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N-Heterocyclic Carbene-Catalyzed Aerobic Oxidative Direct Esterification of Aldehydes with Organoboronic Acids

Jing-Jing Meng, Min Gao, Yu-Ping Wei,* and Wen-Qin Zhang[a]

The ubiquitous nature of the ester functionality in the structures of natural and synthetic molecules makes esterification reactions very important. Numerous methods are available for this transformation, such as nucleophilic reactions of carboxylic acid derivatives with alcohols or phenols, transesterification reactions, as well as Baeyer–Villiger oxidation reactions.[1] Out of those traditional protocols, an oxidative esterification of aldehydes catalyzed by N-heterocyclic carbenes (NHCs) is beginning to emerge as a powerful method in organic synthesis nowadays.[2]

NHCs, first isolated by Arduengo in 1991,[3] have been indeed widely used as versatile ligands in transition-metal catalysis[4] and organocatalysts[5] in organic synthesis. As it is well documented, the esterification of aldehydes is completed via the active Breslow intermediate, resulting from an internal redox reaction[6] or an external oxidation process.[7] Recently, NHC-catalyzed esterification reactions of aldehydes with several nucleophillic reagents, such as hydroxy compounds,[6a,b] aziridines,[8] and alkyl halides,[9] were reported. In particular, for boronic acids several related precedents were established. In 2008, Cheng et al. reported an aromatic esterification reaction of aldehydes and arylboronic acids with 5.0 mol% of a palladium–NHC complex at 120°C under air, which tolerated many functional groups and gave aryl benzoate derivatives with modest yields.[10] Later, Gois et al. improved the process by using 20.0 mol% of iron–NHC complexes, where equimolar amounts of the aldehyde and the boronic acid gave benzoates in yields up to 97% at 90°C after 24 hours.[11] However, these results indicated that those procedures are remarkably dependent on the metal components. Most recently, Anand and co-workers reported an identical NHC-catalyzed reaction, which furnished products in up to 99% isolated yields, and proposed a concerted mechanism.[12] However, further investigations into this protocol disclosed that long reaction times and elevated temperatures (i.e., 24 h at 60°C) were often required. To address this problem, an optimized NHC-catalyzed esterification between arylboronic acids and aldehydes has been reported herein. This reaction proceeded rapidly and provided rate accelerations of up to 48-fold over Anand's protocol. Moreover, to understand this process, a mechanism involving a nucleophilic substitution reaction between $B(OR)_3$ and an acyl azolium species has been proposed.

We used anisaldehyde (0.37 mmol) and phenylboronic acid (0.25 mmol) in the presence of saturated imidazolium **1** in benzene (Table 1) as the initial reaction model. As a result, the reaction was completed in 1 hour and gave **3aa** in 42% isolated yield (Table 1, entry 1). Next, to optimize the reaction conditions, several variables such as, solvent, base, catalyst/base ratios, and reaction temperatures were investigated. Notably, in dimethyl sulfoxide (DMSO), the reaction gave the target product **3aa** in 67% isolated yield after 0.5 hours at 80°C under air (Table 1, entry 9). The selection of the base plays a pivotal role in the reaction efficiency. Diazabicyclo[5.4.0]undecene (DBU) was superior to anionic oxygen bases such as K_2CO_3, Na_2CO_3, K_3PO_4, and KF (Table 1, compare entry 9 with entries 10, 11, 13, and 17).[13] The stronger base, *t*BuOK, and the weaker organic bases, triethylamine (TEA) and pyridine (Py), turned out to be ineffective (Table 1; entries 14–16). The **1**/base ratio also affected the results and a ratio of 20:200 gave the best results, furnishing the product **3aa** in 77% isolated yield (Table 1; entry 21). A higher (Table 1, entry 20) or lower (Table 1, entries 18 and 19) **1**/base ratio is unfavorable for enhancing the yield of **3aa**. The screening of different NHCs indicated that catalysts **3**–**7** were ineffective (Table 1, entry 22). However, catalyst **2** (Table 1, entry 23), which is analogous to **1**, produced **3aa** albeit in a diminished yield (66%). The fine tuning of the proportions of anisaldehyde and phenylboronic acid also greatly improved the yield of **3aa** and a 2:1 ratio gave an isolated yield of 99% (Table 1, entry 25).[14] A lower **1**/base ratio (10:200) required up to 6 hours for completion and afforded **3aa** in 89% yield (Table 1, entry 27). Decreasing the temperature resulted in no product formation, whereas elevating the temperature did not significantly affect the efficiency (Table 1, entries 28 and 29). Therefore, the optimized conditions were determined to be: phenylboronic acid (0.25 mmol), anisaldehyde (0.5 mmol), DBU (0.5 mmol), catalyst **1** (0.05 mmol) in DMSO (4 mL) at 80°C for about 30 min under air. Once the optimal reaction conditions had been established, various arylboronic acids were employed to evaluate the generality of this method. As shown in Table 2, reactions between

[a] Dr. J.-J. Meng, M. Gao, Y.-P. Wei, Prof. W.-Q. Zhang
Department of Chemistry
School of Science Tianjin University
No. 92, Weijin Road, Nan kai District, Tianjin, 300072 (China)
Fax: (+86) 22-27403475
E-mail: ypwei@tju.edu.cn

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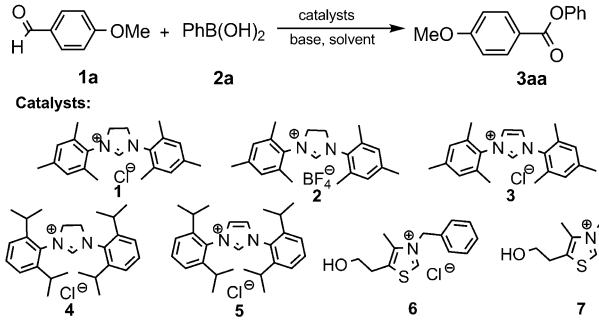
Table 1. Optimization of the esterification reaction of anisaldehyde and phenylboronic acid.[a]

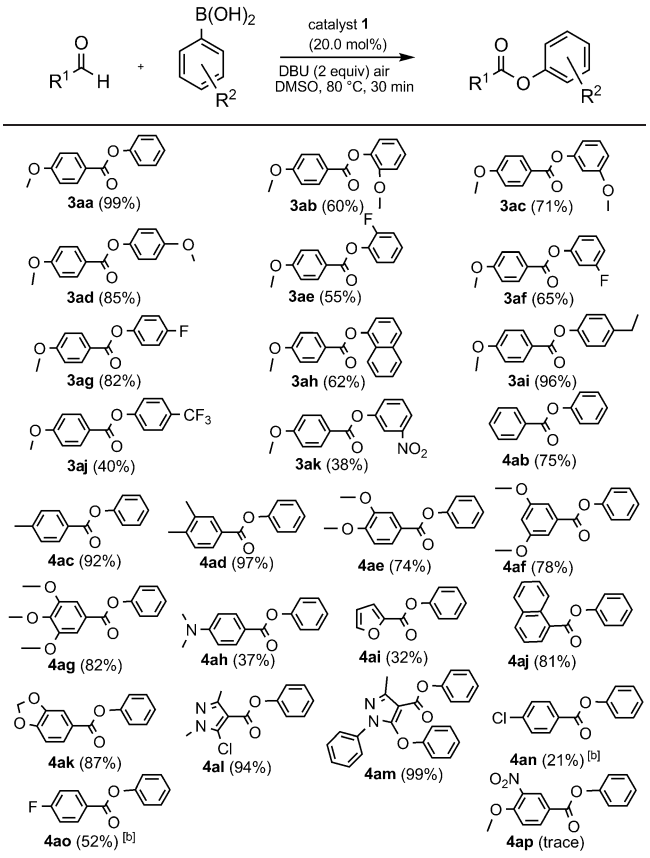


Entry	Catalyst	Base	Solvent	Catalyst/ Base ratio	Isolated yield [%]
1	**1**	DBU	benzene	20:100	42
2	**1**	DBU	toluene	20:100	57
3	**1**	DBU	acetonitrile	20:100	52
4	**1**	DBU	DMF	20:100	48
5	**1**	DBU	1,4-Dioxane	20:100	45
6	**1**	DBU	$PhCF_3$	20:100	21
7	**1**	DBU	anisole	20:100	39
8	**1**	DBU	DMAC	20:100	37
9	**1**	DBU	DMSO	20:100	67
10	**1**	K_2CO_3	DMSO	20:100	63
11	**1**	Na_2CO_3	DMSO	20:100	60
12	**1**	Cs_2CO_3	DMSO	20:100	n.r.
13	**1**	K_3PO_4	DMSO	20:100	35
14	**1**	*t*BuOK	DMSO	20:100	n.r.
15	**1**	TEA	DMSO	20:100	n.r.
16	**1**	Py	DMSO	20:100	n.r.
17	**1**	KF	DMSO	20:100	58
18	**1**	DBU	DMSO	10:50	n.r.
19	**1**	DBU	DMSO	5:20	n.r.
20	**1**	DBU	DMSO	40:100	65
21	**1**	DBU	DMSO	20:200	77
22	**3–7**	DBU	DMSO	20:200	n.r.
23	**2**	DBU	DMSO	20:200	66
24	**1**	DBU	DMSO	20:200	44[b]
25	**1**	DBU	DMSO	20:200	99[c]
26	**1**	DBU	DMSO	20:200	40[d]
27	**1**	DBU	DMSO	10:200	89[c,e]
28	**1**	DBU	DMSO	20:200	n.r.[c,f]
29	**1**	DBU	DMSO	20:200	97[c,g]

[a] Reaction conditions for entries 1–22: **2a** (0.25 mmol), **1a** (0.37 mmol), catalyst/base ratios were based on the amount of relatively little raw material unless otherwise noted, in 4 mL of solvent under air at 80 °C for 30 min. DMF = *N*,*N*-dimethylformamide, DMAC = dimethylacetamide. [b] **2a** (0.5 mmol), **1a** (0.5 mmol). [c] **2a** (0.25 mmol), **1a** (0.5 mmol). [d] **2a** (0.5 mmol), **1a** (0.25 mmol). [e] 6 h. [f] 45 °C. [g] 120 °C, 30 min. n.r. = no reaction.

anisaldehyde (**1a**) and various arylboronic acids (**2a–k**) produced esters (**3aa–ak**) in moderate to excellent isolated yields (38–99%) and no NHC-mediated benzoin condensation reactions took place. Overall, the results show that phenylboronic acids with electron-donating groups were distinctly superior to the electron-withdrawing analogues. Comparison of the methoxy-substituted (Table 2; **3ab–3ad**) and fluoro-substituted (Table 2, **3ae**, **3af**, and **3ag**) phenylboronic acids demonstrates that substitution far away from the boronic acid functional group produces products in a high

Table 2. Substrate scope in the NHC-catalyzed aromatic esterification reactions.[a]

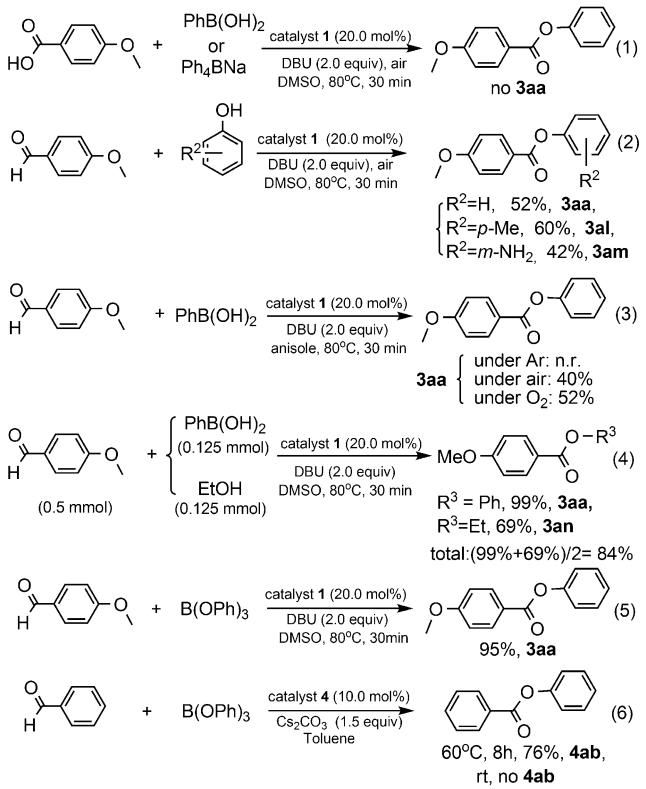


[a] Reactions were carried out under optimal conditions. [b] 5,5-dimethyl-2-phenyl-1,3,2-dioxaborinane was used instead of phenylboronic acid.

yield.[15] Arylboronic acids with *ortho* substituents gave **3ab** and **3ae** in lower yields (Table 2), which probably resulted from steric hinderance, whereas *para*-substituted phenylboronic acid gave **3ad** and **3ag** in the best isolated yields (Table 2).

Next a range of aldehydes (**1b–p**) were screened and found to react well with phenylboronic acid (Table 2, **4ab–ap**). The electron-rich aldehydes reacted with aromatic boronic acids readily and gave the desired products in good to excellent yields. However, reactions with aldehydes bearing electron-withdrawing substituents on the aromatic rings were sluggish (Table 2, **4ap** vs **3ad**).[16] In sharp contrast to the reported one-pot esterification of aldehydes and phenols,[15b] highly hindered aryl aldehydes were also quite reactive and gave **4al** and **4am** in 94% and 99% isolated yields, respectively. It is worth mentioning that many functional groups in both the arylboronic acid and aryl aldehyde substrates are well tolerated. In addition, the esterification reaction also proceeded with some heterocyclic substrates (Table 2) and provided products **4ak**, **4al**, and **4am** in good yields. The low yield of **4ai** may result from the instability of furfural when exposed to some oxidants.

To probe the reaction mechanism, several control experiments were conducted (Scheme 1). Firstly, reactions be-

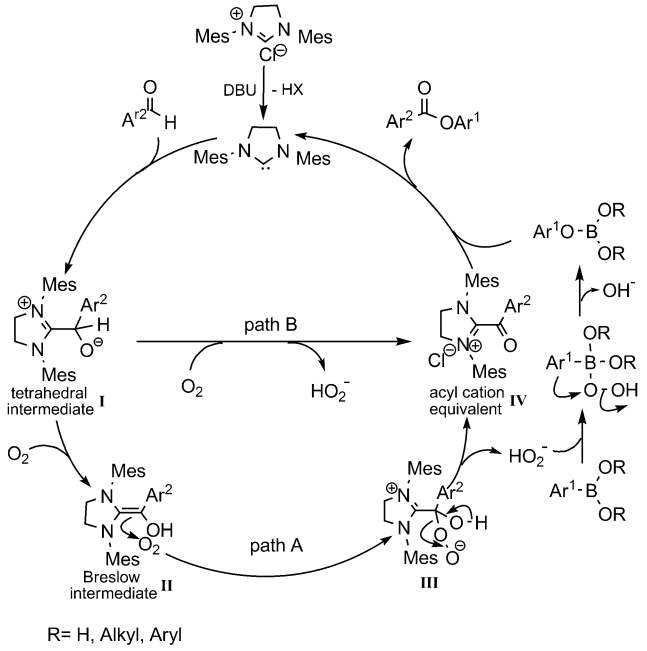


Scheme 1. Control experiments in the NHC precursor-catalyzed esterification procedures. All yields reported are the isolated yields of the products.

tween *para*-anisic acid and phenylboronic acid were investigated under the optimal reaction conditions [Scheme 1, Eq. (1)], but ester **3aa** was not formed.[17] This result tentatively suggests that the reaction does not proceed through the oxidation of the aldehyde to the carboxylic acid followed by esterification with phenylboronic acid.[18] Further, the reaction with the Ph_4BNa substrate also failed. Secondly, when anisaldehyde was exposed to three different phenols, the corresponding products were afforded in 42–60% isolated yields [Scheme 1, Eq. (2)]. These results might indicate that a phenol intermediate was derived from the phenylboronic acid.[19] To verify the appearance of a phenol, GC/MS and in situ NMR spectrocopy (in $[D_6]$DMSO) were performed, however, no phenol species was observed.[10,11] We then speculated that phenylboronic acid must undergo another type of process in this reaction.

Therefore, to elucidate the most probable reaction mechanism, we conducted the reaction between anisaldehyde and phenylboronic acid in anisole under anaerobic conditions; no **3aa** was detected. However, when it was carried out under air, formation of **3aa** was markedly improved to 40% yield. Pure O_2 was used instead of air and enhanced the isolated yield to 52% [Scheme 1, Eq. (3)]. Therefore, it was concluded that oxygen is essential for the transformation of aldehydes to esters.[20] Next, a competitive reaction between phenylboronic acid and nucleophilic EtOH was performed [Scheme 1, Eq. (4)]. Our results indicated that phenylboronic acid was superior to EtOH, as **3aa** and **3an** were furnished in 99% and 69% isolated yield, respectively. Most importantly, the formation of **3an** suggested that an acyl azolium species had been involved in the present research.[21] Moreover, we effected the esterification reaction of anisaldehyde using $B(OPh)_3$ in place of phenylboronic acid, and **3aa** was formed in 95% yield [Scheme 1, Eq. (5)]. However, according to Anand's procedure, the unexpected **4ab** was furnished in 76% isolated yield after 8 hours at 60 °C [Scheme 1, Eq. (6)]. Therefore, we reasoned that arylboronic acids were possibly transformed into the ester functionality function through borate ester $B(OR)_3$ intermediates. In general, the present reaction may undergo a nucleophilic substitution reaction between $B(OR)_3$ and an acyl azolium species.

By analogy with previous work,[12] the most probable mechanism for this method is tentatively postulated. As shown in Scheme 2, of note is the formation of the tetrahedral intermediate via the reaction between the aldehyde and an in situ generated carbene. Then, a proton-transfer event generates the Breslow intermediate **II**. Next, an electrophilic molecule of O_2[15b] was incorporated into **II**, and this resulted in the formation of the corresponding peroxide **III**.[22] Subsequently, intermediate **III** was converted into the well-known acyl cation equivalent **IV**,[23] with simultaneous liberation of the hydroperoxide anion (path A).[24] As a result, in a basic solvent, the hydroperoxide anion exclusively oxidizes substituted borane and simultaneously rearranges into borate esters $B(OR)_3$.[25] This may account for our failure to detect a phenol intermediate under anhydrous conditions. Finally,



Scheme 2. Postulated mechanism of nucleophilic carbene-catalyzed esterification reactions.

the borate ester-type intermediate undergoes an acylation with the acyl cation equivalent **IV**, thus promoting the NHC catalyst turnover and affording esters in a rapid manner. Alternatively, with respect to hydroperoxide anion formation, path B can also not be ruled out.[24a]

In summary, a new reaction pathway to produce benzoates through the reaction between arylboronic acids and aldehydes catalyzed by NHCs has been discovered. In this reaction, the corresponding benzoates are formed and give esters in isolated yields of up to 99% in 30 min under air. This procedure provides a simple, efficient, sustainable, and environmentally friendly route for the transformation of commercially available aldehydes into benzoate analogues.

Experimental Section

Typically, the reactions were carried out as follows: An oven-dried 25 mL Schlenk tube equipped with a magnetic stir bar was charged with NHC precursor (20 mol%) in DMSO (4 mL), and then sealed tightly with a rubber septum. The tube was evacuated and backfilled with argon three times. Then, DBU (2.0 equiv) was added via a syringe. The mixture was stirred for 20 min at room temperature. Then, the aldehyde and arylboronic acid were added sequentially. The tube was then placed into a preheated oil bath and stirred at 80 °C under an ambient air atmosphere. After the reaction was completed, the mixture was extracted with ethyl acetate (5 mL × 3), and washed with water and brine three times, and then dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The residue was purified by preparative thin-layer chromatography eluting with petroleum ether/ethyl acetate (4:1), dichloromethane, or 1,2-dichloroethane to give the corresponding products.

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Keywords: aldehydes · arylboronic acid · carbenes · homogeneous catalysis · synthetic methods

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