DOI: 10.1002/ejoc.201000728

Trichlorosilane-Mediated Stereoselective Reduction of C=N Bonds

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Keywords: Organocatalysis / Amines / Imine reduction / Lewis bases / Chirality

The reduction of C=N bonds represents a powerful and widely used transformation allowing new nitrogen-containing stereocenters to be generated. Chiral amino groups are ubiquitous in a variety of bioactive molecules such as alkaloids, natural products, drugs, and medical agents, so the development of a catalytic stereoselective process for the preparation of enantiomerically enriched amines through ketoimine reduction is attracting increasing interest, especially in view of future industrial applications. Great efforts to develop efficient organocatalytic methods to perform enantioselective imine reductions and reductive amination processes have recently been made. In the last few years, trichlorosilane-mediated reductions have received constantly increasing attention because the potential to generate chiral catalysts for imine reduction simply by coordination of $HSiCl_3$ with a chiral Lewis base has allowed the development of several efficient organocatalytic systems. Here we offer a complete overview of different chiral promoters of stereoselective reductions with trichlorosilane, classified as *N-formyl derivatives*, which may be considered historically the first class of compounds developed as chiral activators of trichlorosilane, *picolinamide derivatives*, and *miscellaneous compounds* presented in that order.

1. Introduction

Recent market analysis showed that global revenues from chiral technology soared from $6.63 billion in 2000 to $16.03 billion in 2007, growing at a compound annual rate of 13.4% during that period. Approximately 80% of all products currently in development for the pharmaceutical industry are based on chiral building blocks, a clear demonstration of why chiral technology has become of fundamental importance, and not only for pharmaceutical companies.[1]

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Among the different methodologies used to synthesize enantiomerically enriched compounds, the use of a chiral catalyst represents in principle the most attractive procedure, because of the small quantities required, the mild (more energy-efficient) reaction conditions, and the more selective (less waste production) courses of the transformations. The achievement of sustainable development is an important goal in the 21st century, and the requirement for the production of single-enantiomer compounds ties in with this because it concerns the reduction of waste in the production of fine chemicals.[2] In this context the possibility of using catalytic amounts of an organic compound of relatively low molecular weight and simple structure to promote reactions that previously required costly transition-

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Maurizio Benaglia was born in Bergamo in 1966. He received his laurea in Chemistry at the University of Milano in 1991 and his PhD in 1994 working with Prof. Mauro Cinquini on the synthesis of β-lactams. He spent two years as a postdoctoral fellow with Prof. Jay Siegel at the University of California at San Diego studying the stereoselective synthesis of supramolecular structures. He then returned to Milano, where he is now Associate Professor. He is author of more than 120 papers in international journals. His research projects concern polymer-supported catalysis, the development of new synthetic methods, stereoselective organocatalysis, and the synthesis of chiral supramolecular systems and molecular devices.

metal-based catalysts can be regarded as a significant step toward the development of truly green chemistry.[3]

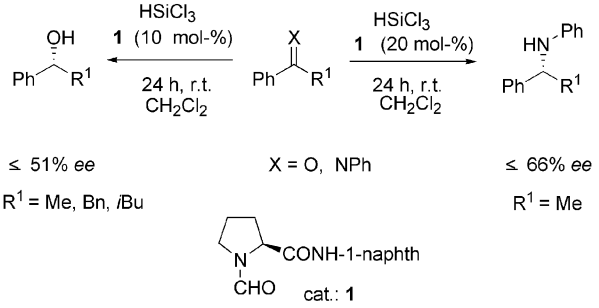
This field includes the problem of developing efficient catalytic methodologies for the stereoselective reduction of C=N bonds, especially ketoimines. Chiral amines are finding applications in an ever-increasing number of fields, such as pharmaceuticals, agrochemicals, and fragrances, so the possibility of developing an organocatalytic approach has gained much attention because it might represent a solution to the problems related to the possible presence of toxic metals, leaching of which could contaminate the products.[4]

Among the metal-free methodologies recently developed,[5] the use of trichlorosilane as a reducing agent is particularly attractive. This cheap reagent is a colorless liquid, easily prepared in the silicon industry, which has already been employed on large scales for transforming phosphane oxides into phosphanes and *N*-acyliminium ions into *N*-acylamines. Although the methodology may present some problems with regard to, for example, the generation of some quantities of halogen waste, it undeniably deserves consideration as a viable tool for the synthesis of chiral secondary amines. The trichlorosilane needs to be activated by coordination with a Lewis base, such as *N*,*N*-dimethylformamide, acetonitrile, or a trialkylamine, to generate hexacoordinate hydridosilicate, the real active reducing agent that operates under mild conditions.[6] The use of chiral Lewis bases[7] offers the potential to control the absolute stereochemistry of the process, and this has been widely explored in the last few years, leading to the development of some really efficient catalysts. Here we offer a complete overview of different catalytic systems reported by many research groups active in a field that has recently attracted considerable attention and has seen the design and the synthesis of different classes of Lewis bases as effective activators of the reduction process. The catalytic systems are classified and presented in the following order: *N-formyl derivatives*, which may be historically considered the first class of compounds developed as chiral activators of trichlorosilane, *picolinamide derivatives*, a second class, intensively investigated in the very last few years, and *miscellaneous compounds*.

2. Discussion

2.1. *N*-Formyl Derivatives

The first example of a stereoselective catalytic reduction with $HSiCl_3$ was reported in 1999: Matsumura and coworkers reported that *N*-formyl cyclic amine compounds [basically (*S*)-proline derivatives] were effective activators for the reduction of ketones in the presence of trichlorosilane.[8a] Catalytic amounts of these Lewis bases were used for obtaining enantiomerically enriched secondary alcohols (up to 51% *ee*, Scheme 1). Two years later the same group found that trichlorosilane, also activated with *N*-formylproline as a chiral Lewis base, is an effective reagent for chemo- and stereoselective reduction of imines (Scheme 1). The corresponding amines were isolated in moderate yields with up to 66% *ee*.[8b]



Scheme 1. *N*-Formylproline as a chiral promoter of $HSiCl_3$-mediated reactions.

The mechanism originally proposed in that study (Figure 1) involved the coordination of the bidentate Lewis basic ligand **1** to the silicon atom, causing the formation of a cationic active species. This species would be able to coordinate the carbonyl oxygen and to transfer the proton via a four-center transition state.

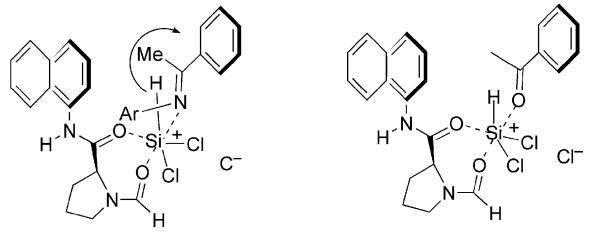


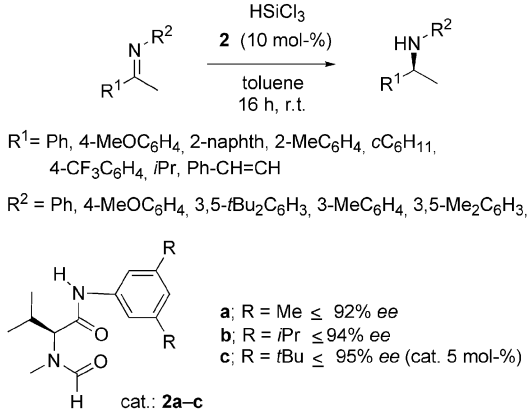
Figure 1. Model for stereoselection.

This hypothesis was later modified by the authors, who in successive publications proposed a transition state more similar to that described by Malkov and Kočovský (see below, Figure 2), in which the silicon atom is not involved in the direct coordination of the substrate.

Matsumura's contribution in designing *N*-formylpyrrolidine derivatives as $HSiCl_3$ activators can be considered a milestone for the asymmetric reduction of ketones and imines through the use of $HSiCl_3$ as reducing agent and paved the road to the synthesis of other related systems. Since then, considerable efforts have been devoted to the development of efficient catalysts for the reduction of C=N bonds, and remarkable progress has been made.

Another important breakthrough in the field was achieved by Malkov and Kočovský in 2004, when they developed the first highly stereochemical efficient catalyst; the compounds of choice were the *N*-methyl-(*S*)-valine-derived Lewis basic organocatalysts of type **2** (Scheme 2), commercially available since 2009.[9]

Two years later,[10] the same authors reported a detailed investigation of the reduction of imines with $HSiCl_3$ catalyzed by *N*-methyl-(*S*)-amino acid derivatives. A library of chiral *N*-formylated amino acids with structural variations at the carboxyamide group was designed and synthesized, with either aromatic or aliphatic substituents. Reductions were carried out in nonpolar solvents; toluene was chosen for its relatively low environmental impact. Different substituted *N*-arylketimines were tested as substrates.



Scheme 2. *N*-Formyl derivative of *N*-methyl-(*S*)-valine.

After screening of a variety of *N*-methyl-(*S*)-amino acids in the reduction of ketomines, valine was selected as chiral element of choice with which to achieve stereocontrol and a few conclusions were proposed: i) the *N*-methylformamide moiety of the catalyst is fundamental for the enantioselectivity, ii) arene–arene interactions may play an important role in determining the stereoselectivity of the catalyst, iii) the anilide moiety of the catalyst has to be a secondary amide (i.e., with an NH group), iv) the silicon atom is activated by coordination with the formamide moiety, v) the configuration of the resulting product depends on the nature of the amino acid side chain, and vi) bulkier groups in the 3,5-positions of the aromatic ring (diisopropyl and di-*tert*-butyl) provide an increase in the enantioselectivity in the reduction of aromatic and non-aromatic ketoimines.

It was suggested that catalyst–substrate hydrogen bonding and coordination of the silicon atom by the two carboxyamide groups played a fundamental role in determining the stereoselectivity of the catalyst. An additional element of stereocontrol in the proposed transition state is the formation of a hydrogen bond between the amide group of the catalyst and the substrate (Figure 2).

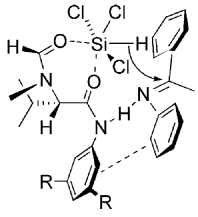
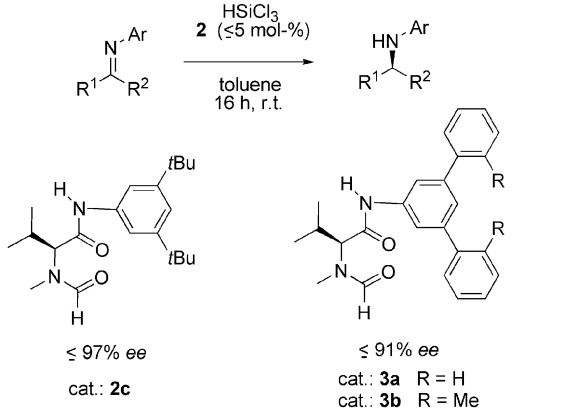


Figure 2. Model of stereoselection for (*S*)-valine-derived organocatalysts.

The general applicability of the catalyst **2c** (known as Sigamide, Scheme 3) in the reduction of multifunctionalized ketoimines bearing heterocyclic and aliphatic substrates was then investigated.[11] The reactions exhibited high enantioselectivities with ketimines derived from aromatic amines and aromatic, heteroaromatic conjugated, and nonaromatic ketones with an appreciable steric difference between the alkyl groups R_1 and R_2. Introduction of a heteroatom into the aromatic system (pyridyl derivatives) afforded the products with almost no enantioselection, probably as a result of the competition of the substrate pyridine nitrogen with the catalyst in the coordinating the silicon atom of $HSiCl_3$.



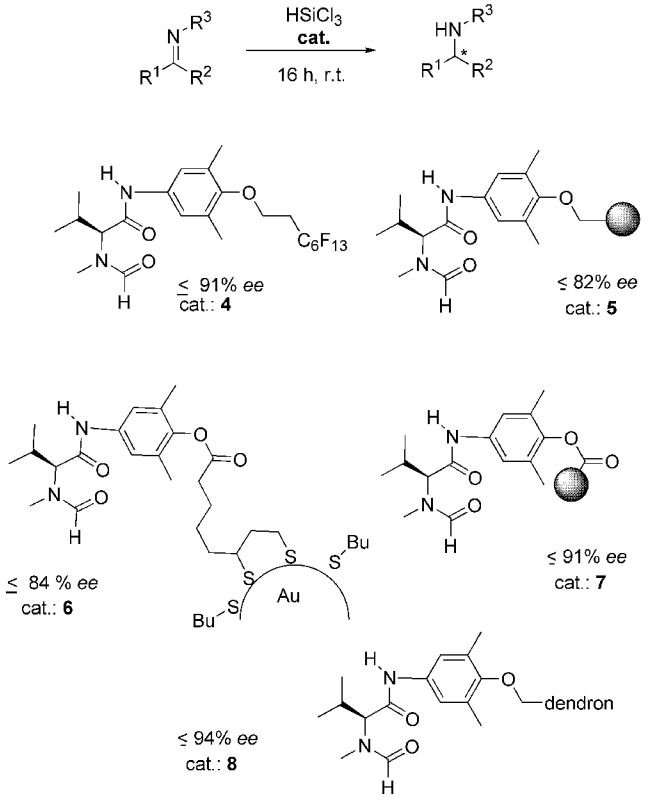
Scheme 3. New (*S*)-valine-derived organocatalysts.

Two new (*S*)-valine-derived organocatalysts (**3a**, **3b**, Scheme 3), each bearing a bulky aromatic substituent at the amidic nitrogen, were recently synthesized.[12] The efficiencies of the new compounds were tested in model reductions of ketoimines derived from aryl methyl ketones and were found to be slightly inferior to that of Sigamide (**2c**).

The recoverability of this family of catalysts has also been studied (Scheme 4). The fluorous-tagged catalyst **4** functions in solution, and showed very little difference from the untagged version in terms of catalytic efficiency.[13a] The products were separated from the catalyst by filtration though a pad of fluorous silica; the catalyst was easily recovered and recycled.

Another study on the development of a polymer-anchored version of the same catalyst was recently reported; different supports were investigated, with Merrifield and extended Merrifield, Wang, TentaGel, and Marshall resins all being employed to immobilize the organocatalysts through ether bonds.[13b] Enantioselective reductions of *N*-aryl ketoimines in the presence of trichlorosilane were typically performed with employment of a 15–25 mol-% amount of the supported catalyst, a higher loading than used with the nonsupported system (typically 5–10 mol-% cat.). The immobilized catalysts showed significant dependence on the reaction solvent; whereas the nonsupported organocatalysts work well in toluene, the polymer-anchored species behave much better in chloroform. Under the best experimental conditions, with the Merrifield-anchored catalyst **5**, the product was isolated in good yield and in 82% *ee*, but this is 10% lower than the enantioselectivity obtained with the nonsupported catalyst. After filtration of the immobilized organocatalyst it was possible to reuse **5** five times always with maintenance of the same level of stereoselectivity, but a reactivation step was required.

A third recoverable version of the catalyst was achieved by connecting the valine-derived formamide Lewis base to gold nanoparticles.[14] This methodology allows one both to work in a homogeneous solution and to simplify the recovery of the catalyst and its separation from the product.



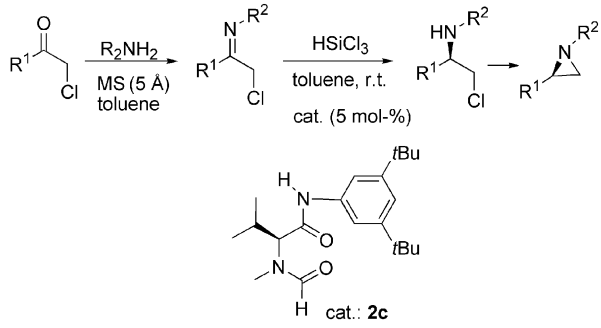
Scheme 4. Recoverable chiral organocatalytic systems.

The nanoparticles can be readily removed from the reaction mixture by precipitation and subsequently recycled. The nanoparticles **6** displayed good solubility in nonpolar solvents (CH_2Cl_2 and toluene) but proved poorly soluble in more polar solvents (CH_3OH). The best result in terms of enantioselectivity (≤84% *ee*) was observed with catalyst **6** in toluene as solvent at room temperature. Recovery experiments showed that the enantioselectivity of **6** dropped in the fourth run, whereas the yield remained virtually unchanged. According to the authors, this behavior is due to partial desorption of the immobilized organocatalyst from the nanoparticle during the workup: in this way the background reaction, catalyzed by the "naked" nanoparticles, becomes competitive. Accordingly, after the third run a decreased solubility of the nanoparticles was observed, and in the fourth run the system was nearly heterogeneous.

A further recyclable catalytic system was produced by anchoring the chiral active species to a new soluble polymeric platform (a block polymethacrylate) that, unlike the classic soluble supports (e.g., PEG), is soluble in apolar solvents and can be precipitated by increasing the solvent polarity.[15] Asymmetric reductions of imines with Cl_3SiH promoted by the soluble polymeric platform **7** (1–7 mol-% catalyst loading) proceed at room temperature, affording chiral amines in high yields and with good enantioselectivities (≤91% *ee*). The catalyst can be recovered and reused at least five times without loss of activity. It was claimed that the polymethacrylate backbone of catalyst **7** allows a high concentration of the catalytic moiety in the polymer.

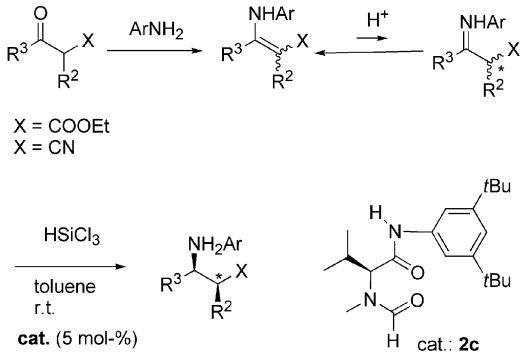
The most recently reported system, published in 2010, relies on an alternative approach: the catalyst is anchored to a dendron.[16] Three generations of dendron-supported *N*-methylvaline derivatives were prepared and employed as organocatalysts for the enantioselective reduction of imines with trichlorosilane. The isolation procedure for the third-generation catalyst proved more successful: 90% of the catalyst was recovered from the mixture by precipitation and centrifugation. After aqueous workup the isolated amine contained a quantity of the catalyst smaller than 1%. The best enantioselectivity (≤94% *ee*) was obtained at room temperature in toluene as solvent. This result is comparable with those obtained with the nonsupported catalysts **2a**–**c**.

The use of (*S*)-valine-derived formamide was also extended to the reduction of α-chloro-imines (Scheme 5). These compounds were generated in situ from the corresponding α-chloroketones and aniline derivatives. Their reduction in the presence of $HSiCl_3$ at room temperature gave the α-chloroamines with high enantioselectivities (up to 96% *ee*) and good yields, and after cyclization the corresponding aziridines as final products.[17]



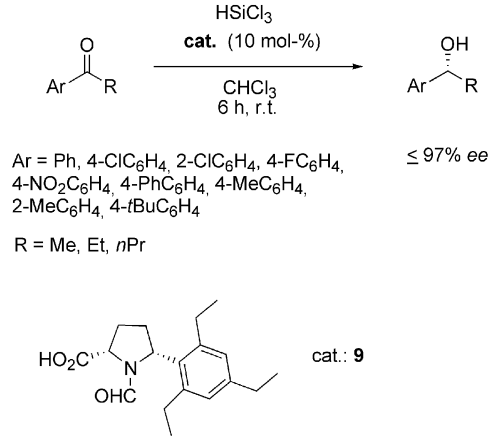
Scheme 5. Stereoselective synthesis of aziridine.

The catalyst **2c** has very recently also proved to be suitable for the development of a new protocol for the enantioselective synthesis of β-amino acid derivatives from enamine precursors (Scheme 6).[18] Treatment of β-ketoesters/-nitriles with *p*-anisidine afforded enamines, which themselves cannot be reduced by Cl_3SiH. Because enamine–imine equilibration is facilitated by Brønsted acids, a number of acid additives were examined, out of which AcOH (one equivalent of which was used) emerged as good compromise between reactivity and selectivity. Enamine was reduced to give the amino ester in high yield and 89% *ee*. The enantiomerically pure product could be obtained by a single crystallization. Nitriles exhibited the same behavior as the esters in terms of reactivity. The authors then focused on the synthesis of $\beta^{2,3}$-amino acids. In this case, because the starting achiral enamines exist in fast equilibrium with the corresponding chiral racemic imines, the reaction can be considered a dynamic kinetic resolution. The corresponding amino esters and amino nitriles were prepared in good yields and with high enantioselectivities (≤90% *ee* values) and diastereoselectivities (≤99% *de* values).



Scheme 6. Stereoselective reduction of enamines.

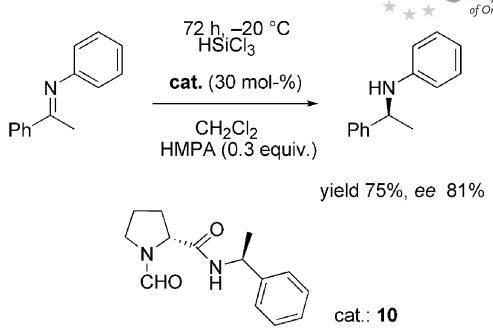
Following his previous studies with prolinamides, in 2006 Matsumura reported the activity of *N*-formylproline derivatives in reductions of ketones in the presence of trichlorosilane.[19] Secondary alcohols could be synthesized with high enantioselectivities (up to 97%, Scheme 7) in the presence of catalytic amounts of *N*-formyl-α′-(2,4,6-triethylphenyl)-(*S*)-proline (catalyst **9**). The selection of the best performing compound was the result of the screening of a series of α′-arylproline derivatives. Both the carbonyl group at the α-position and a 2,4,6-triethylphenyl group at the 5-position in the proline ring play important roles in determining the high enantioselectivity.



Scheme 7. Stereoselective reduction of ketones.

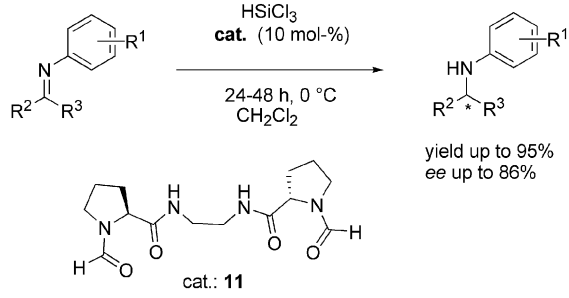
In 2007, Tsogoeva's research group[20] reported the use of chiral formamides in the reduction of ketoimines in the presence of trichlorosilane. A second element of stereocontrol, such as a chiral amine, was coupled to the proline moiety. The catalyst **10** (Scheme 8), the *N*-formylprolinamide of (*R*)-α-methylamine, activated trichlorosilane in the ketoimine reduction, affording the product in 75% yield and 81% *ee* in the presence of an additive. HMPA and *p*-nitrobenzoic acid were tested as additives and, quite surprisingly, the former turned out to be the more effective.

In the same year the Sun group[21] reported the (*S*)-proline-derived C_2-symmetric chiral tetraamide **11** (Scheme 9) as a novel catalyst in the enantioselective hydrosilylation of ketomines. The choice of catalyst **11** was the result of the



Scheme 8. *N*-Formylprolinamides with chiral substitution.

screening of a series of C_2-symmetric chiral tetraamide derivatives, in which the linkage of the two proline diamide units proved to have a significant impact on the enantioselectivity. The presence either of a shorter or of a longer linkage or of aromatic linkages provided products with much lower enantioselectivities.

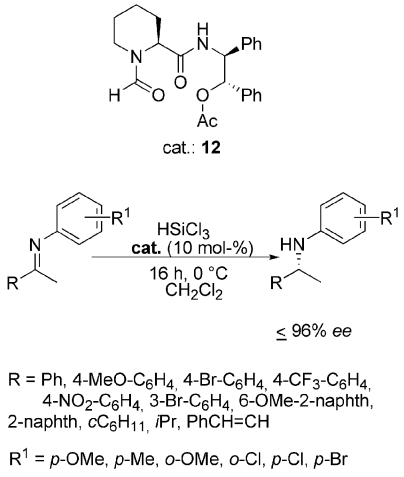


Scheme 9. Chiral bis *N*-formylprolinamides.

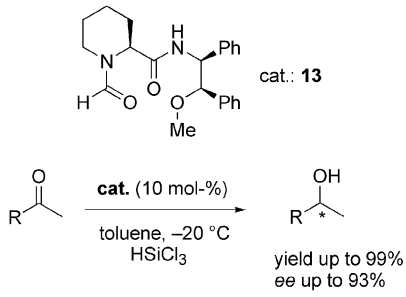
The reaction products were isolated in high yields (up to 95%) and with moderate to high enantioselectivities (up to 86% *ee*) for a broad range of substrates, including aromatic and aliphatic imines. The two diamide units of **11** work cooperatively, showing a synergistic effect.

In 2006 Sun reported that switching from the five-membered ring of proline to a six-membered ring had a beneficial effect on the enantioselectivity (Scheme 10). The first catalyst[22] derived from L-pipecolinic acid, compound **12**, promoted the reduction of *N*-aryl ketoimines with trichlorosilane with high yields and good enantioselectivities.

The use of *N*-formyl-substituted L-pipecolinic acid derivatives as organocatalysts was then extended to the reduction of aromatic and aliphatic ketones.[23] The best catalyst for the reduction of carbonyl compounds was found to be **13** (Scheme 11), characterized by the presence of the methoxy group on the C2′ carbon of the chiral amino alcohol moiety. The methoxy functional group at that position turned out to be crucial for obtaining alcohols with high enantioselectivity. Indeed the replacement of this moiety either with a bigger alkoxy group or with a group with a less electron-rich 2′-oxygen led to decreased reactivity and/or enantioselectivity of the catalyst. According to the authors, the catalyst **13** functions as a tridentate activator and promotes the hydrosilylation of ketones through a heptacoordinate silicon transition structure.

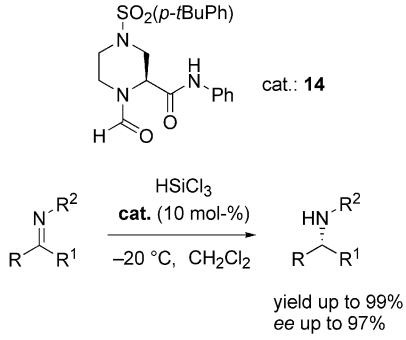


Scheme 10. Pipecolinic acid derivatives.



Scheme 11. Stereoselective reduction of ketones.

A different catalyst was prepared by Sun through the employment of a piperazinyl backbone.[24] The arenesulfonyl group at the 4-position was shown to be a key element for obtaining a high level of enantiocontrol (Scheme 12). The catalyst **14** promoted the reduction of a broad range of imines with good yields and enantioselectivities.

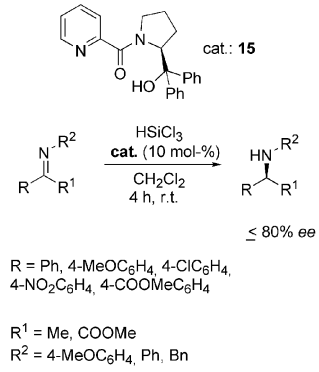


Scheme 12. Chiral piperazinyl derivatives.

Schreiner has very recently published a detailed investigation of the influence that nonaromatic groups in *N*-formylprolinamide may have on the enantiomeric excesses of ketimine reductions, by also employing computational methods in an attempt to achieve some mechanistic insights into the process.[25] By working with a series of novel chiral organocatalysts derived from proline, valine, and pipecolinic acid, the dominant role of the amino acid scaffold for the mode of action in the enantiodifferentiating step was demonstrated. Mechanistic studies based on DFT computations seem to confirm that the catalyst not only coordinates to trichlorosilane, but also reacts as a proton donor in the crucial transition structure; indeed, the importance of the presence of the acidic NH proton of a secondary amide group, able to bind with the basic nitrogen of the reacting imine, has been demonstrated. Although the authors suggest that enantiodifferentiating steps for proline, pipecolinic acid, and valine-derived catalysts might be different, from the computational studies they propose a general picture for the catalytic reduction of ketimines with trichlorosilane, that could be described as a formal H^+/H^- transfer to the C=N double bond.

2.2. Picolinamide Derivatives

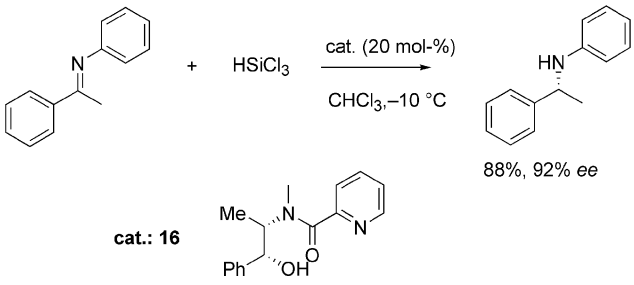
An important contribution to the field came in 2006 from the Matsumura group, who reported that *N*-picolinoylpyrrolidine derivatives can activate trichlorosilane in the reduction of aromatic imines, showing that the *N*-formyl group is not always essential for catalytic activity.[26] *N*-Picolinoyl-(2*S*)-(diphenylhydroxymethyl)pyrrolidine (**15**, Scheme 13) gave the best results, leading to enantioselectivities up to 80%. It was proposed that both the nitrogen atom of picolinoyl group and the carbonyl oxygen play a fundamental role in the coordination of silicon, whereas the hydrogen of the hydroxy group is believed by the authors to be involved in a hydrogen bond with the nitrogen atom of the imine.



Scheme 13. Chiral *N*-picolinoylpyrrolidine derivatives.

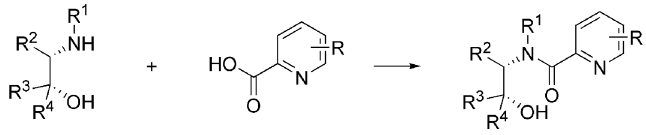
We were especially attracted by Matsumura's work on picolinamides as chiral promoters for imine reductions and decided to focus our attention on a wide class of catalysts prepared by simple condensation of a chiral amino alcohol with picolinic acid or its derivatives. While our investigation led to a patent deposit,[27] Zhang at the same time independently reported the use of ephedrine- and pseudoephedrine-derived picolinamides in the trichlorosilane-promoted reduction of *N*-aryl and *N*-benzyl ketimines in a preliminary communication.[28] With the catalyst **16** (Scheme 14), easily prepared from 2-picolinic acid and (1*R*,2*S*)-ephedrine, a variety of *N*-aryl ketimines and *N*-benzyl ketoimines were

reduced with trichlorosilane in high yields (<93%) and with moderate to excellent *ee* values (<92%) under mild conditions.



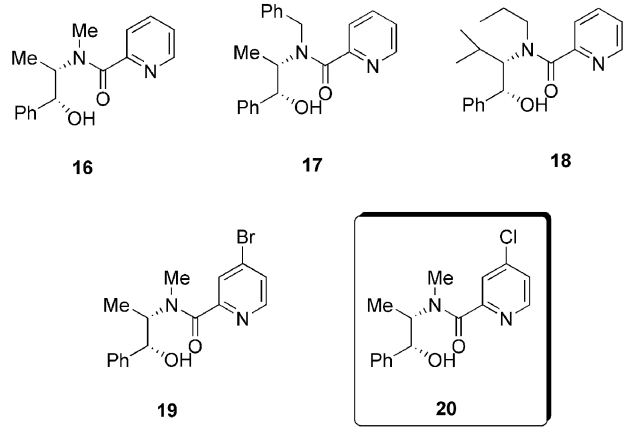
Scheme 14. Ephedrine-derived picolinamide.

Our group systematically investigated this class of organocatalysts.[29] In a single-step procedure, several derivatives were synthesized simply by treatment either of picolinic acid with different enantiomerically pure amino alcohols with mediation by condensing agents or of picolinoyl chloride with the amino alcohols (Scheme 15). In the reduction of the *N*-phenyl imine of acetophenone, selected as model substrate, at 0 °C in dichloromethane in the presence of the *N*-picolinoylamide of (1*R*,2*S*)-ephedrine (**16**, 10 mol-%) the *R* product was isolated after 15 h in quantitative yield and 77% *ee*, in accordance with Zhang's results.



Scheme 15. Synthesis of chiral picolinamides.

The pyridine ring, the free hydroxy group, and *N*-alkyl substitution in the amino alcohol portion were identified as key structural elements necessary to secure good stereocontrol; the effects of different substituents at the nitrogen atom and at the two stereocenters were also studied. Through study of several differently substituted derivatives it was shown that the *N*-benzyl derivative **17** (Scheme 16) catalyzed the reaction with only 10% *ee*, whereas compound **18**, bearing an isopropyl group, was able to promote the reaction, but in lower enantiomeric excess than compound **16** (50% vs. 77% *ee*), confirming ephedrine as the chiral amino alcohol of choice. Lastly, modification of the picolinoyl moiety was studied; a selection of ephedrine derivatives obtained by condensation with picolinic acids bearing different substituents in the 3-, 4-, or 6-positions of the pyridine ring was prepared. It was shown that the introduction of a suitable substituent at the 4-position of the pyridine moiety could improve catalyst efficiency. Indeed, in particular the 4-bromo- and 4-chloropicolinic derivatives **19** and **20** showed remarkable catalytic properties. At 0 °C in dichloromethane with catalyst **20** the chiral amine was obtained in quantitative yield and 83% *ee*; enantioselectivity was increased up to 88% by working in chloroform. A further improvement was observed on performing the reaction at –20 °C, when the enantioselectivity reached 95% with no erosion of the chemical yield, with the reduction product being isolated basically in quantitative yield. Even 1 mol-% of catalyst **20** promoted the reduction in 90% yield in only 2 h.



Scheme 16. Different chiral picolinamides.

The screening of systematically modified organocatalysts of this family led to the identification of the key structural factors that influence their catalytic properties and to the proposal of a tentative model of the stereoselection observed in these reactions promoted by picolinamide derivatives. In this model, the pyridine nitrogen and the CO amidic group of picolinamide activate trichlorosilane by coordination; the hydrogen atom of the hydroxy group plays a fundamental role in coordinating the imine through hydrogen bonding. The presence of two stereogenic centers with the correct relative configuration, as in (1*R*,2*S*)-(–) ephedrine, on the amino alcohol moiety is necessary for stereodirection of the imine attack by trichlorosilane.

The methyl groups on the amide nitrogen and on the stereocenter in the 2-position in the amino alcohol chain are apparently of the optimum size for maximizing the enantiodifferentiation of the process. In the proposed stereoselection model **A** (Figure 3), leading to the major enantiomer, the steric interaction between the pyridine ring and the *N*-aryl group is much less significant than that observed in adduct **B**, which is therefore disfavored.

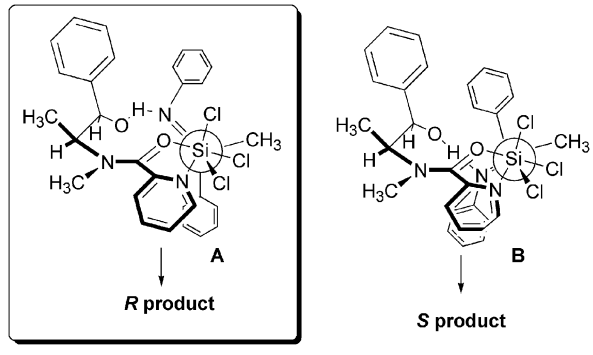
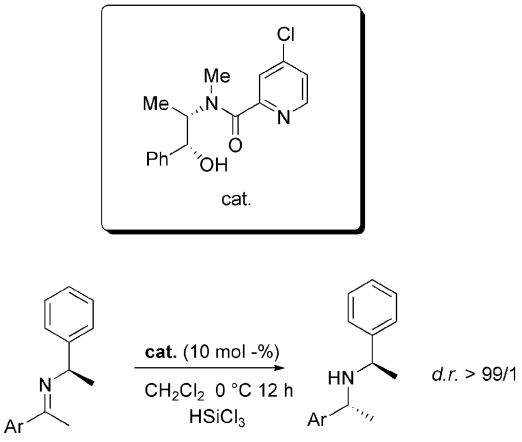


Figure 3. Proposed model of stereoselection for reduction of *N*-aryl ketoimines.

Good results were also obtained in the enantioselective reduction of *N*-alkyl imines,[30] a transformation only recently accomplished organocatalytically.[31] Ephedrine-based picolinamides promoted the reaction with the *N*-butyl imine of acetophenone in excellent yields and with high stereoselectivities: under the best conditions (chloroform, 0 °C, 24 h) the 4-chloropicolinic derivative **20** promoted the reduction in 98% yield and with 91% *ee*.

The organocatalysts have several positive features: i) they are easily prepared, by single condensation steps, from commercially available compounds, ii) they are low-cost catalysts, the sources of stereocontrol being very cheap and readily available amino alcohols such as ephedrine, and iii) the reductions of C=N bonds are performed under very mild reaction conditions and with extremely simple experimental procedures that allow highly pure products to be obtained after aqueous workup. A very convenient enantioselective organocatalytic three-component methodology was also developed; the reductive amination process, starting simply from a mixture of a ketone and an arylamine, gives easy access to chiral amines with a straightforward experimental methodology. All these positive features also make this catalytic method suitable in principle for large-scale applications; its synthetic potentiality was indeed demonstrated by the metal-free catalytic procedure's successful employment in the preparation of (*S*)-metolachlor, a potent and widely used herbicide.[29]

To improve the selectivity of the process further, trichlorosilane-mediated reductions were carried out with ketoimines derived from (*R*)-1-phenylethylamine (Scheme 17). 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.[32] Optimization of the reaction conditions showed that the best results were obtained at –50 °C in chlorinated solvents in the presence of DMF (6 equiv.). Under these conditions, *N*-α-methyl benzyl imines of methyl aryl ketones with different electronic properties were effectively reduced to the corresponding secondary amines in quantitative yields, with 90–99% diastereoselectivities.

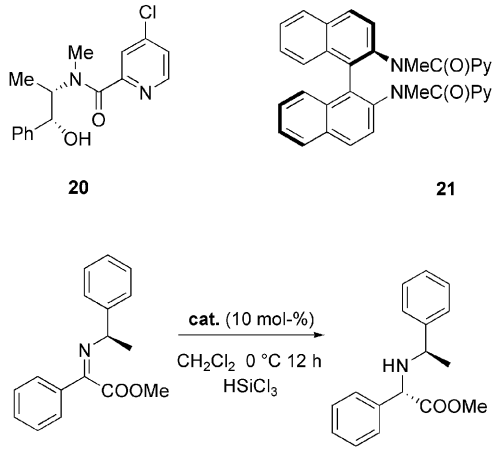


Scheme 17. Stereoselective catalytic reduction of chiral imines.

Control of the stereoselectivity was total when the chiral picolinamide **20** was employed as catalyst, however, providing a demonstration of the existence of a cooperative effect between catalyst **20** and the (*R*)-methyl benzyl residue at the imine nitrogen.[33]

The methodology was extended to the synthesis of enantiomerically pure secondary amines of either C_1 or C_2 symmetry. An imine derived from methyl isobutyl ketone was also readily reduced in >98% yield in the presence of catalyst **20** to afford an enantiomerically pure direct precursor of (*R*)-(1,2-dimethylpropyl)amine. The methodology is attractive because the combination of a low-cost, easy to make metal-free catalyst and an inexpensive chiral auxiliary allowed the reduction of ketimines with different structural features, often with total control of the stereoselectivity.

The wide applicability was also demonstrated in the preparation of α-amino esters (Scheme 18). Catalysts **20** promoted the reduction of the *N*-benzyl iminoester in quantitative yield and up to 71% *ee*. The reduction of *N*-α-methyl benzyl imines of methyl phenylglyoxylate at 0 °C in dichloromethane with the same catalyst, however, afforded the corresponding chiral amino ester in 73% yield and 91% diastereoisomeric excess.



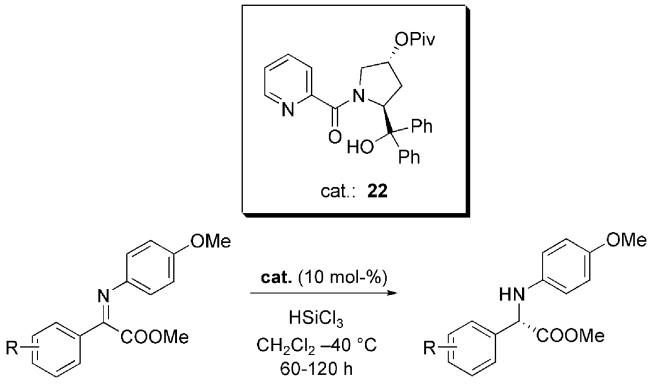
Scheme 18. Stereoselective catalytic reduction of chiral imino esters.

Our group has also developed a second class of chiral picolinamides as efficient chiral organocatalysts for trichlorosilane-mediated reactions. A very short route to chiral Lewis bases was envisaged in reactions between pyridine-2-carboxylic acid and commercially available enantiomerically pure diamines.[34] This straightforward approach was extended to binaphthyldiamine derivatives, commercially available in both enantiomeric forms. Picolinic acid was condensed with (*R*)-*N*,*N*′-dimethyl-1,1′-binaphthyl-2,2′-diamine to afford the catalyst **21** in 73% yield after chromatographic purification.

The mild reaction conditions and the general applicability of the catalyst to a wide variety of substrates are all positive features of this new family of organocatalysts. Notably, binaphthyldiamine-derived bis-picolinamides showed remarkable activity in reductions of *N*-aryl (up to 83% *ee*), *N*-benzyl (up to 87% *ee*), and *N*-alkyl ketoimines (up to

87% *ee*), typically at 0 °C.[35] Furthermore, the catalyst **21** was also employed, although with less success (71% *ee*), in imine reductions of *N*-benzyl imines of keto esters.[33]

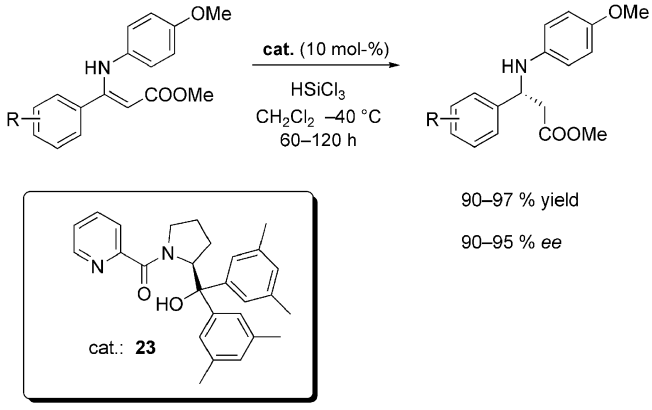
Zhang also very recently reported an efficient protocol for the organocatalytic synthesis of α-amino esters.[36] Novel chiral Lewis base organocatalysts derived from *trans*-4-hydroxy-L-proline were developed (Scheme 19); notably, the catalyst of choice, compound **22**, exhibited only moderate enantioselectivities in the hydrosilylation of *N*-aryl β-enamino esters, but promoted the hydrosilylation of α-imino esters with high enantioselectivities (up to 93% *ee* values). The introduction of a bulky group at C4 of the pyrrolidine ring was decisive for the obtaining of high stereoselectivities. The hydroxy group was functionalized with various bulky groups: whereas benzylation, trimethylsilylation, and isovalerylation of the hydroxy group only caused marginal changes in the enantioselection, an increase in enantioselectivity was observed when the *O*-pivaloyl catalyst **22** was employed. In exploring the applicability of the catalyst to imines of differently substituted aryl glyoxylates it was found that both *para*- and *meta*-functionalized substrates could be reduced with good enantioselectivity (80–93% *ee* values), whereas *ortho* substitution caused a decrease in stereoselection (50–60% *ee*).



Scheme 19. Catalytic reduction of α-imino esters.

The same group has also employed picolinamide derivatives of prolinol to perform efficient enamine reduction (Scheme 20).[37]

Chiral *N*-picolinoylpyrrolidine derivatives and *N*-picolinoylephedrine were evaluated in the hydrosilylation of methyl (*Z*)-3-phenyl-3-(phenylamino)acrylate, leading to the corresponding reduction product with good enantioselectivities in chloroform at 0 °C. The enantioselectivity increased slightly along with increasing size of the aryl groups in the catalysts. The best yield and enantioselectivity were obtained with the catalyst **23** (Scheme 20) at –30 C for 48 h. Under the optimized conditions, the generality of the Lewis-base-organocatalyzed hydrosilylations of various β-enamino esters was examined. In the presence of **23** (10 mol-%), β-enamino esters were reduced in high yields and with enantioselectivities typically ranging from 90–95% *ee*. It is worth mentioning that *N*-acyl β-enamino esters were totally inactive in this organocatalytic system. The



Scheme 20. Catalytic reduction of β-enamino esters.

reaction is believed to proceed through the imine tautomer rather than the enamine tautomer. In the proposed mechanism the nitrogen atom of the pyridine ring and the carbonyl oxygen atom of the catalyst are coordinated to Cl_3SiH, while the imine is activated by the hydroxy group of the Lewis base through hydrogen bonding. It has also been hypothesized that stabilization due to arene–arene interactions between the aromatic systems of the catalyst and the substrate may occur.

2.3 Miscellaneous Derivatives

In 2006 Malkov and Kočovský developed novel chiral Lewis bases, such as oxazolines containing isoquinoline fragments. The catalyst **24** was employed in reductions of aromatic ketones and imines with trichlorosilane, providing the products with good levels of enantioselectivity (Scheme 21).[38]

The maximum levels of enantioselectivity achieved were 87% for the reduction of ketones and 92% for reduction of ketimines. The authors hypothesized that coordination of the trichlorosilane by the catalyst would generate a chiral hexacoordinate silicon species that would act as the actual reducing species. With a ketone as the reactive substrate, further activation would be provided by coordination of a molecule of trichlorosilane by the carbonyl oxygen (Figure 4).

At the end of 2006 a novel designed catalyst featuring a sulfinamide group as the chiral element (Scheme 22) was reported by Sun and co-workers.[39] This family of organocatalysts was found to be able to activate trichlorosilane for the stereoselective reduction of *N*-aryl ketimines with good yields and enantioselectivities.

On the assumption that the mechanism would involve two molecules of Lewis base for the activation of $HSiCl_3$, a novel chiral bis-sulfinamide was developed.[40] After a screening of different derivatives, the compound of choice was found to be a bis-sulfinamide bearing a five-methylene linkage (Scheme 23). Catalyst **26** promoted the reduction of the *N*-phenyl imine of acetophenone as a model substrate with 96% *ee*.

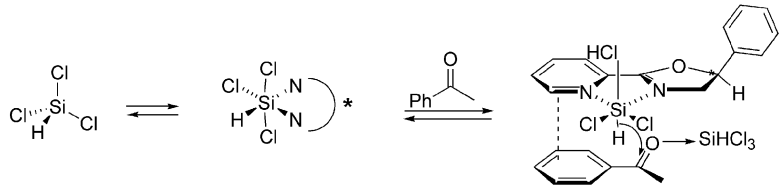
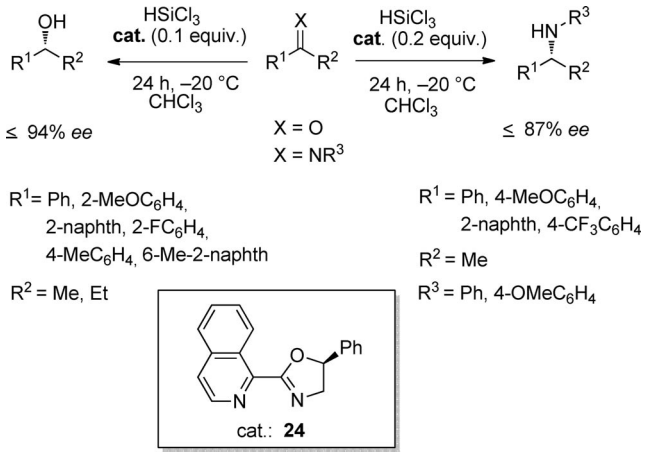
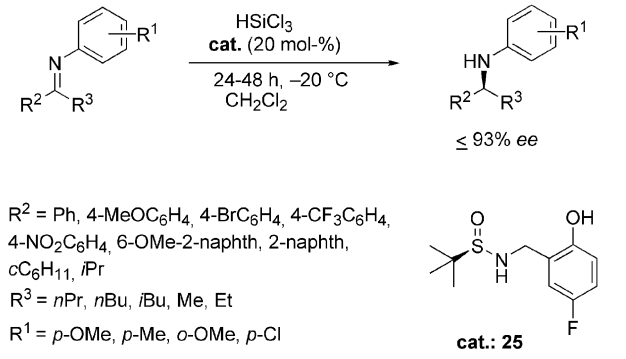


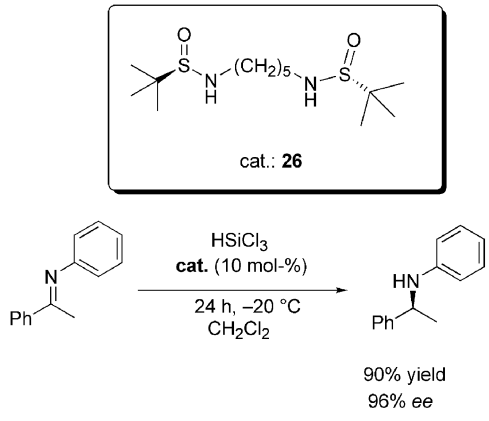
Figure 4. Proposed mechanism for reductions promoted by catalyst **24**.



Scheme 21. Stereoselective catalytic reduction promoted by an oxazoline-based chiral catalyst.

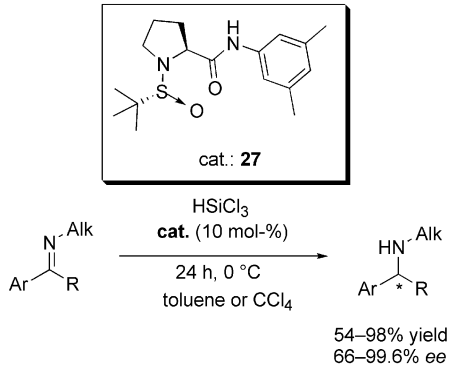


Scheme 22. A chiral sulfinamide as a promoter of imine reductions.



Scheme 23. Novel chiral bis-sulfinamide derivative.

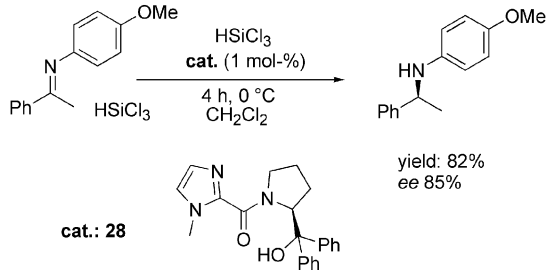
The sulfinamide **27** (Scheme 24) is the most recent catalyst prepared by the Sun group.[31] This derivative incorporates two different elements responsible for the stereochemical control of the process: a sulfinamide group with a stereogenic sulfur atom and a *N*-aryl prolinamide.



Scheme 24. Novel chiral sulfinamide derivative.

This system was employed for reductions of aromatic *N*-alkyl ketimines in the presence of trichlorosilane, providing the corresponding amines with good enantioselectivities (up to 99.6% *ee*) and in high yields.

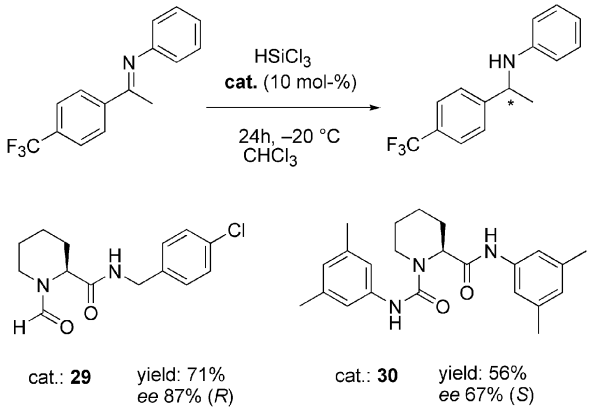
Jones has recently synthesized different bifunctional catalysts containing imidazole rings.[41] The catalyst **28** (Scheme 25), prepared by condensation of diphenyl-(*S*)-prolinol and 1-methylimidazole-2-carboxylate, was evaluated in the asymmetric reductions of a variety of ketimines with low catalyst loadings.



Scheme 25. Imidazole-containing prolinamide.

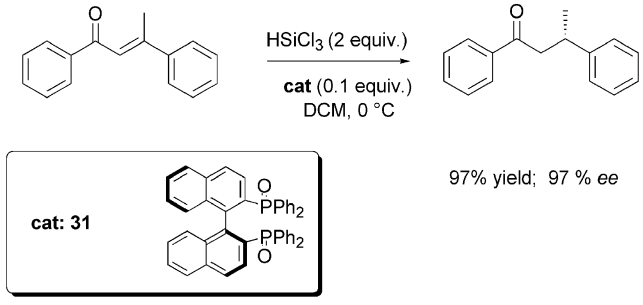
Last year the Ibarra group investigated a series of chiral *N*-formyl derivatives of L-pipecolinic amides.[42] Their catalytic properties in the presence of trichlorosilane were assessed in reductions of the imine obtained from 4′-(trifluoromethyl)acetophenone and aniline (Scheme 26). In that paper the aim of the authors was to explain the role of

the structural components of the systems on the sense of stereocontrol. According to the authors, the obtained results suggest that the asymmetric induction is very highly dependent on the particular structural features of the catalyst. With the *N*-formamide **29** the stereochemical preference was for the *R* enantiomer: in this case, arene–arene interactions and hydrogen bonding between ligand and the nitrogen atom of the imine are important for the enantiodifferentiation process. Instead, when employing catalyst **30** (a urea-amide derivative), the authors verified an inversion of the stereochemical preference. The mechanistic studies demonstrated a new interaction between the N–H group of the urea and the basic nitrogen of the imine.



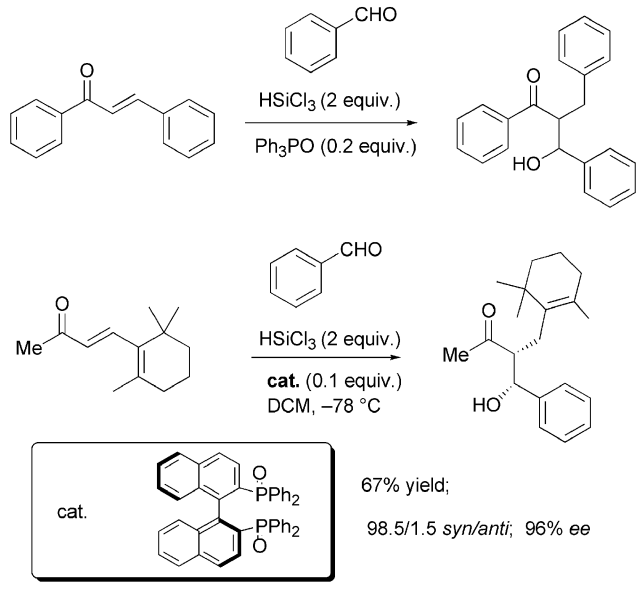
Scheme 26. New derivatives of pipecolinic acid.

Nakajima's group has recently reported the use of chiral phosphane oxides as suitable Lewis bases for activating trichlorosilane in stereoselective transformations, with use of trichlorosilane in conjugate reductions of α,β-unsaturated ketones in the presence of catalytic amounts of chiral Lewis bases (Scheme 27). The reduction of 1,3-diphenylbutenone promoted by catalytic amounts of 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl dioxide (BINAPO, **31**) at 0 °C was successfully accomplished, leading to the corresponding saturated compound in 97% yield and a rather surprising, but very good, 97% *ee*.[43a]



Scheme 27. Reduction of unsaturated ketones.

An alternative methodology for organocatalytic conjugate reductions of enones and subsequent reactions with aldehydes, to achieve reductive aldol reactions, was developed (Scheme 28).[43a] The idea was to activate the silane with a suitable Lewis base to effect the 1,4-reduction via a six-membered transition state; then, with the assistance of the same Lewis base, the generated trichlorosilyl enolate should react with the electrophilic aldehyde.



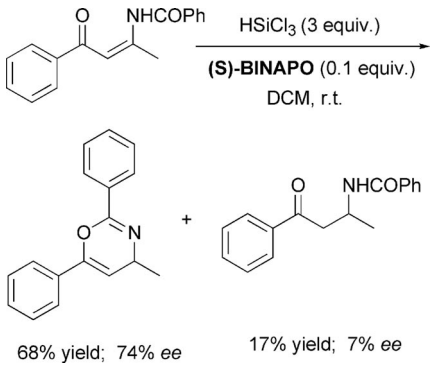
Scheme 28. (*S*)-BINAPO-catalyzed reductive aldol condensation.

Triphenylphosphane oxide was shown to be able to catalyze the three-component reaction of chalcone, benzaldehyde, and trichlorosilane (reductive aldol reaction) to afford the corresponding aldol product in 78% yield. Preliminary experiments with (*S*)-BINAPO as chiral Lewis base were very promising in term of stereocontrol.

2,2′-Bis(diphenylphosphanyl)-1,1′-binaphthyl dioxide (**31**) gave even more appealing results in the reductive aldol reduction of β-ionone with benzaldehyde, in which a very high *syn* stereoselectivity was observed along with 96% enantioselectivity for the *syn* isomer.

A great variety of Lewis-base-catalyzed stereoselective transformations are currently under investigation, and novel synthetic methodologies have been developing as well. One example is from a very recent report in which it was unexpectedly found, in a study of the stereoselective synthesis of *N*-acylated β-amino ketones, that optically active 4*H*-1,3-oxazines could be directly obtained through reductive cyclization of *N*-acylated β-amino enones in the presence of trichlorosilane and chiral Lewis base catalysts (Scheme 29).[43b] The reaction between the (*Z*)-*N*-benzoyl enone derived from 3-amino-1-phenylbutane-1,3-dione and trichlorosilane in the presence of catalytic amounts of BINAPO surprisingly afforded the 4*H*-1,3-oxazine as major product in 56% yield and with 71% enantioselectivity. Similar yields and stereoselectivity (up to 81% *ee*) were obtained on extension of the reaction to five other substrates; of the different chiral phosphane oxides investigated BINAPO was found to give the best performances. From some preliminary experiments it was observed that trichlorosilane acts not only as a reductant, but also as a dehydrating agent. Different ratios of oxazine and the expected β-keto amide were formed in the reaction, depending on

the experimental conditions. Interestingly, it was observed that the two products were obtained with different levels of stereoselection, and sometimes even with different absolute configurations.



Scheme 29. BINAPO-catalyzed synthesis of oxazines.

The result was tentatively explained by assuming that the oxazine was not derived from the ketoamide by simple dehydration. It was proposed that the 4*H*-1,3-oxazine was generated through the conjugate reduction of the *N*-acylated β-amino enone, followed by cyclization of the resulting enolate and elimination of $HOSiCl_3$, whereas the ketoamide originates from the 1,2-reduction of the *N*-acyl imine generated through equilibration of the enamide. Further studies will be necessary for full understanding of the reaction mechanism, in order to design more efficient catalysts.

3. Conclusions

Chiral amines are ubiquitous in a variety of bioactive molecules such as alkaloids, natural products, drugs, pharmaceuticals, and agrochemicals, and so it is not surprising that the development of catalytic stereoselective processes for the preparation of enantiomerically enriched amines is attracting increasing interest both at the academic and at the industrial level. In this context the use of substoichiometric amounts of an organic compound of relatively low molecular weight and simple structure that is capable of promoting reactions in the absence of costly and possibly toxic transition-metal-based catalyst is very attractive. This is the case for trichlorosilane-mediated reactions, in which the use of different chiral Lewis bases has allowed many stereochemically efficient transformations to be developed. It must be considered that $HSiCl_3$ has a number of advantages: it serves as a starting material in the silicon industry and is manufactured in bulk, so that its price is reduced almost to the level typical for common organic solvents. Although trichlorosilane is sensitive to water, the implications are rather modest and the reagent can be easily handled by using standard procedures for moisture-sensitive materials with minimum precautions (in principle, a $CaCl_2$ drying tube could be used instead of an inert atmosphere of nitrogen or argon); the standard reaction workup with aqueous $NaHCO_3$ produces innocuous inorganic materials, namely NaCl and silica, in a protocol that involves relatively low environmental risk.

In conjunction with the low catalyst loadings, all of these features suggest that organocatalyzed reductions with $HSiCl_3$ may become an attractive alternative to the established industrial technologies for asymmetric reductions.

Acknowledgments

Financial support by the Ministero dell' Istruzione, Università e ricerca (MIUR) (Nuovi metodi catalitici stereoselettivi e sintesi stereoselettiva di molecole funzionali) is gratefully acknowledged.

[1] H.-J. Federsel, *Drug News Perspectives* **2008**, *21*, 193. See also H.-J. Federsel, *Acc. Chem. Res.* **2009**, *42*, 671, and references cited therein.
[2] P. T. Anastas, J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press, New York, **1998**. See also: D. J. C. Constable, P. J. Dunn, J. D. Hayler, G. R. Humphrey, J. L. Leazer Jr., R. J. Linderman, K. Lorenz, J. Manley, B. A. Pearlman, A. Wells, A. Zaks, T. Y. Zhang, *Green Chem.* **2007**, *9*, 411.
[3] A. Berkessel, H. Groger (Eds.), *Asymmetric Organic Catalysis*, Wiley-VCH, Weinheim, **2005**.
[4] For recoverable catalysts, see: a) K. J. Ding, F. J. K. Uozomi (Eds.), *Handbook of Asymmetric Heterogeneous Catalysts*, Wiley-VCH, Weinheim, **2008**; b) M. Benaglia (Ed.), *Recoverable and Recyclable Catalysts*, Wiley-VCH, **2009**.
[5] For reductions mediated by chiral phosphoric acids, see: a) S. J. Connon, *Org. Biomol. Chem.* **2007**, *5*, 3407; b) T. Akiyama, *Chem. Rev.* **2007**, *107*, 5744; c) M. Terada, *Chem. Commun.* **2008**, 4098.
[6] Review: M. Benaglia, S. Guizzetti, L. Pignataro, *Coord. Chem. Rev.* **2008**, *252*, 492.
[7] Review: S. E. Denmark, G. L. Beutner, *Angew. Chem. Int. Ed.* **2008**, *47*, 1560.
[8] a) F. Iwasaki, O. Onomura, K. Mishima, T. Maki, Y. Matsumura, *Tetrahedron Lett.* **1999**, *40*, 7507; b) F. Iwasaki, O. Onomura, K. Mishima, T. Kanematsu, T. Maki, Y. Matsumura, *Tetrahedron Lett.* **2001**, *42*, 2525.
[9] A. V. Malkov, A. Mariani, K. N. MacDougal, P. Kočovský, *Org. Lett.* **2004**, *6*, 2253.
[10] A. V. Malkov, S. Stončius, K. N. MacDougal, A. Mariani, G. D. McGeoch, P. Kočovský, *Tetrahedron* **2006**, *62*, 264.
[11] A. V. Malkov, M. Figlus, S. Stončius, P. Kočovský, *J. Org. Chem.* **2009**, *74*, 5839.
[12] A. V. Malkov, K. Vranková, R. C. Sigerson, S. Stončius, P. Kočovský, *Tetrahedron* **2009**, *65*, 9481.
[13] a) A. V. Malkov, M. Figlus, S. Stoncius, P. Kocovský, *J. Org. Chem.* **2007**, *72*, 1315; b) A. V. Malkov, M. Figlus, P. Kocovský, *J. Org. Chem.* **2008**, *73*, 3985.
[14] A. V. Malkov, M. Figlus, G. Cooke, S. T. Caldwell, M. R. Prestly, G. Rabani, P. Kočovský, *Org. Biomol. Chem.* **2009**, *7*, 1878.
[15] A. V. Malkov, M. Figlus, M. R. Prestly, G. Rabani, G. Cooke, P. Kočovský, *Chem. Eur. J.* **2009**, *15*, 9651.
[16] M. Figlus, S. T. Caldwell, D. Walas, G. Yesilbag, G. Cooke, P. Kočovský, A. V. Malkov, A. Sanyal, *Org. Biomol. Chem.* **2010**, *8*, 137.
[17] A. V. Malkov, S. Stončius, P. Kočovský, *Angew. Chem. Int. Ed.* **2007**, *46*, 3722.
[18] A. V. Malkov, S. Stončius, K. Vranková, M. Arndt, P. Kočovský, *Chem. Eur. J.* **2008**, *14*, 8082.
[19] Y. Matsumura, K. Ogura, Y. Kouchi, F. Iwasaki, O. Onomura, *Org. Lett.* **2006**, *8*, 3789.
[20] C. Baudequin, D. Chaturvedi, S. B. Tsogoeva, *Eur. J. Org. Chem.* **2007**, 2623.

[21] Z. Y. Wang, S. Wei, C. Wang, J. Sun, *Tetrahedron: Asymmetry* **2007**, *18*, 705.
[22] Z. Wang, X. Ye, S. Wei, P. Wu, A. Zhang, J. Sun, *Org. Lett.* **2006**, *8*, 999.
[23] L. Zhou, Z. Wang, S. Wei, J. Sun, *Chem. Commun.* **2007**, 2977.
[24] Z. Wang, M. Cheng, P. Wu, S. Wei, J. Sun, *Org. Lett.* **2006**, *8*, 3045.
[25] Z. Zhang, P. Rooshenas, H. Hausmann, P. R. Schreiner, *Synthesis* **2009**, *9*, 1531.
[26] O. Onomura, Y. Kouchi, F. Iwasaki, Y. Matsumura, *Tetrahedron Lett.* **2006**, *47*, 3751.
[27] S. Guizzetti, M. Benaglia, European Patent Application November 30 **2007**; PCT/EP/2008/010079, Nov. 27, **2008**. WO2009068284 (A2), 2009–06–04.
[28] H. Zheng, J. Deng, W. Lin, X. Zhang, *Tetrahedron Lett.* **2007**, *48*, 7934.
[29] S. Guizzetti, M. Benaglia, R. Annunziata, F. Cozzi, *Tetrahedron* **2009**, *65*, 6354–6363.
[30] S. Guizzetti, M. Benaglia, European Patent Appl. n. EP07023240.0, September 22, **2008**.
[31] C. Wang, X. Wu, L. Zhou, J. Sun, *Chem. Eur. J.* **2008**, *14*, 8789.
[32] S. Guizzetti, C. Biaggi, M. Benaglia, G. Celentano, *Synlett* **2010**, 134–136.
[33] S. Guizzetti, M. Benaglia, S. Rossi, *Org. Lett.* **2009**, *11*, 2928–2931.
[34] S. Guizzetti, M. Benaglia, F. Cozzi, S. Rossi, G. Celentano, *Chirality* **2009**, *21*, 233–238.
[35] S. Guizzetti, M. Benaglia, G. Celentano, *Eur. J. Org. Chem.* **2009**, 3683–3687.
[36] Z.-Y. Xue, Y. Jiang, W.-C. Yuan, X.-M. Zhang, *Eur. J. Org. Chem.* **2010**, 616.
[37] H.-J. Zheng, W.-B. Chen, Z.-J. Wu, J.-G. Deng, W.-Q. Lin, W.-C. Yuan, X.-M. Zhang, *Chem. Eur. J.* **2008**, *14*, 9864. For the use of the same catalyst in ketoimine reduction see: O. Onomura, P. G. Kirira, T. Tanaka, S. Tsukada, Y. Matsumura, Y. Demizu, *Tetrahedron* **2008**, *64*, 7498.
[38] A. V. Malkov, A. J. P. S. Liddon, P. Ramírez-López, L. Bendová, D. Haigh, P. Kočovský, *Angew. Chem. Int. Ed.* **2006**, *45*,1432.
[39] D. Pei, Z. Wang, S. Wei, Y. Zhang, J. Sun, *Org. Lett.* **2006**, *8*, 5913.
[40] D. Pei, Z. Wang, S. Wei, M. Wang, J. Sun, *Adv. Synth. Catal.* **2008**, *350*, 619.
[41] F.-M. Gautier, S. Jones, S. J. Martin, *Org. Biomol. Chem.* **2009**, *7*, 229.
[42] J. F. Collados, M. L. Quiroga-Feijóo, C. Alvarez-Ibarra, *Eur. J. Org. Chem.* **2009**, 3357.
[43] a) M. Sugiura, N. Sato, S. Kotani, M. Nakajima, *Chem. Commun.* **2008**, 4309; b) M. Sugiura, M. Kumahara, M. Nakajima, *Chem. Commun.* **2009**, 3585–3587.

Received: May 20, 2010
Published Online: August 16, 2010

