Asymmetric aminohydroxylation of substituted styrenes: applications in the synthesis of enantiomerically enriched arylglycinols and a diamine

Peter O'Brien,*[,a] Simon A. Osborne[b] and Daniel D. Parker[a]

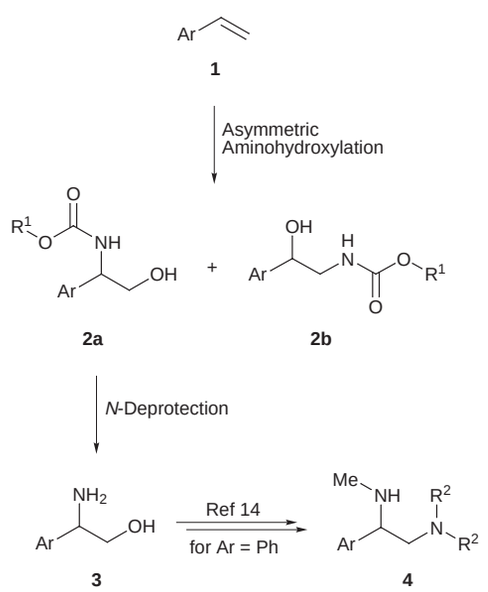
[a] *Department of Chemistry, University of York, Heslington, York, UK YO10 5DD*
[b] *Parke-Davis Neuroscience Research Centre, Forvie Site, Robinson Way, Cambridge, UK CB2 2QB*

The catalytic asymmetric aminohydroxylation of a variety of styrene derivatives and vinyl aromatics using osmium tetroxide in conjunction with alkaloid-derived ligands [*e.g.* $(DHQ)_2PHAL$ or $(DHQD)_2$-PHAL] and haloamine salts of alkyl carbamates (*e.g.* ethyl carbamate or *tert*-butyl carbamate) has been investigated. By observing the effect of different aromatic substituents and alkyl carbamates on the regioselectivity, yield and enantioselectivity of the aminohydroxylation reactions, a number of conclusions have been reached: (i) the 1-aryl-2-hydroxyethylamine regioisomers were obtained as the major products in reasonable yield and high (≥87%) enantiomeric excess; (ii) *tert*-butyl carbamate was superior to ethyl carbamate in terms of yield, enantioselectivity and ease of removal of the *N*-protecting group; (iii) high (≥96%) enantioselectivity was observed with a 4-methoxy-substituted styrene whereas *ortho*-substituted styrenes gave lower enantioselectivities; (iv) chiral ligands $(DHQ)_2PHAL$ and $(DHQD)_2PHAL$ gave essentially equal and opposite senses and degrees of asymmetric induction; (v) regioselectivity was ligand dependent with better regioselectivity (and therefore higher isolated yields) obtained with $(DHQ)_2PHAL$ than with $(DHQD)_2PHAL$. The products of the aminohydroxylation reactions were used to prepare enantiomerically enriched arylglycinols and a chiral diamine.

Introduction

Over the last three years, the catalytic and asymmetric conversion of alkenes into enantiomerically enriched *N*-protected amino alcohols, so-called asymmetric aminohydroxylation (AA), has become a synthetically useful process.[1] Pioneering work by Sharpless and his group[2–4] has shown that the combination of osmium tetroxide with alkaloid-derived ligands [*e.g.* $(DHQ)_2PHAL$ †] and haloamine salts of sulfonamides,[2] alkyl carbamates[3] or amides[4] is suitable for highly enantioselective aminohydroxylation. Sharpless *et al.* have used such transformations to complete syntheses of α-amino acids[5] and the Taxol™ side chain.[4,6] More recently, other research groups have exploited asymmetric aminohydroxylation in the synthesis of amino cyclitols,[7] cyclohexylnorstatine,[8] 2,3-diaminobutanoic acids,[9] α-amino ketones,[10] β-amino-α-hydroxyphosphonic acid derivatives[11] and, in our laboratory, a chiral diamine.[12]

We became interested in asymmetric aminohydroxylation since the amino alcohol products obtained from styrene derivatives are suitable for elaboration into novel chiral diamines using methodology that we had already developed.[13,14] Our proposed route to diamines **4** is summarised in Scheme 1. Asymmetric aminohydroxylation of styrenes **1** could produce two regioisomeric amino alcohols **2a** and **2b**. However, literature precedent[3,5] suggested that amino alcohols **2a** would be generated as the major products and with higher enantiomeric excesses than their regioisomeric counterparts. Thus, we anticipated isolating amino alcohols **2a** and then deprotecting the carbamate substituent (R^1O_2CN) to produce arylglycinols **3**. In the case of phenylglycinol (**3**; Ar = Ph), we had already shown that it could be converted into different diamines **4** (Ar = Ph)



Scheme 1

using a three-step synthesis.[13,14] An alternative and fairly long route to diamines **4** (Ar ≠ Ph) using Sharpless asymmetric dihydroxylation[15] has already been reported.[16]

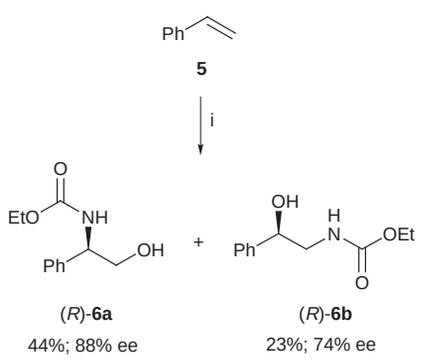
In this paper, we report the full details[12] of a study of the asymmetric aminohydroxylation of substituted styrenes and vinyl aromatic compounds. In particular, for the transformation of alkenes **1** into amino alcohols **2a** and **2b** (see Scheme 1), we describe the effect of different aromatic substituents (Ar) and alkyl carbamates (R^1O_2CN) on the regioselectivity, yield and enantioselectivity of the aminohydroxylation reactions. From a synthetic viewpoint, the potential usefulness of this chemistry is illustrated with the preparation of a number of arylglycinols **3** and one chiral diamine **4**.

† $(DHQ)_2PHAL$ is an alkaloid-derived and commercially available chiral ligand usually used for asymmetric dihydroxylation; the ligand is composed of two hydroquinine portions linked together through a phthalazine (PHAL) "spacer".

Results and discussion

Development of aminohydroxylation methodology

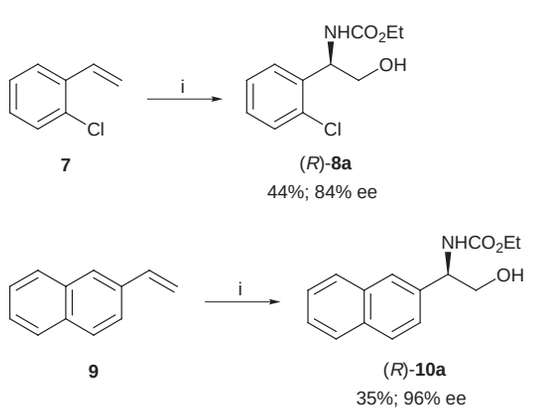
When we started the present study, there were only two reported examples of the asymmetric aminohydroxylation of styrene derivatives.[3] Both examples involved the use of a sodium *N*-chlorocarbamate salt (generated *in situ* from a combination of benzyl carbamate, sodium hydroxide and *tert*-butyl hypochlorite) as Sharpless *et al.* had noted that methods based on sulfonamides failed completely with styrenes.[3,5] Our initial attempts at aminohydroxylations using benzyl carbamate proved fruitless: we were unable to generate any amino alcohol products whatsoever. However, we had more success with ethyl carbamate (urethane) and following the recommended recipe,[3] aminohydroxylation of styrene **5** produced amino alcohol products **6** (Scheme 2).



Scheme 2 *Reagents and conditions*: i, 3.1 equiv. EtO_2CNH_2, 3.05 equiv. NaOH, 3.05 equiv. ^{t}BuOCl, 4 mol% $K_2OsO_2(OH)_4$, 5 mol% $(DHQD)_2$-PHAL, 1:1 ^{n}PrOH–water, 0 °C

After careful chromatography, the two regioisomers were separated from each other and from residual ethyl carbamate: amino alcohol (*R*)-**6a** of 88% ee was obtained in 44% yield and amino alcohol **6b** of 74% ee was obtained in 23% yield. The known[17,18] regioisomers were identified by ^{1}H and ^{13}C NMR spectroscopy and the identity and stereochemistry of **6a** was unequivocally established by independent synthesis from commercially available (*R*)-phenylglycinol; the configuration of **6b** was assigned as (*R*) by comparison of the optical rotation with known (*R*)-**6b** of 63.5% ee.[18]

Two further aminohydroxylation reactions were then carried out and we chose to isolate only the major regioisomer. In fact, it proved difficult to isolate the minor regioisomer separate from the excess ethyl carbamate. The results are summarised in Scheme 3 and the stereochemistry of amino alcohols (*R*)-**8a** and (*R*)-**10a** was assigned by analogy with the result obtained with styrene **5**.



Scheme 3 *Reagents and conditions*: i, 3.1 equiv. EtO_2CNH_2, 3.05 equiv. NaOH 3.05 equiv. ^{t}BuOCl, 4 mol% $K_2OsO_2(OH)_4$, 5 mol%, $(DHQD)_2$-PHAL 1:1 ^{n}PrOH–water, 0 °C

The ethyl carbamate results shown in Schemes 2 and 3 demonstrated that regioisomers **6a**, **8a** and **10a** can be produced in high enantiomeric excess (84–96%). Unfortunately, these amino alcohols were isolated in only moderate yields (35–44%) and as ethyl carbamate deprotection can be problematic,[19] it was possible that they would be of no use to us for diamine synthesis. Thus, we switched our attention to the use of *tert*-butyl carbamate as this would solve our deprotection issue.

For the reactions with *tert*-butyl carbamate, a modified set of reaction conditions {6 mol% of the chiral ligand [$(DHQ)_2$-PHAL or $(DHQD)_2$PHAL] and 2:1 *n*-propanol–water as the solvent} was employed. These conditions were suggested to us by Sharpless[20] as significant levels of *dihydroxylation* had been observed when the usual solvent mixture of 1:1 *n*-propanol–water was used. A wider range of alkene substrates was studied with the *tert*-butyl carbamate reactions and our results are summarised in Table 1. The regioselectivity of all of the reactions was measured from the ^{1}H NMR spectrum of the crude product mixtures; regioisomers **a** were then isolated pure by chromatography and their enantiomeric excesses were determined by chiral HPLC. In general, regioisomers **b** co-eluted with excess *tert*-butyl carbamate and only once did we isolate a pure sample of regioisomer **b** [alkene **11** with $(DHQ)_2$PHAL gave a 25% yield of amino alcohol **16b** of 36% ee, entry 6]. Amino alcohol (*S*)-**13a** (entry 1) is a well documented[21,22] compound and its stereochemistry was corroborated by conversion (TFA deprotection, *vide infra*) into known[23] (*S*)-phenylglycinol; amino alcohol (*R*)-**17a** (entry 9) has previously been synthesised from commercially available (*R*)-4-hydroxyphenylglycine;[24] the stereochemistries of amino alcohols **14a**, **15a** and **16a** reported in Table 1 were assigned by analogy with these results.‡

The results presented in Table 1 illustrate that, as with ethyl carbamate, it is possible to generate amino alcohols **13a**–**17a** in yields which are moderate (34%, entry 7) to good (74%, entry 8) and with enantioselectivities which are high (≥87% ee). Amino alcohols (*S*)-**15a** and (*S*)-**17a** are produced as essentially single enantiomers (98% ee in each case) and the yield of (*S*)-**17a** (74%) is the highest isolated yield that we have obtained from an aminohydroxylation reaction. The main limiting factor with the yield of amino alcohols **13a**–**17a** is in fact the regioselectivity of the reactions which vary from approximately 50:50 to 85:15; careful (and therefore time-consuming) chromatogaphy is also required to isolate pure samples of **13a**–**17a**.

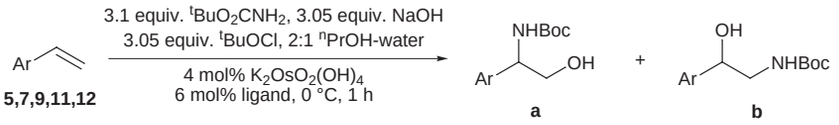
The effect of substrate type and chiral ligand on the enantioselectivity and regioselectivity of the reactions is worthy of further comment.

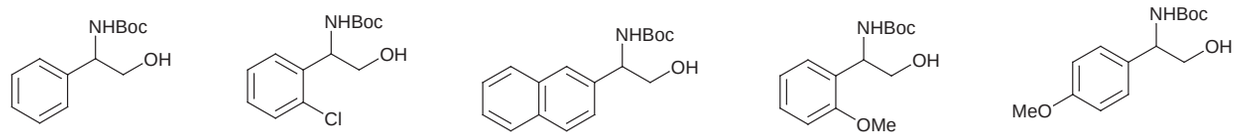
(i) *Enantioselectivity*: the presence of *ortho* substitutents (MeO or Cl) on the aromatic ring is detrimental to the enantioselectivity (compare entries 3, 6 and 7 with the other entries in Table 1); the enantioselectivity is however hardly affected by the nature of the chiral ligand—the "pseudoenantiomeric" ligands $(DHQ)_2$PHAL and $(DHQD)_2$PHAL give essentially equal and opposite senses of asymmetric induction (compare entry 6 with 7 and entry 8 with 9).

(ii) *Regioselectivity*: the regioselectivity observed for these aminohydroxylation reactions depends on the nature of the chiral ligand—*lower levels of regioselectivity are observed with* $(DHQD)_2PHAL$ *when compared with* $(DHQ)_2PHAL$ *in all cases* (even though the enantioselectivities are essentially the same). This effect actually means that aminohydroxylation of styrene **11** with $(DHQD)_2$PHAL generates amino alcohol **16b** as the major product (entry 7). The lower regioselectivities observed with $(DHQD)_2$PHAL manifest themselves in lower isolated yields of regioisomers **16a** and **17a** (compare entry 6 with 7 and

‡ Sharpless *et al.* have prepared amino alcohol **15a** using asymmetric aminohydroxylation with $(DHQ)_2$PHAL and also assigned it as having (*S*) stereochemistry (entry 5).[5]

Table 1 Asymmetric aminohydroxylation of styrenes using *tert*-butyl carbamate





13a 14a 15a 16a 17a

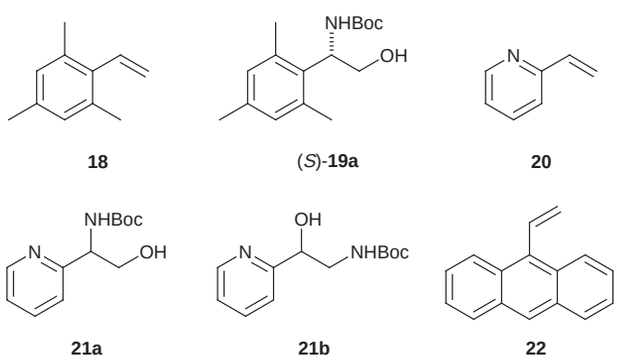
Entry	Ar	Alkene	Ligand	**a**:**b**[a]	Isolated product[b]	Yield of **a** (%)[c]	Ee of **a** (%)[d]
1	Ph	**5**	$(DHQ)_2PHAL$	80:20	(*S*)-**13a**	58	94
2	Ph	**5**	$(DHQD)_2PHAL$	64:36	—	—	—
3	2-ClC_6H_4	**7**	$(DHQ)_2PHAL$	70:30	(*S*)-**14a**	41	92
4	2-ClC_6H_4	**7**	$(DHQD)_2PHAL$	64:36	—	—	—
5	2-Naphthyl	**9**	$(DHQ)_2PHAL$	83:17	(*S*)-**15a**	48	98
6	2-$MeOC_6H_4$	**11**	$(DHQ)_2PHAL$	55:45	(*S*)-**16a**	43[e]	87
7	2-$MeOC_6H_4$	**11**	$(DHQD)_2PHAL$	45:55	(*R*)-**16a**	34	88
8	4-$MeOC_6H_4$	**12**	$(DHQ)_2PHAL$	85:15	(*S*)-**17a**	74	98
9	4-$MeOC_6H_4$	**12**	$(DHQD)_2PHAL$	68:32	(*R*)-**17a**	65	96

[a] Ratio of regioisomers **a** and **b** determined from the ^1H NMR spectrum of the crude product mixture. [b] Regioisomer **a** was isolated by flash column chromatography. [c] Isolated yield of regioisomer **a** after purification by flash column chromatography. [d] Enantiomeric excess of pure regioisomer **a** as determined by chiral HPLC (see Experimental section). [e] 25% yield of amino alcohol (*S*)-**16b** of 36% ee was also isolated from this reaction.

entry 8 with 9) and in lower isolated yields of the (*R*)-enantiomers. Given that $(DHQD)_2PHAL$ and $(DHQ)_2PHAL$ are in fact diastereoisomers ("pseudoenantiomeric" is used to describe their complementary sense of asymmetric induction in dihydroxylation and aminohydroxylation reactions), it is possible that they could exert different effects on the regioselectivity§ of the reactions. Indeed, with other types of alkenes, Sharpless *et al.* have reported really quite dramatic effects of ligand type on regioselectivity levels;[25] the most significant changes are normally observed when different "spacers" are used to link the two alkaloid portions of the ligand.[26] There are no obvious trends in the effect of alkene structure on the observed regioselectivities: a 4-methoxy substituent (alkene **12**, entry 8) gives the highest regioselectivity and a 2-methoxy substituent (alkene **11**, entry 5) gives the lowest regioselectivity.

We have also investigated the *tert*-butyl carbamate-mediated aminohydroxylation of the more elaborate alkene substrates 2,4,6-trimethylstyrene **18**, 2-vinylpyridine **20** and 9-vinylanthracene **22** (Fig. 1). The reaction with 2,4,6-trimethylstyrene **18** was sluggish and after 7.5 hours, only a 21% yield of amino alcohol **19a** was obtained. It was generated with a moderate 56% ee and its stereochemistry was tentatively assigned as (*S*) by analogy with the results in Table 1. Clearly, the presence of two *ortho* substitutents has a detrimental effect on yield and enantioselectivity. A similarly sluggish reaction was encountered with 2-vinylpyridine **20** (which may be a result of the pyridine nitrogen coordinating with the osmium and interfering with the catalytic cycle) and so we left the reaction overnight at room temperature. Even so, we were only able to isolate a 33% yield of an 80:20 mixture of regioisomeric amino alcohols **21a** and **21b** whose enantiomeric excesses were not determined. Aminohydroxylation of 9-vinylanthracene **22** generated an intractable mixture of products which was not purified.

§ Of course, with asymmetric dihydroxylation, there is no issue of regioselectivity. To date, there have been no other reports on the variation of regioselection with type of ligand [$(DHQD)_2PHAL$ *versus* $(DHQ)_2PHAL$].



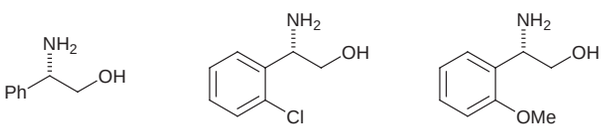
18 (*S*)-19a 20 21a 21b 22

Fig. 1

Use of aminohydroxylation in synthesis

Six of the *N*-Boc protected amino alcohol products from Table 1 have been converted into arylglycinols. The deprotection reactions were carried out using TFA in dichloromethane and the products were isolated in good to excellent yields (81–100%) after basic work up. The enantiomeric excesses of the arylglycinols obtained in this way have not been verified but racemisation during deprotection is unlikely. Full details are shown in Table 2; arylglycinols (*S*)-**23**,[23] *rac*-**25**[27] and (*S*)-**26**[28] (Fig. 2) are known compounds. Thus, aminohydroxylation of styrene derivatives using *tert*-butyl carbamate followed by simple Boc deprotection represents a convenient two step synthesis of enantiomerically enriched arylglycinols.

Finally, to demonstrate that asymmetric aminohydroxylation could be used in diamine synthesis, we have converted one of the arylglycinols into a chiral diamine. The full synthetic sequence is depicted in Scheme 4.



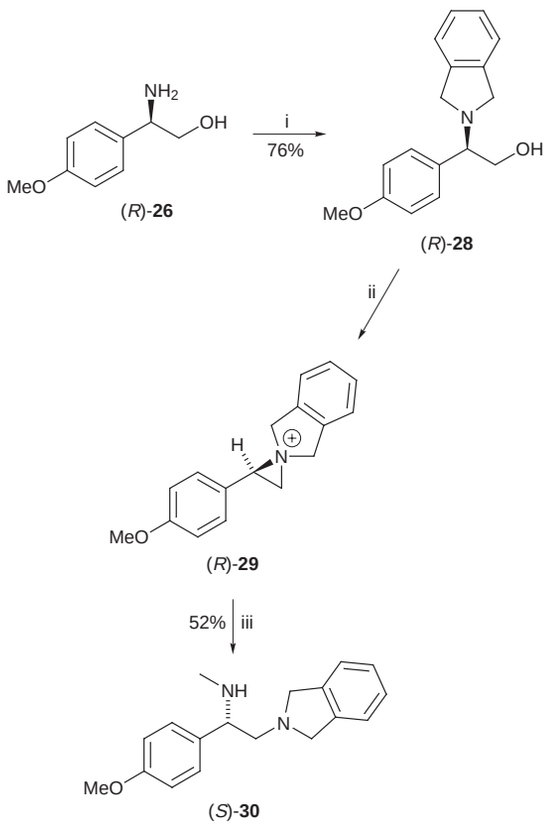
(*S*)-23 (*S*)-24 (*S*)-25

Fig. 2

Table 2 *N*-Boc deprotonation—synthesis of arylglycinols

Entry	SM[a]	Arylglycinol[b]	Yield (%)
1	(*S*)-**13a**	(*S*)-**23**	100
2	(*S*)-**14a**	(*S*)-**24**	98
3	(*S*)-**16a**	(*S*)-**25**	83
4	(*R*)-**16a**	(*R*)-**25**	94
5	(*S*)-**17a**	(*S*)-**26**	81
6	(*R*)-**17a**	(*R*)-**26**	97

[a] Starting material. [b] *Conditions*: TFA, CH_2Cl_2, rt, 1 h.



Scheme 4 *Reagents and conditions*: i, 2 equiv. Na_2CO_3, 1 equiv. α,α′-dibromo-*o*-xylene **27**, 0.1 equiv. tetra-*n*-butylammonium iodide, THF, reflux, 3.5 h; ii, 3 equiv. Et_3N, 1.2 equiv. MsCl, Et_2O, 0 °C, 30 min; iii, 2 equiv. Et_3N, $MeNH_2$, water, rt, 16 h

Standard *N*-Boc deprotection of amino alcohol (*R*)-**17a** of 96% ee afforded arylglycinol (*R*)-**26** in 97% yield (entry 6, Table 2). Then, *N*,*N*-dialkylation using dibromide **27** in refluxing THF generated amino alcohol (*R*)-**28** in 76% yield after chromatography according to our published procedure.[14] Amino alcohol (*R*)-**28** was not characterised but instead treated with triethylamine and mesyl chloride to generate aziridinium ion (*R*)-**29** *in situ*. As expected,[14] reaction of this aziridinium ion with aqueous methylamine produced diamine (*S*)-**30** as a single regioisomer in 52% yield [40% yield from arylglycinol (*R*)-**26**].

Experimental

General

General methods have been described previously.[14] CH_2Cl_2 was dried over calcium hydride and distilled before use. Petrol refers to light petroleum (boiling in the range 40–60 °C and redistilled in Winchester quantities before use). Flash column chromatography was carried out using ICN Biomedicals Gmbh silica (60 Å) according to the method of Still *et al.*[29] Analytical HPLC was performed on Chiralpak AD, Chiralcel OD-H, Chiralcel OJ or Regis (*S*,*S*)-Whelk-O 1 columns and the compounds (detected at 215 nm) were eluted using solutions of 5–20% ^{i}PrOH or EtOH in heptane as the mobile phase at a flow rate of 1.0 mL min^{-1}. Optical rotations were recorded on a Jasco DIP-370 polarimeter (using the sodium D line; 589 nm) at 20 °C and $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}. Microanalyses were carried out at the University of East Anglia. Styrene **5**, 2-chlorostyrene **7**, 2-vinylnaphthalene **9**, 4-methoxystyrene **12**, 2,4,6-trimethylstyrene **18**, 2-vinylpyridine **20** and 9-vinylanthracene **22** are commercially available and were used as supplied. 2-Methoxystyrene **11** was prepared by Wittig homologation of commercially available *o*-anisaldehyde.

General methods

Method A: asymmetric aminohydroxylation using ethyl carbamate

A solution of ethyl carbamate (urethane) (276 mg, 3.1 mmol) in ^{n}PrOH (4 cm^3) was sequentially treated with a freshly prepared solution of sodium hydroxide (122 mg, 3.05 mmol) in water (7.5 cm^3), *tert*-butyl hypochlorite (0.35 cm^3, 3.05 mmol) and a solution of the ligand (40 mg, 0.05 mmol) in ^{n}PrOH (3.5 cm^3). Then, $K_2OsO_2(OH)_4$ (15 mg, 0.04 mmol) was added and after a further 10 min, the alkene (1.0 mmol) was added whereupon the solution turned from pale yellow to dark green. The resulting solution was stirred at room temperature until there was no starting material present by TLC analysis. During this period, the green solution became pale yellow. EtOAc (7 cm^3) was added and the solution was stirred for 10 min. Then, the two layers were separated and the aqueous layer was extracted with EtOAc (3 × 5 cm^3). The combined organic extracts were washed with water (5 cm^3) and then brine (5 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which was purified by flash column chromatography on silica.

Method B: asymmetric aminohydroxylation using *tert*-butyl carbamate

A solution of *tert*-butyl carbamate (545 mg, 4.65 mmol) in ^{n}PrOH (6 cm^3) was sequentially treated with a freshly prepared solution of sodium hydroxide (183 mg, 4.6 mmol) in water (12.2 cm^3) and *tert*-butylhypochlorite (0.53 cm^3, 4.6 mmol). After stirring for 5 min, the solution was cooled to 0 °C and a solution of the ligand (71 mg, 0.09 mmol) in *n*-propanol (6 cm^3) was added. Then, a solution of the alkene (1.5 mmol) in *n*-propanol (12.2 cm^3) was added followed by addition of $K_2OsO_2(OH)_4$ (22.5 mg, 0.06 mmol). After 1 h at 0 °C, the green solution became pale yellow and there was no starting material present by TLC analysis. Saturated aqueous sodium sulfite (10 cm^3) was added and the solution was stirred for 15 min. Then, the two layers were separated and the aqueous layer was extracted with EtOAc (3 × 15 cm^3). The combined organic extracts were washed with brine (20 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which was purified by flash column chromatography on silica.

Method C: Boc deprotection

Trifluoroacetic acid (0.75 cm^3) was added dropwise to a stirred solution of the *N*-Boc protected amino alcohol (0.2 mmol) in CH_2Cl_2 (3 cm^3) at room temperature. After 1 h, the mixture was evaporated under reduced pressure. Then, the residue was dissolved in 20% aqueous sodium hydroxide and extracted with CH_2Cl_2 (6 × 5 cm^3). The combined organic extracts were washed with water (5 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to give the arylglycinol product.

***tert*-Butyl hypochlorite**

Following the literature procedure,[30] a mixture of *tert*-butyl alcohol (37 cm^3, 0.39 mol) and glacial acetic acid (24.5 cm^3, 0.43 mol) was added in one portion to a stirred solution of sodium hypochlorite (500 cm^3, Aldrich ref. 23,930-5) at 0 °C in a 1 L

round bottomed flask covered with foil. The resulting solution was vigorously stirred for 5 min and then the two layers were separated. The yellow organic layer was washed with 10% aqueous sodium carbonate (50 cm^3) and then with water (50 cm^3), dried ($CaCl_2$) and filtered. The resulting yellow liquid (*tert*-butyl hypochlorite) was used without further purification and could be stored in a foil-covered vial in the freezer for up to 3 weeks without any noticeable change in performance.

(1*R*)-*N*-Ethoxycarbonyl-1-phenyl-2-hydroxyethylamine 6a and *N*-ethoxycarbonyl-2-phenyl-2-hydroxyethylamine 6b

Using general procedure A with $(DHQD)_2PHAL$ as the ligand, styrene **5** (104 mg, 1.0 mmol) gave, after 40 min, a crude product which was purified by flash column chromatography on silica with 2:1 petrol–EtOAc as eluent to give known[17,18] amino alcohol (*R*)-**6a** (92 mg, 44%; 88% ee) as a white solid, mp 70–74 °C (from 2:1 petrol–EtOAc) [lit.,[17] 91 °C (decomp.)]; $[\alpha]_D$ −53.8 (*c* 1.0 in EtOH); R_F(1:1 petrol–EtOAc) 0.2 [Found: C, 63.4; H, 7.3; N, 6.3%; $(M + H)^+$, 210.1132. $C_{11}H_{15}NO_3$ requires C, 63.1; H, 7.2; N, 6.7%; *M* + H, 210.1130]; $\nu_{max}(CHCl_3)/cm^{-1}$ 3601 (OH), 3439 (NH), 1711 (C=O) and 1509 (Ph); δ_H(270 MHz, $CDCl_3$) 7.30–7.14 (5 H, m, Ph), 5.49 (1 H, br s, NH), 4.73 (1 H, br s, PhCHN), 4.03 (2 H, q, *J* 7.0, CH_2Me), 3.75–3.67 (2 H, br m, CH_2OH), 2.50 (1 H, br s, OH) and 1.19 (3 H, br m, Me); δ_C(67.5 MHz, $CDCl_3$) 157.3 (C=O), 139.7 (*ipso*-Ph), 129.2 (Ph), 128.2 (Ph), 127.0 (Ph), 66.8 (CH_2OH), 61.6 (CH_2Me), 57.7 (PhCHN) and 14.9 (Me); *m*/*z* (CI; NH_3) 227 [5%, $(M + NH_4)^+$], 210 [100, $(M + H)^+$], 178 (40, M − CH_2OH) and 106 (25); HPLC: Chiralcel OJ, 15% EtOH in heptane, 1.0 mL min^{-1}, 215 nm, 19.6 min [(*R*)-**6a**], 12.0 min [(*S*)-**6a**].

Also obtained from the chromatography was known[18] amino alcohol (*R*)-**6b** (49 mg, 23%; 74% ee) as a white solid, mp 60–63 °C (from 2:1 petrol–EtOAc) (lit.,[18] 92–94 °C); $[\alpha]_D$ −3.7 (*c* 1.0 in EtOH) {lit.,[18] $[\alpha]_D$ −31.8 (*c* 0.48 in $CHCl_3$) for (*R*)-**6b** of 63.5% ee}; R_F(1:1 petrol–EtOAc) 0.4; $\nu_{max}(CHCl_3)/cm^{-1}$ 3611 (OH), 3453 (NH), 1709 (C=O) and 1517 (Ph); δ_H(270 MHz, $CDCl_3$) 7.50–7.31 (5 H, m, Ph), 5.29 (1 H, br s, NH), 4.87 (1 H, br s, PhC*H*OH), 4.31–4.12 (2 H, m, CH_2Me), 3.70–3.56 (1 H, br m, C$H_A$$H_B$N), 3.40–3.25 (1 H, br m, C$H_A$$H_B$N), 3.11 (1 H, br s, OH) and 1.28 (3 H, t, *J* 7.0, Me); δ_C(67.5 MHz, $CDCl_3$) 157.4 (C=O), 141.6 (*ipso*-Ph), 128.5 (Ph), 127.8 (Ph), 125.8 (Ph), 73.5 (PhCHOH), 61.1 (CH_2Me), 48.5 (CH_2N) and 14.5 (Me); *m*/*z* 227 [5%, $(M + NH_4)^+$], 210 [50, $(M + H)^+$] and 192 (100, M − OH) [Found: $(M + H)^+$, 210.1136. $C_{11}H_{15}NO_3$ requires *M* + H, 210.1130]; HPLC: Chiralcel OD-H, 5% ^{i}PrOH in heptane, 1.0 mL min^{-1}, 215 nm, 16.6 min [(*R*)-**6b**], 21.7 min [(*S*)-**6b**].

(1*R*)-*N*-Ethoxycarbonyl-1-(2-chlorophenyl)-2-hydroxyethylamine 8a

Using general procedure A with $(DHQD)_2PHAL$ as the ligand, 2-chlorostyrene **7** (139 mg, 1.0 mmol) gave, after 1.5 h, a crude product which was purified by flash column chromatography on silica with 2:1 petrol–EtOAc as eluent to give amino alcohol (*R*)-**8a** (101 mg, 44%; 84% ee) as a white solid, mp 113–116 °C (from 2:1 petrol–EtOAc); $[\alpha]_D$ −18.0 (*c* 1.0 in EtOH); R_F(1:1 petrol–EtOAc) 0.3 [Found: C, 54.2; H, 5.8; N, 5.4%; $(M + H)^+$, 244.0737. $C_{11}H_{14}NO_3Cl$ requires C, 54.2; H, 5.8; N, 5.7%; *M* + H, 244.0740]; $\nu_{max}(CHCl_3)/cm^{-1}$ 3608 (OH), 3438 (NH), 1711 (C=O) and 1507.5 (Ar); δ_H(270 MHz, $CDCl_3$) 7.18–7.38 (4 H, m, Ar), 5.73 (1 H, br s, NH), 5.23 (1 H, br s, ArCHN), 4.15–4.07 (2 H, m, CH_2Me), 3.90–3.75 (2 H, br m, CH_2OH), 2.53 (1 H, br s, OH) and 1.23 (3 H, br s, Me); δ_C(67.5 MHz, $CDCl_3$) 156.5 (C=O), 132.7 (*ipso*-C_6H_4Cl), 129.9 (Ar), 128.8 (Ar), 127.9 (Ar), 127.0 (Ar), 64.3 (CH_2OH), 61.2 (CH_2Me), 54.3 (PhCHN) and 14.5 (Me); *m*/*z* (CI; NH_3) 261 [15%, $(M + NH_4)^+$], 244 [100, $(M + H)^+$], 212 (25, M − CH_2OH) and 140 (20); HPLC: Chiralcel OD-H, 10% ^{i}PrOH in heptane, 1.0 mL min^{-1}, 215 nm, 8.9 min [(*R*)-**8a**], 6.4 min [(*S*)-**8a**].

(1*R*)-*N*-Ethoxycarbonyl-1-(2-naphthyl)-2-hydroxyethylamine 10a

Using general procedure A with $(DHQD)_2PHAL$ as the ligand, 2-vinylnaphthalene **9** (154 mg, 1.0 mmol) gave, after 3.5 h, a crude product which was purified by flash column chromatography on silica with 1:1 petrol–EtOAc as eluent to give amino alcohol (*R*)-**10a** (91 mg, 35%; 96% ee) as a white solid, mp 112–114 °C (from 1:1 petrol–EtOAc); $[\alpha]_D$ −86.9 (*c* 1.0 in EtOH); R_F(1:1 petrol–EtOAc) 0.25 [Found: C, 69.4; H, 6.6; N, 5.2%; $(M + H)^+$, 260.1281. $C_{15}H_{17}NO_3$ requires C, 69.5; H, 6.6; N, 5.4%; *M* + H, 260.1273]; $\nu_{max}(CHCl_3)/cm^{-1}$ 3601 (OH), 3438 (NH), 1710.5 (C=O) and 1507 (Ar); δ_H(270 MHz, $CDCl_3$) 7.86–7.74 (4 H, m, Ar), 7.48–7.25 (3 H, m, Ar), 5.64 (1 H, br s, NH), 4.96 (1 H, br s, ArCHN), 4.15–4.07 (2 H, m, CH_2Me), 3.88 (2 H, br s, CH_2OH), 2.55 (1 H, br s, OH) and 1.22 (3 H, br s, Me); δ_C(67.5 MHz, $CDCl_3$) 156.7 (C=O), 136.6 (*ipso*-Ar), 133.2 (*ipso*-Ar), 132.8 (*ipso*-Ar), 128.6 (Ar), 127.85 (Ar), 127.6 (Ar), 126.3 (Ar), 126.0 (Ar), 125.3 (Ar), 124.5 (Ar), 66.3 (CH_2OH), 61.2 (CH_2Me), 57.05 (ArCHN) and 14.5 (Me); *m*/*z* (CI; NH_3) 277 [5%, $(M + NH_4)^+$], 260 [80, $(M + H)^+$], 231 (100, M − C_2H_4) and 214 (60, M − OCH_2Me); HPLC: Chiralpak AD, 20% EtOH in heptane, 1.0 mL min^{-1}, 215 nm, 9.7 min [(*R*)-**10a**], 8.2 min [(*S*)-**10a**].

(1*S*)-*N*-(*tert*-Butoxycarbonyl)-1-phenyl-2-hydroxyethylamine 13a

Using general procedure B with $(DHQ)_2PHAL$ as the ligand, styrene **5** (156 mg, 1.5 mmol) gave a crude product which contained an 80:20 mixture of amino alcohols **13a** and **13b** by ^{1}H NMR spectroscopy. Purification by flash column chromatography on silica with 3:1 petrol–EtOAc as eluent gave known[21] amino alcohol (*S*)-**13a** (206 mg, 58%; 94% ee) as a white solid, mp 133–135 °C (from 3:1 petrol–EtOAc) (lit.,[21] 136–137 °C); $[\alpha]_D$ +50.9 (*c* 1.0 in EtOH) {lit.,[21] $[\alpha]_D$ +40 (*c* 1.6 in $CHCl_3$) for (*S*)-**13a**}; R_F(1:1 petrol–EtOAc) 0.4 [Found: C, 65.9; H, 8.15; N, 5.8%; $(M + H)^+$, 238.1447. $C_{13}H_{19}NO_3$ requires C, 65.8; H, 8.1; N, 5.9%; *M* + H, 238.1443]; $\nu_{max}(CHCl_3)/cm^{-1}$ 3597 (OH), 3441.5 (NH), 1707 (C=O) and 1495 (Ph); δ_H(270 MHz, $CDCl_3$) 7.38–7.26 (5 H, m, Ph), 5.28 (1 H, br s, NH), 4.77 (1 H, br s, PhCHN), 3.83 (2 H, br s, CH_2OH), 2.45 (1 H, br s, OH) and 1.43 (9 H, s, CMe_3); δ_C(67.5 MHz, $CDCl_3$) 156.2 (C=O), 139.6 (*ipso*-Ph), 128.7 (Ph), 127.6 (Ph), 126.6 (Ph), 80.0 (CMe_3), 66.7 (CH_2OH), 56.85 (PhCHN) and 28.3 (CMe_3); *m*/*z* (CI; NH_3) 238 [60%, $(M + H)^+$], 199 (35), 182 (75), 138 (100) and 106 (95); HPLC: Regis (*S*,*S*)-Whelk-O 1, 12% EtOH in heptane, 1.0 mL min^{-1}, 215 nm, 5.9 min [(*S*)-**13a**], 8.1 min [(*R*)-**13a**].

Diagnostic signals for amino alcohol **13b** from the ^{1}H NMR spectrum of the crude mixture: δ_H(270 MHz, $CDCl_3$) 5.67 (1 H, br s, NH) and 4.98 (1 H, br s, PhC*H*OH).

(1*R*)-*N*-(*tert*-Butoxycarbonyl)-1-phenyl-2-hydroxyethylamine 13a

Using general procedure B with $(DHQD)_2PHAL$ as the ligand, styrene **5** (156 mg, 1.5 mmol) gave a crude product which contained a 64:36 mixture of amino alcohols **13a** and **13b** by ^{1}H NMR spectroscopy.

(1*S*)-*N*-(*tert*-Butoxycarbonyl)-1-(2-chlorophenyl)-2-hydroxyethylamine 14a

Using general procedure B with $(DHQ)_2PHAL$ as the ligand, 2-chlorostyrene **7** (208 mg, 1.5 mmol) gave a crude product which contained a 70:30 mixture of amino alcohols **14a** and **14b** by ^{1}H NMR spectroscopy. Purification by flash column chromatography on silica with 3:1 petrol–EtOAc as eluent gave amino alcohol (*S*)-**14a** (168 mg, 41%; 92% ee) as a white solid, mp 190–194 °C (from 3:1 petrol–EtOAc); $[\alpha]_D$ +12.1 (*c* 1.0 in EtOH); R_F(1:1 petrol–EtOAc) 0.45 [Found: C, 57.1; H, 6.8; N, 4.7%; $(M + H)^+$, 272.1055. $C_{13}H_{18}NO_3Cl$ requires C, 57.4; H, 6.7; N, 5.1%; *M* + H, 272.1053]; $\nu_{max}(CHCl_3)/cm^{-1}$ 3610 (OH),

3442 (NH), 1708 (C=O) and 1497 (Ar); δ_H(270 MHz, $CDCl_3$) 7.37–7.23 (4 H, m, Ar), 5.43 (1 H, br s, NH), 5.21 (1 H, br s, ArCHN), 3.89 (2 H, br s, CH_2OH), 1.95 (1 H, br s, OH) and 1.43 (9 H, s, CMe_3); *m/z* (CI; NH_3) 289 [20%, $(M + NH_4)^+$], 272 [55, $(M + H)^+$], 233 (100), 215 (35, $M - C_4H_8$) and 172 (35); HPLC: Chiralpak AD, 10% ^{i}PrOH in heptane, 1.0 mL min^{-1}, 215 nm, 9.8 min [(*S*)-**14a**], 8.8 min [(*R*)-**14a**].

Diagnostic signals for amino alcohol **14b** from the ^{1}H NMR spectrum of the crude mixture: δ_H(270 MHz, $CDCl_3$) 5.73 (1 H, br s, NH) and 5.43 (1 H, br s, ArC*H*OH).

(1*R*)-*N*-(*tert*-Butoxycarbonyl)-1-(2-chlorophenyl)-2-hydroxyethylamine 14a

Using general procedure B with $(DHQD)_2$PHAL as the ligand, 2-chlorostyrene **7** (208 mg, 1.5 mmol) gave a crude product which contained a 64:36 mixture of amino alcohols **14a** and **14b** by ^{1}H NMR spectroscopy.

(1*S*)-*N*-(*tert*-Butoxycarbonyl)-1-(2-naphthyl)-2-hydroxyethylamine 15a

Using general procedure B with $(DHQ)_2$PHAL as the ligand, 2-vinylnaphthalene **9** (231 mg, 1.5 mmol) gave a crude product which contained an 83:17 mixture of amino alcohols **15a** and **15b** by ^{1}H NMR spectroscopy. Purification by flash column chromatography on silica with 3:1 petrol–EtOAc as eluent gave known[5] amino alcohol (*S*)-**15a** (207 mg, 48%; 98% ee) as a white solid, mp 150–154 °C (from 3:1 petrol–EtOAc) (lit.,[5] 153–154 °C); $[a]_D$ +45.5 (*c* 1.0 in EtOH) {lit.,[5] $[a]_D$ +55.0 (*c* 0.5 in 95% EtOH) for (*S*)-**15a**}; R_F(1:1 petrol–EtOAc) 0.4 [Found: C, 71.2; H, 7.8; N, 4.5%; $(M + H)^+$, 288.1603. $C_{17}H_{21}NO_3$ requires C, 71.0; H, 7.4; N, 4.9%; *M* + H, 288.1600]; ν_{max}-($CHCl_3$)/cm^{-1} 3600 (OH), 3440 (NH), 1707 (C=O) and 1497.5 (Ar); δ_H(270 MHz, $CDCl_3$) 7.85–7.75 (4 H, m, Ar), 7.51–7.38 (3 H, m, Ar), 5.41 (1 H, br s, NH), 4.92 (1 H, br s, ArCHN), 3.91 (2 H, br s, CH_2OH), 2.44 (1 H, br s, OH) and 1.44 (9 H, s, CMe_3); δ_C(67.5 MHz, $CDCl_3$) 156.1 (C=O), 137.0 (*ipso*-Ar), 133.3 (*ipso*-Ar), 132.9 (*ipso*-Ar), 128.6 (Ar), 127.9 (Ar), 127.7 (Ar), 126.3 (Ar), 126.0 (Ar), 125.4 (Ar), 124.6 (Ar), 80.1 (*C*Me_3), 66.7 (CH_2OH), 57.0 (ArCHN) and 28.3 (C*Me*$_3$); *m/z* (CI; NH_3) 288 [70%, $(M + H)^+$], 256 (15, $M - CH_2OH$), 231 (100, $M - C_4H_8$), 188 (85) and 156 (70); HPLC: Regis (*S*,*S*)-Whelk-O 1, 12% EtOH in heptane, 1.0 mL min^{-1}, 215 nm, 10.3 min [(*S*)-**15a**].

Diagnostic signals for amino alcohol **15b** from the ^{1}H NMR spectrum of the crude mixture: δ_H(270 MHz, $CDCl_3$) 5.0 (1 H, br s, NH) and 4.92 (1 H, br s, ArCHO).

(1*S*)-*N*-(*tert*-Butoxycarbonyl)-1-(2-methoxyphenyl)-2-hydroxyethylamine 16a

Using general procedure B with $(DHQ)_2$PHAL as the ligand, 2-methoxystyrene **11** (201 mg, 1.5 mmol) gave a crude product which contained a 55:45 mixture of amino alcohols **16a** and **16b** by ^{1}H NMR spectroscopy. Purification by flash column chromatography on silica with 3:1 petrol–EtOAc as eluent gave amino alcohol (*S*)-**16a** (172 mg, 43%; 87% ee) as a white solid, mp 147–149 °C (from 3:1 petrol–EtOAc); $[a]_D$ +36.5 (*c* 1.0 in EtOH); R_F(1:1 petrol–EtOAc) 0.4 [Found: C, 63.1; H, 8.1; N, 5.1%; $(M + H)^+$, 268.1552. $C_{14}H_{21}NO_4$ requires C, 62.9; H, 7.9; N, 5.2%; *M* + H, 268.1549]; ν_{max}($CHCl_3$)/cm^{-1} 3600 (OH), 3445 (NH), 1706 (C=O) and 1494 (Ar); δ_H(270 MHz, $CDCl_3$) 7.29–7.22 (2 H, m, Ar), 6.97–6.87 (2 H, m, Ar), 5.57 (1 H, br s, NH), 5.04 (1 H, br s, ArCHN), 3.84 (3 H, s, MeO), 3.80 (2 H, d, *J* 5.1, CH_2OH), 2.17 (1 H, br s, OH) and 1.43 (9 H, s, CMe_3); δ_C(67.5 MHz, $CDCl_3$) 156.9 (*ipso*-C_6H_4OMe), 156.1 (C=O), 128.9 (Ar), 128.5 (Ar), 126.9 (*ipso*-Ar), 120.8 (*p*-C_6H_4OMe), 110.9 (*o*-C_6H_4OMe), 79.6 (*C*Me_3), 65.6 (CH_2OH), 55.4 (MeO), 53.9 (ArCHN) and 28.4 (C*Me*$_3$); *m/z* (CI; NH_3) 268 [35%, $(M + H)^+$], 229 (15), 211 (100, $M - C_4H_8$), 194 (50), 168 (65) and 136 (40); HPLC: Chiralcel OJ, 15% EtOH in heptane, 1.0 mL min^{-1}, 215 nm, 4.5 min [(*S*)-**16a**], 5.0 min [(*R*)-**16a**].

Also obtained from the chromatography was amino alcohol **16b** [of unknown stereochemistry, probably (*S*)] (100 mg, 25%; 36% ee) as a white solid; HPLC: Chiralcel OD-H, 15% ^{i}PrOH in heptane, 1.0 mL min^{-1}, 215 nm, 8.9 min [(*S*)-**16b**], 7.0 min [(*R*)-**16b**]. Diagnostic signal for amino alcohol **16b** from the ^{1}H NMR spectrum of the crude mixture: δ_H(270 MHz, $CDCl_3$) 5.0 (2 H, br s, NH and ArC*H*OH).

(1*R*)-*N*-(*tert*-Butoxycarbonyl)-1-(2-methoxyphenyl)-2-hydroxyethylamine 16a

Using general procedure B with $(DHQD)_2$PHAL as the ligand, 2-methoxystyrene **11** (268 mg, 2.0 mmol) gave a crude product which contained a 45:55 mixture of amino alcohols **16a** and **16b** by ^{1}H NMR spectroscopy. Purification by flash column chromatography on silica with 3:1 petrol–EtOAc as eluent gave amino alcohol (*R*)-**16a** (180 mg, 34%; 88% ee) as a white solid identical (by TLC and ^{1}H NMR spectroscopy) to that obtained previously, $[a]_D$ −33.8 (*c* 1.0 in EtOH); HPLC: Chiralcel OJ, 15% EtOH in heptane, 1.0 mL min^{-1}, 215 nm, 5.0 min [(*R*)-**16a**], 4.5 min [(*S*)-**16a**].

(1*S*)-*N*-(*tert*-Butoxycarbonyl)-1-(4-methoxyphenyl)-2-hydroxyethylamine 17a

Using general procedure B with $(DHQ)_2$PHAL as the ligand, 4-methoxystyrene **12** (201 mg, 1.5 mmol) gave a crude product which contained an 85:15 mixture of amino alcohols **17a** and **17b** by ^{1}H NMR spectroscopy. Purification by flash column chromatography on silica with 2:1 petrol–EtOAc as eluent gave known[24] amino alcohol (*S*)-**17a** (296 mg, 74%; 98% ee) as a white solid, mp 139–141 °C (from 2:1 petrol–EtOAc) [lit.,[24] 130–132 °C for (*R*)-**17a**]; $[a]_D$ +62.6 (*c* 1.0 in EtOH); R_F(1:1 petrol–EtOAc) 0.4 [Found: C, 62.8; H, 8.0; N, 5.0%; $(M + H)^+$, 268.1556. $C_{14}H_{21}NO_4$ requires C, 62.9; H, 7.9; N, 5.2%; *M* + H, 268.1549]; ν_{max}($CHCl_3$)/cm^{-1} 3611 (OH), 3442 (NH), 1707 (C=O) and 1496 (Ar); δ_H(270 MHz, $CDCl_3$) 7.26–7.19 (2 H, m, Ar), 6.90–6.87 (2 H, m, Ar), 5.16 (1 H, br s, NH), 4.73 (1 H, br s, ArCHN), 3.82 (2 H, br s, CH_2OH), 3.80 (3 H, s, MeO) and 1.43 (9 H, s, CMe_3); δ_C(67.5 MHz, $CDCl_3$) 159.1 (*ipso*-C_6H_4OMe), 156.2 (C=O), 131.6 (*ipso*-Ar), 127.7 (*m*-C_6H_4OMe), 114.2 (*o*-C_6H_4OMe), 80.0 (*C*Me_3), 66.9 (CH_2OH), 56.4 (ArCHN), 55.3 (MeO) and 28.3 (C*Me*$_3$); *m/z* 268 (CI; NH_3) [35%, $(M + H)^+$], 229 (45), 211 (100, $M - C_4H_8$), 194 (10), 168 (15) and 136 (25); HPLC: Chiralcel OD-H, 5% ^{i}PrOH in heptane, 1.0 mL min^{-1}, 215 nm, 11.7 min [(*S*)-**17a**], 10.3 min [(*R*)-**17a**].

Diagnostic signals for amino alcohol **17b** from the ^{1}H NMR spectrum of the crude mixture: δ_H(270 MHz, $CDCl_3$) 4.95 (1 H, br s, NH) and 4.68 (1 H, br s, ArC*H*OH).

(1*R*)-*N*-(*tert*-Butoxycarbonyl)-1-(4-methoxyphenyl)-2-hydroxyethylamine 17a

Using general procedure B with $(DHQD)_2$PHAL as the ligand, 4-methoxystyrene **12** (201 mg, 1.5 mmol) gave a crude product which contained a 68:32 mixture of amino alcohols **17a** and **17b** by ^{1}H NMR spectroscopy. Purification by flash column chromatography on silica with 1:1 petrol–EtOAc as eluent gave known[24] amino alcohol (*R*)-**17a** (260 mg, 65%; 96% ee) as a white solid identical (by TLC and ^{1}H NMR spectroscopy) to that obtained previously, $[a]_D$ −61.3 (*c* 1.0 in EtOH) {$[a]_D$ −38.1 (*c* 1.31 in $CHCl_3$) for (*R*)-**17a**}; HPLC: Chiralcel OD-H, 5% ^{i}PrOH in heptane, 1.0 mL min^{-1}, 215 nm, 10.3 min [(*R*)-**17a**], 11.7 min [(*S*)-**17a**].

(1*S*)-*N*-(*tert*-Butoxycarbonyl)-1-(2,4,6-trimethylphenyl)-2-hydroxyethylamine 19a

Using general procedure B with $(DHQ)_2$PHAL as the ligand, 2,4,6-trimethylstyrene **18** (219 mg, 1.5 mmol) gave, after 2 h at 0 °C and 5.5 h at room temperature, a crude product which was purified by flash column chromatography on silica with 4:1 petrol–EtOAc as eluent to give amino alcohol (*S*)-**19a** (87 mg, 21%; 56% ee) as a gum, $[a]_D$ −15.2 (*c* 1.0 in EtOH); R_F(1:1

petrol–EtOAc) 0.4; $\nu_{max}(CHCl_3)/cm^{-1}$ 3612 (OH), 3444 (NH), 1696 (C=O) and 1493 (Ar); δ_H(270 MHz, $CDCl_3$) 6.83 (2 H, s, Ar), 5.18–5.04 (2 H, br m, NH and ArCHN), 4.02–4.01 (1 H, m, CH_AH_BOH), 3.72 (1 H, d, *J* 8.7, CH_AH_BOH), 2.39 (6 H, s, 2 × Me), 2.24 (3 H, s, Me) and 1.42 (9 H, s, CMe_3); δ_C(67.5 MHz, $CDCl_3$) 156.9 (C=O), 137.1 (*ipso*-Ar), 136.1 (*ipso*-Ar), 132.4 (*ipso*-Ar), 130.3 (Ar), 80.1 (CMe_3), 65.7 (CH_2OH), 56.0 (ArCHN), 28.3 (CMe_3), 21.1 (2 × Me) and 20.7 (Me); *m*/*z* (CI; NH_3) 280 [100%, $(M + H)^+$], 241 (60), 224 (30), 223 (30, $M - C_4H_8$), 180 (45) and 148 (45) [Found: $(M + H)^+$, 280.1910. $C_{16}H_{25}NO_3$ requires *M* + H, 280.1913]; HPLC: Chiralcel OD-H, 2% EtOH in heptane, 1.0 mL min^{-1}, 215 nm, 14.7 min [(*S*)-**19a**], 17.9 min [(*R*)-**19a**].

N-(*tert*-Butoxycarbonyl)-1-(2-pyridyl)-2-hydroxyethylamine 21a and *N*-(*tert*-butoxycarbonyl)-2-(2-pyridyl)-2-hydroxyethylamine 21b

Using general procedure B with $(DHQ)_2PHAL$ as the ligand, 2-vinylpyridine **20** (158 mg, 1.5 mmol) gave, after 16 h at room temperature, a crude product which was purified by flash column chromatography on silica with 2:1 EtOAc–petrol as eluent to give an inseparable 80:20 mixture (by ^1H NMR spectroscopy) of amino alcohols **21a** and **21b** (117 mg, 33%) as an orange oil, R_F(2:1 EtOAc–petrol) 0.25–0.2; $\nu_{max}(CHCl_3)/cm^{-1}$ 3610 (OH), 3454 (NH), 1707 (C=O) and 1507 (Ph); *m*/*z* (CI; NH_3) 239 [100%, $(M + H)^+$] and 139 (10).

Amino alcohol **21a**: δ_H(270 MHz, $CDCl_3$) 8.53–8.50 (1 H, m, Ar), 7.74–7.67 (1 H, m, Ar), 7.42–7.36 (1 H, m, Ar), 7.23–7.20 (1 H, m, Ar), 5.13 (1 H, br s, NH), 4.87–4.80 (1 H, br m, ArC*H*OH), 3.70–3.60 (1 H, br m, CH_AH_BN), 3.40–3.28 (1 H, br m, CH_AH_BN) and 1.40 (9 H, s, CMe_3); δ_C(270 MHz, $CDCl_3$) 159.5 (*ipso*-Ar), 156.6 (C=O), 148.0 (Ar), 136.8 (Ar), 122.5 (Ar), 79.4 (CMe_3), 72.6 (ArCHOH), 47.1 (CH_2N) and 28.2 (CMe_3).

Amino alcohol **21b**: δ_H(270 MHz, $CDCl_3$) 8.53–8.50 (1 H, m, Ar), 7.74–7.67 (1 H, m, Ar), 7.42–7.36 (1 H, m, Ar), 7.23–7.20 (1 H, m, Ar), 5.97 (1 H, br s, NH), 4.87–4.80 (1 H, br m, ArCHN), 4.03 (1 H, dd, *J* 4.4 and 11.3, CH_AH_BOH), 3.91 (1 H, dd, *J* 4.3 and 11.1, CH_AH_BOH) and 1.45 (9 H, s, CMe_3); δ_C(270 MHz, $CDCl_3$) 159.0 (*ipso*-Ar), 155.9 (C=O), 148.6 (Ar), 136.9 (Ar), 120.8 (Ar), 79.6 (CMe_3), 65.6 (CH_2OH), 55.8 (ArCHN) and 28.45 (CMe_3).

(*S*)-2-Phenylglycinol 23

Using general procedure C, amino alcohol (*S*)-**13a** (50 mg, 0.2 mmol; 94% ee) gave arylglycinol (*S*)-**23** (29 mg, 100%; 94% ee) as a white solid identical (by ^1H NMR spectroscopy) to an authentic sample, R_F(10:1 CH_2Cl_2–MeOH) 0.1; $[\alpha]_D$ +24.3 (*c* 1.0 in EtOH) [lit.,[23] +32.2 (solvent unspecified) for (*S*)-**23**].

(1*S*)-1-(2-Chlorophenyl)-2-hydroxyethylamine 24

Using general procedure C, amino alcohol (*S*)-**14a** (85 mg, 0.3 mmol; 92% ee) gave arylglcinol (*S*)-**24** (52 mg, 98%; 92% ee) as a gum, R_F(5:1 CH_2Cl_2–MeOH) 0.2; $[\alpha]_D$ +38.4 (*c* 1.0 in EtOH); $\nu_{max}(CHCl_3)/cm^{-1}$ 3667 (NH_2), 3624 (NH_2), 3395 (OH) and 1575 (Ar); δ_H(270 MHz, $CDCl_3$) 7.49–7.16 (4 H, m, Ar), 4.50 (1 H, t, *J* 3.9, ArCHN), 3.82 (1 H, m, CH_AH_BOH), 3.56 (1 H, dd, *J* 7.8 and 10.9, CH_AH_BOH) and 2.18 (3 H, br s, NH_2 and OH); δ_C(67.5 MHz, $CDCl_3$) 139.8 (*ipso*-C_6H_4Cl), 133.1 (*ipso*-Ar), 129.75 (Ar), 128.5 (Ar), 127.4 (Ar), 127.1 (Ar), 65.95 (CH_2OH) and 53.65 (ArCHN); *m*/*z* (CI; NH_3) 172 [100%, $(M + H)^+$] and 140 (10) [Found: $(M + H)^+$, 172.0525. $C_8H_{10}NOCl$ requires *M* + H, 172.0524].

(1*S*)-1-(2-Methoxyphenyl)-2-hydroxyethylamine 25

Using general procedure C, amino alcohol (*S*)-**16a** (120 mg, 0.45 mmol; 87% ee) gave arylglycinol (*S*)-**25** (62 mg, 83%; 87% ee) as a gum, R_F(10:1 CH_2Cl_2–MeOH) 0.15; $[\alpha]_D$ +34.9 (*c* 1.0 in EtOH); $\nu_{max}(CHCl_3)/cm^{-1}$ 3693 (NH_2), 3609 (NH_2), 3399 (OH) and 1600 (Ar); δ_H(270 MHz, $CDCl_3$) 7.27–7.16 (2 H, m, Ar), 6.94–6.74 (2 H, m, Ar), 4.26 (1 H, dd, *J* 3.6 and 8.0, ArCHN), 3.79 (3 H, s, MeO), 3.77–3.50 (2 H, m, CH_2OH), 3.00–2.63 (3 H, br s, NH_2 and OH); δ_C(67.5 MHz, $CDCl_3$) 156.9 (*ipso*-C_6H_4OMe), 130.0 (*ipso*-Ar), 128.4 (Ar), 127.2 (Ar), 120.7 (*p*-C_6H_4OMe), 110.5 (*o*-C_6H_4OMe), 65.6 (CH_2OH), 55.1 (MeO) and 52.8 (ArCHN); *m*/*z* (CI; NH_3) 168 [100%, $(M + H)^+$] and 136 (75, $M - CH_2OH$) [Found: $(M + H)^+$, 168.1025. $C_9H_{13}NO_2$ requires *M* + H, 168.1025].

(1*R*)-1-(2-Methoxyphenyl)-2-hydroxyethylamine 25

Using general procedure C, amino alcohol (*R*)-**16a** (160 mg, 0.6 mmol; 88% ee) gave arylglycinol (*R*)-**25** (94 mg, 94%; 88% ee) as a gum identical (by TLC and ^1H NMR spectroscopy) to that obtained previously, $[\alpha]_D$ −34.5 (*c* 1.0 in EtOH).

(1*R*)-1-(4-Methoxyphenyl)-2-hydroxyethylamine 26

Using general procedure C, amino alcohol (*R*)-**17a** (215 mg, 0.8 mmol; 96% ee) gave known[28] arylglycinol (*R*)-**26** (130 mg, 97%; 96% ee) as a white solid, R_F(5:1 CH_2Cl_2–MeOH) 0.1, $[\alpha]_D$ −21.9 (*c* 1.0 in EtOH); $\nu_{max}(CHCl_3)/cm^{-1}$ 3670 (NH_2), 3626 (NH_2), 3400 (OH) and 1611 (Ar); δ_H(270 MHz, $CDCl_3$) 7.24 (2 H, d, *J* 8.7, *m*-C_6H_4OMe), 6.88 (2 H, d, *J* 8.7, *o*-C_6H_4OMe), 4.0 (1 H, br s, ArCHN), 3.79 (3 H, s, MeO), 3.67 (1 H, br s, CH_AH_BOH), 3.52 (1 H, dd, *J* 8.5 and 10.7, CH_AH_BOH) and 2.43 (3 H, br s, NH_2 and OH); δ_C(67.5 MHz, $CDCl_3$) 159.0 (*ipso*-C_6H_4OMe), 134.6 (*ipso*-Ar), 127.5 (*m*-C_6H_4OMe), 114.0 (*o*-C_6H_4OMe), 68.0 (CH_2OH), 56.7 (ArCHN) and 55.3 (MeO); *m*/*z* (CI; NH_3) 168 [25%, $(M + H)^+$], 151 (100, $M - OH$) and 136 (40, $M - CH_2OH$) [Found: $(M + H)^+$, 168.1022. $C_9H_{13}NO_2$ requires *M* + H, 168.1025].

(1*S*)-1-(4-Methoxyphenyl)-2-hydroxyethylamine 26

Using general procedure C, amino alcohol (*S*)-**17a** (200 mg, 0.75 mmol; 98% ee) gave known[28] arylglycinol (*S*)-**26** (102 mg, 81%; 98% ee) as a white solid identical (by TLC and ^1H NMR spectroscopy) to that obtained previously, $[\alpha]_D$ +22.6 (*c* 1.0 in EtOH) {lit.,[28] $[\alpha]_D$ +38.3 (*c* 0.43 in $CHCl_3$) for (*S*)-**26**}.

(1*S*)-*N*-Methyl-1-(4-methoxyphenyl)-2-(isoindolin-2-yl)ethylamine 30

Sodium carbonate (127 mg, 1.2 mmol) and tetra-*n*-butylammonium iodide (22 mg, 0.06 mmol) were added successively to a stirred solution of arylglycinol (*R*)-**26** (100 mg, 0.6 mmol; 96% ee) in THF (6 cm^3) at room temperature under nitrogen. Then, α,α′-dibromo-*o*-xylene **27** (158 mg, 0.6 mmol) was added and the resulting suspension was heated at reflux for 3.5 h. After cooling to room temperature, the solids were removed by filtration and the filtrate was evaporated under reduced pressure. The residue was dissolved in Et_2O (15 cm^3), washed with water (2 × 6 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product as a yellow solid. Purification by flash chromatography on silica with 20:1 CH_2Cl_2–MeOH as eluent gave amino alcohol (*R*)-**28** (122 mg, 76%) as a pale yellow solid which was not characterised. Under nitrogen, this product was dissolved in Et_2O (5 cm^3), triethylamine (0.19 cm^3, 1.35 mmol) was added and the solution was cooled to 0 °C. Then, methanesulfonyl chloride (0.07 cm^3, 0.9 mmol) was added dropwise. A white precipate formed which made stirring difficult and after 30 min, triethylamine (0.16 cm^3, 0.9 mmol) was added. After warming to room temperature, methylamine (0.6 cm^3 of a 40% aqueous solution, 7.65 mmol) was added and the resulting two phase reaction mixture was vigorously stirred for 16 h. The layers were separated and the light brown aqueous layer was extracted with Et_2O (3 × 3 cm^3). The combined organic extracts were washed with 5% aqueous sodium hydrogen carbonate (3 cm^3) and water (3 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product which was purified by flash chromatography on silica with 20:1 CH_2Cl_2–MeOH as eluent to give diamine (*S*)-**30** [65 mg, 52%, 40% from arylglycinol (*R*)-**26**] as a brown oil, R_F(10:1 CH_2Cl_2–MeOH) 0.3, $[\alpha]_D$ +6.0 (*c* 1.0 in EtOH);

$\nu_{max}(CHCl_3)/cm^{-1}$ 3300 (NH) and 1611 (Ar); δ_H(270 MHz, $CDCl_3$) 7.23 (2 H, d, *J* 8.8, *m*-C_6H_4OMe), 7.10 (4 H, br s, Ar), 6.80 (2 H, d, *J* 8.8, *o*-C_6H_4OMe), 3.96 (2 H, d, *J* 11.9, 2 × ArCH_AH_BN), 3.85 (2 H, d, *J* 11.9, 2 × ArCH_AH_BN), 3.71 (3 H, s, MeO), 3.55 (1 H, dd, *J* 3.3 and 9.7, ArCHN), 3.11 (1 H, br s, NH), 2.93 (1 H, dd, *J* 9.7 and 11.9, CH_AH_BN), 2.62 (1 H, dd, *J* 3.3 and 11.9, CH_AH_BN) and 2.21 (3 H, s, NH*Me*); δ_C(67.5 MHz, $CDCl_3$) 159.0 (*ipso*-C_6H_4OMe), 140.0 (*ipso*-Ar), 133.4 (*ipso*-Ar), 128.55 (Ar), 126.8 (Ar), 122.2 (*m*-C_6H_4OMe), 113.9 (*o*-C_6H_4OMe), 63.5 (NCH_2), 63.1 (ArCHN), 59.5 (2 × NCH_2Ar), 55.2 (OMe) and 34.3 (NHMe); *m/z* (CI; NH_3) 283 [60%, $(M + H)^+$], 252 (25, M − NHMe), 150 (100, ArCHNHMe) and 132 (35) [Found: $(M + H)^+$, 283.1808. $C_{18}H_{22}N_2O$ requires *M* + H, 283.1810].

Acknowledgements

Parke-Davis Neuroscience Research are thanked for funding this project. We are extremely grateful to Mr Tim Underwood and Mr Simon Bryant of GlaxoWellcome Physical Sciences Department for carrying out the chiral HPLC analyses. We also acknowledge Professor K. B. Sharpless for providing us with unpublished results on the use of *tert*-butyl carbamate and Dr Y. Landais for helpful discussions.

References

1 For commentaries, see: (*a*) O. Reiser, *Angew. Chem.*, *Int. Ed. Engl.*, 1996, **35**, 1308; (*b*) G. Casiraghi, G. Rassu and F. Zanardi, *Chemtracts: Org. Chem.*, 1997, **10**, 318.
2 (*a*) G. Li, H.-T. Chang and K. B. Sharpless, *Angew. Chem.*, *Int. Ed. Engl.*, 1996, **35**, 451; (*b*) J. Rudolph, P. C. Sennhenn, C. P. Vlaar and K. B. Sharpless, *Angew. Chem.*, *Int. Ed. Engl.*, 1996, **35**, 2810; (*c*) A. E. Rubin and K. B. Sharpless, *Angew. Chem.*, *Int. Ed. Engl.*, 1997, **36**, 2637.
3 (*a*) G. Li, H. H. Angert and K. B. Sharpless, *Angew. Chem.*, *Int. Ed. Engl.*, 1996, **35**, 2813; (*b*) K. L. Reddy, K. R. Dress and K. B. Sharpless, *Tetrahedron Lett.*, 1998, **39**, 3667.
4 M. Bruncko, G. Schlingloff and K. B. Sharpless, *Angew. Chem.*, *Int. Ed. Engl.*, 1997, **36**, 1483.
5 K. L. Reddy and K. B. Sharpless, *J. Am. Chem. Soc.*, 1998, **120**, 1207.
6 G. Li and K. B. Sharpless, *Acta Chem. Scand.*, 1996, **50**, 649.
7 R. Angelaud, Y. Landais and K. Schenk, *Tetrahedron Lett.*, 1997, **38**, 1407.
8 T. T. Upadhya and A. Sudalai, *Tetrahedron: Asymmetry*, 1997, **8**, 3685.
9 H. Han, J. Yoon and K. D. Janda, *J. Org. Chem.*, 1998, **63**, 2045.
10 P. Phukan and A. Sudalai, *Tetrahedron: Asymmetry*, 1998, **9**, 1001.
11 G. Cravotto, G. B. Giovenzana, R. Pagliarin, G. Palmisano and M. Sisti, *Tetrahedron: Asymmetry*, 1998, **9**, 745.
12 Preliminary communication: P. O'Brien, S. A. Osborne and D. D. Parker, *Tetrahedron Lett.*, 1998, **39**, 4099.
13 (*a*) S. E. de Sousa, P. O'Brien and P. Poumellec, *Tetrahedron: Asymmetry*, 1997, **8**, 2613; (*b*) S. E. de Sousa and P. O'Brien, *Tetrahedron Lett.*, 1997, **38**, 4885; (*c*) P. O'Brien and P. Poumellec, *Tetrahedron Lett.*, 1996, **37**, 5619.
14 S. E. de Sousa, P. O'Brien and P. Poumellec, *J. Chem. Soc.*, *Perkin Trans. 1*, 1998, 1483.
15 H. C. Kolb, M. S. Van Nieuwenhze and K. B. Sharpless, *Chem. Rev.*, 1994, **94**, 2483.
16 G. Miao and B. E. Rossiter, *J. Org. Chem.*, 1995, **60**, 8424.
17 N. Lewis, A. McKillop, R. J. K. Taylor and R. J. Watson, *Synth. Commun.*, 1995, **25**, 561.
18 T. Izumi and K. Fukaya, *Bull. Chem. Soc. Jpn.*, 1993, **66**, 1216.
19 T. W. Greene and P. G. M. Wuts, *Protecting Groups in Organic Synthesis*, Wiley, New York, 1991.
20 K. B. Sharpless, personal communication.
21 J.-N. Denis, A. Correa and A. E. Greene, *J. Org. Chem.*, 1991, **56**, 6939.
22 (*a*) H. Matsunaga, T. Ishizuka and T. Kunieda, *Tetrahedron*, 1997, **53**, 1275; (*b*) R. Caputo, E. Cassano, L. Longobardo and G. Palumbo, *Tetrahedron*, 1995, **51**, 12 337.
23 M. A. Tschantz, L. E. Burgess and A. I. Meyers, *Org. Synth.*, 1996, **73**, 221.
24 F. Matsuura, Y. Hamada and T. Shioiri, *Tetrahedron*, 1994, **50**, 9457.
25 B. Tao, G. Schlingloff and K. B. Sharpless, *Tetrahedron Lett.*, 1998, **39**, 2507.
26 H. Becker and K. B. Sharpless, *Angew. Chem.*, *Int. Ed. Engl.*, 1996, **35**, 448.
27 R. M. Williams, P. P. Ehrlich, W. Zhai and J. Hendrix, *J. Org. Chem.*, 1987, **52**, 2615.
28 K.-I. Kawasaki and T. Katsuki, *Tetrahedron*, 1997, **53**, 6337.
29 W. C. Still, M. Kahn and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.
30 M. J. Mintz and C. Walling, *Org. Synth*. 1983, **Coll. Vol. V**, 183.

Paper 8/03821J
Received 20*th May* 1998
Accepted 25*th June* 1998