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Nucleophilic Carbene and HOAt Relay Catalysis in an Amide Bond Coupling: An Orthogonal Peptide Bond Forming Reaction

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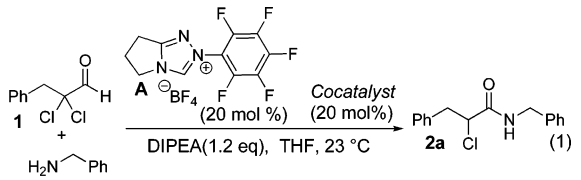
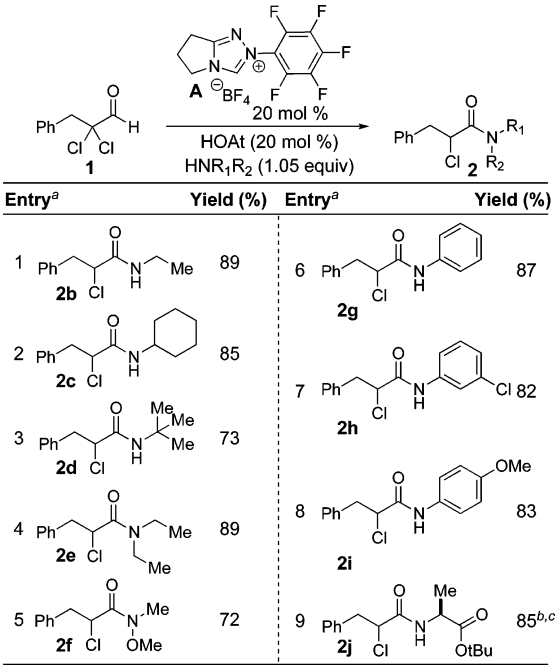
The ubiquity of amides throughout organic, biological, and materials chemistry mandates the development of more efficient methods for their synthesis.[1] Conventional amide bond formation utilizes acids and amines as coupling partners and relies on stoichiometric activating agents for the acid functionality.[2,3] A recent survey of process scale reactions cites a "...pressing need for the development of catalytic environmentally friendly acylation processes".[4,5] We[6] and others[7] have recently illustrated that nucleophilic carbenes[8] catalyze an internal redox reaction whereby α-reducible aldehydes provide α-reduced ester derivatives under catalytic conditions.[9] Surprisingly, among the many nucleophiles reported to participate in this process, there 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-azabenzotriazole[11] (HOAt).

Outside of aniline, our efforts at using amines as nucleophiles in the α-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.



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).

Table 1. Amine Scope



[a] Catalyst **A** (20 mol %), HOAt (20 mol %), Et_3N (1.2 equiv), THF (0.5 M), *t*-BuOH (1.0 equiv), 25 °C, 6 h, unless otherwise noted. [b] HOBt (20 mol %) and Et_3N (2.1 equiv) were used. [c] Diastereomeric ratio 2:1.

A variety of α-haloaldehydes are suitable partners in the α-redox amidation. The reaction is tolerant of branching at the α and *β* position: α,α-dichloroisovaleraldehyde provides **3** in 72% yield, and α-bromocyclohexanecarboxaldehyde provides **4** in 80% yield (Figure 1).

One of the strengths of the redox amidation reaction manifold is that the appropriate choice of α-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 and 5,

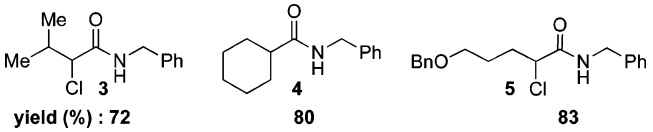


Figure 1. α-Haloaldehyde substrate scope.

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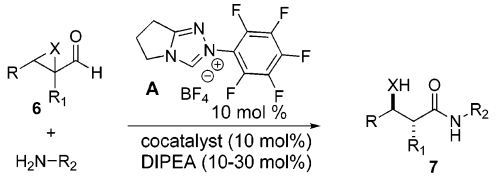
Table 2. Atom-Economical Amidation



Entry	Substrate	Product	Yield (%)	dr
1	(+)-6a	7a	86[a]	>19:1
2	(+)-6a	7b	75[a]	15:1
3	(+/-)-6b	7c	72[a]	>19:1
4	6c	7d	80[b]	-
5	6d	7e	82[b]	-

[a] Catalyst **A** (10 mol %), imidazole (10 mol %), DIPEA (30 mol %), *t*-BuOH (0.1 M), 40 °C, 24 h. [b] Catalyst **A** (10 mol %), HOAt (10 mol %), DIPEA (10 mol %), THF (1.0 M), 45 °C.

Scheme 1. Proposed Catalytic Cycle

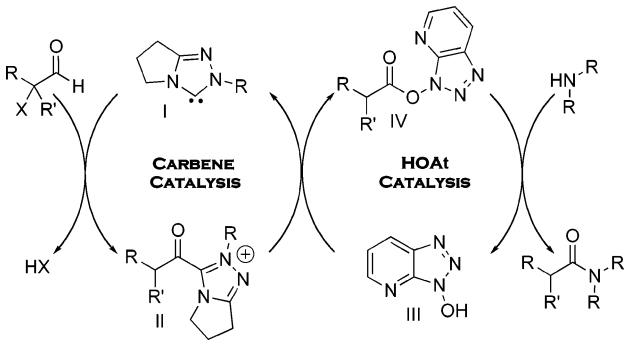
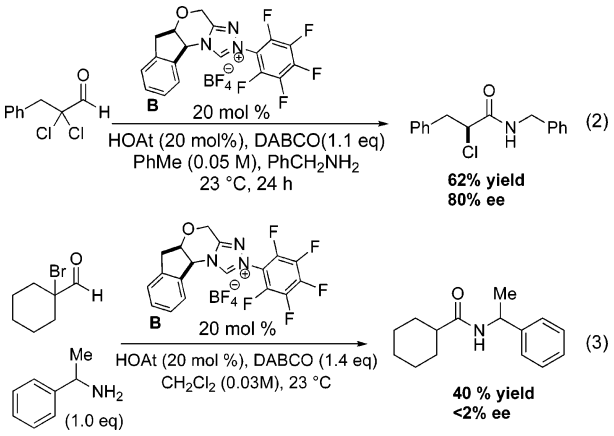


Table 2). Importantly, in each case, the only stoichiometric waste generated is derived from solvent; even the base is used in catalytic amounts.

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 cocatalyst **III** to furnish the activated carboxylate **IV**. Nucleophilic attack by the amine affords the amide and regenerates the cocatalyst.

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-chloroamide 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 the 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 α-reducible aldehydes and amines catalyzed by carbenes in conjunction with common peptide additives as cocatalysts.



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Note Added after ASAP Publication. Reference 11c was added on October 12, 2007.

Supporting Information Available: Experimental procedures and full characterization of all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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