



Intramolecular coupling of chiral diimines using low-valent titanium reagents: stereoselective synthesis of chiral 3,4-disubstituted-2,5-diazabicyclo[4.4.0]decanes

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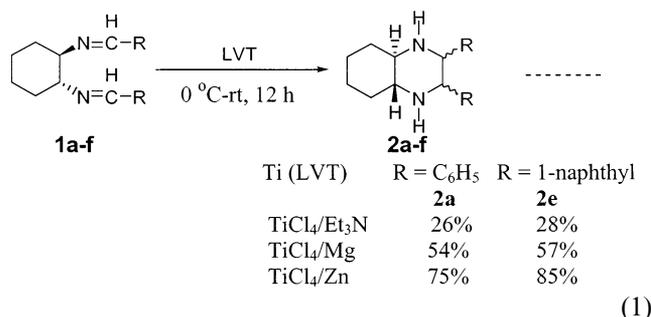
Abstract—Chiral 3,4-disubstituted-2,5-diazabicyclo[4.4.0]decanes are prepared from (1*R*,2*R*)-1,2-diaminocyclohexane derived diimines through intramolecular coupling using low valent titanium reagent systems. © 2001 Elsevier Science Ltd. All rights reserved.

Chiral 1,2 diamines are an important class of organic compounds, useful as ligands in asymmetric synthesis.¹ Synthetic methods based on enantioselective coupling of benzaldimines using a Zn–Cu couple in the presence of (+)-camphorsulphonic acid,² intermolecular reductive coupling of imines and imine derivatives promoted by reducing agents such as alkali metals,³ TiCl₄/Mg–Hg,⁴ Cp₂VCl₂/Zn/CISiH₃,⁵ TiCl₄/Mg⁶ reagents and electroreduction of diimines⁷ have been reported. However, the stereoselectivities realized in these methods are somewhat poor. In continuation of our research efforts towards reductive coupling of imines using TiCl₄/Mg⁸ and TiCl₄/Et₃N,⁹ we have examined the intramolecular reductive coupling of chiral diimines, prepared using chiral 1,2-diaminocyclohexane, using low valent titanium reagents. We wish to report here the results of this investigation.

Initially, the coupling experiments of the diimines derived from (1*R*,2*R*)-cyclohexyldiamine, benzaldehyde and 1-naphthaldehyde were carried out using low-valent titanium-(LVT) species, prepared using the TiCl₄/Et₃N and TiCl₄/Mg reagent systems. Although only one isomer of the product was obtained in each of these cases, the chemical yields were poor (Eq. (1)). Fortunately, the TiCl₄/Zn reagent system gave better yields (Eq. (1)). The X-ray crystal structure analysis revealed that the compound **2a** is (3*S*,4*S*)-diphenyl-2,5-diazabicyclo[4.4.0]decane (Fig. 1).¹⁰

Keywords: diimines; intramolecular coupling; titanium reagents; substituted diazabicyclo decanes.

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We have examined this transformation with different diimines. The results are summarized in Table 1.

In the case of diimines **1b** and **1c**, prepared using chiral (1*R*,2*R*)-cyclohexyldiamine and *p*-Cl and *p*-CH₃ benzaldehydes, only one isomer was obtained in each case. These products have not been reported before but

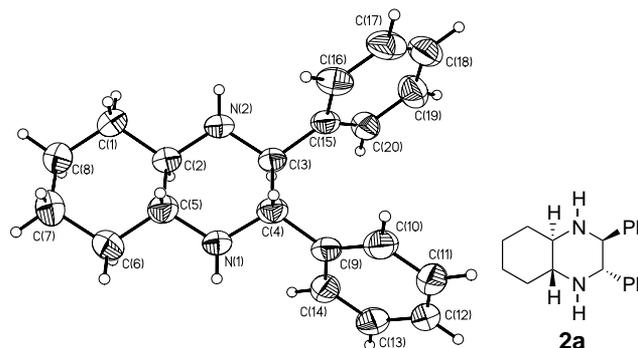


Figure 1. ORTEP diagram of compound **2a**.

Table 1. Reaction of diimines with the TiCl₄/Zn reagent system¹¹

Entry	1	R	2	Yield (%) ^d	[α] _D ²⁵ (c, solvent)
1	1a	C ₆ H ₅	2a ^{a,b}	75	–77.4 (0.93, CHCl ₃) ^b
2	1b	<i>p</i> -ClC ₆ H ₄	2b ^c	73	–136 (1, CHCl ₃)
3	1c	<i>p</i> -CH ₃ C ₆ H ₄	2c ^c	79	–104 (1, CHCl ₃)
4	1d	<i>o</i> -OCH ₃ C ₆ H ₄	2d ^{a,b}	86	+8 (1, CHCl ₃) ^{b,c}
5	1e	1-Naphthyl	2e ^c	85	+200 (1, CHCl ₃)
6	1f	C ₄ H ₉	2f ^c	30	+15.4 (0.26, CHCl ₃)

^a The products **2a** and **2d** were identified by the spectral data (IR, ¹H NMR, ¹³C NMR and MS) and comparison with reported data.⁷

^b Lit⁷ [α]_D –70 (c 1.7, CHCl₃) and +6.1 (c 3.3, CHCl₃) for **2a** and **2d**, respectively.

^c The products **2b**, **2c**, **2e** and **2f** were identified using the spectral data (IR, ¹H NMR, ¹³C NMR and MS¹¹).

^d Yields of isolated products.

^e [α]_D –17 (c 1, MeOH).

comparison of the [α]_D values suggests that the configuration of the new chiral centers in these cases may be also (3*S*,4*S*) as in **2a**. However, on the basis of the [α]_D values of the products **2d** and **2e** obtained from the diimines **1d** and **1e** the configurations of the new chiral centers at C3 and C4 cannot be assigned without ambiguity.

Shono et al.⁷ previously reported the synthesis of compounds **2a** and **2d** through an electroreduction method. They assigned *trans* stereochemistry of the phenyl groups in compound **2a** on the basis of NOE enhancements observed in ¹H NMR (400 MHz) spectrum. Further, these authors suggested *trans* stereochemistry for **2d** and several other derivatives by comparison of ¹H NMR (200 MHz) data. It seems reasonable to assign *trans* stereoconfigurations for the aryl and *t*-butyl derivatives reported here as they exhibit ¹H NMR (200 MHz) signals similar to that reported for **2a** and **2d** and other similar derivatives.⁷ However, these *trans* stereochemical assignments are only tentative.

In conclusion, we anticipate that the simple method of synthesis of chiral 3,4-disubstituted 2,5-diazabicyclo[4.4.0]decane reported here using low-valent titanium species would stimulate further research in the synthetic applications of these chiral derivatives as a 3,4-diaryl-2,5-diazabicyclo[4.4.0]decane derivative has shown excellent chiral discriminating ability (80–99%) in diethylzinc addition to certain aldehydes.⁷

Acknowledgements

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- The X-ray diffraction measurements were carried out at 293 K on an automated Enraf–Nonious MACH 3 diffractometer using graphite-monochromated, Mo-K α ($\lambda = 0.71073$ Å) radiation. Intensity data were collected by the ω -scan mode. The data were reduced using the XTAL program. No absorption correction was applied. **Crystal structure data for compound 2a:** θ range for data collection is 1.64–24.97°. Empirical formula C₂₀H₂₄N₂·0.25H₂O, colorless needles (0.38×0.52×0.8 mm), crystal system is monoclinic, space group C₂, unit cell dimensions: $a = 25.307(2)$, $b = 5.4788(10)$, $c = 15.9953(14)$ Å, $\alpha = 90$, $\beta = 129.11(2)$, $\gamma = 90^\circ$; volume 1721.0(4) Å³, $Z = 4$, $D_{\text{calcd}} = 1.360$ Mg/m³, absorption coefficient is 0.084 mm⁻¹, $F(000) = 744$, index ranges $-30 \leq h \leq 30$, $-6 \leq k \leq 0$, $-18 \leq l \leq 18$, total reflections collected were 3368/1686 reflections with $R_{\text{int}} = 0.0436$. The structure was solved by direct methods and refined by full-matrix least-squares procedure using the SHELX-97 program package. The refinement was carried out using 931 observed [$F > 4\sigma(F)$] reflections and converged to a final $R_1 = 0.0484$, $wR_2 = 0.1369$ and goodness of fit is 0.813 with largest difference peak and hole 0.197 and –0.230 e Å⁻³, respectively. The configuration of the compound **2a** moiety present in the crystal structure was confirmed to be (3*S*,4*S*) by using the platon 98 program, A. L. Spak, version 291198.
- General experimental procedure:** In dry THF (100 ml), TiCl₄ (20 mmol) was added under an N₂ atmosphere at 0°C. Zn (40 mmol) was added with a solid addition flask for 10 min. The reaction mixture was stirred for 0.5 h at 0°C and the imine (5 mmol) in 50 ml of THF was added for 15 min. The reaction mixture was stirred for 0.5 h at 0°C and for 12 h at 25°C. It was quenched with saturated K₂CO₃ (30 ml) and filtered through a Buchner funnel.

The organic layer was separated and the aqueous layer was extracted with ether (2×30 ml). The combined organic extract was washed with brine solution (20 ml) and dried over anhydrous K₂CO₃. The solvent was removed and the residue was chromatographed on basic alumina column using EtOAc/hexane mixture as eluent.

Physical constant and spectroscopic data for compounds 2a–f: **2a:** mp 60–62°C, ¹³C NMR (50 MHz, CDCl₃): δ ppm 24.96, 31.65, 61.61, 66.54, 127.14, 127.61, 128.13, 141.46, mass (*m/z*) 292; **2b:** mp 148–150°C, ¹³C NMR (50 MHz, CDCl₃): δ ppm 24.89, 31.79, 61.47, 68.03,

128.02, 129.40, 132.91, 139.84, mass (*m/z*) 360; **2c:** ¹³C NMR (50 MHz, CDCl₃): δ ppm 21.06, 25.00, 31.88, 61.67, 68.03, 128.02, 128.48, 136.43, 138.73, mass (*m/z*) 320; **2d:** ¹³C NMR (50 MHz, CDCl₃): δ ppm 25.29, 32.17, 55.13, 60.60, 61.99, 110.19, 120.18, 127.57, 129.06, 129.93, 157.09, mass (*m/z*) 352; **2e:** mp 159–161°C, ¹³C NMR (50 MHz, CDCl₃): δ ppm 25.01, 31.81, 60.65, 62.21, 122.53, 124.95, 125.16, 127.62, 128.49, 131.58, 133.60, 137.00, mass (*m/z*) 392; **2f:** ¹³C NMR (50 MHz, CDCl₃): δ ppm 24.86, 27.40, 34.39, 36.14, 55.32, 58.20, mass (*m/z*) 252.