Synthesis of Enantioenriched Alkyl Fluorides by the Fluorination of Boronate Complexes

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Supporting Information

ABSTRACT: The enantiospecific conversion of chiral secondary boronic esters into alkyl fluorides is reported. Boronate complexes derived from boronic esters and PhLi were used as nucleophiles, with Selectfluor II as the electrophilic fluorinating agent, to afford alkyl fluorides 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 alkyl fluorides 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. 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. Consequently, ~20–25% of all pharmaceuticals on the market contain fluorine, 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 $^{18}\text{F}$ into molecules for positron emission tomography (PET).

The high demand for fluorination techniques has resulted in significant recent progress, particularly in the fluorination of aromatic compounds. However, general techniques for aliphatic fluorination remain challenging when the desired site for fluorination is distal to functional groups. Specifically, while enantioselective fluorination adjacent to aromatics, alkynes, heteroatoms, or carbonyl 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 alkyl fluorides by deoxofluorination (Scheme 1a), but the process often suffers from competing elimination. This process has been improved by Ritter with the introduction of PhenoFluor, a thermally more stable reagent. Alternatively, Gandelman has reported an enantioselective nickel-catalyzed Suzuki cross-coupling reaction, but the enantioselectivity was found to be highly substrate dependent (Scheme 1b). In this paper, we demonstrate that enantioenriched boronic esters can be converted into alkyl fluorides in short reaction times and with high levels of enantiospecificity (Scheme 1d).

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

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

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“Reactions 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. Yield of isolated product. Determined by HPLC analysis. 0.2 equiv of 4-tert-butylicate used. 0.25 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). Yield based on 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)₂C₆H₄Li (2) significantly increased the enantiospecificity of the related reaction with diaoicryl azodicarboxylate (DIAD, Figure 1), 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-butylicate, which are added to commercial styrenes to inhibit polymerization, were ruled out as the contributing factor. 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). Pleasingly, using commercially available Selectfluor II (8) increased the enantiospecificity to 94% (entry 12). 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, 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

“Reactions 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. Yield after 16 h reaction. Selectfluor I (7, 1.3 equiv), no styrene or molecular sieves, MeCN, rt, 1 h. Fluorination in 4:1 MeCN/THF mixture (5.0 mL total).

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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 ee 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 benzylc alkyfluoride with high enantioenrichment (6i). Given that the S$_2$2inv pathway is highly dependent on sterics, chiral tertiary boronic esters give rise to racemic products. However, compound 6i 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, including a derivative of cholesterol, was achieved, the products being formed as essentially single diastereoisomers (6k and 6m).

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 scavenger and because Selectfluor is known to react by either S$_2$2 or SET, we probed the possibility of radical intermediates being responsible for the erosion in es (Table 2).

It was expected that if SET competed with the polar pathway then cyclopropyl substrate 4n would give ring-opened homoallylic alkyfluoride 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), thus implicating the existence of a second racemization pathway (see below).

Based on these results, we propose that styrene acts as a radical scavenger. 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$_2$2inv pathway giving the alkyfluoride in high enantiospecificity. A slower SET reaction also competes. However, once the nuclophilic radical 10 is formed it combines rapidly with the fluorine atom within the solvent cage leading to racemic alkyfluoride 6. Alternatively, alkyl radical 10 can escape the solvent cage (11) and then rapidly abstract a fluorine atom from Selectfluor, forming the racemic product and amine radical cation 12. This radical cation then undergoes rapid SET with a new boronate 5 to regenerate radical 11 and complete a propagation cycle. It is possible that this cycle is inhibited by the addition of styrene, which traps radical 11 to afford 13, thus preventing propagation. In the case of the free-radical clock substrate 4n, if 10 escapes the solvent cage it can undergo ring opening to afford 9n, unless it is trapped by styrene or Selectfluor. However, Wong has shown that cyclopropyl radicals often remain intact rather than undergoing ring opening owing to their high rate of reaction with Selectfluor. The low levels of enantiospecificity for this substrate presumably result from a slower rate of S$_2$2inv, 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 sp$^3$ 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. 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.
In conclusion, we have developed the first enantiospecific method to convert chiral secondary boronic esters into alkyl fluorides. 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.

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■ REFERENCES


■ SUPPORTING INFORMATION

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Notes
The authors declare no competing financial interest.