A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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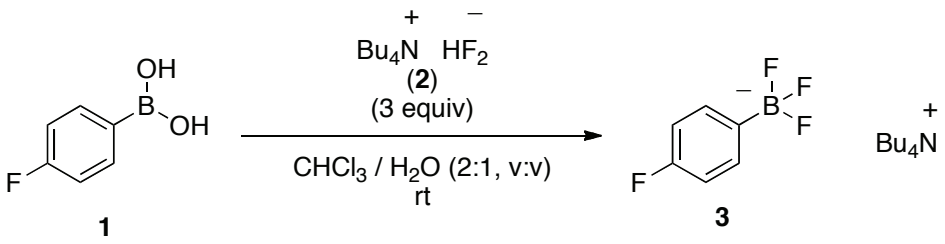
Preparation of Tetrabutylammonium (4-fluorophenyl)trifluoroborate



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Checked by Changming Qin and Huw M. L. Davies.

1. Procedure

A. *Tetrabutylammonium (4-fluorophenyl)trifluoroborate **3***. 4-Fluorophenyl boronic acid **1** (4.00 g, 28.6 mmol, 1.00 equiv) (Note 1) is placed in an open single-necked 1000-mL round-bottomed flask equipped with a magnetic stir bar and suspended in a mixture of chloroform (400 mL) (Note 2) and water (80 mL) (Note 3). Tetrabutylammonium bifluoride (TBABF) **2** (24.2 g, 85.8 mmol, 3.00 equiv) (Note 4) is directly added to a 250-mL pressure-equalizing addition funnel and dissolved with H_2O (120 mL). Open to air, the addition funnel is fitted to the reaction flask and the clear solution of tetrabutylammonium bifluoride **2** is added dropwise to the stirred boronic acid suspension over a period of 1 h (Note 5). Upon addition of the bifluoride solution, the boronic acid dissolves and the biphasic mixture becomes transparent. After 2.5 h (Note 6) the reaction mixture is transferred to a 1000-mL separatory funnel and the two layers are separated. The water layer is extracted with chloroform (4 x 100 mL) and the combined organic phases are washed with water (3 x 200 mL), brine (2 x 150 mL), and dried over anhydrous magnesium sulfate (30 g, 1 h) (Note 7). Magnesium sulfate is removed by vacuum filtration on a Büchner funnel (Note 8) and the filtrate is evaporated by rotary evaporation (bath temp 40 °C), with the final concentration in a 250-mL round bottom flask. The resulting clear transparent oil is placed under high vacuum (0.5 mmHg) for 3 h to afford a white solid (14.5 g). The crude product is purified by recrystallization from ethanol/water (Note 9) as follows. The solid trifluoroborate in the 250-mL

round-bottomed flask is dissolved in ethanol (9.0 mL) upon heating at 50 °C in a water bath. After cooling to 23 °C, water (4.0 mL) is added dropwise to the flask with swirling until the solution becomes cloudy and remains persistently cloudy. This solution is placed in a refrigerator at 0 °C for 3 h. A white solid precipitates from the mixture and is collected by gravity filtration (Note 10). Water (3 x 20 mL) is used to rinse residual solids from the 250 mL flask, and all the rinses are used to wash the solid, which is then dried under high vacuum (0.2 mmHg) over P_2O_5 (30 g) (15 h) to remove traces of ethanol and water, affording a white crystalline solid (11.2 g, 97%) (Note 11).

2. Notes

1. 4-Fluorophenylboronic acid (Sigma-Aldrich) was used as received.
2. Stir bar (VWR) 2x5/16 inch-octagonal was used. Chloroform (≥99.8%, HPLC grade, Sigma-Aldrich) was used as received.
3. ASTM type II water was produced by RO/DI (HARLECO).
4. Tetrabutylammonium bifluoride (> 95.0%, TCI America, Inc.) was used as received. Use of excess reagent was necessary for complete conversion.
5. Rate of addition was approximately 70 drops/min.
6. The reaction was monitored by ^{19}F NMR according to the following procedure: 0.5 mL of the chloroform layer was withdrawn from the mixture, the solvent was evaporated on a rotary evaporator, and the crude mixture was examined by ^{19}F NMR using $CDCl_3$ as solvent. ^{19}F NMR showed complete absence of fluorine signals corresponding to 4-fluorophenyl boronic acid **1** after 2.5 h reaction time**.**
7. Magnesium sulfate (anhydrous, EMD Chemicals) was used as received.
8. 150 mL Büchner funnel, medium Frit.
9. Ethanol (200 proof, DECON Laboratories, Inc) was used as received.
10. Fisherbrand filter paper, Qualitative P8, Porosity-coarse, 24 cm diameter.
11. Tetrabutylammonium (4-fluorophenyl)trifluoroborate **3** has the following physical and spectroscopic properties: mp 83–84 °C; IR (neat):

2964, 2876, 1588, 1489, 1186, 1003, 973, 952, 825, 739 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.94 (t, J = 7.2 Hz, 12 H), 1.26–1.35 (m, 8 H), 1.39–1.45 (m, 8 H), 2.94–2.99 (m, 8 H), 6.86 (t, J = 8.8 Hz, 2 H), 7.55 (t, J = 7.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.3, 19.2, 23.4, 57.8, 112.9 (d, J_{C-F} = 18.6 Hz), 132.9 (d, J_{C-F} = 6.0 Hz), 161.6 (d, J_{C-F} = 238.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: –119.0 (brs, 1F), –141.6 (br, s, 3F); ^{11}B NMR (192 MHz, $CDCl_3$) δ: 3.34; MS (ESI): *m/z* (%) = 163.0349 (100) $[M\text{-}NBu_4]^-$; HRMS (ESI) *m/z* $[M\text{-}NBu_4]^-$ calculated for $C_6H_4BF_4$: 163.0347 found: 163.0349; Anal. Calcd $C_{22}H_{40}BF_4N$: C, 65.18; H, 9.95; N, 3.46. Found: C, 65.13; H, 9.80; N, 3.47 (after first recrystallization).

Handling and Disposal of Hazardous Chemicals

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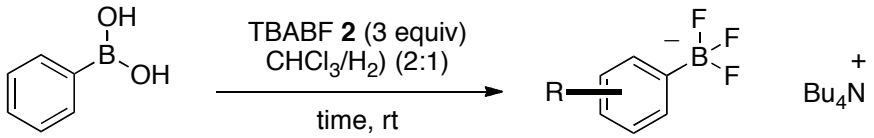
3. Discussion

Since the development of Suzuki–Miyaura cross coupling, boronic acids have gained enormous importance. Despite their widespread use, boronic acids have several distinct drawbacks and limitations. Some boronic acids (cyclopropyl-, heteroaryl-, and vinylboronic acids) show instability upon storage. Boronic acids easily lose water and hence are not monomeric species but, rather, exist as dimeric and cyclic trimeric anhydrides. While this does not affect the cross coupling reactions, uncertainties about the exact stoichiometry of the reaction being performed can be an issue.

Furthermore, under certain reaction conditions, boronic acids are prone to protiodeboronation, resulting in reduced yields. To circumvent these limitations, Vedejs[2] introduced potassium trifluoroborate salts as stable and easy to handle boronic acid substitutes. Although the potassium salts have been synthetically useful, they present the disadvantage of having poor solubility in organic solvents other than methanol, acetonitrile, or water. This characteristic may constitute a problem when apolar substrates, for example, hydrophobic polymeric boronic acids, have to be transformed into the corresponding trifluoroborates. Tetrabutylammonium trifluoroborates[3] are soluble in common organic solvents such as chloroform and dichloromethane, are air-stable, have long shelf-life, and are very easy to handle. Prior to our successful report[4] of one-pot syntheses of a variety of tetrabutylammonium trifluoroborates directly from boronic acids, they were prepared by one of two general methods: by ion exchange from the corresponding potassium salt or from a concentrated methanol solution of a boronic acid treated with three equiv of 48% aqueous hydrofluoric acid (HF), followed by neutralization of the corresponding hydronium trifluoroborate with tetrabutylammonium hydroxide (TBAH).[5] Both methods present some disadvantages. The first requires the preparation of the potassium salts and subsequent cation exchange, while the second requires use of corrosive and hazardous aqueous HF.

The present methodology is a straightforward, one-pot procedure that avoids the use of noxious and highly corrosive HF. By contrast, TBABF is not corrosive and is commercially available in 25 g lots. The reaction can be performed in an open flask without requiring solvent purification and the product is usually isolated in good to excellent yields after purificiation by simple extraction/washing and simple recrystallization procedures. Most importantly, the present protocol is diversely applicable to a variety of substrates as illustrated in Table 1.

Table 1. Synthesis of aromatic and alkyl tetrabutylammonium trifluoroborates



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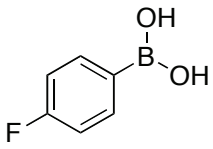
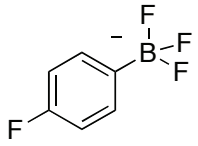
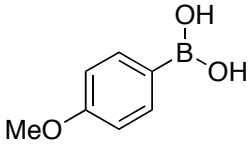
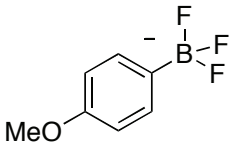
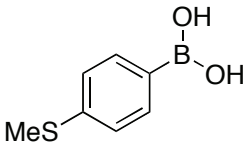
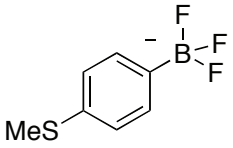
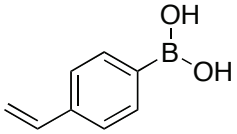
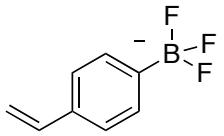
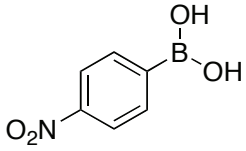
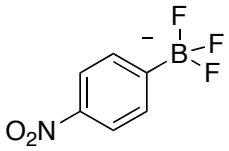
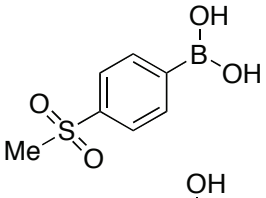
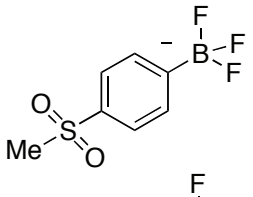
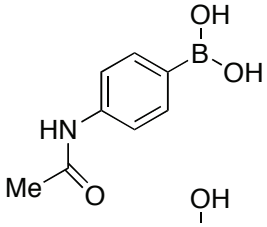
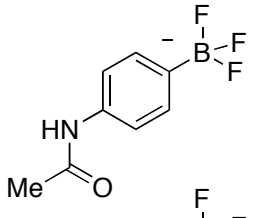
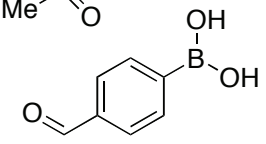
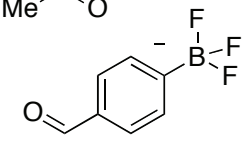
1		1		84
2		1		75
3		1.5		91
4		1.5		93
5		1		96
6		1		97
7		1		95
8		3		96

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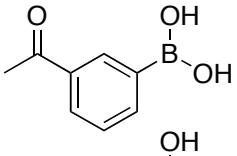
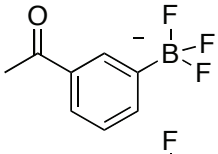
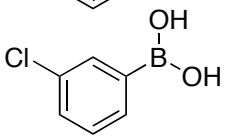
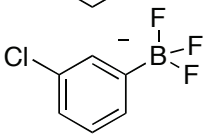
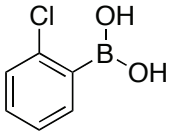
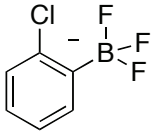
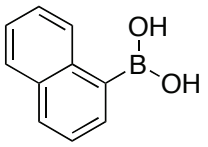
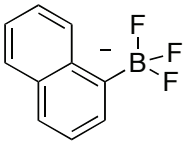
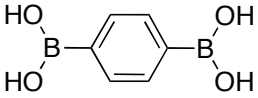
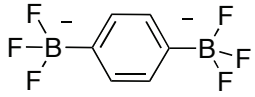
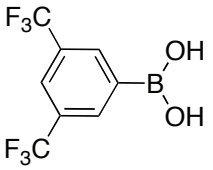
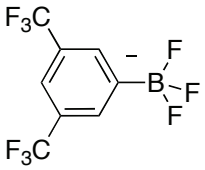
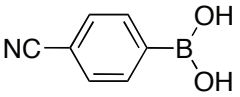
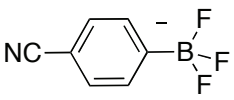
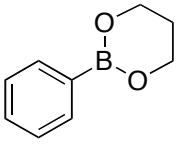
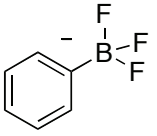
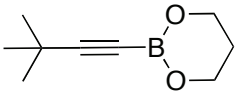
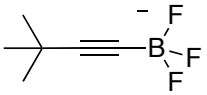
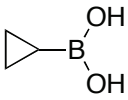
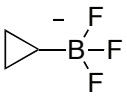
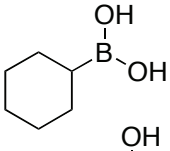
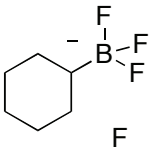
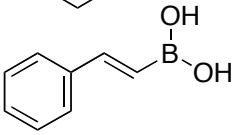
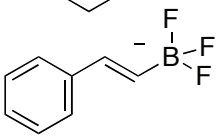
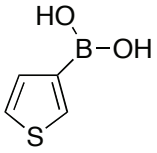
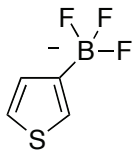
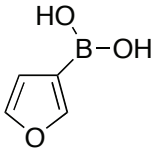
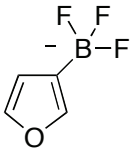
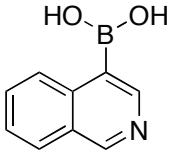
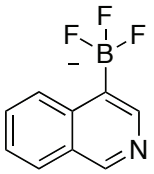
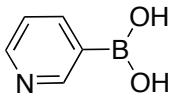
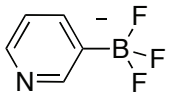
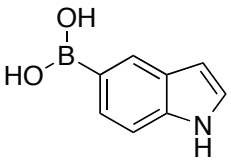
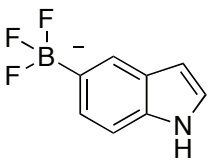
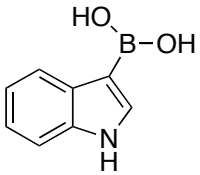
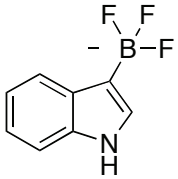
9		45 min		97
10		1		96
11		1		96
12		1		96
13		2		70
14		1.5		97
15		4		74
16		4		80
17		5		50[a,b]
18		5		50[a,b]
19		30 min		86[b]
20		30 min		98

[a] Reaction performed under a nitrogen atmosphere

[b] Crude yield determined by ^{19}F NMR spectroscopic data

The present methodology is quite tolerant of functional groups. Both electron-withdrawing and electron-donating substituents give excellent yields of corresponding trifluoroborates. Even aliphatic boronic acids afford good yields and the difficult to access cyclopropyl, alkynyl, styrenyl and cyclohexyl trifluoroborates are now available in moderate to excellent yields. Boronic esters also appear to react, albeit in moderate conversions as determined by ^{19}F NMR analysis using an internal standard. This protocol can be extended to heteroaromatic systems as exemplified in Table 2. Although the corresponding yields of the trifluoroborates are moderate, the fact that such molecules can be synthesized by this straightforward methodology is important.

Table 2. Synthesis of Heteroaromatic Tetrabutylammonium Trifluoroborates[a]

Entry	Substrate	Time	Product	% Yield
1		6		64
2		24		66[b]
3		7		81[b]
4		6		50
5		6		50
6		2.5		94

[a] Reaction conditions: HetAr (1 equiv), 2 (3 equiv), $CHCl_3$-H_2O (2:1, v:v), rt

[b] Crude yield determined from 19F NMR spectroscopic data

All of the heterocyclic trifluoroborates synthesized by this method can be used as coupling partners in cross-coupling reactions to synthesize a variety of heterocyclic structural motifs that are useful for biological screening.

Potassium trifluoroborates have been used in many transition-metal catalyzed cross-coupling reactions, as illustrated in the literature.[6] Importantly, palladium-catalyzed cross-coupling reactions of tetrabutylammonium trifluoroborates with a variety of aryl halides have also been reported.[5] Lipophilic benzyltrimethylammonium trifluoroborates have also been reported to provide better stereocontrol in alkylation reactions as compared to their potassium counterparts.[7] Applications such as these suggest that tetrabutylammonium trifluoroborates have good, but largely unexplored, potential as coupling partners, especially where the corresponding potassium salts show less promise.

Appendix
Chemical Abstracts Nomenclature; (Registry Number)

4-Fluorophenyl boronic acid: Boronic acid, B-(4-fluorophenyl)-, (CAS 1765-93-1),

Tetrabutylammonium bifluoride: 1-Butanaminium, *N*,*N*,*N*-tributyl-, (hydrogen difluoride) (1:1) (CAS 23868-34-0),

Tetrabutylammonium (4-Fluorophenyl)trifluoroborate): 1-Butanaminium, *N*,*N*,*N*-tributyl-, (*T*-4)-trifluoro(4-fluorophenyl)borate(1-) (1:1) , (CAS 1291068-40-0).

1. Loker Hydrocarbon Research Institute, University of Southern California, Los Angeles, CA 90089-1919, USA.

2. Vedejs, E.; Chapman, R. W.; Fields, S. C.; Lin, S.; Schrimpf, M. R. *J. Org. Chem.* **1995**, *60*, 3020–3027.

3. Tetrabutylammonium bifluoride is commercially available from TCI America. Otherwise, it can be easily prepared from readily available chemicals (KHF_2, Bu_4NHSO_4, $KHCO_3$) according to the literature procedure: Landini, D.; Molinari, H.; Penso, M.; Rampoldi, A., *Synthesis* **1988**, 953–955.

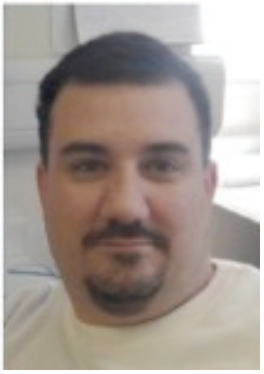
4. Prakash, G. K. S.; Pertusati, F.; Olah, G. A. *Synthesis*, **2011**, 292–302.

5. Batey, R. A.; Quach, T. D. *Tetrahedron Lett.* **2001,** 42, 9099–9103.

6. (a) Darses, S.; Michaund, G.; Genet, J.-P. *Eur. J. Org. Chem.* **1999**, 1875–1883. (b) Molander, G. A.; Ito, T. I. *Org. Lett.* **2001**, *3*, 393–396. (c) Molander, G. A.; Yun, C. S.; Ribagorda, M.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 5534–5539. (d) Saevmarker, J.; Rydfjord, J.; Gising, J.; Odell, L. R.; Larhed, M. *Org. Lett.* **2012**, *14*, 2394–2397. (e) Yao, B.; Liu, Y.; Wang, M.-K.; Li, J.-H.; Tang, R.-Y.; Zhang, X.-G.; Deng, C.-L. *Adv. Synth. Catal.* **2012**, *354*, 1069–1076. (f) Colombel, V.; Presset, M.; Oehlrich, D.; Rombouts, F.; Molander, G. A. *Org. Lett.* **2012**, *14*, 1680–1683. (g) Masuyama, Y.; Sugioka, Y.; Chonan, S.; Suzuki, N.; Fujita, M.; Hara, K.; Fukuoka, A. *J. Mol. Catal. A: Chem.* **2012**, *352*, 81–85. (h) Engle, K. M.; Thuy-Boun, P. S.; Dang, M.; Yu, J. -Q. *J. Am. Chem. Soc.* **2011**, *133*, 18183–18193. (i) Shintani, R.; Takeda, M.; Soh, Y. -T.; Ito, T.; Hayashi, T. *Org. Lett.* **2011**, *13*, 2977–2979. (j) Wu, X.-F.; Neumann, H.; Beller, M. *Adv. Synth. Catal.* **2011**, *353*, 788–792. (k) Li, M.; Wang, C.; Ge, H. *Org. Lett.* **2011**, *13*, 2062–2064.

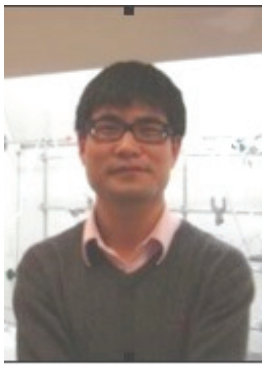
7. Vedejs, E.; Fields, S. C.; Hayashi, R.; Hitchcock, S. R.; Powell, D. R.; Schrimpf, M. R. *J. Am. Chem. Soc.* **1999**, 121, 2460–2470.

G. K. Surya Prakash is a Professor of Chemistry and the Director of the Loker Hydrocarbon Research Institute at the University of Southern California holding the George A. and Judith A. Olah Nobel Laureate Chair in Hydrocarbon Chemistry with research contributions and interests in selective fluorination methods, new synthetic methods, mechanistic studies of organic reactions, electrochemistry, superacid chemistry and hydrocarbon chemistry. He has received many honors and accolades including 2004 ACS award for Creative Work in Fluorine Chemistry, the 2006 George A. Olah Award in Hydrocarbon or Petroleum Chemistry and the 2006 Richard C. Tolman Award.



Fabrizio Pertusati was born in Turin (Italy) in 1972. He did his undergraduate work at the Turin University on surfactant chemistry and after three years in PCB industry obtained his doctorate in organic chemistry at Cardiff University. After a postdoctoral work at Emory University with Professor Fred Menger, he then joined the Prakash group at the Loker Hydrocarbon Institute, University of Southern California, in 2008 working on organotrifluoroborate chemistry. He is currently at the School of Pharmacy at Cardiff University working in the laboratory of Professor Chris McGuigan on the diastereoselective synthesis of phosphoroamidate prodrugs as anti-HCV agents.

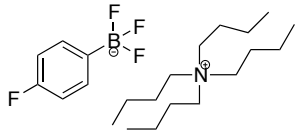
Parag V. Jog was born in Pune, India in 1976. He received his Bachelors (Chemistry, 1996) and Masters (Analytical Chemistry, 1998) at Bombay University. He earned his Ph.D. from Michigan Technological University in organo-sulfur chemistry (Prof. Dallas K. Bates, 2005). After doing his postdoctoral research at University of Urbana-Champaign (Synthetic Ion Channels, Prof. Mary S. Gin) and California Institute of Technology (Conformational Analysis of small organic molecules using NMR, Prof. John D. Roberts), he is currently working at University of Southern California under Prof. G. K. Surya Prakash in the field of organo-fluorine chemistry, specifically, developing direct trifluoromethylation methods.



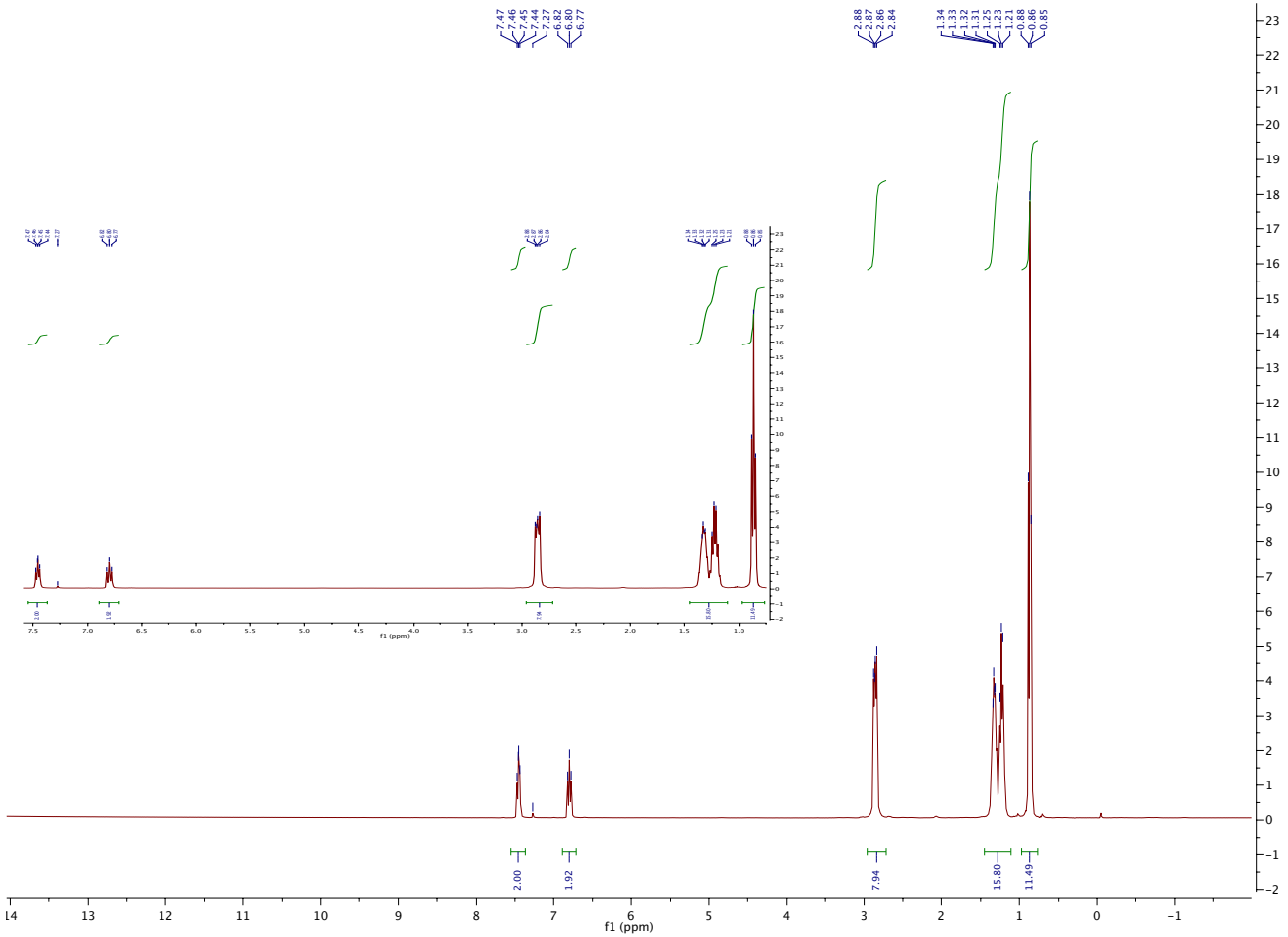
Changming Qin was born in Shandong, China in 1982. He did his undergraduate work at Ludong University on the preparation of polymer nanocomposites under the guidance of Prof. Yucai Hu. He obtained his Masters degree in organic chemistry in 2008 at Wenzhou University under the supervision of Prof. Huayue Wu, working on palladium-catalyzed transformations of aryl boronic acids. After graduation, he worked at the University of Hong Kong with Prof. Chi-Ming Che in 2008-2009, and then joined Prof. Huw Davies' group at Emory University in 2010. His current research is focused on design and synthesis of chiral dirhodium catalysts and their application in novel asymmetric carbeniod transformations.

OS-#3377

^{1}H NMR (400 MHz, $CDCl_3$)

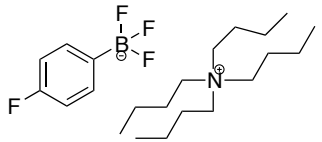


Tetrabutylammonium (4-fluorophenyl)trifluoroborate

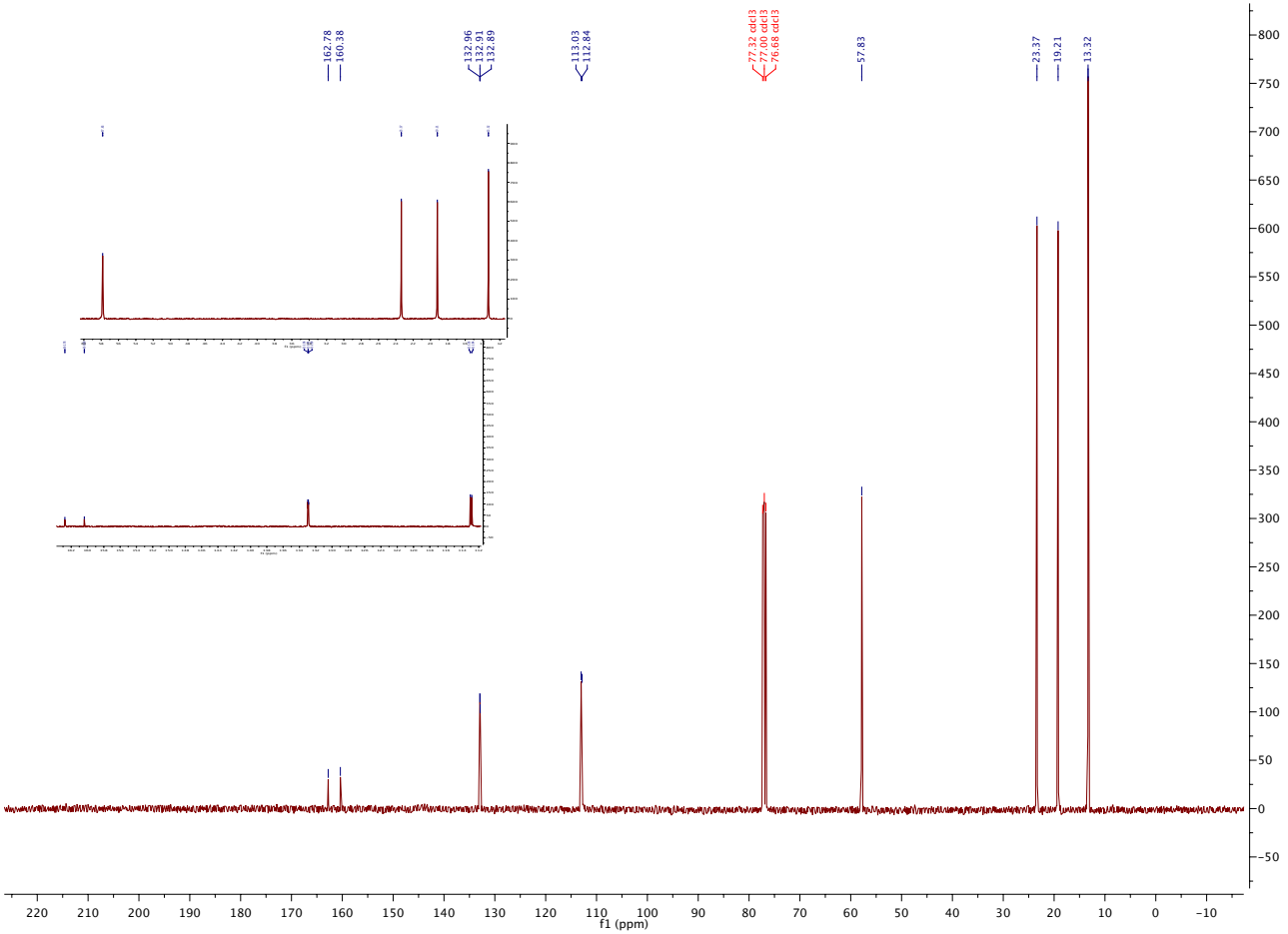


OS-#3377

^{13}C NMR (100 MHz, $CDCl_3$)

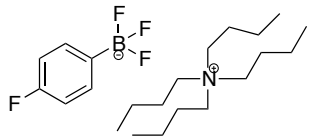


Tetrabutylammonium (4-fluorophenyl)trifluoroborate



OS-#3377

^{11}B NMR (192 MHz, $CDCl_3$)



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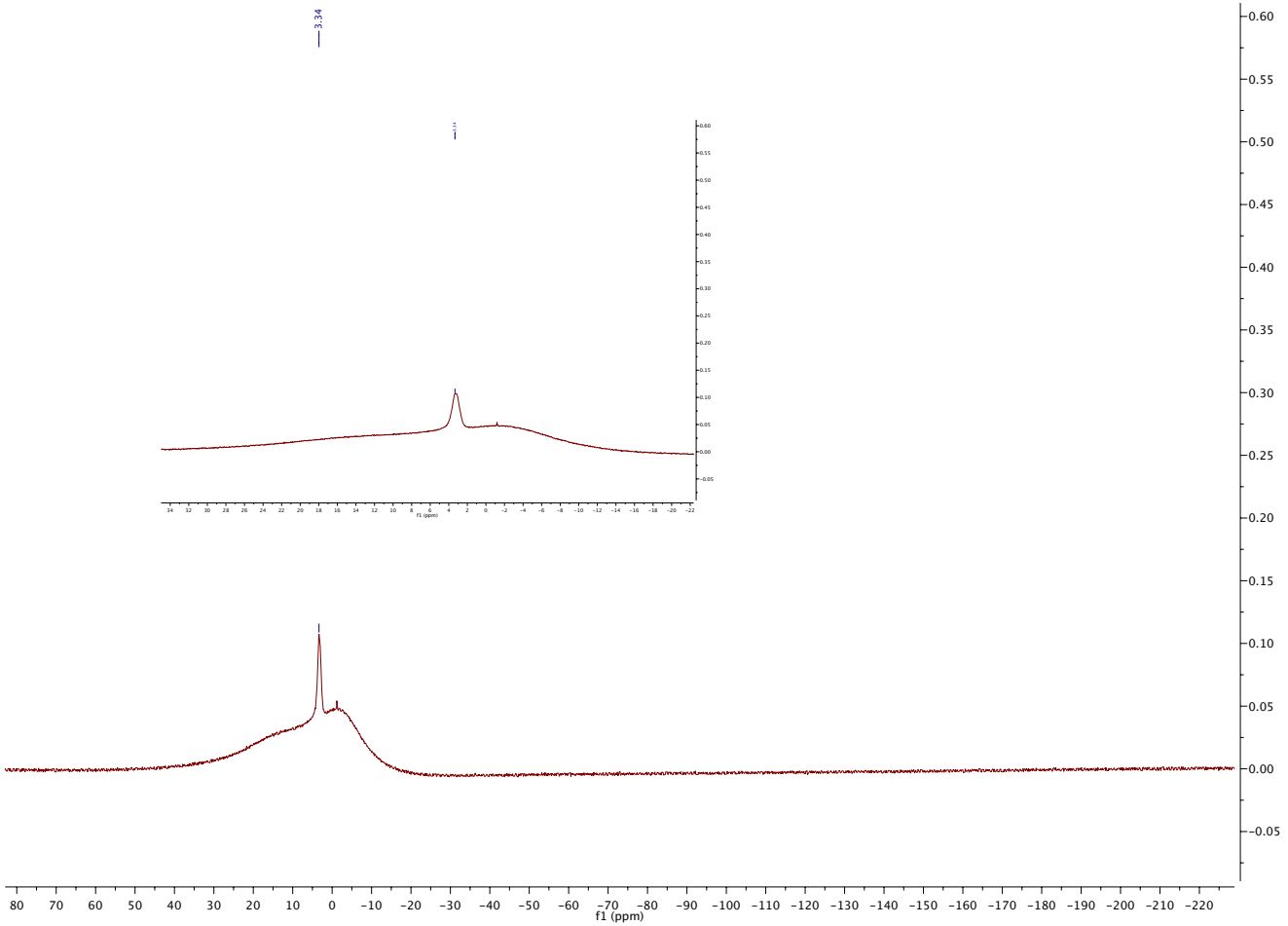
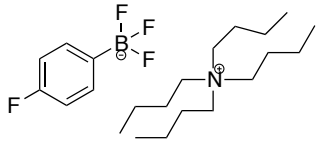


OS-#3377

^{19}F NMR (376 MHz, $CDCl_3$)



Tetrabutylammonium (4-fluorophenyl)trifluoroborate