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A new class of low-loading catalysts for a highly enantioselective, metal-free imine reduction of wide general applicability

Davide Brenna, Riccardo Porta, Elisabetta Massolo, Laura Raimondi, and Maurizio Benaglia*

Abstract: A new class of chiral Lewis bases for the enantioselective $HSiCl_3$-mediated reduction of imines has been developed. Through an extensive catalyst structure optimization, an extremely active species was identified, able to promote the reduction of a large variety of functionalized substrates in high yields and enantioselectivities typically above 90% with catalyst loading as low as 0.1-1% mol. The simple experimental procedure, the low cost of the reagents, the mild reaction conditions, and straightforward isolation of the product, make the methodology attractive also for large scale applications. Its synthetic potentiality was demonstrated by the preparation of advanced intermediates of important APIs, used in the treatment of Alzheimer and Parkinson diseases, hyperparathyroidism, neuropathic pains and neurological disorders.The reaction has also been successfully performed in flow reactors, thus demonstrating the possibility to realize *in continuo* processes yielding multigram quantities of product.

The stereoselective reduction of C=N bonds is probably the most popular approach to synthesize chiral amines.[1] Although in the last few years remarkable progress has been made in the development of efficient chiral organometallic complexes for imines hydrogenation,[2] the high cost of the precious metal species and their lack of general applicability make the discovery of new, highly performant catalysts greatly desirable. Moreover, in the case of C=N bonds reduction, very often quite high catalyst loadings are required.[3] Metal free catalytic methodologies represent a viable alternative option, and some efficient catalytic systems have been reported,[4] but also in these cases high catalyst loadings are necessary.

Despite all the recent achievements in the field, the combination of inexpensive, atoxic, easily available catalyst capable of performing at the very low loadings typical of organometallic catalysis, is an unmet challenge for present-day organocatalysis.[5] Trichlorosilane-based reduction methods may offer an interesting opportunity in this sense.[6] Being a waste product of silicon industry, $HSiCl_3$ is an extremely cheap reagent, readily available in large quantities, that is capable of reducing C=N bonds with amazing chemoselectivity. Its coordination with chiral Lewis bases allowed to develop highly enantioselective catalytic reductions of imines.[7] Here we report the design and the optimization of a new class of enantiopure chiral picolinamides, easily prepared in a few steps from amino acids, such as phenyl-alanine and tyrosine (Figure 1). An extremely active species has been identified, able to promote the reduction on a large variety of functionalized substrates in high yields and enantioselectivities typically higher than 90%, and with catalyst loadings ranging from 0.1 to 1% mol, a level that is exceptionally low for organocatalysis. Remarkably, the new catalysts showed a wide scope and were applied to the synthesis of differently substituted chiral *N*-aryl and *N*-alkyl amines, including α– and β–amino esters and α–nitro amines, easily converted in differently functionalized 1,2-diamino compounds.

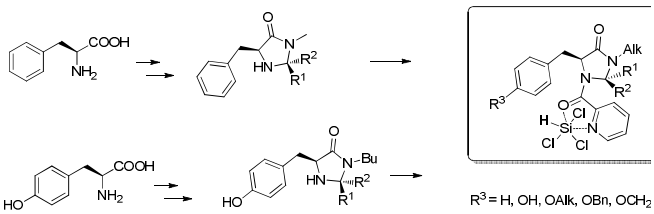

Figure 1. A new class of chiral Lewis bases for enantioselective catalytic hydrosilylation of imines.

Enantiopure picolinamides have been extensively studied as activators of trichlorosilane.[8] In designing a new class of chiral Lewis basic catalysts, we took advantage of the well-established conformational features of chiral imidazolidinones, successfully used in aminocatalysis.[9] While the picolinamide unit is responsible of $HSiCl_3$ coordination and chemical activation, the imidazolidinone scaffold offers many opportunities to tune and modify the steric requirements and the stereoelectronic properties of the catalytic system (Figure 1). Therefore, a series of new chemical entities, featuring different substituents on the imidazolidinone ring and on the aromatic ring of the amino acid moiety, were synthesized (Figure 2).

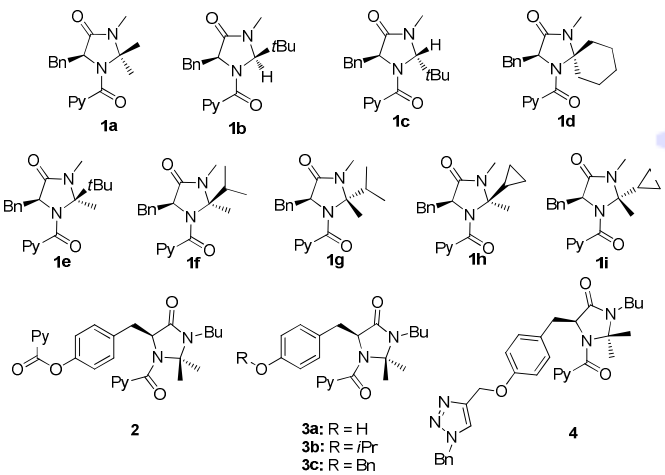

Figure 2. A new class of chiral organocatalysts for the enantioselective trichlorosilane-mediated ketoimines reduction.

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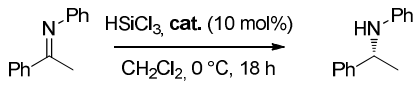
Starting from (S)-phenyl alanine, enantiopure Lewis bases **1a-1i** were synthesized; the imidazolidinone ring was assembled via reaction of the *N*-methyl (S)-phenyl alanine carboxyamide with different carbonyl derivatives, and then conjugated to picolinic acid. Analogously, (S)-tyrosine was used to prepare catalysts **2 – 4** (Figure 2).

A preliminary screening of all new picolinamides **1-4** as catalysts in the trichlorosilane-mediated model reduction of *N*-phenyl acetophenone imine **5a** at 0 ℃ allowed to identify the most promising catalyst candidates (Table 1).

Table 1. Catalyst screening.



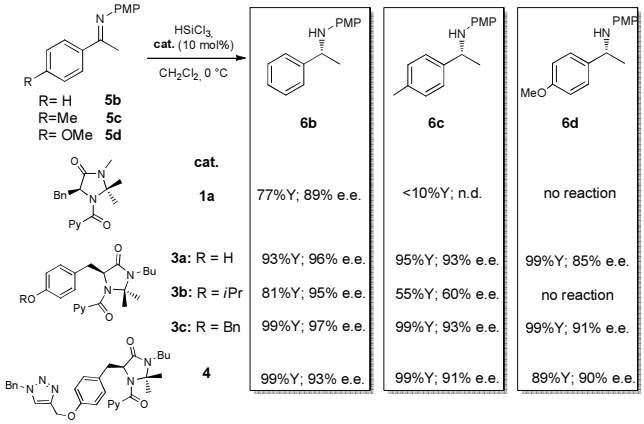
5a **6a**

Entry[a]	Catalyst	Yield (%)[b]	e.e. (%)[c]
1	**1a**	76	85
2[d]	**1a**	73	92
3	**1b**	57	10
4	**1c**	13	<5
5	**1d**	73	64
6	**1e**	90	<5
7	**1f**	80	72
8	**1g**	75	<5
9	**1h**	76	89
10	**1i**	60	48
11	**2**	78	23
12	**3a**	98	94
13	**3b**	81	97
14	**3c**	98	98
15	**4**	99	92

[a] Reaction conditions: **5a** (0.1 mmol), **cat**. 0.01 mmol, $HSiCl_3$ (0.35 mmol, 35 μL) in CH_2Cl_2 (1 mL) at 0℃ for 18 h; [b] isolated yield; [c] de termined by HPLC on chiral stationary phase; absolute configuration established by comparison of optical rotation values; [d] reaction performed at -10 ℃.

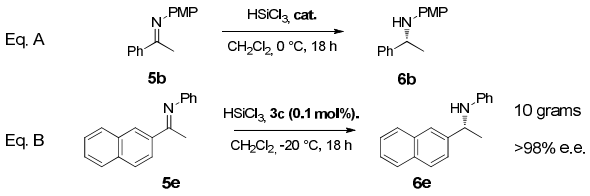
Since catalyst **1a** showed interesting results (entries 1-2), it was envisioned that a modification on the imidazolidinone ring could lead to an improved catalyst efficiency. For example, it was thought the combination of different R^1 and R^2 residues (see Figure 1) could force the phenyl ring of the benzylic unit in a more favourable position, to preferentially shield one face of the imine and improve enantioselectivity.[10] However, the structural variations in catalysts **1b-1i** did not lead to any positive results. On the contrary, the introduction of a substituent in *para* position of the phenyl ring allowed to identify a few very efficient catalysts, like compounds **3a-c.** In view of the immobilization of these chiral Lewis base on solid support, to facilitate the development of continuous flow stereoselective reductions in catalytic reactors,[11] the enantiopure Lewis base **4** was also synthesized, to verify the compatibility of the linker, featuring a triazole ring, with the reaction conditions.[12] Indeed, all catalysts **3a-c** and **4** promoted the reduction, in nearly quantitative yields and with up to 98% enantioselectivity in the case of the *O*-benzyl substituted catalyst **3c** (entries 12-15).

When the behavior of the most promising catalysts **1a, 3a-c** and **4** was studied in the reduction of the electron-rich, and therefore likely poorly reactive, imines **5b-d**, some further differences were evidenced, especially about chemical activity. While catalyst **1a** was unable to promote the reduction of imines **5c-d**, chiral picolinamide **4** and particularly the *O*-benzyl protected imidazolidinone derivative **3c** afforded the expected chiral amines **6b-d** in 99% yield and enantioselectivities ranging from 91 to 97 % (Scheme 1).



Scheme 1. Comparison of different catalytic activities **1a, 3a-3c** and **4**. Reaction conditions: **5** (0.1 mmol), **cat**. 0.01 mmol, $HSiCl_3$ (0.35 mmol, 35 μL) in CH_2Cl_2 (1 mL) at 0℃ C;

Table 2. Studies on catalysts loadings with Lewis bases **3c** and **4**.



Entry[a]	Catalyst	Cat. loading	Yield (%)[b]	e.e. (%)[c]
1	**4**	5 mol%	95	92
2[d]	**4**	5 mol%	95	81
3[e]	**4**	5 mol%	86	92
4	**4**	1 mol%	92	92
5	**3c**	1 mol%	99	97
6	**3c**	0,1 mol%	93	90
7[f]	**3c**	0,1 mol%	80	97

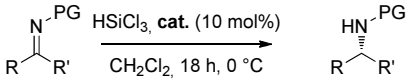
[a] Eq. A. Reaction conditions: **5b** (0.1 mmol), **cat**. 0.01 mmol, $HSiCl_3$ (0.35 mmol, 35 μL) in CH_2Cl_2 (1 mL) at 0℃ for 18 h; [b] isolated yield; [c] de termined by HPLC on chiral stationary phase; [d] reaction performed at 25 ℃; [e] reaction time = 2 hours; [f] reaction performed at -20 ℃.

10.1002/cctc.201700052

Given their exceptional activity, catalysts **3c** and **4** were selected for further studies.[13] In the attempt to lower the catalyst loading, the reduction of imine **5b** was performed with reduced amounts of chiral Lewis base (Eq. A, Table 2). Noteworthy, catalyst **4** still worked efficiently at 1 mol% loading, affording the product in 93% yield and 92% e.e. (entries 1-4); catalyst **3c** showed an even more remarkable activity and promoted the reduction with 0.1% mol loading in 92% yield at 0℃ , and in 80% yield and 97% e.e. at -20℃. It is worth mentioning that, by performing the reaction with 0.1 mol% of chiral base, the ACE (Asymmetric Catalyst Efficiency)[14] of catalyst **3c**, based on entries 6-7 of Table 2, is 375-400, a value that very favourably compares with either organometallic or organic chiral catalysts, which in most cases do not go beyond 50-60 ACE values.[7b] To further demonstrate the efficiency of catalyst **3c**, the synthesis of the chiral amine **6e** was successfully accomplished on multi-gram scale: using 10 mg of catalyst almost 10 grams of enantiopure amine was obtained, after a single crystallization, without the need of any chromatographic purification (Eq. B).[15]

To test the general applicability of catalysts **3c** and **4** the reduction of a wide variety of imines was investigated (Table 3).

Table 3. Reaction scope.



5e-q **6e-q**

Entry	Imine	Cat.	R	R'	PG	Y (%)[a]	e.e (%) [b]
1	**5e**	**3c**	β-napht	CH_3	Ph	99	98
2[c]	**5e**	**4**	β-napht	CH_3	Ph	99	90
3	**5f**	**4**	4-F-C_6H_4	CH_3	PMP	93	95
4	**5g**	**4**	4-CF_3-C_6H_4	CH_3	PMP	92	96
5	**5h**	**3c**	4-NO_2-C_6H_4	CH_3	PMP	99	97
6	**5h**	**4**	4-NO_2-C_6H_4	CH_3	PMP	94	93
7	**5i**	**3c**	4-Cl-C_6H_4	CH_3	PMP	98	96
8	**5i**	**4**	4-Cl-C_6H_4	CH_3	PMP	95	94
9[c]	**5j**	**3c**	3-OMe-C_6H_4	CH_3	PMP	98	90
10	**5j**	**4**	3-OMe-C_6H_4	CH_3	PMP	97	90
11[c]	**5k**	**4**	3-OBn-C_6H_4	CH_3	PMP	80	96
12	**5l**	**4**	3-OBn-C_6H_4	CH_3	Bn	80	93
13[c]	**5m**	**3c**	Ph	CH_3	$(CH_2)_3Ph$	99	98
14[c]	**5m**	**4**	Ph	CH_3	$(CH_2)_3Ph$	99	90
15[c]	**5n**	**3c**	Ph	CH_3	*n*-Bu	80	96
16[c]	**5o**	**3c**	Ph	CO_2CH_3	PMP	99	85
17[c]	**5o**	**4**	Ph	CO_2CH_3	PMP	95	85
18[c]	**5p**	**3c**	Ph	$CH_2CO_2CH_3$	PMP	85	96
19	**5p**	**4**	Ph	$CH_2CO_2CH_3$	PMP	65	95
20[c]	**5q**	**3c**	Ph	CH_2NO_2	PMP	99	93

Reaction conditions: **5a** (0.1 mmol), **cat**. 0.01 mmol, $HSiCl_3$ (0.35 mmol, 35 μL) in CH_2Cl_2 (1 mL) at 0℃ for 18 h; [a] isolated yield; [b] de termined by HPLC on chiral stationary phase; [c] reaction performed at -10 ℃.

Both catalysts **4** and **3c** promoted the reduction of *N*-aryl and *N*- alkyl substituted imines in >90% yield and enantioselectivities constantly ranging from 90% to 98%. The synthesis of α– and β-amino esters was also accomplished, in up to 96% e.e. The reduction of 3-alkoxy-substituted acetophenone imines (**5j-l**), either *N*-benzyl protected (as precursor of primary amine derivatives), or *N*-(3-phenylpropyl) substituted (imine **5m**), represents a practical and efficient entry to the synthesis of enantiomerically pure valuable pharmaceutical compounds, used in the treatment of Alzheimer and Parkinson diseases, hyperparathyroidism, neuropathic pains and neurological disorders (Figure 3). [16]

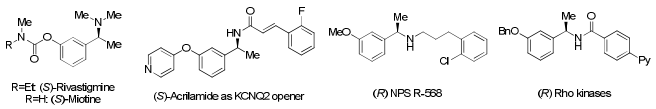
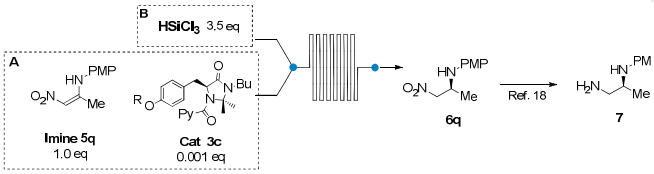


Figure 3. Chiral amines as valuable pharmaceutically active compounds.

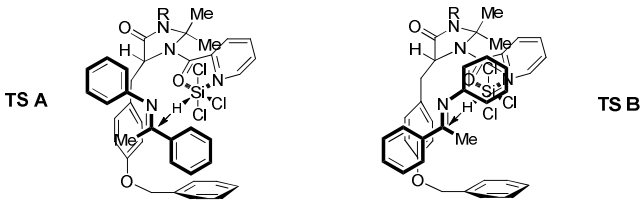
In view of a possible extension of this catalytic methodology to the industrial scale, the possibility to perform the reaction in flow reactors was also preliminarily investigated (Scheme 2).[17] The reduction of model imine **5a** was successfully accomplished under continuous flow conditions. By running the reaction in a 0.5 ml mesoreactor for 20 minutes at 0℃, the chiral amine **6a** was obtained in 96% yield and 97% e.e. (see the SI).



Scheme 2. Continuous flow, organocatalytic enantioselective reduction**.**

In the same fluidic device the chiral α–nitro amine **6q** was also obtained with 88% e.e.; starting from this product the Raney Ni-catalysed reduction[18] afforded the chiral 1,2-diamine **7**, thus offering the possibility to realize a two steps, in flow, metal-free process.

The model tentatively proposed to rationalize the steric course of the enantioselective reduction catalyzed by **3c** is reported in Scheme 3.



Scheme 3. Proposed TS for the reduction promoted by catalyst **3c**.

In model **A**, that leads to the formation of the experimentally preferred (*R*) enantiomer, both the aromatic ring at the imine carbon and the protecting group at the imine nitrogen do not experiment the severe steric repulsions that greatly destabilize TS of model **B**.

In conclusion, a new class of chiral Lewis bases for imines hydrosilylation was developed; the most active catalyst promoted the reduction of a wide variety of functionalized substrates, very often in quantitative yields and enantioselectivities that typically were higher than 90%, and in some instances reached 98%. Remarkably, the chiral Lewis base of choice efficiently catalyzed the reaction with a catalyst loading as low as 0.1% mol without any erosion of its stereoselectivity. The synthesis of enantiopure chiral amines on multi-gram scale, as well as the possibility to perform the organocatalytic enantioselective reduction under continuous flow conditions have been demonstrated.[19] We believe that the simple experimental procedure, the low cost of the reagents, the mild reaction conditions and straightforward isolation of the product after an aqueous work up, the exceptionally low loading of the metal-free catalytic species, and the possibility to realize *in continuo* processes, make the methodology attractive also for industrial applications.

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Keywords: Enantioselective reduction • Trichlorosilane • Chiral amines • Lewis bases • Organocatalysis

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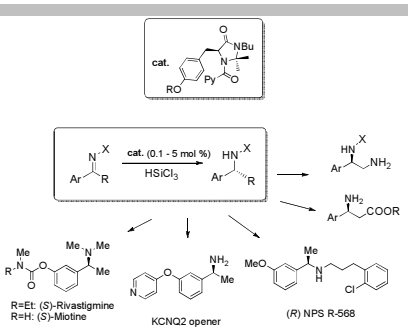
COMMUNICATION

An extremely active Lewis base, able to promote with catalyst loading low as 0.1-1% mol the $HSiCl_3$-mediated reduction of a great variety of imines in high yields and enantioselectivities typically higher than 90%, was discovered. The reaction has been efficiently performed also in flow mesoreactors, thus realizing metal-free enantioselective catalysis *in continuo*. Applications to the synthesis of advanced intermediates of APIs have been successfully accomplished.



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Page No. – Page No.
A new class of low-loading catalysts for a highly enantioselective, metal-free imine reduction of wide general applicability