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Aerobic oxidation of NHC-catalysed aldehyde esterifications with alcohols: benzoin, not the Breslow intermediate, undergoes oxidation†

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Benzoin (and neither the Breslow intermediate nor the NHC–aldehyde tetrahedral adduct) has been unambiguously identified as the oxidised species in aerobic NHC-catalysed aldehyde esterifications.

In the previous communication,[1] the first examples of *broad scope, efficient*, *N*-heterocyclic carbene (NHC)-catalysed aerobic oxidative methyl esterifications of aromatic aldehydes in the absence of alkylating agents, solid stoichiometric oxidants or co-oxidation catalysts were reported. Previously these reactions (when O_2/air had been used as the oxidant) had been postulated to proceed either through the oxidation of the Breslow intermediate or its immediate precursor. We wished to ascertain the nature of the oxidised intermediates that were involved in these aerobic oxidative esterifications, and began by examining the scope of the process with respect to the alcohol component. If the reaction proceeds through a highly electrophilic acyl triazolium **14** (Fig. 1), one would *not* expect to observe significant differences between esterifications using different alcohols (Scheme 1).

Experiments were carried out using two sets of conditions (Scheme 1): a 1 : 1 THF–alcohol solvent mixture (condition set A) and use of 3.0 equivalents of alcohol in THF solvent (condition set B). We commenced our study with a series of alcohols which form esters **3** (amenable to different deprotection methodologies). Both benzylic and allylic alcohols were suitable substrates; providing the corresponding products **4** and **5** in good (condition set B) to excellent yields

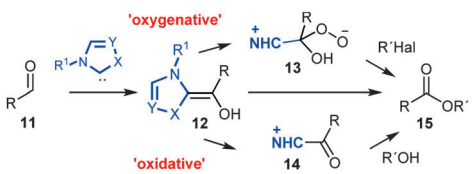
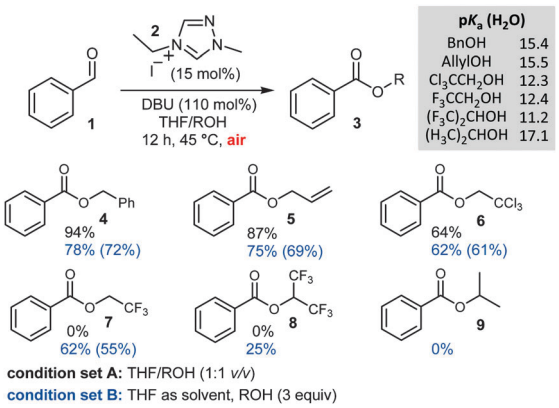
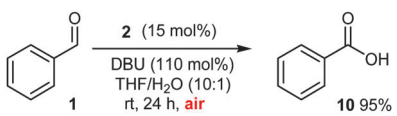


Fig. 1 Current prevalent mechanistic rationales proposed in literature.



Scheme 1 Reaction scope: alcohol component. Yield determined by ^{1}H NMR spectroscopy using styrene (114 μL, 1 mmol, 1 equiv.) as an internal standard; yield of isolated product given in parentheses. Transformation to **7**, **8** and **9** performed at rt.

(condition set A) yields. The formation of the trichloroethanol-derived **6** proceeded in *ca.* 60% yield irrespective of the conditions employed. Interestingly, the synthesis of the corresponding trifluoro-analogue **7** was limited by the volatility of the alcohol, and could only be formed under condition set B. Similar difficulties were encountered with the more hindered hexafluoroisopropanol – resulting in the formation of **8** in low yield. The more hindered and less acidic isopropanol proved resistant to esterification: ester **9** could not be generated.



(1)

Using precatalyst **2** and DBU, **1** could also be cleanly oxidised to the acid **10** in THF/H_2O (10 : 1 v/v) in excellent isolated yield (eqn (1)). Recently disclosed examples of imidazolium ion derived carbene-mediated aerobic oxidations of aromatic aldehydes to carboxylic acids in the presence of water[2] either require significantly elevated temperatures (60 °C) and reaction times >36 h (ref. 2*a*) or are only efficacious with highly activated aldehyde substrates (*e.g.* formation of **10** with <10% yield).[2b]

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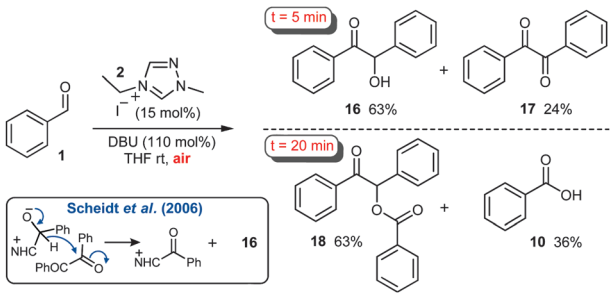
With the breadth of the reaction scope and the intriguing dependency on steric effects established, we attempted to divine some information regarding the reaction mechanism.

The results of our studies (outlined in Scheme 1) are not readily reconciled with either 'oxidative' or 'oxygenative' mechanisms (Fig. 1).[3] For instance, the 'oxygenative' esterification reaction requires alkyl transfer from an electrophile (such as an alkyl halide). The 'oxidative' esterification mechanism is also unsatisfactory here, as the sensitivity of the process described in this work to the steric bulk of *both* the nucleophilic and electrophilic reaction components is not consistent with that we observed in a previous study involving the use of azobenzene as a stoichiometric reactant[4] (*e.g.* in esterifications involving azobenzene as an oxidant, *o*-tolualdehyde and isopropanol served as excellent coupling partners, *while in the current study both are poor substrates*). This strongly indicates that *our aerobic oxidative esterifications outlined above do not proceed via acyl azolium ion intermediates.*

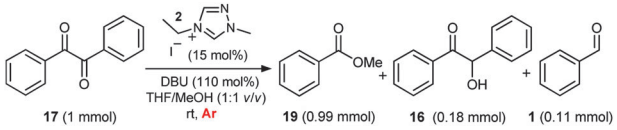
Since the esterifications do not proceed in the absence of O_2, we were forced to consider alternative species which are oxidised in these reactions. The most likely candidate appeared to be benzoin (**16**) – the slow, base-catalysed aerobic oxidation of which to benzil (**17**) by O_2 is known.[5] While we never isolated/observed **17** in any of the reactions outlined above, it is a highly electrophilic species: therefore its rapid destruction in the presence of the relatively unhindered carbene derived from **2** and methanol would not be implausible. In addition, while the sensitivity of the esterifications to steric factors did not match that of known processes involving acyl azolium ions, it was consistent with the influence of steric bulk on the benzoin condensation,[6] which encouraged us to further investigate in the direction of this hypothesis.

We began by subjecting benzaldehyde (**1**) to the esterification conditions *in the absence of methanol*.[7] To our delight, we observed the formation of both **16** and **17** after just 5 min reaction time (Scheme 2). After 20 min, both these species have been replaced by a hydroacylation product **18** (in good yield) and the acid **10** (presumably formed due to the presence of adventitious water).

Chan and Scheidt[8] have previously reported the formation of **18** in the NHC-mediated reaction between **1** and **17**. They rationalised this in terms of a hydride transfer process between the carbene–aldehyde adduct and **17**, which generates an acyl azolium ion and benzoin (Scheme 2, inset). To the best of our knowledge the reaction outlined in Scheme 2 is the first example of the efficient NHC-mediated formation of a hydroacylation product from an aldehyde alone in the presence of air. Next, we attempted to establish if **17** is a catalytically relevant intermediate in the presence of alcohol. Accordingly, benzil was exposed to methanol and the carbene *under an argon atmosphere*.



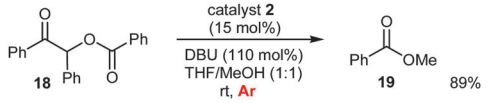
Scheme 2 The observation of benzil in the absence of methanol.



Scheme 3 The anaerobic conversion of benzil to methyl benzoate.

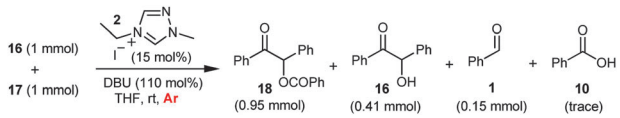
Under these conditions we observed rapid conversion of **17** to methyl benzoate (**19**), **16** and aldehyde **1** at ambient temperature (Scheme 3).[9,10] Similarly, the carbene-catalysed reaction of **16** with an equivalent amount of **17** *in the absence* of both air and MeOH generated the hydroacylation product **18** as the major constituent of the crude reaction mixture (Scheme 4), indicating that benzoin may also be able to play the role of the nucleophilic alcohol in these reactions.[11]

The hydroacylation product **18** is conspicuously absent in the ^{1}H NMR spectra of reactions involving methanol or other smaller alcohols. Therefore we next assessed the stability of **18** under anerobic reaction conditions; whereupon smooth acyl transfer to afford methyl benzoate (**19**) in excellent yield was observed (eqn (2)).

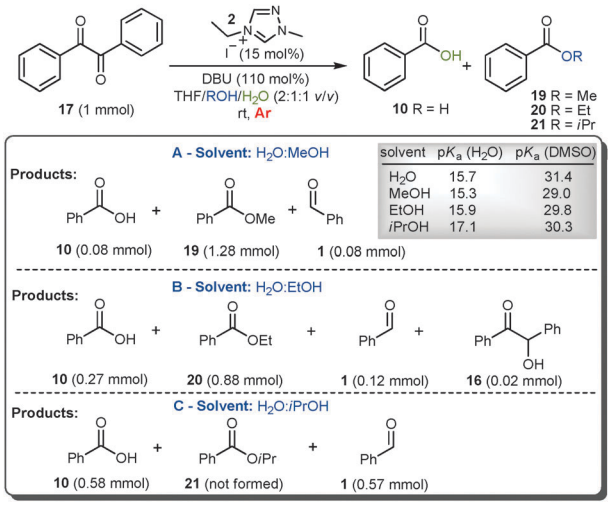


(2)

Finally, to gain some insight regarding the origins of the influence of the alcohol structure on reaction efficiency, benzil (**17**) was reacted in the presence of the NHC under anaerobic conditions in a competition experiment using alcohol and water solvent mixtures (yielding either an ester or acid resp., Scheme 5).[12] We expected products derived from nucleophilic attack of the less hindered water molecule to dominate over the ester analogues stemming from the more hindered alcohols. Surprisingly, the 1 : 1-solvent mixture of methanol and water generated the methyl ester **19** as the major



Scheme 4 The NHC-mediated reaction of benzil with benzoin in the absence of O_2.



Scheme 5 Competition between alcohols and water.

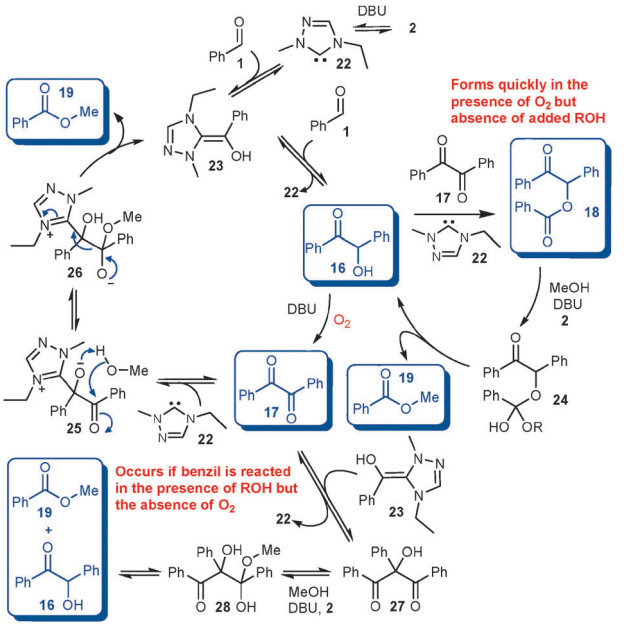
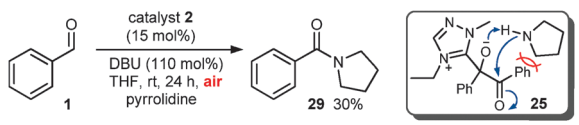


Fig. 2 Mechanistic rationale: all highlighted compounds have been either isolated and/or detected *in situ*.

product (Scheme 5A; only low levels of acid **10** and aldehyde **1**). The use of ethanol as a co-solvent also diverted the process towards the generation of ester **20** (Scheme 5B), however, acid formation was more favourable here (together with of small amounts of aldehyde **1** and benzoin **16**). In aqueous isopropanol conversion is incomplete. No esterification occurs: oxidation to **10** and reversion to aldehyde **1** are the major fates of **17** (Scheme 5C). It appears that the factors which govern selectivity in these processes are not simply related to either acidity or steric bulk, but a confluence of factors: a weak correlation between acidity and propensity for ester formation was found, while the outcome of the experiment involving isopropanol is difficult to rationalise based on its pK_a alone.[13]

Overall, a mechanistic rationale consistent with the data outlined above is shown in Fig. 2. The carbene **22** reacts with **1** to form the enaminol **23**, which, on addition to another molecule of **1** results in the rapid formation of **16** (also see Scheme 2), which is oxidised by air in the presence of base to benzil (**17**).[14] Since our results are not consistent with acyl azolium ion formation, we would propose that the electrophilic diketone **17** is attacked by NHC **22** to give the tetrahedral intermediate **25**, which is converted to **26** (presumably *via* intramolecular general base catalysis – also see Scheme 2). The hemiacetal **26** (ref. 15) can then collapse to reform the enaminol **23** and methyl benzoate **19**. The formation of the hindered hemiacetal **26** would be likely to depend on both the steric bulk and the pK_a of the alcohol. In the absence of added alcohol, it is possible that a similar process occurs involving **16** as the nucleophile, which affords the hydroacylation product **18**. In the presence of MeOH **18** is converted to **16** *via* **24** (also see eqn (2)).[16]



Scheme 6 The NHC-mediated oxidative amidation of **1**.

The formation of benzoin (**16**) from benzil (**17**) in the absence of O_2 (but presence of CH_3OH) also requires explanation: we would suggest that – by analogy with a recent proposal[10] in a distinct but related transformation – attack by the enaminol **23** on diketone **17** would yield **27** (isolated by Massi *et al.*[10]). In the presence of excess base and methanol, the cleavage of **27** to yield ester **19** and **16** *via* hemiacetal **28** is conceivable. This model was supported by the inefficiency of the corresponding amidation chemistry (Scheme 6) involving pyrrolidine – a more nucleophilic but less acidic reagent than MeOH.

We suggest that this may be related to the attack of the more hindered amine on the very bulky ketone **25**. This reaction would also be hampered by considerably less efficient general base catalysis of the attack on the ketone involving the considerably less acidic amine.

In summary these reactions have been shown to be mechanistically distinct from other either NHC-catalysed 'oxidative' or 'oxygenative' esterifications in that the species which reacts with oxygen in the air is *not* the Breslow intermediate, but the aryloin (or more accurately, its enolate). In aqueous solvent benzoic acid (**10**) is accessible from aldehyde **1** in excellent yield. Investigations to further develop the scope and utility of these reactions are underway. Financial support from the IRCSET, Science Foundation Ireland and the DFG is gratefully acknowledged.

Notes and references

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7 Quoted yields within the figures are determined by ^{1}H NMR spectroscopy with an internal standard. See the ESI† for details.
8 A. Chan and K. A. Scheidt, *J. Am. Chem. Soc.*, 2006, **128**, 4558.
9 This process features a comparison of reactions of different molecularity; therefore (to avoid confusion), we have quote the yields as mmol of product.
10 It is noteworthy that Massi *et al.* have recently observed the benzoylation of PEG_{400} on treatment of benzil with a thiazolium ion-derived NHC, see: O. Bortolini, G. Fantin, M. Fogagnolo, P. P. Giovannini, V. Venturi, S. Pacifico and A. Massi, *Tetrahedron*, 2011, **67**, 8110.
11 It must be acknowledged that reversion of **16** to **1**, followed by a hydroacylation reaction as proposed by Scheidt (see Scheme 2) cannot be ruled out at this juncture.
12 For use of an unsymmetrical benzil, see the ESI†.
13 It is noteworthy that in mixtures with MeCN, MeOH has been found to be more nucleophilic than EtOH: (*a*) S. Minegishi, S. Kobayashi and H. Mayr, *J. Am. Chem. Soc.*, 2004, **126**, 5174; (*b*) T. B. Phan and H. Mayr, *Can. J. Chem.*, 2005, **83**, 1554.
14 In a control experiment under standard aerobic conditions in the absence of **2**, **16** (1.0 mmol) was converted to **17** (0.19 mmol) after just one 1 h reaction time.
15 We note that a similar intermediate has been suggested (in a different process) by Massi *et al.*, see ref. 10.
16 This process occurs in both the presence and absence of **2**.