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Short communication

Regioselective hydroboration-oxidation and -amination of fluoro-substituted styrenes

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Abstract

Hydroboration of fluorinated styrenes with common hydroborating agents results in polymerization. However, regioselective hydroboration has been achieved by utilizing iodoborane-dimethyl sulfide. A series of fluorinated β-phenethyl alcohols and amines were synthesized via this methodology.
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1. Introduction

Due to the similarity in size, fluorine has been used as a replacement for hydrogen in many biologically active organic molecules, for use in PET (Positron Emission Tomography) scanning as well as to examine its influence in the biochemistry of such molecules [1]. Fluorine substitution on 2-substituted-1-alkenes substantially modifies the regioselectivity in the transition-metal catalyzed [2] and uncatalyzed [3–5] hydroboration reaction. While the hydroboration-oxidation of 2,3,4,5,6-pentafluorostyrene with BH_3·THF, $BHCl_2$·SMe_2, $BHBr_2$, ChxBClH, catecholborane (CBH), pinacolborane (PBH) yields the Markovnikov product [2,3], CHx_2BH, 9-BBN and Sia_2BH provide the anti-Markovnikov product [4]. Hydroboration with $ThxBH_2$ provides equal amounts of Markovnikov and anti-Markovnikov products [4].

Herein we report a simple and highly regioselective hydroboration of fluoro-substituted styrenes (**1**) for the synthesis of β-fluoroaryl organoboranes (**2**), which were readily converted to the corresponding fluorinated primary alcohols (**3**) and primary amines (**4**) (Scheme 1).

2. Results and discussion

The hydroboration-oxidation of 2-, 3-, and 4-fluorostyrenes under transition-metal catalyzed conditions provide the secondary alcohols (Scheme 2). In continuation of our research on the utilization of organoboranes for the synthesis of various fluorinated amino acids [6], we desired a simple, direct method for the selective access to the hydroboration products, which can be readily converted to the anti-Markovnikov alcohols as oxidation products. The preparation of Markovnikov alcohols from fluoro-substituted styrenes have been reported [7–13]. We expected the anti-Markovnikov products via the non-catalyzed (stoichiometric) hydroboration of fluoro-substituted styrenes with common hydroborating agents [14]. Our assumption was based on the fact that a lone fluorine atom on the benzene ring will have minimal electronic effect.

The initial hydroboration experiments were attempted on 2-fluorostyrene with BH_3·SMe_2 in ethyl ether at 0 °C. To our surprise, the ^{11}B NMR of an aliquot of the reaction mixture showed a quartet (δ −20.3) corresponding to unreacted BH_3·SMe_2. However, a TLC and ^1H NMR analysis revealed consumption of the olefin. Upon careful analysis, we observed that the attempted hydroboration had resulted in the polymerization of the olefin in the presence of borane, with the quantitative recovery of the borane reagent, as determined by hydrolysis [15]. The fluorostyrene met with the same fate in

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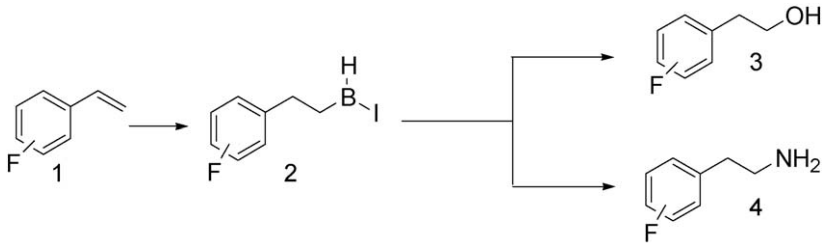
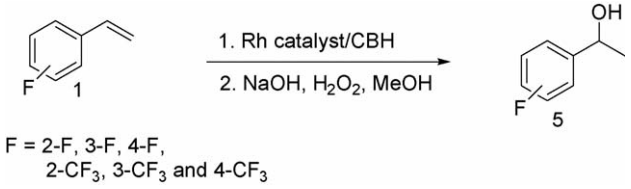
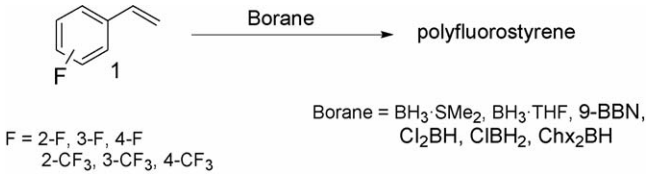


Scheme 1. Regioselective hydroboration, followed by oxidation/amination.



Scheme 2. Hydroboration-oxidation of fluoro-substituted styrenes.

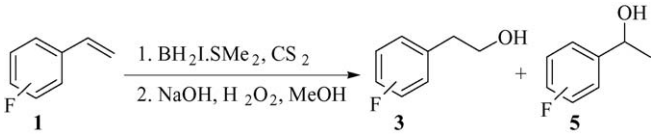


Scheme 3. Attempted hydroboration of fluoro-substituted styrenes with common boranes.

the presence of several other boranes, such as $BHCl_2{\cdot}SMe_2$, 9-BBN, $BHCl_2$, BH_2Cl and CHx_2BH. Hydroboration of 3-, 4-fluoro and 2-CF_3-, 3-CF_3- and 4-CF_3-styrenes also led to polymerization in the presence of $BH_3{\cdot}SMe_2$, $BH_3{\cdot}THF$, 9-BBN, $BHCl_2$, BH_2Cl and CHx_2BH (Scheme 3).

Our quest for a borane reagent that would not polymerize fluorostyrenes, led to the examination of $BH_2I{\cdot}Py$ or $BH_2I{\cdot}SMe_2$. Vedejs and co-workers have recently reported the possibility of activating $Py{\cdot}BH_3$ by replacing one of the hydrogens of borane with iodine and carrying out the hydroboration of alkenes and alkynes [16,17]. We applied the same technique for the hydroboration-oxidation of fluoro-substituted styrenes (Scheme 4). Thus, the hydroboration of 4-fluorostyrene with $BH_2I{\cdot}SMe_2$, prepared via the iodination [18] of $BH_3{\cdot}SMe_2$ in CS_2, was complete within 5 h at RT, as revealed by a doublet at δ −6.5 in the ^{11}B NMR spectrum. The reaction mixture was cooled to 0 °C, quenched with methanol and oxidized under alkaline

Table 1
Regioselective hydroboration-oxidation of fluoro-substituted styrenes[a]



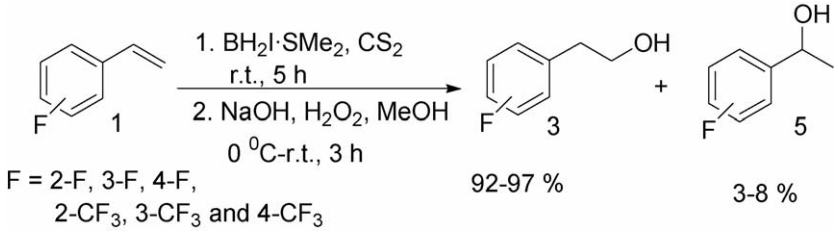
Entry	F	Yield[b] (%)	Product alcohol[c]	
			1°-ol	2°-ol
1	2-F	96	**3a** (97)	**5a** (3)
2	3-F	92	**3b** (94)	**5b** (6)
3	4-F	95	**3c** (97)	**5c** (3)
4	2-CF_3	82	**3d** (93)	**5d** (7)
5	3-CF_3	80	**3e** (92)	**5e** (8)
6	4-CF_3	92	**3f** (95)	**5f** (5)
7	2,3,4,5,6-F_5	72	**3g** (33)	**5g** (67)

[a] Reaction conditions: 1:1 ratio, $BH_2I{\cdot}SMe_2$/fluorostyrene, RT, methanol (2 mL), 1.2 equiv. NaOH, 1.2 equiv. H_2O_2, 0 °C.
[b] Isolated yields.
[c] Isomer ratio determined by ^1H NMR.

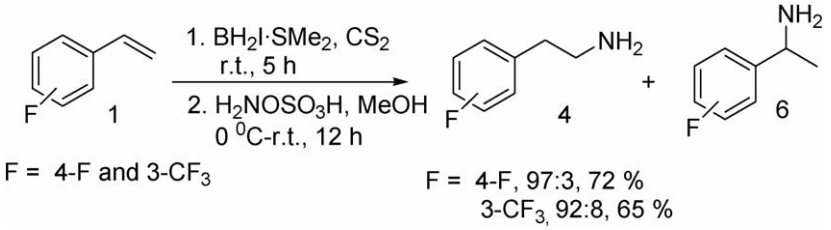
conditions to obtain a 95 % yield of essentially pure primary alcohol product **3c** (**3c**:**5c** = 97:3).

This protocol was then applied to a variety of fluoro-substituted styrenes to provide the corresponding primary alcohols with high selectivity (Table 1). Interestingly, hydroboration of 2,3,4,5,6-pentafluorostyrene with $BH_2I{\cdot}SMe_2$, followed by oxidation with alkaline H_2O_2 provided a 72% yield of a 33:67 mixture of primary and secondary alcohols (**3g** and **5g**) (Table 1, entry 7). This mighty be expected on the basis of our earlier results on the hydroboration of 2,3,4,5,6-pentafluorostyrene with $ThxBH_2$ [4].

Having succeeded in achieving the synthesis of the fluorinated β-phenethanols, we turned our attention to the preparation of representatives of the corresponding β-phenethyl amines [19–22]. Following hydroboration of 4-fluorostyrene



Scheme 4. Hydroboration-oxidation of fluoro-substituted styrenes with iodoborane.



Scheme 5. Hydroboration-amination of fluoro-substituted styrenes with iodoborane.

with $BH_2I{\cdot}SMe_2$, the reaction mixture was cooled to 0 °C, quenched with methanol and aminated using hydroxylamine-*O*-sulfonic acid to obtain a 72% yield of essentially pure primary amine (**4a**:**6a** = 97:3) (Scheme 5). Similarly, the hydroboration-amination of 3-trifluoromethyl styrene gave a 65% yield of primarily the primary amine (**4b**:**6b** = 92:8).

3. Conclusion

In conclusion, we have developed a simple and highly regioselective preparation of β-fluoroaryl organoboranes and converted them to the corresponding fluorinated alcohols and amines.

4. Experimental

Unless otherwise noted, all manipulations were carried out under an inert atmosphere using flame-dried glassware. Iodine was purchased from Fisher Scientific. Carbon disulfide (CS_2), and hydroxylamine-*O*-sulfonic acid were purchased from the Aldrich Chemical Co. Fluorostyrenes were purchased from Apollo Scientific Co. Other chemicals were used without further purification, unless otherwise noted.

The ^1H, ^{11}B and ^{19}F nuclear magnetic resonance (NMR) spectra were plotted on a Varian Gemini-300 spectrometer (300, 75 and 282 MHz, respectively) with a Nalorac-quad probe. ^1H NMR spectra were obtained using $CDCl_3$ as the solvent with either tetramethylsilane (TMS: 0 ppm) or chloroform ($CHCl_3$: 7.2 ppm) as the internal standard. ^{19}F NMR spectra were recorded in $CDCl_3$ using $CFCl_3$ or trifluoroacetic acid (TFA) as the internal standard. ^1H NMR data are reported as chemical shifts (δ, ppm), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant (Hz), and integration. Flash chromatography was performed on 40–60 μm silica gel (230–400 mesh).

5. Representative experimental procedures

5.1. Iodoborane-dimethyl sulfide [18]

An oven-dried, 250 mL round-bottomed flask, equipped with a side arm, was cooled to 0 °C under a stream of nitrogen. In the flask was placed CS_2 (10 mL) and $BH_3{\cdot}SMe_2$ (14.85 mL, 10.0–10.2 M, 0.15 mol). The flask was maintained at 0 °C by immersion in an ice-water bath. To this flask was added a precooled I_2 solution (19.03 g, 0.075 mol) in CS_2 (75 mL) slowly using a double-ended needle. After hydrogen evolution was completed (2 h), the solvent was evaporated under reduced pressure. Fractional distillation yielded iodoborane-dimethyl sulfide (24 g, 80% yield). ^{11}B NMR: δ −20.1 (t).

5.2. Hydroboration-oxidation of fluoro-substituted styrenes

An oven-dried, 50 mL round-bottomed flask, equipped with a side arm, was cooled to 0 °C under a stream of nitrogen. In the flask was placed CS_2 (10 mL) and $BH_3{\cdot}SMe_2$ (1.485 mL, 10.0–10.2 M, 15 mmol). The flask was maintained at 0 °C by immersion in ice-water bath. To this flask was added a precooled I_2 solution (1.903 g, 7.5 mmol) in CS_2 (10 mL) slowly using a double-ended needle. After hydrogen evolution was completed (2 h), the solution was warmed to room temperature and 4-fluorostyrene (15 mmol) was added. After the completion of the reaction (5 h, monitored periodically by ^{11}B NMR doublet at δ −6.5), the reaction mixture was cooled to 0 °C with an ice bath, and quenched with methanol. NaOH (1.2 equiv., 3 M in H_2O) and H_2O_2 (1.2 equiv., 30% aqueous) were added. This mixture was allowed to stir at room temperature for an additional 2 h. The solution was then poured into separatory funnel, diluted with ethyl ether and H_2O, and acidified with HCl (aq). The water layer was washed with ether (2 × 20 mL) and dried with Na_2SO_4. Solvent was removed to afford **3c** (95%, **3c**:**5c** = 97:3). The regioselectivity was determined by ^1H NMR spectroscopic analysis of the final crude reaction mixture after oxidative work-up.

5.2.1. 2-Fluorophenethyl alcohol (*3a*)

^1H NMR (300 MHz, $CDCl_3$): δ 7.30–6.95 (m, 4H), 3.86–3.81 (t, *J*(H,H) = 6.6 Hz, 2H), 2.98–2.86 (t, 2H), 2.22 (brs, 1H).

5.2.2. 3-Fluorophenethyl alcohol (*3b*)

^1H NMR (300 MHz, $CDCl_3$): δ 7.40–7.21 (dd, 2H), 7.02–6.80 (dd, 2H), 3.83–3.79 (t, *J*(H,H) = 6.45 Hz, 2H), 2.90–2.79 (t, 2H), 2.22 (brs, 1H).

5.2.3. 4-Fluorophenethyl alcohol (*3c*)

^1H NMR (300 MHz, $CDCl_3$): δ 7.22–7.14 (dd, 2H) 7.06–6.94 (dd, 2H), 3.85–3.77 (t, 2H), 2.89–2.80 (t, 2H), 1.80 (brs, 1H).

5.2.4. 2-(Trifluoromethyl)phenethyl alcohol (*3d*)

^1H NMR (300 MHz, $CDCl_3$): δ 7.71–7.22 (m, 4H), 3.98–3.82 (t, 2H), 3.12–2.98 (t, 2H), 1.89 (brs, 1H).

*5.2.5. 3-(Trifluoromethyl)phenethyl alcohol (**3e**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61–7.30 (m, 4H), 3.87–3.83 (t, J(H,H) = 6.42 Hz, 2H), 2.98–2.82 (t, 2H), 2.22 (brs, 1H).

*5.2.6. 4-(Trifluoromethyl)phenethyl alcohol (**3f**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59–7.43 (dd, 2H), 7.40–7.30 (dd, 2H), 3.91–3.86 (t, J(H,H) = 6.34 Hz, 2H), 2.99–2.90 (t, 2H), 1.75 (brs, 1H).

*5.2.7. (±)-α-Methyl-2,3,4,5,6,-pentafluorobenzyl alcohol (**5g**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.29–5.12 (s, 1H), 2.82 (brs, 1H), 1.69–1.52 (d, 3H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −54.46 (t).

5.3. Hydroboration-amination of fluoro-substituted styrenes

An oven-dried, 50 mL round-bottomed flask, equipped with a side arm, was cooled to 0 °C under a stream of nitrogen. In the flask was placed CS_2 (10 mL) and $BH_3{\cdot}SMe_2$ (1.485 mL, 10.0–10.2 M, 15 mmol). The flask was maintained at 0 °C by immersion in an ice-water bath. To this flask was added a precooled I_2 solution (1.903 g, 7.5 mmol) in CS_2 (10 mL) slowly using a double-ended needle. After hydrogen evolution was completed, the solution was warmed to room temperature and 4-fluorostyrene (1.79 mL, 15 mmol) was added. After the completion of the reaction (5 h), monitored periodically by ^{11}B NMR doublet at δ −6.5, the reaction mixture was cooled to 0 °C with an ice bath, and quenched with methanol. To this boronic ester, solid hydroxylamine-*O*-sulfonic acid (3.392 g, 30 mmol) was added by using a solid addition tube. The reaction mixture was stirred at RT for 12 h to ensure complete conversion. Water (10 mL) and ethyl ether (15 mL) were added. The acidic aqueous layer was separated, cooled to 0 °C and layered with ethyl ether. The solution was then made strongly alkaline by adding aq. NaOH with stirring. The organic phase was separated and the combined organic phase was dried with Na_2SO_4. Solvent was removed to afford **4a** (72%, **4a**:**6a** = 97:3).

*5.3.1. 4-Fluorophenethyl amine (**4a**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22–6.84 (m, 4H), 2.89–2.60 (m, 4H), 1.16 (s, 2H).

*5.3.2. 3-(Trifluoromethyl)phenethyl amine (**4b**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32–6.82 (m, 4H), 2.89–2.60 (m, 4H), 1.39 (s, 2H).

Acknowledgement

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