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Direct NHC-Catalysed Redox Amidation Using CO₂ for Traceless Masking of Amine Nucleophiles

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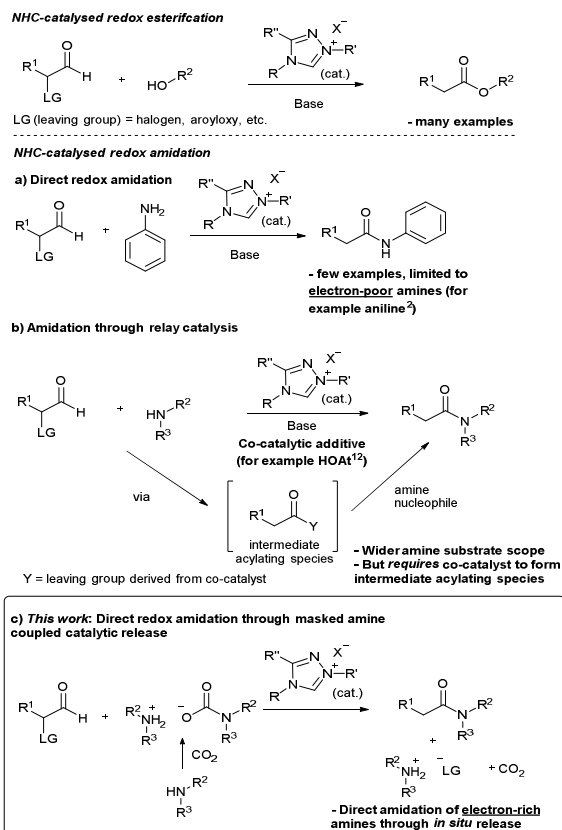
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The N-heterocyclic carbene (NHC)-catalysed redox amidation reaction is poorly developed and usually requires catalytic co-additives for electron-rich amine nucleophiles. We report a masking strategy (using CO₂) that couples release of the free amine nucleophile to catalytic turnover, and in doing so, enables direct catalytic redox amidation of electron-rich amines.

The NHC-catalysed intramolecular-redox formation of acyl azolium intermediates from α -functionalised aldehydes is a powerful method for the catalytic formation of acylating agents as exemplified by numerous examples in the last decade (Scheme 1).^{1–6} The use of oxygen nucleophiles together with such acyl azoliums to give ester products, has been thoroughly investigated.^{2,3,7–11} The corresponding amidation reactions, directly employing amine nucleophiles, have proven to be less accessible.^{6,12,13} There are a few prevalent explanations for this divergent reactivity in the literature, with some suggesting an intrinsic lack of reactivity between acyl azolium species—the key catalytic acylating agents—with amine nucleophiles.^{14–16} However, there are several examples of catalytically generated acyl azolium species acylating electron-poor nitrogen nucleophiles (Scheme 1), including nitrogen-containing heterocycles,^{12,13,15,17} anilines,² and amides and sulfonamides.^{18–21} Likewise, the direct reaction of an acyl azolium with an amine nucleophile has been shown stoichiometrically on separate occasions by Miyashita and Studer; both groups also observed that, whilst alcohol nucleophiles required activation by base or raised temperatures, amines are acylated at room temperature—quantitatively in the example presented by Studer.^{22,23} Therefore while acyl azoliums are clearly capable of acylating nitrogen nucleophiles, it would seem there are significant limitations with direct NHC-catalysed amidation substrate scope and catalytic turnover/side-reactions; especially when

using electron-rich amines. The most plausible reason for such issues is an inherent incompatibility between the amine nucleophile and the aldehyde substrate, due to their propensity for imine formation.^{12,13,15} The effect of this side reactivity is two-fold: 1) imines are typically inactive electrophiles for the NHC catalyst; 2) the water produced in the condensation reaction can act as a competing nucleophile

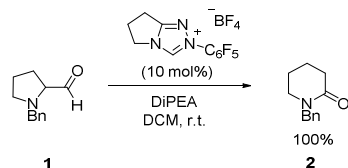


Scheme 1: Prior studies and an overview of the reported work.

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in the redox acylation resulting in the formation of carboxylic acid by-products. It is perhaps telling that Owen and coworkers reported stoichiometric acyl azolium salts to “not react with primary amines *unless water is absent*”.²⁴ Current approaches to overcome such issues rely on the use of co-catalytic additives and/or non-aldehyde substrates (e.g. α' -hydroxyenones as α,β -unsaturated aldehyde surrogates), as well as slow addition of the amine nucleophile.^{4,12–14,17,25,26}

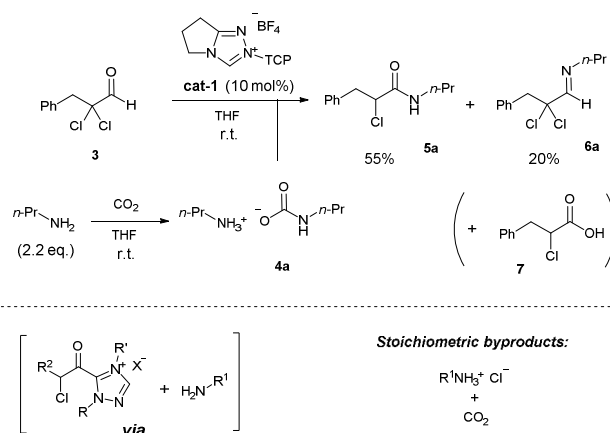


Scheme 2: Gravel's NHC catalyzed redox lactamisation.²⁷

It seemed therefore that there was an opportunity to develop a complementary, more direct approach for catalytic redox amidation using NHCs. The NHC-catalysed rearrangement of pyrrolidine **1** to lactam **2**, depicted in Scheme 2, caught our attention.²⁷ Conceptually this reaction achieves catalytic amidation through the separation of the amine and aldehyde components by a chemical rather than physical means: the amine nucleophile is released as part of the catalytic cycle and consumed before the catalyst turns over. This coupling of amine release to turnover likely simulates slow addition of the amine and limits the concentration of amine that is present in the reaction at any given time. We sought to develop a conceptually similar approach—where amine release is achieved by chemical means—but was not limited to the formation of cyclic (lactam) products. Treatment of amines with CO₂ reversibly produces ammonium carbamate salts comprising an ammonium cation and a carbamate anion (e.g. **4a** in Scheme 3).²⁸ Notably, both the ammonium cation and the carbamate anion would have reduced nucleophilicity towards aldehydes and therefore CO₂ treatment may represent a suitable masking strategy for amines in redox amidation chemistry. Although relatively stable as ammonium carbamate salt pairs, protonation of the carbamate anion results in decarboxylation, to return the amine. We hypothesised that if this protonation event was coupled to deprotonation of the triazolium pre-catalyst (to give the free NHC catalyst), it would be possible to ensure amine release into the reaction mixture is limited and paired to catalytic turnover.

A test reaction was performed using the known redox acylation substrate α,α -dichlorohydrocinnamaldehyde (**3**) together with *n*-propylammonium *N*-*n*-propylcarbamate (**4a**) (as masked propylamine) (Scheme 3). Since the ammonium carbamate reagent formally comprises two equivalents of amine, no further base should be required: one equivalent of the amine should be acylated, while the other acts as a base in the reaction, giving the amine hydrochloride by-product (Scheme 3). Given the likely weakly basic nature of the

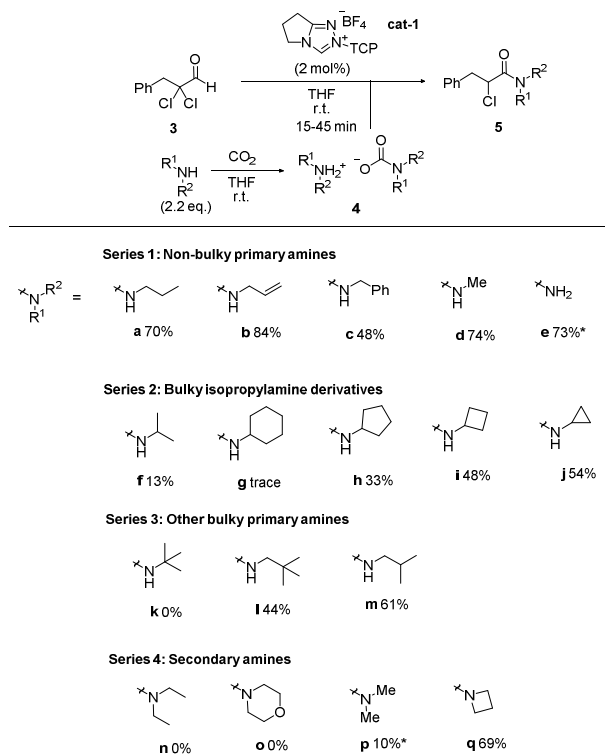
carbamate anion (which is proposed to function as the initiating base), we selected triazolium **cat-1** as the precatalyst,²⁹ where the electron poor aromatic substituent acidifies the C–2 proton.^{30–32} Pleasingly, **cat-1** at 10 mol% loading gave the amide **5a** as the major product (55%), with only 20% competing imine **6a** formation along with an equivalent amount (~20%) of carboxylic acid **7** by-product. The reaction proceeded unexpectedly rapidly, with complete reaction in under 20 minutes - many similar reactions are reported to require reaction times of several hours^{12,13,15,17}. Given the short reaction time, it was envisaged that the catalyst loading could be decreased, particularly in order to further reduce the concentration of free amine released into solution at any given time, and thus further suppress imine formation. A loading of 2 mol% pre-catalyst resulted in an isolated yield of 70% for the desired amide product **5a**.



Scheme 3: Initial test reaction for NHC-catalysed amidation. TCP = 2,4,6-trichlorophenyl

Following the success of using an electron-rich propylamine substrate, the preliminary scope of this methodology was investigated (Scheme 4). It was found that reactions with primary carbonylamines (i.e. H₂NCH₂R, Series 1) generally afforded products **5a–5d** in excellent yield, between 70 and 84% (Scheme 5, top row).³³ As an exception, the use of benzyl amine resulted in the isolation of amide **5c** in moderate yield (48%); something we attribute to increased steric bulk of this substrate (vide infra). Notably, the use of ammonium carbamate (H₂NCOONH₄), a commercially available bench stable solid, was also possible, giving the primary amide **5e** product in an excellent yield (73%). To the best of our knowledge, this is the first example of a primary amide generated using an NHC-catalysed redox amidation protocol. The use of more sterically hindered primary amines such as *iso*-propylamine and derivatives (Series 2, Scheme 4) led to a large decrease in yield presumably for steric reasons; an example being *N*-*iso*-propyl amide **5f** (13%). The steric sensitivity of this reaction is attributed to the reasonably bulky nature of the α,α -dichlorohydrocinnamaldehyde substrate (vide infra). Cyclic amines (*c*-Hex, *c*-Pent, *c*-Bu, *c*-Pr, Series 2) also showed a strong trend towards decreasing yield upon

increasing steric bulk (% yield **5j**>**5i**>**5h**>**5g**). Likewise, the use of even more bulky amines (Series 3), such as *t*-BuNH₂, in an attempt to form **5k**, resulted solely in imine/carboxylic acid byproduct formation. If, however, the steric bulk was moved further from the nucleophilic nitrogen atom (Series 3) the corresponding yields dramatically increased, such as for **5m** and **5l**. Secondary amines generally gave a poor yield, for example dimethylamine **5p** (10%); however again, reduction in steric bulk dramatically improved the yield, such as for azetidine **5q** (69% yield). Electron-poor amines, such as aniline and trifluoroethylamine, were unreactive under the developed conditions. We believe these amines are incapable of forming suitably stable ammonium carbamate adducts.³⁴ We note however, that as opposed to electron-rich amines, such as electron-poor amines (e.g. aniline) are suitable for direct amidation using alternative NHC-catalysed methodologies,² and therefore believe our methodology is complementary to those already available.

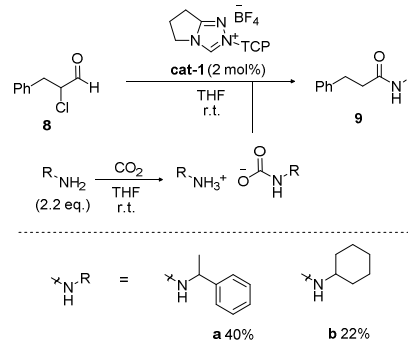


Scheme 4: Substrate scope for direct NHC-catalysed amidation. *Substrate commercially available as pre-formed ammonium carbamate species (1.1 eq. used).

Whilst it would seem that our masking strategy allows for the direct NHC-catalysed amidation using a range of amino (pro)nucleophiles, clearly steric bulk of the amine limits productive reactivity. The main by-product observed in all cases utilising bulky amines was the α -reduced carboxylic acid **7**, which we attribute, not to reaction of advantageous water with the acyl azolium, but instead from hindered amine nucleophiles being outcompeted by the carbamate anions that

are present in much greater concentration (see ESI for more detailed discussion). Ultimately, this would result in the formation of a carboxylic-carbamic mixed anhydride which would subsequently undergo hydrolytic decomposition to give the carboxylic acid and amine.

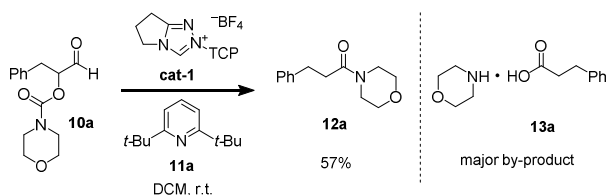
A less bulky α -monochloro hydrocinnamaldehyde substrate **8** was investigated to provide evidence that a reduction in substrate bulk would give a corresponding increased tolerance to amine bulk, and therefore increased (pro)nucleophile scope. Indeed, it was found that by reducing the steric crowding of the substrate, amine nucleophiles that were too hindered for the di-chlorinated substrate could now be acylated (Scheme 5). For example, while cyclohexylamine gave only trace amounts of product for dichloro substrate **3** (Scheme 4), reaction with monochloro substrate **8** gave a significantly improved yield of **9b** (22%). Furthermore, other bulky amines, such as 1-phenylethylamine were suitable nucleophiles using substrate **8**, giving a highly promising yield of **9a** (40%), given the bulky nature of this nucleophile.



Scheme 5. Examples of direct NHC-catalysed amidation using substrate **8**.

Given the success of the above chemistry for intermolecular redox amidation, and the steric limitations in substrate scope that are caused by the use of the α,α -dichloroaldehyde substrate, an alternative α -carbamate aldehyde substrate was considered (see Scheme 6). Conceptually, such carbamate substituents could act as the leaving group, giving rise to a less bulky acyl azolium and a carbamate anion, which could subsequently engage in the methodology developed above. Surprisingly, there are only a few examples in the literature of the related carbonates being used as leaving groups,³⁵⁻³⁸ and of these, only one utilises the displaced alcohol as a nucleophile.³⁸ To the best of our knowledge there are no examples of carbonates being used as leaving groups in related chemistry. A morpholine α -O-carbamoyl aldehyde substrate **10a** was therefore synthesised (see ESI) and tested, using a range of triazolium precatalysts, sub-stoichiometric bases and solvents (see ESI for details). Pleasingly, a preliminary isolated yield of 57% was obtained for the amidation product **12a** (Scheme 6). This result clearly shows that it is possible to mediate direct redox amidation through coupling of amine release to cleavage of an α -leaving group. Through masking of the amine nucleophile as a synthetically accessible carbamate with a concomitant reduction of steric bulk at

the acyl azolium, secondary amines become viable nucleophiles (57% yield of **12a** vs 0% yield of **5o** in Scheme 4).



Scheme 6: Intramolecular variant of direct redox amidation.

While NHC-catalysed redox esterification has been extensively optimised to encompass a wide substrate scope including chiral variants, the corresponding amidation reaction is dramatically underdeveloped. Herein we have developed an amine masking strategy that couples release of the free amine nucleophile to catalytic turnover, and in doing so, enables direct catalytic redox amidation. We predict that this approach should enable the large number of known chiral NHC precursors to now be successfully employed in the field of redox amidation; something that is not possible when employing a co-catalytic additive.³⁹ The success of our methodology stems from the fact that only a low concentration of amine is present at any one time, which in turn limits an important competing side reaction: imine formation. Previous efforts towards NHC-catalysed redox amidation (usually in the presence of co-catalysts) have been seen to employ slow or delayed addition of the amine substrate as a physical means of limiting imine formation. Not only is our approach operationally simpler, it likely also better balances amine presence in the reaction (via *in situ* generation vs slow addition) to formation of the key acyl azolium catalytic intermediate and therefore results in fast reactions. Although clear limitations are present in our methodology, particularly the (substrate and amine) steric sensitivity of the chemistry, we believe this proof of concept work provides an enhanced mechanistic understanding of direct NHC-catalysed redox amidation chemistry that should enable further development to a level comparable with that observed for redox esterification. Such efforts to expand substrate scope, based on the mechanistic understanding gained herein are ongoing and will be reported in due course.

Acknowledgements

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