Communication

Conversion of α-Haloaldehydes into Acylating Agents by an Internal Redox Reaction Catalyzed by Nucleophilic Carbenes

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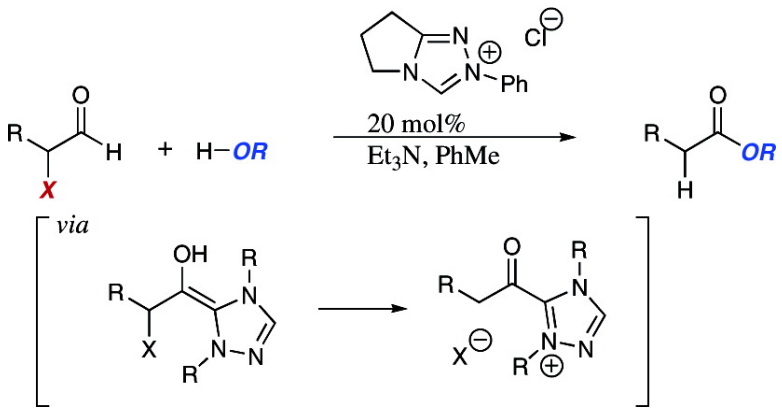

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Conversion of α-Haloaldehydes into Acylating Agents by an Internal Redox Reaction Catalyzed by Nucleophilic Carbenes

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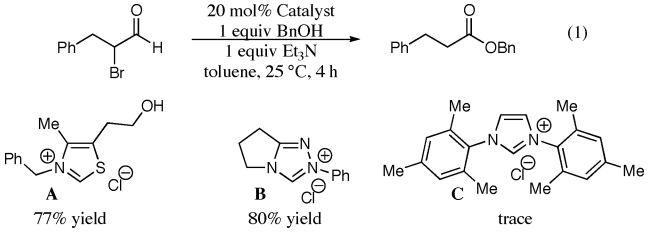
Umpolung reactivity of functional groups allows chemists the opportunity to view bond disconnections in nontraditional ways.[1] A catalyzed umpolung reaction of aldehydes was first discovered in the context of the benzoin reaction.[2] The utility of the proposed acyl anion equivalent was further extended when Stetter discovered that this intermediate reacts with Michael acceptors, affording 1,4-dicarbonyl compounds.[3] The presence of a catalyst coupled with the formation of a new stereocenter in the benzoin and Stetter processes affords an opportunity for asymmetric catalysis of these reactions, a concept that we[4] and others[5] have recently reduced to practice. It has been reported that imidazolylidine carbenes catalyze transesterification reactions, and intermediates such as **IV** (Scheme 1) have been implicated.[6,7,8] In conjunction with our efforts aimed at extending the utility of this umpolung reactivity, we envisioned accessing these intermediates via an unlikely precursor. Herein, we report a new reaction that transforms α-haloaldehydes into dehalogenated acylation agents catalyzed by nucleophilic carbenes.

The activation of aldehydes in the benzoin and Stetter reaction manifolds is proposed to proceed through the nucleophilic alkene intermediate **II** (Scheme 1). We envisioned that, should this intermediate contain a β-leaving group, we may access the enol **III** that, following tautomerization, should provide the acyl azolium **IV**. Interception of this activated ester with an appropriate nucleophile should regenerate the catalyst.



We initiated our investigations by examining α-bromodihydrocinnamaldehyde, easily prepared from hydrocinnamaldehyde and NBS in the presence of proline.[9] The haloaldehyde was treated with benzyl alcohol and triethylamine in the presence of the carbene precursor. Of the three common classes of azolium salts, thiazolium **A** and triazolium **B** proved to be catalytically competent, while imidazolium **C** provided only traces of product (eq 1). The efficiency of this transformation is worth noting: the reaction proceeds well with only one equivalent of alcohol, haloaldehyde, and amine base at ambient temperatures to provide the ester in 80% yield.

With these results in hand, we examined the effect of various haloaldehydes in this reaction. Bromoacetaldehyde provided the desired ester in 60% yield (Table 1, entry 1). Secondary and tertiary bromides were efficient substrates for this reaction (entries 2 and 4), with tertiary bromides requiring a longer reaction time (24 h). As expected, α-bromoaldehydes are more reactive than the chlorinated analogues (entry 2 vs entry 3).

Scheme 1. Proposed Mechanism of the Internal Redox Reaction of α-Haloaldehydes

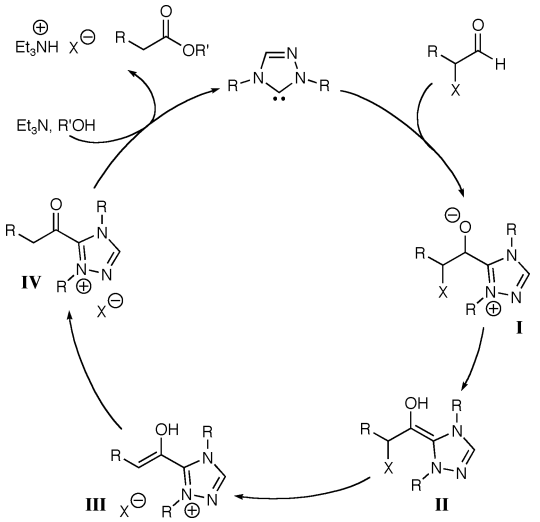
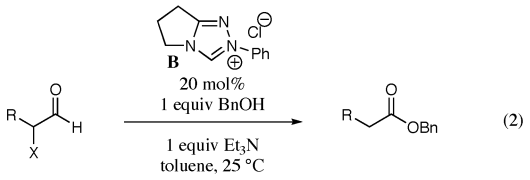
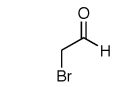
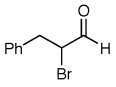
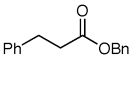
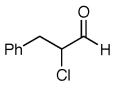
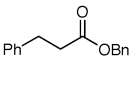
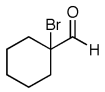
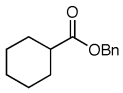


Table 1. Survey of Acylation Precursors



Entry[a]	Aldehyde	Time (h)	Product	Yield (%)
1		4		60
2		4		80
3		4		65
4		24		99

[a] Reactions conducted with one equivalent each of benzyl alcohol and triethylamine in the presence of 20 mol % triazolium catalyst at ambient temperature, unless otherwise stated.

Next, we surveyed the range of nucleophiles that would participate in the reaction. Primary alcohols work well (Table 2, entries 1−3) providing the desired esters in good yield. An increase in reaction time was required to obtain similar yields with secondary alcohols (entries 4−5, 8). Phenols are competent substrates in this chemistry as are anilines, suggesting that imine formation is not a

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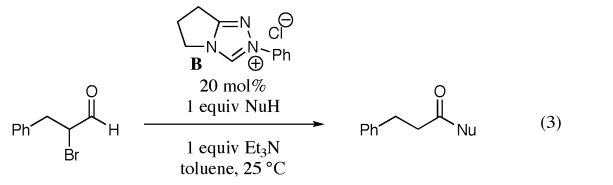
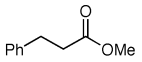
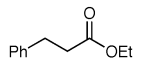
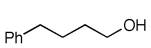
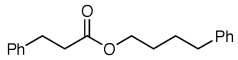
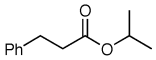
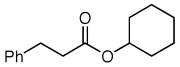
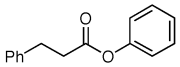
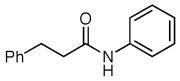
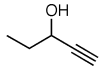
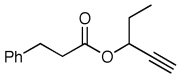
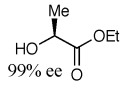
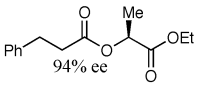
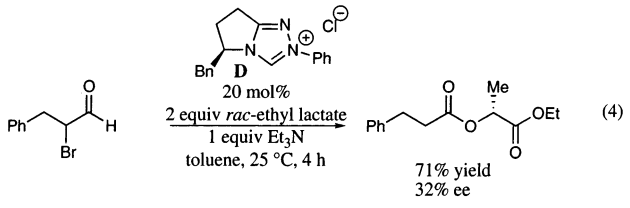
Table 2. Effect of Nucleophile Structure on the Internal Redox Reaction



Entry[a]	Nucleophile	Time (h)	Product	Yield (%)
1	MeOH	4		78
2	EtOH	4		78
3		4		73
4		24		66
5		24		66
6		24		55
7		24		91
8		24		65
9	 99% ee	24	 94% ee	56

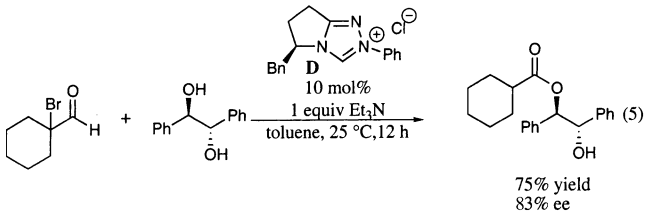
[a] Reactions conducted with one equivalent each of nucleophile and triethylamine in the presence of 20 mol % triazolium catalyst at ambient temperature, unless otherwise stated.

terminal problem. It is significant to note that these reaction conditions are tolerant of epimerizable stereocenters. The use of (S)-ethyl lactate of 99% ee results in the formation of the desired ester with minimal epimerization (94% ee, entry 9).



Since the reaction does not proceed in the absence of triazolium salt, we set out to determine the viability of our proposed intermediate **IV** by subjecting racemic lactate to the reaction in the presence of chiral triazolium salt **D** (eq 4). The product is formed in 71% yield and 32% ee. Because enantioenriched product was obtained, it suggests that the carbene is intimately involved in the bond-forming event, and lends support to our proposed catalytic cycle.

The use of a chiral carbene as a catalyst allows us to desymmetrize meso diols using this approach. Treatment of *meso*-hydrobenzoin with α-bromocyclohexanecarboxaldehyde in the presence of catalyst **D** provides the monoacylated diol in 75% yield and 83% ee. No trace of the corresponding diacylated product was evident by ^{1}H NMR.



In summary, we have discovered a new reaction pathway available to α-haloaldehydes catalyzed by nucleophillic carbenes. Efforts to utilize this reactivity in other transformations are currently underway.

Acknowledgment. We thank the National Science Foundation (CAREER) for partial support of this work. J.R.A. thanks Colorado PEAKS AGEP for a fellowship. T.R. gratefully acknowledges Merck Research Laboratories for unrestricted support, and GlaxoSmithKline and Amgen for young investigator awards.

Note Added in Proof. While this manuscript was in review, a conceptually similar transformation was reported by Bode and Chow; see Chow, K. Y.-K.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 8126−8127.

Note Added after ASAP Publication. After this paper was posted ASAP on July 9, 2004, yield and ee data were added to eq 5. The corrected version was posted July 14, 2004.

Supporting Information Available: Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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