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NHC-catalysed aerobic aldehyde-esterifications with alcohols: no additives or cocatalysts required†

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A highly efficient, broad scope, additive-free mild protocol for the oxidative carbene-catalysed esterification of aldehydes (including the related aqueous oxidation to acids) has been developed.

Esters are a general class of molecules which are so commonplace that their undoubted synthetic importance defies quantification.[1] The ester functional group is most commonly accessed *via* the *stoichiometric* activation of a carboxylic acid as an acyl halide, anhydride or activated ester with subsequent acyl transfer to an alcohol nucleophile.

Recently, interest has grown rapidly in the development of an alternative oxidative esterification of aldehydes with alcohols catalysed by *N*-heterocyclic carbenes (NHCs, **1**, Fig. 1).[2,3] These transformations are purported to involve the addition of the carbene catalyst to an aldehyde **2** to form the Breslow intermediate **3**, which is then converted by a stoichiometric oxidant *e.g.* nitrobenzene,[4] MnO_2,[5,6] TEMPO,[7] diphenoquinone,[8,9] azobenzene,[10,11] phenazine or riboflavin;[12] (the use of anodic electrochemical oxidation to replace the stoichiometric oxidant has also been very recently demonstrated[13]) to an electrophilic acyl azolium ion **4**. This species can then transfer the acyl group to an alcohol **5** to afford ester **6** and the carbene, which re-enters the catalytic cycle. The potential of this novel strategy as a synthetic tool in natural product synthesis has recently begun to be appreciated.[5b,e]

In the presence of molecular oxygen in place of the stoichiometric oxidant it has been proposed that a separate oxidative fate for the Breslow intermediate involving addition of O_2 to **3** affords the internal peroxy zwitterion **7**[14] which then reacts with either the substrate aldehyde **2** (*via* peroxyacid intermediates) or another molecule of **3** to generate a carboxylate ion **8**;[15] this can be trapped by either a proton or an alkyl halide **10**[14–17] to afford either the acid **9** or the ester **11** respectively.[18,19] von Wangelin *et al.*[2a] (Fig. 1) have recently classified these distinct NHC-mediated esterifications as being either 'oxidative' (*i.e.* the oxidation of **3** to **4** by an added oxidant) or 'oxygenative' (*i.e.* the conversion of **3** to **7** by O_2).[20] While significant progress has been made – a mild, additive-free NHC-mediated protocol of broad scope for the aerobic oxidation of aldehydes has yet to be developed.

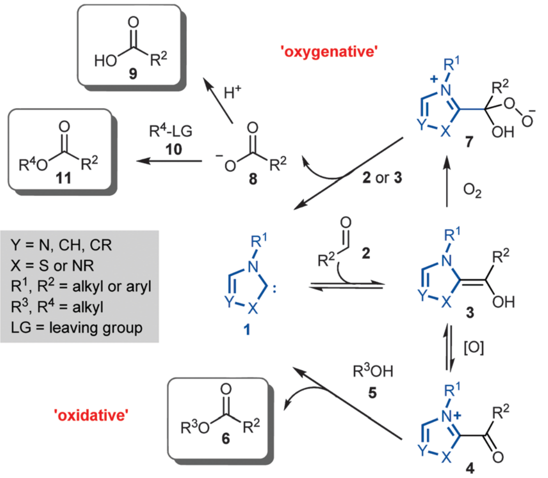

Fig. 1 NHC-mediated aldehyde esterification using either added oxidant or molecular oxygen: current mechanistic rationales.

During an investigation into the use of magnetite nanoparticles as a co-catalyst for the NHC-mediated oxidative esterification of *aldehydes*, we observed partial esterification of benzaldehyde (**12**) in methanol under aerobic conditions *in the absence of the nanoparticle*. After reproducing the result several times, we embarked on a study to determine the factors which influence the efficiency of this catalytic process (Table 1).

Preliminary experiments revealed that **12** could be esterified to a conveniently detectable extent in methanolic THF (1 : 1 v/v) in the presence of triazolium precatalysts (15 mol%) and a

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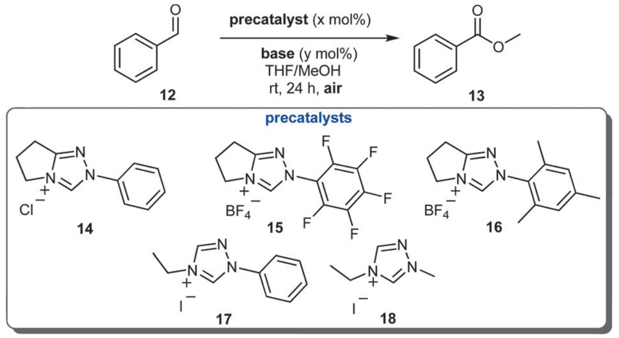
† Electronic supplementary information (ESI) available: Experimental procedures and spectroscopic data for all new compounds. See DOI: 10.1039/c3cc42596g

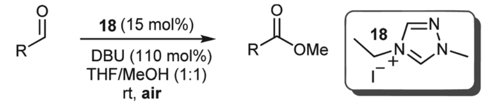
Table 1 NHC-mediated oxidative esterification

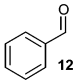
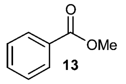
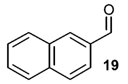
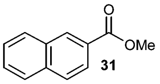
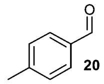
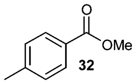
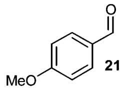
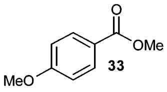
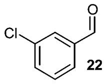
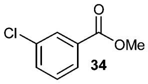
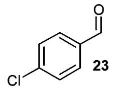
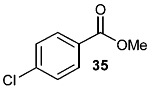
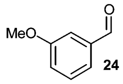
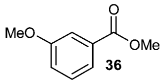
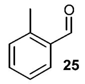
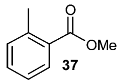
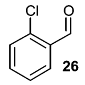
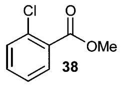
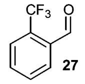
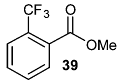
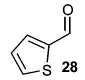
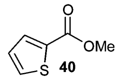
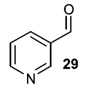
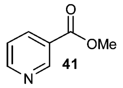
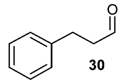
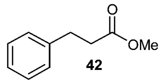


Entry	Precat.	x (mol%)	Base	y (mol%)	Solv.[a] (v/v)	Yield[b] (%)
1	—	0	DBU	110	1:1	0
2	**14**	15	DBU	110	1:1	48
3	**15**	15	DBU	110	1:1	56
4	**16**	15	DBU	110	1:1	61
5	**17**	15	DBU	110	1:1	0
6	**18**	15	DBU	110	1:1	96
7[c]	**18**	15	DBU	110	1:1	73
8	**18**	5	DBU	110	1:1	74
9	**18**	15	DBU	15	1:1	17
10	**18**	15	DBU	50	1:1	54
11	**18**	15	TEA	110	1:1	9
12	**18**	15	DMAP	110	1:1	12
13	**18**	15	DABCO	110	1:1	0
14	**18**	15	K_2CO_3	110	1:1	60
15	**18**	15	DBU	110	12:1	44
16	**18**	15	DBU	110	6:1	61

[a] THF held constant (2.5 mL). [b] Determined by ^{1}H NMR spectroscopy using styrene (114 μL, 1 mmol, 1 equiv.) as an internal standard. [c] THF replaced with CH_2Cl_2 solvent.

Table 2 Reaction scope: aldehyde component



Entry	Substrate	Time	Product	Yield[a] (%)
1	 **12**	24 h	 **13**	94
2	 **19**	12 h	 **31**	90
3	 **20**	30 h	 **32**	92
4	 **21**	92 h	 **33**	90
5	 **22**	24 h	 **34**	92
6	 **23**	12 h	 **35**	72
7[b]	 **24**	68 h	 **36**	77
8	 **25**	24 h	 **37**	28[c]
9	 **26**	24 h	 **38**	53 (53)[d]
10	 **27**	24 h	 **39**	0
11	 **28**	18 h	 **40**	65 (69)[d]
12	 **29**	20 min	 **41**	93
13	 **30**	13	 **42**	15[c]

[a] Yield of isolated product. [b] Reaction at 45 °C. [c] Determined by ^{1}H NMR spectroscopy using styrene (114 μL, 1 mmol, 1 equiv.) as an internal standard. [d] The value in parenthesis is the yield of isolated product obtained when this reaction was repeated in the collaborating research group using independently synthesised/purified materials and precatalyst.

small excess of base (DBU, 110 mol%) under an air atmosphere. We therefore began by examining the influence of precatalyst structure on the efficiency of the process. It is important to note that in the absence of triazolium ions, no conversion to methyl benzoate (**13**) is observed (entry 1). However, in the presence of the *N*-phenyl bicyclic triazolium ion **14** a moderate yield of **13** is formed after 24 h at ambient temperature (entry 2). The use of the more acidic carbene precursor **15**[21] led to a marginal improvement in product yield (entry 3), which increased further when the reaction was mediated by the hindered carbene derived from **16** (entry 4). An open-chain analogue of precatalyst **14** (*i.e.* **17**) proved completely inactive under these conditions (entry 5). Modification of this structure *via* the exchange of the *N*-phenyl substituent for a methyl group (*i.e.* precatalyst **18**) brought about a dramatic increase in activity (entry 6).

Given the mechanistic discussion outlined above (Fig. 1), this efficient, room temperature aerobic oxidative esterification in the absence of either an added stoichiometric oxidant, an alkyl halide or a dedicated catalyst for the activation of triplet oxygen[22–24] is remarkable. We next proceeded to determine the influence of the other reaction components on the process. THF could be exchanged for CH_2Cl_2, with an attendant loss in product yield (entry 7). Reduction of the loading of the triazolium ion to 5 mol% led to a similar reduction in efficacy (entry 8). We were also surprised to find that the oxidation process also strongly depends on both the loading (entries 9 and 10) and the identity (entries 11–14) of the base – with DBU emerging comfortably superior to the others evaluated in this study. The esterification can also be carried out using considerably less MeOH (entries 15 and 16), at the expense of rate.

With a useful protocol in hand, we next investigated the compatibility of the new process with different aldehydes (Table 2). Electron-neutral (*i.e.* **12** and **19**, entries 1 and 2) and deactivated (*i.e.* **20** and **21**, entries 3 and 4) aromatic aldehydes could be converted to the corresponding methyl esters in excellent isolated yield in the presence of **18**, DBU, methanol and air. Activated benzaldehydes provided interesting results: *m*-chlorobenzaldehyde (**22**) proved an excellent substrate, while the esterification of its *para*-substituted isomer **23** and a *m*-methoxy-substituted variant (*i.e.* **24**) proceeded in 77–92% yields (entries 5–7). *Ortho*-substitution is not well tolerated: *o*-tolualdehyde (**25**) and *o*-chlorobenzaldehyde (**26**) underwent conversion to **37** and **38** in low to moderate yields respectively (entries 8 and 9), while *o*-trifluoromethyl-benzaldehyde was inert (entry 10).

Substrates incorporating oxidisable heterocyclic functionality (*i.e.* **28** and **29**) could be converted to their methyl ester analogues in good-excellent yields (entries 11 and 12).[25] In contrast, the aliphatic aldehyde **30** resulted in a poor yield of the ester **42** and a complex product mixture (entry 13).

In summary, we have developed an efficient NHC-catalysed esterification of aldehydes involving alcohols and air (*i.e.* oxygen) as the oxidant. No other added stoichiometric oxidants or catalysts to activate molecular oxygen are required. Unhindered aromatic aldehydes (including heterocyclic analogues) can be converted to the corresponding methyl esters in good to excellent yields at ambient temperature.

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20 Intermediate **7** has also been proposed to for a recent related NHC-catalysed esterification under O_2-atmosphere: I. N. C. Kiran, K. Lalwani and A. Sudalai, *RSC Adv.*, 2013, **3**, 1695.

21 (*a*) M. S. Kerr, J. Read de Alaniz and T. Rovis, *J. Org. Chem.*, 2005, **70**, 5725; (*b*) H. U. Vora, S. P. Lathrop, N. T. Reynolds, M. S. Kerr, J. Read de Alaniz and T. Rovis, *Org. Synth.*, 2010, **87**, 350; (*c*) The pK_a of catalyst **14** (H_2O) has been determined to be 17.7: C. D. Campbell, N. Duguet, K. A. Gallagher, J. E. Thomson, A. G. Lindsay, A. C. O'Donoghue and A. D. Smith, *Chem. Commun.*, 2008, 3528; (*d*) For a recent compilation of more pK_a values of triazolium salts: R. S. Massey, C. J. Collett, A. G. Lindsay, A. D. Smith and A. C. O'Donoghue, *J. Am. Chem. Soc.*, 2012, **134**, 20421.

22 S. Iwahana, H. Iida and E. Yashima, *Chem.–Eur. J.*, 2011, **17**, 8009.

23 For a recent flavin-mediated aerobic oxidation of **12** in a Dakin-type process see: S. Chen and F. W. Foss Jr., *Org. Lett.*, 2012, **14**, 5150.

24 For a recent report concerning the use of Fe^{2+} ions as a co-catalyst and coupling with phenols see: R. S. Reddy, J. N. Rosa, L. F. Veiros, S. Caddick and P. M. P. Gois, *Org. Biomol. Chem.*, 2011, **9**, 3126.

25 In this context it is interesting to note that Goswami and Hazra had previously reported the aerobic esterification of heterocyclic aromatic aldehydes (only) involving thiamine hydrochloride and NEt_3 (2.0 equiv.) in MeOH (heating under reflux was required): S. Goswami and A. Hazra, *Chem. Lett.*, 2009, 484.