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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] We[6] and others[7] have recently illustrated that nucleophilic carbenes[8] 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-azabenzotriazole[11] (HOAt).

Outside of aniline, our efforts at using amines as nucleophilies 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.

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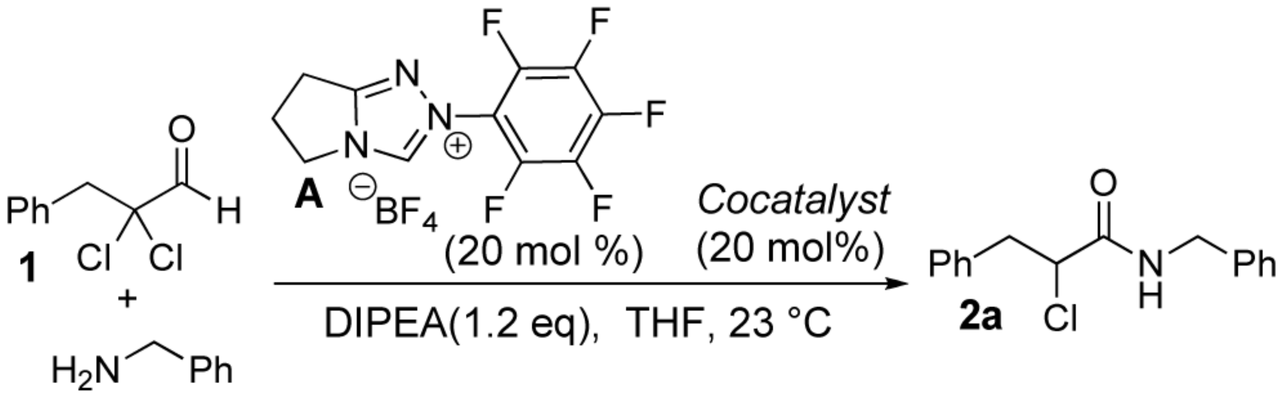


Cocatalyst:	None	HOBt	HOAt	DMAP	Imidazole	PFPOH
Yield (%)	**30**	**92**	**93**	**90**	**85**	**88**

(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).

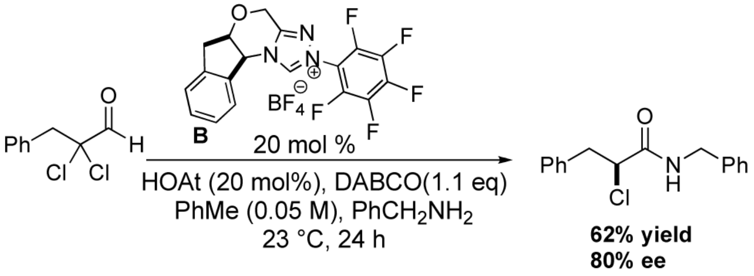
A variety of α-halo aldehydes are suitable partners in the alpha redox amidation. The reaction is tolerant of branching at the α and β position: α,α-dichloro isovaleraldehyde provides **3** in 72% yield, and α-bromo cyclohexanecarboxaldehyde provides **4** in 80% yield (Figure 1).

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.



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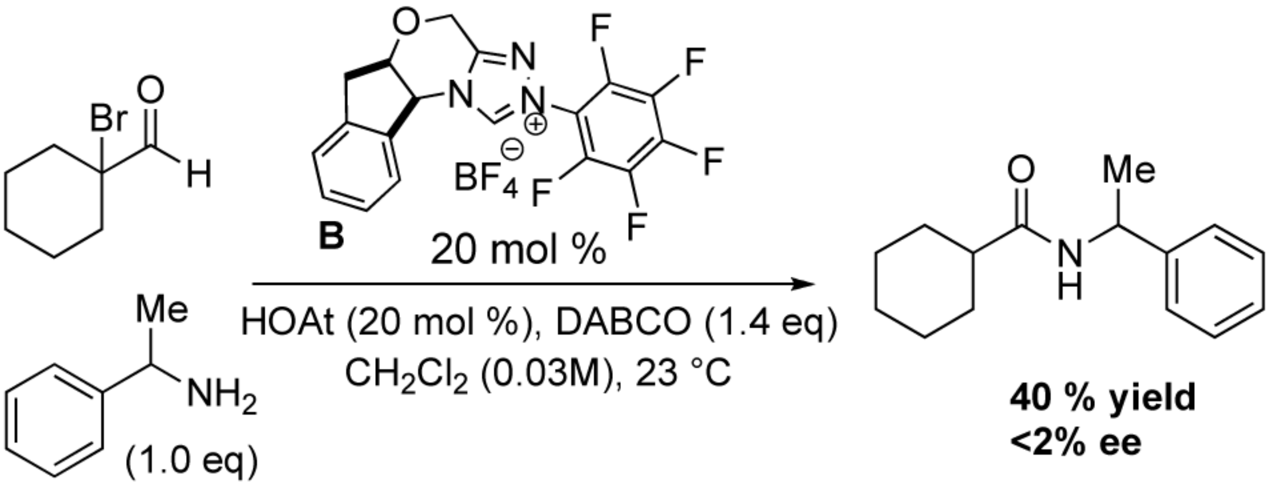

(3)

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

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References

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(14). In the absence of cocatalyst, the reaction generates significant amounts of imine and alpha-reduced carboxylic acid.

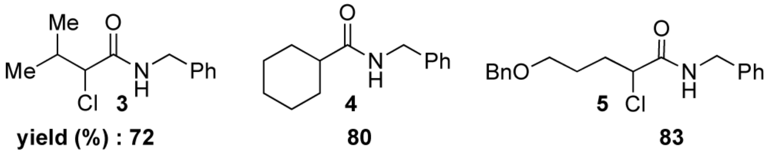
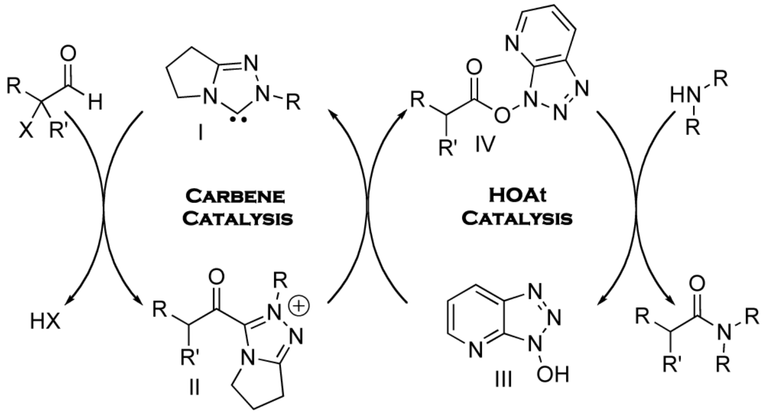


Figure 1.
α-Haloaldehyde substrate scope.

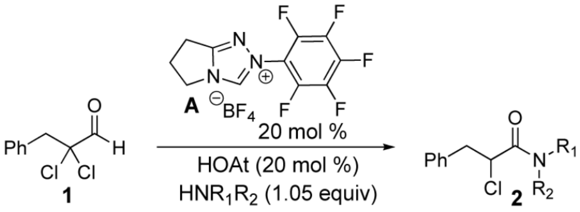
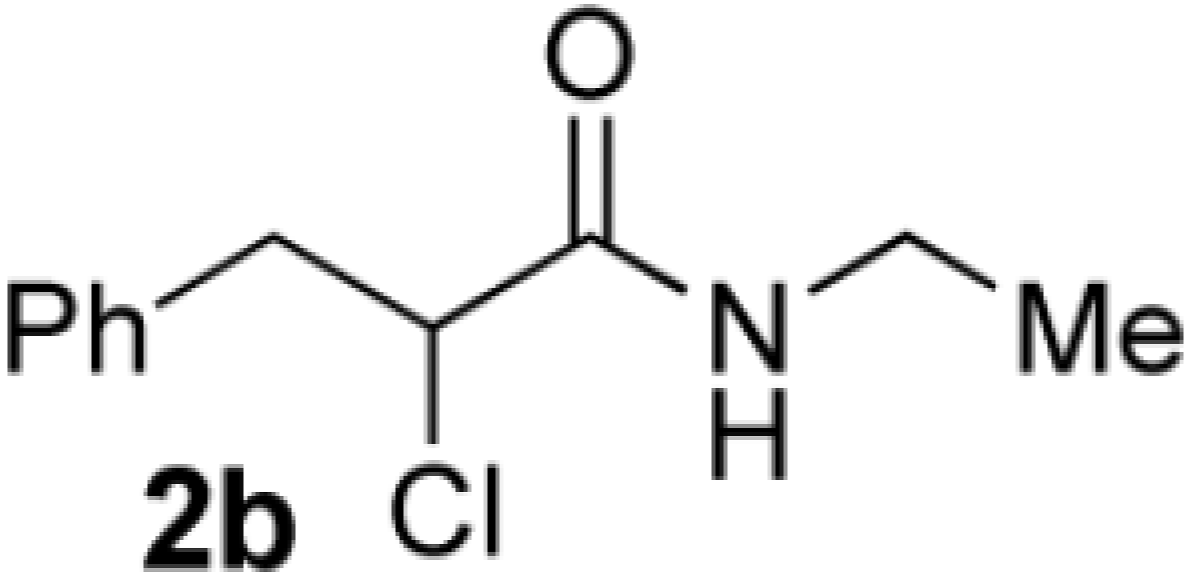
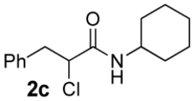


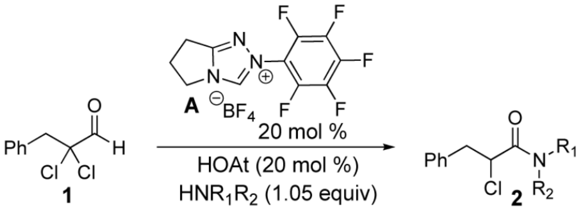
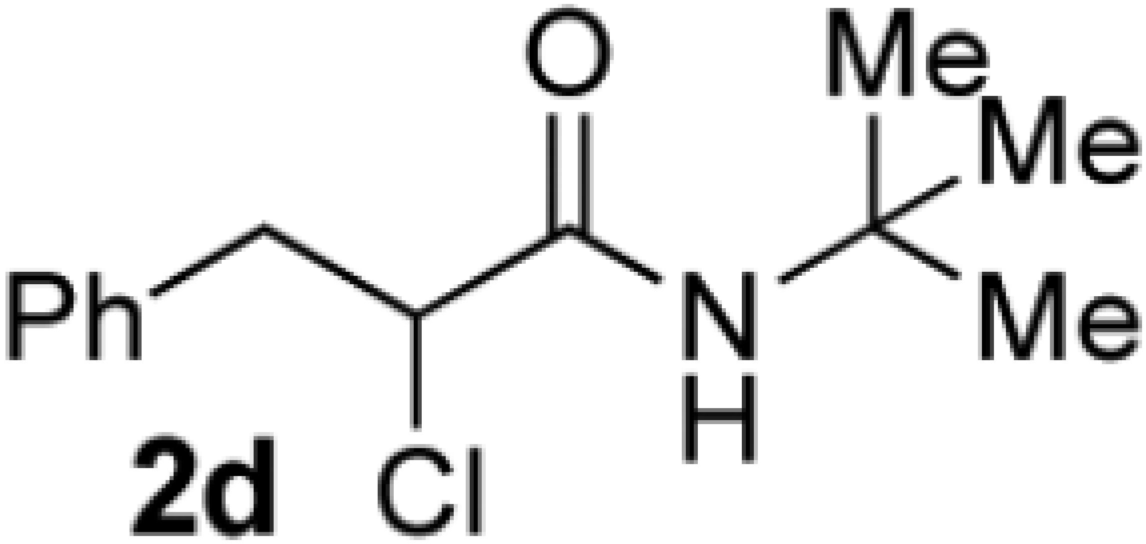
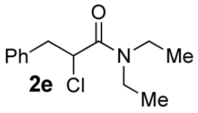
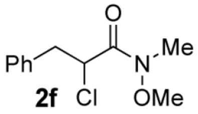
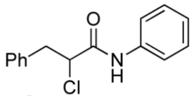
Scheme 1.

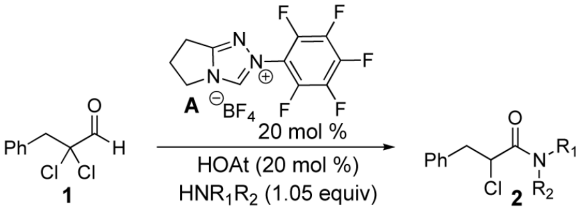
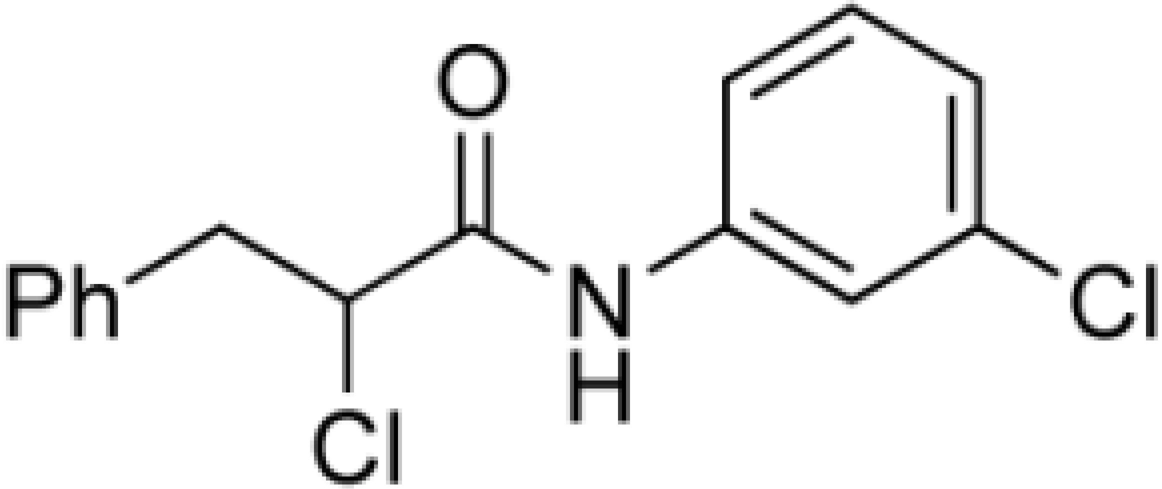
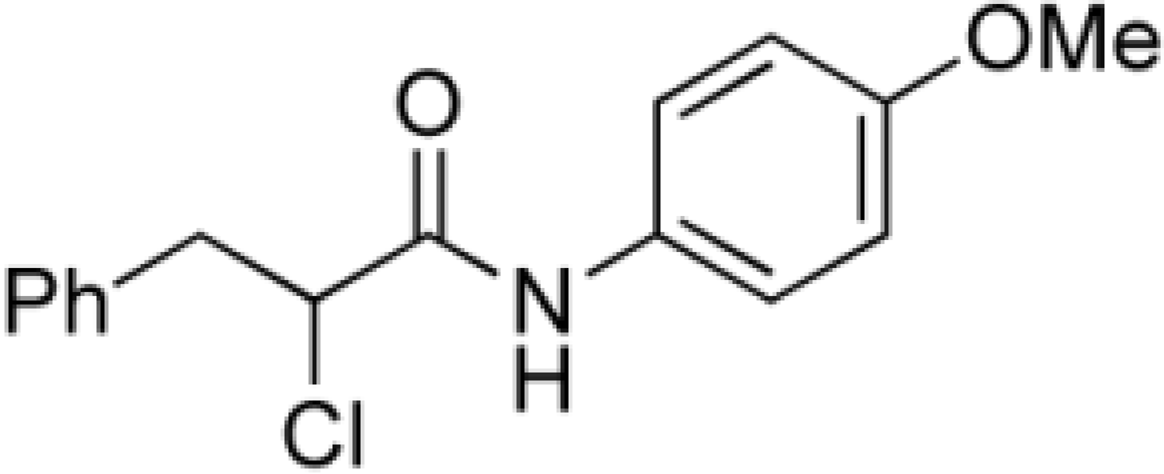
Proposed catalytic cycle.

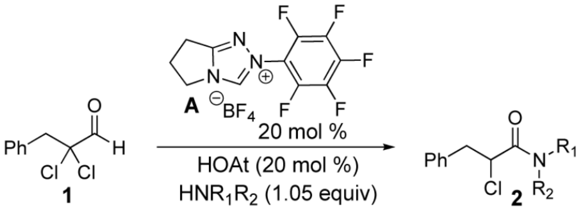
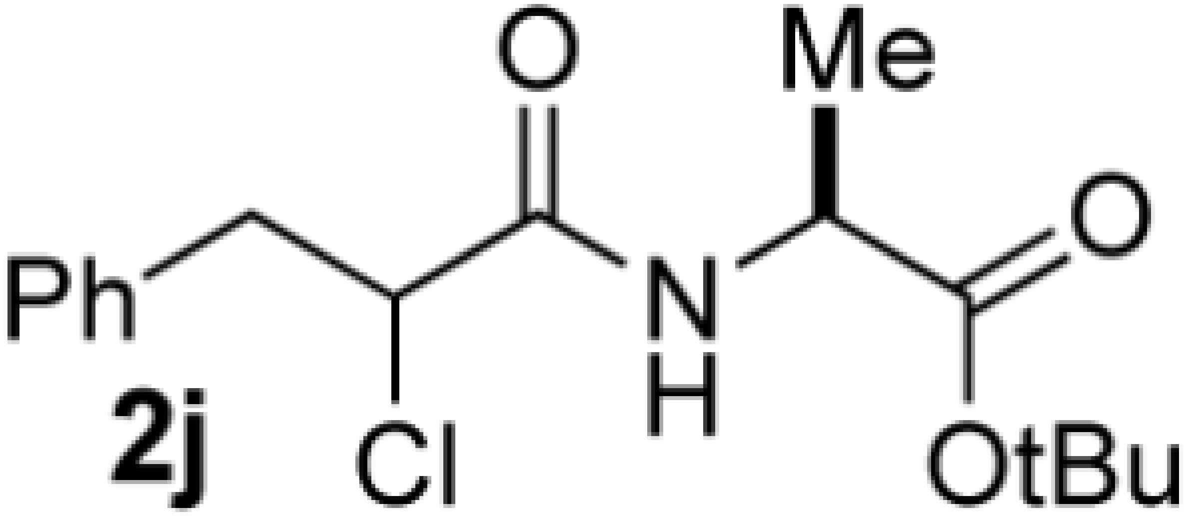
Table 1

Amine Scope

Entry[a]		Yie
1	 **2b**	
2	 **2c**	

Entry[a]		Yie
3	 **2d**	
4	 **2e**	
5	 **2f**	
6	 **2g**	

Entry[a]		**Yie**
7	 **2h**	
8	 **2i**	

Entry[a]		**Yie**
9	2j	8

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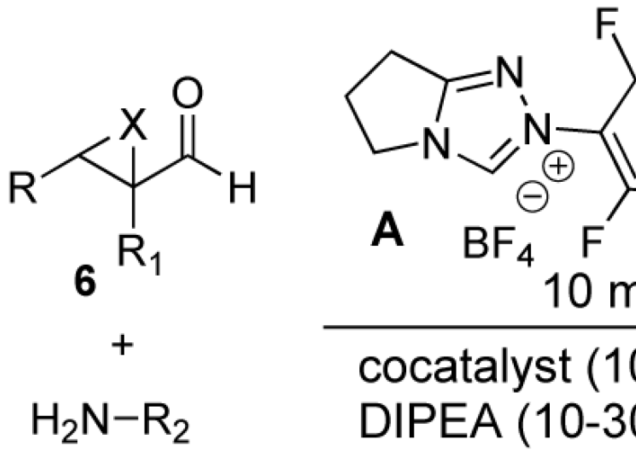
[a] Catalyst **A** (20 mol %), HOAt (20 mol%), Et_3N (1.2 eq), THF (0.5 M), t-BuOH (1.0 eq), 25 °C, 6 h, unless otherwise noted.

[b] HOBt (20 mol%) and Et_3N (2.1 eq) were used.

[c] 2:1 dr.

Table 2

Atom-economical amidation



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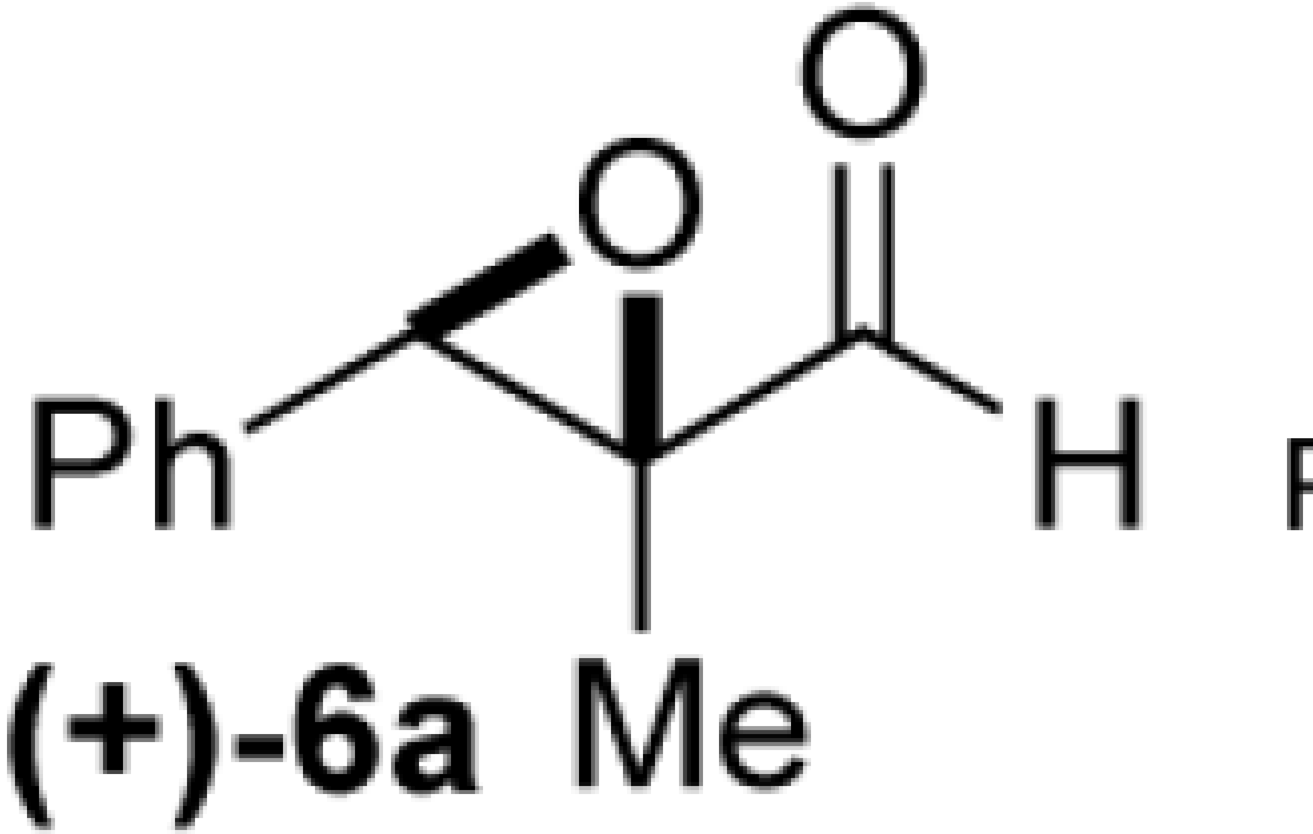
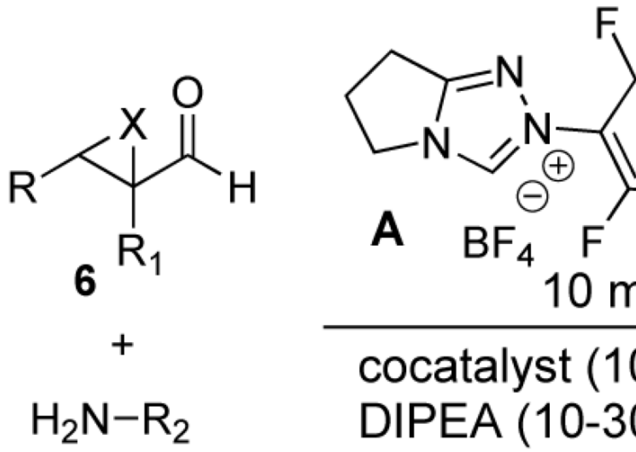
1	 (+)-6a



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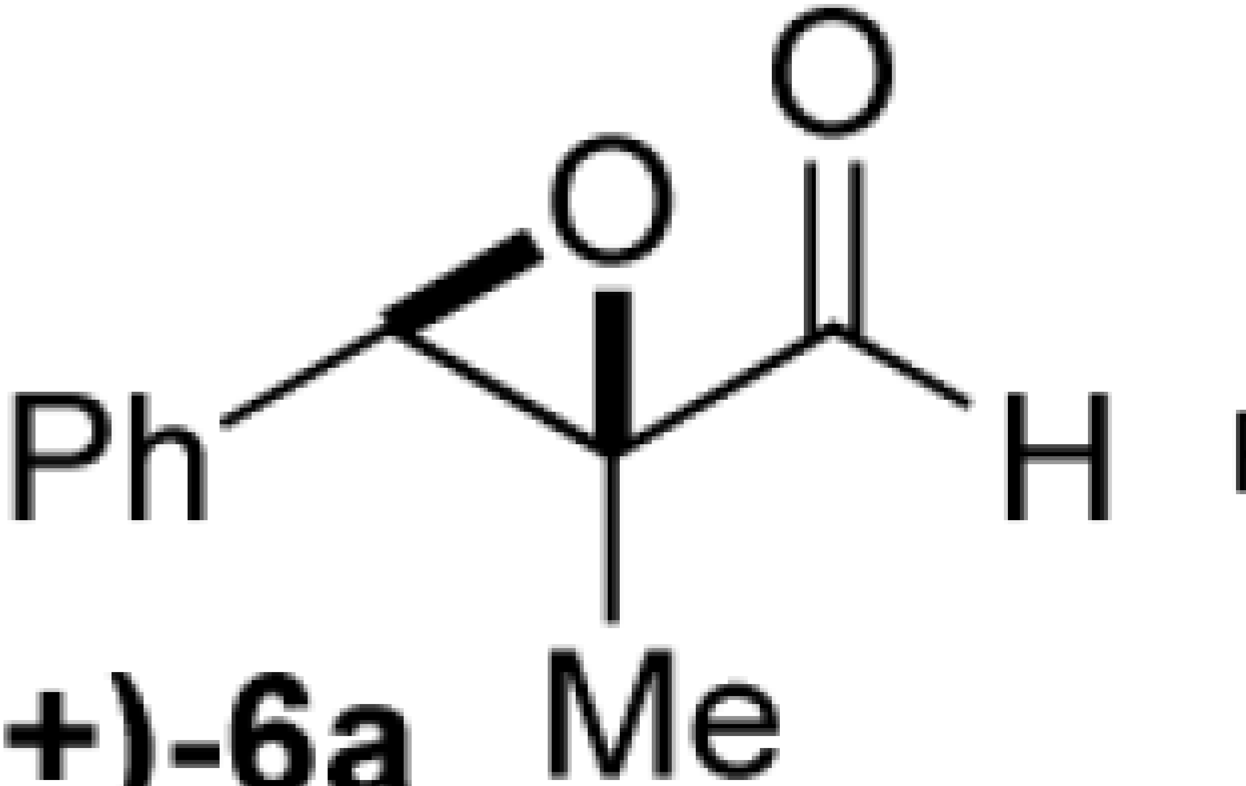
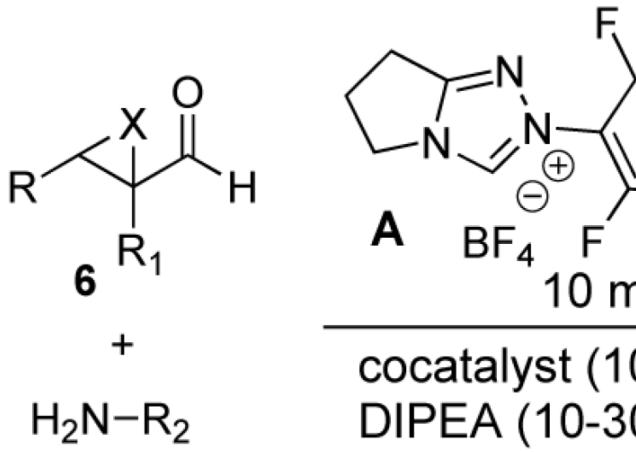
2	 (+)-6a



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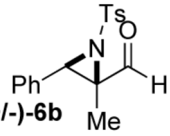
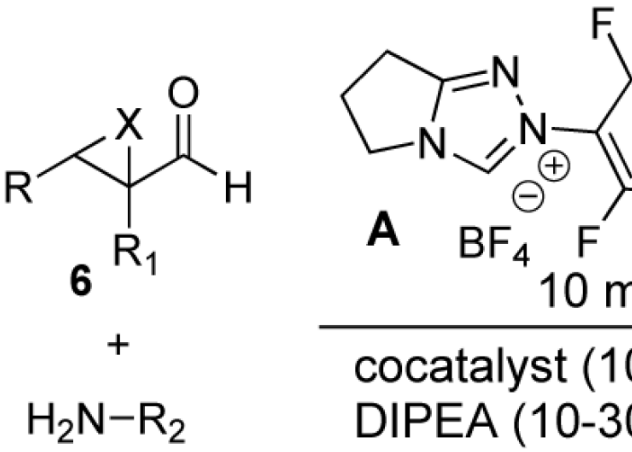
3	 (+/-)-6b



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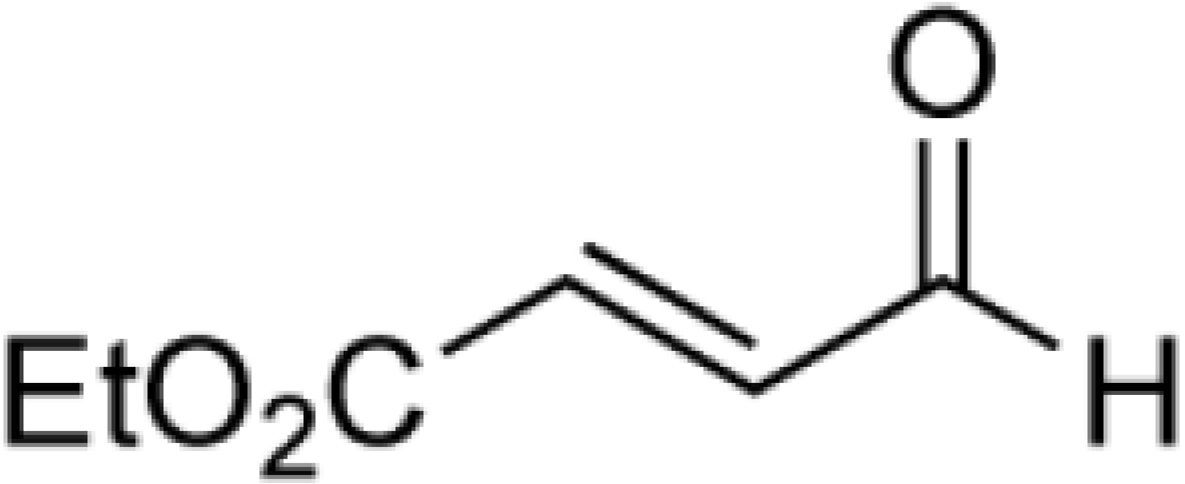
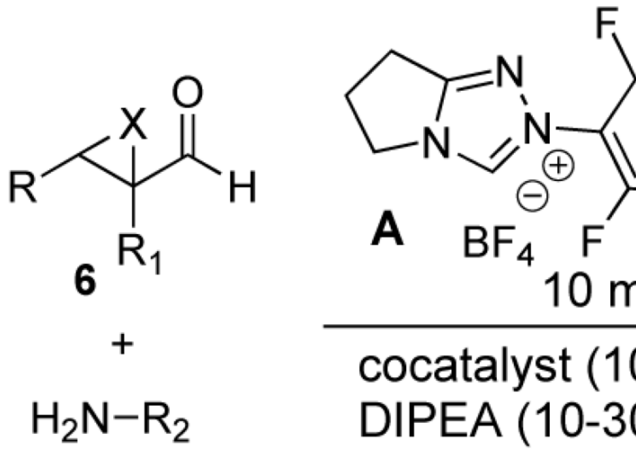
4	 **6c**



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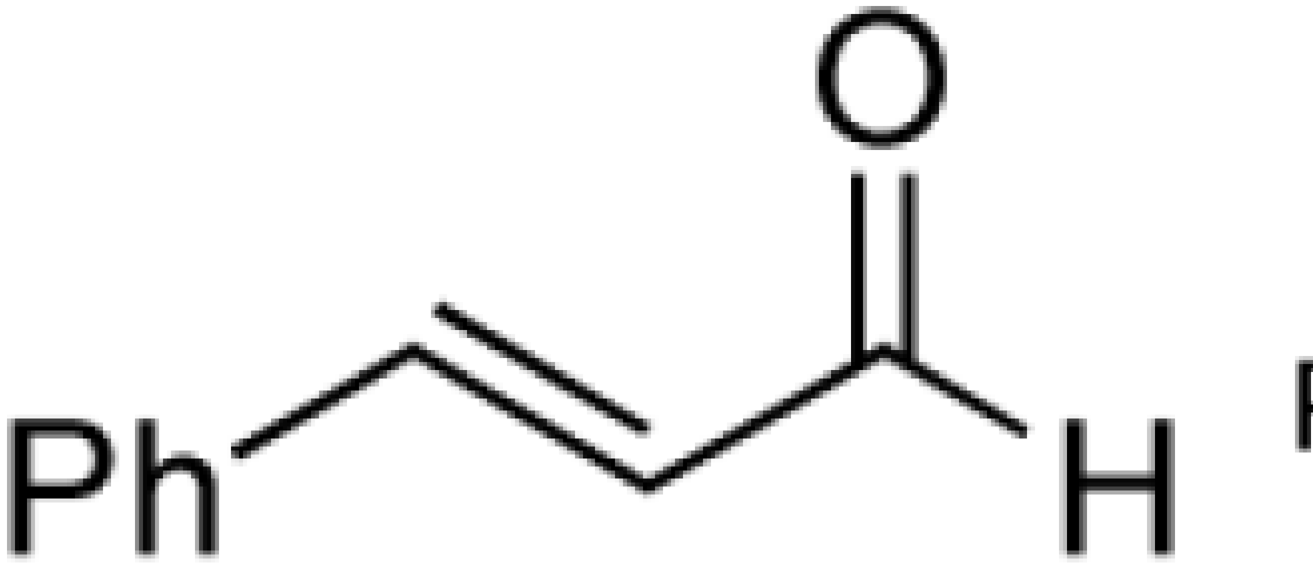
5	 6d

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[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.