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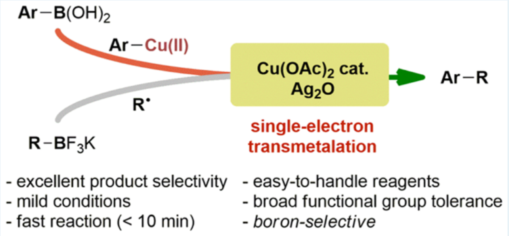
Copper-Catalyzed Boron-Selective $C(sp^2)-C(sp^3)$ Oxidative Cross-Coupling of Arylboronic Acids and Alkyltrifluoroborates Involving a Single-Electron Transmetalation Process

Siyi Ding, Liang Xu, and Pengfei Li*

Center for Organic Chemistry, Frontier Institute of Science and Technology (FIST), Xi'an Jiaotong University, 99 Yanxiang Road, Xi'an, Shaanxi 710054, China

Ⓢ *Supporting Information*

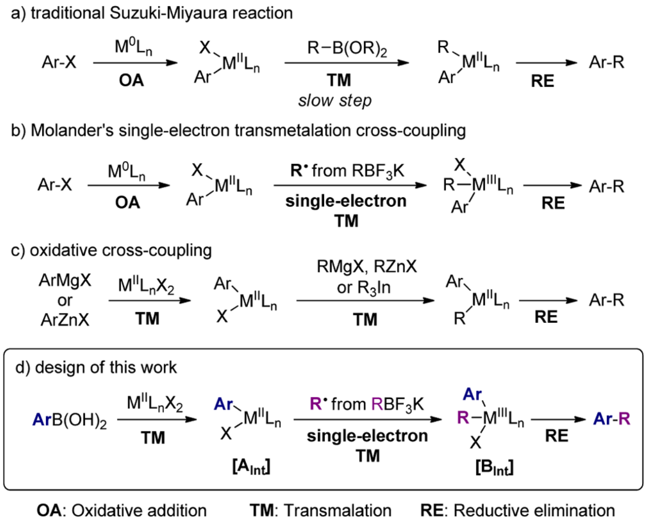
ABSTRACT: A rapid and highly selective oxidative cross-coupling reaction between readily available and shelf-stable arylboronic acids and primary or secondary potassium alkyltrifluoroborates was devised and developed, which works under mild conditions using copper(II) acetate as the catalyst and silver oxide as the oxidant. Initial experimental results indicate that a single-electron transmetalation process is involved. This approach effectively bypasses the problems associated with the traditional cross-coupling reactions of alkylboronates and thus provides a complementary method in building $C(sp^2)-C(sp^3)$ bonds.



KEYWORDS: *cross-coupling, oxidation, single-electron transmetalation, organoboron, copper catalysis*

Palladium-catalyzed carbon−carbon cross-coupling reactions of organometallic reagents and organic electrophiles, especially the Suzuki−Miyaura reaction, have proven to be indispensable tools in organic synthesis.[1,2] Mechanistically, the catalytic cycle includes three two-electron processes that are oxidative addition (OA), transmetalation (TM), and reductive elimination (RE) (Scheme 1a). Although this scenario has been very successful for $C(sp^2)-C(sp^2)$ bond formation, convenient and reliable methods involving $C(sp^3)$-type reactants still remain challenging because for alkyl electrophiles and/or metallic reagents, some or all of these steps are slower,[3] and the reactions are very often complicated due to facile β-hydride elimination of alkyl palladium intermediates.[4] In this regard, first-row transition metals such as nickel have been effective as catalysts in coupling of alkyl electrophiles by overcoming some of the above limitations.[3b,5−8] Highly reactive and air-, moisture-sensitive alkyl nucleophiles such as Grignard reagents, alkylzincs, and alkyl boranes were also successfully used in forming $C(sp^2)-C(sp^3)$ bonds.[3c,9] However, the more user-friendly alkylboronic acid derivatives are much slower in transmetalation, and thus, high temperatures and long reaction times are generally necessary (Scheme 1a),[3a,10] although for some substrates neighboring functional groups may facilitate the transmetalation.[11] Very recently, Molander and co-workers developed an elegant nickel/photoredox dual catalytic method which allowed for efficient use of alkyltrifluoroborates in cross-coupling under mild conditions.[12] Thus, in the presence of visible-light photoredox catalyst, a benzylic or later on a secondary alkyltrifluoroborate can be oxidized to generate an alkyl radical that undergoes facile single-electron transmetalation onto a nickel catalyst (Scheme 1b). Independently, MacMillan and co-workers successfully coupled α-heteroatom aliphatic acids, via photoredox decarboxylation to form the radicals, with aryl halides in a similar manner (Scheme 1b).[13,14]

Scheme 1. Approaches toward $C(sp^2)-C(sp^3)$ Bonds



In the past decade, oxidative cross-coupling reactions, mechanistically via two consecutive transmetalation, have emerged as an alternative approach to construct C−C bonds.[15,16] The inherent challenge of these reactions is to achieve high chemoselectivity between two organometallic reagents avoiding undesired homocoupling processes. For

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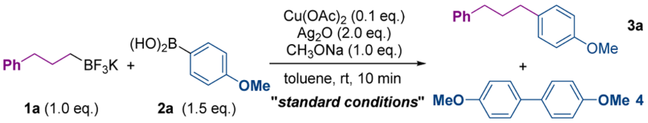
formation of C(sp^2)−C(sp^3) bonds (Scheme 1c), in particular, Lei developed a selective palladium-catalyzed cross-coupling between arylzinc and trialkylindium reagents.[17] Cahiez used diorganozinc to realize this type of coupling in the presence of the iron catalyst.[18] Severin attempted similar reaction with Grignard reagents, but in most cases, a mixture of various coupling products was formed.[19] In contrast, a selective oxidative C(sp^2)−C(sp^3) cross-coupling between two organoboron partners has not been reported. This reaction is interesting and potentially more advantageous because, in comparison with other organometallic reagents, organoboronic acid derivatives are more readily available, stable to air and moisture, and compatible with many functional groups.

In continuing our research on boron-selective reactions,[20] we envisioned that a chemoselective oxidative coupling reaction between an arylboron and an alkylboron might be used to generate a new C(sp^2)−C(sp^3) bond (Scheme 1d). Thus, the arylboron compound may selectively undergo two-electron transmetalation on a transition-metal catalyst to form [$\mathbf{A_{Int}}$],[21,22] while the alkylboron component might be seletively oxidized to an alkyl radical ($\mathbf{R}^\cdot$).[12,23] A single-electron transmetalation process between $\mathbf{R}^\cdot$ and [$\mathbf{A_{Int}}$] then might take place to form the high-valent intermediate [$\mathbf{B_{Int}}$], which should undergo facile reductive elimination to form the desired product.[12−14,24] This design would bypass the low reactivity of alkylboronic acid derivatives in conventional transmetalation as well as the undesired *β*-hydride elimination due to slow reductive elimination. However, several key challenges must be addressed in developing such a reaction. First, suitable oxidant(s) need to be identified to selectively oxidize the alkylboron compound and to regenerate the metal catalyst. Second, the rates of generation of the highly reactive alkyl radical and formation of [$\mathbf{A_{Int}}$] must be balanced to avoid dimerization and/or hydrogenation of the radical, or second transmetalation of arylboron reagents that will lead to a homocoupling product. Third, the competitive C−X reductive elimination from [$\mathbf{B_{Int}}$] should be minimized.

With these considerations in mind, we commenced our investigations toward a boron-selective oxidative cross coupling using potassium 3-phenylpropyl trifluoroborate (**1a**) and 4-methoxyphenylboronic acid (**2a**) as the model substrates (Table 1). After extensive experimental studies, we were able to obtain the desired product **3a** in high efficiency under the “standard” conditions. Thus, using copper(II) acetate (0.1 equiv) as the catalyst, silver(I) oxide (2.0 equiv) as the oxidant, sodium methoxide (1.0 equiv) as a basic additive, a mixture of **1a** (1.0 equiv) and **2a** (1.5 equiv) in toluene (0.2 M) was stirred under nitrogen atmosphere at room temperature for just 10 min and **3a** was formed in 90% GC yield. After filtration and purification by column chromatography, **3a** was isolated in 86% yield (Entry 1). The rapid formation of a C−C bond under exceptionally mild conditions is remarkable. The reaction was not moisture-sensitive, and therefore, rigorous drying of the solvent and reagents was not necessary. More importantly, excellent chemoselectivities were achieved, because the potential protodeboronation products of **1a** and **2a**, homocoupling product of **1a** were only observed in trace amounts, whereas the homocoupling product of **2a** was formed in 6% GC yield.

Table 1. Variations from the “Standard” Reaction Conditions of the Cross-Coupling of 1a and 2a[a]



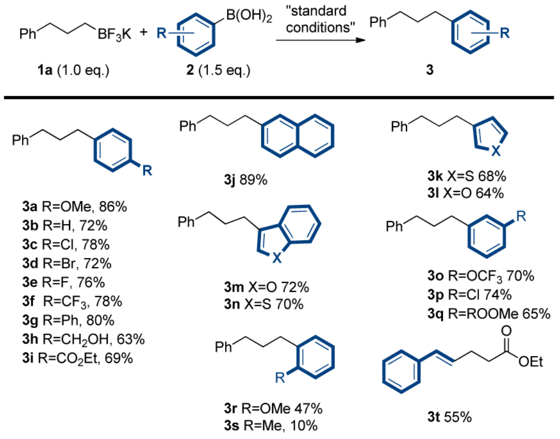
entry	metal	base	yield of **3a** (%)[b]	yield of **4** (%)[b]
1	**Cu(OAc)$_2$**	**CH_3ONa**	**90 (86[c])**	**6**
2	$CuCl_2$	CH_3ONa	67	ND
3	Cu(acac)$_2$	CH_3ONa	50	ND
4	$CoCl_2$	CH_3ONa	28	ND
5	$NiCl_2$	CH_3ONa	56	ND
6	Fe(acac)$_3$	CH_3ONa	30	ND
7	Pd(OAc)$_2$	-	30	15
8	Pd(OAc)$_2$	CH_3ONa	61	31
9	$PdCl_2$	CH_3ONa	trace	10
10	-	CH_3ONa	10	ND
11	Cu(OAc)$_2$	NaOAc	71	9
12	Cu(OAc)$_2$	KOAc	65	ND
13	Cu(OAc)$_2$	Cs_2CO_3	2	ND
14	Cu(OAc)$_2$	K_3PO_4	13	ND
15	Cu(OAc)$_2$	*t*-BuOK	28	ND
16[d]	Cu(OAc)$_2$	CH_3ONa	40	ND
17[e]	Cu(OAc)$_2$	CH_3ONa	15	trace

[a] Reaction conditions: **1a** (0.4 mmol, 1.0 equiv), **2a** (1.5 equiv), catalyst (10 mol %), Ag_2O (2.0 equiv), base (1.0 equiv), solvent (2.0 mL), distilled water (40 μL), room temperature, 10 min. [b] Determined by GC analysis of the reaction mixture using tridecane as an internal standard; the yield was based on **1a**. [c] Yield of the isolated product. [d] The reaction was conducted without addition of distilled water. [e] Reaction was run in air. ND: not determined.

Variations from the “standard” conditions led to significantly lower efficiency, and some representative results are shown in Table 1. Other sources of copper catalyst resulted in lower yields (entries 2 and 3). Under otherwise identical conditions, first-row transition-metal catalysts such as cobalt, nickel, iron were all inferior (entries 4−6), while palladium acetate led to low selectivity as significant amount of 4,4′-dimethoxy-1,1′-biphenyl (**4**) as homocoupling product was observed (entries 7−9). In the absence of copper source, 10% of **3a** was observed (entry 10), presumably due to metal im-purities in commercial Ag_2O.[25] Interestingly, the effect of sodium methoxide as a base additive was dramatic, because other bases only resulted in moderate to low yields (entries 11−15). Furthermore, addition of small amount of distilled water was very important in this reaction, otherwise the yield decreased dramatically (entry 16). When 4-methoxyphenyl pinacol boronate, potassium trifluoroborate, or the corresponding boroxine was used in place of **2a**, little **3a** was formed. These facts suggest that a possible role of water might be keeping the arylboron species in the reactive boronic acid form. In the absence of or using oxidants other than Ag_2O, no reaction was observed, indicating the unique roles of Ag_2O in promoting this reaction. Attempt to run the reaction in air atmosphere resulted in very low yield (entry 17). Finally, the reactions were conducted at 1.0 and 5.0 mmol scales, producing **3a** in 85% and 75% isolated yields, respectively (for more details, see SI).

Having identified the optimal reaction conditions, we next investigated the substrate scope of this transformation. We first varied the arylboronic acid under the standard reaction conditions, and the results are shown in Scheme 2. Various arylboronic acids with electron-donating or -withdrawing substituents at *para*- or *meta*-positions are good substrates, cleanly forming the desired oxidative cross-coupling products in good to high yields. Chlorine and bromine substituents are

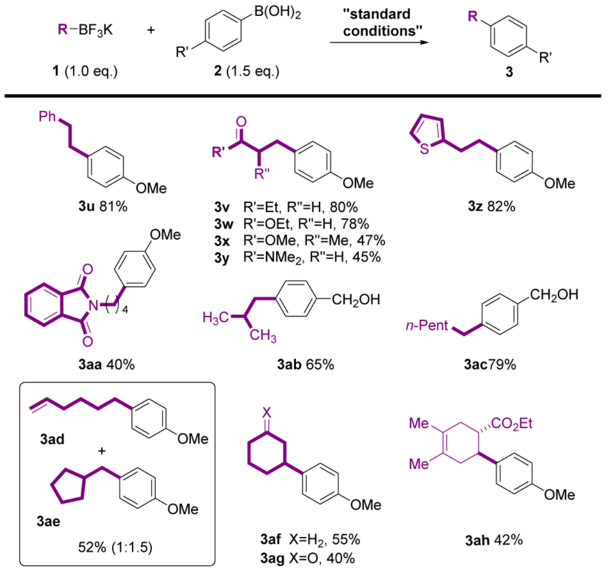
Scheme 2. Scope of the Arylboronic Acid Component



[a]Yield of the isolated product.

compatible (**3c** and **3d**), thus representing orthogonal reactivity with conventional palladium-catalyzed cross-coupling. Alcohol and ester groups, which may not be used in reactions of organomagnesium or organozinc reagents, are also compatible (**3h**, **3i**, **3q**). Furanyl and thiophenyl boronic acids were also found to successfully paticipate the current reaction (**3k**–**3n**). Finally, an alkenylboronic acid also served as a viable substrate, producing the coupling product (**3t**) in 55% yield.

Scheme 3. Scope of the Potassium Alkyltrifluoroborate Component

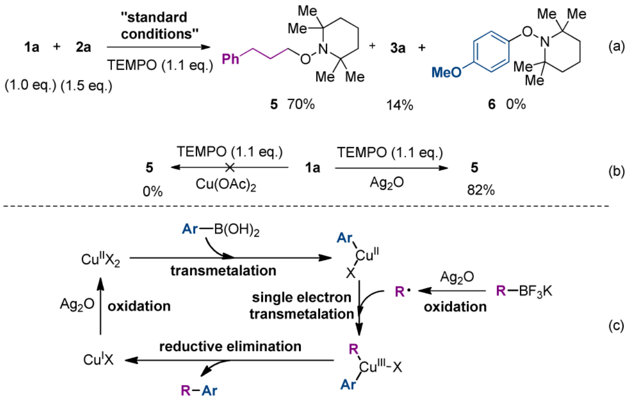


[a]Yield of the isolated product.

Next, we briefly investigated the scope of alkyl trifluoroborates (Scheme 3). Primary alkyl trifluoroborates bearing functional groups such as ester (**3w**, **3x**), amide (**3y**), and even ketone (**3v**) were all suitable coupling partners. Additionally, alkyl trifluoroborates with a thienyl group was compatible (**3z**). When branched alkyl trifluoroborates were used, moderate yields were obtained presumably due to steric hindrance (**3x**, **3ab**). This notion was also consistent with the relatively low yield of **3r** or **3s** where *ortho*-methoxylphenyl boronic acid and *ortho*-methylphenyl boronic acid was used (Scheme 2). When 5-hexenyltrifluoroborate was reacted with **2a** under the standard conditions, a mixture of the normal linear product **3ad** and a cyclized product **3ae** (1:1.5) was obtained, suggesting the intermediacy of primary alkyl radical. Furthermore, secondary alkyltrifluoroborates were also viable substrates under the current conditions, although the yields are moderate (**3af**–**3ah**).

In order to probe the reaction mechanism, 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO, 1.1 equiv) was added as a radical scavenger to the reaction mixture of **1a** and **2a** under the standard conditions. The formation of **3a** (14% yield) was significantly suppressed and the alkyl-TEMPO adduct **5** could be isolated in 70% yield (Scheme 4a). No aryl-TEMPO adduct was observed. The independent oxidation of **1a** using either Ag_2O (2.0 equiv) or $Cu(OAc)_2$ (2.0 equiv) as the sole oxidant in the presence of TEMPO was also conducted (Scheme 4b). Interestingly, while Ag_2O was a very effective oxidant to produce **5** in high yield, $Cu(OAc)_2$ was totally unreactive under the current conditions. This is remarkable because $Cu(OAc)_2$ had been used before in different conditions as effective oxidant of alkyltrifluoroborate.[23]

Scheme 4. Preliminary Mechanistic Studies



On the basis of the experimental results, we propose a catalytic cycle for the present oxidative cross-coupling reaction, as depicted in Scheme 4c. Transmetalation of the arylboronic acid onto the Cu(II) catalyst forms ArCu(II)X species, in analogy to the commonly accepted process in Chan–Lam–Evans reaction.[22] An alkyl radical, generated from Ag_2O-mediated oxidation of the potassium alkyltrifluoroborate, undergoes a single-electron transmetalation onto ArCu(II)X to form a three-valent copper species ArCu(III)RX which then undergoes C–C reductive elimination to produce the desired product ArR and Cu(I)X. Oxidation of Cu(I)X again by Ag_2O regenerates $Cu(II)X_2$ catalyst to close the catalytic cycle.

In summary, we have discovered a copper-catalyzed boron-selective oxidative cross-coupling reaction between readily available arylboronic acids and potassium alkyltrifluoroborates. This reaction features excellent product selectivity, short reaction time, mild reaction conditions, simple operation, and broad functional group tolerance. In comparison with the conventional Suzuki–Miyaura coupling, the current reaction requires one additional step for the preparation of an organoboron reactant from the corresponding halide. However, considering that many shelf-stable aryl and alkyl organoboron compounds are already commercially available, this reaction should be useful in facilitating small-molecule array synthesis due to its characteristics mentioned above. Notably, due to the distinct mechanism, this reaction provides an orthogonal method for coupling of halogen-containing substrates. Although the complete mechanism remains unclear, a novel and highly efficient silver(I) oxide-mediated oxidation of alkyltrifluoroborate and a single-electron transmetalation of the resulting alkyl radical onto copper species are likely involved as the key steps. Future studies on the mechanism and methods for controlled generation of the alkyl radical may further improve this coupling reaction.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.5b02524.

Detailed experimental procedures, spectral data of products (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: lipengfei@mail.xjtu.edu.cn.

Notes

The authors declare no competing financial interest.

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