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

Andrea Genoni [a], Maurizio Benaglia [a,b,*], Emanuele Mattiolo [a], Sergio Rossi [a], Laura Raimondi [a], Pedro C. Barrulas [c], Anthony J. Burke [c,*]

[a] Dipartimento di Chimica, Universita' degli Studi di Milano, via Golgi 19, I-20133 Milano, Italy
[b] Istituto di Scienze e Tecnologie Molecolari, ISTM-CNR, via Golgi 19, I-20133 Milano, Italy
[c] Department of Chemistry and Chemistry Center of Évora, University of Évora, Rua Romão Ramalho, 59, 7000 Évora, Portugal

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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.

* Corresponding authors. Tel.: +39 0250314171; fax: +39 0250314159 (M.B.).
E-mail address: maurizio.benaglia@unimi.it (M. Benaglia).

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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]

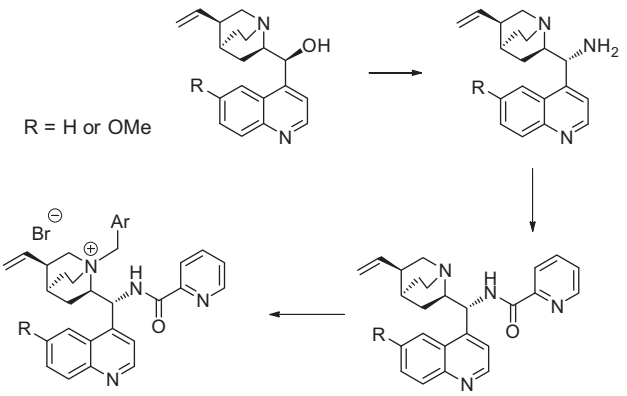
All of these points of molecular variety have been extensively exploited for the facile modification of the naturally occurring alkaloids to develop synthetic, tailor-made compounds for specific applications. It is also known that *Cinchona* alkaloids can adopt in solution several conformations; solvent 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

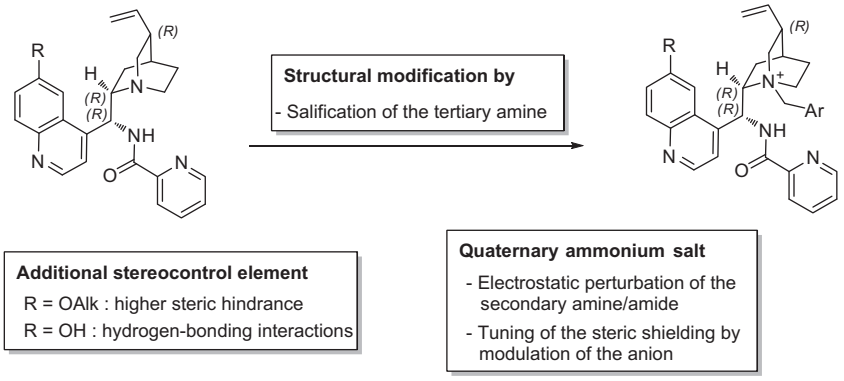


Figure 1. Novel *Cinchona*-based picolinamides featuring quaternary ammonium salts.