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Palladium-Catalyzed Direct Hydroxymethylation of Aryl Halides and Triflates with Potassium Acetoxymethyltrifluoroborate

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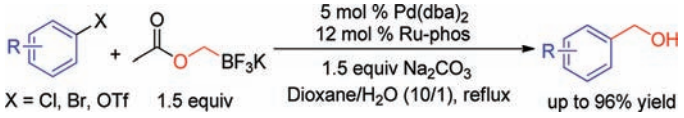
ABSTRACT



Suzuki–Miyaura cross-coupling reactions of aryl halides and triflates with potassium acetoxymethyltrifluoroborate afforded the corresponding aryl and heteroaryl methanol products in moderate to excellent yields.

Compounds with a hydroxymethyl group attached to an aromatic or a heteroaromatic ring are among the most widely used intermediates for the synthesis of bioactive molecules. Common starting materials for the synthesis of hydroxymethyl aromatic compounds include halomethyl-, formyl-, carboxylate-, ester-, and halogen-substituted aromatic compounds. Among these starting materials, aryl halides are attractive because they are generally inexpensive and are commercially available with a wide variety of substitution patterns.

A hydroxymethyl group can be introduced into an aryl halide in the following ways: (i) generation of an arylmetal species by reaction with an organometal reagent such as *n*-BuLi, followed by the addition of formaldehyde or an equivalent;[1] (ii) introduction of a vinyl group and subsequent oxidative cleavage;[2] (iii) introduction of a carbonyl group by reaction with CO gas, followed by reduction;[3] and (iv) hydroxymethylation with acyloxymethylzinc iodides.[4] However, these methods have some limitations, including the scarcity of starting materials that are stable under strongly basic conditions, the need for multiple reaction steps, and the use of toxic CO gas.

In 1985, Migita and co-workers reported the direct hydroxymethylation of aryl bromides with (tributylstannyl)-methanol.[5] This method has the following advantages: the

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(1) For examples, see: (a) Verga, D; Nadai, M.; Doria, F.; Percivalle, C.; Antonio, M. D.; Palumbo, M.; Richter, S. N.; Freccero, M. *J. Am. Chem. Soc.* **2010**, *132*, 14625. (b) Korang, J.; Grither, W. R.; McCulla, R. D. *J. Am. Chem. Soc.* **2010**, *132*, 4466. (c) Watanabe, K.; Iwata, Y.; Adachi, S.; Nishikawa, T.; Yoshida, Y.; Kameda, S.; Ide, M.; Saikawa, Y.; Nakata, M. *J. Org. Chem.* **2010**, *75*, 5573.

(2) For examples, see: (a) Rueeger, H.; Rondeau, J.-M.; McCarthy, C.; Möbitz, H.; Tintelnot-Blomley, M.; Neumann, U.; Desrayaud, S. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1942. (b) Jones, L. H.; Allan, G.; Barba, O.; Burt, C.; Corbau, R.; Dupont, T.; Knöchel, T.; Irving, S.; Middleton, D. S.; Mowbray, C. E.; Perros, M.; Ringrose, H.; Swain, N. A.; Webster, R.; Westby, M.; Phillips, C. *J. Med. Chem.* **2009**, *52*, 1219. (c) Gibson, C.; Schnatbaum, K.; Pfeifer, J. R.; Lacardi, E.; Paschke, M.; Reimer, U.; Richter, U.; Scharn, D.; Faussner, A.; Tradler, T. *J. Med. Chem.* **2009**, *52*, 4370.

(3) For examples, see: (a) Suwandi, L. S.; Agoston, G. E.; Shah, J. H.; Hanson, A. D.; Zhan, X. H.; LaVallee, T. M.; Treston, A. M. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6459. (b) Choquette, D.; Teffera, Y.; Polverino, A.; Harmange, J.-C. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4054. (c) Herzner, H.; Kunz, H. *Tetrahedron* **2007**, *63*, 6423.

(4) (a) Hasník, Z.; Šilhár, P.; Hocek., M. *Synlett* **2008**, 543. (b) Šilhár, P.; Pohl, R.; Votryba, I.; Hocek, M. *Org. Lett.* **2004**, *6*, 3225.

(5) Kosugi, M.; Sumita, T.; Ohhashi, K.; Sano, H.; Migita, T. *Chem. Lett.* **1985**, 997.

(6) (a) Nicolaou, K. C.; Ding, H.; Richard, J.-A.; Chen, D. Y.-K. *J. Am. Chem. Soc.* **2010**, *132*, 3815. (b) Shen, L.; Zhang, M.; Wu, Y.; Qin, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 3618. (c) Williams, D. R.; Heidebrecht, R. W., Jr. *J. Am. Chem. Soc.* **2003**, *125*, 1843. (d) Zanze, I. A.; Patel, J. R.; Hartandi, K.; Brenneman, J.; Winn, M.; Pratt, J. K.; Grynfarb, M.; Nisson, A.; Geldern, T. W.; Kym, P. R. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2079. (e) Yasuda, N.; Yang, D. C.; Wells, K. M.; Jensen, M. S.; Hughes, D. L. *Tetrahedron Lett.* **1999**, *40*, 427.

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reaction conditions are mild, the hydroxymethyl group is introduced directly, no CO gas is required, and aryl bromides are inexpensive and readily available. The method was recently used in the total syntheses of various natural products.[6] However, the method has the following disadvantages: (i) it is shown that the reaction cannot be applied to aryl bromides bearing electron-withdrawing substituents, (ii) only a few examples have been reported for aryl and heteroaryl chlorides,[7] and (iii) organostannic reagents are toxic.

Therefore, we have been working on the development of a novel method for direct hydroxymethylation of aryl halides that addresses the issues of reaction generality, functional group compatibility, and safety.

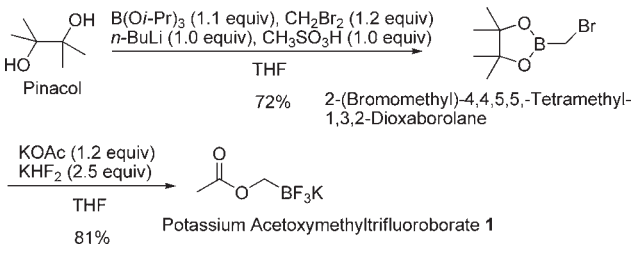
A number of Suzuki–Miyaura cross-coupling reactions[8] of aryl halides with trifluoroborates have been reported over the past decade.[9] Among them, reactions for the introduction of a one-carbon unit into aryl halides were developed by Molander et al.[10] and our group.[11]

In 2005, we succeeded in the direct hydroxymethylation of aryl halides using acyloxymethyltrifluoroborates.[11a] However, the chemical yield of the direct hydroxymethylation was low in some cases; for example, chloropyridine was converted to hydroxymethylpyridine in only 14% yield. Therefore, a more effective direct hydroxymethylation method that would enable us to obtain a variety of products in higher yields was still lacking.

Herein, we describe a versatile method for direct hydroxymethylation of various aryl and heteroaryl halides with potassium acetoxymethyltrifluoroborate **1**.

Potassium acetoxymethyltrifluoroborate **1** was prepared from pinacol in two steps without the need for column chromatography (Scheme 1). 2-(Bromomethyl)-4,4,5,5,-tetramethyl-1,3,2-dioxaborolane was prepared in 72% yield from pinacol via a one-pot distillation process based on a literature procedure.[12] Subsequent reaction with potassium acetate and potassium hydrogen fluoride smoothly provided **1** (81% yield), which showed satisfactory stability to air and moisture.[13]

Scheme 1. Preparation of Potassium Acetoxymethyltrifluoroborate **1**



With **1** in hand, we optimized the conditions for the coupling reaction with 2-chloronaphthalene as a model substrate. For the initial reactions, we selected $Pd(OAc)_2$/S-phos[14] as the catalyst, Cs_2CO_3 as the base, and dioxane/H_2O as the solvent. Because we obtained comparable results with conventional heating (45% yield, reflux, 12 h) and microwave heating (41% yield, 120 °C, 35 min) in preliminary studies, we used microwave heating for the initial studies. A higher-than-usual S-phos/Pd ratio (2.2–3.0/1.0 compared to 2.0/1.0) was required for high reproducibility with commercially available solvents that had not been distilled prior to the reaction. Under these initial reaction conditions, we investigated various ligands, palladium sources, and bases (Table 1 and Figure 1).

The Ru-phos[15] ligand afforded the best yield from the coupling reaction (Table 1, entry 3). Reactions with bidentate ligands such as (*S*)-BINAP and DPE-phos afforded only trace amounts of the desired product (Table 1, entries 7 and 8). The newly reported BI-DIME[16] and Cy-vBRIDP[17] ligands were not as effective as Ru-phos (Table 1, entries 9 and 10). Next, we examined various palladium sources (Table 1, entries 11–17). When we used $Pd_2(dba)_3$•$CHCl_3$, $Pd_2(dba)_3$, or $Pd(dba)_2$, the desired alcohol was obtained in yields ranging from 65% to 68% (Table 1, entries 15–17). The cross-coupling reaction did not proceed in the presence of $Pd_2(dba)_3$•$CHCl_3$ without the phosphine ligand (Table 1, entry 18).

We found that Na_2CO_3 was the optimal base, affording the desired alcohol in 80% yield (Table 1, entry 19). The catalyst loading could be reduced to 5 mol % of $Pd(dba)_2$ and 12 mol % of Ru-phos (Table 1, entries 20 and 21). Moreover, the amounts of **1** and sodium carbonate could be reduced to 1.5 equiv (Table 1, entry 20). Using conventional heating (reflux, 24 h) instead of microwave heating (120 °C, 35 min), we obtained the desired alcohol in 85% yield (Table 1, entry 21).

Next, we applied the optimized reaction conditions to various aryl halides and triflates (Table 2).

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(8) For reviews, see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Kotha, S.; Lahiri, K.; Dhurke, K. *Tetrahedron* **2002**, *58*, 9633.

(9) For reviews, see: (a) Molander, G. A.; Canturk, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 9240. (b) Darses, S.; Genet, J.-P. *Chem. Rev.* **2008**, *108*, 288. (c) Stefani, H. A.; Cella, R.; Vieira, A. S. *Tetrahedron* **2007**, *63*, 3623. (d) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275.

(10) (a) Molander, G. A.; Beaumard, F. *Org. Lett.* **2011**, *13*, 3948. (b) Molander, G. A.; Shin, I. *Org. Lett.* **2011**, *13*, 3956. (c) Raushel, J.; Sandrock, D. L.; Josyula, K. V.; Pakyz, D.; Molander, G. A. *J. Org. Chem.* **2011**, *76*, 2762. (d) Molander, G. A.; Colombel, V.; Braz, V. A. *Org. Lett.* **2011**, *13*, 1852. (e) Molander, G. A.; Flury-Bregeot, N.; Hiebel, M.-A. *Org. Lett.* **2011**, *13*, 1694. (f) Molander, G. A.; Beaumard, F. *Org. Lett.* **2011**, *13*, 1242. (g) Molander, G. A.; Hiebel, M.-A. *Org. Lett.* **2010**, *12*, 4876. (h) Molander, G. A.; Canturk, B. *Org. Lett.* **2008**, *10*, 2135.

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(12) Michnick, T. J.; Matteson, D. S. *Synlett* **1991**, 631.

(13) The NMR spectrum of **1** showed no change after the compound was stored in a vial at room temperature for more than a year (data not shown).

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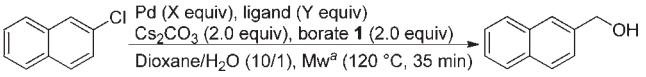
(15) Milne, J. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 13028.

(16) Tang, W.; Capacci, A. G.; Wei, X.; Li, W.; White, A.; Patel, N. D.; Savoie, J.; Gao, J. J.; Rodriguez, S.; Qu, B.; Haddad, N.; Lu, B. Z.; Krishnamurthy, D.; Yee, N. K.; Senanayake, C. H. *Angew. Chem., Int. Ed.* **2010**, *49*, 5879.

(17) (a) Suzuki, K.; Fontaine, A.; Hori, Y.; Kobayashi, T. *Synlett* **2007**, *20*, 3206. (b) Suzuki, K.; Hori, Y.; Nishikawa, T.; Kobayashi, T. *Adv. Synth. Catal.* **2007**, *349*, 2089.

Table 1. Optimization of the Suzuki–Miyaura Cross-Coupling Reaction Conditions



entry	Pd	X	ligand	Y	isolated yield (%)
1	$Pd(OAc)_2$	0.2	PCy_3	0.45	24
2	$Pd(OAc)_2$	0.2	S-phos	0.45	41
3	$Pd(OAc)_2$	0.2	Ru-phos	0.45	47
4	$Pd(OAc)_2$	0.2	Dave-phos	0.45	19
5	$Pd(OAc)_2$	0.2	X-phos	0.45	25
6	$Pd(OAc)_2$	0.2	*t*-BuX-phos	0.45	trace
7	$Pd(OAc)_2$	0.2	DPE-phos	0.22	trace
8	$Pd(OAc)_2$	0.2	(*S*)-BINAP	0.22	7
9	$Pd(OAc)_2$	0.2	BI-DIME	0.45	7
10	$Pd(OAc)_2$	0.2	Cy-vBRIDP	0.22	29
11	Bedford's cat.	0.2	Ru-phos	0.45	38
12	$Pd(Pt\text{-}Bu_3)_2$	0.2	Ru-phos	0.45	38
13	$Pd(dppe)_2$	0.2	Ru-phos	0.45	31
14	$Pd(PPh_3)_4$	0.2	Ru-phos	0.45	trace
15	$Pd_2(dba)_3 \bullet CHCl_3$	0.1	Ru-phos	0.45	68
16	$Pd_2(dba)_3$	0.1	Ru-phos	0.45	65
17	$Pd(dba)_2$	0.2	Ru-phos	0.45	67
18	$Pd_2(dba)_3 \bullet CHCl_3$	0.1	–	–	trace
19[b]	$Pd(dba)_2$	0.1	Ru-phos	0.25	80
20[c]	$Pd(dba)_2$	0.05	Ru-phos	0.12	77
21[c,d]	$Pd(dba)_2$	0.05	Ru-phos	0.12	85

[a] Microwave irradiation. [b] Na_2CO_3 (2.0 equiv) instead of Cs_2CO_3 (2.0 equiv). [c] Na_2CO_3 (1.5 equiv), **1** (1.5 equiv). [d] Reflux, 24 h.

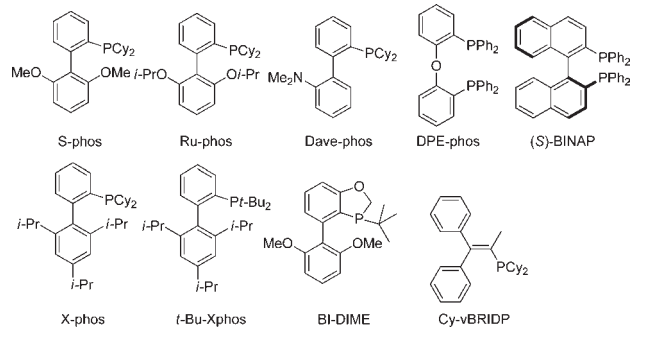
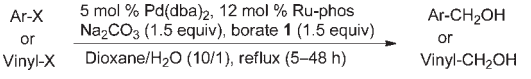
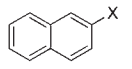
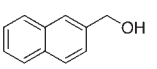
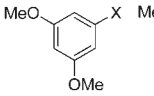
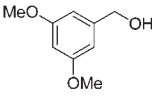
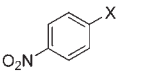
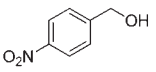
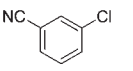
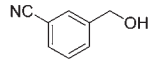
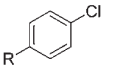
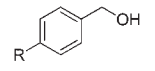
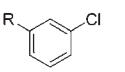
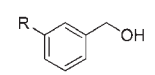
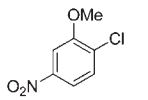
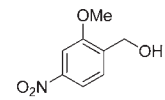
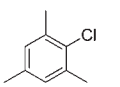
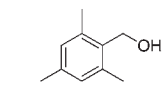
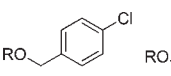
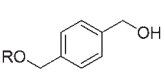
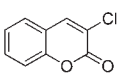
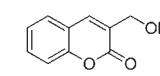
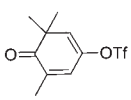
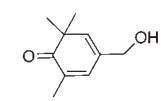


Figure 1. Monodentate and bidentate ligands.

2-Chloronaphthalene and 2-naphthyl trifluoromethanesulfonate were converted to **2a** in good yields, whereas the yield from 2-bromonaphthalene was only moderate (Table 2, entry 1). In addition, the desired alcohol was obtained in a comparable yield when the reaction of 2-chloronaphthalene was conducted on a 1.0 g scale. The yield was nearly independent of the electron density on the benzene ring (Table 2, entries 2–4). Ester, ketone, amide, pyrrole, aldehyde, amine, and alcohol functional groups

Table 2. Suzuki–Miyaura Cross-Coupling Reactions of Aryl Halides and Triflates[a]

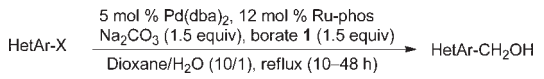


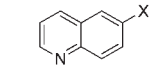
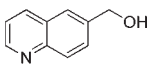
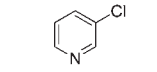
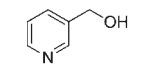
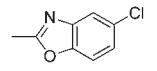
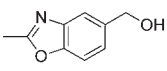
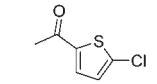
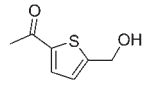
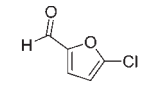
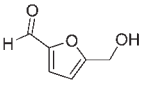
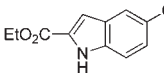
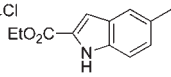
entry	substrate	product		isolated yield (%)
1			X = Cl	85, 79[b]
			Br **2a**	57
			OTf	84
2			X = Cl **2b**	81
			OTf	81
3			X = Cl	94
			Br **2c**	62
			OTf	84
4			**2d**	87
			R = CO_2Et **2e**	86
5			COPh **2f**	91
			$CONH_2$ **2g**	82
			**2h**	85
6			R = CHO **2i**	96
			NH_2 **2j**	56
			OH **2k**	62
7			**2l**	88
8			**2m**	59[c]
9			R = MOM **2n**	73
			TBS **2o**	66
10			**2p**	85
11			**2q**	76

[a] Reaction conditions: 1.0 equiv of substrate, 5 mol % of $Pd(dba)_2$, 12 mol % of Ru-phos, 1.5 equiv of **1**, 1.5 equiv of Na_2CO_3, dioxane/H_2O (10/1), reflux. [b] 1.0 g (6.1 mmol) scale. [c] 10 mol % of $Pd(dba)_2$ and 24 mol % of Ru-phos.

were compatible with the reaction conditions (Table 2, entries 5 and 6). The sterically hindered substrate 1-chloro-2-methoxy-4-nitrobenzene was converted to **2l** in 88% yield (Table 2, entry 7). In contrast, the even more hindered mesityl chloride gave only a moderate yield (Table 2, entry 8). MOM- and TBS-protected alcohol groups were stable under these reaction conditions (Table 2, entry 9). The cross-coupling reactions of a vinyl chloride and triflate smoothly provided desired alcohols **2p** and **2q**, respectively, in good yields (Table 2, entries 10 and 11).

Table 3. Suzuki–Miyaura Cross-Coupling Reactions of Heteroaryl Halides and Triflates[a]



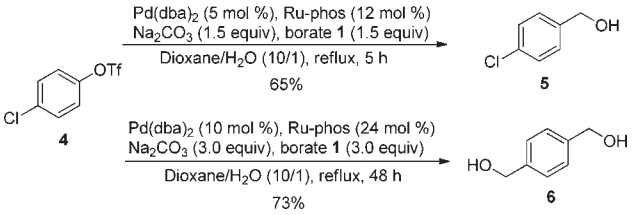
entry	substrate	product		isolated yield (%)
1			X = Cl OTf **3a**	81 84
2			**3b**	52[b]
3			**3c**	80
4			**3d**	84
5			**3e**	80
6			**3f**	57[b, c]

[a] Reaction conditions: 1.0 equiv of substrate, 5 mol % of $Pa(dba)_2$, 12 mol % of Ru-phos, 1.5 equiv of **1**, 1.5 equiv of Na_2CO_3, dioxane/H_2O (10/1), reflux. [b] 10 mol % of $Pd(dba)_2$, 24 mol % of Ru-phos. [c] 2.0 equiv of **1** and Na_2CO_3.

We further investigated the hydroxymethylation reactions of various heteroaryl chlorides and triflates (Table 3). The reactions proceeded in yields ranging from 52% to 84%. 3-Chloropyridine and ethyl-5-chloroindole-2-carboxylate afforded the desired alcohols in moderate yields in the presence of 10 mol % of Pd and 24 mol % of Ru-phos (Table 3, entries 2 and 6).

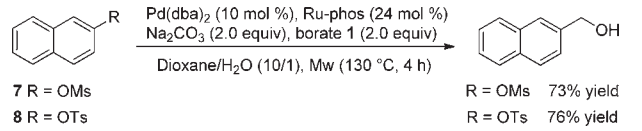
Then, we examined the selectivity for the reaction with chloride and triflate substituents (Scheme 2). When 1-chlorobenzene-4-trifluoromethanesulfonate **4** was used as the substrate, the desired 4-chlorobenzylalcohol **5** was obtained in 65% yield. When the amount of **1** was increased from 1.5 to 3.0 equiv, 1,4-benzenedimethanol **6** was obtained in 73% yield.

Scheme 2. Suzuki–Miyaura Cross-Coupling Reactions of **4**



When we used mesylate **7** or tosylate **8** as a substrate (Scheme 3), microwave irradiation at 130 °C was preferred over conventional heating, and the reactions afforded the desired alcohol in 73% and 76% yields, respectively.

Scheme 3. Suzuki–Miyaura Cross-Coupling Reactions of **7** and **8**



In summary, we developed a versatile method for direct hydroxymethylation of aryl and heteroaryl halides and triflates with potassium acetoxymethyltrifluoroborate **1**. Moreover, we expanded the scope of this method to tosylate and mesylate substrates by using microwave irradiation. Further development of effective methods for the introduction of a one-carbon unit into aryl halides is being undertaken.

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

The authors declare no competing financial interest.