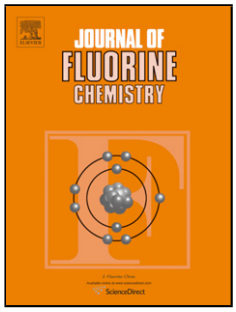

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Geminal Difluorination of α,α'-Disubstituted Styrenes using Fluoro-Benziodoxole Reagent. Migration Aptitude of the α-Substituents

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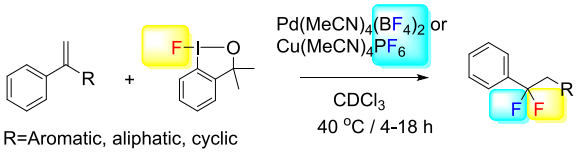
Dedicated to Professor Antonio Togni on the occasion of receiving the ACS Award for Creative Work in Fluorine Chemistry

Graphical abstract



Highlights (see also cover letter):

- Our paper is focused on difluorination of □-substituted styrenes.
- The fluorination reaction was carried out with fluoro-benzoiodoxole reagent 1 in the presence of copper or palladium-catalyst.
- The interesting feature of this process was the appearent migration of the □-substituent.
- We studied the electronic effects of the aryl substituents on the migration aptitude in this reaction.
- In case of an □-aryl and □'-alkyl type of disubstitution the alkyl group underwent migration. In case of cyclic styrenes ring expansion and ring contraction reactions could be performed.

ABSTRACT: α,α'-Disubstituted styrenes undergo a difluorination-rearrangement reaction with fluoro-benzoiodoxole reagent **1**. The reaction is catalyzed by $Pd(MeCN)_4(BF_4)_2$ and $Cu(MeCN)_4PF_6$. We have studied the rearrangement of α,α'-diaryl substituted styrenes, in which the aryl groups have different electronic character. In the case of α-aryl, α'-alkyl substituted styrenes, the aryl substituent has a higher migratory aptitude than the alkyl group. We have also extended the reactions to cycloalkyl styrenes, which underwent interesting ring contraction/expansion reactions. The regioselectivity of the migration can be explained on the basis of the formation of a phenonium intermediate.

KEYWORDS: difluorination, rearrangement, hypervalent fluoroiodine.

1. Introduction

Fluorine substituents have specific effects on the physical, chemical and biological properties of organic molecules [1-4]. Organofluorine compounds are particularly important in pharmaceutical [2, 5, 6] and agrochemical products [4, 7, 8], as well as in medical diagnostics, such as Positron Emission Tomography [9, 10] and Magnetic Resonance Imaging [11]. Although monofluoro- and trifluomethyl compounds have found the widest application in the life sciences, the synthesis and application of difluoromethyl derivatives have received increasing attention, as of late. Difluoromethyl compounds are bioisosters of hydroxyl groups and have the ability to form hydrogen bonds [12] with enzymes and re-

ceptors [13, 14]. The demand for a large variety of new organodifluorides provides an impetus for developing new methodologies for the selective synthesis of geminal difluoroalkanes. Early methodologies for introducing the CF_2 moiety were primarily based on highly reactive fluorinating reagents, such as XeF_2 [15] and DAST [16]. However, application of these reagents may lead to problems with functional group tolerance, selectivity issues, low yields and hazardous HF development upon contact with water. Recently, stable and safe reagents have been utilized, often in the presence of catalysts for difluorination reactions. Typical methods involve cross-coupling reactions with suitable CF_2 carriers [17-22], radical-[23-25], photoredox-difluorination [26] and application of hypervalent iodine reagents [27-30] as the fluorine source. Recently, we employed fluoro-benziodoxole **1** [31-33] as the fluorine source for the difluorination of alkenes [27] and cyclopropane derivatives [34]. Reagent **1** is closely related with the privileged trifluoromethylation reagents, Togni-I and II [31, 35-40], which were employed very successfully in selective introduction of the CF_3 group [41-43].

According to our previous studies [27] into the difluorination of styrenes with **1** and $AgBF_4$, the reaction leads to geminal difluorination with rearrangement of the α and β-carbons of the alkene (Figure 1). The reason for the apparent rearrangement is the formation of a fluoro-phenonium intermediate, which subsequently undergoes a second fluorination mediated by the BF_4 counterion [44] of the silver catalyst. When the reaction was performed with α-methyl styrene (R' = Me), the methyl group was directly bonded to the difluorinated (yellow colored) carbon of the product, indicating that the aryl group preferentially migrated (and not the methyl group). In the present study, we investigated the migratory aptitude of different R' substituents in this reaction, and explored the possibility of employing the above rearrangement for both ring expansion and contraction reactions.

2. Results and discussion

First we directed our studies towards α,α'-diaryl styrenes, with the intention of unearthing any substituent effects of the aryl groups migratory aptitude. Therefore, we first optimized the reaction conditions for the difluorination of **2a**.

*2.1 Variation of the reaction conditions for the difluorination of **2a**.* After careful optimization, we found that **2a** undergoes difluorination and rearrangement using **1** and catalytic amounts (20 mol%) of $Pd(MeCN)_4(BF_4)_2$ as the catalyst affording **4a** in 64% yield (Table 1, header). We employed $CDCl_3$ as the solvent instead of $CHCl_3$, in order to analyze the crude reaction mixture and monitor the conversion of **2a** with ^1H NMR. In this process, we used the same amount (0.1 mmol) of **2a** and **1**. As the isolated yield is higher than 50%, the second fluoride, at least in part, arises from the BF_4 counterion of Pd. We have found a similar secondary fluorination process in our previous studies with styrene derivatives (Figure 1) [27]. When we replaced the Pd-catalyst with $AgBF_4$, only traces of products were observed from **2a** and **1** (Table 1, entry 1). In fluorocyclization reactions [45] with **1,** $Zn(BF_4)_2$ proved to be a very efficient catalyst. However, $Zn(BF_4)_2$ proved to be inefficient as the catalyst in this reaction (entry 2). When the amount of $Pd(MeCN)_4(BF_4)_2$ was reduced to 10% the yield decreased from 64% to 27%. When we replaced **3** with 20 mol% of $Cu(MeCN)_4PF_6$, we obtained **4a** in 32% yield (entry 3). Although, this yield is apparently lower than with the analogous Pd-catalyst, in some other reactions (see below) the Cu-catalyst outperformed **3**. $Cu(MeCN)_4BF_4$ proved to be less efficient than the PF_6 analog (c.f. entries 3 and 4). When we performed the reactions in MeCN or dioxane the yields dropped substantially to 37% and 17%, respectively (entries 5-6). Only traces of product were observed in DCM or THF (entry 7).

2.2 Rearrangements of diaryl substrates. First we studied the migratory aptitude of differentially substituted α,α'-diaryl compounds **2b-e** (Table 2, entries 2-5). In **2b**-**2d** one of the aryl groups was the simple unsubstituted phenyl group, while the others had one electron donating substituent (entries 2-4).

When, these compounds underwent the difluorination-rearrangment reaction the phenyl group was directly bonded to the difluorinated carbon in products **4b-d**. In these reactions the formation of regioisomeric compounds to **4b-d** was not observed. The regioselectivity of the rearrangement indicates that the electron-rich aryl group bearing the Me (entry 2) and OR (entries 3-4) groups forms the fluorinated phenonium ion and therefore also migrates (see also Figure 1). We have also carried out the reaction between electron deficient, fluoro substituted **2e** and an electron-rich OMe substituted aryl group (entry 5). The fluoro substituted aryl group appeared at the difluorinated carbon in **4e**, indicating that the anisyl group underwent migration and not the fluoro-aryl moiety. The structure of **4e** was determined on the basis of the ^{13}C spectrum of **4e** (see Figure 4 in the experimental part). The position of the fluorine atoms could be assigned on the basis of the coupling constants and multiplicity of the C-F couplings. Considering the structural similarity of **4b-4d** to **4e**, we used also used this information for structural assignment of **4b-d**.

2.3 Rearrangement of α-phenyl-α'-alkyl substututed substrates. Similar to the $AgBF_4$ mediated reaction of *α*-methyl styrene (Figure 1) ethyl (**2f**), propyl (**2g**), butyl and isopropyl (**2i**) moieties appeared at the difluorinated carbon (entries 6-9) using $Pd(MeCN)_4(BF_4)_2$ as the catalyst. As we reported previously [34], cyclopropanes bearing alkyl substuents undergo difluorinative ring opening using $AgBF_4$ as the mediator. When we used cyclopropane derivative **2j** as the substrate with **1** and $Pd(MeCN)_4(BF_4)_2$ as the catalyst a complex reaction mixture was obtained. However, when we replaced $Pd(MeCN)_4(BF_4)_2$ with $Cu(MeCN)_4PF_6$ as the catalyst, the reaction gave **4j** with 58% yield (entry 10). In this reaction the aryl ring migrated and the cyclopropane remained unopened. When benzyl derivative **2k** reacted in the presence of $Pd(MeCN)_4(BF_4)_2$, we obtained an inseparable mixture mixture of **4k** and most likely its regioisomer. However, when the catalyst was changed to $Cu(MeCN)_4PF_6$, **4k** formed as the sole product (entry **2k**) in high yield (70%).

[a] A mixture of styrene **2** (0.1 mmol), **1** (0.1 mmol), **3** (0.02 mmol, 20 mol%) was dissolved in $CDCl_3$ under Ar. The reaction mixture was stirred at 40 °C for 18h. The yields refer to isolated yields after chromatography. [b]$Cu(MeCN)_4PF_6$ (0.02 mmol, 20 mol%) was used instead of **3**. [c]**1** (0.2 mmol) was used. [d] The reaction mixture was stirred at 40 °C for 4 h.

2.4 Ring expansion and contraction. We also wanted to study how this migration process would proceed with styrene derivateves embedded within benzofused-cyclic substrates. Dihydronaphthalene (bearing an endocyclic alkene), **2l** underwent an interesting ring contraction to **4l** in a difluorination-rearrangment sequence. The best yield (48%) was obtained using $Cu(MeCN)_4PF_6$ as the catalyst and two equivalents of **1** (entry 12). On the other hand, when exocyclic alkenes **2m** and **2n** were used as substrates, ring expansion products **4m-n** were obtained. In these cases, the $Cu(MeCN)_4PF_6$ catalyst gave the best yields (61 and 50%), when the reaction was carried out at 40 °C for 4 hours (entries 13-14).

2.5. Plausible mechanism for the difluorination-rearrangement reaction. Considering our previous mechanistic studies [27, 46] and recently reported DFT modeling studies [47, 48] for the fluorination of alkenes with **1**, we suggest the mechanism given in Figure 2.

Fluorobenzoiodoxole **1** is activated by coordination of palladium to the fluorine atom. Then, **1** undergoes isomerization providing the more electrophilic complex **5**. Our DFT studies on the mechanism of

fluorination reactions with **1** showed that this metal catalyzed isomerization is a pre-requisite of the efficient fluor transfer from the hypervalent iodine to the organic substrate [47]. The I-F bond undergoes metathesis to form **7** [47]. A possible intermediate or TS of the reaction is iodocyclopropane **6** [48]. Two π-electrons of the aryl group form one of the C-C σ-bond in phenonium ion **8** by displacement of the iodine [48]. If there are two arenes available, as in **2e** the electron-rich arene (i.e. the OMe substituted) will preferentially form the phenonium ion. The next step is nucleophilic attack of the fluoride of the BF_4 counterion at the fluorinated carbon. This attack proceeds with a high level of regioselectivity probably due to the high electrophilicity of the fluorinated carbon atom. This second fluorination leads to formation of product **4e**.

3. Conclusions

In summary, we have studied the difluorination-rearrangement reactions of α,α'-disubstituted styrenes. We have found that the reactions proceed with high selectivity at room temperature using **1** and $Pd(MeCN)_4(BF_4)_2$ or $Cu(MeCN)_4PF_6$ catalysts. In the case of electronically biased 1,1-diarylalkenes, the electron-rich aryl substituent will preferentially undergo migration. Aryl groups have a higher migration aptitude than alkyl groups, which can also be employed for ring contraction and expansion reactions. The reactions outcome can be explained by catalytic activation of **1** followed by selective formation of a phenonium intermediate.

4. Experimental

4.1. General information

Hypervalent iodine **1** [31, 32] and α-substituted styrenes[49] **4a-n** were prepared according to literature procedures. All other chemicals were obtained from commercial sources and used as received. ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded in $CDCl_3$ (internal standard: 7.26 ppm, ^{1}H; 77.2 ppm, ^{13}C) using 400 MHz spectrometers. For column chromatography, silica gel (35-70 microns) was used. Unless otherwise stated, all the reactions were performed under Ar atmosphere. We were not able to obtain proper high-resolution mass data for products **4a-n**, therefore, we provide EI mass data in the characterization.

4.2. General procedure

Reagent **1** (28.0 mg, 0.1 mmol), the corresponding α,α'-substituted styrene **2** (0.1 mmol) $Pd(MeCN)_4(BF_4)_2$ (**3**) (8.9 mg, 0.02 mmol) were mixed in $CDCl_3$ (0.5 ml). This reaction mixture was stirred at 40 ºC for 18 h. The products **4a-n** were isolated by silica gel column chromatography using petroleum ether: ether (100:1) system.

4.2.1. (1,1-difluoroethane-1,2-diyl)dibenzene (**4a**)

This product was prepared according to the above general procedure. Compound **4a** appeared as a white solid (14 mg, 64%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.42-7.31 (m, 5H), 7.25-7.22 (m, 3H), 7.14-7.07 (m, 2H), 3.40 (t, J_{HF} = 15.8 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 137.0 (t, J_{CF} = 26.4 Hz), 132.8 (t, J_{CF} = 4.3 Hz), 130.8, 129.8 (t, J_{CF} = 1.5 Hz), 128.3, 128.3, 127.4, 125.4 (t, J_{CF} = 6.2 Hz), 122.1 (t, J_{CF} = 244.3 Hz), 46.1 (t, J_{CF} = 28.7 Hz). ^{19}F-NMR (377 MHz, $CDCl_3$) δ -94.9 (t, J_{HF} = 15.9 Hz). (EI) m/z (rel intens) 218 (M+, 32), 128 (10), 127 (100), 91 (43), 77 (10). Mp: 63-66 ºC.

4.2.2. 1-(2,2-difluoro-2-phenylethyl)-4-methylbenzene (**4b**)

This product was prepared according to the above general procedure. Compound **4b** appeared as a yellow oil (9 mg, 54%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.44-7.29 (m, 5H), 7.10-6.90 (m, 4H), 3.36 (t, J_{HF} = 15.8 Hz, 2H), 2.31 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 137.1 (t, J_{CF} = 26.2 Hz), 137.0, 130.6, 129.7 (t, J_{CF} = 1.9 Hz), 129.7, 129.0, 128.3, 125.4 (t, J_{CF} = 6.2 Hz), 122.1 (t, J_{CF} = 244.4 Hz), 45.6 (t, J_{CF} =

28.5 Hz), 21.3. ^{19}F-NMR (377 MHz, $CDCl_3$) δ -95.0 (t, J_{HF} = 15.9 Hz). (EI) m/z (rel intens) 232 (M+, 42), 127 (27), 106 (10), 105 (100), 77 (10).

4.2.3. 1-(2,2-difluoro-2-phenylethyl)-4-methoxybenzene (**4c**)
This product was prepared according to the above general procedure. Compound **4c** appeared as a white solid (13 mg, 52%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.45-7.30 (m, 5H), 7.02-6.95 (m, 2H), 6.81-6.73 (m, 2H), 3.78 (s, 3H), 3.34 (t, J_{HF} = 15.8 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 159.0, 137.1 (t, J_{CF} = 26.6 Hz), 131.8, 129.7 (t, J_{CF} = 1.9 Hz), 128.3, 125.4 (t, J_{CF} = 6.0 Hz), 124.9 (t, J_{CF} = 4.3 Hz), 122.2 (t, J_{CF} = 243.9 Hz), 113.8, 55.4, 45.2 (t, J_{CF} = 28.6 Hz). ^{19}F-NMR (377 MHz, CDCl3) δ -95.2 (t, J_{HF} = 15.8 Hz). (EI) m/z (rel intens) 248 (M+, 29), 127 (6), 122 (12), 121 (100), 77 (9). Mp: 90-93 ºC.

4.2.4. 1-(2,2-difluoro-2-phenylethyl)-4-phenoxybenzene (**4d**)
This product was prepared according to the above general procedure. Compound **4d** appeared as a white solid (18 mg, 66%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.44-7.27 (m, 7H), 7.19-6.95 (m, 5H), 6.92-6.85 (m, 2H), 3.38 (t, J_{HF} = 15.8 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 157.3, 156.7, 137.0 (t, J_{CF} = 26.8 Hz), 132.1, 129.9, 129.8 (t, J_{CF} = 2.1 Hz), 128.4, 127.6 (t, J_{CF} = 4.5 Hz), 125.4 (t, J_{CF} = 6.6 Hz), 123.5, 122.1 (t, J_{CF} = 244.0 Hz), 119.1, 118.7, 45.3 (t, J_{CF} = 28.7 Hz). ^{19}F-NMR (377 MHz, $CDCl_3$) δ -95.3 (t, J_{HF} = 15.7 Hz). (EI) m/z (rel intens) 310 (M+, 40), 311 (9), 184 (14), 183 (100), 77 (14). Mp: 76-79 ºC.

4.2.5. 1-(2,2-difluoro-2-(4-fluorophenyl)ethyl)-4-methoxybenzene (**4e**)
This product was prepared according to the above general procedure. Compound **4e** appeared as a yellow oil (18 mg, 67%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.30-7.24 (m, 2H), 7.05-6.95 (m, 4H), 6.82-6.72 (m, 2H), 3.78 (s, 3H), 3.32 (t, J_{HF} = 15.8 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 163.7 (dt, J_{CF} = 248.7, 1.9 Hz), 159.1, 133.1 (td, J_{CF} = 27.5, 3.1 Hz), 131.8, 127.6 (dt, J_{CF} = 8.6, 6.2 Hz), 124.6 (t, J_{CF} = 4.6 Hz), 122.0 (t, J_{CF} = 243.6 Hz), 115.5 (d, J_{CF} = 22.0 Hz), 113.8, 55.4, 45.2 (t, J_{CF} = 28.9 Hz). ^{19}F-NMR (377 MHz, $CDCl_3$) δ – 94.1 (t, J_{HF} = 15.6 Hz), -111.6--111.7 (m). (EI) m/z (rel intens) 266 (M+, 64), 145 (18), 122 (51), 121 (100), 77 (21).

The position of the fluorine atoms were determined on the basis of the ^{13}C NMR spectrum of **4e** by analysis of the coupling constants and their multiplicity (Figure 3). The aromatic C1 carbon has a large doublet C-F coupling of 248.7 Hz and a triplet coupling of 1.9 Hz. In C2 and C3 the doublet C-F couplings are successively decreased (22 Hz and 8.6 Hz) At C4 and C5 the C-F triplet couplings are increasing (27.5 Hz and 243.6 Hz). The benzylic carbon C6 has a C-F triplet coupling of 28.9 Hz and C7 still displays a minor C-F triplet coupling of 4.6 Hz. The other carbons of the anisyl ring do not display any C-F couplings.

4.2.6. (2,2-difluorobutyl)benzene (**4f**)
This product was prepared according to the above general procedure. Compound **4f** appeared as a colorless oil (13 mg, 76%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.36-7.27 (m, 5H), 3.14 (t, J_{HF} = 15.8 Hz, 2H), 1.88-1.68 (m, 2H), 1.02 (t, J = 7.4 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 133.8 (t, J_{CF} = 5.0 Hz), 130.4, 128.6, 127.4, 124.7 (t, J_{CF} = 242.0 Hz), 42.8 (t, J_{CF} = 26.6 Hz), 29.1 (t, J_{CF} = 25.7 Hz), 6.6 (t, J_{CF} = 5.5 Hz). ^{19}F-NMR (377 MHz, $CDCl_3$) δ – 98.6 (tt, J_{HF} = 16.4, 16.3 Hz). (EI) m/z (rel intens) 170 (M+, 22), 92 (11), 91 (100), 79 (2), 65 (6).

4.2.7. (2,2-difluoropentyl)benzene (**4g**)
This product was prepared according to the above general procedure. Compound **4g** appeared as a colorless oil (16 mg, 75%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.35-7.26 (m, 5H), 3.13 (t, J_{HF} = 16.4 Hz, 2H), 1.81-1.64 (m, 2H),1.54-1.44 (m, 2H), 0.92 (t, J = 7.3 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 133.7 (t, J_{CF} = 4.6 Hz), 130.4, 128.6, 127.4, 124.4 (t, J_{CF} = 242.8 Hz), 43.0 (t, J_{CF} = 25.7 Hz), 37.9 (t, J_{CF} = 25.3

Hz), 15.7 (t, J_{CF} = 4.9 Hz), 14.1. ^{19}F-NMR (377 MHz, $CDCl_3$) δ - 96.5 (tt, J_{HF} = 16.0, 15.8 Hz). (EI) m/z (rel intens) 184 (M+, 31), 169 (4), 92 (20), 91 (100), 65 (11).

4.2.8. (2,2-difluoroheptyl)benzene (**4h**)
This product was prepared according to the above general procedure. Compound **4h** appeared as a colorless oil (15 mg, 68%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.35-7.27 (m, 5H), 3.13 (t, J_{HF} = 15.9 Hz, 2H), 1.82-1.64 (m, 2H), 1.53-1.45 (m, 2H), 1.34-1.22 (m, 4H), 0.88 (t, J = 7.3 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 133.8 (t, J_{CF} = 4.6 Hz), 130.5, 128.6, 127.4, 124.5 (t, J_{CF} = 241.8 Hz), 43.1 (t, J_{CF} = 26.6 Hz), 35.9 (t, J_{CF} = 24.8 Hz), 31.7, 22.6, 22.0 (t, J_{CF} = 4.4 Hz), 14.1. ^{19}F-NMR (377 MHz, $CDCl_3$) δ - 96.5 (tt, J_{HF} = 16.5, 16.1 Hz). (EI) m/z (rel intens) 212 (M+, 19), 169 (5), 92 (19), 91 (100), 65 (4).

4.2.9. (2,2-difluoro-3-methylbutyl)benzene (**4i**)
This product was prepared according to the above general procedure. Compound **4i** appeared as a colorless oil (12 mg, 62%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.36-7.27 (m, 5H), 3.14 (t, J_{HF} = 17.1 Hz, 2H), 2.06-1.90 (m, 1H), 1.04 (d, J = 6.9 Hz, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 133.7 (t, J_{CF} = 4.2 Hz), 130.5, 128.5, 127.3, 125.6 (t, J_{CF} = 245.3 Hz), 40.6 (t, J_{CF} = 26.4 Hz), 33.8 (t, J_{CF} = 24.2 Hz), 16.0 (t, J_{CF} = 4.9 Hz). ^{19}F-NMR (377 MHz, $CDCl_3$) δ -105.1 (td, J_{HF} = 16.8, 13.8 Hz). (EI) m/z (rel intens) 184 (M+, 24), 93 (5), 92 (28), 91 (100), 65 (13).

4.2.10. (2-cyclopropyl-2,2-difluoroethyl)benzene (**4j**)
This product was prepared according to the above general procedure. $Cu(MeCN)_4PF_6$ (7.5 mg, 0.02 mmol) was used instead of $Pd(MeCN)_4(BF_4)_2$ (**3**). Compound **4j** appeared as a colorless oil (14 mg, 58%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.35-7.28 (m, 5H), 3.21 (t, J_{HF} = 15.6 Hz, 2H), 1.21-1.05 (m, 1H), 0.67-0.41 (m, 4H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 133.7 (t, J_{CF} = 4.6 Hz), 130.6, 128.5, 127.4, 122.9 (t, J_{CF} = 244.5 Hz), 44.3 (t, J_{CF} = 25.2 Hz), 15.5 (t, J_{CF} = 29.5 Hz), 1.5 (t, J_{CF} = 4.6 Hz). ^{19}F-NMR (377 MHz, $CDCl_3$) δ – 101.8 (dt, J_{HF} = 15.1, 13.1 Hz). (EI) m/z (rel intens) 182 (M+, 14), 147 (17), 117 (11), 91 (100), 65 (11).

4.2.11. (2,2-difluoropropane-1,3-diyl)dibenzene (**4k**)
This product was prepared according to the above general procedure. $Cu(MeCN)_4PF_6$ (7.5 mg, 0.02 mmol) was used instead of $Pd(MeCN)_4(BF_4)_2$ (**3**). Compound **4k** appeared as a colorless oil (15 mg, 70%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.36-7.28 (m, 6H), 7.25-7.23 (m, 4H), 3.10 (t, J_{HF} = 16.2 Hz, 4H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 133.4 (t, J_{CF} = 4.2 Hz), 130.7, 128.6, 127.5, 123.3 (t, J_{CF} = 243.6 Hz), 42.6 (t, J_{CF} = 25.8 Hz). ^{19}F-NMR (377 MHz, $CDCl_3$) δ – 94.8 (tt, J_{HF} = 16.5, 16.2 Hz). (EI) m/z (rel intens) 232 (M+, 51), 141 (16), 92 (35), 91 (100), 65 (11).

4.2.12. 1-(difluoromethyl)-2,3-dihydro-1H-indene (**4l**)
This product was prepared according to the above general procedure using fluoroiodane reagent **1** (56 mg, 0.2 mmol). Compound **4l** appeared as a colorless oil (8 mg, 48%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.39-7.31 (m, 1H), 7.25-7.17 (m, 3H), 5.79 (td, J_{HF} = 57.1, 5.5 Hz, 1H), 3.71-3.51 (m, 1H), 3.09-2.80 (m, 2H), 2.37-2.23 (m, 1H), 2.18-1.95 (m, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 145.1, 128.1, 126.7, 125.6, 125.5, 124.9, 118.3 (t, J_{CF} = 245.2 Hz), 49.2 (t, J_{CF} = 20.1 Hz), 31.6, 25.5 (t, J_{CF} = 4.3 Hz). ^{19}F-NMR (377 MHz, $CDCl_3$) δ – 118.8 (ddd, J_{HF} =56.9, 38.3, 14.2 Hz). (EI) m/z (rel intens) 168 (M+, 27), 118 (9), 117 (100), 115 (30), 91 (6).

4.2.13. 6,6-difluoro-6,7,8,9-tetrahydro-5H-benzo[7]annulene (**4m**)
This product was prepared according to the above general procedure. The reaction mixture was stirred at 40°C for 4 h. Compound **4m** appeared as a colorless oil (10 mg, 61%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.23-7.13 (m, 3H), 7.12-7.06 (m, 1H), 3.32 (t, J_{HF} = 13.4 Hz, 2H), 2.86-2.76 (m, 2H), 2.28-2.15 (m, 2H), 1.82-1.71 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 142.2, 132.6 (t, J_{CF} = 7.3 Hz), 131.4, 129.3,

127.7, 126.8, 121.8 (t, J_{CF} = 243.6 Hz), 44.1 (t, J_{CF} = 28.9 Hz), 39.6 (t, J_{CF} = 26.4 Hz), 34.9, 22.9 (t, J_{CF} = 5.9 Hz). ^{19}F-NMR (377 MHz, $CDCl_3$) δ – 89.4– -90.6 (m). (EI) m/z (rel intens) 182 (M+, 100), 148 (25), 147 (68), 134 (45), 117 (26).

4.2.14. 2,2-difluoro-1,2,3,4-tetrahydronaphthalene (**4n**)
This product was prepared according to the above general procedure. The reaction mixture was stirred at 40°C for 4 h. Compound **4n** appeared as a colorless oil (9 mg, 50%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.23-7.13 (m, 3H), 7.11-7.04 (m, 1H), 3.26 (t, J_{HF} = 15.0 Hz, 2H), 3.02 (t, J_{HF} = 6.6 Hz, 2H), 2.30-2.03 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 134.2, 131.9 (t, J_{CF} = 5.6 Hz), 129.3, 128.7, 126.8, 126.6, 123.3 (t, J_{CF} = 240.0 Hz), 38.2 (t, J_{CF} = 27.9 Hz), 31.3 (t, J_{CF} = 24.0 Hz), 27.2 (t, J_{CF} = 5.5 Hz). ^{19}F-NMR (377 MHz, $CDCl_3$) δ – 95.6 (tt, J_{HF} = 14.3, 14.0 Hz). (EI) m/z (rel intens) 168 (M+, 100), 149 (23), 147 (51), 104 (23), 78 (28).

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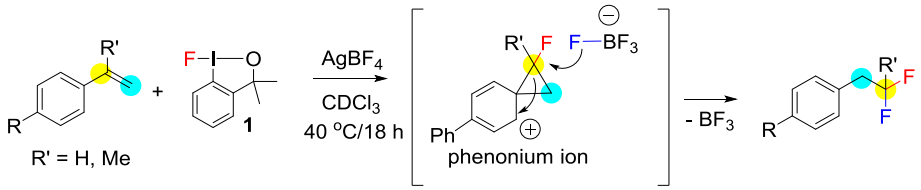


Figure 1. Previously studied difluorination of styrenes [27].

Figure 2. Plausible reaction mechanism exemplified with **2e**.

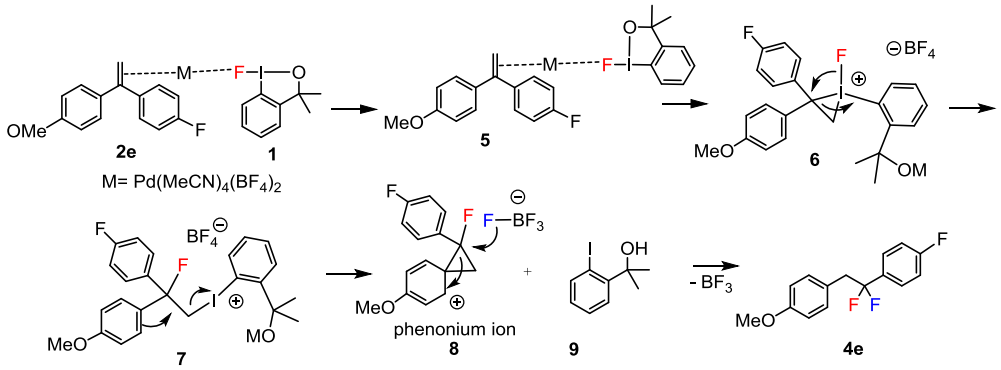


Figure 3. Coupling pattern in ^{13}C-NMR for **4e**

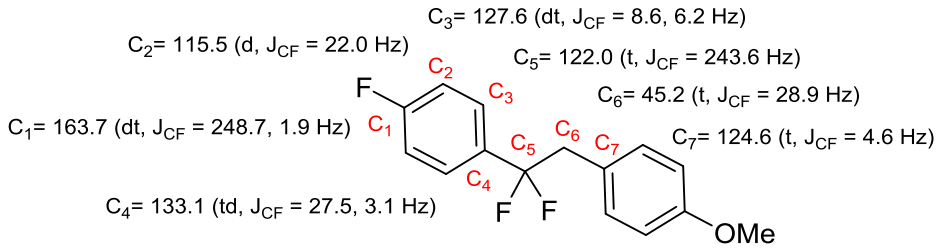
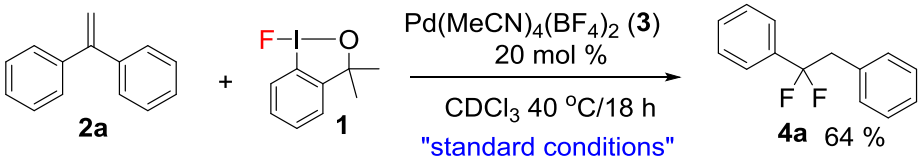
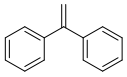
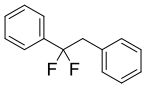
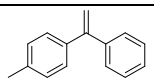
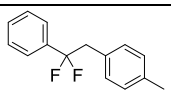
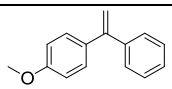
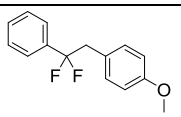
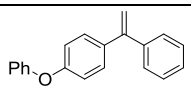
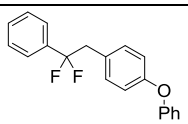
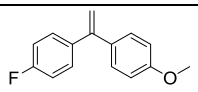
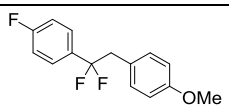
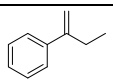
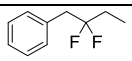
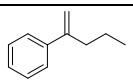
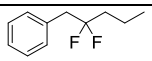
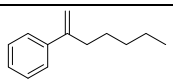
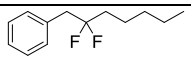
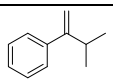
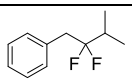


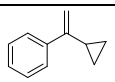
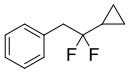
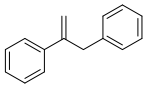
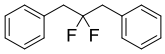
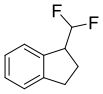
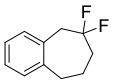
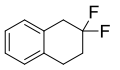
Table 1. Variation of the reaction conditions for β-difluorination reaction.



Entry	Deviation from standard conditions	Product **4a** (%)
1	$AgBF_4$ or $Zn(BF_4)_2$ x H_2O 1 equiv. instead of **3**	<5
2	$Pd(MeCN)_4(BF_4)_2$ 10 mol%	27
3	$Cu(MeCN)_4PF_6$ 20 mol% instead of **3**	32
4	$Cu(MeCN)_4BF_4$ 30 mol% instead of **3**	18
5	MeCN instead of $CDCl_3$	37
6	Dioxane instead of $CDCl_3$	17
7	DCM or THF instead of $CDCl_3$	<5

Table 2. β-Difluorination of various α-substituted styrene derivatives.[a]

Entry[a]	Substrate	Product	Yield (%)
1	 **2a**	 **4a**	64
2	 **2b**	 **4b**	54
3	 **2c**	 **4c**	52
4	 **2d**	 **4d**	66
5	 **2e**	 **4e**	67
6	 **2f**	 **4f**	76
7	 **2g**	 **4g**	75
8	 **2h**	 **4h**	68
9	 **2i**	 **4i**	62

10[b]	 **2j**	 **4j**	58
11[b]	 **2k**	 **4k**	70
12[b,c]	 **2l**	 **4l**	48
13[b,d]	 **2m**	 **4m**	61
14[b,d]	 **2n**	 **4n**	50