

ASYMMETRIC CONJUGATE ADDITION REACTIONS

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for the degree of Doctor of Philosophy

by

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The work described in this thesis was carried out in the Chemistry Research Laboratory, University of Oxford from October 2007 until May 2011, under the supervision of Professor Stephen G. Davies. All of the work is my own unless otherwise stated and has not been submitted previously for any other degree at this or any other university.

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Abstract

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This thesis is concerned with the asymmetric conjugate addition reactions of a range of chiral nucleophiles.

Chapter 1 introduces the conjugate addition reaction as a valuable carbon-carbon and carbon-heteroatom bond forming reaction in organic chemistry, and explores the asymmetric conjugate addition of a range of chiral and achiral carbon and nitrogen nucleophiles to a range of acceptors.

Chapter 2 explores the use of the *N*-benzyl-*N*-(α -methylbenzyl)amino group as a chiral auxiliary, by employing the attempted conjugate additions of both *N*-benzyl-*N*-(α -methylbenzyl)hydrazine and *N*-benzyl-*N*-(α -methylbenzyl)hydroxylamine as chiral ammonia and water equivalents respectively.

Chapter 3 describes the asymmetric and stereoselective preparation of a range of 4,4-disubstituted isoxazolidin-5-ones from the conjugate addition of lithium (*S*)-*N*-*tert*-butyldimethylsilyloxy-*N*-(α -methylbenzyl)amide. The isoxazolidin-5-ones are then globally deprotected *via* hydrogenolysis, giving rise to the corresponding $\beta^{2,2,3}$ -amino acids.

Chapter 4 focuses on the development of a protocol to effect the conjugate addition of a chiral aniline equivalent. The scope of the reaction is delineated by varying both the nucleophile and the α,β -unsaturated ester. Finally, cyclisation of the β -*N*-arylamino esters to the corresponding tetrahydroquinolines is explored, and an application to the synthesis of the natural product (–)-angustureine is presented.

Chapter 5 contains full experimental procedures and characterisation data for all compounds synthesised in Chapters 2, 3 and 4.

For Dad, Mum & Nikki.

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Abbreviations

Δ	reflux
δ_{C}	^{13}C NMR chemical shift
δ_{H}	^1H NMR chemical shift
ν_{max}	infra red absorption
^{13}C NMR	carbon NMR
^1H NMR	proton NMR
Ac	acetyl
aq	aqueous
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
BOX	bisoxazoline

br	broad
Bu	butyl
Bz	benzoyl
C	celsius
cm ⁻¹	wavenumber
Cy	cyclohexyl
dba	dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
d	doublet
DMAP	4-dimethylaminopyridine
DMDO	dimethyldioxirane
DMF	dimethylformamide
DMPU	dimethylpropyleneurea
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
dr	diastereomeric ratio
<i>E</i>	entgegen
ee	enantiomeric excess
equiv	equivalents

ESI	electrospray ionisation
Et	ethyl
EWG	electron-withdrawing group
FI	field ionisation
g	grams
hept	heptyl
h	hours
HMDS	hexamethyldisilazide
HRMS	high resolution mass spectrometry
Hz	hertz
<i>i</i> -Ar	ipso aryl
<i>i</i> -Bu	iso-butyl
<i>i</i> -Ph	ipso phenyl
<i>i</i> -Pr	iso-propyl
IC ₅₀	half maximal inhibitory concentration
<i>J</i>	coupling constant
<i>K</i> _b	binding constant
K	Kelvin
LDA	lithium diisopropylamide

lit	literature
LiTMP	lithium tetramethylpiperidide
$[M]^+$	molecular ion
$[M+H]^+$	protonated molecular ion
$[M+Na]^+$	molecular ion + sodium
<i>m</i> -CPBA	<i>m</i> -chloroperbenzoic acid
m/z	mass to charge ratio
<i>m</i>	meta
Me	methyl
Mes	1,3,5-trimethylphenyl
min	minutes
Moc	methoxycarbonyl
M	molar
MOM	methoxymethyl
MP	Macroporous poly(styrene-co-divinylbenzene)
Ms	methanesulfonyl
m	multiplet
<i>n</i>	normal
Nap	naphthyl

NCS	<i>N</i> -chlorosuccinimide
NMDA	<i>N</i> -methyl-D-aspartate
<i>o</i>	ortho
<i>p</i>	para
pent	pentyl
PG	protecting group
Ph	phenyl
PMP	4-methoxyphenyl
PPA	polyphosphoric acid
ppm	parts per million
PPTS	pyridinium <i>p</i> -toluenesulfonate
Pr	propyl
py	pyridine
q	quartet
RAMP	(<i>R</i>)-1-amino-2-methoxymethylpyrrolidine
r.d.s	rate determining step
RNA	ribonucleic acid
rt	room temperature
SAMP	(<i>S</i>)-1-amino-2-methoxymethylpyrrolidine

sat	saturated
s	singlet
TBAF	tetra- <i>n</i> -butylammonium fluoride
TBDMS	<i>tert</i> -butyldimethylsilyl
TBME	<i>tert</i> -butylmethylether
<i>tert</i>	tertiary
TFAA	trifluoroacetic anhydride
TFA	trifluoroacetic acid
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
THP	tetrahydropyranyl
TMS	trimethylsilyl
Tol	<i>o</i> -tolyl
t	triplet
Ts	<i>p</i> -toluenesulfonyl
v	volume
<i>Z</i>	zusammen

CHAPTER 1

Introduction

1.1 The conjugate addition reaction

The conjugate addition reaction involves the addition of a nucleophile in a 1,4 fashion to an activated alkene such as an α,β -unsaturated ester (Figure 1).

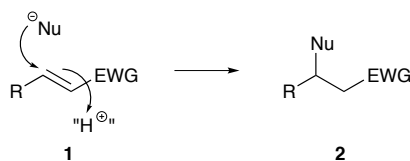
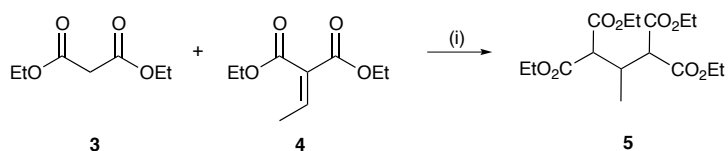


Figure 1: The conjugate addition reaction.

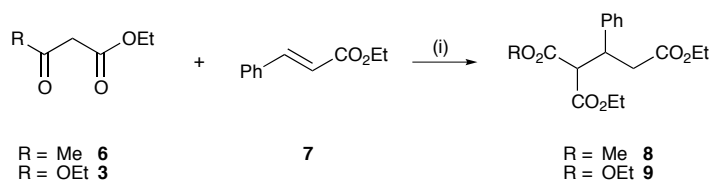
1.2 First examples

The first example of a conjugate addition was reported by Komnenos in 1883, who demonstrated the addition of diethyl malonate **3** to ethylidene malonate **4**, four years before Michael's landmark paper (Scheme 1).¹



Scheme 1: *Reagents & Conditions:* Stir neat.

Michael carried out a more systematic investigation before publishing his 1887 paper entitled “Ueber die Addition von Natriumacetessig und Natriummalonsäureäthern zu den Aethern ungesättigter Säuren”.² Michael showed that the stabilised anions of ethylacetoacetate **6** and diethyl malonate **3** both reacted with ethyl cinnamate **7** affording compounds **8** and **9** (Scheme 2).



Scheme 2: *Reagents & conditions;* (i) NaOEt, EtOH.

Since these initial findings the conjugate addition reaction has been transformed into a powerful tool in the synthetic organic chemist’s reaction arsenal. A wide range of nucleophiles (donors) and α,β -unsaturated carbonyl compounds (acceptors) have been shown to take part in the reaction, meaning that the substrate scope of the reaction is immensely broad. Since addition can be accompanied by the formation of one or more new stereogenic centres, with appropriate control it is possible to engineer the conjugate addition reaction into a highly efficient, diastereoselective or enantioselective process.

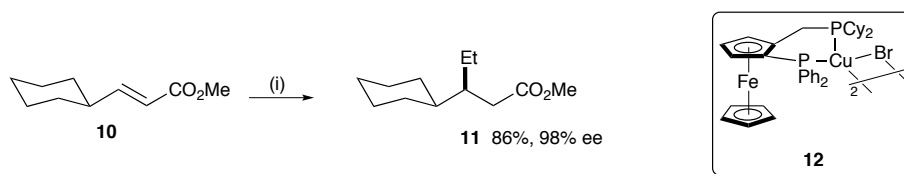
1.3 Asymmetric conjugate addition reactions

The transformation of an sp^2 carbon into an sp^3 carbon can, depending on the substitution pattern, create a new stereogenic centre. Thus, with control, it is possible to make the conjugate addition a highly useful diastereoselective or enantioselective transformation. There are three main ways in which the selectivity can be imparted, by the donor, by

the acceptor, or by a ligand in a metal-catalysed process. As a large portion of this thesis is concerned with the conjugate addition of nitrogen nucleophiles to α,β -unsaturated carbonyl compounds (the aza-Michael reaction) examples with both carbon and nitrogen nucleophiles will be discussed.

1.3.1 Ligand control

Chiral ligand mediated reactions are a very important class of conjugate additions, removing the need for chiral information in either the nucleophile or the acceptor. This group can be further subdivided depending on how the chiral ligand interacts with the reactive species. There are four main classes: the ligand complexing with the nucleophile, the ligand complexing with the acceptor, the ligand coordinating to a Lewis acid (which in turn activates the acceptor), and finally a chiral entity that brings together both the acceptor and the donor. Feringa *et al.* have developed an enantioselective variant of a Grignard addition to an α,β -unsaturated ester, with the enantioselectivity imparted by a copper catalyst with the phosphine ligand “Josiphos” **12**.³ A range of Grignard reagents were reacted with a range of α,β -unsaturated esters, each proceeding in good yield, and with good to excellent selectivities. For example, the reaction of EtMgBr with cyclohexyl substituted acceptor **10** proceeds to give **11** in 86% yield and 98% ee (Scheme 3).



Scheme 3: Reagents & conditions; (i) EtMgBr, **12**, ^tBuOMe, −75 °C, 2 h.

A catalytic cycle was proposed, which was consistent with all the data collected on the reaction. The first step is formation of complex **13** from transmetallation of the Grignard reagent with the pre-catalyst **12**. This new active species **13** then forms π -complex **15** with

acceptor **14**. This species is in a rapid equilibrium with σ -complex **16** from which the final enolate product is able to be formed, regenerating the catalyst (Figure 2).⁴

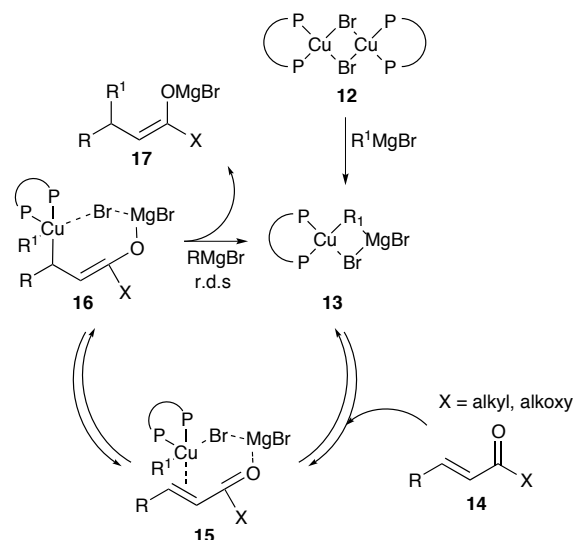


Figure 2: Proposed catalytic cycle.

It is proposed that the enantioselectivity arises from the acceptor approaching the alkyl-copper complex **13** from the least hindered side, adopting a square pyramidal geometry. On changing from the π complex to the σ complex a chairlike 7-membered ring transition state is proposed, with the absolute configuration at the β -position already fixed before the alkyl group is transferred (Figure 3).⁴

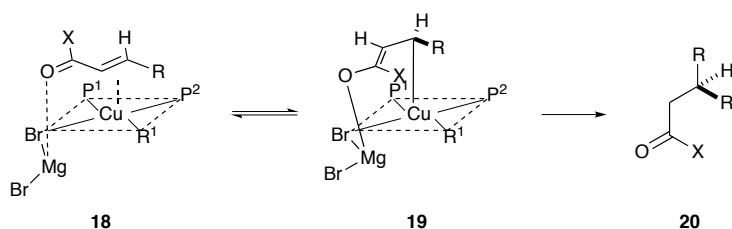
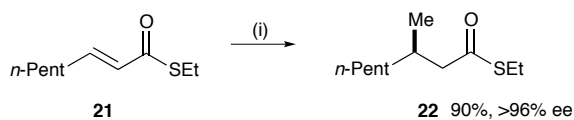


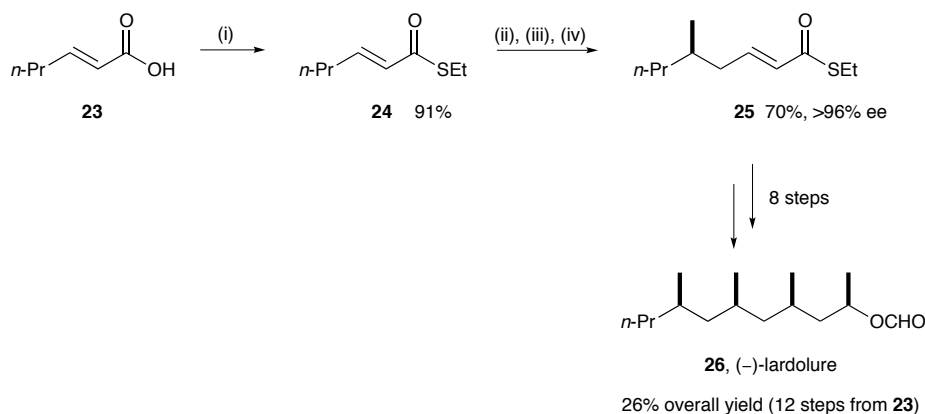
Figure 3: Enantioselectivity rationale.

When EtMgBr is swapped for the less reactive MeMgBr, poor results are obtained, impeding the development of a catalytic iterative methodology for 1,3-dimethyl arrays. Although on switching the α,β -unsaturated esters to the more reactive thioesters, excellent yields and selectivities are observed with MeMgBr. For example the addition of MeMgBr to *n*-pentyl substituted acceptor **21** affords **22** in 90% yield and >96% ee (Scheme 4).⁵



Scheme 4: Reagents & conditions; (i) MeMgBr, **12**, ^tBuOMe, −75 °C, 2 h.

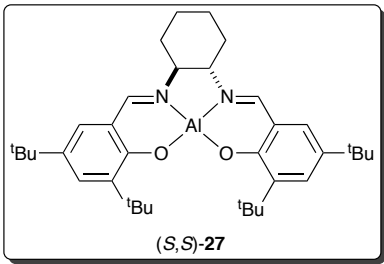
This methodology was applied in the synthesis of the pheromone (−)-lardolure **26** from the acarid mite *Lardoglyphus kono*. This is created *via* an iterative method involving three asymmetric conjugate additions, homologating the carbon chain after each one. (−)-Lardolure **26** is isolated after 12 steps and in 26% overall yield from (*E*)-hex-2-enoic acid **23** (Scheme 5).



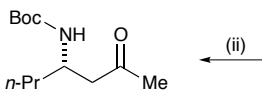
Scheme 5: Reagents & conditions; (i) DCC, EtSH, DMAP, CH₂Cl₂, rt, 16 h; (ii) MeMgBr, **12**, ^tBuOMe −75 °C, 2 h; (iii) 10% Pd/C, Et₃SiH, CH₂Cl₂, rt, 20 min; (iv) Ph₃PCHCOSEt, CH₂Cl₂, Δ, 2 h.

1.3.1.1 Jacobsen's hydrazoic acid conjugate additions

Jacobsen has employed the use of an aluminium-salen complex **27** to develop an enantioselective conjugate addition of a nitrogen nucleophile to an acceptor.⁶ Hydrazoic acid will, in the presence of aluminium-salen complex **27**, add to α,β-unsaturated ketones **28-34** in good to excellent selectivities (61%-94% ee). From the azido intermediates a number of interconversions are possible, including synthesis of the amino ketone **42** in 79% yield and 94 % ee, and triazole **43** in 89% yield and 93% ee (Scheme 6).



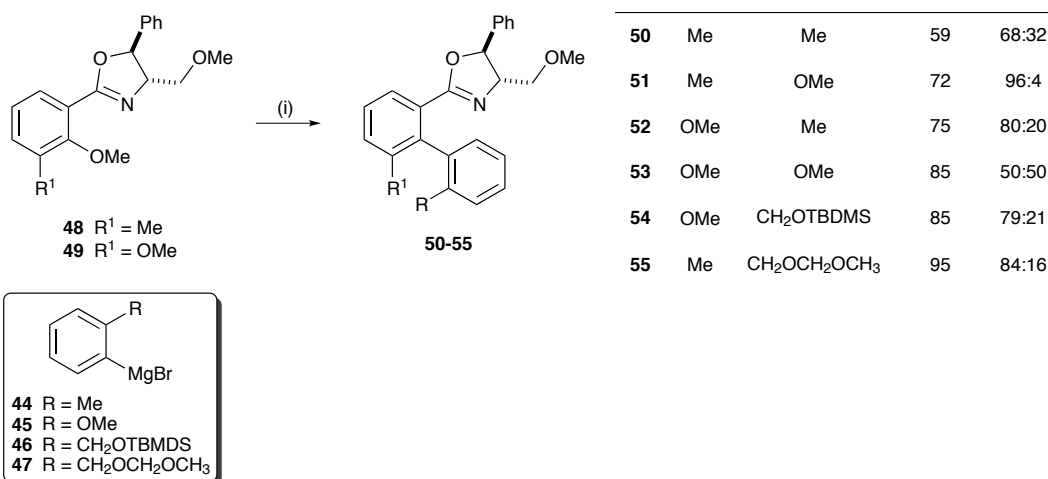
Acceptor	Product	R	R ¹	Yield/%	ee
28	35	<i>n</i> -Pr	Me	88	94
29	36	<i>i</i> -Pr	Me	81	94
30	37	CH ₂ CH ₂ OBn	Me	96	85
31	38	C(CH ₃) ₂ CH ₂ CH ₂ CN	Me	72	84
32	39	<i>n</i> -Pr	<i>n</i> -Bu	88	89
33	40	<i>n</i> -Pr	Ph	90	77
34	41	<i>n</i> -Pr	<i>i</i> -Pr	97	61



Scheme 6: *Reagents & conditions*; (i) HN_3 , $[(S,S)\text{-27}]_2\text{O}$, methylcyclohexane, -40°C , 24 h; (ii) H_2 , Pd/C, Boc_2O , EtOAc, 23°C , 15 h; (iii) Phenyl acetylene, CuSO_4 (1 mol %), sodium ascorbate (10 mol %), EtOH/ H_2O , 23°C , 36 h.

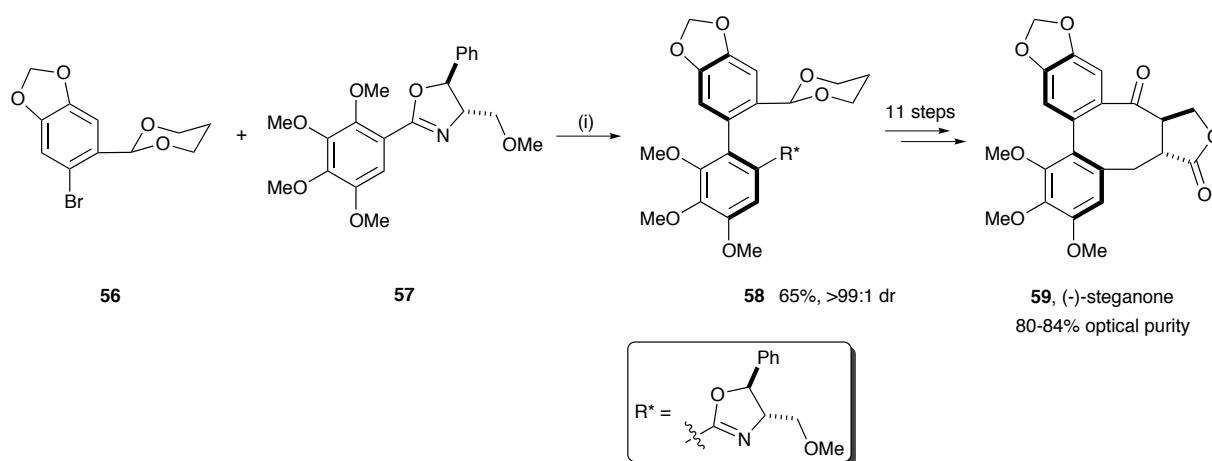
1.3.2 Acceptor control

Traditionally the synthesis of optically active biphenyls was carried out by virtue of a classical or kinetic resolution of a racemic mixture.⁷ In 1985 Meyers *et al.* reported the direct enantioselective synthesis of 2,6,2'-trisubstituted biphenyls *via* a Grignard mediated aryl conjugate addition reaction to a chiral oxazoline acceptor.⁸ The addition of a range of aryl Grignards **44-47** to phenyloxazoline acceptors **48** and **49** was probed, with all reactions proceeding in good yield, and with diastereoselectivities of up to 96:4 dr (Scheme 7).



Scheme 7: Reagents & conditions; (i) **44-47**, THF:Et₂O (v/v 1:1), 24 h, rt.

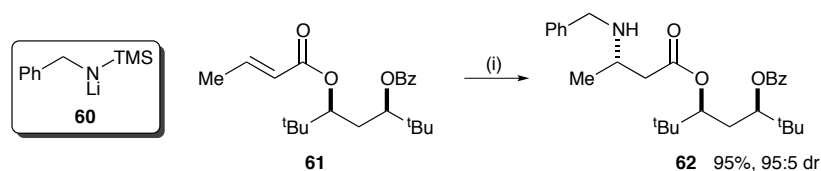
The lack of selectivity obtained in the synthesis of biphenyl **53** is attributed to the inability of the smaller methoxy groups to inhibit racemization. Removal of the chiral oxazoline auxiliary is achieved by means of a 4-step process, which proceeds in good yield and with little or no racemization. This methodology was then applied as a key step in the total synthesis of (–)-steganone **59**, an antileukemic natural product isolated from *Steganotaenia araliacea*. The conjugate addition of the Grignard reagent derived from **56** to **57** gave a 88:12 mixture of diastereoisomers from which the major diastereoisomer **58** was isolated in 65% yield and >99:1 dr. After 11 subsequent chemical operations (–)-steganone **59** was obtained in 80-84% optical purity, implying some racemization had occurred in the latter stages of the synthesis (Scheme 8).⁹



Scheme 8: Reagents & conditions; (i) Mg, THF, reflux, 16 h.

1.3.2.1 Yamamoto's chiral acceptor

Yamamoto *et al.* showed that the use of 2,2,6,6-tetramethyl-3,5-heptanediol as a chiral auxiliary can lead to very high selectivities in the aza-Michael reaction.¹⁰ For example, the reaction of lithium *N*-benzyl-*N*-(trimethylsilyl)amide **60** with the crotonate derived acceptor **61** affords β -amino ester **62** in 95% yield and 95:5 dr (Scheme 9).



Scheme 9: Reagents & conditions; (i) **60**, THF, $-78\text{ }^{\circ}\text{C}$, 10 mins.

The stereochemistry obtained is consistent with ^1H NMR and X-ray crystallographic studies. A model is proposed to rationalise this diastereoselectivity in which the aromatic ring blocks the back face of the double bond in its reactive *s-cis* conformation, forcing the incoming nucleophile to attack from the front face (Figure 4).

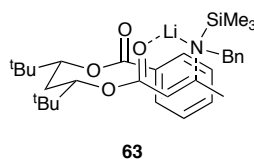
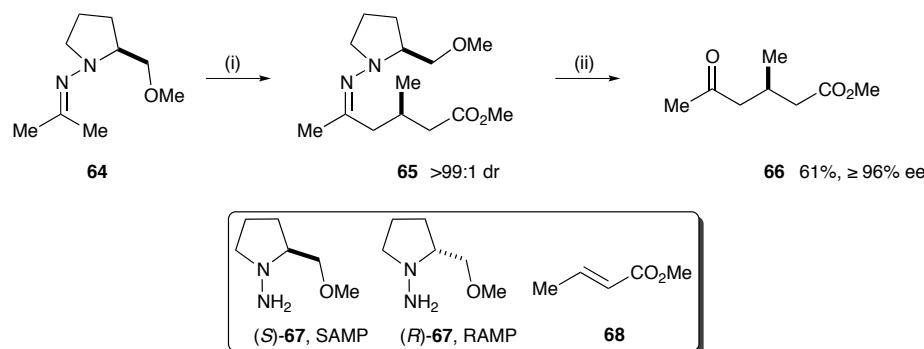


Figure 4: Selectivity rationale.

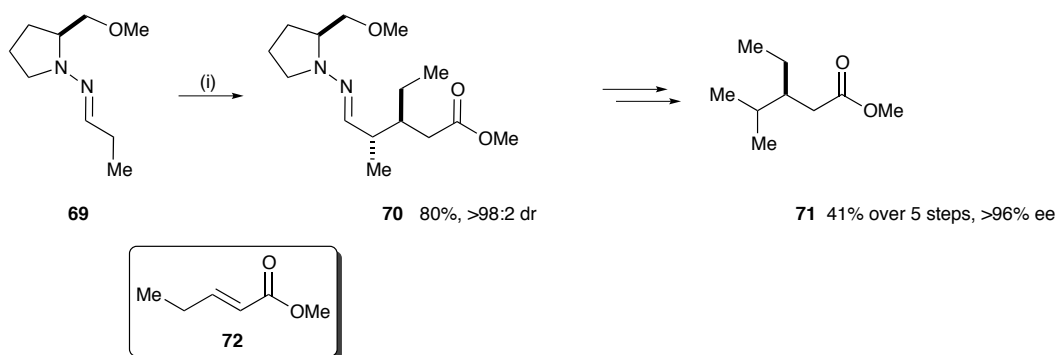
1.3.3 Donor control - Chiral nucleophile

The versatile chiral hydrazines RAMP (*R*)-**67** and SAMP (*S*)-**67** have been utilised as auxiliaries for the asymmetric Michael addition.¹¹ The condensation of one of these auxiliaries with a ketone or aldehyde affords a compound with an enolizable proton, which on metallation, can be added to Michael acceptors. For example, treatment of acetone with SAMP **67** affords hydrazone **64**, and lithiation of this compound with LDA followed by treatment with methyl crotonate **68** gives adduct **65** in >99:1 dr. Finally, removal of the (recyclable) auxiliary with O₃ affords the desired δ -ketoester **66** in 61% overall yield and $\geq 96\%$ ee (Scheme 10).



Scheme 10: Reagents & conditions; (i) LDA, THF, -78 °C, then **68**; (ii) O₃, CH₂Cl₂, -78 °C.

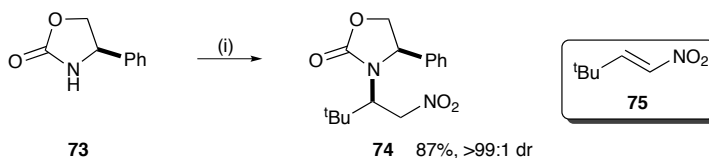
This methodology has been applied to the total synthesis of the pheromones of the small forest ant, *Formica polycтена*, and the red wood ant, *Formica rufa*.¹² Pheromone **71** in particular has shown a strong aggression inhibiting effect in bioassays, and is synthesised in 5 steps from propanal in 41% overall yield and >96% ee. The key step is the Michael addition of **69** to methyl 2-pentenoate **72**, in which two stereocentres are formed with complete control, affording **70** in 80% yield and >98:2 dr (Scheme 11).



Scheme 11: Reagents & conditions; (i) LDA, THF, 0 °C, 3h, then **72**, THF, −100 °C 2 h, then warm to 0 °C, 8-12 h.

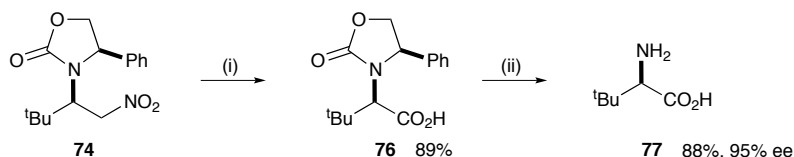
1.3.3.1 Lucet's chiral oxazolidinones

Lucet *et al.* have developed methodology by which the potassium salt of a chiral oxazolidinone can be added to a range of nitroalkenes with excellent diastereoselectivities.¹³ For example, the reaction of oxazolidinone **73** with the *tert*-butyl substituted nitroalkene **75** affords **74** in 87% yield and >99:1 dr (Scheme 12).



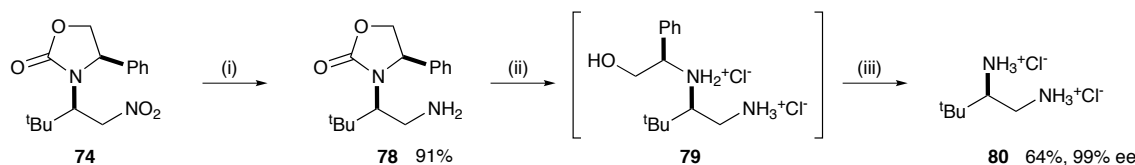
Scheme 12: Reagents & conditions; (i) ^tBuOK, 18-Crown-6, THF, 0 °C, 1 h, then **75**, THF, −78 °C, 2 h.

From these useful intermediates it is possible to synthesise both the requisite α -amino and mono-substituted 1,2-diamines. Firstly the oxidation of the nitro group to a carboxylic acid is achieved by treatment with sodium nitrite and acetic acid, affording **76** in 89% yield with no epimerization. This was followed by removal of the oxazolidinone moiety *via* a Birch reduction to give α -amino acid **77** in 88% yield and 95% ee (Scheme 13).



Scheme 13: Reagents & conditions; (i) NaNO₂, AcOH, DMSO, 18-30 h, 40 °C; (ii) Li/NH₃, THF, ^tBuOH, −78 °C, then DOWEX.

To access the 1,2-diamines firstly the nitro group is reduced by hydrogenation to form primary amine **78**. Then the oxazolidinone is opened with 12 N HCl, and the auxiliary is then cleaved from the resultant intermediate **79** *via* hydrogenolysis in the presence of 1 N HCl to form di-hydrochloride salt **80** in 58% over 3 steps, and in 99% ee (Scheme 14).



Scheme 14: Reagents & conditions; (i) H_2 (30 bar), $\text{Pd}(\text{OH})_2/\text{C}$, MeOH, rt, 14 h; (ii) 12 N HCl, sealed tube, 120 °C, 3.5 days; (iii) H_2 (10 bar), $\text{Pd}(\text{OH})_2/\text{C}$, MeOH/1N HCl, rt, 5 days.

1.4 Lithium amide conjugate addition

The lithium amide conjugate addition reaction, pioneered primarily by Davies *et al.*, is a very efficient method for the synthesis of enantiopure β -amino acids.¹⁴ The highly diastereoselective conjugate addition of a range of enantiopure lithium amides, such as **81–88**, has been reported in a range of structurally diverse systems (Figure 5).

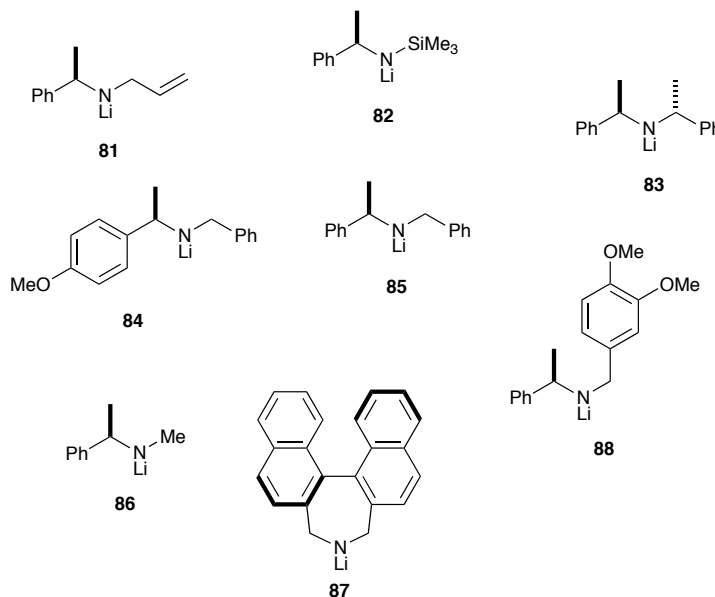
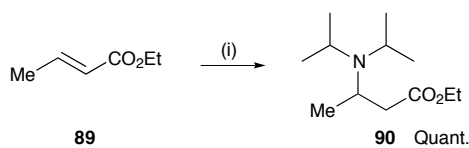


Figure 5: A range of enantiopure lithium amides.

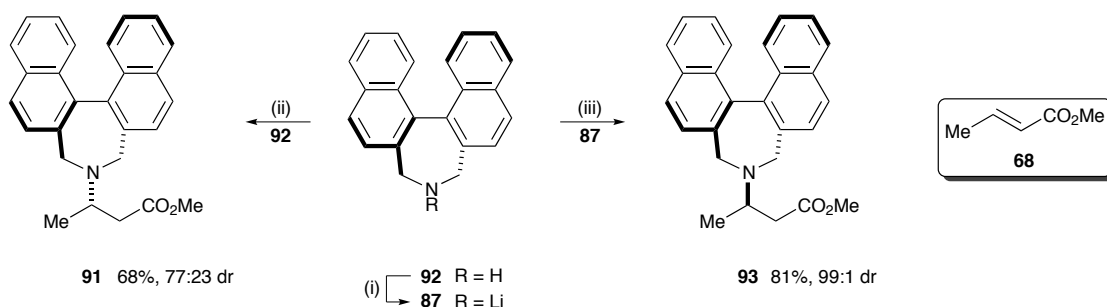
The first reported addition of a lithium amide was by Schlessinger *et al.* in 1973, who demonstrated that LDA could be added in a conjugate fashion to ethyl crotonate **89** in

near quantitative yield (Scheme 15).¹⁵



Scheme 15: Reagents & conditions; (i) LDA, THF, -78 °C, 10 mins.

It then was not until 1986 that an asymmetric variant of the reaction was reported by Hawkins *et al.*¹⁶ The addition of binaphthyl derivative lithium amide **87** to methyl crotonate **68** proceeds in 99:1 dr and 81% isolated yield, compared with just 77:23 dr for the analogous thermal conjugate addition of amine **92** to methyl crotonate **68** (Scheme 16).

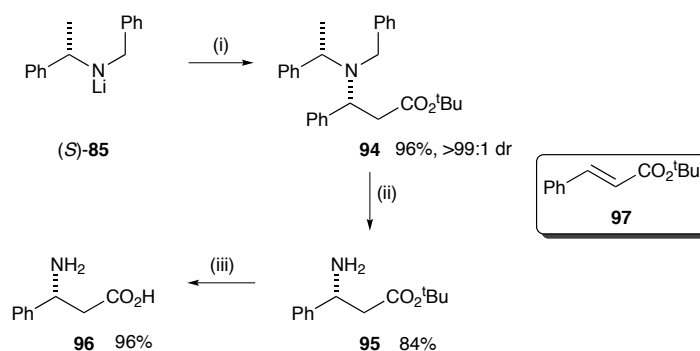


Scheme 16: Reagents & conditions; (i) BuLi, THF, -78 °C, 25 mins; (ii) **68**, Δ, 21 h; (iii) **68**, THF, -78 °C, 30 mins.

The conjugate addition of enantiopure lithium *N*-benzyl-*N*-(α -methylbenzyl)amide **85** has undergone extensive development within the Davies group including the synthesis of β -amino acids,¹⁴ as well as a wide range of natural products.^{17–19}

1.4.1 Synthesis of β -amino acids

As a representative example of the use of this methodology for the preparation of enantiopure β -amino acids, the conjugate addition of lithium amide (*S*)-**85** to *tert*-butyl cinnamate **97** proceeds in 96% yield and >99:1 dr to form β -amino ester **94**.¹⁴ High pressure hydrogenation in the presence of Pd(OH)₂/C affords **95** in 84% yield, followed by deprotection of the *tert*-butyl ester with TFA to give β -amino acid **96** in 96% yield (Scheme 17).



Scheme 17: (i) **97**, THF, -78°C , 2 h; (ii) H_2 , $\text{Pd}(\text{OH})_2/\text{C}$; (iii) $\text{TFA}/\text{CH}_2\text{Cl}_2$.

1.4.2 Natural product synthesis

The β -amino acid motif, and in particular stereogenic centres adjacent to a nitrogen atom, are very prevalent in nature. It has thus been possible to incorporate the lithium amide conjugate addition as a key stereo-defining step in the syntheses of a many natural products, for example sperabillin B **98**,¹⁷ (+)-negamycin **99**,²⁰ (+)-(*S*)-dihydroperiphylline **100**,¹⁸ (*S*)-homopipericolic acid **101**,²¹ thienamycin **102**²² and (–)-lasubine I **103**²³ (Figure 6).

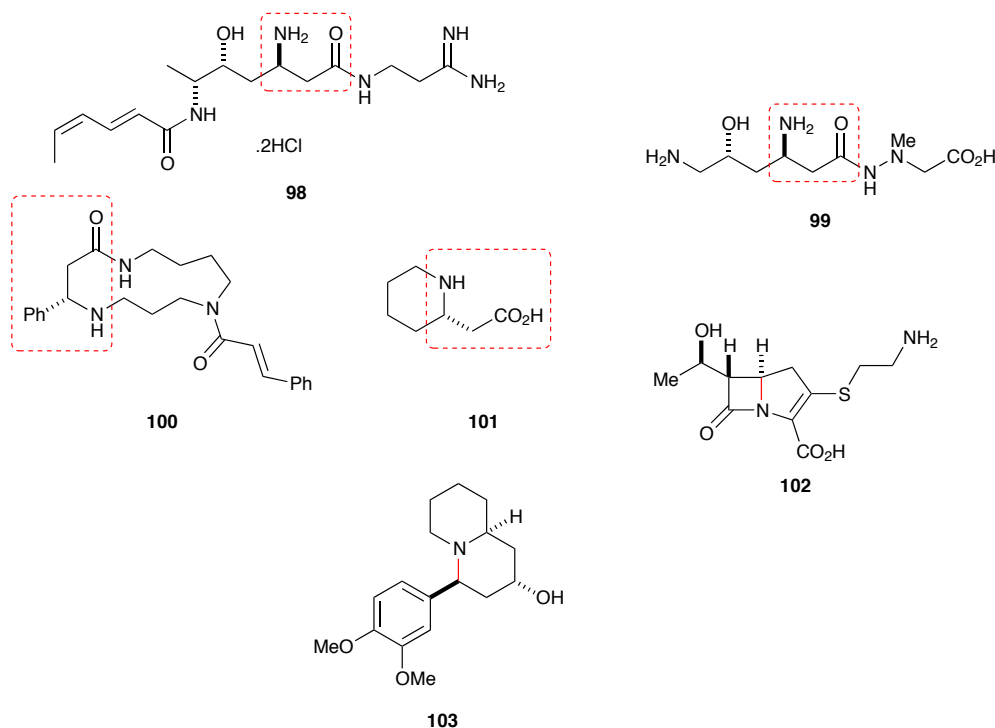


Figure 6: Natural products synthesised with the lithium amide conjugate addition.

1.5 Project aim

This thesis is concerned with the asymmetric conjugate addition reactions of a range of chiral nucleophiles. Chapter 2 discusses the attempted use of *N*-benzyl-*N*-(α -methylbenzyl)amine as a recyclable chiral auxiliary in both aza- and oxy- conjugate additions of nucleophiles derived from hydrazine **104** and hydroxylamine **105** respectively. Chapter 3 discusses the use of lithium amides derived from *N*-*tert*-butyl-dimethylsilyloxy-*N*-(α -methylbenzyl)amine **106** in conjugate addition reactions, and finally Chapter 4 discusses the use of lithium amides derived from *N*-phenyl-*N*-(α -methylbenzyl)amine **107** in conjugate addition reactions (Figure 7).

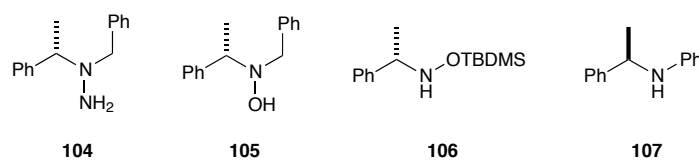


Figure 7: Project Aim.

Bibliography

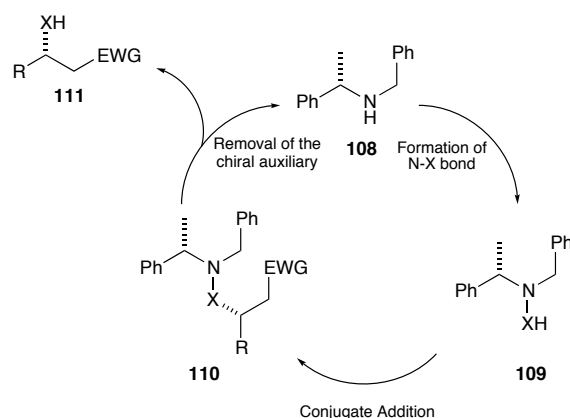
- [1] Komnenos, T. *Liebigs Ann. Chem.* **1883**, *218*, 145–169.
- [2] Michael, A. *J. Prakt. Chem.* **1887**, *35*, 349–356.
- [3] López, F.; Harutyunyan, S. R.; Meetsma, A.; Minnaard, A. J.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2005**, *117*, 2812–2816.
- [4] Harutyunyan, S. R.; López, F.; Browne, W. R.; Correa, A.; Peña, D.; Badorrey, R.; Meetsma, A.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2006**, *128*, 9103–9118.
- [5] Des Mazery, R.; Pullez, M.; López, F.; Harutyunyan, S. R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2005**, *127*, 9966–9967.
- [6] Taylor, M. S.; Zalatan, D. N.; Lerchner, A. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 1313–1317.
- [7] Mislow, K.; Graeve, R.; Gordon, A. J.; Wahl, G. H. *J. Am. Chem. Soc.* **1964**, *86*, 1733–1741.
- [8] Meyers, A. I.; Himmelsbach, R. J. *J. Am. Chem. Soc.* **1985**, *107*, 682–685.
- [9] Meyers, A. I.; Flisak, J. R.; Aitken, R. A. *J. Am. Chem. Soc.* **1987**, *109*, 5446–5452.
- [10] Suzuki, I.; Kin, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **1993**, *115*, 10139–10146.
- [11] Enders, D.; Papadopoulos, K. *Tetrahedron Lett.* **1983**, *24*, 4967–4970.
- [12] Enders, D.; Rendenbach, B. E. M. *Tetrahedron* **1986**, *42*, 2235–2242.
- [13] Lucet, D.; Sabelle, S.; Kostelitz, O.; Le Gall, T.; Mioskowski, C. *Eur. J. Org. Chem.* **1999**, 2583–2591.
- [14] Davies, S. G.; Smith, A. D.; Price, P. *Tetrahedron: Asymmetry* **2005**, *16*, 2833–2891.
- [15] Herrmann, J. L.; Kieczkowski, G. R.; Schlessinger, R. H. *Tetrahedron Lett.* **1973**, *14*, 2433–2436.
- [16] Hawkins, J. M.; Fu, G. C. *J. Org. Chem.* **1986**, *51*, 2820–2822.

- [17] Davies, S. G.; Haggitt, J. R.; Ichihara, O.; Kelly, R. J.; Leech, M. A.; Mortimer, A. J. P.; Roberts, P. M.; Smith, A. D. *Org. Biomol. Chem.* **2004**, *2*, 2630–2649.
- [18] Sergeyev, S. A.; Hesse, M. *Helv. Chim. Acta* **2002**, *85*, 161–167.
- [19] Davies, S. G.; Iwamoto, K.; Smethurst, C. A. P.; Smith, A. D.; Rodriguez-Solla, H. *Synlett* **2002**, 1146–1148.
- [20] Davies, S. G.; Ichihara, O. *Tetrahedron: Asymmetry* **1996**, *7*, 1919–1922.
- [21] Chippindale, A. M.; Davies, S. G.; Iwamoto, K.; Parkin, R. M.; Smethurst, C. A. P.; Smith, A. D.; Rodriguez-Solla, H. *Tetrahedron* **2003**, *59*, 3253–3265.
- [22] Davies, S. G.; Hedgecock, C. J. R.; McKenna, J. M. *Tetrahedron: Asymmetry* **1995**, *6*, 2507–2510.
- [23] Chalard, P.; Remuson, R.; Gelas-Mialhe, Y.; Gramain, J. C. *Tetrahedron: Asymmetry* **1998**, *9*, 4361–4368.

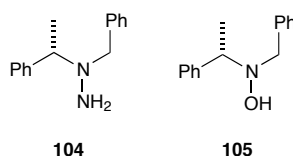
N-Benzyl-*N*-(α -methylbenzyl)amine as a chiral auxiliary

2.1 Chapter aim

All previous studies that employ *N*-benzyl-*N*-(α -methylbenzyl)amine as a chiral nucleophilic source of nitrogen ultimately destroy the chiral information of the α -methylbenzyl group on hydrogenolytic *N*-deprotection. It was envisaged that the entire *N*-benzyl-*N*-(α -methylbenzyl)amino group could be used instead as a chiral auxiliary, by employing the conjugate addition of hydrazine **104** as the chiral ammonia equivalent, followed by N–N cleavage to regenerate *N*-benzyl-*N*-(α -methylbenzyl)amine, which could be recycled. If successful this approach may have the added benefit of being general to a variety of heteroatoms, such as oxygen- and sulfur-based nucleophiles (Figure 8).

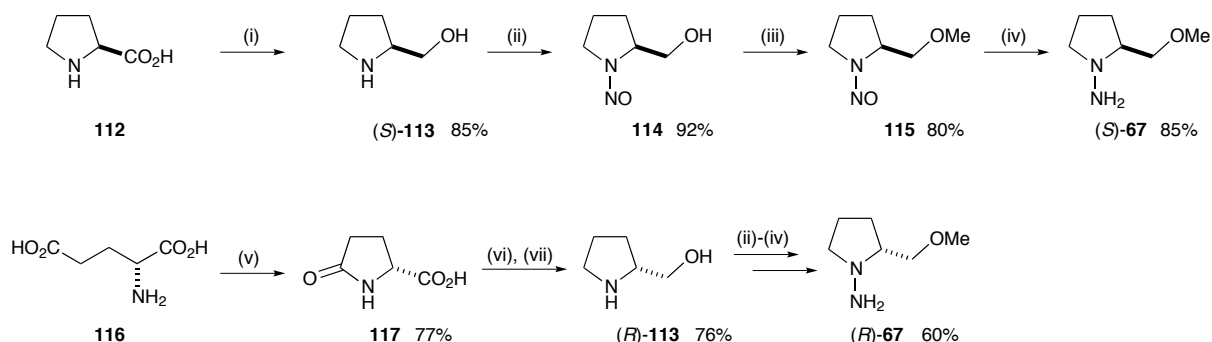
**Figure 8:** Chapter Aim. X = NH, O, S.

This chapter describes the preparation and conjugate addition reactions of hydrazine **104** and hydroxylamine **105** (Figure 9). These two studies were carried out simultaneously.

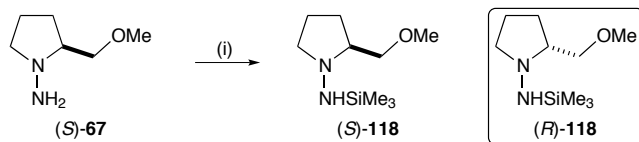
**Figure 9:** Hydrazine **104** and Hydroxylamine **105**.

2.2 RAMP and SAMP hydrazines

SAMP (*S*)-**67** and RAMP (*R*)-**67** hydrazines are versatile chiral auxiliaries synthesised from (*S*)-proline **112**¹ and (*R*)-glutamic acid **116**² respectively. For example, in the synthesis of SAMP (*S*)-**67** the key step is the formation of the N–N bond by reaction of amine (*S*)-**113** with EtONO, giving nitroso species **114** in 92% yield. This functionality is later reduced with LiAlH₄ to give SAMP (*S*)-**67** in 4 steps and 53% overall yield (Scheme 18).

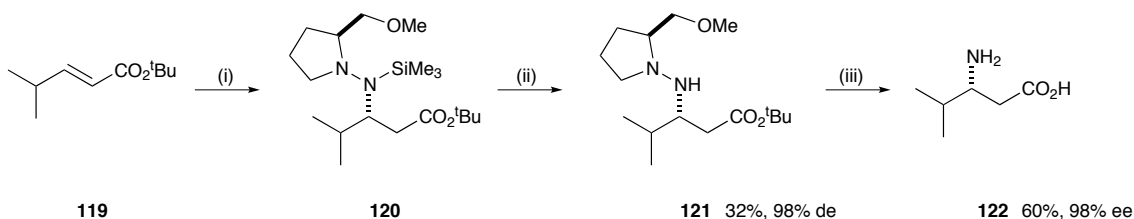
**Scheme 18:** Reagents & conditions: (i) LiAlH₄, THF; (ii) EtONO, THF, rt, 24 h; (iii) NaH, MeI, THF, −40 °C to rt, then 30 min, rt.; (iv) LiAlH₄, THF, 2 h, Δ; (v) H₂O, Δ; (vi) CH₂N₂, Et₂O, 0 °C; (vii) LiAlH₄, THF, Δ, 17 h.

Enders *et al.* demonstrated that it was possible to effect the addition of RAMP and SAMP hydrazines in an aza-Michael fashion, followed by cleavage of the N–N bond to form the desired β -amino acid.³ RAMP (*R*)-**67** and SAMP (*S*)-**67** are first mono-silylated with BuLi and TMSCl to give TMS-RAMP (*R*)-**118** and TMS-SAMP (*S*)-**118** (Scheme 19).



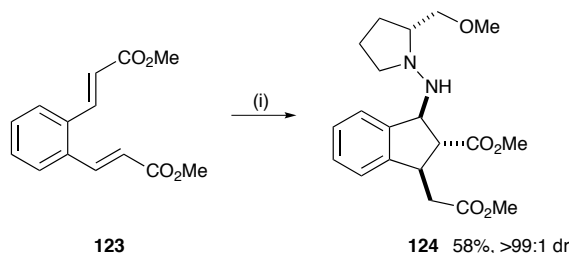
Scheme 19: Reagents & conditions: (i) BuLi, Et₂O, 0 °C, 1 h, then TMSCl, rt, 2 h.

Subsequent reaction of TMS-SAMP (*S*)-**118** with BuLi followed by *tert*-butyl ester **119**, for example, afforded adduct **120**. Treatment of **120** with SiO₂ in EtOAc to remove the TMS group afforded **121** in 32% yield over two steps, and in 99:1 dr. Finally, cleavage of the N–N bond with Raney[®]-Nickel and concomitant saponification of the ester gave the desired β -amino acid **122** in 60% yield and 98% ee (Scheme 20).



Scheme 20: Reagents & conditions: (i) BuLi, (*S*)-**118**, THF, –78 °C; (ii) SiO₂, EtOAc; (iii) Ra-Ni, H₂, H₂O, 65–70 °C.

De Meijere *et al.* extended this methodology for use in tandem aza-Michael additions.⁴ Reaction of TMS-RAMP (*R*)-**118** with BuLi and bis-acceptor **123** afforded polysubstituted aminoindane **124** as a single diastereoisomer in 58% yield (Scheme 21).



Scheme 21: Reagents & conditions: (i) BuLi, TMS-RAMP, THF, –78 °C, 1h, then 5 % HCl, 5 min, rt.

With previous precedent for the aza-Michael addition of chiral hydrazines, studies into the synthesis and reactivity of a hydrazine based on *N*-benzyl-(*N*- α -methylbenzyl)amine **108** therefore began.

2.3 Syntheses of hydrazines

Along with the synthesis *via* the corresponding nitroso compound (*vide supra*), the other major method for hydrazine synthesis involves the coupling of two amines, one electrophilic and one nucleophilic. Hydrazine itself is synthesised *via* either the Raschig process, which produces hydrazine hydrate, or the Olin Raschig process which produces anhydrous hydrazine.⁵ Both are in essence the same and involve the reaction of ammonia with NaOCl to form chloramine, which is then reacted with further ammonia to produce hydrazine (Figure 10).

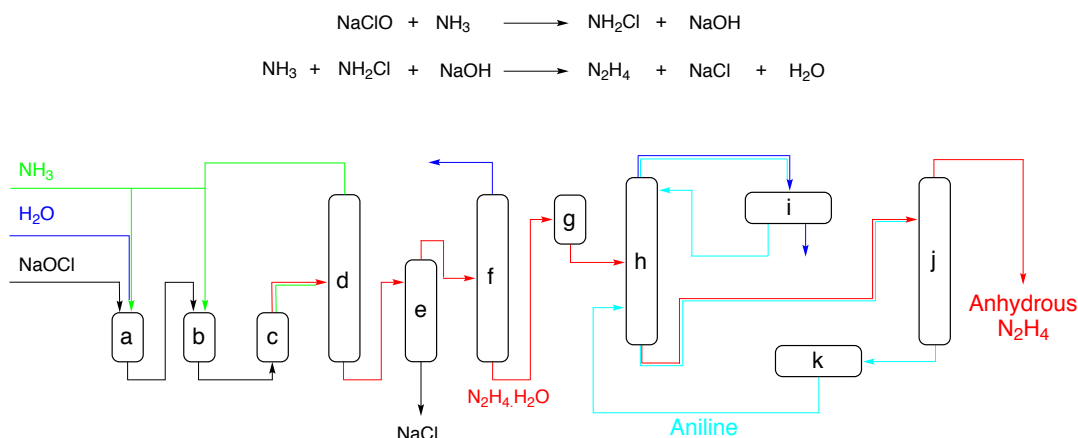
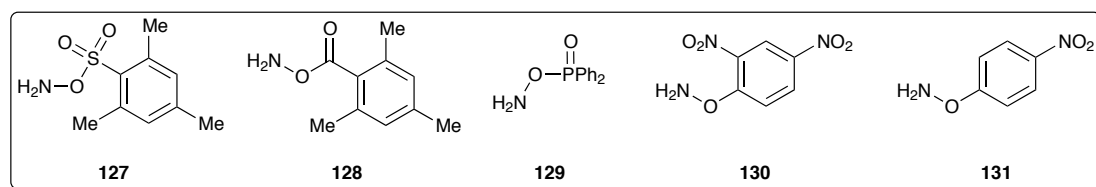


Figure 10: The Olin Raschig Process; (a) Chloramine reactor; (b), (c) Hydrazine Reactors; (d) Ammonia evaporator; (e) Hydrazine-sodium chloride separator; (f) Hydrazine hydrate concentration; (g) Hydrazine hydrate storage; (h) Hydrazine hydrate dehydration; (i) Aniline-water decantation; (j) Anhydrous hydrazine distillation; (k) Aniline storage.

Similar methods can be found in the literature for the synthesis of alkyl hydrazines, for example Friestad *et al.* screened a range of electrophilic sources of “NH₂” for *N*-amination.⁶ Oxazolidinone **125** was treated with either BuLi or NaH, then **127-131**, and the product isolated through conversion to hydrazone **126** (Scheme 22).

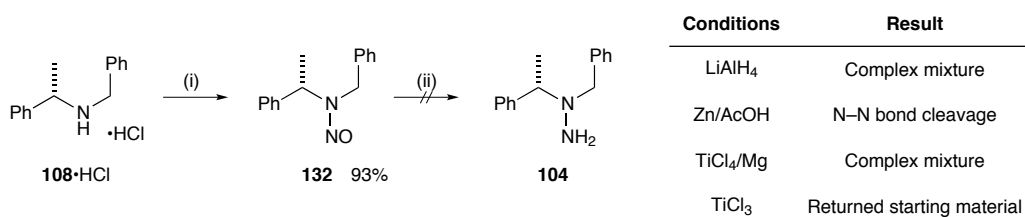


	"NH ₂ "	Yield (BuLi) %	Yield (NaH) %
	127	75	-
	128	22	52
	129	41	73
	130	66	54
	131	0	80

Scheme 22: Reagents & conditions: (i) BuLi, THF, $-78\text{ }^{\circ}\text{C}$, 1 h, then RONH_2 , rt, 24 h or NaH, dioxane, $60\text{ }^{\circ}\text{C}$, 1 h, then RONH_2 , rt, 24 h; (ii) PhCHO, TsOH $\cdot$ H_2O , toluene, Δ , 1 h.

2.4 Attempted synthesis *via* a nitroso species

Reaction of *N*-benzyl-(*N*- α -methylbenzyl)amine hydrochloride **108** $\cdot$ HCl with NaNO_2 and catalytic HCl afforded the desired nitroso compound **132** in 93% yield. A range of reduction methods were screened: LiAlH_4 ,^{1,2} Zn/AcOH ,⁷ TiCl_4/Mg ,⁸ and TiCl_3 ⁹ were all used as the reducing agents. Treatment of **132** with LiAlH_4 and TiCl_4/Mg both gave a complex mixture of inseparable products, Zn/AcOH cleaved the N–N bond to return **108** and TiCl_3 returned the starting nitroso compound **132** (Scheme 23).

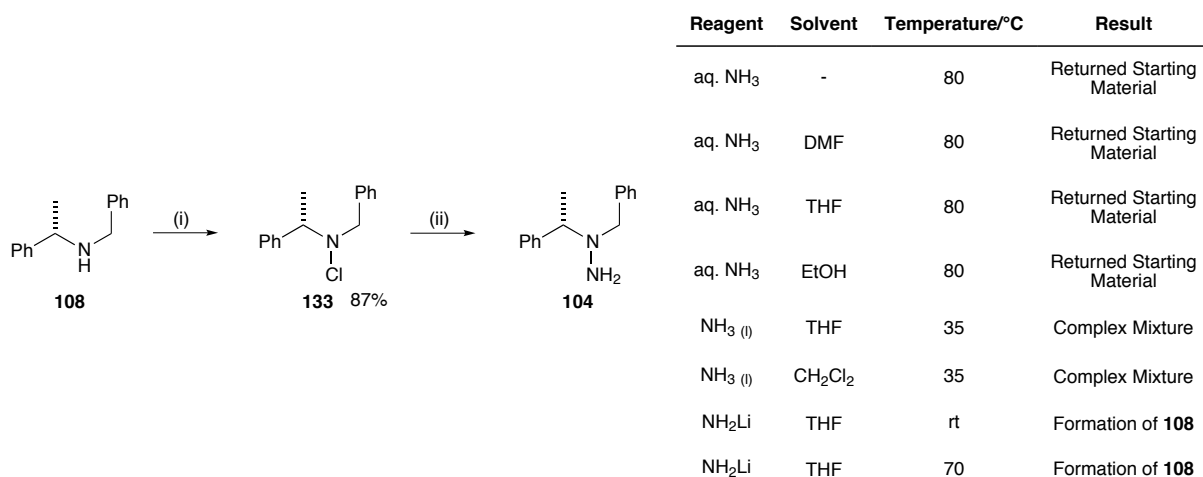


Scheme 23: Reagents & conditions: (i) NaNO_2 , 2 M HCl, H_2O , $75\text{ }^{\circ}\text{C}$, 2.5 h; (ii) See table.

Due to the failure of this method, an alternative synthesis was explored.

2.5 Attempted synthesis *via* *N*-benzyl-*N*-chloro-*N*-(α -methylbenzyl)amine

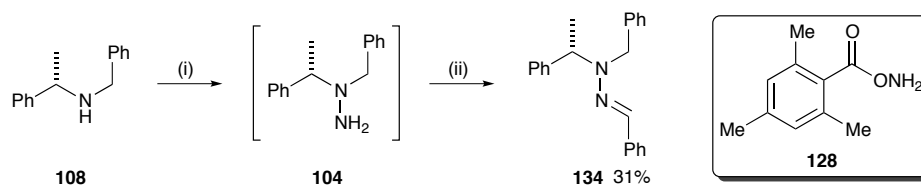
Reaction of *N*-benzyl-(*N*- α -methylbenzyl)amine **108** with NCS formed *N*-chloro species **133** in 87% yield.¹⁰ Subsequent treatment of **133** with aq. NH₃ alone or in a variety of co-solvents gave only returned starting material. On changing to liquid ammonia a complex mixture of inseparable compounds was obtained. Finally reaction with NH₂Li regenerated amine **108** (Scheme 24).



Scheme 24: Reagents & conditions: (i) NCS, CH₂Cl₂, 0 °C, 15 min; (ii) See table.

2.6 Attempted synthesis *via* an electrophilic source of “NH₂”

A variety of electrophilic sources of “NH₂” were screened in an attempt to form hydrazine **104**. Reaction of **108** with chloramine, NH₂–OTs or **128**¹¹ all afforded product mixtures consistent with formation of hydrazine **104**. Due to the requirement of an excess of amine starting material **108** purification was required, but unfortunately the hydrazine was unstable to flash column chromatography and decomposition occurred to give a complex mixture of products. To prove that hydrazine **104** had been formed, the crude material from one of the reactions with **128** was treated with benzaldehyde, and hydrazone **134** was subsequently isolated in 31% yield (Scheme 25).



Scheme 25: Reagents & conditions: (i) **128**, 70 °C; (ii) PhCHO, AcOH, H₂O.

2.7 Synthesis of racemic *N*-benzyl-(*N*- α -methylbenzyl)hydrazine

Due to the instability of hydrazine **104** towards column chromatography, a route was required in which the final step would be clean enough so that no purification would be required. A synthesis from *N*-aminophthalimide **135** was proposed, in which the final step would be an *N*-deprotection. Although this would give the racemate, it was proposed that resolution of either **136** or **137** could be employed, and also that the racemate would give the desired information regarding the diastereoselectivity in its subsequent conjugate addition reactions (Figure 11).¹²

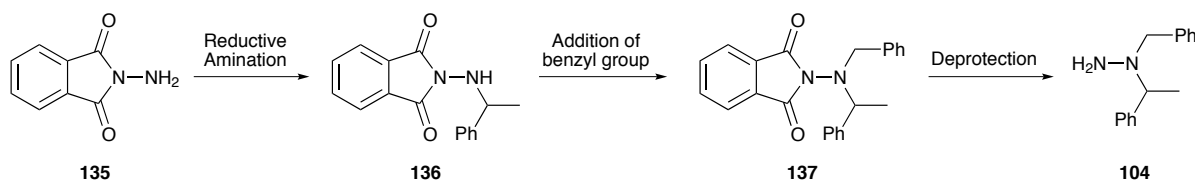
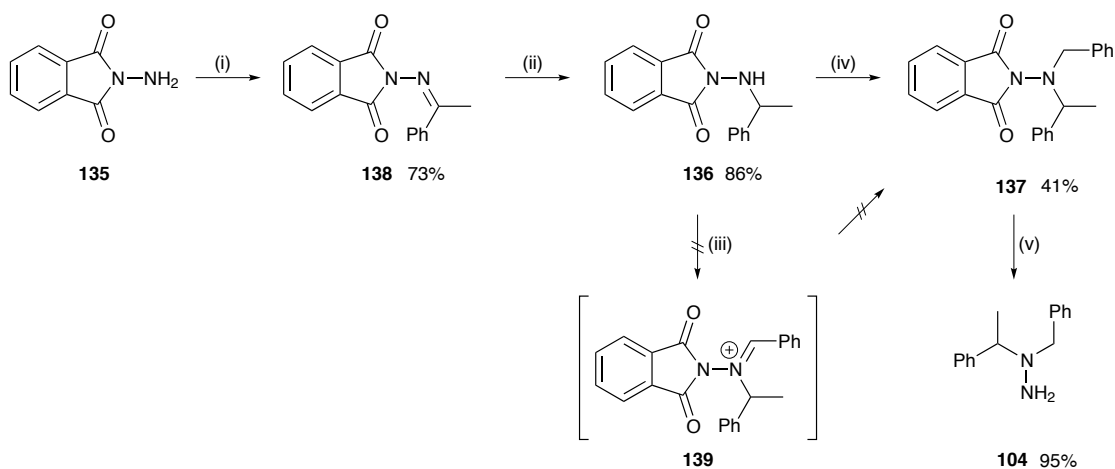


Figure 11: Proposed synthesis of hydrazine **104** from *N*-aminophthalimide.

Reaction of *N*-aminophthalimide **135** with acetophenone in the presence of HCl formed imine **138** in 73% yield (Scheme 26), and subsequent reduction with borane-pyridine complex gave **136** in 86% yield. A further reductive amination with benzaldehyde to install the final benzyl group proved unsuccessful, and thus a direct alkylation protocol was employed.¹³ Treatment of **136** with BnBr and Na₂CO₃ in DMPU afforded **137** in 41% yield,ⁱ and although low yielding it was sufficient for the required purpose. Finally, treatment of

ⁱ37% returned starting material was also recovered

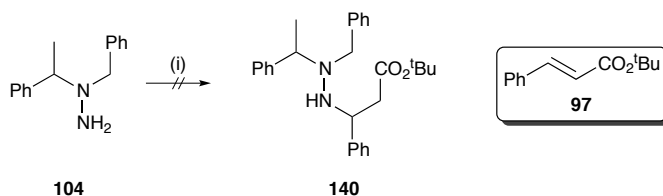
protected hydrazine **137** with hydrazine monohydrate afforded **104** in 95% yieldⁱⁱ (Scheme 26).¹⁴



Scheme 26: *Reagents & conditions:* (i) acetophenone, conc. HCl, 1,4-dioxane, 80 °C, 16 h; (ii) $\text{BH}_3 \cdot \text{py}$, AcOH, rt, 15 min, then 10% HCl, rt, 30 min; (iii) PhCHO, conc. HCl, 1,4-dioxane, 80 °C, 16 h, then $\text{NaBH}(\text{OAc})_3$, rt, 16 h; (iv) BnBr, Na_2CO_3 , DMPU, 100 °C, 5 h; (v) H_2NNH_2 , EtOH, Δ , 4 h.

2.8 Attempted conjugate addition of *N*-benzyl-*N*-(α -methylbenzyl)hydrazine

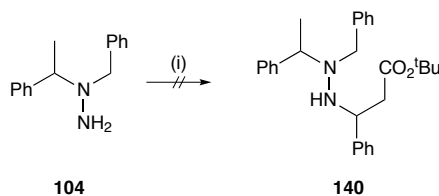
Treatment of hydrazine **104** with BuLi in THF at -78 °C for 30 min, followed by the addition of *tert*-butyl cinnamate **97** afforded a complex mixture of products which included unreacted *tert*-butyl cinnamate **97**. In order to investigate whether the hydrazine anion was stable, treatment of **104** with BuLi was followed by quenching with NH_4Cl after 30 min, and a complex mixture was formed including a major unidentifiable product, consistent with the decomposition of hydrazine **104** (Scheme 27).



Scheme 27: *Reagents & conditions:* (i) BuLi, THF, -78 °C, then **97**, THF, -78 °C, 2 h.

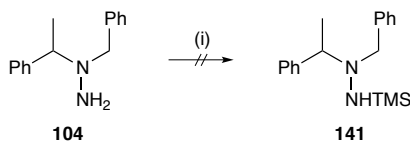
ⁱⁱThis sample was clean enough to use in the conjugate addition reaction.

A pre-mix experiment was next attempted, in an attempt to have an anionic form of **104** around for as little time as possible. Addition of BuLi to a mixture of **104** and **97** in THF at $-78\text{ }^{\circ}\text{C}$ resulted complex mixture, again consistent with decomposition of the hydrazine anion occurring before conjugate addition (Scheme 28).



Scheme 28: Reagents & conditions: (i) **97**, THF, then BuLi, THF, -78 ° , 2 h.

Finally, as with the RAMP and SAMP hydrazines, an attempt was made to mono-TMS protect the hydrazine **104**, but unfortunately treatment with TMSCl and Et₃N resulted only in decomposition of the hydrazine (Scheme 29).



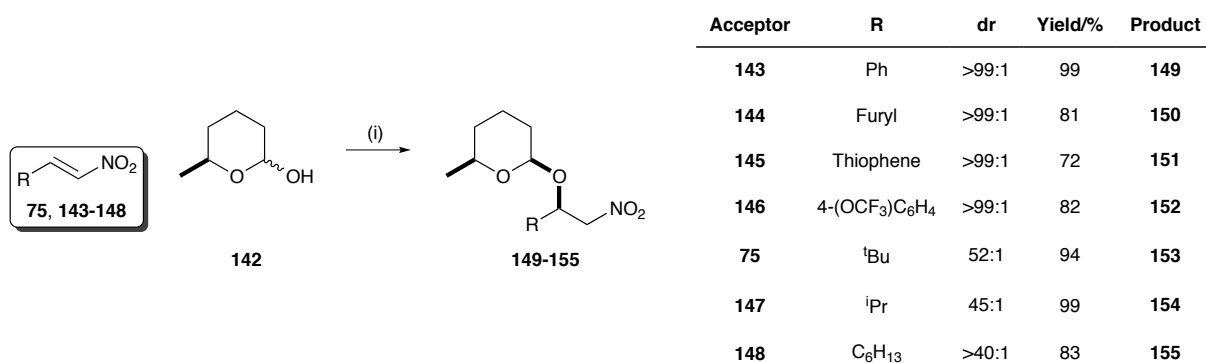
Scheme 29: Reagents & conditions: (i) TMSCl, Et₃N, CH₂Cl₂, rt, 16 h.

2.9 Conclusion

In conclusion, attempts to synthesise and isolate *N*-benzyl-(*N*- α -methylbenzyl)hydrazine **104** enantiopure were unsuccessful, but a racemic sample could be isolated after synthesis from *N*-aminophthalimide. Unfortunately the hydrazine itself was very unstable, and under a variety of conditions decomposition occurred (even upon chromatography). It was therefore not possible to use it in a conjugate addition reaction as hoped, and attention shifted towards investigation of the oxygen analogue, *N*-benzyl-*N*-(α -methylbenzyl)hydroxylamine **105**.

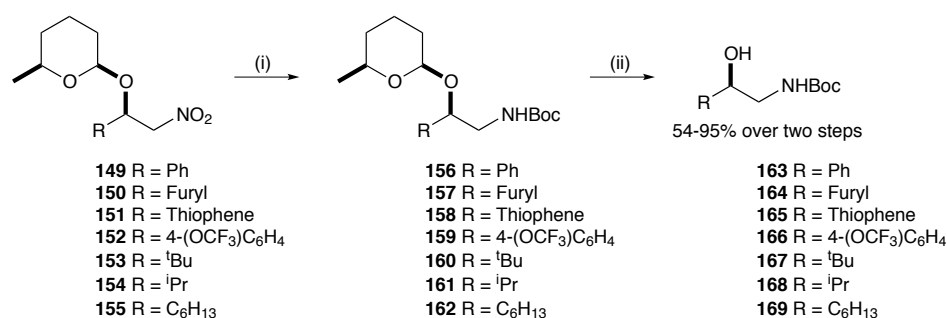
2.10 Oxy-conjugate addition

The oxy-conjugate addition reaction is a highly useful method of introducing an oxygen atom to an α,β -unsaturated system. Dixon *et al.* developed an asymmetric oxy-conjugate addition methodology, with the diastereoselectivity being imparted by the oxygen donor, chiral THP lactol **142**.¹⁵ Treatment of THP lactol **142** with KHMDS followed by 18-crown-6 generates the ‘naked’ anion, which upon reaction with (*E*)- β -nitrostyrene **143** affords the conjugate addition product **149** in 99% yield and >99:1 dr. The scope of the reaction was initially increased by varying the R group on the α,β -unsaturated nitro compound, with each reaction proceeding with excellent yield and diastereoselectivity (Scheme 30).



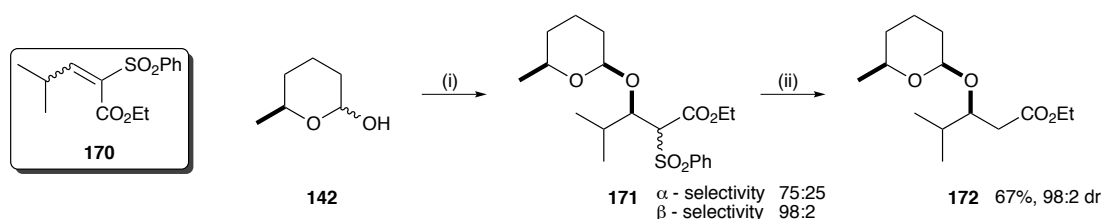
Scheme 30: Reagents & conditions: (i) KHMDS, THF, $-78\text{ }^{\circ}\text{C}$, then 18-crown-6, followed by the requisite acceptor.

Reduction of the nitro group with nickel boride and concomitant *in situ* *N*-Boc protection affords the desired *N*-Boc amine products **156-162**. The THP group can then be removed with a polymer bound acid resin to afford the final *N*-Boc amino alcohols **163-169** in good to excellent yields (Scheme 31).



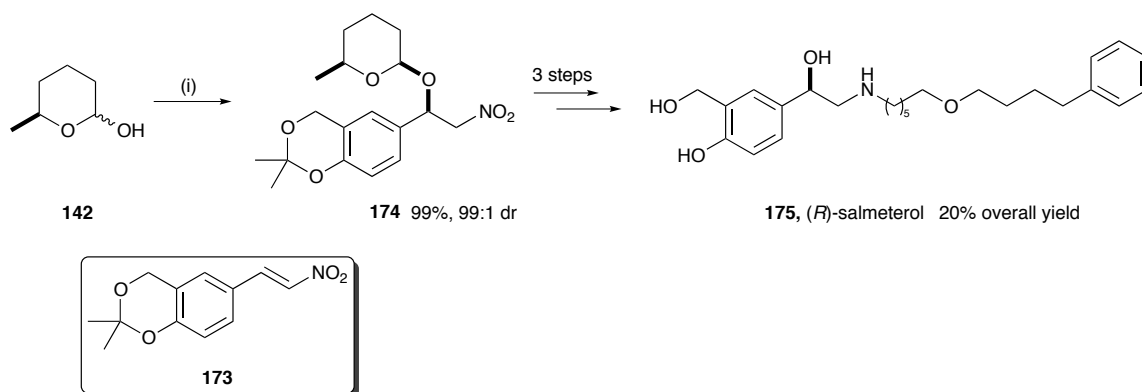
Scheme 31: Reagents & conditions: (i) NiCl₂ · 6 H₂O, NaBH₄, MeOH/THF, 0 °C, then Boc₂O, 0 °C to rt; (ii) MP-TsOH II, MeOH, rt.

The methodology has been extended for use with α,β -unsaturated esters by employing the use of a removable, activating phenyl sulfonyl group.¹⁶ For example, treatment of **170** with the anion of lactol **142** gave **171** with 98:2 dr at the β stereocentre. Protodesulfonylation with SmI₂ gave β -alkoxy ester **172** in 67% yield and 98:2 dr (Scheme 32).



Scheme 32: Reagents & conditions: (i) KHMDS, THF, -78 °C, 15 mins, then 18-crown-6, THF, -78 °C, 30 mins, then **170**, THF, -78 °C, 30 mins; (ii) SmI₂, THF, -78 °C, 12 h.

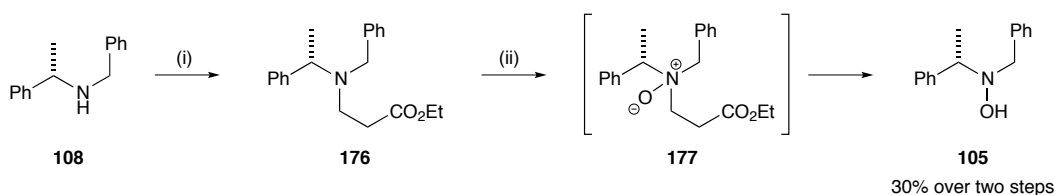
This approach has been used in the synthesis of the natural product (*R*)-salmeterol **175**, with the key step being the conjugate addition of THP lactol **142** to α,β -unsaturated nitro compound **173** (Scheme 33).¹⁷



Scheme 33: Reagents & conditions: (i) KHMDS, 18-crown-6, THF, -78 °C, then **173**.

2.11 Synthesis of the Hydroxylamine

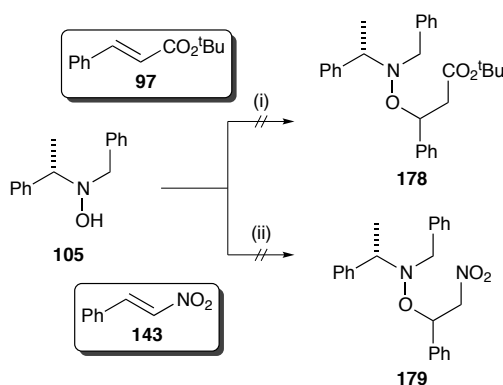
Hydroxylamine **105** was prepared in two steps from *N*-benzyl-*N*-(α -methylbenzyl)amine **108**. The first step involved the thermal addition of **108** to ethyl acrylate, then the resulting product **176** was treated with *m*-CPBA to give hydroxylamine **105** in 30% yield over two steps. The product is consistent with the reaction proceeding *via* *N*-oxidation of **176** followed by in situ Cope elimination to give **105** (Scheme 34).¹⁸



Scheme 34: Reagents & conditions: (i) ethyl acrylate, 110 °C, 48 h; (ii) *m*-CPBA, CH₂Cl₂, rt, 3 h.

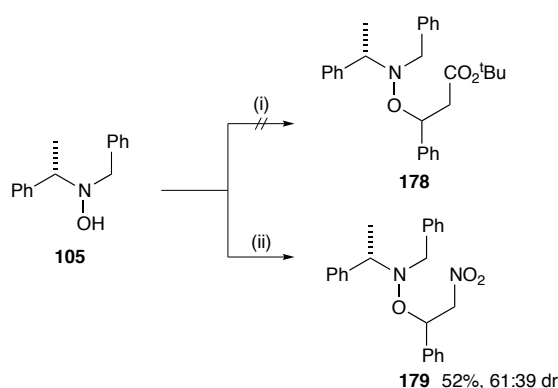
2.12 Initial reactions

Initial reactions probed the propensity of the anion of **105** to undergo conjugate addition to both an α,β -unsaturated ester and α,β -unsaturated nitro compounds. Treatment of **105** with BuLi followed by addition of *tert*-butyl cinnamate **97** formed none of the desired addition product **178** and returned only starting material. Similar treatment of **105** with BuLi followed by addition of *trans*- β -nitrostyrene **143** afforded only starting material (Scheme 35).



Scheme 35: Reagents & conditions: (i) BuLi, THF, -78 °C, 30 min, then **97**, THF, -78 °C, 1 h; (ii) BuLi, THF, -78 °C, 30 min, then **143**, THF, -78 °C, 1 h.

On employing KHMDS to switch from a lithium oxyanion to a potassium oxyanion, the two reactions were repeated, and although the reaction with **97** once again returned only starting material, the reaction with **143** afforded 100% conversion to the desired product **179**ⁱⁱⁱ in 52% isolated yield and 61:39 dr (Scheme 36). These results can be attributed to the relative pKa's of the compounds (hydroxylamine $\sim$ 24, ester $\sim$ 30 and nitroalkane $\sim$ 17 in DMSO¹⁹) which suggest that the conjugate addition reaction to ester **97** is likely to be reversible under the reaction conditions. To explore this hypothesis an attempt was made to trap out the enolate in situ with TMSCl, although unfortunately this proved unsuccessful.



Scheme 36: *Reagents & conditions:* (i) KHMDS, THF, -78°C , 30 min, then **97**, THF, -78°C , 1 h; (ii) KHMDS, THF, -78°C , 30 min, then **143**, THF, -78°C , 1 h.

2.13 Optimisations

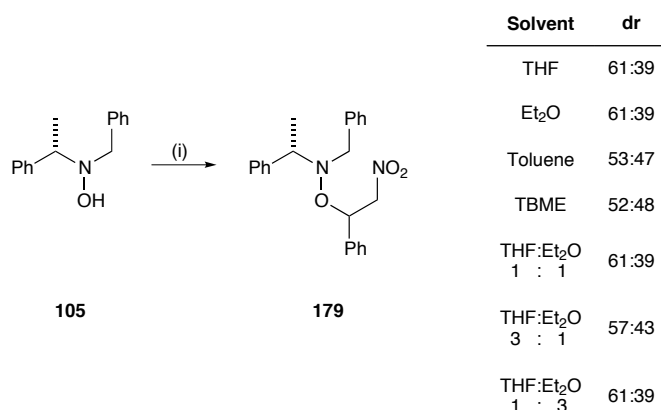
With this first result in hand, attention shifted to attempted reaction optimisation. Three methods to achieve this were envisaged: (i) variation of the solvent; (ii) variation of the temperature; (iii) use of an additive.

2.13.1 Variation of solvent

A range of different solvents were screened in order to determine whether they had an effect on the diastereoselectivity of the reaction. Et₂O, toluene, *tert*-butylmethyl ether as well

ⁱⁱⁱThe reaction was reversible on silica and thus purification gave a 75:25 mixture of product **179**:starting material **143**.

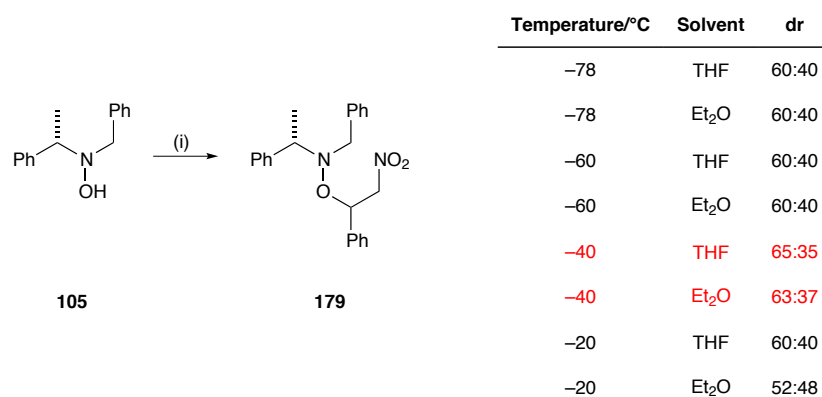
as mixtures of THF and Et₂O were chosen. THF, Et₂O and their respective mixtures all gave diastereoselectivities of around 60:40, with both toluene and *tert*-butylmethyl ether giving lower diastereoselectivities of 53:47 and 52:48 respectively (Scheme 37).^{iv}



Scheme 37: *Reagents & conditions:* (i) KHMDS, solvent, -78 °C, 30 min, then **143**, solvent, -78 °C, 1 h.

2.13.2 Variation of temperature

Varying the temperature of the reaction was next investigated. THF and Et₂O were chosen as solvents due to previous results and a temperature range of -78 to -20 °C was selected. With both THF and Et₂O the diastereoselectivities showed a peak at -40 °C, before a decrease at -20 °C occurred (Scheme 38).

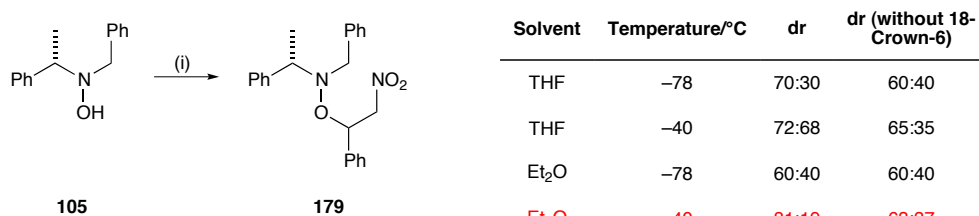


Scheme 38: *Reagents & conditions:* (i) KHMDS, solvent, -78 °C, 30 min, then **143**, solvent, 1 h.

^{iv}Diastereomeric ratios were measured by peak integration of the ¹H NMR spectra.

2.13.3 Addition of 18-crown-6

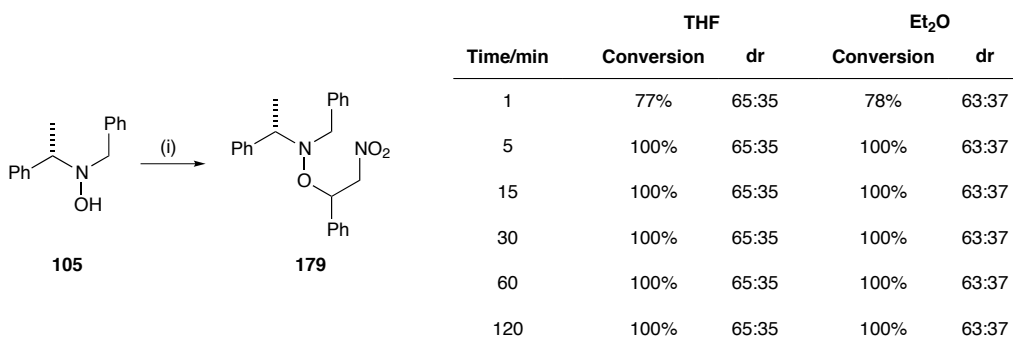
With a slight increase in diastereoselectivity seen from changing the temperature, it was next decided to investigate changing the nature of anion by adding 18-crown-6. Hydroxylamine **105** was deprotonated with KHMDS, then 18-crown-6 was added and the reaction was stirred for 30 min followed by addition of β -nitrostyrene **143**. At -78 °C an increase to 70:30 dr in THF was observed, but with Et₂O there was no observed increase and the reaction diastereoselectivity remained 60:40. On raising the temperature to -40 °C a slight increase in diastereoselectivity was seen in THF, but in Et₂O the diastereoselectivity increased to 81:19 (Scheme 39).



Scheme 39: Reagents & conditions: (i) KHMDS, solvent, 15 mins, then 18-crown-6, solvent, 30 mins, then **143**, solvent, 1 h.

2.14 Time studies

One explanation for the low diastereoselectivity is that under the reaction conditions the addition is reversible, and thus the kinetic product is not obtained. One possible way to probe this is by following the product diastereoisomeric ratio over time. If the reaction is equilibrating then it would be expected that the diastereoisomeric ratio would change over the course of the reaction. Thus a time study was carried out in both THF and Et₂O at -40 °C and the results imply that in this case the addition is not reversible under the reaction conditions, as the selectivity stays constant throughout the reaction (Scheme 40).

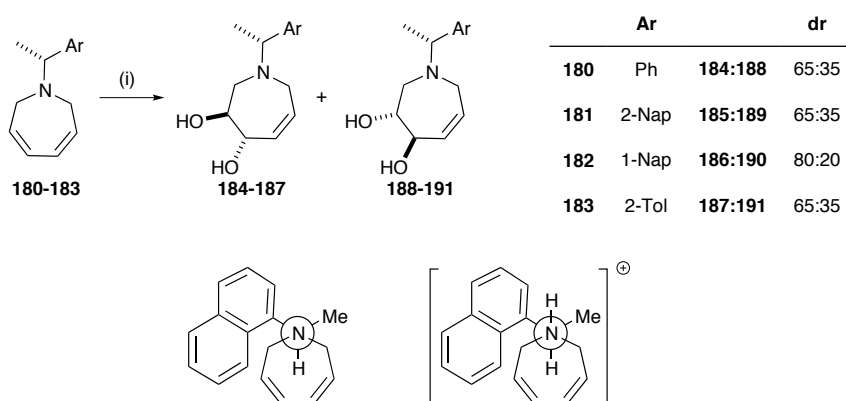


Scheme 40: Reagents & conditions: (i) KHMDS, THF, 30 mins, then **143**, THF, 2 h

After attempted optimisations the selectivity was still not of a synthetically useful level, thus it was decided to alter the chiral auxiliary itself.

2.15 Modifying the hydroxylamine

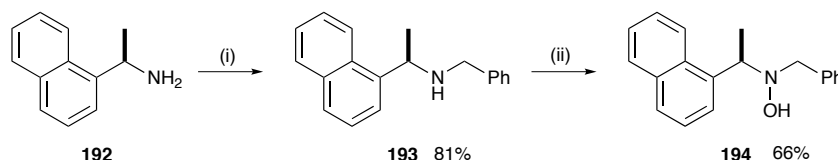
In an effort to introduce some rigidity into the system two modifications to the hydroxylamine structure were envisaged. Firstly, a steric alteration was attempted by replacing the α -methylbenzyl group with a 1-(1'-naphthyl)ethyl group. Some previous work by Davies and co-workers on the oxidation of enantiopure azepines had noted an improvement in diastereoselectivities with this alteration. In this case the C(1')–H bond of the naphthyl group is orientated over one face of the azepine ring, and thus oxidation preferentially occurs on the opposite face (Scheme 41).²⁰



Newman projections along the N-C(1') bond of **182** in the preferred solid-state conformation and the corresponding ammonium ion.

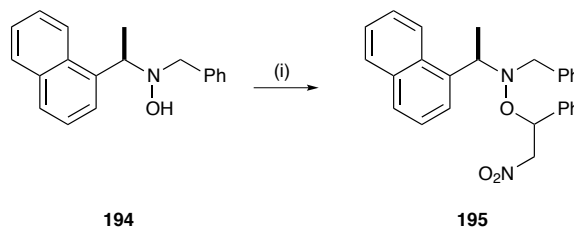
Scheme 41: Reagents & conditions: (i) Cl₃CCO₂H, *m*-CPBA, CH₂Cl₂, rt, 21 h, then NaOH (2 M, aq). [2-Nap = 2-naphthyl. 1-Nap = 1-naphthyl. 2-Tol = 2-tolyl.]

Hydroxylamine **194** was synthesised in two steps from 1-(1'-naphthyl)ethyl]amine **192**. An initial reductive amination with benzaldehyde afforded *N*-benzyl-[1-(1'-naphthyl)ethyl]amine **193** in 81%, followed by oxidation with dimethyldioxirane (DMDO), which afforded the desired hydroxylamine **194** in 66% yield (Scheme 42).^v



Scheme 42: Reagents & conditions: (i) PhCHO, EtOH, 95 °C, 2 h, then NaBH₄, EtOH, rt, 42 h; (ii) DMDO, acetone, 0 °C, 15 min.

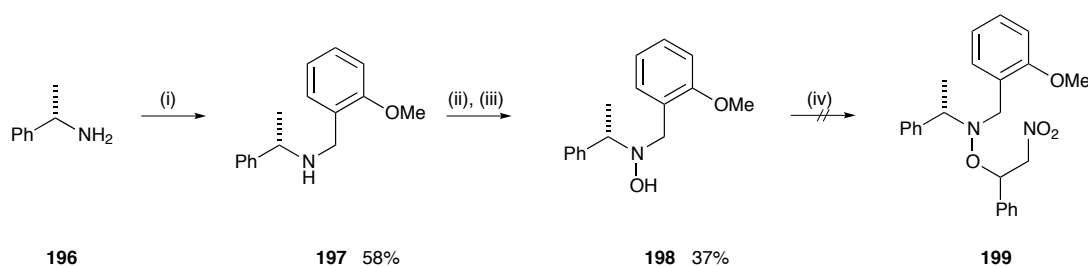
Treatment of **194** with KHMDS in THF, followed by addition of *trans*- β -nitrostyrene **143** gave a complex mixture of inseparable products. Analysis of the crude reaction mixture by both mass spectrometry and ¹H NMR spectroscopy gave indication some of the desired product **195** was present, although it was not isolable and a diastereoisomeric ratio could not be ascertained (Scheme 42).



Scheme 43: Reagents & conditions: (i) KHMDS, THF, -78 °C, 30 mins, then **143**, THF, -78 °C, 1 h.

The second method envisaged was to attempt to introduce some rigidity into the system by chelation. A 2-methoxy substituent was added to the benzyl group in the hope that chelation would occur between the potassium and the oxygen of the methoxy group. Synthesis of the hydroxylamine **198** was carried out by the same method as for the parent hydroxylamine **105**, in 3 steps and 21% overall yield. Treatment of **198** with KHMDS followed by *trans*- β -nitrostyrene **143** returned only starting material (Scheme 44).

^vDMDO was used as opposed to the previous synthetic method employed due to the small amount of **192** available.



Scheme 44: *Reagents & conditions:* (i) *o*-Anisaldehyde, EtOH, 95 °C, 2 h, then NaBH₄, rt, 42 h; (ii) ethyl acrylate, 110 °C, 72 h; (iii) *m*-CPBA, CH₂Cl₂, rt, 3 h; (iv) KHMDS, THF, −78 °C, 30 mins, then **143**, Et₂O, −78 °C, 1 h.

2.16 Conclusion

In conclusion, the conjugate addition of *N*-benzyl-*N*-(α -methylbenzyl)hydroxylamine to β -nitrostyrene proceeds with moderate diastereoselectivities, but due to the inseparable nature of the diastereoisomers, it is not a synthetically useful transformation. Optimisations were attempted, and the selectivity was increased, though only to an 81:19 mixture. Modifications to the hydroxylamine scaffold were also explored although unfortunately none offered an improvement.

Bibliography

- [1] Enders, D.; Eichenauer, H. *Angew. Chem., Int. Ed.* **1976**, *15*, 549–551.
- [2] Enders, D.; Eichenauer, H.; Pieter, R. *Chemische Berichte* **1979**, *112*, 3703–3714.
- [3] Enders, D.; Wahl, H.; Bettray, W. *Angew. Chem., Int. Ed.* **1995**, *34*, 455–457.
- [4] Voigt, K.; Lansky, A.; Noltemeyer, M.; de Meijere, A. *Liebigs Ann. Chem* **1996**, 899–911.
- [5] *Ullmann's Encyclopedia of Industrial Chemicals*; VCH, 1989; Vol. A13.
- [6] Shen, Y.; Friestad, G. K. *J. Org. Chem.* **2002**, *67*, 6236–6239.
- [7] Hatt, H. H. *Org. Synth.* **1936**, *16*, 22.
- [8] Lin, L. S.; Liu, P. WO Patent 2006041797A2.
- [9] Lunn, G.; Sansone, E. B.; Keefer, L. K. *J. Org. Chem.* **1984**, *49*, 3470–3473.
- [10] Goettlich, R. *Synthesis* **2000**, 1561–1564.
- [11] Carpino, L. A. *J. Am. Chem. Soc.* **1960**, *82*, 3133–3135.
- [12] Davies, S. G.; Goodwin, C. J.; Hepworth, D.; Roberts, P. M.; Thomson, J. E. *J. Org. Chem.* **2010**, *75*, 1214–1227.
- [13] Juaristi, E.; Murer, P.; Seebach, D. *Synthesis* **1993**, 1243–1246.
- [14] Brosse, N.; Pinto, M. F.; Jamart-Gregoire, B. *J. Org. Chem.* **2000**, *65*, 4370–4374.
- [15] Adderley, N. J.; Buchanan, D. J.; Dixon, D. J.; Lainé, D. I. *Angew. Chem., Int. Ed.* **2003**, *42*, 4241–4244.
- [16] Hernandez-Juan, F. A.; Xiong, X.; Brewer, S. E.; Buchanan, D. J.; Dixon, D. J. *Synthesis* **2005**, 3283–3286.
- [17] Buchanan, D. J.; Dixon, D. J.; Looker, B. E. *Synlett* **2005**, *16*, 1948–1950.

- [18] Walters, I. A. S. DPhil Thesis, 1993.
- [19] Bordwell, F. G. pKa Table, <http://www.chem.wisc.edu/areas/reich/pkatable>.
- [20] Bagal, S. K.; Davies, S. G.; Lee, J. A.; Roberts, P. M.; Scott, P. M.; Thomson, J. E. *J. Org. Chem.* **2010**, *75*, 215.

Conjugate addition of a chiral hydroxylamine equivalent

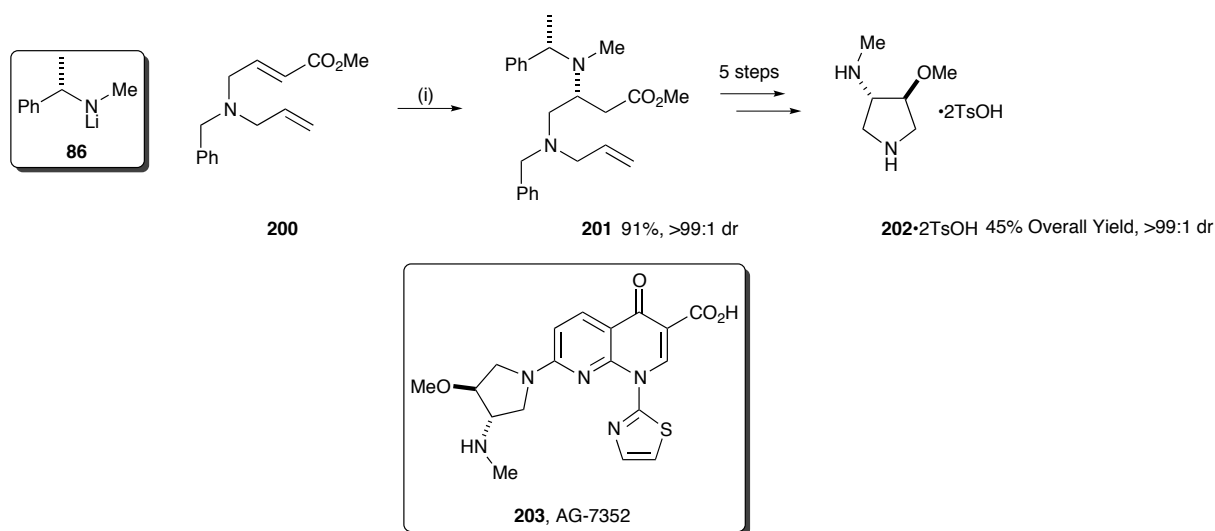
3.1 *N*-Functionalised lithium amides

As stated earlier, the lithium amide conjugate addition reaction is a very efficient method for the synthesis of β -amino acids and their derivatives, but there has been very little study into lithium amides with differing substitution other than the *N*-benzyl group, particularly those which provide some functionalisation.

3.2 *N*-Methyl-*N*-(α -methylbenzyl)amine

A few limited examples exist where the nitrogen substituent is retained in the final product, for example when an *N*-methyl group appears in the target molecule. Although the methyl group could be introduced at a later stage in the synthesis, once both the benzyl and α -methylbenzyl have been removed, in the interests of atom economy it would be more desirable for the *N*-methyl group to be present within the lithium amide reagent. *N*-

Methyl-*N*-(α -methylbenzyl)amide **86** has for example been utilised in the synthesis of *anti*-(3*S*,4*S*)-3-methoxy-4-(*N*-methylamino)pyrrolidine **202**. This is a fragment of a series of synthetic products, such as AG-7352 **203**, which have high *in vivo* and *in vitro* antibacterial activity against Gram positive and Gram negative bacteria, as well as showing potent cytotoxic activity against Murine P388 leukaemia cells.¹⁻³ The key step is the addition of *N*-methyl-*N*-(α -methylbenzyl)amide **86** to acceptor **200** giving β -amino ester **201** in 91% yield and >99:1 dr. Subsequent manipulation and deprotection affords the desired product **202** (isolated as the bis TsOH salt) in 45% overall yield and >99:1 dr (Scheme 45).⁴

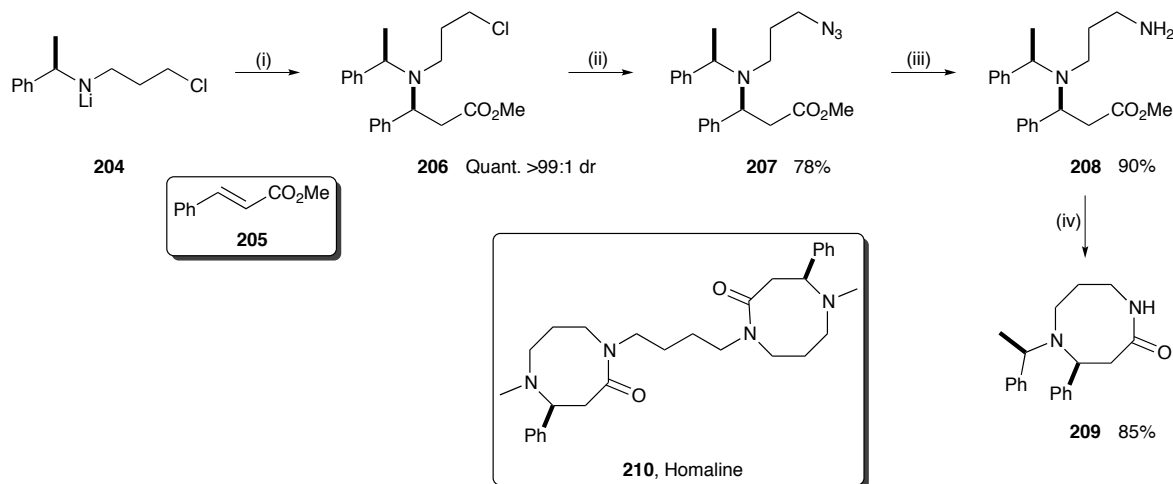


Scheme 45: Reagents & conditions; (i) BuLi, THF, -78°C , 30 mins, then **200**, THF, -78°C , 2 h.

3.3 *N*-(3'-Chloropropyl)-*N*-(α -methylbenzyl)amine

Another example of a lithium amide reagent that incorporates a permanent substituent is *N*-chloropropyl-*N*-(α -methylbenzyl)amide **204**. In this case, the lithium amide has a 3'-chloro substituent present which may be manipulated in the latter steps of the synthesis. For example the conjugate addition of **204** to **205** gives β -amino ester **206** in quantitative yield and >99:1 dr. The presence of the chloro substituent gives the option of many functional group interconversions, for example, displacement with azide provides latent amino functionality. Subsequent Staudinger reduction of **207** affords amine **208** in 90%

isolated yield, which on treatment with $\text{Sb}(\text{OEt})_3$ closes to form 8-membered lactam **209** in 85% isolated yield. This lactam provides a building block for the natural product homaline **210** (Scheme 46).⁵



Scheme 46: Reagents & conditions; (i) **205**, THF, $-78\text{ }^{\circ}\text{C}$ 2 h; (ii) NaN_3 , NaI, DMSO, $50\text{ }^{\circ}\text{C}$, 24 h; (iii) PPh_3 , THF, rt, 30 mins, then H_2O , $50\text{ }^{\circ}\text{C}$, 2 h; (iv) $\text{Sb}(\text{OEt})_3$, Toluene, Δ , 18 h.

3.4 *N*-Allyl-*N*- α -methylbenzylamine

Another alternative lithium amide that has been explored is lithium *N*-allyl-*N*-(α -methylbenzyl)amide (*S*)-**81**.⁶ When coupled with a double bond containing acceptor **211**, ring closing metathesis of the two alkenes within the resultant β -amino ester **212** is possible, giving rise to cyclic β -amino acids **214** after deprotection (Figure 12).

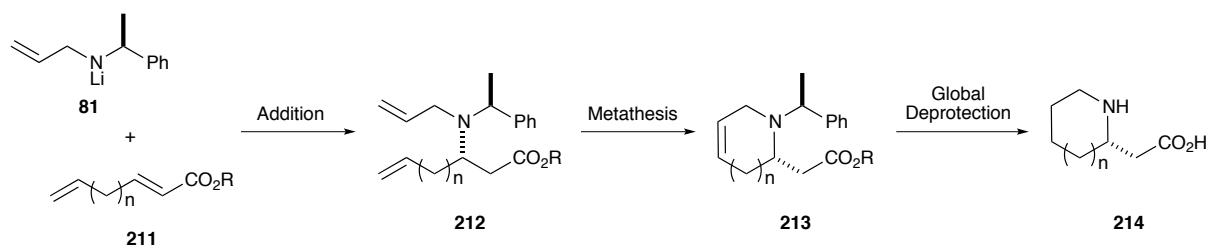
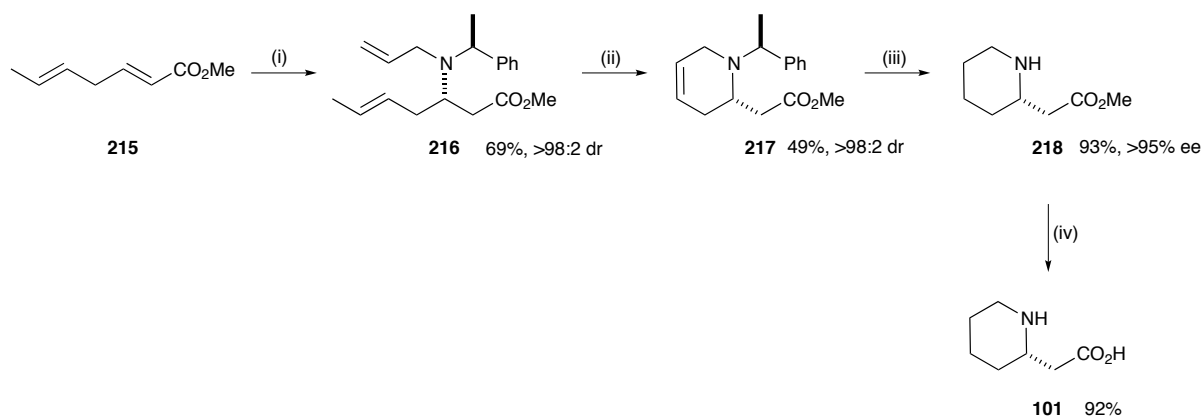


Figure 12: Synthesis of cyclic β -amino acids

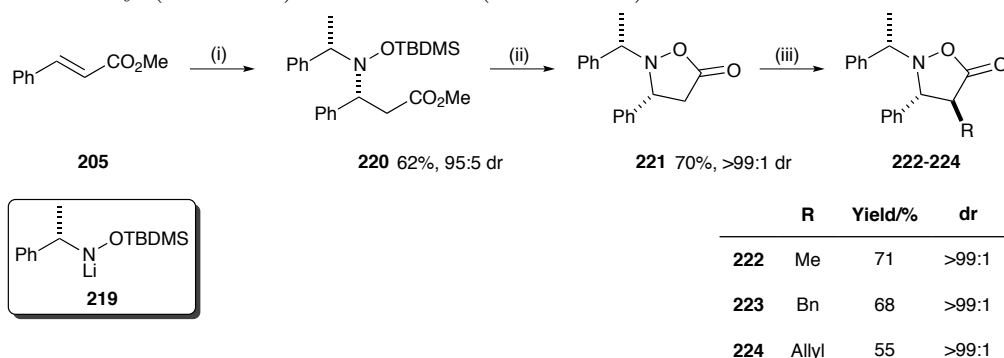
This methodology has been used in the synthesis of (*S*)-homopipicolinic acid **101** in 4 steps and 29% overall yield. The key step is the conjugate addition of lithium amide (*S*)-**81** to skipped diene **215**, creating the C(3)-stereocentre within **216** in >98:2 dr (Scheme 47).



Scheme 47: Reagents & conditions; (i) (*S*)-**81**, THF, $-78\text{ }^{\circ}\text{C}$; (ii) $\text{RuCl}_2(=\text{CHPh})(\text{PCy}_2)_2$, CH_2Cl_2 , Δ , 12 h; (iii) Pd/C, H_2 ; (iv) 2 M HCl, then DOWEX.

3.5 Conjugate addition of a silyl protected hydroxylamine and the asymmetric synthesis of 3-phenyl-4-alkyl-isoxazolidin-5-ones

Davies and Bentley⁷ demonstrated that the conjugate addition of lithium (*S*)-*N*-*tert*-butyldimethylsilyloxy-*N*-(α -methylbenzyl)amide **219** to methyl cinnamate **205** proceeds with high diastereoselectivity (95:5 dr) to give β -amino ester **220** in good isolated yield (62%). Subsequent *O*-silyl deprotection with TBAF promoted *in situ* cyclisation to give isoxazolidin-5-one **221** in 70% isolated yield and >99:1 dr. Alkylation of **221** upon treatment with LiHMDS then either methyl iodide, allyl iodide or benzyl bromide afforded a range of substituted isoxazolidin-5-ones **222-224** in good yields (55-71%) with excellent diastereoselectivity (>99:1 dr) in each case (Scheme 48).



Scheme 48: Reagents & Conditions: (i) (*S*)-**219**, THF, $-78\text{ }^{\circ}\text{C}$, 10 h; (ii) TBAF, THF, rt, 5 h; (iii) LiHMDS, THF, $-78\text{ }^{\circ}\text{C}$, 2 h, then alkyl halide, $-78\text{ }^{\circ}\text{C}$ -rt.

3.6 Chapter aim

It was proposed that this methodology could be extended to facilitate the preparation of a range of 4,4-disubstituted isoxazolidin-5-ones **229**, following sequential diastereoselective alkylation reactions of **227** and **228**, with global hydrogenolysis giving rise to $\beta^{2,2,3}$ -amino acids **230** (Figure 13).

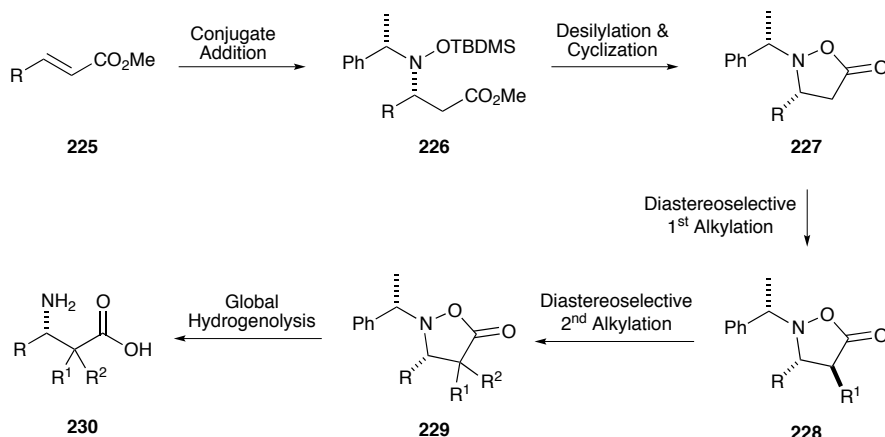


Figure 13: Chapter aim.

3.7 Isoxazolidinones

Less common than 1,3-oxazolidin-2-ones, yet nonetheless occupying an important niche in organic chemistry, 1,2-isoxazolidin-3-ones and 1,2-isoxazolidin-5-ones are popular synthetic targets due to their desirable biological activity⁸ as well as their utility as chiral building blocks, especially in the synthesis of β -amino acids.

3.8 Biological activity of isoxazolidinones

Due to the increasing bacterial resistance to traditional β -lactam based drugs such as the penicillins **231**, the search for suitable replacements is ongoing. Isoxazolidin-3-ones have been studied extensively in this respect, with analogues of β -lactam based drugs such as D-cycloserine **232** and lactavicin **233** showing high antibacterial activity (Figure 14).^{9,10}

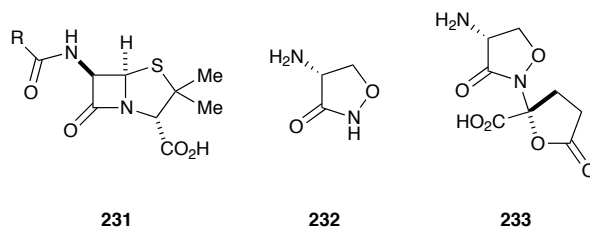


Figure 14: Structures of the penicillin core **231** and isoxazolidin-3-ones **232** and **233**.

As a result of the anti-bacterial activity of isoxazolidin-3-ones, the potential of isoxazolidin-5-ones as anti-bacterials has also been investigated. For instance Chmielewski *et al.* prepared a range of isoxazolidin-5-ones from readily available sugar starting materials, with **234**, **235** and **236** showing limited activity against *Escherichia coli* and *Staphylococcus aureus* (Figure 15).¹¹

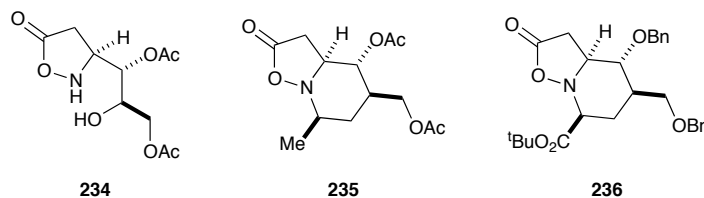


Figure 15: An array of anti-bacterials, **234-236**.

Day *et al.* have shown that appropriately substituted isoxazolidin-5-ones will act as β -lactam mimics and react with penicillin interactive proteins.¹² After screening a variety of differentially substituted isoxazolidin-5-ones, minimum inhibitory concentrationsⁱ obtained were in the same range as pharmaceutically useful β -lactams, e.g. 0.2 $\mu\text{g/mL}$ for **237** (Figure 16).

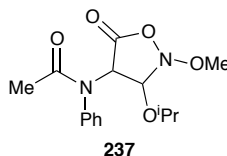


Figure 16: β -Lactam mimic **237**.

Janecki *et al.*⁸ synthesized a range of 4-methylenedisoxazolidin-5-ones, which they then proceeded to evaluate for *in vitro* cytostatic activity against L-1210 mouse leukaemia and

ⁱThis is the lowest concentration of an antimicrobial that will inhibit the visible growth of a microorganism after overnight incubation.

HL60 and NALM-6, human leukaemia, with **238** and **239** showing high levels of activity ($IC_{50} \leq 15 \mu M$) (Figure 17).

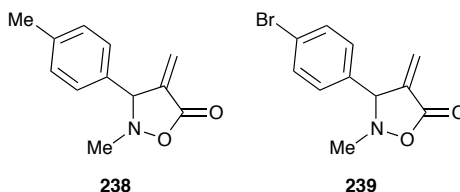
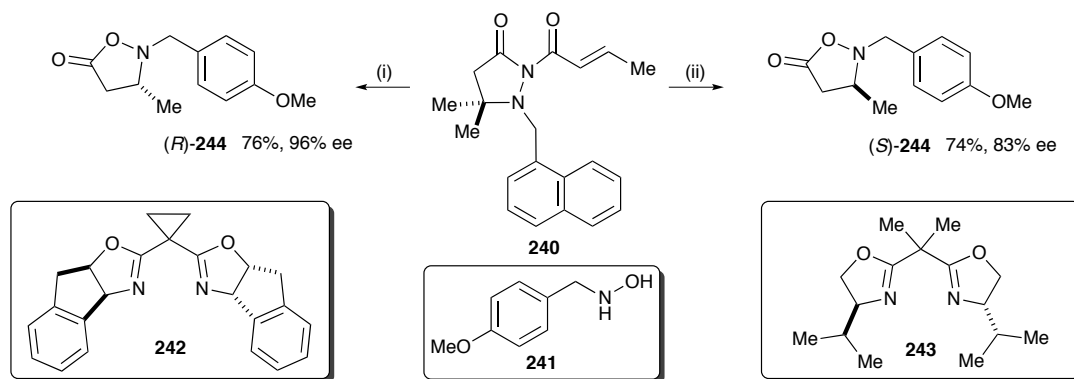


Figure 17: Two highly potent 4-methylideneisoxazolidin-5-ones **238** and **239**.

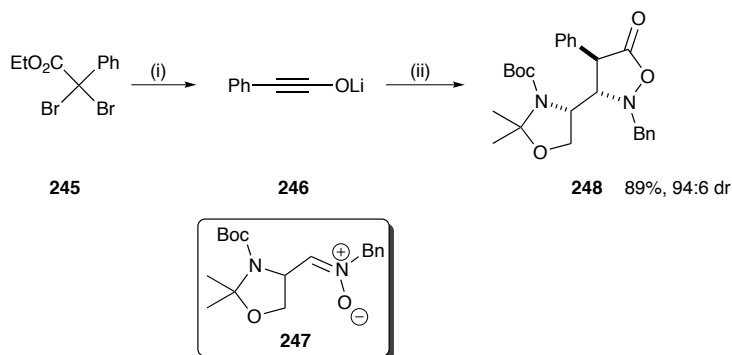
3.9 Syntheses of isoxazolidin-5-ones

Sibi and Liu have utilised the conjugate addition of *N*-(4-methoxybenzyl)hydroxylamine **241** to *N*(2)-enoyl pyrazolidinones in the presence of a chiral Lewis acid bisoxazoline (BOX) catalyst. This results in a highly stereoselective synthesis of isoxazolidin-5-ones.¹³ A simple change of Lewis acid allows access to either enantiomer of product, e.g. the treatment of **240** with BOX **242** and $Mg(ClO_4)_2$ in the presence of *N*-(4-methoxybenzyl)hydroxylamine **241** affords (*R*)-**244** in 76% yield and 96% ee, whilst the treatment of **240** with BOX **243** and $Zn(OTf)_2$ in the presence of hydroxylamine **241** affords (*S*)-**244** in 74% yield and 83% ee. The selectivities are justified *via* a ‘chiral relay’^{14,15} between the catalyst and the *N*(1)-naphthylmethyl substituent of the pyrazolidinone **240**, and although no transition state is proposed, the authors speculate that the switchover in selectivity arises from the different co-ordination geometries around the metal centre (Scheme 49).



Scheme 49: *Reagents & Conditions* (i) **242**, $Mg(ClO_4)_2$, CH_2Cl_2 , rt, 30 min, then **241**, $-25^\circ C$, 24 h; (ii) **243**, $Zn(OTf)_2$, CH_2Cl_2 , rt, 30 min, then **241**, $-25^\circ C$, 24 h.

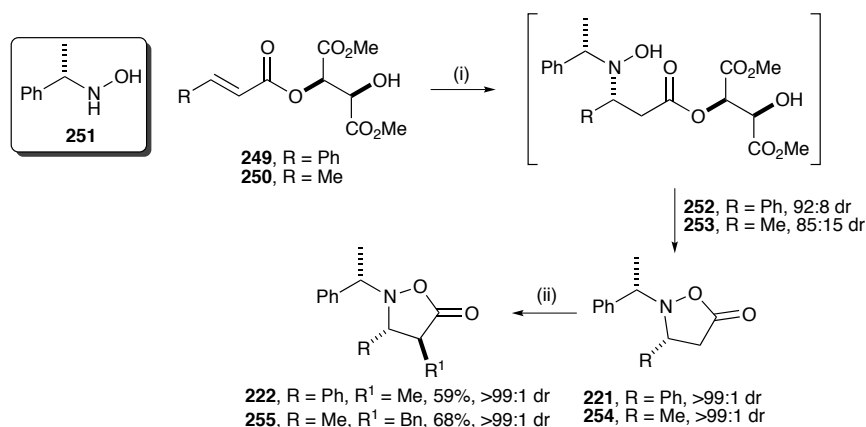
Shindo *et al.* have reported an anionic inverse electron-demand 1,3-dipolar cycloaddition of nitrones with ynolates in the synthesis of isoxazolidin-5-ones.¹⁶ For example, treatment of dibromide **245** with ^tBuLi forms ynolate **246** which on addition of nitrone **247** forms a isoxzolidin-5-one **248** in 89% yield and 94:6 dr (Scheme 50).



Scheme 50: *Reagents & Conditions* (i) ^tBuLi, THF, −78 °C, 3 h; (ii) THF, 0 °C, then **247**, 1 h, then NaHCO₃.

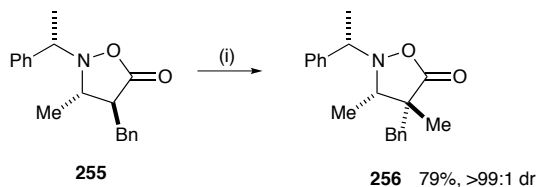
3.10 Synthesis *via* a doubly diastereoselective conjugate addition

Saito *et al.* prepared a range of isoxazolidin-5-ones using a doubly diastereoselective¹⁷ thermal addition of *N*-benzyl-*N*-(α -methylbenzyl)amine **251** to a range of enantiopure α,β -unsaturated esters derived from dimethyl L-tartrate.¹⁸ In particular the addition of **251** to cinnamyl ester **249** and crotonyl ester **250** followed by treatment of the intermediate β -amino esters **252** and **253** with LiHMDS affords isoxazolidin-5-ones **221** and **254** in 92:8 dr and 85:15 dr, respectively, with purification giving both compounds in >99:1 dr. Subsequent treatment of **221** (R = Ph) with LiHMDS then MeI gave isoxazolidin-5-one **222** in >99:1 dr and analogous treatment of **254** (R = Me) with LiHMDS then BnBr gave **255** in >99:1 dr. However these reactions were reported as not proceeding to conversion and the reported 59-68% yields “were corrected for recovered starting material”.¹⁸ The relative configurations within **222** and **255** were assigned on the assumption that the alkylation reactions of the intermediate enoates occur on the face *anti* to the C(3)-stereodirecting group in both cases (Scheme 51).



Scheme 51: *Reagents & Conditions* (i) **251**, PhMe, reflux; (ii) LiHMDS, THF, -65°C , 30 mins, then R¹X, THF, -65°C -rt, 6 h.

The preparation of a C(4)-disubstituted isoxazolidin-5-one was also investigated by Saito and co-workers with a second alkylation of **255**. Thus, treatment of **255** with LiHMDS then MeI gave the product **256** as a single diastereoisomer in 79% yield. The configuration at the newly formed quaternary stereogenic centre within **256** was once again assigned on the assumption that the alkylation reaction occurs on the face *anti* to the C(3)-stereodirecting group (Scheme 52).

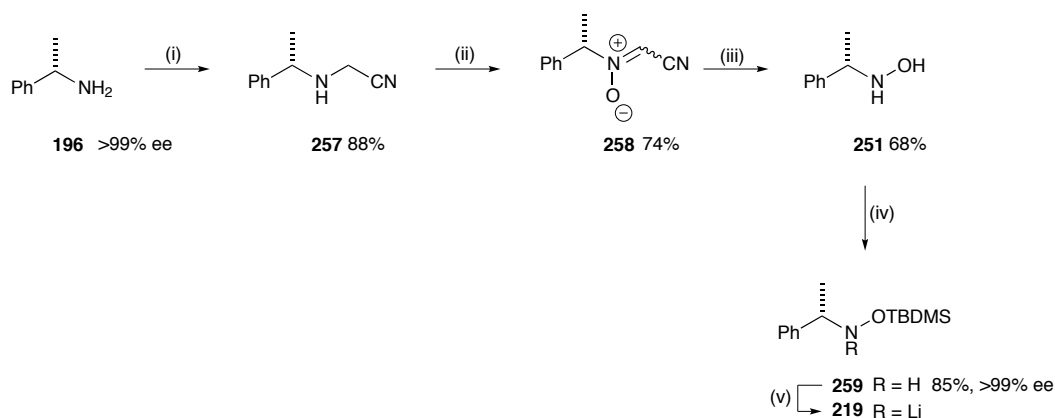


Scheme 52: *Reagents & Conditions* (i) LiHMDS, then MeI.

3.11 Synthesis of the hydroxylamine

O-Silyl protected hydroxylamine **259** was prepared from (*S*)- α -methylbenzylamine **196** in four steps following literature procedures.^{19,20} Alkylation of **196** with bromoacetonitrile gave **257**, which was oxidised with *m*CPBA to give nitron **258**. Hydroxylaminolysis of **258** afforded (*S*)-*N*-(α -methylbenzyl)hydroxylamine **251** in 44% overall yield. Treatment of **251** with TBDMSCl furnished **259** in 85% yield and >99% eeⁱⁱ (Scheme 53).

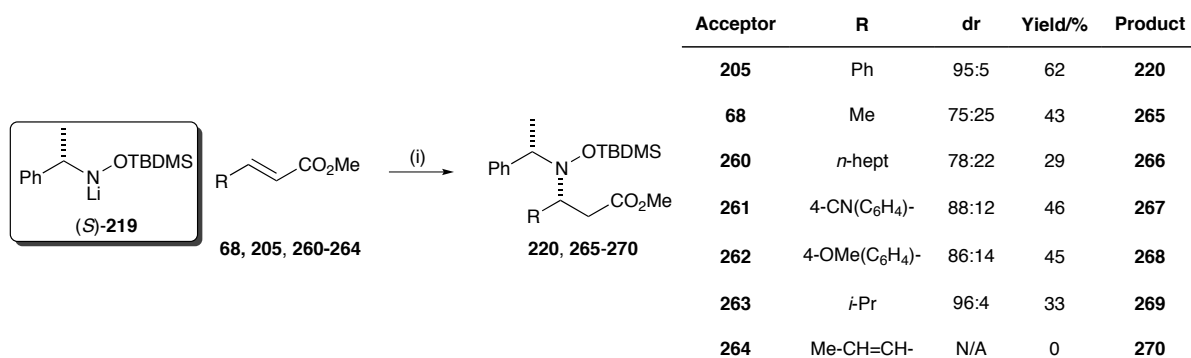
ⁱⁱThe enantiomeric excess of **259** was determined by H NMR spectroscopic analysis in the presence of (*S*)-*O*-acetylmandelic acid as a chiral shift reagent, and comparison with an authentic racemic sample.



Scheme 53: *Reagents & Conditions* (i) BrCH₂CN, iPr₂NEt, MeCN, rt, 16 h; (ii) mCPBA, CH₂Cl₂, 0 °C, 45 min, then rt, 15 min; (iii) NH₂OH, MeOH, 60 °C, 2 h; (iv) TBDMSCl, imidazole, DMF, rt, 16 h; (v) BuLi, THF, -78 °C, 30 min.

3.12 Conjugate additions

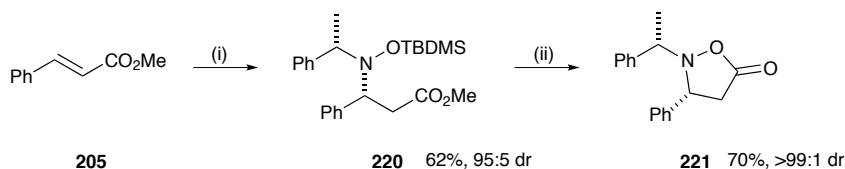
The conjugate addition of lithium amide (*S*)-**219** to a range of α,β -unsaturated esters **68**, **205**, **260-264** was initially investigated under the previously optimised conditions.⁷ Addition to C(3)-*iso*-propyl substituted α,β -unsaturated ester **262** proceeded with 96:4 dr, and to 4-cyano substituted cinnamate **261** and 4-methoxy substituted cinnamate **262** with 88:12 dr and 86:14 dr respectively. The two linear alkyl chain α,β -unsaturated esters **68** and **260** both displayed lower diastereoselectivity with 75:25 and 78:22 dr respectively. The addition to methyl sorbate **264** unfortunately yielded none of the desired product **270** and only returned starting material. Although the crude mass return from the reactions were good, isolated yields were in the range of 29-62% due to instability of the β -amino ester products **220**, **265-269** towards column chromatography which resulted in partial decomposition to a complex mixture of unidentifiable products (Scheme 54). The diastereoselectivity from the addition of lithium *N*-benzyl-*N*-(α -methylbenzyl)amide is >95:5 dr for all the α,β -unsaturated esters screened here, so the lower diastereoselectivity and reactivity of **219** was somewhat unexpected.



Scheme 54: *Reagents & Conditions:* (i) (*S*)-**219**, THF, -78°C , 30 mins, then **68**, **205**, **260-264**, -78°C , 10 h.

3.13 Deprotection studies

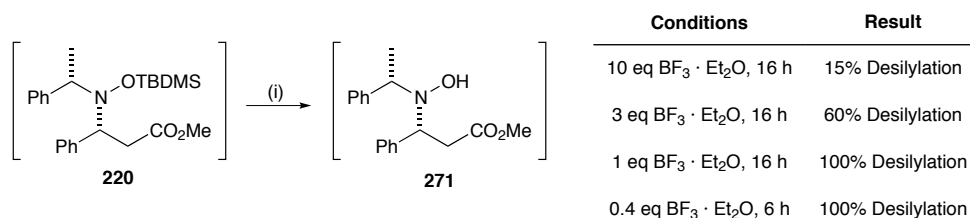
In order to circumvent the mass loss encountered on purification of β -amino esters **220**, **265-269**, it was envisaged that *O*-silyl deprotection of the crude reaction mixture followed by cyclisation and purification of the resultant isoxazolidin-5-one may represent a more efficacious procedure. Although TBAF was an effective desilylating agent in the case of **220**, it was only efficacious when a purified β -amino ester was employed as a substrate, affording phenyl substituted isoxazolidin-5-one **221** in 70% yield (Scheme 55).



Scheme 55: *Reagents & Conditions:* (i) (*S*)-**219**, THF, -78°C , 10 h; (ii) TBAF, THF, rt, 5 h.

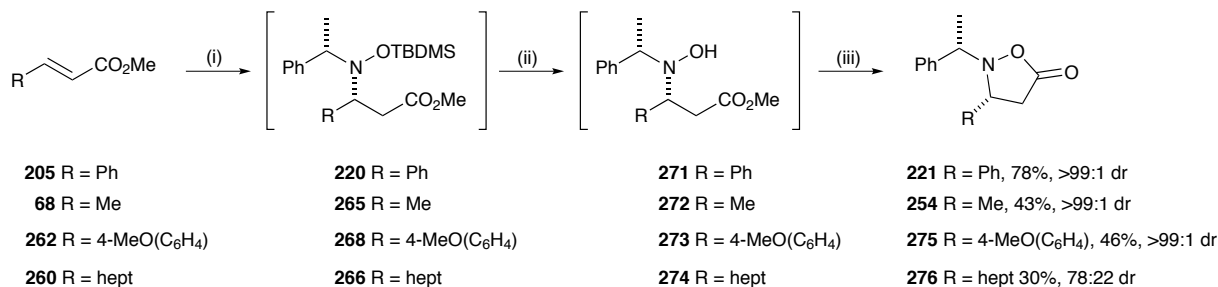
A wide variety of conditions were screened using the crude reaction mixture of **220** (95:5 dr), including treatment with TBAF/AcOH²¹ and TMSOTf²² (which both resulted in a complex mixture of products), and treatment with LiCl/H₂O/DMF²³, and PPTS/EtOH²⁴ (both of which returned starting material). BF₃ · OEt₂²⁵ was also tested as a desilylating agent and upon treatment of crude β -amino ester **220** with 3 equiv of BF₃ · Et₂O, 60% desilylation to give hydroxylamine **271** was observed within 16 h. On increasing this to 10 equiv, an unexpected decrease in reaction conversion was noted and only 15% desilylation

to **271** was observed. Repetition of the reaction with 1 eq of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ gave complete desilylation within 16 h. It was subsequently found that the $\text{BF}_3 \cdot \text{Et}_2\text{O}$ stoichiometry could be dropped to 0.4 equiv, consistent with all three fluorine atoms being active as desilylating agents (Scheme 56).^{26,27}



Scheme 56: *Reagents & Conditions:* (i) See table.

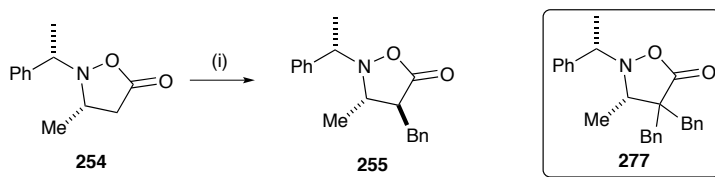
Although this worked reliably with 0.1 mmol of **220**, attempted scale up unfortunately gave capricious results. A large scale alternative procedure was thus required, and desilylation of **220** with hydrogen fluoride-pyridine complex was attempted.²⁸ Treatment of **220** with $\text{HF} \cdot \text{py}$ at 0 °C for 20 min provided 100% conversion to β -amino ester **271**. Subsequent cyclisation of **271** to furnish isoxazolidin-5-one **221** was accomplished by direct treatment of the crude reaction mixture with LiHMDS ,²⁹ giving **221** in 78% yield over 3-steps, and >99:1 dr, after column chromatography. This procedure was applied to α,β -unsaturated esters **68** and **262** giving isoxazolidinones **254** and **275** in 45% and 46% yield respectively, and both in >99:1 dr over 3 steps, whilst reaction of **260** gave isoxazolidin-5-one **276** in 78:22 dr and 30% isolated yield (Scheme 57).



Scheme 57: *Reagents & Conditions:* (i) (*S*)-**219**, −78 °C, 10 h; (ii) $\text{HF} \cdot \text{py}$, THF, 0 °C, 20 min; (iii) LiHMDS , THF, −78 °C, 30 min.

3.14 Mono-alkylations

Studies were next directed towards the investigation of the alkylation reactions of isoxazolidin-5-ones **221** and **254**. Ishikawa *et al.* have previously shown that treatment of diastereoisomerically pure isoxazolidin-5-one **254** with 1.1 equiv of LiHMDS followed by MeI affords exclusively the *anti*-product **255**.¹⁸ Application of this protocol to benzylation of **254** gave predominantly the desired *anti*-product **255**, but was accompanied by the formation of 10% of the dialkylated product **277**, which presumably arises through deprotonation of the product isoxazolidin-5-one by the excess base followed by further alkylation. In order to suppress this side reaction, use of the hindered base LiTMP was investigated. Under these conditions, exclusive mono-benylation of **254** was observed giving **255** as a single diastereoisomer (>99:1 dr) and in 75% isolated yield (Scheme 58).



Scheme 58: *Reagents & Conditions:* (i) LiTMP, THF, -78°C , 30 mins, then BnBr, -78°C - 0°C , 12 h.

The relative configuration within **255** was unambiguously established *via* single crystal X-ray analysis, with the absolute (3*S*,4*S*, α *S*)-configuration being assigned from the known (*S*)-stereocentre of the α -methylbenzyl fragment (Figure 18). This stereochemical outcome is consistent with the alkylation proceeding on the face of the enolate opposite to the C(3)-stereodirecting group.

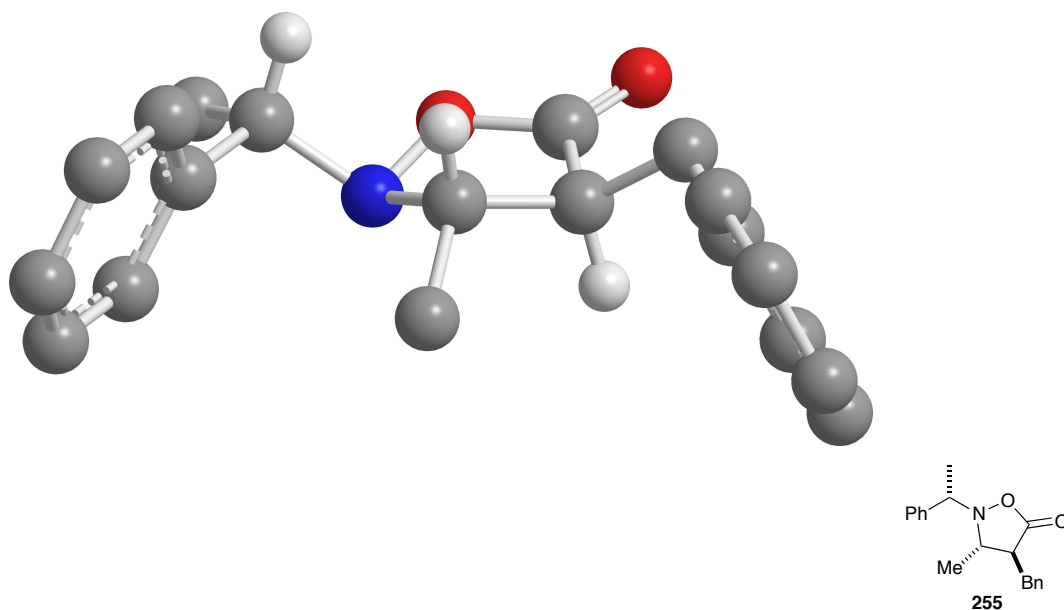
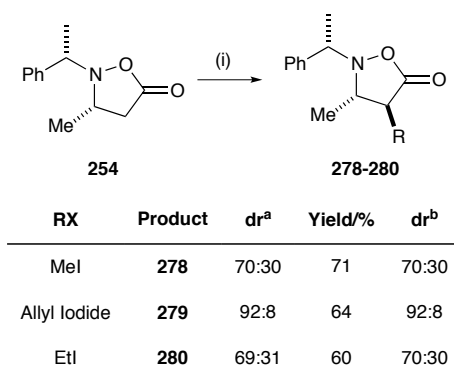


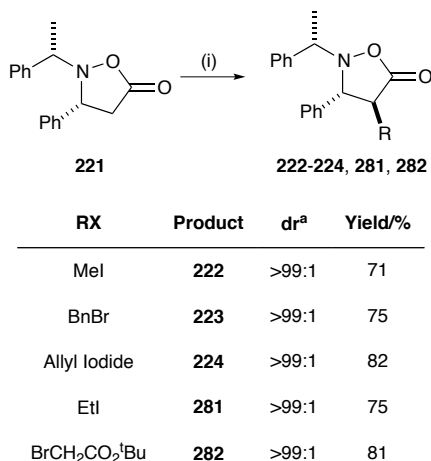
Figure 18: Single crystal X-ray structure of **255**.

Under these optimised conditions isoxazolidin-5-one **254** was alkylated with a range of electrophiles (viz. MeI, allyl iodide and EtI) giving the corresponding C(4)-substituted isoxazolidin-5-ones **278-280** in modest to good diastereoselectivities. Purification *via* flash column chromatography gave **278-280** in good isolated yield. The lower selectivity in the alkylation reactions employing MeI and EtI can be attributed to the smaller size of the incoming electrophiles, coupled with the low steric bulk of the stereodirecting C(3)-methyl group (Scheme 59).



Scheme 59: *Reagents & Conditions:* (i) LiTMP, THF, -78°C , 2 h, then RX, -78°C - 0°C , 16 h; [^acrude, ^bpurified]

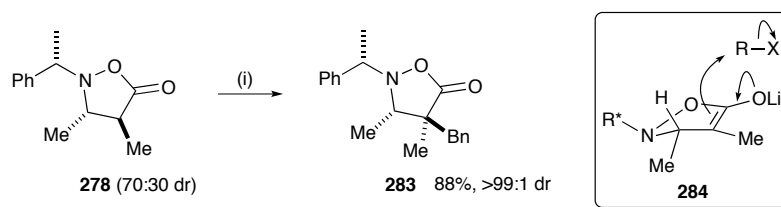
A further series of alkylations (using MeI, BnBr, allyl iodide, EtI and *tert*-butyl bromoacetate) were then applied to isoxazolidin-5-one **221**, bearing a much larger C(3)-phenyl stereodirecting group, which gave alkylated products **222-224**, **281**, **282** in excellent diastereoselectivities (>99:1 dr) and good yields (Scheme 60).⁷



Scheme 60: *Reagents & Conditions:* (i) LiTMP, THF, −78°C, 2 h, then RX, −78 °C-0 °C, 16 h; [^acrude]

3.15 Preparation of C(3)-alkyl-C(4)-dialkyl isoxazolidin-5-ones from C(4)-methyl isoxazolidin-5-ones

Next, the preparation of C(4)-dialkyl isoxazolidin-5-ones *via* alkylation of C(4)-monoalkyl species **222** and **278** was investigated. It was decided to switch the base to LiHMDS as there was now no possibility of overalkylation. Treatment of 3,4-dimethyl isoxazolidin-5-one **278** (70:30 dr) with LiHMDS followed by benzyl bromide gave **283** in >99:1 dr and 88% isolated yield after chromatography. The presence of only one diastereoisomer is consistent with the alkylation being a stereoselective and not stereospecific process, which is to be expected from a reaction proceeding *via* the intermediate enolate **284**, in which the stereocentre at C(4) has been destroyed (Scheme 61).



Scheme 61: Reagents & Conditions: (i) LiHMDS, THF, $-78\text{ }^{\circ}\text{C}$, 2 h, then benzyl bromide, $-78\text{ }^{\circ}\text{C}$ – $0\text{ }^{\circ}\text{C}$, 16 h.

The relative configuration within **283** was unambiguously established by single crystal X-ray analysis, with the absolute (3*S*,4*S*, α *S*)-configuration being assigned from the known (*S*)-stereocentre of the α -methylbenzyl fragment (Figure 19). This stereochemical outcome is also consistent with alkylation of the intermediate enolate **284** proceeding on the face *anti* to the C(3)-stereodirecting group.

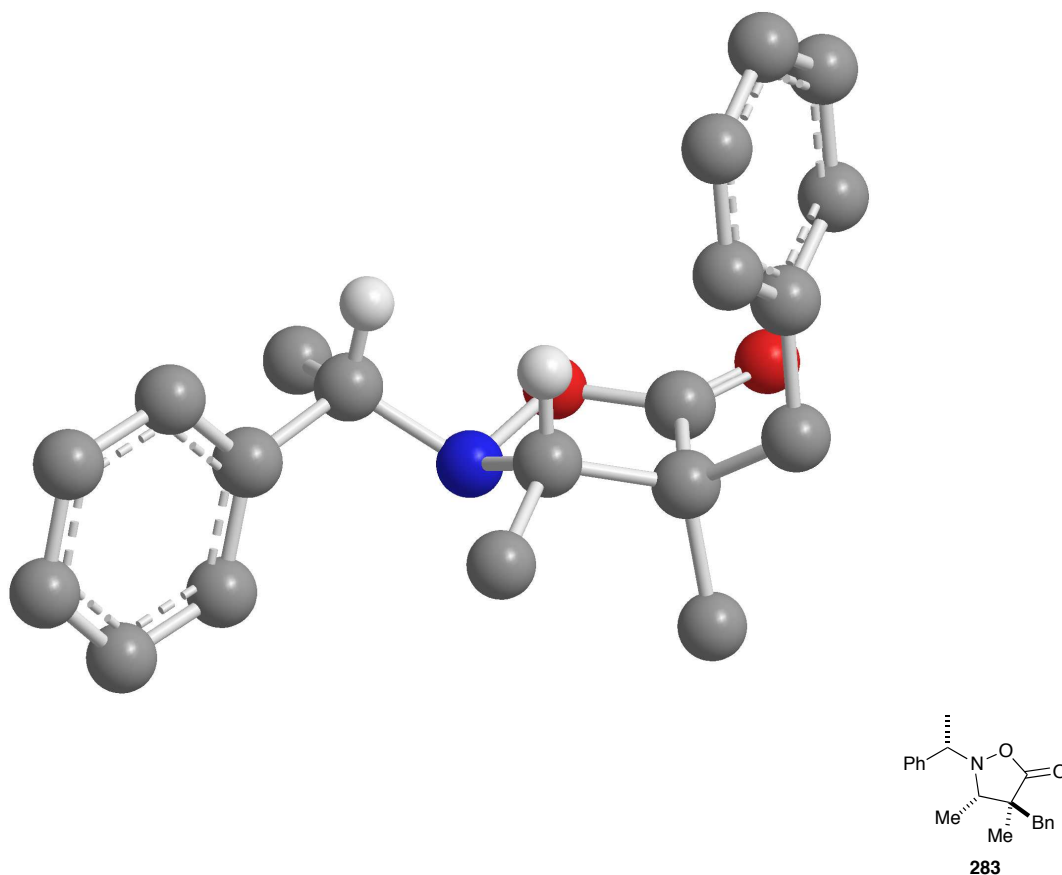
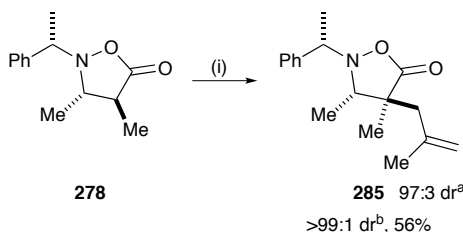


Figure 19: Single crystal X-ray structure of **283**.

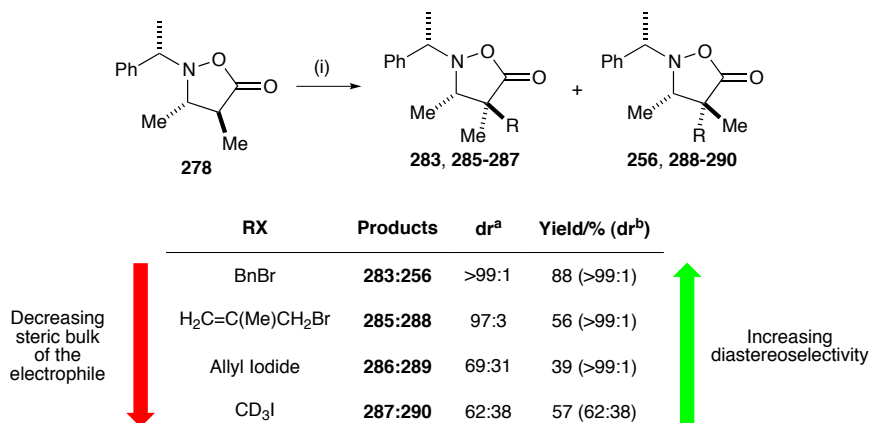
The generality of this protocol was explored and on treatment of isoxazolidin-5-one **278** with LiHMDS, followed by $\text{H}_2\text{C}=\text{C}(\text{Me})\text{CH}_2\text{Br}$, dialkylated isoxazolidin-5-one **285** was af-

forded, albeit in slightly lower diastereoselectivity (97:3 dr). Once again the major diastereoisomer, as determined by nOe analysis, was consistent with that of the electrophile attacking *anti* to the C(3)-methyl group. Separation of the diastereoisomers by flash column chromatography was possible, giving **285** in >99:1 dr and 56% yield (Scheme 62).



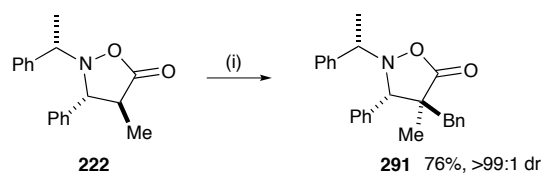
Scheme 62: *Reagents & Conditions:* (i) LiHMDS, THF, -78°C , 2 h, then $\text{H}_2\text{C}=\text{C}(\text{Me})\text{CH}_2\text{Br}$, -78°C - 0°C , 16 h; [^acrude; ^bisolated yield of major diastereoisomer.]

Furthermore, treatment of isoxazolidin-5-one **278** with LiHMDS followed by either allyl iodide or CD_3I afforded **286** and **287** as the major products in 69:31 dr and 62:38 dr respectively. These data were consistent with previous results in that the less sterically demanding the incoming electrophile, the lower the diastereoselectivity of the alkylation reaction (Scheme 63).



Scheme 63: *Reagents & Conditions:* (i) LiHMDS, THF, -78°C , 30 mins, then RX, -78°C - 0°C , 16 h; [^acrude; ^bisolated yield of major diastereoisomer.]

Alkylation of 3-phenyl-4-methyl-isoxazolidin-5-one **222**, bearing a larger C(3)-phenyl stereodirecting group was next investigated. Treatment of **222** with LiHMDS followed by BnBr gave a single diastereoisomer **291**, which was isolated in 76% yield after column chromatography (Scheme 64).



Scheme 64: *Reagents & Conditions:* (i) LiHMDS, THF, -78°C , 2 h, then benzyl bromide, -78°C - 0°C , 16 h.

The relative configuration within **291** was unambiguously established by single crystal X-ray analysis, with the absolute (3*S*,4*S*, α *S*)-configuration being assigned from the known (*S*)-stereocentre of the α -methylbenzyl fragment (Figure 20).

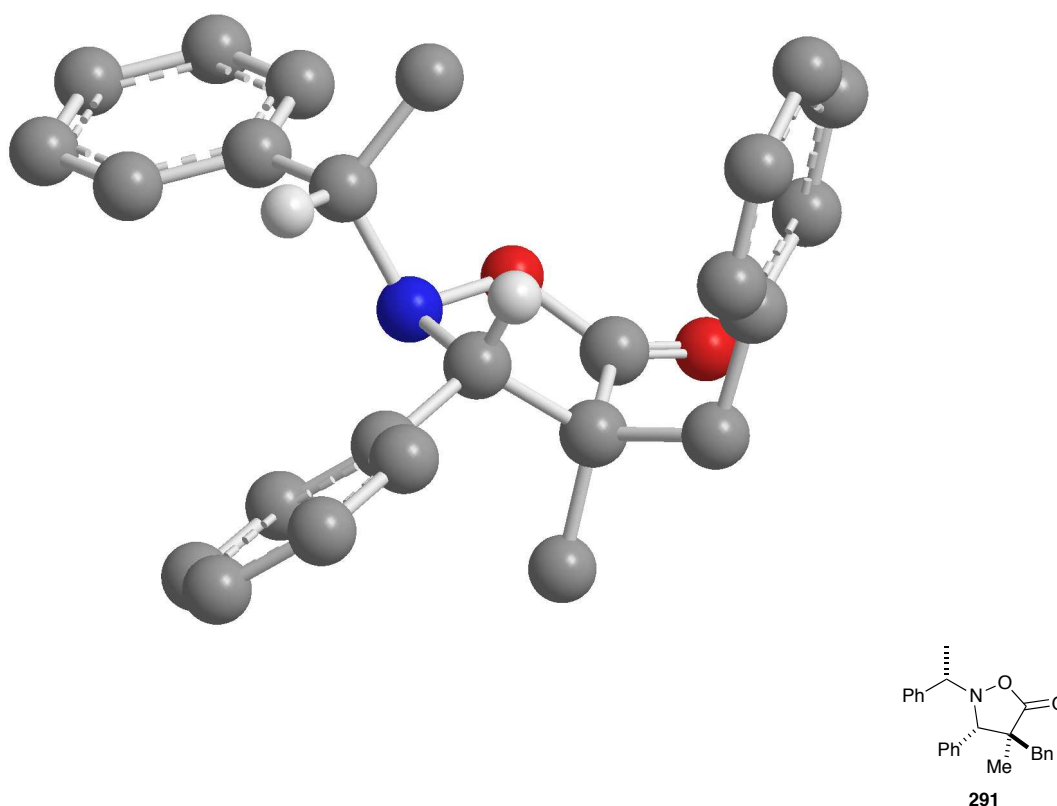
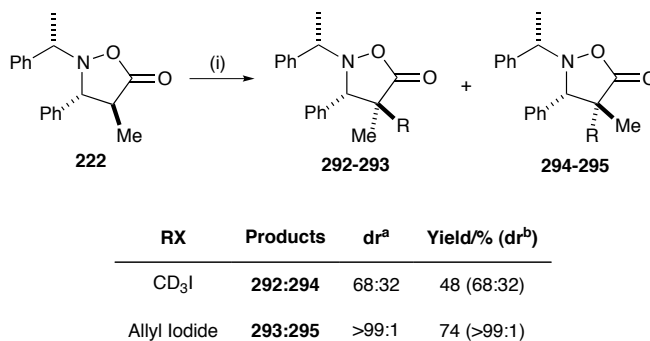


Figure 20: Single crystal X-ray structure of **291**.

Once again this result is consistent with the alkylation reaction occurring *anti* to the C(3)-stereodirecting group. Alkylation of **222** proceeded with excellent levels of diastereoselectivity, furnishing 3-phenyl-4-allyl-4-methyl-isoxazolidin-5-one **293** as a single diastereoisomer which was isolated in 74% yield; the configuration within **293** was determined by nOe analysis. Meanwhile, alkylation of **222** with LiHMDS followed by the sterically small

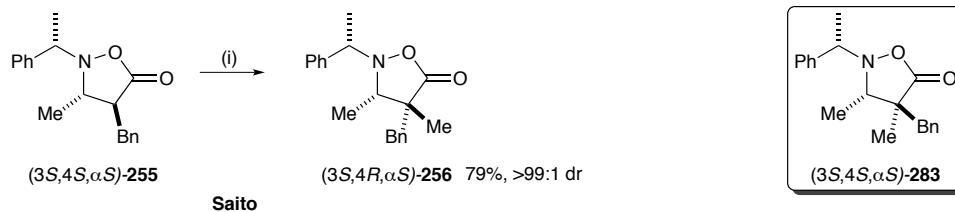
CD₃I gave a 68:32 mixture of the diastereoisomeric isoxazolidin-5-ones **292** and **294**, respectively, which were inseparable by chromatography. The configurations within **292** and **294** were tentatively assigned by analogy to that unambiguously proven for **291** (Scheme 65).



Scheme 65: *Reagents & Conditions:* (i) LiHMDS, THF, −78 °C, 30 mins, then RX, −78 °C–0 °C, 16 h; [^acrude; ^bisolated yield of major diastereoisomer.]

3.16 Preparation of C(3)-alkyl-C(4)-dialkyl isoxazolidin-5-ones from C(4)-benzyl isoxazolidin-5-ones

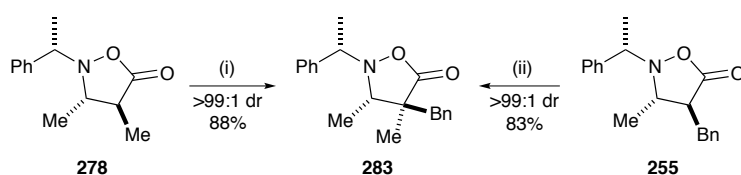
Saito et al. have previously reported that alkylation of the lithium anion of isoxazolidin-5-one **255** with MeI gives (3*S*,4*R*,α*S*)-**256** exclusively (Scheme 66).¹⁸



Scheme 66: *Reagents & Conditions* (i) LiHMDS, then MeI.

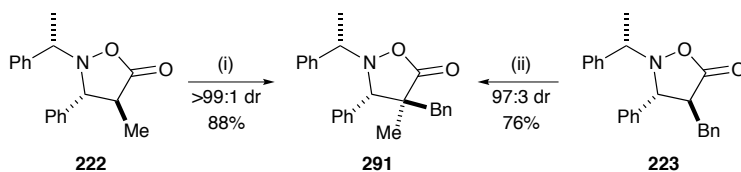
However, the data reported for (3*S*,4*R*,α*S*)-**256** matches those reported in this thesis for (3*S*,4*S*,α*S*)-**283**, suggesting that the stereochemical assignment of *Saito et al.* is in error. Furthermore, these observations imply that the diastereofacial selectivity of alkylation of the C(4)-benzyl substituted isoxazolidin-5-one **255** may not be ascribed simply to preferential reaction of the intermediate enolate on the face *anti* to the C(3)-stereodirecting group.

In order to investigate this apparent discrepancy, the alkylations of 4-benzyl-isoxazolidin-5-ones **255** and **223** were examined. Methylation of 3-methyl-4-benzyl-isoxazolidin-5-one **255** gave **283** in >99:1 dr, i.e. the same major diastereoisomeric product as benzylation of 3-methyl-4-methyl-isoxazolidin-5-one **278**. In the former reaction, methylation of **255** occurs preferentially *syn* to the C(3)-methyl group, whereas in the latter reaction benzylation of **278** occurs preferentially on the face *anti* to the C(3)-methyl group. Since the absolute configuration with **283** had been proved unambiguously by single crystal X-ray analysis these results confirm the misassignment of the configuration by Saito *et al.* (Scheme 67).



Scheme 67: *Reagents & Conditions:* (i) LiHMDS, THF, -78°C , 30 mins, then BnBr, $-78^\circ\text{C-}0^\circ\text{C}$, 16 h; (ii) LiHMDS, THF, -78°C , 30 mins, then MeI, $-78^\circ\text{C-}0^\circ\text{C}$, 16 h.

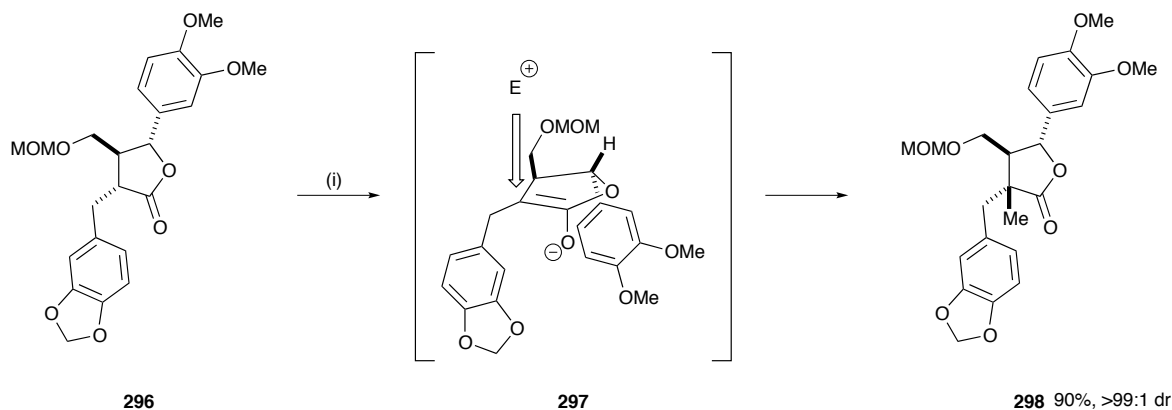
Treatment of the analogous 3-phenyl, 4-benzyl isoxazolidin-5-one **223** under the same conditions again placed the incoming methyl group *syn* to the C(3)-stereodirecting group with 97:3 dr; i.e. the same product as obtained with the benzylation of the 3-phenyl, 4-methyl isoxazolidin-5-one **222** (Scheme 68).



Scheme 68: *Reagents & Conditions:* (i) LiHMDS, THF, -78°C , 30 mins, then BnBr, $-78^\circ\text{C-}0^\circ\text{C}$, 16 h; (ii) LiHMDS, THF, -78°C , 30 mins, then MeI, $-78^\circ\text{C-}0^\circ\text{C}$, 16 h.

A similar phenomenon has been noted during the alkylation reactions of some lactone enolates.³⁰ It would be expected that alkylation of lactone **296** would place the incoming electrophile (MeI) on the bottom face to avoid the tethered MOM group. In fact treatment of **296** with KHMDS and MeI places the methyl group on the top face, proceeding *via* enolate **297**. This can be explained in terms of a ‘chiral relay’ effect^{14,15} in which the MOM

ether within **297** is situated above the top face, which forces the substituted benzyl group down, covering the bottom face. The electrophile thus preferentially attacks from the top face affording **298** as a single diastereoisomer (>99:1 dr) and in 90% yield (Scheme 69).



Scheme 69: Reagents & Conditions (i) KHMDS, THF, $-78\text{ }^{\circ}\text{C}$, then MeI.

In the isoxazolidinone case, it may be expected that the lithium enolates derived from isoxazolidin-5-ones **255** and **223** adopt an envelope conformation with both the C(3)-substituents and the *N*- α -methylbenzyl group occupying pseudo-equatorial sites. Minimization of $A^{1,3}$ strain places one of the C(4)-benzylic hydrogen atoms *syn*-pentane to the enolate oxygen atom. The phenyl ring may then occupy one of two possible sites, with conformation **A** being expected to be favoured over conformation **B** due to minimization of steric repulsions between the C(3)- and C(4)-substituents. During alkylation of the lithium enolate derived from C(3)-methyl substituted **255**, the steric bulk of the phenyl ring of the C(4)-benzyl group is clearly dominant over that of the C(3)-methyl group, and therefore alkylation occurs preferentially through conformation **A**, on the face *syn* to the pseudo-equatorial C(3)-methyl group. In the case of alkylation of the lithium enolate derived from C(3)-phenyl substituted **223**, the steric bulk of the phenyl ring of the C(4)-benzyl group dominates over that of the C(3)-phenyl group, potentially due to the location of the latter in a pseudo-equatorial position somewhat remote from the site of alkylation. Enolate alkylation then occurs preferentially through conformation **A** on the face *syn* to the C(3)-phenyl group. In the case of alkylation of the C(4)-methyl substituted isoxazolidin-5-ones

278 and **222**, the methyl group is unable to protrude over either face of the enolate and therefore the reaction diastereoselectivity is controlled only by the relative steric bulk of the C(3)-substituent (*vide supra*). In both the C(4)-benzyl cases it could be predicted that as the steric demand of the incoming electrophile increases the diastereoselectivity of the reaction would decrease. This would be due to the transition state more closely resembling that of conformation **B** than of conformation **A**, with the larger electrophiles avoiding steric interactions with both the C(3)- and C(4)-substituents. If this is the case then a more pronounced selectivity drop would be expected when the C(3)-substituent is phenyl (Figure 21).

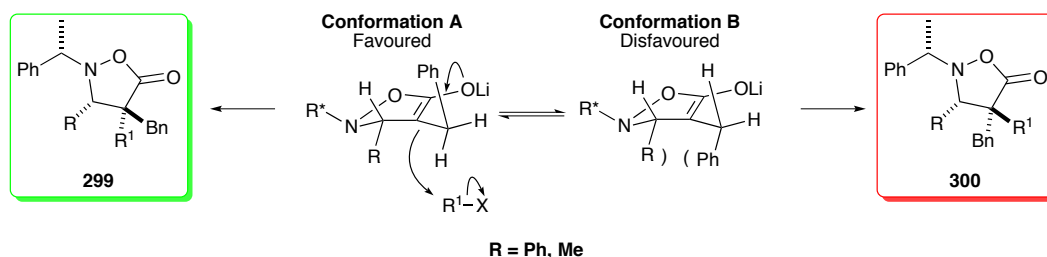
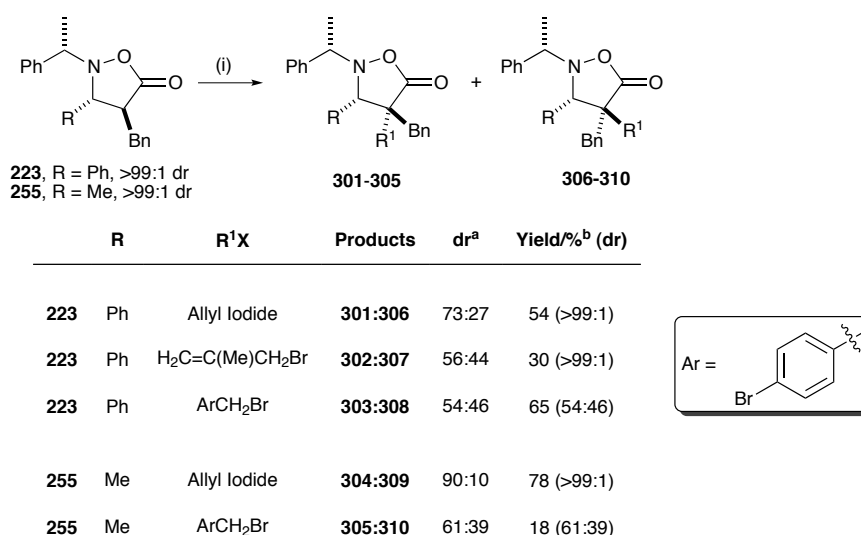


Figure 21: Chiral relay effects in the alkylation of **223** and **255**.

A further series of alkylation reactions applied to both **223** and **255** gave the dialkylated products **301-310**, thus establishing that with increasing steric demand of the electrophile, the diastereoselectivity of the alkylation reaction decreased, and as predicted the drop-off in selectivity is more pronounced with the C(3)-phenyl isoxazolidin-5-one **223** (Scheme 70).



Scheme 70: *Reagents & Conditions:* (i) LiHMDS, THF, $-78\text{ }^{\circ}\text{C}$, 30 mins, then RX, $-78\text{ }^{\circ}\text{C}$ - $0\text{ }^{\circ}\text{C}$, 16 h; [^acrude; ^bisolated yield of major diastereoisomer.]

The relative configuration within **301** was unambiguously established *via* single crystal X-ray analysis, with the absolute (3*S*,4*S*, α *S*)-configuration being assigned from the known (*S*)-stereocentre of the α -methylbenzyl fragment, confirming that the alkylation reaction occurs preferentially on the face *syn* to the C(4)-phenyl group (Figure 22). The stereochemical outcomes resulting from the remaining alkylation reactions were assigned *via* ¹H NMR nOe analyses.

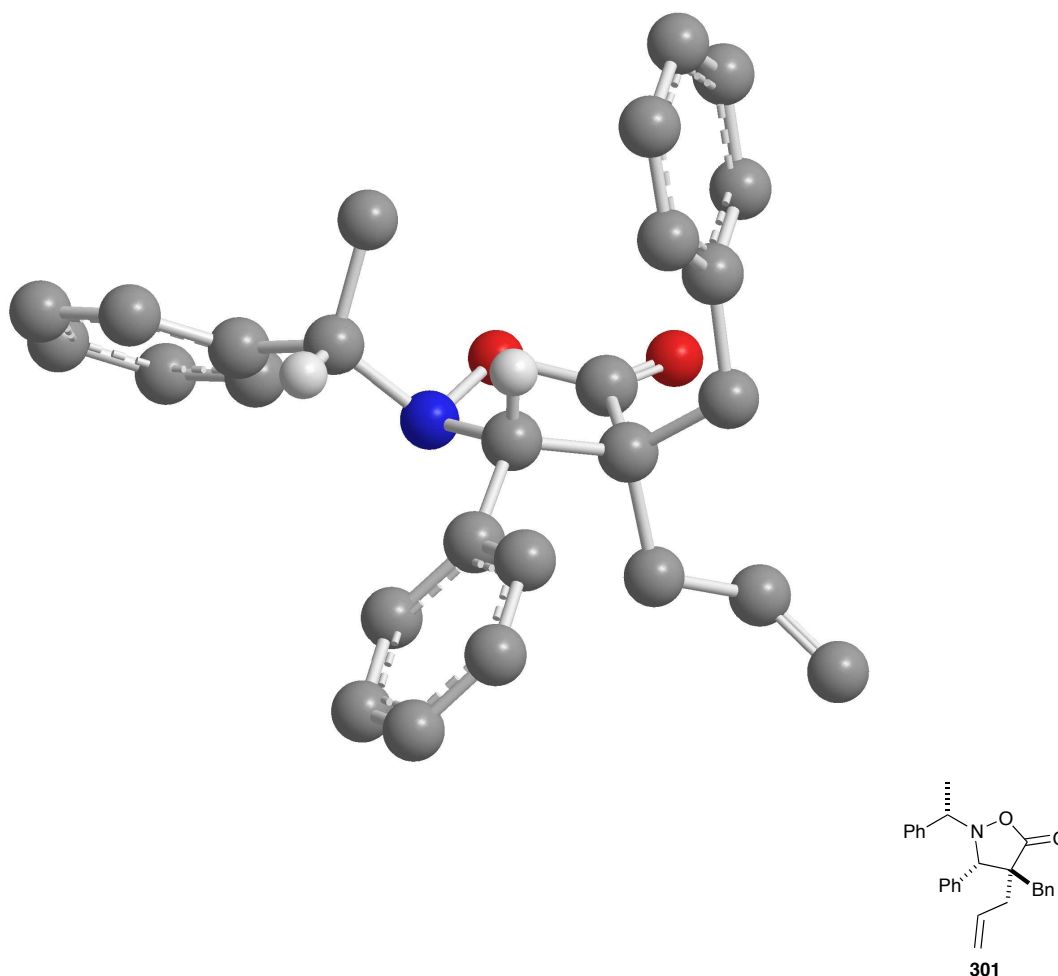
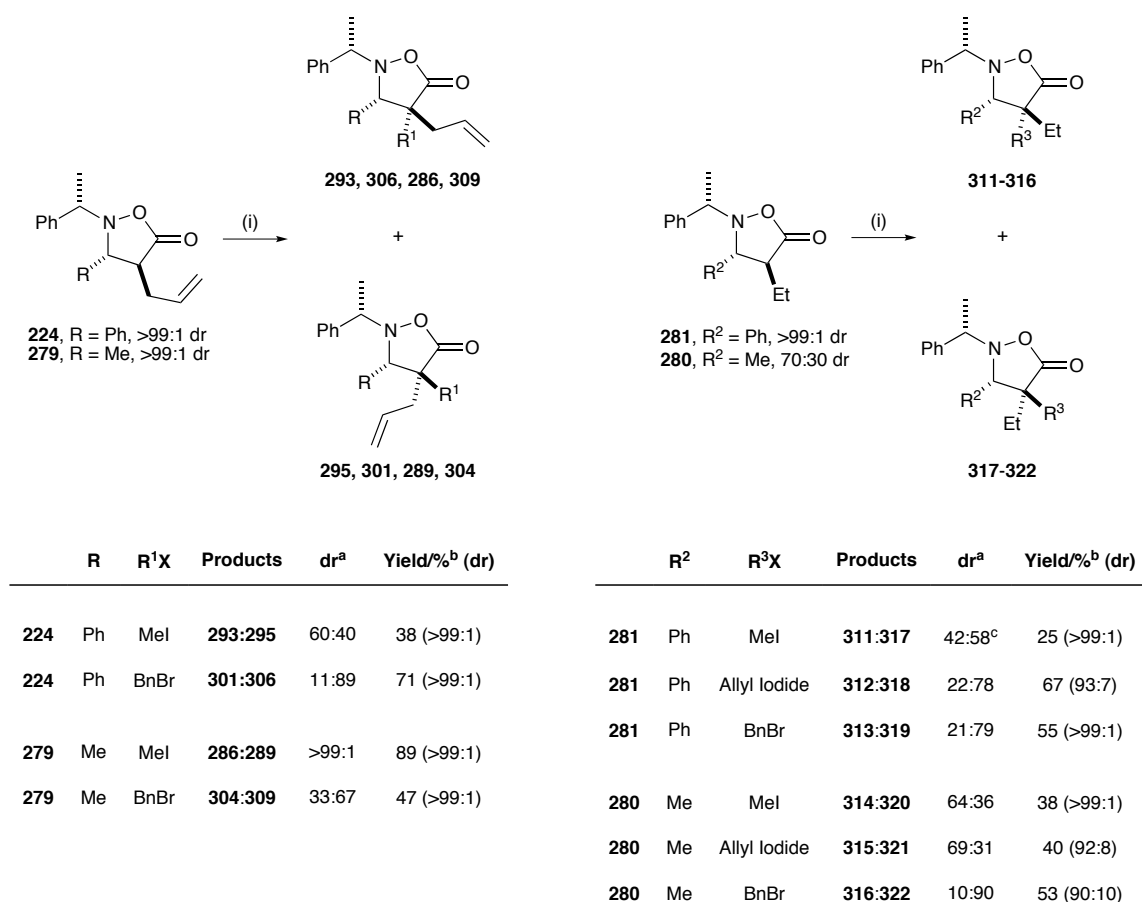


Figure 22: Single crystal X-ray structure of **301**.

3.17 Preparation of C(3)-alkyl-C(4)-dialkyl isoxazolidin-5-ones from C(4)-allyl and C(4)-ethyl isoxazolidin-5-ones

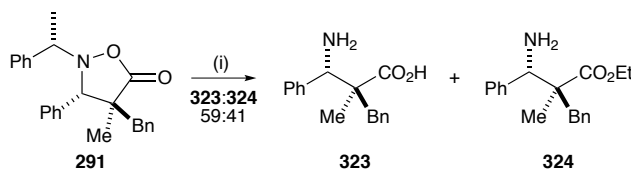
The alkylations of mono-allylated and mono-ethylated isoxazolidin-5-ones **224**, **279**, **280** and **281** were next investigated. Once again a mixture of diastereomeric products were obtained which can again be explained by the payoff between the relative steric bulk of the electrophile and the C(3) and C(4) substituents (Scheme 71).



Scheme 71: *Reagents & Conditions* (i) LiHMDS, THF, $-78\text{ }^{\circ}\text{C}$, 30 mins, then RX, $-78\text{ }^{\circ}\text{C}$ - $0\text{ }^{\circ}\text{C}$, 16 h. [^acrude; ^bisolated yield of major diastereoisomer; ^c Reaction proceeded to 77% conversion.]

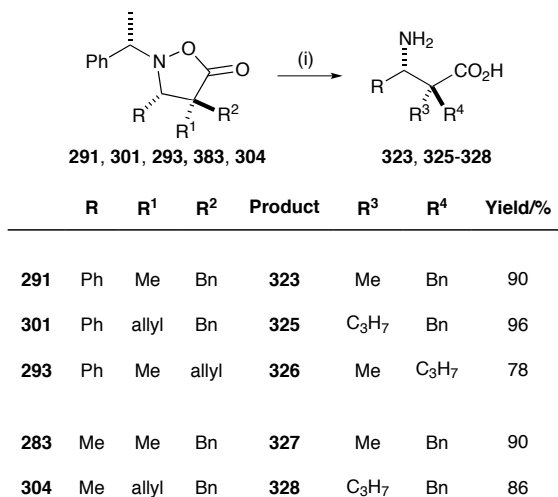
3.18 Deprotection to form $\beta^{2,2,3}$ -trisubstituted amino acids

With a range of 3,4,4,-trisubstituted-isoxazolidin-5-ones in hand, their conversion into the corresponding $\beta^{2,2,3}$ -trisubstituted amino acids was investigated. Attempted hydrogenolysis of **291** using Pearlmans catalyst in EtOH gave a 59:41 mixture of the desired amino acid **323** and amino ester **324**, indicating that competitive ring-opening of the isoxazolidin-5-one ring by the solvent, followed by hydrogenolysis, had occurred (Scheme 72).



Scheme 72: *Reagents & Conditions:* (i) H_2 , $\text{Pd}(\text{OH})_2/\text{C}$, EtOH

It was envisaged that replacing EtOH with a more hindered alcohol as the solvent would prevent the formation of this unwanted side-product. Indeed, when the reaction was run in *t*BuOH, clean formation of **323** was noted. Ion-exchange chromatography gave **323** in 90% yield. Application to isoxazolidin-5-ones **301**, **293**, **283** and **304** gave the corresponding $\beta^{2,2,3}$ -trisubstituted amino acids **325-328** in good yield and in >99:1 dr in all cases (Scheme 73).



Scheme 73: *Reagents & Conditions:* (i) H₂, Pd(OH)₂/C, *t*BuOH.

3.19 Conclusion

In conclusion, the conjugate addition of the chiral hydroxylamine equivalent lithium *N*-*tert*-butyldimethylsilyloxy-*N*-(α -methylbenzyl) amide to a range of α,β -unsaturated esters gives the corresponding β -amino esters in moderate to excellent levels of diastereoselectivity. *O*-Desilylation and subsequent cyclisation furnishes isoxazolidin-5-ones in >99:1 dr after purification. Alkylation of these isoxazolidin-5-one templates proceeds to give the corresponding 3,4-*anti*-disubstituted and 3,4,4-trisubstituted derivatives as single diastereoisomers after purification. The first alkylation occurs with high levels of diastereoselectivity on the face of the enolate *anti* to the C(3)-substituent, whereas the diastereofacial selectivity of the second alkylation is governed by a ‘chiral relay’ effect,^{14,15} between the C(3)- and C(4)-substituents. The magnitude of the diastereoselectivity depends upon the

steric bulk of the electrophile and both the C(3) and C(4) substituents. Subsequent hydrogenolysis promotes cleavage of both the *N*- α -methylbenzyl group and the N–O bond within the isoxazolidin-5-one ring in one pot to give the corresponding $\beta^{2,2,3}$ -trisubstituted amino acids directly. This work has also been published in Tetrahedron.³¹

Bibliography

- [1] Di Cesare, P.; Bouzard, D.; Essiz, M.; Jacquet, J. P.; Ledoussal, B.; Kiechel, J. R.; Remuzon, P.; Kessler, R. E.; Fung-Tomc, J.; Desiderio, J. *J. Med. Chem.* **1992**, *35*, 4205–4213.
- [2] Tomita, K.; Tsuzuki, Y.; Shibamori, K.; Tashima, M.; Kajikawa, F.; Sato, Y.; Kashimoto, S.; Chiba, K.; Hino, K. *J. Med. Chem.* **2002**, *45*, 5564–5575.
- [3] Tsuzuki, Y.; Tomita, K.; Shibamori, K.; Sato, Y.; Kashimoto, S.; Chiba, K. *J. Med. Chem.* **2004**, *47*, 2097–2109.
- [4] Davies, S. G.; Garner, A. C.; Goddard, E. C.; Kruchinin, D.; Roberts, P. M.; Smith, A. D.; Rodriguez-Solla, H.; Thomson, J. E.; Toms, S. M. *Org. Biomol. Chem.* **2007**, 1961–1968.
- [5] Davies, S. G.; Lee, J. A. Unpublished Work.
- [6] Davies, S. G.; Iwamoto, K.; Smethurst, C. A. P.; Smith, A. D.; Rodriguez-Solla, H. *Synlett* **2002**, 1146–1148.
- [7] Bentley, S. A. Part II Thesis, 2007.
- [8] Janecki, T.; Wasek, T.; Rozalski, M.; Krajewska, U.; Studzian, K.; Janecka, A. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1430–1433.
- [9] Baldwin, J. E.; Ng, S. C.; Pratt, A. J. *Tetrahedron Lett.* **1987**, *28*, 4319–4320.
- [10] Harada, S.; Tsubotani, S.; Hida, T.; Koyana, K.; Kondo, M.; Ono, H. *Tetrahedron* **1988**, *44*, 6589–6606.
- [11] Panfil, I.; Urbaczyk-Lipkowska, Z.; Chmielewski, M. *Carbohydr. Res.* **1998**, *306*, 505–515.
- [12] Cao, X.; Iqbal, A.; Patel, A.; Gretz, P.; Huang, G.; Crowder, M.; Day, R. A. *Biochem. Biophys. Res. Commun.* **2003**, *311*, 267–271.
- [13] Sibi, M. P.; Liu, M. *Org. Lett.* **2001**, *3*, 4181–4184.
- [14] Bull, S. D.; Davies, S. G.; Fox, D. J.; Garner, A. C.; Sellers, T. G. R. *Pure Appl. Chem.* **1998**, *70*, 1501–1506.

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- [15] Bull, S. D.; Davies, S. G.; Garner, A. C.; O'Shea, M. D. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3281–3287.
- [16] Shindo, M.; Itoh, K.; Tsuchiya, C.; Shishido, K. *Org. Lett.* **2002**, *4*, 3119–3121.
- [17] Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed.* **1985**, *24*, 1–30.
- [18] Ishikawa, T.; Nagai, K.; Kudoh, T.; Saito, S. *Synlett* **1995**, 1171–1173.
- [19] Tokuyama, H.; Kuboyama, T.; Amano, A.; Yamashita, T.; Fukuyama, T. *Synthesis* **2000**, 1299–1304.
- [20] Costa, M. R.; Curto, M. J.; Davies, S. G.; Sanders, J.; Teixeira, F. C. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2850–2855.
- [21] Smith III, A. B.; Ott, G. R. *J. Am. Chem. Soc.* **1998**, *120*, 3935–3948.
- [22] V. Bou, J. V. *Tetrahedron Lett.* **1990**, *36*, 9479.
- [23] Farras, J.; Serra, C.; Vilarrasa, J. *Tetrahedron Lett.* **1998**, *39*, 327–330.
- [24] Prakash, C.; Saleh, S.; Blair, I. A. *Tetrahedron Lett.* **1989**, *30*, 19–22.
- [25] Kelly, D. R.; Roberts, S. M.; Newton, R. F. *Synth. Commun.* **1979**, *9*, 295.
- [26] Cresswell, A. J.; Davies, S. G.; Lee, J. A.; Roberts, P. M.; Russell, A. J.; Thomson, J. E.; Tyte, M. J. *Org. Lett.* **2010**, *12*, 2936–2939.
- [27] Islas-Gonzalez, G.; Puigjaner, C.; Vidal-Ferran, A.; Moyano, A.; Riera, A.; Pericàs, M. A. *Tetrahedron Lett.* **2004**, *45*, 6337–6341.
- [28] Nicolaou, K. C.; Webber, S. E. *Synthesis* **1986**, 453–461.
- [29] Baldwin, J. E.; Harwood, L. M.; Lombard, M. J. *Tetrahedron* **1984**, *40*, 4363–4370.
- [30] Moritani, Y.; Fukushima, C.; Ogiku, T.; Ukita, T.; Miyagishima, T.; Iwasaki, T. *Tetrahedron Lett.* **1993**, *34*, 2787–2790.
- [31] Bentley, S.; Davies, S.; Lee, J.; Roberts, P.; Russell, A.; Thomson, J.; Toms, S. *Tetrahedron* **2010**, *66*, 4604–4620.

Conjugate addition of a chiral aniline equivalent

4.1 Introduction

It was proposed that development of a process to effect conjugate addition of a chiral aniline equivalent would give access to *N*-aryl β -amino esters. These could then be used as chiral building blocks towards the synthesis of 2-substituted 1,2,3,4-tetrahydroquinolines, which feature as substructural units in a range of natural products such as the *Galipea officinalis* alkaloids angustureine **335**,¹ cuspareine **336**,² galipeine **337**¹ and galipinene **338**.² Two methods for the conversion of *N*-phenyl- β -amino esters **330** into 1,2,3,4-tetrahydroquinolines **334** were envisaged. The first involved an intramolecular Friedel-Crafts acylation type procedure, followed by reduction of the resultant dihydroquinolone **331**. The second involved reduction of the intermediate β -amino ester **330** to the corresponding γ -amino alcohol **332**, followed by an intramolecular Friedel-Crafts alkylation type procedure (Figure 23).

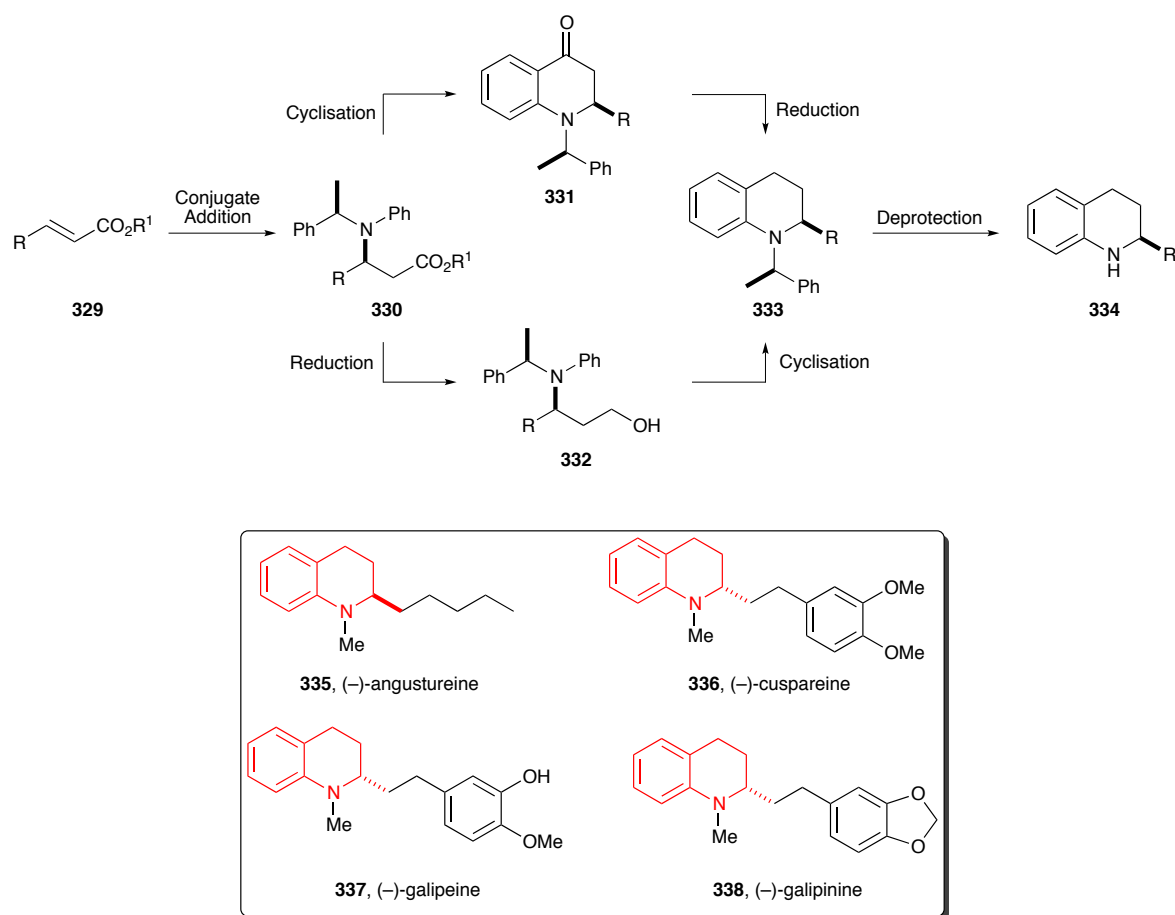


Figure 23: Chapter Aim.

4.2 1,2,3,4-Tetrahydroquinolines

The main interest in 1,2,3,4-tetrahydroquinolines comes from their biological activity. For example 2-methyl-1,2,3,4-tetrahydroquinoline **339** has been found in the human brain,³ and Virantmycin **340** is a 1,2,3,4-tetrahydroquinoline antibiotic which was isolated from the fermentation broth of *Streptomyces nitrosporeus*.⁴ Virantmycin **340** shows potent antiviral activity against both RNA and DNA viruses, as well as antifungal activity. The structure of **340** was first elucidated by Omura *et al.*⁵ in 1981 and the absolute configuration within **340** was assigned by Morimoto *et al.* seven years later in 1988.⁶ Virantmycin has since been the subject of a number of syntheses⁷⁻⁹ (Figure 24).

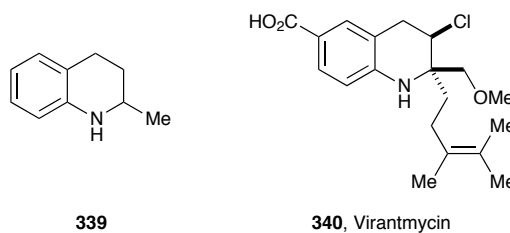


Figure 24: 2-Methyl-1,2,3,4-tetrahydroquinoline **339** and Virantmycin **340**.

L-689,560 **341** (discovered by Merck Sharpe and Dohme) is a very potent NMDAⁱ antagonist. It was screened against the binding of [³H]glycine to rat cortical membranes giving an IC₅₀ value of 7.4 nM and a K_b ⁱⁱ of 130 nM (Figure 25).¹⁰

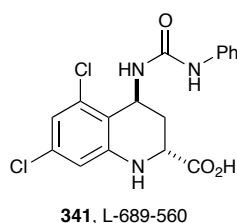


Figure 25: L-689,560 **341**.

4.3 Alkaloids from *Galipea officinalis* Hancock

Galipea officinalis Hancock is a shrub indigenous to the mountainous regions of Venezuela, from the genus *Galipea* Aublet. Its bark has a high content of quinoline derivatives, including the four tetrahydroquinolines **335-338**^{1,2} and the quinolines **342-344**.² Angustureine **335**, cuspareine **336**, galipeine **337** and galipinene **338** were all tested for *in vitro* antimalarial activity on *Plasmodium falciparum*. Three strains were tested and galipinene **338** showed the highest activity, with IC₅₀ values ranging from 0.09 to 2.3 μ g/mL (Figure 26).¹¹

ⁱN-methyl-D-aspartate

ⁱⁱBinding constant

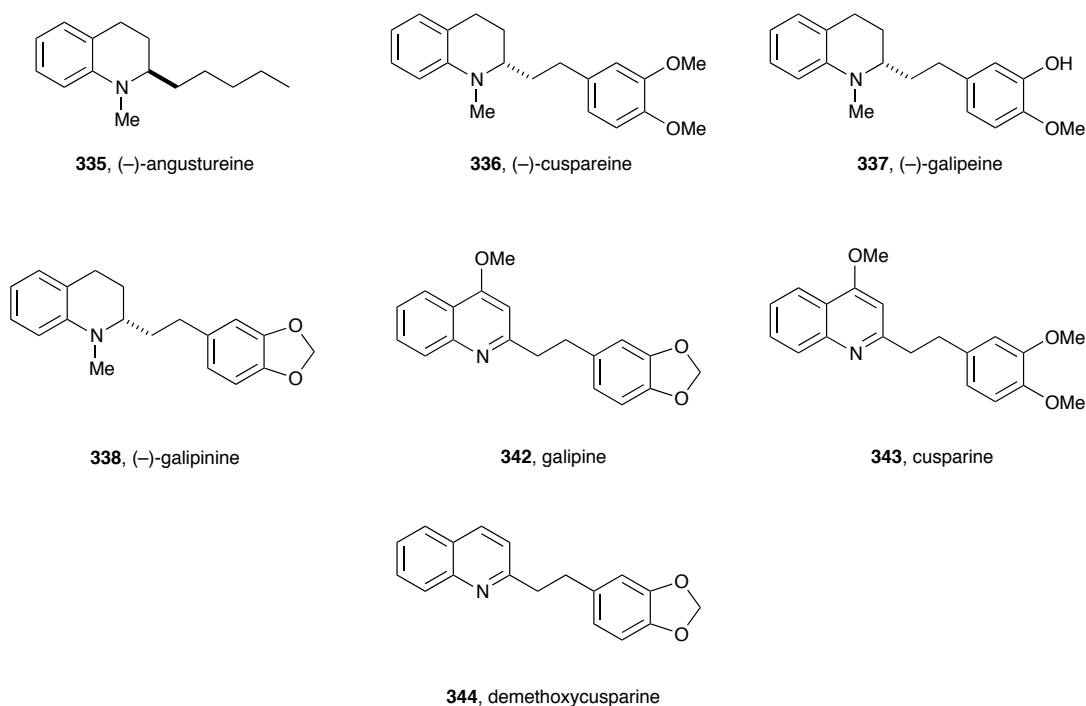
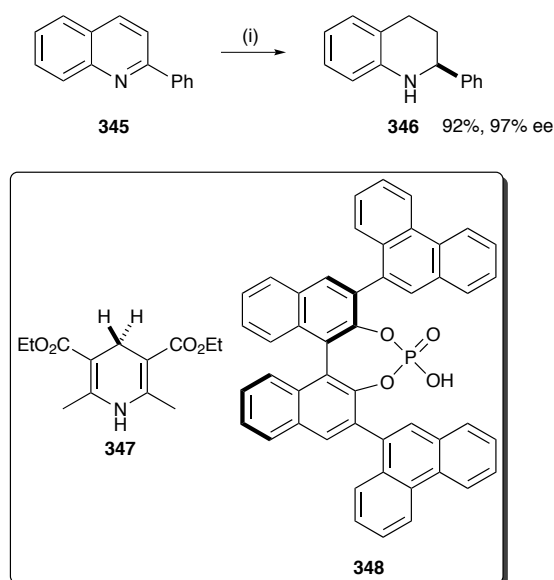


Figure 26: A selection of quinolines and 1,2,3,4-tetrahydroquinolines isolated from the bark of *Galipea officinalis*.

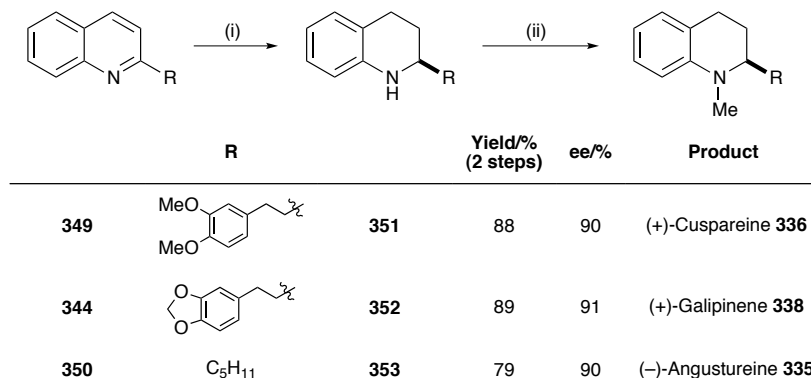
4.4 Syntheses of 1,2,3,4-tetrahydroquinolines

Rueping *et al.* reported a Brønsted acid catalysed bis-reduction in the synthesis of chiral tetrahydroquinolines.¹² For example, treatment of quinoline **345** with dihydropyridine **347** and chiral Brønsted acid **348** gave 1,2,3,4-tetrahydroquinoline **346** in 92% yield and 97% ee. The reaction was applied to a wide range of 2-alkyl and 2-aryl substituted quinolines, each proceeding in good yield and 87->99% ee (Scheme 74).



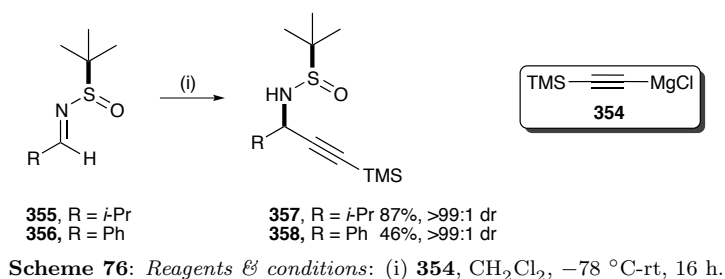
Scheme 74: Reagents & conditions: (i) **347**, 2 mol% **348**, benzene, 60 °C, 12 h.

This methodology was also applied to the synthesis of three of the *Galipea officinalis* alkaloids: (+)-cuspareine **336** (unnatural enantiomer), (+)-galipinene **338** (unnatural enantiomer) and (–)-angustureine **335** (natural enantiomer). Reduction of the requisite quinolines **349**, **344** and **350** gave **351-353** in good yields and 90-91% ee, then *N*-methylation gave the desired natural products **336**, **338** and **335** in excellent yields (Scheme 75).

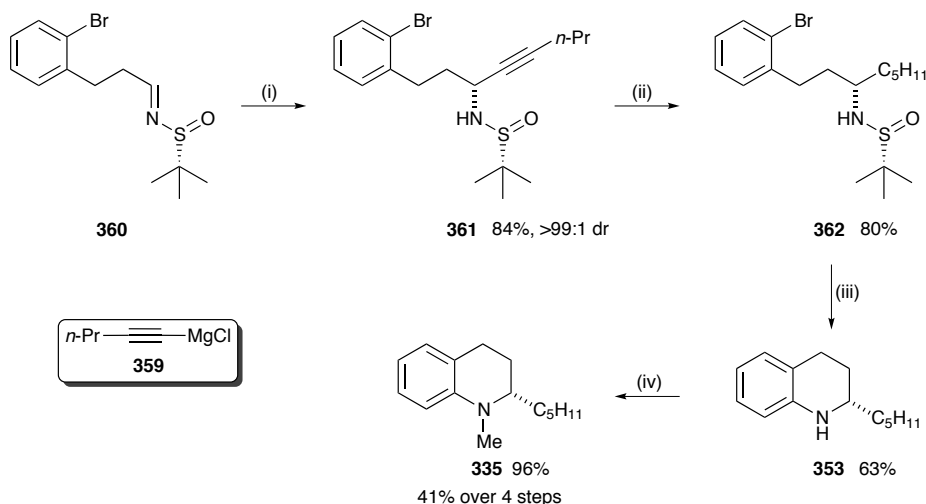


Scheme 75: Reagents & conditions: (i) **347**, 2 mol% **348**, benzene, 60 °C, 12 h; (ii) CH₂O, AcOH, then NaBH₄.

Wang *et al.* reported the highly diastereoselective addition of a range of alkynylmagnesium chlorides to a range of *N*-*tert*-butanesulfinyl aldimines.¹³ For example, addition of alkynylmagnesium chloride **354** to imines **355** and **356** proceed in moderate to good yield and in >99:1 dr (Scheme 76).

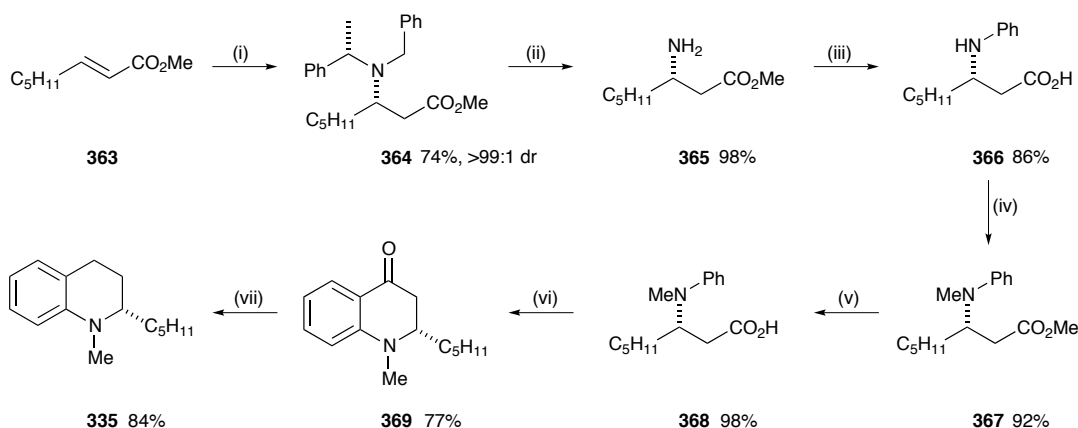


This methodology was utilised in the synthesis of (+)-angustureine **335** (unnatural enantiomer). Addition of alkynyl magnesium chloride **359** to imine **360** gave **361** in 84% yield and >99:1 dr. Hydrogenation of **361** in the presence of PtO₂ gave **362** in 80% yield, then palladium catalysed Buchwald-Hartwig amination¹⁴ and concomitant desulfinylation gave norangustureine **353** in 63% yield. Finally, *N*-methylation of **353** gave (+)-angustureine in 4 steps and 41% yield from imine **360** (Scheme 77).



Ma *et al.* reported a total synthesis of the unnatural enantiomer (+)-angustureine **335**, with the key stereodefining step being the conjugate addition of lithium (*S*)-*N*-benzyl-*N*-(α -methylbenzyl)amide **85** to methyl (*E*)-oct-2-enoate **363**, affording β -amino ester **364** in 74% yield and >99:1 dr.¹⁵ *N*-Deprotection by hydrogenolysis gave primary amine **365** in 98% yield, and subsequent copper catalysed coupling of iodobenzene and concomitant saponification gave **366** in 86% yield. Treatment with MeI/AgO introduced the *N*-methyl

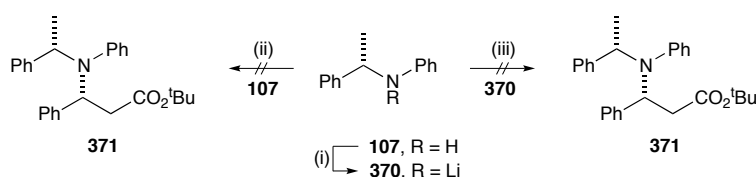
group, as well as forming the methyl ester to give **367** in 92% yield. Saponification followed by acid chloride formation and Friedel-Crafts acylation gave dihydroquinoline **369** in 75% yield over two-steps, and finally reduction of **369** with H₂ and Pd/C gave (+)-angustureine **335** in 36% over 7 steps (Scheme 78).



Scheme 78: Reagents & conditions: (i) (*S*)-**85**, THF, −78 °C, 2 h; (ii) Pd/C, H₂, AcOH, 40 °C, 2 d; (iii) PhI, CuI, K₂CO₃, 110 °C, 48 h; (iv) MeI, AgO, DMF, 60 °C, 16 h; (v) NaOH, MeOH/H₂O, 1:1 (v:v), 60 °C, 2 h; (vi) SOCl₂, CH₂Cl₂, rt, 2 h, then AlCl₃, CH₂Cl₂, rt, 24 h; (vii) Pd/C, MeOH, H₂, AcOH, rt, 16 h.

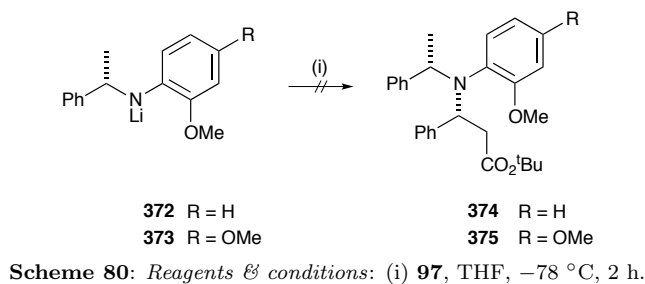
4.5 Lithium *N*-phenyl-*N*-(α -methylbenzyl)amide: Background

Previous work by Davies and co-workers had shown that the attempted conjugate addition of lithium (*S*)-*N*-phenyl-*N*-(α -methylbenzyl)amide **370** to *tert*-butyl cinnamate **97** was unsuccessful, returning only starting material.¹⁶ The same result was also observed on attempting the corresponding thermal addition of amine **107** (Scheme 79).

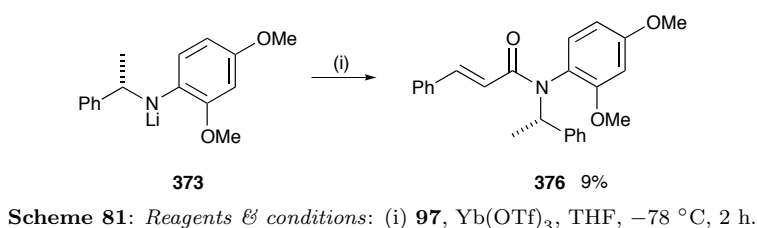


Scheme 79: Reagents & conditions: (i) BuLi, Et₂O, −78 °C, 30 min; (ii) **97**, THF, 48 h, rt; (iii) **97**, Et₂O, −78 °C, 2 h.

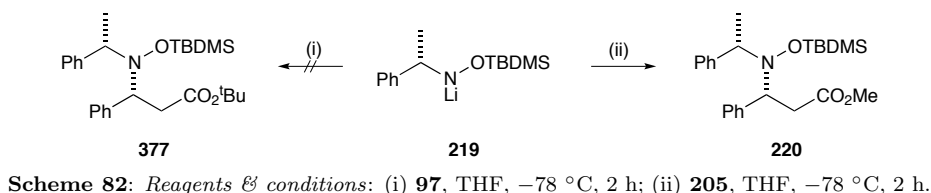
The 2-methoxy and 2,4-dimethoxy derivatives **372** and **373** were also synthesised, and attempts were made to effect their conjugate addition to *tert*-butyl cinnamate **97**, although treatment of both amides **372** and **373** with *tert*-butyl cinnamate **97** again returned only starting material (Scheme 80).



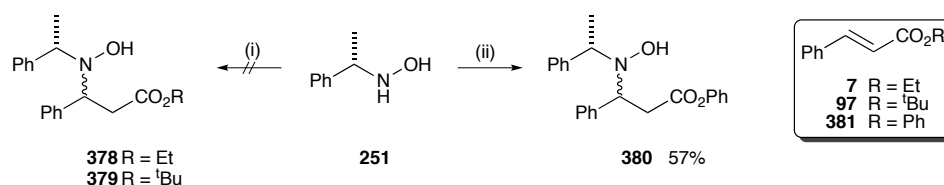
Finally, attempted activation of the ester with a Lewis acid, in this case $\text{Yb}(\text{OTf})_3$, resulted in 9% of 1,2-addition product **376** being isolated, along with returned starting materials (Scheme 81).



The potential of lithium amides **370**, **372** and **373** to undergo conjugate addition to esters other than *tert*-butyl cinnamate **97** was not explored. However, a reactivity difference between esters of cinnamic acid towards conjugate addition of a range of related nucleophiles has since been noted. For instance, lithium *N-tert*-butyldimethylsilyloxy-*N*-(α -methylbenzyl)amide **219** is resistant to conjugate addition to *tert*-butyl cinnamate **97**, but readily gives the addition product **220** when methyl cinnamate **205** is used (Scheme 82).¹⁷



Furthermore, Bew *et al.* observed that the thermal conjugate addition of *N*-(α -methylbenzyl)hydroxylamine **251** to alkyl cinnamates **7** and **97** was unsuccessful, but on switching to phenyl cinnamate **381** the desired product **380** was obtained in modest yield (Scheme 83).¹⁸

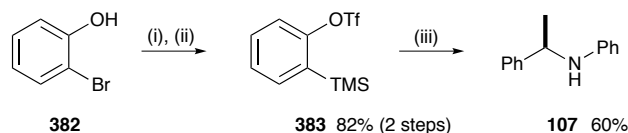


Scheme 83: Reagents & conditions: (i) **7/97**, CH₂Cl₂; (ii) **381**, CH₂Cl₂.

It was thus decided to reinvestigate the conjugate addition of lithium *N*-aryl-*N*-(α -methylbenzyl)amides to a range of esters.

4.6 Synthesis of *N*-phenyl-*N*-(α -methylbenzyl)amine **107**

The synthesis of (*R*)-*N*-phenyl-*N*-(α -methylbenzyl)amine **107** was carried out using a modification of the procedure described by Larock *et al.*¹⁹ The latent benzyne **383** was synthesised in 2 steps from 2-bromophenol **382** in 82% yield. Then, treatment of **383** with (*R*)- α -methylbenzylamine **196** in the presence of CsF gave **107** in 60% yield and >99% eeⁱⁱⁱ (Scheme 84).



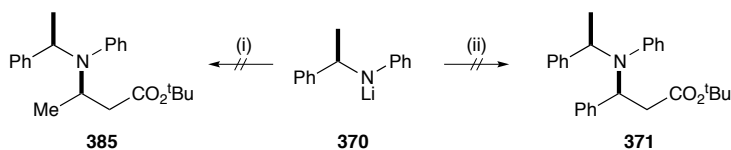
Scheme 84: Reagents & conditions: (i) HMDs, 80 °C, 45 min; (ii) BuLi, THF, -100 °C, 20 min, then Tf₂O, -100 °C, 20 min; (iii) (*R*)-**196**, CsF, MeCN.

4.7 Initial studies: Attempted conjugate addition to *tert*-butyl cinnamate and crotonate

Initially, the previous results were verified, with the attempted conjugate addition of lithium (*R*)-*N*-phenyl-*N*-(α -methylbenzyl)amide **370** to *tert*-butyl cinnamate **97** being undertaken (Scheme 85). Treatment of **97** with **370** in THF at -78 °C returned only

ⁱⁱⁱThe enantiomeric purity of **107** was determined by chiral HPLC analysis kindly provided by Prof. D. J. Dixon and Dr P. Jakubec.

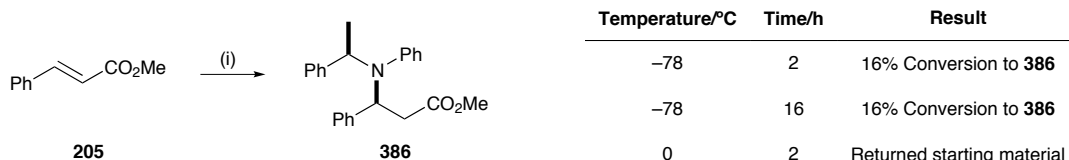
starting material, as expected. Analogous treatment of *tert*-butyl crotonate **384** again returned only starting material (Scheme 85).



Scheme 85: Reagents & conditions: (i) **384**, THF, $-78\text{ }^{\circ}\text{C}$, 2 h; (ii) **97**, THF, $-78\text{ }^{\circ}\text{C}$, 2 h.

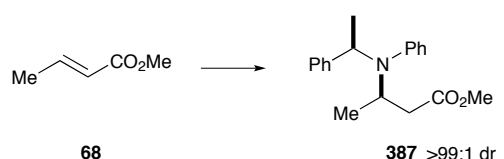
4.8 Conjugate addition to a range of cinnamate and crotonate esters

After confirming the previous results, a change in the ester was proposed. A methyl ester was initially chosen, and reaction of 1.6 equiv of lithium (*R*)-*N*-phenyl-*N*-(α -methylbenzyl) amide **370** with methyl cinnamate **205** for 2 h at $-78\text{ }^{\circ}\text{C}$ gave 16% conversion to the desired β -amino ester **386**. On increasing the reaction time to 16 h, no increase in conversion was observed, and on increasing the reaction temperature to $0\text{ }^{\circ}\text{C}$ only starting material was returned (Scheme 86).



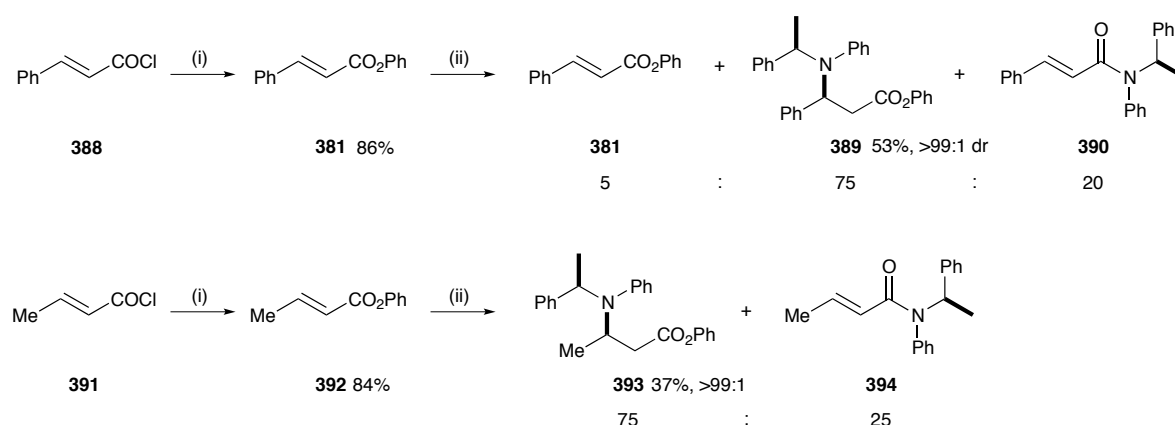
Scheme 86: Reagents & conditions: (i) (*R*)-**370**, THF.

The equivalent reactions were carried out with methyl crotonate **68**, and 34% conversion to **387** was obtained after both 2 h and 16 h. Once again, the reaction at $0\text{ }^{\circ}\text{C}$ returned starting material. The reaction was performed at $-78\text{ }^{\circ}\text{C}$ and then allowed to slowly warm to rt for 16 h, but again only starting material was returned. As an attempt to increase the conversion, the amount of lithium amide **370** was increased to 2 and 5 equiv and in both cases the conversion increased to 40% and 50% respectively, but this did not represent a synthetically useful level (Scheme 87).

	Equiv of 370	Temperature/ $^{\circ}$ C	Time/h	Result
 68 387 >99:1 dr	1.6	-78	2	34% conversion to 387 (28%) ^a
	1.6	-78	16	34% conversion to 387
	1.6	0	2	Returned starting material
	1.6	-78 - rt	16	Returned starting material
	2	-78	2	40% Conversion to 387
	5	-78	2	50% Conversion to 387

Scheme 87: Reagents & conditions: (i) (*R*)-**370**, THF; [^aisolated yield].

Although the use of methyl esters **205** and **68** had proved superior to *tert*-butyl cinnamate and therefore demonstrated a differing reactivity of these esters, complete conversion to either **386** or **387** had not been obtained, so the switch to a phenyl ester was proposed (*vide supra*). Both phenyl cinnamate **381** and phenyl crotonate **392** were synthesised from their respective acid chlorides **388** and **391** in 86% and 84% yield respectively. Reaction of 2 equiv of lithium amide **370** with phenyl cinnamate **381** for 2 hours at -78°C gave a 5:75:20 mixture of **381**:**389**:**390**, which upon purification gave the desired β -amino ester **389** in 53% isolated yield and >99:1 dr. Similar treatment of phenyl crotonate **392** gave a 75:25 mixture of **393**:**394**, which upon purification gave the desired β -amino ester **393** in 37% isolated yield and >99:1 dr (Scheme 88).^{iv}

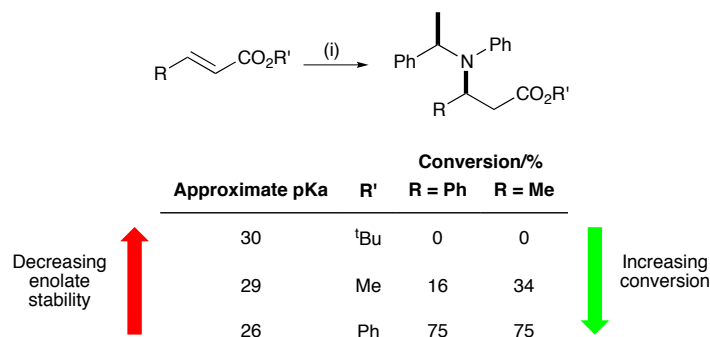


Scheme 88: Reagents & conditions: (i) phenol, Et_3N , CH_2Cl_2 , rt, 16 h; (ii) (*R*)-**370**, THF, -78°C , 2 h.

As can be seen there is a definite increase in conversion as the ester changes from *tert*-butyl to methyl to phenyl. It is worth noting the relative pK_as of the three esters:

^{iv}An authentic sample of the 1,2-addition products **390** and **394** were synthesised from *N*-phenyl-*N*-(α -methylbenzyl)amine **107** and either cinnamoyl chloride **388** or crotonoyl chloride **391**.

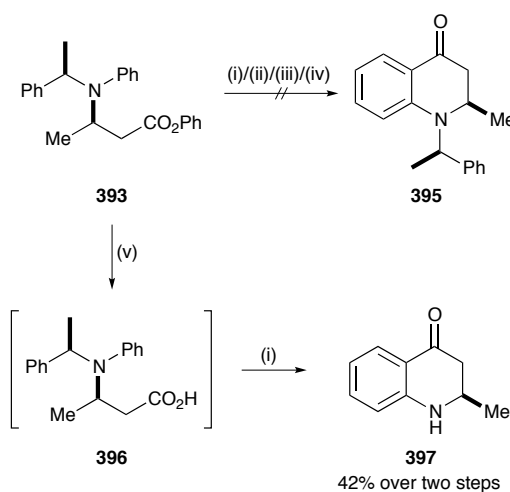
tert-butyl>methyl>>phenyl.²⁰ From these data it is apparent that as the stability of the intermediate enolate increases, the amount of conjugate addition also increases. (Scheme 89).



Scheme 89: Reagents & conditions: (i) (*R*)-**370**, THF, $-78\text{ }^{\circ}\text{C}$, 2 h.

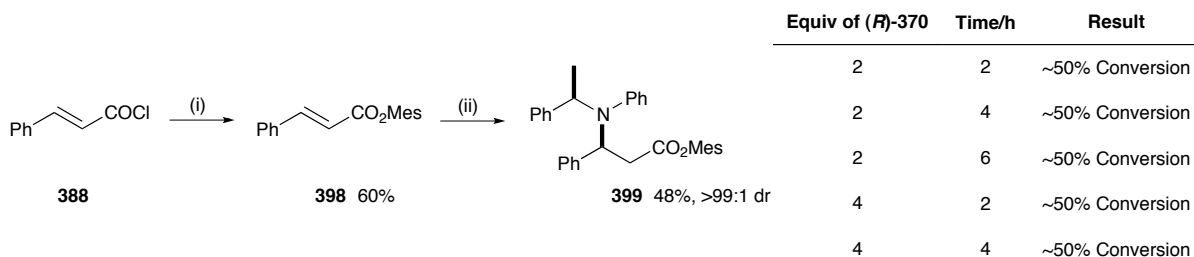
With β -amino ester **393** in hand, a cyclisation to dihydroquinolone **395** was attempted. This would not only give proof of principle that this scaffold could be accessed from the *N*-aryl- β -amino esters, but also proof of the stereochemistry of the addition, as deprotection would give **397**, a known compound.²¹ Attempted cyclisation of **393** with polyphosphoric acid (PPA)^{21,22} or a range of Lewis acids resulted in only the recovery of amine **107**, with no trace of the desired dihydroquinolone **395**, suggesting that decomposition *via* a retro-conjugate addition was occurring. However, saponification of **393** gave a mixture of the corresponding β -amino acid **396** and residual phenol, which on treatment with PPA^{21,22} resulted in cyclisation and *in situ* loss of the α -methylbenzyl group (presumably *via* an S_N1 -type pathway) to give dihydroquinolone **397** in 42% yield over two steps. Comparison of the values of the specific rotation of the sample of **397** with that previously reported for (*R*)-**397** in the literature $\{[\alpha]_D^{25} +174\text{ (}c\text{ 1.0 in C}_6\text{H}_6\text{)}; \text{lit.}^{21} [\alpha]_D^{20} +220\text{ (}c\text{ 1.0 in C}_6\text{H}_6\text{)}\}$ confirmed unambiguously the (*R*)-configuration within **397** and, thus the (*R,R*)-configuration within **393**, since the (*R*)-configuration of the α -methylbenzyl stereocentre was known. The stereinduction elicited by lithium amide **370** in the conjugate addition reaction is therefore the same as that predicted by the transition state mnemonic developed

to rationalise the facial selectivity of other lithium amides of this class (i.e. those bearing an α -methylbenzyl stereodirecting group) (Scheme 90).²³



Scheme 90: Reagents & conditions: (i) PPA, 100 °C, 16 h; (ii) AlCl_3 , CH_2Cl_2 , rt, 16 h; (iii) TiCl_4 , CH_2Cl_2 , rt, 16 h; (iv) SnCl_4 , CH_2Cl_2 , rt, 16 h; (v) NaOH , $\text{CH}_2\text{Cl}_2/\text{MeOH}$, 3:1 (v/v), rt, 2 h.

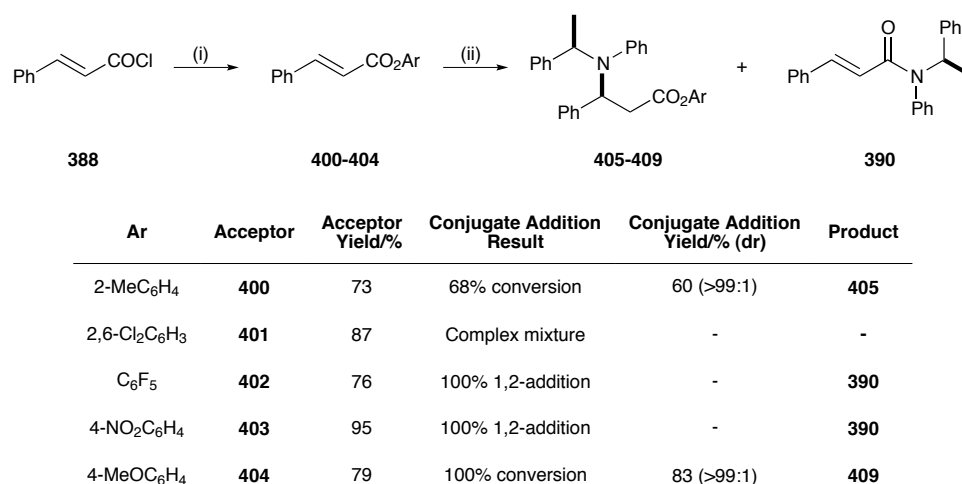
With these promising results in hand, studies turned towards the optimisation of the conjugate addition reaction by suppressing the 1,2-addition. Initially, a mesityl ester was selected as it was proposed that the extra methyl groups would block any 1,2-addition. Mesityl cinnamate **398** was synthesised from cinnamoyl chloride **388** in 60% yield, and on reaction with 2 equiv of lithium amide **370**, 50% conversion to β -amino ester **399** was observed, with no 1,2-addition. β -Amino ester **399** was isolated in 48% yield and >99:1 dr. Unfortunately on increasing both the reaction time and equivalents of lithium amide **370**, the conversion did not increase beyond 50% (Scheme 91).



Scheme 91: Reagents & conditions: (i) mesitol, Et_3N , CH_2Cl_2 , rt, 16 h; (ii) (*R*)-**370**, THF, -78°C .

A further series of substituted phenyl cinnamates were synthesised, varying both the sterics and electronics of the ester. *o*-Cresol **400**, 2,6-dichlorophenyl **401**, pentafluorophenyl **402**,

4-nitrophenyl **403** and 4-methoxyphenyl **404** cinnamate esters were all synthesised from cinnamoyl chloride **388**. Reaction of 2 equiv of lithium amide **370** with *o*-cresol cinnamate **400** gave 68% conversion to β -amino ester **405** (>99:1 dr), with no 1,2-addition, and after column chromatography **405** was isolated in 60% yield and >99:1 dr. Attempted conjugate addition of **370** to 2,6-dichlorophenyl cinnamate **401** gave a complex mixture of products, whilst analogous reaction with pentafluorophenyl ester **402** gave solely 1,2-addition,^v as did 4-nitrophenyl cinnamate **403**. Finally, addition to 4-methoxyphenyl cinnamate **404** gave complete conversion to β -amino ester **409**, which was isolated in 83% yield and >99:1 dr (Scheme 92).

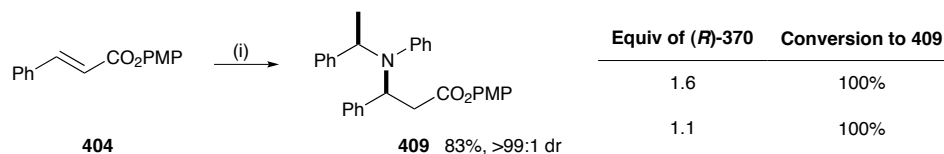


Scheme 92: Reagents & conditions: (i) substituted phenol, Et₃N, CH₂Cl₂, rt, 16 h; (ii) *(R)*-**370**, THF, -78 °C, 2 h.

The 4-methoxyphenyl ester **404** was the obvious candidate to take forwards, as it provided complete conversion to the desired β -amino ester **409** as a single diastereoisomer. Optimisation of the reaction conditions was next carried out to establish whether fewer than 2 equiv of amide **370** were required, and in fact both 1.6 and 1.1 equiv both still provided complete conversion to **409**. The use of only 1.1 equiv of amine represented an optimum protocol since the excess amine could not be removed upon workup by washing the organic phase with 10% aq. citric acid, which is effective to allow separation of

^vAn authentic sample of the 1,2-addition product **390** was synthesised from *N*-phenyl-*N*-(α -methylbenzyl)amine **107** and cinnamoyl chloride **388** (*vide supra*).

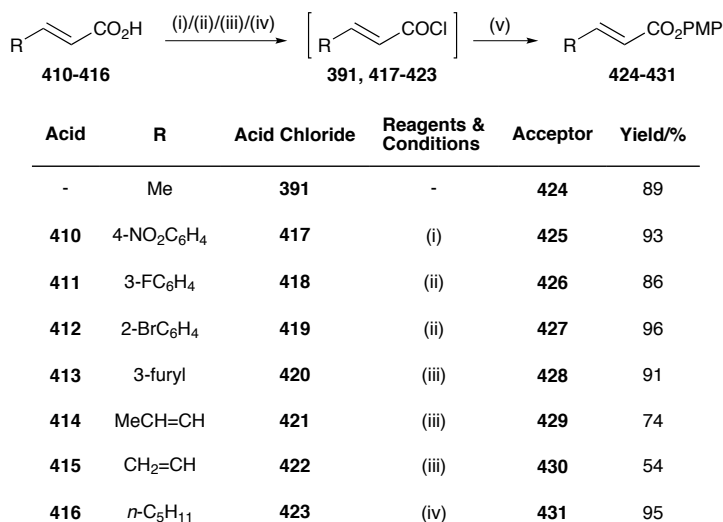
the β -amino ester product of conjugate addition from the remaining amine when using *N*-benzyl-*N*-(α -methylbenzyl)amine **108** (Scheme 93).²⁴



Scheme 93: Reagents & conditions: (i) (*R*)-370, THF, -78°C , 2 h.

4.9 Preparation of a range of 4-methoxyphenyl α,β -unsaturated esters

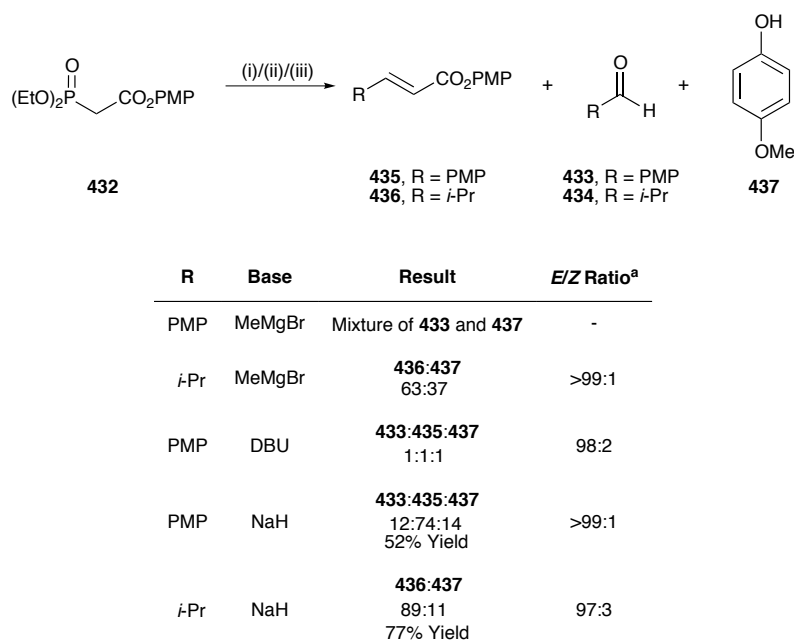
With an optimised procedure in hand, focus turned towards the synthesis of a variety of α,β -unsaturated esters to delineate the scope of the reaction. Two methods were employed: (a) synthesis *via* the acid chloride; (b) Horner-Wadsworth-Emmons olefination. 4-Methoxyphenyl crotonate **424** was synthesised from crotonoyl chloride **391**, whilst **425-431** were all synthesised from the requisite α,β -unsaturated carboxylic acids **410-416** *via* the intermediacy of the corresponding acid chlorides **417-423** (Scheme 94).



Scheme 94: Reagents & conditions: (i) SOCl₂, toluene, Δ , 3 h; (ii) SOCl₂, CHCl₃, Δ , 1 h; (iii) SOCl₂, CH₂Cl₂, Δ , 1 h; (iv) SOCl₂, Δ , 1 h; (v) 4-methoxyphenol, Et₃N, CH₂Cl₂, rt, 16 h.

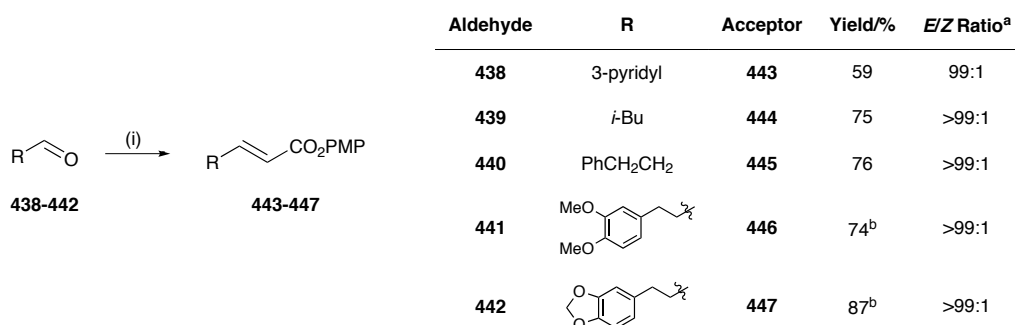
Phosphonate ester **432** was synthesised in two steps from chloroacetyl chloride, in 62% yield overall yield. Initial attempts to effect Horner-Wadsworth-Emmons olefination us-

ing MeMgBr as a base proved relatively unsuccessful:²⁵ on employing *p*-anisaldehyde **433**, a mixture of starting aldehyde and 4-methoxyphenol **437** was returned, and with isobutyraldehyde **434** a mixture of the desired α,β -unsaturated ester **436** and 4-methoxyphenol **437** was obtained in a 63:37 ratio. On switching to the Masamune Roush protocol,²⁶ reaction with *p*-anisaldehyde **433** gave a 1:1:1 mixture of **433:435:437**. One explanation for the formation of 4-methoxyphenol would involve the decomposition of the intermediate enolate to the corresponding ketene. On switching to NaH (which allows quicker reaction times), a 12:74:14 mixture of **433:435:437** was formed, giving **435** in 52% yield.²⁷ Similar reaction with isobutyraldehyde **434** afforded an 89:11 mixture of **436:437**, and **436** was isolated in 77% yield (Scheme 95).



Scheme 95: *Reagents & conditions:* (i) MeMgBr, THF, rt, 15 min, then the requisite aldehyde, Δ , 16 h; (ii) DBU, LiCl, the requisite aldehyde, MeCN, rt, 24 h; (iii) NaH, THF, 0 °C, 20 min, then the requisite aldehyde, rt, 1 h; [^acrude]

This protocol was then applied to 5 further aldehydes **438-442** to give α,β -unsaturated esters **443-447** in good yield, with only 5-12% of side product **437** being formed in each case (Scheme 96).

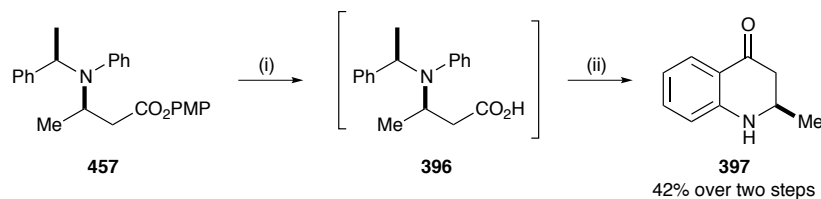


Scheme 96: Reagents & conditions: (i) NaH, **432**, 1 h, rt; [^acrude; ^byield over three steps from the corresponding acid].

4.10 Conjugate addition of lithium *N*-phenyl-*N*-(α -methylbenzyl)amide to a range of 4-methoxyphenyl α,β -unsaturated esters

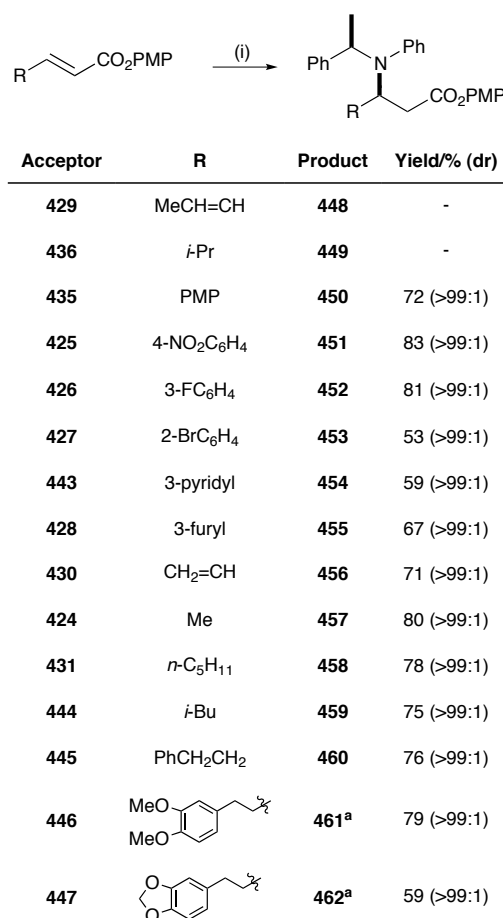
With α,β -unsaturated esters **424-431**, **435**, **436** and **443-447** in hand, the optimised conjugate addition procedure was applied to each in turn. Substituted aryl, heteroaryl, *n*-alkyl and branched alkyl substituents were all well tolerated, although reaction with β -*i*-Pr substituted **436** and the sorbate derived ester **429** returned only starting material under the reaction conditions. Conjugate addition of lithium (*R*)-*N*-phenyl-*N*-(α -methylbenzyl)amide **370** to α,β -unsaturated esters **424-428**, **430**, **431**, **435** and **443-447** under the optimised conditions gave, in each case, complete conversion to single diastereoisomers of the corresponding β -amino esters **450-462**, in 53-83% yield after chromatographic purification (Scheme 97).^{vi} The relative configuration of **457** was unambiguously proven by single crystal X-ray diffraction with the absolute (*R,R*)-configuration being assigned from the known configuration of the (*R*)- α -methylbenzyl stereocentre. The

^{vi}**457** was also cyclised to dihydroquinolone **397** in 44% yield over two steps (Scheme 98).



Scheme 98: Reagents & conditions: (i) LiOH, THF:H₂O, 1:1 (v:v), 40 °C, 3 h; (ii) PPA, 100 °C, 16 h.

configurations of the C(3)-stereogenic centres within **450-456** and **458-462** were assigned by analogy to those unambiguously established for **457** and **393**, and by reference to the lithium amide transition state mnemonic (Figure 27).²³



Scheme 97: Reagents & conditions: (i) **370**, THF, -78 °C, 2 h; [^a(*S*)-enantiomer of amide used].

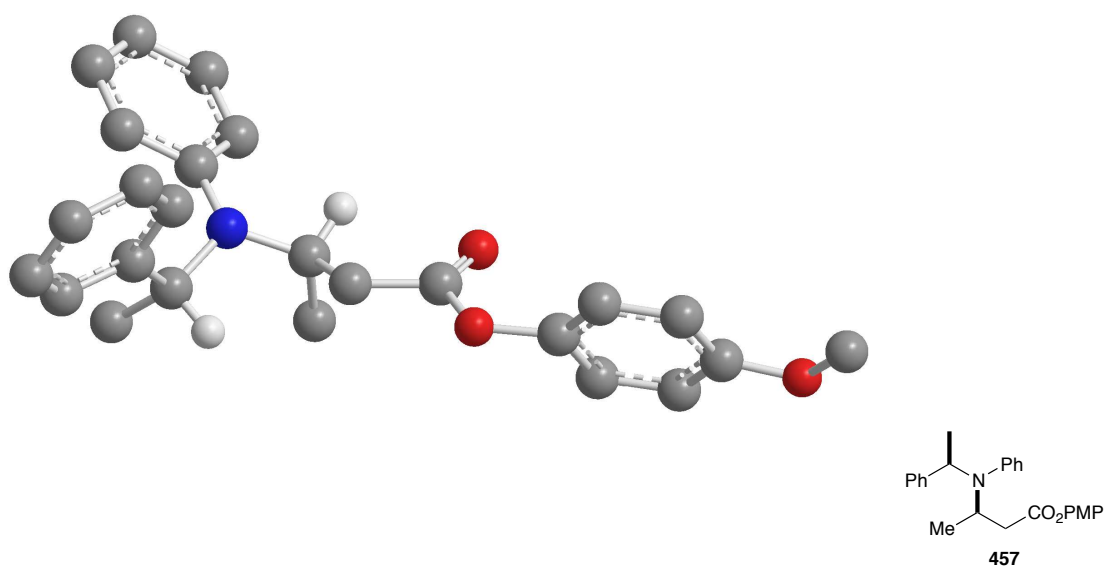
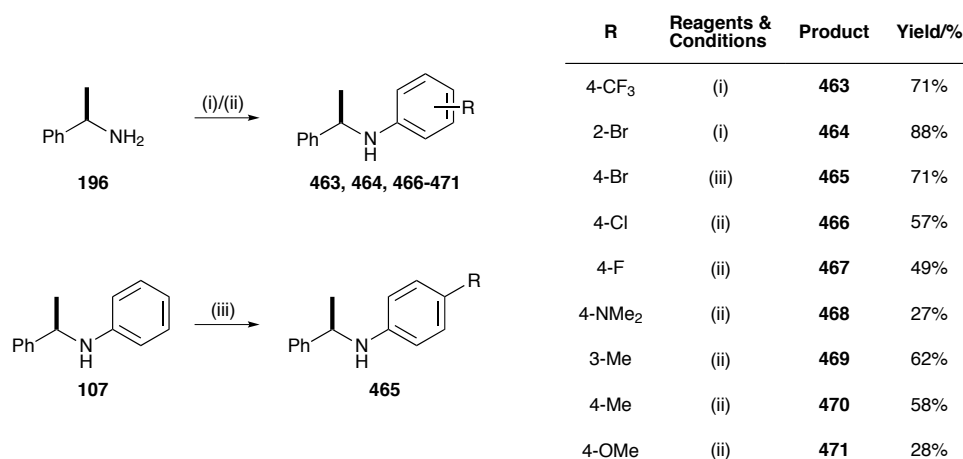


Figure 27: Single crystal X-ray structure of **457**.

4.11 Variation of the structure of the lithium amide: Conjugate addition of a range of lithium *N*-aryl-*N*-(α -methylbenzyl) amides

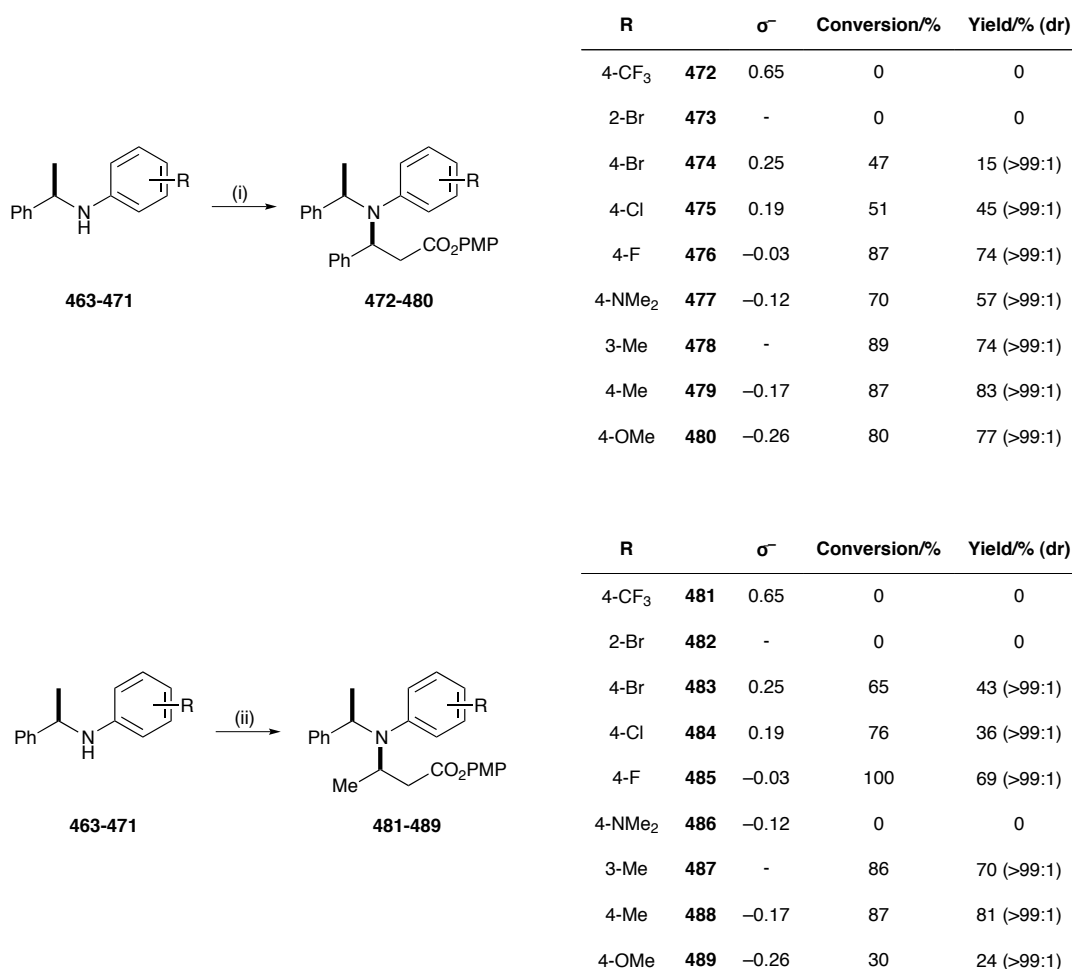
To test further the scope of the reaction, it was decided to investigate whether substituents on the aniline ring were tolerated by the conjugate addition reaction. A variety of electron donating and electron withdrawing substituents were selected, and were placed in *o*-, *m*- and *p*- positions. Alternative syntheses than that employed for the parent compound **107** were required in these cases, due to the method used for the parent amine being non-regioselective when substituents were added to the latent benzyne.¹⁹ The amines **463-471** were synthesised *via* either a palladium or copper mediated *N*-arylation reaction, except in the case of **465** in which it was simply possible to *para* brominate the parent amine **107** (Scheme 99).



Scheme 99: Reagents & conditions: (i) Pd₂(dba)₃, *rac*-BINAP, NaO^tBu, ArBr, toluene, Δ , 90 mins; (ii) CuI, K₃PO₄, ethylene glycol, ArI, *i*-PrOH, 80 °C, 24 h; (iii) KBr, NaBO₃ · 4 H₂O, (NH₄)₆Mo₇O₂₄ · 4 H₂O, AcOH, rt, 3 h.

The addition of lithium amides derived from **463-471** to both 4-methoxyphenyl cinnamate **404** and 4-methoxyphenyl crotonate **424** under the optimised conditions was probed. Both the 4-CF₃ and 2-Br substituted amides gave none of the desired β -amino esters **472**, **473**, **481** or **482** and only starting material was returned. The 4-halo substituted amides gave 47-100% conversion to the desired products **474-476** and **483-485**, and both the methyl substituted amides gave 86-89% conversion to the four desired products **478**, **479**, **487** and

488. On reaction with 4-methoxyphenyl cinnamate **404**, lithium amides derived from 4-NMe₂ amine **468** and 4-OMe amine **471** gave solely the desired β -amino esters **477** and **480** in 70 and 80% conversion respectively, but on reaction with 4-methoxyphenyl crotonate a significant amount of 1,2-addition was observed, the lithium amide derived from **468** giving only 1,2-addition, and with the lithium amide from **471** only 30% conversion to **489** was observed. (Scheme 100).



Scheme 100: Reagents & conditions: (i) BuLi, THF, -78 °C, 30 mins, then **404**, THF, -78 °C, 2 h; (ii) BuLi, THF, -78 °C, 30 mins, then **424**, THF, -78 °C, 2 h

In an effort to see if there was a trend with the reactivities of the amides, the reaction conversions after 2 hours were compared with the respective σ^- Hammett values for each of the *para*-substituted amines, as well as the non-substituted amine **107** (*vide supra*).²⁸ A general trend was seen in each case, the conversion increasing as σ^- decreases, with a

maxima at 0. A drop off is then seen as σ^- decreases further, and in the crotonyl series a large drop off with R = OMe and NMe₂, due to 1,2-addition, suggesting other factors are also contributing (Figure 28).

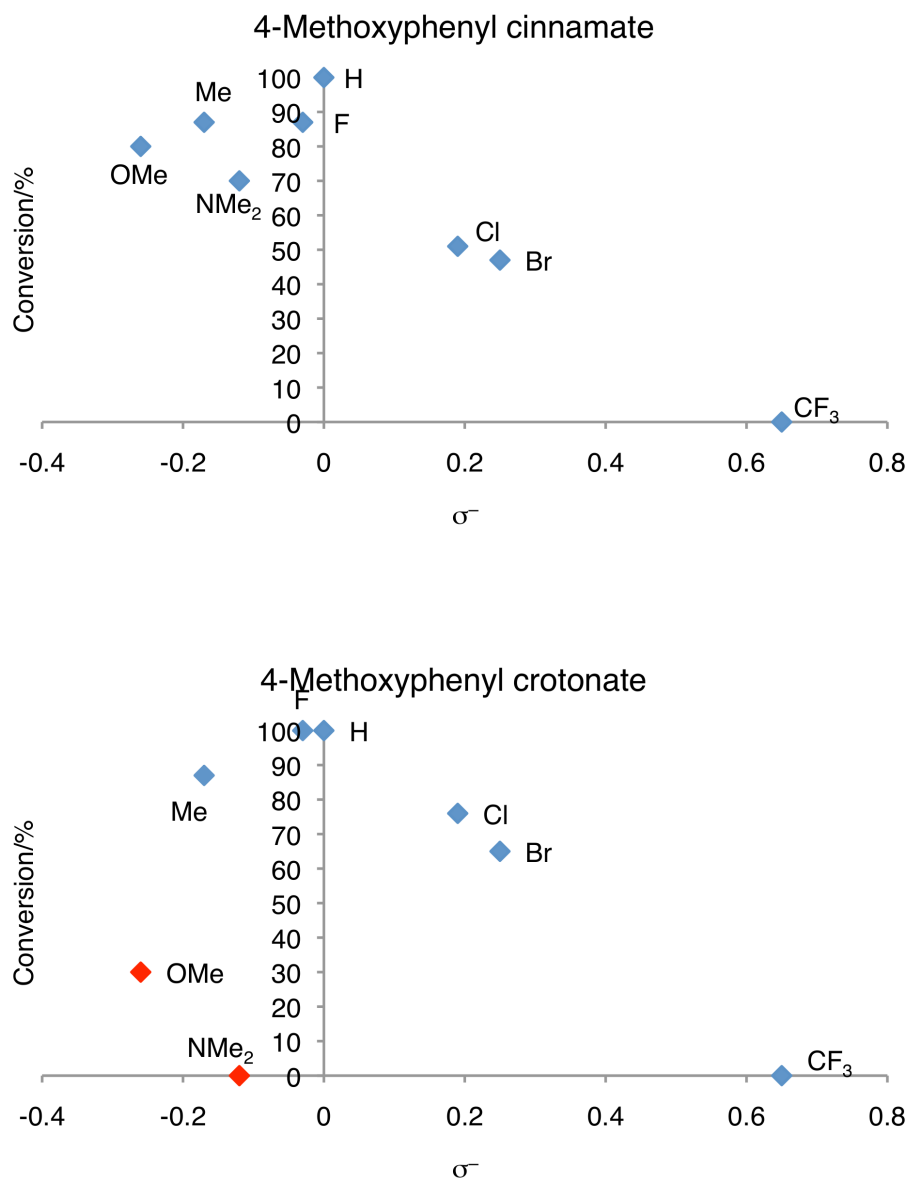
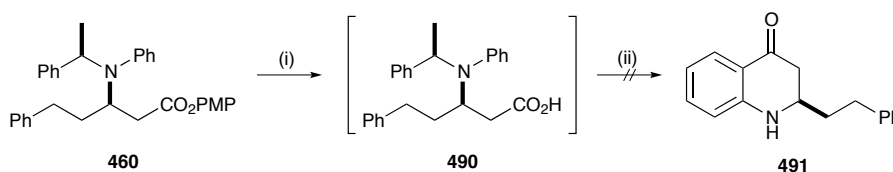


Figure 28: Plotting σ^- vs. conversion.

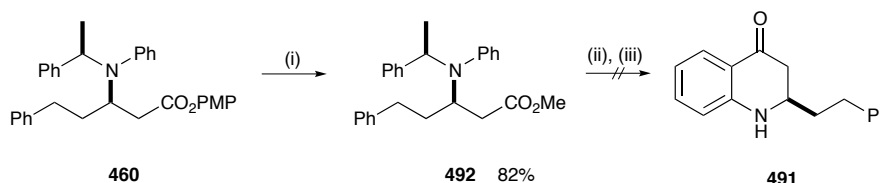
4.12 Attempted cyclisation to form (*R*)-2-(2'-phenylethyl)-2,3-dihydroquinolin-4(1*H*)-one with PPA

Studies then moved back to the cyclisation of the β -amino esters, specifically for the synthesis of the *Galipea officinalis* alkaloids **335**–**338**. With a model system for angustureine **335** already cyclised (β -amino ester **457**), cyclisation of hydrocinnamyl derived β -amino ester **460** was attempted. It was envisaged that this would be a good model system for cuspareine **336**, galipeine **337** and galipinine **338**. Thus, saponification of **460** upon treatment with aqueous LiOH gave the corresponding β -amino acid **490**, which upon exposure to PPA unfortunately gave a complex mixture of unidentifiable products (Scheme 101).



Scheme 101: Reagents & conditions: (i) LiOH, THF:H₂O, 1:1 (v:v), 40 °C, 3 h; (ii) PPA, 100 °C, 16 h.

Although it had not been a problem in the cyclisation of the crotonate derived **393** and **457**, it was felt that perhaps the residual 4-methoxyphenol from the saponification could be involved in undesired side reactions. In an attempt to see if this was true, **460** was transesterified to the corresponding methyl ester **492**, which allowed for chromatographic removal of the residual 4-methoxyphenol. Saponification of **492** then gave acid **490**, which on treatment with PPA once again gave a complex mixture of unidentifiable products. (Scheme 102).

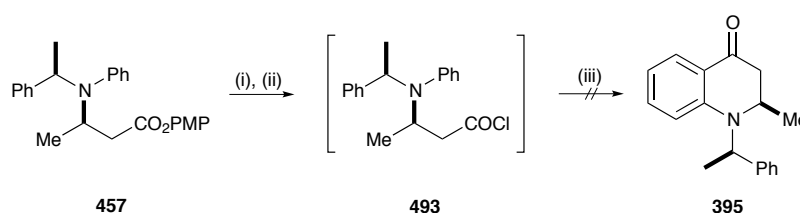


Scheme 102: Reagents & conditions: (i) K₂CO₃, MeOH, rt, 2 h; (ii) LiOH, THF:H₂O, 1:1 (v:v), 40 °C, 16 h; (iii) PPA, 100 °C, 16 h.

With this protocol being unsuccessful, alternative cyclisation methods were therefore screened.

4.13 Friedel-Crafts acylation

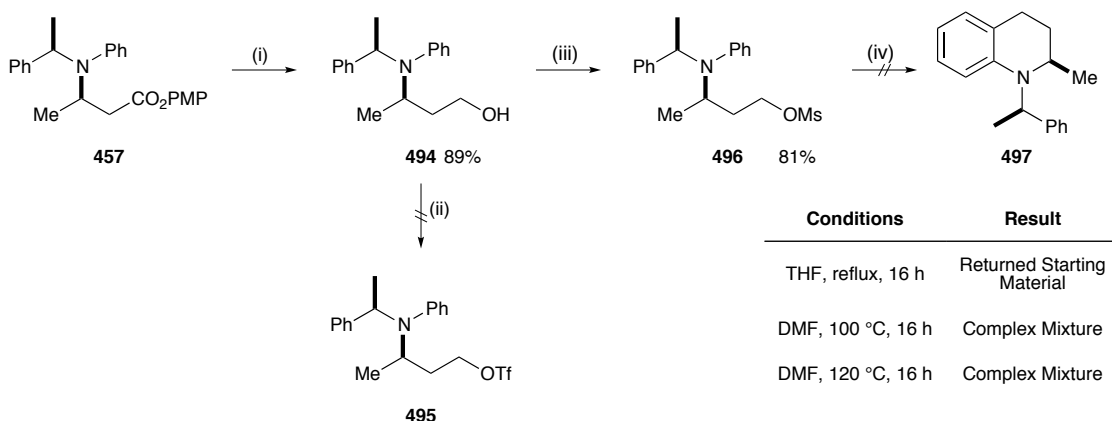
Study switched back to the C(3)-methyl substituted system, with cyclisation from **457** being attempted. Conversion of β -amino ester **457** into the corresponding acid chloride would hopefully allow Friedel-Crafts acylation onto the *N*-phenyl ring. Thus, saponification of **457** afforded the corresponding β -amino acid, although purification *via* flash column chromatography gave poor mass return. Treatment with SOCl_2 gave acid chloride **493** and further treatment with AlCl_3 gave only a complex mixture of products (Scheme 103).



Scheme 103: Reagents & conditions: (i) LiOH, THF:H₂O, 1:1 (v:v), 40 °C, 3 h; (ii) $(\text{COCl})_2$, CH_2Cl_2 , rt, 2 h, then Lewis acid, CH_2Cl_2 , rt, 16 h.

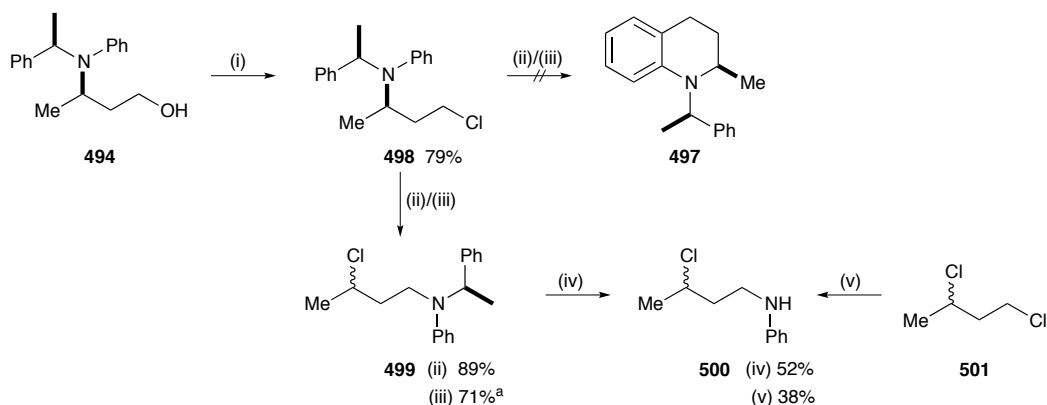
4.14 Friedel-Crafts alkylation

After the failure of the Friedel-Crafts acylation, a switch to Friedel-Crafts alkylation type procedure was envisaged *via* reduction of the ester. Thus, treatment of β -amino ester **457** with LiAlH_4 gave γ -amino alcohol **494** in 89% yield. Initially, formation of triflate **495** was attempted but a complex mixture was returned, potentially due to the very high reactivity of the expected product **495**. A less reactive alternative was therefore investigated, and thus treatment of **494** with MsCl gave mesylate **496** in 81% yield. On heating **496** in THF at reflux only starting material was returned, and on switching the solvent to DMF and increasing the temperature to both 100 °C and 120 °C a mixture of products was obtained, which upon exhaustive chromatography gave no identifiable products (Scheme 104).



Scheme 104: Reagents & conditions: (i) LiAlH_4 , THF, rt, 16 h; (ii) Ti_2O , pyridine, CH_2Cl_2 , rt, 16 h; (iii) MsCl , pyridine, DMAP, rt, 16 h; (iv) See table.

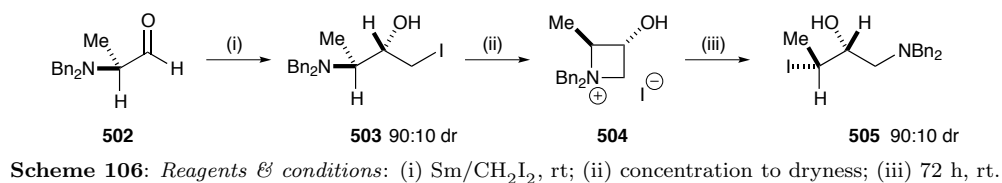
The chloro derivative **498** was next synthesised *via* Appel reaction of **494**. Treatment of **494** with PPh_3 , CCl_4 and Et_3N gave **498** in 79% yield. Heating **498** in DMF at 120 °C gave **499** as a mixture of diastereoisomers, and treatment of **498** with AlCl_3 also gave 41% conversion to **499**. Removal of the α -methylbenzyl group from **499** gave **500**, of which an authentic sample was synthesised from aniline *via* reaction with 1,3-dichlorobutane **501** (Scheme 105).



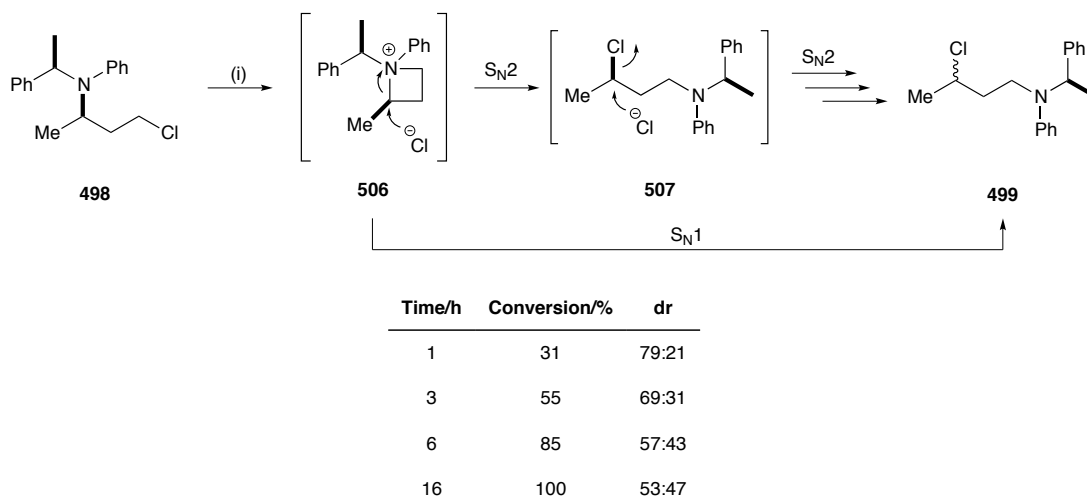
Scheme 105: Reagents & conditions: (i) PPh_3 , CCl_4 , Et_3N , MeCN, Δ , 16 h; (ii) DMF, 120 °C, 16 h; (iii) AlCl_3 , CH_2Cl_2 , rt, 16 h; (iv) H_2 (5 atm), $\text{Pd}(\text{OH})_2$, MeOH, rt, 16 h; (v) aniline, NaH, DMF, Δ , 24 h; [^a59:41 mixture of **499**:**498**].

This outcome is consistent with the formation of an azetidinium intermediate **506**. A similar reaction has been observed previously by Concellón *et al.* in the ring opening and closing of aminoiodohydrins. In this case no loss of stereochemical integrity of the starting material is observed. For example, treatment of **502** with $\text{Sm}/\text{CH}_2\text{I}_2$ gives aminoiodohydrin

503 in 90:10 dr, which after concentration to dryness forms **505** in 90:10 dr *via* azetidinium **504** (Scheme 106).²⁹



In the reaction of **498** in DMF there was a notable degradation of diastereoisomeric ratio in the product (53:47 dr) when compared to the starting material (>99:1 dr). On studying the reaction over time it was evident that as the reaction went further towards completion, the diastereoisomeric ratio decreased. One possible rationale for this observation involves the reaction of chloride ions with **507**, resulting in epimerisation of the C(3) stereogenic centre. This is a known process for iodide and bromide ions,^{30,31} and with the elevated temperatures used in this reaction it maybe that a similar phenomenon with chloride ion is occurring here. Alternatively, a competing S_N1-type ring opening of azetidinium **506** may also be in operation leading to **499** directly (Scheme 107).

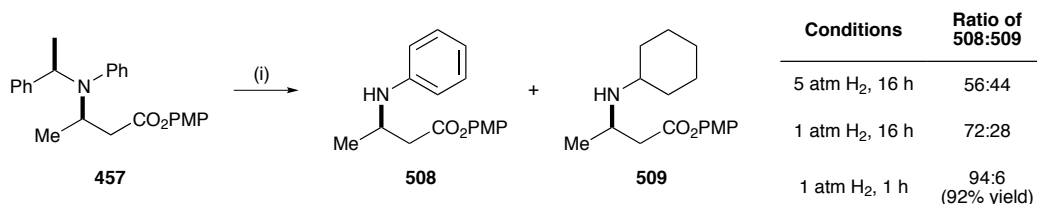


Scheme 107: Reagents & conditions: (i) DMF, 120 °C.

With both of these protocols unsuccessful, it was thought that perhaps the α -methylbenzyl group could be inhibiting the desired cyclisation and attention moved to attempting the cyclisation without it.

4.15 Hydrogenolysis of β -amino ester **457**

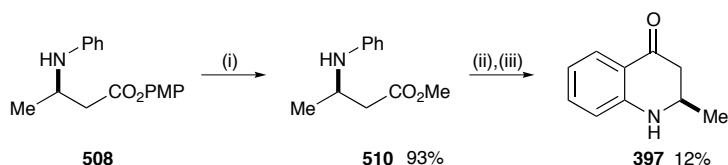
High pressure hydrogenolysis (5 atm) of **457** for 16 h gave a 56:44 mixture of **508** and over reduced product **509**. On reducing the pressure of hydrogen to 1 atm, a 72:28 mixture of **508:509** was present, and finally after reducing the reaction time to 1 hour a 94:6 mixture of **508:509** was afforded, with **508** being isolated in 92% yield after column chromatography (Scheme 108).



Scheme 108: Reagents & conditions: (i) Pd(OH)₂, EtOAc, rt.

4.16 Friedel-Crafts acylation: Deprotected β -amino acid

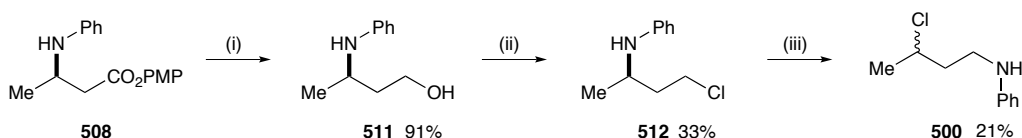
With deprotected β -amino ester **508** in hand the Friedel-Crafts acylation procedure was attempted once again. To avoid the residual 4-methoxyphenol (that would be generated after saponification of **508**) reacting with the acid chloride subsequently formed, once again transesterification to the methyl ester was carried out, affording **510** in 93% yield. Saponification of **510**, followed by formation of the corresponding acid chloride and treatment with AlCl₃ gave the desired dihydroquinolone **397** in 12% yield. The low yield was contributed to by both poor mass return from the saponification of **510**, probably due to the resultant β -amino acid being water soluble, and secondly the cyclisation reaction proceeding to give a mixture of other unidentifiable products (Scheme 109).



Scheme 109: *Reagents & conditions:* (i) MeOH, SOCl₂, Δ, 2 h; (ii) LiOH, THF/H₂O, 1:1 (v/v), 40 °C, 3 h; (iii) (COCl)₂, CH₂Cl₂, rt, 2 h, then AlCl₃, CH₂Cl₂, rt, 16 h.

4.17 Friedel-Crafts alkylation: Deprotected γ -amino chloride

With only a small amount of success with the Friedel-Crafts acylation reaction, the equivalent Friedel-Crafts alkylation was attempted. Reduction of **508** with LiAlH₄ afforded γ -amino alcohol **511** in 91% yield, which was then subjected to Appel conditions to afford chloride **512** in 33% yield. Heating **512** at 120 °C in DMF unfortunately gave a mixture of starting material **512** and **500** (the same product obtained from the earlier Friedel-Crafts alkylation of *N*- α -methylbenzyl protected substrate **498** after deprotection). Once again, the reaction presumably proceeds *via* an azetidinium intermediate (Scheme 110).

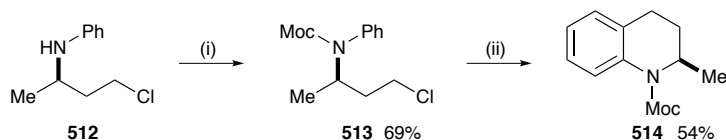


Scheme 110: *Reagents & conditions:* (i) LiAlH₄, THF, rt, 16 h; (ii) PPh₃, CCl₄, Δ, 16 h; (iii) DMF, 120 °C, 2 h.

4.18 Friedel-Crafts alkylation: *N*-Moc protected γ -amino chloride

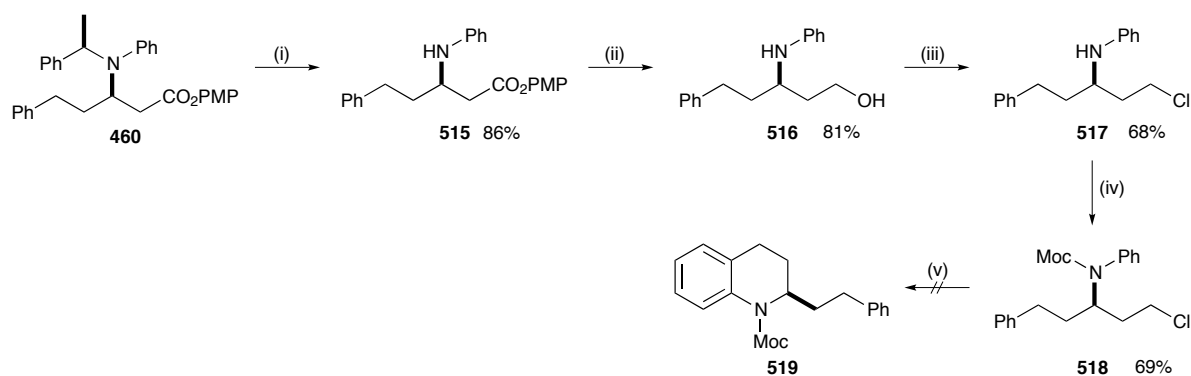
It was envisaged that in order to suppress the azetidinium reaction pathway, an electron withdrawing group must be added to the nitrogen atom in order to reduce the nucleophilicity of the lone pair. Methoxycarbonyl was chosen as a suitable protecting group as not only could it be removed at the end to give an *N*-unsubstituted tetrahydroquinoline, but also reduction with LiAlH₄ would result in formation of an *N*-Me substituent which is

present in the tetrahydroquinoline natural product targets. Treatment of γ -amino chloride **512** with methyl chloroformate gave *N*-Moc protected compound **513** in 69% yield. Subsequent treatment of **513** with AlCl_3 gave the desired tetrahydroquinoline **514** in 54% yield (Scheme 111).



Scheme 111: Reagents & conditions: (i) MocCl, K_2CO_3 , Δ , 16 h; (ii) AlCl_3 , CH_2Cl_2 , rt, 16 h.

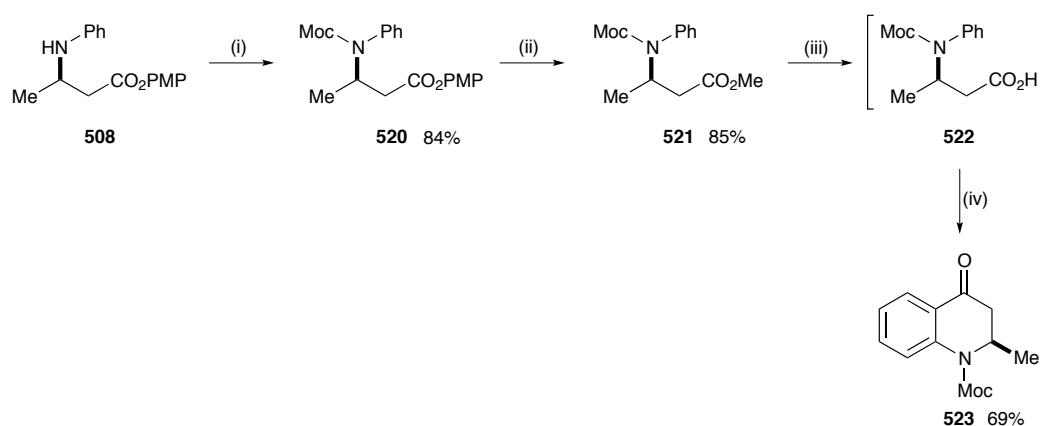
Given this success, β -amino ester **460** (derived from hydrocinnaldehyde) was next chosen as a model system for further reaction optimisation since it mimics the structure of the β -amino esters **461** and **462** required for cuspareine **336** and galipinene **338**. Thus, the α -methylbenzyl group within **460** was removed upon treatment with $\text{H}_2/\text{Pd}(\text{OH})_2$ to give **515** in 86% yield. Subsequent reduction with LiAlH_4 gave γ -amino alcohol **516** in 81% yield, and conversion to the chloride under Appel conditions gave **517** in 68% yield. *N*-Moc protection of **517** gave **518** in 69% yield. Unfortunately, treatment of **518** with AlCl_3 gave a complex mixture of products, which upon exhaustive chromatography gave no identifiable species (Scheme 112).



Scheme 112: Reagents & conditions: (i) $\text{Pd}(\text{OH})_2$, EtOAc, rt, 4 h; (ii) LiAlH_4 , THF, rt, 16 h; (iii) PPh_3 , CCl_4 , 50 °C, 16 h; (iv) MocCl, K_2CO_3 , Δ , 16 h; (v) AlCl_3 , CH_2Cl_2 , rt, 16 h.

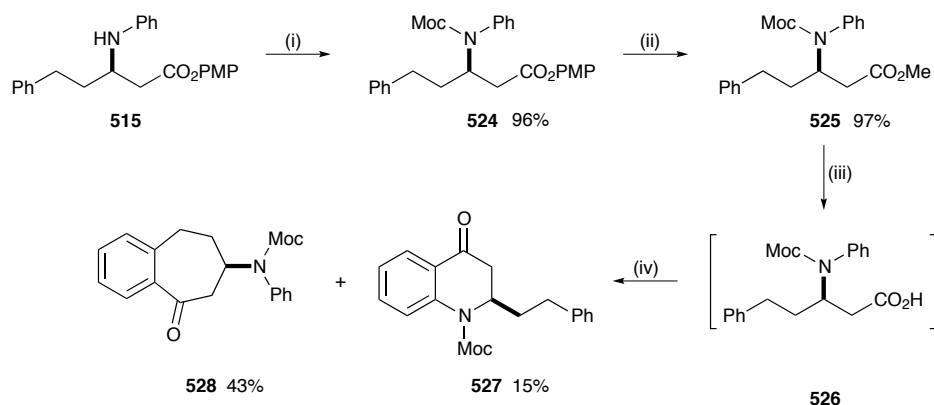
4.19 Friedel-Crafts acylation: *N*-Moc protected β -amino acid

It was then decided to attempt the same approach but for the Friedel-Crafts acylation. Treatment of β -amino ester **508** with methyl chloroformate and K_2CO_3 gave *N*-Moc protected β -amino ester **520** in 84% yield. Again, due to the difficulty of removing the 4-methoxyphenol after saponification, transesterification to the corresponding methyl ester with methanolic HCl was performed, affording **521** in 85% yield. Finally saponification, acid chloride formation and treatment with $AlCl_3$ afforded dihydroquinilone **523** in 69% yield (Scheme 113).



Scheme 113: Reagents & conditions: (i) MocCl, K_2CO_3 , Δ , 16 h; (ii) MeOH, $SOCl_2$, Δ , 2 h; (iii) LiOH, THF/ H_2O , 1:1 (v/v), 40 °C, 3 h; (iv) $(COCl)_2$, CH_2Cl_2 , then $AlCl_3$, CH_2Cl_2 , rt, 16 h.

Switching once again to the hydrocinnamyl derived system, treatment of β -amino ester **515** with methyl chloroformate and K_2CO_3 gave *N*-Moc protected β -amino ester **524** in 96% yield. Transesterification to the methyl ester with methanolic HCl gave **525** in 97% yield, then saponification, acid chloride formation and treatment with $AlCl_3$ gave a 25:75 mixture of the desired dihydroquinilone **527**, and the 7-membered alternative **528**, consistent with competitive cyclisation onto the C(5)-phenyl group. On cooling the reaction to 0 °C the ratio moved further in favour of **528**, giving a 20:80 mixture, but on heating to 50 °C it remained constant at 25:75 (Scheme 114).



Temperature/°C	528:527
0	80:20
20	75:25
50	75:25

Scheme 114: Reagents & conditions: (i) MocCl, K₂CO₃, Δ, 16 h; (ii) MeOH, SOCl₂, Δ, 2 h; (iii) LiOH, THF/H₂O, 1:1 (v/v), 40 °C, 3 h; (iv) (COCl)₂, CH₂Cl₂, then AlCl₃, CH₂Cl₂, 16 h.

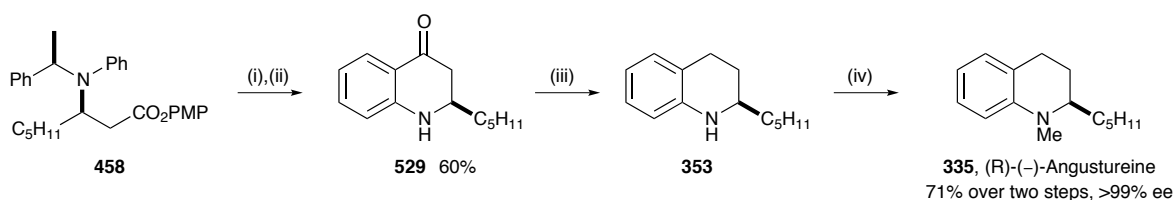
Although it had not been possible to cyclise the hydrocinnamyl derived system, the success of cyclising the C(3)-methyl derived system gave promise to the synthesis of angustureine **335**.

4.20 Synthesis of (*R*)-(-)-angustureine

With β-amino ester **458** already in hand, it was proposed that angustureine could be accessed in four more steps: saponification, cyclisation, reduction of the carbonyl and finally *N*-methylation. Indeed, saponification of **458** upon treatment with aqueous LiOH gave the corresponding β-amino acid which, upon exposure to PPA,^{21,22} underwent cyclisation with concomitant loss of α-methylbenzyl group to give 2-pentyl-2,3-dihydroquinolin-4(1*H*)-one **529** in 60% isolated yield. Reduction of **529** with LiAlH₄²¹ gave tetrahydroquinoline **353** (norangustureine) which was *N*-methylated upon reflux in THF in the presence of MeI and K₂CO₃^{32–35} to give (*R*)-(-)-angustureine **335** in 71% yield over the 2 steps and in >99% ee,^{vii} consistent with the enantiomeric purity of the (*R*)-*N*-phenyl-

^{vii}The enantiomeric purity of (*R*)-(-)angustureine **335** was determined by chiral HPLC analysis kindly provided by Prof. D. J. Dixon and Dr P. Jakubec.

N-(α -methylbenzyl)amine **107** used in the conjugate addition reaction. Overall (*R*)-(-)-angustureine was synthesised in 6 steps and 32% overall yield from commercially available oct-2-enoic acid **416**. The spectroscopic data of the synthetic sample of (*R*)-(-)-**335** were in excellent agreement with those previously reported for the sample isolated from the natural source by Jacquemond-Collet *et al.*,¹ and other synthetic samples.^{12,36–38} Unfortunately, in the original paper describing isolation of the natural product, the conditions under which the specific rotation value was recorded (temperature, solvent, concentration) were not reported by Jacquemond-Collet and co-workers.¹ Nonetheless, on comparing the values obtained from the four synthetic samples of (-)-angustureine **335** in the literature (each of which were in CHCl₃ and with a concentration of either 1.0 or 1.1) only a small deviation was evident $\{[\alpha]_D^{25} -7.0$ (*c* 1.0 in CHCl₃) for >99% ee; lit.¹ for sample isolated from natural source $[\alpha]_D -7.2$;¹ lit.³⁶ $[\alpha]_D^{15} -6.7$ (*c* 1.0 in CHCl₃) for 94% ee; lit.³⁷ $[\alpha]_D^8 -5.5$ (*c* 1.1 in CHCl₃) for 89% ee; lit.¹² $[\alpha]_D^{25} -6.9$ (*c* 1.0 in CHCl₃) for 90% ee; lit.³⁸ $[\alpha]_D^{20} -7.3$ (*c* 1.0 in CHCl₃) for 94% ee} (Scheme 115).



Scheme 115: Reagents & conditions: (i) LiOH, THF:H₂O, 1:1 (v:v), 40 °C, 3 h; (ii) PPA, 100 °C, 16 h; (iii) LiAlH₄, THF, Δ , 16 h; (iv) MeI, K₂CO₃, THF, Δ , 16 h.

4.21 Conclusion and future work

In conclusion, the conjugate addition of lithium (*R*)-*N*-phenyl-*N*-(α -methylbenzyl)amide to α,β -unsaturated 4-methoxyphenyl esters, proceeds with excellent levels of diastereoselectivity to give the corresponding β -amino esters in good yield and as single diastereoisomers (>99:1 dr). The scope of the conjugate addition reaction was delineated by varying the substitution on both the amide and the α,β -unsaturated ester moiety. Cyclisation pro-

protocols to the corresponding tetrahydroquinolines were explored, culminating in the total synthesis of the *Galipea officinalis* alkaloid (–)-angustureine **335** in six steps and 32% overall yield from commercially available oct-2-enoic acid **416**. A portion of this work has also been published in Organic Letters.³⁹ Future work will centre around the key cyclisation step towards the synthesis of the remaining three *Galipea officinalis* tetrahydroquinoline alkaloids, cuspareine **336**, galipeine **337** and galipinine **338**. Although successful cyclisation protocols have been developed, the competing cyclisation from the C(5)-phenyl ring has proved problematic. Two potential solutions to this have been envisaged: (i) decrease the aptitude for the C(5)-ring to cyclise; (ii) add in the ring post-cyclisation. For example if a C(4)-C(5)-*trans* double bond were to be introduced into the system, this would stop the competing cyclisation. It could be introduced pre- or post-conjugate addition, but replacing the α -methylbenzyl group with an *N*-Moc could be problematic as hydrogenolytic cleavage would also reduce the double bond. The use of a 4-methoxy-(α -methylbenzyl) group could be a solution to this, which would allow removal by other non-hydrogenolytic means, e.g. upon treatment with TFA^{40,41} or CAN^{40,42,43} (Figure 29).

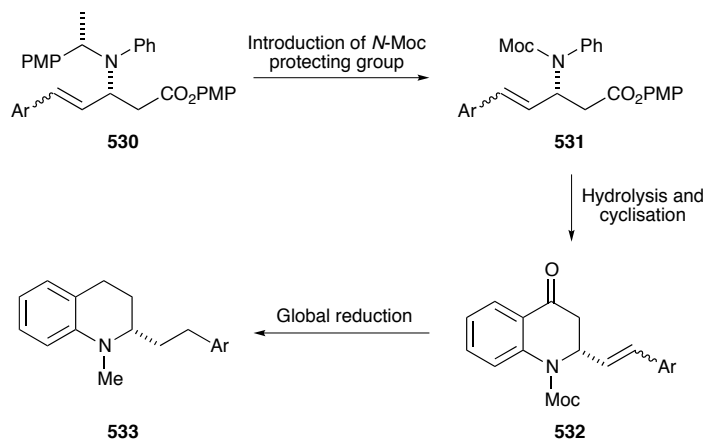


Figure 29: Potential synthetic route.

Alternatively, the aryl ring could be introduced post-cyclisation to remove the option of the competing cyclisation. This could potentially be accomplished by way of alkene metathesis or a Wittig type reaction. In the former, a double bond would need to be

carried through the synthesis, which would once again cause problems with the removal of the α -methylbenzyl group, but again the use of a 4-methoxy-(α -methylbenzyl) group could be a solution. In the latter, the use of a Wittig type reaction would require an oxygen equivalent or a halogen to be carried through the synthesis. This would hopefully be tolerated through the synthesis, then formation of either the corresponding aldehyde or phosphine would allow the olefination (Figure 30).

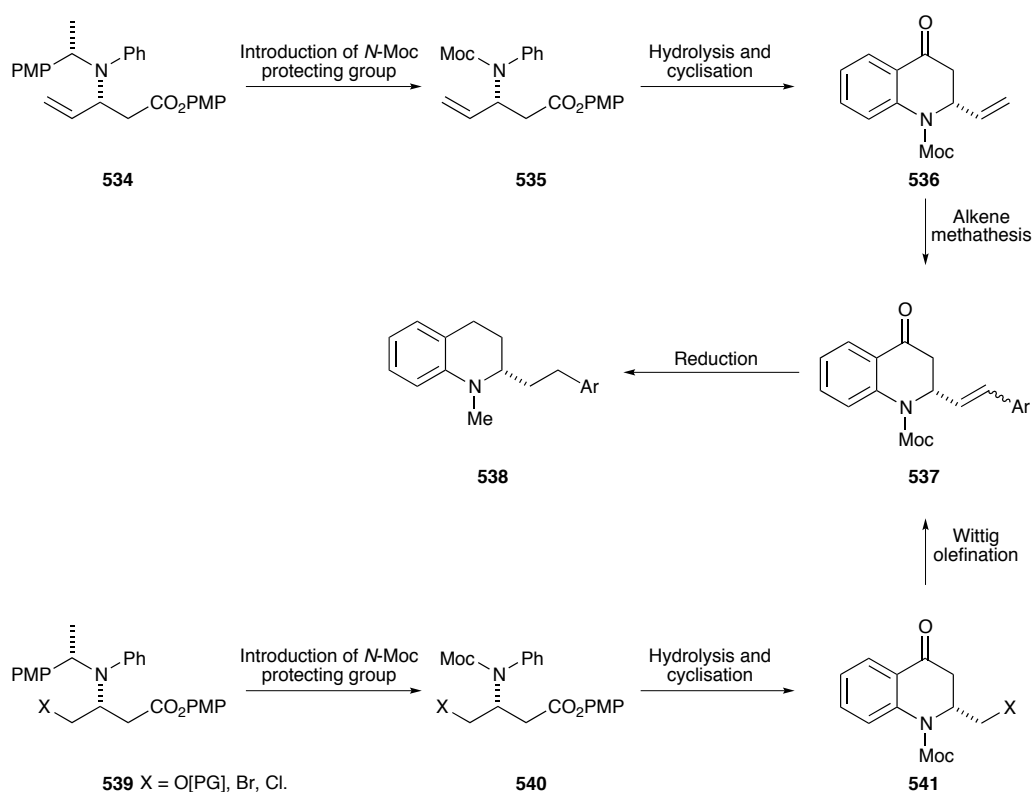


Figure 30: Potential synthetic route.

Bibliography

- [1] Jacquemond-Collet, I.; Hannedouche, S.; Fabre, N.; Fourasté, I.; Moulis, C. *Phytochemistry* **1999**, *51*, 1167–1169.
- [2] Rakotoson, J. H.; Fabre, N.; Jacquemond-Collet, I.; Hannedouche, S.; Fourasté, I.; Moulis, C. *Planta Med.* **1998**, *64*, 762–763.
- [3] Niwa, T.; Takeda, N.; Kaneda, N.; Hashizume, Y.; Nagatsu, T. *Biochem. Biophys. Res. Commun.* **1987**, *144*, 1084 – 1089.
- [4] Nakagawa, A.; Iwai, Y.; Hashimoto, H.; Miyazaki, N.; Oiwa, R.; Takahashi, Y.; Hirano, A.; Shibukawa, N.; Kojima, Y.; Omura, S. *J. Antibiot.* **1981**, *34*, 1408.
- [5] Omura, S.; Nakagawa, A. *Tetrahedron Lett.* **1981**, *22*, 2199–2202.
- [6] Morimoto, Y.; Oda, K.; Shirahama, H.; Matsumoto, T.; Omura, S. *Chem. Lett.* **1988**, *63*, 909–912.
- [7] Hill, M.; Raphael, R. *Tetrahedron Lett.* **1986**, *27*, 1293–1296.
- [8] Steinhagen, H.; Corey, E. J. *Org. Lett.* **1999**, *1*, 823–824.
- [9] Back, T.; Wulff, J. *Angew. Chem., Int. Ed.* **2004**, *116*, 6655–6658.
- [10] Grimwood, S.; Moseley, A.; Carling, R.; Leeson, P.; Foster, A. *Mol. Pharmacol.* **1992**, *41*, 923.
- [11] Jacquemond-Collet, I.; Benoit-Vical, F.; Valentin, A.; Stanislas, E.; Mallié, M.; Fourasté, I. *Planta Med.* **2002**, *68*, 68–69.
- [12] Rueping, M.; Antonchick, A. P.; Theissmann, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3683–3686.
- [13] Chen, B.-L.; Wang, B.; Lin, G.-Q. *J. Org. Chem.* **2010**, *75*, 941–944.
- [14] Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046–2067.
- [15] Lin, X.; Li, Y.; Ma, D. *Chin. J. Chem.* **2004**, *22*, 932–934.
- [16] Masood, M. A. *Post-doc Report*.

- [17] Bentley, S. A. Part II Thesis, 2007.
- [18] Bew, S.; Hughes, D.; Savic, V.; Soapi, K.; Wilson, M. *Chem. Commun.* **2006**, 3513–3515.
- [19] Liu, Z.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 3198–3209.
- [20] Bordwell, F. G. pKa Table, <http://www.chem.wisc.edu/areas/reich/pkatable>.
- [21] Paradisi, M.; Romeo, A. *J. Chem. Soc., Perkin Trans. 1* **1977**, 596–600.
- [22] Liu, J.; Wang, Y.; Sun, Y.; Marshall, D.; Miao, S.; Tonn, G.; Anders, P.; Tocker, J.; Tang, H.; Medina, J. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6840–6844.
- [23] Costello, J. F.; Davies, S. G.; Ichihara, O. *Tetrahedron: Asymmetry* **1994**, *5*, 1999–2008.
- [24] Davies, S. G.; Garrido, N. M.; Kruchinin, D.; Ichihara, O.; Kotchie, L. J.; Price, P. D.; Mortimer, A. J. P.; Russell, A. J.; Smith, A. D. *Tetrahedron: Asymmetry* **2006**, *17*, 1793–1811.
- [25] Claridge, T. D. W.; Davies, S. G.; Lee, J. A.; Nicholson, R. L.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Toms, S. M. *Org. Lett.* **2008**, *10*, 5437.
- [26] Blanchette, M.; Choy, W.; Davis, J.; Essenfeld, A.; Masamune, S.; Roush, W.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183–2186.
- [27] Morgan, A. J.; Masse, C. E.; Panek, J. S. *Org. Lett.* **1999**, *1*, 1949–1952.
- [28] Hansch, C.; Leo, A.; Taft, R. *Chem. Rev.* **1991**, *91*, 165–195.
- [29] Concellón, J.; Bernad, P.; Pérez-Andrés, J. *Tetrahedron Lett.* **2000**, *41*, 1231–1234.
- [30] Hughes, E.; Juliusburger, F.; Masterman, S.; Topley, B.; Weiss, J. *J. Chem. Soc.* **1935**, 1525–1529.
- [31] Hughes, E.; Juliusburger, F.; Scott, A.; Topley, B.; Weiss, J. *J. Chem. Soc.* **1936**, 1173–1175.
- [32] Shahane, S.; Louafi, F.; Moreau, J.; Hurvois, J.; Renaud, J.; van de Weghe, P.; Roisnel, T. *Eur. J. Org. Chem.* **2008**, 4622–4631.
- [33] Kothandaraman, P.; Foo, S. J.; Chan, P. W. H. *J. Org. Chem.* **2009**, *74*, 5947–5952.
- [34] Theeraladanon, C.; Arisawa, M.; Nakagawa, M.; Nishida, A. *Tetrahedron: Asymmetry* **2005**, *16*, 827–831.
- [35] Ryu, J. S. *Bull. Korean Chem. Soc.* **2006**, *27*, 631–634.
- [36] Wang, W. B.; Lu, S. M.; Yang, P. Y.; Han, X. W.; Zhou, Y. G. *J. Am. Chem. Soc.* **2003**, *125*, 10536–10537.
- [37] Lu, S. M.; Wang, Y. Q.; Han, X. W.; Zhou, Y. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 2260–2263.
- [38] Wang, Z. J.; Zhou, H. F.; Wang, T. L.; He, Y. M.; Fan, Q. H. *Green Chem.* **2009**, *11*, 767–769.
- [39] Bentley, S. A.; Davies, S. G.; Lee, J. A.; Roberts, P. M.; Thomson, J. E. *Org. Lett.* **2011**, *13*, 2544–2547.

- [40] Bull, S. D.; Davies, S. G.; Kelly, P. M.; Gianotti, M.; Smith, A. D. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3106–3111.
- [41] Candela-Lena, J.; Davies, S.; Roberts, P.; Roux, B.; Russell, A.; Sanchez-Fernandez, E.; Smith, A. *Tetrahedron: Asymmetry* **2006**, *17*, 1135–1145.
- [42] Bull, S. D.; Davies, S. G.; Delgado-Ballester, S.; Kelly, P. M.; Kotchie, L. J.; Gianotti, M.; Laderas, M.; Smith, A. D. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3112–3121.
- [43] Bull, S. D.; Davies, S. G.; Fox, D. J.; Gianotti, M.; Kelly, P. M.; Pierres, C.; Savory, E. D.; Smith, A. D. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1858–1868.

5.1 General experimental

5.1.1 General techniques

Reactions involving air or moisture sensitive reagents were carried out under nitrogen using standard vacuum line techniques. All glassware for these reactions was flame-dried and allowed to cool under vacuum. Reactions described as being performed at $-78\text{ }^{\circ}\text{C}$ were cooled by means of an acetone/dry ice bath whilst reactions described as being performed at $-78\text{ }^{\circ}\text{C}$ to $0\text{ }^{\circ}\text{C}$ were cooled by means of an acetone bath incompletely saturated with dry ice, or an ice-salt water bath, as appropriate. Organic layers were dried with MgSO_4 .

5.1.2 Solvents

Solvents were dried by passing them through a column of basic alumina, according to the procedure detailed by Grubbs and co-workers.¹ In the case of Et_2O and CH_2Cl_2 this was

Brockman I standard grade *ca.* 150 mesh alumina, whilst for THF it was Alcoa Grade DD-2 alumina. H₂O was purified by either Millipore Mill-Q[®] or Elix[®] UV-10 systems. Solvent ratios are quoted as v/v.

5.1.3 Reagents

n-Butyllithium was used as a solution in hexanes (Aldrich) at the stated concentration, LiHMDS was used as a solution in THF at the concentration stated, KHMDS was used as a solution in toluene at the concentrated stated and *m*-CPBA as a slurry with water and *m*-CBA (Aldrich) at the stated concentration. All other reagents were used as supplied, without further purification. Solutions of DMDO in acetone were prepared² and titrated³ according to the procedures of Adam and co-workers.

5.1.4 Chromatography

Column chromatography was performed either isocratically using a glass column on silica gel (Kieselgel 60) or basic alumina (Brockmann I), or *via* gradient elution using the Biotage SP4 flash chromatography platform. Thin layer chromatography was performed on Merck aluminium sheets coated with 0.2 mm silica gel 60 F₂₅₄. Plates were visualised either by UV light (254 nm), phosphomolybdic acid (10% in ethanol) or potassium permanganate (1% in 2% NaOH solution, containing 7% potassium carbonate).

5.1.5 Infra-red spectroscopy

Infra-red spectra were recorded as a film, a KBr disc or on a diamond ATR module using a Bruker Tensor 27 FT-IR spectrometer. Selected diagnostic peaks only are reported in cm^{-1} .

5.1.6 NMR spectroscopy

^1H NMR spectra were recorded on Bruker AVANCE DPX-200 (200 MHz), DPX250 (250 MHz), DPX-400 (400 MHz), AV-400 (400 MHz), DRX-500 (500 MHz) and AV-500 (500 MHz) spectrometers. Chemical shifts (δ_{H}) are reported in parts per million (ppm) and are referenced to the residual solvent peak. Coupling constants (J) are measured in Hz. ^{13}C NMR spectra were recorded at 62.5 MHz on the Bruker AVANCE DPX-250, 100 MHz on the Bruker AVANCE DPX-400 and AV-400 spectrometers and at 125 MHz on the Bruker AVANCE DRX-500 and AV-500 spectrometers. Chemical shifts (δ_{C}) are quoted in ppm and referenced using residual solvent signals. nOe spectra were recorded on the Bruker AVANCE DRX-500 spectrometer. The spectra recorded on the Bruker AVANCE DRX-500 and AV-500 spectrometers were obtained by Dr. B. Odell of the Chemistry Research Laboratory, University of Oxford.

5.1.7 Mass spectrometry

Low resolution mass spectra (m/z) were recorded on a Micromass LCT Premier instrument (ESI) or a Waters GCT Time of Flight Mass Spectrometer using a temperature programmed solids probe inlet (FI). Major peaks are listed with intensities quoted as percentages of the principal peak. Accurate mass measurements

were recorded by Dr. J. McCullagh, Mr. C. Sparrow, Mr. L. Gong or Mr. R. Procter of the Chemistry Research Laboratory. Accurate Mass ESI measurements were run on a Bruker MicroTof and were internally calibrated with polyalanine in positive and negative modes. Accurate Mass FI measurements were run on a Waters GCT Time of Flight Mass Spectrometer using a temperature programmed solids probe inlet.

5.1.8 Polarimetry

Optical rotations were recorded on a Perkin-Elmer 241 polarimeter with a water jacketed 10 cm cell, with concentrations (c) given in g/100cm³, solvent and temperature as recorded. Specific rotations are quoted in units of 10⁻¹ deg cm² g⁻¹.

5.1.9 Melting points

Melting points were recorded on a Gallenkamp apparatus and are uncorrected.

5.1.10 Chiral HPLC

Chiral HPLC was carried out on an Agilent Technologies 1200 series machine in isocratic mode, using either a Chiralpak[®] OD-H or OJ column, courtesy of Prof. D. J. Dixon and Dr. P. Jakubec.

5.1.11 Elemental analysis

Elemental analyses were recorded by the microanalysis service of the London Metropolitan University, UK.

5.2 General experimental procedures

General Procedure 1: Wittig Olefination

The requisite aldehyde (1 eq) was added to a stirred solution of methyltriphenylphosphenyldiene acetate (1.1 eq) in CH_2Cl_2 and stirred for 16 h at rt. The solution was then concentrated *in vacuo*.

General Procedure 2: Lithium *N-tert*-butyldimethylsilyloxy-*N*-(α -methylbenzyl)amide conjugate addition

BuLi (solution in hexanes, 2 eq) was added dropwise to a stirred solution of *N-tert*-butyldimethylsilyloxy-*N*-(α -methylbenzyl)amine **259** (2 eq) in THF at -78°C . After stirring for 30 min a solution of α,β -unsaturated ester (1 eq) was added in THF *via* cannula. After stirring for a further 10 h at -78°C the reaction mixture was quenched with sat. aq. NH_4Cl . After warming to rt over 15 min the aqueous layer was extracted with three portions of Et_2O , then combined organic extracts were washed with sat. aq. NaCl, then dried and concentrated *in vacuo* to give the crude reaction mixture.

General Procedure 3: Isoxazolidin-5-one Alkylation using LiTMP

Preparation of LiTMP BuLi (solution in hexanes, 1 eq) was added to a stirred solution of 2,2,6,6-tetramethylpiperidine (1.1 eq) in THF at -78°C and left for 1 h.

Alkylation procedure: LiTMP (1.1 eq) was added to a stirred solution of the requisite isoxazolidin-5-one (1 eq) in THF at -78°C and stirred for 2 h. The requisite alkyl halide (3 eq) was then added and the reaction mixture allowed to slowly warm to rt over 16 h, after which time sat. aq. NH_4Cl was added. The aqueous layer was then extracted with three portions of Et_2O , and the combined organic extracts were washed

with sat. aq. NaCl, dried and concentrated *in vacuo* to give the crude reaction mixture.

General Procedure 4: Isoxazolidin-5-one Alkylation using LiHMDS

LiHMDS (solution in THF, 1.2 eq) was added to a stirred solution of the requisite isoxazolidin-5-one in THF at $-78\text{ }^{\circ}\text{C}$ and stirred for 2 h. The requisite alkyl halide (3 eq) was then added and the reaction mixture allowed to slowly warm to rt over 16 h, then sat. aq. NH_4Cl was added. The aqueous layer was then extracted with three portions of Et_2O , and the combined organic extracts were washed with sat. aq. NaCl, dried and concentrated *in vacuo* to give the crude reaction mixture.

General Procedure 5: Hydrogenolysis of Isoxazolidin-5-ones

Pearlman's catalyst (50% by weight) was added to a stirred, degassed solution of the requisite isoxazolidin-5-one in *tert*-butanol. The reaction mixture was then put under 1 atm of hydrogen, heated to $70\text{ }^{\circ}\text{C}$ and stirred for 20 h. Water was added to the solution before filtering through Celite[®]. The Celite[®] was washed with warm water, then the combined water phases were washed with Et_2O , then concentrated *in vacuo* to give the β -amino acid.

General Procedure 6: Lithium *N*-phenyl-*N*-(α -methylbenzyl)amide conjugate addition

BuLi (solution in hexanes, 1.1 eq) was added dropwise *via* syringe to a stirred solution of *N*-phenyl-*N*-(α -methylbenzyl)amine **107** (1.1 eq) in THF at $-78\text{ }^{\circ}\text{C}$ under nitrogen.

After stirring for 30 min, a solution of the requisite α,β -unsaturated ester (1.0 eq) in THF at $-78\text{ }^{\circ}\text{C}$ was added dropwise *via* cannula. After stirring for a further 2 h at $-78\text{ }^{\circ}\text{C}$, sat. aq. NH_4Cl was added. The reaction mixture was allowed to warm to rt over 15 min, and the aqueous layer was extracted with three portions of Et_2O . The combined organic extracts were then washed with brine, dried and concentrated *in vacuo*.

General Procedure 7: Esterification of cinnamoyl chloride

Et_3N (2 eq) was added dropwise to a solution of cinnamoyl chloride (1 eq) and 4-methoxyphenol (1.5 eq) in CH_2Cl_2 at $0\text{ }^{\circ}\text{C}$ and the resultant mixture was stirred for 16 h at rt. H_2O was added, and the aqueous layer was extracted with three portions of CH_2Cl_2 . The combined organic extracts were washed sequentially with 1 M aq. HCl , 10% aq. NaOH and brine, then dried and concentrated *in vacuo*.

General Procedure 8: Horner-Wadsworth-Emmons Olefination

A solution of 4'-methoxyphenyl diethylphosphonoacetate **432** (1.1 eq) in THF was added dropwise to a suspension of NaH (60% dispersion in mineral oil, 1.1 eq) in THF at $0\text{ }^{\circ}\text{C}$. After stirring for 20 min the requisite aldehyde (1.0 eq) was added *via* syringe and the reaction was allowed to stir for a further 1 h at rt. Sat. aq. NH_4Cl was then added, and the aqueous layer was extracted with three portions of EtOAc . The combined organic extracts were washed with brine, dried and concentrated *in vacuo*.

General Procedure 9:⁴ *N*-Arylation I

$\text{Pd}_2(\text{dba})_3$ (4 mol%) and *rac*-BINAP (8 mol%) were dissolved in toluene and degassed with N_2 for 15 mins. The solution was then heated at 110 °C for 10 mins when the colour changed from deep purple to deep orange. After cooling, NaO^tBu (2.05 eq), α -methylbenzyl amine (2.5 eq) and the requisite aryl bromide (1 eq) were added and the reaction was heated at reflux for 90 mins. The solution was allowed to cool and then filtered through a pad of Celite[®], washing with three portions of EtOAc, and the combined organic extracts were concentrated *in vacuo*.

General Procedure 10:⁵ *N*-Arylation II

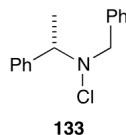
CuI (5 mol%) and K_3PO_4 (2 eq) were added to a round-bottomed flask and purged with N_2 . Iso-propyl alcohol, ethylene glycol (2 eq), α -methylbenzyl amine (1.2 eq) and the requisite aryl iodide (1 eq) were then added. The reaction was heated to 80 °C for 24 h, then cooled and H_2O added. The aqueous layer was extracted with three portions of Et_2O and the combined organic extracts were washed with 10% aq. citric acid and brine, then dried and concentrated *in vacuo*.

General Procedure 11: Methoxycarbonyl Protection

K_2CO_3 (5 eq) was added to a solution of the substrate in methyl chloroformate and heated at reflux for 16 h. The suspension was allowed to cool and then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 and H_2O and the aqueous layer was extracted with three portions of CH_2Cl_2 . The combined organic extracts were washed with brine, dried and concentrated *in vacuo*.

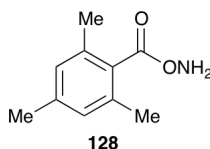
5.3 Experimental for Chapter 2

(*S*)-*N*-Chloro-*N*-benzyl-*N*-(α -methylbenzyl)amine **133**



N-Chlorosuccinimide (126 mg, 0.95 mmol) was added to a solution of **108** (200 mg, 0.95 mmol) in CH₂Cl₂ (4 mL) at 0 °C and stirred for 15 min. The mixture was concentrated *in vacuo*, then 30-40 °C petrol (3 mL) was added and the resulting suspension was filtered and the solid residue washed with further 30-40 °C petrol (2 × 2 mL). The filtrate was concentrated *in vacuo* to give **133** as a colourless oil (189 mg, 81%); $[\alpha]_{\text{D}}^{25}$ -21.2 (c 1.0 in CHCl₃); ν_{max} (ATR) 3030 (C–H); δ_{H} (400 MHz, CDCl₃) 1.69 (3H, d, J 6.6, C(α)Me), 3.93 (1H, d, J 14.0, PhCH_A), 4.05 (1H, d, J 14.0, PhCH_B), 4.21 (1H, q, J 6.6, C(α)H), 7.31-7.49 (10H, m, *Ph*); δ_{C} (100 MHz, CDCl₃) 19.7 (C(α)Me), 62.2 (PhCH₂), 69.0 (C(α)), 126.9, 127.7, 128.0, 128.4, 128.6, 129.0 (*o*-, *m*-, *p*-*Ph*), 137.9, 141.8 (*i*-*Ph*); m/z (FI) 247 ([M]⁺, ³⁷Cl, 100%), 245 ([M]⁺, ³⁷Cl, 100%); HRMS (FI) C₁₅H₁₆³⁷ClN⁺ ([M]⁺) requires 247.0937; found 247.0940; HRMS (FI) C₁₅H₁₆³⁵ClN⁺ ([M]⁺) requires 245.0966; found 245.0966.

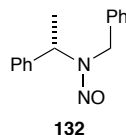
O-Mesityl hydroxylamine **128**⁶



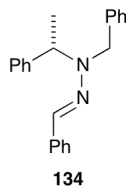
Mesityl chloride (1.00 g, 5.5 mmol) was added to a stirred solution of *N*-Boc hydroxylamine (730 mg, 5.5 mmol) in CH₂Cl₂ (7 mL) at 0 °C and stirred for 4 h, then

stirred for a further 16 h at rt. The mixture was washed with H₂O (7 mL), dried and concentrated *in vacuo*. The residue was dissolved in CH₂Cl₂ (20 mL) and trifluoroacetic acid (20 mL) was added. The mixture was stirred at rt for 15 min then sat. aq. NaHCO₃ was added until CO₂ evolution ceased. The aqueous layer was extracted with CH₂Cl₂ (3 × 100 mL), and the combined organic extracts were dried and concentrated *in vacuo* to give **128** as a colourless oil (896 mg, 91%); δ_H (400 MHz, CDCl₃) 2.30 (9H, s, 3 × *ArMe*), 6.88 (2H, s, *Ar*).

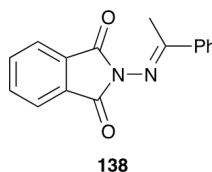
***N*-Benzyl-*N*-(α-methylbenzyl)-*N*-nitrosoamine **132**⁷**



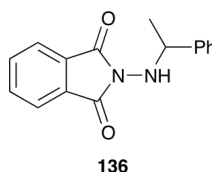
NaNO₂ (1.52 g, 22.0 mmol) was added slowly to a solution of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine hydrochloride (5.00 g, 20.2 mmol) and aq. HCl (2M, 0.25 mL) in H₂O (25 mL) and heated at 75 °C for 2 h. The reaction was cooled, the aqueous layer extracted with Et₂O (3 × 30 mL) and the combined organic extracts dried and concentrated *in vacuo* to give **132** as a pale yellow oil (4.49 g, 93%); [α]_D²⁵ +40.5 (*c* 4.81 in EtOH) {lit.⁸ [α]_D^{30.5} +43.4 (*c* 4.81 in EtOH)}; The *anti* and *syn* isomers could be seen separately as a 87:13 ratio;^{9,10} *anti*: δ_H (400 MHz, CDCl₃) 1.85 (3H, d, *J* 7.1, C(α)*Me*), 4.14 (1H, d, *J* 14.7, PhCH_A), 5.08 (1H, d, *J* 14.7, PhCH_B), 5.41 (1H, q, *J* 7.1, C(α)*H*), 6.99-7.02 (2H, m, *Ph*), 7.25-7.41 (8H, m, *Ph*); *syn*: δ_H (400 MHz, CDCl₃) 1.24 (3H, d, *J* 7.1, C(α)*Me*), 4.69 (1H, d, *J* 15.1, PhCH_A), 5.35 (1H, d, *J* 15.1, PhCH_B), 6.26 (1H, q, *J* 7.1, C(α)*H*), 7.09-7.21 (4H, m, *Ph*), 7.25-7.41 (6H, m, *Ph*).

N*-Benzyl-*N*-(α -methylbenzyl)-*N'*-(benzylidene)hydrazine **134*

108 (2.97 g, 14.1 mmol) and **128** (840 mg, 4.69 mmol) were stirred at rt for 15 min, then at 70 °C for 15 min. Then H₂O (2 mL), AcOH (2.5 mL) and benzaldehyde (0.52 mL, 5.16 mmol) were added and the solution was stirred for a further 15 min. The solution was cooled, H₂O (50 mL) was added and the aqueous extracted with Et₂O (3 × 30 mL). The combined organic extracts were washed with H₂O (50 mL) and 10% aq. NaOH (50 mL). Purification *via* flash column chromatography (gradient elution 30-40 °C petrol/Et₂O 40:1; increased to 20:1) gave **134** as a colourless oil (450 mg, 31%); $[\alpha]_D^{25} +38.7$ (*c* 1.0, CHCl₃); $\nu_{\max}$ (ATR) 1589 (C=N); δ_H (400 MHz, CDCl₃) 1.83 (3H, d, *J* 7.0, C(α)*Me*), 4.24 (1H, d, *J* 16.4, PhCH_A), 4.37 (1H, d, *J* 16.4, PhCH_B), 4.83 (1H, q, *J* 7.0, C(α)*H*), 7.17 (1H, s, C(=N)*H*), 7.21-7.39 (11H, m, *Ph*), 7.43-7.45 (2H, m, *Ph*), 7.56-7.58 (2H, m, *Ph*); δ_C (100 MHz, CDCl₃) 19.9 (C(α)*Me*), 53.7 (PhCH₂), 65.4 (C(α)), 125.6, 126.6, 127.0, 127.1, 127.3, 127.4, 128.5, 128.8, 131.1 (*o*-, *m*-, *p*-*Ph*), 127.6, 127.8, 142.8 (*i*-*Ph*), 153.9 (C=N); *m/z* (ESI⁺) 337 ([M+Na]⁺, 56%), 315 ([M+H]⁺, 100%); HRMS (ESI⁺) C₂₂H₂₃N₂⁺ ([M+H]⁺) requires 315.1856; found 315.1848.

N*-(*N'*-Benzylideneamino)phthalimide **138*

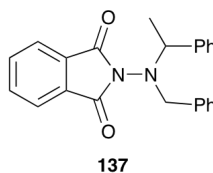
HCl (conc., 0.1 mL) was added to a stirred solution of *N*-amino phthalimide (5 g, 31.0 mmol) and acetophenone (14.3 mL, 123 mmol) in 1,4-dioxane (250 mL). The resultant mixture was then heated to 80 °C for 16 h, then cooled to rt and concentrated *in vacuo*. Purification *via* recrystallisation (1,4-dioxane) gave **138** as a pale yellow solid (5.97 g, 73%); ν_{max} (ATR) 1785 (C=O), 1708 (C=O); δ_{H} (400 MHz, CDCl₃) 2.37 (3H, s, PhCCH₃), 7.43-7.53 (3H, m, *Ph*), 7.75-7.77 (2H, m, *Ph*), 7.89-7.91 (2H, m, *Ar*), 7.98-8.00 (2H, m, *Ar*); δ_{C} (125 MHz, CDCl₃) 18.3 (*Me*), 123.7 (*Ar*), 127.8, 128.6 (*i-Ar*), 131.4, 131.6, 134.4, 136.4 (*Ar*), 164.3 (C=N), 175.5 (C=O); m/z (ESI⁺) 551 ([2M+Na]⁺, 100%), 287 ([M+Na]⁺, 23%), 265 ([M+H]⁺, 10%); HRMS (ESI⁺) C₁₆H₁₃N₂O₂⁺ ([M+H]⁺) requires 265.0972; found 265.0966.

N*-[*N'*-(α -Methylbenzyl)amino]phthalimide **136*

Borane-pyridine complex (11.4 mL, 113 mmol) was added to a stirred solution of **138** (5.79 g, 22.6 mmol) in acetic acid (100 mL) and the reaction was stirred for 15 mins. The acetic acid was then removed *in vacuo* and aq. HCl (10%, 150 mL) was added at 0 °C before the reaction was stirred for a further 30 minutes. Sat. aq. Na₂CO₃ was

added until the solution was neutralised, and it was then extracted with EtOAc (3 × 150 mL). The combined organic extracts were washed with sat. aq. NaCl (300 mL), dried and concentrated *in vacuo* to give a yellow solid. This was washed with petrol to give **136** as a pale yellow solid (5.15 g, 86%); C₁₆H₁₄N₂O₂ requires C, 72.2; H, 5.3; N, 10.5%; found C, 72.1; H, 5.4; N, 10.4%; mp 82-84 °C; $\nu_{\max}$ (ATR) 1784 (C=O), 1704 (C=O); δ_{H} (400 MHz, CDCl₃) 1.47 (3H, d, *J* 6.4, C(α)*Me*), 4.55 (1H, q, *J* 6.4, C(α)*H*), 4.68 (1H, br s, *NH*), 7.23-7.33 (3H, m, *Ph*), 7.45-7.47 (2H, m, *Ph*), 7.69-7.71 (2H, m, *Ar*), 7.78-7.80 (2H, m, *Ar*); δ_{C} (100 MHz, CDCl₃) 20.9 (C(α)*Me*), 59.2 (C(α)), 123.3, 130.0, 134.1 (*Ar*), 127.4, 127.9, 128.4 (*o*, *m*, *p-Ph*), 141.3 (*i-Ph*), 166.8 (C=O); *m/z* (ESI⁺) 555 ([2M+Na]⁺, 82%), 289 ([M+Na]⁺, 100%), 267 ([M+H]⁺, 10%); HRMS (ESI⁺) C₁₆H₁₄NNa₂O₂⁺ ([M+Na]⁺) requires 289.0948; found 289.0944.

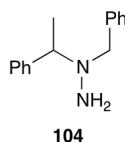
N*-[*N'*-Benzyl-*N'*-(α-methylbenzyl)amino]phthalimide **137*



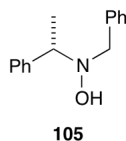
Na₂CO₃ (4.10 g, 38.6 mmol) was added to a stirred solution of **136** (5.15 g, 19.3 mmol) in DMPU (100 mL) under argon. Benzyl bromide (6.90 mL, 67.9 mmol) was added dropwise and the reaction heated to 100 °C for 5 h. The reaction was then cooled to 0 °C then treated with H₂O (100 mL). The aqueous layer was then extracted with Et₂O (3 × 150 mL), the combined organic extracts were washed with H₂O (3 × 300 mL), dried, filtered and concentrated *in vacuo*. Purification *via* flash column chromatography on (gradient elution 30-40 °C petrol/Et₂O 20:1; increased to 3:2) gave **137** as a pale yellow solid (2.80 g, 41%) and recovered **136** (1.88 g, 37%); C₂₃H₂₀N₂O₂;

requires C, 77.5; H, 5.7; N, 7.9%; found C, 77.6; H, 5.8; N, 7.7%; mp 94-96 °C; $\nu_{\max}$ (ATR) 1781 (C=O), 1715 (C=O); δ_{H} (400 MHz, CDCl₃) 1.38 (3H, d, J 6.6, C(α)Me), 4.12 (1H, d, J 13.1, PhCH_A), 4.49 (1H, d, J 13.1, PhCH_B), 4.85 (1H, q, J 6.6, C(α)H), 7.12-7.19 (3H, m, Ar), 7.27-7.39 (5H, m, Ar), 7.61-7.72 (6H, m, Ar); δ_{C} (100 MHz, CDCl₃) 21.9 (C(α)Me), 55.9 (PhCH₂), 63.7 (C(α)), 122.9, 123.4, 127.4, 127.5, 127.7, 128.1, 128.7, 129.1, 129.6, 129.8 (Ar), 134.0, 134.1, 137.0, 143.7 (*i*-Ar), 167.3, 168.2 (C=O); m/z (ESI⁺) 379 ([M+Na]⁺, 100%), 357 ([M+H]⁺, 4%); HRMS (ESI⁺) C₂₃H₂₀N₂NaO₂⁺ ([M+Na]⁺) requires 379.1417; found 379.1402.

N*-Benzyl-*N*-(α -methylbenzyl)hydrazine **104*

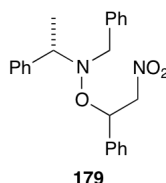


Hydrazine monohydrate (0.24 mL, 4.93 mmol) was added to **137** (700 mg, 1.97 mmol) in EtOH (15 ml) and heated at reflux for 4 h. After cooling the resultant suspension was filtered and then concentrated *in vacuo*. Toluene (10 mL) was added to the residue, the suspension filtered and then concentrated *in vacuo* to give **104** as a pale yellow oil (425 mg, 95%); $\nu_{\max}$ (ATR) 3327 (NH₂); δ_{H} (400 MHz, CDCl₃) 1.56 (3H, d, J 6.7, C(α)Me), 2.81 (2H, br s, NH₂), 3.55 (1H, d, J 13.3, PhCH_A), 3.70 (1H, d, J 13.3, PhCH_B), 3.82 (1H, q, J 6.7, C(α)H), 7.27-7.46 (10H, m, Ph); δ_{C} (100 MHz, CDCl₃) 19.1 (C(α)Me), 62.6 (PhCH₂), 66.0 (C(α)), 127.2, 127.3, 128.1, 128.4, 128.5, 129.1 (*o*-, *m*-, *p*-Ph), 138.7, 142.3 (*i*-Ph); m/z (ESI⁺) 249 ([M+Na]⁺, 15%), 227 ([M+H]⁺, 100%); HRMS (ESI⁺) C₁₅H₁₉N₂⁺ ([M+H]⁺) requires 227.1543; found 227.1543.

(S)-N-(α -methylbenzyl)-N-benzylhydroxylamine **105¹¹**

A mixture of (*S*)-*N*-benzyl-*N*-(α -methylbenzyl)amine **108** (10 g, 47.0 mmol) and ethyl acrylate (5.15 mL, 47 mmol) was stirred neat at 110 °C for 72 h. The reaction mixture was dissolved in CH₂Cl₂ (200 mL) and washed sequentially with aq. citric acid (10%, 200 mL) and sat. aq. NaHCO₃ (200 mL), then dried, filtered and concentrated *in vacuo* to give **176** as a yellow oil (5.50 g). *m*-CPBA (73.7%, 4.13 g, 17.6 mmol) was added to a stirred solution of **176** (5.50 g, 17.6 mmol) at 0 °C, then allowed to warm to rt and stir for a further 2 h. The resultant mixture was passed through a column of basic alumina, eluting first with CH₂Cl₂ to remove impurities, then with CH₂Cl₂:MeOH 3:1. Purification *via* flash column chromatography (gradient elution 30-40 °C petrol/Et₂O 9:1; increased to 3:1) gave **105** as a white solid (3.20 g, 30%); mp 64-66 °C {lit.¹¹ mp 70-74 °C}; [α]_D²⁵ -3.4 (*c* 1.0 in CHCl₃) {lit.¹¹ for enantiomer, [α]_D²² +3.0 (*c* 1.72 in CHCl₃)} δ_{H} (400 MHz, CDCl₃) 1.50 (3H, d, *J* 6.6, C(α)*Me*), 3.65 (1H, d, *J* 13.2, PhCH_A), 3.75 (1H, d, *J* 13.2, PhCH_B), 3.84-3.89 (1H, m, C(α)*H*), 7.24-7.42 (10H, m, *Ph*).

N*-Benzyl-*N*-(α -methylbenzyl)-*O*-(2-nitro-1-phenylethyl)hydroxylamine **179*



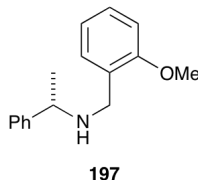
KHMDS (0.5 M in toluene, 0.44 mL, 0.22 mmol) was added to a solution of **105** (50 mg, 0.22 mmol) in THF (2 mL) at $-78\text{ }^{\circ}\text{C}$ and stirred for 30 min, then **143** (22 mg, 0.15 mmol) was added in THF (1 mL) and the reaction stirred for a further 1 h. AcOH (0.1 mL) was added and the solution diluted with H_2O (3 mL). The aqueous was extracted with Et_2O ($3 \times 3\text{ mL}$) and combined organic extracts were washed with sat. aq. NaHCO_3 (10 mL) and brine (10 mL), dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution $30\text{--}40\text{ }^{\circ}\text{C}$ petrol/ Et_2O 4:1; increased to 1:1) gave a 75:25 mixture of **179**:**143** as a pale yellow oil (29 mg, 52%, 61:39 dr); ν_{max} (ATR) 1555 (NO_2 , st as), 1343 (NO_2 , st sy); δ_{C} (100 MHz, CDCl_3) 20.1 ($\text{C}(\alpha)\text{Me}$), 61.5, 63.8 ($\text{C}(1)$), 67.3, 68.6 ($\text{C}(\alpha)$), 80.2, 81.0 ($\text{C}(2)$), 127.2, 127.4, 127.6, 127.6, 127.9, 128.3, 128.4, 128.5, 128.6, 128.7, 129.1, 129.3, 129.4, 129.5, 130.0, 132.3, 137.3, 139.2 (*o*-, *m*-, *p*-Ph), 127.8, 128.1, 130.2, 137.6, 138.6, 143.2 (*i*-Ph); m/z (ESI^+) 399 ($[\text{M}+\text{Na}]^+$, 100%), 377 ($[\text{M}+\text{H}]^+$, 34%); HRMS (ESI^+) $\text{C}_{23}\text{H}_{24}\text{N}_2\text{NaO}_3^+$ ($[\text{M}+\text{Na}]^+$) requires 399.1679, found 399.1674.

Data for major diastereoisomer; δ_{H} (400 MHz, CDCl_3) 1.49 (3H, obs d, J 7.0, $\text{C}(\alpha)\text{Me}$), 3.69 (1H, d, J 13.3, PhCH_A), 3.75–4.04 (2H, m, $\text{C}(\alpha)\text{H}$, PhCH_B), 4.55 (2H, br s, $\text{C}(2)\text{H}_2$), 5.20 (1H, dd, J 7.5, 5.8, $\text{C}(3)\text{H}$), 7.14–7.59 (15H, m, Ph).

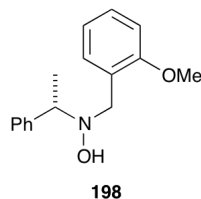
Data for minor diastereoisomer; δ_{H} (400 MHz, CDCl_3) 1.49 (3H, obs d, J 7.0, $\text{C}(\alpha)\text{Me}$), 3.55 (1H, d, J 13.4, PhCH_A), 3.75–4.04 (4H, m, $\text{C}(\alpha)\text{H}$, PhCH_B , $\text{C}(2)\text{H}_2$), 4.90 (1H, dd,

J 7.4, 5.8, C(3) H), 7.14-7.59 (15H, m, Ph).

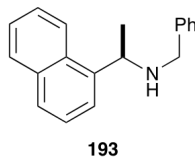
(*S*)-*N*-(α -methylbenzyl)-*N*-(2-methoxy)benzylamine **197¹²**



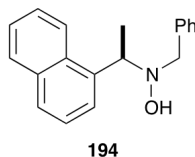
o-Anisaldehyde (1.90 mL, 14.9 mmol) was added to a stirred solution of α -methylbenzylamine **196** (1.72 g, 14.2 mmol) in ethanol (16 mL) and heated at 95 °C for 2 h. The reaction mixture was then cooled to 0 °C and sodium borohydride (538 mg, 14.2 mmol) was slowly added. The reaction was allowed to warm to rt and stirred vigorously for 42 h then concentrated to a white paste. The resulting mixture was partitioned between H₂O (20 mL) and CH₂Cl₂ (20 mL), and the aqueous layer extracted with CH₂Cl₂ (3 $\times$ 20 mL). The combined organic extracts were dried and concentrated *in vacuo*, to give **197** (2.00 g, 58%) with no further purification required; $[\alpha]_{\text{D}}^{25}$ -54.1 (c 1.0 in CHCl₃) {lit.¹² for enantiomer, $[\alpha]_{\text{D}}^{25}$ +56.1 (c 1.0 in CHCl₃)}; δ_{H} (400 MHz, CDCl₃) 1.36 (3H, d, J 6.6, C(α) Me), 3.59 (1H, d, J 13.2, PhCH_A), 3.71 (1H, d, J 13.2, PhCH_B), 3.78 (1H, q, J 6.6, C(α) H), 3.83 (3H, s, OMe), 6.86-6.92 (2H, m, Ar), 7.15-7.19 (1H, m, Ar), 7.22-7.30 (2H, m, Ar), 7.33-7.38 (4H, m, Ar).

(S)-N-(α -methylbenzyl)-N-(2-methoxy)benzylhydroxylamine 198

A mixture of *N*-(α -methylbenzyl)-*N*-(2-methoxy)benzylamine (1.00 g, 4.1 mmol) and ethyl acrylate (0.23 mL, 2.10 mmol) was stirred neat at 110 °C for 72 h. The reaction mixture was dissolved in CH₂Cl₂ (30 mL) and washed sequentially with aq. citric acid (10 %, 30 mL) and sat. aq. NaHCO₃ (30 mL), then dried, filtered and concentrated *in vacuo* to give a yellow oil (400 mg). *m*-CPBA (73.7%, 275 mg, 1.17 mmol) was added to a stirred solution of the crude mixture (400 mg) at 0 °C, then allowed to warm to rt and stir for a further 2 h. The resultant mixture was passed through a column of basic alumina, eluting first with CH₂Cl₂ to remove impurities, then with CH₂Cl₂:MeOH 3:1. Purification *via* flash column chromatography (gradient elution 30-40 °C petrol/Et₂O 9:1; increased to 2:1) gave **198** as a colourless oil (200 mg, 37%); $\nu_{\max}$ (film) 2936 (C–H); $[\alpha]_{\text{D}}^{20.5}$ –21.5 (*c* 1.0 in CHCl₃); δ_{H} (400 MHz, CDCl₃) 1.41 (3H, d, *J* 6.7, C(α)Me), 3.63 (1H, d, *J* 13.2, PhCH_A), 3.70 (1H, q, *J* 6.7, C(α)H), 3.76 (3H, s, OMe), 3.77 (1H, obscured d, *J* 13.2, PhCH_B), 5.91 (1H, br s, OH), 6.83-6.92 (2H, m, Ar), 7.20-7.39 (7H, m, Ar); δ_{C} (100 MHz, CDCl₃) 18.8 (C(α)Me), 55.0 (PhCH₂), 55.2 (OMe), 67.3 (C(α)), 110.4, 120.2, 126.5, 127.2, 128.1, 128.2, 128.4 (Ar), 131.3, 142.8 (*i*-Ar), 157.9 (COMe); *m/z* (ESI⁺) 280 ([M+Na]⁺, 100%), 258 ([M+H]⁺, 66%); HRMS (ESI⁺) C₁₆H₂₀NO₂⁺ ([M+H]⁺) requires 258.1489, found 258.1489.

(*R*)-*N*-benzyl-*N*-[(1'-naphthyl)ethyl]amine **193¹³**

PhCHO (0.62 mL, 6.14 mmol) was added to a solution of (*R*)-1-(1'-naphthyl)ethylamine **192** (0.94 mL, 5.85 mmol) in EtOH (10 mL) and heated at reflux for 2 h. The solution was cooled to 0 °C, NaBH₄ (221 mg, 5.85 mmol) was added and then stirred at rt for 42 h. The resulting suspension was concentrated *in vacuo* to half its volume, then partitioned between H₂O (15 mL) and CH₂Cl₂ (15 mL). The aqueous layer was extracted with CH₂Cl₂ (3 × 15 mL) and the combined organic extracts dried and concentrated *in vacuo* to give **193** as a colourless oil (1.23 g, 81%); [α]_D^{20.5} −5.6 (*c* 1.0 in CHCl₃) {lit.¹³ for enantiomer, [α]_D²⁵ +5.2 (*c* 0.98 in CHCl₃)}; δ_{H} (400 MHz, CDCl₃) 1.54 (3H, d, *J* 6.6, C(α)Me), 3.71 (1H, d, *J* 13.1, PhCH_A), 3.79 (1H, d, *J* 13.1, PhCH_B), 4.71 (1H, q, *J* 6.6, C(α)H), 7.26-7.33 (5H, m, *Ar*), 7.48-7.54 (3H, m, *Ar*), 7.77-7.81 (2H, m, *Ar*), 7.88-7.91 (1H, m, *Ar*), 8.13-8.16 (1H, m, *Ar*).

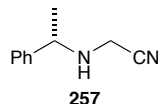
(*R*)-*N*-benzyl-*N*-[(1'-naphthyl)ethyl]hydroxylamine **194**

193 (500 mg, 1.92 mmol) was added to a stirred solution of DMDO (0.044 M in acetone, 43.5 mL, 1.92 mmol) at 0 °C and left for 15 minutes. H₂O (10 mL) was added and the aqueous layer extracted with Et₂O (3 × 15 mL), the combined organic extracts

were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution 30-40 °C petrol/Et₂O 9:1; increased to 4:1) gave **194** as a white solid (350 mg, 66%); $[\alpha]_{\text{D}}^{25} -45.6$ (c 1.0 in CHCl₃); mp 62-64 °C; ν_{max} (ATR) 3061 (O–H); δ_{H} (400 MHz, CDCl₃) 1.62 (3H, d, *J* 6.6, C(**α**)*Me*), 3.69 (1H, d, *J* 13.3, PhCH_A), 3.84 (1H, d, *J* 13.3, PhCH_B), 4.67 (1H, q, *J* 6.6, C(**α**)*H*), 7.26-7.34 (5H, m, *Ph*), 7.49-7.58 (3H, m, *Ar*), 7.72 (1H, d, *J* 7.0, *Ar*), 7.81 (1H, d, *J* 8.1, *Ar*), 7.91 (1H, dd, *J* 7.0, 2.4, *Ar*), 8.31 (1H, d, *J* 8.1, *Ar*); *m/z* (ESI⁺) 300 ([M+Na]⁺, 100%), 278 ([M+H]⁺, 30%); HRMS (ESI⁺) C₁₉H₁₉NNaO⁺ ([M+Na]⁺) requires 300.1359; found 300.1361.

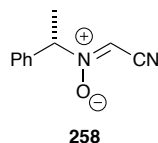
5.4 Experimental for Chapter 3

(*S*)-*N*-Cyanomethyl 2-phenylethylamine **257**



Hünig's base (21.8 mL, 156 mmol) and bromoacetonitrile (6.0 mL, 85.8 mmol) were added sequentially to a stirred solution of (*S*)- α -methylbenzylamine **196** (10.0 mL, 77.7 mmol) in MeCN (200 mL) and stirred for 16 h at rt. The reaction mixture was then concentrated *in vacuo*. The residue was partitioned between sat. aq. NaHCO₃ (200 mL) and CH₂Cl₂ (200 mL), and the aqueous layer was extracted with CH₂Cl₂ (3 $\times$ 200 mL). The combined organic extracts were washed with sat. aq. NaCl (800 mL), then dried and concentrated *in vacuo* to afford **257** as an orange oil (11.0 g, 88%); $[\alpha]_{\text{D}}^{20}$ -210 (c 1.0, CHCl₃) {lit.¹⁴ $[\alpha]_{\text{D}}^{27}$ -217 (c 1.23 CHCl₃)}; δ_{H} (400 MHz, CDCl₃) 1.40 (3H, d, *J* 6.5, C(α)*Me*), 3.27 (1H, d, *J* 17.6, NCH_A), 3.58 (1H, d, *J* 17.6, NCH_B), 4.04 (1H, q, *J* 6.5, C(α)*H*), 7.28-7.36 (5H, m, Ph).

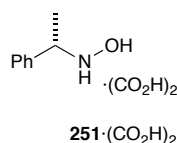
(*S*)-*N*-(Cyanomethylene)-1-phenylethanamine oxide **258**



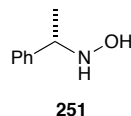
m-CPBA (approx. 70%, 18.5 g, 75.0 mmol) was added in three equal portions over 10 min to a stirred solution of **257** (6.00 g, 37.0 mmol) in CH₂Cl₂ (200 mL) at 0 °C. The resultant mixture was allowed to stir for 15 min, then slowly warmed to rt and stirred for a further 20 min. Sat. aq. Na₂S₂O₃ (200 mL) and sat. aq. NaHCO₃ (200 mL) were then added and the resulting mixture stirred for an additional 20 min. The mixture

was extracted with CH_2Cl_2 (3×200 mL), then the combined organic extracts were washed with sat. aq. NaCl (600 mL), dried and concentrated *in vacuo*. The crude reaction mixture was purified *via* flash column chromatography (gradient elution, 30-40 °C petrol/EtOAc, 2:1; increased to 1:1) affording **258** as a yellow solid (4.80 g, 74%); mp 90-92 °C; {lit.¹⁴ mp 91-92 °C (EtOAc/hexanes)}; $[\alpha]_{\text{D}}^{20} +81.5$ (*c* 1.0, CHCl_3) {lit.¹⁴ $[\alpha]_{\text{D}}^{28} +83$ (*c* 0.494 CHCl_3)}; δ_{H} (400 MHz, CDCl_3) 1.84 (3H, d, *J* 6.9, C(α)Me), 5.18 (1H, q, *J* 6.9, C(α)H), 6.66 (1H, s, NCH), 7.44 (5H, m, *Ph*).

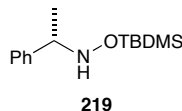
(*S*)-*N*-(α -Methylbenzyl)hydroxylamine oxalate **251·(CO_2H)₂**



Hydroxylamine hydrochloride (8.00 g, 115 mmol) was added to a stirred solution of **258** (4.00 g, 23.0 mmol) in MeOH (120 mL) and stirred for 2 h at 60 °C. The resulting mixture was cooled to rt and diluted with CHCl_3 (400 mL) then filtered through a pad of Celite[®]. The filtrate was concentrated *in vacuo* and then partitioned between CHCl_3 (150 mL) and sat. aq. NaHCO_3 (150 mL). The aqueous was extracted with CHCl_3 (2×150 mL), and the combined organic extracts were washed with sat. aq. NaCl (300 mL) and dried. A solution of oxalic acid (3.10 g, 34.5 mmol) in MeOH (50 mL) was then added to the filtrate, and the resulting suspension was concentrated *in vacuo*, triturated with Et_2O and collected by suction filtration to give **251**·(CO_2H)₂ as a white crystalline solid (3.80 g, 72%); mp 162-164 °C (dec); {lit.¹⁴ mp 163-167 °C (dec)}; $[\alpha]_{\text{D}}^{20} -2.9$ (*c* 1.0, MeOH); {lit.¹⁴ $[\alpha]_{\text{D}}^{28} -3.1$ (*c* 1.06, MeOH)}; δ_{H} (400 MHz, MeOD) 1.67 (3H, d, *J* 6.8, C(α)Me), 4.48 (1H, q, *J* 6.8, C(α)H), 7.46-7.48 (5H, m, *Ph*).

(*S*)-*N*-(α -methylbenzyl)hydroxylamine **251**¹⁵

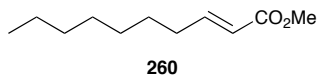
The oxalate salt of (*S*)-*N*-(α -methylbenzyl)hydroxylamine **251**·(CO₂H)₂ (506 mg, 2.22 mmol) was partitioned between Et₂O (50 mL) and sat. aq. NaHCO₃ (50 mL). The layers were separated and the aqueous layer extracted with Et₂O (3 × 50 mL). The organic layers were combined, dried and concentrated *in vacuo* affording **251** as a white crystalline solid (290 mg, 95%); mp 66-68 °C; {lit.¹⁵ mp 69-71 °C} [α]_D²⁵ -43.6 (*c* 1.0 in CH₂Cl₂); {lit.¹⁶ [α]_D²⁰ -43.5 (*c* 1.0 in CH₂Cl₂); δ_{H} (400 MHz, CDCl₃) 1.38 (3H, d, *J* 6.7, C(α)Me), 1.55 (1H, br s, NH), 4.16 (1H, q, *J* 6.7, C(α)H), 7.27-7.37 (5H, m, *Ph*).

(*S*)-*N*-*tert*-butyldimethylsilyloxy-*N*-(α -methylbenzyl)amine **219**¹⁷

tert-Butyldimethylsilyl chloride (514 mg, 3.50 mmol) and imidazole (388 mg, 5.70 mmol) were added sequentially to a stirred solution of (*S*)-*N*-(α -methylbenzyl)hydroxylamine **251** (390 mg, 2.85 mmol) in DMF and the reaction was stirred at rt for 16 h. The resulting mixture was partitioned between EtOAc (10 mL) and sat. aq. NaHCO₃ (10 mL), and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with H₂O (3 x 40 mL), dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30-40 °C petrol/Et₂O, 19:1) gave **219** as a colourless oil (610 mg, 85%); [α]_D²⁵ +12.5 (*c* 1.7, in CHCl₃); {lit.¹⁷ [α]_D²³ +12.0 (*c* 1.69 in CHCl₃)}; δ_{H} (400 MHz, CDCl₃) 0.08 (6H, s,

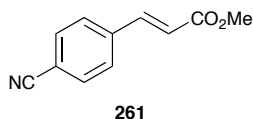
Si(CH₃)₂), 0.90 (9H, s, SiC(CH₃)₃), 1.39 (3H, d, *J* 6.8, C(α)*Me*), 1.57 (1H, br s, *NH*), 4.08 (1H, q, *J* 6.8, C(α)*H*), 7.28-7.34 (5H, m, *Ph*).

(*E*)-Methyl dec-2-eneoate **260**

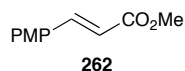


Following *General Procedure 1*, octanal (1.85 mL, 11.7 mmol) and methyl triphenylphosphenylidene acetate (4.30 g, 12.9 mmol) in CH₂Cl₂ (50 mL) gave **260**. Purification *via* flash column chromatography (eluent 30-40 °C petrol/Et₂O, 10:1) gave **260** as a colourless oil (1.70 g, 79%); δ_H (400 MHz, CDCl₃) 0.88 (3H, t, *J* 6.5, C(10)*H*₃), 1.21-1.28 (8H, m, Al-*H*), 1.39-1.47 (2H, m, Al-*H*), 2.18 (2H, app q, *J* 6.9, C(4)*H*₂), 3.73 (3H, s, *OMe*), 5.82 (1H, d, *J* 15.7, C(2)*H*), 6.94-7.02 (1H, m, C(3)*H*).

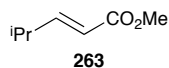
(*E*)-Methyl 3-(4-cyanophenyl)prop-2-enoate **261**



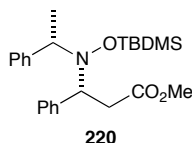
Following *General Procedure 1*, 4-cyanobenzaldehyde (500 mg, 3.82 mmol) and methyl triphenylphosphenylidene acetate (1.40 g, 4.20 mmol) in CH₂Cl₂ (20 mL) gave **261**. Purification *via* flash column chromatography (eluent 30-40 °C petrol/Et₂O, 10:1) gave **261** as a colourless oil (592 mg, 83%); δ_H (400 MHz, CDCl₃) 3.84 (3H, s, *OMe*), 6.53 (1H, d, *J* 16.0, C(2)*H*), 7.61-7.70 (5H, m, *Ar*, C(3)*H*).

(*E*)-Methyl 3-(4-methoxyphenyl)prop-2-enoate **262**¹⁸

Following *General Procedure 1*, *p*-anisaldehyde (1.05 mL, 8.60 mmol) and methyl triphenylphosphenylidene acetate (3.16 g, 9.46 mmol) in CH₂Cl₂ (30 mL) gave **262**. Purification *via* flash column chromatography (eluent 30-40 °C petrol/Et₂O, 10:1) gave **262** as a colourless oil (1.04 g, 82%); δ_H (400 MHz, CDCl₃) 3.80 (3H, s, *OMe*), 3.84 (3H, s, *OMe*), 6.32 (1H, d, *J* 16.3, C(2)*H*), 6.90 (2H, d, *J* 7.1, C(3')*H*, C(5')*H*), 7.49 (2H, d, *J* 7.1, C(2')*H*, C(6')*H*), 7.65 (1H, d, *J* 16.3, C(3)*H*).

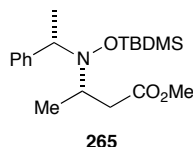
(*E*)-Methyl 4-methylpent-2-enoate **263**¹⁹

Following *General Procedure 1*, isobutyraldehyde (1.20 mL, 13.0 mmol) and methyl triphenylphosphenylidene acetate (4.85 g, 14.5 mmol) in CH₂Cl₂ (50 mL) gave **263**. Purification *via* flash column chromatography (eluent 30-40 °C petrol/Et₂O, 20:1) gave **263** as a colourless oil (1.45 g, 87%); δ_H (400 MHz, CDCl₃) 1.05 (6H, d, *J* 6.7, C(4)*Me*₂), 2.44 (1H, m, C(4)*H*), 3.71 (3H, s, *OMe*), 5.77 (1H, d, *J* 15.6, C(2)*H*), 6.94 (1H, d, *J* 15.6, C(3)*H*).



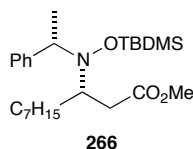
127

Methyl (*S,S*)-3-[*N-tert*-butyldimethylsilyloxy-*N*-(α -methylbenzyl)amino]butanoate **265**



Following *General Procedure 2*, BuLi (2.5 M, 0.16 mL, 0.40 mmol), **259** (100 mg, 0.40 mmol) and **68** (20 mg, 0.20 mmol) in THF (5 mL) gave **265** in 75:25 dr. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 100:1; increased to 40:1) gave **265** as a colourless oil (30 mg, 43%, 75:25 dr); $\nu_{\max}$ (film) 2955 (C-H), 1739 (C=O); δ_{H} (250 MHz, PhMe-*d*₈, 363 K) 0.11 (3H, s, SiMe), 0.14 (3H, s, SiMe), 0.89 (3H, d, *J* 6.7, C(4)*H*₃), 0.97 (9H, s, SiCMe₃), 1.36 (3H, d, *J* 6.7, C(α)Me), 2.19 (1H, dd, *J* 14.8, 8.2, C(2)*H*_A), 2.78 (1H, dd, *J* 14.8, 5.5, C(2)*H*_B), 3.37 (3H, s, OMe), 3.59-3.66 (1H, m, C(3)*H*), 3.92-4.02 (1H, m, C(α)*H*), 6.98-7.30 (5H, m, *Ph*); δ_{C} (62.5 MHz, PhMe-*d*₈, 363 K) -3.7 (SiMe₂), 1.2 (SiCMe₃), 18.6 (C(α)Me), 19.3 (C(4)), 26.6 (SiCMe₃), 39.1 (C(2)), 50.5 (OMe), 57.4 (C(3)), 64.8 (C(α)), 127.3, 128.5 (*o*-, *m*-, *p*-*Ph*), 144.2 (*i*-*Ph*), 171.9 (C(1)); *m/z* (ESI⁺) 352 ([M+H]⁺, 100%); HRMS (ESI⁺) C₁₉H₃₃NNaO₃Si⁺ ([M+Na]⁺) requires 374.2122; found 374.2122.

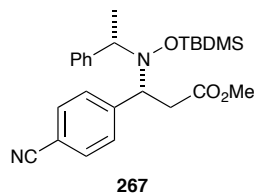
Methyl (*S,S*)-3-[*N-tert*-butyldimethylsilyloxy-*N*-(α -methylbenzyl)amino]decanoate **266**



Following *General Procedure 2*, BuLi (2.5 M, 0.16 mL, 0.40 mmol), **259** (100 mg, 0.40 mmol) and **260** (33 mg, 0.20 mmol) in dry THF (5 mL) gave **266** in 78:22 dr. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O,

100:1; increased to 50:1) gave **266** as a colourless oil (25 mg, 29%, 78:22 dr); $\nu_{\max}$ (film) 2960 (C–H), 1741 (C=O); δ_{H} (250 MHz, PhMe- d_8 , 363 K) 0.02 (3H, s, SiMe), 0.10 (3H, s, SiMe), 0.83–0.89 (3H, m, C(10) H_3), 0.94 (9H, s, SiCMe₃), 1.16–1.26 (12H, m, Al-H), 1.39 (3H, d, J 6.7, C(α)Me), 2.26 (1H, dd, J 15.2, 7.6, C(2) H_A), 2.92 (1H, dd, J 15.2, 4.9, C(2) H_B), 3.46 (3H, s, OMe), 3.90–3.97 (1H, m, C(3) H), 4.02–4.08 (1H, m, C(α) H), 6.85–7.17 (5H, m, Ph); δ_{C} (62.5 MHz, PhMe- d_8 , 363 K) –5.2 (SiMe), –5.0 (SiMe), 1.5 (SiCMe₃), 14.4 (C(10)), 18.3 (C(α)Me), 23.2, 26.7, 28.4, 29.6 (C(4)–C(9)), 26.5 (SiCMe₃), 32.4 (C(2)), 50.8 (OMe), 58.2 (C(3)), 62.6 (C(α)), 127.7, 127.9, 128.5 (σ -, m -, p -Ph), 142.4 (i -Ph), 173.1 (C(1)); m/z (ESI⁺) 436 ([M+H]⁺, 100%); HRMS (ESI⁺) C₂₅H₄₅NNaO₃Si⁺ ([M+Na]⁺) requires 458.3061; found 458.3062.

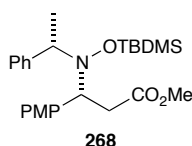
Methyl (3*R*, α *S*)-3-[*N*-*tert*-butyldimethylsilyloxy-*N*-(α -methylbenzyl)amino]-3-(*p*-cyanophenyl)propanoate **267**



Following *General Procedure 2*, BuLi (2.5 M, 0.08 mL, 0.20 mmol), **259** (50 mg, 0.20 mmol) and **261** (18.7 mg, 0.10 mmol) in THF (3 mL) gave **267** in 88:12 dr. Purification *via* flash column chromatography (basic alumina, gradient elution, 30–40 °C petrol/Et₂O, 100:1; increased to 40:1) gave **267** as a colourless oil (20 mg, 46%, 88:12 dr); $\nu_{\max}$ (film) 2955 (C–H), 2230 (C $\equiv$ N), 1740 (C=O); δ_{H} (250 MHz, PhMe- d_8 , 363 K) –0.16 (3H, s, SiMe), 0.00 (3H, s, SiMe), 0.93 (9H, s, SiCMe₃), 1.18 (3H, d, J 6.7, C(α)Me), 2.48 (1H, dd, J 15.9, 9.5, C(2) H_A), 2.90 (1H, dd, J 15.9, 4.5, C(2) H_B), 3.23 (3H, s, OMe), 3.89 (1H, q, J 6.7, C(α) H), 4.54 (1H, dd, J 9.5, 4.5, C(3) H), 6.97–

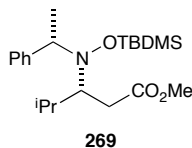
7.26 (9H, m, *Ph*); δ_{C} (62.5 MHz, $\text{PhMe-}d_8$) -4.1 (*SiMe*), -4.0 (*SiMe*), 1.2 (SiCMe_3), 18.0 ($\text{C}(\alpha)\text{Me}$), 26.5 (SiCMe_3), 36.0 ($\text{C}(2)$), 50.8 (*OMe*), 64.9 ($\text{C}(3)$, $\text{C}(\alpha)$), 118.2 (*CN*), 127.8 , 128.5 , 128.6 , 129.5 , 131.7 (*o*-, *m*-, *p-Ph*, *Ar*), 142.8 , 146.0 (*i-Ph*, *Ar*), 171.0 ($\text{C}(1)$); m/z (ESI^+) 439 ($[\text{M}+\text{H}]^+$, 100%); HRMS (ESI^+) $\text{C}_{25}\text{H}_{34}\text{N}_2\text{NaO}_3\text{Si}^+$ ($[\text{M}+\text{Na}]^+$) requires 461.2231 ; found 461.2231 .

Methyl (3*R*, α *S*)-3-[*N-tert*-butyldimethylsilyloxy-*N*-(α -methylbenzyl)amino]-3-(*p*-methoxyphenyl)propanoate **268**

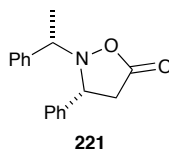


Following *General Procedure 2*, BuLi (1.41 M, 0.42 mL, 0.60 mmol), **259** (150 mg, 0.60 mmol) and **262** (58 mg, 0.30 mmol) in THF (8 mL) gave **268** in 86:14 dr. Purification *via* flash column chromatography (basic alumina, gradient elution, 30-40 °C petrol/ Et_2O , 50:1; increased to 20:1) gave **268** as a colourless oil (60 mg, 45%, 86:14 dr); ν_{max} (film) 1750 ($\text{C}=\text{O}$); δ_{H} (500 MHz, CDCl_3) -0.29 (3H, s, *SiMe*), -0.08 (3H, s, *SiMe*), 0.92 (9H, s, SiCMe_3), 1.29 (3H, d, J 6.5, $\text{C}(\alpha)\text{Me}$), 2.45 - 2.65 (1H, m $\text{C}(2)H_{\text{A}}$), 2.94 - 3.03 (1H, m, $\text{C}(2)H_{\text{B}}$), 3.50 (3H, s, *OMe*), 3.81 (3H, *OMe*), 3.94 (1H, q, J 6.5, $\text{C}(\alpha)H$), 4.40 - 4.48 (1H, m, $\text{C}(3)H$), 6.85 (2H, d, J 8.8, *Ar*), 7.13 - 7.34 (7H, m, *Ar*, *Ph*); δ_{C} (62.5 MHz, $\text{PhMe-}d_8$) -4.3 (*SiMe*), -4.2 (SiMe_2), -3.4 (SiCMe_3), 18.4 ($\text{C}(\alpha)\text{Me}$), 26.4 (SiCMe_3), 37.2 ($\text{C}(2)$), 51.4 (*OMe*), 55.2 (*OMe*), 62.7 ($\text{C}(\alpha)$), 64.4 ($\text{C}(3)$), 113.5 , 127.1 , 128.0 , 128.5 , 129.7 (*Ar*), 143.3 , 146.8 (*i-Ar*), 172.5 ($\text{C}(1)$); m/z (ESI^+) 444 ($[\text{M}+\text{H}]^+$, 100%); HRMS (ESI^+) $\text{C}_{25}\text{H}_{37}\text{NNaO}_4\text{Si}^+$ ($[\text{M}+\text{Na}]^+$) requires 466.2384 ; found 466.2392 .

Methyl (3*R*, α *S*)-3-[*N*-*tert*-butyldimethylsilyloxy-*N*-(α -methylbenzyl)amino]-4-methylbutanoate **269**



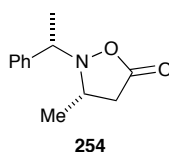
Following *General Procedure 2*, BuLi (1.6 M, 0.63 mL, 1.00 mmol), **259** (250 mg, 1.00 mmol) and **263** (64 mg, 0.50 mmol) in THF (15 mL) gave **269** in 96:4 dr. Purification *via* flash column chromatography (basic alumina, eluent 30-40 °C petrol/Et₂O, 40:1) gave **269** as a colourless oil (63 mg, 33%, 96:4 dr); $[\alpha]_D^{23}$ -8.4 (c 1.0 in CHCl₃); $\nu_{\max}$ (film) 2957 (C–H), 1738 (C=O); δ_H (250 MHz, PhMe-*d*₈, 363 K) 0.07 (3H, s, SiMe), 0.12 (3H, s, SiMe), 0.75 (3H, d, J 6.6, C(4)Me_A), 0.85 (3H, d, J 6.6, C(4)Me_B), 0.94 (9H, s, SiCMe₃), 1.42 (3H, d, J 6.8, C(α)Me), 1.50-1.62 (1H, m, C(4)H), 2.24 (1H, dd, J 16.6, 7.0, C(2)H_A), 3.07 (1H, dd, J 16.6, 3.8, C(2)H_B), 3.27-3.34 (1H, m, C(3)H), 3.42 (3H, s, OMe), 4.06 (1H, q, J 6.8, C(α)H), 6.97-7.36 (5H, m, Ph); δ_C (62.5 MHz, PhMe-*d*₈, 363 K) -3.9 (SiMe), -3.8 (SiMe), 1.2 (SiCMe₃), 17.6 (C(α)Me), 18.6 (C(4)Me_A), 19.0 (C(4)Me_B), 26.5 (SiCMe₃), 31.8 (C(4)), 33.7 (C(2)), 50.7 (OMe), 63.9 (C(α)), 65.8 (C(3)), 127.4, 128.1, 129.0 (*o*-, *m*-, *p*-Ph), 143.8 (*i*-Ph), 173.5 (C(1)); m/z (ESI⁺) 402 ([M+Na]⁺, 42%), 380 ([M+H]⁺, 100%); HRMS (ESI⁺) C₂₁H₃₇NNaO₃Si⁺ ([M+Na]⁺) requires 402.2435; found 402.2435.

(3*R*, α *S*)-N(2)- α -Methylbenzyl-3-phenylisoxazolidin-5-one 221²⁰

BuLi (2.5 M, 0.40 mmol, 0.16 mL) was added to a stirred solution of **259** (100 mg, 0.40 mmol) in THF (4 mL) at $-78\text{ }^{\circ}\text{C}$. After 30 min a solution of **205** (32 mg, 0.20 mmol) in THF (1 mL) was added and the reaction was stirred at $-78\text{ }^{\circ}\text{C}$ for a further 10 h. Sat. aq. NH_4Cl (5 mL) was added and the aqueous layer extracted with Et_2O ($3 \times 5\text{ mL}$). The combined organic extracts were washed with sat. aq. NaCl (15 mL) then dried and concentrated *in vacuo* to give **220** as an orange oil (130 mg, 95:5 dr). Hydrogen fluoride-pyridine complex (12 μL , 0.48 mmol) was added to a stirred solution of **220** (125 mg, 0.40 mmol) in THF (4 mL) at $0\text{ }^{\circ}\text{C}$. After stirring for 20 min the reaction mixture was diluted with Et_2O (25 mL) then quenched with sat. aq. NaHCO_3 (20 mL). The aqueous layer was extracted with Et_2O ($3 \times 20\text{ mL}$) then the combined organic extracts were dried and concentrated *in vacuo* to give **271** (74 mg). This residue was dissolved in THF (3 mL) and cooled to $-78\text{ }^{\circ}\text{C}$. LiHMDS (1.0 M in THF, 0.6 mmol, 0.6 mL) was added and the resultant mixture was left to stir for 30 min. The reaction was then quenched with sat. aq. NH_4Cl (2 mL) and the aqueous layer was extracted with Et_2O ($3 \times 2\text{ mL}$). The combined organic extracts were washed with sat. aq. NaCl, then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent $40\text{--}60\text{ }^{\circ}\text{C}$ petrol/ Et_2O , 20:1) gave **221** as a pale yellow solid (37 mg, 78% over 3 steps, $>99:1$ dr); mp $101\text{--}102\text{ }^{\circ}\text{C}$; $[\alpha]_{\text{D}}^{23} +120$ (c 1.0 in CHCl_3); {lit.²⁰ $[\alpha]_{\text{D}}^{22} +154$ (c 2.05 in CHCl_3)}; δ_{H} (400 MHz, CDCl_3) 1.60 (3H, d, J 6.5,

C(α)Me), 2.91 (1H, dd, J 17.4, 8.9, C(4) H_A), 3.11 (1H, dd, J 17.4, 7.9, C(4) H_B), 4.19 (1H, d, J 6.5, C(α)H), 4.48-4.50 (1H, m, C(3)H), 7.24-7.31 (10H, m, Ph).

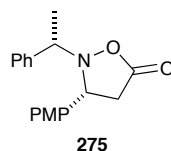
(*S,S*)-*N*(2)- α -Methylbenzyl-3-methylisoxazolidin-5-one **254**²⁰



BuLi (1.41 M, 0.60 mmol, 0.43 mL) was added to a stirred solution of **259** (150 mg, 0.60 mmol) in THF (6 mL) at -78 °C. After 30 min a solution of **68** (30 mg, 0.30 mmol) in THF (2 mL) was added and the reaction was stirred at -78 °C for a further 10 h. Sat. aq. NH_4Cl (8 mL) was added and the aqueous layer was extracted with Et_2O (3×8 mL). The combined organic extracts were washed with sat. aq. NaCl (20 mL) then dried and concentrated *in vacuo* to give **265** as an orange oil (180 mg, 75:25 dr). Hydrogen fluoride-pyridine complex (30 μL , 0.72 mmol) was added to a stirred solution of **265** (180 mg, 0.60 mmol) in THF (6 mL) at 0 °C. After stirring for 20 min the reaction mixture was diluted with Et_2O (35 mL) then quenched with sat. aq. NaHCO_3 (30 mL). The layers were then separated and the aqueous layer was extracted with Et_2O (3×30 mL). The combined organic extracts were dried and concentrated *in vacuo* to give **272** (114 mg). This residue was dissolved in THF (4 mL) and cooled to -78 °C. LiHMDS (1.0 M, 0.90 mmol, 0.9 mL) was added and the mixture was left to stir for 30 min. The reaction was then quenched with sat. aq. NH_4Cl (4 mL) and the aqueous layer was extracted with Et_2O (3×4 mL). The combined organic extracts were washed with sat. aq. NaCl, then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient

elution, 40-60 °C petrol/Et₂O, 20:1; increased to 5:1) gave **254** as a yellow oil (26 mg, 43% over 3 steps, >99:1 dr); [α]_D²³ +76.3 (*c* 1.0 in CHCl₃); {lit.²⁰ [α]_D¹⁹ +84.3 (*c* 2.9 in CHCl₃); δ_{H} (400 MHz, CDCl₃) 1.00 (3H, d, *J* 6.1 C(3)*Me*), 1.55 (3H, d, *J* 6.5, C(α)*Me*), 2.38 (1H, dd, *J* 17.4, 6.5, C(4)*H_A*), 2.84 (1H, dd, *J* 17.4, 7.5, C(4)*H_B*), 3.40-3.60 (1H, m, C(3)*H*), 4.02 (1H, q, *J* 6.5, C(α)*H*), 7.30-7.36 (5H, m, *Ph*).

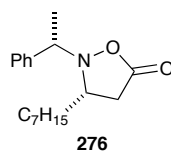
(3*R*, α *S*)-*N*(2)- α -Methylbenzyl-3-(4-methoxyphenyl)isoxazolidin-5-one **275**



BuLi (1.41 M, 0.60 mmol, 0.42 mL) was added to a stirred solution of **259** (150 mg, 0.60 mmol) in THF (6 mL) at −78 °C. After 30 min a solution of **262** (58 mg, 0.3 mmol) in THF (2 mL) was added and the reaction was stirred at −78 °C for a further 10 h. Sat. aq. NH₄Cl (8 mL) was added and the aqueous layer extracted with Et₂O (3 × 8 mL). The combined organic extracts were washed with sat. aq. NaCl (20 mL) then dried and concentrated *in vacuo* to give **268** as an orange oil (190 mg, 86:14 dr). Hydrogen fluoride-pyridine complex (19 μ L, 0.72 mmol) was added to a stirred solution of **268** (190 mg, 0.60 mmol) in THF (6 mL) at 0 °C. After stirring for 20 min the reaction mixture was diluted with Et₂O (40 mL) then quenched with sat. aq. NaHCO₃ (30 mL). The aqueous layer was extracted with Et₂O (3 × 30 mL), then the combined organic extracts were dried and concentrated *in vacuo* to give **273** (110 mg). This residue was dissolved in THF (3 mL) and cooled to −78 °C. LiHMDS (1.0 M, 0.90 mmol, 0.9 mL) was added and the mixture was left to stir for 30 min. The

reaction was then quenched with sat. aq. NH_4Cl (3 mL) and the aqueous layer was extracted with Et_2O (3×3 mL). The combined organic extracts were washed with sat. aq. NaCl (10 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 40-60 °C petrol/ Et_2O , 20:1) gave **275** as a yellow oil (41 mg, 46% over 3 steps, >99:1 dr); $[\alpha]_{\text{D}}^{23} +78.0$ (c 1.0 in CHCl_3); ν_{max} (film) 1778 ($\text{C}=\text{O}$); δ_{H} (400 MHz, CDCl_3) 1.54 (3H, d, J 6.6, $\text{C}(\alpha)\text{Me}$), 2.85 (1H, dd, J 17.3, 9.1, $\text{C}(4)\text{H}_{\text{A}}$), 3.00 (1H, dd, J 17.3, 7.6, $\text{C}(4)\text{H}_{\text{B}}$), 3.79 (1H, s, OMe), 4.13 (1H, q, J 6.6, $\text{C}(\alpha)\text{H}$), 4.41-4.44 (1H, m, $\text{C}(3)\text{H}$), 6.79 (2H, d, J 8.7, Ar), 7.16 (2H, d, J 8.7, Ar), 7.20-7.25 (5H, m, Ph); δ_{C} (100 MHz, CDCl_3) 18.1 ($\text{C}(\alpha)\text{Me}$), 39.2 ($\text{C}(4)$), 55.3 (OMe), 65.7 ($\text{C}(\alpha)$), 65.9 ($\text{C}(3)$), 114.1, 127.8, 127.9, 128.3, 128.4 (Ar) 130.3, 140.4, 159.4 ($i\text{-Ar}$), 173.9 ($\text{C}(5)$); m/z (ESI^+) 617 ($[\text{2M}+\text{Na}]^+$, 100%), 320 ($[\text{M}+\text{Na}]^+$, 78%), 298 ($[\text{M}+\text{H}]^+$, 52%); HRMS (ESI^+) $\text{C}_{18}\text{H}_{19}\text{NNaO}_3^+$ ($[\text{M}+\text{Na}]^+$) requires 320.1257; found 320.1256.

(*S,S*)-*N*(2)- α -Methylbenzyl-3-heptylisoxazolidin-5-one **276**



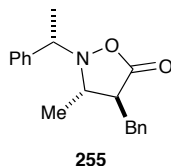
BuLi (1.22 M, 0.33 mmol, 0.27 mL) was added to a stirred solution of **259** (83 mg, 0.33 mmol) in THF (3 mL) at -78 °C. After 30 min a solution of **260** (30 mg, 0.16 mmol) in THF (1 mL) was added and the reaction was stirred at -78 °C for a further 10 h. Sat. aq. NH_4Cl (4 mL) was added and the aqueous layer was extracted with Et_2O (3×4 mL). The combined organic extracts were washed with sat. aq. NaCl (10 mL) then dried and concentrated *in vacuo* to give **266** as an orange oil (105 mg, 78:22 dr). Hydrogen fluoride-pyridine complex (10 μL , 0.40 mmol) was added to a stirred

solution of **266** (105 mg, 0.33 mmol) in THF (5 mL) at 0 °C. After stirring for 20 min the reaction mixture was diluted with Et₂O (35 mL) then quenched with sat. aq. NaHCO₃ (25 mL). The aqueous layer was extracted with Et₂O (3 × 25 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give **274** (75 mg). This residue was dissolved in THF (2 mL) and cooled to -78 °C. LiHMDS (1.0 M, 0.50 mmol, 0.50 mL) was added and the mixture was left to stir for 30 min. The reaction was then quenched with sat. aq. NH₄Cl (3 mL) and the aqueous layer was extracted with Et₂O (3 × 3 mL). The combined organic extracts were washed with sat. aq. NaCl (10 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 40-60 °C petrol/Et₂O, 30:1) gave **276** as a yellow oil (41 mg, 30% over 3 steps, 78:22 dr); $\nu_{\max}$ (film) 1770 (C=O); δ_{C} (100 MHz, CDCl₃) 12.0, 14.1 (*C*(7')), 20.4, 20.5 (*C*(α)*Me*), 22.6, 22.6, 25.5, 25.8, 29.0, 29.0, 29.1, 29.4, 30.1, 30.1, 31.7, 31.7 (*C*(1'), *C*(2'), *C*(3'), *C*(4'), *C*(5'), *C*(6')), 34.2, 35.8 (*C*(4)), 60.9, 61.6 (*C*(3)), 64.7, 64.8 (*C*(α)), 126.0, 127.1, 127.8, 128.4, 128.6 129.2 (*o*-, *m*-, *p*-*Ph*), 136.5 (*i*-*Ph*), 175.0, 176.6 (*C*(5)); *m/z* (ESI⁺) 601 ([2M+Na]⁺, 100%), 312 ([M+Na]⁺, 62%), 290 ([M+H]⁺, 34%); HRMS (ESI⁺) C₁₈H₂₇NNaO₂⁺ ([M+Na]⁺) requires 312.1934; found 312.1945.

Data for Major Diastereoisomer; δ_{H} (400 MHz, CDCl₃) 0.85-0.91 (3H, m, *C*(7')*H*₃), 1.25-1.31 (12H, m, Al-*H*), 1.64 (3H, d, *J* 6.9, *C*(α)*Me*), 2.33-2.35 (2H, m, *C*(4)*H*₂), 3.26 (1H, dd, *J* 7.7, 5.8, *C*(3)*H*), 4.08 (1H, q, *J* 6.9, *C*(α)*H*), 7.32-7.39 (5H, m, *Ph*).

Data for Minor Diastereoisomer; δ_{H} (400 MHz, CDCl₃) 0.85-0.91 (3H, m, *C*(7')*H*₃), 1.25-1.31 (12H, m, Al-*H*), 1.55 (3H, d, *J* 6.5, *C*(α)*Me*), 2.33-2.35 (1H, m, *C*(4)*H*_A), 2.82 (1H, dd, *J* 17.6, 8.2, *C*(4)*H*_B), 3.34-3.37 (1H, m, *C*(3)*H*), 4.04 (1H, q, *J* 6.5, *C*(α)*H*), 7.32-7.39 (5H, m, *Ph*);

(*S,S,S*)-*N*(2)- α -Methylbenzyl-3-methyl-4-benzylisoxazolidin-5-one
255²⁰

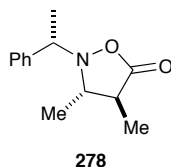


Method 1: Following *General Procedure 3*, LiTMP (0.36 M in THF, 14.9 mL, 5.37 mmol), **254** (1.00 g, 4.88 mmol), benzyl bromide (1.74 mL, 14.6 mmol) and THF (20 mL) gave **255** in >99:1 dr. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 20:1; increased to 5:1) gave **255** as a white solid (1.01 g, 70%, >99:1 dr); mp 79-81 °C (EtOH); [α]_D²⁴ +85.3 (*c* 1.0 in CHCl₃); {lit.²⁰ [α]_D²³ +89.6 (*c* 2.4 in CHCl₃)}; δ_{H} (400 MHz, CDCl₃) 0.67 (3H, d, *J* 5.6, C(3)Me), 1.48 (3H, d, *J* 6.5, C(α)Me), 2.83-2.88 (1H, m, C(4)H), 2.94-2.99 (1H, m, C(4)CH_A), 3.09-3.16 (2H, m, C(3)H, C(4)CH_B), 3.85 (1H, q, *J* 6.5, C(α)H), 7.19-7.36 (10H, m, Ph).

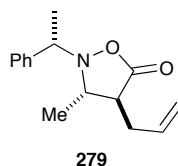
Method 2: Following *General Procedure 4*, LiHMDS (1.0 M in THF, 1.17 mL, 1.17 mmol), **254** (200 mg, 0.98 mmol), benzyl bromide (0.35 mL, 2.94 mmol) and THF (5 mL) gave **255** in >99:1 dr. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 20:1; increased to 5:1) gave **255** as a white solid (162 mg, 56%, >99:1 dr). Further elution gave **277** as a colourless oil (31 mg, 8%, >99:1 dr); [α]_D²⁵ +73.4 (*c* 1.0 in CHCl₃); ν_{max} (film) 1769 (C=O); δ_{H} (400 MHz, CDCl₃) 0.85 (3H, d, *J* 6.4, C(3)Me), 1.36 (3H, d, *J* 6.5, C(α)Me), 2.58 (1H, d, *J* 14.1, C(4)CH_A), 2.78 (1H, d, *J* 13.6, C(4)CH_C), 3.20-3.29 (2H, m, C(3)H, C(4)CH_B), 3.39 (1H, d, *J* 13.6, C(4)CH_D), 3.75 (1H, q, *J* 6.5, C(α)H), 7.12-7.14 (2H, m, Ph), 7.24-7.38 (13H, m, Ph); δ_{C} (100 MHz, CDCl₃) 12.4 (C(3)Me), 18.4 (C(α)Me), 37.9, 38.0 (2 $\times$ PhCH₂), 54.7 (C(4)), 64.8 (C(3)), 66.1 (C(α)), 127.0, 127.1, 127.8, 127.9, 128.1, 128.5, 128.6, 130.3, 130.9 (*o*-, *m*-, *p*-Ph), 135.6, 136.4, 141.7 (*i*-Ph); *m/z* (ESI⁺) 793 ([2M+Na]⁺, 100%), 408

($[M+Na]^+$, 29%), 386 ($[M+H]^+$, 19%); HRMS (ESI^+) $C_{26}H_{27}NNaO_2$ ($[M+Na]^+$) requires 408.1934; found 408.1923.

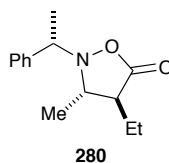
(*S,S,S*)-*N*(2)- α -Methylbenzyl-3,4-dimethylisoxazolidin-5-one **278**



Following *General Procedure 3*, LiTMP (0.23 M in THF, 3.20 mL, 0.73 mmol), **254** (125 mg, 0.61 mmol), methyl iodide (0.11 mL, 1.83 mmol) and THF (3 mL) gave **278** in 70:30 dr. Purification *via* flash column chromatography (eluent 30-40 °C petrol/Et₂O, 20:1) gave **278** as a white solid (80 mg, 71%, 70:30 dr); mp 155-157 °C (dec.); ν_{max} (film) 1768 (C=O); δ_H (400 MHz, CDCl₃) 0.75 (3H, d, *J* 5.8, C(3)*Me*), 1.20 (3H, d, *J* 6.8, C(4)*Me*), 1.58 (3H, d, *J* 6.4, C(α)*Me*), 2.51-2.59 (1H, m, C(4)*H*), 2.97-3.08 (1H, m, C(3)*H*), 3.97 (1H, q, *J* 6.4, C(α)*H*), 7.31-7.39 (5H, m, *Ph*); δ_C (100 MHz, CDCl₃) 11.7 (C(4)*Me*), 17.8 (C(3)*Me*), 19.3 (C(α)*Me*), 44.4 (C(4)), 67.4 (C(α)), 68.1 (C(3)), 127.1, 127.9, 128.6 (*o*-, *m*-, *p*-*Ph*), 140.6 (*i*-*Ph*), 175.7 (C(5)); *m/z* (ESI^+) 461 ($[2M+Na]^+$, 100%), 242 ($[M+Na]^+$, 68%), 220 ($[M+H]^+$, 27%); HRMS (ESI^+) $C_{13}H_{17}NNaO_2^+$ ($[M+Na]^+$) requires 242.1151; found 242.1162.

(*S,S,S*)-*N*(2)- α -Methylbenzyl-3-methyl-4-allylisoxazolidin-5-one 279

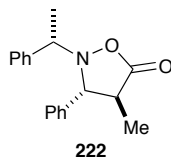
Following *General Procedure 3*, LiTMP (0.43 M in THF, 5 mL, 2.15 mmol), **254** (400 mg, 1.95 mmol), allyl iodide (0.54 mL, 5.85 mmol) and THF (10 mL) gave **279** in 92:8 dr. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 20:1; increased to 5:1) gave **279** as a colourless oil, (307 mg, 64%, 92:8 dr); $[\alpha]_D^{18} +42.2$ (*c* 1.0 in CHCl₃); $\nu_{\max}$ (film) 2935 (C–H), 1771 (C=O); δ_H (400 MHz, CDCl₃) 0.80 (3H, d, *J* 5.9, C(3)*Me*), 1.57 (3H, d, *J* 6.5, C(α)*Me*), 2.44 (2H, app t, *J* 6.3, C(4)*CH*₂), 2.63 (1H, app dt, *J* 11.4, 5.7, C(4)*H*), 3.19 (1H, dq, *J* 11.4, 5.9, C(3)*H*), 3.98 (1H, q, *J* 6.5, C(α)*H*), 5.11-5.15 (2H, m, C(4)*CHCH=CH*₂), 5.73-5.83 (1H, m, C(4)*CHCH=CH*₂), 7.30-7.39 (5H, m, *Ph*); δ_C (100 MHz, CDCl₃) 18.4 (C(3)*Me*), 19.3 (C(α)*Me*), 31.6 (C(4)*CH*₂), 48.8 (C(4)), 64.7 (C(3)), 67.3 (C(α)), 118.4, 133.6, 134.5 (*o*-, *m*-, *p*-*Ph*), 140.8 (*i*-*Ph*), 174.8 (C(5)); *m/z* (ESI⁺) 246 ([M+H]⁺, 100%); HRMS (ESI⁺) C₁₅H₁₉NNaO₂⁺ ([M+Na]⁺ requires 268.1308, found 268.1303.

(*S,S,S*)-*N*(2)- α -Methylbenzyl-3-methyl-4-ethylisoxazolidin-5-one 280

Following *General Procedure 3*, LiTMP (0.25 M in THF, 9.40 mL, 2.34 mmol), **254** (400 mg, 1.95 mmol), ethyl iodide (0.47 mL, 5.85 mmol) and THF (6 mL) gave **280** in

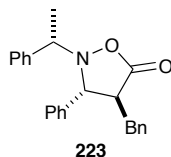
70:30 dr. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 20:1; increased to 5:1) gave **280** as a colourless oil (273 mg, 60%, 70:30 dr); $\nu_{\max}$ (film) 1762 (C=O); δ_{H} (400 MHz, CDCl₃) 0.80 (3H, d, J 6.0, C(3)*Me*), 1.03 (3H, t, J 7.6, C(4)CH₂CH₃), 1.57 (3H, d, J 6.6, C(α)*Me*), 1.65-1.73 (2H, m, C(4)CH₂), 2.47 (1H, dt, J 11.2, 6.0, C(4)*H*), 3.13-3.20 (1H, m, C(3)*H*), 3.98 (1H, q, J 6.6, C(α)*H*), 7.28-7.39 (5H, m, *Ph*); δ_{C} (100 MHz, CDCl₃) 10.9 (C(4)CH₂CH₃), 18.7 (C(3)*Me*), 19.5 (C(α)*Me*), 20.5 (C(4)CH₂), 50.3 (C(4)), 64.8 (C(3)), 67.5 (C(α)), 128.0, 128.2, 128.7 (*o*-, *m*-, *p*-*Ph*), 140.8 (*i*-*Ph*), 175.5 (C(5)); m/z (ESI⁺) 489 ([2M+Na]⁺, 100%), 256 ([M+Na]⁺, 74%); HRMS (ESI⁺) C₁₄H₁₉NNaO₂⁺ ([M+Na]⁺) requires 256.1308; found 256.1306.

(3*R*,4*S*, α *S*)-N(2)- α -Methylbenzyl-3-phenyl-4-methylisoxazolidin-5-one **222²⁰**



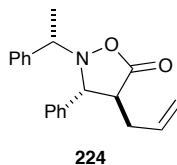
Following *General Procedure 3*, LiTMP (0.2 M in THF, 0.55 mL, 0.11 mmol), **221** (26 mg, 0.10 mmol), MeI (20 μ L, 0.30 mmol) and THF (1 mL) gave **222** in >99:1 dr. Purification *via* flash column chromatography (gradient elution, 40-60 °C petrol/Et₂O, 20:1; increased to 5:1) gave **222** as a colourless oil (20 mg, 71%, >99:1 dr); $[\alpha]_{\text{D}}^{23}$ +102 (*c* 1.0 in CHCl₃); {lit.²⁰ $[\alpha]_{\text{D}}^{25}$ +128 (*c* 1.3 in CHCl₃)}; δ_{H} (400 MHz, CDCl₃) 1.20 (3H, d, J 6.8, C(4)*Me*), 1.58 (3H, d, J 6.6, C(α)*Me*), 2.98-3.02 (1H, m, C(4)*H*), 3.95 (1H, d, J 12.3, C(3)*H*), 4.11 (1H, q, J 6.6, C(α)*H*), 7.16-7.32 (10H, m, *Ph*).

(3*R*,4*S*, α *S*)-*N*(2)- α -Methylbenzyl-3-phenyl-4-benzylisoxazolidin-5-one **223**



Following *General Procedure 3*, LiTMP (0.2 M in THF, 1.45 mL, 0.29 mmol), **221** (70 mg, 0.26 mmol), BnBr (50 μ L, 0.78 mmol) and THF (2 mL) gave **223** in >99:1 dr. Purification *via* flash column chromatography (40-60 °C petrol/Et₂O, 20:1; increased to 5:1) gave **223** as a colourless oil (70 mg, 75%, >99:1 dr); $[\alpha]_D^{23}$ +69.9 (*c* 1.0 in CHCl₃); $\nu_{\max}$ (film) 3031 (C–H), 1773 (C=O); δ_H (400 MHz, CDCl₃) 1.41 (3H, d, *J* 6.6, C(α)Me), 2.87 (1H, dd, *J* 14.5, 5.9, C(4)CH_A), 3.10 (1H, dd, *J* 14.5, 4.9, C(4)CH_B), 3.31-3.38 (1H, m, C(4)H), 3.89 (1H, q, *J* 6.6, C(α)H), 4.03 (1H, d, *J* 11.6, C(3)H), 7.10-7.32 (15H, m, Ph); δ_C (100 MHz, CDCl₃) 17.5 (C(α)Me), 32.8 (C(4)CH₂), 52.8 (C(4)), 66.2 (C(α)), 71.9 (C(3)), 127.3, 128.1, 128.3, 128.4, 128.7, 128.8, 128.9, 129.8, 130.0 (*o*-, *m*-, *p*-Ph), 137.3, 137.9, 140.2 (*i*-Ph), 174.7 (C(5)); *m/z* (ESI⁺) 358 ([M+H]⁺, 100%); HRMS (ESI⁺) C₂₄H₂₄NO₂⁺ ([M+H]⁺) requires 358.1802; found 358.1802.

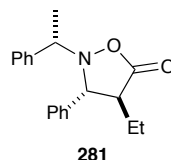
(3*R*,4*S*, α *S*)-*N*(2)- α -Methylbenzyl-3-phenyl-4-allylisoxazolidin-5-one **224**



Following *General Procedure 3*, LiTMP (0.2 M in THF, 1.45 mL, 0.29 mmol), **221** (70 mg, 0.26 mmol), allyl iodide (70 μ L, 0.80 mmol) and THF (2 mL) gave **224** in >99:1 dr. Purification *via* flash column chromatography (40-60 °C petrol/Et₂O, 40:1;

increased to 20:1) gave **224** as a colourless oil (66 mg, 82%, >99:1 dr); $[\alpha]_{\text{D}}^{23} +100$ (c 1.0 in CHCl_3); ν_{max} (film) 3032 (C–H), 1774 (C=O); δ_{H} (400 MHz, CDCl_3) 1.53 (3H, d, J 6.6, C(α)Me), 2.26–2.31 (1H, m, C(4)CH_A), 2.47–2.53 (1H, m, C(4)CH_B), 3.05–3.11 (1H, C(4)H), 4.07 (1H, q, J 6.6, C(α)H), 4.16 (1H, d, J 11.9, C(3)H), 5.07–5.11 (2H, m, C(4)CH₂CH=CH₂), 5.64–5.74 (1H, m, C(4)CH₂CH=CH₂), 7.13–7.24 (10H, m, Ph); δ_{C} (100 MHz, CDCl_3) 17.5 (C(α)Me), 31.0 (C(4)CH₂), 51.2 (C(4)), 66.3 (C(α)), 72.4 (C(3)), 100.0 (C(4)CH₂CH=CH₂), 119.2 (C(4)CH₂CH=CH₂), 128.1, 128.3, 128.5, 128.6, 129.0, 133.6, (*o*-, *m*-, *p*-Ph), 137.9, 140.2 (*i*-Ph), 174.3 (C(5)); m/z (ESI⁺) 308 ([M+H]⁺, 40%); HRMS (ESI⁺) C₂₀H₂₂NO₂⁺ ([M+H]⁺) requires 308.1645; found 308.1645.

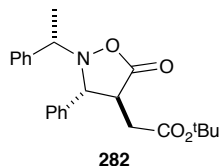
(3*R*,4*S*, α *S*)-*N*(2)- α -Methylbenzyl-3-phenyl-4-ethylisoxazolidin-5-one **281**



Following *General Procedure 3*, LiTMP (0.2 M in THF, 2.05 mL, 0.41 mmol), **221** (100 mg, 0.37 mmol), ethyl iodide (90 μL , 1.12 mmol) and THF (3 mL) gave **281** in >99:1 dr. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et₂O, 20:1) gave **281** as a colourless oil (82 mg, 75%, >99:1 dr); $[\alpha]_{\text{D}}^{24} +49.3$ (c 1.0 in CHCl_3); ν_{max} (film) 1773 (C=O); δ_{H} (400 MHz, CDCl_3) 0.91 (3H, t, J 7.3, C(4)CH₂CH₃), 1.53 (3H, d, J 6.5, C(α)Me), 1.64–1.71 (2H, m, C(4)CH₂), 2.92 (1H, dt, J 12.0, 6.0, C(4)H), 4.03–4.08 (2H, m, C(3)H, C(α)H), 7.12–7.31 (10H, m, Ph); δ_{C} (100 MHz, CDCl_3) 10.8 (C(4)CH₂CH₃), 17.2 (C(α)Me), 20.0 (C(4)CH₂), 52.2 (C(4)), 65.8 (C(α)), 73.0 (C(3)), 127.7, 127.8, 127.8, 128.1, 128.2, 128.6 (*o*-, *m*-, *p*-Ph), 137.9, 139.9 (*i*-Ph), 174.6 (C(5));

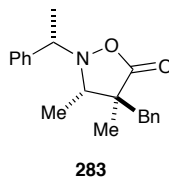
m/z (ESI⁺) 613 ([2M+Na]⁺, 78%), 591 ([2M+H]⁺, 88%), 318 ([M+Na]⁺, 18%), 296 ([M+H]⁺, 100%); HRMS (ESI⁺) C₁₉H₂₁NNaO₂⁺ ([M+Na]⁺) requires 318.1470; found 318.1458.

(3*R*,4*S*, α *S*)-*N*(2)- α -Methylbenzyl-3-phenyl-4-(*tert*-butoxycarbonylmethyl)isoxazolidin-5-one **282**



Following *General Procedure 3*, LiTMP (0.23 M in THF, 2.00 mL, 0.45 mmol), **221** (100 mg, 0.37 mmol), *tert*-butyl bromoacetate (0.16 mL, 1.11 mmol) and THF (2 mL) gave **282** in >99:1 dr. Purification *via* flash column chromatography (eluent 30-40 °C petrol/Et₂O, 20:1) gave **282** as a colourless oil (116 mg, 81%, >99:1 dr); [α]_D²⁴ +69.2 (c 1.0 in CHCl₃); $\nu_{\max}$ (film) 2979 (C–H), 1778 (C=O), 1730 (C=O); δ_{H} (400 MHz, CDCl₃) 1.35 (9H, s, CMe₃), 1.56 (3H, d, J 6.6, C(α)Me), 2.53 (2H, d, J 5.6, C(4)CH₂), 3.31 (1H, ddd, J 11.9, 5.8, 5.6, C(4)H), 4.10 (1H, q, J 6.6, C(α)H), 4.26 (1H, d, J 11.9, C(3)H), 7.10-7.32 (10H, m, Ph); δ_{C} (100 MHz, CDCl₃) 17.2 (C(α)Me), 27.9 (CMe₃), 32.3 (C(4)CH₂), 48.3 (C(4)), 65.9 (C(α)), 73.1 (C(3)), 81.6 (CMe₃), 127.7, 127.8, 128.1, 128.2, 128.4, 128.7 (*o*-, *m*-, *p*-Ph), 137.0, 139.9 (*i*-Ph), 169.2 (CO₂^tBu), 173.4 (C(5)); m/z (ESI⁺) 404 ([M+Na]⁺, 75%), 382 ([M+H]⁺, 100%); HRMS (ESI⁺) C₂₃H₂₇NNaO₄⁺ ([M+Na]⁺) requires 404.1833; found 404.1817.

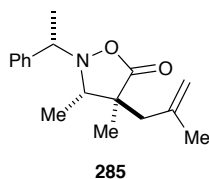
(*S,S,S*)-*N*(2)- α -Methylbenzyl-3,4-dimethyl-4-benzylisoxazolidin-5-one **283**



Method 1: Following *General Procedure 4*, LiHMDS (1.0 M in THF, 0.16 mL, 0.16 mmol), **278** (30 mg, 0.14 mmol), benzyl bromide (20 μ L, 0.42 mmol) and THF (1 mL) gave **283** in >99:1 dr. Purification *via* flash column chromatography (gradient elution, 40-60 °C petrol/Et₂O, 20:1; increased to 5:1) gave **283** as a colourless oil (38 mg, 88%, >99:1 dr). Recrystallisation of an aliquot (EtOH/hexane) gave an analytical sample; mp 71-73 °C; $[\alpha]_D^{25}$ +58.0 (*c* 1.0 in CHCl₃); $\nu_{\max}$ (film) 1768 (C=O); δ_H (400 MHz, CDCl₃) 0.62 (3H, d, *J* 6.5, C(3)*Me*), 1.29 (3H, s, C(4)*Me*), 1.35 (3H, d, *J* 6.5, C(α)*Me*), 2.59 (1H, d, *J* 14.0, C(4)*CH_A*), 3.13-3.18 (1H, m, C(3)*H*), 3.20 (1H, d, *J* 14.0, C(4)*CH_B*), 3.73 (1H, q, *J* 6.5, C(α)*H*), 7.15-7.32 (10H, m, *Ph*); δ_C (100 MHz, CDCl₃) 13.0 (C(3)*Me*), 18.3 (C(α)*Me*), 29.7 (C(4)*Me*), 40.9 (C(4)*CH₂*), 50.4 (C(4)), 64.5 (C(3)), 66.2 (C(α)), 127.0, 127.8, 127.9, 128.5, 129.1, 130.2 (*o*-, *m*-, *p*-*Ph*), 136.3, 141.4 (*i*-*Ph*), 178.1 (C(5)); *m/z* (ESI⁺) 641 ([2M+Na]⁺, 100%), 332 ([M+Na]⁺, 78%), 310 ([M+H]⁺, 23%); HRMS (ESI⁺) C₂₀H₂₃NNaO₂⁺ ([M+Na]⁺) requires 332.1621, found 332.1621.

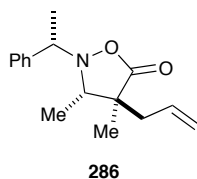
Method 2: Following *General Procedure 4*, LiHMDS (1.0 M in THF, 0.40 mL, 0.40 mmol), **255** (100 mg, 0.34 mmol), methyl iodide (60 μ L, 1.02 mmol) and THF (2.5 mL) gave **283** in >99:1 dr. Purification *via* flash column chromatography (gradient elution, 40-60 °C petrol/Et₂O, 20:1; increased to 5:1) gave **283** as a colourless oil (87 mg, 83%, >99:1 dr).

(*S,S,S*)-*N*(2)- α -Methylbenzyl-3,4-dimethyl-4-methallylisoxazolidin-5-one **285**



Following *General Procedure 4*, LiHMDS (1.0 M in THF, 0.2 mL, 0.22 mmol), **278** (36 mg, 0.17 mmol), methallyl bromide (67 mg, 0.5 mmol) and THF (1 mL) gave **285** in 97:3 dr. Purification *via* flash column chromatography (gradient elution, 40-60 °C petrol/Et₂O, 25:1; increased to 15:1) gave **285** as a colourless oil (25 mg, 56%, >99:1 dr); $[\alpha]_{\text{D}}^{23} +71.0$ (*c* 1.0 in CHCl₃); ν_{max} (film) 2975 (C–H), 1769 (C=O); δ_{H} (400 MHz, CDCl₃) 0.66 (3H, d, *J* 5.9, C(3)*Me*), 1.20 (3H, s, C(4)*Me*), 1.55 (3H, d, *J* 6.7, C(α)*Me*), 1.7 (3H, s, C(2')*Me*), 2.04 (1H, d, *J* 14.2, C(1')*H*_A), 2.60 (1H, d, *J* 14.2, C(1')*H*_B), 3.31 (1H, q, *J* 5.9, C(3)*H*), 3.99 (1H, q, *J* 6.7, C(α)*H*), 4.72 (1H, app s, C(3')*H*_A), 4.88 (1H, app s, C(3')*H*_B), 7.30-7.39 (5H, m, *Ph*); δ_{C} (100 MHz, CDCl₃) 13.0 (C(3)*Me*), 18.7 (C(α)*Me*), 19.4 (C(4)*Me*), 23.5 (C(2')*Me*), 42.7 (C(1')), 48.3 (C(4)), 64.3 (C(3)), 66.4 (C(α)), 115.9 (C(3')), 127.8, 127.9, 128.5 (*o*-, *m*-, *p*-*Ph*), 141.2, 141.4 (C(2'), *i*-*Ph*), 178.4 (C(5)); *m/z* (ESI⁺) 569 ([2M+Na]⁺, 100%), 296 ([M+Na]⁺, 28%), 274 ([M+H]⁺, 18%); HRMS (ESI⁺) C₁₇H₂₃NNaO₂⁺ ([M+Na]⁺) requires 296.1621; found 296.1616.

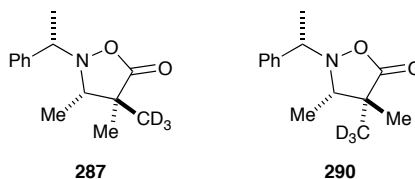
(*S,S,S*)-*N*(2)- α -Methylbenzyl-3,4-dimethyl-4-allylisoxazolidin-5-one
286



Method 1: Following *General Procedure 4*, LiHMDS (1.0 M in THF, 0.27 mL, 0.27 mmol), **278** (50 mg, 0.23 mmol), allyl iodide (0.06 mL, 0.69 mmol) and THF (1 mL) gave **286** in 69:31 dr. Purification *via* flash column chromatography (gradient elution, 40-60 °C petrol/Et₂O, 20:1; increased to 5:1) gave **286** as a colourless oil (23 mg, 39%, >99:1 dr); $[\alpha]_D^{22} +49.3$ (*c* 1.0 in CHCl₃); $\nu_{\max}$ (film) 2937 (C–H), 1770 (C=O); δ_H (400 MHz, CDCl₃) 0.65 (3H, d, *J* 6.0, C(3)*Me*), 1.19 (3H, s, C(4)*Me*), 1.54 (3H, d, *J* 6.6, C(α)*Me*), 2.13 (1H, dd, *J* 14.2, 8.5, C(4)*CH_A*), 2.45 (1H, dd, *J* 14.2, 6.1, C(4)*H_B*), 3.31 (1H, q, *J* 6.0, C(3)*H*), 3.97 (1H, q, *J* 6.6, C(α)*H*), 5.08-5.16 (2H, m, C(4)CH₂CH=CH₂), 5.71-5.82 (1H, m, C(4)CH₂CH=CH₂), 7.28-7.38 (5H, m, *Ph*); δ_C (100 MHz, CDCl₃) 13.0 (C(3)*Me*), 17.3 (C(4)*Me*), 19.0 (C(α)*Me*), 39.4 (C(4)CH₂), 48.7 (C(4)), 65.7 (C(3)), 66.6 (C(α)), 119.4 (C(4)CH₂CH=CH₂), 127.8, 127.9, 128.5 (*o*-, *m*-, *p*-*Ph*), 132.7 (C(4)CH₂CH=CH₂), 141.4 (*i*-*Ph*), 177.9 (C(5)); *m/z* (ESI⁺) 541 ([2M+Na]⁺, 100%), 282 ([M+Na]⁺, 29%), 260 ([M+H]⁺, 16%); HRMS (ESI⁺) C₁₆H₂₁NNaO₂⁺ ([M+Na]⁺) requires 282.1465; found 282.1459.

Method 2: Following *General Procedure 4*, LiHMDS (1.0 M in THF, 0.2 mL, 0.2 mmol), **279** (40 mg, 0.16 mmol), methyl iodide (0.03 mL, 0.48 mmol) and THF (1 mL) gave **286** in >99:1 dr. Purification *via* flash column chromatography (gradient elution, 40-60 °C petrol/Et₂O, 20:1; increased to 5:1) gave **286** as a colourless oil (37 mg, 89%, >99:1 dr).

(3*S*,4*R*, α *S*)- and (*S*,*S*,*S*)-*N*(2)- α -Methylbenzyl-3,4-dimethyl-4-trideuteriomethylisoxazolidin-5-one **287 and **290****

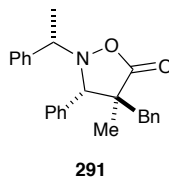


Following *General Procedure 4*, LiHMDS (1.0 M in THF, 0.21 mL, 0.21 mmol), **278** (50 mg, 0.23 mmol), trideuteriomethyl iodide (30 μ L, 0.68 mmol) and THF (1 mL) gave **287** in 62:38 dr. Purification *via* flash column chromatography (gradient elution, 40-60 °C petrol/Et₂O, 20:1; increased to 5:1) gave **287:290** in 62:38 dr as a colourless oil (28 mg, 57%); $\nu_{\max}$ (film) 1772 (C=O); m/z (ESI⁺) 259 ([M+Na]⁺, 100%), 237 ([M+H]⁺, 58%); HRMS (ESI⁺) C₁₄H₁₆D₃NNaO₂⁺ ([M+Na]⁺) requires 259.1496; found 259.1500.

Data for major diastereoisomer **287**: δ_{H} (400 MHz, CDCl₃) 0.62 (3H, d, J 6.3, C(3)*Me*), 1.15 (3H, s, C(4)*Me*), 1.58 (3H, d, J 6.6, C(α)*Me*), 3.07 (1H, q, J 6.3, C(3)*H*), 3.97 (1H, q, J 6.6, C(α)*H*), 7.30-7.39 (5H, m, *Ph*); δ_{C} (125 MHz, CDCl₃) 13.0 (C(3)*Me*), 17.2 (quin, J 20.0, C(4)*CD*₃), 19.3 (C(α)*Me*), 21.3 (C(4)*CH*₃), 45.3 (C(4)), 67.0 (C(3)), 69.7 (C(α)), 127.8, 128.0, 128.5 (*o*-, *m*-, *p*-*Ph*), 141.4 (*i*-*Ph*), 179.0 (C(5)).

Data for minor diastereoisomer **290**: δ_{H} (400 MHz, CDCl₃) 0.62 (3H, d, J 6.3, C(3)*Me*), 1.17 (3H, s, C(4)*Me*), 1.58 (3H, d, J 6.6, C(α)*Me*), 3.07 (1H, q, J 6.3, C(3)*H*), 3.97 (1H, q, J 6.6, C(α)*H*), 7.30-7.39 (5H, m, *Ph*).

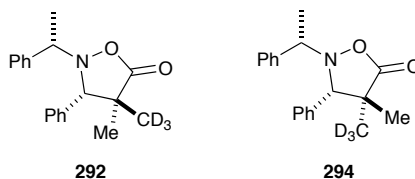
(*S,S,S*)-*N*(2)- α -Methylbenzyl-3-phenyl-4-benzyl-4-methylisoxazolidin-5-one **291**



Method 1: Following *General Procedure 4*, LiHMDS (1.0 M in THF, 0.13 mL, 0.13 mmol), **222** (30 mg, 0.11 mmol), benzyl bromide (40 μ L, 0.39 mmol) and THF (1 mL) gave **291** in >99:1 dr. Purification *via* flash column chromatography (gradient elution, 40-60 °C petrol/Et₂O, 20:1; increased to 5:1) gave **291** as a white solid (31 mg, 76%, >99:1 dr); mp 145-147 °C; $[\alpha]_D^{20}$ +27.0 (*c* 0.4 in CHCl₃); $\nu_{\max}$ (film) 3033 (C–H), 1762 (C=O); δ_H (400 MHz, CDCl₃) 1.11 (3H, s, C(4)*Me*), 1.15 (3H, d, *J* 6.6, C(α)*Me*), 2.53 (1H, d, *J* 14.3, C(4)*CH_A*), 3.35 (1H, d, *J* 14.3, C(4)*CH_B*), 3.82 (1H, q, *J* 6.6, C(α)*H*), 4.41 (1H, s, C(3)*H*), 7.18-7.41 (15H, m, *Ph*); δ_C (100 MHz, CDCl₃) 14.2 (C(α)*Me*), 21.5 (C(4)*Me*), 41.2 (C(4)*CH₂*), 51.8 (C(4)), 63.6 (C(α)), 69.9 (C(3)), 127.2, 127.5, 127.8, 128.1, 128.2, 128.4, 128.6, 128.8, 130.5 (*o*-, *m*-, *p*-*Ph*), 135.2, 136.6, 140.9 (*i*-*Ph*), 177.9 (C(5)); *m/z* (ESI⁺) 430 ([M+MeCN+NH₄]⁺, 100%); HRMS (ESI⁺) C₂₅H₂₅NNaO₂⁺ ([M+Na]⁺) requires 394.1778; found 394.1763.

Method 2: Following *General Procedure 4*, LiHMDS (1.0 M in THF, 0.92 mL, 0.92 mmol), **223** (275 mg, 0.77 mmol), methyl iodide (0.17 mL, 2.76 mmol) and THF (10 mL) gave **291** in 97:3 dr. Purification *via* flash column chromatography (gradient elution, 40-60 °C petrol/Et₂O, 20:1; increased to 5:1) gave **291** as a white solid (206 mg, 72%, >99:1 dr).

(3*S*,4*R*, α *S*)- and (*S,S,S*)-*N*(2)- α -Methylbenzyl-3-phenyl-4-methyl-4-trideuteriomethylisoxazolidin-5-one **292 and **294****

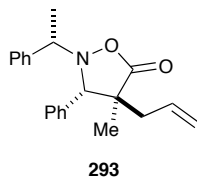


Following *General Procedure 4*, LiHMDS (1.0 M in THF, 0.21 mL, 0.21 mmol), **222** (50 mg, 0.18 mmol), trideuteriomethyl iodide (30 μ L, 0.54 mmol) and THF (1 mL) gave a 68:32 mixture of **292:294**. Purification *via* flash column chromatography (gradient elution, 40-60 °C petrol/Et₂O, 20:1; increased to 5:1) gave **292:294** in 68:32 dr as a colourless oil (26 mg, 48%); ν_{max} (film) 1774 (C=O); δ_{C} (125 MHz, CDCl₃) 14.2 (C(4)*Me*), 19.8 (C(α)*Me*), 46.1 (C(4)), 63.1 (C(α)), 76.3 (C(3)), 127.5, 127.9, 128.2, 128.3, 128.3, 128.4 (*o*-, *m*-, *p*-*Ph*), 134.2, 141.0 (*i*-*Ph*) 178.5 (C(5)); *m/z* (ESI⁺) 619 ([2M+Na]⁺, 100%), 321 ([M+Na]⁺, 32%), 299 ([M+H]⁺, 20%); HRMS (ESI⁺) C₁₉H₁₈D₃NNaO₂⁺ ([M+Na]⁺) requires 321.1653; found 321.1645.

Data for major diastereoisomer **292**: δ_{H} (400 MHz, CDCl₃) 0.99 (3H, s, C(4)*Me*), 1.50 (3H, d, *J* 6.8, C(α)*Me*), 4.14 (1H, q, *J* 6.8, C(α)*H*), 4.23 (1H, s, C(3)*H*), 7.21-7.34 (10H, m, *Ph*).

Data for minor diastereoisomer **294**: δ_{H} (400 MHz, CDCl₃) 1.23 (3H, s, C(4)*CH*₃), 1.50 (3H, d, *J* 6.8, C(α)*Me*), 4.14 (1H, q, *J* 6.8, C(α)*H*), 4.23 (1H, s, C(3)*H*), 7.21-7.34 (10H, m, *Ph*).

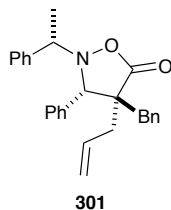
(*S,S,S*)-*N*(2)- α -Methylbenzyl-3-phenyl-4-allyl-4-methylisoxazolidin-5-one **293**



Method 1: Following *General Procedure 4*, LiHMDS (1.0 M in THF, 0.16 mL, 0.16 mmol), **222** (30 mg, 0.11 mmol), allyl iodide (20 μ L, 0.22 mmol) and THF (1 mL) gave **293** in >99:1 dr. Purification *via* flash column chromatography (gradient elution, 40-60 °C petrol/Et₂O, 50:1; increased to 10:1) gave **293** as a colourless oil (26 mg, 74%, >99:1 dr); $[\alpha]_D^{24}$ +50.3 (*c* 1.0 in CHCl₃); $\nu_{\max}$ (film) 2927 (C–H), 1773 (C=O); δ_H (400 MHz, CDCl₃) 1.01 (3H, s, C(4)*Me*), 1.47 (3H, d, *J* 6.7, C(α)*Me*), 2.12 (1H, dd, *J* 14.3, 9.5, C(4)*CH_A*), 2.52 (1H, dd, *J* 14.3, 5.1, C(4)*CH_B*), 4.13 (1H, q, *J* 6.7, C(α)*H*), 4.55 (1H, s, C(3)*H*), 5.22-5.27 (2H, m, C(4)CH₂CH=CH₂), 5.77-5.87 (1H, m, C(4)CH₂CH=CH₂), 7.20-7.34 (10H, m, *Ph*); δ_C (100 MHz, CDCl₃) 17.1 (C(α)*Me*), 19.8 (C(4)*Me*), 39.4 (C(4)CH₂), 49.8 (C(4)), 63.4 (C(α)), 71.3 (C(3)), 119.9 (C(4)CH₂CH=CH₂), 127.6, 127.9, 128.2, 128.3, 128.4, 128.5 (*o*-, *m*-, *p*-*Ph*), 133.2 (C(4)CH₂CH=CH₂), 134.6, 140.9 (*i*-*Ph*), 177.3 (C(5)); *m/z* (ESI⁺) 643 ([2M+H]⁺, 17%), 344 ([M+Na]⁺, 38%), 322 ([M+H]⁺, 100%); HRMS (ESI⁺) C₂₁H₂₃NNaO₂⁺ ([M+Na]⁺) requires 344.1621; found 344.1621.

Method 2: Following *General Procedure 4*, LiHMDS (1.0 M in THF, 0.35 mL, 0.35 mmol), **224** (90 mg, 0.29 mmol), methyl iodide (0.06 mL, 0.87 mmol) and THF (2 mL) gave **293** in a 60:40 dr. Purification *via* flash column chromatography (gradient elution, 40-60 °C petrol/Et₂O, 50:1; increased to 10:1) gave **293** as a colourless oil (35 mg, 38%, >99:1 dr).

(*S,S,S*)-*N*(2)- α -Methylbenzyl-3-phenyl-4-allyl-4-benzylisoxazolidin-5-one **301**

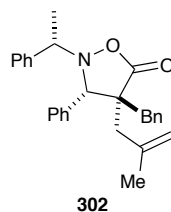


Method 1: Following *General Procedure 4*, LiHMDS (1.0 M in THF, 0.18 mL, 0.18 mmol), **224** (50 mg, 0.16 mmol), benzyl bromide (50 μ L, 0.42 mmol) and THF (1.5 mL) gave **301** in 89:11 dr. Purification *via* flash column chromatography (gradient elution, 40-60 °C petrol/Et₂O, 50:1; increased to 10:1) gave **301** as a white solid (47 mg, 71%, >99:1 dr); C₂₇H₂₇NO₂ requires C, 81.6; H, 6.85; N, 3.5%; found C, 81.5; H, 6.7; N, 3.5%; mp 84-86 °C; [α]_D²⁴ +73.6 (*c* 1.0 in CHCl₃); $\nu_{\max}$ (film) 2921 (C–H) 1771 (C=O); δ_{H} (400 MHz, CDCl₃) 1.12 (3H, d, *J* 6.8, C(α)Me), 1.88 (1H, dd, *J* 14.2, 8.5, C(4)CH_AH_BCH=CH₂), 2.44 (1H, d, *J* 14.4, C(4)CH_AH_BPh), 2.64 (1H, dd, *J* 14.2, 6.1, C(4)CH_AH_BCH=CH₂), 3.47 (1H, d, *J* 14.4, C(4)CH_AH_BPh), 3.83 (1H, q, *J* 6.8, C(α)H), 4.52 (1H, s, C(3)H), 5.00 (1H, app d, *J* 17.0, C(4)CH₂CH=CH_AH_B), 5.10 (1H, app d, *J* 10.1, C(4)CH₂CH=CH_AH_B), 5.69-5.77 (1H, m, C(4)CH₂CH=CH₂), 7.17-7.42 (15H, m, *Ph*); δ_{C} (100 MHz, CDCl₃) 13.5 (C(α)Me), 38.7 (C(4)CH₂CH=CH₂), 38.7 (C(4)CH₂Ph), 54.6 (C(4)), 63.1 (C(α)), 69.5 (C(3)), 119.3 (C(4)CH₂CH=CH₂), 127.2, 127.5, 127.7, 128.2, 128.4, 128.6, 128.7, 128.9, 130.6 (*o*-, *m*-, *p*-*Ph*), 132.2 (C(4)CH₂CH=CH₂), 134.6, 136.9, 141.1 (*i*-*Ph*), 173.9 (C(5)); *m/z* (ESI⁺) 420 ([M+Na]⁺, 50%), 398 ([M+H]⁺, 100%); HRMS (ESI⁺) C₂₇H₂₇NNaO₂⁺ ([M+Na]⁺) requires 420.1934; found 420.1922.

Method 2: Following *General Procedure 4*, LiHMDS (1.0 M in THF, 0.20 mL, 0.20 mmol), **223** (60 mg, 0.17 mmol), allyl iodide (47 μ L, 0.51 mmol) and THF (1 mL) gave

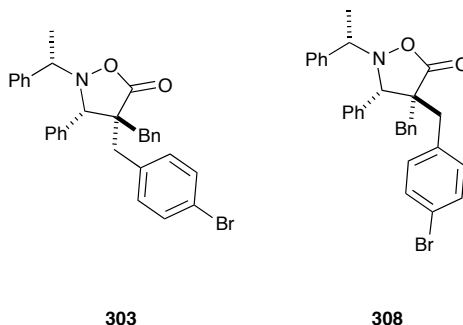
301 in 73:27 dr. Purification *via* flash column chromatography (gradient elution, 40-60 °C petrol/Et₂O, 50:1; increased to 10:1) gave **301** as a white solid (36 mg, 54%, >99:1 dr).

(*S,S,S*)-*N*(2)- α -Methylbenzyl-3-phenyl-4-benzyl-4-methallylisoxazolidin-5-one **302**



Following *General Procedure 4*, LiHMDS (1.0 M in THF, 0.41 mL, 0.41 mmol), **223** (100 mg, 0.34 mmol), methallyl bromide (136 mg, 1.01 mmol) and THF (3 mL) gave **302** in 56:44 dr. Purification *via* flash column chromatography (gradient elution, 40-60 °C petrol/Et₂O, 25:1; increased to 15:1) gave **302** as a colourless oil (42 mg, 30%, >99:1 dr); $[\alpha]_D^{23}$ +88.9 (*c* 1.0 in CHCl₃); $\nu_{\max}$ (film) 1771 (C=O); δ_H (400 MHz, CDCl₃) 1.10 (3H, d, *J* 6.8, C(α)*Me*), 1.72 (1H, d, *J* 13.7, C(1')*H_A*), 1.78 (3H, s, C(2')*Me*), 2.44 (1H, d, *J* 14.2, C(4)*CH_AH_BPh*), 2.70 (1H, d, *J* 13.7, C(1')*H_B*), 3.65 (1H, d, *J* 14.2, C(4)*CH_AH_BPh*), 3.84 (1H, q, *J* 6.8, C(α)*H*), 4.51 (1H, s, C(3)*H*), 4.68 (1H, app s, C(3')*H_A*), 4.95 (1H, app s, C(3')*H_B*), 7.19-7.39 (15H, m, *Ph*); δ_C (125 MHz, CDCl₃) 14.0 (C(α)*Me*), 23.0 (C(2')*Me*), 40.0 (C(1')), 40.7 (C(4)*CH₂Ph*), 51.8 (C(4)), 62.9 (C(α)), 70.2 (C(3)), 117.2 (C(3')), 127.0, 127.6, 127.7, 128.1, 128.3, 128.5, 128.6, 128.9, 130.8 (*o*-, *m*-, *p*-*Ph*), 135.0 (C(2')), 140.8, 141.2, 142.3 (*i*-*Ph*) 175.0 (C(5)); *m/z* (ESI⁺) 434 ([M+Na]⁺, 100%), 412 ([M+H]⁺, 23%); HRMS (ESI⁺) C₂₈H₂₉NNaO₂⁺ ([M+Na]⁺) requires 434.2091; found 434.2098.

(3*S*,4*R*, α *S*)- and (*S*,*S*,*S*)-*N*(2)- α -Methylbenzyl-3-phenyl-4-benzyl-4-(*p*-bromobenzyl)isoxazolidin-5-one **303 and **308****

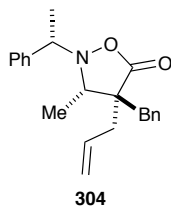


Following *General Procedure 4*, LiHMDS (1.0 M in THF, 0.18 mL, 0.18 mmol), **223** (50 mg, 0.14 mmol), 4-bromobenzyl bromide (80 mg, 0.42 mmol) and THF (2 mL) gave **303:308** in 54:46 dr. Purification *via* flash column chromatography (gradient elution, 40-60 °C petrol/Et₂O, 20:1; increased to 5:1) gave **303:308** in 54:46 dr as a colourless oil (48 mg, 65%); $\nu_{\max}$ (film) 1770 (C=O); δ_{C} (125 MHz, CDCl₃) 13.4, 14.1, 37.4, 38.2, 39.7, 40.3, 54.8, 54.9, 63.0, 63.2, 69.8, 69.9, 121.1, 121.2, 127.1, 127.2, 127.5, 127.6, 127.8, 127.9, 128.0, 128.2, 128.6, 128.6, 128.6, 128.7, 129.0, 130.5, 130.9, 131.0, 131.8, 132.2, 132.6, 134.1, 134.1, 134.3, 134.9, 135.7, 136.4, 140.2, 141.0, 174.8, 175.0; m/z (ESI⁺) 550 ([M+Na]⁺, ⁸¹Br, 97%), 548 ([M+Na]⁺, ⁷⁹Br, 100%); HRMS (ESI⁺) C₃₁H₂₈⁸¹BrNNaO₂⁺ ([M+Na]⁺) requires 550.1180; found 550.1159. HRMS (ESI⁺) C₃₁H₂₈⁷⁹BrNNaO₂⁺ ([M+Na]⁺) requires 548.1196; found 548.1175.

Data for major diastereoisomer: δ_{H} (400 MHz, CDCl₃) 1.13 (3H, d, J 6.6, C(α)Me), 2.19-2.26 (2H, m, 2 $\times$ C(4)CH_A), 3.19-3.30 (2H, m, 2 $\times$ C(4)CH_B), 3.86 (1H, q, J 6.6, C(α)H), 4.60 (1H, s, C(3)H), 6.90-7.44 (19H, m, Ar).

Data for minor diastereoisomer: δ_{H} (400 MHz, CDCl₃) [selected peaks] 1.17 (3H, d, J 6.7, C(α)Me), 2.42-2.47 (2H, m, 2 $\times$ C(4)CH_A), 3.30-3.38 (2H, m, 2 $\times$ C(4)CH_B), 4.02 (1H, q, J 6.7, C(α)H), 4.46 (1H, s, C(3)H).

(*S,S,S*)-*N*(2)- α -Methylbenzyl-3-methyl-4-allyl-4-benzylisoxazolidin-5-one **304**

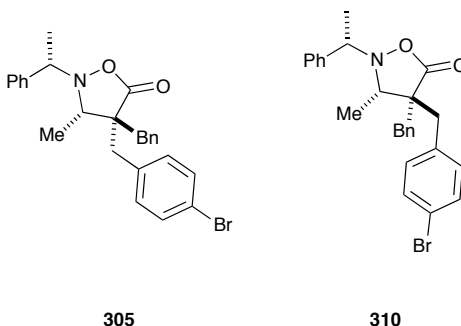


Method 1: Following *General Procedure 4*, LiHMDS (1.0 M in THF, 0.81 mL, 0.81 mmol), **255** (200 mg, 0.68 mmol), allyl iodide (0.19 mL, 2.04 mmol) and THF (5 mL) gave **304** in 90:10 dr. Purification *via* flash column chromatography (gradient elution, 40-60 °C petrol/Et₂O, 20:1; increased to 5:1) gave **304** as a colourless oil (178 mg, 78%, >99:1 dr); $[\alpha]_D^{18} +96.9$ (*c* 1.0 in CHCl₃); $\nu_{\max}$ (film) 2979 (C–H), 1767 (C=O); δ_H (400 MHz, CDCl₃) 0.68 (3H, d, *J* 6.1, C(3)*Me*), 1.33 (3H, d, *J* 6.5, C(α)*Me*), 2.27 (1H, dd, *J* 14.1, 8.6, C(4)CH_AH_BCH=CH₂), 2.53 (1H, d, *J* 14.3, C(4)CH_AH_BPh), 2.72 (1H, dd, *J* 14.1, 6.1, C(4)CH_AH_BCH=CH₂), 3.21 (1H, q, *J* 6.1, C(3)*H*), 3.28 (1H, d, *J* 14.3, C(4)CH_AH_BPh), 3.72 (1H, q, *J* 6.5, C(α)*H*), 5.18-5.23 (2H, m, C(4)CH₂CH=CH₂), 5.95-6.06 (1H, m, C(4)CH₂CH=CH₂), 7.26-7.31 (10H, m, *Ph*); δ_C (100 MHz, CDCl₃) 12.5 (C(3)*Me*), 18.1 (C(α)*Me*), 36.5 (C(4)CH₂=CHCH₂), 38.6 (C(4)CH₂Ph), 53.5 (C(4)), 64.5 (C(3)), 66.1 (C(α)), 107.8 (C(4)CH₂CH=CH₂), 120.0 (C(4)CH₂CH=CH₂), 127.6, 127.7, 128.4, 128.5, 130.1, 132.6 (*o*-, *m*-, *p*-*Ph*), 136.3, 141.4 (*i*-*Ph*), 176.0 (C(5)); *m/z* (ESI⁺) 394 ([M+NH₄+MeCN]⁺, 100%); HRMS (ESI⁺) C₂₂H₂₅NNaO₂⁺ ([M+Na]⁺) requires 358.1778; found 358.1773.

Method 2: Following *General Procedure 4*, LiHMDS (1.0 M in THF, 0.2 mL, 0.2 mmol), **279** (40 mg, 0.16 mmol), benzyl bromide (0.06 mL, 0.48 mmol) and THF (1 mL) gave **304** in 67:33 dr. Purification *via* flash column chromatography on silica gel

(gradient elution, 40-60 °C petrol/Et₂O, 20:1; increased to 5:1) gave **304** as a colourless oil (25 mg, 47%, >99:1 dr).

(3*S*,4*R*, α *S*)- and (3*S*,4*S*, α *S*)-*N*(2)- α -Methylbenzyl-3-methyl-4-benzyl-4-(4-bromobenzyl)isoxazolidin-5-one **305 and **310****



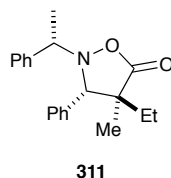
Following *General Procedure 4*, LiHMDS (1.0 M in THF, 0.28 mL, 0.28 mmol), **255** (70 mg, 0.24 mmol), 4-bromobenzyl bromide (176 mg, 0.72 mmol) and THF (2 mL) gave **305:310** in 61:39 dr. Purification *via* flash column chromatography (gradient elution, 40-60 °C petrol/Et₂O, 20:1; increased to 5:1) gave **305:310** in 61:39 dr as a colourless oil (20 mg, 18%); $\nu_{\max}$ (film) 2980 (C–H), 1771 (C=O); δ_{C} (125 MHz, CDCl₃) 12.2, 12.3, 18.1, 18.8, 37.0, 37.3, 37.7, 37.9, 54.5, 54.6, 64.5, 64.7, 65.9, 66.2, 121.0, 121.2, 127.0, 127.1, 127.6, 127.7, 127.8, 127.9, 128.0, 128.1, 128.5, 128.6, 130.2, 130.7, 131.2, 131.6, 131.9, 131.9, 132.4, 134.5, 135.2, 136.0, 141.1, 141.4, 174.7, 174.9; m/z (ESI⁺) 488 ([M+Na]⁺, ⁸¹Br, 96%), 486 ([M+Na]⁺, ⁷⁹Br, 100%), 466 ([M+H]⁺, ⁸¹Br, 30%), 464 ([M+H]⁺, ⁷⁹Br, 38%); HRMS (ESI⁺) C₂₆H₂₆⁸¹BrNNaO₂⁺ ([M+Na]⁺) requires 488.1023, found 488.1027; HRMS (ESI⁺) C₂₆H₂₆⁷⁹BrNNaO₂⁺ ([M+Na]⁺) requires 486.1039, found 486.1042.

Data for major diastereoisomer: δ_{H} (500 MHz, CDCl₃) 0.81 (3H, d, J 6.3, C(3)*Me*), 1.32 (3H, d, J 6.5, C(α)*Me*), 2.52 (1H, d, J 14.2, C(4)*CH_A*), 2.70 (1H, d, J 13.6, C(4)*CH_C*), 3.17-3.19 (1H, m, C(3)*H*), 3.20 (1H, d, J 14.2, C(4)*CH_B*), 3.30 (1H, d, J

13.6, C(4)CH_D), 3.72 (1H, q, *J* 6.5, C(α)*H*), 7.10 (2H, d, *J* 8.2, *Ar*), 7.18-7.34 (10H, m, *Ph*), 7.44-7.45 (2H, d, *J* 8.2, *Ar*).

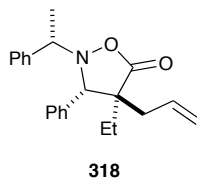
Data for minor diastereoisomer: δ_H (500 MHz, CDCl₃) [selected peaks] 1.39 (3H, d, *J* 6.6, C(α)*Me*), 2.47 (1H, d, *J* 14.2, C(4)CH_A), 2.72 (1H, d, *J* 13.8, C(4)CH_C), 3.09-3.12 (1H, m, C(3)*H*), 3.16 (1H, d, *J* 14.2, C(4)CH_B), 3.38 (1H, d, *J* 13.8, C(4)CH_D), 3.79 (1H, q, *J* 6.6, C(α)*H*), 6.95 (2H, d, *J* 8.2, *Ar*), 7.37 (2H, d, *J* 8.2, *Ar*).

(3*S*,4*R*,α*S*)-*N*(2)-α-Methylbenzyl-3-phenyl-4-ethyl-4-methylisoxazolidin-5-one **311**



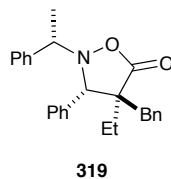
Following *General Procedure 4*, LiHMDS (1.0 M in THF, 0.08 mL, 0.08 mmol), **281** (23 mg, 0.08 mmol), methyl iodide (20 μL, 0.21 mmol) and THF (0.5 mL) gave **311** in 58:42 dr. Purification *via* flash column chromatography (gradient elution, 40-60 °C petrol/Et₂O, 20:1; increased to 5:1) gave **311** as a colourless oil (6 mg, 25%, >99:1 dr); [α]_D²⁴ +69.1 (*c* 0.4 in CHCl₃); ν_{max} (film) 2977 (C–H), 1767 (C=O); δ_H (400 MHz, CDCl₃) 0.81 (3H, app t, *J* 7.5, C(4)CH₂CH₃), 1.25 (3H, s, C(4)*Me*), 1.49 (3H, d, *J* 6.6, C(α)*Me*), 0.92-1.00 (1H, m, C(4)CH_A), 1.86-1.95 (1H, m, C(4)CH_B), 4.13 (1H, q, *J* 6.6, C(α)*H*), 4.32 (3H, s, C(3)*H*), 7.11-7.36 (10H, m, *Ph*); δ_C (125 MHz, CDCl₃) 8.0 (C(4)CH₂CH₃), 17.1 (C(α)*Me*), 18.7 (C(4)*Me*), 25.4 (C(4)CH₂), 49.3 (C(4)), 62.7 (C(α)), 73.0 (C(3)), 127.5, 127.8, 128.1, 128.2, 128.4, 128.6 (*o*-, *m*-, *p*-*Ph*), 134.0, 141.2 (*i*-*Ph*), 177.1 (C(5)); *m/z* (ESI⁺) 332 ([M+Na]⁺, 42%), 310 ([M+H]⁺, 15%); HRMS (ESI⁺) C₂₀H₂₃NNaO₂⁺ ([M+Na]⁺) requires 332.1621; found 332.1626.

(*S,S,S*)-*N*(2)- α -Methylbenzyl-3-phenyl-4-allyl-4-ethylisoxazolidin-5-one **318**



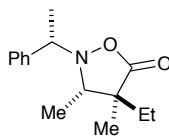
Following *General Procedure 4*, LiHMDS (1.0 M in THF, 0.08 mL, 0.08 mmol), **281** (23 mg, 0.07 mmol), allyl iodide (30 μ L, 0.21 mmol) and THF (0.5 mL) gave **318** in 78:22 dr. Purification *via* flash column chromatography (gradient elution, 40-60 $^{\circ}$ C petrol/Et₂O, 20:1; increased to 5:1) gave **318** as a colourless oil (13 mg, 67%, 93:7 dr); $[\alpha]_{\text{D}}^{24} +44.3$ (*c* 0.5 in CHCl₃); ν_{max} (film) 2975 (C-H), 1768 (C=O); δ_{H} (400 MHz, CDCl₃) 0.83 (3H, app t, *J* 7.5, C(4)CH₂CH₃), 1.00-1.09 (1H, m, C(4)CH_AH_BCH₃), 1.46 (3H, d, *J* 6.7, C(α)Me), 1.83-1.92 (1H, m, C(4)CH_AH_BCH₃), 2.04 (1H, dd, *J* 14.0, 10.7, C(4)CH_AH_BCH=CH₂), 2.74 (1H, dd, *J* 14.0, 4.6, C(4)CH_AH_BCH=CH₂), 4.12 (1H, q, *J* 6.7, C(α)H), 4.69 (1H, s, C(3)H), 5.29 (2H, app d, *J* 13.4, C(4)CH₂CH=CH₂), 5.74-5.84 (1H, m, C(4)CH₂CH=CH₂), 7.21-7.34 (10H, m, *Ph*); δ_{C} (100 MHz, CDCl₃) 8.0 (C(4)CH₂CH₃), 13.9 (C(α)Me), 25.3 (C(4)CH₂CH₃), 36.0 (C(4)CH₂CH=CH₂), 52.9 (C(4)), 62.9 (C(α)), 71.3 (C(3)), 119.9 (C(4)CH₂CH=CH₂), 127.5, 127.9, 128.3, 128.4, 133.7, 134.5 (*o*-, *m*-, *p*-*Ph*), 133.7 (C(4)CH₂CH=CH₂), 141.2, 143.4 (*i*-*Ph*), 175.9 (C(5)); *m/z* (ESI⁺) 693 ([2M+Na]⁺, 100%), 358 ([M+Na]⁺, 33%), 336 ([M+H]⁺, 21%); HRMS (ESI⁺) C₂₂H₂₅NNaO₂⁺ ([M+Na]⁺) requires 358.1778; found 358.1776.

(*S,S,S*)-*N*(2)- α -Methylbenzyl-3-phenyl-4-benzyl-4-ethylisoxazolidin-5-one **319**



Following *General Procedure 4*, LiHMDS (1.0 M in THF, 0.08 mL, 0.08 mmol), **281** (23 mg, 0.07 mmol), benzyl bromide (40 μ L, 0.21 mmol) and THF (0.5 mL) gave **319** in 21:79 dr. Purification *via* flash column chromatography (gradient elution, 40-60 °C petrol/Et₂O, 20:1; increased to 5:1) gave **319** as a colourless oil (20 mg, 55%, >99:1 dr); $[\alpha]_D^{24} +55.4$ (*c* 1.0 in CHCl₃); $\nu_{\max}$ (film) 2950 (C–H), 1770 (C=O); δ_H (400 MHz, CDCl₃) 0.94 (3H, app t, *J* 7.6, C(4)CH₂CH₃), 1.10 (3H, d, *J* 6.7, C(α)Me), 1.17-1.25 (1H, m, C(4)CH_AH_BCH₃), 1.83-1.89 (1H, m, C(4)CH_AH_BCH₃), 2.45 (1H, d, *J* 14.2, C(4)CH_AH_BPh), 3.54 (1H, d, *J* 14.2, C(4)CH_AH_BPh), 3.80 (1H, q, *J* 6.7, C(α)H), 4.50 (1H, s, C(3)H), 7.16-7.41 (15H, m, *Ph*); δ_C (100 MHz, CDCl₃) 8.2 (C(4)CH₂CH₃), 18.1 (C(α)Me), 27.4 (C(4)CH₂CH₃), 38.3 (C(4)CH₂Ph), 54.8 (C(4)), 63.1 (C(α)), 69.8 (C(3)), 127.1, 127.3, 127.7, 128.1, 128.4, 128.5, 128.8, 130.5 (*o*-, *m*-, *p*-*Ph*), 134.9, 137.0, 141.2 (*i*-*Ph*), 176.5 (C(5)); *m/z* (ESI⁺) 408 ([M+Na]⁺, 100%), 386 ([M+H]⁺, 52%); HRMS (ESI⁺) C₂₆H₂₇NNaO₂⁺ ([M+Na]⁺) requires 408.1934; found 408.1929.

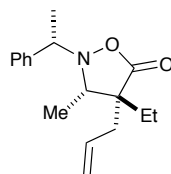
(*S,S,S*)-*N*(2)- α -Methylbenzyl-3,4-dimethyl-4-ethylisoxazolidin-5-one
314



314

Following *General Procedure 4*, LiHMDS (1.0 M in THF, 0.13 mL, 0.13 mmol), **280** (25 mg, 0.11 mmol), methyl iodide (0.02 mL, 0.33 mmol) and THF (0.5 mL) gave **314** in 64:36 *dr*. Purification *via* flash column chromatography (gradient elution, 40-60 °C petrol/Et₂O, 20:1; increased to 5:1) gave **314** as a colourless oil (10 mg, 38%, >99:1 *dr*); $[\alpha]_{\text{D}}^{23} +48.9$ (*c* 0.5 in CHCl₃); ν_{max} (film) 2918 (C–H), 1763 (C=O); δ_{H} (400 MHz, CDCl₃) 0.64 (3H, d, *J* 5.7, C(3)*Me*), 0.95 (3H, app t, *J* 7.4, C(4)CH₂CH₃), 1.17 (3H, s, C(4)*Me*), 1.44-1.51 (1H, m, C(4)CH_A), 1.56 (3H, d, *J* 6.6, C(α)*Me*), 1.69 (1H, dq, *J* 14.5, 7.4, C(4)CH_B), 3.28 (1H, q, *J* 5.7, C(3)*H*), 3.98 (1H, q, *J* 6.6, C(α)*H*), 7.28-7.39 (5H, m, *Ph*); δ_{C} (100 MHz, CDCl₃) 8.6 (C(4)CH₂CH₃), 13.2 (C(3)*Me*), 17.3 (C(4)*Me*), 19.2 (C(α)*Me*), 27.6 (C(4)CH₂), 53.0 (C(4)), 65.6 (C(3)), 70.7 (C(α)), 127.9, 128.0, 128.6 (*o*-, *m*-, *p*-*Ph*), 136.0 (*i*-*Ph*), 174.5 (C(5)); *m/z* (ESI⁺) 517 ([2M+Na]⁺, 100%), 270 ([M+Na]⁺, 54%), 248 ([M+H]⁺, 21%); HRMS (ESI⁺) C₁₅H₂₁NNaO₂⁺ ([M+Na]⁺) requires 270.1454; found 270.1464.

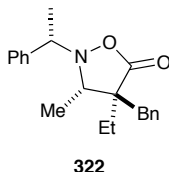
(3*S*,4*R*, α *S*)-*N*(2)- α -Methylbenzyl-3-methyl-4-allyl-4-ethylisoxazolidin-5-one **315**



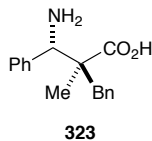
315

Following *General Procedure 4*, LiHMDS (1.0 M in THF, 0.13 mL, 0.13 mmol), **280** (23 mg, 0.11 mmol), allyl iodide (0.03 mL, 0.33 mmol) and THF (0.5 mL) gave **315** in 69:31 dr. Purification *via* flash column chromatography (gradient elution, 40-60 °C petrol/Et₂O, 20:1; increased to 5:1) gave **315** as a colourless oil (12 mg, 40%, 92:8 dr); $\nu_{\max}$ (film) 2935 (C–H), 1766 (C=O); δ_{H} (400 MHz, CDCl₃) 0.71 (3H, d, J 5.5, C(3)*Me*), 0.92 (3H, app t, J 7.5, C(4)CH₂CH₃), 1.34-1.47 (1H, m, C(4)CH_AH_BCH₃), 1.56 (3H, d, J 6.5, C(α)*Me*), 1.81 (1H, dq, J 14.8, 7.5, C(4)CH_AH_BCH₃), 2.15 (1H, dd, J 14.2, 8.5, C(4)CH_AH_BCH=CH₂), 2.63 (1H, dd, J 14.2, 6.3, C(4)CH_AH_BCH=CH₂), 3.40 (1H, q, J 5.5, C(3)*H*), 3.98 (1H, q, J 6.5, C(α)*H*), 5.09-5.14 (2H, m, C(4)CH₂CH=CH₂), 5.83-5.92 (1H, m, C(4)CH₂CH=CH₂), 7.30-7.39 (5H, m, *Ph*); δ_{C} (100 MHz, CDCl₃) 8.5 (C(4)CH₂CH₃), 13.0 (C(3)*Me*), 19.2 (C(α)*Me*), 25.1 (C(4)CH₂CH₃), 35.5 (C(4)CH₂CH=CH₂), 52.5 (C(4)), 65.6 (C(3)), 66.8 (C(α)), 118.6 (C(4)CH₂CH=CH₂), 127.8, 127.9, 128.5 (*o*-, *m*-, *p*-*Ph*), 132.8 (C(4)CH₂CH=CH₂), 141.5 (*i*-*Ph*), 176.3 (C=O); m/z (ESI⁺) 569 ([2M+Na]⁺, 100%), 296 ([M+Na]⁺, 52%), 274 ([M+H]⁺, 30%); HRMS (ESI⁺) C₁₇H₂₃NNaO₂⁺ ([M+Na]⁺) requires 296.1621; found 296.1622.

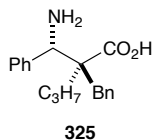
(3*S*,4*R*, α *S*)-*N*(2)- α -Methylbenzyl-3-methyl-4-benzyl-4-ethylisoxazolidin-5-one **322**



Following *General Procedure 4*, LiHMDS (1.0 M in THF, 0.13 mL, 0.13 mmol), **280** (25 mg, 0.11 mmol), benzyl bromide (0.04 mL, 0.33 mmol) and THF (0.5 mL) gave **322** in 90:10 dr. Purification *via* flash column chromatography (gradient elution, 40-60 °C petrol/Et₂O, 20:1; increased to 5:1) gave **322** as a colourless oil (19 mg, 53%, 90:10 dr); ν_{max} (film) 2928 (C-H), 1765 (C=O); δ_{H} (400 MHz, CDCl₃) 0.62 (3H, d, J 6.3, C(3)*Me*), 1.09-1.13 (3H, m, C(4)CH₂CH₃), 1.31 (3H, d, J 6.5, C(α)*Me*), 1.54-1.63 (1H, m, C(4)CH_AH_BCH₃), 1.95 (1H, dq, J 14.3, 7.4, C(4)CH_AH_BCH₃), 2.52 (1H, d, J 13.9, C(4)CH_AH_BPh), 3.16-3.21 (1H, d, J 6.3, C(3)*H*), 3.28 (1H, d, J 13.9, C(4)CH_AH_BPh), 3.67 (1H, q, J 6.5, C(α)*H*), 7.13-7.30 (10H, m, *Ph*); δ_{C} (100 MHz, CDCl₃) 8.5 (C(4)CH₂CH₃), 13.3 (C(3)*Me*), 19.0 (C(α)*Me*), 27.7 (C(4)CH₂CH₃), 38.7 (C(4)CH₂Ph), 53.7 (C(4)), 64.5 (C(3)), 69.1 (C(α)), 127.2, 127.7, 128.1, 128.3, 128.8, 130.3 (*o*-, *m*-, *p*-*Ph*), 136.9, 140.7 (*i*-*Ph*), 175.6 (C(5)); m/z (ESI⁺) 669 ([2M+Na]⁺, 100%), 346 ([M+Na]⁺, 70%), 324 ([M+H]⁺, 38%); HRMS (ESI⁺) C₂₁H₂₅NNaO₂⁺ ([M+Na]⁺) requires 346.1778; found 346.1780.

(*S,S*)-2-Benzyl-2-methyl-3-amino-3-phenylpropanoic acid 323

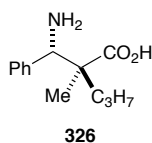
Following *General Procedure 5*, **291** (45 mg, 0.12 mmol), Pearlman's catalyst (23 mg) and *tert*-butanol (1 mL) gave **323** as a white solid (29 mg, 90%, >99:1 dr); mp 168–170 °C; $[\alpha]_{\text{D}}^{25}$ -26.9 (c 1.0 in MeOH); ν_{max} (KBr) 3320 (N–H), 1646 (COO[−] as st); δ_{H} (400 MHz, MeOH- d_4) 0.83 (3H, s, C(2)*Me*), 2.35 (1H, d, J 12.9, C(2) $\text{CH}_\text{A}\text{H}_\text{B}\text{Ph}$), 3.31 (1H, d, J 12.9, C(2) $\text{CH}_\text{A}\text{H}_\text{B}\text{Ph}$), 4.20 (1H, s, C(3)*H*), 7.10–7.40 (10H, m, *Ph*); δ_{C} (100 MHz, CD₃OD) 17.0 (C(2)*Me*), 44.6 (C(2) CH_2Ph), 52.4 (C(2)), 63.2 (C(3)), 126.2, 127.8, 127.9, 128.2, 128.7, 130.5 (*o*-, *m*-, *p*-*Ph*), 138.8, 140.8 (*i*-*Ph*), 182.8 (C(1)); m/z (ESI⁺) 292 ([M+Na]⁺, 73%), 270 ([M+H]⁺, 100%); HRMS (ESI⁺) C₁₇H₂₀NO₂⁺ ([M+H]⁺) requires 270.1489; found 270.1487.

(*S,S*)-2-Benzyl-2-propyl-3-amino-3-phenylpropanoic acid 325

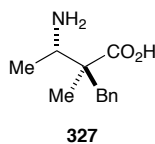
Following *General Procedure 5*, **301** (50 mg, 0.14 mmol), Pearlman's catalyst (25 mg) and *tert*-butanol (3 mL) gave **325** as a white solid (35 mg, 96%, >99:1 dr); mp 150–152 °C; $[\alpha]_{\text{D}}^{25}$ -25.3 (c 1.0 in MeOH); ν_{max} (KBr) 3418 (N–H), 1644 (COO[−] as st); δ_{H} (400 MHz, D₂O) 0.59 (3H, t, J 7.2, C(2) $\text{CH}_2\text{CH}_2\text{CH}_3$), 0.77–0.85 (1H, m, C(2) $\text{CH}_\text{A}\text{H}_\text{B}\text{CH}_2\text{CH}_3$), 1.00–1.08 (1H, m, C(2) $\text{CH}_\text{A}\text{H}_\text{B}\text{CH}_2\text{CH}_3$), 1.28–1.41 (2H, m, C(2) $\text{CH}_2\text{CH}_2\text{CH}_3$), 2.79 (1H, d, J 13.4, C(2) $\text{CH}_\text{A}\text{H}_\text{B}\text{Ph}$), 3.18 (1H, d, J 13.4,

C(2)CH_AH_BPh), 4.22 (1H, s, C(3)*H*), 7.15-7.28 (10H, m, *Ph*); δ_{C} (100 MHz, D₂O) 14.0 (C(2)CH₂CH₂CH₃), 16.3 (C(2)CH₂CH₂CH₃), 33.2 (C(2)CH₂CH₂CH₃), 39.4 (C(2)CH₂Ph), 54.3 (*C*(2)), 59.4 (*C*(3)), 126.9, 128.0, 128.7, 128.8, 129.0, 130.2 (*o*-, *m*-, *p*-*Ph*), 138.2, 147.4 (*i*-*Ph*), 182.2 (*C*(1)); *m/z* (ESI⁻) 296 ([M-H]⁻, 100%); HRMS (ESI⁻) C₁₉H₂₂NO₂⁻ ([M-H]⁻) requires 296.1656; found 296.1656.

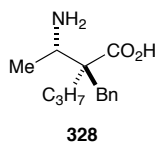
(*S,S*)-2-Methyl-2-propyl-3-amino-3-phenylpropanoic acid **326**



Following *General Procedure 5*, **293** (80 mg, 0.25 mmol), Pearlman's catalyst (40 mg) and *tert*-butanol (3 mL) gave **326** as a white solid (43 mg, 78%, >99:1 dr); mp 144-146 °C; $[\alpha]_{\text{D}}^{25}$ -29.0 (*c* 1.0 in MeOH); ν_{max} (KBr) 3385 (N-H), 1644 (COO⁻ as st); δ_{H} (500 MHz, CD₃OD) 0.94 (3H, s, C(2)*Me*), 0.94 (3H, t, *J* 6.9, C(2)CH₂CH₂CH₃), 1.35-1.41 (1H, m, CH₂), 1.43-1.53 (2H, m, Al-*H*), 1.65-1.71 (1H, m, Al-*H*), 4.21 (1H, s, C(3)*H*), 7.40-7.44 (5H, m, *Ph*); δ_{C} (125 MHz, CD₃OD) 14.9 (C(2)CH₂CH₂CH₃), 19.0 (C(2)CH₂CH₂CH₃), 20.3 (C(2)*Me*), 41.9 (C(2)CH₂CH₂CH₃), 49.5 (*C*(2)), 62.2 (*C*(3)), 129.4, 129.9, 130.0 (*o*-, *m*-, *p*-*Ph*), 137.6 (*i*-*Ph*), 182.0 (*C*(1)); *m/z* (ESI⁺) 465 ([2M+Na]⁺, 100%), 244 ([M+Na]⁺, 58%), 222 ([M+H]⁺, 41%); HRMS (ESI⁺) C₁₃H₁₉NNaO₂⁺ ([M+Na]⁺) requires 244.1308; found 244.1305.

(*S,S*)-2-Benzyl-2-methyl-3-aminobutanoic acid 327

Following *General Procedure 5*, **283** (22 mg, 0.07 mmol), Pearlman's catalyst (11 mg) and *tert*-butanol (1 mL) gave **327** as a white solid (13 mg, 90%, >99:1 dr); mp 184–186 °C; $[\alpha]_{\text{D}}^{25}$ -17.6 (c 0.5 in MeOH); ν_{max} (KBr) 3443 (N–H), 1643 (COO[−] as st); δ_{H} (400 MHz, D₂O) 1.11 (3H, d, J 6.8, C(4) H_3), 1.81 (3H, s, C(2) Me), 2.58 (1H, d, J 13.1, C(2) CH_AH_BPh), 2.87 (1H, d, J 13.1, C(2) CH_AH_BPh), 3.12 (1H, q, J 6.8, C(3) H), 7.09–7.23 (5H, m, Ph); δ_{C} (100 MHz, D₂O) 15.4 (C(2) Me), 16.7 (C(4)), 44.4 (C(2) CH_2Ph), 51.9 (C(2)), 59.3 (C(3)), 128.6, 130.3, 131.2 (o -, m -, p - Ph), 138.3 (i - Ph), 183.2 (C(1)); m/z (ESI⁺) 230 ([M+Na]⁺, 100%), 208 ([M+H]⁺, 41%); HRMS (ESI⁺) C₁₂H₁₇NNaO₂⁺ ([M+Na]⁺) requires 230.1151; found 230.1152.

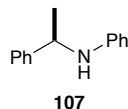
(*S,S*)-2-Benzyl-2-propyl-3-aminobutanoic acid 328

Following *General Procedure 5*, **304** (20 mg, 0.05 mmol), Pearlman's catalyst (10 mg) and *tert*-butanol (1 mL) gave **328** as a white solid (10 mg, 86%, >99:1 dr); mp 156–158 °C; $[\alpha]_{\text{D}}^{25}$ -23.4 (c 0.5 in MeOH); ν_{max} (KBr) 3424 (N–H), 1643 (COO[−] as st); δ_{H} (400 MHz, D₂O) 0.75 (3H, t, J 6.8, C(2) $CH_2CH_2CH_3$), 1.13 (3H, d, J 6.8, C(4) H_3), 1.16–1.21 (2H, m, Al- H), 1.26–1.39 (2H, m, Al- H), 2.77 (1H, d, J 13.4, C(2) CH_AH_BPh), 2.88 (1H, d, J 13.4, C(2) CH_AH_BPh), 3.30 (1H, q, J 6.8, C(3) H), 7.08–7.24 (5H, m, Ph);

δ_{C} (100 MHz, D_2O) 14.3 ($\text{C}(2)\text{CH}_2\text{CH}_2\text{CH}_3$), 15.1 ($\text{C}(2)\text{CH}_2\text{CH}_2\text{CH}_3$), 16.4 ($\text{C}(4)$), 33.3 ($\text{C}(2)\text{CH}_2\text{CH}_2\text{CH}_3$), 39.3 ($\text{C}(2)\text{CH}_2\text{Ph}$), 51.3 ($\text{C}(2)$), 53.1 ($\text{C}(3)$), 127.1, 128.8, 130.1 (*o*-, *m*-, *p*-*Ph*), 138.0 (*i*-*Ph*), 182.3 ($\text{C}(1)$); m/z (ESI^-) 234 ($[\text{M}-\text{H}]^-$, 100%); HRMS (ESI^-) $\text{C}_{14}\text{H}_{20}\text{NO}_2^-$ ($[\text{M}-\text{H}]^-$) requires 234.1500; found 234.1499.

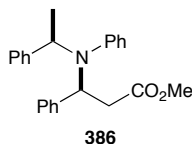
5.5 Experimental for Chapter 4

(*R*)-*N*-Phenyl-*N*-(α -methylbenzyl)amine **107**²¹



A flask containing CsF (2.44 g, 16.1 mmol) was flame dried and placed under an atmosphere of nitrogen. MeCN (60 mL), (*R*)- α -methylbenzylamine (1.28 mL, 10.0 mmol) and 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (2.18 mL, 8.98 mmol) were added to the flask and the reaction mixture was heated at 60 °C for 16 h. The mixture was allowed to cool to rt, brine (60 mL) was added, and the aqueous layer was extracted with Et₂O (3 $\times$ 60 mL). The combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 50:1; increased to 20:1) gave **107** as a white solid (1.05 g, 59%); mp 39-41 °C; {lit.²¹ mp 45.5-47 °C}; [α]_D²⁵ -5.1 (*c* 1.0 in CHCl₃); {lit.²² [α]_D²⁰ -4.9 (*c* 1.0 in CHCl₃)}; δ_{H} (400 MHz, CDCl₃) 1.53 (3H, d, *J* 6.7, C(α)Me), 4.05 (1H, br s, NH), 5.50 (1H, q, *J* 6.7, C(α)H), 6.51-6.54 (2H, m, *Ph*), 6.64-6.68 (1H, m, *Ph*), 7.08-7.13 (2H, m, *Ph*), 7.22-7.27 (1H, m, *Ph*), 7.31-7.40 (4H, m, *Ph*).

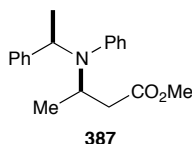
Methyl (3*S*, α *R*)-3-[*N*-phenyl-*N*-(α -methylbenzyl)amino]-3-phenyl propanoate **386**



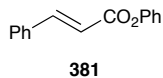
Following *General Procedure 6*, BuLi (2.50 M, 0.61 mL, 1.52 mmol), **107** (300 mg, 1.52 mmol), and **205** (154 mg, 0.95 mmol) in THF (9 mL) gave **386**. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 19:1; increased

to 4:1) gave **386** as a colourless oil (34 mg, 10%, >99:1 dr); $[\alpha]_{\text{D}}^{25}$ -34.5 (c 1.0 in CHCl_3); ν_{max} (film) 1737 (C=O); δ_{H} (400 MHz, CDCl_3) 1.42 (3H, d, J 6.7, C(α)Me), 2.82 (1H, dd, J 15.8, 8.3, C(2) H_{A}), 2.92 (1H, dd, J 15.8, 5.3, C(2) H_{B}), 3.54 (3H, s, OMe), 4.69 (1H, q, J 6.7, C(α)H), 5.24 (1H, dd, J 8.3, 5.3, C(3)H), 6.77 (2H, d, J 8.3, Ph), 6.87 (1H, t, J 7.3, Ph), 7.11 (2H, t, J 7.7, Ph), 7.18-7.22 (1H, m, Ph), 7.25-7.34 (9H, m, Ph); δ_{C} (100 MHz, CDCl_3) 18.0 (C(α)Me), 39.2 (C(2)), 51.8 (OMe), 57.1 (C(α)), 58.3 (C(3)), 121.3, 123.5, 126.9, 127.4, 127.6, 127.9, 128.3, 128.3, 128.4 (*o*-, *m*-, *p*-Ph), 141.5, 144.1, 145.9 (*i*-Ph), 172.5 (C(1));

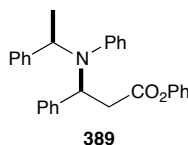
Methyl (*R,R*)-3-[*N*-phenyl-*N*-(α -methylbenzyl)amino]butanoate **387**



Following *General Procedure 6*, BuLi (2.50 M, 0.38 mL, 0.95 mmol), **107** (188 mg, 0.95 mmol), and **68** (48 mg, 0.48 mmol) in THF (5 mL) gave **387**. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 19:1; increased to 4:1) gave **387** as a colourless oil (53 mg, 28%, >99:1 dr); $[\alpha]_{\text{D}}^{25}$ -68.1 (c 1.0 in CHCl_3); ν_{max} (film) 2974 (C–H), 1736 (C=O); δ_{H} (400 MHz, CDCl_3) 1.22 (3H, d, J 6.8, C(4) H_3), 1.50 (3H, d, J 6.8, C(α)Me), 2.36 (1H, dd, J 15.0, 8.7, C(2) H_{A}), 2.66 (1H, dd, J 15.0, 5.1, C(2) H_{B}), 3.62 (3H, s, OMe), 4.10-4.19 (1H, m, C(3)H), 4.73 (1H, q, J 6.8, C(α)H), 6.87-6.93 (3H, m, Ph), 7.18-7.40 (7H, m, Ph); δ_{C} (100 MHz, CDCl_3) 19.0 (C(4)), 20.6 (C(α)Me), 40.3 (C(2)), 60.0 (C(3)), 52.0 (OMe), 56.7 (C(α)), 120.7, 122.3, 127.0, 127.4, 128.7, 128.8 (*o*-, *m*-, *p*-Ph), 144.9, 146.8 (*i*-Ph), 172.0 (C(1)); m/z (ESI⁺) 320 ([M+Na]⁺, 100%), 298 ([M+H]⁺, 54%); HRMS (ESI⁺) C₁₉H₂₄NO₂⁺ ([M+H]⁺) requires 298.1802; found 298.1799.

Phenyl cinnamate **381**²³

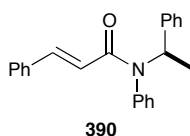
Et₃N (3.35 mL, 24.0 mmol) was added dropwise to a solution of cinnamoyl chloride (2.00 g, 12.0 mmol) and phenol (1.69 g, 18.0 mmol) in CH₂Cl₂ (20 mL) at 0 °C and the resultant mixture was stirred for 16 h at rt. H₂O (20 mL) was added, and the aqueous layer was extracted with CH₂Cl₂ (3 × 20 mL). The combined organic extracts were washed sequentially with 1 M aq. HCl (50 mL), 10% aq. NaOH (50 mL) and brine (50 mL), then dried and concentrated *in vacuo*. Recrystallisation (40-60 °C Petrol) gave **381** as a white solid (2.32 g, 86%); δ_H (400 MHz, CDCl₃) 6.65 (1H, d, *J* 16.0, C(2)*H*), 7.17-7.20 (2H, m, *Ph*), 7.24-7.29 (1H, m, *Ph*), 7.41-7.46 (5H, m, *Ph*), 7.60-7.62 (2H, m, *Ph*), 7.89 (1H, d, *J* 16.0, C(3)*H*).

Phenyl (3*S*,α*R*)-3-(*N*-(α-methylbenzyl)-*N*-phenyl)-3-phenyl propanoate **389**

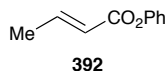
Following *General Procedure 6*, BuLi (2.50 M, 0.83 mL, 5.08 mmol), **107** (1.00 g, 5.08 mmol), and **381** (569 mg, 2.54 mmol) in THF (30 mL) gave a 75:20:5 mixture of **389:390:381**. Purification *via* flash column chromatography (gradient elution 30-40 °C petrol/Et₂O, 19:1; increased to 4:1) gave **389** as a colourless oil (560 mg, 53%, >99:1 dr); C₂₉H₂₇NO₂ requires C, 82.6; H, 6.5; N, 3.3%; found C, 82.7; H, 6.4; N, 3.3%; [α]_D²⁵ -37.2 (*c* 1.0 in CHCl₃); ν_{max} (ATR) 1755 (C=O); δ_H (400 MHz, CDCl₃) 1.51 (3H, d, *J* 6.7, C(α)*Me*), 3.10 (1H, dd, 15.5, 8.8, C(2)*H*_A), 3.23 (1H, dd, *J* 15.5, 5.4, C(2)*H*_B),

4.77 (1H, q, J 6.7, C(α)H), 5.39 (1H, dd, 8.8, 5.4, C(3)H), 6.87-6.93 (4H, m, *Ph*), 6.98-7.02 (1H, m, *Ph*), 7.19-7.47 (15H, m, *Ph*); δ_{C} (100 MHz, CDCl₃) 17.9 (C(α)Me), 39.5 (C(2)), 57.4 (C(α)), 58.9 (C(3)), 121.6, 122.2, 124.8, 125.9, 127.0, 127.7, 127.8, 128.3, 128.3, 128.5, 129.4 (*o*-, *m*-, *p*-*Ph*); 141.0, 145.8, 150.7 (*i*-*Ph*), 170.5 (C=O); m/z (ESI⁺) 444 ([M+Na]⁺, 62%), 422 ([M+H]⁺, 100%); HRMS (ESI⁺) C₂₉H₂₈NO₂ ([M+H]⁺) requires 422.2116; found 422.2096. Further elution gave **390** as a colourless oil (37 mg, 11%); $[\alpha]_{\text{D}}^{25}$ -14.7 (*c* 1.0 in CHCl₃); ν_{max} (ATR) 1652 (C=O), 1617 (C=C); δ_{H} (400 MHz, CDCl₃) 1.51 (3H, d, J 7.1, C(α)Me), 6.12 (1H, d, J 15.5, C(2)H), 6.45 (1H, q, J 7.1, C(α)H), 7.27-7.31 (12H, m, *Ph*), 7.32-7.37 (3H, m, *Ph*), 7.74 (1H, d, J 15.5, C(3)H); δ_{C} (100 MHz, CDCl₃) 17.3 (C(α)Me), 52.6 (C(α)), 119.6 (C(2)), 127.5, 127.9, 128.2, 128.2, 128.3, 128.7, 128.9, 129.5, 130.8 (*o*-, *m*-, *p*-*Ph*), 135.3, 138.2, 141.2 (*i*-*Ph*), 142.0 (C(3)), 165.8 (C(1)); m/z (ESI⁺) 677 ([2M+Na]⁺, 100%), 655 ([2M+H]⁺, 14%), 350 ([M+H]⁺, 13%); HRMS (ESI⁺) C₂₃H₂₂NO⁺ ([M+H]⁺) requires 328.1696; found 328.1691.

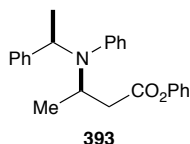
(*R*)-*N*-Phenyl-*N*-(α -methylbenzyl) cinnamide **390**



Cinnamoyl chloride **388** (85 mg, 0.51 mmol) was added to a solution of **107** (200 mg, 1.02 mmol) in CH₂Cl₂ (2 mL) at 0 °C and the resultant mixture was stirred for 16 h at rt. H₂O (2 mL) was added, the layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 × 2 mL). The combined organic extracts were washed with brine (5 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 2:1; increased to 1:1) gave **390** as a colourless oil (142 mg, 85%).

Phenyl crotonate **392²⁴**

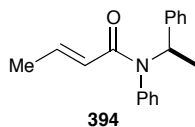
Et₃N (3.35 mL, 24.0 mmol) was added dropwise to a solution of crotonoyl chloride **391** (1.15 mL, 12.0 mmol) and phenol (1.69 g, 18.0 mmol) in CH₂Cl₂ (20 mL) at 0 °C and the resultant mixture was stirred for 16 h at rt. H₂O (20 mL) was added, and the aqueous layer was extracted with CH₂Cl₂ (3 × 20 mL). The combined organic extracts were washed sequentially with 1 M aq. HCl (50 mL), 10% aq. NaOH (50 mL) and brine (50 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 9:1; increased to 4:1) gave **392** as a colourless oil (1.63 g, 84%); δ_H (400 MHz, CDCl₃) 1.98 (3H, dd, *J* 6.9, 1.7, C(4)*H*₃), 6.06 (1H, dq, *J* 15.5, 1.7, C(2)*H*), 7.11-7.14 (2H, m, *Ph*), 7.16-7.27 (2H, m, C(3)*H*, *Ph*), 7.37-7.41 (2H, m, *Ph*).

Phenyl (*R,R*)-3-[*N*-phenyl-*N*-(α-methylbenzyl)amino]butanoate **393**

Following *General Procedure 6*, BuLi (2.24 M, 1.70 mL, 3.80 mmol), **107** (749 mg, 3.80 mmol), and **392** (308 mg, 1.90 mmol) in THF (9 mL) gave a 75:25 mixture of **393:394**. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 19:1; increased to 4:1) gave **393** as a colourless oil (250 mg, 37%, >99:1 dr); [α]_D²⁵ −85.5 (*c* 1.0 in CHCl₃); ν_{max} (film) 1755 (C=O); δ_H (400 MHz, CDCl₃) 1.37 (3H, d, *J* 6.8, C(4)*H*₃), 1.58 (3H, d, *J* 6.7, C(α)*Me*), 2.64 (1H, dd, *J* 15.2, 8.5, C(2)*H*_A),

2.94 (1H, J 15.2, 5.3, C(2) H_B), 4.27-4.35 (1H, m, C(3) H), 4.85 (1H, q, J 6.7, C(α) H), 6.97-7.01 (1H, m, Ph), 7.05-7.10 (4H, m, Ph), 7.26-7.32 (4H, m, Ph), 7.37-7.45 (4H, m, Ph), 7.49-7.51 (2H, m, Ph); δ_C (100 MHz, $CDCl_3$) 18.8 (C(4)), 20.5 (C(α) Me), 40.2 (C(2)), 50.7 (C(3)), 56.9 (C(α)), 121.0, 121.5, 122.7, 125.8, 126.8, 127.2, 128.5, 128.5, 129.4 (o -, m -, p - Ph), 144.6, 146.3, 150.7 (i - Ph), 170.7 (C(1)); m/z (ESI⁺) 382 ([M+Na]⁺, 100%), 360 ([M+H]⁺, 78%); HRMS (ESI⁺) C₂₄H₂₆NO₂⁺ ([M+H]⁺) requires 360.1958; found 360.1948. Further elution gave **394** as a colourless oil (38 mg, 8%); $[\alpha]_D^{25}$ +23.2 (c 1.0 in $CHCl_3$) ν_{max} (film) 2976 (C–H), 1664 (C=O), 1626 (C=C); δ_H (400 MHz, $CDCl_3$) 1.44 (3H, d, J 7.2, C(α) Me), 1.69 (3H, dd, J 7.1, 1.5, C(4) H_3), 5.49 (1H, dd, J 14.9, 1.5, C(2) H), 6.37 (1H, q, J 7.2, C(α) H), 6.96 (1H, dq, J 14.9, 7.1, C(3) H), 7.19-7.32 (10H, m, Ph); δ_C (100 MHz, $CDCl_3$) 17.2 (C(α) Me), 18.1 (C(4)), 52.2 (C(α)), 123.6 (C(2)), 127.5, 128.0, 128.1, 128.2, 128.8, 130.8 (o -, m -, p - Ph), 138.3 (i - Ph), 141.4 (C(3)), 141.5 (i - Ph), 165.8 (C(1)); m/z (ESI⁺) 288 ([M+Na]⁺, 100%), 266 ([M+H]⁺, 42%); HRMS (ESI⁺) C₁₈H₂₀NO⁺ ([M+H]⁺) requires 266.1539; found 266.1538.

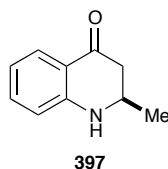
(*R*)-*N*-Phenyl-*N*-(α -methylbenzyl) crotonamide **394**



Crotonoyl chloride **391** (23 μ L, 0.24 mmol) was added dropwise to a solution of **107** (95 mg, 0.48 mmol) in CH_2Cl_2 (1 mL) at 0 °C and the resultant mixture was stirred for 16 h at rt. H_2O (1 mL) was added, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 $\times$ 1 mL). The combined organic extracts were washed with brine (3 mL), then dried and concentrated *in vacuo*. Purification *via*

flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 2:1; increased to 1:1) gave **394** as a colourless oil (53 mg, 83%).

(*R*)-2-Methyl-2,3-dihydroquinolin-4(1*H*)-one 397²⁵

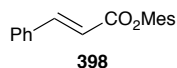


Method 1: NaOH (82 mg, 2.05 mmol) was added to a solution of **393** (183 mg, 0.51 mmol) in CH₂Cl₂/MeOH (6 mL/1.5mL) and stirred at rt for 2 h. The mixture was concentrated *in vacuo*, acidified to pH 1 with 1 M aq. HCl, and then extracted with CH₂Cl₂ (3 × 10 mL). The combined organic extracts were dried and concentrated *in vacuo*. PPA (2 mL) was added to the residue and this mixture was heated at 100 °C for 16 h. The mixture was allowed to cool to rt, basified to pH 14 with 10% aq. NaOH, and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine, dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 9:1; increased to 2:1) gave **397** as a pale yellow solid (34 mg, 42%); mp 49-51 °C; [α]_D²⁵ +174 (*c* 1.0 in C₆H₆); {lit.²⁵ [α]_D²⁰ +220 (*c* 1.0 in C₆H₆)}; δ _H (400 MHz, CDCl₃) 1.35 (3H, d, *J* 6.3, C(2)*Me*), 2.49 (1H, dd, *J* 16.1, 13.0, C(3)*H*_A), 2.65 (1H, dd, *J* 16.1, 3.7, C(3)*H*_B), 3.74-3.84 (1H, m, C(2)*H*), 6.67 (1H, dd, *J* 8.3, 0.7, C(8)*H*), 6.75 (1H, app td, *J* 7.7, 0.7, C(6)*H*), 7.29-7.33 (1H, m, C(7)*H*), 7.84 (1H, dd, *J* 7.7, 1.6, C(5)*H*).

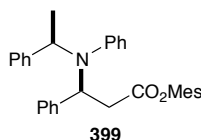
Method 2: LiOH (114 mg, 4.97 mmol) was added to a solution of **457** (387 mg, 0.99 mmol) in THF/H₂O (15 mL/15mL) and the resultant mixture was heated at 40 °C for 3 h. The mixture was allowed to cool to rt, acidified to pH 1 with 1 M aq. HCl,

and then extracted with EtOAc (3×20 mL). The combined organic extracts were dried and concentrated *in vacuo*. PPA (4 mL) was added to the residue and this mixture was heated at 100 °C for 16 h. The mixture was allowed to cool to rt, basified to pH 14 with 10% aq. NaOH, and the aqueous layer was extracted with EtOAc (3×35 mL). The combined organic extracts were washed with brine, dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 9:1; increased to 2:1) gave **397** as a pale yellow solid (70 mg, 44%); $[\alpha]_D^{25} +183$ (*c* 1.0 in CHCl₃).

Method 3: LiOH (218 mg, 9.10 mmol) was added to a stirred solution of **510** (350 mg, 1.81 mmol) in a mixture of THF (14 mL) and H₂O (14 mL). The resultant solution was stirred at 40 °C for 3 h, then allowed to cool and 1 M aq. HCl (10 mL) was added. The aqueous layer was extracted with CHCl₃:IPA 3:1 (3×20 mL), and the combined organic extracts were dried and concentrated *in vacuo* to afford the crude product as a white solid (110 mg). The crude product was dissolved in CH₂Cl₂ (3 mL), DMF (1 drop) and (COCl)₂ (64 µL, 0.78 mmol) were added and the mixture stirred at rt for 2 h. The solution was concentrated *in vacuo*, and the residue dissolved in CH₂Cl₂ (3 mL). The solution was cooled to 0 °C, and AlCl₃ (218 mg, 1.64 mmol) was added, then the reaction was stirred for 16 h at rt. Sat. aq. NaHCO₃ (4 mL) was added and the aqueous layer extracted with CH₂Cl₂ (3×4 mL). The combined organic extracts were washed with brine (10 mL), dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 9:1; increased to 2:1) gave **397** as a pale yellow solid (35 mg, 12%).

2,4,6-Trimethylphenyl cinnamate 398

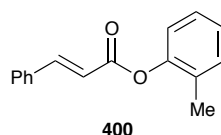
Following *General Procedure 7*, Et₃N (3.3 mL, 24.0 mmol), cinnamoyl chloride **388** (2.00 g, 12.0 mmol) and mesitol (2.45 g, 18.0 mmol) in CH₂Cl₂ (20 mL) gave **398**. Recrystallisation (40-60 °C petrol) gave **398** as white needles (1.90 g, 60%); C₁₈H₁₈O₂ requires C, 81.2; H, 6.8%; found C, 81.3; H, 6.95%; mp 82-84 °C; $\nu_{\max}$ (ATR) 2921 (C–H), 1724 (C=O), 1634 (C=C); δ_{H} (400 MHz, CDCl₃) 2.21 (6H, s, 2 × ArCH₃), 2.33 (3H, s, ArCH₃), 6.74 (1H, d, *J* 16.0, C(2)*H*), 6.95 (2H, s, *Ar*), 7.46-7.47 (3H, m, *Ph*), 7.63-7.66 (2H, m, *Ph*), 7.96 (1H, d, *J* 16.0, C(3)*H*); δ_{C} (100 MHz, CDCl₃) 16.3 (*ArMe*), 20.8 (2 × *ArMe*), 117.0 (*C*(2)), 128.3, 129.0, 129.3, 130.7 (*Ar*), 129.9, 134.2, 135.3, 146.0 (*i-Ar*), 146.4 (*C*(3)), 164.9 (*C*(1)); *m/z* (ESI⁺) 555 ([2M+Na]⁺, 100%), 289 ([M+Na]⁺, 54%); HRMS (ESI⁺) C₁₈H₁₈NaO₂⁺ ([M+Na]⁺) requires 289.1199; found 289.1194.

Mesityl (*R,R*)-3-(*N*-(α -methylbenzyl)-*N*-phenyl)-3-phenyl propanoate 399

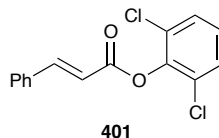
Following *General Procedure 6*, BuLi (2.50 M, 0.30 mL, 0.76 mmol), **107** (150 mg, 0.76 mmol), and **398** (101 mg, 0.38 mmol) in THF (4.5 mL) gave **399** in >99:1 dr. Purification *via* flash column chromatography (gradient elution 30-40 °C petrol/Et₂O, 39:1; increased to 4:1) gave a 62:38 mixture of **399:398** as a colourless oil (115 mg, 48%); $\nu_{\max}$ (ATR) 1731 (C=O); δ_{H} (400 MHz, CDCl₃) 1.42 (3H, d, *J* 6.7, C(α)*Me*), 1.79 (6H, s, 2 × *ArMe*), 2.18 (3H, s, *ArMe*), 3.10-3.22 (2H, m, C(2)*H*₂), 4.67 (1H, q, *J*

6.7, C(α)H), 5.30 (1H, dd, J 9.3, 4.9, C(3)H), 6.8 (2H, s, Ar), 6.82-6.85 (2H, m, Ph), 6.94-6.98 (1H, m, Ph), 7.13-7.40 (12H, m, Ph); δ_{C} (100 MHz, CDCl₃) 16.1 (ArMe), 17.9 (C(α)Me), 20.8 (2 $\times$ ArMe), 38.4 (C(2)), 57.5 (C(α)), 58.6 (C(3)), 122.3, 125.0, 127.0, 127.6, 127.7, 128.3, 128.4, 128.5, 129.2, 129.4 (Ar), 129.8, 135.3, 141.0, 144.2, 145.7, 145.8 (*i*-Ar), 169.9 (C(1)); m/z (ESI⁺) 486 ([M+Na]⁺, 40%), 464 ([M+H]⁺, 100%); HRMS (ESI⁺) C₃₂H₃₄NO₂⁺ ([M+H]⁺) requires 464.2584; found 464.2572.

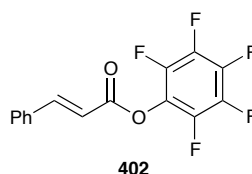
2'-Methylphenyl cinnamate **400**



Following *General Procedure 7*, Et₃N (3.3 mL, 24.0 mmol), cinnamoyl chloride **388** (2.00 g, 12.0 mmol) and *o*-cresol (1.95 g, 18.0 mmol) in CH₂Cl₂ (20 mL) gave **400**. Recrystallisation (40-60 °C petrol) gave **400** as white crystals (2.08 g, 73%); C₁₆H₁₄O₂ requires C, 80.65; H, 5.9%; found C, 80.8; H, 5.9%; mp 75-77 °C (40-60 °C petrol); ν_{max} (ATR) 1731 (C=O), 1634 (C=C); δ_{H} (400 MHz, CDCl₃) 2.28 (3H, s, C(2')Me), 6.72 (1H, d, J 16.0, C(2)H), 7.13-7.31 (4H, m, Ar), 7.45-7.47 (3H, m, Ph), 7.62-7.65 (2H, m, Ph), 7.94 (1H, d, J 16.0, C(3)H); δ_{C} (100 MHz, CDCl₃) 16.3 (ArMe), 117.2 (C(2)), 122.0, 126.1, 127.0, 128.4, 129.1, 130.8, 131.2 (Ar), 130.4 (C(2')), 134.3 (*i*-Ph), 146.6 (C(3)), 149.5 (C(1')), 165.2 (C(1)); m/z (ESI⁺) 499 ([2M+Na]⁺, 74%), 261 ([M+Na]⁺, 100%), 239 ([M+H]⁺, 3%); HRMS (ESI⁺) C₁₆H₁₄NaO₂⁺ ([M+Na]⁺) requires 261.0886; found 261.0881.

2',6'-Dichlorophenyl cinnamate 401

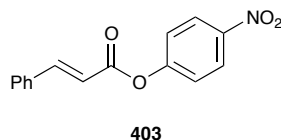
Following *General Procedure 7*, Et₃N (3.3 mL, 24.0 mmol), cinnamoyl chloride **388** (2.00 g, 12.0 mmol) and 2,6-dichlorophenol (2.93 g, 18.0 mmol) in CH₂Cl₂ (20 mL) gave **401** as a grey solid (3.07 g, 87%); mp 77-79 °C; $\nu_{\max}$ (ATR) 1727 (C=O), 1627 (C=C); δ_{H} (400 MHz, CDCl₃) 6.73 (1H, d, *J* 16.0, C(2)*H*), 7.17 (1H, t, *J* 8.2, C(4')), 7.40 (2H, d, *J* 8.2, C(3'), C(5')), 7.45-7.46 (3H, m, *Ph*), 7.62-7.64 (2H, m, *Ph*), 7.99 (2H, d, *J* 16.0, C(3)*H*); δ_{C} (100 MHz, CDCl₃) 115.7 (C(2)), 127.2, 128.6, 128.8, 129.1, 131.1 (*Ar*), 129.2 (C(2')), C(6')), 134.0 (*i-Ph*), 144.3 (C(1')), 148.2 (C(3)), 163.3 (C(1)); *m/z* (ESI⁺) 611 ([2M+Na]⁺, ³⁷Cl, ³⁷Cl, 54%), 609 ([2M+Na]⁺, ³⁷Cl, ³⁵Cl, 100%), 607 ([2M+Na], ³⁵Cl, ³⁵Cl, 77%), 319 ([M+Na]⁺, ³⁷Cl, ³⁷Cl, 5%), 317 ([M+Na]⁺, ³⁷Cl, ³⁵Cl, 24%), 315 ([M+Na]⁺, ³⁵Cl, ³⁵Cl, 34%); HRMS (ESI⁺) C₁₅H₁₀³⁷Cl₂NaO₂⁺ ([M+Na]⁺) requires 318.9892; found 318.9912; HRMS (ESI⁺) C₁₅H₁₀³⁷Cl³⁵ClNaO₂⁺ ([M+Na]⁺) requires 316.9921; found 316.9924; HRMS (ESI⁺) C₁₅H₁₀³⁵Cl₂NaO₂⁺ ([M+Na]⁺) requires 314.9950; found 314.9942.

Pentafluorophenyl cinnamate 402²⁶

Following *General Procedure 7*, Et₃N (3.3 mL, 24.0 mmol), cinnamoyl chloride **388**

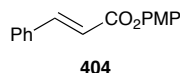
(2.00 g, 12.0 mmol) and pentafluorophenol (3.30 g, 18.0 mmol) in CH_2Cl_2 (20 mL) gave **402** as a colourless oil (2.87 g, 76%); δ_{H} (400 MHz, CDCl_3) 6.62 (1H, d, J 16.0, C(2) H), 7.43-7.50 (3H, m, Ph), 7.61-7.64 (2H, m, Ph), 7.97 (1H, d, J 16.0, C(3) H).

4'-Nitrophenyl cinnamate **403**



Following *General Procedure 7*, Et_3N (3.3 mL, 24.0 mmol), cinnamoyl chloride **388** (2.00 g, 12.0 mmol) and 4-nitrophenol (2.50 g, 18.0 mmol) in CH_2Cl_2 (20 mL) gave **403**. Trituration with Et_2O gave **403** as a pale yellow solid (2.87 g, 89%); mp 136-138 °C; ν_{max} (ATR) 1732 (C=O), 1632 (C=C); δ_{H} (400 MHz, CDCl_3) 6.64 (1H, dd, J 16.0, 1.4, C(2) H), 7.37-7.40 (2H, m, Ar), 7.44-7.48 (3H, m, Ph), 7.60-7.63 (2H, m, Ph), 7.93 (1H, d, J 16.0, C(3) H), 8.29-8.32 (2H, m, Ar); δ_{C} (100 MHz, CDCl_3) 116.3 (C(2)), 122.6 (C(2'), C(6')), 125.3 (C(3'), C(5')), 128.6, 129.2, 131.3 (o -, m -, p - Ph), 133.9 (i - Ph), 145.4 (C(4')), 148.2 (C(3)), 155.7 (C(1')), 164.5 (C(1)); m/z (ESI⁺) 561 ([2M+Na]⁺, 100%), 292 ([M+Na]⁺, 38%); HRMS (ESI⁺) $\text{C}_{15}\text{H}_{11}\text{NNaO}_4^+$ ([M+Na]⁺) requires 292.0580; found 292.0588.

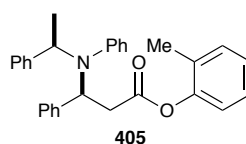
4'-Methoxyphenyl cinnamate **404**²⁷



Following *General Procedure 7*, Et_3N (3.3 mL, 24.0 mmol), cinnamoyl chloride **388** (2.00 g, 12.0 mmol) and 4-methoxyphenol (2.23 g, 18.0 mmol) in CH_2Cl_2 (20 mL) gave

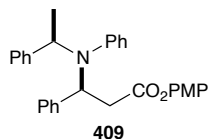
404. Purification *via* recrystallisation from 40-60 °C petrol gave **404** as a white solid (2.41 g, 79%); mp 93-95 °C; {lit.²⁷ mp 99-101 °C}; δ_{H} (400 MHz, CDCl_3) 3.83 (3H, s, *OMe*), 6.64 (1H, d, *J* 16.0, *C*(2)*H*), 6.92-6.95 (2H, m, *C*(3')*H*, *C*(5')*H*), 7.09-7.12 (1H, m, *C*(2')*H*, *C*(6')*H*), 7.43-7.45 (3H, m, *Ph*), 7.59-7.61 (2H, m, *Ph*), 7.87 (1H, d, *J* 16.0, *C*(3)*H*).

2'-Methylphenyl (3*S*, α *R*)-3-[*N*-phenyl-*N*-(α -methylbenzyl)amino]-3-phenylpropanoate **405**



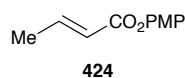
Following *General Procedure 6*, BuLi (2.50 M, 0.30 mL, 0.76 mmol), **107** (150 mg, 0.76 mmol), and **400** (91 mg, 0.38 mmol) in THF (4.5 mL) gave **405** in >99:1 dr. Purification *via* flash column chromatography (gradient elution 30-40 °C petrol/ Et_2O , 39:1; increased to 4:1) gave **405** as a colourless oil (99 mg, 60%, >99:1 dr); $[\alpha]_{\text{D}}^{25}$ -20.8 (*c* 1.0 in CHCl_3); ν_{max} (ATR) 1756 (C=O); δ_{H} (400 MHz, CDCl_3) 1.44 (3H, d, *J* 6.7, *C*(α)*Me*), 1.89 (3H, s, *ArMe*), 3.09 (1H, dd, *J* 15.6, 9.4, *C*(2)*H*_A), 3.19 (1H, dd, *J* 15.6, 4.9, *C*(2)*H*_B), 4.69 (1H, q, *J* 6.7, *C*(α)*H*), 5.31 (1H, dd, *J* 9.4, 4.9, *C*(3)*H*), 6.70 (1H, d, *J* 7.5, *Ar*), 6.84-6.86 (2H, m, *Ar*), 6.95-6.99 (1H, m, *Ar*), 7.09-7.18 (5H, m, *Ph*), 7.23-7.42 (10H, m, *Ph*); δ_{C} (100 MHz, CDCl_3) 16.0 (*ArMe*), 17.7 (*C*(α)*Me*), 39.0 (*C*(2)), 57.4 (*C*(α)), 58.9 (*C*(3)), 121.8, 122.4, 125.0, 126.0, 126.9, 127.0, 127.7, 127.8, 128.3, 128.4, 128.5 (*Ar*), 130.2 (*i-Ar*), 131.1 (*Ar*), 141.0, 144.1, 145.7, 149.3 (*i-Ar*), 170.2 (*C*(1)); *m/z* (ESI⁺) 458 ([*M*+*Na*]⁺, 48%), 436 ([*M*+*H*]⁺, 100%); HRMS (ESI⁺) $\text{C}_{30}\text{H}_{30}\text{NO}_2$ ([*M*+*H*]⁺) requires 436.2271; found 436.2253.

4'-Methoxyphenyl (3*S*, α *R*)-3-[*N*-phenyl-*N*-(α -methylbenzyl)amino]-3-phenylpropanoate **409**



Following *General Procedure 6*, BuLi (2.10 M, 0.76 mL, 1.60 mmol), **107** (314 mg, 1.60 mmol) and **404** (368 mg, 1.45 mmol) in THF (9 mL) gave **409** in >99:1 dr. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O 19:1, increased to 3:2) gave **409** as a colourless oil (540 mg, 83%, >99:1 dr); [α]_D²⁵ -26.9 (*c* 1.0 in CHCl₃); $\nu_{\max}$ (film) 1754 (C=O); δ_{H} (400 MHz, CDCl₃) 1.46 (3H, d, *J* 6.7, C(α)*Me*), 3.03 (1H, dd, 15.5, 8.8, C(2)*H*_A), 3.16 (1H, dd, *J* 15.5, 5.5, C(2)*H*_B), 3.79 (3H, s, OMe), 4.71 (1H, q, *J* 6.7, C(α)*H*), 5.33 (1H, dd, 8.8, 5.5, C(3)*H*), 6.73-6.75 (2H, m, C(3')*H*, C(5')*H*), 6.83-6.87 (4H, m, C(2')*H*, C(6')*H*), 6.94-6.97 (1H, m, *Ar*), 7.14-7.42 (12H, m, *Ar*); δ_{C} (100 MHz, CDCl₃) 17.7 (C(α)*Me*), 39.4 (C(2)), 55.6 (OMe), 57.2 (C(α)), 58.8 (C(3)), 114.4 (C(3'), C(5')), 122.0, 122.2, 124.6, 126.8, 127.6, 127.6, 128.1, 128.2, 128.4 (*Ar*), 140.9, 145.6 (*i-Ph*), 144.0 (C(1')), 157.2 (C(4')), 170.8 (C(1)); *m/z* (ESI⁺) 474 ([M+Na]⁺, 100%), 452 ([M+H]⁺, 90%); HRMS (ESI⁺) C₃₀H₃₀NO₃⁺ ([M+H]⁺) requires 452.2220; found 452.2212.

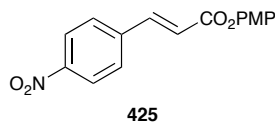
4'-Methoxyphenyl crotonate **424**



Et₃N (10.6 mL, 76.4 mmol) was added dropwise to a solution of crotonoyl chloride **391** (3.66 mL, 38.2 mmol) and 4-methoxyphenol (7.12 g, 57.4 mmol) in CH₂Cl₂ (40 mL) at 0 °C and the resultant mixture was stirred for 16 h at rt. H₂O (40 mL) was

added, and the aqueous layer was extracted with CH_2Cl_2 (3×40 mL). The combined organic extracts were washed sequentially with 1 M aq. HCl (100 mL), 10% aq. NaOH (100 mL) and brine (100 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/ Et_2O , 9:1; increased to 4:1) gave **424** as a colourless oil (6.53 g, 89%); ν_{max} (film) 2950 (C–H), 1738 (C=O), 1656 (C=C); δ_{H} (400 MHz, CDCl_3) 1.96 (3H, dd, J 6.9, 1.7, $\text{C}(4)\text{H}_3$), 3.78 (3H, s, OMe), 6.04 (1H, dq, J 15.5, 1.7, $\text{C}(2)\text{H}$), 6.88-6.92 (2H, m, $\text{C}(3')\text{H}$, $\text{C}(5')\text{H}$), 7.02-7.06 (2H, m, $\text{C}(2')\text{H}$, $\text{C}(6')\text{H}$), 7.18 (1H, dq, J 15.5, 6.9, $\text{C}(3)\text{H}$); δ_{C} (100 MHz, CDCl_3) 18.2 ($\text{C}(4)$), 55.6 (OMe), 114.5 ($\text{C}(3')$, $\text{C}(5')$), 122.2 ($\text{C}(2')$, $\text{C}(6')$), 122.4 ($\text{C}(2)$), 144.3 ($\text{C}(1')$), 146.8 ($\text{C}(3)$), 157.2 ($\text{C}(4')$), 165.3 ($\text{C}(1)$); m/z (ESI^+) 215 ($[\text{M}+\text{Na}]^+$, 100%), 193 ($[\text{M}+\text{H}]^+$, 12%); HRMS (ESI^+) $\text{C}_{11}\text{H}_{12}\text{NaO}_3^+$ ($[\text{M}+\text{Na}]^+$) requires 215.0679; found 215.0679.

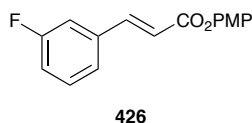
4''-Methoxyphenyl (*E*)-3-(4'-nitrophenyl)propenoate **425**



A few drops of DMF were added to a suspension of 4-nitrocinnamic acid **410** (5.00 g, 25.9 mmol) and thionyl chloride (5.66 mL, 77.8 mmol) in toluene (250 mL). The resultant solution was heated at reflux for 3 h, then allowed to cool to rt then concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (50 mL), cooled to 0 °C and 4-methoxyphenol (4.82 g, 38.9 mmol) was added. Et_3N (7.22 mL, 51.8 mmol) was then added dropwise and the resultant mixture was stirred for 16 h at rt. H_2O (50 mL) was added, and the aqueous layer was extracted with CH_2Cl_2 (3×50 mL). The combined organic extracts were washed sequentially with 1 M aq. HCl (120 mL), 10%

aq. NaOH (120 mL) and brine (120 mL), then dried and concentrated *in vacuo* to give **425** as a beige solid (7.22 g, 93%); mp 145-147 °C; $\nu_{\max}$ (KBr) 1725 (C=O), 1634 (C=C); δ_{H} (400 MHz, CDCl_3) 3.82 (3H, s, OMe), 6.75 (1H, d, J 16.0, C(2)*H*), 6.92-6.94 (2H, m, C(3'')*H*, C(5'')*H*), 7.09-7.11 (2H, m, C(2'')*H*, C(6'')*H*), 7.72-7.75 (2H, m, C(2')*H*, C(6')*H*), 7.88 (1H, d, J 16.0, C(3)*H*), 8.26-8.30 (2H, m, C(3')*H*, C(5')*H*); δ_{C} (100 MHz, CDCl_3) 55.7 (OMe), 114.6 (C(3''), C(5'')), 122.3 (C(2''), C(6'')), 124.4 (C(3'), C(5')), 129.0 (C(2'), C(6')), 121.8 (C(2)), 140.3 (C(1')), 143.4 (C(3)), 144.1 (C(1'')), 148.8 (C(4')), 157.5 (C(4'')), 165.0 (C(1)); m/z (ESI⁺) 322 ([M+Na]⁺, 100%); HRMS (ESI⁺) $\text{C}_{16}\text{H}_{13}\text{NNaO}_5^+$ ([M+Na]⁺) requires 322.0686; found 322.0681.

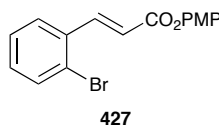
4''-Methoxyphenyl (*E*)-3-(3'-fluorophenyl)propenoate **426**



Thionyl chloride (0.96 mL, 13.2 mmol) was added to a suspension of 3-fluorocinnamic acid **411** (1.35 g, 8.81 mmol) in CHCl_3 (30 mL). The resultant solution was heated at reflux for 1 h, then allowed to cool to rt then concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (30 mL), cooled to 0 °C and 4-methoxyphenol (1.64 g, 13.21 mmol) was added. Et_3N (2.46 mL, 17.6 mmol) was then added dropwise and the resultant mixture was stirred for 16 h at rt. H_2O (30 mL) was added, the layers separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed sequentially with 1 M aq. HCl (80 mL), 10% aq. NaOH (80 mL) and brine (80 mL), then dried and concentrated *in vacuo* to give **426** as a white solid (2.05 g, 86%); mp 76-78 °C; $\nu_{\max}$ (KBr) 1726 (C=O), 1640 (C=C), 1248 (C-F); δ_{H} (400 MHz, CDCl_3) 3.82 (3H, s, OMe), 6.62 (1H, d, J 16.0, C(2)*H*), 6.92-6.95 (1H, m,

$C(3'')H$, $C(5'')H$), 7.09-7.13 (3H, m, *Ar*), 7.27-7.30 (1H, m, *Ar*), 7.35-7.43 (2H, m, *Ar*), 7.82 (1H, d, J 16.0, $C(3)H$); δ_C (100 MHz, $CDCl_3$) 55.7 (*OMe*), 114.6 (d, J 22.4, $C(2')$), 114.6 ($C(3'')$, $C(5'')$), 117.6 (d, J 22.2, $C(4')$), 118.9 ($C(2)$), 122.4 ($C(2'')$, $C(6'')$), 124.4 (d, J 3.2, $C(6')$), 130.7 (d, J 8.1, $C(5')$), 136.5 (d, J 8.0, $C(1')$), 144.3 ($C(1'')$), 145.0 (d, J 3.0, $C(3)$), 157.4 ($C(4'')$), 163.3 (d, J 247.7, $C(3')$), 165.5 ($C(1)$); m/z (ESI^+) 567 ($[2M+Na]^+$, 100%), 295 ($[M+Na]^+$, 97%), 273 ($[M+H]^+$, 35%); HRMS (ESI^+) $C_{16}H_{13}FNaO_3^+$ ($[M+Na]^+$) requires 295.0741; found 295.0737.

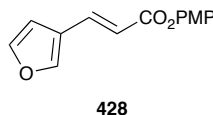
4''-Methoxyphenyl (*E*)-3-(2'-bromophenyl)propenoate **427**



Thionyl chloride (0.96 mL, 13.2 mmol) was added to a suspension of 2-bromocinnamic acid **412** (2.00 g, 8.81 mmol) in $CHCl_3$ (30 mL). The resultant solution was heated at reflux for 1 h, then allowed to cool to rt then concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (30 mL), cooled to 0 °C and 4-methoxyphenol (1.64 g, 13.2 mmol) was added. Et_3N (2.46 mL, 17.6 mmol) was then added dropwise and the resultant mixture was stirred for 16 h at rt. H_2O (30 mL) was added, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3×30 mL). The combined organic extracts were washed sequentially with 1 M aq. HCl (80 mL), 10% aq. NaOH (80 mL) and brine (80 mL), then dried and concentrated *in vacuo* to give **427** as a white solid (2.83 g, 96%); mp 75-77 °C; ν_{max} (KBr) 2952 (C–H), 1730 (C=O), 1634 (C=C); δ_H (400 MHz, $CDCl_3$) 3.82 (3H, s, *OMe*), 6.58 (1H, d, J 15.9, $C(2)H$), 6.93 (2H, d, J 8.9, $C(3'')H$, $C(5'')H$), 7.12 (2H, d, J 8.9, $C(2'')H$, $C(6'')H$), 7.26 (1H, td, J 7.7, 1.6, *Ar*), 7.34-7.38 (1H, m, *Ar*), 7.63-7.69 (2H, m, *Ar*), 8.24 (1H, d, J 15.9, $C(3)H$); δ_C (100 MHz,

CDCl₃) 55.7 (*OMe*), 114.5 (*C*(3''), *C*(5'')), 120.3 (*C*(2)), 122.4 (*C*(2''), *C*(6'')), 125.6 (*C*(2')), 127.9, 128.0, 131.6, 133.6 (*C*(3'), *C*(4'), *C*(5'), *C*(6')), 134.3 (*C*(1')), 144.3 (*C*(1'')), 144.7 (*C*(3)), 157.3 (*C*(4'')), 165.2 (*C*(1)); *m/z* (ESI⁺) 691 ([2M+Na]⁺, ⁸¹Br/⁸¹Br, 65%), 689 ([2M+Na]⁺, ⁸¹Br/⁷⁹Br, 100%), 687 ([2M+Na]⁺, ⁷⁹Br/⁷⁹Br, 76%), 357 ([M+Na]⁺, ⁸¹Br, 39%), 355 ([M+Na]⁺, ⁷⁹Br, 41%), 335 ([M+H]⁺, ⁸¹Br, 9%), 333 ([M+H]⁺, ⁷⁹Br, 9%); HRMS (ESI⁺) C₁₆H₁₃⁸¹BrNaO₃⁺ ([M+Na]⁺) requires 356.9920; found 356.9915; C₁₆H₁₃⁷⁹BrNaO₃⁺ ([M+Na]⁺) requires 354.9940; found 354.9933.

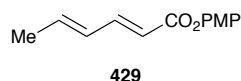
4''-Methoxyphenyl (*E*)-3-(3'-furyl)propenoate **428**



Thionyl chloride (0.79 mL, 10.9 mmol) was added to a suspension of (*E*)-3-(3'-furyl)propenoic acid **420** (1.00 g, 7.24 mmol) in CH₂Cl₂ (10 mL). The resultant solution was heated at reflux for 1 h, then allowed to cool to rt then concentrated *in vacuo*. The residue was dissolved in CH₂Cl₂ (10 mL), cooled to 0 °C and 4-methoxyphenol (1.36 g, 10.9 mmol) was added. Et₃N (2.02 mL, 14.5 mmol) was then added dropwise and the resultant mixture was stirred for 16 h at rt. H₂O (10 mL) was added, and the aqueous layer was extracted with CH₂Cl₂ (3 × 10 mL). The combined organic extracts were washed sequentially with 1 M aq. HCl (25 mL), 10% aq. NaOH (25 mL) and brine (25 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 9:1; increased to 4:1) gave **428** as a white solid (1.60 g, 91%); mp 67-69 °C; ν_{max} (KBr) 1723 (C=O), 1645 (C=C); δ_{H} (400 MHz, CDCl₃) 3.81 (3H, s, *OMe*), 6.35 (1H, app br s, *C*(2)*H*), 6.66 (1H, dd, *J* 1.8, 0.5, *C*(4')*H*), 6.92 (2H, d, *J* 9.0, *C*(3'')*H*, *C*(5'')*H*), 7.08

(2H, d, J 9.0, $C(2'')H$, $C(6'')H$), 7.47 (1H, dd, J 1.8, 1.1, $C(5')H$), 7.71 (1H, br s, $C(2')H$), 7.76 (1H, d, J 15.8, $C(3)H$); δ_c (100 MHz, $CDCl_3$) 55.7 (OMe), 107.5 ($C(4')$), 114.6 ($C(3'')$, $C(5'')$), 117.2 ($C(2)$), 122.5 ($C(2'')$, $C(6'')$), 122.7 ($C(3')$), 136.5 ($C(3)$), 144.3 ($C(1'')$), 144.7 ($C(5')$), 145.1 ($C(2')$), 157.3 ($C(4'')$), 165.9 ($C(1)$); m/z (ESI^+) 267 ($[M+Na]^+$, 100%), 245 ($[M+H]^+$, 20%); HRMS (ESI^+) $C_{14}H_{12}NaO_4^+$ ($[M+Na]^+$) requires 267.0628; found 267.0631.

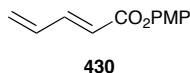
4-Methoxyphenyl sorbate **429**



Thionyl chloride (1.95 mL, 26.6 mmol) was added to a suspension of sorbic acid **414** (2.00 g, 17.8 mmol) in CH_2Cl_2 (24 mL). The resulting solution was heated at reflux for 1 h, then cooled to rt and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (24 mL), cooled to 0 °C and 4-methoxyphenol (3.30 g, 26.6 mmol) was added. Et_3N (4.96 mL, 35.6 mmol) was then added dropwise and the resultant mixture was stirred for 16 h at rt. H_2O (20 mL) was added, the layers separated, and the aqueous layer was extracted with CH_2Cl_2 (3 $\times$ 20 mL). The combined organic extracts were washed sequentially with 1.0 M aq. HCl (60 mL), 10% aq. NaOH (60 mL) and brine (60 mL), then dried and concentrated *in vacuo*. Recrystallisation (40-60 °C petrol) gave **429** as a white solid (3.22 g, 74%); 52-54 °C; ν_{max} (ATR) 1726 (C=O), 1639 (C=C); δ_H (400 MHz, $CDCl_3$) 1.90 (3H, d, J 5.4, $C(6)H_3$), 3.80 (3H, s, OMe), 5.96 (1H, dd, J 15.3, 0.5, $C(2)H$), 6.19-6.32 (2H, m, $C(4)H$, $C(5)H$), 6.88-6.92 (2H, m, $C(3')H$, $C(5')H$), 7.03-7.07 (2H, m, $C(2')H$, $C(6')H$), 7.40-7.47 (1H, m, $C(3)H$); δ_c (100 MHz, $CDCl_3$) 18.6 ($C(6)$), 55.7 (OMe), 114.5 ($C(3')$, $C(5')$), 118.2 ($C(2)$), 122.5 ($C(2')$, $C(6')$), 129.9, 140.6 ($C(4)$,

$C(5)$), 144.4 ($C(1')$), 146.8 ($C(3)$), 157.2 ($C(4')$), 166.1 ($C(1)$); m/z (ESI^+) 241 ($[M+Na]^+$, 100%), 218 ($[M+H]^+$, 10%); HRMS (ESI^+) $C_{13}H_{14}NaO_3^+$ ($[M+Na]^+$) requires 241.0835; found 241.0837.

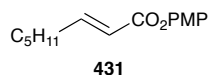
4'-Methoxyphenyl (*E*)-penta-2,4-dienoate **430**



Malonic acid (10.2 g, 98.4 mmol) was added portionwise to pyridine (10.4 mL, 127.9 mmol) and stirred for 30 min at rt. Acrolein (7.4 mL, 110.7 mmol) was added dropwise over 30 mins and the resulting solution was stirred for a further 1 h at rt then poured onto ice. Conc. H_2SO_4 (7 mL) was added and the aqueous layer extracted with CH_2Cl_2 (3×15 mL). The combined organic extracts were dried and concentrated *in vacuo* to give the acid. The acid (1.51 g, 15.4 mmol) was dissolved in CH_2Cl_2 (15 mL) and thionyl chloride (1.69 mL, 23.1 mmol) was added. The resulting solution was heated at reflux for 1 h, then cooled to rt and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (15 mL), cooled to 0 °C and 4-methoxyphenol (2.87 g, 23.1 mmol) was added. Et_3N (4.29 mL, 30.8 mmol) was then added dropwise and the resultant mixture was stirred for 16 h at rt. H_2O (15 mL) was added, the layers separated, and the aqueous layer was extracted with CH_2Cl_2 (3×15 mL). The combined organic extracts were washed sequentially with 1.0 M aq. HCl (45 mL), 10% aq. NaOH (45 mL) and brine (45 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution 30-40 °C petrol/ Et_2O , 49:1; increased to 19:1) gave **430** as a white solid (1.69 g, 8%); mp 46-48 °C; ν_{max} (ATR) 1725 (C=O), 1640 (C=C); δ_H (400 MHz, $CDCl_3$) 3.81 (3H, s, *OMe*), 5.58 (1H, d, J 10.0, $C(5)H_A$),

5.70 (1H, d, J 16.9, C(5) H_B), 6.11 (1H, d, J 15.4, C(2) H), 6.50-6.59 (1H, m, C(4) H), 6.89-6.93 (2H, m, Ar), 7.04-7.07 (2H, m, Ar), 7.42-7.48 (1H, m, C(3) H); δ_C (100 MHz, $CDCl_3$) 55.7 (OMe), 114.6 ($C(3')$, $C(5')$), 121.5 ($C(2)$), 122.4 ($C(2')$, $C(6')$), 126.7 ($C(5)$), 134.8 ($C(4)$), 144.3 ($C(1')$), 146.5 ($C(3)$), 157.3 ($C(4')$), 165.7 ($C(1)$); m/z (ESI^+) 227 ($[M+Na]^+$, 100%), 205 ($[M+H]^+$, 37%); HRMS (ESI^+) $C_{12}H_{13}O_3^+$ ($[M+H]^+$) requires 205.0859; found 205.0860.

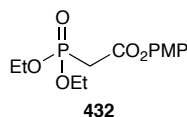
4'-Methoxyphenyl (*E*)-oct-2-enoate **431**



Thionyl chloride (3.83 mL, 52.7 mmol), was added to (*E*)-oct-2-enoic acid **416** (5.30 mL, 35.2 mmol). The resultant solution was heated at reflux for 1 h, then allowed to cool to rt then concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (80 mL), cooled to 0 °C and 4-methoxyphenol (6.54 g, 52.7 mmol) was added. Et_3N (9.81 mL, 70.4 mmol) was then added dropwise and the resultant mixture was stirred for 16 h at rt. H_2O (80 mL) was added, and the aqueous layer was extracted with CH_2Cl_2 (3 $\times$ 80 mL). The combined organic extracts were washed sequentially with 1 M aq. HCl (200 mL), 10% aq. NaOH (200 mL) and brine (200 mL), then dried and concentrated *in vacuo* to give **431** as a colourless oil (8.30 g, 95%); ν_{max} (film) 2931 (C–H), 1738 (C=O), 1652 (C=C); δ_H (400 MHz, $CDCl_3$) 0.93 (3H, t, J 7.0, C(8) H_3), 1.33-1.37 (4H, m, CH_2), 1.49-1.56 (2H, m, CH_2), 2.25-2.31 (2H, m, C(4) H_2), 3.81 (3H, s, OMe), 6.01 (1H, dt, J 15.6, 1.5, C(2) H), 6.90 (2H, d, J 9.0, C(3') H , C(5') H), 7.04 (2H, d, J 9.0, C(2') H , C(6') H), 7.18 (1H, dt, J 15.6, 7.0, C(3) H); δ_C (100 MHz, $CDCl_3$) 14.1 ($C(8)$), 22.6, 27.8, 31.5 ($C(5)$, $C(6)$, $C(7)$), 32.5 ($C(4)$), 55.7 (OMe), 114.5 ($C(3')$, $C(5')$), 120.6 ($C(2)$), 122.5 ($C(2')$, $C(6')$), 144.4 ($C(1')$), 151.8 ($C(3)$), 157.2 ($C(4')$), 165.6 ($C(1)$);

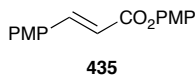
m/z (ESI⁺) 271 ([M+Na]⁺, 100%), 249 ([M+H]⁺, 26%); HRMS (ESI⁺) C₁₅H₂₀NaO₃⁺ ([M+Na]⁺) requires 271.1305; found 271.1305.

4'-Methoxyphenyl diethylphosphonoacetate **432**²⁸



4-Methoxyphenyl acetylchloride (16.0 g, 79.6 mmol) and P(OEt)₃ (15.0 mL, 87.5 mmol) were heated at 100 °C for 20 hours. Concentration *in vacuo* gave **432** as a pale yellow oil (20.4 g, quant); δ_H (400 MHz, CDCl₃) 1.38 (6H, t, *J* 7.1, MeCH₂), 3.18 (2H, d, *J* 21.7, C(2)H₂), 3.80 (3H, s, OMe), 4.20-4.27 (4H, m, MeCH₂), 6.88-6.90 (2H, m, C(3')H, C(5')H), 7.02-7.05 (2H, m, C(2')H, C(6')H).

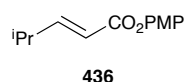
4''-Methoxyphenyl (*E*)-3-(4'-methoxyphenyl)propenoate **435**



Following *General Procedure 8*, NaH (60% dispersion in mineral oil, 160 mg, 4.00 mmol) was reacted with 4'-methoxyphenyl diethylphosphonoacetate **432** (1.22 g, 4.00 mmol) and *p*-anisaldehyde **433** (0.45 mL, 3.7 mmol) in THF (19 mL). Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 9:1; increased to 4:1) gave **435** as a white solid (534 mg, 52%); mp 104-106 °C; ν_{max} (KBr) 1715 (C=O); δ_H (400 MHz, CDCl₃) 3.82 (3H, s, OMe), 3.86 (3H, s, OMe), 6.50 (1H, d, *J* 15.9, C(2)H), 6.92-6.96 (4H, m, *Ar*), 7.10 (2H, d, *J* 9.0, *Ar*), 7.54 (2H, d, *J* 9.0, *Ar*), 7.83 (1H, d, *J* 15.9, C(3)H); δ_C (100 MHz, CDCl₃) 55.5 (OMe), 55.7 (OMe), 114.5

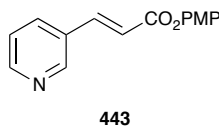
($C(2)$), 114.8 ($C(3')$, $C(5')$, $C(3'')$, $C(5'')$), 122.5 ($C(2'')$, $C(6'')$), 130.1 ($C(2')$, $C(6')$), 127.1 ($C(1')$), 144.5 ($C(1'')$), 146.2 ($C(3)$), 157.3 ($C(4'')$), 161.8 ($C(4')$), 166.2 ($C(1)$); m/z (ESI⁺) 307 ([M+Na]⁺, 100%); HRMS (ESI⁺) $C_{17}H_{16}NaO_4^+$ ([M+Na]⁺) requires 307.0941; found 307.0958.

4'-Methoxyphenyl (*E*)-4-methylpent-2-enoate **436**²⁹



Following *General Procedure 8*, NaH (60% dispersion in mineral oil, 31 mg, 0.77 mmol) was reacted with 4'-methoxyphenyl diethylphosphonoacetate **432** (231 mg, 0.77 mmol) and isobutyraldehyde **434** (0.06 mL, 0.70 mmol) in THF (4 mL). Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 19:1; increased to 4:1) gave **436** as a colourless oil (119 mg, 77%); δ_H (400 MHz, CDCl₃) 1.13 (6H, d, J 6.8, $C(4)Me_2$), 2.50-2.59 (1H, m, $C(4)H$), 3.81 (3H, s, OMe), 5.97 (1H, dd, J 15.7, 1.50, $C(2)H$), 6.89-6.92 (2H, m, $C(3')H$, $C(5')H$), 7.03-7.05 (2H, m, $C(2')H$, $C(6')H$), 7.15 (1H, dd, J 15.7, 6.6, $C(3)H$).

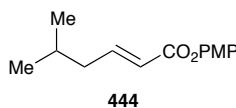
4''-Methoxyphenyl (*E*)-3-(3'-pyridyl)propenoate **443**



Following *General Procedure 8*, NaH (60% dispersion in mineral oil, 154 mg, 3.85 mmol) was reacted with 4'-methoxyphenyl diethylphosphonoacetate **432** (1.10 g, 3.85 mmol) and 3-pyridinecarboxaldehyde **438** (0.33 mL, 3.50 mmol) in THF (19 mL). Purification *via* flash column chromatography (gradient elution, 30-40 °C

petrol/EtOAc, 9:1; increased to neat EtOAc) gave **443** as a colourless oil (667 mg, 75%); $\nu_{\max}$ (film) 2954 (C–H), 1730 (C=O), 1640 (C=C), 1587 (C=N); δ_{H} (400 MHz, CDCl_3) 3.77 (3H, s, OMe), 6.67 (1H, d, J 16.1, C(2) H), 6.89 (2H, d, J 8.9, C(3'') H , C(5'') H), 7.07 (2H, d, J 8.9, C(2'') H , C(6'') H), 7.32 (1H, dd, J 7.8, 4.8, C(4') H), 7.81 (1H, d, J 16.1, C(3) H), 7.84–7.87 (1H, m, C(5') H), 8.61 (1H, dd, J 4.8, 1.8, C(6') H), 8.77 (1H, d, J 1.8, C(2') H); δ_{C} (100 MHz, CDCl_3) 55.6 (OMe), 114.6 (C(3''), C(5'')), 119.6 (C(2)), 122.3 (C(2''), C(6'')), 123.9 (C(4')), 130.0 (C(3')), 134.4 (C(5')), 142.7 (C(3)), 144.1 (C(1'')), 150.0 (C(2')), 151.4 (C(6')), 157.4 (C(4'')), 165.1 (C(1)); m/z (ESI⁺) 278 ([M+Na]⁺, 100%), 256 ([M+H]⁺, 64%); HRMS (ESI⁺) $\text{C}_{15}\text{H}_{14}\text{NO}_3^+$ ([M+H]⁺) requires 256.0968; found 256.0973.

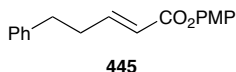
4'-Methoxyphenyl (*E*)-5-methylhex-2-enoate **444**



Following *General Procedure 8*, NaH (60% dispersion in mineral oil, 193 mg, 4.39 mmol) was reacted with 4-methoxyphenyl diethylphosphonoacetate **432** (1.33 g, 4.39 mmol) and isovaleraldehyde **439** (0.43 mL, 3.99 mmol), in THF (21 mL). Purification *via* flash column chromatography (gradient elution, 30–40 °C petrol/Et₂O, 9:1; increased to 4:1) gave **444** as a colourless oil (674 mg, 72%); $\nu_{\max}$ (film) 2958 (C–H), 1738 (C=O), 1652 (C=C); δ_{H} (400 MHz, CDCl_3) 0.98 (6H, d, J 6.7, C(5) Me_2), 1.76–1.88 (1H, m, C(5) H), 2.18 (2H, td, J 7.3, 1.3, C(4) H_2), 3.81 (3H, s, OMe), 6.01 (1H, dt, J 15.5, 1.3, C(2) H), 6.88–6.92 (2H, m, C(3') H , C(5') H), 7.03–7.07 (2H, m, C(2') H , C(6') H), 7.15 (1H, dt, J 15.5, 7.3, C(3) H); δ_{C} (100 MHz, CDCl_3) 22.5 (C(5) Me_2), 27.9 (C(5)), 41.8 (C(4)), 55.7 (OMe), 114.5 (C(3'), C(5')), 121.7 (C(2)), 122.5 (C(2')),

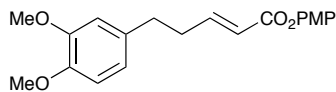
$C(6')$), 144.3 ($C(1')$), 150.6 ($C(3)$), 157.2 ($C(4')$), 165.4 ($C(1)$); m/z (ESI^+) 257 ($[\text{M}+\text{Na}]^+$, 100%), 235 ($[\text{M}+\text{H}]^+$, 27%); HRMS (ESI^+) $\text{C}_{14}\text{H}_{18}\text{NaO}_3^+$ ($[\text{M}+\text{Na}]^+$) requires 257.1148; found 257.1146.

4'-Methoxyphenyl (*E*)-5-phenylpent-2-enoate **445**



Following *General Procedure 8*, NaH (60% dispersion in mineral oil, 164 mg, 4.10 mmol) was reacted with 4-methoxyphenyl diethylphosphonoacetate **432** (1.24 g, 4.10 mmol) and hydrocinnamaldehyde **440** (0.49 mL, 3.72 mmol), in THF (19 mL). Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 9:1; increased to 4:1) gave **445** as a white solid (795 mg, 72%); mp 54-56 °C; ν_{max} (KBr) 2938 (C-H), 1735 (C=O), 1645 (C=C); δ_{H} (400 MHz, CDCl_3) 2.60-2.66 (2H, m, $C(4)H_2$), 2.86 (2H, t, J 7.8, $C(5)H_2$), 3.82 (3H, s, OMe), 6.04-6.09 (1H, m, $C(2)H$), 6.92 (2H, d, J 8.9, $C(3')H$, $C(5')H$), 7.06 (2H, d, J 8.9, $C(2')H$, $C(6')H$), 7.19-7.27 (4H, m, Ph), 7.32-7.36 (2H, m, Ph , $C(3)H$); δ_{C} (100 MHz, CDCl_3) 34.2 ($C(4)$), 34.4 ($C(5)$), 55.7 (OMe), 114.5 ($C(3')$, $C(5')$), 122.5 ($C(2')$, $C(6')$), 121.3 ($C(2)$), 126.4, 128.4, 128.7 (σ -, m -, p - Ph), 140.7 (i - Ph), 144.3 ($C(1')$), 150.3 ($C(3)$), 157.3 ($C(4')$), 165.4 ($C(1)$); m/z (ESI^+) 587 ($[2\text{M}+\text{Na}]^+$, 100%), 305 ($[\text{M}+\text{Na}]^+$, 98%), 283 ($[\text{M}+\text{H}]^+$, 45%); HRMS (ESI^+) $\text{C}_{18}\text{H}_{18}\text{NaO}_3^+$ ($[\text{M}+\text{Na}]^+$) requires 305.1148; found 305.1150.

4''-Methoxyphenyl (*E*)-5-(3',4'-dimethoxyphenyl)pent-2-enoate
446

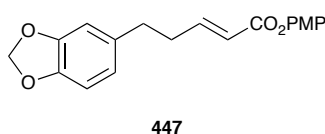


446

LiAlH₄ (308 mg, 7.98 mmol) was added to a suspension of 3-(3',4'-dimethoxyphenyl)propanoic acid (798 mg, 3.80 mmol) in Et₂O (25 mL) at 0 °C and stirred for 16 h at rt. The resulting solution was cooled to 0 °C and H₂O (1 mL) was slowly added and the mixture then stirred for 15 min. The suspension was filtered and the filtrate concentrated *in vacuo* to give the crude product (700 mg). The crude product was dissolved in DMSO (8 mL), IBX (1.17 g, 4.18 mmol) was added and the suspension was stirred for 16 h at rt. The resultant solution was partitioned between Et₂O (15 mL) and H₂O (15 mL) and the aqueous layer extracted with Et₂O (3 × 15 mL). The combined organic extracts were washed with H₂O (2 × 40 mL) and brine (40 mL), then dried and concentrated *in vacuo* to give the crude aldehyde. Then following *General Procedure 8*, NaH (60% dispersion in mineral oil, 104 mg, 2.60 mmol) was reacted with 4'-methoxyphenyl dimethylphosphonoacetate **432** (785 g, 2.60 mmol) and the crude aldehyde (429 mg, 2.36 mmol) in THF (12 mL). Purification *via* flash column chromatography (gradient elution 30-40 °C petrol/Et₂O, 9:1; increased to 2:1) gave **446** as a white solid (962 mg, 74%); mp 65-67 °C; $\nu_{\max}$ (ATR) 1728 (C=O), 1650 (C=C); δ_{H} (400 MHz, CDCl₃) 2.59 (2H, dt, *J* 8.0, 6.9, C(4)*H*₂), 2.79 (2H, t, *J* 8.0, C(5)*H*₂), 3.80 (3H, s, *OMe*), 3.87 (3H, s, *OMe*), 3.89 (3H, s, *OMe*), 6.04 (1H, dt, *J* 15.6, 1.4, C(2)*H*), 6.73-6.77 (2H, m, *Ar*), 6.82 (1H, d, *J* 8.1, *Ar*), 6.89-6.92 (2H, m, C(3')*H*, C(5')*H*), 7.01-7.05 (2H, m, C(2')*H*, C(6')*H*), 7.20 (1H, dt, *J* 15.6, 6.9, C(3)*H*); δ_{C} (100 MHz, CDCl₃) 34.0 (C(5)), 34.4 (C(4)), 55.7, 55.9, 56.0 (3 ×

OMe), 111.4, 111.8 ($C(2')$, $C(5')$), 114.5 ($C(3'')$, $C(5'')$), 120.3 ($C(6')$), 121.2 ($C(2)$), 122.4 ($C(2'')$, $C(6'')$), 133.3 ($C(1')$), 144.3 ($C(1'')$), 147.6, 149.0 ($C(3')$, $C(4')$), 150.4 ($C(3)$), 157.3 ($C(4'')$), 165.3 ($C(1)$); m/z (ESI⁺) 707 ([2M+Na]⁺, 76%), 365 ([M+Na]⁺, 100%), 343 ([M+H]⁺, 7%); HRMS (ESI⁺) $C_{20}H_{22}NaO_5^+$ ([M+Na]⁺) requires 365.1359; found 365.1357.

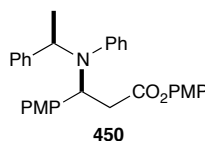
4''-Methoxyphenyl (*E*)-5-(3',4'-methylenedioxyphenyl)pent-2-enoate **447**



LiAlH₄ (902 mg, 23.7 mmol) was added to a suspension of 3-(3',4'-methylenedioxyphenyl)propanoic acid (2.19 g, 11.3 mmol) in Et₂O (100 mL) at 0 °C and stirred for 16 h at rt. The resulting solution was cooled to 0 °C and H₂O (4 mL) was slowly added and the mixture then stirred for 15 min. The suspension was filtered and the filtrate concentrated *in vacuo* to give the crude product (2.04 g). The crude product was dissolved in DMSO (25 mL), IBX (3.49 g, 12.5 mmol) was added and the suspension was stirred for 16 h at rt. The resultant solution was partitioned between Et₂O (40 mL) and H₂O (40 mL) and the aqueous layer extracted with Et₂O (3 × 40 mL). The combined organic extracts were washed with H₂O (2 × 100 mL) and brine (100 mL), then dried and concentrated *in vacuo* to give the crude aldehyde. Then following *General Procedure 8*, NaH (60% dispersion in mineral oil, 475 mg, 11.9 mmol) was reacted with 4'-methoxyphenyl dimethylphosphonoacetate **432** (3.59 g, 11.9 mmol) and the crude aldehyde (1.92 g, 10.8 mmol) in THF (57 mL). Purification *via* flash column chromatography (gradient elution 30-40 °C petrol/Et₂O, 9:1;

increased to 2:1) gave **447** as a white solid (3.20 g, 87%); mp 52-54 °C; $\nu_{\max}$ (ATR) 1735 (C=O), 1656 (C=C); δ_{H} (400 MHz, CDCl_3) 2.54-2.59 (2H, m, C(4) H_2), 2.76 (2H, t, J 7.7, C(5) H_2), 3.81 (3H, s, OMe), 5.95 (2H, s, OCH $_2$), 6.03 (1H, dt, J 15.6, 1.6, C(2) H), 6.65-6.67 (1H, m, Ar), 6.70 (1H, d, J 1.6, Ar), 6.76 (1H, d, J 7.9, Ar), 6.89-6.92 (2H, m, C(3') H , C(5') H), 7.01-7.04 (2H, m, C(2') H , C(6') H), 7.17 (1H, dt, J 15.6, 6.9, C(3) H); δ_{C} (100 MHz, CDCl_3) 34.1, 34.5 (C(4), C(5)), 55.7 (OMe), 101.0 (OCH $_2$), 108.4, 108.9 (C(2'), C(5')), 114.5 (C(3''), C(5'')), 121.2, 121.3 (C(2), Ar), 122.5 (C(2''), C(6'')), 134.5 (*i*-Ar), 144.3 (C(1'')), 146.1, 147.8 (*i*-Ar), 150.2 (C(3)), 157.3 (C(4'')), 165.3 (C(1)); m/z (ESI $^+$) 675 ([2M+Na] $^+$, 100%), 349 ([M+Na] $^+$, 68%), 327 ([M+H] $^+$, 20%); HRMS (ESI $^+$) C $_{19}$ H $_{18}$ NaO $_5$ $^+$ ([M+Na] $^+$) requires 349.1046; found 349.1040.

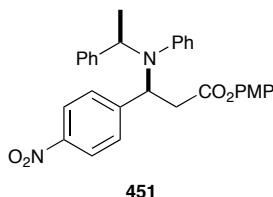
4''-Methoxyphenyl (3*S*, α *R*)-3-[*N*-phenyl-*N*-(α -methylbenzyl)amino]-3-(4'-methoxyphenyl)propanoate **450**



Following *General Procedure 6*, BuLi (2.35 M, 0.28 mL, 0.66 mmol), **107** (130 mg, 0.66 mmol), and **435** (171 mg, 0.60 mmol) in THF (4.5 mL) gave **450** in >99:1 dr. Purification *via* flash column chromatography (gradient elution, toluene/CH $_2$ Cl $_2$, 19:1; increased to 3:2) gave **450** as a colourless oil (207 mg, 72%, >99:1 dr); $[\alpha]_{\text{D}}^{25}$ -14.6 (c 1.0 in CHCl $_3$); $\nu_{\max}$ (film) 2963 (C-H), 1753 (C=O); δ_{H} (400 MHz, CDCl_3) 1.43 (3H, d, J 6.7, C(α)Me), 2.97 (1H, dd, J 15.3, 9.0, C(2) H_{A}), 3.14 (1H, dd, J 15.3, 5.5, C(2) H_{B}), 3.78 (3H, s, OMe), 3.84 (3H, s, OMe), 4.66 (1H, q, J 6.7, C(α) H), 5.27 (1H, dd, J 9.0, 5.5, C(3) H), 6.74-6.76 (2H, m, Ar), 6.83-6.87 (4H, m, Ar), 6.90-6.97 (3H, m, Ar), 7.14-7.32 (9H, m, Ar); δ_{C} (100 MHz, CDCl_3) 17.8 (C(α)Me), 39.4 (C(2)), 55.4, 55.7 (OMe), 57.2 (C(3)), 58.4 (C(α)), 113.8, 114.4, 122.2, 122.3, 125.0, 125.4, 126.9, 127.7, 129.2,

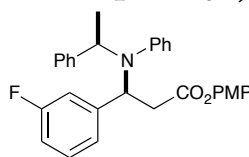
129.4, 132.9, 144.1, 144.2, 145.8, 157.3, 159.1 (*Ar*), 170.9 (*C*(1)); m/z (ESI^+) 504 ($[\text{M}+\text{Na}]^+$, 90%), 482 ($[\text{M}+\text{H}]^+$, 100%); HRMS (ESI^+) $\text{C}_{31}\text{H}_{32}\text{NO}_4^+$ ($[\text{M}+\text{H}]^+$) requires 482.2326; found 482.2315.

4''-Methoxyphenyl (3*S*, α *R*)-3-[*N*-phenyl-*N*-(α -methylbenzyl)amino]-3-(4'-nitrophenyl)propanoate **451**



Following *General Procedure 6*, BuLi (2.10 M, 0.55 mL, 1.16 mmol), **107** (229 mg, 1.16 mmol) and **425** (316 mg, 1.06 mmol) in THF (7.5 mL) gave **451** in >99:1 dr. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 5:1; increased to 1:1) gave **451** as a yellow oil (434 mg, 83%, >99:1 dr); $[\alpha]_{\text{D}}^{25}$ -9.1 (c 1.0 in CHCl_3); ν_{max} (film) 2964 (C-H), 1752 (C=O); δ_{H} (400 MHz, CDCl_3) 1.45 (3H, d, J 6.7, C(α)*Me*), 3.00 (1H, dd, J 16.0, 9.1, C(2)*H*_A), 3.18 (1H, dd, J 16.0, 4.8, C(2)*H*_B), 3.77 (3H, s, O*Me*), 4.71 (1H, q, J 6.7, C(α)*H*), 5.20 (1H, dd, J 9.1, 4.8, C(3)*H*), 6.73-6.84 (6H, m, *Ar*), 6.99-7.02 (1H, m, *Ar*), 7.16-7.20 (2H, m, *Ar*), 7.25-7.34 (5H, m, *Ar*), 7.42-7.46 (2H, m, (C(2')*H*, C(6')*H*), 8.15-8.19 (2H, m, (C(3')*H*, C(5')*H*); δ_{C} (100 MHz, CDCl_3) 19.1 (C(α)*Me*), 38.4 (C(2)), 55.7 (O*Me*), 58.3 (C(3)), 58.5 (C(α)), 114.5 (C(3''), C(5'')), 122.1 (C(2''), C(6'')), 123.3, 123.6, 127.5, 127.8, 128.6, 128.6 (*Ar*) 125.5 (C(3'), C(5')), 129.0 (C(2'), C(6')), 143.5, 145.0, 147.3, 149.1 (*Ar*), 143.9, (C(1''), 157.4, (C(4''), 170.4 (C(1)); m/z (ESI^+) 519 ($[\text{M}+\text{Na}]^+$, 92%), 497 ($[\text{M}+\text{H}]^+$, 100%); HRMS (ESI^+) $\text{C}_{30}\text{H}_{29}\text{N}_2\text{O}_5^+$ ($[\text{M}+\text{H}]^+$) requires 497.2071; found 497.2062.

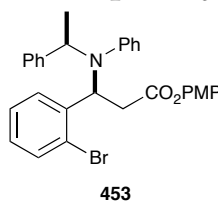
4''-Methoxyphenyl (3*S*, α *R*)-3-[*N*-phenyl-*N*-(α -methylbenzyl)amino]-3-(3'-fluorophenyl)propanoate **452**



452

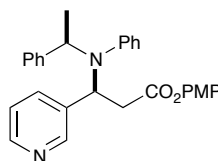
Following *General Procedure 6*, BuLi (2.29 M, 0.45 mL, 1.02 mmol), **107** (200 mg, 1.02 mmol), and **426** (250 mg, 0.92 mmol) in THF (6 mL) gave **452** in >99:1 dr. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 99:1; increased to 9:1) gave **452** as a colourless oil (349 mg, 81%, >99:1 dr); [α]_D²⁵ -15.2 (*c* 1.0 in CHCl₃); $\nu_{\max}$ (film) 1753 (C=O); δ_{H} (400 MHz, CDCl₃) 1.48 (3H, d, *J* 6.7, C(α)*Me*), 2.99 (1H, dd, *J* 15.7, 8.9, C(2)*H*_A), 3.14 (1H, dd, *J* 15.7, 5.2, C(2)*H*_B), 3.79 (3H, s, OMe), 4.72 (1H, q, *J* 6.7, C(α)*H*), 5.25 (1H, dd, *J* 8.9, 5.2, C(3)*H*), 6.76-6.80 (2H, m, *Ar*), 6.84-6.88 (4H, m, *Ar*), 6.96-7.05 (2H, m, *Ar*), 7.09-7.20 (4H, m, *Ar*), 7.23-7.35 (6H, m, *Ar*); δ_{C} (100 MHz, CDCl₃) 18.2 (C(α)*Me*), 39.1 (C(2)), 55.7 (OMe), 57.7 (C(α)), 58.4 (C(3)), 114.4 (C(3''), C(5'')), 114.5 (d, *J* 21.3, C(2')), 115.1 (d, *J* 20.9, C(4')), 122.2 (*Ar*), 122.5 (C(2''), C(6'')), 123.7, 124.9, 127.1, 127.7, 128.4 (*Ar*), 129.9 (d, *J* 8.0, C(5')), 143.8 (C(1'')), 144.0 (d, *J* 6.0, C(1')), 145.5 (*Ar*), 157.3 (C(4'')), 163.0 (d, *J* 246, C(3')), 170.6 (C(1)); *m/z* (ESI⁺) 492 ([M+Na]⁺, 67%), 470 ([M+H]⁺, 100%); HRMS (ESI⁺) C₃₀H₂₉FNO₃⁺ ([M+H]⁺) requires 470.2126; found 470.2111.

4''-Methoxyphenyl (3*S*, α *R*)-3-[*N*-phenyl-*N*-(α -methylbenzyl)amino]-3-(2'-bromophenyl)propanoate **453**



Following *General Procedure 6*, BuLi (2.29 M, 0.45 mL, 1.02 mmol), **107** (200 mg, 1.02 mmol), and **427** (306 mg, 0.92 mmol) in THF (6 mL) gave **453** in >99:1 dr. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 49:1; increased to 4:1) gave **453** as a colourless oil (256 mg, 53%, >99:1 dr); [α]_D²⁵ -44.1 (*c* 1.0 in CHCl₃); ν_{max} (film) 2966 (C-H), 1753 (C=O); δ_{H} (400 MHz, CDCl₃) 1.40 (3H, d, *J* 6.8, C(α)Me), 2.95 (1H, dd, *J* 15.0, 9.5, C(2)*H*_A), 3.23 (1H, dd, *J* 15.0, 5.6, C(2)*H*_B), 3.77 (3H, s, OMe), 4.46 (1H, q, *J* 6.8, C(α)H), 5.72 (1H, dd, *J* 9.5, 5.6, C(3)H), 6.68-6.71 (2H, m, C(2'')H, C(6'')H), 6.79-6.82 (2H, m, C(3'')H, C(5'')H), 6.90-6.92 (2H, m, Ar), 6.98-7.02 (1H, m, Ar), 7.15-7.27 (8H, m, Ar), 7.34-7.38 (1H, m, Ar), 7.57-7.59 (1H, m, Ar), 7.63-7.65 (1H, m, Ar); δ_{C} (100 MHz, CDCl₃) 16.9 (C(α)Me), 39.7 (C(2)), 55.7 (OMe), 57.3 (C(α)), 59.2 (C(3)), 114.4 (C(3''), C(5'')), 122.2 (C(2''), C(6'')), 123.1, 125.9, 126.2, 126.8, 127.6, 127.9, 128.0, 128.2, 129.3, 130.1, 133.4, 140.3, 143.5, 145.3 (Ar), 144.0 (C(1'')), 157.4 (C(4'')) 169.8 (C(1)); *m/z* (ESI⁺) 554 ([M+Na]⁺, ⁸¹Br, 45%), 552 ([M+Na]⁺, ⁷⁹Br, 48%), 532 ([M+H]⁺, ⁸¹Br, 93%), 530 ([M+H]⁺, ⁷⁹Br, 100%), 428 ([M-C₈H₈]⁺, ⁸¹Br, 31%), 426 ([M-C₈H₈]⁺, ⁷⁹Br, 33%); HRMS (ESI⁺) C₃₀H₂₉⁸¹BrNO₃⁺ ([M+H]⁺) requires 532.1305, found 532.1295; C₃₀H₂₉⁷⁹BrNO₃⁺ ([M+H]⁺) requires 530.1325; found 530.1313.

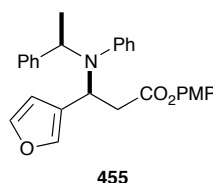
4''-Methoxyphenyl (3*S*, α *R*)-3-[*N*-phenyl-*N*-(α -methylbenzyl)amino]-3-(3'-pyridyl)propanoate **454**



454

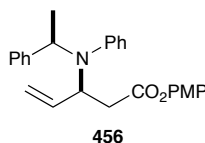
Following *General Procedure 6*, BuLi (2.29 M, 0.45 mL, 1.02 mmol), **107** (200 mg, 1.02 mmol), and **443** (235 mg, 0.92 mmol) in THF (6 mL) gave **454** in >99:1 dr. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/EtOAc, 2:1; increased to 1:2) gave **454** as a colourless oil (245 mg, 59%, >99:1 dr); $[\alpha]_{\text{D}}^{25} +5.2$ (*c* 1.0 in CHCl₃); ν_{max} (film) 1752 (C=O), 1596 (C=N); δ_{H} (400 MHz, CDCl₃) 1.43 (3H, d, *J* 6.7, C(α)*Me*), 2.97 (1H, dd, *J* 15.5, 9.1, C(2)*H_A*), 3.18 (1H, dd, *J* 15.5, 5.3, C(2)*H_B*), 3.76 (3H, s, *OMe*), 4.65 (1H, q, *J* 6.7, C(α)*H*), 5.16 (1H, dd, *J* 9.1, 5.3, C(3)*H*), 6.73-6.76 (2H, m, *Ar*), 6.80-6.83 (4H, m, *Ar*), 6.99-7.02 (1H, m, *Ar*), 7.15-7.34 (8H, m, *Ar*), 7.48-7.51 (1H, m, *Ar*), 8.53-8.57 (2H, m, *Ar*); δ_{C} (100 MHz, CDCl₃) 19.3 (C(α)*Me*), 38.2 (C(2)), 55.6 (*OMe*), 57.0 (C(3)), 58.4 (C(α)), 114.5 (C(3'')), C(5'')), 122.1 (C(2''), C(6'')), 123.2, 123.5, 126.3, 127.3, 127.7, 128.4, 128.4 (*Ar*, C(5')), 135.6 (C(4')), 136.5, 145.1 (*Ar*), 143.8, (C(3')) 143.9 (C(1'')), 148.9, 149.9 (C(2'), C(6')), 157.3 (C(4'')) 170.4 (C(1)); *m/z* (ESI⁺) 475 ([M+Na]⁺, 85%), 453 ([M+H]⁺, 100%); HRMS (ESI⁺) C₂₉H₂₉N₂O₃⁺ ([M+H]⁺) requires 453.2173; found 453.2159.

4''-Methoxyphenyl (3*S*, α *R*)-3-[*N*-phenyl-*N*-(α -methylbenzyl)amino]-3-(3'-furyl)propanoate **455**



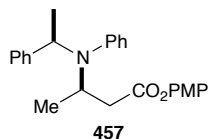
Following *General Procedure 6*, BuLi (2.29 M, 0.45 mL, 1.02 mmol), **107** (200 mg, 1.02 mmol), and **428** (225 mg, 0.92 mmol) in THF (6 mL) gave **455** in >99:1 dr. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 19:1; increased to 4:1) gave **455** as a colourless oil (272 mg, 67%, >99:1 dr); $[\alpha]_{\text{D}}^{25}$ -59.1 (*c* 1.0 in CHCl₃); ν_{max} (film) 1754 (C=O), 1505 (C=C); δ_{H} (400 MHz, CDCl₃) 1.52 (3H, d, *J* 6.8, C(α)Me), 2.96 (1H, dd, *J* 15.5, 8.4, C(2)*H*_A), 3.05 (1H, dd, *J* 15.5, 5.8, C(2)*H*_B), 3.80 (3H, s, OMe), 4.82 (1H, q, *J* 6.8, C(α)H), 5.30 (1H, dd, *J* 8.4, 5.8, C(3)H), 6.38 (1H, dd, *J* 1.6, 0.7, C(4')H), 6.88 (4H, app br s, C(2'')H, C(3'')H, C(5'')H, C(6'')H), 6.90-6.94 (3H, m, *Ar*), 7.17-7.27 (3H, m, *Ar*), 7.31-7.35 (2H, m, *Ar*), 7.37-7.43 (4H, m, *Ar*); δ_{C} (100 MHz, CDCl₃) 19.5 (C(α)Me), 39.1 (C(2)), 51.3 (C(3)), 55.7 (OMe), 57.1 (C(α)), 110.4 (C(4')), 114.5 (C(3''), C(5'')), 121.2, 122.8, 126.9, 127.5, 128.4 (*o*-, *m*-, *p*-Ph), 122.2 (C(2''), C(6'')), 125.6 (C(3')), 140.3 (C(5')), 143.2 (C(2')), 144.1, 146.1 (*i*-Ph), 144.3 (C(1'')), 157.3 (C(4'')), 170.6 (C(1)); *m/z* (ESI⁺) 905 ([2M+Na]⁺, 100%), 464 ([M+Na]⁺, 77%), 442 ([M+H]⁺, 80%); HRMS (ESI⁺) C₂₈H₂₈NO₄⁺ ([M+H]⁺) requires 442.2013; found 442.2013.

4'-Methoxyphenyl (3*S*, α *R*)-3-[*N*-phenyl-*N*-(α -methylbenzyl)amino]pent-4-enoate **456**



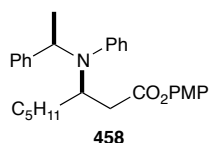
Following *General Procedure 6*, BuLi (2.50 M, 3.98 mL, 9.94 mmol), **107** (1.96 g, 9.94 mmol), and **430** (1.69 g, 8.28 mmol) in THF (60 mL) gave **456** in >99:1 dr. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 49:1; increased to 19:1) gave **456** as a white solid (2.37 g, 71%, >99:1 dr); C₂₆H₂₇NO₃ requires C, 77.8; H, 6.8; N, 3.5%; found C, 77.7; H, 6.9; N, 3.55%; mp 72-74 °C; $[\alpha]_D^{25}$ -71.5 (*c* 1.0 in CHCl₃); $\nu_{\max}$ (ATR) 1754 (C=O); δ_H (400 MHz, CDCl₃) 1.57 (3H, d, *J* 6.8, C(α)Me), 2.82-2.84 (2H, m, C(2)H₂), 3.81 (3H, s, OMe), 4.69-4.75 (1H, m, C(3)H), 4.87 (1H, q, *J* 6.8, C(α)H), 5.28 (1H, d, *J* 1.4, C(5)H_A), 5.32 (1H, app dt, *J* 7.7, 1.2, C(5)H_B), 5.99-6.08 (1H, m, C(4)H), 6.86-6.96 (7H, m, *Ar*), 7.33-7.17 (5H, m, *Ph*), 7.37-7.40 (2H, m, *Ph*); δ_C (100 MHz, CDCl₃) 19.2 (C(α)Me), 38.6 (C(2)), 55.7 (OMe), 57.2, 57.3 (C(α), C(3)), 114.5 (C(3'), C(5')), 116.8 (C(4)), 120.6, 121.7 (*o*-, *m*-, *p*-*Ph*), 122.3 (C(2'), C(6')), 126.9, 127.5, 128.4, 128.5 (*o*-, *m*-, *p*-*Ph*), 138.0 (C(5)), 144.1 (C(1')), 144.2, 146.5 (*i*-*Ph*), 157.3 (C(4')), 170.6 (C=O); *m/z* (ESI⁺) 424 ([M+Na]⁺, 12%), 402 ([M+H]⁺, 100%); HRMS (ESI⁺) C₂₆H₂₈NO₃⁺ ([M+H]⁺) requires 402.2064; found 402.2049.

4'-Methoxyphenyl (*R,R*)-3-[*N*-phenyl-*N*-(α -methylbenzyl)amino]butanoate **457**



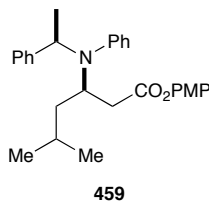
Following *General Procedure 6*, BuLi (2.10 M, 0.76 mL, 1.60 mmol), **107** (314 mg, 1.60 mmol), and **424** (278 mg, 1.45 mmol) in THF (9 mL) gave **457** in >99:1 dr. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 19:1; increased to 4:1) gave **457** as a white solid (450 mg, 80%, >99:1 dr); C₂₅H₂₇NO₃ requires C, 77.1; H, 7.0; N, 3.6%; found C, 77.2; H, 6.9; N, 3.4%; mp 95-97 °C; $[\alpha]_D^{25}$ -68.2 (*c* 1.0 in CHCl₃); $\nu_{\max}$ (KBr) 2973 (C-H), 1753 (C=O); δ_H (400 MHz, CDCl₃) 1.33 (3H, d, *J* 6.8, C(4)*H*₃), 1.54 (3H, d, *J* 6.7, C(α)*Me*), 2.59 (1H, dd, *J* 15.2, 8.5, C(2)*H*_A), 2.88 (1H, *J* 15.2, 5.3, C(2)*H*_B), 3.82 (3H, s, *OMe*), 4.25-4.27 (1H, m, C(3)*H*), 4.81 (1H, q, *J* 6.7, C(α)*H*), 6.90-7.03 (7H, m, *Ar*), 7.24-7.28 (3H, m, *Ar*), 7.34-7.37 (2H, m, *Ar*), 7.45-7.47 (2H, m, *Ar*); δ_C (100 MHz, CDCl₃) 18.7 (C(4)), 20.4 (C(α)*Me*), 40.1 (C(2)), 50.7 (C(3)), 55.6 (*OMe*), 56.8 (C(α)), 114.4 (C(3'), C(5')), 120.9, 122.2, 122.6, 126.7, 127.2, 128.4, 128.5 (*Ar*), 144.1 (C(1')), 144.6, 146.3 (*Ar*), 157.2 (C(4')), 171.0 (C(1)); *m/z* (ESI⁺) 412 ([M+Na]⁺, 90%), 390 ([M+H]⁺, 100%); HRMS (ESI⁺) C₂₅H₂₈NO₃⁺ ([M+H]⁺) requires 390.2064; found 390.2059.

4'-Methoxyphenyl (*R,R*)-3-[*N*-phenyl-*N*-(α -methylbenzyl)amino]octanoate **458**



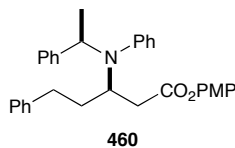
Following *General Procedure 6*, BuLi (2.29 M, 2.43 mL, 5.58 mmol), **107** (1.10 g, 5.58 mmol) and **431** (1.26 g, 5.07 mmol) in THF (45 mL) gave **458** in >99:1 dr. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 19:1; increased to 4:1) gave **458** as a colourless oil (1.75 g, 78%, >99:1 dr); [α]_D²⁵ -26.1 (*c* 1.0 in CHCl₃); ν_{max} (film) 2931, 2857 (C-H), 1754 (C=O); δ_{H} (400 MHz, CDCl₃) 0.89 (3H, t, *J* 7.1, C(8)*H*₃), 1.19-1.42 (6H, m, C(5)*H*₂, C(6)*H*₂, C(7)*H*₂), 1.44-1.58 (1H, m, C(4)*H*_A), 1.50 (3H, d, *J* 6.7, C(α)*Me*), 1.65-1.72 (1H, m, C(4)*H*_B), 2.52 (1H, dd, *J* 15.4, 7.8, C(2)*H*_A), 2.78 (1H, dd, *J* 15.4, 5.2, C(2)*H*_B), 3.81 (3H, s, O*Me*), 3.93-4.00 (1H, m, C(3)*H*), 4.79 (1H, q, *J* 6.7, C(α)*H*), 6.87-6.96 (5H, m, *Ar*), 7.02 (2H, d, *J* 8.6, *Ar*), 7.23-7.27 (3H, m, *Ar*), 7.31-7.34 (2H, m, *Ar*), 7.41-7.43 (2H, m, *Ar*); δ_{C} (100 MHz, CDCl₃) 14.2 (C(8)), 20.8 (C(α)*Me*), 22.7, 26.6, 31.9 (C(5), C(6), C(7)), 33.4 (C(4)), 38.4 (C(2)), 55.2 (C(3)), 55.7 (O*Me*), 57.7 (C(α)), 114.5 (C(3'), C(5')), 121.1, 123.1, 126.9, 127.5, 128.4, 128.5 (*o*-, *m*-, *p*-*Ph*), 122.3 (C(2'), C(6')), 144.2 (C(1')), 144.5, 146.6 (*i*-*Ph*), 157.3 (C(4')), 171.5 (C(1)); *m/z* (ESI⁺) 468 ([M+Na]⁺, 83%), 446 ([M+H]⁺, 100%); HRMS (ESI⁺) C₂₉H₃₅NNaO₃⁺ ([M+Na]⁺) requires 468.2509; found 468.2511.

4'-Methoxyphenyl (*R,R*)-3-[*N*-phenyl-*N*-(α -methylbenzyl)amino]-5-methylhexanoate **459**



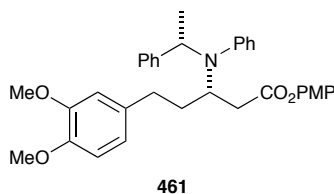
Following *General Procedure 6*, BuLi (2.35 M, 0.43 mL, 1.02 mmol), **107** (200 mg, 1.02 mmol) and **444** (216 mg, 0.92 mmol) in THF (6 mL) gave **459** in >99:1 dr. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 19:1; increased to 4:1) gave **459** as a colourless oil (298 mg, 75%, >99:1 dr); $[\alpha]_{\text{D}}^{25}$ -3.4 (*c* 1.0 in CHCl₃); ν_{max} (film) 2956 (C-H), 1752 (C=O); δ_{H} (400 MHz, CDCl₃) 0.80 (3H, d, *J* 6.5, C(5)*Me*_A), 0.93 (3H, d, *J* 6.5, C(5)*Me*_B), 1.19-1.26 (1H, m, C(4)*H*_A), 1.45 (3H, d, *J* 6.6, C(α)*Me*), 1.51-1.59 (1H, m, C(4)*H*_B), 1.89 (1H, app nonet, *J* 6.7, C(5)*H*), 2.43 (1H, dd, *J* 15.0, 8.1, C(2)*H*_A), 2.91 (1H, dd, *J* 15.0, 5.1, C(2)*H*_B), 3.81 (3H, s, OMe), 3.95-4.02 (1H, m, C(3)*H*), 4.71 (1H, q, *J* 6.6, C(α)*H*), 6.88-6.95 (4H, m, *Ar*), 7.01-7.10 (3H, m, *Ph*), 7.26-7.36 (5H, m, *Ph*), 7.45-7.47 (2H, m, *Ph*); δ_{C} (100 MHz, CDCl₃) 21.5 (C(α)*Me*), 22.7 (C(5)*Me*_A), 23.0 (C(5)*Me*_B), 24.6 (C(5)), 37.6 (C(2)), 42.8 (C(4)), 53.5 (C(3)), 55.6 (OMe), 58.1 (C(α)), 114.4 (C(3'), C(5')), 122.1, 124.9, 126.9, 127.5, 128.4 (*o*-, *m*-, *p*-*Ph*), 122.2 (C(2'), C(6')), 144.2 (C(1')), 144.7, 146.2 (*i*-*Ph*), 157.2 (C(4')), 171.5 (C(1)); *m/z* (ESI⁺) 885 ([2M+Na]⁺, 100%), 454 ([M+Na]⁺, 75%), 432 ([M+H]⁺, 75%); HRMS (ESI⁺) C₂₈H₃₃NNaO₃⁺ ([M+Na]⁺) requires 454.2353; found 454.2350.

4'-Methoxyphenyl (*R,R*)-3-[*N*-phenyl-*N*-(α -methylbenzyl)amino]-5-phenylpentanoate **460**



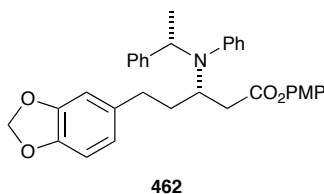
Following *General Procedure 6*, BuLi (2.35 M, 0.43 mL, 1.02 mmol), **107** (200 mg, 1.02 mmol), and **445** (272 mg, 0.92 mmol) in THF (6 mL) gave **460** in >99:1 dr. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 49:1; increased to 4:1) gave **460** as a colourless oil (344 mg, 76%, >99:1 dr); [α]_D²⁵ -8.0 (*c* 1.0 in CHCl₃); ν_{max} (film) 2933 (C-H), 1752 (C=O); δ_{H} (400 MHz, CDCl₃) 1.52 (3H, d, *J* 6.7, C(α)Me), 1.80-1.89 (1H, m, C(4)*H*_A), 1.97-2.06 (1H, m, C(4)*H*_B), 2.56-2.68 (2H, m, C(2)*H*_A, C(5)*H*_A), 2.83-2.94 (1H, m, C(2)*H*_B, C(5)*H*_B), 3.83 (3H, s, OMe), 4.04 (1H, m, C(3)*H*), 4.83 (1H, q, *J* 6.7, C(α)*H*), 6.91 (4H, app br s, *Ar*), 7.00-7.04 (1H, m, *Ph*), 7.09-7.16 (4H, m, *Ph*), 7.20-7.39 (8H, m, *Ph*), 7.46-7.48 (2H, m, *Ph*); δ_{C} (100 MHz, CDCl₃) 20.9 (C(α)Me), 33.3 (C(5)), 35.4 (C(4)), 38.3 (C(2)), 54.9 (C(3)), 55.6 (OMe), 58.2 (C(α)), 114.4 (C(3'), C(5')), 121.7, 122.1, 123.6, 125.9, 127.0, 127.5, 128.4, 128.4, 128.6 (*o*-, *m*-, *p*-*Ph*), 122.2 (C(2'), C(6')), 142.1, 144.2, 146.1 (*i*-*Ph*), 144.1 (C(1')), 157.2 (C(4')), 171.3 (C(1)); *m/z* (ESI⁺) 502 ([M+Na]⁺, 94%), 480 ([M+H]⁺, 100%); HRMS (ESI⁺) C₃₂H₃₃NNaO₃⁺ ([M+Na]⁺) requires 502.2353; found 502.2353.

4''-Methoxyphenyl (*S,S*)-3-[*N*-phenyl-*N*-(α -methylbenzyl)amino]-5-(3',4'-dimethoxyphenyl)pentanoate **461**

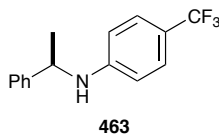


Following *General Procedure 6*, BuLi (2.50 M, 1.45 mL, 3.63 mmol), **107** (716 mg, 3.63 mmol), and **446** (1.13 g, 3.30 mmol) in THF (21 mL) gave **461** in >99:1 dr. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 19:1; increased to 3:1) gave **461** as a pale yellow solid (1.41 g, 79%, >99:1 dr); $[\alpha]_{\text{D}}^{25} +9.2$ (*c* 1.0 in CHCl₃); ν_{max} (ATR) 1752 (C=O); δ_{H} (400 MHz, CDCl₃) 1.48 (3H, d, *J* 6.7, C(α)Me), 1.75-1.84 (1H, m, C(4)*H*_A), 1.90-2.00 (1H, m, C(4)*H*_B), 2.51-2.58 (2H, m, C(2)*H*_A, C(5)*H*_A), 2.75-2.82 (2H, m, C(2)*H*_B, C(5)*H*_B), 3.80 (3H, s, OMe), 3.81 (3H, s, OMe), 3.86 (3H, s, OMe), 3.98 (1H, tt, *J* 8.2, 5.2, C(3)*H*), 4.80 (1H, q, *J* 6.7, C(α)*H*), 6.59 (1H, d, *J* 2.0, C(2')*H*), 6.64 (1H, dd, *J* 8.1, 2.0, C(6')*H*), 6.76 (1H, d, *J* 8.1, C(5')*H*), 6.86 (4H, s, C(2'')*H*, C(3'')*H*, C(5'')*H*, C(6'')*H*), 6.95-6.99 (1H, m, *Ph*), 7.05-7.07 (2H, m, *Ph*), 7.23-7.34 (5H, m, *Ph*), 7.40-7.42 (2H, m, *Ph*); δ_{C} (100 MHz, CDCl₃) 20.8 (C(α)Me), 32.9 (C(5)), 35.6 (C(4)), 38.5 (C(2)), 54.8 (C(3)), 55.7, 55.9, 56.1 (OMe), 58.3 (C(α)), 111.3, 111.8 (C(2'), C(5')), 114.5 (C(3''), C(5'')), 120.2, 121.6 (*Ar*), 122.3 (C(2''), C(6'')), 123.5, 127.1, 127.6, 128.5, 128.7 (*Ar*), 134.8, 144.2, 144.2 (C(1''), *i*-Ar), 146.5, 147.3, 148.9 (*i*-Ar), 157.2 (C(4'')), 171.2 (C(1)); *m/z* (ESI⁺) 562 ([M+Na]⁺, 82%), 540 ([M+H]⁺, 100%); HRMS (ESI⁺) C₃₄H₃₇NNaO₅⁺ ([M+Na]⁺) requires 562.2564, found 562.2560.

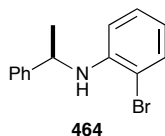
4''-Methoxyphenyl (*S,S*)-3-[*N*-phenyl-*N*-(α -methylbenzyl)amino]-5-(3',4'-methylenedioxyphenyl)pentanoate **462**



Following *General Procedure 6*, BuLi (2.50 M, 2.36 mL, 5.90 mmol), **107** (1.16 g, 5.90 mmol), and **447** (1.75 g, 5.37 mmol) in THF (36 mL) gave **462** in >99:1 dr. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 19:1; increased to 3:1) gave **462** as a pale yellow solid (1.66 g, 59%, >99:1 dr); C₃₃H₃₃NO₅ requires C, 75.7; H, 6.35; N, 2.7%; found C, 75.5; H, 6.2; N, 2.8%; mp 62-64 °C; $[\alpha]_D^{25} +2.2$ (*c* 1.0 in CHCl₃); $\nu_{\max}$ (ATR) 1752 (C=O); δ_H (400 MHz, CDCl₃) 1.48 (3H, d, *J* 6.7, C(α)Me), 1.71-1.80 (1H, m, C(4)*H*_A), 1.87-1.97 (1H, m, C(4)*H*_B), 2.48-2.56 (2H, m, C(2)*H*_A, C(5)*H*_A), 2.73-2.84 (2H, m, C(2)*H*_B, C(5)*H*_B), 3.81 (3H, s, OMe), 3.95 (1H, m, C(3)*H*), 4.79 (1H, q, *J* 6.7, C(α)*H*), 5.91 (2H, s, OCH₂), 6.54-6.58 (2H, m, *Ar*), 6.69-6.71 (1H, m, *Ar*), 6.88 (4H, s, C(2'')*H*, C(3'')*H*, C(5'')*H*, C(6'')*H*), 7.00 (1H, td, *J* 7.3, 0.9, *Ar*), 7.06-7.08 (2H, m, *Ar*), 7.26-7.35 (5H, m, *Ar*), 7.43 (2H, d, *J* 7.7, *Ar*); δ_C (100 MHz, CDCl₃) 21.0 (C(α)Me), 33.1 (C(5)), 35.8 (C(4)), 38.4 (C(2)), 54.9 (C(3)), 55.7 (OMe), 58.3 (C(α)), 100.9 (OCH₂), 108.3, 108.9 (C(2'), C(5')), 114.5 (C(3''), C(5'')), 121.1, 121.8 (*Ar*), 122.3 (C(2''), C(6'')), 123.8, 127.1, 127.6, 128.5, 128.7 (*Ar*), 136.0, 144.2 (*i-Ar*), 144.3 (C(1'')), 145.7, 146.4, 147.6 (*i-Ar*), 157.3 (C(4'')), 171.3 (C(1)); *m/z* (ESI⁺) 524 ([M+H]⁺, 100%); HRMS (ESI⁺) C₃₃H₃₄NO₅⁺ ([M+H]⁺) requires 524.2431; found 524.2420.

(*R*)-*N*-(4-(Trifluoromethyl)phenyl)-*N*-(α -methylbenzyl)amine **463**³⁰

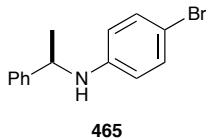
Following *General Procedure 9*, Pd₂(dba)₃ (137 mg, 0.15 mmol), *rac*-BINAP (210 mg, 0.3 mmol), NaO^tBu (770 mg, 8.00 mmol), α -methylbenzyl amine **196** (1.29 mL, 10.0 mmol) and 1-bromo-4-trifluoromethyl benzene (0.56 mL, 4.00 mmol) in toluene (10 ml) gave **463**. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 24:1; increased to 9:1) gave **463** as a pale yellow oil (755 mg, 71%); [α]_D²⁵ -1.0 (*c* 1.0 in CHCl₃); {lit.³⁰ [α]_D²⁰ -1.0 (*c* 0.99 in CHCl₃)}; δ_{H} (400 MHz, CDCl₃) 1.56 (3H, d, *J* 6.7, C(α)*Me*), 4.53 (1H, q, *J* 6.7, C(α)*H*), 6.55 (2H, d, *J* 8.2, *Ar*), 7.25-7.28 (1H, m, *Ph*), 7.31-7.36 (6H, m, *Ar*).

(*R*)-*N*-(2-Bromophenyl)-*N*-(α -methylbenzyl)amine **464**⁴

Following *General Procedure 9*, Pd₂(dba)₃ (81 mg, 0.09 mmol), *rac*-BINAP (110 mg, 0.18 mmol), NaO^tBu (430 mg, 4.51 mmol), α -methylbenzyl amine **196** (0.70 mL, 5.5 mmol) and 1,2-dibromobenzene (0.27 mL, 2.2 mmol) in toluene (6 ml) gave **464**. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 49:1; increased to, 30-40 °C petrol/Et₂O, 20:1) gave **464** as a pale yellow oil (530 mg, 88%); [α]_D²⁵ -2.5 (*c* 1.0 in CHCl₃); δ_{H} (400 MHz, CDCl₃) 1.60 (3H, d, *J* 6.7, C(α)*Me*), 4.54 (1H, q, *J* 6.7, C(α)*H*), 4.94 (1H, br s, *NH*), 6.42 (1H, dt, *J* 8.2, 1.3, *Ar*), 6.51-6.55 (1H, ddd, *J* 7.9, 7.4, 1.3, *Ar*), 7.00 (1H, ddd, *J* 8.2, 7.4, 1.5, *Ar*), 7.22-7.27 (1H, m, *Ph*),

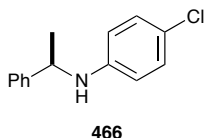
7.31-7.37 (4H, m, *Ph*), 7.42 (1H, dd, *J* 7.9, 1.5, *Ar*).

(*R*)-*N*-(4-Bromophenyl)-*N*-(α -methylbenzyl)amine **465³¹**



Following *General Procedure 9*, Pd₂(dba)₃ (81 mg, 0.09 mmol), *rac*-BINAP (110 mg, 0.18 mmol), NaO^tBu (430 mg, 4.51 mmol), α -methylbenzyl amine **196** (0.70 mL, 5.50 mmol) and 1,4-dibromobenzene (0.28 mL, 2.20 mmol) in toluene (6 mL) gave **465**. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 49:1; increased to 19:1) gave **465** as a pale yellow oil (287 mg, 47%); [α]_D²⁵ +13.9 (*c* 1.0 in CHCl₃) {lit.³¹ [α]_D²⁵ +7.6 (*c* 0.53 in CHCl₃)}; δ_{H} (400 MHz, CDCl₃) 1.52 (3H, d, *J* 6.7, C(α)*Me*), 4.07 (1H, br s, *NH*), 4.43 (1H, q, *J* 6.7, C(α)*H*), 6.36-6.39 (2H, m, *Ar*), 7.14-7.17 (2H, m, *Ar*), 7.23-7.26 (1H, m, *Ph*), 7.30-7.35 (4H, m, *Ph*).

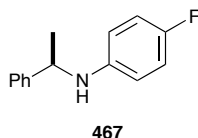
(*R*)-*N*-(4-Chlorophenyl)-*N*-(α -methylbenzyl)amine **466³²**



Following *General Procedure 10*, CuI (44 mg, 0.23 mmol), K₃PO₄ (1.95 g, 9.18 mmol), isopropyl alcohol (5 mL), ethylene glycol (0.5 mL, 9.18 mmol), α -methylbenzyl amine **196** (0.71 mL, 5.50 mmol) and 4-iodochlorobenzene (1.09 g, 4.59 mmol) gave **466**. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 49:1; increased to 19:1) gave **466** as a pale yellow oil (600 mg, 57%); [α]_D²⁵ +9.5 (*c* 1.0 in CHCl₃) {lit.³² [α]_D²⁵ -8.0 (*c* 1.13 in CHCl₃) for enantiomer}; δ_{H} (400 MHz, CDCl₃)

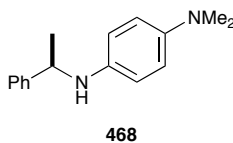
1.52 (3H, d, J 6.7, C(α)Me), 4.06 (1H, br s, NH), 4.44 (1H, q, J 6.7, C(α)H), 6.41-6.44 (2H, m, Ar), 7.01-7.05 (2H, m, Ar), 7.23-7.27 (1H, m, Ph), 7.32-7.35 (4H, m, Ph).

(*R*)-*N*-(4-Fluorophenyl)-*N*-(α -methylbenzyl)amine **467²²**



Following *General Procedure 10*, CuI (44 mg, 0.23 mmol), K₃PO₄ (1.95 g, 9.18 mmol), isopropyl alcohol (5 mL), ethylene glycol (0.5 mL, 9.18 mmol), α -methylbenzyl amine **196** (0.71 mL, 5.50 mmol) and 4-iodofluorobenzene (0.53 mL, 4.59 mmol) gave **467**. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 49:1; increased to 19:1) gave **467** as a colourless oil (480 mg, 49%); [α]_D²⁵ -23.8 (c 1.0 in CHCl₃) {lit.²² [α]_D²⁰ -24.8 (c 1.0 in CHCl₃)}; δ_{H} (400 MHz, CDCl₃) 1.53 (3H, d, J 6.7, C(α)Me), 3.95 (1H, br s, NH), 4.44 (1H, q, J 6.7, C(α)H), 6.42-6.48 (2H, m, Ar), 6.78-6.85 (2H, m, Ar), 7.23-7.28 (1H, m, Ph), 7.32-7.39 (4H, m, Ph).

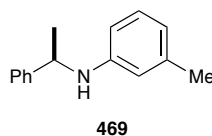
(*R*)-*N*-(4-(*N,N*-Dimethylamino)phenyl)-*N*-(α -methylbenzyl)amine **468³³**



Following *General Procedure 10*, CuI (139 mg, 0.73 mmol), K₃PO₄ (6.20 g, 29.2 mmol), isopropyl alcohol (15 mL), ethylene glycol (1.63 mL, 29.2 mmol), α -methylbenzyl amine **196** (4.69 mL, 36.4 mmol) and 4-iodo-*N,N*-dimethylaniline (3.6 g, 14.6 mmol) at 90 °C for 48 h gave **468**. Purification *via* flash column chromatography (gradient elution, 30-

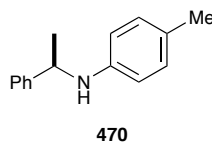
40 °C petrol/EtOAc, 3:1; increased to 1:1) gave **468** as a grey solid (943 mg, 27%); $[\alpha]_{\text{D}}^{25} +20.3$ (c 1.0 in CHCl_3); δ_{H} (400 MHz, CDCl_3) 1.51 (3H, d, J 6.7, C(α)Me), 2.80 (6H, s, NMe_2), 3.72 (1H, br s, NH), 4.43 (1H, q, J 6.7, C(α)H), 6.52 (2H, d, J 8.7, Ar), 6.68 (2H, d, J 8.7, Ar), 7.22-7.27 (1H, m, Ph), 7.32-7.35 (2H, m, Ph), 7.39-7.41 (2H, m, Ph).

(*R*)-*N*-(3-Methylphenyl)-*N*-(α -methylbenzyl)amine **469³⁴**



Following *General Procedure 10*, CuI (44 mg, 0.23 mmol), K_3PO_4 (1.95 g, 9.18 mmol), iso-propyl alcohol (5 mL), ethylene glycol (0.5 mL, 9.18 mmol), α -methylbenzyl amine **196** (0.71 mL, 5.50 mmol) and 3-iodotoluene (0.59 mL, 4.59 mmol) gave **469**. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/ Et_2O , 49:1; increased to 19:1) gave **469** as a colourless oil (600 mg, 62%); $[\alpha]_{\text{D}}^{25} -1.4$ (c 1.0 in CHCl_3) {lit.³⁴ $[\alpha]_{\text{D}} +1.9$ (c 1.0 in CHCl_3) for enantiomer}; δ_{H} (400 MHz, CDCl_3) 1.56 (3H, d, J 6.7, C(α)Me), 2.27 (3H, s, C(3)Me), 4.01 (1H, br s, NH), 4.54 (1H, q, J 6.7, C(α)H), 6.36 (1H, dd, J 7.8, 2.2, Ar), 6.42 (1H, s, Ar), 6.53 (1H, dd, J 7.8, 0.6, Ar), 7.03 (1H, t, J 7.8, Ar), 7.26-7.29 (1H, m, Ph), 7.35-7.44 (4H, m, Ph).

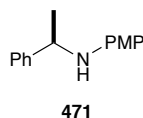
(*R*)-*N*-(4-Methylphenyl)-*N*-(α -methylbenzyl)amine **470²²**



Following *General Procedure 10*, CuI (44 mg, 0.23 mmol), K_3PO_4 (1.95 g, 9.18 mmol), isopropyl alcohol (5 mL), ethylene glycol (0.5 mL, 9.18 mmol), α -methylbenzyl amine

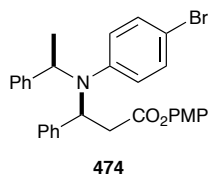
196 (0.71 mL, 5.50 mmol) and 4-iodotoluene (1 g, 4.59 mmol) gave **470**. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 49:1; increased to 19:1) gave **470** as a colourless oil (560 mg, 58%); $[\alpha]_{\text{D}}^{25} +6.9$ (*c* 1.0 in CHCl₃) {lit.²² $[\alpha]_{\text{D}}^{20} +4.4$ (*c* 1.0 in CHCl₃)}; δ_{H} (400 MHz, CDCl₃) 1.52 (3H, d, *J* 6.7, C(α)*Me*), 2.20 (3H, s, Ar*Me*), 3.92 (1H, br s, NH), 4.47 (1H, q, *J* 6.7, C(α)*H*), 6.44-6.46 (2H, m, Ar), 6.91-6.93 (2H, m, Ar), 7.22-7.27 (1H, m, Ph), 7.31-7.40 (4H, m, Ph).

(*R*)-*N*-(4-Methoxyphenyl)-*N*-(α -methylbenzyl)amine 471³⁵



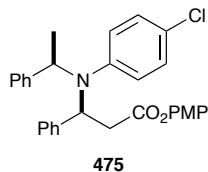
Following *General Procedure 10*, CuI (19 mg, 0.1 mmol), K₃PO₄ (849 mg, 3.00 mmol), isopropyl alcohol (2 mL), ethylene glycol (0.22 mL, 3.00 mmol), α -methylbenzyl amine **196** (0.31 mL, 2.40 mmol) and 4-iodoanisole (468 mg, 2.00 mmol) gave **471**. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 24:1; increased to 9:1) gave **471** as a colourless oil (129 mg, 28%); $[\alpha]_{\text{D}}^{25} +2.0$ (*c* 1.0 in CHCl₃) {lit.³⁵ $[\alpha]_{\text{D}}^{25} +1.9$ (*c* 1.0 in CHCl₃)}; δ_{H} (400 MHz, CDCl₃) 1.51 (3H, d, *J* 6.7, C(α)*Me*), 3.70 (3H, s, O*Me*), 4.42 (1H, q, *J* 6.7, C(α)*H*), 6.47-6.50 (2H, m, Ar), 6.68-6.72 (2H, m, Ar), 7.21-7.25 (1H, m, Ph), 7.30-7.38 (4H, m, Ph).

4'-Methoxyphenyl (3*S*, α *R*)-3-[*N*-(4''-bromophenyl)-*N*-(α -methylbenzyl)amino]-3-phenylpropanoate **474**



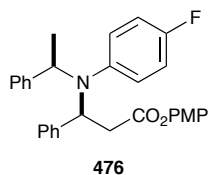
Following *General Procedure 6*, BuLi (2.50 M, 0.10 mL, 0.24 mmol), **465** (67 mg, 0.24 mmol), and **404** (56 mg, 0.22 mmol) in THF (1.5 mL) gave **474** in >99:1 dr. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 19:1; increased to 4:1) gave **474** as a colourless oil (18 mg, 15%, >99:1 dr); $[\alpha]_{\text{D}}^{25}$ -38.8 (*c* 1.0 in CHCl₃); ν_{max} (ATR) 1754 (C=O); δ_{H} (500 MHz, CDCl₃) 1.42 (3H, d, *J* 6.7, C(α)Me), 3.00 (1H, dd, *J* 15.6, 8.4, C(2)*H*_A), 3.09 (1H, dd, *J* 15.6, 5.8, C(2)*H*_B), 3.78 (23H, s, OMe), 4.66 (1H, q, *J* 6.7, C(α)H), 5.31 (1H, dd, *J* 8.4, 5.8, C(3)H), 6.67-6.70 (2H, m, *Ar*), 6.72-6.75 (2H, m, *Ar*), 6.81-6.84 (2H, m, *Ar*), 7.20-7.38 (12H, m, *Ar*); δ_{C} (125 MHz, CDCl₃) 17.7 (C(α)Me), 39.3 (C(2)), 55.7 (OMe), 57.2 (C(α)), 58.7 (C(3)), 114.5 (C(3'), C(5')), 114.6 (C(4'')), 122.2 (C(2'), C(6')), 125.7, 127.1, 127.6, 127.9, 128.1, 128.4, 128.7, 131.3 (*Ar*), 140.5 (*i-Ar*), 143.5 (*i-Ar*), 144.1 (C(1')), 145.0 (*i-Ar*), 157.4 (C(4')), 170.7 (C(1)); *m/z* (ESI⁺) 554 ([M+Na]⁺, ⁸¹Br, 72%), 552 ([M+Na]⁺, ⁷⁹Br, 70%), 532 ([M+H]⁺, ⁸¹Br, 100%), 530 ([M+H]⁺, ⁷⁹Br, 98%); HRMS (ESI⁺) C₃₀H₂₈⁸¹BrNNaO₃⁺ ([M+Na]⁺) requires 554.1126; found 554.1119; HRMS (ESI⁺) C₃₀H₂₈⁷⁹BrNNaO₃⁺ ([M+Na]⁺) requires 552.1145; found 552.1137.

4'-Methoxyphenyl (3*S*, α *R*)-3-[*N*-(4''-chlorophenyl)-*N*-(α -methylbenzyl)amino]-3-phenylpropanoate **475**



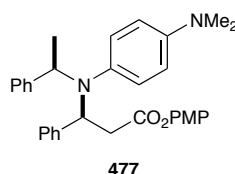
Following *General Procedure 6*, BuLi (2.50 M, 0.21 mL, 0.52 mmol), **466** (120 mg, 0.52 mmol), and **404** (120 mg, 0.47 mmol) in THF (3 mL) gave **475** in >99:1 dr. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 19:1; increased to 4:1) gave **475** as a colourless oil (82 mg, 36%, >99:1 dr); [α]_D²⁵ -36.6 (*c* 1.0 in CHCl₃); $\nu_{\max}$ (ATR) 1754 (C=O); δ_{H} (400 MHz, CDCl₃) 1.42 (3H, d, *J* 6.7, C(α)Me), 2.97 (1H, dd, *J* 15.4, 8.5, C(2)*H*_A), 3.10 (1H, dd, *J* 15.4, 5.8, C(2)*H*_B), 3.78 (3H, s, OMe), 4.62 (1H, q, *J* 6.7, C(α)H), 5.27 (1H, dd, *J* 8.5, 5.8, C(3)H), 6.71-6.75 (4H, m, *Ar*), 6.81-6.84 (2H, m, *Ar*), 7.07-7.09 (2H, m, *Ar*), 7.21-7.37 (10H, m, *Ph*); δ_{C} (100 MHz, CDCl₃) 17.7 (C(α)Me), 39.3 (C(2)), 55.7 (OMe), 57.4 (C(α)), 59.0 (C(3)), 114.5 (C(3'), C(5')), 122.2 ((C(2'), C(6'))), 126.1, 127.1 (*Ar*), 127.5 (C(4')), 127.7, 127.9, 128.2, 128.3, 128.4, 128.6 (*Ar*), 140.5, 143.7 (*i-Ph*), 144.1 C(1'), 144.4 C(1''), 157.3 (C(4')), 170.7 (C(1)); *m/z* (ESI⁺) 510 ([M+Na]⁺, ³⁷Cl, 35%), 508 ([M+Na]⁺, ³⁵Cl, 95%), 486 ([M+H]⁺, ³⁵Cl, 100%); HRMS (ESI⁺) C₃₀H₂₈³⁷ClNNaO₃⁺ ([M+Na]⁺) requires 510.1623; found 510.1633; HRMS (ESI⁺) C₃₀H₂₈³⁵ClNNaO₃⁺ ([M+Na]⁺) requires 508.1650; found 508.1649.

4'-Methoxyphenyl (3*S*, α *R*)-3-[*N*-(4''-fluorophenyl)-*N*-(α -methylbenzyl)amino]-3-phenylpropanoate **476**



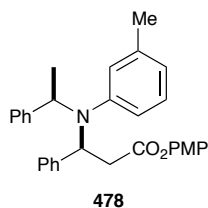
Following *General Procedure 6*, BuLi (2.50 M, 0.38 mL, 0.95 mmol), **467** (204 mg, 0.95 mmol), and **404** (219 mg, 0.86 mmol) in THF (6 mL) gave **476** in >99:1 dr. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 19:1; increased to 4:1) gave **476** as a colourless oil (300 mg, 74%, >99:1 dr); [α]_D²⁵ -17.2 (*c* 1.0 in CHCl₃); ν_{max} (ATR) 1754 (C=O); δ_{H} (400 MHz, CDCl₃) 1.42 (3H, d, *J* 6.6, C(α)Me), 2.86 (1H, dd, *J* 14.8, 8.9, C(2)*H*_A), 3.12 (1H, dd, *J* 14.8, 6.1, C(2)*H*_B), 3.78 (3H, s, OMe), 4.45 (1H, q, *J* 6.6, C(α)H), 5.10 (1H, dd, *J* 8.9, 6.1, C(3)H), 6.71-6.73 (2H, m, *Ar*), 6.78-6.86 (6H, m, *Ar*), 7.21-7.27 (5H, m, *Ph*), 7.34-7.39 (5H, m, *Ph*); δ_{C} (100 MHz, CDCl₃) 17.8 (C(α)Me), 39.4 (C(2)), 55.7 (OMe), 58.2 (C(α)), 60.2 (C(3)), 114.5 (C(3'), C(5')), 114.6 (d, *J* 22.3, C(3''), C(5'')), 122.3 (C(2'), C(6')), 127.0, 127.9, 128.0, 128.2, 128.5, 128.6 (*Ar*), 129.9 (d, *J* 8.0, C(2''), C(6'')), 140.4 (*Ar*), 141.1 (d, *J* 3.0, C(1'')), 144.1, 144.2 (*Ar*), 157.3 (C(4')), 159.7 (d, *J* 243, C(4'')), 170.7 (C(1)); *m/z* (ESI⁺) 961 ([2M+Na]⁺, 100%), 492 ([M+Na]⁺, 43%), 470 ([M+H]⁺, 38%); HRMS (ESI⁺) C₃₀H₂₈FNNaO₃⁺ ([M+Na]⁺) requires 492.1945; found 492.1938.

4'-Methoxyphenyl (3*S*, α *R*)-3-[*N*-(4''-*N,N*-dimethylaminophenyl)-*N*-(α -methylbenzyl)amino]-3-phenylpropanoate **477**



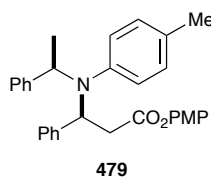
Following *General Procedure 6*, BuLi (2.50 M, 0.44 mL, 1.10 mmol), **468** (264 mg, 1.10 mmol), and **404** (254 mg, 1.00 mmol) in THF (8 mL) gave **477** in >99:1 dr. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 4:1; increased to 1:2) gave **477** as a colourless oil (281 mg, 57%, >99:1 dr); [α]_D²⁵ -11.3 (*c* 1.0 in CHCl₃); ν_{max} (ATR) 1747 (C=O); δ_{H} (400 MHz, CDCl₃) 1.34 (3H, d, *J* 6.6, C(α)*Me*), 2.76 (1H, dd, *J* 14.6, 9.6, C(2)*H*_A), 2.88 (6H, s, NMe₂), 3.10 (1H, dd, *J* 14.6, 5.6, C(2)*H*_B), 3.76 (3H, s, OMe), 4.33 (1H, q, *J* 6.6, C(α)*H*), 4.95 (1H, dd, *J* 9.6, 5.6, C(3)*H*), 6.52-6.54 (2H, m, *Ar*), 6.61-6.63 (2H, m, *Ar*), 6.72-6.81 (4H, m, *Ar*), 7.18-7.26 (5H, m, *Ph*), 7.31-7.39 (5H, m, *Ph*); δ_{C} (100 MHz, CDCl₃) 17.2 (C(α)*Me*), 39.7 (C(2)), 41.0 (NMe₂), 55.7 (OMe), 58.3 (C(α)), 60.9 (C(3)), 112.0 (*Ar*), 114.4 (C(3'), C(5')), 122.3 (C(2'), C(6')), 126.7, 127.6, 127.9, 128.2, 128.3, 128.8, 130.5, 134.2, 141.4 (*Ar*), 144.1 (C(1')), 145.0, 148.1 (*Ar*), 157.2 (C(4')), 171.1 (C(1)); *m/z* (ESI⁺) 517 ([M+Na]⁺, 42%), 495 ([M+H]⁺, 100%); HRMS (ESI⁺) C₃₂H₃₅N₂O₃⁺ ([M+H]⁺) requires 495.2642; found 495.2639.

4'-Methoxyphenyl (3*S*, α *R*)-3-[*N*-(3''-methylphenyl)-*N*-(α -methylbenzyl)amino]-3-phenylpropanoate **478**



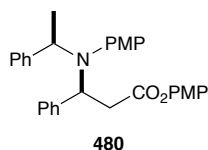
Following *General Procedure 6*, BuLi (2.50 M, 0.38 mL, 0.95 mmol), **469** (200 mg, 0.95 mmol), and **404** (219 mg, 0.86 mmol) in THF (6 mL) gave **478** in >99:1 dr. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 19:1; increased to 4:1) gave **478** as a colourless oil (294 mg, 74%, >99:1 dr); [α]_D²⁵ -43.0 (*c* 1.0 in CHCl₃); $\nu_{\max}$ (ATR) 1754 (C=O); δ_{H} (400 MHz, CDCl₃) 1.43 (3H, d, *J* 6.7, C(α)Me), 2.24 (3H, s, ArMe), 3.00 (1H, dd, *J* 15.4, 9.0, C(2)*H*_A), 3.15 (1H, dd, *J* 15.4, 5.3, C(2)*H*_B), 3.78 (3H, s, OMe), 4.68 (1H, q, *J* 6.7, C(α)H), 5.27 (1H, dd, *J* 9.0, 5.3, C(3)H), 6.65-6.66 (2H, m, Ar), 6.70-6.73 (2H, m, Ar), 6.77-6.79 (1H, m, Ar), 6.82-6.84 (2H, m, Ar), 7.03-7.07 (1H, m, Ar), 7.23-7.42 (10H, m, Ar); δ_{C} (100 MHz, CDCl₃) 17.6 (C(α)Me), 21.7 (ArMe), 39.4 (C(2)), 55.7 (OMe), 57.3 (C(α)), 58.9 (C(3)), 114.4 (C(3'), C(5')), 121.9 (Ar), 122.3 ((C(2'), C(6')), 123.0, 125.6, 126.9, 127.6, 127.8, 128.0, 128.2, 128.3, 128.4 (Ar), 137.8 (C(3'')), 141.2 (*i*-Ph), 144.1, 144.2 (C(1'), C(1'')), 145.6 (*i*-Ph), 157.2 (C(4')), 170.8 (C(1)); *m/z* (ESI⁺) 953 ([2M+Na]⁺, 100%), 488 ([M+Na]⁺, 65%), 466 ([M+H]⁺, 57%); HRMS (ESI⁺) C₃₁H₃₁NNaO₃⁺ ([M+Na]⁺) requires 488.2196; found 488.2185.

4'-Methoxyphenyl (3*S*, α *R*)-3-[*N*-(4''-methylphenyl)-*N*-(α -methylbenzyl)amino]-3-phenylpropanoate **479**



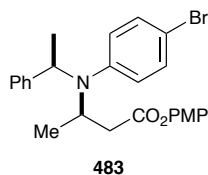
Following *General Procedure 6*, BuLi (2.50 M, 0.38 mL, 0.95 mmol), **470** (200 mg, 0.95 mmol), and **404** (219 mg, 0.86 mmol) in THF (6 mL) gave **479** in >99:1 dr. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 19:1; increased to 4:1) gave **479** as a colourless oil (331 mg, 83%, >99:1 dr); [α]_D²⁵ -20.6 (*c* 1.0 in CHCl₃); ν_{max} (ATR) 1754 (C=O); δ_{H} (400 MHz, CDCl₃) 1.42 (3H, d, *J* 6.7, C(α)*Me*), 2.29 (3H, s, Ar*Me*), 2.93 (1H, dd, *J* 15.1, 9.2, C(2)*H*_A), 3.15 (1H, dd, *J* 15.1, 5.5, C(2)*H*_B), 3.78 (3H, s, O*Me*), 4.57 (1H, q, *J* 6.7, C(α)*H*), 5.19 (1H, dd, *J* 9.2, 5.5, C(3)*H*), 6.70-6.72 (2H, m, Ar), 6.77 (2H, d, *J* 8.5, Ar), 6.82-6.84 (2H, d, Ar), 6.97 (2H, d, *J* 8.5, Ar), 7.22-7.42 (10H, m, Ph); δ_{C} (100 MHz, CDCl₃) 17.5 (C(α)*Me*), 20.9 (Ar*Me*), 39.5 (C(2)), 55.6 (O*Me*), 57.6 (C(α)), 59.6 (C(3)), 114.4 ((C(3'), C(5')), 122.3 ((C(2'), C(6')), 126.6, 126.8, 127.7, 127.9, 128.1, 128.4, 128.5, 128.8 (Ar), 132.7 (C(4')), 141.1, 142.8 (*i*-Ph), 144.1 C(1'), 144.5 C(1''), 157.2 (C(4')), 170.9 (C(1)); *m/z* (ESI⁺) 488 ([M+Na]⁺, 37%), 466 ([M+H]⁺, 100%); HRMS (ESI⁺) C₃₁H₃₂NO₃⁺ ([M+H]⁺) requires 466.2377; found 466.2365.

4'-Methoxyphenyl (3*S*, α *R*)-3-[*N*-(4''-methoxyphenyl)-*N*-(α -methylbenzyl)amino]-3-phenylpropanoate **480**



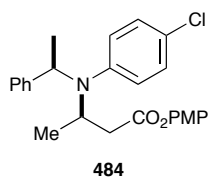
Following *General Procedure 6*, BuLi (2.35 M, 0.41 mL, 0.96 mmol), **471** (216 mg, 0.96 mmol), and **404** (221 mg, 0.87 mmol) in THF (6 mL) gave **480** in >99:1 dr. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 4:1; increased to 1:1) gave **480** as a colourless oil (323 mg, 77%, >99:1 dr); C₃₁H₃₁NO₄ requires C, 77.3; H, 6.5; N, 2.9%; found C, 77.2; H, 6.4; N, 2.9%; [α]_D²⁵ -9.2 (*c* 1.0 in CHCl₃); $\nu_{\max}$ (ATR) 1753 (C=O); δ_{H} (400 MHz, CDCl₃) 1.37 (3H, d, *J* 6.6, C(α)*Me*), 2.79 (1H, dd, *J* 14.7, 9.3, C(2)*H*_A), 3.10 (1H, dd, *J* 14.7, 5.9, C(2)*H*_B), 3.75 (3H, s, *OMe*), 3.76 (3H, s, *OMe*), 4.37 (1H, q, *J* 6.6, C(α)*H*), 4.99 (1H, dd, *J* 9.3, 5.9, C(3)*H*), 6.64-6.69 (4H, m, *Ar*), 6.76-6.81 (4H, m, *Ar*), 7.18-7.27 (5H, m, *Ph*), 7.31-7.36 (5H, m, *Ph*); δ_{C} (100 MHz, CDCl₃) 17.6 (C(α)*Me*), 39.5 (C(2)), 55.4, 55.7 (2 $\times$ *OMe*), 58.3 (C(α)), 60.6 (C(3)), 113.1 (C(3''), C(5'')), 114.4 (C(3'), C(5')), 122.3 (C(2'), C(6')), 126.8, 127.8, 128.0, 128.1, 128.4, 128.8, 130.5 (*Ar*), 137.9 (C(1'')), 140.9 (*i-Ph*), 144.1 (C(1')), 144.7 (*i-Ph*), 156.7 (C(4'')), 157.2 (C(4')), 170.9 (C(1)); *m/z* (ESI⁺) 504 ([M+Na]⁺, 31%), 482 ([M+H]⁺, 100%); HRMS (ESI⁺) C₃₁H₃₂NO₄⁺ ([M+H]⁺) requires 482.2326; found 482.2307.

4'-Methoxyphenyl (*R,R*)-3-[*N*-(4''-bromophenyl)-*N*-(α -methylbenzyl)amino]butanoate **483**



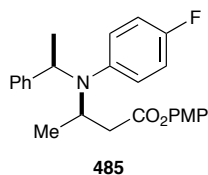
Following *General Procedure 6*, BuLi (2.50 M, 0.07 mL, 0.18 mmol), **465** (50 mg, 0.18 mmol), and **424** (31 mg, 0.16 mmol) in THF (1.5 mL) gave **483** in >99:1 dr. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 19:1; increased to 4:1) gave **483** as a colourless oil (32 mg, 43%, >99:1 dr); [α]_D²⁵ -69.0 (*c* 1.0 in CHCl₃); ν_{max} (ATR) 1753 (C=O); δ_{H} (500 MHz, CDCl₃) 1.30 (3H, d, *J* 6.8, C(4)*H*₃), 1.53 (3H, d, *J* 6.8, C(α)*Me*), 2.57 (1H, dd, *J* 15.4, 8.2, C(2)*H*_A), 2.81 (1H, dd, *J* 15.4, 5.7, C(2)*H*_B), 3.80 (3H, s, *OMe*), 4.24-4.31 (1H, m, C(3)*H*), 4.76 (1H, q, *J* 6.8, C(α)*H*), 6.79-6.83 (2H, m, *Ar*), 6.87-6.90 (2H, m, *Ar*), 6.92-6.95 (2H, m, *Ar*), 7.22-7.38 (7H, m, *Ar*); δ_{C} (125 MHz, CDCl₃) 18.5 (C(4)), 20.0 (C(α)*Me*), 40.3 (C(2)), 50.8 (C(3)), 55.7 (*OMe*), 56.4 (C(α)), 112.9 (C(4'')), 114.6 (C(3'), C(5')), 122.3 (C(2'), C(6')), 123.3, 127.0, 127.1, 128.6, 131.5 (*Ar*), 144.0 (*i-Ar*), 144.1 (C(1')), 145.6 (*i-Ar*), 157.4 (C(4')), 170.9 (C(1)); *m/z* (ESI⁺) 494 ([M+Na]⁺, ⁸¹Br, 26%), 492 ([M+Na]⁺, ⁷⁹Br, 72%), 470 ([M+H]⁺, ⁸¹Br, 100%), 468 ([M+H]⁺, ⁷⁹Br, 95%); HRMS (ESI⁺) C₂₅H₂₇⁸¹BrNO₃⁺ ([M+H]⁺) requires 470.1150; found 470.1145; HRMS (ESI⁺) C₂₅H₂₇⁷⁹BrNO₃⁺ ([M+H]⁺) requires 468.1169; found 468.1156.

4'-Methoxyphenyl (*R,R*)-3-[*N*-(4''-chlorophenyl)-*N*-(α -methylbenzyl)amino]butanoate **484**



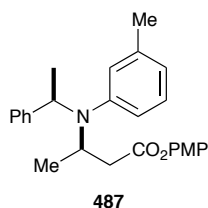
Following *General Procedure 6*, BuLi (2.50 M, 0.21 mL, 0.52 mmol), **466** (120 mg, 0.52 mmol), and **424** (91 mg, 0.47 mmol) in THF (3 mL) gave **484** in >99:1 dr. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 19:1; increased to 4:1) gave **484** as a colourless oil (90 mg, 45%, >99:1 dr); [α]_D²⁵ -82.7 (*c* 1.0 in CHCl₃); ν_{max} (ATR) 1754 (C=O); δ_{H} (400 MHz, CDCl₃) 1.28 (3H, d, *J* 6.8, C(4)*H*₃), 1.51 (3H, d, *J* 6.8, C(α)*Me*), 2.54 (1H, dd, *J* 15.3, 8.1, C(2)*H*_A), 2.81 (1H, dd, *J* 15.3, 5.7, C(2)*H*_B), 3.80 (3H, s, *OMe*), 4.20-4.28 (1H, m, C(3)*H*), 4.73 (1H, q, *J* 6.8, C(α)*H*), 6.87-6.90 (4H, m, *Ar*), 6.92-6.95 (2H, m, *Ar*), 7.15-7.17 (2H, m, *Ar*), 7.23-7.26 (1H, m, *Ph*), 7.30-7.33 (2H, m, *Ph*), 7.36-7.38 (2H, m, *Ph*); δ_{C} (100 MHz, CDCl₃) 18.5 (C(4)), 20.3 (C(α)*Me*), 40.3 (C(2)), 50.9 (C(3)), 55.7 (*OMe*), 56.8 (C(α)), 114.6 (C(3'), C(5')), 122.3 (C(2'), C(6')), 123.7 (*Ar*), 126.0 (C(4')), 127.0, 127.1, 128.5, 128.6 (*Ar*), 142.2 (*i-Ph*), 144.2 C(1'), 145.0 C(1''), 157.4 (C(4')), 170.9 (C(1)); *m/z* (ESI⁺) 448 ([M+Na]⁺, ³⁷Cl, 35%), 446 ([M+Na]⁺, ³⁵Cl, 100%), 424 ([M+H]⁺ ³⁵Cl, 92%); HRMS (ESI⁺) C₂₅H₂₆³⁷ClNNaO₃⁺ ([M+Na]⁺) requires 448.1466; found 448.1475; HRMS (ESI⁺) C₂₅H₂₆³⁵ClNNaO₃⁺ ([M+Na]⁺) requires 446.1493; found 446.1485.

4'-Methoxyphenyl (*R,R*)-3-[*N*-(4''-fluorophenyl)-*N*-(α -methylbenzyl)amino]butanoate **485**



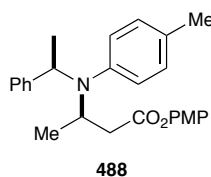
Following *General Procedure 6*, BuLi (2.50 M, 0.38 mL, 0.95 mmol), **467** (204 mg, 0.95 mmol), and **424** (165 mg, 0.86 mmol) in THF (6 mL) gave **485** in >99:1 dr. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 19:1; increased to 4:1) gave **485** as a colourless oil (240 mg, 69%, >99:1 dr); [α]_D²⁵ -51.5 (*c* 1.0 in CHCl₃); ν_{max} (ATR) 1752 (C=O); δ_{H} (400 MHz, CDCl₃) 1.18 (3H, d, *J* 6.7, C(4)*H*₃), 1.39 (3H, d, *J* 6.6, C(α)*Me*), 2.39 (1H, dd, *J* 14.7, 7.9, C(2)*H*_A), 2.82 (1H, dd, *J* 14.7, 6.1, C(2)*H*_B), 3.83 (3H, s, *OMe*), 3.99-4.09 (1H, m, C(3)*H*), 4.59 (1H, q, *J* 6.6, C(α)*H*), 6.89-6.99 (6H, m, *Ar*), 7.01-7.06 (2H, m, *Ar*), 7.20-7.24 (1H, m, *Ar*), 7.27-7.32 (2H, m, *Ar*), 7.36-7.39 (2H, m, *Ar*); δ_{C} (100 MHz, CDCl₃) 18.8 (C(4)), 22.0 (C(α)*Me*), 39.7 (C(2)), 51.5 (C(3)), 55.7 (*OMe*), 58.6 (C(α)), 114.6 (C(3'), C(5')), 114.9 (d, *J* 22.2, C(3''), C(5'')), 122.3 (C(2'), C(6')), 127.0, 127.4, 128.5 (*o*-, *m*-, *p*-*Ph*), 128.3 (d, *J* 7.6, C(2''), C(6'')), 141.9 (d, *J* 2.8, C(1'')), 144.2 (C(1')), 145.1 (*i*-*Ph*), 157.3 (C(4')), 158.9 (d, *J* 242.0, C(4'')), 171.3 (C(1)); *m/z* (ESI⁺) 837 ([2M+Na]⁺, 93%), 430 ([M+Na]⁺, 68%), 408 ([M+H]⁺, 100%); HRMS (ESI⁺) C₂₅H₂₆FNNaO₃⁺ ([M+Na]⁺) requires 430.1789; found 430.1774.

4'-Methoxyphenyl (*R,R*)-3-[*N*-(3''-methylphenyl)-*N*-(α -methylbenzyl)amino]butanoate **487**



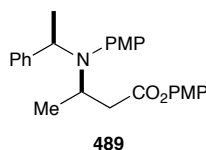
Following *General Procedure 6*, BuLi (2.50 M, 0.38 mL, 0.95 mmol), **469** (200 mg, 0.95 mmol), and **424** (165 mg, 0.86 mmol) in THF (6 mL) gave **487** in >99:1 dr. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 19:1; increased to 4:1) gave **487** as a colourless oil (244 mg, 70%, >99:1 dr); [α]_D²⁵ -36.6 (*c* 1.0 in CHCl₃); ν_{max} (ATR) 1754 (C=O); δ_{H} (400 MHz, CDCl₃) 1.31 (3H, d, *J* 6.8, C(4)*H*₃), 1.51 (3H, d, *J* 6.7, C(α)*Me*), 2.33 (3H, s, *ArMe*), 2.56 (1H, dd, *J* 15.1, 8.8, C(2)*H*_A), 2.86 (1H, dd, *J* 15.1, 5.0, C(2)*H*_B), 3.81 (3H, s, *OMe*), 4.14-4.21 (1H, m, C(3)*H*), 4.78 (1H, q, *J* 6.7, C(α)*H*), 6.76-6.81 (2H, m, *Ar*), 6.83-6.85 (1H, m, *Ar*), 6.88-6.91 (2H, m, *Ar*), 6.93-6.96 (2H, m, *Ar*), 7.13 (1H, t, *J* 7.8, *Ar*); 7.23-7.27 (1H, m, *Ph*), 7.32-7.36 (2H, m, *Ph*), 7.43-7.45 (2H, m, *Ph*); δ_{C} (100 MHz, CDCl₃) 19.0 (C(4)), 20.5 (C(α)*Me*), 21.9 (*ArMe*), 40.1 (C(2)), 50.7 (C(3)), 55.7 (*OMe*), 57.0 (C(α)), 114.5 (C(3'), C(5')), 120.0, 121.9 (*Ar*), 122.3 (C(2'), C(6')), 123.4, 126.8, 127.3, 128.3, 128.5 (*Ar*), 138.2 (C(3'')), 144.2 C(1'), 144.7 C(1''), 146.4 (*i-Ph*), 157.3 (C(4')), 171.2 (C(1)); *m/z* (ESI⁺) 829 ([2M+Na]⁺, 100%), 426 ([M+Na]⁺, 67%), 404 ([M+H]⁺, 54%); HRMS (ESI⁺) C₂₆H₂₉NNaO₃⁺ ([M+Na]⁺) requires 426.2040; found 426.2035.

4'-Methoxyphenyl (*R,R*)-3-[*N*-(4''-methylphenyl)-*N*-(α -methylbenzyl)aminobutanoate **488**



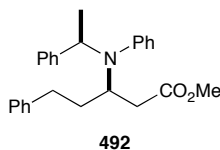
Following *General Procedure 6*, BuLi (2.50 M, 0.38 mL, 0.95 mmol), **470** (200 mg, 0.95 mmol), and **424** (165 mg, 0.86 mmol) in THF (6 mL) gave **488** in >99:1 dr. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 19:1; increased to 4:1) gave **488** as a white solid (279 mg, 81%, >99:1 dr); C₂₆H₂₉NO₃ requires C, 77.4; H, 7.2; N, 3.5%; found C, 77.3; H, 7.3; N, 3.4%; [α]_D²⁵ -57.3 (*c* 1.0 in CHCl₃); mp 83-85 °C; $\nu_{\max}$ (ATR) 1754 (C=O); δ_{H} (400 MHz, CDCl₃) 1.26 (3H, d, *J* 6.7, C(4)*H*₃), 1.46 (3H, d, *J* 6.7, C(α)*Me*), 2.33 (3H, s, *ArMe*), 2.48 (1H, dd, *J* 14.8, 8.5, C(2)*H*_A), 2.89 (1H, dd, *J* 14.8, 5.5, C(2)*H*_B), 3.82 (3H, s, *OMe*), 4.07-4.16 (1H, m, C(3)*H*), 4.71 (1H, q, *J* 6.7, C(α)*H*), 6.90-6.93 (2H, m, *Ar*), 6.97-7.70 (4H, m, *Ar*), 7.09 (2H, d, *J* 8.4, *Ar*), 7.24-7.28 (1H, m, *Ph*), 7.33-7.37 (2H, m, *Ph*), 7.45-7.47 (2H, m, *Ph*); δ_{C} (100 MHz, CDCl₃) 19.0 (C(4)), 20.8 (C(α)*Me*), 21.5 (*ArMe*), 39.7 (C(2)), 51.1 (C(3)), 55.7 (*OMe*), 57.8 (C(α)), 114.5 (C(3'), C(5')), 122.3 (C(2'), C(6')), 125.1, 126.8, 127.3, 128.4, 129.1 (*Ar*), 131.7 (C(4'')), 143.4 (*i-Ph*), 144.2 C(1'), 145.2 C(1''), 157.3 (C(4')), 171.3 (C(1)); *m/z* (ESI⁺) 426 ([M+Na]⁺, 53%), 404 ([M+H]⁺, 90%); HRMS (ESI⁺) C₂₆H₃₀NO₃⁺ ([M+H]⁺) requires 404.2220; found 404.2213.

4'-Methoxyphenyl (*R,R*)-3-[*N*-(4''-methoxyphenyl)-*N*-(α -methylbenzyl)]aminobutanoate **489**

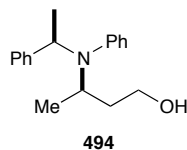


Following *General Procedure 6*, BuLi (2.35 M, 0.41 mL, 0.96 mmol), **471** (216 mg, 0.96 mmol), and **424** (167 mg, 0.87 mmol) in THF (6 mL) gave **489** in >99:1 dr. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 4:1; increased to 1:1) gave **489** as a colourless oil (77 mg, 24%, >99:1 dr); [α]_D²⁵ -42.0 (*c* 1.0 in CHCl₃); ν_{max} (ATR) 1752 (C=O); δ_{H} (400 MHz, CDCl₃) 1.12 (3H, d, *J* 6.7, C(4)*H*₃), 1.31 (3H, d, *J* 6.6, C(α)*Me*), 2.31 (1H, dd, *J* 14.4, 8.1, C(2)*H*_A), 2.84 (1H, dd, *J* 14.4, 5.9, C(2)*H*_B), 3.79 (3H, s, *OMe*), 3.80 (3H, s, *OMe*), 3.87-3.94 (1H, m, C(3)*H*), 4.53 (1H, q, *J* 6.6, C(α)*H*), 6.79-6.82 (2H, m, *Ar*), 6.87-6.91 (2H, m, *Ar*), 6.94-6.98 (2H, m, *Ar*), 7.05-7.07 (2H, m, *Ar*), 7.20-7.23 (1H, m, *Ph*), 7.27-7.31 (2H, m, *Ph*), 7.38-7.41 (2H, m, *Ph*); δ_{C} (100 MHz, CDCl₃) 19.2 (C(4)), 22.8 (C(α)*Me*), 39.2 (C(2)), 51.7 (C(3)), 55.5, 55.7 (2 $\times$ *OMe*), 59.4 (C(α)), 113.5 (C(3''), C(5'')), 114.5 (C(3'), C(5')), 122.4 (C(2'), C(6')), 126.9, 127.5, 128.4, 129.8 (*Ar*), 138.4 (C(1'')), 144.3 (C(1')), 145.8 (*i-Ph*), 156.5 (C(4'')), 157.3 (C(4')), 171.6 (C(1)); *m/z* (ESI⁺) 442 ([M+Na]⁺, 32%), 420 ([M+H]⁺, 100%); HRMS (ESI⁺) C₂₆H₃₀NO₄⁺ ([M+H]⁺) requires 420.2169; found 420.2166.

Methyl (*R,R*)-3-[*N*-phenyl-*N*-(α -methylbenzyl)amino]-5-phenylpentanoate **492**

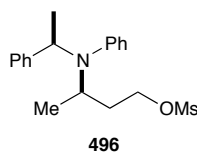


K₂CO₃ (95 mg, 0.69 mmol) was added to a solution of **460** (300 mg, 0.63 mmol) in MeOH (6 mL) at rt and stirred for 2 h. The resulting mixture was partitioned between EtOAc (10 mL) and H₂O (10 mL) and the aqueous layer extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with 10% aq. NaOH (30 mL), dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution 30-40 °C petrol/Et₂O, 19:1; increased to 4:1) gave **492** as a colourless oil (200 mg, 82%); [α]_D²⁵ -15.4 (*c* 1.0 in CHCl₃); $\nu_{\max}$ (ATR) 1735 (C=O); δ_{H} (400 MHz, CDCl₃) 1.47 (d, *J* 6.7, C(α)Me), 1.73 (1H, app ddt, *J* 13.8, 11.1, 5.4, C(4)*H*_A), 1.91 (1H, dddd, *J* 13.8, 11.1, 8.2, 5.4, C(4)*H*_B), 2.36 (1H, dd, *J* 15.2, 8.2, C(2)*H*_A), 2.56 (1H, ddd, *J* 13.7, 11.1, 5.4, C(5)*H*_A), 2.63 (1H, dd, *J* 15.2, 5.4 (C(2)*H*_B), 2.85 (1H, ddd, *J* 13.7, 11.1, 5.4, C(5)*H*_B), 3.59 (3H, s, OMe), 3.93 (1H, app tt, *J* 8.2, 5.4, C(3)*H*), 4.75 (1H, q, *J* 6.7, C(α)*H*), 6.94-7.03 (1H, m, *Ph*), 7.01-7.03 (1H, m, *Ph*), 7.11-7.13 (1H, m, *Ph*), 7.19-7.41 (10H, m, *Ph*); δ_{C} (100 MHz, CDCl₃) 20.8 (C(α)Me), 33.4 (C(5)), 35.6 (C(4)), 38.2 (C(2)), 51.7 (OMe), 55.0 (C(3)), 57.9 (C(α)), 121.3, 123.1, 125.9, 127.0, 127.5, 128.4, 128.5, 128.6 (*o*-, *m*-, *p*-*Ph*), 142.2, 144.3, 146.5 (*i*-*Ph*), 172.9 (C(1)); *m/z* (ESI⁺) 410 ([M+Na]⁺, 100%), 388 ([M+H]⁺, 53%); HRMS (ESI⁺) C₂₆H₃₀NO₂ ([M+H]⁺) requires 388.2271; found 388.2299.

(*R,R*)-3-[*N*-Phenyl-*N*-(α -methylbenzyl)]aminobutanol 494

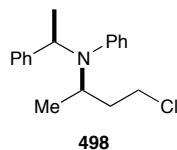
LiAlH₄ (394 mg, 10.4 mmol) was added to a solution of **457** (2.02 g, 5.19 mmol) in THF (30 mL) at 0 °C and stirred at rt for 16 h. The solution was cooled to 0 °C and 10 % NaOH (6 mL) was added dropwise. The mixture was diluted with H₂O (20 mL) and the aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic extracts were washed with brine (60 mL), dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 9:1; increased to 2:1) gave **494** as a colourless oil (1.24 g, 89%); [α]_D²⁵ −78.4 (*c* 1.0 in CHCl₃); ν_{max} (ATR) 3369 (O–H), 2966 (C–H); δ_{H} (400 MHz, CDCl₃) 1.23 (3H, d, *J* 6.8, C(4)*H*₃), 1.58 (3H, d, *J* 6.8, C(α)*Me*), 1.61-1.69 (1H, m, C(2)*H*_A), 1.85 (1H, br s, OH), 1.88-1.96 (1H, m, C(2)*H*_B), 3.50-3.56 (1H, m, C(1)*H*_A), 3.60-3.65 (1H, m, C(1)*H*_B), 3.85-3.77 (1H, m, C(3)*H*), 4.85 (1H, q, *J* 6.8, C(α)*H*), 6.82-6.86 (1H, m, *Ph*), 6.91-6.94 (2H, m, *Ph*), 7.16-7.27 (3H, m, *Ph*), 7.30-7.34 (2H, m, *Ph*), 7.37-7.40 (2H, m, *Ph*); δ_{C} (100 MHz, CDCl₃) 18.4 (*C*(4)), 19.1 (*C*(α)*Me*), 38.1 (*C*(2)), 50.6 (*C*(3)), 56.3 (*C*(α)), 61.3 (*C*(1)), 119.7, 121.0, 126.8, 127.5, 128.4, 128.5 (*o*-, *m*-, *p*-*Ph*), 144.3, 147.0 (*i*-*Ph*); *m/z* (ESI⁺) 292 ([M+Na]⁺, 100%), 270 ([M+H]⁺, 95%); HRMS (ESI⁺) C₁₈H₂₄NO⁺ ([M+H]⁺) requires 270.1852; found 270.1854.

(*R,R*)-*O*-Mesyl-3-[(*N*-phenyl-*N*-(α -methylbenzyl)amino]butanol
496

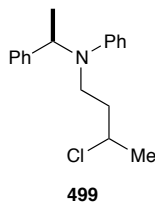


Methanesulfonyl chloride (58 μ L, 0.75 mmol) was added to a solution of **494** (100 mg, 0.37 mmol) and DMAP (3 crystals) in pyridine (2 mL) and stirred at rt for 16 h. H₂O was added (2 mL) and the aqueous extracted with EtOAc (3 $\times$ 2 mL). The combined organic extracts were washed with HCl (6 mL), NaHCO₃ (6 mL) and brine (6 mL), dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 19:1; increased to 1:4) gave **496** as a colourless yellow oil (89 mg, 69%); [α]_D²⁵ -42.3 (*c* 1.0 in CHCl₃); $\nu_{\max}$ (film) 1355 (S=O, st as), 1175 (S=O, st sy); δ_{H} (400 MHz, CDCl₃) 1.26 (3H, d, *J* 6.7, C(4)*H*₃), 1.53 (3H, d, *J* 6.8, C(α)*Me*), 1.75-1.83 (1H, m, C(2)*H*_A), 2.05-2.14 (1H, m, C(2)*H*_B), 2.87 (3H, s, *SMe*), 3.73 (1H, app s, C(3)*H*), 4.10 (2H, app td, *J* 6.6, 1.0, C(1)*H*₂), 4.80 (1H, q, *J* 6.8, C(α)*H*), 6.87-6.95 (3H, m, *Ph*), 7.20-7.28 (3H, m, *Ph*), 7.33-7.37 (2H, m, *Ph*), 7.41-7.43 (2H, m, *Ph*); δ_{C} (100 MHz, CDCl₃) 18.5 (C(4)), 19.7 (C(α)*Me*), 34.7 (C(2)), 37.3 (*SMe*), 49.8 (C(3)), 56.4 (C(α)), 68.1 (C(1)), 120.3, 121.4, 126.9, 127.3, 128.4, 128.6 (*o*-, *m*-, *p*-*Ph*), 144.5, 146.9 (*i*-*Ph*); *m/z* (ESI⁺) 370 ([M+Na]⁺, 100%), 348 ([M+H]⁺, 33%); HRMS (ESI⁺) C₁₉H₂₆NO₃S ([M+H]⁺) requires 348.1628; found 348.1617.

(*R,R*)-1-Chloro-3-[(*N*-phenyl-*N*-(α -methylbenzyl)amino]butane
498



CCl_4 (1.08 mL, 11.15 mmol) was added to a suspension of **494** (300 mg, 1.12 mmol), solid supported PPh_3 (2.50-3.00 mmol/g, 930 mg, 2.79 mmol) and Et_3N (1.56 mL, 11.15 mmol) in MeCN (4 mL) and heated at reflux for 16 h. The mixture was allowed to cool and then filtered through a plug of Celite[®], which was washed with EtOAc (3 $\times$ 5 mL) and the combined organic extracts were concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/ Et_2O , 39:1; increased to 9:1) gave **496** as a pale yellow oil (253 mg, 79%); $[\alpha]_{\text{D}}^{25} -42.7$ (*c* 1.0 in CHCl_3); ν_{max} (ATR) 2976 (C–H); δ_{H} (400 MHz, CDCl_3) 1.24 (3H, d, *J* 6.8, C(4) H_3), 1.54 (3H, d, *J* 6.8, C(α)*Me*), 1.81 (1H, dq, *J* 13.8, 7.0, C(2) H_{A}), 2.12 (1H, dq, *J* 13.8, 7.0, C(2) H_{B}), 3.35-3.48 (2H, m, C(1) H_2), 3.82 (1H, app d, *J* 6.7, C(3)*H*), 4.79 (1H, q, *J* 6.8, C(α)*H*), 6.82-6.91 (3H, m, *Ph*), 7.17-7.41 (7H, m, *Ph*); δ_{C} (100 MHz, CDCl_3) 18.2 (C(4)), 19.7 (C(α)*Me*), 38.4 (C(2)), 43.1 (C(1)), 50.9 (C(3)), 56.1 (C(α)), 119.7, 120.8, 126.8, 127.3, 128.4, 128.6 (*o*-, *m*-, *p*-*Ph*), 144.6, 147.0 (*i*-*Ph*); *m/z* (ESI^+) 290 ($[\text{M}+\text{H}]^+$, ^{37}C , 38%), 288 ($[\text{M}+\text{H}]^+$, ^{35}Cl , 100%); HRMS (ESI^+) $\text{C}_{18}\text{H}_{23}^{37}\text{ClN}$ ($[\text{M}+\text{H}]^+$) requires 290.1485; found 290.1486; HRMS (ESI^+) $\text{C}_{18}\text{H}_{23}^{35}\text{ClN}$ ($[\text{M}+\text{H}]^+$) requires 288.1514; found 288.1512.

(*R*)-*N*-3-Chlorobutyl-*N*-phenyl-*N*-(α -methylbenzyl)amine 499

Method 1: **498** (115 mg, 0.40 mmol) was heated in DMF (1.5 mL) at 120 °C for 16 h. The solution was cooled to rt and sat. aq. NaHCO₃ (2 mL) was added. The aqueous was extracted with EtOAc (3 × 2 mL) and combined organic extracts were washed with H₂O (2 × 6 mL) and brine (6 mL), then dried and concentrated *in vacuo* to give **499** as a pale yellow oil (102 mg, 89%); $\nu_{\max}$ (ATR) 2973 (C–H); δ_{C} (100 MHz, CDCl₃) 17.0, 17.6 (C(α)Me), 22.6, 25.7 (C(4)), 38.4, 38.8 (C(2)), 43.2, 43.6 (C(1)), 56.9, 57.1 (C(3)), 57.7, 58.1 (C(α)), 114.8, 115.1, 117.5, 117.7, 126.8, 127.1, 127.3, 127.4, 128.4, 128.5, 129.4 (*o*-, *m*-, *p*-Ph), 142.6, 142.8, 148.7, 148.8 (*i*-Ph); m/z (ESI⁺) 290 ([M+H]⁺, ³⁷Cl, 43%), 288 ([M+H]⁺, ³⁵Cl, 100%); HRMS (ESI⁺) C₁₈H₂₃³⁷ClN ([M+H]⁺) requires 290.1485, found 290.1477; HRMS (ESI⁺) C₁₈H₂₃³⁵ClN ([M+H]⁺) requires 288.1514, found 288.1506.

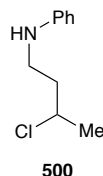
Data for major diastereoisomer; δ_{H} (400 MHz, CDCl₃) 1.42 (3H, d, *J* 6.4, C(4)*H*₃), 1.57 (3H, d, *J* 6.9, C(α)Me), 1.73-1.84 (1H, m, C(2)*H*_A), 1.85-1.94 (1H, m, C(2)*H*_B), 3.12-3.23 (1H, m, C(1)*H*_A), 3.28-3.35 (1H, ddd, *J* 14.6, 9.4, 5.1, C(1)*H*_B), 3.97-4.05 (1H, m, C(3)*H*), 5.06 (1H, q, *J* 6.9, C(α)*H*), 6.74-6.79 (1H, m, *Ph*), 6.85-6.87 (2H, m, *Ph*), 7.23-7.34 (7H, m, *Ph*).

Data for minor diastereoisomer; δ_{H} (400 MHz, CDCl₃) 1.42 (3H, d, *J* 6.4, C(4)*H*₃), 1.59 (3H, d, *J* 6.9, C(α)Me), 1.73-1.84 (1H, m, C(2)*H*_A), 1.85-1.94 (1H, m, C(2)*H*_B), 3.12-3.23 (1H, m, C(1)*H*_A), 3.38-3.45 (1H, ddd, *J* 14.8, 9.8, 5.0, C(1)*H*_B), 3.84-3.92 (1H, m,

C(3)*H*), 5.06 (1H, q, *J* 6.9, C(α)*H*), 6.74-6.79 (1H, m, *Ph*), 6.85-6.87 (2H, m, *Ph*), 7.23-7.34 (7H, m, *Ph*).

Method 2: AlCl₃ (35 mg, 0.26 mmol) was added to a solution of **498** (30 mg, 0.10 mmol) in CH₂Cl₂ (0.5 ml) and stirred for 16 h at rt. Sat. aq. NaHCO₃ (3 mL) was added and the aqueous extracted with CH₂Cl₂ (3 × 3 mL). The combined organic extracts were washed with brine (10 mL), dried and concentrated *in vacuo* to give a 59:41 mixture of **499**: **498** (21 mg, 70%).

N*-3-Chlorobutyl-*N*-phenylamine **500*



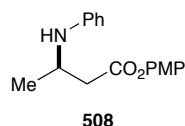
Method 1: A solution of **499** (40 mg, 0.14 mmol) in EtOAc (1 mL) was degassed with N₂ for 10 mins. Pd(OH)₂ (20 mg) was added, and the suspension was put under 5 atm of H₂. After stirring for 1 h the suspension was filtered through a plug of Celite[®], washing with EtOAc (3 × 2 mL), the washings were combined and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 19:1; increased to 4:1) gave **500** as a colourless oil (13 mg, 52%); *v*_{max} (ATR) 3414 (N–H); δ_H (400 MHz, CDCl₃) 1.57 (3H, d, *J* 6.6, C(4)*Me*), 1.95 (1H, dddd, *J* 14.4, 9.3, 7.0, 5.1, C(2)*H*_A), 2.07 (1H, dtd, *J* 14.4, 7.3, 3.9, C(2)*H*_B), 3.31-3.43 (2H, m, C(1)*H*₂), 4.15-4.22 (1H, m, C(3)*H*), 6.63-6.65 (2H, m, *Ph*), 6.71-6.74 (1H, m, *Ph*), 7.18-7.21 (2H, m, *Ph*); δ_C (100 MHz, CDCl₃) 25.7 (*C*(4)), 39.8 (*C*(2)), 41.4 (*C*(1)), 56.5 (*C*(3)), 113.0, 117.7, 129.5 (*o*-, *m*-, *p*-*Ph*), 148.0 (*i*-*Ph*); *m/z* (ESI⁺) 186 ([M+H]⁺,

^{37}Cl , 29%), 184 ($[\text{M}+\text{H}]^+$, ^{35}Cl , 100%); HRMS (ESI^+) $\text{C}_{10}\text{H}_{15}^{37}\text{ClN}$ ($[\text{M}+\text{H}]^+$) requires 186.0858, found 186.0860; HRMS (ESI^+) $\text{C}_{10}\text{H}_{15}^{35}\text{ClN}$ ($[\text{M}+\text{H}]^+$) requires 184.0888, found 184.0887.

Method 2: NaH (60% in mineral oil, 44 mg, 1.10 mmol) was added to a solution of aniline (0.10 ml, 1.10 mmol) in DMF (2 mL) at 0 °C and stirred for 30 min. 1,3-dichlorobutane **501** (0.13 ml, 1.10 mmol) was added and the resulting mixture stirred at 100 °C for 24 h. The solution was cooled to rt and NH_4Cl (2 mL) was added. The aqueous layer was extracted with EtOAc (3×3 mL) and the combined organic extracts were washed with H_2O (2×10 mL) and brine (10 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/ Et_2O , 19:1; increased to 4:1) gave **500** as a colourless oil (77 mg, 38%).

Method 3: **512** (30 mg, 0.16 mmol) was heated in DMF (0.5 mL) at 120 °C for 16 h. The solution was cooled to rt and sat. aq. NaHCO_3 (1 mL) is added. The aqueous was extracted with EtOAc (3×1 mL) and combined organic extracts were washed with H_2O (2×3 mL) and brine (3 mL), then dried and concentrated *in vacuo* to give **500** as a colourless oil (6 mg, 21%).

4'-Methoxyphenyl (*R*)-3-(*N*-phenylamino)butanoate **508**



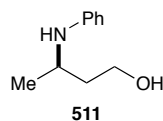
Method 1: A solution of **457** (1.87 g, 4.82 mmol) in EtOAc (20 mL) was degassed with N_2 for 10 mins. Pearlman's catalyst (937 mg) was added and the suspension was put under 1 atm of H_2 . After stirring for 1 h the suspension was filtered through a plug of

Celite[®], washing with EtOAc (3 × 10 mL), the washings were combined and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 19:1; increased to 4:1) gave **508** as a colourless oil (1.26 g, 92%); $[\alpha]_{\text{D}}^{25} +4.8$ (*c* 1.0 in CHCl₃); ν_{max} (film) 1748 (C=O); δ_{H} (400 MHz, CDCl₃) 1.41 (3H, d, *J* 6.4, C(4)*H*₃), 2.70 (1H, dd, *J* 16.0, 6.8, C(2)*H*_A), 2.88 (1H, dd, *J* 16.0, 5.5, C(2)*H*_B), 3.82 (3H, s, *OMe*), 3.87 (1H, br s, *NH*), 4.12 (1H, app sextet, *J* 6.3, C(3)*H*), 6.69-6.72 (2H, m, *Ph*), 6.76-6.80 (1H, m, *Ph*), 6.90-6.93 (2H, m, C(3')*H*, C(5')*H*), 6.97-7.00 (2H, m, C(2')*H*, C(6')*H*), 7.22-7.26 (2H, m, *Ph*); δ_{C} (100 MHz, CDCl₃) 20.8 (C(4)), 41.1 (C(2)), 46.3 (C(3)), 55.7 (*OMe*), 113.8, 118.0, 129.5 (*o*-, *m*-, *p*-*Ph*), 114.5 (C(3'), C(5')), 122.4 (C(2'), C(6')), 144.1 (C(1')), 146.8 (*i*-*Ph*), 157.4 (C(4')), 170.8 (C(1)); *m/z* (ESI⁺) 593 ([2M+Na]⁺, 100%), 308 ([M+Na]⁺, 97%), 286 ([M+H]⁺, 91%); HRMS (ESI⁺) C₁₇H₂₀NO₃⁺ ([M+H]⁺) requires 286.1438; found 286.1434.

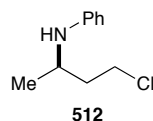
Method 2: A solution of **457** (913 mg, 2.35 mmol) in EtOAc (10 mL) was degassed with N₂ for 10 mins. Pearlman's catalyst (457 mg) was added and the suspension was put under 5 atm of H₂. After stirring for 16 h the suspension was filtered through a plug of Celite[®], washing with EtOAc (3 × 6 mL), the washings were combined and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 19:1; increased to 4:1) gave **508** as a colourless oil (295 mg, 44%); further elution with EtOAc gave **509** as a colourless oil (212 mg, 31%); $[\alpha]_{\text{D}}^{25} -4.6$ (*c* 1.0 in CHCl₃); ν_{max} (ATR) 1753 (C=O); δ_{H} (400 MHz, CDCl₃) 1.04-1.09 (2H, m, *Cy*), 1.17-1.20 (4H, m, C(a)*Me*, *Cy*), 1.23-1.33 (2H, m, *Cy*), 1.59-1.63 (1H, m, *Cy*), 1.71-1.75 (2H, m, *Cy*), 1.86-1.92 (2H, m, *Cy*), 2.53-2.59 (3H, m, C(2)*H*_A, C(1'')*H*), 2.66 (1H, dd, *J* 15.1, 6.5, C(2)*H*_B), 3.38 (1H, app sextet, *J* 6.5, C(3)*H*), 3.80 (3H, s, *OMe*), 6.88-6.90 (2H, m, C(3')*H*, C(5')*H*), 6.99-7.01 (2H, m, C(2')*H*, C(6')*H*); δ_{C} (100

MHz, CDCl₃) 21.2 (*C*(a)Me), 25.1, 25.2, 26.1, 33.7, 34.3 (*C*(2''), *C*(3''), *C*(4''), *C*(5''), *C*(6'')), 42.1 (*C*(2)), 46.8 (*C*(3)), 53.4 (*C*(1'')), 55.6 (*OMe*), 114.4 (*C*(3'), *C*(5')), 122.3 (*C*(2'), *C*(6')), 144.1 (*C*(1')), 157.2 (*C*(4')), 171.3 (*C*(1)); *m/z* (FI) 291 ([M]⁺, 100%); HRMS (FI) C₁₇H₂₅NO₃⁺ ([M]⁺) requires 291.1830; found 291.1834.

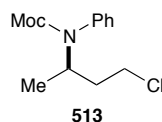
(*R*)-3-(*N*-Phenylamino)butanol **511**



LiAlH₄ (321 mg, 8.45 mmol) was added to a solution of **508** (1.20 g, 4.23 mmol) in THF (20 mL) at 0 °C and stirred at rt for 16 h. The solution was cooled to 0 °C and 10 % NaOH (5 mL) was added dropwise. The mixture was diluted with H₂O (20 mL) and the aqueous layer was extracted with Et₂O (3 × 20 mL). The combined organic extracts were washed with brine (50 mL), dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 9:1; increased to 0:1) gave **511** as a colourless oil (580 mg, 83%); [α]_D²⁵ −76.2 (*c* 1.0 in CHCl₃); ν_{max} (film) 3362 (O–H), 2963 (C–H); δ_H (400 MHz, CDCl₃) 1.22 (3H, d, *J* 6.4, *C*(4)*H*₃), 1.75-1.78 (2H, m, *C*(2)*H*₂), 3.71 (1H, app sextet, *C*(3)*H*), 3.77-3.86 (2H, m, *C*(1)*H*₂), 6.66-6.69 (2H, m, *Ph*), 6.75 (1H, tt, *J* 7.3, 1.1, *Ph*), 7.17-7.22 (2H, m, *Ph*); δ_C (100 MHz, CDCl₃) 21.2 (*C*(4)), 39.4 (*C*(2)), 48.1 (*C*(3)), 61.2 (*C*(1)), 114.2, 118.0, 129.4 (*o*-, *m*-, *p*-*Ph*), 147.4 (*i*-*Ph*); *m/z* (ESI⁺) 188 ([M+Na]⁺, 87%), 166 ([M+H]⁺, 100%); HRMS (ESI⁺) C₁₀H₁₆NO⁺ ([M+H]⁺) requires 166.1226; found 166.1229.

(*R*)-1-Chloro-3-(*N*-phenylamino)butane 512

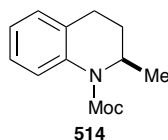
PPh₃ (1.19 g, 4.55 mmol) was added to a solution of **511** (250 mg, 1.52 mmol) in CCl₄ (10 mL) and stirred at reflux for 16 h. H₂O (10 mL) was added, the aqueous layer extracted with CH₂Cl₂ (3 × 10 mL) and the combined organic extracts dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 19:2; increased to 4:1) gave **512** as a pale yellow oil (92 mg, 33%); $[\alpha]_D^{25}$ -45.6 (*c* 1.0 in CHCl₃); $\nu_{\max}$ (film) 2965 (C-H); δ_H (400 MHz, CDCl₃) 1.26 (3H, d, *J* 6.3, C(4)*H*₃), 1.93 (1H, app dq, *J* 13.8, 6.8, C(2)*H*_A), 2.04 (1H, app dq, *J* 13.8, 6.9, C(2)*H*_B), 3.35 (1H, s, NH), 3.62-3.72 (2H, m, C(1)*H*₂), 3.75-3.82 (1H, m, C(3)*H*), 6.66 (2H, d, *J* 8.2, *Ph*), 6.72-6.75 (1H, m, *Ph*), 7.19-7.23 (2H, m, *Ph*); δ_C (100 MHz, CDCl₃) 20.9 (*C*(4)), 40.1 (*C*(2)), 42.2 (*C*(1)), 46.3 (*C*(3)), 113.6, 117.5, 129.5 (*o*-, *m*-, *p*-*Ph*), 147.4 (*i*-*Ph*); *m/z* (ESI⁺) 184 ([M+H]⁺, 100%); HRMS (ESI⁺) C₁₀H₁₅ClN⁺ ([M+H]⁺) requires 184.0888, found 184.0891.

Methyl (*R*)-*N*-(1-chlorobutan-3-yl)-*N*-phenylcarbamate 513

Following *General Procedure 11*, potassium carbonate (274 mg, 1.98 mmol), **512** (60 mg, 0.33 mmol), in methyl chloroformate (0.33 mL) gave **513**. Purification *via* flash

column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 19:1; increased to 3:2) gave **513** as a pale yellow oil (58 mg, 73%); $[\alpha]_{\text{D}}^{25}$ -26.8 (*c* 1.0 in CHCl₃); ν_{max} (film) 2958 (C-H), 1704 (C=O); δ_{H} (400 MHz, CDCl₃) 1.21 (3H, d, *J* 6.9, C(4)*H*₃), 1.83 (1H, dt, *J* 14.3, 7.1, C(2)*H*_A), 2.14-2.23 (1H, m, C(2)*H*_B), 3.56-3.68 (2H, m, C(1)*H*₂), 3.64 (3H, s, OMe), 4.46-4.55 (1H, m, C(3)*H*), 7.11-7.13 (2H, m, *Ph*), 7.31-7.41 (3H, m, *Ph*); δ_{C} (100 MHz, CDCl₃) 19.3 (C(4)), 38.0 (C(2)), 42.1 (C(1)), 52.2 (C(3)), 52.9 (OMe), 127.7, 129.1, 129.4 (*o*-, *m*-, *p*-*Ph*), 139.1 (*i*-*Ph*), 156.3 (C=O); *m/z* (ESI⁺) 507 ([2M+Na]⁺, ³⁷Cl, 95%), 505 ([2M+Na]⁺, ³⁵Cl, 100%), 266 ([M+Na]⁺ ³⁷Cl, 66%), 264 ([M+Na]⁺ ³⁵Cl, 95%), 244 ([M+H]⁺ ³⁷Cl, 17%), 242 ([M+H]⁺ ³⁵Cl, 39%); HRMS (ESI⁺) C₁₂H₁₇³⁷ClNO₂ ([M+H]⁺) requires 244.0914; found 244.0916; HRMS (ESI⁺) C₁₂H₁₇³⁵ClNO₂ ([M+H]⁺) requires 242.0942; found 242.0944.

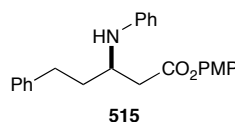
(*R*)-*N*-(Methoxycarbonyl)-2-methyl-1,2,3,4-tetrahydroquinoline **514**



AlCl₃ (42 mg, 0.31 mmol) was added to a stirred solution of **513** (25 mg, 0.1 mmol) in CH₂Cl₂ (0.5 mL) at 0 °C and then stirred for 16 h at rt. Sat. aq. NaHCO₃ (0.5 mL) was added and the aqueous layer extracted with CH₂Cl₂ (3 × 0.5 mL). The combined organic extracts were washed with brine (2 mL), dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 19:1; increased to 1:2) gave **514** as a colourless oil (11 mg, 54%); $[\alpha]_{\text{D}}^{25}$ -34.0 (*c* 1.0 in CHCl₃); ν_{max} (film) 2955 (C-H), 1700 (C=O); δ_{H} (400 MHz, CDCl₃) 1.18 (3H, d, *J* 6.5, C(2)*Me*), 1.53 (1H, dddd, *J* 13.4, 8.0, 6.8, 5.5, C(3)*H*_A), 2.21-2.28 (1H, m, C(3)*H*_B),

2.61-2.73 (2H, m, C(4) H_2), 3.78 (3H, s, OMe), 4.62 (1H, app sextet, J 6.6, C(2) H), 7.04 (1H, td, J 7.4, 1.2, C(6) H), 7.10 (1H, dd, J 7.4, 1.2, C(5) H), 7.18 (1H, td, J 7.7, 1.2, C(7) H), 7.52 (1H, d, J 8.1, C(8) H); δ_C (100 MHz, CDCl₃) 19.6 (C(2)Me), 23.6 (C(4)), 31.3 (C(3)), 49.8 (C(2)), 52.9 (OMe), 124.2 (C(6)), 125.6 (C(8)), 126.2 (C(7)), 127.9 (C(5)), 132.1 (C(4A)), 136.7 (C(8A)), 155.4 (C=O); m/z (ESI⁺) 433 ([₂M+Na]⁺, 100%), 228 ([M+Na]⁺, 91%), 206 ([M+H]⁺, 38%); HRMS (ESI⁺) C₁₂H₁₆NO₂⁺ ([M+H]⁺) requires 206.1176; found 206.1180.

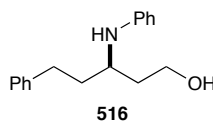
4-Methoxyphenyl (*R*)-(3-anilido-5-phenyl)pentanoate **515**



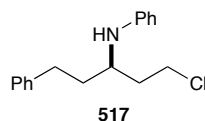
A solution of **460** (2.00 g, 4.18 mmol) in EtOAc (20 mL) was degassed with N₂ for 10 mins. Pearlman's catalyst (1.00 g) was added and the suspension was put under 1 atm of H₂. After stirring for 4 h the suspension was filtered through a plug of Celite[®], washing with EtOAc (3 × 10 mL), the washings were combined and washed with citric acid (20 mL), dried and concentrated *in vacuo* to give **515** as a colourless oil (1.35 g, 86%). Purification of an analytical sample *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 5:1; increased to 1:2) gave **515** as a colourless oil; $[\alpha]_D^{25} +21.0$ (c 1.0 in CHCl₃); $\nu_{\max}$ (ATR) 1748 (C=O); δ_H (400 MHz, CDCl₃) 1.98-2.12 (2H, m, C(4) H_2), 2.77-2.92 (4H, m, C(2) H_2 , C(5) H_2), 3.82 (3H, s, OMe), 3.86 (1H, br s, NH), 3.99 (1H, br s, C(3) H), 6.68 (2H, d, J 8.5, *Ar*), 6.78 (1H, td, J 7.3, 0.6, *Ar*), 6.87-6.93 (4H, m, *Ar*), 7.21-7.27 (5H, m, *Ar*), 7.32-7.36 (2H, m, *Ar*); δ_C (100 MHz, CDCl₃) 32.6 (C(5)), 36.9 (C(4)), 39.4 (C(2)), 50.1 (C(3)), 55.7 (OMe), 113.8 (*o*-, *m*-,

p-Ph), 114.5 (*C*(3'), *C*(5')), 117.9 (*o*-, *m*-, *p*-Ph), 122.4 (*C*(2'), *C*(6')), 126.1, 128.6, 129.6 (*o*-, *m*-, *p*-Ph), 141.5 (*i*-Ph), 144.0 (*C*(1')), 147.1 (*i*-Ph), 157.4 (*C*(4')), 170.8 (*C*(1)); *m/z* (ESI⁺) 773 ([2M+Na]⁺, 89%), 398 ([M+Na]⁺, 86%), 376 ([M+H]⁺, 100%); HRMS (ESI⁺) C₂₄H₂₅NNaO₃⁺ ([M+Na]⁺) requires 398.1727; found 398.1718.

(*R*)-(3-Anilido-5-phenyl)pentan-1-ol **516**

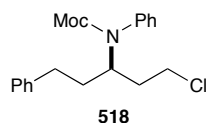


LiAlH₄ powder (120 mg, 3.15 mmol) was added to a solution of **515** (590 mg, 1.57 mmol) in THF (10 mL) at 0 °C and stirred at rt for 16 h. The solution was cooled to 0 °C and 10% NaOH (3 mL) was added dropwise. The mixture was diluted with H₂O (15 mL) and the aqueous layer was extracted with Et₂O (3 × 15 mL). The combined organic extracts were washed with brine (35 mL), dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 3:1; increased to 1:1) gave **516** as a colourless oil (324 mg, 81%); [α]_D²⁵ −44.0 (*c* 1.0 in CHCl₃); ν_{max} (ATR) 3393 (O–H), 2939 (C–H), 1601 (C=O); δ_H (400 MHz, CDCl₃) 1.69-1.77 (1H, m, C(2)*H*_A), 1.85-1.97 (3H, m, C(2)*H*_B, C(4)*H*₂), 2.23 (1H, br s, OH), 2.72 (2H, dd, *J* 8.9, 6.9, C(5)*H*₂), 3.51 (1H, br s, NH), 3.58-3.65 (1H, m, C(3)*H*), 3.82 (2H, dd, *J* 6.4, 5.3, C(1)*H*₂), 6.59-6.62 (2H, m, *Ph*), 6.71-6.75 (1H, m, *Ph*), 7.15-7.23 (5H, m, *Ph*), 7.27-7.31 (2H, m, *Ph*); δ_C (100 MHz, CDCl₃) 32.4 (*C*(5)), 37.2, 37.4 (*C*(2), *C*(4)), 51.7 (*C*(3)), 61.1 (*C*(1)), 113.9, 117.9, 126.0, 128.5, 129.5 (*o*-, *m*-, *p*-Ph), 141.9, 147.7 (*i*-Ph); *m/z* (ESI⁺) 533 ([2M+Na]⁺, 39%), 278 ([M+Na]⁺, 92), 256 ([M+H]⁺, 100%); HRMS (ESI⁺) C₁₇H₂₂NO⁺ ([M+H]⁺) requires 256.1696; found 256.1698.

(*R*)-1-Chloro-3-anilido-5-phenyl pentane 517

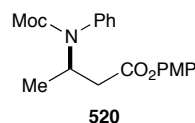
Solid supported PPh₃ (1.63 g, 2.28 mmol) was added to a solution of **516** (280 mg, 1.14 mmol) in CCl₄ (10 mL) and stirred at 50 °C for 16 h. The resulting suspension was filtered through a plug of Celite[®], which was washed with CH₂Cl₂ (3 × 10 mL) and the combined organic extracts concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 19:1; increased to 4:1) gave **517** as a colourless oil (260 mg, 84%); $[\alpha]_D^{25}$ -30.3 (*c* 1.0 in CHCl₃); $\nu_{\max}$ (ATR) 2941 (C-H); δ_H (400 MHz, CDCl₃) 1.81-2.01 (3H, m, C(2)*H*_A, C(4)*H*₂), 2.09 (1H, dtd, *J* 14.4, 7.2, 4.7, C(2)*H*_B), 2.69-2.82 (1H, m, C(5)*H*₂), 3.37 (1H, br s, NH), 3.64-3.72 (3H, m, C(1)*H*₂, C(3)*H*), 6.59-6.62 (2H, m, *Ph*), 6.71-6.75 (1H, m, *Ph*), 7.17-7.25 (5H, m, *Ph*), 7.30-7.33 (2H, m, *Ph*); δ_C (100 MHz, CDCl₃) 32.4 (*C*(5)), 37.2 (*C*(4)), 38.6 (*C*(2)), 42.2 (*C*(1)), 50.3 (*C*(3)), 113.3, 117.5, 126.1, 128.5, 128.6, 129.5 (*o*-, *m*-, *p*-*Ph*), 141.7, 147.7 (*i*-*Ph*); *m/z* (ESI⁺) 276 ([M+H]⁺, ³⁷Cl, 62%), 274 ([M+H]⁺, ³⁵Cl, 100%); HRMS (ESI⁺) C₁₇H₂₁³⁷ClN⁺ ([M+H]⁺) requires 276.1328; found 276.1344; HRMS (ESI⁺) C₁₇H₂₁³⁵ClN⁺ ([M+H]⁺) requires 274.1357; found 274.1359.

Methyl (R)-N-(1-chloro-5-phenylpentan-3-yl)-N-phenylcarbamate **518**

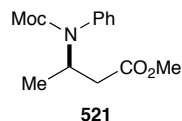


Following *General Procedure 11*, potassium carbonate (301 mg, 2.20 mmol), **517** (119 mg, 0.44 mmol), in methyl chloroformate (0.5 mL) gave **518**. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 9:1; increased to 1:1) gave **518** as a colourless oil (83 mg, 69%); $[\alpha]_{\text{D}}^{25} +5.0$ (c 1.0 in CHCl₃); ν_{max} (ATR) 1702 (C=O); δ_{H} (400 MHz, CDCl₃) 1.73-1.82 (1H, m, C(4)*H*_A), 1.90-2.00 (2H, m, C(2)*H*_A, C(4)*H*_B), 2.12-2.21 (1H, m, C(2)*H*_B), 2.68-2.85 (2H, m, C(5)*H*₂), 3.64-3.68 (5H, m, C(1)*H*₂, OMe), 4.45 (1H, tt, J 9.3, 4.9, C(3)*H*), 7.15-7.22 (5H, m, *Ph*), 7.27-7.36 (3H, m, *Ph*), 7.38-7.43 (2H, m, *Ph*); δ_{C} (100 MHz, CDCl₃) 33.2 (C(5)), 35.4 (C(4)), 36.6 (C(2)), 42.0 (C(1)), 53.1 (OMe), 56.9 (C(3)), 126.2, 127.7, 128.4, 128.6, 129.1, 129.2 (*o*-, *m*-, *p*-*Ph*), 139.3, 141.6 (*i*-*Ph*), 156.7 (C=O); m/z (ESI⁺) 356 ([M+Na]⁺ ³⁷Cl, 37%), 354 ([M+Na]⁺, ³⁵Cl, 94%), 334 ([M+H]⁺ ³⁷Cl, 40%), 332 ([M+H]⁺ ³⁵Cl, 100%); HRMS (ESI⁺) C₁₉H₂₃³⁷ClNO₂ ([M+H]⁺) requires 334.1384; found 334.1378; HRMS (ESI⁺) C₁₉H₂₃³⁵ClNO₂ ([M+H]⁺) requires 332.1412; found 332.1404.

4-Methoxyphenyl (*R*)-3-[*N*-methoxycarbonyl-*N*-phenylamino]butanoate **520**

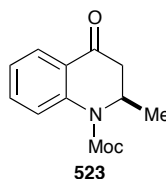


Method 1: Following *General Procedure 11*, potassium carbonate (822 mg, 5.95 mmol), **508** (338 mg, 1.19 mmol), in methyl chloroformate (1.2 mL) gave **520**. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 4:1; increased to 1:1) gave **520** as a colourless oil (343 mg, 84%); $[\alpha]_{\text{D}}^{25}$ -35.0 (c 1.0 in CHCl₃); ν_{max} (film) 2957 (C–H), 1754 (C=O, ester), 1704 (C=O, carbamate); δ_{H} (400 MHz, CDCl₃) 1.31 (3H, d, J 6.9, C(4) H_3), 2.62 (1H, dd, J 15.1, 6.4, C(2) H_A), 2.90 (1H, dd, J 15.1, 8.4, C(2) H_B), 3.65 (3H, s, C=O(OMe)), 3.80 (3H, s, ArOMe), 4.98 (1H, app d, J 7.3, C(3) H), 6.88-6.92 (2H, m, *Ar*), 7.01-7.04 (2H, m, *Ar*), 7.21-7.23 (2H, m, *Ph*), 7.33-7.43 (3H, m, *Ph*); δ_{C} (100 MHz, CDCl₃) 19.8 (*C*(4)), 40.1 (*C*(2)), 51.3 (*C*(3)), 52.9 (C=O(OMe)), 55.7 (ArOMe), 114.5 (*C*(3'), *C*(5')), 122.3 (*C*(2'), *C*(6')), 127.8, 129.1, 129.7 (*o*-, *m*-, *p*-*Ph*), 138.7 (*i*-*Ph*), 144.1 (*C*(1')), 156.1 ((*C*=O)OMe), 157.4 (*C*(4')), 170.2 (*C*(1)); m/z (ESI⁺) 366 ([M+Na]⁺, 100%), 344 ([M+H]⁺, 43%); HRMS (ESI⁺) C₁₉H₂₂NO₅⁺ ([M+H]⁺) requires 344.1492; found 344.1492.

Methyl (*R*)-3-[*N*-methoxycarbonyl-*N*-phenylamino]butanoate **521**

Thionyl chloride (50 μ L, 0.69 mmol) was added to a solution of **520** (50 mg, 0.15 mmol) in MeOH (2 mL) and heated to reflux for 2 h. On cooling the solution was concentrated *in vacuo* and the residue was partitioned between CH₂Cl₂ (2 mL) and sat. aq. NaHCO₃ (2 mL) and the aqueous layer was extracted with CH₂Cl₂ (3 $\times$ 2 mL). The combined organic extracts were washed with brine (6 mL), dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 30-40 $^{\circ}$ C petrol/Et₂O, 3:1; increased to 1:3) gave **521** as a colourless oil (31 mg, 85%); $[\alpha]_{\text{D}}^{25}$ -21.7 (c 1.0 in CHCl₃); ν_{max} (film) 2956 (C–H), 1704 (C=O); δ_{H} (400 MHz, CDCl₃) 1.22 (3H, d, J 7.0, C(4) H_3), 2.39 (1H, dd, J 15.2, 7.0, C(2) H_A), 2.68 (1H, dd, J 15.2, 7.8, C(2) H_B), 3.63 (3H, s, OMe), 3.69 (3H, s, OMe), 4.78 (1H, app sextet, J 7.0, C(3) H), 7.13-7.15 (2H, m, *Ph*), 7.30-7.40 (3H, m, *Ph*); δ_{C} (100 MHz, CDCl₃) 19.7 (C(4)), 40.0 (C(2)), 51.4 (C(3)), 51.9 (OMe), 52.9 (OMe), 127.8, 129.1, 129.6 (*o*-, *m*-, *p*-*Ph*), 138.9 (*i*-*Ph*), 156.0 ((C=O)OMe), 171.8 (C(1)); m/z (ESI⁺) 525 ([2M+Na]⁺, 100%), 274 ([M+Na]⁺, 94%), 252 ([M+H]⁺, 38%); HRMS (ESI⁺) C₁₃H₁₇NNaO₄ ([M+Na]⁺) requires 274.1050; found 274.1047.

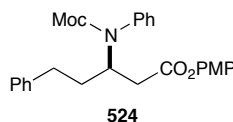
(*R*)-*N*-(Methoxycarbonyl)-2-methyl-1,2-dihydroquinolin-4(1*H*)-one
523



LiOH (44 mg, 1.85 mmol) was added to a stirred solution of **521** (93 mg, 0.37 mmol) in a mixture of THF (2 mL) and H₂O (2 mL). The resultant solution was stirred at 40 °C for 3 h, then allowed to cool and 1 M aq. HCl (2 mL) was added. The aqueous layer was extracted with EtOAc (3 × 2 mL), and the combined organic extracts were dried and concentrated *in vacuo* to afford the crude product as a colourless oil (87 mg). The crude product was dissolved in CH₂Cl₂ (2 mL), DMF (1 drop) and (COCl)₂ (47 µL, 0.56 mmol) were added and the mixture stirred at rt for 2 h. The solution was concentrated *in vacuo*, and the residue dissolved in CH₂Cl₂ (2 mL). The solution was cooled to 0 °C, and AlCl₃ (158 mg, 1.18 mmol) was added, then the reaction was stirred for 16 h at rt. Sat. aq. NaHCO₃ (2 mL) was added and the aqueous layer extracted with CH₂Cl₂ (3 × 2 mL). The combined organic extracts were washed with brine (6 mL), dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 4:1; increased to 1:1) gave **523** as a colourless oil (55 mg, 69%); $[\alpha]_D^{25}$ -143.9 (*c* 1.0 in CHCl₃); $\nu_{\max}$ (ATR) 2960 (C-H), 1712 (C=O, carbamate), 1687 (C=O, quinoline); δ_H (400 MHz, CDCl₃) 1.22 (3H, d, *J* 7.0, C(2)*Me*), 2.56 (1H, dd, *J* 17.3, 1.8, C(3)*H_A*), 3.04 (1H, dd, *J* 17.3, 5.9, C(3)*H_B*), 3.85 (3H, s, *OMe*), 5.10-5.17 (1H, m, C(2)*H*), 7.13-7.17 (1H, m, C(6)*H*), 7.51 (1H, ddd, *J* 8.5, 7.1, 1.7, C(7)*H*), 7.79 (1H, d, *J* 8.5, C(8)*H*), 7.98 (1H, dd, *J* 7.8, 1.7, C(5)*H*); δ_C (100 MHz, CDCl₃) 17.9 (C(2)*Me*), 44.4 (C(3)), 50.0 (C(2)), 53.4 (*OMe*), 124.0 (C(6)), 124.3 (C(8)), 124.4 (C(4A)), 126.9 (C(5)), 134.6 (C(7)), 141.1 (C(8A)),

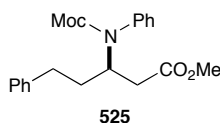
154.4 ($C=O(OMe)$), 193.4 ($C(4)$); m/z (ESI^+) 461 ($[2M+Na]^+$, 100%), 242 ($[M+Na]^+$, 97%), 220 ($[M+H]^+$, 14%); HRMS (ESI^+) $C_{12}H_{14}NO_3^+$ ($[M+H]^+$) requires 220.0968; found 220.0970.

4-Methoxyphenyl (*R*)-3-[*N*-methoxycarbonyl-*N*-phenylamino]-5-phenylpentanoate **524**



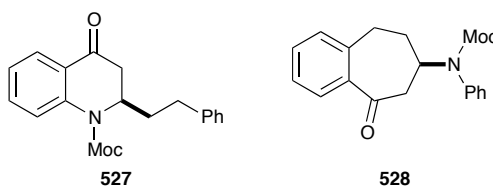
Following *General Procedure 11*, potassium carbonate (2.37 g, 17.1 mmol) and **515** (1.29 g, 3.43 mmol) in methyl chloroformate (3.5 mL) gave **524** as a colourless oil (1.41 g, 96%). Purification of an analytical sample of *via* flash column chromatography (gradient elution, 30-40 °C petrol/ Et_2O , 4:1; increased to 1:1) gave **524** as a colourless oil; $[\alpha]_D^{25} +1.3$ (c 1.0 in $CHCl_3$); ν_{max} (ATR) 1754 ($C=O$, ester), 1702 ($C=O$, carbamate); δ_H (400 MHz, $CDCl_3$) 1.84-1.93 (1H, m, $C(4)H_A$), 2.06 (1H, dddd, J 14.1, 10.4, 8.9, 5.5, $C(4)H_B$), 2.71-2.93 (4H, m, $C(2)H_2$, $C(5)H_2$), 3.70 (3H, s, $C=O(OMe)$), 3.81 (3H, s, $ArOMe$), 4.95 (1H, tt, J 8.9, 5.5, $C(3)H$), 6.93-6.89 (2H, m, Ar), 6.99-7.03 (2H, m, Ar), 7.21-7.45 (10H, m, Ph); δ_C (100 MHz, $CDCl_3$) 33.1 ($C(5)$), 35.6 ($C(4)$), 38.8 ($C(2)$), 53.1 ($C=O(OMe)$), 55.7, 55.8 ($ArOMe$, $C(3)$), 114.5 ($C(3')$, $C(5')$), 122.3 ($C(2')$, $C(6')$), 126.2, 127.8, 128.4, 128.6, 129.2, 129.4 (o -, m -, p - Ph), 138.9, 141.3 (i - Ph), 144.1 ($C(1')$), 156.5 ($(C=O)OMe$), 157.4 ($C(4')$), 170.3 ($C(1)$); m/z (ESI^+) 889 ($[2M+Na]^+$, 100%), 456 ($[M+Na]^+$, 99%), 434 ($[M+H]^+$, 14%); HRMS (ESI^+) $C_{26}H_{27}NNaO_5^+$ ($[M+Na]^+$) requires 456.1781; found 456.1778.

Methyl (*R*)-3-[*N*-methoxycarbonyl-*N*-phenylamino]-5-phenylpentanoate **525**



Thionyl chloride (1.2 mL, 16.4 mmol) was added to a solution of **524** (1.33 g, 3.07 mmol) in MeOH (30 mL) and heated at reflux for 2 h. On cooling the solution was concentrated *in vacuo* and the residue was partitioned between CH₂Cl₂ (20 mL) and sat. aq. NaHCO₃ (20 mL) and the aqueous layer was extracted with CH₂Cl₂ (3 × 20 mL). The combined organic extracts were washed with brine (6 mL), dried and concentrated *in vacuo* to give **525** as a colourless oil (974 mg, 97%). Purification of an analytical sample *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 4:1; increased to 1:1) gave **525** as a colourless oil; C₂₀H₂₃NO₄ requires C, 70.4; H, 6.8; N, 4.1%; found C, 70.2; H, 6.65; N, 4.1%; [α]_D²⁵ +9.1 (*c* 1.0 in CHCl₃); ν_{max} (ATR) 1735 (C=O, ester), 1703 (C=O, carbamate); δ_H (400 MHz, CDCl₃) 1.75-1.84 (1H, m, C(4)*H*_A), 1.93-2.02 (1H, m, C(4)*H*_B), 2.51 (1H, dd, *J* 15.5, 6.2, C(2)*H*_A), 2.64-2.76 (2H, m, C(2)*H*_B, C(5)*H*_A), 2.80-2.87 (1H, m, C(5)*H*_B), 3.68 (3H, s, OMe), 3.69 (3H, s, OMe), 4.76 (1H, tt, *J* 8.6, 5.8, C(3)*H*), 7.17-7.22 (5H, m, *Ph*), 7.27-7.42 (5H, m, *Ph*); δ_C (100 MHz, CDCl₃) 33.1 (*C*(5)), 35.4 (*C*(4)), 38.6 (*C*(2)), 51.9, 53.0 (OMe), 55.9 (*C*(3)), 126.1, 127.7, 128.4, 128.6, 129.2, 129.3 (*o*-, *m*-, *p*-*Ph*), 139.1, 141.4 (*i*-*Ph*), 156.4 ((*C*=O)OMe), 171.8 (*C*(1)); *m/z* (ESI⁺) 705 ([2M+Na]⁺, 100%), 364 ([M+Na]⁺, 95%), 342 ([M+H]⁺, 32%); HRMS (ESI⁺) C₂₀H₂₄NO₄⁺ ([M+H]⁺) requires 342.1700; found 342.1695.

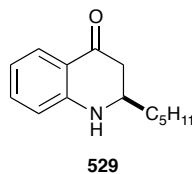
(*R*)-*N*-(Methoxycarbonyl)-2-(2'-phenylethyl)-1,2-dihydroquinolone 527 and (*R*)-3-(*N*-methoxycarbonyl-*N*-phenylamino)benzosuber-1-one 528



LiOH (18 mg, 0.73 mmol) was added to a stirred solution of **525** (52 mg, 0.15 mmol) in THF/H₂O (1 mL/1 mL). The resultant solution was stirred at 40 °C for 3 h, then allowed to cool and 1 M aq. HCl (1 mL) was added. The aqueous layer was extracted with EtOAc (3 × 2 mL), and the combined organic extracts were dried and concentrated *in vacuo* to afford the crude product as a colourless oil (48 mg). The crude product was dissolved in CH₂Cl₂ (1 mL), DMF (1 drop) and (COCl)₂ (19 µL, 0.23 mmol) were added and the mixture stirred at rt for 2 h. The solution was concentrated *in vacuo*, and the residue dissolved in CH₂Cl₂ (1 mL). The solution was cooled to 0 °C, and AlCl₃ (64 mg, 0.48 mmol) was added, then the reaction was stirred for 16 h at rt. Sat. aq. NaHCO₃ (2 mL) was added and the aqueous layer extracted with CH₂Cl₂ (3 × 2 mL). The combined organic extracts were washed with brine (5 mL), dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 4:1; increased to 1:1) gave **527** as a colourless oil (7 mg, 15%); $[\alpha]_{\text{D}}^{25}$ -93.2 (*c* 0.5 in CHCl₃); ν_{max} (ATR) 1711 (C=O, carbamate), 1688 (C=O, quinoline); δ_{H} (500 MHz, CDCl₃) 1.76-1.83 (1H, m, C(1')H_A), 1.95 (1H, dtd, *J* 14.0, 9.8, 5.6, C(1')H_B), 2.60-2.68 (3H, m, C(3)H_A, C(2')H₂), 3.07 (1H, dd, *J* 17.6, 5.8, C(3)H_B), 3.85 (3H, s, OMe), 5.01-5.05 (1H, m, C(2)H), 7.05-7.07 (1H, m, C(6)H), 7.16-7.25 (5H, m, *Ph*), 7.53 (1H, ddd, *J* 8.5, 7.4, 1.7, C(7)H), 7.70 (1H, d, *J* 7.4, C(8)H), 7.99 (1H, dd, *J* 7.8, 1.7, C(5)H); δ_{C} (125 MHz, CDCl₃) 32.7 (C(2')), 33.2

(*C*(1')), 43.5 (*C*(3)), 53.5 (*OMe*), 53.9 (*C*(2)), 124.5, 125.0, 125.1, 126.2, 127.0, 128.4, 128.5 (*C*(4A), *C*(5), *C*(6), *C*(8), *o*-, *m*-, *p*-*Ph*) 134.6 (*C*(7)), 140.9 (*C*(8A)), 140.9 (*i*-*Ph*) 154.9 (*C*=*O*(*OMe*)), 193.4 (*C*(4)); *m/z* (ESI⁺) 332 ([*M*+*Na*]⁺, 100%), 310 ([*M*+*H*]⁺, 27%); HRMS (ESI⁺) C₁₉H₂₀NO₃⁺ ([*M*+*H*]⁺) requires 310.1438; found 310.1438; further elution gave **528** as a colourless oil (20 mg, 43%); [α]_D²⁵ -32.8 (*c* 1.0 in CHCl₃); $\nu_{\max}$ (ATR) 1730 (*C*=*O*, carbamate), 1677 (*C*=*O*); δ_{H} (500 MHz, CDCl₃) 2.06-2.13 (1H, m, *C*(4)*H*_A), 2.18-2.25 (1H, m, *C*(4)*H*_B), 2.80-2.85 (1H, m, *C*(5)*H*_A), 2.90-2.96 (1H, m, *C*(5)*H*_B), 3.06 (1H, ddd, *J* 16.0, 3.1, 0.4, *C*(2)*H*_A), 3.17 (1H, dd, *J* 16.0, 11.0, *C*(2)*H*_B), 3.63 (3H, s, *OMe*), 4.50-4.56 (1H, m, *C*(3)*H*), 7.12-7.16 (3H, m, *Ar*), 7.27-7.42 (5H, m, *Ph*), 7.69 (1H, dd, *J* 7.7, 1.4, *Ar*); δ_{C} (125 MHz, CDCl₃) 30.6 (*C*(4)), 31.1 (*C*(5)), 48.0 (*C*(2)), 53.0 (*OMe*), 53.9 (*C*(3)), 127.2, 127.9, 128.8, 129.3, 129.4, 129.8, 132.7 (*Ar*), 138.1, 139.6, 140.3 (*i*-*Ar*), 155.9 (*C*=*O*(*OMe*)), 202.3 (*C*(1)); *m/z* (ESI⁺) 332 ([*M*+*Na*]⁺, 100%), 310 ([*M*+*H*]⁺, 33%); HRMS (ESI⁺) C₁₉H₂₀NO₃⁺ ([*M*+*H*]⁺) requires 310.1438; found 310.1433.

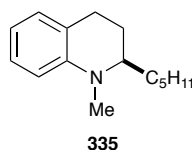
(*R*)-2-Pentyl-2,3-dihydroquinolin-4(1*H*)-one **529**



LiOH (439 mg, 19.1 mmol) was added to a solution of **458** (1.70 g, 3.82 mmol) in THF/H₂O (60 mL/60mL) and the resultant solution was heated at 40 °C for 3 h. The mixture was allowed to cool to rt, acidified to pH 1 with 1 M aq. HCl, and then extracted with EtOAc (3 × 80 mL). The combined organic extracts were dried and concentrated *in vacuo*. PPA (15 mL) was added to the residue and the resultant mixture was heated at 100 °C for 16 h. The mixture was allowed to cool to rt, basified

to pH 14 with 10% aq. NaOH, and the aqueous layer was extracted with EtOAc (3×150 mL). The combined organic extracts were washed with brine, dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/Et₂O, 9:1; increased to 2:1) gave **529** as a yellow oil (497 mg, 60%); $[\alpha]_{\text{D}}^{25} +144$ (c 1.0 in CHCl₃); ν_{max} (film) 3341 (N–H), 2929 (C–H), 1653 (C=O); δ_{H} (400 MHz, CDCl₃) 0.91 (3H, t, J 7.0, C(5')H₃), 1.29-1.44 (6H, m, C(2')H₂, C(3')H₂, C(4')H₂), 1.56-1.68 (2H, m, C(1')H₂), 2.48 (1H, dd, J 16.1, 12.7, C(3)H_A), 2.68 (1H, dd, J 16.1, 3.7, C(3)H_B), 3.63 (1H, app dtd, J 12.7, 6.4, 3.7, C(2)H), 4.37 (1H, br s, NH), 6.67 (1H, app dt, J 8.3, 0.7, C(8)H), 6.73 (1H, ddd, J 7.9, 7.1, 0.7, C(6)H), 7.30 (1H, ddd, J 8.3, 7.1, 1.6, C(7)H), 7.82 (1H, dd, J 7.9, 1.6, C(5)H); δ_{C} (100 MHz, CDCl₃) 14.1 (C(5')), 22.7, 25.1, 31.8 (C(2'), C(3'), C(4')), 35.3 (C(1')), 44.1 (C(3)), 53.5 (C(2)), 115.9 (C(8)), 118.0 (C(6)), 119.2 (C(4A)), 127.6 (C(5)), 135.3 (C(7)), 151.6 (C(8A)), 194.3 (C(4)); m/z (ESI⁺) 240 ([M+Na]⁺, 100%), 218 ([M+H]⁺, 52%); HRMS (ESI⁺) C₁₄H₁₉NNaO⁺ ([M+Na]⁺) requires 240.1359; found 240.1360.

(*R*)-*N*(1)-Methyl-2-pentyl-1,2,3,4-tetrahydroquinoline [(*R*)-(-)-angustureine] 335³⁶



LiAlH₄ (98 mg, 2.44 mmol) was added to a solution of **529** (212 mg, 0.98 mmol) in THF (4 mL) and the resultant mixture was heated at reflux for 16 h. The mixture was allowed to cool to rt, ice was added, followed by 1 M aq. NaOH (3 mL), and the aqueous layer was extracted with Et₂O (3×5 mL). The combined organic extracts were dried and concentrated *in vacuo*. The residue was dissolved in THF (5 mL), then

MeI (0.31 mL, 4.91 mmol) and K_2CO_3 (113 mg, 0.82 mmol) were added sequentially. The resultant mixture was heated at reflux for 16 h. The mixture was allowed to cool to rt, H_2O was added (5 mL), and the aqueous layer was extracted with Et_2O (3×5 mL). The combined organic extracts were washed with brine (10 mL), dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 30-40 °C petrol/ Et_2O , 9:1; increased to 2:1) gave **335** as a colourless oil (151 mg, 71%); $[\alpha]_D^{25} -7.0$ (*c* 1.0 in $CHCl_3$); {lit.³⁶ for sample isolated from natural source $[\alpha]_D -7.2$; lit.³⁷ $[\alpha]_D^{15} -6.7$ (*c* 1.0 in $CHCl_3$) for 94% ee; lit.³⁸ $[\alpha]_D^8 -5.5$ (*c* 1.1 in $CHCl_3$) for 89% ee; lit.³⁹ $[\alpha]_D^{25} -6.9$ (*c* 1.0 in $CHCl_3$) for 90% ee; lit.⁴⁰ $[\alpha]_D^{20} -7.3$ (*c* 1.0 in $CHCl_3$) for 94% ee}; δ_H (400 MHz, $CDCl_3$) 0.92 (3H, t, *J* 6.8, $C(5')H_3$), 1.28-1.44 (7H, m, $C(1')H_A$, $C(2')H_2$, $C(3')H_2$, $C(4')H_2$), 1.60-1.62 (1H, m, $C(1')H_B$), 1.88-1.93 (2H, m, $C(3)H_2$), 2.67 (1H, dt, *J* 16.4, 4.2, $C(4)H_A$), 2.78-2.87 (1H, m, $C(4)H_B$), 2.95 (3H, s, *NMe*), 3.22-3.28 (1H, m, $C(2)H$), 6.54 (1H, d, *J* 8.1, $C(8)H$), 6.60 (1H, app t, *J* 7.3, $C(6)H$), 7.00 (1H, d, *J* 7.3, $C(5)H$), 7.10 (1H, app t, *J* 8.1, $C(7)H$); δ_C (100 MHz, $CDCl_3$) 14.1 ($C(5')$), 22.7, 23.6, 24.4, 25.8, 31.2, 32.1 ($C(1')$, $C(2')$, $C(3')$, $C(4')$, $C(3)$, $C(4)$), 38.0 (*NMe*), 58.9 ($C(2)$), 110.4 ($C(8)$), 115.1 ($C(6)$), 121.8 ($C(4A)$), 127.0 ($C(7)$), 128.6 ($C(5)$), 145.4 ($C(8A)$).

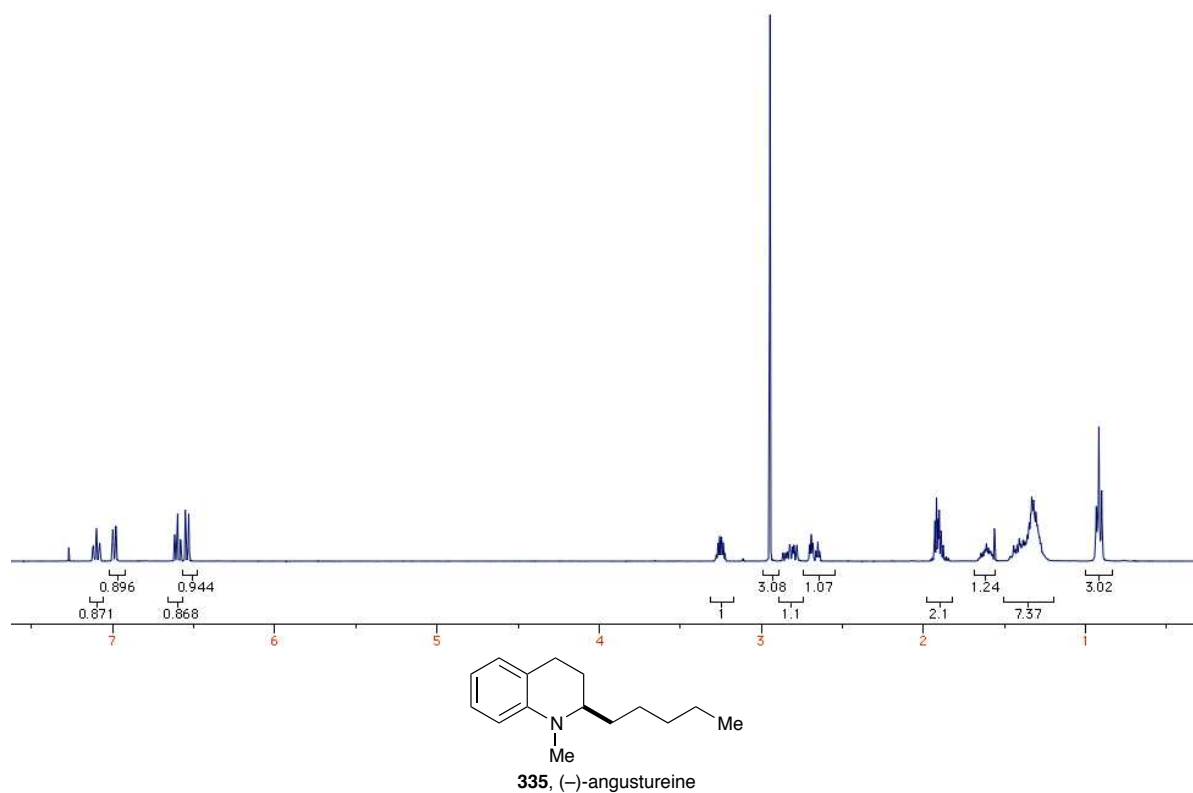
Bibliography

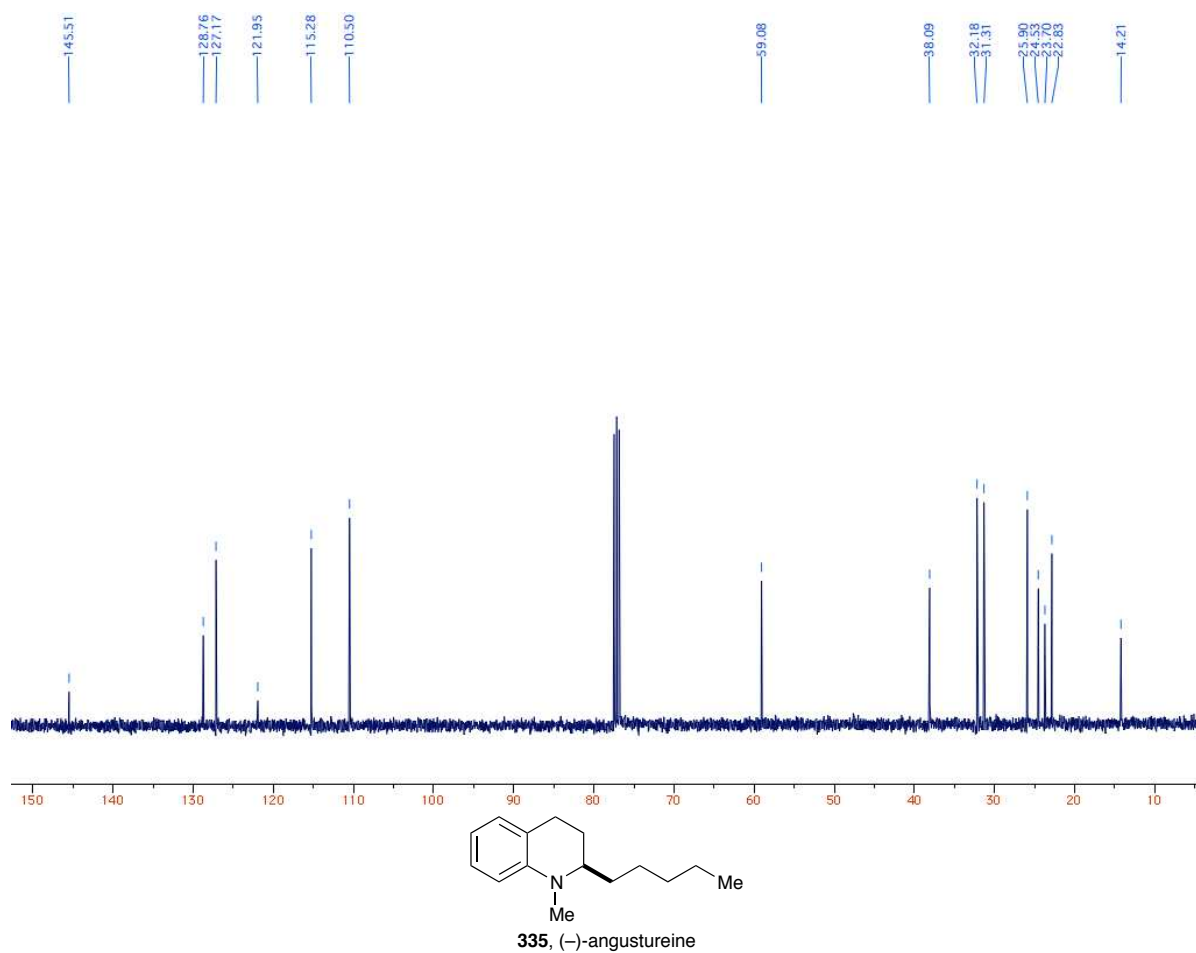
- [1] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518–1520.
- [2] Adam, W.; Bialas, J.; Hadjiarapoglou, L. *Chem. Ber.* **1991**, *124*, 2377–2377.
- [3] Adam, W.; Chan, Y.; Cremer, D.; Gauss, J.; Scheutzow, D.; Schindler, M. *J. Org. Chem.* **1987**, *52*, 2800–2803.
- [4] Rivas, F. M.; Riaz, U.; Giessert, A.; Smulik, J. A.; Diver, S. T. *Org. Lett.* **2001**, *3*, 2673–2676.
- [5] Kwong, F. Y.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 581–584.
- [6] Carpino, L. A. *J. Am. Chem. Soc.* **1960**, *82*, 3133–3135.
- [7] Fraser, R.; Boussard, G.; Postescu, I.; Whiting, J.; Wigfield, Y. *Can. J. Chem.* **1973**, *51*, 1109–1115.
- [8] Terashima, S.; Wagatsuma, M.; Yamada, S. *Chem. Pharm. Bull.* **1970**, *18*, 1137–1144.
- [9] Chow, Y.; Colon, C. *Can. J. Chem.* **1968**, *46*, 2827–2833.
- [10] Karabatsos, G.; Taller, R. *J. Am. Chem. Soc.* **1964**, *86*, 4373–4378.
- [11] Davies, S. G.; Smyth, G. D. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2467–2477.
- [12] Price, P. DPhil Thesis, 2005.
- [13] Smith, C. R.; RajanBabu, T. V. *Org. Lett.* **2008**, *10*, 1657–1659.
- [14] Tokuyama, H.; Kuboyama, T.; Amano, A.; Yamashita, T.; Fukuyama, T. *Synthesis* **2000**, 1299–1304.
- [15] Heydari, A.; Aslanzadeh, S. *Adv. Synth. Catal.* **2005**, *347*, 1223–1225.
- [16] Belzecki, C.; Panfil, I. *J. Org. Chem.* **1979**, *44*, 1212–1218.
- [17] Costa, M. R.; Curto, M. J.; Davies, S. G.; Sanders, J.; Teixeira, F. C. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2850–2855.

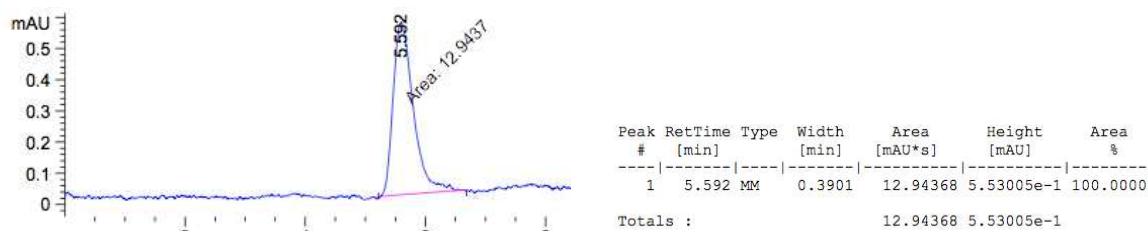
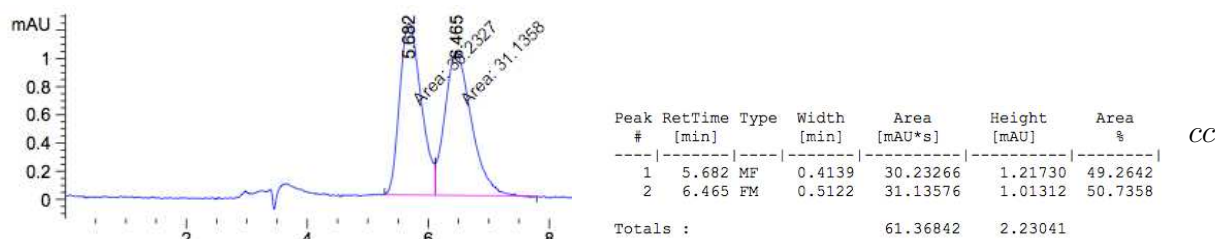
- [18] Ruan, J.; Li, X.; Saidi, O.; Xiao, J. *J. Am. Chem. Soc.* **2008**, *130*, 2424–2425.
- [19] Soucy, F.; Grenier, L.; Behnke, M. L.; Destree, A. T.; McCormack, T. A.; Adams, J.; Plamondon, L. *J. Am. Chem. Soc.* **1999**, *121*, 9967–9976.
- [20] Ishikawa, T.; Nagai, K.; Kudoh, T.; Saito, S. *Synlett* **1995**, 1171–1173.
- [21] Tsuchihashi, G.-I.; Iriuchijima, S.; Maniwa, K. *Tetrahedron Lett.* **1973**, *14*, 3389 – 3392.
- [22] Li, W.; Hou, G.; Chang, M.; Zhang, X. *Adv. Synth. Catal.* **2009**, *351*, 3123–3127.
- [23] Sarkar, S. D.; Grimme, S.; Studer, A. *J. Am. Chem. Soc.* **2010**, *132*, 1190–1191.
- [24] Jabin, I.; Revial, G.; Tomas, A.; Lemoine, P.; Pfau, M. *Tetrahedron: Asymmetry* **1995**, *6*, 1795–1812.
- [25] Paradisi, M.; Romeo, A. *J. Chem. Soc., Perkin Trans. 1* **1977**, 596–600.
- [26] Tan, E. W.; Chan, B.; Blackman, A. G. *J. Am. Chem. Soc.* **2002**, *124*, 2078–2079.
- [27] Ruiz, D.; Romanelli, G.; Vázquez, P.; Autino, J. *Appl. Catal., A* **2010**, *374*, 110–119.
- [28] Shelkov, R.; Nahmany, M.; Melman, A. *Org. Biomol. Chem.* **2004**, *2*, 397–401.
- [29] Morgan, A. J.; Masse, C. E.; Panek, J. S. *Org. Lett.* **1999**, *1*, 1949–1952.
- [30] Imamoto, T.; Iwadate, N.; Yoshida, K. *Org. Lett.* **2006**, *8*, 2289–2292.
- [31] Zhu, C.; Akiyama, T. *Org. Lett.* **2009**, *11*, 4180–4183.
- [32] Zhu, S.-F.; Xie, J.-B.; Zhang, Y.-Z.; Li, S.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2006**, *128*, 12886–12891.
- [33] Strekowski, L.; Wydra, R. L.; Cegła, M. T.; Czarny, A.; Patterson, S. *J. Org. Chem.* **1989**, *54*, 6120–6123.
- [34] Malkov, A. V.; Figlus, M.; Stončius, S.; Kočovský, P. *J. Org. Chem.* **2007**, *72*, 1315–1325.
- [35] Baeza, A.; Pfaltz, A. *Chem.–Eur. J.* **2010**, *16*, 4003–4009.
- [36] Jacquemond-Collet, I.; Hannedouche, S.; Fabre, N.; Fourasté, I.; Moulis, C. *Phytochemistry* **1999**, *51*, 1167–1169.
- [37] Wang, W. B.; Lu, S. M.; Yang, P. Y.; Han, X. W.; Zhou, Y. G. *J. Am. Chem. Soc.* **2003**, *125*, 10536–10537.
- [38] Lu, S. M.; Wang, Y. Q.; Han, X. W.; Zhou, Y. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 2260–2263.
- [39] Rueping, M.; Antonchick, A. P.; Theissmann, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3683–3686.
- [40] Wang, Z. J.; Zhou, H. F.; Wang, T. L.; He, Y. M.; Fan, Q. H. *Green Chem.* **2009**, *11*, 767–769.

APPENDIX A

^1H and ^{13}C NMR spectra of (–)-angustureine **335**

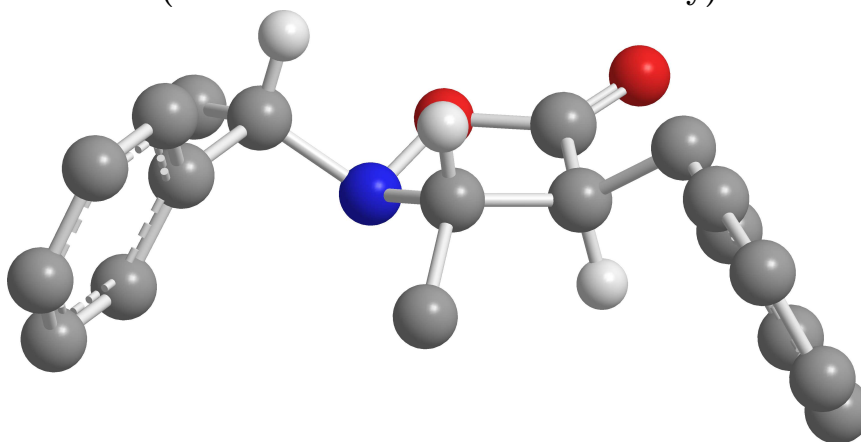




Chiral HPLC analysis of (–)-angustureine **335**

X-Ray crystal structure data for (*S,S,S*)-**255**

(Some H atoms omitted for clarity)



X-ray crystal structure determination for **255**

Data were collected using an Enraf-Nonius κ -CCD diffractometer with graphite monochromated Mo-K α radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined

using CRYSTALS.¹

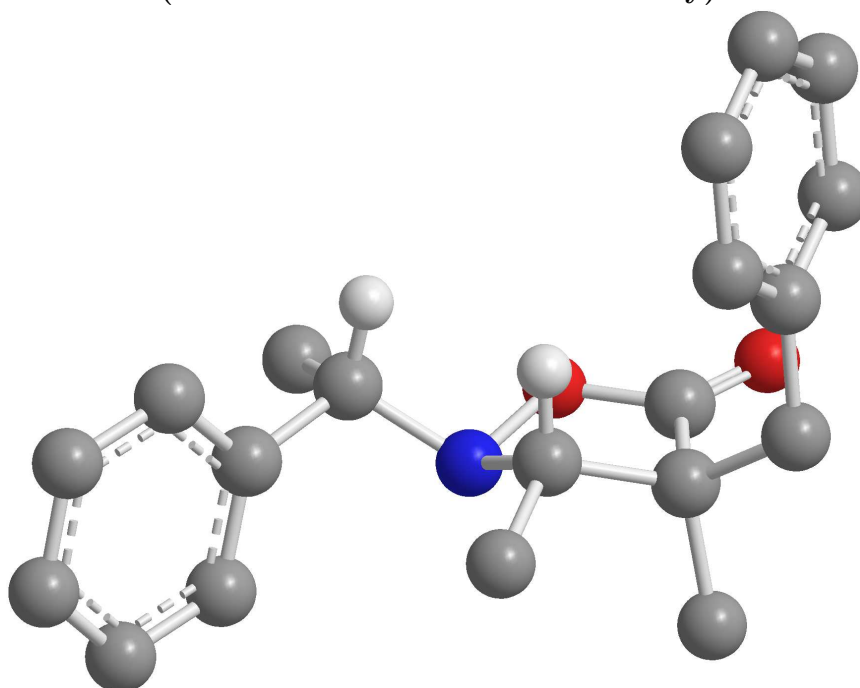
X-ray crystal structure data for **255** [C₁₉H₂₁NO₂]: M = 295.38, orthorhombic, space group $P 2_1 2_1 2_1$, $a = 5.8643(2)$ Å, $b = 9.9505(4)$ Å, $c = 27.5990(12)$ Å, $V = 1610.48(11)$ Å³, $Z = 4$, $\mu = 0.08$ mm⁻¹, colourless plate, crystal dimensions = $0.10 \times 0.10 \times 0.20$ mm³. A total of 2106 unique reflections were measured for $5 < \theta < 27$ and 1210 reflections were used in the refinement. The final parameters were $wR_2 = 0.058$ and $R_1 = 0.087$ [$I > 1.0\sigma(I)$]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

¹Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.

APPENDIX D

X-Ray crystal structure data for (*S,S,S*)-**283**

(Some H atoms omitted for clarity)



X-ray crystal structure determination for **283**

Data were collected using an Enraf-Nonius κ -CCD diffractometer with graphite monochro-

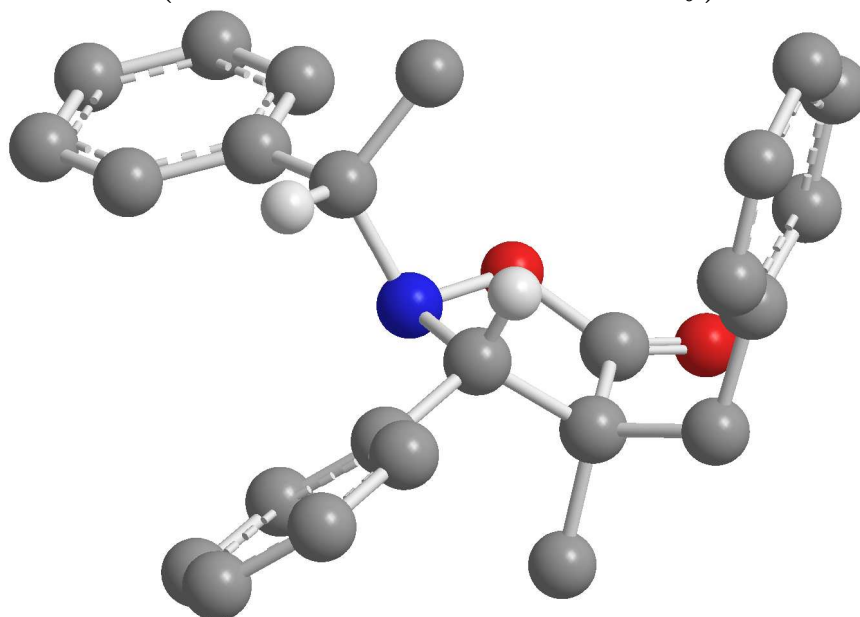
mated Mo-K α radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.¹

X-ray crystal structure data for **283** [C₂₀H₂₃NO₂]: M = 309.41, orthorhombic, space group *P* 2₁ 2₁ 2₁, *a* = 10.6697(2) Å, *b* = 7.2058(2) Å, *c* = 22.4278(5) Å, *V* = 1724.33(7) Å³, *Z* = 4, μ = 0.08 mm¹, colourless plate, crystal dimensions = 0.09 × 0.13 × 0.26 mm³. A total of 2256 unique reflections were measured for 5 < θ < 27 and 1853 reflections were used in the refinement. The final parameters were wR_2 = 0.074 and R_1 = 0.042 [$I > -3.0\sigma(I)$]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

¹Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.

X-Ray crystal structure data for (*S,S,S*)-**291**

(Some H atoms omitted for clarity)



X-ray crystal structure determination for **291**

Data were collected using an Enraf-Nonius κ -CCD diffractometer with graphite monochromated Mo-K α radiation using standard procedures at 150 K. The structure was solved by

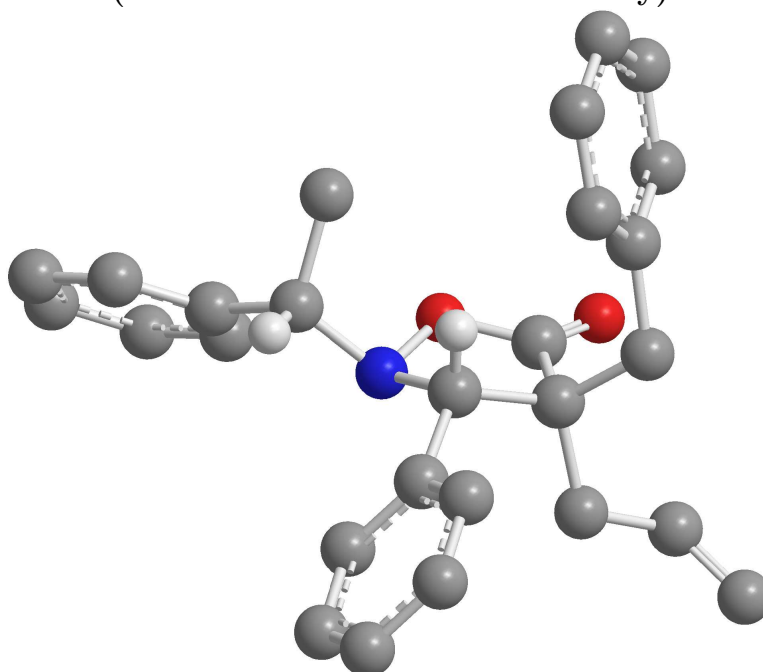
direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.¹

X-ray crystal structure data for **291** [C₂₅H₂₅NO₂]: M = 371.48, orthorhombic, space group *P* 2₁ 2₁ 2₁, *a* = 7.473100(10) Å, *b* = 12.1146(2) Å, *c* = 22.5635(4) Å, *V* = 2031.25(6) Å³, *Z* = 4, μ = 0.08 mm⁻¹, colourless plate, crystal dimensions = 0.05 × 0.05 × 0.20 mm³. A total of 2639 unique reflections were measured for 5 < θ < 27 and 2639 reflections were used in the refinement. The final parameters were *wR*₂ = 0.100 and *R*₁ = 0.058 [*I* > -3.0 σ (*I*)]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

¹Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.

X-Ray crystal structure data for (*S,S,S*)-**301**

(Some H atoms omitted for clarity)

**X-ray crystal structure determination for 301**

Data were collected using an Enraf-Nonius κ -CCD diffractometer with graphite monochromated Mo-K α radiation using standard procedures at 150 K. The structure was solved by

direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.¹

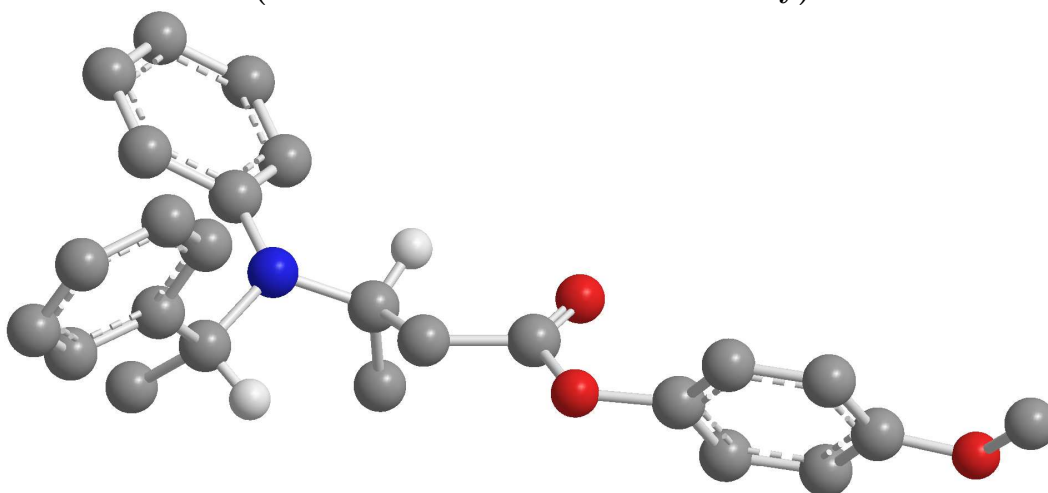
X-ray crystal structure data for **301** [C₂₇H₂₇NO₂]: M = 397.52, orthorhombic, space group *P* 2₁ 2₁ 2₁, *a* = 9.98060(10) Å, *b* = 12.3492(2) Å, *c* = 35.5508(6) Å, *V* = 4389.72(11) Å³, *Z* = 8, μ = 0.08 mm⁻¹, colourless plate, crystal dimensions = 0.20 × 0.20 × 0.40 mm³. A total of 5516 unique reflections were measured for 5 < θ < 27 and 3517 reflections were used in the refinement. The final parameters were *wR*₂ = 0.055 and *R*₁ = 0.060 [*I* > 1.5 σ (*I*)]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

¹Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.

APPENDIX G

X-Ray crystal structure data for (*R,R*)-**457**

(Some H atoms omitted for clarity)



X-ray crystal structure determination for **457**

Data were collected using an Enraf-Nonius κ -CCD diffractometer with graphite monochromated Mo-K α radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined

using CRYSTALS.¹

X-ray crystal structure data for **457** [C₂₅H₂₇NO₃]: *M* = 389.59, orthorhombic, space group *P* 2₁ 2₁ 2₁, *a* = 9.6818(4) Å, *b* = 14.3637(5) Å, *c* = 15.1077(6) Å, *V* = 2100.97(14) Å³, *Z* = 4, *μ* = 0.08 mm¹, colourless plate, crystal dimensions = 0.14 × 0.15 × 0.27 mm³. A total of 2687 unique reflections were measured for 5 < *θ* < 27 and 2278 reflections were used in the refinement. The final parameters were *wR*₂ = 0.090 and *R*₁ = 0.034 [*I* > −3.0σ(*I*)]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

¹Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.