

SYNLETT Spotlight 115

Cinchona Alkaloid Derivatives as Chiral Organocatalysts

Compiled by Ciarán Ó Dálaigh



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

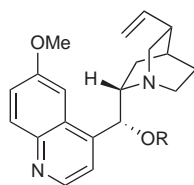
Ciarán Ó Dálaigh was born in 1981 in Dublin, Ireland and received a B.A. (Mod.) from the University of Dublin, Trinity College in 2003. In the same year he commenced his Ph.D. studies under the supervision of Dr. Stephen Connon. His research interests are in the field of asymmetric organocatalysis, particularly the design of enantioselective acyl-transfer catalysts.

Department of Organic Chemistry, University of Dublin, Trinity College, Dublin 2, Ireland
E-mail: odalaigc@tcd.ie

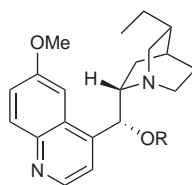
Introduction

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

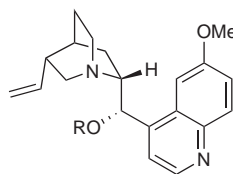
particular synthetic utility as they are inexpensive, readily available natural products and are obtainable in either of their *pseudo*-enantiomeric forms. In addition to ready availability, cinchona alkaloids also possess both Lewis acidic (H-bonding) and Lewis basic (quinuclidine nitrogen) sites, thus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



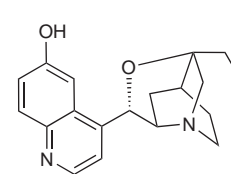
1 R = H Quinine
cat **A**: R = COPh
cat **B**: R = Me



cat **C**: R = H



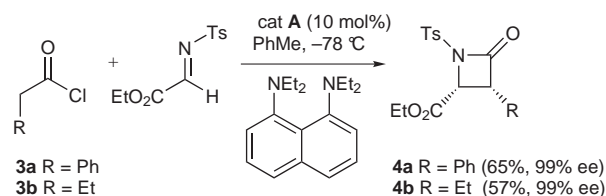
2 R = H Quinidine
cat **D**: R = SiMe₃



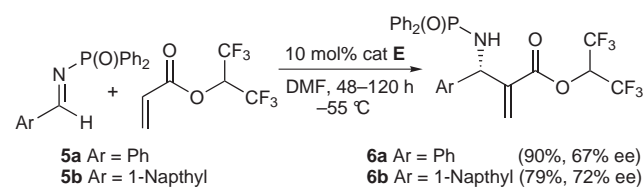
cat **E**

Abstracts

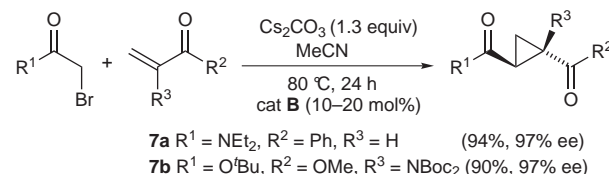
(A) The nucleophile-catalysed Staudinger reaction² (not to be confused with its azide-reduction³ namesake) is a process of considerable interest from a medicinal chemistry standpoint.⁴ Lectka et al.⁵ were the first to report the catalytic asymmetric [2+2] cycloaddition of ketenes with imines to form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



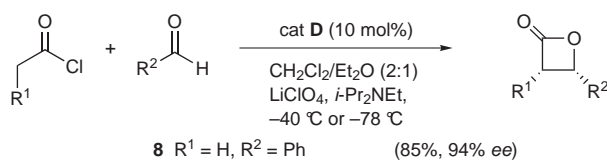
(B) The reaction of imines with activated alkenes (the aza-Baylis–Hillman reaction) catalysed by modified cinchona alkaloids has been reported. The use of a modified Quinidine-derived catalyst, i.e. β -isocupreidine, allowed the reaction between 1,1,1,3,3,3-hexafluoroisopropylacrylate and aromatic imines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



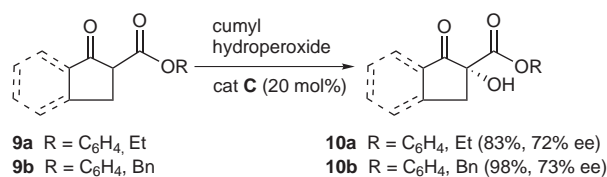
(C) Gaunt and co-workers have described a novel enantioselective organocatalytic synthesis of functionalised cyclopropanes⁸ via intermediate ammonium ylides.⁹ These reactions yielded exceptional enantio- and diastereoselectivities with a range of functional groups.



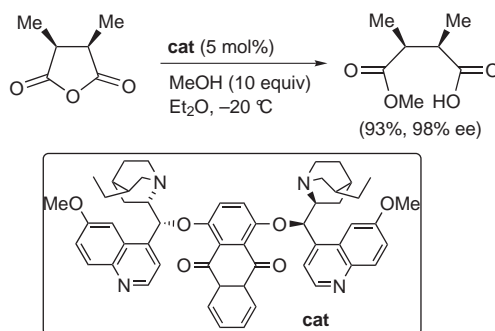
(D) Cinchona alkaloids have been used as nucleophilic catalysts for the cycloaddition reactions involving ketenes and aldehydes.¹⁰ *O*-Trimethylsilyl derivatives of **1** and **2**, along with structurally diverse aldehydes, provided access to a range of optically active β -lactones.



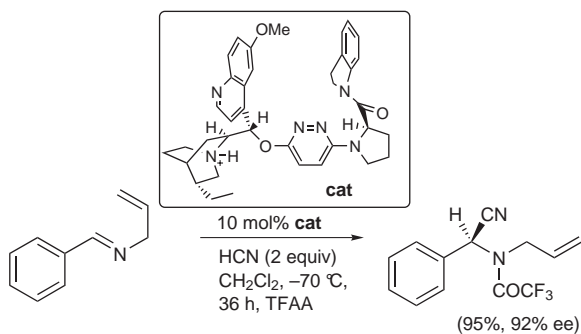
(E) Reaction of dihydroquinine with the β -keto ester **9** gives rise to a chiral ammonium enolate, which reacts with an electrophilic peroxide in a face-selective manner to form α -hydroxy- β -keto esters **10** with moderate enantioselectivity. Subsequent diastereoselective reduction of **10** affords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



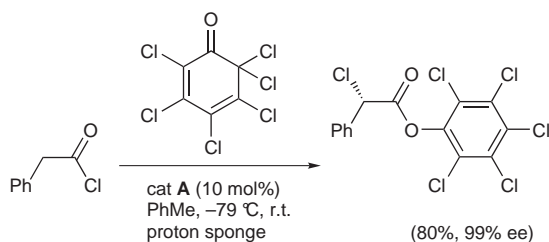
(F) The cinchona alkaloid derivative-catalysed desymmetrisation of *meso*-anhydrides in the presence of methanol is an efficient strategy for the synthesis of non-racemic dicarboxylic acid monoesters.¹² The products were formed with high enantioselectivity (up to 98% ee) with 100% conversion of the anhydride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



(G) Corey and Huang have developed a cinchona alkaloid derivative¹⁴ capable of catalysing the Strecker reaction of *N*-allylbenzaldimines 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.



References

- Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2004**, *43*, 5138.
- Staudinger, H. *Justus Liebigs Ann. Chem.* **1907**, *356*, 51.
- Staudinger, H.; Meyer, J. *Helv. Chim. Acta* **1919**, 635.
- Chemistry and Biology of Beta-Lactam Antibiotics*, Vol. 1–3; Morin, R. B.; Gorman, M., Eds.; Academic Press: New York, **1982**.
- Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Ferraris, D.; Lectka, T. *J. Am. Chem. Soc.* **2002**, *124*, 6626.
- Kawahara, S.; Nakano, A.; Esumi, T.; Iwabuchi, Y.; Hatakeyama, S. *Org. Lett.* **2003**, *5*, 3103.
- Iwabuchi, Y.; Nakatani, M.; Yokoyama, N.; Hatakeyama, S. *J. Am. Chem. Soc.* **1999**, *121*, 10219.
- Papageorgiou, C. D.; Cubillo de Dios, M. A.; Ley, S. V.; Gaunt, M. J. *Angew. Chem. Int. Ed.* **2004**, *43*, 4641.
- Jonczyk, A.; Konarska, A. *Synlett* **1999**, 1085.
- Zhu, C.; Shen, X.; Nelson, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 5352.
- Acocella, M. R.; Mancheno, O. G.; Bella, M.; Jorgensen, K. A. *J. Org. Chem.* **2004**, *69*, 8165.
- Chen, Y.; Tian, S. K.; Deng, L. *J. Am. Chem. Soc.* **2000**, *122*, 9542.
- Sharpless, K. B.; Amberg, W.; Beller, M.; Chen, H.; Hartung, J.; Kawanami, Y.; Lubben, D.; Manoury, E.; Ogino, Y.; Shibata, T.; Ukita, T. *J. Org. Chem.* **1991**, *56*, 4585.
- Huang, J.; Corey, E. J. *Org. Lett.* **2004**, *6*, 5027.
- France, S.; Wack, H.; Taggi, A. E.; Hafez, A. M.; Wagerle, T. R.; Shah, M. H.; Dusich, C. L.; Lectka, T. *J. Am. Chem. Soc.* **2004**, *126*, 4245.