Catalytic Redox Amidations of Aldehydes with a Polymer-Supported Peptide–N-Heterocyclic Carbene Multifunctional Catalyst

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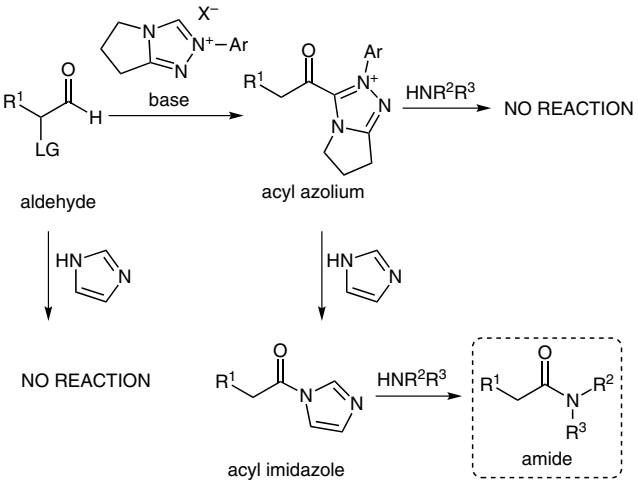
Abstract: We have prepared an oligomeric histidine-bound N-heterocyclic carbene precursor by coupling a carboxylic acid functionalized 1,2,4-triazolium salt to a peptide using solid-phase peptide synthesis. We have demonstrated that the resulting multifunctional resin-bound catalyst cooperatively facilitates redox amidation reactions of aldehydes and amines, a reaction not catalyzed by N-heterocyclic carbenes alone.

Key words: N-heterocyclic carbenes, catalysis, immobilization, amides, solid-phase synthesis

Due to the ubiquity of the amide linkage in peptides, polymers, and drugs,[1] amide-bond-forming reactions are among the most executed and important transformations in organic chemistry.[2] The conventional method of condensing an amine and carboxylic acid to form an amide requires the addition of a stoichiometric amount of a coupling reagent, rendering it uneconomical and wasteful.[3] Our group and others have therefore sought to develop catalytic alternatives.[4]

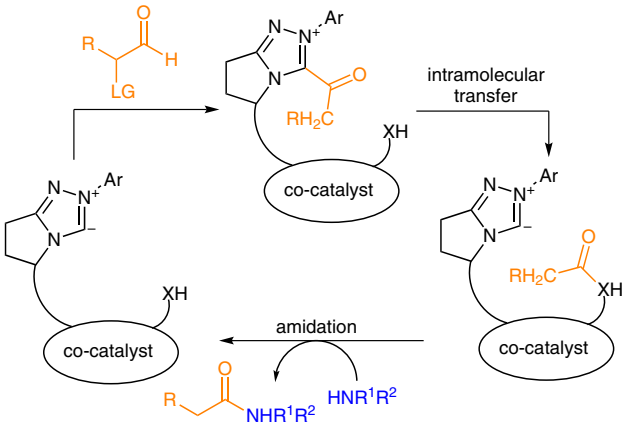
N-Heterocyclic carbene (NHC) catalysts have the potential to make a significant contribution,[5] as they can catalytically generate transient activated carboxylates from α-functionalized aldehydes such as α-haloaldehydes,[6] formyl cyclopropanes,[7] epoxyaldehydes,[8] aziridinyl aldehydes,[9] α,β-unsaturated aldehydes,[10] or their surrogates, α-hydroxyenones.[11] Although the catalytically generated acyl azoliums critical to these reactions react smoothly and in high yield with nucleophilic species, such as alcohols to form esters, the synthesis of amides from similar reactions with amines is often unsuccessful.[12] The reason is threefold; first, amines do not react with the acyl azoliums to form amides directly and a cocatalyst is needed. Second, amines have a propensity to condense with aldehydes and form imines or enamines. Third, the water released upon imine formation destroys the acyl azolium intermediate, which is extremely prone to hydrolysis.

To circumvent these shortcomings, our group and others have discovered that a number of additives such as imidazole,[9,13] triazole,[11a] hydroxamic acids,[14] 1-hydroxy-7-azabenzotriazole (HOAt),[9,15] 1-hydroxybenzotriazole (HOBt),[9] and pentafluorophenol (PFPOH)[9] can promote the reaction (Scheme 1). Such additives act as cocatalysts, first undergoing a reaction with the NHC-generated acyl azoliums to form a traditional activated carboxylate that readily couples with amines to form amides.



Scheme 1 NHC-catalyzed redox amidation of aldehydes and amines cocatalyzed by imidazole

The redox amidations fall under the category of cascade catalysis, in which two catalysts work cooperatively to activate one reactant in a sequential manner.[16] The development of new organocatalytic methods has been an area of intense research in recent years, and the chemical literature abounds with examples of other multicatalytic mechanisms that allow access to otherwise difficult or unattainable transformations. These include synergistic



Scheme 2 Design concept for multifunctional NHC

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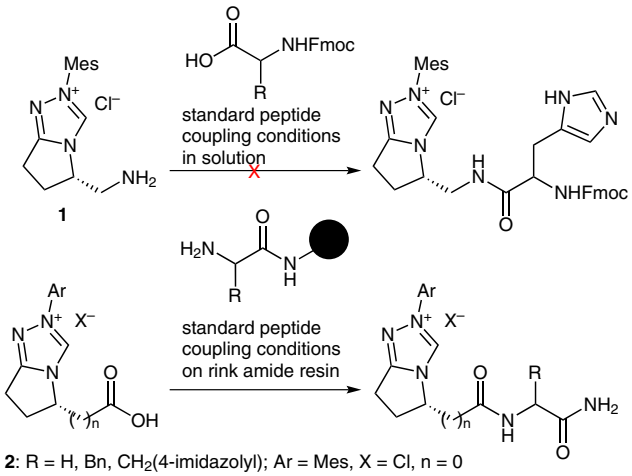
catalysis,[17] double activation catalysis[18] and bifunctional catalysis.[19] Enzymes, by far the most sophisticated examples of multicatalytic systems, do not fall under any single category, but often execute specific transformations through the cooperation of several catalytic moieties within an active site.[20]

We set out to design a catalyst capable of using discrete functional groups on a single molecule to facilitate a redox amidation reaction between aldehydes and amines. The ideal structure we envisioned would consist of an azolium salt NHC precursor covalently bound to a cocatalyst (Scheme 2). The biggest hurdle in identifying an active catalyst is the need for an intramolecular transfer of the acyl group between the catalytically generated acyl azolium and the pendant cocatalyst. Furthermore, preparing such multifunctional NHC requires a difficult synthesis and purification of azolium salt precursors that can be readily appended to the cocatalysts.[21]

The few routes for the synthesis of the bicyclic 1,2,4-triazolium salts, which are the most general NHC precursors, require numerous steps and are based on a limited number of scaffolds. Any functionality is typically introduced early in the synthesis because the harsh conditions required for the cyclization of the azolium ring preclude many functional groups.[22] Attempting to modify the catalysts even slightly usually invokes the need to reoptimize the entire synthesis, making the preparation and screening of diverse libraries of NHC a tedious process.

In our synthetic planning, we turned to the amino acid histidine as a means of introducing the cocatalytic functionality to NHC, due to the presence of an imidazole moiety on the side chain. We envisioned the synthesis of a triazolium salt functionalized with an exploitable functional handle and therefore capable of being coupled to histidine containing peptides.

Starting from the readily available (*S*)-pyroglutamic acid, we prepared triazolium salts **1** and **2**, equipped with an amine and a carboxylic acid (Scheme 3).[22a] We first attempted to couple **1** and various N-protected amino acids but were hampered by the fact that it is insoluble in most organic solvents, challenging to purify and couples only reluctantly to amino acids in solution. In contrast, carboxylic acid functionalized triazolium salt **2** was successfully coupled to various amino acids including histidine using standard conditions for solid-phase peptide synthesis.[23] However, the resulting catalyst did not facilitate a redox amidation in the absence of an external cocatalyst, probably due to suboptimal distance between the acyl azolium and the histidine imidazole. Furthermore, the chiral center positioned α to the carbonyl of the catalyst was prone to epimerization, and the use of **2** was therefore abandoned. To overcome these problems, we prepared carboxylic acid functionalized triazolium salts **3** and **4**, with unfunctionalized chiral centers that should not be prone to epimerization. The synthesis began with the homologation of (*S*)-pyroglutamic acid. A one-carbon homologation by a known procedure was successful, but overly long and low-yielding.[24] A more reliable procedure by a two carbon extension through the condensation and reduction of Meldrum's acid adducts was adopted and gave carboxylic acid **7** (Scheme 4).



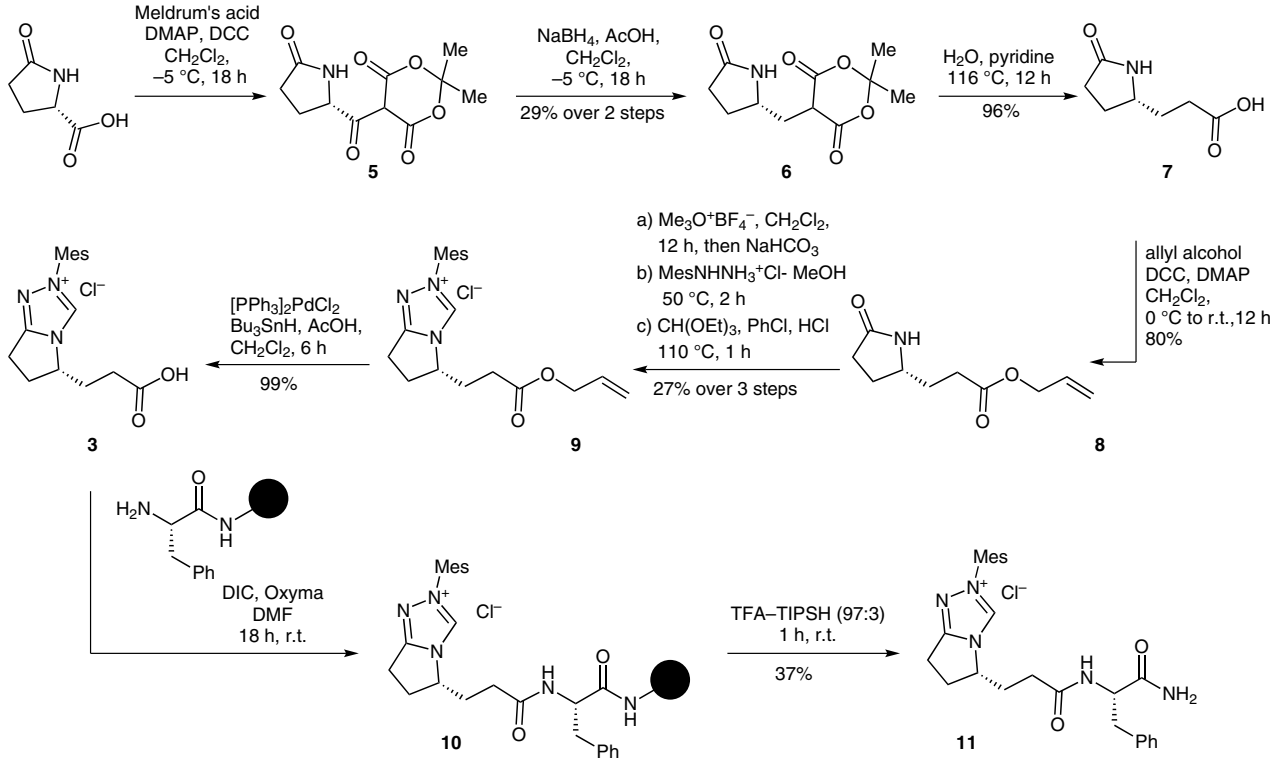
2: R = H, Bn, CH_2(4-imidazolyl); Ar = Mes, X = Cl, n = 0
3: R = Bn, CH_2(4-imidazolyl); Ar = Mes, X = Cl, n = 2
4: R = Bn, CH_2(4-imidazolyl); Ar = C_6F_5, X = BF_4, n = 2

Scheme 3 Functionalized triazolium salts prepared from pyroglutamic acid

Carboxylic acid **7** was protected with an allyl group and converted into the *N*-mesityl-substituted triazolium salt **9** using a protocol developed in our group[25] and based on protocols from Rovis[26] and Knight and Leeper (Scheme 4).[27] After the allyl deprotection, **3** was obtained as a white crystalline solid, which was used without further purification. The *N*-pentafluorophenyl-substituted triazolium salt **4** was also synthesized from **7** using a similar reaction protocol, although this catalyst was more prone to decomposition during purification.

We performed an extensive screen of conditions for coupling **3** and **4** to amino acids, both in solution and on Rink amide resin, using L-phenylalanine as the test amine. Although traces of the coupled products were observed using standard peptide coupling reagents such as HBTU and HOBT, extensive decomposition occurred under these conditions. Considering that the decomposition was much more pronounced with the more acidic perfluorinated **4**, it was hypothesized that stoichiometric DIPEA used in the coupling was deprotonating the triazolium salt and leading to undesired side reactions. When base-free conditions such as diisopropyl carbodiimide (DIC) and the additive ethyl 2-cyano-2-(hydroxyimino)acetate (Oxyma) were used, the coupling proceeded with improved efficiency and reliability. L-Phenylalanine-bound **3** was cleaved from the solid support with trifluoroacetic acid and purified by HPLC to give the clean product **11** in isolated yield of 37% (Scheme 4).

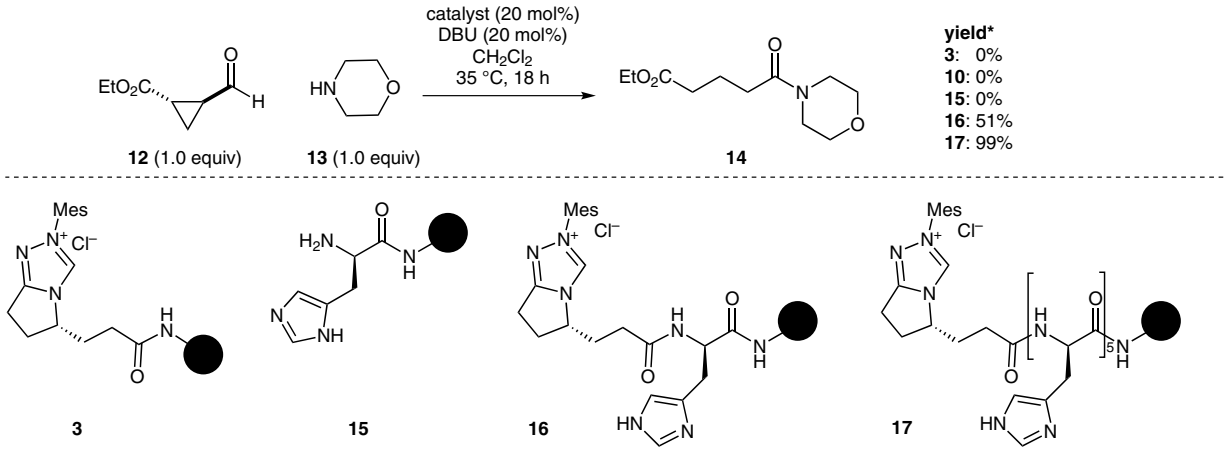
As an initial test of the catalytic activity of such peptide-bound NHC precursors, we performed a redox amidation reaction between ethyl 2-formylcyclopropanecarboxylate (**12**) and morpholine (**13**), to form ethyl 5-morpholino-5-



Scheme 4 Synthesis of chiral carboxylic acid functionalized triazolium salt **3** and coupling to phenylalanine on solid phase

oxopentanoate (**14**, Scheme 5). Using imidazole as a co-catalyst, the reaction proceeded well. In the absence of imidazole, no reaction was observed. Motivated by the advantages of using resin-bound catalysts, such as their recyclability and ease of handling,[28] we tested the activity of **10**, the solid-supported precatalyst on TentaGel resin. We were pleased to find that **10** was also an active catalyst and obviates the tedious and low-yielding purification procedure. The synthesis and screening of diverse peptide-bound catalysts is greatly accelerated when the post-synthetic cleavage from resin and chromatographic purification is avoided. Unlike the soluble NHC, the resin-bound catalyst can be used twice with no loss of activity and multiple times at a higher loading. Having found appropriate synthetic conditions, we prepared **16** by coupling the carboxylic acid functionalized triazolium salt to **15**, a single resin-bound histidine (Scheme 5). Our standard test reaction between **12** and **13** revealed that the resulting histidine-bound NHC facilitates the redox amidation reaction in 51% conversion, in the absence of an external cocatalyst. In contrast, we determined that neither the solid-supported triazolium salt without histidine **3**, nor the solid-supported histidine without the triazolium salt **15** were able to facilitate the redox amidation reaction alone.

Hypothesizing that more molecules of histidine would facilitate the reaction more efficiently, we prepared **17**, a triazolium salt bound oligomeric pentapeptide containing five units of histidine. We were pleased to find that this



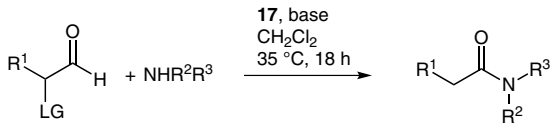
Scheme 5 Screening of peptide-bound NHC precursors for redox amidation reaction. (Resin = TentaGel 0.29 mmol/g). * Calculated by ^1H NMR.

solid-supported catalyst drives the test reaction to complete conversion.

The catalyst and reaction conditions were subsequently optimized (not shown). Various bases and solvents were tested for the reaction, with the combination of DBU and CH_2Cl_2 remaining optimal for the test reaction. Polystyrene and TentaGel resins of loadings ranging from 0.09 mmol/g to 2.2 mmol/g were screened with the best loading found to be 0.2–0.3 mmol/g. When polystyrene resin was utilized, we studied the effects of placing 0 to 5 linkers of 6-aminohexanoic acid between the peptide and the solid support, with the effect of several linkers being similar to that of decreasing the loading. Although polystyrene resin is more chemically stable, TentaGel is a more hydrophilic support that swells in a wider range of polar solvents.[29] We also deemed it appropriate for our chemistry because the tethered catalysts project into the solution in a manner that allows the conditions to more closely resemble solution-phase chemistry. Ultimately, TentaGel resin of 0.29 mmol/g loading was the most general and optimal solid support. For reactions that went to complete conversion in the catalytic screening, the clean amidation products were obtained simply by filtration from the resin-bound catalyst and washing with aqueous NH_4Cl to remove DBU.

A survey of aldehyde and amine substrates was conducted to demonstrate the generality of the new catalytic system (Table 1). Reactions between **12** and various primary and secondary amines were conducted with amides being obtained in moderate to excellent yields. Other aldehyde partners such as α,β-unsaturated aldehydes and α-chloro aldehydes were employed, as were simple unsubstituted aldehydes, where an external oxidant is utilized.[30] These reactions also give amides in moderate to excellent yields.

Table 1 Catalytic Redox Amidations and Oxidative Amidations of Amines and Aldehydes



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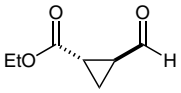
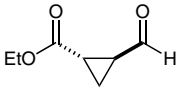
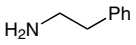
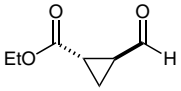
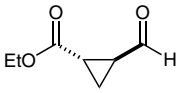
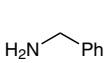
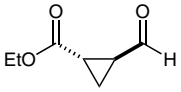
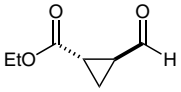
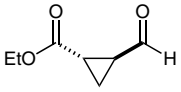
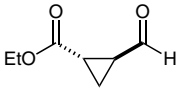
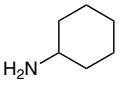
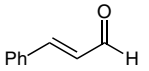
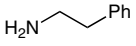
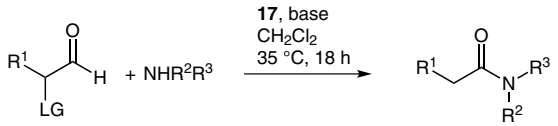
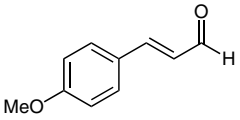
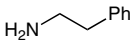
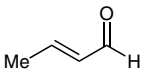
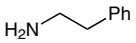
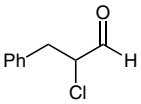
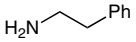
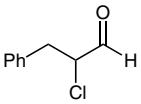
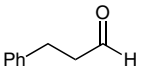
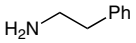
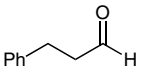
1			99
2			87
3			89
4			82
5			61
6			76
7			93
8			78
9			99

Table 1 Catalytic Redox Amidations and Oxidative Amidations of Amines and Aldehydes (continued)



Entry	Aldehyde	Amine	Yield (%)[a,d]
10			61
11			66
12			87[b]
13			75[b]
14			77[c]
15			85[c]

[a] Conditions: aldehyde (1.0 equiv), **17** (0.2 equiv), DBU (0.2 equiv; or 1.2 equiv DBU when **17** is recycled). Shake at 35 °C for 30 min prior to addition of amine (1.0 equiv). Shake at 35 °C for 18 h.
[b] Using 1.2 equiv of DIPEA instead of DBU.
[c] With the addition of 1.0 equiv of quinone oxidant 3,3′,5,5′-tetra-*tert*-butyl-[1,1′-bi(cyclohexylidene)]-2,2′,5,5′-tetraene-4,4′-dione.
[d] Isolated yield after chromatographic purification.

In conclusion, we have developed an efficient approach for the synthesis of immobilized, recyclable, multifunctional NHC precatalysts by coupling carboxylic acid functionalized triazolium salts to peptides using solid-phase synthesis. We have used this method to develop a competent catalyst for redox amidation reactions: an oligomeric histidine-bound 1,2,4-triazolium salt.

This work represents one of very few examples of immobilized organocatalytic triazolium salt derived N-heterocyclic carbenes.[31] To the best of our knowledge, it is the first example of a redox amidation using a solid-supported or a multifunctional N-heterocyclic carbene. Our current and future efforts will be focused on the further development of multifunctional N-heterocyclic carbenes, particularly for enantioselective redox amidations for the kinetic resolution of amines or peptide synthesis.

Representative Procedure for Redox Amidation Reaction: Ethyl 5-Morpholino-5-oxopentanoate (Table 1, Entry 1)
A 10 mL fritted syringe was charged with **17** (250 mg, 0.073 mmol, 0.20 equiv), ethyl 2-formylcyclopropanecarboxylate (52.5 mg, 0.363 mmol, 1.00 equiv), DBU (11.0 mg, 0.073 mmol, 0.20 equiv), and CH_2Cl_2 (3.6 mL). The solution was transferred to a shaker at 35 °C for 30 min. Morpholine (31.6 mg, 0.363 mmol, 1.00 equiv) was added to the reaction mixture. The reaction was shaken at 35 °C overnight, upon which the reaction vessel was allowed to cool to r.t. The solution was filtered from the resin and purified further using column chromatography [gradient; CH_2Cl_2 to MeOH–CH_2Cl_2 (1:10)] to yield the clean product (85 mg, 99%). IR: ν = 3297.7, 2977.6, 2934.2, 1732.7, 1646.0, 1546.6, 1196.6, 1153.2 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.12 (q, *J* = 7.1 Hz, 2 H), 3.69–3.63 (m, 4 H), 3.63–3.57 (m, 2 H), 3.50–3.42 (m, 2 H), 2.38 (dt, *J* = 7.6, 6.1 Hz, 4 H), 2.00–1.89 (m, 2 H), 1.25 (t, *J* = 7.1 Hz, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.3, 1709, 66.9, 66.7, 60.3, 45.9, 41.9, 33.4, 32.0, 20.4, 14.2. HRMS: *m/z* calcd for $C_{11}H_{20}NO_4^+$ $[M + H]^+$: 230.1392; found: 230.1387.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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