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Highly chemoselective, sterically sensitive NHC-catalysed amine acylation with pyridil†

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A new strategy for the protection of amines has been developed involving reaction with pyridil under the influence of N-heterocyclic carbene catalysis. The methodology is capable of distinguishing between two amines characterised by small differences in steric bulk and the resulting pyridoyl amides can be cleaved without requiring either strongly acidic or basic hydrolysis.

The wide utility of amide bonds[1] continues to inspire chemists to develop new and unconventional methods for their synthesis.[2] We recently[3] developed an N-heterocyclic carbene (NHC)-catalysed oxidative amidation of aldehydes[4,5] which allows the coupling of benzaldehydes **1** with a range of primary and secondary amines **2** in the presence of precatalyst **3**, 1,2,4-triazole, stoichiometric DBU and phenazine (**4**) to produce amides **5** in good to excellent yields at ambient temperature. We could show that the reaction proceeded through symmetrical 1,2-diketones of general type **6** (Fig. 1A). In addition, in the absence of the 1,2,4-triazole nucleophilic co-catalyst, it was postulated that amidation occurred *via* the sterically hindered pre-transition state assembly **7**.

The steric congestion associated with **7**[6,7] (see the ESI† for a mechanistic rationale) led us to speculate that the system could potentially be adapted to bring about highly chemoselective amine acylation with a view to developing a new, sterically sensitive strategy for the protection of the least hindered amino functionality in a molecule. Despite impressive advances in protection–free synthesis,[8] the temporary masking of amine (Lewis)-basicity and nucleophilicity *via* a variety of methods[9] usually remains a *sine qua non* in the synthesis of complex molecules.

While the selective acylation of primary over secondary amines in polyamines is often possible,[10] and the exploitation of biomolecules to achieve high selectivity has been reported,[11,12] the use of a small molecule to discriminate between two amines when the steric discrepancy between amino groups is exceedingly small has been considerably less successful.[13]

The state-of-the-art in this domain is the recent comprehensive study of the use of **9** as an acylating agent by Doyle *et al.* (Fig. 1B).[14] The heterocycle could transfer a single benzoyl group with consistently (and uniformly) outstanding selectivity to a range of polyamines: for instance – diamine **8** could be transformed into the monobenzoyl-protected **10** in excellent yield; driven by the formation of an aromatic conjugate base of the leaving group **11**. While the selectivity possible is akin to that which one would expect from biocatalysis – the harsh acidic/basic conditions required to cleave *N*-benzoyl amides[15] (no aroyl variants of **9** were reported) and the non-trivial synthesis of **9** from simple starting materials[16] are two obstacles to the adoption of this technology as a protection group strategy in complex molecule synthesis.

Herein we report the development of an NHC-catalysed highly chemoselective acylation of amines and challenging diamines

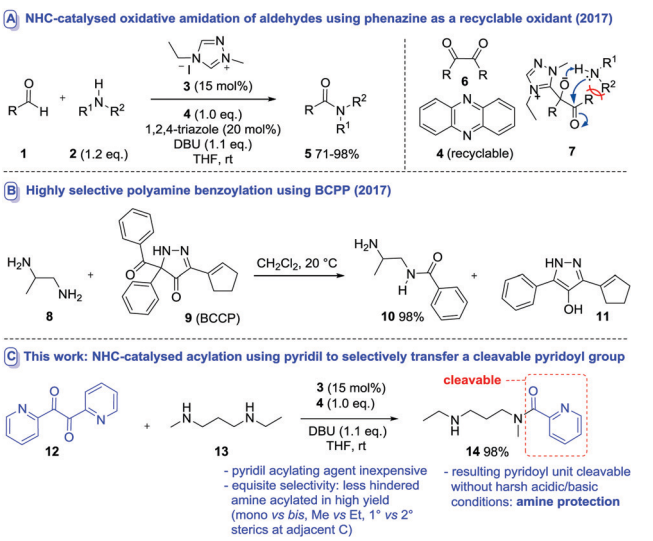

Fig. 1 NHC catalysed oxidative amination of aldehydes, chemoselective amine acylation using a pyrazol-4-one and amine acylation using pyridil.

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(*e.g.* **13**) using pyridil (**12**) as a commercially available unconventional acylating agent to give products such as **14** in excellent yield (Fig. 1C). Significantly, we show that the pyridoyl-unit is demonstrably cleavable without resorting to either strongly acidic or basic aqueous conditions.

We began by examining the ability of pyridil (**12**) to acylate a range of amines of general type **2** under the influence of carbene catalysis (in the absence of catalyst, no reaction occurs) in the presence of phenazine (**4**)[17] to generate product amides **15–26** (Table 1). Simple primary benzyl-, allyl- and propargyl[18] amines could be acylated in good-excellent yields to yield pyridine derivatives **15–18** respectively. Substitution at the β-carbon of a primary amine is well tolerated (*i.e.* amide **19**), however, while acylation of primary amines substituted at the α-carbon atom is possible in good yield (*i.e.* products **20** and **21**), these are clearly more difficult substrates for the system – pointing to the possibility of being able to discriminate between these groups in acylation events.

The cyclic secondary amines pyrrolidine and piperidine could be smoothly transformed to **22** and **23**, however, the installation of an electron-withdrawing group on the piperidine-ring led to significantly decreased efficacy (*i.e.* amide **24**). More sterically encumbered secondary amines such as dipropylamine and *N*-methylbenzylamine gave rise to **25** and **26** respectively in moderate yield.

Next, a small library of diamines was selected to further probe the acylation proclivities of the system and its ability to discriminate between amino groups in different steric environments (Table 2).

The acylation of diamine **29** – which incorporates both a primary amine and a cyclic secondary amino unit – with **12** proceeded chemoselectively to afford **30** in excellent yield (entry 1). Since the piperidine amine is sterically encumbered by the chain at the 2-position, the acylation of **31** was next examined. Here the competition is between a primary and a secondary amine differing only by one *N*-methyl substituent. Gratifyingly, acylation occurred exclusively at the less hindered site to furnish **32** in near quantitative yield (entry 2). In a similar vein, the system is capable of selecting between two primary amines distinguished only by an α-methyl group at carbon (*i.e.* **8**) to product **33** in 98% yield (entry 3).

None of the reactions outlined above produced bis-acylated products. To provide a significant challenge in this context; we examined the monoacylation of diamine **34** (an important molecule in asymmetric catalysis); which is notoriously difficult to monoacylate chemoselectively without using excess amine.[19–21] Under NHC catalysis the reaction formed the monoacyl product **35** in reduced yet appreciable yield; with the remainder bis-acylated material (entry 4).

The methodology can also act upon steric variations between two different secondary amines. For instance, the preference for efficient reaction at the *N*-Me group associated with diamine **36** over its *N*-iPr counterpart is clear (entry 5). More strikingly, complete *N*-Me *vs.* *N*-Et selectivity is possible under these conditions – affording amide **38** from amine **13** in 98% yield (entry 6). We are not aware of another small molecule-based system capable of such discriminatory ability in the acylation of secondary amines in the literature.

To put these results in context: in our hands the acylation of either **29**, **31** or **33** by either one equivalent of benzoyl chloride (1.0 eq.) or $(Boc)_2O$ (1.0 eq.) in either THF or CH_2Cl_2 (0.1 M) in the presence of NEt_3 at temperatures from ambient to −78 °C provided only bis-acylated products and starting materials. No monoacyl compounds were formed.

We considered that intramolecular hydrogen bonding may be an actor in the experiments summarised in Table 2. Accordingly, we carried out the competition experiments outlined in Scheme 1.

Table 1 Influence of amine structure on NHC-catalysed acylation by pyridil

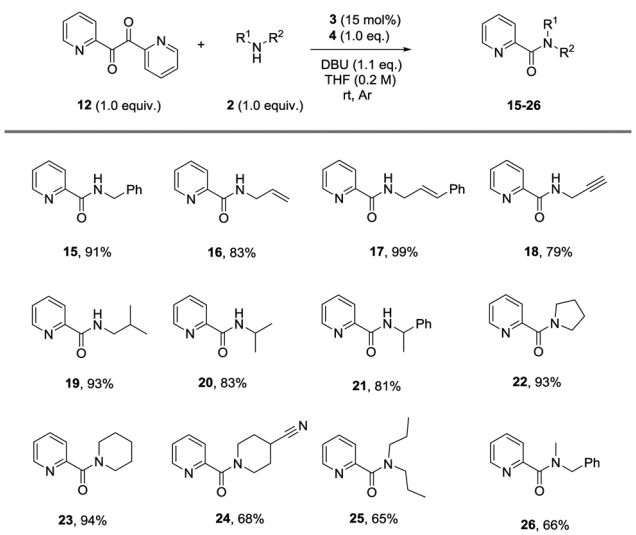
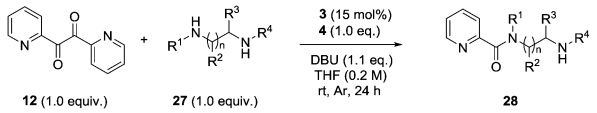
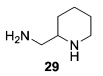
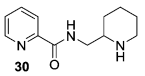
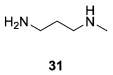
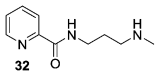
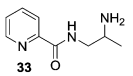
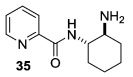
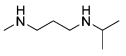
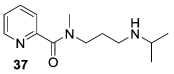
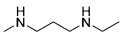
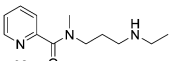
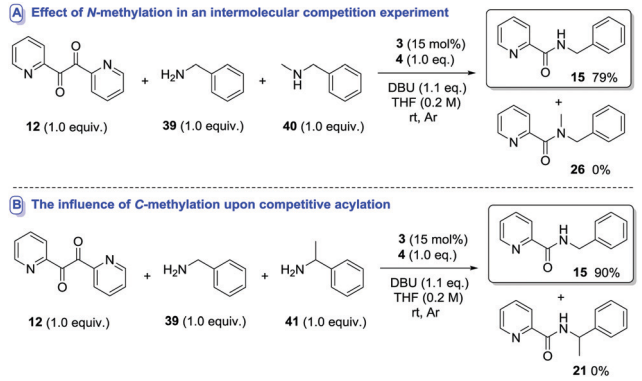


Table 2 Chemoselective acylation of diamines



Entry	Diamine	Product	Yield[a] (%)
1[b]	 29	 30	94
2	 31	 32	98
3	 8	 33	98
4[b]	 34	 35	77
5	 36	 37	94
6	 13	 38	98

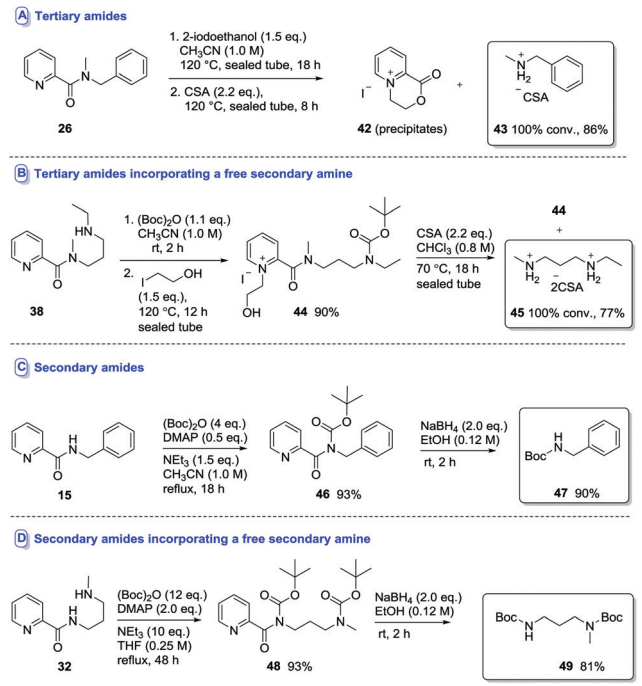
[a] Isolated yield. [b] 0.5 eq. of **12** utilised.



Scheme 1 Influence of *N*- and *C*-substitution on competition experiments.

When pyridil was offered a choice between benzylamine (**39**) and equimolar loadings of its *N*-methyl analogue **40**, **15** was the sole amide detected and isolated (Scheme 1A). Similarly, competition for acylation between **39** and its α-methyl variant **41** resulted in the smooth and exclusive formation of **15** and the complete absence of the more hindered product **21** (Scheme 1B). Thus it would appear that the ability of the system to acylate the least hindered N-atom in a diamine is related to steric sensitivity and not the formation of intramolecular hydrogen bonds between the termini of either the substrates or products.

While dramatic levels of chemoselectivity are possible, for the system to be considered of potential utility relative to (for example) benzoylation, the amide must be cleavable under milder conditions. After considerable experimentation, a suite of conditions were developed under which any amide generated by the study could be deprotected in high yield without requiring heating under strongly acidic or basic aqueous conditions (Scheme 2).



Scheme 2 Pyridoyl-amide cleavage.

Tertiary amides can be deprotected in an *ad hoc*-designed one-pot procedure involving alkylation with iodoethanol followed by ring closure in the presence of dry camphorsulfonic acid (CSA) to generate the corresponding heterocyclic lactone **42** – which precipitates from solution and facilitates purification – and the deprotected salt **43** (Scheme 2A). Amides which are the product of chemoselective acylation and incorporate free amino groups on the pendant chain such as **38** can be first Boc-protected and then subjected to similar conditions to generate the double ammonium salt **45** *via* **44** (Scheme 2B).

Simple secondary amides (*e.g.* **15**) can be deprotected *via* initial carbamate formation to give **46**, followed by treatment with sodium borohydride[22] to afford the Boc-protected **47** (Scheme 2C), whereas a similar strategy involving installation of two Boc-groups allows the cleavage of secondary amides incorporating a secondary amine such (*e.g.* formation of **49** from **32** *via* **48**, (Scheme 2D)).

In summary, the use of pyridil as an unconventional acylating agent for reaction with a range of primary and secondary amines in the presence of an N-heterocyclic carbene catalyst is reported. The system is able to easily discriminate between amines in a diamine – always reacting at the least hindered N-atom. Thus, in general, primary amines can be acylated in preference to secondary analogues (even when the steric difference derives from a methyl group), while two primary amines can be distinguished based on substituents at the adjacent C-atom (again, discrepancies as small as a methyl group are sufficient for total control). In the case of secondary amines, the reaction is unprecedentedly sterically discerning for a small molecule-based system: an *N*-Me group can be exclusively acylated in the presence of an *N*-Et unit.

Competition experiments demonstrated that the origin of this selectivity is not ascribable to intramolecular hydrogen bonding between the amines. Novel methods were developed which allow the resulting monoacylated pyridoyl amides to be cleaved without requiring the harsh acidic and basic hydrolytic conditions associated with benzoyl protection of aliphatic amines; thereby allowing the methodology to potentially serve as a highly chemoselective protection group strategy for amino groups.

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Conflicts of interest

There are no conflicts to declare.

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