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Synthesis of novel cinchona-amino acid hybrid organocatalysts for asymmetric catalysis

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ABSTRACT

Three novel subclasses of cinchonidine derivatives coupled to diverse amino acids were prepared in very good overall yield and tested in a benchmark organocatalytic aldol reaction, between acetone and aromatic aldehydes. These subclasses are a family of amino acid-cinchonidine (subclass A), *N*-formamides-cinchonidine (subclass B) and dipeptide-cinchonidine (subclass C) hybrids. Our main goal, besides obtaining very good yields and enantioselectivities, was to understand the influence of the amino acid side chain residues on the enantioselectivity of the asymmetric aldol reactions. Different amino acid tethered cinchonidine hybrids were compared and their catalytic behaviour was evaluated, allowing good enantioselectivities to be achieved, 92% ee in one case. Other reactions such as Biginelli, Michael addition and ketimine hydrosilylation reactions were screened with these ligands, but the outcome was less successful.

1. Introduction

One of the most powerful means for obtaining enantiomerically enriched compounds is via asymmetric catalysis.[1,2] The most common way of achieving this is with metal based catalysts or enzymes. Over the last 15 years, organocatalysts have become important alternatives to these traditional catalysts.[2,3]

In the early 70s, Eder et al.[4a] and Hajos and Parrish[4b] reported ground-breaking work on the proline catalysed Robinson annulation, thus giving rise to the field of organocatalysis. However, only in 2000 did this field experience a remarkable renaissance, with key reports by List[5a] (aldol condensation with L-proline) and MacMillan[5b] (Diels–Alder reaction with imidazolidinone). From this time this field has witnessed significant and exponential growth.

Due to their considerable success, cinchona alkaloid based organocatalysts are considered to be 'privileged chiral catalysts'.[6,7] Cinchona alkaloids are recognized as having many medicinal applications, particularly with regard to malaria,[8] and also functioning as antiarrythmics,[9] sodium-channel blockers[10] as well as potential cytostatic agents.[11]

On the other hand, due to their structural complexity and ready availability, they can be used as chiral resolving agents, ligands for asymmetric catalysis,[12–14] and also as NMR discriminating agents.[15] Cinchona alkaloids have a bifunctional nature, which is apparent in the case of both quinine **QN** and cinchonidine **CD** (Fig. 1).

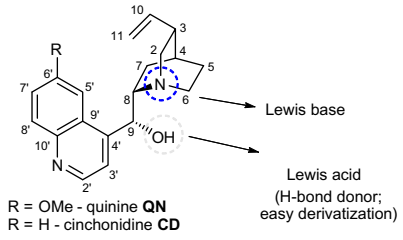

Figure 1. Structural attributes of quinine **QN** and cinchonidine **CD** alkaloids.

One of the beneficial characteristics of these molecules is the presence of a chiral cavity, and the potential to functionalize the 9-OH group; for instance, the functionalization of the OH group into more acidic groups or ones which are more effective as hydrogen bond donors. With regard to their organocatalytic activity, several key reactions can be successfully carried out, such as: Michael additions, Mannich, aldol, Baylis–Hillman, cycloadditions and Henry reactions.[12–14]

Amino acids are another class of natural compounds that play a very important role in asymmetric synthesis.[16,17] They have many

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diverse applications, and have been successfully applied in asymmetric organocatalytic reactions such as: Michael additions,[18] ketimine reductions with trichlorosilane,[19,20] multicomponent Biginelli reactions[21] and aldol reactions.[22–26]

Our main goal herein was the synthesis of three novel subclasses of cinchonidine-amino acid hybrids for asymmetric organocatalysis, using a benchmark aldol condensation as the test reaction. The subclasses that we targeted were amino acid hybrids based on cinchonidine (subclass A), *N*-formamides of some compounds from subclass A (subclass B) and dipeptide hybrids based on cinchonidine (subclass C) (Fig. 2).

Subclass A, has already been reported on,[27] however, our goal was to develop further specific examples of this class, with diverse amino side-chains. Subclass B is currently unknown in the literature, although *N*-formylated amine organocatalysts have already been extensively studied for organocatalyzed imine hydrosilylation reactions. Some molecules belonging to subclass C, are already known,[28] but to the best of our knowledge have not been exploited in catalysis to date. Our main motive was to carefully study and compare these three structural subgroups in a bench-mark aldol reaction (and other reactions) with a view to obtaining: (a) new efficient modular catalytic systems whose reactivity and asymmetry inducing capabilities could be easily tuned, and (b) to gain an insight into the most basic structural requirements within the molecule's chemical structure for controlling the reaction enantioselectivity. These molecules contain a number of structural and functional group diversity points, such as: the amino acid side-chain (aliphatic, aromatic or hydrogen), the amino acid nitrogen (primary, secondary cyclic or acyclic), as well as the incorporation of a carbonyl group or a new amino acid residue, which all have a potential influence on the stereochemical outcome of the reaction.

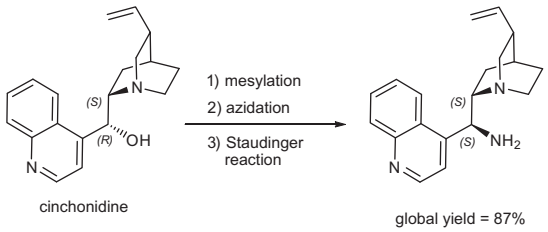
The first organocatalytic application of this type of compound was published by Chen et al.[27b] in 2008 when they synthesized Cinchona-(cinchonidine, cinchonine, quinidine and quinine)proline (D and L) hybrids, and applied them to enantioselective aldol reactions, affording very good results (97% yield and 98% ee).

Zhao et al.[27c] suggested a transition state model for the same prolinamides synthesized by Chen et al. that involves hydrogen bonding interactions between the protonated organocatalyst and the electrophile.

Recently, Huang et al.[29] reported on the synthesis of a small library of cinchona alkaloids (cinchonine and quinine) with a diverse range of amino acid residues in their structure (Ala, Val, Leu). They were screened in a series of asymmetric aldol reactions, giving very good yields (up to 96%) and enantioselectivities (up to 92% ee).

2. Results and discussion

The synthesis of all subclasses A, B and C was achieved using a common precursor; the amine (8S,9S)-9-amino(9-deoxy)-epi-cinchonidine, which was easily obtained in three reaction steps according to the literature from commercially available cinchonidine[30–32] (Scheme 1).



Scheme 1. General synthesis of amine (8S,9S)-9-amino(9-deoxy)-epi-cinchonidine.

With amine **4** in hand, we proceeded with the synthesis of our first library of cinchonidine derivatives: subclass A, and for this purpose we used the mixed anhydride method of Girgis and Prashad (Scheme 2).[33]

With this method we were able to successfully obtain a library of eight compounds with good results for subsequent screening in asymmetric aldol reactions (Fig. 3).

After concluding the synthesis of subclass A, we advanced with the synthesis of the respective *N*-formamide derivatives, subclass B, which were prepared (with the exception of compounds **1g** and **1h**) by *N*-formylation, including **2g** the formamide of amine **4**. Malkov and Kočovský have shown the importance of the presence of an *N*-formyl group in a variety of organocatalysts used in this reaction.[34] We wished to determine if the presence of this group might enhance the catalytic activity for other reaction types, such as: asymmetric aldol reactions,[35,36] Biginelli,[21] Michael[18] and ketone hydrosilylation reactions.[34,37,38,41,42]

Accordingly, based on the method used by Malkov and Kočovský[34a] for the *N*-formylation of L-valine derivatives, we created a library of amino acid cinchonidine *N*-formamide hybrids in good to excellent yields 62–99%, with overall yields of between 43% and 77% (Fig. 4).

Finally, subclass C was easily obtained in good yields using **1a** as the substrate by the mixed anhydride method (Fig. 5).

At this point, we started to evaluate the organocatalytic potential of these catalysts. Based on the pioneering work of Xiao[27] and Liu[27c] on the synthesis and application of prolinamides derived from Cinchona alkaloids in the asymmetric aldol reaction, we began studying the influence of various amino acid units on the outcome of a bench-mark aldol reaction. This was followed by their evaluation in various other asymmetric catalytic reactions such as Michael, Biginelli and hydrosilylation reactions.

In the case of the aldol reactions, we examined the bench-mark aldol reaction between acetone and *p*-nitrobenzaldehyde (Table 1) using the three subclasses of catalysts (see Table 1). It was possible to verify the reliability of our results; in the case of the cinchonidine-amino acid hybrids (subclass A) the results compared well to those of Xiao[27b] for the same reaction with prolinamide **1f**. Using the same conditions, Xiao obtained the desired product **6a**

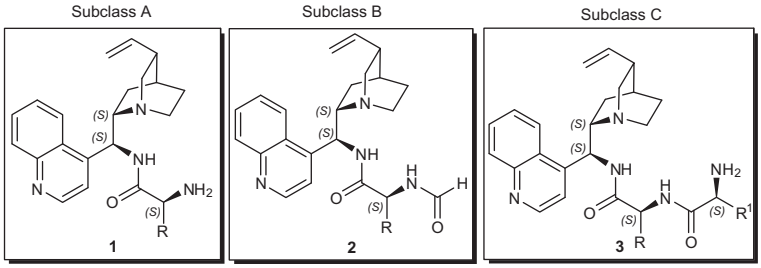


Figure 2. Novel subclasses of cinchonidine derivatives synthesized in this work.