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Catalytic amide-formation with α' -hydroxyenones as acylating reagents[†]

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Abstract

α' -Hydroxyenones undergo clean, catalytic amidations with amines promoted by the combination of an N-heterocyclic carbene and 1,2,4-triazole.

The ubiquity of amide-containing organic compounds coupled with the generally expensive and wasteful methods for their formation have engendered intense, recent efforts in the identification and development of catalytic methods for amide-bond formation.¹ The most attractive approach, the direct catalytic coupling of carboxylic acids and amines,² can be achieved with certain boronic acids as catalysts under conditions involving high temperatures^{2a,b} or the use of molecular sieves.^{2c} Elegant work with transition metal catalysts has made possible the formation of amides from amines and alcohols, with the formation of H₂ as the only stoichiometric byproduct.³ Chemoselective, reagentless amide-formations, are an exciting area for the synthesis of peptides and biomolecules,⁴ but the need for specialized starting materials limits the utility of these processes for the synthesis of simple amides.⁵

In seeking to develop simple, waste-free methods for the synthesis of carboxylic acid derivatives, we have advanced the concept of redox esterifications and amidations.⁶ These reactions, promoted by N-heterocyclic carbenes,⁷ proceed via transient activated carboxylates catalytically generated by internal redox reactions of α -functionalized aldehydes including epoxyaldehydes,⁸ α -haloaldehydes,⁹ formyl cyclopropanes,¹⁰ and α,β -unsaturated aldehydes.¹¹ Such esterifications proceed smoothly in high yield without stoichiometric amounts of reagents or byproducts. The amidations, however, are often complicated by competing imine formation and proceed only in the presence of a suitable additive such as imidazole or HOAt.¹² Thus, while feasible, this redox amidation requires further refinement to improve the yields, catalyst loadings, and scope to impact the need for simple amidation reactions. In this communication, we report such an advance in the form of catalytic amidations of α' -hydroxyenones in the presence of a triazolium precatalyst and 1,2,4-triazole as a co-catalyst.

The use of α' -hydroxyenones as substrates for NHC-catalyzed reactions stems from our recent studies on their use as surrogates for α,β -unsaturated aldehydes.¹³ These starting materials are attractive due to their facile, one-step preparation from widely available starting materials,¹⁴ their stability towards long-term storage, and their tendency to be crystalline products. In contrast, the corresponding α,β -unsaturated aldehydes often require multi-step syntheses employing expensive and wasteful reagents.¹⁵ We also recognized that the use of α' -

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hydroxyenones could overcome the imine formation that complicates the use of aldehydes in catalytic amidation reactions.

The interaction of an N-heterocyclic carbene with the α' -hydroxyenone leads to the conjugated Breslow intermediate via a retro-benzoin reaction that expels acetone. This intermediate must be protonated in order to form the key acyl azolium intermediate that serves as the catalytically generated activated carboxylate.^{11b} We were pleased to see that esterifications from alcohols and the α' -hydroxyenones proceeded smoothly, but initial attempts to extend this to amidations gave rise to only small amounts of the desired products. Reasoning that the use of a suitable co-catalyst was essential for the success of the amidation, we screened a number of additives and found that imidazole and related heterocycles were effective at promoting the amidation (See Supporting Information).¹⁶ From a number of active co-catalysts, we selected 1,2,4-triazole¹⁷ for further development. Additional optimization identified the conditions showed in Scheme 1 as preferred. A screen of alternative azolium precatalysts confirmed the unique reactivity of N-mesitylsubstituted triazolium salt **1**.¹⁸

Table 1 shows the scope of the amidation reaction with primary amines and the phenyl substituted α' -hydroxyenone **2** (Table 1). The products are the corresponding hydrocinnamyl amides. Excellent results were obtained for most substrates, with only the sterically demanding *tert*-butyl amine giving lower yields. Chemoselective amidation of the primary amine occurs with tryptamine. Anilines, despite being less reactive, turned out to be excellent substrates if the reactions were performed at lower concentration for 12 h.

The amidation reaction also works well for secondary amines (Table 2). For the preparation of Weinreb amide **19**, we found it necessary to first form the free base the hydroxylamine prior to the amidation. For reasons that we do currently understand, simply using the hydrochloride salt and an additional equivalent of base did not allow for amidation under these conditions.

We also examined the use of various α' -hydroxyenones in the amidation reaction (Table 3). The advantage of these substrates is that they are easily prepared from aromatic aldehydes, under conditions that readily tolerate diverse functionalities including heterocycles. We were pleased to find that these substrates participated in the amidation reactions without modification of the reaction conditions. An initial attempt with an aliphatic substituted hydroxyenone gave the expected amide **30** in inferior yield. We anticipate that further substrate dependent optimization will be possible.

An intriguing feature of NHC-catalyzed redox reactions is that while esterification processes generally work extremely well without the need for any additive, amidations reactions in the absence of a suitable co-catalyst generally fail. We were therefore interested in the chemoselectivity of the amidation reaction when amino alcohols were used as substrates.¹⁹ Table 4 shows our preliminary investigations on NHC-catalyzed amidations of various aminoalcohols in the presence of 1,2,4-triazole as a co-catalyst. In the absence of the co-catalyst, NHC-catalyzed acylations of the aminoalcohols usually gave mixtures of the amide and ester products, including bis-acylated compounds. With 10 mol % 1,2,4-triazole, however, the desired amides were chemoselectively formed in moderate to good yield.

We believe that this NHC-catalyzed redox amidation proceeds according to the tandem catalytic cycle shown in Scheme 1. Attack of the NHC-catalyst onto the α' -hydroxyenone gives **I**, which expels acetone to generate Breslow intermediate **II**. The conjugate acid of the catalytic base, formed during the deprotonation of the triazolium precatalyst, protonates the Breslow intermediate, which may be considered as a formal homoenolate equivalent. Tautomerization of **III** affords activated carboxylate **IV**. This intermediate is a competent acylating agent for alcohols, but reacts only slowly with amines and is turned over by the triazole co-catalyst to

regenerate the precatalyst and form acyl triazole **V**. This is the active acylating agent with amines.²⁰

In summary, we have documented a new method for catalytic amide formation. No stoichiometric reagents are required, the reaction proceeds under mild conditions, and the only byproduct is one equivalent of acetone. The use of readily prepared α' -hydroxyenones overcomes the two major limitations of α,β -unsaturated aldehydes as substrates in similar amidation reactions: 1) their relative difficulty of preparation and 2) their tendency to form imines that complicate the reaction protocols or contaminate the desired amide product. The two distinct catalytic cycles involved in this reaction offer the opportunity to develop new chemo- and stereoselective processes for amine acylation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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16. In some cases, modest yields (5–30%) of amide products could be obtained without a co-catalyst. For many substrates, however, no amide products were obtained in the absence of 1,2,4-triazole or similar promoter.

17. During the course of this work, Birman reported that the combination of 1,2,4-triazole and base catalyzes the acylations of amines and esters: Yang X, Birman VB. *Org. Lett* 2009;11:1499–1502. [PubMed: 19281231]
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20. We have detected this intermediate during the reaction and studied it by ^1H NMR and ^{13}C NMR. This data supports the regiochemical assignment shown in Scheme 1.

Scheme 1.

Postulated tandem catalytic cycles for amide formation from α' -hydroxyenones.

Table 1

NHC-catalyzed amidations of primary amines

$\text{Ph}-\text{CH}=\text{CH}-\text{C}(\text{OH})(\text{Me})_2 + \text{H}_2\text{N}-\text{R}^1 \xrightarrow[\text{0.5 M CH}_2\text{Cl}_2, 40^\circ\text{C}, 3\text{ h}]{\text{NHC (1, 5 mol \%), (iPr)}_2\text{NEt (20 mol \%), 1,2,4-triazole (10 mol \%)}} \text{Ph}-\text{CH}_2-\text{CH}_2-\text{C}(=\text{O})-\text{NHR}^1$ 2 (1.2 equiv) (1.0 equiv)	
3 84%	4 92%
5 73%	6 69%
7 90%	8 90%
9 84%	10 90%
11 56%	12 90%
13 47%	14 98%
15 98%^a	16 99%^a

^a Reaction conditions: 0.1 M CH₂Cl₂ for 12 h

Table 2

Catalytic amidations of secondary amines.

Table 3 Variation of the α' -hydroxyenone in catalytic amidations.

Table 4 Chemoselective amidations of aminoalcohols. ^a

 31 51%	 32 66%
 33 38%	 34 74%

^aReaction conditions: 5 mol % **1**, 10 mol % 1,2,4-triazole, 20 mol % (iPr)₂NEt, 0.1 M CH₂Cl₂, 40 °C, 3 h.