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One-pot synthesis of diaryl ketones from aldehydes via palladium-catalyzed reaction with aryl boronic acids

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Abstract

A Pd-catalyzed coupling-type reaction of aldehydes and organoboronic acids was achieved in the presence of P(1-nap)$_3$, using Cs_2CO_3 in toluene, providing diaryl ketones with yields ranged from moderate to excellent. The efficiency of this reaction was demonstrated by the compatibility with nitro, cyano, trifluoromethyl, fluoro and chloro groups. Moreover, the rigorous exclusion of air/moisture is not required in these transformations.

Keywords: Diarylketone; One-pot; Aldehyde; Arylboronic acid; Palladium-catalyzed

Diaryl and aryl-alkyl ketones are important building blocks in the synthesis of natural products and pharmacological compounds as well as material science target molecules.[1] General methods for the preparation of these compounds include Friedel–Crafts acylation reactions,[2] and acylation of organometallic reagents reactions.[3] However, these methods suffer from their lack of atom economy due to the use of a stoichiometric amount of aluminum trichloride or anhydrous conditions required for both partners. Alternative transformations used to construct these diaryl ketones involve the metal-catalyzed coupling reactions of carboxylic anhydrides,[4] esters,[5] thiol esters[6] with organometallic compounds. These reports, nevertheless, had a limited substrate scope or might need the additives. Some other approaches involve a metal-catalyzed reaction between aryl halide and an aldehyde or its derivative. Hartwig and co-workers reported a rhodium-catalyzed coupling of aryl iodides with *N*-pyrazyl aldimines[7] and a palladium-catalyzed coupling of aryl bromides with *N*-*tert*-butylhydrazones.[8] The formation of ketones by this methods required two steps and strong base NaOBu^t. Aryl iodides coupled with aldehydes in the presence of Ni(dppe)Br_2 and Zn to give the corresponding biaryl ketones have also been described by Cheng and co-workers.[9] Cooperative catalysis by Ru and Pd for the direct coupling of achelating aldehyde with iodoarenes or organostannanes was reported by Chang and co-workers.[10] The high availability of aldehydes renders this route particularly attractive.

Recently, Genet and co-workers have reported direct access to ketones from aldehydes via rhodium-catalyzed cross-coupling reaction with potassium tifluoro(organo)-borates.[11] To the best of our knowledge, one-pot synthesis diaryl ketones from aldehydes by palladium-catalyzed reaction with organoboronic acids have been unexplored ever before.

Recent studies in our group have focused on extending the scope and utility of the reaction between organoboron

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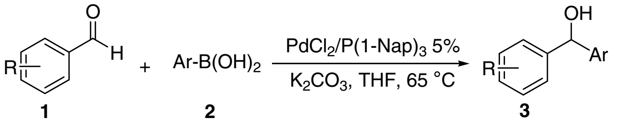
reagents and aldehydes. In our previous work, we reported the combination of $PdCl_2$ and $P(1\text{-nap})_3$ could promote the arylation of aldehydes to furnish the secondary alcohols in good to excellent yields at 65 °C Eq. 1.[12]



(1)

Herein, we report an efficient one-pot synthesis of diaryl ketones from aldehydes via Pd-catalyzed reaction of arylboronic acids, using inorganic base and easily prepared $P(1\text{-nap})_3$ in common organic solvent, providing arylarylketones with yields ranged from moderate to excellent.

Initial studies focused on the screening of the bases, oxidative additives and solvents using $PdCl_2$ as the palladium source and $P(1\text{-nap})_3$ as the ligand with the reaction of phenylboronic acid (**1a**) and 4-nitrobenzaldehyde (**2a**) as the model reaction. The screening results of the bases, additives and solvents are listed in Table 1.

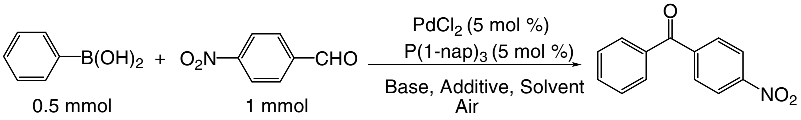
Through the screening process, no target product was detected in the presence of a series of oxidative additives; however, we were delighted to find that the yield could be improved to 32% when the combination of Cs_2CO_3 and undried toluene was employed in the air atmosphere. Encouraged by this promising result, we further optimized the reaction conditions, such as palladium catalysts, ligands (Fig. 1), ratio of L/Pd for phenylation of 4-nitrobenzaldehyde (Table 2).

As shown in Table 2, PPh_3 was totally ineffective in such transformation. Electron-deficient ligand such as **L6** and bidentate phosphine such as **L4** were non effective at all. Aminophosphine ligands **L2** and **L3** could improve the yield to 74% and 68%, respectively. The bulky, electron-rich monodentate phosphine ligand **L5** unexpectedly inhibited the reaction, nevertheless, **L1** was tested to be the best and the yield was dramatically increased to 93% with the combination of $Pd_2(dba)_3$ and **L1** (Table 2, entry 12). Increasing the amount of **L1** (Table 1, entries 17, 18) or decreasing the amount of Cs_2CO_3 (Table 2, entries 15, 16) in the system reduced the yield slightly.

With optimal conditions in hand, the reaction of different organoboronic acids with various aryl aldehydes was examined to explore the scope of the reaction (Table 3).

As shown in Table 3, the reaction proceeded smoothly in the presence of a variety of functional groups including nitro, cyano, acetoxy, trifluoromethyl and chloro groups. Nitro-substituted aryl aldehydes reacted with arylboronic acids easily and gave biarylketones in high yield partly due to the withdrawing group on aryl increased the activity of C=O bond. Generally, electronically neutral and rich aldehydes except furan-2-carbaldehyde **2f** gave poor yield. Aliphatic aldehydes have no reactivity at all. Arylboronic acids with electron-withdrawing substitution group are prone to homocoupling and protodeboronation side

Table 1
Selected results of bases, additives and solvents screening[a]



Entry	Base (equiv)	Additive (equiv)	Solvent	Yield[b] (%)
1	K_2CO_3 (3)	$PhI(OAc)_2$ (1)	THF	<5
2	K_2CO_3 (3)	Benzoquinone (2)	THF	<5
3	K_2CO_3 (3)	PCC (1)	THF	<5
4	K_2CO_3 (3)	Ag_2O (3)	THF	<5
5	K_2CO_3 (2)	NaOH (1)	THF	<5
6	K_2CO_3 (1)	NaOH (2)	THF	8
7	NaOH (3)	None	THF	10
8	KOH (3)	None	THF	<5
9	CsOH (3)	None	THF	<5
10	$KOBu^t$ (3)	None	THF	<5
11	Ag_2CO_3 (3)	None	THF	<5
12	Chloroamine-T (3)	None	Toluene	<5
13	Rb_2CO_3 (3)	None	Dioxane	<5
14	Cs_2CO_3 (3)	None	DMF	<5
15	Cs_2CO_3 (3)	None	DMA	<5
16	Cs_2CO_3 (3)	None	DMSO	<5
17	Cs_2CO_3 (3)	None	$BrCH_2CH_2Br$	<5
18	Cs_2CO_3 (3)	None	$CH_3CH_2NO_2$	<5
19	Cs_2CO_3 (3)	None	THF	<5
20	Cs_2CO_3 (3)	None	Toluene	32[c]

[a] All of the reaction were run with $PdCl_2$ (5 mol %), $P(1\text{-nap})_3$ (5 mol %) at 65 °C in THF and 120 °C in other solvents in sealed tube for 24 h.
[b] GC yield.
[c] Isolated yield.

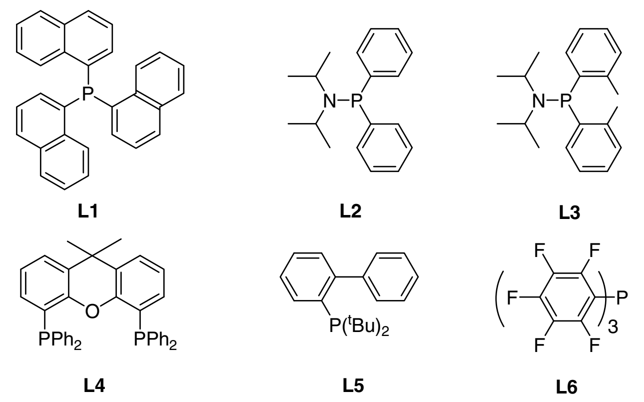
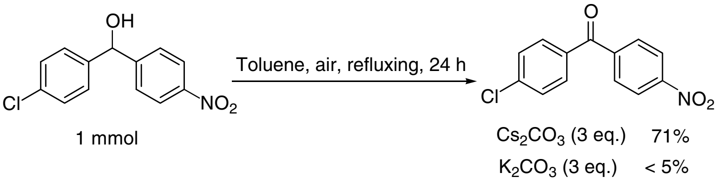


Fig. 1. Ligands screening.

reactions.[13] In our system, however, **1b** and **le** could proceed smoothly with **2a** and **3ba** and **3ea** were isolated in 91% and 82% yield, respectively (Table 3, entries 7, 10).

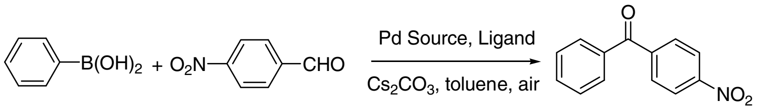
Hetero-aryl boronic acid, such as **1f**, was still good partner in this procedure, albeit the yield was decreased to 56%, which may be owing to the fact that heteroatom in the hetero-aryl boronic acid may deactivate the transition metal.[14] Hetero-aryl aldehyde, such as furfural **2f**, had good activity in the reaction, and **3af** was isolated in 71% yield. 4-Chlorophenylboronic acid **1c** could proceed smoothly with **2a** to afford **3ca** in 75% isolated yield and keep the chloro group intact. A mono substitution in the *ortho* position of the coupling partners reduced reactivity slightly. For example, **3ha** and **3ia** were isolated in 66% and 65% yield, respectively. Compared with most of the previous reports, it should be noted that bulky and cheap aldehydes were relatively excess to the boronic acids in our system. The feasibility of access to highly hindered diarylketones by use of di-*ortho*-substituted and electron-rich 2,6-dimethoxyl-benzaldehyde or mesitylboronic acid failed.



(2)

Table 2

Effects of Pd sources, ligands, the amount of base and L/Pd ratio on the palladium-catalyzed phenylation of 4-nitrobenzaldehyde[a]

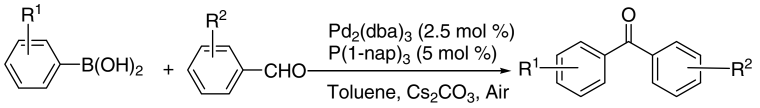


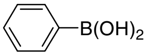
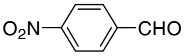
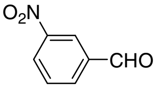
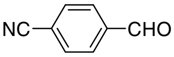
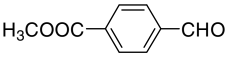
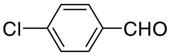
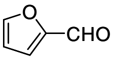
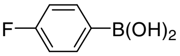
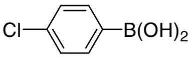
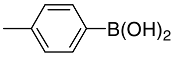
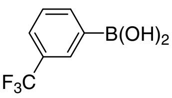
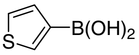
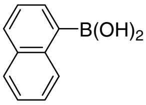
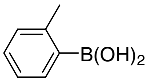
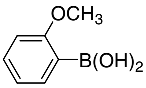
Entry	Pd source	Base (equiv)	Ligand	L/Pd ratio	Yield[b] (%)
1	$Pd(OAc)_2$	Cs_2CO_3 (3)	**L1**	1	85
2	$Pd(OAc)_2$	Cs_2CO_3 (3)	**L2**	1	74
3	$Pd(OAc)_2$	Cs_2CO_3 (3)	**L3**	1	68
4	$Pd(OAc)_2$	Cs_2CO_3 (3)	**L4**	1	<5
5	$Pd(OAc)_2$	Cs_2CO_3 (3)	**L5**	1	<5
6	$Pd(OAc)_2$	Cs_2CO_3 (3)	**L6**	1	<5
7	$Pd(OAc)_2$	Cs_2CO_3 (3)	**PPh_3**	1	<5
8	$PdCl_2$	Cs_2CO_3 (3)	**L1**	1	28
9	$PdCl_2(PPh_3)_2$	Cs_2CO_3 (3)	**L1**	1	78
10	$PdCl_2(PhCN)_2$	Cs_2CO_3 (3)	**L1**	1	73
11	$Pd(PPh_3)_4$	Cs_2CO_3 (3)	**L1**	1	53
12	$Pd_2(dba)_3$	Cs_2CO_3 (3)	**L1**	1	93
13	$Pd_2(dba)_3CHCl_3$	Cs_2CO_3 (3)	**L1**	1	83
14	$PdCl_2(Py)_2$	Cs_2CO_3 (3)	**L1**	1	59
15	$Pd_2(dba)_3$	Cs_2CO_3 (2)	**L1**	1	83
16	$Pd_2(dba)_3$	Cs_2CO_3 (1)	**L1**	1	81
17	$Pd_2(dba)_3$	Cs_2CO_3 (3)	**L1**	2	82
18	$Pd_2(dba)_3$	Cs_2CO_3 (3)	**L1**	3	80
19	$Pd_2(dba)_3$	Cs_2CO_3 (3)	**L1**	1	86

[a] All reactions were run with 4-nitrobenzaldehyde (151 mg, 1.0 mmol), phenylboronic acid (61 mg, 0.5 mmol), Pd source (5 mol %), Cs_2CO_3, and indicated L/Pd ratio in 5 mL undried toluene at 120 °C for 24 h.

[b] Isolated yield.

Table 3
Palladium-catalyzed one-pot synthesis of diaryl ketones[a]



Entry	Boronic acids	Aldehydes	Products	Yield[b] (%)
1	 **1a**	 **2a**	**3aa**	93
2	**1a**	 **2b**	**3ab**	89
3	**1a**	 **2c**	**3ac**	42
4	**1a**	 **2d**	**3ad**	28
5	**1a**	 **2e**	**3ae**	72
6	**1a**	 **2f**	**3af**	71[c]
7	 **1b**	**2a**	**3ba**	91
8	 **1c**	**2a**	**3ca**	75
9	 **1d**	**2a**	**3da**	72
10	 **1e**	**2a**	**3ea**	82
11	 **1f**	**2a**	**3fa**	56
12	 **1g**	**2a**	**3ga**	70
13	 **1h**	**2a**	**3ha**	66
14	 **1i**	**2a**	**3ia**	65[d]

[a] All reactions were run with aldehyde (1.0 mmol), organoboronic acid (0.5 mmol), Cs_2CO_3 (488 mg, 1.5 mmol), $Pd_2(dba)_3$ (11.4 mg, 2.5 mol %) and **L1** (5 mol %, 10.3 mg) in 3 mL undried toluene at 120 °C in sealed tube for 24 h.

[b] Isolated yield.

[c] **1a** 1.0 mmol, **2f** 0.5 mmol.

[d] **1i** 1.0 mmol, **2a** 0.5 mmol.

During the reaction process, we initially found some secondary alcohols were produced by GC–MS. However, we found that these secondary alcohols gradually disappeared during the process of the reaction. Thus we supposed that in our system Cs_2CO_3 could mediate the aerobic oxidation of the addition products formed in situ to aromatic ketones. To further confirm the supposition, we tested the different activities of K_2CO_3 and Cs_2CO_3 in the reaction.

We found that the corresponding product could be generated in 72% yield in the presence of Cs_2CO_3 (3.0 equiv), while no product was detected when K_2CO_3 was used in the reaction (Eq. 2). Thus, we suppose that Cs_2CO_3 might exhibit a dual ability in our system. (1) Facilitating the addition of organoboronic acids to aldehydes, affording carbinol derivatives, while strong bases such as KOH have no activity in this step due to the incompatibility with aldehydes. (2) Prompting the aerobic oxidation of the carbinol derivatives in situ to aromatic ketones, while K_2CO_3 could not promote this step due to the weaker base than Cs_2CO_3.

In summary, this reaction represents an approach to synthesize diarylketones with yields ranged from moderate to excellent in air atmosphere. Since the aryl aldehydes can be facilely transformed from various functional groups such as methyl, hydroxylmethyl, carboxyl, cyano and ester,[15] this methodology appears to be versatile and may provide potential opportunities in the synthesis of complex natural organic compounds.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.12.074.

References and notes

1. (a) Dieter, R. K. *Tetrahedron* **1999**, *55*, 4177; (b) Lawrence, N. J. *J. Chem. Soc. Perkin Trans. 1* **1998**, 1739; (c) Krause, N. *Modern Organocopper Chemistry*; Wiley-VCH: Weinheim, 2002.
2. (a) Furstner, A.; Voigtlander, D.; Schrader, W.; Giebel, D.; Reetz, M. T. *Org. Lett.* **2001**, *3*, 417; (b) Song, C. E.; Shim, W. H.; Roh, E. J.; Choi, J. H. *Chem. Commun.* **2000**, 1695; (c) Ross, J.; Xiao, J. *Green Chem.* **2002**, *4*, 129; (d) Gmouh, S.; Yang, H.; Vaultier, M. *Org. Lett.* **2003**, *5*, 2219; (e) Nara, S. J.; Harjani, J. R.; Salunkhe, M. M. *J. Org. Chem.* **2001**, *66*, 8616; (f) Fillion, E.; Fishlock, D.; Wilsily, A.; Goll, J. M. *J. Org. Chem.* **2005**, *70*, 1316; (g) Furstner, A.; Voigtlander, D.; Schrader, W.; Giebel, D.; Reetz, M. T. *Org. Lett.* **2001**, *3*, 417; (h) Gooßen, L. J.; Ghosh, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 3458; (i) Sarvari, M. H.; Sharghi, H. *J. Org. Chem.* **2004**, *69*, 6953; (j) Ichikawa, J.; Jyono, H.; Kudo, T.; Fujiwara, M.; Yokota, M. *Synthesis* **2005**, 39.
3. (a) Larock, R. C. *Comprehensive Organic Transformations*; VCH: New York, 1989; (b) Groves, J. K. *Chem. Soc. Rev.* **1972**, *1*, 73; (c) Shirley, D. A. In *Organic Reactions*; Wiley: New York, 1954; Vol. 8, p 28; (d) Wakefield, B. J. *Organomagnesium Methods in Organic Synthesis*; Academic Press: London, 1995; (e) Silverman, G. S.; Rakita, P. E. *Handbook of Grignard Reagents*; Marcel Dekker: New York, 1996; (f) Goure, W. F.; Wright, M. E.; Davis, P. D.; Labadie, S. S.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 6417; (g) Cho, C. S.; Itotani, K.; Uemura, S. J. *J. Organomet. Chem.* **1993**, *433*, 253; (h) Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390; (i) Posner, G. H.; Whitten, C. E.; McFarland, P. E. *J. Am. Chem. Soc.* **1972**, *94*, 5106; (j) Karpov, A. S.; Muller, T. J. *Org. Lett.* **2003**, *5*, 3451; (k) Kim, S.-H.; Rieke, R. D. *J. Org. Chem.* **2000**, *65*, 2322; (l) Lee, P. H.; Lee, S. W.; Seomoon, D. *Org. Lett.* **2003**, *5*, 4963; (m) Larock, R. C.; Lu, Y. *J. Org. Chem.* **1993**, *58*, 2846; (n) Hart, D. W.; Schwartz, J. *J. Am. Chem. Soc.* **1974**, *96*, 8115; (o) Hegedus, L. S.; Kendall, R. M.; Lo, S. M.; Sheats, J. R. *J. Am. Chem. Soc.* **1975**, *97*, 5448; (p) Duplais, C.; Bures, F.; Sapountzis, I.; Korn, T. J.; Cahiez, G.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2968; (q) Zhang, Y.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 15964; (r) Wang, X.-J.; Zhang, L.; Sun, X.; Xu, Y.; Krishnamurthy, D.; Senanayake, C. H. *Org. Lett.* **2005**, *7*, 5593.
4. (a) Xin, B. W.; Zhang, Y. H.; Cheng, K. *J. Org. Chem.* **2006**, *71*, 5725; (b) Kakino, R.; Shimizu, I.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 371; (c) Kakino, R.; Yasumi, S.; Shimizu, I.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 137; (d) Kakino, R.; Narahashi, H.; Shimizu, I.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 1333; (e) Kakino, R.; Narahashi, H.; Shimizu, I.; Yamamoto, A. *Chem. Lett.* **2001**, 1242; (f) Goossen, L. J.; Ghosh, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 3458; (g) Goossen, L. J.; Ghosh, K. *Eur. J. Org. Chem.* **2002**, 3254; (h) Goossen, L. J.; Ghosh, K. *Chem. Commun.* **2001**, 2084; (i) Goossen, L. J.; Winkel, L.; Doehring, A.; Ghosh, K.; Paetzold, J. *Synlett* **2002**, 1237; (j) Wang, D.; Zhang, Z. *Org. Lett.* **2003**, *5*, 4645.
5. Tatamidani, H.; Kakiuchi, F.; Chatani, N. *Org. Lett.* **2004**, *6*, 3597.
6. (a) Zeysing, B.; Gosch, C.; Terfort, A. *Org. Lett.* **2000**, *2*, 1843; (b) Savarin, C.; Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2000**, *2*, 3229; (c) Liebeskind, L. S.; Srogl, J. *J. Am. Chem. Soc.* **2000**, *122*, 11260; (d) Yu, Y.; Liebeskind, L. S. *J. Org. Chem.* **2004**, *69*, 3554.
7. Ishiyama, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2000**, *122*, 12043.
8. Akemiya, A. T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 14800.
9. Huang, Y.-C.; Majumdar, K. K.; Cheng, C.-H. *J. Org. Chem.* **2002**, *67*, 1682.
10. Ko, S.; Kang, B.; Chang, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 455.
11. Pucheault, M.; Darses, S.; Genet, J. P. *J. Am. Chem. Soc.* **2004**, *126*, 15356.
12. Qin, C.; Wu, H.; Cheng, J.; Chen, X.; Liu, M.; Zhang, W.; Su, W.; Ding, J. *J. Org. Chem.* **2007**, *72*, 4102.
13. Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685; and references cited therein.
14. (a) Yang, Y. *Synth. Commun.* **1989**, *19*, 1001; (b) Menard, F.; Chapman, T. M.; Dockendorff, C.; Lautens, M. *Org. Lett.* **2006**, *8*, 4569.
15. Ferguson, L. N. *Chem. Rev.* **1946**, *38*, 227.