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Synthesis of Fluorinated Olefins via the Palladium Catalyzed Cross-Coupling Reaction of 1-Fluorovinyl Halides with Organoboranes

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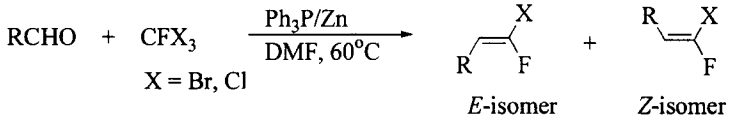
Abstract: The palladium catalyzed cross-coupling reaction of 1-fluorovinyl halides **1-4** with organoboranes proceeds under Suzuki conditions with retention on configuration to give 1-substituted 1-fluoroolefins **6-8** in good to excellent yields.

Keywords: Palladium catalyzed cross-coupling; fluoroolefins; oranoboranes; stereospecific

New synthetic methods to fluoroorganic compounds have received considerable attention in recent years,[1] in part because of the observation that biological activity is often observed on the introduction of fluorine into a class of compounds that is being synthesized to obtain biologically active agents.[2] For this reason fluorinated olefins[3] have attracted much attention as potential enzyme inhibitors.[4] Recently we communicated the stereospecific Pd(0)/Cu(I) catalyzed cross-coupling of 1-fluorovinylstannanes with aryl iodides under Stille conditions to afford substituted fluoroolefins.[5] In this Letter we report a new palladium-catalyzed cross-coupling reaction[6] of 1-fluorovinyl bromides or chlorides with organoboranes that provides a stereospecific route to 1-substituted 1-fluoroolefins.

The required 1-fluorovinyl bromides or chlorides **1-4** are readily available by the condensation of aldehydes with fluorotribromomethane or fluorotrichloromethane in the presence of triphenylphosphine and zinc,[7] as a mixture of *E, Z* isomers that are separable by gas chromatography (Scheme 1). Alternatively,

Scheme 1



E-isomer *Z*-isomer

***Z*-1 or *E*-1**: R = Ph, X = Br;
2: R = Ph, X = Cl;
3: R = p-MeOPh, X = Cl;
4: R = $PhCH_2CH_2$, X = Cl

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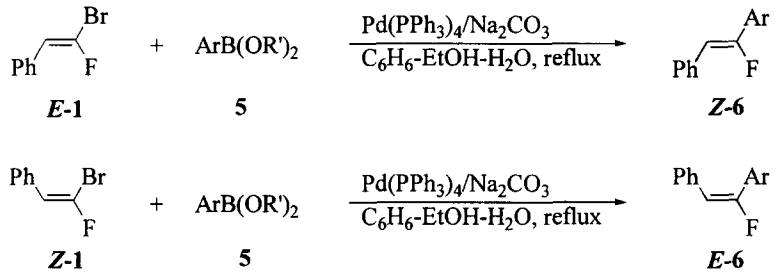
bromination of *E*-1-fluorophenylacrylic acid[6] followed by debromocarboxylation gives pure isomer *Z*-**1**. The corresponding *E*-isomer[8] *E*-**1** was obtained in 92% isomeric purity by isomerization of *Z*-**1** with a catalytic amount of bromine in chloroform.

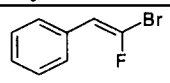
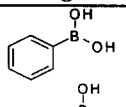
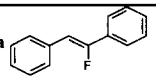
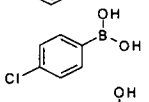
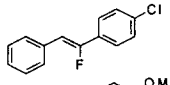
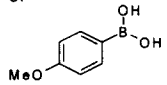
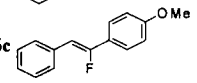
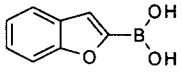
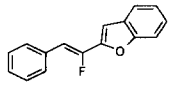
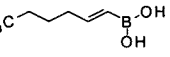
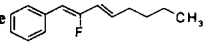
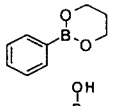
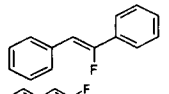
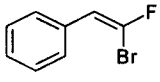
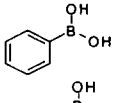
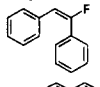
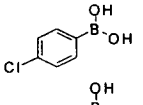
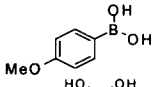
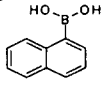
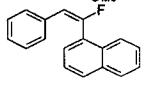
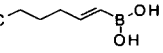
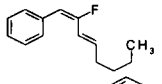
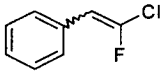
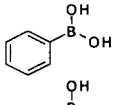
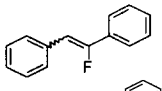
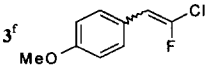
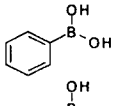
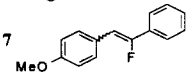
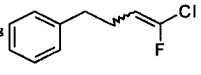
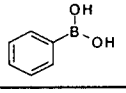
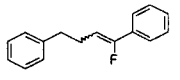
The coupling of (*E*)-1-fluoro-2-phenylvinyl bromide *E*-**1** with phenylboronic acid (**5a**) proceeded in the presence of 5 mole % of $Pd(PPh_3)_4$ under Suzuki conditions (2N aq. Na_2CO_3, benzene-ethanol, reflux)[9] to afford 1-fluorostilbene *Z*-**6a**[10] exclusively in 86% isolated yield (Scheme 2).[11] Under these conditions *E*-**1** coupled with a variety of arylboronic acids **5a-d**, vinylboronic acid **5e** and phenylborate **5g** to give fluoroolefins *Z*-**6a-e** in 81-91% yields. The coupling reaction of the *Z*-isomer *Z*-**1** with organoboronic acids **5a-c** and **5e-f** also proceeded smoothly to give the corresponding *E* isomeric compounds *E*-**6a-c** and *E*-**6e-f** exclusively in 78-92% yields (see Table 1).

Scheme 2



This coupling reaction also proceeded with 1-fluorovinyl chlorides **2-4**. Reaction of 1-fluoro-2-phenylvinyl chloride **2** (mixture of *E/Z* isomers with a ratio of E/Z = 44/56) with phenylboronic acid (**5a**) under Suzuki conditions gave the fluorinated olefin **6a** as a mixture of *E* and *Z* isomers with an 1:1 ratio based on GC-MS and fluorine NMR analysis of the crude reaction mixture. These two isomers were separated by chromatography (*Z*-**6a**, 43% and *E*-**6a**, 49%) (Scheme 3). The coupling reaction of 1-vinyl chloride **3** (*E/Z* = 44:56) with phenylboronic acid (**5a**) provided the products *Z*-**7** and *E*-**7** in 80% isolated yields (Z/E = 47:53). It is interesting to note that this reaction required approximately 8 hr. versus 4 hr. for the unsubstitiuted phenyl fluoroolefin, which can be attributed to the electron-donating methoxy group. Reaction of 1-fluoro-2-phenethylvinyl chloride **4** with phenylboronic acid (3 equivalents) was not complete after 48 hr. when catalyzed by tetrakis(triphenylphosphine)-palladium(0). However, the reaction did proceed to completion in 24 hr. when catalyzed by $Pd(PPh_3)_2Cl_2$ in refluxing dioxane to afford the desired product in 83% yield as an inseperable mixture of *Z*-**8** and *E*-**8** in a ratio of 45:55.

Table 1. Synthesis of Fluoroolefins from 1-Fluorovinyl Halides and Organoboranes

Entry	Vinyl Halide	Reagent	Method[a]	Time (hr)	Product	Yield (%)[b]
1	*E*-**1**[c] 	**5a** 	A	1	*Z*-**6a** 	86[d]
2		**5b** 	A	1	*Z*-**6b** 	89
3		**5c** 	A	3	*Z*-**6c** 	91
4		**5d** 	A	3	*Z*-**6d** 	83
5		**5e** 	A	3	*Z*-**6e** 	81
6		**5g** 	A	1	*Z*-**6a** 	94[e]
7	*Z*-**1** 	**5a** 	A	4	*E*-**6a** 	92
8		**5b** 	A	4	*E*-**6b** 	90
9		**5c** 	A	6	*E*-**6c** 	85
10		**5f** 	A	5	*E*-**6d** 	78
11		**5e** 	A	4	*E*-**6a** 	82
12	**2**[f] 	**5a** 	A	4	**6a** 	92 (50:50)[h]
13	**3**[f] 	**5a** 	A	8	**7** 	80 (47:53)[h]
14	**4**[g] 	**5a** 	B	24	**8** 	83 (45:55)[h]

a) Method A: $Pd(PPh_3)_4$ (5 mole%), Na_2CO_3 (2 eq.), benzene-EtOH-H_2O, reflux; Method B: $Pd(PPh_3)_2Cl_2/Na_2CO_3$/dioxane-H_2O, reflux.

b) Isolated yields.

c) Contaminated by about 8% of *Z*-isomer (*Z*-**1**).

d) *E*-isomer (*E*-**6a**) was also isolated in about 5%.

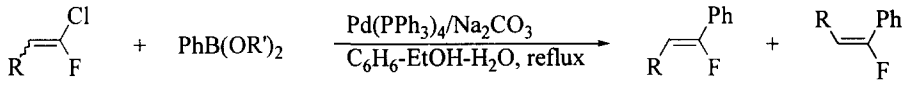
e) GC-MS yield.

f) E/Z = 44:56.

g) *E*/*Z* = 47:53.

h) Isolated as a mixture of *Z*/*E* isomers. The ratio was determined by GC-MS and ^{19}F NMR analysis of the crude reaction mixture.

Scheme 3



2: R = Ph
3: R = p-MeOPh
4: R = $PhCH_2CH_2$

Z-isomer *E*-isomer

6: R = Ph
7: R = p-MeOPh
8: R = $PhCH_2CH_2$

In summary, the palladium-catalyzed cross-coupling reactions of 1-fluorovinyl bromides and chlorides with various organoboranes provide a very efficient and convenient method for the stereospecific synthesis of 1-substituted 1-fluoroolefins in high yields.

References and Footnotes

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10 The E or Z configuration of the product olefins was assigned from the $^3J_{H\text{-}F}$ coupling constant: 14-18Hz for a *cis* H-F coupling. 33-36Hz for a *trans* coupling.

11 Typical procedure: A solution of 0.5 mmole of (*Z*)-1-bromo-1-fluorostyrene ***Z*-1** in benzene (10 mL) was treated with phenylboronic acid (0.6 mmol), sodium carbonate (1.5 mmol), ethanol (0.5 mL), water (0.5 ml) and $Pd(PPh_3)_4$ (30 mg, 0.025 mmol) under nitrogen. This mixture was stirred and heated at reflux for 4 hours. The reaction mixture was diluted with ether, dried over $MgSO_4$, filtrated and concentrated *in vacuo*. Chromatography on silica gel with hexanes gave (*E*)-1-fluorostilbene (91 mg, 92 %) as a colorless oil.[12] ^1H NMR (TMS/$CDCl_3$): 6.31 (d, J = 39.6Hz, 1H), 7.02-7.42 (m, 6H), 7.62 (m, 4H); ^{19}F NMR: -108.3 (d, J = 40Hz); GC-MS: 198 (M+).

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