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Chiral Lewis base promoted trichlorosilane reduction of ketimines. An enantioselective organocatalytic synthesis of chiral amines

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ABSTRACT

The reduction of the carbon–nitrogen double bond is an important transformation. Here we report our studies on a family of chiral organic catalysts able to promote the stereoselective reduction of ketimines with trichlorosilane. The very cheap, metal-free catalysts were easily prepared in one step from commercially available products, namely a chiral aminoalcohol and picolinic acid derivatives. The catalyst structure was extensively modified in a study that allowed to identify an extremely active species, able to promote the reduction on a large variety of substrates with high efficiency (up to 95% ee). A three component methodology has been also developed, where the enantiomerically enriched amine was isolated after performing the reaction by mixing a ketone and an amine in the presence of trichlorosilane and the catalyst. Its synthetic potentiality was demonstrated by employing the present metal-free catalytic procedure in the preparation of (*S*)-metolachlor, a potent and widely used herbicide.

1. Introduction

Chiral amines are ubiquitous in a variety of bioactive molecules such as alkaloids, natural products, drugs, pharmaceuticals and agrochemicals. Therefore it is not surprising that the development of a catalytic stereoselective process for the preparation of enantiomerically enriched amines is attracting an increasing interest both at the academic and the industrial levels.[1] The reduction of ketimines represents a powerful and widely used transformation for the generation of a new nitrogen-bearing stereocenter. However the few efficient chiral catalytic organometallic systems currently available suffer from some drawbacks.[2] Indeed, the catalysts are generally quite expensive species, typically constituted by an enantiomerically pure ligand (whose synthesis may be costly, long and difficult), and a metal species, in many cases a precious and toxic metal, whose leaching can contaminate the product. A solution to some of these problems can be represented by the use of metal-free catalysts. 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.[3]

In this context, the reduction of carbon–nitrogen double bonds has been the subject of an intense research activity that has allowed the development of efficient organocatalytic methods to perform enantioselective imine reductions and reductive amination processes.[4] Two methodologies have been successfully developed; in one approach, 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. However, it must be noted that the procedure involves the use of high molecular weight and quite expensive compounds as catalysts and it requires separation of the oxidized form of the Hantzsch ester from the reaction product.[5] Another methodology exploits trichlorosilane as the reducing species, that needs to be activated by co-ordination with Lewis bases, such as *N*,*N*-dimethylformamide, acetonitrile, trialkylamines, to generate a hexacoordinated hydridosilicate acting as the actual reducing agent.[6] Among the employed Lewis bases activators, *N*-formyl derivative of amino acids have so far played a major role. Derivatives of this type have been shown to promote the reduction, in some cases with high enantioselectivity.[7] Recently other chiral *N*-formamide derivatives were prepared from commercially available (*S*)-pipecolinic acid and enantiopure 2-amino-1,2-diphenylethanol, and successfully employed in the reduction of ketimines.[8] In addition to formamides, it was shown that quinoline, isoquinoline and pyridine-derived chiral oxazolines may be efficient promoters for the addition of trichlorosilane to ketones and imines.[9] The stereoselective reduction of a broad range of *N*-aryl ketimines was also catalyzed in the presence of a chiral sulfinamide featuring a stereogenic sulfur atom.[10] However many of these systems present some drawbacks, due to the stability of the activators, or their difficult synthesis and limited applicability, and to sometimes

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unsatisfactory levels of chemical and stereochemical efficiency. Finally *N*-picolinoylpyrrolidine derivatives were also reported to act as promoters for this reaction.[11]

Despite all these reported methods, however, the development of a really efficient system, of general applicability and suitable for large scale preparations is still a task of extreme interest. It is clear now that organocatalysis has entered a new phase; many fundamental reactions of organic chemistry can now be run in the presence of metal-free promoters, but the challenge today is to design novel organocatalysts of great efficiency, low cost, high stability and capable to promote enantioselective reactions on a wide variety of substrates. In other words, the real challenge is the development of metal-free catalysts of interest for industrial applications.[12]

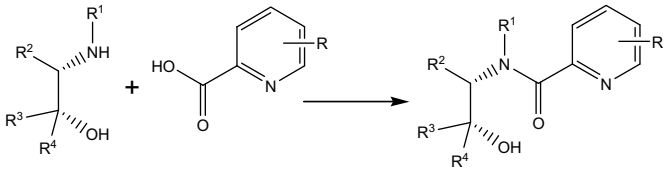
In this context we wish to report here our studies on a low cost catalytic system, easily prepared from commercially available products, able to promote the enantioselective reduction of carbon–nitrogen double bonds with trichlorosilane with great efficiency.

2. Results and discussion

2.1. Catalyst structure/activity study

Our project aimed to the development of structurally simple chiral Lewis bases as catalysts for the enantioselective reduction of imines with trichlorosilane; the catalysts should be obtained by modification of an inexpensive, commercially available, enantiopure material whose manipulation must be kept to minimum.[13] We were specially attracted by Matsumura's work on picolinamides as chiral promoters for the imine reduction[11] and we decided to focus our attention onto a wide class of catalysts prepared by simple condensation of a chiral aminoalcohol with picolinic acid or its derivatives.[14] At that time Zhang reported in a preliminary communication the use of ephedrine and pseudoephedrine-derived picolinamides in the reduction of *N*-aryl and *N*-benzyl ketimines promoted by trichlorosilane.[15]

We decided to study in detail this class of organocatalyst. In a single step procedure several derivatives were synthesized simply by reaction of picolinic acid and different enantiomerically pure amino alcohols mediated by condensing agents or by reaction of picolinoyl chloride and the amino alcohol (see Experimental section) (Scheme 1).



Scheme 1. General scheme for the synthesis of chiral picolinamides.

Some of the structurally diversified organocatalysts synthesized and employed to promote the trichlorosilane reduction of ketimines are reported in Chart 1.

The *N*-phenyl imine of acetophenone was selected as model substrate to investigate the catalytic behaviour of compounds **1**–**21** in the reaction with trichlorosilane under different conditions of solvent and temperature. (Scheme 2) After preliminary experiments, chlorinated solvents were found to be the medium of choice for this kind of transformation.

In a typical procedure, to a stirred solution of catalyst and the imine in the proper solvent and temperature conditions under nitrogen, trichlorosilane was added drop wise by means of a syringe. After usual aqueous work up allowed to isolate the crude product.

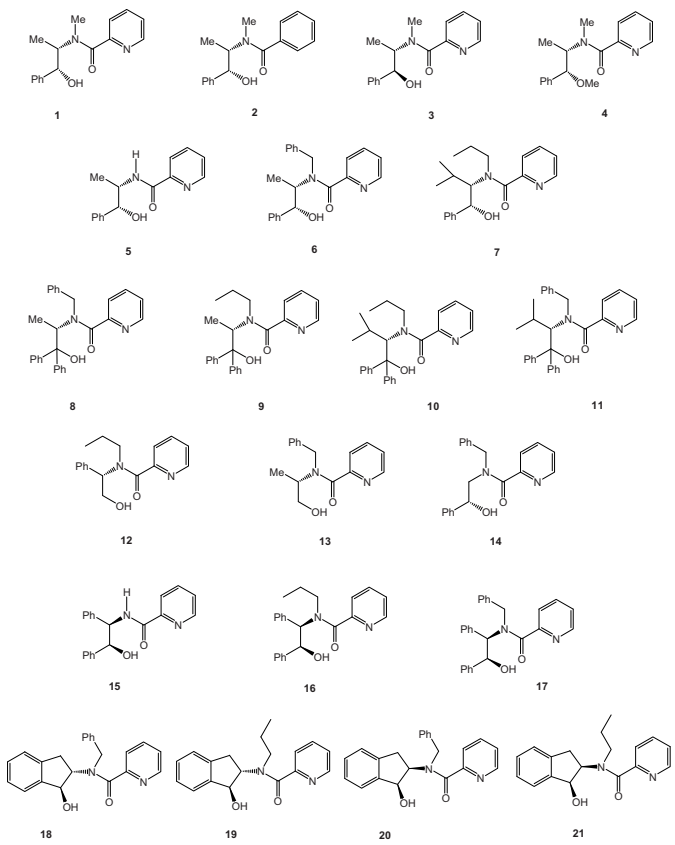
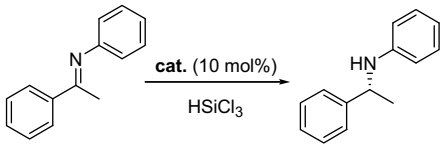


Chart 1. Chiral catalysts for enantioselective reduction of imines.



Scheme 2. Enantioselective reduction of *N*-phenyl imine of acetophenone.

The results of these exploratory experiments are reported in Table 1 and Table 2. By running the reaction at 0 °C in dichloromethane in the presence 10 mol % amount of *N*-picolinoylamide of (1*R*,2*S*)-ephedrine **1** the (*R*) product was isolated after 15 h in quantitative yield and 77% ee (entry 1, Table 1), in accordance with Zhang's result.[15] The high chemical efficiency and the good level of enantioselectivity showed by catalyst **1** are very interesting in light of the low cost of ephedrine as the source of absolute stereocontrol in the reduction. On this basis we undertook a detailed investigation of the structure–activity relationship of this kind of organocatalysts. First benzamide **2** was prepared where the pyridyl group has been replaced by phenyl ring. In the hypothesis that both the nitrogen atom of picolinoyl group and the carbonyl oxygen play a fundamental role in the activation of trichlorosilane by coordination of silicon atom catalyst **2** was expected to perform worse than **1**. Indeed, compound **2** promoted the reaction in 40% yield and only 27% ee.

As already reported[15] the relative stereochemistry of the aminoalcohol stereocenters and the presence of the hydroxyl groups played a decisive role in controlling the stereochemistry; indeed also in our hands the already known catalysts[15] **3** and **4** performed less efficiently. The result seems to point out at an active role of the OH group in controlling the stereochemical outcome of the trichlorosilane mediated reduction, possibly by a H-bond mediated coordination of the imine nitrogen with the hydroxyl

Table 1
Enantioselective reduction of *N*-phenyl imine of acetophenone performed in DCM at 0 °C with 10 mol % amount of catalyst

Entry	Catalyst	Yield[a] (%)	ee[b] (%)
1	**1**	98	77 (*R*)
2	**2**	40	27 (*R*)
3	**3**	98	28 (*R*)
4	**4**	98	59 (*R*)
5	**5**	98	<5
6	**6**	98	11 (*S*)
7	**7**	98	50 (*R*)
8	**8**	76	<5
9	**9**	98	60 (*R*)
10	**10**	41	<5
11	**11**	81	10 (*R*)
12	**12**	94	25 (*R*)
13	**13**	98	21 (*S*)
14	**14**	98	16 (*S*)
15	**15**	98	<5
16	**16**	73	40 (*R*)
17	**17**	98	15 (*S*)
18	**18**	98	10 (*R*)
19	**19**	96	7 (*R*)
20	**20**	98	30 (*R*)
21	**21**	92	37 (*R*)

[a] Yields determined after chromatographic purification.
[b] Enantiomeric excess determined by HPLC on chiral stationary phase.

Table 2
Enantioselective reduction of *N*-phenyl imine of acetophenone performed with 10 mol % amount of catalyst

Entry	Catalyst	Solvent	Temp	Yield[a] (%)	ee[b] (%)
1	**1**	DCM	0 °C	98	77 (*R*)
2	**1**	$CHCl_3$	0 °C	98	82 (*R*)
3	**22**	DCM	0 °C	8	77 (*R*)
4	**23**	DCM	0 °C	97	71 (*R*)
5	**23**	DCM	−20 °C	91	75 (*R*)
6	**23**	$CHCl_3$	−20 °C	95	78 (*R*)
7	**24**	$CHCl_3$	−20 °C	98	73 (*R*)
8	**25**	$CHCl_3$	−20 °C	47	61 (*R*)
9	**26**	$CHCl_3$	−20 °C	49	57 (*R*)

[a] Yields determined after chromatographic purification.
[b] Enantiomeric excess determined by HPLC on chiral stationary phase.

group of the aminoalcohol. Finally the catalyst obtained starting from (L)-nor-ephedrine **5** was tested and it showed to promote the reduction with excellent chemical yield but without any stereocontrol (entry 5, Table 1).

Having identified the pyridine ring, free hydroxyl group and *N*-alkyl substitution in the aminoalcohol portion as key structural elements, necessary to secure good stereocontrol, the effect of different substituents at the nitrogen atom and at the two stereocenters was then studied. *N*-Benzyl derivative **6** catalyzed the reaction in only 10% ee (isomer *R* was obtained as major isomer), while compound **7** bearing an isopropyl group was able to afford the (*S*) isomer in lower enantiomeric excess than compound **1** (50% vs 77%, entries 7 vs 1).

From the data collected with catalysts **8**–**11** it was shown that only structure **9** was able to assure a good level of enantioselectivity (60% ee, entry 9, Table 1), that however was slightly inferior than that observed with **1**. This clearly indicates once again that a *N*-alkyl derivative behaved better than a *N*-benzyl one and that increasing the steric hindrance at the stereocenter bearing the OH group does not bring to any improvement of enantioselectivity. The activity of molecules **12**–**14** with one stereocenter only was also investigated but no improvement in the stereoselectivity was observed (entries 12–14). The same held true with compounds **15**–**17** obtained by condensation of picolinic acid with 1,2-diphenyl amino ethanol. Finally very disappointing results were observed also working with both *trans* and *cis* enantiomerically pure aminoindanol derivatives **18**–**21** (entries 18–21, Table 1).

We moved our attention also to the modification of the picolinoyl moiety. A selection of ephedrine-derivatives obtained by condensation with picolinic acids bearing different substituents in positions 3, 4 or 6 of the pyridine ring is shown in Chart 2. The new catalysts were evaluated in the usual test reduction of acetophenone imine under the same experimental conditions employed for compounds **1**–**21**.

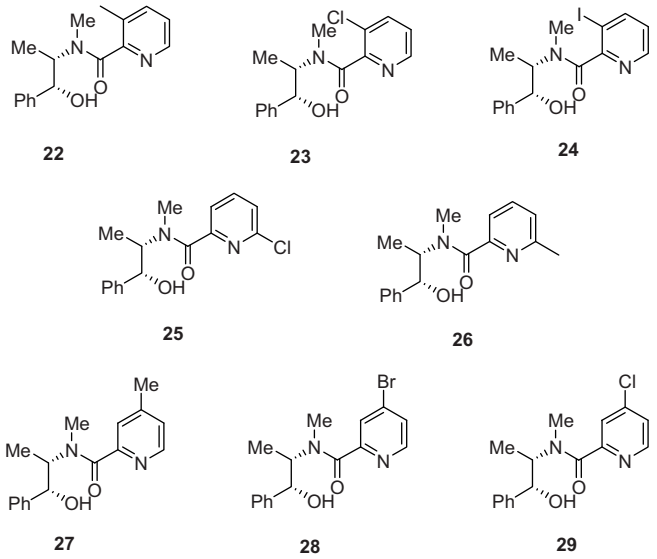


Chart 2. Modified Chiral catalysts for reduction of imines.

From the results collected in Table 2 it was clear that a substituent in position 3 did not seem to influence the reactivity or the stereochemical behavior of the catalyst. Indeed compounds **22**, **23** and **24**, bearing a 3-methyl, chloro and iodo substituted pyridine ring respectively, promoted the reaction in similar yields and enantioselectivities comparable to those of catalyst **1** (up to 77% ee). As general observation these catalysts usually performed better in chloroform than in dichloromethane (see for example entry 1 vs 2 in Table 2, but also entry 5 vs 6), while the lowering of the reaction temperature often did not bring any substantial modification in the enantioselectivity and not in a predictable way.[16]

A substitution at the 6 position on the pyridine was shown to be deleterious for the stereochemical efficiency of the catalyst; 6-chloro and 6-methyl picolinamides **25** and **26** promoted the reduction with lower enantioselectivities than **1** (entries 8–9, Table 2).

On the other hand the introduction of an appropriate substituent in the 4 position of the pyridine moiety was decisive to improve catalyst efficiency. Indeed specially 4-bromo and 4-chloro picolinic derivatives **28** and **29** showed remarkable catalytic properties (Table 3). Working at 0 °C in dichloromethane with catalyst **29** 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 by performing the reaction at −20 °C when enantioselectivity reached 95% with no

Table 3
Enantioselective reduction of *N*-phenyl imine of acetophenone performed with 10 mol % amount of catalyst

Entry	Catalyst	Solvent	Temp	Yield[a] (%)	ee[b] (%)
1	**27**	$CHCl_3$	−20 °C	98	80 (*R*)
2	**29**	DCM	0 °C	98	83 (*R*)
3	**29**	$CHCl_3$	0 °C	98	88 (*R*)
4	**29**	$CHCl_3$	−20 °C	98	95 (*R*)
5	**28**	$CHCl_3$	−20 °C	95	93 (*R*)

[a] Yields determined after chromatographic purification.
[b] Enantiomeric excess determined by HPLC on chiral stationary phase.

erosion of the chemical yield, being the reduction product isolated basically in quantitative yield (entries 2–4 of Table 3). Also 4-bromo picolinic acid derivative **28** was able to promote the reaction with high chemical and stereochemical efficiency (93% ee, entry 5).

It is worth mentioning that not only the stereochemical ability but also the chemical activity of 4-chloropicolinic acid derivative **29** was superior to that of picolinamide **1**. The performances of the two catalysts at different loadings were investigated and the results collected in Table 4. When the ketimine reduction was performed at 0 °C in chloroform in the presence of 10 mol % amount of catalyst **1** the product was isolated in 83% ee; by lowering the catalyst loading picolinamide of (L) ephedrine still showed to efficiently catalyze the reaction even in 5% or even 1 mol % amount, affording the chiral amine in 88% and 86% yield respectively after 15 h; however a small but significant decrease of enantioselectivity was observed, from 83% to 78% and 70% (entries 1, 3 and 4 of Table 4). 4-Chloropicolinic acid derivative **29** proved to be a superior catalyst, able to maintain a very high chemical efficiency and a satisfactory stereoselectivity even at low catalyst loadings. Indeed by employing 5 mol % amount of **29** it was possible to obtain the product in 93% yield after only 2 h and unchanged enantioselectivity (entry 5, Table 4).

Table 4
Catalyst efficiency of compounds **1** and **29** in chloroform in the reduction of *N*-phenyl imine of acetophenone

Entry	Catalyst	Cat. Load.	Time	Temp	Yield[a] (%)	ee[b] (%)
1	**1**	10%	15 h	0 °C	98	83 (*R*)
2	**29**	10%	15 h	0 °C	98	88 (*R*)
3	**1**	5%	15 h	0 °C	88	78 (*R*)
4	**1**	1%	15 h	0 °C	86	70 (*R*)
5	**29**	5%	2 h	0 °C	93	88 (*R*)
6	**29**	1%	2 h	0 °C	90	86 (*R*)
7	**29**	10%	15 h	−20 °C	98	95 (*R*)
8	**29**	1%	15 h	−20 °C	98	88 (*R*)
9	**29**	1%	4 h	−20 °C	77	90 (*R*)

[a] Yields determined after chromatographic purification.
[b] Enantiomeric excess determined by HPLC on chiral stationary phase.

Even by working with 1 mol % amount catalyst **29** offered a really interesting performance, promoting the reduction in 90% yield after only 2 h (entry 6, Table 4). By comparing the catalytic behavior of catalysts **1** and **29** it was observed once again that while the use of 1 mol % of catalyst **1** at −20 °C did not bring to any improvement in the enantioselectivity, 4-chloropicolinic acid derivative **29** maintained a high level of efficiency leading to the product after only 4 h in 77% yield and still 90% ee (entry 9, Table 4).

The screening of systematically modified organocatalysts of this family led to identify the key structural factors that influence their catalytic properties and to propose a tentative model of stereoselection observed in the reaction promoted by picolinamide derivatives. In this model pyridine nitrogen and CO amidic group of picolinamide activate trichlorosilane by coordination; the hydrogen atom of hydroxyl group plays a fundamental role in coordinating the imine through hydrogen bonding. The presence of two stereogenic centers on the aminoalcohol moiety with the correct relative configuration such as in (1*R*,2*S*)-(−) ephedrine is necessary to stereodirect the imine attack by trichlorosilane. The methyl groups on the amide nitrogen and on the stereocenter in position 2 of the aminoalcohol chain apparently have the optimum size for maximizing the enantiodifferentiation of the process. In the proposed stereoselection model **A**, leading to the major enantiomer, the steric interaction between the pyridine ring and *N*-aryl group is much less significant than that observed in adduct **B**, that is thus disfavored.[17]

The importance of the role played by the substituent at the imine nitrogen was supported by the observation that the same organocatalysts were able to promote the enantioselective reduction of aryl-alkyl ketones in lower enantioselectivity Figure 1 For instance the reaction of acetophenone with trichlorosilane at 0 °C in chloroform in the presence of **1** or **29** afforded the corresponding chiral alcohol in 86% yield and 65% ee, and 80% yield and 66% ee, respectively.[18]

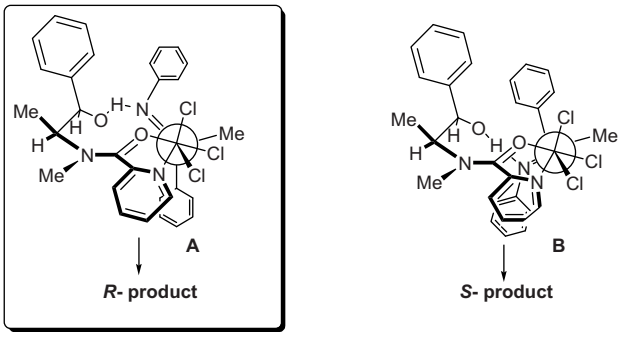
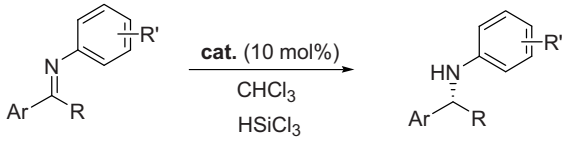


Figure 1. Proposed model of stereoselection for enantioselective reduction of *N*-aryl ketoimines.

2.2. General applicability

4-Chloropicolinamide of (1*R*,2*S*)-ephedrine **29** was then selected as the catalyst of choice and employed in a series of experiments aimed to test its general applicability to substituted *N*-aryl imine of alkyl-aryl ketones (Scheme 3).



30	Ar=β–naphthyl, R=Me, R'=H	**35**
31	Ar= 4-CF_3-C_6H_4, R=Me, R'=H	**36**
32	Ar= Ph; R=Me, R'=2-OMe	**37**
33	Ar= Ph; R=Me, R'=4-OMe	**38**
34	Ar= Ph, R=Et, R'=H	**39**

Scheme 3. Enantioselective reduction of *N*-aryl imine of different ketones.

Different *N*-aryl ketimines were reduced with trichlorosilane in the presence of 10 mol % of catalyst **1** in $CHCl_3$ at 0 °C and catalyst **29** at −20 °C (Table 5).

Table 5
Enantioselective catalytic reduction of imines **30**–**34**

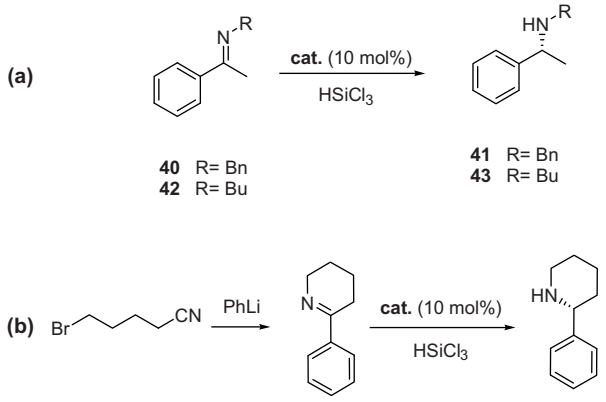
Entry	Catalyst	Imine	Yield[a] (%)	ee[b] (%)
1[c]	**1**	**30**	95	82
2	**29**	**30**	95	95
3	**1**	**31**	98	77
4	**29**	**31**	85	91
5	**1**	**32**	98	83
6	**29**	**32**	98	82
7	**1**	**33**	98	87
8	**29**	**33**	98	91
9	**1**	**34**	90	71
10	**29**	**34**	91	81

[a] Yields determined after chromatographic purification.
[b] Enantiomeric excess determined by HPLC on chiral stationary phase.
[c] Reaction run at −20 °C with 10 mol % of catalyst.

With all the substrates both catalysts displayed a high catalytic activity, affording the products very often in quantitative yields. In terms of enantioselectivity, catalyst **29** performed generally better than catalyst **1**, often leading to products in more than 90% enantioselectivities.[19] For example, with imine **30**, catalyst **29** was able to catalyze the reduction in 95% ee (entries 1–2, Table 5). This is also the case for imine **31** (entries 3–4, Table 5) and, more importantly, of

N-4-methoxyphenyl imine **33**; the chiral amine **38** was isolated in quantitative yield and 91% ee. It must be noted that both products **37** and **38** represent potential precursors of primary amines, since both the *ortho*-methoxyphenyl ring as well as the *para*-methoxyphenyl moiety are easily removed by oxidative degradation of the anisol ring.

Zhang has already reported that ephedrine-derived picolinamide **1** was also active in the reduction of *N*-benzyl imines.[15] (Scheme 4, Eq. a) In our hands imine **40** of acetophenone was reduced by reaction with trichlorosilane in the presence of 10% of catalyst **1** at 0 °C in 85% yield and 71% ee (entry 1, Table 6). Also for this substrate, 4-chloropicolinamide **29** promoted the reaction in better yield and enantioselectivities, performing at its best at −20 °C in dichloromethane; under these conditions chiral amine **41**, direct precursor of a primary amine, was synthesized in quantitative yield and 80% ee (entry 4, Table 6).



Scheme 4. Enantioselective reduction of *N*-benzyl and *N*-alkyl imines.

Table 6
Enantioselective catalytic reduction of imines **40**–**42**

Entry	Catalyst	Imine	Solvent	Temp	Yield[a] (%)	ee[b] (%)
1	**1**	**40**	DCM	0 °C	85	71
2	**29**	**40**	DCM	−20 °C	98	77
3	**29**	**40**	$CHCl_3$	0 °C	98	78
4	**29**	**40**	DCM	0 °C	98	80
5	**1**	**42**	DCM	0 °C	95	70
6	**29**	**42**	DCM	0 °C	98	77
7	**29**	**42**	$CHCl_3$	0 °C	98	91
8	**29**	**42**	$CHCl_3$	−20 °C	98	83
9[c]	**29**	**42**	$CHCl_3$	0 °C	77	87

[a] Yields determined after chromatographic purification.
[b] Enantiomeric excess determined by HPLC on chiral stationary phase.
[c] Reaction was performed with 1 mol % amount of catalyst.

Even better results were obtained in the enantioselective reduction of *N*-alkyl imines.[20] It is worth mentioning that an efficient organocatalyzed reduction of *N*-alkyl substituted ketoimines has been described for the first time only very recently.[21] Previously only two examples were reported where the catalyst was shown to be stereochemically inefficient, affording the product as racemic mixture[7b] or in low enantioselectivity.[10a]

However ephedrine-based picolinamides promoted the reaction of *N*-butyl imine of acetophenone **42** in excellent yields and pleasingly in high stereoselectivities. While the reaction run at 0 °C in dichloromethane with **1** afforded the product **43** in 95% yield and 70% ee, with catalyst **29** the *N*-butyl amine **43** was isolated in quantitative yield and 77% ee (entries 5–6, Table 6).

Under the best conditions (chloroform, 0 °C, 24 h) 4-chloro picolinic derivative **29** promoted the reduction in 98% yield and 91% ee (entry 7, Table 6). It was demonstrated that it was possible to carry out the reaction with just 1 mol % amount of catalyst and still to maintain a very high level of enantioselectivity (entry 9, Table 6). The wide applicability and generally high stereochemical efficiency shown by ephedrine-based picolinamides in the enantioselective reduction of both *N*-aryl and *N*-alkyl ketoimines is remarkable considering the extremely simple preparation and the low cost of such a class of organocatalysts.

Catalyst **29** was also successfully employed in the enantioselective reduction of a cyclic *N*-alkyl imine, a structural motif of great interest in view of future possible application in pharmaceutical chemistry. The reduction of 2-phenyl-(3,4-5,6-tetrahydro)-pyridine promoted by 4-chloropicolinic derivative **29** afforded the corresponding cyclic amine in 98% yield and 81% ee.

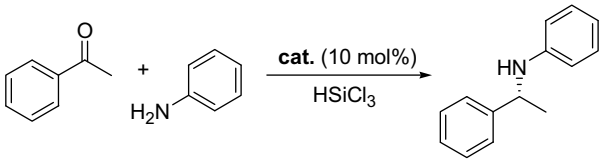
Another positive feature is represented by the possibility to recover and reuse the catalyst. After a simple aqueous work up the crude reaction mixture is often constituted by just the product and the catalyst. An easy purification through a short plug of silica allows to separate the product from the organocatalyst that was recovered in higher than 95% yield, and recycled with no loss of chemical and stereochemical efficiency.

2.3. Three component methodology

The development of a three component version of the reaction was also explored; we reasoned that since the preparation of the ketimines is not straightforward and requires long reaction times and relatively high temperatures, the possibility to perform an enantioselective reductive amination process starting directly from a ketone/amine mixture would be very attractive and would make the methodology even more synthetically appealing.

Asymmetric reductive amination of ketones has been performed with organometallic as well as with organic catalysts.[22] However it must be noted that a reductive multicomponent methodology for the trichlorosilane promoted reduction has been so far underdeveloped.[23] One of the reasons may be that a reductive amination process mediated by trichlorosilane competes with ketone reduction, since also these substrates are easily reduced by $HSiCl_3$ in the presence of by Lewis bases, even at low temperatures. For instance the reduction of acetophenone promoted by **1** afforded the corresponding alcohol in 86% at 0 °C, 64% at −20 °C and 55% yield at −40 °C after 12 h only in dichloromethane.[18]

A detailed study allowed us to find the correct experimental conditions and to develop a successful organocatalyzed reductive amination starting from a ketone and an aromatic amine. The reaction of acetophenone and aniline was investigated as model transformation (Scheme 5).



Scheme 5. Enantioselective reductive amination process.

When an equimolar mixture of ketone and aniline was reacted in the presence of 10 mol % amount of catalyst **1** and 3.5 mol equiv of trichlorosilane for 48 h at 0 °C in dichloromethane the chiral amine was recovered in only 50% yield along with 10% of 1-phenyl-1-ethanol. The enantioselectivity was comparable to that obtained in the direct reduction of *N*-phenyl imine of acetophenone (78% ee, entry 1, Table 7). A longer reaction time increased the yield of both the chiral amine and the undesired alcohol (entry 2). However, by working on the stoichiometry of the reagents it was possible to secure better results; an increase of the aniline equivalents was found to be crucial for obtaining only amine in good yields and

unchanged enantioselectivity. After 24 h the reductive amination process successfully lead to the chiral amine in quantitative yield and 76% ee at 0 °C in chloroform (entry 5). However a reaction time as short as six hours gave the product in 87% (entry 7). Also in the three components reaction catalyst **29** proved to be really efficient. Working with this catalyst at 0 °C the product was obtained in quantitative yield and 83% ee, that was further increased up to 87% enantioselectivity by performing the reaction at −20 °C, with no loss of chemical efficiency (entries 8–9, Table 7). The reductive amination methodology was also applied to other substrates (Table 8).

Table 7
Reductive amination process for the synthesis of *N*-phenyl-1-phenylethylamine at 0 °C

Entry	Catalyst	Aniline (equiv)	Solvent	Time	Yield[a] (%)	Yield[a] alcohol (%)	ee[b] (%)
1	**1**	1	DCM	48 h	50	10	78
2	**1**	1	DCM	72 h	67	29	78
3	**1**	1.5	DCM	72 h	78	12	77
4	**1**	2.5	$CHCl_3$	72 h	96	—	77
5	**1**	2.5	$CHCl_3$	24 h	98	—	76
6	**1**	2.5	$CHCl_3$	12 h	94	—	75
7	**1**	2.5	$CHCl_3$	6 h	87	—	75
8	**29**	2.5	$CHCl_3$	72 h	98	—	83
9[c]	**29**	2.5	$CHCl_3$	40 h	98	—	87

[a] Yields determined after chromatographic purification.
[b] Enantiomeric excess determined by HPLC on chiral stationary phase.
[c] Reaction performed at −20 °C.

Table 8
Reductive amination process for the synthesis of *N*-4-methoxyphenyl 1-phenyl ethylamine **38**

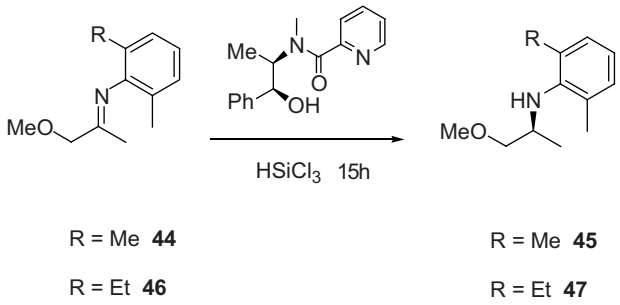
Entry	Catalyst	Temperature	Solvent	Time	Yield[a] (%)	ee[b] (%)
1	**1**	0 °C	DCM	12 h	15	73
2	**29**	0 °C	DCM	72 h	90	77
3	**29**	−20 °C	$CHCl_3$	90 h	80	87

[a] Yields determined after chromatographic purification.
[b] Enantiomeric excess determined by HPLC on chiral stationary phase.

For example also 4-methoxyaniline was reacted with acetophenone in the presence of catalyst **29** (10 mol %) under different experimental conditions to afford the chiral amine **38** (Scheme 3), immediate precursor of a primary amine. In this case longer reaction times were required in order to have high yields of the product. By working in chloroform at −20 °C 4-chloro picolinamide derivative was able to catalyze the synthesis of amine **38** in 80% yield and 87% ee (entry 3, Table 8).

As a synthetic application of the present methodology, a synthesis of (*S*)-metolachlor was attempted. This is a very popular herbicide belonging to the class of α-chloroacetanilides. Since 1996, a mixture of metolachlor constituted by 88% of the (*S*)-isomer and 12% of the (*R*)-isomer is commercialized by Syngenta (Chart 3). The preparation on ton scale of the enantiomerically enriched product relies on the enantioselective imine reduction through an extremely active and efficient, but very expensive iridium-chiral ferrocenyl phosphine complex.[24]

The use of picolinamides **1** and **29** as organocatalysts in the enantioselective reduction of *N*-2,6-dimethylphenyl imine of methoxyacetone **44** was first explored (Scheme 6). After 15 h at 0 °C in dichloromethane catalyst **1** derived from (1*S*,2*R*)-(+) ephedrine afforded the product in quantitative yield and 65% ee (Table 9, entry 1). The catalyst performed better in chloroform; when the reaction temperature was lowered from 0 °C to −20 °C, the product was obtained in 75% yield and 75% ee (entry 3). Based on these promising results the methodology was employed in the enantioselective reduction of imine **46** to afford chiral amine **47**, an immediate precursor of metolachlor. Under the best conditions ($CHCl_3$, −20 °C, 15 h, entry 5, Table 9) the product was isolated in 53% yield and 72% ee, that is a 86:14 enantiomeric ratio, very similar to that of the commercial product. In this case catalyst **29** afforded comparable results and led to the formation of product **47** at −20 °C in 67% yield and 70% ee (entry 7, Table 9).



Scheme 6. Enantioselective reduction of *N*-aryl imine of methoxyacetone.

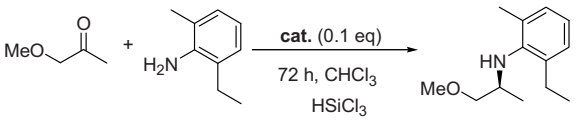
Table 9
Enantioselective reduction of *N*-aryl imine of methoxyacetone

Entry	Catalyst	Imine	Solvent	Temp	Yield[a] (%)	ee[b] (%)
1	**1**	**44**	DCM	0 °C	98	65
2	**1**	**44**	DCM	0 °C	80	70
3	**1**	**44**	$CHCl_3$	−20 °C	75	75
4	**1**	**46**	$CHCl_3$	0 °C	84	67
5	**1**	**46**	$CHCl_3$	−20 °C	53	72
6	**29**	**46**	$CHCl_3$	0 °C	68	55
7	**29**	**46**	$CHCl_3$	−20 °C	67	70

[a] Yields determined after chromatographic purification.
[b] Enantiomeric excess determined by HPLC on chiral stationary phase.

To the best of our knowledge this is the first organocatalytic example of reduction for an industrially relevant compound occurring with efficiency comparable to the existing organometallic process.

Since the preparation of the imine precursor for these important chiral amines is quite difficult and it requires long reaction times, the development of a three component reductive amination process was especially attractive. We were pleased to find that when a mixture of methoxyacetone and 2-ethyl, 6-methyl aniline was reacted at 0 °C in chloroform for 70 h with 10 mol % amount of picolinamide **1** and 3.5 mol equiv of trichlorosilane, chiral amine **47** was obtained in 86% yield and 70% ee (Scheme 7).



Scheme 7. Multicomponent enantioselective organocatalyzed preparation of an immediate precursor of metolachlor.

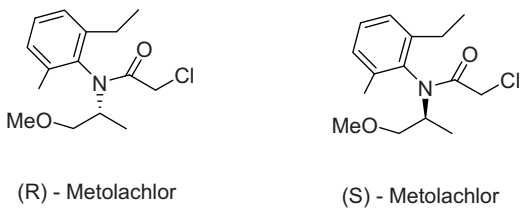


Chart 3. Metolachlor: a potent herbicide.

3. Conclusion

In conclusion, we have studied and developed a new class of metal-free chiral catalysts able to promote the enantioselective

reduction of ketimines mediated by trichlorosilane with high chemical and stereochemical efficiency.[25] The organocatalysts have several positive features: they are easily prepared, by a single condensation step, from commercially available compounds; they are low cost catalysts, the source of stereocontrol being a very cheap and largely available aminoalcohol, such as ephedrine; the reduction of carbon–nitrogen double bond is performed under very mild reaction conditions and with an extremely simple experimental procedure. The catalytic methodology can be applied to a large variety of substrates; noteworthy the ephedrine-derived picolinamides promoted the reduction not only of *N*-aryl but also of *N*-alkyl ketimines; the catalyst could be used in loading as low as 1 mol %. A convenient enantioselective organocatalytic three component methodology was also developed; the reductive amination process, starting simply by a mixture of a ketone and an aryl amine, opens an easy access to chiral amines with a straightforward experimental methodology. All these positive features make the present catalytic method in principle suitable also for large scale applications; its synthetic potentiality was demonstrated by successfully employing the present metal-free catalytic procedure in the preparation of (*S*)-metolachlor, a potent and widely used herbicide.

4. Experimental

4.1. General methods

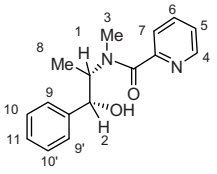
All reactions were carried out in oven-dried glassware with magnetic stirring under nitrogen atmosphere, unless otherwise stated. Dry solvents were purchased by Fluka and stored under nitrogen over molecular sieves (bottles with crown cap). Reactions were monitored by analytical thin-layer chromatography (TLC) using silica gel 60 F_{254} pre-coated glass plates (0.25 mm thickness) and visualized using UV light or phosphomolibdic acid. Proton NMR spectra were recorded on spectrometers operating at 200, 300 or 500 MHz respectively. Proton chemical shifts are reported in ppm (δ) with the solvent reference relative to tetramethylsilane (TMS) employed as the internal standard ($CDCl_3$, δ=7.26 ppm). The following abbreviations are used to describe spin multiplicity: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad signal, dd=doublet of doublets. ^{13}C NMR spectra were recorded on 300 or 500 MHz spectrometers operating at 75 and 125 MHz respectively, with complete proton decoupling. Carbon chemical shifts are reported in ppm (δ) relative to TMS with the respective solvent resonance as the internal standard ($CDCl_3$, δ=77.0 ppm). Optical rotations were obtained on a polarimeter at 589 nm using a 5 mL cell with a length of 1 dm. HPLC for ee determination was performed on Agilent 1100 instruments under the conditions reported below. Mass spectra (MS) were performed on a hybrid quadrupole time of flight mass spectrometer equipped with an ESI ion source. Microwave-accelerated reactions were performed in CEM Discover class S instrument.

4.1.1. Synthesis of the catalysts

4.1.1.1. General procedure A. To a stirred solution of the picolinic acid (1 mol equiv) or its derivatives in chloroform (5 mL/mmol substrate) kept under nitrogen at 0 °C, chloroform solutions of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC, 1.2 mol equiv), and 1-hydroxybenzotriazole (HOBT, 1.2 mol equiv), and aminoalcohol (1.2 mol equiv) were added in this order (the volume of each added solution was 1–3 mL; the total final volume of the solution was 8–25 mL). The reaction was stirred at room temperature overnight, and concentrated under vacuum to give the crude product. Purification by flash chromatography afforded the products.

4.1.1.2. General procedure B. A stirred solution of the picolinic acid (1 mol equiv) or its derivatives in thionyl chloride (1 mL/mmol substrate) was refluxed for 2 h, then the solvent was evaporated under vacuum; the residue, dissolved in THF (2 mL) with a few drops of DMF, was added to a solution of chiral aminoalcohol (1 mol equiv) and TEA (3 mol equiv) in THF; the reaction mixture was stirred for 12 h at reflux. The organic phase was quenched with aqueous saturated solution $NaHCO_3$, and brine. The organic phase was then dried over Na_2SO_4, filtered and concentrated under vacuum to give the crude product. Purification by flash chromatography afforded the products.

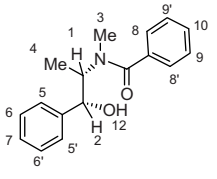
*4.1.1.3. Catalyst **1** (procedure A).*



Following procedure A, starting from (1*R*,2*S*)-ephedrine (1.2 mmol, 0.198 g) catalyst **1** was isolated as white solid (70% yield, 0.189 g) (purification through silica gel, eluent: 99:1 CH_2Cl_2/CH_3OH).

Rotamer 1. ^1H NMR (300 MHz, $CDCl_3$): δ 8.53 (s, 1H, 4), 7.85–7.65 (m, 1H, 6), 7.55–7.45 (m, 1H, 7), 7.40–7.30 (m, 1H, 5), 7.30–7.25 (m, 5H, 9, 9′, 10, 10′, 11), 4.81 (d, *J*=4.6 Hz, 1H, 2), 4.35 (br s, 1H, 1), 2.8 (s, 3H, 3), 1.33 (d, *J*=4.9 Hz, 3H, 8). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169, 154.2, 147.3, 141.5, 137.4, 128.2 (2C), 127.4, 126.7 (2C), 124.5, 123.1, 76.1, 58.3, 29.7, 14.5. *Rotamer 2.* ^1H NMR (300 MHz, $CDCl_3$): δ 8.53 (s, 1H, 4), 7.78–7.73 (m, 1H, 6), 7.53–7.47 (m, 1H, 7), 7.40–7.36 (m, 1H, 5), 7.30–7.25 (m, 5H, 9, 9′, 10, 10′, 11), 5.09 (br s, 1H, 2), 4.57 (br s, 1H, 1), 2.87 (s, 3H, 3), 1.28 (d, *J*=4.8 Hz, 3H, 8). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.8, 154.8, 148.3, 142.1, 137.1, 128.2 (2C), 127.1, 126.3 (2C), 124.5, 124.3, 76.4, 58.6, 35, 11.2. IR (DCM): $\nu_{C=O}$=1725 cm^{-1}. Mp=99–101 °C. $[\alpha]_D^{25}$ −19 (*c* 0.55 g/100 mL, DCM, λ=589 nm). Mass (ESI^+): *m*/*z*=271 $[M]^+$, 293 $[M+Na]^+$. Anal. Calcd for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.15; H, 6.57; N, 10.35.

*4.1.1.4. Catalyst **2**.*

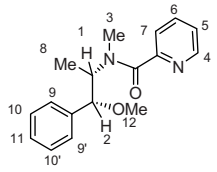


To a solution of (1*R*,2*S*)-ephedrine (1.2 mmol, 0.198 g), TEA (1.2 mmol, 0.165 mL) and DMAP (10 mg) in dry THF a solution of benzoyl chloride (1 mmol, 0.140 g) in THF was slowly added dropwise. The mixture was stirred for 12 h at room temperature. The obtained residue, after evaporation of solvent, was purified by silica gel flash chromatography (eluent: 100 mL of 7:3 hexane/ethyl acetate, then 300 mL of 6:4 hexane/ethyl acetate) allowed to obtain as white solid **2** (98% yield, 0.26 g).

Rotamer 1. ^1H NMR (300 MHz, $CDCl_3$): δ 7.4–7.1 (m, 10H, 8, 8′, 9, 9′, 10, 5, 5′, 6, 6′, 7), 6.98 (s, 1H, 12), 4.81 (s, 1H, 2), 4. 5 (br s, 1H, 1), 2.6 (s, 3H, 3), 1.33 (d, *J*=5.5 Hz, 3H, 4). *Rotamer 2.* ^1H NMR (300 MHz, $CDCl_3$): δ 7.4–7.1 (m, 10H, 8, 8′, 9, 9′, 10, 5, 5′, 6, 6′, 7), 6.90 (s, 1H, 12), 4.5 (s, 1H, 2), 4.3 (br s, 1H, 1), 2.9 (s, 3H, 3), 1.4 (d, *J*=5.1 Hz, 3H, 4). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168, 155.2, 141.3, 141.0, 137.4, 128.3 (2C), 128.0, 127.7 (2C), 126.5 (2C), 124.5 (2C), 123.1, 120.1 (2C), 77.1, 59.3,

30.7, 15.5. IR (DCM): $\nu_{C=O}$=1700 cm^{-1}. Mp=122–124 °C. $[\alpha]_D^{25}$ −140.6 (*c* 0.46 g/100 mL, DCM, λ=589 nm). Mass (ESI$^+$): *m*/*z*=270 [M]$^+$. Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.85; H, 7.12; N, 5.15.

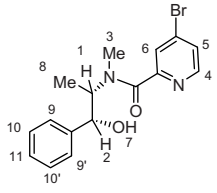
*4.1.1.5. Catalyst **4**.*



Compound **1** (0.5 mmol, 0.135 g) was added to a suspension of 50% NaH (0.55 mmol, 26.4 mg) in THF (3 mL) and the mixture was stirred at room temperature for 2 h. MeI (1 mmol, 0.142 g) was added and the resulting mixture was stirred for 20 h. The residue obtained after evaporation of solvent was purified by silica gel flash chromatography (eluent: 200 mL of 9:1 CH_2Cl_2/CH_3OH). Compound **4** was isolated as white solid (29% yield, 47 mg).

Rotamer 1. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.59 (s, 1H, 4), 7.70–7.65 (m, 1H, 6), 7.49–7.39 (m, 2H, 9, 9′), 7.38–7.35 (m, 1H, 11), 7.35–7.31 (m, 2H, 10, 10′), 7.30–7.25 (m, 1H, 5), 7.08 (d, *J*=7.5 Hz, 1H, 7), 4.36 (d, *J*=5.5 Hz, 1H, 2), 4.20–4.15 (m, 1H, 1), 3.27 (s, 3H, 12), 3.12 (s, 3H, 3), 1.36 (d, *J*=6.5 Hz, 3H, 8). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169, 154, 148, 139.5, 136, 128.4 (2C), 127.9, 126.8 (2C), 124.1, 124, 86.1, 58.6, 57.1, 28.6, 13.5. *Rotamer 2.* ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.59 (s, 1H, 4), 7.80–7.73 (m, 1H, 6), 7.35–7.25 (m, 2H, 5, 7), 7.30–7.25 (m, 1H, 11), 7.30–7.20 (m, 2H, 10, 10′), 7.08 (d, *J*=7.6 Hz, 2H, 9, 9′), 4.80–4.70 (m, 1H, 1), 4.57 (d, *J*=4.5 Hz, 1H, 2), 3.32 (s, 3H, 12), 2.92 (s, 3H, 3), 1.36 (d, *J*=5.5 Hz, 3H, 8). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.5, 154, 148, 140, 136, 128.4 (2C), 127.7, 127.1 (2C), 124, 122.5, 86.1, 57.1, 55.5, 31.3, 11.7. IR (DCM): $\nu_{C=O}$=1720 cm^{-1}. Mp=81–91 °C. $[\alpha]_D^{25}$ −35.31 (*c* 0.32 g/100 mL, DCM, λ=589 nm). Mass (ESI$^+$): *m*/*z*=285. Anal. Calcd for $C_{17}H_{20}N_2O_2$: C, 71.81; H, 7.09; N, 9.85. Found: C, 71.83; H, 7.11; N, 9.81.

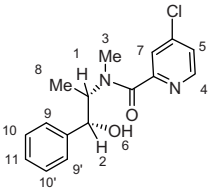
*4.1.1.6. Catalyst **28** (procedure A).*



Starting from (1*R*,2*S*) ephedrine (1.2 mmol, 0.198 g) and 4-bromopicolinic acid (1 mmol, 0.2 g) catalyst **28** was isolated as white solid (60% yield, 0.21 g) (purification through silica gel, eluent: 500 mL of 97:3 CH_2Cl_2/MeOH).

Rotamer 1. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.30 (d, *J*=5.3 Hz, 1H, 4), 7.55–7.48 (m, 1H, 5), 7.35–7.28 (m, 3H, 10, 10′, 11), 7.25–7.15 (m, 3H, 6, 9, 9′), 4.75 (d, *J*=6.6 Hz, 1H, 2), 4.28–4.22 (m, 1H, 1), 2.89 (s, 3H, 3), 1.36 (d, *J*=6.7 Hz, 3H, 8). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.7, 155.1, 148, 141.4, 133.7, 128.1 (2C), 127.8, 127.4, 126.2 (2C), 126.1, 75.6, 58.6, 29.2, 14.4. *Rotamer 2.* ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.30 (d, *J*=5.3 Hz, 1H, 4), 7.55–7.45 (m, 3H, 5, 9, 9′), 7.40–7.35 (m, 2H, 10, 10′), 7.35–7.30 (m, 1H, 11), 7.25–7.18 (m, 1H, 6), 5.05 (d, *J*=3.8 Hz, 1H, 2), 4.65–4.55 (m, 1H, 1), 2.86 (s, 3H, 3), 1.33 (d, *J*=3.1 Hz, 3H, 8). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.2, 155.6, 148.9, 141.7, 133.6, 128.1 (2C), 127.8, 127.4, 126.2 (2C), 126.1, 76.3, 58.3, 34.7, 11.1. IR (DCM): $\nu_{C=O}$=1723 cm^{-1}. Mp=143–145 °C. $[\alpha]_D^{25}$ −24.12 (*c* 0.23 g/100 mL, DCM, λ=589 nm). HMRS Mass (ESI$^+$): *m*/*z*=[M+H]$^+$ calcd for $C_{16}H_{17}BrN_2O_2$ 348.0473, found 348.0469 [M+H]$^+$.

*4.1.1.7. Catalyst **29** (procedure B).*



Starting from (1*R*,2*S*) ephedrine (1.2 mmol, 0.198 g) and 4-choloropicolinic chloride (1 mmol, 0.180 g) catalyst **29** was isolated as white solid (71% yield, 0.21 g) (purification through silica gel, eluent: 400 mL of 98:2 CH_2Cl_2/MeOH, 600 mL of 95:5 CH_2Cl_2/MeOH, then 400 mL of 9:1 CH_2Cl_2/MeOH).

Rotamer 1. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.35–8.30 (m, 1H, 4), 7.29–7.20 (m, 3H, 5, 10, 10′), 7.25–7.18 (m, 1H, 11), 7.08 (d, *J*=6.1 Hz, 2H, 9, 9′), 6.48 (br s, 1H, 7), 4.63 (d, *J*=4.0 Hz, 1H, 2), 4.12–4.06 (m, 1H, 1), 2.86 (s, 3H, 3), 1.31 (d, *J*=6.7 Hz, 3H, 8). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.9, 155.4, 148.3, 144.9, 141.7, 128 (2C), 127.6, 126.1 (2C), 124.3, 124.1, 75.2, 58.8, 28.8, 14.2. *Rotamer 2.* ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.33–8.28 (m, 1H, 4), 7.45–7.35 (m, 2H, 9, 9′), 7.33–7.27 (m, 3H, 7, 10, 10′), 7.25–7.20 (m, 1H, 5), 7.22–7.18 (m, 1H, 11), 5.11–5.01 (m, 1H, 2), 4.60–4.50 (m, 1H, 1), 2.80 (s, 3H, 3), 1.25 (d, *J*=7 Hz, 3H, 8). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.1, 155.8, 149.1, 145, 141.8, 128 (2C), 127.3, 126.1 (2C), 124.3, 123.3, 75.9, 57.6, 34.2, 11.1. Mp=139–141 °C. IR (DCM): $\nu_{C=O}$=1721 cm^{-1}. $[\alpha]_D^{25}$ −36.06 (*c* 0.244 g/100 mL, DCM, λ=589 nm). HRMS Mass (ESI$^+$): *m*/*z*=[M+Na]$^+$ calcd for $C_{16}H_{17}ClN_2O_2$ 327.0871, found 327.0869 [M+Na]$^+$.

4.1.2. General procedures for reduction reaction

4.1.2.1. Imine reduction. General procedure. To a stirred solution of catalyst (0.1–0.01% mol/eq mmol) in the chosen solvent (2 mL), the imine (1 mmol/eq) was added. The mixture was then cooled to the chosen temperature and trichlorosilane (3.5 mmol/eq) was added drop wise by means of a syringe. After stirring at the proper temperature, the reaction was quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (1 mL). The mixture was allowed to warm up to room temperature and water (2 mL) and dichloromethane (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 at room temperature to afford the crude product. If necessary, the amine was purified by flash chromatography. Yields and enantiomeric excesses for each reaction are indicated in the Tables. The assignment of absolute configuration to the predominant isomer formed in each reaction rests on comparison of sign of optical rotation with those reported in the literature.

4.1.2.2. Three component reaction. General procedure. Amine (2.5 mmol/eq), ketone (1 mmol/eq) and trichlorosilane (3.5 mmol/eq) in the chosen solvent (2 mL) were stirred for 30 min and then the catalyst (0.1 mmol/eq) was added. After stirring at the chosen temperature the reaction was quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (1 mL). The mixture was allowed to warm up to room temperature and water (2 mL) and dichloromethane (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 at room temperature to afford the crude product. If necessary, the amine was purified by flash chromatography. Yields and enantiomeric excesses for each reaction are

indicated in the Tables. The assignment of absolute configuration to the predominant isomer formed in each reaction rests on comparison of sign of optical rotation with those reported in the literature.

*4.1.2.3. General procedure for the synthesis of imines **30**, **31**, **32**, **33**, **34**, **40**, **42**[26].* In a typical experiment: amine (1 equiv) was reacted in toluene with ketone (1 equiv) in the presence of montmorillonite (250 mg for 5 mmol of reagent) in a microwave reactor (PW=200 W; T=130 °C; time: 4 h and 30 min). The product was purified by fractional distillation at P=1 mbar: the starting material distilled at about 120 °C, the desired product at about 160 °C.

4.1.3. Characterization of products

4.1.3.1. N-(1-Phenylethyl)aniline. This product was purified with a 98:2 hexane/ethyl acetate mixture as eluent. Its ^{1}H NMR data were in agreement with those reported in the literature.[26]

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35–7.10 (m, 5H), 7.01 (t, J=7.80 Hz, 2H), 6.57 (t, J=6.60 Hz, 1H), 6.44 (d, J=7.90 Hz, 2H), 4.41 (q, J=6.70 Hz, 1H), 3.94 (br s, 1H), 1.41 (d, J=6.70 Hz, 3H).

The enantiomeric excess was determined by HPLC on a Chiralcel IB column (99:1 hexane/isopropanol; flow rate: 0.8 mL/min; λ=254 nm): t_S=9.3 min, t_R=10.4 min.

*4.1.3.2. N-(1-(Naphthalen-2-yl)ethyl)aniline (**35**).* This product was purified with a hexane/ethyl acetate 98:2 mixture as eluent. It had ^{1}H NMR data in agreement with those reported in the literature.[26]

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.91–7.86 (m, 4H), 7.55–7.45 (m, 3H), 7.1 (t, J=7.70 Hz, 2H), 6.80–6.60 (m, 3H), 4.6 (q, J=6.80 Hz, 1H), 3.97 (br s, 1H), 1.6 (d, J=6.80 Hz, 3H).

The enantiomeric excess was determined by HPLC on a Chiralcel OD column (98:2 hexane/isopropanol; flow rate: 1 mL/min; λ=254 nm): t_S=14.7 min, t_R=15.7 min.

*4.1.3.3. N-(1-(4-(Trifluoromethyl)phenyl)ethyl)aniline (**36**).* This product was purified with a 98:2 hexane/ethyl acetate mixture as eluent. Its ^{1}H NMR data were in agreement with those reported in the literature.[7]

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51 (d, J=7.80 Hz, 2H), 7.41 (d, J=7.70 Hz, 2H), 7.02 (t, J=6.90 Hz, 2H), 6.59 (t, J=6.80 Hz, 1H), 6.38 (d, J=6.90 Hz, 2H), 4.46 (q, J=6.50 Hz, 1H), 3.97 (br s, 1H), 1.46 (d, J=6.50 Hz, 3H).

The enantiomeric excess was determined by HPLC on a Chiralcel OD column (9:1 hexane/isopropanol; flow rate: 1 mL/min; λ=254 nm): t_S=9.9 min, t_R=12.4 min.

*4.1.3.4. 2-Methoxy-N-(1-phenylethyl)aniline (**37**).* This product was purified with a 98:2 hexane/ethyl acetate mixture as eluent. Its ^{1}H NMR data were in agreement with those reported in the literature. [7]

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43–7.26 (m, 6H), 6.80–6.72 (m, 2H), 6.66 (d, J=7.50 Hz, 1H), 6.40 (d, J=7.50 Hz, 1H), 4.53 (q, J=6.50 Hz, 1H), 3.93 (s, 3H), 1.60 (d, J=6.50 Hz, 3H).

The enantiomeric excess was determined by HPLC on a Chiralcel IB column (99:1 hexane/isopropanol; flow rate: 0.8 mL/min; λ=254 nm): t_S=7.3 min, t_R=9.5 min.

*4.1.3.5. 4-Methoxy-N-(1-phenylethyl)aniline (**38**).* This product was purified with a 98:2 hexane/ethyl acetate mixture as eluent. Its ^{1}H NMR data were in agreement with those reported in the literature.[7]

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43–7.26 (m, 5H), 6.73 (d, J=8.00 Hz, 2H), 6.58 (d, J=8.00 Hz, 2H), 4.46 (q, J=6.90 Hz, 1H), 3.74 (s, 3H), 1.58 (d, J=6.90 Hz, 3H).

The enantiomeric excess was determined by HPLC on a Chiralcel ODH column (98:2 hexane/isopropanol; flow rate 0.8 mL/min; λ=230 nm): t_R=13.6 min, t_S=15.5 min.

*4.1.3.6. N-(1-Phenylpropyl)aniline (**39**).* This product was purified with a 98:2 hexane/ethyl acetate mixture as eluent. Its ^{1}H NMR data were in agreement with those reported in the literature.[26]

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31 (m, 4H), 7.25–7.18 (m, 1H), 7.07 (t, J=7.50 Hz, 2H), 6.62 (t, J=6.90 Hz, 1H), 6.50 (d, J=6.90 Hz, 2H), 4.21 (t, J=6.70 Hz, 1H), 4.05 (br s, 1H), 1.81 (m, 2H), 0.94 (t, J=6.70 Hz, 3H).

The enantiomeric excess was determined by HPLC on a Chiralcel IB column (99:1 hexane/isopropanol; flow rate: 0.8 mL/min; λ 254 nm): t_S=7.9 min, t_R=8.5 min.

*4.1.3.7. N-Benzyl-1-phenylethanamine (**41**).* This product was purified with a 8:2 hexane/ethyl acetate mixture as eluent. Its ^{1}H NMR data were in agreement with those reported in the literature.[26]

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38–7.24 (m, 10H), 3.82 (q, J=6.50 Hz, 1H), 3.67, (d, J=7.00 Hz, 1H, A proton of AB system), 3.60 (d, J=7.00 Hz, 1H, B proton of AB system), 1.57 (br s, 1H), 1.37 (d, J=6.50 Hz, 3H).

The enantiomeric excess was determined by HPLC on a Chiralcel ODH column (99:1 hexane/isopropanol; flow rate: 0.8 mL/min; λ=210 nm): t_R=7.8 min, t_S=8.4 min.

*4.1.3.8. N-(1-Phenylethyl)butan-1-amine (**43**).* This product was purified with a 8:2 hexane/ethyl acetate mixture as eluent. Its ^{1}H NMR data were in agreement with those reported in the literature.[7]

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.3–7.1 (m, 5H), 3.73 (q, J=6.50 Hz, 1H), 2.45–2.35 (m, 2H), 1.40–1.30 (m, 2H), 1.32 (d, J=6.50 Hz, 3H), 1.22–1.15 (m, 2H), 0.79 (t, J=7.50 Hz, 3H).

The enantiomeric excess was determined by analysis of the acetamide obtained by reaction of the isolated amine with acetic anhydride at room temperature for 12 h.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45–7.35 (m, 5H), 6.0 (q, J=6.70 Hz, 1H), 5.0* (q, J=6.80 Hz, 1H), 3.3–2.8 (m, 2H), 2.2 (s, 3H), 2.1* (s, 3H), 1.6 (d, J=6.70 Hz, 3H), 1.5* (d, J=6.580 Hz, 3H), 1.45–1.35 (m, 2H), 1.25–1.10 (m, 2H), 0.8 (t, J=6750 Hz, 3H).

The enantiomeric excess was determined by HPLC on a Chiralcel IB column (9:1 hexane/isopropanol; flow rate: 0.8 mL/min; λ 210 nm): t_R=8.5 min, t_S=9.4 min.

4.1.3.9. 2-Phenylpiperidine. The imine was prepared following the procedure reported below:[27]

PhLi (1.13 equiv, solution 1.9 M), was added dropwise to a solution of 5-bromovaleronitrile (1 equiv) in dry benzene (0.1 M). The resulting solution was refluxed for 20 h, cooled and quenched with 1 mL of water. The organic solution was dried ($MgSO_4$) and the solvents were removed under reduced pressure. The oily residue was separated by chromatography on neutral alumina (eluent: 400 mL of 97:3 hexane/AcOEt, then 300 mL of 95:5 hexane/AcOEt).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.90–7.70 (m, 2H), 7.50–7.30 (m, 3H), 3.80–3.70 (m, 2H), 2.70–2.60 (m, 2H), 1.90–1.80 (m, 2H), 1.75–1.60 (m, 2H). Mass (ESI^+): m/z=160.2.

The reduction product was purified with a 98:2 CH_2Cl_2/MeOH mixture as eluent. Its ^{1}H NMR data were in agreement with those reported in the literature.[28]

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38–7.20 (m, 5H), 3.65–3.55 (m, 1H), 3.22–3.18 (m, 1H), 2.85–2.75 (m, 1H), 1.90–1.48 (m, 6H).

The enantiomeric excess was determined by analysis of trifluoroacetamide obtained by reaction of the isolated amine with trifluoroacetic anhydride at 0 °C for 3 h.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44–7.35 (m, 5H), 6.0 (q, J=6.65 Hz, 1H), 5.4* (q, J=6.55 Hz, 1H), 4.4 (d, J=6.65 Hz, 1H), 3.8* (d, J=6.55 Hz, 1H), 3.20–3.00 (m, 1H), 2.66–2.55* (m, 1H), 3.45–3.35 (m, 1H), 2.1–2.0 (m, 2H), 1.5–1.3 (m, 3H).

The enantiomeric excess was determined by HPLC on a Chiralcel OD column (98:2 hexane/isopropanol; flow rate: 0.8 mL/min; λ=210 nm): t_S=6.7 min, t_R=7.3 min.

*4.1.3.10. N-(1-Methoxypropan-2-yl)-2,6-dimethylaniline (**45**).* This product was purified with a 98:2 hexane/ethyl acetate mixture as eluent. Its ^{1}H NMR data were in agreement with those reported in the literature.[29]

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.0 (d, J=7.50 Hz, 2H), 6.8 (t, J=7.50 Hz, 1H), 3.40–3.30 (m, 7H), 2.2 (s, 6H), 1.2 (d, J=6.90 Hz, 3H).

The enantiomeric excess was determined by HPLC on a Chiralcel OD column (99.5:0.5 hexane:isopropanol; flow rate 0.8 mL/min; λ 254 nm): t_R=9.7 min, t_S=11.6 min.

*4.1.3.11. 2-Ethyl-N-(1-methoxypropan-2-yl)-6-methylaniline (**47**).* This product was purified with a 98:2 hexane/ethyl acetate mixture as eluent. Its ^{1}H NMR data were in agreement with those rerported in the literature.[29]

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.00 (d, J=7.80 Hz, 2H), 6.8 (t, J=7.80 Hz, 1H), 3.25–3.05 (m, 7H), 2.7 (q, J=5.80 Hz, 2H), 2.2 (s, 3H), 1.3 (t, J=5.80 Hz, 3H), 1.2 (d, J=6.70 Hz, 3H).

The enantiomeric excess was determined by HPLC on a Chiralcel OD column (99.5:0.5 hexane/isopropanol; flow rate 0.8 mL/min; λ=254 nm): t_R=7.8 min, t_S=9.1 min.

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