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Asymmetric synthesis via aziridinium ions: exploring the stereospecificity of the ring opening of aziridinium ions and a formal synthesis of (−)-swainsonine

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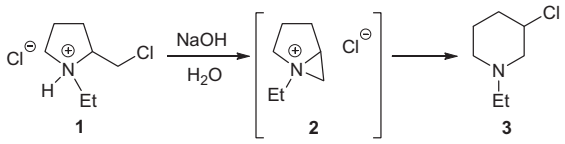
Dedicated to Professor H. B. Kagan in celebration of his 80th birthday

ABSTRACT

The use of aziridinium ions in two different projects is described. First, the stereospecificity of the ring opening of aziridinium ions with $MeNH_2$ as a route to chiral diamines has been explored. When the aziridinium ion contained a phenyl or *para*-methoxyphenyl substituent, stereospecific ring opening occurred. In contrast, switching the *para*-methoxy group to a *para*-*N*,*N*-dimethylamino group gave a *racemic* diamine product. Second, starting from *N*-Boc pyrrolidine, asymmetric lithiation-trapping-ring expansion (via an aziridinium ion) was used to synthesise a piperidine alcohol. In this way, a formal synthesis of **(−)**-swainsonine was completed.

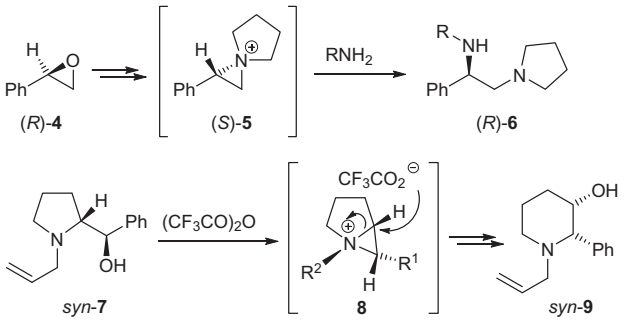
1. Introduction

Aziridinium ions were first implicated as reaction intermediates in 1946 during investigations of the reactions of the nitrogen mustard gases.[1,2] One year later, the structure of the analgesic amidone was determined and the regioselectivity of its synthesis from a chloro-amine could only be rationalised via the intermediacy of an aziridinium ion.[3] The first example of a ring enlargement via an aziridinium ion was described by Fuson and Zirkle in 1948.[4] Thus, treatment of pyrrolidine hydrochloride salt **1** with NaOH gave chloro-piperidine **3** as the only product, with the rearrangement proceeding via aziridinium ion **2** (Scheme 1). Since these early beginnings, aziridinium ions are now established as useful intermediates in natural product synthesis[5,6] and synthetic methodology.[7,8]



Scheme 1. Seminal report on the ring expansion of a pyrrolidine to a piperidine via an aziridinium ion intermediate.

Our group has a long-standing interest in the use of aziridinium ions in synthesis. In 1996, we reported a one-pot method for the conversion of (*R*)-styrene oxide (*R*)-**4** into chiral diamines such as (*R*)-**6** via aziridinium ion (*S*)-**5** (Scheme 2).[9] More recently, we described the ring expansion of pyrrolidinyl amino alcohol *syn*-**7**, via aziridinium ion **8**, into piperidinyl alcohol *syn*-**9** (Scheme 2) as a key step in the synthesis of (+)-L-733,060, a neuronkinin-1 substance P receptor antagonist.[10]



Scheme 2. Previous work by the O'Brien group with aziridinium ions.

In this paper, our latest developments in the use of aziridinium ions in synthesis are reported. First, a study on the stereospecificity of the ring opening of aziridinium ions (*S*)-**10** equipped with an electron-donating group in the *para* position (e.g., X = OMe, NMe_2) is described (Scheme 3). Here, we anticipated that the stereospecificity of the ring opening could be compromised with the intervention of an S_N1-like pathway in aziridinium ions such as (*S*)-**10**. With this study,

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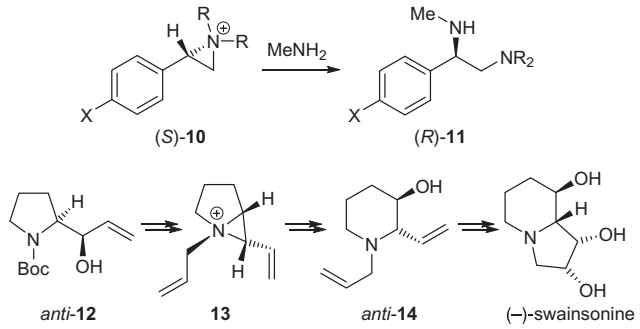


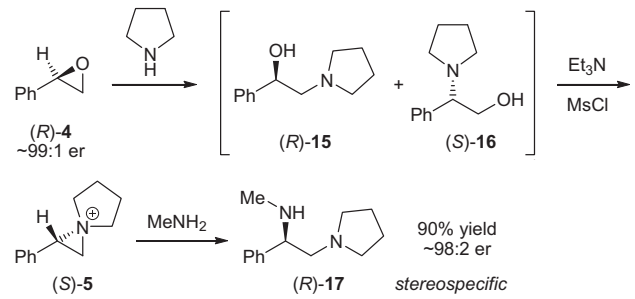
Scheme 3. Synthesis of chiral diamines and (−)-swainsonine via aziridinium ions.

we hoped to map out the scope and limitations of the aziridinium ion route to chiral diamines such as (*R*)-**11**. We also report the successful application of our *N*-Boc pyrrolidine lithiation-aldehyde trapping-ring expansion methodology (*anti*-**12**→**13**→*anti*-**14**, Scheme 3) to the formal synthesis of **(−)**-swainsonine, an inhibitor of lysosomal α-mannosidase and mannosidase II.[11]

2. Results and discussion

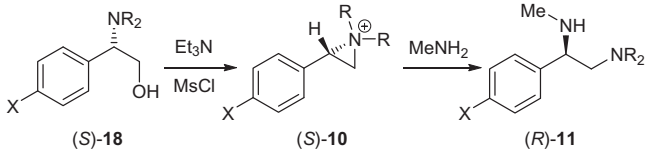
2.1. Investigation of the stereospecificity of ring opening of aziridinium ions

Chiral diamines are important building blocks in synthesis, and are useful precursors to chiral ligands/catalysts.[12] Our one-pot method for the conversion of (*R*)-styrene oxide (*R*)-**4** (⩾99:1 er) into chiral diamines such as (*R*)-**17** is summarised in Scheme 4.[9] The approach was based on a step-wise process previously developed by Dieter et al.[13] and Miao and Rossiter.[14] First, (*R*)-styrene oxide (*R*)-**4** was ring opened with pyrrolidine to give a mixture of (*R*)-**15** and (*S*)-**16**. Then, mesylation of this mixture gave an aziridinium ion (*S*)-**5** in situ which was ring opened at the benzylic position to give diamine (*R*)-**17**. Our subsequent efforts focused on developing a route starting from phenylglycinol,[15] preparing new chiral bases from norephedrine,[16] synthesising a range of Koga bases[17] and exploring the regiochemistry of ring opening different aziridinium ions.[18]



Scheme 4. One-pot synthesis of a chiral diamine.

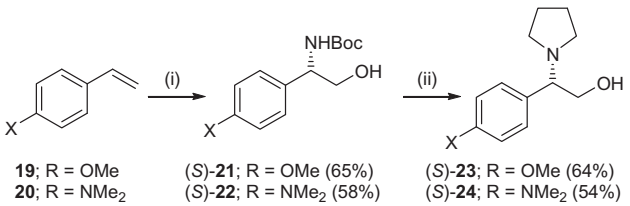
The styrene oxide/aziridinium ion approach to these types of chiral diamines has proved useful in academic and industrial laboratories: Kerr and co-workers prepared some new chiral diamines;[19] researchers at Pfizer prepared 6.3 kg of a κ-opioid receptor agonist[20] and 1.3 kg of a Koga base was synthesised by researchers at Amgen.[21] In all but two cases,[13,22] diamines such as (*R*)-**17** contain a phenyl ring (derived from styrene oxide,[9,15,17,20,21] phenylglycinol[15] or mandelic acid[23]). With a view to extending the methodology to non-phenyl-containing diamines, we have now explored the stereospecificity of the ring opening of aziridinium ions with different aromatic substituents as outlined in Scheme 5.



Scheme 5. Proposed investigation of the stereospecificity of the ring opening of aziridinium ions.

The stereospecificity of the S_N2 ring opening of aziridinium ions (*S*)-**10** with X = H (phenyl ring) by amines to give (*R*)-**11** (X = H) has previously been demonstrated by us[9,15] and by researchers at Pfizer[20] and Amgen.[21] To probe the effect of X and to ultimately map out the scope of the aziridinium ion route to non-phenyl-containing diamines, we prepared amino alcohols (*S*)-**18** with X = OMe and NMe_2 and studied the stereospecificity of their transformation into diamines (*R*)-**11**.

To start with, amino alcohols (*S*)-**23** and (*S*)-**24** were prepared using the route outlined in Scheme 6. Sharpless asymmetric aminohydroxylation (AA)[24,25] of commercially available 4-methoxystyrene **19** using $K_2OsO_2(OH)_4$, $(DHQ)_2PHAL$ and $^tBuO_2CNH_2$/NaOH/^{t}BuOCl gave Boc-protected amino alcohol (*S*)-**21** in 65% yield. In a similar way, substituted styrene **12** (prepared by a Wittig reaction on the corresponding aldehyde[26]) gave Boc-protected amino alcohol (*S*)-**22** in 58% yield.

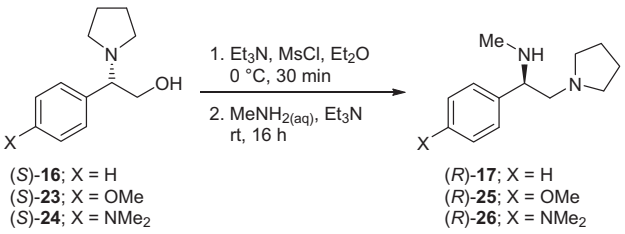


Scheme 6. Synthesis of amino alcohols (*S*)-**15** and (*S*)-**16**. Reagents and conditions: (i) 4 mol % $K_2OsO_2(OH)_4$, 6 mol % $(DHQ)_2PHAL$, 3 equiv $^tBuO_2CNH_2$/NaOH/^{t}BuOCl, ^{n}PrOH–water, 0 °C, 1 h; (ii) TFA, CH_2Cl_2, rt, 1 h then 1,4-dibromobutane, Na_2CO_3, $^nBu_4N^+I^-$, THF, reflux, 40 h.

Next, both (*S*)-**21** and (*S*)-**22** were converted into their corresponding pyrrolidinyl-substituted amino alcohols (*S*)-**23** and (*S*)-**24** via a 2-step process of Boc-deprotection and N,N-dialkylation using 1,4-dibromobutane.[15] This delivered (*S*)-**23** (64% yield) and (*S*)-**24** (54% yield), both of which were shown to be ⩾97:3 er by chiral shift ^{1}H NMR spectroscopy in the presence of (*S*)-1-(9-anthryl)-2,2,2-trifluoroethanol.

With amino alcohols (*S*)-**23** and (*S*)-**24** in hand, their conversion into diamines (*R*)-**25** and (*R*)-**26**, respectively, was studied. A comparison with the known[15] stereospecific synthesis of diamine (*R*)-**5** (entry 1) is shown in Table 1. Treatment of amino alcohol (*S*)-**23** (⩾97:3 er) with Et_3N and MsCl (0 °C, Et_2O, 1 h) followed by reaction with aqueous methylamine (rt, 16 h) gave diamine (*R*)-**25** in 58% yield. Analysis of (*R*)-**25** by chiral shift ^{1}H NMR spectroscopy in the presence of (*S*)-1-(9-anthryl)-2,2,2-trifluoroethanol indicated that its er was ⩾97:3 (entry 2). Thus, despite the presence of an electron-donating *para*-methoxy group, the ring opening of the intermediate aziridinium ion was stereospecific. In contrast, reaction of amino alcohol (*S*)-**24** (⩾97:3 er) under the same mesylation-ring-opening conditions delivered diamine (*R*)-**26** in 50% yield and ~50:50 er (entry 3). With a more electron-donating *N*,*N*-dimethylamino substituent in the *para* position, complete loss of er was observed. Thus, it can be concluded that this methodology will not tolerate aromatic groups with a strongly electron-donating *para*-substituent.

Table 1
Investigation of the stereospecificity of the ring opening of aziridinium ions derived from (*S*)-**16**, (*S*)-**23** and (*S*)-**24**

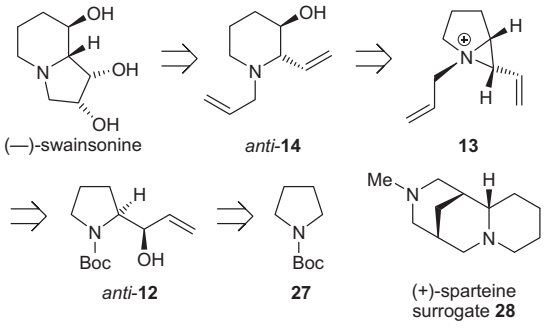


Entry	X	SM	er *S*:*R*	Prod	Yield[a] (%)	er *S*:*R*[b]
1	H	(*S*)-**16**	⩾99:1	(*R*)-**17**	—[c]	⩾98:2
2	OMe	(*S*)-**23**	⩾97:3	(*R*)-**25**	58	⩾97:3
3	NMe_2	(*S*)-**24**	⩾97:3	(*R*)-**26**	50	~50:50

[a] Yield after purification by Kugelrohr distillation.
[b] Enantiomer ratio (er) determined by chiral shift ^{1}H NMR spectroscopy in the presence of (*S*)-1-(9-anthryl)-2,2,2-trifluoroethanol.
[c] 90% yield of (*R*)-**17** from (*R*)-styrene oxide (*R*)-**4** (see Scheme 4).[2,5]

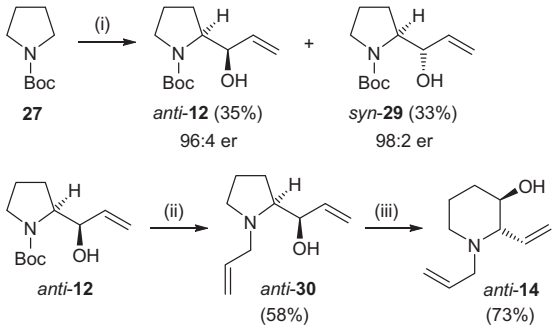
2.2. From pyrrolidines to piperidines via aziridinium ions: formal synthesis of (−)-swainsonine

(−)-Swainsonine, an inhibitor of lysosomal α-mannosidase and mannosidase II,[11] has been the subject of extensive synthetic efforts.[6,27] Using our recently developed *N*-Boc pyrrolidine lithiation-aldehyde trapping-ring expansion methodology, we realised that a concise synthesis of (−)-swainsonine could be attempted. Thus, previous work had established that piperidinyl alcohol *anti*-**14** could be converted into (−)-swainsonine (Scheme 7).[6,28] We envisaged that piperidinyl alcohol *anti*-**14** would be derived from *N*-Boc pyrrolidinyl alcohol *anti*-**12** via ring expansion through the key aziridinium ion intermediate **13**.[4,29] Asymmetric lithiation of *N*-Boc pyrrolidine **27** and trapping with acrolein would give amino alcohol *anti*-**12**. Notably, to ultimately complete a formal synthesis of the naturally occurring (−)-antipode, it would be necessary to use the (+)-sparteine surrogate **28** developed in our group.[30]



Scheme 7. Proposed formal synthesis of (−)-swainsonine.

Our planned synthesis started with the Beak-style[31] asymmetric lithiation of *N*-Boc pyrrolidine **27**. Thus, *N*-Boc pyrrolidine **27** was lithiated using *s*-BuLi/(+)-sparteine surrogate **28** and then trapped with acrolein to give a ~50:50 mixture of diastereomeric adducts *anti*-**12** and *syn*-**29**. Purification by column chromatography delivered *anti*-**12** (35% yield; 96:4 er) and *syn*-**29** (33% yield; 98:2 er) (Scheme 8). The relative stereochemistry was established by comparison with the literature data[32] and the ers were determined by chiral HPLC of the corresponding *N*-benzamide (formed by Boc deprotection and N-acylation with benzoyl chloride). Amino alcohol *anti*-**12** was then subjected to Boc deprotection and N-allylation to give *anti*-**30** in 58% yield. Finally, Cossy-style ring



Scheme 8. Synthesis of piperidine alcohol *anti*-**14**. Reagents and conditions: (i) *s*-BuLi, (+)-sparteine surrogate **28**, Et_2O, −78 °C, 3 h then acrolein; (ii) TFA, CH_2Cl_2, rt, 20 h then K_2CO_3, allyl bromide, MeOH, rt, 12 h; (iii) (a) $(CF_3CO)_2O$, Et_3N, CH_2Cl_2, −78 °C, 1 h; (b) reflux, 48 h; (c) $NaOH_{(aq)}$, rt, 2 h.

expansion of pyrrolidinyl alcohol *anti*-**30** to piperidinyl alcohol *anti*-**14** was accomplished using trifluoroacetic anhydride at reflux (followed by ester hydrolysis using NaOH). In this way, piperidinyl alcohol *anti*-**14** was generated in 73% yield.

We had anticipated converting *anti*-**14** into its TBDMS-protected analogue which is an intermediate in Blechert's synthesis of (−)-swainsonine.[28] However, whilst our work was in progress, Cossy et al. reported a formal synthesis of (−)-swainsonine[6] that proceeded via piperidinyl alcohol *anti*-**14** (prepared in five steps from (*S*)-proline). Thus, our three-step synthesis of a piperidinyl alcohol *anti*-**14** represents a formal synthesis of (−)-swainsonine.

3. Conclusion

In conclusion, we report the first example of a non-stereospecific ring opening of aromatic aziridinium ions (*S*)-**10**. Thus, diamine (*R*)-**25** (X = OMe) was formed in ⩾97:3 er but *racemic* diamine **26** (X = NMe_2) was generated. As a result, the scope and limitations of this aziridinium ion route to chiral diamines is now established. In addition, we also report a formal synthesis of (−)-swainsonine with a shorter synthesis of the key intermediate, piperidinyl alcohol *anti*-**14**. Of note, this synthesis of the natural (−)-antipode required the use of the (+)-sparteine surrogate **28**.

4. Experimental

4.1. General

All solvents were distilled before use. Et_2O and THF were freshly distilled from sodium benzophenone ketyl whereas CH_2Cl_2 was freshly distilled from calcium hydride. Et_3N was stored over KOH pellets. *n*-BuLi and *s*-BuLi were titrated against *N*-benzylbenzamide before use. All non-aqueous reactions were carried out under O_2-free N_2 or Ar using flame-dried glassware. Petrol refers to the fraction of petroleum ether boiling in the range 40–60 °C. Brine refers to a saturated aqueous solution. Flash chromatography was carried out using Fluka Chemie GmbH silica (220–440 mesh). Thin layer chromatography was carried out using commercially available Merck F_{254} aluminium-backed silica plates. Proton (400 MHz) and carbon (100.6 MHz) NMR spectra were recorded on a Jeol ECX-400 instrument using an internal deuterium lock. For samples recorded as solutions in $CDCl_3$, chemical shifts are quoted in parts per million relative to $CHCl_3$ (δ_H 7.27) and $CDCl_3$ (δ_C 77.0, central line of triplet). Carbon NMR spectra were recorded with broad band proton decoupling and were assigned using DEPT experiments. Coupling constants (*J*) are quoted in hertz. Melting points were carried out on a Gallenkamp melting point apparatus. Infrared spectra were recorded on an ATI Mattson Genesis FT-IR spectrometer. Chemical ionisation high and low resolution mass

spectra were recorded on a Fisons Analytical (VG) Autospec spectrometer. Electrospray high and low resolution mass spectra were recorded on a Bruker Daltronics microOTOF spectrometer. Optical rotations were recorded at room temperature on a Jasco DIP-370 polarimeter (using the sodium D line; 259 nm) and $[\alpha]_D$ given in units of 10^{-1} deg cm^3 g^{-1}. Chiral stationary phase HPLC was performed on an Agilent 1200 series chromatograph.

4.2. General procedure A: aminohydroxylation

A solution of $NaOH_{(aq)}$ was freshly prepared by dissolving NaOH (4.6 mmol) in water (12.2 mL). *t*-Butyl hypochlorite (4.6 mmol) and then 10 mL of the $NaOH_{(aq)}$ solution were added sequentially to a stirred solution of *t*-butyl carbamate (4.65 mmol) in *n*-PrOH (6 mL). After stirring for 5 min, the solution was cooled to 0 °C and a solution of DHQ_2PHAL or $DHQD_2PHAL$ (0.09 mmol) in *n*-PrOH (6 mL) was added. Then, a solution of alkene (1.5 mmol) in *n*-PrOH (12.2 mL) was added followed by addition of a solution of $K_2OsO_2(OH)_4$ (0.06 mmol) in the remaining 2.2 mL of the $NaOH_{(aq)}$ solution. After stirring for 1 h at 0 °C, saturated $Na_2SO_{3(aq)}$ solution (10 mL) was added and the mixture was stirred for 15 min. Then, the two layers were separated and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product.

4.3. General procedure B: Boc deprotection–dialkylation

At first, TFA (3.5 mL) was added dropwise to a stirred solution of the N-Boc-protected amino alcohol (0.90 mmol) in CH_2Cl_2 (10 mL) at rt under N_2. After stirring for 1 h, the solvent was evaporated under reduced pressure and 20% $NaOH_{(aq)}$ solution (1 mL) was added. The mixture was extracted with CH_2Cl_2 (4 × 10 mL) and the combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude amino alcohol which was sufficiently pure (by ^{1}H NMR spectroscopy) for use in the next step. Na_2CO_3 (2.70 mmol), tetra-*n*-butylammonium iodide (0.45 mmol) and then 1,4-dibromobutane (0.90 mmol) were added successively to a stirred solution of the crude amino alcohol in THF (10 mL) at rt under N_2. The resulting suspension was heated at reflux for 40 h. After being allowed to cool to rt, the solids were removed by filtration and the filtrate was evaporated under reduced pressure. The residue was dissolved in Et_2O (10 mL), washed with water (10 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product.

4.4. General procedure C: diamine synthesis

At first, MsCl (0.04 mL, 0.46 mmol) was added dropwise to a stirred solution of the amino alcohol (0.38 mmol) and Et_3N (0.96 mmol) in THF (5 mL) at 0 °C under N_2. After stirring at 0 °C for 30 min, Et_3N (0.58 mmol) was added and the solution was allowed to warm to rt. Then, $MeNH_2$ (40% aqueous solution, 5.75 mmol) was added and the resulting two-phase reaction mixture was stirred vigorously for 16 h. The two layers were separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with 5% $NaHCO_{3(aq)}$ (20 mL) and water (20 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product.

4.5. *N*,*N*-Dimethyl-4-vinylaniline 20

At first, *n*-BuLi (6.2 mL of a 1.45 M solution in hexanes, 8.95 mmol) was added dropwise to a stirred solution of methyltriphenylphosphonium bromide (3.20 g, 8.95 mmol) in THF (20 mL) at rt under N_2. After stirring for 15 min, a solution of 4-(dimethylamino)benzaldehyde (1.14 g, 7.65 mmol) in THF (10 mL) was added dropwise and the resulting mixture was stirred at rt for 16 h. Then, water (30 mL) and Et_2O (30 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 40 mL) and the combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography with 2:1 petrol–Et_2O as eluent gave styrene **20** (990 mg, 82%) as a pale yellow oil, R_F (1:1 petrol–Et_2O) 0.5; δ_H (400 MHz, $CDCl_3$) 7.34 (d, J = 9.0 Hz, 2H, *m*-$C_6H_4NMe_2$), 6.71 (d, J = 9.0 Hz, 2H *o*-$C_6H_4NMe_2$), 6.67 (dd, J = 17.0, 10.5 Hz, 1H, ArCH), 5.58 (dd, J = 17.0, 2.0 Hz, 1H, =CH), 5.06 (dd, J = 10.5, 2.0 Hz, 1H, =CH), 2.99 (s, 6H, NMe_2); δ_C (100.6 MHz, $CDCl_3$) 150.2 (*ipso*-Ar), 136.6 (=CH), 127.1 (Ar), 126.2 (*ipso*-Ar), 112.3 (Ar), 109.3 (=CH_2), 40.5 (NMe_2). Spectroscopic data were consistent with those reported in the literature.[26]

4.6. *tert*-Butyl (1*S*)-2-hydroxy-1-(4-methyoxyphenyl)-ethylcarbamate (*S*)-21

Using general procedure A, *t*-butyl carbamate (545 mg, 4.65 mmol), NaOH (183 mg, 4.6 mmol) in water (12.2 mL), *t*-butyl hypochlorite (0.53 mL, 4.6 mmol), $(DHQ)_2PHAL$ (71 mg, 0.09 mmol), 4-methoxystyrene (0.12 mL, 1.5 mmol) and $K_2OsO_2(OH)_4$ (22.5 mg, 0.06 mmol) in *n*-PrOH (24.2 mL) gave the crude product. Purification by flash column chromatography with 3:1 petrol–EtOAc as eluent gave carbamate (*S*)-**21** (260 mg, 65%) as a white solid, mp 140–142 °C (lit.,[22b] mp 139–141 °C); R_F (3:1 petrol–Et_2O) 0.2; $[\alpha]_D$ = +59.3 (*c* 1.0, EtOH) {lit.,[22b] $[\alpha]_D$ = +62.6 (*c* 1.0, EtOH) for 98% ee}; δ_H (400 MHz, $CDCl_3$) 7.21 (d, J = 8.5 Hz, 2H, *m*-C_6H_4OMe), 6.88 (d, J = 8.5 Hz, 2H, *o*-C_6H_4OMe), 5.24 (br s, 1H, NH), 4.71 (br s, 1H, CHN), 3.82–3.74 (m, 2H, CH_2O), 3.80 (s, 3H, OMe), 2.51 (br s, 1H, OH), 1.43 (s, 9H, CMe_3). Spectroscopic data were consistent with those reported in the literature.[22b]

4.7. *tert*-Butyl (1*S*)-1-[4-(dimethylamino)phenyl]-2-hydroxyethylcarbamate (*S*)-22

Using general procedure A, *t*-butyl carbamate (545 mg, 4.65 mmol), NaOH (183 mg, 4.6 mmol) in water (12.2 mL), *t*-butyl hypochlorite (0.53 mL, 4.6 mmol), $(DHQ)_2PHAL$ (71 mg, 0.09 mmol), styrene **20** (1.2 mL, 1.5 mmol) and $K_2OsO_2(OH)_4$ (22.5 mg, 0.06 mmol) in *n*-PrOH (24.2 mL) gave the crude product. Purification by flash column chromatography with 3:1 petrol–EtOAc as eluent gave carbamate (*S*)-**22** (244 mg, 58%) as an off-white solid, mp 165–167 °C; R_F (1:1 petrol–Et_2O) 0.2; $[\alpha]_D$ = +58.9 (*c* 1.0, $CHCl_3$); ν_{max} ($CDCl_3$) 3247 (NH), 3054, 2972, 1670 (C=O), 1524, 1364, 1264, 1056, 737 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.16 (d, J = 8.5 Hz, 2H, *m*-$C_6H_4NMe_2$), 6.72 (d, J = 8.5 Hz, 2H, *o*-$C_6H_4NMe_2$), 5.09 (br d, J = 6.0 Hz, 1H, NH), 4.71–4.67 (m, 1H, CHN), 3.81 (br s, 2H, CH_2O), 2.94 (s, 6H, NMe_2), 1.44 (s, 9H, CMe_3); δ_C (100.6 MHz, $CDCl_3$) 150.2 (*ipso*-Ar), 128.1 (*ipso*-Ar), 127.4 (Ar), 112.8 (Ar), 79.8 (*C*Me_3), 67.2 (CH_2), 56.6 (CHN), 40.6 (NMe_2), 28.3 (*CMe*$_3$); *m*/*z* (CI, NH_3) 281 [27%, $(M+H)^+$], 225 (68, M−55), 207 (43, M−73), 164 (100, M−116) [Found: $(M+H)^+$, 281.1867. $C_{15}H_{24}N_2O_3$ requires *M*+H, 281.1865].

4.8. (2*S*)-2-(4-Methoxyphenyl)-2-(1-pyrrolidinyl)ethanol (*S*)-23

Using general procedure B, TFA (3.5 mL, 45.0 mmol) and N-Boc-protected amino alcohol (*S*)-**21** (240 mg, 0.90 mmol) in CH_2Cl_2 (10 mL) followed by Na_2CO_3 (286 mg, 2.70 mmol), tetra-*n*-butylammonium iodide (165 mg, 0.45 mmol) and 1,4-dibromobutane (0.11 mL, 0.90 mmol) in THF (10 mL) gave the crude product. Purification by flash column chromatography with 9:1 CH_2Cl_2–MeOH as eluent gave amino alcohol (*S*)-**23** (127 mg, 64%, >97:3 er by ^{1}H NMR spectroscopy in the presence of (*S*)-1-(9-anthryl)-2,2,2-tri-

fluoroethanol) as a colourless oil, $[\alpha]_D$ = +54.8 (*c* 1.0, $CHCl_3$); ν_{max} ($CDCl_3$) 3390 (OH), 2954, 2841, 1650, 1514, 1249, 1180, 1024 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.24 (d, *J* = 8.5 Hz, 2H, *m*-C_6H_4OMe), 6.88 (d, *J* = 8.5 Hz, 2H, *o*-C_6H_4OMe), 3.88 (dd, *J* = 10.5, 6.0 Hz, 1H, CH_AH_BO), 3.80 (s, 3H, OMe), 3.78 (dd, *J* = 10.5, 6.0 Hz, 1H, CH_AH_BO), 3.49 (t, *J* = 6.0 Hz, 1H, CHN), 3.07 (br s, 1H, OH), 2.59–2.50 (m, 4H, CH_2N), 1.78–1.71 (m, 4H, CH_2); δ_C (100.6 MHz, $CDCl_3$) 159.1 (*ipso*-Ar), 130.5 (*ipso*-Ar), 129.7 (Ar), 113.7 (Ar), 69.0 (CHN), 64.1 (CH_2O), 55.2 (OMe), 51.1 (CH_2N), 23.0 (CH_2); *m*/*z* (CI, NH_3) 222 [100%, $(M+H)^+$], 190 (75) [Found: $(M+H)^+$, 222.1495. $C_{13}H_{19}NO_2$ requires *M*+H, 222.1494].

4.9. (2*S*)-2-[4-(Dimethylamino)phenyl]-2-(1-pyrrolidinyl)-ethanol (*S*)-24

Using general procedure B, TFA (3.15 mL, 40.5 mmol) and N-Boc-protected amino alcohol (*S*)-**22** (228 mg, 0.81 mmol) in CH_2Cl_2 (10 mL) followed by Na_2CO_3 (256 mg, 2.41 mmol), tetra-*n*-butylammonium iodide (149 mg, 0.40 mmol) and 1,4-dibromobutane (0.10 mL, 0.81 mmol) in THF (10 mL) gave the crude product. Purification by flash column chromatography with 10:1 CH_2Cl_2–MeOH as eluent gave amino alcohol (*S*)-**24** (103 mg, 54%, >97:3 er by ^1H NMR spectroscopy in the presence of (*S*)-1-(9-anthryl)-2,2,2-trifluoroethanol) as a yellow oil, R_F (10:1 CH_2Cl_2–MeOH) 0.1; $[\alpha]_D$ = −127.4 (*c* 0.5, $CHCl_3$); ν_{max}($CDCl_3$) 3382 (OH), 3052, 2963, 2878, 1613, 1522, 1351, 1265, 1164, 1064, 820, 740 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.17 (d, *J* = 8.5 Hz, 2H, *m*-$C_6H_4NMe_2$), 6.71 (d, *J* = 8.5 Hz, 2H, *o*-$C_6H_4NMe_2$), 3.87 (dd, *J* = 10.5, 6.5 Hz, 1H, CH_AH_BO), 3.74 (dd, *J* = 10.5, 6.0 Hz, 1H, CH_AH_BO), 3.46 (dd, *J* = 6.5, 6.0 Hz, 1H, CHN), 2.95 (s, 6H, NMe_2), 2.64 (br s, 1H, OH), 2.54–2.50 (m, 4H, CH_2N), 1.74–1.71 (m, 4H, CH_2); δ_C (100.6 MHz, $CDCl_3$) 150.1 (*ipso*-Ar), 129.5 (Ar), 125.8 (*ipso*-Ar), 112.2 (Ar), 68.4 (CHN), 63.9 (CH_2O), 50.6 (CH_2N), 40.5 (NMe), 23.0 (CH_2); *m*/*z* (CI, NH_3) 235 [69%, $(M+H)^+$], 164 (100, M−70) [Found: $(M+H)^+$, 235.1810. $C_{14}H_{22}N_2O$ requires *M*+H, 235.1810].

4.10. *N*-[-[(1*R*)-4-Methoxyphenyl)-2-(1-pyrrolidinyl)ethyl]-*N*-methylamine (*R*)-25

Using general procedure C, MsCl (0.05 mL, 0.65 mmol), amino alcohol (*S*)-**23** (120 mg, 0.54 mmol, >97:3 er) and Et_3N (0.19 mL, 1.36 mmol) in THF (5 mL) followed by Et_3N (0.19 mL, 1.36 mmol) and $MeNH_2$ (0.60 mL of a 40% aqueous solution, 7.73 mmol) gave the crude product. Purification by Kugelrohr distillation gave diamine (*R*)-**25** (74 mg, 58%, >97:3 er by ^1H NMR spectroscopy in the presence of (*S*)-1-(9-anthryl)-2,2,2-trifluoroethanol) as a colourless oil, bp 150–160 °C/0.3 mmHg; $[\alpha]_D$ = −73.2 (*c* 1.0 in $CHCl_3$); ν_{max} ($CDCl_3$)/ 3321 (NH), 2962, 1604, 1511, 1440, 1265, 1176, 1034, 738 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.27 (d, *J* = 8.5 Hz, 2H, *m*-C_6H_4OMe), 6.88 (d, *J* = 8.5 Hz, 2H, *o*-C_6H_4OMe), 3.81 (s, 3H, OMe), 3.55 (dd, *J* = 10.5, 3.5 Hz, 1H, CHAr), 2.84 (dd, *J* = 12.0, 10.5 Hz, 1H, CH_AH_BN), 2.65–2.61 (m, 2H, CH_2N), 2.50–2.45 (m, 2H, CH_2N), 2.29 (s, 3H, NMe), 2.25 (dd, *J* = 12.0, 3.5 Hz, 1H, CH_AH_BN), 2.16 (br s, 1H, NH), 1.83–1.73 (m, 4H, CH_2); δ_C (100.6 MHz, $CDCl_3$) 158.8 (*ipso*-Ar), 132.1 (*ipso*-Ar), 128.4 (Ar), 113.8 (Ar), 63.6 (CH_2N), 63.4 (CHN), 55.2 (OMe), 54.2 (CH_2N), 34.5 (NMe), 23.6 (CH_2); *m*/*z* (CI, NH_3) 235 [100%, $(M+H)^+$] [Found: $(M+H)^+$, 235.1811. $C_{14}H_{22}N_2O$ requires *M*+H, 235.1810].

4.11. *N*-[1-[4-(Dimethylamino)phenyl]-2-(1-pyrrolidinyl)ethyl]-*N*-methylamine *rac*-26

Using general procedure C, MsCl (0.04 mL, 0.46 mmol), amino alcohol (*S*)-**24** (90 mg, 0.38 mmol, >97:3 er) and Et_3N (0.14 mL, 0.96 mmol) in THF (5 mL) followed by Et_3N (0.08 mL, 0.58 mmol) and $MeNH_2$ (0.43 mL of a 40% aqueous solution, 5.75 mmol) gave the crude product. Purification by Kugelrohr distillation gave diamine *rac*-**26** (48 mg, 50%, ~50:50 er by ^1H NMR spectroscopy in the presence of (*S*)-1-(9-anthryl)-2,2,2-trifluoroethanol) as a colourless oil, bp 220–230 °C/1 mmHg; ν_{max} ($CDCl_3$) 3324 (NH), 2962, 1614, 1522, 1442, 1349, 1161, 819 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.21 (d, *J* = 8.5 Hz, 2H, *m*-$C_6H_4NMe_2$), 6.73 (d, *J* = 8.5 Hz, 2H, *o*-$C_6H_4NMe_2$), 3.50 (dd, *J* = 10.5, 3.5 Hz, 1H, CHN), 2.94 (s, 6H, NMe_2), 2.87 (dd, *J* = 12.0, 10.5 Hz, 1H, CH_AH_BN), 2.65–2.60 (m, 4H, CH_2N), 2.30 (s, 3H, NMe), 2.25 (dd, *J* = 12.0, 3.5 Hz, 1H, CH_AH_BN), 1.81–1.73 (m, 4H, CH_2); δ_C (100.6 MHz, $CDCl_3$) 149.9 (*ipso*-Ar), 130.2 (*ipso*-Ar), 128.1 (Ar), 112.6 (Ar), 63.8 (CH_2N), 63.5 (CHN), 54.2 (CH_2N), 40.7 (NMe_2), 34.5 (NMe), 23.5 (CH_2); *m*/*z* (CI, NH_3) 248 [46%, $(M+H)^+$], 217 (100, M−30) [Found: $(M+H)^+$, 248.2124. $C_{15}H_{25}N_3$ requires *M*+H, 248.2127].

4.12. 2-(1-Hydroxyallyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (1*S*,2*S*)-29 (*anti*-29) and (1*R*,2*S*)-12 (*syn*-12)

At first, *s*-BuLi (7.0 mL of a 1.1 M solution in cyclohexanes, 7.6 mmol, 1.3 equiv) was added dropwise to a stirred solution of *N*-Boc pyrrolidine **27** (1.00 g, 5.84 mmol) and (+)-sparteine surrogate **28** (1.47 g, 7.6 mmol, 1.3 equiv) in Et_2O (14 mL) at −78 °C under Ar. The resulting pale yellow solution was stirred at −78 °C for 3 h. Then, a solution of acrolein (0.78 mL, 11.7 mmol) in Et_2O (2 mL) was added dropwise and the resulting solution was allowed to warm to rt over 20 h. Saturated $NH_4Cl_{(aq)}$ (20 mL) was added and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 20 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product, which contained a ~50:50 mixture (by ^1H NMR spectroscopy) of pyrrolidines (1*S*,2*S*)-**29** and (1*R*,2*S*)-**12**. Purification by flash column chromatography on silica with $CHCl_3$–EtOAc (6:1) as eluent gave pyrrolidine (1*S*,2*S*)-**29** (435 mg, 33%, 98:2 er by chiral HPLC of the *N*-benzamide) as a pale yellow oil, R_F (6:1 $CHCl_3$–EtOAc) 0.2; $[\alpha]_D$ = −67.1 (*c* 1.0 in $CHCl_3$) [lit.,[32] $[\alpha]_D$ = −86.2 (*c* 0.905 in $CHCl_3$)]; δ_H (400 MHz, $CDCl_3$) 5.82 (ddd, *J* = 17.0, 10.5, 7.0 Hz, 1H, C*H*=CH_2), 5.32 (dt, *J* = 17.0, 1.5 Hz, 1H, *trans*-CH=CH_AH_B), 5.24 (br s, 1H, OH), 5.19 (br d, *J* = 10.5 Hz, 1H, *cis*-CH=CH_AH_B), 3.96 (br s, 1H, CHO), 3.87–3.81 (br m, 1H, CHN), 3.51–3.43 (br m, 1H, CH_AH_BN), 3.36–3.30 (m, 1H, CH_AH_BN), 1.94–1.72 (m, 4H), 1.48 (s, 9H, CMe_3) and pyrrolidine (1*R*,2*S*)-**12** (467 mg, 35%, 96:4 er) as a colourless oil, R_F (6:1 $CHCl_3$–EtOAc) 0.2; $[\alpha]_D$ = −51.4 (*c* 1.0, $CHCl_3$) [lit.,[32] $[\alpha]_D$ = −63.8 (*c* 0.853, $CHCl_3$)]; δ_H (400 MHz, $CDCl_3$) 5.80 (ddd, *J* = 17.0, 10.5, 6.5 Hz, 1H, C*H*=CH_2), 5.31 (dt, *J* = 17.0, 1.5 Hz, 1H, *trans*-CH=CH_AH_B), 5.25 (br s, 1H, OH), 5.19 (dt, *J* = 10.5, 1.5 Hz, 1H, *cis*-CH=CH_AH_B), 4.16 (br s, 1H, CHO), 4.07 (br s, 1H, CHN), 3.48 (br s, 1H, CH_AH_BN), 3.21 (br s, 1H, CH_AH_BN), 2.05 (br s, 1H), 1.85 (br s, 1H), 1.78–1.69 (m, 2H), 1.46 (s, 9H, CMe_3). Spectroscopic data were identical with those reported in the literature.[32]

The er of pyrrolidine (1*S*,2*S*)-**29** was determined by chiral HPLC of the *N*-benzamide: Chiralcel OD (95:5 hexane-*iso*-PrOH, 1.0 mL min^{-1}) (1*S*,2*S*) 14.9 (major), (1*R*,2*R*) 19.1 min (minor).

The er of pyrrolidine (1*R*,2*S*)-**12** was determined by chiral HPLC of the *N*-benzamide: Chiralcel OD (95:5 hexane-*iso*-PrOH, 1.0 mL min^{-1}) (1*R*,2*S*) 14.6 (major), (1*S*,2*R*) 27.5 min (minor).

4.13. 1-(1-Allylpyrrolidin-2-yl)prop-2-en-1-ol (1*R*,2*S*)-30 (*anti*-30)

At first, TFA (1.00 mL, 11.6 mmol) was added to a stirred solution of pyrrolidine (1*R*,2*S*)-**12** (263 mg, 1.16 mmol, 96:4 er) in CH_2Cl_2 (5 mL) at 0 °C under N_2. The resulting pale yellow solution was allowed to warm to rt then stirred for 20 h. 33% $NH_4OH_{(aq)}$ (2 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the

crude amino alcohol. To a stirred suspension of the crude amino alcohol and K_2CO_3 (240 mg, 1.74 mmol) in MeOH (4 mL) at 0 °C under N_2 was added allyl bromide (0.12 mL, 1.39 mmol). The resulting suspension was allowed to warm to rt and stirred for 12 h. Water (5 mL) and CH_2Cl_2 (5 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Immediate purification by flash column chromatography on silica with CH_2Cl_2–MeOH (95:5) then (9:1) as eluent gave pyrrolidine (1*R*,2*S*)-**30** (113 mg, 58%) as a yellow oil, R_F (9:1 CH_2Cl_2–MeOH) 0.2; $[\alpha]_D$ = −51.2 (*c* 0.75, $CHCl_3$) [lit.,[6] = −54.3 (*c* 1.0, $CHCl_3$)]; δ_H (400 MHz, $CDCl_3$) 5.90 (dddd, *J* = 17.5, 10.0, 7.5, 5.5 Hz, 1H, CH_2-C*H*=CH_2), 5.77 (ddd, *J* = 17.0, 10.5, 5.0 Hz, 1H, CH-C*H*=CH_2), 5.35 (dt, *J* = 17.0, 1.5 Hz, 1H, *trans*-CH=C*H*$_A$H$_B$), 5.21 (dd, *J* = 17.5, 1.5 Hz, 1H, *trans*-CH=C*H*$_A$H$_B$), 5.16 (dt, *J* = 10.5, 1.5 Hz, *cis*-CH=C*H*$_A$H$_B$), 5.12 (d, *J* = 10.5 Hz, 1H, *cis*-CH=C*H*$_A$H$_B$), 4.27–4.22 (m, 1H, CHO), 3.49 (dd, *J* = 13.5, 5.5 Hz, 1H, C*H*$_A$H$_B$CH=CH_2), 3.33 (br s, 1H, OH), 3.17–3.13 (m, 1H, C*H*$_A$H$_B$N), 2.94 (dd, *J* = 13.5, 7.5 Hz, 1H, CH$_A$*H*$_B$CH=CH_2), 2.58–2.53 (m, 1H), 2.31 (q, *J* = 9.0 Hz, 1H, CH$_A$*H*$_B$N), 1.84–1.78 (m, 1H), 1.74–1.60 (m, 3H). Spectroscopic data were consistent with those reported in the literature.[6]

4.14. 1-Allyl-2-vinylpiperidin-3-ol (2*S*,3*R*)-14 (*anti*-14)

At first, trifluoroacetic anhydride (0.11 mL, 0.81 mmol) was added to a stirred solution of pyrrolidine (1*R*,2*S*)-**30** (90 mg, 0.54 mmol) in THF (4 mL) at −78 °C under Ar. The resulting colourless solution was stirred at −78 °C for 1 h and then Et_3N (0.23 mL, 1.62 mmol) was added. The resulting colourless solution was stirred at −78 °C for 1 h and then heated at reflux for 48 h. The resulting brown solution was cooled to 0 °C and 2.0 M $NaOH_{(aq)}$ (2 mL) was added. The resulting brown mixture was warmed to rt and stirred for 2 h. CH_2Cl_2 (5 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with CH_2Cl_2–MeOH–NH_4OH (95:4.5:0.5) as eluent gave piperidine (2*S*,3*R*)-**14** (68 mg, 73%) as a brown oil, R_F (95:4.5:0.5 CH_2Cl_2–MeOH–NH_4OH) 0.3; $[\alpha]_D$ = +68.6 (*c* 1.5, $CHCl_3$) [lit.,[6] = +50.2 (*c* 1.03, $CHCl_3$)]; δ_H (400 MHz, $CDCl_3$) (dddd, *J* = 17.0, 10.5, 8.0, 5.5 Hz, 1H, CH_2-C*H*=CH_2), 5.76 (ddd, *J* = 17.0, 10.5, 8.5 Hz, 1H, CH-C*H*=CH_2), 5.36 (d, *J* = 10.5 Hz, 1H, *cis*-CH=C*H*$_A$H$_B$), 5.34 (d, *J* = 17.0 Hz, 1H, *trans*-CH=C*H*$_A$H$_B$), 5.14 (d, *J* = 17.0 Hz, 1H, *trans*-CH=C*H*$_A$H$_B$), 5.13 (d, *J* = 10.5 Hz, 1H, *cis*-CH=CH$_A$*H*$_B$), 3.39–3.33 (m, 2H, CHO and C*H*$_A$H$_B$CH=CH_2), 2.87 (dt, *J* = 11.5, 4.0 Hz, 1H, C*H*$_A$H$_B$N), 2.81 (dd, *J* = 14.0, 8.0 Hz, 1H, CH$_A$*H*$_B$CH=C H_2), 2.51 (t, *J* = 8.5 Hz, 1H, CHN), 2.23 (br s, 1H, OH), 2.06–2.00 (m, 2H), 1.72 (d quintet, *J* = 13.5, 4.0 Hz, 1H), 1.62–1.51 (m, 1H), 1.31 (dtd, *J* = 12.0, 10.0, 4.0 Hz, 1H). Spectroscopic data were consistent with those reported in the literature.[6]

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