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Palladium-Catalyzed Aromatic Esterification of Aldehydes with Organoboronic Acids and Molecular Oxygen

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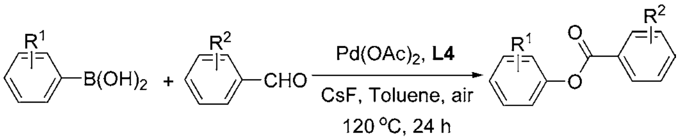
ABSTRACT



A palladium-catalyzed aromatic esterification reaction of aldehydes with arylboronic acids under an air atmosphere was achieved. This reaction tolerates many functional groups and provides aryl benzoate derivatives with yields ranging from moderate to good. Dioxygen takes part in the reaction and is crucial for this transformation.

Direct transformation of aldehydes to esters under mild conditions holds promise in organic synthesis, particularly in the synthesis of natural products.[1] In the past few years, great progress has been made in the synthesis of alkyl benzoate derivatives through aldehydes.[2] Recently, Wolf and co-workers reported an efficient oxidative conversion of aldehydes to ester using siloxanes and palladium−phosphinous acid.[3] More recently, Kiyooka and co-workers reported $[IrCl(cod)]_2$-catalyzed direct oxidative esterification of aldehydes with alcohols.[4]

However, less attention has been paid to the synthesis of aryl benzoate derivatives, which are important building blocks in the synthesis of natural and pharmacological compounds.[5] Traditional methods for preparation of these compounds include esterification[6] and transesterification reactions[7] as well as Baeyer−Villiger oxidation reactions.[8] The esterification and transesterification reactions were often conducted under strongly acidic or basic conditions, which might limit the scope of functional groups. In the Baeyer−

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(1) (a) Larock, R. C. *Comprehensive Organic Transformation*; VCH: New York, 1989; p 840. (b) McDonald, C.; Holcomb, H.; Kennedy, K.; Kirkpatrick, E.; Leathers, T.; Vanemon, P. *J. Org. Chem.* **1989**, *54*, 1213. (c) Corey, E. J.; Gilman, N. W.; Ganem, B. E. *J. Am. Chem. Soc.* **1968**, *90*, 5616. (d) Ogawa, T.; Matsui, M. *J. Am. Chem. Soc.* **1976**, *98*, 1629. (e) Garegg, P. J.; Olsson, L.;. Oscarson, S. *J. Org. Chem.* **1995**, *60*, 2200. (f) Sundararaman, P.; Walker, E. C.; Djerassi, C. *Tetrahedron Lett.* **1978**, *19*, 1627.

(2) (a) Gopinath, R.; Patel, B. K. *Org. Lett.* **2000**, *5*, 577. (b) Gopinath, R.; Paital, A. R.; Patel, B. K *Tetrahedron Lett.* **2002**, *43*, 5123. (c) Espenson, J. H.; Zhu, Z.; Zauche, T. H. *J. Org. Chem.* **1999**, *64*, 1191. (d) Barkakaty, B.; Talukdar, B.; Patel, B. K. *J. Org. Chem.* **2003**, *68*, 2944. (e) Travis, B. R.; Sivakumar, M.; Hollist, G. O.; Borhan, B. *Org. Lett.* **2003**, *5*, 1031. (f) Okimoto, M.; Chiba, T. *J. Org. Chem.* **1988**, *53*, 218. (g) Wuts, P. G. M.; Bergh, C. L. *Tetrahedron Lett.* **1986**, *27*, 3995. (h) McDonald, C. E.; Nice, L. E.; Shaw, A. W.; Nestor, N. B. *Tetrahedron Lett.* **1993**, *34*, 2741.

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(4) Kiyooka, S. -I.; Wada, Y.; Ueno, M.; Yokoyama, T.; Yokoyama, R. *Tetrahedron* **2007**, *63*, 12695.

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(6) (a) Sarvari, M. H.; Sharghi, H. *Tetrahedron* **2005**, *61*, 10903. (b) Tamaddon, F.; Amrollahi, M. A.; Sharafat, L. *Tetrahedron Lett.* **2005**, *46*, 7841. (d) Shah, S. T. A.; Khan, K. M.; Hussain, H.; Anwar, M. U.; Fecker, M.; Voelter, W. *Tetrahedron* **2005**, *61*, 6652.

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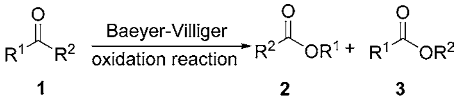
10.1021/ol800176p CCC: $40.75

Scheme 1. Regioselectivity in the Baeyer−Villiger Oxidation Reaction



Villiger oxidation reaction (Scheme 1), given that the migratory rate of R^1 is faster than that of R^2, it is hard to synthesize **3** via this route. Moreover, if R^1 and R^2 have similar migratory rates, the mixtures of **2** and **3** will be obtained with low regioselectivity. An alternative approach for the synthesis of esters from aromatic aldehydes involves the Tischenko−Claisen dismutation reaction, which was limited in the synthesis of benzyl esters. Thus, developing versatile approaches to the synthesis of aryl benzoate derivatives is still a highly desired goal in organic synthesis.

In our previous work, we reported the palladium-catalyzed synthesis of carbinol derivatives and diaryl ketone derivatives by employing aromatic boronic acids,[9] which enjoy high prestige in metal-catalyzed C−C bond formation thanks to their advantages of low toxicity, stability to air and moisture, and good functional group tolerance.[10] Our interest in the development of organoboron reactions led us to explore the potential reactions between organoboron reagents and aldehydes. Herein, we report a palladium-catalyzed aromatic esterification reaction of aldehydes with aromatic boronic acids under an air atmosphere, affording aryl benzoate derivatives in moderate to good yield.

Initial studies were concentrated on reactions between phenylboronic acid (**1a**) and piperonal (**2a**) as a model reaction. After careful screening, to our delight, a 28% yield of phenyl benzo[*d*][1,3]dioxole-5-carboxylate (**3aa**) was obtained by employing the combination of $Pd(OAc)_2$ (5.0 mol %), **L1** as a precursor of an *N*-heterocyclic carbene (NHC), (5.0 mol %), and CsF (3.0 equiv) in refluxing dry toluene under air. Encouraged by this result, we further optimized the reaction conditions using some other NHC precursors (Figure 1). The selected results, such as palladium catalysts, the ratio of **L**/Pd, bases, and solvents, are listed in Table 1.

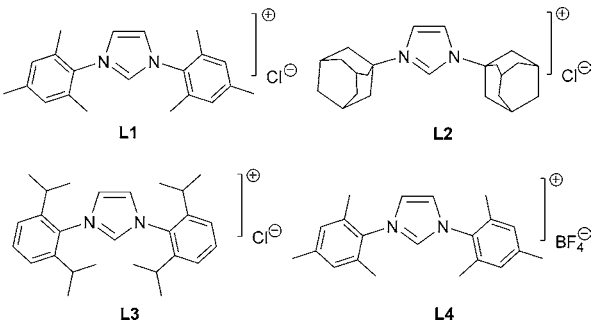
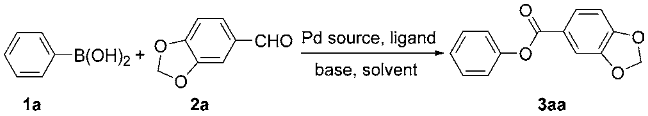


Figure 1. Selected imidazolium salts screened.

Table 1. Effects of Pd Source, Base, Solvent, Imidazolium Salts **L**, and Ratio of **L**/Pd on the Palladium-Catalyzed Esterifications of Aldehydes with Organoboronic Acids[a]



entry	Pd source	base	solvent	ligand	**L**/Pd ratio	yield (%)[b]
1	$PdCl_2$	CsF	toluene	**L1**	1	16
2	$Pd(OAc)_2$	CsF	toluene	**L1**	1	28
3	$Pd_2(dba)_3$	CsF	toluene	**L1**	1	<5
4	$Pd_2(dba)_3{\cdot}CHCl_3$	CsF	toluene	**L1**	1	<5
5	$Pd(PPh_3)_4$	CsF	toluene	**L1**	1	16
6	$PdCl_2(Py)_2$	CsF	toluene	**L1**	1	17
7	$Pd(OAc)_2$	CsF	DMA	**L1**	1	<5
8	$Pd(OAc)_2$	CsI	toluene	**L1**	1	<5
9	$Pd(OAc)_2$	CsCl	toluene	**L1**	1	<5
10	$Pd(OAc)_2$	KF	toluene	**L1**	1	<5
11	$Pd(OAc)_2$	LiF	toluene	**L1**	1	<5
12	$Pd(OAc)_2$	Cs_2CO_3	toluene	**L1**	1	18
13	$Pd(OAc)_2$	CsF	toluene	**L2**	1	<5
14	$Pd(OAc)_2$	CsF	toluene	**L3**	1	16
15	$Pd(OAc)_2$	CsF	toluene	**L4**	1	59 (53)[c]
16	$Pd(OAc)_2$	CsF	toluene	**L4**	2	57
17	$Pd(OAc)_2$	CsF	toluene	**L4**	3	52
18	$Pd(OAc)_2$	CsF	DMF	**L4**	1	<5
19	$Pd(OAc)_2$	CsF	1,4-dioxane	**L4**	1	<5
20	$Pd(OAc)_2$	CsF	$MeOCH_2CH_2OMe$	**L4**	1	<5
21	$Pd(OAc)_2$	CsF	toluene	**L4**	1	<5
22	$Pd(OAc)_2$	CsF	toluene	**L4**	1	54[d]
23	$Pd(OAc)_2$	CsF	toluene	**L4**	1	<5[e]
24	$Pd(OAc)_2$	CsF	toluene		1	<5
25	$Pd(OAc)_2$	CsF	toluene	**L1**	1	7[f]
26	$Pd(OAc)_2$	CsF	toluene	**L1**	1	8[g]
27	$Pd(OAc)_2$	CsF	toluene	**L1**	1	9[h]
28	$Pd(OAc)_2$	CsF	toluene	**L4**	1	41[i]

[a] All reactions were run with piperonal (75 mg,0.5 mmol), phenylboronic acid (122 mg, 1.0 mmol), base (1.5 mmol), Pd source (5.0 mol %), and indicated **L**/Pd ratio in 3 mL of dry solvent in air at 120 °C for 24 h. [b] GC yield. [c] Undried toluene. [d] O_2 atm. [e] N_2 atm. [f] 5.0 mol % $AgBF_4$ was added. [g] 5.0 mol % $AgSbF_6$was added. [h] 5.0 mol % $AgPF_6$ was added. [i] 80 °C

Among the palladium sources used, such as $PdCl_2$, $Pd(OAc)_2$, $PdCl_2(Py)_2$, $Pd_2(dba)_3$, $Pd_2(dba)_3{\cdot}CHCl_3$, and $Pd(PPh_3)_4$, $Pd(OAc)_2$ exhibited the highest catalytic reactivity. The imidazolium chlorides **L3** and **L1** with bulky aromatic substituent groups on their nitrogen atoms gave poor to moderate results, respectively, and imidazolium salts **L2** containing *N*-alkyl groups turned out to be totally ineffective. Interestingly, only when the ligand changed to the imidazolium salts **L4** did the yield dramatically increase to 59%.

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(10) (a) Suzuki, A. *Acc. Chem. Res.* **1982**, *15*, 178. (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (c) Suzuki, A. *J. Organomet. Chem.* **1998**, *576*, 147. (d) Darses, S.; Genet, J. P. *Eur. J. Org. Chem.* **2003**, 4313.

However, no good yield was obtained when $AgBF_4$, $AgSbF_6$, or $AgPF_6$ was added with **L1** in the system, respectively. We also found that no desired product was delivered when $AgBF_4$ was added with **L2** in the reaction.

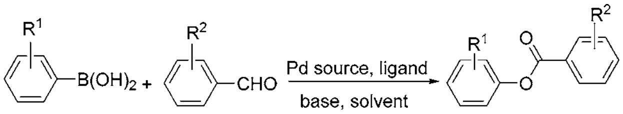
Increasing the amount of **L4** in the system had little influence on the yield (Table 1, entries 16 and 17), which might be owing to its difficulty to dissociate from the metal center to produce the bulk metal.[11] CsF was superior to some other cesium or fluoride salts such as Cs_2CO_3, KF, LiF, CsCl, and CsI. The choice of solvent was also crucial to the success of the catalytic reaction. Toluene appeared to be the best among the common solvents such as DMF, DMA, 1,4-dioxane, and 1,2- dimethoxyethane. Moreover, dioxygen played a significant role in the reaction since no desired products were obtained under a N_2 atmosphere. It should be noted that **3aa** was still obtained in 41% yield at 80 °C for 30 h.

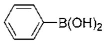
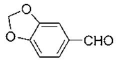
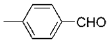
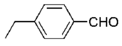
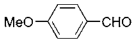
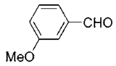
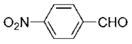
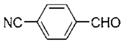
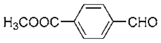
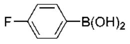
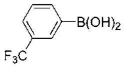
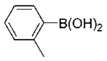
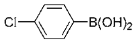
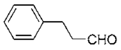
Under the optimized conditions, various aromatic aldehydes and aromatic boronic acids were subjected to this kind of esterification process (Table 2).

As expected, the reaction proceeded smoothly with yields ranging from moderate to good and tolerated various functional groups such as nitro, cyano, acetoxy, trifluoromethyl, chloro, and fluoro groups. Electron-rich aldehydes reacted with aromatic boronic acids easily and gave the desired products in good yields. Nevertheless, the reaction became sluggish by using aldehydes with electron-withdrawing groups. Aliphatic aldehydes, such as **2i**, were not good substrates in the reaction. Arylboronic acids with electron-withdrawing substituted groups, which are less nucleophilic and transmetalate more slowly than electron-neutral analogues, are prone to homocoupling and protodeboronation side reactions.[12] In our system, however, **1b** and **1c** could proceed smoothly with **2a**, and the products **3ba** and **3ca** were isolated in 68% and 62% yields, respectively (Table 2, entries 9 and 10).

It is noteworthy that **3ca** is difficult to prepare from corresponding diaryl ketones via Baeyer−Villiger oxidation since the electron-withdrawing groups on the aryl will decrease its migratory rate. However, in our procedure, **1c** reacted smoothly with **2a** and produced **3ca** in 62% isolated yield. The *ortho* substituents on the aromatic boronic acids had little effect in the reaction. For example, **3da** and **3dd** were isolated in 55% and 56% yield, respectively (Table 2, entries 11, 16). Since the aromatic aldehydes can be facilely synthesized from a lot of functional groups such as methyl, hydroxylmethyl, carboxyl, cyano, and ester,[13] this method appears to be versatile and might provide potential opportunities in the synthesis of complex molecules possessing interesting biological and pharmacological properties.

Table 2. Substrate Scope in the Palladium-Catalyzed Aromatic Esterification of Aromatic Aldehydes with Arylboronic Acids[a]



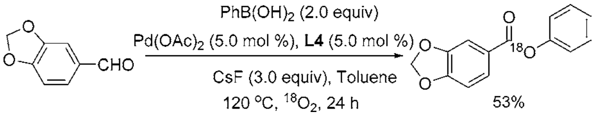
entry	boronic acids		aldehydes		products	yields[%][b]
1		**1a**		**2a**	**3aa**	59
2	**1a**			**2b**	**3ab**	55
3	**1a**			**2c**	**3ac**	56
4	**1a**			**2d**	**3ad**	62
5	**1a**			**2e**	**3ae**	42
6	**1a**			**2f**	**3af**	11
7	**1a**			**2g**	**3ag**	24
8	**1a**			**2h**	**3ah**	41
9		**1b**	**2a**		**3ba**	68
10		**1c**	**2a**		**3ca**	62
11		**1d**	**2a**		**3da**	55
12		**1e**	**2d**		**3ed**	34[c]
13	**1b**		**2d**		**3bd**	51
14	**1b**		**2h**		**3bh**	24
15	**1c**		**2b**		**3cb**	41
16	**1d**		**2d**		**3dd**	56
17	**1a**			**2i**	**3ai**	<5

[a] All reactions were run with aldehyde (0.5 mmol), arylboronic acid (1.0 mmol), CsF (228 mg, 1.5 mmol), $Pd(OAc)_2$ (5.6 mg, 5 mol %), **L4** (9.9 mg, 5 mol %) in 3 mL of dry toluene in air at 120 °C for 24 h. [b] Isolated yield. [c] 36 h.

Employing benzoic acid or benzophenone instead of benzaldehyde under the same procedure, no target product was detected in this reaction. This result suggested that they might not be the intermediates of the reaction. Analysis of the crude reaction mixtures between phenyl boronic acids and benzaldehyde by GC-MS showed that the 2-hydroxy-1,2-diphenylethanone was produced in situ, which was formed due to the NHC-mediated benzil condensation.[14] However, 2-hydroxy-1,2-diphenylethanone or benzil did not deliver the desired product under the standard reaction conditions either.

To understand the mechanism more clearly, labeling studies were conducted using $^{18}O_2$ (Scheme 2). We found that the reaction proceeded smoothly under an $^{18}O_2$ atmo-

Scheme 2. Study on $^{18}O_2$ Incorporation into the Desired Product



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[13] Ferguson, L. N. *Chem. Rev.* **1946**, *38*, 227.

sphere to provide the desired product in 53% yield. The ESI-MS spectrum showed that m/z at 244.8 and 266.8 were attributed to $[M + H]^+$ and $[M + Na]^+$ ions, respectively. The MS^2 spectrum of the precursor ion at m/z 244.8 exhibited intensive characteristic fragment at m/z 148.7, which was attributed to the fragment of $[244.8 - Ph^{18}OH]^+$. This result showed that dioxygen took part in this reaction and was essential for the transformation.

In summary, we have demonstrated a palladium-catalyzed aromatic esterification reaction between aldehydes and organoboronic acids under an air atmosphere. This procedure represents a simple, direct method in the synthesis of functionalized phenyl benzoate derivatives from the bulky commercially available aldehydes. Indeed, this method appears to be versatile and might have potential application in the synthesis of complex natural compounds. Furthermore, this transformation might involve a new type of dioxygen activity, and further investigation to understand this mechanism as well as its application are ongoing in our laboratory.

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Supporting Information Available: Experimental procedures along with copies of spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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