Copper-Catalyzed Arylation of Arylboronic Acids with Aldehydes

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Abstract: A novel copper-catalyzed arylation of arylboronic acids with aldehydes under oxygen atmosphere was achieved in the presence of $Cu(OTf)_2$ and Xantphos, affording diaryl ketone derivatives in moderate to good yields. The efficiency of this reaction was demonstrated by the compatibility with fluoro, bromo, chloro, nitro, methylsulfonyl, and trifluoromethyl groups.

Key words: arylation, diaryl ketones, copper, catalysis

Diaryl ketone derivatives constitute an important building block for the synthesis of natural products and pharmacologically active compounds.[1] Common synthetic routes for the preparation of these compounds involve Friedel–Crafts acylation reactions[2] and acylation reactions using organometallic reagents.[3] However, these methods suffer from a lack of atom economy because a stoichiometric amount of aluminum trichloride is used. Anhydrous conditions are often required for both partners. Alternative approaches to construct diaryl ketones include metal-catalyzed coupling reactions of carboxylic acid derivatives such as acyl halides,[4] carboxylic anhydrides,[5] esters,[6] or thiol esters[7] with organometallic compounds. These reports, nevertheless, either had a limited substrate scope or required additives.

Some other general methods involve reactions between an aryl halide and an aldehyde or its derivative catalyzed by palladium,[8] rhodium,[9] or nickel.[10] Chang and co-workers have reported cooperative catalysis by Ru and Pd for the direct coupling of a chelating aldehyde with iodoarenes or organostannanes.[11] The high availability of aldehydes renders this route particularly attractive.

Organoboron reagents are highly regarded due to their advantages of stability to air and moisture, and good functional group tolerance.[12] In recent years, the method for the synthesis of diaryl ketones by palladium-[13] and nickel[14]-catalyzed addition of arylboronic acids to nitriles has been developed. However, less attention has been paid to the synthesis of diaryl ketones by the reaction of aldehydes with organoboron reagents. In 2004, Genet and co-workers reported the direct access to ketones from aldehydes via rhodium-catalyzed cross-coupling reaction with potassium trifluoro(organo)borates.[15] In our previous report, we have developed a palladium-catalyzed arylation of aldehydes to produce diaryl ketones in good yields.[16] Recently, Xu and co-workers have reported palladium-catalyzed direct C–H bond arylation of 2-hydroxybenzaldehydes with arylboronic acids.[17] Although another new method has also been developed, it suffered from the limited range of 2-hydroxybenzaldehydes.

Recently, the use of copper salts as catalysts has gained much prominence in organic synthesis due to their economic attractiveness, good functional group tolerance, and scalability in large-scale synthetic procedures.[18] Very recently, we have reported the copper-catalyzed synthesis of carbinol derivatives by addition of arylboronic acids to aromatic aldehydes in good to excellent yields.[19]

To our knowledge, a general and efficient copper-catalyzed method for the arylation of arylboronic acids with aldehydes to give the corresponding diaryl ketone derivatives has not been developed. Continuation of our interest in the development of organoboron reactions led us to explore the potential reactions between organoboron reagents and aldehydes or aldimines.[16,19,20] Herein, we report that copper-catalyzed arylation of arylboronic acids with aldehydes, using Xantphos as the ligand under oxygen atmosphere, provides diaryl ketone derivatives with yields ranging from moderate to good.

As suggested by our previous work,[19] initial studies focused on screening of oxidative additives, bases, and solvents using $Cu(OAc)_2{\cdot}H_2O$ as the copper source and dppf as the ligand with the reaction of 4-nitrobenzaldehyde (**1a**) and phenylboronic acid (**2a**) as a model reaction. Screening results are listed in Table 1. No target product was detected in the presence of various oxidative additives such as $PhI(OAc)_2$, Ag_2O, DDQ, and Oxone (Table 1, entries 1–4). However, it was satisfying to find that the reaction could proceed and afforded **3aa** in 12% yield when the combination of CsF and toluene was employed under air (Table 1, entry 13).

Considering ligands always play important roles in metal-catalyzed chemistry,[21] we focused on ligand screening (Scheme 1). Through screening, we found that bidentate phosphine ligands with electron-rich, large bite angles, or small bite angles had poor catalytic activity (Scheme 1, **L1**–**L5**). The small hindrance of the monodentate phosphine ligands resulted in poor yields (Scheme 1, **L6**, **L8**, and **L9**). Electron-rich phosphine ligands such as Xantphos (**L13**) were effective for this transformation, affording 42% yield. In addition, we examined the aminophosphine ligands (Scheme 1, **L15**–**L17**) and nitro-

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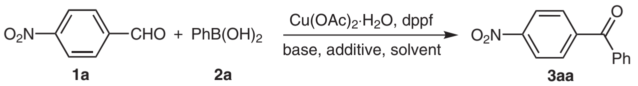
Table 1 Selected Results of Screening for Optimal Conditions[a]



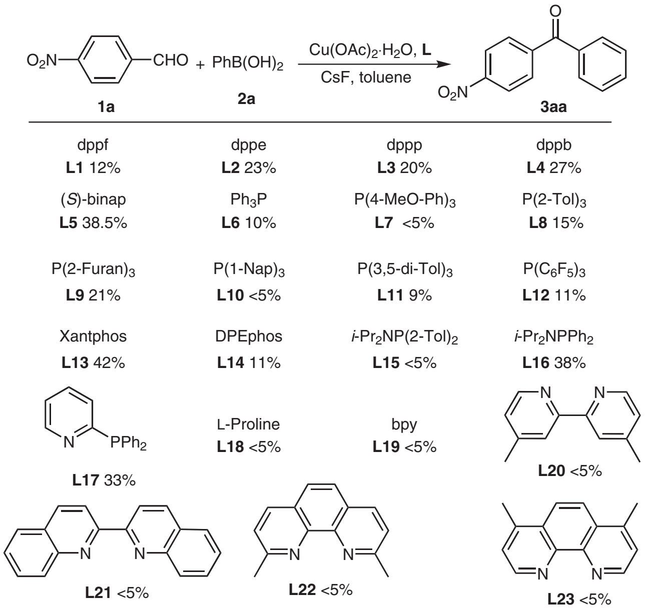
Entry	Base	Additive	Solvent	Yield (%)[b]
1	NaOAc	$PhI(OAc)_2$	toluene	<5
2	NaOAc	Ag_2O	toluene	<5
3	NaOAc	DDQ	toluene	<5
4	NaOAc	Oxone	toluene	<5
5	NaOAc		toluene	<5
6	NaOH		toluene	<5
7	CsOH		toluene	<5
8	Na_2CO_3		toluene	<5
9	K_2CO_3		toluene	<5
10	Cs_2CO_3		toluene	5
11	DABCO		toluene	<5
12	KO*t*-Bu		toluene	<5
13	CsF		toluene	12
14	CsF		chlorobenzene	10
15	CsF		xylene	9
16	CsF		DMF	<5
17	CsF		DMSO	<5
18	CsF		NMP	<5

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.6 mmol), base (0.9 mmol), $Cu(OAc)_2\cdot H_2O$ (10 mol%), additive (0.1 mmol), dppf (10 mol %) air, solvent (2 mL), 120 °C, 24 h.

[b] Isolated yield.

gen ligands (Scheme 1, **L18–L23**) which had no activity except for ligands **L16** and **L17**. Finally, we chose the commercially available **L13** as the best ligand for our system.

Encouraged by this promising result, we further optimized the reaction conditions, such as bases, copper source, and ratio of **L13**/Cu for phenylation of 4-nitrobenzaldehyde, and the results are listed in Table 2. Among the bases, $KF\cdot 2H_2O$ was superior to some others such as NaOAc, K_2CO_3, Cs_2CO_3, and $CsOH\cdot H_2O$ (Table 2, entries 1–5). Then using $KF\cdot 2H_2O$ as the base we screened the influence of the copper sources, $Cu(OTf)_2$ exhibited the highest catalytic activity compared with $Cu(OAc)_2\cdot H_2O$, $CuBr_2$, $CuCl_2$, CuF_2, CuBr, CuCl, and Cu_2O, affording a 70% yield (Table 2, entries 5–12). Decreasing the amount of $KF\cdot 2H_2O$ to 2.0 equivalents increased the yield to 73% (Table 2, entry 17). Increasing the ratio of Cu/**L13** or decreasing the ratio of Cu/**L13** in the system reduced the yield slightly (Table 2, entries 13–15). To our delight, the yield was improved to 85% when the reaction was carried out under oxygen (Table 2, entry 18).

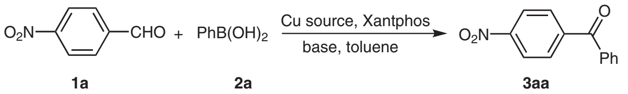


Scheme 1 Ligand screening. *Reagents and conditions*: **1a** (0.3 mmol), **2a** (0.6 mmol), base (0.9 mmol), $Cu(OAc)_2\cdot H_2O$ (10 mol%), ligand (10 mol%), CsF (0.9 mmol), air, toluene (2 mL), 120 °C, 24 h. Isolated yields are given.

With optimal conditions in hand, the reaction of different aldehydes with various arylboronic acids was examined to explore the scope of the reaction (Table 3). In our system, the electronic effect of substituents on the arylboronic acids had little influence on the reaction (Table 3, entries 1–6). Electron-neutral **2a** and electron-rich **2b**,**c** arylboronic acids reacted smoothly with 4-nitrobenzaldehyde (**1a**) to afford **3aa**, **3ab**, and **3ac** in 85%, 86%, and 72% yields, respectively (Table 3, entries 1–3). Electron-withdrawing arylboronic acids, which are less nucleophilic, and hence transmetalate more slowly than their electron-neutral analogues, are prone to homocoupling and protodeboronation side reactions.[21c] However, in our catalytic system, 4-bromophenylboronic acid (**2d**), 4-chlorophenylboronic acid (**2e**), 4-fluorophenylboronic acid (**2f**), and 4-(trifluoromethyl)phenylboronic acid (**2g**) reacted with **1a** to afford **3ad**, **3ae**, **3af**, and **3ag** in 70%, 82%, 87%, and 60% yields, respectively (Table 3, entries 4–7). Moreover, 1-naphthylboronic acid (**2h**) and 2-naphthylboronic acid (**2i**) also gave the corresponding diaryl ketones **3ah** and **3ai** in 71% and 65% yields, respectively (Table 3, entries 8 and 9). On the other hand, the products of **3ad** and **3eb** had the bromo group untouched, showed high selectivity (Table 3, entries 4 and 13).

As shown in Table 3, the influence of a monosubstituent group at the *ortho*, *meta*, and *para* position for both arylboronic acids (Table 3, entries 1–3) and aromatic aldehydes (Table 3, entries 1, 10, and 11) was investigated to examine the steric effect in our system. For example, **2b** proceeded with aldehydes **1a**, **1b**, and **1c** efficiently and **3ab**, **3bb**, and **3cb** were obtained in 86%, 88%, and 89%

Table 2 Effects of Base, Cu Source, and **L13**/Cu Ratio[a]



Entry	Cu source	Base (equiv)	**L13**/Cu ratio	Yield (%)[b]
1	$Cu(OAc)_2$	NaOAc (3)	1.5	<5
2	$Cu(OAc)_2$	K_2CO_3 (3)	1.5	52
3	$Cu(OAc)_2$	Cs_2CO_3 (3)	1.5	<5
4	$Cu(OAc)_2$	$CsOH·H_2O$ (3)	1.5	<5
5	$Cu(OAc)_2$	$KF·2H_2O$ (3)	1.5	57
6	$CuBr_2$	$KF·2H_2O$ (3)	1.5	<5
7	$CuCl_2$	$KF·2H_2O$ (3)	1.5	<5
8	CuF_2	$KF·2H_2O$ (3)	1.5	<5
9	CuBr	$KF·2H_2O$ (3)	1.5	56
10	CuCl	$KF·2H_2O$ (3)	1.5	<5
11	Cu_2O	$KF·2H_2O$ (3)	1.5	<5
12	$Cu(OTf)_2$	$KF·2H_2O$ (3)	0.5	70
13	$Cu(OTf)_2$	$KF·2H_2O$ (3)	1	20
14	$Cu(OTf)_2$	$KF·2H_2O$ (3)	2	48
15	$Cu(OTf)_2$	$KF·2H_2O$ (3)	1.5	53
16	$Cu(OTf)_2$	$KF·2H_2O$ (1)	1.5	50
17	$Cu(OTf)_2$	$KF·2H_2O$ (2)	1.5	73
18	$Cu(OTf)_2$	$KF·2H_2O$ (2)	1.5	85[c]

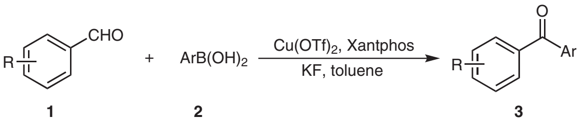
[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.6 mmol), base, Cu source (10 mol %), air, toluene (2 mL), 120 °C, 24 h.
[b] Isolated yield.
[c] The reaction was run under an oxygen atmosphere.

yields, respectively (Table 3, entries 2, 10, and 11), demonstrating little steric effect on the yields in the reaction.

For the aldehydes, electron-withdrawing and electron-rich aromatic aldehydes reacted with **2b** and gave diaryl ketones (**3bb**–**jb**) with moderate to good yields (Table 3, entries 10–18). Aldehydes such as **1e**, **1f**, and **1g** reacted well with **2a**, and the products **3ea**, **3fa**, and **3ga** were isolated in 88%, 67%, and 61% yields, respectively (Table 3, entries 13–15).

Aldehydes containing a strongly electron-withdrawing group, such as 4-(methylsulfonyl)benzaldehyde (**1d**) and 2,4-dinitrobenzaldehyde (**1h**) afforded the corresponding diaryl ketones **3db**[22] and **3hb** in 67% and 63% yields, respectively (Table 3, entries 12 and 16). Benzaldehyde (**1i**) and 4-methylbenzaldehyde (**1j**) coupled with **2b** to afford **3ib** and **3jb** in 60% and 75% isolated yields, respectively (Table 3, entries 17 and 18). Unfortunately, the reaction was unsuccessful using aldehydes with a heteroatom, aliphatic aldehydes, and heteroarylboronic acid (Table 3, entries 19–21). However, treatment of an alkylboronic acid such as cyclopropylboronic acid (**2k**) with *p*-nitrobenzaldehyde under the optimized conditions, the desired product **3ak** was obtained in 19% yield (Table 3, entry 22).

Table 3 Substrate Scope in the Copper-Catalyzed Arylation of Arylboronic Acids with Aldehydes[a]



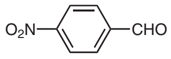
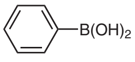
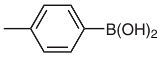
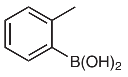
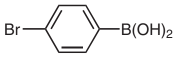
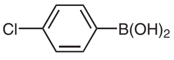
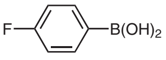
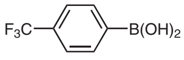
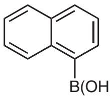
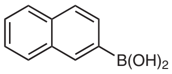
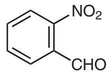
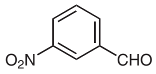
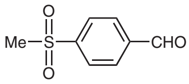
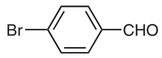
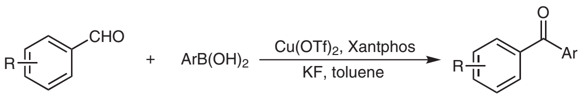
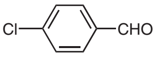
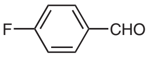
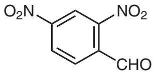
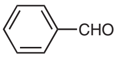
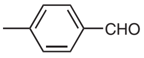
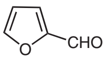
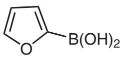
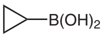
Entry	Aldehyde	Boronic acid	Product	Yield (%)[b]
1	 **1a**	 **2a**	**3aa**	85
2	**1a**	 **2b**	**3ab**	86
3	**1a**	 **2c**	**3ac**	72
4	**1a**	 **2d**	**3ad**	70
5	**1a**	 **2e**	**3ae**	82
6	**1a**	 **2f**	**3af**	87
7	**1a**	 **2g**	**3ag**	60
8	**1a**	 **2h**	**3ah**	71
9	**1a**	 **2i**	**3ai**	65
10	 **1b**	**2b**	**3bb**	88
11	 **1c**	**2b**	**3cb**	89
12	 **1d**	**2b**	**3db**	67
13	 **1e**	**2b**	**3eb**	88

Table 3 Substrate Scope in the Copper-Catalyzed Arylation of Arylboronic Acids with Aldehydes[a] (continued)



1 **2** **3**

Entry	Aldehyde	Boronic acid	Product	Yield (%)[b]
14	 **1f**	**2b**	**3fb**	67
15	 **1g**	**2b**	**3gb**	61
16	 **1h**	**2b**	**3hb**	63
17	 **1i**	**2b**	**3ib**	60
18	 **1j**	**2b**	**3jb**	75
19	 **1k**	**2b**	**3kb**	trace
20	n-$C_9H_{19}CHO$ **1l**	**2b**	**3lb**	trace
21	**1a**	 **2j**	**3aj**	trace
22	**1a**	 **2k**	**3ak**	19

[a] Reaction conditions: **1** (0.3 mmol), **2** (0.6 mmol), $Cu(OTf)_2$ (10 mol%), Xantphos (15 mol%), $KF·2H_2O$ (0.6 mmol), toluene (2 mL), 120 °C, 24 h, O_2 atmosphere.

[b] Isolated yields.

In summary, we have developed a novel copper-catalyzed method for the synthesis of diaryl ketones in moderate to good yields from the reaction of various aldehydes and arylboronic acids in the presence of $Cu(OTf)_2$ and Xantphos under oxygen atmosphere. Work to probe the detailed mechanism and apply the reaction in organic synthesis is currently under way in our laboratory.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(22) **General Procedure for the Synthesis of Diaryl Ketones**
Under nitrogen atmosphere, a Schlenk tube was charged with aldehyde (0.3 mmol), arylboronic acid (0.6 mmol), Cu(OTf)$_2$ (10 mol%), Xantphos ligand (15 mol%), and KF·2H$_2$O (0.6 mmol) in toluene (2 mL) under ice-salt (–20 °C). The mixture was stirred for 6 h at r.t. under nitrogen atmosphere. Then pass into the oxygen, the mixture was stirred for 0.5 h at r.t. and heated up to reflux temperature (about 120 °C) for 24 h under oxygen atmosphere. After the completion of the reaction, as monitored by TLC, the solvent was concentrated in vacuo, and the residue was purified by flash column chromatography on silica gel (300–400 mesh) with PE–EtOAc as eluent to give the desired product.

Naphthalen-2-yl(4-nitrophenyl)methanone (3ai, Table 3, Entry 9)
^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.57–7.69 (m, 2 H), 7.91–8.00 (m, 6 H), 8.23 (s, 1 H), 8.22–8.40 (m, 2 H). ^{13}C NMR (125 MHz, CDCl$_3$): δ = 123.6, 125.2, 127.2, 127.9, 128.8, 129.0, 129.5, 130.7, 132.1, 132.4, 133.5, 135.6, 143.2, 149.8, 194.8. ESI-MS: *m/z* (%) = 278 (100) $[M + 1]^+$. Anal. Calcd for C$_{17}$H$_{11}$NO$_3$: C, 73.64; H, 4.00. Found: C, 73.66; H, 4.05.

4-Methylsulfonylphenyl(4-tolyl)methanone (3db, Table 3, Entry 12)
^{1}H NMR (300 MHz, CDCl$_3$): δ = (s, 3 H), 3.12 (s, 3 H), 7.32 (d, *J* = 8.1 Hz, 2 H), 7.71 (d, *J* = 8.1 Hz, 2 H), 7.93 (d, *J* = 8.4 Hz, 2 H), 8.06 (d, *J* = 8.4 Hz, 2 H). ^{13}C NMR (125 MHz, CDCl$_3$): δ = 21.7, 44.4, 127.4, 129.3, 130.3, 133.7, 142.7, 143.2, 144.5, 194.8. ESI-MS: *m/z* (%) = 275 (100) $[M + 1]^+$. Anal. Calcd for C$_{15}$H$_{14}$O$_3$S: C, 65.67; H, 5.14. Found: C, 65.82; H, 5.22.

2,6-Dinitrophenyl(4-tolyl)methanone (3hb, Table 3, Entry 16)
^{1}H NMR (300 MHz, CDCl$_3$): δ = (s, 3 H), 7.29 (d, *J* = 8.1 Hz, 2 H), 7.63 (d, *J* = 8.1 Hz, 2 H), 7.70 (d, *J* = 8.1 Hz, 2 H), 8.62 (d, *J* = 8.1 Hz, 2 H), 9.08 (s, 1 H). ^{13}C NMR (125 MHz, CDCl$_3$): δ = 21.8, 120.1, 128.4, 129.6, 129.8, 130.3, 132.4, 141.7, 146.0, 146.0, 148.4, 190.9. MS (EI): *m/z* (%) = 287 (100) $[M + 1]^+$. Anal. Calcd for C$_{14}$H$_{10}$N$_2$O$_5$: C, 58.74; H, 3.52. Found: C, 58.83; H, 3.63.