SYNLETT
Spotlight 224

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

MacMillan's Imidazolidinones: Powerful Chiral Organocatalysts

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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]

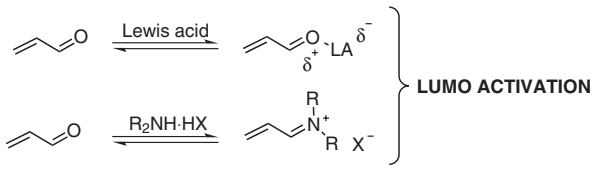


Figure 1 Lewis acid activation vs iminium activation

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 compounds[4] and cascade catalysis.[5]

Furthermore, these chiral imidazolidinones can be used for the classical enamine activation of ketone or aldehyde[6] in aldol or addition reactions.[5]

This concept first reported by MacMillan[3] is now an efficient tool in organocatalysis.[7] Indeed, this reagent is a good alternative to toxic, hazardous and expensive metals.

Numerous catalysts are commercially available (Figure 2), or can be easily prepared from inexpensive natural amino acids.[3]

Moreover, it has been recently reported that the commercially available chiral amine salts derived from these imidazolidinones can be used for iminium activation in total synthesis, demonstrating that this concept can be applied to the preparation of complex target molecules.[8]

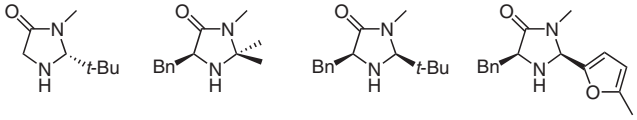
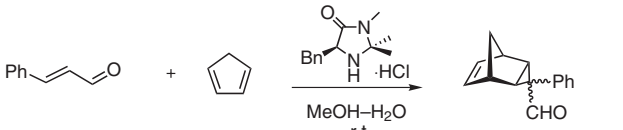


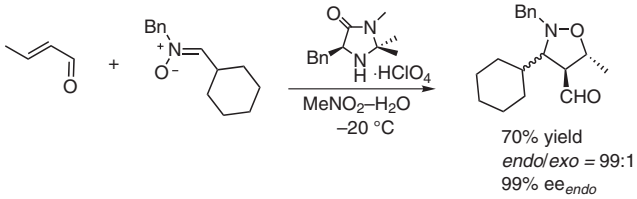
Figure 2 Commercially available chiral imidazolidinone catalysts

Abstract

(A) MacMillan and co-workers[3] 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]

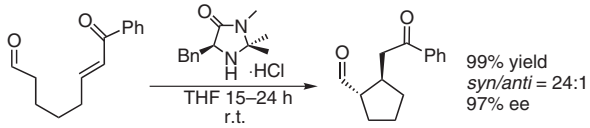


(B) Isoxazolidines are useful synthons in amino acid synthesis.[10] MacMillan and co-workers[11] were the first to report organocatalysed 1,3-dipolar cycloaddition of nitrones with α,β-unsaturated aldehydes. This reaction led to the formation of isoxazolidines with high enantio- and diastereoselectivities.

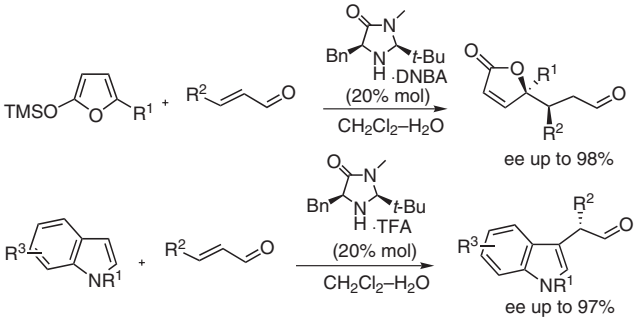


SYNLETT 2008, No. 1, pp 0147–0148
Advanced online publication: 11.12.2007
DOI: 10.1055/s-2007-990914; Art ID: V22807ST

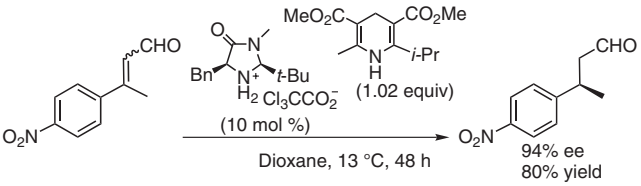
(C) Hechavarria Fonseca and List[12] have reported the asymmetric intramolecular Michael addition of a formyl enone providing a ketoaldehyde with good diastereoselectivity and high enantiomeric purity.



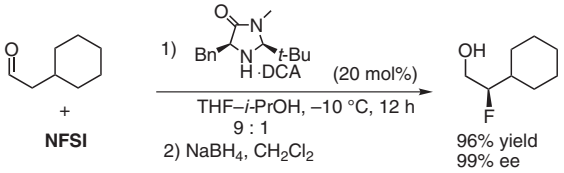
(D) Chiral imidazolidinones have been used in the addition of π-nucleophiles (pyrroles, indoles, anilines and silyloxyfuranes) to α,β-unsaturated aldehydes.[2,13] The resulting chiral adducts are important building blocks for the preparation of natural products.[14]



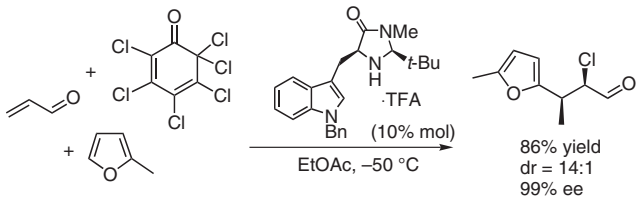
(E) Organocatalytic reduction of α,β-unsaturated aldehydes was performed by List and and co-workers.[4] The iminium generated in situ reacted with the Hantzsch ester hydride donor to provide enantiomerically pure hydrogenated aldehydes. The authors noticed that the enantiomeric excess is not related 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-workers[5] 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.



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