A New Efficient Synthesis of (*R*,*R*)-2,2′-Bipyrrolidine: An Interesting Chiral 1,2-Diamine with C_2 Symmetry**

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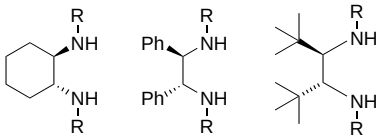
Chiral C_2-symmetrical diamines emerged recently as versatile auxiliaries or ligands in many asymmetric transformations.[1] For example, *N*,*N*′-dialkyl-1,2-cyclohexanediamine (**1**), *N*,*N*′-dialkyl-1,2-diphenyl-1,2-ethanediamine (**2**), *N*,*N*′-dialkyl-1,2-di(*tert*-butyl)-1,2-ethanediamine (**3**)[2] have given excellent results in many reactions.[1a]



1 **2** **3**

To understand why the corresponding chiral aminals are such efficient auxiliaries, one must first examine the particular conformation under which they react. Most studies show that in such cyclic aminals (imidazolidine in this case), the preferred conformation is one with the N substituent located *trans* to the substituent on the adjacent carbon. In this conformation, each nitrogen atom becomes a stereogenic center with different stereodirecting and/or chelation ability; one lone pair participates in an anomeric effect, whereas the other one does not, making the nitrogen center more basic. This is easily seen from the X-ray structure of **4**, an aminal derived from the monohydrazone of glyoxal (Figure 1).[3]

However, is this conformation necessary? To answer this question we needed to prepare an imidazolidine where the N substituent and the substituent on the adjacent carbon are *cis* to each other. This may be attained by taking advantage of the preferential *cis* ring junction of the bicyclo[3.3.0]azaoctane ring system (see analogous tricyclic system in Scheme 1). Aminals of (*R*,*R*)-2,2′-bipyrrolidine, which contains two nitrogen atoms in five-membered rings, are good examples of such a conformational restriction.

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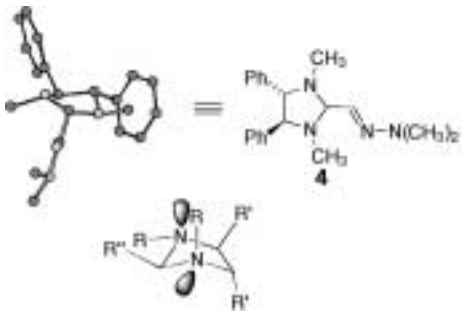
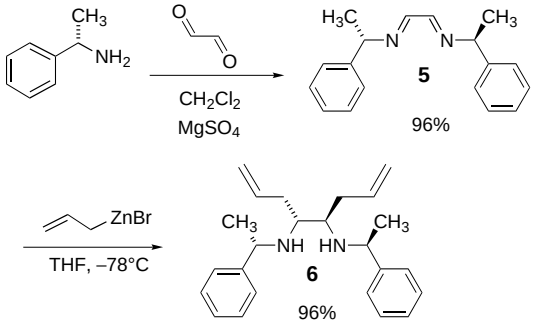


Figure 1. Conformation of chiral imidazolidine **4** and, below, a general representation of the conformation of these compounds.

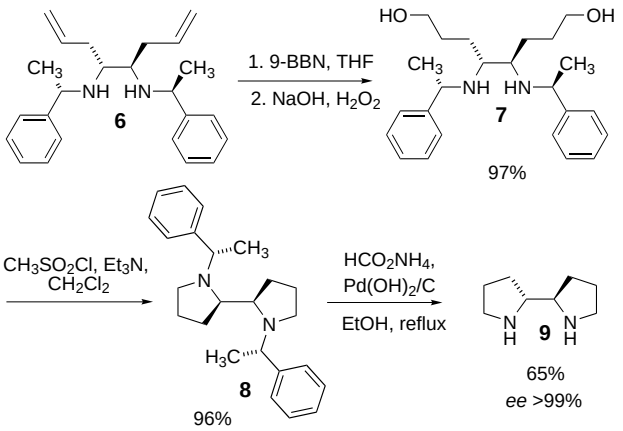
Scheme 1. Comparison of the conformations of monocyclic and tricyclic imidazolidines.

(*R*,*R*)-2,2′-bipyrrolidine (**9**) was first prepared by Hirama and co-workers, by resolution with tartaric acid.[5] Another synthesis has been reported by Kotsuki et al., starting from mannitol or tartaric acid.[6] We have developed an alternative shorter strategy, which is feasible on a large scale (no chromatographic purifications are required). The first steps are based on the chiral diamine synthesis reported by Neumann et al.,[7] latterly improved by Savoia and co-workers,[8] which starts from *N*,*N*-bis[(*S*)-1-phenylethyl]ethanediimine (**5**; Scheme 2).[9]



Scheme 2. Preparation of starting material **6**.

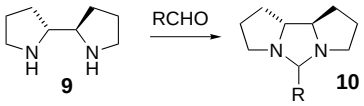
By this method, *N*,*N*-bis[(*S*)-1-phenylethyl]-(*R*,*R*)-4,5-diamino-1,7-octadiene (**6**) is obtained in good yield (60%) and excellent diastereoselectivity (>99%) when isolated and purified. Alternatively, a simple acid–base washing procedure afforded a quantitative yield of material suitable for further transformation. Double hydroboration of this diamine using 9-BBN in tetrahydrofuran,[10] gave **7** in good yield with complete regiocontrol (Scheme 3). The cyclisation was carried out on the crude material by formation of the bismesylate (=bis-methane sulfonate) with methanesulfonyl chloride and subsequent treatment with triethylamine in dichloromethane.[11] The resulting cyclic compound **8** (*N*,*N*-bis[(*S*)-1-phenylethyl]-(*R*,*R*)-2,2′-bipyrrolidine) was isolated



Scheme 3. Preparation of 2,2′-bipyrrolidine (**9**) starting from **6**. 9-BBN = 9-borabicyclo[3.3.1]nonane.

in 60 % yield or simply purified by acid – base washing to give 95 % yield. The final step is the debenzylation of the nitrogen groups with Pearlmann's catalyst, using ammonium formate as a hydrogen source, in refluxing ethanol (Scheme 3). This synthesis of (*R*,*R*)-2,2′-bipyrrolidine (**9**) could be carried out on a large scale (0.4 mol) in 61 % overall yield, starting from **6** and using only acid – base wash purifications and a final distillation, with an *ee* value of >99 % (the *ee* value was determined by ^{31}P NMR spectroscopy).[12]

With (*R*,*R*)-2,2′-bipyrrolidine (**9**) in hand, we easily prepared the corresponding aminals **10** with several aldehydes,[13] by simple stirring of the diamine with the aldehyde, in diethyl ether at room temperature (Scheme 4). None of the reactions however, gave products suitable for X-ray crystallography.



Scheme 4. Formation of aminals **10**. R = Ph, *p*-FC_6H_4, *p*$NO_2C_6H_4$.

In order to prove that the preferred conformation is as shown in Scheme 4, we relied on the coordination of the nitrogens to a metal salt. Thus, we were able to form two solid complexes **11** and **12**, obtained from reactions of **8** and **9**, respectively, with zinc chloride in diethyl ether. Compounds **11** and **12** were recrystallized from ethanol to obtain crystals suitable for analysis.

As can be seen from the X-ray structure (Figure 2) of complex **11**, the 2,2′-bipyrrolidine framework adopts a stair-like conformation, perfectly fitting our hypothesis. In particular, the hybridization of the nitrogens remains clearly sp^3, as may be found by the sum of the bond angles, 322°. The mean N–Zn bond is 2.125(3) Å. We may assume that aminals **10** also adopt such a stair-like conformation.

Compound **12** displayed a more complex crystal structure, where two monomeric forms (diamine:zinc = 1:1) **12a** and a dimeric form (diamine:zinc = 2:1) **12b** alternate (Figure 3). This behavior reflects, in fact, the strong basicity of the pyrrolidine unit, which allows for the replacement of the chlorine atom by a nitrogen. It should be noted, however, that

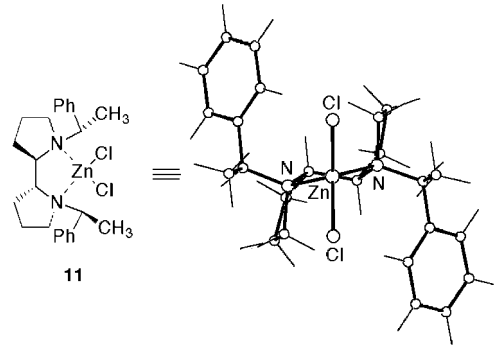


Figure 2. X-ray structure of **11**, the complex formed between *N*,*N*-bis[(*S*)-1-phenylethyl]-(*R*,*R*)-2,2′-bipyrrolidine (**8**) and $ZnCl_2$.

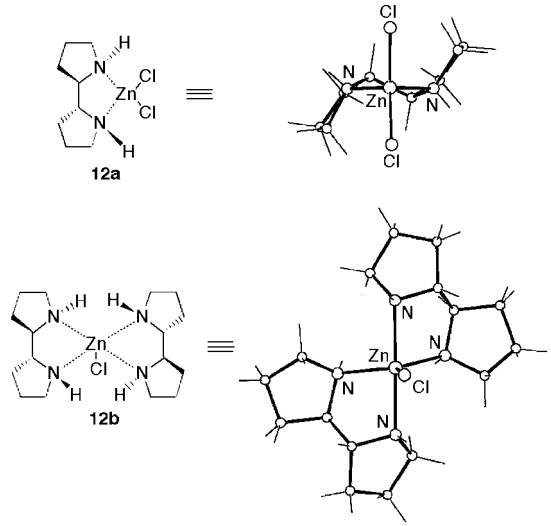


Figure 3. X-ray structures of **12a** and **12b**, the complexes formed between 2,2′-bipyrrolidine (**9**) and $ZnCl_2$.

both the monomeric and dimeric structures adopt the same stair-like conformation, exactly as in complex **11**. The angle formed by the two adjacent five-membered rings is lower, that is, the molecule is less bent and shows a slightly lower degree of pyramidalization of the nitrogen atoms. The monomeric form has quasi perfect C_2 symmetry, again with a tetrahedral zinc atom. The dimeric form is a remarkable trigonal bipyramid, with two nitrogens in the apical positions, and two nitrogens and the chlorine atom in equatorial positions. The N–Zn apical bonds are longer than the N–Zn equatorial bonds (2.203(4) Å and 2.095(4) Å, respectively). The dimeric complex is located on a cristallographic C_2 axis passing through the Zn^+, Cl, and Cl^- atoms. The Cl^- atom is located 3.941(1) Å from the Zn^+ atom and is involved in hydrogen bonds with two nitrogen atoms of the pyrrolidine rings: N–H = 0.93(4) Å, H ··· Cl = 3.388(4) Å, N–H ··· Cl = 152(4)°.

The behavior of this diamine is being actively studied in asymmetric synthesis and the results will be reported in due course.

Experimental Section

Compound **6** was prepared as reported by Savoia and co-workers[8] on a large scale (0.4 mol).

Compound **7**: *cis*,*cis*-1,5-Cyclooctadiene (0.178 L, 1.45 mol) was added dropwise to a stirred solution of $BH_3 \cdot Me_2S$ complex (95 %, 0.144 L,

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1.45 mol) in dry THF (1.45 L) at $-5\,^{\circ}C$ under N_2. The mixture was stirred for 45 min at $-5\,^{\circ}C$ (a white solid was formed). The resulting mixture was heated at reflux for 1 h, and then cooled to room temperature. A solution of **6** (127 g, 0.36 mol) in anhydrous THF (1.00 L) was added under N_2. The mixture was stirred for 1 h and cooled to $0\,^{\circ}C$. An aqueous solution of 3 M NaOH (0.40 L) was added dropwise followed by an aqueous solution of 30% H_2O_2 (0.56 L). The mixture was stirred for 30 min at $0\,^{\circ}C$ and NaOH (74 g) was added. The mixture was extracted 3 times with Et_2O (3×1.00 L) and the combined organic layers were dried over K_2CO_3, filtered, and concentrated to give an orange oil. The crude product was purified by acid–base washing to give 135 g (97%) of *N*,*N*′-bis[(*S*)-1-phenylethyl]-(*R*,*R*)-4,5-diamino-1,8-octanediol (**7**) with a good purity (a small sample was purified on silicagel (CH_2Cl_2/MeOH 90/10) with 83% yield for spectroscopic analysis). ^1H NMR (200 MHz, $CDCl_3$, $25\,^{\circ}C$): $\delta = 1.30$ (d, 6H, $J = 6.6$ Hz), 1.38–1.24 (m, 12H), 2.41–2.25 (m, 2H), 3.56–3.49 (m, 4H), 3.77 (q, 2H, $J = 6.6$ Hz), 7.40–7.28 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$, $25\,^{\circ}C$): $\delta = 26.6$, 28.2, 29.6, 55.6, 62.4, 126.8, 127.8, 128.1, 145.2; IR: $\tilde{\nu} = 3331$, 3026, 2926, 2859, 1492, 1452, 1370, 1300, 1270, 1215, 1110, 1059, 1009, 907, 763, 701 cm^{-1}; GC-MS (electron ionization (EI)) *m*/*z* (%): 192 (100) $[C_{12}H_{18}NO]$, 174 (12) $[C_{12}H_{16}N]$, 105 (79) $[C_8H_6]$, 70 (12) $[C_4H_8N]$.

Compound **8**: Et_3N (0.15 L, 1.05 mol) and CH_3SO_2Cl solution (0.08 L, 1.05 mol) were added to a stirred solution of **7** (135 g, 0.35 mol) in anhydrous CH_2Cl_2 (1.00 L) under nitrogen cooled to $0\,^{\circ}C$. The mixture was warmed to room temperature and stirred for 10 min. The solvent was removed and the crude product was purified by acid–base washing to give 118 g (96%) of *N*,*N*-bis[(*S*)-1-phenylethyl]-(*R*,*R*)-2,2′-bipyrrolidine **8** (a small sample was purified on silicagel (CH_2Cl_2/MeOH 90/10) with 60% yield, for spectroscopic analysis). ^1H NMR: (200 MHz, $CDCl_3$, $25\,^{\circ}C$): $\delta =$ 1.20 (d, 6H, $J = 6.6$ Hz), 1.68–1.45 (m, 4H), 1.90–1.70 (m, 4H), 2.55–2.35 (m, 2H), 2.83–2.65 (m, 2H), 3.10–2.85 (m, 2H), 3.54 (q, 2H, $J = 6.6$ Hz), 7.40–7.15 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$, $25\,^{\circ}C$): $\delta = 16.9$, 24.3, 26.4, 50.6, 61.4, 63.8, 127.2, 127.4, 128.3, 144.0; IR: $\tilde{\nu} = 2968$, 2199, 1493, 1451, 1372, 905, 732 cm^{-1}; GC-MS (EI) *m*/*z* (%): 174 (100) $[C_{12}H_{16}N]$, 105 (60) $[C_8H_6]$, 70 (49) $[C_4H_8N]$; MS (electron spectroscopy imaging) *m*/*z* (%): 349 (100) $[M^{+}+1]$, 245 (45) $[C_{16}H_{23}N_2^{2+}]$, 174 (23) $[C_{12}H_{16}N]$, 142 (40) $[C_8H_{16}N_2^{++}]$, 106 (69) $[C_8H_6^{+}]$.

In the synthesis of compounds **7** and **8**, 5–10% of 1,5-cyclooctanediol contaminated the product but it can be removed in the final distillation.

Compound **9**: $Pd(OH)_2$/C (20%, 16 g) and anhydrous HCO_2NH_4 (128 g, 2.03 mol) were added to a solution of **8** (118 g, 0.34 mol) in EtOH (2.00 L). The mixture was refluxed 1.5 h with vigorous stirring under N_2. After cooling to room temperature the mixture was filtered through celite, the residue was washed with EtOH, and the filtrate was concentrated. The residue was dissolved in Et_2O (1.00 L) and stirred for 15 min over K_2CO_3, before being filtered and concentrated to give the crude diamine as a pale yellow oil. The crude product was purified by distillation under reduced pressure to yield 31 g (65% overall based on **7**) of **9**. ^1H NMR: (200 MHz, $CDCl_3$, $25\,^{\circ}C$): $\delta = 1.2$–2.3 (m, 8H), 2.6–3.3 (m, 6H), 4.0 (br.s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$, $25\,^{\circ}C$): $\delta = 25.9$, 29.7, 46.9, 64.2; IR: $\tilde{\nu} = 3278$, 2957, 2868, 1560, 1457, 1398, 1368, 1336, 1074, 908, 814, 763, 700, 600 cm^{-1}; GC-MS (EI) *m*/*z* (%): 70 (100) $[C_4H_8N]$, 43 (6) $[C_2H_5N]$, 18 (6) $[C_2H_4]$; ^{31}P NMR (162 MHz, $CDCl_3$, $25\,^{\circ}C$): $\delta = 146.7$ $[(N)_2P{-}(-)$menthol], 147.4 $[(N)_2P{-}(+)$menthol].

General procedure for the synthesis of aminals **10**: Aldehyde (1 mmol) was added to a stirred solution of 2,2′-bipyrrolidine (140 mg, 1 mmol) in Et_2O (10 mL). The mixture was stirred at room temperature (1–5 h) until none of starting material remained (determined by GC). The solvent was removed under reduced pressure to give the crude aminal.

Compound **11**: Anhydrous $ZnCl_2$ (50 mg, 0.37 mmol) was added to a stirred solution of **8** (130 mg, 0.37 mmol) in Et_2O (10 mL). After solubilization, a white precipitate was formed and collected by filtration. This solid was recrystallized from EtOH.

12a and **12b**: Anhydrous $ZnCl_2$ (135 mg, 1 mmol) was added to a stirred solution of **9** (140 mg, 1 mmol) in Et_2O (10 mL). After solubilization, a white precipitate was formed and collected by filtration. This solid was recrystallized from EtOH.

Crystal structure determinations: Cell dimensions and intensities were measured at 200 K on a Stoe IPDS diffractometer with graphite-monochromated $Mo_{K\alpha}$ radiation ($\mu = 0.71069$ Å). Data were corrected for linear prediction and for absorption. The structures were solved by direct methods using MULTAN 87[14], all other calculations used the XTAL system.[15] $[ZnCl_2(C_{24}H_{32}N_2)] \cdot (CH_3OH)_{0.25}$ (**11**): $M_r = 492.8$, $\mu = 1.25$ mm^{-1}, T_{min}, $T_{max} = 0.7363$, 0.7735, $\rho_x = 1.35$ $g\,cm^{-3}$, orthorhombic, $P2_12_12_1$, $Z = 4$, $a = 10.4081(7)$, $b = 12.8932(8)$, $c = 18.0095(11)$ Å, $U = 2416.8(3)$ Å^3. 30376 measured reflections, 4719 unique reflections of which 4253 were observable $|F_o| > 4\sigma(F_o)$); R_{int} for equivalent reflections = 0.026. Full-matrix least-squares refinement (on *F*) using weight of $1/[\sigma^2(F_o) + 0.0003(F_o^2)]$ gave final values $R = 0.025$, $wR = 0.030$, for 271 variables and 4253 contributing reflections. Flack parameter:[16] $x = -0.01(1)$. Hydrogen atoms were placed in calculated positions.

$[ZnCl(C_8H_{16}N_2)_2]^{+}Cl^{-}[ZnCl_2(C_8H_{16}N_2)]_2$ (**12**): $M_r = 969.9$, $\mu = 2.11$ mm^{-1}; T_{min}, $T_{max} = 0.6732$, 0.7366, $\delta_x = 1.53$g cm^{-3}, tetragonal, $P4_12_12$, $Z = 4$, $a =$ 13.8279(6), $c = 22.0358(12)$ Å, $U = 4213.5(4)$ Å^3. 52049 measured reflections, 4110 unique reflections of which 3231 were observable $|F_o| > 4\sigma(F_o)$); R_{int} for equivalent reflections = 0.043. Full-matrix least-squares refinement (on *F*) using weight of $1/[\sigma^2(F_o) + 0.0002(F_o^2)]$ gave final values $R = 0.027$, $wR = 0.030$, for 230 variables and 3231 contributing reflections. Flack parameter:[16] $x = 0.00(2)$. Hydrogen atoms were placed in calculated positions except for hydrogens bound to the nitrogen atoms which were observed and refined with a fixed value of U_{iso}. The Zn and Cl atoms of the dimer moiety (and the Cl^{-}) are located on twofold axes in special positions 4a. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-143123 (for **11**) and CCDC-143124 (for **12**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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