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Synthesis of an advanced precursor of Rivastigmine: *Cinchona*-derived quaternary ammonium salts as organocatalysts for stereoselective imine reductions

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ABSTRACT

The enantioselective reduction of ketoimines has been successfully realized, using trichlorosilane as the stoichiometric reducing agent in the presence of catalytic amounts of a Lewis base, specifically a *Cinchona* derivative. For the first time, a novel class of derivatives was studied, featuring a picolinamide unit bound to the alkaloid scaffold, further functionalized as quaternary ammonium salt at the quinuclidine ring. Excellent yields and from good to high enantioselectivities (up to 92% ee) were obtained in the reduction of ketoimines. The novel catalysts were successfully employed in the synthesis of an enantiomerically pure advanced precursor of the blockbuster drug Rivastigmine.

The reduction of carbon–carbon and carbon–nitrogen double bonds is one of the most important chemical transformations since it leads very often to the generation of new stereocenters in the molecule. The control of the stereochemical outcome of the reduction process, in an attempt to obtain preferentially one stereoisomer over the other ones, requires the use of a 'chiral technology'. Despite several difficulties and many open questions, enantioselective catalysis is the modern answer to this question and the key of all future technologies.[1] The replacement of organometallic systems with equally efficient metal-free catalysts[2] represents a further attractive opportunity, in view of possible applications in the future of non toxic, low cost, and environmentally friendly promoters on industrial scale.[3]

This holds true also in the case of enantioselective reduction of carbon–nitrogen double bond, that leads to the formation of chiral amines, compounds of extraordinary importance in different fields,[4] specially as pharmaceutical products, where complexity and multifunctionality call for methodologies with high chemo-, regio-, diastereo-, and enantiocontrol. Catalytic asymmetric hydrogenation[5] of imines represents a versatile method for access to chiral nitrogen-containing substrates;[6] however, stereoselective hydrogenation of carbon–nitrogen double bonds is not very well explored, due also to the possible deactivation and/or poisoning of catalysts by molecules containing nitrogen and sulfur atoms. Therefore organocatalytic methodologies[7] offer an appealing alternative, since they may avoid problems due to the presence of toxic metal, whose leaching could contaminate the product, a key point for pharmaceuticals, agrochemicals, and fragrances.

One of the most developed metal-free methodologies to enantioselectively reduce ketoimines relies on the use of the very cheap and readily available trichlorosilane as the reducing agent in the presence of a chiral Lewis base.[8] Among the most successful basic ligands used to activate $HSiCl_3$, picolinamides have found great success,[9] due also to the easiness of their preparation, simply connecting picolinic acid to a chiral carbon skeleton.[10]

We have recently reported a novel group of *Cinchona*-based picolinamides, which gave excellent results in the ketoimine hydrosilylation.[11] Noteworthy, remarkably high TOFs and very short reaction times for imine hydrosilylation were observed, the catalyst of choice being successfully active even at 1 mol % only. Based on those very encouraging results, we decided to take advantage of the great richness of functionalities featuring the *Cinchona* alkaloids and explore a further structure variation of this new family of catalysts.

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Indeed, quinine (and quinidine) derivatives are small yet complex molecules containing five stereogenic centers, a basic and nucleophilic quinuclidine, a quinoline unit, a secondary alcohol, an aryl methyl ether, and a terminal olefin (Fig. 1).[12]

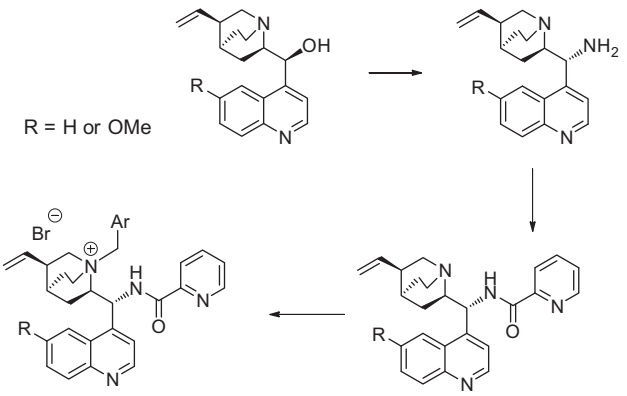
All of these points of molecular variety have been extensively exploited for the facile modification of the naturally occurring alkaloids to develop synthetic, tailor-made compounds for specific applications. It is also known that *Cinchona* alkaloids can adopt in solution several conformations; solvent change, protonation, or quaternarization of the *N*-quinuclidine moiety may induce three-dimensional structural modifications. Therefore we decided to exploit the unique molecular recognition abilities of this natural scaffold and to further explore the catalytic behavior of newly modified *Cinchona*-derived picolinamides, characterized by the presence of quaternary ammonium salt as additional steric and electronic element of stereocontrol (Fig. 1).

In synthesizing the novel metal-free catalysts, we followed the synthetic plan described in Scheme 1. Starting from the naturally occurring alkaloid, the C9-hydroxyl group was easily converted into the corresponding amine in a three step preparation and a single purification;[13] the amino-*Cinchona* derivative was then reacted with picolinic acid to afford an enantiomerically pure picolinamide.[11] Finally the reaction with benzyl bromide (or analog activated bromide) afforded the desired novel chiral Lewis base, featuring a quaternary ammonium salt.

This straightforward and experimentally very simple synthesis allowed the preparation of different *Cinchona* alkaloid derivatives in good and reliable yields. Some representatives of this new family of catalysts for enantioselective hydrosilylation of ketoimines are reported in Figure 2. *Epi*-cinchonine and *epi*-cinchonidine quaternary ammonium salts **1**–**3** were prepared, as well as analogous *epi*-quinidine derivatives **4**–**6**, typically by quaternarization of the quinuclidine ring by reaction with benzyl or methyl bromide.[14] For the sake of comparison in picolinamides **7**–**9**, non functionalized at the quinuclidine ring, are reported in Figure 2.[15]

All the catalysts were preliminarily tested in the model reaction, the hydrosilylation of the *N*-phenyl-imine of acetophenone (Table 1), using 3 mol equiv of trichlorosilane and 10 mol% of the catalyst in dry DCM, for 18 h at 0 °C (Scheme 2).

In all cases excellent yields were obtained; as expected, Cinchonine and Cinchonidine derivatives behaved as *quasi-enantiomers* and led to the formation of the products with opposite absolute configuration. Enantioselectivities range from modest to very good (up to 87% ee), with *epi*-cinchonine derivative **2** performing clearly better than *epi*-quininidine-derived catalysts **4**–**6** (Table 1). From the reported results, it can be noted that the benzyl salt **2** showed an improvement compared to the parent catalyst **7** and that the picolinamides derived from Cinchonine (**2**) performed slightly better than the catalyst synthesized from Cinchonidine **1**,



Scheme 1. Synthetic sequence for the preparation of novel *Cinchona*-based catalysts for enantioselective hydrosilylation of imines.

thus confirming the trend already observed in our previous work.[11] However, poorer results were obtained with compound **3**, which features a more sterically hindering arylmethyl moiety at the quinuclidine nitrogen, clearly showing that it is not possible to directly correlate the catalyst stereochemical efficiency with the bulkiness of the ammonium salt substituent.

It is worth noting that molecules **1**–**9** are representatives of a wide class of multifunctional chiral Lewis bases, as chiral catalysts for stereoselective reductions, characterized by multiple possible modes of action. Indeed, while compounds **7**–**8** feature the picolinamide group as coordinating unit to $HSiCl_3$, and the basic quinuclidine ring that can also play a role in the activation of the reducing agent, catalyst **2** has the only picolinamides as activating unit of trichlorosilane. Furthermore, catalyst **9** might still behave as a bifunctional catalyst, presenting a different coordination mode, with the carboxyamide group and the quinuclidine nitrogen atom, while catalyst **6** probably functions as a monodentate catalyst. Further studies are required in order to further determine the different possibilities that the *Cinchona* scaffold can offer, principally for tuning the catalyst behavior by exploiting steric and electronic modifications in the catalyst structure.

Once **2** was identified as the most promising catalyst, a screening of the reaction conditions, that is, solvent and temperature, was performed; the results are reported in Table 2.

While high chemical yields could be obtained in different reaction media, chlorinated solvents seem to be the best option to guarantee high levels of enantioselectivity at 0 °C; while the reaction at 22 °C led to the formation of the chiral amine in lower enantioselection, by decreasing the temperature it was possibly to further improve the enantioselection of the process, up to 92% ee, although with a harsh drop in chemical yield. Finally, the catalyst loading was

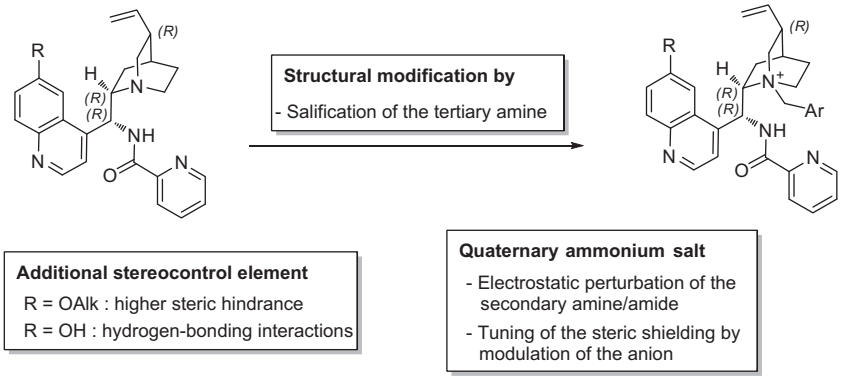


Figure 1. Novel *Cinchona*-based picolinamides featuring quaternary ammonium salts.

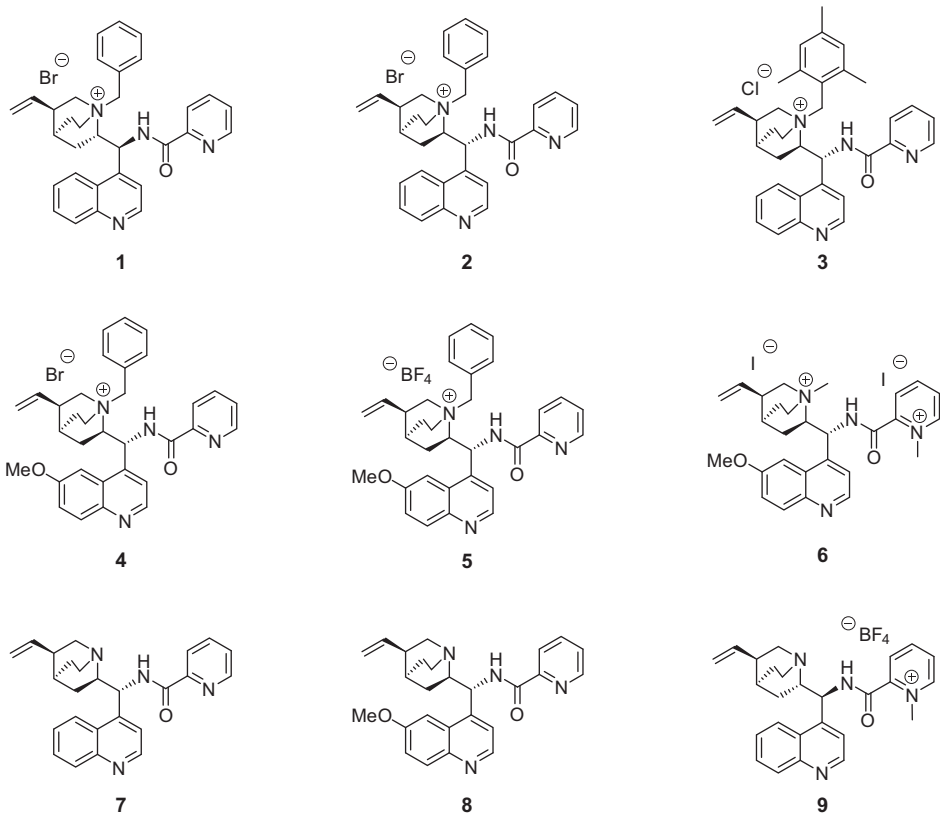


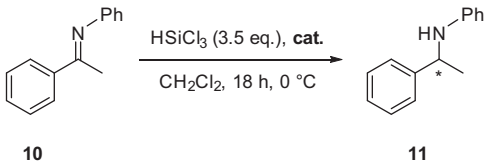
Figure 2. *Cinchona* alkaloid quaternary ammonium salts and analogs as catalysts for enantioselective trichlorosilane addition to imines.

Table 1
Stereoselective hydrosilylation of *N*-phenyl-imine of acetophenone promoted by catalyst **1**–**9**[a]

Entry	Catalyst	Yield %[b]	ee %[c]
1	**1**	91	75 (*S*)
2	**2**	98	87 (*R*)
3	**3**	67	67 (*R*)
4	**4**	93	43 (*R*)
5	**5**	91	51 (*R*)
6	**6**	87	65 (*R*)
7	**7**	97	77 (*R*)
8[d]	**8**	98	87 (*R*)
9[d]	**9**	75	90 (*S*)

[a] Typical experimental conditions: 0.1 mol equiv of catalyst, 1 mol equiv of imine, 3,5 mol equiv of trichlorosilane, 18 h reaction time in DCM at 0 °C.
[b] Yields of isolated products.
[c] As determined by HPLC on a chiral stationary phase; yields and ee are average of duplicate experiments.
[d] As reported in the literature (see Ref. 13).

also briefly investigated; we were happy to see that catalyst **2** could maintain its activity also when used at loadings of 5 mol% or even 1 mol% (entries 8 and 9 of Table 2), always affording the chiral amine with comparable enantioselectivity.



Scheme 2. Screening of catalysts **1**–**9** in the enantioselective hydrosilylation of *N*-phenyl imine of acetophenone.

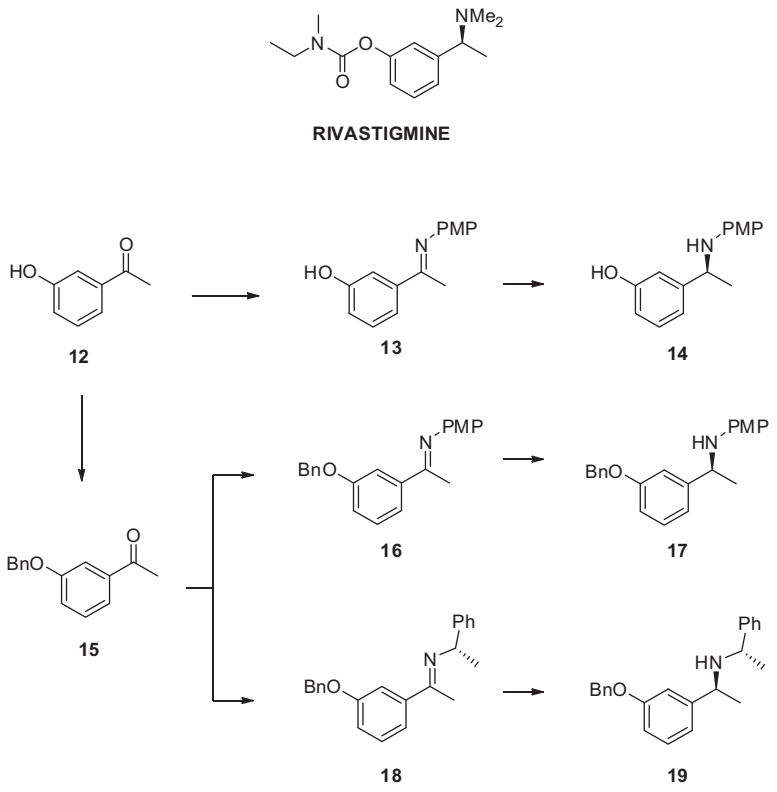
In the attempt to test the applicability of the new catalysts in the synthesis of a product of pharmaceutical interest, we performed a preliminary investigation directed at the synthesis of an advanced Rivastigmine precursor.[16]

At the beginning of our studies, we investigated the possibility to perform the enantioselective reduction directly on the *N*-PMP imine **13** easily obtained from the commercially available ketone **12**. However the modest enantioselectivities observed prompted us to protect the phenolic group as benzyl ether, to give ketone **15** (Scheme 3).

Table 2
Optimization studies for the enantioselective reduction of *N*-phenyl-imine of acetophenone **10** catalyzed by **2**[a]

Entry	*T* (°C)	Solvent	Yield %[b]	ee %[c]
1	0	DCM	98	87
2	0	$CHCl_3$	95	87
3	0	Et_2O	97	31
4	0	THF	98	23
5	0	CH_3CN	98	53
6	−20	DCM	67	83
7	−40	DCM	33	92
8[d]	0	DCM	95	86
9[e]	0	DCM	83	85
10	22	DCM	91	71
11	22	$CHCl_3$	92	73

[a] Unless different specifications, typical experimental conditions were: 0.1 mol equiv of catalyst, 1 mol equiv of imine, 3,5 mol equiv of trichlorosilane, 18 h reaction time at 0 °C.
[b] Yields of isolated products.
[c] Enantiomeric excess determined by HPLC analysis on a chiral stationary phase.
[d] Reaction was run with 5 mol% cat. at 0 °C.
[e] Reaction was run with 1 mol% cat. at 0 °C.



Scheme 3. Preliminary studies on the synthesis of Rivastigmine.

The *O*-benzyl protected ketone was then converted into two different ketimines, the *N*-PMP protected imine **16** and imine **18** obtained through the reaction with (*S*)-phenyl ethylamine.[17] The reduction of imine **16** afforded the product in good yield but modest enantioselectivity,[18] even at a lower reaction temperature (entries 3 and 4, Table 3).[19]

However, the reduction of imine **18** led to the formation of the expected chiral amine **19** in 81% yield with virtually complete diastereocontrol as observed by NMR spectroscopy.[20] The same chiral amine was obtained with high stereoselectivity using catalyst **9**, while, as expected, less stereocontrol was observed when the mismatch combination of imine **18** and catalyst **8** was employed. The deprotection by hydrogenolysis of intermediate **19** would afford an advanced precursor of the target molecule,[21] thus providing a very promising and straightforward route to enantiomerically pure Rivastigmine.

Table 3
Preliminary investigation on the possible synthetic strategies for the enantioselective synthesis of Rivastigmine[a]

Entry	Catalyst	Substrate	Reduction product	Yield %[b]	ee %[c]
1	**1**	**13**	**14**	44	65
2	**Ent-8**	**13**	**14**	35	55
3	**1**	**16**	**17**	85	43
4[d]	**1**	**16**	**17**	51	65
5	**1**	**18**	**19**	81	>96[e]
6	**8**	**18**	**19**	73	68[e]
7	**9**	**18**	**19**	65	94[e]

[a] Unless different specifications, typical experimental conditions were: 0.1 mol equiv of catalyst, 1 mol equiv of imine, 3,5 mol equiv of trichlorosilane, 18 h reaction time at 0 °C.
[b] Yields of isolated products.
[c] As determined by HPLC on a chiral stationary phase; yields and ee are average of duplicate experiments.
[d] Reaction was run at −20 °C.
[e] dr ratio was determined by ^{1}H MR spectroscopic on the crude reaction mixture and confirmed after chromatographic purification.

In conclusion, we have reported a new class of *Cinchona* derivatives, featuring a picolinamide unit bound to the alkaloid scaffold, further functionalized as a quaternary ammonium salt at the quinuclidine ring. The best catalyst was able to promote the reduction of *N*-phenyl imine of acetophenone in up to 92% ee. The new catalysts were also successfully employed in preliminary studies aimed at the development of an easy and straightforward preparation of the blockbuster drug Rivastigmine. The main feature of the described class of catalysts is their high tunability, coupled with the capacity to modulate both the electronic and the steric properties as well as to explore different coordination modes, experimenting with different combinations of the coordinating units (carboxyamide, pyridine ring, and quinuclidine moiety).

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Supplementary data

Supplementary data (copies of ^{1}H and ^{13}C NMR spectra of new catalysts. ^{1}H NMR spectra and HPLC chromatograms on chiral stationary phase of products of reduction of ketoimines) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.08.086.

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18. Typical imine reduction: the catalyst (0.02 mmol, 0.1 equiv) and a solution 0.9 M of the imine in dry CH_2Cl_2 (0.2 mmol, 1 equiv) were introduced in a 10 mL vial under N_2 atmosphere and further diluted in 2 mL of dry CH_2Cl_2. The mixture was cooled to the desired temperature and stirred for 15 min, after which a solution 1.6 M in CH_2Cl_2 of $HSiCl_3$ (0.7 mmol, 3.5 equiv) was added. The mixture was stirred for 18 h, then quenched with NaOH 10% aq. until a basic pH was reached, stirred at room temperature for 30 min, filtered over celite pad, and washed with CH_2Cl_2 (10 mL) and ethyl acetate (10 mL). The solvent was removed under reduced pressure and the desired amines were purified by flash column chromatography on silica gel. Absolute configuration was determined by comparison of the sign of the optical rotation of the product with literature data.
19. The reduction with catalyst **1** of the 3-methoxy-protected *N*-PMP ketoimine at 0 °C gave comparable results (81% yield, 37% ee).
20. *N-(1-(S)-Phenylethyl)-ethan-1-(3-(benzyloxy)phenyl)-1-amine* ***19***. The crude NMR showed the presence of product with >96% diastereoisomeric ratio. The product was purified by flash column chromatography on silica gel with a 8:2 hexane/ethyl acetate mixture as eluent. R_f = 0.21. title compound was obtained in 81% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.47–7.20 (m, 11H), 6.89–6.87 (m, 2H), 6.81 (d, 1H, J = 7.5 Hz), 5.08 (s, 2H), 3.49 (m, 2H) 1.26 (d, 6H, J = 6.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.05, 147.72, 145.77, 137.16, 129.42, 128.60, 128.42, 127.95, 127.56, 126.71, 119.41, 113.08, 69.96, 55.11, 24.94. MS (ESI+): m/z = calcd for $C_{23}H_{25}NO^+$ = 331.19, found 332.0 [M+H].
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