Enantioselective synthesis of β-hydroxy amines and aziridines using asymmetric transfer hydrogenation of α-amino ketones

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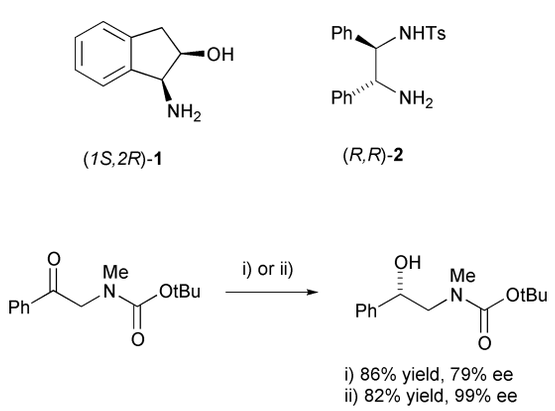
Enantioselective transfer hydrogenation of α-amino ketones is an effective method for the asymmetric synthesis of β-hydroxy amines and aziridines.

Introduction

Aziridines are valuable synthetic reagents and intermediates. In particular they benefit from high reactivity due to the small, strained, nitrogen-containing rings, thus permitting their rapid conversion into a range of derivatives. The synthesis of enantiomerically pure aziridines is a desirable objective since the physiological properties of both the aziridines themselves and the products formed from them are likely to be dependent on the absolute configuration.[1]

Enantiomerically enriched aziridines may be formed by the enantioselective catalysis of the addition of a nitrene onto one face of a prochiral alkene.[2] However, the most conceptually simple approach to these targets is probably through the cyclisation of an appropriate enantiomerically pure β-amino alcohol precursor.[1] Whilst a number of homochiral β-amino alcohols are available from natural sources such as amino acids, the range of materials is limited. In this paper we describe a simple and expedient route for the enantioselective synthesis of aziridines *via* α-amido ketone reduction followed by cyclisation.

We have previously described the use of enantioselective transfer hydrogenation[3–5] for the reduction of ketones containing α-amido groups (Scheme 1).[5] In the example shown we first



Scheme 1 *Reagents and conditons:* i) 0.5 mol% $[Ru(cymene)Cl_2]_2$ 1 mol% **1**, iPrOH, 2.5 mol% KOH, rt. ii) 0.5 mol% $[Ru(cymene)Cl_2]_2$ 1 mol% **2**, HCO_2H, Et_3N, rt.

employed a catalyst formed by the combination of (1*S*,2*R*)-*cis*-1-aminoindan-2-ol **1** with $[Ru(cymene)Cl_2]_2$ and propan-2-ol–KOH as the hydrogen source,[5a] which gave a product of 79% ee. In subsequent studies we found that the combination of (*R*,*R*)-TsDPEN **2** with the same ruthenium complex, a system first reported by Noyori,[3] gave superior results (Scheme 1) when used with the formic acid–triethylamine hydrogen source.[5b] Since the enantioselectivies of the reduction were high, we considered that this might be a suitable method for the synthesis of aziridines of high enantiomeric excess.

Results and discussion

The racemic reduction of α-amino ketones is generally routinely carried out through the use of sodium borohydride or other hydride reagents. Enantioselective reduction of such substrates by transfer hydrogenation had not been reported prior to our initial studies, and we feared that it may be inhibited by chelation of the metal of the catalyst by the reduction product. Recent work in our group has revealed that the use of an amide or carbamate derivative to protect the amine prevents this and renders the reaction high yielding and selective.[5] Following conversion of the hydroxy group to a tosylate and deprotection of the amine it is possible to cyclise the product through an S_N2 mechanism, to give the aziridine in high ee.[5b]

During the last two decades, the conversion of 2-amino alcohols to aziridines[6,7] has been achieved by one-pot cyclisations employing triphenylphosphine–carbon tetrachloride–triethylamine[8] or triphenylphosphine dibromide–triethylamine.[9] Although the combination of triphenylphosphine–diethyl azodicarboxylate (Mitsunobu reagent) has been used for intramolecular dehydrations,[10] application of this reagent to the synthesis of aziridines has also been reported.[11,12] According to Pfister,[13] aziridines are generally obtained successfully if there is at least one substituent attached to either of the two carbon atoms between oxygen and nitrogen.

For the synthesis of *N*-benzyl-2-phenylaziridine **3** we began with the preparation of α-(*N*-benzyl-amino) ketone from readily available and inexpensive bromoacetophenone and benzylamine, followed by tBoc-protection of the NH group to give α-(*N*-benzyl-*N*-tBoc)amino ketone **4** in 79% yield. Reduction of **4** using sodium borohydride gave the racemic alcohol *rac*-**5** in 98% yield. Enantioselective reduction of **4** was successfully achieved using both the (1*S*,2*R*)-*cis*-aminoindanol–propan-2-ol and (1*R*,2*R*)-TsDPEN–formic acid systems. In both cases the enantiomeric excesses (ee) were determined by chiral HPLC. The aminoindanol system afforded *S*-(+)-**5** in 60% yield and 88% ee, while the (1*R*,2*R*)-TsDPEN–formic acid system gave *S*-(+)-**5** in 74% yield and 98% ee. The absolute configuration was confirmed by conversion to the *O*-*tert*-butyldimethylsilyl ether *S*-(+)-**6** (see later discussion) by treatment of the precursor alcohol **5** with *tert*-butylchloro-

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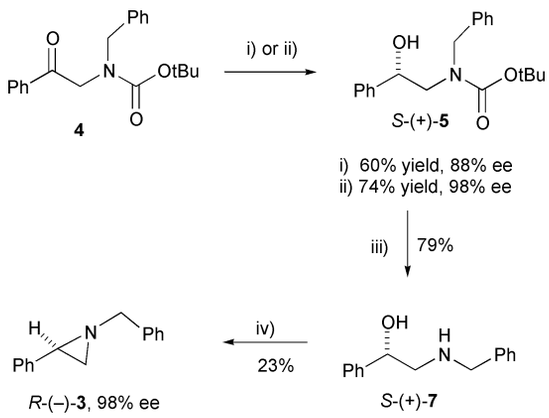
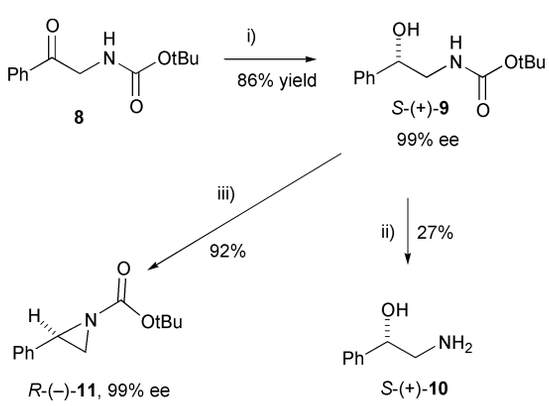
dimethylsilane and imidazole (49% yield). Deprotection of the nitrogen atom in *S*-(+)-**5** gave the amino alcohol *S*-(+)-**7** which was the subject of cyclisation studies. Attempts to achieve this *via* *O*-tosylation followed by base treatment failed,[14] however the use of Mitsunobu conditions resulted in formation in low yield (23%), but high enantiomeric excess, of the aziridine *R*-(−)-**3**.[10] The ee of the aziridine **3** was determined to be 98% by ^{1}H NMR analysis using 6 mol% Eu(hfc)$_3$[15] chiral shift reagent. The racemic aziridine was also synthesised in an identical manner (27% yield for the cyclisation step) (Scheme 2).



Scheme 2 *Reagents and conditions:* i) 0.5 mol% [Ru(cymene)Cl$_2$]$_2$ 1 mol% **1**, iPrOH, 2.5 mol% KOH, rt. ii) 0.5 mol% [Ru(cymene)Cl$_2$]$_2$ 1 mol% **2**, HCO$_2$H, Et$_3$N, rt. iii) TFA, CH$_2$Cl$_2$. iv) DEAD, PPh$_3$, THF.

In an attempt to identify an improved route, the synthesis of *N*-tBoc-2-phenylaziridine was also an objective of our study. *N*-Acylaziridine has been prepared according to essentially three synthetic routes from *N*-acyl-α-amino alcohols. The first method involves activation of the hydroxy group by converting it into a tosylate or mesylate and subsequent ring-closure by means of a strong base (LiHMDS or NaH).[16] The second method is most frequently used and requires the Mitsunobu conditions.[17,18] Thirdly *N*-acylaziridines have been prepared using the expensive and hazardous diethylaminosulfur trifluoride (DAST).[19] For this project we employed the straightforward cyclisation method of *N*-tBoc-amino alcohols described by Wessig *et al.*[14a]

The synthetic route began with 2-(*N*-*tert*-butoxycarbonylamino)acetophenone **8** and is summarised in Scheme 3. Our

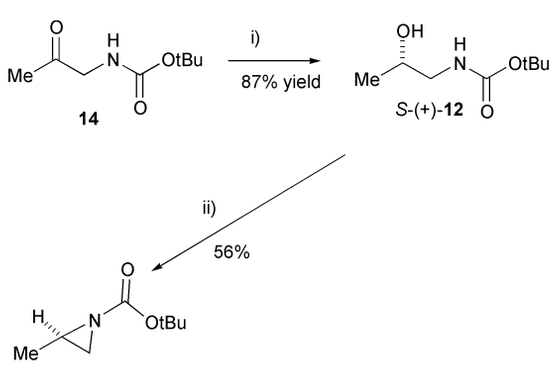


Scheme 3 *Reagents and conditions:* i) 0.5 mol% [Ru(cymene)Cl$_2$]$_2$ 1 mol% **2**, HCO$_2$H, Et$_3$N, rt. ii) TFA, CH$_2$Cl$_2$. iii) DEAD, PPh$_3$, THF.

studies revealed that the monotosylated diamine system was highly efficient at the reduction of **8**, furnishing alcohol *S*-(+)-**9** in 86% yield, $[a]_D^{20}$ +0.8 (*c* = 2 ethanol), and 99% ee as measured by chiral HPLC. In contrast the (1*S*,2*R*)-*cis*-aminoindanol–Ru(II)–propan-2-ol system totally failed in this application. The reasons for this dramatic difference are not fully clear, however we have previously speculated that chelating reduction products (as might be obtained from the reduction of **8**) may inhibit, and lead to subsequent decomposition of, the aminoalcohol–Ru(II) complex.[3] In contrast the monotosylated diamine may well form much stronger complexes with the same metal, and be resistant to such chelation-initiated decomposition. The configuration of *S*-(+)-**9** was determined by deprotection of the nitrogen atom with TFA to give the known amino alcohol *S*-(+)-**10**[20] in 27% yield. Conversion of the same sample of *S*-(+)-**9** to *S*-(+)-**6** with *tert*-butylchlorodimethylsilane and imidazole, and subsequently with phenyl bromide and sodium hydride, served to confirm the absolute configuration of the product of reduction of **4** as described previously (Scheme 2).

Alcohol *S*-(+)-**9** was cyclised to the *N*-tBoc-aziridine *R*-(−)-**11** in 92% yield and 99% ee (determined by ^{1}H NMR analysis using 6 mol% Eu(hfc)$_3$ chiral shift reagent) through treatment with tosyl chloride and base,[14a] thus delivering an efficient synthesis of aziridines in high yield and enantioselectivity.[21] Cyclisation of racemic (±)-1-phenyl-2-(*tert*-butoxycarbonylamino)ethanol was also achieved in 92% yield through treatment with tosyl chloride and base (in order to supply a racemic standard).

2-Methylaziridine has been prepared using the classic method of Wenker,[21,22] through cyclisation of the sulfate ester of 1-aminopropan-2-ol. In an attempt to improve the synthetic method of formation of 2-methylaziridine, cyclisation with tosyl chloride and KOH was used. Boc-protection of the NH group of (±)-1-aminopropan-2-ol gave the (±)-1-tBoc-aminopropan-2-ol **12** in 95% yield, which was then used in two different reactions. It was i) cyclised to the *N*-tBoc aziridine **13** through treatment with tosyl chloride and base (57%), and ii) oxidised with pyridium dichromate to give (±)-1-tBoc-aminopropan-2-one **14** in 88% yield. Reduction of **14** using the ruthenium based catalyst, with TsDPEN **2** and formic acid, was achieved in 87% yield and gave a product of $[a]_D^{20}$ +27.5 (*c* = 1, CH$_2$Cl$_2$). We have assigned, on the basis of the sense of reduction of **8**, *S* configuration to compound **12**. Alcohol **12** was then cyclised to *N*-tBoc-2-methylaziridine *R*-(−)-**13** in 56% yield, through treatment with tosyl chloride and base (Scheme 4). The

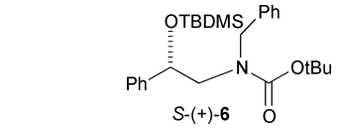


Scheme 4 *Reagents and conditions:* i) 0.5 mol% [Ru(cymene)Cl$_2$]$_2$ 1 mol% **2**, HCO$_2$H, Et$_3$N, rt. ii) TsCl, KOH, THF.

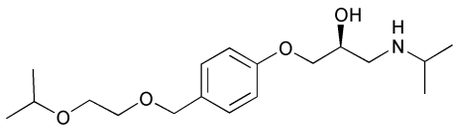
resulting aziridine exhibits $[a]_D^{20}$ −42.2 (*c* = 1, dichloromethane). Since the alcohol is not UV active, the exact enantiomeric excess of the pure compound could not be measured by chiral HPLC. However Wessig *et al.*[14a] have previously referred to the synthesis of enantiomerically pure (*S*)-*N*-tBoc-2-methylaziridine, which has $[a]_D^{20}$ +39.2 (*c* = 1, CH$_2$Cl$_2$). Since aziridine **13** has $[a]_D^{20}$ −42.2 (*c* = 1, CH$_2$Cl$_2$), we can then conclude that it is of high ee and *R* configuration as expected since the cyclisation process normally occurs with an inversion of configuration.

In view of the importance of 2-hydroxy-2-propylamine derivatives, such as bisprolol **15**,[23] as β-selective adrenoceptor blocking agents (β-blockers) used in the treatment of hypertension, angina pectoris, cardiac arrhythmias, glaucoma, and

prevention of migraine attacks, we chose to examine the synthetic approach to such targets through the enantioselective transfer hydrogenation of the corresponding ketone precursor.

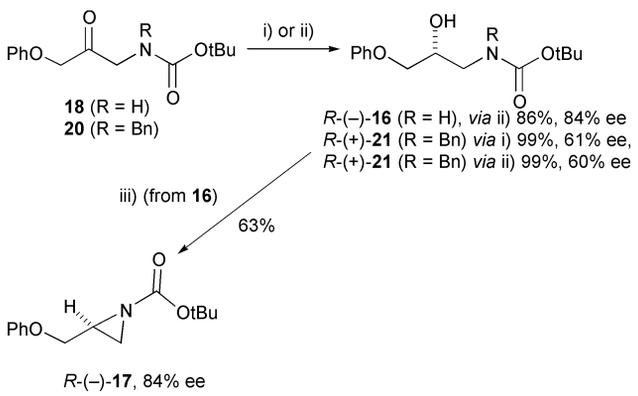


S-(+)-**6**



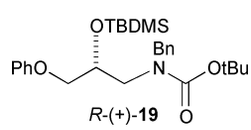
Bisprolol **15**

The route to 2-hydroxy-2-propylamine and its corresponding aziridine derivative is outlined is Scheme 5. The substrate was



Scheme 5 *Reagents and conditions:* i) 0.5 mol% $[Ru(cymene)Cl_2]_2$ 1 mol% **1**, iPrOH, 2.5 mol% KOH, rt. ii) 0.5 mol% $[Ru(cymene)Cl_2]_2$ 1 mol% **2**, HCO_2H, Et_3N, rt. iii) TsCl, KOH, THF.

prepared by tBoc-protection of the NH group of allylamine (98% yield), oxidation with *m*-chloroperoxybenzoic acid (88%), ring opening with phenol (to give racemic **16**, 92% yield). Compound *rac*-**16** was then i) cyclised to *rac*-*N*-tBoc-2-(phenoxymethyl)aziridine **17** in 66% yield, and ii) oxidised with pyridine dichromate to afford **18** in 31% yield. Reaction of ketone **18** using the (1*R*,2*R*)-TsDPEN–formic acid system gave the corresponding alcohol *R*-(−)-**16** in 84% ee (measured by chiral HPLC) and 86% yield. The configuration is based on analogy with the synthesis of (*R*)-propranolol described in the next section. In contrast the (1*S*,2*R*)-*cis*-aminoindanol–Ru(II)–propan-2-ol system totally failed in this application. Conversion of the same sample of *R*-(−)-**16** to *R*-(+)-**19** with *tert*-butylchlorodimethylsilane and imidazole, followed by benzyl bromide and sodium hydride, was undertaken to confirm the absolute sense of the product of reduction of **20** as described in the next section.

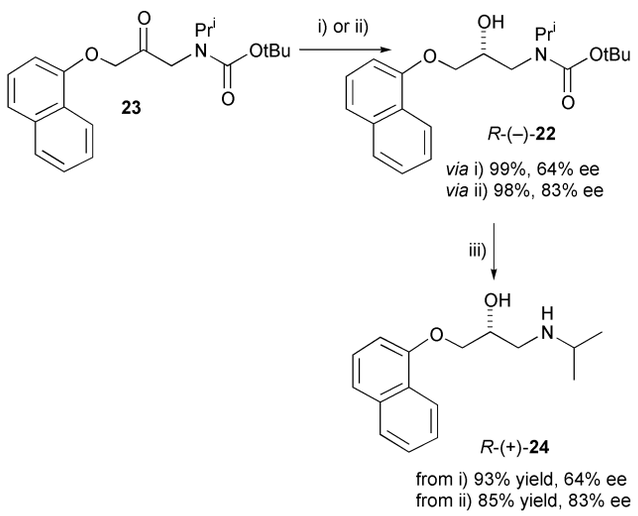


R-(+)-**19**

Alcohol *R*-(−)-**16** was then cyclised to the corresponding aziridine *R*-(−)-**17** in 63% yield, through treatment with tosyl chloride and base. The resulting aziridine has a high $[\alpha]_D^{20}$ (−68.9 ($c = 1$, ethanol)), and enantiopurity (84% ee). We believe that this represents a competitive, and highly practical approach for the reduction of this class of ketones, which are normally regarded as 'difficult' substrates due to the lack of steric differentiation between the groups flanking the C=O group.

Considering the importance of 2-hydroxy-3-phenoxypropylamine derivatives, some alternative routes to produce the corresponding ketone precursors were examined. (*R*)-(+)-1-(*N*-butoxycarbonyl-*N*-benzylamino)-2-oxo-3-phenoxypropane **20** was prepared from the reaction of 2-(chloromethyl)allyl phenyl ether with benzyl amine, tBoc protection and ozonolysis. Enantioselective reduction of ketone **20** was successfully achieved using both (1*R*,2*R*)-TsDPEN–formic acid and (1*S*,2*R*)-(+)-*cis*-1-aminoindan-2-ol–propan-2-ol systems. The (1*S*,2*R*)-*cis*-aminoindanol system afforded (*R*)-(+)-**21** in 99% yield with 61% ee, while the (1*R*,2*R*)-TsDPEN–formic acid system gave (*R*)-(+)-**21** in 99% yield with 60% ee. That the absolute configurations of *R*-(+)-**21** and *R*-(+)-**16** were both identical was confirmed by conversion of *R*-(+)-**21** to the *O*-*tert*-butyldimethylsilyl ether *R*-(+)-**19** by treatment with *tert*-butylchlorodimethylsilane and imidazole. Deprotection of the nitrogen atom in *R*-(+)-**21** gave the corresponding amino alcohol (not illustrated) for which attempts to cyclise using Mitsunobu conditions failed.

Our assignment of the configuration of compound *R*-(+)-**21** was based on analogy with the result from a short synthesis of *R*-(−)-propranolol, a known β-adrenergic blocking agent[24] (Scheme 6). Reaction of 1-naphthol with epichlorohydrin



Scheme 6 *Reagents and conditions:* i) 0.5 mol% $[Ru(cymene)Cl_2]_2$ 1 mol% **1**, iPrOH, 2.5 mol% KOH, rt. ii) 0.5 mol% $[Ru(cymene)Cl_2]_2$ 1 mol% **2**, HCO_2H, Et_3N, rt. iii) TFA, DCM.

afforded (±)-3-(1-naphthyloxy)-1,2-epoxypropane in 61% yield, which was followed by a ring opening reaction with isopropylamine to give the racemic amino alcohol, (±)-*N*-isopropyl-*N*-[2-hydroxy-3-(1-naphthyloxy)propyl]amine **24** in 93% yield. tBoc-protection of the amino group of this alcohol gave the (±)-*N*-tBoc-*N*-isopropyl-*N*-[2-hydroxy-3-(1-naphthyloxy)-propyl]amine **22** in 99% yield. Oxidation of compound **22** with pyridinium dichromate afforded the ketone, *N*-(tBoc)-isopropyl-*N*-[2-oxo-3-(1-naphthyloxy)propyl]amine, **23** in 68.5% yield. Enantioselective reduction of ketone **23** was successfully achieved using both (1*R*,2*R*)-TsDPEN–formic acid and (1*S*,2*R*)-(+)-*cis*-1-aminoindan-2-ol–propan-2-ol systems. The (1*S*,2*R*)-*cis*-aminoindanol system afforded *R*-(+)-**22** in 99% yield with $[\alpha]_D^{20}$ −1.9 ($c = 0.89$, ethanol), while the (1*R*,2*R*)-TsDPEN–formic acid system gave *R*-(−)-**22** in 98% yield with $[\alpha]_D^{20}$ −2.92 ($c = 0.96$, ethanol). Deprotection of the amine gave the amino acid, (*R*)-(+)-*N*-isopropyl-*N*-[2-hydroxy-3-(1-naphthyloxy)propyl]amine (propranolol) **24**, in 85% yield and 83.0% ee as measured by chiral HPLC, with $[\alpha]_D^{20}$ +5.19 ($c = 1.6$, ethanol) for (1*R*,2*R*)-TsDPEN–formic system, and 93% yield, 64% ee, with $[\alpha]_D^{20}$ +6.26 ($c = 0.74$ ethanol) for (1*S*,2*R*)-*cis*-aminoindanol system.

According to the literature,[24] *S*-(−)-propranolol has $[\alpha]_D^{20}$ −23.2 ($c = 1.08$, ethanol). Therefore, comparing the values of $[\alpha]_D^{20}$ of both compounds, we can conclude that our route for the enantioselective reduction of ketone **22** leads to *R*-(+)-propranolol **24**. By confirming the configuration of *R*-(+)-

propranolol, and considering the steric and electronic similarity of the groups OPh with Onaphthyl, and benzyl with isopropyl, we have assigned the configuration of compound **16** and consequently compound **21**, as also *R*-configured.

Conclusion

In conclusion, we have demonstrated that the use of monotosylated diamine–formic acid–triethylamine and *cis*-1-aminoindan-2-ol–propan-2-ol systems are highly effective at the enantioselective reduction of tBoc-protected α-aminoketones and this process provides an efficient method for the enantioselective syntheses of enantiomerically enriched β-amino alcohol and aziridines.

Experimental

All reactions, unless otherwise stated, were run under an atmosphere of nitrogen. Room temperature refers to ambient temperature (20–22 °C), 0 °C refers to an ice slush bath and −78 °C refers to a dry ice–acetone bath. Heated experiments were conducted using thermostatically controlled oil baths. Reactions were monitored by TLC using aluminium backed silica gel 60 (F254) plates, visualised using UV 254 nm and phosphomolybdic acid, ninhydrin or potassium permanganate dips as appropriate. Flash column chromatography was carried out routinely using 60 Å silica gel (Merck). Reagents were used as received from commercial sources unless otherwise stated. Acetophenone was purified by short path distillation before use. Formic acid–triethylamine (5 : 2 molar) is a commercially available azeotrope (Fluka). NMR spectra were recorded on a Bruker DPX (300 MHz) spectrometer. The spectra solutions were in deuterated chloroform ($CDCl_3$) unless otherwise stated. Chemical shifts are reported in δ units, parts per million downfield from TMS. Coupling constants (J) are measured in hertz. IR spectra were recorded on a Perkin–Elmer 1310 FTIR instrument using sodium chloride plates. Mass spectra were recorded on a 7070E VG mass spectrometer. Melting points were recorded on a Stuart Scientific SMP 1 instrument and are uncorrected. Optical rotations were measured with an AA-1000 polarimeter and are given in 10^{-1} deg cm^2 g^{-1}. Determination of enantiomeric excesses by HPLC analysis was achieved using a Waters 501 HPLC pump, Water tuneable absorbance detector, Waters 746 data module and a Daicel Chiral OD 4.6 × 25 cm column.

α-(*N*-*tert*-Butoxycarbonyl-*N*-benzylamino)acetophenone 4

Benzylamine (1.02 g, 9.5 mmol) and triethylamine (5.06 g, 50.0 mmol) were stirred in dichloromethane (20 mL) for 30 minutes. 2-Bromoacetophenone (**3**) (1.99 g, 10.0 mmol) in dichloromethane (10 mL) was added dropwise and the reaction stirred for 3 hours. Di-*tert*-butyl dicarbonate (2.18 g, 10.0 mmol) in dichloromethane (10 mL) was added and the reaction mixture was stirred overnight. Ammonium chloride saturated solution (30 mL) was added. The phases were separated and the aqueous layer extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and the solvent removed *in vacuo*, to give **4** as a yellow oil. Purification by flash chromatography on silica eluting with 5–10% ethyl acetate–petroleum ether 40 : 60, gave a light yellow solid (2.45 g, 79.3%), mp 66–67 °C; $\nu_{max}(CDCl_3)$/cm^{-1} 2960, 1703 (C=O), 1450, 1365, 1245, 1224, 1164; δ_H(300 MHz, $CDCl_3$) (1 : 1 mixture of NCO rotamers) 1.41 (4.5 H, s, CH_3), 1.50 (4.5 H, s, CH_3), 4.47 (1 H, s, CHH-Ph), 4.55 (1 H, s, CHH-Ph), 4.61 (1 H, s, C(=O)-CHH), 4.63 (1 H, s, C(=O)-CHH), 7.22–7.90 (10 H, m, Aryl H); δ_C (75.5 MHz, $CDCl_3$) 28.64 ((*C*H$_3$)$_3$C), 51.45 (C(=O)*C*H$_2$), 52.56 (N(Boc)*C*H$_2$), 80.72 ((CH$_3$)$_3$*C*), 127.82, 127.94, 128.09, 128.31, 128.53, 129.01, 129.16, 133.89 (Ar-*ipso*), 196.56 (C=O); *m*/*z* (CI) 326 ([M + H]$^+$, 42%), 270 (46), 227 (67), 226 (100), 169 (22), 120 (56), 106 (40), 91 (34) (Found: [M + H]$^+$, 326.1753. $C_{20}H_{23}NO_3$ requires *m*/*z*, 326.1756).

rac-2-(*N*-*tert*-Butoxycarbonyl-*N*-benzylamino)-1-phenylethanol 5

α-(*N*-*tert*-Butoxycarbonyl-*N*-benzylamino)acetophenone **4** (1.60 g, 5.00 mmol) was dissolved in 20 ml of MeOH–H_2O (9 : 1), in an ice bath. Sodium borohydride (0.25 g, 7.00 mmol) dissolved in 10 mL of MeOH–H_2O (9 : 1) was added slowly to the ketone solution. The reaction mixture was allowed to warm up to room temperature. When the reaction was completed (TLC), it was concentrated under reduced pressure. The residue was dissolved in diethyl ether (30 mL) and worked up with ammonium chloride saturated solution (30 mL). The phases were separated and the aqueous layer extracted with diethyl ether (2 × 20 mL). The organic layers were dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude compound was purified using medium pressure flash chromatography eluting with 15% ethyl acetate–petroleum 40 : 60 to give 2-(*N*-*tert*-butoxycarbonyl-*N*-benzylamino)-1-phenylethanol **5** as a white solid (1.60 g, 98%), mp 66–68 °C (Found: C, 73.24; H, 7.66; N, 4.20. $C_{20}H_{25}NO_3$ requires C, 73.37; H, 7.70; N, 4.28%); $\nu_{max}(CDCl_3)$/cm^{-1} 3509 (OH), 2927, 2365, 2357, 1669 (C=O), 1454, 1415, 1246, 1164, 731, 699; δ_H(300 MHz, $CDCl_3$) 1.48 (9 H, s, CH_3), 3.32 (1 H, br d, *J* 12.4, CH(OH)CHH), 3.51–3.59 (1 H, m, CH(OH)CHH), 4.07–4.46 (1 H, m, CHH-Ar), 4.44 (2 H, br d, *J* 14.3, CHH-Ar, OH), 4.88 (1 H, m, C(OH)H), 7.18–7.36 (10 H, m, Aryl H); δ_C (75.5 MHz, $CDCl_3$) 28.80 ((*C*H$_3$)$_3$C), 52.89 (*C*H$_2$), 56.04 (*C*H$_2$), 74.53 (*C*H(OH)), 81.42 ((CH$_3$)$_3$*C*), 126.21, 127.36, 127.76, 128.80, 129.01, 129.16, 130.17, 138.34, 142.78 (Ar-*ipso*), 164.19 (C=O); *m*/*z* (FAB) 326 ([M + H]$^+$, 14%), 254 (84%), 226 (10%), 164 (22%), 154 (55%), 91 (100).

2-(*N*-Benzylamino)-1-phenylethanol 7

Benzylamine (1.29 g, 12.1 mmol) and triethylamine (7.6 g, 75.0 mmol) were stirred in dichloromethane (50 mL) for 30 minutes. 2-Bromoacetophenone (3.0 g, 15.1 mmol) in dichloromethane (10 mL) was added dropwise and the reaction stirred for 6 hours. Ammonium chloride saturated solution (30 mL) was added. The phases were separated and the aqueous layer extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and the solvent removed *in vacuo*, to give α-(*N*-benzylamino)acetophenone as a yellow oil, which was then dissolved in 20 ml of MeOH–H_2O (9 : 1), in an ice bath. Sodium borohydride (0.86 g, 22.6 mmol) dissolved in 10 ml of MeOH–H_2O (9 : 1) was added slowly to the ketone solution. The reaction mixture was allowed to warm up to room temperature. When the reaction was completed (TLC), it was concentrated under reduced pressure. The residue was dissolved in diethyl ether (30 mL) and worked up with ammonium chloride saturated solution (30 mL). The phases were separated and the aqueous layer extracted with diethyl ether (2 × 20 mL). The organic layers were dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. Recrystallisation of crude compound ethyl acetate–petroleum 40 : 60 gave 2-(*N*-benzylamino)-1-phenylethanol as a white solid (0.98 g, 35.8%), mp 93–96 °C; $\nu_{max}(CDCl_3)$/cm^{-1} 3400, 3000, 2950, 2850, 2254, 1444, 903, 728; δ_H(300 MHz, $CDCl_3$) 2.40 (2 H, br s, OH, NH), 2.75 (1 H, dd, *J* 8.8, 12.0, C(OH)CHH), 2.93 (1 H, dd, *J* 3.6, 12.0, C(OH)CHH), 3.83 (2 H, AB_{system}, J^{AB} 13.2), 4.73 (1 H, dd, *J* 3.6, 8.8, C(OH)H), 7.25–7.35 (10 H, m, Aryl H); δ_C(75.5 MHz, $CDCl_3$) 53.93 (*C*H$_2$), 56.94 (*C*H$_2$), 72.20 (*C*H), 126.22, 127.56, 127.91, 128.51, 128.78, 128.91 (Ar-*ipso*); *m*/*z* (CI) 228 ([M + H]$^+$, 100%), 226 (45), 212 (20), 210 (66), 150 (10), 120 (65), 108 (36), 91 (55) (Found: [M + H]$^+$, 228.1380. $C_{15}H_{17}NO$ requires *m*/*z*, 228.1388).

rac-*N*-Benzyl-2-phenylaziridine 3

To a solution of (±)-2-benzylamino-1-phenylethanol **7** (0.9 g, 3.98 mmol) and triphenylphosphine (1.36 g, 5.20 mmol) in THF (30 mL), stirred under nitrogen in an ice bath, was slowly added diethyl azodicarboxylate (0.9 g, 5.20 mmol) *via* syringe. The ice bath was removed and the mixture stirred at room temperature for 6 hours. It was then worked up with sodium bicarbonate saturated solution (20 mL). The phases were separated and the aqueous layer extracted with ethyl acetate (2 × 20 mL). The organic layers were dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude compound was purified using medium pressure flash chromatography eluting with 5% ethyl acetate–petroleum 40 : 60 to give the aziridine **3** as a pale oil (0.22 g, 26.5%); ν_{max}(neat)/cm^{-1} 3028, 2970, 2824, 1597, 1488, 1444, 1349, 1137, 1086, 1027, 823, 735; δ_H(300 MHz, $CDCl_3$) 1.84 (1 H, d, *J* 6.6, CHH_{az}), 1.98 (1 H, d, *J* 3.2, C*H*H$_{az}$), 2.49 (1 H, dd, *J* 3.4, 6.6, CH_{az}), 3.59 (1 H, d, *J* 13.8, CH*H*Ph), 3.68 (1 H, d, *J* 13.8, CH*H*Ph), 7.21–7.38 (10 H, m, Aryl H); δ_C(75.5 MHz, $CDCl_3$) 38.38 (Ph-*C*H$_2$), 41.93 (*C*H$_{2az}$), 65.17 (*C*H$_{az}$), 126.66, 127.29, 127.38, 128.26, 128.71, 128.77, 139.53, 140.54 (Ar-*ipso*); *m*/*z* (EI) 210 ([M + H]$^+$, 100%), 208 (23), 120 (10), 118 (20), 91 (26) (Found: [M + H]$^+$, 210.1309. $C_{15}H_{15}N$ requires *m*/*z*, 210.1304).

(*S*)-(+)-2-[*N*-(*tert*-Butoxycarbonyl)-*N*-(benzyl)amino]-1-phenylethanol 5

A mixture of (*p*-cymene)ruthenium(II) chloride dimer (0.13 mg, 0.0021 mmol) and (1*R*,2*R*)-TsDPEN **2** (0.15 mg, 0.0042 mmol) in a 5 : 2 formic acid–triethylamine mixture (2.5 mL) was stirred at 28 °C for 15 min. 2-[*N*-(*tert*-Butoxycarbonyl)-*N*-benzylamino]-1-phenylethanone **4** (0.27 g, 0.83 mmol) was added and the solution was stirred at 28 °C for 24 hours. Then the mixture was filtered through silica and washed with ethyl acetate (50 mL). The solvent was evaporated under reduced pressure to give the crude compound, which was purified by flash chromatography (5% v/v ethyl acetate–petroleum ether 40 : 60) to give the product *S*-(+)-**5** as a white solid (0.20 g, 74.0%). The product was determined to be of 98% ee by HPLC analysis (Chiral OD, hexane–ethanol–diethylamine = 95 : 5 : 0.1 (0.5 mL min^{-1}), *R* isomer 13.93 min, *S* isomer 15.27 min), mp 64–65 °C; $[\alpha]_D^{20}$ +3.3 (*c* = 2 ethanol); ν_{max}($CDCl_3$)/cm^{-1} 3435 (OH), 3029, 2975, 2931, 1667 (C=O), 1494, 1454, 1414, 1366, 1314, 1246, 1165, 1123, 1086, 1060, 1028, 878, 746; δ_H(300 MHz, $CDCl_3$) 1.48 (9 H, s, CH_3), 3.32 (1 H, d, *J* 12.8, CH(OH)CH*H*), 3.52–3.50 (1 H, m, CH(OH)C*H*H), 4.18 (1 H, d, *J* 15.6, CH*H*Ph), 4.43–4.46 (2 H, m, C*H*H-Ar, O*H*), 4.85–4.96 (1 H, m, C(OH)*H*), 7.18–7.35 (10 H, m, Aryl H); δ_C (75.5 MHz, $CDCl_3$) 28.81 ((*C*H$_3$)$_3$C), 52.89 (*C*H$_2$), 56.05 (*C*H$_2$), 74.55 (*C*H(OH)), 81.44 ((CH$_3$)$_3$*C*), 126.21, 127.76, 127.94, 128.81, 129.01, 129.16, 138.32, 142.78 (Ar-*ipso*); *m*/*z* (FAB) 326 ([M + H]$^+$, 43%), 254 (100), 220 (24), 164 (22), 120 (49) (Found: [M + H]$^+$, 328.1915. $C_{20}H_{25}NO_3$ requires *m*/*z*, 328.1913). The reduction using (1*S*,2*R*)-**1**–propan-2-ol was carried out using identical conditions to those reported.[4b] The product, *S*-(+)-**5** was formed in 60% yield and 88% ee as determined by chiral HPLC analysis.

(*S*)-(+)-2-(*N*-Benzylamino)-1-phenylethanol 7

To a solution of 2-(*N*-*tert*-butoxycarbonyl-*N*-benzylamino)-1-phenylethanol *S*-(−)-**5** (0.2 g, 0.61 mmol) in dichloromethane (2 mL), TFA (2 mL) was added slowly. After 2 hours the solvent was removed and the resulting product was dissolved in ethyl acetate and NaOH solution 0.2 M was added until the pH = 7. The product was then extracted with ethyl acetate and the combined organic layers were dried over magnesium sulfate, filtered and the solvent removed *in vacuo*. Recrystallisation (ethyl acetate–petroleum ether 40 : 60) gave (*S*)-2-(*N*-benzylamino)-1-phenylethanol **7** as a white solid (0.11 g, 78.6% yield). The product was determined to be of 99% ee by HPLC analysis (Chiral OD, hexane–ethanol–diethylamine = 97 : 3 : 0.1 (0.5 mL min^{-1}), *S* isomer 31.97 min, *R* isomer 33.19 min), mp 105–107 °C; $[\alpha]_D^{20}$ +33.8 (*c* = 2, ethanol); ν_{max}($CDCl_3$)/cm^{-1} 3414, 2248, 1637, 1452, 1201, 908, 728; δ_H(300 MHz, $CDCl_3$) 2.35 (2 H, br s, OH, NH), 2.77 (1 H, dd, *J* 9.0, 12.2, C(OH)CHH), 2.95 (1 H, dd, *J* 3.6, 12.2, C(OH)CHH), 3.86 (2 H, AB_{system}, J^{AB} 13), 4.75 (1 H, dd, *J* 3.6, 9.0, C(OH)H), 7.20–7.38 (10 H, m, Aryl H); δ_C(75.5 MHz, $CDCl_3$) 53.77 (CH$_2$), 56.69 (CH$_2$), 71.20 (CH), 126.19, 127.75, 127.99, 128.62, 128.81, 128.97 (Ar-*ipso*); *m*/*z* (CI) 228 ([M + H]$^+$, 100%), 226 (7), 210 (10), 120 (36), 108 (11), 91 (11) (Found: [M + H]$^+$, 228.1384. $C_{15}H_{17}NO$ requires *m*/*z*, 228.1388).

(*R*)-(−)-*N*-Benzyl-2-phenylaziridine 3

To a solution of (*S*)-2-benzylamino-1-phenylethanol **5** (0.33 g, 1.45 mmol) and triphenylphosphine (0.58 g, 2.20 mmol) in THF (15 mL), stirred under nitrogen in an ice bath, was slowly added diethyl azodicarboxylate (0.38 g, 2.20 mmol) *via* syringe. The ice bath was removed and the mixture was stirred at room temperature for 6 hours. It was then worked up with sodium bicarbonate saturated solution (10 mL). The phases were separated and the aqueous layer extracted with ethyl acetate (2 × 10 mL). The organic layers were dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude compound was purified using medium pressure flash chromatography eluting with 5% ethyl acetate–petroleum ether 40 : 60 to give the aziridine *R*-(−)-**3** as a pale oil (0.07 g, 23%). The product was determined to be of 98% ee by chiral shift reagent ([Eu(hfc)$_3$], 6 mol%); $[\alpha]_D^{20}$ −49 (*c* = 2, ethanol); ν_{max}(neat)/cm^{-1} 3350, 3058, 3021, 2977, 1734, 1604, 1495, 1453, 1259, 1172, 1028, 940, 733, 697; δ_H(300 MHz, $CDCl_3$) 1.84 (1 H, d, *J* 6.6, CHH_{az}), 1.98 (1 H, d, *J* 3.2, C*H*H$_{az}$), 2.50 (1 H, dd, *J* 3.2, 6.6, CH_{az}), 3.69 (1 H, d, *J* 13.8, C*H*HPh), 3.58 (1 H, d, *J* 13.8, CH*H*Ph), 7.21–7.42 (10 H, m, Aryl H); δ_C(75.5 MHz, $CDCl_3$) 38.36 (Ph-*C*H$_2$), 41.92 (*C*H$_{2az}$), 65.15 (*C*H$_{az}$), 126.65, 127.28, 127.38, 128.25, 128.70, 139.51, 140.54 (Ar-*ipso*); *m*/*z* (CI) 210 ([M + H]$^+$, 100%), 209 (45), 120 (7), 108 (17), 91 (24) (Found: [M + H]$^+$, 210.1279. $C_{15}H_{15}N$ requires *m*/*z*, 210.1283).

(±)-2-(*N*-*tert*-Butoxycarbonylamino)-1-phenylethanol 9

To a solution of (±)-2-amino-1-phenylethanol (1.37 g, 10.0 mmol) in dichloromethane (30 mL), triethylamine (1.52 g, 15.0 mmol) followed by di-*tert*-butyl dicarbonate (2.18 g, 10.0 mmol) were added. The reaction mixture was stirred overnight then saturated ammonium chloride solution (30 mL) added. The phases were separated and the aqueous layer extracted with dichloromethane (2 × 30 mL). The combined organic layers were dried over magnesium sulfate, filtered, and the solvent removed *in vacuo* to give *rac*-**9** as a white solid (2.25 g, 95%), mp 120–121 °C; ν_{max}(Nujol)/cm^{-1} 3362, 1675, 1531, 1276, 1166, 962, 957, 903, 750; δ_H(300 MHz, $CDCl_3$) 1.44 (9 H, s, CH_3), 3.18–3.27 (1 H, m, CH*H*), 3.39 (1 H, br s, O*H*), 3.42–3.49 (1 H, m, C*H*H), 4.78–4.81 (1 H, m, C*H*), 5.03 (1 H, br s, N*H*), 7.26–7.35 (5 H, m, Aryl H); δ_C(75.5 MHz, $CDCl_3$) 28.75 ((*C*H$_3$)$_3$C), 48.73 (*C*H$_2$), 74.3 (*C*H), 80.23 ((CH$_3$)$_3$*C*), 126.28, 128.16, 128.87, 142.22 (Ar-*ipso*), 157.36 (C=O); *m*/*z* (FAB) 238 ([M + H]$^+$, 40%), 182 (63), 164 (100), 154 (29), 137 (26), 120 (29) (Found: [M + H]$^+$, 238.1449. $C_{13}H_{19}NO_3$ requires *m*/*z*, 238.1443).

(±)-*N*-(*tert*-Butoxycarbonyl)-2-phenylaziridine 11

To a solution of (±)-2-(*N*-*tert*-butoxycarbonylamino)-1-phenylethanol **9** (0.3 g, 1.10 mmol) and tosyl chloride (0.23 g, 1.20 mmol) in dry THF (20 mL) was added KOH (0.30 g, 5.40 mmol) freshly powered (with the help of a ball mill) at room temperature. The reaction mixture was left stirring overnight. It was then dissolved in diethyl ether (30 mL) and filtered. The

solvent was removed under reduced pressure to give pure aziridine *R*-(−)-**11** as a pale oil (0.22 g, 92.0%). ν_{max}(neat)/cm^{-1} 2366, 2336, 2319, 1717, 1655, 1469, 1391, 1317, 1303, 1280, 1253, 1229, 1153, 852, 794; δ_H(300 MHz, $CDCl_3$) 1.50 (9 H, s, $(CH_3)_3C$), 2.31 (1 H, d, *J* 3.58, CH_{az}), 2.67 (1 H, d, *J* 6.40, CH_{az}), 3.48 (1 H, dd, *J* 3.58, 6.41, CH_{az}), 7.31–7.40 (5 H, m, Aryl H); δ_C(75.5 MHz, $CDCl_3$) 28.29 ($(CH_3)_3C$), 35.24 (CH_2), 39.70 (*C*H), 81.76 ($(CH_3)_3C$), 126.74, 128.15, 128.84, 137.67 (Ar-*ipso*), 162.52 (C=O); *m*/*z* (CI) 220 ([M + H]$^+$, 47%), 181 (100), 164 (90), 146 (10), 120 (70) (Found: [M + H]$^+$, 220.1334. $C_{13}H_{17}NO_2$ requires *m*/*z*, 220.1338).

2-[*N*-(*tert*-Butoxycarbonyl)amino]acetophenone 8

(±)-2-(*N*-*tert*-Butoxycarbonylamino)-1-phenylethanol **9** (2.55 g, 10.75 mmol) was added to an ice cold solution of pyridinium dichromate (15.0 g, 39.83 mmol) in anhydrous *N*,*N*-dimethylformamide (50 mL). The reaction mixture was stirred overnight, then worked up with brine (60 mL). The compound was extracted with diethyl ether (3 × 60 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give the crude compound which was purified by flash chromatography eluting with 10% ethyl acetate–petroleum ether 40 : 60 to give 2-[*N*-(*tert*-butoxycarbonyl)amino]acetophenone **8** as a white solid (2.23 g, 88.1%), mp 55–58 °C; ν_{max}($CDCl_3$)/cm^{-1} 3425, 2970, 2342, 2247, 1685, 1582, 1488, 1444, 1363, 1217, 1159, 1049, 984, 903, 867; δ_H(300 MHz, $CDCl_3$) 1.48 (9 H, s, CH_3), 4.66 (2 H, d, *J* 4.52, CH_2), 5.60 (1 H, br s, N*H*), 7.46–7.97 (5 H, m, Aryl H); δ_C(75.5 MHz, $CDCl_3$) 28.74 ($(CH_3)_3C$), 47.89 (CH_2), 80.19 ($(CH_3)_3C$), 128.20, 129.24, 134.30, 134.92 (Ar-*ipso*), 156.15 (C=O), 193.5 (C=O); *m*/*z* (FAB) 236 ([M + H]$^+$, 23%), 180 (87), 154 (27), 136 (100), 105 (30), 97 (47) (Found: [M + H]$^+$, 236.1284. $C_{13}H_{17}NO_3$ requires *m*/*z*, 236.1287).

(*S*)-2-(*N*-*tert*-Butoxycarbonylamino)-1-phenylethanol *S*-(+)-9

A mixture of (*p*-cymene)ruthenium(II) chloride dimer (0.34 mg, 0.006 mmol) and (1*R*,2*R*)-TsDPEN **2** (0.40 mg, 0.011 mmol) in a 5 : 2 formic acid–triethylamine mixture (3.0 mL) was stirred at 28 °C for 15 min. 2-[*N*-(*tert*-Butoxycarbonyl)amino]acetophenone **8** (0.50 g, 2.13 mmol) was added and the solution was stirred at 28 °C for 24 hours. Then the mixture was filtered through silica and washed with ethyl acetate (60 mL). The solvent was evaporated under reduced pressure to give the crude compound, which was purified by flash chromatography (5% v/v ethyl acetate–petroleum ether 40 : 60) to give the *S*-(+)-**9** as a white solid (0.44 g, 86.3%). The product was determined to be of 99% ee by HPLC analysis (Chiral OD, hexane–ethanol–diethylamine = 95 : 5 : 0.1 (0.5 mL min^{-1}), *S* isomer 17.86 min, *R* isomer 19.49 min), mp 66–68 °C $[\alpha]_D^{20}$ +3.5 (*c* = 1, ethanol); ν_{max}($CDCl_3$)/cm^{-1} 3423, 2978, 2931, 1693, 1514, 1454, 1392, 1367, 1251, 1170, 1094, 1065, 910, 733, 700; δ_H(300 MHz, $CDCl_3$) 1.43 (9 H, s, CH_3), 3.16–3.25 (1 H, m, CH*H*), 3.41–3.47 (1 H, m, C*H*H), 3.56 (1 H, br s, O*H*), 4.76–4.79 (1 H, m, C*H*(OH)), 5.08 (1 H, br s, N*H*), 7.24–7.34 (5 H, m, Aryl H); δ_C(75.5 MHz, $CDCl_3$) 28.75 ($(CH_3)_3C$), 48.70 (CH_2), 74.19 (*C*H), 80.19 ($(CH_3)_3C$), 126.29, 128.14, 128.85, 142.24 (Ar-*ipso*), 157.34 (C=O); *m*/*z* (FAB) 238 ([M + H]$^+$, 52%), 182 (72), 164 (100), 154 (40), 137 (35), 120 (30) (Found: [M + H]$^+$, 238.1448. $C_{13}H_{19}NO_3$ requires *m*/*z*, 238.1443). The reduction using (1*S*,2*R*)-**1**–propan-2-ol was carried out using identical conditions to those reported; however no reduction product was isolated.[4b]

(*R*)-(−)-*N*-(*tert*-Butoxycarbonyl)-2-phenylaziridine 11

To a solution of (*S*)-2-(*N*-*tert*-butoxycarbonylamino)-1-phenylethanol *S*-(+)-**9** (0.3 g, 1.10 mmol) and tosyl chloride (0.23 g, 1.20 mmol) in dry THF (20 mL) was added KOH (0.30 g, 5.40 mmol) freshly powered (with the help of a ball mill) at room temperature. The reaction mixture was left stirring overnight. Then it was dissolved in diethyl ether (30 mL) and filtered. The solvent was removed under reduced pressure to give a pale oil as a pure aziridine *R*-(−)-**11** (0.22 g, 92.0%). The product was determined to be 99% ee by chiral shift reagent ([Eu(hfc)$_3$], 6 mol%), $[\alpha]_D^{20}$ −137 (*c* = 2, ethanol); ν_{max}(neat)/cm^{-1} 3408, 3058, 2977, 2933, 1719, 1663, 1597, 1473, 1318, 1155, 1020, 962, 852, 765; δ_H(300 MHz, $CDCl_3$) 1.44 (9 H, s, $(CH_3)_3C$), 2.26 (1 H, d, *J* 3.5, CH_{az}), 2.62 (1 H, d, *J* 6.2, CH_{az}), 3.42 (1 H, dd, *J* 3.5, 6.2, CH_{az}), 7.24–7.33 (5 H, m, Aryl H); δ_C(75.5 MHz, $CDCl_3$) 28.29 ($(CH_3)_3C$), 35.24 (CH_2), 39.70 (*C*H), 81.82 ($(CH_3)_3C$), 126.73, 128.15, 128.84, 137.66 (Ar-*ipso*), 162.54 (C=O); *m*/*z* (CI) 220 ([M + H]$^+$, 97%), 181 (77), 164 (100), 146 (10), 120 (18) (Found: [M + H]$^+$, 220.1332. $C_{13}H_{17}NO_2$ requires *m*/*z*, 220.1338).

(*S*)-(−)-*O*-(*tert*-Butyldimethylsilyl)-2-(*N*-*tert*-butoxycarbonylamino)-1-phenylethanol

(*S*)-2-(*N*-*tert*-Butoxycarbonylamino)-1-phenylethanol *S*-(+)-**9** (0.3 g, 1.26 mmol) and imidazole (0.21 g, 3.15 mmol) were dissolved in 10 mL of DMF and treated with *tert*-butylchlorodimethylsilane (TBDMSCl) (0.23 g, 1.52 mmol). The mixture was stirred at 35–45 °C until the starting materials were completely consumed (followed by TLC). The reaction was then treated with sodium bicarbonate saturated solution (20 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give the crude compound which was purified by flash chromatography eluting with 5% ethyl acetate–petroleum ether 40 : 60 to give the product as a pale liquid (0.37 g, 84.1%). This was determined to be of 92% ee by HPLC analysis (Chiral OD hexane–ethanol–diethylamine = 97 : 3 : 0.1 (0.5 mL min^{-1}), *S* isomer 7.59 min, *R* isomer 9.96 min), $[\alpha]_D^{20}$ +55.7 (*c* = 2, ethanol); ν_{max}(neat)/cm^{-1} 3460, 3373, 2956, 2885, 1716, 1504, 1435, 1390, 1252, 1171, 1098, 976, 870, 700; δ_H(300 MHz, $CDCl_3$) 0.00 (3 H, s, $SiCH_3(CH_3)$), 0.14 (3 H, s, $SiCH_3(CH_3)$), 1.01 (9H, s, Si-C(CH_3)$_3$), 1.54 (9 H, s, CH_3), 3.11–3.20 (1 H, m, CH*H*), 3.42–3.56 (1 H, m, C*H*H), 4.86–4.90 (1H, m, C*H*), 7.35–7.43 (5 H, m, Aryl H); δ_C(75.5 MHz, $CDCl_3$) −4.65 ($SiCH_3(CH_3)$), −4.34 ($SiCH_3(CH_3)$), 18.61 (Si-*C*(CH_3)$_3$), 26.22 (Si-C(CH_3)$_3$), 28.81 ($(CH_3)_3C$), 49.50 (CH_2), 74.20 (*C*H), 79.60 ($(CH_3)_3C$), 126.37, 127.82, 128.60, 142.80 (Ar-*ipso*), 156.25 (C=O); *m*/*z* (CI) 352 ([M + H]$^+$, 96%), 296 (100), 278 (16), 252 (77), 221 (82), 181 (72).

(*S*)-*O*-(*tert*-Butyldimethylsilyl)-2-[*N*-(*tert*-butoxycarbonyl)-*N*-benzylamino]-1-phenylethanol *S*-(+)-6

To a suspension of sodium hydride (0.05 g, 1.14 mmol) in dry THF (10 mL), (*S*)-*O*-(*tert*-butyldimethylsilyl)-2-[*N*-)*tert*-butoxycarbonyl)amino]-1-phenylethanol (0.2 g, 0.57 mmol) was added at room temperature and it was stirred for 1 hour. Then a solution of benzyl bromide (0.15 g, 0.85 mmol) in dry THF (5 mL) was added slowly. The reaction was left stirring until the starting materials had been completely consumed (followed by TLC). The reaction was then treated with sodium bicarbonate saturated solution (20 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give the crude compound which was purified by flash chromatography eluting with 5% ethyl acetate–petroleum ether 40 : 60 to give the protected compound as a pale liquid (0.25 g, 100%). The product was determined to be of 92% ee by HPLC analysis (Chiral OD, hexane–ethanol–diethylamine = 97 : 3: 0.1 (0.5 mL min^{-1}), *S* isomer 8.63 min, *R* isomer 9.45 min), $[\alpha]_D^{20}$ +52.3 (*c* = 2, ethanol); ν_{max}(neat)/cm^{-1} 3058, 3028, 2955, 2919, 2846, 1700, 1693, 1458, 1440, 1363, 1247, 1167, 1020, 947, 838, 779; δ_H(300 MHz, $CDCl_3$) (1 : 1 mixture of NCO rotamers) 0.00 (1.5 H, s, $SiCH_3(CH_3)$), 0.004

(1.5 H, s, SiCH_3(CH$_3$)), 0.17 (1.5 H, s, SiCH_3(CH$_3$)), 0.19 (1.5 H, s, SiCH_3(CH$_3$)), 1.02 (4.5 H, s, Si-C(CH_3)$_3$), 1.06 (4.5 H, s, Si-C(CH_3)$_3$), 1.56 (4.5 H, s, C(CH_3)$_3$), 1.65 (4.5 H, s, C(CH_3)$_3$), 3.13 (0.5 H, dd, *J* 9.1, 14.2, CH), 3.23 (0.5 H, dd, *J* 7.9, 14.3, CH), 3.40 (0.5 H, dd, *J* 4.7, 14.5, CH), 3.60 (0.5 H, dd, *J* 3.4, 13.8, CH), 4.46 (0.5 H, d, *J* 5.8, H), 4.48 (0.5 H, d, *J* 6.8, CH), 4.58 (0.5 H, d, *J* 6.8, CH), 4.72 (0.5 H, d, *J* 5.8, CH), 5.08 (0.5 H, dd, *J* 5.0, 8.0, CH), 5.24 (0.5 H, dd, *J* 3.6, 9.0, CH), 7.25–7.49 (10 H, m, Aryl H); δ_C(75.5 MHz, CDCl$_3$) 26.31 (Si*C*H$_3$(CH$_3$)), 28.85 (Si-C(*C*H$_3$)$_3$), 28.96 ((*C*H$_3$)$_3$C), 51.81, 53.25 (*C*H$_2$), 55.54, 56.45 (*C*H$_2$), 68.37 (Si-*C*(CH$_3$)$_3$), 73.84, 74.52 (*C*H), 80.12 ((CH$_3$)$_3$*C*), 126.35, 127.03, 127.35, 127.44, 127.63, 127.99, 128.47, 128.61, 128.78, 128.82, 138.78, 139.12, 143.36 (Ar-*ipso*), 156.10 (C=O); *m*/*z* (FAB) 442 ([M + H]$^+$, 29%), 342 (44), 328 (45), 254 (88), 221 (74), 164 (29), 120 (59), 91 (100).

A sample of *S*-(+)-**6** with identical data to that cited above was also prepared by the reaction of *S*-(+)-**5** with TBDMSCl and imidazole in DMF following the same procedure as that previously described for *S*-(+)-**9**. The product was formed in 49% yield and exhibited $[\alpha]_D^{20}$ +36.0 (*c* = 2, ethanol).

(±)-1-(*N*-*tert*-Butoxycarbonylamino)propan-2-ol 12

To a solution of (±)-1-aminopropan-2-ol (2.0 g, 26.62 mmol) in dichloromethane (50 mL), triethylamine (3.95 g, 15.0 mmol) followed by di-*tert*-butyl dicarbonate (2.18 g, 39.0 mmol) were added. The reaction mixture was stirred overnight, then saturated ammonium chloride solution (30 mL) was added. The phases were separated and the aqueous layer extracted with dichloromethane (2 × 30 mL). The combined organic layers were dried over magnesium sulfate, filtered, and the solvent removed *in vacuo*. Purification by flash chromatography on silica with 20% ethyl acetate–petroleum ether 40 : 60, gave the compound *rac*-**12** as colourless liquid of high viscosity (4.44 g, 95.3%); ν_{max}(neat)/cm^{-1} 2977, 2357, 1685, 1517, 1363, 1276, 1159, 1108, 976, 750; δ_H(300 MHz, CDCl$_3$) 1.17 (3 H, d, *J* 6.41, CH_3), 1.45 (9 H, s, C(CH_3)$_3$), 2.95–3.04 (2 H, m, CH*H*, O*H*), 3.23–3.29 (1 H, m, C*H*), 3.88–3.90 (1H, m, C*H*H), 5.12 (1 H, br s, N*H*); δ_C(75.5 MHz, CDCl$_3$) 20.32 (*C*H$_3$), 28.47 ((*C*H$_3$)$_3$C), 47.91 (*C*H$_2$), 67.06 (*C*H), 79.83 ((CH$_3$)$_3$*C*), 164.25 (C=O); *m*/*z* (FAB) 176 ([M + H]$^+$, 74%), 154 (6), 137 (9), 120 (100), 103 (13) (Found: [M + H]$^+$, 176.1286. $C_8H_{17}NO_3$ requires *m*/*z*, 176.1287).

(±)-*N*-(*tert*-Butoxycarbonyl)-2-methylaziridine 13

To a solution of (±)-1-(*N*-*tert*-butoxycarbonylamino)propan-2-ol **12** (2.0 g, 11.41 mmol) and tosyl chloride (3.05 g, 15.98 mmol) in dry THF (40 mL) was added KOH (3.10 g, 56.11 mmol) freshly powered (with the help of a ball mill) at room temperature. The reaction mixture was left stirring overnight. Then it was dissolved in diethyl ether (50 mL) and filtered. The solvent was removed under reduced pressure and the crude compound was purified using flash chromatography eluting with 20% ethyl acetate–petroleum ether 40 : 60 to give the aziridine *rac*-**13** as a colourless liquid (1.27 g, 56.7%); ν_{max}(neat)/cm^{-1} 3006, 2989, 2357, 1714, 1451, 1275, 1260, 1159, 749; δ_H(300 MHz, CDCl$_3$) 1.22 (3 H, d, *J* 5.6, CH_3), 1.41 (9 H, s, (CH_3)$_3$C), 1.82 (1 H, d, *J* 3.8, CHH_{az}), 2.19 (1 H, d, *J* 5.8, C*H*H$_{az}$), 2.14–2.43 (1 H, m, CH_{az}); δ_C(75.5 MHz, CDCl$_3$) 17.28 (*C*H$_3$), 28.12 ((*C*H$_3$)$_3$C), 32.41 (*C*H$_2$), 33.69 (*C*H), 80.92 ((CH$_3$)$_3$*C*), 162.58 (C=O); *m*/*z* (FAB) 158 ([M + H]$^+$, 16%), 156 (10), 128 (6), 119 (15), 108 (37), 58 (100) (Found: [M + H]$^+$, 158.1181. $C_8H_{15}NO_2$ requires *m*/*z*, 158.1181).

(±)-1-(*N*-*tert*-Butoxycarbonylamino)propan-2-one 14

(±)-1-(*N*-*tert*-Butoxycarbonylamino)propan-2-ol (1.0 g, 5.71 mmol) was added to an ice cold solution of pyridinium dichromate (6.44 g, 17.13 mmol) in anhydrous *N*,*N*-dimethylformamide (20 mL). The reaction mixture was stirred overnight, then worked up with brine (30 mL). The compound was extracted with diethyl ether (3 × 30 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give the crude compound which was purified by flash chromatography eluting with 40% ethyl acetate–petroleum ether 40 : 60 to give (±)-1-(*N*-*tert*-butoxycarbonylamino)propan-2-one **14** as a colourless liquid (0.88 g, 88.0%); ν_{max}(neat)/cm^{-1} 3357, 2977, 2926, 1699, 1510, 1356, 1283, 1247, 1159, 1071, 955, 882, 779; δ_H(300 MHz, CDCl$_3$) 1.45 (9 H, s, C(CH_3)$_3$), 2.18 (3 H, s, CH_3), 4.03 (2 H, d, *J* 4.71, CH_2), 5.24 (1 H, br s, N*H*); δ_C(75.5 MHz, CDCl$_3$) 27.49 (*C*H$_3$), 28.69 ((*C*H$_3$)$_3$C), 51.31 (*C*H$_2$), 80.23 ((CH$_3$)$_3$*C*), 164.05 (C=O); *m*/*z* (CI) 174 ([M + H]$^+$, 100%), 163 (12), 147 (25) (Found: [M + H]$^+$, 174.1127. $C_8H_{15}NO_3$ requires *m*/*z*, 174.1130).

S-(+)-1-(*N*-*tert*-Butoxycarbonylamino)propan-2-ol 12

A mixture of (*p*-cymene)ruthenium(II) chloride dimer (0.62 mg, 0.010 mmol) and (1*R*,2*R*)-TsDPEN **2** (0.74 mg, 0.02 mmol) in a 5 : 2 formic acid–triethylamine mixture (3.0 mL) was stirred at 28 °C for 15 min. (±)-1-(*N*-*tert*-Butoxycarbonylamino)-propan-2-one **14** (0.70 g, 4.04 mmol) was added and the solution was stirred at 28 °C for 24 hours. Then the mixture was filtered through silica and washed with ethyl acetate (60 mL). The solvent was evaporated under reduced pressure to give the crude compound, which was purified by flash chromatography (30% v/v ethyl acetate–petroleum ether 40 : 60) to give *S*-(+)-**12** as a colourless liquid (0.62 g, 87.3%). $[\alpha]_D^{20}$ +27.5 (*c* = 2, dichloromethane); ν_{max}(neat)/cm^{-1} 3355, 2974, 2934, 1691, 1528, 1458, 1393, 1368, 1276, 1252, 1173, 1039, 991, 942, 901, 865, 838; δ_H(300 MHz, CDCl$_3$) 1.18 (3 H, d, *J* 6.41, CH_3), 1.45 (9 H, s, C(CH_3)), 2.96–3.05 (2 H, m, CH*H*, O*H*), 3.23–3.30 (1 H, m, C*H*H), 3.85–3.95 (1H, m, C*H*H), 5.01 (1H, br s, N*H*); δ_C(75.5 MHz, CDCl$_3$) 21.03 (*C*H$_3$), 28.75 ((*C*H$_3$)$_3$C), 48.35 (*C*H$_2$), 68.09 (*C*H), 80.07 ((CH$_3$)$_3$*C*), 155.60 (C=O); *m*/*z* (FAB) 176 ([M + H]$^+$, 27%), 155 (100), 154 (100), 136 (80), 120 (50), 107 (31) (Found: [M + H]$^+$, 176.1279. $C_8H_{17}NO_3$ requires *m*/*z*, 176.1287).

R-(−)-*N*-(*tert*-Butoxycarbonyl)-2-methylaziridine 13

To a solution of (+)-1-(*N*-*tert*-butoxycarbonylamino)propan-2-ol *S*-(+)-**12** (1.0 g, 5.71 mmol) and tosyl chloride (1.63 g, 8.56 mmol) in dry THF (20 mL) was added KOH (1.60 g, 28.55 mmol) freshly powered (with the help of a ball mill) at room temperature. The reaction mixture was left stirring overnight. Then it was dissolved in diethyl ether (40 mL) and filtered. The solvent was removed under reduced pressure and the crude compound was purified using flash chromatography eluting with 20% ethyl acetate–petroleum ether 40 : 60 to give the *R*-(−)-**13** as a colourless liquid (0.50 g, 55.7%) $[\alpha]_D^{20}$ −42.2 (*c* = 1, dichloromethane); ν_{max}(neat)/cm^{-1} 3064, 2977, 2932, 1718, 1600, 1475, 1458, 1407, 1393, 1368, 1310, 1257, 1224, 1154, 1088, 1063, 1028, 940, 908, 867, 831, 769; δ_H(300 MHz, CDCl$_3$) 1.27 (3 H, d, *J* 5.5, CH_3), 1.46 (9 H, s, (CH_3)$_3$C), 1.89 (1 H, d, *J* 3.8, CHH_{az}), 2.24 (1 H, d, *J* 5.8, C*H*H$_{az}$), 2.24–2.49 (1 H, m, CH_{az}); δ_C(75.5 MHz, CDCl$_3$) 17.77 (*C*H$_3$), 28.31 ((*C*H$_3$)$_3$C), 32.86 (*C*H$_2$), 33.95 (*C*H), 81.29 ((CH$_3$)$_3$*C*), 162.58 (C=O); *m*/*z* (FAB) 158 ([M + H]$^+$, 16%), 156 (10), 128 (6), 119 (15), 108 (37), 58 (100) (Found: [M + H]$^+$, 158.1181. $C_8H_{15}NO_2$ requires *m*/*z*, 158.1181).

N-(*tert*-Butoxycarbonyl)allylamine

To a solution of allylamine (3.0 g, 52.54 mmol) in dichloromethane (80 mL), triethylamine (6.91 g, 68.30 mmol) followed by di-*tert*-butyl dicarbonate (11.57 g, 53.0 mmol) were added. The reaction mixture was stirred overnight, then saturated ammonium chloride solution (50 mL) added. The phases were separated and the aqueous layer extracted with dichloro-

methane (2 × 50 mL). The combined organic layers were dried over magnesium sulfate, filtered, and the solvent removed *in vacuo*. Purification by flash chromatography on silica with 10% ethyl acetate–petroleum ether 40 : 60, gave the product as white solid (8.1 g, 98.1%); $\nu_{max}(CDCl_3)/cm^{-1}$ 3352, 2976, 1693, 1519, 1366, 1250, 1173, 990, 917, 862, 780; δ_H(300 MHz, $CDCl_3$) 1.45 (9 H, s, C(CH_3)$_3$), 3.73–3.75 (2 H, m, CH_2=CH-CH_2), 4.71 (1 H, br s, NH), 5.10 (1 H, dq, *J* 10.2, 1.5, CHH^{cis}), 5.18 (1 H, dq, *J* 17.1, 1.5, CHH^{trans}), 5.84 (1 H, ddt, *J* 10.2, 17.1, 5.5, =CH-CH_2); δ_C(75.5 MHz, $CDCl_3$) 28.75 ((CH_3)$_3$C), 43.42 (CH_2=CH-CH_2), 79.69 ((CH_3)$_3C$), 116.01 (CH_2=CH-CH_2), 135.30 (CH_2=CH-CH_2), 156.17 (C=O).

rac-*N*-(*tert*-Butoxycarbonyl)-2,3-epoxypropylamine

A solution of *N*-(*tert*-butoxycarbonyl)allylamine (3 g, 19.08 mmol) in anhydrous dichloromethane (60 mL) was added dropwise to a stirred solution of *m*-chloroperoxybenzoic acid (9.87 g, 57.24 mmol) at room temperature. Then it was refluxed for 6 hours and worked up with sodium bicarbonate saturated solution (40 mL). The compound was extracted with ethyl acetate (3 × 40 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give the crude compound which was purified by flash chromatography eluting with 10% ethyl acetate–petroleum ether 40 : 60 to give *N*-(*tert*-butoxycarbonyl)-2,3-epoxypropylamine as a pale liquid (2.75 g, 88.3%) of high viscosity which crystallised on the bench after one week; $\nu_{max}(CDCl_3)/cm^{-1}$ 3451, 2980, 2931, 2252, 1704, 1510, 1454, 1391, 1367, 1332, 1251, 1170, 1097, 1041, 1020, 908, 849, 735, 648; δ_H(300 MHz, $CDCl_3$) 1.45 (9 H, s, C(CH_3)$_3$), 2.60 (1 H, dd, *J* 2.6, 4.5, OCHHCH-CH_2), 2.78 (1 H, dd, *J* 4.5, 4.3, OCHHCH-CH_2), 3.07–3.12 (1 H, m, CH- CH_2-NH), 3.17–3.29 (1 H, m, CHH-NH), 3.51–3.56 (1 H, m, CHH-NH), 4.76 (1 H, br s, NH); δ_C(75.5 MHz, $CDCl_3$) 28.73 ((CH_3)$_3$C), 42.01 (O-CH_2-CH-CH_2), 45.41 (O- CH_2-CH-CH_2), 51.23 (O-CH_2-CH-CH_2), 80.03 ((CH_3)$_3C$), 164.29 (C=O); *m*/*z* (CI) 174 ([M + H]$^+$, 62%), 135(100), 118(84), 74(35), 57(7) (Found: [M + H]$^+$, 174.1131. $C_8H_{15}NO_3$ requires *m*/*z*, 174.1130).

rac-1-(*N*-*tert*-Butoxycarbonylamino)-2-hydroxy-3-phenoxypropane 16

Potassium hydroxide (0.65 g, 11.6 mmol), in water (15 mL), was cooled at 0 °C, then *N*-(*tert*-butoxycarbonyl)-2,3-epoxypropylamine (1 g, 5.77 mmol) and phenol (1.08 g, 11.6 mmol) were added to the solution. The reaction was warmed up to room temperature, left stirring overnight, then neutralised with 2 M hydrochloric acid. The compound was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give the crude compound which was purified by flash chromatography eluting with 20% ethyl acetate–petroleum ether 40 : 60 to give 1-(*N*-*tert*-butoxycarbonylamino)-2-hydroxy-3-phenoxypropane *rac*-**16** as a pale liquid (2.49 g, 92.2%); ν_{max}(neat)/cm^{-1} 3359, 3060, 2977, 2931, 1690, 1599, 1587, 1497, 1456, 1391, 1366, 1245, 1170, 1123, 1070, 1044, 993, 925, 855, 813, 781, 754, 737, 691; δ_H(300 MHz, $CDCl_3$) 1.46 (9 H, s, C(CH_3)$_3$), 3.26–3.35 (2 H, m, CH_2), 3.44–3.52 (1 H, m, C(OH)H), 3.90–4.01 (2 H, m, CH_2), 4.08 (1 H, br s, OH), 5.01 (1 H, br s, NH), 6.86–7.32 (5 H, m, Aryl-H); δ_C(75.5 MHz, $CDCl_3$) 28.74 ((CH_3)$_3$C), 48.89 (CH_2), 69.66 (CH_2), 70.35 (CH), 80.34 ((CH_3)$_3C$), 114.87, 121.62, 129.94 (Ar-*ipso*), 158.75 (C=O); *m*/*z* (CI) 268 ([M + H]$^+$, 50%), 212 (100), 209 (15) (Found: [M + H]$^+$, 268.1551. $C_{14}H_{21}NO_4$ requires *m*/*z*, 268.1549).

rac-*N*-(*tert*-Butoxycarbonyl)-2-phenoxymethylaziridine 17

To a solution of 1-(*N*-*tert*-butoxycarbonylamino)-2-hydroxy-3-phenoxypropane *rac*-**16** (0.5 g, 1.87 mmol) and tosyl chloride (0.53 g, 2.81 mmol) in dry THF (10 mL) was added KOH (0.52 g, 9.35 mmol) freshly powered (with the help of a ball mill) at room temperature. The reaction mixture was left stirring overnight. Then it was dissolved in diethyl ether (20 mL) and filtered. The solvent was removed under reduced pressure and the crude compound was purified using flash chromatography eluting with 10% ethyl acetate–petroleum ether 40 : 60 to give the aziridine as a pale liquid (0.31 g, 66.4%). ν_{max}(neat)/cm^{-1} 2977, 2931, 2874, 1719, 1599, 1587, 1496, 1457, 1426, 1392, 1367, 1307, 1244, 1222, 1157, 1079, 1038, 996, 968, 854, 754, 691; δ_H(300 MHz, $CDCl_3$) 1.44 (9 H, s, (CH_3)$_3$C), 2.25 (1 H, d, *J* 4.0, CHH_{az}), 2.38 (1 H, d, *J* 6.0, CHH$_{az}$), 2.80–2.86 (1 H, m, CH_{az}), 4.0 (1 H, dd, *J* 4.9, 10.6, C-CHH-O-Ph), 4.16 (1 H, dd, *J* 4.9, 10.6, C-CHH-O-Ph), 6.89–7.33 (5 H, m, Aryl H); δ_C(75.5 MHz, $CDCl_3$) 27.65 ((CH_3)$_3$C), 29.31 (CH_2), 35.57 (CH_2), 67.24 (CH), 81.25 ((CH_3)$_3C$), 114.36, 120.92, 129.24 (Ar-*ipso*), 158.06 (C=O); *m*/*z* (FAB) 250 ([M + H]$^+$, 80%), 249 (70), 194 (100), 176 (15), 154 (80), 136 (34), 107 (29) (Found: [M + H]$^+$, 250.1441. $C_{14}H_{19}NO_3$ requires *m*/*z*, 250.1443).

rac-1-(*N*-*tert*-Butoxycarbonylamino)-2-oxo-3-phenoxypropane 18

1-(*N*-*tert*-Butoxycarbonylamino)-2-hydroxy-3-phenoxypropane *rac*-**16** (1.77 g, 6.62 mmol) was added to an ice cold solution of pyridinium dichromate (8.51 g, 23.17 mmol) in anhydrous *N*,*N*-dimethylformamide (30 mL). The reaction mixture was stirred overnight, then worked up with brine (40 mL). The compound was extracted with diethyl ether (3 × 40 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give the crude compound which was purified by flash chromatography eluting with 10% ethyl acetate–petroleum ether 40 : 60 to give 1-(*N*-*tert*-butoxycarbonylamino)-2-oxo-3-phenoxypropane **18** as a white solid (0.54 g, 31.0%), mp 65 °C; ν_{max}(neat)/cm^{-1} 3438, 2983, 2254, 1711, 1600, 1496, 1369, 1246, 1170, 1066, 909, 732; δ_H(300 MHz, $CDCl_3$) 1.46 (9 H, s, C(CH_3)$_3$), 4.34 (2 H, d, *J* 5.1, CH_2-NH), 4.64 (2 H, s, O-CH_2-C(=O)), 5.23 (1 H, br s, NH), 6.86–7.35 (5 H, m, Aryl-H); δ_C(75.5 MHz, $CDCl_3$) 28.69 ((CH_3)$_3$C), 48.81 (CH_2), 72.16 (CH_2), 80.46 ((CH_3)$_3C$), 114.83, 122.43, 130.18 (Ar-*ipso*), 157.82 (C=O), 164.50 (C=O); *m*/*z* (CI) 266 ([M + H]$^+$, 87%), 265 (100), 258 (10), 242 (7), 239 (5) (Found: [M + H]$^+$, 266.1392. $C_{14}H_{19}NO_4$ requires *m*/*z*, 266.1392).

R-(−)-1-(*N*-*tert*-Butoxycarbonylamino)-2-hydroxy-3-phenoxypropane 16

A mixture of (*p*-cymene)ruthenium(II) chloride dimer (0.31 mg, 0.0051 mmol) and (1*R*,2*R*)-TsDPEN **2** (0.37 mg, 0.0102 mmol) in a 5 : 2 formic acid–triethylamine mixture (2.5 mL) was stirred at 28 °C for 15 min. 1-(*N*-*tert*-Butoxycarbonylamino)-2-oxo-3-phenoxypropane **18** (0.54 g, 2.04 mmol) was added and the solution was stirred at 28 °C for 24 hours. Then the mixture was filtered through silica and washed with ethyl acetate (60 ml). The solvent was evaporated under reduced pressure to give the crude compound, which was purified by flash chromatography (20% v/v ethyl acetate–petroleum ether 40 : 60) to give the *R*-(−)-**16** as a white solid (0.47 g, 86.2%). The product was determined to be of 84% ee by HPLC analysis (Chiral OD, hexane–ethanol–diethylamine = 95 : 5 : 0.1 (0.5 mL min^{-1}), *R* isomer 22.48 min, *S* isomer 41.64 min), mp 70–72 °C; $[\alpha]_D^{20}$ −7.2 (*c* = 1, ethanol); ν_{max}(neat)/cm^{-1} 3359, 3060, 2977, 2931, 1690, 1599, 1587, 1497, 1456, 1391, 1366, 1245, 1170, 1123, 1070, 1044, 993, 925, 855, 813, 781, 754, 737, 691; δ_H(300 MHz, $CDCl_3$) 1.46 (9 H, s, C(CH_3)$_3$), 3.26–3.35 (2 H, m, CHH, C(OH)H), 3.44–3.52 (1 H, m, CHH), 3.90–4.01 (2 H, m, CH_2), 4.11 (1 H, br s, OH), 4.99 (1 H, br s, NH), 6.88–7.33 (5 H, m, Aryl-H); δ_C(75.5 MHz, $CDCl_3$) 28.74 ((CH_3)$_3$C), 43.89 (CH_2), 69.62 (CH_2), 70.39 (CH), 80.34 ((CH_3)$_3$C), 114.87, 121.64, 129.95 (Ar-*ipso*), 158.74

(C=O); *m*/*z* (CI) 268 ([M + H]$^+$, 35%), 212 (63), 192 (11), 168 (35), 154 (100), 136 (70), 107 (26) (Found: [M + H]$^+$, 268.155464. $C_{14}H_{21}NO_4$ requires *m*/*z*, 268.154883). The reduction using (1*S*,2*R*)-**1**–propan-2-ol was attempted using identical conditions to those reported however no reduction product was isolated.[4b]

(*R*)-(−)-*N*-(*tert*-Butoxycarbonyl)-2-phenoxymethylaziridine 17

To a solution of chiral 1-*N*-(*tert*-butoxycarbonylamino)-2-hydroxy-3-phenoxypropane *R*-(−)-**16** (0.38 g, 1.42 mmol) and tosyl chloride (0.41 g, 2.13 mmol) in dry THF (10 mL) was added KOH (0.40 g, 7.10 mmol) freshly powdered (with the help of a ball mill) at room temperature. The reaction mixture was left stirring overnight. Then it was dissolved in diethyl ether (20 mL) and filtered. The solvent was removed under reduced pressure and the crude compound was purified using flash chromatography eluting with 20% diethyl ether–hexane to give the aziridine *R*-(−)-**17** as a colourless liquid (0.22 g, 62.9%). The product was determined to be of 83.7% ee by HPLC analysis (Chiral OD, hexane–ethanol–diethylamine = 95 : 5 : 0.1 (0.5 mL min^{-1}), *R* isomer 22.48 min, *S* isomer 41.64 min); $[\alpha]_D^{20}$ −68.9 (*c* = 1, ethanol); ν_{max}(neat)/cm^{-1} 2979, 2932, 2360, 1722, 1600, 1497, 1458, 1393, 1308, 1245, 1222, 1156, 1110, 1080, 1039, 996, 968, 853, 832, 754, 692; δ_H(300 MHz, $CDCl_3$) 1.44 (9 H, s, $(CH_3)_3C$), 2.25 (1 H, d, *J* 3.6, CH_{az}), 2.38 (1 H, d, *J* 6.0, CH_{az}), 2.80–2.87 (1 H, m, CH_{az}), 4.0 (1 H, dd, *J* 4.9, 10.6, C-CH-O-Ph), 4.16 (1 H, dd, *J* 4.9, 10.6, C-CH-O-Ph), 6.89–7.31 (5 H, m, Aryl H); δ_C(75.5 MHz, $CDCl_3$) 27.65 ($(CH_3)_3C$), 29.32 (CH_2), 35.57 (CH_2), 67.25 (CH), 81.26 ($(CH_3)_3C$), 114.36, 120.92, 129.24 (Ar-*ipso*), 158.05 (C=O); *m*/*z* (FAB) 250, ([M]$^+$, 80%), 249 (70), 194 (100), 176 (15), 154 (80), 136 (34), 107 (29) (Found: [M + H]$^+$, 250.1441. $C_{14}H_{19}NO_3$ requires *m*/*z*, 250.1443).

2-(Chloromethyl)allyl phenyl ether

Sodium hydride (0.10 g, 2.5 mmol) was stirred in DMF (7 mL) at 0 °C and to this phenol (0.094 g, 1 mmol) was added slowly. Once the addition was complete the reaction was stirred for 20 minutes. The cooling bath was removed and the stirring was continued for a further hour at room temperature. 3-Chloro-2-chloromethylprop-1-ene (0.125 g, 1 mmol) was added and the reaction was stirred overnight. Saturated ammonium chloride solution (10 mL) was added to quench the reaction and then the aqueous solution was extracted with ethyl acetate. The organic layers were dried over magnesium sulfate, filtered and concentrated under reduced pressure to give the crude compound which was purified using medium pressure flash chromatography eluting with 1% ether–hexane to give the product as a pale oil (0.08 g, 43.7%). ν_{max}(neat)/cm^{-1} 3062, 3039, 2925, 2867, 1930, 1840, 1775, 1702, 1654, 1597, 1495, 1456, 1443, 1407, 1368, 1334, 1299, 1241, 1172, 1079, 1056, 1033, 993, 919, 883, 814, 753, 691, 665; δ_H(300 MHz, $CDCl_3$) 4.19 (2 H, br d, *J* 0.7, CH_2), 4.63 (2 H, br s, CH_2), 5.37 (1 H, m, =CH*H*), 5.39 (1 H, m, =CH*H*), 6.90–7.00 (3 H, m, Ar-H), 7.25–7.35 (2 H, m, Ar-*H*); δ_C(75.5 MHz, $CDCl_3$) 45.52 (CH_2), 68.26 (CH_2), 115.17, 117.93, 121.56, 129.91, 141.25 (Ar-*ipso*), 158.80 (C=CH_2), 164.35 (C=CH$_2$); *m*/*z* (EI) 184, 182 ([M + H]$^+$ 62, 86%), 148, 147 (57, 100), 133, 131 (50, 26), 119, 118 (15, 7), 94, 93 (36, 6) (Found: [M + H]$^+$, 184.0472, 182.0501. $C_{14}H_{19}NO_4$ requires *m*/*z*, 184.0469, 182.0498).

N-(*tert*-Butoxycarbonyl)-*N*-(benzyl)-2-(phenoxymethyl)allylamine

Sodium hydride (0.62 g, 5.80 mmol) was stirred in DMF (20 mL) and to this benzylamine (0.62 g, 5.80 mmol) in 5 mL of DMF was added slowly. Once the addition was completed the reaction was stirred for a further 1 hour at room temperature. Then 2-(chloromethyl)allyl phenyl ether in 5 mL of DMF was added and the reaction mixture was stirred overnight. The reaction was then filtered and DMF was removed. Dichloromethane (30 mL) was then added followed by di-*tert*-butyl dicarbonate (1.27 g, 5.80 mmol) dissolved in 10 mL of dichloromethane. The reaction mixture was stirred overnight, then saturated ammonium chloride solution (30 mL) added. The phases were separated and the aqueous layer extracted with dichloromethane (2 × 30 mL). The combined organic layers were dried over magnesium sulfate, filtered, and the solvent removed *in vacuo*. Purification by flash chromatography on silica with 10% ethyl acetate–hexane 60 : 80, gave the product as a colourless liquid (0.56 g, 27.3%); ν_{max}(neat)/cm^{-1} 3366, 3064, 3030, 2976, 2929, 1950, 1809, 1694, 1599, 1587, 1495, 1454, 1409, 1365, 1339, 1301, 1243, 1169, 1119, 1078, 1053, 1031, 993, 915, 882, 816, 754, 692; δ_H(300 MHz, $CDCl_3$) 1.45 (9 H, s, $C(CH_3)_3$), 3.91 (2 H, m, Ph-O-CH_2), 4.45 (4 H, br m, =C-CH_2, CH_2-Ph), 5.04 (1 H, s, =CHH), 5.11 (1 H, br s, =CHH), 6.88–7.38 (10 H, m, Ar-H); δ_C(75.5 MHz, $CDCl_3$) 28.76 ($(CH_3)_3C$), 48.63 (CH_2), 49.40 (CH_2), 50.07 (CH_2), 60.15 (C=CH_2), 71.27 ($C(CH_3)_3$), 80.49 (C=CH_2), 114.53, 115.07, 121.32, 127.65, 127.87, 128.38, 128.92, 129.83, 138.38, 140.91 (Ar-*ipso*), 158.89 (C=O); *m*/*z* (FAB) 354 ([M]$^+$, 70%), 307 (25), 298 (87), 254 (70), 204 (90), 160 (23), 154 (90), 136 (62), 107 (27) (Found: [M + H]$^+$, 354.2064. $C_{22}H_{27}NO_3$ requires *m*/*z*, 354.2069).

1-(*N*-Butoxycarbonyl-*N*-benzylamino)-2-oxo-3-phenoxypropane 20

N-(*tert*-Butoxycarbonyl)-*N*-(benzyl)-2-(phenoxymethyl)allylamine (0.17 g, 0.48 mmol) was stirred in dichloromethane (10 mL) at −78 °C. An empty trap followed by a trap containing a solution of 5% potassium iodide in 50% acetic acid–water were connected to the outlet. Ozone was passed through the reaction mixture for 20 minutes after which time the solution appeared pale blue. Oxygen was bubbled through the solution for 10 minutes followed by nitrogen for 20 minutes. Triphenylphosphine (0.19 g, 0.72 mmol) was added and the cooling bath removed. The reaction was stirred overnight, the solvent removed and purified by column chromatography yielding the product **20** as a colourless liquid of high viscosity (0.08 g, 47% yield). ν_{max}(neat)/cm^{-1} 3371, 3064, 2977, 2930, 1740, 1694, 1599, 1589, 1495, 1454, 1427, 1393, 1366, 1292, 1245, 1165, 1126, 1080, 1060, 967, 886, 754, 692; δ_H(300 MHz, $CDCl_3$, 1 : 1 mixture of NCO rotamers) 1.44 (4.5 H, s, $C(CH_3)_3$), 1.49 (4.5 H, s, $C(CH_3)_3$), 4.12 (1 H, s, N-CHH-Ph), 4.20 (1 H, s, N-CHH-Ph), 4.48 (1 H, s, C(=O)-CHH), 4.51 (2 H, s, Ph-O-CH_2), 4.59 (1 H, s, C(=O)-CHH), 6.80–7.35 (10 H, m, Ar-H); δ_C(75.5 MHz, $CDCl_3$) 28.64 ($(CH_3)_3C$), 51.60 (CH_2), 53.70 (CH_2), 72.24 (CH_2), 81.06 ($C(CH_3)_3$), 80.49 (C=CH_2), 114.78, 122.18, 127.98, 128.59, 129.05, 130.07, 137.88 (Ar-*ipso*), 156.21 (C=O), 157.97 (C=O); *m*/*z* (FAB) 356 ([M + H]$^+$, 31%), 307 (20), 300 (100), 289 (10), 256 (26), 220 (21), 154 (69), 136 (45), 120 (32) (Found: [M + H]$^+$, 356.1862. $C_{21}H_{25}NO_4$ requires *m*/*z*, 356.1862).

R-(+)-1-(*N*-*tert*-Butoxycarbonyl-*N*-benzylamino)-2-hydroxy-3-phenoxypropane 21

A mixture of (*p*-cymene)ruthenium(II) chloride dimer (0.26 mg, 0.0043 mmol) and (1*R*,2*R*)-TsDPEN **2** (0.30 mg, 0.0086 mmol) in a 5 : 2 formic acid–triethylamine mixture (2.5 mL) was stirred at 28 °C for 15 min. 1-(*N*-*tert*-Butoxycarbonyl-*N*-benzylamino)-2-oxo-3-phenoxypropane (0.61 g, 1.72 mmol) was added and the solution was stirred at 28 °C for 24 hours. Then the mixture was filtered through silica and washed with ethyl acetate (60 ml). The solvent was evaporated under reduced pressure to give the crude compound, which was purified by flash chromatography (20% v/v ethyl acetate–petroleum ether 40 : 60) to give the product **21** as a colourless liquid (0.61 g, 99.0%). The product was determined to be of 59.7% ee by HPLC analysis (Chiral OD, hexane–ethanol–diethylamine = 95 : 5 : 0.1 (0.5 mL min^{-1}), *S* isomer 21.09 min, *R* isomer 22.98 min); $[\alpha]_D^{20}$ +7.45

($c = 2$, ethanol); ν_{max}(neat)/cm^{-1} 3430, 3061, 3028, 2973, 2928, 1947, 1736, 1694, 1598, 1586, 1495, 1453, 1413, 1391, 1365, 1288, 1244, 1168, 1132, 1077, 995, 967, 924, 881, 814, 754, 691; δ_H(300 MHz, $CDCl_3$) 1.47 (9 H, s, $C(CH_3)_3$), 3.44–3.53 (2 H, m, C(O*H*)H, O*H*), 3.82–3.94 (2 H, m, Boc-N-CH_2-Ph), 4.06–4.23 (2 H, m, CH(OH)-CH_2-N-Boc), 4.48 (2 H, AB system, J^{AB} 14.7, Ph-O-CH_2), 6.87–7.36 (10 H, m, Aryl-*H*); δ_C(75.5 MHz, $CDCl_3$) 28.15 ($(CH_3)_3C$), 50.41 (CH_2), 52.40 (CH_2), 68.78 (CH_2), 69.98 (CH), 81.00 ($(CH_3)_3C$), 114.21, 120.86, 127.16, 128.39, 129.31, 137.74 (Ar-*ipso*), 164.09 (C=O); *m*/*z* (FAB) 358 ([M + H]$^+$, 71%), 302 (90), 282 (15), 258 (91), 208 (35), 194 (10), 154 (86), 164 (16), 136 (60), 120 (44) (Found: [M + H]$^+$, 358.2014. $C_{21}H_{27}NO_4$ requires *m*/*z*, 358.2018). The reduction using (1*S*,2*R*)-**1**–propan-2-ol was carried out using identical conditions to those reported.[4b] The product, *R*-(+)-**21** was formed in 99% yield and 61% ee as determined by chiral HPLC analysis.

1-(*N*-*tert*-Butoxycarbonyl-*N*-benzylamino)-2-hydroxy-3-phenoxypropane *rac*-21

1-(*N*-*tert*-Butoxycarbonyl-*N*-benzylamino)-2-oxo-3-phenoxypropane (0.70 g, 1.97 mmol) was dissolved in 15 mL of MeOH–H_2O (9 : 1), in an ice bath. Sodium borohydride (0.25 g, 7.00 mmol) dissolved in 10 mL of MeOH–H_2O (9 : 1) was added slowly to the ketone solution. The reaction mixture was allowed to warm up to room temperature. When the reaction was completed (TLC), it was concentrated under reduced pressure. The residue was dissolved in diethyl ether (30 mL) and worked up with saturated ammonium chloride solution (30 mL). The phases were separated and the aqueous layer extracted with diethyl ether (2 × 20 mL). The organic layers were dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude compound was purified using medium pressure flash chromatography eluting with 20% ethyl acetate–petroleum ether 40 : 60 to give 1-(*N*-*tert*-butoxycarbonyl-*N*-benzylamino)-2-hydroxy-3-phenoxypropane **21** as a colourless liquid (0.70 g, 99%); ν_{max}(neat)/cm^{-1} 3425, 3061, 3028, 2973, 2928, 1948, 1693, 1598, 1586, 1537, 1494, 1453, 1413, 1365, 1288, 1244, 1169, 1133, 1077, 1043, 995, 966, 923, 881, 814, 753, 691; δ_H(300 MHz, $CDCl_3$) 1.47 (9 H, s, $C(CH_3)_3$), 3.44–3.57 (2H, m, C(OH)*H*, O*H*), 3.88–3.94 (2 H, m, N(Boc)-CH_2-Ph), 4.06–4.17 (2 H, m, CH(OH)CH_2), 4.48 (2 H, AB system, J^{AB} 14.7, Ph-O-CH_2), 6.87–7.36 (10 H, m, Aryl H); δ_C(75.5 MHz, $CDCl_3$) 28.77 ($(CH_3)_3C$), 51.02 (CH_2), 53.02 (CH_2), 69.42 (CH_2), 70.61 (*C*H), 86.50 ($(CH_3)_3C$), 114.82, 121.46, 127.78, 129.01, 129.93, 137.50 (Ar-*ipso*), 164.14 (C=O); *m*/*z* (FAB) 358 ([M + H]$^+$, 31%), 307 (27), 302 (40), 289 (16), 258 (43), 208 (17), 154 (100), 136 (72), 120 (30) (Found: [M + H]$^+$, 358.2021. $C_{21}H_{27}NO_4$ requires *m*/*z*, 358.2018).

R-(+)-1-(*N*-Benzylamino)-2-hydroxy-3-phenoxypropane

To a solution of 1-(*N*-*tert*-butoxycarbonyl-*N*-benzylamino)-2-hydroxy-3-phenoxypropane *R*-(+)-**21** (0.48 g, 1.34 mmol) in dichloromethane (2 mL) TFA (2 mL) was added slowly. After 2 hours the solvent was removed and the resulting product was dissolved in ethyl acetate and 0.2 M NaOH solution was added until the pH = 7. The product was then extracted with ethyl acetate and the combined organic layers were dried over magnesium sulfate, filtered and the solvent removed *in vacuo*. Recrystallisation (ethyl acetate–petroleum ether 40 : 60) gave 1-(*N*-benzylamino)-2-hydroxy-3-phenoxypropane as a white solid (0.34 g, 47.0% yield). The product was determined to be of 45.6% ee by HPLC analysis (Chiral OD, hexane–ethanol–diethylamine = 95 : 5 : 0.1 (0.5 mL min^{-1}), *S* isomer 21.27 min, *R* isomer 60.49 min), mp 64–66 °C; $[\alpha]_D^{20}$ +9.4 ($c = 2$, ethanol); ν_{max}($CDCl_3$)/cm^{-1} 3375, 2926, 2252, 1681, 1599, 1495, 1454, 1244, 1043, 908, 732, 649; δ_H(300 MHz, $CDCl_3$) 2.24 (2 H, br s, OH, NH), 2.81 (1 H, dd, J^{ab} 12.1, J^{bc} 7.7, C*H*^{b}H^{a}CH^c(OH)), 2.91 (1 H, dd, J^{ab} 12.2, J^{ac} 3.9, CH^b*H*^{a}CH^c(OH)), 3.85 (2 H, AB_{system}, J^{AB} 13.0, NHCH_2-Ph), 3.98 (2 H, d, J 5.3, Ph(O)-CH_2), 4.05–4.13 (1 H, m, C*H*(OH)), 6.89–7.35 (10 H, m, Aryl H); δ_C(75.5 MHz, $CDCl_3$) 51.48 (CH_2), 54.10 (CH_2), 68.66 (CH), 70.64 (CH_2), 114.92, 121.48, 127.69, 128.59, 128.95, 129.89 (Ar-*ipso*); *m*/*z* (CI) 258 ([M + H]$^+$, 80%), 240 (5), 148 (7), 120 (18), 108 (8), 91 (10) (Found: [M + H]$^+$, 258.1498. $C_{16}H_{19}NO_2$ requires *m*/*z*, 258.1494).

rac-1-(*N*-Benzylamino)-2-hydroxy-3-phenoxypropane

To a solution of 1-(*N*-*tert*-butoxycarbonyl-*N*-benzylamino)-2-hydroxy-3-phenoxypropane *rac*-**21** (0.76 g, 2.11 mmol) in dichloromethane (2 mL) TFA (2 mL) was added slowly. After 2 hours the solvent was removed and the resulting product was dissolved in ethyl acetate and NaOH solution 0.2 M was added until the pH = 7. The product was then extracted with ethyl acetate and the combined organic layers were dried over magnesium sulfate, filtered and the solvent removed *in vacuo*. Recrystallisation (ethyl acetate–petroleum ether 40 : 60) gave 1-(*N*-benzylamino)-2-hydroxy-3-phenoxypropane (racemic) as a white solid (0.34 g, 47% yield). Mp 74–76 °C; ν_{max}($CDCl_3$)/cm^{-1} 3402, 2925, 1644, 1599, 1587, 1453, 1301, 1245, 1173, 1078, 1041, 909, 752, 691; δ_H(300 MHz, $CDCl_3$) 2.55 (2 H, br s, OH, NH), 2.78 (1 H, dd, J^{ab} 12.06, J^{bc} 7.72, C*H*^{b}H^{a}CH^c(OH)), 2.88 (1 H, dd, J^{ab} 12.25, J^{ac} 3.96, CH^b*H*^{a}CH^c(OH)), 3.83 (2 H, AB_{system}, J^{AB} 13.37, NHCH_2-Ph), 3.96 (2 H, d, J 5.09, Ph(O)-CH_2), 4.04–4.15 (1 H, m, C*H*(OH)), 6.84–7.38 (10 H, m, Aryl H); δ_C(75.5 MHz, $CDCl_3$) 51.48 (CH_2), 54.10 (CH_2), 68.66 (CH), 70.64 (CH_2), 114.93, 121.44, 127.58, 128.55, 128.92, 129.45, 129.89, 140.24 (Ar-*ipso*); *m*/*z* (CI) 258 ([M + H]$^+$, 90%), 256 (17), 168 (21), 164 (18), 162 (12), 146 (8), 120 (31), 106 (10) (Found: [M + H]$^+$, 258.1498. $C_{16}H_{19}NO_2$ requires *m*/*z*, 258.1494).

O-(*tert*-Butyldimethylsilyl)-1-(*N*-*tert*-butoxycarbonylamino)-2-hydroxy-3-phenoxypropane and subsequently *R*-(+)-19 from *R*-(+)-16

1-(*N*-*tert*-Butoxycarbonylamino)-2-hydroxy-3-phenoxypropane *R*-(−)-**16** (0.3 g, 1.12 mmol) and imidazole (0.19 g, 2.80 mmol) were dissolved in 10 mL of DMF and treated with *tert*-butylchlorodimethylsilane (TBDMSCl) (0.21 g, 1.35 mmol). The mixture was stirred at 35–45 °C until the starting materials were completely consumed (followed by TLC). The reaction was then treated with sodium bicarbonate saturated solution (20 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give the crude compound which was purified by flash chromatography eluting with 20% ethyl acetate–petroleum ether 40 : 60 to give *O*-(*tert*-butyldimethylsilyl)-1-(*N*-*tert*-butoxycarbonylamino)-2-hydroxy-3-phenoxypropane as a colourless liquid (0.42 g, 99%); $[\alpha]_D^{20}$ −12.05 ($c = 2$, ethanol); ν_{max}(neat)/cm^{-1} 2929, 1703, 1674, 1652, 1600, 1497, 1390, 1366, 1328, 1245, 1172, 1062, 987, 937, 836, 777, 752, 691; δ_H(300 MHz, $CDCl_3$) −0.0001 (3 H, s, $SiCH_3(CH_3)_3$), 0.0231 (3 H, s, $SiCH_3(CH_3)_3$), 0.80 (9 H, s, Si-$C(CH_3)_3$), 1.33 (9 H, s, $C(CH_3)_3$), 3.08–3.16 (1 H, m, CH*H*-NH), 3.26–3.34 (1 H, m, C*H*H-NH), 3.76 (2 H, dd, J 1.32, 5.75, Ph-O-CH_2), 3.98–4.04 (1 H, m, C*H*), 4.70 (1 H, br s, N*H*), 6.75–7.25 (5 H, m, Aryl H); δ_C(75.5 MHz, $CDCl_3$) −4.46 ($SiCH_3(CH_3)_3$), −4.11 ($SiCH_3(CH_3)_3$), 26.20 (Si-$C(CH_3)_3$), 28.79 ($(CH_3)_3C$), 44.65 (CH_2), 70.31 (CH_2), 70.40 (*C*H), 114.78, 121.29, 122.29, 129.86, 135.54 (Ar-*ipso*), 163.97 (C=O); *m*/*z* (FAB) 382 ([M + H]$^+$, 25%), 326 (26), 282 (63), 268 (100), 232 (6), 174 (8), 154 (20), 136 (16), 107 (10) (Found: [M + H]$^+$, 382.2413. $C_{20}H_{35}NSiO_4$ requires *m*/*z*, 382.2413). This was converted into *R*-(+)-**19** (100 mg scale) by treatment with sodium hydride–benzyl bromide using the same procedure as employed for *S*-(+)-**6** previously described. The product was formed in 50% yield and exhibited $[\alpha]_D^{20}$ +0.70 ($c = 2$, ethanol).

O-(*tert*-Butyldimethylsilyl)-1-(*N*-*tert*-butoxycarbonyl-*N*-benzylamino)-2-hydroxy-3-phenoxypropane *S*-(+)-19 from *R*-(+)-21

R-(+)-1-(*N*-*tert*-Butoxycarbonyl-*N*-benzylamino)-2-hydroxy-3-phenoxypropane **21** (0.2 g, 0.56 mmol) and imidazole (0.08 g, 1.12 mmol) were dissolved in 10 mL of DMF and treated with *tert*-butylchlorodimethylsilane (TBDMSCl) (0.13 g, 0.84 mmol). The mixture was stirred at 35–45 °C until the starting materials had been completely consumed (followed by TLC). The reaction was then treated with sodium bicarbonate saturated solution (20 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give the crude compound which was purified by flash chromatography eluting with 20% ethyl acetate–petroleum ether 40 : 60 to give *O*-(*tert*-butyldimethylsilyl-1-(*N*-*tert*-butoxycarbonyl-*N*-benzylamino)-2-hydroxy-3-phenoxypropane *R*-(+)-**19** as a colourless liquid (0.25 g, 99%); $[\alpha]_D^{20}$ +0.7 (*c* = 2, ethanol); ν_{max}(neat)/cm^{-1} 3429, 3064, 3031, 2955, 2929, 2857, 1696, 1600, 1587, 1496, 1462, 1409, 1366, 1245, 1171, 1135, 1078, 1049, 980, 880, 836, 808, 775, 753, 691; δ_H(300 MHz, $CDCl_3$) −0.10 (6 H, s, Si(CH_3)$_2$), 0.90 (9 H, s, Si-C(CH_3)$_3$), 1.44 (4.5 H, s, C(CH_3)$_3$), 1.51 (4.5 H, s, C(CH_3)$_3$), 3.13–3.20 (1 H, m, C(O)Si-CH*H*-NBoc), 3.44–3.59 (1 H, m, C(O)SiC*H*H-NBoc), 3.80–3.93 (2 H, m, N-CH_2-Ph), 4.40 (2H, d, *J* 15.45, Ph-O-CH_2), 4.70–4.74 (1 H, m, Ph-O-CH$_2$-C*H*(OSi)), 6.80–7.30 (10 H, m, Aryl H); δ_C(75.5 MHz, $CDCl_3$) −4.33 (Si*C*H$_3$(CH$_3$)$_3$), −4.14 (SiCH$_3$(*C*H$_3$)$_3$), 18.48 (Si-*C*(CH$_3$)$_3$), 26.27 ((*C*H$_3$)$_3$C), 28.81 (Si-C(*C*H$_3$)$_3$), 50.26, 50.83 (*C*H$_2$), 51.95, 52.92 (*C*H$_2$), 69.31 (*C*H$_2$), 70.26, 70.64 (*C*H), 77.42, 77.85 (*C*(CH$_3$)$_3$), 105.42, 114.78, 117.77, 120.77, 121.07, 122.48, 125.57, 126.18, 126.78, 127.55, 127.84, 128.14, 128.91, 129.82, 133.73, 163.95 (C=O); *m*/*z* (FAB) 472 ([M + H]$^+$, 27%), 372 (100), 358 (95), 322 (7), 154 (14), 136 (12), 120 (17) (Found: [M + H]$^+$, 472.2883. $C_{27}H_{41}NSiO_4$ requires *m*/*z*, 472.2883).

(±)-3-(1-Naphthyloxy)-1,2-epoxypropane

To a solution of 1-naphthol (2 g, 13.87 mmol) in 20 mL of dry DMF was added NaH (1.11 g, 27.74 mmol) and the mixture was heated to 80 °C for 1 hour. To this solution was added epichlorohydrin (2.57 g, 27.74 mmol) and it was stirred for 4 hours at 80 °C. The solution was cooled and poured into 30 mL of water. The product was then extracted with diethyl ether (3 × 30 mL), dried with $MgSO_4$ and concentrated to give the crude compound which was purified by flash chromatography (10% v/v ethyl acetate–hexane) to give the product as a colourless liquid (1.69 g, 61%); ν_{max}(neat)/cm^{-1} 3053, 3000, 2926, 1628, 1595, 1580, 1576, 1508, 1465, 1440, 1349, 1271, 1241, 1179, 1157, 1109, 1101, 1083, 1069, 1020, 999, 960, 916, 862, 841, 793, 772, 728, 635, 614; δ_H(300 MHz, $CDCl_3$) 2.83 (1 H, dd, *J* 2.6, 4.9, CH-O-C*H*H), 2.94 (1 H, t, *J* 4.2, CH-O-CH*H*), 3.45–3.50 (1 H, m, Ar-O-CH$_2$-C*H*-O-CH$_2$), 4.11 (1 H, dd, *J* 5.6, 11.1, Ar-O-C*H*H-CH-O-CH$_2$), 4.37 (1 H, dd, *J* 3.2, 11.1, Ar-O-CH*H*-CH-O-CH$_2$), 6.77–6.79 (1 H, m, Ar-H), 7.32–7.52 (4 H, m, Ar-H), 7.75–7.82 (1 H, m, Ar-H), 8.27–8.32 (1 H, m, Ar-H); δ_C(75.5 MHz, $CDCl_3$) 45.17 (*C*H$_2$), 50.67 (*C*H$_2$), 69.34 (*C*H), 105.36, 121.26, 122.44, 125.75, 125.98, 126.14, 126.94, 127.88, 134.92, 154.63 (Ar-*ipso*); *m*/*z* (CI) 201 ([M + H]$^+$, 100%), 200 (13), 185 (53), 144 (17), 115 (10).

(±)-*N*-Isopropyl-*N*-[2-hydroxy-3-(1-naphthyloxy)propyl]amine 24

A solution of the epoxide (0.2 g, 1.0 mmol) in acetonitrile (1 mL) was treated with anhydrous metal salt ($CaCl_2$) (0.11 g, 1.0 mmol), then stirred until the salt had completely dissolved. The resulting solution was treated under stirring, at room temperature, with the required amount of the amine (0.12 g, 2.0 mmol). After the addition of the amine was complete, the reaction mixture was stirred until the reagents had been consumed. The reaction was then treated with water (5 mL) and extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give the crude compound which was recrystallised with ether to give (±)-*N*-isopropyl-*N*-[2-hydroxy-3-(1-naphthyloxy)propyl]amine **24** as a white solid (0.24 g, 93%). Mp 88–89 °C; ν_{max}($CDCl_3$)/cm^{-1} 3429, 2253, 1655, 1581, 1461, 1396, 1268, 1103, 908, 734, 650; δ_H(300 MHz, $CDCl_3$) 1.11 (6 H, d, *J* 6.4, CH(CH_3)$_2$), 1.51 (2 H, br s, O*H*, N*H*), 2.82–2.90 (2 H, m, CH_2NH), 2.89–3.03 (1 H, m, C*H*(CH$_3$)$_2$), 4.11–4.24 (3 H, m, CH_2C*H*(OH)), 6.84 (1 H, dd, *J* 1.2, 7.4, Ar-H), 7.34–7.52 (4 H, m, Ar-H), 7.76–7.83 (1 H, m, Ar-H), 8.21–8.26 (1 H, m, Ar-H); δ_C(75.5 MHz, $CDCl_3$) 23.51 (*C*H$_3$), 23.65 (*C*H$_3$), 49.31 (*C*H), 49.85 (*C*H$_2$), 68.98 (*C*H), 71.06 (*C*H$_2$), 105.28, 121.00, 122.21, 125.65, 126.23, 126.83, 127.93 (Ar-*ipso*); *m*/*z* (CI) 260 ([M + H]$^+$, 77%), 242 (7), 145 (34), 128 (6), 116 (74), 100 (100), 98 (28), 84 (13), 72 (31), 58 (30) (Found: [M + H]$^+$, 260.1646. $C_{16}H_{21}NO_2$ requires *m*/*z*, 260.1650).

N-*tert*-Butoxycarbonyl-*N*-isopropyl-*N*-[2-hydroxy-3-(1-naphthyloxy)propyl]amine *rac*-22

To a solution of (±)-*N*-isopropyl-*N*-[2-hydroxy-3-(1-naphthyloxy)propyl]amine (0.95 g, 3.66 mmol) in dichloromethane (40 mL), triethylamine (1.85 g, 18.30 mmol) followed by di-*tert*-butyl dicarbonate (1.60 g, 7.32 mmol) were added. The reaction mixture was stirred overnight, then saturated ammonium chloride solution (30 mL) was added. The phases were separated and the aqueous layer extracted with dichloromethane (2 × 40 mL). The combined organic layers were dried over magnesium sulfate, filtered, and the solvent removed *in vacuo*. Purification by flash chromatography on silica with 10% ethyl acetate–hexane, gave the product **22** as a colourless liquid (1.45 g, 98.7%); ν_{max}(neat)/cm^{-1} 3416, 3053, 2975, 2931, 2876, 1865, 1658, 1596, 1581, 1509, 1476, 1457, 1403, 1367, 1347, 1269, 1241, 1213, 1164, 1128, 1103, 1069, 1020, 1001, 922, 900, 878, 861, 792, 771, 735, 571; δ_H(300 MHz, $CDCl_3$) 1.15 (3 H, d, *J* 6.6, CH(CH$_3$)C*H*$_3$), 1.24 (3 H, d, *J* 6.9, CH(C*H*$_3$)CH$_3$), 1.51 (9 H, s, C(C*H*$_3$)$_3$), 3.52 (2 H, d, *J* 4.3, C*H*$_2$-N(tBoc)), 4.05–4.07 (1 H, m, C*H*(CH$_3$)$_2$), 4.17–4.25 (3 H, m, CH_2C*H*(OH)), 5.29 (1 H, br s, O*H*), 6.85 (1 H, d, *J* 7.4, Ar-H), 7.35–7.52 (4 H, m, Ar-H), 7.78–7.85 (1 H, m, Ar-H), 8.19–8.24 (1 H, m, Ar-H); δ_C(75.5 MHz, $CDCl_3$) 20.89 (CH(*C*H$_3$)CH$_3$), 21.40 (C(CH$_3$)*C*H$_3$), 28.86 (C(*C*H$_3$)$_3$), 47.46 (*C*H), 66.24 (*C*H$_2$), 70.24 (*C*H$_2$), 72.50 (*C*H), 81.17 (*C*(CH$_3$)$_3$), 105.16, 120.99, 122.04, 125.64, 125.82, 126.30, 126.80, 127.99, 134.89 (Ar-*ipso*), 154.53 (C=O); *m*/*z* (FAB) 360 ([M + H]$^+$, 12%), 304 (20), 260 (42), 160 (100), 154 (25), 136 (20) (Found: [M + H]$^+$, 360.2170. $C_{21}H_{29}NO_4$ requires *m*/*z*, 360.2174).

N-*tert*-Butoxycarbonyl-*N*-isopropyl-*N*-[2-oxo-3-(1-naphthyloxy)propyl] amine 23

N-*tert*-Butoxycarbonyl-*N*-isopropyl-*N*-[2-hydroxy-3-(1-naphthyloxy)propyl]amine **22** (1.40 g, 3.89 mmol) was added to a solution of pyridinium dichromate (5.13 g, 13.63 mmol) in anhydrous *N*,*N*-dimethylformamide (30 mL). The reaction mixture was stirred overnight, then worked up with brine (40 mL). The compound was extracted with diethyl ether (3 × 40 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give the crude compound which was purified by flash chromatography eluting with 10% ethyl acetate–hexane to give *N*-*tert*-butoxycarbonyl-*N*-isopropyl-*N*-[2-oxo-3-(1-naphthyloxy)propyl]amine **23** (0.95 g, 68.5%); ν_{max}(neat)/cm^{-1} 3054, 2976, 2930, 1742, 1699, 1695, 1651, 1597, 1581, 1509, 1464, 1398, 1365, 1270, 1243, 1214, 1165, 1105, 1077, 1021, 902, 875, 792, 771; δ_H(300 MHz, $CDCl_3$) 1.06, 1.09 (6 H, 2 × dd, ratio 60 : 40, *J* 6.8, 6.9, CH(CH_3)$_2$), 1.41, 1.49 (9 H, 2 × s, ratio 60 : 40, C(CH_3)$_3$), 4.21, 4.25 (2 H, 2 × s, ratio 60 : 40, CH_2),

4.44–4.65 (1 H, m, C*H*(CH_3)$_2$), 4.80, 4.88 (2 H, 2 × s, ratio 60 : 40, CH_2), 6.71–6.75 (1 H, m, Ar-H), 7.34–7.56 (4 H, m, Ar-H), 7.79–7.87 (1 H, m, Ar-H), 8.30–8.33 (1 H, m, Ar-H); δ_C(75.5 MHz, $CDCl_3$) 20.88, 21.30 (CH(*C*H_3)$_2$), 28.69, 28.84 (C(*C*H_3)$_3$), 46.44 (*C*H), 49.13 (*C*H_2), 72.67 (*C*H_2), 80.54 (*C*(CH_3)$_3$), 105.25, 121.80, 122.10, 126.16, 127.06, 128.08, 135.03 (Ar-*ipso*); *m*/*z* (FAB) 357 ([M]$^+$, 64%), 339 (16), 313 (18), 302 (98), 289 (14), 258 (61), 158 (59), 154 (100), 136 (95), 116 (58), 107 (65), 95 (79) (Found: [M]$^+$, 357. $C_{21}H_{27}NO_4$ requires *m*/*z*, 357).

(*R*)-(−)-*N*-*tert*-Butoxycarbonyl-*N*-isopropyl-*N*-[2-hydroxy-3-(1-naphthyloxy)propyl]amine 22

A mixture of (*p*-cymene)ruthenium(II) chloride dimer (0.17 mg, 0.0028 mmol) and (1*R*,2*R*)-TsDPEN **2** (0.21 mg, 0.0021 mmol) in a 5 : 2 formic acid–triethylamine mixture (2.5 mL) was stirred at 28 °C for 15 min. *N*-Isopropyl-*N*-[2-oxo-3-(1-naphthyloxy)-propyl]amine (0.37 g, 1.12 mmol) was added the solution was stirred at 28 °C for 24 hours. Then the mixture was filtered through silica and washed with ethyl acetate (60 ml). The solvent was evaporated under reduced pressure to give the crude compound, which was purified by flash chromatography (20% v/v ethyl acetate–petroleum ether 40 : 60) to give *R*-(−)-**22** as a colourless liquid (0.36 g, 98.4%); $[\alpha]_D^{20}$ −2.92 (*c* = 0.96, ethanol); ν_{max}(neat)/cm^{-1} 3418, 3053, 2974, 2931, 1738, 1687, 1596, 1581, 1509, 1403, 1366, 1269, 1164, 1103, 1069, 1020, 1001, 899, 861, 792, 771, 736; δ_H(300 MHz, $CDCl_3$) 1.15 (3 H, d, *J* 6.6, CH(CH_3)CH_3), 1.24 (3 H, d, *J* 6.8, CH(CH_3)CH_3), 1.51 (9 H, s, C(CH_3)$_3$), 3.52 (2 H, d, *J* 4.5, CH_2-N(tBoc)), 4.04–4.11 (1 H, m, C*H*(CH_3)$_2$), 4.17–4.25 (3 H, m, CH_2C*H*(OH)), 5.17 (1 H, br s, O*H*), 6.85 (1 H, d, *J* 7.4, Ar-H), 7.34–7.52 (4 H, m, Ar-H), 7.77–7.84 (1 H, m, Ar-H), 8.19–8.25 (1 H, m, Ar-H); δ_C(75.5 MHz, $CDCl_3$) 20.88 (CH(*C*H_3)CH_3), 21.39 (C(CH_3)*C*H_3), 28.86 (C(*C*H_3)$_3$), 49.08 (*C*H), 66.27 (*C*H_2), 70.21 (*C*H_2), 72.90 (*C*H), 81.17 (*C*(CH_3)$_3$), 105.15, 120.99, 122.04, 125.64, 125.81, 126.30, 126.80, 127.99, 134.89 (Ar-*ipso*), 154.53 (C=O); *m*/*z* (CI) 360 ([M + H]$^+$, 13%), 304 (21), 260 (36), 160 (98), 136 (19), 133 (100) (Found: [M + H]$^+$, 360.2177. $C_{21}H_{29}NO_4$ requires *m*/*z*, 360.2175). The reduction using (1*S*,2*R*)-**1**–propan-2-ol was carried out using identical conditions to those reported.[4b] The product, *R*-(−)-**22** was formed in 99% yield and 64% ee as determined by chiral HPLC analysis.

(*R*)-(+)-*N*-Isopropyl-*N*-[2-hydroxy-3-(1-naphthyloxy)propyl]-amine 24

To a solution of (*R*)-*N*-*tert*-butoxycarbonyl-*N*-isopropyl-*N*-[2-hydroxy-3-(1-naphthyloxy)propyl]amine *R*-(−)-**22** (0.32 g, 0.90 mmol) in dichloromethane (2 mL) TFA (2 mL) was added slowly. After 2 hours the solvent was removed and the resulting product was dissolved in ethyl acetate and NaOH solution 0.2 M was added until the pH = 7. The product was then extracted with ethyl acetate and the combined organic layers were dried over magnesium sulfate, filtered and the solvent removed *in vacuo*. Recrystallisation (ethyl acetate–petroleum ether 40 : 60) gave (*R*)-*N*-isopropyl-*N*-[2-hydroxy-3-(1-naphthyloxy)-propyl]amine *R*-(+)-**24** as a light yellow solid (0.20 g, 84.5% yield). The product was determined to be of 83.0% ee by HPLC analysis (Chiral OD, hexane–ethanol–diethylamine = 95 : 5 : 0.1 (0.5 mL min^{-1}), *R* isomer 32.91 min, *S* isomer 54.76 min), mp 88–89 °C; $[\alpha]_D^{20}$ +5.1 (*c* = 1.6, ethanol); ν_{max}($CDCl_3$)/cm^{-1} 3429, 2253, 1655, 1581, 1461, 1396, 1268, 1103, 908, 734, 650; δ_H(300 MHz, $CDCl_3$) 1.11 (6 H, d, *J* 6.4, CH(CH_3)$_2$), 2.14 (2 H, br s, O*H*, N*H*), 2.81–2.91 (2 H, m, CH_2NH), 2.98–3.04 (1 H, m, C*H*(CH_3)$_2$), 4.11–4.21 (3 H, m, CH_2C*H*(OH)), 6.83 (1 H, dd, *J* 0.9, 7.5, Ar-H), 7.34–7.53 (4 H, m, Ar-H), 7.78–7.83 (1 H, m, Ar-H), 8.21–8.28 (1 H, m, Ar-H); δ_C(75.5 MHz, $CDCl_3$) 23.45 (CH(*C*H_3)CH_3), 23.59 (C(CH_3)*C*H_3), 49.36 (*C*H), 49.83 (*C*H_2), 69.81 (*C*H), 71.04 (*C*H_2), 80.05 (*C*(CH_3)$_3$), 105.27, 121.01, 122.21, 125.65, 126.23, 126.84, 127.93 (Ar-*ipso*); *m*/*z* (CI) 260 ([M + H]$^+$, 77%), 242 (7), 145 (34), 128 (6), 116 (74), 100 (100), 98 (28), 84 (13), 72 (31), 58 (30) (Found: [M + H]$^+$, 260.1650. $C_{16}H_{21}NO_2$ requires *m*/*z*, 260.1650). The compound from reduction of **23** using Ru(II)–aminoindanol **1** was deprotected in an identical manner to give *R*-(+)-**24** in 93% yield and 64% ee.

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