SYNLETT Spotlight 115

Cinchona Alkaloid Derivatives as Chiral Organocatalysts

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This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

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Introduction

The last five years have witnessed a resurgence of interest in the cinchona alkaloids¹ [e.g. Quinine (**1**) and Quinidine (**2**)] due to their potential to serve as air- and moisture-insensitive asymmetric organocatalysts for a variety of enantioselective transformations. These materials are of

particular synthetic utility as they are inexpensive, readily available natural products and are obtainable in either of their *pseudo*-enantiomeric forms. In addition to ready availability, cinchona alkaloids also possess both Lewis acidic (H-bonding) and Lewis basic (quinuclidine nitrogen) sites, thus making them potentially useful for the promotion of a variety of reactions via *bifunctional catalysis*.

Abstracts

(A) The nucleophile-catalysed Staudinger reaction² (not to be confused with its azide-reduction³ namesake) is a process of considerable interest from a medicinal chemistry standpoint.⁴ Lectka et al.⁵ were the first to report the catalytic asymmetric [2+2] cycloaddition of ketenes with imines to form a variety of β -lactam compounds.

(B) The reaction of imines with activated alkenes (the aza-Baylis–Hillman reaction) catalysed by modified cinchona alkaloids has been reported. The use of a modified Quinidine-derived catalyst, i.e. β -isocupreidine, allowed the reaction between 1,1,1,3,3,3-hexafluoroisopropylacrylate and aromatic imines **5** to proceed in good yield with high enantioselectivity.⁶ Interestingly, the corresponding aldehyde substrates (the Baylis–Hillman reaction) gave products with the opposite configuration.⁷

(C) Gaunt and co-workers have described a novel enantioselective organocatalytic synthesis of functionalised cyclopropanes⁸ via intermediate ammonium ylides.⁹ These reactions yielded exceptional enantio- and diastereoselectivities with a range of functional groups.

(D) Cinchona alkaloids have been used as nucleophilic catalysts for the cycloaddition reactions involving ketenes and aldehydes.¹⁰ *O*-Trimethylsilyl derivatives of **1** and **2**, along with structurally diverse aldehydes, provided access to a range of optically active β -lactones.

(E) Reaction of dihydroquinine with the β -keto ester **9** gives rise to a chiral ammonium enolate, which reacts with an electrophilic peroxide in a face-selective manner to form α -hydroxy- β -keto esters **10** with moderate enantioselectivity. Subsequent diastereoselective reduction of **10** affords *anti*-1,2-diols.¹¹

(F) The cinchona alkaloid derivative-catalysed desymmetrisation of *meso*-anhydrides in the presence of methanol is an efficient strategy for the synthesis of non-racemic dicarboxylic acid monoesters.¹² The products were formed with high enantioselectivity (up to 98% ee) with 100% conversion of the anhydride using nucleophilic Sharpless AD ligands.¹³

(G) Corey and Huang have developed a cinchona alkaloid derivative¹⁴ capable of catalysing the Strecker reaction of *N*-allyl-benzaldimines with HCN. This provides a concise, versatile route to a variety of α -amino acids.

(H) An example of a cinchona alkaloid-catalysed asymmetric α -halogenation/esterification transformation involving ketenes has also been described.¹⁵ Synthetically useful enantiopure α -chloroesters are readily accessible from commercially available acid chlorides using this process.

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