Use of in Situ Isopropoxide Protection in the Metal−Halogen Exchange of Arylboronates

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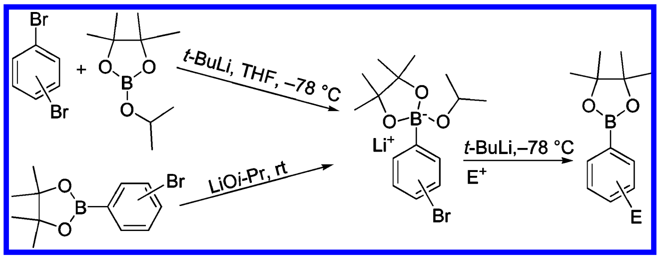
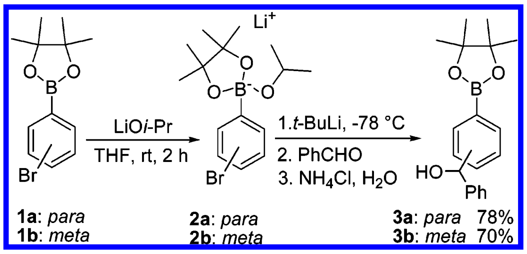


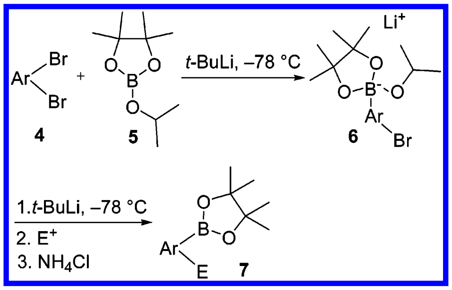
Isopropoxide protection of arylboronates allowed their use in metal−halogen exchange reactions. The isopropoxide-protected borate species were obtained from a boronate or in situ from dibromoarenes. *meta*- and *para*-dibromoarenes were converted via these intermediates into functionalized arylboronates in a one-pot manner.

Metal−halogen exchange is an important and widely used method of selective functionalization of organic compounds. It has been clear since the first unsuccessful attempt by Gilman in 1958 that a "halogen−metal interconversion in bromosubstituted benzeneboronic acids [...] would have provided many possibilities for new syntheses."[1] However, until very recently there have been no precedents of a successful metal−halogen exchange employing molecules containing a boronate or boronic acid moiety. This can be explained by the fact that boronates, being Lewis acids, actively react with most organometallic reagents used in metal−halogen exchange.[2] In 2005, Knochel established that iodo-substituted aryl boronates could be metalated with *i*-PrMgCl·LiCl.[3] Although Knochel's method has a wide applicability, the substrates are not commercially available and are prepared from expensive diiodoarenes. In 2006, Molander proposed metalation of readily available potassium bromoaryltrifluoroborates with *n*-BuLi−TMEDA as an alternative approach.[4] However, as trifluoroborates are purified by crystallization, his method is applicable only to 1,4-substituted benzenes. When the products are less crystalline, as in the case of 1,3-disubstituted benzenes, the purification becomes problematic.[4]

SCHEME 1. Protection of Boronates with Lithium Isopropoxide



SCHEME 2. Synthesis of Functionalized (Hetero)arylboronates



In this Note we disclose a method for effecting a metal−halogen exchange in halogenated arylboronates, which is free from the disadvantages of the above two methods. Inexpensive dibromoarenes or commercially available and easily prepared bromoarylpinacolatoboronates are employed in our method as the starting materials. The reaction affords pinacolatoboronates which can be purified by flash chromatography.[5]

The key to preventing side reactions with the metalating agent is the reversible protection of the boron atom as an aryltrialkoxyborate anion. To the best of our knowledge, this paper is the first reported case of such protection. The choice of protecting pinacolatoisopropoxyborate group is important. Pinacolatoboronates are more stable than isopropoxyboronates; therefore, isopropoxide can be cleaved selectively, avoiding the scrambling of the ester.[6] For example, *p*-bromophenylpinacolatoboronate (**1a)** was protected by a reaction with commercially available lithium isopropoxide to provide anionic species **2a**. The subsequent metal−halogen exchange and quench with benzaldehyde followed by a standard aqueous workup afforded the desired product **3a** (Scheme 1). This reaction is also applicable to meta-substituted aryl boronates as illustrated by conversion of **1b** into **3b** (Scheme 1). Boronates **1a**,**b** are commercially available[7] and can also be easily prepared from the corresponding boronic acids (see the Supporting Information). The yield of **3a** (78%) and **3b** (70%) was similar to the yield reported by Knochel (83% of **3a** and 71% of **3b**) starting with iodophenylboronates. Lower yield (62%) of the trifluo-

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(1) Santucci, L.; Gilman, H. *J. Am. Chem. Soc.* **1958**, *80*, 193.

(2) For example, see: (a) Letsinger, R. L.; Remes, N. *J. Am. Chem. Soc.* **1955**, *77*, 2489. (b) Letsinger, R. L.; Skoog, I. *J. Am. Chem. Soc.* **1955**, *77*, 2491. (c) Brown, H. C.; Cole, T. E.; Srebnik, M. *Organometallics* **1985**, *4*, 1788. (d) Brown, H. C.; Srebnik, M.; Cole, T. E. *Organometallics* **1986**, *5*, 2300.

(3) Baron, O.; Knochel, P. *Angew. Chem., Int. Ed.* **2005**, *44*, 3133.

(4) Molander, G. A.; Ellis, N. M. *J. Org. Chem.* **2006**, *71*, 7491.

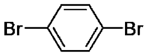
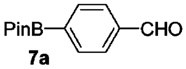
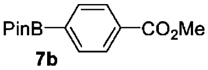
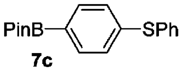
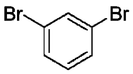
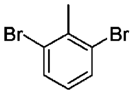
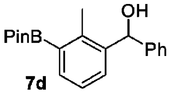
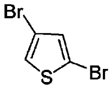
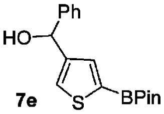
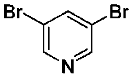
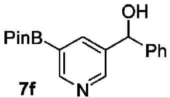
(5) (a) Tucker, C. E.; Davidson, J.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 3482. (b) Pereira, S.; Srebnik, M. *Tetrahedron Lett.* **1996**, *37*, 3283.

(6) Pinacolatoboronates have been prepared via hydrolysis of pinacolatoisopropoxyborate intermediate, for example, see: (a) Hoffmann, R. W.; Metternich, R.; Lanz, J. W. *Liebigs Ann. Chem.* **1987**, 881. (b) Krueger, J.; Hoffmann, R. W. *J. Am. Chem. Soc.* **1997**, *119*, 7499. (c) Mohacrishnan, A. K.; Hucke, A.; Lyon, M. A.; Lakshmikantham, M. V.; Cava, M. P. *Tetrahedron* **1999**, *55*, 11745. (d) Karsten, M.; Dimichele, L.; Mills, P.; Frantz, D. E.; Nelson, T. D.; Kress, M. H. *Synlett* **2006**, 1948.

(7) Combi-Blocks: **1a** (cat. no. PN-2629) and **1b** (cat. no. PN-2655).

10.1021/jo0710329 CCC: $37.00

TABLE 1. Synthesis of Functionalized (Hetero)arylboronates

Entry	Starting material	E^+	Product	Yield (%)
1	 **4a**	PhCHO	**3a**	71
2	**4a**	DMF	 **7a**	74
3	**4a**	MeO_2CCN	 **7b**	76
4	**4a**	PhSSPh	 **7c**	63
5		PhCHO	**3b**	66
6		PhCHO	 **7d**	78
7		PhCHO	 **7e**	61
8		PhCHO	 **7f**	47

roborate derivative corresponding to **3a** was obtained by Molander from potassium *p*-bromophenyltrifluoroborate.

As a more economical alternative, the protected "*ate*" intermediate can be generated in situ in a one-pot procedure starting with dibromoarene (**4**, Scheme 2).[8] Due to its simplicity, this procedure was preferred. To minimize side reactions, *t*-BuLi (2 equiv) was added to a mixture of **4** and **5** at −78 °C ("in situ quench" protocol).[9] After 30 min, formation of intermediate **6** was complete, and the metal−halogen exchange was effected by a further addition of *t*-BuLi. The resulting anion was quenched with various electrophiles to afford functionalized arylboronates **3** and **7** (Table 1).

The use of triisopropylborate in place of **5** gave the corresponding boronic acids. However, they were difficult to purify, and that approach was abandoned. An attempt to substitute *n*-BuLi for *t*-BuLi in this reaction was unsuccessful, causing decomposition of the "*ate*" intermediate.

The yield of **3a** (entry 1) and **3b** (entry 5) was similar to the yield obtained in the stepwise procedure in Scheme 1. Starting with *p*-dibromobenzene (**4a**), the corresponding formyl (entry 2), methoxycarbonyl (entry 3), and phenylsulfanyl (entry 4) substituted boronates were prepared in good yield. To further probe the scope of the synthesis, benzaldehyde was used as a

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(8) For the metalation of dibromobenzenes, see: (a) Gilman, H.; Langham, W.; Moore, F. W. *J. Am. Chem. Soc.* **1940**, *62*, 2327. (b) Caron, S.; Nga, M. D. *Synlett* **2004**, 1440 and references cited therein.

(9) For the use of triisoporopylborate with the following bases, see: (a) *n*-BuLi: Yasuda, N.; Huffman, M. A.; Ho, G.-J.; Xavier, L. C.; Yang, C.; Emerson, K. M.; Tsay, F.-R.; Li, Y.; Kress, M. H.; Rieger, D. L.; Karady, S.; Sohar, P.; Abramson, N. L.; DeCamp, A. E.; Mathre, D. J.; Douglas, A. W.; Dolling, U.-H.; Grabowski, E. J. J.; Reider, P. J. *J. Org. Chem.* **1998**, *63*, 5438. (b) *n*-BuLi: Li, W.; Nelson, D. P.; Jensen, M. S.; Hoerrner, R. S.; Cai, D.; Larsen, R. D.; Reider, P. J. *J. Org. Chem.* **2002**, *67*, 5394. (c) LTMP: Kristensen, J.; Lysén, M.; Vedso, P.; Begtrup, M. *Org. Lett.* **2001**, *3*, 1435. (d) LDA: Caron, S.; Hawkins, J. M.; *J. Org. Chem.* **1998**, *63*, 2054.

model electrophile. The reaction proceeded smoothly with hindered dibromoarene (entry 6) and also afforded good to moderate yields of *m*-phenylcarbinol substituted thiophene (entry 7) and pyridine (entry 8) boronates. Unfortunately, unlike Knochel's approach, application of our method to the preparation of ortho-substituted arylboronates was unsuccessful, with the second step leading instead to decomposition products.

In conclusion, a new method for metal−halogen exchange on bromoarylboronate molecules via an in situ isopropoxide protection has been developed. The desired protected intermediates can also be generated from dibromoarenes, making this procedure a convenient alternative for the preparation of functionalized (hetero)arylboronates.

Experimental Section

Typical Experimental Procedure A: Preparation of Phenyl-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanol[3] (3a) from 1a. To a solution of **1a** (1.32 g, 4.66 mmol) in anhydrous THF (20 mL) was added LiO*i*-Pr (2.33 mL, 2 M in THF, 4.66 mmol) at room temperature under N_2. After 2 h the reaction mixture was cooled to −78 °C; *t*-BuLi (5.50 mL, 1.7 M in pentane, 9.35 mmol) was added dropwise over 3 min, and the reaction was stirred for an additional 20 min at −78 °C. After this time benzaldehyde (0.588 g, 5.54 mmol) was added; the reaction was stirred for 20 min and quenched with saturated aq NH_4Cl (20 mL). The resulting mixture was extracted with ethyl acetate (3 × 50 mL). The combined extracts were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash column chromatography (silica gel, 85:15 hexanes/ethyl acetate) to provide **3a** (1.13 g, 78%) as a colorless oil: ^1H NMR (500 MHz, DMSO-d_6) δ 7.61 (d, J = 8.0 Hz, 2H), 7.39 (d, J = 8.0 Hz, 2H), 7.35 (d, J = 7.3 Hz, 2H), 7.31−7.27 (m, 2H), 7.19 (t, J = 7.3 Hz, 1H), 5.93 (d, J = 4.0 Hz, 1H), 5.71 (d, J = 4.0 Hz, 1H), 1.27 (s, 12H).

Typical Experimental Procedure B: Preparation of Phenyl-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanol (3a) from 4a. To a solution of **4a** (1.17 g, 5.00 mmol) and **5** (0.948 g, 5.10 mmol) in anhydrous THF (20 mL) was added *t*-BuLi (5.90 mL, 1.7 M in pentane, 10.0 mmol) dropwise over 3 min at −78 °C under N_2. After 30 min at −78 °C, additional *t*-BuLi (5.90 mL, 1.7 M in pentane, 10.0 mmol) was added dropwise over 3 min, and the reaction was stirred for a further 20 min. After this time benzaldehyde (0.588 g, 5.54 mmol) was added, and the reaction was stirred for 20 min and quenched with saturated aq NH_4Cl (20 mL). The workup was carried out as described above, affording **3a** in 71% yield (1.10 g).

Acknowledgment. The authors would like to thank Dr. R. Jason Herr for helpful suggestions to this manuscript.

Supporting Information Available: Full experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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