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Transition-Metal-Free Cross-Coupling Using Tertiary Benzylic Organoboronates

Mitsutaka Takeda,[a] Kazunori Nagao,[a] and Hirohisa Ohmiya*[a][b]

Abstract: The transition-metal-free cross-coupling of alkyl or aryl electrophiles using tertiary benzylic organoboronates is reported. This reaction involves the generation of tertiary alkyl anions from organoboronates in the presence of an alkoxide base and then their substitution reactions. This protocol allows the simple and efficient construction of quaternary carbon centers.

The preparation of quaternary carbon centers using cross-coupling reactions has been identified as a key challenge in organic synthesis. Cross-coupling reactions using a tertiary alkyl organometallic nucleophile are a direct and reliable approach for realizing highly congested quaternary carbon centers. Tertiary alkylboron compounds are particularly attractive organometallic reagents due to their high chemical stability and widespread availability (Figure 1A, top).[1] Recent progress in the catalytic preparation of tertiary alkylborons from various simple organic molecules has been remarkable.[2] Nevertheless, cross-coupling using tertiary alkylborons is still in its infancy given the limited progress in recent years.[3,4] In particular, $C(sp^3)$–$C(sp^3)$ cross-coupling between tertiary alkylborons and alkyl electrophiles is quite difficult. Obstacles to transition-metal catalysis are the slow transmetalation from sterically encumbered nucleophiles and the reductive elimination from the *in situ*-generated alkylmetal complex, which is prone to β-hydride elimination.

Alkylborons serve as alkyl anion equivalents through the formation of borate species in the presence of an appropriate base. However, cross-coupling using borate species, which is derived from a tertiary alkylboron and a base, is underdeveloped (Figure 1A, bottom). For example, Aggarwal and co-workers demonstrated S_E2'-type $C(sp^3)$–$C(sp^3)$ cross-couplings between trisubstituted allylboronates and activated alkyl electrophiles such as tropylium cation, benzodithiolylium, and Eschenmoser's salt using organolithium reagents as a base (Figure 1B).[5] Morken and co-workers revealed that the borate complex, which is derived from 1,1-diborylalkanes and alkoxide bases, could undergo deborylative $C(sp^3)$–$C(sp^3)$ cross-coupling using alkyl halides (Figure 1C).[6a] On the other hand, the process using tertiary alkylborate species has not yet been applied to $C(sp^3)$–$C(sp^2)$ cross-coupling using aryl electrophiles.

Here, we report tertiary alkylative cross-coupling of alkyl or aryl electrophiles using benzylic organoboronates (Figure 1D).[7] The reaction involves the generation of tertiary alkyl anions from organoboronates in the presence of an alkoxide base and then their substitution reactions under mild and transition-metal-free conditions. This protocol allows the simple and efficient construction of quaternary carbon centers.

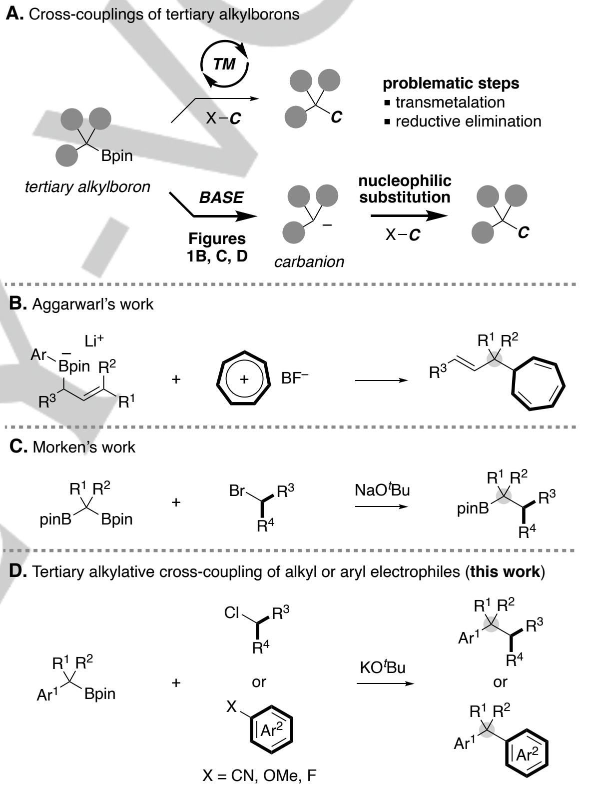

Figure 1. Construction of quaternary carbon centers through cross-couplings using tertiary alkylborons.

In numerous studies in this laboratory, we found that the reaction of tertiary benzylboronate **1a** (0.3 mmol) and 4-chlorotetrahydro-2H-pyran (**2a**) (0.2 mmol) with a stoichiometric amount of KO*t*Bu (0.3 mmol) occurred in dioxane (1 mL) at 100 °C to produce the cross-coupling product **3aa** in 87% isolated yield (Table 1, entry 1).

The choice of bases was critical in the cross-coupling reaction (Table 1, entries 2–6). The use of other alkali metal-based tertiary butoxide bases, NaO*t*Bu and LiO*t*Bu, resulted in moderate and no product yield, respectively (entries 2 and 3). Highly basic and sterically demanding KHMDS was less effective (entry 4). A small alkoxide base, KOMe, slightly diminished the product yield (entry 5). The reaction efficiency tended to increase as the ionic radius of the metal increased (Li+ < Na+ < K+).[6a] PhLi showed moderate reactivity (entry 6).[5]

The effect of the leaving group of the alkyl electrophile was

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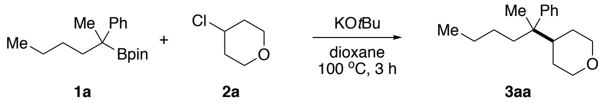
also evaluated (Table 1, entries 7–11). The reaction with secondary alkyl fluoride resulted in recovery of the substrate (entry 7). Secondary alkyl bromide and iodide gave a trace amount of the desired alkylation product, along with an alkene as the E2 elimination product (entries 8 and 9). Alkyl tosylate underwent the desired alkylation reaction (entry 10), but alkyl mesylate did not afford the product (entry 11).

Table 1. Screening of conditions for cross-coupling between **1a** and **2a**.[a]



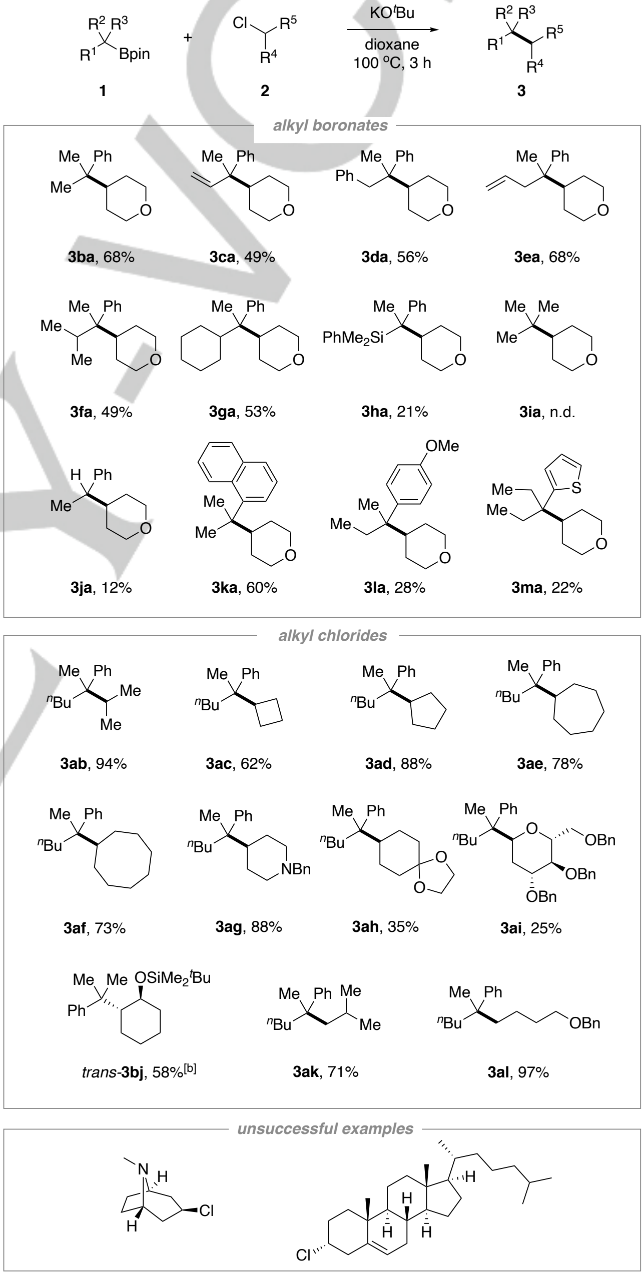
Entry	Change from standard conditions	Yield (%) of **3aa**^{b}
1	none	97 (87)
2	NaO*t*Bu instead of KO*t*Bu	53
3	LiO*t*Bu instead of KO*t*Bu	0
4	KHMDS instead of KO*t*Bu	47
5	KOMe instead of KO*t*Bu	60
6	PhLi instead of KO*t*Bu	51
7	F as leaving group instead of Cl	0
8	Br as leaving group instead of Cl	0
9	I as leaving group instead of Cl	3
10	OTs as leaving group instead of Cl	31
11	OMs as leaving group instead of Cl	0

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.2 mmol), KO*t*Bu (0.3 mmol), dioxane (1 mL), 100 °C, 3 h. [b] 1H NMR yield. Yield of the isolated product is in parentheses. KHMDS, potassium hexamethyldisilazide. OTs, tosylate. OMs, mesylate.

With these optimized reaction conditions in hand, the scope of the alkylboronates was investigated (Table 2, top).[8] Methyl, vinyl, benzyl, and allyl groups instead of the butyl group of **1a** were tolerated (**3ba**–**ea**). The benzyl boronates having a bulky substituent such as an isopropyl or cyclohexyl group participated in the reactions to construct the highly congested contiguous sp^3 carbon centers (**3fa**, **3ga**). Replacement of the butyl group with a SiMe$_2$Ph substituent was tolerated, although the product yield was low (**3ha**). The reaction with a non-benzyl boronate resulted in no product being formed (**3ia**). Thus, the applicability of this protocol seems to be limited to benzyl boronates, the results indicating that the reaction would proceed through the formation of the benzyl anion from the organoboronate (*vide infra*). A secondary benzyl boronate drastically diminished the reaction efficiency (**3ja**). Conversion of the phenyl group to other aromatic rings such as the 1-naphthyl group was allowed in the reaction (**3ka**). A methoxy substituent at the *para*-position of the aromatic ring of the benzyl boronate resulted in low yield (**3la**). Thiophene underwent the reaction, although the yield was moderate (**3ma**).

The scope of alkyl chlorides was also examined in cross-coupling using tertiary benzyl boronates (Table 2, middle). Acyclic alkyl chloride was a suitable substrate (**3ab**). This protocol was applied to various cyclic alkyl chlorides. Thus, 4-, 5-, 6-, 7- and 8-membered aliphatic rings could be utilized as coupling partners (**3ac**–**3af**). The piperidine derivative and acetal-substituted cyclohexyl chloride were allowed (**3ag**, **3ah**). A sugar derivative could be tertiary-alkylated with three benzyl ether moieties remaining untouched (**3ai**). When a substrate having a stereogenic center next to the halogenated carbon was subjected to the reaction conditions, *trans* alkylated product **3bj** was obtained due to the steric nature. Primary alkyl chlorides were found to be competent coupling partners (**3ak**, **3al**). Two enantioenriched secondary alkyl chlorides were examined, but the reactions didn't proceed (Table 2, bottom).

Table 2. Substrate scope of C(sp^3)–C(sp^3) cross-coupling [a]



[a] Reaction conditions: **1** (0.3 mmol), **2** (0.2 mmol), KO*t*Bu (0.3 mmol), dioxane (1 mL), 100 °C, 3 h. [b] The product was isolated after desilylation.

To understand how the borate intermediate, which is derived from a tertiary alkylboronate and an alkoxide base, reacted with the alkyl chloride, several experiments were conducted (Figure

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2). First, when enantioenriched chiral tertiary alkylboronate (*R*)-**1a** was used as a substrate, a complete loss of chirality in the product was observed (Figure 2A).[9] Subsequently, the reaction of alkyl chloride **2a** and benzyl potassium reagent, prepared by the treatment of cumene **1b**-H and Schlosser's base,[10] was examined (Figure 2B). The result was comparable to the reaction of **1b** and **2a** shown in Table 2. In addition, NMR spectroscopic studies support the formation of a benzyl carbanion through an alkoxide-mediated deborylative pathway (see Figures S1–S6 in Supporting Information). These experimental results indicated significant C–B bond cleavage before the reaction with **2a**. [11] Although the reduction potential of the alkyl chloride is high, the reaction pathway involving single electron transfer from the tertiary alkylborate to the alkyl chloride followed by radical–radical coupling could also be considered.[12] To gain further mechanistic information, the reaction with a *cis*/*trans* mixture of **2m**, which is used in typical radical clock experiments, was conducted (Figure 2C). As a result, *trans* alkylated product **3bm** was obtained with recovery of the *trans* isomer of substrate **2m**. This result supported the idea that the reaction would proceed through the S_N2 type mechanism with the alkyl chloride.

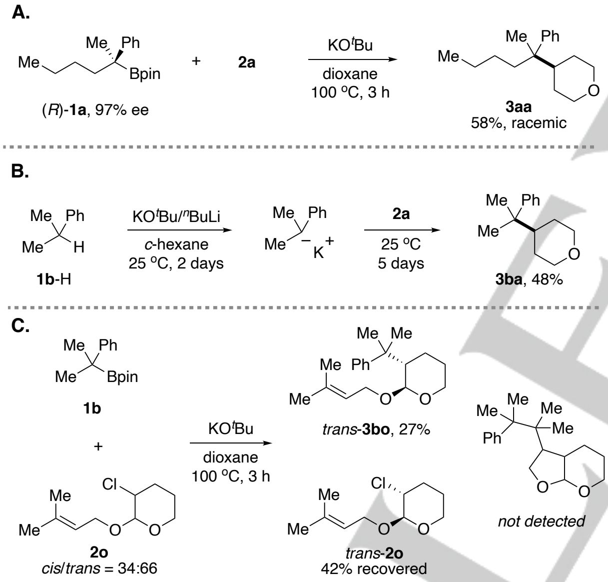


Figure 2. Mechanistic studies

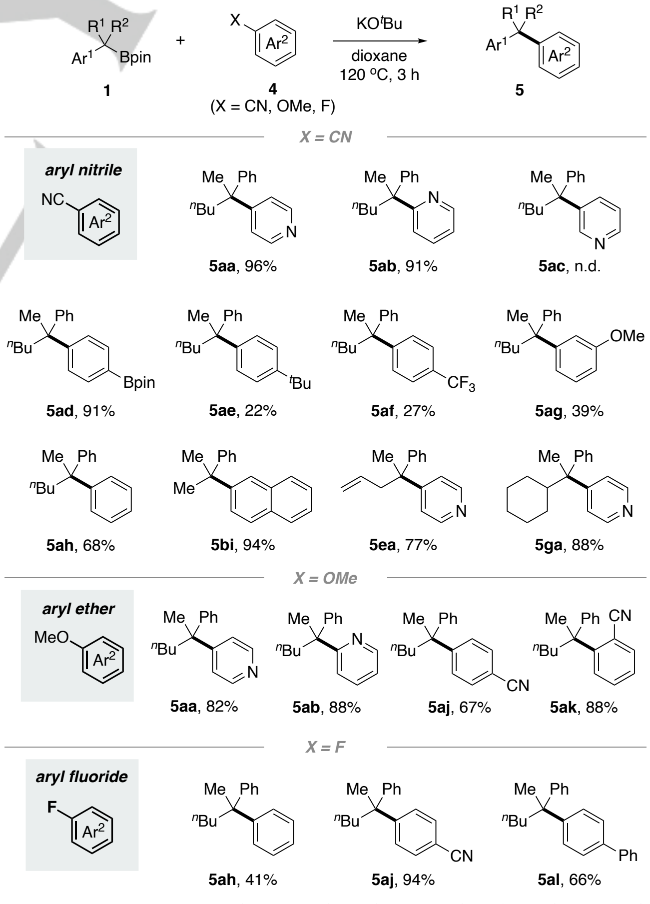
Encouraged by the results shown above, we turned our attention to C(sp^3)–C(sp^2) cross-coupling with aryl electrophiles. The high nucleophilicity of the tertiary benzylborate would be effective for S_NAr-type cross-coupling. Indeed, our protocol was applicable to C(sp^3)–C(sp^2) cross-couplings using aryl electrophiles having CN,[13] OMe[14] and F[15] leaving groups. Specifically, the C(sp^3)–C(sp^2) cross-coupling between tertiary alkylboronate **1a** (0.2 mmol) and 4-cyanopyridine (**4a**) (0.1 mmol) occurred with a stoichiometric amount of KO*t*Bu (0.2 mmol) in dioxane (0.5 mL) at 120 °C to produce the cross-coupling product **5aa** in 96% yield.

With the optimized reaction conditions in hand, a variety of aryl nitriles were subjected to this reaction (Table 3, top). 2-Cyanopyridine was also tolerated, however, 3-cyanopyridine yielded no product. The boron-substituted benzonitrile was possible (**5ad**). Aryl nitriles having *t*Bu, CF_3, or OMe substituents participated in the reaction, although the product yields were low (**5ae**–**5ag**). Importantly, this reaction with the simple benzonitrile afforded the corresponding product in good yield (**5ah**). Replacement of the butyl with methyl, allyl, or cyclohexyl substituents in the tertiary alkylboronate also provided the products in high yield (**5bi**, **5ea** and **5ga**). 2-Cyanothiophene, 2-cyanofurane and 2-pyrimidinecarbonitrile didn't participate in this reaction (data not shown).

The reactions with aryl electrophiles having other leaving groups were examined (Table 3, middle). When **1a** was subjected to the reaction with 4- or 2-methoxypyridine, C–OMe bond cleavage was observed (**5aa** and **5ab**). 4- or 2-Cyanomethoxybenzenes reacted with the tertiary alkylboronate (**5aj** and **5ak**). It was found that cyanomethoxybenzene has different functional groups that can be activated depending on the position of the substituent (see **5ag** in Table 3, top). This selectivity depended on the conjugative effect, electrostatic attraction, and inductive effects. [14g]

The protocol was applicable to fluorobenzene derivatives (Table 3, bottom). Simple fluorobenzene participated in this reaction (**5ah**). When substrates having cyano or phenyl groups were subjected to the reaction, the corresponding products were obtained in good yields (**5aj** and **5al**).

Table 3. Substrate scope of C(sp^3)–C(sp^2) cross-coupling [a]



[a] Reaction conditions: **1** (0.2 mmol), **4** (0.1 mmol), KO*t*Bu (0.2 mmol), dioxane (0.5 mL), 120 °C, 3 h.

Considering that aryl ethers or aryl fluorides are effective, the reaction with aryl electrophiles would proceed through an ionic S_NAr mechanism. However, the reaction with aryl nitriles gave the low yield and the small amount of homo-coupled product which stems from tertiary benzylboronate was detected. Thus, the reaction pathway of aryl nitriles would be contaminated with a radical S_NAr mechanism involving a single electron transfer from tertiary benzylborate.[4c, 5a, 16]

In summary, a transition-metal-free cross-coupling reaction for the construction of quaternary carbon centers from tertiary benzylboronates has been demonstrated. The protocol enabled the use of alkyl or aryl electrophiles. Thus, this transformation has expanded the scope of tertiary alkylative cross-coupling using organoboronates. The reaction involves the generation of tertiary alkyl anions from organoboronates in the presence of an alkoxide base followed by their substitution reactions. Extending the scope of this reaction to electrophiles is in progress.

Acknowledgements

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Keywords: cross-coupling · tertiary alkylation · tertiary alkylboronate · quaternary carbon center · transition-metal-free

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[9] Treatment of (*R*)-**1a** and KO*t*Bu in dioxane at 100 ˚C afforded the deborylprotonated product. When PhLi was used instead of KO*t*Bu on the reaction between (*R*)-**1a** and **2a**, a complete loss of chirality in **3aa** was observed

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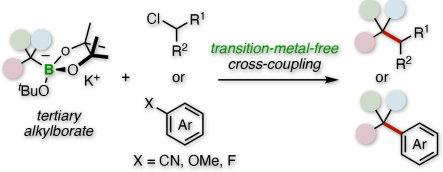

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