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Copper-Catalyzed *N*- and *O*-Alkylation of Amines and Phenols using Alkylborane Reagents

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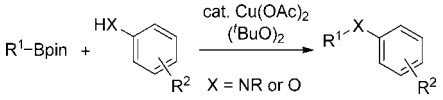
ABSTRACT



By the reaction of amines with alkylborane reagents in the presence of a catalytic amount of copper(II) acetate $Cu(OAc)_2$ and di-*tert*-butyl peroxide, a cross-coupling reaction proceeded and alkylated amines were obtained in good to excellent yields. Phenols are also applicable for this reaction, and the corresponding alkyl aryl ethers were produced.

Many bioactive compounds,[1] drugs, and organic functional materials[2] contain amino and ether functional groups. Therefore, carbon–nitrogen (C–N) and carbon–oxygen (C–O) bond formation reactions play an important role in the synthesis of such compounds. A large number of C–N and C–O bond formation reactions have been reported. In the case of C–N bond formation, however, it is usually difficult to prevent overalkylation (formation of multialkylated amines and ammonium salts).[3] Moreover, protection–deprotection of primary amines is necessary for the synthesis of secondary amines.[4] To overcome the problem, a cross-coupling reaction is one of the most useful and promising synthetic methods (Figure 1). Buchwald–Hartwig amination[5] is a well-known robust and practical synthetic method of anilines, but this reaction requires a strong base and β-hydride elimination occurs as a side reaction in the synthesis of aliphatic amines.[6] On the other hand, a Chan–Lam–Evans cross-coupling reaction between organoboronic acids and amines gives both arylated and alkylated amines.[7] The yields of the products in this cross-coupling reaction are high, although this reaction

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usually requires excess amounts of copper salts and substrates, and the stability of some boronic acids is low. In addition, there have been only a few reports on alkyl-type cross-coupling reactions.[7o,p,w] Recently, Yamamoto, Miyaura, and co-workers reported novel arylation and alkylation of amines using aryl and alkyl triol borates, which are prepared in basic conditions.[8] This method could be used in neutral conditions and gives multisubstituted amines in good to excellent yields. We report herein a copper-catalyzed cross-coupling reaction between alkylborane reagents and amines that gave the corresponding alkylated amines in good to excellent yields. The reaction conditions are applicable for alkylation of phenol derivatives. In these reactions, stable boronates can be used as substrates, and addition of a strong base is not necessary for a cross-coupling reaction.

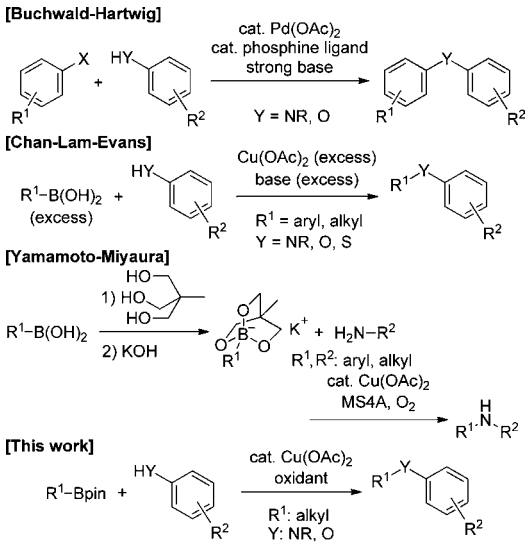


Figure 1. Several types of cross-coupling reactions for the formation of carbon–heteroatom bonds.

This reaction is a rare example of catalytic alkylation of amines and could be applicable to the synthesis of useful compounds such as lavendustin A[9] and methotrexate,[10] which behave as tyrosine kinase and folic acid antagonists, respectively (Figure 2).

At first, we investigated reactions between benzyl boronic acid pinacol ester (**1a**) and *N*-methylaniline (**2a**) with several copper salts and oxidants (Table 1). A cross-coupling reaction between **1a** and **2a** proceeded in the presence of a catalytic amount of $Cu(OAc)_2$ in toluene at 100 °C for 24 h; however, *N*-benzyl-*N*-methylaniline (**3a**) was formed in only 4% yield (entry 1). By adding 2 equiv of $(^tBuO)_2$ as an oxidant, the yield of **3a** was improved to 47% yield (entry 2), and **3a** was obtained quantitatively

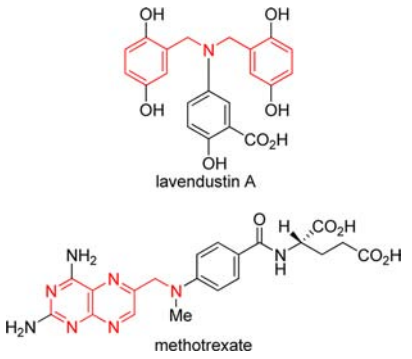


Figure 2. Examples of drugs that contain benzylic amine moieties.

when the reaction temperature was decreased to 50 °C (entry 3).[11–14] The copper salt $Cu(OAc)_2$ is indispensable to promote the cross-coupling reaction (entry 4). The yields of **3a** were low when using other copper salts[15] or oxidants[16] (entries 5–13 and 16). The yield of **3a** was comparable to that in entries 2 and 3 when silver carbonate Ag_2CO_3 was used as an oxidant. The following investigations were carried out using $(^tBuO)_2$, however, because $(^tBuO)_2$ is much less expensive than Ag_2CO_3.

Next, the scope of alkylborane reagents was investigated (Table 2). Benzyl boronic acid pinacol ester (**1a**) showed higher reactivity compared with the corresponding *B*-benzyl-9-borabicyclo[3.3.1]nonane **1b** and borate **1c** (entries 1–3). Therefore, the following investigations were performed using boronic acid pinacol esters. In a 1.0 mmol scale reaction, the desired product **3a** was obtained in 90% yield (in the parentheses in entry 1). The cross-coupling reactions proceeded using benzylic boronic acid pinacol esters with an electron-donating or -withdrawing group, **1d**–**f** (entries 4–6). Primary and secondary aliphatic boronic acid pinacol esters **1g**–**j** also produced the corresponding coupling products **3e**–**h** in 51–82% yields (entries 7–10).[17,18] Notably, although the ethoxycarbonyl and cyano groups are sensitive to bases, the cross-coupling reaction proceeded by this method without the loss of functional groups.

Reactions of benzyl boronic acid pinacol ester (**1a**) with several amines were investigated (Table 3). The corresponding

(8) Pd: (a) Yamamoto, Y.; Takizawa, M.; Yu, Z.-Q.; Miyaura, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 928. Cu: (b) Yu, Z.-Q.; Yamamoto, Y.; Miyaura, N. *Chem.—Asian J.* **2008**, *3*, 1517.

(9) Onoda, T.; Iinuma, H.; Sasaki, Y.; Hamada, M.; Isshiki, K.; Naganawa, H.; Takeuchi, T.; Tatsuta, K.; Umezawa, K. *J. Nat. Prod.* **1989**, *52*, 1252.

(10) Kremer, J. M.; Lee, J. K. *Arthritis Rheum.* **1986**, *29*, 822.

(11) The amount of catalyst was reduced to 3 mol % and 1 mol %, and the yield of **3a** was decreased to 70% and 32%, respectively.

(12) The amount of $(^tBuO)_2$ was decreased to 1 equiv, and the yield of **3a** was 69%.

(13) When the reaction time was shortened to 12 h, the yield of **3a** was decreased to 49%.

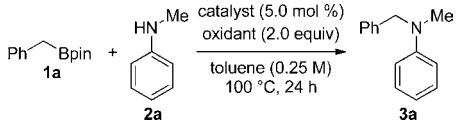
(14) Investigation of several solvents, see: hexane, 48%; 1,4-dioxane, 9%; THF, 9%; 1,2-dichloroethane, 50%; *N*,*N*-dimethylformamide, 0%; acetonitrile, 32%; DMSO, 0%.

(15) Several copper (I) salts were less effective than $Cu(OAc)_2$ for the cross-coupling reaction: CuCl, 9%; CuBr, 9%; CuI, 5%; CuOAc, 19%; CuOTf·$^1/_2$toluene, 19%; MesCu, 5%. Other transition metals were also investigated under the same reaction conditions; however, any satisfactory results were not obtained: $Pd(OAc)_2$, 3%. No reaction: $Mn(OAc)_2$, $Mn(OAc)_3$, $Fe(OAc)_2$, $Co(OAc)_2$, $Ni(OAc)_2$.

(16) No reaction: 1,4-benzoquinone, $Ce(SO_4)_2$, OXONE, TEMPO, pyridine *N*-oxide. Urea–hydrogen peroxide complex (UHP), 8%.

(17) The reactions did not give the corresponding cross-coupling product using phenylboronic acid pinacol ester, *N*-methyliminodiacetic acid protected phenyl boronate, and phenylboronic acid neopentylglycol ester.

Table 1. Investigation of Several Transition-Metal Salts and Oxidants[a]



entry	catalyst	oxidant	yield[b] (%)
1	$Cu(OAc)_2$	none	4
2	$Cu(OAc)_2$	$(^tBuO)_2$	47
3[c]	$Cu(OAc)_2$	$(^tBuO)_2$	99
4	none	$(^tBuO)_2$	1
5	$CuCl_2$	$(^tBuO)_2$	17
6	$CuBr_2$	$(^tBuO)_2$	4
7	$Cu(OTf)_2$	$(^tBuO)_2$	6
8	$Cu(OMe)_2$	$(^tBuO)_2$	4
9	$Cu(OAc)_2$	^tBuOOBz	12
10	$Cu(OAc)_2$	$PhI(OAc)_2$	<1
11	$Cu(OAc)_2$	$K_2S_2O_8$	5
12	$Cu(OAc)_2$	Me_3NO	33
13	$Cu(OAc)_2$	AgOAc	31
14	$Cu(OAc)_2$	Ag_2CO_3	55
15[c]	$Cu(OAc)_2$	Ag_2CO_3	96
16	$Cu(OAc)_2$	O_2 (1.0 atm)	13

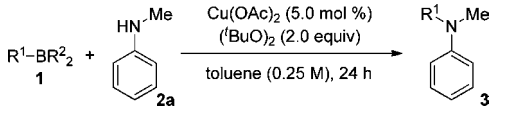
[a] **2a** (1.1 equiv). [b] Yield was determined by ^1H NMR. [c] 50 °C. Bpin: pinacol borate.

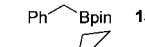
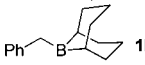
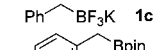
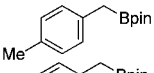
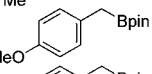
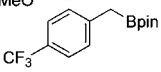
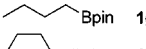
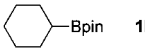
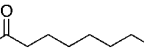
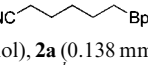
cross-coupling products **3i**–**l** were obtained in excellent yields without the loss of the functional groups using aniline derivatives with an electron-donating or -withdrawing group **2b**–**e** (entries 1–4). The cross-coupling reaction also proceeded in the presence of a steric hindrance (entry 5). The desired product was also produced when tosylamide **2g** was used as a substrate (entry 6). Functional group selectivity is important for the synthesis of highly functionalized complex molecules. The cross-coupling reaction proceeded only at the amino group, even in the presence of a hydroxy group (entry 7). When using primary anilines **2i** and **2j**, both mono- and dialkylated products can be formed. Interestingly, only monoalkylated products **3p** and **3q** were provided in 78% and 97% yields, respectively (entries 8 and 10). In entry 8, the reaction was carried out using 2 equiv of **1a**. As a result, monobenzylated product **3p** and dibenzylated product (*N*, *N*-dibenzyl-4-methoxyaniline) **3q** were obtained in 20% and 60% yields, respectively (entry 9). In this reaction system, a nitrogen-containing heteroaromatic compound could also be applicable, and the desired benzylated product **3s** was afforded using carbazole (**2k**) (entry 11). The corresponding product **3t** was obtained in 65% yield using phthalimide (**2l**) as a substrate (entry 12). The desired cross-coupling reaction did not proceed using aliphatic amines, such as butylamine and morpholine.

Based on the result in Table 3, entry 9, introduction of two different benzylic groups was investigated. The reaction of **2i** with 1.0 equiv of **1a** and successive treatment with

(18) The cross-coupling reaction did not proceed using butylboronic acid instead of butylboronic acid pinacol ester.

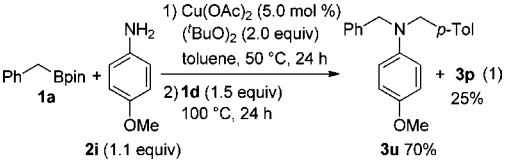
Table 2. Copper-Catalyzed Cross-Coupling Reactions between Several Organoboron Reagents **1** and *N*-Methylaniline (**2a**)[a]



entry	organoboron reagent		temp / °C	yield / %
1		**1a**	50	**3a** 99 (90)[b]
2		**1b**	100	**3a** 14
3		**1c**	100	**3a** 59
4		**1d**	50	**3b** 78
5		**1e**	100	**3c** 57
6[c]		**1f**	100	**3d** 48
7[c]		**1g**	100	**3e** 82
8[c,d]		**1h**	80	**3f** 51
9[e]		**1i**	100	**3g** 61
10[c]		**1j**	100	**3h** 51

[a] **1a** (0.125 mmol), **2a** (0.138 mmol, 1.1 equiv). [b] **1a** (1.0 mmol), 70 °C. [c] **2a** (1.5 equiv), 0.50 M. [d] Hexane was used as a solvent. [e] **1i** (2.0 equiv). Bpin = pinacol borate.

1.5 equiv of **1d** gave **3p** and the desired product **3u** in 25% and 70% yields, respectively (eq 1).



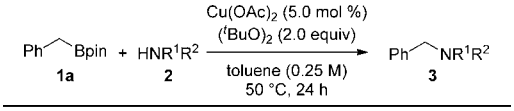
Phenols could be used instead of amines (Table 4).[19] The reaction of benzyl boronic acid pinacol ester (**1a**) with phenol derivatives bearing an electron-donating or -withdrawing group gave the corresponding benzyl aryl ethers **5a**–**d** in 42–70% yields (entries 1–4). In entry 3, the yield of **5a** was 62% (1.0 mmol scale). The reaction with *p*-cyanophenol (**4e**) gave the product **5e** in 44% yield with functional group tolerance (entry 5). It is noteworthy that the reactions using tyrosine derivative **4f** and 17β-estradiol (**4g**) provided the *O*-benzylated products **5f**[20] and **5g** in 91% and 44% yields, respectively (entries 6 and 7). In entry 6, racemization of the stereocenter of the tyrosine derivative occurred in ca. 5%. The reaction did not proceed with thiophenol.

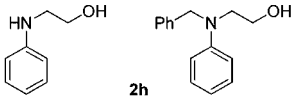
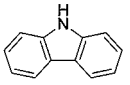
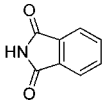
The proposed mechanism for the cross-coupling reaction is shown in Scheme 1: (1) formation of copper(II) amide (or aryloxycopper(II)) intermediate **A** from $Cu(OAc)_2$ and an

(19) (a) Evans, D. A.; Katz, J. F.; West, T. R. *Tetrahedron Lett.* **1998**, *39*, 2937. (b) Quach, T. D.; Batey, R. A. *Org. Lett.* **2003**, *5*, 1381. (c) Shade, R. E.; Hyde, A. M.; Olsen, J.-C.; Merlic, C. A. *J. Am. Chem. Soc.* **2010**, *132*, 1202. (d) Medda, A.; Pal, G.; Singha, R.; Hossain, T.; Saha, A.; Das, A. R. *Synth. Commun.* **2013**, *43*, 169. See also ref 7a,7x–7z.

(20) Compound **5f** is a intermediate for synthesis of some biologically active compounds; see: (a) Yuan, W.; Munoz, B.; Wong, C.-H. *J. Med. Chem.* **1993**, *36*, 211. (b) Cheng, X.-C.; Wang, R.-C.; Dong, Z.-K.; Li, J.; Li, Y.-Y.; Li, R.-R. *Bioorg. Med. Chem.* **2012**, *20*, 5738.

Table 3. Copper-Catalyzed Cross-Coupling Reactions between Benzylpinacolborane (**1a**) and Several Amines **2**[a]

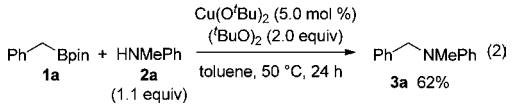


entry	R^1	R^2		yield / %
1	4-$MeOC_6H_4$	Me	**2b**	**3i** 84
2	4-MeC_6H_4	Me	**2c**	**3j** 92
3[b]	4-$CF_3C_6H_4$	Me	**2d**	**3k** 97
4[b]	4-BrC_6H_4	Me	**2e**	**3l** >99
5[b,c]	2-MeC_6H_4	Me	**2f**	**3m** 78
6	Ts	Me	**2g**	**3n** 70
7[c,d]			**2h**	**3o** 82
8	4-$MeOC_6H_4$	H	**2i**	**3p** 78
9[e]	4-$MeOC_6H_4$	H	**2i**	**3p** 20
10[c]	4-$CF_3C_6H_4$	H	**2j**	**3r** 97
11[c]			**2k**	**3s** 45
12[c]			**2l**	**3t** 65

[a] **2** (1.1 equiv). [b] 0.5 M. [c] 100 °C. [d] *O*-Benzylated product was not formed. [e] **1a** (2.0 equiv).

amine (or phenol);[7s] (2) generation of alkylcopper(II) species **B** by transmetalation between **A** and an alkylboronic acid pinacol ester;[19a] and (3) oxidative–reductive elimination[21] of the copper catalyst with $(^tBuO)_2$ to give the cross-coupling product.

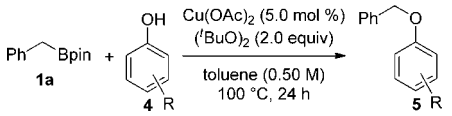
In the above estimated catalytic cycle, $Cu(O^tBu)_2$ is a possible catalytic species. To examine this further, a reaction of benzyl boronic acid pinacol ester (**1a**) with *N*-methylaniline (**2a**) was performed in the presence of a catalytic amount of $Cu(O^tBu)_2$ and $(^tBuO)_2$ (eq 2). *N*-Benzyl-*N*-methylaniline (**3a**) was obtained in 62% yield. This result suggests that $Cu(O^tBu)_2$ is a catalytic species after the first cycle.

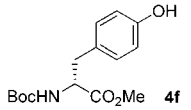
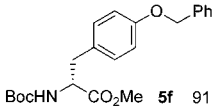
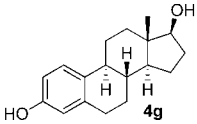
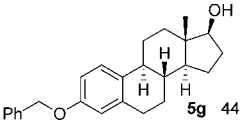


In the ^{11}B NMR spectrum in benzene-d_6, the signal of **1a** (32.5 ppm) disappeared completely following treatment of **1a** with **2a** (1.1 equiv) in the presence of $Cu(OAc)_2$ (5.0 mol %, 50 °C, 24 h) and new signals (1.01 ppm in ^1H NMR and 22.2 ppm in ^{11}B NMR) appeared. The chemical shifts are consistent with the reported ^1H and ^{11}B NMR spectra of HO-Bpin,[22] which must be generated from ^{t}BuO-Bpin by hydrolysis in the workup operation. This result shows that boronate **C** should be formed in situ.

(21) Grimes, K. D.; Gupte, A.; Aldrich, C. C. *Synthesis* **2010**, 1441.
(22) Bettinger, H. F.; Filthaus, M.; Bornemann, H.; Oppel, I. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4744.

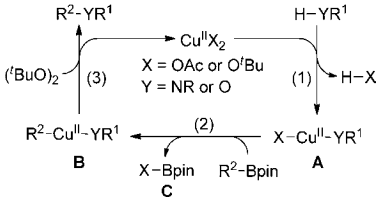
Table 4. Copper-Catalyzed Cross-Coupling Reactions between Benzylpinacolborane (**1a**) and Several Phenols **4**[a]



entry	R		yield / %
1	3,5-Me_2	**4a**	**5a** 56
2	4-MeO	**4b**	**5b** 42
3	4-NO_2	**4c**	**5c** 70 (62)[b]
4	4-Br	**4d**	**5d** 61
5	4-CN	**4e**	**5e** 44
6		**4f**	 **5f** 91
7		**4g**	 **5g** 44

[a] **1a** (0.125 mmol), **4** (0.138 mmol, 1.1 equiv). [b] **1a** (1.0 mmol).

Scheme 1. Proposed Mechanism of Copper-Catalyzed Cross-Coupling Reactions between Alkylborane Reagents **1** and Amines **2** (or Phenols **4**)



In summary, we achieved a copper-catalyzed cross-coupling reaction between aliphatic pinacol boronic acid esters and amines. Corresponding secondary and tertiary amines were obtained in good to excellent yields. Although the generated $Cu(O^tBu)_2$ may work as a base, this reaction does not require strong basic conditions, which is obtained by using an oxidant, therefore, it can be applicable for use with substrates having base-sensitive functional groups. In addition, this reaction system could also be applicable for alkylation of aza-heteroaromatic compounds and phenols. We think that this reaction will become a useful synthetic method for multisubstituted amines and aryl ethers.

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Supporting Information Available. General experimental procedure and characterization data for cross-coupling products **3a**–**u** and **5a**–**g**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.