

Palladium-Catalyzed Benzylic C–H Borylation of Alkylbenzenes with Bis(pinacolato)diboron or Pinacolborane

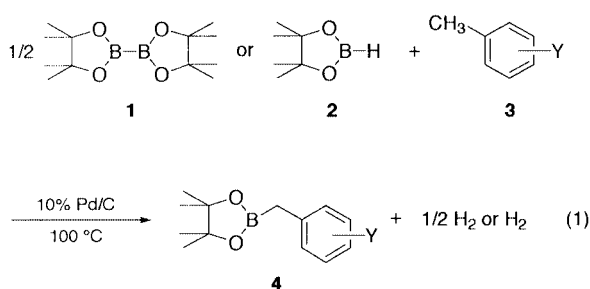
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Borylation at the benzylic C–H bond of alkylbenzenes with bis(pinacolato)diboron [(Me₄C₂O₂)B–B(O₂C₂Me₄)] or pinacolborane [(Me₄C₂O₂)B–H] was carried out at 100 °C in the presence of a catalytic amount of 10% Pd/C. The reaction selectively afforded pinacol benzylboronates in good yields directly from various alkylbenzenes.

The transition metal-catalyzed C–C and C–X bond formation accompanied with activation of inactive C–H bonds has emerged as an interesting and important alternative to the conventional bond-forming reactions involving functionalized substrates.¹ Since organoboron compounds are versatile intermediates in organic synthesis,² an extension of the methodology to borylation reactions would have significant synthetic value. Indeed, several pioneering studies have been made on the coupling reactions of bis(pinacolato)diboron (**1**) or pinacolborane (**2**). The direct borylation of alkanes and benzene with the diboron **1** was catalyzed by Cp*Re(CO)₃ under photochemical conditions³ or by Cp*Rh(η⁴-C₆Me₆) under thermal conditions.⁴ The latter complex,⁵ Cp*Ir(PMe₃)(H)[B(O₂C₂Me₄)],^{5,6} and (Cp*RhCl₂)₂⁷ have been successfully used for aromatic C–H borylation with pinacolborane **2**, and RhCl[P(*i*-Pr)₃]₂(N₂)⁷ for benzylic C–H borylation. In the course of our studies on the transition metal-catalyzed reactions of diboron compounds,⁸ we recently found that Pd/C is an efficient catalyst for selective benzylic C–H borylation of alkylbenzenes (**3**) with the diboron **1** or pinacolborane **2** to produce the corresponding pinacol benzylboronates (**4**) in good yields (eq 1).⁹



The borylation of toluene (60 mmol) with bis(pinacolato)diboron **1** (1.0 mmol) was carried out at 100 °C for 16 h in the presence of various metal complexes (3 mol%) to optimize the catalyst system. Pd(OAc)₂ and PdCl₂ produced pinacol benzylboronate as the sole product in 11% and 33% yields, respectively. In contrast, NiCl₂, PtCl₂(COD), RhCl₃, IrCl₃, and RuCl₃ exhibited no catalytic activity at all. Instantaneous formation of palladium black observed for Pd(OAc)₂ and PdCl₂ prompted us to use ligands; however, the addition of PPh₃, P(*c*-Hex)₃, P(OPh)₃, AsPh₃, and SbPh₃ completely retarded the reaction, thus suggesting the superiority of

ligand-free metallic palladium. Although commercial palladium black did not catalyze the reaction, a palladium on carbon (10% Pd/C) finally achieved the selective coupling in high yields. Very interestingly, two boryl groups in **1** participated in the reaction to provide 74% yield of the product based on the boron atom.¹⁰ Other heterogeneous catalysts such as Pt/C, Rh/C, and Ru/C were totally ineffective.

In order to obtain further information on the formation of two moles of benzylboronate from one mole of the diboron, the Pd/C-catalyzed reaction of **1** with toluene at 100 °C was followed by GC analysis. The diboron was completely consumed after 2.5 h, but the yield of benzylboronate was 49%. Further prolongation of the reaction time increased the yield even after the complete consumption of the diboron. Finally, the reaction gave 74% yield of benzylboronate after 9 h. The results indicated a two-step process involving a very fast and quantitative reaction of toluene with the diboron **1**, followed by a slow reaction with pinacolborane **2** generated by the former process. A 52% yield of pinacol benzylboronate was obtained indeed when pinacolborane was treated with toluene at 100 °C in the presence of Pd/C (3 mol%).¹⁰

The representative results are summarized in Table 1. All reactions of bis(pinacolato)diboron **1** or pinacolborane **2** were carried out at 100 °C in the presence of 10% Pd/C (3–6 mol%).¹⁰ Not only toluene (Entry 1), but also polymethylated benzenes are viable substrates. *o*-, *m*-, and *p*-Xylenes smoothly underwent the selective monoborylation to provide the corresponding benzylboronates **4** in good yields in the presence of 3 mol% catalyst (Entries 2–4), while mesitylene required 6 mol% of catalyst to achieve a satisfactory yield (Entry 5). Ethylbenzene yielded a 3:1 mixture of the benzylboronate and the homobenzyl derivative. The latter product can be derived from positional isomerization of the benzylpalladium intermediate to a homobenzylpalladium species via the β-hydride elimination–insertion process (Entry 6).¹¹ Another probable pathway involving a direct C–H activation at the β-carbon should be ruled out by the fact that no reaction was observed for *tert*-butylbenzene. Isopropylbenzene exclusively afforded the homobenzyl derivative due to large steric hindrance at the benzylic carbon (Entry 7). On the other hand, the borylation of 4-isopropyltoluene selectively occurred at the methyl group, though the reaction was accompanied with a small amount of 2-(4-methylphenyl)-1-propylboronate (Entry 8). In all reactions, the diboron **1** gave higher yields than pinacolborane **2**.

In contrast to the results of unfunctionalized alkylbenzenes, the reaction was highly sensitive to the presence of heteroatoms. For example, 4-methylanisole and 4-fluorotoluene resulted in 13% and 26% yields, respectively, even at higher catalyst loading or prolongation of reaction time. All attempts at the borylation of 4-methylacetophenone, 2-methylthiophene, and 2-methylfuran were unsuccessful.

Table 1. Synthesis of Pinacol Benzylboronates via Direct Benzylic C–H Borylation (eq 1)^a

Entry	3	Product ^b	Yield/% ^c	
			1	2
1			74	52
2			77	
3			79	
4			72	51
5			64 ^d	45
6			39 ^d	15 ^d
			15 ^d	6 ^d
7			38 ^d	13 ^d
8			39 ^d	42 ^d
			9 ^d	5 ^d

^aThe experimental procedure, see Reference 10. ^bThe pinB abbreviates 4,4,5,5-tetramethyl-1,3,2-dioxaborolanyl group. ^cGLC yields based on boron atom in 1 or 2. ^dA 6 mol% of catalyst was used.

In conclusion, Pd/C was found to be an efficient catalyst for the selective benzylic C–H borylation of alkylbenzenes with bis(pinacolato)diboron and pinacolborane. The method provides a simple and direct route for the synthesis of benzylboronic esters which have been prepared via transmetalation between benzylmagnesium halide and trialkyl borate. The cat-

alytic direct borylation of other hydrocarbons is being actively investigated.

Dedicated to Prof. Hideki Sakurai on the occasion of his 70th birthday.

References and Notes

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- A representative procedure for 4: To 10% Pd/C (0.03 mmol) were successively added toluene (60 mmol) and 1 or 2 (1.0 mmol), and the resulting mixture was stirred at 100 °C for 16 h under nitrogen. The product was extracted with benzene, washed with water, and dried over MgSO₄. Filtration and Kugelrohr distillation gave analytically pure pinacol benzylboronate: ¹H NMR (400 MHz, CDCl₃) δ 1.23 (s, 12 H), 2.29 (s, 2 H), 7.1–7.3 (m, 5 H); ¹³C NMR (100 MHz, CDCl₃) δ 24.69, 83.38, 124.79, 128.22, 128.96, 138.61 (Due to quadrupolar relaxation, the carbon attached to the boron atom was not detected); HRMS *m/z* Found: M⁺, 218.1470. Calcd for C₁₃H₁₉BO₂: 218.1478.
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