CSIRO PUBLISHING

Aust. J. Chem. **2014**, *67*, 675–678
http://dx.doi.org/10.1071/CH13642

Full Paper

Transition Metal-Free Synthesis of Pinacol Arylboronate: Regioselective Boronation of 1,3-Disubstituted Benzenes

Yan Wang,[A] *Le Wang,*[A] *Ling-Yan Chen,*[A] *Pinaki S. Bhadury,*[A] *and Zhihua Sun*[A,B]

[A]College of Chemistry and Chemical Engineering, Shanghai University of Engineering Science, Shanghai, 201620, China.
[B]Corresponding author. Email: sungaris@gmail.com

The regioselective synthesis of pinacol arylboronate has been achieved from 1,3-disubstituted benzene through directed *ortho*-metallation (D*o*M)–borylation sequence. A wide range of substituents and borylating reagents were investigated. In situ lithiation and subsequent boronation predominantly occurred at the *ortho*-position to afford the desired products in moderate yields.

Manuscript received: 20 November 2013.
Manuscript accepted: 13 December 2013.
Published online: 17 January 2014.

Introduction

Boronation of arenes and heteroaromatic compounds often leads to reactive synthetic intermediates, which are used to execute useful synthetic transformations via transition metal-catalyzed cross-coupling reactions[1–4] and conversion into other functional groups.[5–8] In fact, selective transition metal-mediated incorporation of boryl moiety into arene system has gained widespread attention in recent times.[9–12] However, the reported methods have several disadvantages such as harsh reaction conditions, long reaction times, and use of expensive metal catalysts associated with poor yields.[13–15] Moreover, the reaction system is not eco-friendly as the borylated arene is often contaminated with heavy metals.[16] Consequently, development of a practical, transition metal-free approach for the incorporation of boron into an organic core has become highly desirable.[17,18]

Although some examples of regioselective borylation of mono- and poly-substituted arenes are available,[19,20] the literature furnishes much less information for 1,3-disubstituted aromatic systems which possess multiple active sites that are prone to attack by electrophilic agents. In our earlier study,[21] 1,3-disubstituted arenes were subjected to deprotonation/metallation sequence with *n*-butyl lithium. The in situ lithiated species generated through directed *ortho*-metallation (D*o*M) was reacted with the electrophile, dimethylformamide, under optimal conditions to afford formylated products in good yields and regioselectivities. The practical utility of this transition metal-free protocol was further extended in the current investigation to prepare a more important type of synthetic intermediate, pinacol arylboronate. The results of our finding are reported in this article.

Results and Discussion

At the outset, we varied the reaction parameters such as time, temperature, and molar ratios of the reagents to obtain optimal selectivity and yield of the borylated regioisomer. Due to its excellent D*o*M property,[21] 1,3-difluorobenzene was selected as the model compound to prepare the regioisomer **1b** using different electrophilic borylating reagents (Fig. 1).

The results of our initial exploration are presented in Table 1. The regioisomeric distribution of products was established using ^{19}F NMR spectroscopy. It is evident from the data presented in Table 1 that in situ lithiation of the substrate **1a** by *n*-BuLi/*N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA)/diisopropylamine (DIPA) and subsequent reaction with the electrophile, *i*-PrOBPin,[17,18] afforded inferior result when 1.1 equivalents (equiv.) of the electrophile was employed (Table 1, entry 1). To our delight, excellent regioselectivity (>98 %) and much higher yield (67 %) for the isomer **1b** were obtained by increasing the reaction time from 1 to 12 h and by increasing the amount of the boron reagent to 1.5 equiv. (Table 1, entry 2). However, the yield of the product was not affected significantly by increasing the amount of *i*-PrOBPin to 3.0 equiv. or by prolonging the reaction time to 24 h (Table 1, entry 3). Under comparable conditions, B_2Pin_2 afforded similar results in terms of selectivity albeit lower yield of the isomer (Table 1, entry 4). The outcome of the reaction practically remained unaltered in the presence of the CuCl catalyst (Table 1, entry 5). On the other hand, the electrophilic reagents $(MeO)_3B$,[22] PinB-BR_e,[23] and Ph_3SiB-Pin[24,25] proved to be far less effective (Table 1, entries 6–8).

Having established the optimal conditions, regioselective borylation of a series of 1,3- disubstituted benzene was conducted either with 1.5 equiv. of *i*-PrOBPin or 1.5 equiv. of B_2Pin_2 at room temperature for 12 h. From the data presented in Table 2, borylation of 1,3-disubstituted benzene, in general, afforded the desired product in moderate to high yields (28–69 %). However, the electrophile *i*-PrOBPin proved to be more efficient compared with B_2Pin_2 in terms of overall yields of the final products (entries 1–11). In situ lithiation and subsequent borylation of 1,3-disubstituted benzene preferentially leads to the generation of 2,6-disubstituted phenylboronic acid pinacol ester. In a few cases for compounds bearing

trifluoromethyl groups, the incoming electrophile was directed to the *ortho*-position (Table 2, entries 10–11). This is perhaps attributed to the fact that the relatively bulky CF_3 group not only imposes steric restrictions to the incoming borylating agent adjacent to it but also greatly polarizes the π-electrons at other positions.[26]

Conclusion

In summary, we developed a transition metal-free regioselective boronation protocol to prepare a series of pinacol boronates, which are useful synthetic intermediates in many organic transformations. The method is operationally simple and cheap, with a wide substrate scope, and utilises both *i*-PrOBPin and B_2Pin_2 as electrophilic sources. This novel approach is expected to find vast applications for the synthesis of aromatic boron compounds.

Experimental

General Experimental Procedure

THF was heated at reflux over sodium benzophenone ketyl before use. All reactions were carried out under N_2 atmosphere using oven-dried glassware. NMR spectra were recorded on Bruker Avance II spectrometer at 400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR, and 396 MHz for ^{19}F NMR; chemical shifts are given in parts per million. Electrospray ionization–atmospheric pressure ionization (ESI–API) analyses were carried out with an Agilent 1100 LC/MSD trap mass spectrometer. Gas chromatography–mass spectrometry (electron impact ionization, EI) analyses were carried out on a Thermo Fisher DSQ apparatus (70 eV) with ions given in *m*/*z*. High-resolution mass spectra were recorded on a Shimadzu liquid chromatograph mass spectrometer (LCMS-IT-TOF).

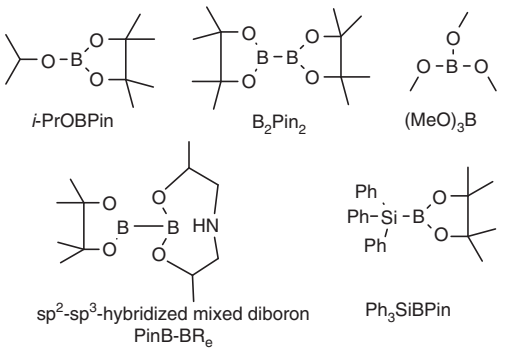


Fig. 1. Different electrophilic borylating reagents employed for optimization.

General Procedure for Metallation–Boronation of 1,3-Disubstituted Benzene

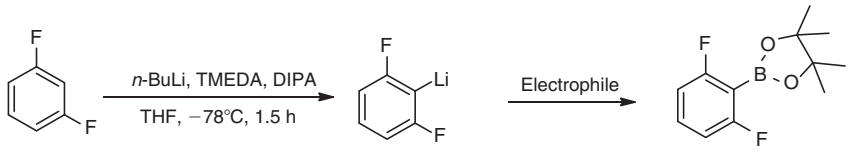
Method A

To a oven-dried 100 mL flask was added 1,3-disubstituted benzene (3.0 mmol), TMEDA (1.1 equiv., 3.3 mmol), DIPA (5 mol-%, 0.16 mmol), and THF (10.0 mL). The solution was cooled to −78°C for 10 min and then *n*-BuLi (1.1 equiv., 3.3 mmol) was added dropwise. The mixture was maintained at this temperature for 1.5 h followed by the addition of B_2Pin_2 (1.5 equiv., 4.5 mmol). The mixture was stirred for another 30 min at −78°C. The system was allowed to warm up to room temperature (r.t.) and stirring was continued for 1–12 h and a saturated aqueous NH_4Cl solution (5 mL) was added to quench the reaction. The mixture was extracted using ethyl acetate (3 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. The regioselectivity of the crude product was confirmed by ^{19}F NMR and then subjected to flash chromatography to obtain the desired products, which were characterized by ^{1}H, ^{13}C, and ^{19}F NMR spectral data, and liquid chromatography mass spectrometry analyses.

Method B

Instead of the B_2Pin_2 electrophile, *i*-PrOBPin was used. The rest of the procedure was the same as that of Method A.

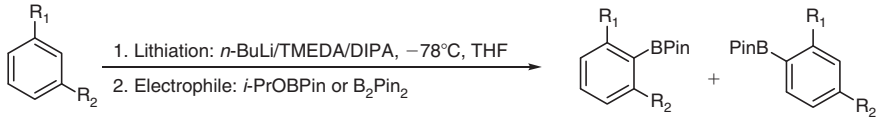
Table 1. Regioselective *ortho*-borylation of 1,3-difluorobenzene



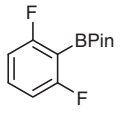
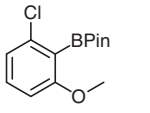
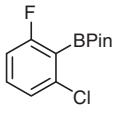
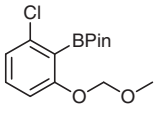
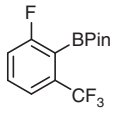
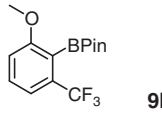
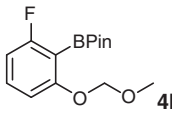
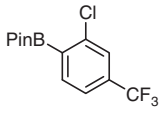
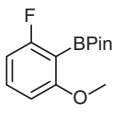
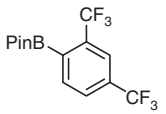
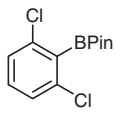
Entry	Reaction conditions[A]	Isomer selectivity[B] [%]	Yield[E] [%]
1	*i*-PrOBPin 1.1 equiv., r.t., 1 h	n.d.[C]	<10
2	*i*-PrOBPin 1.5 equiv., r.t., 12 h	>98	67
3	*i*-PrOBPin 3.0 equiv., r.t., 24 h	>95	64
4	B_2Pin_2 1.5 equiv., r.t., 12 h	>98	43
5	CuCl, 1.1 equiv. in first step, B_2Pin_2 1.5 equiv., r.t., 12 h	>95	40
6[D]	PinB-BR_e, 5.0 equiv., r.t., 24 h	n.d.[C]	<5
7	$(MeO)_3B$, 5.0 equiv., r.t., 24 h	n.d.[C]	<5
8	$Ph_3SiBPin$, 5.0 equiv., r.t., 24 h	n.d.[C]	<5

[A]Unless otherwise noted, all the reactions were carried out with 1.0 equiv. of the substrate **1a**, 1.1 equiv. each of *n*-BuLi and TMEDA, and 5 mol-% of DIPA at −78°C for 1.5 h followed by 1.1–5.0 equiv. of the electrophile.
[B]Determined by ^{19}F NMR.
[C]Not determined.
[D]2.2 equiv. of *n*-BuLi was added before reaction with the electrophile.
[E]Overall crude yield.

Table 2. Regioselective boronation of 1,3-disubstituted benzene under optimal conditions with electrophiles, *i*-PrOBPin and B_2Pin_2[A]



1-11a **1-11b** **1-11c**

Entry	Product	Yield[B] [%] *i*-PrOBPin	Yield[B] [%] B_2Pin_2	Entry	Product	Yield[B] [%] *i*-PrOBPin	Yield[B] [%] B_2Pin_2
1	 **1b**	67	43	7	 **7b**	64	35
2	 **2b**	69	45	8	 **8b**	53	28
3	 **3b**	57	34	9	 **9b**	55	34
4	 **4b**	52	33	10	 **10c**	56	34
5	 **5b**	63	44	11	 **11c**	59	31
6	 **6b**	68	47				

[A]Unless otherwise noted, all reactions were carried out with 1.0 equiv. of the substrate **1a**, 1.1 equiv. each of *n*-BuLi and TMEDA, and 5 mol-% of DIPA at −78°C for 1.5 h, followed by 1.5 equiv. of the electrophile.
[B]Isolated yields using electrophiles, *i*-PrOBPin and B_2Pin_2.

*2,6-Difluorophenylboronic Acid Pinacol Ester (**1b**)*

Yellow solid, mp 50.1–51.8°C. δ_H ($CDCl_3$) 7.38 (m, 1H), 6.86 (t, *J* 8.0, 2H), 1.41 (s, 12H). δ_C ($CDCl_3$) 167.8, 165.3, 133.1, 111.1, 84.3, 77.0, 24.8. δ_F ($CDCl_3$) −100.66. *m/z* (HR-MS ESI) 241.1211; $[M+H]^+$ requires 241.1133.

*2-Chloro-6-fluorophenylboronic Acid Pinacol Ester (**2b**)*

Yellow solid, mp 68.3–69.6°C. δ_H ($CDCl_3$) 7.29 (m, 1H), 7.15 (d, *J* 8.0, 1H), 6.94 (t, *J* 8.0, 1H), 1.43 (s, 12H). δ_C ($CDCl_3$) 166.7, 164.2, 138.4, 131.9, 124.7, 113.2, 84.8, 77.0, 24.7. δ_F ($CDCl_3$) −102.64. *m/z* (HR-MS ESI) 257.0895; $[M+H]^+$ requires 257.0838.

*2-Fluoro-6-trifluoromethylphenylboronic Acid Pinacol Ester (**3b**)*

Yellow oil. δ_H ($CDCl_3$) 7.47 (m, 2H), 7.22 (d, *J* 8.0, 1H), 1.42 (s, 12H). δ_C ($CDCl_3$) 131.5, 131.5, 121.3, 118.4, 118.1, 85.1, 24.6. δ_F ($CDCl_3$) −59.94 (3F), −103.13 (F). *m/z* (HR-MS ESI) 291.1168; $[M+H]^+$ requires 291.1101.

*2-Fluoro-6-methoxymethylphenylboronic Acid Pinacol Ester (**4b**)*

Yellow solid, mp 96.3–97.2°C. δ_H ($CDCl_3$) 7.27 (m, 1H), 6.82 (d, *J* 8.4, 1H), 6.70 (t, *J* 8.0, 1H), 5.18 (s, 2H), 3.49 (s, 3H), 1.40 (s, 12H). δ_C ($CDCl_3$) 167.4, 164.9, 161.3, 161.2, 132.1, 109.6, 94.6, 83.5, 77.0, 56.6, 25.0. δ_F ($CDCl_3$) −103.88. *m/z* (EI) 282 $[M^+]$.

*2-Fluoro-6-methoxyphenylboronic Acid Pinacol Ester (**5b**)*

Yellow solid, mp 68.6–70.1°C. δ_H ($CDCl_3$) 7.29 (m, 1H), 6.64 (m, 2H), 1.41 (s, 12H), 3.56 (s, 3H). δ_C ($CDCl_3$) 167.5, 165.1, 164.0, 132.1, 107.7, 105.8, 84.1, 77.0, 56.0, 24.7. δ_F ($CDCl_3$) −104.17. *m/z* (HR-MS ESI) 253.1400; $[M+H]^+$ requires 253.1333.

*2,6-Dichlorophenylboronic Acid Pinacol Ester (**6b**)*

Yellow solid, mp 78.5–79.6°C. δ_H ($CDCl_3$) 7.24 (s, 3H), 1.45 (s, 12H). δ_C ($CDCl_3$) 138.1, 131.2, 126.8, 85.0, 77.0, 24.8. *m/z* (ESI) 295 $[M+Na]^+$. *m/z* (HRMS ESI) 273.0610; $[M+H]^+$ requires 273.0542.

*2-Chloro-6-methoxyphenylboronic Acid Pinacol Ester (**7b**)*

Yellow solid, mp 78.4–79.7°C. δ_H ($CDCl_3$) 7.23 (d, *J* 8.0, 1H), 6.93 (d, *J* 8.0, 1H), 6.72 (d, *J* 8.4, 1H), 3.80 (s, 3H), 1.42 (s, 12H). δ_C ($CDCl_3$) 163.1, 137.8, 132.6, 131.3, 121.2, 108.0, 84.4, 77.0, 55.8, 24.7. *m/z* (HR-MS ESI) 269.1101; $[M+H]^+$ requires 269.1038.

*2-Chloro-6-methoxymethylphenylboronic Acid Pinacol Ester (**8b**)*

Yellow solid, mp 100.6–101.3°C. δ_H ($CDCl_3$) 7.22 (t, *J* 8.0, 1H), 6.98 (d, *J* 8.0, 1H), 6.93 (d, *J* 8.4, 1H), 5.16 (s, 2H), 3.48 (s, 3H), 1.42 (s, 12H). δ_H ($CDCl_3$) 160.4, 137.7, 131.2, 122.2, 111.6, 94.3, 77.0, 56.1, 29.7, 24.7. *m/z* (EI) 298 $[M^+]$.

*2-Methoxy-6-trifluoromethylphenylboronic Acid Pinacol Ester (**9b**)*

Yellow oil. δ_H ($CDCl_3$) 7.43 (t, *J* 8.0, 1H), 7.22 (d, *J* 8.0, 1H), 7.00 (d, *J* 8.0, 1H), 3.85 (s, 3H), 1.41 (s, 12H). δ_C ($CDCl_3$) 162.7, 134.4, 130.8, 117.7, 112.9, 84.5, 77.0, 55.9, 24.6 . δ_F ($CDCl_3$) −63.24. *m/z* (HR-MS ESI) 303.1365; $[M+H]^+$ requires 303.1301.

*2-Chloro-4-trifluoromethylphenylboronic Acid Pinacol Ester (**10c**)*

Yellow oil. δ_H ($CDCl_3$) 7.82 (d, *J* 7.6, 1H), 7.63 (s, 1H), 7.50 (d, *J* 7.6, 1H), 1.40 (s, 12H). δ_C ($CDCl_3$) 140.1, 136.8, 133.9, 133.5, 126.1, 122.4, 84.6, 77.0, 24.8. δ_F ($CDCl_3$) −63.21. *m/z* (ESI) 307 $[M+H]^+$.

*2,4-Di-trifluoromethylphenylboronic Acid Pinacol Ester (**11c**)*

Yellow oil. δ_H ($CDCl_3$) 7.93 (s, 1H), 7.89 (d, *J* 8.0, 1H), 7.79 (d, *J* 8.0, 1H), 1.40 (s, 12H). δ_C ($CDCl_3$) 135.5, 134.7, 132.2, 127.3, 124.9, 122.2, 85.0, 77.0, 24.6. δ_F ($CDCl_3$) −60.13, −63.27. *m/z* (ESI) 363 $[M+Na]^+$.

Supplementary Material

Details of experimental procedures, characterization data of compounds as well as ^1H, ^{13}C, and ^{19}F NMR spectra are available on the Journal's website.

Acknowledgements

Financial support for this work was provided by Shanghai Municipal Education Commission (14ZZ159) and Shanghai Municipal Science and Technology Commission (No.12430501300). The authors are also grateful for financial support from the Special Scientific Foundation for Outstanding Young Teachers in Shanghai Higher Education Institutions (shgcjs023, ZZGJD13020), and Start-up Funding of Shanghai University of Engineering Science (2013–01).

References

[1] R. Jana, T. P. Pathak, M. S. Sigman, *Chem. Rev.* **2011**, *111*, 1417. doi:10.1021/CR100327P

[2] *Boronic Acids: Preparation and Applications in Organic Synthesis and Medicine* (Ed. D. G. Hall) **2005** (Wiley-VCH: Weinheim).

[3] A. Suzuki, *Angew. Chem.* **2011**, *123*, 6854. doi:10.1002/ANGE.201101379

[4] N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457. doi:10.1021/CR00039A007

[5] (a) P. Anbarasan, H. Neumann, M. Beller, *Angew. Chem.* **2011**, *123*, 539. doi:10.1002/ANGE.201006044
(b) P. Anbarasan, H. Neumann, M. Beller, *Angew. Chem.* **2011**, *50*, 519. doi:10.1002/ANIE.201006044

[6] T. Furuya, H. M. Kaiser, T. Ritter, *Angew. Chem.* **2008**, *120*, 6082. doi:10.1002/ANGE.200802164

[7] L. Chu, F. Qing, *Org. Lett.* **2010**, *12*, 5060. doi:10.1021/OL1023135

[8] K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem.* **2005**, *117*, 4516. doi:10.1002/ANGE.200500368

[9] G. A. Chotana, M. A. Rak, M. R. Smith III, *J. Am. Chem. Soc.* **2005**, *127*, 10539. doi:10.1021/JA0428309

[10] K. I. Goldberg, A. S. Goldman, *Activation and Functionalization of C-H Bonds* **2004** (American Chemical Society: Washington, D.C.).

[11] T. Ishiyama, Y. Nobuta, J. F. Hartwig, N. Miyaura, *Chem. Commun.* **2003**, 2924. doi:10.1039/B311103B

[12] L. Iannazzo, K. P. C. Vollhardt, M. Malacria, C. Aubert, V. Gandon, *Eur. J. Org. Chem.* **2011**, 3283. doi:10.1002/EJOC.201100371

[13] A. Maderna, H. Pritzkow, W. Siebert, *Angew. Chem.* **1996**, *108*, 1664. doi:10.1002/ANGE.19961081339

[14] H. Yoshida, K. Okada, S. Kawashima, K. Tanino, J. Ohshita, *Chem. Commun.* **2010**, *46*, 1763. doi:10.1039/B919407J

[15] H. Yoshida, S. Kawashima, Y. Takemoto, K. Okada, J. Ohshita, K. Takaki, *Angew. Chem.* **2012**, *124*, 239. doi:10.1002/ANGE.201106706

[16] L. Zhu, J. Duquette, M. Zhang, *J. Org. Chem.* **2003**, *68*, 3729. doi:10.1021/JO0269114

[17] F. Mo, Y. Jiang, D. Qiu, Y. Zhang, J. Wang, *Angew. Chem.* **2010**, *122*, 1890. doi:10.1002/ANGE.200905824

[18] H. Li, L. Wang, Y. Zhang, J. Wang, *Angew. Chem.* **2012**, *51*, 2943. doi:10.1002/ANIE.201108139

[19] M. Alessi, A. L. Larkin, K. A. Ogilvie, L. A. Green, S. Lai, S. Lopez, V. Snieckus, *J. Org. Chem.* **2007**, *72*, 1588. doi:10.1021/JO0620359

[20] M. Burger, G. Nishiguchi, T. D. Machajewki, A. Rico, R. L. Simmons, A. R. Smith, V. Tamez, H. Tanner, L. Wan, *U. S. Patent 2012/0225062 A1* **2012**.

[21] L. Wang, Y. Wang, F.-X. Guo, Y. Zheng, P. S. Bhadury, Z. Sun, *Tetrahedron Lett.* **2013**, *54*, 6053. doi:10.1016/J.TETLET.2013.08.098

[22] T. Leermann, F. R. Leroux, F. Colobert, *Org. Lett.* **2011**, *13*, 4479. doi:10.1021/OL2016252

[23] M. Gao, S. B. Thorpe, W. L. Santos, *Org. Lett.* **2009**, *11*, 3478. doi:10.1021/OL901359N

[24] T. Ohmura, T. Torigoe, M. Suginome, *J. Am. Chem. Soc.* **2012**, *134*, 17416. doi:10.1021/JA307956W

[25] T. Kurahashi, T. Hata, H. Masai, H. Kitagawa, M. Shimizu, T. Hiyama, *Tetrahedron* **2002**, *58*, 6381. doi:10.1016/S0040-4020(02)00648-8

[26] R. F. Leroux, B. Manteau, J. P. Vors, S. Pazenok, *Beilstein J. Org. Chem.* **2008**, *13*, 1.