Highly Stereoselective Metal-Free Catalytic Reduction of Imines: An Easy Entry to Enantiomerically Pure Amines and Natural and Unnatural α-Amino Esters

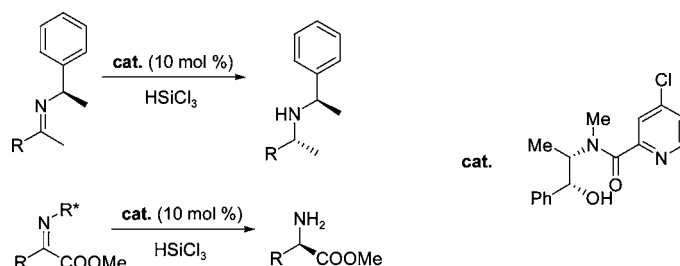Stefania Guizzetti, Maurizio Benaglia,* and Sergio Rossi

Dipartimento di Chimica Organica e Industriale, Università degli Studi di Milano, Via Golgi 19, I-20133 Milano, Italy

maurizio.benaglia@unimi.it

ABSTRACT

A highly efficient catalytic stereoselective ketimine reduction is described. The combination of an inexpensive chiral organocatalyst, easily prepared in a single step, and of a very cheap removable chiral auxiliary allowed us to obtain enantiomerically pure amino compounds. The methodology allowed synthesis of chiral secondary and primary amines and natural and unnatural amino esters in high yields often with total control of the absolute stereochemistry.

Chiral amines are key structural elements of many biologically active compounds, which find application as fragrances, agrochemicals, and pharmaceuticals.[1]

Among the different approaches, the reduction of ketimines represents a powerful and widely used transformation.[2] However, only a few efficient chiral catalytic organometallic systems are currently available.[3] The organocatalytic approach[4] may offer new possibilities.[5] In this context, the past few years have witnessed the flourishing of an impressive

activity on the development of organocatalytic methodologies in the reductive amination process[6] or ketimine reductions. 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.[7] Alternatively, trichlorosilane was exploited as the reducing species; once activated by coordination with Lewis bases, it generates a hexacoordinated hydridosilicate which is the actual reducing agent.[8] Recently, different chiral Lewis bases were reported to be efficient activators of the ketimine reduction, sometimes in very high stereoselectivity.[9] Chiral organocatalytic methodologies rep-

(1) (a) Tararov, V. L.; Borner, A. *Synlett* **2005**, 203. (b) Blaser, H.-U.; Malan, C.; Pugin, B.; Spindler, F.; Steiner, H.; Studer, M. *Adv. Synth. Catal.* **2003**, *345*, 103. For pertinent reviews, see also: (c) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069–1094. (d) Vilaivan, T.; Bhanthumnavin, W.; Sritana-Anant, Y. *Curr. Org. Chem.* **2005**, *9*, 1315.

(2) Constable, D. J. C.; Dunn, P. J.; Hayler, J. D.; Humphrey, G. R.; Leazer, J. L.; Linderman, R. J.; Lorenz, K.; Manley, J.; Pearlman, B. A.; Wells, A.; Zaks, A.; Zhang, J. *Green Chem.* **2007**, *9*, 411.

(3) Blaser, H.-U.; Pugin, B.; Spindler, F.; Thommen, M. *Acc. Chem. Res,* **2007**, *40*, 1240, and references cited thereinFor a special issue on hydrogenation and transfer hydrogenation, see: Krische, M. J.; Sun, Y. *Acc. Chem. Res.* **2007**, *40*, 12.

(4) Reviews: (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138. (b) Dondoni, A.; Massi, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 4638. For reviews on supported organic catalysts, see: (c) Puglisi, A.; Cozzi, F.; Benaglia, M. *Chem. Rev.* **2003**, *103*, 3401–3430. (d) Cozzi, F. *Adv. Synth. Catal.* **2006**, *344*, 1267–1290. (e) Benaglia, M. *New J. Chem.* **2006**, *30*, 1525–1533.

(5) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press: New York, 1998.

resent an opportunity, but they must point at two main directions: higher chemical and stereochemical efficiency and lower cost of the catalytic system. To obtain an enantiopure compound with a metal-free, inexpensive catalyst would open unexplored synthetic routes with relevant consequences also in terms of novel patent strategies.

In this context, we wish to report here our studies on a low cost catalytic system, easily prepared from commercially available products, able to promote the enantioselective reduction of ketimines with trichlorosilane with great efficiency. A wide class of catalysts prepared by simple condensation of picolinic acid[9m] or its derivatives with a chiral amino alcohol[9i,10] or diamine[11] was investigated. In a one-step procedure, several derivatives were synthesized simply by reaction of a chiral amino alcohol or diamine with picolinoyl chloride or picolinic acid in the presence of condensing agents. Among the different synthesized compounds, (1R,2S)-ephedrine-derived N-picolinoylamide **1**[9i] and N-4-chloropicolinoylamide **2**[10] and the bis(N-methyl-N-picolinoylamide) of 1,1′-binaphthyldiamine **3**[12] were selected for this study (Figure 1).
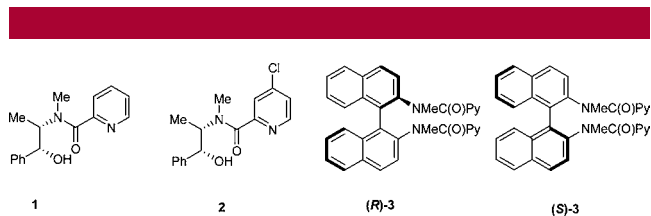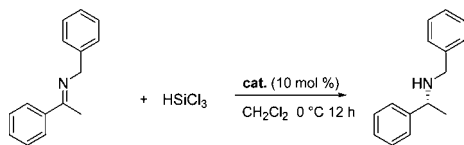

Figure 1. Catalysts for stereoselective ketimine reduction.

In the reduction of the N-benzylimine of acetophenone, by employing 10% of catalyst **1** at 0 °C in dichloromethane the product was isolated in 85% yield and 71% ee (Scheme 1).

**Scheme 1.** Enantioselective Reduction of N-Benzylimines

Higher performances were obtained with ephedrine-based 4-chloropicolinamide **2** that promoted the reaction in quantitative yield and 80% ee. Catalyst (S)-**3** promoted the reaction in quantitative yield and 85% ee.

Even if both catalysts **2** and **3** showed excellent chemical efficiency and interesting levels of enantioselectivity, the control of the absolute stereochemistry was not satisfactory. In order to improve the selectivity of the process, the trichlorosilane-mediated reduction of acetophenone imines (R)-**4** and (S)-**4** derived from (R)- and (S)-1-phenylethylamine, respectively, was studied (Scheme 2).[13] The reaction

Scheme 2. Stereoselective Reduction of Imine **4**
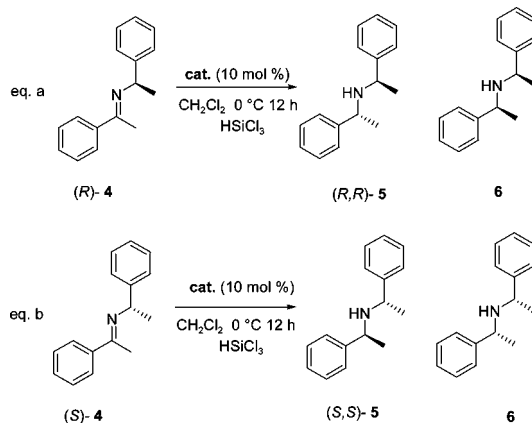
product is the bis-α-methylbenzylamine, a compound that has found numerous applications as chiral base and chiral ligand.[14] The diastereoselective reduction of these chiral substrates through hydrogenation with different catalytic systems has been investigated.[15] However, to the best of our knowledge, no examples of analogous studies with organocatalytic systems have been reported so far.

(6) Reductive amination: for selected recent references for organometallic systems see ref 2 and: (a) Reetz, M. T.; Bondarev, O. *Angew. Chem., Int. Ed.* **2007**, *46*, 4523. (b) Graves, C. R.; Scheidt, K. A.; Nguyen, S. T. *Org. Lett.* **2006**, *8*, 1229. For organic catalysts, see: (c) Ouellet, S. G.; Walji, A.; MacMillan, D. W. C. *Acc. Chem. Res.* **2007**, *40*, 1327. (d) Rueping, M.; Antonchick, A. P.; Theissmann, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3683. (e) Zhou, J.; List, B. *J. Am. Chem. Soc.* **2007**, *129*, 7498. (f) Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 84. For a recent biocatalytic reductive amination, see: (g) Koszelewski, D.; Lavandera, I.; Clay, D.; Guebitz, G. M.; Rozzell, D.; Kroutil, W. *Angew. Chem., Int. Ed.* **2008**, *47*, 9337. (h) Koszelewski, D.; Lavandera, I.; Clay, D.; Rozzell, D.; Kroutil, W. *Adv. Synth. Catal.* **2008**, *350*, 2761. See also: (i) Kadyrov, R.; Riermeier, T. H. *Angew. Chem., Int. Ed.* **2003**, *43*, 5472.

(7) Connon, S. J. *Org. Biomol. Chem.* **2007**, *5*, 3407.

(8) Reviews: (a) Benaglia, M.; Guizzetti, S.; Pignataro, L. *Coord. Chem. Rev.* **2008**, *252*, 492. (b) Denmark, S. E.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1560.

(9) Selected references: (a) Malkov, A. V.; Mariani, A.; MacDougal, K. N.; Kočovský, P. *Org. Lett.* **2004**, *6*, 2253. (b) Malkov, A. V.; Stončius, S.; Kočovský, P. *Angew. Chem., Int. Ed.* **2007**, *46*, 3722. (c) Malkov, A. V.; Figlus, M.; Kočovský, P. *J. Org. Chem.* **2008**, *73*, 3985. (d) Matsumura, Y.; Ogura, K.; Kouchi, Y.; Iwasaki, F.; Onomura, O. *Org. Lett.* **2006**, *8*, 3789. (e) Wang, Z.; Ye, X.; Wei, S.; Wu, P.; Zhang, A.; Sun, J. *Org. Lett.* **2006**, *8*, 999. (f) Pei, D.; Wang, Z.; Wei, S.; Zhang, Y.; Sun, J. *Org. Lett.* **2006**, *8*, 5913. (g) Pei, D.; Zhang, Y.; Wei, S.; Wang, M.; Sun, J. *Adv. Synth. Catal.* **2008**, *350*, 619. (h) Wu, P.; Wang, Z.; Cheng, M.; Zhou, L.; Sun, J. *Tetrahedron* **2008**, *64*, 11304. (i) Zheng, H.; Deng, J.; Lin, W.; Zhang, X. *Tetrahedron Lett.* **2007**, *48*, 7934. (l) Gautier, F.-M.; Jones, S.; Martin, S. J. *Org. Biomol. Chem.* **2009**, *7*, 229. (m) For the first report where chiral amides were used as catalysts, see: Iwasaki, F.; Onomura, O.; Mishima, K.; Kanematsu, T.; Maki, T.; Matsumura, Y. *Tetrahedron Lett.* **2001**, *42*, 2525.

(10) Guizzetti, S.; Benaglia, M. European Patent Appl. Nov 30, 2007; PCT/EP/2008/010079, Nov 27, 2008.

(11) Guizzetti, S.; Benaglia, M. European Patent Appl. no. EP07023240.0, Sep 22, 2008.

(12) Guizzetti, S.; Benaglia, M.; Cozzi, F.; Rossi, S.; Celentano, G. *Chirality* **2009**, *21*, 233.

(13) For a review on the use of methylbenzylamine, see: Juaristi, E.; Leon-Romo, J. L.; Reyes, A.; Escalante, J. *Tetrahedron: Asymmetry* **1999**, *10*, 2441.

(14) See: Alexakis, A.; Gille, S.; Prian, F.; Rosset, S.; Ditrich, K. *Tetrahedron Lett.* **2004**, *45*, 1449, and references cited therein.

(15) Nugent, T. C.; El-Shazly, M.; Wachaure, V. N. *J. Org. Chem.* **2008**, *73*, 1297, and references cited thereinSee also: *Adv. Synth. Catal.* **2006**, *10*, 5433.

Therefore, the reduction with trichlorosilane of imines (R)-**4** and (S)-**4** was performed in dichloromethane in the presence of either achiral or chiral ligands (Table 1). For

Table 1. Catalytic Reduction of Acetophenone-Imine **4**

entry	cat.	imine	product	yield[a] (%)	dr **5/6**[b]
1[c]		(R)-**4**	(R,R)-**5**	98	80/20
2		(R)-**4**	(R,R)-**5**	37	88/12
3	DMF	(R)-**4**	(R,R)-**5**	72	95/5
4	**2**	(R)-**4**	(R,R)-**5**	**98**	>99/1
5	**2**	(R)-**4**	(R,R)-**5**	98	76/24
6	(R)-**3**	(S)-**4**	(R,R)-**5**	98	95/5
7	(R)-**3**	(R)-**4**	(R,R)-**5**	98	80/20

[a] Reactions were run with 3.5 molar equiv of HSiCl$_3$ and 10 mol % of catalyst; yields were determined after chromatographic purification. [b] Diastereoisomeric ratio was determined by ^{1}H NMR and confirmed by HPLC. [c] Reduction was performed with NaBH$_4$.

the sake of comparison, first the reduction of imine (R)-**4** with NaBH$_4$ was accomplished; in our hands the reaction afforded the products in quantitative yield and 80/20 (R,R)-**5**/**6** diastereoisomeric ratio (Table 1, entry 1).

In the absence of any organic promoter, trichlorosilane reduced ketimine (R)-**4** in poor yield; when the reaction was performed in the presence of 2 molar equiv of N,N-dimethylformamide, chiral amine **5** was obtained in 72% yield and, interestingly, in 90% diastereoselectivity (entry 3). However, the real improvement was observed when picolinamide **2** was employed as catalyst; it promoted the reduction in quantitative yield and with a total control of the stereoselectivity (Table 1, entry 4).[16]
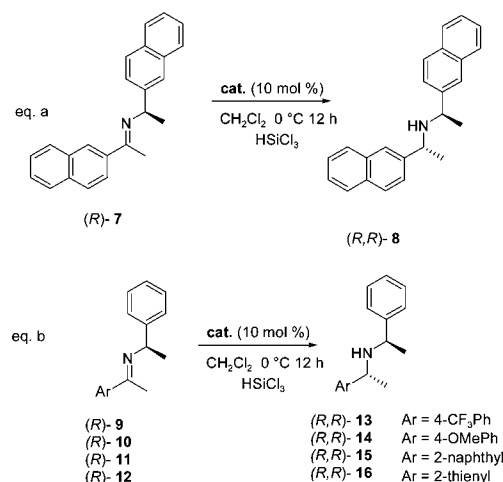
As a demonstration of the presence of a cooperative effect of catalyst **2** with the (R)-methyl benzyl residue at the imine nitrogen, the reduction of imine (S)-**4** in the presence of **2** led to the formation of isomer (S,S)-**5** as major product but in only 76/24 isomeric ratio (entry 5). Also binaphthyl-derived bis-picolinamide **3** catalyzed efficiently the reduction of chiral imines **4**, although with a lower selectivity. In this case, the matching pair was represented by (R)-binaphthyl-diamine derivative **3** and imine (S)-**4** prepared from (S)-methylbenzylamine; such a combination allowed us to obtain (S,S)-**5** with 90% de.

The methodology was extended to the synthesis of an enantiomerically pure secondary amine of either C_1 or C_2 symmetry. For example, the reduction of the (R)-N-1-β-naphthylethylimine of 2-acetonaphthone **7** with trichlorosilane and catalyst **2** was successfully accomplished (eq a, Scheme 3); amine **8** was obtained at 0 °C as single isomer in 98% yield.[17]

Scheme 3. Stereoselective Reduction of Imines **9**−**12**

The general applicability of such a methodology was demonstrated; N-α-methylbenzylimines 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 (eq b, Scheme 3). Amines **13**−**15** were all obtained in >99/1 stereoisomeric ratio (Table 2).[18] It is noteworthy that the correct match pair of (R)-**9**

Table 2. Catalytic Reduction of Imines **9**−**12**

entry	cat.	imine	product	yield[a] (%)	dr[b] (%)
1	**2**	(R)-**7**	(R,R)-**8**	98	>99/1
2	**2**	(R)-**9**	(R,R)-**13**	98	>99/1
3	(S)-**3**	(R)-**9**	(R,R)-**13**	86	>99/1
4	**2**	(R)-**10**	(R,R)-**14**	98	>99/1
5	**2**	(R)-**11**	(R,R)-**15**	98	>99/1
6	(S)-**3**	(R)-**11**	(R,R)-**15**	98	>99/1
7	**2**	(R)-**12**	(R,R)-**16**	98	>99/1

[a] Reactions were run with 3.5 molar equiv of HSiCl$_3$ and 10 mol % of catalyst; yields were determined after chromatographic purification; [b] Diastereoisomeric ratio was determined by ^{1}H NMR and by HPLC.

imine and (S)-**3** also afforded the secondary amine as an enantiomerically pure compound. Amine **13** can be converted to 4-trifluoromethylphenylmethylamine by simple hydrogenation,[19] thus demonstrating the feasibility of the approach for the preparation of an enantiomerically pure primary amine. The methodology can also be used for the reduction of heteroaromatic alkyl ketimines; catalyst **2** promoted the reduction of 2-thenyl methyl ketone-derived imine **12** in >99/1 dr (entry 7).

The trichlorosilane-mediated reduction was also applied to imines of dialkyl ketones.

(16) By ^{1}H NMR analysis on the crude reaction mixture and then confirmed after purification only one product was detected. HPLC analysis showed the presence of the other diastereoisomer to be <0.5%; see the Supporting Information. For a recent contribution on the analytical aspect, see: Claridge, T. D. W.; Davies, S. G. M.; Polywka, E. C.; Roberts, P. M.; Russell, A. J.; Savory, E. D.; Edward, D.; Smith, A. D. *Org. Lett.* **2008**, *10*, 5433.

(17) The reduction of imine **7** with NaBH$_4$ afforded the product with 78% diastereoselectivity.

(18) See the Supporting Information for a table containing the results obtained in the reduction of the chiral ketimines with NaBH$_4$.

(19) For selective debenzylation reactions, see: Kanai, M.; Yasumoto, M.; Kuriyama, Y.; Inomiya, K.; Katsuhara, Y.; Higashiyama, K.; Ishii, A. *Org. Lett.* **2003**, *5*, 1007.

Imine **17** derived from methyl isobutyl ketone was readily reduced in >98% yield in the presence of both catalysts **2** and **3**. With ephedrine-based catalyst **2**, amine **18**, the direct precursor of (*R*)-isopropylmethylamine, was isolated as an isomerically pure compound (Scheme 4).

Scheme 4. Stereoselective Reduction of Imine **17**
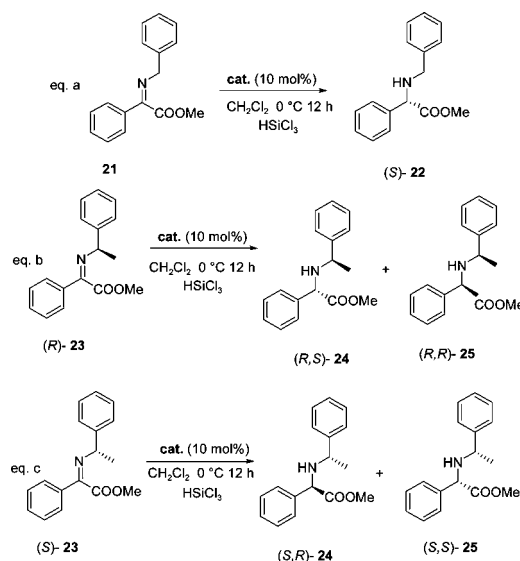

98% yield; 99% d.e.

(*R*)- **17**   (*R,R*)- **18**
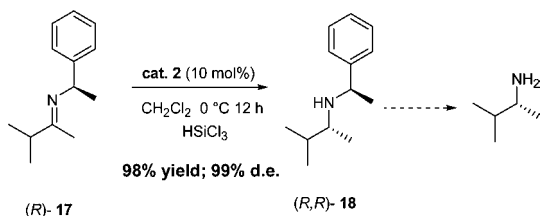
A tentative model of stereoselection observed in the reaction promoted by catalyst **2** was proposed: pyridine nitrogen and a CO amidic group of picolinamide would activate trichlorosilane by coordination. In the (*R*)-phenyl-ethylamine-derived imine reduction, a working model of the low energy conformer of *trans*-ketimine determining the facial selectivity was already proposed.[15] It involves the presence of the imine nitrogen and the carbon and the hydrogen atoms of the stereocenter on the same plane. Based on these considerations, the sense of the hydrogen attack on the imine S_i-face determined by the (*R*)-stereocenter of the chiral auxiliary is in accordance with the sense of addition dictated by catalyst **2**; the cooperative effect of the two chiral elements responsible for the stereoselection explains the sense of the experimentally observed absolute stereochemistry.

Finally, we decided to test our methodology in the preparation of unnatural α-amino acids.[20] Very few successful transition-metal-catalyzed hydrogenations of α-imino esters were reported.[21] In addition, organocatalysis has offered only in the last 3 years the first examples of phosphoric acid-promoted ketoimine reduction.[6c] A very limited number of cyclic α-imino esters were studied,[22] and only one reduction of acyclic imino esters is known.[23]

Catalysts **2** and **3** promoted the reduction of *N*-benzyl iminoester **21** in quantitative yield and up to 71% ee. However picolinamide **2** catalyzed the reduction of chiral imine (*R*)-**23** at 0 °C in dichloromethane to afford the formation of (*R,S*)-**24** in 73% yield and 91% diastereoisomeric excess (Scheme 5). The use of (1*S*,2*R*)-ephedrine-derived catalyst **en-2** led to the unnatural α-aminoester.

(20) Ma, J.-A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4290.
(21) Review: (a) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029. (b) Shang, G.; Yang, Q.; Zhang, X. *Angew. Chem., Int. Ed.* **2006**, *45*, 6360.
(22) See ref 8 and also: (a) Rueping, M.; Sugiono, E.; Azap, C.; Theissmann, T.; Bolte, M. *Org. Lett.* **2005**, *7*, 3781. (b) Hoffmann, S.; Seayad, A. M.; List, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 7424.
(23) Li, G.; Liang, Y.; Antilla, J. C. *J. Am. Chem. Soc.* **2007**, *129*, 5830.

Scheme 5. Stereoselective Synthesis of Amino Esters

In conclusion, we have developed a highly efficient synthesis of enantiomerically pure primary and secondary amines; the combination of low cost, easy to make metal-free catalyst, and an inexpensive chiral auxiliary allowed us
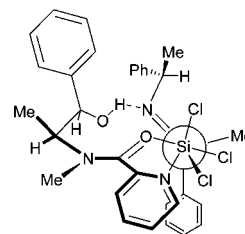

Figure 2. Proposed model of stereoselection.

to reduce ketimines with different structural features often with total control of the stereoselectivity.

Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra of **2** and **3**, table for the reduction of chiral imines by NaBH[4], characterization of new compounds, and selected ^{1}H NMR, ^{13}C spectra, and HPLC chromatograms of chiral amines. This material is available free of charge via the Internet at http://pubs.acs.org.

OL900945H