A Convenient, Highly Stereoselective, Metal-Free Synthesis of Chiral Amines

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Abstract: A low cost, efficient, metal-free highly stereoselective reduction of ketimines to chiral amines was developed. Different imines bearing a very cheap and removable chiral auxiliary were reduced simply by trichlorosilane in the presence of *N*,*N*-dimethylformamide, often in quantitative yield and complete control of the absolute stereochemistry, to afford highly enantiomerically enriched amines.

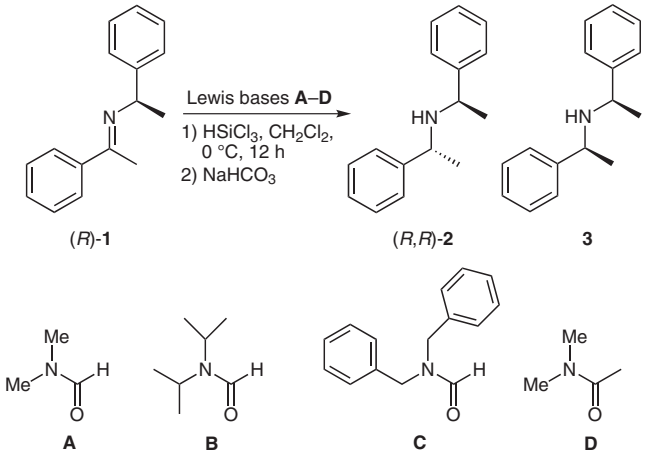
Key words: imine reduction, Lewis base, trichlorosilane, chiral auxiliary, chiral amine

The advent of organocatalysis over the last few years has led to the discovery and development of new activation modes and novel transformations, sometimes complementary to those established in the field of organometallic catalysis.[1] A paradigmatic example comes from the stereoselective carbon–nitrogen double-bond reduction; for this fundamental transformation that generates a new nitrogen-bearing stereocenter, both organometallic catalytic systems[2] and organic catalysts[3] have been recently developed. However, the search of inexpensive but highly efficient procedures for imines reduction, with total control of the absolute stereochemistry, is still very active. Among the different possibilities, an attractive methodology exploits trichlorosilane as the reducing species that needs to be activated by co-ordination with Lewis bases, such as *N*,*N*-dimethylformamide, acetonitrile, and trialkylamines, to generate a hexacoordinated hydridosilicate acting as the actual reducing agent.[4]

Already in 1999 in his pioneering works Matsumura reported the use of *N*-formyl proline to promote enantioselective reduction of ketones and later of imines.[5] Since then several chiral activators for trichlorosilane-mediated reduction have been developed.[4,6] In the course of our work on the topic[7] very recently we have demonstrated that it is possible to reach often a complete stereocontrol in the ketoimines reduction by combining the use of a proper catalyst with a very cheap, removable chiral auxiliary at the imine nitrogen.[8]

Now we wish to report that by working with the proper experimental conditions, the reduction of ketoimines derived from (*R*)- or (*S*)-1-phenylethylamine may be accomplished in very high chemical and stereochemical efficiency simply by addition of trichlorosilane in the presence of an achiral Lewis base such as *N*,*N*-dimethylformamide.

During our studies on the organocatalytic reduction of chiral ketimines[8] it was found that a catalytic amount of *N*,*N*-dimethylformamide was able to promote $HSiCl_3$ addition with good stereoselectivity, although in low yield. We decided to further investigate the reaction; not only DMF (**A**) but also other achiral formamide derivatives were employed, like *N*,*N*-diisopropylformamide (**B**), *N*,*N*-dibenzylformamide (**C**), and *N*,*N*-dimethylacetamide (**D**). In preliminary studies the reduction of imine (*R*)-**1** was performed at 0 °C in dichloromethane for 12 hours in the presence of different equivalents of different Lewis bases (Scheme 1).



Scheme 1 Stereoselective reduction of chiral imine **1**

A few selected results are collected in Table 1. All activators promoted the trichlorosilane addition often in quantitative yield, besides *N*,*N*-dimethylacetamide that was less effective also as stereochemical controller (Scheme 1). Generally, the use of six mol equivalents of Lewis base allowed to obtain amine (*R*,*R*)-**2** in higher diastereoselectivities, with *N*,*N*-dimethylformamide leading to the best result (99% yield, dr = 97:3, entry 2).

With DMF having been identified as the Lewis base of choice, a few experiments were dedicated to the individuation of the best experimental conditions (Table 2).

At 0 °C in dichloromethane a variation of the amount of DMF from 2 mol equivalents to 8 mol equivalents does

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Table 1 Different Lewis Bases in the Stereoselective Reduction of (*R*,*R*)-**1** with $HSiCl_3$

Entry	Lewis base	Lewis base (equiv)	Yield (%)[a]	dr of (*R*,*R*)-**2**/**3**[b]
1	**A**	2	99	95:5
2	**A**	6	99	97:3
3	**B**	2	99	89:11
4	**B**	6	99	90:10
5	**C**	2	99	91:9
6	**C**	6	99	92:8
7	**D**	2	95	87:13

[a] Reaction run at 0 °C, yields determined by ^{1}H NMR and confirmed after chromatographic purification.
[b] Diastereomeric excess determined by ^{1}H NMR and confirmed by HPLC (see Supporting Information).

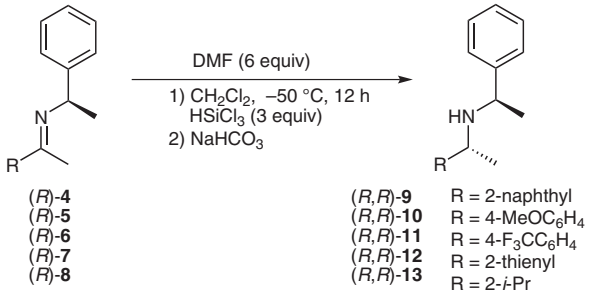
not seem to influence the stereoselectivity decisively. However, 6 mol equivalents of DMF and 3 mol equivalents of $HSiCl_3$ in CH_2Cl_2 seem to be the best combination. In other solvents, like toluene, acetonitrile, or chloroform lower stereoselectivities were obtained. A decisive improvement came from lowering the reaction temperature; at –50 °C, after only 12 hours, the chiral amine **2**[9] was obtained in 98% yield and basically as single diastereomer.[10]

The general applicability of the methodology was then investigated (Scheme 2).[11] *N*-α-Methyl benzyl imines of methyl aryl ketones of different electronic properties were effectively reduced to the corresponding secondary amines in quantitative yields, always maintaining an absolute control of the stereoselectivity of the process (Table 3).

Table 2 Stereoselective Reduction of Imine **1** Promoted by DMF–$HSiCl_3$

Entry	Temp (°C)	Lewis base (equiv)	Solvent	Yield (%)[a]	dr of (*R*,*R*)-**2**/**3**[b]
1	0	0.3	CH_2Cl_2	91	94:6
2	0	2	CH_2Cl_2	99	95:5
3	0	4	CH_2Cl_2	99	94:6
4	0	5	CH_2Cl_2	99	93:7
5	0	6	CH_2Cl_2	99	97:3
6	0	8	CH_2Cl_2	99	96:4
7	0	6	toluene	72	94:6
8	0	6	MeCN	99	87:13
9	0	6	$CHCl_3$	90	95:5
10	–20	6	CH_2Cl_2	95	94:6
11	–50	6	CH_2Cl_2	98	>99:1

[a] Reaction run at 0 °C, yields determined by ^{1}H NMR and confirmed after chromatographic purification.
[b] Diastereomeric excess determined by ^{1}H NMR and confirmed by HPLC (see Supporting Information).



Scheme 2 Stereoselective reduction of chiral imine **4**–**8**

Both aromatic and heteroaromatic alkyl ketimines can be converted to the corresponding amines with great efficiency and stereocontrol (entries 1–4, Table 3). It is worth mentioning that amine **11** has been converted to 4-trifluoromethylphenylmethylamine by simple hydrogenation,[12] thus demonstrating the feasibility of the approach for the preparation of an enantiomerically pure primary amine.

Imine **8** derived from methyl isobutyl ketone was also readily reduced in >98% yield in the presence of *N*,*N*-dimethylformamide at –50 °C (entry 5, Table 3). Chiral amine **13**, obtained as single isomer, represents a direct precursor of (*R*)-isopropylmethylamine.[13]

Table 3 Stereoselective Reduction of Chiral Imines

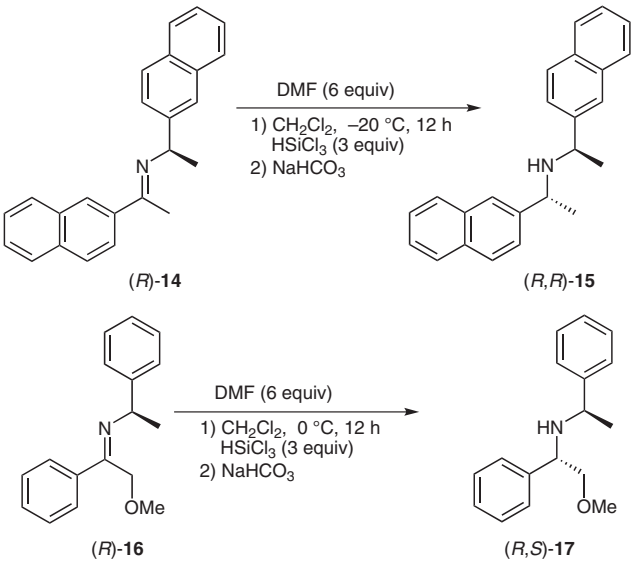
Entry	Imine	Product	Yield (%)[a]	dr[b]
1	**4**	**9**	71	>99:1
2	**5**	**10**	90	91:9
3	**6**	**11**	83	99:1
4	**7**	**12**	65	>99:1
5	**8**	**13**	90	>99:1
6[c]	**14**	**15**	99	98:2
7	**14**	**15**	67	98:2
8[c]	**16**	**17**	71	91:9
9	**16**	**17**	51	88:12

[a] Reaction run at 0 °C, yields determined by ^{1}H NMR and confirmed after chromatographic purification.
[b] Diastereomeric excess determined by ^{1}H NMR and confirmed by HPLC (see Supporting Information).
[c] Reaction run at 0 °C.

The procedure was successfully employed in the preparation of other chiral secondary amines of C_2 symmetry. For example, the reduction of (*R*)-*N*-1-β-naphthyl ethyl imine of 2-acetonaphthone **14** with trichlorosilane was accomplished (Scheme 3). In this case amine **15** was obtained already at 0 °C in quantitative yield and 98:2 stereoisomeric

ratio; running the reaction at lower temperature did not improve the stereoselectivity (entries 6 and 7, Table 3).

Finally, as further demonstration of the versatility of the methodology, the addition of trichlorosilane to imine **16**, derived from reaction of 2-methoxyacetophenone and (*R*)-1-phenylethylamine, was studied (Scheme 3). The reduction at 0 °C after only 12 hours afforded the 1,2-methoxyamino derivative **17** in 71% yield and 91:9 diastereomeric ratio (entry 8, Table 3).[14] Also for this transformation a lower reaction temperature did not modify significantly the stereochemical result.



Scheme 3 Stereoselective reduction of chiral imines **14** and **16**

In conclusion, we have developed a very convenient, low cost protocol for a highly stereoselective reduction of ketimines[15] bearing a very cheap and removable chiral auxiliary, promoted by an achiral inexpensive Lewis base. A very simple experimental procedure allows to obtain the products often with very high diastereomeric excess.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett. It includes characterization of reaction products, ^{1}H NMR spectra, and HPLC chromatograms on chiral stationary phase of chiral amines.

Acknowledgment

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(15) **Typical Experimental Procedure for the Reduction of Ketimines**
To a stirred solution of the imine (1 mmol/equiv, for the imine synthesis see Supporting Information) in CH_2Cl_2 (2 mL), DMF (6 mmol/equiv) was added. The mixture was then cooled to –50 °C and $HSiCl_3$ (3 mmol/equiv) was added dropwise by means of a syringe. The reaction was quenched by the addition of $NaHCO_3$ sat. soln (2 mL). The mixture was allowed to warm up to r.t. and H_2O (2 mL) and CH_2Cl_2 (5 mL) were added. The organic phase was separated and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated under vacuum to afford the crude product.