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Practical Radical Cyclizations with Arylboronic Acids and Trifluoroborates

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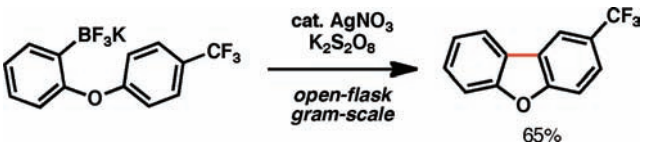
ABSTRACT



Practical radical cyclizations using organoboronic acids and trifluoroborates take place in water, open to air, and in a scalable fashion employing catalytic silver nitrate and stoichiometric potassium persulfate. Both Pschorr-type cyclizations and tandem radical cyclization/trap cascades are described, illustrating the utility of these mild conditions for the generation of polycyclic scaffolds.

Radical cyclizations have proven to be a valuable tactic widely employed in organic synthesis.[1] Often, however, the appeal they exhibit in generating molecular complexity is attenuated by the drawback of using toxic tin species and inert (oxygen-free) reaction conditions. In the case of aryl-centered radicals, diazonium salts serve as one means for entry into radical processes, although their preparation and handling offset their synthetic value. Among the recent developments[2] aimed at circumventing such drawbacks, the recently discovered Minisci-type reactivity of organoboronic acids[3] and trifluoroborates[3b,4] (Figure 1) addresses many of these. Indeed, the conditions involve the use of ubiquitous boronic acids and cheap inorganic salts (silver nitrate and potassium persulfate), can be performed in an open-flask without recourse to high temperatures, and can be safely conducted on gram scale. In this letter, the chemistry of aryl radicals derived from boronic acids and trifluoroborates is explored in an intramolecular setting.

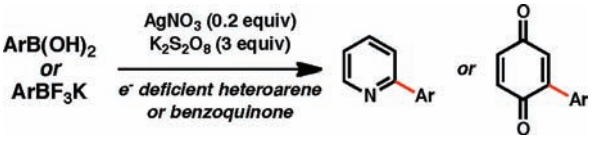


Figure 1. Previously reported intermolecular C–H functionalization of heteroarenes[3a] and benzoquinones.[3b]

The preparation of tricyclic scaffolds such as dibenzofurans and fluorenones has received significant attention,

(1) (a) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon Press: New York, 1986. (b) Abeywickrema, A. N.; Beckwith, A. L. J. *Tetrahedron Lett.* **1986**, *27*, 109–112. (c) Barton, D. H. R.; da Silva, E.; Zard, S. Z. *J. Chem. Soc., Chem. Commun.* **1988**, 285–287. (d) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237–1286. (e) Thebtaranonth, C.; Thebtaranonth, Y. *Cyclization Reactions*; CRC Press: Boca Raton, FL, 1994; pp 77–167. (f) *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001. (g) *Topics in Current Chemistry: Radicals in Synthesis I*; Gansauer, A., Ed.; Springer: Berlin, 2006; Vol. 263. (h) *Topics in Current Chemistry: Radicals in Synthesis II*; Gansauer, A., Ed.; Springer: Berlin, 2006; Vol. 264.

(2) (a) Devin, P.; Fensterbank, L.; Malacria, M. *Tetrahedron Lett.* **1999**, *40*, 5511–5514. (b) Heinrich, M. R.; Kirchstein, M. D. *Tetrahedron Lett.* **2000**, *47*, 2115–2118. (c) Kita, Y.; Nambu, H.; Ramesh, N. G.; Anilkumar, G.; Matsugi, M. *Org. Lett.* **2001**, *3*, 1157–1160. (d) Gagosz, F.; Zard, S. Z. *Org. Lett.* **2002**, *4*, 4345–4348. (e) Khan, T. A.; Tripoli, R.; Crawford, J. J.; Martin, C. G.; Murphy, J. A. *Org. Lett.* **2003**, *5*, 2971–2974. (f) Bowman, W. R.; Storey, J. M. D. *Chem. Soc. Rev.* **2007**, *36*, 1803–1822. (g) Biechy, A.; Zard, S. Z. *Org. Lett.* **2009**, *11*, 2800–2803. (h) Wang, B.; Ramirez, A. P.; Slade, J. J.; Morken, J. P. *J. Am. Chem. Soc.* **2010**, *132*, 16380–16382. (i) Sorin, G.; Martinez Mallorquin, R.; Contie, Y.; Baralle, A.; Malacria, M.; Goddard, J.-P.; Fensterbank, L. *Angew. Chem., Int. Ed.* **2010**, *49*, 8721–8723. (j) Braun, M.-G.; Zard, S. Z. *Org. Lett.* **2011**, *13*, 1230–1233.

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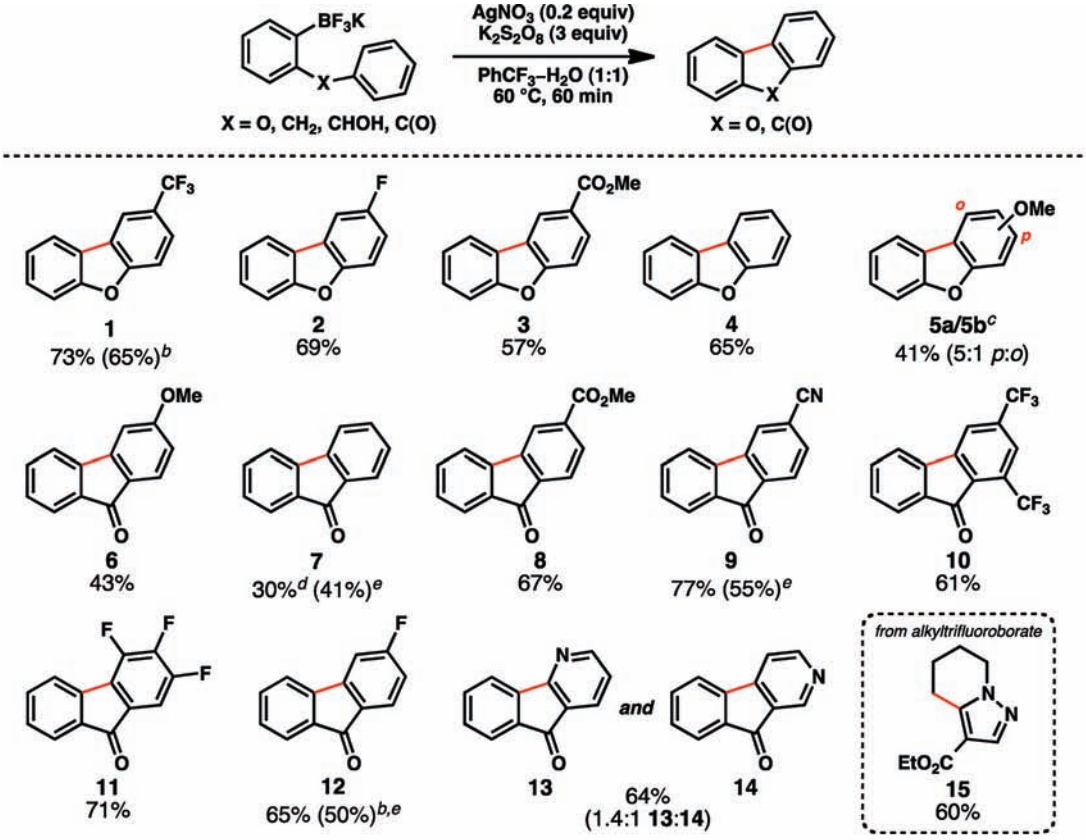


[a]Aryltrifluoroborate (0.1 mmol), $AgNO_3$ (0.02 mmol), $K_2S_2O_8$ (0.3 mmol), $PhCF_3$–H_2O (1:1 v/v, 1.0 mL), 60 °C, 60 min; yields for chromatographically and spectroscopically pure products. [b]Yield of reaction performed on gram-scale. [c]Inseparable mixture. [d]Yield from X = CH_2. [e]Yield from X = CHOH.

Figure 2. Pschorr-type cyclization using organotrifluoroborates as radical precursors.[a]

owing to their presence in natural products and compounds of medicinal interest.[5] One of the earliest means for access to such molecules involves the radical-based method known as the Pschorr cyclization,[6] which dates back to 1896. This powerful transformation relies upon an arenediazonium salt as a radical precursor and typically employs superstoichiometric iron or copper salts for radical generation. Figure 2 illustrates the invention and scope of a "borono-Pschorr" reaction that obviates the need for potentially dangerous arenediazonium salt preparation. Additionally, this method complements Pd-mediated processes recently described by Harvey,[7a] Fagnou,[7b] and Glorius.[7c] A variety of functional groups are tolerated, such as nitriles, esters, and Lewis basic heteroatoms, and products are obtained in synthetically useful yields. Concomitant benzylic oxidation is observed, and this can be exploited to increase step economy. For instance, fluorenone (**7**) was obtained from a diarylmethane precursor under the standard conditions.

The boronic acid is installed onto the substrate through lithium−halogen exchange followed by borate trapping,[8] or by transition-metal-mediated borylation.[9] For a substrate bearing a pinacol boronate ester, conversion to the trifluoroborate salt is accomplished by treatment with

(5) (a) Wang, W.; Snieckus, V. *J. Org. Chem.* **1992**, *57*, 424–426. (b) Cone, M. C.; Melville, C. R.; Gore, M. P.; Gould, S. J. *J. Org. Chem.* **1993**, *58*, 1058–1061. (c) Jones, W. D., Jr.; Ciske, F. L. *J. Org. Chem.* **1996**, *61*, 3920–3922. (d) Kaniwa, K.; Ohtsuki, T.; Yamamoto, Y.; Ishibashi, M. *Tetrahedron Lett.* **2006**, *47*, 1505–1508. (e) Yu, M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2008**, *130*, 2783–2785. (f) Ye, Y. Q.; Koshino, H.; Onose, J.; Yoshikawa, K.; Abe, N.; Takahashi, S. *Org. Lett.* **2009**, *11*, 5074–5077. (g) Kemnitzer, W.; Sirisoma, N.; Jiang, S.; Kasibhatla, S.; Crogan-Grundy, C.; Tseng, B.; Drewe, J.; Cai, S. X. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1288–1292. (h) Teng, H.; Thakur, G. A.; Makriyannis, A. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 5999–6002.

(6) (a) Pschorr, R. *Ber.* **1896**, *29*, 496–501. (b) Leake, P. H. *Chem. Rev.* **1956**, *56*, 27–48. (c) Cano-Yelo, H.; Deronzier, A. *J. Chem. Soc., Perkin Trans. 2* **1984**, 1093–1098. (d) Wassmundt, F. W.; Kiesman, W. F. *J. Org. Chem.* **1995**, *60*, 196–201. (e) 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*, 5438–5346. (f) Moorthy, J. N.; Samanta, S. *J. Org. Chem.* **2007**, *72*, 9786–9789.

(7) (a) ArOTf, cat. $PdCl_2(Ph_3P)_2$, 145 °C: Wang, J.-Q.; Harvey, R. G. *Tetrahedron* **2002**, *58*, 5927–5931. (b) ArH, cat. $Pd(OAc)_2$, PivOH, 120 °C: Liegault, B.; Lee, D.; Huestis, M. P.; Stuart, D. R.; Fagnou, K. *J. Org. Chem.* **2008**, *73*, 5022–5028. (c) $ArCO_2H$, cat. $Pd(TFA)_2$, Ag_2CO_3, 150 °C: Wang, C.; Piel, I.; Glorius, F. *J. Am. Chem. Soc.* **2009**, *131*, 4194–4195.

(8) Li, W.; Nelson, D. P.; Jensen, M. S.; Hoerrner, R. S.; Cai, D.; Larsen, R. D.; Reider, P. J. *J. Org. Chem.* **2002**, *67*, 5394–5397.

(9) Billingsley, K. L.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 5589–5591.

aqueous KHF_2 followed by repeated evaporation with MeOH−H_2O (1:1 v/v) to remove pinacol.[10]

Given the durability of pinacol boronate esters under a variety of conditions, we secured (as proof-of-principle) three examples of fluorenone synthesis utilizing a bifunctional reagent, 2-formylphenylboronic acid pinacol ester (Figure 3). Direct addition of an aryl Grignard, followed by treatment with aqueous KHF_2, provided radical cyclization precursors which, upon exposure to $Ag^+/S_2O_8^{2-}$, furnished the corresponding fluorenones. Such a strategy can prove useful in situations where a masked radical precursor is carried through subsequent steps and then unmasked for the radical cyclization step.

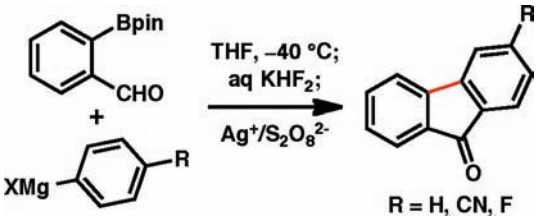
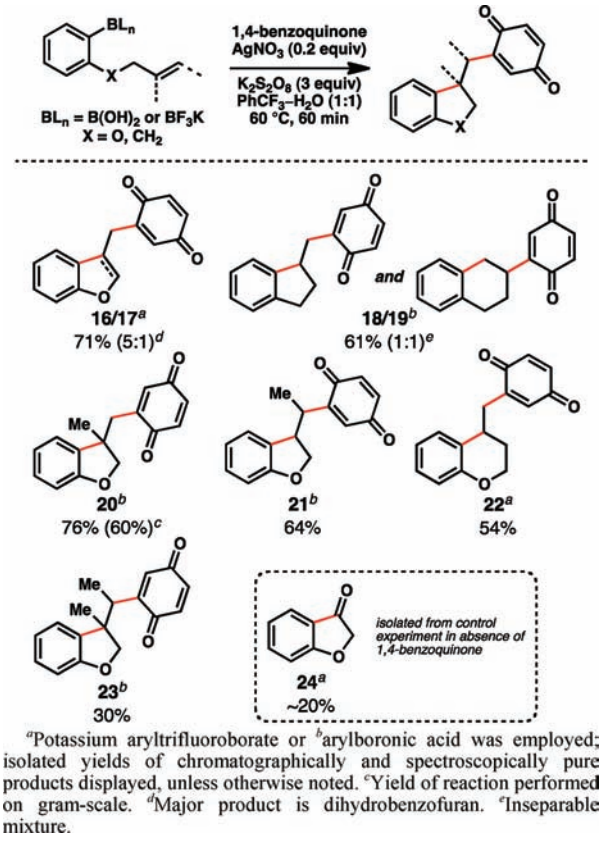


Figure 3. Three-step sequence to fluorenones.

Vicinal olefin difunctionalization, in which multiple carbon−carbon bonds are forged in concert, is a valuable tactic for complexity generation in synthesis.[11] Such a process is exemplified by the results in Figure 4. In this tandem radical cyclization/benzoquinone trap protocol, 5-exo, 6-exo, and 6-endo radical cyclizations are combined with an intermolecular radical capture.[12] The trend in isolated yields (for products **16**−**23**) suggests that increasing degrees of olefin substitution attenuate the efficiency of the tandem process. Importantly, this protocol stands in contradistinction to the more classic tributyltin hydride based radical cyclization and the palladium-catalyzed Heck-type process, both of which were found to be incompatible with the use of benzoquinone in this context.[13]

Incidentally, we have isolated benzofuranone (**24**) in a control experiment (in the absence of 1,4-benzoquinone). In lieu of a competent radical trapping agent, oxygen from the air intercepts the radical intermediate. This,



[a]Potassium aryltrifluoroborate or [b]arylboronic acid was employed; isolated yields of chromatographically and spectroscopically pure products displayed, unless otherwise noted. [c]Yield of reaction performed on gram-scale. [d]Major product is dihydrobenzofuran. [e]Inseparable mixture.

Figure 4. Tandem radical cyclization/trap using 1,4-benzoquinone as the terminating radicophile.

accompanied by benzylic C−H oxidation of the substrate, leads to oxidative carbon−carbon bond cleavage.[14,15]

While the results described in this letter demonstrate a capacity for performing open-flask radical cyclizations, it is important to note its limitations. Although high chemoselectivity has been observed under these biphasic conditions,[3] persulfate ($S_2O_8^{2-}$) is a strong oxidizing agent and therefore motifs such as benzylic C−H bonds and vicinal diols may not be compatible. Radical ring closure and intermolecular radicophile capture must outpace the capture of oxygen (O_2) or H-abstraction (either from an intramolecular donor or from solvent). Such considerations must be taken into account when planning a reaction using the $Ag^+/S_2O_8^{2-}$ system.[16]

The mechanism by which an organoboronic acid gives rise to a reactive radical species upon exposure to $Ag^+/S_2O_8^{2-}$ will be the subject of future work. The working hypothesis involves (1) Ag^+-mediated decomposition of

(10) (a) Darses, S.; Michaud, G.; Genet, J.-P. *Eur. J. Org. Chem.* **1999**, 1875–1883. (b) Bagutski, V.; Ros, A.; Aggarwal, V. K. *Tetrahedron* **2009**, *65*, 9956–9960.

(11) Ho, T.-L. *Tandem Organic Reactions*; Wiley-Interscience: New York, 1992; pp 398−415.

(12) Other examples of quinones in radical capture: (a) Demchuk, O. M.; Pietrusiewicz, K. M. *Synlett* **2009**, *7*, 1149–1153. (b) Luthy, M.; Darmency, V.; Renaud, P. *Eur. J. Org. Chem.* **2011**, 547–552.

(13) A standard Bu_3SnH reaction was performed using 1-(allyloxy)-2-bromobenzene in the presence of 1,4-benzoquinone. Analysis by TLC and ^1H NMR showed only recovered bromide and no cyclization product. Similar results were obtained upon performing a Pd-catalyzed Heck cyclization reaction using 1-(allyloxy)-2-bromobenzene in the presence of 1,4-benzoquinone.

(14) Benzofuranone was not observed in reactions containing 1,4-benzoquinone.

(15) It is known that persulfate can cleave vicinal diols: Kumar, A. *J. Am. Chem. Soc.* **1981**, *103*, 5179–5182.

(16) (a) Snyder, H. R.; Kuck, J. A.; Johnson, J. R. *J. Am. Chem. Soc.* **1938**, *60*, 105–111. (b) Lewin, A. H.; Cohen, T. *J. Org. Chem.* **1967**, *32*, 3844–3850. (c) Minisci, F.; Citterio, A.; Giordano, C. *Acc. Chem. Res.* **1983**, *16*, 27–32. (d) Karady, S.; Cummins, J. M.; Dannenberg, J. J.; del Rio, E.; Dormer, P. G.; Marcune, B. F.; Reamer, R. A.; Sordo, T. L. *Org. Lett.* **2003**, *5*, 1175–1178.

(17) A similar proposal has previously been put forth in which phenylcarbonyloxy radical (generated in situ) attack at boron leads to carbon−boron bond homolysis: Cadot, C.; Cossy, J.; Dalko, P. I. *Chem. Commun.* **2000**, 1017–1018.

$S_2O_8^{2-}$ to give $SO_4^{\bullet-}$, (2) attack at boron by $SO_4^{\bullet-}$, and (3) carbon–boron bond homolysis.[17]

We emphasize that this open-air[18] radical chemistry does not involve high temperatures and avoids the use of toxic and/or expensive metals. Additionally, this method circumvents recourse to potentially hazardous entities such as arenediazonium salts,[19] and can be safely conducted on gram scale.[20,21] With the emergence of noncryogenic[22] and C–H borylation[23] protocols to complement classic methods for preparing organoboron species, we anticipate increased use of boronic acids and trifluoroborates as radical precursors in synthesis.

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Supporting Information Available. Experimental procedures, copies of all spectral data, and full characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

(18) It was found that conducting these $Ag^+/S_2O_8^{2-}$ reactions under a nitrogen atmosphere did not result in an appreciable difference in yield.

(19) Arenediazonium salts are also utilized in Meerwein arylation of electron-deficient olefins: Heinrich, M. R.; Wetzel, A.; Kirchstein, M. *Org. Lett.* **2007**, *9*, 3833–3835. We have performed a vicinal difunctionalization of acrylonitrile employing 4-methoxyphenylboronic acid and TEMPO, obtaining the oxyarylation product in 50% yield. See Supporting Information and:Dickschat, A.; Studer, A. *Org. Lett.* **2010**, *12*, 3972–3974.

(20) **Representative experimental procedure for Pschorr-type cyclization:** To a solution of aryltrifluoroborate (0.1 mmol, 1.0 equiv) in trifluorotoluene (0.5 mL) and water (0.5 mL) was added silver(I) nitrate (0.02 mmol, 0.2 equiv). Potassium persulfate (0.3 mmol, 3.0 equiv) was added in one portion, and the reaction mixture was stirred vigorously at 60 °C for 60 min. The mixture was extracted with EtOAc (5 × 3 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by silica gel chromatography (hexanes/EtOAc) afforded the product.

(21) **Representative experimental procedure for tandem radical cyclization/trap:** To a solution of 1,4-benzoquinone (0.1 mmol, 1.0 equiv) in trifluorotoluene (0.5 mL) and water (0.5 mL) were added arylboronic acid (0.15 mmol, 1.5 equiv), silver(I) nitrate (0.02 mmol, 0.2 equiv), and potassium persulfate (0.3 mmol, 3.0 equiv). The reaction mixture was stirred vigorously at 60 °C for 60 min, diluted with EtOAc (3 mL), and washed with 5% aqueous $NaHCO_3$ (3 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 3 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by silica gel chromatography (hexanes/Et_2O) afforded the product.

(22) Molander, G. A.; Trice, S. L. J.; Dreher, S. D. *J. Am. Chem. Soc.* **2010**, *132*, 17701–17703.

(23) (a) Liskey, C. W.; Wei, C. S.; Pahls, D. R.; Hartwig, J. F. *Chem. Commun.* **2009**, *37*, 5603–5605. (b) Chotana, G. A.; Vanchura, B. A., II.; Tse, M. K.; Staples, R. K.; Maleczka, R. E., Jr.; Smith, M. R., III. *Chem. Commun.* **2009**, *37*, 5731–5733. (c) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890–931.