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Tetrahedron Letters 49 (2008) 1233–1236
Tetrahedron Letters

# New chiral titanium complexes for enantioselective reductive cyclizations of diimines to *trans*-2,3-diarylpiperazines

Pothiappan Vairaprakash, Mariappan Periasamy *

*School of Chemistry, University of Hyderabad, Central University PO, Hyderabad 500 046, India*

Received 28 October 2007; revised 29 November 2007; accepted 6 December 2007
Available online 14 December 2007

**Abstract**

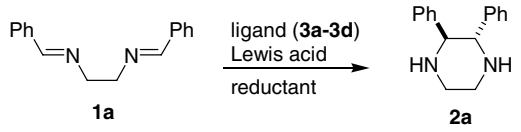
Enantioselective intramolecular reductive coupling of diimines by chiral titanium complexes, prepared using a titanium(IV) reagent and hemisalen ligands derived from chiral β-amino alcohols, gives *trans*-2,3-diarylpiperazines in up to 97% ee.


*Keywords:* Enantioselective reductive coupling; Diimine; Hemisalen ligand; 2,3-Diarylpiperazines

Though enantioselective pinacol couplings of aromatic aldehydes using chiral titanium and chromium complexes[1] are widely reported, very few reports are available for the enantioselective reductive coupling of chiral imines.[2] Recently, we reported intramolecular reductive coupling of diimines in the presence of the $Ti(O^iPr)_2Cl_2/Zn$ reagent system to afford (±)-*trans*-2,3-diarylpiperazines.[3] Herein, we report the enantioselective intramolecular reductive coupling of diimines derived from ethylenediamine leading to enantiomerically pure 2,3-diarylpiperazines **2** using various chiral titanium complexes consisting of a chiral diamide, a chiral diol or a chiral β-amino alcohol.

Initially, we examined the enantioselective reductive coupling of *N*,*N*′-dibenzylidene-1,2-ethanediamine **1a** using different chiral ligands (Scheme 1, Fig. 1). The results are summarized in Table 1.

In the case of diamide *R*,*R*-**3a**, only racemic 2,3-diphenylpiperazine **2a** was obtained when the $TiCl_4/^iPrMgBr$ reagent system was used (Table 1, entry 1). Lowering the temperature to −40 °C did not result in any enantioselectivity; instead the yield of the product decreased (Table 1, entry 2). A slight enhancement in the enantioselectivity was achieved using the $Ti(O^iPr)_2Cl_2/Zn$ reagent system




Scheme 1. Reductive coupling of diimine **1a** in the presence of chiral ligands **3a**–**d**.

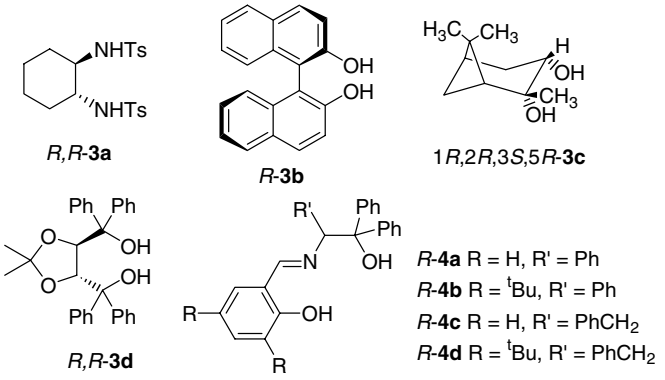



Fig. 1. Chiral ligands examined for reductive coupling of diimine.

(Table 1, entry 3). Although 2,3-diphenylpiperazine was obtained in higher yields in the presence of chiral *R*-BINOL **3b**, the enantioselectivity was poor (Table 1, entries

* Corresponding author. Tel.: +91 40 2313 4814; fax: +91 40 2301 2460.
*E-mail address:* mpsc@uohyd.ernet.in (M. Periasamy).

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doi:10.1016/j.tetlet.2007.12.038

Table 1
Reductive coupling of diimine **1a** in the presence of chiral ligands **3a–d**[a]

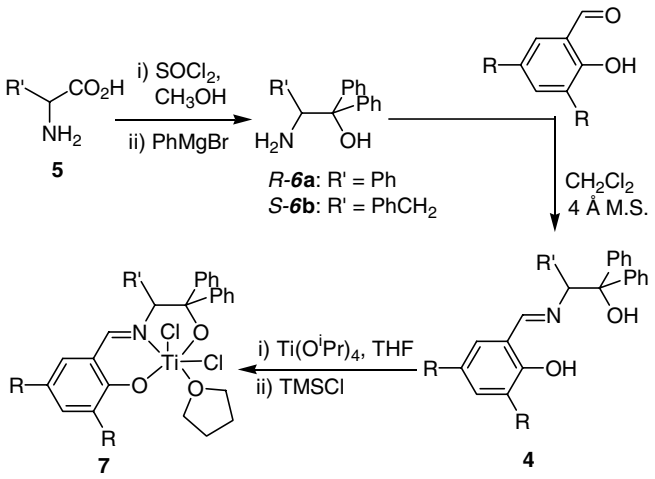
| Entry | Ligand | Lewis acid | $T$ (°C) | Yield[b] (%) | ee/conf[c] (%) |
|---|---|---|---|---|---|
| 1[d] | *R*,*R*-**3a** | $TiCl_4$ | 25 | 60 | — |
| 2[d] | *R*,*R*-**3a** | $TiCl_4$ | −40 | 40 | — |
| 3[d] | *R*,*R*-**3a** | $Ti(O^iPr)_2Cl_2$ | 25 | 75 | 12 (*S*,*S*) |
| 4 | *R*-**3b** | $Ti(O^iPr)_4$ | 25 | 65 | — |
| 5 | *R*-**3b** | $Ti(O^iPr)_4$ | −70 | 60 | 5 (*R*,*R*) |
| 6 | *R*-**3b** | $Ti(O^iPr)_2Cl_2$ | 25 | 82 | — |
| 7[e] | **3c** | $TiCl_4$ | 25 | 75 | — |
| 8[e] | **3c** | $TiCl_4$ | −70 | 70 | 10 (*R*,*R*) |
| 9 | *R*,*R*-**3d** | $TiCl_4$ | 25 | 40 | 10 (*S*,*S*) |

[a] Unless noted otherwise, all the reactions were carried out with 1.0 mmol of diimine **1a**, 2.5 mmol of chiral ligands **3a**, **b** and **d**, 2.2 mmol of Lewis acid and 5 mmol of Zn dust in $CH_2Cl_2$.
[b] Yield of isolated product after flash column chromatography on silica.
[c] All ee values reported here are based on HPLC analysis on a Chiralcel OD-H column.
[d] THF was used as a solvent and $^i$PrMgBr was used as a reductant.
[e] 4.0 mmol of diimine **1a**, 11.0 mmol of chiral ligand **3c**, 10.0 mmol of $TiCl_4$ and 25 mmol of Zn were used.

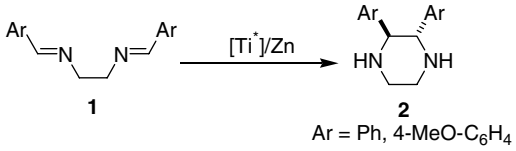
4–6). The use of pinanediol **3c** and (*R*,*R*)-*trans*-α,α′-(2,2-dimethyl-1,3-dioxalane-4,5-diyl)bis(diphenylmethanol) TADDOL **3d** gave enantioselectivity of only up to 10% (Table 1, entries 7–9).

Previously, the chiral titanium complex **7d** prepared from tridentate hemisalen ligand **4d** was used in the enantioselective pinacol coupling of aldehydes.[1d,4] We have prepared the chiral titanium complexes **7a–d** in situ (Scheme 2) and used them for the reductive coupling of diimines **1**.[5] When the titanium complexes **7b** and **7d** were used in catalytic amounts (10 mol %), products **2** were obtained in moderate to good yields but the enantioselectivities obtained were poor (Scheme 3, Table 2).

When a stoichiometric amount of complex **7a** was used, moderate enantioselectivity was achieved (Table 3, entry 1). Encouraged by this result, we carried out the reductive coupling under different conditions and also with chiral




Scheme 2. Synthesis of chiral titanium complexes **7a–d**.




Scheme 3. Reductive coupling of diimines **1** using chiral titanium complex **7** [Ti*]/Zn.

Table 2
Asymmetric synthesis of 2,3-diarylpiperazine **2** using a catalytic amount of chiral titanium complexes **7b** and **7d**[a]

| Entry | Chiral titanium complex | Ar | Yield[b] (%) | ee/conf[c] (%) |
|---|---|---|---|---|
| 1 | *R*-**7b** | Ph | 77 | 15 (*R*,*R*) |
| 2 | *R*-**7b** | 4-MeO–$C_6H_4$ | 60 | 18 (*R*,*R*) |
| 3 | *S*-**7d** | Ph | 54 | 15 (*S*,*S*) |
| 4 | *S*-**7d** | 4-MeO–$C_6H_4$ | 48 | 28 (*S*,*S*)[d] |

[a] Unless noted otherwise, all the reactions were carried out with 2.5 mmol of diimine **1**, 0.5 mmol of chiral titanium complex **7** (prepared in situ), 10.0 mmol of Zn dust in $CH_2Cl_2$ (20 mL), $CH_3CN$ (5 mL) and TMSCl (5.0 mmol) at 25 °C.
[b] Yield of isolated product after flash column chromatography on silica.
[c] All ee values reported here are based on HPLC analysis on a Chiralcel OD-H column.[6]
[d] Absolute configuration was assigned as (*S*,*S*) by single crystal X-ray analysis of the corresponding (*S*)-camphorsulfonate salt.[7]

Table 3
Asymmetric synthesis of 2,3-diarylpiperazines **2** using a stoichiometric amount of chiral titanium complexes **7**[a]

| Entry | Chiral Ti complex | Ar | $T$ (°C) | Yield[b] (%) | ee/conf[c] (%) |
|---|---|---|---|---|---|
| 1 | *R*-**7a** | Ph | 25 | 45 | 60 (*R*,*R*) |
| 2 | *R*-**7b** | Ph | 25 | 72 | 76 (*R*,*R*) |
| 3 | *S*-**7c** | Ph | 25 | 55 | 50 (*S*,*S*) |
| 4 | *S*-**7c** | Ph | −10 | 40 | 55 (*S*,*S*) |
| 5 | *S*-**7d** | Ph | 25 | 75 | 88 (*S*,*S*) |
| 6 | *S*-**7d** | 4-MeO–$C_6H_4$ | 25 | 55 | 97 (*S*,*S*)[d] |

[a] Unless noted otherwise, all the reactions were carried out with 0.5 mmol of diimine **1**, 1.25 mmol of chiral titanium complexes **7a–d** (prepared in situ), and 2.5 mmol of Zn dust in $CH_2Cl_2$ (10 mL), $CH_3CN$ (5 mL).
[b] Yield of isolated product after flash column chromatography on silica.
[c] All ee values reported here are based on HPLC analysis.[6]
[d] Absolute configuration was assigned (*S*,*S*) by single crystal X-ray analysis of the corresponding (*S*)-camphorsulfonate salt.[7]

titanium complexes containing different substitution patterns **7b–d** (Table 3). We observed that the presence of a bulky group such as the *tert*-butyl group on the phenyl ring had a significant role in enhancing the enantioselectivity as well as the yield. The chiral titanium complexes **7b** and **7d** gave the 2,3-diphenylpiperazine product **2a** in good ee (Table 3, entries 2 and 5). Decreasing the reaction temperature (−10 °C) did not lead to any improvement in enantioselectivity (Table 3, entry 4). By using the chiral

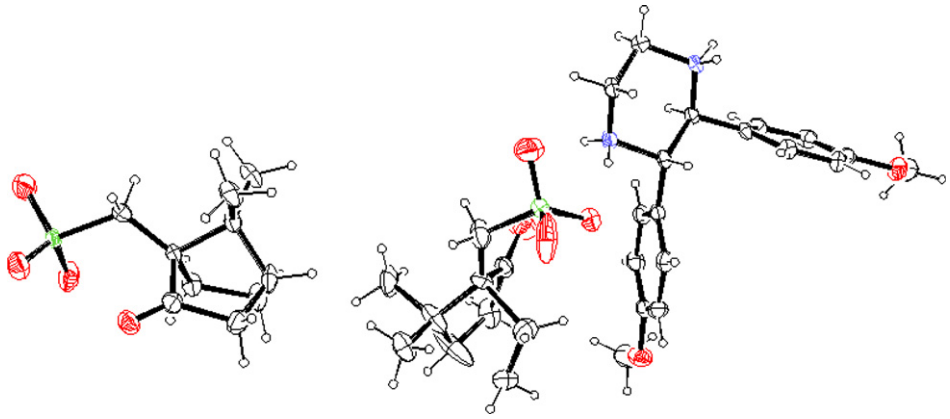


Fig. 2. ORTEP diagram of the (*S*)-camphorsulfonate salt **8** (thermal ellipsoids are drawn at 20% probability).

titanium complex **7d**, 2,3-bis(4-methoxyphenyl)piperazine **2b** was obtained with very good enantioselectivity, up to 97% ee (Table 3, entry 6). The absolute configurations of the newly formed chiral centres in **2b** were assigned (*S*,*S*) by single crystal X-ray analysis of the corresponding (*S*)-camphorsulfonate salt **8** (Fig. 2).[7]

It has been reported that ligand **4** forms hexacoordinated complex **7b**, which is monomeric in nature.[1d] Presumably, complexes **7a**, **7c** and **7d** could also form hexacoordinate complexes that are monomeric in nature.

In summary, we have developed new chiral titanium reagents for the enantioselective intramolecular reductive cyclizations of diimines yielding chiral 2,3-diarylpiperazines with good enantioselectivity. In view of the potential applications of the chiral piperazine products in asymmetric catalysis,[8] organocatalysis[9] and also the biological activity reported for molecules containing this skeleton,[10] the synthetic method reported here has potential for further exploitation.

## Acknowledgements

P.V. is thankful to the CSIR and NATCO for a research fellowship. We are thankful to the ILS-UOH-MOU for a research grant. UGC support under the 'University with Potential for Excellence (UPE)' and 'Centre for Advance Study (CAS-SAP)' programmes is gratefully acknowledged. We are thankful to the DST for a 400 MHz NMR spectrometer and National XRD-CCD facilities in the School of Chemistry, University of Hyderabad. The award of the JC Bose Fellowship grant to M.P. is gratefully acknowledged.

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5. *Representative procedure for the enantioselective intramolecular reductive coupling of diimines* **1** *using chiral titanium complexes* **7a**–**d** *and Zn*: In a 25 mL two necked flask equipped with a dropping funnel and an air condenser protected by a mercury trap, were placed $CH_2Cl_2$ (5 mL), 2-hydroxy-3,5-di(*tert*-butyl)benzaldehyde (340 mg, 1.1 mmol), (*R*)-2-amino-1,1,2-triphenylethanol (*R*)-6a (320 mg, 1.1 mmol) and 4 Å molecular sieves (1.0 g) under nitrogen and the reaction stirred for 6–8 h. To this, $Ti(O^iPr)_4$ (284 mg, 1.0 mmol) and THF (1 mL) were added and stirring was continued for another 1 h. The chiral titanium complex **7b** was formed by the addition of TMSCl (220 mg, 2.0 mmol) in $CH_3CN$ (5 mL), followed by stirring for 15 min. To this, activated zinc powder (325 mg, 5.0 mmol) was added and stirring was continued for another 1 h after which the reaction was cooled to the appropriate temperature. Then, diimine (0.5 mmol) dissolved in $CH_3CN$ (5 mL) was added dropwise. After the addition was complete, the reaction mixture was stirred at the same temperature for 24 h. The reaction mixture was poured into saturated aqueous $K_2CO_3$ solution at 0 °C and then filtered. The organic layer was separated and the aqueous layer was extracted with $CH_2Cl_2$ (2 × 20 mL). The combined organic extract was washed with water and brine and then dried over anhydrous $K_2CO_3$. The solvent was evaporated and the product was purified by flash column chromatography (silica gel, $CHCl_3$ and then $CHCl_3/CH_3OH = 9:1$). The ee of the product was obtained from HPLC analysis using a Chiralcel OD-H column. Physical and spectral data for products **2a** and **2b**: Compound **2a**: mp: 88–90 °C; FTIR (KBr) $\nu_{max}$ ($cm^{-1}$): 3318, 3280, 3030, 2949, 2820, 1603, 1491; $^1H$ NMR (400 MHz, $CDCl_3$, $\delta$ ppm) 2.00 (br s, 2H, NH), 3.15 (s, 4H), 3.72 (s, 2H), 7.07–7.12 (m, 10H); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 47.0, 68.1, 127.3, 127.8, 128.0, 141.2. Compound **2b**: mp: 90–92 °C; FTIR (KBr) $\nu_{max}$ ($cm^{-1}$): 3271, 3040, 3003, 2957, 1612, 1584 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$, $\delta$ ppm) 2.27 (br s, 2H, NH), 3.10 (s, 4H), 3.63 (s, 2H), 3.70 (s, 6H), 6.65 (d, 4H, $J = 8.0$ Hz), 7.00 (d, 4H, $J = 8.0$ Hz); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 47.0, 55.1, 67.4, 113.2, 129.0, 133.6, 158.6.
6. *HPLC analysis of the trifluoroacetamide derivatives of 2,3-diarylpiperazines*: Piperazines (**2a**,**b**) (0.5 mmol) in $CH_2Cl_2$ (5 mL) were stirred overnight with excess trifluoroacetic anhydride (TFAA). The solution was concentrated under reduced pressure to remove the solvent and

excess TFAA and the residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 19:1). The trifluoroacetamide derivatives were dissolved in isopropanol (~10 mg/mL) and HPLC analyses were performed using a Chiralcel OD-H column supplied by Daicel Chemical Industries, Ltd with a binary gradient method using hexane/isopropanol (98:2) with a flow rate of 0.5 mL/min. Retention times for the trifluoroacetamide derivatives of 2,3-diphenylpiperazine were 10.5 min for the (*R*,*R*) and 12.3 min for the (*S*,*S*) salts, and for the trifluoroacetamide derivatives of 2,3-bis(4-methoxyphenyl)piperazine, were 17.6 min for the (*R*,*R*) and 23.1 min for the (*S*,*S*) salts.

7. *Crystal data*: Compound **8**: Molecular formula: $C_{38}H_{54}N_2O_{10}S_2$ [$C_{18}H_{24}N_2O_2$ 2($C_{10}H_{15}O_4S$)], $M_w = 762.95$, monoclinic, space group: *P*2(1), $a = 6.7095(10)$ Å, $b = 17.741(3)$ Å, $c = 16.365(3)$ Å, $\beta = 99.641(2)°$, $V = 1920.5(5)$ Å$^3$, $Z = 2$, $\rho_c = 1.319$ mg m$^{-3}$, $\mu = 0.198$ mm$^{-1}$, $T = 298(2)$ K. Of the 13,082 reflections collected, 6705 were unique ($R_{int} = 0.0317$). Refinement on all data converged at $R_1 = 0.0781$, $wR_2 = 0.2063$ (CCDC Deposition Number: CCDC 664992).
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