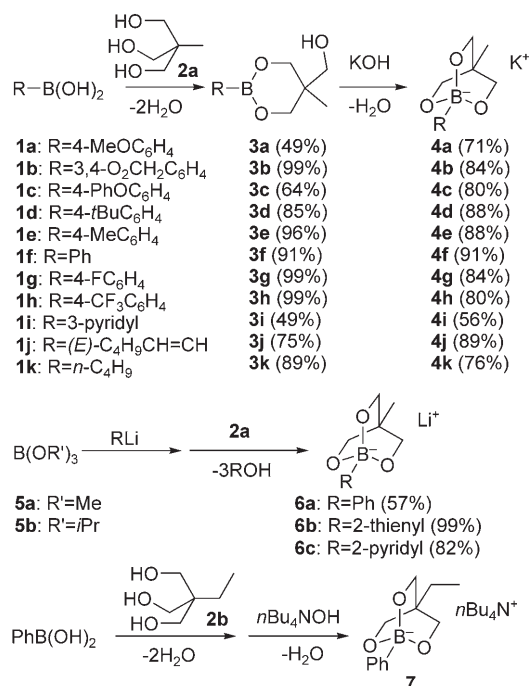


Cyclic Triolborates: Air- and Water-Stable Ate Complexes of Organoboronic Acids

Yasunori Yamamoto,* Miho Takizawa, Xiao-Qiang Yu, and Norio Miyaura*

The C–B bond of organoboronic acids is totally covalent and therefore inert to ionic reactions; however, the nucleophilicity of organic groups attached to a boron atom is enhanced significantly by quaternarization with an anionic ligand.^[1] Thus, tetracoordinated ate complexes have been used successfully for most nucleophilic addition and coupling reactions of organoboron compounds, including metal-catalyzed reactions of organoboronic acids.^[1,2] Although the in situ preparation of such complexes from an organoborane and a base is most common, the method has limitations. Therefore, attempts have been made to prepare stable ate complexes. Air- and water-stable trifluoroborates $M[RBF_3]$ ($M = K, NR_4$)^[3] are typical compounds that exist as pure and water-stable crystalline materials and have advantages over boronic acids in terms of their preparation and handling. However, their metal-catalyzed bond-forming reactions are very slow in the absence of a base because of the low nucleophilicity of the fluorine atoms.^[3] Sodium trihydroxyborates $[RB(OH)_3]Na$ were synthesized recently as isolated discrete species for cross-coupling in anhydrous solvents without the aid of an additional base.^[4] Other isolable ate complexes are 1-alkynyl borates $Li[RC\equiv CB(OiPr)_3]$ ^[5] and tetraaryl borates $M[Ar_4B]$.^[6] We describe herein novel cyclic triolborates^[7] that are exceptionally stable in air and water and more soluble in organic solvents than potassium trifluoroborates. We also demonstrate the high transmetalation efficiency of lithium and potassium triolborates in palladium- and copper-catalyzed C–C^[2] and C–N^[8] bond-forming reactions.

We developed methods for the synthesis of the cyclic triolborates **4** and **6** (Scheme 1). The azeotropic removal of water upon the treatment of organoboronic acids **1** with the triol **2a** gave boronic esters **3**, which were converted readily into triolborates **4** by treatment with KOH. Compounds **4** were also obtained in high yields when the esterification was followed directly by quaternization with KOH in the same flask without the isolation of **3**. The triolborates **4** are insoluble in toluene (the solvent used) and precipitated as white solids in high yields. The corresponding lithium salts **6** were synthesized by the alkylation of $B(OMe)_3$ (**5a**) or



Scheme 1. Synthesis of potassium, lithium, and ammonium triolborates.

$B(OiPr)_3$ (**5b**) with RLi, followed by the removal of MeOH or *i*PrOH through ester exchange with **2a**. By using this protocol, the 2-pyridyl borate **6c**, which is sensitive to B–C bond cleavage in the presence of water, was obtained in high yield. The treatment of $PhB(OH)_2$ with the triol **2b** followed by nBu_4NOH afforded a single crystal of the ammonium salt monohydrate^[9] $(NBu_4)[C_6H_5B(OCH_2)_3CCH_2CH_3] \cdot H_2O$ (**7**) for X-ray crystal analysis.

An ORTEP plot of **7** showed that the molecular structure contains a bicyclo[2.2.2]octane ring that includes a tetrahedral boron atom (Figure 1). The C–B bond (1.60 Å) is slightly longer than that of neutral $PhB(OR)_2$ ($R = H, alkyl$; 1.56 Å) as a result of the sp^3 hybridization of the boron atom.^[10] There is some distortion of the three boatlike rings owing to hydrogen bonding between a hydrogen atom of the water molecule and one of the three borate oxygen atoms. Triolborates **4** and **6** are bench-stable ate complexes that can be handled and stored without special precautions. When **4e** was dissolved in D_2O/CD_3OD , a ^{11}B NMR signal characteristic of tetrahedral boron species was observed at $\delta = 6.76$ ppm, and there was no change in the 1H NMR spectrum due to any hydrolysis of **4e**.

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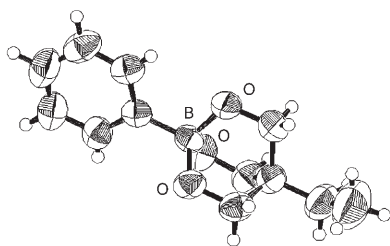
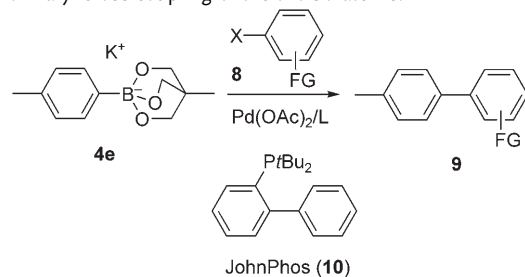


Figure 1. An ORTEP plot of the anion of **7**. Thermal ellipsoids at 50% probability.

Such borate anions are key intermediates for transmetalation between organoboron compounds and complexes of the type $\text{Ni}^{\text{II}}\text{-X}$,^[11,12] $\text{Pd}^{\text{II}}\text{-X}$,^[13–15] $\text{Pt}^{\text{II}}\text{-X}$,^[16] $\text{Rh}^{\text{I}}\text{-X}$,^[17] and $\text{Cu}^{\text{I}}\text{-X}$ ^[18] during metal-catalyzed C–C or carbon–heteroatom bond-forming reactions. It became apparent immediately that these borates can be used conveniently for palladium- and copper-catalyzed coupling reactions. The cross-coupling reaction of the 4-tolyl triolborate **4e** with representative bromoarenes was complete within 5 h at room temperature in the presence of $\text{Pd}(\text{OAc})_2$. The ligand johnphos (**10**) was also added for the reaction with 4-chloroacetophenone (Table 1, entry 4) and hindered 2,6-dimethylbromobenzene (entry 14). The use of aqueous *N,N*-dimethylformamide (DMF) to give a homogeneous solution was critical for the reactions carried out at room temperature.

Low yields are often observed for cross-coupling reactions of aryl boronic acids in aqueous solvents as a result of

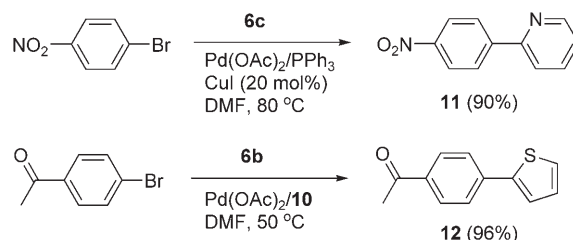
Table 1: Biaryl cross-coupling of the triolborate **4e**.^[a]



| Entry | X | FG | Catalyst | t [h] | Yield [%] ^[b] |
|-------------------|-----|----------------------|---------------------------------------|-------|--------------------------|
| 1 | Br | 4-NO ₂ | $\text{Pd}(\text{OAc})_2$ | 5 | 99 |
| 2 | Br | 4-CF ₃ | $\text{Pd}(\text{OAc})_2$ | 5 | 93 |
| 3 | Br | 4-COMe | $\text{Pd}(\text{OAc})_2$ | 5 | 99 |
| 4 | Cl | 4-COMe | $\text{Pd}(\text{OAc})_2/\mathbf{10}$ | 22 | 90 |
| 5 | Br | 4-CO ₂ Me | $\text{Pd}(\text{OAc})_2$ | 5 | 99 |
| 6 | Br | 4-Cl | $\text{Pd}(\text{OAc})_2$ | 5 | 99 |
| 7 | Br | 2-OMe | $\text{Pd}(\text{OAc})_2$ | 5 | 98 |
| 8 | Br | 3-OMe | $\text{Pd}(\text{OAc})_2$ | 5 | 98 |
| 9 | Br | 4-OMe | $\text{Pd}(\text{OAc})_2$ | 5 | 97 |
| 10 | OTf | 4-OMe | $\text{Pd}(\text{OAc})_2$ | 22 | 89 |
| 11 | Br | 4-OH | $\text{Pd}(\text{OAc})_2$ | 5 | 96 |
| 12 ^[c] | Br | 4-NH ₂ | $\text{Pd}(\text{OAc})_2$ | 5 | 92 |
| 13 | Br | 4-NMe ₂ | $\text{Pd}(\text{OAc})_2$ | 22 | 92 |
| 14 | Br | 2,6-Me ₂ | $\text{Pd}(\text{OAc})_2/\mathbf{10}$ | 5 | 80 |

[a] Reaction conditions: **8** (1 mmol), **4e** (1.1 mmol), $\text{Pd}(\text{OAc})_2$ (3 mol%), **10** (6.6 mol%, if used), DMF/H₂O (5:1), 20 °C. [b] Yield of the isolated product after chromatography. [c] The reaction was carried out at 50 °C. FG = functional group.

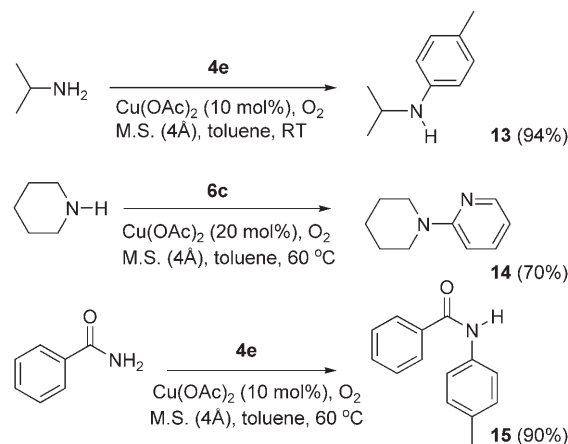
competitive hydrolytic B–C bond cleavage.^[19] 2-Pyridyl- and 2-thiophenylboronic acid and their boronic ester derivatives are typical boron compounds for which such cleavage with water occurs during cross-coupling reactions.^[19] However, the triolborates **6b–c** reacted quantitatively with bromoarenes in anhydrous DMF (Scheme 2). The presence of CuI led to an increase in the coupling yield with the 2-pyridyl boronate **6c**.^[19c]



Scheme 2. Coupling reactions of triolborates that are sensitive to protodeboronation.

The copper-promoted coupling of aryl boronic acids with heteroatoms reported by Lam et al.^[20a] has found broad application in the arylation of N–H, O–H, and S–H bonds.^[8] The simple protocol in air at room temperature was expanded to catalytic reactions by using a reoxidant of the copper species.^[20b] The catalytic arylation of the N–H bond of isopropylamine, piperidine, and benzoyl amide provided the aryl amines **13–15** in high yields in the presence of $\text{Cu}(\text{OAc})_2$ (10–20 mol%) under an atmosphere of oxygen (Scheme 3). Again, the 2-pyridyl boronate **6c** underwent the desired coupling reaction to afford the product in good yield. In both catalytic and stoichiometric reactions, aryl boronic acids undergo coupling with water as a side reaction to provide phenol and diaryl ether by-products.^[20,21] Such by-products were also formed in yields of a few percent in the reactions of the triolborates, but their formation is prevented completely in the presence of molecular sieves.

In conclusion, we have described a simple and practical synthetic approach to stable ate complexes of organoboronic acids. As such complexes are key species in various ionic



Scheme 3. Copper-catalyzed arylation of N–H bonds. M.S. = molecular sieves.

reactions of boron compounds, including metal-catalyzed bond-forming reactions, studies towards their application to other addition and coupling reactions are in progress.

Experimental Section

4f: Phenylboronic acid (**1f**; 100 mmol) and 1,1,1-tris(hydroxymethyl)ethane (**2a**; 100 mmol) were dissolved in toluene (200 mL). Water was removed by azeotropic distillation by the Dean–Stark method for 4 h. The solvents were then removed to give crude **3f**. ¹H NMR (400 MHz, [D₆]DMSO): δ = 0.87 (s, 3 H), 3.33 (d, J = 4.9 Hz, 2 H), 3.75 (d, J = 10.5 Hz, 2 H), 3.94 (d, J = 10.5 Hz, 2 H), 4.85 (t, J = 4.9 Hz, 1 H), 7.31–7.44 (m, 3 H), 7.68 ppm (d, J = 7.8 Hz, 2 H); ¹³C NMR (100 MHz, [D₆]DMSO): δ = 17.4, 36.7, 63.1, 67.7, 127.8, 130.9, 133.7 ppm (C–B is not observed); ¹¹B NMR (128 MHz, [D₆]DMSO): δ = 30.1 ppm; MS (EI): m/z (%): 43 (14), 57 (36), 72 (39), 78 (16), 91 (14), 105 (100), 117 (55), 122 (38), 132 (43), 151 (17), 159 (15), 173 (35), 188 (16), 206 (83, M^+); HRMS (EI): m/z calcd for C₁₁H₁₅BO₃: 206.1114; found: 206.1102. The crude **3f** and KOH (90 mmol) were dissolved in toluene and heated at reflux for 4 h by the Dean–Stark method. The potassium triolborate **4f** that precipitated was collected by filtration, washed with acetone, and dried under reduced pressure. ¹H NMR (400 MHz, [D₆]DMSO): δ = 0.47 (s, 3 H), 3.56 (s, 6 H), 6.88–6.98 (m, 3 H), 7.30 ppm (d, J = 6.8 Hz, 2 H); ¹³C NMR (100 MHz, [D₆]DMSO): δ = 16.5, 73.9, 124.2, 125.7, 132.3 ppm (C–B is not observed); ¹¹B NMR (128 MHz, [D₆]DMSO): δ = 4.39 ppm; MS (FAB[–]): m/z (%): 56 (5), 104 (100), 148 (27), 205 (10, [M–K][–]); HRMS (FAB[–]): m/z calcd for C₁₁H₁₄BO₃[–]: 205.1041; found: 205.1041; elemental analysis: calcd (%) for C₁₁H₁₄BKO₃: C 54.12, H 5.78; found: C 52.76, H 5.65.

6c: *n*BuLi (110 mmol) in hexane was added to a stirred solution of 2-bromopyridine (100 mmol) in THF (400 mL) at –78 °C. The resulting mixture was stirred for 1 h at –78 °C, then a solution of triisopropyl borate (**5b**; 120 mmol) was added. The mixture was stirred for 2 h at –78 °C and then allowed to warm to room temperature. A solution of 1,1,1-tris(hydroxymethyl)ethane (**2a**; 100 mmol) in THF (150 mL) was then added, and the resulting mixture was stirred for 5 h. Concentration to dryness under reduced pressure gave **6c** (82 %). ¹H NMR (400 MHz, [D₆]DMSO): δ = 0.54 (s, 3 H), 3.67 (s, 6 H), 7.06–7.51 (m, 3 H), 8.24 ppm (br s, 2 H); ¹³C NMR (100 MHz, [D₆]DMSO): δ = 15.9, 73.5, 120.8, 127.8, 134.4, 146.9 ppm; ¹¹B NMR (128 MHz, [D₆]DMSO): δ = 3.25 ppm.

7: A solution of *n*Bu₄NOH (10 mmol, 1 M in H₂O) was added to a solution of **4f** (10 mmol) in MeOH (5 mL) at 0 °C, and the resulting mixture was stirred for 2 h at room temperature. The product was extracted with CH₂Cl₂, washed with water, dried over MgSO₄, and concentrated in vacuo. The solid obtained was recrystallized from CH₂Cl₂/EtOAc to give **7** (98 %).

Crystal data for **7**: C₂₈H₃₄BO₄N, M_r = 479.55, monoclinic, space group *C2/c*, a = 22.102(15), b = 16.568(11), c = 17.512(11) Å, β = 107.53(5)°, V = 6115.4(70) Å³, Z = 8, ρ_{calcd} = 1.042 g cm^{–3}, $\mu(\text{MoK}\alpha)$ = 0.669 cm^{–1}; $2\theta_{\text{max}}$ = 55.0°, 29236 reflections, 7018 unique reflections (R_{int} = 0.039), reflection/parameter ratio = 19.39, $R_1(I > 2.00\sigma(I))$ = 0.0696; R (all reflections) = 0.1568, wR_2 (all reflections) = 0.1991, goodness-of-fit indicator = 0.980, maximum shift/error in final cycle = 0.00, $\rho(\text{min/max})$ = –0.35/0.53 e[–] Å^{–3}. CCDC 669817 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

General procedure for cross-coupling reactions: The triolborate (1.1 mmol), the aryl halide (1.0 mmol), and palladium acetate (3 mol %) were placed in a flask under an atmosphere of nitrogen. DMF/H₂O (5:1; 3 mL) was added, and the reaction mixture was stirred at room temperature for 5 h.

General procedure for the arylation of amines: A mixture of the triolborate salt (1.5 mmol), the amine (1.0 mmol), molecular sieves

(4 Å; 300 mg), and copper acetate (10 mol %) in toluene (6 mL) was stirred at room temperature for 20 h under an atmosphere of oxygen.

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