

SYNLETT Spotlight 476

N-Mesityl-Substituted Triazolium Salts

Compiled by Egor Chirkin



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

Egor Chirkin was born in Moscow, Russia, in 1986. He studied pharmacy at Peoples' Friendship University in Moscow and medicinal chemistry at the Université d'Auvergne in Clermont-Ferrand, France. After a six-month research internship in the group of Professor Klaus T. Wanner at Ludwig Maximilians University of Munich, Germany, he started to pursue doctoral studies under the supervision of Dr. François-Hugues Porée at Université René Descartes in Paris. His research interests include the total synthesis of bioactive natural products and semi-synthetic modifications of their structure for medicinal applications.

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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 transfor-

mations, 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.

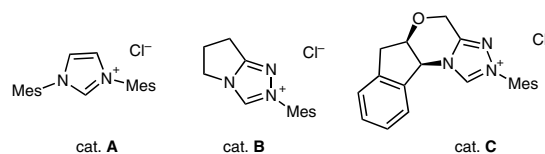
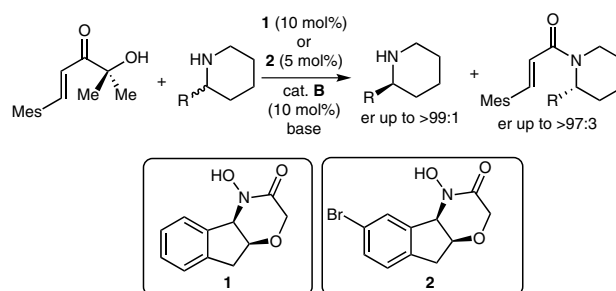


Figure 1 *N*-Mesityl-substituted imidazolium (cat. **A**) and triazolium (cat. **B** and **C**) carbene precursors. Chiral pre-catalyst **C** is commercially available (Mes = 1,3,5-trimethylphenyl).

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}



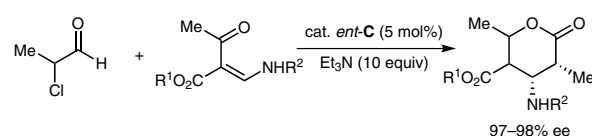
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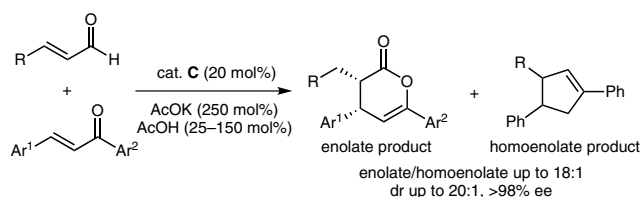
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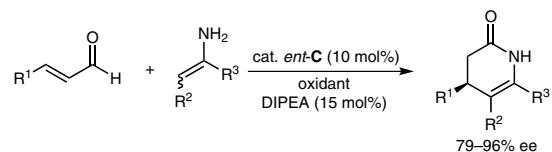
(B) Ester enolate equivalents generated from α -halo- and α,β -unsaturated aldehydes underwent enantioselective oxa- and aza-Diels-Alder reactions.^{1a} Strikingly, bench-stable bisulfite adducts of α -halo aldehydes could be directly used for this transformation. Kobayashi et al. reported the synthesis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



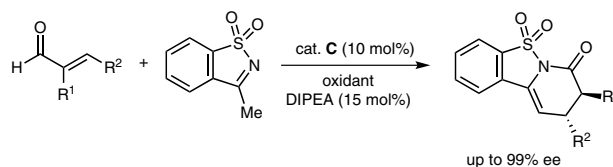
(C) Although imidazolium-derived catalysts are generally superior to triazolium precursors in γ -lactonization and γ -lactamization reactions, triazolium salts also efficiently promote the annulation of highly reactive electrophiles via the homoenolate pathway.⁹ In 2013, Chi et al. developed a selective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



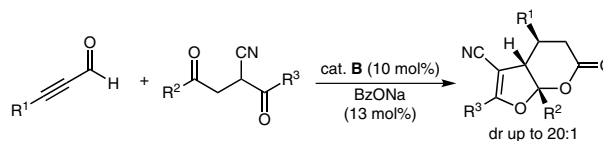
(D) In course of their work on kojic acids, Bode and co-workers discovered a new enantioselective azolium-catalyzed annulation of ynals via a Coates-Claisen rearrangement. The reaction pathway was different from enolate, homoenolates, and acyl anion activation.^{11a,b} Further, the substrate scope of 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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