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Nucleophilic Carbene and HOAt Relay Catalysis in a Waste Free Amide Bond Coupling:

An Orthogonal Peptide Bond Forming Reaction

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The ubiquity of amides throughout organic, biological and materials chemistry mandates the development of more efficient methods for their synthesis.¹ Conventional amide bond formation utilizes acids and amines as coupling partners and relies on stoichiometric activating agents for the acid functionality.^{2,3} A recent survey of process scale reactions cites a “...pressing need for the development of catalytic environmentally friendly acylation processes.”^{4,5} We⁶ and others⁷ have recently illustrated that nucleophilic carbenes⁸ catalyze an internal redox reaction whereby alpha reducible aldehydes provide alpha reduced ester derivatives under catalytic conditions.⁹ Surprisingly, among the many nucleophiles reported to participate in this process are only two amines: we^{6a} have shown that aniline participates and Scheidt^{7b} has shown that a vinylogous imide could be used.¹⁰ Clearly, the salient features of this redox manifold, a waste free catalyzed acylation, provide a strong impetus to identify a general solution to the problem of NHC catalyzed amidation. Herein, we report one such solution relying on relay catalysis by a nucleophilic carbene and a common peptide cocatalyst such as 1-hydroxy-7-azabenzotriazole¹¹ (HOAt).

Outside of aniline, our efforts at using amines as nucleophiles in the alpha redox reaction were met with uniform failure. Since we had established that phenols are competent partners, we hypothesized that the use of a cocatalyst such as HOAt could provide a relay shuttle.^{12,13} HOAt should participate in the redox chemistry to generate activated ester which would undergo the in situ amidation thereby regenerating the catalyst. The viability of a concerted catalytic system using N-heterocyclic carbenes and HOAt to generate amides was investigated utilizing 2,2-dichloro-3-phenylpropanal as the redox substrate and benzyl amine as the nucleophile. The desired chemical transformation took place to afford the benzyl amide **2a** in 93% yield (eq 1). In the absence of HOAt, only minor amidation product is observed.¹⁴ A cocatalyst screen revealed that 1-hydroxybenzotriazole (HOBt), 4-(dimethylamino) pyridine (DMAP), imidazole and pentafluorophenol (PFPOH) are effective at promoting the reaction, affording the desired amide products.

(1)

Experiments that probe the scope of useful amine partners are summarized in Table 1. A variety of primary and secondary amines partake in the reaction (entries 1-5, Table 1) to afford the desired amide in good to excellent yields. Of particular interest is the generation of the Weinreb amide **2f** in 72% yield (entry 5, Table 1). Electron rich and poor aryl amines **2f-h** (entries 6-8, Table 1) also undergo the transformation readily to give the desired anilides in 82-87% yield. Amino esters are also competent partners (entry 9, Table 1).

A variety of α -halo aldehydes are suitable partners in the alpha redox amidation. The reaction is tolerant of branching at the α and β position: α,α -dichloro isovaleraldehyde provides **3** in 72% yield, and α -bromo cyclohexanecarboxaldehyde provides **4** in 80% yield (Figure 1).

One of the strengths of the redox amidation reaction manifold is that the appropriate choice of alpha reducible aldehyde provides an opportunity for a waste free amidation. Treatment of α,β -epoxy and aziridino aldehydes under the redox amidation conditions affords β -hydroxy and β -amino amides (entries 1-3, Table 2) in good yields and excellent diastereoselectivities. α,β -Unsaturated aldehydes provide the alkanamides in good yield (entries 4-5, Table 2). Importantly, in each case, the only stoichiometric waste generated is derived from solvent; even the base is used in catalytic amounts.

The catalytic cycle is postulated to initiate upon formation of carbene **I**, which undergoes nucleophilic addition to the aldehyde, Scheme 1. Generation of the acyl azolium intermediate **II** sets the stage for an acyl transfer event with co-catalyst **III** to furnish the activated carboxylate **IV**. Nucleophilic attack by the amine affords the amide, and regenerates the co-catalyst.

Experimental support for the proposed mechanism is provided by the use of chiral carbenes in this process. The use of catalyst **B** leads to an asymmetric α -chloro amide synthesis in modest ee (eq 2), validating the role of the carbene in controlling the protonation event. In contrast, the use of **B** provides no selectivity in the kinetic resolution of α -methylbenzyl amine (eq 3). In addition, the use of stoichiometric HOAt in absence of amine provides the HOAt ester **IV** in 64% yield. Addition of BnNH_2 generates the amide quantitatively.

In summary, we have developed a waste-free amide bond forming reaction using alpha reducible aldehydes and amines catalyzed by carbenes in conjunction with common peptide additives as cocatalysts.

(2)

(3)

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

- (1). Humphrey JM, Chamberlin AR. Chem Rev 1997;97:2243. [PubMed: 11848900]
- (2). Larock, RC. Comprehensive Organic Transformations. VCH; New York: 1999.
- (3). For some recent exceptions, see:(a)Shangguan N, Katukojvala S, Greenberg R, Williams LJ. J. Am. Chem. Soc 2003;125:7754. [PubMed: 12822965](b)Bode JW, Fox RM, Baucom KD. Angew. Chem. Int. Ed 2006;45:1248.(c)Carillo N, Davalos EA, Russak JA, Bode JW. J. Am. Chem. Soc 2006;128:1452. [PubMed: 16448107]
- (4). Carey JS, Laffan D, Thomson C, Williams MT. Org. Biomol. Chem 2006;4:2337. [PubMed: 16763676]Also see:Dugger RW, Ragan JA, Brown Ripin DH. Org. Proc. Res. Dev 2005;9:253.

- (5). For a sampling of recent contributions in this area, see:(a)Ishihara K, Ohara S, Yamamoto H. J. Org. Chem 1996;61:4196. [PubMed: 11667313](b)Eldred SE, Stone DA, Gellman SH, Stahl SS. J. Am. Chem. Soc 2003;125:3422–3423.3423 [PubMed: 12643691](c)Yoo WJ, Li CJ. J. Am. Chem. Soc 2006;128:13064. [PubMed: 17017781](d)Ekoue-Kovi K, Wolf C. Org. Lett 2007;9:3429. [PubMed: 17655318]
- (6)(a). Reynolds NT, Read de Alaniz J, Rovis T. J. Am. Chem. Soc 2004;126:9518. [PubMed: 15291537] (b) Reynolds NT, Rovis T. J. Am. Chem. Soc 2005;127:16406. [PubMed: 16305222]
- (7)(a). Chow KY-K, Bode JW. J. Am. Chem. Soc 2004;126:8126. [PubMed: 15225048] (b) Chan A, Scheidt KA. Org. Lett 2005;7:905. [PubMed: 15727471] (c) Sohn SS, Bode JW. Org. Lett 2005;7:3873. [PubMed: 16119920] (d) Sohn SS, Bode JW. Angew. Chem. Int. Ed 2006;45:6021. (e) Zeitler K. Org. Lett 2006;8:637. [PubMed: 16468730] (f) Grasa GA, Güveli T, Singh R, Nolan SP. J. Org. Chem 2003;68:2812. [PubMed: 12662057]
- (8). Reviews:(a)Enders D, Balensiefer T. Acc. Chem. Res 2004;37:534. [PubMed: 15311952](b)Johnson JS. Angew. Chem. Int. Ed 2004;43:1326.(c)Zeitler K. Angew. Chem. Int. Ed 2005;44:7506.(d) Marion N, Díez-Gonzalez S, Nolan SP. Angew. Chem. Int. Ed 2007;46:2988.
- (9). This reactivity was first described by Wallach, who found that treatment of chloral with aqueous cyanide provides dichloroacetic acid:Wallach O. Ann. Chem 1873;6:114.
- (10). Movassaghi has shown that amide products can be obtained from treatment of ester with amino alcohols using N-heterocyclic carbenes. This reactivity has been shown to proceed via an intramolecular O→N acyl transfer to generate the amide.Movassaghi M, Schmidt MA. Org. Lett 2005;7:2453. [PubMed: 15932221]
- (11)(a). König W, Geiger R. Ber. Dtsch. Chem. Ges 1970;103:788. (b) König W, Geiger R. Ber. Dtsch. Chem. Ges 1970;103:2024.
- (12). Catalytic HOAt and HOBt in ester amidation:Han C, Lee JP, Lobkovsky E, Porco JA. J. Am. Chem. Soc 2005;127:10039. [PubMed: 16011366]
- (13). Cascade catalysis:(a)Hourai AF, Xu Z, Cogan DA, Hoveyda AH. J. Am. Chem. Soc 1995;117:2943. (b)Bruggink A, Schoevaart R, Kieboom T. Org. Proc. Res. Dev 2003;7:622.(c)Huang Y, Walji AM, Larsen CH, MacMillan DWC. J. Am. Chem. Soc 2005;127:15051. [PubMed: 16248643](d) Concurrent tandem catalysis:Wasilke J-C, Obrey SJ, Baker RT, Bazan GC. Chem. Rev 2005;105:1001. [PubMed: 15755083]
- (14). In the absence of cocatalyst, the reaction generates significant amounts of imine and alpha-reduced carboxylic acid.

Figure 1.
 α -Haloaldehyde substrate scope.

Scheme 1.
Proposed catalytic cycle.

Table 1

Amine Scope

Yield
Entry ^a		

1

2

Entry^a

Yie

Entry^a

Yie

7

8

Entry^a

Yie

9

^aCatalyst **A** (20 mol %), HOAt (20 mol%), Et₃N (1.2 eq), THF (0.5 M), t-BuOH (1.0 eq), 25 °C, 6 h, unless otherwise noted.

^bHOBt (20 mol%) and Et₃N (2.1 eq) were used.

^c2:1 dr.

Table 2

Atom-economical amidation

Entry	Substrate
	<p>6 + H₂N-R₂</p> <p>A BF₄⁻</p> <p>cocatalyst (10) DIPEA (10-30)</p>

1

cocatalyst (10-30)
DIPEA (10-30)

Entry

Substrate

2

Entry

Substrate

3

Entry

Substrate

4

Entry

Substrate

5

^a **A** (10 mol %), imid. (10 mol %), DIPEA (30 mol %), *t*-BuOH (0.1 M), 40 °C, 24 h.

^b **A** (10 mol %), HOAt (10 mol %), DIPEA (10 mol%), THF (1.0 M), 45 °C.