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Nucleophilic carbene-catalysed oxidative esterification reactions

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Abstract

The first synthetically useful protocol of broad scope for the oxidative esterification of aldehydes with equimolar amounts of primary and secondary alcohols at room temperature catalysed by N-heterocyclic carbenes is reported.
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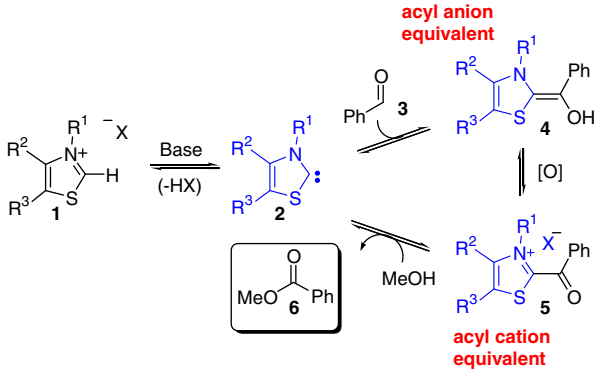
The most common strategy for the synthesis of carboxylic acid ester derivatives under mild conditions involves the stoichiometric activation of the parent acid as an acyl halide, anhydride or activated ester (in situ or otherwise) amenable to subsequent nucleophilic substitution.[1] An interesting and potentially valuable alternative transformation in which there has been a recent resurgence in interest is the (catalysed) oxidative esterification of aldehydes under mild conditions.[1b,2]

N-Heterocyclic carbenes (NHCs)[3] derived from thiazolium ions have been shown to catalyse the oxidative esterification of aldehydes with simple alcohols.[4] Deprotonation of thiazolium salt **1** gives rise to carbene **2**, the addition of which to benzaldehyde **3** gives the Breslow intermediate **4**,[5] which in the presence of a suitable oxidant[6–12] can be diverted from the benzoin condensation pathway through the formation of 2-benzoyl thiazolium ion[13] **5** which is capable of transferring its acyl group to an alcohol nucleophile to regenerate the catalyst (Scheme 1).[14–16]

While these carbene-catalysed oxidative esterifications are of mechanistic interest, their synthetic utility is curtailed by narrow substrate scope: only primary alcohols and simple aromatic aldehydes give acceptable isolated yields.[6–12] In addition, the general requirement for the use of the alcohol as solvent and the employment of stoichiometric amounts of base and excess oxidant render the process unsuitable for either the efficient use of more complex coupling partners or application on industrial scale. We therefore set out to examine this reaction with a view towards its development into a synthetically useful and efficient coupling methodology.



Scheme 1. Proposed mechanism of nucleophilic carbene-catalysed aldehyde esterification.

Our investigation began with the oxidative esterification of benzaldehyde with methanol as solvent catalysed by thiazolium salt **8** (5 mol %) in the presence of catalytic loadings of base and one equivalent of acridine as the oxidant at ambient temperature (Table 1). This initial experiment afforded ester **6** in moderate yield (entry 1). We were encouraged to subsequently find that a more efficient oxidative esterification could be carried out in THF using just one equivalent of the alcohol without requiring elevated reaction temperatures (entry 2).

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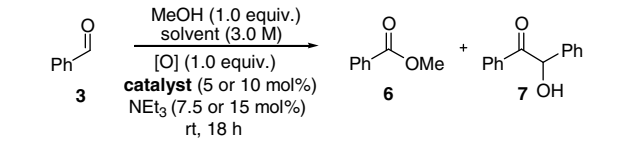
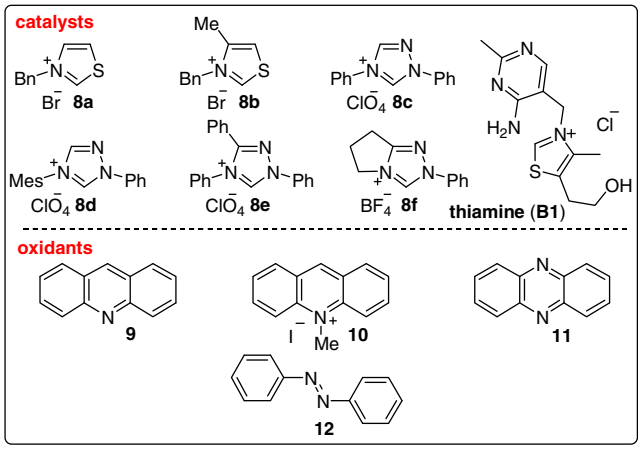
Table 1
Catalytic oxidative aldehyde esterification: initial studies





Entry	Cat.	Loading (mol %)	[O]	Solvent	Yield of 7[a] (%)	Yield of 6[a] (%)
1	**8a**	5	**9**	MeOH	0	31
2	**8a**	5	**9**	THF	10	41
3	**8a**	5	**10**	THF	0	<1
4	**8a**	5	**11**	THF	0	71
5	**8a**	5	**12**	THF	4	85
6	**8b**	5	**12**	THF	5	83
7	**B1**	5	**12**	THF	0	<1
8	**8c**	5	**12**	THF	0	1
9	**8d**	5	**12**	THF	0	0
10	**8e**	5	**12**	THF	0	4
11	**8f**	5	**12**	THF	5	2
12[b]	**8a**	5	**12**	THF	0	84
13[c]	**8a**	5	**12**	THF	0	50
14[d]	**8a**	2	**12**	THF	0	5
15[d]	**8a**	10	**12**	THF	0	81
16[d]	**8a**	10	**12**	MTBE	0	71
17[d]	**8a**	10	**12**	EtOAc	0	81
18[d]	**8a**	10	**12**	CH_2Cl_2	3	66

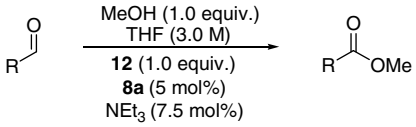
[a] Determined by ^{1}H NMR spectroscopy using either (*E*)-stilbene or 2,5-diphenylfuran as an internal standard.
[b] In the presence of DMAP (5 mol %) co-catalyst.
[c] NEt_3 used at 100 mol % levels.
[d] 1.0 M reaction concentration, 18 h.

The detection of significant levels of benzoin in this experiment prompted us to explore the use of alternative oxidants under otherwise identical conditions. While the *N*-methyl acridinium ion **10** proved ineffective, use of either phenazine (**11**) or azobenzene (**12**) allowed the formation of **6** in good to high (85%) yields, respectively (entries 3–5). A 4-methyl analogue of catalyst **8a** (i.e., **8b**) provided similar levels of performance (entry 6); however, thiamine (**B1**) and triazolium ion-based pre-catalysts **8c–f** proved essentially inactive under otherwise identical conditions (entries 7–11). This latter finding was somewhat surprising given the general utility of triazolium ion-based systems in a variety of organocatalytic transformations reported recently.[3]

With the optimal NHC pre-catalyst and oxidant in hand we subsequently examined the effect of an added nucleophilic co-catalyst (entry 12), catalyst/base loading (entries 13 and 14), concentration and solvent polarity on the efficacy of the process without identifying any one factor which improved the yield significantly.

Attention now turned to the question of reaction scope with respect to the aldehyde component (Table 2). Gratifyingly, aromatic aldehydes incorporating either electron

Table 2
Evaluation of substrate scope



Entry	Substrate	Product	*T* (°C)	*t* (h)	Yield[a] (%)
1	**13**	**21**	rt	24	97
2	**14**	**22**	40	24	83
3	**15**	**23**	rt	40	80
4	**16**	**24**	60	48	48
5	**17**	**25**	rt	40	46
6	**18**	**26**	40	40	77
7	**19**	**27**	rt	24	54[b]
8	**20**	**28**	40	48	16

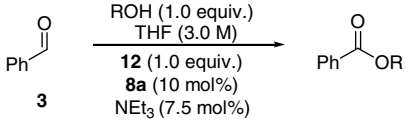
[a] Refers to isolated yield after chromatography.
[b] Determined by ^{1}H NMR using 2,5-diphenylfuran as an internal standard.

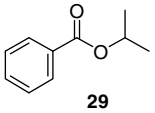
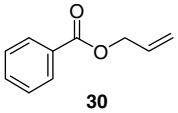
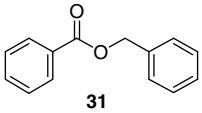
donating or electron withdrawing substituents were found to be compatible with the methodology at ambient temperature (entries 1, 3 and 5–8)—only the strongly deactivated substrates **14** and **16** required elevated temperatures of 40–60 °C (entries 2 and 4). Interestingly, *o*-substituted aldehydes provided the corresponding methyl esters in (reproducibly) higher yields than their *p*-substituted counterparts, the reason for which is unclear at this time. Cinnamaldehyde (**18**) and 2-naphthaldehyde (**19**) could also be esterified under the influence of thiazolium ion catalysis, however, aliphatic aldehydes such as hexanal (**20**) proved problematic, furnishing **28** in low yield.

The use of alternative alcohol nucleophiles was also investigated. We were pleased to find that the oxidative esterification was not confined to primary alcohols—isopropanol could be smoothly coupled with benzaldehyde to give **29** in good yield at ambient temperature.[17] Synthetically relevant allyl and benzyl esters **30** and **31** could also be similarly prepared (Table 3).

In summary, we have studied the oxidative esterification of aldehydes catalysed by N-heterocyclic carbenes. Optimal conditions[18] were identified under which aromatic and α,β-unsaturated aldehydes could be coupled efficiently with either a primary or secondary alcohol in the presence of a stoichiometric oxidant. Both activated and deactivated aldehydes can be esterified, however aliphatic aldehydes give poor results. Thiazolium catalysts proved superior to their triazolium analogues and can be employed at low loadings in conjunction with a single equivalent of the alcohol nucleophile at ambient temperature for the first time. We would contend that this convenient methodology represents a significant step forward for a process that had been regarded as little more than a mechanistic curiosity previously—and allows the possibility of the development of related synthetically useful coupling processes using alternative nucleophiles. Investigations along these lines are currently underway in our laboratory.

Table 3
Variation of the alcohol coupling partner



Entry	Product	Yield[a] (%)
1	 **29**	87
2	 **30**	76
3	 **31**	55

[a] Refers to isolated yield after chromatography.

Acknowledgements

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18. In a 5 cm^3 flask fitted with a stirring bar and a reflux condenser under an atmosphere of Ar (balloon), methanol (162 μL, 4.0 mmol) and triethylamine (42 μL, 0.3 mmol) were added via syringe to a solution of azobenzene (728 mg, 4.0 mmol), 3-benzyl-4-methylthiazolium bromide (54 mg, 0.20 mmol) and **14** (545 mg, 4.0 mmol) in THF (1.0 cm^3). The resulting solution was stirred at 40 °C for 24 h. The solution was then diluted with EtOAc (30 cm^3), washed with HCl (aq 0.2 M, 2 cm^3), water (2 cm^3) and brine (2 cm^3), respectively, and dried over $MgSO_4$. Removal of the solvent in vacuo and purification by column chromatography gave **22** as a pale yellow oil (551 mg, 83%). ^1H NMR ($CDCl_3$, 400 MHz) 7.28 (dd, $J = 12.0$, 2.0, 1H), 7.49 (app. dt, $J = 9.0$, 2.0, 1H), 7.00 (m, 2H), 3.91 (s, 3H), 3.93 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) 166.3, 158.6, 133.1, 131.2, 119.7, 119.5, 111.5, 55.5, 51.6. HRMS (ESI) calcd for [$C_9H_{10}O_3$+Na] requires 189.0528, found 189.0529.