New, Readily Available Organocatalysts for the Enantioselective Reduction of α-Imino- and β-Imino Esters

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Dedicated to Professor Alberto Brandi on the occasion of his 60th birthday

Abstract: Novel metal-free, readily available chiral catalytic systems for the enantioselective reduction of keto imines are reported. Different β-imino esters were reduced by trichlorosilane in the presence of 10 mol% of a chiral Lewis base easily obtained in one step only from prolinol, in high yields and in up to 85% enantioselectivity; imines bearing an inexpensive and removable chiral auxiliary, were reduced with complete control of the absolute stereochemistry. The methodology was successfully extended to the stereoselective synthesis of α-amino esters.

Key words: trichlorosilane, Lewis base, β-imino esters, stereoselective reduction, imines

Recently great efforts have been made to develop efficient organocatalytic methods to perform enantioselective imine reductions and reductive amination processes.[1] Binaphthol-derived phosphoric acids were successfully employed as catalytic activators in the reduction of ketimines by using a dihydropyridine-based Hantzsch ester-type reagent as the reducing agent.[2] Alternatively in the last few years trichlorosilane-mediated reductions have encountered a constantly increasing attention; the simple coordination of a chiral Lewis base to $HSiCl_3$ allows to generate a chiral catalytic species active in the stereoselective keto imine reduction.[3]

Already in 1999 in his pioneering works Matsumura reported the use of *N*-formyl proline to promote enantioselective reduction of ketones and imines.[4] Since then several chiral activators for trichlorosilane-mediated reduction have been developed. They may be classifieds mainly in two classes: a) chiral *N*-formyl derivatives, usually prepared starting from α-amino acids, b) picolinamides derivatives, typically synthesized by reacting picolinic acid with chiral amino alcohols.[3] Less frequently trichlorosilane has been used in the reduction of imines derived from α-keto esters, leading to the synthesis of natural and unnatural α-amino acids,[5] and in the reduction of β-enamino esters,[6] as valid alternative to the metal-catalyzed hydrogenations.[7] In the course of our studies on the organocatalytic reduction of chiral ketimines,[8] a method for the synthesis of b-amino esters, easily converted into highly enantiomerically enriched β-lactams, was recently developed.[9]

In the attempt to further enlarge the number and types of chiral coordinating Lewis bases suitable for $HSiCl_3$-promoted reductions we have decided to explore the use of novel enantiomerically pure phosphoroamides. We wish to report here the results of our preliminary investigation that allowed us to select at least two new chiral organocatalysts, readily synthesized in one step from cheap, commercially available sources, like prolinol, and employed with success in the reduction of α- and β-imino esters.

In our approach structurally simple chiral Lewis bases should be obtained by modification of an inexpensive, commercially available, enantiopure material whose manipulation must be kept to minimum. Indeed several derivatives were synthesized in a single-step procedure, by reaction of different enantiomerically pure amino alcohols, typically (*S*)-prolinol or similar derivatives, and diphenyl phosphinoyl chloride (compounds **1**–**6**, see supporting information). Based on our previous studies[3,8,9] also ephedrine was used as chiral scaffold for the preparation of derivative **7** (Figure 1).

In preliminary experiments the reduction of *N*-benzyl enamine **8** of 3-oxo-3-phenylpropionic acid methyl ester,[10] was studied. In a typical procedure the reaction was

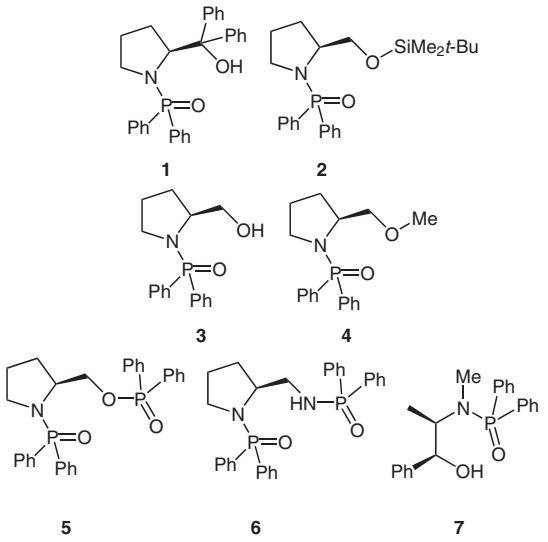

Figure 1 Novel chiral organocatalysts for keto imine reduction

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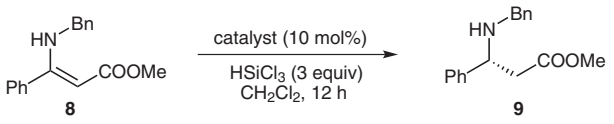
performed at 0 °C in dichloromethane for 12 hours in the presence of 10 mol% of chiral Lewis base (Scheme 1).



Scheme 1 Stereoselective reduction of enamines **8** and **9**

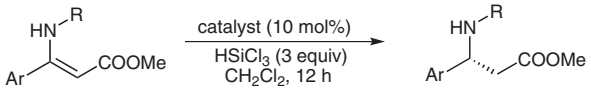
A few selected results are collected in Table 1. All activators were able to promote the trichlorosilane addition, often in very high yield. As one may expect on the basis of previous studies,[3] monodentate organocatalysts **1**–**4** and **7** showed to be less efficient catalysts and afforded the product generally in lower yield than biscoordinating systems, like compounds **5** and **6**. At 0 °C only modest enantioselectivities were observed; however, at lower temperature (–40 °C, entries 8 and 9 of Table 1) good stereoselectivities were achieved: by employing catalysts **5** and **6** the reduction of enamine **8** afforded the product in 75% ee and 85% ee, respectively.

Table 1 Stereoselective Reduction of Enamine **8** Promoted by Chiral Organocatalysts **1**–**7**[a]

Entry	Temp. (°C)	Catalyst	Yield (%)[b]	ee (%)[c]
1	0	**1**	41	21
2	0	**2**	70	7
3	0	**3**	98	5
4	0	**4**	47	7
5	0	**5**	99	35
6	0	**6**	98	31
7	0	**7**	47	11
8	–40	**5**	53	75
9	–40	**6**	50	85

[a] Reaction was run for 12 h in CH_2Cl_2.
[b] Determined by ^1H NMR and confirmed after chromatographic purification.
[c] Determined by HPLC (see Supporting Information).

In the attempt to find the best protecting group at the nitrogen, the *N*-4-methoxyphenyl (PMP) enamine **10** was reduced in different experimental conditions (Scheme 2). Although good chemical efficiency was achieved, lower enantioselectivities were observed even at –40 °C (entry 3, Table 2). At this time it is not possible to give an easy explanation of this result. It is noteworthy that the analogue *N*-phenyl derivative **12** was reduced by catalyst **5** at 0 °C with 65% ee. Therefore in further studies of the performance of catalysts of choice **5** and **6** both *N*-benzyl and *N*-aryl enamines of differently substituted substrates were taken in consideration. The general applicability of the methodology was thus investigated (Scheme 2).[10]



8	Ar = Ph	R = Bn	**9**
10	Ar = Ph	R = PMP	**11**
12	Ar = Ph	R = Ph	**13**
14	Ar = 4-$MeOC_6H_4$	R = Bn	**15**
16	Ar = 4-$MeOC_6H_4$	R = PMP	**17**
18	Ar = 4-$F_3CC_6H_4$	R = Bn	**19**
20	Ar = 4-$F_3CC_6H_4$	R = PMP	**21**
22	Ar = 4-BrC_6H_4	R = PMP	**23**
24	Ar = 4-$O_2NC_6H_4$	R = Bn	**25**
26	Ar = 4-$O_2NC_6H_4$	R = PMP	**27**

Scheme 2 Stereoselective reduction of different β-enamino esters

The organocatalytic reduction of *N*-benzyl and *N*-PMP imines of different β-aryl β-keto esters was accomplished. The corresponding β-amino esters were obtained in very good yields, especially when the aryl residue bears electron-withdrawing groups (see for example entries 8 and 10–12 in Table 3).

Table 2 $HSiCl_3$-Mediated Reduction of Different of β-Enamino Esters[a]

Entry	Temp (°C)	Catalyst	Imine	Yield (%)[b]	ee (%)[c]
1	–40	**5**	**8**	53	75
2	–40	**6**	**8**	50	85
3	–40	**5**	**10**	73	21
4	0	**5**	**12**	83	65
5	0	**6**	**12**	81	45

[a] Reaction was run for 12 h in CH_2Cl_2.
[b] Determined by ^1H NMR and confirmed after chromatographic purification.
[c] Determined by HPLC (see Supporting Information).

Based on the results it is not possible to clearly select a protecting group of choice. For example *N*-benzyl enamine **8** was reduced in enantioselectivites higher than those of *N*-PMP derivative **10**, while for enamines **14** and **16**, *N*-4-methoxyphenyl-substituted derivative **16** offered the best results (entry 3, Table 3). Catalyst **6** did not confirm the excellent result shown with substrate **8** and behaved quite unpredictably in several attempted reactions. Therefore (*S*)-prolinol derivative **5** was preferably employed with other substrates.

Generally PMP-substituted compounds were reduced in higher enantioselectivities than *N*-benzyl derivatives, always affording β-amino esters with ee value higher than 70% and up to 83% in the case of enamine **26**.[11] Addition of $HSiCl_3$ to imines **24** and **26** afforded the products with 80% ee and 70% ee, respectively, even at 0 °C.

In the attempt to improve the selectivity of the process, we decided to take advantage of the presence of a removable chiral auxiliary at the imine nitrogen;[5b] therefore trichlorosilane-mediated reduction[9] of enamine **28** derived from

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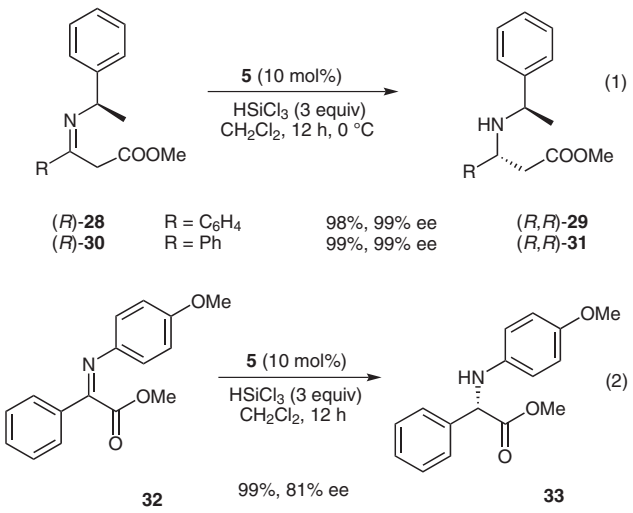
Table 3 Stereoselective Reduction of Different of β-Enamino Esters[a]

Entry	Temp (°C)	Catalyst	Imine	Yield (%)[b]	ee (%)[c]
1	0	**5**	**14**	87	43
2	0	**5**	**16**	99	50
3	–40	**5**	**16**	71	70
4	–40	**6**	**16**	70	21
5	–40	**5**	**18**	73	60
6	–40	**5**	**20**	55	63
7	0	**5**	**22**	99	70
8	–40	**5**	**22**	77	75
9[d]	0	**5**	**24**	99	80
10[d]	–40	**5**	**24**	75	78
11[d]	0	**6**	**24**	90	40
12[d]	0	**5**	**26**	99	70
13[d]	–40	**5**	**26**	85	83

[a] Reaction was run for 12 h in CH_2Cl_2.
[b] Determined by ^1H NMR and confirmed after chromatographic purification.
[c] Determined by HPLC (see Supporting Information).
[d] Ethyl ester was used.

(*R*)-1-phenylethyl amine was studied[12] (Scheme 3, equation 1). By running the reaction at 0 °C the chiral β-amino ester **29** was obtained after 12 hours in 98% yield with a total control of the stereoselectivity.[13] Also *N*-α-methylbenzyl imine **30** was effectively reduced in quantitative yield, to afford the product as a single stereoisomer, as determined by NMR analysis.

Finally we decided to test our methodology in the preparation of α-amino acids. A very limited number of cyclic α-imino esters were studied in organocatalysis[14] and only very recently metal-free catalytic reductions of acyclic imino esters were reported.[15] Both catalysts **5** and **6** promoted the reduction of *N*-4-methoxyphenyl imino ester **32** in quantitative yield at 0 °C and with 81% and 70% enantioselectivity, respectively (Scheme 3, equation 2).



Scheme 3 Stereoselective reduction of α-imino esters

In conclusion, we have developed novel, inexpensive, easy to make, metal-free chiral catalysts, able to promote the trichlorosilane-mediated stereoselective reduction of α-imino and β-imino esters. Further studies on the new catalytic systems and their application in the reduction of heterocyclic rings are currently under way.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett. Included are the synthesis and characterization of chiral catalysts, characterization of reaction products, ^1H NMR spectra and HPLC chromatograms of chiral amino esters.

Acknowledgment

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