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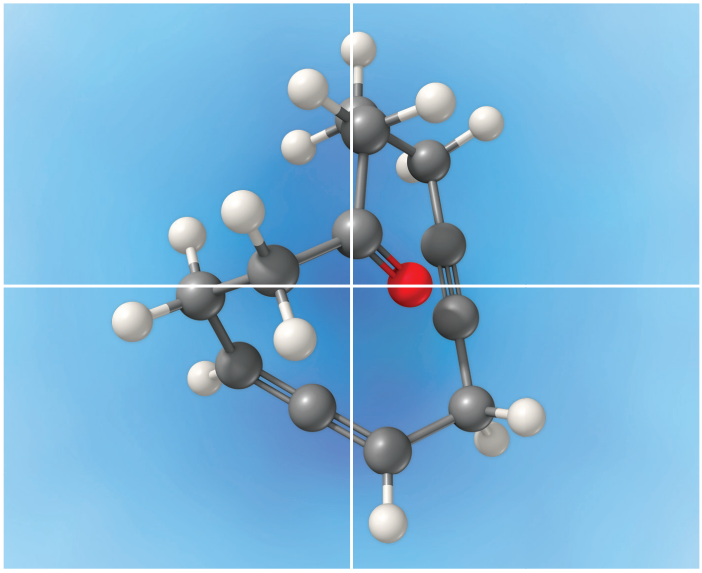

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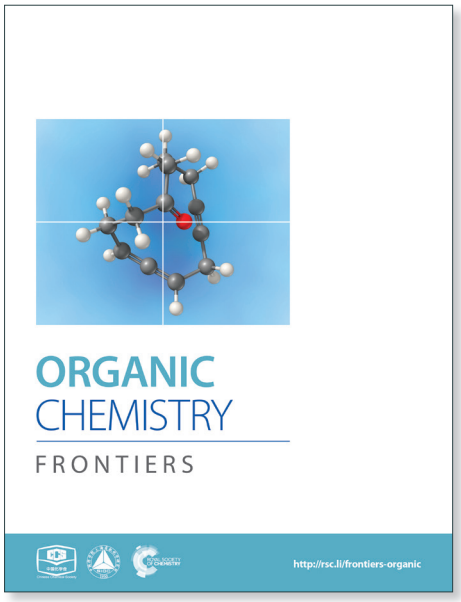

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ARTICLE TYPE

Direct Borylation of Benzyl Alcohol and Its Analogues in the Absence of Base

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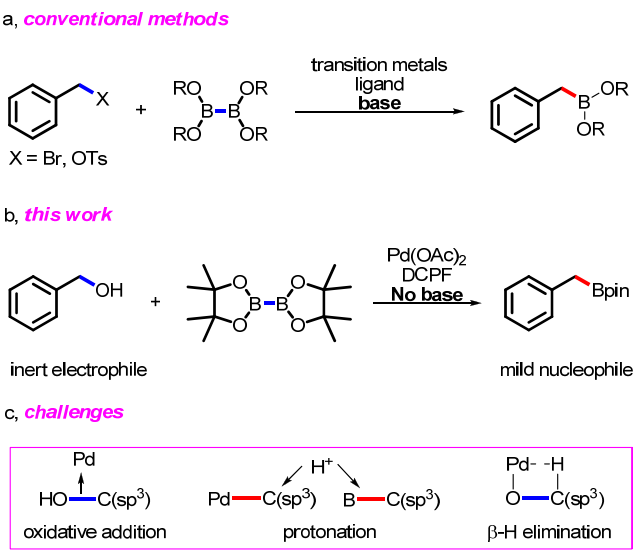
Direct borylation of arylmethanols to facilitate important and useful benzylboronates was carried out through $Pd(OAc)_2$-catalyzed sp^3 C-O activation. This borylation is compatible with various functional groups under mild conditions in the absence of any bases, offering an atom- and step- economic way to produce benzylboron compounds.

Alcohol is not only one of the most popular and abundant structural motif in natural and synthetic world, [1] but also used as a versatile building block in organic synthesis. [2] Conventional direct applications of alcohols are limited in C-C bond formation, majorly focused on Friedel-Crafts alkylation which featured as harsh conditions. [3] In recent decades, cross-coupling reactions by employing C-O electrophiles partially updated the application of alcohols in C-C formation. Various alcohol derivatives, such as carbonates, [4] sulfonates, [5] ethers, [6] and so on, have been successfully applied in cross couplings. However, direct catalytic transformation of alcohols, other than relatively active allyl, [7] propargyl, [8] and allenyl [9] alcohols, remained challenging due to their inertness of C-O bond and the Bronsted acidity of OH, resulting the protonation of the active R-M intermediate in desirable transformations. As one of the most important alcohols, benzyl alcohol exhibited its limited reactivity in few transformations recently reported by Yi [10] and ourselves. [11] Herein, we reported a reliable and simple method to synthesize arylmethylboronic esters from easily and commercially available arylmethanols *via* Pd catalysis under mild conditions.

Organoboron compounds are featured as one of the most important ingredients in Suzuki-Miyaura coupling [12] and other important transformations [13] due to their high functional group tolerance, easy working-up, non-toxicity, as well as their increasingly commercial availability. They became the most versatile nucleophiles in organic synthesis, providing powerful ways to construct C-C, C-O and other functionalities. [12, 13] As one of the common and important organoboron compounds, not only do benzylboron compounds show their great application potential in traditional cross-couplings and organic synthesis, [14] but also exhibit its special features. For example, Molander and co-workers discovered a new reaction, in which benzylic trifluoroborates released benzyl radicals, followed by carbon-carbon bond formation through a single-electron transfer pathway[15].

Obviously, extensive methods to synthesize benzylboron compounds have significant synthetic value. Indeed, many efforts have been carried out to meet such a goal. [16] The most common method for preparation of benzylboron compounds is nucleophilic borylation with Grignard or lithium reagents, which held a poor compatibility with functionalities and presented complicated manipulation. [16a] Development of Miyaura borylation starting from benzyl halides and sulfonic benzyl ester partially solved the problems (Scheme **1a**).[16f-l] However, the use of the irritative benzyl halides and preparation of sulfonates limited their practical applications. Direct borylation of benzyl C-H bonds was ideal, unfortunately with poor functional group compatibility and limited substrate scope. [16m, 16n] Another beautiful pathway to produce the benzylboronic esters has been recently carried out by Wang and co-workers starting from the tosylhydrazone and diboron reagents without transition-metal catalysis. [16o] Up to date, reliable methods to furnish such important organoboron compounds from simple and easily available chemicals under mild conditions were still appealed. During the preparation of this manuscript, Martin and coworkers reported an elegant example to produce benzylboronates from benzyl ethers through C-O activation.[16p] Considering the importance of benzylboron compounds and easy availability of benzyl alcohols, we conceived a Pd catalytic system to carry out the direct borylation of benzyl alcohols to produce benzylboron reagents under mild conditions (Scheme **1b**).

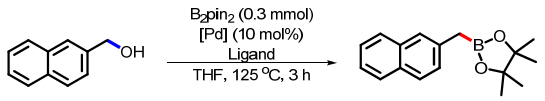


Scheme 1. Construction of benzylic boronates via C-O bond activation

Only few examples of the direct borylation *via* cleavage of active C-O bond were reported. [17] However, to the best of our knowledge, there was no sufficient way to carry out the direct borylation of benzyl alcohols. In fact, direct borylation of

inactivated benzyl alcohols through transition-metal catalysis faces three challenges (Scheme **1c**): 1) the Bronsted acidity of benzyl alcohols potentially accelerated the protonation of key R-M species and final benzylboron compounds, leading the formation of toluene derivatives (pKa of benzyl alcohol: 15.4, pKa of allylic alcohol: 15.52); [18] 2) high bond dissociation energy (BDE) of unactivated benzyl C-OH bond increased the difficulty of oxidative addition to transition metal. [19] (Bond dissociation energy: C-OH bond in benzyl alcohol: 340 kJ/mol, C-Cl bond in benzyl chloride: 300 kJ/mol, C-Br bond in benzyl bromide: 251kJ/mol, C-I bond in benzyl iodide: 183 kJ/mol); 3) last but not the least, the coordination of benzoxyl toward transition-metal ($ArCH_2O$-M) induced the potential oxidation through β-hydride elimination, competing with the desired borylation process. [20]

Table 1. Selected exploration of optimized conditions[a,b]



1a, 0.2 mmol **2a**

Entry	catalyst	ligand (loading/mol%)	Y^b (%)	Entry	catalyst	ligand (loading/mol%)	Y^b (%)
1	$Pd(OAc)_2$	PPh_3 (40)	0	11	$Pd(PPh_3)_4$	DCPF (20)	0
2	$Pd(OAc)_2$	PCy_3 (40)	0	12	$Pd(OTf)_2$	DCPF (20)	0
3	$Pd(OAc)_2$	P^tBu_3 (40)	0	13	$PdCl_2$	DCPF (20)	0
4	$Pd(OAc)_2$	XPhos (40)	0	14[c]	$Pd(OAc)_2$	DCPF (20)	50
5	$Pd(OAc)_2$	DPPB (20)	0	15[cd]	$Pd(OAc)_2$	DCPF (20)	57
6	$Pd(OAc)_2$	DPPM (20)	0	16[ce]	$Pd(OAc)_2$	DCPF (20)	<10
7	$Pd(OAc)_2$	DCPE (20)	0	17[cf]	$Pd(OAc)_2$	DCPF (20)	68
8	$Pd(OAc)_2$	DPPF (20)	0	***18[cf]***	***$Pd(OAc)_2$***	***DCPF (15)***	***78*** (0, 15, 1)
9	$Pd(OAc)_2$	DCPF (20)	48	19[cfg]	$Pd(OAc)_2$	DCPF (15)	0
10	$Pd(OAc)_2$	D^tBuPF (20)	0	20[cfh]	$Pd(OAc)_2$	DCPF (15)	0

[a] The reactions were carried out on 0.2 mmol scale, [b] NMR yield, numbers in parenthesis are the ratio of 1a, 2-methylnaphthalene, and diarylethane, [c] the temperature was 100 °C, [d] benzene was used as the solvent, [e] Et_2O was used as the solvent, [f] benzene/Et_2O (0.1 mL/0.9 mL) was used as the solvent, [g] HBpin was used as the borylation reagent, [h] B_2cat_2 was used as the borylation reagent.

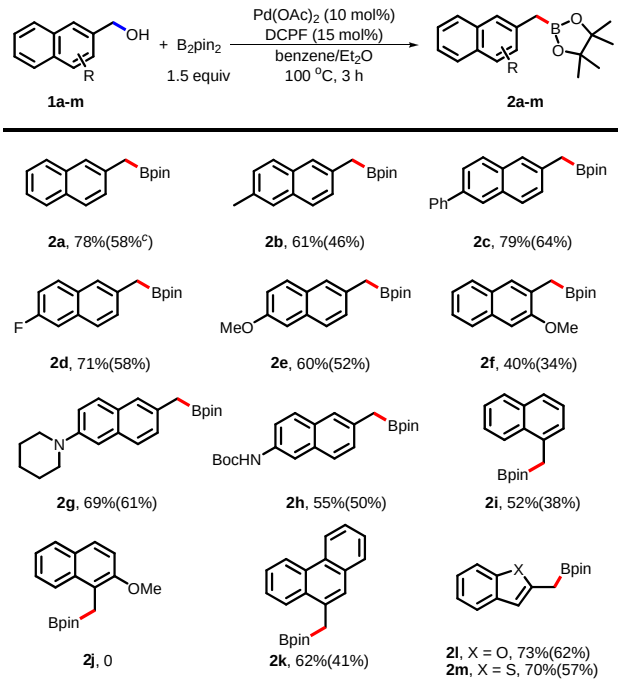
According to the unique reactivity of naphthylmethanol, **1a** was selected as the model substrate. The other important point to choose **1a** as an objective because the desired product was also easily isolated due to the good fluorescent of **2a** (**Table 1**). We first chose $Pd(OAc)_2$ in THF as catalyst set due to its stability, commercial availability and broad application in conventional Miyaura borylation. The ligand played a crucial role in this borylation and the desired product (**2a**) was obtained in 48% NMR yield when bidentate phosphine ligand DCPF[21] was employed (entry 9), while all other tested monodentate phosphine ligands failed (entries 1-4). Notably, other bidentate phosphine ligands, such as DPPB (entry 5), DPPM (entry 6), DCPE (entry 7), DPPF (entry 8) and D^tBuPF (entry 10) were also not suitable, probably due to their different electron density or unsuitable bite angle.

We further investigated different Pd catalysts and found that, Pd catalysts were also critical to this borylation. For example, $Pd(PPh_3)_4$, $PdCl_2$ and $Pd(OTf)_2$ all failed. By screening the temperature we found that, the full conversion of the naphthylmethanol (**1a**) was reached at 100 °C after 3 h. Unfortunately, 30% of protonated product 2-methylnaphthalene was observed, lowering the efficiency of this borylation. As demonstrated as one of the challenges, this by-product might be generated by protonating the final benzylic boronates or active benzyl-Pd species.

To avoid this by-product, the solvent's effect was systematically investigated. With the use of non-polar benzene as solvent, the best result was 57% NMR yield of (**2a**) while the by-product remained. To our satisfactory, only the desired product was observed if with diethyl ether as the solvent. [22] Due to the volatility of diethyl ether, we finally selected benzene/diethyl ether as co-solvent and the highest yield was obtained when 15 mol% DCPF was used with 15% of the by-product, which can be easily isolated (entry 18). [23]

Different diboron reagents were further studied with 2-naphthylmethanol (**1a**) (entry 19, entry 20). To our interest, only bis(pinacolato)diboron showed a credible reactivity. Other borylation reagents, for example, HBpin and B_2cat_2, completely failed in this transformation.

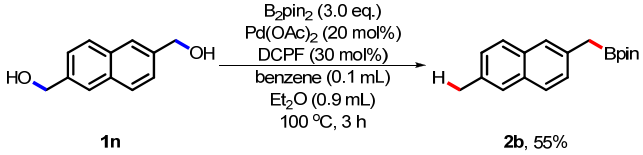
Table 2. Investigation of functional group tolerance[a,b]



[a] Reaction conditions: benzyl alcohol (0.2 mmol), B_2pin_2 (0.3 mmol), $Pd(OAc)_2$ (10 mol%), DCPF (15 mol%), benzene and diethyl ether as the mixed solvent, 100 °C oil bath, 3 h.
[b] NMR yield, and isolated yield in parentheses, decomposition is occurring through column chromatography.
[c] the reaction was performed in 1.0 mmol.

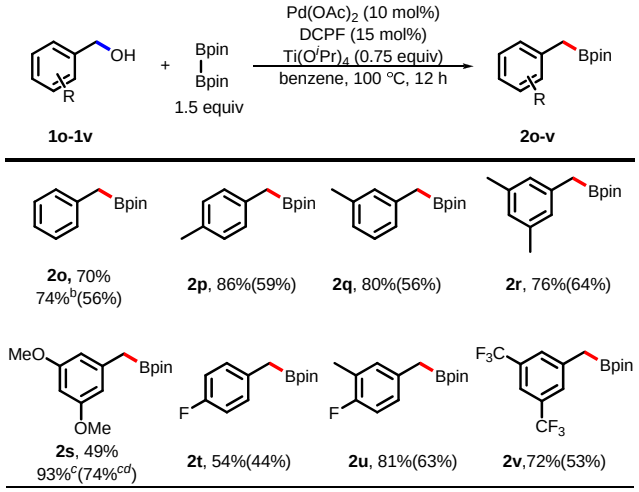
With the optimized conditions in hand, we applied this borylation to a variety of functionalized naphthylmethanols (**Table 2**). Substituted naphthylmethanols, such as alkyl- and aryl- substituents, were suitable for this borylation and the desired naphthylmethylboron compounds (**2a** and **2b**) were obtained in moderate to good yields. Both electron-rich (**2e**, **2g**, and **2h**) and electron-poor (**2d**) substituents did not obviously affect the efficacy and the desired products were produced in credible yields. It was important to note that the heterocycle-containing substrates, such as 2-benzofuranmethanol (**2l**) and benzo[*b*]thiophene-2-methanol (**2m**), were also suitable and the corresponding arylmethylboronates were obtained in good yields. To test the effect of the steric hindrance, steric demanding substrates **1i**, **1j**, as well as **1f**, were submitted to the reaction system to test the reactivity. Both **1f** and **1i** gave the desired products (**2f** and **2i**) albeit in the relatively poor yields. To our interest, **1j** completely failed in this borylation, demonstrating that the increased steric hindrance is critical by combining these two steric effects. The diol 2,6-naphthalenedimethanol **1n** was also investigated for this borylation under slightly changed conditions (**Scheme 2**). Notably, product **2b** was obtained as

major one in 55% isolated yield. This result was also concordance with the hypothesis of challenge in protonation.



Scheme 2. Investigation of the reactivity of 2,6-naphthalenedimethanol

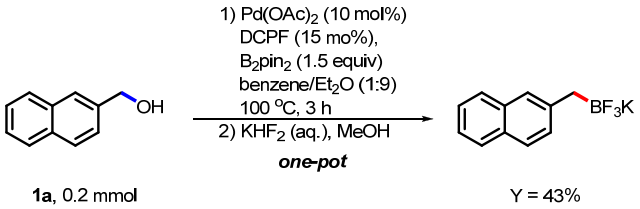
Table 3. Reactivity of simple benzenmethanol[a]



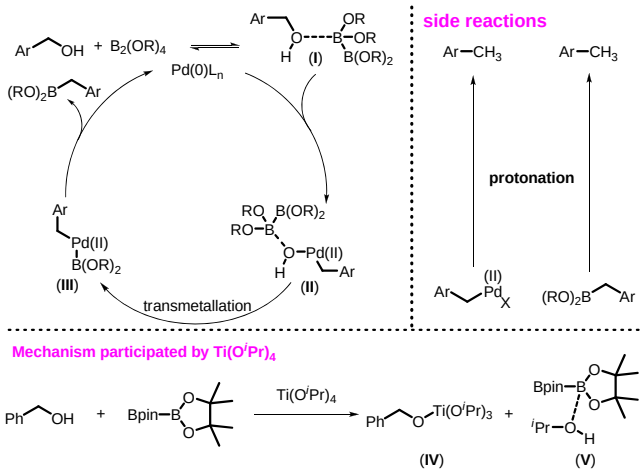
[a] Reaction conditions: benzyl alcohols (0.2 mmol), B_2pin_2 (0.3 mmol), $Pd(OAc)_2$, (10 mol%), DCPF (15 mol%), $Ti(OiPr)_4$.(0.75 equiv), benzene (1 mL), 100 °C oil bath, 12 h, NMR yield, isolated yield in parentheses, decomposition is occurring through column chromatography.
[b] benzene (0.2 mL) and Et_2O (0.8 mL) as the solvent,
[c] n[$Ti(OiPr)_4$] = 0.2 mmol,
[d] the reaction was performed in 1.0 mmol.

The success of the borylation of naphthylmethanols inspired us to apply for such a borylation to simple benzyl alcohols. Unfortunately, no desired products were observed under the standard conditions. To our delight, a variation of the standard conditions by adding 0.75 equivalent amount of $Ti(O^iPr)_4$ promoted such a borylation reaction in high efficiency (**Table 3**). Such an effect inducing by $Ti(O^iPr)_4$ was also observed in previous studies in the transformation of alcohols. [24] To further explore the applications, benzyl alcohols bearing *mono-* or *multi-*substituent groups were investigated and the desired products were obtained in good to excellent yields (by NMR). Both electron-rich and electron-poor ones gave the desired products in high efficiency. It was worthy to note that, the product (**2t**) was obtained in a relative low yield, probably arising from the electron-withdraw effect and/or coordinating effect of F-atom without the steric hindrance.

To solidify the possibility of the application, we conducted the borylation of both naphthylmethanol (**1a**) and 3,5-dimethoxylbenzyl alcohol (**2s**) in mmol scale under the corresponding developed conditions. To our delight, the desired boron reagents were isolated in comparable yields although those benzylboron esters were considered very reactive and difficult to isolate (see SI). Moreover, the transformation of the desired benzylic boronates to stable and versatile benzylic trifluoroborates was also conducted (**Scheme 3**). To our delight, the catalytic system was treated by KHF_2 in one-pot and the desired product **3** was isolated in 43% isolated yield. This development also extended the application potential of this borylation.

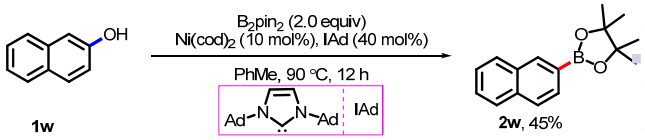


Scheme 3. Transformation of benzylic boronate to benzylic trifluoroborates



Scheme 4. Proposed mechanism

Based on the previous reports [11b, 25] and our observations, the catalytic cycle was proposed as **Scheme 4**. Arylmethanols **1** might have a weak and reversible interaction with B_2pin_2 to form the key intermediate I. While this weak interaction influence the catalytic process in two aspects: 1) such a coordination between B_2pin_2 and benzyl alcohols weakened the benzylic C-O bond, facilitating the oxidative addition of benzylic C-O toward Pd(0) species; 2) the alcohols could act as an inner-base to activate the B-B bond of B_2pin_2, further promoting the transmetallation. The intermediate I further undergoes oxidative addition to the Pd(0) to generate the Pd(II) species **II**, which subsequently proceeded either intramolecular or intermolecular transmetallation to form intermediate **III**. The reductive elimination of **III** fulfilled the catalytic cycle by releasing the desired product and regenerated the active Pd(0) species. For relative inert benzyl alcohol, the Lewis acidity of B_2pin_2 might not be strong enough to activate it. Thus, $Ti(O^iPr)_4$ was required to activate the benzylic C-O bonds by alkoxide exchange to form BnO-Ti species **IV** to facilitate the desired borylation. The formation of by-products in the borylation system could be also well documented based on this catalytic cycle, such as the toluene derivatives may be formed *via* the protonation of either the desired product **2** or active intermediate **II** and **III**.



Scheme 5. Direct borylation of phenol

In principle, this proposed catalytic mechanism might also be suitable for the borylation of phenol and its derivatives. Unfortunately, both conditions have been submitted to the direct borylation of phenol derivates via Pd catalysis while failed. After the hard-working we found that, the borylation of 2-naphthol took place with Ni catalysis and 45% yield of **2w** was isolated (Scheme 5). Further efforts to promote the efficacy of this transformation are still struggled in our lab.

Conclusions

In summary, we developed a simple and efficient borylation of arylmethanols with B_2pin_2 through palladium-catalyzed sp^3 C-O bond activation for the first time. Most importantly, such a transformation is atom- and step- economy to construct benzylboron compounds from arylmethanols in the absence of any bases under mild conditions. This method can be a privileged alternative to construct benzylboron derivatives, thereby complemented earlier catalytic methods typically from benzyl halides. Further investigations to expend the substrate scope, to promote the efficiency and detailed mechanism are underway.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

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