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Stereoselective Preparation of (Z)-α,β-Difluorostyrenes

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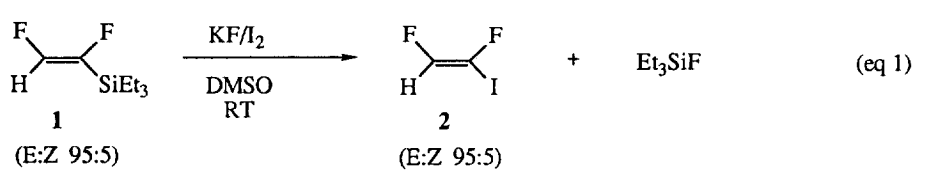
Abstract: *Substituted aromatic iodides couple with (E)-HFC=CFZnI, under mild conditions, in the presence of catalytic $Pd(PPh_3)_4$ in DMF to give the title compounds in good yield.*

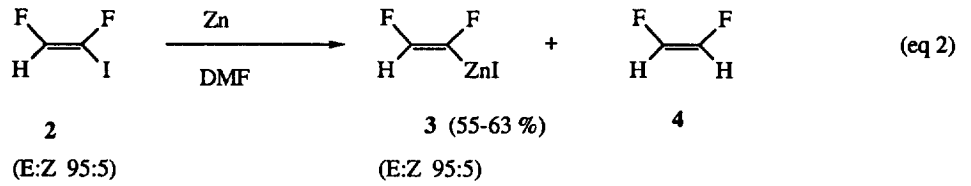
Fluorinated styrenes are useful building blocks in organofluorine chemistry and have found application as monomers,[1] and as precursors for antiinflammatory[2] and antifertility[3] compounds. Previous reports from our laboratories have described the general preparation of α,β,β-trifluorostyrenes, 1-arylperfluoropropenes,[4] and β,β-difluoro-α-(trifluoromethyl)styrenes[5] by Pd(0) catalyzed arylation of the thermally stable perfluoroalkenylzinc reagents F_2C=CFZnX, (Z) and (E)-CF_3CF=CFZnX, and CF_3(ZnX)C=CF_2, respectively. A general, stereoselective preparation of (Z)-α,β-difluorostyrenes, however, has not been previously reported. α,β-Difluorostyrene has been prepared in low yield by dehalogenation of 1-chloro-1-phenyl-1,2,2-trifluoroethane.[6] The stereochemistry of the resultant styrene was not reported. Dehydrofluorination of 1-phenyl-1,1,2-trifluoroethane resulted in a low yield of α,β-difluorostyrene and this dehydrofluorination was not extended to other 1-aryl-1,1,2-trifluoroethanes.[7] Low temperature metallation of several isomeric α,β-difluoro-β-chlorostyrenes with an alkyllithium reagent followed by hydrolysis has been reported to give predominantly (E)-α,β-difluorostyrenes.[8] Protodesilyation of (Z)-1,2-difluoro-2-arylvinylsilanes by potassium fluoride in aqueous dimethylsulfoxide gave (E)-α,β-difluorostyrenes.[9,10] Efforts in our laboratory to prepare the (Z)-analogs by isomerization of the corresponding (E)-styrenes, however, have resulted in oligomerization of the starting materials.[11]

Here we report a general, stereospecific method for the preparation of (Z)-α,β-difluorostyrenes. Our recent report on the development of (Z) and (E)-difluoroethylenyl synthons[12] suggested a route to the title compounds which avoids oligomerization processes, as outlined below. (E)-1,2-difluoroethylenylzinc, **3**, was prepared in two steps from (E)-HFC=CF$SiEt_3$, **1**, which is readily prepared from bromotrifluoroethylene[12] or chlorotrifluoroethylene.[13] Cleavage of the silane moiety with KF/I_2 gave a mixture of (E)-HFC=CFI (**2**) and Et_3SiF (eq 1).



1 (E:Z 95:5) **2** (E:Z 95:5) (eq 1)

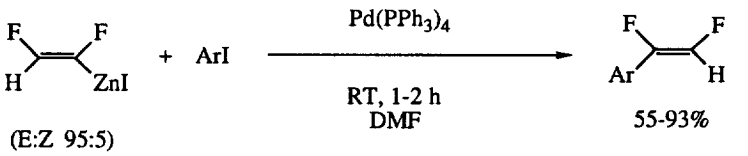
The mixture of Et_3SiF and **2**, after distillation from the reaction mixture, was treated with zinc metal in DMF to give **3** (55-63%, based on **1**, as determined by internal $PhCF_3$ standard) and 1,2-difluoroethylene **4** (eq 2). The zinc reagent **3** exhibits excellent thermal stability. Significant loss of molarity, with concomitant formation of **4**, occurred only after extended heating (12 h) at temperatures at or above 100 °C.



2 (E:Z 95:5) **3** (55-63 %) (E:Z 95:5) **4**

Substituted aromatic iodides couple smoothly under mild conditions with (E)-HFC=CFZnI in the presence of catalytic $Pd(PPh_3)_4$ to give (Z)-α,β-difluorostyrenes in good to excellent yields. **Table I** summarizes our results.

Table I. $Pd(PPh_3)_4$ Catalyzed Arylation of (E)-HFC=CFZnI



(E:Z 95:5)

ArI	Product	Yield (%)[a]
C_6H_5I	$C_6H_5CF{=}CFH$	65
p-$MeOC_6H_4I$	*p*-$MeOC_6H_4CF{=}CFH$	88
p-$NO_2C_6H_4I$	*p*-$NO_2C_6H_4CF{=}CFH$	66 [b]
o-$NO_2C_6H_4I$	*o*-$NO_2C_6H_4CF{=}CFH$	78
p-$CH_3C_6H_4I$	*p*-$CH_3C_6H_4CF{=}CFH$	72
p-$EtO_2CC_6H_4I$	*p*-$EtO_2CC_6H_4CF{=}CFH$	93
p-$CH_3C(O)C_6H_4I$	*p*-$CH_3C(O)C_6H_4CF{=}CFH$	71
m-ClC_6H_4I	*m*-$ClC_6H_4CF{=}CFH$	60
1,4-$C_6H_4I_2$	*p*-$HFC{=}CFC_6H_4CF{=}CFH$	80
p-$CF_3C_6H_4I$	*p*-$CF_3C_6H_4CF{=}CFH$	70
o-(^{i}Pr)C_6H_4I	*o*-(^{i}Pr)$C_6H_4CF{=}CFH$	55 [c]

[a] Isolated yield of (Z)-isomer only; all products gave satisfactory ^{19}F, ^1H, and ^{13}C NMR, IR, and HRMS data. [b] Isolated as 95:5 (Z:E) mixture; reaction was carried out at 0 °C. [c] Reaction conditions: 60 °C, 8 h.

The coupling reaction is tolerant of a variety of functionalities and no significant difference in reaction time or yield was observed between electron-releasing and electron-donating groups. *p*-Diiodobenzene coupled with (E)-HFC=CFZnI to give the 1,4-disubstituted product. Except for the *p*-NO_2 case, the major (Z)-isomer was readily separated from the (E)-isomer impurity by column chromatography.

In a typical procedure for preparation of the (E)-HFC=CFZnI, a 250 mL three-neck flask equipped with a magnetic stir bar, thermometer adapter, cold-finger condenser set to -40 °C, and N_2 source, was charged with anhydrous KF (12.7 g, 219 mmol), I_2 (38 g, 150 mmol), and 90 mL dry DMSO. To the stirred mixture was added (E)-HFC=CFSiEt$_3$ (13.0 g, 73 mmol, E:Z 95:5)*via* syringe, in one portion. An exotherm resulted (60-70 °C) followed by cooling to room temperature. The mixture was stirred at room temperature for 36 h or until no starting material was detected by ^{19}F NMR analysis of the reaction mixture. The reaction flask was connected to a liquid N_2 cooled receiver and flash distilled (*ca.* 60 °C bath temperature/10 mm Hg). The contents of the reaction flask were periodically analyzed by ^{19}F NMR to determine when all product had been removed from the reaction mixture. The cooled receiver contained (E)-HFC=CFI, Et$_3$SiF, and DMSO. The distillate was then redistilled through a short path apparatus at atmospheric pressure and a mixture of (E)-HFC=CFI, and Et$_3$SiF was collected and used without further purification (bp 50-105 °C). ^{19}F NMR for (E)-HFC=CFI ($CDCl_3$, *vs.* internal $CFCl_3$) -106.5 (d, $^3J_{F,H}$ = 15.2 Hz, 1F),-130.7 (d, $^2J_{F,H}$ = 73.7 Hz, 1F). A 50 mL flask equipped with a dry ice/IPA condenser, magnetic stir bar, N_2 source, and septum port, was charged with acid-washed Zn metal (4.9 g, 75 mmol) and 30 mL dry DMF. To this mixture was added *via* syringe a volume of (E)-HFC=CFI/Et$_3$SiF (*ca.* 50 mmol) mixture in one portion. Induction occurred within 20-30 min. and an exotherm was observed. The remainder of the starting material was then slowly added dropwise, maintaining the temperature at ≤ 60 °C. The dark-colored reaction mixture was stirred an additional 45 min. and formation of the vinyl zinc reagent **3** was confirmed by ^{19}F NMR analysis of the reaction mixture (3:4 93:7). The molarity was determined by internal $PhCF_3$ standard. The excess Zn was allowed to settle or filtered through a medium-fritted funnel and the zinc reagent was stored under N_2 at room temperature. ^{19}F NMR for (E)-HFC=CFZnX (DMF solution, *vs.* internal $CFCl_3$) -149.2 (d, $^2J_{F,H}$ = 83 Hz, 1F), -146.8 (d, $^3J_{F,H}$ = 29 Hz, 1F); ^{19}F NMR for (Z)-HFC=CFH (DMF solution, *vs.* internal $CFCl_3$) -164.2 (dd, $^2J_{F,H}$ = 66 Hz, $^3J_{F,H}$ = 32 Hz).

In a typical coupling reaction, a two-neck 25 mL round botton flask equipped with a N_2 source, magnetic stir bar, and rubber septum, was charged with $Pd(PPh_3)_4$ (0.29 g, 0.25 mmol) and *p*-$CO_2EtC_6H_4I$ (2.3 g, 8.3 mmol). A DMF solution of (E)-HFC=CFZnI (12 mmol) was then added *via* syringe and the mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with cold water (75 mL) and extracted with 1:1 pentane:Et$_2$O (4 x 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Chromatography on SiO_2 (20% EtOAc:pentane, R_f 0.5) gave 1.63 g (93%) of (Z)-*p*-$CO_2EtC_6H_4CF$=CFH as a pale yellow solid: mp 52-53 °C; HRMS calcd. for $C_{11}H_{10}F_2O_2$ 212.0649, found 212.0641.; FTIR (CCl_4) 3122 (w), 2984 (w), 1724 (s), 1694 (s), 1411 (m), 1275 (s), 1146 (s), 1108 (s), 1013 (m) cm^{-1}; ^{19}F NMR ($CDCl_3$, *vs.* internal $CFCl_3$) -143.7 (dd, $^3J_{F,H}$ = 15.7 Hz, $^3J_{F,F}$ = 10.2 Hz, 1F), -161.2 (dd, $^2J_{F,H}$ = 71.9 Hz, $^3J_{F,F}$ = 10.2 Hz, 1F); ^1H NMR ($CDCl_3$) 1.4 (t, 7.1 Hz, 3H), 4.4 (q, 7.1 Hz, 2H), 7.1 (dd, 72.5, 16.9 Hz, 1H), 7.5 (d, 8.4 Hz, 2H), 8.0 (d, 8.3 Hz, 2H); ^{13}C NMR ($CDCl_3$) 14.3, 61.3, 123.2 (t, 4.2 Hz), 130.0, 131.2, 133.1 (d, 23.5 Hz), 135.4 (dd, 260.6, 15.1 Hz), 145.7 (dd, 247.5, 10.9 Hz) 165.8.

In conclusion, we have developed a general method for the stereospecific preparation of (Z)-α,β-difluorostyrenes from (E)-HFC=CFSiEt$_3$. Work aimed at utilizing the resultant styrenes in the stereospecific construction of functionalized fluorinated alkenes is in progress.

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