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# Diastereoselective Synthesis of 1,2-Diphenyl-1,2-diaminoethanes by Yb(OTf)3 Accelerated Reductive Coupling of Imines

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**Abstract**

New reaction protocols have been established to perform the reductive coupling of *N*-benzyl benzaldimines to 1,2-diphenyl-1,2-diaminoethanes in mild, stereoselective, and catalytic conditions by the use of $SmI_2$ and $Yb(OTf)_3$. 

*Keywords:* Diamines; Reduction; Stereoselection; Lanthanides.

The importance of the 1,2-diamine functionality in medicinal chemistry [1,2], stereoselective synthesis [3-6], and analytical chemistry [7,8] prompted a great deal of research toward the development of new methods for the synthesis of these compounds [9-11].

Among these methods, the metal-promoted reductive coupling of aldimines, although generally limited to the preparation of symmetrical products, is receiving increasing attention[12-20]. Recently, $SmI_2$ [21], that has been extensively exploited for the pinacol coupling of carbonyls [22], proved to be a useful promoter of aldimine coupling, provided that either a large excess of reagent [23-25] or high reaction temperatures [23,24] or very activated aldimines [25] were used.[1]

We here report that: i) the combined use of $SmI_2$ and $Yb(OTf)_3$ allows the homocoupling of *N*-benzyl benzaldimines to occur at room temperature and in the presence of only 2.0 mol

[1] The system $Sm(0)/Cp_2TiCl_2$ has also been used [26] for imine coupling, but it is likely that in this case the reaction is promoted by an *in situ* generated Ti(III) species. For a similar example in carbonyl pinacol coupling see ref. [27].

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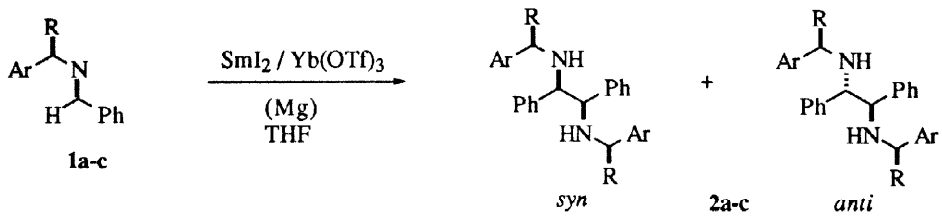
equiv of $SmI_2$ to give the corresponding diamine with low to complete *syn* stereoselectivity; ii) the reaction can be made catalytic in $SmI_2$ by the use of a large excess of Mg metal; and iii) when an enantiomerically pure amine is used to generate the imine, a fair level of stereocontrol can be achieved in the coupling reaction.

**Table 1**
**Diastereoselective coupling of aldimines 1a-c to diamines 2a-c**




| Entry | Imine 1 | R | Ar | $SmI_2$ mol equiv | Mg mol equiv | T °C | Diamine 2 | Y%[a] | *syn/anti*[b] ratio |
|---|---|---|---|---|---|---|---|---|---|
| 1 | a | H | Ph | 2.0 | 0 | 65 | a | 53[c] | 57/43 |
| 2 | a | H | Ph | 2.0 | 0 | 20 | a | 81 | >98/2 |
| 3 | a | H | Ph | 2.0 | 0 | 65 | a | 84 | 63/37 |
| 4 | a | H | Ph | 2.0 | 0 | -20 | a | 83 | 80/20 |
| 5 | a | H | Ph | 2.0 | 8 | 65 | a | 96[c] | 50/50 |
| 6 | a | H | Ph | 0.2 | 8 | 65 | a | 42[c] | 56/44 |
| 7 | a | H | Ph | 0.2 | 8 | 65 | a | 62 | 63/37 |
| 8 | b | Me | Ph | 2.0 | 0 | 20 | b | 86 | 62/38[d] |
| 9 | b | Mc | Ph | 2.0 | 0 | -20 | b | 85 | 64/36[e] |
| 10 | c | Me | α-Napht | 2.0 | 0 | 20 | c | 23 | 65/35[f] |

[a] Isolated yield after flash chromatography. [b] As determined by 300 MHz $^1H$ NMR analysis of the crude products. [c] In the absence of $Yb(OTf)_3$. [d] Two *syn* isomers were obtained in a 75/25 ratio. [e] Two *syn* isomers were obtained in a 89/11 ratio. [f] A single *syn* isomer was detected. For 2b and 2c, only the major *syn* isomer is depicted.

As can be seen from the data collected in Table 1 the coupling reaction of imine **1a** promoted by $SmI_2$ occurred in *refluxing* THF to afford a 53/47 mixture of *syn* and *anti* isomers of diamine **2a** (entry 1).[2] No reaction was observed at room temperature. On the basis of the recognized [29-32] ability of $Yb(OTf)_3$ to activate imines toward nucleophilic attack at carbon, we attempted the coupling reaction in the presence of 1 mol equiv of this Lewis acid.[3] We found that not only the reaction occurred at room temperature, but also the *syn* diastereoselectivity was increased to >98/2 (entry 2). Running the reaction at -20 or at 65°C (entries 3 and 4) depressed the diastereoselectivity at different extent.

Prompted by a recent report describing a $SmI_2$ catalyzed pinacol coupling of aldehydes [33]

[2] Configurational assignment resided on comparison of $^1H$ NMR data of the isomers of compound **2a** with those reported [28].

[3] Also the use of $BF_3OEt_2$ allowed to run the reaction at room temperature, but the diastereoselection was lower, **2a** being obtained in 67% yield as a 63/37 *syn/anti* mixture of diastereoisomers.

we also realized a catalytic version of our imine coupling process. To this end, the reaction of imine **1a** was carried out in refluxing THF in the presence of 0.2 mol equiv of $SmI_2$ and of 8 mol equiv of Mg metal to afford a 56/44 mixture of *syn* and *anti* isomers of diamine **2a** in 42% yield (entries 5 and 6). Addition of $Yb(OTf)_3$ (entry 7) did not allow to lower the reaction temperature but increased both the yield (up to 62%) and, slightly, the diastereoselection (*syn/anti* = 63/37).

Finally, control of the absolute stereochemistry of the products was attempted by using an enantiomerically pure residue at the imine nitrogen. When imine (R)-**1b** was coupled in the presence of $SmI_2$ (2.0 mol equiv) and $Yb(OTf)_3$ (1.0 mol equiv) at room temperature (entry 8), a 68/32 mixture of two *syn* and one *anti* isomers was obtained in 86% yield. The major *syn* isomer had the (R,R,R,R) configuration and was obtained in a 75/25 excess over the (R,S,S,R)-one [34].[4] The ratio between the *syn* isomers was increased to 89/11 by lowering the temperature down to -20°C (entry 9). Replacement of the (R)-1-phenylethanamine residue of **1b** by the bulkier (R)-1-α-naphthylethanamine one of **1c** led to a higher stereocontrol even at room temperature (a single *syn* isomer of **2c** was obtained), but also to a marked decrease of the chemical yield (entry 10).

In conclusion, new reaction protocols have been established that allow efficient imine reductive homocoupling to generate 1,2-diphenyl-1,2-diaminoethanes in mild, stereoselective, and catalytic conditions.[5] Work is in progress to extend this reaction to the stereocontrolled preparation of other vicinal diamines.[6]

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[4] *Syn* and *anti* isomers are easily distinguished by $^1H$ NMR spectroscopy on the basis of the Ph-C*H*-NH-CH(Me)Ph signals: these are homotopic and isochronous in the $C_2$ symmetric *syn* isomers, and diastereotopic and anisochronous in the $C_1$ symmetric *anti* isomer. The $^1H$ NMR spectrum of the (R,S,S,R) isomer of **2b** reported in ref. [33] is identical to that of the minor component of our mixture. Therefore, the major *syn* isomer has the (R,R,R,R) configuration. For a very recent application of the lithium salt of diamine *syn* **2b** to stereoselective synthesis see ref. [35].

[5] Commercially available 0.1 M solutions of $SmI_2$ in THF were employed throughout this work. To ensure reproducible results, a freshly opened bottle of reagent must be used. *In situ* generation of $SmI_2$ from $CH_2I_2$ and Sm metal led to similar but less reproducible results. The imines were freshly prepared and aldehyde free (by NMR) compounds that were used as crude products.

[6] In ancillary experiments it was found that also the following imines could be coupled in the conditions of entry 2, Table 1: *N*-benzyl 4-fluorobenzaldimine (95% yield, *syn/anti* = 60/40); *N*-benzyl 4-methoxybenzaldimine (28% yield, *syn/anti* = 70/30); *N*-t-butyl benzaldimine ( 80% yield, *syn/anti* = 65/35).

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