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The preparation of β-substituted amines from mixtures of epoxide opening products via a common aziridinium ion intermediate

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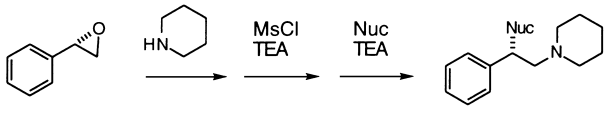
Abstract

Here we describe a one-pot synthesis of a series of β-substituted amines as single enantiomers from an initial regioisomeric mixture of styrene oxide ring-opening products. We also report the isolation and characterization of a key β-chloro intermediate and provide additional insight into the mechanism of the reported alkylations. These results require that the reaction proceeds through a common aziridinium ion intermediate on two separate occasions in order to account for the observed overall net retention of configuration in proceeding from (*S*)-styrene oxide to the desired β-substituted amine products.

1. Introduction

Stereoselective syntheses of chiral molecules are important in drug design and action,[1,2] as well as in the discovery and implementation of chiral catalysts.[3–7] Here we report the preparation of a series of enantiomerically pure amines using a high yielding, one-pot synthesis.



Procedures exist for the preparation of vicinal diamine ligands from readily available styrene oxide.[4–6] Dieter et al.[4] reported a synthesis of two chiral triamines and Rossiter et al.[5] a synthesis of a series of chiral diamine derivatives. During the progress of our studies, a one-pot synthesis of chiral diamines from

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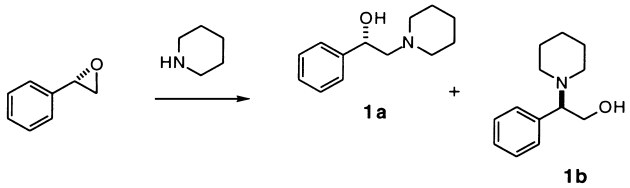
(*R*)-styrene oxide was reported by O'Brien and Poumellec.[7] Herein, we report the inclusion of non-amine nucleophiles to expand the utility of this synthetic route and the isolation and characterization of a key β-chloro intermediate.

2. Results and discussion

The first step in the synthesis of the desired β-substituted amines is the reaction of a secondary amine with styrene oxide. A common problem with these alkylations is the formation of two regioisomers, which result from opening of the styrene oxide at either the α- or β-center.[8] In the first example (Scheme 1), the oxirane ring of (*S*)-styrene oxide was cleaved using piperidine. This reaction was conducted in two separate solvent systems. When ring cleavage was conducted in refluxing toluene, conversion to product was complete in 24 h to provide a 95:5‡ mixture of **1a** and **1b**. In isopropanol at room temperature, conversion to the ring-opened product was complete in 24 h to provide a 70:30‡ mixture of **1a** and **1b**. Although most of the reactions reported herein were carried out in toluene, the isopropanol example containing the higher amount of the α-isomer was carried through to demonstrate that the α-isomer is also converted into the desired material.



Scheme 1.

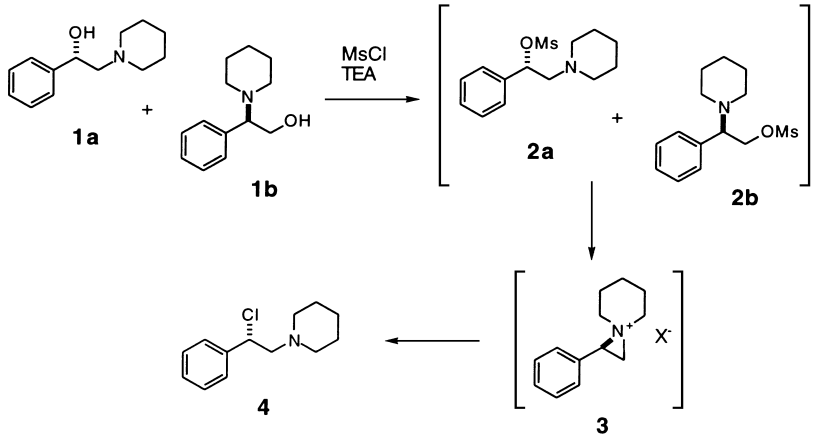
The mixture of regioisomers **1a** and **1b** was then treated with methanesulfonyl chloride in toluene at room temperature. After 1–2 h at room temperature, an aqueous workup provided the β-chloro amine **4** as a single regioisomer (Scheme 2). Production of a single β-chloro amine isomer was independent of the relative population of the two regioisomers going into the activation step. ^{1}H NMR and mass spectral data indicate that both mesylate intermediates are fully converted to **4**. The structure of **4** was confirmed by ^{1}H NMR and mass spectral data.[9] The presence of a single regioisomer at this point is consistent with the inclusion of an aziridinium ion intermediate (**3**).[10] Cleavage of the aziridinium ion proceeds via a regioselective and stereospecific attack of the chloride ion at the more activated benzylic position.

Previous literature reports identify the activated intermediate which is carried into the second alkylation reaction as a mixture of mesylates and/or aziridinium ion **3**. Based on the spectral characterization of the intermediate and its observed stability,§ we propose that this activated intermediate is actually the β-chloro amine **4**.

The final step in the synthesis involves substituting the desired nucleophile for the chloro substituent of **4**. Diamine **5** was prepared by refluxing **4** with diethylamine in 50% (v/v) THF in toluene (Scheme 3). The reaction was complete in 48–72 h. An aqueous workup yielded **5**, with an overall yield of 65–75%

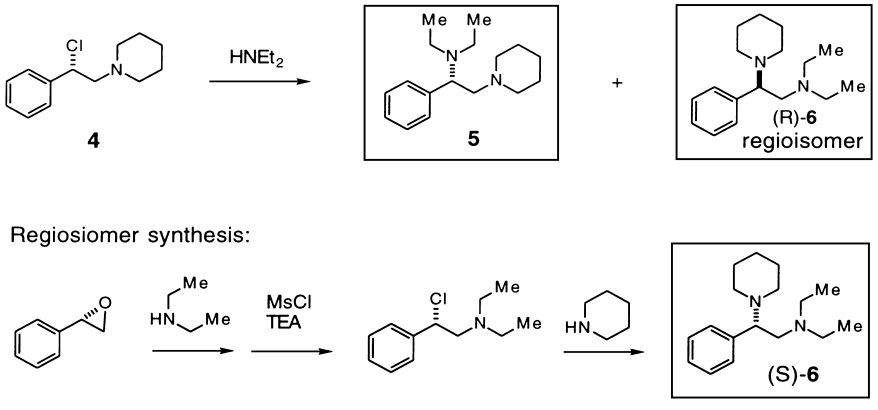
‡ Based on ^{1}H NMR ratios.

§ The β-amino chloride was surprisingly stable. It was isolated via an aqueous workup and could be stored at 4°C for a week before side products started to become apparent by ^{1}H NMR. In the presence of moisture, **4** begins to revert to the amino alcohol **1a**.



Scheme 2.

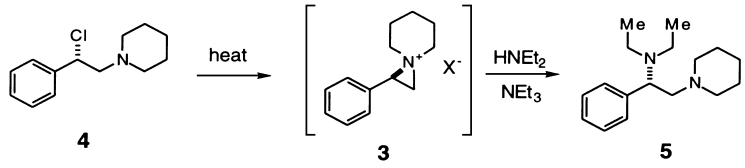
from the styrene oxide. The absence of the second regioisomer was confirmed by independent synthesis. Diamine **6** was produced by inverting the order in which the two secondary amines were added. At the limits of ^{1}H NMR detection, there was no contamination of **6** in **5** or vice versa.[¶]



Scheme 3.

Chiral HPLC assays of (*S*)-**5** and (*S*)-**6** indicate that the reaction sequence results in a single enantiomer. Optical rotation showed that there was net overall retention of configuration at the benzylic stereocenter in proceeding from styrene oxide to the final product. This is consistent with previously reported results.[4–7] These reports argue that the net retention of stereochemistry reflects a total of two inversions at the benzylic position, the first occurring prior to the formation of the common aziridinium ion **3** and the second upon cleavage of **3**. Our characterization of the chloro amine **4**, however, requires a total of four inversions at the benzylic carbon in order to account for the net retention of configuration. The initial conversion of the mixture of regioisomeric mesylates **2a** and **2b** into a single regioisomer of the β-amino chloride **4** requires the intermediacy of aziridinium ion **3**. This would account for two inversions of stereochemistry at the benzylic carbon. The β-amino chloride is then postulated to return to aziridinium ion **3** when heated, and this aziridinium ion is trapped by the incoming nucleophile to yield the final product. The result is a total of four inversions at the benzylic carbon, with each inversion occurring in a regioselective and stereospecific manner (Scheme 4).

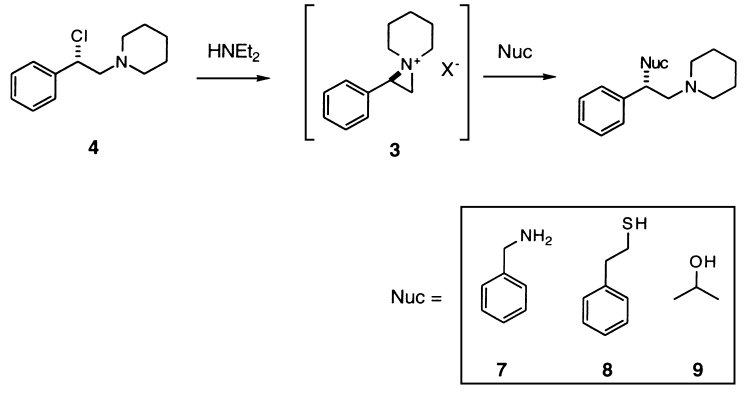
[¶] Product **6** is the enantiomer of the potential regioisomer that would form in the preparation of **5**, as indicated in Scheme 3.



Scheme 4.

This sequence was conducive to the implementation of a one-pot synthesis of **5** from styrene oxide.[||] The styrene oxide substrate was carried through the epoxide cleavage (compounds **1a** and **1b**), the chlorination (compound **4**), and the final aziridinium cleavage (compound **5**) without workup (Schemes 1, 2 and 4). Using this approach, it was unnecessary to separate the original mixture of regioisomers, or to isolate the potentially moisture-sensitive β-amino chloride. An aqueous workup of the final product mixture yielded **5** in 70–76% yield.

In order to ascertain the generality of this one-pot synthesis, we considered the ability of a series of nucleophiles to cleave the aziridinium ring (Scheme 5).[††] The described one-pot procedure was found to be synthetically viable for all of the nucleophiles tested (Table 1). Although this methodology is applicable only when a secondary amine does the initial alkylation of styrene oxide, the scope of the second nucleophile has been shown to include primary and secondary amines, as well as alcohols and thiols. A single crystal of diamine **7** was obtained that was suitable for X-ray crystallography (Fig. 1). This structure made conclusive the regiochemistry assignments made for diamines **5** and **6**. Products **7**, **8** and **9** were all produced with reasonable yields and with complete regioselectivity and stereospecificity.



Scheme 5.

3. Conclusions

We have reported a one-pot synthesis of a series of β-substituted amines as single enantiomers from an initial regioisomeric mixture of styrene oxide ring-opening products. Our characterization of the β-chloro amine **4** provides some additional insight into the mechanism of these alkylations, i.e. two separate passes through aziridinium ion **3** must occur for this reaction to proceed with overall net retention of configuration. Although this methodology is applicable only for systems where a secondary amine does

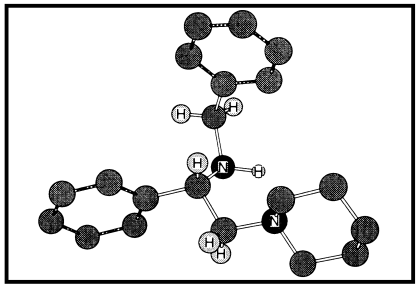
[||] At the time we were completing our work in this area, the same observation was reported by O'Brien and co-workers (see the literature[7]).

[††] For examples of other non-amine nucleophiles that are alkylated by aziridinium intermediates, see the literature.[3]

Table 1
Yields and selectivities of aziridinium alkylations

Compound	Nucleophile 1	Nucleophile 2	Overall % Yield	Enantiomeric Ratio (S:R)
5[a]	piperidine	diethylamine	65-78	>99:1
5[b]	piperidine	diethylamine	70-76	>99:1
6	diethylamine	piperidine	67-84	>98.7:1.3
7	piperidine	benzylamine	63-66	>99:1
8	piperidine	phenethylthiol	80	>99:1
9	piperidine	isopropanol	79	>99:1

[a] The amino alcohol and β-amino chloride were isolated enroute to **5**.
[b] One-pot synthesis of **5**.



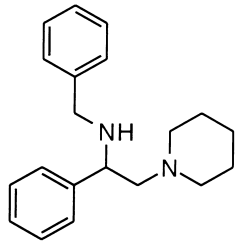


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Figure 1. Single crystal X-ray structure of benzyl-(1-phenyl-2-piperidin-1-yl-ethyl)-amine **7**

the initial alkylation of a styrene oxide derivative, the scope of the second nucleophile has been expanded to include alcohols and thiols. Such a one-pot synthesis should be useful in the preparation of molecules of biological significance as well as in the preparation of chiral ligands for asymmetric syntheses.

4. Experimental

4.1. General

^{1}H NMR spectra were obtained on a General Electric QE-300 instrument at 300 MHz. Spectra were recorded in $CDCl_3$. Chemical shifts are reported in ppm (δ) relative to a TMS standard. Mass spectra were obtained on a Micromass Platform II mass spectrometer using APcI ($APcI^+$) with a 50:50 water: acetonitrile mobile phase. $[\alpha]_D$ values were determined on a Perkin–Elmer 243 polarimeter. The single crystal X-ray structure was obtained at room temperature on a Siemens R3RA/v diffractometer with a resolution of 1 Å. Crystallographic calculations were facilitated by the SHELXTL system.

(*S*)-Styrene oxide, piperidine, diethylamine, benzylamine, isopropanol, phenethyl mercaptan, triethylamine, and methanesulfonyl chloride were purchased from Fisher, Acros, or Aldrich chemicals. All solvents were reagent grade.

*4.2. Preparation of a 1-phenyl-2-piperidin-1-yl-ethanol **1a** and 2-phenyl-2-piperidin-1-yl-ethanol **1b** mixture in toluene*

Piperidine (4.3 mL, 43.7 mmol) was added to (*S*)-styrene oxide (5.0 mL, 43.7 mmol) in 50 mL of toluene. The solution was refluxed for 24 h. The solution was washed with saturated sodium bicarbonate (3×25 mL), dried over sodium sulfate, and concentrated in vacuo to yield an oily residue. The product mixture was isolated, analyzed, and carried into the next reaction without further purification. ^{1}H NMR analysis showed a 95:5 ratio of **1a**:**1b**. ^{1}H NMR resonances ($CDCl_3$, 300 MHz) characteristic of **1a** are: δ 1.38–1.55 (m, 2H), 1.55–1.90 (m, 4H), 2.22–2.60 (m, 4H), 2.72 (b s, 2H), 4.75 (dd, 1H, *J*=10.45 and 3.55 Hz), 7.18–7.60 (m, 5H). Although there is much overlap in the ^{1}H NMR spectra of **1a** and **1b**, well-separated NMR resonances exist for each regioisomer: **1a**: δ 4.75 (dd, 1H, *J*=10.45 and 3.55 Hz) and **1b**: δ 3.59–3.71 (m, 2H), 3.99 (t, 1H, *J*=9.98 Hz). APCI–MS *m/z* 206 (M+1).

*4.3. Preparation of a 1-phenyl-2-piperidin-1-yl-ethanol **1a** and 2-phenyl-2-piperidin-1-yl-ethanol **1b** mixture in isopropanol*

Piperidine (4.3 mL, 43.7 mmol) was added to (*S*)-styrene oxide (5.0 mL, 43.7 mmol) in 50 mL of isopropanol. The solution was stirred for 24 h at room temperature. The solution was concentrated in vacuo to remove the isopropanol. The product was redissolved in 50 mL of ethyl acetate, washed with saturated sodium bicarbonate (3×25 mL), dried over sodium sulfate, and concentrated in vacuo to yield an oily residue. The product mixture was isolated, analyzed, and carried into the next reaction without further purification. ^{1}H NMR analysis showed a 70:30 ratio of **1a**:**1b**. ^{1}H NMR resonances ($CDCl_3$, 300 MHz) characteristic of **1a** are: δ 1.38–1.55 (m, 2H), 1.55–1.90 (m, 4H), 2.22–2.60 (m, 4H), 2.72 (b s, 2H), 4.75 (dd, 1H, *J*=10.45 and 3.55 Hz), 7.18–7.60 (m, 5H). Although there is much overlap in the ^{1}H NMR spectra of **1a** and **1b**, well-separated NMR resonances exist for each regioisomer: **1a**: δ 4.75 (dd, 1H, *J*=10.45 and 3.55 Hz) and **1b**: δ 3.59–3.71 (m, 2H), 3.99 (t, 1H, *J*=9.98 Hz). APCI–MS *m/z* 206 (M+1).

*4.4. Preparation of 1-(2-chloro-2-phenylethyl)-piperidine **4***

The mixture of regioisomers **1a** and **1b** was dissolved in 50 mL of toluene. Methanesulfonyl chloride (3.7 mL, 48 mmol) and triethylamine (7.3 mL, 52 mmol) were added at 4°C with stirring. The mixture was stirred for an additional 1–2 h at room temperature. The solution was washed with saturated sodium bicarbonate (3×25 mL), dried over sodium sulfate, and concentrated in vacuo to yield an oily residue. The crude product was isolated, analyzed, and identified as the β-chloro intermediate **4**. ^{1}H NMR and mass spectral data indicate that both mesylate intermediates had been fully converted to **4**. Although the β-chloro intermediate was surprisingly stable, permitting the acquisition of both NMR and MS spectra, its reactive nature was not conducive to further purification (either via a silica plate/column or HPLC chromatography). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.35–1.48 (m, 2H), 1.48–1.80 (m, 4H), 2.35–2.65 (b s, 4H), 2.80 (dd, 1H, *J*=13.49 and 8.00 Hz), 3.01 (dd, 1H, *J*=13.87 and 6.02 Hz), 5.05 (t, 1H, *J*=7.03 Hz), 7.25–7.75 (m, 5H). APCI–MS *m/z* 224 (M+1).

*4.5. Preparation of diethyl-(1-phenyl-2-piperidin-1-yl-ethyl)-amine **5***

β-Amino chloride **4** was dissolved in 50 mL of 1:1 THF:toluene. Diethylamine (5.4 mL, 52.2 mmol) and triethylamine (12.2 mL, 87.4 mmol) were added, and the mixture was allowed to reflux for 24 h.

The solution was washed with saturated sodium bicarbonate (3×25 mL), dried over sodium sulfate, and concentrated in vacuo to yield an oily residue.

Diamine **5** was further purified by extraction. Diamine **5** was dissolved in 100 mL of ethyl acetate and extracted with 2 M HCl (2×100 mL). The combined aqueous layers were basified with 4 M NaOH (75 mL), and the neutral amine was back-extracted into hexane (3×125 mL). The organic layers were combined, dried over sodium sulfate, and concentrated in vacuo to yield 8.9 g (78% overall yield) of a light brown oil. HPLC analysis of **5** using a Chiralpak AD column (4.6×25 cm, hexane:isopropanol 50:50, flow=1.0 ml/min, λ=205 nm) showed that the enantiomeric ratio for **5** was >99:1 *S*:*R* with t_R (*S*)=3.80 min and t_R (*R*)=3.54 min. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.15 (t, 6H, *J*=7.12 Hz), 1.35–1.46 (m, 2H), 1.46–1.70 (m, 4H), 2.35–2.61 (m, 6H), 2.61–2.78 (m, 3H), 2.78–2.92 (m, 1H), 3.95 (t, 1H, *J*=6.26 Hz), 7.20–7.65 (m, 5H). APCI–MS *m/z* 261 (M+1).

*4.6. General procedure for the one-pot preparation of the β-substituted amines **5**, **7**, **8** and **9***

Piperidine (4.3 mL, 43.7 mmol) was added to (*S*)-styrene oxide (5.0 mL, 43.7 mmol) in 50 mL of toluene. The solution was refluxed for 24 h. Methanesulfonyl chloride (3.7 mL, 48 mmol) and triethylamine (7.3 mL, 52 mmol) were added at 4°C with stirring. The mixture was stirred for an additional 2 h at room temperature before the nucleophilic reagent (1.2 equiv.), triethylamine (12.2 mL, 87.4 mmol), and THF (30 mL) were added. This mixture was refluxed for 24 h. The solution was washed with saturated sodium bicarbonate (3×25 mL), dried over sodium sulfate, and concentrated in vacuo to yield an oily residue.

*4.7. Diethyl-(1-phenyl-2-piperidin-1-yl-ethyl)-amine **5***

Diethyl-(1-phenyl-2-piperidin-1-yl-ethyl)-amine **5** was further purified as described above. The one-pot process yielded 8.6 g (76%) of a light brown oil. HPLC analysis of **5** using a Chiralpak AD column (4.6×25 cm, hexane:isopropanol 50:50, flow=1.0 ml/min, λ=205 nm) showed that the enantiomeric ratio for **5** was >99:1 *S*:*R* with t_R (*S*)=3.80 min and t_R (*R*)=3.54 min. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.15 (t, 6H, *J*=7.12 Hz), 1.35–1.46 (m, 2H), 1.46–1.70 (m, 4H), 2.32–2.59 (m, 6H), 2.59–2.76 (m, 3H), 2.76–2.92 (m, 1H), 3.95 (t, 1H, *J*=6.26), 7.20–7.65 (m, 5H); APCI–MS *m/z* 261 (M+1). HPLC purity (Zorbax C8, 4.6×150 mm; 54% water, 46% acetonitrile containing 0.2% triethylamine and 0.1% acetic acid; 1 mL/min flow rate; 220 nm detection) — t_R 5.3 min, 97.9%.

*4.8. Benzyl-(1-phenyl-2-piperidin-1-yl-ethyl)-amine **7***

Benzyl-(1-phenyl-2-piperidin-1-yl-ethyl)-amine **7** formed crystals upon sitting as an oil on the bench top. The crystalline product was dissolved in hot methanol, and water was added to give a 2:1 ratio of methanol and H_2O. The solution was stirred slowly at room temperature. Small crystals formed and were isolated via filtration. The mother liquor was concentrated to dryness, and the recrystallization procedure repeated to form a second crop of crystals, yielding a total of 8.5 g (66%) of a crystalline product: mp 65–68°C. HPLC analysis of **7** using a Chiralpak AD column (4.6×25 cm, hexane:isopropanol:diethylamine 80:20:0.1, flow=1.0 ml/min, λ=205 nm) showed that the enantiomeric ratio for **7** was >99:1 *S*:*R* with t_R (*S*)=3.64 min and t_R (*R*)=3.45 min. $[\alpha]_D$ +120 (*c* 1.98, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.25–1.46 (m, 2H), 1.46–1.82 (m, 4H), 2.10–2.33 (m, 3H), 2.33–2.62 (m, 3H), 3.47 (d, 1H, *J*=13.69 Hz), 3.73 (dd, 1H, *J*=11.48 and 2.87 Hz), 3.81 (d, 1H, *J*=13.69 Hz), 7.20–7.70 (m, 10H). APCI–MS *m/z* 295 (M+1). HPLC purity (Zorbax C8, 4.6×150 mm; 54% water, 46% acetonitrile

containing 0.2% triethylamine and 0.1% acetic acid; 1 mL/min flow rate; 220 nm detection) — t_R 6.2 min, 98.5%.

4.9. 1-(2-Phenethylsulfanyl-2-phenylethyl)-piperidine **8**

The 1-(2-phenethylsulfanyl-2-phenylethyl)-piperidine **8** was converted into the corresponding HCl salt. The oil obtained was dissolved in 10 mL of ethyl acetate and added to 10 mL of ethyl acetate containing 1 equiv. of concentrated HCl. The resulting solution was concentrated in vacuo. Ether (10 mL) was added and the mixture was concentrated to dryness. This process was repeated to yield a brittle foam. The foam was crushed, washed with a 50:50 (v/v) mixture of ether and ethyl acetate, and dried in vacuo to yield 12.7 g (80%) of a light yellow powder. HPLC analysis of **8** using a Chiralpak AD column (4.6×25 cm, hexane:isopropanol:diethylamine 5:95:0.1, flow=1.0 ml/min, λ=205 nm) showed that the enantiomeric ratio for **8** was >99:1 *S*:*R* with t_R (*S*)=4.65 min and t_R (*R*)=4.27 min. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.25–1.46 (m, 2H), 1.46–1.75 (m, 4H), 2.36–2.48 (m, 4H), 2.54 (t, 2H, *J*=7.87 Hz), 2.62–3.00 (m, 4H), 4.08 (t, 1H, *J*=7.15 Hz), 7.05–7.65 (m, 10H). APCI–MS *m/z* 326 (M+1). HPLC purity (Zorbax C8, 4.6×150 mm; 54% water, 46% acetonitrile containing 0.2% triethylamine and 0.1% acetic acid; 1 mL/min flow rate; 220 nm detection) — t_R 8.8 min, 98.9%.

4.10. 1-(2-Isopropoxy-2-phenylethyl)-piperidine **9**

The 1-(2-isopropoxy-2-phenylethyl)-piperidine **9** was purified using a two-step process. The oil obtained was dissolved in 100 mL of ethyl acetate and extracted with 2 M HCl (2×100 mL). The combined aqueous layers were basified with 4 M NaOH (75 mL), and the neutral amine was back-extracted into hexane (3×125 mL). The organic layers were combined, dried over sodium sulfate, and concentrated in vacuo. Subsequent purification by flash chromatography (1–20% methanol in methylene chloride) yielded 8.8 g (79%) of a yellow oil. HPLC analysis of **9** using a Chiralpak AD column (4.6×25 cm, hexane:isopropanol 50:50, flow=1.0 ml/min, λ=205 nm) showed that the enantiomeric ratio for **9** was >99:1 *S*:*R* with t_R (*S*)=3.52 min and t_R (*R*)=3.29 min. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.08 (d, 3H, *J*=6.14 Hz), 1.18 (d, 3H, *J*=6.14 Hz), 1.34–1.50 (m, 2H), 1.50–1.80 (m, 4H), 2.28–2.50 (m, 3H), 2.50–2.65 (m, 2H), 2.65–2.90 (m, 1H), 3.42–3.62 (m, 1H), 4.61 (dd, 1H, *J*=8.37 and 3.66 Hz), 7.22–7.62 (m, 5H). APCI–MS *m/z* 248 (M+1). HPLC purity (Zorbax C8, 4.6×150 mm; 54% water, 46% acetonitrile containing 0.2% triethylamine and 0.1% acetic acid; 1 mL/min flow rate; 220 nm detection) — t_R 4.0 min, 92.4%.

4.11. One-pot preparation of diethyl-(2-phenyl-2-piperidin-1-yl-ethyl)-amine **6**

Diethylamine (18 mL, 174.0 mmol) was added to (*S*)-styrene oxide (5.0 mL, 43.7 mmol) in 50 mL of toluene. The solution was refluxed for 48–72 h. The resulting product was concentrated in vacuo to remove excess diethylamine. The product was redissolved in 50 mL of toluene, and methanesulfonyl chloride (3.7 mL, 48 mmol) and triethylamine (7.3 mL, 52 mmol) were added at 4°C with stirring. The mixture was stirred for an additional 2 h at room temperature. Piperidine (5.2 mL, 52.4 mmol), triethylamine (12.2 mL, 87.4 mmol), and THF (30 mL) were added, and the mixture was refluxed for 24 h. The solution was extracted with saturated sodium bicarbonate (3×25 mL), dried over sodium sulfate, and concentrated in vacuo to yield an oily residue.

Diamine **6** was further purified by extraction. The oil obtained was dissolved in 100 mL of ethyl acetate and extracted with 2 M HCl (2×100 mL). The combined aqueous layers were basified with 4 M NaOH

(75 mL), and the neutral amine was back-extracted into hexane (3×125 mL). The organic layers were combined, dried over sodium sulfate, and concentrated in vacuo to yield 9.6 g (84%) of a light brown oil. HPLC analysis of **6** using a Chiral OJ-R column (4.6 mm × 15 cm, acetonitrile:pH 11.3 H_3PO_4 buffer 30:70, flow=0.5 ml/min, λ=210 nm) showed that the enantiomeric ratio for **6** was 98.7:1.3 *S*:*R* with t_R (*S*)=17.6 min and t_R (*R*)=16.7 min. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.95 (t, 6H, *J*=7.10 Hz), 1.22–1.42 (m, 2H), 1.42–1.75 (m, 4H), 2.39 (b s, 4H), 2.46–2.70 (m, 4H), 2.82 (dd, 1H, *J*=13.08 and 5.49 Hz), 2.96 (dd, 1H, *J*=13.07 and 5.36 Hz), 3.54 (t, 1H, *J*=6.39 Hz), 7.15–7.55 (m, 5H). APCI–MS *m/z* 261 (M+1). HPLC purity (Zorbax C8, 4.6×150 mm; 54% water, 46% acetonitrile containing 0.2% triethylamine and 0.1% acetic acid; 1 mL/min flow rate; 220 nm detection) — t_R 5.6 min, 95.2%.

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