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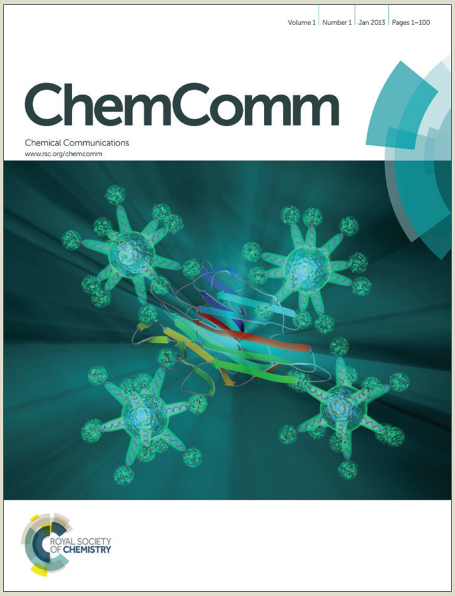

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Cu-Catalyzed Suzuki-Miyaura Reactions of Primary and Secondary Benzyl Halides with Arylboronates

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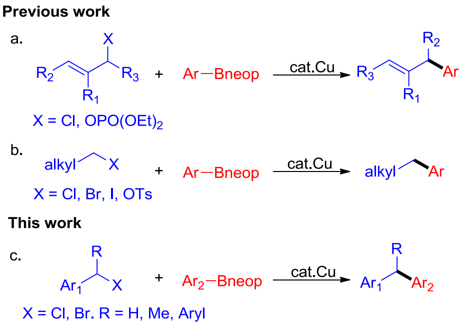
A copper-catalyzed Suzuki-Miyaura coupling of benzyl halides with arylboronates is described. Varieties of primary benzyl halides as well as more challenging secondary benzyl halides with β hydrogens or steric hindrance could be successfully converted into the corresponding products. Thus it provides access to diarylmethanes, diarylethanes and triarylmethanes.

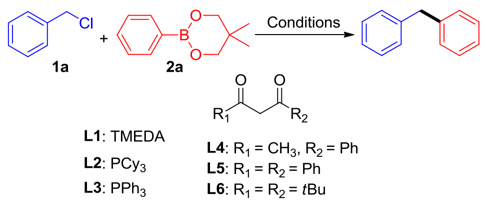
Transition metal catalyzed cross-coupling reactions provide efficient approaches for the construction of C-C bonds and plays an important role in organic synthesis.[1] Apart from Kumada[2,3] and Negishi,[4] the Suzuki-Miyaura reaction is widely used due to the superior features of organoboron compounds, such as easy manipulation, ready availability and low toxicity. Extensive studies on palladium or nickel catalyzed Suzuki-Miyaura reactions have been investigated during the past few decades.[5,6a-f] Recently, more attentions have been paid to the inexpensive and environmentally benign copper catalyst.[6g] For instance, Sawamura[7] and Lalic[8] have reported S_N2'-selective arylation of allylic electrophiles with arylboronates using copper as catalyst (Scheme 1a). In 2011 the copper-catalyzed cross-coupling reaction of alkyl electrophlic reagents and arylboronates was also reported (Scheme 1b),[9] which was recognized as the pioneering work in this area. Notwithstanding these advances, the Cu-catalyzed Suzuki-Miyaura reaction of benzyl electrophiles with arylboronates *has surprisingly never been reported*.

Herein, we report the first example of copper-catalyzed cross-coupling reaction of benzyl halides with arylboronates (Scheme 1c). The primary benzyl halides could be converted successfully into the desired products, even more challenging partners-*secondary benzyl halides* with β hydrogens or extra steric hindrance performed well under such catalytic system.[10] This reaction expands the scope of copper-catalyzed cross-coupling benzylation in a fundamental sense, and simultaneously complements nickel- and palladium-catalyzed Suzuki-Miyaura reaction. Also, this methodology provides a fruitful and efficient synthesis for functionalized diarylmethanes, diarylethanes and triarylmethanes,[11d-g] which are emerged as structural constituents in pharmacologically interesting molecules (e.g. Papaverin and Piritrexim).[11a-c]



Scheme 1 Copper catalyzed reactions of alkyl electrophiles with arylboronates. Neop = $(OCH_2CMe_2CH_2O)$.

Table 1 Optimization of the Reaction conditions.[a]



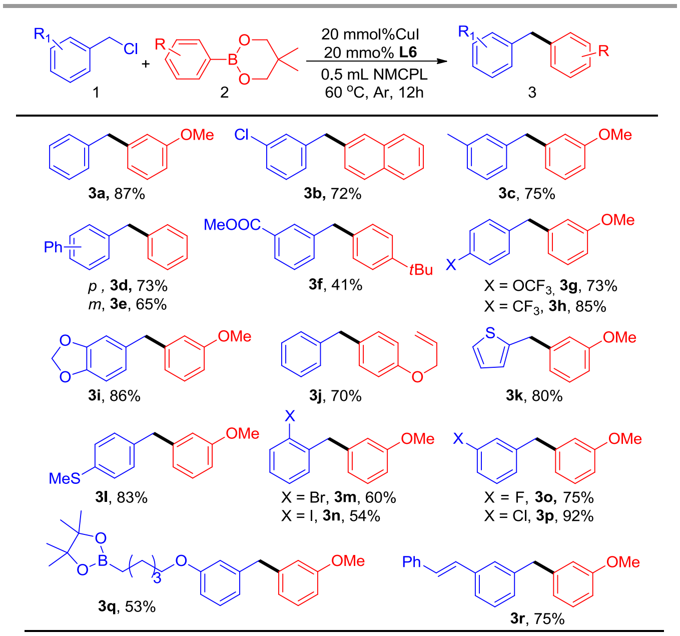
Entry	Catalyst	Solvent	Ligand	Yield[a]
1	CuI	DMF	-	35[b]
2	CuI	DMF	-	40
3	CuI	DMF	**L1**	33
4	CuI	DMF	**L2**	28
5	CuI	DMF	**L3**	25
6	CuI	DMF	**L4**	65
7	CuI	DMF	**L5**	70
8	CuI	DMF	**L6**	75
9	CuI	NMP	**L6**	66
10	CuI	DMPU	**L6**	68
11	CuI	THF	**L6**	20
12	CuI	NMCPL	**L6**	90(85[c])

13	CuCl	NMCPL	**L6**	50
14[d]	Pd(OAc)$_2$	NMCPL	**L6**	18
15[d]	NiI$_2$	NMCPL	**L6**	trace
16	-	NMCPL	**L6**	0

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.75 mmol), CuI (20 mol%), LiO*t*Bu(3 equiv), ligand (20 mol%) in 0.5 mL solvent at 60 °C for 12h under Ar atmosphere. The yield was determined by GC using benzophenone as internal standard (average of two GC runs).[b] CuI (10 mol%), LiO*t*Bu(2 equiv) in 0.5 mL solvent at 60 °C for 12h under Ar atmosphere.[c] Isolated yield. [d] catalyst loading: 2 mol%. DMF = N, N-dimethylformamide. NMP = 1-methyl-2-pyrrolidinone. DMPU = 1,3-dimethyl-3, 4, 5, 6-tetrahydro-2(1H)-pyrimidinone, THF = tetrahydrofuran. NMCPL = N-methylcaprolactam.

We commenced our study by choosing benzyl chloride (**1a**) and phenylboronate (**2a**) as the model substrates (Table 1). First we tested the previously reported catalytic system.[9] Gratifyingly, the desired product was obtained in 35% GC yield (entry 1). The result indicated that the conditions previously reported for the coupling of primary alkyl electrophiles, were not suitable for benzyl halides. Thus, we devoted our efforts to improve the yield by screening various ligands. Bidentate nitrogen ligands (e.g. TMEDA) and monodentate phosphine ligands (e.g. PPh$_3$, PCy$_3$) were examined first, but gave a lower yield (entry 3-5 vs entry 1-2). To our delight, we observed 65% yields with **L4** (entry 6). This finding encouraged us to test the diketone family ligands (entry 6-8). Surprisingly, the ligand **L6** dramatically increased the yield to 75%. In a further evaluation of various solvents (entry 9-12), the desired product was obtained in 90% yield employing N-methylcaprolactam (NMCPL) as a solvent (entry 12). Notably, to rule out the probable involvement of Ni or Pd contamination in the reaction, we conducted the reaction using Pd(OAc)$_2$ or NiI$_2$, and found that only a very low amount of product was formed (entry 14-15). Furthermore, blank experiment demonstrated that copper catalyst is necessary for the reaction (entry 16).

Table 2 Scope of primary benzyl chlorides[a,b]

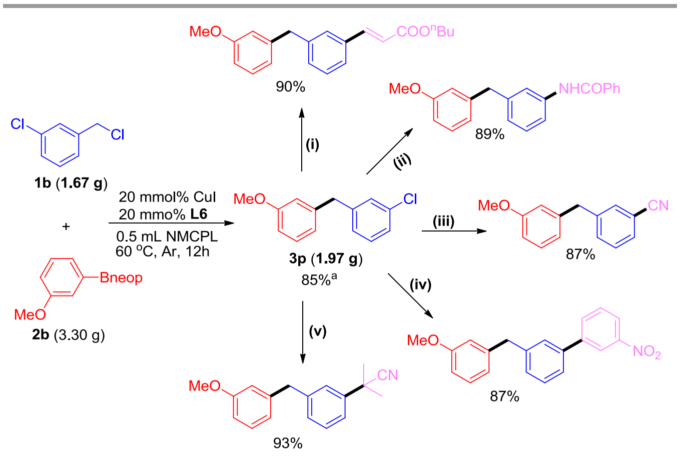


[a] Reaction conditions: Benzyl chlorides (0.5 mmol), arylboronic esters (1.5 equiv), LiO*t*Bu (3 equiv), NMCPL= N-methylcaprolactam. [b] Isolated yields.

Under the optimized conditions, we decided to investigate the scope of this transformation (Table 2). To our delight, a series of synthetically relevant functional groups including ether (**3a**), naphthyl (**3b**), *meta-/para*-substitued methyl/phenyl (**3c**, **3d**, **3e**), ester (**3f**), trifluoromethoxy (**3g**), trifluoromethyl (**3h**), ketal (**3i**), olefin (**3j**) can be well tolerated in yield of 41-87%. Compounds bearing sulphur atom, which were another interesting substrates, can also participate in the reaction (**3k**, **3l**). It is noteworthy that aryl-X (X= F, Cl, Br, I) bonds (in products **3m**, **3n**, **3o**, **3p**) do not interfere with the reaction and could be tolerated with the yield of 54-92%, which may thus give the possibility for further functionalizations of C-X. Significantly, we observed selective cross-coupling of an aryl boronate ester over of alkyl pinacol boronate ester (**3q**). This feature makes additional transformation possible at C-B bond. Finally, phenylethylene substrate was also successfully employed to prepare the corresponding styrene compounds and derivatives (**3r**).

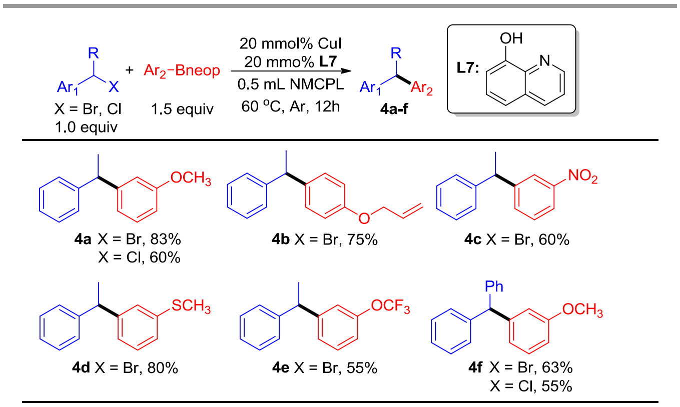
Gram-scale reaction was carried out (Fig. 1), furnishing 1.97 g of the desired product with a yield of 85 % isolation. No detrimental effect on the yield was observed upon increasing the reaction scale. Further functionalizations via palladium-catalyzed cross-coupling reactions at the halogenated sites were also proceeded to excellent yield, which supplies a general approach to an array of useful compounds[12] such as styrenes, benzamides, nitrobenzoates, benzonitrile.

Fig 1. Gram-Scale Synthesis and functionalization of the products[a,b]



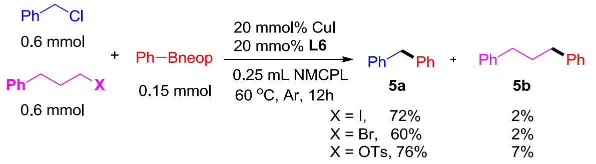
[a] Reaction conditions: LiO*t*Bu (3 equiv), neop = (OCH$_2$CMe$_2$CH$_2$O). [b]Isolated yields. NMCPL = N-methylcaprolactam. For reaction conditions of **i-v**, see ref.[12]

Table 3 Scope of secondary benzyl halides[a,b]



[a] Reaction conditions: Benzyl halides (0.5 mmol), arylboronic esters (1.5 equiv), LiO*t*Bu (3 equiv), NMCPL = N-methylcaprolactam. [b] Isolated yields.

Since varieties of primary benzyl halides could be successfully converted into the corresponding products, we envisioned whether more challenging secondary benzyl electrophiles with β hydrogens, could involve in the reaction. Fortunately, after a considerable number of screening experiments, the desired product (**4a**) through the reaction of (1-bromoethyl)benzene and arylboronate (**2b**) was indeed obtained in 83% yield (see Supporting Information). As illustrated in Table 3, secondary benzyl bromides containing β hydrogens, which tended to suffer undesired β-hydride elimination in palladium-catalyzed reaction,[10] are suitable substrates (**4a-4e**). Interestingly, secondary benzyl halides, such as (bromomethylene)dibenzene, could also perform well in the coupling (**4f**). In addition, the reaction could tolerate an array of functional groups, such as ether (**4a**), olefin (**4b**), nitro group (**4c**), thioether (**4d**), trifluoromethoxy (**4e**) in 55%-83% yield, thus offering an easy access to diarylethanes and triarylmethanes.[13]



Scheme 2 Selectivity in competitive experiments[14]

To better understand the selectivity trend between benzyl chlorides and alkyl electrophiles, we conducted a few competitive experiments. As illustrated in Scheme 2, we observed that highly selective coupling was carried out at the benzyl C-Cl site over of alkyl C-X (X=OTs, Br. I) under the present catalytic system.

To demonstrate the mechanism of the reaction, we carried out the radical scavenger experiment and found that the effect of TMEPO is not similar for different substrates (For more details, see Supporting Information). Further investigations on the possible mechanism are underway.[15,16]

In summary, an efficient and practical copper-catalyzed cross-coupling reaction of benzyl halides with arylboronates has been developed for the first time. A series of primary benzyl halides as well as more challenging secondary benzyl halides with β hydrogens or steric hindrance could be successfully converted into the corresponding products. Additionally, this reaction conceptually broadens the scope of copper catalyzed cross-coupling, and complements palladium- and nickel-catalyzed Suzuki-Miyaura reaction of benzyl electrophiles. The reaction provides a straightforward, effective means for the synthesis of diarylmethanes, diarylethanes and triarylmethanes with various functional groups. Further studies on the mechanism are ongoing in our laboratory.

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