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Preparation, Properties, and Synthetic Potentials of Novel Boronates in a Fluorous Version (Fluorous Boronates)

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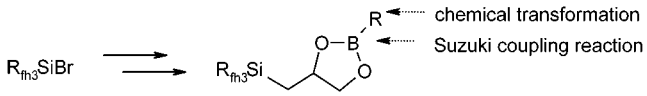
ABSTRACT



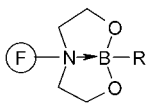
4a-j R = aryl, alkenyl, alkyl

A series of boronic acids were attached to a fluorous tag by esterification. Functional transformations of these boronates together with the fluorous Suzuki coupling reaction illustrated their usefulness in fluorous-phase techniques.

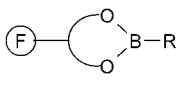
Since the pioneering work of Harváth and Rábai,[1] the fluorous property of highly fluorinated compounds has been exploited to influence phase behavior and thereby simplify separation in organic synthesis. With the expansion and generalization of fluorous concepts, the fluorous-phase-oriented synthesis is developing into a viable alternative to solid-phase techniques in organic synthesis.[2] In this context, we were interested in examining how the fluorous-phase approach could be applied to boron chemistry. To facilitate the synthesis and separation of functionalized arylboronic acids, several groups have recently resorted to solid-phase techniques and achieved much success in their effort.[3] However, to the best of our knowledge, no attempt has been made to tag boronic acids with a fluorinated label as fluorous reagents or substrates in fluorous synthesis. In this Letter, we report the first synthesis of fluorous boronic acid esters, along with a preliminary assessment of their application in fluorous-phase techniques.

Boronic acids rapidly and reversibly form cyclic esters with diols albeit in basic aqueous media. In light of this known reaction, it seems promising to immobilize boronic acids in the fluorocarbon phase via a boronate linkage, which could be readily cleaved or detached by simple hydrolysis. As potential candidates for fluorous analogues of boronates, we considered two types of model compounds originating from different diol moieties.

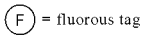
Initial experiments showed that compounds of type **I** were mostly undesirable using a criterion of fluorous attributes. Due to the coordination between nitrogen and oxygen, diethanolamine boronate derivatives are usually endowed with polar character, which affects their fluorous-phase affinity. In this regard, compounds of type **II** derived from simple 1,2 or 1,3 diol moieties might provide a more convenient access to the fluorous boronic acid esters.



I



II



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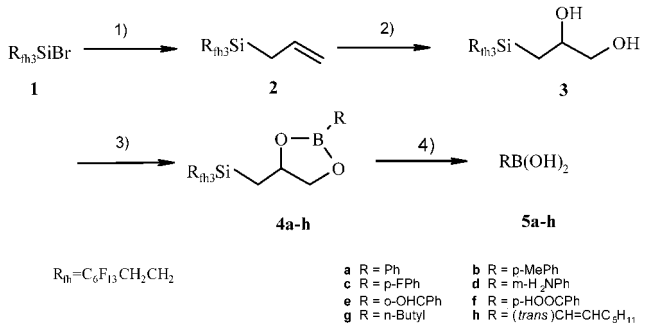
As usual, fluorous bromosilane **1** was employed as a fluorous-phase label. Treatment of **1** with excess allyl Grignard reagent afforded fluorous allylsilane **2** in quantitative yield. The dihydroxylation of **2** with *N*-methylmorpholine *N*-oxide (NMNO) and catalytic osmium tetraoxide in aqueous acetone provided the desired fluorous diol **3** in quantitative yield. As the only fluorous product, compound **3** was obtained in high purity by simple extractive workup (FC-77/aqueous acetone). Subsequent experiments were then conducted to verify the effectiveness of fluorous diol **3** in immobilizing boronic acid templates. Encouraging results showed that compound **3** could couple to 1.0 equiv or a slight excess of arylboronic acids in quantitative yields. Depending on the solubility of boronic acids, the reaction time may be varied. Nevertheless, the formation of fluorous boronates **4** was highly favored in anhydrous solvents such as THF, ether, pentane, or benzotrifluoride (BTF), and total conversion of **3** was achieved with the aid of 4 Å MS. The fluorous boronates **4**, purified by FC-77/CH_3CN extraction if necessary, were provided in high purity without contaminated by any diol components. As shown in Scheme 1, this reaction

Scheme 1[a]



[a] Reagents and conditions: (1) CH_2=$CHCH_2MgBr$ (4.0 equiv), Et_2O reflux overnight, 98%; (2) 4% aqueous OsO_4 (cat.), NMNO (1.2 equiv), acetone/H_2O 10:1, 8 h, 99%; (3) $RB(OH)_2$, **5a**−**h** (1.0−1.1 equiv), 4 Å MS, anhydrous ether, 0.5−12 h, >90%; (4) (a) THF/HOAc/H_2O 80:10:10, 2−4 h, 57−70%.

is applicable to a wide variety of electron-rich and electron-poor arylboronic acids. These prepared boronates, which were fully characterized by ^{1}H NMR, ^{19}F NMR, IR, MS, and EA, are mostly colorless or pale yellow viscous liquids.[4] Since prolonged exposure of moisture might detach the fluorous tag by hydrolysis, they were kept in dry vessels and showed adequate storage stability for long periods of time.

To assess the fluorous affinity of these boronates, we chose compound **4a** as representative and determined its partition coefficient K_D in several fluorous biphasic solvent combinations. As shown in Table 1, boronate **4a** behaves as a "fluorous compound" for most solvent pairs. With appropriate selection of organic solvents, the K_D values are high enough for effective fluorous extraction.

Table 1. Partition Coefficients of Boronate **4a** (K_D = *C*(fluorous solvent)/*C*(organic solvent), at 10 °C)[a]

organic solvents	K_D	organic solvents	K_D
acetonitrile	13.3	ethyl acetate	0.88
dichloromethane	7.53	acetone	2.73
chloroform	5.43	toluene	7.69
hexane	6.50	THF	2.91

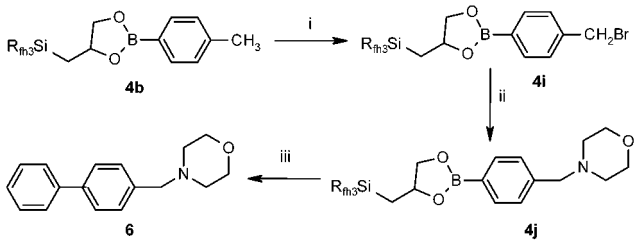
[a] The fluorous solvent is FC-77.

A search for hydrolytic cleavage conditions was then undertaken. Since hydrolysis under neutral conditions requires a prolonged reaction time, an acidic aqueous media is advisable for the release of free boronic acids. The released boronic acids were recovered intact by liquid−liquid extraction in reasonable yields. Meanwhile, the fluorous diol **3**, which was distributed into FC-77, could be recycled without additional treatment.

As robust and general methods for carbon−carbon bond formation, the Suzuki reaction has emerged as an important tool in parallel synthesis and combinatorial chemistry.[5] In consideration of this fact, we sought to plan different transformations of these boronates in fluorous synthesis and then carry out the Suzuki reaction as a detagging process.[6] In comparison with simple hydrolysis methods to provide novel boronic acids, we believe such a synthesis should hold greater interest for the combinatorial chemistry community.

As a significant demonstration of our approach, we focused our attention on the synthesis of aminomethylbiaryls, which are of marked interest in biological and pharmaceutical research (Scheme 2).[7] The fluorous boronate **4b**, produced

Scheme 2[a]



[a] Reagents and conditions: (1) NBS (1.5 equiv), AIBN (cat.), BTF, reflux, overnight, 67%; (2) morphline (1.2 equiv), $(i\text{-Pr})_2NEt$ (1.0 equiv), THF, rt, 18 h, 88%; (3) $Pd(PPh_3)_4$ (2 mol %), 2 M K_3PO_4 (2.0 equiv), dioxane, PhI (1.0 equiv), 12 h, 75 °C; 76%.

by the general method of esterification, was treated with NBS (1.5 equiv) in BTF at reflux. In a radical process, fluorous benzyl bromide **4i** was obtained and purified by repeated FC-77/CH_3CN extractions. Compound **4i** was further treated

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(4) Compound **4f** was a white waxy solid, mp 59−60 °C. Because of the action of 4 Å MS, it was formed as an anhydride, since no hydroxyl signal was detected in ^{1}H NMR or IR.

with morpholine and totally converted to the corresponding aminomethyl derivative **4j**. After extractive workup, the latter reacted with phenyl iodide under standard Suzuki reaction conditions in aqueous dioxane.[8] Although normal boronic acids or esters were replaced by fluorous boronates, we did not find any retardant effect for the Suzuki reaction from perfluoroalkyl chains. From a synthetic point of view, while we regard this reaction as the detagging process in fluorous synthesis, boronates such as **4a**−**j** might also serve as potential fluorous reagents. Finally, biaryl **6** was obtained by a crude extraction followed by chromatography (silica gel, petroleum ether/EtOAc 5:1).

To summarize, we have developed a fluorous approach to the chemistry of boronic acids and preliminarily demonstrated its application in fluorous-phase techniques. Further studies are currently underway in the following aspects: First, to separate complicated boronates with low fluorine content, the technique of solid−liquid extraction would be adopted,[9] and the stability of boronate linkage to chromatography should be considered. Second, fluorous asymmetric boronic esters may be useful for asymmetric synthesis.[10]

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

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