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Stereospecific synthesis of (*E*)-α,β-difluorostyrenes

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Abstract

Isomerically pure (*Z*)-HFC=CFZnI undergoes $Pd(PPh_3)_4$/CuBr co-catalyzed cross-coupling reactions with aryl iodides in DMAC to give the title compounds in good yields, under mild conditions. In the absence of CuBr, the reaction is sluggish, requires more vigorous reaction conditions, and gives lower yields. © 2000 Elsevier Science Ltd. All rights reserved.

Fluorinated styrenes are useful building blocks in organofluorine chemistry and have found applications 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-difluorostyrenes, 1-arylperfluoropropenes,[4] β,β-difluoro-α-(trifluoromethyl)styrenes,[5] and (*Z*)-α,β-difluorostyrenes,[6] by the corresponding $Pd(PPh_3)_4$ catalyzed arylation of the thermally stable perfluorovinylzinc reagents, CF_2=CFZnX, (*Z*) and (*E*)-CF_3CF=CFZnX, CF_3(ZnX)C=CF_2, and (*E*)-HFC=CFZnI. A few reports have described the formation of (*E*)-α,β-difluorostyrenes; however, a general and stereospecific preparation of these compounds has not been reported. Low temperature metallation of several isomeric β,β-difluoro-α-chlorostyrenes with an alkyllithium reagent followed by hydrolysis has been reported to give predominantly (*E*)-α,β-difluorostyrenes.[7] Protodesilylation of (*Z*)-1,2-difluoro-3-arylvinylsilanes with KF/H_2O gave (*E*)-α,β-difluorostyrenes.[8] In the chemical literature, the palladium catalyzed coupling reaction (Stille reaction) of an organobromide or iodide with organostannane or zinc reagents has been well documented.[9] In general, the Stille reaction with an organostannane needs a Cu(I) salt as a co-catalyst. However, only one report has noted co-catalysis of a Cu(I) salt in the Stille reaction with an organozinc reagent.[10]

We now report a general and stereospecific method for the preparation of (*E*)-1,2-difluorostyrenes. This method utilizes isomerically pure (*Z*)-HFC=CFZnI coupling with aryl iodides in DMAC under $Pd(PPh_3)_4$/CuBr co-catalysis. (*Z*)-HFC=CFZnI, **3**, was prepared via a two-step procedure as described below.

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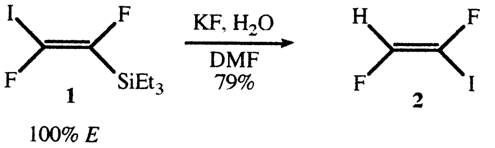
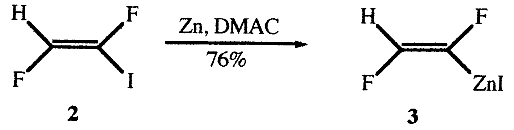


(1)

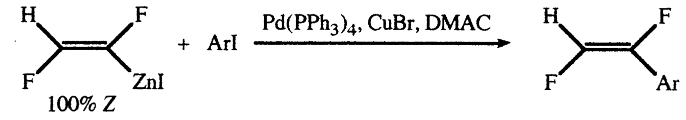


(2)

Via a modification of Normant's procedure,[11] (Z)-HFC=CFI, **2**, was prepared in 79% yield via protodesilylation of **1** with KF/H_2O, whereas Normant employed DMSO as the solvent and obtained **2**, in a lower isolated yield (66%). (Z)-HFC=CFI,[12] **2**, was treated with acid-washed zinc dust in DMAC to give **3** in good NMR yield (determined with $PhCF_3$ internal standard in the ^{19}F NMR spectrum). A higher yield (76%) was obtained in DMAC (*N*,*N*-dimethylacetamide) solvent than in DMF (<50%) (*N*,*N*-dimethylformamide).

(Z)-1,2-Difluoroethenylzinc iodide undergoes cross-coupling reactions with aryl iodides under mild conditions in the presence of $Pd(PPh_3)_4$ and CuBr. Under similar conditions, the coupling reaction was incomplete in the absence of CuBr. It has been found that addition of CuBr greatly accelerates the sluggish palladium catalyzed coupling reaction of the (Z)-1,2-difluoroethenylzinc iodide. In the presence of CuBr, all the coupling reactions were completed in a short period of time (normally 2 hours) under mild conditions. Table 1 summarizes these results. The CuBr presumably complexes the triphenylphosphine ligands and generates a higher concentration of the active catalyst.

Table 1
Preparation of (E)-1,2-difluorostyrenes



Entry	Ar	Conditions	Isolated yield (%)[a]
1	4-F-C_6H_4	40°C/3 h	89
2	4-Cl-C_6H_4	rt/1 h	95
3	4-Br-C_6H_4	rt/1 h	94[b]
4	4-I-C_6H_4	rt/2 h	92[c]
5	C_6H_5	rt/4 h	74[d]
6	4-OMe-C_6H_4	40°C/6 h	94
7	3-$CF_3C_6H_4$	40°C/1.5 h	84
8	1-Naphthalene	40°C/2.5 h	87
9	3-NO_2-C_6H_4	rt/1 h	93
10	4-NO_2-C_6H_4	rt/20 min	87
11	2-Thiophene	rt/1 h	73

[a] All products gave satisfactory ^{19}F, ^{1}H, ^{13}C NMR and HRMS data.

[b] No bis-adduct detected.

[c] Bis-adduct; 3 equiv. of zinc reagent used.

[d] Without CuBr, the reaction with a 94:6 isomeric mixture of (Z) and (E)-1,2-difluoroethenylzinc iodides took six hours at 50°C; the product was isolated in a yield of 41%, GLPC purity = 95%.

Our initial preparation of (*E*)-α,β-difluorostyrenes utilized a sequence similar to that used for the synthesis of (*Z*)-α,β-difluorostyrenes.[6] Thus, a 94:6 isomeric mixture of (*Z*) and (*E*)-1,2-difluoroethenylzinc iodides was utilized in the $Pd(PPh_3)_4$ catalyzed cross-coupling with aryl iodides. However, the problem with using an isomeric mixture of (*Z*) and (*E*)-1,2-difluorooethenylzinc iodides to prepare (*E*)-α,β-difluorostyrenes is that the *cis*/*trans* isomer ratio increases in the products. The reason for this unsuccessful preparation of (*E*)-α,β-difluorostyrenes from a mixture of (*Z*) and (*E*)-zinc reagents is that the (*E*)-1,2-difluoroethylzinc iodide undergoes the palladium catalyzed cross-coupling reaction with aryl iodides faster than the (*Z*)-isomer. Thus, pure (*Z*)-1,2-difluoroiodoethene must be employed in the preparation of the zinc reagent.

In a typical procedure for the preparation of the (*Z*)-HFC=CFZnI, a two-neck 1 L round bottom flask equipped with a Teflon-coated stir bar, dry ice/isopropanol condenser and rubber septum, was charged with DMF (300 mL), (*E*)-1,2-difluoro-3-iodo-1-triethylsilylethylene (92.1 g, purity 95%, 288 mmol), and KF (18.2 g, 314 mmol). Water (5.2 g, 289 mmol) was then gradually introduced into the solution via a syringe over 5 minutes. A mild exothermic reaction was observed. The reaction mixture was stirred at room temperature for 0.5 h, then distilled by flash distillation and the distillate trapped in a liquid nitrogen cooled flask. The resultant colorless distillate was dried over 5 g of P_2O_5 and distilled by flash distillation at rt/1 mmHg. Further fractional distillation of the distillate through a 10 cm Vigreux column yielded 42.7 g (79%) of a colorless liquid, GLPC purity = 100%, bp = 44–45°C. ^{19}F NMR (δ) −132.1 (d, J = 145 Hz), −158.8 (dd, J = 145, 76 Hz); ^{1}H NMR (δ) 7.47 (dd, J = 76, 1 Hz); {^{1}H}^{13}C NMR (δ) 146.31 (dd, J = 248, 56 Hz), 104.16 (dd, J = 315, 57 Hz); GCMS (*m*/*e*) 190 (M^+, 100), 127 (49), 63 (76), 59 (42); HRMS: calcd for C_2HF_2I: 189.9090, observed: 189.9106. A two-neck 500 mL round bottom flask equipped with a Teflon-coated stir bar, a dry ice/isopropanol condenser attached to a nitrogen source and a rubber septum, was charged with 190 mL of DMAC, 30 g (461.5 mmol) of acid-washed zinc dust and 39.8 g (209.8 mmol) of (*Z*)-1,2-difluoroiodoethene. After the reaction mixture had been stirred for 0.5 h, a strong exothermic reaction was observed. After the exotherm had subsided, the solution was stirred for an additional 1.5 h. The ^{19}F NMR spectrum of the reaction mixture indicated complete consumption of the (*Z*)-1,2-difluoroiodoethene. The NMR yield ($PhCF_3$ as the internal standard) of the (*Z*)-1,2-difluoroethenylzinc iodide was 76%. ^{19}F NMR (δ) (DMAC) −172.28 (dd, J = 104, 12 Hz, 1F), −184.46 (dd, J = 104, 87 Hz, 1 F).

In a typical coupling reaction, a two-neck 50 mL round bottom flask equipped with a Teflon-coated stir bar, a cold water condenser attached to a nitrogen source and a septum, was charged with 4-chloroiodobenzene (1.79 g, 7.43 mmol, 99%), $Pd(PPh_3)_4$ (0.50 g, 0.43 mmol, 5.8 mol%), CuBr (1.0 g, 6.9 mmol, 0.9 equiv.) and (*Z*)-1,2-difluoroethenylzinc iodide (19 mL, 11.4 mmol, 0.60 M, 1.5 equiv.) in DMAC. The reaction mixture was stirred at room temperature for 1 h. ^{19}F NMR analysis of the reaction mixture showed the formation of the 4-chloro-(*E*)-α,β-difluoro-β-hydrostyrene; GCMS of a pre-chromatographed reaction mixture showed the complete disappearance of the 4-chloroiodobenzene. The dark reaction mixture was poured onto a silica gel column and eluted with pentane, R_f = 0.57. Eluents with similar UV-active TLC spots were combined and a majority of the pentane was removed by simple distillation. Removal of the remaining trace amount of solvent at −35°C/1 mmHg yielded 1.23 g (95%) of a colorless liquid, GLPC purity >99%. ^{19}F NMR (δ), −167.0 (dd, J = 126, 5 Hz, 1 F), −172.69 (dd, J = 126, 75 Hz, 1 F); ^{1}H NMR (δ) 7.47–7.07 (m, 5 H); {^{1}H}^{13}C NMR (δ) 151.36 (dd, J = 228, 31 Hz), 141.34 (dd, J = 252, 72 Hz), 135.64 (d, J = 3 Hz), 129.10 (s), 127.73 (dd, J = 25, 6 Hz), 126.73 (dd as t, $J = 8$ Hz); GCMS (m/e) 174 (M^+, 100), 139 (27), 138 (14), 119 (40), 99 (12); FTIR: 3110 (w), 1598 (m), 1494 (s), 1399 (m), 1354 (m), 1151 (versus), 1121 (m), 1107 (s), 1098 (m); HRMS calcd for $C_8H_5Cl^{35}F_2$: 174.0048, observed: 174.0049.

In conclusion, we have developed a general method for the stereospecific preparation of (E)-α,β-difluoro-β-hydrostyrenes from (Z)-HFC=CFZnI via an unusual $Pd(PPh_3)_4/CuBr$ co-catalyzed cross-coupling reaction. Detailed mechanistic study and applications of these fluorinated styrenes is in progress.

Acknowledgements

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References

1. Reynolds, D. W.; Cassidy, P. E.; Johnson, C. G.; Cameron, M. L. *J. Org. Chem.* **1990**, *55*, 4448.
2. Middleton, W. J.; Bingham, E. M. *J. Fluorine Chem.* **1983**, *22*, 561.
3. Middleton, W. J.; Metzger, D.; Snyder, J. A. *J. Med. Chem.* **1971**, *14*, 1193.
4. Heinze, P. L.; Burton, D. J. *J. Org. Chem.* **1988**, *53*, 2714.
5. Morken, P. A.; Burton, D. J. *J. Org. Chem.* **1993**, *58*, 1167.
6. Davis, C. R.; Burton, D. J. *Tetrahedron Lett.* **1996,** *37*, 7237; Davis, C. R.; Burton, D. J. *J. Org. Chem.* **1997**, *62*, 9217.
7. Martin, S.; Sauvetre, R.; Normant, J. F. *Tetrahedron Lett.* **1982**, *23*, 4329.
8. Yagupol'skii, L. M.; Cherednichenko, P. G.; Kremlev, M. M. *J. Org. Chem. USSR* (*Engl. Transl.*) **1987**, *23*, 246; Martin, S.; Sauvetre, R.; Normant, J. F. *Tetrahedron Lett.* **1983**, *24*, 5615.
9. Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *41*, 6139.
10. Labaudiniere, L.; Normant, J. F. *Tetrahedron Lett.* **1992**, *41*, 6139.
11. Martin, S.; Sauvetre, R.; Normant, J. F. *J. Organomet. Chem.* **1989**, *367*, 1.
12. (Z)-HFC=CFI should be dried by flash distillation of the liquid from anhydrous P_2O_5.