Organic &
Biomolecular
Chemistry

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 848

www.rsc.org/obc

PAPER

N-Heterocyclic carbene catalysed aerobic oxidation of aromatic aldehydes to aryl esters using boronic acids†

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Received 13th September 2011, Accepted 19th October 2011
DOI: 10.1039/c1ob06566a

The organocatalytic behavior of *N*-heterocyclic carbenes in the aerobic oxidation of aromatic aldehydes to esters with boronic acids has been explored. This transition metal-free protocol allows access to a wide variety of aromatic esters in good to excellent yields under mild reaction conditions.

Although the concept of organocatalysis has been utilised since the beginnings of chemistry, the applications of organocatalysts in organic transformations and asymmetric synthesis have been realised to a great extent in the past two decades.[1] *N*-Heterocyclic carbenes (NHCs) have contributed in this revolution significantly due to their unique reactivity towards carbonyl group activation.[2] The umpolung reactivity of NHCs has been explored in many organic transformations employing a variety of acyl anion acceptors.[3] Recently, the utility of NHCs has been extended to some redox reactions[4] and oxidation reactions where NHC was used in combination with molecular oxygen[5] or carbon dioxide[6] or with an organic oxidant.[7]

The ester functionality has been recognised as an important synthetic target because it serves as a building block for a number of natural products and active pharmaceutical ingredients (APIs).[8] Traditional methods for the construction of the ester functionality include acid catalysed esterification and transesterification.[9] Alternative methods involve Lewis acid catalysed esterification,[10] Baeyer–Villiger oxidation,[11] esterification with hypervalent iodine reagents,[12] organocatalytic esterification[13] and transition metal catalysed coupling reactions.[14] Recently, Wu's group has reported palladium catalysed aromatic esterification of aldehydes with boronic acids and molecular oxygen.[15] Though most of the functional groups were tolerated, this methodology was performed at harsh conditions (120 °C) and the products were obtained in low yields (5–68%). Gois' group has reported a modified procedure, in which palladium was replaced with iron, and by using this protocol a variety of aryl esters could be prepared in moderate to good yields at elevated temperature (90 °C).[16] However, since NHC catalysed oxidative esterification of aryl aldehydes with alkyl halides or alcohols has been well documented in the literature,[5–7] we believed that NHC itself, without any assistance from a metal catalyst, would promote the aerobic oxidation of aryl aldehydes in the presence of boronic acids to furnish the corresponding esters.

We became interested in exploring the organocatalytic activity of NHCs in this particular aerobic oxidation reaction using a few commercially available *N*-heterocyclic carbene precursors **1–4** (Fig. 1).

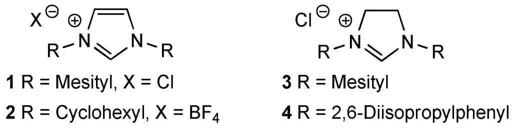

Fig. 1 NHC precursors.

We began the optimisation studies using *p*-chlorobenzaldehyde (**5**) and phenylboronic acid (**6**) as model substrates (Table 1). The initial experiments on the reaction between **5** and **6** under aerobic conditions were discouraging as no desired product (**7**) was obtained using either **1** or **2** (10 mol%) at RT (Entries 1 and 2, Table 1). Surprisingly, when the same reaction was performed at RT in toluene using **3** as a catalyst and Cs_2CO_3 as a base, **7** was isolated in 64% yield (Entry 3).

Encouraged by this result, further optimisation experiments were carried out by employing 10 mol% of **3** or **4** as a catalyst (Entries 3–19). In all the cases, ester **7** was formed in moderate to excellent yields and, in most of the cases, **4** was found to be more active than **3**. Use of a slight excess of aldehyde helped in improving the yield of **7** considerably (Entries 17–19). No product was obtained when the reaction was carried out in the absence of NHC. It was also observed that 1.5 equivalent of base is essential to carry out this transformation. Based on the above observations, the optimal reaction was found to be the reaction where the ester **7** was obtained almost in quantitative yield using 1.3 equivalent of **5** with respect to **6** in the presence of 10 mol% of **4** (Entry 17).

To generalise this synthetic methodology, the aerobic oxidative esterification of **5** with a variety of boronic acids was evaluated under the optimised reaction conditions and the results are summarised in Table 2.

It is apparent from Table 2 that boronic acids with various substituents having different electronic and steric properties reacted smoothly with **5** under the given reaction conditions and produced the corresponding aryl esters in good to excellent yields.

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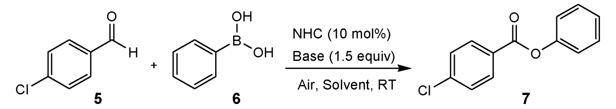
† Electronic supplementary information (ESI) available: Experimental procedures and characterisation data. See DOI: 10.1039/c1ob06566a

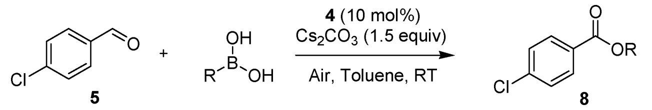
Table 1 Optimisation of reaction conditions[a]

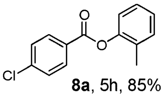


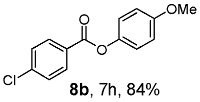
Entry	NHC	Base	Solvent	Time [h]	Yield [%][b]
1	**1**	DBU	Toluene	24	0
2	**2**	Cs_2CO_3	Toluene	24	0
3	**3**	Cs_2CO_3	Toluene	6	64
4	**3**	Cs_2CO_3	Dioxane	8	58
5	**3**	Cs_2CO_3	THF	8	60
6	**3**	Cs_2CO_3	DCE	8	28
7	**3**	Cs_2CO_3	MeCN	8	38
8	**3**	Cs_2CO_3	DME	8	56
9	**3**	KO^{t}Bu	Toluene	12	48
10	**3**	DBU	Toluene	8	53
11	**3**	NaH	Toluene	8	24
12	**3**	DBU	THF	8	45
13	**4**	Cs_2CO_3	THF	5	50
14	**4**	Cs_2CO_3	Dioxane	5	64
15	**4**	Cs_2CO_3	Toluene	6	75
16	**4**	Cs_2CO_3	DMF	5	19
17[c]	**4**	**Cs_2CO_3**	**Toluene**	**5**	**99**
18[d]	**4**	Cs_2CO_3	Toluene	5	95
19[e]	**4**	Cs_2CO_3	Toluene	5	86

[a] Reaction conditions: **5**/**6** = 1/1.1, 0.06 M of **5** in solvent, RT = 31 °C. [b] Isolated yield. [c] **5**/**6** = 1.3/1. [d] **5**/**6** = 1.2/1. [e] **5**/**6** = 1.1/1.

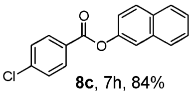
Table 2 Oxidative esterification of **5** with boronic acids[a]

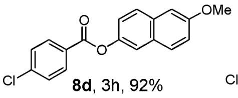



8a, 5h, 85%

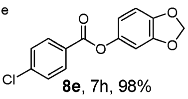


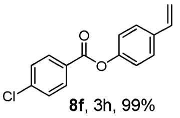
8b, 7h, 84%

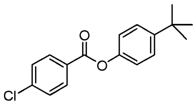

8c, 7h, 84%

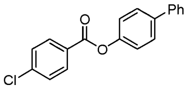


8d, 3h, 92%

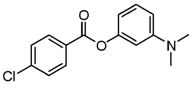

8e, 7h, 98%


8f, 3h, 99%

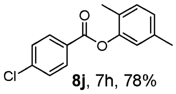

8g, 3h, 86%

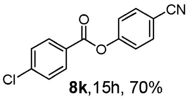


8h, 7h, 90%

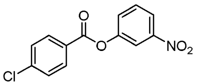


8i, 12h, 80%

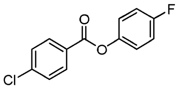

8j, 7h, 78%



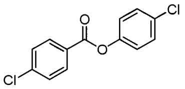
8k,15h, 70%



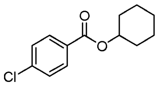
8l, 15h, 68%



8m, 45h, 88%[b]

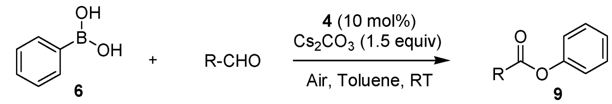


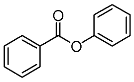
8n, 6h, 95%[c]

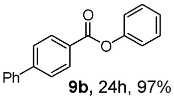

8o, 30h, 0%

[a] Reaction conditions: **5**/R–B(OH)$_2$ = 1.3/1, 0.06 M of **5** in toluene, RT = 31–33 °C. [b] Conversion started after 24 h. [c] Performed at 60 °C.

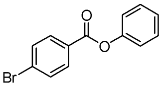
Table 3 Substrate scope of the oxidative esterification reaction of aldehydes with phenylboronic acid[a]



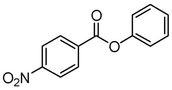

9a, 6h, 86%



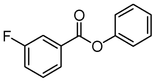
9b, 24h, 97%



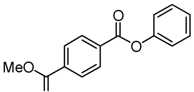
9c, 6h, 99%



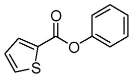
9d, 6h, 95%



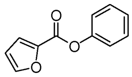
9e, 6h, 90%



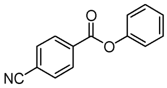
9f, 3h, 96%



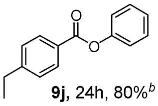
9g, 34h, 82%

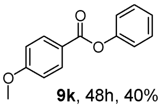


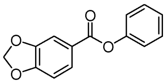
9h, 24h, 60%

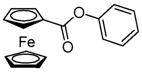


9i, 2 h, 93%

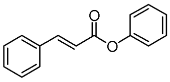

9j, 24h, 80%[b]

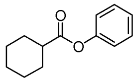

9k, 48h, 40%[b]


9l, 24 h, 75%[b]



9m, 24h, 33%[b]


9n, 24h, 25%[b]


9o, 48h, 0%[b]

[a] Reaction conditions: R–CHO/R–B(OH)$_2$ = 1.3/1, 0.06 M of R–CHO in toluene, RT = 31–33 °C. [b] Performed at 60 °C.

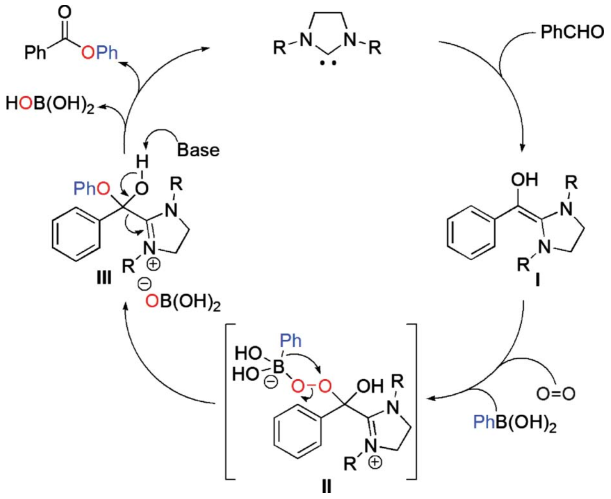
Electron rich boronic acids (Examples **8b**, **8d**, **8e**, **8g** and **8i**) reacted faster than electron deficient boronic acids (Examples **8k**, **8l**, **8m** and **8n**) as expected. Interestingly, esters were obtained in excellent yields in the cases of other activated boronic acids (Examples **8c**, **8f** and **8h**). Sterically hindered boronic acids (Examples **8a** and **8j**) also underwent smooth conversion under standard conditions. It was observed that this transformation is applicable only for aromatic boronic acids as cyclohexylboronic acid (Example **8o**) failed to react with **5** even at 80 °C.

In order to explore the significance of this transformation further, phenylboronic acid (**6**) was treated with different aromatic and heteroaromatic aldehydes under standard conditions and the results are tabulated in Table 3.

Except in a few cases, aromatic esters were obtained in modest to excellent yields. The reactivity of the aldehyde was greatly influenced by the electronic and steric properties of the substituents attached to it. Electron poor aldehydes reacted at a faster rate when compared to electron rich aldehydes. For example, *p*-cyanobenzaldehyde was converted to its corresponding ester **9i** in 93% yield in just 2 h. Other electron poor aldehydes such as *p*-nitrobenzaldehyde and methyl-4-formyl benzoate reacted with **6** efficiently and provided esters **9d** and **9f** in 95% and 96% yields respectively. But, electron rich aldehydes (Examples **9j–9l**) did not react with **6** at RT, but were converted to the esters in reasonably good yields at 60 °C. Activated aldehydes such as *p*-phenylbenzaldehyde and *p*-bromobenzaldehyde were oxidised to their corresponding esters in excellent yields at RT (Examples **9b** and **9c**). It is also evident from Table 3 that the substrate scope was not limited to aromatic aldehydes as heteroaromatic aldehydes (Examples **9g** and **9h**) could also be converted to esters in moderate to good yields. Ferrocene carboxaldehyde reacted at a much slower rate and the ester **9m** was obtained in only 33% yield even at

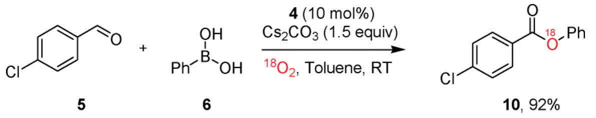
60 °C. In the case of cinnamaldehyde, a considerable amount of cinnamic acid was formed during the reaction. As a result, ester **9n** was isolated only in 25% yield. Since the reaction is carried out under basic conditions, aliphatic aldehydes could not be used as substrates. For example, cyclohexane carboxaldehyde did not give **9o** but decomposed under the given reaction conditions.

In order to comprehend the mechanism in detail, the reaction between **5** and **6** under standard reaction conditions was carefully monitored by TLC at equal time intervals. Interestingly, phenol was not detected during the course of the reaction, which is in parallel with the findings reported by Gois' group.[16] Moreover, phenol was not at all formed when the reaction was conducted in the absence of aldehyde, without changing other parameters. Although, NHC-metal catalysed oxidative esterification of aldehydes with phenol at elevated temperature has been reported very recently,[17] we strongly believe that phenol is not involved as an intermediate in our methodology based on the above experimental observations. To obtain a better understanding of this transformation, an experiment was run using **5** and phenol under optimal aerobic conditions, but the ester **7** was obtained only in 18% yield even after stirring the reaction for a long period (over 24 h). Addition of 1 equivalent of boric acid to the reaction mixture helped in improving the yield of **7** but not significantly (28% yield after 24 h).[18] But, as discussed earlier, the reaction of phenylboronic acid with **5** under the same conditions provided **7** in quantitative yield in less than 5 h (Entry 17, Table 1). This clearly indicates a different kind of mechanism is operating in the boronic acid case, without the involvement of phenol as an intermediate. Based on the above experimental observations, a plausible mechanism has been proposed (Scheme 1). We presume that the intermediate **II** is formed by the reaction of **I** with oxygen and boronic acid, and decomposes rapidly to **III** *i.e.*, transfer of the phenyl group to the peroxy linkage and formation of the borate anion, both are probably occurring in a concerted manner. Finally, intermediate **III** expels the NHC along with the ester and boric acid.



Scheme 1 Plausible mechanism for the oxidative esterification.

To confirm the participation of atmospheric oxygen in this transformation, an isotopic labelling experiment was conducted using $^{18}O_2$ (Scheme 2). The HRMS spectrum clearly showed the presence of the ester **10** (calcd for $C_{13}H_9ClO^{18}O$ 235.0412 [M + H], found 235.0419). The EI MS spectrum also showed a strong peak at m/z 234.91, which is attributed to the $[M + H]^+$ ion of ester **10**. The fragmentation pattern showed the base peak at m/z 139.03 (100%), which could be attributed to the $[ClC_6H_4CO]^+$ fragment. An additional peak appeared at m/z 141.00 (34% with respect to the base peak), which could be due to the presence of the chlorine isotope or oxygen isotope of $[ClC_6H_4CO]^+$. But, we strongly believe that the peak at m/z 141.00 does not correspond to the $[ClC_6H_4CO^{18}]^+$ fragment because the peak (at m/z 143.00) for the chlorine isotope of $[ClC_6H_4CO^{18}]^+$ was not at all observed in the spectrum. So, it is conclusive from the mass spectral data that the oxygen labelling did not take place at the carbonyl oxygen, which sturdily supports the concerted mechanism operating in the reaction (Scheme 1). The above experiment also indicates the involvement of atmospheric oxygen in the esterification reaction.



Scheme 2 Isotopic labelling experiment using $^{18}O_2$.

To conclude, the studies described in this article have led to the development of a mild and efficient method for the oxidative esterification of aromatic aldehydes using NHC as an organocatalyst under aerobic conditions. The practicability of this methodology has been demonstrated using various boronic acids and aldehydes.

Acknowledgements

The authors acknowledge IISER Mohali for providing financial support and infrastructure. PA, VR and BTR thank CSIR for the research fellowship. The NMR group of IISER Mohali is also gratefully acknowledged.

Notes and references

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