ChemComm

COMMUNICATION

View Article Online
View Journal

Cite this: DOI: 10.1039/c7cc05561g

Received 18th July 2017,
Accepted 24th August 2017

DOI: 10.1039/c7cc05561g

rsc.li/chemcomm

Direct, efficient NHC-catalysed aldehyde oxidative amidation: *in situ* formed benzils as unconventional acylating agents†

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A new N-heterocyclic carbene-catalysed oxidative amidation of aldehydes has been developed which converts the aldehyde to a benzil acylating agent *in situ*. The process uses an air-recyclable oxidant and a nucleophilic co-catalyst and does not require the use of a large excess of either one coupling partner or catalyst.

The ubiquity and importance of amide bonds in natural product and pharmaceutical chemistry is not easily understated,[1] and thus new methods for their formation involving unconventional coupling partners are highly prized. The most common methodology for the formation of amides involves the transformation of a carboxylic acid into a more electrophilic derivative (or its *in situ* activation using a coupling agent) followed by reaction with an amine. A relatively underexplored approach involves the use of an amine in conjunction with an aldehyde with concomitant oxidation in the presence of an N-heterocyclic carbene (NHC) catalyst.[2] There are a plethora of methodologies for the analogous reaction leading to esters, however progress towards amides has been considerably slower.[3,4]

In 2007 two groups independently demonstrated the concept of 'internal redox' amidation of aldehydes. Rovis and Vora disclosed that α,α-dichloro aldehydes (*inter alia*) such as **1** could be converted to α-chloro amides **2** in the presence of an amine, a base, a triazolium ion precatalyst **3**, HOAt and *tert*-butanol.[5] Contemporaneously, Bode and John[6] reported that cyclopropyl aldehydes **4** could be transformed into amides of general type **6** with cleavage of the cyclopropyl ring balancing (from a redox standpoint) the oxidative coupling of an aldehyde with an amine (Fig. 1A).[7,8] Studer and De Sarkar[9] were the first to carry out NHC-mediated oxidative coupling between simple aldehydes **7** and amines in the presence of a stoichiometric quinone-based oxidant **8** (Fig. 1B). This process is an oxidative esterification:[10] in the presence of stoichiometric alcohol additive **9** and triazolium ion precatalyst **10** the initially formed active ester **12** is subsequently reacted with an amine in one pot to give amides **11**. Yields are high to excellent; however a substantial excess of amine (2.5 eq.) and only amidations involving primary amines and pyrrolidine were reported.

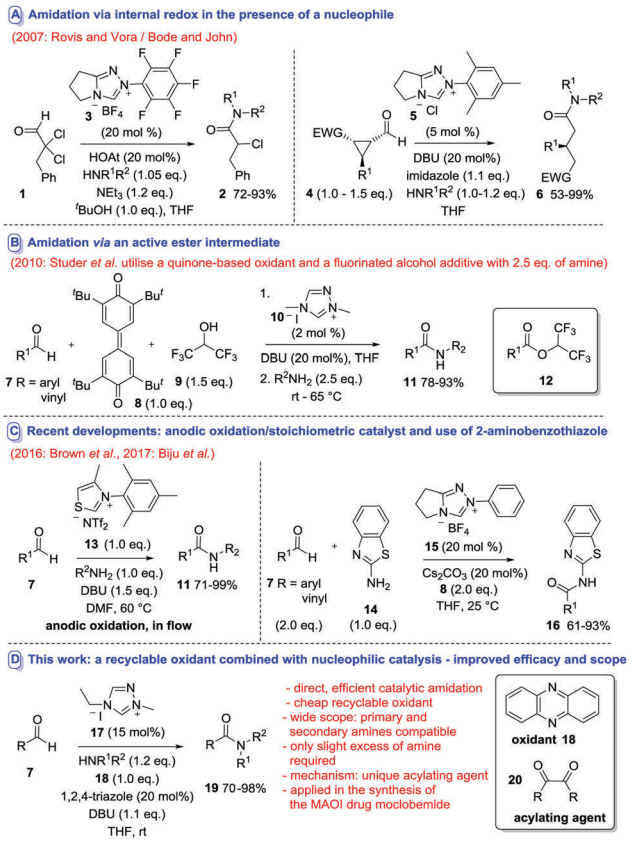

Fig. 1 NHC catalysed oxidative amination of aldehydes.

Very recently Brown *et al.*[11] published an innovative study involving the use of anodic oxidation in flow to bring about the synthesis of amides **11** from aldehydes – often with excellent

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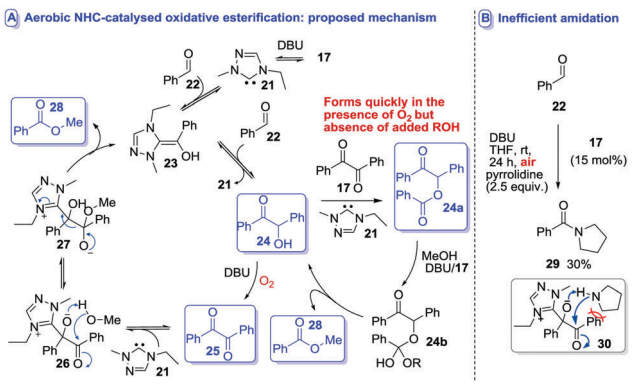
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c7cc05561g

yield – in the presence of stoichiometric loadings of thiazolium ion precatalyst **13** and primary amines, while Biju *et al.*[12] have just reported oxidative amidations of aldehydes (in two-fold excess) using oxidant **8** and the specialised amine 2-amino-benzothiazole **14** (Fig. 1C). Maheswari *et al.* have also recently reported aldehyde amidations with NBS (3.0 eq.) as a stoichiometric oxidant. Amide yields were high, with obvious restrictions on substrate scope given the reactivity of NBS.[13,14]

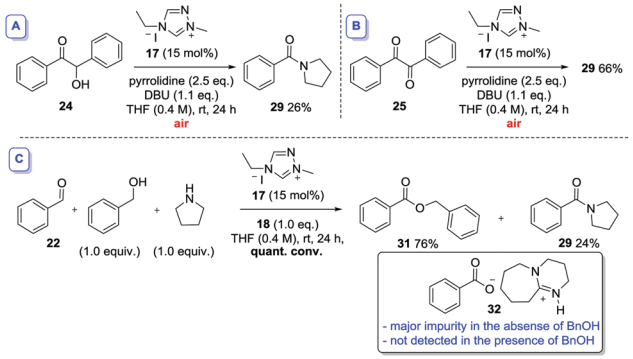
Herein we report the development of an efficient, general oxidative amidation methodology of wide scope with respect to the amine component (used in only slight excess) utilising a cheap recyclable oxidant in conjunction with the cooperation of nucleophilic and NHC-based catalysis. The mechanism is unconventional and involves neither internal redox nor the intermediacy of an acylazolium ion (Fig. 1D).

In 2013 we reported that benzaldehydes underwent efficient oxidative esterification in the presence of a carbene catalyst in alcoholic media using air as the terminal oxidant.[15] A precis of the extended catalytic cycle is shown in Scheme 1A.[16] The process is distinct from analogous literature processes in that the species which is oxidised is neither the Breslow intermediate nor its 1,2-catalyst-aldehyde adduct precursor, but aldehyde-derived benzoin. Addition of the carbene **21** to benzaldehyde (**22**) generates the Breslow intermediate **23**. This reacts with **22** to form benzoin (**24**), which, in the presence of oxygen and base oxidises to benzil (**25**). This electrophilic diketone is attacked by carbene **21** to afford **26**, which, in the crucial step, is attached by the alcohol nucleophile – most likely under the influence of general base catalysis – to give the sterically hindered **27**, which collapses to form the product ester **28** and regenerates the **23**.

When amidation in the presence of precatalyst **17** was attempted under similar conditions using the more nucleophilic but less acidic pyrrolidine nucleophile (2.5 eq.), yields reduced dramatically (Scheme 1B). Therefore our study began with an attempt to optimise the reaction conditions. Variation of the solvent, concentration, temperature, base, catalyst structure (both triazolium and thiazolium salt precatalysts) and loading of the amine nucleophile failed to lead to significant improvements in product yield. We therefore endeavoured to pinpoint the step(s) in the catalytic cycle which were proving problematic (Scheme 2). These experiments were instructive: use of **24** led to inefficient



Scheme 1 NHC-Catalysed aerobic oxidative esterification and amidation.

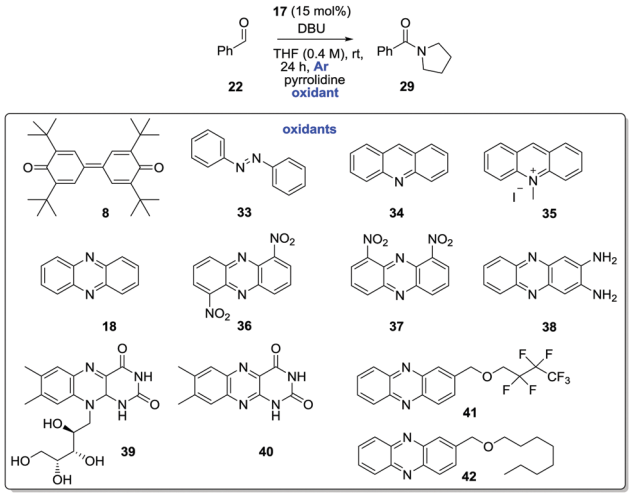


Scheme 2 Oxidative amidation of benzoin and benzil.

amidation (Scheme 2A), while its replacement with **25**[17] led to the formation of amide **29** in greatly improved yield (Scheme 2B). The magnitude of the product yields seemed to support a hypothesis involving efficient amidation from the benzil stage of the catalytic cycle forwards, but problematic conversion of benzoin to benzil under these conditions,[18] despite the fact it occurs without problems in the analogous esterification chemistry (albeit in alcoholic media).[13,14] The inferiority of the amine nucleophile in these processes was underlined by a competition experiment in which **22** was amidated with pyrrolidine in the presence of stoichiometric benzyl alcohol (Scheme 2C): not only was **31** formed in preference to **29** – the major salt side product **32** identified in the reactions summarised in Scheme 2A and B was completely absent.[15,19] It is noteworthy that rigorous drying of reagents/solvents (even the air) failed to lead to suppress the formation of **32**; indicating that it does not derive from a hydrolytic process.

It is clear that in the case of the amidation reaction, sluggish (relative to esterification) amide formation allows the intervention of an alternative, deleterious, aerobic oxidation pathway which leads to the formation of **32**. Focus therefore shifted to the use of oxidant additives under an inert atmosphere (Table 1). We began with the use of the quinone-like oxidant **8** at stoichiometric levels used successfully by Studer.[9] Using 2.5 equivalents of pyrrolidine the amide **29** was obtained in 43% yield (entry 1). This was higher than that in the presence of air (Scheme 1B) but is some way short of being synthetically useful. Azobenzene (**33**) had previously been shown to be a serviceable added oxidant in an aldehyde esterification methodology,[20] but was ineffective here (entry 2) Acridine (**34**) and its *N*-methylated analogue **35** (entries 3–4) were less efficacious oxidants than **8**. Use of the inexpensive phenazine (**18**) however, allowed smooth amidation to occur in 86% yield (entry 5). While increasing the oxidant loading proved ineffectual (entry 6), the reaction could be carried out using just 1.2 equivalents of the amine in 83% yield (entry 7). Importantly, we observed that on exposure to air, the dihydrophenazine (detected by ^{1}H NMR spectroscopy) oxidised rapidly to **18**, and we could recover the oxidant in 98% isolated yield after column chromatography. Thus while the process is inefficient in air due to side reactions, air can be used to recycle the oxidant – thereby lowering the cost of the process considerably. Lowering the loading of the oxidant to 25 mol% led to only a 5% reduction in product yield (entry 8).

Table 1 Influence of added oxidant under an argon atmosphere

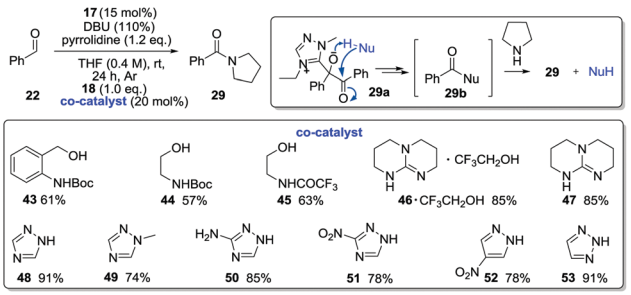


Entry	Pyrrolidine loading (eq.)	DBU loading (mol%)	Oxidant	Oxidant loading (eq.)	Yield[a] (%)
1	2.5	110	**8**	1.00	43
2	2.5	110	**33**	1.00	>5
3	2.5	110	**34**	1.00	21
4	2.5	110	**35**	1.00	33
5	2.5	110	**18**	1.00	86
6	2.5	110	**18**	1.50	86
7	**1.2**	**110**	**18**	**1.00**[b]	**83**
8	1.2	110	**18**	0.25	78
9	1.2	110	**36**	0.25	68
10	1.2	110	**37**	0.25	44
11	1.2	110	**38**	0.25	70
12	1.2	110	**49**	0.25	67
13	1.2	110	**40**	0.25	68
14	1.2	110	**41**	0.25	64
15	1.2	110	**42**	0.25	46

[a] Determined by ^{1}H NMR spectroscopy using styrene as an internal standard. [b] Recovered in 98% yield after chromatography.

Variation of the electronic characteristics (*i.e.* **36–40**, entries 9–13) and the solubility[21] (*i.e.* **41–42**, entries 14–15) of the phenazine core failed to provide further improvements.

We now attempted to influence the other (putative) challenging step in the catalytic cycle – the attack of the amine on the catalyst-benzil adduct (*i.e.* **29a**, Scheme 3). It had hypothesised that (*vide supra*) this step was both general base catalysed and – as it forms a product with adjacent quaternary carbon centres – exquisitely sensitive to steric bulk in the nucleophile. We therefore sought to establish if this step could be accelerated by nucleophilic catalysis. Initial attempts involved the use of alcohols (known to be good nucleophiles in this step) **43–45** incorporating a hydrogen bond-donating unit to facilitate subsequent amidation of the ester product by pyrrolidine to release the catalyst. Addition of these alcohols at 20 mol% loading led to decreased product yields. The guanidine base TBD had been shown to serve as an effective catalyst ester amidation processes,[22] but had little effect on the NHC catalysed process either in the presence or absence of an added alcohol nucleophile (*i.e.* **46**·CF_3CO_2H and **47**). Gratifyingly, use of 1,2,4-triazole (**48**) – who Birman *et al.*[23] had reported served as an efficient catalyst (in the presence of DBU) for the amidation

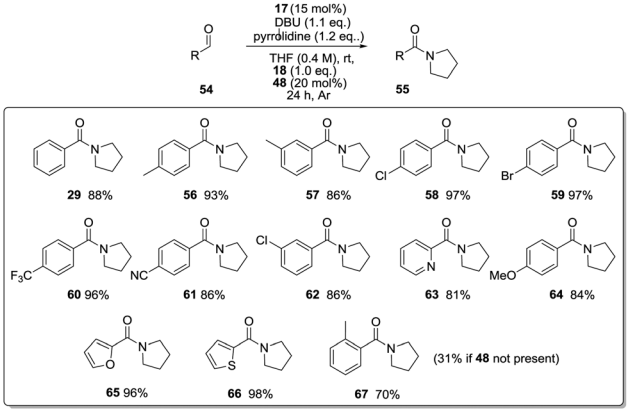


Scheme 3 Intervention of nucleophilic co-catalysis.

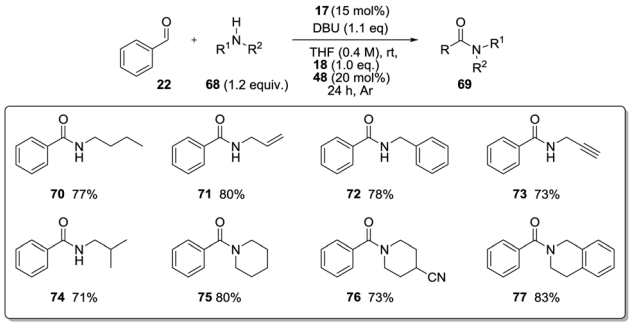
of active esters generated amide **29** in 91% yield. It seems likely that the conjugate base of **48** is the active co-catalyst, as the *N*-methylated analogue **49** failed to promote amidation. Of the other similar heterocycles (**50–53**) evaluated, only 1,2,3-triazole was comparable in efficacy to **48**.

Attention now turned to substrate scope (Scheme 4). Under optimised conditions a range of benzaldehydes could be amidated with pyrrolidine (1.2 eq.) in the presence of precatalyst **17**, DBU, co-catalyst **48** and recyclable oxidant **18** to form amides **29** and **56–67** in good to excellent isolated yields. Electron rich, electron deficient and heterocyclic variants were all compatible. The lower (but still synthetically useful) yield of the *o*-substituted product **67** supports the rationale that the mechanism involves oxidation of the corresponding benzoin (the formation of which is sterically sensitive[24]) and not the formation of an acyl azolium ion (much less sterically sensitive[18]) and highlights the contribution from the nucleophilic co-catalyst **48**.

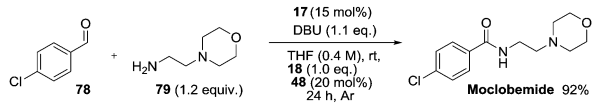
The scope was also broad with respect to the amine component (Scheme 5): **22** could be efficiently amidated by 1.2 equivalents of straight chain-, benzylic-, allylic- and propargylic primary amines to give amides **70–73**. β-Branching is also tolerated (*i.e.* product **74**), while both functionalised and unfunctionalised secondary amines could also be used – leading to amides **75–77**. One of the distinct advantages associated with this process is that large excesses of either coupling partner are not required. To demonstrate the potential utility of the methodology, we prepared the MAO-inhibitor drug moclobemide (Hoffman-La Roche) from the



Scheme 4 Substrate scope: aldehyde component.



Scheme 5 Substrate scope: amine component.



Scheme 6 Synthesis of moclobemide.

oxidative amidation of *p*-chlorobenzaldehyde (**78**) with the commercially available amine **79** in 92% yield (Scheme 6).

In conclusion, a new NHC-catalysed oxidative amidation of aldehydes has been developed. The methodology is mechanistically distinct (involving benzils as acylating agents) and unique among such methodologies in that a large excess of neither the amine, aldehyde nor catalyst are required. Phenazine proved superior to the often used **8**, and could be recycled and recovered efficiently after the reaction by exposure to air. A carbene catalyst and a nucleophilic co-catalyst operate synergistically to allow the smooth amidation of a range of aromatic aldehydes with either primary or secondary amines in good-excellent yields, and the utility of the technology was demonstrated through the efficient synthesis of an anti-depression drug. Efforts to further explore the scope and mechanism of this reaction are underway.

We are grateful to Science Foundation Ireland the Solid State Pharmaceutical Centre (12/RC/2275) for financial support.

Conflicts of interest

There are no conflicts to declare.

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