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N-Heterocyclic carbene catalyzed esterification of aromatic aldehydes with alcohols under aerobic conditions†

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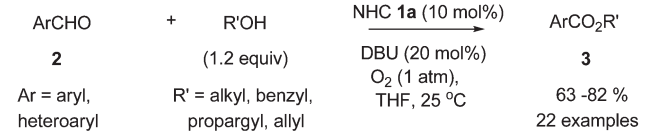
A simple, organocatalytic procedure for the direct oxidative esterification of a variety of aromatic aldehydes with alcohols has been described that affords the corresponding aromatic esters in high yields. The method employs *N*-heterocyclic carbenes as catalysts and molecular O_2 as an oxidant under ambient conditions.

Aromatic esters are important and useful structural elements finding tremendous applications in a wide range of fields encompassing solvents, lubricants, plasticizing agents, perfumes, pharmaceuticals, agrochemicals, *etc.*[1] Aromatic esters are generally prepared using one of these methods: Fischer esterification,[2] Mitsunobu reaction,[3] Favorskii rearrangement,[4] Baeyer–Villiger oxidation[5] and Pinner reaction.[6] In addition, the halogen–metal exchange of aryl halides with either carbon monoxide,[7] ethyl chloroformate[8] or DMF[9] has emerged as an alternative method of synthesis. However, these methods have several limitations such as the reversibility of the conventional esterification reaction, the use of expensive Pd catalysts, the handling of toxic CO gas and variable yields often obtained in some cases. In this respect, a new strategy involving the direct oxidative esterification of aromatic aldehydes to aromatic esters under mild conditions has assumed special importance in the synthesis of natural products.[10] This useful transformation generally involves an oxidative pathway, often requiring more than stoichiometric amounts of oxidants (*e.g.*, oxone,[11a] SnO_2/SBA–H_2O_2,[11b] hypervalent iodine,[11c] pyridinium bromide perbromide,[11d] V_2O_5–H_2O_2[11e] and acetone cyanohydrin/base[11f]) and long reaction times. In addition, some of these reagents are less effective for substrates with electron-withdrawing groups.

In recent years, *N*-heterocyclic carbenes (NHCs) have emerged as an important and powerful class of organocatalysts[12] with tremendous applications in a variety of synthetic transformations and as versatile ligands[13] in transition metal catalysis. Recently, NHC catalyzed oxidative esterification of aldehydes with alcohols,[14] alkyl halides[15] and boronic acids[16] has been reported. However, the use of heavy metals (Pd, Mn, Fe, *etc.*) as oxidants, the use of excess alkyl halides and bases and higher reaction temperatures are some of the drawbacks associated with them.[14,15] Herein, we report the NHC catalyzed direct esterification of aromatic aldehydes (**2**) with a variety of alcohols using a catalytic amount of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in low to high yields under ambient conditions (Scheme 1).

Fig. 1 shows the NHC precatalysts **1a–f** that were examined for the oxidative esterification of aldehydes. Catalysts **1a–d** and **1f** were prepared following a modified procedure[17] while **1e** was purchased from Aldrich, USA.

When 4-nitrobenzaldehyde was subjected to oxidative esterification with MeOH (1 equiv.) in the presence of **1a** (10 mol%) and DBU (20 mol%) as a base in THF under an N_2 atmosphere at room temperature, no trace of ester **3f** was formed. When the same reaction was conducted in open air, **3f** was indeed isolated in low yields (45%). However, a dramatic increase in yield (70%) was realized when the experiment was carried out under an O_2 atmosphere (O_2 balloon, 1 atm). Out of several NHC catalysts screened, imidazolium salt **1a** showed higher catalytic activity,[18] providing the desired product **3f** in 70% yield, while **1b** and **1c** gave **3f** in moderate yields (Table 1). However, other catalysts **1d**, **1e** and **1f** were found to be less effective for the esterification reaction. Also, either increasing the NHC catalyst quantity from 10 mol% up to 20 mol% or increasing the temperature from 25 °C to 50 °C did not improve the yield of the product. Surprisingly, increasing the amount of alcohol from 1 equiv. to 1.2 equiv. resulted in an improved yield (76%) of the ester product. However,



Scheme 1 NHC catalyzed direct esterification of aromatic aldehydes with alcohols.

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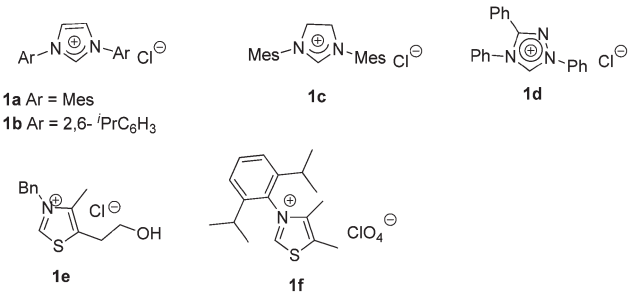
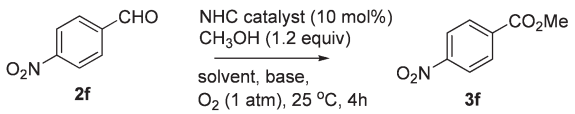


Fig. 1 *N*-Heterocyclic carbene precatalysts screened for the oxidative esterification.

further increase in the amount of alcohol (3 equiv.) had no effect on the yield. Among several solvents and bases screened for the reaction, THF and DBU were found to be the most effective (Table 1).

In order to gauge the scope and generality of the reaction, a variety of aromatic aldehydes having both electron-donating and withdrawing groups were screened.[20] The results of such studies are presented in Table 2. As can be seen, several aromatic aldehydes underwent oxidative esterification with methanol smoothly under mild conditions. Remarkably, substrates with electron-withdrawing groups showed higher reactivity than those with electron-releasing substituents. Heteroaromatic aldehydes such as 3-pyridine carboxaldehyde and furfural also gave the corresponding esters in high yields. In the case of cinnamaldehydes, an inseparable mixture of saturated and unsaturated methyl esters were obtained,[19] while aliphatic aldehydes failed to undergo this reaction, which may be a limitation.

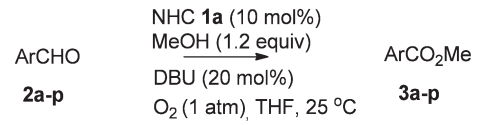
Table 1 Oxidative esterification of 4-nitrobenzaldehyde: optimization studies[a]



Entry	Catalyst (10 mol%)	Base (20 mol%)	Solvent	Yield of **3f** (%)[b]
1	No catalyst	DBU	THF	—
2	**1a**	DBU	THF	76 (45)[c]
		DBU	CH_2Cl_2	60
		DBU	CH_3CN	58
		DBU	DMSO	27
		DBU	Toluene	60
3	**1a**	K_2CO_3	THF	56
		Et_3N	THF	40
		^nBuLi	THF	16
		KO^tBu	THF	12
4	**1b**	DBU	THF	36
5	**1c**	DBU	THF	54
6	**1d**	DBU	THF	14
7	**1e**	DBU	THF	27
8	**1f**	DBU	THF	26

[a] Reaction conditions: 4-nitrobenzaldehyde (5 mmol), methanol (6 mmol), NHC catalyst (10 mol%), base (20 mol%), 25 °C, O_2 (1 atm), 4 h. [b] Isolated yield after column chromatographic purification. [c] In air.

Table 2 Oxidative esterification of aryl aldehydes: substrate scope[a]



Entry	Substrate, Ar **2a–p**	Time (h)	Yield of **3a–p** (%)[b]
a	*m*-Tolualdehyde	10	78
b	4-OMe-benzaldehyde	30	72
c	3,4-$(OMe)_2$-benzaldehyde	36	70
d	3,4,5-$(OMe)_3$-benzaldehyde	36	65
e	4-SMe-benzaldehyde	28	68
f	4-NO_2-benzaldehyde	4	76
g	3-NO_2-benzaldehyde	10	82
h	4-Br-benzaldehyde	14	78
i	3-Br-benzaldehyde	18	72
j	4-Cl-benzaldehyde	18	79
k	3-Cl-benzaldehyde	14	70
l	4-F-benzaldehyde	10	76
m	4-CF_3-benzaldehyde	7	69
n	4-CN-benzaldehyde	6	72
o	3-Pyridinecarboxaldehyde	20	76
p	Furfural	24	63

[a] Reaction conditions: aldehyde (5 mmol), methanol (6 mmol), NHC **1a** (10 mol%), base (20 mol%), 25 °C, O_2 (1 atm). [b] Isolated yield after column chromatographic purification.

A wide range of alcohols were then examined for oxidative esterification with 4-nitrobenzaldehyde as the substrate; the results are summarized in Table 3.

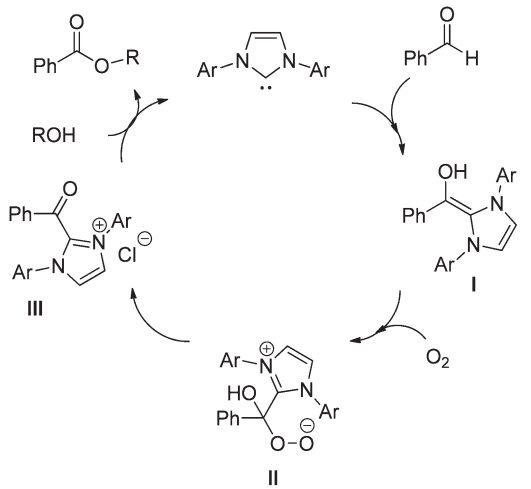
Both primary and secondary alcohols including allylic, propargylic and benzylic alcohols underwent this reaction to give the corresponding esters in excellent yields.

In order to gain insight into the mechanistic details of the reaction, the following experiments were conducted: (i) for **2f**, no esterification took place under an N_2 atmosphere while at the same time a low yield (45%) was obtained in air, suggesting the necessity of O_2 for realizing higher yields; (ii) the esterification reaction between *p*-nitrobenzoic acid and methanol did not proceed under the reaction conditions, confirming the absence of carboxylic acid as the intermediate; (iii) when (*S*) or (*R*)-tetrahydrofuran-3-ol was used as the alcohol partner, the retention of the configuration was obtained, thereby confirming the incorporation of alcohol oxygen into the ester moiety; (iv) when

Table 3 Oxidative esterification of 4-nitrobenzaldehyde: alcohol scope[a]

Entry	Alcohol components	Time (h)	Yield of ester (%)[b]
1	Ethanol	4	80
2	2-Propanol	7	76
3	Benzyl alcohol	4	80
4	Allyl alcohol	4	76
5	Propargyl alcohol	5	82
6	(*S*)-Tetrahydrofuran-3-ol[c]	16	66 (99% ee)

[a] Reaction conditions: 4-nitrobenzaldehyde (5 mmol), alcohol (6 mmol), NHC **1a** (10 mol%), DBU (20 mol%), 25 °C, O_2 (1 atm). [b] Isolated yield after column chromatographic purification. [c] The (*R*)-tetrahydrofuran-3-ol gave the corresponding ester in 64% yield and 99% ee.



Scheme 2 Probable mechanistic pathway for the oxidative esterification.

1 equiv. of sodium methoxide was used as the alcohol component, the corresponding methyl ester was obtained in 46% yield, suggesting the possibility of alkoxide anion formation as the intermediate. Based on this result and on precedents set by the literature,[16,18] we have proposed a catalytic cycle in which the peroxy anion **II**[16] formed from the reaction between the Breslow intermediate **I** and O_2 is depicted as the key intermediate in the esterification process (Scheme 2). Upon decomposition this results in the formation of the acyl intermediate **III**.[16b] Subsequently, the alkoxide ion[18] formed from the alcohol reacts with **III** to give the corresponding ester with the liberation of NHC.

In conclusion, we have developed a simple organocatalytic procedure for the direct oxidative esterification of aromatic aldehydes with alcohols employing NHC as a catalyst and oxygen as an oxidant at ambient conditions. The reaction is simple to carry out and the products are obtained in high yields and purity from stoichiometric amounts of alcohol and catalytic amounts of organic base.

Acknowledgements

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References

1 (*a*) *The Art of Drug Synthesis*, ed. D. S. Johnson and J. J. Li, John Wiley and Sons, Hoboken, NJ, 2007; (*b*) A. Zapf and M. Beller, *Top. Catal.*, 2002, **19**, 101; (*c*) J. Stetter and F. Lieb, *Angew. Chem., Int. Ed.*, 2000, **39**, 1724.

2 (*a*) E. Fischer and A. Speier, *Ber. Dtsch. Chem. Ges.*, 1895, **28**, 3252; (*b*) R. C. Larock, *Comprehensive Organic Transformations*, VCH, New York, USA, 2nd edn, 1989, pp. 881; (*c*) S. P. Bew, D. L. Hughes and S. V. Sharma, *J. Org. Chem.*, 2006, **71**, 7881.

3 O. Mitsunobu, *Synthesis*, 1981, 1.

4 A. E. Favorskii, *J. Prakt. Chem.*, 1895, **51**, 533.

5 A. Baeyer and V. Villiger, *Ber. Dtsch. Chem. Ges.*, 1899, **32**, 3625.

6 A. Pinner and F. Klein, *Ber. Dtsch. Chem. Ges.*, 1883, **16**, 1643.

7 (*a*) D. A. Watson, X. Fan and S. L. Buchwald, *J. Org. Chem.*, 2008, **73**, 7096; (*b*) J. R. Martinelli, D. A. Watson, D. M. M. Freckmann, T. E. Barder and S. L. Buchwald, *J. Org. Chem.*, 2008, **73**, 7102; (*c*) R. H. Munday, J. R. Martinelli and S. L. Buchwald, *J. Am. Chem. Soc.*, 2008, **130**, 2754; (*d*) X. Wu, H. Neumann and B. Matthlas, *ChemCatChem*, 2010, **2**, 509; (*e*) W. Yang, W. Han, W. Zhang, L. Shan and J. Sun, *Synlett*, 2011, 2253; (*f*) Z. Xin, T. M. Gogsig, A. T. Lindhardt and T. Skrydstrup, *Org. Lett.*, 2012, **14**, 284.

8 L. D. Bratton, H. Huh and R. A. Bartsch, *J. Heterocycl. Chem.*, 2000, **37**, 2599.

9 S. Ushijima, K. Moriyama and H. Togo, *Tetrahedron*, 2012, **68**, 4701.

10 (*a*) E. J. Corey, N. W. Gilman and B. E. Ganem, *J. Am. Chem. Soc.*, 1968, **90**, 5616; (*b*) P. Sundararaman, E. C. Walker and C. Djerassi, *Tetrahedron Lett.*, 1978, **19**, 1627; (*c*) P. J. Garegg, L. Olcson and S. Oscarson, *J. Org. Chem.*, 1995, **60**, 2200; (*d*) T. Ogawa and M. Matsui, *J. Am. Chem. Soc.*, 1976, **98**, 1629; (*e*) K. Lee, H. Kim and J. Hong, *Angew. Chem., Int. Ed.*, 2012, **51**, 5735.

11 (*a*) B. R. Travis, M. Sivakumar, G. O. Hollist and B. Borhan, *Org. Lett.*, 2003, **5**, 1031; (*b*) G. Quian, Z. Rui, D. Ji, G.-M. Lu, Y.-X. Qi and J.-S. Suo, *Chem. Lett.*, 2004, **33**, 834; (*c*) N. N. Karade, V. H. Budhewar, A. N. Katkar and G. B. Tiwari, *ARKIVOC*, 2006, **xi**, 162; (*d*) S. Sayama and T. Onami, *Synlett*, 2004, 2739; (*e*) R. Gopinath and B. K. Patel, *Org. Lett.*, 2000, **2**, 577; (*f*) I. V. P. Raj and A. Sudalai, *Tetrahedron Lett.*, 2005, **46**, 8303.

12 (*a*) J. L. Moore and T. Rovis, *Top. Curr. Chem.*, 2009, **291**, 77; (*b*) E. M. Phillips, A. Chan and K. A. Scheidt, *Aldrichimica Acta*, 2009, **42**, 55; (*c*) V. Nair, S. Vellalath and B. P. Babu, *Chem. Soc. Rev.*, 2008, **37**, 2691; (*d*) D. Enders, O. Niemeier and A. Henseler, *Chem. Rev.*, 2007, **107**, 5606; (*e*) N. Marion, S. Diez-Gonzalez and S. P. Nolan, *Angew. Chem., Int. Ed.*, 2007, **46**, 2988; (*f*) K. Zeitler, *Angew. Chem., Int. Ed.*, 2005, **44**, 7506; (*g*) D. Enders and T. Balensiefer, *Acc. Chem. Res.*, 2004, **37**, 534.

13 (*a*) S. Diez-Gonzalez, N. Marion and S. P. Nolan, *Chem. Rev.*, 2009, **109**, 3612; (*b*) S. Wurtz and F. Glorius, *Acc. Chem. Res.*, 2008, **41**, 1523; (*c*) E. A. B. Kantchev, C. J. Obrien and M. G. Organ, *Angew. Chem., Int. Ed.*, 2007, **46**, 2768; (*d*) S. Diez-Gonzalez and S. P. Nolan, *Coord. Chem. Rev.*, 2007, **251**, 874; (*e*) F. Glorius, *N-Heterocyclic carbenes in Transition Metal Catalysis*, Springer, Berlin, 2007; (*f*) S. P. Nolan, *N-Heterocyclic carbenes in Synthesis*, Wiley-VCH, Weinheim, Germany, 2006.

14 (*a*) S. De Sarkar, S. Grimme and A. Studer, *J. Am. Chem. Soc.*, 2010, **132**, 1190; (*b*) S. De Sarkar and A. Studer, *Angew. Chem., Int. Ed.*, 2010, **48**, 9266; (*c*) C. A. Rose and K. Zeitler, *Org. Lett.*, 2010, **12**, 4552; (*d*) B. E. Maki, A. Chan, E. M. Phillips and K. A. Scheidt, *Tetrahedron*, 2009, **65**, 3102; (*e*) C. Noonan, L. Baragwanath and S. J. Connon, *Tetrahedron Lett.*, 2008, **49**, 4003; (*f*) B. E. Maki and K. A. Scheidt, *Org. Lett.*, 2008, **10**, 4331; (*g*) B. E. Maki, A. Chan, E. M. Phillips and K. A. Scheidt, *Org. Lett.*, 2007, **9**, 371; (*h*) H. Inoue and K. Higashiura, *J. Chem. Soc., Chem. Commun.*, 1980, 549; (*i*) R. S. Reddy, J. N. Rosa, L. F. Veiros, S. Caddick and P. M. P. Gois, *Org. Biomol. Chem.*, 2011, **9**, 3126.

15 (*a*) Y. C. Xin, S. H. Shi, D. D. Xie, X. P. Hui and P. F. Xu, *Eur. J. Org. Chem.*, 2011, 6527; (*b*) B. Maji, S. Vedachalan, X. Ge, S. Cai and X.-W. Liu, *J. Org. Chem.*, 2011, **76**, 3016.

16 (*a*) P. Arde, B. T. Ramanjaneyulu, V. Reddy, A. Saxena and V. Anand, *Org. Biomol. Chem.*, 2012, **10**, 848; (*b*) J.-J. Meng, M. Gao, Y.-P. Wei and W.-Q. Zhang, *Chem.–Asian J.*, 2012, **7**, 872.

17 (*a*) A. J. Arduengo, R. Krafczyk, R. Schmutzler, H. A. Craig, J. R. Goerlich, W. J. Marshall and M. Unverzagt, *Tetrahedron*, 1999, **55**, 14523; (*b*) M. Scholl, S. Ding, C. W. Lee and R. H. Grubbs, *Org. Lett.*, 1999, **1**, 953; (*c*) D. Enders, K. Breuer, U. Kallfass and T. Balensiefer, *Synthesis*, 2003, **8**, 1292; (*d*) L. Benhamou, E. Chardon, G. Lavigne, S. Bellemin-laponnaz and V. Cesar, *Chem. Rev.*, 2011, **111**, 2705.

18 E. M. Phillips, M. Riedrich and K. A. Scheidt, *J. Am. Chem. Soc.*, 2010, **132**, 13179.

19 B. E. Maki, A. Chan and K. A. Scheidt, *Synlett*, 2008, 1306.

20 **General experimental procedure for esterification of aromatic aldehydes:** to a flame-dried round bottom flask equipped with a magnetic stir bar was added imidazolium salt **1a** (10 mol%), DBU (20 mol%) and THF (10 mL). The flask was evacuated and the contents were covered with molecular oxygen in a balloon. The resultant reaction mixture was kept stirring at 25 °C for 45 min. To this mixture was added aromatic aldehydes **2a–p** (5 mmol) and alcohol (6 mmol) successively. It was allowed to stir at 25 °C. After completion of the reaction (monitored by TLC), THF was evaporated, H_2O (50 mL) was added and the mixture was extracted with EtOAc (3 × 50 ml). The combined organic layers were dried over anhyd. Na_2SO_4 and concentrated to give crude ester, which was purified by silica gel-packed column chromatography to obtain pure esters, **3a–p**. Spectral data for (*S*)-tetrahydrofuran-3-yl 4-nitrobenzoate: **Yield**: 66%; colorless gum; $[\alpha]_D^{25}$ −31.24 (c 1.2, CH_2Cl_2) (ref. 19 $[\alpha]_D^{25}$ +31.26 (c 1, CH_2Cl_2) for the corresponding (*R*)-enantiomer); IR ($CHCl_3$): 720, 878, 1086, 1106, 1122, 1529, 1604, 1718, 2877, 2933, 3076 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.14–2.21 (m, 1H), 2.29–2.43 (m, 1H), 3.91–4.07 (m, 4H), 5.57–5.60 (m, 1H), 8.21 (d, J = 8.8 Hz, 2H), 8.30 (d, J = 8.8 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 32.8, 66.9, 72.9, 76.4, 123.5, 130.7, 135.2, 150.7, 164.1; **Analysis**: $C_{11}H_{11}NO_5$ requires C 55.70, H 4.67, N 5.90%, found C 55.62, H 4.51, N 5.79%.

