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Suzuki–Miyaura Cross-Coupling of Benzylic Carbonates with Arylboronic Acids

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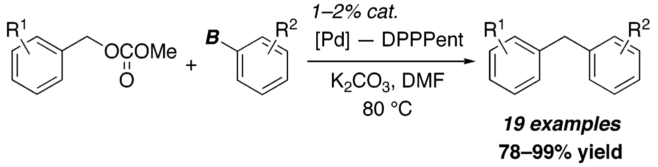
ABSTRACT



The cross-coupling of benzylic carbonates with arylboronic acids gave the corresponding diarylmethanes in high yields by use of the palladium catalyst generated in situ from [Pd(η^3-C_3H_5)Cl]$_2$ and 1,5-bis(diphenylphosphino)pentane (DPPPent). The Suzuki–Miyaura reaction using DPPPent–palladium catalyst is applicable to syntheses of a broad range of functionalized diarylmethanes.

During the last several years, tremendous progress has been made in palladium-catalyzed cross-couplings of organometallic compounds with unactivated aryl chlorides,[1] which had been regarded as unsuitable electrophilic coupling partners. The catalytic cross-coupling can now be conducted even with alkyl chloride.[2] However, the use of carboxylate functionality as a leaving group on an electrophilic substrate is unexplored except for the reactions of allylic esters.[3] The acyl C−O bond of carboxylate is usually cleaved by palladium(0) complex (path a), and aryl carboxylates are often employed in the catalytic acylation of organometallic compounds (Figure 1).[4] The oxidative addition of the C−O bond leading to (alkyl)(carboxylato)palladium **A** (path b) is desirable for the development of the cross-coupling using an ester, but the C−O bond is difficult to activate by a low-valent metal complex in general. Only one example of the formation of **A** through path b has been reported in the reaction of benzyl trifluoroacetate with palladium(0) complex.[5,6]

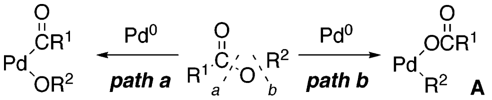


Figure 1. Oxidative Addition of Carboxylate to Palladium(0).

Recently, we reported catalytic benzylic substitutions of benzylic carbonates, where a DPPF-ligated palladium complex was found to be the best catalyst.[7] The catalytic reaction may involve the formation of (η^3-benzyl)palladium through path b, and it suggests that the DPPF−palladium catalyst is efficient for the activation of the benzylic C−O bond. The

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(1) Reviews: (a) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176−4211. Examples: (b) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3387−3388. (c) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722−9723. (d) Kataoka, N.; Shelby, Q.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553−5566.

(2) (a) Kirchhoff, J. H.; Dai, C.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 1945−1947. (b) Frisch, A. C.; Shaikh, N.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4056−4059. (c) Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 12527−12530. (d) Frisch, A. C.; Rataboul, F.; Zapf, A.; Beller, M. *J. Organomet. Chem.* **2003**, *687*, 403−409.

(3) Examples: (a) Del Valle, L.; Stille, J. K.; Hegedus, L. S. *J. Org. Chem.* **1990**, *55*, 3019−3023. (b) Uozumi, Y.; Danjo, H.; Hayashi, T. *J. Org. Chem.* **1999**, *64*, 3384−3388. (c) Bouyssi, D.; Gerusz, V.; Balme, G. *Eur. J. Org. Chem.* **2002**, 2445−2448.

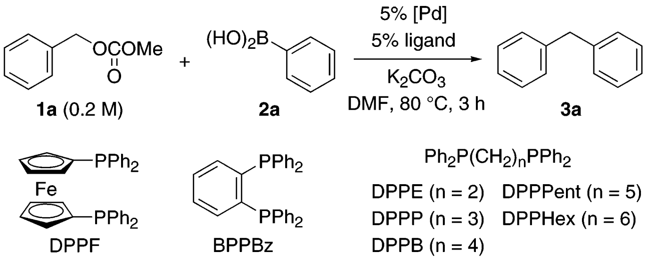
(4) (a) Kakino, R.; Shimizu, I.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **2001**, *72*, 371−376. (b) Tatamidani, H.; Kakiuchi, F.; Chatani, N. *Org. Lett.* **2004**, *6*, 3597−3599.

(5) Nagayama, K.; Shimizu, I.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 799−803.

(6) Narahashi, H.; Yamamoto, A.; Shimizu, I. *Chem. Lett.* **2004**, *33*, 348−349.

10.1021/ol050078q CCC: $30.25

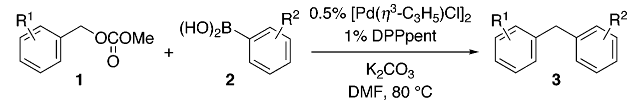
Table 1. Effect of Phosphine−Palladium Complex on the Cross-Coupling of Benzyl Methyl Carbonate with Phenylboronic Acid[a]

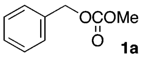
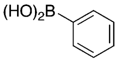
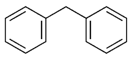
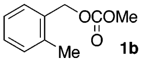
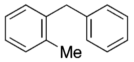
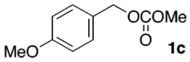
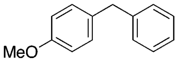
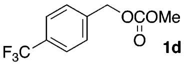
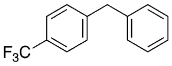
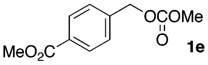
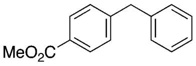
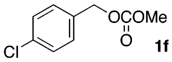
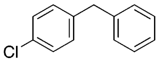
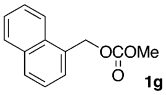
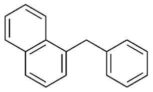
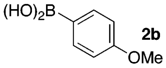
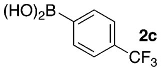
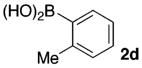
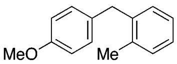
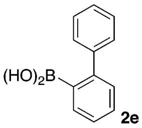
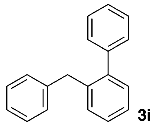
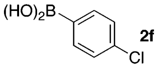
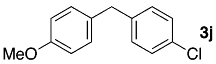
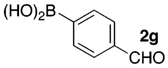
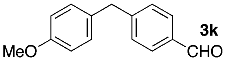
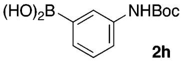
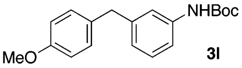
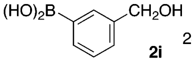
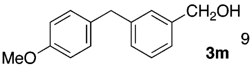
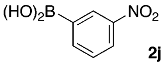
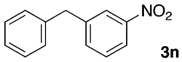
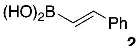
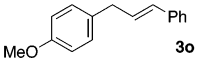


entry	ligand	[Pd]	yield, %[b]
1	DPPF	$[Pd(\eta^3\text{-}C_3H_5)(cod)]BF_4$	3
2	PPh_3	$[Pd(\eta^3\text{-}C_3H_5)(cod)]BF_4$	2
3	$P(C_6H_4\text{-}o\text{-}Me)$	$[Pd(\eta^3\text{-}C_3H_5)(cod)]BF_4$	0
4	$P(t\text{-}Bu)_3$	$[Pd(\eta^3\text{-}C_3H_5)(cod)]BF_4$	0
5	DPPBz	$[Pd(\eta^3\text{-}C_3H_5)(cod)]BF_4$	1
6	DPPE	$[Pd(\eta^3\text{-}C_3H_5)(cod)]BF_4$	3
7	DPPP	$[Pd(\eta^3\text{-}C_3H_5)(cod)]BF_4$	1
8	DPPB	$[Pd(\eta^3\text{-}C_3H_5)(cod)]BF_4$	24
9	DPPPent	$[Pd(\eta^3\text{-}C_3H_5)(cod)]BF_4$	32
10	DPPHex	$[Pd(\eta^3\text{-}C_3H_5)(cod)]BF_4$	13
11	DPPPent	$PdBr_2(cod)$	16
12	DPPPent	$Pd(OAc)_2$	23
13	DPPPent	$Pd(dba)_2$	<1
14	DPPPent	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	50 (89[c])

[a] Reactions were conducted in DMF (1.0 mL) at 80 °C for 3 h. The ratio of **1a** (0.2 mmol):**2a**:K_2CO_3:[Pd]:ligand was 20:30:60:1:1. [b] GC yield (average of two runs). [c] GC yield at 24 h.

Table 2. Cross-Coupling of Benzylic Carbonates (**1**) with Arylboronic Acids (**2**)[a]



entry	1	2	time, h	product (3)	yield, %[b]
1[c]	 **1a**	 **2a**	24	 **3a**	80
2[c]	 **1b**	**2a**	5	 **3b**	88
3	 **1c**	**2a**	5	 **3c**	94
4	 **1d**	**2a**	12	 **3d**	94
5	 **1e**	**2a**	3	 **3e**	82
6	 **1f**	**2a**	24	 **3f**	84
7	 **1g**	**2a**	5	 **3g**	90
8	**1a**	 **2b**	24	**3c**	90
9	**1a**	 **2c**	24	**3d**	81
10	**1c**	 **2d**	24	 **3h**	99
11	**1a**	 **2e**	48	 **3i**	87
12	**1c**	 **2f**	72	 **3j**	85
13	**1c**	 **2g**	72	 **3k**	78
14	**1c**	 **2h**	3	 **3l**	92
15	**1c**	 **2i**	24	 **3m**	92
16[c]	**1a**	 **2j**	72	 **3n**	83
17	**1c**	 **2k**	48	 **3o**	82

[a] Reactions were conducted in DMF (1.0 mL) at 80 °C. The ratio of **1** (1.0 mmol):**2**:K_2CO_3:$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$:DPPPent was 100:110:220:0.5:1. [b] Isolated yield. [c] Reactions were conducted with 2 mol % palladium.

above consideration prompted us to develop a new class of cross-couplings using benzylic carbonates as electrophiles. In this paper, we report the Suzuki−Miyaura cross-coupling of benzylic carbonates.[8,9] The catalytic reaction offered a new straightforward approach to diverse diarylmethanes,[10] which is a ubiquitous structural constituent of pharmacologically interesting compounds.[11]

First, we attempted the cross-coupling of benzyl methyl carbonate (**1a**) with phenylboronic acid (**2a**) in the presence of DPPF−$[Pd(\eta^3\text{-}C_3H_5)(cod)]BF_4$, which was the most effective catalyst for the benzylation of malonate carbanions by benzylic carbonate.[7a] However, the reaction failed to yield diphenylmethane (**3a**). We evaluated a broad range of phosphine ligands, palladium catalyst precursors, bases, and solvents. Selected results are shown in Table 1. The palladium catalyst generated in situ from $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and bidentate bisphosphine 1,5-bis(diphenylphosphino)pen-

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(7) (a) Kuwano, R.; Kondo, Y.; Matsuyama, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12104−12105. (b) Kuwano, R.; Kondo, Y. *Org. Lett.* **2004**, *6*, 3545−3547.

(8) Reviews: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483. (b) Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, 2419−2440.

(9) Examples of cross-coupling of benzyl halides with organoboron compounds: (a) Chowdhury, S.; Georghiou, P. *Tetrahedron Lett.* **1999**, *40*, 7599−7603. (b) Langle, S.; Abarbri, M.; Duchêne, A. *Tetrahedron Lett.* **2003**, *44*, 9255−9258. (c) Chahen, L.; Doucet, H.; Santelli, M. *Synlett* **2003**, 1668−1672.

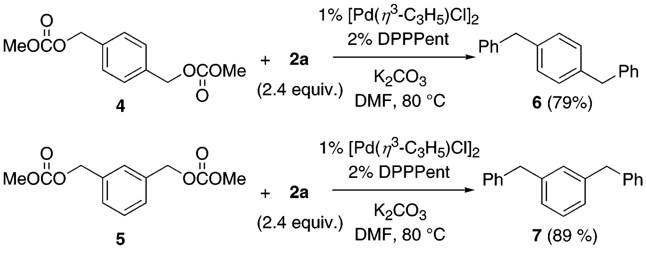
(10) Examples of diarylmethane synthesis through cross-coupling: (a) Negishi, E.-i.; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, *42*, 1821−1823. (b) Vanier, C.; Lorgé, F.; Wagner, A.; Mioskowski, C. *Angew. Chem., Int. Ed.* **2000**, *39*, 1679−1683. (c) Molander, G. A.; Ito, T. *Org. Lett.* **2001**, *3*, 393−396. (d) Itami, K.; Mineno, M.; Kamei, T.; Yoshida, J. *Org. Lett.* **2002**, *4*, 3635−3638.

(11) (a) Wai, J. S.; Egbertson, M. S.; Payne, L. S.; Fisher, T. E.; Embrey, M. W.; Tran, L. O.; Melamed, J. Y.; Langford, H. M.; Guare, J. P., Jr.; Zhuang, L.; Grey, V. E.; Vacca, J. P.; Holloway, M. K.; Naylor-Olsen, A. M.; Hazuda, D. J.; Felock, P. J.; Wolfe, A. L.; Stillmock, K. A.; Schleif, W. A.; Gabryelski, L. J.; Young, S. D. *J. Med. Chem.* **2000**, *43*, 4923−4926. (b) Long, Y.-Q.; Jiang, X.-H.; Dayam, R.; Sanchez, T.; Shoemaker, R.; Sei, S.; Neamati, N. *J. Med. Chem.* **2004**, *47*, 2561−2573.

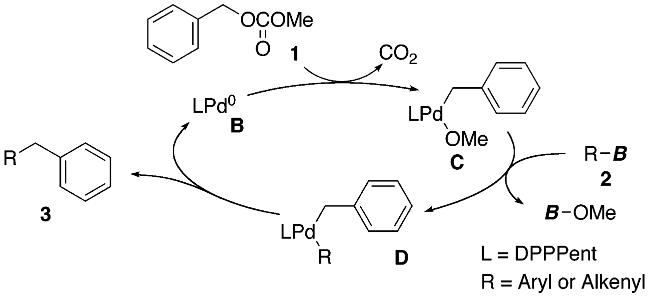
tane (DPPPent) recorded the highest yield of **3a**. The choice of a phosphine ligand is essential for the catalysis. Monophosphine-ligated palladium complexes exhibited poor catalytic activity for the cross-coupling. Bidentate phosphine ligands possessing a small bite angle were ineffective, while increasing the ligand bite angle enhanced the reaction rate and the yield of **3a**. The yield of **3a** reached a maximum when DPPPent was used. DPPHex, providing a larger P−Pd−P angle, was less effective than DPPPent.[12] [Pd(η^3-C_3H_5)Cl]$_2$ was superior to the other palladium catalyst precursors. DMF was the solvent of choice. K_3PO_4 and Cs_2CO_3, as well as K_2CO_3, were suitable bases for the cross-coupling of **1a** with **2a**, but K_2CO_3 is economically preferred.[13] The catalyst loading was successfully reduced to 2 mol % palladium at a high concentration of **1a** (1.0 M) under the optimal reaction conditions, and **3a** was obtained in 80% isolated yield (Table 2, entry 1).

The optimal palladium catalyst and reaction conditions proved to be useful for cross-couplings of diverse benzylic carbonates and boronic acids, as shown in Table 2. Both electron-rich and electron-poor benzylic esters, **1c** and **1d**, respectively, were more reactive than **1a**,[14] and their reactions with **2a** afforded diarylmethane **3c** and **3d** in high yields at a catalyst loading of 1 mol % palladium. On the other hand, the rate of the reaction of electron-rich boronic acid **2b** was almost equal to that of **2a**, but the electron-withdrawing group on arylboronic acid **2c** accelerated the cross-coupling.[14] The ortho substitutents of arylboronic acids **2d** and **2e** did not hinder the catalytic reaction. A variety of diarylmethanes bearing chloro, carboxylate, aldehyde, carbamate, alcohol, and nitro functionalities were prepared in high yields by means of the DPPPent−palladium catalyst. Alkenylboronic acid **2k** was transformed into allylarene **3o** in high yield, and no undesirable migration of the double bond was observed. However, alkylboronic acids failed to react with **1a**, and the desired cross-coupling product was not obtained. Xylene-α,α′-diol dicarbonates **4** and **5** underwent two-directional cross-coupling with **2a**, as shown in Scheme 1, and yielded *p*- (**6**) and *m*-dibenzylbenzene (**7**), respectively.

Scheme 1. Syntheses of Dibenzylbenzenes



Scheme 2. Proposed Mechanism



A proposed mechanism of the present reaction is shown in Scheme 2. The benzylic C−O bond of **1** is cleaved by DPPPent-ligated palladium(0) **B**, and (η^1-benzyl)(alkoxo)-palladium intermediate **C** was formed through decarboxylation of the carbonate leaving group. The alkoxo ligand on palladium is more effective for transmetalation with organoboron **2** than acetato and halo ligands.[15] No cross-coupling of benzyl acetate with **2a** occurred in the presence of the DPPPent−palladium catalyst. The resulting (alkyl)(benzyl)-palladium **D** provides diarylmethane **3** and regenerates palladium(0) **B** through reductive elimination.

In conclusion, we have proved that benzylic carbonates are a new class of coupling partners in Suzuki−Miyaura cross-coupling. The palladium catalyst generated from [Pd(η^3-C_3H_5)Cl] and bidentate bisphosphine DPPPent is most effective for the cross-coupling using benzylic carbonates. The catalytic reaction showed high functional group compatibility, and a wide range of arylboronic acids are now commercially available. Therefore, this methodology developed by us will offer a fruitful and general synthetic method for diarylmethanes.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) We speculate that the cleavage of the benzylic C−O bond proceeded through a pathway similar to the formation of (η^3-allyl)palladium from allylic ester. The activation energy of the process would depend on the potential energy of (η^3-benzyl)palladium. The angle of P−Pd−P was 104.37° in the DFT-optimized structure (B3LYP/6-31G(d) & LANL2DZ for Pd) of [$(H_3P)_2$-Pd(η^3-benzyl)]$^+$. DPPPent might provide a bite angle close to 104.37° and might form undistorted (η^3-benzyl)palladium, which immediately isomerized to (η^1-benzyl)palladium.

(13) When the reaction was conducted with 1.0 equiv of Cs_2CO_3 to **2a**, no formation of **3a** was observed. The acidic proton of boronic acid might cause hydrolysis of Pd−OR bond of the intermediate **C** in Scheme 2.

(14) Relative reactivities of **1a**,**c**,**d** and **2a**,**b**,**c** were estimated by competitive experiments using **2a** and **1a**, respectively. See Supporting Information.

(15) Miyaura, N.; Yamada, K.; Suginome, H.; Suzuki, A. *J. Am. Chem. Soc.* **1985**, *107*, 972−980.