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Cross-Coupling Reactions

Copper-Catalyzed Cross-Coupling Reaction of Organoboron Compounds with Primary Alkyl Halides and Pseudohalides[**]

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Cross-coupling reactions of organocopper reagents with alkyl halides are among the most useful C−C bond-forming reactions in organic synthesis.[1] One drawback of these reactions has been the need to use an excess of the organocopper reagent for high conversion of the starting material.[2] This requirement causes serious waste of the precious organometallic species, in particular in the case of cuprate reagents (R_2CuLi), which contain two transferable R groups.[3] To solve this problem, several research groups have developed copper-catalyzed alkylation reactions of Grignard reagents.[3–5] It was found that these catalytic reactions are much easier to carry out and considerably less expensive. Additives, such as 1-methyl-2-pyrrolidinone and 1-phenylpropyne, were originally used to promote the alkylation reactions,[4] and the slow addition of the Grignard reagent was found to provide similar results in a recent study.[5] Although primary alkyl halides (as well as mesylates and tosylates) are mostly used in these catalytic alkylation reactions, some studies have indicated that secondary and even tertiary alkyl halides may also be possible coupling partners.[3,6]

Our interest in copper-catalyzed cross-coupling[7] prompted us to consider the possibility of using organoboron compounds in such alkylation reactions. The advantages of replacing Grignard reagents with organoboron reagents are well-known, including the better commercial availability of the reagents and the higher functional-group tolerance.[8] However, whereas certain complexes of Pd,[9] Ni,[10,11] and Fe[12] have been reported to be competent catalysts for the coupling of alkyl halides with organoboron compounds, until now the catalysis of such transformations by Cu complexes has not been reported.[13] Therefore, we were surprised to find that in the presence of LiO*t*Bu as a base, CuI could efficiently catalyze the cross-coupling of aryl boronate esters with primary halides and pseudohalides containing a C−X bond (X = I, Br, Cl, OTs, and OMs; Ts = *p*-toluenesulfonyl, Ms = methanesulfonyl). This new transformation not only expands the concept and utility of copper-catalyzed alkylation reactions in a fundamental sense, but also provides practically useful reactivities. It may thus complement palladium- and nickel-catalyzed Suzuki–Miyaura coupling reactions of alkyl halides.[9–11]

We began our study by examining the coupling of *n*-dodecyl *p*-toluenesulfonate with an aryl boronate ester **1**. We initially used CuI as the catalyst and tested several different bases (Table 1, entries 1–7). Although the yield of the desired product was very low with most bases, LiO*t*Bu provided a good yield of 83% at 110 °C (Table 1, entry 7). Interestingly, when the temperature was lowered to 60 °C, the yield increased slightly to 87% (Table 1, entry 8). The reaction also proceeded at room temperature, but more slowly (Table 1, entry 9). The use of other Li bases, Cu catalysts, and solvents did not improve the reaction (Table 1, entries 10–17). Other organoboron substrates, **2**–**4**, could also be used (Table 1, entries 18–20). Alkyl iodides, bromides, mesylates, and even chlorides are also acceptable coupling partners (Table 1, entries 21–24). The amount of the CuI catalyst could be decreased to 2 mol% (Table 1, entry 25); however, no product was formed with Pd and Ni salts (Table 1, entries 26 and 27). Thus, we could rule out the possible involvement of Pd or Ni contamination in the catalysis. In the absence of a catalyst, the reaction did not occur (Table 1, entry 28). The reaction was also sensitive to water (Table 1, entry 29). Finally, under the present conditions, the reaction of cyclohexyl *p*-toluenesulfonate with **1** gave only a trace amount of the desired product. Thus, with this catalyst system, secondary alkyl electrophiles do not undergo the coupling reaction.

The above results indicate that CuI is a competent catalyst for the cross-coupling of organoboron reagents with primary halides and pseudohalides. To test the scope of this method, we examined a variety of substrates (Table 2). We found that alkyl halide and pseudohalide reagents with different chain lengths and branching could participate in the reaction (to give **5aa**–**5af**). A variety of substituents were well-tolerated on the alkyl reagent, including an olefin (product **5ag**), an ether (product **5ah**), an aryl group (product **5aj**), an ester (product **5ak**), a cyano group (product **5al**), and an amide (product **5am**). This feature compares favorably with previous examples of the copper-catalyzed coupling of primary alkyl halides with Grignard reagents, in which nearly all reported alkyl groups were hydrocarbons.[3–5] Furthermore, for the synthesis of **5ab**, we changed the catalyst from CuI to CuO*t*Bu generated in situ through the equimolar reaction of anhydrous CuI with LiO*t*Bu in THF at room temperature under nitrogen. The yield with CuO*t*Bu was 90%, which is slightly higher than that observed with CuI (86%). Finally,

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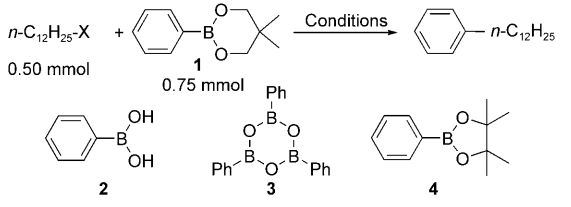
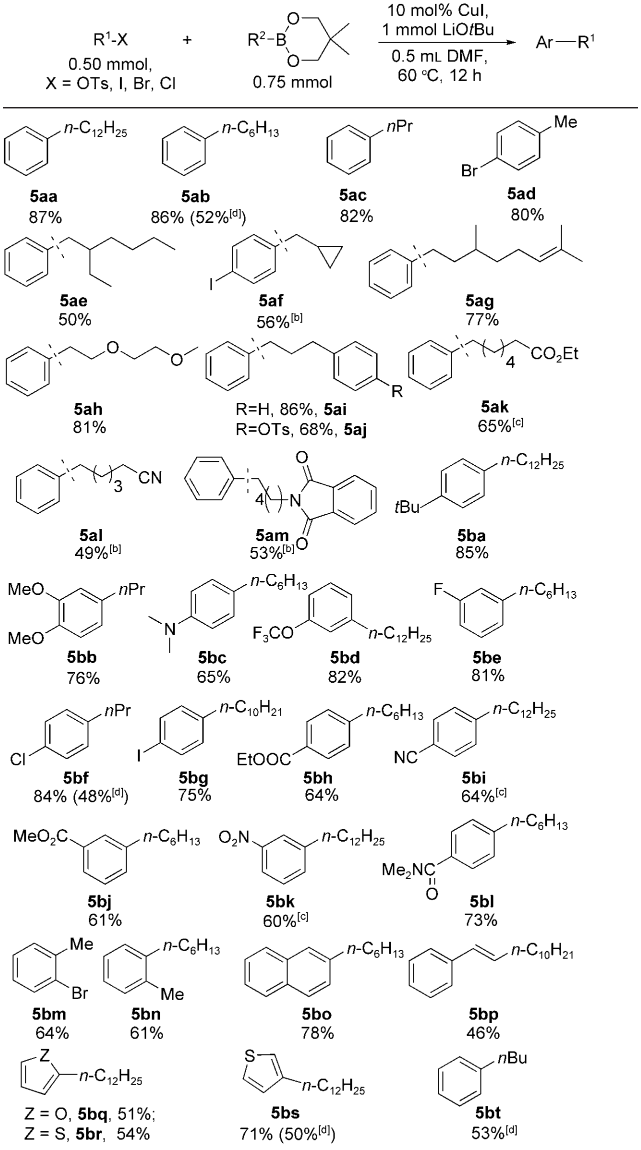
Table 1: Cross-coupling of $n\text{-}C_{12}H_{25}\text{–}X$ under various conditions.



Entry	X	Catalyst (10 mol%)	Base	Solvent	T [°C]	t [h]	Yield [%][a]
1	OTs	CuI	Cs_2CO_3	DMF	110	12	6
2	OTs	CuI	K_3PO_4	DMF	110	12	7
3	OTs	CuI	CsOAc	DMF	110	12	trace
4	OTs	CuI	$NaN(SiMe_3)_2$	DMF	110	12	10
5	OTs	CuI	KO*t*Bu	DMF	110	12	33
6	OTs	CuI	NaO*t*Bu	DMF	110	12	35
7	OTs	CuI	LiO*t*Bu	DMF	110	12	83
8	**OTs**	**CuI**	**LiO*t*Bu**	**DMF**	**60**	**12**	**87**
9	OTs	CuI	LiO*t*Bu	DMF	RT	24	38 (76[b])
10	OTs	CuI	LiOMe	DMF	60	12	54
11	OTs	CuI	LiOEt	DMF	60	12	47
12	OTs	CuI	Li_2CO_3	DMF	60	12	8
13	OTs	CuBr	LiO*t*Bu	DMF	60	12	54
14	OTs	CuCl	LiO*t*Bu	DMF	60	12	20
15	OTs	$Cu(OTf)_2$	LiO*t*Bu	DMF	60	12	4
16	OTs	CuI	LiO*t*Bu	DMSO	60	12	67
17	OTs	CuI	LiO*t*Bu	PhMe	60	12	18
18[c]	OTs	CuI	LiO*t*Bu	DMF	60	12	76
19[d]	OTs	CuI	LiO*t*Bu	DMF	60	12	70
20[e]	OTs	CuI	LiO*t*Bu	DMF	60	12	65
21	I	CuI	LiO*t*Bu	DMF	RT	12	78
22	Br	CuI	LiO*t*Bu	DMF	80	12	69
23	Cl	CuI	LiO*t*Bu	DMF	110	12	56
24	OMs	CuI	LiO*t*Bu	DMF	110	12	71
25	OTs	CuI[f]	LiO*t*Bu	DMF	60	24	83
26	OTs	$Pd(OAc)_2$[f]	LiO*t*Bu	DMF	60	12	0
27	OTs	NiI_2[f,g]	LiO*t*Bu	DMF	60	12	0
28	OTs	–	LiO*t*Bu	DMF	60	12	0
29	OTs	CuI[h]	LiO*t*Bu	DMF	60	12	14

[a] The yield was determined by GC (average of two GC runs). [b] Yield after 72 h. [c] Boronic acid **2** was used in the coupling. [d] Boroxine **3** was used in the coupling. [e] Boronic ester **4** was used in the coupling. [f] Catalyst loading: 2 mol%. [g] NiI_2 was used first because it is an anhydrous salt. $NiCl_2$ and $NiBr_2$ were also tested as hydrated salts and gave the same negative result. [h] Water (10 μL) was added. DMF = *N*,*N*-dimethylformamide, DMSO = dimethyl sulfoxide.

Table 2: Scope of the coupling reaction.[a]



[a] Yields were determined by isolation of the desired product. [b] R–Br (0.5 mmol) was used to facilitate product separation; the reaction was carried out at 80 °C for 24 h. [c] R–I (0.5 mmol) was used to improve the yield; the reaction was carried out at 25 °C for 24 h. [d] The reaction was carried out with R–Cl (0.5 mmol) at 110 °C for 24 h.

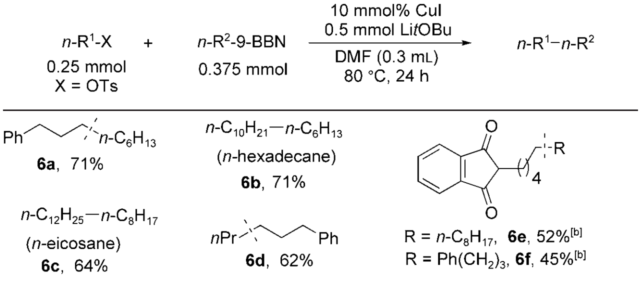
moderate yields were observed when alkyl chlorides were used as substrates (for the synthesis of **5ab**, **5bf**, **5bs**, and **5bt**).

The reaction also tolerates an array of substituents on the organoboron substrate (products **5ba**–**bl**). Importantly, aryl–X (X = F, Cl, Br, I) bonds (in products **5be**–**bg**, **5ad**, and **5af**) do not interfere with the transformation, so that additional cross-coupling reactions at the halogenated positions are possible. Reactive groups that were previously not compatible with Grignard reagents (i.e. ester (**5bh**, **5bj**), cyano (**5bi**), amide (**5bl**), and even nitro groups (**5bk**)) can be present in this new reaction. Furthermore, steric hindrance at the *ortho* position is tolerated to some extent (products **5bm**, **5bn**). Naphthyl, vinyl, and heteroaryl boronate esters can also participate in the reaction (products **5bo**–**bs**).

Under the present conditions, alkyl boronate esters are not viable substrates. However, when alkyl 9-BBN reagents (9-BBN = 9-borabicyclo[3.3.1]nonane) were used as nucleophiles, the copper-catalyzed coupling reaction also proceeded to form a sp^3–sp^3 bond (Table 3). Both alkyl tosylates and alkyl bromides could be used in the reaction. The products were formed in moderate yields.

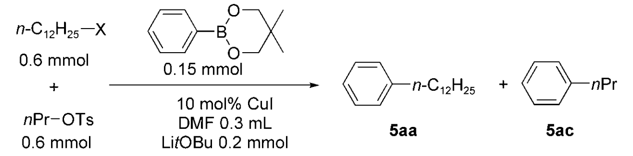
In Table 1 it is shown that for different leaving groups, the required reaction temperature is not the same. To further compare the reactivity trend, we conducted the competitive experiments described in Table 4. According to the results, alkyl iodides are the most reactive electrophiles (Table 4, entry 1), and alkyl bromides are slightly more reactive than alkyl tosylates (Table 4, entry 2). On the other hand, alkyl

Table 3: Cross-coupling of alkyl 9-BBN reagents.[a]



[a] Yields were determined by isolation of the desired product. [b] R–Br (0.25 mmol) was used.

Table 4: Selectivity in competitive experiments.



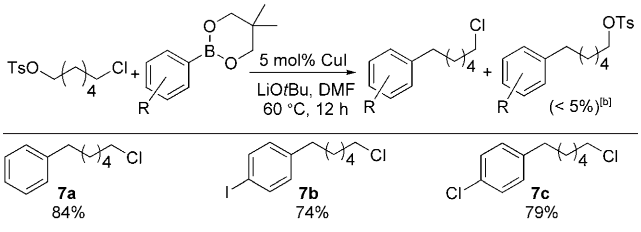
Entry	X	*T* [°C]	*t* [h]	Yield of **5aa** [%][a]	Yield of **5ac** [%][a]
1	I	RT	24	62	11
2	Br	60	24	40	10
3	Cl	60	24	2	68
4[b]	Cl	110	24	9	54

[a] The yield was determined by GC relative to the boronate ester (average of two GC runs). [b] *n*Pr–OMs was used in place of *n*Pr–OTs.

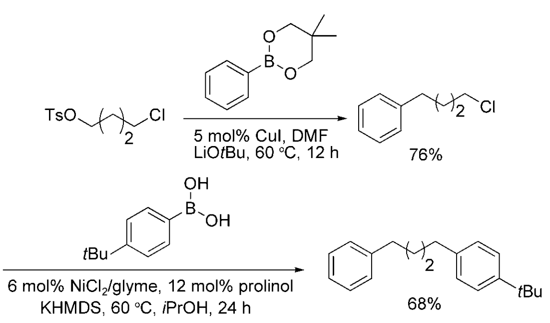
tosylates (and to a lesser extent, alkyl mesylates) are much more reactive than alkyl chlorides (Table 4, entries 3 and 4). These results are consistent with previous results for the copper-catalyzed coupling of Grignard reagents with alkyl electrophiles and confirm that the reactivity increases in the order: chloride < mesylate < tosylate < bromide < iodide.[4c] The copper-catalyzed coupling of alkyl tosylates with boronate esters is particularly interesting on the basis of synthetic considerations because of the difficulties experienced in the past with other metal catalysts. Although Netherton and Fu reported a Pd/P*t*Bu$_2$Me-based system,[9e] the reaction requires the use of organoboron reagents containing 9-BBN–carbon bonds. It was once reported that alkyl tosylates were unreactive in nickel-catalyzed Suzuki reactions of alkyl halides, possibly owing to their reluctance to undergo oxidative addition through a radical pathway.[10b]

We took advantage of the above observations and subjected 6-chlorohexyl tosylate to selective coupling at the C–OTs site (Table 5). Conversion at the C–Cl site was determined to be less than 5 % under these conditions. This interesting chemoselectivity enables the design of sequential cross-coupling reactions on aliphatic chains. Copper-catalyzed cross-coupling at the C(sp^3)–OTs site of 4-chlorobutyl tosylate was followed by nickel-catalyzed cross-coupling at the C(sp^3)–Cl site (Scheme 1).[10b] Note that the boronate ester moiety in Table 5 can contain a halogenated C(sp^2) site that may be further functionalized through cross-coupling. It is expected that the use of selective cross-coupling reactions at various sp^2 and sp^3 sites will greatly expand the utility of cross-coupling reactions for the synthesis of complex target molecules.

Table 5: Site-selective cross-coupling.[a]

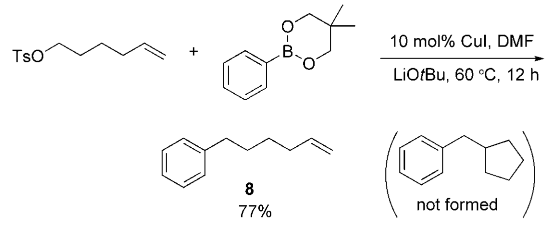


[a] Reaction conditions: *n*-C$_{12}$H$_{25}$–OTs (0.5 mmol), LiO*t*Bu (0.5 mmol), boronate ester (0.75 mmol), DMF (0.5 mL). Yields were determined by isolation of the desired product. [b] The yield of the tosylate by-product was determined by GC.



Scheme 1. Site-selective cross-coupling. KHMDS = potassium hexamethyldisilazide.

To understand the mechanism of the new copper-catalyzed coupling reaction, we first tested the effect of 1,4-cyclohexadiene as a radical scavenger (see the Supporting Information). The addition of 1,4-cyclohexadiene did not produce any negative effect on the reaction yields. Moreover, when hex-5-enyl tosylate was used, **8** was obtained as the sole coupling product in 77 % yield (Scheme 2). These results rule out the possible involvement of a radical mechanism such as that reported for the nickel-catalyzed Suzuki reaction of alkyl halides.[10b] Therefore, a more likely mechanism for the transformation may involve transmetalation between Cu^I and the boronate ester to form an organocopper intermediate. In the following step, the organocopper species should react with the alkyl electrophile through an S$_N$2-type substitution to afford the final product. The reason that LiO*t*Bu is crucial to



Scheme 2. Radical-trapping experiment.

the reaction is twofold: 1) the lithium cation may help stabilize the organocopper intermediate by forming certain cuprate-like complexes;[14] 2) the tBuO$^-$ anion facilitates the transmetalation by coordinating to the boron atom.[15] By ^{11}B NMR spectroscopy, we observed a significant change in the position of the boron peak from $\delta = 26.9$ ppm to $\delta = 3.1$ ppm after the addition of LiOtBu to compound **1** under the reaction conditions. The peak at $\delta = 3.1$ ppm should correspond to a negatively charged boron complex with tBuO$^-$.[16]

To summarize, we have developed a copper-catalyzed cross-coupling of non-activated alkyl electrophiles with organoboron compounds. The use of LiOtBu as a base was found to be crucial to the reaction. The reaction is applicable to alkyl iodides, bromides, tosylates, mesylates, and even chlorides, and tolerates many more functional groups than the previously described copper-catalyzed coupling of Grignard reagents. It provides practically useful reactivities and may thus complement palladium and nickel-catalyzed Suzuki–Miyaura coupling reactions of alkyl halides. Our next challenge is to extend the reaction to secondary alkyl halides.

Experimental Section

Typical procedure: CuI (9.5 mg, 0.05 mmol), LiOtBu (80 mg, 1 mmol), and 5,5-dimethyl-2-phenyl-1,3,2-dioxaborinane (**1**; 142 mg, 0.75 mmol) were added to a Schlenk tube equipped with a stir bar. The vessel was evacuated and filled with argon (this process was repeated three times). n-$C_{12}H_{25}$OTs (170 mg, 0.5 mmol) and DMF (0.5 mL) were added in turn with a syringe. The resulting reaction mixture was stirred vigorously at 60 °C for 12 h. It was then diluted with Et_2O, filtered through silica gel (which was rinsed with EtOAc), and concentrated. Purification of the residue by column chromatography (silica gel, hexanes/EtOAc) yielded dodecylbenzene (**5aa**; 107 mg, 87 %) as a colorless liquid. The spectroscopic data of **5aa** matched previously described data.

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