Communication

N-Heterocyclic Carbene-Catalyzed Redox Amidations of α-Functionalized Aldehydes with Amines

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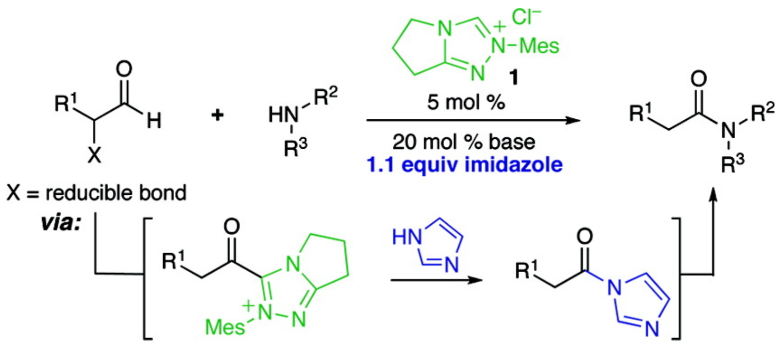

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COMMUNICATIONS

N-Heterocyclic Carbene-Catalyzed Redox Amidations of α-Functionalized Aldehydes with Amines

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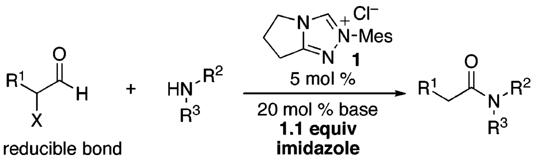
Despite the quintessential importance of carboxylic acid amides in organic chemistry, there are few catalytic methods for their preparation from simple starting materials.[1] Established approaches for amide synthesis continue to rely on the stoichiometric generation of an activated carboxylate via the reaction of a carboxylic acid and a coupling reagent, a process that not only generates copious byproducts but also requires extensive protection of other functional groups.[2]

As part of a program aimed at developing new reactions for amide bond formation, we have pioneered isohypsic approaches to carboxylic acid derivatives that obviate the need for stoichiometric reagents or reaction byproducts. For example, we have disclosed that α-ketoacids and various hydroxylamines undergo reagentless, chemoselective couplings to afford amides.[3] In parallel, we have developed a method for the catalytic generation of activated carboxylates via N-heterocyclic carbene-catalyzed internal redox reactions of α-functionalized aldehydes.[4] These developments have allowed us and others to identify conditions for the synthesis of esters and thioesters from α,*β*-epoxy aldehydes,[5] α-haloaldehydes,[6] α,*β*-unsaturated aldehydes,[7] ynals,[8] formyl cyclopropanes,[9] and formyl *β*-lactams[10] without the need for stoichiometric reagents or the production of byproducts.

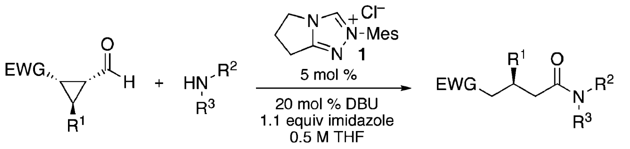
Despite these impressive and rapid advances in catalytic, stereoselective approaches to carboxylic acid derivatives, reliable protocols for the synthesis of the corresponding amides have remained elusive.[11] This difficulty stems from the unsurprising finding that the combination of aldehyde substrates and amine nucleophiles results in rapid formation of carbonyl imines, leading to extensive inhibition of the desired catalytic amidation reactions. We now report an effective and general solution via the unexpected role of imidazole as promoter that makes possible catalytic amidations of a wide range of α-functionalized aldehydes (eq 1).[12]

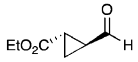
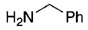
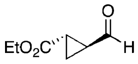
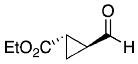
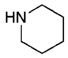
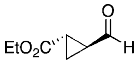
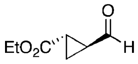
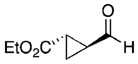
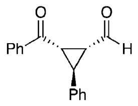
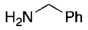
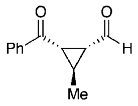
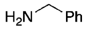
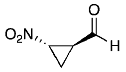
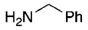
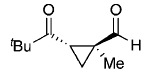
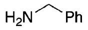


(1)

For reaction development, we considered the redox amidation of a formyl cyclopropane **2** with benzyl amine, catalyzed by a combination of triazolium precatalyst **1** and DBU. In the absence of a suitable promoter, less than 5% of the desired amide was isolated, and NMR analyses revealed that the bulk of the aldehyde starting material was converted to the corresponding imine (**4**). Cognizant of our studies suggesting a key role for a suitable proton source in accelerating the NHC-catalyzed generation of the activated carboxylate, we screened a number of suitable additives. While a number of nucleophilic co-catalysts (0.2 equiv) commonly employed in acylation reactions, including HOBt, DMAP, pentafluorophenol, and *ortho*-nitrophenol, offered little or no improvement in the amidation reaction, we were pleased to find that protic N-heterocycles greatly benefited the amidation reaction (see the Supporting Information).

Table 1. NHC-Catalyzed Amidations of Formyl Cyclopropanes[a]



entry	aldehyde	amine	conditions	% yield[b]
1			A	88
2			B	90
3		$H_2N-n\text{-}C_8H_{17}$	A	65
4			B	74
5		NH_2–Phe–O^{t}Bu	B	99[c]
6		H_2N-Ph	B	70
7		H_2N-OBn	B	53
8			B	81
9			B	83
10			B	54
11			A	68

[a] Conditions A: 1 equiv of aldehyde, 1.1 equiv of imidazole, 5 mol % of **1**, 20 mol % of DBU at 40 °C for 20 min prior to addition of 1.2 equiv of amine at rt, 15 h. Conditions B: 1.5 equiv of aldehyde, 1 equiv of amine, 1.1 equiv of imidazole, 40 °C, 15 h. [b] Isolated yield after chromatography. [c] With 3 equiv of aldehyde.

Useful yields of the desired amide were obtained using 20 mol % of imidazole as an additive, and employing 1.1 equiv of imidazole completely suppressed imine formation and led to amide formation in excellent yield. A wide range of amines, including primary, secondary, aniline, and hydroxylamines, were viable reaction partners for catalytic amidations (Table 1, entries 1−7). Likewise, a range of substituted formyl cyclopropanes served as efficient acyl donors in catalytic amidation reactions with benzyl amine (entries 8−11). α-Chloroaldehydes, which are exceptionally reactive toward

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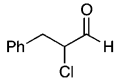
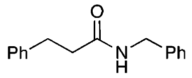
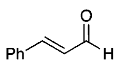
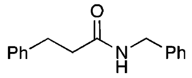
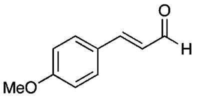
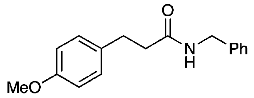
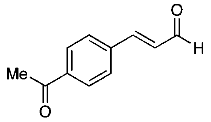
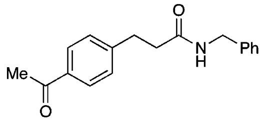
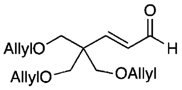
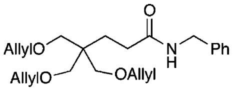
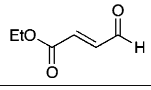
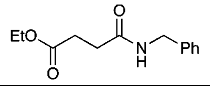
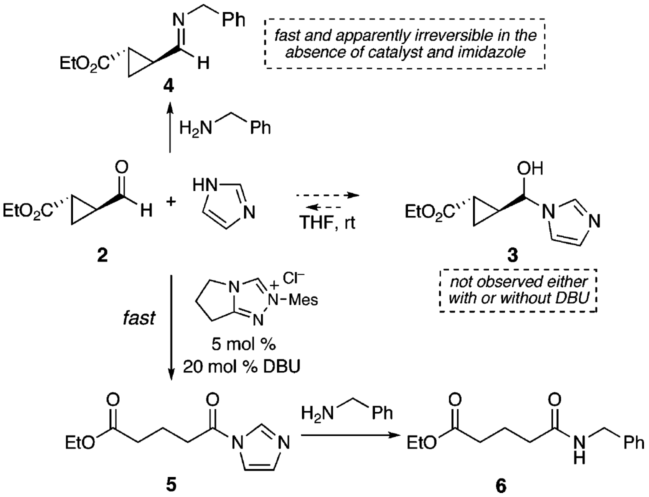
10.1021/ja0768136 CCC: $37.00

Table 2. Catalytic Redox Amidations of Enals

entry	aldehyde	product	% yield[d]
1			63[a,c]
2			96
3			68[a]
4			96[b]
5			63[b]
6			56[a]
7			78[a]
8			90[b]
9			52[a]

[a] Conditions: 1 equiv of aldehyde, 1.1 equiv of imidazole, 5 mol % of **1** and 20 mol % of DIPEA amine at 40 °C for 20 min prior to addition of 1.2 equiv of amine at rt, 15 h. [b] Amine added after 15 h, and rxn stirred at rt for 1 h. [c] With 1 equiv of DIPEA employed. [d] Isolated yield after chromatography.

Scheme 1. Consideration of Reaction Pathways in Imidazole-Promoted Redox Amidation of α-Functionalized Aldehydes



the NHC catalyst,[13] afforded the amide product in good yield without competing reactions (Table 2, entries 1 and 2).

Unlike other classes of α-functionalized aldehydes, including α-halo- and α,*β*-epoxyaldehydes, α,*β*-unsaturated aldehydes are less reactive and their redox reactions can be complicated by competing lactone-forming dimerization reactions.[14] However, their wide availability and relative stability renders them the most attractive class of acyl donors. We were therefore pleased to identify conditions suitable for direct redox amidations of enals, again using imidazole as an essential, inexpensive, promoter (Table 2). Consistent with our previous studies, the use of Hünig's base, rather than DBU, was critical to the success of the reaction.

The ability of imidazole and related N-heterocycles to facilitate the catalytic amidation reaction raises several mechanistic questions, particularly, in light of the failure, in the case of formyl cyclopropanes, of other common additives to successfully promote the amidations. Initially, we considered three explanations for the role of imidazole: (1) rapid reaction of imidazole with the aldehyde, forming a known, metastable hemiaminal **3** that acts as an in situ protecting group;[15] (2) a role in promoting the decomposition of the imine to the aldehyde and amine substrates;[16] and (3) a tandem catalysis approach via chemoselective reaction of the acyl triazolium activated carboxylate with imidazole, leading to an acyl imidazolium species that is eventually converted to the desired amide product.

Given the previous failures of nitrogen-based nucleophiles to participate in these redox-type reactions,[17] we initially favored for imidazole a role as a transient aldehyde-protecting group. However, exposure of formyl cyclopropane **1** to imidazole, without precatalyst **1**, in either the presence or absence of DBU led to no observable reactions by NMR analysis (Scheme 1). Upon addition of benzyl amine, in the absence of **1**, imine formation occurred readily, discounting a role for imidazole in suppressing or reversing imine formation. In contrast, when **2**, imidazole, precatalyst **1**, and DBU were combined in the absence of benzyl amine, the aldehyde was quickly consumed and new product formed. Analysis by ^{1}H NMR (see Supporting Information) identified this species as the acyl imidazole **5**. Treatment of this intermediate with amines or alcohols leads cleanly to amide or esters products, respectively.

In summary, we have documented a straightforward solution to the seemingly intractable problem of competing imine formation in the NHC-catalyzed redox amidation of α-functionalized aldehydes. These studies provide a valuable addition to ongoing efforts on developing catalytic, stereoselective, and atom-economical approaches to carboxylic acid derivatives.

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

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(17) For the only two exceptions, see examples cited in refs 6a and 7b.

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