Boronyl-Group-Assisted Decatungstate-Catalyzed Benzylic C(sp^3)-H Alkylation

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バージョン：

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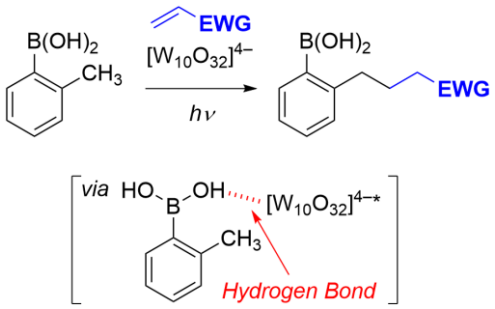
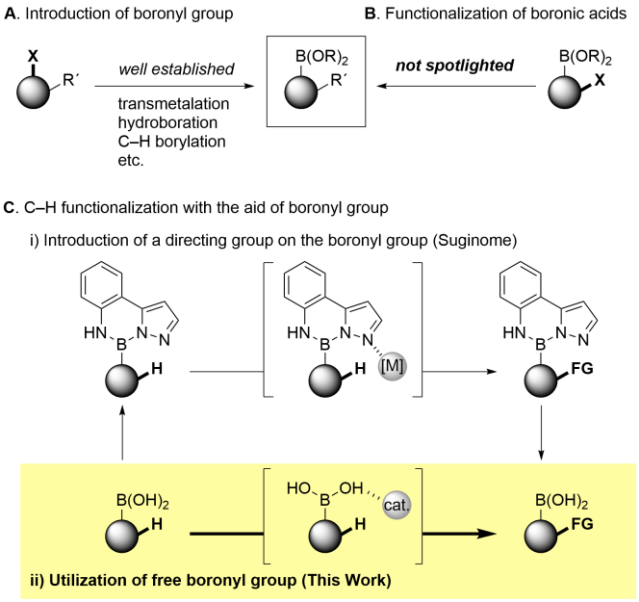
Supporting Information Placeholder



ABSTRACT: Boronic acid synthesis primarily involves the introduction of boronyl groups. However, an alternative route that involves the functionalization of boronic acids, has not received much attention. This study describes the catalytic C(sp^3)–H alkylation of *ortho*-tolylboronic acids utilizing the interaction between a free boronyl group [–$B(OH)_2$] and decatungstate photocatalyst $[W_{10}O_{32}]^{4-}$. The boronyl groups of the alkylated products could be converted without isolation of the alkylated product.

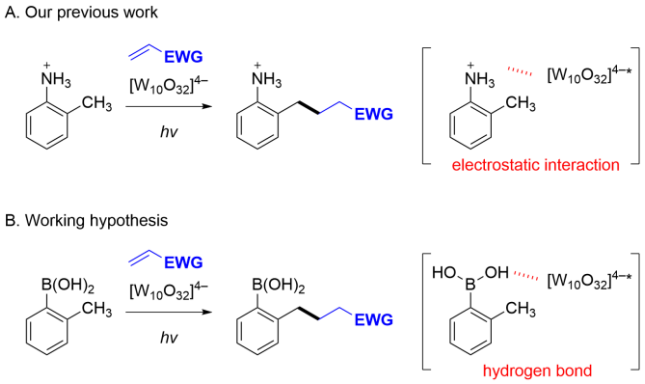
Boronic acid derivatives are essential molecules for synthetic organic chemistry because their carbon-boron bonds can be easily converted to carbon-carbon and carbon-heteroatom bonds, despite their high bench-stability.[1] In addition, boronates diversify out of simple synthetic intermediates and contribute significantly in modern pharmaceutical and materials sciences.[1–3] The general synthetic route to boronic acid derivatives involves the introduction of boronyl or boronate groups through transmetallation, hydroboration, catalytic borylation of carbon-halogen bond, and C–H borylation (Scheme 1A).[1,4,5] In contrast, functionalization of boronic acids with the retention of their boronyl groups has received limited attention (Scheme 1B). Although boronates have often been used as substrates in recent chemical reaction developments, the preparation of functionalized boronates with the aid of boronyl groups has been less explored. As a representative example of such a transformation, Suginome and colleagues developed directing groups on boron atoms and realized proximal C–H functionalization of boronates using transition metal catalysts (Scheme 1C-i).[6] Although this strategy is elegant, synthetic chemists want to avoid the preparation and introduction of directing groups. Hence, development of catalytic C–H functionalization using a free boronyl group [–$B(OH)_2$] is highly desirable (Scheme 1C-ii).

Scheme 1. Synthetic Methods of Boronic acids



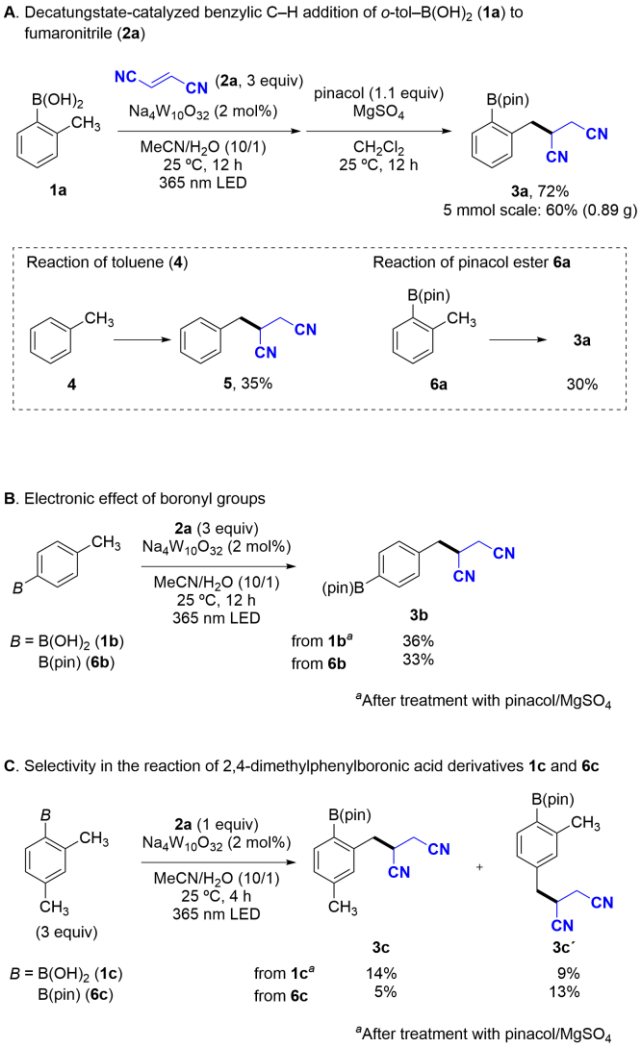
We recently developed the C(sp^3)–H alkylation of ammonium salts using the decatungstate photocatalyst, $[W_{10}O_{32}]^{4-}$ (Scheme 2A).[7–11] In these reactions, electrostatic interactions between the cationic ammonium group ($-^+NH_3$) and anionic $[W_{10}O_{32}]^{4-}$ play a key role. We envisioned that the electron-rich $[W_{10}O_{32}]^{4-}$ could function as a hydrogen bond acceptor and interact with a boronyl group, which could function as a hydrogen bond donor. This conceptualization led us to hypothesize the realization of catalytic functionalization of free boronic acids utilizing their boronyl groups (Scheme 2B).

Scheme 2. Noncovalent Interactions for Decatungstate-Catalyzed C(sp^3)–H Alkylation



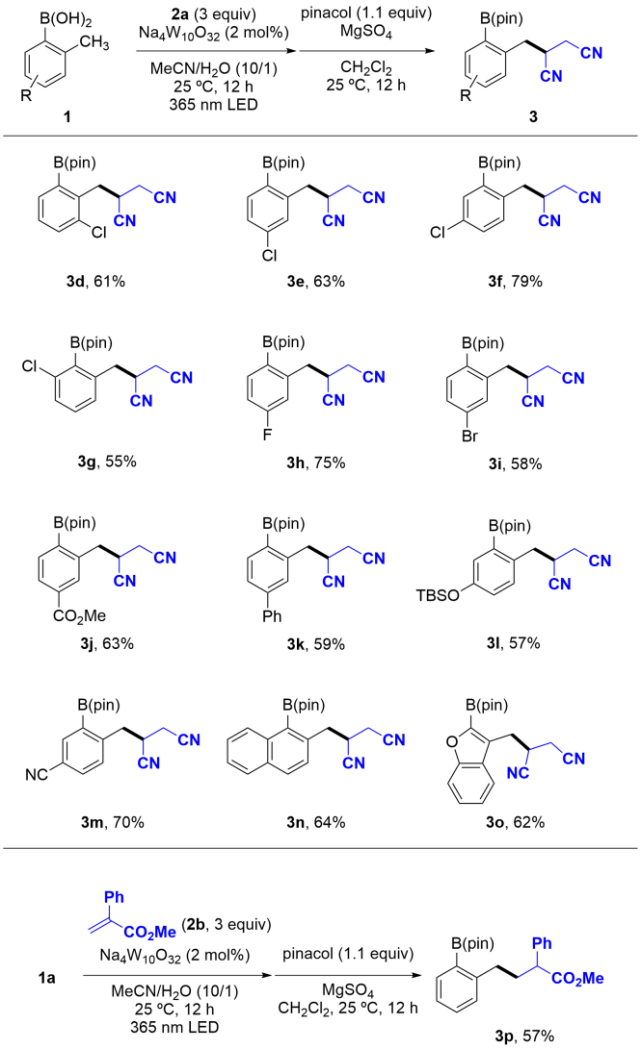
The reaction conditions were optimized and the details are provided in the Supporting Information (Table S1). The reaction of *ortho*-tolylboronic acid (**1a**; 0.500 mmol; 1.0 equiv.) with fumaronitrile (**2a**; 1.50 mmol; 3.0 equiv.) in the presence of $Na_4W_{10}O_{32}$ (2 mol%) in MeCN/H_2O (10/1; 5.0 mL) under the irradiation of UV light (365 nm LED), afford the best yield (Scheme 3A). After treatment of the formed alkylated boronic acid with pinacol in the presence of $MgSO_4$, alkylated product **3a** was obtained in 72% yield. Under the optimized reaction conditions, a gram-scale reaction (**1a**: 5.00 mmol) was performed, and product **3a** was obtained in 60% yield (Scheme 3A). In contrast, alkylation of toluene (**4**) under identical conditions afforded the corresponding alkylated product **5** in only 35% yield, indicating that the reaction of **1a** was accelerated by the boronyl group despite steric hindrance (Scheme 3A). In addition, the reaction of pinacol ester **6a** afforded **3a** in low yields (Scheme 3A). These results show the importance of free hydroxy group(s) (–OH), and we concluded that the interaction between the boronyl group and $[W_{10}O_{32}]^{4-}$ is not a Lewis acid-base interaction but a hydrogen bond.[12,13] The electronic effects of the boronyl group were investigated using *para*-tolylboronic acid (**1b**) and pinacol ester **6b** (Scheme 3B). The yields of the reactions were almost the same as those of reaction **4**, indicating the small electronic effect of the boronyl group. The strength of the interaction between the boronyl group and $[W_{10}O_{32}]^{4-}$ was estimated based on the reaction of 2,4-dimethylphenylnoronic acid (Scheme 3C). To avoid the formation of the dialkylated product, the reaction was carried out using 3 equivalents of a substrate relative to **2a** for 4 h. The reaction of boronic acid **1c** afforded the proximal alkylated **3c** and distal alkylated **3c´** in 14 and 9% yields, respectively. In contrast, pinacol ester **6c** was converted to **3c** and **3c´** with 5 and 13% yields, respectively. These results indicate that, although not strong, interactions between the boronyl group and decatungstate catalyst exists.

Scheme 3. Decatungstate-Catalyzed Addition of Benzylic C(sp^3)–H Bonds of Boronic Acids



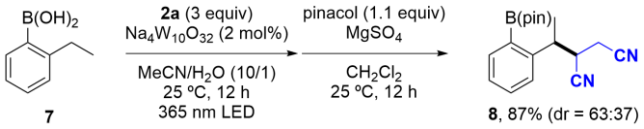
The reactions of *ortho*-tolylboronic acid derivatives **1** and **2a** were investigated (Scheme 4). The reaction of (3-chloro-2-methylphenyl)boronic acid (**1d**) afforded product **3d** in 61% yield, despite the steric hindrance around the reaction site. Substrates **1e** and **1f** with a chlorine atom at *para* or *meta* to the boronyl group were converted into the corresponding alkylated products **3e** and **3f** in 63 and 79% yields, respectively. The alkylation of (2-chloro-6-methylphenyl)boronic acid (**1g**) gave the corresponding alkylated product **3g** in 55% yield, indicating that sterically congested boronyl groups interacted with $[W_{10}O_{32}]^{4-}$. Both fluorine and bromine atoms remained unchanged after the reactions, and other functional groups such as ester, phenyl, silyloxy, and nitrile groups were tolerated, affording **3h**–**3m** in good yields. C(sp^3)–H alkylation also proceeded using 1-naphthylboronic acid (**1n**) to give the alkylated product **3n** in 64% yield. Boronyl-group-assisted C(sp^3)–H alkylation is applicable to five-membered heteroaromatic compounds; the reaction of benzofuran derivative **1o** afforded the corresponding alkylated product **3o** in 62% yield. The addition of C(sp^3)–H bond to methyl 2-phenylacrylate (**2b**) was also successful, giving **3p** in 57% yield.

Scheme 4. Boronyl-Assisted Benzylic C(sp^3)–H Alkylation of Boronic Acids 1



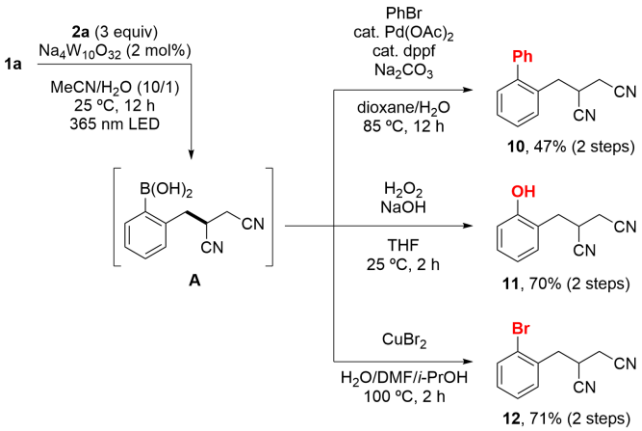
Alkylation of methylene C(sp^3)–H bonds was also successful (Scheme 5). The reaction of (2-ethylphenyl)boronic acid (**7**) afforded the corresponding alkylated product **8** in 87% yield, as a mixture of diastereomers (dr = 63:37). However, when (2-isopropylphenyl)boronic acid (**9**) was reacted with **2a**, the yield of the alkylated product was less than 5%, probably due to the steric effect.

Scheme 5. Methylene C(sp^3)–H Alkylation of (2-Ethylphenyl)boronic Acid (7)



We investigated the conversion of the boronyl group of the alkylated products (Scheme 6). Detailed reaction conditions are presented in SI. After the alkylation of **1a** with **2a**, the solvent was removed in vacuo, and a crude mixture containing alkylated boronic acid **A** was used for subsequent conversions without purification. Suzuki–Miyaura cross-coupling with bromobenzene afforded biaryl **10** in 47% yield. Oxidation with H_2O_2/NaOH afforded the corresponding phenol derivative **11** in 70% yield. Bromination with $CuBr_2$ successfully afforded aryl bromide **12** in 71% yield.

Scheme 6. Synthetic Conversion of Alkylated Products



In summary, we developed a free boronyl group-assisted benzylic C(sp^3)–H alkylation method using electron-deficient alkenes. The decatungstate-catalyzed benzylic C–H alkylation of *ortho*-tolylboronic acid proceeded more efficiently than the reactions of toluene or pinacol ester, indicating the existence of noncovalent interactions between the free boronyl group and electron rich $[W_{10}O_{32}]^{4-}$. A variety of *ortho*-tolylboronic acid derivatives were alkylated, and the methylene C–H alkylation of (2-ethylphenyl)boronic acid was successful. The boronyl group of the alkylated product was converted to other functional groups such as phenyl, hydroxy, and bromo groups without purification of the alkylated products. Furthermore, biaryl, phenol, and aryl bromides were obtained in moderate to good yields.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its online Supporting Information.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

General considerations, experimental details, characterization data of the compounds, additional experimental results, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(12) No difference of chemical shifts in ^{11}B NMR analysis between **1a** and a 1:1 mixture of **1a** and $Na_4W_{10}O_{32}$ was observed, indicating there are no Lewis acid-base interactions. For details, see SI.

(13) When increasing the ratio of water in the solvent (changing the ratio of MeCN/H_2O from 10:1 to 5:1), the yield of the alkylated product significantly decreased from 72% to 54% (see Table S1). This result indicates that an excess amount of water weakens the hydrogen bond, whereas an appropriate amount of water facilitates the reaction.