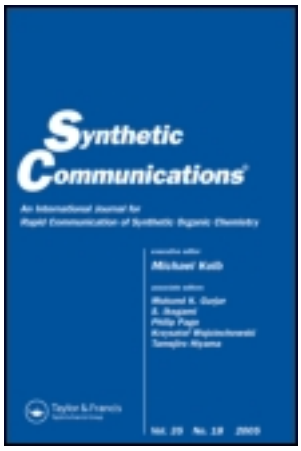

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An Easy and Clean Synthesis of Chiral 3,4-Diaryl-2,5-diazabicyclo[4.4.0]decanes by Reductive Intramolecular Coupling of Chiral Diimines

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An Easy and Clean Synthesis of Chiral 3,4-Diaryl-2,5-diazabicyclo[4.4.0]decanes by Reductive Intramolecular Coupling of Chiral Diimines

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ABSTRACT

A clean and efficient reductive intramolecular coupling of diimines prepared from (1*R*,2*R*)-cyclohexanediamine gave chiral 2,3-diaryl-piperazines.

Key Words: Diimines; Reductive intramolecular coupling; Chiral building blocks.

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Environmental considerations and safety regulations define new challenges and objectives for current chemical research. Chemistry at interphases offers possibilities to suggest organic process alternatives for reducing the generation of waste and bringing benefits providing advantageous synthetic routes.[1] Our interest in advanced materials led us to study chiral organic–inorganic solids[2] and chiral organic polymers[3] as enantioselective catalytic materials. Rigid and chiral organic molecules are compounds of growing interest for macromolecular chemistry due to their influence on the physical and chemical properties of the materials.[4] Recent report on the stereoselective synthesis of chiral 3,4-disubstituted-2,5-diazabicyclo[4.4.0]decanes using low-valent titanium reagents[5] prompt us to communicate a more practical and efficient method for the synthesis of various chiral 3,4-diaryl-2,5-diazabicyclo[4.4.0]decanes which are useful building blocks for our studies.

The synthesis of aromatic diimines **2(a–f)** by usual procedure involved the reaction of (1*R*,2*R*)-cyclohexanediamine with 2 equivalents of the corresponding substituted benzaldehyde in ethanol under reflux.[6] Isolation of the Schiff bases was facilitated by the precipitation of the products out of the mixture upon cooling. In Table 1, the results of the reactions of various benzaldehyde derivatives are summarized.[7]

The piperazine core could be prepared either by use of low-valent titanium species[9] or by an electroreductive method.[10] In view of the synthesis of nitrogen-containing macrocycles, Kise et al.[11] reported the strong protic acid–zinc powder combination as an efficient reductive

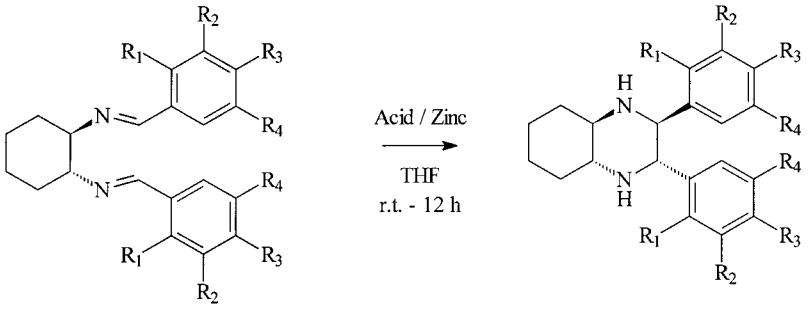
Table 1. Preparation of various diaryl (1*R*,2*R*)-cyclohexanediimine.

Reagent	R^1	R^2	R^3	R^4	Product	Yield (%)[d]
1a	H	H	H	H	**2a**[b]	87
1b	H	H	Br	H	**2b**[b]	94
1c	H	H	OMe	H	**2c**[b]	98
1d	H	H	CO_2Me	H	**2d**[b]	81
1e	H	H	$C{\equiv}CSiMe_3$[a]	H	**2e**[b]	88
1f	OMe	H	H	Br	**2f**[c]	81

[a]Prepared by the Krause et al. method.[8]
[b]Prepared from (1*R*,2*R*)-cyclohexanediamine.
[c]Prepared from racemic *trans*-(1,2)-cyclohexanediamine.
[d]Isolated yield.

intramolecular diimines coupling reagent. This simple chemical reduction was surprisingly only applied to compound **3a**. By use of this method, we observed that chiral diimines **2(a–f)** are readily conversed to *trans*-3,4-diaryl-2,5-diazabicyclo[4.4.0]decanes **3(a–f)** in very high yield (Sch. 1).[12]

In addition, the reaction treatment was reduced to a simple basic neutralization–filtration–extraction sequence. Interestingly, the electronic nature of substituents on the aromatic ring plays a critical role for the choice of the protic acid used. Indeed the synthesis of compounds **3c** and **3f** failed when using methanesulfonic acid (MSA), but the use of trifluoroacetic acid (TFA) led to single products. The results are summarized in Table 2.[13]

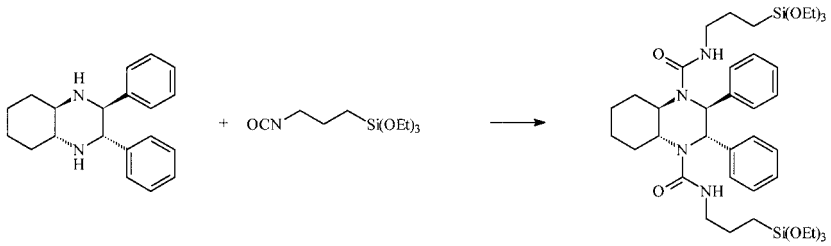


Scheme 1.

Table 2. Reaction of diimines with the strong protic acid/zinc reagent system.

Reagent	R^1	R^2	R^3	R^4	Acid[a]	Product	Yield (%)[d]
2a	H	H	H	H	MSA	**3a**[b]	98
2b	H	H	Br	H	MSA	**3b**	95
2c	H	H	OMe	H	TFA	**3c**	98
2d	H	H	CO_2Me	H	MSA	**3d**	98
2e	H	H	$C{\equiv}CSiMe_3$	H	MSA	**3e**	94
2f	OMe	H	H	Br	TFA	**3f**[c]	89

[a]Acid: MSA (Methanesulfonic acid) or TFA (Trifluoroacetic acid).
[b]The product **3a** was identified by spectral data (^{1}H NMR, ^{13}C NMR, IR and MS) and comparison with reported data.[5,10]
[c]Synthesized starting with racemic diamine.
[d]Yield of isolated products.



Scheme 2.

trans Stereochemistry was previously assigned for compound **3a** and other (1*R*,2*R*)-cyclohexanediamine derivatives on the basis of NMR analysis.[5,10] The similarity between **3a** and the other products **3(b–f)** suggested the same (3*S*,4*S*) stereochemistry for the newly formed chiral centers.

These piperazine derivatives are of interest for the elaboration of organic inorganic hybrid materials. As an example, condensation of **3a** with trialkoxysilyl isocyanate provided the *bis*-triethoxysilylated piperazine precursor **4a** (Sch. 2).[14]

In summary, the method described here is a simple and economical synthetic methodology. Various chiral, rigid and bicyclic piperazines have been prepared in high yield by a cleanly two step sequence from (1*R*,2*R*)-cyclohexanediamine. Access to organic–inorganic solids and polymers with these building blocks are in progress.

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7. Physical constant and spectroscopic data for Schiff bases **2(a–f)**.
   2a: $[\alpha]_D^{20} = -202.0$ (c 0.5, $CHCl_3$). M.p.: 98–100°C. ^{1}H NMR (200 MHz, $CDCl_3$) δ ppm 8.21 (s, 2H), 7.59 (d, 4H, $J = 2.2$ Hz), 7.33 (d, 4H, $J = 2.2$ Hz), 7.29 (m, 2H), 3.42 (m, 2H), 1.86 (sl, 6H), 1.50 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ ppm 160.94, 136.33, 130.16, 128.32, 127.87, 73.76, 32.93, 24.46. Mass (FAB+) m/z (relative intensity): 291 ($M+H^+$, 100).
   2b: $[\alpha]_D^{20} = -266.0$ (c 1.2, $CHCl_3$). M.p.: 124–126°C. ^{1}H NMR (200 MHz, $CDCl_3$) δ ppm 8.11 (s, 2H), 7.44 (s, 8H), 3.38 (m, 2H), 1.86 (m, 6H), 1.49 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ ppm 159.74, 135.15, 131.67, 129.32, 124.69, 73.77, 32.81, 24.42. Mass (FAB+) m/z (relative intensity): 499 ($M+H^+$, 100).
   2c: $[\alpha]_D^{20} = -291.0$ (c 1.0, $CHCl_3$). M.p.: 105–107°C. ^{1}H NMR (200 MHz, $CDCl_3$) δ ppm 8.12 (s, 2H), 7.52 (d, 4H, $J = 8.8$ Hz), 6.81 (d, 4H, $J = 8.8$ Hz), 3.77 (s, 6H), 3.35 (m, 2H), 1.84 (m, 6H), 1.48 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ ppm 161.28, 160.32, 129.46, 113.78, 73.82, 55.28, 33.15, 24.63. Mass (FAB+) m/z (relative intensity): 351 ($M+H^+$, 100).
   2d: $[\alpha]_D^{20} = -318.0$ (c 1.0, $CHCl_3$). M.p.: 118–120°C. ^{1}H NMR (200 MHz, $CDCl_3$) δ ppm 8.22 (s, 2H), 7.97 (d, 4H, $J = 8.3$ Hz), 7.63 (d, 4H, $J = 8.3$ Hz), 3.89 (s, 6H), 3.44 (m, 2H), 1.88 (m, 6H), 1.51 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ ppm 166.71, 160.23, 140.20, 131.63, 129.80, 127.82, 73.98, 52.26, 32.81, 24.44. Mass (FAB+) m/z (relative intensity): 407 ($M+H^+$, 100).
   2e: $[\alpha]_D^{20} = -440.0$ (c 0.5, $CHCl_3$). M.p.: 173–175°C. ^{1}H NMR (200 MHz, $CDCl_3$) δ ppm 8.12 (s, 2H), 7.49 (d, 4H, $J =$

8.2 Hz), 7.39 (d, 4H, $J = 8.2$ Hz), 3.39 (m, 2H), 1.88 (m, 6H), 1.49 (m, 2H), 0.24 (s, 18H). ^{13}C NMR (50 MHz, $CDCl_3$) δ ppm 160.52, 136.14, 132.09, 127.69, 125.03, 104.82, 96.06, 73.86, 32.87, 24.50, −0.02. Mass (FAB+) m/z (relative intensity): 483 ($M+H^+$, 80).
2f (racemic)**:** ^{1}H NMR (200 MHz, $CDCl_3$) δ ppm 8.50 (s, 2H), 7.91 (d, 2H, $J = 2.6$ Hz), 7.36 (dd, 2H, $J = 8.8$ and 2.6 Hz), 6.67 (d, 2H, $J = 8.8$ Hz), 3.73 (s, 6H), 3.39 (m, 2H), 1.82 (m, 6H), 1.47 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ ppm 157.79, 156.22, 133.85, 129.83, 113.28, 112.78, 73.90, 55.84, 32.92, 24.53. Mass (FAB+) m/z (relative intensity): 509 ($M+H^+$, 40).

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12. General experimental procedure for compounds **3(a–f)**: To a mixture of the diimine (1–5 mmoles) and zinc (10 equivalents) in dry THF (10 mL/mmole of diimine), acid (5 equivalents) was added under an N_2 atmosphere at 0°C. The ice bath was removed and the reaction mixture was stirred for 12 h at room temperature. It was quenched with saturated $NaHCO_3$ until basic pH, the mixture was diluted with $CHCl_3$ and filtered through a pad of celite. The organic phase was washed with brine and dried over $MgSO_4$ before concentration. The crude products **3(a–f)** gave satisfactory analytical data and can be used without further purification in a next step.
13. Physical constant and spectroscopic data for compounds **3(a–f)**
3a: $[\alpha]_D^{20} = -72.0$ (c 0.5, $CHCl_3$). M.p.: 64–66°C. ^{1}H NMR (200 MHz, $CDCl_3$) δ ppm 7.12 (s, 10H), 3.84 (s, 2H), 2.61 (m, 2H), 1.80 (m, 6H), 1.42 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ ppm 141.40, 128.07, 127.75, 127.08, 68.48, 61.50, 31.78, 24.91.

Mass (FAB+) m/z (relative intensity): 293 ($M+H^+$, 100).

3b: $[\alpha]_D^{20} = -126.0$ (c 1.1, $CHCl_3$). M.p.: 149–151°C. ^1H NMR (200 MHz, $CDCl_3$) δ ppm 7.26 (d, 4H, $J = 8.4$ Hz), 6.96 (d, 4H, $J = 8.4$ Hz), 3.72 (s, 2H), 2.57 (m, 2H), 1.73 (m, 6H), 1.39 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$): δ ppm 140.23, 131.06, 129.81, 121.12, 67.96, 61.40, 31.76, 24.88. Mass (FAB+) m/z (relative intensity): 451 ($M+H^+$, 85).

3c: $[\alpha]_D^{20} = -102.0$ (c 0.5, $CHCl_3$). M.p.: 105–107°C. ^1H NMR (200 MHz, $CDCl_3$) δ ppm 7.03 (d, 4H, $J = 8.6$ Hz), 6.86 (d, 4H, $J = 8.6$ Hz), 3.75 (s, 2H), 3.72 (s, 6H), 2.59 (sl, 2H), 1.73 (m, 6H), 1.40 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$): δ ppm 158.48, 133.86, 129.04, 113.12, 67.76, 61.54, 55.05, 31.77, 24.90. Mass (FAB+) m/z (relative intensity): 353 ($M+H^+$, 40).

3d: $[\alpha]_D^{20} = -148.0$ (c 0.5, $CHCl_3$). M.p.: 173–175°C. ^1H NMR (200 MHz, $CDCl_3$) δ ppm 7.76 (d, 4H, $J = 8.3$ Hz), 7.12 (d, 4H, $J = 8.3$ Hz), 3.85 (s, 8H), 2.61 (sl, 2H), 1.88 (sl, 2H), 1.73 (m, 4H), 1.40 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$): δ ppm 166.93, 146.22, 129.25, 128.11, 68.44, 61.39, 52.01, 31.76, 24.90. Mass (FAB+) m/z (relative intensity): 409 ($M+H^+$, 100).

3e: $[\alpha]_D^{20} = -232.0$ (c 0.5, $CHCl_3$). M.p.: 217–219°C. ^1H NMR (200 MHz, $CDCl_3$) δ ppm 7.22 (d, 4H, $J = 8.2$ Hz), 6.99 (d, 4H, $J = 8.2$ Hz), 3.75 (s, 2H), 2.61 (m, 2H), 1.70 (m, 6H), 1.39 (m, 4H), 0.23 (m, 12H). ^{13}C NMR (50 MHz, $CDCl_3$): δ ppm 141.66, 131.56, 127.97, 121.95, 105.17, 93.87, 68.38, 61.38, 31.76, 24.92, 0.04. Mass (FAB+) m/z (relative intensity): 485 ($M+H^+$, 40).

3f (racemic)**:** ^1H NMR (200 MHz, $CDCl_3$) δ ppm 7.60 (d, 2H, $J = 2.5$ Hz), 7.13 (dd, 2H, $J = 8.7$ and 2.5 Hz), 6.42 (d, 2H, $J = 8.7$ Hz), 4.28 (s, 2H), 3.47 (s, 6H), 2.52 (s, 2H), 1.74 (m, 6H), 1.35 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$): δ ppm 155.88, 133.74, 130.43, 112.57, 111.70, 61.72, 55.38, 31.90, 25.06. Mass (FAB+) m/z (relative intensity): 511 ($M+H^+$, 100).

14. Selected spectroscopical data for compound **4a:** ^1H NMR (200 MHz, $CDCl_3$) δ ppm 7.50–7.25 (m, 10H), 5.77 (s, 2H), 4.27 (t, 2H), 3.80 (q, 12H, $J = 7.0$ Hz), 3.10 (m, 4H), 2.70 (m, 2H), 1.70 (m, 8H), 1.46 (m, 4H), 1.22 (t, 18H, $J = 7.0$ Hz), 0.51 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$): δ ppm 159.63, 140.94, 128.89, 127.54, 125.89, 61.61, 58.44, 56.74, 42.93, 32.50, 24.80, 23.54, 18.35, 7.59. ν_{max} (KBr)/cm^{-1} 3442, 2977, 2930, 2888, 1654, 1508, 1102, 1078.

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