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Synthesis of an *N*-Mesityl Substituted Chiral Imidazolium Salt for NHC-Catalyzed Reactions

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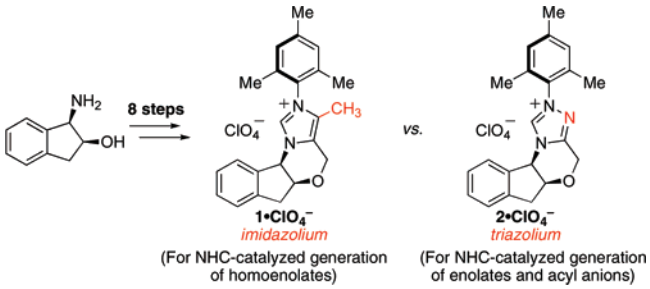
ABSTRACT



A new synthetic approach to chiral imidazolium salts makes possible the first synthesis of an *N*-mesityl substituted, aminoindanol-derived N-heterocyclic carbene precursor, 1·ClO_4. The successful synthesis allows the first direct comparison of otherwise identical imidazolium and triazolium precursors across a number of NHC-catalyzed processes. These studies confirm striking differences in reactivity and mechanism between the two classes.

N-Heterocyclic carbenes derived from azolium salts are remarkable and versatile catalysts for a wide range of organic transformations.[1] The classical benzoin and Stetter reactions of simple aldehydes are catalyzed by thiazolium and triazolium-derived carbenes.[2] More recently, an extensive array of new processes operating via reactive intermediates catalytically generated by internal redox reactions of α-functionalized aldehydes have been discovered.[3] Successful developments from our lab include enantioselective *N*-mesityl substituted triazolium-catalyzed annulations affording *cis*-disubstituted dihydropyranones and dihydropyridinones,[4a,b] cyclopentenes,[4c] and bicyclic β-lactams,[4d] all with exceptional levels of diastereo- and enantioselectivity. We and Glorius also documented diastereoselective annulations of enals and aldehydes to afford γ-butyrolactones using imidazolium catalysts.[5]

The starting materials for many of these annulation processes are similar or identical, but the reaction outcomes differ dramatically by the choice of imidazolium vs triazolium precatalysts. These disparate results have led to considerable confusion over the difference between the imidazolium and triazolilum precatalysts. Direct comparisons between the reactivity and mechanistic pathways of these two classes have been precluded by the use of structurally different catalyst classes in each case.

(1) For a recent, comprehensive review, see: Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606−5655.

(2) For recent reviews, see: (a) Johnson, J. S. *Angew. Chem., Int. Ed.* **2003**, *42*, 2534−2536. (b) Christmann, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 2632−2634.

(3) For the first reports of this concept, see: (a) Chow, K. Y.-C.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 8126−8127. (b) Reynolds, N. T.; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 9518−9519. (c) For a highlight, see: Zeitler, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 7506−7510.

(4) (a) He, M.; Uc, G. J.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 15088−15089. (b) He, M.; Struble, J. R.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 8148−8150. (c) Chiang, P.-C.; Kaeobamrung, J.; Bode, J. W. *J. Am. Chem. Soc.* **2007**, *129*, 3520−3521. (d) He, M.; Bode, J. W. *J. Am. Chem. Soc.* **2008**, *130*, 418−419.

(5) (a) Sohn, S. S.; Rosen, E. L.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 14370−14371. (b) Burstein, C.; Glorius, F. *Angew. Chem., Int. Ed.* **2004**, *43*, 6205−6208. (c) Burstein, C.; Tschan, S.; Xie, X.; Glorius, F. *Synthesis* **2006**, 2418−2439.

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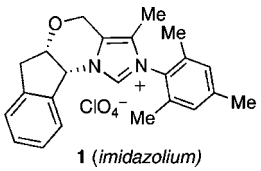
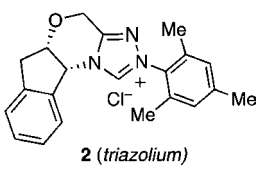
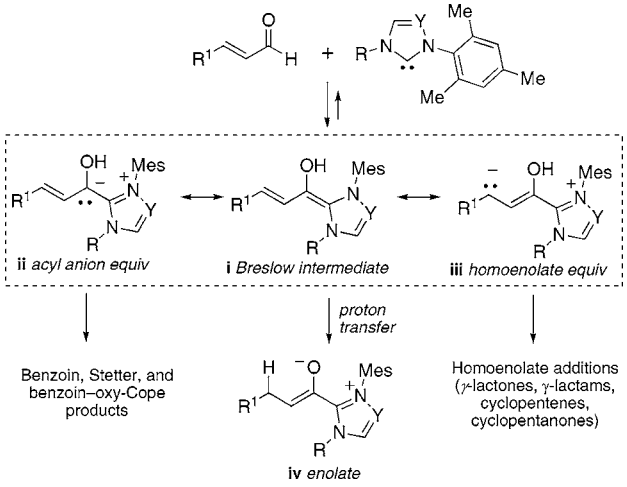




In the present communication, we address these important issues through the synthesis of chiral imidazolium salt **1**, which corresponds to the *N*-mesityl aminoindanol-derived triazolium salt **2** that has served as the most reactive and selective precatalyst in numerous annulation processes. The successful synthesis of **1** allows the first direct comparison between these two catalyst classes, differing only by a single atom at a site removed from the reactive center. The distinct reactivity of these two classes provides valuable insight into the mechanistic differences and the challenges associated with developing enantioselective variants.

Scheme 1. Reactive Intermediates Catalytically Generated by NHC-Promoted Redox Reactions of α,β-Unsaturated Aldehydes

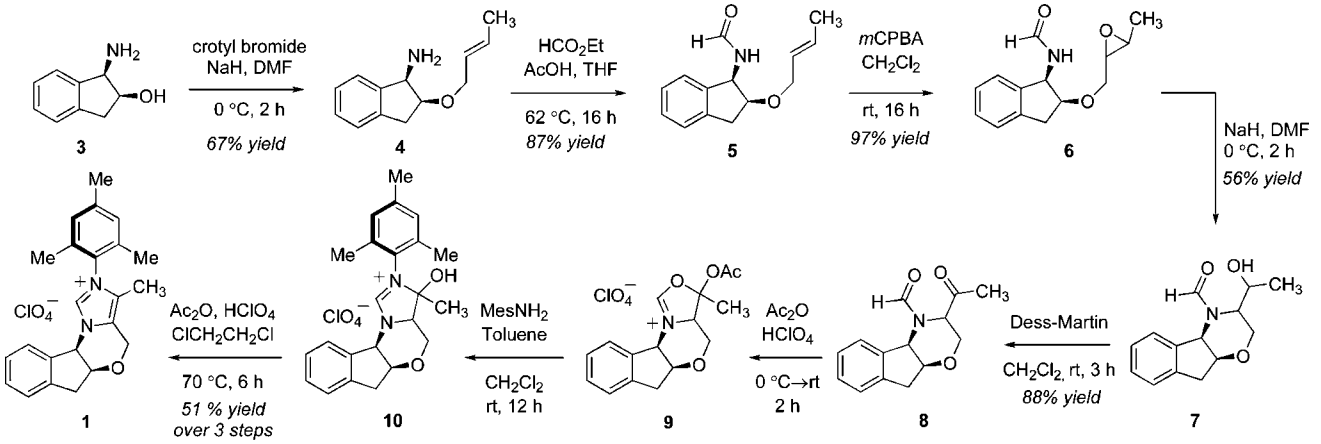


The basis of the novel annulation reactions of α,β-unsaturated aldehydes and electrophiles is the catalytic generation of unique reactive intermediates by internal redox reactions promoted by the association of an N-heterocyclic carbene and the enal (Scheme 1). Depending on the structure of the catalyst and the facility of proton-transfer events, the initially formed Breslow intermediate **i** can ultimately serve as acyl anion equivalent **ii**, homoenolate equivalent **iii**, or enolate **iv**. In the latter two cases, the aldehyde is simultaneously oxidized to the carboxylic acid oxidation state. As this communication demonstrates, the fate of the Breslow intermediate is intimately controlled not by the steric demands of the catalyst but rather by the choice of imidazolium vs triazolium-derived NHCs.

At the outset of our studies, we sought to address two recurring issues in our development of novel, NHC-catalyzed reactions. First, numerous annulation processes were promoted exclusively by one catalyst type (imidazolium or triazolium) but not the other. Even in the few instances where a given transformation is promoted by either catalyst class, such as cyclopentene-forming annulations, we and Nair have demonstrated that different mechanisms may be operating.[4c,6] Second, although highly enantioselective *triazolium*-catalyzed processes have been achieved for diverse reaction types, no examples of highly selective *imidazolium*-catalyzed processes have been documented. For example, despite extensive efforts from our group and others, no highly enantioselective NHC-catalyzed γ-lactam and γ-lactone formations have been achieved.

A key feature of the chiral triazolium salts designed by Leeper,[7] Enders,[8] and Rovis[9] is their unsymmetrical, polycyclic structure, which has proven exceptionally successful in the levels of selectivity provided. They are also readily prepared by a convenient, modular route from chiral amino alcohols. Unfortunately, the synthesis of similar chiral imidazolium salts has proven challenging. With a few notable exceptions,[10] the chiral imidazolium-derived carbenes reported to date are constructed from either a chiral, C-2 symmetric diamine backbone or with the chiral centers resident on the *N*-substitutent.[11] The requirement, in many of the annulation reactions, of an ortho,ortho′-disubsituted aromatic on the *N*-substituent further increases the synthetic challenge.

Scheme 2. Synthesis of Aminoindanol-Derived Imidazolium Salt **1**·ClO_4

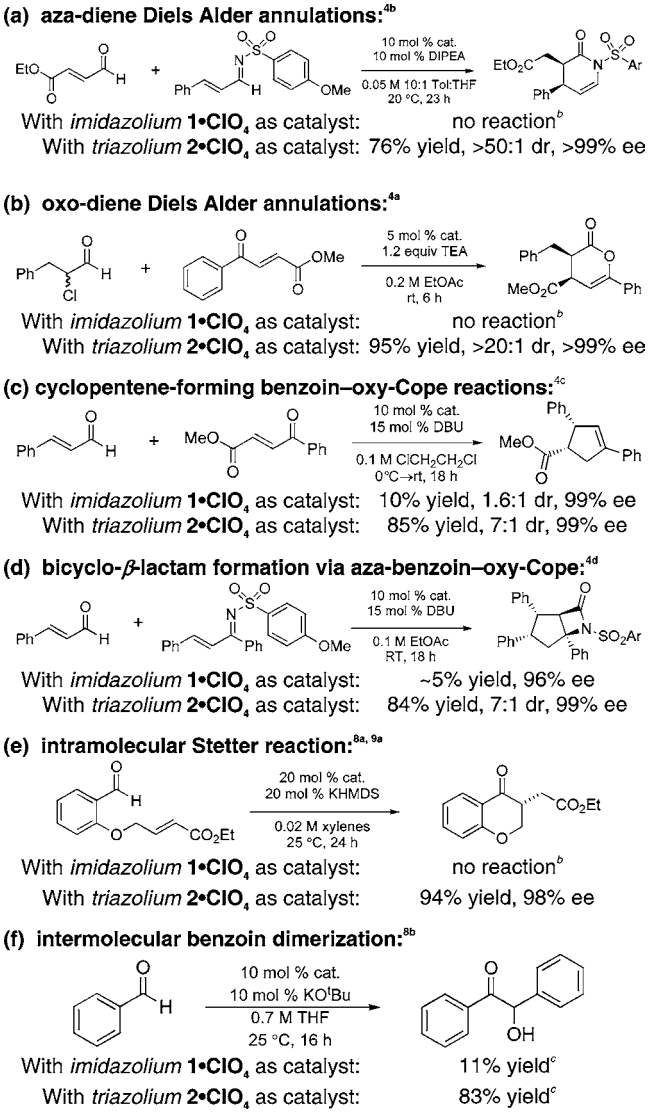


Our initial attempts to prepare chiral, bicyclic imidazolium salts bearing the essential *N*-mesityl substituent were unsuccessful using established methods such as those reported by Arduengo,[12] Kuhn,[13] and Waymouth and Hendrick.[14] We were intrigued, however, by a recent, elegant approach to unsymmetrical imidazolium salts disclosed by Fürstner.[15] This approach allowed for a redesign of our synthetic strategy, by reducing the synthetic challenge to the preparation of *N*-formyl bicyclic ketone **8**. This precursor, in turn, was prepared from *cis*-aminoindanol **3** by alkylation, formylation, epoxidation, intramolecular epoxide opening,[16] and oxidation as shown in Scheme 2. With **8** in hand, a slight modification of Fürstner's protocol allowed the introduction of the *N*-mesityl substituent and formation of the imidazolium ring. This approach proved to be robust and reliable and allowed for the preparation of a range of *N*-substituents.[17]

With chiral imidazolium precatalyst **1** in hand, we undertook a systematic comparison of imidazolium vs triazolium precatalysts in reactions known to be catalyzed by N-heterocyclic carbenes. Our previous studies employed triazolium salt **2·Cl** as the precatalyst, but our corresponding imidazolilum salt was most easily prepared and handled as the perchlorate salt (**1·ClO$_4$**). To avoid any concern over counterion effects, we prepared and employed triazolium **2·ClO$_4$** for comparison. A brief survey showed that this salt had identical reactivity as the chloride variant.

The results of the catalyst comparison confirmed, for the first time, that profound reactivity differences exist between the two classes of NHC-precatalysts. Of nine discrete reaction types screened, six processes were promoted almost exclusively by the triazolium precatalyst (**2·ClO$_4$**) (Scheme 3). Another three processes, all of which invoke catalytically generated homoenolates as the putative reactive intermediates, were preferentially promoted by the imidazolium salt **1·ClO$_4$** (Scheme 4). In all cases, the reaction conditions screened were identical, save for the catalyst structure, and no attempts were made to optimize the reacton conditions for improved yields or stereoselectivities. As we anticiapted from our results using achiral imidazolium salts,[18] precatalyst **1·ClO$_4$** was ineffective for NHC-catalyzed inverse electron-demand Diels−Alder processes. This was true regardless of how the key catalyst-bound enolate was generated, either via redox reactions of electron-deficient enals (Scheme 3a) or α-chloro aldehydes (Scheme 3b).[19] They were also unreactive in our recently disclosed annulation of enals and electron-deficient enones (Scheme 3c) or *N*-sulfonyl imines

Scheme 3. Reactions Catalyzed Preferentialy by Triazolium NHC-Precatalyst **2·ClO$_4$**[a]



[a] All reactions run under identical conditions with the two different precatalysts. No attempts were made to optimize the reaction conditions. [b]Unreacted enal was detected by ^{1}H NMR analysis of the unpurified reaction mixture. [c]% ee not determined.

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(10) Glorius, F.; Altenhoff, G.; Goddard, R.; Lehmann, C. *Chem. Commun.* **2002**, 2704−2705.

(11) For an excellent review of chiral N-heterocyclic carbenes, see: Perry, M. C.; Burgess, K. *Tetrahedron: Asymmetry* **2003**, *14*, 951−961.

(12) Arduengo, A. J.; Krafczyk, R.; Schmutzler, R.; Craig, H. A.; Goerlich, J. R.; Marshall, W. J.; Unverzagt, M. *Tetrahedron* **1999**, *55*, 14523−14534.

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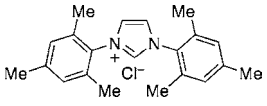
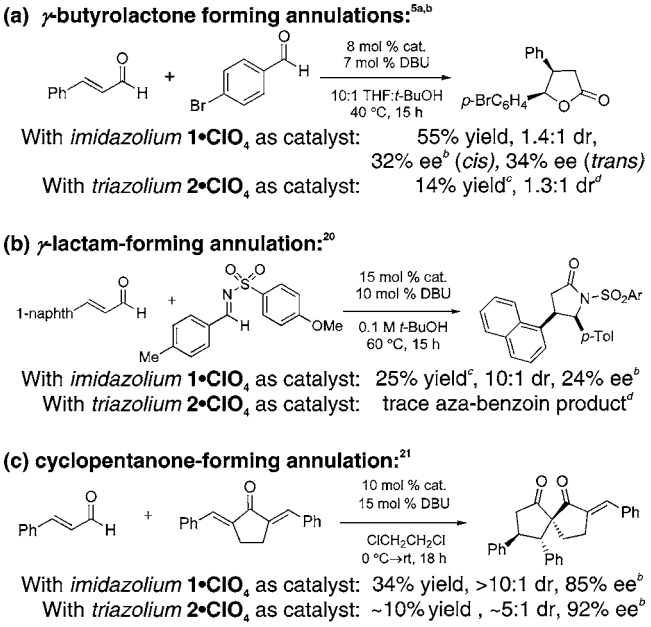
(16) Potter, G. W. H.; Monro, A. M. *J. Heterocycl. Chem.* **1972**, 299−301.

(17) See the Supporting Information for complete experimental procedures for the synthesis of **1·ClO$_4$**. Further details on the development of this route and its use to prepare a range of *N*-substituted derivatives is the subject of forthcoming full account.

(18) The most common achiral imidazolium salt employed for homoenolate based annulations is IMesCl:



Scheme 4. Reactions Catalyzed Preferentialy by *Imidazolium* NHC-Precatalyst **1**[a]



[a] All reactions run under identical conditions with the two different precatalysts. No attempts were made to optimize the reaction conditions. [b]Absolute configuration not determined. Unreacted enal was detected by ^{1}H NMR analysis of the unpurified reaction mixture. [c]% ee not determined.

(Scheme 3d), processes that we believe proceed via a benzoin−oxy-Cope reaction. Interestingly, triazolium precatalyst **2**, but not its imidazolium counterpart, was highly effective for intramolecular Stetter (Scheme 3e) and intermolecular benzoin reactions (Scheme 3f). Although these reactions are well-known to be catalysed by other triazolium-derived NHCs, this was the first time the *N*-mesityl substituted variant had been employed. These results strongly suggest that the lack of benzoin products observed when *N*-mesityl substituted imidazolium-derived NHCs are employed stem from the properties of the imidazolium ring rather than steric restrictions of the *N*-mesityl moeity.

In contrast, NHC-catalyzed annulation process that we and others have postulated to occur via catalytically generated homoenolate equivalents operate preferentially with imidazolium-derived precatalysts. The three reactions shown in Scheme 2 have all been reported to proceed in good yields in the presence of catalytic amounts of IMesCl. Although these processes work well with this catalyst, only a single report of an enantioselective variant has appeared in the work of Glorius, who obtained a maximum of 25% ee for a related annulation.[5c] Despite the high reactivity of triazolium-derived carbenes for the processes shown in Scheme 3, **2·ClO$_4$** and related triazolium salts are almost ineffective for the reactions shown in Scheme 4. The difference in reactivity between the annulations shown in Scheme 3d and Scheme 4b is particularly striking.

The cyclopentanone-forming annulation shown in Scheme 4c was recently reported by Nair and co-workers,[21] who believe that it proceeds via the intermediacy of a catalytically generated homoenolate. In support of this hypothesis, triazolioum **2**, which is typically a poor catalyst for homoenolate-based annulations, is almost unreactive. In contrast, imidazolium **1** effects the expected transformation in 85% ee, the highest level of enantioselectivity yet reported for any transformation catalyzed by a chiral imidazolium-derived NHC.

In summary, we have reported the synthesis of chiral *N*-mesityl substituted imidazolium salt **1**. In addition to providing a viable, potentially modular route to synthetically challenging chiral imidazolium salts, its successful synthesis allowed for the first time direct comparisons of otherwise structurally identical chiral imidazolium and triazolium NHC-precatalysts. The distinct reactivity profiles of these two classes reveal pronounced and unexpected differences in reactivity from a molecular replacement remote from the catalyst active site. The origin of this discrepancy, and the development of new catalytic reactions and enantioselective variants are the subject of ongoing investigations.

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Supporting Information Available: Full experimental procedures and characterization for the preparation of catalyst **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Under these reaction conditions the chloroaldehyde was not consumed when imidazolium salt **1·ClO$_4$** was employed. When DBU was used as base, the aldehyde was consumed but the dihydropyranone product was not observed.

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