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Transition-metal-free cross-coupling reaction of benzylic halides with arylboronic acids leading to diarylmethanes

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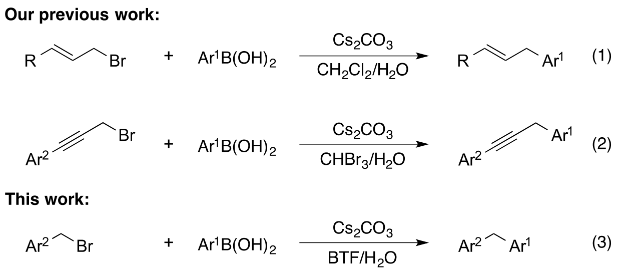
ABSTRACT

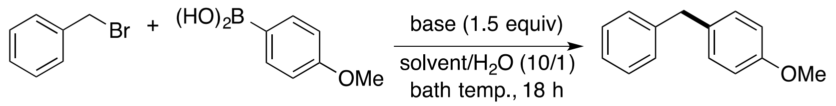
The cross-coupling reaction between arylboronic acids and various benzylic halides proceeded without using a transition-metal catalyst to give the corresponding diarylmethanes in moderate to good yields.

We recently reported the transition-metal-free Suzuki–Miyaura coupling reaction of allylic bromides[1] with arylboronic acids, which gave the corresponding allylated products (Scheme 1, eq 1). We also reported the transition-metal-free Suzuki–Miyaura coupling reaction of propargylic bromides[2] with arylboronic acids, which gave the corresponding propargylated products (Scheme 1, eq 2). We thought that a similar catalyst-free system could be extended to arylation of benzylic bromides. Herein we would like to report the transition-metal-free cross-coupling reaction of benzylic bromides with arylboronic acids (eq 3).[3,4,5]



Scheme 1. Transition-metal-free cross-coupling reaction

Table 1. Screening of reaction conditions[a]



1a **2a** (1.3 equiv) **3a**

Entry	Base	Solvent	Temp (°C)	Yield (%)[b]
1	Cs_2CO_3	CH_2Cl_2	60	32
2	Cs_2CO_3	$CHBr_3$	110	47
3	Cs_2CO_3	Toluene	110	38
4	Cs_2CO_3	BTF[c]	110	57
5	CsF	BTF	110	41
6	K_2CO_3	BTF	110	14
7	KF	BTF	110	14

[a] Reaction conditions: **1a** (1.0 equiv), **2a** (1.3 equiv), base (1.5 equiv), solvent/H_2O (0.4 M for **1a**), bath temp. (°C), 18 h.

[b] Isolated yield. [c] Benzotrifluoride.

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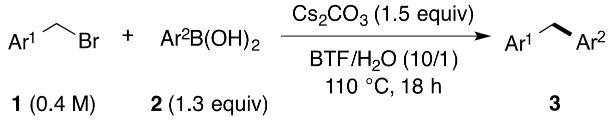
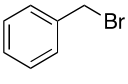
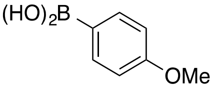
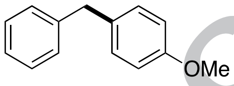
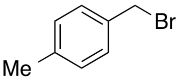
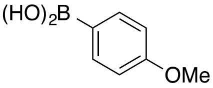
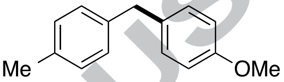
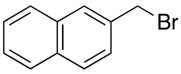
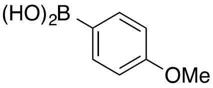
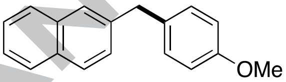
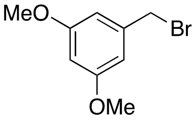
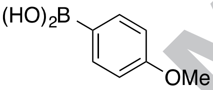
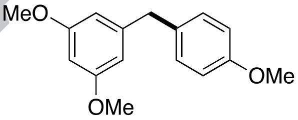
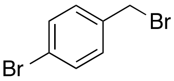
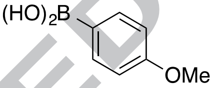
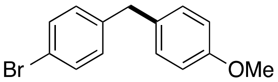
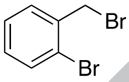
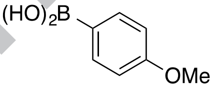
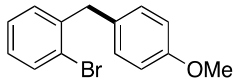
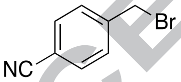
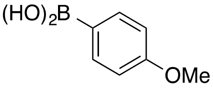
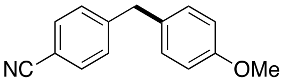
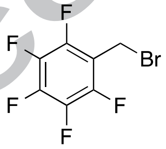
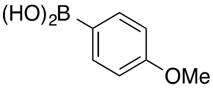
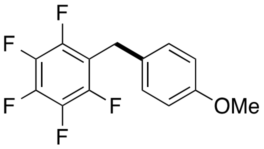
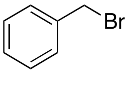
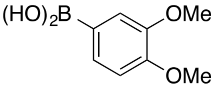
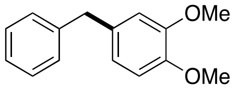
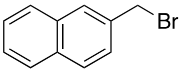
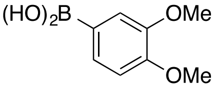
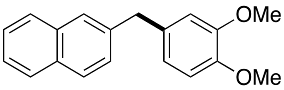
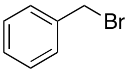
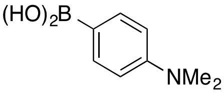
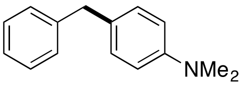
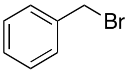
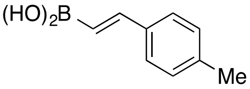
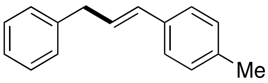
Treatment of benzyl bromide (**1a**) with 4-methoxyphenylboronic acid (**2a**: 1.3 equiv) and Cs_2CO_3 (1.5 equiv, purchased from Wako Pure Chemical Industries, Ltd.) in a mixed solvent of CH_2Cl_2/H_2O (10/1) at 60 °C for 18 h gave 1-benzyl-4-methoxybenzene (**3a**) in 32% yield (Table 1, entry 1).

In this reaction, water is necessary to dissolve boronic acid **2a** and benzyl alcohol was formed as by-product (21%), which was obtained by hydrolysis of **1a**. We then surveyed the effects of solvent and reaction temperature. The reaction using $CHBr_3/H_2O$ (10/1) as the solvent at the elevated temperature such as 110 °C

Table 2. Transition-metal-free cross-coupling reaction of benzylic bromides **1** with arylboronic acids **2**[a]



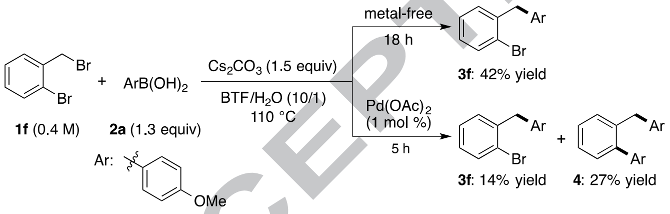
Entry	1	2	Product 3	Yield (%)[b]
1	 **1a**	 **2a**	 **3a**	57
2	 **1b**	 **2a**	 **3b**	55
3	 **1c**	 **2a**	 **3c**	68
4	 **1d**	 **2a**	 **3d**	49
5	 **1e**	 **2a**	 **3e**	46
6	 **1f**	 **2a**	 **3f**	42
7	 **1g**	 **2a**	 **3g**	42
8	 **1h**	 **2a**	 **3h**	22
9	 **1a**	 **2b**	 **3i**	41
10	 **1c**	 **2b**	 **3j**	57
11	 **1a**	 **2c**	 **3k**	29
12	 **1a**	 **2e**	 **3l**	30[c]

[a] Reaction conditions: **1** (1.0 equiv), **2** (1.3 equiv), Cs_2CO_3 (1.5 equiv), BTF/H_2O (0.4 M for **1**), 110 °C, 18 h. [b] Isolated yield.

[c] Only the (*E*)-isomer of **3l** was obtained.

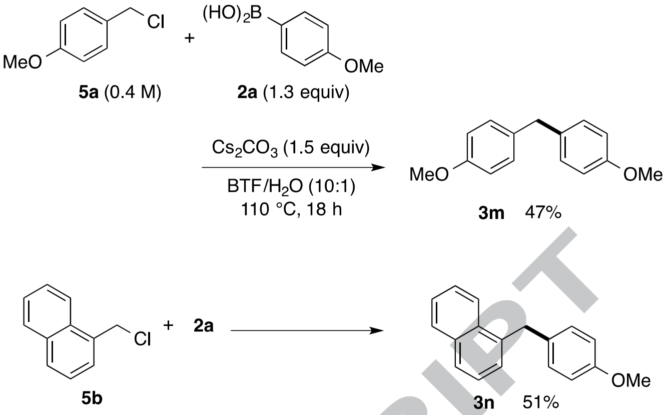
afforded **3a** in 47% yield (entry 2). Whereas toluene/H_2O (10/1) was less effective (38%; entry 3), further improvement of the yield was achieved using BTF(benzotrifluoride)/H_2O (10/1) (57%; entry 4). The use of CsF in BTF/H_2O (10/1) as a base gave **3a** in 41% yield (entry 5). However, the use of K_2CO_3 and KF was far less effective (entries 6 and 7).

With the optimized reaction conditions of entry 4 in hand (Table 1), the scope of the present metal-free Suzuki–Miyaura coupling reaction was investigated (Table 2). 4-Methylbenzyl bromide (**1b**) showed comparable reactivity with benzyl bromide (**1a**) (55%; entry 2). The reaction of 2-(bromomethyl)naphthalene (**1c**) with **2a** gave the corresponding product **3c** in 68% yield (entry 3). 3,5-Dimethoxybenzyl bromide (**1d**) also reacted with **2a** to afford **3d** in 49% yield (entry 4).[6] It is interesting to note that bromine-containing benzyl bromides (**1e** and **1f**) tolerated the reaction conditions to furnish the corresponding cross-coupling product **3e** and **3g** in 46% and 42% yields, respectively without the formation of any trace amount of double arylated products (entries 5 and 6). These are interesting, since the palladium-catalyzed Suzuki-Miyaura coupling reaction of **1e** with **2a** is known to give the biaryl product as major product.[7] Indeed, when 1 mol % of $Pd(OAc)_2$ was added to the reaction mixture under our standard reaction conditions, the biaryl product **4** was obtained as a major product after 5 h (Scheme 2). *p*-Cyano-substituted benzyl bromide **1g** gave **3g** in 42 % yield (entry 7). Electron-poor aryl boronic acid was less reactive as in the cases of our former studies on allylation and propargylation (entry 8). Whereas 3,4-dimethoxyphenylboronic acid (**2b**) worked well for the present metal-free coupling reaction (entries 9 and 10), dimethylamino-substituted phenylboronic acid **2c** gave a poor result (entry 11). The cross-coupling reaction of trans-2-(4-methylphenyl)vinylboronic acid (**2e**) with benzyl bromide (**1a**) proceeded to give the benzylated *E*-form alkene **3l** in 30% yield (entry 12). Electron-poor aryl boronic acid, such as *p*-CF_3-phenylboronic acid, did not react with **1a**.[8] This is in contrast with the good result by palladium-catalyzed reaction.[4]



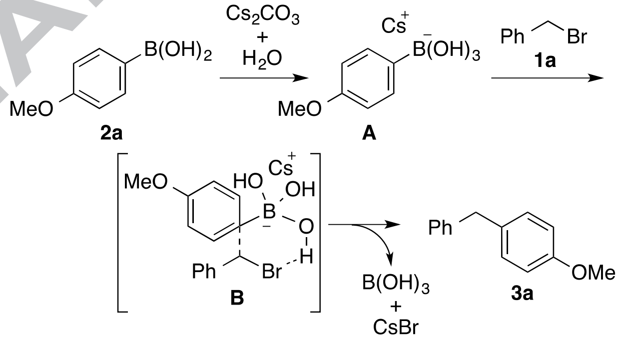
Scheme 2. Palladium-catalyzed Suzuki–Miyaura coupling reaction of **1f** with **2a**

These catalyst-free conditions were also applicable to the cross-coupling reaction of benzylic chlorides (Scheme 3). Thus, the reaction of 4-methoxybenzyl chloride (**5a**) with **2a** gave **3m** in 47% yield. Similarly, 1-(chloromethyl)naphthalene (**5b**) reacted with **2a** to give **3n** in 51% yield.



Scheme 3. Transition-metal-free cross-coupling reaction of benzylic chlorides **5** with 4-methoxyphenyl boronic acid (**2a**)

Scheme 4 illustrates a possible rationale for the present cross-coupling reaction, in which we assume an *ipso*-attack of arylboronic acid is involved.[1a,2] As a first step, **2a** would be converted to borate anion **A** by H_2O and Cs_2CO_3. **A** would then react with benzyl bromide (**1a**) through six-membered ring transition state **B** to give the cross-coupling product **3a**, accompanied by the liberation of boronic acid.[9,10]



Scheme 4. Possible mechanism for the formation of **3a** from **2a** and **1a.**

In summary, we have shown that, in the presence of cesium carbonate as a base and H_2O as a co-solvent, cross-coupling reaction of benzylic bromides and chlorides with arylboronic acids can take place without the use of any transition-metal catalysts. Though the yields are not so high, this protocol provides a mild method to prepare diarylmethanes, which are potentially useful compounds.[11] Additional applications of metal-free cross-coupling reactions are currently underway in our Laboratory.

Acknowledgments

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6. **Typical Procedure for a Transition-Metal-Free Suzuki–Miyaura Cross-Coupling Reaction of Benzylic Halides with Arylboronic Acids**: A mixture of 3,5-dimethoxybenzyl bromide (**1d**; 0.5 mmol), 4-methoxyphenylboronic acid (**2a**; 0.65 mmol, 1.3 equiv), and Cs_2CO_3 (0.75 mmol, 1.5 equiv) in BTF/H_2O (1.65 mL, 10/1) was stirred at 110 °C for 18 h. Then, the reaction mixture was treated with aq 1 N HCl, extracted with EtOAc and the organic layer was dried over $MgSO_4$. The organic layer was concentrated and the resulting residue was purified by column chromatography on silica gel (hexane-EtOAc, 10:1) to give 1,3-dimethoxy-5-(4-methoxybenzyl)benzene (**3d**) as a yellow liquid in 49% yield (63.29 mg, 0.245 mmol); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.75 (s, 6H), 3.80 (s, 3H), 3.86 (s, 2H), 6.32 (m, 3H), 6.82 (m, 2H), 7.11 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 41.7, 55.7(two peaks overlap), 98.3, 107.4, 107.5, 114.3, 130.3, 133.2, 144.3, 158.4, 161.2; IR(neat): 3001, 2934, 2836, 1607, 1470, 1428, 1348, 1206, 1107, 821 cm^{-1}; HRMS (EI) *m/z* calcd. for $C_{16}H_{18}O_3$: 258.1256, found: 258.1250.
7. Bandgar, B. P.; Bettigeri, S. V.; Phopase, J. *Tetrahedron Lett.* **2004**, *45*, 6959-6962.
8. Some previous work of metal-free Suzuki-Miyaura reactions was actually catalyzed by contaminated transition metals in inorganic base or solvent. See: Na_2CO_3; (a) Arvela, R. K.; Leadbeater, N. E.; Sangi, M. S.; Williams, A.; Granados, P.; Singer, R. D. *J. Org. Chem.* **2005**, *70*, 161-168. Dimethyl carbonate; (b) Inamoto, K.; Campbell, L. D.; Doi, T.; Koide, K. *Tetrahedron Lett.* **2012**, *53*, 3147-3148.
9. We tested four different purity/source of Cs_2CO_3 [TCI, Wako, Aldrich (99.9%), and Aldrich (99.995%)] suing the reaction of entry 6 in Table 2. In all cases, nearly the same results were provided.
10. For pharmaceuticals having diarylmethane structures, see: (a) Juteau, H.; Gareau, Y.; Labelle, M.; Sturino, C. F.; Sawyer, N.; Tremblay, N.; Lamontagne, S.; Carrière, M.-C.; Denis, D.; Metters, K. M. *Bioorg. Med. Chem.* **2001**, *9*, 1977-1984. (b) Rosowsky, A.; Chen, H.; Fu, H.; Queener, S. F. *Bioorg. Med. Chem.* **2003**, *11*, 59-67. (c) Forsch, R. A.; Queener, S. F.; Rosowsky, A. *Bioorg. Med. Chem.* **2004**, *14*, 1811-1815.
11. Compounds **3a**, **3b**, **3c**, **3e**, **3f**, **3g**, **3h**, **3i**, **3k**, **3l**, **3m**, and **3n** are known in literature. **3a**, **3b**, **3c**, **3k**, **3n**: Chang, S.-T.; Li, Q.; Chiang, R.-T.; Gau, H.-M. *Tetrahedron* **2012**, *68*, 3956-3962. **3e**: Brown, C. A.; Nile, T. A.; Mahon, M. F.; Webster, R. L. *Dalton Trans.* **2015**, *44*, 12189-12195. **3f**: Treu, M.; Jordis, U. *Molecules* **2002**, *7*, 18-25. **3g**: Benischke, A. D.; Knoll, I.; Rérat, A.; Gosmini, C.; Knochel, P. *Chem. Commun.* **2016**, *52*, 3171-3174. **3h**: Fan, S.; He, C.-Y.; Zhang, X. *Chem. Commun.* **2010**, *46*, 4926-4928. **3i**: Chen, C.-R.; Zhou, S.; Biradar, D. B.; Gau, H.-M. *Adv. Synth. Catal.* **2010**, *352*, 1718-1727. **3l**: Mino, T.; Kogure, T.; Abe, T.; Koizumi, T.; Fujita, T.; Sakamoto, M. *Eur. J. Org. Chem.* **2013**, 1501-1505. **3m**: Deshmukh, M. S.; Srivastava, A.; Das, B.; Jain, N. *J. Org. Chem.* **2015**, *80*, 10041-10048.

Graphical Abstract

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Transition-metal-free cross-coupling reaction of benzylic halides with arylboronic acids leading to diarylmethanes

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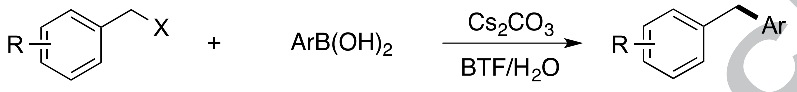
Mitsuhiro Ueda,* Daiki Nakakoji, Yuki Kuwahara, Kota Nishimura, and Ilhyong Ryu



R = H, Me, MeO,
Br, CN, F
X = Br, Cl

Ar = electron-rich aryl

14 examples
up to 68% yield

Highlights:

Transition-metal-free cross-coupling of benzylic halides with arylboronic acids.

Ionic substitution mechanism via a six-membered ring transition state is proposed.

Arylboronic acids react with benzylic halides at *ipso*-position of $B(OH)_2$.