Route to Air and Moisture Stable β-Difluoroboryl Acrylamides

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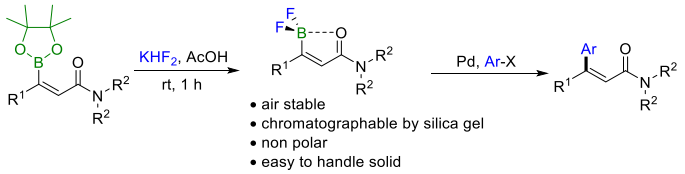
Supporting Information Placeholder



ABSTRACT: A method for the preparation of air stable difluoroboryl acrylamides is reported. In contrast to the ubiquitous organotrifluoroborate salts, difluoroboryl acrylamides are relatively nonpolar and are readily purified by silica chromatography. Difluoroboryl acrylamides serve as efficient substrates in cross-coupling reactions to afford the corresponding trisubstituted acrylamides in good to excellent yields. The utility of the difluoroboryl group in various chemical transformations is presented.

Boron containing compounds are commonplace in organic synthesis. Transformations involving organoboron substrates are fundamental in any organic chemist's toolkit. Specifically, the Suzuki-Miyaura cross-coupling reaction has become a "household" name in organic chemistry and continues to demonstrate the usefulness of organoboron substrates as synthetic intermediates.[1] Such cross-coupling reactions are ubiquitous and allow for the construction of otherwise difficult C-C bonds. In recent years, a large fraction of synthesis in the pharmaceutical industry consists of such cross-coupling reactions.[2] To meet the needs of increasingly complex and niche syntheses as well as practicality and commercial accessibility, a balance of stability and reactivity in organoboron substrates is necessary. For example, disubstituted acrylamides can be assembled *via* cross-coupling reactions from organoboron building blocks, which can be subsequently cyclized to 2-quinolones (Figure 1).[3] Quinolone tipifarnib is a the farnesyltransferase inhibitor that is currently in phase II clinical trials.[4]

Among the prevalent organoboron ancillary motifs, potassium trifluoroborate salts have received much attention due to their air and moisture stability. These compounds efficiently undergo cross-coupling reactions,[5] which has led to the

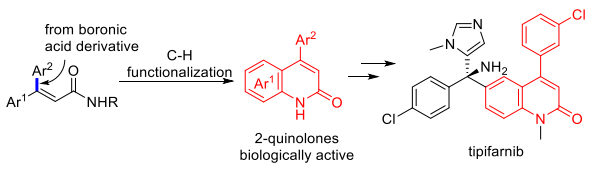


Figure 1. Diaryl substituted acrylamides derived from boronic acid derivatives as synthetic building blocks.

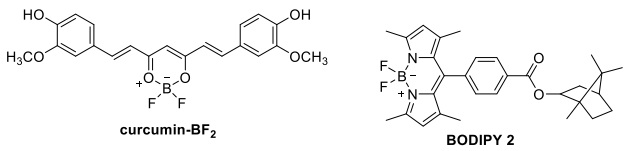
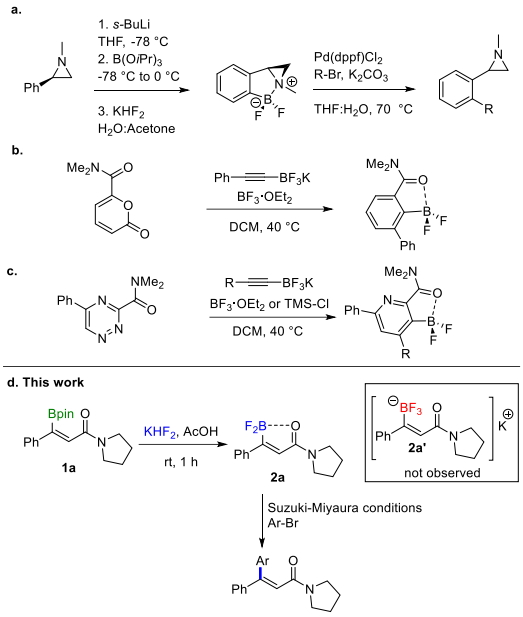


Figure 2. Fluorescent difluoroborates used in sensing and imaging.

widespread commercial availability of trifluoroborate salts. Exhaustive work by Molander and co-workers demonstrates the utility of organotrifluoroborates in the synthesis of important commodity materials.[1b] Fortunately, access to trifluoroborates is relatively straightforward as fluoride sources such as potassium fluoride or potassium bifluoride readily produce the tetravalent borate salts.[5a, 5b] While the polar nature of these compounds endows themselves air and moisture stability, their purification is limited to crystallization procedures that is often contaminated by the fluoride source or through tedious Soxhlet extraction. In contrast, the complementary difluoroborate counterparts have received far less attention in synthesis. In biology, however, BF_2-containing dyes such as BODIPY, curcumin-BF_2, and other related structures have been extensively explored primarily for their use as dyes, chelators, and imaging tools (Figure 2).[6] For example, BODIPY **2** recently reported by Yang and co-workers demonstrates high quantum yield, cell permeability, and utility in live cell imaging (Figure 2).[7] Additionally, organodifluoroborates have served as efficient catalysts in conjugate addition reactions[8] and as frustrated Lewis pair catalysts in C–H activation borylations.[9] Unfortunately, these difluoroborates often share the same polarity and purification burdens as trifluoroborate salts. While organic difluoroborates are typically generated *in situ* due to stability, handling, and the

Scheme 1. Previous Work



propensity of boron to form trifluoroborate salts,[10] intramolecular Lewis acid-base pair formation often affords stable adducts.

Seminal work by Florio and co-workers reported the synthesis of aryl tetra-coordinated difluoroborates and demonstrated their reactivity towards cross-coupling reactions (Scheme 1a).[11] Recently, Harrity and co-workers disclosed a benzannulation reaction mediated by difluoroborates generated *in situ* that afforded difluoroboryl benzamides in good yield (Scheme 1b). Intramolecular Lewis acid-base interactions with an amide or N-heterocycle directing group mediated the transformation and stabilized the resulting difluoroborate complex.[12] In follow-up work, an aza-Diels-Alder cycloaddition reaction between 1,2,4-triazines and alknyldifluoroboranes afforded

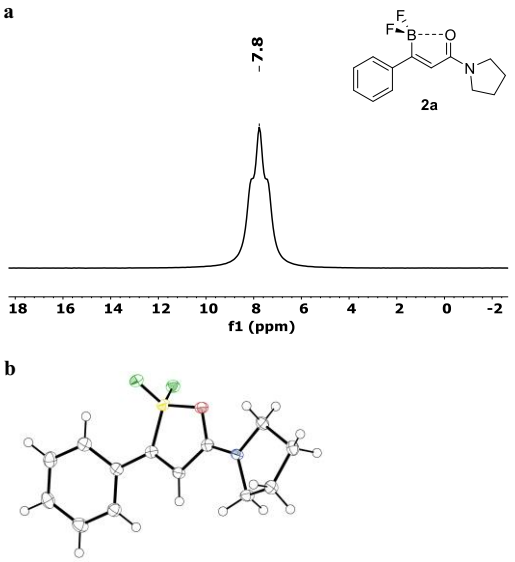


Figure 3. ^{11}B NMR (**a**) and X-ray Crystal Structure (b) for **2a** (CDC 1948315).

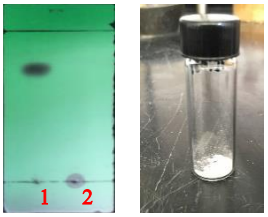
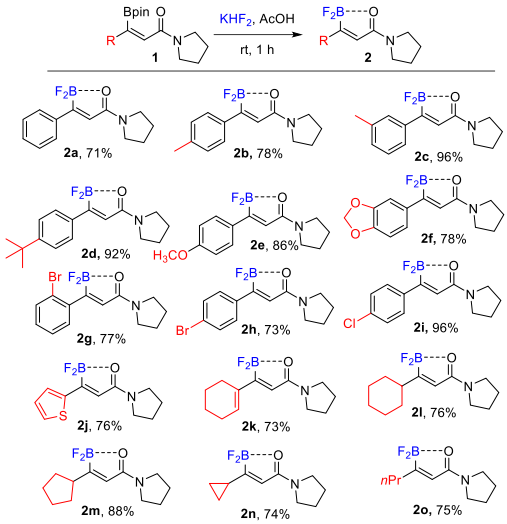


Figure 4. (a) Thin layer chromatography of **2a** (lane 1) and methyl (*E*)-3-phenyl-3-(trifluoroboryl)acrylate (lane 2) (b) Representative difluoroborate after months of storage under room air on the benchtop.

Scheme 2. Synthesis of Difluoroboryl Acrylamides[a]



[a]Reaction conditions: **1** (0.2 mmol) and KHF_2 (0.6 mmol) were dissolved in acetic acid (2 mL) at room temperature for 0.5-1 h. Isolated yields are shown.

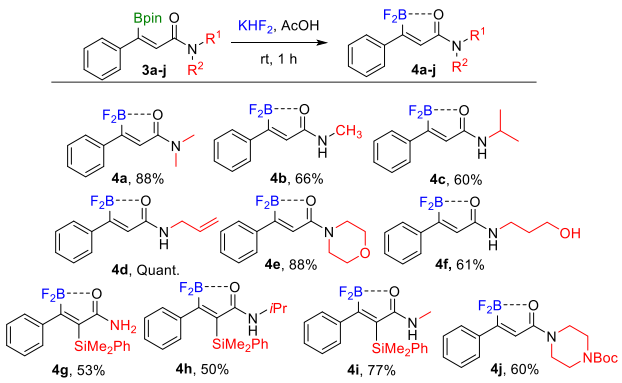
similar difluoroboryl picolinamide complexes (Scheme 1c).[13] In both examples, the resulting difluoroborate complexes served as effective substrates in subsequent cross-coupling reactions as the boron moiety is attached to the aryl ring.

Inspired by these previous studies and our work in conjugate borylation reactions with α,β-unsaturated carbonyls,[14] we were interested in stable vinyl boron derivatives and their potential application in organic synthesis. As such, we attempted to synthesize trifluoroborate salts from (*E*)-β-boryl acrylamides (**1**) and KHF_2 (Scheme 1d). To our surprise, the expected trifluoroborate salt **2a'** was not formed; instead a significantly less polar product was observed by thin layer chromatography. Isolation and extensive characterization of the product revealed difluoroboryl acrylamide (**2a**) (Scheme 1d). ^{11}B NMR indicated a strong amide O-B coordination as suggested by a single peak at 7.8 ppm, which is indicative of a tetrahedral geometry on boron (Figure 3a). We note that the corresponding fully saturated β-boryl amides reported in the literature demonstrate no intramolecular coordination at least on the ^{11}B NMR time scale (peak at 28 ppm indicates trigonal boron center) and readily form trifluoroborate salts;[15] however, recently reported (*E*)-β-boryl acrylamides exhibit intramolecular coordination and a tetrahedral boron center as determined by ^{11}B NMR.[16] This suggests that internal coordination of the carbonyl oxygen must be sufficiently stable to replace one of the fluorine atom in a trifluoroborate, which is also entropically driven because of the increase in effective molarity of the Lewis base. To demonstrate

necessity of the (*Z*)-configuration for difluoroborate synthesis, (*Z*)-**1a** was prepared.[14a] Upon treatment of (*Z*)-**1a** with KHF_2 in acetic acid, the corresponding difluoroboryl acrylamide was not observed. An X-ray crystal structure of **2a** unequivocally identified the difluoroboryl structure and revealed a B–O coordinate bond length of 1.535 Å (Figure 3b). In contrast to the expected trifluoroborate or difluoroborate salts, **2a** was relatively nonpolar relative to the boronate ester starting material and was readily purified by silica gel chromatography. Thin layer chromatography highlighted the stark contrast in polarity between **2a** and potassium trifluoroborates as well as the well-delineated migration of **2a** on silica (Figure 4a). Furthermore, we observed that these difluoroboryl acrylamides could be stored as a dry white solid at room temperature without special storage conditions as no physical changes or degradation products were observed during the course of this study (at least 18 months, see Figure 4b). From our observations, these difluoroboryl acrylamides share the desirable stability and reactivity (*vide infra*) as trifluoroborate salts but with the added advantage of ease of handling and purification.

To determine the nature and reactivity of these compounds, we investigated whether a variety of pinacol protected substrates can be readily transformed to difluoroboryl acrylamides (Scheme 2). Using previously reported methods to access the (*E*)-β-boryl acrylamide starting material,[16a] difluoroboryl acrylamides **2a-2o** were efficiently synthesized under mild conditions using potassium bifluoride in acetic acid (Scheme 2). Difluoroboryl acrylamides containing alkyl groups (**2a-2d**) and electron donating groups such as methoxy (**2e**) and methylenedioxy (**2f**) on the phenyl ring were synthesized from their corresponding pinacol boronate acrylamides in good to excellent yields with no significant bias with respect to electronics or sterics observed. Difluoroboryl acrylamide products bearing halides such as bromine (**2g**, **2h**) and chlorine (**2i**) were also synthesized in excellent yield. Heterocycle such as thiophene derivative (**1j**) was also effectively transformed to the diborylacrylamide product (**2j**) in good yield. Dienamide (**1k**) served as an efficient substrate to afford **2k** in good yield. Cyclohexyl (**1l**), cyclopentyl (**1m**) or cyclopropyl (**1n**) substituted vinyl boronic acid derivatives were readily converted to the corresponding difluoroborates (**2l-2n**). Furthermore, linear alkanes were likewise tolerated generating compound **2o**. These results suggest the wide substrate tolerance of the reaction.

Scheme 3. Synthesis of Difluoroboryl Acrylamides[a]

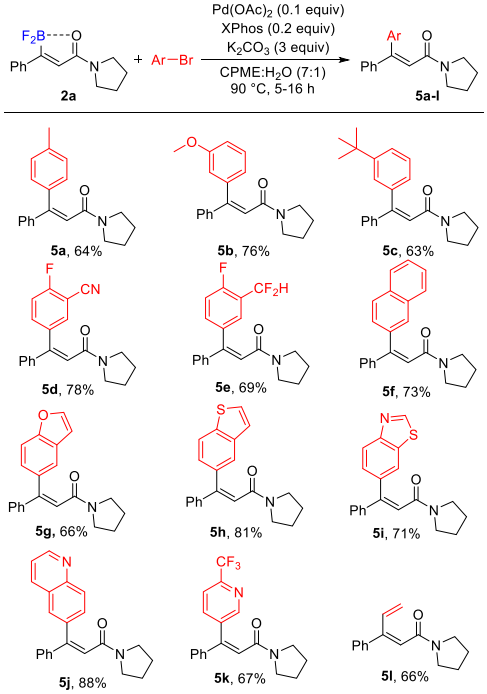


[a]General procedure: **1** (0.2 mmol) and KHF_2 (0.6 mmol) were dissolved in acetic acid (2 mL) at room temperature for 0.5-1 h. Isolated yields are shown.

Next, we found it prudent to determine whether substitutions on nitrogen affect the ability of the amide oxygen to form an internally coordinated boron center. As such, (*E*)-β-boryl acrylamides **3a-3j** were prepared and converted to the corresponding difluoroboryl acrylamides (Scheme 3). The tertiary dimethyl amide difluoroborate (**4a**) was synthesized in excellent yield. Secondary amides bearing a methyl (**4b**) or isopropyl (**4c**) groups were synthesized from their corresponding substrates in good yield, albeit at slightly lower yields. Further, an allyl substituted amide (**3d**) very efficiently afforded the product **4d** in excellent yield. Morpholinamide (**3e**) was also a competent substrate for the reaction to afford **4e**. In the case of a TBS-protected alcohol (**3f**), fluorination proceeded with conversion to the difluoroborate with concurrent cleavage of the silyl protecting group to generate the corresponding alcohol **4f**. In the presence of dimethylphenylsilyl containing substrates **3g-3i,**[17] **4g-4i** were isolated in moderate to good yields. To our delight, the dimethylphenylsilyl group was well tolerated. We also found that the reaction was compatible with other protecting groups such as Boc as the Boc-protected piperazine **4j** was isolated in good yield.

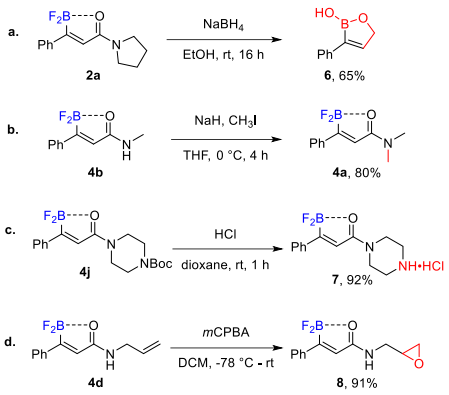
Next we turned our attention to the reactivity of the difluoroboryl acrylamides in cross-coupling reactions. To our delight, difluoboryl acrylamides served as efficient substrates under standard Suzuki-Miyaura cross-coupling conditions (Scheme 4).[15f] For example, difluoroboryl acrylamide **2a** effectively underwent the cross-coupling reaction against a variety of electron rich and electron deficient aryl bromides to afford the corresponding trisubstituted acrylamides **5a-5e**. Napthalene as well as other heteroaromatics such as benzofu-

Scheme 4. Suzuki-Miyaura Cross-Coupling of Difluoroboryl Acrlyamides[a]



[a]General procedure: **2a** (0.2 mmol), aryl bromide (0.22 mmol), $Pd(OAc)_2$ (0.02 mmol), XPhos (0.04 mmol), and K_2CO_3 (0.6 mmol) in CPME:H_2O (1 mL:0.4 mL) at 90 °C for 5-16 h. Isolated yields are shown. CPME: cyclopentyl methyl ether.

Scheme 5. Transformations of Difluoroboryl Acrylamides



ran, benzothiophene, benzothiazole, quinoline and pyridine substituents served as excellent substrates generating **5f-5k** in good to excellent yields. Furthermore, vinyl bromide was productively cross-coupled to yield the conjugated dieneamide **5l**.

In addition to cross-coupling reactions, we investigated the versatility of the organoboron derivative toward other transformations. Recent interest in benzoxaboroles as pharmacophores in medicinal chemistry[18] such as in the FDA approved drugs Crisaborole (Eucrisa)[19] and Tavaborole (Kerydin)[20] are increasing. Thus, synthetic methods towards these important class of compounds are important. Fortunately, we found that treating **2a** with sodium borohydride in ethanol afforded 3-phenyl oxaborole **6** in 65% yield (Scheme 5a). We previously demonstrated the similar transformation using the corresponding ester[16a] but this is the first example of the conversion from an amide. In contrast, attempts to reduce the corresponding pinacol protected version of **2a** under similar conditions were unsuccessful.

Because the boron center in difluoroboryl acrylamides are tetrahedral in nature, we hypothesized that they will likewise serve a dual purpose of acting as protecting group. For example, secondary amide **4b** was subjected to simple alkylation with sodium hydride and methyl iodide to produce tertiary amide **4a** in 80% yield (Scheme 5b). Under these basic conditions, we did not observe any protodeboration. Furthermore, the difluoroboryl group remained intact during the hydrogen chloride-mediated Boc-deprotection of **4j** affording the HCl salt **7** in excellent yield (Scheme 5c). Stability under oxidative condition was also explored using allyl substituted amide **4d** (Scheme 5d). Oxidization with mCPBA proceeded in excellent yield affording epoxide **8**. This chemoselectivity demonstrates the utility of difluoroboryl group in modern synthetic chemistry.

In conclusion, we have discovered a class of readily accessible difluoroboryl compounds with excellent potential towards further transformation. A notable property of these molecules is their stability and nonpolar nature affording the capacity to purification using silica gel column chromatography. The versatility of these substrates was demonstrated not only in their ability to undergo Suzuki-Miyaura cross-coupling reaction but also as carbon protecting groups in oxidation as well as other reactions. The potential application of these compounds is currently under investigation in our labs and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental details and characterization data for all new compounds.

Accession Codes

CCDC 1948315 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing da-ta_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.).

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