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Base-Promoted Protodeboronation of 2,6-Disubstituted Arylboronic Acids

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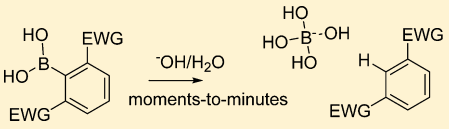
Supporting Information

ABSTRACT: Facile based promoted deboronation of electron-deficient arylboronate esters was observed for arylboronates containing two ortho electron-withdrawing group (EWG) substituents. Among 30 representative boronates, only the diortho-substituted species underwent facile C−B fission in aqueous basic conditions (200 mM hydroxide). These results provide fundamental insight into deboronative mechanisms with implications for cross-coupling reactions, regioselective deuteration/tritiation for isotopic labeling, and the design of new ^{18}F-trifluoroborate radioprosthetics.



Boronic acids have been explored for diverse aims including artificial lectins,[1−3] precursors in ^{11}C-labeling,[4] applications in ^{18}F-ArBF$_3^-$ imaging agents,[5,6] and as substrates in transition-metal-catalyzed C−C bond cross-coupling reactions.[7−10] In particular, Suzuki and Miyaura showed the versatility of arylboronic acids to form carbon−carbon bonds.[11,12] Cross-coupling reactions between aryl boronic acids and aryl halides are often noted for high yields and clean conversion under basic conditions.[13] Variable aryl substitution may increase or decrease relative rates and yields[14] and have been featured in many studies.[9,15−20] Typically, palladium-catalyzed cross-coupling reactions are performed in water or mixed aqueous−organic solvents that include 2 equiv of base, e.g. Ba(OH)$_2$, NaOH, K$_2$CO$_3$, and K$_3$PO$_4$.[10,21−23] With the corresponding aryltrifluoroborate, base, as well as silica,[24] is added to facilitate defluoridation[25] whereas, with an arylboronate, base is used to enhance C−B bond scission with concomitant aryl insertion into the metal catalyst.[26] The mechanism of cross-coupling is now well understood to include oxidative addition, transmetalation, and reductive elimination during which the C−B bond breaks so that the aryl enters the catalytic cycle.[10,11,15] Yet any uncontrolled C−B bond scission that occurs without concomitant catalyst loading will lead to unproductive protodeboronation. Hence understanding molecular components that lead to C−B bond scission is of paramount importance to designing catalytic C−C cross-coupling processes.[9,10] Besides synthetic applications, such understanding has ramifications for other applications in materials and designing boron-based ^{18}F-radioprosthetics (*vide infra*).

Despite a number of studies directed at understanding the mechanism of metal catalyzed cross-couplings,[10,17] few studies have described the stability of the C−B bond under conditions used in catalysis. In contrast, rapid, acid-catalyzed protodeboronation of *p*-anisoleboronic acid in 3% H$_2$SO$_4$ was reported 50 years ago.[27] Kinetic isotope effects suggested rate-limiting arene ipso-protonation followed by deboronation.[27] A Hammett analysis showed that EWG modifications retard acid-catalyzed protodeboronation.[28] Both general acid and specific base (OH$^-$) catalyzed protodeboronation had been inferred from the reaction of 2,6-dimethoxyphenylboronic acid at 90−150 °C in malonic acid/malonate buffer pH 2−6.7. Nevertheless, protodeboronation rates at pH 6.7 and at 90 °C with a single electron-withdrawing group (EWG) group at any position were generally slow ($k_{obs} \approx 10^{-7}$ min^{-1}), with the exception of 2-fluoro- and 2,6,-dimethoxyphenyl-boronic acid: $k_{obsd} \approx 10^{-5}$ min^{-1} and 1.8×10^{-5} min^{-1} respectively. Notably, single EWG substitution at various positions (o, m, p) retarded deboronation.[27] Yet these early studies never examined reaction under alkaline conditions that are commonly used in Suzuki−Miyaura reactions. Furthermore, no other diortho arylboronic or heteroarylboronic acid was examined. Indeed, base-mediated deboronation of electron-deficient aryl systems has little precedent. Interest in EWG-modified arylboronic acids now includes use as *in vivo* stable ^{18}F-ArBF$_3$ radioprosthetics that do not liberate fluoride due to both steric and electronic effects at the ortho positions.[29] Here we show that the same EWG-substituents that retard B−F bond solvolysis greatly enhance base-mediated C−B bond scission at ambient temperature.

Our interest in designing boronates for aqueous ^{18}F-fluoride capture initially led us to examine the rate of fluoridation of *p*-anisole-boronic acid in 1 M KHF$_2$ under acidic conditions (pH 2, HF-as-buffer). Under these conditions fluoridation is quantitative on mixing. At pH ≈ 2, the *p*-anisole-BF$_3^-$ appears as a broad singlet (−137 ppm) due to rapid exchange with fluoride atoms.[29] Unexpectedly, tetraborate (BF$_4^-$) rapidly appears with concomitant loss of *p*-anisole-BF$_3^-$. Under these conditions, the deborylation reaction is complete within 13 min.

Acid catalyzed deboronation likely occurs via ipso-protonation of the aryltrifluoroborate followed by loss of BF$_3$, which fluoridates in the presence of excess fluoride; however, it is possible that this proceeds via direct loss of B(OH)$_3$, followed by conversion to BF$_4^-$ (Figure 1, Scheme 1).

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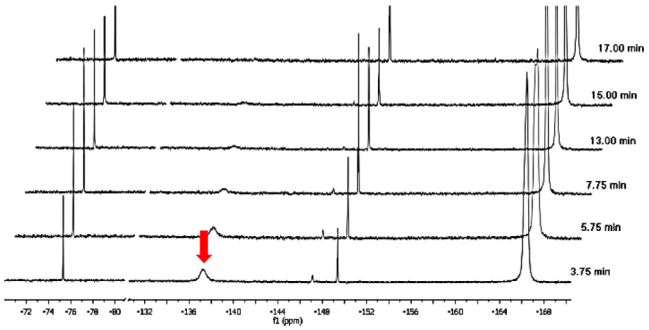
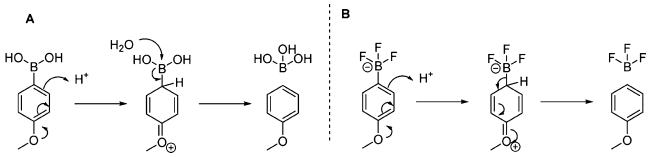


Figure 1. ^{19}F NMR spectroscopy of loss of the $ArBF_3^-$ and linear increase in BF_4^-; CF_3CH_2OH (−75 ppm), *p*-anisole-BF_3^- (−137 ppm) denoted by red arrow; BF_4^- (−149 ppm), HF (−165 ppm), borosilicate etching appears at −147 ppm.

Scheme 1. (A) Proposed Mechanism for Protodeboronation of *p*-Anisoleboronic Acid; (B) Proposed Mechanism for the Aryltrifluoroborate

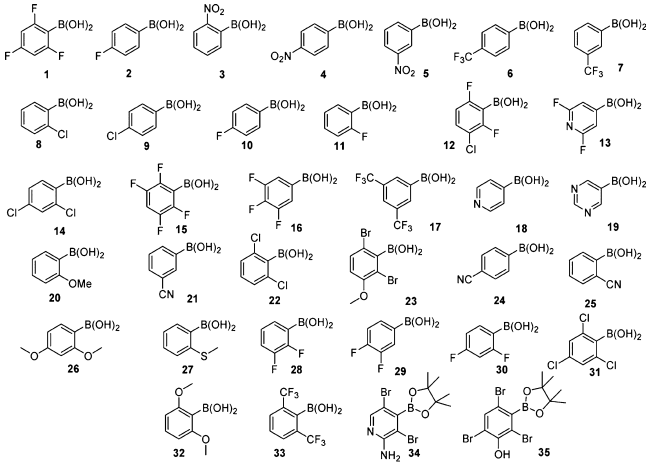


This observation recapitulates previous reports on acid catalyzed protodeboronation, yet deboronation of the *p*-anisole-BF_3^- occurs more rapidly than previously reported. One explanation is that the BF_3^- may be a better leaving group than the $B(OH)_3^-$ or that fluoride may act as a nucleophile or base thereby promoting deboronation. Distinguishing these mechanisms is difficult due to the extreme lability of the B−F bonds under these conditions.[29] Under the same conditions no acid-catalyzed protodeboronation was observed for phenytrifluoroborate (data not shown). This suggests that only EDG-modified $ArBF_3^-$s readily undergo acid catalyzed protodeboronation. By contrast, neither phenylboronic acid nor *p*-anisoleboronic acid deboronated at pH 12, room temperature (data not shown).

Because B−F bonds in EDG-modified $ArBF_3^-$s solvolyze at immeasurably rapid rates,[29] we have focused on EWG-modified arylboronic acids, whose corresponding trifluoroborates solvolyze slowly making them useful for ^{18}F-labeling.[5,6,29−34] In the course of this work, we have observed significant amounts of protodeboronated arene in commercially available EWG-modified arylboronic acid precursors, and in those we synthesized without precedent.[6,31,34] While *a priori* this could be due to acid or base mediated protodeboronation, because EWG-groups are known to retard acid-catalyzed protodeboronation, along with the fact that in our hands all EWG-arylboronic acids were stable in 0.1 M HCl over a period of days, we turned our attention to reaction with a base.

Commercially available 2,4,6-trifluorophenyl-boronic acid (compound **1**, Table 1) was reacted in aqueous 200 mM NaOH. A ^{19}F NMR spectrum revealed conversion of free boronic acid with two peaks (2:1) to trifluorobenzene, which appears as a singlet (Figure 2B). When the reaction was repeated in the presence of KOD/D_2O, 1D-trifluorobenzene is produced (Figure 2C and Scheme 2).

Table 1. Structures of Boronic Acids 1−35 That Were Tested



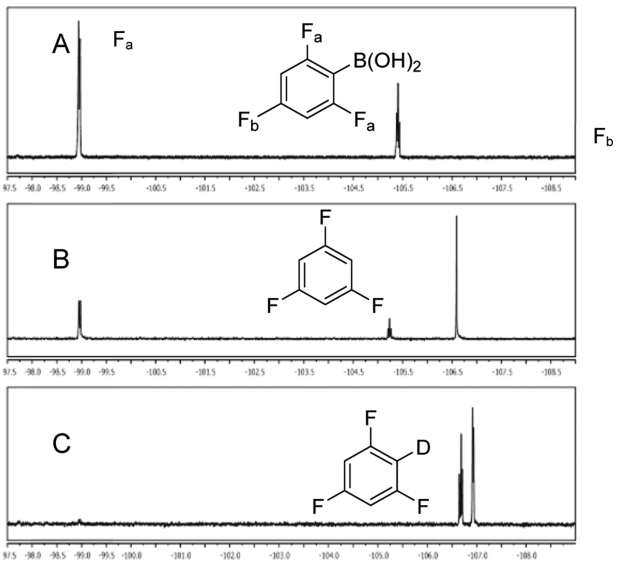


Figure 2. (A) ^{19}F NMR spectrum of 2,4,6-trifluorophenylboronic acid **1**; (B) ^{19}F NMR of crude reaction of **1** in base resulting in 80% completion giving 1,3,5-trifluorobenzene that appears as a singlet; (C) ^{19}F NMR spectrum of 2-D-1,3,5-trifluorobenzene that is produced by reaction in KOD/D_2O.

Scheme 2. Deuteration of 1 Following Deboronation

Surprisingly, deboronation of **1** is quantitative within 20 min at room temperature. Figure 3 shows an HPLC run that indicates the rapidity of protodeboronation.

Initial rates were linearly proportional with hydroxide concentration from 50 to 200 mM (data not shown) suggesting that the reaction is first order in both base and arylboronate. As the boronic acid is likely hydrated as the arylborate, we suggest a mechanism (Scheme 3) involving deprotonation of the boronate that undergoes C−B bond fission with concomitant arene protonation, thereby regenerating hydroxide to give tetraborate.

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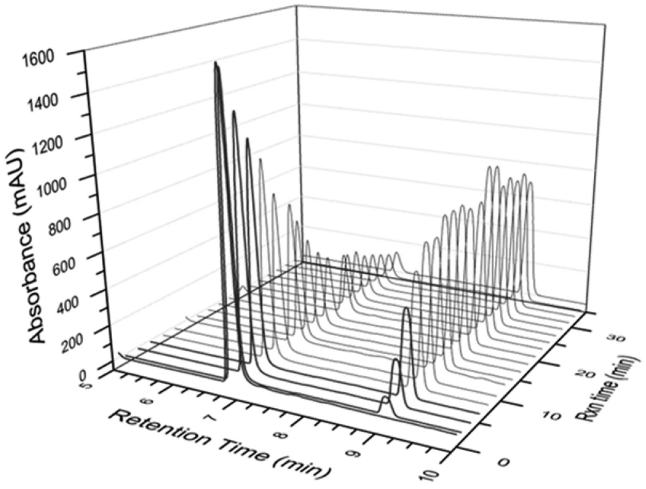
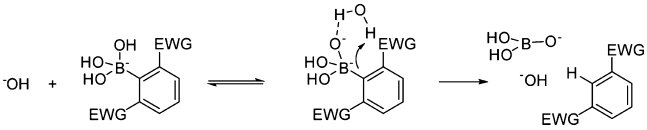


Figure 3. Kinetic profile of protodeboronation of **1** analyzed by HPLC; data are fitted to a first-order rate equation (k_{obs} = 0.074 min^{-1}; see Table 2).

Scheme 3. Mechanism for Base Mediated Protodeboronation



Given the impressive rapidity of this reaction, we tested 34 other arylboronic acids (Table 1), of which only eight showed significant reactivity: **12**, **15**, **22**, **23**, **31**, **33**, **34**, and **35**. Time-dependent deboronation in 200 mM KOH provided pseudo-first-order rate constants for each deboronation reaction (see Supporting Information); compounds **15** and **35** underwent protodeboronation too rapidly to measure, while, in the case of **35**, further degradation to unidentified products was also observed.

Of these EWG arylboronates, including electron-deficient heteroarylboronates, e.g. **13** and **19**, only diortho-substituted ones rapidly protodeboronated (Table 2). Observed pseudo-first order rate constants are listed in Table 2. Taken together, ortho-steric and electronic effects greatly enhance the rate of protodeboronation.

While it is difficult to separate steric from electronic effects of ortho substituents,[35−37] a purely steric argument is unlikely to apply as the relatively bulky 2,6-dimethoxyphenylboronic acid, **32**, did not react under these conditions. By contrast, EWGs such as halogens and trifluoromethyl groups are needed. The trifluorophenylboronic acid is less reactive than the trichloro analogue, suggesting that added steric bulk from the chlorine atoms contribute to higher reactivity despite the greater inductive effects of fluorine substituents. Alternatively the greater mesomeric effect of fluorine compared to that of chlorine might also contribute to a lower reactivity. The tetrafluorinated species, **15**, with two additional fluorine atoms at remote positions 3 and 5 was so reactive that a rate constant could not be measured. Strikingly, **15**, in distilled water/DMSO (pH ∼7) decomposed within a day although solutions of the same in very dry DMSO were indefinitely stable (data not shown). Interestingly, a single EWG ortho substituent does not result in deboronation (e.g., **3**, **20**, **25**), even in the cases of heteroarylboronic acids that are considerably more electron-deficient. Hence this reaction appears to be limited to various diortho-EWG-substituted arylboronates, even when considering heteroaryl species.

Table 2. Observed Rate Constants of Base-Labile Boronic Acids Featured in Table 1

compound	k_{obs} (min^{-1})
35	too fast
15	too fast
31	0.88
34	0.47
23	0.39
12	0.32
22	0.19
33	0.10
1	0.074

Using ESI mass spectrometry, we found no evidence of phenolates, which would have formed via a benzyne intermediate following the action of $^{-}$OH. Therefore, C−B fission likely accompanies σ-bond protonation. Alternatively, if an aryl anion forms it protonates more rapidly than ortho halide elimination.

These results have important implications for Suzuki−Miyaura cross-coupling reactions involving disubstituted arylboronic acids and aryltrifluoroborates. We previously showed that EWG-modified $ArBF_3$s are solvolytically stable and that ortho-substitution retards solvolytic loss of fluoride through a combination of steric and electronic effects.[29] Nevertheless, EWG-modified aryltrifluoroborates are reported to undergo Suzuki−Miyaura cross-coupling in reasonable yields.[15,16] One explanation may be that while 2,6-disubstituted aryltrifluoroborates release fluoride slowly, once solvolyzed they may rapidly undergo C−B fission to supply the metal catalyst with the aryl ligand. If the metal catalyst is preordered in an η^6-arene interaction, insertion could compete with protodeboronation. However, if the catalyst is not properly positioned, protodeboronation is likely to be rapid and irreversible thereby lowering yields.

Besides these implications, this work enables selective deuteration at the ispo position, and the same should extend to tritiation. Other applications include the potential for improving the rate of Cu-mediated $^{11}CO_2$ capture for PET studies,[4] or electrophilic fluorination by reaction with F^+-reagents such as NFSI. For the synthesis of EWG-arylboronates as ^{18}F-capture reagents, care must be taken during bioconjugation. Hence, sterically encumbered protecting groups such as a tetraphenylpinacol, or 1,8-diaminonaphthalene that forms a base-stable borimidine (B(dan)), should be used.[38,39] We have used both for ^{18}F-$ArBF_3$-based radiotracers.[5,6]

■ CONCLUSIONS

Deboronation was studied on a series of electron-deficient aryl and heteroarylboronic acids. Of these, the 2,6-disubstituted boronic acids underwent rapid and quantitative protodeboronation within minutes at pH 12. Acidic exposure to the same did not promote C−B cleavage indicating that protodeboronation is base mediated. These findings provide insight into the stability of ortho-substituted arylboronates for use in Suzuki−Miyaura cross-couplings and for other diverse purposes.

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EXPERIMENTAL SECTION

ESI-HRMS data was obtained with a time-of-flight (TOF) detector in negative ion mode. All NMR spectra were recorded at room temperature on a 300 or 400 MHz spectrometer. *p*-Anisoleboronic acid (20 mM) was converted to the $ArBF_3^-$ using a solution of 1 M KHF_2 in 1 M HCl (buffered HF pH ~2). For base-mediated protodeboronation, commercially available boronic acids listed in Table 1 were obtained from commercially available sources or prepared according to our previous reports.[6,34] For **35**, commercially available 3-phenolboronylpincacolate was brominated in NBS according to the following method. A flame-dried round-bottom flask was charged with 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (330 mg, 1.5 mmol), 3.2 equiv of *N*-bromosuccinimide (854 mg, 4.8 mmol), and 0.02 equiv of $AuCl_3$ (10 mg, 0.03 mmol) along with 3 mL of dry 1,2-dichloroethane (DCE). The reaction was heated up to 80 °C for 12 h before quenching with 20 mL of water. The aqueous layer was extracted twice with 20 mL of CH_2Cl_2. The organic layers were combined and concentrated under vacuum. The crude residue was chromatographed on using a gradient (0−20%) of ethyl acetate in hexane to give 410 mg (2.2 equiv) as a white powder. Yield: 64%. ^{1}H NMR (300 MHz, $CDCl_3$): 1.47 (s, 12H), 5.91 (s, 1H), 7.64 (s, 1H). ^{13}C NMR: 24.89, 77.02, 85.30, 110.93, 113.48, 116.06, 134.55, 148.42. HRMS (ESI-TOF) *m*/*z*: $[M]^-$ Calcd for $C_{12}H_{14}BBr_3O_3^-$ 451.8544; Found 451.8552.

To measure deboronation rates, stock solutions (20 mM) of the boronic acids in Table 1 were prepared in water. Arylboronate (1 equiv) was reacted with 200 mM KOH for various time points. Reactions were quenched with 1 equiv of HCl. For fluorinated arylboronic acids, protodeboronation was monitored using ^{19}F NMR spectroscopy (300 MHz) using trifluoroethanol (TFE) as an internal standard at −75 ppm (Figure 1). In most cases, starting material and product were resolved by HPLC, and time-dependent rates of deboronation were fitted to pseudo-first-order rate equations. Product composition was confirmed by mass spectrometry (ESIMS and EI-MS). For most compounds in question, conversion to a single protodeboronated product was observed.

ASSOCIATED CONTENT

Supporting Information

Analysis of screening techniques, UV, HPLC, and ^{19}F NMR spectra, corresponding mass spectra of products and graphical extrapolation to rate constants, and characterization of compound **35**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Springsteen, G.; Wang, B. H. *Tetrahedron* **2002**, *58*, 5291.
(2) Pal, A.; Berube, M.; Hall, D. G. *Angew. Chem., Int. Ed.* **2010**, *49*, 1492.
(3) Schumacher, S.; Katterle, M.; Hettrich, C.; Paulke, B. R.; Hall, D. G.; Scheller, F. W.; Gajovic-Eichelmann, N. *J. Mol. Recognit.* **2011**, *24*, 953.
(4) Riss, P. J.; Lu, S. Y.; Telu, S.; Aigbirhio, F. I.; Pike, V. W. *Angew. Chem., Int. Ed.* **2012**, *51*, 2698.
(5) Li, Y.; Guo, J.; Tang, S.; Lang, L.; Chen, X.; Perrin, D. M. *Am. J. Nucl. Med. Mol. Imaging* **2013**, *3*, 44.
(6) Ting, R.; Harwig, C. W.; auf dem Keller, U.; McCormick, S.; Austin, P.; Overall, C. M.; Adam, M. J.; Ruth, T. J.; Perrin, D. M. *J. Am. Chem. Soc.* **2008**, *130*, 12045.
(7) Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, 2419.
(8) Suzuki, A.; Yamamoto, Y. *Chem. Lett.* **2011**, *40*, 894.
(9) Lennox, A. J. J.; Lloyd-Jones, G. C. *Chem. Soc. Rev.* **2014**, *43*, 412.
(10) Amatore, C.; Le Duc, G.; Jutand, A. *Chem.—Eur. J.* **2013**, *19*, 10082.
(11) Butters, M.; Harvey, J. N.; Jover, J.; Lennox, A. J. J.; Lloyd-Jones, G. C.; Murray, P. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 5156.
(12) Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.* **1979**, *20*, 3437.
(13) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
(14) Wallow, T. I.; Novak, B. M. *J. Org. Chem.* **1994**, *59*, 5034.
(15) Lennox, A. J. J.; Lloyd-Jones, G. C. *Isr. J. Chem.* **2010**, *50*, 664.
(16) Lennox, A. J. J.; Lloyd-Jones, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 7431.
(17) Lennox, A. J. J.; Lloyd-Jones, G. C. *Angew. Chem., Int. Ed.* **2013**, *52*, 7362.
(18) Weissman, H.; Milstein, D. *Chem. Commun.* **1999**, 1901.
(19) Hoshi, T.; Honma, T.; Mori, A.; Konishi, M.; Sato, T.; Hagiwara, H.; Suzuki, T. *J. Org. Chem.* **2013**, *78*, 11513.
(20) Eseola, A. O.; Geibig, D.; Gorls, H.; Sun, W. H.; Hao, X.; Woods, J. A. O.; Plass, W. *J. Organomet. Chem.* **2014**, *754*, 39.
(21) Batey, R. A.; Quach, T. D. *Tetrahedron Lett.* **2001**, *42*, 9099.
(22) Quach, T. D.; Batey, R. A. *Org. Lett.* **2003**, *5*, 4397.
(23) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633.
(24) Molander, G. A.; Cavalcanti, L. N.; Canturk, B.; Pan, P. S.; Kennedy, L. E. *J. Org. Chem.* **2009**, *74*, 7364.
(25) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275.
(26) Molander, G. A.; Canturk, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 9240.
(27) Kuivila, H. G.; Reuwer, J. F.; Mangravi, J. A. *Can. J. Chem.* **1963**, *41*, 3081.
(28) Nahabedian, K.; Kuivila, H. G. *J. Am. Chem. Soc.* **1961**, *83*, 2167.
(29) Ting, R.; Harwig, C.; Lo, J.; Li, Y.; Adam, M. J.; Ruth, T. J.; Perrin, D. M. *J. Org. Chem.* **2008**, *73*, 4662.
(30) Ting, R.; Lo, J.; Adam, M. J.; Ruth, T. J.; Perrin, D. M. *J. Fluor. Chem.* **2008**, *129*, 349.
(31) Li, Y.; Asadi, A.; Perrin, D. M. *J. Fluor. Chem.* **2009**, *130*, 377.
(32) Ting, R.; Aguilera, T. A.; Crisp, J. L.; Hall, D. J.; Eckelman, W. C.; Vera, D. R.; Tsien, R. Y. *Bioconjugate Chem.* **2010**, *21*, 1811.
(33) Liu, Z.; Li, Y.; Lozada, J.; Wong, M. Q.; Greene, J.; Lin, K.-S.; Yapp, D.; Perrin, D. M. *Nucl. Med. Biol.* **2013**, *40*, 841.
(34) Liu, Z.; Hundal-Jabal, N.; Wong, M.; Yapp, D.; Lin, K. S.; Benard, F.; Perrin, D. M. *MedChemComm* **2014**, *5*, 171.
(35) Charton, M. *J. Am. Chem. Soc.* **1969**, *91*, 615.
(36) Charton, M. *J. Am. Chem. Soc.* **1969**, *91*, 6649.
(37) Charton, M. *Can. J. Chem.* **1960**, *38*, 2493.
(38) Noguchi, H.; Shioda, T.; Chou, C. M.; Suginome, M. *Org. Lett.* **2008**, *10*, 377.
(39) Iwadate, N.; Suginome, M. *J. Organomet. Chem.* **2009**, *694*, 1713.