Two expedient methods for the preparation of chiral diamines

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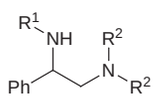
A study on the development of methodology for the synthesis of chiral diamines is reported. Two synthetic approaches are described both of which involve the generation and subsequent reaction of aziridinium ions. One of the methods is a one-pot preparation from (*R*)-styrene oxide to give several diamines and a C_2 symmetric triamine in yields of 63–93%. The other method is a sequential two-step approach from (*R*)- or (*S*)-phenylglycinol and four diamines have been prepared in yields of 62–82%. Both approaches start from readily available materials and are simple, high yielding, and shorter than previous synthetic routes and can be used to prepare either enantiomer of a range of chiral diamines. Such chiral diamines are useful reagents for asymmetric synthesis and are intermediates in the preparation of non-opioid analgesics.

Introduction

The development of new methods for the preparation of enantiomerically pure chiral diamines **1** is highly desirable since such



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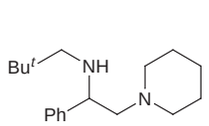
compounds have been widely used as chiral reagents for asymmetric synthesis and as intermediates in the synthesis of analgesics (*vide infra*). We recently [1–3] communicated two related methods for diamine synthesis and in this paper, we describe the full synthetic and mechanistic details of our syntheses as well as commenting on their scope and potential limitations. In particular, the general usefulness of our methods is demonstrated with the preparation of twelve enantiomerically pure diamines, many of which are novel compounds.

For over ten years, Koga and co-workers [4] have been using chiral lithium amide bases derived from diamines such as (*R*)- or (*S*)-**2** and (*R*)- or (*S*)-**3** in the enantioselective deprotonation of prochiral cyclic ketones.[5] More recently, Singh and co-workers [6,7] have introduced chiral lithium amide bases generated from diamines (*R*)- or (*S*)-**4** and (*R*)- or (*S*)-**5** as useful reagents for the enantioselective rearrangement of epoxides to allylic alcohols.[8] We have also reported epoxide rearrangement reactions using the lithium amide derived from diamine **4** [9,10] which is the reason why we have had recourse to investigate new methods for diamine synthesis. In addition, Rossiter and co-workers [11,12] have reported the use of lithium amides prepared from diamines **1** as chiral ligands in asymmetric conjugate addition reactions.[13] Diamines **1** have also been used as intermediates in the synthesis of non-opioid analgesics.[14–16] For example, amide (*S*)-**6**, prepared from diamine (*S*)-**4**, is a κ agonist with potent naloxone-reversible analgesic effects [14] and a patent [17] has recently been filed on a series of pyrrolidinyl hydroxamic acid derivatives which are prepared from intermediates similar in structure to diamines **1**.



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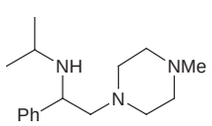

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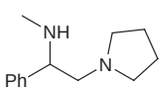

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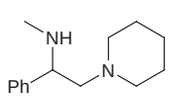

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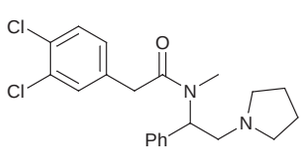

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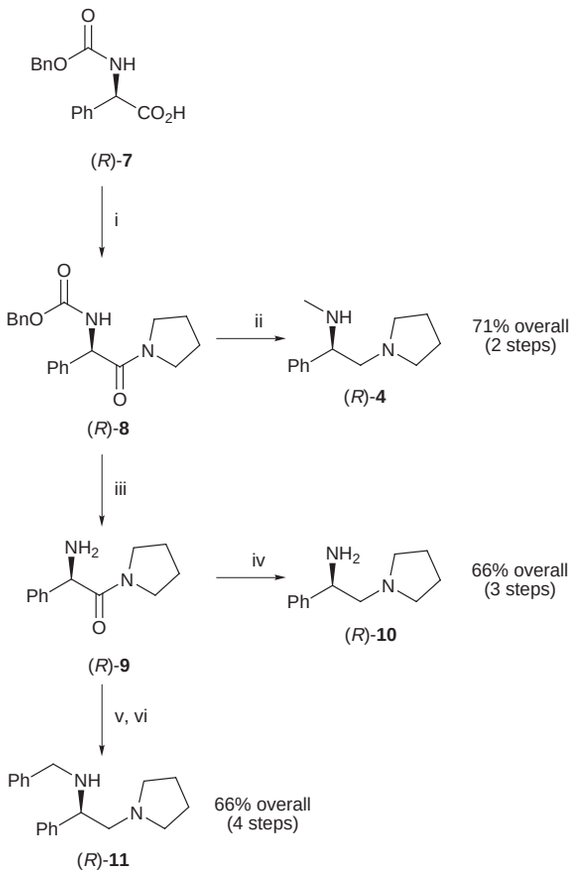
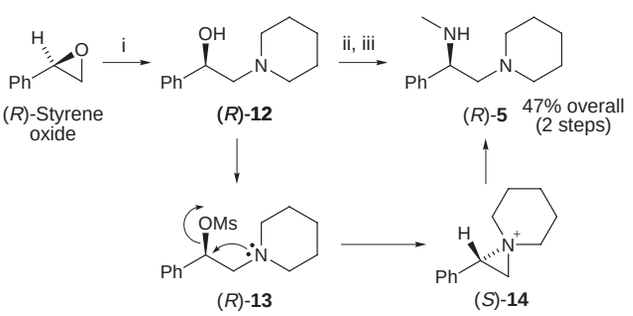
Prior to our diamine synthetic studies, the most frequently employed route started with phenylglycine and involved *N*-protection, amide formation [with $(R^2)_2NH$] and subsequent synthetic manipulations. Singh and co-workers,[6,7] Rossiter *et al.*[11] and Koga and co-workers [18] have all independently used this general approach for the synthesis of a wide range of diamines **1** and representative examples of Singh's synthesis of diamines (*R*)-**4**, (*R*)-**10** and (*R*)-**11** from *N*-protected phenylglycine (*R*)-**7** are summarised in Scheme 1.[6,7] Although each of the diamines can be prepared in either enantiomeric form and in >60% yield, there are some limitations: (i) the overall route to diamine (*R*)-**11** is four steps from (*R*)-**7** [which itself has to be prepared from (*R*)-phenylglycine]; (ii) the amide coupling conditions need to be carefully controlled in order to prevent racemisation;[19] (iii) the route is not flexible enough for the easy synthesis of different diamines.

An alternative method for the preparation of diamines **1** has been reported by Rossiter *et al.* Their idea (Scheme 2) for a completely different approach to the synthesis of diamines **1** was based on earlier work by Dieter and co-workers [20] who had prepared chiral triamines from ephedrine and pseudoephedrine. Initially, (*R*)-styrene oxide was reacted with piperidine to afford amino alcohol (*R*)-**12** as a single regioisomer (73% yield after recrystallisation). Subsequent mesylation gave (*R*)-**13** which is not isolated, as it was believed to convert into aziridinium ion (*S*)-**14** *in situ*. Reaction with methylamine then gave diamine (*R*)-**5** as a single regioisomer and enantiomer in 65% yield from amino alcohol (*R*)-**12**. The intermediacy of the aziridinium ion [21] was required to explain the stereochemical outcome of this synthesis [overall retention of stereochemistry from (*R*)-styrene oxide] and was consistent with Dieter's inability to isolate amino methanesulfonates (mesylates) from the attempted mesylation of a number of amino alcohols similar in structure to (*R*)-**12**.[20]

Of the two methods that had been previously used to prepare diamines **1**, we felt that the route from phenylglycine was



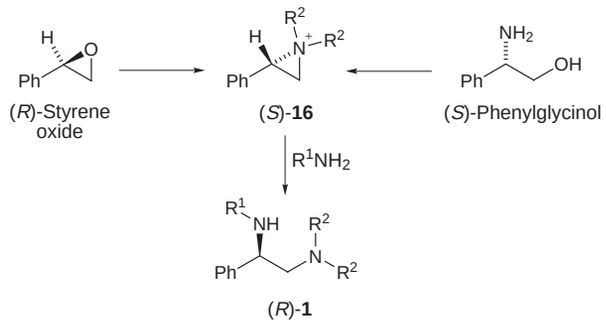
Scheme 1 Singh's synthesis of diamines. *Reagents and conditions:* i, Pyrrolidine, DCC, 1-hydroxybenzotriazole, $CuCl_2$, DMF, 0 °C→rt, 20 h (90%); ii, $LiAlH_4$, THF, reflux, 6 h (79%); iii, 10% Pd–C, H_2, MeOH, rt, 2 h (95% crude); iv, $LiAlH_4$, THF, reflux, 6 h (77%); v, PhCHO, 4 Å molecular sieves, benzene, rt, 7 h (quant.); vi, $LiAlH_4$, THF, reflux, 8 h (79%)



Scheme 2 Rossiter's synthesis of diamine (*R*)-**5**. *Reagents and conditions:* i, Piperidine, reflux, 30 min (73%); ii, Et_3N, MsCl, Et_2O, 0 °C, 30 min; iii, Et_3N, $MeNH_2$, water (65%)

lengthy, had a potentially problematic amide formation step and was not amenable to the easy preparation of a wide range of structurally diverse diamines. In contrast, Rossiter's aziridinium ion route (Scheme 2), although less well developed, appeared to have the potential of being a much more flexible synthetic route.

Thus, we embarked on a programme of research aimed at developing further the methods introduced by Rossiter and by Dieter for the preparation of chiral diamines and triamines. Our plan was to prepare amino alcohols like (*R*)-**12** since we imagined that diamines (*R*)-**1** could be obtained upon mesylation [to give aziridinium ions (*S*)-**16**] and reaction with a range of amines (R^1NH_2) as outlined in Scheme 3. Of the two approaches that we have developed, the one from phenylglycinol is similar to a route used by Gibson and Fulton to make a β-amino thioacetate[22] and the route used to make some pyrrolidinyl hydroxamic acid derivatives.[17] Singh and Saravanan[23] have very recently reported a useful modification of our methods: amino alcohols (*R*)- or (*S*)-**12** were prepared in high yield from either enantiomer of mandelic acid and then converted into diamines **1** *via* aziridinium ions.



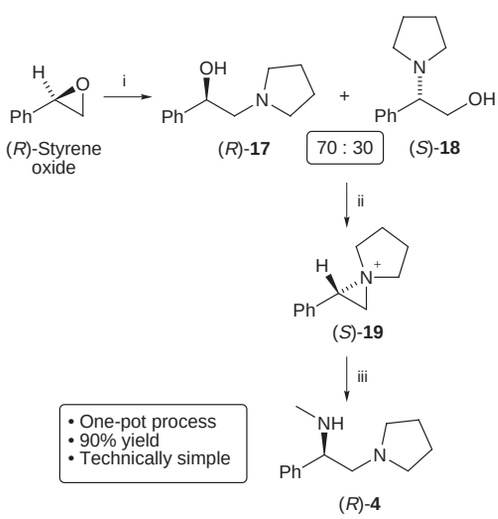
Scheme 3 Our methods for diamine synthesis

Results and discussion

Chiral diamines from styrene oxide

Both enantiomers of styrene oxide are commercially available[24] but since (*R*)-styrene oxide is considerably cheaper, virtually all of the synthetic studies were carried out with (*R*)-styrene oxide. As a starting point, we decided to attempt the preparation of diamine (*R*)-**4** using a modified version of Rossiter's method.

Reaction of pyrrolidines with (*R*)-styrene oxide in refluxing ethanol for 2 h afforded a quantitative yield of a crude product which crystallised slowly after removal of the volatiles and high vacuum drying.† Analysis at this stage by ^1H NMR spectroscopy revealed that a 70:30 mixture of regioisomeric amino alcohols (*R*)-**17**[25] and (*S*)-**18** had been generated (Scheme 4).

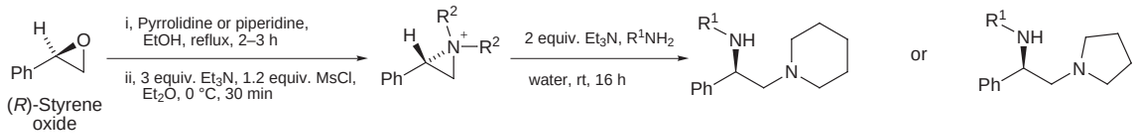


Scheme 4 *Reagents and conditions:* i, Pyrrolidine, EtOH, reflux, 2 h (quant.); ii, 3 equiv. Et_3N, 1.2 equiv. MsCl, Et_2O, 0 °C, 30 min; iii, 2 equiv. Et_3N, $MeNH_2$, water, rt, 16 h (90%)

According to Rossiter's procedure,[11] we should have isolated the major amino alcohol regioisomer (*R*)-**17** by recrystallisation. However, it appeared to us that this was unnecessary since *both* amino alcohols (*R*)-**17** and (*S*)-**18** should generate the

† In general, we prefer to see the crude mixture of amino alcohols (*R*)-**17** and (*S*)-**18** crystallise and, in most of our attempts, this was the case. If, however, after 1 h of drying on the high vacuum crystallisation had not occurred, we continued with the next steps and we have never observed any adverse effects on yield or purity of the diamine products produced in this way.

Table 1 One-pot synthesis of chiral diamines from (*R*)-styrene oxide

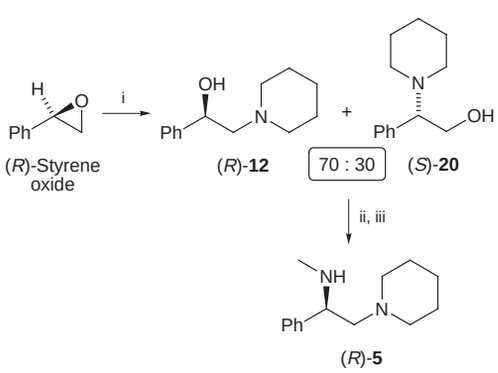


Entry	R^1NH_2 (equiv.)	Diamine product	Yield (%)	Purification method
1	Ammonia (50)	(*R*)-**21**	79	Distillation
2	*tert*-Butylamine (11)	(*R*)-**22**	90	Distillation
3	Aniline (1)	(*R*)-**23**	79	Chromatography
4	Benzylamine (1)	(*R*)-**24**	81	Chromatography
5	Benzylamine (1)	(*R*)-**25**	93	Chromatography
6	(*S*)-α-methylbenzylamine (1)	(*S*,*R*)-**26**	74	Chromatography
7	(*R*)-α-methylbenzylamine (1)	(*R*,*R*)-**26**	80	Chromatography

same aziridinium ion (*S*)-**19** upon mesylation. Thus, mesylation of the *crude* mixture of amino alcohols (*R*)-**17** and (*S*)-**18** *in the same flask* followed by reaction with aqueous methylamine as described by Rossiter gave diamine (*R*)-**4** in 90% isolated yield after Kugelrohr distillation (Scheme 4).

As both Rossiter and Dieter had found, only a single regioisomer of the diamine (*R*)-**4** was obtained and its ^{1}H NMR spectrum and optical rotation {$[\alpha]_D^{20}$ −65.4 (*c* 1.7 in EtOH)} were in accord with the data {$[\alpha]_D^{25}$ −64.0 (*c* 1.6 in EtOH)} reported by Singh and co-workers for the same compound prepared from (*R*)-phenylglycine.[7] We established that diamine (*R*)-**4** of ⩾95% ee had been produced by carrying out ^{1}H NMR spectroscopy experiments with diamines *rac*- and (*R*)-**4** in the presence of the chiral solvating agent, (*R*)-1-phenyl-2,2,2-trifluoroethanol.[26] Thus, the conversion of (*R*)-styrene oxide into diamine (*R*)-**4** proceeds with overall retention of configuration *via* regio- and stereo-specific opening of aziridinium ion (*S*)-**19** at the activated benzylic position. This is in contrast to episelenium[27] and episulfonium[28] ions derived from (*R*)-styrene oxide which partially racemise (presumably *via* the open chain carbocations) during Ritter-type substitution reactions at room temperature. It is important to emphasise that our synthesis of diamine (*R*)-**4** from (*R*)-styrene oxide is a *one-pot reaction* and as such is a significant improvement on Rossiter's two-step synthesis. Additionally, we carried out the synthesis of diamine (*R*)-**5** using our new one-pot protocol and obtained an 89% yield after purification by chromatography (Scheme 5) [*cf.* Rossiter's 47% yield of (*R*)-**5** over two steps; Scheme 2].

To show that our one-pot method was general for the preparation of pyrrolidinyl and piperidinyl diamines **1**, we have varied the amine (R^1NH_2) that intercepts the aziridinium ions (*S*)-**14** and (*S*)-**19** and the results are summarised in Table 1. Only methylamine and ammonia are available as aqueous solutions



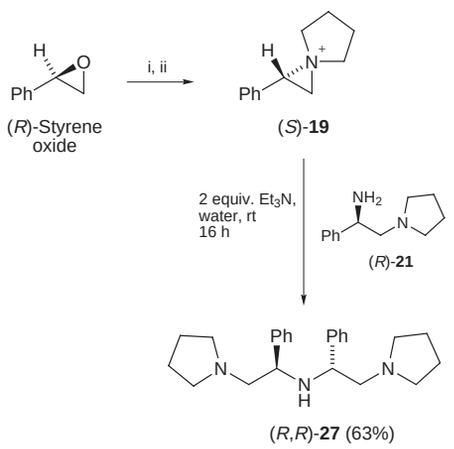
Scheme 5 *Reagents and conditions:* i, Piperidine, EtOH, reflux, 3 h (quant.); ii, 3 equiv. Et_3N, 1.2 equiv. MsCl, Et_2O, 0 °C, 30 min; iii, 2 equiv. Et_3N, $MeNH_2$, water, rt, 16 h (89%)

so with the other amines (entries 2–7) it was necessary to add a reasonable amount of water just prior to the addition of the amine. Also, we preferred to use a large molar excess of the volatile amines (methylamine, ammonia and *tert*-butylamine) but only one equivalent of the non-volatile amines (aniline, benzylamine and α-methylbenzylamine) as this facilitated purification of the products. In general, diamines prepared from the volatile amines (entries 1 and 2) were best purified by Kugelrohr distillation whilst those synthesised from the non-volatile amines (entries 3–7) were more easily purified by chromatography.

As can be seen in Table 1, good yields of a range of (*R*)-diamines were obtained from (*R*)-styrene oxide: sterically hindered amines (*e.g. tert*-butylamine; entry 2) and less nucleophilic amines (*e.g.* aniline; entry 3) work just as well as methyl-

amine. In all cases, the absolute stereochemistry was assigned by analogy with the preparation of diamine (*R*)-**4**, only one regioisomer was observed and the products had ≥95% ee as shown by ^{1}H NMR spectroscopy in the presence of (*R*)-1-phenyl-2,2,2-trifluoroethanol[26] or, in the cases of (*S*,*R*)-**26** and (*R*,*R*)-**26** by the formation of a single diastereoisomeric product.

The most structurally complex amine that we have prepared using our methodology is the C_2 symmetric *triamine* (*R*,*R*)-**27**. Its synthesis was accomplished by reacting aziridinium ion (*S*)-**19** [generated in the usual manner from (*R*)-styrene oxide] with diamine (*R*)-**21** [previously prepared from (*R*)-styrene oxide; entry 1, Table 1] to give (*R*,*R*)-**27** in 63% yield (Scheme 6).



Scheme 6 *Reagents and conditions:* i, Pyrrolidine, EtOH, reflux, 2 h (quant.); ii, 3 equiv. Et_3N, 1.2 equiv. MsCl, Et_2O, 0 °C, 30 min

This is essentially a two-step synthesis from (*R*)-styrene oxide, pyrrolidine and ammonia (50% overall yield) and as such is highly convergent and efficient. Indeed, it is difficult to imagine an alternative synthetic route to triamine (*R*,*R*)-**27** of just two steps with complete control of the absolute and relative stereochemistry.

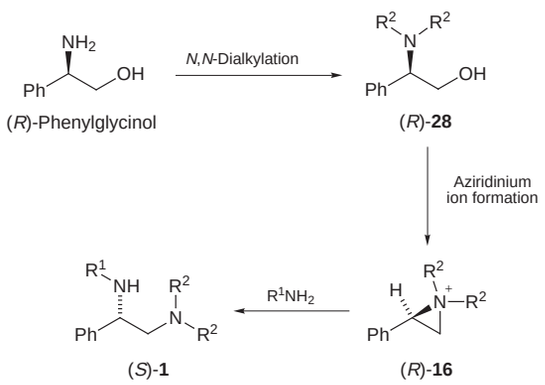
Some of the practical points in our one-pot synthesis are worthy of further explanation. The use of aqueous amine in the final step is unusual but completely necessary. At the end of the mesylation step it is impossible to stir the reaction mixture due to the precipitation of triethylamine hydrochloride and addition of neat amine at this stage does not lead to the efficient formation of the diamine.[29] In contrast, when aqueous amine is added, the hydrochloride salt is solubilised and efficient stirring of the now two-phase reaction mixture for 16 h leads to high yields of diamine. We have also observed that stirring for 16 h after addition of the aqueous amine is required for formation of the diamine product. In one reaction, we left the reaction mixture for just 3 h before working it up and no diamine product was obtained. We have also shown that THF can be used in place of Et_2O as the solvent for the mesylation–diamine formation steps (89% yield of *rac*-**4** was obtained using THF in place of Et_2O).

Although we generally prepared diamines on <1 g scale, we have demonstrated that it is possible to carry out the preparation of diamine *rac*-**4** on a larger scale. For example, 2.9 g of diamine *rac*-**4** has been prepared in one synthesis. Thus, by developing the methods originally reported by Dieter and Rossiter, we have uncovered a very useful one-pot method for the synthesis of chiral diamines on a reasonable scale.

Chiral diamines from phenylglycinol

The one-pot method for diamine synthesis described in the previous section is simple to carry out, high yielding and improves on previous syntheses of diamines (*R*)-**1**. However, it is not appropriate for the synthesis of diamines (*S*)-**1** since (*S*)-styrene oxide is much more expensive than its enantiomer.[24] In order to remedy this limitation, we have investigated an alternative method of preparing diamines.

When developing a different route to diamines **1**, there were two aspects of the original method that we wanted to maintain: (i) the generation and regioselective opening of aziridinium ions and (ii) the fact that no purification of any intermediates was required, *i.e.* the one-pot nature of the process. Thus, we decided to attempt an alternative preparation of amino alcohols like (*R*)-**12** as we knew that they could be converted into diamines in an efficient manner using mesylation and reaction with an amine. Our proposed route to amino alcohols (*R*)-**28** involved *N*,*N*-dialkylation of phenylglycinol (readily available in both enantiomeric forms[30,31]) with R^2Br and the full synthetic approach to diamines (*S*)-**1** is outlined in Scheme 7. A bonus



Scheme 7

associated with this proposed route is that it should enable us to prepare diamines with substituents other than pyrrolidinyl and piperidinyl rings.

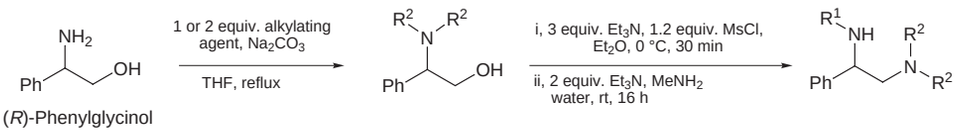
We began our study by investigating the conversion of (*R*)-phenylglycinol into the known[32] dibenzyl amino alcohol (*R*)-**29**. Of the methods previously used for *N*,*N*-dialkylation of amino alcohols,[33–36] we developed a useful method by slightly modifying the procedure reported by Brown and coworkers.[33,34] Thus, refluxing (*R*)-phenylglycinol for 19 h with two equivalents of benzyl bromide in THF containing two equivalents of sodium carbonate and 0.1 equivalents of tetra-*n*-butylammonium iodide (TBAI) gave amino alcohol (*R*)-**29** in 79% isolated yield after chromatography. In the absence of TBAI, the reaction proceeded at a considerably slower rate. As expected, treatment of amino alcohol (*R*)-**29** sequentially with mesyl chloride and then methylamine in the usual way produced novel diamine (*S*)-**31** {$[a]_D^{20}$ +74.1 (*c* 1.0 in $CHCl_3$)} in 83% yield (Scheme 8).

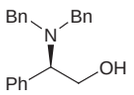
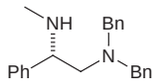
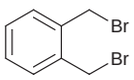
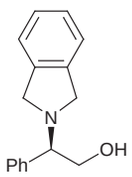
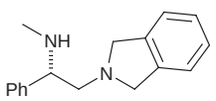
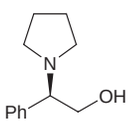
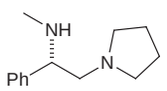
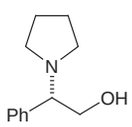
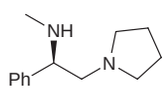
By analogy with the conversions of (*S*)-**18** and (*S*)-**20** into diamines (*R*)-**4** and (*R*)-**5** respectively (Schemes 4 and 5), we have assigned diamine **31** as having an (*S*)-configuration: formation of diamine (*S*)-**31** presumably proceeds *via* aziridinium ion (*R*)-**30**. Also in line with our earlier results, diamine (*S*)-**31** was the only regioisomer detected (by ^{1}H NMR spectroscopy) and it had ≥95% ee as shown by ^{1}H NMR spectroscopy in the presence of (*R*)-1-phenyl-2,2,2-trifluoroethanol.[26]

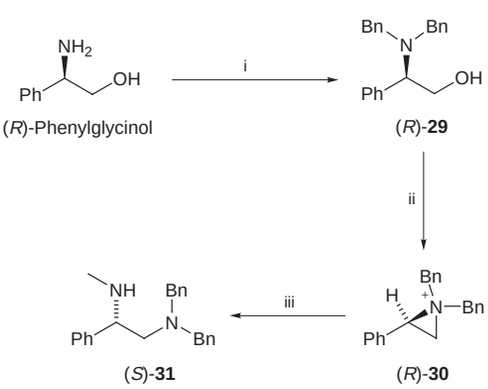
The preparation of diamine (*S*)-**31** outlined in Scheme 8 is a two-step synthesis (66% overall yield) with purification of the intermediate amino alcohol (*R*)-**29** using chromatography. Therefore, we decided to try and develop a procedure that did not require purification of any intermediates and was suitable for the preparation of a range of (*S*)-diamines.

Ideally, we hoped to develop another one-pot method for diamine synthesis starting from (*R*)- or (*S*)-phenylglycinol. However, despite an extensive study, this proved not to be possible and, in the end, we settled for a compromise. Our optimised protocol is a *sequential* two-step synthesis of diamines involving: (i) *N*,*N*-dialkylation of (*R*)-phenylglycinol in reflux-

Table 2 Sequential two-step synthesis of chiral diamines from phenylglycinol



Entry	Alkylating agent	Na_2CO_3 (equiv.)	TBAI (equiv.)	Reflux time/h	Amino alcohol	Diamine product	Yield (%)
1	2 equiv. BnBr	2	0.1	19	 (*R*)-**29**	 (*S*)-**31**	62
2	1 equiv. 	2	0.1	3	 (*R*)-**32**	 (*S*)-**33**	69
3	1 equiv. 	3	0.5	20	 (*R*)-**18**	 (*S*)-**4**	76
4	1 equiv. 	3	0.5	20	 (*S*)-**18**	 (*R*)-**4**	82



Scheme 8 *Reagents and conditions:* i, 2 equiv. BnBr, 2 equiv. Na_2CO_3, 0.1 equiv. TBAI, THF, reflux, 19 h (79%); 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 (83%)

ing THF containing the appropriate bromide, sodium carbonate and TBAI followed by removal of the solids by filtration and an aqueous work-up to give a crude product; (ii) treatment of the crude product, dissolved in Et_2O, with mesyl chloride and then methylamine in the usual manner. The intermediate aqueous work-up was necessary to remove any dissolved inorganic salts and the TBAI catalyst. Using this procedure, we have prepared four diamines in good yields from (*R*)- or (*S*)-phenylglycinol and the results are summarised in Table 2.

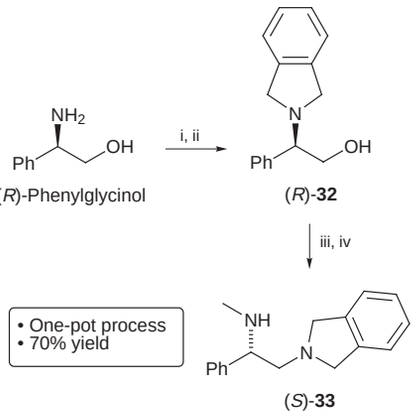
The main problem we encountered when developing the sequential two-step method was the *N*,*N*-dialkylation step which proved to be very difficult to drive to completion. Indeed, with 1,4-dibromobutane (entries 3 and 4), 0.5 equivalents of the TBAI catalyst and three equivalents of sodium carbonate were used to ensure that the *N*,*N*-dialkylation was essentially complete after a reasonable length of time (20 h reflux time). In contrast, *N*,*N*-dialkylation using 1,2-bis(bromomethyl)benzene (entry 2) presented no such problems: the reaction was complete after 3 h of reflux (and probably sooner). The corresponding reaction in the absence of the TBAI catalyst did, however, have to be refluxed for 19 h to reach completion.

As mentioned previously, the role of the intermediate aqueous work-up in the sequential two-step method was to remove the TBAI catalyst prior to the diamine forming step. Given that we knew we could prepare amino alcohol (*R*)-**32** [*via* *N*,*N*-dialkylation using 1,2-bis(bromomethyl)benzene] in THF without added TBAI and given that we had already shown that mesylation and diamine formation could be carried out in THF, we wondered whether we could omit the aqueous work-up and carry out a one-pot synthesis of diamine (*S*)-**33**. With this in mind, amino alcohol (*R*)-**32** was prepared in the absence of TBAI (refluxing THF, 19 h) and the reaction mixture filtered to remove the solids. Then, this THF solution of the crude amino alcohol (*R*)-**32** was treated sequentially with mesyl chloride and then methylamine to give diamine (*S*)-**33** in 70% isolated yield (Scheme 9). Thus, we were able to prepare diamine (*S*)-**33** *via* an essentially one-pot process.

The *N*,*N*-dialkylation route for diamine synthesis was not as easy to develop as the styrene oxide approach. However, *via* a sequential two-step process, it did enable us to prepare diamines (*S*)-**1** with substituents other than pyrrolidinyl or piperidinyl rings.

Conclusions

The development of useful methods for the preparation of either enantiomer of chiral diamines **1** is an issue that is still attracting synthetic interest.[23] Using Dieter's and Rossiter's seminal contributions, we have developed a particularly useful and high yielding synthesis from styrene oxide. One limitation of this method is that (*S*)-styrene oxide is expensive. Thus, the *N*,*N*-dialkylation route from (*R*)-phenylglycinol is the method of choice for the synthesis of diamines (*S*)-**1**. Alternatively, Singh's recently published route[23] to diamines (*S*)-**1** from (*S*)-mandelic acid is as good if not better than our route from



Scheme 9 *Reagents and conditions:* i, 2 equiv. Na_2CO_3, equiv. 1,2-bis(bromomethyl)benzene, THF, reflux, 19 h; ii, filter and dilute with THF; iii, 3 equiv. Et_3N, 1.2 equiv. MsCl, Et_2O, 0 °C, 30 min; iv, 2 equiv. Et_3N, $MeNH_2$, water, rt, 16 h (70%)

(*R*)-phenylglycinol. In contrast, for the synthesis of diamines (*R*)-**1**, we recommend the use of our one-pot method from (*R*)-styrene oxide.

Experimental

General

Et_2O and THF were dried over sodium–benzophenone and distilled before use. Petrol refers to the fraction of light petroleum boiling in the range 40–60 °C and was redistilled in Winchester quantities before use. Triethylamine was stored over potassium hydroxide pellets. All non-aqueous reactions were carried out under oxygen-free nitrogen using over-dried glassware. Flash column chromatography[37] was carried out using Merck 7734 silica gel or ICN Biomedicals GmbH 33–63 silica (60 Å). Thin layer chromatography was carried out on commercially available Merck 5554 aluminium-backed silica plates.

Proton (270 MHz) and carbon (67.5 MHz) NMR spectra were recorded on a JEOL EX-270 spectrometer using an internal deuterium lock. Proton (500 MHz) NMR spectra were recorded on a Bruker AMX-500 spectrometer using an internal deuterium lock. All samples were recorded as solutions in deuteriated chloroform and chemical shifts are quoted in parts per million downfield of tetramethylsilane. Coupling constant (*J*) values are given in Hz. Carbon NMR spectra were recorded with broad band proton decoupling and were assigned using DEPT experiments.

Melting points were measured on an Electrothermal IA 9100 digital or a Gallenkamp melting point apparatus and are uncorrected. Boiling points given for compounds purified by Kugelrohr distillation correspond to the oven temperature during the distillation. Infrared spectra were recorded on an ATI Mattson Genesis FTIR spectrometer as neat films, as solutions in chloroform or as Nujol mulls. Chemical ionisation and high resolution mass spectra were recorded on a Fisons Analytical (VG) Autospec spectrometer. Optical rotations were recorded on a JASCO DIP-370 polarimeter (using the sodium D line; 589 nm) at 20 °C and $[\alpha]_D$ are given in units of 10^{-1} deg cm^{-2} g^{-1}.

Details of the synthesis of diamines (*R*)- and (*S*)-**4** using *both* methods have been reported in full elsewhere.[3]

General methods for diamine synthesis

Method A: one-pot synthesis from styrene oxide. (*R*)-Styrene oxide (4.4 mmol) was added to a stirred solution of pyrrolidine or piperidine (7.2 mmol) in EtOH (15 cm^3) and the resulting mixture was heated under reflux for 2–3 h. After cooling, the solvent was evaporated under reduced pressure to give the crude product which was thoroughly dried for at least 1 h under high vacuum (during which time the product usually crystallised). Under nitrogen, this crude product was dissolved in Et_2O (20 cm^3), triethylamine (13.2 mmol; 3 equiv.) was added and the solution was cooled to 0 °C. Then, methanesulfonyl (mesyl) chloride (5.3 mmol; 1.2 equiv.) was added dropwise. A white precipitate formed which made stirring difficult and after 30 min, triethylamine (8.8 mmol; 2 equiv.) was added. After being allowed to warm to room temperature, the amine (1–50 equiv.) and then water‡ (2.5 cm^3) were added and the resulting two-phase reaction mixture was vigorously stirred. After 16 h, the layers were separated and the light-brown aqueous layer was extracted with Et_2O (3 × 30 cm^3). The combined organic extracts were washed with 5% aqueous sodium hydrogen carbonate (30 cm^3) and water (30 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product as an oil or a solid which was purified by Kugelrohr distillation or flash chromatography.

Method B: sequential two-step synthesis from phenylglycinol. Sodium carbonate (2 or 3 equiv.), tetra-*n*-butylammonium iodide (0.1 or 0.5 equiv.) and alkylating agent [2 equiv. of benzyl bromide; 1 equiv. of 1,2-bis(bromomethyl)benzene or 1,4-dibromobutane] were added successively to a stirred solution of (*R*)-phenylglycinol (500 mg, 3.6 mmol) in THF (15 cm^3) at room temperature under nitrogen. The resulting suspension was heated at reflux for 3–20 h. After being allowed to cool to room temperature, the solids were removed by filtration and the filtrate was evaporated under reduced pressure. The residue was dissolved in Et_2O (20 cm^3), washed with water (3 × 20 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product as a yellow oil. Under nitrogen, this crude product was dissolved in Et_2O (15 cm^3), triethylamine (10.8 mmol; 3 equiv.) was added and the solution was cooled to 0 °C. Then, methanesulfonyl chloride (7.2 mmol; 2 equiv.) was added dropwise. A white precipitate formed which made stirring difficult and after 30 min, triethylamine (7.2 mmol; 2 equiv.) was added. After being allowed to warm to room temperature, aqueous methylamine (4.5 cm^3 of a 40% solution, 61.2 mmol; 17 equiv.) was added and the resulting two-phase reaction mixture was vigorously stirred. After 16 h, the layers were separated and the light-brown aqueous layer was extracted with Et_2O (3 × 20 cm^3). The combined organic extracts were washed with 5% aqueous sodium hydrogen carbonate (20 cm^3) and water (20 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product as an oil which was purified by Kugelrohr distillation or flash chromatography.

General procedure for determination of enantiomeric excess of diamines using (*R*)-1-phenyl-2,2,2-trifluoroethanol as a chiral solvating agent

The purity of both racemic and optically active diamines was established by initially recording 270 MHz ^{1}H NMR spectra in the presence of no additives. Then, a sample containing 1–2 mg of *racemic* diamine and 8–15 mg of (*R*)-1-phenyl-2,2,2-trifluoroethanol (4–6 equiv.) in 2 cm^3 of $CDCl_3$ was prepared. The 270 MHz ^{1}H NMR spectrum of this sample was recorded and the peaks due to the two enantiomers of the diamines were identified. Next, a sample containing 1–2 mg of *optically active* diamine and 8–15 mg of (*R*)-1-phenyl-2,2,2-trifluoroethanol (4–6 equiv.) in 2 cm^3 of $CDCl_3$ was prepared and the 270 MHz ^{1}H NMR spectrum of this sample was recorded. In all cases, the presence of only one set of peaks indicated that the *optically active* diamines had ⩾95% ee.

(*R*)-2-(Pyrrolidin-1-yl)-1-phenylethanol (*R*)-17 and (*S*)-2-(pyrrolidin-1-yl)-2-phenylethanol (*S*)-18

(*R*)-Styrene oxide (4.4 mmol) was added to a stirred solution of

‡ With aqueous methylamine (40%) and aqueous ammonia (30%), water was not added.

pyrrolidine (7.2 mmol) in EtOH (15 cm^3) and the resulting mixture was heated under reflux for 2 h. After cooling, the solvent was evaporated under reduced pressure to give the crude product which was thoroughly dried for at least 1 h under high vacuum. Analysis by ^1H NMR spectroscopy indicated that a 70:30 mixture of amino alcohols (*R*)-**17** and (*S*)-**18** had been generated. Diagnostic signals for known[25] amino alcohol (*R*)-**17**: δ_H(270 MHz; $CDCl_3$) 4.76 (1 H, dd, *J* 3.2 and 10.4, PhC*H*OH); δ_C(67.5 MHz; $CDCl_3$) 70.7 (PhCHOH), 64.1 (CH*C*H_2N), 53.8 (CH_2NCH_2) and 23.6 (CH_2CH_2). Diagnostic signals for amino alcohol (*S*)-**18**: δ_H(270 MHz; $CDCl_3$) 3.92 (1 H, dd, *J* 5.8 and 10.7, CH_AH_BOH), 3.84 (1 H, dd, *J* 5.3 and 10.7, CH_AH_BOH) and 3.54 (1 H, t, *J* 5.8, PhC*H*N); δ_C(67.5 MHz; $CDCl_3$) 69.9 (PhCHN), 64.3 (CH_2OH), 51.2 (CH_2NCH_2) and 23.0 (CH_2CH_2).

(*R*)-2-(Piperidin-1-yl)-1-phenylethanol (*R*)-12 and (*S*)-2-(piperidin-1-yl)-2-phenylethanol (*S*)-20

(*R*)-Styrene oxide (4.4 mmol) was added to a stirred solution of piperidine (7.2 mmol) in EtOH (15 cm^3) and the resulting mixture was heated under reflux for 3 h. After cooling, the solvent was evaporated under reduced pressure to give the crude product which was thoroughly dried for at least 1 h under high vacuum. Analysis by ^1H NMR spectroscopy indicated that a 70:30 mixture of amino alcohols (*R*)-**12** and (*S*)-**20** had been generated. Diagnostic signal for known[25] amino alcohol (*R*)-**12**: δ_H(500 MHz, $CDCl_3$) 4.71 (1 H, dd, *J* 3.5 and 10.6, PhC*H*OH). Diagnostic signals for amino alcohol (*S*)-**20**: δ_H(500 MHz; $CDCl_3$) 3.97 (1 H, t, *J* 10.0, PhC*H*N), 3.67 (1 H, dd, *J* 5.2 and 9.9, CH_AH_BOH) and 3.61 (1 H, dd, *J* 5.2 and 10.3, CH_AH_BOH).

(*R*)-*N*-Methyl-1-phenyl-2-(piperidin-1-yl)ethanamine (*R*)-5

Using general method A, (*R*)-styrene oxide (0.5 cm^3, 4.4 mmol), piperidine (0.65 cm^3, 6.6 mmol) and aqueous methylamine (6.0 cm^3; 40%, 81.6 mmol) gave a crude product which was purified by flash chromatography on silica with CH_2Cl_2–MeOH (20:1→10:1) as eluent to give diamine (*R*)-**5** (852 mg, 89%) as a colourless oil, R_f (10:1 CH_2Cl_2–MeOH) 0.3; $[\alpha]_D$ −94.4 (*c* 1.9 in $CHCl_3$) {lit.,[11] $[\alpha]_D$ −107 (*c* 1.23 in $CHCl_3$)}; ν_{max}($CHCl_3$)/cm^{-1} 3683 (NH), 1603 (Ph) and 1520 (Ph); δ_H(270 MHz; $CDCl_3$) 7.39–7.21 (5 H, m, Ph), 3.64 (1 H, dd, *J* 3.4 and 10.9, PhC*H*NH), 3.26 (1 H, br s, NH), 2.60–2.45 (2 H, m, CH_2N), 2.51 (1 H, dd, *J* 10.9 and 12.6, CH_AH_BN), 2.33–2.27 (3 H, m, CH_2N and CH_AH_BN), 2.30 (3 H, s, NH*Me*), 1.65–1.54 (4 H, m, 2 × CH_2) and 1.47–1.41 (2 H, m, CH_2); δ_C(67.5 MHz; $CDCl_3$) 142.6 (*ipso*-Ph), 128.2 (Ph), 127.4 (Ph), 127.0 (Ph), 66.6 (CH*C*H_2N), 62.3 (PhCHN), 54.7 (CH_2NCH_2), 34.6 (NHMe), 26.1 (2 × CH_2) and 24.4 (CH_2); *m*/*z* 219 [100%, $(M + H)^+$], 188 (5, M − NHMe) and 98 (75, $CH_2NC_5H_{10}$) [Found: $(M + H)^+$, 219.1862. $C_{14}H_{22}N_2$ requires *M* + H, 219.1861].

(*R*)-1-Phenyl-2-(pyrrolidin-1-yl)ethanamine (*R*)-21

Using general method A, (*R*)-styrene oxide (0.5 cm^3, 4.4 mmol), pyrrolidine (0.6 cm^3, 7.2 mmol) and aqueous ammonia (12.5 cm^3 of a 30% solution, 220 mmol) gave a crude product which was purified by Kugelrohr distillation to give diamine (*R*)-**21** (663 mg, 79%) as a colourless liquid, bp 140–150 °C/1 mmHg (lit.,[7] 110–120 °C/0.2 mmHg); R_f (10:1 CH_2Cl_2–MeOH) 0.4; $[\alpha]_D$ −42.6 (*c* 1.6 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3384 (NH), 2964, 2796, 1602 (Ph), 1454, 1351, 759 and 700; δ_H(270 MHz; $CDCl_3$) 7.40–7.21 (5 H, m, Ph), 4.09 (1 H, dd, *J* 3.6 and 10.4, PhC*H*NH_2), 2.76 (1 H, dd, *J* 10.4 and 11.9, CH_AH_BN), 2.69–2.66 (2 H, m, CH_2N), 2.52–2.48 (2 H, m, CH_2N), 2.38 (1 H, dd, *J* 3.6 and 11.9, CH_AH_BN), 2.95 (2 H, br s, NH_2) and 1.81–1.76 (4 H, m, CH_2CH_2); δ_C(67.5 MHz; $CDCl_3$) 144.5 (*ipso*-Ph), 128.4 (Ph), 127.1 (Ph), 126.6 (Ph), 65.0 (CH*C*H_2N), 54.6 (PhCHN), 54.3 (CH_2NCH_2) and 23.6 (CH_2CH_2); *m*/*z* 191 [100%, $(M + H)^+$], 106 (15, M − $CH_2NC_4H_8$) and 84 (25, $CH_2NC_4H_8$) [Found: $(M + H)^+$, 191.1543. $C_{13}H_{20}N_2$ requires *M* + H, 191.1548].

(*R*)-*N*-(1,1-Dimethylethyl)-1-phenyl-2-(pyrrolidin-1-yl)-ethanamine (*R*)-22

Using general method A, (*R*)-styrene oxide (0.5 cm^3, 4.4 mmol), pyrrolidine (0.6 cm^3, 7.2 mmol) and *tert*-butylamine (5.4 cm^3, 47.0 mmol) gave a crude product which was purified by Kugelrohr distillation to give diamine (*R*)-**22** (986 mg, 90%) as a pale yellow oil, bp 150–160 °C/1 mmHg; R_f (10:1 CH_2Cl_2–MeOH) 0.4; $[\alpha]_D$ −78.7 (*c* 1.6 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3296 (NH), 2964, 2800, 1602 (Ph), 1363, 1230, 759 and 701; δ_H(270 MHz; $CDCl_3$) 7.41 (2 H, d, *J* 7.0, *o*-Ph), 7.27–7.22 (2 H, m, *m*-Ph), 7.20 (1 H, d, *J* 7.0, *p*-Ph), 3.86 (1 H, dd, *J* 3.6 and 10.9, PhC*H*NH), 2.70 (1 H, t, *J* 11.4, CH_AH_BN), 2.66–2.63 (2 H, m, CH_2N), 2.45–2.42 (2 H, m, CH_2N), 2.15 (1 H, dd, *J* 3.6 and 12.1, CH_AH_BN), 1.73–1.77 (4 H, m, CH_2CH_2) and 0.97 (9 H, s, CMe_3); δ_C(67.5 MHz; $CDCl_3$) 146.5 (*ipso*-Ph), 128.0 (Ph), 127.3 (Ph), 126.6 (Ph), 64.6 (CH*C*H_2N), 56.4 (PhCHN), 53.8 (CH_2NCH_2), 50.9 (*C*Me), 30.3 (C*Me*$_3$) and 23.6 (CH_2CH_2); *m*/*z* 247 [100%, $(M + H)^+$], 162 (15, M − $CH_2NC_4H_8$) and 84 (20, $CH_2NC_4H_8$) [Found: $(M + H)^+$, 247.2177. $C_{13}H_2N_2$ requires *M* + H, 247.2174].

(*R*)-*N*-Phenyl-1-phenyl-2-(pyrrolidin-1-yl)ethanamine (*R*)-23

Using general method A, (*R*)-styrene oxide (0.5 cm^3, 4.4 mmol), pyrrolidine (0.6 cm^3, 7.2 mmol) and aniline (0.5 cm^3, 4.4 mmol) gave a crude product which was purified by flash chromatography on silica with CH_2Cl_2–MeOH (40:1→10:1) as eluent to give diamine (*R*)-**23** (897 mg, 78%) as a white solid, mp 61–62 °C [from CH_2Cl_2–MeOH (10:1)]; R_f (10:1 CH_2Cl_2–MeOH) 0.4; $[\alpha]_D$ + 13.4 (*c* 1.8 in $CHCl_3$); ν_{max}(Nujol)/cm^{-1} 3351 (NH), 1606 (Ph) and 1602 (Ph); δ_H(270 MHz; $CDCl_3$) 7.44–7.21 (5 H, m, Ph), 7.06 (2 H, dd, *J* 7.3 and 8.5, *m*-PhNH), 6.65 (1 H, t, *J* 7.4, *p*-NHPh), 6.53 (2 H, dd, *J* 1.0 and 8.5, *o*-NHPh), 5.29 (1 H, br s, NH), 4.27 (1 H, dd, *J* 4.1 and 11.2, PhC*H*NH), 2.92 (1 H, t, *J* 11.6, CH_AH_BN), 2.65–2.55 (2 H, m, CH_2N), 2.53–2.50 (2 H, m, CH_2N), 2.49 (1 H, dd, *J* 4.1 and 12.3, CH_AH_BN) and 1.82–1.77 (4 H, m, CH_2CH_2); δ_C(67.5 MHz; $CDCl_3$) 148.4 (*ipso*-NHPh), 143.0 (*ipso*-Ph), 128.9 (Ph), 128.6 (Ph), 127.1 (Ph), 126.3 (Ph), 117.4 (*p*-NHPh), 114.1 (*o*-NHPh), 63.3 (CH*C*H_2N), 57.4 (PhCHN), 53.6 (CH_2NCH_2) and 23.6 (CH_2CH_2); *m*/*z* 267 [100%, $(M + H)^+$], 182 (30, M − $CH_2NC_4H_8$), 94 (20, NH_3Ph) and 84 (95, $CH_2NC_4H_8$) [Found: $(M + H)^+$, 267.1866. $C_{13}H_{20}N_2$ requires *M* + H, 267.1861].

(*R*)-*N*-Benzyl-1-phenyl-2-(pyrrolidin-1-yl)ethanamine (*R*)-24

Using general method A, (*R*)-styrene oxide (0.5 cm^3, 4.4 mmol), pyrrolidine (0.6 cm^3, 7.2 mmol) and benzylamine (0.5 cm^3, 4.4 mmol) gave a crude product which was purified by flash chromatography on silica with CH_2Cl_2–MeOH (40:1→10:1) as eluent to give diamine (*R*)-**24** (980 mg, 80%) as a colourless oil, R_f (10:1 CH_2Cl_2–MeOH) 0.2; $[\alpha]_D$ −92.2 (*c* 1.8 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3305 (NH), 2964, 2796, 1602 (Ph), 1452, 757 and 700; δ_H(270 MHz; $CDCl_3$) 7.43–7.19 (10 H, m, 2 × Ph), 3.76 (1 H, d, *J* 13.6, PhCH_AH_BN), 3.72 (1 H, dd, *J* 3.4 and 11.9, PhC*H*NH), 3.47 (1 H, d, *J* 13.6, PhCH_AH_BN), 3.05 (1 H, br s, NH), 2.88 (1 H, t, *J* 11.9, CH_AH_BN), 2.54–2.41 (4 H, m, CH_2NCH_2), 2.25 (1 H, dd, *J* 3.4 and 11.9, CH_AH_BN) and 1.76–1.71 (4 H, m, CH_2CH_2); δ_C(67.5 MHz; $CDCl_3$) 142.7 (*ipso*-Ph), 140.8 (*ipso*-Ph), 128.4 (Ph), 128.2 (Ph), 127.5 (Ph), 127.2 (Ph), 126.7 (Ph), 63.5 (CH*C*H_2N), 60.3 (PhCHN), 53.9 (CH_2NCH_2), 51.3 ($NHCH_2Ph$) and 23.5 (CH_2CH_2); *m*/*z* 281 [100%, $(M + H)^+$], 196 (25, M − $CH_2NC_4H_8$), 106 (15, $NHCH_2Ph$) and 84 (70, $CH_2NC_4H_8$) [Found: $(M + H)^+$, 281.2018. $C_{19}H_{24}N_2$ requires *M* + H, 281.2018].

(*R*)-*N*-Benzyl-1-phenyl-2-(piperidin-1-yl)ethanamine (*R*)-25

Using general method A, (*R*)-styrene oxide (0.5 cm^3, 4.4 mmol), pyrrolidine (0.65 cm^3, 6.6 mmol) and benzylamine (0.5 cm^3, 4.4 mmol) gave a crude product which was purified by flash

chromatography on silica with CH_2Cl_2–MeOH (40:1→10:1) as eluent to give diamine (*R*)-**25** (1.2 g, 93%) as a white solid, mp 63–67 °C (lit.,[11] 57–61 °C); R_f (10:1 CH_2Cl_2–MeOH) 0.2; $[\alpha]_D$ −108.6 (*c* 2.0 in $CHCl_3$) {lit.,[11] $[\alpha]_D$ +107 (*c* 1.98 in $CHCl_3$) for (*S*)-**25**}; ν_{max}($CHCl_3$)/cm^{-1} 3683 (NH), 1602 (Ph) and 1520 (Ph); δ_H(270 MHz; $CDCl_3$) 7.42–7.20 (10 H, m, 2 × Ph), 3.78 (1 H, d, *J* 13.6, PhCH_AH_BN), 3.72 (1 H, dd, *J* 3.4 and 11.2, PhC*H*NH), 3.46 (1 H, d, *J* 13.6, PhCH_AH_BN), 2.90 (1 H, br s, NH), 2.45–2.38 (2 H, m, CH_2N), 2.45 (1 H, dd, *J* 11.2 and 12.4, CH_AH_BN), 2.24–21.8 (2 H, m, CH_2N), 2.20 (1 H, dd, *J* 3.4 and 12.4, CH_AH_BN), 1.59–1.144 (4 H, m, 2 × CH_2) and 1.42–1.38 (2 H, m, CH_2); δ_C(67.5 MHz; $CDCl_3$) 142.85 (*ipso*-Ph), 140.9 (*ipso*-Ph), 128.3 (Ph), 128.2 (Ph), 127.9 (Ph), 127.6 (Ph), 127.0 (Ph), 126.6 (Ph), 66.3 (CH*C*H_2N), 58.0 (PhCHN) 54.4 (CH_2NCH_2), 51.15 ($NHCH_2Ph$), 26.1 (2 × CH_2) and 24.4 (CH_2); *m*/*z* 295 [100%, $(M + H)^+$], 196 (15, M − $CH_2NC_5H_{10}$), 106 (10, $NHCH_2Ph$) and 98 (80, $CH_2NC_5H_{10}$) [Found: $(M + H)^+$, 295.2172. $C_{20}H_{26}N_2$ requires *M* + H, 295.2174].

(1*R*)-*N*-[(1*S*)-1-Phenylethyl]-1-phenyl-2-(pyrrolidin-1-yl)-ethanamine (*S*,*R*)-26

Using general method A, (*R*)-styrene oxide (0.5 cm^3, 4.4 mmol), pyrrolidine (0.6 cm^3, 7.2 mmol) and (0.6 cm^3, 4.6 mmol) gave a crude product which was purified by flash chromatography on silica with CH_2Cl_2–MeOH (20:1→10:1) as eluent to give diamine (*S*,*R*)-**26** (960 mg, 74%) as a colourless oil, R_f (10:1 CH_2Cl_2–MeOH) 0.2; $[\alpha]_D$ −131.4 (*c* 2.3 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3305 (NH), 1603 (Ph) and 1585 (Ph); δ_H(270 MHz; $CDCl_3$) 7.35–7.14 (10 H, m, 2 × Ph), 3.48 (1 H, q, *J* 6.8, C*H*Me), 3.40 (1 H, dd, *J* 3.4 and 11.4, PhC*H*NH), 2.90 (1 H, br s, NH), 2.81 (1 H, dd, *J* 11.4 and 11.9, CH_AH_BN), 2.33–2.29 (4 H, m, CH_2NCH_2), 2.07 (1 H, dd, *J* 3.4 and 11.9, CH_AH_BN), 1.75–1.68 (4 H, m, CH_2CH_2) and 1.34 (3 H, d, *J* 6.8, CH*Me*); δ_C(67.5 MHz; $CDCl_3$) 146.1 (*ipso*-Ph), 143.2 (*ipso*-Ph), 128.2 (Ph), 128.0 (Ph), 127.5 (Ph), 127.0 (Ph), 126.6 (Ph), 126.5 (Ph), 63.6 (CH*C*H_2N), 58.3 (PhCHN), 54.8 (NH*C*HMe), 53.8 (CH_2NCH_2), 24.5 (CH*Me*) and 23.5 (CH_2CH_2); *m*/*z* 295 [100%, $(M + H)^+$], 210 (30, M − $CH_2NC_4H_8$) and 84 (70, $CH_2NC_4H_8$) [Found: $(M + H)^+$, 295.2174. $C_{20}H_{26}N_2$ requires *M* + H, 295.2174].

(1*R*)-*N*-[(1*R*)-1-Phenylethyl]-1-phenyl-2-(pyrrolidin-1-yl)-ethanamine (*R*,*R*)-26

Using general method A, (*R*)-styrene oxide (0.5 cm^3, 4.4 mmol), pyrrolidine (0.6 cm^3, 7.2 mmol) and (*R*)-α-methylbenzylamine (0.6 cm^3, 4.6 mmol) gave a crude product which was purified by flash chromatography on silica with CH_2Cl_2–MeOH (20:1→10:1) as eluent to give diamine (*R*,*R*)-**26** (1.04 g, 80%) as a colourless viscous oil, R_f (10:1 CH_2Cl_2–MeOH) 0.2; $[\alpha]_D$ −29.7 (*c* 2.1 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3302 (NH) and 1603 (Ph); δ_H(270 MHz; $CDCl_3$) 7.35–7.11 (10 H, m, 2 × Ph), 3.93 (1 H, dd, *J* 4.1 and 10.2, PhC*H*NH), 3.68 (1 H, q, *J* 6.6, C*H*Me), 2.83 (1 H, dd, *J* 10.2 and 12.1, CH_AH_BN), 2.59–2.50 (2 H, m, CH_2N), 2.50–2.44 (3 H, m, CH_2N and NH), 2.32 (1 H, dd, *J* 4.1 and 12.1, CH_AH_BN), 1.78–1.73 (4 H, m, CH_2CH_2) and 1.36 (3 H, d, *J* 6.6, CH*Me*); δ_C(67.5 MHz; $CDCl_3$) 146.4 (*ipso*-Ph), 143.6 (*ipso*-Ph), 128.1 (Ph), 128.0 (Ph), 127.4 (Ph), 126.8 (Ph), 126.6 (Ph), 126.4 (Ph), 63.8 (CH*C*H_2N), 59.5 (PhCHN), 54.6 (NH*C*HMe), 54.0 (CH_2NCH_2), 23.6 (CH*Me*) and 21.5 (CH_2CH_2); *m*/*z* 295 [100%, $(M + H)^+$], 210 (30, M − $CH_2NC_4H_8$) and 84 (60, $CH_2NC_4H_8$) [Found: $(M + H)^+$, 295.2175. $C_{20}H_{26}N_2$ requires *M* + H, 295.2174].

Bis[(*R*)-1-phenyl-2-pyrrolidin-1-ylethyl]amine 27

Using general method A, (*R*)-styrene oxide (0.18 cm^3, 1.6 mmol), pyrrolidine (0.21 cm^3, 2.53 mmol) and diamine (*R*)-**21** (300 mg, 1.6 mmol) gave a crude product which was purified by Kugelrohr distillation to give diamine (*R*,*R*)-**27** (359 mg, 63%) as a yellow solid, mp 59–62 °C, bp 210–220 °C/1 mmHg; R_f (10:1 CH_2Cl_2–MeOH) 0.1; $[\alpha]_D$ −125.2 (*c* 1.8 in $CHCl_3$); ν_{max}(Nujol)/cm^{-1} 1602 (Ph) and 1525 (Ph); δ_H(270 MHz; $CDCl_3$) 7.34–7.21 (10 H, m, 2 × Ph), 3.45 (2 H, dd, *J* 4.4 and 9.9, 2 × PhC*H*NH), 2.96 (1 H, br, NH), 2.92 (2 H, dd, *J* 9.9 and 11.9, 2 × CH_AH_BN), 2.32–2.29 (8 H, br s, 2 × CH_2NCH_2), 2.23 (2 H, dd, *J* 4.4 and 11.9, 2 × CH_AH_BN) and 1.71–1.66 (8 H, m, 2 × CH_2CH_2); δ_C(67.5 MHz; $CDCl_3$) 143.6 (2 × *ipso*-Ph), 128.2 (2 × Ph), 127.4 (2 × Ph), 126.9 (2 × Ph), 63.4 (2 × CH*C*H_2N), 58.7 (2 × PhCHN), 54.1 (2 × CH_2NCH_2) and 23.4 (2 × CH_2CH_2); *m*/*z* 364 [100%, $(M + H)^+$], 279 (20, M − $CH_2NC_4H_8$), 106 (20, $PhCHNH_2$) and 84 (20, $CH_2NC_4H_8$) [Found: $(M + H)^+$, 364.2755. $C_{24}H_{33}N_2$ requires *M* + H, 364.2753].

(*R*)-2-(*N*,*N*-Dibenzylamino)-2-phenylethan-1-ol (*R*)-29

Sodium carbonate (510 mg, 4.8 mmol), tetra-*n*-butylammonium iodide (90 mg, 0.24 mmol) and benzyl bromide (0.58 cm^3, 4.8 mmol) were added successively to a stirred solution of (*R*)-phenylglycinol (330 mg, 2.4 mmol) in THF (10 cm^3) at room temperature under nitrogen. The resulting suspension was heated at reflux for 19 h. After being allowed to cool to room temperature, the solids were removed by filtration and the filtrate was evaporated under reduced pressure. The residue was dissolved in Et_2O (10 cm^3), washed with water (20 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product as a yellow oil. Purification by flash chromatography on silica with light petroleum–Et_2O (4:1) as eluent gave known[32] amino alcohol (*R*)-**29** (600 mg, 79%) as an oil, R_f (4:1 EtOAc–light petroleum) 0.6; $[\alpha]_D$ −118.2 (*c* 5.5 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3444 (OH), 3028, 1493 and 1450; δ_H(270 MHz; $CDCl_3$) 7.45–7.22 (15 H, m, 3 × Ph), 4.14 (1 H, t, *J* 10.6, CH_AH_BOH), 3.96–3.90 (1 H, m, CH_AH_BOH), 3.93 (2 H, d, *J* 13.3, 2 × PhCH_AH_BN), 3.60 (1 H, dd, *J* 5.1 and 10.6, PhCHN), 3.19 (2 H, d, *J* 13.3, 2 × $PhCH_AH_B$N) and 3.02 (1 H, br s, OH); δ_C(67.5 MHz; $CDCl_3$) 139.1 (*ipso*-NCH_2Ph), 135.1 (*ipso*-PhCHN), 129.3 (Ph), 129.0 (Ph), 128.6 (Ph), 128.4 (Ph), 128.0 (Ph), 127.3 (Ph), 63.0 (PhCHN), 60.4 (CH_2OH) and 53.5 (2 × NCH_2Ph); *m*/*z* 318 [100%, $(M + H)^+$], 300 (5, M − OH), 286 (50, M − CH_2OH), 196 (15) and 91 (55, $PhCH_2$) [Found: $(M + H)^+$, 318.1853. $C_{22}H_{23}NO$ requires *M* + H, 318.1857].

(*S*)-*N*-Methyl-2-(*N*,*N*-dibenzylamino)-1-phenylethanamine (*S*)-31

Triethylamine (0.63 cm^3, 4.5 mmol) was added dropwise to a stirred solution of amino alcohol (*R*)-**29** (473 mg, 1.5 mmol) in Et_2O (10 cm^3) at 0 °C under nitrogen. Then, methanesulfonyl chloride (0.14 cm^3, 1.8 mmol) was added dropwise. A white precipitate formed which made stirring difficult and after 30 min, triethylamine (0.42 cm^3, 3.0 mmol) was added. After being allowed to warm to room temperature, aqueous methylamine (1.9 cm^3; 40%; 25.8 mmol) was added and the resulting two-phase reaction mixture was vigorously stirred. After 16 h, the layers were separated and the light-brown aqueous layer was extracted with Et_2O (3 × 30 cm^3). The combined organic extracts were washed with 5% aqueous sodium hydrogen carbonate (20 cm^3) and water (20 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product as a yellow oil. Purification by flash chromatography on silica with CH_2Cl_2–MeOH (10:1) as eluent gave diamine (*S*)-**31** (410 mg, 83%) as a yellow oil, R_f (4:1 EtOAc–light petroleum) 0.2; $[\alpha]_D$ +74.1 (*c* 1.0 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3329 (NH), 2792, 1493, 1446 and 1115; δ_H(270 MHz; $CDCl_3$) 7.35–7.18 (5 H, m, 3 × Ph), 3.73 (2 H, d, *J* 13.8, 2 × PhCH_AH_BN), 3.51 (2 H, d, *J* 13.8, 2 × $PhCH_AH_B$N), 3.48 (1 H, dd, *J* 4.0 and 10.2, PhCHN), 2.72 (1 H, dd, *J* 10.2 and 12.7, CH_AH_BN), 2.50 (1 H, dd, *J* 4.0 and 12.7, CH_AH_BN), 2.30 (1 H, br s, NH) and 2.14 (3 H, s, NH*Me*); δ_C(67.5 MHz; $CDCl_3$) 142.4 (*ipso*-Ph), 139.2 (*ipso*-Ph), 128.9 (Ph), 128.7 (Ph), 128.3 (Ph), 128.25 (Ph), 127.5 (Ph), 127.3 (Ph), 63.4 (PhCHN), 62.3 (CH*C*H_2N), 59.2 (2 × NCH_2Ph) and 34.6 (NHMe); *m*/*z* 331 [100%, $(M + H)^+$], 210 (45, M − PhCHNHMe) and 120 [20, M −

$CH_2N(CH_2Ph)_2$] [Found: $(M + H)^+$, 331.2174. $C_{23}H_{26}N_2$ requires $M + H$, 321.2172].

(*S*)-*N*-Methyl-2-(*N*,*N*-dibenzylamino)-1-phenylethanamine (*S*)-31

Using general method B, sodium carbonate (760 mg, 7.2 mmol), tetra-*n*-butylammonium iodide (140 mg, 0.36 mmol), benzyl bromide (0.87 cm^3, 7.2 mmol), (*R*)-phenylglycinol (500 mg, 3.6 mmol) and aqueous methylamine (4.5 cm^3 of a 40% solution, 61.2 mmol) gave a crude product which was purified by flash chromatography on silica with EtOAc–light petroleum (4:1) as eluent to give diamine (*S*)-**31** (740 mg, 62%) as a yellow oil, R_f (4:1 EtOAc–light petroleum) 0.2; $[a]_D$ +80.6 (*c* 1.9 in $CHCl_3$).

(*S*)-*N*-Methyl-2-(isoindolin-2-yl)-1-phenylethanamine (*S*)-33

Using general method B, sodium carbonate (760 mg, 7.2 mmol), tetra-*n*-butylammonium iodide (140 mg, 0.36 mmol), 1,2-bis(bromomethyl)benzene (950 mg, 3.6 mmol), (*R*)-phenylglycinol (500 mg, 3.6 mmol) and aqueous methylamine (4.5 cm^3; 40%; 61.2 mmol) gave a crude product which was purified by flash chromatography on silica with EtOAc–petrol (4:1) as eluent to give diamine (*S*)-**33** (630 mg, 69%) as a yellow oil, R_f (20:1 CH_2Cl_2–MeOH) 0.25; $[a]_D$ −6.2 (*c* 1.8 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3325 (NH), 2935, 2785, 1466 and 1146; δ_H(270 MHz; $CDCl_3$) 7.43–7.03 (9 H, m, Ph and Ar), 4.07 (2 H, d, *J* 11.2, 2 × ArCH_AH_BN), 3.95 (2 H, d, *J* 11.2, 2 × ArCH_AH_BN), 3.67 (1 H, dd, *J* 3.5 and 10.9, PhCHN), 2.99 (1 H, dd, *J* 10.9 and 12.1, CH_AH_BN), 2.73 (1 H, dd, *J* 3.5 and 12.1, CH_AH_BN), 2.32 (3 H, s, NH*Me*) and 2.18–2.16 (1 H, br s, NH); δ_C(67.5 MHz; $CDCl_3$) 142.3 (*ipso*-Ar), 139.9 (*ipso*-Ar), 128.4 (Ar), 127.4 (Ar), 127.2 (Ar), 126.8 (Ar), 122.2 (Ar), 64.2 (PhCHN), 63.4 (CHCH_2N), 59.5 (2 × NCH_2Ar) and 34.8 (NHMe); *m*/*z* 253 [100%, $(M + H)^+$], 132 (20, M − PhCHNHMe) and 120 (20, M − $CH_2NC_8H_8$) [Found: $(M + H)^+$, 253.1705. $C_{17}H_{20}N_2$ requires $M + H$, 253.1702].

(*S*)-*N*-Methyl-1-phenyl-2-(pyrrolidin-1-yl)ethanamine (*S*)-4

Using general method B, sodium carbonate (770 mg, 7.2 mmol), tetra-*n*-butylammonium iodide (450 mg, 1.2 mmol), 1.4-dibromobutane (0.29 cm^3, 2.4 mmol), (*R*)-phenylglycinol (330 mg, 2.4 mmol) and aqueous methylamine (3.0 cm^3; 40%; 40.4 mmol) gave a crude product which was purified by Kugelrohr distillation to give known[3,7] diamine (*S*)-**4** (370 mg, 76%) as a colourless oil, bp 170–180 °C/1 mmHg (lit.,[7] 100–110 °C/0.,2 mmHg); R_f (10:1 CH_2Cl_2–MeOH) 0.4; $[a]_D$ +61.7 (*c* in EtOH) {lit.,[7] $[a]_D$ −64.0 (*c* 1.4 in EtOH) for (*R*)-**4**}.

(*S*)-*N*-Methyl-2-(isoindolin-2-yl)-1-phenylethanamine (*S*)-33

Sodium carbonate (760 mg, 7.2 mmol) and 1,2-bis(bromomethyl)benzene or 1,4-dibromobutane (950 mg, 3.6 mmol) were added successively to a stirred solution of (*R*)-phenylglycinol (500 mg, 3.6 mmol) in THF (15 cm^3) at room temperature under nitrogen. The resulting suspension was heated at reflux for 20 h. After being allowed to cool to room temperature, the solids were removed by filtration and THF (5 cm^3) was added. Triethylamine (1.5 cm^3, 10.8 mmol) was added to the THF solution under nitrogen and the solution was cooled to 0 °C. Then, methanesulfonyl chloride (0.42 cm^3, 7.2 mmol) was added dropwise. A white precipitate formed which made stirring difficult and after 30 min, triethylamine (1.0 cm^3, 7.2 mmol) was added. After being allowed to warm to room temperature, aqueous methylamine (4.5 cm^3; 40%; 61.2 mmol) was added and the resulting two-phase reaction mixture was vigorously stirred. After 16 h, the layers were separated and the light-brown aqueous layer was extracted with Et_2O (3 × 30 cm^3). The combined organic extracts were washed with 5% aqueous sodium hydrogen carbonate (20 cm^3) and water (20 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product as a yellow oil. Purification by flash chromatography on silica with CH_2Cl_2–MeOH (10:1) as eluent gave diamine (*S*)-**33** (630 mg, 70%) as a yellow oil, R_f (20:1 CH_2Cl_2–MeOH) 0.25; $[a]_D$ −5.7 (*c* 1.6 in $CHCl_3$).

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References

1 P. O'Brien and P. Poumellec, *Tetrahedron Lett.*, 1996, **37**, 5619.
2 S. E. de Sousa and P. O'Brien, *Tetrahedron Lett.*, 1997, **38**, 4885.
3 S. E. de Sousa, P. O'Brien and P. Poumellec, *Tetrahedron: Asymmetry*, 1997, **8**, 2613.
4 (*a*) R. Shirai, M. Tanaka and K. Koga, *J. Am. Chem. Soc.*, 1986, **108**, 543; (*b*) H. Kim, R. Shirai, H. Kawasaki, M. Nakajima and K. Koga, *Heterocycles*, 1990, **30**, 307; (*c*) R. Shirai, D. Sato, K. Aoki, M. Tanaka, H. Kawasaki and K. Koga, *Tetrahedron*, 1997, **53**, 5963.
5 For reviews, see: (*a*) P. J. Cox and N. S. Simpkins, *Tetrahedron: Asymmetry*, 1991, **2**, 1; (*b*) P. O'Brien, *J. Chem. Soc., Perkin Trans. 1*, 1998, 1439.
6 (*a*) D. Bhuniya and V. K. Singh, *Synth. Commun.*, 1994, **24**, 1475; (*b*) D. Bhuniya, A. DattaGupta and V. K. Singh, *Tetrahedron Lett.*, 1995, **36**, 2847.
7 D. Bhuniya, A. DattaGupta and V. K. Singh, *J. Org. Chem.*, 1996, **61**, 6108.
8 For a review, see: D. M. Hodgson, A. R. Gibbs and G. P. Lee, *Tetrahedron*, 1996, **52**, 14 361.
9 P. O'Brien and P. Poumellec, *Tetrahedron Lett.*, 1996, **37**, 8057.
10 P. O'Brien and J. J. Tournayre, *Tetrahedron*, 1997, **53**, 17 527.
11 B. E. Rossiter, M. Eguchi, G. Miao, N. M. Swingle, A. E. Hernández, E. Fluckiger, D. Vickers, R. G. Patterson and K. V. Reddy, *Tetrahedron*, 1993, **49**, 965.
12 G. Miao and B. E. Rossiter, *J. Org. Chem.*, 1995, **60**, 8424.
13 For a review, see: J. Leonard, *Contemp. Org. Synth.*, 1994, **1**, 387.
14 (*a*) G. F. Costello, R. James, J. S. Shaw, A. M. Slater and N. C. Stutchbury, *J. Med. Chem.*, 1991, **34**, 181; (*b*) J. J. Barlow, T. P. Blackburn, G. F. Costello, R. James, D. J. Le Count, B. G. Main, R. J. Pearce, K. Russell and J. S. Shaw, *J. Med. Chem.*, 1991, **34**, 3149.
15 (*a*) A.-C. Chang, A. E. Takemori and P. S. Portoghese, *J. Med. Chem.*, 1994, **37**, 1547; (*b*) S. A. Weerawarna, R. D. Davis and W. L. Nelson, *J. Med. Chem.*, 1994, **37**, 2856; (*c*) A.-C. Chang, A. E. Takemori, W. H. Ojala, W. B. Gleason and P. S. Portoghese, *J. Med. Chem.*, 1994, **37**, 4490; (*d*) G. A. Pinna, E. Gavini, G. Cignarella, S. Scolastico and P. Fadda, *Eur. J. Med. Chem.*, 1995, **30**, 515.
16 N. C. Law and W. Brose, *Chem. Ind.*, 1997, 306.
17 F. Ito (Pfizer Inc.) 1996, JP-00820 (*Chem. Abstr.*, 1996, **125**, 86 487y).
18 R. Shirai, K. Aoki, D. Sato, H.-D. Kim, M. Murakata, T. Yasukata and K. Koga, *Chem. Pharm. Bull.*, 1994, **42**, 690.
19 Racemisation during reactions of *N*-protected phenylglycine-derivatives is well documented. See for example: J.-N. Denis, A. Correa and A. E. Greene, *J. Org. Chem.*, 1991, **56**, 6939.
20 (*a*) R. K. Dieter, B. Lagu, J. W. Dieter, N. Deo and W. T. Pennington, *Synlett*, 1990, 109; (*b*) R. K. Dieter, N. Deo, B. Lagu and J. W. Dieter, *J. Org. Chem.*, 1992, **57**, 1663.
21 For examples of aziridinium ion intermediates in synthesis, see: (*a*) Q. Liu, A. P. Marchington and C. M. Rayner, *Tetrahedron*, 1997, **53**, 15 729; (*b*) Q. Liu, A. P. Marchington, N. Boden and C. M. Rayner, *J. Chem. Soc., Perkin Trans. 1*, 1997; 511; (*c*) C. M. Rayner, *Synlett*, 1997, 11; (*d*) M. Okuda and K. Tomioka, *Tetrahedron Lett.*, 1994, **35**, 4585; (*e*) P. Gmeiner, D. Junge and A. Kärtner, *J. Org. Chem.*, 1994, **59**, 6766; (*f*) J. Freedman, M. J. Vaal and E. W. Huber, *J. Org. Chem.*, 1991, **56**, 670; (*g*) D. R. Williams, D. L. Brown and J. W. Benbow, *J. Am. Chem. Soc.*, 1989, **111**, 1923; (*h*) T. Rosen, S. W. Fesik, D. T. W. Chu and A. G. Pernet, *Synthesis*, 1988, 40; (*i*) T. Kametani and T. Honda, *Adv. Heterocycl. Chem.*, 1986, **39**, 181.
22 D. A. Fulton and C. L. Gibson, *Tetrahedron Lett.*, 1997, **38**, 2019.
23 P. Saravanan and V. K. Singh, *Tetrahedron Lett.*, 1998, **39**, 167.

24 (*R*)- and (*S*)-styrene oxide are available from the Aldrich Chemical Company.
25 S. Miyano, L. D.-L. Lu, S. M. Viti and K. B. Sharpless, *J. Org. Chem.*, 1985, **50**, 4350.
26 W. H. Pirkle and D. J. Hoover, *Top. Stereochem.*, 1982, **13**, 263.
27 A. Toshimitsu, C. Hirosawa and K. Tamao, *J. Chem. Soc.*, *Chem. Commun.*, 1989, 530.
28 A. Toshimitsu, C. Hirosawa and K. Tamao, *Tetrahedron*, 1994, **50**, 8997.
29 Dr Simon A. Osborne, personal communication.
30 (*R*)- and (*S*)-phenylglycinol are commercially available from Lancaster Synthesis.
31 (*R*)- and (*S*)-phenylglycinol can be prepared by reduction of (*R*)- and (*S*)-phenylglycine respectively. Using a method reported by Meyers ($NaBH_4$ and $BF_3{\cdot}Et_2O$), we have prepared 3.26 g of (*R*)-phenylglycinol (73% yield): M. A. Tschantz, L. E. Burgess and A. I. Meyers, *Org. Synth.*, 1996, **73**, 221.
32 M. Meguro, N. Asao and Y. Yamamoto, *J. Chem. Soc.*, *Perkin Trans. 1*, 1994, 2597.
33 E. Brown, A. Lézé and J. Touet, *Tetrahedron: Asymmetry*, 1996, **7**, 2029.
34 E. Brown, A. Penfornis, J. Bayma and J. Touet, *Tetrahedron: Asymmetry*, 1991, **2**, 339.
35 P. L. Beaulieu and D. Wernic, *J. Org. Chem.*, 1996, **61**, 3635.
36 J. Juárez, D. Gnecco, A. Galindo, R. G. Enríquez, C. Marazano and W. F. Reynolds, *Tetrahedron: Asymmetry*, 1997, **8**, 203.
37 W. C. Still, M. Kahn and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.

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