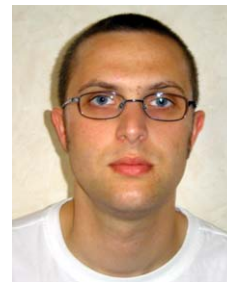


SYNLETT Spotlight 224

MacMillan's Imidazolidinones: Powerful Chiral Organocatalysts

Compiled by Thomas Poisson



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

Thomas Poisson was born in Normandie in 1982, and received his Master degree in 2005 from the University of Rouen under the supervision of Prof. G. Dupas. In the same year he started his PhD research under the supervision of Dr. V. Levacher. His research interests involve the development of new asymmetric organocatalytic reactions.

Laboratoire de Chimie Organique Fine et Hétérocyclique UMR 6014 IRCOF, Université et INSA de Rouen, BP 08, 76131 Mont Saint Aignan Cedex, France
E-mail: thomas.poisson@insa-rouen.fr

Introduction

During the last seven years, many research groups have developed the concept of iminium activation. The advantage of this approach is that the iminium generated in situ by equilibrium between an α,β -unsaturated carbonyl compound (ketone or aldehyde) and a secondary amine salt can replace the traditional use of Lewis acid to lower the LUMO of the electrophile (Figure 1).¹

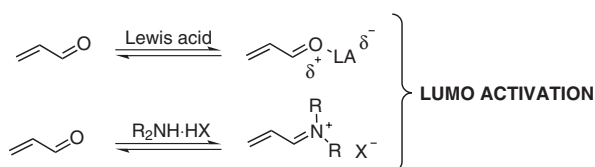
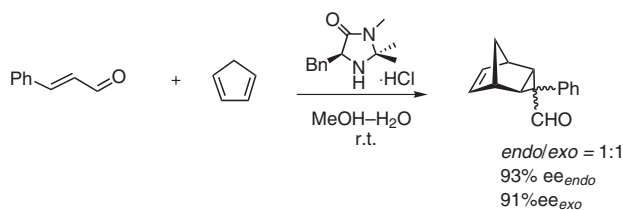


Figure 1 Lewis acid activation vs iminium activation

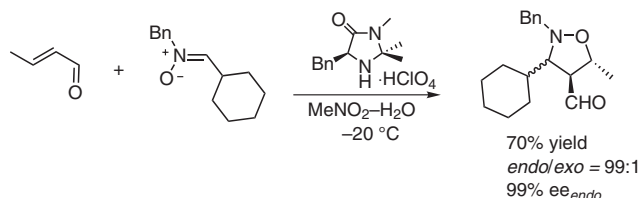
A small collection of chiral imidazolidinone salts have been shown to be widely efficient for a broad range of asymmetric transformations such as Friedel–Crafts alkylation,² Diels–Alder cycloaddition,³ hydrogenation of α,β -unsaturated carbonyl compounds⁴ and cascade catalysis.⁵

Abstract

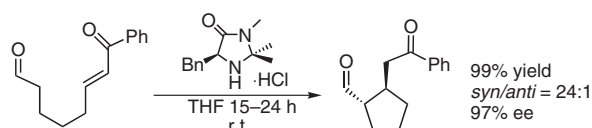
(A) MacMillan and co-workers³ have reported the first enantioselective organocatalytic Diels–Alder cycloaddition under mild conditions with excellent enantioselectivities for both stereoisomers (*exo* and *endo*). This methodology can also be applied to an intramolecular version.⁹



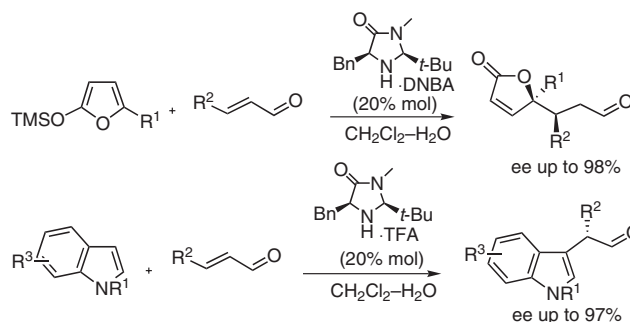
(B) Isoxazolidines are useful synthons in amino acid synthesis.¹⁰ MacMillan and co-workers¹¹ were the first to report organocatalysed 1,3-dipolar cycloaddition of nitrones with α,β -unsaturated aldehydes. This reaction led to the formation of isoxazolidines with high enantio- and diastereoselectivities.



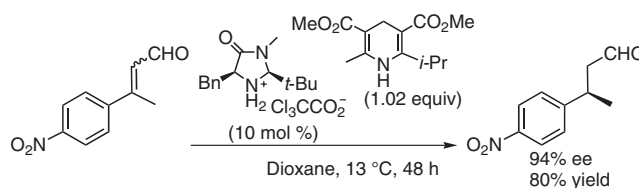
(C) Hechavarría Fonseca and List¹² have reported the asymmetric intramolecular Michael addition of a formyl enone providing a ketoaldehyde with good diastereoselectivity and high enantiomeric purity.



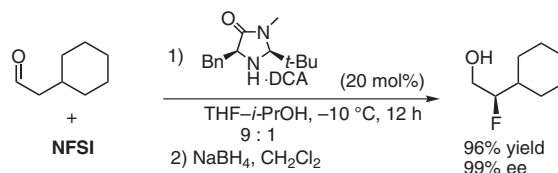
(D) Chiral imidazolidinones have been used in the addition of π -nucleophiles (pyroles, indoles, anilines and silyloxyfuranes) to α,β -unsaturated aldehydes.^{2,13} The resulting chiral adducts are important building blocks for the preparation of natural products.¹⁴



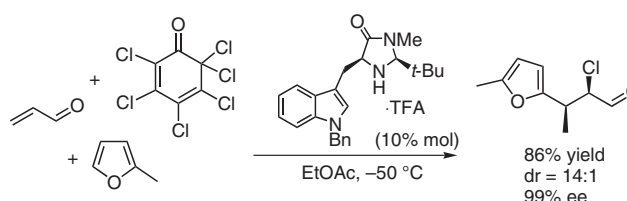
(E) Organocatalytic reduction of α,β -unsaturated aldehydes was performed by List and co-workers.⁴ The iminium generated in situ reacted with the Hantzsch ester hydride donor to provide enantiomerically pure hydrogenated aldehydes. The authors noticed that the enantiomeric excess is not related to the geometry of the double bond.



(F) Asymmetric electrophilic fluorination can be performed by reaction of *N*-fluorobenzenesulfonimide (NFSI) with the enamine intermediate generated during the catalytic cycle.^{15a} This highly enantioselective fluorination process provides a concise and versatile route to a variety of α -fluoro alcohols or aldehydes (chlorination reactions are also possible).^{15b}



(G) MacMillan and co-workers⁵ reported a cascade reaction where the imidazolidinone is first used to promote the formation of an iminium intermediate. Then, the latter reacts with the furan resulting in the formation of an enamine which is finally chlorinated. This cascade reaction was performed with good diastereoselectivity and high enantioselectivity.



References

- (1) Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007.
- (2) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370.
- (3) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243.
- (4) Yang, J. W.; Hechavarría, F. o. n. s. e. c. a. M. T.; Vignola, N.; List, B. *Angew. Chem. Int. Ed.* **2005**, *44*, 108.
- (5) Huang, Y.; Walji, A. M.; Larsen, C. H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 15051.
- (6) (a) List, B. *Chem. Commun.* **2006**, 819. (b) List, B. *Acc. Chem. Res.* **2004**, *37*, 548. (c) Marigo, M.; Jørgensen, K. A. *Chem. Commun.* **2006**, 2001.
- (7) (a) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2004**, *43*, 5138. (b) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis*; Wiley-VCH: Weinheim, **2005**.
- (8) (a) Kinsman, A. C.; Kerr, M. A. *J. Am. Chem. Soc.* **2003**, *125*, 14120. (b) Robichaud, J.; Tremblay, F. *Org. Lett.* **2006**, *8*, 597. (c) King, H. D.; Meng, Z.; Denhart, D.; Mattson, R.; Kimura, R.; Wu, D.; Qi, G.; Macor, J. E. *Org. Lett.* **2005**, *7*, 3437.
- (9) Wilson, R. M.; Jen, W. S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 11616.
- (10) Fredrickson, F. *Tetrahedron* **1997**, *53*, 403.
- (11) Jen, W. S.; Wiener, J. J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 9874.
- (12) Hechavarría Fonseca, M. T.; List, B. *Angew. Chem. Int. Ed.* **2004**, *43*, 3958.
- (13) (a) Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172. (b) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 7894. (c) Brown, S. P.; Goodwin, N. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 1192.
- (14) (a) Pederson, R. L.; Fellows, I. M.; Ung, T. A.; Ishihara, H.; Hajela, S. P. *Adv. Synth. Catal.* **2002**, *344*, 728. (b) Kim, S. G.; Kim, J.; Jung, H. *Tetrahedron Lett.* **2005**, *46*, 2437.
- (15) (a) Beeson, T.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 8826. (b) Brochu, M. P.; Brown, S. P.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2004**, *126*, 4108.