SYNLETT
Spotlight 476

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

N-Mesityl-Substituted Triazolium Salts

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Introduction

Metal-free organocatalysis employing N-heterocyclic carbenes (NHCs) has attracted great interest because of its use in the construction of intricate molecular architectures from simple starting materials under mild reaction conditions.[1] The catalytic pathway of NHCs mimics that of thiamine-dependent enzymatic processes and passes through discrete reactive species, such as acyl anions and enolate or homoenolate equivalents.[2] This enables the selective generation of a set of versatile electrophilic (acyl azoliums) and nucleophilic (enolates, homoenolates) intermediates and makes NHCs efficient catalysts in such various reactions as acylation, cycloaddition, β-borylation, and elimination.

N-Mesityl substituted imidazolium (cat. **A**) and triazolium (cat. **B**) salts were introduced by Bode and co-workers as stable NHC precursors.[3] The imidazolium derivative favors the homoenolate pathway, whereas the triazolium precursor promotes almost all NHC-catalyzed transformations, except for benzoin and Stetter reactions. Chiral pre-catalysts like **C** and its enantiomer are also commercially available.[4]

It should be noted that the N-substituent is of crucial importance; for example, an *N*-phenyl substituents might not provide any product, while the Bode (*N*-mesityl) or Rovis (*N*-pentafluorophenyl)[5] catalysts are highly catalytically active.

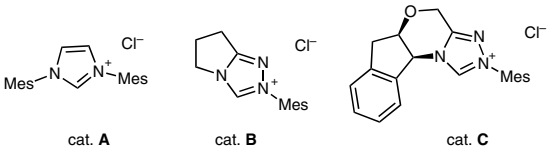
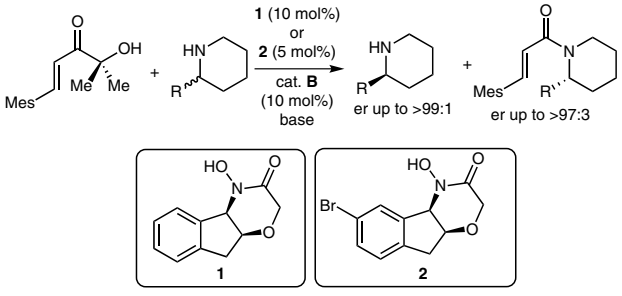


Figure 1 *N*-Mesityl-substituted imidazolium (cat. **A**) and triazolium (cat. **B** and **C**) carbene precursors. Chiral pre-catalyst **C** is commercially available (Mes = 1,3,5-trimethylphenyl).

Abstracts

(A) Bode catalysts were first found to be efficient for the esterification of aldehydes via the activated carboxylates generated from α,β-epoxyaldehydes, enals, and cyclopropanes. You et al. used a similar methodology for the ring expansion of formylcyclopropanes to afford 3,4-dihydro-α-pyrones.[6] Although in situ generated acyl azoliums did not react directly with amines, amidation was possible using a co-catalyst with additives such as imidazole, triazole, hydroxamic acid, HOBt, HOAt, or pentafluorophenol.[7a] This approach was successfully in the catalytic kinetic resolution of cyclic amines using the chiral hydroxamic acid **1** or **2** as co-catalyst.[7b,c] Recent development includes the use of a polymer-supported histidine-bound NHC precursor in which the histidine moiety acts as co-catalyst.[7d]



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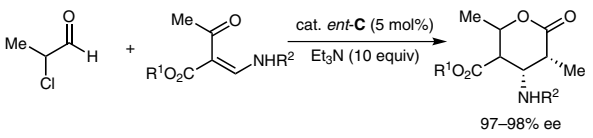
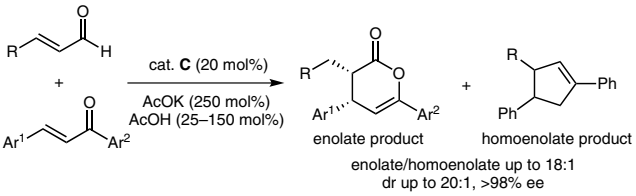
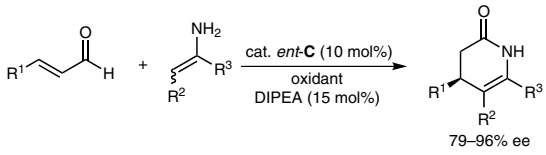
(B) Ester enolate equivalents generated from α-halo- and α,β-unsaturated aldehydes underwent enantioselective oxa- and aza-Diels–Alder reactions.[1a] Strikingly, bench-stable bisulfite adducts of α-halo aldehydes could be directly used for this transformation. Kobayashi et al. reported the synthesis of 1β-methylcarbapenem antibiotic intermediates using vinylogous amides as dienes.[8]



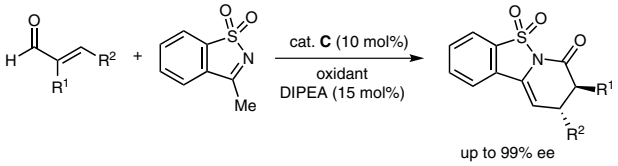
(C) Although imidazolium-derived catalysts are generally superior to triazolium precursors in γ-lactonization and γ-lactamization reactions, triazolium salts also efficiently promote the annulation of highly reactive electrophiles via the homoenolate pathway.[9] In 2013, Chi et al. developed a selective β-protonation of homoenolate equivalents.[10] This enabled the synthesis of previously inaccessible enolate products by the reaction of enals with chalcones.



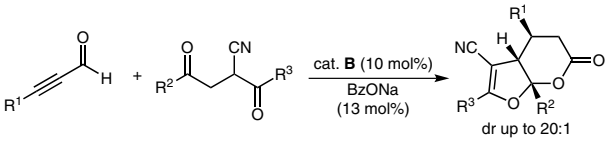
(D) In course of their work on kojic acids, Bode and co-workers discovered a new enantioselective azolium-catalyzed annulation of ynals via a Coates–Claisen rearrangement. The reaction pathway was different from enolate, homoenolates, and acyl anion activation.[11a,b] Further, the substrate scope of the reaction was extended to enals. Mechanistical insights into this transformation led to the NHC-catalyzed aza-Claisen rearrangement of enals with vinylogous amides.[11c]



(E) The NHC-promoted addition of enals to imine electrophiles represents a particular reactivity. Ketimines derived from saccharine were found to be excellent electrophiles in annulation reactions proceeding via homoenolate and acyl azolium pathways.[12] In the latter case, the pre-catalyst **C** ensured the first annulation of α- and β,β′-substituted enals with a high enantio- and diastereoselectivity.



(F) Recently, Alexakis and co-workers reported the stereoselective annulation between α-cyano-1,4-diketones and ynals.[13] Starting from achiral material and in the presence of achiral pre-catalyst **B**, this transformation furnished a functionalized bicyclic scaffold possessing three contiguous stereogenic centers with a good diastereoselectivity.



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