires 548.1516].

The complexity of the ^{13}C NMR data means that each signal has been reported with no interpretation.

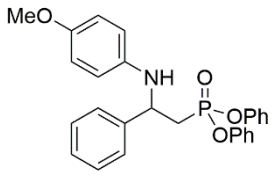
{2-[(4-methoxyphenyl)amino]-2-phenylethenyl}-bis(2,2,2-trifluoroethyl) ester phosphonic acid 347 and {2-[(4-methoxyphenyl)imino]-2-phenylethyl}-bis(2,2,2-trifluoroethyl) ester phosphonic acid 348



(2-Oxo-2-phenylethyl)-bis(2,2,2-trifluoroethyl) ester phosphonic acid (285 mg, 0.80 mmol), *p*-anisidine (123 mg, 1.00 mmol) and *p*-toluenesulfonic acid monohydrate (6 mg, 0.04 mmol) were dissolved in dry toluene (50 mL) and heated under Dean-Stark conditions overnight. After cooling to rt., the solvent was removed under reduced pressure. Purification via flash column chromatography on silica gel pre-treated with triethylamine (ethyl acetate:hexane 25:75) afforded the product mixture as an orange oil (0.09 g, 32%, 88:12 enamine:imine, 75:25 enamine geometric isomers); ν_{max}/cm^{-1} (thin film) 3284, 2964, 2839, 1608, 1589, 1572, 1513; δ_H (400 MHz, $CDCl_3$) 3.63 (0.24H, d, *J* 23.9, *imine* PC*H*$_2$), 3.72 (1.98H, s, *major enamine* OC*H*$_3$), 3.85 (0.36H, s, *imine* OC*H*$_3$), 3.86 (0.66H, s, *minor enamine* OC*H*$_2$), 4.20 (0.66H, d, *J* 13.2, *major enamine* C*H*), 4.36-4.64 (4H, m, OC*H*$_2$), 4.58 (0.22H, d, *J* 11.6, *minor* enamine), 6.64-6.66 (4H, m, ArC*H*), 7.19-7.96 (5H, m, ArC*H*); δ_C (100 MHz, $CDCl_3$) 55.4, 55.51, 55.54, 61.9 (dq, *J* 37.5, 4.0), 74.6, 76.5, 114.0, 114.9, 124.5, 126.7, 128.4, 128.6, 129.9, 133.3, 136.3, 156.0, 164.6; δ_P (162 MHz, $CDCl_3$) 25.2, 27.4 (*major enamine*), 27.6; *m/z* (ESI^+) 470.0970 [100%, $(M+H)^+$, $C_{19}H_{18}F_6NO_4P$ requires 470.0950].

The complexity of the ^{13}C NMR data means that each signal has been reported with no interpretation.

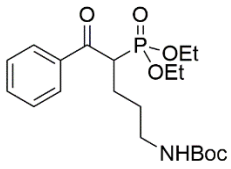
{2-[(4-Methoxyphenyl)amino]-2-phenylethyl}-diphenyl ester phosphonic acid 349



{2-[(4-Methoxyphenyl)amino]-2-phenyl-ethenyl}-diphenyl ester phosphonic acid (0.23 g, 0.50 mmol), benzoic acid (6.0 mg, 0.005 mmol), and dimethylformamide (0.01 mL, 0.50 mmol) were dissolved in DCM (0.6 mL) under nitrogen and cooled to 0 °C. Trichlorosilane (0.20 mL, 2.0 mmol) was added dropwise, the reaction was warmed to rt, and stirred overnight. After diluting with DCM (3 mL), the reaction was quenched with aq. 1M NaOH (6 mL) and stirred for 20 min. The layers were separated, and the aqueous layer extracted using DCM (3 × 10 mL). The combined organic layers were washed with brine (30 mL), dried ($MgSO_4$), filtered, and solvent removed under reduced pressure. Purification via recrystallisation from ethyl acetate afforded the product as a white solid (0.15 g, 65%); mpt.150-152 °C; v_{max}/cm^{-1} (thin film) 3435 (NH), 2103, 1644; δ_H (400 MHz, $CDCl_3$) 2.58-2.68 (2H, m, C*H*$_2$), 3.72 (3H, d, *J* 0.8, OC*H*$_3$), 4.86 (1H, dt *J* 13.5, 6.9, C*H*), 6.48-6.54 (2H, m, ArC*H*), 6.65-6.73 (2H, m, ArC*H*), 7.09 (4H, dddd, *J* 11.0, 8.6, 2.2, 1.1, ArC*H*), 7.13-7.21 (2H, m, ArC*H*), 7.24-7.40 (7H, m, ArC*H*), 7.45 (2H, d, *J* 7.6, ArC*H*); δ_C (100 MHz, $CDCl_3$) 37.2 (d, $J_{C\text{-}P}$ 131.0, P*C*H$_2$), 55.1 (O*C*H$_3$), 57.1 (N*C*H), 114.7 (Ar*C*H), 115.9 (Ar*C*H), 118.5 (Ar*C*H), 120.3 (d, $J_{C\text{-}P}$ 4.0, Ar*C*H), 124.2 (Ar*C*H), 127.8 (Ar*C*H), 129.1 (Ar*C*H), 141.0 (Ar*C*), 145.1 (Ar*C*), 152.3 (Ar*C*), 154.7 (d, $J_{C\text{-}P}$ 10.5, Ar*C*) ; δ_P (162 MHz, $CDCl_3$) 20.9 [C*P*(O)(OEt)$_2$]; *m/z* (ESI$^+$) 460.1681 [100%, $(M^+H)^+$, $C_{27}H_{26}NO_4P$ requires 460.1672].

The complexity of the ^{13}C NMR data means that each signal has been reported with very little interpretation.

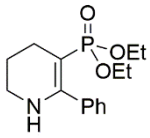
α-{[[(1,1-Dimethylethoxy)carbonyl]amino]propyl}-β-oxo-benzenepropanphosphonic acid diethyl ester 350



Sodium hydride (60% dispersion in mineral oil, 0.120 g, 3.0 mmol) was washed using hexane (3 × 1 mL) under nitrogen and the suspended in dry THF (1 mL). Diethyl 2-oxo-2-phenylethylphosphonate (0.512 g, 2.0 mmol) in dry THF (2 mL) was added dropwise and the reaction mixture was heated at 35 °C for 30 min. *N*-Boc-3-bromopropylamine (0.571 g, 2.4 mmol) in dry THF (3 mL) was added dropwise followed by tetrabutylammonium iodide (0.739 g, 2.0 mmol) in one portion. The reaction was heated a 60 °C overnight. After cooling to rt., the reaction was quenched via the addition of aq. saturated ammonium chloride (2 mL) and diluted with water (10 mL). The layers were separated, and the aqueous layer was extracted using ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure. Purification on silica gel (30:70 ethyl acetate:hexane) afforded the product as a pale-yellow oil (0.136 g, 16%, some contamination from starting material); δ_H (400 MHz, $CDCl_3$) 1.19 (3H, t, *J* 7.0, C*H*$_3$), 1.27 (3H, t, *J* 7.0, C*H*$_3$), 1.43 [9H, s, C(C*H*$_3$)$_3$], 1.51 (2H, dp, *J* 15.2, 5.5, C*H*$_2$), 1.94-2.11 (1H, m, C*H*H), 2.17-2.34 (1H, m, C*H*H), 3.06-3.18 (2H, m, C*H*$_2$), 3.98-4.22 (5H, m, OC*H*$_2$ and C*H*), 4.60 (1H, bs, N*H*), 7.46 (2H, m, ArC*H*), 7.55-7.64 (1H, m, ArC*H*), 7.97-8.04 (2H, m, ArC*H*); δ_P (162 MHz, $CDCl_3$) 22.0.

Selected data from contaminated ^{1}H NMR spectrum.

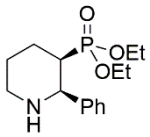
1,4,5,6-Tetrahydro-2-phenyl-4H-pyrridyl-3-phosphonic acid diethyl ester **351**



α-{[[(1,1-Dimethylethoxy)carbonyl]amino]propyl}-β-oxo-benzenepropanphosphonic acid diethyl ester (0.130 g, 0.31 mmol) was dissolved in DCM (3 mL) under argon and cooled to 0 °C. TFA (0.24 mL, 3.10 mmol) was added dropwise. After addition was complete, the reaction was warmed to rt. and stirred for 2.5 h. An ice/water slurry (10 mL) was added, the mixture neutralised using solid sodium hydrogen carbonate, and the mixture stirred for 1.5 h. The layers were separated, and the aqueous layer was extracted using DCM (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure affording the product as a yellow oil (0.09 g, 98%, some contamination from starting material) which was used directly in the next step without further purification; δ_H (400 MHz, $CDCl_3$) 1.10 (6H, t, *J* 7.1, C*H*$_3$), 1.85-1.96 (2H, m, C*H*$_2$), 2.45 (2H, q, *J* 6.4, C*H*$_2$), 3.30-3.38 (2H, m, C*H*$_2$), 3.59-4.02 (4H, m, OC*H*$_2$), 7.31-7.76 (5H, m, ArC*H*); δ_P (162 MHz, $CDCl_3$) 24.6; *m/z* (ESI$^+$) 296.15 [100%, $(M+H)^+$], 125.99 (3).

Selected data from crude ^{1}H NMR spectrum.

(±)-*cis*-2-Phenylpiperidine-3-phosphonic acid diethyl ester 352



1,4,5,6-Tetrahydro-2-phenyl-4H-pyrridyl-3-phosphonic acid diethyl ester (36.9 mg, 0.125 mmol) was dissolved in methanol (2.5 mL). Hydrogenation was performed employing the H-Cube® reactor (30 bar, 35 °C) with 5% Pd/C CatCart®. The reaction mixture was cycled through three times. The solvent was removed under reduced pressure. Purification via small

scale column chromatology on silica gel (3:97 methanol:DCM) afforded the product as a pale-yellow oil (32.5 mg, 87%); ν_{max}/cm^{-1} (thin film, ATR) 2980, 2931, 1662, 1448; δ_H (400 MHz, $CDCl_3$, dr >99:1) 0.88 (3H, t, *J* 7.1, C*H*$_3$), 1.23 (3H, t, *J* 7.0, C*H*$_3$), 1.52-1.60 (1H, m, C*H*H), 1.84-2.27 (3H, m, C*H*H and N*H*), 2.37-2.54 (2H, m, C*H*H), 2.84 (1H, ddd, *J* 13.5, 12.1, 3.4, C*H*H), 3.19 (1H, ddq, *J* 10.1, 8.7, 7.1, OC*H*H), 3.42 (1H, ddt, *J* 13.5, 4.2, 2.0, C*H*^{A}), 3.48-3.62 (1H, m, OC*H*H), 3.89-4.03 (2H, m, OC*H*$_2$), 4.14 (1H, dd, *J* 39.2, 3.7, PC*H*), 7.18-7.26 (1H, m, ArC*H*), 7.28-7.40 (4H, m, ArC*H*); δ_C (100 MHz, $CDCl_3$) 16.0 (d, $J_{C\text{-}P}$ 6.5, *C*H$_3$), 16.3 (d, $J_{C\text{-}P}$ 6.5, *C*H$_3$), 23.3 (*C*H$_2$), 27.3 (d, $J_{C\text{-}P}$ 2.5, *C*H$_2$), 39.1 (d, $J_{C\text{-}P}$ 136.5, P*C*H), 60.7 (d, $J_{C\text{-}P}$ 7.0, O*C*H$_2$), 60.9 (d, $J_{C\text{-}P}$ 3.0, *C*H), 61.0 (d, $J_{C\text{-}P}$ 7.0, O*C*H$_2$), 126.50 (2 × Ar*C*H), 126.54 (Ar*C*H), 127.9 (2 × Ar*C*H), 142.1 (Ar*C*); δ_P (162 MHz, $CDCl_3$) 29.5; *m*/*z* (ESI$^+$) 298.1578 [100%, (M+H)$^+$, $C_{15}H_{25}NO_3P$ requires 298.1567].

References

1 G. M. Keseru and G. M. Makara, *Drug Discov. Today*, 2006, 11, 741–748.

2 C. A. Lipinski, F. Lombardo, B. W. Dominy and P. J. Feeney, *Adv. Drug Deliv. Rev.*, 2001, **46**, 3–26.

3 I. J. P. De Esch, D. A. Erlanson, W. Jahnke, C. N. Johnson and L. Walsh, *J. Med. Chem.*, 2022, **65**, 84–99.

4 D. A. Erlanson, S. W. Fesik, R. E. Hubbard, W. Jahnke and H. Jhoti, *Nat. Rev. Drug Discov. 2016 159*, 2016, **15**, 605–619.

5 L. H. Yuen and R. M. Franzini, *ChemBioChem*, 2017, 18, 829–836.

6 I. Wagner and H. Musso, *Angew. Chemie Int. Ed. English*, 1983, 22, 816–828.

7 M. A. T. Blaskovich, *J. Med. Chem.*, 2016, **59**, 10807–10836.

8 C. F. O'Brien, R. Jimenez, R. A. Hauser, S. A. Factor, J. Burke, D. Mandri and J. C. Castro-Gayol, *Mov. Disord.*, 2015, **30**, 1681–1687.

9 P. Pevarello, A. Bonsignori, P. Dostert, F. Heidempergher, V. Pinciroli, M. Colombo, R. A. McArthur, P. Salvati, C. Post, R. G. Fariello and M. Varasi, *J. Med. Chem.*, 1998, **41**, 579–590.

10 E. Juaristi and V. A. Soloshonok, *Enantioselective Synthesis of beta-Amino Acids, 2nd Ed*, John Wiley & Sons, Inc., United States of America, Second Edi., 2005.

11 F. Lipmann, *Microbiol. Mol. Biol. Rev.*, 1953, **17**, 1–16.

12 E. E. van Tamelen, J. R. Dyer, H. A. Whaley, H. E. Carter and G. B. Whitfield, *J. Am. Chem. Soc*, 1961, **83**, 4295–4296.

13 Z. Ji, M. Wang, J. Zhang, S. Wei and W. Wu, *J. Antibiot. (Tokyo).*, 2007, **60**, 739–744.

14 M. C. Cone, X. Yin, L. L. Grochowski, M. R. Parker and T. M. Zabriskie, *ChemBioChem*, 2003, **4**, 821–828.

15 S. Abele, G. Guichard and D. Seebach, *Helv. Chim. Acta*, 1998, **81**, 2141–2156.

16 G. A. Khoury, R. C. Baliban and C. A. Floudas, *Sci. Rep.*, 2011, **1**, 1–5.

17 S. K. Kang, G. H. Cho, H. J. Leem, B. K. Soh, J. Sim and Y. G. Suh, *Tetrahedron Asymmetry*, 2017, **28**, 34–40.

18 U. Schöllkopf, U. Groth and C. Deng, *Angew. Chemie Int. Ed. English*, 1981, **20**, 798–799.

19 B. U. Schollkopf, W. Hartwig and U. Groth, *Angew. Chem. Int. Ed.*, 1979, **18**, 863–864.

20 T. K. Chakraborty and A. Ghosh, *Tetrahedron Lett.*, 2002, **43**, 9691–9693.

21 X. Lu, J. Yi, Z.-Q. Q. Zhang, J.-J. J. Dai, J.-H. H. Liu, B. Xiao, Y. Fu and L. Liu, *Chem. - A Eur. J.*, 2014, **20**, 15339–15343.

22 R. F. W. Jackson, N. Wishart, A. Wood, K. James and M. J. Wythes, *J. Org. Chem.*, 1992, **57**, 3397–3404.

23 A. Strecker, *Justus Liebigs Ann. Chem.*, 1850, **75**, 27–45.

24 K. Harada, *Nature*, 1963, **200**, 1201.

25 J. Wang, X. Liu and X. Feng, *Chem. Rev.*, 2011, **111**, 6947–6983.

26 M. S. Iyer, K. M. Gigstad, N. D. Namdev and M. Lipton, *J. Am. Chem. Soc*, 1996, **11**, 259–268.

27 S. J. Zuend, M. P. Coughlin, M. P. Lalonde and E. N. Jacobsen, *Nature*, 2009, **461**, 968–970.

28 J. H. Xie, S. F. Zhu and Q. L. Zhou, *Chem. Rev.*, 2011, 111, 1713–1760.

29 J. Chen, F. Li, F. Wang, Y. Hu, Z. Zhang, M. Zhao and W. Zhang, *Org. Lett.*, 2019, **21**, 9060–9065.

30 G. Shang, Q. Yang and X. Zhang, *Angew. Chemie - Int. Ed.*, 2006, **45**, 6360–6362.

31 C. Zhu and T. Akiyama, *Adv. Synth. Catal.*, 2010, **352**, 1846–1850.

32 A. S. Saghyan and P. Langer, *Asymmetric Synthesis of Non-Proteinogenic Amino Acids*, John Wiley & Sons, Incorporated, Weinheim, 1st edn., 2016.

33 R. O. Duthaler, *Tetrahedron*, 1994, **50**, 1539–1650.

34 F. Kudo, A. Miyanaga and T. Eguchi, *Nat. Prod. Rep.*, 2014, **31**, 1056–1073.

35 S. G. Davies and O. Ichihara, *Tetrahedron: Asymmetry*, 1991, **2**, 183–186.

36 S. G. Davies, A. D. Smith and P. D. Price, *Tetrahedron Asymmetry*, 2005, 16, 2833–2891.

37 S. G. Davies, A. M. Fletcher, P. M. Roberts and J. E. Thomson, *Tetrahedron: Asymmetry*, 2012, **23**, 1111–1153.

38 M. Liu and M. P. Sibi, *Tetrahedron*, 2002, **58**, 7991–8035.

39 F. A. Davis, R. T. Reddy and R. E. Reddy, *J. Org. Chem.*, 1992, **57**, 6387–6389.

40 J. Vesely, R. Rios, I. Ibrahem and A. Córdova, *Tetrahedron Lett.*, 2007, **48**, 421–425.

41 K. L. Klettke, S. Sanyal, W. Mutatu and K. D. Walker, *J. Am. Chem. Soc.*, 2007, **129**, 6988–6989.

42 W. D. Lubell, M. Kitamura and R. Noyori, *Tetrahedron: Asymmetry*, 1991, **2**, 543–554.

43 Q. Dai, W. Yang and X. Zhang, *Org. Lett.*, 2005, **7**, 5343–5345.

44 J. H. Xie, S. F. Zhu and Q. L. Zhou, *Chem. Soc. Rev.*, 2012, **41**, 4126–4139.

45 P. Yang, H. Xu and J. Zhou, *Angew. Chemie - Int. Ed.*, 2014, **53**, 12210–12213.

46 N. J. A. Martin, X. Cheng and B. List, *J. Am. Chem. Soc.*, 2008, **130**, 13862–13863.

47 F. Iwasaki, O. Onomura, K. Mishima, T. Kanematsu, T. Maki and Y. Matsumura, *Tetrahedron Lett.*, 2001, **42**, 2525–2527.

48 A. V. Malkov, A. J. P. Stewart Liddon, P. Ramírez-López, L. Bendová, D. Haigh and P. Kočovský, *Angew. Chemie - Int. Ed.*, 2006, **45**, 1432–1435.

49 O. Onomura, Y. Kouchi, F. Iwasaki and Y. Matsumura, *Tetrahedron Lett.*, 2006, **47**, 3751–3754.

50 C. Wang, X. Wu, L. Zhou and J. Sun, *Chem. - A Eur. J.*, 2008, **14**, 8789–8792.

51 C. Wang, X. Wu, L. Zhou and J. Sun, *Org. Biomol. Chem.*, 2015, **13**, 577–582.

52 S. Guizzetti, M. Benaglia, F. Cozzi and R. Annunziata, *Tetrahedron*, 2009, **65**, 6354–

6363.

53 T. Kanemitsu, A. Umehara, R. Haneji, K. Nagata and T. Itoh, *Tetrahedron*, 2012, **68**, 3893–3898.

54 Y. Xing, S. Wu, M. Dong, J. Wang, L. Liu and H. Zhu, *Tetrahedron*, 2019, **75**, 130495.

55 S. Jones and C. J. A. Warner, *Org. Biomol. Chem.*, 2012, **10**, 2189.

56 C. J. A. Warner, A. T. Reeder and S. Jones, *Tetrahedron: Asymmetry*, 2016, **27**, 136–141.

57 C. J. A. Warner, S. S. Berry and S. Jones, *Tetrahedron*, , DOI:10.1016/j.tet.2019.130733.

58 W. Pan, Y. Deng, J. B. He, B. Bai and H. J. Zhu, *Tetrahedron*, 2013, **69**, 7253–7257.

59 Y. N. Pei, Y. Deng, J. L. Li, L. Liu and H. J. Zhu, *Tetrahedron Lett.*, 2014, **55**, 2948–2952.

60 M. Bonsignore, M. Benaglia, L. Raimondi, M. Orlandi and G. Celentano, *Beilstein J. Org. Chem.*, 2013, **9**, 633–640.

61 Q. Li, Y. Li, J. Wang, Y. Lin, Z. Wei, H. Duan, Q. Yang, F. Bai and Y. Li, *New J. Chem.*, 2018, **42**, 827–831.

62 F.-M. Gautier, S. Jones and S. J. Martin, *Org. Biomol. Chem.*, 2009, **7**, 229–231.

63 X. Li, A. T. Reeder, F. Torri, H. Adams and S. Jones, *Org. Biomol. Chem.*, 2017, **15**, 2422–2435.

64 M. Sugiura, M. Kumahara and M. Nakajima, *Chem. Commun.*, 2009, **0**, 3585.

65 Z.-Y. Xue, Y. Jiang, X.-Z. Peng, W.-C. Yuan and X.-M. Zhang, *Adv. Synth. Catal.*, 2010, **352**, 2132–2136.

66 X. Chen, Y. Zheng, C. Shu, W. Yuan, B. Liu and X. Zhang, *J. Org. Chem.*, 2011, **76**, 9109–9115.

67 Z.-Y. Xue, L.-X. Liu, Y. Jiang, W.-C. Yuan and X.-M. Zhang, *European J. Org. Chem.*, 2012, **2012**, 251–255.

68 L. Chen, C. Wang, L. Zhou and J. Sun, *Adv. Synth. Catal.*, 2014, **356**, 2224–2230.

69 M. Sugiura, Y. Ashikari, Y. Takahashi, K. Yamaguchi, S. Kotani and M. Nakajima, *J. Org. Chem.*, 2019, **84**, 11458–11473.

70 C. Wagner, A. F. Kotthaus and S. F. Kirsch, *Chem. Commun.*, 2017, **53**, 4513–4516.

71 S. Gulzzettl, M. Benaglia and S. Rossi, *Org. Lett.*, 2009, **11**, 2928–2931.

72 M. Bonsignore, M. Benaglia, R. Annunziata and G. Celentano, *SYNLETT*, 2011, **8**, 1085–1088.

73 Z.-Y. Xue, Y. Jiang, W.-C. Yuan, X.-M. Zhang, X. Zhou-Yang, J. Yan, Y. Wei-Cheng and Z. Xiao-Mei, *European J. Org. Chem.*, 2010, **2010**, 616–619.

74 A. V. Malkov, S. Stončius, K. Vranková, M. Arndt and P. Kočovský, *Chem. - A Eur. J.*, 2008, **14**, 8082–8085.

75 H.-J. Zheng, W.-B. Chen, Z.-J. Wu, J.-G. Deng, W.-Q. Lin, W.-C. Yuan and X.-M. Zhang, *Chem. - A Eur. J.*, 2008, **14**, 9864–9867.

76 X. Wu, Y. Li, C. Wang, L. Zhou, X. Lu and J. Sun, *Chem. - A Eur. J.*, 2011, **17**, 2846–2848.

77 S. Jones and X. Li, *Tetrahedron*, 2012, **68**, 5522–5532.

78 X. Chen, X. Y. Hu, C. Shu, Y. H. Zhang, Y. S. Zheng, Y. Jiang, W. C. Yuan, B. Liu and X. M. Zhang, *Org. Biomol. Chem.*, 2013, **11**, 3089–3093.

79 Y. Jiang, X. Chen, Y. Zheng, Z. Xue, C. Shu, W. Yuan and X. Zhang, *Angew. Chemie Int. Ed.*, 2011, **50**, 7304–7307.

80 Y. Jiang, X. Chen, X. Y. Hu, C. Shu, Y. H. Zhang, Y. S. Zheng, C. X. Lian, W. C. Yuan and X. M. Zhang, *Adv. Synth. Catal.*, 2013, **355**, 1931–1936.

81 X. Dai, M. Liu, M. Huang, J. Zhang, X. Xu, W. Yuan and X. Zhang, *Asian J. Org. Chem.*, 2019, **8**, 456–461.

82 P. Zhang, C. Wang, L. Zhou and J. Sun, *Chinese J. Chem.*, 2012, **30**, 2636–2640.

83 C. Shu, X. Y. Hu, S. S. Li, W. C. Yuan and X. M. Zhang, *Synlett*, 2014, **25**, 1879–1882.

84 D. J. Hamilton, M. Beemsterboer, C. M. Carter, J. Elsayed, R. E. M. Huiberts, H. F. Klein, P. O'Brien, I. J. P. de Esch and M. Wijtmans, *ChemMedChem*, , DOI:10.1002/cmdc.202200113.

85 C. Lambruschini, D. Galante, L. Moni, F. Ferraro, G. Gancia, R. Riva, A. Traverso, L. Banfi and C. D'Arrigo, *Org. Biomol. Chem.*, 2017, **15**, 9331–9351.

86 X. Xiao, X. X. Zhang, M. M. Zhan, K. Cheng, S. Li, Z. Xie and C. Liao, *Eur. J. Med. Chem.*, 2018, **145**, 588–593.

87 A. Gironda-Martínez, E. J. Donckele, F. Samain and D. Neri, *ACS Pharmacol. Transl. Sci.*, 2021, 4, 1265–1279.

88 D. Damour, F. Herman, R. Labaudinière, G. Pantel, M. Vuilhorgne and S. Mignani, *Tetrahedron*, 1999, **55**, 10135–10154.

89 S. Hanessian, G. McNaughton-Smith, H. G. Lombart and W. D. Lubell, *Tetrahedron*, 1997, 53, 12789–12854.

90 S. K. Panday, *Tetrahedron Asymmetry*, 2011, 22, 1817–1847.

91 Y. Matsumura, K. Ogura, Y. Kouchi, F. Iwasaki and O. Onomura, *Org. Lett.*, 2006, **8**, 3789–3792.

92 R. D. Birkenmeyer and F. Kagan, *J. Med. Chem.*, 1970, **13**, 616–619.

93 F. Manfré and J. P. Pulicani, *Tetrahedron: Asymmetry*, 1994, **5**, 235–238.

94 E. A. Severino, E. R. Costenaro, A. L. L. Garcia and C. R. D. Correia, *Org. Lett.*, 2003, **5**, 305–308.

95 M. Haddad, H. Imogai and M. Larcheveque, *J. Org. Chem.*, 1998, **63**, 5680–5683.

96 B. C. J. Van Esseveldt, P. W. H. Vervoort, F. L. Van Delft and F. P. J. T. Rutjes, *J. Org. Chem.*, 2005, **70**, 1791–1795.

97 D. Stead, P. O'Brien and A. Sanderson, *Org. Lett.*, 2008, **10**, 1409–1412.

98 F. A. Davis, T. Fang and R. Goswami, *Org. Lett.*, 2002, **4**, 1599–1602.

99 A. C. Rudolph, R. Machauer and S. F. Martin, *Tetrahedron Lett.*, 2004, **45**, 4895–

4898.

100 Y. G. Wang, T. Kumano, T. Kano and K. Maruoka, *Org. Lett.*, 2009, **11**, 2027–2029.

101 M. Lee, Y. J. Lee, E. Park, Y. Park, M. W. Ha, S. Hong, Y. J. Lee, T. S. Kim, M. H. Kim and H. G. Park, *Org. Biomol. Chem.*, 2013, **11**, 2039–2046.

102 P. W. R. Harris, M. A. Brimble, V. J. Muir, M. Y. H. Lai, N. S. Trotter and D. J. Callis, *Tetrahedron*, 2005, **61**, 10018–10035.

103 P. Liu, X. Huo, B. Li, R. He, J. Zhang, T. Wang, F. Xie and W. Zhang, *Org. Lett.*, 2018, **20**, 6564–6568.

104 S. S. Berry and S. Jones, *Org. Biomol. Chem.*, 2021, 19, 10493–10515.

105 J. Yun and S. L. Buchwald, *Chirality*, 2000, **12**, 476–478.

106 J. Yun and S. L. Buchwald, *J. Org. Chem.*, 2000, **65**, 767–774.

107 D. Imbri, N. Netz, M. Kucukdisli, L. M. Kammer, P. Jung, A. Kretzschmann and T. Opatz, *J. Org. Chem.*, 2014, **79**, 11750–11758.

108 I. Oura, K. Shimizu, K. Ogata and S. I. Fukuzawa, *Org. Lett.*, 2010, **12**, 1752–1755.

109 D. S. Timofeeva, A. R. Ofial and H. Mayr, *Tetrahedron*, 2019, **75**, 459–463.

110 A. Momotake, H. Togo and M. Yokoyama, *J. Chem. Soc. - Perkin Trans. 1*, 1999, 1193–1200.

111 M. Arbour, S. Roy, C. Godbout and C. Spino, *J. Org. Chem.*, 2009, **74**, 3806–3814.

112 F. R. Stermitz, M. M. Miller and M. J. Schneider, *J. Nat. Prod.*, 1990, **53**, 1019–1020.

113 M. Amat, N. Llor, R. Griera, M. Pérez and J. Bosch, *Nat. Prod. Commun.*, 2011, 6, 515–526.

114 K. E. Andersen, C. Braestrup, F. C. Grønwald, A. S. Jørgensen, E. B. Nielsen, U. Sonnewald, P. O. Sørensen, P. D. Suzdak and L. J. S. Knutsen, *J. Med. Chem.*, 2002, **36**, 1716–1725.

115 A. Lee, *Drugs 2021 821*, 2021, **82**, 79–85.

116 E. Vitaku, D. T. Smith and J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 10257–10274.

117 T. D. Downes, S. P. Jones, H. F. Klein, M. C. Wheldon, M. Atobe, P. S. Bond, J. D. Firth, N. S. Chan, L. Waddelove, R. E. Hubbard, D. C. Blakemore, C. De Fusco, S. D. Roughley, L. R. Vidler, M. A. Whatton, A. J. A. Woolford, G. L. Wrigley and P. O'Brien, *Chem. – A Eur. J.*, 2020, **26**, 8969–8975.

118 A. Bari, A. Iqbal, Z. A. Khan, S. A. Shahzad and M. Yar, *Synth. Commun.*, 2020, 50, 2572–2589.

119 P. M. Weintraub, J. S. Sabol, J. M. Kane and D. R. Borcherding, *Tetrahedron*, 2003, **59**, 2953–2989.

120 S. Källström and R. Leino, *Bioorg. Med. Chem.*, 2008, **16**, 601–635.

121 N. M. Garrido, M. García, D. Díez, M. R. Sánchez, F. Sanz and J. G. Urones, *Org. Lett.*, 2008, **10**, 1687–1690.

122 A. R. Mohite, P. R. Sultane and R. G. Bhat, *Tetrahedron Lett.*, 2012, **53**, 30–35.

123 C. M. Pedersen and M. Bols, *Tetrahedron*, 2005, **61**, 115–122.

124 E. Semina, F. Colpaert, K. Van Hecke, N. De Kimpe and S. Mangelinckx, *European J. Org. Chem.*, 2015, **2015**, 4847–4859.

125 Q. Zhou, L. Zhang, W. Meng, X. Feng, J. Yang and H. Du, *Org. Lett.*, 2016, **18**, 5189–5191.

126 Z. Y. Yang, H. Luo, M. Zhang and X. C. Wang, *ACS Catal.*, 2021, **11**, 10824–10829.

127 S. Jedrzejczak, University of Sheffield, 2021.

128 T. Hughes, G. P. Simon and K. Saito, *Polym. Chem.*, 2018, **9**, 5585–5593.

129 K. Achiwa, K. Sugiyama and M. Sekiya, *Chem. Pharm. Bull.*, 1985, **33**, 1975–1981.

130 P. Kafarski and B. Lejczak, *Phosphorus. Sulfur. Silicon Relat. Elem.*, 1991, **63**, 193–215.

131 K. D. Troev, *Chemistry and application of H-phosphonates*, Elsevier, Amsterdam, 2006.

132 X. Cheng, R. Goddard, G. Buth and B. List, *Angew. Chemie Int. Ed.*, 2008, **47**, 5079–5081.

133 H. Park, C. W. Cho and M. J. Krische, *J. Org. Chem.*, 2006, **71**, 7892–7894.

134 F. Palacios, C. Alonso and J. M. de los Santos, *Chem. Rev.*, 2005, **105**, 899–932.

135 Y. V Rassukana, P. P. Onys'ko, M. V Kolotylo, A. D. Sinitsa, P. Łyzwa and M. Mikołajczyk, *Tetrahedron Lett.*, 2009, **50**, 288–290.

136 H. Brachwitz, M. Ölke, J. Bergmann and P. Langen, *Bioorganic Med. Chem. Lett.*, 1997, **7**, 1739–1742.

137 G. Cravotto, G. B. Giovenzana, R. Pagliarin, G. Palmisano and M. Sisti, *Tetrahedron Asymmetry*, 1998, **9**, 745–748.

138 S. Hanessian, Y. L. Bennani and Y. Herve, *SYNLETT*, 1993, 35–36.

139 M. Mikołajczyk, P. Lyzwa, J. Drabowicz, M. W. Wieczorek and J. Blaszczyk, *Chem. Commun.,* 1996, **27**, 1503–1504.

140 T. Hashimoto and K. Maruoka, *J. Am. Chem. Soc.*, 2007, **129**, 10054–10055.

141 Y. Peng, Y. Ning, S. Tan, D. Li and N. Liao, *Synlett*, 2018, **29**, 678–682.

142 S. Doherty, J. G. Knight, A. L. Bell, S. El-Menabawey, C. M. Vogels, A. Decken and S. A. Westcott, *Tetrahedron Asymmetry*, 2009, **20**, 1437–1444.

143 R. Kadyrov, J. Holz, B. Schäffner, O. Zayas, J. Almena and A. Börner, *Tetrahedron: Asymmetry*, 2008, **19**, 1189–1192.

144 M. Zhou, Z. Xue, M. Cao, X. Q. Dong and X. Zhang, *Org. Biomol. Chem.*, 2016, **14**, 4582–4584.

145 A. Mishra and I. Deb, *Adv. Synth. Catal.*, 2016, **358**, 2267–2272.

146 K. Molnar, L. Takacs, M. Kadar, Z. Kardos and F. Faigl, *Synthesis (Stuttg).*, 2015, **47**, 1085–1090.

147 A. Solladié-Cavallo, K. Azyat, M. Schmitt and R. Welter, *Tetrahedron: Asymmetry*, 2005, **16**, 1055–1060.

148 E. J. Corey, R. K. Bakshi, S. Shibata, C. pin Chen and V. K. Singh, *J. Am. Chem.*

Soc., 1987, **109**, 7925–7926.

149 J. Haddow, C. J. Suckling and H. C. S. Wood, *J. Chem. Soc. Perkin Trans. 1*, 1989, 1297–1304.

150 G. C. Look, M. M. Murphy, D. A. Campbell and M. A. Gallop, *Tetrahedron Lett.*, 1995, **36**, 2937–2940.

151 P. Karoyan, J. Quancard, J. Vaissermann and G. Chassaing, , DOI:10.1021/jo026535n.

152 T. Jakusch, Á. Dörnyei, I. Correia, L. M. Rodrigues, G. K. Tóth, T. Kiss, J. Costa Pessoa and S. Marcão, *Eur. J. Inorg. Chem.*, 2003, **2003**, 2113–2122.

153 D. A. Rowlands and G. T. Young, *J. Chem. Soc.*, 1952, **0**, 3937–3940.

154 S. Bozkurt, M. Durmaz, M. Yilmaz and A. Sirit, *Tetrahedron Asymmetry*, 2008, **19**, 618–623.

155 R. S. Coffey, M. Green and G. W. Kenner, *J. Chem. Soc.*, 1959, 4100.

156 A. Armstrong, I. D. Edmonds, M. E. Swarbrick and N. R. Treweeke, *Tetrahedron*, 2005, **61**, 8423–8442.

157 N. Ikota, K. Achiwa and S.-I. Yamada, *Chem. Pharm. Bull.*, 1983, **3**, 887–894.

158 H. Imagawa, Y. Asai, H. Takano, H. Hamagaki and M. Nishizawa, *Org. Lett.*, 2006, **8**, 447–450.

159 M. J. O'Donnell and R. L. Polt, *J. Org. Chem.*, 1982, **47**, 2663–2666.

160 T. Niu, W. Zhang, D. Huang, C. Xu, H. Wang and Y. Hu, *Org. Lett.*, 2009, **11**, 4474–4477.

161 L. Kumar, A. Sarswat, N. Lal, A. Jain, S. Kumar, S. T. V. S. Kiran Kumar, J. P. Maikhuri, A. K. Pandey, P. K. Shukla, G. Gupta and V. L. Sharma, *Bioorganic Med. Chem. Lett.*, 2011, **21**, 176–181.

162 Z. Wang and S. F. Martin, *Tetrahedron*, 2022, **103**, 132551.

163 A. Gomtsyan, *Org. Lett.*, 2000, **2**, 11–13.

164 H. K. Hall, *J. Am. Chem. Soc.*, 1958, **80**, 6404–6409.

165 K. Usami, E. Yamaguchi, N. Tada and A. Itoh, *Org. Lett.*, 2018, **20**, 5714–5717.

166 A. Turočkin, W. Raven and P. Selig, *European J. Org. Chem.*, 2017, **2017**, 296–305.

167 S. K. V. Vernekar, H. Y. Hallaq, G. Clarkson, A. J. Thompson, L. Silvestr, S. C. R. Lummis and M. Lochner, *J. Med. Chem.*, 2010, **53**, 2324–2328.

168 C. V. Galliford and K. A. Scheidt, *Chem. Commun.*, 2008, 1926–1928.

169 L. Li, E. Babaoglu, K. Harms and G. Hilt, *European J. Org. Chem.*, 2017, **2017**, 4543–4547.

170 Y. Zhang and Y. Zhang, *J. Chem. Res.*, 2004, 510–512.

171 E. Cogné-Laage, J. F. Allemand, O. Ruel, J. B. Baudin, V. Croquette, M. Blanchard-Desce and L. Jullien, *Chem. – A Eur. J.*, 2004, **10**, 1445–1455.

172 S. Lethu, M. Ginisty, D. Bosc and J. Dubois, *J. Med. Chem.*, 2009, **52**, 6205–6208.

173 J. S. Yadav, B. V. Subba Reddy, B. Eeshwaraiah and P. N. Reddy, *Tetrahedron*,

2005, **61**, 875–878.

174 N. S. Y. Loy, S. Choi, S. Kim and C. M. Park, *Chem. Commun.*, 2016, **52**, 7336–7339.

175 J. Chen, D. Joseph, Y. Xia and S. Lee, *J. Org. Chem.*, 2021, **86**, 5943–5953.

176 J. Fan, Y. Peng, W. Xu, A. Wang, J. Xu, H. Yu, X. Lin and Q. Wu, *Org. Lett.*, 2020, **22**, 5446–5450.

177 Y. F. Chen, Y. C. Lin, P. K. Huang, H. C. Chan, S. C. Kuo, K. H. Lee and L. J. Huang, *Bioorganic Med. Chem.*, 2013, **21**, 5064–5075.

178 J. D. White, R. Juniku, K. Huang, J. Yang and D. T. Wong, *J. Med. Chem.*, 2009, **52**, 5872–5879.

179 K. E. Borbas and J. I. Bruce, *Org. Biomol. Chem.*, 2007, **5**, 2274–2282.

180 J. Simonin, S. K. V. Vernekar, A. J. Thompson, J. D. Hothersall, C. N. Connolly, S. C. R. Lummis and M. Lochner, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 1151–1155.

181 R. R. Milburn, K. McRae, J. Chan, J. Tedrow, R. Larsen and M. Faul, *Tetrahedron Lett.*, 2009, **50**, 870–872.

182 X. H. Hu, X. F. Yang and T. P. Loh, *Angew. Chemie Int. Ed.*, 2015, **54**, 15535–15539.

183 C. McWhirter, E. A. Lund, E. A. Tanifum, G. Feng, Q. I. Sheikh, A. C. Hengge and N. H. Williams, *J. Am. Chem. Soc*, 2008, **130**, 13673–13682.

184 F. P. F. P. Touchard, *European J. Org. Chem.*, 2005, **2005**, 1790–1794.

185 S. K. Perumal, S. A. Adediran and R. F. Pratt, *Bioorganic Med. Chem.*, 2008, **16**, 6987–6994.

186 P. Sampson, G. B. Hammond and D. F. Wiemer, *J. Org. Chem.*, 1986, **51**, 4342–4347.

Appendix

Crystal structure determination of 241

Crystal Data for $C_{14}H_{17}NO_3$ (*M* =247.28 g/mol): monoclinic, space group $P2_1/n$ (no. 14), *a* = 9.6335(19) Å, *b* = 10.079(2) Å, *c* = 13.695(3) Å, *β* = 99.152(7)°, *V* = 1312.8(5) Å^3, *Z* = 4, *T* = 100 K, μ(CuKα) = 0.717 mm^{-1}, *Dcalc* = 1.251 g/cm^3, 15980 reflections measured (10.948° ≤ 2Θ ≤ 133.2°), 2291 unique (R_{int} = 0.0529, R_{sigma} = 0.0315) which were used in all calculations. The final R_1 was 0.0408 (I > 2σ(I)) and wR_2 was 0.1086 (all data).

*Table 27: Crystal data and structure refinement for **241***

Identification code	OSJ247v_0m
Empirical formula	$C_{14}H_{17}NO_3$
Formula weight	247.28
Temperature/K	100
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	9.6335(19)
b/Å	10.079(2)
c/Å	13.695(3)
α/°	90
β/°	99.152(7)
γ/°	90
Volume/Å^3	1312.8(5)
Z	4
ρ_{calc}g/cm^3	1.251
μ/mm^{-1}	0.717
F(000)	528.0
Crystal size/mm^3	0.34 × 0.31 × 0.15
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection/°	10.948 to 133.2
Index ranges	-11 ≤ h ≤ 10, -10 ≤ k ≤ 11, -16 ≤ l ≤ 14
Reflections collected	15980
Independent reflections	2291 [R_{int} = 0.0529, R_{sigma} = 0.0315]
Data/restraints/parameters	2291/0/168
Goodness-of-fit on F^2	1.071
Final R indexes [I>=2σ (I)]	R_1 = 0.0408, wR_2 = 0.1011
Final R indexes [all data]	R_1 = 0.0515, wR_2 = 0.1086
Largest diff. peak/hole / e Å^{-3}	0.27/-0.23

*Table 28: Fractional Atomic Coordinates (×104) and Equivalent Isotropic Displacement Parameters (Å2×103) for **241**. Ueq is defined as 1/3 of of the trace of the orthogonalised UIJ tensor.*

Atom	*x*	*y*	*z*	U(eq)
O1	7056.7(12)	7782.9(12)	7877.1(8)	25.3(3)
O2	4980.7(12)	9302.2(11)	6785.1(9)	27.7(3)
O3	5051.1(12)	8010.2(11)	5445.4(8)	22.5(3)
N1	7550.2(14)	5384.1(14)	6399.0(10)	22.1(3)

Atom	*x*	*y*	*z*	U(eq)
C1	6619.1(16)	6157.3(15)	6648.2(11)	18.9(3)
C2	6813.6(17)	7656.0(16)	6826.7(12)	21.3(4)
C3	8060.3(17)	8183.8(17)	6366.3(13)	25.2(4)
C4	9295.1(18)	7248.7(19)	6620.9(14)	29.5(4)
C5	8898.8(17)	5899.2(18)	6183.3(13)	26.9(4)
C6	5248.2(16)	5549.5(15)	6795.3(12)	19.7(4)
C7	4758.0(17)	4459.9(16)	6216.6(12)	22.1(4)
C8	3494.4(17)	3863.7(17)	6319.8(13)	26.5(4)
C9	2699.8(18)	4354.6(17)	6998.4(14)	29.3(4)
C10	3173.1(18)	5444.7(18)	7574.1(14)	29.5(4)
C11	4439.6(17)	6048.0(17)	7476.4(13)	24.4(4)
C12	5498.8(17)	8419.6(15)	6373.6(12)	21.1(4)
C13	3745.6(18)	8598.9(18)	4937.7(13)	26.4(4)
C14	2495.3(19)	7896(2)	5228.1(14)	34.9(5)

*Table 29: Anisotropic Displacement Parameters (Å2×103) for **241**. The Anisotropic displacement factor exponent takes the form: -2π2[h2a*2U11+2hka*b*U12+…].*

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O1	29.5(7)	20.9(7)	24.4(6)	0.1(5)	0.6(5)	-3.3(5)
O2	29.8(7)	23.6(7)	30.2(7)	-3.7(5)	6.2(5)	2.0(5)
O3	21.9(6)	21.2(6)	23.6(6)	0.0(4)	1.0(5)	1.4(4)
N1	16.1(7)	24.3(8)	26.0(8)	2.4(5)	3.9(6)	0.8(5)
C1	18.8(8)	18.8(8)	18.4(8)	2.3(6)	0.9(6)	-1.1(6)
C2	22.2(9)	20.7(9)	20.7(8)	-1.4(6)	2.9(6)	-3.6(6)
C3	23.6(9)	24.1(9)	27.8(9)	0.0(7)	3.8(7)	-8.1(7)
C4	17.0(9)	38.5(11)	33.2(10)	2.9(8)	4.2(7)	-6.8(7)
C5	16.9(8)	32.8(10)	31.7(10)	5.5(7)	6.0(7)	2.2(7)
C6	18.1(8)	16.4(8)	24.0(8)	5.3(6)	1.5(6)	1.4(6)
C7	19.2(8)	20.7(9)	25.8(9)	1.8(6)	1.9(7)	1.0(6)
C8	21.1(9)	22.6(9)	33.4(10)	3.7(7)	-3.0(7)	-3.8(7)
C9	18.2(9)	28.2(10)	41.6(11)	10.5(8)	4.6(8)	-2.5(7)
C10	25.2(9)	28.8(10)	37.3(10)	6.9(7)	13.6(8)	5.1(7)
C11	23.0(9)	20.3(9)	30.9(9)	2.1(7)	7.3(7)	0.6(6)
C12	23.8(9)	16.0(8)	24.4(8)	0.8(6)	6.6(7)	-5.2(6)
C13	24.0(9)	25.7(9)	28.0(9)	3.6(7)	-0.5(7)	2.1(7)
C14	26.1(10)	44.8(12)	33.6(10)	-0.3(8)	4.1(8)	-1.4(8)

*Table 30: Bond Lengths for **241***

Atom	Atom	Length/Å	Atom	Atom	Length/Å
O1	C2	1.4260(19)	C3	C4	1.514(2)
O2	C12	1.203(2)	C4	C5	1.511(3)
O3	C12	1.341(2)	C6	C7	1.392(2)
O3	C13	1.463(2)	C6	C11	1.400(2)
N1	C1	1.275(2)	C7	C8	1.385(2)

Atom	Atom	Length/Å	Atom	Atom	Length/Å
N1	C5	1.472(2)	C8	C9	1.386(3)
C1	C2	1.537(2)	C9	C10	1.387(3)
C1	C6	1.498(2)	C10	C11	1.389(2)
C2	C3	1.537(2)	C13	C14	1.504(3)
C2	C12	1.527(2)			

*Table 31: Bond Angles for **241***

Atom	Atom	Atom	Angle/˚	Atom	Atom	Atom	Angle/˚
C12	O3	C13	116.65(13)	N1	C5	C4	114.42(14)
C1	N1	C5	121.27(14)	C7	C6	C1	118.19(15)
N1	C1	C2	124.76(14)	C7	C6	C11	119.21(15)
N1	C1	C6	117.30(14)	C11	C6	C1	122.58(15)
C6	C1	C2	117.93(14)	C8	C7	C6	120.55(16)
O1	C2	C1	104.17(12)	C7	C8	C9	120.12(16)
O1	C2	C3	111.66(13)	C8	C9	C10	119.84(16)
O1	C2	C12	110.93(13)	C9	C10	C11	120.44(17)
C1	C2	C3	111.00(14)	C10	C11	C6	119.83(16)
C12	C2	C1	111.00(13)	O2	C12	O3	125.22(15)
C12	C2	C3	108.09(13)	O2	C12	C2	124.16(15)
C4	C3	C2	109.05(14)	O3	C12	C2	110.55(13)
C5	C4	C3	109.23(14)	O3	C13	C14	110.34(14)

*Table 32: Hydrogen Bonds for **241***

D	H	A	d(D-H)/Å	d(H-A)/Å	d(D-A)/Å	D-H-A/°
O1	H1	N1[a]	0.90(3)	1.91(3)	2.8073(19)	173(2)

[a]3/2-X,1/2+Y,3/2-Z

*Table 33: Torsion Angles for **241***

A	B	C	D	Angle/˚	A	B	C	D	Angle/˚
O1	C2	C3	C4	70.46(17)	C3	C2	C12	O3	74.56(16)
O1	C2	C12	O2	20.2(2)	C3	C4	C5	N1	-49.7(2)
O1	C2	C12	O3	-162.71(12)	C5	N1	C1	C2	-4.7(2)
N1	C1	C2	O1	-102.73(17)	C5	N1	C1	C6	176.53(14)
N1	C1	C2	C3	17.6(2)	C6	C1	C2	O1	76.03(16)
N1	C1	C2	C12	137.82(16)	C6	C1	C2	C3	-163.66(14)
N1	C1	C6	C7	-32.3(2)	C6	C1	C2	C12	-43.42(19)
N1	C1	C6	C11	148.77(16)	C6	C7	C8	C9	0.4(2)
C1	N1	C5	C4	20.9(2)	C7	C6	C11	C10	0.7(2)
C1	C2	C3	C4	-45.30(18)	C7	C8	C9	C10	0.0(3)

A	B	C	D	Angle/˚	A	B	C	D	Angle/˚
C1	C2	C12	O2	135.48(16)	C8	C9	C10	C11	-0.1(3)
C1	C2	C12	O3	-47.39(17)	C9	C10	C11	C6	-0.3(3)
C1	C6	C7	C8	-179.73(14)	C11	C6	C7	C8	-0.8(2)
C1	C6	C11	C10	179.62(15)	C12	O3	C13	C14	-82.36(18)
C2	C1	C6	C7	148.84(14)	C12	C2	C3	C4	-167.26(14)
C2	C1	C6	C11	-30.1(2)	C13	O3	C12	O2	-6.6(2)
C2	C3	C4	C5	61.85(18)	C13	O3	C12	C2	176.35(13)
C3	C2	C12	O2	-102.56(18)					

Table 34: Hydrogen Atom Coordinates (Å×104) and Isotropic Displacement Parameters (Å2×103) for ***241***

Atom	*x*	*y*	*z*	U(eq)
H1	7170(20)	8640(30)	8057(17)	51(7)
H3A	7793.69	8246.45	5639.17	30
H3B	8322.39	9081.31	6626.12	30
H4A	10117.83	7597.69	6352.16	35
H4B	9552	7175.95	7348.09	35
H5A	8852.49	5950.28	5456.97	32
H5B	9651	5261.45	6438.8	32
H7	5294.92	4122.52	5747.01	26
H8	3171.59	3116.96	5924.67	32
H9	1833.05	3945.21	7068.86	35
H10	2627.16	5781.11	8038.57	35
H11	4756.67	6797.16	7870.69	29
H13A	3714.72	8532.05	4213.37	32
H13B	3713.87	9550.21	5112.55	32
H14A	1630.36	8257.43	4847.43	52
H14B	2483.68	8027.94	5935.79	52
H14C	2557.35	6945.94	5090.36	52

Crystal structure determination of 233.HCl

Crystal Data for $C_{14}H_{20}ClNO_2$ (*M* =269.76 g/mol): triclinic, space group P-1 (no. 2), *a* = 7.673(8) Å, *b* = 8.567(9) Å, *c* = 11.448(12) Å, *α* = 86.72(2)°, *β* = 87.035(18)°, *γ* = 84.943(18)°, *V* = 747.6(13) Å^3, *Z* = 2, *T* = 100 K, μ(MoKα) = 0.250 mm^{-1}, *Dcalc* = 1.198 g/cm^3, 9941 reflections measured (3.568° ≤ 2Θ ≤ 54.53°), 3316 unique (R_{int} = 0.0685, R_{sigma} = 0.0888) which were used in all calculations. The final R_1 was 0.0809 (I > 2σ(I)) and wR_2 was 0.2229 (all data).

*Table 35: Crystal data and structure refinement for **233**.HCl*

Identification code	OSJ249s_0m
Empirical formula	$C_{14}H_{20}ClNO_2$
Formula weight	269.76
Temperature/K	100
Crystal system	triclinic
Space group	P-1
a/Å	7.673(8)
b/Å	8.567(9)
c/Å	11.448(12)
α/°	86.72(2)
β/°	87.035(18)
γ/°	84.943(18)
Volume/Å^3	747.6(13)
Z	2
ρ_{calc}g/cm^3	1.198
μ/mm^{-1}	0.250
F(000)	288.0
Crystal size/mm^3	0.45 × 0.06 × 0.012
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	3.568 to 54.53
Index ranges	-9 ≤ h ≤ 9, -11 ≤ k ≤ 11, -14 ≤ l ≤ 13
Reflections collected	9941
Independent reflections	3316 [R_{int} = 0.0685, R_{sigma} = 0.0888]
Data/restraints/parameters	3316/0/172
Goodness-of-fit on F^2	1.133
Final R indexes [I>=2σ (I)]	R_1 = 0.0809, wR_2 = 0.2064
Final R indexes [all data]	R_1 = 0.1217, wR_2 = 0.2229
Largest diff. peak/hole / e Å^{-3}	0.54/-0.34

*Table 36: Fractional Atomic Coordinates (×104) and Equivalent Isotropic Displacement Parameters (Å2×103) for **233**.HCl. Ueq is defined as 1/3 of the trace of the orthogonalised UIJ tensor.*

Atom	***x***	***y***	***z***	**U(eq)**
O1	7707(4)	9106(4)	849(3)	39.0(9)
O2	5791(4)	8095(4)	2193(3)	36.8(8)
N1	7034(4)	6492(4)	4262(3)	22.9(8)
C1	8574(5)	6436(5)	3389(4)	24.5(9)
C2	8746(5)	8047(5)	2727(4)	26.1(10)

Atom	*x*	*y*	*z*	U(eq)
C3	8755(5)	9375(5)	3609(4)	29.2(10)
C4	7177(5)	9363(5)	4499(4)	28.4(10)
C5	7107(6)	7741(5)	5138(4)	28.4(10)
C6	8560(6)	5113(5)	2554(4)	27.2(10)
C7	7061(6)	4424(6)	2287(5)	38.2(12)
C8	7167(8)	3253(7)	1456(5)	47.5(14)
C9	8765(8)	2778(6)	903(5)	44.3(13)
C10	10267(7)	3460(6)	1168(5)	39.3(12)
C11	10182(6)	4610(5)	2000(4)	32.4(11)
C12	7406(5)	8471(5)	1803(4)	25.2(10)
C13	4307(6)	8473(7)	1440(4)	38.3(12)
C14	3192(6)	9872(6)	1886(5)	39.3(12)
Cl1	7074.2(12)	3429.4(13)	5824.7(10)	27.5(3)

*Table 37: Anisotropic Displacement Parameters (Å2×103) for **233**.HCl. The Anisotropic displacement factor exponent takes the form: -2π2[h2a*2U11+2hka*b*U12+…].*

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O1	38.7(19)	47(2)	30.0(19)	4.6(16)	5.4(15)	-8.0(16)
O2	17.8(15)	56(2)	35.1(19)	10.1(16)	-0.5(13)	-1.3(14)
N1	15.2(17)	28(2)	25(2)	0.4(16)	-1.4(14)	0.7(14)
C1	11.0(17)	29(2)	32(2)	-3.1(19)	3.1(16)	4.4(15)
C2	14.0(18)	26(2)	37(3)	-4.0(19)	5.7(17)	0.1(16)
C3	22(2)	28(2)	38(3)	-4(2)	0.7(18)	-3.3(17)
C4	21(2)	29(2)	34(3)	-6(2)	-0.6(18)	4.0(17)
C5	23(2)	32(3)	30(2)	-5(2)	1.4(17)	1.9(17)
C6	27(2)	29(2)	24(2)	1.1(19)	2.9(17)	1.1(17)
C7	31(2)	40(3)	44(3)	-7(2)	4(2)	-5(2)
C8	48(3)	43(3)	55(4)	-15(3)	0(3)	-18(3)
C9	62(4)	33(3)	38(3)	-7(2)	5(3)	0(2)
C10	43(3)	36(3)	37(3)	-5(2)	5(2)	8(2)
C11	30(2)	29(2)	38(3)	-4(2)	-1(2)	5.5(19)
C12	25(2)	20(2)	30(3)	-5.3(19)	3.7(17)	-1.3(16)
C13	28(2)	53(3)	33(3)	5(2)	-7(2)	1(2)
C14	32(3)	44(3)	41(3)	9(2)	-5(2)	-3(2)
Cl1	13.6(5)	29.9(6)	38.0(7)	5.1(5)	-0.6(4)	-0.4(4)

*Table 38: Bond Lengths for **233**.HCl.*

Atom	Atom	Length/Å	Atom	Atom	Length/Å
O1	C12	1.213(5)	C3	C4	1.543(6)
O2	C12	1.355(5)	C4	C5	1.537(6)
O2	C13	1.466(5)	C6	C7	1.394(7)
N1	C1	1.507(5)	C6	C11	1.412(6)
N1	C5	1.515(6)	C7	C8	1.416(8)
C1	C2	1.549(6)	C8	C9	1.389(8)
C1	C6	1.524(6)	C9	C10	1.391(8)

Atom	Atom	Length/Å	Atom	Atom	Length/Å
C2	C3	1.564(6)	C10	C11	1.404(7)
C2	C12	1.520(6)	C13	C14	1.508(7)

*Table 39: Bond Angles for **233**.HCl*

Atom	Atom	Atom	Angle/˚	Atom	Atom	Atom	Angle/˚
C12	O2	C13	119.3(4)	C7	C6	C11	119.1(4)
C1	N1	C5	112.7(3)	C11	C6	C1	116.5(4)
N1	C1	C2	111.6(3)	C6	C7	C8	120.2(5)
N1	C1	C6	112.7(4)	C9	C8	C7	120.3(5)
C6	C1	C2	112.1(4)	C8	C9	C10	119.7(5)
C1	C2	C3	110.7(4)	C9	C10	C11	120.5(5)
C12	C2	C1	114.6(3)	C10	C11	C6	120.2(5)
C12	C2	C3	111.4(3)	O1	C12	O2	123.4(4)
C4	C3	C2	111.7(4)	O1	C12	C2	125.2(4)
C5	C4	C3	110.8(3)	O2	C12	C2	111.3(4)
N1	C5	C4	110.2(4)	O2	C13	C14	109.4(4)
C7	C6	C1	124.3(4)				

*Table 40: Hydrogen Bonds for **233**.HCl*

D	H	A	d(D-H)/Å	d(H-A)/Å	d(D-A)/Å	D-H-A/°
N1	H1A	Cl1	0.98(4)	2.12(4)	3.089(5)	171(3)
N1	H1B	O2	0.90(5)	2.26(5)	2.835(5)	122(4)

*Table 41: Torsion Angles for **233**.HCl*

A	B	C	D	Angle/˚	A	B	C	D	Angle/˚
N1	C1	C2	C3	52.4(4)	C3	C4	C5	N1	-56.9(5)
N1	C1	C2	C12	-74.6(5)	C5	N1	C1	C2	-56.3(5)
N1	C1	C6	C7	23.7(6)	C5	N1	C1	C6	176.4(3)
N1	C1	C6	C11	-158.4(4)	C6	C1	C2	C3	180.0(3)
C1	N1	C5	C4	58.2(4)	C6	C1	C2	C12	53.0(4)
C1	C2	C3	C4	-52.3(4)	C6	C7	C8	C9	0.2(8)
C1	C2	C12	O1	-139.8(4)	C7	C6	C11	C10	1.6(7)
C1	C2	C12	O2	42.2(5)	C7	C8	C9	C10	-0.1(9)
C1	C6	C7	C8	176.9(5)	C8	C9	C10	C11	0.8(8)
C1	C6	C11	C10	-176.3(4)	C9	C10	C11	C6	-1.6(7)
C2	C1	C6	C7	-103.2(5)	C11	C6	C7	C8	-0.9(7)
C2	C1	C6	C11	74.7(5)	C12	O2	C13	C14	-104.9(5)
C2	C3	C4	C5	54.9(5)	C12	C2	C3	C4	76.5(5)
C3	C2	C12	O1	93.5(5)	C13	O2	C12	O1	-0.5(7)
C3	C2	C12	O2	-84.5(4)	C13	O2	C12	C2	177.6(4)

*Table 42: Hydrogen Atom Coordinates (Å×104) and Isotropic Displacement Parameters (Å2×103) for **233**.HCl*

Atom	*x*	*y*	*z*	U(eq)
H1	9647.78	6206.31	3849.57	29
H2	9921.3	7980.33	2303.82	31
H3A	9853.97	9232.45	4033.73	35
H3B	8723.39	10406.22	3169.21	35
H4A	7272.26	10163.37	5078.05	34
H4B	6080.7	9637.01	4086.08	34
H5A	8156.75	7503.72	5605.08	34
H5B	6058.84	7744.52	5680.05	34
H7	5964.66	4741.68	2662.75	46
H8	6140.58	2788.92	1275.23	57
H9	8832.08	1991.12	347.04	53
H10	11357.24	3145.46	782.81	47
H11	11218.85	5050.29	2189.58	39
H13A	3597.61	7561.83	1440.63	46
H13B	4741.64	8711.4	625.41	46
H14A	2133.96	10056.28	1436.34	59
H14B	3857.1	10800.69	1797.37	59
H14C	2859.53	9669.44	2715.64	59
H1A	7090(50)	5460(50)	4680(40)	13(10)
H1B	6050(60)	6560(50)	3850(40)	25(12)

HPLC chromatogram for **166** from Onyx Scientific