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Suzuki–Miyaura Coupling Reaction Using Pentafluorophenylboronic Acid

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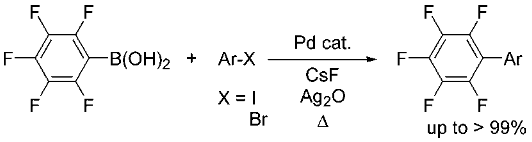
ABSTRACT



We have found new conditions for the Suzuki–Miyaura coupling reaction applicable to pentafluorophenylboronic acid ($C_6F_5B(OH)_2$) (1), which is an inactive substrate under normal conditions. The reactions of 1 with phenyl iodide or bromide under $Pd(PPh_3)_4/CsF/Ag_2O$ or $Pd_2(dba)_3/P(t\text{-}Bu)_3/CsF/Ag_2O$ catalytic system conditions gave 2,3,4,5,6-pentafluoro-1,1′-biphenyl (3a) in more than 90% yields. Combination of CsF and Ag_2O was essential for promoting these reactions.

The palladium-catalyzed cross-coupling reaction of arylboronic acid with aryl halide, known as the Suzuki−Miyaura coupling reaction, is one of the most useful methods for the synthesis of biaryl compounds.[1] However, pentafluorophenylboronic acid ($C_6F_5B(OH)_2$, **1**) is an inactive substrate under the usual reaction conditions,[2] probably because the transmetalation of the highly electron-deficient C_6F_5 group to the Pd center proceeds only with difficulty.[3,4] Recently, Pd-catalyzed and Ag_2O-promoted coupling reactions[5,6] of **1** with 2-iodopyridine[7] and the reactions of modified C_6F_5−boron compounds ($C_6F_5B(OMe)_3Li$[8a] or $C_6F_5BF_3K$[8b,c]) with aryl iodides have been reported. In the reaction with $C_6F_5BF_3K$, yields were reported to exceed 90%.[8b] However, these methods have limited utility because more widely used aryl bromides are not usable.[8] Here, we have developed an efficient Suzuki−Miyaura coupling reaction, using the commercially available compound **1**, which is applicable not only to aryl iodides but also to aryl bromides (condition A [$Pd(PPh_3)_4/CsF/Ag_2O$] and condition B [$Pd_2(dba)_3/P(t\text{-}Bu)_3/CsF/Ag_2O$]). The yield of the resulting pentafluorobiphenyl

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(2) (a) Havelková, M.; Dvořák, D.; Hocek, M. *Synthesis* **2001**, 1704. (b) Havelková, M.; Hocek, M.; Česnek, M.; Dvořák, D. *Synlett* **1999**, 1145. (c) Thiemann, T.; Umeno, K.; Ohira, D.; Inohae, E.; Sawada, T.; Mataka, S. *New J. Chem.* **1999**, *23*, 1067.

(3) The Mulliken charges of C^1 atoms in $ArB(OH)_2$ ($Ar = C_6F_5$: −0.11, Ar = Ph: +0.07) and in $ArB(OH)_3^-$ ($Ar = C_6F_5$: −0.21, Ar = Ph: −0.92) were calculated at the B3LYP/6-31G*//B3LYP/6-31+G* level. The results showed that the nucleophilicity of the C_6F_5 group on the boron atom was scarcely enhanced by the addition of the base (OH^-) to **1** in contrast to that of the Ph group. All calculations were performed by Gaussian 03W. Gaussian 03, Revision B.04: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.;. Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. Gaussian, Inc., Pittsburgh, PA, 2003.

(4) Another possibility for the low reactivity of $C_6F_5B(OH)_2$ which originates from the very slow reductive elimination step due to high stability of $Pd-C_6F_5$ bond is excluded as follows. We examined the reaction of $C_6F_5B(OH)_2$ with PhBr and that of $PhB(OH)_2$ with C_6F_5Br under the same conditions ($Pd(PPh_3)_4$, CsF), because both reactions should give C_6F_5-Ph via the identical intermediate (Ph-Pd-C_6F_5), i.e., through the same reductive elimination step. Although the former gave no product, the latter afforded the desired product of C_6F_5-Ph in 62% yield. The results show that the reductive elimination step does not have the problem in this case.

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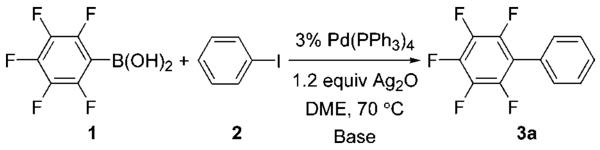
compounds **3** was as high as 97%, even in the reaction with aryl bromide.

First, we investigated the coupling reaction of **1** with iodobenzene (**2**) (Table 1) in the presence of Ag_2O, using the following procedure: a mixture of **1**, **2**, $Pd(PPh_3)_4$ (3 mol %), Ag_2O (1.2 equiv), and the appropriate base in DME was stirred at 70 °C for 6 h under an argon atmosphere. The reaction in the absence of the base yielded 2,3,4,5,6-pentafluoro-1,1′-biphenyl (**3a**) in a yield of only 29% (entry 1). Addition of K_2CO_3, the most commonly used base in the Suzuki−Miyaura coupling reaction, was not effective in accelerating this reaction (entry 2). Although *t*-BuOK accelerated the reaction, this also resulted in the formation of the 4-(*t*-BuO)-substituted byproduct in 30% yield (entry 3).[9] We then focused on the possibility of using fluoride ions as a mild base; this method is often used for base-sensitive substrates.[10] However, the use of KF decreased the yield of **3** to only 9% (entry 4), as observed previously for the reaction of **1** with 2-iodopyridine.[7] In contrast, we found that the use of CsF as a base markedly increased the yield to 69% (entry 5), indicating the importance of the countercation.[11] The yield was further increased to 90% by prolonging the reaction time (condition A, entry 6).

Table 1. Coupling Reaction of $C_6F_5B(OH)_2$ with PhI[a]

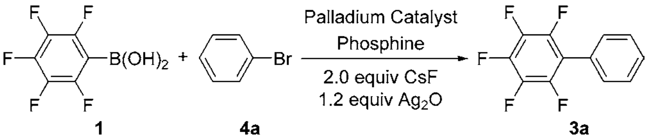


entry	base	time (h)	yield[b] (%)
1	none	6	29
2	2.0 equiv of K_2CO_3	6	31
3	2.0 equiv of *t*-BuOK	6	40[c]
4	2.0 equiv of KF	6	9
5	2.0 equiv of CsF	6	69
6	2.0 equiv of CsF	12	90

[a] All reactions were performed under an argon atmosphere. [b] Isolated yield after silica gel chromatography. [c] *p*-*t*-BuO-C_6F_4-C_6H_5 was obtained in 30% yield.

Next, we attempted to improve the method for bromobenzene (**4a**), which gave **3a** in only 7% yield under the above conditions (Table 2, entry 1), by optimizing the phosphine ligands. Although the reaction with the less hindered tri-*n*-butylphosphine gave no product (entry 2), the use of bulkier[12] and more basic[13] ligands such as TTMPP, PCy_3, and $P(t\text{-}Bu)_3$ accelerated the reaction in the presence of $Pd_2(dba)_3$, CsF, and Ag_2O (entries 3−5). Among the ligands examined, tri-*tert*-butylphosphine performed the best, giving **3a** in 56% yield (entry 5).[14] The role of the bulky strong base may be to activate the Pd−Br bond to dissociate Br^- in the Ag_2O-promoted transmetalation step.[15] After optimization of the reaction conditions, i.e., solvent, temperature, and reaction time (entries 6−8), we obtained **3a** in 97% yield (condition B, entry 8).

Table 2. Coupling Reaction of $C_6F_5B(OH)_2$ with PhBr[a]



entry	catalyst	solvent	*T* (°C)	time (h)	yield[b] (%)
1	3.0% $Pd(PPh_3)_4$	DME	70	6	7
2	1.5% $Pd_2(dba)_3$/3.6% $P(n\text{-}Bu)_3$	DME	70	6	0
3	1.5% $Pd_2(dba)_3$/3.6% TTMPP [c]	DME	70	6	20
4	1.5% $Pd_2(dba)_3$/3.6% PCy_3	DME	70	6	19
5	1.5% $Pd_2(dba)_3$/3.6% $P(t\text{-}Bu)_3$	DME	70	6	56
6	1.5% $Pd_2(dba)_3$/3.6% $P(t\text{-}Bu)_3$	Toluene	100	6	34
7	1.5% $Pd_2(dba)_3$/3.6% $P(t\text{-}Bu)_3$	DMF	100	6	72
8	2.5% $Pd_2(dba)_3$/6.0% $P(t\text{-}Bu)_3$	DMF	100	12	97

[a] All reactions were performed under an argon atmosphere. [b] Isolated yield after silica gel chromatography. [c] Tris(2,4,6-trimethoxyphenyl)phosphine.

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(5) Ag_2O has often been employed for promoting the Suzuki−Miyaura coupling reaction: (a) Lopez, L. C.; Strohriegl, P.; Stubinger, T. *Macromol. Chem. Phys*. **2002**, *203*, 1926. (b) Occhiato, E. G.; Trabocchi, A.; Guarna, A. *J. Org. Chem*. **2001**, *66*, 2459. (c) Zou, G.; Reddy, K.; Falck, J. R. *Tetrahedron Lett*. **2001**, *42*, 7213. (d) Yao, M.-L.; Deng, M.-Z. *J. Org. Chem*. **2000**, *65*, 5034. (e) Zhou, S.-M.; Deng, M.-Z. *Tetrahedron Lett*. **2000**, *41*, 3951. (f) Chen, H.; Deng, M.-Z. *Org. Lett*. **2000**, *2*, 1649. (g) Chen, H.; Deng, M.-Z. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1609. (h) Ruel, F. S.; Braun, M. P.; Johnson, C. R. *Org. Synth*. **1998**, *75*, 69. (i) Mu, Y.; Gibbs, R. A. *Tetrahedron Lett*. **1995**, *36*, 5669. (j) Gillmann, T.; Weeber, T. *Synlett* **1994**, 649. (k) Uenishi, J.; Beau, J.-M.; Armstrong, R. W.; Kishi, Y. *J. Am. Chem. Soc*. **1987**, *109*, 4756.

(6) The role of Ag_2O for activation of transmetalation: Nishihara, Y.; Onodera, H.; Osakada, K. *Chem. Commun*. **2004**, 192.

(7) Chen, J.; Cammers-Goodwin, A. *Tetrahedron Lett*. **2003**, *44*, 1503.

(8) (a) Frohn, H.-J.; Adonin, N. Y.; Bardin, V. V.; Starichenko, V. F. *J. Fluorine Chem*. **2003**, *122*, 195. (b) Frohn, H.-J.; Adonin, N. Y.; Bardin, V. V.; Starichenko, V. F. *Tetrahedron Lett*. **2002**, *43*, 8111. (c) without Ag_2O: Molander, G. A.; Biolatto, B. *J. Org. Chem*. **2003**, *68*, 4302.

(9) *t*-BuOK was effective for the reaction of $C_6F_5B(OH)_2$ with 2-iodopyridine in the presence of $Pd(PPh_3)_4$ and Ag_2O, giving 72% of coupling product (see ref 7).

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(11) The fluoride ion, irrespective of the type of countercation, can activate the boronic acid to accelerate the transmetalation step inherently (See ref 9). However, in our reaction with **1** and Ag_2O the countercation played a significant role. The countercation most likely affects the activation process of Ar−Pd−I by the assistance of Ag_2O, and **1** is not concerned here. In the ^{31}P NMR analysis in DME with a capillary containing benzene-d_6, independently prepared *trans*-$[PdPh(I)(PPh_3)_2]$ (**5**)[11a] showed a signal at δ 23.7. Addition of Ag_2O and heating at 70 °C for 1 h shifted the signal to δ 24.4, probably generating *trans*-$[PdPh(OH)(PPh_3)_2]$[11b] (**6**) by activation of **5** with Ag_2O and subsequent anion exchange with hydroxide due to the trace of water content. Addition of CsF to the mixture of **5** and Ag_2O was found to form **6** as a major product together with a small amount of *trans*-$[PdPh(F)(PPh_3)_2]$[11c] that was detected by ^{31}P NMR (δ 19.1). In contrast, the addition of KF yielded **6** and two unidentified complexes (δ 20.4 and 33.4) (with similar ^{31}P NMR intensities), which might disturb the catalytic activity. (a) Grushin, V. V. *Organometallics* **2000**, *19*, 1888. (b) Matos, K.; Soderquist, J. A. *J. Org. Chem*. **1998**, *63*, 461. (c) Fraser, S. L.; Antipin, M. Y.; Khroustalyov, V. N.; Grushin, V. V. *J. Am. Chem. Soc*. **1997**, *119*, 4769.

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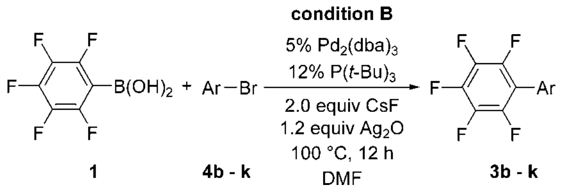
The optimized conditions (condition B) were effectively applied to a variety of aryl bromides (Table 3).[16] In particular, the bromides bearing electron-donating groups (**4b**,**c**,**e**−**g**) gave excellent yields of more than 90% (entries 1, 2, 4−6), except for the sterically hindered *o*-methyl-substituted bromide **4d** (54% yield) (entry 3). The bromides bearing electron-withdrawing groups (**4h**−**k**) gave the products **3h**−**k** in yields that were moderate to good (64−90%) (entries 7−10) but lower than those obtained using bromides with electron-donating groups. In general, electron-withdrawing groups on the aryl halide enhance reactivity compared to electron-donating groups because the oxidative addition step is often the rate-determining step in the catalytic cycle.[17] Although the trend of reactivities shown in Table 3 is opposite to the general one, this trend has been observed in Ag_2O-promoted cross-coupling reactions.[5f,18]

Table 3. Coupling Reaction of $C_6F_5B(OH)_2$ with ArBr[a]



entry	Ar	product	yield[b] (%)
1	*p*-Me-C_6H_4 (**4b**)	**3b**	93
2	*m*-Me-C_6H_4 (**4c**)	**3c**	95
3	*o*-Me-C_6H_4 (**4d**)	**3d**	54
4	*p*-MeO-C_6H_4 (**4e**)	**3e**	94
5	*m*-MeO-C_6H_4 (**4f**)	**3f**	93
6	2-naphthyl (**4g**)	**3g**	91
7	*p*-F-C_6H_4 (**4h**)	**3h**	90
8	*p*-EtO_2C-C_6H_4 (**4i**)	**3i**	79
9	*p*-F_3C-C_6H_4 (**4j**)	**3j**	73
10	*p*-O_2N-C_6H_4 (**4k**)	**3k**	64

[a] All reactions were performed under an argon atmosphere. [b] Isolated yield after silica gel chromatography.

The reactivity of phenyl halides and triflate in this reaction (condition B) was further examined, and the order of reactivity was found to be as follows: I > Br > Cl > OTf (Table 4). The yields for chlorobenzene and phenyl trifluoromethanesulfonate were very low (entries 3, 4), indicating that aryl iodide and bromide are more suitable substrates for biaryl synthesis (entries 1, 2).

Table 4. Coupling Reaction of $C_6F_5B(OH)_2$ with PhX under Condition B[a,b]

entry	X	yield of **3a**[c] (%)
1	I	quant
2	Br	97
3	Cl	39
4	OTf	4

[a] Catalyst: 2.5% $Pd_2(dba)_3$/6% $P(t\text{-}Bu)_3$. [b] All reactions were performed under an argon atmosphere. [c] Isolated yield after silica gel chromatography.

Using these optimized conditions, it was found that $C_6F_5B(OH)_2$ was no longer an inactive substrate for the Suzuki−Miyaura coupling reaction. Under condition A [$Pd(PPh_3)_4$/CsF/Ag_2O] for iodobenzene and condition B [$Pd_2(dba)_3$/$P(t\text{-}Bu)_3$/CsF/Ag_2O] for aryl bromides and iodide, a variety of pentafluorobiphenyls were obtained in good to excellent yields. The reaction conditions may prove to be useful for highly electron-deficient arylboronic acids such as **1**.

Acknowledgment. This work was partially supported by the Okayama Foundation for Science and Technology and a Grant-in-Aid for Young Scientists (B) from the Ministry of Education, Culture, Sports, Science and Technology, Japan. We thank the SC-NMR Laboratory of Okayama University for ^1H, ^{13}C, ^{19}F, and ^{31}P NMR measurements.

Supporting Information Available: General experimental procedure, ^1H NMR spectra of products, Cartesian coordinates of boronic compounds, and ^{31}P NMR spectra of Pd complexes. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Activation of Ph-Pd-Br by Ag_2O is more difficult as compared to that of Ph-Pd-I, because the affinity of $Pd(II)^+$ to bromide ion is stronger than that of iodide ion, and the affinity of $Ag(I)^+$ to halide is the opposite of the above order: (a) Flemming, J. P.; Pilon, M. C.; Borbulevitch, O. Y.; Antipin, M. Y.; Grushin, V. V. *Inorg. Chim. Acta* **1998**, *280*, 87. (b) Lee, J. D. *A New Concise Inorganic Chemistry*, 3rd ed.; Van Nostrand Reinhold Co.: London, 1977.

(16) Twice the amount of catalyst (5% $Pd_2(dba)_3$/12% $P(t\text{-}Bu)_3$) was used for good reproducibility.

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(18) (a) Hirabayashi, K.; Mori, A.; Kawashima, J.; Suguro, M.; Nishihara, Y.; Hiyama, T. *J. Org. Chem.* **2000**, *65*, 5342. (b) Hirabayashi, K.; Kawashima, J.; Nishihara, Y.; Mori, A.; Hiyama, T. *Org. Lett.* **1999**, *1*, 299.