

The conjugate addition of enantiomerically pure lithium amides as chiral ammonia equivalents part

III: 2012–2017

Stephen G. Davies,* Ai M. Fletcher, Paul M. Roberts and James E. Thomson

Department of Chemistry, Chemistry Research Laboratory, University of Oxford, Mansfield Road, Oxford, OX1 3TA, U.K.

E-mail: steve.davies@chem.ox.ac.uk

Abstract

This review covers further applications of the conjugate addition of enantiomerically pure lithium amides as chiral ammonia equivalents in asymmetric synthesis and provides an update since our last review of this area, which was published in 2012.

Contents:

1. Introduction	XX
2. The conjugate addition of enantiomerically pure lithium amides	XX
2.1 Conjugate addition of enantiomerically pure lithium amides to β -alkyl and β -aryl- α,β -unsaturated esters and amides	XX
2.2 Conjugate addition to chiral substrates: doubly diastereoselective reactions	XX
3. Enolate functionalisation	XX
3.1. Synthesis of α -hydroxy- β -amino acid derivatives	XX
3.2 Synthesis of α -alkyl- β -amino acid derivatives	XX
4. Global and selective deprotection strategies	XX
4.1. Global deprotection: synthesis of primary β -amino esters	XX
4.2. Selective deprotection strategies	XX
4.3. Ester hydrolysis: synthesis of β -amino acids	XX
5. Synthetic applications: target syntheses	XX
6. Conclusion	XX
References	XX

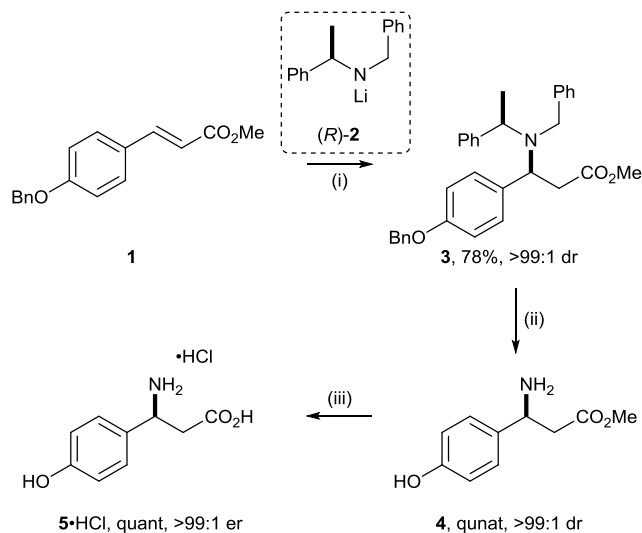
1. Introduction

We published a comprehensive review concerning the development, scope and application of the conjugate additions of enantiomerically pure lithium amides (which act as chiral ammonia equivalents) in 2005¹ and an

update covering 2005–2011 was published 2012.² Since then, this methodology has continued to be employed in asymmetric synthesis: particularly, numerous applications have been reported which elaborate the resultant β -amino esters/amides to a wide range of biologically important targets. Accordingly, several synthetic methodologies have also been developed which utilise the enantiopure β -amino esters/amides to access various other synthetic motifs. This review will provide a further update on reports and applications of the conjugate additions of enantiomerically pure lithium amides in asymmetric synthesis covering the period of 2012 to date.

2. The conjugate addition of enantiomerically pure lithium amides

The highly diastereoselective conjugate addition of enantiomerically pure lithium *N*-benzyl-*N*-(α -methylbenzyl)amide **2** to α,β -unsaturated esters was originally reported in 1991.³ The conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(α -methylbenzyl)amide (*R*)-**2** to methyl *p*-benzyloxycinnamate **1** in THF at $-78\text{ }^{\circ}\text{C}$ gave β -amino ester **3** in 78% yield as a single diastereoisomer ($>99:1$ dr). Hydrogenolysis of the *N*-benzyl and *O*-benzyl groups in the presence of $\text{Pd}(\text{OH})_2/\text{C}$ and subsequent acid-mediated ester hydrolysis in aq HCl under reflux gave (*S*)- β -tyrosine·hydrochloride **5**·HCl in quantitative yield and $>99:1$ er (Scheme 1). Since this original report, this methodology has been employed routinely in organic synthesis,⁴ demonstrating a wide range of substrate scope (~ 300 examples) and consistently high diastereoselectivity (typically $>95:5$ dr).



Scheme 1. Reagents and conditions: (i) (*R*)-**2**, THF, $-78\text{ }^{\circ}\text{C}$, 15 min; (ii) H_2 (1 atm), $\text{Pd}(\text{OH})_2/\text{C}$, $\text{MeOH}/\text{H}_2\text{O}/\text{AcOH}$ (v/v 40:4:1), $20\text{ }^{\circ}\text{C}$, 18 h; (iii) aq HCl, reflux, 16 h.

In addition to lithium *N*-benzyl-*N*-(α -methylbenzyl)amide **2**, which has been utilised most commonly, several other enantiomerically pure lithium amides have also been employed. The lithium amide reagents that appeared in the literature since 2011 are listed below (Figure 1).

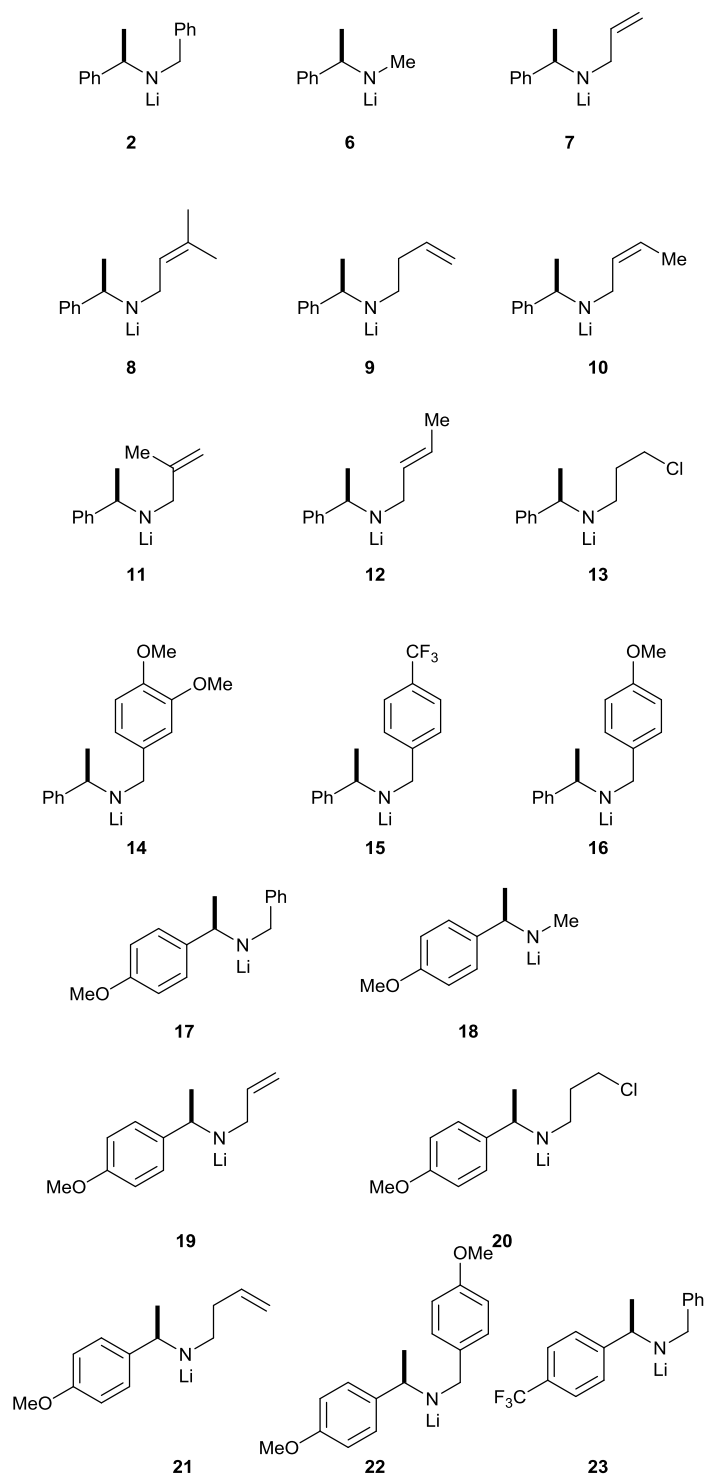


Figure 1.^a Enantiomerically pure lithium amides **2** and **6–23** as chiral “ammonia equivalents”. ^a Chiral lithium amide reagents are depicted here as their (*R*)-enantiomers in all cases, regardless of which antipode was employed in the original reports.

Based upon molecular modelling calculations, a transition state mnemonic was proposed to rationalise the diastereoselectivity observed upon conjugate addition.⁵ In order to gain further insight into the mechanism of this process, some studies towards elucidating the structure of lithium amide reagents in solution have been reported more recently.⁶ We have determined the solution structure of both enantiopure and racemic, doubly labelled ⁶lithium ¹⁵N-benzyl-¹⁵N-(α -methylbenzyl)amide, which exists as dimers in THF, as determined by ⁶Li and ¹⁵N NMR spectroscopic analysis at low temperature.^{7,8} Garrido et. al employed QM calculations in combination with MM sampling to explore the conformational structure of the transition state in this

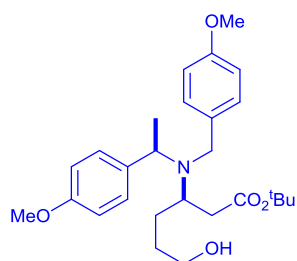
reaction. Their results suggested that the main potential transition state geometries are two conformers in a “V-stacked” orientation of the lithium amide’s phenyl rings.⁹

2.1 Conjugate addition of enantiomerically pure lithium amides to β -alkyl and β -aryl- α,β -unsaturated esters and amides

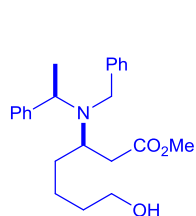
The conjugate addition of enantiomerically pure lithium amides has been applied to a number of α,β -unsaturated esters and amides, with a wide range of functionality including protected amino groups, halides, protected and free-hydroxyl groups, carboxylic acids, alkenyl groups, and heterocycles. All of the recent examples, reported since 2011, are listed below (Table 1).

Table 1.

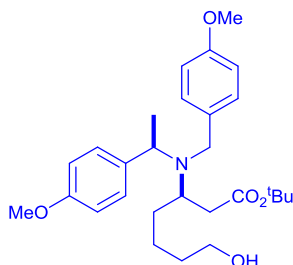
24 Ref 10: -78 °C, >97:3 dr Ref 11: -78 °C, 90% Ref 12: -78 °C	25 Ref 13: -78 °C, 95%, >99:1 dr Ref 14: -78 °C, 85% [α] _D ²⁶ -14.2 (c 1.85, CHCl ₃)	25 Ref 15: -78 °C, 85% [α] _D ²¹ +18.7 (c 0.75, CHCl ₃)	26 Ref 13: -78 °C, 96%, >99:1 dr
27 Ref 15: -78 °C, 69% [α] _D ²¹ +18.0 (c 5.0, CHCl ₃)	28 Ref 11: -78 °C Ref 12: -78 °C	29 Ref 15: -78 °C, 78% [α] _D ²¹ +3.4 (c 2.95, CHCl ₃)	30 Ref 16: -78 °C, 45%
30 Ref 17: -78 °C, 89% [α] _D ²³ +12.4 (c 0.9, CHCl ₃)	31 Ref 18: -78 °C, 82% [α] _D ²⁰ -2.8 (c 1.0, CHCl ₃)	32 Ref 14: -78 °C, 75% [α] _D ²⁶ -51.4 (c 1.45, CHCl ₃)	33 Ref 16: -78 °C
34 Ref 16: -78 °C	35 Ref 16: -78 °C	36 Ref 19: -78 °C, 81% [α] _D ²³ +6.27 (c 1.0, CHCl ₃)	36 Ref 19: -78 °C, 80% [α] _D ²³ -7.6 (c 1.4, CHCl ₃)
37 Ref 20: -78 °C, 81%, >99:1 dr [α] _D ²⁴ -13.6 (c 1.0, CHCl ₃)	38 Ref 20: -78 °C, 73%, >99:1 dr [α] _D ²⁴ -13.6 (c 1.0, CHCl ₃)	39 Ref 11: -78 °C Ref 12: -78 °C	40 Ref 15: -78 °C, 68% [α] _D ²⁵ +11.0 (c 6.7, CHCl ₃)



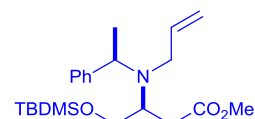
41
Ref 21: $-78\text{ }^{\circ}\text{C}$, 40%
 $[\alpha]_{\text{D}}^{20} +37.7$ (c 1.0, CHCl_3)



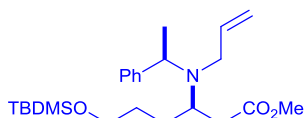
42
Ref 22: $-78\text{ }^{\circ}\text{C}$, 77%
 $[\alpha]_{\text{D}}^{20} +8.1$ (c 0.7, CHCl_3)



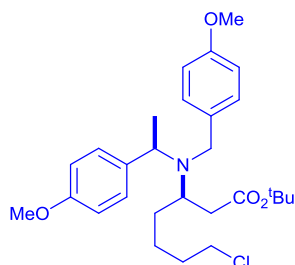
43
Ref 23:
Ref 21: $-78\text{ }^{\circ}\text{C}$, 43%
 $[\alpha]_{\text{D}}^{22} +30.7$ (c 1.0, CHCl_3)



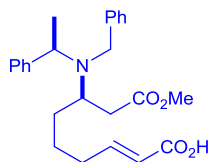
44
Ref 14: $-78\text{ }^{\circ}\text{C}$, 91%
 $[\alpha]_{\text{D}}^{28} -18.8$ (c 1.4, CHCl_3)



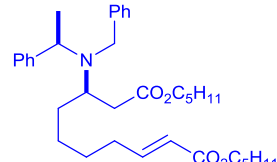
45
Ref 14: $-78\text{ }^{\circ}\text{C}$, 100%
 $[\alpha]_{\text{D}}^{26} -11.9$ (c 1.75, CHCl_3)



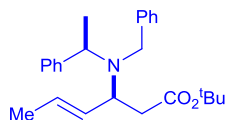
46
Ref 23:
Ref 21: $-78\text{ }^{\circ}\text{C}$, 82%
 $[\alpha]_{\text{D}}^{22} +34.3$ (c 1.0, CHCl_3)



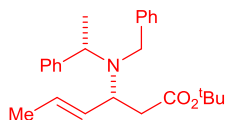
47
Ref 22: $-78\text{ }^{\circ}\text{C}$, 84%
 $[\alpha]_{\text{D}}^{20} +4.6$ (c 1.6, CHCl_3)



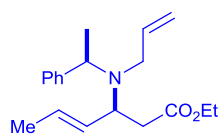
48
Ref 22: $-78\text{ }^{\circ}\text{C}$, 42%
 $[\alpha]_{\text{D}}^{20} +6.2$ (c 2.62, CHCl_3)



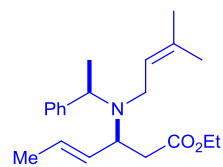
49
Ref 24: $-78\text{ }^{\circ}\text{C}$, 80%, 98:2 dr
 $[\alpha]_{\text{D}}^{25} -22.2$ (c 2.0, CHCl_3)



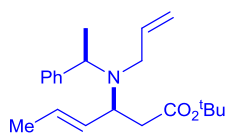
49
Ref 25:
 $-78\text{ }^{\circ}\text{C}$, 89%, >99:1 dr
 $[\alpha]_{\text{D}}^{20} +23.6$ (c 1.0, CHCl_3)
Ref 26:
 $-78\text{ }^{\circ}\text{C}$, 89%, >99:1 dr



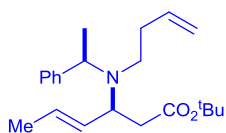
50^a
Ref 13:
 $-40\text{ }^{\circ}\text{C}$, 72%, 90:10 dr



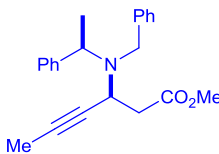
51^a
Ref 13:
 $-40\text{ }^{\circ}\text{C}$, 67%, 88:12 dr



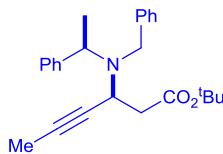
52
Ref 27: $-78\text{ }^{\circ}\text{C}$, 89%
 $[\alpha]_{\text{D}}^{20} -4.7$ (c 1.0, CHCl_3)
Ref 28: $-78\text{ }^{\circ}\text{C}$, 89%
 $[\alpha]_{\text{D}}^{25} -3.5$ (c 2.0, CHCl_3)



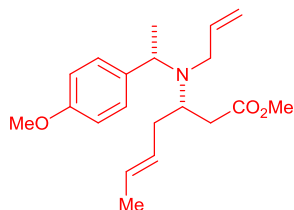
53
Ref 29: $-78\text{ }^{\circ}\text{C}$, 69%
 $[\alpha]_{\text{D}}^{20} -14.6$ (c 1.0, CHCl_3)
Ref 28: $-78\text{ }^{\circ}\text{C}$, 69%
 $[\alpha]_{\text{D}}^{25} -15.4$ (c 2.0, CHCl_3)



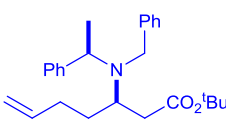
54
Ref 30: $-78\text{ }^{\circ}\text{C}$
61%, 93:7 dr
 $[\alpha]_{\text{D}}^{20} -136.5$ (c 1.0, CHCl_3)



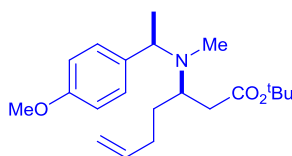
55
Ref 30: $-78\text{ }^{\circ}\text{C}$
70%, 92:8 dr
 $[\alpha]_{\text{D}}^{20} -66.5$ (c 1.0, CHCl_3)



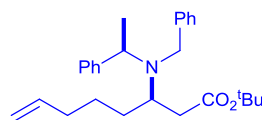
56
Ref 31: $-78\text{ }^{\circ}\text{C}$
59%, >95:5 dr
 $[\alpha]_{\text{D}}^{20} +13.0$ (c 1.0, CHCl_3)
Ref 32: $-78\text{ }^{\circ}\text{C}$
87%, >95:5 dr
 $[\alpha]_{\text{D}}^{25} +2.8$ (c 1.0, CHCl_3)



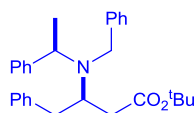
57
Ref 33:
 $-78\text{ }^{\circ}\text{C}$, 89%, >99:1 dr
 $[\alpha]_{\text{D}}^{20} +8.7$ (c 1.0, CHCl_3)



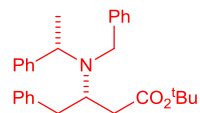
58
Ref 34:
 $-78\text{ }^{\circ}\text{C}$, 74%, >99:1 dr
 $[\alpha]_{\text{D}}^{20} -3.2$ (c 1.3, CHCl_3)



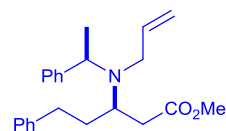
59
Ref 33:
 $-78\text{ }^{\circ}\text{C}$, 97%, >99:1 dr
 $[\alpha]_{\text{D}}^{20} +6.5$ (c 1.0, CHCl_3)



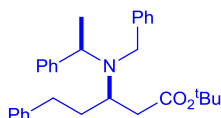
60
Ref 35:
 -78 °C, 98%, >99:1 dr



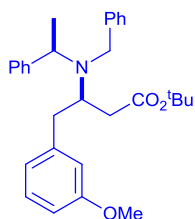
61
Ref 36:
 -78 °C, 56%
 $[\alpha]_D^{25} -19.3$ (c 1.0, CHCl₃)



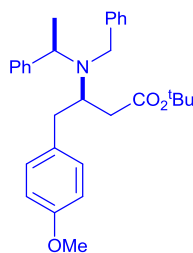
62
Ref 14:
 -78 °C, 94%
 $[\alpha]_D^{25} -12.6$ (c 0.95, CHCl₃)



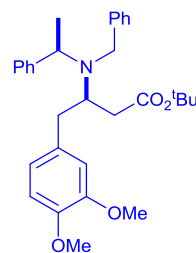
63
Ref 35:
 -78 °C, quant, >99:1 dr



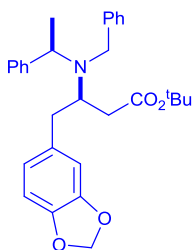
64
Ref 35:
 -78 °C, 97%, >99:1 dr



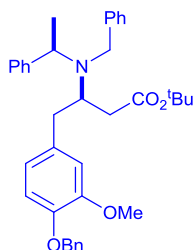
65
Ref 35:
 -78 °C, 96%, >99:1 dr



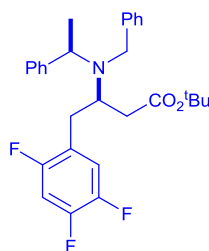
66
Ref 37:
 -78 °C, 93%, >99:1 dr
 $[\alpha]_D^{25} -14.0$ (c 1.0, CHCl₃)



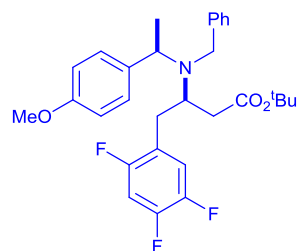
67
Ref 37:
 -78 °C, 72%, >99:1 dr
 $[\alpha]_D^{20} -7.7$ (c 0.9, CHCl₃)



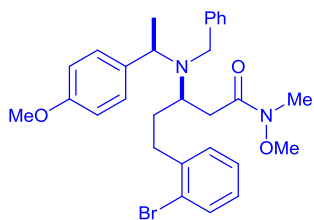
68
Ref 37:
 -78 °C, 47%, >99:1 dr
 $[\alpha]_D^{25} +24.1$ (c 1.0, CHCl₃)



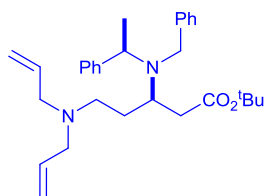
69
Ref 38:
 -78 °C, 87%, >99:1 dr
 $[\alpha]_D^{25} +10.2$ (c 1.0, CHCl₃)



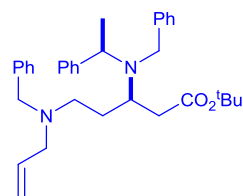
70
Ref 38:
 -78 °C, 86%, >99:1 dr
 $[\alpha]_D^{25} +27.0$ (c 1.0, CHCl₃)



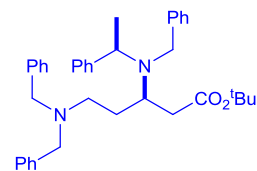
71
Ref 39:
 -78 °C, 80%, >95:5 dr
 $[\alpha]_D^{25} +21.8$ (c 1.0, CHCl₃)



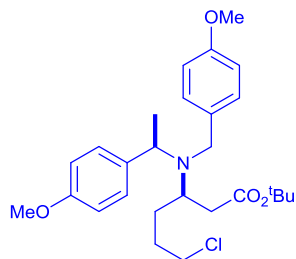
72
Ref 40:
 -78 °C, 82%, >99:1 dr
 $[\alpha]_D^{22} +3.4$ (c 1.2, CHCl₃)



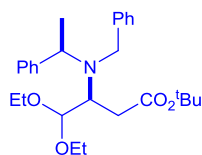
73
Ref 40:
 -78 °C, 88%, >99:1 dr
 $[\alpha]_D^{22} -2.9$ (c 1.3, CHCl₃)



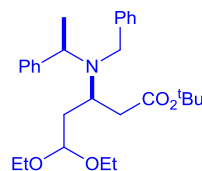
74
Ref 40:
 -78 °C, 52%, >99:1 dr
 $[\alpha]_D^{25} -9.0$ (c 1.8, CHCl₃)



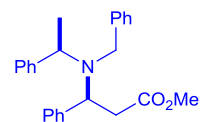
75
Ref 21: -78 °C, >99:1 dr



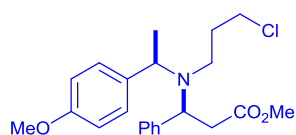
76
Ref 24:
 -78 °C, 87%, 99:1 dr
 $[\alpha]_D^{25} -33.6$ (c 1.0, CHCl₃)



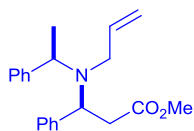
77
Ref 24:
 -78 °C, 91%, 99:1 dr
 $[\alpha]_D^{25} -42.2$ (c 1.0, CHCl₃)



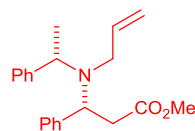
78
Ref 10:
 -78 °C, >97:3 dr
Ref 11:
 -78 °C, 78%, >97:3 dr
Ref 12: -78 °C



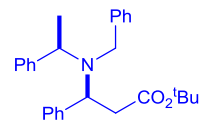
79
Ref 20, 41:
 -78 °C, >99:1 dr



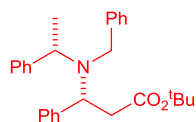
80
Ref 13:
 -78 °C, 92%, >99:1 dr
Ref 14:
 -78 °C, 90%
 $[\alpha]_D^{26} -3.6$ (c 0.85, CHCl₃)



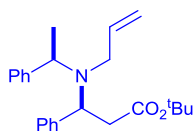
80
Ref 15:
 -78 °C, 90%
 $[\alpha]_D^{21} +1.5$ (c 4.1, CHCl₃)



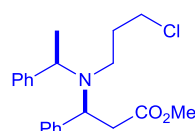
81
Ref 35:
 -78 °C, quant., >99:1 dr



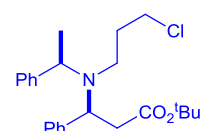
81
Ref 26:
−78 °C, 82%, >99:1 dr



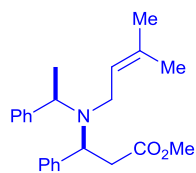
82
Ref 13:
−78 °C, 56%, >99:1 dr



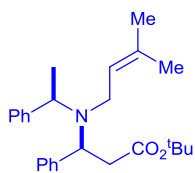
83
Ref 20:
−78 °C, quant, >99:1 dr
[α]_D²⁴ −7.0 (c 1.0, CHCl₃)



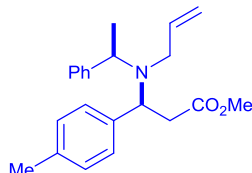
84
Ref 20:
−78 °C, 84%, >99:1 dr
[α]_D²⁰ −4.2 (c 1.0, CHCl₃)



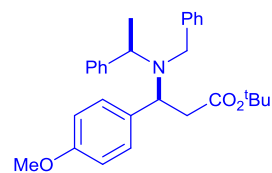
85
Ref 13:
−78 °C, 39%, >78:22 dr



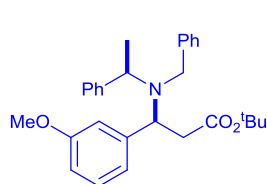
86
Ref 13:
−78 °C, 95%, >93:7 dr



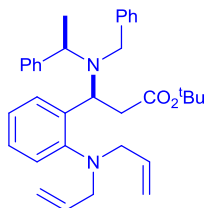
87
Ref 14: −78 °C, 95%
[α]_D²⁷ −0.04 (c 1.35, CHCl₃)



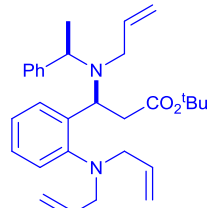
88
Ref 35:
−78 °C, 95%, >99:1 dr



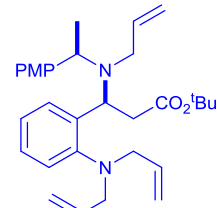
89
Ref 35:
−78 °C, 93%, >99:1 dr



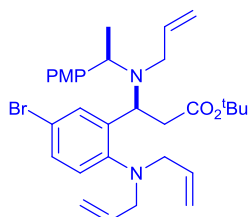
90
Ref 42:
−78 °C, 97%, >99:1 dr
[α]_D²⁵ −9.5 (c 1.1, CHCl₃)



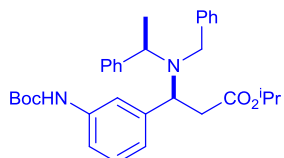
91
Ref 42:
−78 °C, 85%, >99:1 dr
[α]_D²⁵ +8.7 (c 2.1, CHCl₃)



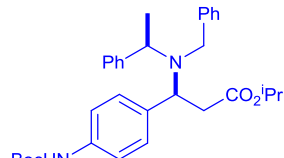
92
Ref 42:
−78 °C, 89%, >99:1 dr
[α]_D²⁰ +19.9 (c 1.3, CHCl₃)



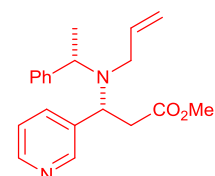
93
Ref 43:
−78 °C, quant, >99:1 dr
[α]_D²⁰ −5.6 (c 1.0, CHCl₃)



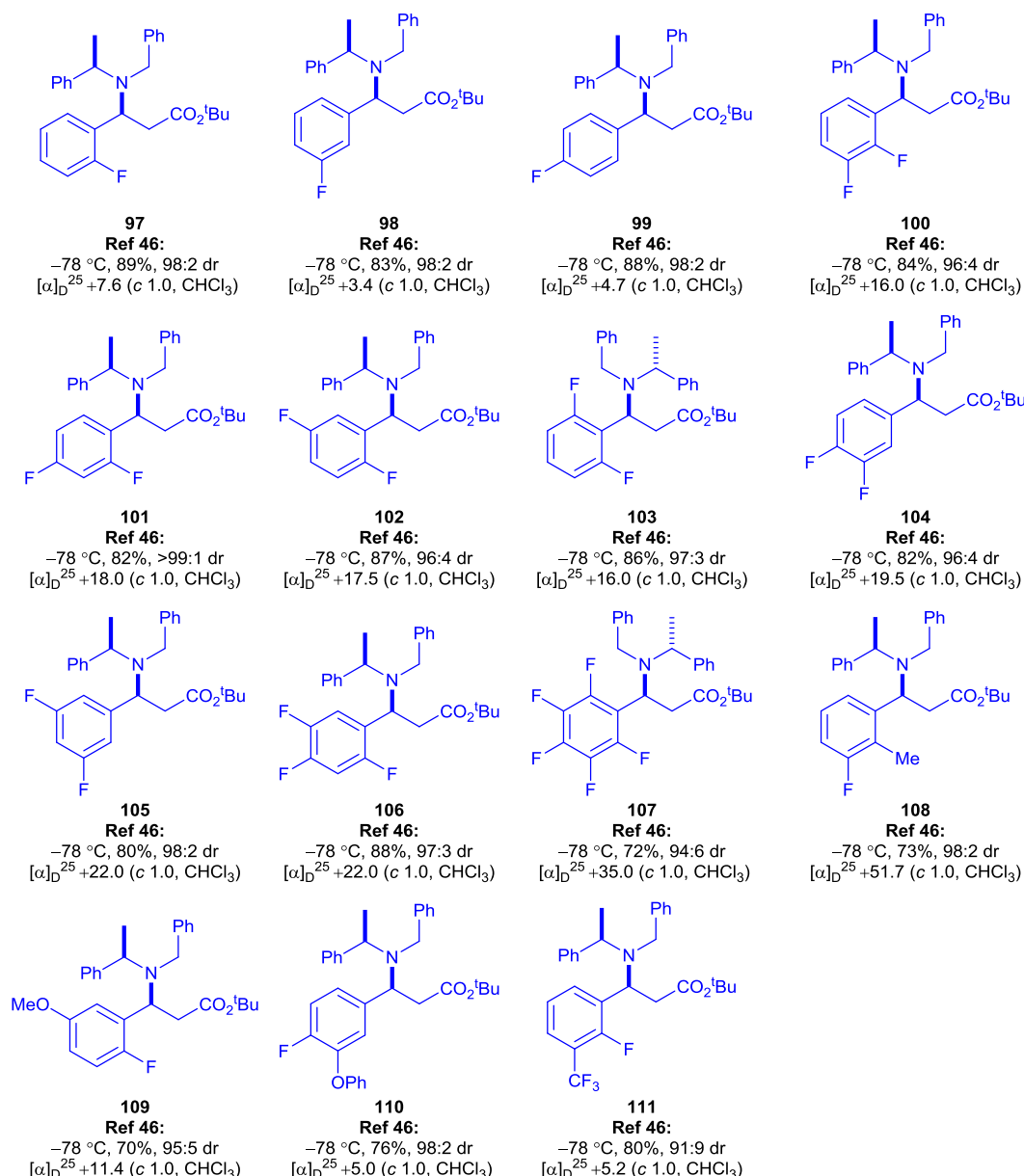
94
Ref 44: −78 °C, 41%



95
Ref 45: −78 °C



96
Ref 15: −78 °C, 48%
[α]_D²¹ −0.6 (c 1.7, CHCl₃)



^a The reaction was carried in the presence of catalytic amount of LiCl.

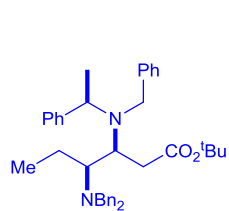
2.2 Conjugate addition to chiral substrates: doubly diastereoselective reactions

The stereochemical outcome of conjugate additions of enantiomerically pure lithium amide reagents to chiral α,β -unsaturated carbonyl compounds is also influenced by the stereochemistry of the substrate in a doubly diastereoselective reaction. When the two chiral species (i.e., chiral lithium amide reagent and chiral α,β -unsaturated carbonyl compound) favour formation of the same diastereoisomeric product, this reaction would lead to very high diastereoselectivity, which is called a “matched” reaction, whereas when the two chiral species favour opposite stereochemical outcomes, lower diastereoselectivity is generally observed, which is termed a “mismatched” reaction. The inherent level of substrate control of the chiral α,β -unsaturated ester can be predicted upon conjugate addition of an achiral lithium amide, such as *N*-benzyl-*N*-isopropylamide, which we have found to be a good model for lithium *N*-benzyl-(*N*- α -methylbenzyl)amide **2**.

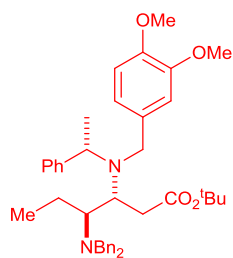
In general, reagent control from the chiral lithium amide is dominant over substrate control for chiral α,β -unsaturated carbonyl compound, with a few notable exceptions. Depending on the nature of the chiral α,β -unsaturated carbonyl compound (especially incorporating dense heteroatom functionality such as protected hydroxyl groups and amino groups at the γ -position in particular), a major diastereoisomer can also be formed under dominant substrate control in some cases. Examples of conjugate addition reactions to chiral α,β -unsaturated carbonyl compounds reported since 2011 are presented below (Table 2).

Table 2.

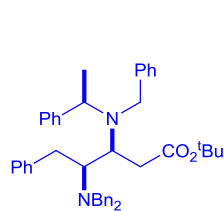
<p>112 Ref 47: –78 °C, 88% [α]_D²⁰ +93.0 (c 0.25, MeOH)</p>	<p>113 Ref 48: –78 °C, 84%, >99:1 dr [α]_D²⁴ –16.2 (c 1.0, CHCl₃)</p>	<p>114 Ref 49: –78 °C, 64%, >99:1 dr [α]_D²⁰ –27.4 (c 0.5, CHCl₃)</p>	<p>115 Ref 49: –78 °C, 71%, >99:1 dr [α]_D²⁰ –7.2 (c 2.0, CHCl₃)</p>
<p>116 Ref 50: –78 °C, 73%, >99:1 dr [α]_D²⁵ –0.6 (c 1.0, CHCl₃)</p>	<p>117 Ref 50: –78 °C, 74%, >99:1 dr [α]_D²⁵ –1.1 (c 0.9, CHCl₃)</p>	<p>118 Ref 28: –78 °C, 98%, >99:1 dr [α]_D²⁵ +45.1 (c 1.0, CHCl₃)</p>	<p>119 Ref 28: –78 °C, 92%, >99:1 dr [α]_D²⁵ +72.8 (c 1.0, CHCl₃)</p>
<p>120 Ref 28: –78 °C, 97%, >99:1 dr [α]_D²⁵ +23.8 (c 1.0, CHCl₃)</p>	<p>121 Ref 28: –78 °C, 94%, >99:1 dr [α]_D²⁵ +68.1 (c 1.0, CHCl₃)</p>	<p>122 Ref 51:^a –78 °C, 40%, >99:1 dr [α]_D²⁴ +3.5 (c 3.2, CHCl₃)</p>	<p>123 Ref 51:^a –78 °C, 43%, >99:1 dr [α]_D²⁴ –6.4 (c 2.0, CHCl₃)</p>



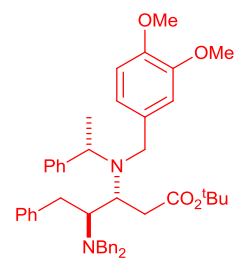
124
Ref 51:^a
–78 °C, 31%, >99:1 dr
[α]_D²⁴ –21.2 (c 1.0, CHCl₃)



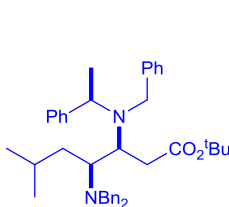
125
Ref 51:^a
–78 °C, 40%, >99:1 dr
[α]_D²⁴ +13.0 (c 2.7, CHCl₃)



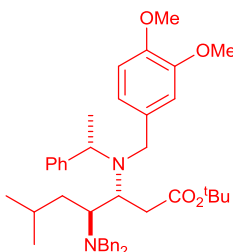
126
Ref 51:^a
–78 °C, 42%, >99:1 dr
[α]_D²⁴ +6.8 (c 2.3, CHCl₃)



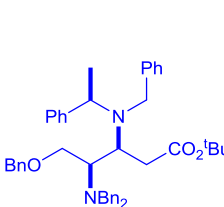
127
Ref 51:^a
–78 °C, 43%, >99:1 dr
[α]_D²⁴ –18.0 (c 1.0, CHCl₃)



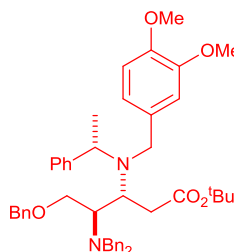
128
Ref 51:^a
–78 °C, 39%, >99:1 dr
[α]_D²⁴ +0.7 (c 2.9, CHCl₃)



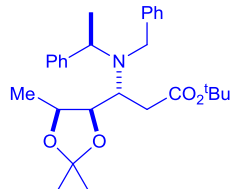
129
Ref 51:^a
–78 °C, 43%, >99:1 dr
[α]_D²⁴ –0.6 (c 2.0, CHCl₃)



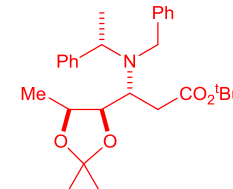
130
Ref 51:^a
–78 °C, 37%, >99:1 dr
[α]_D²⁴ +11.3 (c 2.6, CHCl₃)



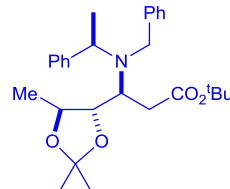
131
Ref 51:^a
–78 °C, 40%, >99:1 dr
[α]_D²⁴ –12.4 (c 2.5, CHCl₃)



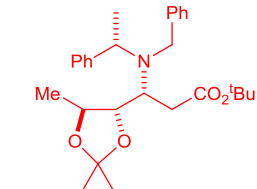
132
Ref 52:
–20 °C, Et₂O, 60:40 crude dr
38%, >99:1 dr
[α]_D²⁴ +65.2 (c 1.0, CHCl₃)



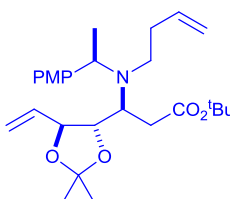
133
Ref 52:
–20 °C, Et₂O, 85:15 crude dr
39%, >99:1 dr
[α]_D²⁴ +8.7 (c 1.0, CHCl₃)



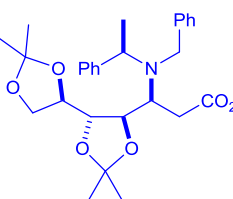
134
Ref 52:
–78 °C, 76:24 crude dr
47%, 98:2 dr
[α]_D²⁴ –22.4 (c 1.0, CHCl₃)



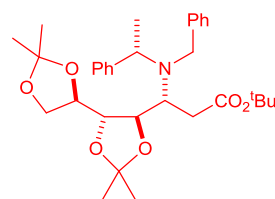
135
Ref 52:
–78 °C, 84:16 crude dr
57%, >99:1 dr
[α]_D²⁴ –8.0 (c 1.0, CHCl₃)



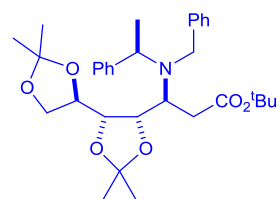
136
Ref 53:
–78 °C, 65%, >99:1 dr
[α]_D²⁵ –23.6 (c 0.6, CHCl₃)



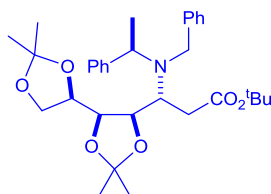
137
Ref 54:
–78 °C, 81:19 crude dr
60%, 85:15 dr



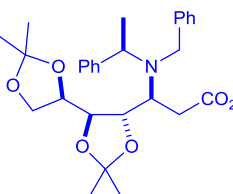
138
Ref 54:
–78 °C, >99:1 crude dr
73%, >99:1 dr
[α]_D²⁵ +23.5 (c 1.0, CHCl₃)



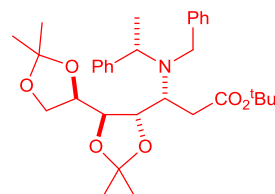
139
Ref 54:
–78 °C, >99:1 crude dr
94%, >99:1 dr
[α]_D²⁵ –18.8 (c 1.0, CHCl₃)



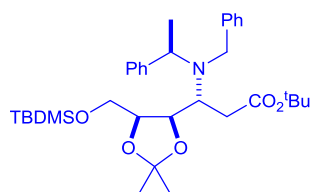
140
Ref 54:
–20 °C, Et₂O, 66:34 crude dr
42%, >99:1 dr
[α]_D²⁵ +44.2 (c 1.0, CHCl₃)



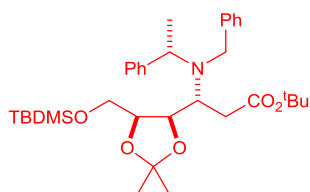
141
Ref 54:
–78 °C, 65:35 crude dr
52%, 96:4 dr
[α]_D²⁵ –26.2 (c 1.0, CHCl₃)



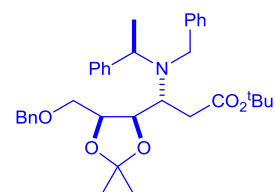
142
Ref 54:
–78 °C, 90:10 crude dr
41%, >99:1 dr
[α]_D²⁵ +4.7 (c 1.0, CHCl₃)



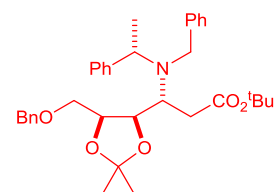
143
Ref 55:
–20 °C, Et₂O, 82:18 crude dr
58%, >99:1 dr
[α]_D²⁵ +34.7 (c 1.0, CHCl₃)



144
Ref 55:
–20 °C, Et₂O, >99:1 crude dr
90%, >99:1 dr
[α]_D²⁵ +13.8 (c 1.0, CHCl₃)



145
Ref 55:
–20 °C, Et₂O, 83:17 crude dr
44%, >99:1 dr
[α]_D²⁵ +25.8 (c 1.0, CHCl₃)



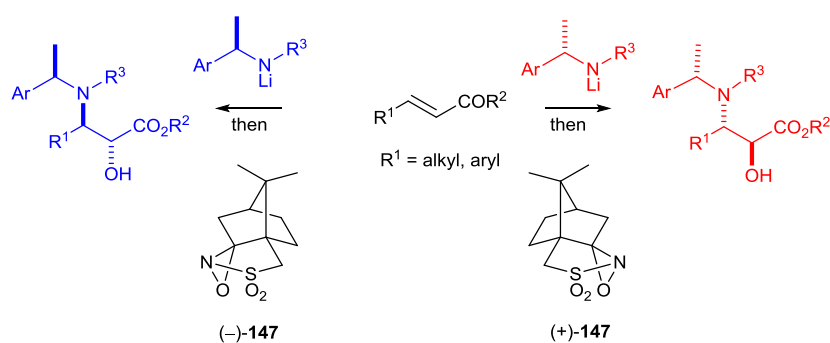
146
Ref 55:
–20 °C, Et₂O, 93:7 crude dr
79%, 93:7 dr
[α]_D²⁵ +3.3 (c 1.0, CHCl₃)

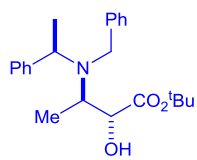
^a The reaction was performed under parallel kinetic resolution conditions [i.e., conjugate addition of a 50:50 pseudoenantiomeric mixture (*R*)-**2** and (*S*)-**14** to racemic α,β -unsaturated esters].

3. Enolate functionalisation

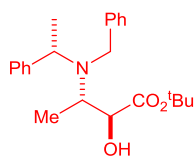
3.1. Synthesis of α -hydroxy- β -amino acid derivatives

Conjugate addition of an enantiomerically pure lithium amide followed by *in situ* oxidation of the resultant enolate with either (+)- or (–)-(camphorsulfonyl)oxaziridine (CSO) **147** gives the corresponding α -hydroxy β -amino esters. This reaction is highly diastereoselective and affords the corresponding 2,3-*anti*-products in most cases. In addition, enantiorecognition between CSO **147** and the intermediate β -amino enolate is not significant, thus the use of either enantiomer of CSO **147** can give comparable diastereoselectivity in this aminohydroxylation process,^{56,57} although the pairings of (*S*)-**2** [or the other (*S*)-lithium amide reagent such as **6–23**] or with (+)-CSO **147**, and (*R*)-**2** [or the other (*R*)-lithium amide reagent such as **6–23**] with (–)-CSO **147** are usual. All the recent examples reported since 2011 are presented below (Table 3).

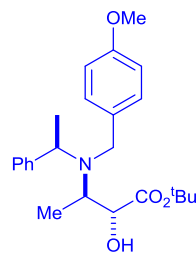
Table 3.



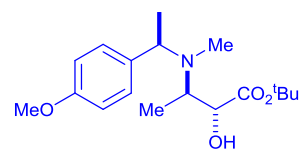
148
Ref 58: 58%, >99:1 dr
 $[\alpha]_D^{20}$ -27.9 (c 1.0, CHCl₃)
Ref 59: 91%, >99:1 dr
 $[\alpha]_D^{23}$ -35.5 (c 1.0, CHCl₃)
Ref 60: 91%, >99:1 dr
 $[\alpha]_D^{23}$ -35.5 (c 1.0, CHCl₃)



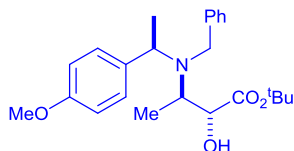
148
Ref 61: 64%, >99:1 dr
 $[\alpha]_D^{25}$ +33.0 (c 1.0, CHCl₃)



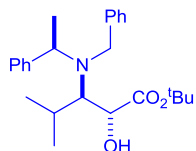
149
Ref 58: 80%, >99:1 dr
 $[\alpha]_D^{20}$ -7.2 (c 1.0, CHCl₃)



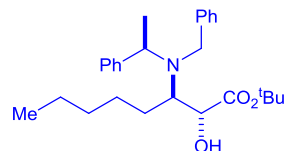
150
Ref 58: 71%, >99:1 dr
 $[\alpha]_D^{20}$ -23.5 (c 1.0, CHCl₃)



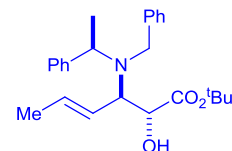
151
Ref 58: 82%, >99:1 dr
 $[\alpha]_D^{20}$ -8.4 (c 1.0, CHCl₃)



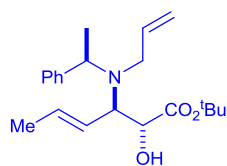
152
Ref 60: 56%, >99:1 dr
 $[\alpha]_D^{23}$ -32.2 (c 1.0, CHCl₃)



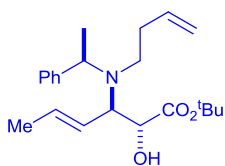
153
Ref 62: -78 °C, 84%, >99:1 dr
 $[\alpha]_D^{25}$ -27.0 (c 1.0, CHCl₃)



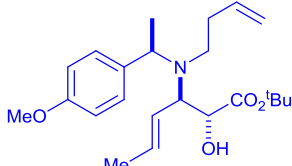
154
Ref 24: -78 °C, 69%, >99:1 dr
 $[\alpha]_D^{25}$ -63.1 (c 1.0, CHCl₃)



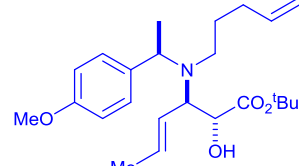
155
Ref 27: -78 °C, 61%, >99:1 dr
 $[\alpha]_D^{20}$ -60.4 (c 1.0, CHCl₃)



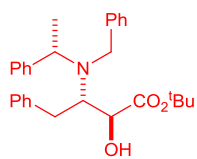
156
Ref 29, 63: -78 °C, 64%
 $[\alpha]_D^{23}$ -82.7 (c 1.0, CHCl₃)



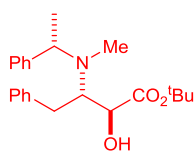
157
Ref 63: -78 °C, 70%
 $[\alpha]_D^{23}$ -80.4 (c 1.0, CHCl₃)



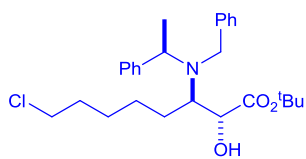
158
Ref 63: -78 °C, 66%
 $[\alpha]_D^{20}$ -44.6 (c 1.0, CHCl₃)



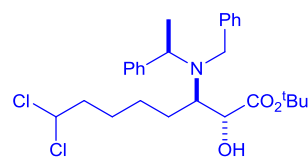
159
Ref 36: -78 °C, 71%, >99:1 dr
 $[\alpha]_D^{25}$ +46.5 (c 1.0, CHCl₃)



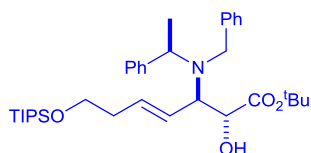
160
Ref 36: -78 °C, 44%
 $[\alpha]_D^{25}$ +60.8 (c 1.0, CHCl₃)



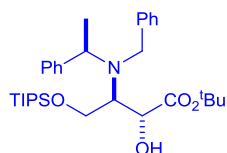
161
Ref 62: -78 °C, 80%, >99:1 dr
 $[\alpha]_D^{25}$ -23.7 (c 1.0, CHCl₃)



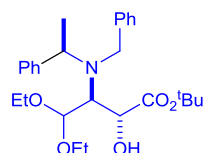
162
Ref 62: -78 °C, 60%, >99:1 dr
 $[\alpha]_D^{25}$ -19.0 (c 1.0, CHCl₃)



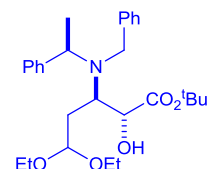
163
Ref 64:
72%, >99:1 dr
[α]_D²⁵ -41.2 (c 1.0, CHCl₃)



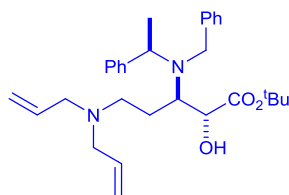
164
Ref 65:
80%, >99:1 dr



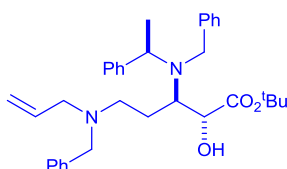
165
Ref 24:
-78 °C, 68%, >99:1 dr
[α]_D²⁵ -41.2 (c 1.0, CHCl₃)



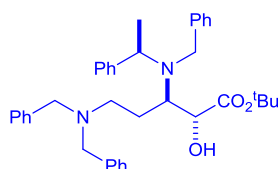
166
Ref 24:
-78 °C, 77%, 92:8 dr
[α]_D²⁵ -33.6 (c 1.0, CHCl₃)



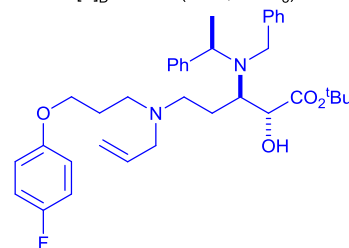
167
Ref 40:
68%, >99:1 dr
[α]_D²⁵ -5.1 (c 1.0, CHCl₃)



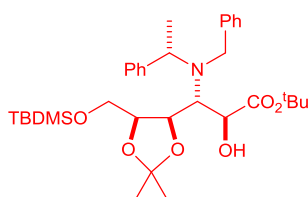
168
Ref 40:
42%, >99:1 dr
[α]_D²⁵ -27.3 (c 1.0, CHCl₃)



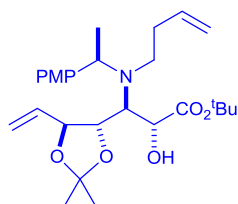
169
Ref 40:
33%, >99:1 dr
[α]_D²⁵ -22.5 (c 1.0, CHCl₃)



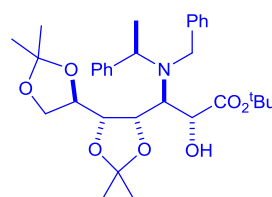
170
Ref 40:
64%, >99:1 dr
[α]_D²⁵ -19.4 (c 1.0, CHCl₃)



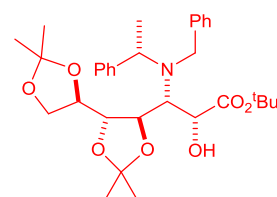
171
Ref 57b: -78 °C
60%, >99:1 dr
[α]_D²⁵ -4.1 (c 1.0, CHCl₃)



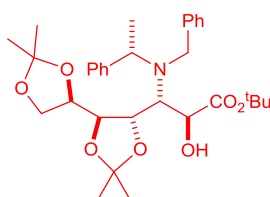
172
Ref 53: -78 °C
58%, >99:1 dr
[α]_D²⁵ -57.8 (c 0.6, CHCl₃)



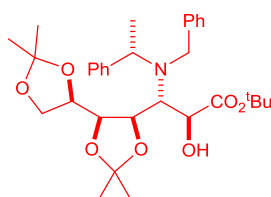
173
Ref 57c:
-78 °C, 76%, >99:1 dr
[α]_D²⁵ +9.7 (c 1.0, CHCl₃)



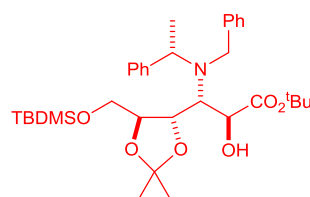
174
Ref 57c: -78 °C
82%, 64:40 dr, 39%, >99:1 dr
[α]_D²⁵ +25.0 (c 2.0, CHCl₃)



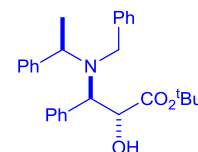
175
Ref 57c: -78 °C
65%, 70:30 dr, 37%, >99:1 dr
[α]_D²⁰ +17.0 (c 0.5, CHCl₃)



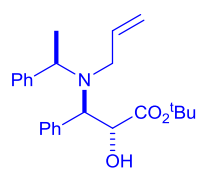
176
Ref 57c: -78 °C
35%, >99:1 dr
[α]_D²⁰ +26.5 (c 1.0, CHCl₃)



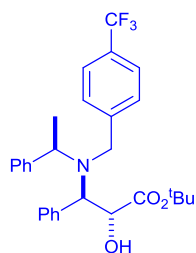
177
Ref 57b: -78 °C
66%, >99:1 dr
[α]_D²⁵ +3.5 (c 1.0, CHCl₃)



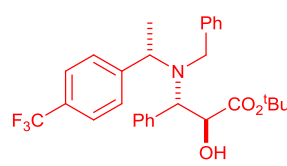
178
Ref 59:
93%, >99:1 dr
[α]_D²³ -26.7 (c 1.0, CHCl₃)



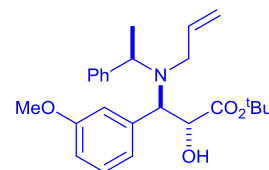
179
Ref 66:
-78 °C, 73%
[α]_D²⁰ +4.5 (c 1.0, CHCl₃)



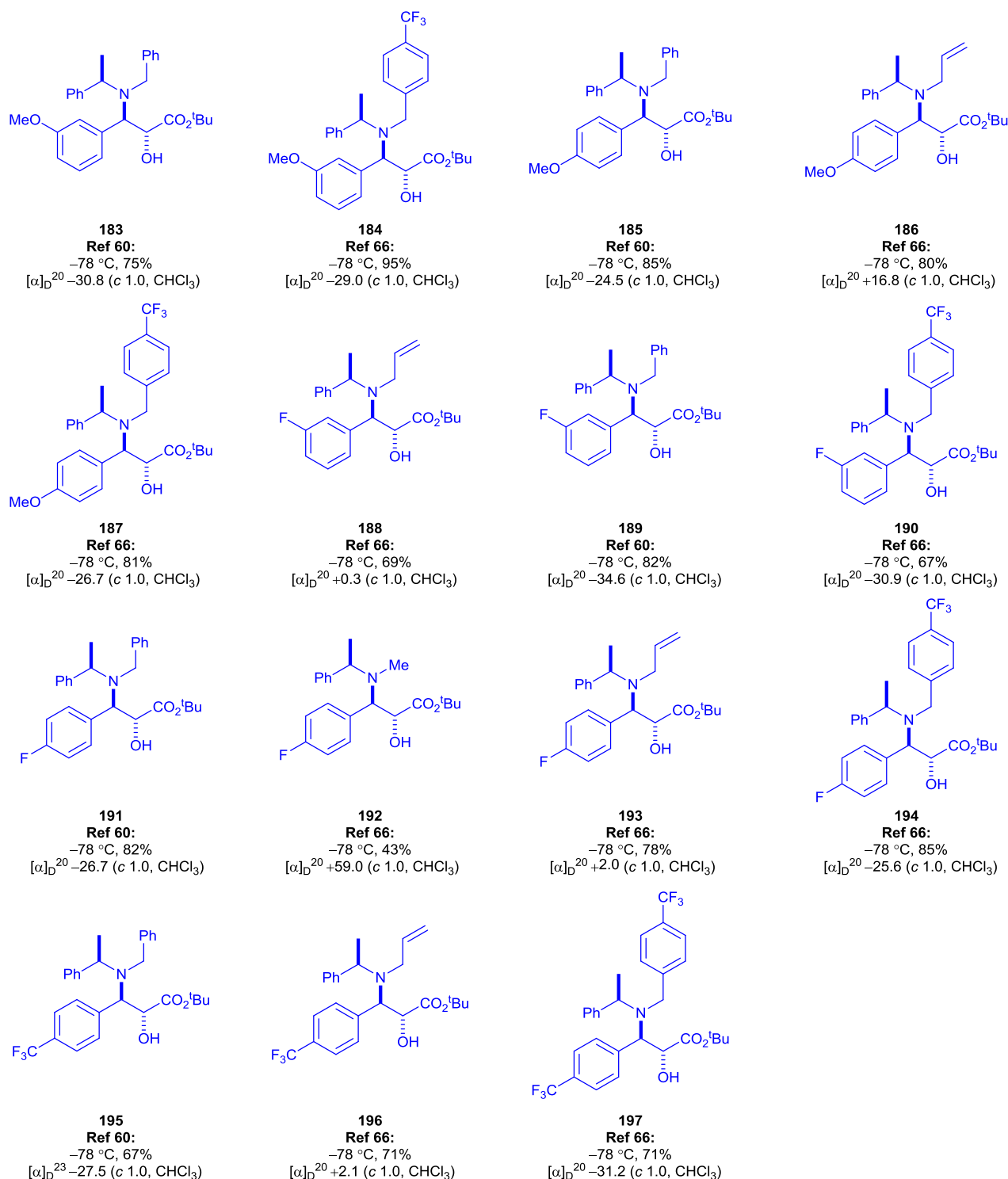
180
Ref 66:
-78 °C, 65%
[α]_D²⁰ -25.6 (c 1.0, CHCl₃)



181
Ref 66:
-78 °C, 94%
[α]_D²⁰ +27.8 (c 1.0, CHCl₃)

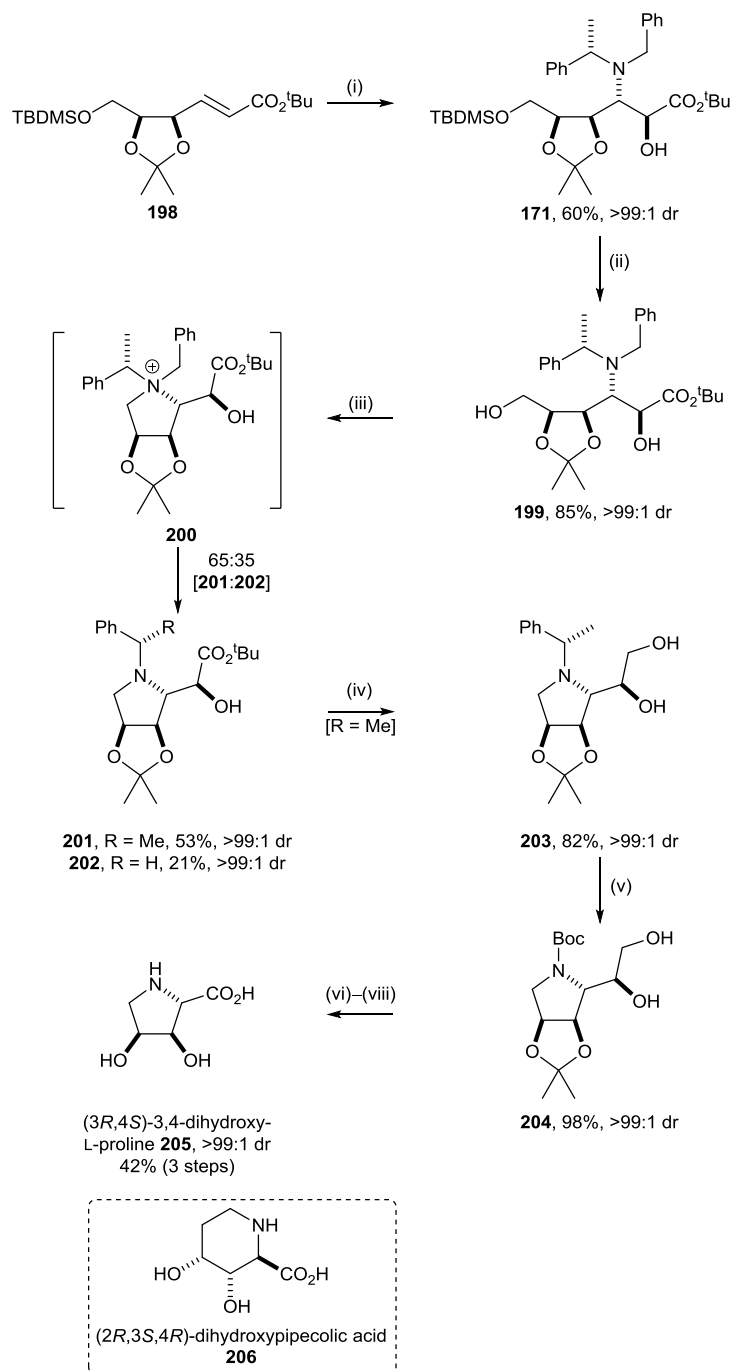


182
Ref 66:
-78 °C, 70%
[α]_D²⁰ +3.0 (c 1.0, CHCl₃)



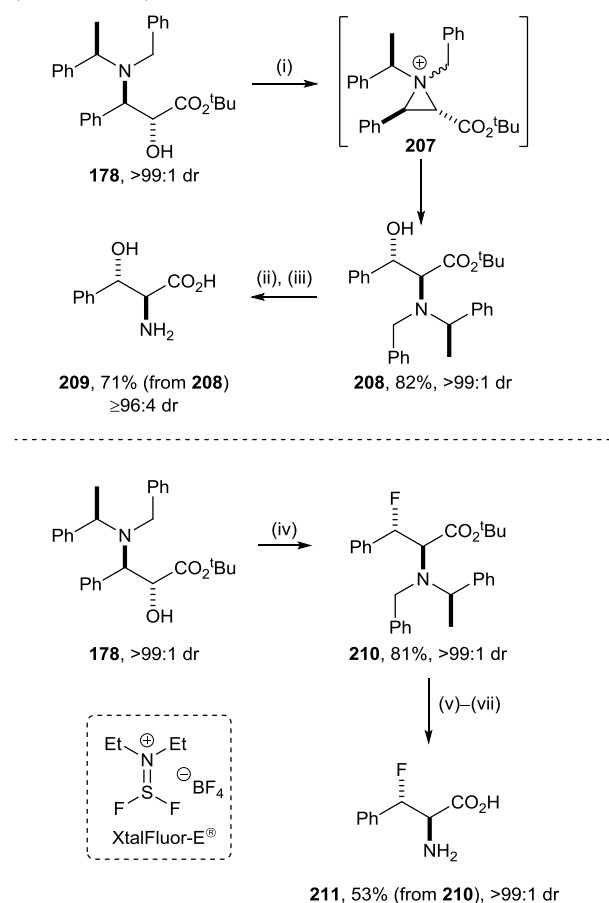
As an application of this aminohydroxylation, elaboration of the resultant α -hydroxy- β -amino esters to α -amino acids has also been developed. For example, aminohydroxylation of **198** using lithium amide (*S*)-**2** and (-)-CSO **147** gave α -hydroxy- β -amino ester **171** as the major product, which was isolated in 60% yield and >99:1 dr. Desilylation of α -hydroxy- β -amino ester **171** with TBAF gave diol **199** in 85% yield and >99:1 dr. Selective activation of the diol **199** at the primary hydroxyl group under Appel conditions promoted cyclisation to form initially pyrrolizidinium ion **200** followed by *in situ* *N*-debenzylation to give **201** (derived from the loss of *N*-benzyl group) in 53% yield and **202** (derived from the loss of *N*- α -

methylbenzyl group) in 21% yield as single diastereoisomer in each case. Reduction of **201** (R = Me) with LiAlH₄ gave diol **203** in 82% yield and >99:1 dr. Hydrogenolysis of pyrrolidine **203** in the presence of Boc₂O gave **204** in 98% yield and >99:1 dr. The cleavage of diol unit within **204** with NaIO₄ followed by oxidation and subsequent acid-mediated global hydrolysis gave 3,4-dihydroxy-L-proline **205** in 42% yield (from **204**) and >99:1 dr (Scheme 2).^{57a} Following a similar approach, employing oxidative cleavage of diol followed by oxidation to the corresponding α -amino acid, synthesis of (2*R*,3*S*,4*R*)-dihydroxypipecolic acid **206** was also reported.²⁹



Scheme 2. Reagents and conditions: (i) (*S*)-**2**, THF, −78 °C, 2 h, then (−)-CSO **147**, −78 °C to rt, 12 h; (ii) TBAF, THF, rt, 16 h; (iii) I₂, imidazole, PPh₃, PhMe, MeCN, 60 °C, 1 h; (iv) LiAlH₄, THF, −78 °C to rt, 16 h; (v) Boc₂O, H₂, Pd/C, MeOH, rt, 18 h; (vi) NaIO₄, EtOH, H₂O, rt, 15 min; (vii) NaClO₂, KH₂PO₄, cyclohexene, ^tBuOH, H₂O, rt, 18 h; (viii) HCl (2.0 M, aq), reflux, 8 h, then DOWEX 50WX8-200.

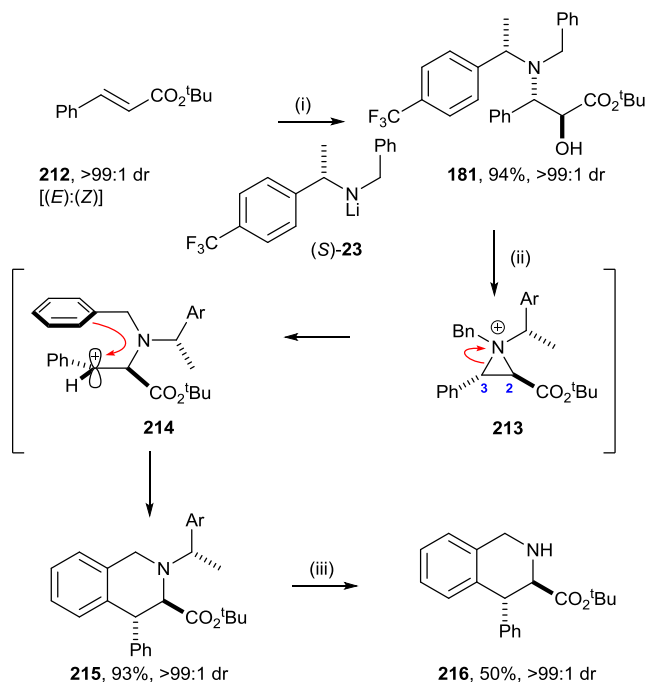
More general synthetic methodology to access enantiopure α -amino acid derivatives from α -hydroxy- β -amino esters via the corresponding aziridine⁵⁹ or aziridinium⁶⁰ intermediates was also developed. For example, treatment of **178** with Ms_2O in the presence of Et_3N activated the α -hydroxy group within **178**, which facilitated the formation of aziridinium intermediate **207**. The subsequent addition of H_2O promoted regioselective ring-opening to give the corresponding β -hydroxy- α -amino ester **208** in 82% yield and >99:1 dr. Hydrogenolytic removal of *N*-protecting groups within **208** and acid-mediated hydrolysis of the ester moiety gave β -hydroxyphenylalanine **209** in 71% yield (from **208**) and $\geq 96:4$ dr. α -Hydroxy- β -amino ester **128** was also converted into β -fluorophenylalanine **211** upon treatment with deoxyfluorination reagent combination XtalFluor-E and $\text{Et}_3\text{N}\cdot 3\text{HF}$, which promoted *in situ* formation of the corresponding aziridinium intermediate followed by regioselective ring-opening by fluoride to give β -fluoro- α -amino ester **210** in 81% yield and >99:1 dr. Oxidative *N*-debenzylation of **210** with NaBrO_3 and $\text{Na}_2\text{S}_2\text{O}_4$ (*vide infra*) followed by acid-mediated ester hydrolysis gave β -fluorophenylalanine **211** in 53% yield (from **210**) and >99:1 dr (Scheme 3).⁶⁷



Scheme 3. Reagents and conditions: (i) Ms_2O , Et_3N , CH_2Cl_2 , rt, 1 h then H_2O , rt, 24 h; (ii) H_2 (5 atm), $\text{Pd}(\text{OH})_2/\text{C}$, MeOH , rt, 16 h; (iii) 6.0 M aq HCl , 90 °C, 18 h; (iv) XtalFluor-E®, $\text{Et}_3\text{N}\cdot 3\text{HF}$, CH_2Cl_2 , rt, 2 h; (v) NaBrO_3 , $\text{Na}_2\text{S}_2\text{O}_4$, $\text{EtOAc}/\text{H}_2\text{O}$ (3:2), rt, 1 h; (vi) 1.0 M aq HCl ; (vii) propylene oxide, $^i\text{PrOH}$, rt, 6 h.

Enantiopure 3-(*tert*-butoxycarbonyl)-1,2,3,4-tetrahydroisoquinolines can also be accessed upon elaboration of α -hydroxy- β -amino esters.⁶⁶ For example, aminohydroxylation of **212** with (*S*)-**23** and (+)-CSO **147** gave α -hydroxy- β -amino ester **181** in 94% yield and >99:1 dr. Treatment of **181** with Tf_2O initially formed

aziridinium intermediate **213**, and subsequent rupture of the C(3)–N bond generates the corresponding benzylic carbenium ion **214**, which undergoes selective Friedel-Crafts type cyclisation of the more electron rich benzyl group to give 1,2,3,4-tetrahydroisoquinoline **215** as the sole product in 93% yield and >99:1 dr. The *p*-trifluoromethyl group within **181** is necessary to ensure high chemoselectivity in this cyclisation step. Hydrogenolytic *N*-deprotection of **215** gave 1,2,3,4-tetrahydroisoquinoline **216** in 50% yield and >99:1 dr (Scheme 4).

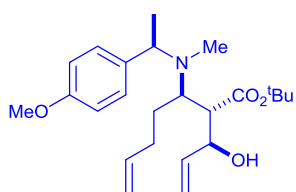
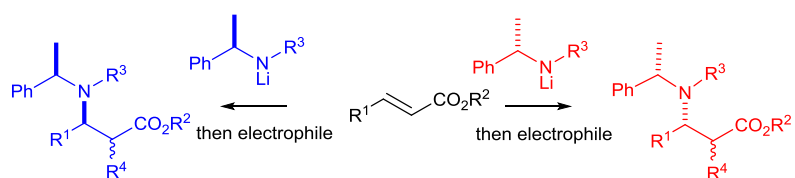


Scheme 4. Reagents and conditions: (i) (S)-23, THF, -78°C , 2 h then (+)-CSO **147**, -78°C to rt, 18 h; (ii) TiF_2O , DTBMP, CH_2Cl_2 , rt, 6 h; (iii) HCO_2NH_4 , Pd/C, MeOH, reflux, 3 h. [Ar = *p*-trifluoromethylphenyl].

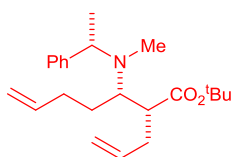
3.2 Synthesis of α -alkyl- β -amino acid derivatives

α -Alkylation of the β -amino ester products from conjugate addition is possible via treatment of the corresponding β -amino enolate with an electrophile (e.g., alkyl halides and aldehydes). Two different procedures, a “tandem” approach and a “stepwise” approach, are employed routinely: in the “tandem” approach, treatment of the intermediate lithium (Z)- β -amino enolate⁶⁸ (arising from conjugate addition of a lithium amide to an α,β -unsaturated carbonyl compound) with an electrophile gives the corresponding α -substituted β -amino ester; in the “stepwise” approach, the lithium β -amino enolate (arising from deprotonation of the corresponding β -amino ester) is reacted with the electrophile “E⁺”. The outcome of these procedures in terms of reaction conversion, identity of the major diastereoisomeric product and level of diastereoselectivity vary depending on the nature of the substrate, electrophile and reaction conditions. And the origin of those observations remains unclear. All the recent examples of α -alkylation of β -amino enolates, reported since 2011, are presented below (Table 4 for “tandem” enolate alkylations, Table 5 for “step-wise” enolate alkylations).

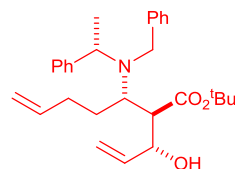
Table 4.



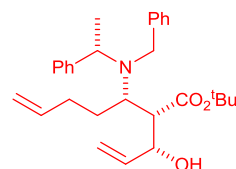
217
Ref 34:
 77:13:6:4 dr,
 59%, >99:1 dr
 $[\alpha]_D^{25} +7.6$ (c 1.9, CHCl₃)



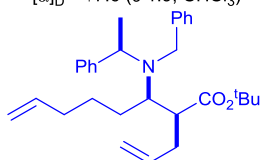
218
Ref 69:
 85:15 dr
 60%, 85:15 dr



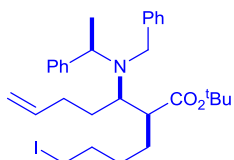
219
Ref 70:
 49:15:23:13 dr
 22%, >99:1 dr
 $[\alpha]_D^{25} +14.3$ (c 1.1, CHCl₃)



220
Ref 70:
 12:7:28:53 dr
 41%, >99:1 dr
 $[\alpha]_D^{25} +3.7$ (c 1.0, CHCl₃)

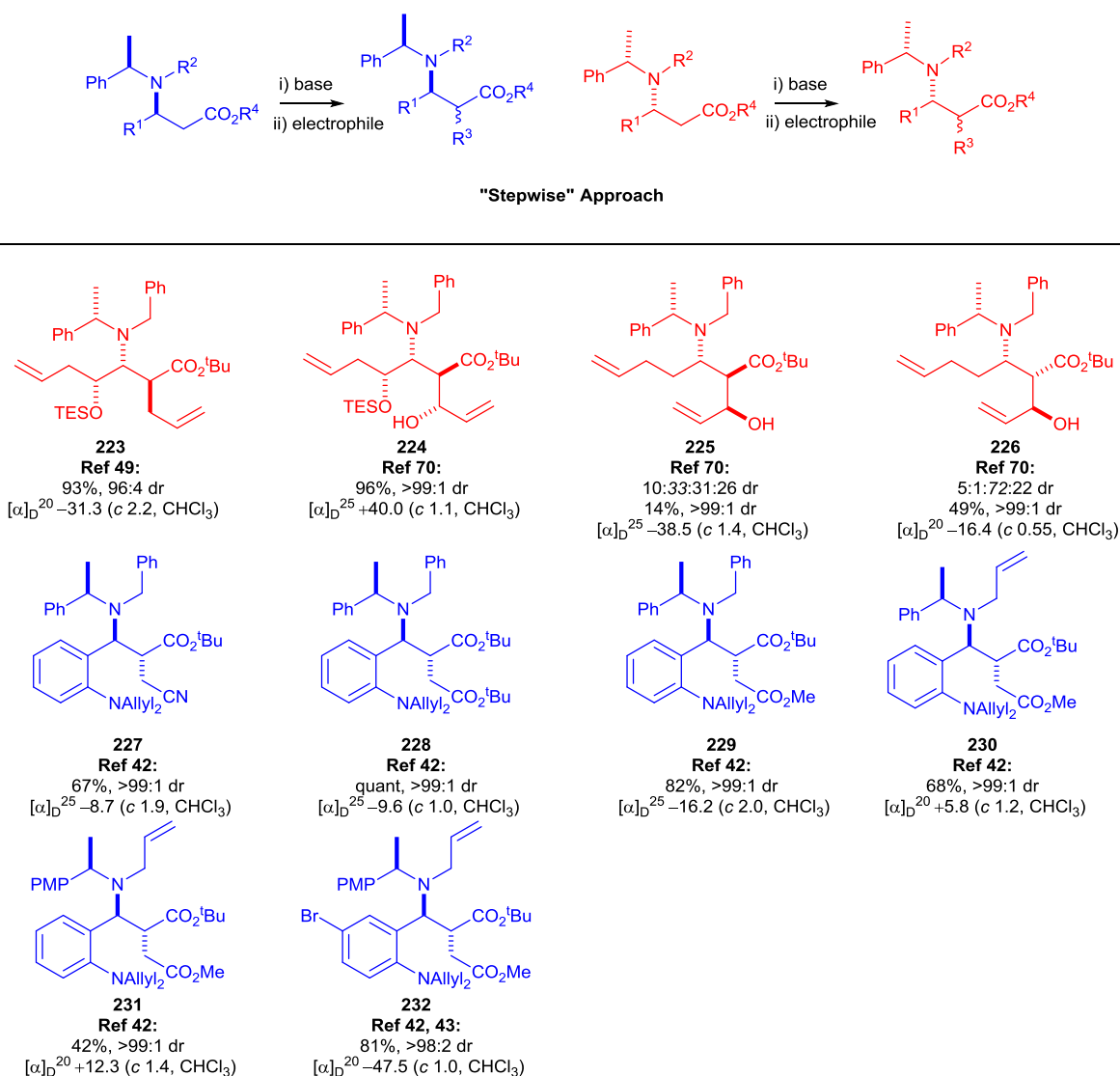


221
Ref 33:
 65:35 dr
 5%, >99:1 dr
 $[\alpha]_D^{20} +36.5$ (c 1.0, CHCl₃)



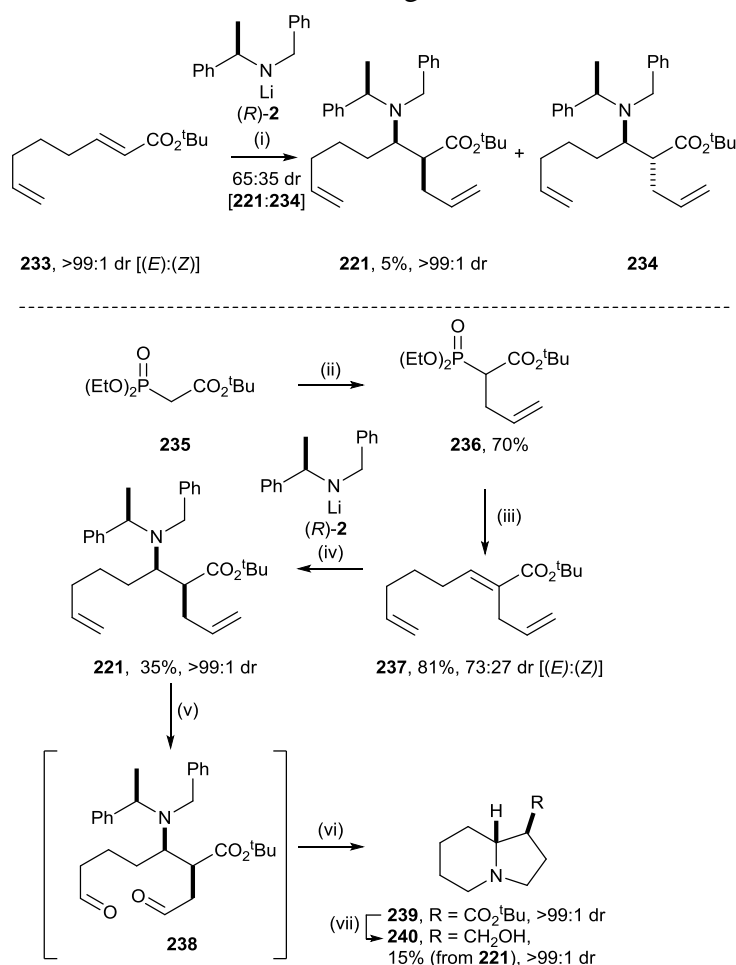
222
Ref 33:
 60:40 dr
 36%, >99:1 dr
 $[\alpha]_D^{20} +12.7$ (c 1.0, CHCl₃)

Table 5.



As an alternative approach to access α -alkyl- β -amino esters, the conjugate addition of an enantiopure lithium amide reagent to an α -substituted- α,β -unsaturated ester, followed by diastereoselective protonation of the resultant enolate can be achieved.^{71,33,72} For example, conjugate addition of lithium amide (*R*)-**2** to α,β -unsaturated ester **223** followed by addition of allyl bromide gave a 65:35 mixture of **221** and **234**, respectively, which were partially separable by flash column chromatography. Thus, after exhaustive purification, **221** was isolated in only 5% yield as a single diastereoisomer (>99:1 dr). Instead, conjugate addition to α -alkenyl- α,β -unsaturated ester **237** was employed: deprotonation of **235** with NaH followed by addition of allyl bromide gave **236** in 70% yield. Treatment of **236** with 5-hexenal following a modified Wadsworth-Emmons protocol⁷³ gave **237** in 81% yield and 73:27 dr [(*E*):(*Z*)]. Under the optimised conditions, conjugate addition of lithium amide (*R*)-**2** to **237** in PhMe followed by addition of 2,6-di-*tert*-

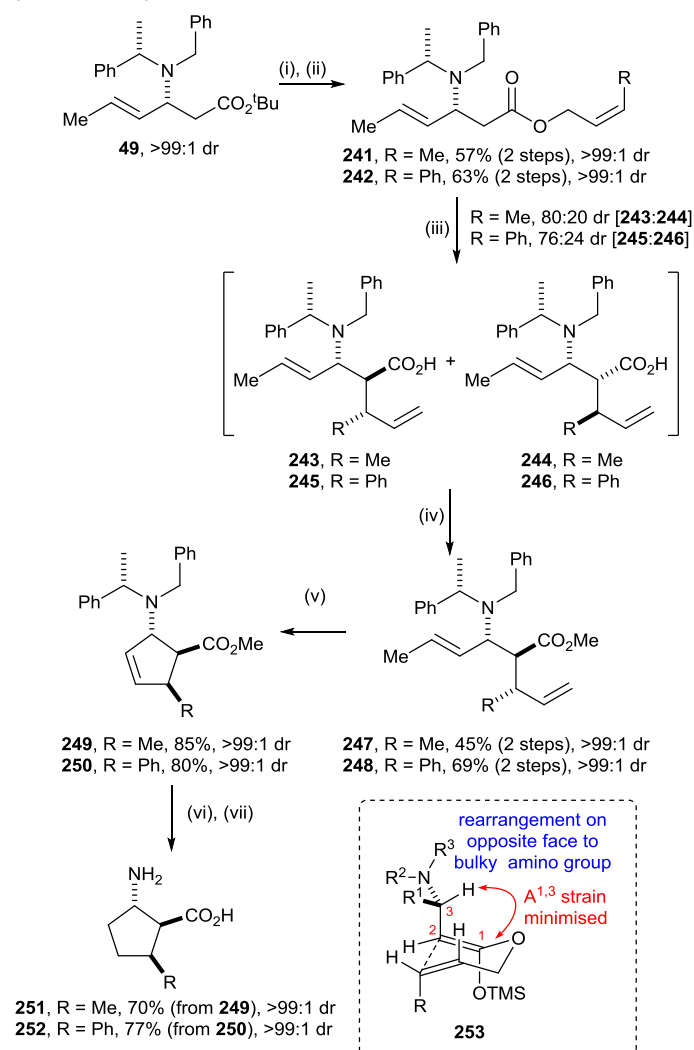
butylphenol in THF gave **221** in 35% yield as single diastereoisomer. The one-pot oxidative cleavage of the olefinic units within **221** gave dialdehyde **238** and subsequent hydrogenolysis of *N*-protecting groups facilitated *in situ* cyclisation and hydrogenation of the resultant iminium intermediate gave indolizidine **239**. Treatment of **239** with LiAlH₄ gave indolizidine **240** in 15% yield (from **221**) and >99:1 dr (Scheme 5).



Scheme 5. Reagents and conditions: (i) (R)-**2**, THF, −78 °C, 2 h then allyl bromide, −78 °C to rt, 12 h; (ii) NaH, THF, rt, 1 h then allyl bromide, 70 °C, 36 h; (iii) MeMgBr, THF, rt, 15 min then 5-hexenal, 70 °C, 3 h; (iv) (R)-**2**, PhMe, −78 °C, 1 h then −30 °C, 2 h then THF, −78 °C, 30 min then 2,6-di-*tert*-butylphenol, −78 °C to rt, 30 min; (v) OsO₄, NaIO₄, 2,6-lutidine, 1,4-dioxane/H₂O (3:1), rt, 40 min; (vi) H₂ (5atm), Pd(OH)₂/C, MeOH, rt, 120 h; (vii) LiAlH₄, THF, −78 °C to rt, 2 h.

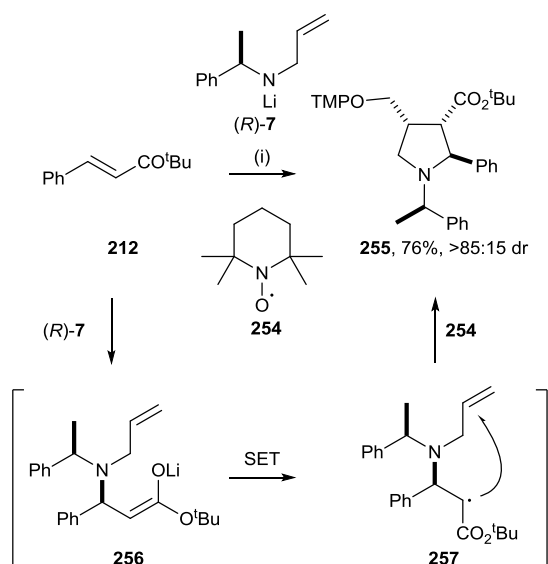
Ireland-Claisen rearrangement of the β-amino ester products of the conjugate addition has also been shown to achieve overall diastereoselective α-functionalisation.^{25,26} The benefit of this methodology is that it can create two more stereogenic centres within the β-amino ester scaffold in a single chemical operation. For example, transesterification of the known β-amino ester **49** gave the corresponding allylic ester rearrangement precursors **241** (R = Me) and **242** (R = Ph) in 57 and 63% yield, respectively. Ireland-Claisen rearrangement of **241** and **242** was achieved by deprotonation with LiHMDS and treatment of the resultant lithium (*E*)-β-amino enolates with TMSCl, followed by heating at reflux in PhMe. This gave an ~80:20 mixture of the corresponding carboxylic acids **243** and **244**, and **245** and **246**, respectively. After conversion to the corresponding methyl esters, **247** and **248** were isolated in 45 and 69% yield, respectively, as single diastereoisomers in each case. The stereochemical outcome of this rearrangement was rationalised via chair-like transition state **253** where 1,3-allylic strain between the C(3)-alkyl group and the C(1)–O bond is

minimised, and rearrangement occurs on the face opposite to the bulky *N*-benzyl-*N*-(α -methylbenzyl) group. α -Alkenyl- β -amino esters **247** and **248** were elaborated to 1,2-*anti*-1,5-*syn*-transpentacines **251** and **252** via ring-closing metathesis followed by hydrogenolysis/hydrogenation and ester hydrolysis in good overall yield (Scheme 6).



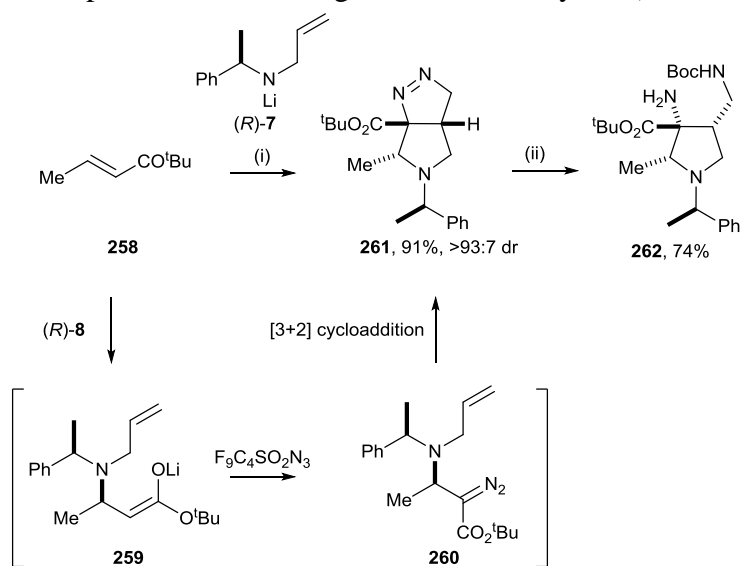
Scheme 6. Reagents and conditions: (i) CH₂Cl₂/TFA (2:1), rt, 16 h; (ii) (COCl)₂, CH₂Cl₂, DMF, 0 °C to rt, 1 h then *cis*-RCH=CHCH₂OH (R = Me or Ph), CH₂Cl₂, 0 °C to rt, 16 h; (iii) LiHMDS, TMSCl, PhMe, −78 °C, 15 min, then reflux, 1 h; (iv) DBU, MeI, MeCN, rt, 16 h; (v) Grubbs I, CH₂Cl₂, 40 °C, 24 h; (vi) H₂ (1 atm), Pd(OH)₂/C, MeOH, rt, 24 h; (vii) HCl (6.0 M aq), reflux, 16 h then DOWEX 50WX8.

Jahn and co-workers reported a one-pot protocol for lithium amide conjugate addition followed by radical cyclisation of an α -radical intermediate and oxygenation by ferrocenium hexafluorophosphate and TEMPO to form highly functionalised pyrrolidines. Treatment of α,β -unsaturated ester **212** with lithium amide (*R*)-**7** gave initially the corresponding enolate intermediate **256** and subsequent addition of ferrocenium hexafluorophosphate and TEMPO **254** facilitated the tandem SET oxidation/5-exo radical cyclisation/oxygenation sequence *in situ* to give pyrrolidine **255** in 76% yield and >85:15 dr (Scheme 7).¹³



Scheme 7. Reagents and conditions: (i) **(R)-7**, THF, -78°C , 30 min then ferrocenium hexafluorophosphate, TEMPO **254**, -78°C , 40–60 min.

Jahn and co-workers also developed another domino reaction using lithium amide conjugate addition/[3+2]cycloaddition to access diamino-pyrrolidines. β -Amino enolate **259** (derived from **258**) was treated with nonafllyl azide to form the corresponding α -diazo ester **260** and *in situ* 1,3-dipolar cycloaddition gave bicyclic pyrazoline **261** in 91% yield and >93:7 dr. Hydrogenolytic ring-opening of **261** with Raney-Ni in the presence of Boc_2O gave **262** in 74% yield (Scheme 8).⁷⁴



Scheme 8. Reagents and conditions: (i) **(R)-7**, THF, -78°C , 30 min then nonafllyl azide, 15 min then AcOH, rt overnight; (ii) H_2 (10 bar), Raney-Ni, Boc_2O , MeOH, 50°C , 2 h.

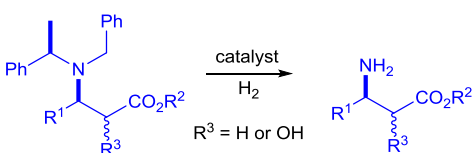
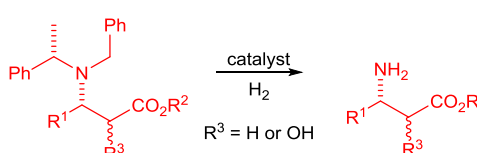
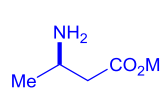
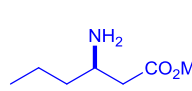
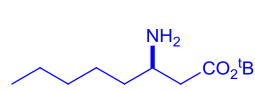
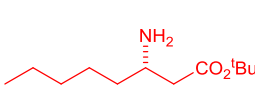
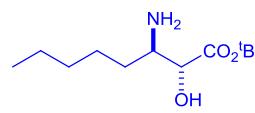
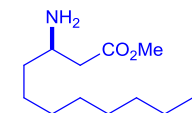
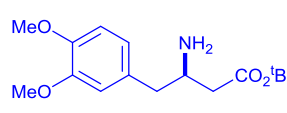
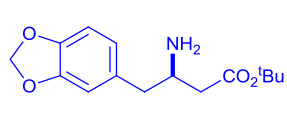
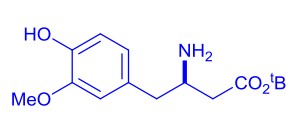
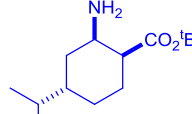
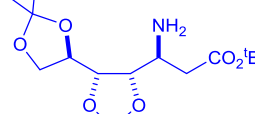
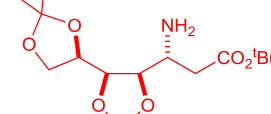
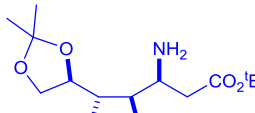
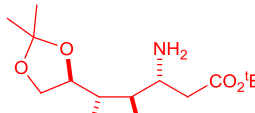
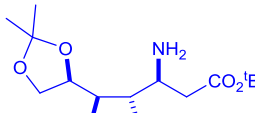
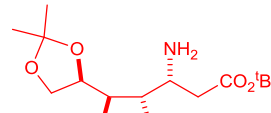
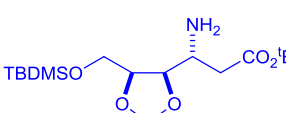
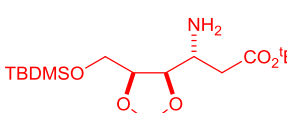
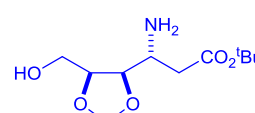
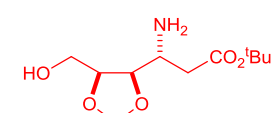
4. Global and selective deprotection strategies

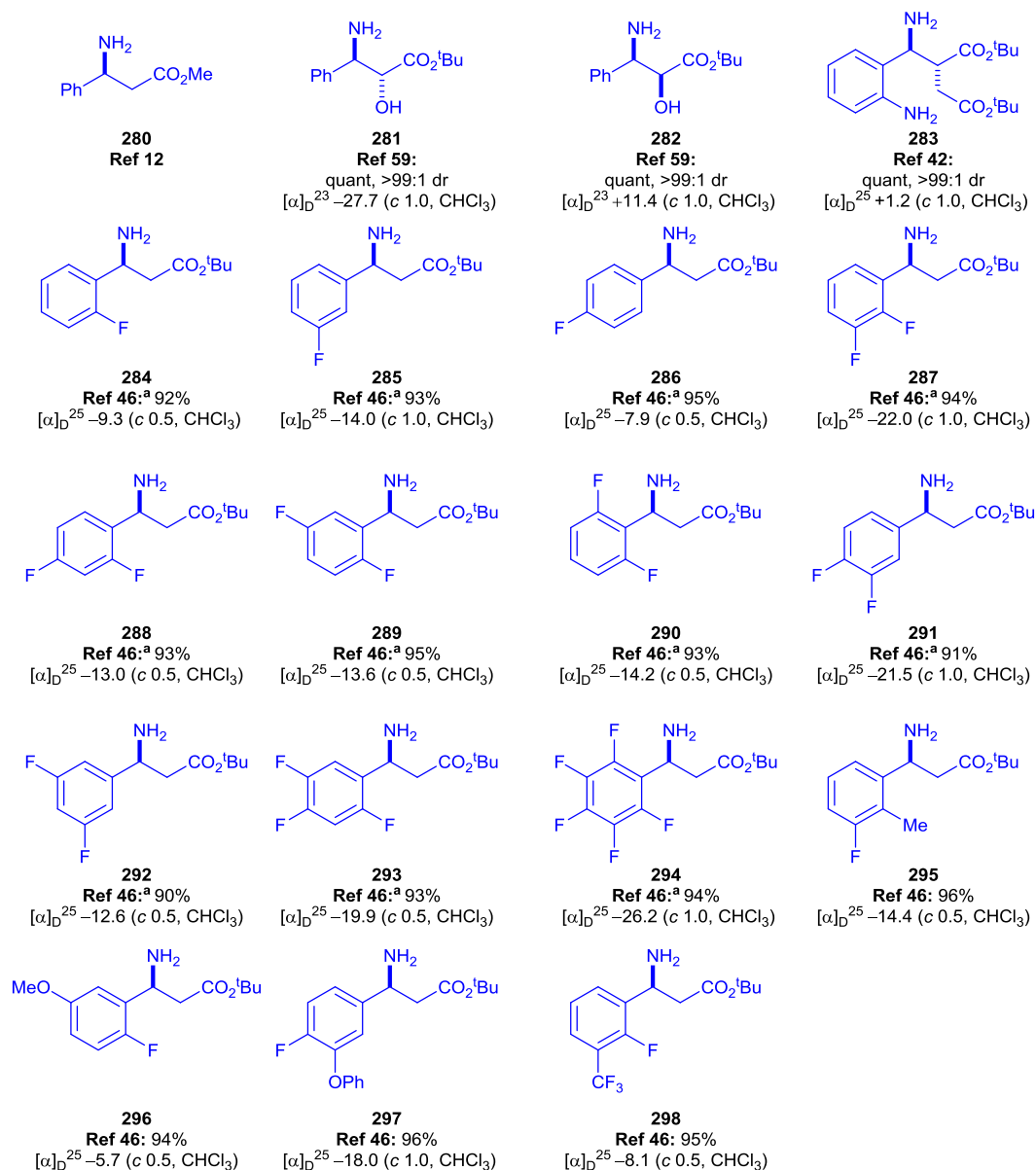
4.1. Global deprotection: synthesis of primary β -amino esters

Hydrogenolytic *N*-deprotection under the established conditions (either 1 or 5 atm of hydrogen in MeOH or EtOAc with a Pd catalyst) facilitates global *N*-deprotection of *N*-benzyl-*N*- α -methylbenzyl substituted β -amino esters derived from conjugate addition. This protocol gives the corresponding primary β -amino esters

in excellent yield, typically with no need for purification. A list of examples reported since 2011 is presented below (Table 6).

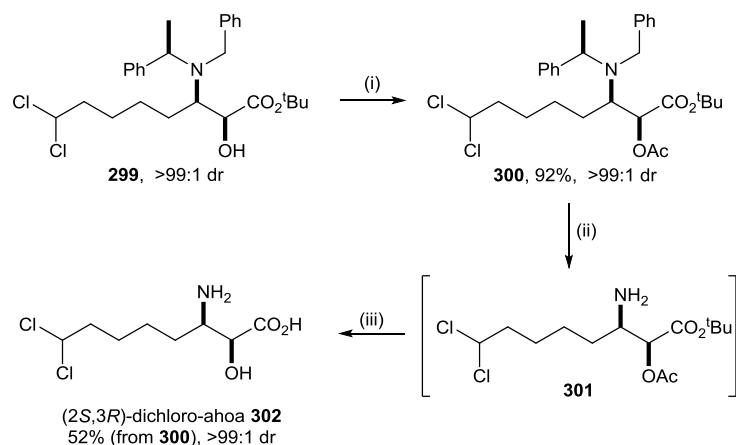
Table 6.

			
 263 Ref 11, 12: 80%	 264 Ref 12, 17: 91% $[\alpha]_D^{24} -16.6$ (c 1.0, CHCl ₃)	 265 Ref 19: 90% $[\alpha]_D^{23} -13.3$ (c 0.7, CHCl ₃)	 265 Ref 19: 81% $[\alpha]_D^{23} +13.8$ (c 0.7, CHCl ₃)
 266 Ref 62: 96%, >99:1 dr $[\alpha]_D^{25} +8.3$ (c 1.0, CHCl ₃)	 267 Ref 12	 268 Ref 37: $[\alpha]_D^{25} +1.1$ (c 0.75, CHCl ₃)	 269 Ref 37: $[\alpha]_D^{25} -1.8$ (c 0.8, CHCl ₃)
 270 Ref 37: $[\alpha]_D^{25} +2.9$ (c 1.6, CHCl ₃)	 271 Ref 47: 90% $[\alpha]_D^{20} -39.0$ (c 0.125, MeOH)	 272 Ref 54: quant, >99:1 dr $[\alpha]_D^{25} +25.0$ (c 1.0, CHCl ₃)	 273 Ref 54: 76%, >99:1 dr $[\alpha]_D^{25} +1.4$ (c 1.0, CHCl ₃)
 274 Ref 54: 87%, 85:15 dr	 275 Ref 54: quant, >99:1 dr $[\alpha]_D^{25} +18.3$ (c 1.0, CHCl ₃)	 276 Ref 54: 94%, 96:4 dr $[\alpha]_D^{25} -18.4$ (c 1.0, CHCl ₃)	 277 Ref 54: 77%, >99:1 dr $[\alpha]_D^{25} -10.0$ (c 1.0, CHCl ₃)
 278 Ref 55: 89%, >99:1 dr	 278 Ref 55: 64%, >99:1 dr $[\alpha]_D^{25} -6.7$ (c 1.0, CHCl ₃)	 279 Ref 55: 42%, >99:1 dr $[\alpha]_D^{25} +20.7$ (c 1.0, CHCl ₃)	 279 Ref 55: 81%, 93:7 dr



^a Pd(OH)₂/C (6% w/w), H₂ (5 atm), MeOH, rt, 24 h. ^b Pd(OH)₂/C (26% w/w), H₂ (5 atm), MeOH, rt, 24 h.

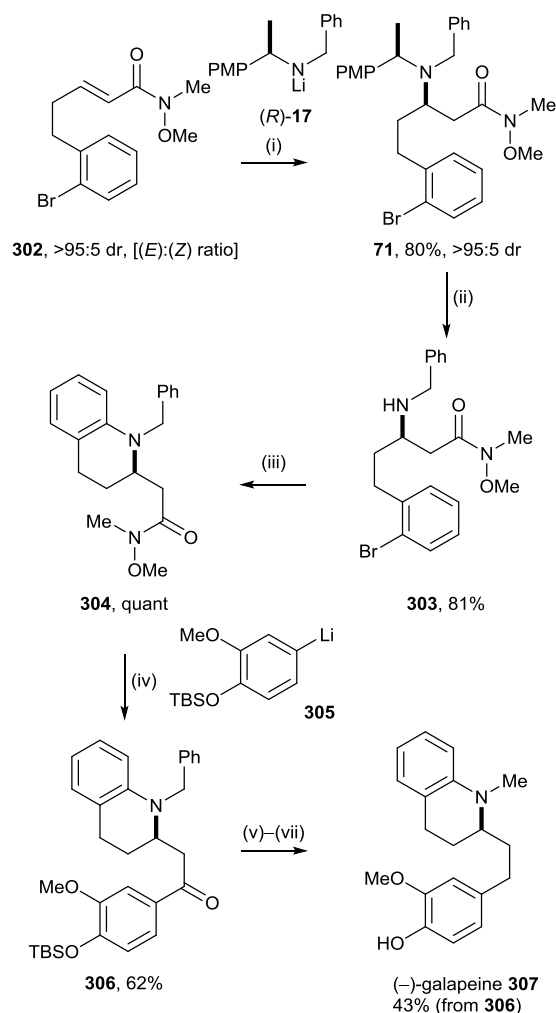
The hydrogenolytic *N*-debenzylation strategy for the β-amino esters incorporating olefinic functionalities and/or halides is not applicable as the undesired hydrogenation/hydrogenolysis would also occur. Thus, oxidative *N*-debenzylation with NaBrO₃ and Na₂S₂O₄ was employed for oxidative global removal of *N*-benzyl-*N*-α-methylbenzyl groups. For example, efficient chemoselective hydrogenolytic *N*-deprotection of dichloroalkyl α-hydroxy-β-amino ester **299** was not possible due to the competitive dehalogenation, however, the corresponding acetate **300**, which was prepared by treatment of **299** with Ac₂O in 92% yield, was treated with NaBrO₃ and Na₂S₂O₄ to give primary amine **301**. The immediate treatment of **301** with 6.0 M aq HCl gave **302**, the *N*-terminal α-hydroxy-β-amino acid component of microginin 680, in 52% yield from **300** (Scheme 9).⁶²



Scheme 9. Reagents and conditions: (i) Ac₂O, DMAP, pyridine, rt, 18 h; (ii) NaBrO₃, Na₂S₂O₄, EtOAc/H₂O (1:2), rt, 4 h; (iii) 6.0 M aq HCl, rt, 18 h then Dowex.

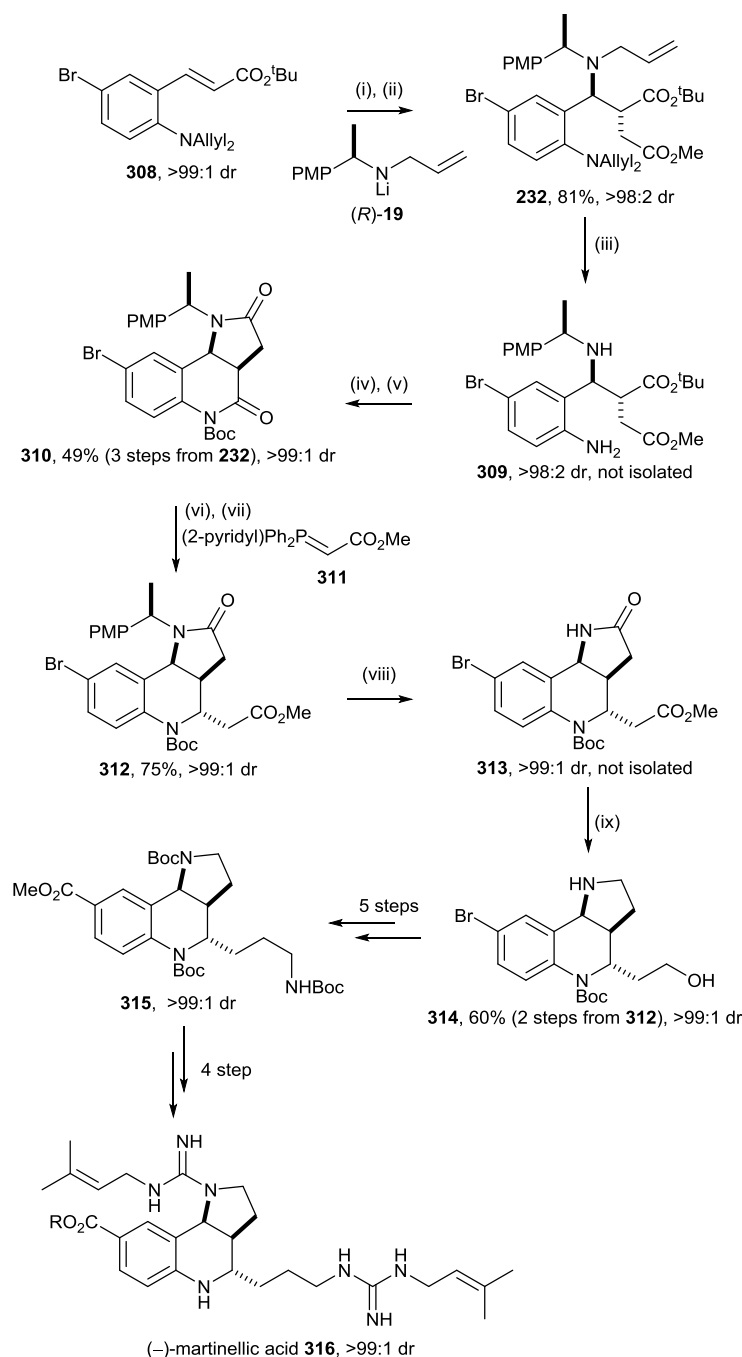
4.2. Selective deprotection strategies

Chemoselective procedures for the oxidative cleavage of benzyl groups employing either CAN or DDQ have been developed,⁷⁵ which allows selective removal of one of the benzyl groups and a discussion of this has been included in our previous reviews.^{1,2} In this section, other strategies for selective removal of *N*-protecting groups reported since 2011 are discussed. Due to the strongly electron donating nature of *p*-methoxybenzyl group (i.e., ability to stabilise the corresponding benzylic cation), selective *N*-deprotection of α -methyl *p*-methoxybenzyl groups can be achieved by treatment under various acidic conditions. For example, this approach was utilised in the asymmetric synthesis of the tetrahydroquinoline alkaloid (–)-galipeine **307**, and this study provided the unambiguous structural determination and resulted in the structural revision of galipenine.³⁹ Conjugate addition of lithium amide (*R*)-**17** to α,β -unsaturated Weinreb amide **302** gave β -amino amide **71** in 80% yield as a single diastereoisomer. Treatment of **71** with HCO₂H in the presence of Et₃SiH effected selective *N*-deprotection of the *N*- α -methyl-*p*-methoxybenzyl group to give **303** in 81% yield. Pd-Catalysed intramolecular amination of **303** gave tetrahydroquinoline **304** quantitatively. Treatment of **304** with aryl lithium **305** gave ketone **306** in 62% yield and subsequent reductive deoxygenation followed by *N*-methylation gave (–)-galipeine **307** in 43% yield over three steps from **306** (Scheme 10). Other methods of removal of *N*- α -methyl-*p*-methoxybenzyl groups under acidic conditions include treatment with TFA,^{41,20} and aq HCl.^{38,63}



Scheme 10. *Reagents and conditions:* (i) (*R*)-**17**, THF, $-78\text{ }^{\circ}\text{C}$, 2 h; (ii) HCO_2H , Et_3SiH , $90\text{ }^{\circ}\text{C}$, 16 h; (iii) $\text{Pd}(\text{OAc})_2$, X-Phos, Cs_2CO_3 , PhMe, reflux, 24 h; (iv) **305**, $-78\text{ }^{\circ}\text{C}$, 90 min; (v) LiAlH_4 , THF, reflux, 16 h; (vi) TFA, Et_3SiH , rt, 16 h; (vii) H_2 , Pd/C, formalin, MeOH, rt, 24 h.

Lithium *N*-allyl-*N*-(α -methylbenzyl)amide **7** and the corresponding *p*-methoxybenzyl analogue amides **19** have often been employed in synthesis for the purpose of distinguishing between the two groups on the nitrogen. For example, lithium *N*-allyl-*N*-(α -methyl-*p*-methoxybenzyl)amide **19** was used in the asymmetric synthesis of (–)-martinellic acid **316**. Conjugate addition of lithium amide (*R*)-**19** to α,β -unsaturated ester **308**, followed by “stepwise” enolate alkylation with methylbromoacetate gave **232** in 81% yield and >98:2 dr (from **308**). Chemoselective *N*-deallylation of **232** was readily achieved by treatment with $\text{Pd}(\text{PPh}_3)_4$ and DMBA to give secondary amine **309**, and subsequent cyclisation and *N*-Boc protection gave **310** in 49% yield (from **232**). Chemoselective reduction of **310** with $\text{LiAl}(\text{O}^i\text{Bu})_3\text{H}$ gave the corresponding hemiaminal followed by treatment with yild **311** gave **312** in 75% yield over the two steps. The removal of *N*- α -methyl-*p*-methoxybenzyl group within **312** was achieved by treatment with CAN and reduction of methyl ester **313** gave **314** in 60% yield (from **312**). Azacyclic intermediate **314** was elaborated to (–)-martinellic acid **316** in nine further steps (Scheme 11).^{42,43} *N*-Deallylation of *N*-allyl-*N*- α -methylbenzyl amine was also reported using Wilkinson’s catalyst in aq MeCN under reflux.¹⁵



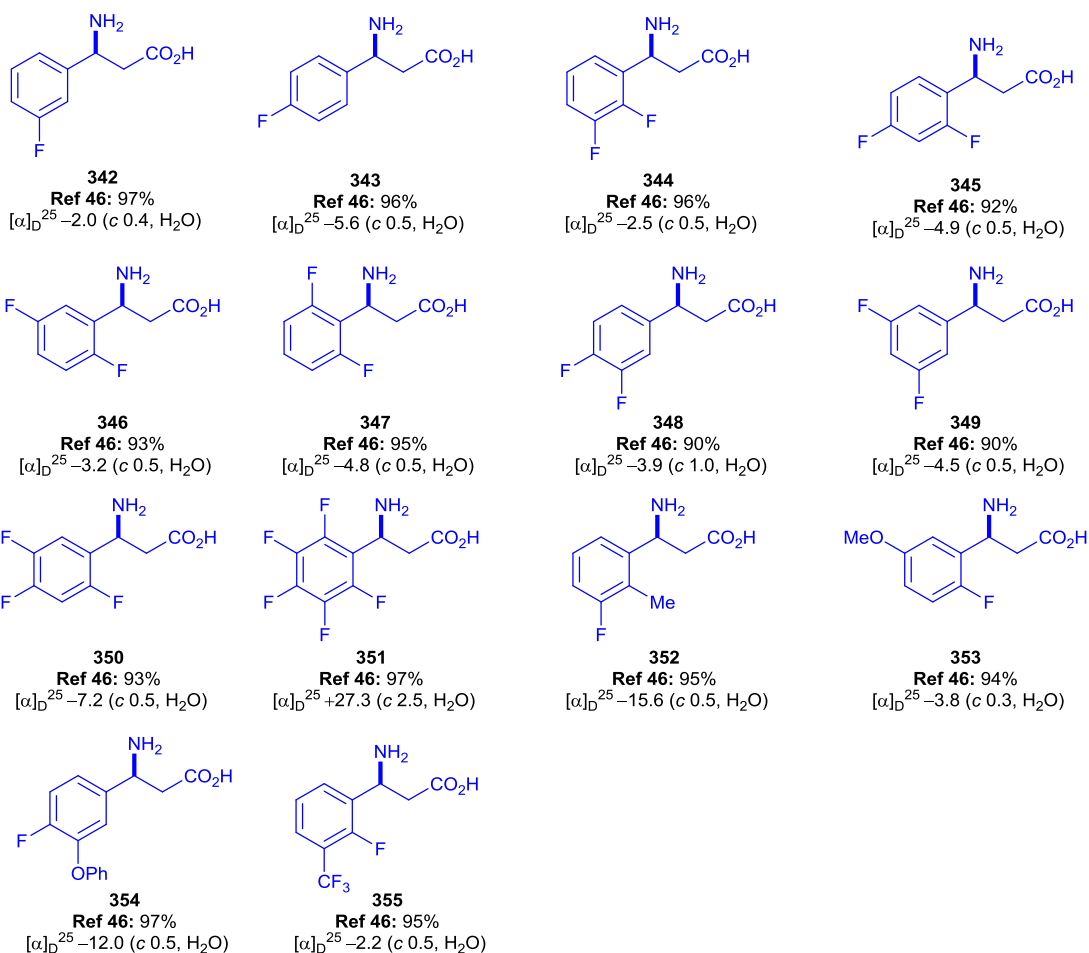
Scheme 11. Reagents and conditions: (i) (R)-19, THF, -78 °C, 2 h; (ii) LDA, THF, -78 °C, 1 h then MeO₂CCH₂Br, -78 °C to rt, 16 h; (iii) Pd(PPh₃)₄, DMBA, CH₂Cl₂, 35 °C, 16 h; (iv) PhCO₂H, PhMe, reflux, 16 h; (v) Boc₂O, DMAP, CH₂Cl₂, 35 °C, 16 h; (vi) LiAl(O^tBu)₃H, THF, 0 °C, 1 h; (vii) 311, PhMe, 80 °C, 72 h; (viii) CAN, MeCN/H₂O (1:1), rt, 1 h; (ix) BH₃·THF, reflux, 3 h then MeOH, reflux, 48 h.

4.3. Ester hydrolysis: synthesis of β-amino acids

Hydrolysis of β-amino esters derived from conjugate addition of enantiopure lithium amides provides the corresponding β-amino acids, via an either acid-mediated protocol (e.g., HCl or TFA) or base-mediated protocol (e.g., aq KOH). β-Amino acids derived from lithium amide adducts reported since 2011 are listed below (Table 7).

Table 7.

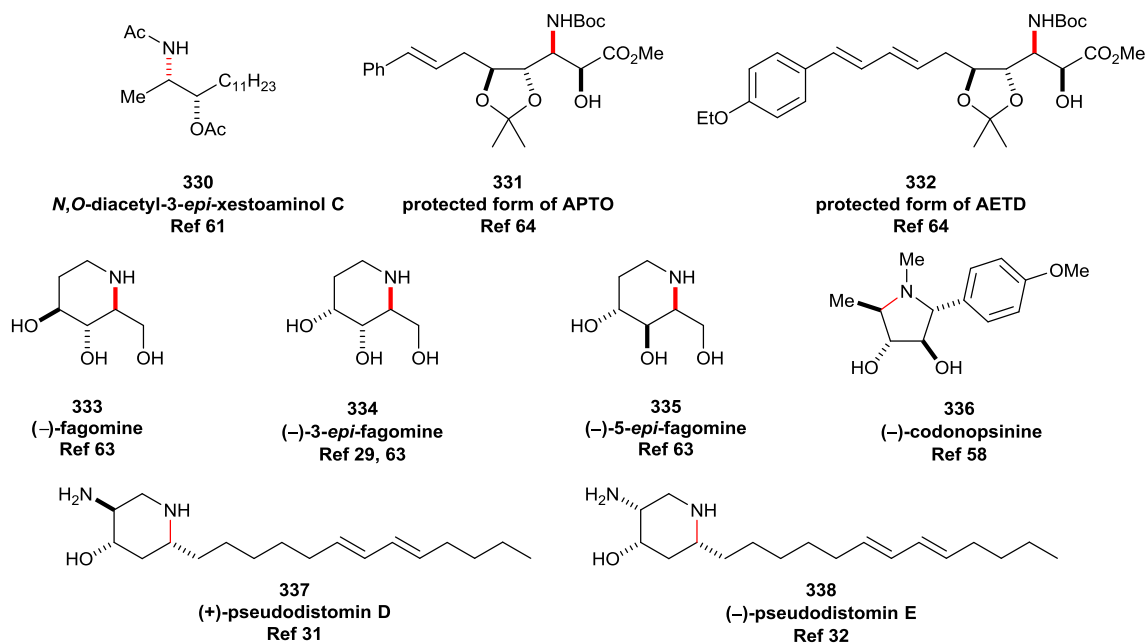
<p>317 Ref 62: 60%, >99:1 dr [α]_D²⁵ +3.6 (c 1.0, MeOH)</p>	<p>318 Ref 62: 79%, >99:1 dr [α]_D²⁵ -6.0 (c 1.0, H₂O/MeOH (1:1))</p>	<p>319 Ref 62: 91%, >99:1 dr [α]_D²⁵ +20.4 (c 1.0, MeOH)</p>	<p>320 Ref 62: 89%, >99:1 dr [α]_D²⁵ -4.9 (c 0.5, MeOH)</p>
<p>321 Ref 62: 47%, >99:1 dr [α]_D²⁵ +32.7 (c 0.5, MeOH)</p>	<p>322 Ref 62: 52%, >99:1 dr [α]_D²⁵ -7.7 (c 0.5, MeOH)</p>	<p>323 Ref 26: 88%, >99:1 dr [α]_D²⁰ -19.6 (c 0.2, H₂O)</p>	<p>324 Ref 26: 91%, 96:4 dr [α]_D²⁰ +27.1 (c 0.3, H₂O)</p>
<p>324 Ref 76: 85%, >99:1 dr [α]_D²⁰ +73.3 (c 1.0, H₂O) Ref 26: 85%, >99:1 dr [α]_D²⁰ +73.3 (c 1.0, H₂O)</p>	<p>325 Ref 76: 94%, >99:1 dr [α]_D²⁰ +6.0 (c 0.2, H₂O) Ref 26: 94%, >99:1 dr [α]_D²⁰ +6.0 (c 0.2, H₂O)</p>	<p>326 Ref 76: 63%, >99:1 dr [α]_D²⁰ +91.3 (c 0.2, H₂O)</p>	<p>327 Ref 76: 81%, >99:1 dr [α]_D²⁰ +70.4 (c 0.5, H₂O)</p>
<p>251 Ref 26: 84%, >99:1 dr Ref 25: 84%, >99:1 dr [α]_D²⁰ +67.0 (c 1.0, H₂O)</p>	<p>328 Ref 26: quant, >99:1 dr [α]_D²⁰ +4.7 (c 1.0, H₂O)</p>	<p>252 Ref 76: 89%, >99:1 dr [α]_D²⁰ +17.5 (c 0.5, H₂O) Ref 26: 89%, >99:1 dr Ref 25: 89%, >99:1 dr [α]_D²⁰ +17.5 (c 0.5, H₂O)</p>	<p>329 Ref 77: quant</p>
<p>330 Ref 54: 92%, >99:1 dr [α]_D²⁵ -43.5 (c 1.0, H₂O) Ref 27: 78%, 99:1 dr [α]_D²⁰ -40.4 (c 1.0, H₂O)</p>	<p>331 Ref 27: 73%, >95:5 dr [α]_D²⁰ -35.6 (c 1.0, 1.0 M aqHCl)</p>	<p>332 Ref 27: 51%, >99:1 dr [α]_D²⁰ +3.2 (c 0.5, H₂O)</p>	<p>333 Ref 27: 67%, >99:1 dr [α]_D²⁰ +14.8 (c 0.5, H₂O)</p>
<p>334 Ref 54: 84%, >99:1 dr [α]_D²⁵ -9.9 (c 1.0, H₂O)</p>	<p>335 Ref 57b: 94%, >99:1 dr [α]_D²⁵ -12.7 (c 0.9, H₂O)</p>	<p>336 Ref 27: quant, >99:1 dr [α]_D²⁰ +14.6 (c 1.0, MeOH)</p>	<p>337 Ref 29: 77%, >99:1 dr [α]_D²⁰ -72.6 (c 0.5, MeOH)</p>
<p>338 Ref 29: 80%, >99:1 dr [α]_D²⁰ -46.4 (c 0.5, H₂O)</p>	<p>339 Ref 29: quant, >99:1 dr [α]_D²⁰ +3.8 (c 0.5, H₂O)</p>	<p>340 Ref 29: quant, >99:1 dr [α]_D²⁰ -19.3 (c 0.4, H₂O)</p>	<p>341 Ref 46: 96% [α]_D²⁵ -2.7 (c 0.3, H₂O)</p>

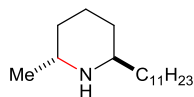


5. Synthetic applications: target syntheses

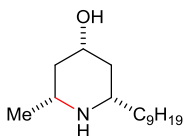
The conjugate addition of enantiomerically pure lithium amides to α,β -unsaturated esters has been employed in a wide range of target orientated asymmetric syntheses as the key stereodefining step, typically installing nitrogen bearing stereogenic centre in a wide range of synthetic targets. The recent achievements in this area (reported since 2011) are presented below (Table 8). The stereogenic centre formed in this conjugate addition reaction is highlighted in red in each of these target molecules.

Table 8.

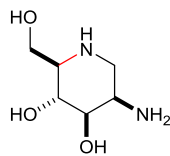




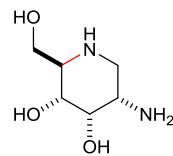
339
(-)-solenopsine A
Ref 12



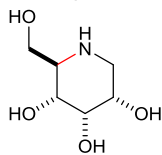
340
(+)-alkaloid 241D
Ref 12



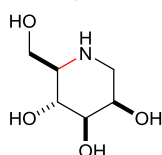
341
(-)-ADMJ
Ref 78



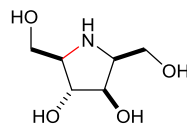
342
(+)-ADANJ
Ref 78



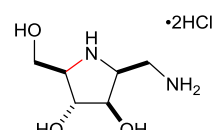
343
(+)-1-deoxyallonojirimycin
Ref 65



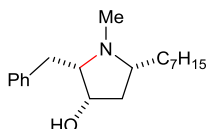
344
(-)-1-deoxymannojirimycin
Ref 65



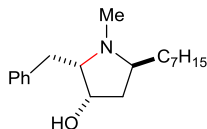
345
(+)-DGBP
Ref 79



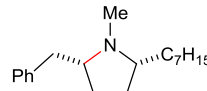
346·2HCl
(+)-ADGDP·2HCl
Ref 79



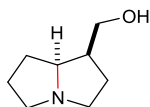
347
(+)-preussin B
Ref 36



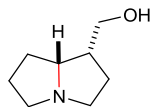
348
5-epi-(+)-preussin B
Ref 36



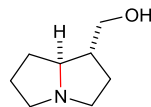
349
3-deoxy-(+)-preussin B
Ref 36



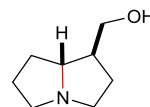
350
(-)-isoretronecanol
Ref 69



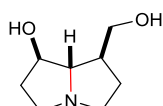
350
(+)-isoretronecanol
Ref 21



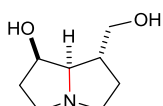
351
(-)-trachelanthamidine
Ref 69



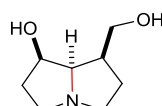
351
(+)-trachelanthamidine
Ref 33



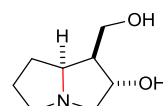
352
(-)-hastanecine
Ref 49



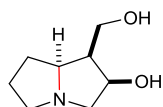
353
(-)-turnefordicine
Ref 49



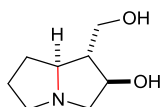
354
(-)-platynecine
Ref 49



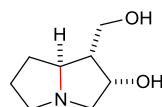
355
(-)-1-epi-macronecine
Ref 70



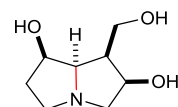
356
(-)-petasinecine
Ref 70



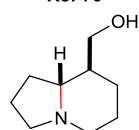
357
(+)-1-epi-petasinecine
Ref 70



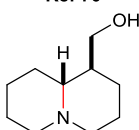
358
(-)-macronecine
Ref 70



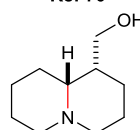
359
(+)-2-epi-rosmarinecine
Ref 70



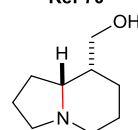
360
(+)-tashiromine
Ref 33



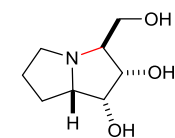
361
(+)-epilupinine
Ref 33



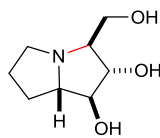
362
(-)-lupinine
Ref 21, 23



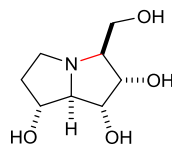
363
(+)-5-epi-tashiromine
Ref 21



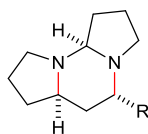
364
(-)-hyacinthacine A1
Ref 53



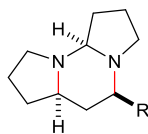
365
(-)-hyacinthacine A2
Ref 53



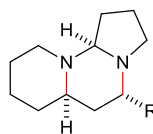
366
(-)-1-epi-alexine
Ref 53



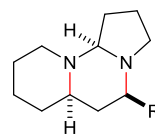
367, tetraponerine T1, R = C₃H₇
368, tetraponerine T5, R = C₅H₁₁
Ref 28



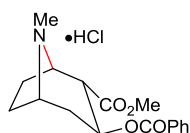
369, tetraponerine T2, R = C₃H₇
370, tetraponerine T6, R = C₅H₁₁
Ref 28



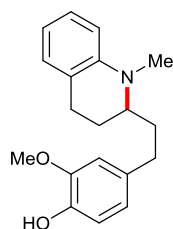
371, tetraponerine T3, R = C₃H₇
Ref 28
372, tetraponerine T7, R = C₅H₁₁
Ref 19, 28



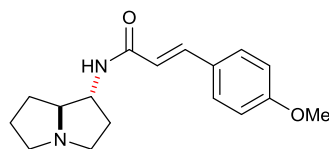
373, tetraponerine T4, R = C₃H₇
Ref 28
374, tetraponerine T8, R = C₅H₁₁
Ref 19, 28



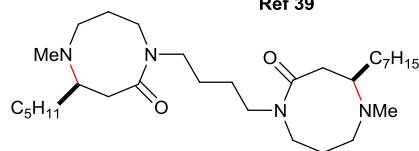
375·HCl
(+)-pseudococaine·HCl
Ref 34



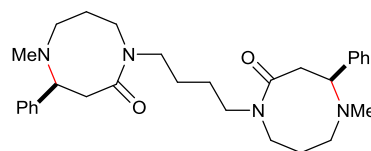
307
(-)-galipeine
Ref 39



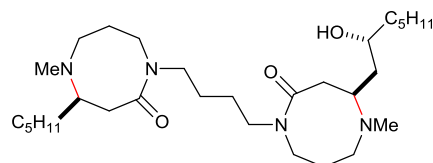
376
(-)-(1R,7aS)-absoulone
Ref 50



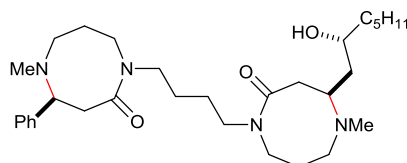
377
(-)-(R,R)-hopromine
Ref 41



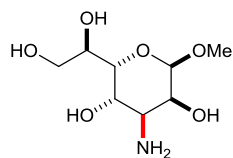
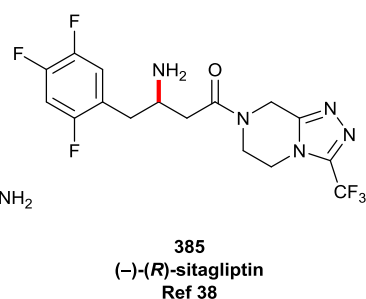
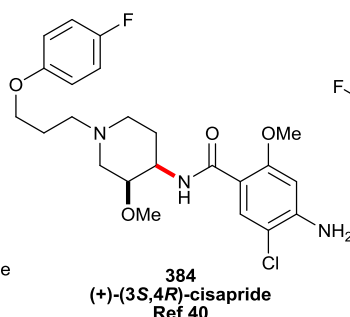
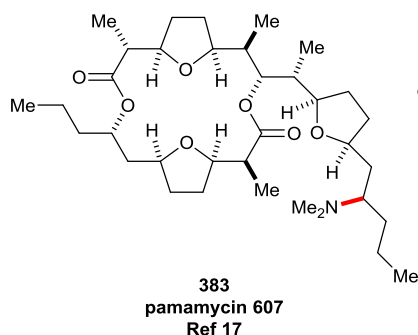
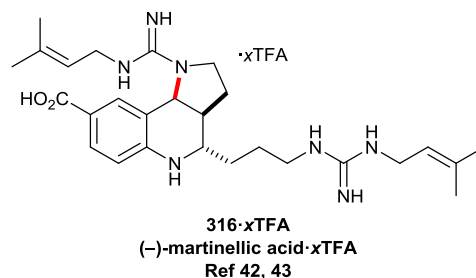
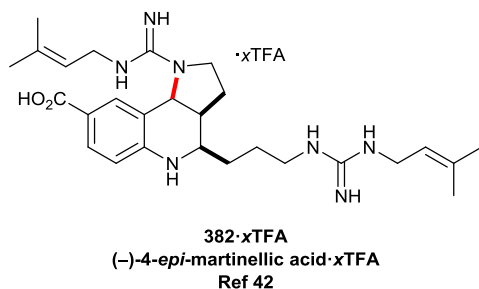
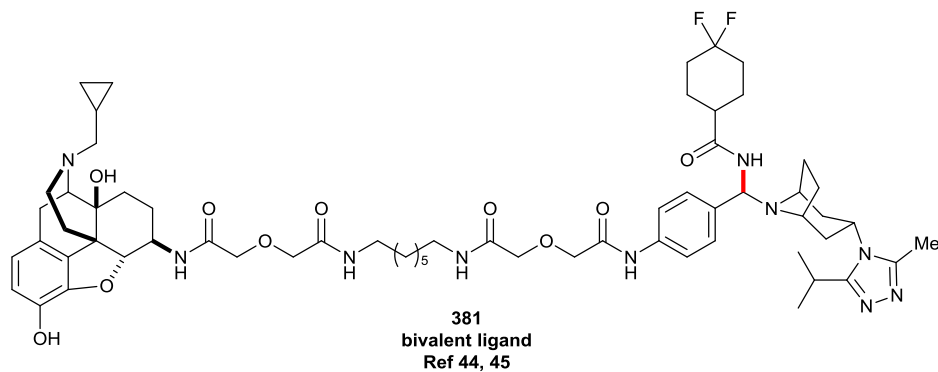
378
(-)-(S,S)-homaline
Ref 20, 41



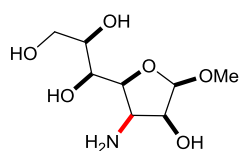
379
(-)-(R,R,R)-hoprominol
Ref 48



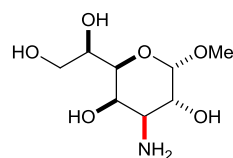
380
(-)-(4'S,4''R,2'''R)-hopromalinol
Ref 48



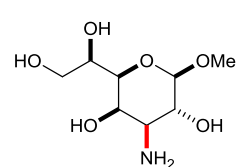
386
methyl 3-deoxy-3-amino-D-glycero-
α-L-gulo-heptopyranoside
Ref 80



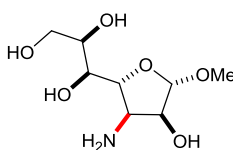
387
methyl 3-deoxy-3-amino-D-glycero-β-L-gulo-
heptofuranoside
Ref 80



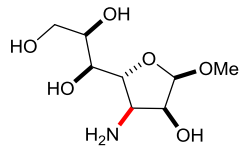
388
methyl 3-deoxy-3-amino-D-glycero-
α-D-galacto-heptopyranoside,
Ref 80



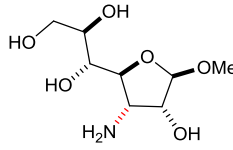
389
3-deoxy-3-amino-D-glycero-α-D-
galacto-heptopyranoside
Ref 80



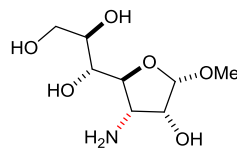
390
methyl 3-deoxy-3-amino-
D-glycero-β-L-allo-heptofuranoside
Ref 80



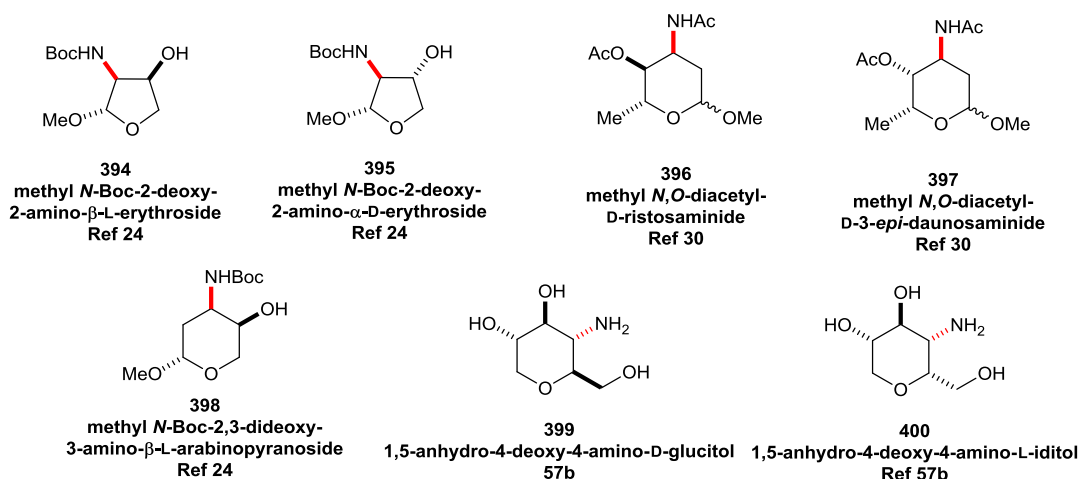
391
methyl 3-deoxy-3-amino-D-glycero-
α-L-allo-heptofuranoside
Ref 80



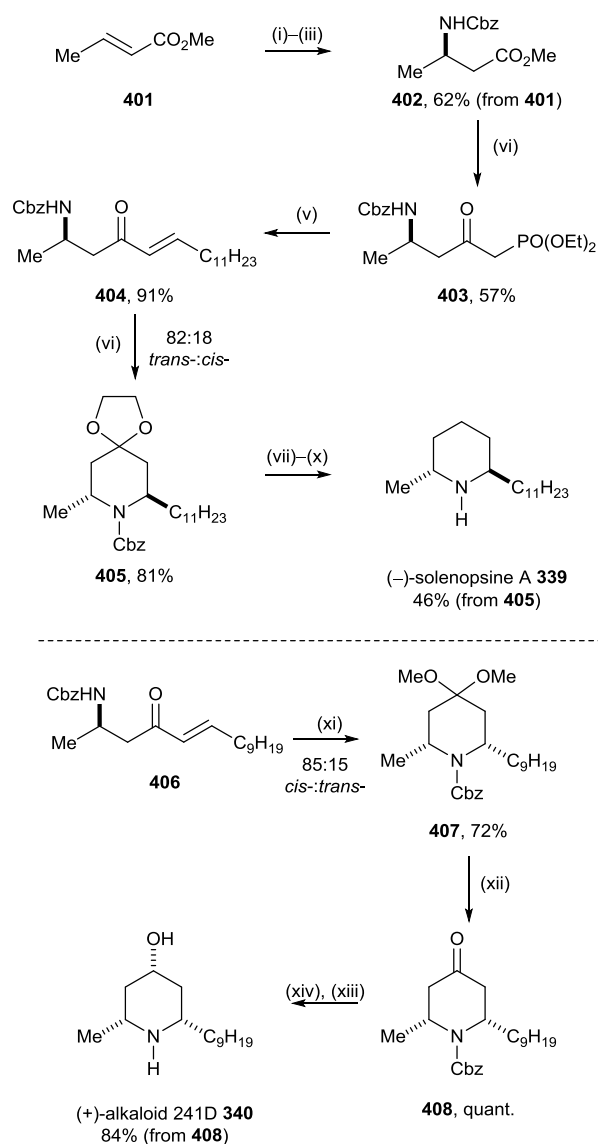
392
methyl 3-deoxy-3-amino-D-
glycero-β-D-allo-heptofuranoside
Ref 80



393
methyl 3-deoxy-3-amino-
D-glycero-α-D-allo-heptofuranoside
Ref 80



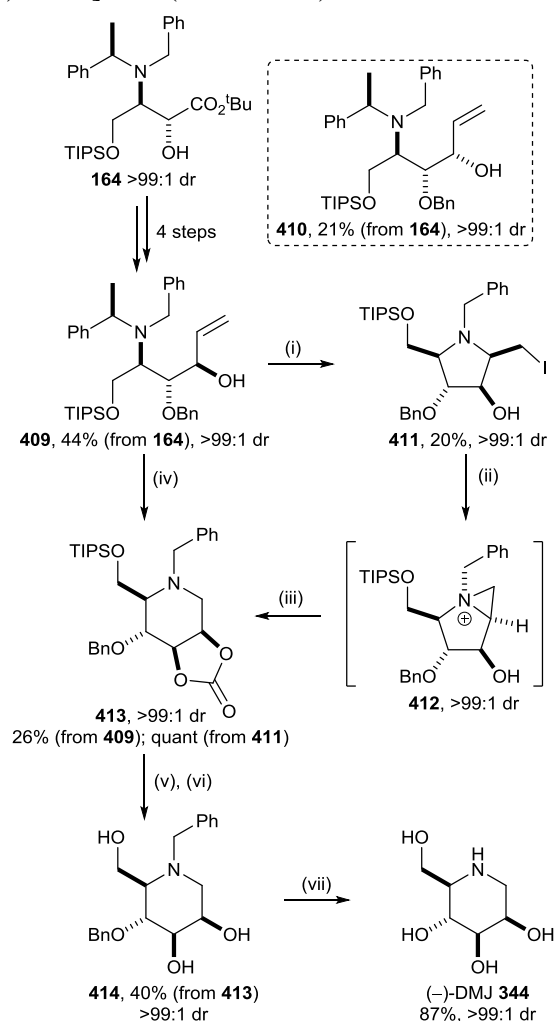
Troin et al. demonstrated an intramolecular Michael type cyclisation of (protected) β -amino ketone to selectively form 2,6-*cis*- or 2,6-*trans*-disubstituted piperidines.¹² Conjugate addition of lithium amide (*R*)-**2** to α,β -unsaturated ester **401**, followed by protecting group manipulation afforded carbamate **402** in 62% yield (from **401**). α,β -Unsaturated ketone **404**, the cyclisation precursor, was accessed via Wadsworth-Emmons reaction of the phosphonate derivative **403** with the required aldehyde. Treatment of **404** under kinetic cyclisation conditions (i.e., using ethylene glycol and a catalytic amount of *p*-TsOH) gave *trans*-piperidine **405** in 81% yield with high *trans*-diastereoselectivity (82:18 dr). Subsequent four step sequential transformations including thioketalation, *N*-Boc protection, desulfuration and acid-promoted *N*-deprotection gave (–)-solenpsine A **339** in 46% yield over four steps. By tuning the conditions, It was demonstrated that cyclisation under thermodynamic control to access 2,6-*cis*-piperidines could be possible: treatment of **406** with trimethylorthoformate and stoichiometric amount of *p*-TsOH gave 2,6-*cis*-piperidine **407** in 72% yield. Treatment of **407** with TFA gave the corresponding ketone **408**, followed by hydrogenolytic *N*-deprotection and diastereoselective reduction gave (+)-alkaloid 241D **340** in 84% yield over two steps (Scheme 12).



Scheme 12. Reagents and conditions: (i) (*R*)-**2**, THF, $-78\text{ }^{\circ}\text{C}$, 3.5 h; (ii) H_2 (60 psi), $\text{Pd}(\text{OH})_2/\text{C}$, MeOH, rt, 4 d; (iii) Na_2CO_3 , BnCO_2Cl , $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$, rt, 3 h; (iv) BuLi, $(\text{EtO})_2\text{P}(\text{O})\text{Me}$, THF, $-78\text{ }^{\circ}\text{C}$, 30 min then $0\text{ }^{\circ}\text{C}$, 1 h; (v) $\text{Ba}(\text{OH})_2$, THF/ H_2O (40:1), $\text{C}_{11}\text{H}_{23}\text{CHO}$, rt, 1 h; (vi) $\text{HO}(\text{CH}_2)_2\text{OH}$, $(\text{MeO})_3\text{CH}$, *p*-TsOH, rt, 1 h; (vii) $\text{SH}(\text{CH}_2)_2\text{SH}$, $\text{BF}_3\cdot\text{Et}_2\text{O}$, CH_2Cl_2 , rt, 24 h; (viii) $(\text{Boc})_2\text{O}$, DMAP, CH_2Cl_2 , rt, 1 h; (ix) Raney Ni, EtOH, reflux, 2 h; (x) TFA, CH_2Cl_2 , rt, 2 h. (xi) $(\text{MeO})_3\text{CH}$, *p*-TsOH, rt, 1 h; (xii) TFA, $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$, rt, 1 h; (xiii) Pd/C, H_2 (1 atm), MeOH, rt, 24 h; (xiv) NaBH_4 , MeOH, rt, 15 min.

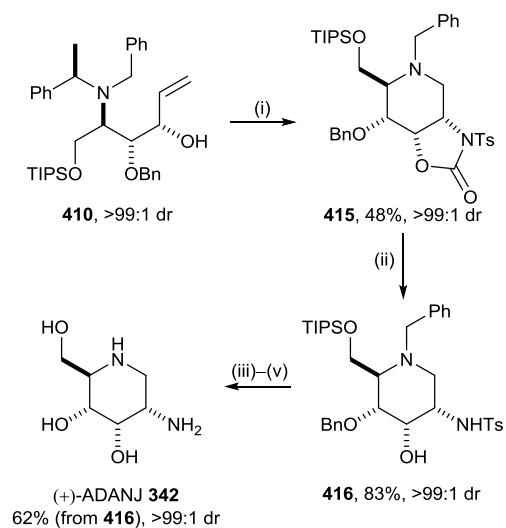
An intramolecular nucleophilic substitution, especially with tethered nucleophiles, can be very attractive functionalisation strategy with high regio- and diastereoselectivity. This approach has been employed in highly functionalised piperidine natural product syntheses in combination with conjugate addition of enantiopure lithium amide methodology. Aminohydroxylation product **164** was converted to **409** and **410** in 44 and 21% yield, respectively, over four steps. Treatment of the major diastereoisomer **409** with I_2 and NaHCO_3 in MeCN promoted ring-closing iodoamination with concomitant *N*-debenzylation to give pyrrolidine **411** in 20% yield and >99:1 dr. Subsequent treatment of **411** with AgBF_4 promoted the formation of aziridinium intermediate **412**. Treatment of **412** with NaHCO_3 in dioxane/ H_2O (3:1) gave carbonate **413** in quantitative yield (from **411**). Under the optimised conditions, carbonate **413** could be obtained directly from **409** via one-pot iodoamination, *in situ* aziridinium ion formation, followed by ring-opening by a tethered

nucleophile (carbonic acid half ester) to give carbonate **413** in 26% yield (from **409**) and >99:1 dr. Subsequent three steps deprotection protocol facilitated the total synthesis of (–)-1-deoxymannojirimycin [(–)-DMJ] **344** (Scheme 13).⁶⁵



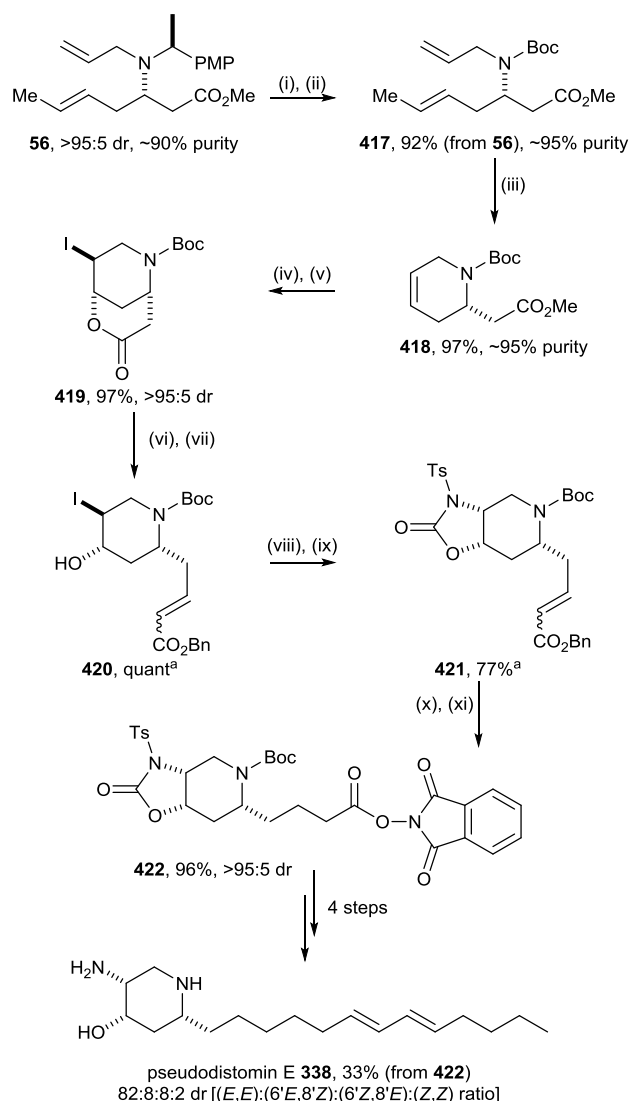
Scheme 13. Reagents and conditions: (i) I_2 , $NaHCO_3$, MeCN, rt, 16 h; (ii) $AgBF_4$, CH_2Cl_2 , rt, 1 h; (iii) $NaHCO_3$, dioxane/ H_2O (3:1), rt, 16 h; (iv) I_2 , $NaHCO_3$, dioxane/ H_2O (3:1), rt, 16 h then Ac_2O , pyridine, DMAP, 0 °C to rt, 16 h; (v) $HF \cdot pyridine$, THF, 0 °C to rt, 16 h; (vi) K_2CO_3 , MeOH, rt, 16 h; (vii) $Pd(OH)_2/C$, H_2 (5 atm), MeOH, rt, 48 h.

Ring-expansion of the aziridinium intermediate via the trapping of “ $X=C=Y$ ” electrophile in the place of CO_2 was applied in the synthesis of (+)-ADANJ **342**, the 2-deoxy-2-amino analogue of (+)-1-deoxyallonojirimycin. One-pot ring-closing iodoamination/ring-expansion of bishomoallylic amine **410** upon treatment with I_2 followed by addition of $TsNCO$ gave oxazolidinone **415** in 48% yield. The stereochemical outcome of this reaction is consistent with the mechanism via the corresponding aziridinium ion intermediate followed by trapping $TsNCO$ and opening the aziridinium ion with the tethered cyanate anion (OCN^-). Treatment of **415** with K_2CO_3 in MeOH gave piperidine **416** in 83% yield and >99:1 dr. Deprotection of the *N*-Ts group by Na and naphthalene and *O*-silyl group with HCl and subsequent hydrogenolysis of *N*-benzyl group gave (+)-ADANJ **342** in 62% yield (from **416**) and >99:1 dr (Scheme 14).⁷⁸



Scheme 14. *Reagents and conditions:* (i) I_2 , NaHCO_3 , MeCN, rt, 16 h then p -TsNCO, rt, 16 h; (ii) K_2CO_3 , MeOH, rt, 16 h; (iii) Na, naphthalene, DME, -78°C to rt, 16 h; (iv) 6.0 M aq HCl, MeOH, 40°C , 16 h; (v) H_2 (5 atm), $\text{Pd}(\text{OH})_2/\text{C}$, MeOH, rt, 48 h then Dowex 50WX8.

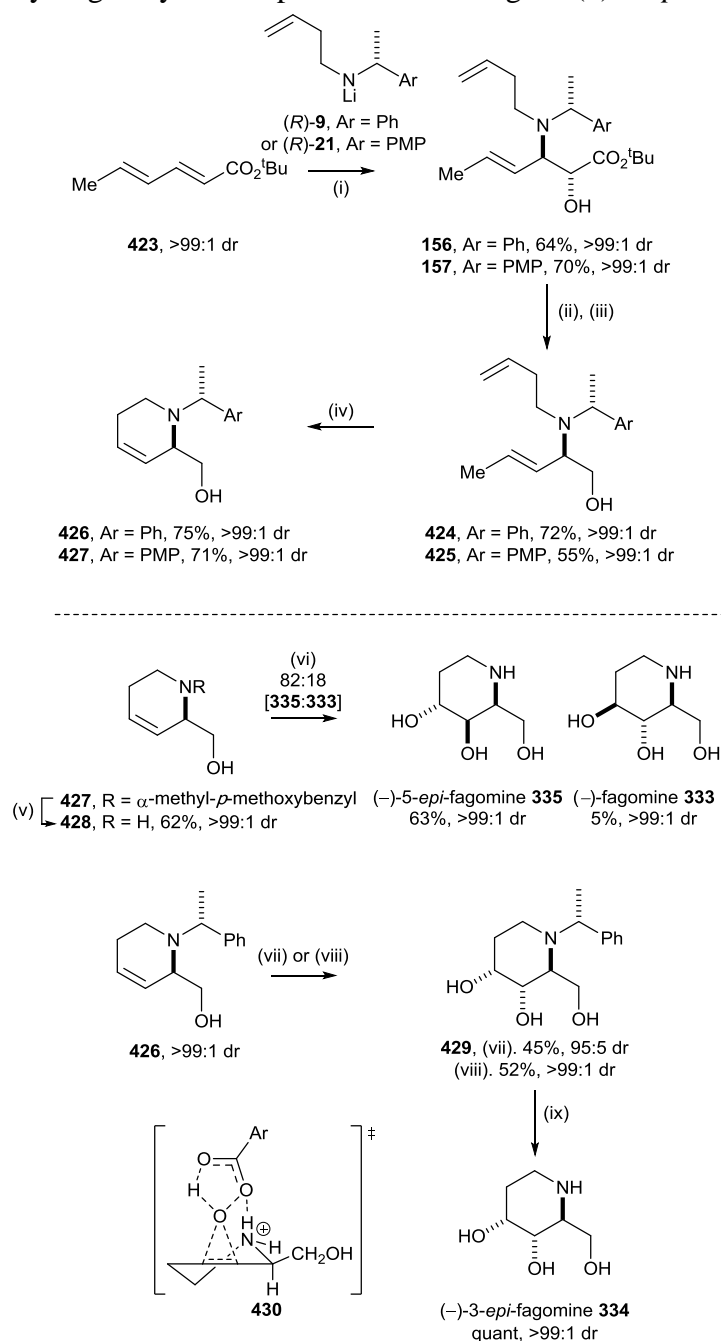
Trapping TsNCO with a hydroxyl group followed by substitution with the tethered cyanate anion (OCN^-) to form a highly substituted piperidine was employed as one of the key steps in the first asymmetric synthesis of (–)-pseudodistomin E **338**.³² Chemoselective removal of the N - α -methyl- p -methoxybenzyl group within **56**³¹ was achieved upon treatment with HCO_2H in the presence of Et_3SiH and subsequent N -Boc protection gave **417**. Ring-closing metathesis of **417** with Grubbs I catalyst gave tetrahydropyridine **418** in 97% yield. Methyl ester hydrolysis upon treatment with LiOH was followed by iodolactonisation upon treatment with I_2 and NaHCO_3 to give **419** in 97% yield (from **418**) and >95:5 dr. Reduction of lactone **419** with DIBAL-H followed by Wittig olefination gave **420** in quantitative yield (from **419**) as a 68:32 mixture of olefinic geometric isomers. Treatment of **420** with TsNCO gave the corresponding N -Ts carbamates and addition of Et_3N promoted formation of N -Ts oxazolidinone **421** in 77% yield. Tandem hydrogenolysis and hydrogenation of **421** followed by coupling with PhthNOH gave the activated ester **422** in 96% yield (from **421**) and >99:1 dr, which was elaborated to pseudodistomin E **338** over four steps (Scheme 15).



Scheme 15. Reagents and conditions: (i) HCO_2H , Et_3SiH , 90 °C, 16 h; (ii) Boc_2O , NaHCO_3 , MeOH , rt, 16 h; (iii) Grubbs I, CH_2Cl_2 , rt, 16 h; (iv) LiOH , H_2O , THF , 50 °C, 16 h; (v) I_2 , NaHCO_3 , MeCN , -20 °C, 2 h then rt, 16 h; (vi) DIBAL-H , CH_2Cl_2 , -78 °C, 90 min; (vii) $\text{PhP=CHCO}_2\text{Bn}$, CH_2Cl_2 , rt, 16 h; (viii) TsNCO , THF , 0 °C to rt, 3 h; (ix) Et_3N , acetone, 60 °C, 3 h; (x) H_2 , $\text{Pd}(\text{OH})_2/\text{C}$, EtOAc , rt, 6 h; (xi) PhthNOH , DIC , DMAP , CH_2Cl_2 , rt, 16 h. ^a 68:32 dr [(*E*):(*Z*) ratio].

Diastereoselective *syn*- and *anti*-dihydroxylation of enantiopure tetrahydropyridines were employed to access polyhydroxylated piperidine alkaloids, such as (–)-fagomine **333** and its epimers. Aminohydroxylation of (*R*)-**9** [Ar = Ph] or (*R*)-**21** [Ar = PMP] with α,β -unsaturated ester **423** gave α -hydroxy- β -amino esters **156** and **157** in 64 and 70% yield, respectively, as single diastereoisomers in both cases. Reduction of **156** and **157** with LiAlH_4 gave the corresponding 1,2-diols, subsequent sequential oxidative cleavage the resultant 1,2-diol unit and reduction with NaBH_4 gave alcohols **424** and **425** in 72 and 55% yield, respectively. Ring-closing metathesis of **424** and **425** with Grubbs II catalyst gave tetrahydropyridines **426** and **427** in 75 and 71% yield, respectively. The removal of α -methyl-*p*-methoxybenzyl group within **427** was achieved by treatment with 6.0 M aq HCl under reflux to give **428** in 62% yield. Chemo and diastereoselective oxidation⁸¹ of **428** with *m*-CPBA and HBF_4 gave an 82:18 mixture of **335** and **333**, from which (–)-5-*epi*-fagomine **335** and (–)-fagomine **333** were isolated in 63 and 5% yield, respectively as single diastereoisomers. The stereochemical outcome of this dihydroxylation reaction was

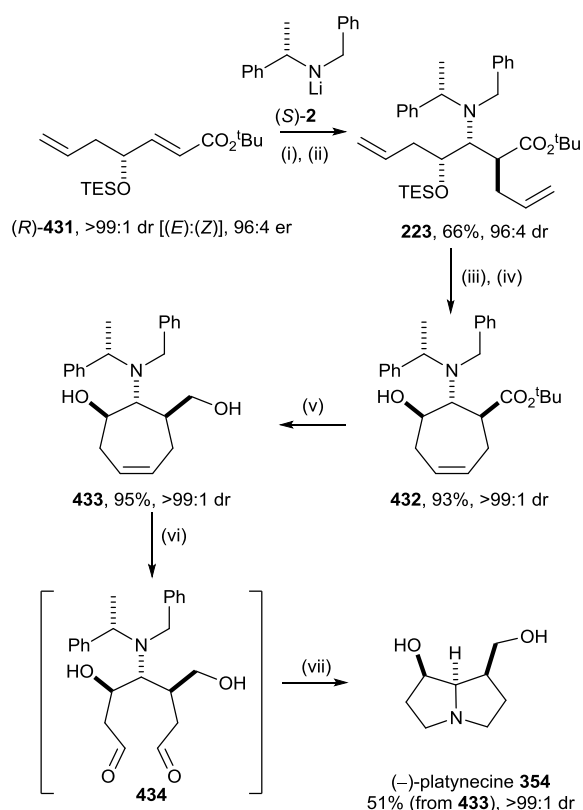
rationalised by H-bonding from an axial N–H bond derived from the corresponding ammonium group within **430** to the peracid to form initially the corresponding epoxide followed by regioselective ring-opening with H₂O to give 3,4-*anti*-**335** as the major diastereoisomeric product. Instead, *syn*-dihydroxylation of **426** under Upjohn conditions⁸² (i.e., catalytic amount of OsO₄ and NMO) or Donohoe conditions⁸³ (i.e., OsO₄ and TMEDA) occurred on the less hindered face to give triol **429** in 45 and 52% yield, respectively. Hydrogenolytic *N*-deprotection of **429** gave (–)-3-*epi*-fagomine **334** in quantitative yield (Scheme 16).⁶³



Scheme 16. Reagents and conditions: (i) (*R*)-**9** or (*R*)-**21**, THF, –78 °C, 2 h then (–)-CSO **147**, –78 °C to rt, 12 h; (ii) LiAlH₄, THF, –78 °C to rt, 16 h; (iii) NaIO₄, EtOH/H₂O (5:1), rt, 20 min then NaBH₄, 0 °C to rt, 12 h; (iv) Grubbs II, CH₂Cl₂, 35 °C, 48 h; (v) 6.0 M aq HCl, reflux, 3 days; (vi) *m*-CPBA, aq HBF₄, CH₂Cl₂, rt, 48 h; (vii) OsO₄, NMO, THF/H₂O (4:1), rt, 12 h; (viii) OsO₄, TMEDA, CH₂Cl₂, –78 °C, 2 h then P(CH₂OH)₃, Et₃N, silica, CH₂Cl₂, rt, 48 h; (ix) H₂ (1 atm), Pd(OH)₂/C, MeOH, rt, 12 h.

Rapid construction of azabicyclic scaffolds can be achieved from β -amino esters derived from conjugate addition of an enantiopure lithium amide. A double reductive cyclisation protocol was developed as a

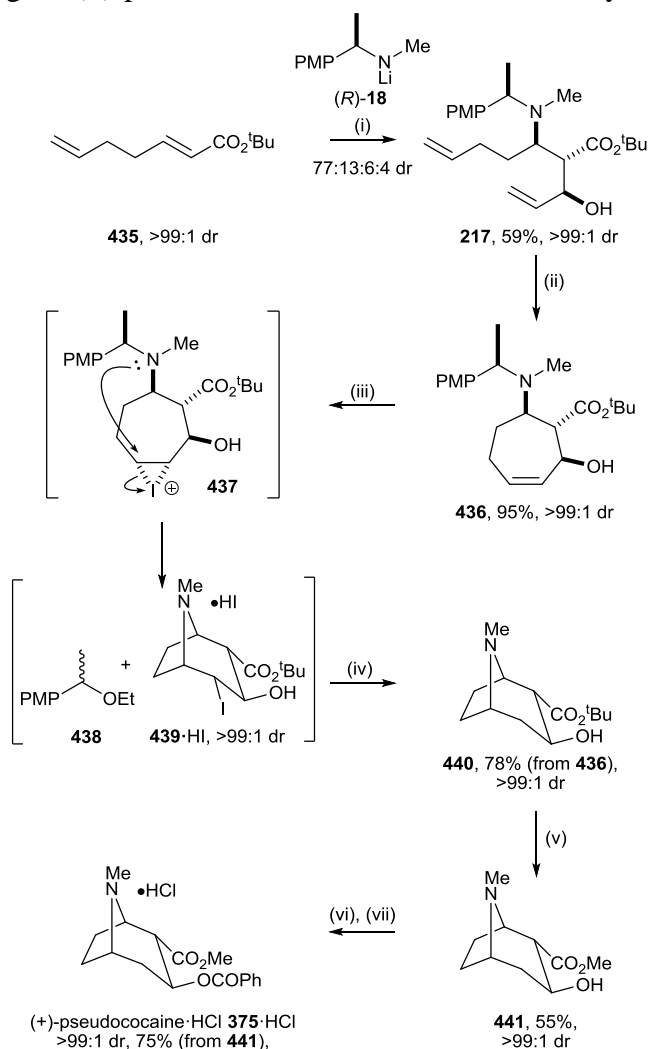
general and efficient method for construction of pyrrolizidines, indolizidines and quinolizidines, and has been employed in more than ten syntheses of azabicyclic alkaloids and their analogues syntheses.³⁹ For example, conjugate addition of lithium amide (*S*)-**2** to α,β -unsaturated ester **431**, followed by stepwise alkylation of the corresponding β -amino enolate gave **223** in 66% yield (from **431**) and 96:4 dr. *O*-Desilylation of **223** with TBAF followed by ring-closing metathesis gave cycloheptene **432** in 93% yield (from **223**) and >99:1 dr. Reduction of **432** with LiAlH₄ gave diol **433** in 95% yield and >99:1 dr. The amino group was first protected as the corresponding ammonium HCl salt from oxidation and ozonolysis of the corresponding HCl salt of **433** revealed dialdehyde and subsequent hydrogenolytic removal of the *N*-protecting groups facilitated *in situ* cyclisation followed by reduction of the corresponding iminium intermediate to give (–)-platynecine **354** in 51% yield (from **433**) and >99:1 dr (Scheme 17).⁴⁹



Scheme 17. Reagents and conditions: (i) (*S*)-**2**, THF, –78 °C, 2 h; (ii) LDA, THF, 0 °C, 1 h then allyl bromide, 0 °C to rt, 2 h; (iii) Grubbs I, CH₂Cl₂, 35 °C, 18 h; (iv) HF·pyridine, THF, rt, 18 h; (v) LiAlH₄, THF, –78 °C to rt, 18 h; (vi) HCl (2.0 M in Et₂O), rt, then O₃, CH₂Cl₂/MeOH, –78 °C then polymer-bound PPh₃, rt, 2 h; (vii) H₂ (5 atm), Pd(OH)₂/C, MeOH/AcOH (10:1), rt, 48 h.

Transannular iodoamination was also employed for elaboration of β -amino esters derived upon lithium amide conjugate addition to azabicyclic scaffold. Conjugate addition of lithium amide (*R*)-**18** to dienyl ester **435** followed by *in situ* aldol reaction with acrolein gave a 77:13:6:4 mixture of diastereoisomeric products, from which the major product **217** was isolated in 59% yield and >99:1 dr. Ring-closing metathesis of **217** with Grubbs I catalyst gave cycloheptene **436** in 95% yield and >99:1 dr. Treatment of **436** with I₂ in CH₂Cl₂ facilitated transannular iodoamination to give a mixture of **439**·HI and **438** (resulting from trapping α -

methyl-*p*-methoxybenzyl carbocation by-product with EtOH). Recrystallisation of this mixture from CH₂Cl₂/Et₂O gave **439**·HI. Subsequent reduction of iodide upon treatment with Bu₃SnH gave **440** in 78% yield (from **437**) and >99:1 dr. Transesterification of **440** to the corresponding methyl ester **441** by treatment with SOCl₂ in MeOH followed by *O*-benzoylation of the hydroxyl group within **441** and treatment with HCl gave (+)-pseudococaine·HCl **375**·HCl in 75% yield (Scheme 18).³⁴



Scheme 18. Reagents and conditions: (i) (R)-**18**, THF, −78 °C, 2 h then acrolein, −78 °C to rt, 2 h; (ii) Grubbs I, CH₂Cl₂, 30 °C, 12 h; (iii) I₂, CH₂Cl₂, rt, 12 h; (iv) Bu₃SnH, AIBN, toluene/MeOH (v/v 5:1), 80 °C, 5 h; (v) SOCl₂, MeOH, 50 °C, 5 h; (vi) PhCOCl, DMAP, Et₃N, CH₂Cl₂, 12 h; (vii) HCl, MeOH, rt, 5 min.

6. Conclusion

In conclusion, the conjugate addition of enantiomerically pure lithium amides as chiral ammonia equivalents has continued to be a powerful C–N bond forming reaction with very high diastereoselectivity and an extremely wide substrate scope. This methodology has been routinely employed particularly in the area of natural product, alkaloid, and pharmaceutically important target synthesis. Significant development for further elaboration of the resultant β -amino ester products towards other synthetic scaffolds such as α - and β -amino acids, azacyclic molecules, peptides, aminosugars and iminosugars has also been reported and this methodology will continue to find its application in synthesis.

References

- ¹ Davies, S. G.; Smith, A. D.; Price, P. D. *Tetrahedron: Asymmetry* **2005**, *16*, 2833.
- ² Davies, S. G.; Fletcher, A. M.; Roberts, P. M.; Thomson, J. E. *Tetrahedron: Asymmetry* **2012**, *23*, 1111.
- ³ Davies, S. G.; Ichihara, O. *Tetrahedron: Asymmetry* **1991**, *2*, 183.
- ⁴ For an alternative review of this area, see: Kiss, L.; Cherepanova, M.; Fülöp, F. *Tetrahedron* **2015**, *71*, 2049.
- ⁵ Costello, J. F.; Davies, S. G.; Ichihara, O. *Tetrahedron: Asymmetry* **1994**, *5*, 1999.
- ⁶ (a) Armstrong, D. R.; Henderson, K. W.; Kennedy, A. R.; Kerr, W. K.; Mair, F. S.; Moir, J. H.; Moran, P. H.; Snaith, R. *J. Chem. Soc., Dalton Trans.* **1999**, 4063; (b) Andrews, P. C.; Duggan, P. J.; Fallon, G. D.; McCarthy, T. D.; Peatt, A. C. *J. Chem. Soc., Dalton Trans.* **2000**, 1937; (c) Sugawara, K.; Shindo, M.; Noguchi, H.; Koga, K. *Tetrahedron Lett.* **1996**, *37*, 7377.
- ⁷ Claridge, T. D. W.; Davies, S. G.; Kruchinin, D.; Odell, B.; Roberts, P. M.; Russell, A. J.; Thomson, J. E.; Toms, S. M. *Tetrahedron: Asymmetry* **2013**, *24*, 947.
- ⁸ For another study concerning on solvent effects on the aggregation of a chiral lithium amide, see: Barozzino-Consiglio, G.; Rouen, M.; Ouladi, H.; Harrison-Marchand, A.; Maddaluno, J. *Dalton Trans.* **2014**, *43*, 14219.
- ⁹ Nieto, C. T.; Díez, D.; Garrido, N. M. *J. Comput. Chem.* **2014**, *35*, 1846.
- ¹⁰ Plas, A.; Marchand, F.; Eschaliér, A.; Troin, Y.; Chalard, P. *Eur. J. Org. Chem.* **2012**, 6070.
- ¹¹ Abrunhosa-Thomas, I.; Plas, A.; Kandepedu, N.; Chalard, P.; Trion, Y. *Beilstein J. Org. Chem.* **2013**, *9*, 486.
- ¹² Abrunhosa-Thomas, I.; Plas, A.; Vogrig, A.; Kandepedu, N.; Chalard, P.; Troin, Y. *J. Org. Chem.* **2013**, *78*, 2511.
- ¹³ Kafka, F.; Pohl, R.; Císařová, I.; Mackman, R.; Bahador, G.; Jahn, U. *Eur. J. Org. Chem.* **2016**, 3862.

- ¹⁴ Chen, B.-L.; Wang, B.; Lin, G.-Q. *Sci. China Chem.* **2014**, *57*, 945.
- ¹⁵ Marson, C. M.; Yau, K. C. *Tetrahedron* **2015**, *71*, 7459.
- ¹⁶ McGowan, D.; Herschke, F.; Pauwels, F.; Stoops, B.; Last, S.; Pieters, S.; Scholliers, A.; Thoné, T.; Schoubroeck, V.; De Pooter, D.; Mostmans, W.; Daoubi, M.; Embrechts, W.; Dhuyvetter, D.; Smyej, I.; Arnoult, E.; Demin, S.; Borghys, H.; Fanning, G.; Vlach, J.; Roboisson, P. *J. Med. Chem.* **2016**, *59*, 7936.
- ¹⁷ Gernay, O.; Kumar, N.; Moore, C. G.; Thomas, E. J. *Org. Biomol. Chem.* **2012**, *10*, 9709.
- ¹⁸ Chouhan, M.; Sharma, R.; Nair, V. A. *Org. Lett.* **2012**, *14*, 5672.
- ¹⁹ Strassnig, I.; Körber, K.; Hüniger, U.; Kunz, H. *Synthesis* **2015**, 2299.
- ²⁰ Davies, S. G.; Lee, J. A.; Roberts, P. M.; Stonehouse, J. P.; Thomson, J. E. *J. Org. Chem.* **2012**, *77*, 7028.
- ²¹ Davies, S. G.; Fletcher, A. M.; Foster, E. M.; Houlsby, I. T. T.; Roberts, P. M.; Scofield, T. M.; Thomson, J. E. *Org. Biomol. Chem.* **2014**, *12*, 9223.
- ²² Nieto, C. T.; Salgado, M. M.; Domínguez, S. H.; Díez, D.; Garrido, N. M. *Tetrahedron: Asymmetry* **2014**, *25*, 1046.
- ²³ Davies, S. G.; Fletcher, A. M.; Foster, E. M.; Houlsby, I. T. T.; Roberts, P. M.; Schofield, T. M.; Thomson, J. E. *Chem. Commun.* **2014**, *50*, 8309.
- ²⁴ Brambilla, M.; Davies, S. G.; Fletcher, A. M.; Hao, L.; Lv, L.; Roberts, P. M.; Thomson, J. E. *Tetrahedron* **2014**, *70*, 3491.
- ²⁵ Davies, S. G.; Fletcher, A. M.; Roberts, P. M.; Thomson, J. E.; Zammit, C. M. *Chem. Commun.* **2013**, *49*, 7037.
- ²⁶ Davies, S. G.; Fletcher, A. M.; Lee, J. A.; Roberts, P. M.; Souleymanou, M. Y.; Thomson, J. E.; Zammit, C. M. *Org. Biomol. Chem.* **2014**, *12*, 2702.
- ²⁷ Csatayová, K.; Davies, S. G.; Figuccia, A. L. A.; Fletcher, A. M.; Ford, J. G.; Lee, J. A.; Roberts, P. M.; Saward, B. G.; Song, H.; Thomson, J. E. *Tetrahedron* **2015**, *71*, 9131.
- ²⁸ Davies, S. G.; Fletcher, A. M.; Houlsby, I. T. T.; Roberts, P. M.; Thomson, J. E. *J. Org. Chem.* **2017**, *82*, 6689.
- ²⁹ Csatayová, K.; Davies, S. G.; Fletcher, A. M.; Ford, J. G.; Klauber, D. J.; Roberts, P. M.; Thomson, J. E. *J. Org. Chem.* **2014**, *79*, 10932.
- ³⁰ Csatayová, K.; Davies, S. G.; Ford, J. G.; Lee, J. A.; Roberts, P. M.; Thomson, J. E. *J. Org. Chem.* **2013**, *78*, 12397.
- ³¹ Davies, S. G.; Fletcher, A. M.; Lee, J. A.; Roberts, P. M.; Russell, A. J.; Taylor, R. J.; Thomson, A. D.; Thomson, J. E. *Org. Lett.* **2012**, *14*, 1672.
- ³² Davies, S. G.; Fletcher, A. M.; Roberts, P. M.; Thomson, J. E.; Zimmer, D. *Org. Lett.* **2017**, *19*, 1638.

- ³³ Brambilla, M.; Davies, S. G.; Fletcher, A. M.; Roberts, P. M.; Thomson, J. E.; Zimmer, D. *Tetrahedron* **2016**, 72, 7417.
- ³⁴ Brock, E. A.; Davies, S. G.; Lee, J. A.; Roberts, P. M.; Thomson, J. E. *Org. Lett.* **2012**, 14, 4278.
- ³⁵ Davies, S. G.; Goddard, E. C.; Roberts, P. M.; Russell, A. J.; Thomson, J. E. *Synlett* **2015**, 1541.
- ³⁶ Buchman, M.; Csatayová, K.; Davies, S. G.; Fletcher, A. M.; Houlsby, I. T. T.; Roberts, P. M.; Rowe, S. M.; Thomson, J. E. *J. Org. Chem.* **2016**, 81, 4907.
- ³⁷ Davies, S. G.; Goddard, E. C.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E.; Withey, J. M. *Tetrahedron: Asymmetry* **2016**, 27, 274.
- ³⁸ Davies, S. G.; Fletcher, A. M.; Lv, L.; Roberts, P. M.; Thomson, J. E. *Tetrahedron Lett.* **2012**, 53, 3052.
- ³⁹ Davies, S. G.; Fletcher, A. M.; Houlsby, T. T. I.; Roberts, P. M.; Thomson, J. E. *J. Org. Chem.* **2017**, 82, 10673.
- ⁴⁰ Davies, S. G.; Huckvale, R.; Lee, J. A.; Lorkin, T. J. A.; Roberts, P. M.; Thomson, J. E. *Tetrahedron* **2012**, 68, 3263.
- ⁴¹ Davies, S. G.; Lee, J. A.; Roberts, P. M.; Stonehouse, J. P.; Thomson, J. E. *Tetrahedron Lett.* **2012**, 53, 1119.
- ⁴² Davies, S. G.; Fletcher, A. M.; Lee, J. A.; Lorkin, T. J. A.; Roberts, P. M.; Thomson, J. E. *Tetrahedron* **2013**, 69, 9779.
- ⁴³ Davies, S. G.; Fletcher, A. M.; Lee, J. A.; Lorkin, T. J. A.; Roberts, P. M.; Thomson, J. E. *Org. Lett.* **2013**, 15, 2050.
- ⁴⁴ Arnatt, C. K.; Falls, B. A.; Yuan, Y.; Raborg, T. J.; Masvekar, R. R.; El-Hage, N.; Selley, D. E.; Nicola, A. V.; Knapp, P. E.; Hauser, K. F.; Zhang, Y. *Bioorg. Med. Chem.* **2016**, 24, 5969.
- ⁴⁵ Yuan, Y.; Arnatt, C. K.; Li, G.; Haney, K. M.; Ding, D.; Jacob, J. C.; Selley, D. E.; Zhang, Y. *Org. Biomol. Chem.* **2012**, 10, 2633.
- ⁴⁶ Davies, S. G.; Fletcher, A. M.; Lv, L.; Roberts, P. M.; Thomson, J. E. *Tetrahedron: Asymmetry* **2012**, 23, 910.
- ⁴⁷ Szakonyi, Z.; Sillanpää, R.; Fülöp, F. *Beilstein J. Org. Chem.* **2014**, 10, 2738.
- ⁴⁸ Davies, S. G.; Lee, J. A.; Roberts, P. M.; Stonehouse, J. P.; Thomson, J. E. *J. Org. Chem.* **2012**, 77, 9724.
- ⁴⁹ Brambilla, M.; Davies, S. G.; Fletcher, A. M.; Roberts, P. M.; Thomson, J. E. *Tetrahedron* **2016**, 72, 4523.
- ⁵⁰ Davies, S. G.; Fletcher, A. M.; Lebée, C.; Roberts, P. M.; Thomson, J. E.; Yin, J. *Tetrahedron* **2013**, 69, 1369.
- ⁵¹ Davies, S. G.; Lee, J. A.; Roberts, P. M.; Thomson, J. E.; Yin, J. *Org. Lett.* **2012**, 14, 218.

- ⁵² Davies, S. G.; Foster, E. M.; Frost, A. B.; Lee, J. A.; Roberts, P. M.; Thomson, J. E. *Org. Biomol. Chem.* **2012**, *10*, 6186.
- ⁵³ Brock, E. A.; Davies, S. G.; Lee, J. A.; Roberts, P. M.; Thomson, J. E. *Org. Biomol. Chem.* **2013**, *11*, 3187.
- ⁵⁴ Davies, S. G.; Foster, E. M.; Lee, J. A.; Roberts, P. M.; Thomson, J. E. *Tetrahedron* **2013**, *69*, 8680.
- ⁵⁵ Davies, S. G.; Foster, E. M.; Lee, J. A.; Roberts, P. M.; Thomson, J. E. *Tetrahedron: Asymmetry* **2014**, *25*, 534.
- ⁵⁶ For example, highly diastereoselective aminohydroxylation of α,β -unsaturated ester with either combination of (*R*)-**2** and (+)-**147**, or (*S*)-**2** and (+)-**147** was observed: see Bunnage, M. E.; Burke, A. J.; Davies, S. G.; Goodwin, C. J. *Tetrahedron: Asymmetry* **1995**, *6*, 165.
- ⁵⁷ For selected few examples of “matching” and “mismatching” being observed upon aminohydroxylation, see: (a) Bunnage, M. E.; Davies, S. G.; Goodwin, C. J.; Ichihara, O. *Tetrahedron* **1994**, *50*, 3975; (b) Davies, S. G.; Foster, E. M.; Lee, J. A.; Roberts, P. M.; Thomson, J. E. *J. Org. Chem.* **2014**, *79*, 9686; (c) Davies, S. G.; Fletcher, A. M.; Foster, E. M.; Lee, J. A.; Roberts, P.; Thomson, J. E.; Waul, M. A. *Tetrahedron* **2014**, *70*, 7106.
- ⁵⁸ Davies, S. G.; Lee, J. A.; Roberts, P. M.; Thomson, J. E.; West, C. J. *Tetrahedron* **2012**, *68*, 4302.
- ⁵⁹ Davies, S. G.; Fletcher, A. M.; Frost, A. B.; Lee, J. A.; Roberts, P. M.; Thomson, J. E. *Tetrahedron* **2013**, *69*, 8885.
- ⁶⁰ Davies, S. G.; Fletcher, A. M.; Frost, A. B.; Roberts, P. M.; Thomson, J. E. *Tetrahedron* **2014**, *70*, 5849.
- ⁶¹ Archer, S. G.; Csatayová, K.; Davies, S. G.; Fletcher, A. M.; Roberts, P. M.; Thomson, J. E. *Tetrahedron Lett.* **2016**, *57*, 1270.
- ⁶² Davies, S. G.; Fletcher, A. M.; Hanby, A. R.; Roberts, P. M.; Thomson, J. E. *Tetrahedron: Asymmetry* **2017**, DOI: 10.1016/j.tetasy.2017.09.022.
- ⁶³ Csatayová, K.; Davies, S. G.; Fletcher, A. M.; Ford, J. G.; Klauber, D. J.; Roberts, P. M.; Thomson, J. E. *Tetrahedron* **2015**, *71*, 7170.
- ⁶⁴ Davies, S. G.; Fletcher, A. M.; Foster, E. M.; Lee, J. E.; Roberts, P. M.; Thomson, J. E. *J. Org. Chem.* **2013**, *78*, 2500.
- ⁶⁵ Davies, S. G.; Figuccia, A. L. A.; Fletcher, A. M.; Roberts, P. M.; Thomson, J. E. *Org. Lett.* **2013**, *15*, 2042.
- ⁶⁶ Davies, S. G.; Fletcher, A. M.; Frost, A. B.; Kennedy, M. S.; Roberts, P. M.; Thomson, J. E. *Tetrahedron* **2016**, *72*, 2139.
- ⁶⁷ Davies, S. G.; Fletcher, A. M.; Frost, A. B.; Roberts, P. M.; Thomson, J. E. *Org. Lett.* **2015**, *17*, 2254.

- ⁶⁸ (a) Davies, S. G.; Walters, I. A. S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 9, 1129; (b) Davies, S. G.; Fletcher, A. M.; Hermann, G. J.; Poce, G.; Roberts, P. M.; Smith, A. D.; Sweet, M. J.; Thomson, J. E. *Tetrahedron: Asymmetry* **2010**, 21, 6135; (c) Davies, S. G.; Foster, E. M.; McIntosh, C. R.; Roberts, P. M.; Rosser, T. E.; Smith, A. D.; Thomson, J. E. *Tetrahedron: Asymmetry* **2011**, 22, 1035.
- ⁶⁹ Brambilla, M.; Davies, S. G.; Fletcher, A. M.; Roberts, P. M.; Thomson, J. E. *Tetrahedron* **2014**, 70, 204.
- ⁷⁰ Brambilla, M.; Davies, S. G.; Fletcher, A. M.; Roberts, P. M.; Thomson, J. E. *Tetrahedron* **2016**, 72, 7449.
- ⁷¹ Davies, S. G.; Ichihara, O.; Walters, I. A. S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1141.
- ⁷² Rangel, H.; Carrillo-Morales, M.; Galindo, J. M.; Castillo, E.; Obregón-Zúñiga, A.; Juaristi, E.; Escalante, J. *Tetrahedron: Asymmetry* **2015**, 26, 325.
- ⁷³ 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.
- ⁷⁴ Kapras, V.; Pohl, R.; Císařová, I.; Jahn, U. *Org. Lett.* **2014**, 16, 1088.
- ⁷⁵ (a) Bull, S. D.; Davies, S. G.; Fenton, G.; Mulvany, A. W.; Prasad, R. S.; Smith, A. D. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3765; (b) Bull, S. D.; Davies, S. G.; Fenton, G.; Mulvaney, A. W.; Prasad, R. S.; Smith, A. D. *Chem. Commun.* **2000**, 337.
- ⁷⁶ Davies, S. G.; Fletcher, A. M.; Roberts, P. M.; Thomson, J. E.; Zammit, C. M. *Tetrahedron: Asymmetry* **2016**, 27, 208.
- ⁷⁷ Garrido, N. M.; Nieto, C. T.; Díez, D. *Synlett* **2013**, 169.
- ⁷⁸ Davies, S. G.; Figuccia, A. L. A.; Fletcher, A. M.; Roberts, P. M.; Thomson, J. E. *J. Org. Chem.* **2016**, 81, 6481.
- ⁷⁹ Davies, S. G.; Figuccia, A. L. A.; Fletcher, A. M.; Roberts, P. M. *Tetrahedron* **2014**, 70, 3601.
- ⁸⁰ Brambilla, M.; Davies, S. G.; Diment, W. T.; Fletcher, A. M.; Lee, J. A.; Roberts, P. M.; Thomson, J. E.; Waul, M. A. *Tetrahedron: Asymmetry* **2016**, 27, 31.
- ⁸¹ (a) Aciro, C.; Claridge, T. D. W.; Davies, S. G.; Roberts, P. M.; Russell, A. J.; Thomson, J. E. *Org. Biomol. Chem.* **2008**, 6, 3751; (b) Aciro, C.; Davies, S. G.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2008**, 6, 3762; (c) Bond, C. W.; Cresswell, A. J.; Davies, S. G.; Fletcher, A. M.; Kurosawa, W.; Lee, J. A.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E. *J. Org. Chem.* **2009**, 74, 6735; (d) Brennan, M. B.; Claridge, T. D. W.; Compton, R. G.; Davies, S. G.; Fletcher, A. M.; Henstridge, M. C.; Hewings, D. S.; Kurosawa, W.; Lee, J. A.; Roberts, P. M.; Schoonen, A. K.; Thomson, J. E. *J. Org. Chem.* **2012**, 77, 7241; (e) Brennan, M. B.; Davies, S. G.; Fletcher, A. M.; Lee, J. A.; Roberts, P. M.; Russell, A. J.; Thomson, J. E. *Aust. J. Chem.* **2015**, 68, 610; (f) Brennan, M. B.; Csatayová, K.; Davies, S. G.; Fletcher, A. M.; Green, W. D.; Lee, J. A.; Roberts, P. M.; Russell, A. J.;

Thomson, J. E. *J. Org. Chem.* **2015**, *80*, 6609; (g) Brambilla, M.; Brennan, M. B.; Csatayová, K.; Davies, S. G.; Fletcher, A. M.; Kennett, A. M.; Lee, J. A.; Roberts, P. M.; Russell, A. J.; Thomson, J. E. *J. Org. Chem.* **2017**, *82*, 6689; (h) Davies, S. G.; Fletcher, A. M.; Thomson, J. E. *Org. Biomol. Chem.* **2014**, *12*, 4544.

⁸² VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *17*, 1973.

⁸³ a) Donohoe, T. J.; Moore, P. R.; Waring, M. J.; Newcombe, N. J. *Tetrahedron Lett.* **1997**, *38*, 5027; (b) Donohoe, T. J.; Blades, K.; Moore, P. R.; Winter, J. J. G.; Helliwell, M.; Stemp, G. *J. Org. Chem.* **1999**, *64*, 2980; (c) Donohoe, T. J. *Synlett* **2002**, 1223; (d) Donohoe, T. J.; Blades, K.; Moore, P. R.; Waring, M. J.; Winter, J. J. G.; Helliwell, M.; Newcombe, N. J.; Stemp, G. *J. Org. Chem.* **2002**, *67*, 7946.