SYNLETT
Spotlight 476

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

**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. 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 homoenoate equivalents. This enables the selective generation of a set of versatile electrophilic (acyl azoliums) and nucleophilic (enolates, homoenoates) intermediates and makes NHCs efficient catalysts in such various reactions as acylation, cycloaddition, β-borylation, and elimination.

*N*-Mesityl substituted imidazolium (cat. **A**), triazolium (cat. **B**) and triazolium (cat. **C**) salts were introduced by Bode and co-workers as stable NHC precursors. The imidazolium derivative favors the homoenoate 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.

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

![Figure 1](image_url)  
**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 formycyclopropanes to afford 3,4-dihydro-α-pyrone. 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. This approach was successfully in the catalytic kinetic resolution of cyclic amines using the chiral hydroxamic acid 1 or 2 as co-catalyst. Recent development includes the use of a polymer-supported histidine-bound NHC precursor in which the histidine moiety acts as co-catalyst.
(B) Ester enolate equivalents generated from α-halo- and α,β-unsaturated aldehydes underwent enantioselective oxa- and aza-Diels–Alder reactions.\textsuperscript{1a} Strikingly, bench-stable bisulfite adducts of aldehydes could be directly used for this transformation. Kobayashi et al. reported the synthesis of 1β-methylcarbapenem antibiotic intermediates using vinylogous amides as dienes.\textsuperscript{9}

(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.\textsuperscript{12} In 2013, Chi et al. developed a selective β-protonation of homoenolate equivalents.\textsuperscript{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 yna 1s via a Coates–Claisen rearrangement. The reaction pathway was different from enolate, homoenolates, and acyl anion activated ynals via a Coates–Claisen rearrangement. The reaction pathway was different from enolate, homoenolates, and acyl anion activation.\textsuperscript{11a,b} Further, the substrate scope of the reaction was extended to ynals. Mechanistical insights into this transformation led to the NHC-catalyzedaza-Claisen rearrangement of enals with vinylogous imines derived from saccharine and acetates.\textsuperscript{11c}

(E) The NHC-promoted addition of enals to imine electrophiles represents a particular reactivity. Ketenimes derived from saccharine and acetates were found to be excellent electrophiles in annulation reactions proceeding via homoenolate and acyl azolium pathways.\textsuperscript{12} In the latter case, the pre-catalyst ensured the first annulation of α-[25] and β-[26] substituted enals with a high enantio- and diastereoselectivity.

(F) Recently, Alexakis and co-workers reported the stereoselective annihilation between α-cyano-1,4-diketones and yna 1s.\textsuperscript{13} Starting from achiral material and in the presence of achiral pre-catalyst, this transformation furnished a functionalized bicyclic scaffold possessing three contiguous stereogenic centers with a good diastereoselectivity.

References