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The conjugate addition of enantiomerically pure lithium amides as homochiral ammonia equivalents: scope, limitations and synthetic applications

Stephen G. Davies,* Andrew D. Smith and Paul. D. Price

Department of Organic Chemistry, University of Oxford, Chemistry Research Laboratory, Mansfield Road, Oxford OX1 3TA, UK

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Abstract—This review delineates the scope and limitations of the conjugate addition of homochiral lithium amides to act as homochiral ammonia equivalents for the asymmetric synthesis of a range of β-amino carboxylic acid derivatives and its widespread applications in synthesis.

Contents

* Corresponding author. Tel.: +44 (0)1865 275646; fax: +44 (0)1865 275633; e-mail: steve.davies@chem.ox.ac.uk

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1. Introduction

Chiral lithium amides have been extensively used and studied[1] within organic synthesis as effective reagents for a range of transformations including enantioselective reduction,[2] alkylation,[3] deprotonation,[4] desymmetrisation[5] and kinetic resolution.[6] Although many of these procedures rely upon lithium amides to act as chiral bases and readily discriminate between enantiotopic protons, lithium amides may also act as nucleophiles. In this arena, lithium amides have been widely used in conjugate addition reactions, particularly as homochiral ammonia equivalents for the asymmetric synthesis of β-amino acid derivatives. This review aims to showcase the widespread applications of this reaction manifold within asymmetric synthesis, including the preparation of β-amino acids, the total synthesis of a range of natural products and the development of kinetic resolution methodologies.

2. Conjugate addition of nitrogen nucleophiles

2.1. Amine additions: thermodynamic control

The conjugate addition reaction is undoubtedly one of the most synthetically useful reactions in synthesis.[7] A range of carbon and heteroatom based nucleophiles have been shown to participate in this reaction manifold, since Komnenos first reported the addition of diethyl sodiomalonate to diethyl ethylidenemalonate in 1883,[8] with a plethora of nitrogen based nucleophiles readily participating in this reaction manifold. Ammonia, the simplest amine, has long been known to add in a conjugate sense, with Fischer and Scheibler first reporting the conjugate addition of ammonia to crotonic acid **1** in 1910, giving methyl (*RS*)-3-amino butyrate **2** in reasonable yield (61%).[9] Feuer and Swarts later showed that addition of ammonia in EtOH to diethyl glutaconate **3** gave diethyl 3-amino-glutarate **4** in 60% yield (Fig. 1).[10]

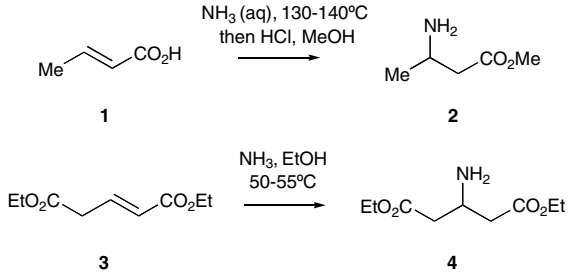
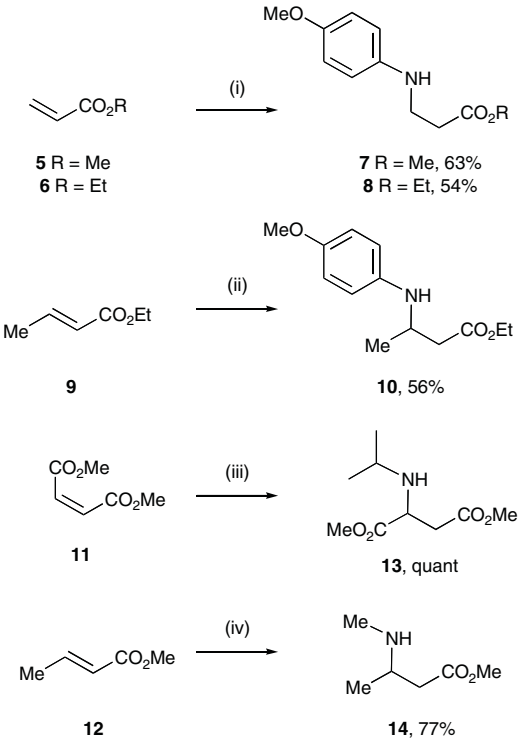


Figure 1. Conjugate addition of ammonia to α,β-unsaturated acceptors.

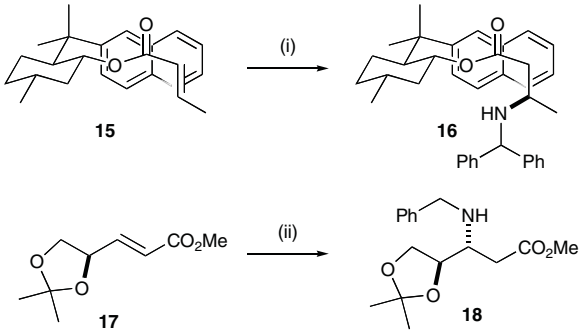
A range of primary *N*-alkyl, *N*-aryl and *N*-benzylamines also participate in conjugate addition reactions. In the 1940's, Elderfield et al.[11] and subsequently Johnson et al.[12] showed that *p*-anisidine could add to methyl and ethyl acrylate **5** and **6**, respectively, in the presence of acetic acid to give the corresponding β-amino esters **7** and **8** in reasonable yield. MacPhillamy et al. subsequently extended this protocol to addition to ethyl crotonate **9**, giving β-amino ester **10** in 56% yield,[13] with the generality of this transformation subsequently demonstrated by Kano et al. (Scheme 1).[14] While primary amines such as isopropylamine and methylamine add to dimethyl maleate **11**[15] and methyl crotonate **12**,[16] respectively, to give the corresponding β-amino esters **13** and **14** in good yield (Scheme 1), the additions of *N*-benzylamines to α,β-unsaturated esters typically



Scheme 1. Reagents and conditions: (i) *p*-anisidine, Δ; (ii) *p*-anisidine, benzene, Δ; (iii) $^{i}PrNH_2$, (10 equiv), Δ; (iv) $MeNH_2$, MeOH, 60 °C.

require either high temperature,[17] high pressure,[18] microwave irradiation,[19] Lewis acid catalysis[20] or a combination of these methods to proceed to completion.

Attempts to induce stereoselectivity in the conjugate addition of primary amines to α,β-unsaturated acceptors have been investigated by numerous research groups, typically through the use of either a chiral acceptor or chiral amine component in the reaction. For example, d'Angelo and Maddaluno showed that the addition of (diphenylmethyl)amine to the bulky chiral acceptor 8-β-naphthyl-menthyl crotonate **15** proceeded with excellent diastereoselectivity (>99% de) at 15 kbar pressure, giving the desired β-amino ester **16** in 50% isolated yield.[21] Similarly, *N*-benzylamine adds stereoselectively to the chiral α,β-unsaturated ester **17** derived from glyceraldehyde at −50 °C, giving β-amino ester **18** as a single diastereoisomer (Scheme 2).[22]



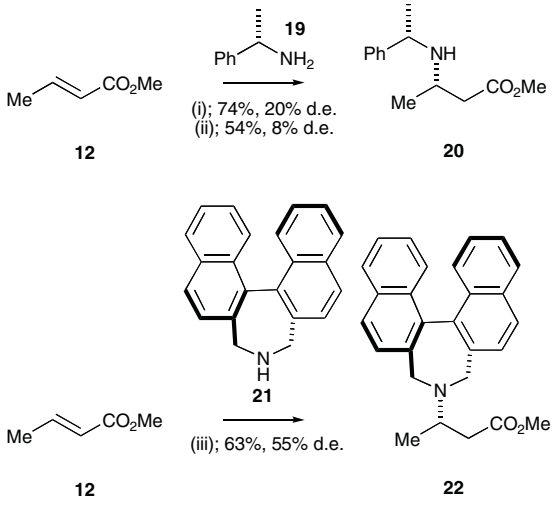
Scheme 2. Reagents and conditions: (i) diphenylmethylamine, MeOH, 15 kbar, rt; (ii) benzylamine, −50 °C, 50 h.

The diastereoselective thermal addition of readily available homochiral (*R*)- or (*S*)-α-methylbenzylamine **19** to α,β-unsaturated acceptors has also been investigated, with addition to methyl crotonate proceeding with low stereocontrol to give either a 60:40 (20% de)[23] or 54:46 (8% de)[24] mixture of diastereoisomers with **20** predominating. Interestingly, Hawkins and Fu showed that the thermal addition of the C_2 symmetric amine 3,5-dihydro-4*H*-dinaphth[2,1-*c*:1′,1′-*e*]azepine **21** to methyl crotonate gave a 77:23 mixture of diastereoisomers with **22** predominating under kinetic control, which upon standing gave a thermodynamic 50:50 mixture of diastereoisomers (Scheme 3).[30]

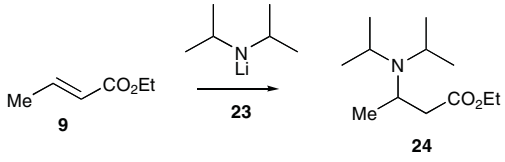
The observation of kinetic and thermodynamic product ratios in the thermal addition reactions of chiral amines implies that these reactions are reversible, with high stereocontrol seldom achievable.

2.2. Metal amide additions: kinetic control

In contrast to the thermal addition of amines that proceed under thermodynamic control, the addition of metal amides, derived from the corresponding amines by treatment with an alkyllithium or Grignard reagent, proceeds under kinetic control. This reaction manifold was first reported by Schlessinger et al. in the early 1970's, who observed that LDA **23** added in a conjugate



Scheme 3. Reagents and conditions: (i) (*S*)-α-methylbenzylamine **19** (1 equiv), EtOH, Δ, 12 h; (ii) (*S*)-α-methylbenzylamine **19** (1.16 equiv), MeOH, Δ, 96 h; (iii) 3,5-dihydro-4*H*-dinaphth[2,1-*c*:1′,1′-*e*]azepine **21** (0.1 equiv), Δ, 21 h.

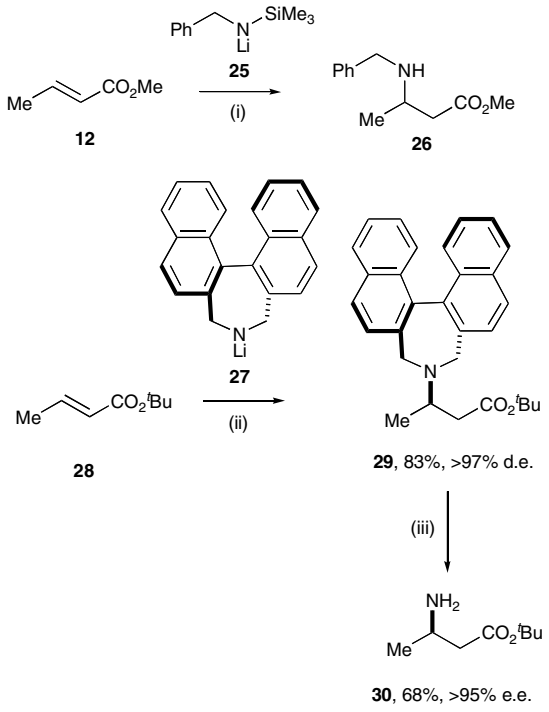


Scheme 4. Reagents and conditions: (i) LDA **23**, THF, −78 °C, then H^+.

manner to ethyl crotonate **9** to give **24** in near quantitative yield, although the use of LDA in HMPA resulted in predominant γ-deprotonation (Scheme 4).[25]

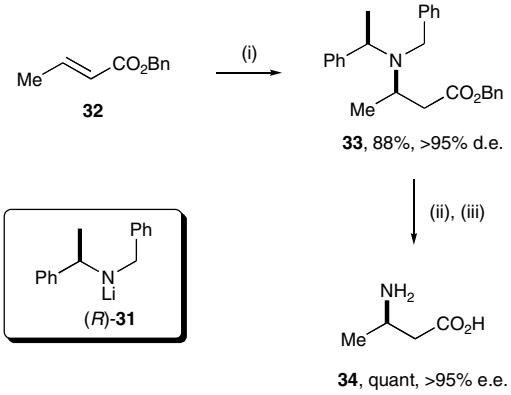
This conjugate addition reaction remained largely ignored until the mid-1980's with the seminal work of the groups of both Yamamoto and Hawkins. Within this area, Yamamoto introduced lithium *N*-benzyl-*N*-trimethylsilyl amide (LSA) **25**, and demonstrated that LSA added in a conjugate fashion to methyl crotonate **12**.[26] This methodology was extended to the conjugate addition of amido cuprates to homochiral α,β-unsaturated acceptors[27] and applied to a range of further applications,[28] an area of research that has been reviewed.[29] Hawkins et al. first showed in 1986 that an enantiomerically pure lithium amide could induce asymmetry in the conjugate addition reaction manifold. The C_2 symmetric lithium amide **27** derived from 3,5-dihydro-4*H*-dinaphth[2,1-*c*:1′,1′-*e*]azepine **21** undergoes highly diastereoselective conjugate addition to a range of α,β-unsaturated acceptors (>97% de to *tert*-butyl crotonate **28** to give **29**),[30] although it was not until 1992 that rather severe deprotection conditions for removal of the binaphthyl derived *N*-protecting groups were reported, requiring an excess of palladium hydroxide for hydrogenolysis, furnishing **30** (Scheme 5).[31]

In 1991, Davies and Ichihara described the conjugate addition of lithium *N*-benzyl-*N*-α-methylbenzylamide **31** to benzyl crotonate **32**. While conjugate addition of lithium *N*-α-methylbenzylamide to α,β-unsaturated



Scheme 5. Reagents and conditions: (i) LSA **25**, THF, −78 °C, then H^+; (ii) amide **27**, THF, −78 °C or DME, −78 °C, then H^+; (iii) $Pd(OH)_2$ on C, ammonium formate, EtOH, 50 °C.

esters proceeds with low diastereoselectivity, addition of a THF solution of benzyl crotonate at −78 °C to a THF solution of lithium amide **31** gave the corresponding β-amino ester **33** in >95% de and in good yield. In contrast to the severe conditions necessary for the deprotection of the binaphthyl derived *N*-protecting groups within the β-amino esters derived from lithium amide **27**, global deprotection of β-amino ester **33** by hydrogenolysis proceeded under mild conditions, requiring only 1 atm of H_2 in a MeOH, AcOH and H_2O mixture to give (*R*)-3-aminobutanoic acid **34** in quantitative yield and >95% ee (Scheme 6).[32]



Scheme 6. Reagents and conditions: (i) lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide (1.6 equiv), THF, −78 °C, then NH_4Cl(aq); (ii) $Pd(OH)_2$ on C, MeOH, H_2 (5 atm); (iii) crystallisation; (iv) $Pd(OH)_2$ on C, MeOH, AcOH, H_2O (40:4:1), H_2 (1 atm); (v) HCl(aq), Δ.

Since the first communication of this methodology, a range of homochiral lithium amides **35**–**45** that are readily derived from commercially available homochiral α-methylbenzylamines have been developed. As both enantiomers of the parent α-methylbenzylamines are commercially available, both enantiomers of lithium amides **35**–**45** may be used in synthesis. All members of this family of lithium amides undergo highly diastereoselective conjugate addition to a wide range of α,β-unsaturated esters and amides, and allow for either differential deprotection of the *N*-atom within the β-amino ester product of conjugate addition or further functionalisation in synthesis (Fig. 2).

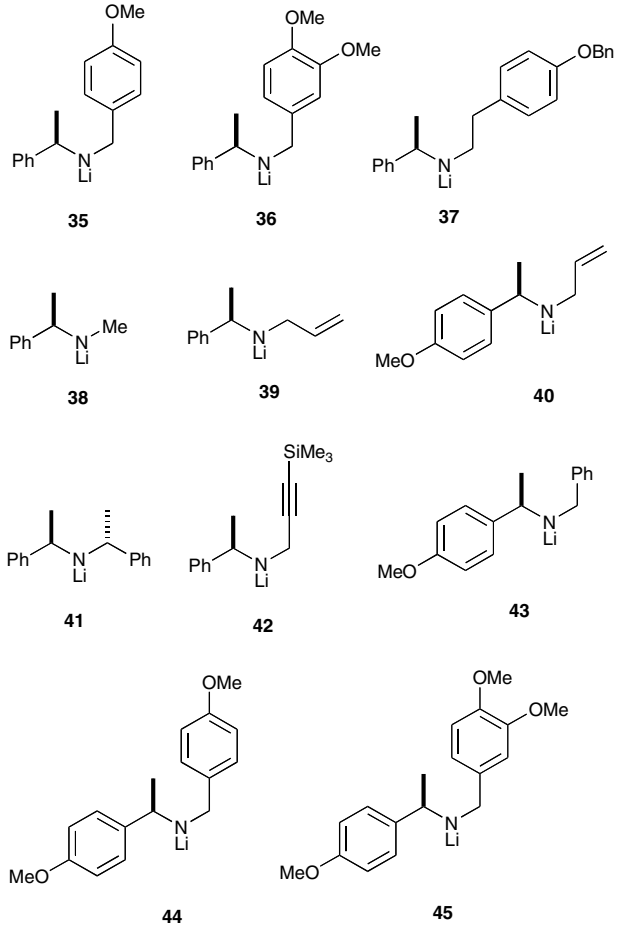
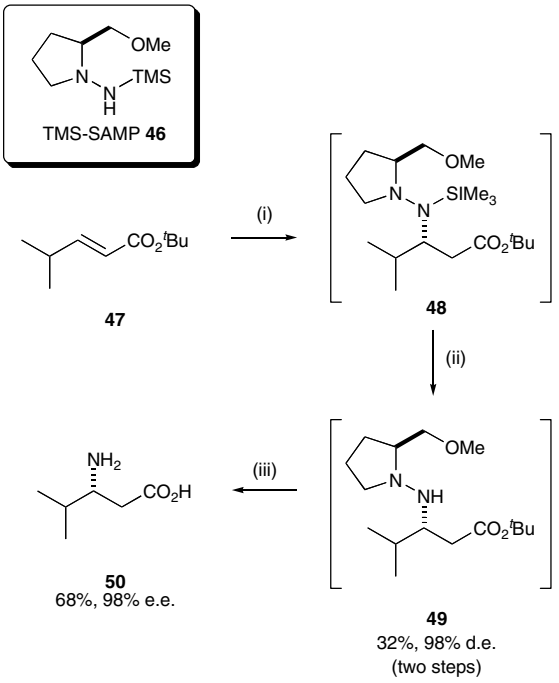


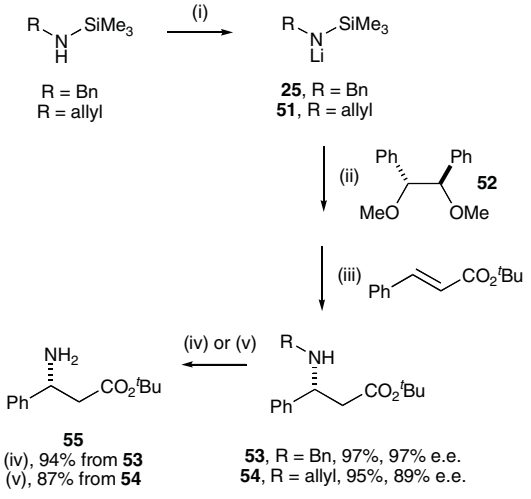
Figure 2. Homochiral lithium amides as asymmetric ammonia equivalents.

Following the first development of this conjugate addition methodology, Enders et al. modified their established SAMP and RAMP auxiliary methodology, introducing TMS-SAMP **46** as a chiral ammonia equivalent. Lithiation of TMS-SAMP **46** via deprotonation with *n*-BuLi and subsequent addition of a solution of *tert*-butyl 4-methyl-pent-2-enoate **47** gave the corresponding *N*-silyl-β-hydrazinoester **48**, which after stirring on silica and purification gave the β-hydrazinoester **49** in 98% de and 32% yield over two steps. The β-hydrazinoester **49** can be converted to the corresponding β-amino acid **50** in 68% yield and 98% ee by treatment with Raney nickel and saponification (Scheme 7).[33]



Scheme 7. Reagents and conditions: (i) TMS-SAMP (1.3 equiv), *n*-BuLi (1.3 equiv), THF, −78 °C, then $NaHCO_3$(satd., aq); (ii) SiO_2, EtOAc, HCl, then chromatographic purification; (iii) Raney nickel, H_2O, 60–75 °C, H_2 (7.5–9.5 bar), then chromatography, then recrystallisation.

As an alternative strategy, Tomioka et al. have shown that the homochiral diether **52** confers stereocontrol in the conjugate addition of *N*-trimethylsilyl-*N*-benzyl- and *N*-trimethylsilyl-*N*-allyl-lithium amides **25** and **51** to α,β-unsaturated esters, giving the corresponding β-amino esters **53** and **54** in high ee, which can be subsequently *N*-deprotected by either hydrogenolysis or deallylation to β-amino ester **55** (Scheme 8).[34]



Scheme 8. Reagents and conditions: (i) amine (1.5 equiv), *n*-BuLi (1.5 equiv), toluene, −78 °C, then H^+; (ii) ligand **52** (1.8 equiv), toluene, −78 °C; (iii) *tert*-butyl cinnamate, toluene, −78 °C; (iv) $Pd(OH)_2$ on C, MeOH, H_2; (v) $Rh(PPh_3)_3Cl$, MeCN(aq), Δ.

This introduction has showcased the variety of systems that are available for the asymmetric conjugate addition of lithium amides to α,β-unsaturated acceptors. In the subsequent sections of this review, the products of these conjugate addition reactions are categorised according to reaction type and substitution.

3. Conjugate addition reaction of homochiral lithium amides

3.1. Conjugate addition of chiral lithium amides to β-alkyl-acrylates

The conjugate addition of chiral lithium amides has been applied to an enormous range of β-alkyl-acrylates. In general, the addition reactions of lithium *N*-benzyl- or *N*-allyl-protected *N*-α-methylbenzylamides proceed with high diastereoselectivities at −78 °C (generally >95% de), with only a modest decrease in stereoselectivity at higher temperatures (~80% de at 0 °C). However, conjugate additions of lithium *N*-methyl-*N*-α-methylbenzylamide generally proceed with slightly lower levels of stereoselectivity (~90% at −78 °C) to β-alkyl-acrylates. Higher isolated yields of the β-amino ester products are normally achieved upon addition to *tert*-butyl esters than the corresponding methyl, ethyl or benzyl esters, the *tert*-butyl ester functionality protecting the carbonyl carbon effectively against 1,2 addition, which can become competitive in the other esters, especially if the β-position is hindered. The reaction is tolerant of straight chain and branched β-alkyl substitution on the acrylates, with high diastereoselectivity being independent of the length of the alkyl chain of the β-alkyl substituent (Table 1).

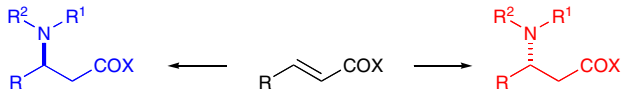
3.2. Conjugate addition of chiral lithium amides to β-aryl-acrylates

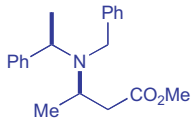
A similar general trend in reactivity to that observed upon addition of lithium amides to β-alkyl-acrylates is seen upon addition of β-aryl-acrylates, with the reaction generally tolerant of addition to acrylates containing β-aryl groups with either electron donating or electron withdrawing substituents. The conjugate additions of lithium *N*-benzyl protected *N*-α-methylbenzylamide **31** generally proceed with excellent stereoselectivity (>95% de), although lithium *N*-benzyl-*N*-4-methoxy-α-methylbenzylamide **43** adds with slightly lower stereoselectivity (typically 88–92% de). Fortunately, the β-amino ester products derived from addition of lithium *N*-benzyl-*N*-4-methoxy-α-methylbenzylamide **43** can often be purified to homogeneity by crystallisation, allowing the β-amino esters to be isolated in diastereomerically pure form. Alternatively, salt formation imparts crystallinity to many β-amino ester products, facilitating their purification to homogeneity by crystallisation (Table 2).

3.3. Scale-up possibilities: premixing

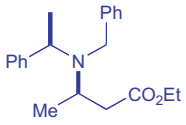
The standard experimental protocol for this lithium amide conjugate addition reaction that can be carried out readily on a multigram scale in the laboratory

Table 1.

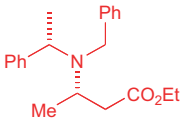




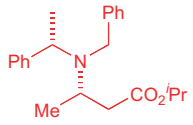
56
Ref 32: -78ºC, 85%, 95% d.e.
Ref 35: -78ºC, 83%, >99% d.e .
Ref 36



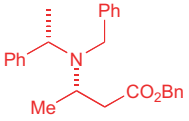
57
Ref 37: 0ºC, 83%, 82 d.e.



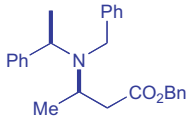
58
Ref 38: -78ºC, 68%, 94% d.e.
Ref 37: 0ºC, 85%, 82 d.e.
Ref 39: -78ºC, 85%, >97% d.e.



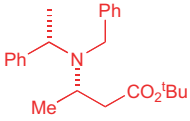
59
Ref 40: -78ºC, 85%, >95% d.e.
$[\alpha]_D^{24}$ +4.4 (c=1.0, $CHCl_3$)



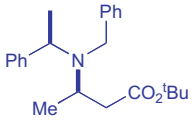
33
Ref 41: -78ºC, 64%, >99% d.e.



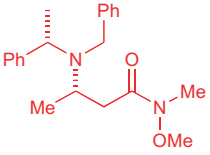
33
Ref 32: -78ºC, 88%, 95% d.e.



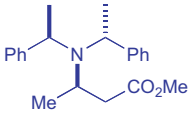
59
Ref 38, Ref 42



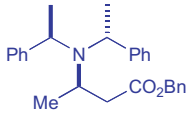
59
Ref 32: -78ºC, 82%, 99% d.e.



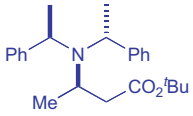
60
Ref 43: -78ºC; quant, >98% d.e
Ref 44: -78ºC; 96%, >95% d.e.
$[\alpha]_D^{22}$ -29.1 (c=1.1, $CHCl_3$)



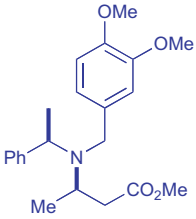
61
Ref 32: -78ºC, 57%, 95% d.e.



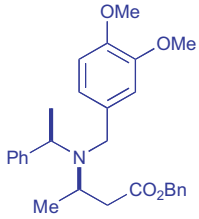
62
Ref 32: 0ºC, 23%, 95% d.e.



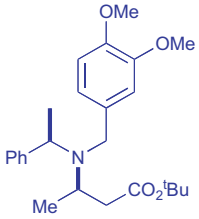
63
Ref 32: -78ºC, 27%, 99% d.e.



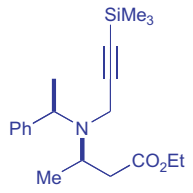
64
Ref 32: -78ºC, 68%, 95% d.e.



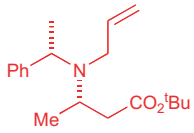
65
Ref 32: -78ºC, 74%, 96% d.e.



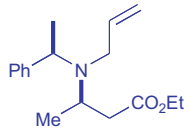
66
Ref 32: -78ºC; 83%, 99% d.e.



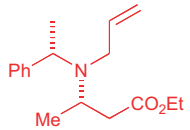
67
Ref 45: -78ºC; 72%, 90% d.e.
Ref 46



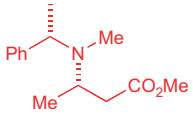
68
Ref 47: -78ºC ,92%, >99:1 d.s.



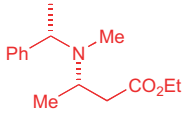
69
Ref 45: -78ºC; 73%, 97.5:2.5 d.s.
Ref 46



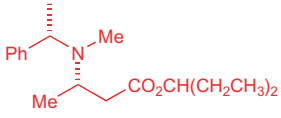
69
Ref 48



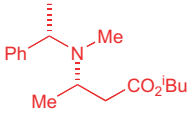
70
Ref 38: -78ºC; 73%, 89% d.e.



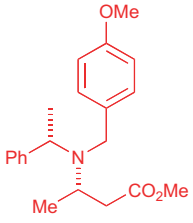
71
Ref 38: -78ºC; 84%, 89% d.e.



72
Ref 38: -78ºC, 49%, 60% d.e.

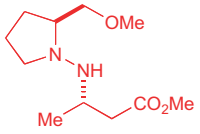


73
Ref 38: -78ºC, 88%, 89% d.e.

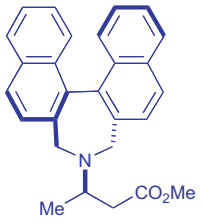


74
Ref 49: -78ºC, 69%, 95% d.e.
Ref 50: -78ºC, 67%, >95% d.e.

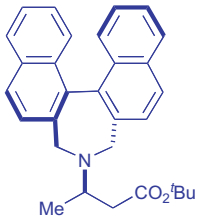
Table 1 (*continued*)



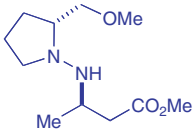
75
Ref 33: -78°C, 48%, 95% d.e.
$[\alpha]_D^{22}$ -97.6 (c=1.04, $CHCl_3$)



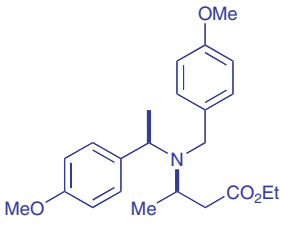
22
Ref 30: -78°C, 83%, >97% d.e.



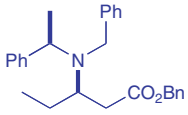
29
Ref 31: -78°C, 83%, >97% d.e.



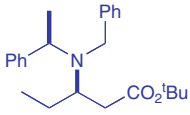
75
Ref 33: -78°C, 47%, 95% d.e.
$[\alpha]_D^{22}$ +96.4 (c=0.87, $CHCl_3$)



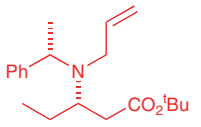
76
Ref 51: -78°C, 41%, >90% d.e.
$[\alpha]_D^{20}$ +22 (c=0.9, $CHCl_3$)



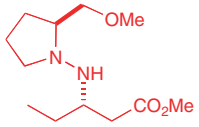
77
Ref 52: -78°C, 67%, 95% d.e.



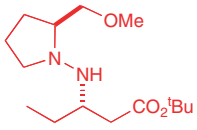
78
Ref 52: -78°C, 92%, >95% d.e.



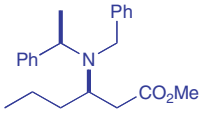
79
Ref 47: -78°C, 85%, >98% d.e.
$[\alpha]_D^{21}$ +18.5 (c = 1.88, $CHCl_3$)



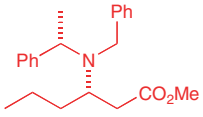
80
Ref 33: -78°C, 37%, 95% d.e.
$[\alpha]_D^{22}$ -100.0 (c=1.02, $CHCl_3$)



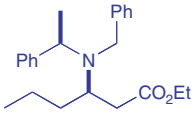
81
Ref 33: -78°C, 49%, 98% d.e.
$[\alpha]_D^{22}$ -93.2 (c=1.09, $CHCl_3$)



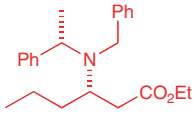
82
Ref 53, Ref 54



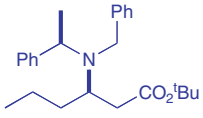
82
Ref 36



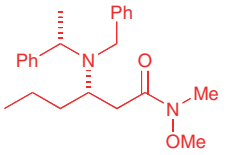
83
Ref 55: 0°C, 93%, >92% d.e.
Ref 56: -78°C, 50%, >98% d.e.
Ref 37: 0°C, 70%, 82% d.e



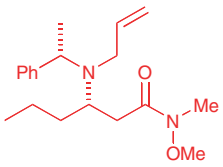
83
Ref 37: -78°C, 70%, 82% d.e.



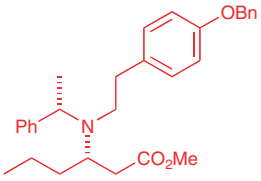
84
Ref 57: -78°C, 74%, >98% d.e.
$[\alpha]_D^{30}$ +7.3 (c = 1.24, EtOH)
Ref 58
Ref 59: -78°C, 85%
$[\alpha]_D^{15}$ +6 (c = 0.6, $CHCl_3$)
Ref 60: 89%



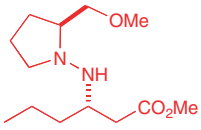
85
Ref 44: -78°C, 96%, >95% d.e.
$[\alpha]_D^{22}$ -41.9 (c = 1.0, $CHCl_3$)



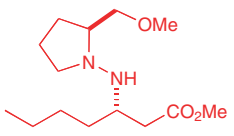
86
Ref 61: -78°C, 65%, >95% d.e.
$[\alpha]_D^{23}$ -7.5 (c = 2.09, $CHCl_3$)
Ref 62



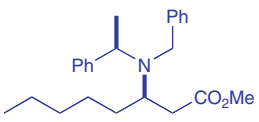
87
Ref 63: -78°C, 82%, >97% d.e.



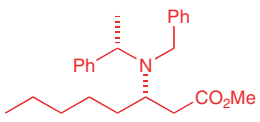
88
Ref 33: -78°C, 40%, 95% d.e.
$[\alpha]_D^{22}$ -105.0 (c=1.00, $CHCl_3$)



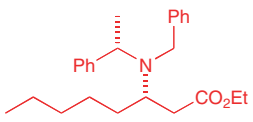
89
Ref 33: -78°C, 39%, >94% d.e
$[\alpha]_D^{22}$ -108.8 (c=0.98, $CHCl_3$).



90
Ref 64 : 90%
Ref 65



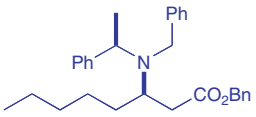
90
Ref 66: 74%
$[\alpha]_D^{20}$ -9.9 (c = 1.2, $CHCl_3$)



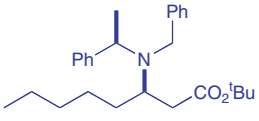
91
Ref 67

(*continued on next page*)

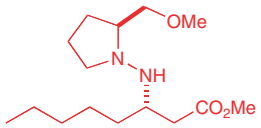
Table 1 (*continued*)



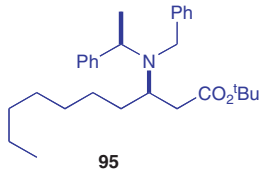
92
Ref 52: -78°C, 75%, >95% d.e.



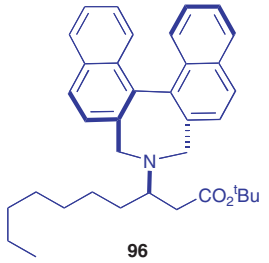
93
Ref 68: -78°C, 90%, >98% d.e.
$[\alpha]_D^{25}$ +5.1 (c = 1.07, EtOH)



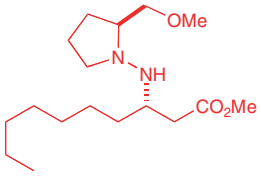
94
Ref 33: -78°C, 39%, >94% d.e.
$[\alpha]_D^{22}$ -102.0 (c=1.05, $CHCl_3$)



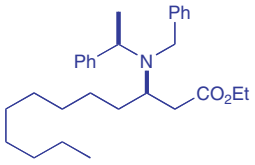
95
Ref 69: -78°C, 91%, >95% d.e.
$[\alpha]_D^{22}$ +5.3 (c = 1.03, $CHCl_3$)



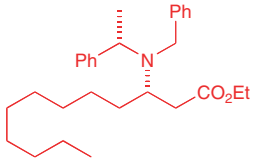
96
Ref 31: -78°C, 96% d.e., 80% yield



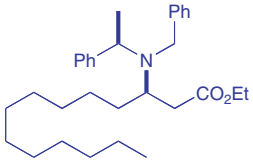
97
Ref 33: -78°C, 36%, 95% d.e.
$[\alpha]_D^{22}$ -87.9 (c=1.78, $CHCl_3$)



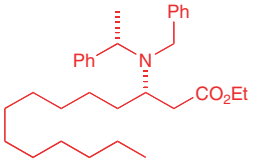
98
Ref 70: -78°C, 99%, >98% d.e.
$[\alpha]_D^{20}$ +7.7 (c = 0.04, $CHCl_3$)
Ref 37: 0°C, 71%, 80% d.e.



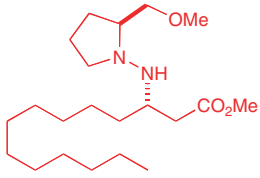
98
Ref 70: -78°C, 99%, >98% d.e.
$[\alpha]_D^{20}$ -7.7 (c = 0.05, $CHCl_3$)
Ref 37: 0°C, 69%, 80% d.e.



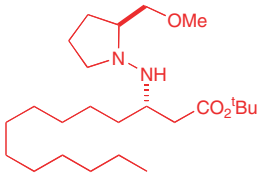
99
Ref 37: 0°C, 88%, 80% d.e.



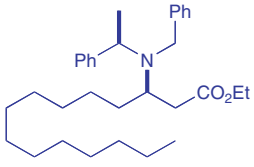
99
Ref 37: 0°C, 76%, 80% d.e.



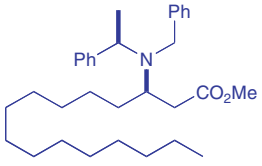
100
Ref 33: -78°C, 35%, 95% d.e.
$[\alpha]_D^{22}$ -67.0 (c=1.10, $CHCl_3$)



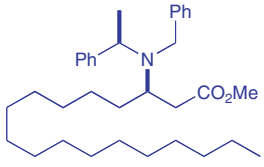
101
Ref 33: -78°C, 67%, 97% d.e.
$[\alpha]_D^{22}$ -98.5 (c=1.21, $CHCl_3$)



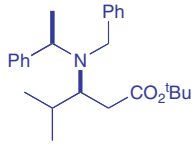
102
Ref 71: 88%



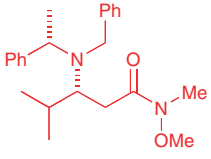
103
Ref 72: 88%



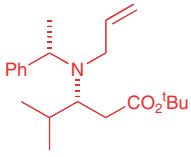
104
Ref 53, **Ref 54**



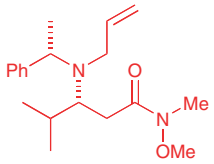
105
Ref 52: -78°C, 91%, 95% d.e.



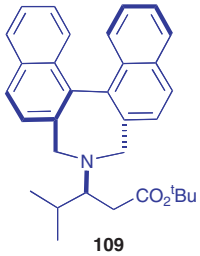
106
Ref 44: -78°C, 95%, >95% d.e.
$[\alpha]_D^{22}$ -37.4 (c = 1.0, $CHCl_3$)
Ref 43: quantitative, 98% d.e.



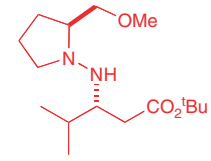
107
Ref 47: -78°C, 88%, >98% d.e.
$[\alpha]_D^{21}$ +52.7 (c = 1.85, $CHCl_3$)



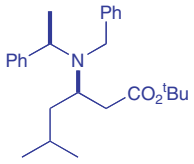
108
Ref 61: -78°C, 63%, >95% d.e.
$[\alpha]_D^{23}$ +8.0 (c = 1.1, $CHCl_3$)



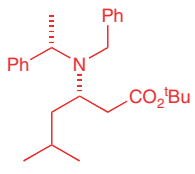
109
Ref 31: -78°C, 69%, 94% d.e.



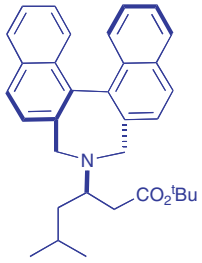
49
Ref 33: -78°C, 32%, 98% d.e.
$[\alpha]_D^{22}$ -69.4 (c=1.08, $CHCl_3$)



110
Ref 73: -78°C, 96%, 97% d.e.
$[\alpha]_D^{25}$ +3.2 (c = 1.6, $CHCl_3$)

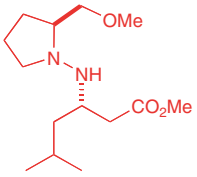


110
Ref 73: -78°C, 95%, 96% d.e.
$[\alpha]_D^{25}$ -3.0 (c = 1.4, $CHCl_3$)

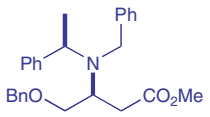


111
Ref 31: -78°C, 74%, 97% d.e.

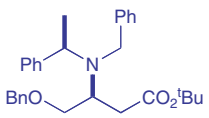
Table 1 (*continued*)



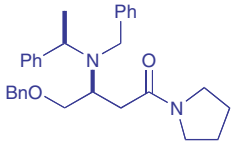
112
Ref 33: -78°C, 35%, >93% d.e.
$[\alpha]_D^{22}$ -113.8 (c=1.02, $CHCl_3$)



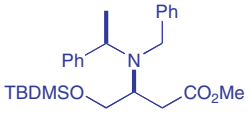
113
Ref 74: -78°C, 47%, >98% d.e.
$[\alpha]_D^{22}$ -14.5 (c = 1.00, EtOH)



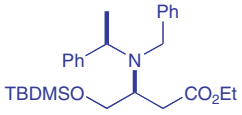
114
Ref 74: -78°C, 42%, >98% d.e.
$[\alpha]_D^{25}$ -72.9 (c = 0.75, $CHCl_3$)



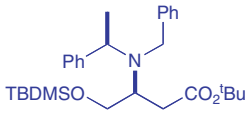
115
Ref 74: -78°C, 89%, >95% d.e.
$[\alpha]_D^{21}$ -0.16 (c = 1.22, $CHCl_3$)



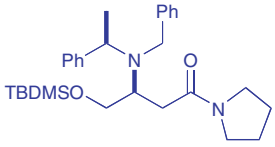
116
Ref 74: -78°C, 60%, >95% d.e.



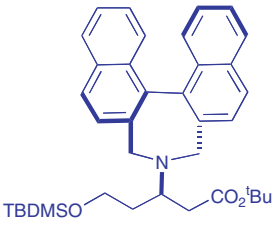
117
Ref 74: -78°C, 72%, >95% d.e.
$[\alpha]_D^{25}$ -7.9 (c = 2.00, $CHCl_3$)



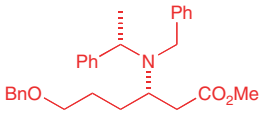
118
Ref 74: -78°C, 76%, >95% d.e.
$[\alpha]_D^{25}$ -13.7 (c = 1.00, $CHCl_3$)



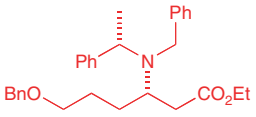
119
Ref 74: -78°C, 53%, >95% d.e.
$[\alpha]_D^{21}$ +8.4 (c = 1.97, $CHCl_3$)



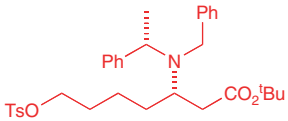
120
Ref 31: -78°C, 86%, 95% d.e.



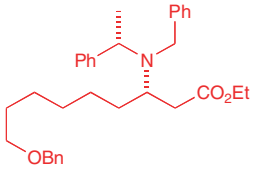
121
Ref 75: -78°C, 83%, >98% d.e.
Ref 76: -78°C, 81%, >98% d.e.
$[\alpha]_D^{20}$ -8.7 (c = 1.0, $CHCl_3$)



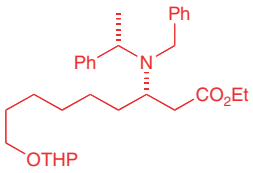
122
Ref 76: -78°C, 83%, >98% d.e.
$[\alpha]_D^{20}$ -4.9 (c = 1.6, $CHCl_3$)
Ref 77



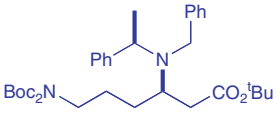
123
Ref 78: 75%



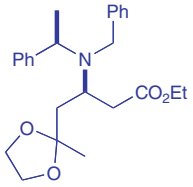
124
Ref 53



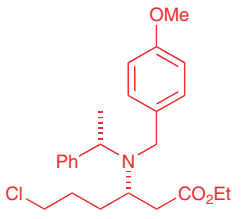
125
Ref 71: 88%



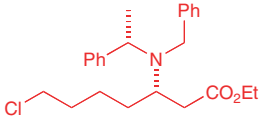
126
Ref 79: -78°C, >95% d.e.



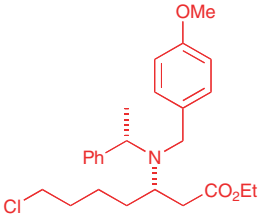
127
Ref 80: -78°C, 91%, >95% d.e.
$[\alpha]_D^{20}$ +8.2 (c = 0.55, $CHCl_3$)



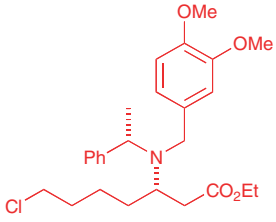
128
Ref 81: -78°C, 72%, 95% d.e.



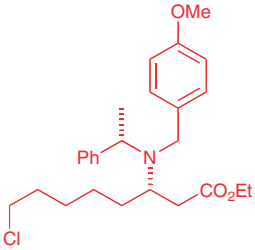
129
Ref 81: -78°C, 62%, 95% d.e.



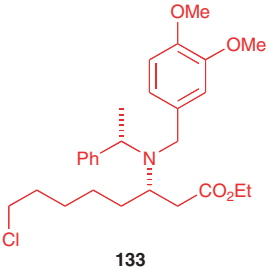
130
Ref 81: -78°C, 88%, 95% d.e.
$[\alpha]_D$ -17.1 (c = 1.0, $CHCl_3$)



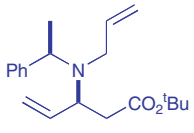
131
Ref 81: -78°C, 60%, 95% d.e.



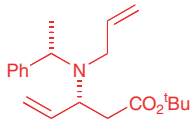
132
Ref 81: -78°C, 87%, 95% d.e.



133
Ref 81: -78°C, 70%, 95% d.e.



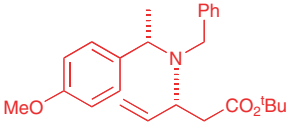
134
Ref 82: -78°C, 87%, 98% d.e.



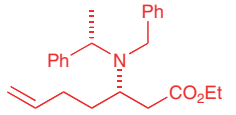
134
Ref 61: -78°C, 62%, >95% d.e.
$[\alpha]_D^{26}$ +8.3 (c = 1.04, $CHCl_3$)

(*continued on next page*)

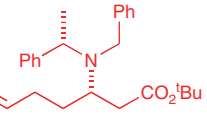
Table 1 (*continued*)



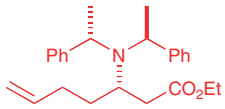
135
Ref 83: -78°C, 81%, 98% d.e.
$[\alpha]_D^{24}$ +8.7 (c = 1.0, $CHCl_3$)



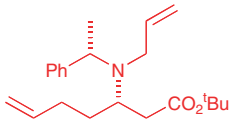
136
Ref 84: -78°C, 93%, >90% d.e.



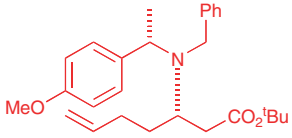
137
Ref 85: -78°C, 77%, >98% d.e.
$[\alpha]_D^{26}$ -8.1 (c = 0.88, $CHCl_3$)



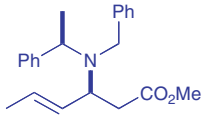
138
Ref 84: -78°C, 53%, >90% d.e.



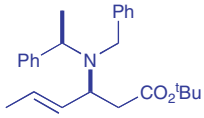
139
Ref 85: -78°C, 89%, 96% d.e.
$[\alpha]_D^{26}$ +21.8 (c = 1.32, $CHCl_3$)



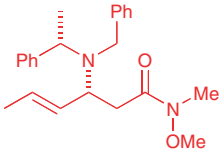
140
Ref 85: -78°C, 85%, 93% d.e.
$[\alpha]_D^{25}$ -19.3 (c = 1.02, $CHCl_3$)



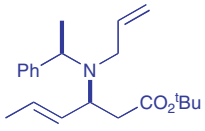
141
Ref 86: -78°C, 71%, 95% d.e.
$[\alpha]_D^{24}$ -25.4 (c = 3.38, $CHCl_3$)
Ref 87



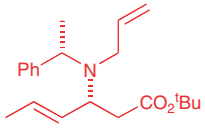
142
Ref 88: -78°C, 77%, 94% d.e.
$[\alpha]_D^{24}$ -23.3 (c = 2.04, $CHCl_3$)
Ref 86



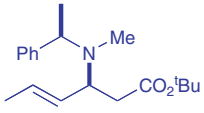
143
Ref 43: -78°C, 95%, 98% d.e.



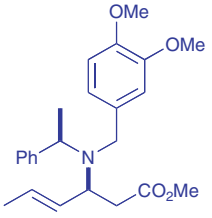
144
Ref 89: -78°C, 85%, >95% d.e.



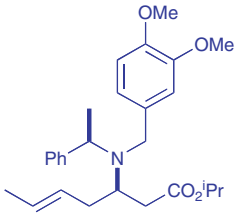
144
Ref 62
Ref 61: -78°C, 78%, >95% d.e.
$[\alpha]_D^{24}$ +6.4 (c = 1.32, $CHCl_3$)
Ref 90: -78°C, 78%, 96% d.e.
Ref 47: -78°C, 78%, >96% d.e.
$[\alpha]_D^{21}$ +2.7 (c = 1.67, $CHCl_3$)



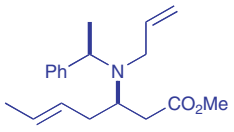
145
Ref 88: -78°C, 71%, 91% d.e.
$[\alpha]_D^{24}$ +27.5 (c = 2.08, $CHCl_3$)
Ref 91



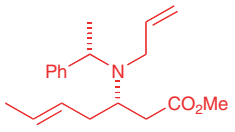
146
Ref 92: -78°C, 90%, 96% d.e.



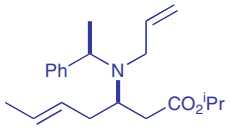
147
Ref 93: -78°C, 53%, >95% d.e.
$[\alpha]_D^{25}$ +1.86 (c = 1.0, $CHCl_3$)



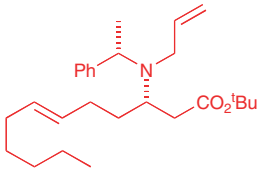
148
Ref 93: -78°C, 73%, >96% d.e.
$[\alpha]_D^{22}$ -6.0 (c = 1.2, $CHCl_3$)
Ref 94



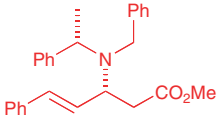
148
Ref 61: -78°C, 69%, >95% d.e.
$[\alpha]_D^{23}$ +6.4 (c = 1.3, $CHCl_3$)
Ref 62



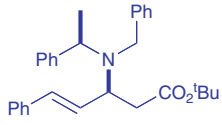
149
Ref 93: -78°C, 64%, 91% d.e.
$[\alpha]_D^{25}$ -12.0 (c = 1.9, $CHCl_3$)
Ref 95



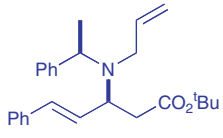
150
Ref 96: -78°C, 90%, >95% d.e.
$[\alpha]_D^{26}$ +19.2 (c=1.00, $CHCl_3$)



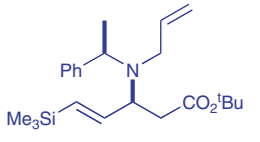
151
Ref 97: 61%, $[\alpha]_D$ +89 (c = 10, CH_2Cl_2)



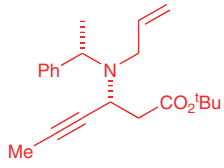
152
Ref 98: -78°C, quant., >99% d.e.



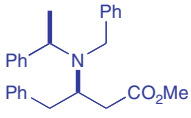
153
Ref 99: -78°C, 79%, 98% d.e.
$[\alpha]_D^{25}$ -31.5 (c = 1.25, $CHCl_3$)



154
Ref 100: -78°C, 94%, >98% d.e.
$[\alpha]_D^{23}$ -17.5 (c = 0.60, $CHCl_3$)

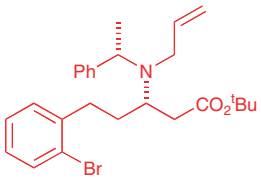


155
Ref 96: -78°C, 55%, >95% d.e.
$[\alpha]_D^{23}$ +35.8 (c=0.84, $CHCl_3$)

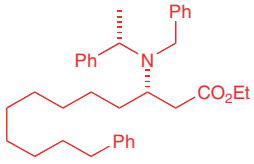


156
Ref 53, **Ref 54**

Table 1 (*continued*)

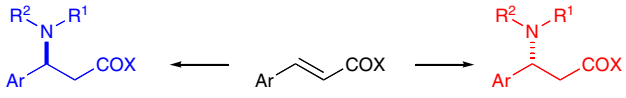


157
Ref 96: -78°C, 89%, >95% d.e.
$[\alpha]_D^{23}$ +10.1 (c=0.92, $CHCl_3$)

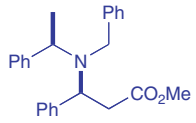


158
Ref 101: -78°C, 89%, >97% d.e
$[\alpha]_D^{20}$ -3.4 (c = 0.75, $CHCl_3$).

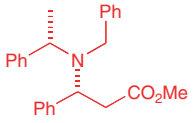
Table 2.



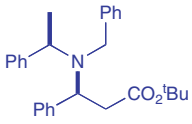
X = OR', N(R')(R'')



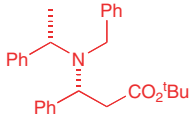
159
Ref 37: 0°C, 86%, 84% d.e.



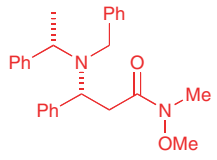
159
Ref 37: 0°C, 79%, 84% d.e.



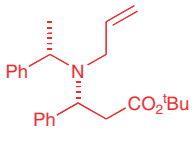
160
Ref 102: 100%
Ref 103, **Ref 104**: -78°C, 96%, >95% d.e.
. **Ref 105**: -78°C, >95% d.e
Ref 106: -78°C, 92%, >95% d.e.



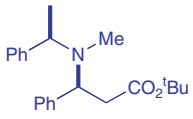
160
Ref 107: -78°C, 96%, >98% d.e.
Ref 40: -78°C, 89%, >95% d.e.
$[\alpha]_D^{23}$ -4.0 (c = 1.0, $CHCl_3$)



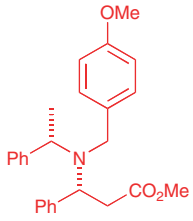
161
Ref 44: -78°C, 92%, >95% d.e.
$[\alpha]_D^{22}$ -23.8 (c = 1.1, $CHCl_3$)
Ref 43: -78°C, quant, 98% d.e.



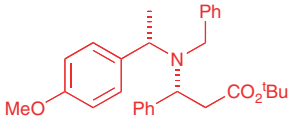
162
Ref 107, **Ref 108**: -78°C, 88%, >98% d.e.
Ref 46: -78°C, 97%, >98% d.e.
$[\alpha]_D^{21}$ -2.1 (c = 3.24, $CHCl_3$)



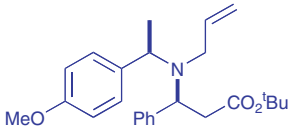
163
Ref 108: 94%, 88% d.e.



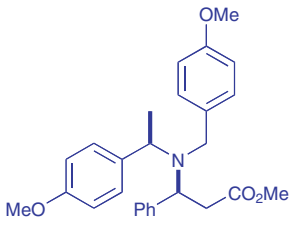
164
Ref 49: -78°C, 72%, 95% d.e.



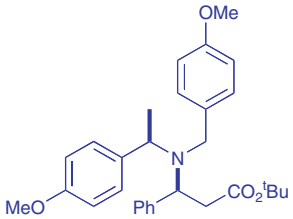
165
Ref 107: -78°C, 77%, 92% d.e.
$[\alpha]_D^{20}$ -14.2 (c = 1.0, $CHCl_3$)
Ref 83, **Ref 107**
Ref 109: -78°C, 82%, 92% d.e.



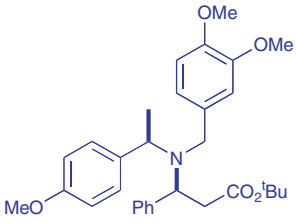
166
Ref 51: -78°C, 84%, >90% d.e.
$[\alpha]_D^{20}$ +11 (c = 0.6, $CHCl_3$)



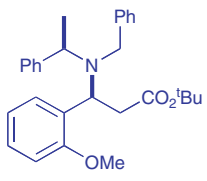
167
Ref 51: -78°C, 44%, >90% d.e.
$[\alpha]_D^{20}$ +16 (c = 1.1, $CHCl_3$)



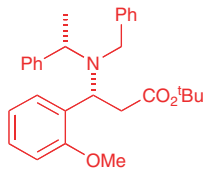
168
Ref 51: -78°C, 88%, >90% d.e.
$[\alpha]_D^{20}$ +21 (c = 0.4, $CHCl_3$)



169
Ref 110: -78°C, 95%, >95% d.e.
$[\alpha]_D^{24}$ +26.1 (c = 1.0, $CHCl_3$)



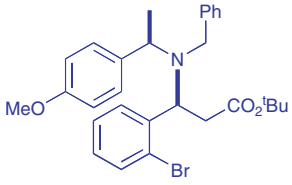
170
Ref 73: -78°C, 88%, 95% d.e.
$[\alpha]_D^{25}$ +13.6 (c = 2.6, $CHCl_3$)



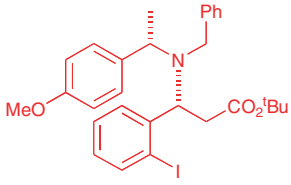
170
Ref 73: -78°C, 86%, 97% d.e.
$[\alpha]_D^{25}$ -13.7 (c = 2.0, $CHCl_3$)

(*continued on next page*)

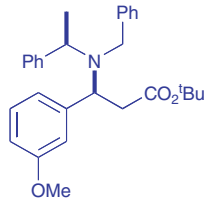
Table 2 (*continued*)



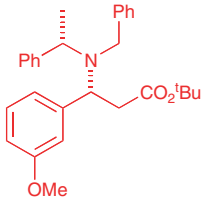
171
Ref 111: -78°C, 82%, 90% d.e.
$[\alpha]_D^{23}$ +59.4 (c = 1.03, $CHCl_3$)



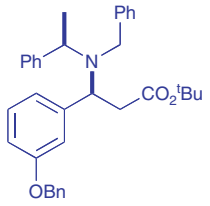
172
Ref 111: -78°C, 76%, 92% d.e.
$[\alpha]_D^{22}$ -34.5 (c = 1.0, $CHCl_3$)



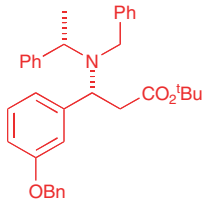
173
Ref 73: -78°C, 94%, 95% d.e.
$[\alpha]_D^{25}$ +3.3 (c = 1.4, $CHCl_3$)



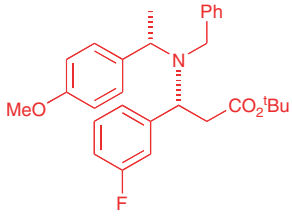
173
Ref 73: -78°C, 94%, 96% d.e.
$[\alpha]_D^{25}$ -3.2 (c = 2.8, $CHCl_3$)



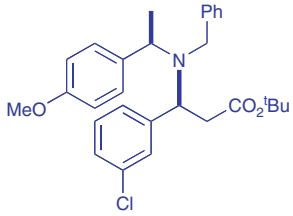
174
Ref 73: -78°C, 87%, 96% d.e.
$[\alpha]_D^{25}$ +2.7 (c = 1.1, $CHCl_3$)



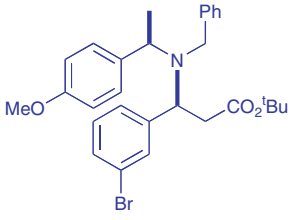
174
Ref 73: -78°C, 90%, 96% d.e.
$[\alpha]_D^{25}$ -2.5 (c = 1.5, $CHCl_3$)



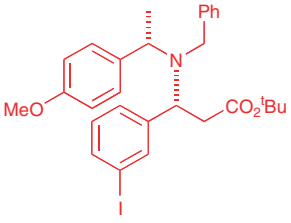
175
Ref 111: -78°C, 77%, 92% d.e.
$[\alpha]_D^{20}$ -25.0 (c = 1.0, $CHCl_3$)
Ref 109



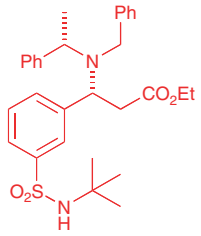
176
Ref 109: -78°C, 80%, 90% d.e.
Ref 111: -78°C, 78%, 88% d.e.
$[\alpha]_D^{20}$ -19.2 (c = 1.0, $CHCl_3$)



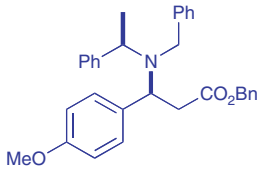
177
Ref 111: -78°C, 80%, 90% d.e
$[\alpha]_D^{20}$ +18.6 (c = 1.03, $CHCl_3$).
Ref 109



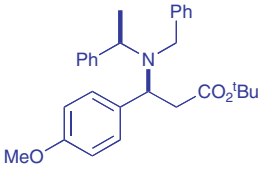
178
Ref 111: -78°C, 74%, 88% d.e.
$[\alpha]_D^{20}$ -18.0 (c = 1.0, $CHCl_3$)
Ref 109



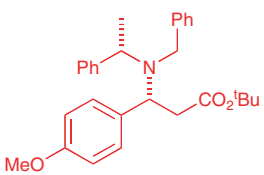
179
Ref 112: -78°C, 87%, >99% d.e.
$[\alpha]_D$ +5.6 (MeOH)



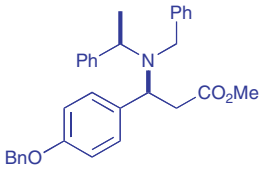
180
Ref 52: -78°C, 72%, 90% d.e.



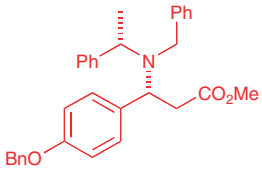
181
Ref 73: -78°C, 91%, 96% d.e
$[\alpha]_D^{25}$ +2.0 (c = 2.1, $CHCl_3$).



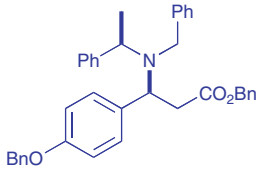
181
Ref 73: -78°C, 89%, 96% d.e.
$[\alpha]_D^{25}$ -1.8 (c = 3.2, $CHCl_3$)



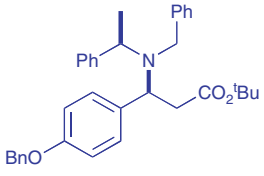
182
Ref 40: -78°C, 78%, >95% d.e.
Ref 113



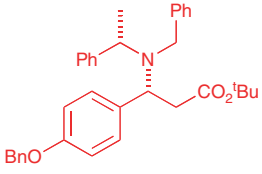
182
Ref 114: >98% d.e.



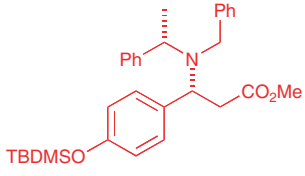
183
Ref 115: 64%, 91% d.e.



184
Ref 73: -78°C, 90%, 96% d.e.
$[\alpha]_D^{25}$ +2.0 (c = 1.0, $CHCl_3$)

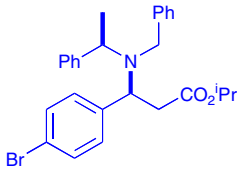


184
Ref 73: -78°C, 93%, 96% d.e.
$[\alpha]_D^{25}$ -2.1 (c = 1.4, $CHCl_3$)

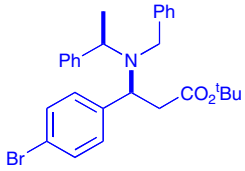


185
Ref 116: -78°C, 95%, >95% d.e.
$[\alpha]_D$ +1.9 (c = 1.61, $CHCl_3$)

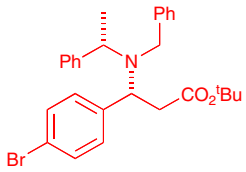
Table 2 (*continued*)



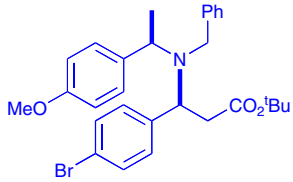
186
Ref 107: -78°C, 82%, 95% d.e.
$[\alpha]_D^{23}$ +5.1 (c = 1.0, $CHCl_3$)
Ref 117



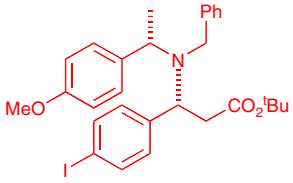
187
Ref 118: -78°C, 95%, 94% d.e.



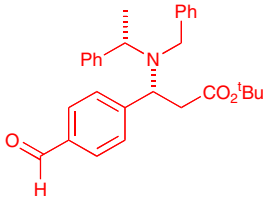
187
Ref 107: -78°C, 92%, 97% d.e.
$[\alpha]_D^{23}$ +3.6 (c = 1.8, $CHCl_3$)



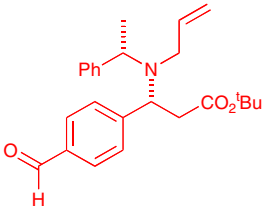
188
Ref 111: -78°C, 86%, 92% d.e.
$[\alpha]_D^{24}$ +10.4 (c = 1.0, $CHCl_3$)



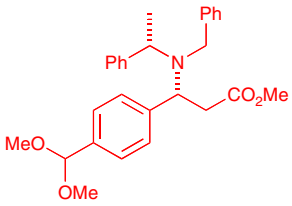
189
Ref 111: -78°C, 74%, 94% d.e.
$[\alpha]_D^{20}$ -6.9 (c = 1.0, $CHCl_3$)



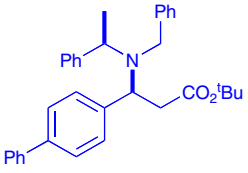
190
Ref 107: -78°C, 81%, 97% d.e
$[\alpha]_D^{23}$ +18.0 (c = 1.0, $CHCl_3$).
Ref 117



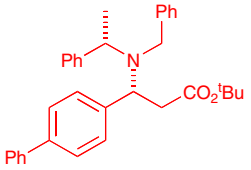
191
Ref 107: -78°C, 63%, 92% d.e.
$[\alpha]_D^{23}$ +18.7 (c = 1.0, $CHCl_3$)



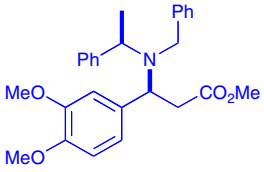
192
Ref 107: -78°C, 58%, 82% d.e.



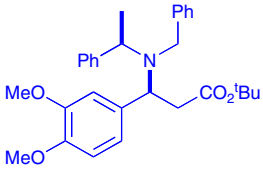
193
Ref 73: -78°C, 89%, 96% d.e.
$[\alpha]_D^{25}$ -1.6 (c = 1.1, $CHCl_3$)



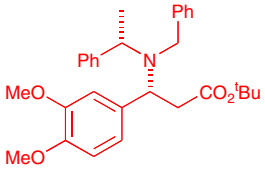
193
Ref 73: -78°C, 91%, 96% d.e.
$[\alpha]_D^{25}$ +1.7 (c = 1.2, $CHCl_3$)



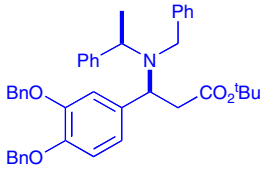
194
Ref 119: -78°C, 81%, >92% d.e.
$[\alpha]_D^{25}$ +2 (c = 5.3, $CHCl_3$)



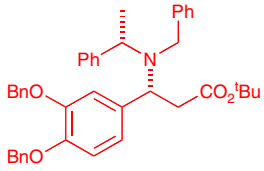
195
Ref 120: -78°C, 97%, >95% d.e.
Ref 73:-78°C, 95%, 96% d.e.
$[\alpha]_D^{25}$ -1.0 (c = 1.1, $CHCl_3$)



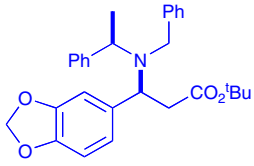
195
Ref 73: -78°C, 88%, 96% d.e.
$[\alpha]_D^{25}$ +1.0 (c = 1.0, $CHCl_3$)



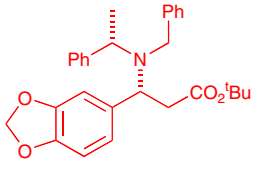
196
Ref 73: -78°C, 89%, 96% d.e.
$[\alpha]_D^{25}$ -2.0 (c = 2.2, $CHCl_3$)



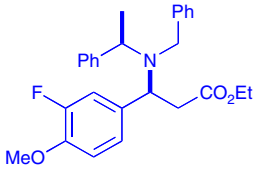
196
Ref 73: -78°C, 94%, 96% d.e.
$[\alpha]_D^{25}$ +2.2 (c = 2.3, $CHCl_3$)



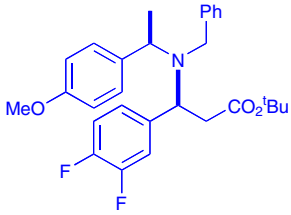
197
Ref 73: -78°C, 91%, 97% d.e.
$[\alpha]_D^{25}$ +5.9 (c = 1.2, $CHCl_3$)



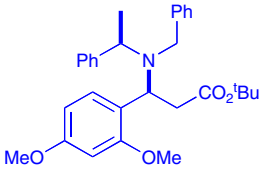
197
Ref 73: -78°C, 93%, 96% d.e.
$[\alpha]_D^{25}$ -6.3 (c = 1.5, $CHCl_3$)



198
Ref 121



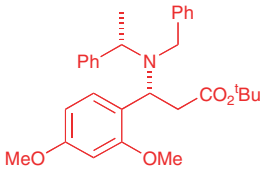
199
Ref 111: -78°C, 86%, 90% d.e.
$[\alpha]_D^{26}$ +13.9 (c = 1.0, $CHCl_3$)



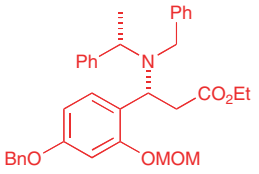
200
Ref 73: -78°C, 79%, 96% d.e.
$[\alpha]_D^{25}$ +8.6 (c = 8.6, $CHCl_3$)

(*continued on next page*)

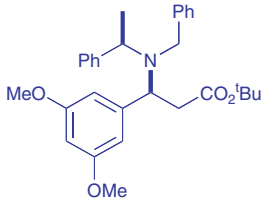
Table 2 (*continued*)



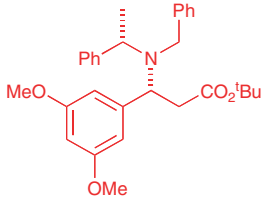
200
Ref 73: -78°C, 84%, 97% d.e.
$[\alpha]_D^{25}$ -8.4 (c = 0.8, $CHCl_3$)



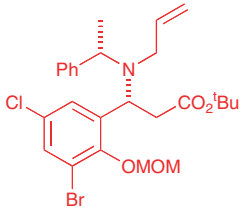
201
Ref 122: $[\alpha]_D^{23}$ -16.3 (c = 1.04, $CHCl_3$)
Ref 123



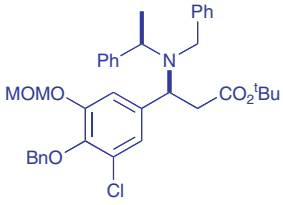
202
Ref 73: -78°C, 96%, 95% d.e.
$[\alpha]_D^{25}$ +1.8 (c = 1.0, $CHCl_3$)



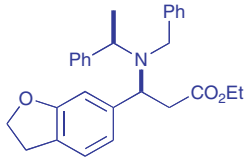
202
Ref 73: -78°C, 98%, 96% d.e.
$[\alpha]_D^{25}$ -1.6 (c = 1.1, $CHCl_3$)



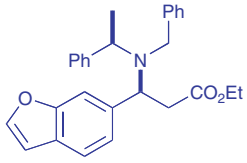
203
Ref 124: -78°C, 75%, >98% d.e.



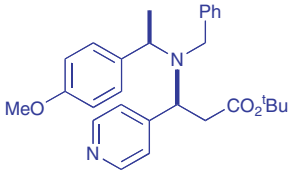
204
Ref 125: 83%, 90% d.e.



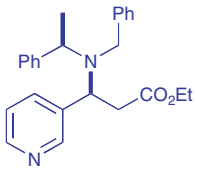
205
Ref 121



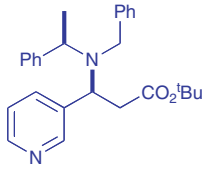
206
Ref 126: 72%, >90% d.e.



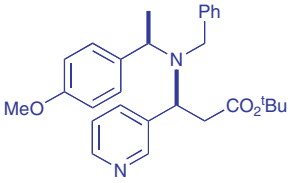
207
Ref 127: -78°C, 68%, 84% d.e.
$[\alpha]_D^{22}$ +39.3 (c = 1.1, $CHCl_3$)



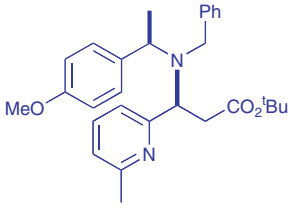
208
Ref 121



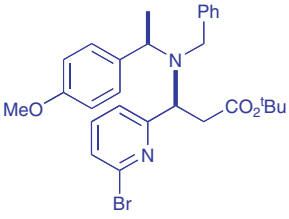
209
Ref 128: -78°C, 88%, >98% d.e.
Ref 127: -78°C, 83%, 98% d.e.
$[\alpha]_D^{24}$ +4.2 (c = 1.0, $CHCl_3$)
Ref 129



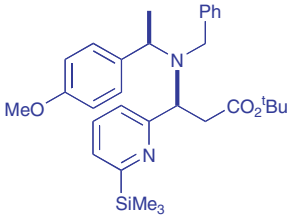
210
Ref 127: -78°C, 83%, 84% d.e.
$[\alpha]_D^{24}$ +16.8 (c = 1.0, $CHCl_3$)



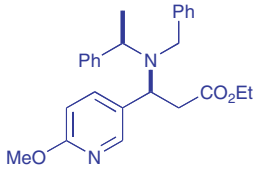
211
Ref 127: -78°C, 85%, 61% d.e.



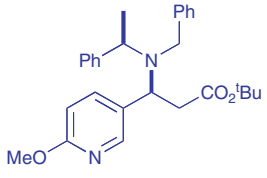
212
Ref 127: -78°C, 45%, 81% d.e.



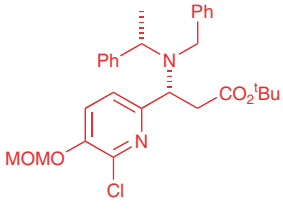
213
Ref 127: -78°C, 86%, 83% d.e.



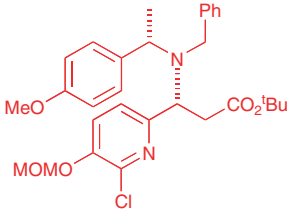
214
Ref 130: -78°C, 80%, >94% d.e.
Ref 121: 80%



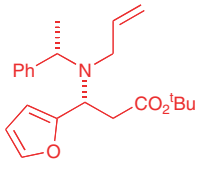
215
Ref 131: 71%



216
Ref 132: 83%, 86% d.e.



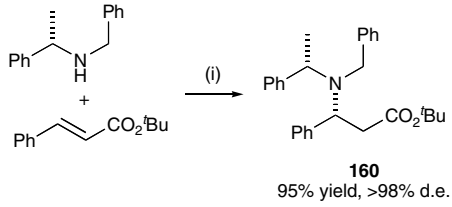
217
Ref 127: 69%,80% d.e.
$[\alpha]_D^{22}$ +25.4 (c = 1.0, $CHCl_3$)



218
Ref 47: -78°C, 97%, >98% d.e.

involves pre-making the lithium amide reagent by deprotonation of the corresponding amine in THF with *n*-BuLi at −78 °C, followed by addition of a solution of the α,β-unsaturated ester in THF at −78 °C via cannula

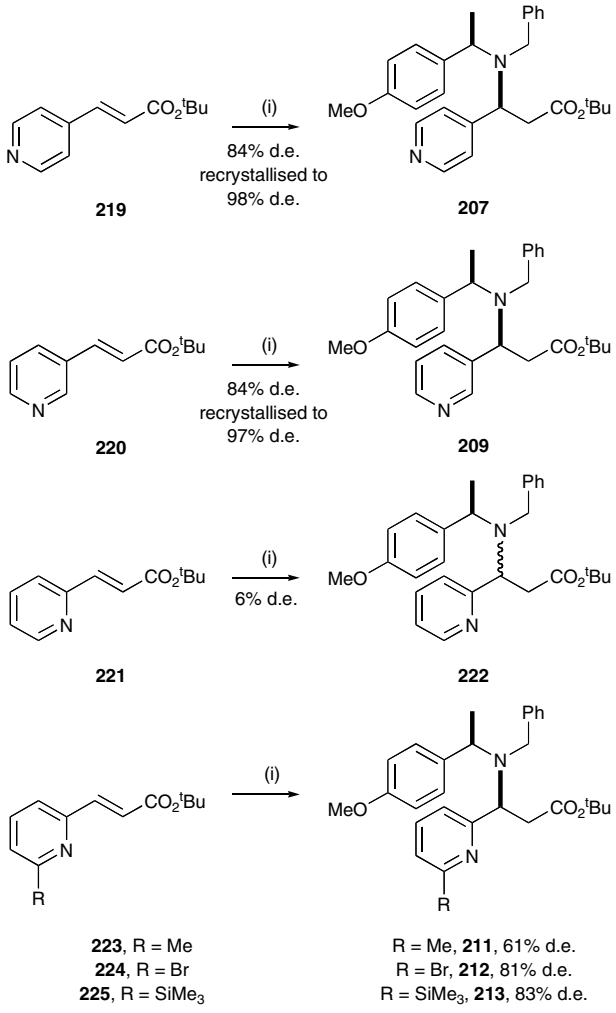
to the amide solution. This protocol preempts alternative reaction manifolds such as conjugate addition, 1,2 addition or γ-deprotonation of the α,β-unsaturated ester by *n*-BuLi that might compete with lithium amide addition. In order to simplify further this reaction procedure, the viability of a one-pot reaction protocol has been investigated,[78,133] in which deprotonation of the amine by an alkyl lithium reagent and subsequent conjugate addition is in direct competition with any alternative reactions. Using the conjugate addition to *tert*-butyl cinnamate as a model, *n*-BuLi (1.55 equiv) was added to a solution of (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (1.6 equiv) and *tert*-butyl cinnamate (1 equiv) in THF at −78 °C, giving, after addition of NH_4Cl(aq) and standard work up, the desired β-amino ester (3*R*,α*S*)-**160** in >98% de and 95% isolated yield. This reaction protocol is readily reproducible on a multigram scale, has been applied to a range of other α,β-unsaturated esters, and should facilitate further the application of this methodology on an industrial scale (Scheme 9).[133]



Scheme 9. Reagents and conditions: (i) *n*-BuLi, (*S*)-*N*-benzyl-*N*-α-methylbenzylamine, *tert*-butyl cinnamate, THF, −78 °C, then NH_4Cl(aq).

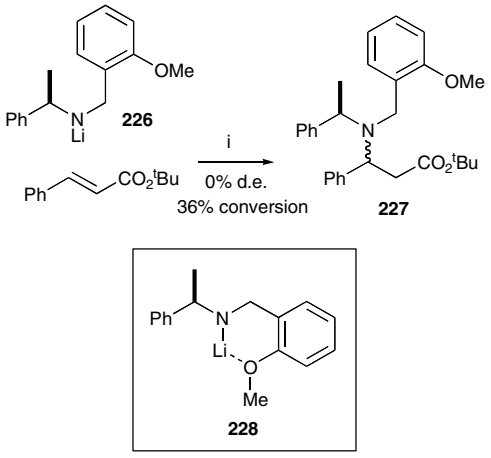
3.4. Limitations of the conjugate addition methodology

Although extremely versatile, this diastereoselective conjugate addition methodology is not universally applicable. Conjugate addition to (*E*)-β-substituted acrylates generally proceeds with high and predictable levels of diastereoselectivity. However, treatment of the corresponding (*Z*)-β-substituted acrylates with lithium amides results predominantly in deprotonation, either at the γ-position (if possible) or at the α-position.[134] In certain β-substituted acrylates or lithium amides that contain a heteroatom capable of disrupting the transition state complex by complexation of lithium ions, significant reductions in reactivity and diastereoselectivity have been observed. For example, while the addition of lithium amide (*R*)-**43** (1.6 equiv) to *tert*-butyl 3-(4′-pyridyl) or *tert*-butyl 3-(3′-pyridyl)-prop-2-enoate **219** and **220** proceeds readily in high yield and de, the analogous addition to *tert*-butyl 3-(2′-pyridyl)-prop-2-enoate **221** proceeds to only 50% conversion. Three equivalents of lithium amide (*R*)-**43** are required to drive the conjugate addition reaction to completion, giving the β-amino ester **222** in a poor 6% de. The low level of diastereoselectivity in this addition is presumably due to disruption of the normal chelation controlled lithium amide transition state (vide infra) by chelation of the pyridyl nitrogen to lithium ions, affording a competing, non-stereoselective pathway for conjugate addition. However, the introduction of steric blocking groups at the 6-position within the 2-pyridyl motif serves to impede the co-ordinating ability of the pyridyl nitrogen, leading to a significant improvement in the diastereoselectivity of the addition, with additions to the 6′-Me, 6′-Br and 6′-$SiMe_3$ substituted esters **223**–**225** proceeding in 61%, 81% and 83% de, respectively (Scheme 10).[127]

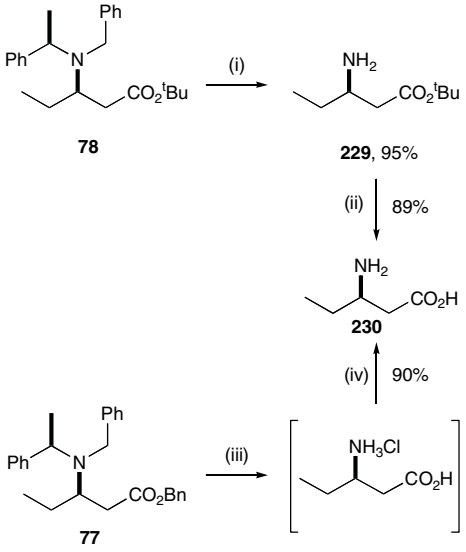


Scheme 10. Reagents and conditions: (i) lithium (*R*)-*N*-benzyl-*N*-(α-methyl-4-methoxybenzyl)amide **43**, THF, −78 °C, then NH_4Cl(aq).

A similar reduction in reactivity and selectivity has also been observed upon conjugate addition of lithium *N*-(2-methoxybenzyl)-*N*-α-methylbenzylamide **226** to *tert*-butyl cinnamate. Under standard conditions, the reaction proceeded to only 36% conversion, furnishing a 50:50 mixture of diastereoisomers **227**. In this case, the reduced reactivity and low stereoselectivity may arise from the formation of a chelated lithium amide species such as **228**, resulting in disruption of the normal chelation controlled lithium amide transition state and a corresponding decrease in stereoselectivity (Scheme 11).[85]



Scheme 11. Reagents and conditions: (i) lithium *N*-(2-methoxybenzyl)-*N*-α-methylbenzylamide **226**, THF, −78 °C, then NH_4Cl(aq).



Scheme 12. Reagents and conditions: (i) Pd/C, H_2 (5 atm), MeOH; (ii) TFA, DCM (1:1), then 2 N HCl, then Dowex 50WX-200; (iii) Pd/C, H_2 (5 atm), AcOH, then 2 N HCl; (iv) Dowex 50WX-200.

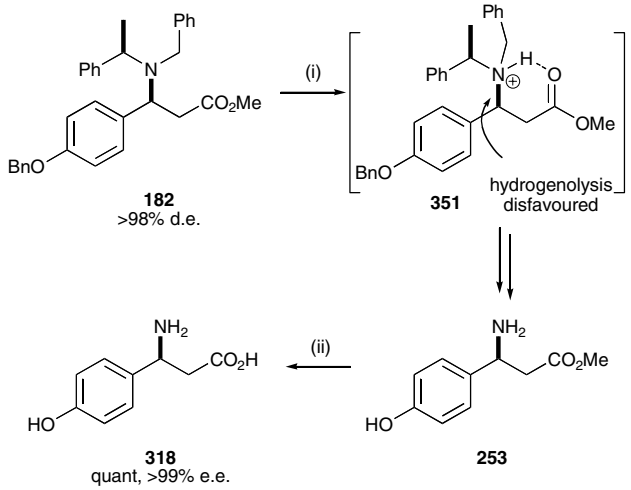
4. Global and selective deprotection strategies of β-amino esters

The *N*-protected β-amino esters arising from conjugate addition are useful building blocks for synthesis. Both chemoselective and global *N*-deprotection strategies of these products have been extensively investigated, allowing the synthesis of β-amino acids, β-lactams and differential protection of the nitrogen centre within the β-amino ester products of conjugate addition.

4.1. Global deprotection: synthesis of β-amino acids

The most straightforward application of the *N*-benzyl-*N*-α-methylbenzyl-β-amino alkyl esters (alkyl = Me, Et, ^{t}Bu) arising from conjugate addition is for the synthesis of β-amino acids. *N*-Deprotection of both *N*-benzyl protecting groups in these β-amino esters is readily achieved by Pd promoted hydrogenolysis, using either 1 atm of H_2 in a MeOH–AcOH–H_2O mixture, 5 atm of H_2 in either MeOH, AcOH or EtOAc, or using transfer hydrogenation with formic acid and ammonium formate, giving the corresponding primary β-amino ester in excellent yield and without compromising the stereoselectivity (Table 3). These primary β-amino esters are readily further deprotected by ester hydrolysis to the corresponding β-amino acids without racemisation. Furthermore, application of these hydrogenolysis conditions to *N*-benzyl-*N*-α-methylbenzyl-β-amino benzyl esters allows direct access to the corresponding β-amino acids in high ee and in good yields after ion exchange chromatography (Scheme 12, Table 4).

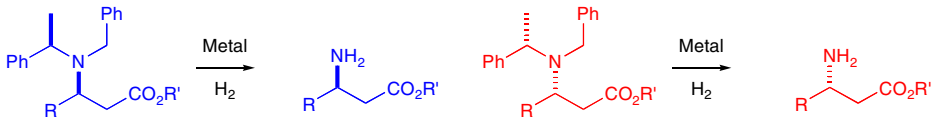
Chemoselective *N*-debenzylation of the tertiary β-amino esters derived from conjugate addition to β-aryl acrylates is seen, with the benzylic C(3)–*N* bond remaining intact and selective removal of the *N*-benzyl and *N*-α-methylbenzyl protecting groups from the nitrogen centre being observed. For example, treatment of β-amino ester **182** with $Pd(OH)_2$ on C and H_2 (1 atm) gave the corresponding methyl β-amino ester **253** in quantitative yield, with ester hydrolysis giving β-amino acid **318**. In this debenzylation step, four benzylic bonds could possibly be cleaved, but only the *N*-protecting groups derived from the lithium amide and the *O*-benzyl ether are susceptible to hydrogenolysis. The chemoselectivity in this debenzylation is thought to arise through the intermediacy of an intramolecularly hydrogen bonded intermediate **351**, which holds the C(3)-β-aryl group in a conformation that disfavours hydrogenolysis and cleavage of the benzylic C(3)–*N* bond (Scheme 13).

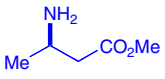


Scheme 13. Reagents and conditions: (i) $Pd(OH)_2$ on C, MeOH, AcOH, H_2O (40:4:1), H_2 (1 atm); (ii) HCl(aq), Δ.

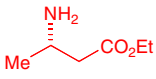
While these *N*-debenzylation protocols are versatile, *N*-deprotection via hydrogenolysis in this manner does not always allow for differential deprotection of the *N*-centre, and is also incompatible with a number of functional groups that are sensitive to hydrogenolysis. For

Table 3.

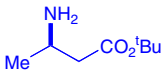




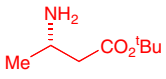
2
Ref 35: 81%
$[\alpha]_D$ -29.0 (c 0.45, $CHCl_3$)



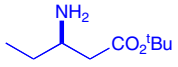
231
Ref 39: 89%
Ref 38



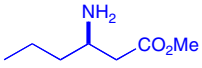
30
Ref 73: 84%
$[\alpha]_D^{25}$ -22.2 (c 0.5, $CHCl_3$)



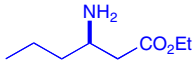
30
Ref 73: 73%
$[\alpha]_D^{25}$ +24.1 (c 0.5, $CHCl_3$)
Ref 38, **Ref 42**



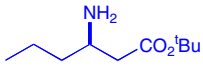
229
Ref 52: 95%



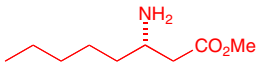
232
Ref 53, **Ref 54**



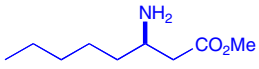
233
Ref 55: 90%



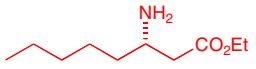
234
Ref 57: 70%
Ref 59



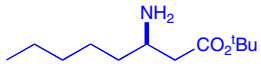
235
Ref 66: 98%



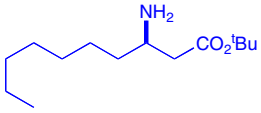
235
Ref 64



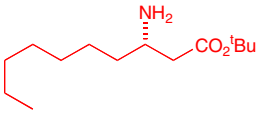
236
Ref 67: 89%



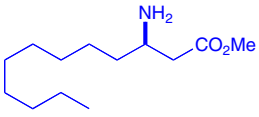
237
Ref 68: 76%



238
Ref 69: 92%
Ref 73: 87%
$[\alpha]_D^{25}$ -11.3 (c 1.3, $CHCl_3$)



238
Ref 73: 83%
$[\alpha]_D^{25}$ +11.2 (c 1.4, $CHCl_3$)



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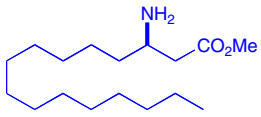
Ref 70: 98%



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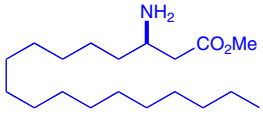
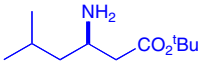
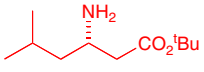
Ref 72: 100%



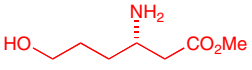
241
Ref 53, Ref 54



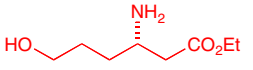
242
Ref 73: 91%
$[\alpha]_D^{25}$ -21.1 (c 2.5, $CHCl_3$)



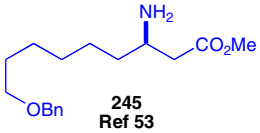
242
Ref 73: 90%
$[\alpha]_D^{25}$ +21.2 (c 2.9, $CHCl_3$)



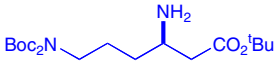
243
Ref 135: 97%



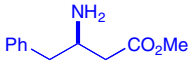
244
Ref 77: 95%
Ref 136



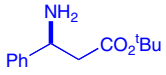
245
Ref 53



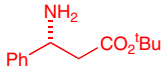
246
Ref 79
$[\alpha]_D^{23}$ -5.7 (c 1.08, $CHCl_3$)



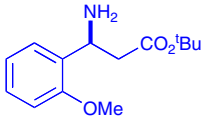
247
Ref 53, **Ref 54**



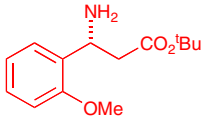
55
Ref 73: 84%
$[\alpha]_D^{20}$ -21.0 (c 1.0, $CHCl_3$)
Ref 104: 75%



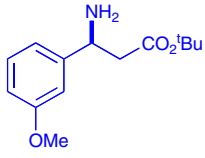
55
Ref 73: 89%
$[\alpha]_D^{25}$ +18.3 (c 2.9, $CHCl_3$)



248
Ref 73: 88%
$[\alpha]_D^{25}$ -22.0 (c 2.4, $CHCl_3$)



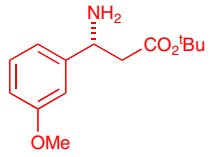
248
Ref 73: 90%
$[\alpha]_D^{25}$ +22.4 (c 2.4, $CHCl_3$)



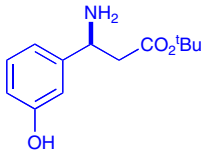
249
Ref 73: 87%
$[\alpha]_D^{25}$ -15.5 (c 1.4, $CHCl_3$)

(*continued on next page*)

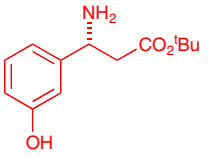
Table 3 (*continued*)



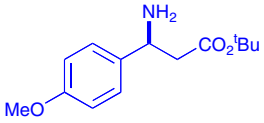
249
Ref 73: 86%
$[\alpha]_D^{25}$ +15.4 (c 1.5, $CHCl_3$)



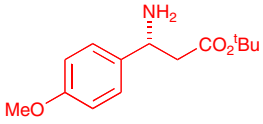
250
Ref 73: 77%
$[\alpha]_D^{25}$ -7.8 (c 1.3, $CHCl_3$)



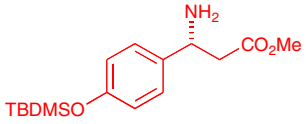
250
Ref 73: 77%
$[\alpha]_D^{25}$ +7.8 (c 1.2, $CHCl_3$)



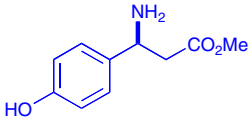
251
Ref 73: 93%
$[\alpha]_D^{25}$ +16.5 (c 1.4, $CHCl_3$)



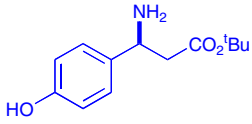
251
Ref 73: 90%
$[\alpha]_D^{25}$ -16.4 (c 1.5, $CHCl_3$)



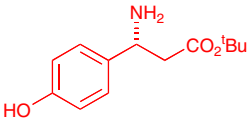
252
Ref 116: 90%



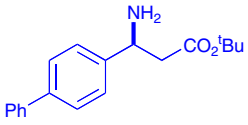
253
Ref 32: 100%
$[\alpha]_D^{20}$ +10.55 (c 1.9, H_2O)
Ref 113



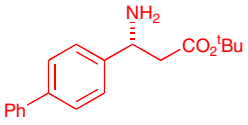
254
Ref 73: 82%
$[\alpha]_D^{25}$ -8.5 (c 1.1, $CHCl_3$)



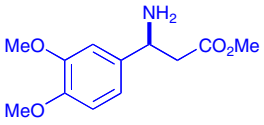
255
Ref 73: 81%
$[\alpha]_D^{25}$ +9.0 (c 1.1, $CHCl_3$)



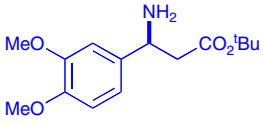
255
Ref 73: 76%
$[\alpha]_D^{25}$ -11.3 (c 1.1, $CHCl_3$)



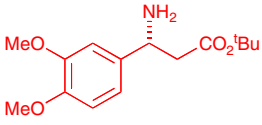
255
Ref 73: 81%
$[\alpha]_D^{25}$ +11.8 (c1.4, $CHCl_3$)



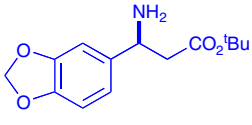
256
Ref 38: 90%



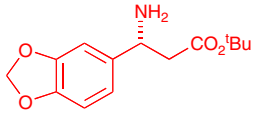
257
Ref 73: 85%
$[\alpha]_D^{25}$ -11.0 (c 2.5, $CHCl_3$)
Ref 120



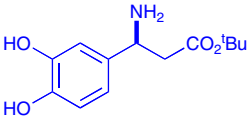
257
Ref 73: 87%
$[\alpha]_D^{25}$ +11.1 (c 2.5, $CHCl_3$)



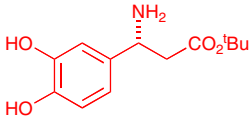
258
Ref 73: 87%
$[\alpha]_D^{25}$ -13.0 (c 2.2, $CHCl_3$)



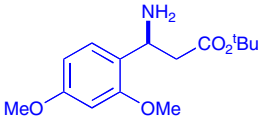
258
Ref 73: 83%
$[\alpha]_D^{25}$ +13.2 (c 2.2, $CHCl_3$)



259
Ref 73: 85%
$[\alpha]_D^{25}$ +8.0 (c 0.4, MeOH)

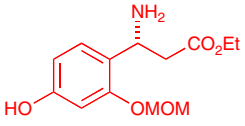


259
Ref 73: 82%
$[\alpha]_D^{25}$ -7.9 (c 0.3, MeOH)

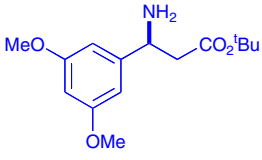


260
Ref 73: 85%
$[\alpha]_D^{25}$ -16.9 (c 2.5, $CHCl_3$)

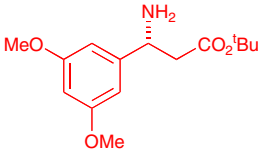
260
Ref 73: 82%
$[\alpha]_D^{25}$ +17.0 (c 2.2, $CHCl_3$)



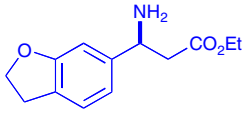
261
Ref 122, Ref 123



262
Ref 73: 87%
$[\alpha]_D^{25}$ -11.7 (c 2.7, $CHCl_3$)

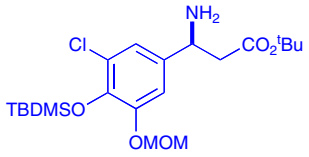


262
Ref 73: 88%
$[\alpha]_D^{25}$ +12.3 (c 2.2, $CHCl_3$)

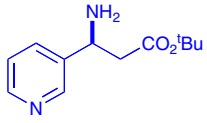


263
Ref 126: 75%

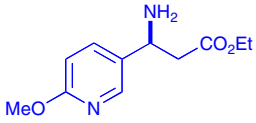
Table 3 (*continued*)



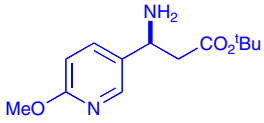
264
Ref 125



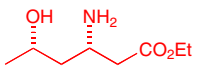
265
Ref 128: 93%



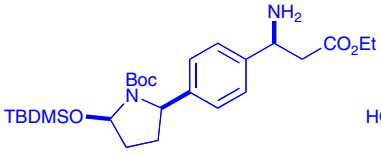
266
Ref 130: 83%
Ref 121



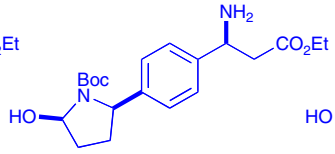
267
Ref 131: 93%



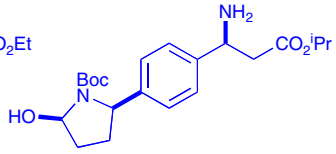
268
Ref 137



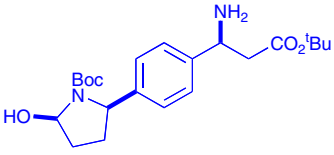
269
Ref 138



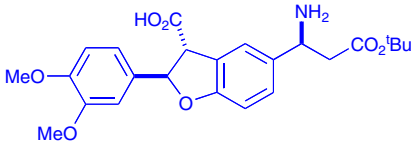
270
Ref 138



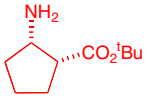
271
Ref 138



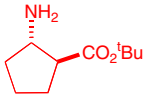
272
Ref 138: 98%



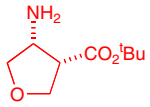
273
Ref 139: 68%
Ref 140



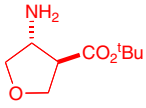
274
Ref 141
Ref 142: XX%
$[\alpha]_D^{25}$ -5.6 (c 0.63, $CHCl_3$)



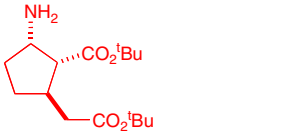
275
Ref 142



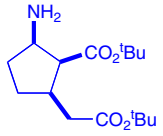
276
Ref 143
$[\alpha]_D^{24}$ -3.2 (c 1.0, $CHCl_3$)



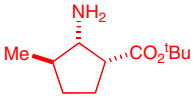
277
Ref 143
$[\alpha]_D^{24}$ +61.9 (c 2.1, $CHCl_3$)



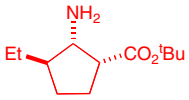
278
Ref 144: 71%
$[\alpha]_D^{26}$ +28.4 (c 1.45, $CHCl_3$)



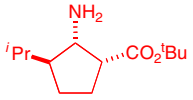
279
Ref 144: 77%
$[\alpha]_D^{26}$ +25.8 (c 1.47, $CHCl_3$)



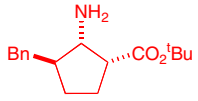
280
Ref 145
$[\alpha]_D^{22}$ -51.8 (c 1.02, $CHCl_3$)



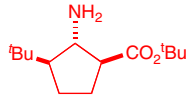
281
Ref 146
$[\alpha]_D^{22}$ -44.7 (c 1.0, $CHCl_3$)



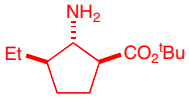
282
Ref 146
$[\alpha]_D^{22}$ -20.0 (c 0.35, $CHCl_3$)



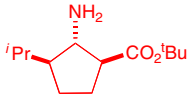
283
Ref 146
$[\alpha]_D^{22}$ -32.7 (c 1.0, $CHCl_3$)



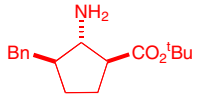
284
Ref 146
$[\alpha]_D^{22}$ +34.2 (c 0.7, $CHCl_3$)



285
Ref 146
$[\alpha]_D^{22}$ +36.7 (c 1.0, $CHCl_3$)



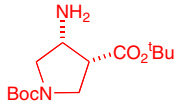
286
Ref 146
$[\alpha]_D^{22}$ +30.6 (c 0.5, $CHCl_3$)



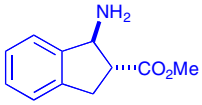
287
Ref 146
$[\alpha]_D^{22}$ +44.2 (c 1.2, $CHCl_3$)

(*continued on next page*)

Table 3 (*continued*)

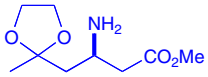


288
Ref 143
$[\alpha]_D^{24}$ +4.7 (c 0.90, $CHCl_3$)

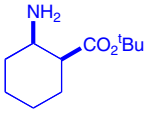


289
Ref 147
55%

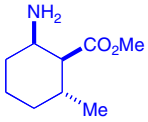
290
Ref 148
86%



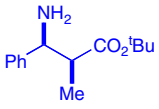
291
Ref 80: 95%
$[\alpha]_D^{20}$ -13.0 (c 1.50, $CHCl_3$)



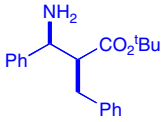
292
Ref 149: 86%



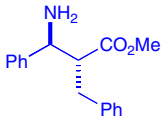
293
Ref 150: 97%
$[\alpha]_D^{22}$ -31.0 (c 1.03, $CHCl_3$)



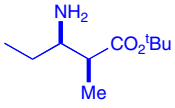
294
Ref 151: 81%
$[\alpha]_D^{25}$ +19.3 (c 2.37, $CHCl_3$)
Ref 106



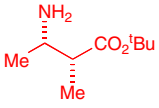
295
Ref 151: 57%
$[\alpha]_D^{25}$ -28.5 (c 0.90, $CHCl_3$)



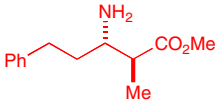
296
Ref 152: 49%
$[\alpha]_D^{25}$ +3.3 (c 0.48, $CHCl_3$)



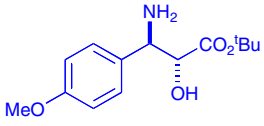
297
Ref 153



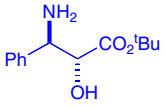
298
Ref 154



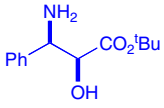
299
Ref 97: 71%
$[\alpha]_D$ -2.4 (c 10, CH_2Cl_2)



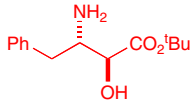
300
Ref 155: 96%
$[\alpha]_D^{25}$ -1.2 (c 2.1, $CHCl_3$)



301
Ref 156 : 99%
$[\alpha]_D^{25}$ -29.0 (c 0.50, $CHCl_3$)

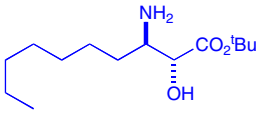


302
Ref 157

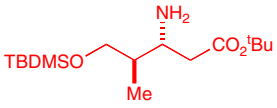


303
Ref 158: 62%
$[\alpha]_D^{21}$ +19.1 (c 1.02, $CHCl_3$)
Ref 159

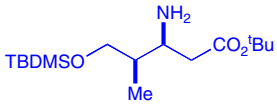
304
Ref 160 : 98%



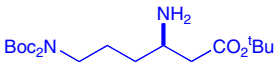
305
Ref 161 : 91%



306
Ref 98 :70%



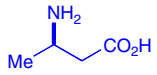
307
Ref 98: 73%



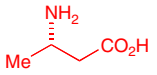
308
Ref 79: 51% from α,β-unsaturated ester
$[\alpha]_D^{23}$ -5.7 (c 1.08, $CHCl_3$)

example, β-haloaryl-β-amino acids and β-pyridyl-β-amino acids are important β-amino acid sub-classes that are widely employed within medicinal chemistry: although lithium amide conjugate addition proceeds with high stereocontrol to the corresponding α,β-unsaturated ester, attempted debenzylation by hydrogenolysis results in halogen–carbon bond cleavage or reduction of the pyridine ring; unsaturated β-amino ester derivatives are also susceptible to hydrogenolysis. Alternative *N*-deprotection routes to allow the stereoselective

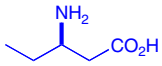
Table 4.



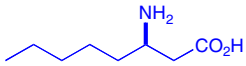
34
Ref 32
$[\alpha]_D^{19}$ -39.8 (c 0.47, H_2O)



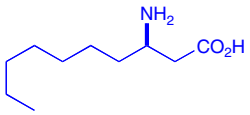
34
Ref 73
$[\alpha]_D^{25}$ +32.0 (c 0.6, H_2O)
Ref 42



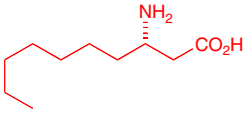
230
Ref 52



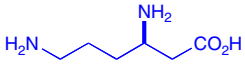
309
Ref 52



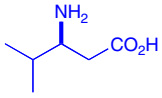
310
Ref 73
$[\alpha]_D^{25}$ -2.4 (c 0.2, H_2O)
Ref 69
$[\alpha]_D^{24}$ -13.1 (c 0.41, 1N HCl)



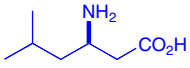
310
Ref 73
$[\alpha]_D^{25}$ +2.5 (c 0.1, H_2O)



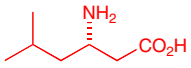
311
Ref 79
$[\alpha]_D^{21}$ -19.3 (c 0.63, 1M HCl)



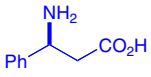
50
Ref 52



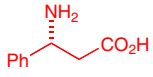
312
Ref 73
$[\alpha]_D^{25}$ -27.9 (c 0.7, H_2O)



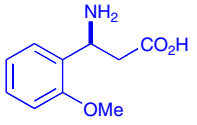
312
Ref 73
$[\alpha]_D^{25}$ +27.8 (c 0.6, H_2O)



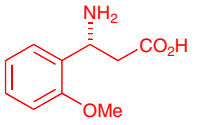
313
Ref 106
$[\alpha]_D^{20}$ -7.0 (c 1.0, $CHCl_3$)



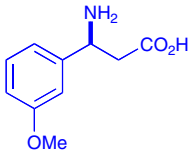
313
Ref 83
$[\alpha]_D^{25}$ +6.8 (c 0.9, H_2O)



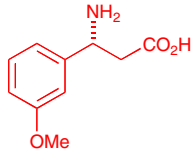
314
Ref 73
$[\alpha]_D^{25}$ +18.8 (c 0.6, H_2O)



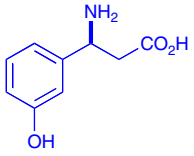
314
Ref 73
$[\alpha]_D^{25}$ -18.5 (c 0.5, H_2O)



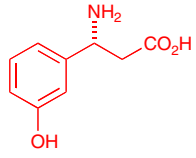
315
Ref 73
$[\alpha]_D^{25}$ -3.9 (c 1.0, H_2O)



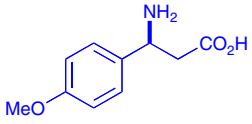
315
Ref 73
$[\alpha]_D^{25}$ +3.8 (c 0.9, H_2O)



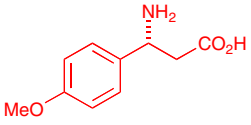
316
Ref 73
$[\alpha]_D^{25}$ -7.2 (c 0.3, H_2O)



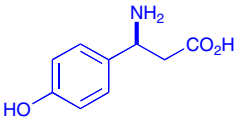
316
Ref 73
$[\alpha]_D^{25}$ +7.2 (c 0.5, H_2O)



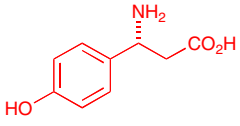
317
Ref 73
$[\alpha]_D^{25}$ +0.8 (c 0.2, H_2O)



317
Ref 73
$[\alpha]_D^{25}$ -0.6 (c 0.1, H_2O)



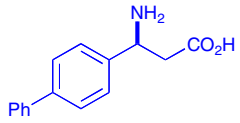
318
Ref 73
$[\alpha]_D^{25}$ -5.9 (c 0.5, H_2O)
Ref 32 (HCl salt)
$[\alpha]_D^{25}$ +3.55 (c 1.38, H_2O)



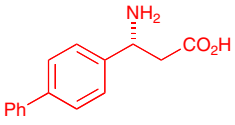
318
Ref 73
$[\alpha]_D^{25}$ +6.0 (c 0.6, H_2O)

(*continued on next page*)

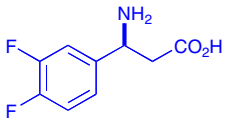
Table 4 (*continued*)



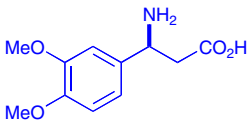
319
Ref 73
$[\alpha]_D^{25}$ +3.3 (c 0.8, MeOH)



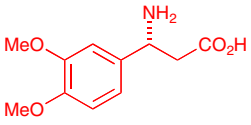
319
Ref 73
$[\alpha]_D^{25}$ -3.3 (c 0.8, MeOH)



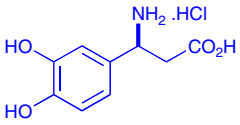
320
Ref 111



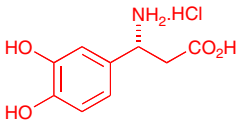
321
Ref 73
$[\alpha]_D^{25}$ +0.9 (c 0.7, H_2O)



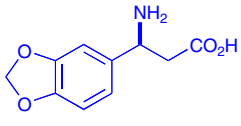
321
Ref 73
$[\alpha]_D^{25}$ -0.9 (c 0.7, H_2O)



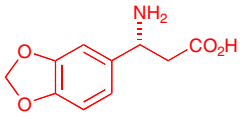
322
Ref 73
$[\alpha]_D^{25}$ +4.8 (c 0.2, MeOH)



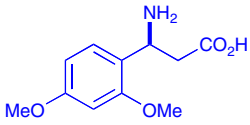
322
Ref 73
$[\alpha]_D^{25}$ -4.6 (c 0.5, MeOH)



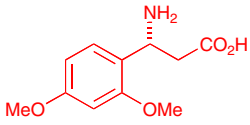
323
Ref 73
$[\alpha]_D^{25}$ +42.4 (c 0.3, H_2O)



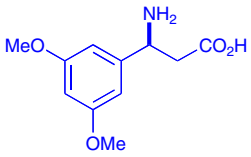
323
Ref 73
$[\alpha]_D^{25}$ -42.0 (c 0.3, H_2O)



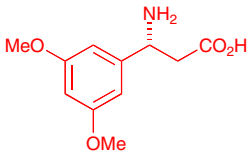
324
Ref 73
$[\alpha]_D^{25}$ +5.3 (c 0.6, H_2O)



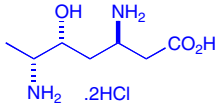
324
Ref 73
$[\alpha]_D^{25}$ -5.1 (c 0.8, H_2O)



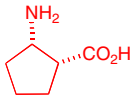
325
Ref 73
$[\alpha]_D^{25}$ +0.7 (c 0.8, H_2O)



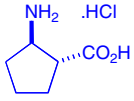
325
Ref 73
$[\alpha]_D^{25}$ -0.8 (c 0.7, H_2O)



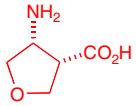
326
Ref 95
$[\alpha]_D^{25}$ -3.1 (c 0.68, H_2O)



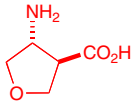
327
Ref 141
Ref 142
$[\alpha]_D^{23}$ -8.8 (c 1.00, H_2O)



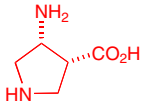
328
Ref 142
$[\alpha]_D^{25}$ -50.7 (c 0.75, H_2O)



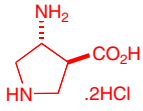
329
Ref 143
$[\alpha]_D^{23}$ +19.3 (c 0.80, H_2O)



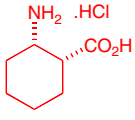
330
Ref 143
$[\alpha]_D^{23}$ +17.8 (c 1.0, H_2O)



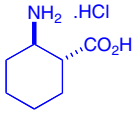
331
Ref 143
$[\alpha]_D^{25}$ +17.1 (c 2.5, H_2O)



332
Ref 143
$[\alpha]_D^{25}$ +22.9 (c 0.50, H_2O)

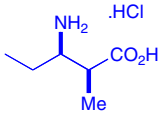


333
Ref 142
$[\alpha]_D^{25}$ +1.7 (c 0.60, MeOH)



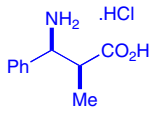
334
Ref 142
$[\alpha]_D^{25}$ -45.4 (c 1.04, H_2O)

335
Ref 142
$[\alpha]_D^{25}$ +47.4 (c 1.14, H_2O)

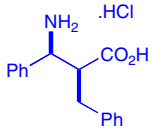


336
Ref 151
$[\alpha]_D^{25}$ +1.7 (c 1.06, H_2O)
Ref 153

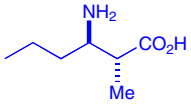
Table 4 (*continued*)



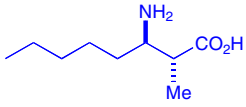
337
Ref 151
$[\alpha]_D^{25}$ +5.0 (c 2.60, H_2O)
Ref 106



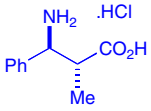
338
Ref 151
$[\alpha]_D^{25}$ -16.4 (c 0.28, MeOH)



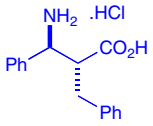
339
Ref 56
50% d.e.



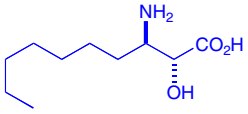
340
Ref 65
43% d.e.



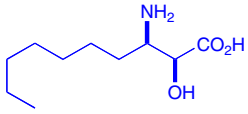
341
Ref 152
$[\alpha]_D^{25}$ +10.2 (c 1.94, MeOH)
Ref 106



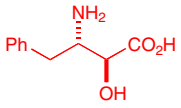
342
Ref 162
80% d.e.



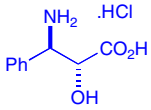
343
Ref 69
$[\alpha]_D^{25}$ +3.4 (c 0.7, 1N HCl)
Ref 161



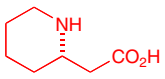
344
Ref 69
$[\alpha]_D^{25}$ +5.4 (c 0.59, 1N HCl)



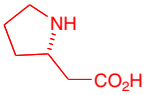
345
Ref 158
$[\alpha]_D^{20}$ -5.4 (c 0.51, 1N HCl)



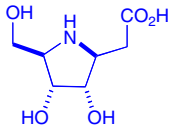
346
Ref 156
$[\alpha]_D^{20}$ +25.1 (c 0.98, MeOH)



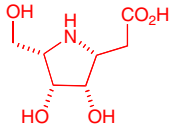
347
Ref 61
$[\alpha]_D^{26}$ +24.0 (c 0.87, H_2O)
Ref 62



348
Ref 61
$[\alpha]_D^{23}$ +3.4 (c 1.0, H_2O)
Ref 62



349
Ref 163
$[\alpha]_D^{24}$ +20.3 (c 0.89, H_2O)



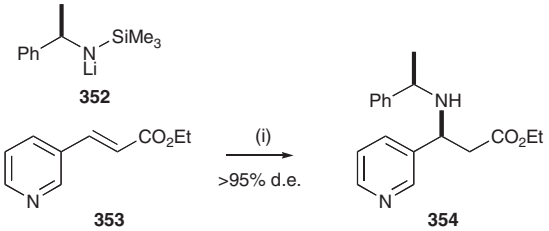
350
Ref 85
$[\alpha]_D^{23}$ -30.3 (c 0.83, H_2O)

syntheses of these desirable β-amino acids have been investigated that utilise oxidative or selective *N*-deprotection strategies.

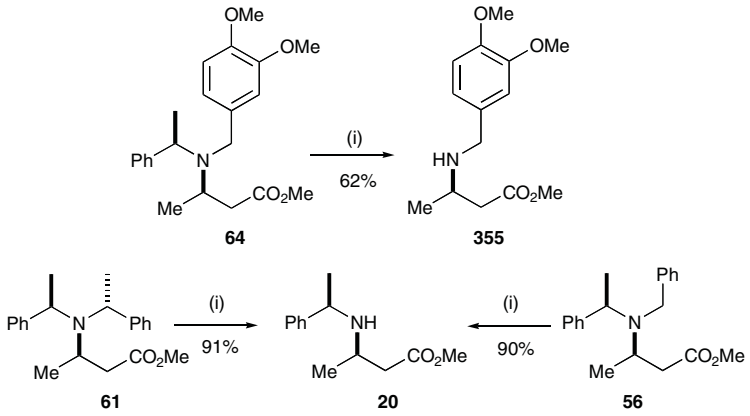
4.2. Selective deprotection strategies

A range of selective deprotection strategies have been developed to allow selective functionalisation of the *N*-centre within β-amino esters by differential deprotection; this strategy has proven useful for the synthesis of a range of products such as β-lactams.

4.2.1. Conjugate addition of lithium *N*-trimethylsilyl-*N*-α-methylbenzylamides. One strategy for the asymmetric synthesis of *N*-α-methylbenzyl protected β-amino esters uses the conjugate addition of lithium *N*-trimethylsilyl-*N*-α-methylbenzylamide **352** to α,β-unsaturated esters. Removal of the silyl protecting group is achieved readily upon purification, giving the corresponding *N*-α-methylbenzyl protected β-amino ester. While high stereoselectivity in the addition of lithium amide (*R*)-**352** to ethyl 3-(3′-pyridyl)-prop-2-enoate **353** to give β-amino ester **354** has been reported by Bovy et al.,[129] and this protocol has been developed further by Sewald et al.[164,165] using lithium amidocuprates derived from **352**, the generality of this protocol has yet to be demonstrated (Scheme 14).



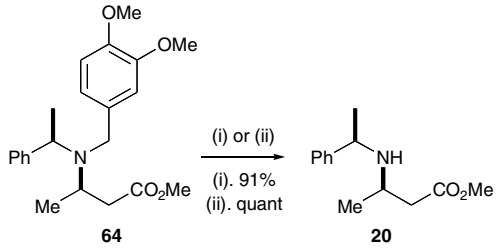
Scheme 14. Reagents and conditions: (i) lithium (*R*)-*N*-benzyl-*N*-trimethylsilylamide, THF, −78 °C.



Scheme 15. Reagents and conditions: (i) $Pd(OH)_2$ on C, MeOH, H_2 (1 atm).

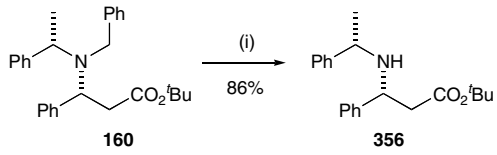
4.2.2. Selective hydrogenation protocols. Hydrogenolysis can be used for the selective removal of one of the *N*-benzyl protecting groups from β-amino esters derived from lithium *N*-benzyl-*N*-α-methylbenzylamide and lithium *N*-methoxybenzyl-*N*-α-methylbenzylamides. As *N*-4-methoxybenzyl protected amines are known to be less susceptible to hydrogenolysis than the corresponding *N*-benzyl protected amine,[166] while being readily removed by oxidative processes,[167] differential protection of the nitrogen atom within β-amino ester **64** could be readily achieved, as hydrogenolysis results in selective *N*-α-methylbenzyl group cleavage, giving β-amino ester **355**. Furthermore, as the ease of hydrogenolysis of *N*-benzyl groups increases from primary > secondary > tertiary amines,[168] selective mono-debenzylation of β-amino esters **56** and **61** to give **20** can be achieved through careful monitoring of the progress of the reaction at low catalyst loadings (Scheme 15).[92]

4.2.3. Selective and global oxidative deprotection methods. The well-documented susceptibility of *N*-4-methoxybenzyl and *N*-3,4-dimethoxybenzyl protecting groups to oxidative deprotection allows mono *N*-deprotection of the nitrogen centre within *N*-3,4-dimethoxybenzyl-*N*-α-methylbenzyl-β-amino ester **64** to be readily achieved, giving *N*-α-methylbenzyl protected β-amino ester **20** in excellent yield upon treatment with either CAN or DDQ (Scheme 16, Table 5).



Scheme 16. Reagents and conditions: (i) CAN, MeCN–H_2O (5:1), rt; (ii) DDQ, DCM, H_2O (5:1), rt.

Furthermore, as simple *N*-benzyl groups are readily deprotected chemoselectively upon treatment with CAN,[40,169] oxidative treatment of *N*-benzyl-*N*-α-methylbenzylamine protected esters such as **160** allows chemoselective *N*-benzyl deprotection, giving β-amino ester **356** in excellent yield (Scheme 17, Table 5).

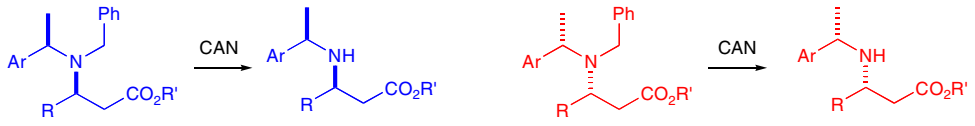


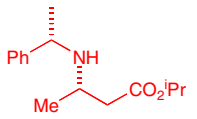
Scheme 17. Reagents and conditions: (i) CAN, MeCN–H_2O (5:1), rt.

This oxidative deprotection protocol has been further investigated in order to obviate the need for removal of the stereodirecting *N*-α-methylbenzylamine protecting group by hydrogenolysis from within β-amino esters. Using *N*-4-methoxy-α-methylbenzylamine as the stereodirecting fragment within a group of oxidatively cleavable lithium amides, the corresponding β-amino ester products can be treated to allow orthogonal deprotection of the nitrogen centre. For example, selective removal of the *N*-4-methoxy-α-methylbenzyl protecting group (with concomitant ester hydrolysis) can be achieved by treatment of **165** with TFA, giving acid **372** in good yield. However, treatment of **165** with CAN gives preferential removal of the unbranched *N*-benzyl protecting group over the branched *N*-α-methylbenzyl protecting group, allowing orthogonal deprotection of the nitrogen centre to give **373**. Further treatment of **373** with CAN facilitates removal of the *N*-4-methoxy-α-methylbenzyl protecting group, giving the corresponding β-amino ester **55**. This methodology has proven particularly versatile for the synthesis of β-haloaryl-β-amino acid derivatives (Scheme 18, Table 6).

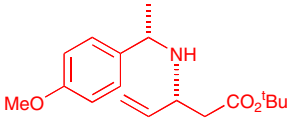
This oxidative *N*-deprotection strategy with CAN allows *N*-debenzylation of both *N*-protecting groups by treatment of β-amino esters with excess CAN. For example, treatment of (3*S*,α*R*)-**199** with CAN (6 equiv) and subsequent treatment with aqueous acid gave β-3,4-difluorophenyl-3-aminopropanoic acid **320** in 63% yield and 97% ee (Scheme 19).[111]

Table 5.

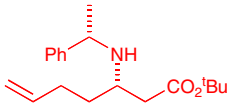




357
Ref 170: 85%
Ref 40



358
Ref 83: 73%



359
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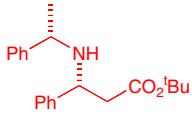

356
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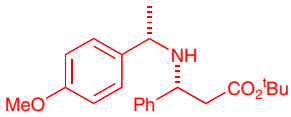
Ref 40



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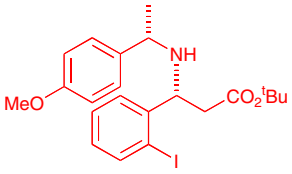

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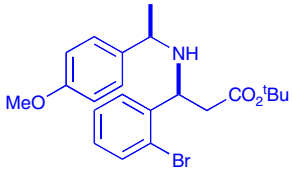

362
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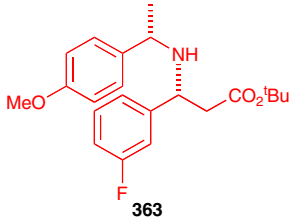

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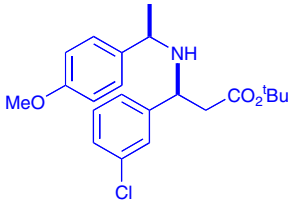
Ref 111: 86%
Ref 109



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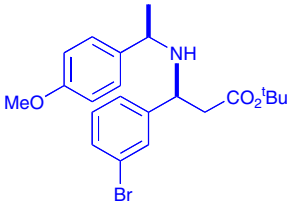

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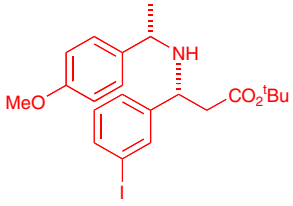
Ref 109



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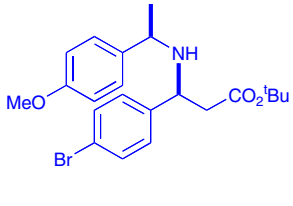
Ref 109



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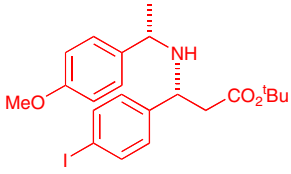

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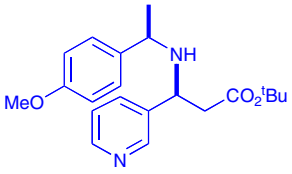
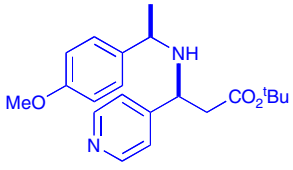


369
Ref 127: 80%



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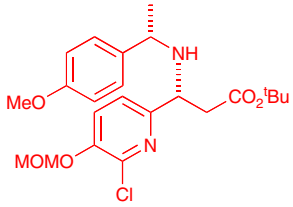
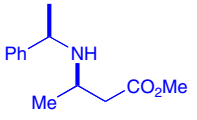
Ref 127: 86%

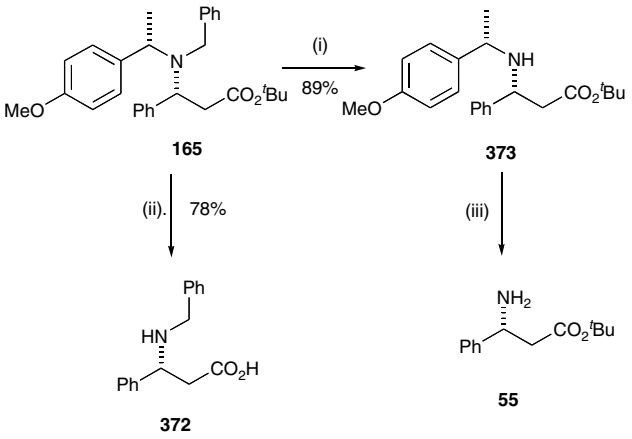


371
Ref 127: 68%

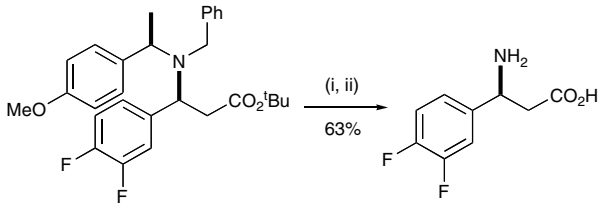


20
Ref 92: 91%

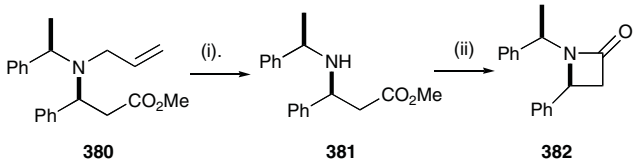
4.2.4. Selective deprotection strategies of β-amino esters derived from lithium *N*-allyl-*N*-α-methylbenzylamide. The β-amino esters derived from addition of lithium *N*-allyl-*N*-α-methylbenzylamide allow differential protection of the nitrogen centre via either deallylation with Wilkinson's catalyst in refluxing acetonitrile[170] or palladium-mediated deallylation using $Pd(PPh_3)_4$ and *N*,*N*-dimethylbarbituric acid.[171] This methodology has



Scheme 18. Reagents and conditions: (i) CAN (2.1 equiv), MeCN–H_2O (5:1), rt; (ii) TFA–DCM (1:1), rt; (iii) CAN (4.0 equiv), MeCN–H_2O (5:1), rt.



Scheme 19. Reagents and conditions: (i) CAN (6.0 equiv), MeCN–H_2O (5:1), then HCl(aq); (ii) Dowex 50W-X8.

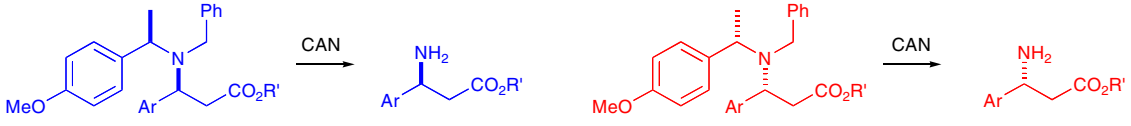


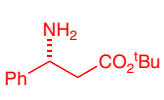
Scheme 20. Reagents and conditions: (i) $RhCl(PPh_3)_3$, MeCN–H_2O (5:1), Δ; (ii) MeMgBr, Et_2O, 0 °C.

proven ideal for the synthesis of β-lactams, from where the stereodirecting *N*-α-methylbenzyl protecting group is readily removable by treatment with sodium in liquid ammonia. For example, treatment of β-amino ester **380** with Wilkinson's catalyst gave **381**, and subsequent treatment of **381** with MeMgBr gave β-lactam **382** in excellent yield (Scheme 20).[47]

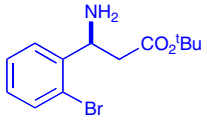
Highly chemoselective deallylation of the *N*-allyl protecting group derived from the lithium amide is seen using this mono-deprotection strategy. For example, treatment of β-amino ester **144** with Wilkinson's catalyst,[90] or α-hydroxy-β-amino ester **383** with $Pd(PPh_3)_4$ and *N*,*N*-dimethylbarbituric acid results in selective deallylation,[172] giving **384** and **385**, respectively, leaving the disubstituted C=C bond intact. Further elaboration gives β-amino esters containing unsaturated functionality within the skeletal framework (Scheme 21). This selective deallylation methodology has been used for the synthesis of a range of β-amino esters (Table 7). Fur-

Table 6.

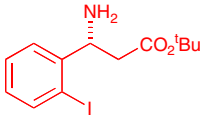




55
Ref 109: 64%



374
Ref 111: 68%



375
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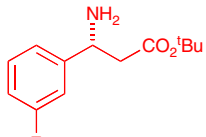

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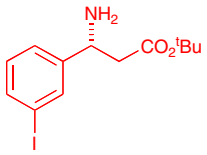

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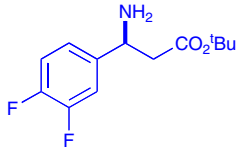
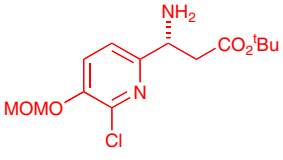
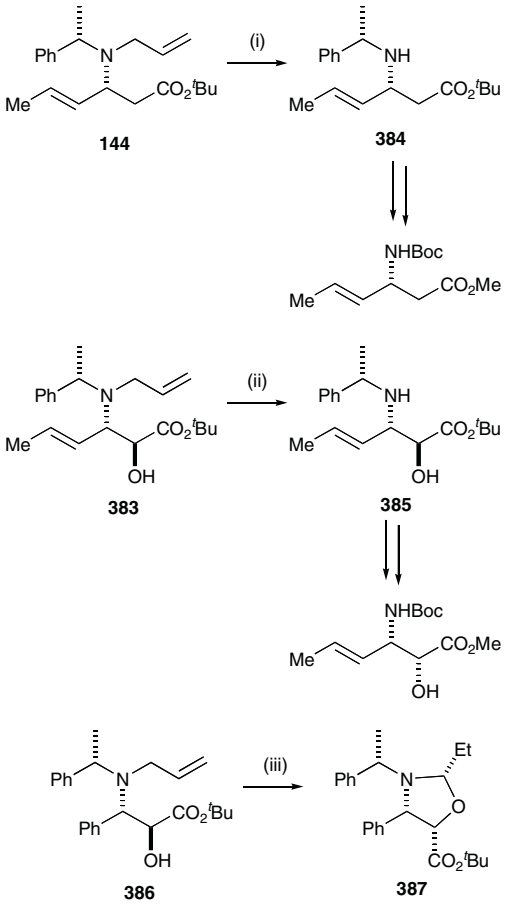
Ref 111: 49%



378
Ref:111



379
Ref 127: 49%

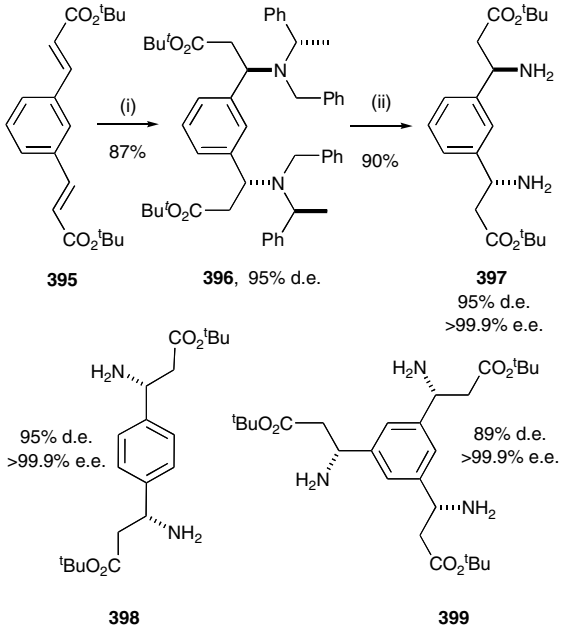


Scheme 21. Reagents and conditions: (i) $RhCl(PPh_3)_3$, MeCN–H_2O (5:1), Δ; (ii) $Pd(PPh_3)_4$, *N*,*N*-dimethylbarbituric acid; (iii) $RhCl(PPh_3)_3$, MeCN, Δ.

thermore, the isomerisation implicit in the mechanism of *N*-allyl deprotection using Wilkinson's catalyst allows for the in situ protection of adjacent hydroxyl functionality in the absence of water. For example, treatment of α-hydroxy-β-amino ester **386** with Wilkinson's catalyst gives the corresponding oxazolidine **387** as an 89:11 mixture of diastereoisomers.[173]

5. Asymmetric synthesis of β-amino acid scaffolds

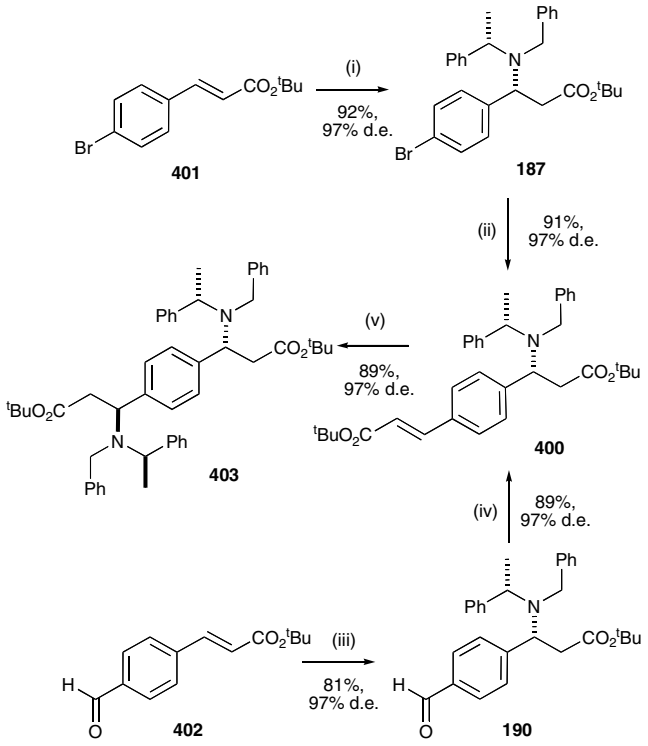
The combination of this conjugate addition and chemoselective deprotection methodology has been used for the synthesis of complex molecules that contain multiple β-amino ester fragments. The addition of 2 or 3 equiv of lithium amide (*S*)-**31** to conjugate acceptors containing two or three α,β-unsaturated ester fragments, respectively, around a central arene core, and subsequent hydrogenolytic deprotection affords homochiral bis- or tris-β-amino esters containing two or three new stereogenic centres in high de. For example, conjugate addition of lithium amide (*S*)-**31** to **395** gave C_2 symmetric bis-β-amino ester **396** in 95% de, with hydrogenolysis giving **397** in 90% yield and 95% de and, due to the operation of a double asymmetric synthesis in this reaction, a conservative estimate of >99.9% ee (Scheme 22).[174] This strategy was successfully applied to the synthesis of homochiral bis- or tris-β-amino esters **398** and **399**.



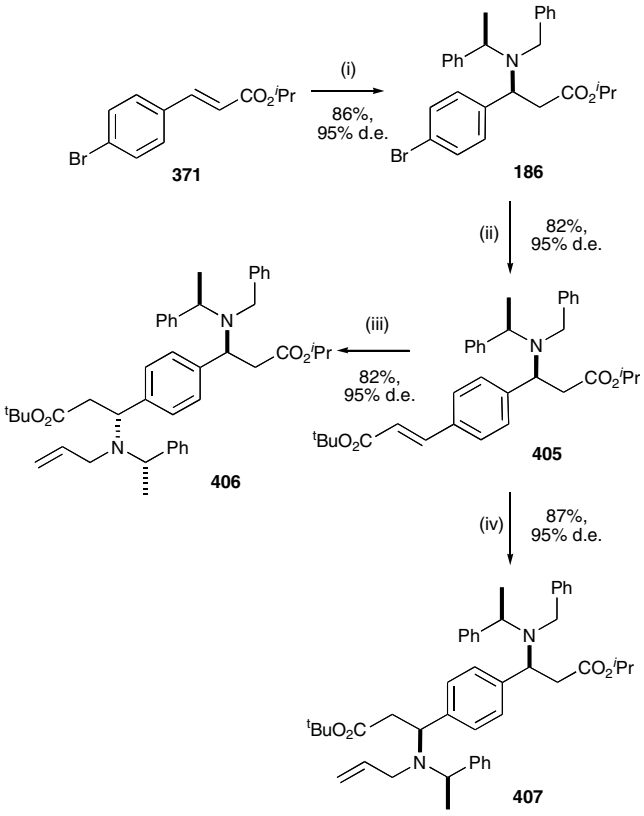
Scheme 22. Reagents and conditions: (i) lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide, THF, −78 °C; (ii), $Pd(OH)_2$ on C, MeOH, H_2 (5 atm).

While this one-pot multiple addition strategy allows the synthesis of homochiral (*R*,*R*)- or (*S*,*S*)-β-amino esters, a related strategy allows the asymmetric synthesis of *meso*-(*R*,*S*)-bis-β-amino acid scaffolds, formally resulting from the stepwise conjugate addition of two enantiomeric lithium amides to two α,β-unsaturated esters attached to a central arene (Scheme 23).[107,117] The desired substrate **400** containing both an α,β-unsaturated ester and a β-amino ester can be prepared by two different routes following either a Heck coupling or Wadsworth–Horner–Emmons strategy. In the Heck strategy, conjugate addition of lithium amide (*S*)-**31** to 4-bromoaryl acceptor **401** and subsequent Heck coupling of the β-amino ester product **187** gave **400** in high yield. Alternatively, inverse addition of an excess of lithium amide (*S*)-**31** to 4-formyl acceptor **402** gave β-amino ester **190**, which after treatment with the lithium anion of *tert*-butyl diethylphosphonoacetate gave **400** in good yield. Subsequent addition of lithium amide (*R*)-**31** to β-amino ester **400** gave *meso*-β-amino ester **403** in good yield and selectivity (Scheme 23).

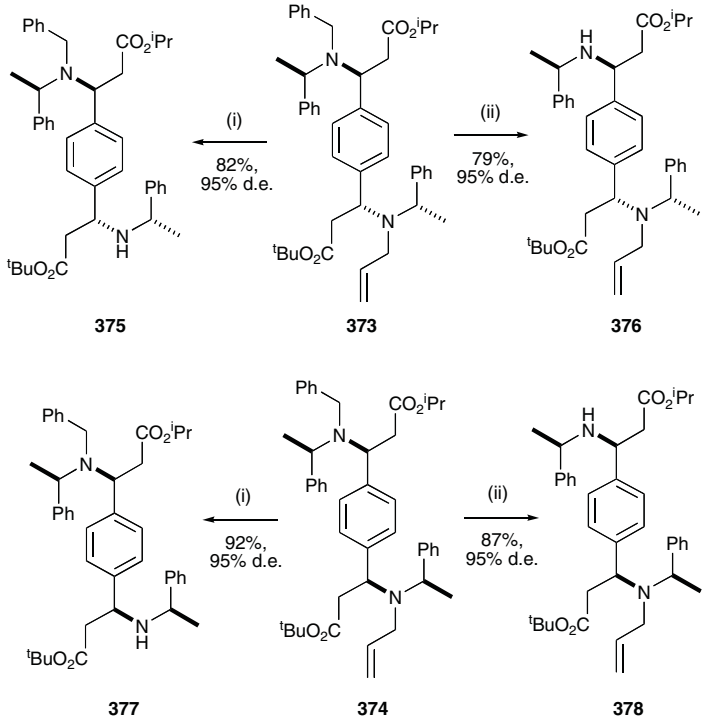
Subsequent investigations were directed towards the preparation of second generation bis-β-amino ester templates with either pseudo-C_2 or pseudo-*meso* symmetry, with the incorporation of differentially protected amino and carboxylate functionalities used to allow these molecules to act as novel peptide scaffolds. The availability of lithium *N*-benzyl-*N*-α-methylbenzylamide **31** and lithium *N*-allyl-*N*-α-methylbenzylamide **39** in either homochiral form was used to allow differentiation of the *N*-protecting groups, with the ability to deprotect the *N*-allyl functionality using Wilkinson's catalyst, coupled



Scheme 23. Reagents and conditions: (i) lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide **31** (1.6 equiv), THF, −78 °C, then NH_4Cl(aq); (ii) $Pd(OAc)_2$ (5 mol %), NEt_3, *tert*-butyl acrylate (1.5 equiv), tri-(*o*-tolyl)-phosphine (20 mol %); (iii) lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide **31** (3.0 equiv), THF, −78 °C, inverse addition; (iv) *tert*-butyl diethylphosphonoacetate (1.15 equiv), *n*-BuLi (1.1 equiv), THF, −78 °C to rt; (v) lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide **31** (3.0 equiv), THF, −78 °C, then NH_4Cl(aq).

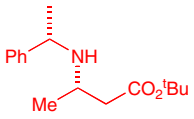


Scheme 24. Reagents and conditions: (i) lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide **31** (1.6 equiv), THF, −78 °C, then NH_4Cl(aq); (ii) $Pd(OAc)_2$ (5 mol %), NEt_3, *tert*-butyl acrylate (1.5 equiv), tri-(*o*-tolyl)-phosphine (20 mol %); (iii) lithium (*S*)-*N*-allyl-*N*-α-methylbenzylamide **39** (3.0 equiv), THF, −78 °C, then NH_4Cl(aq); (iv) lithium (*R*)-*N*-allyl-*N*-α-methylbenzylamide **39** (3.0 equiv), THF, −78 °C, then NH_4Cl(aq).

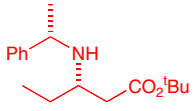


Scheme 25. Reagents and conditions: (i) $Rh(PPh_3)_3Cl$ (0.1 equiv), MeCN–H_2O (8.5:1.5), Δ; (ii) CAN (2.1 equiv), MeCN–H_2O (5:1), rt.

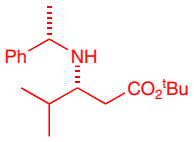
Table 7.



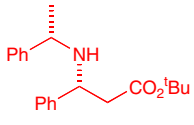
388
Ref 47: 96%
$[\alpha]_D^{21}$ -36.3 (c 1.78, $CHCl_3$)



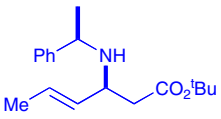
389
Ref 47: 92%
$[\alpha]_D^{21}$ -54.0 (c 1.81, $CHCl_3$)



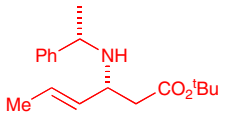
390
Ref 47: 95%
$[\alpha]_D^{21}$ -52.7 (c 1.57, $CHCl_3$)



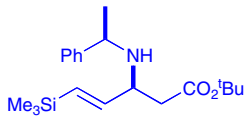
356
Ref 47, 95%
$[\alpha]_D^{21}$ -16.3 (c 1.45, $CHCl_3$)



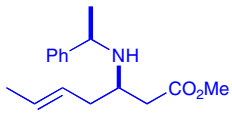
384
Ref 89: 59%
Ref 86: 90%



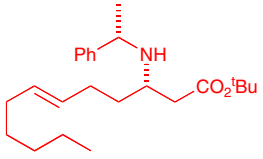
384
Ref 47: 78%
$[\alpha]_D^{21}$ -45.1 (c 1.69, $CHCl_3$)
Ref 90: 92%



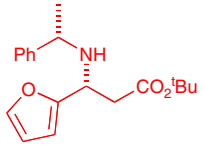
391
Ref 100: 93%
$[\alpha]_D^{23}$ +31.9 (c 1.65, $CHCl_3$)



392
Ref 93: 97%
Ref 94



393
Ref 96: 77%
$[\alpha]_D^{26}$ -26.8 (c=0.95, $CHCl_3$)



394
Ref 47: 80%
$[\alpha]_D^{21}$ -1.5 (c 1.74, $CHCl_3$)

with the ability of *N*-benzyl tertiary amines to be chemoselectively debenzylated upon treatment with CAN, allowing selective deprotection and subsequent elaboration at nitrogen. The relative acid and base lability of *tert*-butyl and isopropyl esters would allow selective access to the carboxylate functionality. The desired pseudo-C_2 symmetric or pseudo-*meso* bis-β-amino esters **406** and **407**, respectively, were readily constructed using the Heck coupling and lithium amide conjugate addition strategy developed previously (Scheme 24).

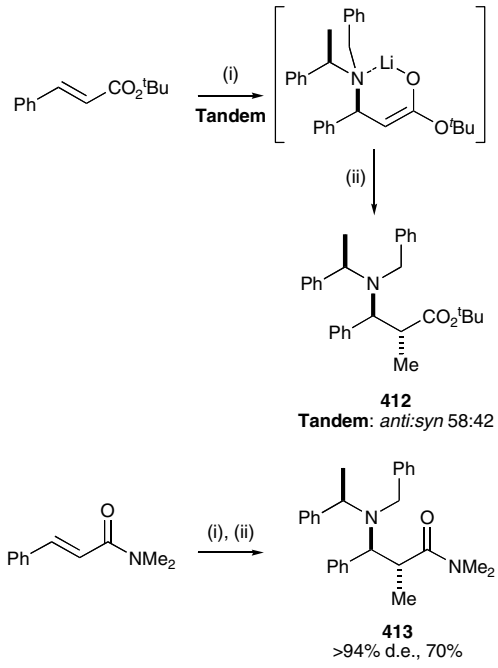
Differential protection of these pseudo-*meso* or pseudo-C_2-symmetric β-amino esters via selective *N*-benzyl or *N*-allyl deprotection strategies enabled regio-, stereo- and chemoselective functionalisation of these templates (Scheme 25).

6. Functionalised β-amino acids: enolate elaboration

6.1. Synthesis of β-amino-α-alkyl acid derivatives

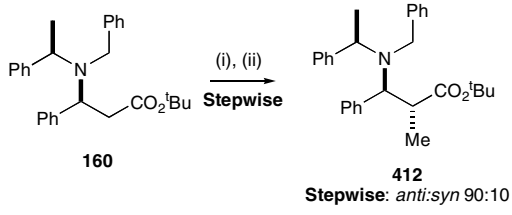
The synthetic versatility of this conjugate addition methodology has been extended to allow the preparation of a variety of α-substituted-β-amino acid derivatives via enolate elaboration. Both *syn*- and *anti*-α-alkyl-β-amino acid derivatives are readily prepared. The *anti*-derivatives may be prepared by a tandem conjugate addition–alkylation procedure, giving a mixture of diastereoisomers that are epimeric at the α-position. In these reactions, conjugate addition occurs readily at −78 °C to give the (*Z*)-enolate, although enolate alkylation generally only occurs upon warming to 0 °C, resulting in a compromise in α-stereoselectivity. For example, conjugate addition of lithium amide (*R*)-**31** to *tert*-butyl cinnamate and subsequent alkylation with methyl iodide gave a 58:42 mixture of *anti*-:*syn*-α-methyl-β-amino ester **412**.[152] Although the tandem addition–alkylation reactions proceed with low stereoselectivity in the ester series, conjugate addition to α,β-unsaturated amides and subsequent alkylation proceed with high *anti*-selectivity;[162] for example, conjugate addition of lithium amide (*R*)-**31** to dimethyl cinnamide and alkylation with methyl iodide gave *anti*-α-methyl-β-amino amide **413** in >94% de and 70% yield (Scheme 26, Table 8).

However, in the ester series, high levels of *anti*-selectivity can be obtained using an overall stepwise rather than a tandem strategy by deprotonation of a β-amino ester and subsequent alkylation of the (*E*)-lithium enolate



Scheme 26. Reagents and conditions: (i) lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide, THF, −78 °C; (ii) MeI, −78 °C to rt.

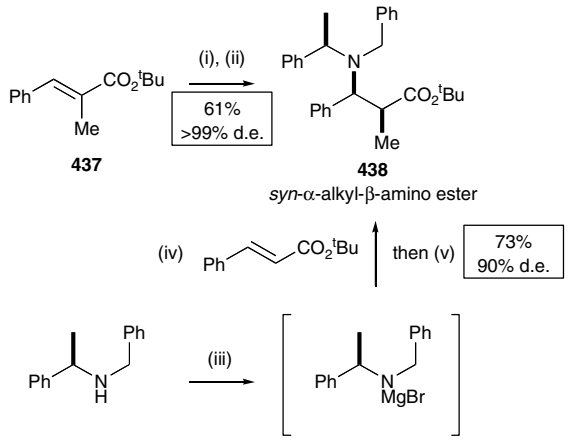
with an alkyl halide. For example, deprotonation of β-amino ester **160** with LDA and subsequent alkylation with methyl iodide gave a 90:10 mixture of *anti*-:*syn*-α-methyl-β-amino ester **412** (Scheme 27, Table 9).[152]



Scheme 27. Reagents and conditions: (i) LDA, THF, −78 °C; (ii) MeI, −78 °C to rt.

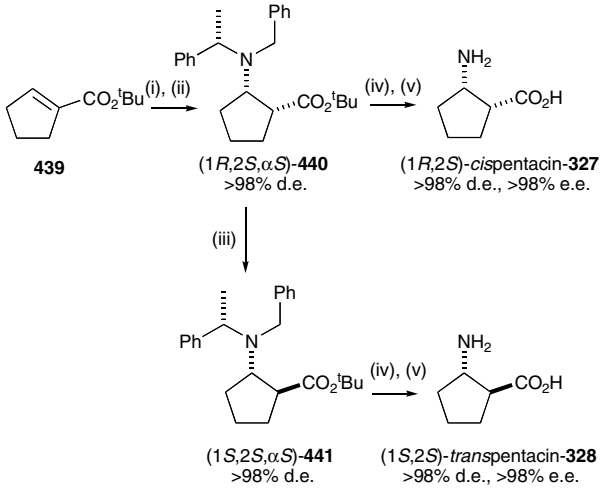
syn-α-Alkyl-β-amino ester derivatives may be prepared by conjugate addition to α-alkyl-α,β-unsaturated esters and subsequent diastereoselective protonation with 2,6-di-*tert*-butyl phenol. For example, conjugate addition of lithium amide (*R*)-**31** to **437** and addition of 2,6-di-*tert*-butyl phenol gave *syn*-β-amino ester **438** as a single diastereoisomer (Scheme 28).[151] Alternatively, conjugate addition of the magnesium amide of (*R*)-*N*-benzyl-*N*-α-methylbenzylamine to *tert*-butyl cinnamate and methylation of the resultant enolate with methyl iodide also gives rise to *syn*-β-amino ester **438** in >90% de. This result indicates that the same sense of asymmetric induction in the conjugate addition step is seen with both lithium and magnesium amides of (*R*)-*N*-benzyl-*N*-α-methylbenzylamine, although the resultant β-amino enolates undergo stereodivergent reactions with methyl iodide.[175]

This conjugate addition and stereoselective protonation methodology has been applied to the synthesis of a num-



Scheme 28. Reagents and conditions: (i) lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide, toluene, −78 °C; (ii) 2,6-di-*tert*-butyl phenol, THF, −78 °C to rt; (iii) (*R*)-*N*-benzyl-*N*-α-methylbenzylamine, MeMgBr, THF, rt, then cool to −78 °C; (iv) *tert*-butyl cinnamate, −78 °C; (v) MeI, −78 °C to rt.

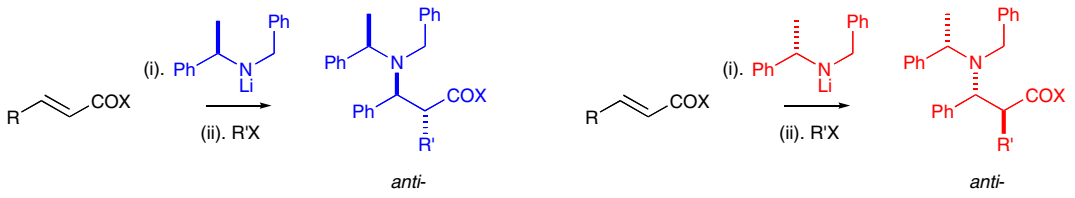
ber of β-amino acid derivatives, including the synthesis of the natural product (1*R*,2*S*)-cispentacin **327**. Conjugate addition of homochiral lithium amide (*S*)-**31** to *tert*-butyl cyclopentene-1-carboxylate **439** followed by addition of 2,6-di-*tert*-butyl phenol gave β-amino ester **440** in excellent yield, with subsequent *N*-deprotection and ester hydrolysis giving (1*R*,2*S*)-cispentacin. Rapid and complete epimerisation of β-amino ester (1*R*,2*S*,α*S*)-**440** to the thermodynamic epimer (1*S*,2*S*,α*S*)-**441** and further deprotection gives (1*S*,2*S*)-transpentacin **328** (Scheme 29, Table 10).

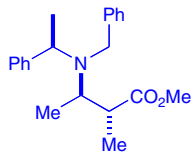


Scheme 29. Reagents and conditions: (i) lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide, THF, −95 °C; (ii) 2,6-di-*tert*-butyl phenol, THF, −78 °C to rt; (iii) KO^{t}Bu, ^{t}BuOH, rt (7 days) or KO^{t}Bu, ^{t}BuOH, Δ (3 h); (iv) Pd–C, MeOH, H_2 (5 atm), rt; (v) TFA, then Dowex 50X8-200.

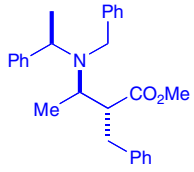
The consistent *anti*-preference within this series for enolate alkylation or protonation is consistent with reaction of the electrophile upon the least hindered face of the enolate, *anti*- to the C(3)-amino group arising from con-

Table 8.

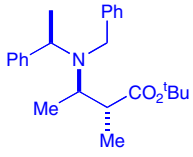




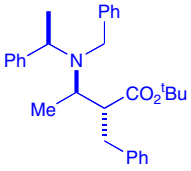
414
50%, 9% d.e.
Ref 152



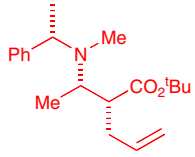
415
54%, 50% d.e.
Ref 152



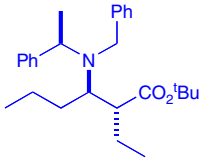
416
60%, 15% d.e.
Ref 152



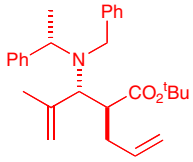
417
42%, 0% d.e.
Ref 152



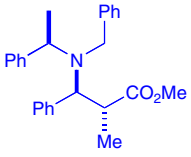
418
75-80%, 50% d.e.
Ref 38



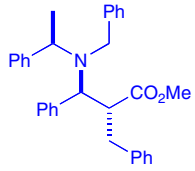
419
16% d.e.
Ref 58



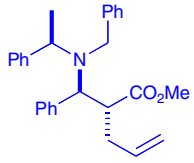
420
36%, 5% d.e.
Ref 61



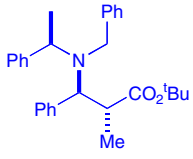
421
61%, >86% d.e.
Ref 152



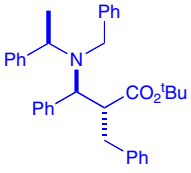
422
55%, 50% d.e.
Ref 152



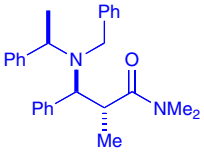
423
79%, 50% d.e.
Ref 152



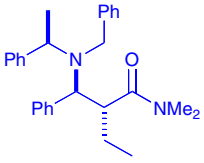
412
78%, 15% d.e.
Ref 152



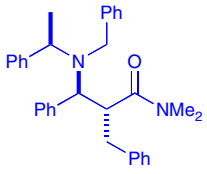
424
46%, 43% d.e.
Ref 152



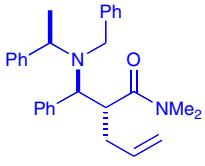
413
70%, >94% d.e.
Ref 162



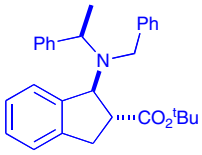
425
80%, 82% d.e.
Ref 162



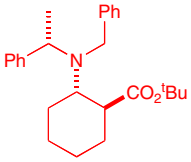
426
89%, >94% d.e.
Ref 162



427
71%, >94% d.e.
Ref 162



428
80%, 87% d.e.
Ref 147

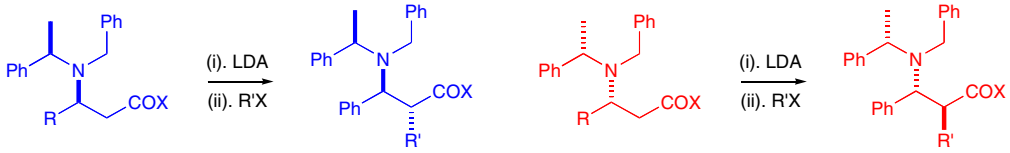


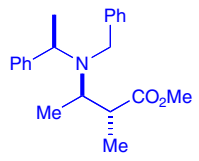
429
28%, >95% d.e.
Ref 78

jugate addition as depicted pictorially (**463**–**464**) in Figure 3.[179]

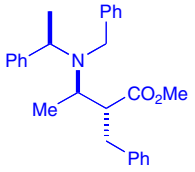
An alternative conjugate addition and intramolecular alkylation strategy has been investigated by

Table 9.

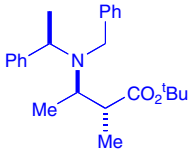




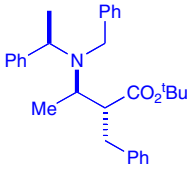
414
Ref 152: 89%, 67% d.e.



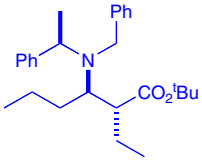
415
Ref 152: 52%, 15% d.e.



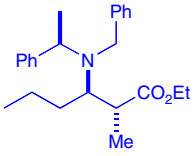
416
Ref 152: 69%, 80% d.e.



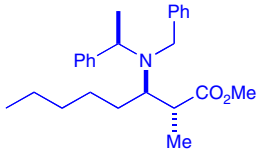
417
Ref 152: 83%, 0% d.e.



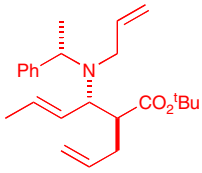
419
Ref 58: 88%, 12% d.e.



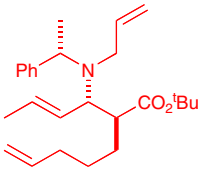
430
Ref 56: 50%, 50% d.e.



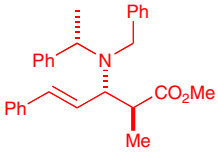
431
Ref 65: 43% d.e.



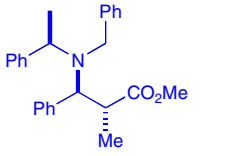
432
Ref 61: 99%, 75% d.e.



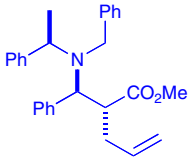
433
Ref 61: 92%, 21% d.e.



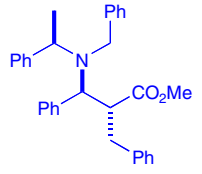
434
Ref 61: 57%, 60% d.e.



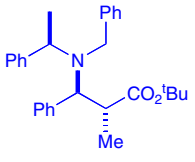
421
Ref 106: 76%, >90% d.e.
Ref 152: 70%, 94% d.e.



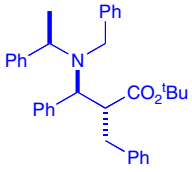
423
Ref 152: 70%, 78% d.e.



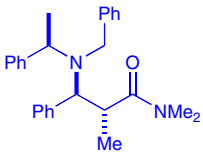
422
Ref 152: 80%, 67% d.e.



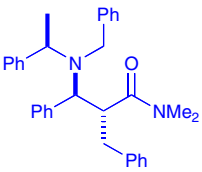
412
Ref 152: 70%, 94% d.e.



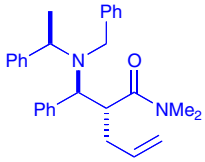
424
Ref 152: 41%, 11% d.e.



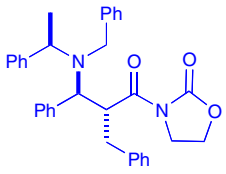
413
80%, >94% d.e.
Ref 162



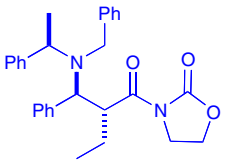
426
79%, >94% d.e.
Ref 162



427
75%, >94% d.e.
Ref 162



435
62%, >90% d.e.
Ref 162



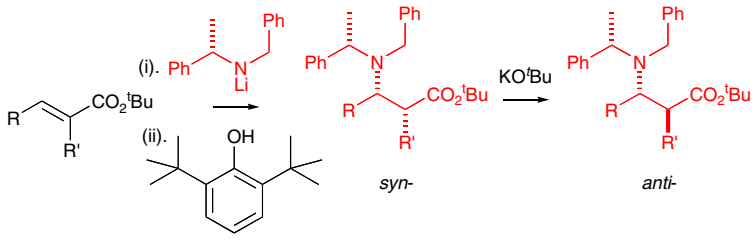
436
63%, >80% d.e.
Ref 162

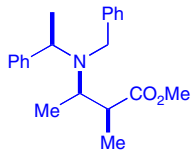
Price for the synthesis of the constrained β-amino ester **428**. Conjugate addition of lithium amide (*R*)-**31** to acceptor **465** generated the intermediate lithium (*Z*)-enolate, with subsequent alkylation giving cyclic β-amino ester **428** in good yield.[147] In a similar fashion, Riss et al. have demonstrated that conjugate addition to the OTs protected acceptor **466** and subsequent intramolecular alkylation upon warming gives **429** as the exclusive product with high stereoselectivity (Scheme 30).[78] High levels of stereoselectivity are seen in these alkylation reactions presumably as a consequence of the intramolecular nature of these reactions facilitating fast alkylation at low temperature.

6.2. Synthesis of α-hetero-β-amino acid derivatives

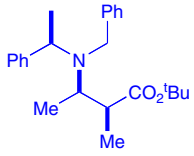
Elaboration of β-amino enolates to incorporate α-heteroatom functionality has also been investigated, with conjugate addition of lithium amide (*R*)-**31** and subsequent in situ diastereoselective enolate oxidation with (−)-(camphorsulfonyl)oxaziridine **467** giving the corresponding *anti*-β-amino-α-hydroxyesters in high de and in good yields. Although the oxaziridine used in this reaction is homochiral, it exerts only low stereocontrol in this reaction manifold. Conjugate addition of lithium amide (*R*)-**31** and addition of either (+)- or

Table 10.

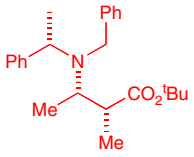




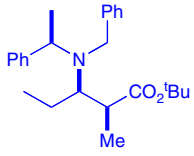
442
Ref 151: -78°C, 40%, 82% d.e.



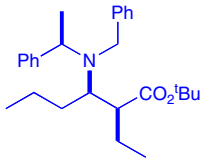
443
Ref 151: -78°C, 72%, >98% d.e.



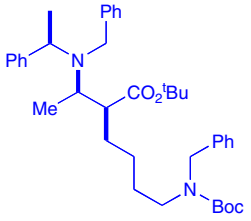
443
Ref 154



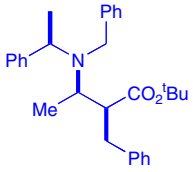
444
Ref 151: -78°C, 65%, >98% d.e.
$[\alpha]_D^{20}$ +46.1 (c 1.41, $CHCl_3$)
Ref 153



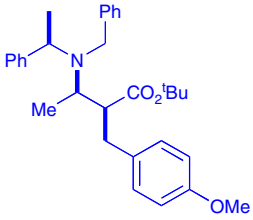
445
Ref 178: -78°C, 67%, >98% d.e.
Ref 177



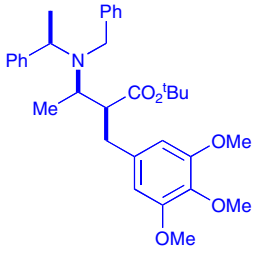
446
Ref 177: -78°C, 90% d.e.



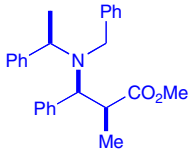
447
Ref 177: -78°C, 89% d.e.



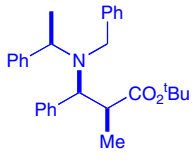
448
Ref 177: -78°C, 86% d.e.



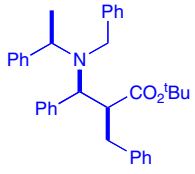
449
Ref 177: -78°C, 89% d.e.



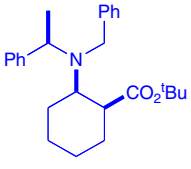
450
Ref 151: -78°C, 37%, 93% d.e.



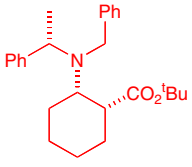
438
Ref 151: -78°C, 61%, >98% d.e.
Ref 106



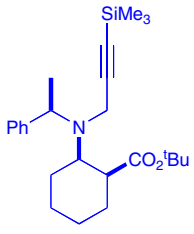
451
Ref 151: -78°C, 45%, 96% d.e.



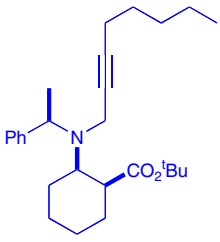
452
Ref 149: -78°C, 47%, >96% d.e.
$[\alpha]_D^{23}$ +85.3 (c 1.00, $CHCl_3$)
Ref 142: -78°C, 70%, >95% d.e.
$[\alpha]_D^{25}$ +88.3 (c 1.00, $CHCl_3$)
Ref 141



452
Ref 142: -78°C, 63%, >96% d.e
$[\alpha]_D^{25}$ 92.0 (c 1.00, $CHCl_3$).



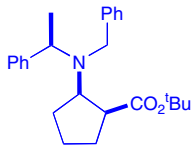
453
Ref 46



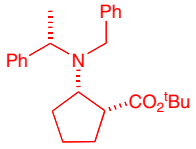
454
Ref 46

(*continued on next page*)

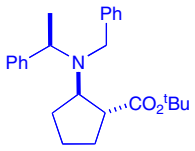
Table 10 (*continued*)



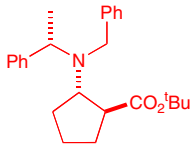
440
Ref 178: >98% d.e.



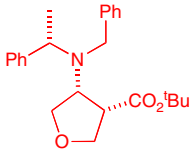
440
Ref 178: >98% d.e.
Ref 142: -95°C, 65%, >98% d.e.
$[\alpha]_D^{25}$ -69.1 (c 1.14, $CHCl_3$)
Ref 141



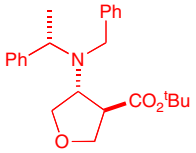
441
Ref 142: >98% d.e.



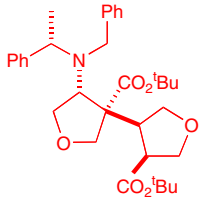
441
Ref 142: >98% d.e.



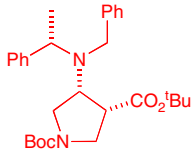
455
Ref 143: -78°C, 68%, 78% d.e.
$[\alpha]_D^{24}$ -48.0 (c 1.5, $CHCl_3$)



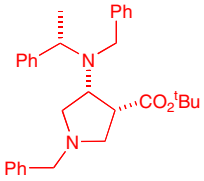
456
Ref 143: >98% d.e.
$[\alpha]_D^{24}$ +67.7 (c 1.5, $CHCl_3$)



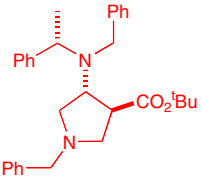
457
Ref 143: >98% d.e.
$[\alpha]_D^{24}$ -38.0 (c 0.25, $CHCl_3$)



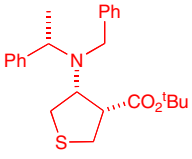
458
Ref 143: -78°C, 46%, >98% d.e.
$[\alpha]_D^{25}$ -18.5 (c 1.8, $CHCl_3$)



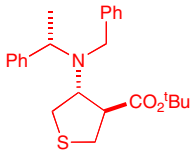
459
Ref 143: -78°C, 79%, >98% d.e.
$[\alpha]_D^{25}$ +32.0 (c 1.0, $CHCl_3$)



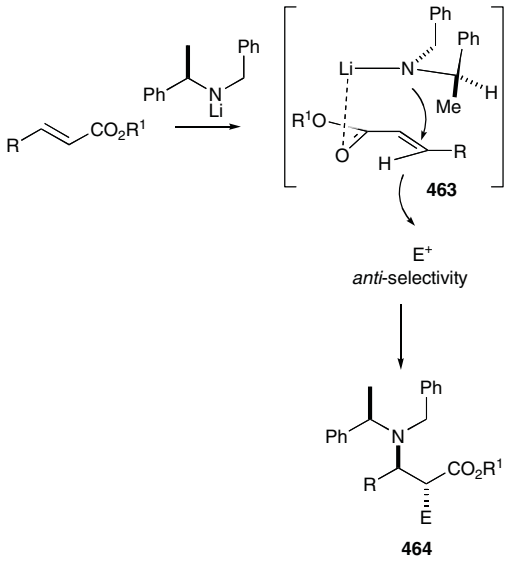
460
Ref 143: >98% d.e.
$[\alpha]_D^{25}$ +51.6 (c 1.1, $CHCl_3$)



461
Ref 143: -78°C, 52%, 38% d.e.



462
Ref 143: -78°C, 52%, 38% d.e.



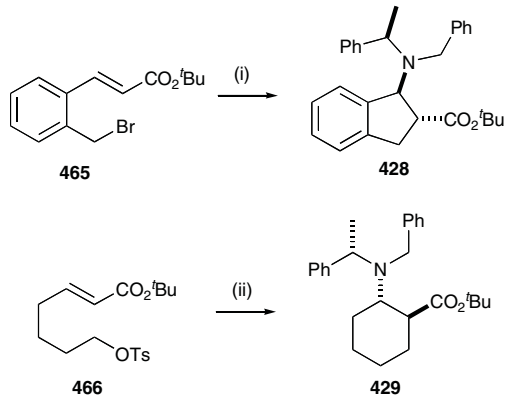
463

464

anti-selectivity

Figure 3. Simplistic model to account for *anti*-preference for enolate alkylation or protonation of β-amino enolates.

(−)-enantiomers of the oxaziridine give high *anti*-selectivity (>90% de) irrespective of the configuration of the oxidant, consistent with the reaction proceeding under the predominant control of the β-amino ester enolate. For example, conjugate addition of lithium amide (*S*)-**31** to *tert*-butyl cinnamate and oxidation with (+)-**467** gave *anti*-β-amino-α-hydroxyester **468** in 89% yield and >95% de (Scheme 31, Table 11).



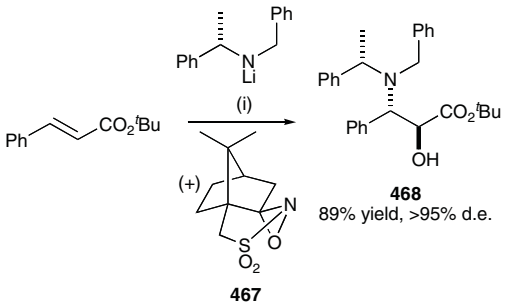
465

428

466

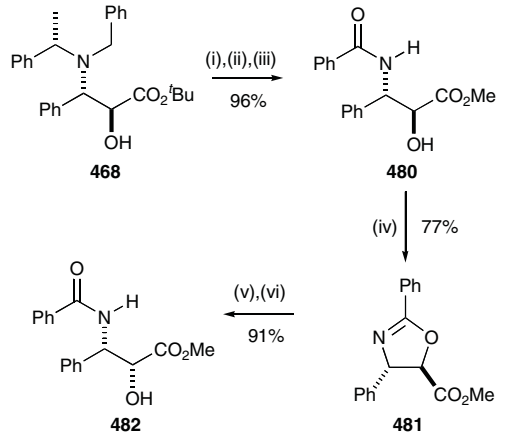
429

Scheme 30. Reagents and conditions: (i) lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide, THF, −78 °C, then NH_4Cl(aq); (ii) lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide, DME, −60 to 0 °C, then NH_4Cl(aq).



Scheme 31. Reagents and conditions: (i) lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide (1.6 equiv), THF, −78 °C, 2 h, then (1*R*)-(−)-(camphorsulfonyl) oxaziridine, THF, −78 °C to rt.

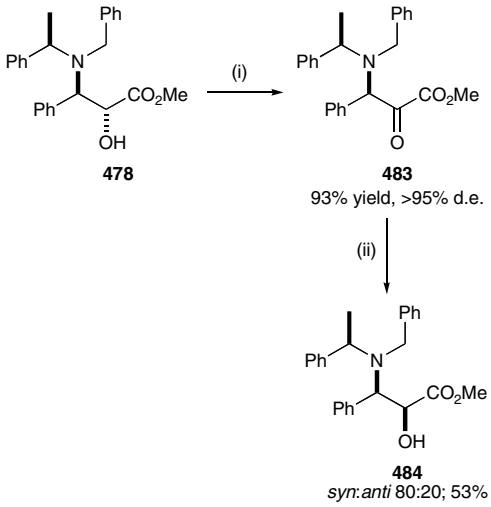
syn-β-Amino-α-hydroxyesters can be prepared from the corresponding *anti*-products by two different strategies. In the first strategy, hydrogenolysis of **468** and transesterification, followed by *N*-benzoyl protection gave **480** in good yield, with inversion of configuration at C(2) achieved through the formation of dihydrooxazole **481**, formed through intramolecular participation of the *N*-benzoyl group. Subsequent hydrolysis gives *syn*-β-amino-α-hydroxyester **482**, the side chain of the natural product Taxol (Scheme 32).[157]



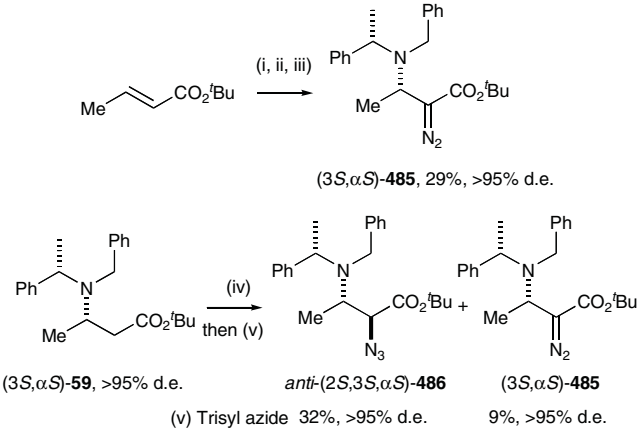
Scheme 32. Reagents and conditions: (i) H_2 (7 atm), Pd/C, AcOH; (ii) HCl, MeOH; (iii) PhCOCl (1 equiv), NEt_3; (iv) DEAD, PPh_3, THF, 0 °C; (v) HCl (0.5 M), MeOH; (vi) $NaHCO_3$.

Alternatively, Swern oxidation of *anti*-β-amino-α-hydroxyester **478** to the ketone **483** and subsequent reduction with $NaBH_4$ gives an 80:20 *syn*:*anti* mixture of the desired β-amino-α-hydroxyester **484** (Scheme 33).[183]

While β-amino enolate oxidation is readily achieved, the direct incorporation of an α-amino functionality through the analogous reaction with an electrophilic nitrogen source is difficult. Although conjugate addition of lithium amide (*S*)-**31** to *tert*-butyl crotonate **28** and in situ amination with trisyl azide results in the exclusive formation of the corresponding 2-diazo-3-amino ester **485** in >95% de, amination of the (*E*)-lithium enolate of β-amino ester **59** with trisyl azide gives the (2*S*,3*S*,α*S*)-*anti*-2-azido-3-amino ester **486** in >95% de but in low yield (32%) (Scheme 34).[184]



Scheme 33. Reagents and conditions: (i) $(COCl)_2$, DMSO, DCM, −60 to −10 °C, then NEt_3; (ii) $NaBH_4$, MeOH.



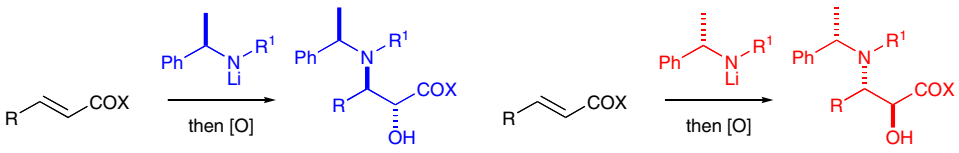
Scheme 34. Reagents and conditions: (i) lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide, THF, −78 °C; (ii) trisyl azide, −78 °C; (iii) AcOH; (iv) LDA, THF, −78 °C; (v) trisyl azide, −78 °C, then AcOH; (vi) diphenylphosphorylazide, −78 °C, then AcOH.

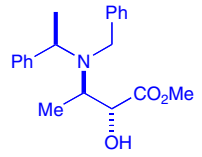
Alternatively, *anti*-β-amino-α-hydroxyester **470** may be converted selectively to the *anti*-α-azido-β-aminoester **486** by aziridinium ion formation and regioselective opening with azide (with overall retention of configuration at the α-position), with deprotection via Staudinger reduction, hydrogenolysis and ester hydrolysis furnishing *anti*-(2*S*,3*S*)-diaminobutanoic acid **488** in 98% de and 98% ee (Scheme 35).

The synthesis of the diastereoisomeric *syn*-(2*R*,3*S*)-diaminobutanoic acid **489** (98% de and 98% ee) was accomplished via functional group manipulation of *anti*-β-amino-α-hydroxyester **470** in a protocol involving azide inversion of *N*-Boc-3-amino mesylate **490** and subsequent deprotection (Scheme 36).[185]

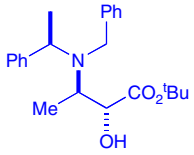
The extension of this methodology for the asymmetric synthesis of β-amino-α-thioesters has also been accomplished, with conjugate addition of lithium amide (*R*)-**31** to *tert*-butyl cinnamate and addition of toluene-4-thiosulfonic acid *S*-*tert*-butyl ester as an electrophilic

Table 11.

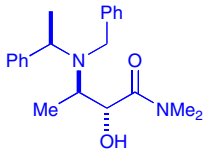




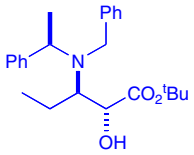
469
Ref 156: -78°C, 55%, 75% d.e.
$[\alpha]_D^{25}$ -9.2 (c = 0.97, $CHCl_3$)



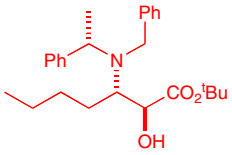
470
Ref 156: -78°C, 36%, >90% d.e.
$[\alpha]_D^{22}$ -35.2 (c = 1.00, $CHCl_3$)
Ref 179; Ref 180: 89%, >90% d.e.



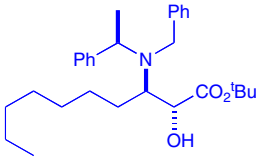
471
Ref 156: -78°C, 42%, >93% d.e.
$[\alpha]_D^{21}$ -92.5 (c = 0.93, $CHCl_3$)



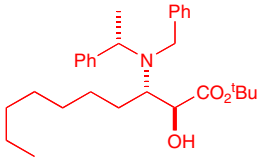
472
Ref 156: -78°C, 53%, >90% d.e.
$[\alpha]_D^{20}$ -12.5 (c = 1.00, $CHCl_3$)



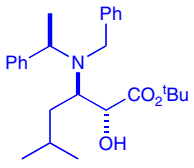
473
Ref 160: -78°C, 85%, >98% d.e.



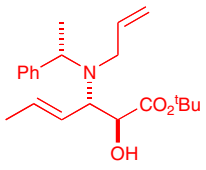
474
Ref 69: -78°C, 63%, 88% d.e.
$[\alpha]_D^{25}$ -24.6 (c = 1.02, $CHCl_3$)
Ref 161



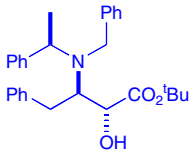
474
Ref 69: -78°C, 85%, 92% d.e.
$[\alpha]_D^{26}$ +23.4 (c = 2.28, $CHCl_3$)



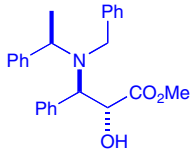
475
Ref 179: Ref 180
-78°C, 91%, >90% d.e.
$[\alpha]_D^{22}$ -18.9 (c = 1.0, $CHCl_3$)



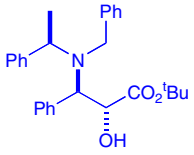
476
Ref 174: -78°C, 63%, 96% d.e.
$[\alpha]_D^{22}$ +50.4 (c = 1.99, $CHCl_3$)
Ref 90



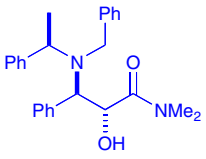
477
Ref 158: -78°C, 41%, 20% d.e.



478
Ref 156: -78°C, 43%, >90% d.e.
$[\alpha]_D^{23}$ -5.5 (c = 1.10, $CHCl_3$)



468
Ref 179, Ref 180: -78°C, 70%, >90% d.e.
Ref 156: 89%, >98% d.e.
$[\alpha]_D^{20}$ -27.2 (c = 0.98, $CHCl_3$)
Ref 158, Ref 181, Ref 182



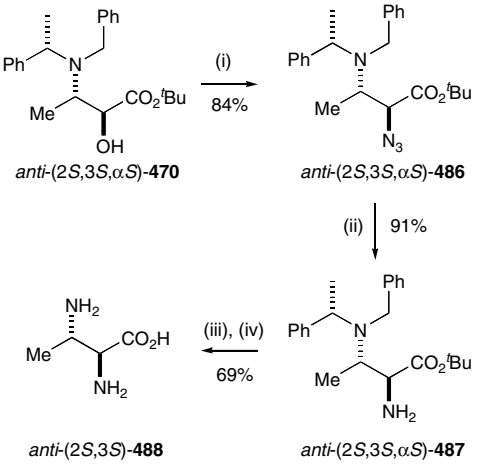
479
Ref 156: -78°C, 85%, >95% d.e.
$[\alpha]_D^{20}$ -73.9 (c = 1.03, $CHCl_3$)

source of sulfur giving *anti*-β-amino-α-thio-ester **492** in 78% yield and 97% de (Scheme 37).[186]

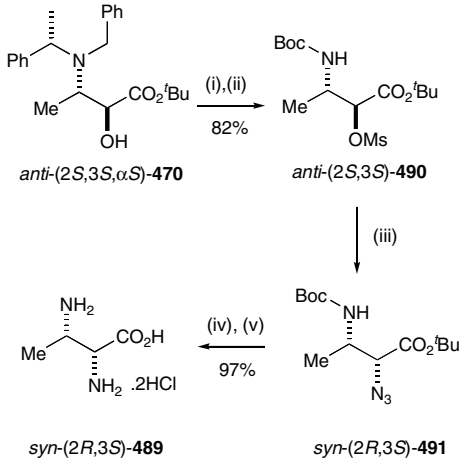
Attempted use of S_8 as an electrophilic source of sulfur after addition of lithium amide (*R*)-**31** to *tert*-butyl cinnamate gave a complex mixture of polysulfur containing compounds represented by **493**, which upon treatment with $NaBH_4/S_8$ gave a 67:33 mixture of thiomorpholines **494** and **495**, presumably through a stereoselective radical cyclisation of the intermediate α-thiol (Scheme 38).[186]

6.3. Aldol reactions

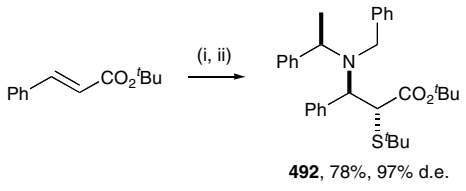
Yamamoto et al. have demonstrated that enolate geometry plays an important part in determining the stereoselectivity of aldol reactions of β-amino enolates. For example, conjugate addition of LSA **25** to methyl croto-



Scheme 35. Reagents and conditions: (i) hydrazoic acid (4.5 equiv), PPh_3 (4.3 equiv), DEAD (4.3 equiv), benzene, rt; (ii) PPh_3, THF/H_2O, rt; (iii) $Pd(OH)_2$ on C, MeOH, H_2 (5 atm); (iv) TFA, rt, then 1 M HCl(aq), then Dowex 50X8-200.

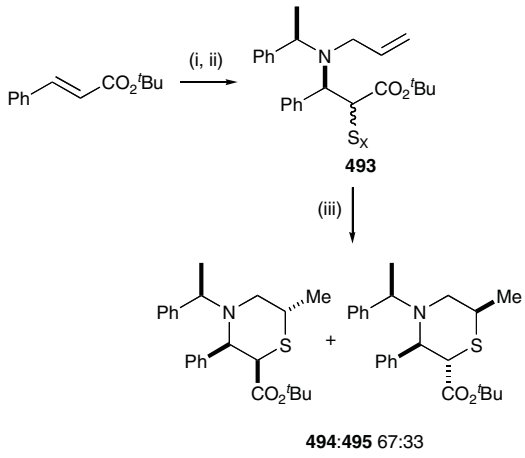


Scheme 36. Reagents and conditions: (i) $Pd(OH)_2$ on C, H_2 (5 atm), Boc_2O (3.7 equiv), EtOAc, rt; (ii) $MeSO_2Cl$ (1.1 equiv), NEt_3 (1.5 equiv), DCM, 0 °C (30 min), then rt; (iii) NaN_3 (4.6 equiv), DMF, 55 °C; (iv) Pd/C, H_2 (5 atm), EtOAc, rt; (v) TFA, rt overnight, then 1 M HCl(aq), rt.

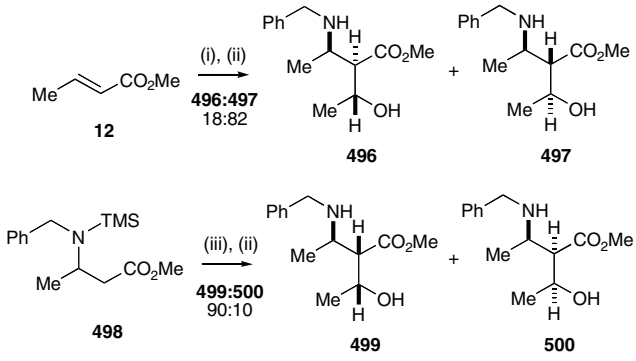


Scheme 37. Reagents and conditions: (i) lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide, THF, −78 °C; (ii) toluene-4-thiosulfonic acid *S*-*tert*-butyl ester, −78 °C.

nate (generating the corresponding (*Z*)-enolate) and subsequent aldol reaction with acetaldehyde gave an 18:82 mixture of diastereoisomers **496**:**497**. Treatment of β-amino ester **498** with LDA (generating the corresponding (*E*)-enolate) gave a 90:10 mixture of diastereoisomers **499**:**500** (Scheme 39).[187]

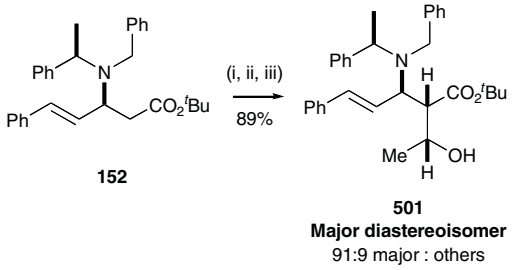


Scheme 38. Reagents and conditions: (i) lithium (*R*)-*N*-allyl-*N*-α-methylbenzylamide, THF, −78 °C; (ii) S_8, −78 °C; (iii) $NaBH_4$, S_8, EtOH, rt.



Scheme 39. Reagents and conditions: (i) LSA, THF, −78 °C; (ii) MeCHO, −78 °C to rt; (iii) LDA, −78 °C, then TMSCl.

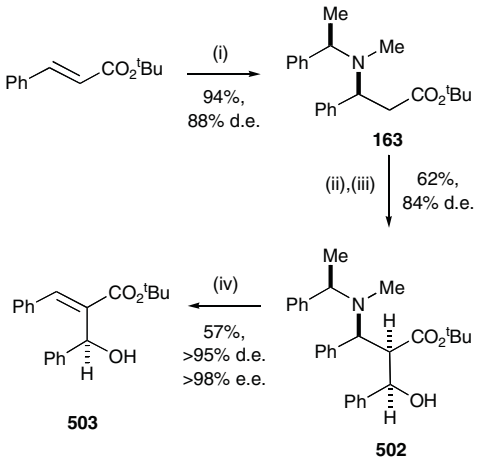
In the homochiral series, the effect of Lewis acid derivatives on the stereoselectivity of the aldol reaction has been investigated. Generation of the (*E*)-enolate of β-amino ester **152**, followed by transmetallation with trimethyl borate and addition of acetaldehyde, gave a 91:9 mixture of the major diastereoisomer **501** to other diastereoisomers (Scheme 40).[188]



Scheme 40. Reagents and conditions: (i) LDA, THF, −78 °C; (ii) $B(OMe)_3$, −78 °C; (iii) MeCHO.

This methodology has been used as the basis for the development of the asymmetric synthesis of β-substituted Baylis–Hillman products. Diastereoselective conjugate addition of lithium (*R*)-*N*-methyl-*N*-α-methylbenzylamide **38** to *tert*-butyl cinnamate gave

163, with subsequent generation of the (*E*)-enolate and boron mediated aldol reaction giving **502** in high de. Purification of the major aldol diastereoisomer **502** to homogeneity, and subsequent *N*-oxidation and Cope elimination gives the β-substituted Baylis–Hillman product **503** in >95% de and >98% ee (Scheme 41).[108]



Scheme 41. Reagents and conditions: (i) lithium (*R*)-*N*-methyl-*N*-α-methylbenzylamide **38**, −78 °C, THF, then NH_4Cl(aq); (ii) LDA, −78 to 0 °C; (iii) $B(OMe)_3$, −78 °C, then PhCHO; (iv) mCPBA, $CHCl_3$.

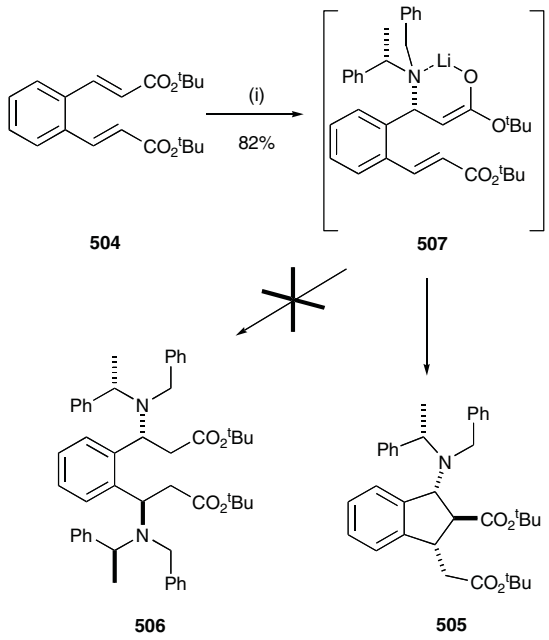
7. Cascade reactions for the preparation of multiple stereogenic centres: double conjugate addition and addition–cyclisation reactions

While a range of functionalities can be incorporated into the β-amino ester structure by enolate elaboration, the one-pot generation of multiple stereocentres via conjugate addition–cyclisation reactions and multiple conjugate addition reactions has also been investigated. For example, conjugate addition of lithium amide (*S*)-**31** to *o*-substituted bis-α,β-unsaturated acceptor **504** gave exclusively benzo transpentacin analogue **505** rather than the bis-β-amino ester **506**. This observation is consistent with the intermediate enolate **507** generated by addition of 1 equiv of lithium amide (*S*)-**31** to acceptor **504** undergoing intramolecular conjugate addition to the tethered α,β-unsaturated ester fragment to afford **505** at a much greater rate than addition of a second equivalent of lithium amide (*S*)-**31** to afford **506** (Scheme 42).[174,189]

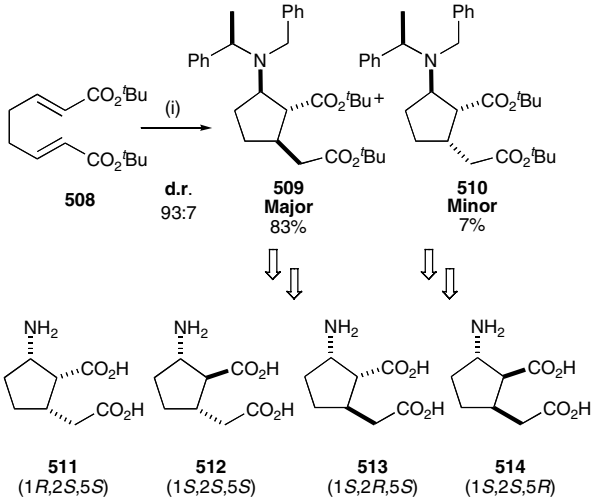
Similarly, conjugate addition of lithium amide (*R*)-**31** to di-*tert*-butyl (*E*,*E*)-octa-2,6-dienoate **508** generated a mixture of two diastereoisomers **509**:**510** in good yield and with reasonable selectivity. This protocol was subsequently utilised for the selective generation of all stereoisomers of 2-amino-5-carboxymethyl-cyclopentane-1-carboxylate **511**–**514** (Scheme 43).[144]

Conjugate addition of lithium amide (*R*)-**31** to homologous di-methyl (*E*,*E*)-nona-2,7-diendioate **515** allows the reaction manifold to be diverted to two distinct pathways, allowing competition between intramolecular cyclisation and double conjugate addition. While conjugate addition of 1.1 equiv of lithium amide (*R*)-**31** promoted selectively the addition–cyclisation reaction giving **516** as a single diastereoisomer, addition of excess lithium amide (12 equiv) gave a 60:40 mixture of **516** and the diaddition product **517** as a single diastereoisomer (Scheme 44).[190]

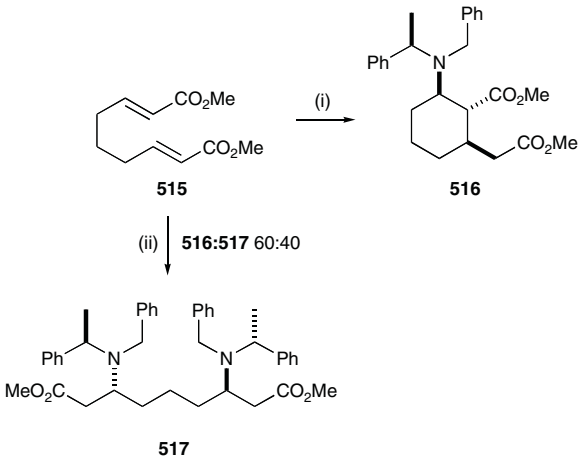
To extend this methodology, lithium amide addition and cyclisation of ε-oxo-α,β-unsaturated esters have been investigated. Addition of ε-oxo-α,β-unsaturated ester **518** to a solution of lithium amide (*S*)-**31** (2.4 equiv) at −78 °C followed by warming to −20 °C gave a 9:91 mixture of **519**:**520**, giving **519** in 7% yield (>98% de) and cyclic β-amino ester **520** in 66% yield (>98% de) (Scheme 45).[190]



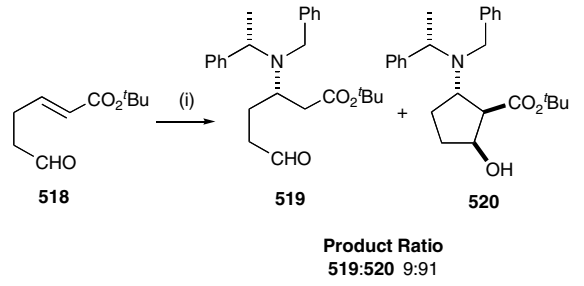
Scheme 42. Reagents and conditions: (i) lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide (3.0 equiv), THF, −78 °C, then NH_4Cl(aq).



Scheme 43. Reagents and conditions: (i) lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide, THF, −78 °C, then NH_4Cl(aq).



Scheme 44. Reagents and conditions: (i) lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide, THF, −78 °C, then NH_4Cl(aq).



Scheme 45. Reagents and conditions: (i) lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide, THF, −78 to −20 °C, then NH_4Cl(aq).

8. Conjugate addition to chiral α,β-unsaturated acceptors

The high levels of diastereoselectivity offered by chiral lithium amides upon conjugate addition to α,β-unsaturated acceptors offer numerous opportunities for investigating chiral recognition phenomena via kinetic resolution and double diastereoselective synthesis through addition to chiral α,β-unsaturated acceptors.

8.1. Addition to chiral acyclic α,β-unsaturated acceptors: double diastereoselective reactions

The addition of achiral lithium amides to chiral acyclic α,β-unsaturated acceptors containing a γ-alkoxy bearing stereogenic centre has been reported by a number of groups. Reasonable levels of stereocontrol are observed in these reactions that proceed under substrate control. For example, Yamamoto et al. have demonstrated that lithium *N*-benzyl-*N*-trimethylsilylamide **25** undergoes preferential *syn*-addition to the lactate-derived ester **521**, while exclusive *anti*-addition to the mandelate-derived ester **523** was observed.[191] Reasonable levels of stereocontrol have also been observed in the conjugate addition of lithium dibenzylamide to (*RS*)-**525**, giving preferentially the *anti*-diastereoisomer **526** (Fig. 4).[192]

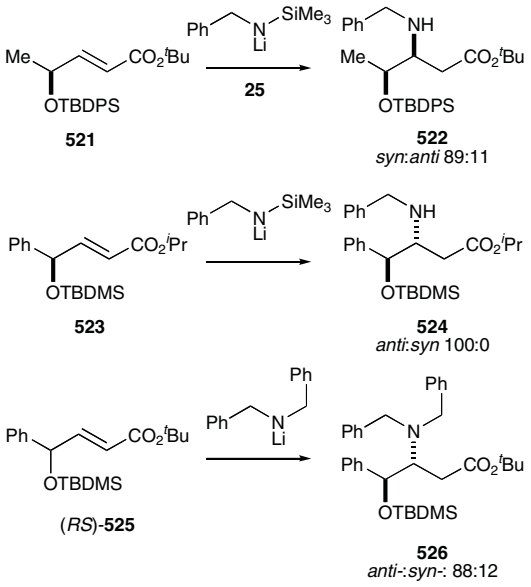
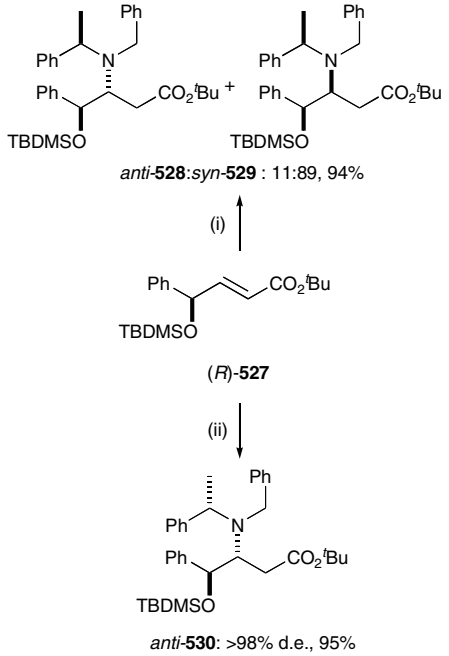


Figure 4. Conjugate addition of lithium *N*-benzyl-*N*-trimethylsilylamide and lithium dibenzylamide to γ-silyloxy-α,β-unsaturated esters.

As chiral acceptors such as **521** and **523** generally show reasonable levels of stereocontrol upon conjugate addition of an achiral lithium amide, double diastereoselectivity upon conjugate addition of the lithium amides (*S*)-**31** and (*R*)-**31** to similar chiral acceptors may be expected. Indeed, conjugate addition of lithium amide (*R*)-**31** to the acceptor **527** gives an 11:89 mixture of the inseparable *anti*-:*syn*-diastereoisomers **528**:**529** in 94% isolated yield, corresponding to the mismatched reaction pair. In the matched series, conjugate addition of lithium amide (*S*)-**31** gave *anti*-**530** as a single diastereoisomer in 95% yield (Scheme 46). These product



Scheme 46. Reagents and conditions: (i) lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide, THF, −78 °C, then NH_4Cl(aq); (ii) lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide, THF, −78 °C, then NH_4Cl(aq).

distributions indicate that the asymmetric induction from the enantiomerically pure lithium amide dominates in these reactions, even in the mismatched reaction case.[192]

Within this area, Sewald et al. have shown that conjugate addition of homochiral lithium *N*-α-methylbenzyl-*N*-trimethylsilylamide **352** to the glyceraldehyde derived homochiral ester (*S*)-**531** proceeds under the stereocontrol of the chiral acceptor, with high *syn*-selectivity noted independent of the absolute configuration of the nucleophile in Et_2O, although no stereocontrol was observed in THF (Fig. 5).[164]

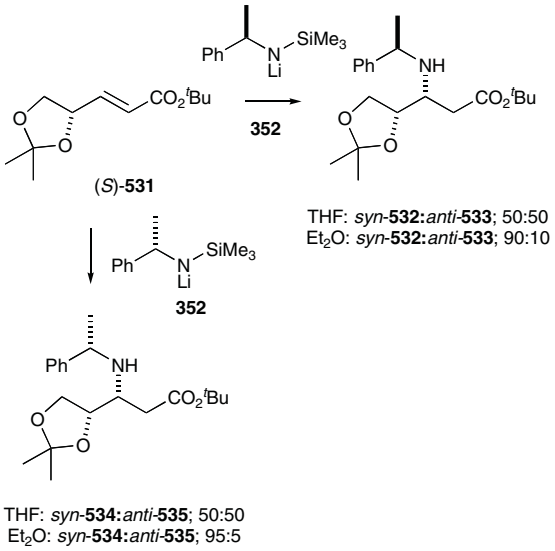
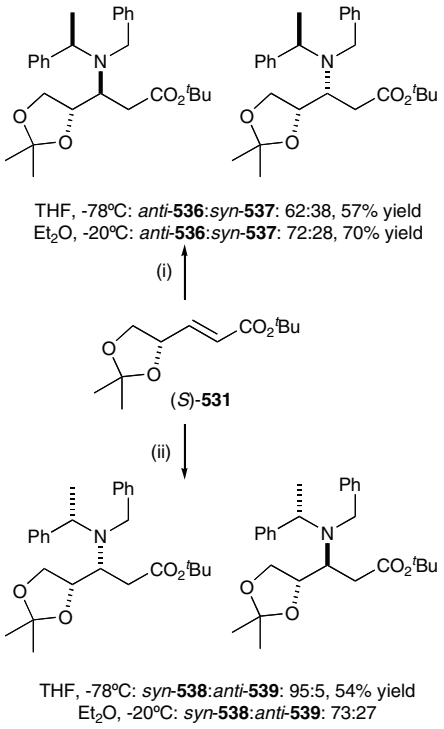


Figure 5. Conjugate addition of lithium *N*-α-methylbenzyl-*N*-trimethylsilylamide **352** to (*S*)-**531**.

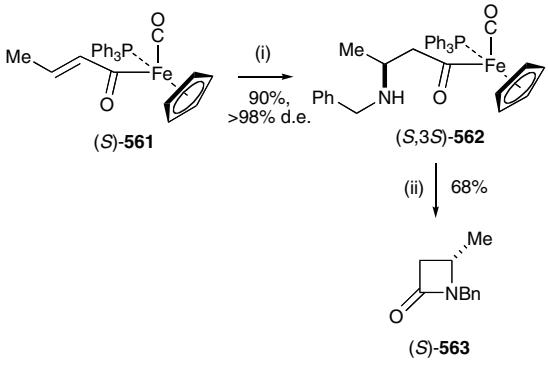
In the same series, conjugate addition of lithium amide (*R*)-**31** to **531** in Et_2O at −20 °C gave a 72:28 mixture of *anti*- and *syn*-diastereoisomers **536**:**537**, while in THF at −78 °C a 62:38 *anti*:*syn* mixture of diastereoisomers was observed. Furthermore, conjugate addition of lithium amide (*S*)-**31** to **531** in Et_2O at −20 °C gave a 73:27 mixture of *syn*:*anti* diastereoisomers **538**:**539**, while high *syn*-selectivity is seen in THF at −78 °C (95:5 *syn*:*anti*) (Scheme 47). These results indicate that these conjugate addition reactions proceed predominantly under the stereocontrol of the chiral lithium amide, consistent with the stereodirecting effect of lithium *N*-benzyl-*N*-α-methylbenzylamide > lithium *N*-trimethylsilyl-*N*-α-methylbenzylamide (Scheme 47, Table 12).



Scheme 47. Reagents and conditions: (i) lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide, solvent, temp; (ii) lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide, solvent, temp.

8.2. Conjugate addition to chiral iron acceptors

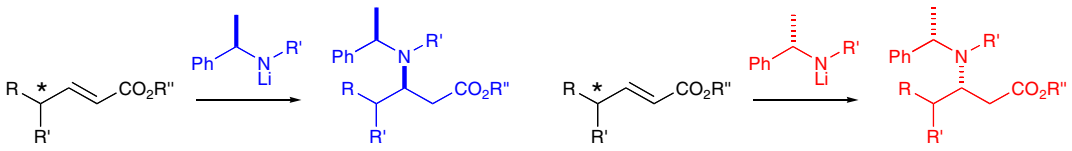
The iron chiral auxiliary [(η^5-C_5H_5)Fe(CO)(PPh_3)] shows remarkable levels of stereocontrol upon reaction of its attached alkyl and acyl ligands for a range of transformations, including alkylations, aldol reactions, conjugate addition reactions and Diels Alder reactions.[197] For example, conjugate addition of lithium benzylamide to the (*S*)-iron crotonyl complex **561** affords the (*S*,3*S*)-β-amino complex-**562** in 90% yield as a single diastereoisomer (>98% de), which upon oxidative decomplexation with bromine affords homochiral (*S*)-4-methyl-*N*-benzylazetidin-2-one **563** (Scheme 48).[198]

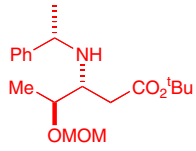


Scheme 48. Reagents and conditions: (i) BnNHLi (1.2 equiv), THF, −78 °C; (ii) Br_2 (2 equiv), DCM, −78 °C, then NEt_3, −78 °C to rt.

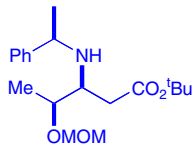
As both the chiral iron auxiliary and homochiral lithium amides show high levels of control in conjugate addition reactions, high levels of chiral recognition may be expected between the racemic iron crotonoyl complex (*RS*)-[(η^5-C_5H_5)Fe(CO)(PPh_3)(COCH=CHMe)] **561**

Table 12.

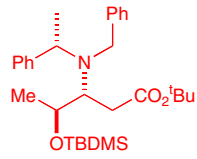




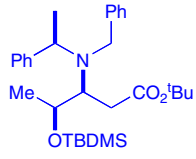
540
Ref 194: 95%, 92% d.e.
$[\alpha]_D^{20}$ -36 (c = 1, $CHCl_3$)



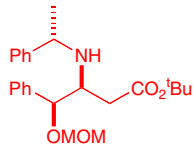
541
Ref 194: 74%, 72% d.e.
$[\alpha]_D^{20}$ +47 (c = 1, $CHCl_3$)



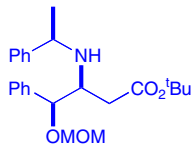
542
Ref 192: 96%, >98% d.e.
$[\alpha]_D^{22}$ +14.2 (c = 1.22, $CHCl_3$)



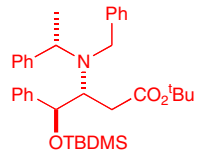
543
Ref 192: 95%, 90% d.e.
$[\alpha]_D^{21}$ +39.1 (c =1.34, $CHCl_3$)



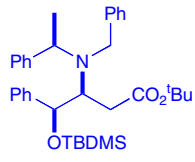
544
Ref 194: 27%, 98% d.e.
$[\alpha]_D^{20}$ +46 (c = 1, $CHCl_3$)



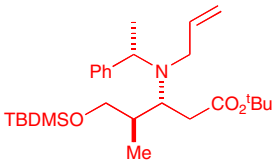
545
Ref 194: 39%, 76% d.e.
$[\alpha]_D^{20}$ +36 (c = 1, $CHCl_3$)



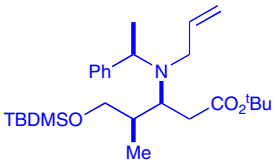
530
Ref 192: 95%, >98% d.e.
$[\alpha]_D^{20}$ +50.3 (c = 1.13, $CHCl_3$)



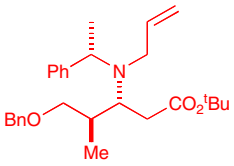
529
Ref 192: 94%, 78% d.e.
$[\alpha]_D^{20}$ +22.6 (c = 0.76, $CHCl_3$)



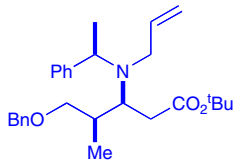
546
Ref 195: 84%, 97% d.e.
$[\alpha]_D^{23}$ +35.1 (c = 1.22, $CHCl_3$)



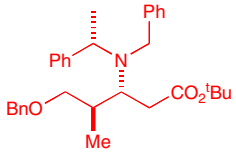
547
Ref 195: 84%, 88% d.e.
$[\alpha]_D^{23}$ -46.6 (c = 1.55, $CHCl_3$)



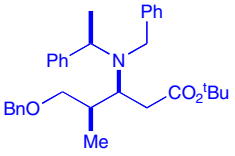
548
Ref 195: 77%, 91% d.e.
$[\alpha]_D^{23}$ +38.1 (c = 1.25, $CHCl_3$)



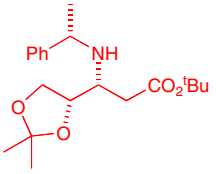
549
Ref 195: 80%, 73% d.e.
$[\alpha]_D^{23}$ -53.8 (c = 2.00, $CHCl_3$)



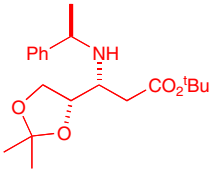
550
Ref 98: 95%, ~100% d.e.
$[\alpha]_D^{27}$ +3.8 (c = 1.05, $CHCl_3$)



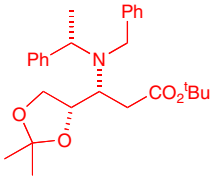
551
Ref 98: 80%, 73% d.e.
$[\alpha]_D^{27}$ -11.1 (c = 0.96, $CHCl_3$)



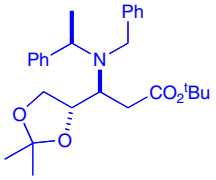
534
Ref 194, Ref 129: 75%, 90% d.e.
$[\alpha]_D^{20}$ -32 (c = 1, $CHCl_3$)
Ref 195: 92%, 66% d.e.



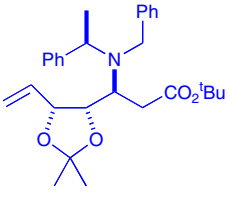
532
Ref 194, Ref 129: 75%, 90% d.e.
$[\alpha]_D^{20}$ +24 (c = 1, $CHCl_3$)
Ref 192: 83%, 76% d.e.
$[\alpha]_D^{20}$ +22.7 (c = 1.04, $CHCl_3$)



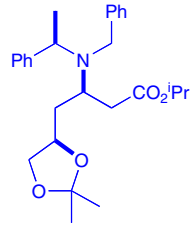
538
Ref 193: 54%, 90% d.e.
$[\alpha]_D^{20}$ -0.7 (c = 1.18, $CHCl_3$)



536
Ref 193: 52%, 24% d.e.



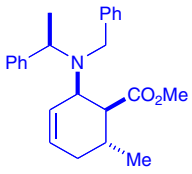
552
Ref 163: 70%, >98% d.e.
$[\alpha]_D^{22}$ +1.7 (c = 0.30, $CHCl_3$)



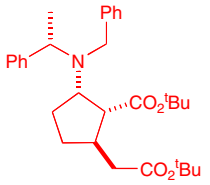
553
Ref 196: 85%, 95% d.e.
$[\alpha]_D^{21}$ -23.9 (c = 2.0, $CHCl_3$)

(*continued on next page*)

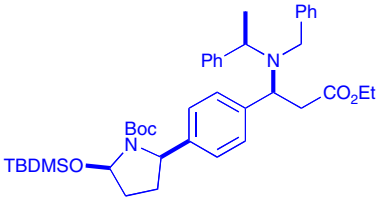
Table 12 (*continued*)



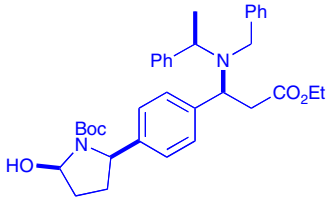
554
Ref 150: 86%, >95% d.e.
$[\alpha]_D^{23}$ -226.0 (c = 1.17, $CHCl_3$)



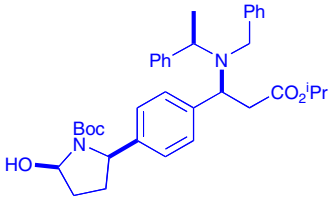
555
Ref 144: -78°C, 68%, >98% d.e.
$[\alpha]_D^{26}$ -46.8 (c 1.72, $CHCl_3$)



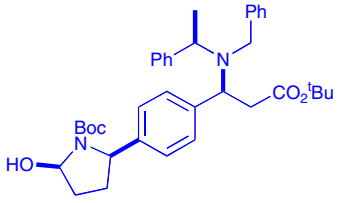
556
Ref 138



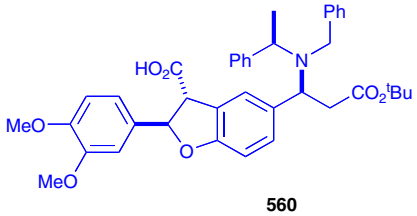
557
Ref 138



558
Ref 138



559
Ref 138: 99%
$[\alpha]_D^{20}$ +33.6 (c = 1.0, $CHCl_3$)

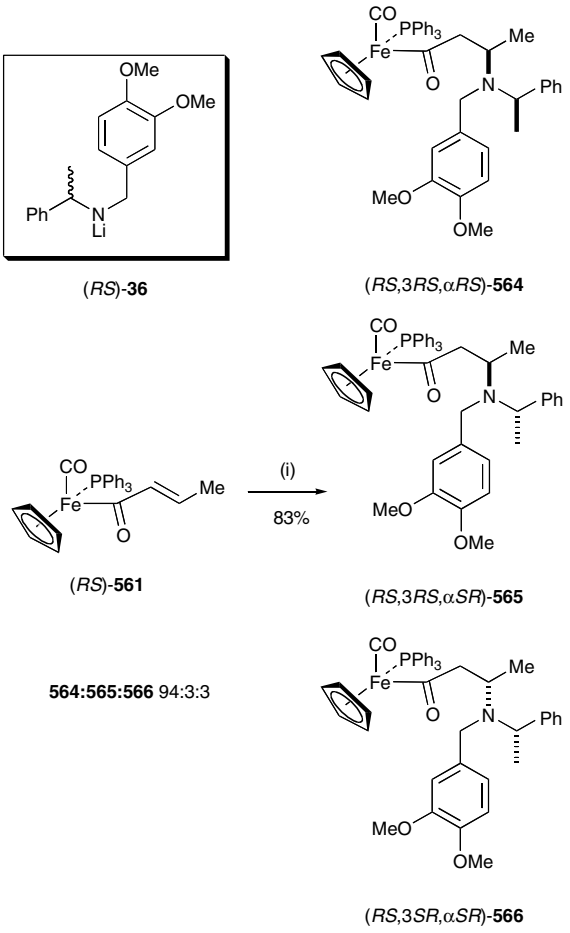


560
Ref 139: 48%
$[\alpha]_D$ -35 (c = 0.1, $CHCl_3$)
Ref 140: 48%, >98% d.e.

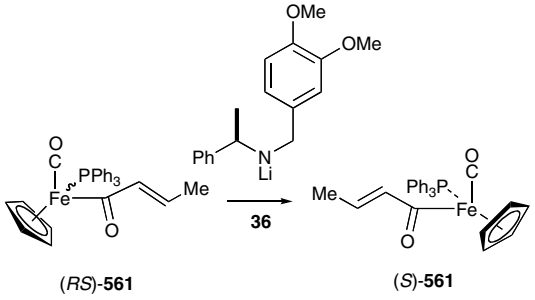
and racemic (*RS*)-lithium *N*-3,4-dimethoxybenzyl-*N*-α-methylbenzylamide **36**. As first demonstrated by Horeau,[199] this mutual kinetic resolution approach allows the maximum stereoselectivity factor (*E*) for the reactants to be evaluated independent of the reaction conversion, assuming that non-linear effects do not operate. Conjugate addition of lithium amide (*RS*)-**36** to iron complex (*RS*)-**561** gave a crude product mixture containing three diastereoisomers **564**:**565**:**566** in a 94:3:3 ratio ($E = 15$) (Scheme 49). This product distribution indicates that the stereodirecting capability of the chiral iron auxiliary is effectively counteracted by the stereocontrol imposed by the chiral lithium amide in these reactions.

This 94:3:3 ratio of diastereoisomers suggests a >15:1 rate difference between the addition of the matched pair {lithium amide (*R*)-**36** and (*R*)-[(η^5-C_5H_5)Fe(CO)(PPh_3)(COCH=CHMe)] **561**} and the mismatched pair {lithium amide (*R*)-**36** and (*S*)-[(η^5-C_5H_5)Fe(CO)(PPh_3)(COCH=CHMe)] **561**}. This rate difference was used as the basis for a kinetic resolution of (*RS*)-**561** by homochiral lithium amide (*R*)-**36** (Scheme 50).[200]

Further reactions in this series indicated that the reaction of (*RS*)-lithium amide **31** with either (*RS*)- or homochiral iron acyl complex **561** shows 2:1 stoichiometry (2 equiv of amide needed for the reaction to go to completion), while the homochiral lithium amide **31** showed 1:1 stoichiometry with either (*RS*)- or homochiral iron acyl complex **561**. While Seebach et al. have commented that addition of lithium amide (*R*)-**31** to methyl crotonate requires 2 equiv of amide to proceed to completion (~40% conversion with 1 eq amide),[35] in our hands the addition of lithium amide **31** to achiral acceptors requires only 1 equiv of lithium amide to proceed to completion; only with the iron complex **561** and (*RS*)-lithium amide **31** is this 2:1 stoichiometry observed. Upon the assumption that chiral lithium amide **31** reacts predominantly as a dimeric complex, conjugate addition reactions involving a single enantiomer of lithium amide can involve only homochiral [(*R*,*R*) or (*S*,*S*)] dimers, while in the racemic series both homochiral [(*R*,*R*) and (*S*,*S*)] and heterochiral [(*R*,*S*)] dimers can be formed. The differences in the reaction stoichiometry in these reactions imply that heterochiral [(*R*,*S*)] lithium amide dimers play an essential role in the conjugate addition reaction of the racemic amide.[201]



Scheme 49. Reagents and conditions: (i) (*RS*)-*N*-3,4-dimethoxybenzyl-*N*-α-methylbenzylamide (2.0 equiv), THF, −78 °C, then NH_4Cl(aq).



Conversion (%)	SpecificRotation (c 0.15, benzene)	e.e (%)
4	+6.3	4
18	+33.5	19
34	+73.8	42
56	+145.0	83
70	+181.4	>95
80	+178.1	>95

authentic (*S*)-**561** $[\alpha]_D^{23}$ +175.3 (c 0.15, benzene)

Scheme 50. Reagents and conditions: (i) lithium (*R*)-*N*-3,4-dimethoxybenzyl-*N*-α-methylbenzylamide (2.0 equiv), THF, −78 °C.

8.3. Kinetic resolutions of cyclopentene-1-carboxylates

In order to enhance the structural diversity of monomeric cispentacin and transpentacin derivatives available for secondary structural and bioactivity studies, an approach to substituted analogues, which maintain the saturated five-membered ring backbone and (1*R*,2*S*)-absolute configuration essential for biological activity, is desired.[202] To solve this synthetic problem, the conjugate addition of homochiral lithium amide (*S*)-**31** to effect a kinetic resolution of *tert*-butyl (*RS*)-3-methylcyclopentene-1-carboxylate **567** has been demonstrated.[145,203] As efficient kinetic resolution requires both reacting partners to show high levels of stereocontrol, the level of chiral recognition between acceptor **567** and lithium (*RS*)-amide **31** was evaluated through their mutual kinetic resolution [addition of (*RS*)-**567** to an excess of (*RS*)-lithium amide **31**]. The enantiorecognition between the two chiral but racemic components in this strategy is identical to the diastereoselectivity observed in the reaction (since the effects of mass action are eliminated), on the assumption that there are no non-linear effects operating.[204] Four diastereoisomeric products **568**–**571** arising from this reaction are possible [ignoring C(1) protonation selectivity], although based upon the stereodirecting capabilities of the (*RS*)-lithium amide and the (*RS*)-acceptor, the major product was predicted to have the C(2)–C(3) *anti*-relative configuration corresponding to **568**, in which synergistic combination of both stereodirecting components of the amide and acceptor is favoured (Fig. 6).

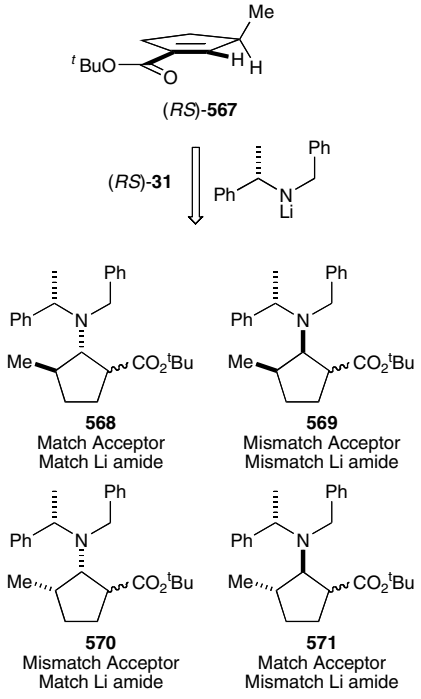
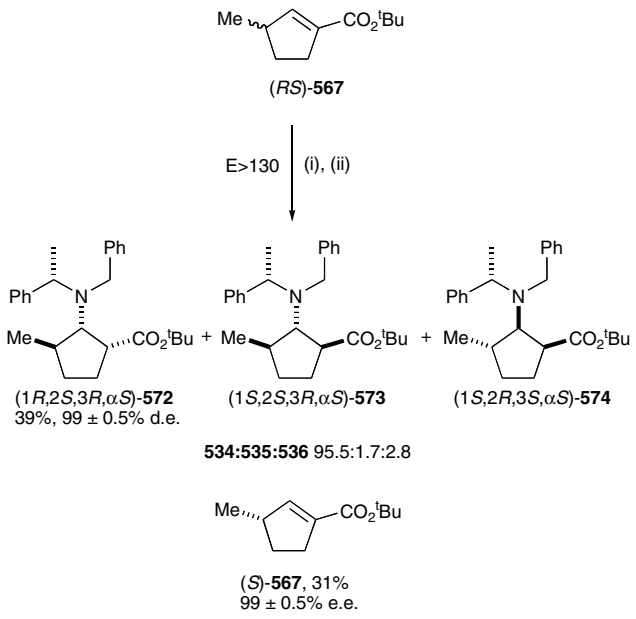


Figure 6. Possible diastereoisomeric β-amino ester products obtained upon addition of lithium (*RS*)-amide **31** to (*RS*)-**567**.

Addition of (*RS*)-**567** to an excess of lithium (*RS*)-amide **31** gave a mixture of three diastereoisomers (±)-**572**:(±)-**573**:(±)-**574** in a 90.2:9.1:0.7 ratio, consistent with *E*

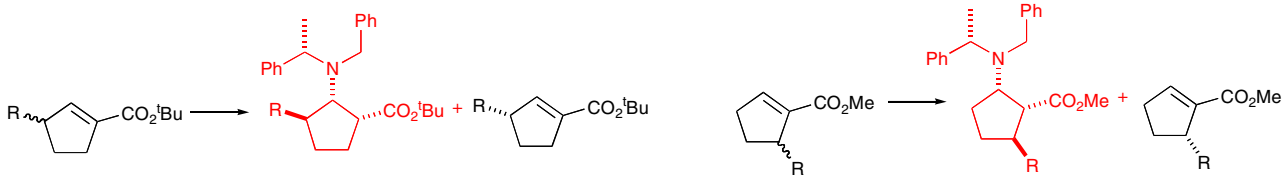
>140 in this enantiorecognition protocol. With high levels of enantiorecognition observed between (*RS*)-**567** and (*RS*)-lithium amide **31**, the kinetic resolution of (*RS*)-**567** was achieved by treatment of (*RS*)-**567** with 0.7 equiv of lithium amide (*S*)-**31** to give, at 51% conversion, a mixture of three β-amino ester diastereoisomers **572**:**573**:**574** in a 95.5:1.7:2.8 ratio. Chromatographic purification and subsequent recrystallisation gave β-amino ester **572** in 39% yield and 99 ± 0.5% de and (*S*)-**567** in 31% yield and 99 ± 0.5% ee, consistent with *E* >130 (Scheme 51, Table 13).

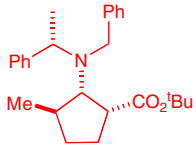
Deprotection to the desired β-amino acid was readily achieved, with Pd mediated *N*-debenzylation and treatment with TFA giving (1*R*,2*S*,3*R*)-3-methylcispentacin **584** in >98% de and 98 ± 1% ee after purification by ion exchange chromatography. The diastereoisomeric (1*S*,2*S*,3*R*)-3-methyltranspentacin was also prepared by epimerisation of (1*R*,2*S*,3*R*,α*S*)-**572** to the C(1) epimer (1*S*,2*S*,3*R*,α*S*)-**585**, with hydrogenolysis, ester hydrolysis and recrystallisation giving (1*S*,2*S*,3*R*)-3-methyltranspentacin hydrochloride **586** in >98% de and 97 ± 1% ee (Scheme 52). This methodology has been applied to the kinetic resolution of a number of



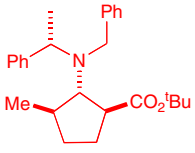
Scheme 51. Reagents and conditions: (i) lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide **31** (0.7 equiv), THF, −78 °C; (ii) 2,6-di-*tert*-butylphenol, THF, −78 °C to rt.

Table 13.

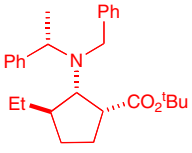




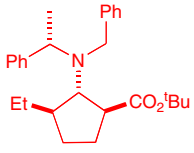
572
Ref 203 39%
Ref 145



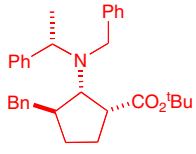
573
Ref 145



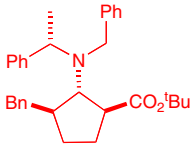
575
Ref 146 32%



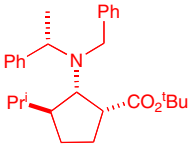
576
Ref 146



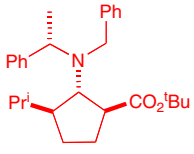
577
Ref 146 41%



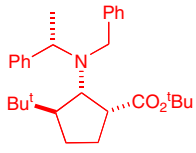
578
Ref 146



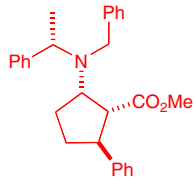
579
Ref 146 35%



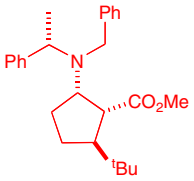
580
Ref 146



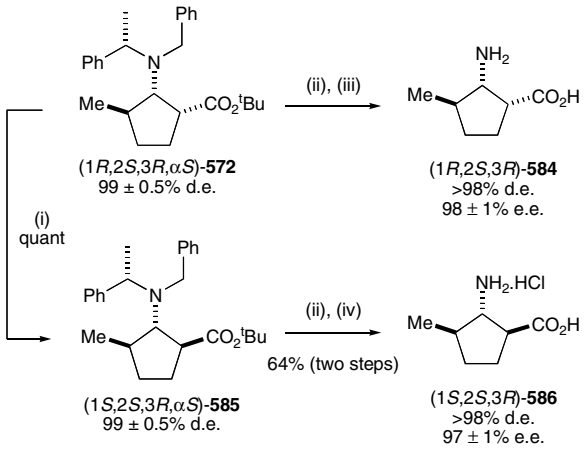
581
Ref 146 37%



582
Ref 206 28%



583
Ref 205 42%
Ref 206



Scheme 52. Reagents and conditions: (i) KO^{t}Bu, ^{t}BuOH, Δ, 3 h; (ii) $Pd(OH)_2$ on C, MeOH, H_2 (5 atm); (iii) TFA, then Dowex 50X8-200; (iv) TFA, then HCl(aq) and recrystallisation.

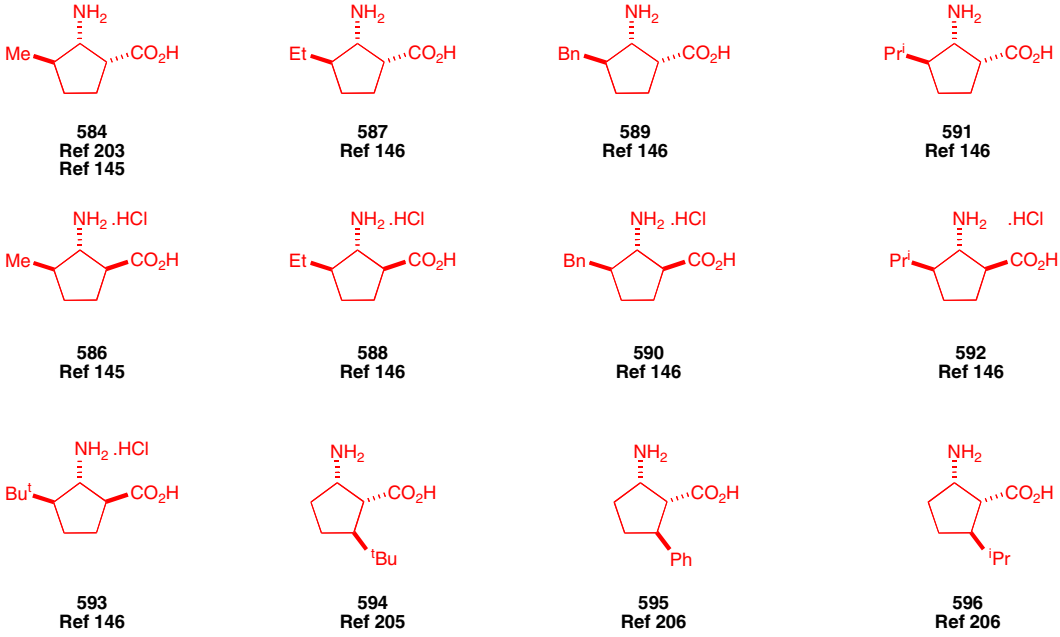
3-alkyl- and 5-alkyl-cis and transpentacin derivatives (Table 14).

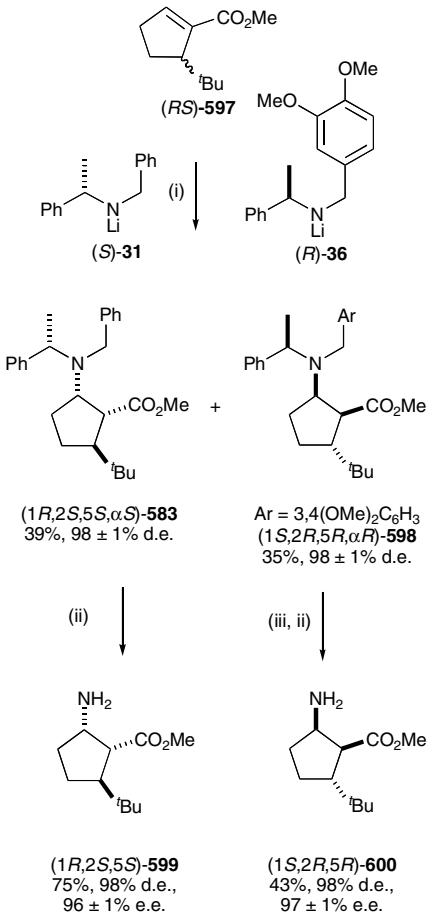
Although this kinetic resolution methodology leads to the generation of only one stereoisomeric reaction product, practically it is limited by the need to compromise either yield or selectivity in the reaction, due to the negative effects of mass action as the reaction progresses. The development of a parallel kinetic resolution protocol would maximise the ee of the product and facilitate the isolation of both product enantiomers from a single reaction.[207] As an extension of this kinetic resolution methodology, the parallel kinetic resolution of methyl (*RS*)-5-*tert*-butyl-cyclopentene-1-carboxylate **597** with a pseudoracemic mixture of chiral lithium amides was investigated in order to eliminate the deleterious effect of mass action during kinetic resolution processes. Lithium amides (*S*)-**31** (98% ee) and (*R*)-**36** (98% ee) were chosen as the components of the pseudoracemic mixture required for this protocol, as they show complementary stereoselectivity upon addition to achiral α,β-unsaturated acceptors; furthermore, it was predicted that the polar nature of the *N*-3,4-dimethoxybenzyl protecting group would facilitate the separation of the β-amino ester products arising from conjugate addition. (*RS*)-**597** (1 equiv) in THF was added to a 50:50 mixture of amides (*S*)-**31** (1.5 equiv):(*R*)-**36** (1.5 equiv) in THF and stirred for 2 h prior to the addition of NH_4Cl(aq). Examination of the ^{1}H NMR spectra of the crude reaction mixture showed a 50:50 mixture of β-amino esters **583** and **598** in 98 ± 1% de in each case, consistent with E >65 for each process. Chromatographic purification gave the two readily separable β-amino esters **583** and **598** in 39% and 35% yield, respectively, and in 98 ± 1% de. Subsequent *N*-debenzylation of **583** by hydrogenolysis gave β-amino ester **599** in 75% yield, 98% de and 96 ± 1% ee, while *N*-deprotection of **598** via oxidative deprotection with DDQ and subsequent hydrogenolysis gave β-amino ester **600** in 98% de and 97 ± 1% ee (Scheme 53, Table 15).

8.4. Probing conjugate addition mechanisms by double asymmetric induction

N-Enoyl derivatives of oxazolidinones have been used extensively for the conjugate addition of organocuprates, Grignard reagents and radicals. In these reactions, it is possible for the α,β-unsaturated carbonyl component to undergo 1,4-addition via either of the

Table 14.





Scheme 53. Reagents and conditions: (i) (*S*)-**31** (1.5 equiv), (*R*)-**36** (1.5 equiv), THF, −78 °C, then NH_4Cl(aq); (ii) $Pd(OH)_2$ on C, MeOH, H_2 (5 atm), rt; (iii) DDQ (2.1 equiv), DCM–H_2O (3:1), rt.

syn- or *anti*-, and *s-cis* or the *s-trans* conformations (Fig. 7).[209]

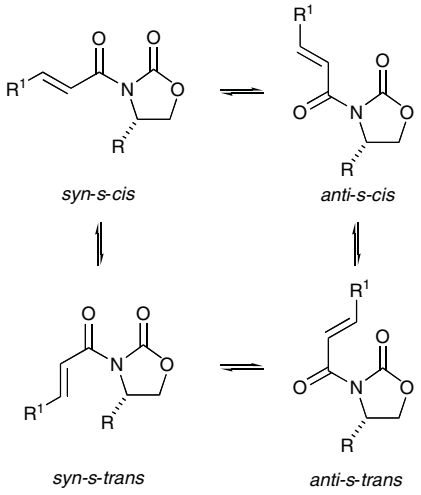
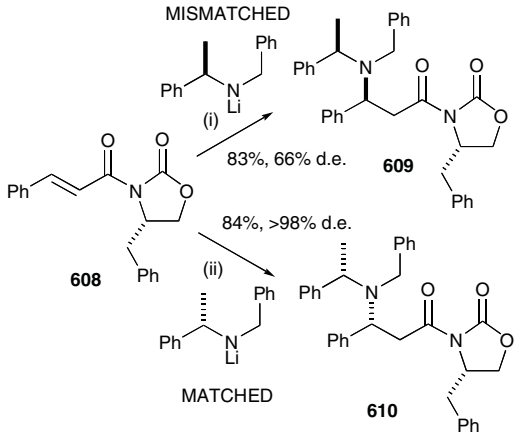


Figure 7. Possible conformations of *N*-acyl-oxazolidinones for conjugate addition.

The diastereoselective conjugate addition of organocuprates has been proposed to occur via the Lewis acid chelated *syn-s-cis* conformation,[210] with the levels of diastereoselectivity postulated to reflect the populations of the reactive conformers of these substrates.[211] As lithium *N*-benzyl-*N*-α-methylbenzylamide adds with high diastereoselectivity to α,β-unsaturated acceptors in the *s-cis* conformation,[187b,152] double asymmetric induction in the reaction of lithium amides and *N*-enoyl oxazolidinones may be used as a mechanistic probe, with the sense of the matched and mismatched pairings used to determine the reactive conformation of the acceptor in this manifold.[212] Conjugate addition of lithium amide (*R*)-**31** to acceptor (*S*)-**608** furnished an inseparable mixture of diastereoisomers **609** with low diastereoselectivity (66% de), and in 83% isolated yield after chromatographic purification. However, conjugate addition of lithium amide (*S*)-**31** to (*S*)-**608** gave (5*S*,3′*R*,α*S*)-**610** as a single diastereoisomer (>98% de) in 84% yield after crystallisation from the crude reaction mixture (Scheme 54).



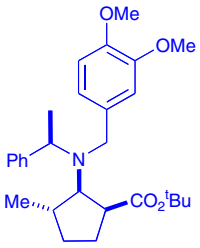
Scheme 54. Reagents and conditions: (i) lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide **31** (1.6 equiv), THF, −78 °C, then NH_4Cl(aq); (ii) lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide **31** (1.6 equiv), THF, −78 °C, then NH_4Cl(aq).

Given the known preference for lithium amides to react with α,β-unsaturated acceptors exclusively in the *s-cis* conformation, the observed sense of asymmetric induction upon addition of both (*S*)-**31** and (*R*)-**31** to **608** is consistent with the stereocontrol of the lithium amide, not the oxazolidinone, dominating the reaction selectivity. In the matched case, addition of lithium amide (*S*)-**31** to acceptor **608** in the *anti-s-cis* conformation results in the preferential formation of (5*S*,3′*R*,α*S*)-**610**. In the mismatched case, addition of lithium amide (*R*)-**31** to acceptor **608** in the *anti-s-cis* conformation results in the preferential formation of (5*S*,3′*S*,α*R*)-**609**, but with reduced levels of diastereoselectivity (Fig. 8).

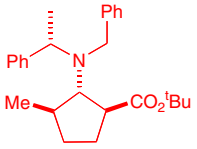
8.5. Asymmetric synthesis of β²-amino acids

The concept of lithium amide conjugate addition has been extended to allow the asymmetric synthesis of α-substituted-β-amino acids (β^2-amino acids) via lithium amide addition to *N*-acryloyl-oxazolidinones.

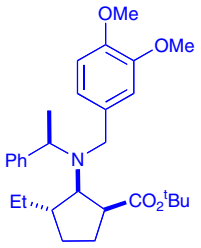
Table 15.



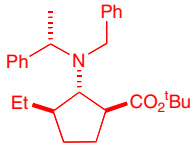
601
40%, >98% d.e.
Ref 208



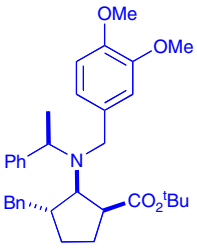
572
34%, >98% d.e.
Ref 208



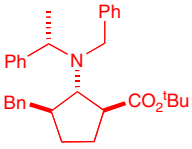
602
30%, >98% d.e.
Ref 208



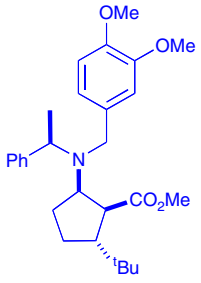
574
34%, >98% d.e.
Ref 208



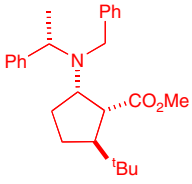
603
36%, >98% d.e
Ref 208.



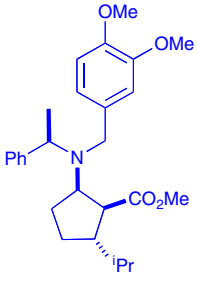
576
40%, >98% d.e.
Ref 208



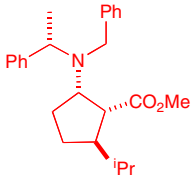
598
35%, 9 ± 1% d.e.
Ref 205, Ref 206



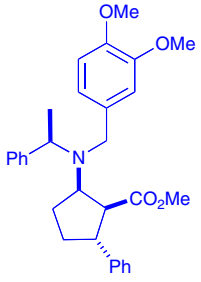
583
39%, 98 ± 1% d.e.
Ref 205, Ref 206



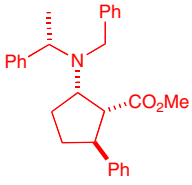
604
30%, 93 ± 1% d.e.
Ref 206



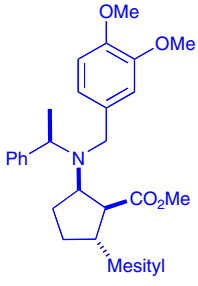
581
30%, 93 ± 1% d.e.
Ref 206



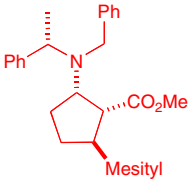
605
43%, 93 ± 1% d.e.
Ref 206



582
38%, 93 ± 1% d.e.
Ref 206



606
45%, 98 ± 1% d.e.
Ref 206



607
41%, 98 ± 1% d.e.
Ref 206

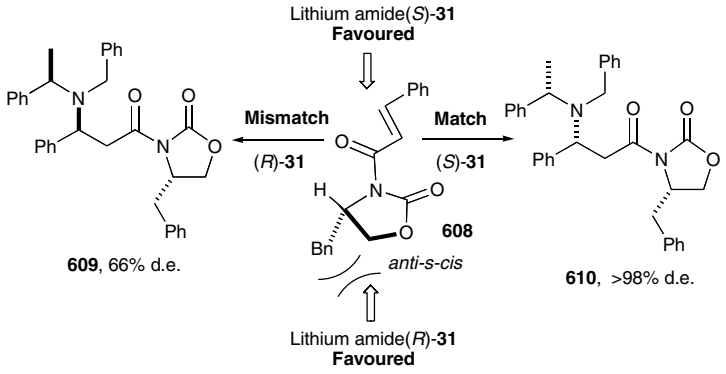
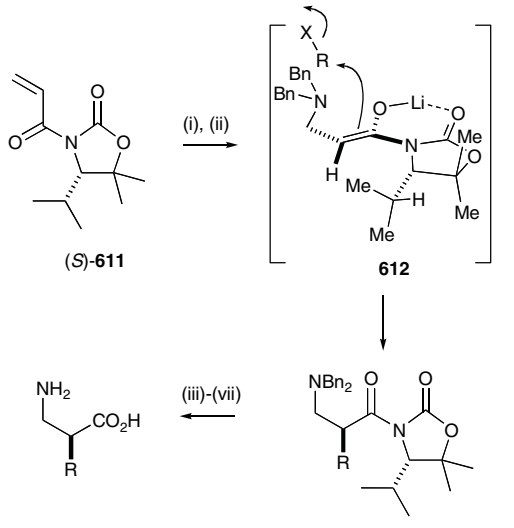


Figure 8. Model to explain double diastereoselectivity in the conjugate addition of lithium amides (*R*)- and (*S*)-**31** to **609**.

Complementary diastereoselectivity can be achieved through two alternative approaches to these substrates, via either tandem conjugate addition to *N*-acryloyl-oxazolidinones and subsequent stereoselective enolate alkylation, or conjugate addition to *N*-2′-alkylacryloyl-oxazolidinones and stereoselective protonation. Conjugate addition of lithium dibenzylamide to *N*-acryloyl-oxazolidinone **611** and in situ elaboration of the enolate **612** arising from conjugate addition by alkylation with a range of alkyl halides gave the corresponding β-amino oxazolidinone derivatives **613**–**615** in good yield and stereoselectivity. Deprotection to the corresponding β^2-amino acids **616**–**618** was readily achieved under standard conditions (Scheme 55).



R		e.e. (%)	Yield (%)
Me	**616**	96	93
Et	**617**	>95	89
Bn	**618**	97	88

R		d.e. (%)	Yield (%)
Me	**613**	96	88
Et	**614**	96	62
Bn	**615**	97	85

Scheme 55. Reagents and conditions: (i) lithium dibenzylamide, THF, −78 °C; (ii) RX, −78 °C to rt; (iii) LiOMe, 0 °C; (iv) Pd/C, H_2 (1 atm), MeOH, rt; (v) LiOH, THF, H_2O, Δ; (vi) HCl(aq); (vii). Dowex 50W-X8.

Alternatively, conjugate addition of lithium dibenzylamide to 2′-isopropyl-**619** and addition of 2-pyridone to achieve stereoselective protonation gave an inseparable 95:5 mixture of diastereoisomers with (4*S*,2′*R*)-**620** predominating (90% de), while the same procedure with 2′-phenyl-**621** gave an inseparable 88:12 mixture of diastereoisomers with (4*S*,2′*S*)-**622** predominating (76% de). The diastereoselectivity could be improved in these cases, through the conjugate addition of homochiral lithium amides to the oxazolidinones **619** and **621** and subsequent protonation. For example, conjugate addition of lithium amide (*S*)-**31** to 2′-isopropyl-**619** and addition of 2-pyridone as the proton source gave (4*S*,2′*R*)-**623** in 85% yield and 94% de, while conjugate addition of lithium amide (*R*)-**31** to 2′-phenyl-**621** and protonation with 2-pyridone gave, after purification, (5*S*,2′*S*)-**624** in 73% yield and 96% de (Scheme 56).[213]

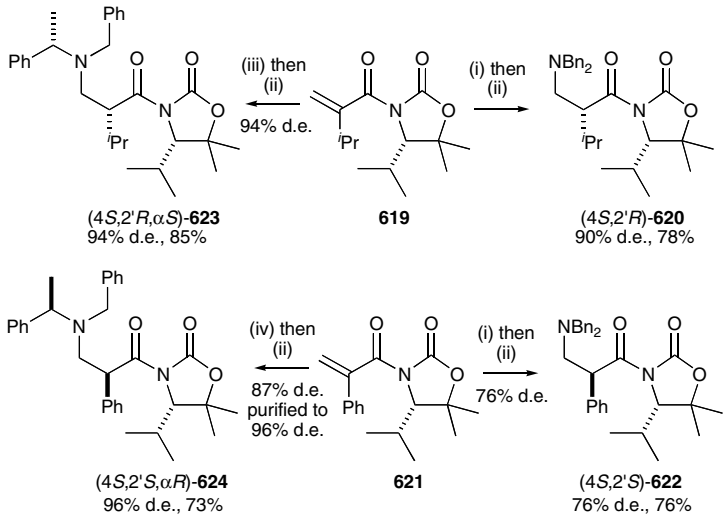
9. Heterocycle synthesis

This lithium amide conjugate addition methodology has been utilised as the cornerstone of numerous target directed syntheses of heterocyclic products and natural products of biological significance.

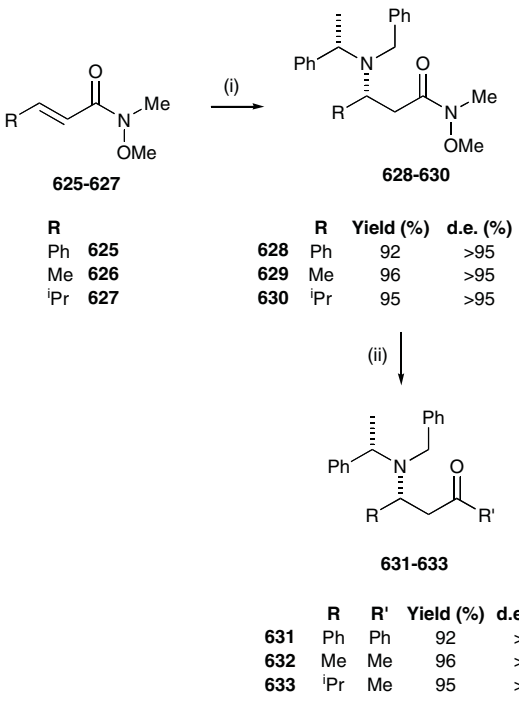
9.1. Asymmetric synthesis of piperidine and pyrrolidine skeletons

N-Protected α-amino aldehydes and ketones have been widely used as building blocks in natural product synthesis,[214] with notable targets employing this molecular class including amino sugars,[215] amino acids[216] and pyrrolidines.[217] In contrast, there is a lack of general methods for the asymmetric synthesis of homochiral β-amino aldehydes and ketones, partially due to their inherent instability.[218] However, conjugate addition of lithium amide (*S*)-**31** to α,β-unsaturated Weinreb amides **625**–**627** gave the corresponding β-amino Weinreb amides **628**–**630** in >95% de and in excellent (>90%) isolated yields, which upon treatment with Grignard reagents or alkyllithiums gave good conversion to the corresponding β-amino ketones **631**–**633** (Scheme 57).[43,44]

Alternatively, treatment of β-amino Weinreb amides **628**–**630** with DIBAL in THF at −78 °C gave the corresponding aldehydes in quantitative yield, although these products proved unstable to chromatographic purification. However, trapping the aldehyde in situ through



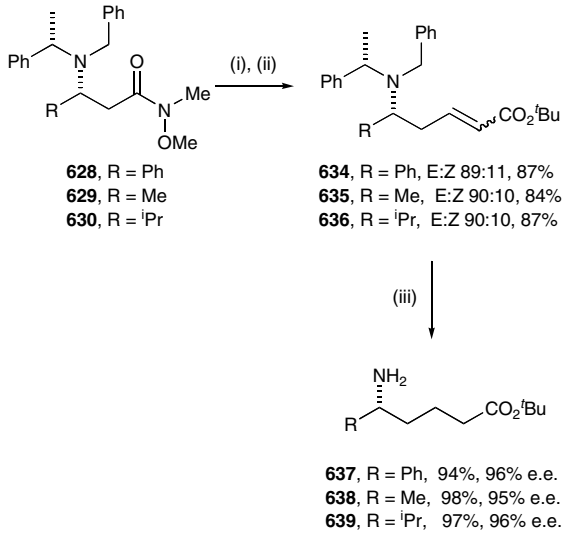
Scheme 56. Reagents and conditions: (i) lithium dibenzylamide, THF, −78 °C; (ii) 2-pyridone, THF, −78 °C to rt; (iii) lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide, THF, −78 °C; (iv) lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide, THF, −78 °C.



R		R	Yield (%)	d.e. (%)
Ph	**625**	**628** Ph	92	>95
Me	**626**	**629** Me	96	>95
^{i}Pr	**627**	**630** ^{i}Pr	95	>95

	R	R'	Yield (%)	d.e. (%)
631	Ph	Ph	92	>95
632	Me	Me	96	>95
633	^{i}Pr	Me	95	>95

Scheme 57. Reagents and conditions: (i) lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide (1.6 equiv), THF, −78 °C, then NH_4Cl(aq); (ii) R′MgBr (3 equiv), THF, 0 °C to rt.

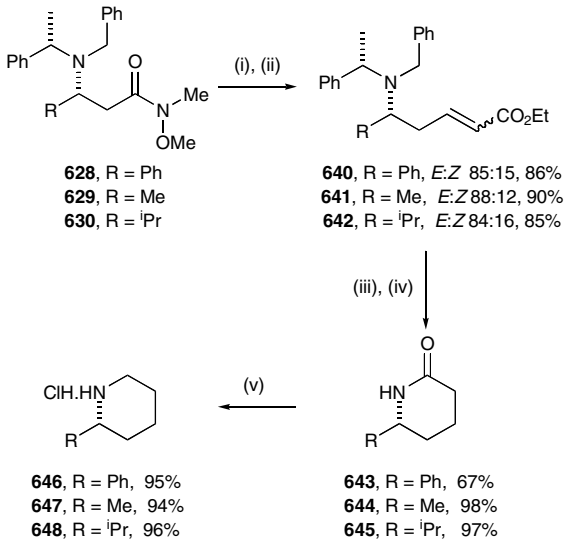


Scheme 58. Reagents and conditions: (i) DIBAL, hexanes, THF, 0 °C, then acetone, satd $C_4H_4KNaO_{6(aq)}$; (ii) $(EtO)_2POCH_2CO_2{}^{t}Bu$, *n*-BuLi, THF, −78 °C to rt; (iii) H_2 (5 atm), $Pd(OH)_2$ on C, MeOH.

Wadsworth–Emmons reaction on the crude mixture with the lithium anion of *tert*-butyl diethylphosphonoacetate gave excellent conversion to δ-amino α,β-unsaturated acceptors **634–636**, which after hydrogenation gave the δ-amino acid *tert*-butyl esters **637–639** in 94–98% yield and >95% ee (Scheme 58).[44]

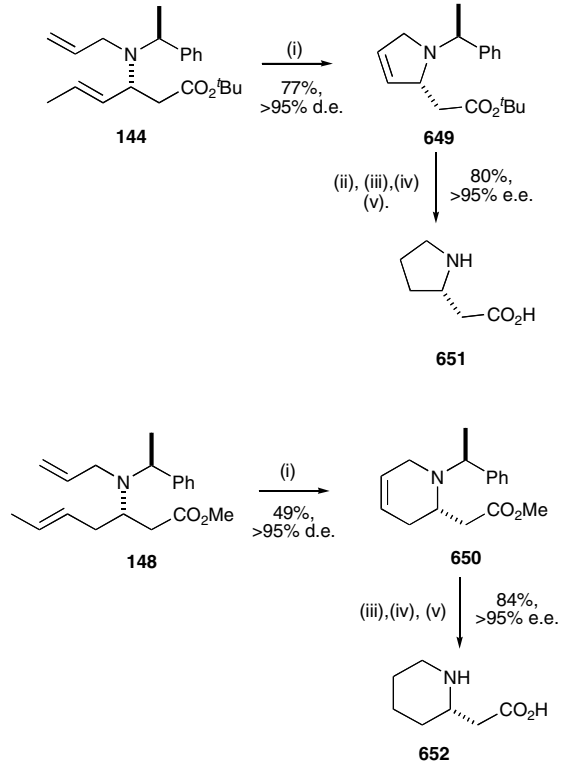
The combination of this conjugate addition and DIBAL/olefination methodology has been applied to the asymmetric synthesis of homochiral δ-lactams and 2-alkylpiperidines. Treatment of β-amino amides **628–630** with DIBAL-H and reaction of the crude reaction mixture with the lithium anion of triethylphosphonoacetate gave the ethyl δ-amino α,β-unsaturated esters **640–642** in high yields and with high diastereoselectivity. Concurrent *N*-debenzylation and reduction of the C=C upon hydrogenation, and treatment of the resulting mixture in toluene at reflux gave δ-lactams **643–645** in high yields. Reduction of δ-lactams **643–645** with $LiAlH_4$ gave, after treatment with HCl in Et_2O and purification by flash column chromatography on silica gel, 2-alkyl piperidines **646–648** as their hydrochloride salts (Scheme 59).[44]

As an alternative route to heterocyclic compounds, the *N*-allyl functionality contained within β-amino esters arising from conjugate addition of the *N*-allyl lithium amide **39** can be manipulated in a protocol involving



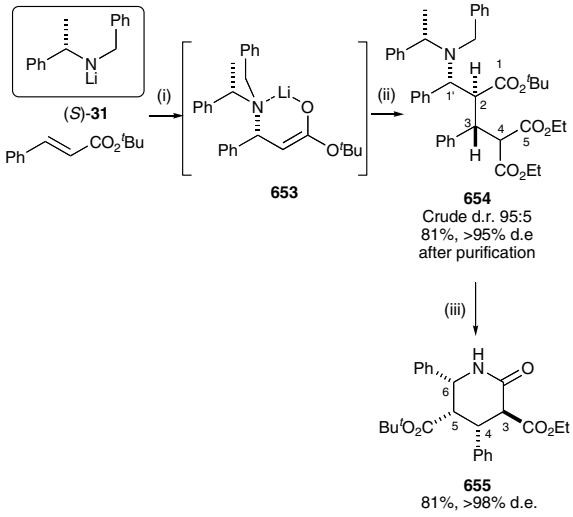
Scheme 59. Reagents and conditions: (i) DIBAL, hexanes, THF, 0 °C then acetone, satd $C_4H_4KNaO_{6(aq)}$; (ii) $(EtO)_2POCH_2CO_2{}^tBu$, *n*-BuLi, THF, −78 °C to rt; (iii) H_2 (5 atm), $Pd(OH)_2$ on C, MeOH; (iv) PhMe, Δ; (v) $LiAlH_4$, Et_2O, Δ then HCl.

functionalisation, rather than deprotection. For example, ring closing olefin metathesis of β-amino esters **144** and **148** gave the five- and six-membered cyclic β-amino esters **649** and **650**, respectively, with subsequent deprotection giving (*S*)-homoproline **651** and (*S*)-homopipecolic acid **652**, respectively, in high ee and in good overall yields (Scheme 60).[61,62]



Scheme 60. Reagents and conditions: (i) $(Cyc_3P)_2Cl_2Ru{=}CHPh$, DCM; (ii) $RhCl(PPh_3)_3$, H_2; (iii) H_2, $Pd(OH)_2$; (iv) 6 M HCl; (v) Dowex ion exchange.

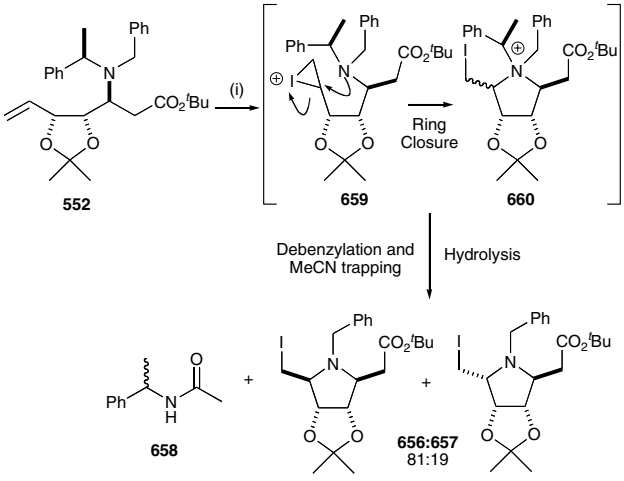
As an alternative strategy, the consecutive conjugate additions of a lithium amide to an α,β-unsaturated ester, followed by subsequent β-amino enolate conjugate addition, have been reported. For example, addition of lithium amide (*S*)-**31** (2 equiv) to *tert*-butyl cinnamate (1 equiv) gave the lithium (*Z*)-β-amino enolate **653** and subsequent addition of diethyl benzyl- idenemalonate (2 equiv) gave (2*S*,3*S*,1′*R*,α*S*)-**654** in 90% de (crude product ratio **654**:one minor diastereoisomer 95:5), with chromatographic purification giving **654** in 81% yield and in >95% de. Hydrogenolysis of β-amino ester **654** gave the tetrasubstituted piperidinone (3*S*,4*R*,5*S*,6*R*)-**655** in 81% yield and as a single diastereoisomer (>98% de) after purification (Scheme 61).[219]



Scheme 61. Reagents and conditions: (i) lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide **31**, THF, −78 °C; (ii) diethyl benzylidenemalonate (1 equiv), THF, −78 to 0 °C; (iii) $Pd(OH)_2$ on C, MeOH, H_2.

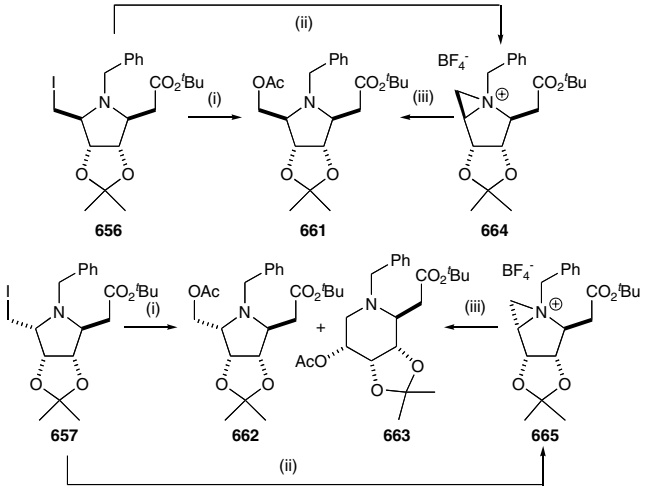
There has been much recent interest in the stereocontrolled synthesis of polyhydroxylated pyrrolidine derivatives, as these sugar mimics exhibit a diverse range of biological activities, including potential as anti-HIV candidates[220] and as glycosidase inhibitors.[221] A novel iodine mediated ring closing-debenzylation protocol provides directly the polyhydroxylated pyrrolidine skeleton from homochiral β-amino acid derivatives. Treatment of β-amino ester **552** with iodine in MeCN in the presence of $NaHCO_3$ gave a separable 81:19 mixture of *N*-benzyl pyrrolidines **656**:**657** in 63% and 17% yield, respectively, and in >95% de in each case, in which ring closure to the pyrrolidine and chemoselective *N*-deprotection had been effected in a single step. Further purification by chromatography furnished *N*-α-methylbenzylacetamide **658**, whose specific rotation $\{[\alpha]_D^{25} = -3.8$ (*c* 0.7, $CHCl_3$); lit.,[222] $[\alpha]_D^{25} = +129.5$ (*c* 1.0, $CHCl_3$)$\}$ indicated that essentially complete racemisation of the *N*-α-methylbenzyl stereocentre had occurred during the reaction. These observations are consistent with a mechanism involving formation of iodonium ion **659** and intramolecular trapping by the tethered tertiary amine to give quaternary ammonium species

660. Preferential S_N1 loss of the *N*-α-methylbenzyl protecting group accounts for the remarkable chemoselectivity observed in this reaction, with subsequent trapping with MeCN and hydrolysis giving (*RS*)-*N*-α-methylbenzylacetamide **658** (Scheme 62).[163]



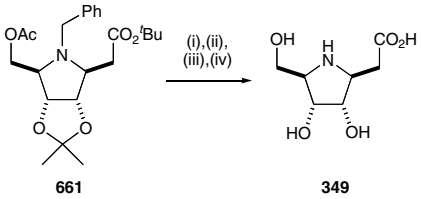
Scheme 62. Reagents: (i) I_2, $NaHCO_3$, MeCN.

Subsequent functionalisation of the primary iodide within the major diastereoisomer **656** with AgOAc in toluene gave the acetate **661** as a single diastereoisomer in 77% yield, although similar exposure of the diastereoisomeric iodide **657** gave an inseparable 45:55 mixture of the pyrrolidine and piperidine acetates **662**:**663** in 82% overall yield. The intermediacy of a bicyclic aziridinium ion in these transformations was proven by treatment of iodides **656** and **657** with $AgBF_4$, giving the corresponding isolable bicyclic aziridinium species **664** and **665**, which upon treatment with NaOAc in toluene gave identical product distributions to that observed in the direct transformation of iodides **656** and **657** to the corresponding acetates (Scheme 63).[163]



Scheme 63. Reagents and conditions: (i) AgOAc, toluene, rt; (ii) $AgBF_4$, DCM, rt; (iii) NaOAc, toluene, rt.

Further synthetic manipulation of acetate **661** by *N*-debenzylation, basic hydrolysis of the acetate, acidic hydrolysis and ion exchange gave the polyhydroxylated pyrrolidine β-amino acid **349** (Scheme 64).[163]



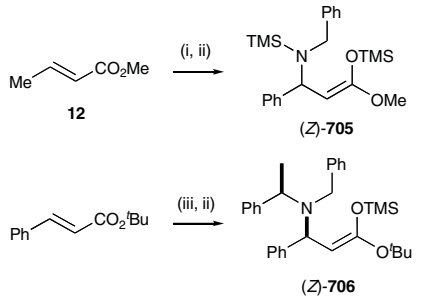
Scheme 64. Reagents and conditions: (i) $Pd(OH)_2$ on C, MeOH, H_2 (1 atm); (ii) K_2CO_3, MeOH; (iii) TFA, then H_2O; (iv) Dowex 50W-X8.

10. Synthetic applications: natural product synthesis

The conjugate addition of chiral lithium amides to α,β-unsaturated acceptors has been applied as the key step for numerous natural product syntheses (Table 16). The stereocentre formed in this conjugate addition reaction is highlighted in red in each of these natural products.

11. Mechanism of lithium amide conjugate addition

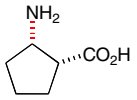
This review has demonstrated that the conjugate addition of lithium amides is widely applicable in synthesis. Despite its widespread utility, a full mechanistic picture of this reaction has yet to be delineated. However, Yamamoto et al. have demonstrated that conjugate addition of LSA **25** to methyl crotonate **12** and subsequent addition of TMSCl gives the (*Z*)-silylketene acetal **705** as a single diastereoisomer, while Davies et al. have similarly shown that conjugate addition of lithium amide (*R*)-**31** to *tert*-butyl cinnamate and addition of TMSCl generate the (*Z*)-silylketene acetal **706**.[152] Both of these selectivities are consistent with addition of the lithium amide to the corresponding α,β-unsaturated acceptor in the *s-cis* conformation (Scheme 65).



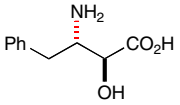
Scheme 65. Reagents and conditions: (i) LSA, THF, −78 °C; (ii) TMSCl, −78 °C to rt; (iii) lithium (*R*)-*N*-benzyl-*N*-a-methylbenzylamide, THF, −78 °C.

Using this information, the high diastereoselectivity observed upon addition of homochiral lithium amide (*R*)-**31** to α,β-unsaturated esters has been rationalised

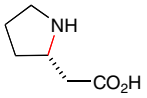
Table 16.



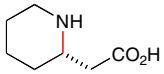
327
Cispentacin
Ref 141, Ref 142



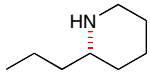
345
Allophenylnorstatine
Ref 158



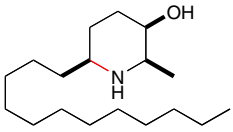
347
(*S*)-Homoproline
Ref 61, Ref 62



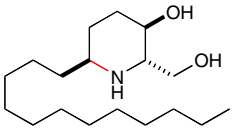
348
(*S*)-Homopipecolic Acid
Ref 61, Ref 62



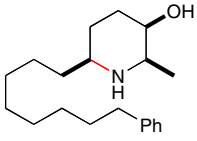
667
(*S*)-Coniine
Ref 44, Ref 61
Ref 62



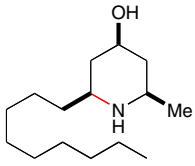
668
(-)-Deoxocassine
Ref 71



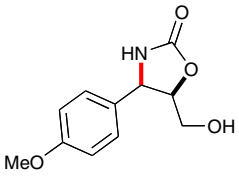
669
(-)-Deoxoprosophylline
Ref 223



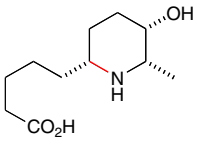
670
(-)-Irnigaine
Ref 101



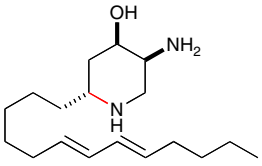
671
Dendrobate Alkaloid (+)-241D
Ref 136



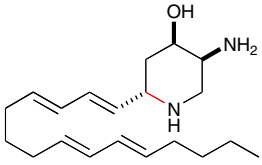
666
Cytoxazone
Ref 155



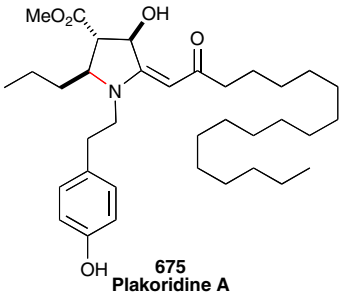
672
(+)-Azimic Acid
Ref 71



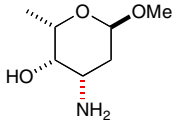
673
Pseudodistomin B
Ref 53



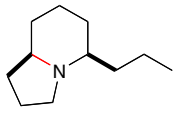
674
Pseudodistomin F
Ref 53



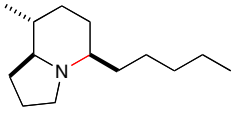
675
Plakoridine A
Ref 63



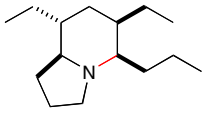
676
L-Daunosamine
Ref 86, Ref 87



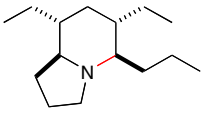
677
(-)-Indolizidine 167B
Ref 57, Ref 136: Formal Synthesis
Ref 55: Total Synthesis



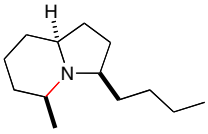
678
(-)-Indolizidine 209B
Ref 64, Ref 68



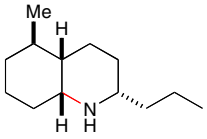
679
Indolizidine 223A
Ref 176



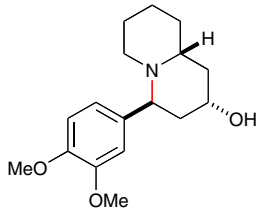
680
6-*epi*-Indolizidine 223A
Ref 59



681
(+)-Monomorine
Ref 224

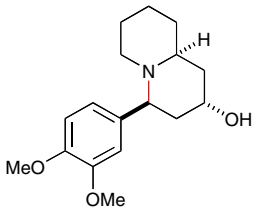


682
(-)-Pumiliotoxin
Ref 150

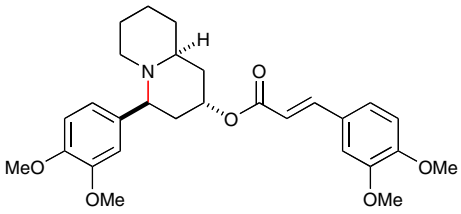


683
(-)-Lasubine I
Ref 119

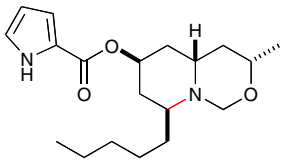
Table 16 (*continued*)



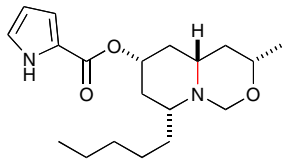
684
(-)-Lasubine II
Ref 119



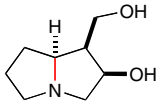
685
(+)-Subcosine II
Ref 119



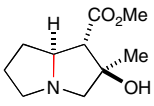
690
Hyperaspine
Ref 67



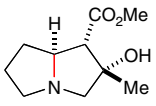
691
(-)-8-*epi*-Hyperaspine
Ref 137



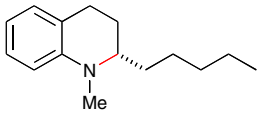
687
(-)-Petasinecine
Ref 76



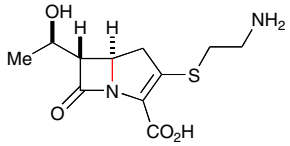
688
Isotussilagine
Ref 75, Ref 76



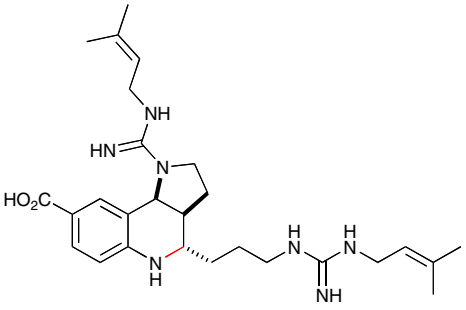
689
Tussilagine
Ref 75, Ref 76



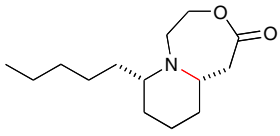
686
(+)-Angustureine
Ref 66



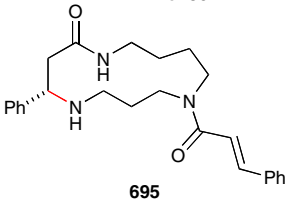
693
Thienamycin
Ref 82, Ref 100



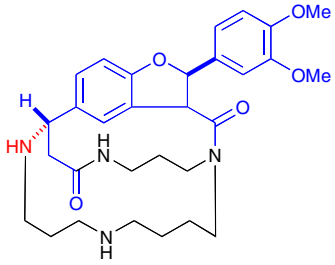
694
Martinellic Acid
Ref 135, Ref 77



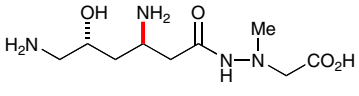
692
(+)-Calvine
Ref 80



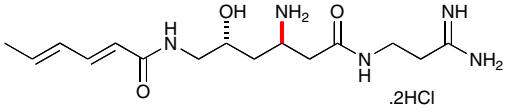
695
(+)-(*S*)-Dihydroperiphylline
Ref 102



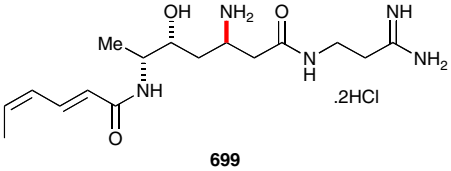
696
Ephedradine C (Northern segment)
Ref 139, Ref 140



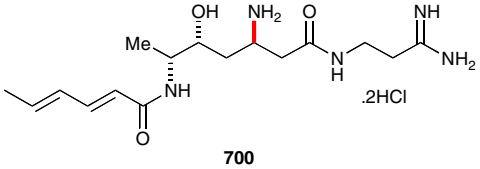
697
(+)-Negamycin
Ref 199



698
Sperabillin C
Ref 115



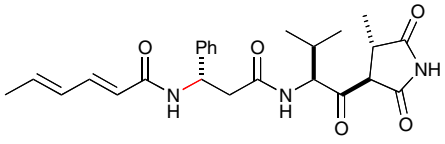
699
Sperabillin B
Ref 93, Ref 94



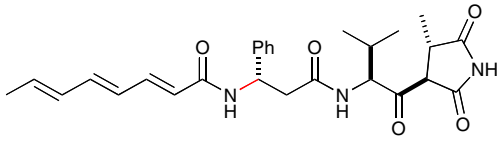
700
Sperabillin D
Ref 93, Ref 94

(*continued on next page*)

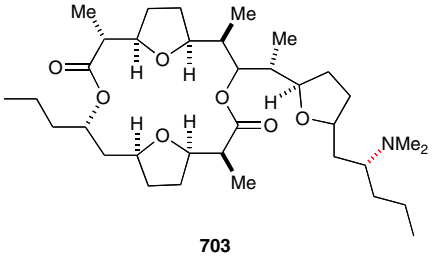
Table 16 (*continued*)



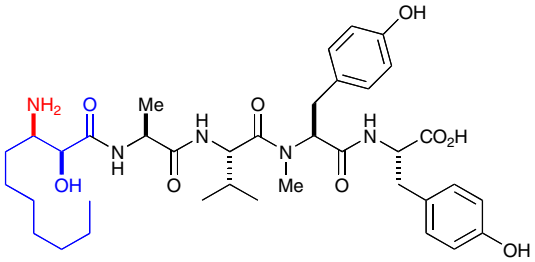
701
Moiramide B
Ref 103, Ref 104



702
Andrimid
Ref 104



703
Pamamycin 607
Ref 60



704
Microginin (β-amino acid fragment)
Ref 69, Ref 161

by simple molecular modelling calculations, allowing the development of a mnemonic that predicts the sense of asymmetric induction in these reactions.[225] Allowing for lithium chelation between the amide nitrogen and the ester carbonyl, at distances between the amide nitrogen and the β-carbon of approximately 3.0–4.5 Å the phenyl rings of the lithium amide are thought to adopt a splayed arrangement about the developing bond (**707**). At distances of 1.7–3.0 Å (close to initial bonding interaction distances) a conformational reorganisation occurs, placing the phenyl rings approximately parallel (**708**). To minimise steric interactions in the transition state, the *N*-α-methyl group prefers to occupy the position above the C(3) olefinic hydrogen atom rather than above the carbon chain. Analysis of Newman projections **709**–**712**, viewed along the developing N–C bond, illustrates why transition state **709** is favoured, since only in this conformation can the methyl group occupy a sterically undemanding position, meaning that the (*R*)-amide favours addition to the *Si* face of *tert*-butyl cinnamate (Fig. 9). A molecular modelling approach has also been used by Hawkins to rationalise the stereochemical outcome of the addition of lithium amide **27** to α,β-unsaturated esters.[226]

These studies have furnished only limited insight into the mechanism of this transformation. As racemic lithium amide (*RS*)-**31** shows 2:1 stoichiometry but the homochiral lithium amide **31** shows 1:1 stoichiometry with either (*RS*)- or homochiral iron acyl complex **561**, it is tempting to invoke a dimeric lithium amide complex as the reactive species in the conjugate addition reaction. However, kinetic analysis of the reaction is hampered by the reaction efficiency, as under typical concentrations the reaction is essentially complete instantaneously at −78 °C. There is clearly a need for the development of

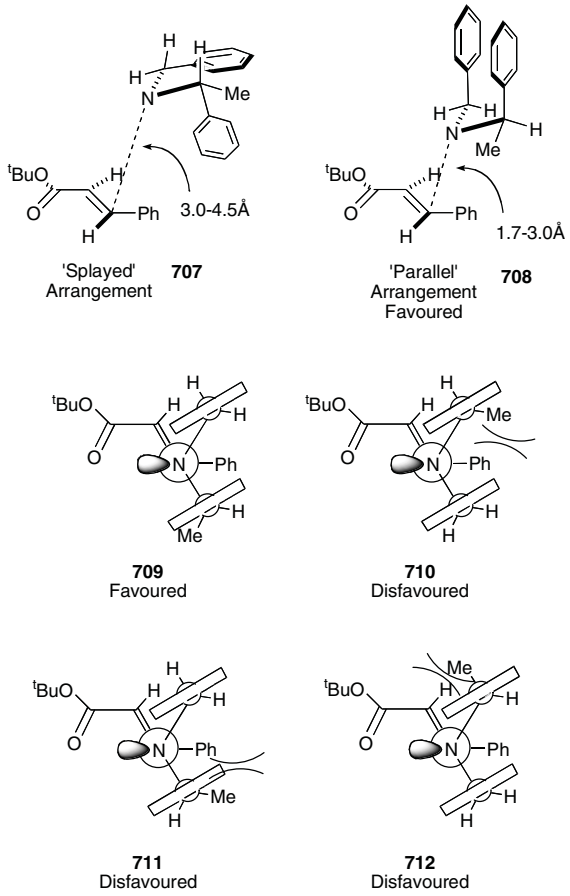


Figure 9. Proposed transition states for conjugate addition (Li omitted for clarity).

a more detailed understanding of this reaction; current investigations within our laboratory are focused upon

the further understanding and synthetic applications of this successful methodology.

12. Conclusion

In conclusion, the ability of homochiral lithium amides to act as homochiral ammonia equivalents through their conjugate addition to α,β-unsaturated acceptors has been shown to be a highly versatile, reliable and scaleable methodology that has been applied to an enormous variety of synthetic transformations. This ever-expanding area of research has been widely adapted by the synthetic community over the last fifteen years and continues to find novel and interesting applications in synthesis today.

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