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Cinchona Alkaloid Derivatives as Chiral Organocatalysts

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Introduction

The last five years have witnessed a resurgence of interest in the cinchona alkaloids [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 reaction (not to be confused with its azide-reduction namesake) is a process of considerable interest from a medicinal chemistry standpoint. Lectka et al. 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 to proceed in good yield with high enantioselectivity. Interestingly, the corresponding aldehyde substrates (the Baylis–Hillman reaction) gave products with the opposite configuration.

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

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

(E) Reaction of dihydroquinine with the \(\beta\)-keto ester \(9\) gives rise to a chiral ammonium enolate, which reacts with an electrophilic peroxide in a face-selective manner to form \(\alpha\)-hydroxy-\(\beta\)-keto esters \(10\) with moderate enantioselectivity. Subsequent diastereoselective reduction of \(10\) affords anti-1,2-diols.\textsuperscript{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.\textsuperscript{12} The products were formed with high enantioselectivity (up to 98\% ee) with 100\% conversion of the anhydride using nucleophilic Sharpless AD ligands.\textsuperscript{13}

(G) Corey and Huang have developed a cinchona alkaloid derivative\textsuperscript{14} capable of catalysing the Strecker reaction of \(N\)-allyl-benzalaldimines with HCN. This provides a concise, versatile route to a variety of \(\alpha\)-amino acids.

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

References