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Stereocontrol in the Reduction of 1,2-Diimine with an Oxazaborolidine Catalyst. Highly Stereoselective Preparation of (*R*,*R*)-1,2-Diphenylethylenediamine

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Abstract: Highly enantioselective reduction of 1,2-bis(*p*-methoxyphenylimino)-1,2-diphenylethane was conducted even with 0.5 mol% of new oxazaborolidine derived form L-threonine and a stoichiometric amount of BH_3•THF to give 1,2-diphenylethylenediamine derivative in excellent enantiomeric purity. The subsequent deprotection of nitrogen atoms afforded (*R*,*R*)-1,2-diphenylethylenediamine in enantiomerically pure form.

Widespread use of chiral 1,2-diphenylethylenediamine[1] coupled with some difficulties associated with its preparation prompted us to investigate highly efficient methods for its synthesis. Generally accepted methods for chiral 1,2-diphenylethylenediamines involve resolution of racemic compounds with certain chiral carboxylic acids[2a-c] or enantioselective 1,2-dihydroxylation of olefins followed by introduction of nitrogen atoms.[2d] Although these offer practical procedures, more straightforward methods have been highly desirable. On the other hand, enantioselective reduction of 1,2-diimines appears to be attractive due to the ready accessibility of the substrates via diimination of the parent 1,2-dicarbonyl compounds. However, there appear to be two non-trivial problems for the control of stereochemistry: one concerns diastereofacial selectivity and the other enantiofacial discrimination. We have been interested in the pinacol type coupling of imino compounds and have already disclosed a highly efficient enantioselective procedure for the synthesis of 1,2-diphenylethylenediamine by using Zn-Cu couple in the presence of (+)-camphorsulfonic acid as chiral auxiliary.[3] With the properties of these 1,2-diamine derivatives in hand we investigated enantioselective reduction of 1,2-diimines. Among various procedures for the enantioselective reductions of ketones and imines,[4] the oxazaborolidine-borane reagent[5] appears to be the method of choice due to the simplicity of the procedure, and of particular interest is the stereochemical outcome of bis-reduction of 1,2-diimine.[6] We have now found that in the presence of a catalytic amount of new chiral amino alcohol **3**, prepared from L-

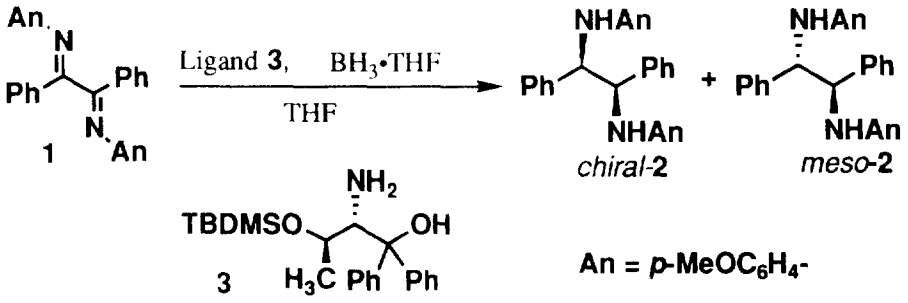
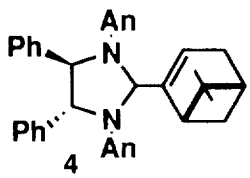


Table 1. Reduction of Diimime 1.[a)]

Entry	Ligand **3** (mol%)	BH_3•THF (eq)	Yield of **2** (%)[b)]	*chiral* : *meso*[c)]	%ee[d)]
1	0.1	3.0	71	95 : 5	73
2	0.5	3.0	90	95 : 5	99
3	1	3.0	82	95 : 5	99
4	2	3.0	81	95 : 5	99
5	5	3.0	86	95 : 5	99
6	10	3.1	93	96 : 4	99
7	25	3.3	89	96 : 4	99
8	50	3.5	96	96 : 4	99
9	100	4.0	90	>99 : <1	99

a) The reaction was carried out according to the typical experimental procedure. b) Isolated yield. c) Ratio determined by ^1H NMR and/or HPLC. d) Determined by HPLC analysis of aminal **4** prepared from **2** and (-)-myrtenal, and for determination of the absolute configuration, see text.

threonine, 1,2-bis(*p*-methoxyphenylimino)-1,2-diphenylethane **1** was reduced with borane in a highly diastereo- and enantioselective fashion to give 1,2-diphenylethylenediamine derivative **2** in excellent chemical and optical yields. The reaction was carried out as follows: to a solution of (2*S*,3*R*)-2-amino-3-(*t*-butyldimethylsiloxy)-1,1-diphenylbutanol **3**[7] (8×10^{-3} M in THF, 0.15 mL, 0.0012 mmol) in 0.15 mL of THF was added a solution of BH_3•THF complex (1 N in THF, 0.72 mL, 0.72 mmol), and the mixture was stirred for one hour at room temperature. A solution of 1,2-bis(*p*-methoxyphenylimino)-1,2-diphenylethane **1**[8] (100 mg, 0.24 mmol) in THF (2.5 mL) was added dropwise during 30 min. After stirring for 2 hours at room temperature, the reaction mixture was quenched by adding a solution of phosphate buffer (5 mL). The entire mixture was extracted with ether (5 mL x 3), and the combined extracts were dried and concentrated in vacuo to leave a crude oil, which was purified on preparative silica gel TLC (eluent : *n*-Hex / AcOEt = 4 /1 x 2) to give diamine **2** as a colorless oil (91.2 mg, 90 %). The ratio of *chiral*- vs. *meso*-isomer and the enantiomeric purity of the *chiral* diamine were determined by HPLC after transformation into aminal **4** with (-)-myrtenal. The results of the reduction are summarized in Table 1.



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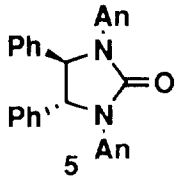

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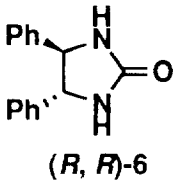
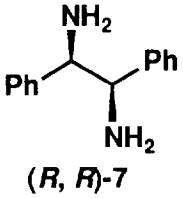


(*R*, *R*)-6

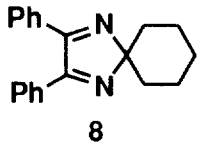


(*R*, *R*)-7

As shown, the reaction was effected by the use of a catalytic amount of oxazaborolidine to give the diamine **2** in excellent chemical and optical yields, in which *chiral* vs. *meso* ratios were higher than 95 : 5 (entries 2-8). Even in the presence of 0.5 mol% of the ligand **3**, the high efficacy of this catalytic system was still maintained to give *chiral*-**2** in 99%ee (entry 2). Separation of *chiral* from *meso*-isomer was readily performed in the transformation into enantiomerically pure 1,2-diphenylethylenediamine **7** as described later. The formation of *meso*-isomer was completely suppressed, when the reduction was carried out with 100 mol% of the ligand **3**, in which case *chiral*-**2** was obtained exclusively with 99%ee (entry 9). The transformation of **2** into **7** was readily conducted via formation of imidazolidinone **5**. It was at this stage the separation of *chiral*- from *meso*-isomer was carried out, either by silica gel chromatography or by simple recrystallization from ethyl acetate.

Oxidative removal of the *p*-anisyl groups was followed by acidic hydrolysis of the imidazolidinone ring: diamine **2** was converted into imidazolidinone **5** in 89% yield with 1.5 equiv of trichloromethyl chloroformate-triethylamine in toluene in the presence of a catalytic amount of 4-*N*,*N*-dimethylaminopyridine at 0° C~room temperature. The *p*-anisyl groups were removed on treatment with 7 equiv of ammonium cerium (IV) nitrate[9] in acetonitrile-water at -20~0° C to give **6** in 60% yield, and the subsequent hydrolysis was carried out with 47% aq HBr in refluxing acetic acid[10] to give (*R*,*R*)-1,2-diphenylethylenediamine **7** in 98% yield. The sign and the value of the optical rotation obtained for **7** ($|\alpha|^{23}_D$ +106.0 (*c* 0.18, CH_3OH))[11] indicated that the absolute configuration and the enantiomeric purity of **7** were (*R*,*R*) and >99%ee, respectively.

Attempts to use other 1,2-diimino-1,2-diphenylethane derivatives such as 1,2-dioxime met with disappointing results. Either the reaction did not reach completion or only poor diastereo- and enantio-discrimination was observed. In order to clarify the origin of the selectivity of the new ligand **3**, reduction of 1,2-diimine **8**[2b] possessing an *s-cis*-diimino moiety was carried out. Under the conditions used for the reduction of **1** with a stoichiometric amount of **3**, diimine **8** underwent mono-reduction to give **9** in 28% yield with 26%ee. This result indicated that the six-membered cyclic transition state involving coordination of the imino nitrogen to the electrophilic boron of the oxazaborolidine and hydride transfer from the NBH_3^- unit which was similar to the one proposed by Corey et al,[5f] might work in the present system (*vide infra*), since *s-cis*-diimine **8** experienced a severe steric interaction between the cyclohexyl moiety and the oxazaborolidine ring in such a six-membered metallo-cycle, resulting in mono-reduction with low enantiofacial discrimination. As for diimine **1**, such a steric interaction was released by taking an *s-trans*-conformation, having an ideal six-membered cyclic transition state **10** to give bis-reduction product **2** in a highly diastereo- and enantioselective manner.



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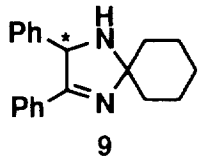

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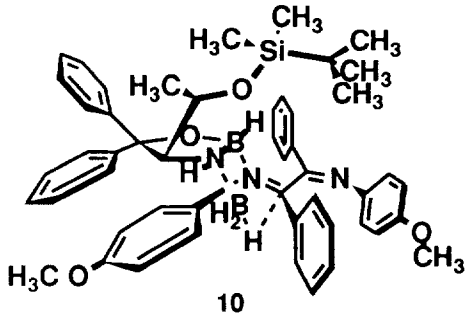

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In summary, we have developed a highly stereocontrolled way for enantiomerically pure (*R*,*R*)-1,2-diphenylethylenediamine by reduction of 1,2-diimine with BH_3 and oxazaborolidine derived from L-threonine, which worked with a catalytic amount as low as 0.5 mol%. Since a variety of 1,2-diketones are readily available[2c] and the transformation into diimines holds no particular problem, this procedure offers a straightforward access to a highly useful class of compounds.

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7. Ligand **3** was prepared from L-threonine in five steps: L-threonine was treated with Cbz-Cl and NaOH in H_2O-dioxane followed by methylation with CH_2N_2 to give methyl (2*S*,3*R*)-2-(benzyloxycarbonylamino)-3-hydroxybutyrate in 61% yield, which was *t*-butyldimethylsilylated at the hydroxy group with TBDMS-Cl and imidazole in DMF in 98% yield. The reaction with phenylmagnesium bromide in THF gave diphenylcarbinol in 93% yield, and the subsequent debenzylation with H_2/Pd-C in MeOH gave **3** in 91% yield: $[\alpha]_D^{23}$ -37.0 (*c* 1.06, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 0.00 (s, 3H), 0.10 (s, 3H), 0.99 (s, 9H), 1.34 (d, *J* = 6.60 Hz, 3H), 1.63 (brs, 2H), 3.63 (d, *J* = 1.65 Hz, 1H), 4.19 (dd, *J* = 1.65 and 6.60 Hz, 1H), 4.99 (brs, 1H), 7.20-7.42 (m, 6H), 7.65-7.72 (m, 4H).

8. Diimine **2** was prepared in 90% yield from the reaction of benzil with 2 equiv of *p*-anisidine in 1,2-dichloroethane at 70°C in the presence of molecular sieves 4A: ^1H NMR (270 HMz, $CDCl_3$) δ 3.72 (s, 6H), 6.61-6.68 (m, 8H), 7.32-7.87 (m, 6H), 7.85 (dd, *J* = 0.99 and 1.98 Hz, 4H).

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11. Lit.[2a] $[\alpha]_D^{22}$+106.5 (*c* 1.09, CH_3OH)

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