Practical One-Step Synthesis of Koga's Chiral Bases

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Abstract: A simple, efficient and practical method for the preparation of Koga's chiral bases is described. The method involves attack of an amine on a styrene oxide-derived aziridinium ion and has allowed the synthesis of novel diamines which cannot be prepared using Koga's original route.

Key words: amines, chirality, amino alcohols, aziridinium ions

The use of lithium amide bases derived from chiral amines and diamines continues to be an important method in asymmetric synthesis.[1,2] In particular, enantioselective deprotonation of prochiral cyclic ketones using the chiral bases from amine (*R*,*R*)-**1**, popularised by Simpkins,[3] or diamines (*R*)-**2**–**6**, introduced by Koga,[4] have been used with success in a number of synthetic endeavours. In general, the two types of chiral bases give similar enantioselectivity in ketone deprotonations but amine (*R*,*R*)-**1** is the more popular as it is easy to prepare and commerically available; there is a reluctance to use Koga's bases presumably because of the length and difficulty of their synthesis.[5] Although difficult to access, Koga's chiral bases have been used to prepare intermediates for the total synthesis of penitrem B, reiswigin A and a range of indolizidine and tropinone alkaloids.[6] In an attempt to increase the popularity of Koga's bases, we now report that (*R*)-styrene oxide **7** can be converted into diamines (*R*)-**2**–**4** via a simple and efficient one-pot process. Furthermore, the methodology has been extended to include the synthesis of some novel chiral diamines and chiral bases not previously accessible using Koga's original route.[5]

Koga's published synthesis of diamines (*R*)-**2**–**4** involves a four step synthesis of diamine (*R*)-**10** from (*R*)-phenylglycine and subsequent synthetic manipuations to give the required diamines (e.g. reductive amination with pivaldehyde or amide formation followed by reduction). This route is long and technically demanding. An alternative route starting from mandelic acid has recently been reported by Singh and Saravanan[7] but this approach is still three steps. In contrast, our previously reported[8] synthesis of diamines from styrene oxide is simple and effectively one-step; we reasoned that it would be a simple matter to extend this to the synthesis of Koga's diamines. To test this out, we prepared Koga's important intermediate (*R*)-**10** in 71% yield starting from (*R*)-styrene oxide as outlined in the Scheme. The aziridinium ion (*S*)-**9** was prepared in the usual manner (ring opening of the epoxide with piperidine followed by mesylation) and was successfully intercepted by ammonia. By synthesising diamine (*R*)-**10** we had completed a formal synthesis of virtually all of the diamines previously prepared by Koga. However, the power of our methodology is demonstrated by the direct synthesis of Koga's chiral diamines from (*R*)-styrene oxide. Our results with a range of amine nucleophiles are presented in the Table.

The preparation of each of Koga's chiral diamines (*R*)-**2**–**4** proceeded in high yield (79–85%) and with stereochemical integrity[9] (entries 1–3). For the synthesis of diamine (*R*)-**3**, neopentylamine was prepared from pivalonitrile using a published procedure[10] and for the preparation of (*R*)-**4**, trifluoroethylamine was generated in situ from the corresponding hydrochloride salt using an extra equivalent of triethylamine. The 85% yield obtained for diamine (*R*)-**3** (entry 2), arguably the most useful of the Koga bases, is particularly noteworthy.

We have also successfully extended the one-pot procedure to diamines (*R*)-**11**, (*R*,*R*)-**12** and (*S*,*R*)-**13** (Entries 5, 6 and 7), compounds which are not accesible using Koga's reductive amination or amide formation routes. A different type of phenylglycine-derived amine, diamine (*R*)-**15**,

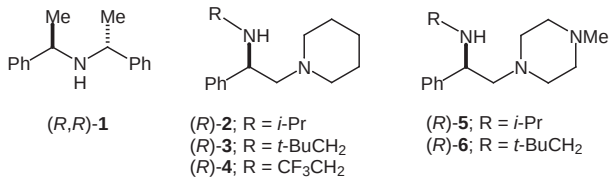
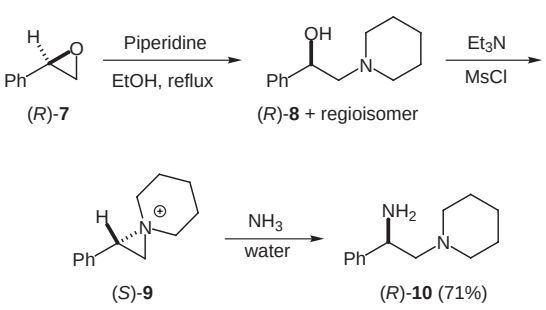


Figure 1 Structures of known chiral bases **1**–**6**



Scheme

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is particularly useful for enantioselective α-alkylation.[11] We have prepared diamine (*R*)-**15** (entry 9) and a related compound (*R*)-**14** (entry 8) in good yields using the one-pot reaction with known[12] 2-(2-methoxyethoxy)ethylamine and di(ethylene glycol) methyl ether respectively. The conversion of diamine (*R*)-**14** into (*R*)-**15** by methylation using sodium hydride was unsuccessful. The "dimeric" tetraamine (*R*,*R*)-**16** has recently been described as an excellent ligand for enantioselective α-alkylation[13] and enantioselective protonation.[14] As a final example, we were able to prepare this very useful tetraamine in 67% yield using a one-pot reaction in which half an equivalent of 1,3-diaminopropane was reacted with aziridinium ion (*S*)-**9**.

In conclusion, a simple, efficient and practical method for the preparation of Koga's chiral bases and related novel chiral bases has been described. The continued use of these compounds in synthesis emphasises the need for a simple method for their preparation.

Water is distilled water. The boiling points reported are for compounds purified by Kugelrohr distillation and correspond to the oven temperature during the distillation. Optical rotations were recorded on a Jasco DIP-370 polarimeter (using the sodium D line; 589 nm) and $[\alpha]_D$ are given in units of 10^{-1} deg cm^2 g^{-1}. Diamines (*R*)-**2**–**4**, (*R*)-**10** and (*R*)-**15** have been fully characterised previously by Koga and our data is in agreement with that reported in the literature.[5]

Amines 11–16 from (*R*)-Styrene Oxide; General Procedure

A solution of (*R*)-styrene oxide **7** (4.4 mmol) and piperidine (7.2 mmol) in EtOH (15 mL) 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. Under N_2, this crude product was dissolved in Et_2O (20 mL), Et_3N (7.1 mmol, 1.6 equiv) was added and the solution was cooled to 0 °C. Then, MsCl (5.3 mmol, 1.2 equiv) was added dropwise. A white precipitate formed which made stirring difficult and after 30 min, Et_3N (8.8 mmol, 2 equiv) was added. At r.t., the amine (1–50 equiv, either neat or generated in situ from the hydrochloride salt and one mole equiv of Et_3N) and then H_2O (2.5 mL) 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 mL). The combined organic extracts were washed with aq 5% $NaHCO_3$ solution (30 mL) and H_2O (30 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product as an oil which was purified by Kugelrohr distillation. For yields and equivalents of amine used, see Table.

(*R*)-*N*-(1,1-Dimethylethyl)-1-phenyl-2-(piperidin-1-yl)ethanamine [(*R*)-**11**]

Colourless oil; bp 125–135 °C/0.5 Torr; $[\alpha]_D$ -77 (*c* = 1.0, $CHCl_3$).

IR ($CDCl_3$): ν = 3294 cm^{-1}.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.43–7.15 (m, 5 H), 3.90 (dd, 1 H, *J* = 4, 11 Hz), 2.56 (br s, 2 H), 2.32–2.13 (m, 3 H), 2.27 (dd, 1 H, *J* = 11, 12 Hz), 2.17 (dd, 1 H, *J* = 4, 12 Hz), 1.62–1.41 (m, 6 H), 0.98 (s, 9 H).

^{13}C NMR (67.9 MHz, $CDCl_3$): δ = 146.7, 127.9, 127.3, 126.4, 67.0, 54.2, 50.8, 30.1, 26.2, 24.5.

MS (CI, NH_3): *m/z* = 261 $(M + H)^+$, 98.

HRMS (CI, NH_3): *m/z* Calcd for $C_{17}H_{29}N_2$ $(M + H)^+$ 261.2331, found 261.2328.

(1*R*)-*N*-[(1*R*)-Phenylethyl]-1-phenyl-2-(piperidin-1-yl)ethanamine [(*R*,*R*)-**12**]

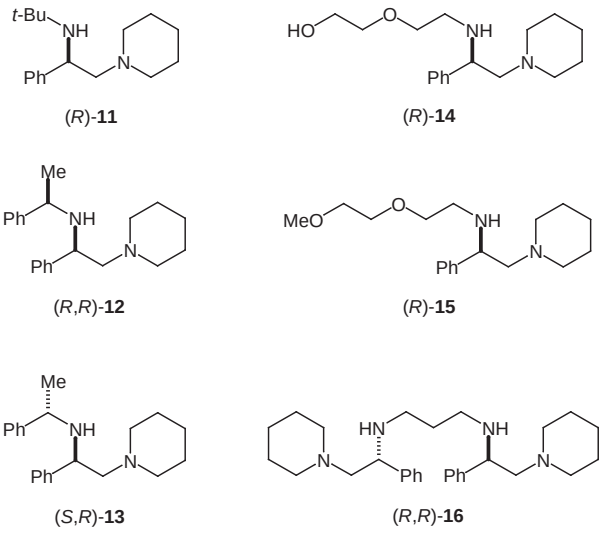

Figure 2 Structures of synthesised chiral bases **11**–**16**

Table Synthesis of Diamines and a Tetraamine from (*R*)-Styrene Oxide

Entry	Amine (equiv)	Product	Yield (%)
1	*i*-$PrNH_2$ (17.0)	(*R*)-**2**	79
2	*t*-$BuCH_2NH_2$ (3.0)	(*R*)-**3**	85
3	CF_3CH_2NH2 (1.1)[a]	(*R*)-**4**	82
4	NH_3 (50.0)	(*R*)-**10**	71
5	*t*-$BuNH_2$ (11.0)	(*R*)-**11**	83
6	(*R*)-$PhCH(Me)NH_2$ (1.1)	(*R*,*R*)-**12**	71
7	(*S*)-$PhCH(Me)NH_2$ (1.1)	(*S*,*R*)-**13**	70
8	$HO(CH_2)_2O(CH_2)_2NH_2$	(*R*)-**14**	63
9	$MeO(CH_2)_2O(CH_2)_2NH_2$ (1.0)[a]	(*R*)-**15**	69
10	$H_2N(CH_2)_3NH_2$ (0.5)	(*R*,*R*)-**16**	67

[a] A 1:1 ratio of the hydrochloride salt and triethylamine was used.

Colourless oil; bp 190–220 °C/0.3 Torr; $[\alpha]_D$ -46 (*c* = 1.0, $CHCl_3$).

IR ($CDCl_3$): ν = 3303 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 7.39–7.16 (m, 10 H), 3.98 (dd, 1 H, *J* = 4, 10 Hz), 3.70 (q, 1 H, *J* = 7 Hz), 2.80–2.28 (m, 7 H), 1.68–1.39 (m, 6 H), 1.36 (d, 3 H, *J* = 7 Hz).

^{13}C NMR (67.9 MHz, $CDCl_3$): δ = 146.4, 143.6, 128.1, 127.5, 126.8, 126.6, 126.3, 66.3, 57.5, 54.8, 54.5, 26.1, 24.5, 21.5.

MS (CI, NH_3): *m/z* = 309 $(M + H)^+$, 98.

HRMS (CI, NH_3): *m/z* Calcd for $C_{21}H_{29}N_2$ $(M + H)^+$ 309.2331, found 261.2329.

(1*R*)-*N*-[(1*S*)-Phenylethyl]-1-phenyl-2-(piperidin-1-yl)ethanamine [(*S*,*R*)-**13**]

Colourless oil; bp 190–220 °C/0.3 Torr; $[\alpha]_D$ -141 (*c* = 1.0, $CHCl_3$).

IR ($CDCl_3$): ν = 3273 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 7.36–7.17 (m, 10 H), 3.50 (q, 1 H, *J* = 7 Hz), 3.44 (dd, 1 H, *J* = 3, 11 Hz), 2.94 (br s, 1 H), 2.50–2.10 (m, 6 H), 1.58–1.42 (m, 6 H), 1.37 (d, 3 H, *J* = 7 Hz).

^{13}C NMR (67.9 MHz, $CDCl_3$): δ = 146.2, 143.2, 128.3, 128.2, 127.6, 127.0, 126.6, 126.5, 66.2, 56.2, 54.7, 54.4, 26.0, 24.6, 24.4.

MS (CI, NH_3): *m/z* = 309 $(M + H)^+$, 210, 98.

HRMS (CI, NH_3): *m/z* Calcd for $C_{21}H_{29}N_2$ $(M + H)^+$ 309.2331, found 261.2328.

(*R*)-*N*-[2-(2-Hydroxyethyloxy)ethyl]-1-phenyl-2-(piperidin-1-yl)ethanamine [(*R*)-**14**]

Colourless oil; bp 205–220 °C/0.5 Torr; $[\alpha]_D$ +55 (*c* = 1.0, EtOH).

IR ($CDCl_3$): ν = 3595, 3275 cm^{-1}.

1H NMR (270 MHz, $CDCl_3$): δ = 7.38–7.20 (m, 5 H), 3.80–3.73 (m, 3 H), 3.61–3.55 (m, 4 H), 2.68–2.44 (m, 5 H), 2.30–2.24 (m, 5 H), 1.68–1.40 (m, 6 H).

^{13}C NMR (67.9 MHz, $CDCl_3$): δ = 142.6, 128.3, 127.4, 127.1, 72.2, 70.4, 66.4, 61.9, 59.9, 54.7, 47.1, 26.0, 24.4.

MS (CI, NH_3): *m/z* = 293 $(M + H)^+$, 98.

HRMS (CI, NH_3): *m/z* Calcd for $C_{17}H_{28}N_2O_2$ $(M + H)^+$ 293.2229, found 293.2227.

N,*N*-bis[(*R*)-1-Phenyl-2-(piperidin-1-yl)ethyl]-1,3-propanediamine [(*R*,*R*)-**16**]

Colourless oil; bp 230–240 °C/0.3 Torr; $[\alpha]_D$ -99 (*c* = 1.0, $CHCl_3$).

IR ($CDCl_3$): ν = 3278 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 7.37–7.19 (m, 10 H), 3.72 (dd, 2 H, *J* = 4, 11 Hz), 2.53–2.20 (m, 18 H), 1.69–1.38 (m, 14 H).

^{13}C NMR (67.9 MHz, $CDCl_3$): δ = 143.3, 128.8, 127.3, 126.9, 66.6, 60.2, 54.6, 46.3, 30.7, 26.1, 24.5.

MS (CI, NH_3): *m/z* = 449 $(M + H)^+$, 350, 98, 86.

HRMS (CI, NH_3): *m/z* Calcd for $C_{29}H_{45}N_4$ $(M + H)^+$ 449.3644, found 449.3639.

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