

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

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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.

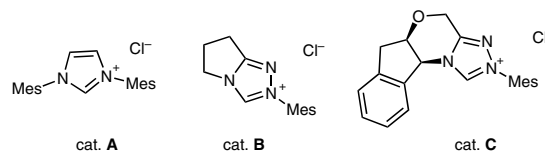
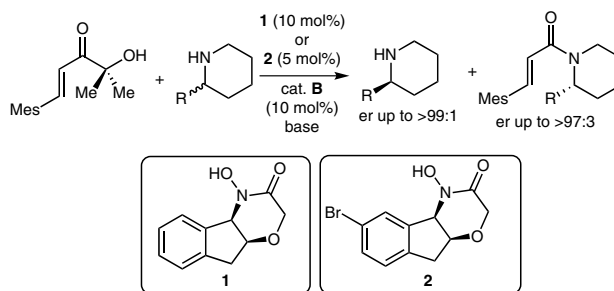


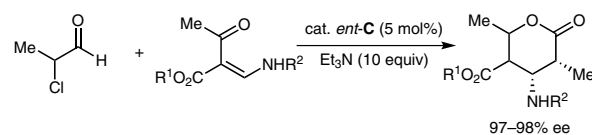
Figure 1 *N*-Mesityl-substituted imidazolium (cat. **A**) and triazolium (cat. **B** and **C**) carbene precursors. Chiral pre-catalyst **C** is commercially available (Mes = 1,3,5-trimethylphenyl).

Abstracts

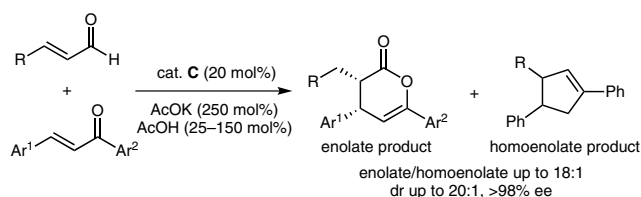
(A) Bode catalysts were first found to be efficient for the esterification of aldehydes via the activated carboxylates generated from α,β -epoxyaldehydes, enals, and cyclopropanes. You et al. used a similar methodology for the ring expansion of formylcyclopropanes to afford 3,4-dihydro- α -pyrones.⁶ 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}



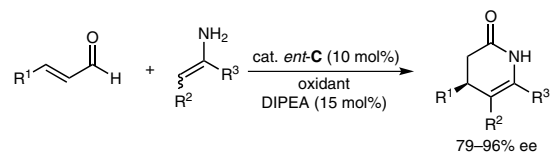
(B) Ester enolate equivalents generated from α -halo- and α,β -unsaturated aldehydes underwent enantioselective oxa- and aza-Diels–Alder reactions.^{1a} Strikingly, bench-stable bisulfite adducts of α -halo aldehydes could be directly used for this transformation. Kobayashi et al. reported the synthesis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



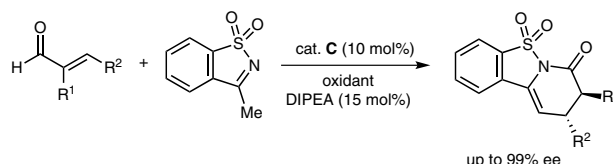
(C) Although imidazolium-derived catalysts are generally superior to triazolium precursors in γ -lactonization and γ -lactamization reactions, triazolium salts also efficiently promote the annulation of highly reactive electrophiles via the homoenolate pathway.⁹ In 2013, Chi et al. developed a selective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



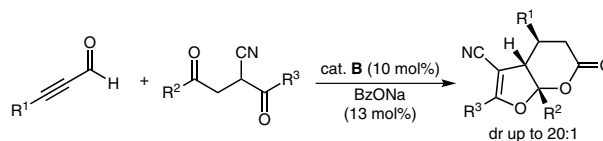
(D) In course of their work on kojic acids, Bode and co-workers discovered a new enantioselective azolium-catalyzed annulation of ynals via a Coates–Claisen rearrangement. The reaction pathway was different from enolate, homoenolates, and acyl anion activation.^{11a,b} Further, the substrate scope of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



References

- (1) For recent reviews see: (a) Chiang, P.-C.; Bode, J. W. *TCL MAIL* **2011**, 149, 2. (b) Grossmann, A.; Enders, D. *Angew. Chem. Int. Ed.* **2012**, 51, 314. Book chapters: (c) Mahatthananchai, J.; Bode, J. W. In *Contemporary Carbene Chemistry*; Moss, R. A.; Doyle, M. P., Eds.; Wiley: Hoboken, **2013**, 237. (d) Mahatthananchai, J.; Bode, J. W. In *Asymmetric Synthesis: The Essentials II*; Christmann, M.; Bräse, S., Eds.; Wiley: Weinheim, **2012**, 67. (e) Gondo, C. A.; Bode, J. W. In *Science of Synthesis: Houben Weyl Methods of Molecular Transformations Vol. 13.33*; List, B., Ed.; Georg Thieme Verlag: Stuttgart, New York, **2012**, 199. (f) Chiang, P.-C.; Bode, J. W. In *Science of Synthesis: Asymmetric Organocatalysis Vol. 1*; List, B., Ed.; Georg Thieme Verlag: Stuttgart, New York, **2012**, 639.
- (2) For a review on the mechanism of NHC-catalyzed reactions, see: Mahatthananchai, J.; Bode, J. W. *Acc. Chem. Res.* **2014**, 47, 696.
- (3) Sohn, S. S.; Bode, J. W. *Org. Lett.* **2005**, 7, 3873.
- (4) He, M.; Struble, J. R.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, 128, 8418.
- (5) Kerr, M. S.; Rovis, T. J. *J. Am. Chem. Soc.* **2004**, 126, 8876.
- (6) Li, G.-Q.; Dai, L.-X.; You, S.-L. *Org. Lett.* **2009**, 11, 1623.
- (7) (a) Chiang, P.-C.; Kim, Y.; Bode, J. W. *Chem. Commun.* **2009**, 30, 4566. (b) Hsieh, S.-Y.; Binanzer, M.; Kreituss, I.; Bode, J. W. *Chem. Commun.* **2012**, 48, 8892. (c) Binanzer, M.; Hsieh, S.-Y.; Bode, J. W. *J. Am. Chem. Soc.* **2011**, 133, 19698. (d) Gondo, C. A.; Bode, J. W. *Synlett* **2013**, 24, 1205.
- (8) Kobayashi, S.; Kinoshita, T.; Uehara, H.; Sudo, T.; Ryu, S. *Org. Lett.* **2009**, 11, 3934.
- (9) For the recent review on the homoenolates see: Nair, V.; Menon, R. S.; Biju, A. T.; Sinu, C. R.; Paul, R. R.; Jose, A.; Sreekumar, V. *Chem. Soc. Rev.* **2011**, 40, 5336.
- (10) Fu, Z.; Sun, H.; Chen, S.; Tiwari, B.; Li, G.; Chi, Y. R. *Chem. Commun.* **2013**, 49, 261.
- (11) (a) Mahatthananchai, J.; Kaeobamrung, J.; Bode, J. W. *ACS Catal.* **2012**, 2, 494. (b) Kaeobamrung, J.; Mahatthananchai, J.; Zheng, P.; Bode, J. W. *J. Am. Chem. Soc.* **2010**, 132, 8810. (c) Wanner, B.; Mahatthananchai, J.; Bode, J. W. *Org. Lett.* **2011**, 13, 5378.
- (12) (a) Rommel, M.; Fukuzumi, T.; Bode, J. W. *J. Am. Chem. Soc.* **2008**, 130, 17266. (b) Kravina, A. G.; Mahatthananchai, J.; Bode, J. W. *Angew. Chem. Int. Ed.* **2012**, 51, 9433.
- (13) Romanov-Michailidis, F.; Besnard, C.; Alexakis, A. *Org. Lett.* **2012**, 14, 4906.