Date: 14-10-14 13:48:39

Eurjoen Journal of Organic Chemistry

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DOI: 10.1002/ejoc.201403180

# Cinchona-Derived Picolinamides: Effective Organocatalysts for Stereoselective Imine Hydrosilylation

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Keywords: Alkaloids / Imines / Reduction / Organocatalysis / Lewis bases

Picolinamide–cinchona organocatalysts for the successful enantioselective reduction of ketomines were developed. For the first time, a new type of chiral Lewis base, a cationic species, is reported to efficiently organocatalyze the addition of trichlorosilane to imines. Excellent yields with good to high enantioselectivities (up to 91%) were obtained in the reduction of differently substituted substrates. Noteworthy,

## Introduction

Organocatalysis<sup>[1]</sup> has already made significant contributions to the production and discovery of new pharmaceuticals, agrochemicals, and other high added-value compounds.<sup>[2]</sup> Metal-free catalysts based on the cinchona skeleton are well known and have been employed for a diversity of reactions.<sup>[3]</sup> On the other hand, Lewis base based organocatalysts have been exploited with success in the stereoselective trichlorosilane-mediated reduction of N-substituted ketoimines<sup>[4]</sup> and in the asymmetric Biginelli reaction.<sup>[5]</sup> The hydrosilvlation reaction is a widely employed method for accessing enantiomerically enriched amines,<sup>[6]</sup> and it is extremely useful from an industrial perspective, as it affords chiral products by using typically very cheap reducing agents.<sup>[7]</sup> Several groups have used the organocatalytic strategy for the hydrosilylation of ketoimines.<sup>[8]</sup> Among the most successful Lewis bases used to activate HSiCl<sub>3</sub> are the picolinamides, simply synthesized by connecting picolinic acid to a chiral carbon skeleton.<sup>[9]</sup>

We now wish to report our preliminary results on the application of novel picolinamide–cinchona organocatalysts for the successful highly enantioselective trichlorosilanemediated reduction of ketomines to chiral amines; more-

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- Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201403180.

remarkably high turnover frequencies for the hydrosilylation of imines were observed; the catalyst of choice proved to be active even at a loading of only 1 mol-%. The loading was further reduced to 0.5 mol-%, and for very short reaction times (15 min) very impressive asymmetric catalyst efficiency speed values were reached.

over, as far as we are aware, we have achieved the highest turnover frequency for the hydrosilylation of imines to date.<sup>[10]</sup>

## **Results and Discussion**

Two types of picolinamide–cinchona catalysts were studied: neutral derivatives and pyridine-*N*-methylated compounds (methylated pyridinium salts **4** and **5**, Figure 1). Our rationale was that in the former case the picolinamide unit would coordinate to the silicon atom with the carboxyamide group and the pyridine nitrogen atom in an octahedral hexacoordinate complex, as usual for this class of catalysts; in the latter case, different HSiCl<sub>3</sub> activation modes may be envisaged: hexacoordination of the Si atom with the CO amide group and the quinuclidine N atom or complexation of trichlorosilane with the only amide oxygen atom to generate a pentacoordinate silane are both possible.

Organocatalysts 1–7 were prepared by using amide coupling and methylation (in the case of 4 and 5) procedures (Figure 1, for further details see the Supporting Information).<sup>[10]</sup> All the catalysts were screened in a preliminarily test reaction: the hydrosilylation of the *N*-phenyl imine of acetophenone by using trichlorosilane (3 equiv.) and the catalyst (10 mol-%) in dry CH<sub>2</sub>Cl<sub>2</sub> (Scheme 1;  $\mathbb{R}^1 = \mathbb{H}$ ,  $\mathbb{R}^2$ = Ph,  $\mathbb{R}^3 = \mathbb{M}e$ ).<sup>[11]</sup>

In all cases, excellent yields and high enantioselectivities ranging from 77 to 90% *ee* were obtained (Table 1). Whereas *epi*-quinine derivatives **2** and **3** catalyzed the reaction generally with 80% *ee*, *epi*-quinidine derivatives **6** and 7 were more efficient in terms of both chemical and stereochemical efficiency; they afforded the chiral amine (with the opposite absolute configuration) in up to 90% *ee*. Lowering the reaction temperature resulted in only a marginal Date: 14-10-14 13:48:39

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Figure 1. Cinchona-pyridinecarboxyamide catalysts studied in this work.



Scheme 1. Enantioselective organocatalytic reduction of ketoimines.

increase in the enantioselectivity. Noteworthy, *epi*-quininederived methylated pyridinium salts **4** and **5** promoted the formation of the (*S*) enantiomer, as did corresponding neutral compound **1**, with higher enantioselectivity, up to 90%*ee* in the case of tetrafluoroborate salt **5** (Table 1, Entry 5).

Table 1. Screening results with catalysts 1-7 in the hydrosilylation of the *N*-phenyl imine of acetophenone.

Entry	Catalyst	<i>T</i> [°C]	Yield <sup>[a]</sup> [%]	ee <sup>[b]</sup> [%]
1	1	0	97	80 (S)
2	2	0	91	77 (S)
3	3	0	83	81 (S)
4	4	0	77	79 (S)
5	5	0	75	90 (S)
6	6	0	98	81 ( <i>R</i> )
7	7	0	99	90 (R)
8	6	-20	51	83 ( <i>R</i> )
9	6	-40	23	84 ( <i>R</i> )

[a] Yield of isolated product. [b] Determined by HPLC on a chiral stationary phase.

The catalytic behavior of neutral picolinamides 1, 6, and 7 in the reduction of different substrates was then briefly investigated (Scheme 1, Table 2). *epi*-Quinidine-based catalyst 7 featuring a hydroxy group on the quinoline ring proved to be constantly the best performer; it often afforded the corresponding chiral amines in quantitative yields with 90% *ee*.

Table 2. Reduction of ketoimines promoted by neutral chiral picolinamides.

Entry	R <sup>1</sup> /R <sup>2</sup> /R <sup>3[a]</sup>	Catalyst	Т [°С]	Yield [%]	ee [%]
1	H/Ph/Et	1	25	77	81 (S)
2	H/Ph/Me	1	0	97	80 (S)
3	H/Ph/Me	6	0	93	81 ( <i>R</i> )
4	H/Ph/Me	7	0	99	90 ( <i>R</i> )
5	H/PMP/Me	7	0	97	90 ( <i>R</i> )
6	4-Cl/PMP/Me	7	0	99	91 ( <i>R</i> )
7	4-Br/PMP/Me	7	0	98	88 (R)
8	3-Br/PMP/Me	7	0	77	89 (R)
9	H/PMP/CO <sub>2</sub> Me	7	0	93	80 (S)
10	H/PMP/CH <sub>2</sub> CO <sub>2</sub> Me	6	0	87	83 (R)
11	H/PMP/CH <sub>2</sub> CO <sub>2</sub> Me	7	0	99	90 ( <i>R</i> )

[a] PMP = p-methoxyphenyl.

We also looked at imino esters: whereas  $\alpha$ -imino derivatives were reduced with decent enantioselectivity (Table 2, Entry 9; 93% yield with 80% *ee*),  $\beta$ -imino esters were converted into  $\beta$ -amino esters in up to 99% yield with 90% *ee* (Table 2, Entries 10 and 11).

The activity of methylated, cationic catalysts was also investigated (Table 3). By using cationic species 4 and 5, derived from *epi*-cinchonidine, in the reduction of the *N*phenyl imine of propiophenone, the corresponding (*S*) chiral amine was obtained as the major enantiomer; this indicated that the mechanism for the hydrosilylation of imines was equivalent to that operating with neutral picolinamides 1–3. The product was isolated in up to 84% *ee* at room temperature (Table 3, Entry 3).

Table 3. Hydrosilylation of ketoimines promoted by cationic picolinamide 5.

Entry	$R^{1}/R^{2}/R^{3[a]}$	<i>Т</i> [°С]	Yield [%]	ее [%]
1	H/Ph/Et	0	80	80 (S)
2	H/Ph/Et	-20	79	80 (S)
3	H/Ph/Et	25	86	84 (S)
4 <sup>[b]</sup>	H/Ph/Et	25	47	65(S)
5	4-NO <sub>2</sub> /Ph/Me	25	68	83 (S)
6	4-MeO/Ph/Me	25	58	84 (S)
7	4-MeO/4-BrC <sub>6</sub> H <sub>4</sub> /Me	25	10	69 (S)
8	$4-NO_2/3-BrC_6H_4/Me$	25	75	76 <sup>[c]</sup>
9	4-MeO/3-BrC <sub>6</sub> H <sub>4</sub> /Me	25	20	69 <sup>[c]</sup>
10	H/Ts/Et	25	73	73(S)
11	H/PMP/Me	0	71	89( <i>S</i> )
12	Cl/PMP/Me	0	85	83( <i>S</i> )
13	H/PMP/CO <sub>2</sub> Me	0	93	81 ( <i>R</i> )
14	H/Ph/CH <sub>2</sub> CO <sub>2</sub> Et	25	72	70 <sup>[c]</sup>
15	Br/PMP/CH <sub>2</sub> CO <sub>2</sub> Me	0	> 99	85 (S)

[a] Ts = *p*-tolylsulfonyl. [b] Reaction was run in chloroform. [c] Major enantiomer configuration unknown.

The catalyst promoted the reaction with good chemical and stereochemical efficiency for a wide range of aryl ketoimines. Interestingly, a good level of enantioselectivity was maintained in the reduction of *N*-tosyl imines (Table 3, Entry 10), whereas higher *ee* values were obtained with *N*-*p*methoxyphenyl-substituted ketoimines (Table 3, Entries 11– 13 and 15).

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Effective Organocatalysts for Stereoselective Imine Hydrosilylation

Having thus determined the scope of catalyst **5** in the hydrosilylation reaction, we studied various loadings of this novel organocatalyst and looked at the turnover frequency (TOF), with a view to its industrial application. The results were very encouraging (Table 4): the loading of the catalyst was reduced to 1 mol-%, but the product was still obtained in 86% yield with 80% *ee* after a reaction time of 18 h (Table 4, Entry 4). Upon reducing the quantity of trichlorosilane to 1.5 equiv., the highest TOF of 31.0 h<sup>-1</sup> (at a loading of 10 mol-% catalyst) was reached with a remarkable 87% *ee*. Noteworthy, these results favorably compare with the best results so far obtained with organocatalysts.

Table 4. Catalyst loading optimization studies of **5** in the hydrosilylation of the *N*-phenyl imine of propiophenone.

Entry	<b>5</b> [mol-%]	Yield <sup>[a]</sup> [%]	ее <sup>[b]</sup> [%]	TOF [h <sup>-1</sup> ]	ACES <sup>[12]</sup> [h <sup>-1</sup> ]
1 <sup>[c]</sup>	20	85	85	0.24	0.08
2 <sup>[c]</sup>	10	86	84	0.48	0.17
3[c]	5	88	82	0.98	0.34
4 <sup>[c]</sup>	1	86	80	4.78	1.61
5 <sup>[c]</sup>	0.5	80	72	8.67	2.64
6 <sup>[d]</sup>	10	81 <sup>[e]</sup>	90	8.1	3.08
7 <sup>[d]</sup>	5	67 <sup>[e]</sup>	88	13.4	4.98
8 <sup>[d]</sup>	10	77 <sup>[f]</sup>	88	15.4	5.72
9 <sup>[d]</sup>	10	55 <sup>[g]</sup>	87	31.0	8.03

[a] Yield of isolated product. [b] Determined by HPLC on a chiral stationary phase. [c] Reaction time: 18 h. [d] HSiCl<sub>3</sub> (1.5 equiv.) was added. [e] Reaction time: 1 h. [f] Reaction time: 30 min. [g] Reaction time: 15 min.

We also evaluated the asymmetric catalyst efficiency speed (ACES) on the basis of the asymmetric catalyst efficiency equation that was originally developed by El-Fayyoumy et al. in 2009.<sup>[12]</sup> This formula allows one to unambiguously compare the overall efficiency and briskness of any asymmetric catalytic process; the central dogma is that an asymmetric catalyst may be considered more efficient if fewer atoms are utilized to give a product with a specific *ee* value. The best result was obtained at a catalyst loading of 10 mol-% with 1.5 equiv. of silane over 15 min (8.03 h<sup>-1</sup>; Table 4, Entry 9).

Overall, by using the ACES formula, this represents an excellent performance in terms of catalytic efficiency for the imine hydrosilylation reaction. For instance, in the case of this reaction the best ACES values were between 0.1 and 0.3 h<sup>-1</sup>. To date, only the imidazole-based catalyst reported by Jones's group in 2009 favorably compares with catalyst **5**.<sup>[4b,13]</sup> For the sake of comparison, in the case of the pion-eering Hajos–Parrish–Eder–Sauer–Wiechert reaction<sup>[1]</sup> with L-proline, the best ACES of 2.31 h<sup>-1</sup> was obtained.

## Conclusions

We reported a group of picolinamide–cinchona derivatives, including for the first time a chiral cationic picolinamide, that give excellent results in the hydrosilylation of ketoimines. Our studies revealed that we could reduce the loading of the catalyst down to 0.5 mol-% and still obtain satisfactory results and very impressive ACES values. The newly developed multifunctional chiral Lewis bases represent an easy entry in an unexplored class of catalysts for stereoselective reductions that are characterized by multiple possible modes of action. We are currently investigating the mechanism of these catalysts, looking at their application in the synthesis of biologically active targets, and optimizing their immobilization to solid supports.

## **Experimental Section**

**General Remarks:** Cinchonidine and all other reagents and solvents used in this work were purchased from Sigma–Aldrich, Fluka, or Acros Organics and were used as received. The imine substrates were prepared by using known methods.<sup>[14,15]</sup> All details on the synthesis of the catalysts, analyses of the products, and characterization data are reported in the Supporting Information.

General Procedure for the Catalytic Asymmetric Hydrosilylation with Catalysts 1–7: The ketoimine (0.33 mmol) and the organocatalyst (0.1–20 mol-%) were dissolved in dry  $CH_2Cl_2$  (1 mL). The mixture was then cooled in an ice bath; after 15 min, HSiCl<sub>3</sub> (1.5– 3 equiv.) was added dropwise. Once the addition was complete, the mixture was stirred at room temperature for 15 min to 18 h. The reaction was quenched by the addition of a saturated solution of NaHCO<sub>3</sub> (2 mL). The organic phase was extracted with  $CH_2Cl_2$ (3 × 10 mL), dried with anhydrous MgSO<sub>4</sub>, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography with silica gel by using literature conditions. The enantiomeric excess was determined by using HPLC with chiral columns (for further details see the Supporting Information).

**Supporting Information** (see footnote on the first page of this article): Synthesis and characterization of the catalysts, synthesis of the imine, enantioselective reduction procedures, NMR and mass spectra, and HPLC traces of the organocatalytic reductions.

### Acknowledgments

P. C. B. is grateful to the Fundação para a Ciência e a Tecnologia (FCT) for the award of a Ph.D. grant (SFRH/BD/61913/2009). This work was conducted by using finances from the FCT through strategic project PEst-OE/QUI/UI0619/2011. We acknowledge LabRMN at FCT-UNL for the acquisition of the NMR spectra; the NMR spectrometers are part of the National NMR Facility supported by the Fundação para a Ciência e a Tecnologia (RECI/ BBB-BQB/0230/2012). The staff at the MS laboratory at CACTI, University of Vigo, is acknowledged for the MS analyses. We thank Dr. Olivia Furtado Burke, Laboratório Nacional de Energia e Geologia (LNEG), Lisbon, for performing some of the optical rotation measurements. Chiratecnics Lda (www.chiratecnecnics.com) is acknowledged for its interest in this project and its valuable support. M. B. thanks European Cooperation in Science and Technology (COST) action CM9505 "ORCA" Organocatalysis. A. G. acknowledges the Università degli Studi di Milano for a Ph.D. fellowship.

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Received: September 8, 2014 Published Online: ■

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Date: 14-10-14 13:48:39

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**Organocatalysis** 

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Cinchona derivatives for the successful enantioselective addition of trichlorosilane to ketimines are developed. Excellent yields with good to high enantioselectivities (up to 91%) are obtained in the reduction of differently substituted substrates. Remarkably high turnover frequencies for imine hydrosilylation are observed at a catalyst loading of only 1 mol-%.



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