SYNLETT
Spotlight 115

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

Cinchona Alkaloid Derivatives as Chiral Organocatalysts

Compiled by Ciarán Ó Dálaigh

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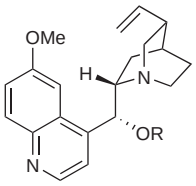
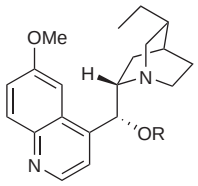
Introduction

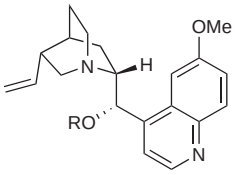
The last five years have witnessed a resurgence of interest in the cinchona alkaloids[1] [e.g. Quinine (**1**) and Quinidine (**2**)] due to their potential to serve as air- and moisture-insensitive asymmetric organocatalysts for a variety of enantioselective transformations. These materials are of particular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



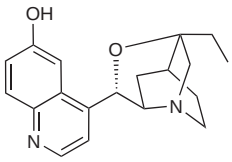
1 R = H Quinine
cat **A**: R = COPh
cat **B**: R = Me



cat **C**: R = H



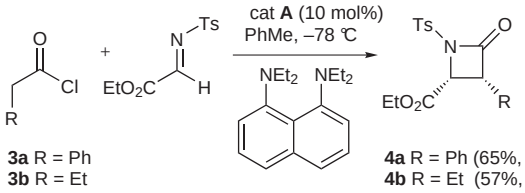
2 R = H Quinidine
cat **D**: R = $SiMe_3$



cat **E**

Abstracts

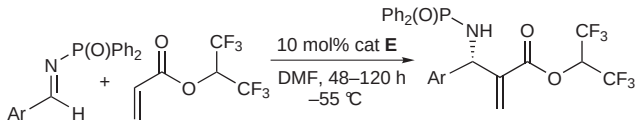
(A) The nucleophile-catalysed Staudinger reaction[2] (not to be confused with its azide-reduction[3] namesake) is a process of considerable interest from a medicinal chemistry standpoint.[4] Lectka et al.[5] were the first to report the catalytic asymmetric [2+2] cycloaddition of ketenes with imines to form a variety of β-lactam compounds.



3a R = Ph
3b R = Et

4a R = Ph (65%, 99% ee)
4b R = Et (57%, 99% ee)

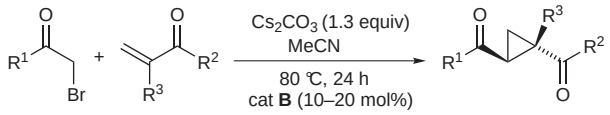
(B) The reaction of imines with activated alkenes (the aza-Baylis–Hillman reaction) catalysed by modified cinchona alkaloids has been reported. The use of a modified Quinidine-derived catalyst, i.e. β-isocupreidine, allowed the reaction between 1,1,1,3,3,3-hexafluoroisopropylacrylate and aromatic imines **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]



5a Ar = Ph
5b Ar = 1-Napthyl

6a Ar = Ph (90%, 67% ee)
6b Ar = 1-Napthyl (79%, 72% ee)

(C) Gaunt and co-workers have described a novel enantioselective organocatalytic synthesis of functionalised cyclopropanes[8] via intermediate ammonium ylides.[9] These reactions yielded exceptional enantio- and diastereoselectivities with a range of functional groups.



7a $R^1 = NEt_2$, R^2 = Ph, R^3 = H (94%, 97% ee)
7b $R^1 = O^tBu$, R^2 = OMe, $R^3 = NBoc_2$ (90%, 97% ee)

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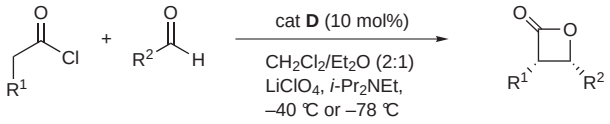
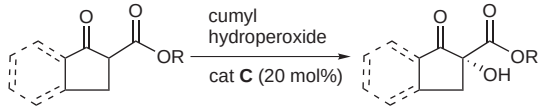
(D) Cinchona alkaloids have been used as nucleophilic catalysts for the cycloaddition reactions involving ketenes and aldehydes.[10] *O*-Trimethylsilyl derivatives of **1** and **2**, along with structurally diverse aldehydes, provided access to a range of optically active β-lactones.



8 R^1 = H, R^2 = Ph (85%, 94% *ee*)

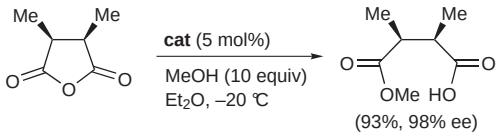
(E) Reaction of dihydroquinine with the β-keto ester **9** gives rise to a chiral ammonium enolate, which reacts with an electrophilic peroxide in a face-selective manner to form α-hydroxy-β-keto esters **10** with moderate enantioselectivity. Subsequent diastereoselective reduction of **10** affords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



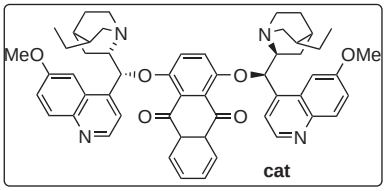
9a R = C_6H_4, Et
9b R = C_6H_4, Bn

10a R = C_6H_4, Et (83%, 72% ee)
10b R = C_6H_4, Bn (98%, 73% ee)

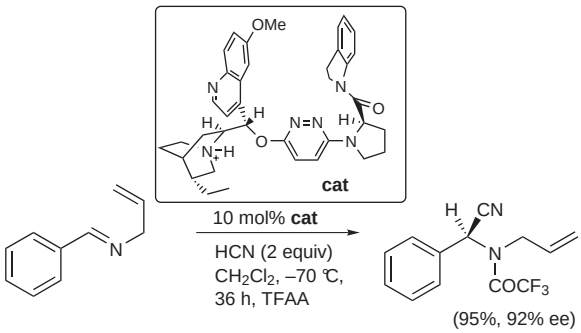
(F) The cinchona alkaloid derivative-catalysed desymmetrisation of *meso*-anhydrides in the presence of methanol is an efficient strategy for the synthesis of non-racemic dicarboxylic acid monoesters.[12] The products were formed with high enantioselectivity (up to 98% ee) with 100% conversion of the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



(93%, 98% ee)

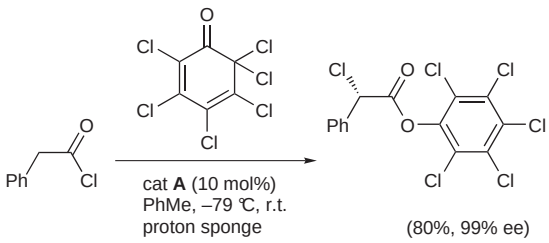


(G) Corey and Huang have developed a cinchona alkaloid derivative[14] capable of catalysing the Strecker reaction of *N*-allylbenzaldimines with HCN. This provides a concise, versatile route to a variety of α-amino acids.



(95%, 92% ee)

(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.



(80%, 99% ee)

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