

Synthesis of Enantioenriched Alkylfluorides by the Fluorination of Boronate Complexes

Christopher Sandford, Ramesh Rasappan, and Varinder K. Aggarwal*

School of Chemistry, University of Bristol, Cantock's Close, Bristol BS8 1TS, United Kingdom

S Supporting Information

ABSTRACT: The enantiospecific conversion of chiral secondary boronic esters into alkylfluorides is reported. Boronate complexes derived from boronic esters and PhLi were used as nucleophiles, with Selectfluor II as the electrophilic fluorinating agent, to afford alkylfluorides in short reaction times. The addition of styrene as a radical trap was found to enhance enantiospecificity. A broad range of alkyl boronic esters were converted into alkylfluorides with almost complete enantiospecificity by this method.

Organofluorine compounds are of increasing importance in pharmaceuticals, agrochemicals, and functional materials due to the element's unique properties.¹ In medicinal chemistry, the incorporation of fluorine into an organic compound can result in improved metabolic stability and bioavailability and enhance the binding efficacy when compared to the non-fluorinated analogue.² Consequently, ~20–25% of all pharmaceuticals on the market contain fluorine,³ and the development of novel procedures to introduce fluorine are highly sought after. Late-stage fluorination techniques are of particular importance because they can be used to introduce ¹⁸F into molecules for positron emission tomography (PET).⁴

The high demand for fluorination techniques has resulted in significant recent progress, particularly in the fluorination of aromatic compounds.⁵ However, general techniques for aliphatic fluorination remain challenging when the desired site for fluorination is distal to functional groups.⁶ Specifically, while enantioselective fluorination⁷ adjacent to aromatics,⁸ alkenes,⁹ heteroatoms,¹⁰ or carbonyl¹¹ functional groups has been achieved successfully, enantioselective fluorination of remote positions is largely unexplored. The most direct current method to create such entities is the conversion of chiral secondary alcohols into alkylfluorides by deoxyfluorination (Scheme 1a), but the process often suffers from competing elimination.¹² This process has been improved by Ritter with the introduction of PhenoFluor, a thermally more stable reagent.¹³ Alternatively, Gandelman has reported an enantioselective nickel-catalyzed Suzuki cross-coupling reaction, but the enantioselectivity was found to be highly substrate dependent (Scheme 1b).¹⁴ In this paper, we demonstrate that enantioenriched boronic esters can be converted into alkylfluorides in short reaction times and with high levels of enantiospecificity (Scheme 1d).

Recently, Li reported the silver-catalyzed fluorination of primary, secondary, and tertiary alkylboronates with Selectfluor as the electrophilic fluorinating agent (Scheme 1c).¹⁵ The

Scheme 1. Synthesis of Fluorine-Bearing Stereocenters Distal to Functional Groups

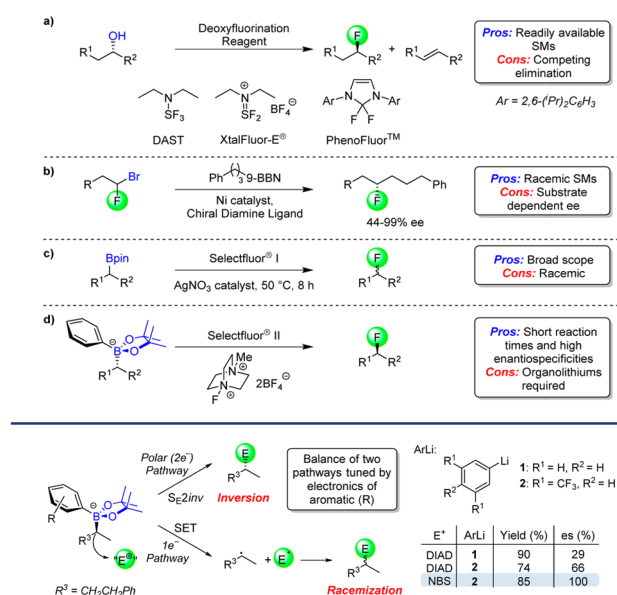


Figure 1. Reaction pathways of boronate complexes with electrophiles, and previous results with diisopropyl azodicarboxylate (DIAD) and *N*-bromosuccinimide (NBS) as electrophiles (E⁺). SET = single-electron transfer.^{16a}

reaction was found to proceed through a radical mechanism. We reasoned that if a protocol could be found which proceeded via a polar (two-electron) pathway rather than a radical pathway, then enantioenriched alkylfluorides would be obtained. We previously reported that the addition of an aryllithium to a secondary boronic ester afforded a boronate complex, which reacted with a range of electrophiles with high selectivity (Figure 1), the reactions proceeding by a polar pathway. This enabled the conversion of the C–B bond into C–I, C–Br, C–Cl, C–N, C–O, and C–C (bromination exemplified in Figure 1).¹⁶ However, the conversion of the C–B bond into C–F was more challenging, but has now been realized and is reported herein.

Initially, chiral secondary boronic ester **4a** was treated with phenyllithium to afford the intermediate boronate complex **5a** (Table 1), but no reaction with Selectfluor I (**7**) was observed in THF. However, when THF was used for ate complex formation and then exchanged for acetonitrile for the reaction with

Received: June 10, 2015

Published: August 5, 2015

Table 1. Investigation into the Fluorination of Boronate Complex 5a^a

ArLi: R^1 , R^2 , R^3

1: $R^1 = H, R^2 = H$
 2: $R^1 = CF_3, R^2 = H$
 3: $R^1 = H, R^2 = CH=CH_2$

7: $R^3 = Cl$, Selectfluor[®] I
 8: $R^3 = H$, Selectfluor[®] II

entry	ArLi	Selectfluor	additive	yield ^b (%)	es ^c (%)
1	1	Selectfluor I	none	78	37
2	2	Selectfluor I	none	61	47
3	3	Selectfluor I	none	61	59
4	1	Selectfluor I	styrene	81	89
5	1	Selectfluor I	4-MeO styrene	>99	74
6	1	Selectfluor I	4-CF ₃ styrene	78	87
7	1	Selectfluor I	4- <i>tert</i> -butyl catechol ^d	67	24
8	1	Selectfluor I	1-octene	>99	78
9	1	Selectfluor I	toluene	72	46
10	1	Selectfluor I	<i>n</i> -octane	>99	33
11	1	Selectfluor I	styrene ^e	89	89
12	1	Selectfluor II	styrene ^e	72	94
13 ^f	1	Selectfluor II	styrene ^e	83 ^g	100
14 ^f	1	Selectfluor II	none	72 ^g	80

^aReactions were carried out with 0.10 mmol of **4a** and 1.3 equiv of ArLi. Conditions: 1.0 mL of THF for ate complex formation, 2.0 mL of MeCN (total) for fluorination, PMP = *para*-methoxy phenyl. ^bYield of isolated product. ^cDetermined by HPLC analysis. ^d0.2 equiv of 4-*tert*-butylcatechol used. ^e0.5 equiv of styrene used. ^f0.25 mmol of **4a** and 0.95 equiv of PhLi. Conditions: Ate complex formation at 0 °C (30 min) in 2.5 mL of THF, fluorination at -10 °C (2 h) in 5.0 mL of MeCN (total), with 1.3 equiv of Selectfluor and 3 Å molecular sieves (powder, 100 mg). ^gYield based on the 0.95 equiv of PhLi.

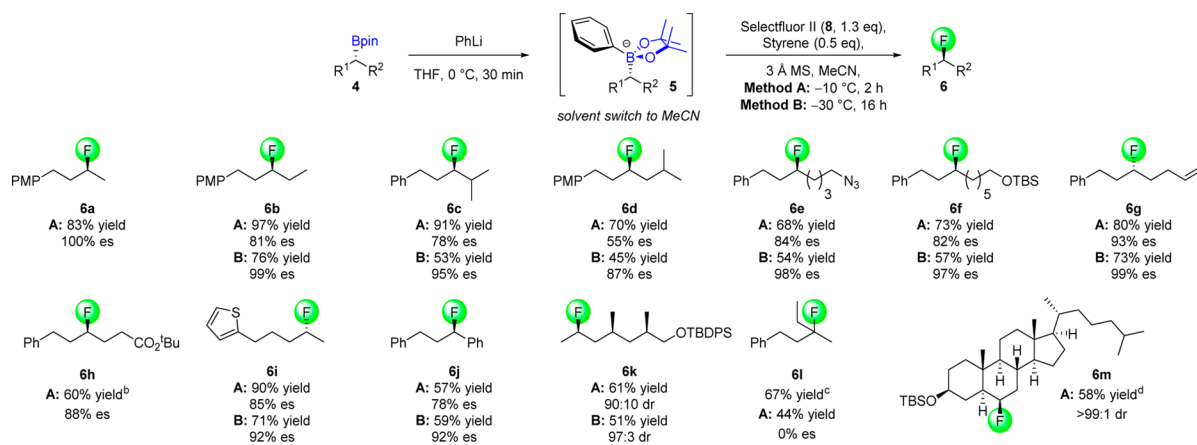
Selectfluor (acetonitrile used to solubilize Selectfluor), the corresponding secondary alkylfluoride **6a** was formed in 78% yield and 37% es (entry 1). Reasoning that a single-electron transfer (SET) process was dominating because of the high oxidation potential of Selectfluor I, we attempted to tune the reactivity by altering the nature of the aryl group on boron. We have previously reported that replacing PhLi (**1**) with 3,5-

(CF₃)₂C₆H₃Li (**2**) significantly increased the enantiospecificity of the related reaction with diisopropyl azodicarboxylate (DIAD, Figure 1),^{16a} presumably by reducing the reduction potential of the boronate complex and favoring the polar (two-electron) pathway. However, the boronate complex derived from **2** was found to afford only a small improvement to 47% es in the fluorination reaction (entry 2).


Somewhat surprisingly, using an aryl organolithium formed from 4-bromostyrene increased the enantiospecificity to 59% (entry 3). To ascertain whether the alkene substituent was altering the reaction, 1.3 equiv of styrene was added to the reaction mixture, with phenyllithium being used for ate complex formation. Pleasingly, product **6a** was afforded in 81% yield and 89% es (entry 4). Notably, ate complex **5a** is fluorinated within only 30 min at 0 °C.

Different additives were tested in the model reaction, but no improvements in enantiospecificity were observed when compared to styrene (entries 5–10). Specifically, using either electron-deficient or -rich styrenes had no significant effect on the level of enantiospecificity; small amounts of 4-*tert*-butylcatechol, which are added to commercial styrenes to inhibit polymerization, were ruled out as the contributing factor.¹⁷ When the alkene additive was replaced with toluene or an alkane such as *n*-octane, the enantiospecificity was found to be reduced, signifying the importance of the alkene functionality. It was also found that the number of equivalents of styrene could be reduced to 0.5 before the level of enantiospecificity was found to decrease (entry 11).

To further increase the enantiospecificity, we turned to tuning the fluorinating agent to favor the desired polar pathway. It was reported by Banks that the electrophilicity (and, consequently, the oxidation potential) could be reduced by decreasing the electron-withdrawing power of the alkyl group attached to nitrogen (CH₂R³).¹⁸ Pleasingly, using commercially available Selectfluor II (**8**) increased the enantiospecificity to 94% (entry 12).¹⁹ When the scale of the reaction was increased to 0.25 mmol it was found that reducing the equivalents of PhLi to 0.95 was necessary to maintain high enantiospecificity. Upon final optimization,²⁰ it was determined that adding molecular sieves and reducing the temperature to -10 °C gave alkylfluoride **6a** in

Scheme 2. Scope of the Fluorination Reaction^a

^aReactions were carried out with 0.25 mmol of boronic ester and 0.95 equiv of PhLi. Conditions: 2.5 mL of THF for ate complex formation, 5.0 mL of MeCN (total) for fluorination, 3 Å molecular sieves (powder, 100 mg), unless stated otherwise. Yields recorded are those of isolated material based on 0.95 equiv of PhLi; es determined by HPLC or GC analysis; dr determined by ¹⁹F NMR analysis. ^bYield after 16 h reaction. ^cSelectfluor I (7, 1.3 equiv), no styrene or molecular sieves, MeCN, rt, 1 h. ^dFluorination in 4:1 MeCN/THF mixture (5.0 mL total).

Table 2. Radical Clock Experiment^a


entry	temp/°C (time)	additive	yield ^b (%)	ratio ^c 6n:9n	es ^d (6n) (%)
1	25 (1 h)	none	62	95:5	52
2	25 (1 h)	styrene	69	>99:1	56
3	-30 (16 h)	none	52	97:3	56
4	-30 (16 h)	styrene	74	>99:1	64

^aReactions were carried out with 0.25 mmol of **4n** and 0.95 equiv of PhLi. Conditions: 2.5 mL of THF for ate complex formation, 5.0 mL of MeCN (total) for fluorination, 3 Å molecular sieves (powder, 100 mg). ^bYield of isolated product based on 0.95 equiv of PhLi. ^cDetermined by ¹⁹F NMR analysis. ^dDetermined by HPLC analysis.

83% yield with complete enantiospecificity (100% es, 91% ee, entry 13). Under these optimized conditions, but without styrene, the enantiospecificity was only 80% (entry 14).

With optimized conditions established for the model reaction, the scope of the transformation was investigated (Scheme 2). Upon changing the methyl substituent at the stereogenic center for ethyl, the es of the reaction was found to drop to 81%. Pleasingly, 99% es was achieved by simply decreasing the temperature to -30 °C, albeit with a slightly reduced yield. The two methods (A and B) were thus used to exemplify the high reactivity and enantiospecificity, respectively, allowing the conditions to be chosen depending on the application of the procedure.

The reaction scope shows that the conditions tolerate a range of functional groups including azides, protected alcohols, alkenes, and *tert*-butyl esters. Additionally, the reaction can be used to afford a benzylic alkylfluoride with high enantioenrichment (**6j**). Given that the S_E2*inv* pathway is highly dependent on sterics, chiral tertiary boronic esters give rise to racemic products. However, compound **6l** could be obtained in 67% yield within 1 h at rt using Selectfluor I (**7**), and hence this transformation provides a rapid late-stage method to obtain such functionality. Furthermore, the fluorination of complex boronic ester structures with additional stereogenic centers,²¹ including a derivative of cholesterol, was achieved, the products being formed as essentially single diastereoisomers (**6k** and **6m**).²²

The mechanism, and in particular the role of styrene, was briefly explored. Styrene was not consumed at a detectable level during the course of the reaction, and no reaction between styrene and Selectfluor was observed under the reaction conditions in the absence of the boronate complex. Because styrene is a known radical scavenger²³ and because Selectfluor¹⁹ is known to react by either S_N2 or SET, we probed the possibility of radical intermediates being responsible for the erosion in es (Table 2).^{6c,g,24} It was expected that if SET competed with the polar pathway then cyclopropyl substrate **4n** would give ring-opened homoallylic alkylfluoride **9n** together with the fluorinated cyclopropane **6n** in high enantiospecificity. In practice, in the absence of styrene, very little ring-opened product **9n** was observed, but in the presence of styrene, formation of **9n** was completely suppressed. However, the levels of enantiospecificity for this substrate were lower than those for all the other boronic esters tested (in agreement with previous reactions with DIAD^{16a}), thus implicating the existence of a second racemic pathway (see below).

Based on these results, we propose that styrene acts as a radical scavenger.²⁵ However, because the yield of this transformation is not diminished by the presence of styrene, it seems probable that styrene is trapping a radical propagating species (Figure 2). We propose that boronate **5** reacts with Selectfluor predominantly through a polar S_E2*inv* pathway giving the alkylfluoride in high enantiospecificity. A slower SET reaction also competes. However, once the nucleophilic radical **10** is formed it combines rapidly with the fluorine atom within the solvent cage leading to racemic alkylfluoride **6**. Alternatively, alkyl radical **10** can escape the solvent cage (**11**) and then rapidly abstract a fluorine atom from Selectfluor, forming the racemic product and amine radical cation **12**.^{6g-i} This radical cation then undergoes rapid SET with a new boronate **5** to regenerate radical **11** and complete a propagation cycle. It is possible that this cycle is inhibited by the addition of styrene, which traps radical **11** to afford **13**, thus preventing propagation.²⁶ In the case of the free-radical clock substrate **4n**, if **10** escapes the solvent cage it can undergo ring opening to afford **9n**, unless it is trapped by styrene or Selectfluor. However, Wong has shown that cyclopropyl radicals often remain intact rather than undergoing ring opening owing to their high rate of reaction with Selectfluor.²⁷ The low levels of enantiospecificity for this substrate presumably result from a slower rate of S_E2*inv*, with the radical combination following SET contributing significantly. Because the effect of added styrene is small, it suggests that radical propagation is not the primary cause of the low levels of enantiospecificity in this case.

To probe the presence of amine radical cation **12**, we considered its application to the fluorination of sp³ C–H bonds. Lectka has demonstrated that intermediate **12** is capable of abstracting a H atom from adamantane, with the corresponding radical reacting with Selectfluor to form 1-fluoroadamantane and regenerate **12**.^{6g,h} When adamantane was added to our system (Scheme 3), we observed the formation of 1-fluoroadamantane **14** in 4.4% yield after 3 h at rt. The formation of **14** was reduced to 1.0% upon the addition of 1.3 equiv of styrene, demonstrating its ability to inhibit the radical propagation cycle.

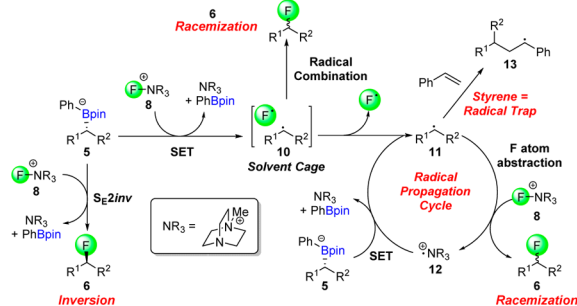
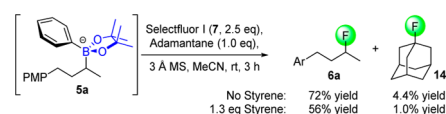


Figure 2. Proposed pathways for the reaction of boronate complex **5** with Selectfluor (**8**, F⁻+NR₃).

Scheme 3. Radical Fluorination of sp³ C–H Bonds^a



^aReactions were carried out with 0.25 mmol of boronic ester and 0.95 equiv of PhLi. Conditions: 2.5 mL of THF for ate complex formation, 5.0 mL of MeCN (total) for fluorination. Yields determined by crude ¹⁹F NMR analysis. Ar = C₆H₄OMe or C₆H₃FOMe (~11:1 mixture).

In conclusion, we have developed the first enantiospecific method to convert chiral secondary boronic esters into alkylfluorides. Very high levels of enantiospecificity can be afforded at low temperatures using styrene, an additive which we believe acts as a radical trap that prevents a radical propagation cycle. Alternatively, the reaction can be conducted at higher temperature to achieve reaction times of 30 min. The transformation reported herein represents a significant addition to the range of aliphatic fluorination reactions because it enables the introduction of fluorine-bearing stereogenic centers at remote positions, which were previously challenging to obtain.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and characterization data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b05848.

■ AUTHOR INFORMATION

Corresponding Author

*v.aggarwal@bristol.ac.uk

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank EPSRC (EP/I038071/1) and Bristol University for financial support, Dr. E. Myers and Dr. D. Leonori for valuable discussions, and Dr. H. Sparkes for X-ray analysis of **6m**.

■ REFERENCES

- (1) (a) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308. (b) Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature* **2011**, *473*, 470. (c) Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 8214.
- (2) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320.
- (3) (a) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (b) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, *114*, 2432.
- (4) (a) Ametamey, S. M.; Honer, M.; Schubiger, P. A. *Chem. Rev.* **2008**, *108*, 1501. (b) Brooks, A. F.; Topczewski, J. J.; Ichiishi, N.; Sanford, M. S.; Scott, P. J. H. *Chem. Sci.* **2014**, *5*, 4545. (c) Neumann, C. N.; Ritter, T. *Angew. Chem., Int. Ed.* **2015**, *54*, 3216.
- (5) Campbell, M. G.; Ritter, T. *Chem. Rev.* **2015**, *115*, 612.
- (6) (a) Chambers, R. D.; Parsons, M.; Sandford, G.; Bowden, R. *Chem. Commun.* **2000**, 959. (b) Liu, W.; Huang, X.; Cheng, M.-J.; Nielsen, R. J.; Goddard, W. A.; Groves, J. T. *Science* **2012**, *337*, 1322. (c) Yin, F.; Wang, Z.; Li, Z.; Li, C. *J. Am. Chem. Soc.* **2012**, *134*, 10401. (d) Rueda-Becerril, M.; Chatalova Sazepin, C.; Leung, J. C. T.; Okbinoglu, T.; Kennepohl, P.; Paquin, J.-F.; Sammis, G. M. *J. Am. Chem. Soc.* **2012**, *134*, 4026. (e) Cochrane, N. A.; Nguyen, H.; Gagné, M. R. *J. Am. Chem. Soc.* **2013**, *135*, 628. (f) Halperin, S. D.; Fan, H.; Chang, S.; Martin, R. E.; Britton, R. *Angew. Chem., Int. Ed.* **2014**, *53*, 4690. (g) Pitts, C. R.; Bloom, S.; Woltonist, R.; Auvenshine, D. J.; Ryzhkov, L. R.; Siegler, M. A.; Lectka, T. *J. Am. Chem. Soc.* **2014**, *136*, 9780. (h) Bloom, S.; Knippel, J. L.; Lectka, T. *Chem. Sci.* **2014**, *5*, 1175. (i) Ventre, S.; Petronijevic, F. R.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2015**, *137*, 5654.
- (7) For selected reviews of enantioselective fluorination, see: (a) Lectard, S.; Hamashima, Y.; Sodeoka, M. *Adv. Synth. Catal.* **2010**, *352*, 2708. (b) Hollingworth, C.; Gouverneur, V. *Chem. Commun.* **2012**, 48, 2929. (c) Wu, J. *Tetrahedron Lett.* **2014**, *55*, 4289. (d) Yang, X.; Wu, T.; Phipps, R. J.; Toste, F. D. *Chem. Rev.* **2015**, *115*, 826.
- (8) (a) Emer, E.; Pfeifer, L.; Brown, J. M.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2014**, *53*, 4181. (b) Huang, X.; Liu, W.; Ren, H.; Neelamegam, R.; Hooker, J. M.; Groves, J. T. *J. Am. Chem. Soc.* **2014**, *136*, 6842. (c) Talbot, E. P. A.; Fernandes, T. D. A.; McKenna, J. M.; Toste, F. D. *J. Am. Chem. Soc.* **2014**, *136*, 4101.
- (9) (a) Katcher, M. H.; Doyle, A. G. *J. Am. Chem. Soc.* **2010**, *132*, 17402. (b) Katcher, M. H.; Sha, A.; Doyle, A. G. *J. Am. Chem. Soc.* **2011**, *133*, 15902. (c) Wu, J.; Wang, Y.-M.; Drljevic, A.; Rauniyar, V.; Phipps, R. J.; Toste, F. D. *Proc. Natl. Acad. Sci. U. S. A.* **2013**, *110*, 13729.
- (10) (a) Kalow, J. A.; Doyle, A. G. *J. Am. Chem. Soc.* **2010**, *132*, 3268. (b) Rauniyar, V.; Lackner, A. D.; Hamilton, G. L.; Toste, F. D. *Science* **2011**, *334*, 1681.
- (11) (a) Differding, E.; Lang, R. W. *Tetrahedron Lett.* **1988**, *29*, 6087. (b) Shibata, N.; Suzuki, E.; Takeuchi, Y. *J. Am. Chem. Soc.* **2000**, *122*, 10728. (c) Hamashima, Y.; Yagi, K.; Takano, H.; Tamás, L.; Sodeoka, M. *J. Am. Chem. Soc.* **2002**, *124*, 14530. (d) Beeson, T. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 8826. (e) Liang, Y.; Fu, G. C. *J. Am. Chem. Soc.* **2014**, *136*, 5520. (f) Yang, X.; Phipps, R. J.; Toste, F. D. *J. Am. Chem. Soc.* **2014**, *136*, 5225.
- (12) (a) Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574. (b) Messina, P. A.; Mange, K. C.; Middleton, W. J. *J. Fluorine Chem.* **1989**, *42*, 137. (c) Shellhamer, D. F.; Briggs, A. A.; Miller, B. M.; Prince, J. M.; Scott, D. H.; Heasley, V. L. *J. Chem. Soc., Perkin Trans. 2* **1996**, 973. (d) Lal, G. S.; Pez, G. P.; Pesaresi, R. J.; Prozonc, F. M. *Chem. Commun.* **1999**, 215. (e) L'Heureux, A.; Beaulieu, F.; Bennett, C.; Bill, D. R.; Clayton, S.; LaFlamme, F.; Mirmehrabi, M.; Tadayon, S.; Tovell, D.; Couturier, M. *J. Org. Chem.* **2010**, *75*, 3401. Triflates can be displaced by fluoride, but elimination also often occurs; see: (f) Hunter, L.; O'Hagan, D.; Slawin, A. M. Z. *J. Am. Chem. Soc.* **2006**, *128*, 16422. (g) Keddie, N. S.; Slawin, A. M. Z.; Lebl, T.; Philp, D.; O'Hagan, D. *Nat. Chem.* **2015**, *7*, 483.
- (13) (a) Sladojevich, F.; Arlow, S. I.; Tang, P.; Ritter, T. *J. Am. Chem. Soc.* **2013**, *135*, 2470. (b) Fujimoto, T.; Becker, F.; Ritter, T. *Org. Process Res. Dev.* **2014**, *18*, 1041. For a recent development in deoxyfluorination, see: (c) Nielsen, M. K.; Ugaz, C. R.; Li, W.; Doyle, A. G. *J. Am. Chem. Soc.* **2015**, ASAP.
- (14) (a) Jiang, X.; Sakthivel, S.; Kulbitski, K.; Nisnevich, G.; Gandelman, M. *J. Am. Chem. Soc.* **2014**, *136*, 9548. (b) Jiang, X.; Gandelman, M. *J. Am. Chem. Soc.* **2015**, *137*, 2542.
- (15) (a) Li, Z.; Wang, Z.; Zhu, L.; Tan, X.; Li, C. *J. Am. Chem. Soc.* **2014**, *136*, 16439. See also: (b) Cazorla, C.; Métay, E.; Andrioletti, B.; Lemaire, M. *Tetrahedron Lett.* **2009**, *50*, 3936.
- (16) (a) Larouche-Gauthier, R.; Elford, T. G.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2011**, *133*, 16794. (b) Mohiti, M.; Rampalakos, C.; Feeney, K.; Leonori, D.; Aggarwal, V. K. *Chem. Sci.* **2014**, *5*, 602. (c) Feeney, K.; Berionni, G.; Mayr, H.; Aggarwal, V. K. *Org. Lett.* **2015**, *17*, 2614.
- (17) Styrene was distilled using a Hickman distillation head prior to use to remove 4-*tert*-butylcatechol.
- (18) (a) Banks, R. E.; Mohialdin-Khaffaf, S. N.; Lal, G. S.; Sharif, I.; Syvret, R. G. *J. Chem. Soc., Chem. Commun.* **1992**, 595. (b) Banks, R. E.; Besheesh, M. K.; Mohialdin-Khaffaf, S. N.; Sharif, I. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2069.
- (19) Nyffeler, P. T.; Durón, S. G.; Burkart, M. D.; Vincent, S. P.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2005**, *44*, 192.
- (20) For complete optimization studies, see [Supporting Information](#).
- (21) (a) Bonet, A.; Odachowski, M.; Leonori, D.; Essafi, S.; Aggarwal, V. K. *Nat. Chem.* **2014**, *6*, 584. (b) Rasappan, R.; Aggarwal, V. K. *Nat. Chem.* **2014**, *6*, 810.
- (22) Stereochemistry of compound **6m** confirmed by X-ray crystallography; see [Supporting Information](#).
- (23) (a) Moad, G.; Rizzardo, E.; Solomon, D. H. *Macromolecules* **1982**, *15*, 909. (b) Li, K.; Alexakis, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 7600.
- (24) (a) Griller, D.; Ingold, K. U. *Acc. Chem. Res.* **1980**, *13*, 317. (b) Bowry, V. W.; Luszyk, J.; Ingold, K. U. *J. Am. Chem. Soc.* **1991**, *113*, 5687.
- (25) Other radical traps (TEMPO, *p*-quinone, BHT) were also tested but found to inhibit reactivity completely owing to their ability to oxidize the boronate complex or react with Selectfluor.
- (26) It is also possible that amine radical cation **12** is trapped by styrene, thereby preventing the radical propagation cycle.
- (27) (a) Vincent, S. P.; Burkart, M. D.; Tsai, C.-Y.; Zhang, Z.; Wong, C.-H. *J. Org. Chem.* **1999**, *64*, S264. (b) Piana, S.; Devillers, L.; Togni, A.; Rothlisberger, U. *Angew. Chem., Int. Ed.* **2002**, *41*, 979.