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Asymmetric synthesis of β-substituted Baylis–Hillman products via lithium amide conjugate addition

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Abstract—A three-step protocol for the asymmetric synthesis of a range of β-substituted Baylis–Hillman products has been developed. This procedure involves the diastereoselective conjugate addition of lithium (*R*)-*N*-methyl-*N*-(α-methylbenzyl)amide to an α,β-unsaturated ester to generate an *N*-protected β-amino ester in high de. Subsequent asymmetric aldol reaction via deprotonation with LDA, transmetallation with $B(OMe)_3$ and addition of an aldehyde gives a range of *syn*-aldol products in moderate to high de. Purification of the *syn*-aldol products to homogeneity followed by tandem N-oxidation and Cope elimination gives the desired β-substituted Baylis–Hillman products in good yield and high de and ee.

1. Introduction

Carbon–carbon bond forming reactions are of fundamental importance in organic chemistry, with a plethora of stoicheiometric and catalytic methods having been developed for use in synthesis. Among these different strategies, the condensation of an aldehyde and an acrylate ester catalysed by a tertiary amine[1] or phosphine[2] to afford α-methylene-β-hydroxy-esters (commonly known as the Morita–Baylis–Hillman reaction) has been exploited widely.[3] These compounds have proven to be useful synthetic intermediates, often used to provide practical synthons in stereoselective synthesis.[4] As this efficient reaction produces polyfunctional chiral molecules in a single step, various endeavours seeking to develop asymmetric versions of this reaction to afford allylic alcohols in enantiomerically enriched form have been reported. In principle, asymmetry in the Morita–Baylis–Hillman reaction may be induced through the use of a chiral source in any or all of the reaction components. For instance, chiral acrylates have been widely used, with menthyl,[5] carbohydrate[6] and pyrazolidinone[7] derived auxiliaries giving reasonable to high levels of stereocontrol. The first highly enantioselective approach in this area was that of Leahy et al., who reported asymmetric Baylis–Hillman reactions using a derivative of Oppolzer's camphor sultam auxiliary **1**, which generated **2** in >99% ee upon treatment with DABCO and propanaldehyde.[8] Chiral amines have also been evaluated as catalysts for the asymmetric Baylis–Hillman reaction, with DABCO derivatives,[9] pyrrolizidines[10] and derivatives of cinchona alkaloids[11] all showing some success. For example, amine **4** promotes the coupling of acrylate **5** with a range of aldehydes in up to 99% ee;[12] a strategy that has been used in natural product synthesis.[13] Chiral phosphines have also been used to promote efficient catalysis.[14] Furthermore, a range of chiral aldehydes have been used to induce stereoselectivity,[15] with enantiomerically pure azetidine carboxaldehydes such as **7** undergoing highly selective Baylis–Hillman reactions with methyl vinyl ketone and DABCO (Fig. 1).[16] A double diastereoselective Baylis–Hillman variant that uses a chiral carbohydrate

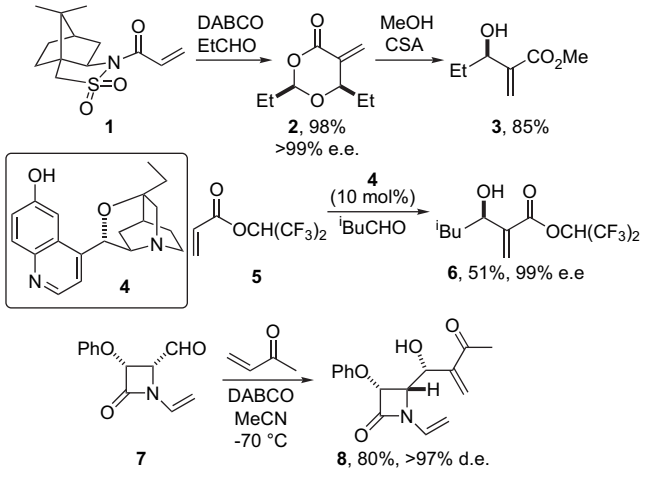

Figure 1. Asymmetric Baylis–Hillman reactions.

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derived acrylate and an enantiomerically pure aldehyde has also been reported.[17]

Although efficient, these approaches are restricted to the use of β-unsubstituted acrylate components, generating α-methylene-β-hydroxy compounds. Methods for the preparation of β-substituted Baylis–Hillman products have been reported, although examples are limited. Racemic β-substituted Baylis–Hillman products may be prepared from α-silyl-alkenoates but with low levels of (*E*)/(*Z*) stereocontrol,[18] whilst hydroalumination of β-propiolates in the presence of HMPA and subsequent reaction with an aldehyde gives the desired products with high (*Z*)-stereocontrol.[19] Enantiomerically enriched β-substituted Baylis–Hillman products may be prepared by α-functionalisation of chiral α,β-unsaturated sulfoxides with aldehydes,[20] and through the reaction of silyl allenolates with aldehydes catalysed by a chiral oxazaborolidine,[21] although the synthetic generality of these procedures has yet to be demonstrated. In order to address this structural limitation, we became interested in the development of methodology that is capable of the stereoselective synthesis of enantiomerically pure β-substituted Baylis–Hillman products. Previous investigations from this laboratory have demonstrated that the conjugate addition of homochiral lithium amides derived from α-methylbenzylamine to α,β-unsaturated esters allows the asymmetric synthesis of β-amino acid derivatives in high de[22] and it was proposed that this methodology could be used as the cornerstone of a three-step strategy for the asymmetric synthesis of β-substituted Baylis–Hillman products. This protocol would involve the diastereoselective conjugate addition of lithium (*R*)-*N*-methyl-*N*-(α-methylbenzyl)amide[23] to an α,β-unsaturated ester to generate stereoselectively the corresponding β-amino ester. Subsequent asymmetric aldol reaction and tandem N-oxidation and Cope elimination would generate the desired β-substituted Baylis–Hillman products. As the Cope elimination is known to proceed via a stereospecific *syn*-elimination[24] the relative configuration of C(2) and C(3) within the aldol products will determine the formation of the corresponding (*E*)- or (*Z*)-β-substituted Baylis–Hillman products (Fig. 2). We report herein our full investigations in this area, part of which has been communicated previously.[25]

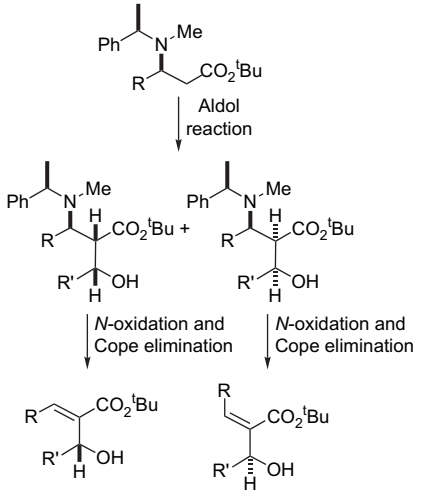
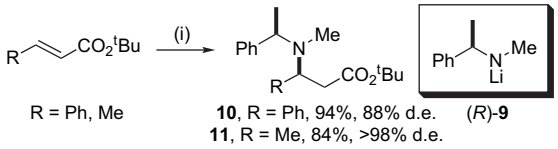


Figure 2. Proposed route to β-substituted Baylis–Hillman products.

2. Results and discussion

2.1. Model studies: preparation of (*E*)- and (*Z*)-1′-hydroxyethyl-3-alkyl-prop-2-enoates

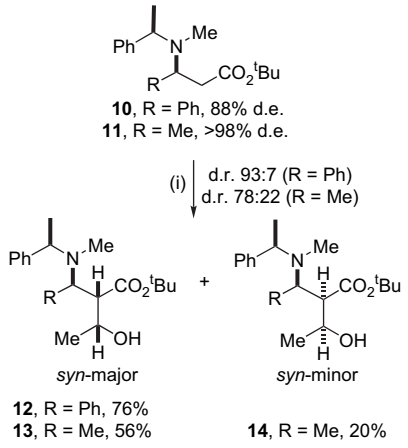
Initial studies concentrated on the application of this proposed three-step methodology to enable the synthetic equivalent of coupling an α,β-unsaturated ester (*tert*-butyl cinnamate and *tert*-butyl crotonate) with acetaldehyde. Thus, conjugate addition of lithium (*R*)-*N*-methyl-*N*-(α-methylbenzyl)amide **9** (>98% ee)[26] to *tert*-butyl cinnamate and *tert*-butyl crotonate gave the corresponding β-amino esters (3*S*,α*R*)-**10** and (3*R*,α*R*)-**11** in 88 and >98% de, respectively.[27] The configuration at C(3) within β-amino esters **10** and **11** was assigned by analogy to the transition state model previously developed for the addition of this class of lithium amide to α,β-unsaturated esters.[28] Exhaustive chromatography did not enhance the diastereomeric excess of **10**, which was thus isolated in 94% yield and 88% de, whilst chromatography allowed the isolation of **11** in 84% yield and in >98% de (Scheme 1).



Scheme 1. *Reagents and conditions*: (i) (*R*)-**9** (1.6 equiv), THF, −78 °C.

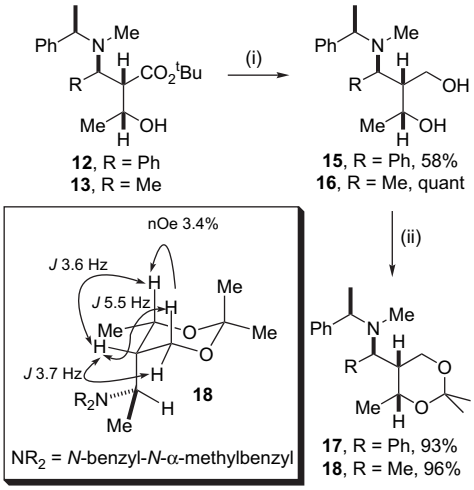
β-Amino esters **10** and **11** were next subjected to an asymmetric boron aldol reaction. Previous investigations within this area have demonstrated that lithium (*Z*)- and (*E*)-β-amino enolates (generated from conjugate addition of a lithium amide to an α,β-unsaturated ester, and deprotonation of a β-amino ester, respectively) offer stereodivergent reaction manifolds upon reaction with aldehydes;[29] however, the use of trimethylborate to transmetallate the lithium (*E*)-enolate offers high levels of C(2)–C(1′) *syn*-selectivity,[30] and therefore this protocol was applied to β-amino esters **10** and **11**. Deprotonation of **10** and **11** with LDA to form the corresponding lithium (*E*)-enolate was followed by the addition of $B(OMe)_3$ before the addition of acetaldehyde, giving the crude aldol products. Very high levels of diastereoselectivity were observed upon aldol reaction of the cinnamate derived β-amino ester (3*S*,α*R*)-**10** in this protocol, furnishing a 93:7 mixture of diastereoisomers, with the major diastereoisomeric aldol product purified to homogeneity by flash chromatography, giving (2*S*,3*S*,1′*R*,α*R*)-**12** in 76% yield. Reaction of β-amino ester (3*R*,α*R*)-**11** under identical conditions showed lower levels of diastereoselectivity, furnishing a 78:22 mixture of diastereoisomers. Purification to homogeneity by chromatography allowed the isolation of the separable diastereoisomers (2*S*,3*R*,1′*R*,α*R*)-**13** and (2*R*,3*R*,1′*S*,α*R*)-**14** in 76% combined yield (Scheme 2).

In order to establish unambiguously the relative configuration of the two new stereogenic centres formed during the aldol protocol, the major diastereoisomeric β-amino aldol products **12** and **13** were converted into the corresponding acetonides. Reduction of **12** and **13** with $LiAlH_4$ in THF and treatment of the resulting diols **15** and **16** with 2,2-dimethoxypropane and camphorsulfonic acid (CSA) in acetone



Scheme 2. *Reagents and conditions*: (i) LDA (3 equiv), THF, −78 to 0 °C, then $B(OMe)_3$, then MeCHO.

gave the acetonides **17** and **18** in good yield. In each case, analysis of the coupling constants in the ^1H NMR spectra allowed the assignment of axial and equatorial relationships between the ring protons, with 1,3-diaxial relationships confirmed through NOE difference analysis as demonstrated for **18** (Scheme 3). This analysis confirmed the expected *syn*-selectivity for the aldol reaction, consistent with the predicted configurations of the major diastereoisomeric β-amino ester aldol products **12** and **13**.



Scheme 3. *Reagents and conditions*: (i) $LiAlH_4$, THF, 0 °C to rt; (ii) 2,2-dimethoxypropane, acetone, CSA.

Single crystal X-ray analysis of **17** allowed unambiguous confirmation of the relative configuration, with the absolute (4*R*,5*R*,1′*S*,α*R*) configuration assigned relative to the known (*R*)-α-methylbenzyl fragment (Fig. 3).

In a similar fashion, reduction of minor diastereoisomeric β-amino aldol product **14** in the crotonate derived series with $LiAlH_4$ gave the diol **19** in quantitative yield. Elaboration of **19** to the acetonide **20** and subsequent ^1H NMR spectroscopic analysis also confirmed the *syn*-configuration within **14** (Scheme 4).

X-ray crystallographic analysis of **19** allowed unambiguous assignment of the relative configuration, with the

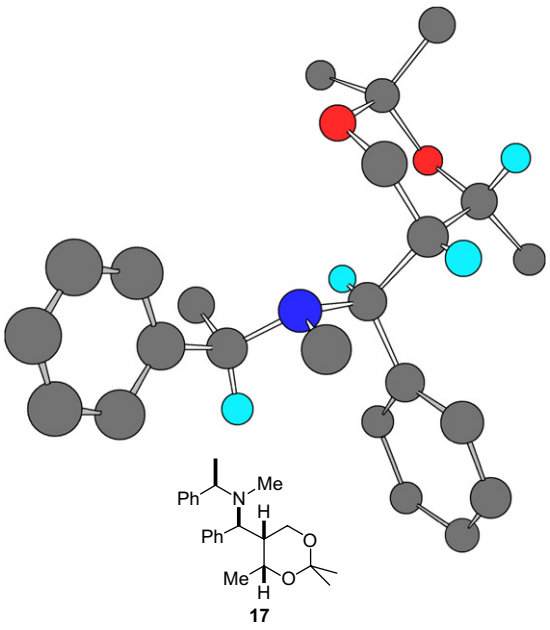
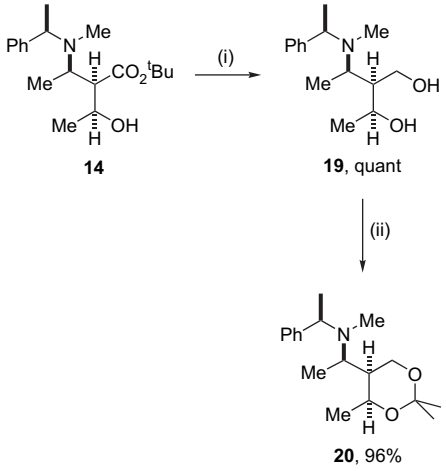


Figure 3. Chem 3D representation of the X-ray crystal structure of **17** (some H atoms were removed for clarity).



Scheme 4. *Reagents and conditions*: (i) $LiAlH_4$, THF, 0 °C to rt.

(2*S*,3*R*,1′*S*,α*R*) absolute configuration assigned from the known (*R*)-α-methylbenzyl fragment (Fig. 4).

Having established unambiguously the stereoselectivity of the aldol reactions of β-amino esters **10** and **11** with acetaldehyde, the tandem N-oxidation and Cope elimination of the β-amino aldol products **12**–**14** to the desired β-phenyl or β-methyl Baylis–Hillman products were investigated. Stereospecific *syn*-elimination from **12** and **13** was predicted to give rise to the corresponding (*E*)-β-substituted Baylis–Hillman products, while **14** was anticipated to yield the corresponding (*Z*)-β-substituted product. As expected, treatment of the *syn*-aldol products **12** and **13** with *m*CPBA in $CHCl_3$ resulted in the formation of the desired products (2*E*,1′*R*)-**21** and (2*E*,1′*R*)-**22** as single diastereoisomers in 74 and 58% isolated yield, respectively. Further application of this methodology to the aldol product **14** gave the corresponding (*Z*)-β-methyl Baylis–Hillman product **23** in 59%

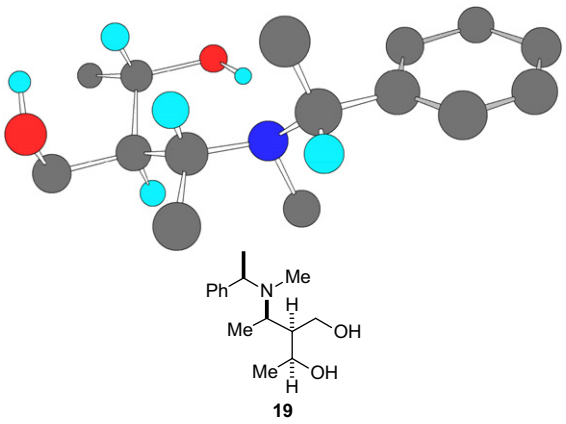
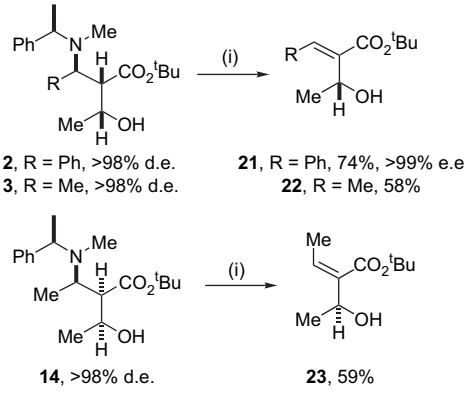


Figure 4. Chem 3D representation of the X-ray crystal structure of **19** (some H atoms were removed for clarity).

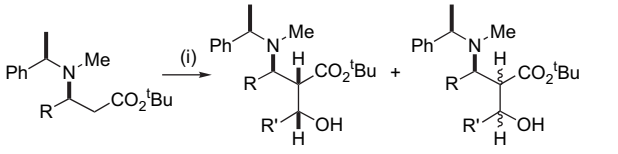
yield. ^{1}H NMR NOE difference experiments were indicative of the assigned alkene configurations within (2*E*,1′*R*)-**21**, (2*E*,1′*R*)-**22** and (2*Z*,1′*S*)-**23**. The ee of **21** was determined to be >99% by chiral HPLC analysis[31] and comparison with an authentic scalemic sample,[32] indicating that the N-oxidation protocol proceeds without epimerisation of the C(1′) stereogenic centre. Although the ee of Baylis–Hillman products **22** and **23** could not be unambiguously determined, similar high levels of enantiomeric excess are assumed due to their isolation as single diastereoisomers, and their formation from single diastereoisomers of enantiomerically pure aldol products **13** and **14** (Scheme 5).



Scheme 5. *Reagents and conditions*: (i) *m*CPBA, $CHCl_3$, rt.

2.2. Preparation of a range of (*E*)-1′-hydroxyalkyl-3-alkyl-prop-2-enoates

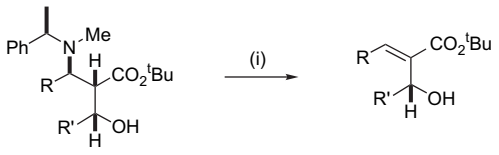
Having demonstrated the utility of this methodology for the synthesis of model (*E*)- and (*Z*)-β-substituted Baylis–Hillman products, the generality of this three-step protocol was probed. Aldol reaction of β-amino esters (3*S*,α*R*)-**10**, (3*R*,α*R*)-**11** and the known β-amino ester (3*R*,4*E*,α*R*)-**24**[23a] with a range of aldehydes was therefore evaluated. Aldol reaction of the boron (*E*)-enolate derived from **10** with benzaldehyde, *iso*-butyraldehyde and pivaldehyde gave aldol products **25**–**27** with high to reasonable levels of stereoselectivity (93:7, 85:15 and 71:29, respectively), with the major *syn*-diastereoisomer[33] purified to homogeneity in each case. Markedly lower levels of diastereoselectivity were observed upon reaction of the boron (*E*)-enolate derived from **11** with benzaldehyde, and with the boron (*E*)-enolate of **24** with acetaldehyde. In each of these cases, three diastereoisomers were observed by ^{1}H NMR spectroscopic analysis of the crude reaction product, with the major diastereoisomer purified to homogeneity in each case and assigned the *syn*-configuration by analogy to that previously proven unambiguously (Scheme 6).



β-Amino ester	R	Major aldol product	R'	d.r.	Yield %[a]
10	Ph	**25**	Ph	93:7	65
10	Ph	**26**	^{i}Pr	85:15	66
10	Ph	**27**	^{t}Bu	71:29	66
11	Me	**28**	Ph	46:38:16	54
24	(*E*)-MeCH=CH	**29**	Me	60:30:10	69

Scheme 6. *Reagents and conditions*: (i) LDA (3 equiv), THF, −78 to 0 °C, then $B(OMe)_3$, then R′CHO. [[a]Combined isolated yield of all diastereoisomers.]

With a range of homogenous *syn*-aldol products **25**–**29** in hand, their conversion to the corresponding β-substituted Baylis–Hillman products was investigated. Treatment of aldol products **25**–**29** with *m*CPBA gave, in each case, the corresponding (*E*)-β-substituted Baylis–Hillman products **30**–**34** in good (59–70%) yield and in >95% de. The (*E*)-configuration within **30**–**34** was identified by NOE difference NMR spectroscopic analysis, consistent with the assigned configuration of the aldol precursors and *syn*-elimination during the Cope elimination. The ee of **30** was unambiguously established as >99% by HPLC analysis,[34] although the ees of **31**–**34** could not be unambiguously identified either via derivatisation, chiral shift or HPLC analysis. However, the isolation of **26**–**29** as essentially single diastereoisomers (>95% de) allows an ee of >98% (consistent with the >98% ee of the *N*-methyl-*N*-(α-methylbenzyl)amine used to initiate the conjugate addition reaction) to be assumed (Scheme 7).



Aldol product	R	R'	Product	Yield %	d.e.
25	Ph	Ph	**30**	63	>95
26	Ph	^{i}Pr	**31**	66	>95
27	Ph	^{t}Bu	**32**	59	>95
28	Me	Ph	**33**	62	>95
29	(*E*)-MeCH=CH	Me	**34**	70	>95

Scheme 7. *Reagents and conditions*: (i) *m*CPBA, $CHCl_3$, rt.

3. Conclusion

A three-step protocol for the diastereoselective synthesis of β-substituted Baylis–Hillman products has been developed,

involving conjugate addition of lithium (*R*)-*N*-methyl-*N*-(α-methylbenzyl)amide to an α,β-unsaturated ester, followed by asymmetric aldol reaction and subsequent tandem N-oxidation and Cope elimination. The aldol reactions proceed with moderate to good levels of diastereoselectivity and the generality of this protocol towards a range of α,β-unsaturated esters and aldehydes has been demonstrated. The further application of this methodology for natural product synthesis is currently underway within this laboratory.

4. Experimental

4.1. General experimental

All reactions described as being carried out under nitrogen were performed using standard vacuum line techniques using glassware that was flame-dried and subsequently cooled in vacuo. THF was distilled under nitrogen from sodium benzophenone ketyl. Butyllithium was purchased as a 1.6 M solution in hexanes and titrated against diphenylacetic acid prior to use. Di-*iso*-propylamine was distilled from (and stored over) potassium hydroxide pellets. Aldehydes were freshly distilled before use. All other solvents and reagents were used as supplied, without further 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 and are uncorrected. Elemental analyses were recorded by the microanalysis service of the Dyson–Perrins Laboratory, University of Oxford. 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 Perkin–Elmer 1750 FT spectrometer as a KBr disc (KBr), a thin film on an NaCl plate (film) or as a solution in $CHCl_3$ using 1.0 mm NaCl cells ($CHCl_3$). Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded on a Bruker AC200, Bruker WH300, Bruker AV400 or Bruker AM500 spectrometer in $CDCl_3$. The field was locked by external referencing to the deuteron resonance. Mass spectra were obtained on a VG Masslab 20–250 Quadrupole instrument (CI, NH_3) or a VG BIO-Q instrument (ESI^+).

4.2. General procedure 1 for aldol reaction

BuLi (3 equiv) was added dropwise to a solution of di-*iso*-propylamine (3.5 equiv) in THF (20 mL) at −78 °C and warmed to 0 °C for 30 min before a solution of the β-amino ester in THF (30 mL) was added via cannula and stirred for 2 h at 0 °C under nitrogen. After recooling to −78 °C, $B(OMe)_3$ (4 equiv) was added and the reaction mixture was stirred for 30 min before the addition of freshly distilled aldehyde (excess). After 2 h, satd aq NH_4Cl (5 mL) was added and the mixture warmed to rt before being partitioned between brine (50 mL) and Et_2O (3×40 mL), dried and concentrated in vacuo.

4.3. General procedure 2 for tandem N-oxidation and Cope elimination

A solution of *m*CPBA (50% pure, 2 equiv) in $CHCl_3$ (10 mL) was added to the aldol product in $CHCl_3$ (5 mL) and stirred at rt under nitrogen. Satd aq $NaHCO_3$ (5 mL) was added when no sign of starting material was apparent by TLC and starch/KI paper. The resultant material was extracted with DCM (2×15 mL), dried and concentrated in vacuo.

4.3.1. *tert*-Butyl (3*S*,α*R*)-3-[*N*-methyl-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 10. Following the literature procedure,[35] BuLi (1.4 M in hexanes, 10.5 mL, 14.7 mmol), (*R*)-*N*-methyl-*N*-(α-methylbenzyl)amine (2.12 g, 15.7 mmol) in THF (20 mL) and *tert*-butyl cinnamate (2.0 g, 9.8 mmol) in THF (30 mL) gave, after purification by column chromatography (40–60 °C petrol/Et_2O 12:1), **10** as a clear yellow oil (3.13 g, 94%, 88% de). Found: C, 77.65; H, 8.9; N, 4.3%. $C_{22}H_{29}NO_2$ requires: C, 77.8; H, 8.6; N, 4.1%. $[\alpha]_D^{22}$ +33.3 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1729 (C=O); δ_H (500 MHz, $CDCl_3$) 1.30 (9H, s, C*Me*$_3$), 1.36 (3H, d, *J* 6.6, C(α)*Me*), 2.08 (3H, s, N*Me*), 2.62 (1H, dd, *J* 14.3, 8.6, C(2)H_A), 2.88 (1H, dd, *J* 14.3, 6.4, C(2)H_B), 3.66 (1H, q, *J* 6.6, C(α)*H*), 4.30 (1H, dd, *J* 8.6, 6.4, C(3)*H*), 7.19–7.37 (10H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 16.7 (C(α)*Me*), 27.9 (C*Me*$_3$), 33.1 (N*Me*), 38.5 (*C*(2)), 59.2, 60.9 (*C*(3), *C*(α)), 80.2 (*C*Me$_3$), 126.6, 127.2 (*Ph*$_p$), 127.4, 128.1, 128.3 (*Ph*$_o$, *Ph*$_m$), 140.9, 145.3 (*Ph*$_i$), 171.4 (*C*(1)); *m/z* (CI, NH_3) 340 ($[M+H]^+$, 100%).

4.3.2. *tert*-Butyl (3*R*,α*R*)-3-[*N*-methyl-*N*-(α-methylbenzyl)amino]butanoate 11. Following the literature procedure,[35] BuLi (1.5 M in hexanes, 10.5 mL, 15.8 mmol), (*R*)-*N*-methyl-*N*-(α-methylbenzyl)amine (2.3 g, 16.9 mmol) in THF (20 mL) and *tert*-butyl crotonate (1.5 g, 10.5 mmol) in THF (30 mL) gave, after purification by column chromatography (eluent toluene/acetone 70:1), **11** as a clear yellow oil (2.5 g, 84%, >98% de). Found: C, 73.6; H, 10.0; N, 5.6%. $C_{17}H_{27}NO_2$ requires: C, 73.6; H, 9.8; N, 5.1%. $[\alpha]_D^{22}$ −2.9 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1730 (C=O); δ_H (500 MHz, $CDCl_3$) 0.97 (3H, d, *J* 6.6, C(4)H_3), 1.34 (3H, d, *J* 6.6, C(α)*Me*), 1.44 (9H, s, C*Me*$_3$), 2.07 (3H, s, N*Me*), 2.15 (1H, dd, *J* 13.9, 7.8, C(2)H_A), 2.44 (1H, dd, *J* 13.9, 6.6, C(2)H_B), 3.48 (1H, app sextet, *J* 7.0, C(3)*H*), 3.56 (1H, q, *J* 6.6, C(α)*H*), 7.19–7.34 (5H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 14.2, 21.8 (*C*(4), C(α)*Me*), 28.1 (C*Me*$_3$), 32.1 (N*Me*), 40.1 (*C*(2)), 51.2, 62.1 (*C*(3), *C*(α)), 79.8 (*C*Me$_3$), 126.6 (*Ph*$_p$), 127.2, 128.2 (*Ph*$_o$, *Ph*$_m$), 146.2 (*Ph*$_i$), 172.0 (*C*(1)); *m/z* (ESI^+) 300 ($[M+Na]^+$, 50%), 278 ($[M+H]^+$, 100%).

4.3.3. *tert*-Butyl (2*S*,3*S*,1′*R*,α*R*)-2-(1′-hydroxyethyl)-3-[*N*-methyl-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 12. Following *general procedure 1*, BuLi (1.4 M in hexanes, 3.16 mL, 4.42 mmol) and di-*iso*-propylamine (0.72 mL, 5.2 mmol) in THF (60 mL), **10** (500 mg, 1.47 mmol) in THF (40 mL), $B(OMe)_3$ (0.50 mL, 4.42 mmol) and acetaldehyde (~1 mL, excess) gave, after purification by column chromatography (eluent 40–60 °C petrol/Et_2O 2:1) **12** as a clear colourless oil (430 mg, 76%). Found: C, 75.45; H, 8.9; N, 3.6%. $C_{24}H_{33}NO_3$ requires: C, 75.2; H, 8.7; N, 3.65%. $[\alpha]_D^{22}$ +68.0 (*c* 0.95 in $CHCl_3$); ν_{max} (film)

3450 (br, O–H), 1728 (C=O); δ_H (300 MHz, $CDCl_3$) 1.16 (3H, d, *J* 6.1, C(2′)H_3), 1.28 (3H, d, *J* 6.7, C(α)*Me*), 1.38 (9H, s, CMe_3), 2.14 (3H, s, N*Me*), 3.18 (1H, dd, *J* 8.5, 6.4, C(2)*H*), 3.84 (1H, q, *J* 6.7, C(α)*H*), 4.21 (1H, dq, *J* 8.5, 6.1, C(1′)*H*), 4.29 (1H, d, *J* 6.4, C(3)*H*), 5.88 (1H, br s, O*H*), 7.20–7.46 (10H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 13.5, 21.3 (*C*(2′), C(α)*Me*), 28.0 (CMe_3), 34.3 (N*Me*), 53.4 (*C*(2)), 58.0, 66.7, 68.0 (*C*(3), *C*(1′), *C*(α)), 80.0 (*C*Me$_3$), 126.9 (Ph_p), 127.6 (Ph_o/Ph_m), 128.0 (Ph_p), 128.2, 128.3, 129.6 (Ph_o, Ph_m), 135.8, 143.4 (Ph_i), 171.2 (*C*(1)); *m*/*z* (CI, NH_3) 384 ([M+H]$^+$, 40%).

4.3.4. *tert*-Butyl (2*S*,3*R*,1′*R*,α*R*)- and (2*R*,3*R*,1′*S*,α*R*)-2-(1′-hydroxyethyl)-3-[*N*-methyl-*N*-(α-methylbenzyl)amino]butanoate (2*S*,3*R*,1′*R*,α*R*)-13 and (2*R*,3*R*,1′*S*,α*R*)-14. Following *general procedure 1*, BuLi (1.5 M in hexanes, 7.2 mL, 10.8 mmol) and di-*iso*-propylamine (1.77 mL, 12.6 mmol) in THF (100 mL), **11** (1.0 g, 3.60 mmol) in THF (50 mL), $B(OMe)_3$ (1.22 mL, 10.8 mmol) and acetaldehyde (~2 mL, excess) gave, after purification by column chromatography (eluent 40–60 °C petrol/Et_2O 7:1 then toluene/acetone 40:1), **13** and **14** (875 mg, 76% combined yield).

First to elute: **14** as a clear colourless oil (229 mg, 20%). Found: C, 71.1; H, 10.0; N, 4.55%. $C_{19}H_{31}NO_3$ requires: C, 71.0; H, 9.7; N, 4.4%. $[\alpha]_D^{22}$ +9.3 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3190 (br, O–H), 1722 (C=O); δ_H (500 MHz, $CDCl_3$) 0.91 (3H, d, *J* 6.5, C(4)H_3), 1.18 (3H, d, *J* 6.1, C(2′)H_3), 1.47 (9H, s, CMe_3), 1.47 (3H, d, *J* 6.6, C(α)*Me*), 1.98 (3H, s, N*Me*), 2.32 (1H, dd, *J* 10.7, 9.3, C(2)*H*), 3.62 (1H, q, *J* 6.6, C(α)*H*), 3.73 (1H, dq, *J* 10.7, 6.5, C(3)*H*), 4.13 (1H, dq, *J* 9.3, 6.1, C(1′)*H*), 7.23–7.33 (5H, m, *Ph*), 7.93 (1H, br s, O*H*); δ_C (50 MHz, $CDCl_3$) 10.2, 21.4, 21.5 (*C*(4)H_3, *C*(2′)H_3, C(α)*Me*), 28.0 (CMe_3), 32.7 (N*Me*), 56.2, 56.9, 62.8, 71.2 (*C*(2), *C*(3), *C*(1′), *C*(α)), 81.0 (*C*Me$_3$), 127.1, 127.4, 128.7 (Ph_o, Ph_m, Ph_p), 143.8 (Ph_i), 172.1 (*C*(1)); *m*/*z* (CI, NH_3) 322 ([M+H]$^+$, 100%).

Second to elute: **13** as a clear yellow oil (646 mg, 56%). Found: C, 70.9; H, 9.6; N, 4.4%. $C_{19}H_{31}NO_3$ requires: C, 71.0; H, 9.7; N, 4.4%. $[\alpha]_D^{22}$ −7.9 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3436 (br, O–H), 1727 (C=O); δ_H (500 MHz, $CDCl_3$) 1.25 (6H, overlapping 2×3H d, C(4)H_3, C(2′)H_3), 1.38 (3H, d, *J* 6.9, C(α)*Me*), 1.49 (9H, s, CMe_3), 2.11 (3H, s, N*Me*), 2.83 (1H, dd, *J* 9.3, 4.4, C(3)*H*), 3.19 (1H, qd, *J* 6.6, 4.4, C(3)*H*), 4.20–4.29 (2H, m, C(1′)*H*, C(α)*H*), 6.36 (1H, br s, O*H*), 7.24–7.35 (5H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 12.8, 14.7, 22.0 (*C*(4), *C*(2′), C(α)*Me*), 28.1 (CMe_3), 32.5 (N*Me*), 53.4, 57.1, 57.5, 66.0 (*C*(2), *C*(3), *C*(1′), *C*(α)), 80.7 (*C*Me$_3$), 127.1, 128.1 (Ph_o, Ph_m, Ph_p), 141.4 (Ph_i), 172.0 (*C*(1)); *m*/*z* (CI, NH_3) 322 ([M+H]$^+$, 80%).

4.3.5. (2*R*,3*S*,1′*R*,α*R*)-2-(1′-Hydroxyethyl)-3-[*N*-methyl-*N*-(α-methylbenzyl)amino]-3-phenylpropan-1-ol 15. A solution of **12** (100 mg, 0.26 mmol) in THF (5 mL) was added to a suspension of $LiAlH_4$ (100 mg, 2.50 mmol) in THF (5 mL) and stirred at rt for 24 h, before the sequential dropwise addition of water (0.5 mL), 1 M aq NaOH (0.1 mL) and more water (0.5 mL). EtOAc (15 mL) was added and the mixture was stirred for 3 h before being filtered through Celite, dried and concentrated in vacuo. The residue was purified by column chromatography (eluent Et_2O) to give **15** (47 mg, 58%) as a clear colourless oil. Found: C, 76.7; H, 8.5; N, 4.4%. $C_{20}H_{27}NO_2$ requires: C, 76.6; H, 8.7; N 4.5%. $[\alpha]_D^{23}$ +77.7 (*c* 1.1 in $CHCl_3$); ν_{max} (film) 3369 (br, O–H); δ_H (300 MHz, $CDCl_3$) 1.07 (3H, d, *J* 6.5, C(2′)H_3), 1.41 (3H, d, *J* 6.6, C(α)*Me*), 2.04 (3H, s, N*Me*), 2.50–2.58 (1H, m, C(2)*H*), 3.59–3.66 (2H, m, C(1)H_A, C(α)*H*), 3.76 (1H, app quintet, *J* 6.3, C(1′)*H*), 3.88 (1H, dd, *J* 11.0, 3.8, C(1)H_B), 4.24 (1H, d, *J* 8.1, C(3)*H*), 4.37 (1H, br s, O*H*), 7.18–7.42 (10H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 16.2, 19.3 (*C*(2′), C(α)*Me*), 34.9 (N*Me*), 45.2 (*C*(2)), 59.5 (*C*(α)), 62.8 (*C*(1)), 66.7, 67.0 (*C*(3), *C*(1′)), 127.0, 127.3, 127.8, 128.3, 128.5, 129.6 (Ph_o, Ph_m, Ph_p), 134.9, 143.7 (Ph_i); *m*/*z* (ESI$^+$) 314 ([M+H]$^+$, 100%).

4.3.6. (2*R*,3*R*,1′*R*,α*R*)-2-(1′-Hydroxyethyl)-3-[*N*-methyl-*N*-(α-methylbenzyl)amino]butan-1-ol 16. $LiAlH_4$ (1.0 M in THF, 2.5 mL, 2.5 mmol) was added to a stirred solution of **13** (500 mg, 1.55 mmol) in THF (50 mL) at 0 °C and warmed to rt for 15 h before the dropwise addition of water (0.5 mL). EtOAc (15 mL) was added and the mixture was stirred for 3 h before being filtered through Celite, dried and concentrated in vacuo. The residue was purified by column chromatography (eluent 40–60 °C petrol/Et_2O 4:1) to give **16** as a clear colourless oil (389 mg, quant); ν_{max} (film) 3364 (br, O–H); δ_H (300 MHz, $CDCl_3$) 1.01 (3H, d, *J* 6.7, C(4)H_3), 1.16 (3H, d, *J* 6.4, C(2′)*H*), 1.40 (3H, d, *J* 6.7, C(α)*Me*), 1.92–1.97 (1H, m, C(2)*H*), 2.03 (3H, s, N*Me*), 3.28 (1H, m, C(3)*H*), 3.73–3.83 (2H, m, C(1)H_A, C(α)*H*), 3.92–4.03 (2H, m, C(1)H_B, C(1′)*H*), 7.22–7.34 (5H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 11.0 (C(α)*Me*), 18.9, 19.1 (*C*(4), *C*(2′)), 33.0 (N*Me*), 47.8, 56.3, 61.2, 67.4 (*C*(2), *C*(3), *C*(1′), *C*(α)), 63.2 (*C*(1)), 127.2, 127.5, 128.5 (Ph_o, Ph_m, Ph_p), 143.8 (Ph_i); *m*/*z* (CI, NH_3) 252 ([M+H]$^+$, 100%); HRMS (CI, NH_3) found: 252.1964; $C_{15}H_{26}NO_2^+$ ([M+H]$^+$) requires: 252.1964.

4.3.7. (4*R*,5*R*,1′*S*,α*R*)-2,2,4-Trimethyl-5-{1′-[*N*-methyl-*N*-(α-methylbenzyl)amino]benzyl}-1,3-dioxane 17. A solution of 2,2-dimethoxypropane and acetone (1:1, 10 mL) was added to a mixture of **15** (40 mg, 0.13 mmol) and (+)-CSA (2 mg), and heated at reflux for 8 h. Na_2CO_3 was added until neutral pH was reached, and the mixture filtered, dried and concentrated in vacuo. Purification by column chromatography (eluent 40–60 °C petrol/Et_2O 5:1) and recrystallisation (40–60 °C petrol/Et_2O) gave **17** as white plates (42 mg, 93%). Found: C, 78.1; H, 8.6; N, 3.7%. $C_{23}H_{31}NO_2$ requires: C, 78.15; H, 8.8; N 4.0%. Mp 138–143 °C; $[\alpha]_D^{26}$ +43.4 (*c* 1.3 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 0.65 (3H, d, *J* 6.8, C(4)*Me*), 1.52 (6H, s, C(2)Me_2), 1.60 (3H, d, *J* 6.4, C(α)*Me*), 1.72 (3H, s, N*Me*), 2.27 (1H, app dq, *J* 10.7, 3.1, C(5)*H*), 3.27 (1H, q, *J* 6.4, C(α)*H*), 4.05 (1H, dd, *J* 11.1, 3.1, C(6)H_A), 4.28 (1H, qd, *J* 6.8, 3.0, C(4)*H*), 4.48 (1H, dd, *J* 11.1, 3.3, C(6)H_B), 4.72 (1H, d, *J* 10.7, C(1′)*H*), 7.18–7.38 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 20.6, 21.0, 22.6, 29.1 (*C*(2)Me_2, C(4)*Me*, C(α)*Me*), 34.6 (N*Me*), 38.5 (*C*(5)), 55.9, 61.4 (*C*(1′), *C*(α)), 62.5 (*C*(6)), 68.3 (*C*(4)), 98.6 (*C*(2)), 126.5, 126.8, 127.3, 127.8, 128.2, 129.2 (Ph_o, Ph_m, Ph_p), 137.3, 147.0 (Ph_i); *m*/*z* (ESI$^+$) 354 ([M+H]$^+$, 100%).

4.3.7.1. X-ray crystal structure determination for 17. Data were collected using an Enraf–Nonius CAD4

diffractometer with graphite monochromated Cu Kα radiation using standard procedures at rt. The structure was solved by direct methods, all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[36]

X-ray crystal structure data for **17** [$C_{23}H_{31}NO_2$]: M=353.51, monoclinic, space group P 1 21 1, a=7.0424(9) Å, b=9.548(1) Å, c=15.797(2) Å, β=97.84(1)°, V=1052.3Å^3, Z=2, μ=5.1 cm^{-1}, colourless block, crystal dimensions=0.2×0.3×0.3 mm^3. A total of 2125 unique reflections were measured for $1<\theta<70$ and 1801 reflections were used in the refinement. The final parameters were wR_2=0.030 and R_1=0.028 [$I>3\sigma(I)$]. Crystallographic data (excluding structural factors) have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 634751. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

4.3.8. (4*R*,5*R*,1′*R*,α*R*)-2,2,4-Trimethyl-5-{1′-[*N*-methyl-*N*-(α-methylbenzyl)amino]ethyl}-1,3-dioxane 18. A solution of 2,2-dimethoxypropane (0.3 mL) in acetone (10 mL) was added to a mixture of **16** (300 mg, 1.2 mmol), (+)-CSA (140 mg) and $CuSO_4$ (100 mg, 0.63 mmol) and stirred for 5 days at rt. Na_2CO_3 was added until neutral pH was reached, and the mixture was filtered, dried and concentrated in vacuo. Purification by column chromatography (eluent 40–60 °C petrol/Et_2O 10:1) gave **18** as a clear oil (340 mg, 96%). $[\alpha]_D^{25}$ +2.7 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2974 (C–H), 1453, 1378; δ_H (400 MHz, $CDCl_3$) 0.97 (3H, d, *J* 6.5, C(2′)H_3), 1.28 (3H, d, *J* 6.9, C(4)*Me*), 1.33 (3H, d, *J* 6.6, C(α)*Me*), 1.45, 1.46 (2×3H, s, C(2)Me_2), 1.67 (1H, m, C(5)*H*), 1.88 (3H, s, N*Me*), 3.44 (1H, dq, *J* 10.1, 6.5, C(1′)*H*), 3.54 (1H, q, *J* 6.6, C(α)*H*), 3.92 (1H, dd, *J* 11.4, 3.7, C(6)H_A), 4.17 (1H, dd, *J* 11.4, 5.2, C(6)H_B), 4.28 (1H, qd, *J* 6.9, 3.6, C(4)*H*), 7.18–7.35 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 11.6 (*C*(2′)), 19.9 (C(4)*Me*), 22.1 (C(α)*Me*), 23.2, 28.4 (C(2)Me_2), 33.0 (N*Me*), 42.6 (*C*(5)), 48.4 (*C*(1′)), 62.0 (*C*(6)), 62.4 (*C*(α)*Me*), 68.6 (*C*(4)), 98.2 (*C*(2)), 126.5, 127.2, 128.2 (Ph_o, Ph_m, Ph_p), 147.2 (Ph_i); *m*/*z* (CI, NH_3) 292 ([M+H]$^+$, 100%); HRMS (CI, NH_3) found: 292.2276; $C_{18}H_{30}NO_2^+$ ([M+H]$^+$) requires: 292.2277.

4.3.9. (2*S*,3*S*,1′*R*,α*R*)-2-(1′-Hydroxyethyl)-3-[*N*-methyl-*N*-(α-methylbenzyl)amino]butan-1-ol 19. $LiAlH_4$ (1.0 M in THF, 2.5 mL, 2.5 mmol) was added to a stirred solution of **14** (500 mg, 1.55 mmol) in THF (5 mL) at 0 °C and warmed to rt for 15 h before the dropwise addition of water (0.5 mL). EtOAc (15 mL) was added and the mixture was stirred for 3 h before being filtered through Celite, dried and concentrated in vacuo to give **19** as a white solid (389 mg, quant). Found: C, 71.6; H, 10.1; N, 5.6%. $C_{15}H_{25}NO_2$ requires: C, 71.7; H, 10.0; N, 5.6%. $[\alpha]_D^{25}$ +27.8 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3367 (br, O–H); δ_H (400 MHz, $CDCl_3$) 1.05 (3H, d, *J* 6.6, C(4)H_3), 1.31 (3H, d, *J* 6.1, C(2′)H_3), 1.45 (3H, d, *J* 6.7, C(α)*Me*), 1.50 (1H, m, C(2)*H*), 1.75 (1H, br, O*H*), 1.96 (3H, s, N*Me*), 3.64 (1H, q, *J* 6.7, C(α)*H*), 3.68–3.75 (2H, m, C(1)H_A, C(3)*H*), 3.85 (1H, dd, *J* 11.6, 2.9, C(1)H_B), 4.21 (1H, dq, *J* 9.0, 6.1, C(1′)*H*), 7.20–7.33 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 9.7 (*C*(4)), 21.2 (C(α)*Me*), 21.8 (*C*(2′)), 32.7 (N*Me*), 47.9 (*C*(2)), 55.1 (*C*(3)), 61.0 (*C*(1)), 62.6 (*C*(α)), 70.3 (*C*(1′)), 127.2, 128.6 (Ph_o, Ph_m, Ph_p), 144.4 (Ph_i); *m*/*z* (CI, NH_3) 252 ([M+H]$^+$, 100%).

4.3.9.1. X-ray crystal structure determination for 19. Data were collected using an Enraf–Nonius κ-CCD diffractometer with graphite monochromated Mo Kα radiation using standard procedures at 190 K. The structure was solved by direct methods, all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[36]

X-ray crystal structure data for **19** [$C_{15}H_{25}NO_2$]: M=251.37, orthorhombic, space group P 21 21 21, a=7.1930(1) Å, b=9.3005(2) Å, c=22.3709(5) Å, V=1496.58(5) Å^3, Z=4, μ=0.073 mm^{-1}, colourless plate, crystal dimensions=0.2×0.2×0.4 mm^3. A total of 2001 unique reflections were measured for $0<\theta<30$ and 1811 reflections were used in the refinement. The final parameters were wR_2=0.043 and R_1=0.041 [$I>3\sigma(I)$]. Crystallographic data (excluding structural factors) have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 634752. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

4.3.10. (4*S*,5*S*,1′*R*,α*R*)-2,2,4-Trimethyl-5-{1′-[*N*-methyl-*N*-(α-methylbenzyl)amino]ethyl}-1,3-dioxane 20. A solution of 2,2-dimethoxypropane (0.3 mL) in acetone (5 mL) was added to a mixture of **19** (300 mg, 1.2 mmol), (+)-CSA (140 mg) and $CuSO_4$ (100 mg, 0.63 mmol) and stirred for 5 days at rt. Na_2CO_3 was added until neutral pH was reached, and the mixture was filtered, dried and concentrated in vacuo. Purification by column chromatography (eluent 40–60 °C petrol/Et_2O 10:1) gave **20** (340 mg, 96%) as a clear oil. $[\alpha]_D^{25}$ +6.6 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2988 (C–H), 1454, 1378, 1197; δ_H (400 MHz, $CDCl_3$) 1.05 (3H, d, *J* 6.9, C(2′)H_3), 1.34 (3H, d, *J* 6.7, C(4)*Me*), 1.41 (3H, d, *J* 6.6, C(α)*Me*), 1.42, 1.45 (2×3H, s, C(2)Me_2), 1.65 (1H, m, C(5)*H*), 1.98 (3H, s, N*Me*), 3.43 (1H, app quintet, *J* 6.9, C(1′)*H*), 3.67 (1H, q, *J* 6.6, C(α)*H*), 3.92 (2H, app d, *J* 3.8, C(6)H_2), 4.27 (1H, dq, *J* 6.7, 3.4, C(4)*H*), 7.20–7.33 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 10.6 (*C*(2′)), 19.3 (*C*(4)*Me*), 20.3 (C(α)*Me*), 21.8, 28.8 (C(2)Me_2), 33.1 (N*Me*), 40.0 (*C*(5)), 50.4 (*C*(1′)), 61.8 (*C*(6)), 62.0 (*C*(α)*Me*), 68.9 (*C*(4)), 98.0 (*C*(2)), 126.5, 127.3, 128.2 (Ph_o, Ph_m, Ph_p), 145.1 (Ph_i); *m*/*z* (CI, NH_3) 292 ([M+H]$^+$, 100%); HRMS (CI, NH_3) found: 292.2274; $C_{18}H_{30}NO_2^+$ ([M+H]$^+$) requires: 292.2277.

4.3.11. *tert*-Butyl (2*E*,1′*R*)-2-(1′-hydroxyethyl)-3-phenyl-prop-2-enoate 21. Following *general procedure 2*, *m*CPBA (0.18 g, 0.52 mmol) in $CHCl_3$ (5 mL) was added to **12** (100 mg, 0.26 mmol) in $CHCl_3$ (5 mL) and the reaction was quenched after 1 h. Purification by column chromatography (eluent 40–60 °C petrol/Et_2O 12:1) gave **21** as a clear colourless oil (48 mg, 74%, >99% ee). Found: C, 72.4; H, 8.35%. $C_{15}H_{20}O_3$ requires: C, 72.55; H, 8.1%. $[\alpha]_D^{22}$ +93.7 (*c* 0.75 in $CHCl_3$); ν_{max} (film) 3500 (br, O–H), 1688 (C=O); δ_H (500 MHz, $CDCl_3$) 1.52 (3H, d, *J* 6.6,

C(2′)H_3), 1.59 (9H, s, CMe_3), 3.64 (1H, d, J 11.2, OH), 4.84 (1H, dq, J 11.2, 6.6, C(1′)H), 7.27–7.41 (5H, m, Ph), 7.55 (1H, s, C(3)H); δ_C (125 MHz, $CDCl_3$) 23.3 (C(2′)), 28.2 (CMe_3), 65.0 (C(1′)), 82.0 (CMe$_3$), 128.4, 129.0, 129.1 (Ph_o, Ph_m, Ph_p), 134.8, 136.0 (C(2), Ph_i), 138.7 (C(3)), 167.1 (C(1)); m/z (CI, NH_3) 249 ([M+H]$^+$, 8%), 210 ([M−C_4H_8+NH_4]$^+$, 100%); HRMS (CI, NH_3) found: 210.1130; $C_{11}H_{16}NO_3^+$ [M−C_4H_8+NH_4]$^+$ requires: 210.1131.

4.3.12. *tert*-Butyl (2*E*,1′*R*)-2-(1′-hydroxyethyl)but-2-enoate 22. Following *general procedure 2*, *m*CPBA (129 mg, 0.37 mmol) in $CHCl_3$ (5 mL) was added to **13** (60 mg, 0.19 mmol) in $CHCl_3$ (5 mL) and the reaction was quenched after 90 min. Purification by column chromatography (eluent 40–60 °C petrol/Et_2O 12:1) gave **22** (21 mg, 58%) as a colourless oil. Found: C, 64.75; H, 10.0%. $C_{10}H_{18}O_3$ requires: C, 64.5; H, 9.7%. $[\alpha]_D^{22}$ +31.7 (*c* 1.1 in $CHCl_3$); ν_{max} ($CHCl_3$) 3526 (br, O–H), 1684 (C=O); δ_H (500 MHz, $CDCl_3$) 1.44 (3H, d, J 6.6, C(2′)H_3), 1.56 (9H, s, CMe_3), 1.84 (3H, d, J 7.3, C(4)H_3), 3.80 (1H, d, J 10.9, OH), 4.74 (1H, dq, J 10.9, 6.6, C(1′)H), 6.72 (1H, q, J 7.3, C(3)H); δ_C (125 MHz, $CDCl_3$) 13.5, 23.2 (C(4), C(2′)), 28.2 (CMe_3), 64.7 (C(1′)), 81.3 (CMe$_3$), 136.1 (C(2)), 136.6 (C(3)), 166.7 (C(1)); m/z (CI, NH_3) 204 ([M+NH_4]$^+$, 10%), 187 ([M+H]$^+$, 100%).

4.3.13. *tert*-Butyl (2*Z*,1′*S*)-2-(1′-hydroxyethyl)but-2-enoate 23. Following *general procedure 2*, *m*CPBA (644 mg, 1.87 mmol) in $CHCl_3$ (5 mL) was added to **14** (200 mg, 0.62 mmol) in $CHCl_3$ (5 mL) and the reaction was quenched after 2 h. Purification by column chromatography (eluent 40–60 °C petrol/Et_2O 12:1) gave **23** (68 mg, 59%) as a colourless oil. Found: C, 64.3; H, 9.9%. $C_{10}H_{18}O_3$ requires: C, 64.5; H, 9.7%. $[\alpha]_D^{22}$ −7.4 (*c* 1.4 in $CHCl_3$); ν_{max} ($CHCl_3$) 3601 (br, O–H), 1687 (C=O); δ_H (300 MHz, $CDCl_3$) 1.34 (3H, d, J 6.4, C(2′)H_3), 1.54 (9H, s, CMe_3), 1.95 (3H, d, J 7.1, C(4)H_3), 2.81 (1H, br s, OH), 4.43 (1H, m, C(1′)H), 6.12 (1H, q, J 7.1, C(3)H); δ_C (50 MHz, $CDCl_3$) 15.3, 22.3 (C(4), C(2′)), 28.3 (CMe_3), 70.1 (C(1′)), 81.6 (CMe$_3$), 134.6 (C(3)), 137.1 (C(2)), 167.2 (C(1)); m/z (CI, NH_3) 187 ([M+H]$^+$, 100%).

4.3.14. *tert*-Butyl (2*S*,3*S*,1′*S*,α*R*)-2-(1′-hydroxybenzyl)-3-[*N*-methyl-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 25. Following *general procedure 1*, BuLi (1.5 M in hexanes, 3.0 mL, 4.42 mmol) and di-*iso*-propylamine (0.68 mL, 5.15 mmol) in THF (15 mL), **10** (500 mg, 1.47 mmol) in THF (15 mL), B(OMe)$_3$ (0.66 mL, 5.9 mmol) and benzaldehyde (1.5 mL, 14.7 mmol) gave, after purification by column chromatography (eluent 40–60 °C petrol/Et_2O 8:1), two partially separable diastereoisomeric products (424 mg, 65% combined yield).

First to elute: **25** as a colourless oil (203 mg, 31%). Found: C, 78.0; H, 7.7; N, 3.0%. $C_{29}H_{35}NO_3$ requires: C, 78.2; H, 7.9; N, 3.1%. $[\alpha]_D^{22}$ +68.0 (*c* 0.95 in $CHCl_3$); ν_{max} (film) 3568 (br, O–H), 1729 (C=O); δ_H (500 MHz, $CDCl_3$) 1.12 (9H, s, CMe_3), 1.29 (3H, d, J 6.8, C(α)Me), 2.33 (3H, s, NMe), 3.62 (1H, dd, J 9.8, 5.2, C(2)H), 4.08 (1H, q, J 6.8, C(α)H), 4.35 (1H, d, J 5.2, C(3)H), 5.21 (1H, d, J 9.8, C(1′)H), 7.21–7.58 (15H, m, Ph); δ_C (125 MHz, $CDCl_3$) 11.2 (C(α)Me), 27.5 (CMe_3), 34.3 (NMe), 53.1, 57.1, 70.2, 73.5 (C(2), C(3), C(1′), C(α)), 80.8 (CMe$_3$), 126.9, 127.5, 127.6, 127.8, 128.1, 128.2, 128.4, 129.6 (Ph_o, Ph_m, Ph_p), 135.8, 142.3, 142.6 (Ph_i), 170.0 (C(1)); m/z (CI, NH_3) 446 ([M+H]$^+$, 70%).

Second to elute: a mixture of diastereoisomers as a colourless oil (201 mg, 31%).

Third to elute: a minor diastereoisomer, contaminated with ~5% of an unknown impurity, as a colourless oil (20 mg, 3%); selected data: ν_{max} (film) 3446 (br, O–H), 1707 (C=O); δ_H (500 MHz, $CDCl_3$) 0.76 (9H, s, CMe_3), 1.78 (3H, d, J 6.4, C(α)Me), 1.96 (3H, s, NMe), 3.36 (1H, dd, J 11.2, 9.2, C(2)H), 3.42 (1H, q, J 6.4 C(α)H), 4.98 (1H, d, J 11.2, C(3)H), 5.15 (1H, d, J 9.2, C(1′)H), 7.21–7.48 (15H, m, Ph); δ_C (125 MHz, $CDCl_3$) 22.0 (C(α)Me), 27.0 (CMe_3), 35.4 (NMe), 54.1, 62.2, 65.2, 79.1 (C(2), C(3), C(1′), C(α)), 80.4 (CMe$_3$), 127.2, 127.3, 127.4, 127.5, 127.8, 127.9, 128.0, 129.0, 130.0 (Ph_o, Ph_m, Ph_p), 133.1, 141.6, 144.0 (Ph_i), 172.4 (C(1)); m/z (CI, NH_3) 446 ([M+H]$^+$, 10%).

4.3.15. *tert*-Butyl (2*S*,3*S*,1′*S*,α*R*)-2-(1′-hydroxy-2′-methyl)propyl-3-[*N*-methyl-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 26. Following *general procedure 1*, BuLi (1.5 M in hexanes, 3.0 mL, 4.42 mmol) and di-*iso*-propylamine (0.68 mL, 5.15 mmol) in THF (15 mL), **10** (500 mg, 1.47 mmol) in THF (15 mL), B(OMe)$_3$ (0.66 mL, 5.9 mmol) and *iso*-butyraldehyde (1.35 mL, 14.7 mmol) gave, after purification by column chromatography (eluent 40–60 °C petrol/Et_2O 7:1 then toluene/acetone 40:1), two partially separable diastereoisomeric products (396 mg, 66% combined yield).

First to elute: a minor diastereoisomer as a colourless oil (18 mg, 3%). $[\alpha]_D^{22}$ +41.9 (*c* 0.4 in $CHCl_3$); ν_{max} (film) 3420 (br, O–H), 1703 (C=O); δ_H (500 MHz, $CDCl_3$) 0.90 (3H, d, C(2′)Me_A), 0.93 (3H, d, C(2′)Me_B), 1.50 (3H, d, J 6.4, C(α)Me), 1.57 (9H, s, CMe_3), 1.51–1.62 (1H, m, C(2′)H), 1.97 (3H, s, NMe), 2.69 (1H, m, C(1′)H), 3.20 (1H, q, J 6.4, C(α)H), 3.35 (1H, dd, J 11.8, 2.2, C(2)H), 3.40 (1H, d, J 11.0, OH), 4.91 (1H, d, J 11.8, C(3)H), 7.16–7.52 (10H, m, Ph); δ_C (50 MHz, $CDCl_3$) 19.0, 20.0 (C(2′)Me_2), 21.9 (C(α)Me), 28.3 (CMe_3), 34.1, 35.1 (C(2′), NMe), 50.0, 61.4, 62.3, 75.8 (C(2), C(3), C(1′), C(α)), 81.3 (CMe$_3$), 126.6, 127.4, 127.5, 128.0, 128.1, 129.4 (Ph_o, Ph_m, Ph_p), 134.7, 146.2 (Ph_i), 174.3 (C(1)); m/z (ESI$^+$) 412 ([M+H]$^+$, 100%).

Second to elute: a mixture of diastereoisomers as a colourless oil (131 mg, 22%).

Third to elute: **26** as a colourless oil (248 mg, 41%). Found: C, 75.9; H, 8.8; N, 3.2%. $C_{26}H_{37}NO_3$ requires: C, 75.9; H, 9.1; N, 3.4%. $[\alpha]_D^{22}$ +45.2 (*c* 0.25 in $CHCl_3$); ν_{max} (film) 3587 (br, O–H), 1723 (C=O); δ_H (500 MHz, $CDCl_3$) 0.94 (3H, d, C(2′)Me_A), 0.98 (3H, d, C(2′)Me_B), 1.25 (3H, d, J 6.7, C(α)Me), 1.32 (9H, s, CMe_3), 1.52–1.60 (1H, m, C(2′)), 2.19 (3H, s, NMe), 3.31 (1H, dd, J 9.9, 5.4, C(2)H), 3.90 (1H, q, J 6.7, C(α)H), 4.04 (1H, dd, J 9.9, 2.7, C(1′)H), 4.25 (1H, d, J 5.4, C(3)H), 6.23 (1H, br s, OH), 7.21–7.52 (10H, m, Ph); δ_C (125 MHz, $CDCl_3$) 11.0, 15.2 (C(2′)Me_2), 20.3 (C(α)Me), 27.9 (CMe_3), 31.4 (C(2′)), 34.2

(N*Me*), 49.0, 57.2, 70.0, 74.2 (*C*(2), *C*(3), *C*(1′), *C*(α)), 80.7 (*C*Me$_3$), 126.9, 127.7, 128.1, 128.2, 128.4, 129.7 (*Ph*$_o$, *Ph*$_m$, *Ph*$_p$), 136.3, 142.7 (*Ph*$_i$), 171.0 (*C*(1)); *m*/*z* (CI, NH$_3$) 412 ([M+H]$^+$, 20%).

4.3.16. *tert*-Butyl (2*S*,3*S*,1′*S*,α*R*)-2-(1′-hydroxy-2′,2′-dimethyl)propyl-3-[*N*-methyl-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 27. Following *general procedure 1*, BuLi (1.5 M in hexanes, 3.0 mL, 4.42 mmol) and di-*iso*-propylamine (0.68 mL, 5.15 mmol) in THF (15 mL), **10** (500 mg, 1.47 mmol) in THF (15 mL), B(OMe)$_3$ (0.66 mL, 5.9 mmol) and pivaldehyde (1.26 mL, 14.7 mmol) gave, after purification by column chromatography (eluent 40–60 °C petrol/Et$_2$O 7:1 then toluene/acetone 40:1), two partially separable diastereoisomeric products (413 mg, 66% combined yield).

First to elute: **27** as a clear colourless oil (125 mg, 20%). Found: C, 76.0; H, 9.4; N, 3.5%. $C_{27}H_{39}NO_3$ requires: C, 76.2; H, 9.2; N, 3.3%. $[\alpha]_D^{22}$ +19.7 (*c* 1.0 in CHCl$_3$); ν_{max} (film) 3500 (br, O–H), 1740 (C=O); δ_H (500 MHz, CDCl$_3$) 0.95 (9H, s, C(2′)*Me*$_3$), 1.25 (3H, d, *J* 6.8, C(α)*Me*), 1.28 (9H, s, C*Me*$_3$), 2.17 (3H, s, N*Me*), 3.28 (1H, dd, *J* 10.2, 4.6, C(2)*H*), 4.01 (1H, q, *J* 6.8, C(α)*H*), 4.12 (1H, d, *J* 4.6, C(1′)*H*), 4.13 (1H, d, *J* 10.2, C(3)*H*), 7.15–7.42 (10H, m, *Ph*); δ_C (50 MHz, CDCl$_3$) 10.0 (C(α)*Me*), 26.0, 27.7 (C*Me*$_3$, C(2′)*Me*$_3$), 33.7 (N*Me*), 36.7 (*C*(2′)Me$_3$), 46.2, 56.4, 72.2, 77.2 (*C*(2), *C*(3), *C*(1′), *C*(α)), 80.7 (*C*Me$_3$), 127.0, 128.0, 128.1, 128.2, 128.4, 130.1 (*Ph*$_o$, *Ph*$_m$, *Ph*$_p$), 136.8, 141.6 (*Ph*$_i$), 171.1 (*C*(1)); *m*/*z* (CI, NH$_3$) 426 ([M+H]$^+$, 50%).

Second to elute: a mixture of diastereoisomers as a colourless oil (288 mg, 46%).

Third to elute: a minor diastereoisomer (80% de); selected data: ν_{max} (film) 3436 (br, O–H), 1716 (C=O); δ_H (500 MHz, CDCl$_3$) 0.95, 1.01 (2×9H, s, C*Me*$_3$, C(2′)*Me*$_3$), 1.66 (3H, d, *J* 6.4, C(α)*Me*), 1.91 (3H, s, N*Me*), 3.14–3.19 (2H, m, C(2)*H*, C(α)*H*), 4.03 (1H, d, *J* 9.1, C(1′)*H*), 4.82 (1H, d, *J* 11.2, C(3)*H*), 7.14–7.38 (10H, m, *Ph*), 8.70 (1H, br s, O*H*); δ_C (50 MHz, CDCl$_3$) 21.7 (C(α)*Me*), 26.0 (C(2′)*Me*$_3$), 27.0 (C*Me*$_3$), 34.9 (N*Me*), 36.5 (*C*(2′)Me$_3$), 47.3, 62.1, 64.8, 81.9 (*C*(2), *C*(3),*C*(1′), *C*(α)), 80.9 (*C*Me$_3$), 127.2, 127.6, 128.0, 128.7, 130.6 (*Ph*$_o$, *Ph*$_m$, *Ph*$_p$), 131.9, 143.9 (*Ph*$_i$), 172.2 (*C*(1)); *m*/*z* (CI, NH$_3$) 426 ([M+H]$^+$, 30%).

4.3.17. *tert*-Butyl (2*S*,3*R*,1′*S*,α*R*)-2-(1′-hydroxy)benzyl-3-[*N*-methyl-*N*-(α-methylbenzyl)amino]butanoate 28. Following *general procedure 1*, BuLi (1.5 M in hexanes, 2.95 mL, 4.33 mmol) and di-*iso*-propylamine (0.66 mL, 5.05 mmol) in THF (15 mL), **11** (400 mg, 1.44 mmol) in THF (15 mL), B(OMe)$_3$ (0.64 mL, 5.8 mmol) and benzaldehyde (1.47 mL, 14.4 mmol) gave, after exhaustive purification by column chromatography (eluent 40–60 °C petrol/Et$_2$O 12:1 then 40–60 °C petrol/Et$_2$O 6:1) three partially separable diastereoisomeric products (298 mg, 54% combined yield).

First to elute: **28** as a clear colourless oil (132 mg, 24%). Found: C, 75.4; H, 8.6; N, 3.2%. $C_{24}H_{33}NO_3$ requires: C, 75.2; H, 8.7; N 3.65%. $[\alpha]_D^{22}$ +39.6 (*c* 0.25 in CHCl$_3$); ν_{max} (CHCl$_3$) 3343 (br, O–H), 1687 (C=O); δ_H (500 MHz, CDCl$_3$) 1.08 (3H, d, *J* 6.5, C(4)*H*$_3$), 1.18 (9H, s, C*Me*$_3$), 1.35 (3H, d, *J* 6.6, C(α)*Me*), 2.01 (3H, s, N*Me*), 2.80 (1H, dd, *J* 10.9, 2.9, C(2)*H*), 3.56 (1H, q, *J* 6.6, C(α)*H*), 3.96 (1H, dq, *J* 10.9, 6.5, C(3)*H*), 4.46 (1H, d, *J* 10.5, O*H*), 4.86 (1H, dd, *J* 10.5, 2.9, C(1′)*H*), 7.19–7.35 (10H, m, *Ph*); δ_C (50 MHz, CDCl$_3$) 9.3 (C(4)*H*$_3$), 21.9 (C(α)*Me*), 27.9 (C*Me*$_3$), 32.5 (N*Me*), 53.0, 57.9, 63.1, 71.7 (*C*(2), *C*(3), *C*(1′), *C*(α)), 81.0 (*C*Me$_3$), 125.4, 126.7, 127.0, 127.5, 128.1 (*Ph*$_o$, *Ph*$_m$, *Ph*$_p$), 142.9, 146.2 (*Ph*$_i$), 183.8 (*C*(1)); *m*/*z* (ESI$^+$) 384 ([M+H]$^+$, 100%).

Second to elute: a 67:33 mixture of two minor diastereoisomers **A** and **B** (166 mg, 30%); *m*/*z* (ESI$^+$) 384 ([M+H]$^+$, 100%).

Selected data for **A**: δ_H (500 MHz, CDCl$_3$) 0.96 (3H, d, *J* 6.5, C(4)*H*$_3$), 1.11 (9H, s, C*Me*$_3$), 1.56 (3H, d, *J* 6.6, C(α)*Me*), 2.11 (3H, s, N*Me*), 2.74 (1H, dd, *J* 10.8, 9.5, C(2)*H*), 3.60 (1H, q, *J* 6.6, C(α)*H*), 3.91 (1H, dq, *J* 10.8, 6.5, C(3)*H*), 5.00 (1H, d, *J* 9.5, C(1′)*H*), 7.23–7.45 (10H, m, *Ph*), 8.47 (1H, br s, O*H*); δ_C (50 MHz, CDCl$_3$) 10.5, 21.4 (C(4)*H*$_3$, C(α)*Me*), 27.5 (C*Me*$_3$), 32.8 (N*Me*), 56.0, 57.3, 62.9, 78.7 (*C*(2), *C*(3), *C*(1′), *C*(α)), 80.7 (*C*Me$_3$), 127.4, 127.7, 127.8, 128.7 (*Ph*$_o$, *Ph*$_m$, *Ph*$_p$), 141.5, 143.7 (*Ph*$_i$), 171.1 (*C*(1)).

Selected data for **B**: δ_H (500 MHz, CDCl$_3$) 1.26 (9H, s, C*Me*$_3$), 1.39 (3H, d, *J* 6.8, C(α)*Me*), 1.43 (3H, d, *J* 6.9, C(4)*H*$_3$), 2.21 (3H, s, N*Me*), 3.23 (1H, dd, *J* 9.5, 3.9, C(2)*H*), 3.29 (1H, dq, *J* 6.9, 3.9, C(3)*H*), 4.31 (1H, q, *J* 6.8, C(α)*H*), 5.17 (1H, d, *J* 9.5, C(1′)*H*), 7.11 (1H, br s, O*H*), 7.22–7.49 (10H, m, *Ph*); δ_C (125 MHz, CDCl$_3$) 13.0, 14.4 (C(4)*H*$_3$, C(α)*Me*), 27.8 (C*Me*$_3$), 32.7 (N*Me*), 53.5, 57.5, 57.8, 72.9 (*C*(2), *C*(3), *C*(1′), *C*(α)), 80.7 (*C*Me$_3$), 127.1, 127.2, 127.5, 128.0, 128.2 (*Ph*$_o$, *Ph*$_m$, *Ph*$_p$), 141.3, 143.1 (*Ph*$_i$), 171.2 (*C*(1)).

4.3.18. *tert*-Butyl (2*S*,3*R*,4*E*,1′*R*,α*R*)-2-(1′-hydroxyethyl)-3-[*N*-methyl-*N*-(α-methylbenzyl)amino]hex-4-enoate 29. Following *general procedure 1*, BuLi (1.5 M in hexanes, 3.6 mL, 5.4 mmol) and di-*iso*-propylamine (0.88 mL, 6.3 mmol) in THF (60 mL), **24** (547 mg, 1.80 mmol) in THF (20 mL), B(OMe)$_3$ (0.61 mL, 5.4 mmol) and acetaldehyde (~1 mL, excess) gave, after exhaustive purification by column chromatography (eluent 40–60 °C petrol/Et$_2$O 3:1), two diastereoisomeric products (430 mg, 69% overall).

First to elute: a minor diastereoisomer as a white solid (130 mg, 21%). Found: C, 72.4; H, 9.95; N, 3.8%. $C_{21}H_{33}NO_3$ requires: C, 72.6; H, 9.6; N 4.0%. Mp 76–78 °C; $[\alpha]_D^{21}$ +61.6 (*c* 1.4 in CHCl$_3$); ν_{max} (KBr) 3450 (br, O–H), 1726 (C=O); δ_H (300 MHz, CDCl$_3$) 1.20 (3H, d, *J* 6.0, C(2′)*H*$_3$), 1.40 (9H, s, C*Me*$_3$), 1.47 (3H, d, *J* 6.5, C(α)*Me*), 1.72 (3H, dd, *J* 6.5, 1.2, C(6)*H*$_3$), 1.96 (3H, s, N*Me*), 2.47 (1H, app t, *J* 10.0, C(2)*H*), 3.45 (1H, q, *J* 6.5, C(α)*H*), 4.01 (1H, app t, *J* 10.0, C(3)*H*), 4.16 (1H, dq, *J* 9.3, 6.0, C(1′)*H*), 5.38 (1H, ddq, *J* 15.3, 9.6, 1.2, C(4)*H*), 5.66 (1H, dq, *J* 15.3, 6.5, C(5)*H*), 7.20–7.32 (5H, m, *Ph*), 7.91 (1H, br s, O*H*); δ_C (50 MHz, CDCl$_3$) 17.9, 21.5 (*C*(6), *C*(2′), C(α)*Me*), 27.9 (C*Me*$_3$), 34.4 (N*Me*), 54.7 (*C*(2)), 62.5, 63.7, 71.1 (*C*(3), *C*(1′), *C*(α)), 80.6 (*C*Me$_3$), 123.6 (*C*(5)), 127.1, 127.2, 128.6 (*Ph*$_o$, *Ph*$_m$, *Ph*$_p$), 131.6 (*C*(4)),

144.2 (*Ph*$_i$), 171.2 (*C*(1)); *m/z* (CI, NH_3) 348 ([M+H]$^+$, 80%).

Second to elute: **29** as a clear colourless oil (300 mg, 48%). Found: C, 72.3; H, 9.8; N, 4.3%. $C_{21}H_{33}NO_3$ requires: C, 72.6; H, 9.6; N 4.0%. $[\alpha]_D^{21}$ +10.1 (*c* 1.6 in $CHCl_3$); ν_{max} (film) 3433 (br, O–H), 1729 (C=O); δ_H (300 MHz, $CDCl_3$) 1.23 (3H, d, *J* 6.0, C(2′)*H*$_3$), 1.28 (3H, d, *J* 6.7, C(α)*Me*), 1.45 (9H, s, C*Me*$_3$), 1.75 (3H, d, *J* 6.0, C(6)*H*$_3$), 2.07 (3H, s, N*Me*), 2.81 (1H, dd, *J* 9.5, 4.9, C(2)*H*), 3.57 (1H, dd, *J* 9.5, 4.9, C(3)*H*), 4.12 (1H, q, *J* 6.7, C(α)*H*), 4.25 (1H, dq, *J* 9.5, 6.0, C(1′)*H*), 5.64 (1H, dq, *J* 15.3, 6.5, C(5)*H*), 5.76 (1H, dd, *J* 15.3, 9.5, C(4)*H*), 6.45 (1H, br s, O*H*), 7.19–7.31 (5H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 12.8, 17.8, 22.1 (*C*(6), *C*(2′), C(α)*Me*), 28.0 (C*Me*$_3$), 33.1 (N*Me*), 53.5 (*C*(2)), 57.9, 66.7, 67.1 (*C*(3), *C*(1′), *C*(α)), 80.5 (*C*Me$_3$), 126.9, 127.0, 127.9, 128.1 (*C*(5), *Ph*$_o$, *Ph*$_m$, *Ph*$_p$), 130.5 (*C*(4)), 142.5 (*Ph*$_i$), 171.0 (*C*(1)); *m/z* (ESI$^+$) 348 ([M+H]$^+$, 100%).

4.3.19. *tert*-Butyl (2*E*,1′*R*)-2-(1′-hydroxybenzyl)-3-phenylprop-2-enoate 30. Following *general procedure 2*, *m*CPBA (194 mg, 0.45 mmol) in $CHCl_3$ (5 mL) was added to **25** (100 mg, 0.22 mmol) in $CHCl_3$ (5 mL) and the reaction was quenched after 1 h. Purification by column chromatography (eluent 40–60 °C petrol/Et_2O 12:1) gave **30** (44 mg, 63%) as a colourless oil.[18] $[\alpha]_D^{22}$ +209.3 (*c* 0.6 in $CHCl_3$); ν_{max} ($CHCl_3$) 3436 (br, O–H), 1707 (C=O); δ_H (500 MHz, $CDCl_3$) 1.36 (9H, s, C*Me*$_3$), 3.89 (1H, d, *J* 11.7, O*H*), 5.83 (1H, d, *J* 11.7, C(1′)*H*), 7.27–7.42 (10H, m, *Ph*), 7.88 (1H, s, C(3)*H*); δ_C (125 MHz, $CDCl_3$) 27.9 (C*Me*$_3$), 69.5 (*C*(1′)), 82.2 (*C*Me$_3$), 125.3, 127.0, 128.3, 128.6, 128.9, 129.1 (*Ph*$_o$, *Ph*$_m$, *Ph*$_p$), 134.2, 134.6 (*Ph*$_i$), 141.1 (*C*(3)), 143.3 (*C*(2)), 166.8 (*C*(1)); *m/z* (CI, NH_3) 311 ([M+H]$^+$, 8%), 254 (100%).

4.3.20. *tert*-Butyl (2*E*,1′*R*)-2-(1′-hydroxy-2′-methyl)-propyl-3-phenylprop-2-enoate 31. Following *general procedure 2*, *m*CPBA (209 mg, 0.49 mmol) in $CHCl_3$ (5 mL) was added to **26** (100 mg, 0.24 mmol) in $CHCl_3$ (5 mL) and the reaction was quenched after 1 h. Purification by column chromatography (eluent 40–60 °C petrol/Et_2O 15:1) gave **31** (44 mg, 66%) as a colourless oil. $[\alpha]_D^{22}$ −12.8 (*c* 0.1 in $CHCl_3$); ν_{max} ($CHCl_3$) 1685 (C=O); δ_H (500 MHz, $CDCl_3$) 0.71 (3H, d, *J* 6.9, C(2′)*Me*$_A$), 1.02 (3H, d, *J* 6.6, C(2′)*Me*$_B$), 1.57 (9H, s, C*Me*$_3$), 1.99–2.06 (1H, m, C(2′)*H*), 3.38 (1H, d, *J* 11.2, O*H*), 4.18 (1H, dd, *J* 11.2, 9.3, C(1′)*H*), 7.31–7.41 (5H, m, *Ph*), 7.61 (1H, s, C(3)*H*); δ_C (125 MHz, $CDCl_3$) 19.5, 19.7 (C(2′)*Me*$_2$), 28.2 (C*Me*$_3$), 33.7 (*C*(2′)), 74.9 (*C*(1′)), 81.9 (*C*Me$_3$), 128.3, 128.5, 129.0 (*Ph*$_o$, *Ph*$_m$, *Ph*$_p$), 135.0, 135.1 (*C*(2), *Ph*$_i$), 167.7 (*C*(1)); *m/z* (CI, NH_3) 277 ([M+H]$^+$, 10%), 238 ([M−C_4H_8+NH_4]$^+$, 100%).

4.3.21. *tert*-Butyl (2*E*,1′*R*)-2-(1′-hydroxy-2′,2′-dimethyl)-propyl-3-phenylprop-2-enoate 32. Following *general procedure 2*, *m*CPBA (132 mg, 0.31 mmol) in $CHCl_3$ (5 mL) was added to **27** (65 mg, 0.16 mmol) in $CHCl_3$ (5 mL) and the reaction was quenched after 1 h. Purification by column chromatography (eluent 40–60 °C petrol/Et_2O 12:1) gave **32** (26 mg, 59%) as a colourless oil. $[\alpha]_D^{22}$ −230.7 (*c* 0.45 in $CHCl_3$); ν_{max} ($CHCl_3$) 1682 (C=O); δ_H (500 MHz, $CDCl_3$) 0.79 (9H, s, C(2′)*Me*$_3$), 1.57 (9H, s, C*Me*$_3$), 4.52 (1H, d, *J* 10.3, C(1′)*H*), 4.80 (1H, d, *J* 10.3, O*H*), 7.28–7.42 (5H, m, *Ph*), 7.57 (1H, s, C(3)*H*); δ_C (125 MHz, $CDCl_3$) 26.5, 28.1 (C*Me*$_3$, C(2′)*Me*$_3$), 37.3 (*C*(2′)), 76.5 (*C*(1′)), 82.1 (*C*Me$_3$), 128.0, 128.5, 128.6 (*Ph*$_o$, *Ph*$_m$, *Ph*$_p$), 133.3, 135.6 (*C*(2), *Ph*$_i$), 140.6 (*C*(3)), 169.5 (*C*(1)); *m/z* (CI, NH_3) 291 ([M+H]$^+$, 15%), 252 ([M−C_4H_8+NH_4]$^+$, 100%).

4.3.22. *tert*-Butyl (2*E*,1′*R*)-2-(1′-hydroxybenzyl)but-2-enoate 33. Following *general procedure 2*, *m*CPBA (72 mg, 0.21 mmol) in $CHCl_3$ (5 mL) was added to **29** (40 mg, 0.10 mmol) in $CHCl_3$ (5 mL) and the reaction was quenched after 90 min. Purification by column chromatography (eluent 40–60 °C petrol/Et_2O 12:1) gave **34** (16 mg, 62%) as a colourless oil.[37] $[\alpha]_D^{22}$ −181.5 (*c* 0.25 in $CHCl_3$); ν_{max} ($CHCl_3$) 1685 (C=O); δ_H (500 MHz, $CDCl_3$) 1.36 (9H, s, C*Me*$_3$), 1.96 (3H, d, *J* 7.3, C(4)*H*$_3$), 4.12 (1H, d, *J* 11.0, O*H*), 5.68 (1H, d, *J* 11.0, C(1′)*H*), 6.99 (1H, q, *J* 7.3, C(3)*H*), 7.23–7.38 (5H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 14.1 (*C*(4)), 28.0 (C*Me*$_3$), 69.1 (*C*(1′)), 81.7 (*C*Me$_3$), 125.2, 128.2, 126.9 (*Ph*$_o$, *Ph*$_m$, *Ph*$_p$), 134.7, 143.2 (*C*(2), *Ph*$_i$), 139.0 (*C*(3)), 166.5 (*C*(1)).

4.3.23. *tert*-Butyl (2*E*,4*E*,1′*R*)-2-(1′-hydroxyethyl)hexa-2,4-dienoate 34. Following *general procedure 2*, *m*CPBA (340 mg, 0.99 mmol) in $CHCl_3$ (8 mL) was added to **29** (171 mg, 0.49 mmol) in $CHCl_3$ (5 mL) and the reaction was quenched after 2 h. Purification by column chromatography (eluent 40–60 °C petrol/Et_2O 5:1) gave **34** as a colourless oil (73 mg, 70%). Found: C, 68.1; H, 9.3%. $C_{12}H_{20}O_3$ requires: C, 67.9; H, 9.5%. $[\alpha]_D^{21}$ +18.2 (*c* 1.8 in $CHCl_3$); ν_{max} ($CHCl_3$) 3520 (br, O–H), 1675 (C=O); δ_H (300 MHz, $CDCl_3$) 1.42 (3H, d, *J* 6.6, C(2′)*H*$_3$), 1.52 (9H, s, C*Me*$_3$), 1.87 (3H, d, *J* 6.8, C(6)*H*$_3$), 3.74 (1H, br s, O*H*), 4.80 (1H, br s, C(1′)*H*), 6.13 (1H, dq, *J* 14.7, *J* 6.8, C(5)*H*), 6.42 (1H, dd, *J* 14.7, 11.5, C(4)*H*), 6.98 (1H, d, *J* 11.5, C(3)*H*); δ_C (50 MHz, $CDCl_3$) 18.9, 23.6 (*C*(6), *C*(2′)), 28.2 (C*Me*$_3$), 65.3 (*C*(1′)), 81.3 (*C*Me$_3$), 125.9 (*C*(5)), 131.6 (*C*(2)), 138.1, 139.7 (*C*(3), *C*(4)), 167.3 (*C*(1)); *m/z* (CI, NH_3) 213 ([M+H]$^+$, 40%).

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31. HPLC performed using a Daicel ChiralPak OD column with a solvent system of *iso*-propanol/hexanes 5:95; flow rate 1.0 mL min^{-1}; retention times: (*S*)-enantiomer 9 min, (*R*)-enantiomer 16 min.
32. A known scalemic mixture of lithium *N*-methyl-*N*-(α-methylbenzyl)amide **9** (33% ee, enriched in (*R*)-**9**) was used in the same three-step protocol (conjugate addition, aldol and Cope elimination) to generate authentic material of 33% ee to allow unambiguous ee determination.
33. The major diastereoisomer in each case was assigned the *syn*-configuration by analogy to that unambiguously confirmed upon aldol reaction of **10** and **11** with acetaldehyde.
34. HPLC performed using a Daicel ChiralPak OD column with a solvent system of *iso*-propanol/hexanes 5:95; flow rate 1.0 mL min^{-1}; retention times: (*S*)-enantiomer 11 min, (*R*)-enantiomer 18 min.
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