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Double asymmetric induction as a mechanistic probe: the doubly diastereoselective conjugate addition of enantiopure lithium amides to enantiopure α,β-unsaturated esters and enantiopure α,β-unsaturated hydroxamates

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ABSTRACT

The doubly diastereoselective conjugate addition of the antipodes of lithium *N*-benzyl-*N*-(α-methylbenzyl)amide to a range of enantiopure α,β-unsaturated esters [derived from Corey's 8-phenylmenthol chiral auxiliary] and enantiopure α,β-unsaturated hydroxamates [derived from our 'chiral Weinreb amide' auxiliary (*S*)-*N*-1-(1′-naphthyl)ethyl-*O*-*tert*-butylhydroxylamine] has been used as a mechanistic probe to determine the reactive conformations of these acceptors.

1. Introduction

Previous investigations from this laboratory have demonstrated that the conjugate addition of enantiopure secondary lithium amides (derived from α-methylbenzylamine) to α,β-unsaturated esters represents a general and efficient synthetic protocol for the synthesis of β-amino esters and their derivatives.[1] This methodology has found numerous applications, including the total syntheses of natural products,[2] molecular recognition phenomena[3] and resolution protocols[4] and has been reviewed.[5] For instance, we have recently elaborated the use of double asymmetric induction as a mechanistic probe to elucidate the reactive conformation of enantiopure *N*-enoyl oxazolidin-2-ones upon the conjugate addition of an enantiopure lithium amide.[5,6] In this study, the doubly diastereoselective conjugate additions of the antipodes of lithium *N*-benzyl-*N*-(α-methylbenzyl)amide **1** to a range of enantiopure *N*-enoyl oxazolidin-2-ones were investigated. For example, the conjugate addition of (*R*)-**1** to *N*-enoyl oxazolidin-2-one **2** gave **3** with relatively low diastereoselectivity (83:17 dr) representing the doubly diastereoselective 'mismatched' pairing of chiral reagents, whereas the corresponding addition of (*S*)-**1** gave **4** as a single diastereoisomer (>99:1 dr) representing the doubly diastereoselective 'matched' reaction pairing. These data, in combination with the well established diastereofacial preference observed upon addition of lithium *N*-benzyl-*N*-(α-methylbenzyl) amide **1** to achiral α,β-unsaturated esters and amides,[1] allowed the *anti-s-cis* form of *N*-enoyl oxazolidin-2-one **2** to be identified as the reactive conformation (Fig. 1).

We envisaged that double asymmetric induction could be further exploited as a mechanistic probe to elucidate the reactive conformation of other chiral α,β-unsaturated carbonyl compounds upon conjugate addition. We proposed to investigate the diastereoselectivity elicited upon conjugate addition of the antipodes of lithium *N*-benzyl-*N*-(α-methylbenzyl)amide **1** to enantiopure α,β-unsaturated carbonyl compounds, such as ester **5** [derived from Corey's 8-phenylmenthol chiral auxiliary **6**[7]] and hydroxamate **7** [derived from our 'chiral Weinreb amide' auxiliary (*S*)-*N*-1-(1′-naphthyl)ethyl-*O*-*tert*-butylhydroxylamine **8**[8]] (Fig. 2). We report herein our findings within this area.

2. Results and discussion

2.1. Conjugate additions to chiral α,β-unsaturated esters

Corey's 8-phenylmethol auxiliary **8** has shown considerable versatility in synthesis[9] and found use in, for example, nucleophilic addition reactions,[10] cycloadditions,[11] intermolecular ene reactions,[12]

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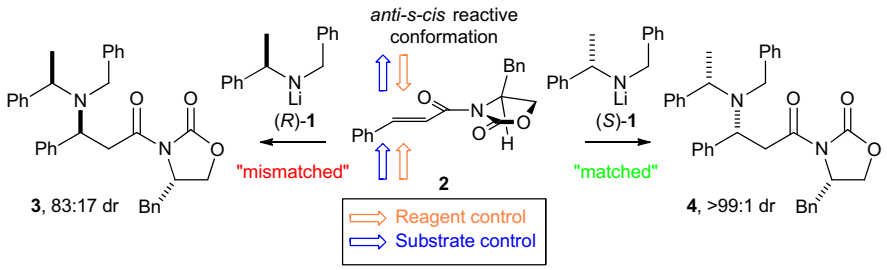


Fig. 1. The doubly diastereoselective conjugate addition of the antipodes of lithium *N*-benzyl-*N*-(α-methylbenzyl)amide **1** to enantiopure *N*-enoyl oxazolidin-2-one **2** in the *anti-s-cis* reactive conformation.

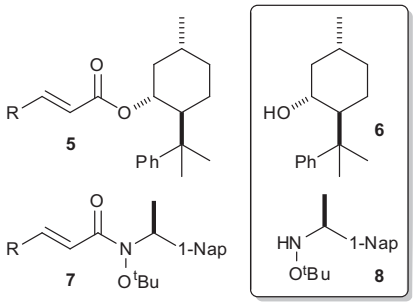
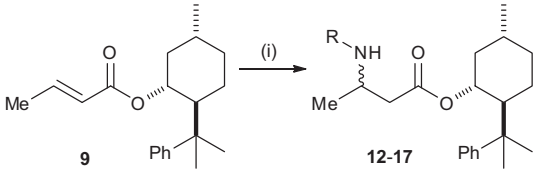


Fig. 2. Enantiopure α,β-unsaturated esters **5** [derived from Corey's 8-phenylmenthol chiral auxiliary **6**] and enantiopure α,β-unsaturated hydroxamates **7** [derived from (*S*)-*N*-1-(1′-naphthyl)ethyl-*O*-*tert*-butylhydroxylamine **8**]. [1-Nap=1-naphthyl].

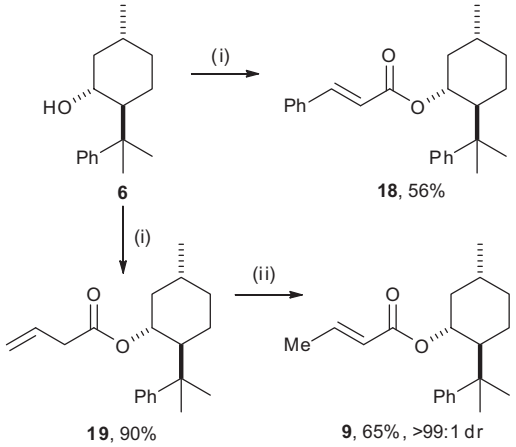
oxidation reactions,[13] reduction reactions,[14] rearrangement processes,[15] photochemical/radical reactions[16] and as a resolving agent.[17] α,β-Unsaturated esters of this chiral alcohol have also shown application as substrates in diastereoselective conjugate addition reactions.[18] One notable example reported by d'Angelo and Maddaluno, however, describes the high pressure induced conjugate addition of primary amines to chiral α,β-unsaturated esters, such as **9**.[19] The authors report that whilst moderate levels of diastereoselectivity were obtained upon conjugate addition of primary amines to **9** it is noteworthy that '*the double diastereodifferentiation phenomenon was not observed*' upon addition of either (*R*)- or (*S*)-α-methylbenzylamine **10** to **9** (Scheme 1). This finding is consistent with the poor diastereoselectivity observed upon thermal addition of (*S*)-α-methylbenzylamine **10** to methyl crotonate, which has been reported to give a 54:46 epimeric mixture of β-amino esters.[20] In contrast, the conjugate addition of secondary lithium amides, such as lithium *N*-benzyl-*N*-(α-methylbenzyl)amide **1** to a range of achiral α,β-unsaturated esters at −78 °C in THF has consistently been shown to proceed with extremely high levels of diastereoselectivity (typically >95:5 dr).[5] We therefore proposed to use this reaction to identify the reactive conformations of 8-phenylmenthyl α,β-unsaturated esters upon the conjugate addition of a lithium amide using the tool of double asymmetric induction.



RNH_2	R	products	dr	combined yield (%)
(*R*)-**10**	(*R*)-CHMePh	**12**:**13**	75:25	60
(*S*)-**10**	(*S*)-CHMePh	**14**:**15**	80:20	60
11	Bn	**16**:**17**	80:20	90

Scheme 1. Reagents and conditions: (i) RNH_2, MeOH, 15 kbar, 50 °C, 24 h.

8-Phenylmenthyl crotonate **9** and 8-phenylmenthyl cinnamate **18** were selected as model substrates for this investigation and were therefore synthesised by coupling the requisite acid chlorides and 8-phenylmenthol **6**. Thus, auxiliary **6** was prepared on a >10 g scale in 36% overall yield from (+)-(*R*)-pulegone[21] according to a literature procedure.[22] Subsequent treatment of **6** with cinnamoyl chloride in the presence of Hünig's base gave **18** in 56% isolated yield. However, treatment of **6** with crotonoyl chloride under the same conditions gave β,γ-unsaturated ester **19** in 90% yield as the only product isolated; subsequent isomerisation of **19** upon treatment with DBU gave α,β-unsaturated ester **9** in 65% yield and >99:1 dr (Scheme 2).



Scheme 2. Reagents and conditions: (i) RCOCl, $^{i}Pr_2NEt$, THF, rt, 18 h; (ii) DBU, THF, rt, 18 h.

^{1}H NMR spectroscopic analysis of 8-phenylmenthyl α,β-unsaturated esters **9** and **18** and the corresponding methyl esters suggests that the phenyl group of the auxiliary effectively shields one face of the olefin.[23] There are four conformations of an 8-phenylmenthyl α,β-unsaturated ester where this shielding is possible: two *s-cis* conformations **20A** and **20B**, and two *s-trans* conformations **20C** and **20D** (Fig. 3).[24] Upon conjugate addition, the same product would arise from attack on the least hindered face of both conformations **20A** and **20D**, and the other diastereoisomer would result from attack on the least hindered face of both conformations **20B** and **20C**. Several enolate trapping studies following the conjugate addition of lithium amides to both chiral[6b] and achiral[25] substrates have concluded that the lithium (*Z*)-β-amino enolate arises from conjugate addition to the acceptor in an *s-cis* reactive conformation. Assuming that these findings are consistent with the conjugate addition of a lithium amide to 8-phenylmenthyl α,β-unsaturated esters **9** and **18**, either conformation **20A** or **20B** will be the reactive conformation upon conjugate addition.

The doubly diastereoselective conjugate addition of both antipodes of lithium *N*-benzyl-*N*-(α-methylbenzyl)amide **1** to **9** and **18**

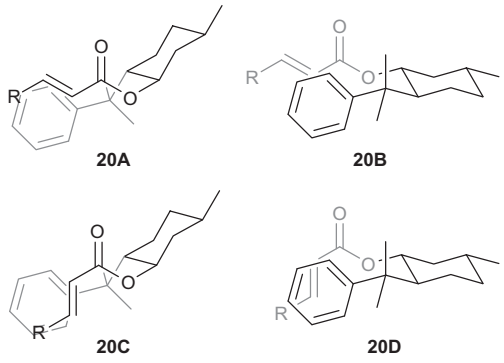


Fig. 3. Possible conformations of **20**: *s-cis* **20A** and **20B**, and *s-trans* **20C** and **20D**.

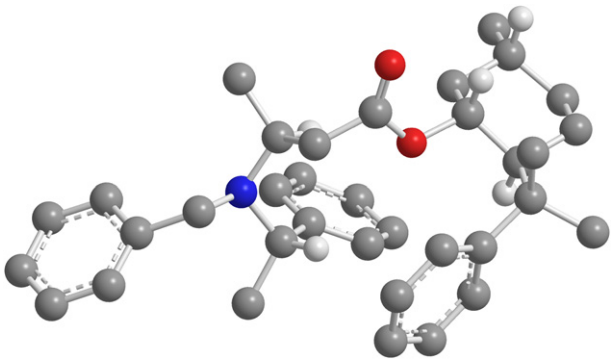
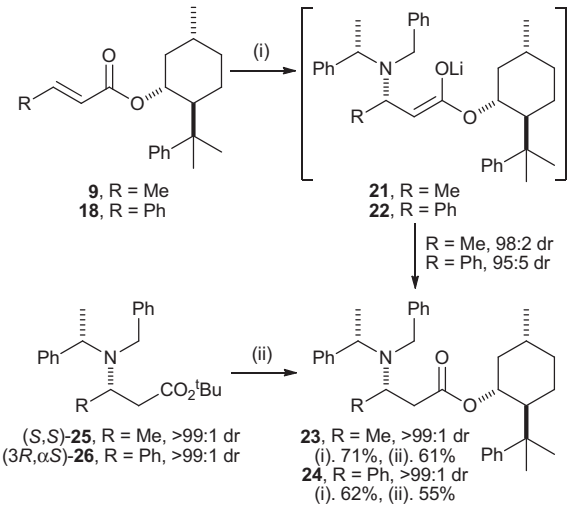


Fig. 4. X-ray crystal structure of (3*S*,1′*R*,2′*S*,5′*R*,α*S*)-**23** (some H atoms are omitted for clarity).

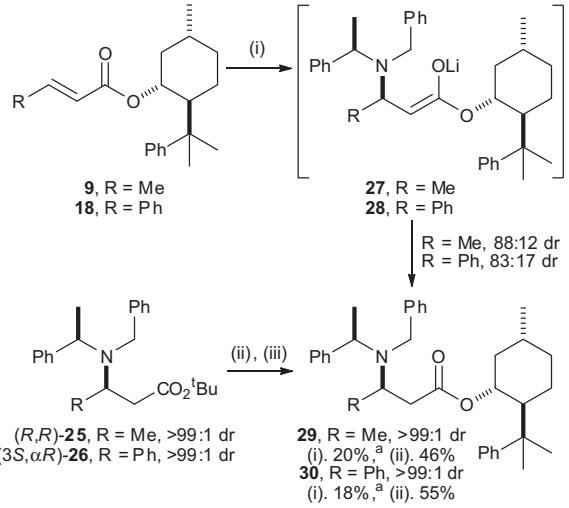
were next investigated. Thus, the conjugate additions of (*S*)-**1** to both **9** and **18** proceeded with high diastereoselectivity giving **23** and **24** in 98:2 and 95:5 dr, respectively; in both cases the major diastereoisomeric products were isolated as single diastereoisomers (>99:1 dr) after chromatographic purification. The configurations at C(3) within β-amino esters **23** and **24** were unambiguously established by a separate chemical synthesis in each case: β-amino esters (*S*,*S*)-**25** and (3*R*,α*S*)-**26** [obtained from the conjugate addition of lithium amide (*S*)-**1** to *tert*-butyl crotonate and *tert*-butyl cinnamate, respectively][1a,26] were treated with TFA to give the corresponding carboxylic acids, which were coupled with Corey's auxiliary **6** via the intermediacy of the corresponding acid chlorides. The spectroscopic properties, including specific rotation values, of the samples of β-amino esters **23** and **24** prepared in this manner were identical to the major diastereoisomers arising from the conjugate addition of lithium amide (*S*)-**1** to **9** and **18**, providing unequivocal evidence of the sense of stereoinduction observed in these reactions (Scheme 3). Furthermore, the relative configuration within **23** was also unambiguously assigned by single crystal X-ray diffraction analysis,[27] with the absolute (3*S*,1′*R*,2′*S*,5′*R*,α*S*)-configuration assigned relative to the known configurations of both the (+)-(*R*)-pulegone derived auxiliary **6** and the (*S*)-α-methylbenzyl stereocentre (Fig. 4).



Scheme 3. Reagents and conditions: (i) (*S*)-**1**, THF, −78 °C, 2 h; (ii) TFA/CH_2Cl_2 (v/v 1:1), rt, 2 h, then $(COCl)_2$, DMF, CH_2Cl_2, 0 °C to rt, 1 h then **6**, CH_2Cl_2, rt, 18 h.

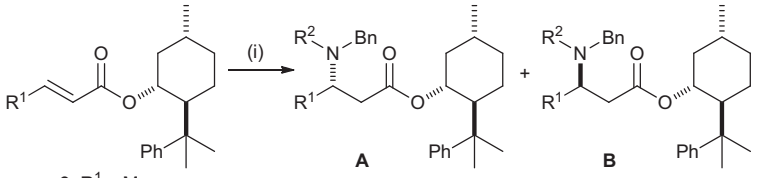
Upon conjugate addition of (*R*)-**1** to both **9** and **18** lower levels of diastereoselectivity were observed, giving **29** and **30** as the major products in 88:12 and 83:17 dr, respectively; in both cases the major diastereoisomeric products were isolated as single diastereoisomers (>99:1 dr) after chromatographic purification.[28]

Again, the configurations at C(3) within β-amino esters **29** and **30** were established unambiguously by a separate chemical synthesis in each case. β-Amino esters (*R*,*R*)-**25** and (3*S*,α*R*)-**26** [obtained from the conjugate addition of lithium amide (*R*)-**1** to *tert*-butyl crotonate and *tert*-butyl cinnamate, respectively][26] were treated with TFA to give the corresponding carboxylic acids, which were coupled with Corey's auxiliary **6** via the intermediacy of the corresponding acid chlorides. The spectroscopic properties, including specific rotation values, of the samples of β-amino esters **29** and **30** prepared in this manner were identical to the major diastereoisomers arising from the conjugate addition of lithium amide (*R*)-**1** to **9** and **18**, providing unequivocal evidence of the sense of stereoinduction observed in these reaction pairings (Scheme 4). The conjugate additions of (*S*)-**1** to both **9** and **18** therefore represent the doubly diastereoselective 'matched' reaction pairings, and the conjugate additions of (*R*)-**1** to both **9** and **18** proceeded under the dominant stereocontrol of the lithium amide reagent representing the doubly diastereoselective 'mismatched' reaction pairings.



Scheme 4. Reagents and conditions: (i) (*R*)-**1**, THF, −78 °C, 2 h; (ii) TFA/CH_2Cl_2 (v/v 1:1), rt, 2 h, then $(COCl)_2$, DMF, CH_2Cl_2, 0 °C to rt, 1 h; (iii) **6**, CH_2Cl_2, rt, 18 h [[a] mixed fractions were also isolated, see Ref. 28].

In addition, the conjugate additions of achiral lithium dibenzylamide **31**[29] and lithium *N*-isopropyl-*N*-benzylamide **32**[4a–c] to these substrates were also conducted to assess the extent of substrate control in these systems. The conjugate additions of both achiral lithium amides **31** and **32** to both **9** and **18** proceeded with the same sense of stereoinduction and modest levels of diastereoselectivity (up to 80:20 dr). In the case of addition of these lithium amides to **9** the major diastereoisomers were isolated in >99:1 dr, although



Michael acceptor	lithium amide	R^1	R^2	A	B	crude dr (A:B)	yield of A (%)	yield of B (%)
9	**31**	Me	Bn	**33**	**37**	78:22	25 (>99:1 dr)	10 (63:37 dr)
9	**32**	Me	^{i}Pr	**34**	**38**	72:28	9[a] (>99:1 dr)	--
18	**31**	Ph	Bn	**35**	**39**	65:35	85 (65:35 dr)	--
18	**32**	Ph	^{i}Pr	**36**	**40**	80:20	78 (80:20 dr)	--

Scheme 5. Reagents and conditions: (i) LiNR^{2}Bn, THF, −78 °C, 2 h [[a] a mixed fraction was also isolated, see Ref. 30].

the addition products derived from **18** proved to be inseparable and were therefore isolated as mixtures of C(3)-epimers (Scheme 5).[30]

In order to assign the configurations within β-amino esters **33**–**40** the stereochemical outcomes of these reactions were next correlated with the products arising from conjugate addition of lithium amides (*S*)-**1** and (*R*)-**1** to **9** and **18**. Thus, the *N*-benzyl and *N*-α-methylbenzyl groups within β-amino esters **23**, **24**, **29** and **30** were removed via hydrogenolysis in the presence of Pearlman's catalyst [$Pd(OH)_2$/C] to give **41**–**44** in 61–98% yield as single diastereoisomers (>99:1 dr) in each case. β-Amino esters **41**–**44** were then treated with BnBr in the presence of K_2CO_3 at 100 °C to provide authentic samples of the *N*,*N*-dibenzyl substituted β-amino esters **33**, **35**, **37** and **39** in 86–95% yield and >99:1 dr. β-Amino esters **41**–**44** were also subjected to a reductive alkylation procedure to give single diastereoisomers of the *N*-isopropyl substituted analogues **45**–**48** in 62–83% yield and >99:1 dr. Finally, treatment of **45**–**48** with BnBr provided access to authentic samples of the *N*-isopropyl-*N*-benzyl substituted β-amino esters **34**, **36**, **38** and **40** in 75–90% yield and >99:1 dr (Scheme 6). Furthermore, the relative configuration within **33** was also unambiguously assigned by single crystal X-ray diffraction analysis,[27] with the absolute (3*S*,1′*R*,2′*S*,5′*R*)-configuration assigned relative to the known configuration of the (+)-(*R*)-pulegone derived auxiliary **6** (Fig. 5).

2.2. The origins of diastereoselectivity observed upon conjugate addition to 8-phenylmenthyl α,β-unsaturated esters

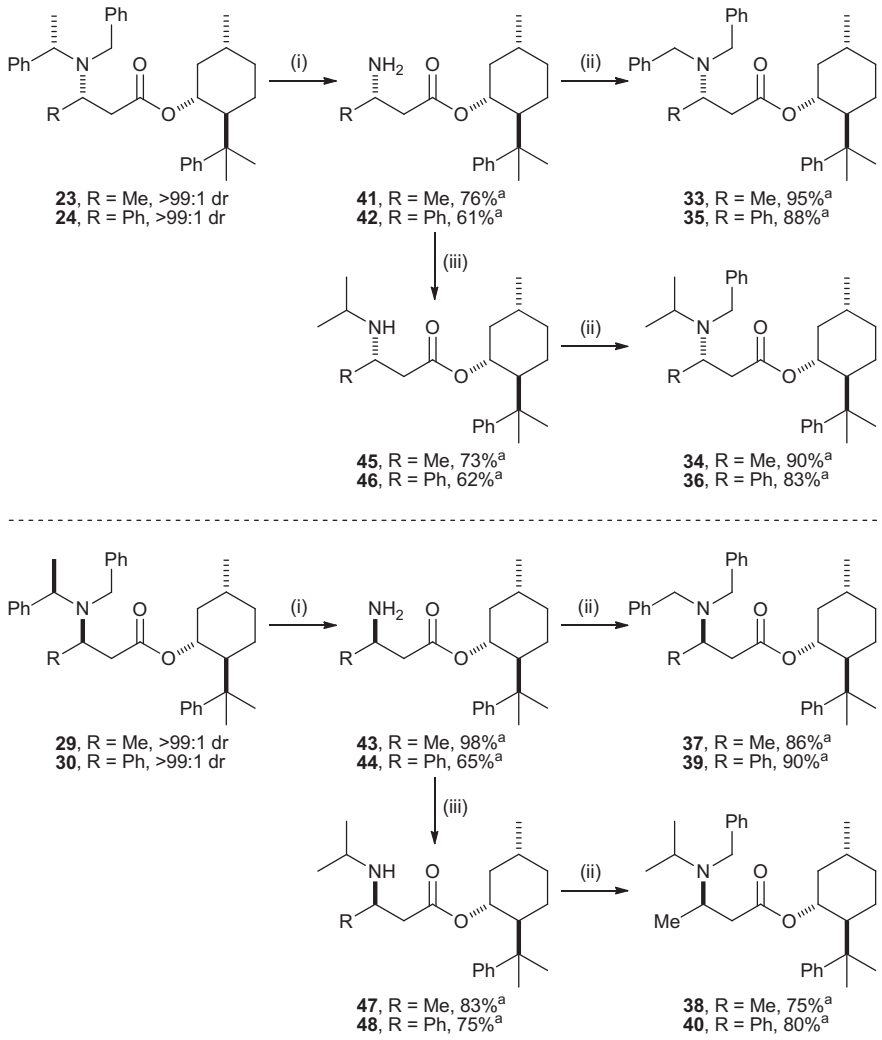
Considering the double asymmetric induction observed upon addition of the antipodes of lithium *N*-benzyl-*N*-(α-methylbenzyl) amide **1** to both **9** and **18**, in the 'matched' cases conjugate addition of (*S*)-**1** to **9** results in the preferential formation of **23** in 98:2 dr, and addition of (*S*)-**1** to **18** results in the preferential formation of **24** in 95:5 dr. In the 'mismatched' cases, conjugate addition of (*R*)-**1** to **9** results in the formation of **29** in 88:12 dr, and the addition of (*R*)-**1** to **18** results in the formation of **30** in 83:17 dr. These empirical 'matched' and 'mismatched' product distributions cannot be achieved if the reaction were to proceed through *s-cis* conformation **20A**, but is consistent with addition of lithium amides (*S*)-**1** and (*R*)-**1** to **9** and **18** in *s-cis* conformation **20B**. In this model, the preferential addition of lithium amide (*S*)-**1** to the back face of the double bond as drawn within **20B** (reagent control) coincides with addition opposite to the bulky stereodirecting group of the auxiliary (substrate control), and is consistent with the formation of **23** and **24** in the 'matched' reactions. The formation of **29** and **30** as the major diastereoisomers in the 'mismatched' cases may occur via approach of the lithium amide (*R*)-**1** on the same face as the stereodirecting phenyl group of the auxiliary in conformation **20B**, although these data do not discount the possibility that the formation of **29** and **30** may occur via preferential addition of (*R*)-**1** to **9** and **18** in an alternative conformation (Fig. 6).

2.3. Conjugate additions to chiral α,β-unsaturated hydroxamates

We have previously established that the alkylations of enolates derived from *N*-1-(1′-naphthyl)ethyl-*O*-*tert*-butylhydroxamates, such as **49** proceed with high levels of diastereoselectivity (>95:5 dr) to give access to the corresponding enantiopure α-stereogenic aldehydes or ketones **52** in >95:5 er following treatment of the intermediate hydroxamates **51** with either $LiAlH_4$ or MeLi.[8a,c] A combination of evidence gained through experimental observations (including modification of the auxiliary structure), physical measurements, and molecular mechanics calculations, was found to validate a 'chiral relay'[31] mechanism, which was proposed to rationalise the observed stereochemical outcome in these reactions.[8b] It was shown that deprotonation of **49** with KHMDS leads to a non-chelated (*Z*)-enolate **50** with the oxygen atoms adopting an *anti*-periplanar conformation. The configuration of the *N*-1-(1′-naphthyl)ethyl group dictates the position of the *O*-*tert*-butyl group and the configuration adopted by the pyramidal nitrogen atom. Subsequent enolate alkylation occurs on the face *anti* to both the *O*-*tert*-butyl group (steric control) and *N*-lone pair (stereoelectronic control). Based on these alkylation studies we envisaged that α,β-unsaturated hydroxamates **7** [derived from our 'chiral Weinreb amide' auxiliary (*S*)-*N*-1-(1′-naphthyl)ethyl-*O*-*tert*-butylhydroxylamine **8**] may undergo conjugate addition reactions with high levels of diastereocontrol at the β-position. We therefore proposed to evaluate this hypothesis upon the conjugate addition of **31**, **32** and the antipodes of **1** to α,β-unsaturated hydroxamates **7**, and also use the tool of double asymmetric induction to identify the reactive conformation of **7** in this case (Fig. 7).

Enantiopure α,β-unsaturated hydroxamates **54** and **55** were prepared in 88 and 94% yield by reaction of (*S*)-*N*-1-(1′-naphthyl) ethyl-*O*-*tert*-butylhydroxylamine **8** with crotonyl and cinnamoyl chlorides, respectively (Scheme 7). The ^{1}H and ^{13}C NMR spectra of **54** and **55** were indicative of these compounds being rotameric in $CDCl_3$ at rt; however, ^{1}H NMR spectroscopic analysis of both **54** and **55** at 343 K in PhMe-d_8 revealed that peak coalescence had occurred.

The solid state conformations of **54** and **55** were also investigated by single crystal X-ray diffraction (Fig. 8).[27] In both cases the conformation of the 'chiral Weinreb amide' auxiliary was found to be consistent with our previous observations concerning this class of hydroxamates,[32] i.e., that the oxygen atoms adopt an *anti*-periplanar conformation, the *O*-*tert*-butyl group is approximately perpendicular to this plane, the nitrogen atom is pyramidalized, and the nitrogen



Scheme 6. Reagents and conditions: (i) H_2 (5 atm), $Pd(OH)_2/C$, MeOH, AcOH, rt, 18 h; (ii) BnBr, K_2CO_3, 100 °C, 7 h; (iii) acetone, $NaBH_3CN$, MeOH, rt, 18 h [[a] isolated in >99:1 dr].

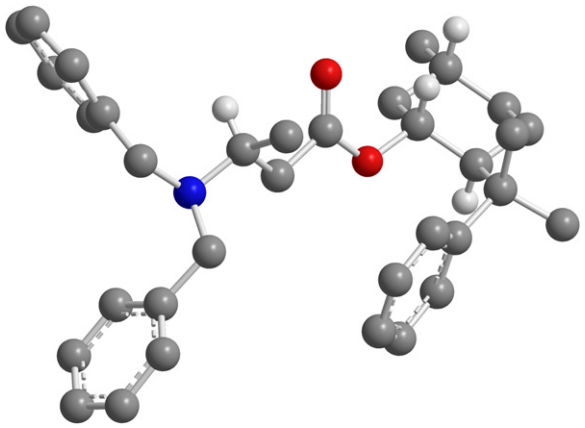


Fig. 5. X-ray crystal structure of (3*S*,1′*R*,2′*S*,5′*R*)-**33** (some H atoms are omitted for clarity).

lone-pair lies *syn*-periplanar to the *O*-*tert*-butyl group. It is notable that these structures also bear a striking resemblance to that proposed for enolate **50**. Assuming that **54** and **55** adopt similar conformations in solution it may therefore be reasoned that their reactive conformations upon conjugate addition are similar also. In this case the conjugate addition of lithium amide (*R*)-**1** would be predicted to be the doubly diastereoselective 'matched' reaction pairing with nucleophilic attack preferentially occurring on the face *anti* to both the *O*-*tert*-butyl group and *N*-lone pair.

The conjugate addition of lithium dibenzylamide **31**, lithium *N*-isopropyl-*N*-benzylamide **32** and the antipodes of lithium *N*-benzyl-*N*-(α-methylbenzyl)amide **1** to α,β-unsaturated hydroxamates **54** and **55** were next undertaken. The addition of lithium amide (*R*)-**1** to both **54** and **55** gave, in each case, the corresponding β-amino hydroxamates **56** and **60** in >95:5 dr,[33] representing the doubly diastereoselective 'matched' reaction pairings. The levels of diastereoselectivity observed upon conjugate addition of lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl) amide (*S*)-**1** to **54** and **55** were much lower, representing the doubly diastereoselective 'mismatched' reaction pairings. In the case of the C(3)-methyl substituted α,β-unsaturated hydroxamate **54** the conjugate addition of (*S*)-**1** proceeded under the predominant stereocontrol of the lithium amide giving a mixture of **57** and **65** in 25:75 dr, respectively. Upon purification of the crude reaction mixture it was possible to enrich the diastereoisomeric purity of the major product giving **65** in 46% yield and 90:10 dr. In the case of the C(3)-phenyl substituted α,β-unsaturated hydroxamate **55** conjugate addition of (*S*)-**1** gave a 60:40 mixture of **61** and **69**, respectively; in this case the major diastereoisomer **61** was isolated in 18% yield and 85:15 dr.[34] The conjugate additions of the achiral lithium amides **31** and **32** to α,β-unsaturated hydroxamates **54** and **55** all proceeded with the same sense of stereoinduction and with modest levels of diastereoselectivity (≥70:30 dr) to give **58**, **59**, **62** and **63** as the major products. In these

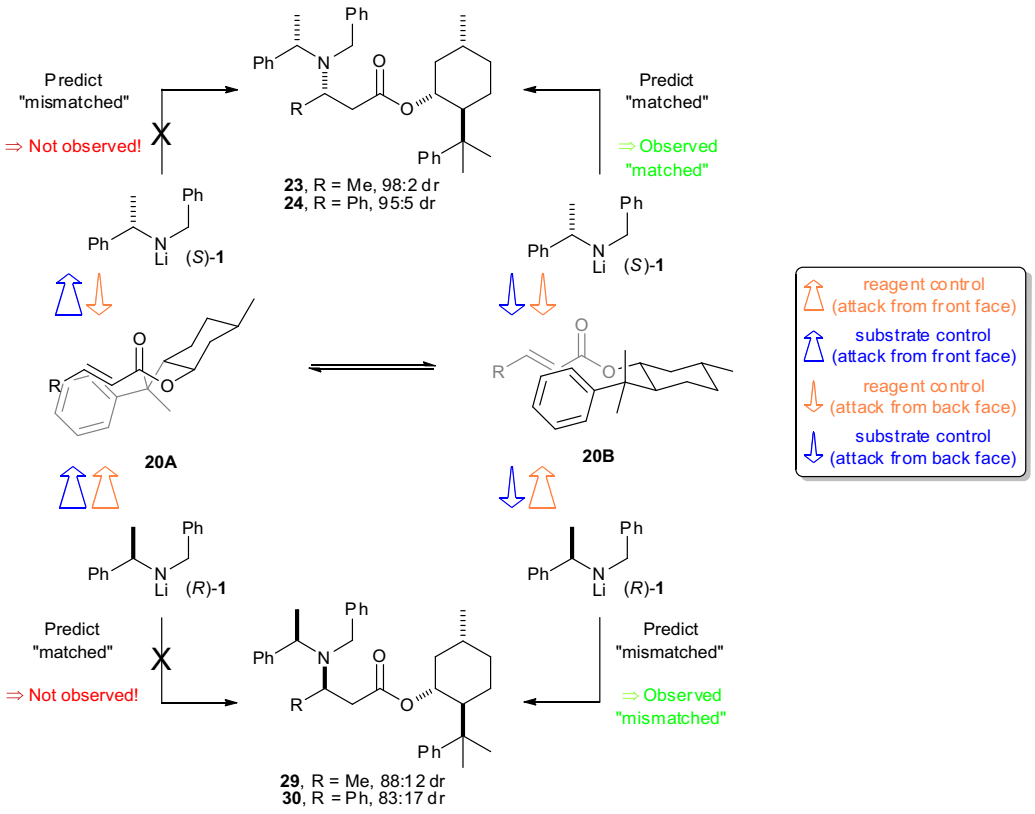


Fig. 6. Model to rationalise the observed 'matched' and 'mismatched' double asymmetric induction; given the observed 'matched' and 'mismatched' reaction pairings, the reactive conformation cannot be **20A**.

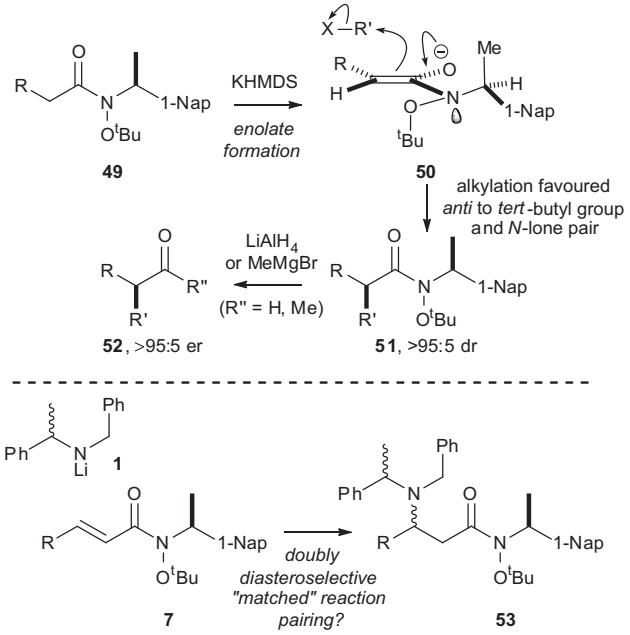
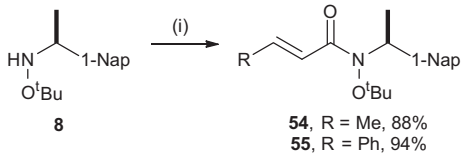


Fig. 7. Alkylation of chiral hydroxamates **49** and the doubly diastereoselective conjugate addition of the antipodes of **1** to α,β-unsaturated hydroxamates **7**. [1-Nap=1-naphthyl].



Scheme 7. Reagents and conditions: (i) RCH=CHCOCl, CH_2Cl_2, rt, 18 h [1-Nap=1-naphthyl].

cases, separation of the diastereoisomeric products could not be achieved upon purification, even after exhaustive flash column chromatography (Scheme 8).

The configurations at C(3) within **56**, **60**, **65** and **69** were established unambiguously by a separate chemical synthesis in each case, thereby also confirming the assigned configurations within **57**, **61**, **64** and **68**: both enantiomers of β-amino esters **25** and **26** were hydrolysed with TFA then the resultant carboxylic acids were coupled with (*S*)-*N*-1-(1′-naphthyl)ethyl-*O*-*tert*-butylhydroxylamine **8** to give authentic samples of **56**, **60**, **65** and **69** as single diastereoisomers (>95:5 dr), although the overall yields obtained in the coupling step were relatively low. The spectroscopic properties, including specific rotation values, of the samples of **56**, **60**, **65** and **69** prepared in this manner were consistent with the major diastereoisomers[35] arising from the conjugate addition of lithium amides (*R*)-**1** and (*S*)-**1** to α,β-unsaturated hydroxamates **54** and **55**, providing unequivocal evidence of the sense of stereoinduction observed in these reaction pairings (Scheme 9). Furthermore, the relative configuration within **56** was unambiguously assigned by single crystal X-ray diffraction analysis,[27] with the absolute (3*R*,1′*S*,α*R*)-configuration assigned relative to the known configurations of both the (*R*)-α-methylbenzyl stereocentre and the (*S*)-*N*-1-(1′-naphthyl)ethyl-*O*-*tert*-butylhydroxylamine **8** derived 'chiral Weinreb amide' auxiliary (Fig. 9).

Authentic samples of the products arising from the conjugate addition of **31** and **32** to α,β-unsaturated hydroxamates **54** and **55** were produced by conversion of (*R*,*R*)-**25** and (3*S*,α*R*)-**26** into the corresponding enantiopure *N*,*N*-dibenzyl substituted derivatives **58** and **62** and *N*-isopropyl-*N*-benzyl substituted derivatives **59** and **63**, although the yields of the coupling steps were again found to be

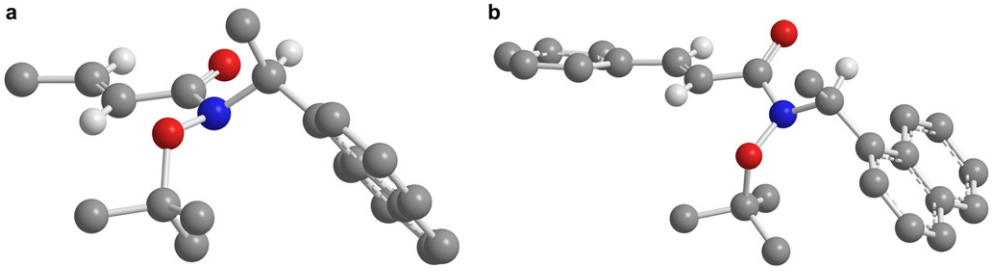
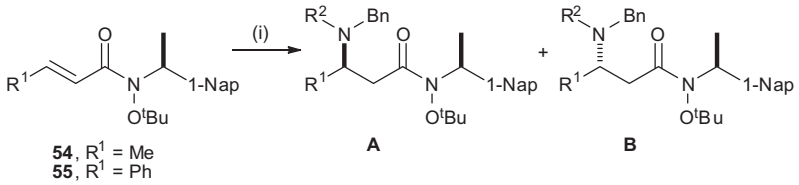


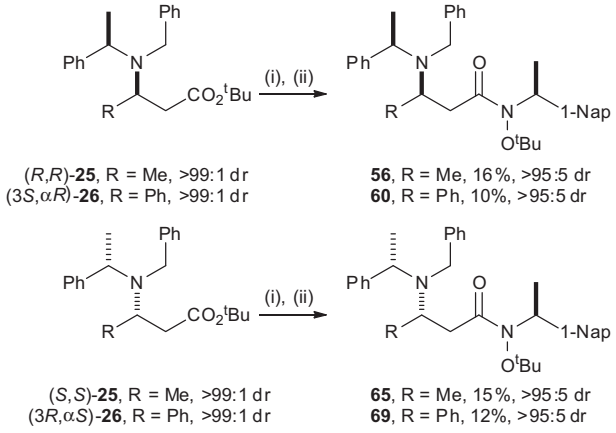
Fig. 8. X-ray crystal structures of (a) **54** and (c) **55** (some H atoms are omitted for clarity). [1-Nap=1-naphthyl].



54, R^1 = Me
55, R^1 = Ph

Michael acceptor	lithium amide	R^1	R^2	A	B	conv (%)	crude dr (A:B)	yield of A (%)	yield of B (%)
54	(*R*)-**1**	Me	(*R*)-CHMePh	**56**	**64**	quant	>95:5	81 (>95:5 dr)	--
54	(*S*)-**1**	Me	(*S*)-CHMePh	**57**	**65**	91	25:75	--	46[a] (90:10 dr)
54	**31**	Me	Bn	**58**	**66**	83	80:20	66 (80:20 dr)	--
54	**32**	Me	^{i}Pr	**59**	**67**	83	80:20	70 (80:20 dr)	--
55	(*R*)-**1**	Ph	(*R*)-CHMePh	**60**	**68**	94	>95:5	80 (>95:5 dr)	--
55	(*S*)-**1**	Ph	(*S*)-CHMePh	**61**	**69**	90	60:40	18[a] (85:15 dr)	--
55	**31**	Ph	Bn	**62**	**70**	92	70:30	62 (70:30 dr)	--
55	**32**	Ph	^{i}Pr	**63**	**71**	65	80:20	60 (80:20 dr)	--

Scheme 8. Reagents and conditions: (i) LiNR^{2}Bn, THF, −78 °C, 2 h [1-Nap=1-naphthyl; [a] mixed fractions were also isolated, see Ref. 34].



(*R*,*R*)-**25**, R = Me, >99:1 dr
(3*S*,α*R*)-**26**, R = Ph, >99:1 dr

56, R = Me, 16%, >95:5 dr
60, R = Ph, 10%, >95:5 dr

(*S*,*S*)-**25**, R = Me, >99:1 dr
(3*R*,α*S*)-**26**, R = Ph, >99:1 dr

65, R = Me, 15%, >95:5 dr
69, R = Ph, 12%, >95:5 dr

Scheme 9. Reagents and conditions: (i) TFA/CH_2Cl_2 (v/v 1:1), rt, 2 h; (ii) $(COCl)_2$, DMF, CH_2Cl_2, rt, 1 h then (*S*)-**8**·(+)-CSA, CH_2Cl_2, 16 h [1-Nap=1-naphthyl].

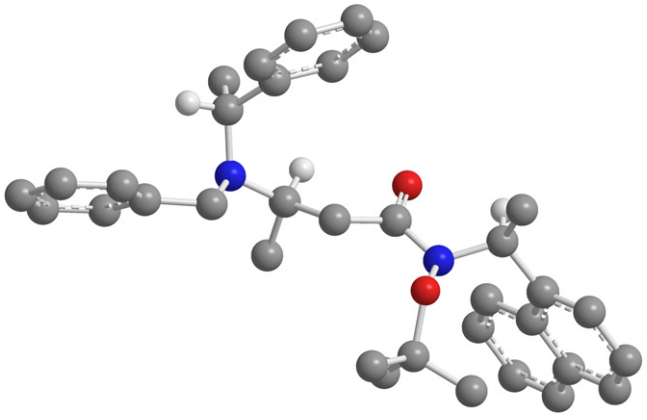
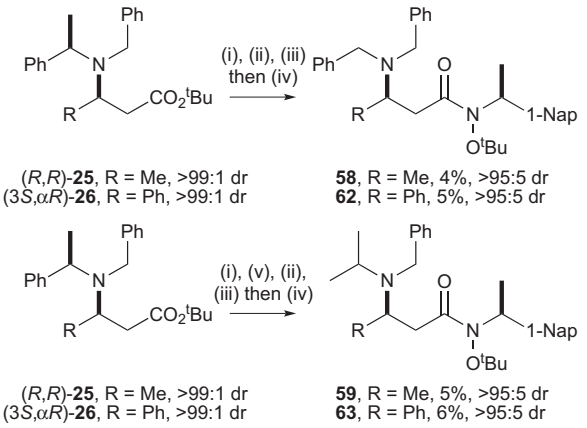


Fig. 9. X-ray crystal structure of (3*R*,1′*S*,α*R*)-**56** (some H atoms are omitted for clarity). [1-Nap=1-naphthyl].

relatively poor.[36] The spectroscopic properties, including specific rotation values, of the samples of **58**, **59**, **62** and **63** prepared in this manner were consistent with the major diastereoisomers arising from the conjugate addition of lithium amides **31** and **32** to α,β-unsaturated hydroxamates **54** and **55**, providing unequivocal evidence of the sense of stereoinduction observed in these reactions (Scheme 10).

2.4. The origins of diastereoselectivity observed upon conjugate addition to α,β-unsaturated hydroxamates

As predicted, the conjugate addition of (*R*)-**1** to enantiopure α,β-unsaturated hydroxamates **54** and **55** proceeded with high diastereoselectivity (>95:5 dr in each case) and represents the doubly diastereoselective 'matched' reaction pairings, whereas reaction of (*S*)-**1** with **54** and **55** proceeded with much poorer levels of diastereoselectivity (25:75 and 60:40 dr, respectively) and represents the 'mismatched' reaction pairings. These empirical 'matched' and 'mismatched' product distributions are consistent with the preferential addition of lithium amide (*R*)-**1** to the top face of the double bond (reagent control) as drawn within *s-cis* reactive conformation **72**, which coincides with addition opposite to the stereodirecting *tert*-butyl group and *N*-lone pair within the auxiliary (substrate control). The poor diastereoselectivity observed in the 'mismatched' cases may occur via approach of lithium amide (*S*)-**1** on the same face as the stereodirecting *tert*-butyl group of the auxiliary, although these data do not discount the possibility that preferential addition of (*S*)-**1** to **54** and **55** proceeds via an alternative conformation of the α,β-unsaturated hydroxamate.



Scheme 10. Reagents and conditions: (i) H_2 (5 atm), $Pd(OH)_2$/C, MeOH, rt, 36 h; (ii) BnBr, K_2CO_3, 100 °C, 7 h; (iii) TFA/CH_2Cl_2 (v/v 1:1), rt, 2 h; (iv) $(COCl)_2$, DMF, CH_2Cl_2, 0 °C to rt, 1 h then (*S*)-**8**·(+)-CSA, K_2CO_3, CH_2Cl_2, 18 h; (v) acetone, $NaBH_3CN$, MeOH, rt, 16 h [1-Nap=1-naphthyl].

These findings are consistent with our previous observations concerning the alkylation of the of enolates derived from *N*-1-(1′-naphthyl) ethyl-*O*-*tert*-butylhydroxamates[8] in that a 'chiral relay'[31] mechanism may be proposed to rationalise the observed stereochemical outcome of the reaction: the configuration of the *N*-1-(1′-naphthyl)ethyl group dictates the position of the *O*-*tert*-butyl group and also the configuration adopted by the pyramidal nitrogen atom. A fully staggered arrangement is adopted in which minimisation of steric interactions between the C(1′)-methyl and *O*-*tert*-butyl groups leaves the C(1′)-hydrogen and carbonyl oxygen atoms eclipsing, minimising *syn*-pentane interactions. Minimisation of lone pair–lone pair repulsion controls the configuration of the pyramidal nitrogen atom; the doubly diastereoselective 'matched' conjugate addition of (*R*)-**1** then occurs on the opposite face to both the nitrogen lone-pair and the bulky *O*-*tert*-butyl group (Fig. 10).

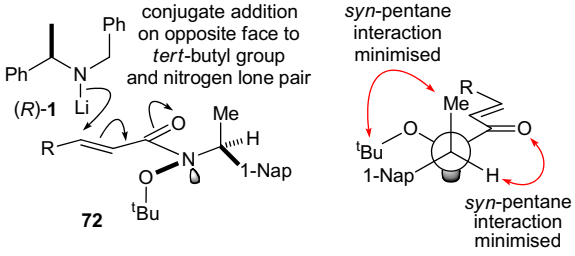


Fig. 10. A 'chiral relay' mechanism in the doubly diastereoselective conjugate addition of (*R*)-**1** to **54** (R=Me) and **55** (R=Ph). [1-Nap=1-naphthyl].

3. Conclusion

In conclusion, the doubly diastereoselective conjugate additions of the antipodes of lithium *N*-benzyl-*N*-(α-methylbenzyl)amide to a range of enantiopure α,β-unsaturated esters and enantiopure α,β-unsaturated hydroxamates have been used as a mechanistic probe to determine the reactive conformations in these systems. In all cases, conjugate addition occurs with the α,β-unsaturated carbonyl compounds adopting *s*-*cis* reactive conformations. High levels of diastereoselectivity (≥95:5 dr) were observed in the doubly diastereoselective 'matched' reaction pairings. In all but one case the dominant stereocontrolling element in the 'mismatched' reaction pairings was found to be the lithium amide reagent. Intermediate levels of diastereoselectivity were observed upon conjugate addition of achiral lithium amides, providing an indication of the level of substrate control in these systems. In the doubly diastereoselective 'matched' cases the known diastereofacial preference exerted by lithium *N*-benzyl-*N*-(α-methylbenzyl)amide was found to be in accord with conjugate addition to the face opposite to the stereodirecting groups within these auxiliaries (i.e., the phenyl group within Corey's 8-phenylmenthol auxiliary and both the *tert*-butyl group and *N*-lone pair within our 'chiral Weinreb amide' auxiliary).

4. Experimental

4.1. General experimental

All reactions involving organometallic or other moisture-sensitive reagents were carried out under a nitrogen or argon atmosphere using standard vacuum line techniques and glassware that was flame dried and cooled under nitrogen before use. Solvents were dried according to the procedure outlined by Grubbs and co-workers.[37] Water was purified by an Elix® UV-10 system. ^{i}PrOH was distilled from CaO. BuLi was purchased from Sigma–Aldrich (as solution in hexanes) and titrated against diphenylacetic acid before use. All other reagents were used as supplied (analytical or HPLC grade) without prior purification. Organic layers were dried over $MgSO_4$. Thin layer chromatography was performed on aluminium plates coated with 60 F_{254} silica. Plates were visualised using UV light (254 nm), iodine, 1% aq $KMnO_4$, or 10% ethanolic phosphomolybdic acid. Flash column chromatography was performed on Kieselgel 60 silica.

Melting points were recorded on a Gallenkamp Hot Stage apparatus. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter with a water-jacketed 10 cm cell. Specific rotations are reported in 10^{-1} deg cm^2 g^{-1} and concentrations in g/100 mL. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer as either a thin film on NaCl plates (film) or a KBr disc (KBr), as stated. Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded on Bruker Avance spectrometers in the deuterated solvent stated. Spectra were recorded at rt unless otherwise stated. The field was locked by external referencing to the relevant deuteron resonance. Low-resolution mass spectra were recorded on either a VG MassLab 20–250 or a Micromass Platform 1 spectrometer. Accurate mass measurements were run on either a Bruker MicroTOF internally calibrated with polyalanine, or a Micromass GCT instrument fitted with a Scientific Glass Instruments BPX5 column (15 m×0.25 mm) using amyl acetate as a lock mass.

4.2. General procedure 1: conjugate addition of lithium amide

BuLi (1.6 equiv) was added to a solution of the requisite amine (2.0 equiv) in THF at −78 °C. After 30 min, a solution of the requisite substrate (1.0 equiv) in THF at −78 °C was added dropwise via cannula. After a further 2 h, satd aq NH_4Cl was added and the reaction mixture was allowed to warm to rt before being concentrated in vacuo. 10% aq Citric acid solution was then added and the resultant mixture was extracted with three portions of CH_2Cl_2. The combined organic extracts were washed with satd aq $NaHCO_3$ and brine, then dried and concentrated in vacuo.

4.3. General procedure 2: deprotection with TFA

A solution of the requisite substrate in TFA/CH_2Cl_2 (v/v 1:1) was stirred at 0 °C for 5 min. The reaction mixture was then allowed to warm to rt over 2 h then concentrated in vacuo. In the case of tertiary amino ester starting materials, the residue was dissolved in CH_2Cl_2 and the resultant solution was washed with satd aq $NaHCO_3$, then dried and concentrated in vacuo.

4.4. General procedure 3: N/O-acylation of a chiral auxiliary with a carboxylic acid derivative

A solution of the requisite carboxylic acid (1.0–2.5 equiv) in CH_2Cl_2 at 0 °C was treated with $(COCl)_2$ (1.00–5.00 equiv) and DMF (1 drop). The reaction mixture was allowed to warm to rt over 1 h then concentrated in vacuo. The residue was dissolved in CH_2Cl_2 and the resultant mixture was added to a solution of the requisite chiral auxiliary (1.00 equiv) in CH_2Cl_2 at 0 °C. The reaction mixture was then allowed to warm to rt and stirred for 18 h. Satd aq $NaHCO_3$ was then added and the resultant mixture was extracted with three portions of CH_2Cl_2. The combined organic extracts were washed with brine, then dried and concentrated in vacuo.

4.5. General procedure 4: hydrogenolysis with Pearlman's catalyst

$Pd(OH)_2/C$ (20% by weight as supplied, load 25–50% by weight of substrate for reaction) was added to a vigorously stirred solution of the requisite substrate in either (i) degassed EtOAc; (ii) degassed MeOH; or (iii) degassed MeOH:AcOH (v/v 40:1), at rt. The resultant suspension was stirred under hydrogen at either: (i) 1 atm or (ii) 5 atm, as stated, for 18–36 h. The reaction mixture was filtered through Celite® [eluent either (i) EtOAc or (ii) MeOH] and concentrated in vacuo. For reactions which required AcOH, the residue was dissolved in CH_2Cl_2 and the resultant solution was washed with satd aq $NaHCO_3$ and brine, then dried and concentrated in vacuo.

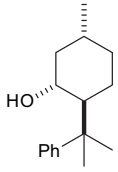
4.6. General procedure 5: N-benzylation of primary or secondary amines

K_2CO_3 (10.0 equiv) was added to a stirred solution of the requisite amine (1.0 equiv) in BnBr (10.0 equiv). The resultant mixture was heated at 100 °C for 7 h then allowed to cool to rt and partitioned between satd aq $NaHCO_3$ and CH_2Cl_2. The aqueous layer was extracted with three portions of CH_2Cl_2 and the combined organic extracts were then dried and concentrated in vacuo.

4.7. General procedure 6: reductive amination with $NaBH_3CN$

Acetone (2.0 equiv) and $NaBH_3CN$ (4.0 equiv) were added sequentially to a solution of the requisite primary amine (1.0 equiv) in MeOH at rt. The resultant mixture was stirred at rt for 18 h then concentrated in vacuo. The residue was partitioned between CH_2Cl_2 and H_2O and the aqueous layer was extracted with three portions of CH_2Cl_2. The combined organic extracts were then dried and concentrated in vacuo.

4.7.1. (1R,2S,5R)-2-(2′-Phenylpropan-2′-yl)-5-methylcyclohexanol ***6****.*

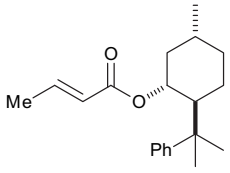


Step 1: PhMgBr (3.0 M in Et_2O, 26.4 mL, 78.8 mmol) was added dropwise to a stirred solution of copper(I) bromide (1.12 g, 7.82 mmol) in Et_2O (20 mL) at −20 °C. After 30 min, a solution of (*R*)-(+)-pulegone (10.0 g, 65.7 mmol) in Et_2O (13 mL) was added over a period of 15 min and the resultant mixture was stirred at −20 °C for 16 h. The reaction mixture was then added to 2.0 M aq HCl (80 mL) at 0 °C and the aqueous layer was saturated with NH_4Cl and extracted with Et_2O (3×80 mL). The combined organic extracts were washed with satd aq $NaHCO_3$ (80 mL) and brine (80 mL), then dried and concentrated in vacuo to give a yellow oil (14.0 g, 93%).

Step 2: The residue (14.0 g, 60.8 mmol) was dissolved in EtOH (150 mL) and H_2O (20 mL) then KOH (17.5 g, 300 mmol) was added. The resultant mixture was heated at reflux for 3 h and concentrated in vacuo to a volume of 50 mL. H_2O (125 mL) was then added, and the resultant mixture was saturated with NaCl and extracted with Et_2O (3×50 mL). The combined organic extracts were washed with brine (80 mL), then dried and concentrated in vacuo to give a pale yellow oil (13.0 g, 93%).

Step 3: The residue (13.0 g, 56.4 mmol) was dissolved in freshly distilled ^{i}PrOH (12.6 mL) and the resultant solution was added to a mixture of Na (3.82 g, 164 mmol) in toluene (54 mL) at a rate as to keep the reaction at a gentle reflux. Once the addition was complete, the mixture was heated at reflux for 8 h and then cooled to 0 °C. The mixture was diluted with Et_2O (60 mL) and poured into water (70 mL) at 0 °C. The aqueous layer was saturated with NaCl and extracted with with Et_2O (3×50 mL). The combined organic extracts were washed with brine (50 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (gradient elution, 1%→10% Et_2O in 30–40 °C petrol) gave **6** as a colourless oil (5.50 g, 36%, >99:1 dr); $[\alpha]_D^{22}$ −26.5 (*c* 1.0 in EtOH); {lit.[7] for enantiomer $[\alpha]_D^{20}$ +26.3 (*c* 2.02 in EtOH)}; δ_H (400 MHz, $CDCl_3$) 0.85–1.20 (3H, m, CH_2, C*H*) overlapping 0.87 (3H, d, *J* 6.5, C(5)*Me*), 1.29 (3H, s, C(1′)H_3), 1.42 (3H, s, C(3′)H_3), 1.43–1.78 (4H, m, 2× CH_2), 1.81–1.89 (1H, m, C*H*), 3.48 (1H, app td, *J* 10.6, 4.4, C(1)*H*), 7.15–7.47 (5H, m, *Ph*).

4.7.2. (1′R,2′S,5′R)-2′-(2″-Phenylpropan-2″-yl)-5′-methylcyclohexyl (E)-but-2-enoate ***9****.*

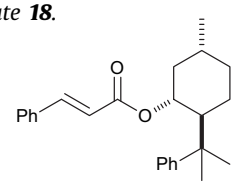


Step 1: Crotonoyl chloride (2.40 mL, 25.0 mmol) and ^{i}Pr$_2$NEt (4.20 mL, 25.0 mmol) was added to a stirred solution of **6** (2.90 g, 12.5 mmol) in THF (30 mL) at 0 °C. The resultant solution was allowed to warm to rt and stirred for 18 h. The reaction mixture was partitioned between satd aq $NaHCO_3$ (30 mL) and CH_2Cl_2 (30 mL). The aqueous layer was extracted with CH_2Cl_2 (3×30 mL). The combined organic extracts were washed with brine (30 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (gradient elution, 1%→20% Et_2O in 30–40 °C petrol) gave **19** as a colourless oil (3.38 g, 90%);[13] $[\alpha]_D^{25}$ +10.5 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2955, 2924 (C–H), 1730 (C=O), 1643 (C=C); δ_H (400 MHz, $CDCl_3$) 0.89 (3H, d, *J* 6.3, C(5′)*Me*), 0.90–1.20 (3H, m, CH_2, C*H*), 1.23 (3H, s, C(1″)H_3), 1.33 (3H, s, C(3″)H_3), 1.42–2.10 (5H, m, 2× CH_2, C*H*), 2.43 (1H, dd, *J* 16.7, 6.8, C(2)H_A), 2.48 (1H, dd, *J* 16.7, 6.8, C(2)H_B), 4.85 (1H, app td, *J* 10.6, 4.4, C(1′)*H*), 5.02 (1H, dd, *J* 16.7, 1.3, C(4)H_A), 5.08 (1H, dd, *J* 10.1, 1.3, C(4)H_B), 5.64–5.77 (1H, m, C(3)*H*), 7.10–7.35 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 22.2 (C(5′)*Me*), 24.9 (*C*(3″)), 26.9 (*C*H_2), 28.9 (*C*(1″)), 31.7 (*C*H), 35.0 (*C*H_2), 39.4 (*C*(2″)), 40.0 (*C*H_2), 42.1 (*C*(2)), 50.7 (*C*H), 74.6 (*C*(1′)), 118.0 (*C*(4)), 125.0 (*C*(3)), 125.4, 127.9, 130.5 (*o*,*m*,*p*-*Ph*), 151.7 (*i*-*Ph*), 170.8 (*C*(1)); *m*/*z* (ESI$^+$) 323 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{20}H_{28}NNaO_2^+$ ([M+Na]$^+$) requires 323.1982; found 323.1978.

Step 2: DBU (5.00 mL, 33.6 mmol) was added to a stirred solution of **19** (3.36 g, 11.2 mmol) in THF (35 mL) at rt and the resultant solution was stirred at rt for 18 h. The reaction mixture was then partitioned between 2.0 M aq HCl (30 mL) and CH_2Cl_2 (30 mL). The aqueous layer was extracted with CH_2Cl_2 (3×30 mL), and the combined organic extracts were washed with brine

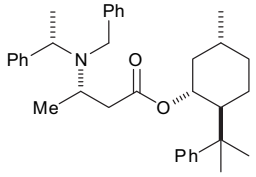
(30 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (gradient elution, 1%→20% Et_2O in 30–40 °C petrol) gave **9** as a colourless oil (2.20 g, 65%, >99:1 dr); $[\alpha]_D^{25}$ −10.0 (*c* 1.1 in hexane); {lit.[38] $[\alpha]_D^{25}$ −9.8 (*c* 13.1 in hexane)}; δ_H (400 MHz, $CDCl_3$) 0.91 (3H, d, *J* 6.5, C(5′)*Me*), 0.95–1.27 (3H, m, CH_2, C*H*) overlapping 1.26 (3H, s, C(1″)H_3), 1.35 (3H, s, C(3″)H_3), 1.49–2.01 (4H, m, 2× CH_2), 1.78 (3H, dd, *J* 7.2, 1.7, C(4)H_3), 2.04–2.16 (1H, m, C*H*), 4.88 (1H, app td, *J* 10.6, 4.4, C(1′)*H*), 5.38 (1H, dd, *J* 15.7, 1.7, C(2)*H*), 6.50 (1H, dd, *J* 15.7, 7.2, C(3)*H*), 7.14–7.48 (5H, m, *Ph*).

4.7.3. (1′R,2′S,5′R)-2′-(2″-Phenylpropan-2″-yl)-5′-methylcyclohexyl (E)-3-phenylpropenoate ***18****.*



$^i Pr_2NEt$ (289 mg, 2.37 mmol) was added in one portion to a stirred solution of cinnamoyl chloride (358 mg, 2.15 mmol) in THF (16 mL) at 0 °C. An immediate precipitate was observed and the resultant suspension was stirred for 15 min before a solution of **6** (500 mg, 2.15 mmol) in CH_2Cl_2 (4 mL) was added. The resultant mixture was allowed to warm to rt and stirred for 18 h. The reaction mixture was partitioned between satd aq $NaHCO_3$ (10 mL) and CH_2Cl_2 (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were washed with brine (10 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (gradient elution, 1%→20% Et_2O in 30–40 °C petrol) gave **18** as a colourless oil (436 mg, 56%, >99:1 dr); $[\alpha]_D^{25}$ +10.2 (*c* 2.2 in $CHCl_3$); {lit.[39] $[\alpha]_D^{25}$ +9.9 (*c* 2.23 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 0.94 (3H, d, *J* 6.5, C(5′)*Me*), 0.96–1.27 (3H, m, CH_2, C*H*), 1.29 (3H, s, C(1″)H_3), 1.38 (3H, s, C(3″)H_3), 1.52–2.03 (4H, m, 2× CH_2), 2.13–2.22 (1H, m, C*H*), 4.96 (1H, app td, *J* 10.6, 4.4, C(1′)*H*), 5.81 (1H, d, *J* 16.0, C(2)*H*), 7.11–7.48 (11H, m, C(3)*H*, *Ph*).

4.7.4. (1′R,2′S,5′R)-2′-(2″-Phenylpropan-2″-yl)-5′-methylcyclohexyl (S,S)-3-[N-benzyl-N-(α-methylbenzyl)amino]butanoate ***23****.*



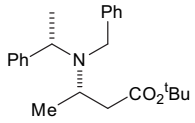
Method A: Following general procedure 1, a solution of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (0.20 mL, 0.96 mmol) in THF (2 mL) at −78 °C was treated with BuLi (1.6 M in hexanes, 0.48 mL, 0.77 mmol) and **9** (143 mg, 0.48 mmol, >99:1 dr) in THF (2 mL) to give **23** in 98:2 dr. Purification via flash column chromatography (gradient elution, 1%→10% Et_2O in 30–40 °C petrol) gave **23** as a colourless oil that crystallised upon standing (175 mg, 71%, >99:1 dr); $C_{35}H_{45}NO_2$ requires C, 82.2; H, 8.9; N, 2.7%; found C, 82.3; H, 8.9; N, 2.7%; mp 72–74 °C; $[\alpha]_D^{20}$ +6.4 (*c* 0.5 in $CHCl_3$); ν_{max} (KBr) 2959, 2924 (C–H), 1723 (C=O); δ_H (500 MHz, $CDCl_3$) 0.79–1.12 (3H, m, CH_2, C*H*), 0.88 (3H, d, *J* 6.3, C(5′)*Me*), 1.07 (3H, d, *J* 6.6, C(4)H_3), 1.19 (3H, s, C(1″)H_3), 1.25 (3H, s, C(3″)H_3), 1.31 (3H, d, *J* 6.9, C(α)*Me*), 1.38–1.67 (4H, m, 2× CH_2), 1.76–1.82 (1H, m, C(2)H_A), 1.87 (1H, dd, *J* 14.5, 4.1, C(2)H_B), 1.91–1.98 (1H, m, C*H*), 3.22–3.31 (1H, m, C(3)*H*), 3.61 (2H, AB system, J_{AB} 14.8, NCH_2Ph), 3.78 (1H, q, *J* 6.9, C(α)*H*), 4.72 (1H, app td, *J* 10.6, 4.3, C(1′)*H*), 7.10–7.40 (15H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 18.5 (*C*(4)), 19.1 (C(α)*Me*), 21.8 (C(5′)*Me*), 25.5 (*C*(3″)), 26.6 (*C*(1″)), 27.5 (*C*H_2), 31.2 (*C*H), 34.5 (*C*H_2), 39.0 (*C*(2)), 39.7 (*C*(2″)), 41.5 (*C*H_2), 49.7 (*C*H), 49.9 (NCH_2Ph), 50.3 (*C*(3)), 58.4 (*C*(α)), 73.9 (*C*(1′)), 125.0, 125.5, 126.4, 126.7, 127.6, 128.0, 128.2 (*o*,*m*,*p*-*Ph*), 142.1, 144.5, 151.6 (*i*-*Ph*), 171.8 (*C*(1)); *m*/*z* (ESI$^+$) 512 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{35}H_{46}NO_2^+$ ([M+H]$^+$) requires 512.3523; found 512.3520.

Method B: Following general procedure 2, a solution of (*S*,*S*)-**25** (1.75 g, 4.95 mmol) in CH_2Cl_2 (17.0 mL) was treated with TFA (17.0 mL) to give a white foam (1.32 g). Then, following general procedure 3, a solution of the residue (131 mg) in CH_2Cl_2 (2 mL) was reacted with $(COCl)_2$ (40 μL, 0.46 mmol) and a solution of **6** (50 mg, 0.22 mmol) in CH_2Cl_2 (1 mL). Purification via flash column chromatography (gradient elution, 1%→10% Et_2O in 30–40 °C petrol) gave **23** as a colourless oil that crystallised upon standing (76 mg, 61%, >99:1 dr); mp 72–74 °C; $[\alpha]_D^{21}$ +6.5 (*c* 1.0 in $CHCl_3$).

4.7.4.1. X-ray crystal structure determination for ***23****.* Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[40]

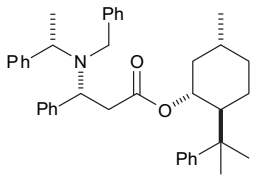
X-ray crystal structure data for **23** [$C_{35}H_{45}NO_2$]: *M*=511.75, triclinic, space group *P*1, *a*=8.7141(2) Å, *b*=9.8528(2) Å, *c*=10.1472(2) Å, α=98.8224(7)°, β=111.4837(8)°, γ=105.3920(9)°, *V*=750.51(3) Å^3, *Z*=1, μ=0.069 mm^{-1}, colourless block, crystal dimensions=0.17×0.21×0.24 mm^3. A total of 3396 unique reflections were measured for 5<θ<27 and 2765 reflections were used in the refinement. The final parameters were wR_2=0.067 and R_1=0.032 [*I*>−3.0σ(*I*)]. Crystallographic data (excluding structure factors) has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 815826. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

4.7.5. tert-Butyl (S,S)-3-[N-benzyl-N-(α-methylbenzyl)amino]butanoate ***25****.*



Following general procedure 1, a solution of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (2.38 g, 11.3 mmol) in THF (20 mL) at −78 °C was treated with BuLi (2.5 M, 5.10 mL, 10.9 mmol) and *tert*-butyl crotonate (1.00 g, 7.03 mmol) to give (*S*,*S*)-**25** in >99:1 dr. Purification via flash column chromatography (gradient elution, 1%→20% Et_2O in 30–40 °C petrol) gave (*S*,*S*)-**25** as a pale yellow oil (2.18 g, 88%, >99:1 dr);[1c] $[\alpha]_D^{24}$ +3.6 (*c* 1.0 in $CHCl_3$); {lit.[1c] $[\alpha]_D^{24}$ +3.6 (*c* 0.8 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.12 (3H, d, *J* 6.5, C(4)H_3), 1.34 (3H, d, *J* 7.0, C(α)*Me*), 1.39 (9H, s, CMe_3), 2.02 (1H, dd, *J* 14.1, 9.0, C(2)H_A), 2.26 (1H, dd, *J* 14.1, 4.8, C(2)H_B), 3.39–3.48 (1H, m, C(3)*H*), 3.69 (2H, AB system, J_{AB} 15.0, NCH_2Ph), 3.89 (1H, q, *J* 7.0, C(α)*H*), 7.19–7.42 (10H, m, *Ph*).

4.7.6. (1′R,2′S,5′R)-2′-(2″-Phenylpropan-2″-yl)-5′-methylcyclohexyl (3R,αS)-3-[N-benzyl-N-(α-methylbenzyl)amino]-3-phenylpropanoate ***24****.*

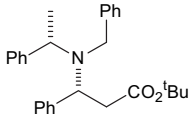


Method A: Following general procedure 1, a solution of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (0.10 mL, 0.50 mmol) in THF

(1 mL) at −78 °C was treated with BuLi (1.6 M in hexanes, 0.25 mL, 0.40 mmol) and **18** (90 mg, 0.25 mmol) in THF (1 mL) to give **24** in 95:5 dr. Purification via flash column chromatography (gradient elution, 1%→10% Et_2O in 30–40 °C petrol) gave **24** as a colourless oil (89 mg, 62%, >99:1 dr); $[\alpha]_D^{20}$ −10.3 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2963, 2924 (C–H), 1725 (C=O); δ_H (500 MHz, $CDCl_3$) 0.57–1.03 (3H, m, CH_2, C*H*), 0.79 (3H, d, *J* 6.3, C(5′)*Me*), 1.13 (3H, s, C(1″)H_3), 1.19 (3H, s, C(3″)H_3), 1.21 (3H, d, *J* 6.9, C(α)*Me*), 1.25–1.61 (4H, m, 2× CH_2), 1.84–1.92 (1H, m, C*H*), 2.26 (1H, dd, *J* 15.3, 5.4, C(2)H_A), 2.11 (1H, dd, *J* 15.3, 9.8, C(2)H_B), 3.64 (2H, app s, NCH_2Ph), 3.94 (1H, q, *J* 6.9, C(α)*H*), 4.25 (1H, dd, *J* 9.8, 5.4, C(3)*H*), 4.62 (1H, app td, *J* 10.6, 4.3, C(1′)*H*), 7.13–7.45 (20H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 16.1 (C(α)*Me*), 21.7 (C(5′)*Me*), 26.1 (*C*(3″)), 26.7 (*C*(1″)), 26.8 (*C*H_2), 31.1 (*C*H), 34.5 (*C*H_2), 37.7 (*C*(2)), 39.7 (*C*(2″)), 41.2 (*C*H_2), 50.2 (NCH_2Ph), 50.6 (*C*H), 56.9 (*C*(α)), 59.3 (*C*(3)), 74.4 (*C*(1′)), 125.1, 125.5, 126.4, 126.7, 127.1, 127.9, 128.0, 128.3 (*o*,*m*,*p*-*Ph*), 141.5, 141.7, 144.4, 151.4 (*i*-*Ph*), 170.9 (*C*(1)); *m*/*z* (ESI$^+$) 574 ($[M+H]^+$, 100%); HRMS (ESI$^+$) $C_{40}H_{48}NO_2^+$ ($[M+H]^+$) requires 574.3680; found 574.3680. Data for the (3*S*,1′*R*,2′*S*,5′*R*,α*S*)-diastereoisomer: δ_H (400 MHz, $CDCl_3$) [selected peaks] 3.63 (2H, app s, NCH_2Ph), 3.96 (1H, q, *J* 6.9, C(α)*H*), 4.32–4.38 (1H, m, C(3)*H*), 4.69 (1H, app td, *J* 10.6, 4.3, C(1′)*H*).

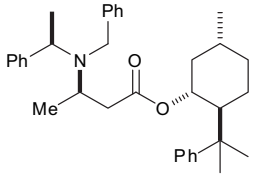
Method B: Following general procedure 2, a solution of (3*R*,α*S*)-**26** (1.66 g, 3.99 mmol) in CH_2Cl_2 (16.0 mL) was treated with TFA (16.0 mL) to give a white foam (1.32 g). Then, following general procedure 3, a solution of the residue (475 mg, 1.32 mmol) in CH_2Cl_2 (5 mL) was reacted with $(COCl)_2$ (0.11 mL, 1.39 mmol) and a solution of **6** (154 mg, 0.66 mmol) in CH_2Cl_2 (2 mL). Purification via flash column chromatography (gradient elution, 1%→10% Et_2O in 30–40 °C petrol) gave **24** as a colourless oil (227 mg, 55%, >99:1 dr); $[\alpha]_D^{22}$ −10.5 (*c* 1.1 in $CHCl_3$).

*4.7.7. tert-Butyl (3R,αS)-3-[N-benzyl-N-(α-methylbenzyl)amino]-3-phenylpropanoate **26**.*



Following general procedure 1, a solution of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (1.66 g, 7.84 mmol) in THF (20 mL) at −78 °C was treated with BuLi (2.5 M, 3.00 mL, 7.60 mmol) and *tert*-butyl cinnamate (1.00 g, 4.90 mmol) to give (3*R*,α*S*)-**26** in >99:1 dr. Purification via flash column chromatography (gradient elution, 1%→20% Et_2O in 30–40 °C petrol) gave (3*R*,α*S*)-**26** as a pale yellow oil (1.67 g, 84%, >99:1 dr);[41] $[\alpha]_D^{24}$ −4.2 (*c* 1.0 in $CHCl_3$); {lit.[41] $[\alpha]_D^{23}$ −4.0 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.22 (9H, s, CMe_3), 1.26 (3H, d, *J* 6.9, C(α)*Me*), 2.48–2.56 (2H, m, C(2)H_2), 3.68 (2H, app s, NCH_2Ph), 4.00 (1H, q, *J* 6.9, C(α)*H*), 4.40 (1H, dd, *J* 9.9, 5.4, C(3)*H*), 7.18–7.43 (15H, m, *Ph*).

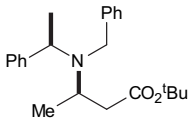
*4.7.8. (1′R,2′S,5′R)-2′-(2″-Phenylpropan-2″-yl)-5′-methylcyclohexyl (R,R)-3-[N-benzyl-N-(α-methylbenzyl)amino]butanoate **29**.*



Method A: Following general procedure 1, a solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (212 mg, 1.00 mmol) in THF (2 mL) at −78 °C was treated with BuLi (2.5 M in hexanes, 0.32 mL, 0.80 mmol) and **9** (150 mg, 0.50 mmol) in THF (2 mL) to give **29** in 88:12 dr. Purification via flash column chromatography (gradient elution, 1%→10% Et_2O in 30–40 °C petrol) gave **29** as a colourless oil (51 mg, 20%, >99:1 dr); $[\alpha]_D^{20}$ +11.3 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2965, 2925 (C–H), 1723 (C=O); δ_H (500 MHz, $CDCl_3$) 0.79–1.14 (3H, m, CH_2, C*H*), 0.86 (3H, d, *J* 6.3, C(5′)*Me*), 0.98 (3H, d, *J* 6.6, C(4)H_3), 1.18 (3H, s, C(1″)H_3), 1.23 (3H, s, C(3″)H_3), 1.31 (3H, d, *J* 6.9, C(α)*Me*), 1.38–1.69 (4H, m, 2× CH_2), 1.53 (1H, dd, *J* 14.6, 9.8, C(2)H_A), 1.90 (1H, dd, *J* 14.6, 4.4, C(2)H_B), 1.93–1.99 (1H, m, C*H*), 3.22–3.30 (1H, m, C(3)*H*), 3.58 (2H, AB system, J_{AB} 15.1, NCH_2Ph), 3.82 (1H, q, *J* 6.9, C(α)*H*), 4.71 (1H, app td, *J* 10.6, 4.3, C(1′)*H*), 7.09–7.40 (15H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 18.4 (*C*(4)), 19.1 (C(α)*Me*), 21.8 (C(5′)*Me*), 25.1 (*C*(3″)), 26.5 (*C*(1″)), 27.7 (*C*H_2), 31.2 (*C*H), 34.6 (*C*H_2), 39.2 (*C*(2)), 39.6 (*C*(2″)), 41.7 (*C*H_2), 49.7 (*C*H), 49.9 (NCH_2Ph), 50.3 (*C*(3)), 58.4 (*C*(α)), 74.1 (*C*(1′)), 124.9, 125.3, 126.5, 126.7, 127.7, 127.9, 128.1 (*o*,*m*,*p*-*Ph*), 142.0, 144.3, 151.7 (*i*-*Ph*), 171.8 (*C*(1)); *m*/*z* (ESI$^+$) 512 ($[M+H]^+$, 100%); HRMS (ESI$^+$) $C_{35}H_{46}NO_2^+$ ($[M+H]^+$) requires 512.3523; found 512.3522. Further elution gave an 85:15 mixture of **29** and its C(3)-epimer as colourless oil (128 mg, 50%). Data for the (3*S*,1′*R*,2′*S*,5′*R*,α*R*)-diastereoisomer: δ_H (500 MHz, $CDCl_3$) [selected peaks] 0.72 (3H, d, *J* 6.3, C(5′)*Me*), 0.90 (3H, d, *J* 6.6, C(4)H_3), 3.33–3.43 (1H, m, C(3)*H*), 3.66 (2H, AB system, J_{AB} 15.1, NCH_2Ph), 3.87 (1H, q, *J* 6.9, C(α)*H*), 4.81 (1H, app td, *J* 10.6, 4.3, C(1′)*H*); δ_C (125 MHz, $CDCl_3$) [selected peaks] 18.7 (*C*(4)), 19.4 (C(α)*Me*), 22.0 (C(5′)*Me*), 25.2 (*C*(3″)), 27.1 (*C*(1″)), 27.8 (*C*H_2), 31.2 (*C*H), 34.6 (*C*H_2), 58.7 (*C*(α)), 74.0 (*C*(1′)), 141.8, 143.8, 149.9 (*i*-*Ph*), 171.9 (*C*(1)).

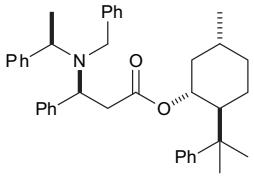
Method B: Following general procedure 2, a solution of (*R*,*R*)-**25** (1.67 g, 4.72 mmol) in CH_2Cl_2 (16.0 mL) was treated with TFA (16.0 mL) to give a white foam (1.36 g). Then, following general procedure 3, a solution of the residue (131 mg, 0.44 mmol) in CH_2Cl_2 (2 mL) was reacted with $(COCl)_2$ (40 μL, 0.46 mmol) and a solution of **6** (50 mg, 0.22 mmol) in CH_2Cl_2 (1 mL). Purification via flash column chromatography (gradient elution, 1%→10% Et_2O in 30–40 °C petrol) gave **29** as a colourless oil (52 mg, 46%, >99:1 dr); $[\alpha]_D^{22}$ +11.5 (*c* 1.1 in $CHCl_3$).

*4.7.9. tert-Butyl (R,R)-3-[N-benzyl-N-(α-methylbenzyl)amino]butanoate **25**.*



Following general procedure 1, a solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (5.94 g, 28.1 mmol) in THF (40 mL) at −78 °C was treated with BuLi (2.5 M, 10.9 mL, 27.3 mmol) and *tert*-butyl crotonate (2.50 g, 17.6 mmol) to give (*R*,*R*)-**25** in >99:1 dr. Purification via flash column chromatography (gradient elution, 1%→20% Et_2O in 30–40 °C petrol) gave (*R*,*R*)-**25** as a pale yellow oil (5.60 g, 90%, >99:1 dr);[1c] $[\alpha]_D^{25}$ −3.9 (*c* 1.0 in CH_2Cl_2); {lit.[1c] $[\alpha]_D^{20}$ −3.7 (*c* 1.1 in CH_2Cl_2)}.

*4.7.10. (1′R,2′S,5′R)-2′-(2″-Phenylpropan-2″-yl)-5′-methylcyclohexyl (3S,αR)-3-[N-benzyl-N-(α-methylbenzyl)amino]-3-phenylpropanoate **30**.*

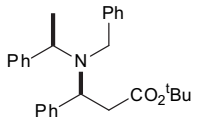


Method A: Following general procedure 1, a solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (350 mg, 1.66 mmol) in THF (3 mL) at −78 °C was treated with BuLi (2.5 M in hexanes, 0.53 mL, 1.33 mmol) and **18** (300 mg, 0.83 mmol) in THF (3 mL) to give **30** in 83:17 dr. Purification via flash column chromatography (gradient elution, 1%→10% Et_2O in 30–40 °C petrol) gave an 83:17 mixture of

30 and its C(3)-epimer as a colourless oil (334 mg, 70%); ν_{max} (film) 2964, 2924 (C–H), 1722 (C=O); *m*/*z* (ESI$^+$) 574 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{40}H_{48}NO_2^+$ ([M+H]$^+$) requires 574.3680; found 574.3680. Data for the (3*R*,1′*R*,2′*S*,5′*R*,α*R*)-diastereoisomer: δ_H (500 MHz, $CDCl_3$) [selected peaks] 0.76 (3H, d, *J* 6.3, C(5′)*Me*), 1.19 (3H, s, C(1″)H_3), 2.42 (2H, app d, *J* 7.8, C(2)H_2), 3.65 (2H, AB system, J_{AB} 15.1, NCH_2Ph), 4.22 (1H, app t, *J* 7.8, C(3)*H*); δ_C (125 MHz, $CDCl_3$) [selected peaks] 19.3 (C(α)*Me*), 21.8 (C(5′)*Me*), 25.9 (*C*(3″)), 26.6 (*C*(1″)), 27.0 (*C*H$_2$), 37.9 (*C*(2)), 39.7 (*C*(2″)), 41.2 (*C*H$_2$), 50.2 (NCH_2Ph), 58.2 (*C*(α)), 59.3 (*C*(3)), 74.3 (*C*(1′)), 140.4, 142.4, 144.6, 151.4 (*i*-*Ph*), 170.9 (*C*(1)). Further elution gave **30** as a colourless oil (86 mg, 18%, >99:1 dr); $[\alpha]_D^{24}$ +87.8 (*c* 1.2 in $CHCl_3$); ν_{max} (film) 2964, 2924 (C–H), 1722 (C=O); δ_H (500 MHz, $CDCl_3$) 0.51–1.06 (3H, m, CH_2, C*H*), 0.76 (3H, d, *J* 6.3, C(5′)*Me*), 1.14 (3H, s, C(1″)H_3), 1.16 (3H, s, C(3″)H_3), 1.26 (3H, d, *J* 6.9, C(α)*Me*), 1.29–1.66 (4H, m, 2× CH_2), 1.81–1.89 (1H, m, C*H*), 2.02 (1H, dd, *J* 14.8, 10.8, C(2)H_A), 2.11 (1H, dd, *J* 14.8, 3.8, C(2)H_B), 3.61 (2H, AB system, J_{AB} 15.1, NCH_2Ph), 3.92 (1H, q, *J* 6.9, C(α)*H*), 4.33 (1H, dd, *J* 10.8, 3.8, C(3)*H*), 4.59 (1H, app td, *J* 10.6, 4.3, C(1′)*H*), 7.00–7.47 (20H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 16.4 (C(α)*Me*), 21.7 (C(5′)*Me*), 24.8 (*C*(3″)), 26.5 (*C*(1″)), 27.7 (*C*H$_2$), 31.1 (*C*H), 34.5 (*C*H$_2$), 37.0 (*C*(2)), 39.5 (*C*(2″)), 41.1 (*C*H$_2$), 50.3 (NCH_2Ph), 50.9 (*C*H), 57.0 (*C*(α)), 59.2 (*C*(3)), 74.1 (*C*(1′)), 125.0, 125.3, 125.4, 126.5, 126.9, 127.1, 127.8, 127.9, 128.0, 128.1 (*o*,*m*,*p*-*Ph*), 141.6, 141.8, 143.9, 151.5 (*i*-*Ph*), 171.2 (*C*(1)).

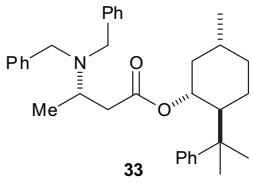
Method B: Following general procedure 2, a solution of (3*S*,α*R*)-**26** (1.72 g, 4.14 mmol) in CH_2Cl_2 (17.0 mL) was treated with TFA (17.0 mL) to give a white foam (1.41 g). Then, following general procedure 3, a solution of the residue (378 mg, 1.05 mmol) in CH_2Cl_2 (4 mL) was reacted with $(COCl)_2$ (93 μL, 1.10 mmol) and a solution of **6** (122 mg, 0.53 mmol) in CH_2Cl_2 (2 mL). Purification via flash column chromatography (gradient elution, 1%→10% Et_2O in 30–40 °C petrol) gave **30** as a colourless oil (176 mg, 55%, >99:1 dr); $[\alpha]_D^{25}$ +88.0 (*c* 1.0 in $CHCl_3$).

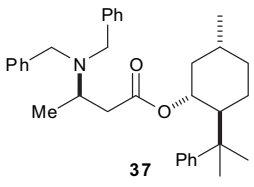
*4.7.11. tert-Butyl (3S,αR)-3-[N-benzyl-N-(α-methylbenzyl)amino]-3-phenylpropanoate **26**.*



Following general procedure 1, a solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (6.62 g, 31.3 mmol) in THF (80 mL) at −78 °C was treated with BuLi (2.5 M, 12.0 mL, 30.4 mmol) and *tert*-butyl cinnamate (4.00 g, 19.6 mmol) to give (3*S*,α*R*)-**26** in >99:1 dr. Purification via flash column chromatography (gradient elution, 1%→20% Et_2O in 30–40 °C petrol) gave (3*S*,α*R*)-**26** as a pale yellow oil (6.70 g, 83%, >99:1 dr);[41] $[\alpha]_D^{22}$ +4.1 (*c* 1.0 in $CHCl_3$); {lit.[41] for enantiomer $[\alpha]_D^{23}$ −4.0 (*c* 1.0 in $CHCl_3$)}.

*4.7.12. (1′R,2′S,5′R)-2′-(2″-Phenylpropan-2″-yl)-5′-methylcyclohexyl (S)-3-(N,N-dibenzylamino)butanoate **33** and (1′R,2′S,5′R)-2′-(2″-phenylpropan-2″-yl)-5′-methylcyclohexyl (R)-3-(N,N-dibenzylamino) butanoate **37**.*



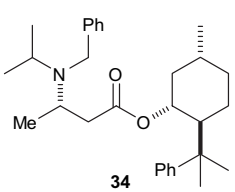


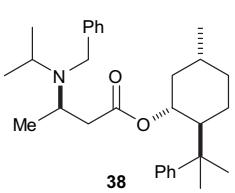
Following general procedure 1, a solution of dibenzylamine (0.64 mL, 3.33 mmol) in THF (5 mL) at −78 °C was treated with BuLi (2.5 M in hexanes, 1.07 mL, 2.67 mmol) and **9** (500 mg, 1.67 mmol) in THF (5 mL) to give a 78:22 mixture of **33** and **37**. Purification via flash column chromatography (gradient elution, 1%→5% Et_2O in 30–40 °C petrol) gave a 37:63 mixture of **33** and **37** as a colourless oil (83 mg, 10%); ν_{max} (film) 2961, 2925 (C–H), 1725 (C=O); *m*/*z* (ESI$^+$) 498 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{34}H_{44}NO_2^+$ ([M+H]$^+$) requires 498.3367; found 498.3368. Data for **37**: δ_H (400 MHz, $CDCl_3$) 0.86–1.22 (3H, m, CH_2, C*H*), 0.94 (3H, d, *J* 6.6, C(5′)*Me*), 1.00 (3H, d, *J* 6.9, C(4)H_3), 1.24 (3H, s, C(1″)H_3), 1.32 (3H, s, C(3″)H_3), 1.45–1.80 (3H, m, CH_2, C*H*), 1.67 (1H, dd, *J* 14.5, 8.5, C(2)H_A), 2.24 (1H, dd, *J* 14.5, 5.7, C(2)H_B), 1.91–2.06 (2H, m, CH_2), 3.02–3.31 (1H, m, C(3)*H*), 3.53 (4H, AB system, J_{AB} 13.9, N(CH_2Ph)$_2$), 4.80 (1H, app td, *J* 10.6, 4.3, C(1′)*H*), 7.14–7.46 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.7 (*C*(4)), 21.9 (C(5′)*Me*), 24.6 (*C*(3″)), 26.5 (*C*H$_2$), 28.4 (*C*(1″)), 31.3 (*C*H), 34.7 (*C*H$_2$), 38.6 (*C*H$_2$), 39.6 (*C*(2″)), 41.6 (*C*H), 50.2 (*C*(2)), 50.5 (*C*(3)), 53.5 (N(*C*H$_2$Ph)$_2$), 74.2 (*C*(1′)), 124.9, 125.4, 126.8, 128.0, 128.2, 128.4, 128.6, 128.8 (*o*,*m*,*p*-*Ph*), 140.1, 151.9 (*i*-*Ph*), 171.7 (*C*(1)). Further elution gave **33** as a colourless oil that crystallised upon standing (208 mg, 25%, >99:1 dr); $C_{34}H_{43}NO_2$ requires C, 82.05; H, 8.7; N, 2.8%; found C, 82.2; H, 8.8; N, 2.7%; mp 71–72 °C; $[\alpha]_D^{24}$ +12.6 (*c* 1.0 in $CHCl_3$); ν_{max} (KBr) 2961, 2925 (C–H), 1725 (C=O); δ_H (500 MHz, $CDCl_3$) 0.81–1.14 (3H, m, CH_2, C*H*), 0.88 (3H, d, *J* 6.6, C(5′)*Me*), 1.03 (3H, d, *J* 6.9, C(4)H_3), 1.20 (3H, s, C(1″)H_3), 1.28 (3H, s, C(3″)H_3), 1.42–1.71 (3H, m, CH_2, C*H*), 1.74 (1H, dd, *J* 14.5, 8.5, C(2)H_A), 2.09 (1H, dd, *J* 14.5, 5.7, C(2)H_B), 1.85–2.03 (2H, m, CH_2), 3.08–3.16 (1H, m, C(3)*H*), 3.46 (4H, AB system, J_{AB} 13.9, N(CH_2Ph)$_2$), 4.76 (1H, app td, *J* 10.6, 4.3, C(1′)*H*), 7.11–7.38 (15H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 15.1 (*C*(4)), 21.8 (C(5′)*Me*), 25.0 (*C*(3″)), 26.5 (*C*H$_2$), 27.8 (*C*(1″)), 31.3 (*C*H), 34.5 (*C*H$_2$), 38.0 (*C*H$_2$), 39.7 (*C*(2″)), 41.6 (*C*H), 50.3 (*C*(2)), 50.5 (*C*(3)), 53.5 (N(*C*H$_2$Ph)$_2$), 74.0 (*C*(1′)), 124.9, 125.4, 126.7, 128.0, 128.1, 128.7 (*o*,*m*,*p*-*Ph*), 140.1, 151.7 (*i*-*Ph*), 171.7 (*C*(1)).

*4.7.12.1. X-ray crystal structure determination for **33**.* Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[40]

X-ray crystal structure data for **33** [$C_{34}H_{43}NO_2$]: *M*=497.72, monoclinic, space group $P2_1$, *a*=6.21350(10) Å, *b*=35.5431(5) Å, *c*=13.2219(2) Å, β=91.2327(5)°, *V*=2919.34(8) Å^3, *Z*=4, μ=0.069 mm^{-1}, colourless block, crystal dimensions=0.10×0.14×0.15 mm^3. A total of 6339 unique reflections were measured for 5<θ<27 and 4973 reflections were used in the refinement. The final parameters were wR_2=0.251 and R_1=0.090 [*I*>−3.0σ(*I*)]. Crystallographic data (excluding structure factors) has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 815827. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

*4.7.13. (1′R,2′S,5′R)-2′-(2″-Phenylpropan-2″-yl)-5′-methylcyclohexyl (S)-3-(N-isopropyl-N-benzylamino)butanoate **34** and (1′R,2′S,5′R)-2′-(2″-phenylpropan-2″-yl)-5′-methylcyclohexyl (R)-3-(N-isopropyl-N-benzylamino)butanoate **38**.*

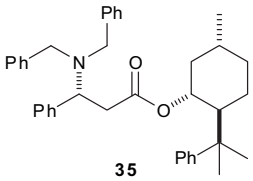




Following general procedure 1, a solution of *N*-benzyl-*N*-isopropylamine (0.56 mL, 3.33 mmol) in THF (5 mL) at −78 °C was treated with BuLi (2.5 M in hexanes, 1.07 mL, 2.67 mmol) and **9** (500 mg, 1.67 mmol) in THF (5 mL) to give a 72:28 mixture of **34**

and **38**. Purification via flash column chromatography (gradient elution, 1%→10% Et_2O in 30–40 °C petrol) gave an 83:17 mixture of **34** and **38** as a colourless oil (300 mg, 40%). Data for **38**: δ_H (500 MHz, $CDCl_3$) 0.83–1.18 (3H, m, CH_2, C*H*), 0.88 (3H, d, *J* 6.6, C(5′)*Me*), 0.96 (3H, d, *J* 6.6, C(4)H_3), 0.99 (3H, d, *J* 6.6, NCHMe_A), 1.00 (3H, d, *J* 6.6, NCHMe_B), 1.21 (3H, s, C(1″)H_3), 1.30 (3H, s, C(3″)H_3), 1.44–1.75 (3H, m, CH_2, C*H*), 1.88–2.06 (2H, m, CH_2), 1.60 (1H, dd, *J* 14.5, 8.2, C(2)H_A), 2.09 (1H, dd, *J* 14.5, 6.0, C(2)H_B), 2.87 (1H, septet, *J* 6.6, C*H*Me$_2$), 3.09–3.16 (1H, m, C(3)*H*), 3.56 (2H, AB system, J_{AB} 14.8, NCH_2Ph), 4.78 (1H, app td, *J* 10.6, 4.3, C(1′)*H*), 7.10–7.35 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 18.1 (*C*(4)), 20.1, 21.0 (NCHMe_2), 21.8 (C(5′)*Me*), 24.5 (*C*(3″)), 26.5 (*C*H$_2$), 28.3 (*C*(1″)), 31.3 (*C*(2)), 34.6 (*C*H), 39.6 (*C*H$_2$), 40.9 (*C*H$_2$), 41.7 (*C*(2″)), 48.5 (*C*H), 48.8 (N*C*H$_2$Ph), 49.3 (*C*HMe$_2$), 50.3 (*C*(3)), 74.1 (*C*(1′)), 124.9, 125.3, 126.3, 127.8, 128.0, 128.1 (*o*,*m*,*p*-*Ph*), 142.1, 151.9 (*i*-*Ph*), 171.9 (*C*(1)). Further elution gave **34** as a colourless oil (68 mg, 9%, >99:1 dr); $[\alpha]_D^{25}$ +22.2 (*c* 0.5 in $CHCl_3$); ν_{max} (film) 2963, 2926 (C–H), 1725 (C=O); δ_H (500 MHz, $CDCl_3$) 0.73–1.20 (3H, m, CH_2, C*H*), 0.93 (3H, d, *J* 6.6, C(5′)*Me*), 0.99 (3H, d, *J* 6.6, C(4)H_3), 1.04 (3H, d, *J* 6.6, NCHMe_A), 1.06 (3H, d, *J* 6.6, NCHMe_B), 1.25 (3H, s, C(1″)H_3), 1.34 (3H, s, C(3″)H_3), 1.37–1.80 (4H, m, 2× CH_2), 1.72 (1H, dd, *J* 14.7, 7.6, C(2)H_A), 1.99 (1H, dd, *J* 14.7, 7.8, C(2)H_B), 2.02–2.06 (1H, m, C*H*), 2.86 (1H, septet, *J* 6.6, C*H*Me$_2$), 3.28–3.38 (1H, m, C(3)*H*), 3.57 (2H, s, NCH_2Ph), 4.85 (1H, app td, *J* 10.6, 4.3, C(1′)*H*), 7.12–7.42 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 18.7 (*C*(4)), 20.1, 21.6 (NCHMe_2), 22.3 (C(5′)*Me*), 25.6 (*C*(3″)), 27.0 (*C*H$_2$), 28.3 (*C*(1″)), 30.2 (*C*(2)), 31.7 (*C*H), 35.0 (*C*H$_2$), 40.1 (*C*H$_2$), 41.2 (*C*(2″)), 48.8 (*C*H), 49.3 (N*C*H$_2$Ph), 49.4 (*C*HMe$_2$), 50.7 (*C*(3)), 74.4 (*C*(1′)), 125.4, 125.8, 128.3, 128.6 (*o*,*m*,*p*-*Ph*), 142.5, 152.1 (*i*-*Ph*), 172.5 (*C*(1)); *m*/*z* (ESI^+) 450 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{30}H_{44}NO_2^+$ ($[M+H]^+$) requires 450.3367; found 450.3362.

4.7.14. (1′R,2′S,5′R)-2′-(2″-Phenylpropan-2″-yl)-5′-methylcyclohexyl (R)-3-(N,N-dibenzylamino)-3-phenylpropanoate ***35*** *and (1′R,2′S,5′R)-2′-(2″-phenylpropan-2″-yl)-5′-methylcyclohexyl (S)-3-(N,N-dibenzylamino)-3-phenylpropanoate* ***39***.



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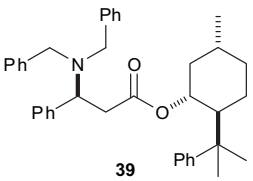

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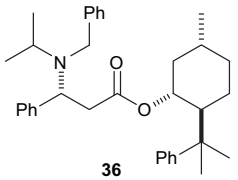
Following general procedure 1, a solution of dibenzylamine (0.32 mL, 1.66 mmol) in THF (3 mL) at −78 °C was treated with BuLi (2.5 M in hexanes, 0.53 mL, 1.33 mmol) and **18** (300 mg, 0.83 mmol) in THF (3 mL) to give a 65:35 mixture of **35** and **39**. Purification via flash column chromatography (gradient elution, 1%→10% Et_2O in 30–40 °C petrol) gave a 65:35 mixture of **35** and **39** as a colourless oil (394 mg, 85%); ν_{max} (film) 2954, 2924 (C–H), 1725 (C=O); *m*/*z* (ESI^+) 560 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{39}H_{46}NO_2^+$ ($[M+H]^+$) requires 560.3523; found 560.3523. Data for **35**: δ_H (400 MHz, $CDCl_3$) 0.75–1.15 (3H, m, CH_2, C*H*), 0.88 (3H, d, *J* 6.3, C(5′)*Me*), 1.22 (3H, s, C(1″)H_3), 1.30 (3H, s, C(3″)H_3), 1.37–1.80 (4H, m, 2× CH_2), 1.96–2.05 (1H, m, C*H*), 2.39–2.54 (2H, m, C(2)H_2), 3.45 (4H, AB system, J_{AB} 13.6, N(CH_2Ph)$_2$), 4.19 (1H, app t, *J* 7.6, C(3)*H*), 4.76 (1H, app td, *J* 10.6, 4.3, C(1′)*H*), 7.12–7.45 (20H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.9 (C(5′)*Me*), 25.4 (*C*(3″)), 26.6 (*C*H$_2$), 27.7 (*C*(1″)), 31.2 (*C*H), 34.6 (*C*H$_2$), 36.3 (*C*(2)), 39.7 (*C*(2″)), 41.5 (*C*H$_2$), 50.3 (*C*H), 53.8 (N(*C*H$_2$Ph)$_2$), 58.7 (*C*(3)), 74.5 (*C*(1′)), 125.0, 125.5, 126.9, 127.3, 128.0, 128.2, 128.4, 128.6, 128.7, 128.8 (*o*,*m*,*p*-*Ph*), 138.1, 139.8, 151.7 (*i*-*Ph*), 171.0 (*C*(1)). Data for **39**: δ_H (400 MHz, $CDCl_3$) 0.72–1.15 (3H, m, CH_2, C*H*), 0.85 (3H, d, *J* 6.3, C(5′)*Me*), 1.20 (3H, s, C(1″)H_3), 1.27 (3H, s, C(3″)H_3), 1.33–1.76 (4H, m, 2× CH_2), 1.93–2.02 (1H, m, C*H*), 2.26 (1H, dd, *J* 14.9, 9.2, C(2)H_A), 2.55 (1H, dd, *J* 14.9, 6.2, C(2)H_B), 3.45 (4H, AB system, J_{AB} 13.6, N(CH_2Ph)$_2$), 4.09 (1H, dd, *J* 9.2, 6.2, C(3)*H*), 4.72 (1H, app td, *J* 10.6, 4.3, C(1′)*H*), 7.10–7.42 (20H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.8 (C(5′)*Me*), 24.6 (*C*(3″)), 26.5 (*C*H$_2$), 28.2 (*C*(1″)), 31.2 (*C*H), 34.6 (*C*H$_2$), 35.9 (*C*(2)), 39.6 (*C*(2″)), 41.4 (*C*H$_2$), 50.2 (*C*H), 53.8 (N(*C*H$_2$Ph)$_2$), 58.7 (*C*(3)), 74.3 (*C*(1′)), 125.0, 125.4, 126.9, 127.2, 127.9, 128.2, 128.4, 128.6, 128.8 (*o*,*m*,*p*-*Ph*), 138.3, 139.8, 151.8 (*i*-*Ph*), 171.0 (*C*(1)).

4.7.15. (1′R,2′S,5′R)-2′-(2″-Phenylpropan-2″-yl)-5′-methylcyclohexyl (R)-3-(N-isopropyl-N-benzylamino)-3-phenylpropanoate ***36*** *and (1′R,2′S,5′R)-2′-(2″-phenylpropan-2″-yl)-5′-methylcyclohexyl (S)-3-(N-isopropyl-N-benzylamino)-3-phenylpropanoate* ***40***.



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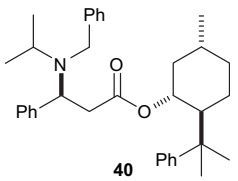
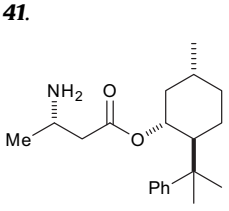


40

Following general procedure 1, a solution of *N*-benzyl-*N*-isopropylamine (0.10 mL, 0.56 mmol) in THF (1 mL) at −78 °C was treated with BuLi (2.5 M in hexanes, 0.17 mL, 0.44 mmol) and **18** (100 mg, 0.28 mmol) in THF (1 mL) to give a 80:20 mixture of **36** and **40**. Purification via flash column chromatography (gradient elution, 1%→10% Et_2O in 30–40 °C petrol) gave a 80:20 mixture of **36** and **40** as a colourless oil (112 mg, 78%); ν_{max} (film) 2961, 2925 (C–H), 1725 (C=O); *m*/*z* (ESI^+) 512 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{35}H_{46}NO_2^+$ ($[M+H]^+$) requires 512.3523; found 512.3525. Data for **36**: δ_H (400 MHz, $CDCl_3$) 0.66–1.09 (3H, m, CH_2, C*H*), 0.79 (3H, d, *J* 6.3, C(5′)*Me*), 0.81 (3H, d, *J* 6.6, NCHMe_A), 0.99 (3H, d, *J* 6.6, NCHMe_B), 1.14 (3H, s, C(1″)H_3), 1.21 (3H, s, C(3″)H_3), 1.30–1.65 (4H, m, 2× CH_2), 1.90–1.99 (1H, m, C*H*), 2.25–2.39 (2H, m, C(2)H_2), 2.97 (1H, septet, *J* 6.6, C*H*Me$_2$), 3.63 (2H, AB system, J_{AB} 15.4, NCH_2Ph), 4.11 (1H, dd, *J* 8.8, 6.3, C(3)*H*), 4.67 (1H, app td, *J* 10.6, 4.3, C(1′)*H*), 7.13–7.44 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 18.7, 21.2 (NCHMe_2), 21.8 (C(5′)*Me*), 25.5 (*C*(3″)), 26.6 (*C*H$_2$), 27.4 (*C*(1″)), 31.1 (*C*H), 34.5 (*C*(2)), 38.8 (*C*H$_2$), 39.6 (*C*(2″)), 41.4 (*C*H$_2$), 48.1 (*C*H), 49.2 (NCH_2Ph), 50.3 (*C*HMe$_2$), 59.9 (*C*(3)), 74.4 (*C*(1′)), 125.1, 125.5, 126.5, 127.0, 127.9, 128.0, 128.3, 128.6, 128.7 (*o*,*m*,*p*-*Ph*), 141.6, 142.2, 151.6 (*i*-*Ph*), 171.2 (*C*(1)). Data for **40**: δ_H (400 MHz, $CDCl_3$) 0.51–1.12 (3H, m, CH_2, C*H*), 0.78 (3H, d, *J* 6.3, C(5′)*Me*), 0.86 (3H, d, *J* 6.6, NCHMe_A), 1.03 (3H, d, *J* 6.6, NCHMe_B), 1.18 (3H, s, C(1″)H_3), 1.24 (3H, s, C(3″)H_3), 1.27–1.73 (4H, m, 2× CH_2), 1.87–1.95 (1H, m, C*H*), 2.03 (1H, dd, *J* 14.4, 10.4, C(2)H_A), 2.33 (1H, dd, *J* 14.4, 4.8, C(2)H_B), 2.96 (1H, septet, *J* 6.6, C*H*Me$_2$), 3.66 (2H, AB system, J_{AB} 15.4, NCH_2Ph), 4.14 (1H, dd, *J* 10.4, 4.8, C(3)*H*), 4.65 (1H, app td, *J* 10.6, 4.3, C(1′)*H*), 7.00–7.44 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 18.8, 20.9 (NCHMe_2), 21.7 (C(5′)*Me*), 24.2 (*C*(3″)), 26.4 (*C*H$_2$), 28.3 (*C*(1″)), 31.1 (*C*H), 34.5 (*C*(2)), 38.4 (*C*H$_2$), 39.5 (*C*(2″)), 41.2 (*C*H$_2$), 48.2 (*C*H), 49.4 (N*C*H$_2$Ph), 50.3 (*C*HMe$_2$), 60.4 (*C*(3)), 74.9 (*C*(1′)), 125.1, 125.5, 126.5, 126.9, 127.8, 128.0, 128.2, 128.6, 128.8 (*o*,*m*,*p*-*Ph*), 141.8, 142.2, 151.6 (*i*-*Ph*), 171.4 (*C*(1)).

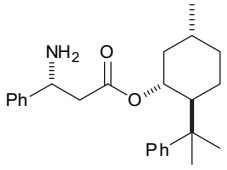
4.7.16. (1′R,2′S,5′R)-2′-(2″-Phenylpropan-2″-yl)-5′-methylcyclohexyl (S)-3-aminobutanoate ***41***.



Following general procedure 4, **23** (410 mg, 0.80 mmol) and $Pd(OH)_2$/C (205 mg) in EtOAc (5 mL) under H_2 (5 atm) for 18 h gave **41**. Purification via flash column chromatography (eluent 30–40 °C petrol (1% Et_3N)/Et_2O, 3:1, increased to 1:3) gave **41** as a pale yellow

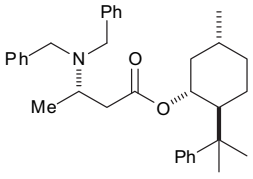
oil (192 mg, 76%, >99:1 dr); $[\alpha]_D^{25}$ +12.9 (*c* 2.0 in $CHCl_3$); ν_{max} (film) 3374 (N–H), 2959, 2924 (C–H), 1723 (C=O); δ_H (500 MHz, $CDCl_3$) 0.87–1.22 (3H, m, CH_2, C*H*), 0.91 (3H, d, *J* 6.6, C(5′)*Me*), 1.03 (3H, d, *J* 6.3, C(4)H_3), 1.24 (3H, s, C(1″)H_3), 1.35 (3H, s, C(3″)H_3), 1.46–1.92 (4H, m, 2× CH_2), 1.65–1.73 (2H, m, NH_2), 1.74–1.82 (2H, m, C(2)H_2), 2.04–2.11 (1H, m, C*H*), 3.10–3.19 (1H, m, C(3)*H*), 4.87 (1H, app td, *J* 10.6, 4.3, C(1′)*H*), 7.14–7.35 (5H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 21.8 (C(5′)*Me*), 23.2 (*C*(4)), 24.2 (*C*(3″)), 26.4 (*C*H$_2$), 28.6 (*C*(1″)), 31.3 (*C*H), 34.5 (*C*H$_2$), 39.5 (*C*(2″)), 41.8 (*C*H$_2$), 43.7 (*C*H), 43.9 (*C*(2)), 50.2 (*C*(3)), 73.9 (*C*(1′)), 124.9, 125.4, 127.9 (*o*,*m*,*p*-*Ph*), 151.7 (*i*-*Ph*), 171.8 (*C*(1)); *m*/*z* (ESI$^+$) 318 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{20}H_{32}NO_2^+$ ([M+H]$^+$) requires 318.2428; found 318.2428.

4.7.17. (1′R,2′S,5′R)-2′-(2″-Phenylpropan-2″-yl)-5′-methylcyclohexyl (R)-3-amino-3-phenylpropanoate ***42***.



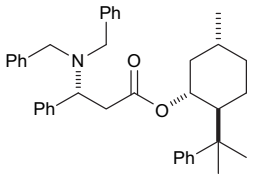
Following general procedure 4, **24** (168 mg, 0.29 mmol) and Pd(OH)$_2$/C (85 mg) in MeOH/AcOH (v/v 40:1, 4.1 mL) under H_2 (5 atm) for 18 h gave **42**. Purification via flash column chromatography (eluent 30–40 °C petrol (1% Et_3N)/Et_2O, 3:1, increased to 1:3) gave **42** as a colourless oil (67 mg, 61%, >99:1 dr); $[\alpha]_D^{25}$ +42.8 (*c* 0.5 in $CHCl_3$); ν_{max} (film) 3385 (N–H), 2955, 2923 (C–H), 1722 (C=O); δ_H (500 MHz, $CDCl_3$) 0.82–1.16 (3H, m, CH_2, C*H*), 0.86 (3H, d, *J* 6.3, C(5′)*Me*), 1.18 (3H, s, C(1″)H_3), 1.28 (3H, s, C(3″)H_3), 1.39–1.83 (4H, m, 2× CH_2), 1.73 (2H, br s, NH_2), 1.97–2.04 (1H, m, C*H*), 1.99 (1H, dd, *J* 16.1, 4.4, C(2)H_A), 2.15 (1H, dd, *J* 16.1, 9.5, C(2)H_B), 4.15 (1H, dd, *J* 9.5, 4.4, C(3)*H*), 4.82 (1H, app td, *J* 10.7, 4.4, C(1′)*H*), 7.05–7.35 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 21.8 (C(5′)*Me*), 24.6 (*C*(3″)), 26.5 (*C*H$_2$), 28.3 (*C*(1″)), 31.3 (*C*H), 34.5 (*C*H$_2$), 39.7 (*C*(2″)), 41.6 (*C*H$_2$), 43.8 (*C*(2)), 50.3 (*C*H), 52.2 (*C*(3)), 74.2 (*C*(1′)), 125.1, 125.4, 126.3, 127.2, 128.0, 128.4 (*o*,*m*,*p*-*Ph*), 144.6, 151.5 (*i*-*Ph*), 171.4 (*C*(1)); *m*/*z* (ESI$^+$) 380 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{25}H_{34}NO_2^+$ ([M+H]$^+$) requires 380.2584; found 380.2581.

4.7.18. (1′R,2′S,5′R)-2′-(2″-Phenylpropan-2″-yl)-5′-methylcyclohexyl (S)-3-(N,N-dibenzylamino)butanoate ***33***.



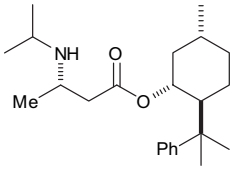
Following general procedure 5, **41** (100 mg, 0.31 mmol) was reacted with K_2CO_3 (435 mg, 3.15 mmol) in BnBr (0.37 mL, 3.15 mmol). Purification via flash column chromatography (gradient elution, 1%→10% Et_2O in 30–40 °C petrol) gave **33** as a white solid (147 mg, 95%, >99:1 dr); mp 71–72 °C; $[\alpha]_D^{25}$ +12.8 (*c* 0.5 in $CHCl_3$).

4.7.19. (1′R,2′S,5′R)-2′-(2″-Phenylpropan-2″-yl)-5′-methylcyclohexyl (R)-3-(N,N-dibenzylamino)-3-phenylpropanoate ***35***.



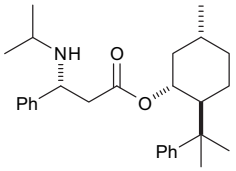
Following general procedure 5, **42** (55 mg, 0.15 mmol) was reacted with K_2CO_3 (200 mg, 1.45 mmol) in BnBr (0.17 mL, 1.45 mmol). Purification via flash column chromatography (gradient elution, 1%→10% Et_2O in 30–40 °C petrol) gave **35** as a colourless oil (71 mg, 88%, >99:1 dr).

4.7.20. (1′R,2′S,5′R)-2′-(2″-Phenylpropan-2″-yl)-5′-methylcyclohexyl (S)-3-(N-isopropylamino)butanoate ***45***.



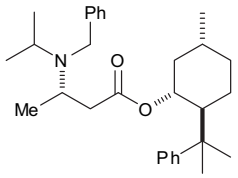
Following general procedure 6, **41** (76 mg, 0.24 mmol), acetone (35 μL, 0.48 mmol) and $NaBH_3CN$ (60 mg, 0.96 mmol) were reacted in MeOH (2 mL). Purification via flash column chromatography (gradient elution, 1%→50% Et_2O in 30–40 °C petrol) gave **45** as a colourless oil (63 mg, 73%, >99:1 dr); $[\alpha]_D^{25}$ −2.2 (*c* 0.5 in $CHCl_3$); ν_{max} (film) 3321 (N–H), 2962, 2925 (C–H), 1725 (C=O); δ_H (400 MHz, $CDCl_3$) 0.87 (3H, d, *J* 6.3, C(5′)*Me*), 0.90–1.18 (3H, m, CH_2, C*H*), 0.98 (3H, d, *J* 6.6, C(4)H_3), 1.01 (3H, d, *J* 6.3, NCH*Me*$_A$), 1.03 (3H, d, *J* 6.3, NCH*Me*$_B$), 1.20 (3H, s, C(1″)H_3), 1.31 (3H, s, C(3″)H_3), 1.39–1.89 (4H, m, 2× CH_2), 1.42–1.45 (1H, m, N*H*), 1.70 (1H, dd, *J* 15.4, 6.3, C(2)H_A), 1.93 (1H, dd, *J* 15.4, 6.3, C(2)H_B), 1.97–2.07 (1H, m, C*H*), 2.80 (1H, septet, *J* 6.3, C*H*Me$_2$), 2.94–3.03 (1H, m, C(3)*H*), 4.82 (1H, app td, *J* 10.6, 4.3, C(1′)*H*), 7.08–7.32 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.6 (*C*(4)), 21.8 (C(5′)*Me*), 22.8, 23.3 (NCH*Me*$_2$), 24.7 (*C*(3″)), 26.6 (*C*H$_2$), 28.1 (*C*(1″)), 29.7 (*C*H$_2$), 31.3 (*C*H), 34.6 (*C*H$_2$), 39.7 (*C*(2″)), 41.7 (*C*(2)), 45.3 (*C*H), 47.0 (*C*HMe$_2$), 50.2 (*C*(3)), 74.1 (*C*(1′)), 125.0, 125.3, 128.0 (*o*,*m*,*p*-*Ph*), 150.6 (*i*-*Ph*), 171.6 (*C*(1)); *m*/*z* (ESI$^+$) 360 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{23}H_{38}NO_2^+$ ([M+H]$^+$) requires 360.2897; found 360.2897.

4.7.21. (1′R,2′S,5′R)-2′-(2″-Phenylpropan-2″-yl)-5′-methylcyclohexyl (R)-3-(isopropylamino)-3-phenylpropanoate ***46***.



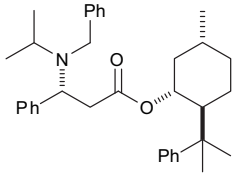
Following general procedure 6, **42** (125 mg, 0.33 mmol), acetone (48 μL, 0.66 mmol) and $NaBH_3CN$ (83 mg, 1.32 mmol) were reacted in MeOH (3 mL). Purification via flash column chromatography (gradient elution, 1%→50% Et_2O in 30–40 °C petrol) gave **46** as a colourless oil (86 mg, 62%, >99:1 dr); $[\alpha]_D^{25}$ +26.8 (*c* 0.5 in $CHCl_3$); ν_{max} (film) 3407 (N–H), 2959, 2924 (C–H), 1725 (C=O); δ_H (500 MHz, $CDCl_3$) 0.80–1.15 (3H, m, CH_2, C*H*), 0.88 (3H, d, *J* 6.6, C(5′)*Me*), 0.98 (3H, d, *J* 6.3, NCH*Me*$_A$), 1.06 (3H, d, *J* 6.3, NCH*Me*$_B$), 1.19 (3H, s, C(1″)H_3), 1.27 (3H, s, C(3″)H_3), 1.39–1.72 (4H, m, 2× CH_2), 1.72–1.80 (1H, m, N*H*), 1.96–2.04 (1H, m, C*H*), 2.07 (1H, dd, *J* 15.7, 6.1, C(2)H_A), 2.23 (1H, dd, *J* 15.7, 8.2, C(2)H_B), 2.52–2.62 (1H, m, C*H*Me$_2$), 4.01 (1H, dd, *J* 8.2, 6.1, C(3)*H*), 4.80 (1H, app td, *J* 10.6, 4.3, C(1′)*H*), 7.08–7.38 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 21.7 (C(5′)*Me*), 21.9, 24.2 (NCH*Me*$_2$), 25.1 (*C*(3″)), 26.5 (*C*H$_2$), 27.5 (*C*(1″)), 31.2 (*C*H), 34.5 (*C*H$_2$), 39.6 (*C*(2″)), 41.6 (*C*H$_2$), 43.1 (*C*(2)), 45.5 (*C*H), 50.3 (*C*HMe$_2$), 56.5 (*C*(3)), 74.4 (*C*(1′)), 125.1, 125.4, 127.1, 127.8, 128.4 (*o*,*m*,*p*-*Ph*), 143.1, 151.5 (*i*-*Ph*), 171.1 (*C*(1)); *m*/*z* (ESI$^+$) 422 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{40}NO_2^+$ ([M+H]$^+$) requires 422.3054; found 422.3054.

4.7.22. (1′R,2′S,5′R)-2′-(2″-Phenylpropan-2″-yl)-5′-methylcyclohexyl (S)-3-(N-isopropyl-N-benzylamino)butanoate ***34***.



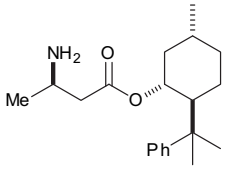
Following general procedure 5, **45** (62 mg, 0.17 mmol) was reacted with K_2CO_3 (238 mg, 1.72 mmol) in BnBr (0.21 mL, 1.72 mmol). Purification via flash column chromatography (gradient elution, 1%→10% Et_2O in 30–40 °C petrol) gave **34** as a colourless oil (70 mg, 90%, >99:1 dr).

4.7.23. (1′R,2′S,5′R)-2′-(2″-Phenylpropan-2″-yl)-5′-methylcyclohexyl (R)-3-(N-isopropyl-N-benzylamino)-3-phenylpropanoate ***36***.



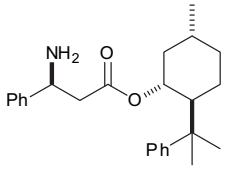
Following general procedure 5, **46** (67 mg, 0.16 mmol) was reacted with K_2CO_3 (221 mg, 1.59 mmol) in BnBr (0.19 mL, 1.59 mmol). Purification via flash column chromatography (gradient elution, 1%→10% Et_2O in 30–40 °C petrol) gave **36** as a colourless oil (68 mg, 83%, >99:1 dr).

4.7.24. (1′R,2′S,5′R)-2′-(2″-Phenylpropan-2″-yl)-5′-methylcyclohexyl (R)-3-aminobutanoate ***43***.



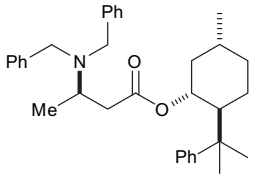
Following general procedure 4, **29** (160 mg, 0.31 mmol) and $Pd(OH)_2/C$ (80 mg) in EtOAc (4 mL) under H_2 (5 atm) for 18 h gave **43** as a colourless oil (97 mg, 98%, >99:1 dr); $[\alpha]_D^{25}$ −25.0 (*c* 0.5 in $CHCl_3$); ν_{max} (film) 3378 (N–H), 2957, 2924 (C–H), 1724 (C=O); δ_H (400 MHz, $CDCl_3$) 0.82–1.17 (3H, m, CH_2, C*H*), 0.85 (3H, d, *J* 6.6, C(5′)*Me*), 0.94 (3H, d, *J* 6.3, C(4)H_3), 1.18 (3H, s, C(1″)H_3), 1.30 (3H, s, C(3″)H_3), 1.32–1.78 (4H, m, 2× CH_2), 1.61–1.73 (2H, m, NH_2), 1.79–1.90 (2H, m, C(2)H_2), 1.95–2.08 (1H, m, C*H*), 2.97–3.10 (1H, m, C(3)*H*), 4.80 (1H, app td, *J* 10.6, 4.3, C(1′)*H*), 7.09–7.31 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.7 (C(5′)*Me*), 23.2 (*C*(4)), 24.4 (*C*(3″)), 26.5 (*C*H_2), 28.4 (*C*(1″)), 31.5 (*C*H), 34.5 (*C*H_2), 39.7 (*C*(2″)), 41.3 (*C*H_2), 43.7 (*C*H), 44.3 (*C*(2)), 50.2 (*C*(3)), 74.5 (*C*(1′)), 125.1, 125.5, 128.0 (*o*,*m*,*p*-*Ph*), 151.8 (*i*-*Ph*), 171.2 (*C*(1)); *m*/*z* (ESI$^+$) 318 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{20}H_{32}NO_2^+$ ([M+H]$^+$) requires 318.2428; found 318.2427.

4.7.25. (1′R,2′S,5′R)-2′-(2″-Phenylpropan-2″-yl)-5′-methylcyclohexyl (S)-3-amino-3-phenylpropanoate ***44***.



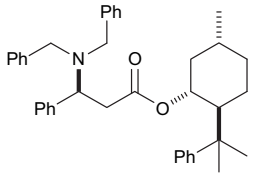
Following general procedure 4, **30** (189 mg, 0.33 mmol) and $Pd(OH)_2/C$ (95 mg) in MeOH/AcOH (v/v 40:1, 4.1 mL) under H_2 (5 atm) for 18 h gave **44**. Purification via flash column chromatography (eluent 30–40 °C petrol (1% Et_3N)/Et_2O, 3:1, increased to 1:3) gave **44** as a colourless oil (81 mg, 65%, >99:1 dr); $[\alpha]_D^{21}$ +4.2 (*c* 2.1 in $CHCl_3$); ν_{max} (film) 3385 (N–H), 2955, 2923 (C–H), 1722 (C=O); δ_H (400 MHz, $CDCl_3$) 0.80–1.17 (3H, m, CH_2, C*H*), 0.86 (3H, d, *J* 6.3, C(5′)*Me*), 1.21 (3H, s, C(1″)H_3), 1.32 (3H, s, C(3″)H_3), 1.38–1.83 (4H, m, 2× CH_2), 1.60–1.77 (2H, m, NH_2), 1.97–2.04 (1H, m, C*H*), 2.04–2.13 (2H, m, C(2)H_2), 4.11 (1H, dd, *J* 8.3, 5.1, C(3)*H*), 4.82 (1H, app td, *J* 10.9, 4.6, C(1′)*H*), 7.13–7.45 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.8 (C(5′)*Me*), 24.6 (*C*(3″)), 26.5 (*C*H_2), 28.3 (*C*(1″)), 31.3 (*C*H), 34.5 (*C*H_2), 39.7 (*C*(2″)), 41.6 (*C*H_2), 44.2 (*C*(2)), 50.2 (*C*H), 52.4 (*C*(3)), 74.4 (*C*(1′)), 125.1, 125.4, 126.3, 127.2, 128.0, 128.4 (*o*,*m*,*p*-*Ph*), 144.7, 151.7 (*i*-*Ph*), 171.2 (*C*(1)); *m*/*z* (ESI$^+$) 380 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{25}H_{34}NO_2^+$ ([M+H]$^+$) requires 380.2584; found 380.2581.

4.7.26. (1′R,2′S,5′R)-2′-(2″-Phenylpropan-2″-yl)-5′-methylcyclohexyl (R)-3-(N,N-dibenzylamino)butanoate ***37***.



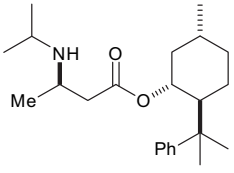
Following general procedure 5, **43** (86 mg, 0.27 mmol) was reacted with K_2CO_3 (375 mg, 2.71 mmol) in BnBr (0.32 mL, 2.71 mmol). Purification via flash column chromatography (gradient elution, 1%→10% Et_2O in 30–40 °C petrol) gave **37** as a colourless oil (116 mg, 86%, >99:1 dr).

4.7.27. (1′R,2′S,5′R)-2′-(2″-Phenylpropan-2″-yl)-5′-methylcyclohexyl (S)-3-(N,N-dibenzylamino)-3-phenylpropanoate ***39***.



Following general procedure 5, **44** (60 mg, 0.16 mmol) was reacted with K_2CO_3 (218 mg, 1.58 mmol) in BnBr (0.19 mL, 1.58 mmol). Purification via flash column chromatography (gradient elution, 1%→10% Et_2O in 30–40 °C petrol) gave **39** as a colourless oil (80 mg, 90%, >99:1 dr).

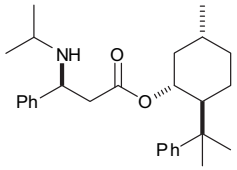
4.7.28. (1′R,2′S,5′R)-2′-(2″-Phenylpropan-2″-yl)-5′-methylcyclohexyl (R)-3-(N-isopropylamino)butanoate ***47***.



Following general procedure 6, **43** (96 mg, 0.32 mmol), acetone (47 μL, 0.64 mmol) and $NaBH_3CN$ (80 mg, 1.26 mmol) were reacted in MeOH (2 mL). Purification via flash column chromatography (gradient elution, 1%→50% Et_2O in 30–40 °C petrol) gave **47** as a colourless oil (95 mg, 83%, >99:1 dr); $[\alpha]_D^{25}$ +6.0 (*c* 0.5 in $CHCl_3$); ν_{max} (film) 3320 (N–H), 2960, 2924 (C–H), 1725 (C=O); δ_H (500 MHz, $CDCl_3$) 0.88 (3H, d, *J* 6.3, C(5′)*Me*), 0.90–1.18 (3H, m, CH_2, C*H*), 0.97 (3H, d, *J* 6.6, C(4)H_3), 1.00 (3H, d, *J* 6.3, NCHMe_A), 1.02 (3H, d, *J* 6.3, NCHMe_B), 1.22 (3H, s, C(1″)H_3), 1.31 (3H, s, C(3″)H_3), 1.39–1.89 (4H, m, 2× CH_2), 1.42–1.45 (1H, m, N*H*), 1.71 (1H, dd, *J* 15.4, 6.3, C(2)H_A), 2.00 (1H, dd, *J* 15.4, 6.3, C(2)H_B), 1.97–2.07 (1H, m,

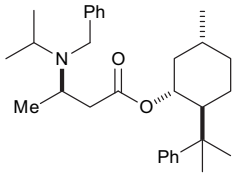
CH), 2.79 (1H, septet, *J* 6.3, CHMe$_2$), 2.88–2.95 (1H, m, C(3)*H*), 4.80 (1H, app td, *J* 10.6, 4.3, C(1′)*H*), 7.08–7.32 (5H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 20.1 (*C*(4)), 21.8 (C(5′)*Me*), 22.2, 22.8 (NCH*Me*$_2$), 25.2 (*C*(3″)), 26.6 (*C*H$_2$), 27.8 (*C*(1″)), 31.0 (*C*H$_2$), 31.3 (*C*H), 34.5 (*C*H$_2$), 39.7 (*C*(2″)), 41.8 (*C*(2)), 45.6 (*C*H), 47.2 (*C*HMe$_2$), 50.3 (*C*(3)), 74.6 (*C*(1′)), 125.1, 125.4, 127.9 (*o*,*m*,*p*-*Ph*), 151.5 (*i*-*Ph*), 171.4 (*C*(1)); *m*/*z* (ESI$^+$) 360 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{23}H_{38}NO_2^+$ ([M+H]$^+$) requires 360.2897; found 360.2897.

4.7.29. (1′R,2′S,5′R)-2′-(2″-Phenylpropan-2″-yl)-5′-methylcyclohexyl (S)-3-(N-isopropylamino)-3-phenylpropanoate ***48****.*



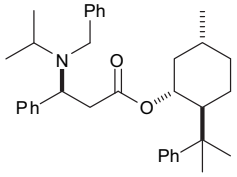
Following general procedure 6, **44** (85 mg, 0.22 mmol), acetone (38 μL, 0.52 mmol) and $NaBH_3CN$ (65 mg, 1.04 mmol) were reacted in MeOH (2 mL). Purification via flash column chromatography (gradient elution, 1%→50% Et_2O in 30–40 °C petrol) gave **48** as a colourless oil (82 mg, 75%, >99:1 dr); $[\alpha]_D^{25}$ −11.6 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3426 (N–H), 2970, 2927 (C–H), 1726 (C=O); δ_H (400 MHz, $CDCl_3$) 0.73–1.14 (3H, m, C*H*$_2$, C*H*), 0.84 (3H, d, *J* 6.6, C(5′)*Me*), 0.96 (3H, d, *J* 6.3, NCH*Me*$_A$), 1.00 (3H, d, *J* 6.3, NCH*Me*$_B$), 1.21 (3H, s, C(1″)*H*$_3$), 1.30 (3H, s, C(3″)*H*$_3$), 1.34–1.72 (4H, m, 2× C*H*$_2$), 1.59–1.66 (1H, m, N*H*), 1.93–2.01 (1H, m, C*H*), 2.04 (1H, dd, *J* 15.2, 5.8, C(2)*H*$_A$), 2.15 (1H, dd, *J* 15.2, 8.6, C(2)*H*$_B$), 2.54 (1H, septet, *J* 6.3, C*H*Me$_2$), 3.94 (1H, dd, *J* 8.6, 5.8, C(3)*H*), 4.76 (1H, app td, *J* 10.6, 4.3, C(1′)*H*), 7.09–7.34 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.7 (C(5′)*Me*), 21.9, 24.2 (NCH*Me*$_2$), 25.0 (*C*(3″)), 26.5 (*C*H$_2$), 27.9 (*C*(1″)), 31.2 (*C*H), 34.5 (*C*H$_2$), 39.7 (*C*(2″)), 41.5 (*C*H$_2$), 43.5 (*C*(2)), 45.4 (*C*H), 50.3 (*C*HMe$_2$), 56.7 (*C*(3)), 74.3 (*C*(1′)), 125.1, 125.4, 127.0, 127.9, 128.3 (*o*,*m*,*p*-*Ph*), 143.3, 151.6 (*i*-*Ph*), 171.1 (*C*(1)); *m*/*z* (ESI$^+$) 422 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{40}NO_2^+$ ([M+H]$^+$) requires 422.3054; found 422.3054.

4.7.30. (1′R,2′S,5′R)-2′-(2″-Phenylpropan-2″-yl)-5′-methylcyclohexyl (R)-3-(N-isopropyl-N-benzylamino)butanoate ***38****.*



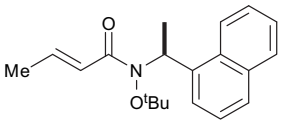
Following general procedure 5, **47** (76 mg, 0.21 mmol) was reacted with K_2CO_3 (292 mg, 2.11 mmol) in BnBr (0.25 mL, 2.11 mmol). Purification via flash column chromatography (gradient elution, 1%→10% Et_2O in 30–40 °C petrol) gave **38** as a colourless oil (71 mg, 75%, >99:1 dr).

4.7.31. (1′R,2′S,5′R)-2′-(2″-Phenylpropan-2″-yl)-5′-methylcyclohexyl (S)-3-(N-isopropyl-N-benzylamino)-3-phenylpropanoate ***40****.*



Following general procedure 5, **48** (60 mg, 0.14 mmol) was reacted with K_2CO_3 (196 mg, 1.42 mmol) in BnBr (0.17 mL, 1.42 mmol). Purification via flash column chromatography (gradient elution, 1%→10% Et_2O in 30–40 °C petrol) gave **40** as a colourless oil (58 mg, 80%, >99:1 dr).

4.7.32. (S)-N-tert-Butoxy-N-1′-(1″-naphthyl)ethyl (E)-but-2-enamide ***54****.*

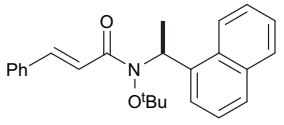


K_2CO_3 (5.80 g, 42.0 mmol) and crotonoyl chloride (1.00 mL, 10.5 mmol) were added sequentially to a stirred solution of (*S*)-**8**·(+)-CSA[8a] (2.00 g, 4.20 mmol) in CH_2Cl_2 (40 mL) at rt. The resultant mixture was stirred at rt for 12 h then quenched with H_2O (40 mL). The aqueous layer was extracted with CH_2Cl_2 (3×40 mL) and the combined organic extracts were washed with brine (40 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (gradient elution, 1%→20% Et_2O in 30–40 °C petrol) gave **54** as a colourless oil that crystallised upon standing (1.15 g, 88%, >99:1 dr); $C_{20}H_{25}NO_2$ requires C, 77.1; H, 8.1; N, 4.5%; found C, 77.0; H, 8.2; N, 4.4%; mp 68–70 °C; $[\alpha]_D^{24}$ −87.6 (*c* 1.0 in $CHCl_3$); ν_{max} (KBr) 2979, 2937, 2913 (C–H), 1657 (C=O), 1624 (C=C); δ_H (250 MHz, PhMe-d_8, 343 K) 0.69 (9H, s, C*Me*$_3$), 1.55 (3H, dd, *J* 6.7, 1.5, C(4)*H*$_3$), 1.68 (3H, d, *J* 7.0, C(1′)*Me*), 6.35–6.56 (1H, br m, C(1′)*H*), 6.63 (1H, dq, *J* 15.2, 1.5, C(2)*H*), 7.03–7.29 (3H, m, C(3)*H*, *Ar*), 7.31–7.42 (1H, m, *Ar*), 7.48–7.66 (3H, m, *Ar*), 8.48–8.72 (1H, br m, *Ar*); δ_C (100 MHz, $CDCl_3$) 16.2 (C(1′)*Me*), 18.4 (*C*(4)), 27.8 (C*Me*$_3$), 55.4 (*C*(1′)), 82.6 (*C*Me$_3$), 123.3 (*C*(2)), 126.5 (*C*(3)), 124.1, 124.2, 124.4, 124.9, 125.6, 126.0, 128.6, 133.6, 136.4, 142.9 (*Ar*), 173.7 (*C*(1)); *m*/*z* (ESI$^+$) 334 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{20}H_{25}NNaO_2^+$ ([M+Na]$^+$) requires 334.1778; found 334.1780.

4.7.32.1. X-ray crystal structure determination for ***54****.* Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[40]

X-ray crystal structure data for **54** [$C_{20}H_{25}NO_2$]: *M*=622.85, monoclinic, space group *P*2$_1$, *a*=13.1038(2) Å, *b*=9.7412(2) Å, *c*=14.4605(3) Å, *β*=101.4490(9)°, *V*=1809.11(6) Å^3, *Z*=4, *μ*=0.073 mm^{-1}, colourless block, crystal dimensions=0.16×0.19×0.21 mm^3. A total of 4332 unique reflections were measured for $5<\theta<27$ and 4332 reflections were used in the refinement. The final parameters were wR_2=0.106 and R_1=0.051 [$I>-3.0\sigma(I)$]. Crystallographic data (excluding structure factors) has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 815828. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

4.7.33. (S)-N-tert-Butoxy-N-1′-(1″-naphthyl)ethyl (E)-3-phenylpropanamide ***55****.*



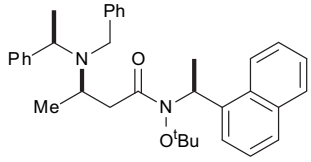
K_2CO_3 (5.80 g, 42.0 mmol) and cinnamoyl chloride (1.76 g, 10.5 mmol) were added sequentiallly to a stirred solution of (*S*)-**8**·(+)-CSA[8a] (2.00 g, 4.20 mmol) in CH_2Cl_2 (40 mL) at rt. The resultant mixture was stirred at rt for 12 h then quenched with

H_2O (40 mL). The aqueous layer was extracted with CH_2Cl_2 (3×40 mL) and the combined organic extracts were washed with brine (40 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (gradient elution, 1%→20% Et_2O in 30–40 °C petrol) gave **55** as a colourless oil that crystallised upon standing (1.47 g, 94%, >99:1 dr); mp 85–86 °C; $[\alpha]_D^{17}$ −44.5 (*c* 1.0 in $CHCl_3$); ν_{max} (KBr) 2975, 2932 (C–H), 1648 (C=O), 1623 (C=C); δ_H (250 MHz, PhMe-d_8, 343 K) 0.73 (9H, s, CMe_3), 1.73 (3H, d, *J* 6.7, C(1′)*Me*), 6.47–6.64 (1H, br m, C(1′)*H*), 7.05–7.15 (2H, m, *Ar*), 7.18–7.45 (7H, m, C(2)*H*, *Ar*, *Ph*), 7.53–7.66 (3H, m, *Ar*), 7.92 (1H, d, *J* 15.8, C(3)*H*), 8.56–8.76 (1H, br m, *Ar*); δ_C (100 MHz, $CDCl_3$) 16.4 (C(1′)*Me*), 27.8 (CMe_3), 55.6 (*C*(1′)), 83.1 (*C*Me_3), 118.8 (*C*(2)), 126.6 (*C*(3)), 124.5, 124.9, 125.7, 126.1, 128.0, 128.6, 128.9, 129.9, 133.7, 135.4, 143.3 (*Ar*, *Ph*), 173.8 (*C*(1)); *m*/*z* (ESI$^+$) 396 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{25}H_{27}NNaO_2^+$ ([M+Na]$^+$) requires 396.1934; found 396.1932.

*4.7.33.1. X-ray crystal structure determination for **55**.* Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[40]

X-ray crystal structure data for **55** [$C_{25}H_{27}NO_2$]: *M*=373.49, orthorhombic, space group $P2_12_12_1$, *a*=8.11180(10) Å, *b*=26.0315(4) Å, *c*=9.7014(2) Å, *V*=2048.75(6) Å^3, *Z*=4, μ=0.076 mm^{-1}, colourless plate, crystal dimensions=0.16×0.20×0.28 mm^3. A total of 2632 unique reflections were measured for 5<θ<27 and 2028 reflections were used in the refinement. The final parameters were wR_2=0.065 and R_1=0.031 [*I*>−3.0σ(*I*)]. Crystallographic data (excluding structure factors) has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 815829. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

*4.7.34. (S)-N-tert-Butoxy-N-1′-(1″-naphthyl)ethyl (R,R)-3-[N-benzyl-N-(α-methylbenzyl)amino]butanamide **56**.*



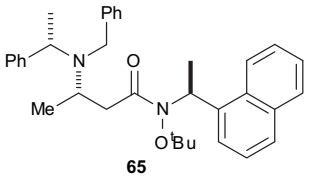
Method A: Following general procedure 1, a solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (101 mg, 0.48 mmol) in THF (1 mL) at −78 °C was treated with BuLi (2.5 M in hexanes, 0.15 mL, 0.39 mmol) and **54** (75 mg, 0.24 mmol) in THF (1 mL) to give **56** in >95:5 dr. Purification via flash column chromatography (gradient elution, 1%→10% Et_2O in 30–40 °C petrol) gave **56** as a colourless oil that crystallised upon standing (102 mg, 81%, >95:5 dr); $C_{35}H_{42}N_2O_2$ requires C, 80.4; H, 8.1; N, 5.4%; found C, 80.5; H, 8.2; N, 5.3%; mp 155–158 °C; $[\alpha]_D^{25}$ +33.8 (*c* 0.5 in $CHCl_3$); ν_{max} (KBr) 2972, 2928 (C–H), 1660 (C=O); δ_H (250 MHz, PhMe-d_8, 343 K) 0.67 (9H, s, CMe_3), 1.23 (3H, d, *J* 6.4, C(1′)*Me*), 1.29 (3H, d, *J* 6.9, C(α)*Me*), 1.59 (3H, d, *J* 7.0, C(4)H_3), 2.30–2.43 (1H, br m, C(2)H_A), 2.48–2.60 (1H, br m, C(2)H_B), 3.66 (2H, AB system, J_{AB} 14.6, NCH_2Ph), 3.88 (1H, q, *J* 6.9, C(α)*H*), 3.80–3.90 (1H, m, C(3)*H*), 6.12–6.26 (1H, br m, C(1′)*H*), 6.92–7.40 (13H, m, *Ar*, *Ph*), 7.50–7.63 (3H, m, *Ar*, *Ph*), 8.25–8.39 (1H, br m, *Ar*); δ_C (100 MHz, $CDCl_3$) 14.2 (C(1′)*Me*), 18.9 (C(α)*Me*), 19.4 (*C*(4)), 27.8 (CMe_3), 29.8 (*C*(2)), 39.4 (*C*(α)), 49.7 (*C*(3)), 50.1 (NCH_2Ph), 58.8 (*C*(1′)), 82.3 (*C*Me_3), 124.9, 125.5, 126.1, 126.4, 126.5, 126.7, 127.7, 128.2, 128.6, 133.6, 142.4, 144.4 (*Ar*, *Ph*), 186.0 (*C*(1)); *m*/*z* (ESI$^+$) 523 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{35}H_{43}N_2O_2^+$ ([M+H]$^+$) requires 523.3319; found 523.3320.

Method B: Following general procedure 2, a solution of (*R*,*R*)-**25** (1.67 g, 4.72 mmol) in CH_2Cl_2 (16.0 mL) was treated with TFA (16.0 mL) to give a white foam (1.36 g). Then, following general procedure 3, a solution of the residue (156 mg) in CH_2Cl_2 (2 mL) was reacted with $(COCl)_2$ (0.10 mL, 1.04 mmol) and a mixture of (*S*)-**8**·(+)-CSA[8a] (100 mg, 0.21 mmol) and K_2CO_3 (290 mg, 2.10 mmol) in CH_2Cl_2 (1 mL). Purification via flash column chromatography (gradient elution, 1%→10% Et_2O in 30–40 °C petrol) gave **56** as a colourless oil that crystallised upon standing (18 mg, 16%, >95:5 dr); mp 155–158 °C; $[\alpha]_D^{25}$ +33.9 (*c* 1.0 in $CHCl_3$).

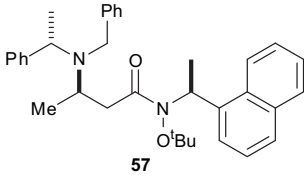
*4.7.34.1. X-ray crystal structure determination for **56**.* Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[40]

X-ray crystal structure data for **56** [$C_{35}H_{42}N_2O_2$]: *M*=522.73, monoclinic, space group $P2_1$, *a*=11.6903(3) Å, *b*=10.8507(3) Å, *c*=12.1629(3) Å, β=104.3593(14)°, *V*=1494.64(7) Å^3, *Z*=2, μ=0.071 mm^{-1}, colourless plate, crystal dimensions=0.11×0.13×0.24 mm^3. A total of 3557 unique reflections were measured for 5<θ<27 and 3120 reflections were used in the refinement. The final parameters were wR_2=0.079 and R_1=0.035 [*I*>−3.0σ(*I*)]. Crystallographic data (excluding structure factors) has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 815830. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

*4.7.35. (S)-N-tert-Butoxy-N-1′-(1″-naphthyl)ethyl (S,S)-3-[N-benzyl-N-(α-methylbenzyl)amino]butanamide **65** and (S)-N-tert-butoxy-N-1′-(1″-naphthyl)ethyl (3R,αS)-3-[N-benzyl-N-(α-methylbenzyl)amino] butanamide **57**.*



65



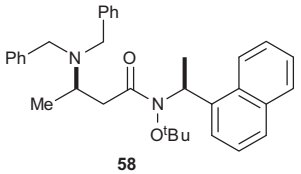
57

Method A: Following general procedure 1, a solution of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (101 mg, 0.48 mmol) in THF (1 mL) at −78 °C was treated with BuLi (2.5 M in hexanes, 0.15 mL, 0.39 mmol) and **54** (75 mg, 0.24 mmol) in THF (1 mL) to give a 75:25 mixture of **65** and **57**. Purification via flash column chromatography (gradient elution, 1%→10% Et_2O in 30–40 °C petrol) gave a 60:40 mixture of **65** and **57** as a colourless oil (38 mg, 30%); ν_{max} (film) 2974, 2932 (C–H), 1658 (C=O); *m*/*z* (ESI$^+$) 523 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{35}H_{43}N_2O_2^+$ ([M+H]$^+$) requires 523.3319; found 523.3316. Data for **65**: δ_H (250 MHz, PhMe-d_8, 343 K) 0.62 (9H, s, CMe_3), 1.15 (3H, d, *J* 6.4, C(1′)*Me*), 1.33 (3H, d, *J* 7.0, C(α)*Me*), 1.59 (3H, d, *J* 6.7, C(4)H_3), 2.26–2.41 (1H, br m, C(2)H_A), 2.50–2.67 (1H, br m, C(2)H_B), 3.67 (2H, AB system, J_{AB} 14.9, NCH_2Ph), 3.89 (1H, q, *J* 7.0, C(α)*H*), 3.87–4.01 (1H, m, C(3)*H*), 6.15–6.35 (1H, br m, C(1′)*H*), 6.95–7.46 (13H, m, *Ar*, *Ph*), 7.46–7.68 (3H, m, *Ar*, *Ph*), 8.35–8.50 (1H, br m, *Ar*); δ_C (125 MHz, $CDCl_3$) 17.4 (C(1′)*Me*), 18.8 (C(α)*Me*), 19.1 (*C*(4)), 27.7 (CMe_3), 29.7 (*C*(2)), 38.9 (*C*(α)), 49.8 (*C*(3)), 50.1 (NCH_2Ph), 58.4 (*C*(1′)), 82.3 (*C*Me_3), 124.8, 125.5, 126.1, 126.3, 126.5, 126.7, 127.7, 127.8, 128.1, 128.2, 128.6, 133.6, 136.2, 142.2, 144.1 (*Ar*, *Ph*), 179.5 (*C*(1)). Data for **57**: δ_H (250 MHz, PhMe-d_8, 343 K) [selected peaks] 0.72 (9H, s, CMe_3), 0.98 (3H, d, *J* 6.4, C(1′)*Me*), 1.68 (3H, d, *J* 6.7, C(4)H_3), 2.84–3.02 (1H, br m,

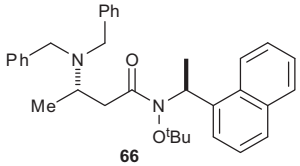
C(2)H_B); δ_C (125 MHz, $CDCl_3$) [selected peaks] 17.4 (C(1′)*Me*), 18.4 (C(α)*Me*), 19.1 (*C*(4)), 26.6 (C*Me*$_3$), 54.9 (*C*(1′)), 82.4 (*C*Me$_3$). Further elution gave a 90:10 mixture of **65** and **57** as a colourless oil (58 mg, 46%).

Method B: Following general procedure 2, a solution of (*S*,*S*)-**25** (1.75 g, 4.95 mmol) in CH_2Cl_2 (17.0 mL) was treated with TFA (17.0 mL) to give a white foam (1.32 g). Then, following general procedure 3, a solution of the residue (156 mg) in CH_2Cl_2 (2 mL) was reacted with $(COCl)_2$ (0.10 mL, 1.04 mmol) and a mixture of (*S*)-**8**·(+)-CSA[8a] (100 mg, 0.21 mmol) and K_2CO_3 (290 mg, 2.10 mmol) in CH_2Cl_2 (1 mL). Purification via flash column chromatography (gradient elution, 1%→10% Et_2O in 30–40 °C petrol) gave **65** as a colourless oil (16 mg, 15%, >95:5 dr); $[\alpha]_D^{25}$ −51.2 (*c* 0.5 in $CHCl_3$).

*4.7.36. (S)-N-tert-Butoxy-N-1′-(1″-naphthyl)ethyl (R)-3-(N,N-dibenzylamino)butanamide **58** and (S)-N-tert-butoxy-N-1′-(1″-naphthyl)ethyl (S)-3-(N,N-dibenzylamino)butanamide **66**.*



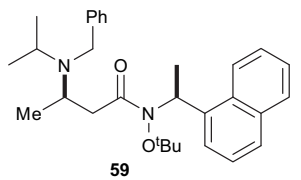
58



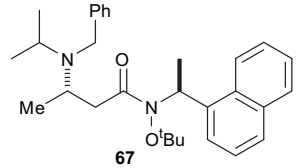
66

Following general procedure 1, a solution of dibenzylamine (0.14 mL, 0.71 mmol) in THF (1 mL) at −78 °C was treated with BuLi (1.2 M in hexanes, 0.47 mL, 0.57 mmol) and **54** (110 mg, 0.35 mmol) in THF (1 mL) to give a 80:20 mixture of **58** and **66**. Purification via flash column chromatography (gradient elution, 1%→10% Et_2O in 30–40 °C petrol) gave an 80:20 mixture of **58** and **66** as a colourless oil (119 mg, 66%); ν_{max} (film) 2973, 2928 (C–H), 1660 (C=O); *m*/*z* (ESI$^+$) 509 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{34}H_{41}N_2O_2^+$ ([M+H]$^+$) requires 509.3163; found 509.3164. Data for **58**: δ_H (500 MHz, PhMe-d_8, 343 K) 0.78 (9H, s, C*Me*$_3$), 1.15 (3H, d, *J* 6.6, C(1′)*Me*), 1.64 (3H, d, *J* 6.6, C(4)H_3), 2.43 (1H, dd, *J* 15.1, 9.1, C(2)H_A), 3.00 (1H, dd, *J* 15.1, 3.5, C(2)H_B), 3.53 (4H, AB system, J_{AB} 13.9, N(CH_2Ph)$_2$), 3.59–3.65 (1H, m, C(3)*H*), 6.19 (1H, q, *J* 6.6, C(1′)*H*), 6.89–7.36 (13H, m, *Ar*, *Ph*), 7.47–7.63 (3H, m, *Ar*, *Ph*), 8.28–8.39 (1H, br m, *Ar*); δ_C (125 MHz, $CDCl_3$) 14.4 (C(1′)*Me*), 15.7 (*C*(4)), 27.7 (C*Me*$_3$), 29.8 (*C*(2)), 38.1 (*C*(3)), 50.5 (*C*(1′)), 53.7 (N(*C*H$_2$Ph)$_2$), 82.4 (*C*Me$_3$), 124.1, 125.5, 126.2, 126.4, 126.7, 128.2, 128.5, 128.7, 129.0, 133.6, 140.3 (*Ar*, *Ph*), 179.4 (*C*(1)). Data for **66**: δ_H (500 MHz, PhMe-d_8, 343 K) 0.72 (9H, s, C*Me*$_3$), 1.09 (3H, d, *J* 6.6, C(1′)*Me*), 1.62 (3H, d, *J* 6.6, C(4)H_3), 2.61 (1H, dd, *J* 15.1, 9.1, C(2)H_A), 2.85–2.90 (1H, br m, C(2)H_B), 3.52 (4H, AB system, J_{AB} 13.9, N(CH_2Ph)$_2$), 3.65–3.71 (1H, m, C(3)*H*), 6.19 (1H, q, *J* 6.6, C(1′)*H*), 6.89–7.36 (13H, m, *Ar*, *Ph*), 7.47–7.63 (3H, m, *Ar*, *Ph*), 8.28–8.39 (1H, br m, *Ar*); δ_C (125 MHz, $CDCl_3$) 14.4 (C(1′)*Me*), 18.1 (*C*(4)), 27.7 (C*Me*$_3$), 31.8 (*C*(2)), 38.1 (*C*(3)), 50.5 (*C*(1′)), 55.0 (N(*C*H$_2$Ph)$_2$), 82.4 (*C*Me$_3$), 124.1, 125.5, 126.2, 126.4, 126.7, 128.2, 128.5, 128.7, 129.0, 133.6, 140.3 (*Ar*, *Ph*), 179.4 (*C*(1)).

*4.7.37. (S)-N-tert-Butoxy-N-1′-(1″-naphthyl)ethyl (R)-3-(N-isopropyl-N-benzylamino)butanamide **59** and (S)-N-tert-butoxy-N-1′-(1″-naphthyl)ethyl (S)-3-(N-isopropyl-N-benzylamino)butanamide **67**.*



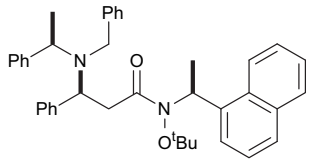
59



67

Following general procedure 1, a solution of *N*-benzyl-*N*-isopropylamine (0.13 mL, 0.77 mmol) in THF (1 mL) at −78 °C was treated with BuLi (1.2 M in hexanes, 0.51 mL, 0.62 mmol) and **54** (120 mg, 0.39 mmol) in THF (1 mL) to give an 80:20 mixture of **59** and **67**. Purification via flash column chromatography (gradient elution, 1%→10% Et_2O in 30–40 °C petrol) gave an 80:20 mixture of **59** and **67** as a colourless oil (124 mg, 70%); ν_{max} (film) 2972 (C–H), 1660 (C=O); *m*/*z* (ESI$^+$) 461 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{30}H_{41}N_2O_2^+$ ([M+H]$^+$) requires 461.3163; found 461.3158. Data for **59**: δ_H (250 MHz, PhMe-d_8, 343 K) 0.73 (9H, s, C*Me*$_3$), 0.97 (3H, d, *J* 6.6, NCH*Me*$_A$), 0.99 (3H, d, *J* 6.6, NCH*Me*$_B$), 1.17 (3H, d, *J* 6.6, C(1′)*Me*), 1.68 (3H, d, *J* 6.9, C(4)H_3), 2.39 (1H, dd, *J* 15.5, 8.8, C(2)H_A), 2.87 (1H, dd, *J* 15.5, 4.0, C(2)H_B), 2.91–2.97 (1H, m, C*H*Me$_2$), 3.59 (2H, AB system, J_{AB} 14.8, NCH_2Ph), 3.67–3.76 (1H, m, C(3)*H*), 6.19–6.36 (1H, br m, C(1′)*H*), 6.90–7.63 (11H, m, *Ar*, *Ph*), 8.32–8.49 (1H, br m, *Ar*); δ_C (125 MHz, $CDCl_3$) 18.4, 18.6 (NCH*Me*$_2$), 19.8 (C(1′)*Me*), 21.0 (*C*(4)), 27.9 (C*Me*$_3$), 29.7 (*C*(2)), 40.7 (*C*HMe$_2$), 47.2 (*C*(3)), 49.3 (NCH_2Ph), 54.7 (*C*(1′)), 82.3 (*C*Me$_3$), 123.2, 124.9, 125.5, 126.1, 126.3, 126.5, 128.0, 128.2, 128.6, 133.6, 142.3 (*Ar*, *Ph*), 179.7 (*C*(1)). Data for **67**: δ_H (250 MHz, PhMe-d_8, 343 K) [selected peaks] 0.70 (9H, s, C*Me*$_3$), 0.99 (3H, d, *J* 6.6, NCH*Me*$_A$), 1.01 (3H, d, *J* 6.6, NCH*Me*$_B$), 1.12 (3H, d, *J* 6.6, C(1′)*Me*), 1.65 (3H, d, *J* 6.9, C(4)H_3), 2.62–2.71 (2H, m, C(2)H_2); δ_C (125 MHz, $CDCl_3$) [selected peaks] 18.5 (NCH*Me*$_2$), 21.6 (*C*(4)), 27.6 (C*Me*$_3$), 49.0 (NCH_2Ph), 82.4 (*C*Me$_3$).

*4.7.38. (S)-N-tert-Butoxy-N-1′-(1″-naphthyl)ethyl (3S,αR)-3-[N-benzyl-N-(α-methylbenzyl)amino]-3-phenylpropanamide **60**.*



Method A: Following general procedure 1, a solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (114 mg, 0.54 mmol) in THF (1 mL) at −78 °C was treated with BuLi (2.5 M in hexanes, 0.17 mL, 0.43 mmol) and **55** (100 mg, 0.27 mmol) in THF (1 mL) to give **60** in >95:5 dr. Purification via flash column chromatography (gradient elution, 1%→10% Et_2O in 30–40 °C petrol) gave **60** as a colourless oil (126 mg, 80%, >95:5 dr); $[\alpha]_D^{25}$ +47.5 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3060, 2965, 2934 (C–H), 1659 (C=O); δ_H (500 MHz, PhMe-d_8, 343 K) 0.68 (9H, s, C*Me*$_3$), 1.29 (3H, d, *J* 6.9, C(1′)*Me*), 1.47 (3H, d, *J* 6.9, C(α)*Me*), 2.71 (1H, br m, C(2)H_A), 3.12 (1H, br m, C(2)H_B), 3.74 (2H, AB system, J_{AB} 14.8, NCH_2Ph), 4.06 (1H, q, *J* 6.9, C(α)*H*), 4.93 (1H, dd, *J* 10.1, 3.8, C(3)*H*), 5.82–6.01 (1H, br m, C(1′)*H*), 7.05–7.68 (21H, m, *Ar*, *Ph*), 7.91–8.05 (1H, br m, *Ar*); δ_C (100 MHz, $CDCl_3$) 27.3 (C*Me*$_3$), 27.8 (C(1′)*Me*), 30.9 (C(α)*Me*), 38.0 (*C*(2)), 51.1 (NCH_2Ph), 53.4 (*C*(α)), 56.7 (*C*(3)), 61.6 (*C*(1′)), 82.2 (*C*Me$_3$), 125.3, 125.9, 126.2, 126.4, 126.7, 127.0, 127.8, 128.1, 128.6, 133.5, 135.3, 142.7, 144.3 (*Ar*, *Ph*), 176.9 (*C*(1)); *m*/*z* (ESI$^+$) 585 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{40}H_{45}N_2O_2^+$ ([M+H]$^+$) requires 585.3476; found 585.3481.

Method B: Following general procedure 2, a solution of (3*S*,α*R*)-**26** (1.72 g, 4.14 mmol) in CH_2Cl_2 (17.0 mL) was treated with TFA (17.0 mL) to give a white foam (1.41 g). Then, following general procedure 3, a solution of the residue (170 mg) in CH_2Cl_2 (2 mL) was reacted with $(COCl)_2$ (80 μL, 0.95 mmol) and a mixture of (*S*)-**8**·(+)- CSA[8a] (90 mg, 0.19 mmol) and K_2CO_3 (263 mg, 1.90 mmol) in CH_2Cl_2 (1 mL). Purification via flash column chromatography (gradient elution, 1%→10% Et_2O in 30–40 °C petrol) gave **60** as a colourless oil (11 mg, 10%, >95:5 dr); $[\alpha]_D^{23}$ +46.9 (*c* 1.1 in $CHCl_3$).

4.7.39. (S)-N-tert-Butoxy-N-1′-(1″-naphthyl)ethyl (S,S)-3-[N-benzyl-N-(α-methylbenzyl)amino]-3-phenylpropanamide ***61*** *and (S)-N-tert-butoxy-N-1′-(1″-naphthyl)ethyl (3R,αS)-3-[N-benzyl-N-(α-methylbenzyl)amino]-3-phenylpropanamide* ***69***

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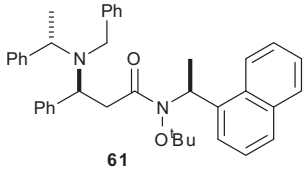
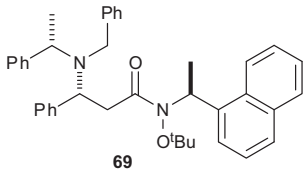


61

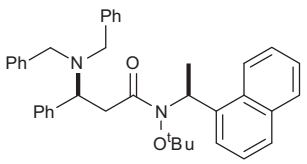


69

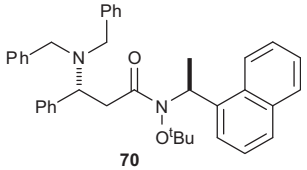
Following general procedure 1, a solution of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (114 mg, 0.54 mmol) in THF (1 mL) at −78 °C was treated with BuLi (2.5 M in hexanes, 0.17 mL, 0.43 mmol) and **55** (100 mg, 0.27 mmol) in THF (1 mL) to give a 60:40 mixture of **61** and **69**. Purification via flash column chromatography (gradient elution, 1%→10% Et_2O in 30–40 °C petrol) gave an 85:15 mixture of **61** and **69** as a colourless oil (28 mg, 18%); ν_{max} (film) 2974 (C–H), 1654 (C=O); *m*/*z* (ESI$^+$) 585 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{40}H_{45}N_2O_2^+$ ([M+H]$^+$) requires 585.3476; found 585.3481. Data for **61**: δ_H (250 MHz, PhMe-d_8, 343 K) 0.71 (9H, s, CMe_3), 1.27 (3H, d, *J* 6.7, C(1′)*Me*), 1.48 (3H, d, *J* 7.0, C(α)*Me*), 2.91–3.09 (1H, br m, C(2)H_A), 3.10–3.29 (1H, br m, C(2)H_B), 3.74 (2H, AB system, J_{AB} 15.2, NCH_2Ph), 4.07 (1H, q, *J* 7.0, C(α)*H*), 4.91 (1H, dd, *J* 9.1, 4.9, C(3)*H*), 5.84–6.09 (1H, br m, C(1′)*H*), 7.04–7.71 (21H, m, *Ar*, *Ph*), 7.91–8.12 (1H, br m, *Ar*); δ_C (125 MHz, $CDCl_3$) 18.7 (C(1′)*Me*), 27.5 (CMe_3), 31.0 (C(α)*Me*), 38.0 (*C*(2)), 50.4 (NCH_2Ph), 51.2 (*C*(α)), 56.4 (*C*(1′)), 57.8 (*C*(3)), 82.4 (CMe_3), 125.3, 125.9, 126.2, 126.4, 126.7, 127.0, 127.7, 127.8, 128.0, 128.1, 128.2, 128.6, 128.8, 133.5, 141.8, 142.8, 143.9 (*Ar*, *Ph*).[42] Data for **69**: δ_H (250 MHz, PhMe-d_8, 343 K) 0.44 (9H, s, CMe_3), 1.19 (3H, d, *J* 6.9, C(1′)*Me*), 1.33 (3H, d, *J* 7.0, C(α)*Me*), 2.40–2.51 (1H, br m, C(2)H_A), 3.25–3.40 (1H, br m, C(2)H_B), 3.70 (2H, AB system, J_{AB} 14.9, NCH_2Ph), 4.03 (1H, q, *J* 7.0, C(α)*H*), 4.95 (1H, dd, *J* 11.2, 3.1, C(3)*H*), 6.26 (1H, q, *J* 6.9, C(1′)*H*), 7.04–7.62 (21H, m, *Ar*, *Ph*), 8.51 (1H, d, *J* 8.2, *Ar*); δ_C (125 MHz, $CDCl_3$) 15.2 (C(1′)*Me*), 27.5 (CMe_3), 27.8 (C(α)*Me*), 37.8 (*C*(2)), 51.2 (NCH_2Ph), 54.0 (*C*(α)), 56.4 (*C*(3)), 61.6 (*C*(1′)), 82.3 (CMe_3), 124.4, 124.7, 125.6, 126.0, 126.3, 126.4, 126.7, 127.1, 127.7, 128.0, 128.1, 128.2, 128.4, 128.6, 128.9, 129.9, 132.4, 133.5, 136.3, 142.5, 144.0 (*Ar*, *Ph*).[42] Further elution gave a 50:50 mixture of **61** and **69** as a colourless oil (63 mg, 40%).

Method B: Following general procedure 2, a solution of (3*R*,α*S*)-**26** (1.66 g, 3.99 mmol) in CH_2Cl_2 (16.0 mL) was treated with TFA (16.0 mL) to give a white foam (1.32 g). Then, following general procedure 3, a solution of the residue (187 mg) in CH_2Cl_2 (2 mL) was reacted with $(COCl)_2$ (0.10 mL, 1.04 mmol) and a mixture of (*S*)-**8**·(+)-CSA[8a] (100 mg, 0.21 mmol) and K_2CO_3 (290 mg, 2.10 mmol) in CH_2Cl_2 (1 mL). Purification via flash column chromatography (gradient elution, 1%→10% Et_2O in 30–40 °C petrol) gave **69** as a colourless oil (15 mg, 12%, >95:5 dr).

4.7.40. (S)-N-tert-Butoxy-N-1′-(1″-naphthyl)ethyl (S)-3-(N,N-dibenzylamino)-3-phenylpropanamide ***62*** *and (S)-N-tert-butoxy-N-1′-(1″-naphthyl)ethyl (R)-3-(N,N-dibenzylamino)-3-phenylpropanamide* ***70***.



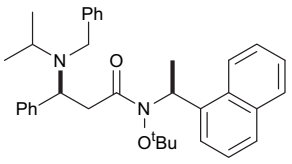
62



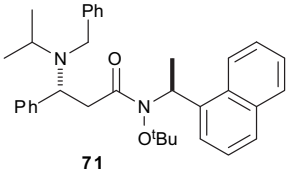
70

Following general procedure 1, a solution of dibenzylamine (77 μL, 0.40 mmol) in THF (1 mL) at −78 °C was treated with BuLi (2.5 M in hexanes, 0.13 mL, 0.32 mmol) and **55** (75 mg, 0.20 mmol) in THF (1 mL) to give a 70:30 mixture of **62** and **70**. Purification via flash column chromatography (gradient elution, 1%→10% Et_2O in 30–40 °C petrol) gave a 70:30 mixture of **62** and **70** as a colourless oil (71 mg, 62%); ν_{max} (film) 2977 (C–H), 1659 (C=O); *m*/*z* (ESI$^+$) 571 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{39}H_{43}N_2O_2^+$ ([M+H]$^+$) requires 571.3319; found 571.3316. Data for **62**: δ_H (250 MHz, PhMe-d_8, 343 K) 0.75 (9H, s, CMe_3), 1.54 (3H, d, *J* 7.0, C(1′)*Me*), 3.12–3.28 (2H, br m, C(2)H_2), 3.56 (4H, AB system, J_{AB} 14.0, N(CH_2Ph)$_2$), 4.78 (1H, app t, *J* 7.3, C(3)*H*), 5.98–6.19 (1H, br m, C(1′)*H*), 7.10–7.68 (21H, m, *Ar*, *Ph*), 8.05–8.22 (1H, br m, *Ar*); δ_C (100 MHz, $CDCl_3$) 28.0 (CMe_3), 36.0 (C(1′)*Me*), 53.5 (*C*(1′)), 54.5 (*C*(2)), 54.7 (N(CH_2Ph)$_2$), 54.8 (*C*(3)), 82.3 (CMe_3), 125.5, 126.1, 126.4, 127.0, 127.2, 128.0, 128.3, 128.4, 128.8, 128.9, 133.6, 139.3, 140.1, 140.3 (*Ar*, *Ph*).[42] Data for **70**: δ_H (250 MHz, PhMe-d_8, 343 K) 0.62 (9H, s, CMe_3), 1.29 (3H, d, *J* 7.0, C(1′)*Me*), 2.85–2.97 (2H, br m, C(2)H_2), 3.58 (4H, AB system, J_{AB} 13.7, N(CH_2Ph)$_2$), 4.77 (1H, app t, *J* 4.6, C(3)*H*), 6.26 (1H, q, *J* 7.0, C(1′)*H*), 7.10–7.68 (21H, m, *Ar*, *Ph*), 8.48 (1H, d, *J* 8.8, *Ar*); δ_C (100 MHz, $CDCl_3$) 29.8 (CMe_3), 36.0 (C(1′)*Me*), 53.5 (*C*(1′)), 54.5 (*C*(2)), 54.7 (N(CH_2Ph)$_2$), 54.8 (*C*(3)), 82.3 (CMe_3), 125.5, 126.1, 126.4, 127.0, 127.2, 128.0, 128.3, 128.4, 128.8, 128.9, 133.6, 139.3, 140.1, 140.3 (*Ar*, *Ph*).[42]

4.7.41. (S)-N-tert-Butoxy-N-1′-(1″-naphthyl)ethyl (S)-3-(N-isopropyl-N-benzylamino)-3-phenylpropanamide ***63*** *and (S)-N-tert-butoxy-N-1′-(1″-naphthyl)ethyl (R)-3-(N-isopropyl-N-benzylamino)-3-phenylpropanamide* ***71***.



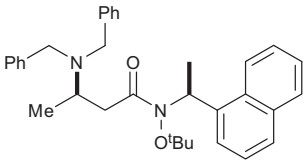
63



71

Following general procedure 1, a solution of *N*-benzyl-*N*-isopropylamine (67 μL, 0.40 mmol) in THF (1 mL) at −78 °C was treated with BuLi (2.5 M in hexanes, 0.13 mL, 0.32 mmol) and **55** (75 mg, 0.20 mmol) in THF (1 mL) to give an 80:20 mixture of **63** and **71**. Purification via flash column chromatography (gradient elution, 1%→10% Et_2O in 30–40 °C petrol) gave an 80:20 mixture of **63** and **71** as a colourless oil (63 mg, 60%); ν_{max} (film) 2973, 2930 (C–H), 1655 (C=O); *m*/*z* (ESI$^+$) 523 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{35}H_{43}N_2O_2^+$ ([M+H]$^+$) requires 523.3319; found 523.3319. Data for **63**: δ_H (500 MHz, PhMe-d_8, 343 K) 0.67 (9H, s, CMe_3), 0.86 (3H, d, *J* 6.6, NCHMe_A), 0.97 (3H, d, *J* 6.4, NCHMe_B), 1.49 (3H, d, *J* 7.0, C(1′)*Me*), 2.90–3.10 (2H, br m, C(2)H_2), 3.07–3.11 (1H, m, C*H*Me$_2$), 3.66 (2H, AB system, J_{AB} 15.2, NCH_2Ph), 4.79 (1H, app t, *J* 6.7, C(3)*H*), 5.88–6.12 (1H, br m, C(1′)*H*), 7.04–7.67 (16H, m, *Ar*, *Ph*), 8.57–8.75 (1H, br m, *Ar*); δ_C (125 MHz, $CDCl_3$) 17.3, 19.5 (NCHMe_2), 21.3 (C(1′)*Me*), 36.1 (*C*(2)), 27.6 (CMe_3), 39.0 (CHMe$_2$), 41.4 (*C*(1′)), 48.7 (NCH_2Ph), 54.1 (*C*(3)), 82.3 (CMe_3), 124.5, 124.9, 125.7, 126.3, 126.5, 126.8, 127.9, 128.2, 128.6, 128.8, 130.0, 133.6, 135.4, 143.1 (*Ar*, *Ph*), 179.3 (*C*(1)). Data for **71**: δ_H (500 MHz, PhMe-d_8, 343 K) 0.49 (9H, s, CMe_3), 0.88 (3H, d, *J* 6.6, NCHMe_A), 0.98 (3H, d, *J* 6.4, NCHMe_B), 1.49 (3H, d, *J* 7.0, C(1′)*Me*), 2.70–2.79 (1H, br m, C(2)H_A), 3.35–3.43 (1H, br m, C(2)H_B), 3.07–3.11 (1H, m, C*H*Me$_2$), 3.66 (2H, AB system, J_{AB} 15.2, NCH_2Ph), 4.74 (1H, app t, *J* 6.7, C(3)*H*), 6.27 (1H, q, *J* 7.0, C(1′)*H*), 7.04–7.67 (16H, m, *Ar*, *Ph*), 8.51 (1H, d, *J* 8.2, *Ar*); δ_C (125 MHz, $CDCl_3$) 15.2, 18.8 (NCHMe_2), 21.1 (C(1′)*Me*), 27.7 (CMe_3), 29.1 (*C*(2)), 33.7 (CHMe$_2$), 41.4 (*C*(1′)), 49.6 (NCH_2Ph), 62.7 (*C*(3)), 82.3 (CMe_3), 124.5, 124.9, 125.7, 126.3, 126.5, 126.8, 127.9, 128.2, 128.6, 128.8, 130.0, 133.6, 135.4, 143.1 (*Ar*, *Ph*), 179.3 (*C*(1)).

4.7.42. (S)-N-tert-Butoxy-N-1′-(1″-naphthyl)ethyl (R)-3-(N,N-dibenzylamino)butanamide ***58***.

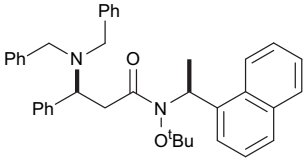


Step 1: Following general procedure 4, (*R*,*R*)-**25** (5.27 g, 14.9 mmol) and $Pd(OH)_2/C$ (1.32 g) in MeOH (50 mL) under H_2 (5 atm) for 36 h gave *tert*-butyl (*R*)-3-aminobutanoate as a colourless oil (1.48 g, 62%);[43] $[\alpha]_D^{23}$ −22.0 (*c* 1.0 in $CHCl_3$); {lit.[43] $[\alpha]_D^{25}$ −22.2 (*c* 0.5 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.13 (3H, d, *J* 6.5, C(4)H_3), 1.46 (9H, s, CMe_3), 1.85 (2H, br s, NH_2), 2.23 (1H, dd, *J* 15.4, 8.2, C(2)H_A), 2.34 (1H, dd, *J* 15.4, 4.8, C(2)H_B), 3.31–3.40 (1H, m, C(3)*H*).

Step 2: Following general procedure 5, *tert*-butyl (*R*)-3-aminobutanoate (740 mg, 4.65 mmol) was reacted with K_2CO_3 (6.43 g, 46.5 mmol) in BnBr (5.50 mL, 46.5 mmol). Purification via flash column chromatography (gradient elution, 1%→20% Et_2O in 30–40 °C petrol) gave *tert*-butyl (*R*)-3-(*N*,*N*-dibenzylamino)butanoate as a colourless oil that crystallised upon standing (1.02 g, 64%); mp 42–45 °C; $[\alpha]_D^{25}$ −12.3 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2974, 2933 (C–H), 1727 (C=O); δ_H (400 MHz, $CDCl_3$) 1.20 (3H, d, *J* 6.8, C(4)H_3), 1.54 (9H, s, CMe_3), 2.29 (1H, dd, *J* 13.9, 7.8, C(2)H_A), 2.70 (1H, dd, *J* 13.9, 6.6, C(2)H_B), 3.37–3.47 (1H, m, C(3)*H*), 3.66 (4H, AB system, J_{AB} 13.6, N(CH_2Ph)$_2$), 7.25–7.58 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.8 (*C*(4)), 28.3 (CMe_3), 40.1 (*C*(2)), 51.1 (*C*(3)), 53.6, 69.8 (N(CH_2Ph)$_2$), 80.1 (*C*Me$_3$), 126.9, 128.2, 128.4, 128.7, 128.9, 135.4 (*o*,*m*,*p*-*Ph*), 140.2, 155.1 (*i*-*Ph*), 171.9 (*C*(1)); *m*/*z* (ESI$^+$) 340 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{22}H_{30}NO_2^+$ ([M+H]$^+$) requires 340.2271; found 340.2270.

Step 3: Following general procedure 2, a solution of *tert*-butyl (*R*)-3-(*N*,*N*-dibenzylamino)butanoate (600 mg, 1.77 mmol) in CH_2Cl_2 (6.0 mL) was treated with TFA (6.0 mL) to give a white foam (501 mg). Then, following general procedure 3, a solution of the residue (298 mg) in CH_2Cl_2 (3 mL) was reacted with $(COCl)_2$ (0.18 mL, 2.10 mmol) and a mixture of (*S*)-**8**·(+)-CSA[8a] (200 mg, 0.42 mmol) and K_2CO_3 (580 mg, 4.20 mmol) in CH_2Cl_2 (2 mL). Purification via flash column chromatography (gradient elution, 1%→10% Et_2O in 30–40 °C petrol) gave **58** as a colourless oil (24 mg, 11%, >95:5 dr).

4.7.43. (S)-N-tert-Butoxy-N-1′-(1″-naphthyl)ethyl (S)-3-(N,N-dibenzylamino)-3-phenylpropanamide ***62***.

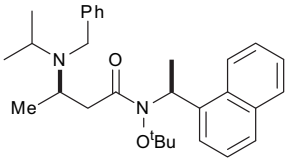


Step 1: Following general procedure 4, (3*S*,α*R*)-**26** (6.70 g, 16.1 mmol) and $Pd(OH)_2/C$ (1.70 g) in MeOH (65 mL) under H_2 (5 atm) for 36 h gave *tert*-butyl (*S*)-3-amino-3-phenylpropanoate as a colourless oil (2.48 g, 72%);[26a] $[\alpha]_D^{23}$ −22.0 (*c* 1.0 in $CHCl_3$); {lit.[26a] $[\alpha]_D^{20}$ −21.0 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.43 (9H, s, CMe_3), 1.71 (2H, br s, NH_2), 2.59 (2H, d, *J* 7.2, C(2)H_2), 4.38 (1H, app t, *J* 6.8, C(3)*H*), 7.24–7.40 (5H, m, *Ph*).

Step 2: Following general procedure 5, *tert*-butyl (*S*)-3-amino-3-phenylpropanoate (1.20 g, 5.42 mmol) was reacted with K_2CO_3 (7.50 g, 54.2 mmol) in BnBr (6.46 mL, 54.2 mmol). Purification via flash column chromatography (gradient elution, 1%→20% Et_2O in 30–40 °C petrol) gave *tert*-butyl (*S*)-3-(*N*,*N*-dibenzylamino)-3-phenylpropanoate as a white solid (1.54 g, 71%);[25a] mp 64–67 °C; {lit.[25a] mp 64–66 °C}; $[\alpha]_D^{25}$ −78.4 (*c* 2.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.34 (9H, s, CMe_3), 2.72 (1H, dd, *J* 14.3, 8.5, C(2)H_A), 3.00 (1H, dd, *J* 14.3, 6.8, C(2)H_B), 3.50 (4H, AB system, J_{AB} 13.7, N(CH_2Ph)$_2$), 4.28 (1H, app t, *J* 7.2, C(3)*H*), 7.18–7.40 (15H, m, *Ph*).

Step 3: Following general procedure 2, a solution of *tert*-butyl (*S*)-3-(*N*,*N*-dibenzylamino)-3-phenylpropanoate (938 mg, 2.34 mmol) in CH_2Cl_2 (10.0 mL) was treated with TFA (10.0 mL) to give a white foam (703 mg). Then, following general procedure 3, a solution of the residue (363 mg) in CH_2Cl_2 (4 mL) was reacted with $(COCl)_2$ (0.18 mL, 2.10 mmol) and a mixture of (*S*)-**8**·(+)-CSA[8a] (200 mg, 0.42 mmol) and K_2CO_3 (580 mg, 4.20 mmol) in CH_2Cl_2 (2 mL). Purification via flash column chromatography (gradient elution, 1%→10% Et_2O in 30–40 °C petrol) gave **62** as a colourless oil (26 mg, 10%, >95:5 dr).

4.7.44. (S)-N-tert-Butoxy-N-1′-(1″-naphthyl)ethyl (R)-3-(N-isopropyl-N-benzylamino)butanamide ***59***.

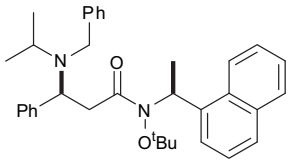


Step 1: Following general procedure 6, *tert*-butyl (*R*)-3-aminobutanoate (1.40 g, 8.79 mmol), acetone (1.29 mL, 17.6 mmol) and $NaBH_3CN$ (2.21 g, 35.2 mmol) were reacted in MeOH (40 mL). Purification via flash column chromatography (gradient elution, 1%→30% Et_2O in 30–40 °C petrol) gave *tert*-butyl (*R*)-3-(*N*-isopropylamino)butanoate as a colourless oil (1.33 g, 75%);[44] $[\alpha]_D^{23}$ −20.1 (*c* 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.41 (3H, d, *J* 6.5, C(4)H_3), 1.46 (3H, d, *J* 6.5, NCHMe_A), 1.47 (9H, s, CMe_3), 1.48 (3H, d, *J* 6.5, NCHMe_B), 2.70 (1H, dd, *J* 17.1, 6.8, C(2)H_A), 2.97 (1H, dd, *J* 17.1, 6.1, C(2)H_B), 3.33–3.44 (1H, m, NC*H*Me$_2$), 3.53–3.62 (1H, m, C(3)*H*).

Step 2: Following general procedure 5, *tert*-butyl (*R*)-3-(*N*-isopropylamino)butanoate (850 mg, 4.22 mmol) was reacted with K_2CO_3 (5.83 g, 42.2 mmol) in BnBr (5.00 mL, 42.2 mmol). Purification via flash column chromatography (gradient elution, 1%→20% Et_2O in 30–40 °C petrol) gave *tert*-butyl (*R*)-3-(*N*-isopropyl-*N*-benzylamino)butanoate as a colourless oil (849 mg, 69%); $[\alpha]_D^{25}$ −36.7 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2970, 2932 (C–H), 1729 (C=O); δ_H (400 MHz, $CDCl_3$) 1.08 (3H, d, *J* 6.6, NCHMe_A), 1.10 (3H, d, *J* 6.6, NCHMe_B), 1.16 (3H, d, *J* 6.8, C(4)H_3), 1.53 (9H, s, CMe_3), 2.21 (1H, dd, *J* 13.9, 6.8, C(2)H_A), 2.54 (1H, dd, *J* 13.9, 7.3, C(2)H_B), 2.93–3.04 (1H, m, NC*H*Me$_2$), 3.48–3.54 (1H, m, C(3)*H*), 3.70 (2H, AB system, J_{AB} 14.7, NCH_2Ph), 7.22–7.48 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 18.1, 19.5 (NCHMe_2), 21.3 (*C*(4)), 28.2 (CMe_3), 42.2 (*C*(2)), 48.6 (NCHMe$_2$), 49.0 (NCH_2Ph), 49.6 (*C*(3)), 79.9 (*C*Me$_3$), 127.8, 128.0, 128.3 (*o*,*m*,*p*-*Ph*), 142.0 (*i*-*Ph*), 172.1 (*C*(1)); *m*/*z* (ESI$^+$) 292 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{18}H_{30}NO_2^+$ ([M+H]$^+$) requires 292.2271; found 292.2270.

Step 3: Following general procedure 2, a solution of *tert*-butyl (*R*)-3-(*N*-isopropyl-*N*-benzylamino)butanoate (849 mg, 2.91 mmol) in CH_2Cl_2 (9.0 mL) was treated with TFA (9.0 mL) to give a white foam (516 mg). Then, following general procedure 3, a solution of the residue (396 mg) in CH_2Cl_2 (4 mL) was reacted with $(COCl)_2$ (0.14 mL, 1.68 mmol) and a mixture of (*S*)-**8**·(+)-CSA[8a] (160 mg, 0.34 mmol) and K_2CO_3 (470 mg, 3.40 mmol) in CH_2Cl_2 (4 mL). Purification via flash column chromatography (gradient elution, 1%→10% Et_2O in 30–40 °C petrol) gave **59** as a colourless oil (14 mg, 9%, >95:5 dr).

4.7.45. (S)-N-tert-Butoxy-N-1′-(1″-naphthyl)ethyl (S)-3-(N-isopropyl-N-benzylamino)-3-phenylpropanamide ***63****.*



Step 1: Following general procedure 6, *tert*-butyl (*S*)-3-amino-3-phenylpropanoate (1.00 g, 4.50 mmol), acetone (0.66 mL, 9.00 mmol) and $NaBH_3CN$ (1.13 g, 18.0 mmol) were reacted in MeOH (30 mL). Purification via flash column chromatography (gradient elution, 1%→30% Et_2O in 30–40 °C petrol) gave *tert*-butyl (*S*)-3-(*N*-isopropylamino)-3-phenylpropanoate as a colourless oil (1.12 g, 94%); $[\alpha]_D^{25}$ −23.1 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3328 (N–H), 2968, 2932 (C–H), 1727 (C=O); δ_H (400 MHz, $CDCl_3$) 0.98 (3H, d, *J* 6.3, NCH*Me*$_A$), 1.04 (3H, d, *J* 6.3, NCH*Me*$_B$), 1.38 (9H, s, C*Me*$_3$), 1.86 (1H, br s, N*H*), 2.51 (1H, dd, *J* 15.2, 6.1, C(2)*H*$_A$), 2.61 (1H, dd, *J* 15.2, 8.3, C(2)*H*$_B$), 2.56–2.65 (1H, m, NC*H*Me$_2$), 4.15 (1H, dd, *J* 8.3, 6.1, C(3)*H*), 7.20–7.38 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.9, 24.2 (NCH*Me*$_2$), 28.0 (C*Me*$_3$), 44.7 (*C*(2)), 45.6 (NCHMe$_2$), 57.0 (*C*(3)), 80.6 (*C*Me$_3$), 127.1, 127.2, 128.4 (*o*,*m*,*p*-*Ph*), 143.1 (*i*-*Ph*), 171.0 (*C*(1)); *m*/*z* (ESI^+) 264 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{16}H_{26}NO_2^+$ ($[M+H]^+$) requires 264.1958; found 264.1956.

Step 2: Following general procedure 5, *tert*-butyl (*S*)-3-(*N*-isopropylamino)-3-phenylpropanoate (1.12 g, 4.18 mmol) was reacted with K_2CO_3 (5.25 g, 41.8 mmol) in BnBr (4.50 mL, 41.8 mmol). Purification via flash column chromatography (gradient elution, 1%→20% Et_2O in 30–40 °C petrol) gave *tert*-butyl (*S*)-3-(*N*-isopropyl-*N*-benzylamino)-3-phenylpropanoate as a colourless oil (1.22 g, 83%); $[\alpha]_D^{25}$ −17.0 (*c* 0.5 in $CHCl_3$); ν_{max} (film) 2972, 2932 (C–H), 1728 (C=O); δ_H (400 MHz, $CDCl_3$) 0.86 (3H, d, *J* 6.6, NCH*Me*$_A$), 1.07 (3H, d, *J* 6.6, NCH*Me*$_B$), 1.28 (9H, s, C*Me*$_3$), 2.56 (1H, dd, *J* 14.2, 9.5, C(2)*H*$_A$), 2.81 (1H, dd, *J* 14.2, 5.9, C(2)*H*$_B$), 3.02–3.11 (1H, m, NC*H*Me$_2$), 3.71 (2H, AB system, J_{AB} 15.1, NC*H*$_2$Ph), 4.29 (1H, dd, *J* 9.5, 5.9, C(3)*H*), 7.21–7.43 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 18.5, 21.1 (NCH*Me*$_2$), 27.9 (C*Me*$_3$), 40.1 (*C*(2)), 48.2 (NCHMe$_2$), 49.4 (NCH$_2$Ph), 60.5 (*C*(3)), 80.1 (*C*Me$_3$), 126.4, 126.9, 128.0, 128.1, 128.3, 128.8 (*o*,*m*,*p*-*Ph*), 141.8, 142.2 (*i*-*Ph*), 171.3 (*C*(1)); *m*/*z* (ESI^+) 354 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{23}H_{32}NO_2^+$ ($[M+H]^+$) requires 354.2428; found 354.2427.

Step 3: Following general procedure 2, a solution of *tert*-butyl (*S*)-3-(*N*-isopropyl-*N*-benzylamino)-3-phenylpropanoate (1.13 g, 4.14 mmol) in CH_2Cl_2 (12.0 mL) was treated with TFA (12.0 mL) to give a white foam (1.00 g). Then, following general procedure 3, a solution of the residue (312 mg) in CH_2Cl_2 (4 mL) was reacted with $(COCl)_2$ (0.18 mL, 2.10 mmol) and a mixture of (*S*)-**8**·(+)-CSA[8a] (200 mg, 0.42 mmol) and K_2CO_3 (580 mg, 4.20 mmol) in CH_2Cl_2 (2 mL). Purification via flash column chromatography (gradient elution, 1%→10% Et_2O in 30–40 °C petrol) gave **63** as a colourless oil (19 mg, 8%, >95:5 dr).

Acknowledgements

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References and notes

1. (a) Davies, S. G.; Ichihara, O. *Tetrahedron: Asymmetry* **1991**, *2*, 183; (b) Costello, J. F.; Davies, S. G.; Ichihara, O. *Tetrahedron: Asymmetry* **1994**, *5*, 1999; (c) Davies, S. G.; Garrido, N. M.; Kruchinin, D.; Ichihara, O.; Kotchie, L. J.; Price, P. D.; Price Mortimer, A. J.; Russell, A. J.; Smith, A. D. *Tetrahedron: Asymmetry* **2006**, *17*, 1793; (d) Davies, S. G.; Nicholson, R. L.; Price, P. D.; Roberts, P. M.; Russell, A. J.; Savory, E. D.; Smith, A. D.; Thomson, J. E. *Tetrahedron: Asymmetry* **2009**, *20*, 758; (e) Davies, S. G.; Garner, A. C.; Nicholson, R. L.; Osborne, J.; Roberts, P. M.; Savory, E. D.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2009**, *7*, 2604; (f) Davies, S. G.; Mujtaba, N.; Roberts, P. M.; Smith, A. D.; Thomson, J. E. *Org. Lett.* **2009**, *11*, 1959; (g) Bentley, S. A.; Davies, S. G.; Lee, J. A.; Roberts, P. M.; Russell, A. J.; Thomson, J. E.; Toms, S. M. *Tetrahedron* **2010**, *66*, 4604; (h) Abraham, E.; Bailey, C. W.; Claridge, T. D. W.; Davies, S. G.; Ling, K. B.; Odell, B.; Rees, T. L.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Smith, L. J.; Storr, H. R.; Sweet, M. J.; Thompson, A. L.; Thomson, J. E.; Tranter, G. E.; Watkin, D. J. *Tetrahedron: Asymmetry* **2010**, *21*, 1797.

2. For selected examples from this laboratory, see: (a) Bunnage, M. E.; Burke, A. J.; Davies, S. G.; Goodwin, C. J. *Tetrahedron: Asymmetry* **1994**, *5*, 203; (b) Davies, S. G.; Kelly, R. J.; Price Mortimer, A. J. *Chem. Commun.* **2003**, 2132; (c) Davies, S. G.; Burke, A. J.; Garner, A. C.; McCarthy, T. D.; Roberts, P. M.; Smith, A. D.; Rodriguez-Solla, H.; Vickers, R. J. *Org. Biomol. Chem.* **2004**, *2*, 1387; (d) Davies, S. G.; Haggitt, J. R.; Ichihara, O.; Kelly, R. J.; Leech, M. A.; Price Mortimer, A. J.; Roberts, P. M.; Smith, A. D. *Org. Biomol. Chem.* **2004**, *2*, 2630; (e) Abraham, E.; Candela-Lena, J. I.; Davies, S. G.; Georgiou, M.; Nicholson, R. L.; Roberts, P. M.; Russell, A. J.; Sánchez-Fernández, E. M.; Smith, A. D.; Thomson, J. E. *Tetrahedron: Asymmetry* **2007**, *18*, 2510; (f) Abraham, E.; Davies, S. G.; Millican, N. L.; Nicholson, R. L.; Roberts, P. M.; Smith, A. D. *Org. Biomol. Chem.* **2008**, *6*, 1655;
(g) Abraham, E.; Brock, E. A.; Candela-Lena, J. I.; Davies, S. G.; Georgiou, M.; Nicholson, R. L.; Perkins, J. H.; Roberts, P. M.; Russell, A. J.; Sánchez-Fernández, E. M.; Scott, P. M.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2008**, *6*, 1665; (h) Davies, S. G.; Fletcher, A. M.; Roberts, P. M.; Smith, A. D. *Tetrahedron* **2009**, *65*, 10192; (i) Davies, S. G.; Hughes, D. G.; Price, P. D.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E.; Williams, O. M. H. *Synlett* **2010**, 567; (j) Davies, S. G.; Ichihara, O.; Roberts, P. M.; Thomson, J. E. *Tetrahedron* **2011**, *67*, 216.

3. For selected examples from this laboratory, see: (a) Cailleau, T.; Cooke, J. W. B.; Davies, S. G.; Ling, K. B.; Naylor, A.; Nicholson, R. L.; Price, P. D.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2007**, *5*, 3922; (b) Davies, S. G.; Durbin, M. J.; Goddard, E. C.; Kelly, P. M.; Kurosawa, W.; Lee, J. A.; Nicholson, R. L.; Price, P. D.; Roberts, P. M.; Russell, A. J.; Scott, P. M.; Smith, A. D. *Org. Biomol. Chem.* **2009**, *7*, 761.

4. For selected examples from this laboratory, see: (a) Davies, S. G.; Garner, A. C.; Long, M. J. C.; Morrison, R. M.; Roberts, P. M.; Smith, A. D.; Sweet, M. J.; Withey, J. M. *Org. Biomol. Chem.* **2005**, *3*, 2762; (b) Abraham, E.; Davies, S. G.; Docherty, A. J.; Ling, K. B.; Roberts, P. M.; Russell, A. J.; Thomson, J. E.; Toms, S. M. *Tetrahedron: Asymmetry* **2008**, *19*, 1356; (c) Davies, S. G.; Durbin, M. J.; Hartman, S. J. S.; Matsuno, A.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E.; Toms, S. M. *Tetrahedron: Asymmetry* **2008**, *19*, 2870; (d) Aye, Y.; Davies, S. G.; Garner, A. C.; Roberts, P. M.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2008**, *6*, 2195.

5. Davies, S. G.; Smith, A. D.; Price, P. D. *Tetrahedron: Asymmetry* **2005**, *16*, 2833.

6. (a) Davies, S. G.; Hermann, G. J.; Sweet, M. J.; Smith, A. D. *Chem. Commun.* **2004**, 1128; (b) Davies, S. G.; Fletcher, A. M.; Hermann, G. J.; Poce, G.; Roberts, P. M.; Smith, A. D.; Sweet, M. J.; Thomson, J. E. *Tetrahedron: Asymmetry* **2010**, *21*, 1635.

7. Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908.

8. (a) Chernega, A. N.; Davies, S. G.; Goodwin, C. J.; Hepworth, D.; Kurosawa, W.; Roberts, P. M.; Thomson, J. E. *Org. Lett.* **2009**, *11*, 3254; (b) Davies, S. G.; Goodwin, C. J.; Hepworth, D.; Roberts, P. M.; Thomson, J. E. *J. Org. Chem.* **2010**, *75*, 1214; (c) Chernega, A. N.; Davies, S. G.; Fletcher, A. M.; Goodwin, C. J.; Hepworth, D.; Prasad, R. S.; Roberts, P. M.; Savory, E. D.; Smith, A. D.; Thomson, J. E. *Tetrahedron* **2010**, *66*, 4167.

9. For a review, see: Whitesell, J. *Chem. Rev.* **1992**, *92*, 953.

10. For instance, see: (a) Kaneko, T.; Turner, D. L.; Newcomb, M.; Bergbreiter, D. E. *Tetrahedron Lett.* **1979**, *20*, 103; (b) Whitesell, J. K.; Bhattacharya, A.; Henke, K. *J. Chem. Soc., Chem. Commun.* **1982**, 988; (c) Yamamoto, Y.; Maeda, M.; Maruyama, K. *J. Chem. Soc., Chem. Commun.* **1983**, 774; (d) Comins, D. L.; Goehring, R. R.; Joseph, S. P.; O'Connor, S. *J. Org. Chem.* **1990**, *55*, 2574.

11. For instance, see: (a) Boeckman, R. K., Jr.; Naegely, P. C.; Arthur, S. D. *J. Org. Chem.* **1980**, *45*, 752; (b) Swindell, C. S.; Tao, M. *J. Org. Chem.* **1993**, *58*, 5889; (c) Rigby, J. H.; Sugathapaia, P.; Heeg, M. J. *J. Am. Chem. Soc.* **1995**, *117*, 8851; (d) Serells, A. K.; Simpson, G. W. *Tetrahedron Lett.* **1997**, *38*, 4277; (e) Oppolzer, W.; Kurth, M.; Reichlin, D.; Chapuis, C.; Mohnhaupt, M.; Moffatt, F. *Helv. Chim. Acta* **1981**, *64*, 2802.

12. For instance, see: (a) Oppolzer, W.; Robbiani, C.; Bättig, K. *Helv. Chim. Acta* **1980**, *63*, 2015; (b) Whitesell, J. K.; Bhattacharya, A.; Aguilar, D. A.; Henke, K. *J. Chem. Soc., Chem. Commun.* **1982**, 989.

13. Muniz, K.; Iesato, A.; Nieger, M. *Chem.—Eur. J.* **2003**, *9*, 5581.

14. For instance, see: (a) Donohoe, T. J.; Guyo, P. M.; Helliwell, M. *Tetrahedron Lett.* **1999**, *40*, 435; (b) Sebek, M.; Holz, J.; Börner, A.; Jähnisch, K. *Synlett* **2009**, 461.

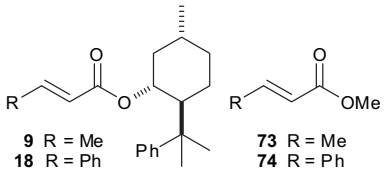
15. For instance, see: (a) Anderson, J. C.; O'Loughlina, J. M. A.; Tornosb, J. A. *Org. Biomol. Chem.* **2005**, *3*, 2741; (b) Tayama, E.; Kimura, H. *Angew. Chem., Int. Ed.* **2007**, *46*, 8869; (c) Tayama, E.; Orihara, K.; Kimura, H. *Org. Biomol. Chem.* **2008**, *6*, 3673.

16. For instance, see: (a) Koch, H.; Runsink, J.; Scharf, H.-D. *Tetrahedron Lett.* **1983**, *24*, 3217; (b) Little, R. D.; Moeller, K. D. *J. Org. Chem.* **1983**, *48*, 4487.

17. For instance, see: (a) Kozikowski, A. P.; Tückmantel, W.; Liao, Y.; Manev, H.; Ikonomovic, S.; Wroblewskil, J. T. *J. Med. Chem.* **1993**, *36*, 2706; (b) Kozikowski, A. P.; Zhao, L.; Zhang, A.; Wang, C. Z.; Flippen-Anderson, J.; Johnson, K. M. *ChemMedChem* **2006**, *1*, 58.

18. For instance, see: (a) Oppolzer, W.; Löher, H. J. *Helv. Chim. Acta* **1981**, *64*, 2808; (b) Barluenga, J.; Montserrat, J. M.; Flórez, J.; García-Granda, S.; Martín, E. *Angew. Chem.* **1994**, *106*, 1451; (c) Murthy, K. S. K.; Rey, A. W.; Tjepkema, M. *Tetrahedron Lett.* **2003**, *44*, 5355; (d) Lee, C. K. Y.; Herlt, A. J.; Simpson, G. W.; Willis, A. C.; Easton, C. J. *J. Org. Chem.* **2006**, *71*, 3221; (e) Ikeda, S.; Shibuya, M.; Kanoh, N.; Iwabuchi, Y. *Org. Lett.* **2009**, *11*, 1833.

19. d'Angelo, J.; Maddaluno, J. *J. Am. Chem. Soc.* **1986**, *108*, 8112.
20. Under these conditions the conjugate addition reaction is known to be reversible, see: Furukawa, M.; Okawara, T.; Terawaki, Y. *Chem. Pharm. Bull.* **1977**, *25*, 1319.
21. (+)-(*R*)-Pulegone was purchased from the Aldrich chemical company.
22. Ort, O. *Org. Synth.* **1987**, *65*, 203.
23. A comparative study of the ^{1}H NMR spectra for **9** and **18**, and the corresponding methyl esters **73** and **74**, reveals that the peaks corresponding to the olefinic C(2)*H* and C(3)*H* protons within both **9** and **18** are shifted upfield with respect to the corresponding resonances in the ^{1}H NMR spectra of **73** and **74**, consistent with the phenyl group of the auxiliary shielding one face of the olefin. [[a] approximate value (±0.05 ppm) due to peak overlap].



9 R = Me
18 R = Ph

73 R = Me
74 R = Ph

Ester	R	δ_H (ppm) for C(2)*H*	δ_H (ppm) for C(3)*H*
9	Me	5.38	6.50
73	Me	5.76	6.81
18	Ph	5.81	7.20[a]
74	Ph	6.53	7.73

24. A search of the Cambridge Crystallographic Database revealed that the structures of a range of different 8-arylmenthol α,β-unsaturated esters all adopt conformations similar to **20B** (Fig. 3) in the solid state.
25. (a) Davies, S. G.; Walters, I. A. S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1129; (b) Uyehara, T.; Asao, N.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1989**, 753; (c) Asao, N.; Uyehara, T.; Yamamoto, Y. *Tetrahedron* **1990**, *46*, 4563; (d) Jahn, U.; Müller, M.; Aussieker, S. *J. Am. Chem. Soc.* **2000**, *122*, 5212; (e) Davies, S. G.; Foster, E. M.; McIntosh, C. R.; Roberts, P. M.; Rosser, T. E.; Smith, A. D.; Thomson, J. E. *Tetrahedron: Asymmetry*, **2011**, doi:10.1016/j.tetasy.2011.06.008.
26. (a) Davies, S. G.; Garrido, N. M.; Ichihara, O.; Walters, I. A. S. *J. Chem. Soc., Chem. Commun.* **1993**, 1153; (b) Davies, S. G.; Dixon, D. J. *Chem. Commun.* **1996**, 1797; (c) Davies, S. G.; Dixon, D. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2635.
27. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 815826(**23**), 815827 (**33**), 815828(**54**), 815829 (**55**) and 815860 (**56**).
28. In some cases mixed fractions were also obtained after purification by flash column chromatography: following reaction of (*R*)-**1** with **9** an 85:15 mixture of **29** and its C(3)-epimer was also isolated in 50% combined yield, and following reaction of (*R*)-**1** with **18** an 83:17 mixture of **30** and its C(3)-epimer was also isolated in 70% combined yield.
29. (a) Bunnage, M. E.; Chippindale, A. M.; Davies, S. G.; Parkin, R. M.; Smith, A. D.; Withey, J. M. *Org. Biomol. Chem.* **2003**, *1*, 3698; (b) Bunnage, M. E.; Davies, S. G.; Parkin, R. M.; Roberts, P. M.; Smith, A. D.; Withey, J. M. *Org. Biomol. Chem.* **2004**, *2*, 3337 See also Ref. 4.
30. Upon conjugate addition of **32** to **9** a mixed fraction containing an 83:17 mixture of **34** and **38** was also isolated in 40% yield after chromatographic purification.
31. (a) Bull, S. D.; Davies, S. G.; Fox, D. J.; Garner, A. C.; Sellers, T. G. R. *Pure Appl. Chem.* **1998**, *70*, 1501; (b) Bull, S. D.; Davies, S. G.; Fox, D. J.; Sellers, T. G. R. *Tetrahedron: Asymmetry* **1998**, *9*, 1483; (c) Bull, S. D.; Davies, S. G.; Epstein, S. W.; Ouzman, J. V. A. *Chem. Commun.* **1998**, 659; (d) Bull, S. D.; Davies, S. G.; Epstein, S. W.; Leech, M. A.; Ouzman, J. V. A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2321; (e) Bull, S. D.; Davies, S. G.; Garner, A. C.; Mujtaba, N. *Synlett* **2001**, 781; (f) Bull, S. D.; Davies, S. G.; Garner, A. C.; O'Shea, M. D. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3281; (g) Sibi, M. P.; Venkatraman, L.; Liu, M.; Jasperse, C. P. *J. Am. Chem. Soc.* **2001**, *123*, 8444; (h) Quaranta, L.; Corminboeuf, O.; Renaud, P. *Org. Lett.* **2002**, *4*, 39; (i) Corminboeuf, O.; Quaranta, L.; Renaud, P.; Liu, M.; Jasperse, C. P.; Sibi, M. P. *Chem.—Eur. J.* **2003**, *9*, 29; (j) Malkov, A. V.; Hand, J. B.; Kocovsky, P. *Chem. Commun.* **2003**, 1948; (k) Hitchcock, S. R.; Casper, D. M.; Vaughn, J. F.; Finefield, J. M.; Ferrence, G. M.; Esken, J. M. *J. Org. Chem.* **2004**, *69*, 714; (l) Sibi, M. P.; Stanley, L. M. *Tetrahedron: Asymmetry* **2004**, *15*, 3353; (m) Sibi, M. P.; Prabagaran, N. *Synlett* **2004**, 2421; (n) Clayden, J.; Vassiliou, N. *Org. Biomol. Chem.* **2006**, *4*, 2667; (o) Bull, S. D.; Davies, S. G.; Epstein, S. W.; Garner, A. C.; Mujtaba, N.; Roberts, P. M.; Savory, E. D.; Smith, A. D.; Tamayo, J. A.; Watkin, D. J. *Tetrahedron* **2006**, *62*, 7911; (p) Parrott, R. W., II; Hitchcock, S. R. *Tetrahedron: Asymmetry* **2007**, *18*, 377; (q) Bull, S. D.; Davies, S. G.; Garner, A. C.; Parkes, A. L.; Roberts, P. M.; Sellers, T. G. R.; Smith, A. D.; Tamayo, J. A.; Thomson, J. E.; Vickers, R. J. *New J. Chem.* **2007**, *31*, 486.
32. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 733577, 745789 and 745790; see also Refs. 8a,c.
33. Due to the highly rotameric nature of all the β-amino hydroxamates described herein more accurate determinations of the reaction diastereoselectivities were not possible.
34. In some cases mixed fractions were also obtained after purification by flash column chromatography: following reaction of (*S*)-**1** with **54** a 60:40 mixture of **65** and **57** was also isolated in 30% combined yield, and following reaction of (*S*)-**1** with **55** a 50:50 mixture of **61** and **69** was also isolated in 40% combined yield.
35. The conjugate addition of (*S*)-**1** to **55** produced a 60:40 mixture of **61** and **69**, respectively. In this case the spectroscopic data for the authentic sample of **69** were consistent with the minor diastereoisomer from the conjugate addition reaction.
36. Attempted hydrogenolysis of **56** was not successful and returned a complex mixture of products: ^{1}H NMR spectroscopic and mass spectrometric analyses of the crude reaction mixture indicated the presence of products arising from cleavage of the N–O, N–C(1′) and *N*-benzyl bonds.
37. Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.
38. Carpita, A.; Magistris, E.; Rossi, R. *Gazz. Chim. Ital.* **1989**, *119*, 99.
39. Ye, S.; Tang, Y.; Dai, L. *J. Org. Chem.* **2001**, *66*, 5717.
40. Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.
41. Bull, S. D.; Davies, S. G.; Fenton, G.; Mulvaney, A. W.; Prasad, R. S.; Smith, A. D. *J. Chem. Soc., Perkin Trans. 1* **2000**, *22*, 3765.
42. A peak corresponding to *C*(1) was not observed in the ^{13}C NMR spectrum for this compound.
43. Davies, S. G.; Mulvaney, A. W.; Russell, A. J.; Smith, A. D. *Tetrahedron: Asymmetry* **2007**, *18*, 1554.
44. Hank, Z.; Bruneau, C.; Renaud, J. *Synthesis* **2009**, *15*, 2627.