Facile Preparation of Fluorine-containing Alkenes, Amides and Alcohols *via* the Electrophilic Fluorination of Alkenyl Boronic Acids and Trifluoroborates

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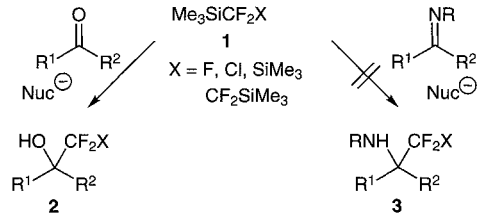
Abstract: Reaction of alkenyl boronic acids, or preferably alkenyl trifluoroborates, with one equivalent of Selectfluor™ gives the corresponding alkenyl fluorides. A similar reaction with two equivalents of Selectfluor™ in water or a nitrile solvent gives difluoromethyl-substituted alcohols and amides respectively.

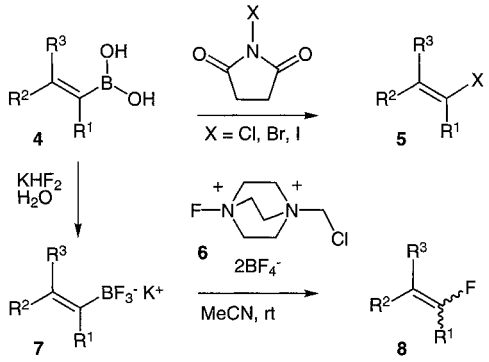
The profound ability of fluorine to modulate the physical, chemical and biological properties of organic molecules, continues to present new opportunities for the design of novel enzyme inhibitors, biochemical probes, agrochemicals, and polymeric materials. In view of the unique features of fluorine-containing compounds,[1] there has been an increasing interest in the development of novel and practical methods for the synthesis of fluorinated molecules.[2]

Among recent developments in this area that have received particular attention, are several convenient fluoroalkylation methods developed in our laboratories which allow the introduction of trifluoromethyl,[3] and difluoromethyl[4] groups. These methods involve silicon-containing reagents of the general type **1** and rely on nucleophilic catalysis to deliver the fluoroalkyl groups onto carbonyl compounds and other electrophiles. Although these procedures allow the preparation of various fluoroalkyl-containing alcohols (**2**), they are not suitable for the analogous formation of fluoroalkylated amines (**3**) *via* similar additions to the corresponding imines.[5] This difference in the reactivity between imines and carbonyl compounds may be attributed to the weaker Si-N bond as compared to the Si-O bond.



Herein, we report a novel method for the convenient synthesis of alkenyl fluorides as well as difluoromethyl-substituted[6] alcohols and amides *via* the electrophilic fluorination[7] of alkenyl boronic acids and trifluoroborates. Recent studies on the chemistry of alkenyl boronic acids (**4**) in our laboratories have revealed that these readily available and experimentally convenient intermediates undergo facile reactions with *N*-halosuccinimides to give geometrically pure alkenyl halides (**5**).[8] As an extension of this method, we anticipated that an electrophilic fluorine source under similar conditions may lead to the corresponding alkenyl fluorides (**8**). Although there was a recent report on the use of electrophilic fluorination for the conversion of alkenyl organometallics to the corresponding alkenyl fluorides,[9] these reactions employed organotin derivatives and were performed at elevated temperatures. We, therefore, explored the reactivity of alkenyl boronic acids with Selectfluor™ (**6**), a commercially available and synthetically useful electrophilic fluorinating agent.[10]

While the reaction of **4** with **6** produced alkenyl fluorides (**8**) as expected, this reaction was usually quite slow and the product was contaminated with variable amounts of the corresponding fluorine-free alkene. Consequently, we examined the related chemistry of alkenyl trifluoroborates (**7**), easily prepared from **4**[11] or directly from alkynes,[12] by adapting the method of Vedejs.[13] Indeed, reaction of **7** with one equiv. of **6** gave the corresponding fluorinated alkenes (**8**) in good yields.[14] This method is quite mild and synthetically appealing since it utilizes relatively non-toxic reagents and can be performed either in acetonitrile or water. Unlike the conversion of **4** to **5**, however, which proceeded in a stereocontrolled manner, fluorides **8** were obtained as *Z*/*E* mixtures.



R¹	R²	R³	Product	Yield	E/Z Ratio
H	Ph	H	**8a**	89 %	50/50
H	Bu	H	**8b**	58 %	50/50
H	4-MeC$_6$H$_4$	H	**8c**	87 %	50/50
H	4-ClC$_6$H$_4$	H	**8d**	78 %	50/50
Ph	Ph	H	**8e**	71 %	85/15
H	Ph	Br	**8f**	65 %	50/50

We have also found that when a second equivalent of **6** is used, the alkenyl fluorides being formed undergo further reaction to produce a putative carbocationic intermediate which is quenched with the solvent. Although we have not examined in detail the effect of carbocation stability in this process, we noted that the reaction worked well only with compounds leading to benzylic carbocations (R^2=Ar). When the reaction is performed in water the products are the corresponding difluoromethyl alcohol derivatives.[15] Similarly, when the reaction is performed in acetonitrile or propionitrile it leads to the corresponding difluoromethyl amide products.[16] In this case, the reaction can be considered as the fluoro analog of the Ritter reaction[17,18] ("fluoro-Ritter" reaction). In both cases the experimental procedure and work-up are quite simple, allowing the isolation of the corresponding alcohol or amide in good yields.

In terms of mechanism, the reaction of **4** or **7** with **6** to give **8** presumably proceeds differently than the conversion of **4** to **5**. Rather than a direct transfer of the alkenyl moiety to the fluorine atom, which would give geometrically pure **8**, the reaction presumably involves an addition-elimination pathway *via* a carbocation intermediate. The formation of a mixture of geometrical isomers and the faster reaction with the more nucleophilic trifluoroborates are consistent with this mechanism.

Overall, the reaction of alkenylboron compounds with electrophilic fluorinating agents provides a simple and experimentally convenient route to alkenyl fluorides as well as difluoromethylated alcohols and amides. This chemistry complements previously reported methods for the synthesis of such compounds, while further manipulation of the

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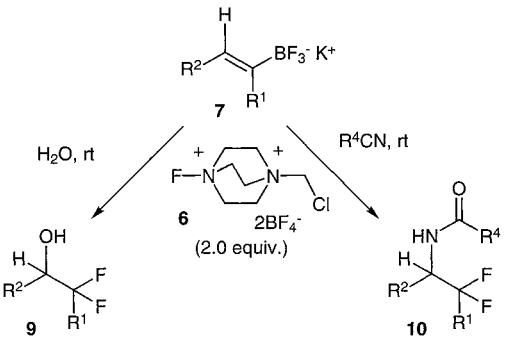

R1	R2	Alcohol	Yield
H	Ph	**9a**	69 %
H	4-MeC6H4	**9b**	71 %
H	4-ClC6H4	**9c**	67 %
Ph	Ph	**9d**	58 %
Me	Ph	**9e**	75%

R1	R2	R4	Amide	Yield
H	Ph	Me	**10a**	82 %
H	4-MeC6H4	Me	**10b**	68 %
H	4-ClC6H4	Me	**10c**	81 %
Ph	Ph	Me	**10d**	77 %
H	Ph	Et	**10e**	62 %

substituents can potentially lead to other types of fluorine-containing functional groups which continue to be of great importance in the design of bioactive substances and other molecules.

Acknowledgments

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12) Typical experimental procedure: Phenylacetylene (5 g, 5.38 mL, 49 mmol) was slowly added into a flame-dried flask containing neat catecholborane (6 g, 5.33 mL, 50 mmol) stirred under an argon atmosphere. This exothermic reaction (caution!) was stirred at room temperature and was occasionally cooled with a cold water bath so that the temperature did not exceed 70 °C. After about 1 hr, when the reaction stopped producing heat, the flask was sealed and heated at 75 °C for 4 hours. The reaction mixture was then cooled to ambient temperature and opened to the air. Excess saturated aqueous solution of KHF_2 (50 mL, ca. 4.5 M) was then added slowly with vigorous stirring (exothermic reaction). After 15 min, the precipitated product was collected and washed with cold methanol. Recrystallization from minimal acetonitrile gave pure potassium (E)-(2-phenylethenyl)trifluoroborate (8.3 g, 81 % yield). ^{1}H-NMR (360 MHz, CD_3CN) δ 7.1-7.4 (m, 5H), 6.6 (d, J=18.8 Hz, 1H), 6.28 (dq, J=18.8 Hz, 4.1 Hz, 1H). ^{13}C-NMR (90 MHz, CD_3CN) δ 141.7, 134.9 (q), 129.2, 127.0, 126.6. ^{19}F-NMR (339 MHz, CD_3CN) δ -140 (br).

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14) Typical experimental procedure: Selectfluor™ (354 mg, 1.0 mmol) was added to a solution of potassium (*E*)-(2-phenylethenyl) trifluoroborate (210 mg, 1.0 mmol) in acetonitrile (10 mL) and the resulting mixture was stirred at room temperature for 24 hr. The solvent was evaporated and the residue was treated with aqueous NaOH (5 mL, 1.0 M). Extraction with diethyl ether (3 x 10 mL), solvent evaporation and purification by flash-column chroma-tography (silica gel, hexanes) yielded pure 1-fluoro-2-phenylethylene (109 mg, 89 % yield, 1:1 E/Z mixture). For (*Z*)-isomer: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.3-7.5 (m, 5H), 6.65 (dd, J = 84 Hz, 5.4 Hz, 1H), 5.60 (dd, J = 45 Hz, 5.4 Hz, 1H). ^{19}F NMR (339 MHz, $CDCl_3$) δ -122.6 (dd, J = 84 Hz, 45 Hz).

15) Typical experimental procedure: Selectfluor™ (708 mg, 2.5 mmol) was added to a solution of potassium (*E*)-(2-phenylethenyl) trifluoroborate (210 mg, 1.0 mmol) in water (10 mL) and the resulting mixture was stirred at room temperature for 48 hr. The reaction mixture was quenched with aqueous NaOH (10 mL, 1.0ÊM) and extracted with diethyl ether (3 x 10 mL). Solvent evaporation and purification by flash-column chromatography (silica gel, hexanes-ethyl acetate 7:3) yielded pure 2,2-difluoro-l-phenylethanol (109 mg, 69 % yield). ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.30 (br m, 5H), 5.68 (td, J = 55.9 Hz, 4.8 Hz, 1H), 4.82 (td, J = 10 Hz, 4.8 Hz, 1H), 2.4 (br, 1H); ^{19}F NMR (339 MHz, $CDCl_3$) δ -128.6 (ddd, J = 280 Hz, 56 Hz, 10.5 Hz, 1F), - 126.2 (ddd, J = 280 Hz, 56 Hz, 10.5 Hz, 1F). (Lit.: Hagiwara, T.; Fuchikami, T. *Synlett*, **1995**, 717).

16) Typical experimental procedure: Selectfluor™ (708 mg, 2.5 mmol) was added to a solution of potassium (*E*)-(2-phenylethenyl) trifluoroborate (210 mg, 1 mmol) in acetonitrile (10 mL) and the resulting mixture was stirred at room temperature

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for 48 hr. The solvent was evaporated and the residue was treated with aqueous NaOH (5 mL, 1.0M). Extraction with diethyl ether (3 x 10 mL), followed by purification by flash-column chromatography (silica gel, hexanes-ethyl acetate 7:3) yielded pure (*N*-acetyl)-2,2-difluoro-l-phenylethylamine (164 mg, 82 % yield) as an off-yellow powder. ^{1}H NMR(360 MHz, $CDCl_3$) δ 7.32 (m, 5H), 6.45 (d, J = 8.6 Hz, 1H), 5.98 (td, J = 55.3 Hz, 2.4 Hz, 1H), 5.37 (tdd, J = 15.1 Hz, 8.6 Hz, 2.4 Hz, 1H), 2.00 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 170.4, 133.9, 128.9, 128.8, 127.8, 114.6 (t, J = 245.6 Hz), 54.8 (t, J = 21.5 Hz), 23.0; ^{19}F NMR (339 MHz, $CDCl_3$) δ -125.5 (ddd, J = 281.3 Hz, 58.1 Hz, 15.6 Hz, 1F), -127.7 (ddd, J = 281.0 Hz, 55.2 Hz, 14.7 Hz, 1F); HRMS calcd for $C_{10}H_{12}NOF_2$ 200.0889, found 200.0887.

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