Oxidative esterification of aldehydes with alcohols and phenols in air

Shuanghua Cheng[a], Jiuxi Chen[a], Wenxia Gao[a], Huile Jin[a], Jinchang Ding[a,b] and Huayue Wu[a]*

[a]*College of Chemistry and Materials Engineering, Wenzhou University, Wenzhou 325035, P. R. China*

[b]*Wenzhou Vocational and Technical College, Wenzhou, 325035, P. R. China*

Nucleophilic carbene-catalysed oxidative esterification of aldehydes with alcohols and phenols without additional oxidant under an air atmosphere has been achieved, which provides a metal-free new methodology for the oxidative esterification of aldehydes.

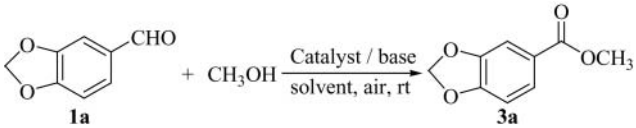
Keywords: oxidative esterification, alcohols, phenols, nucleophilic carbene

Direct transformation of aldehydes to esters under mild conditions is an extremely useful conversion in organic synthesis, particularly in the synthesis of natural products.[1–3] Several conversions using environmentally unacceptable complexes of different heavy metal oxidants such as rhenium,[4] rhodium,[5] ruthenium,[6] MnO_2,[7] pyridinium dichromate,[8] $[IrCl(cod)]_2$,[9] and the highly expensive silver[10] have been reported. The efficiency of this protocol has been enhanced by using reagents including hydrogen peroxide[11] as the principal oxidant coupled with V_2O_5[12] and titanosilicates.[13] Other oxidative esterification protocols involved in the presence of chlorites,[14] N-halosuccinimide,[15] $PhI(OAc)_2$[16] and by photochemical[17] as well as electrochemical means.[18] Connon and co-workers[19] reported direct oxidative esterification of aldehydes with alcohols in the presence of a stoichiometric oxidant catalysed by the *N-hetero*cyclic carbenes (NHCs) from thiazolium salts. Very recently, Cao and co-workers[20] reported that gold supported on nanocrystalline β-Ga_2O_3 was a versatile bifunctional catalyst for oxidative transformation of aldehydes into esters. However, most of the methods are associated with some drawbacks, which include the use of hazardous reagents, drastic reaction conditions, metal-catalyst and tedious work up procedure. Moreover, less attention has been paid to the esterification reaction of aldehydes with phenols. Thus, developing versatile approaches to the oxidative esterification reaction of aldehydes with alcohols or phenols is still a highly desired goal in organic synthesis.

Recently, we reported the palladium-catalysed aromatic esterification of aldehydes with organoboronic acids and molecular oxygen.[21] Here, we report the nucleophilic carbene-catalysed oxidative esterification reaction of aldehydes with alcohols and phenols without additional oxidant under an air atmosphere.

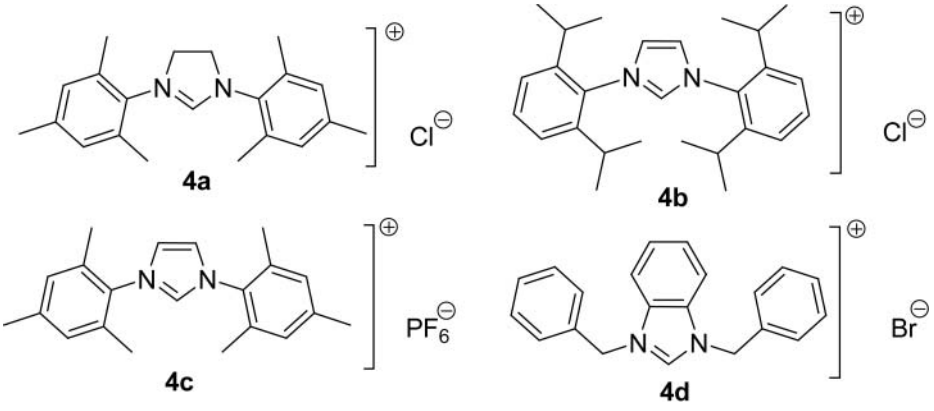
The model reaction of piperonal **1a** with methanol was conducted to screen for optimal reaction conditions. After careful screening, to our delight, a 67 % yield of methyl benzo[*d*][1,3]dioxole-5-carboxylate (**3a**) was obtained by employing the combination of **4a** as a precursor of an *N*-heterocyclic carbene (NHC) (15 mol %), and Cs_2CO_3 (2.0 equiv) in dry cyclohexane at 25 °C in air (Table 1, entry 9). Encouraged by this result, we further optimised the reaction conditions using other NHC precursors (Scheme 1). The

Table 1 Screening conditions[a]



Entry	Catalyst	Base/equiv	Solvent	Yield/%[b]
1	None	Cs_2CO_3 (2)	Cyclohexane	0
2	**4a**	None	Cyclohexane	0
3	**4a**	CsF (2)	Cyclohexane	40
4	**4a**	Na_2CO_3 (2)	Cyclohexane	<5
5	**4a**	K_2CO_3 (2)	Cyclohexane	57
6	**4a**	NaOH (2)	Cyclohexane	51
7	**4a**	DABCO(2)	Cyclohexane	<5
8	**4a**	Et_3N (2)	Cyclohexane	<5
9	**4a**	Cs_2CO_3 (2)	Cyclohexane	67
10	**4a**	Cs_2CO_3 (2)	Toluene	52
11	**4a**	Cs_2CO_3 (2)	Dioxane	50
12	**4a**	Cs_2CO_3 (2)	Methanol	58
13	**4a**	Cs_2CO_3 (2)	THF	12
14	**4a**	Cs_2CO_3 (2)	DMF	15
15	**4b**	Cs_2CO_3 (2)	Cyclohexane	<5
16	**4c**	Cs_2CO_3 (2)	Cyclohexane	<5
17	**4d**	Cs_2CO_3 (2)	Cyclohexane	15
18	**4a**	Cs_2CO_3 (1)	Cyclohexane	72
19	**4a**	Cs_2CO_3 (0.6)	Cyclohexane	80
20	**4a**	Cs_2CO_3 (0.2)	Cyclohexane	42

[a] All reactions were run with piperonal (60 mg, 0.4 mmol), methanol (48 μL, 1.2 mmol), catalyst (15 mol%) and base in 2 mL of dry solvent for 10 h at 25 °C in air.
[b] Isolated yields.



Scheme 1 Precursors of *N*-heterocyclic carbene.

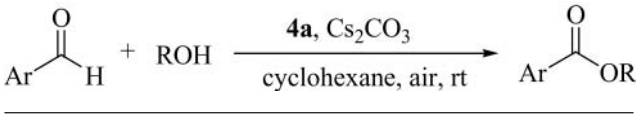
* Correspondent. E-mail: huayuewu@wzu.edu.cn

selected results, for catalysts, solvents and bases are listed in Table 1.

Reaction with **4d** as catalyst provided the corresponding methylester in 15% yield and **4b** and **4c** proved nearly inactive (Table 1, entries 15–17), so it was known to us that **4a** was the most active catalyst among those above (Table 1, entry 9). Among the screened solvents, toluene, methanol, dioxane, THF and DMF afforded products in 52%, 58%, 50%, 12% and 15% yields respectively (Table 1, entries 10–14). However, the reaction with cyclohexane as solvent gave product in 67% yield (Table 1, entry 9). Among Na_2CO_3, K_2CO_3, NaOH, CsF, Cs_2CO_3 and DABCO, Cs_2CO_3 is the best base, but reaction with NEt_3 as base could hardly provide the corresponding ester (entries 3–9). Subsequently, we examined the effect of the amount of base for the esterification reaction (Table 1, entries 18–20), and reaction with 0.6 equiv of Cs_2CO_3 as base provided the product in 80% yield. So we adopted the conditions with **4a** (15 mol %), and Cs_2CO_3 (0.6 equiv.) at 25 °C in air in the present protocol.

With the optimised conditions in hand, the reactions of different aldehydes with methanol were examined (Table 2). A series of substituted aromatic aldehydes with electron-donating or electron-withdrawing groups attached to the aromatic ring were investigated. Aldehydes with electron-donating groups such as piperonal **1a** and *p*-methylbenzaldehyde **1b** provided the corresponding methyl ester in 80 % and 75% yields respectively (Table 2, entries 1 and 6). Electron-withdrawing substituents on the aromatic ring of aldehyde decrease the yields, **1c**–**h** (Table 2, entries 7–12). Moreover, *o*-nitrobenzaldehyde **1f** (Table 2, entry 10) provided the corresponding product **3j** in 34% yield, which is lower than *m*-substituted (40 %, Table 2, entry 11) and *p*-substituted (51%, Table 2, entry 12) analogues which may be partly due to a steric hindrance effect.

Table 2 Esterification reactions of aldehydes with alcohols[a]



Entry	Ar	R	Product	Yield/%[b]
1	3,4-(OCH_2O)-C_6H_3 **1a**	CH_3	**3a**	80
2	**1a**	CH_3CH_2	**3b**	68
3	**1a**	$CH_3(CH_2)_4$	**3c**	50
4	**1a**	$(CH_3)_2CH(CH_2)_2$	**3d**	52
5	**1a**	$(CH_3)_2CH$	**3e**	57
6	*p*-MeC_6H_4 **1b**	CH_3	**3f**	75
7	*p*-ClC_6H_4 **1c**	CH_3	**3g**	59
8	*p*-BrC_6H_4 **1d**	CH_3	**3h**	70
9	2,4-$Cl_2C_6H_3$ **1e**	CH_3	**3i**	51
10	*o*-$NO_2C_6H_4$ **1f**	CH_3	**3j**	34
11	*m*-$NO_2C_6H_4$ **1g**	CH_3	**3k**	40
12	*p*-$NO_2C_6H_4$ **1h**	CH_3	**3l**	51

[a] All reactions were run with alcohols (1.2 mmol), aldehydes (0.4 mmol), **4a** (20.6 mg, 15 mol %) and Cs_2CO_3 (78 mg, 0.6 equiv) in 2 mL of dry cyclohexane for 10 hours at 25 °C in air.
[b] Isolated yields.

On the other hand, the use of other alcohols was investigated. In addition to ethanol, piperonal could be esterified with pentanol and *iso*-amyl alcohol (Table 2, entries 2–4). The secondary alcohol isopropanol also reacted with piperonal to give the ester **3e** in 57% yield (Table 2, entry 5).

Furthermore, the oxidative esterification reactions of piperonal with the phenols were also investigated under the same conditions. To our delight, **3m** and **3n** were obtained in 55% and 53% yields respectively (Scheme 2). This procedure represents a simple, direct method for the synthesis of aryl benzoate derivatives.

In summary, we have developed the direct oxidative esterification of aldehydes with alcohols and phenols catalysed by *N*-heterocyclic carbenes without the additional oxidant at ambient temperature under an air atmosphere. Investigations on the application of the protocol are currently underway in our laboratory.

Experimental

Chemicals and solvents were either used as purchased or purified by standard techniques. IR spectra were recorded on a Bruker-EQUINOX55 spectrometer. NMR spectroscopy was performed on a Bruker-300 spectrometer or Bruker-500 spectrometer using $CDCl_3$ as the solvent with tetramethylsilane (TMS) as an internal standard at room temperature. Chemical shifts are given in δ relative to TMS, the coupling constants *J* are given in Hz. Mass spectra (MS) was measured with a Thermo Finnigan LCQ-Advantage. Elemental analyses were carried out using a Carlo-Erba EA1112 instrument. Column chromatography was performed using EM Silica gel 60 (300–400 mesh).

General procedure

A Schlenk reaction tube was charged with aldehyde (0.4 mmol), **4a** (20.6 mg, 15 mol %), Cs_2CO_3 (78 mg, 0.6 equiv), alcohol (1.2 mmol) and 2 mL of dry cyclohexane in an air atmosphere, then the mixture was stirred for 10 hours at room temperature. After completion of the reaction, as indicated by TLC, the reaction mixture was extracted with ethyl acetate (3×10 mL), concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel to give the desired product **3**. The physical and spectroscpic data of the compounds **3a**–**n** are as follows.

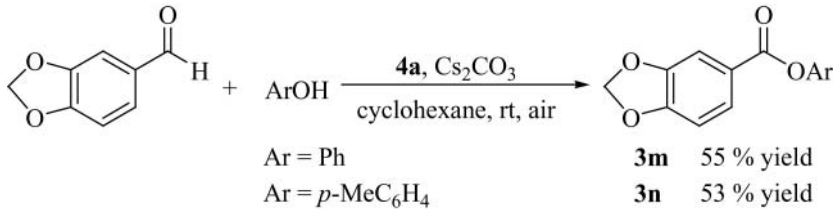
Methyl benzo[d][1,3]dioxole-5-carboxylate (**3a**)[22]: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.80 (s, 3H), 5.96 (s, 2H), 6.74–7.59 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 52.2, 101.9, 108.1, 109.7, 124.3, 125.5, 147.9, 151.7, 166.6.

Methyl benzo[d][1,3]dioxole-5-carboxylate (**3b**)[23]: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.37 (t, J = 7.1 Hz, 3H), 4.33 (q, J = 7.1 Hz, 2H), 6.02 (s, 2H), 6.81–7.67 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.3, 61.0, 101.9, 108.0, 109.6, 124.7, 125.4, 147.8, 151.6, 166.1.

Pentyl benzo[d][1,3]dioxole-5-carboxylate (**3c**)[24]: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.88–0.95 (m, 3H), 1.34–1.44 (m, 4H), 1.70–1.77 (m, 2H), 4.27 (t, J = 6.7 Hz, 2H), 6.03 (s, 2H), 6.82–7.67 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.1, 22.5, 28.4, 28.6, 65.2, 101.9, 108.1, 109.6, 124.7, 125.4, 147.8, 151.6, 166.2.

Isopentyl benzo[d][1,3]dioxole-5-carboxylate (**3d**)[25]: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.95–0.98 (m, 6H), 1.60–1.67 (m, 3H), 4.28–4.33 (m, 2H), 6.02 (s, 2H), 6.81–7.66 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 22.7, 25.4, 37.6, 63.7, 101.9, 108.1, 109.6, 124.7, 125.4, 147.8, 151.6, 166.2.

Isopropyl benzo[d][1,3]dioxole-5-carboxylate (**3e**)[26]: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.28 (d, J = 6.24 Hz, 6H), 5.10–5.18 (m, 1H), 5.95 (s, 2H), 6.75–7.59 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 22.0, 68.2, 101.7, 107.9, 109.5, 125.0, 125.2, 147.6, 151.4, 165.5.



Scheme 2 Reactions of piperonal with phenols.

Methyl 4-methylbenzoate (**3f**)[23]: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.33 (s, 3H), 3.82 (s, 3H), 7.15–7.19 (m, 2H), 7.84–7.87 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.6, 51.9, 127.4, 129.0, 129.6, 143.5, 167.2.

Methyl 4-chlorobenzoate (**3g**)[23]: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.93 (s, 3H), 7.42 (d, J = 8.4 Hz, 2H), 7.98 (d, J = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 52.2, 128.6, 128.7, 131.0, 139.4, 166.2.

Methyl 4-bromobenzoate (**3h**)[27]: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.83 (s, 3H), 7.47–7.51 (m, 2H), 7.79–7.83 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 52.2, 128.0, 129.0, 131.1, 131.7, 166.3.

Methyl 2,4-dichlorobenzoate (**3i**)[28]: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.94 (s, 3H), 7.29–7.83 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 52.5, 127.0, 128.3, 131.0, 132.5, 135.0, 138.3, 165.2.

Methyl 2-nitrobenzoate (**3j**)[29]: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.93 (s, 3H), 7.64–7.94 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 53.2, 123.9, 127.6, 129.8, 131.7, 132.9, 148.3, 165.8.

Methyl 3-nitrobenzoate (**3k**)[30]: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.00 (s, 3H), 7.64–8.88 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 52.5, 124.3, 127.1, 129.4, 131.6, 135.0, 148.0, 164.7.

Methyl 4-nitrobenzoate (**3l**)[29]: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.90 (s, 3H), 8.12–8.23 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 52.8, 123.5, 130.7, 135.5, 150.6, 165.2.

Phenyl benzo[d][1,3]dioxole-5-carboxylate (**3m**)[21]: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.07 (s, 2H), 6.90–7.86 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 102.2, 108.3, 110.1, 121.9, 123.6, 126.0, 126.4, 129.6, 148.1, 151.2, 152.4, 164.7.

p-Tolyl benzo[d][1,3]dioxole-5-carboxylate (**3n**): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.30 (s, 3H), 6.00 (s, 2H), 6.81–7.76 (m, 7H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.9, 101.9, 108.1, 109.9, 121.3, 123.6, 126.1, 129.9, 135.4, 147.9, 148.7, 152.1, 164.7. IR (KBr, cm^{-1}) 3422, 2904, 1719, 1611, 1494, 1267, 1218, 1164, 1107, 905, 756. ESI-MS: *m/z* (%): 256 ([M+H]$^+$, 100). Anal. Calcd for $C_{15}H_{12}O_4$: C, 70.31; H, 4.72; Found: C, 70.26; H, 4.78%.

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Electronic Supplementary Information

NMR spectra may be downloaded via http://www.ingentaconnect.com/content/stl/jcr/supp-data

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