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Palladium/Copper (I) Halide-Cocatalyzed Stereospecific Coupling of 1-Fluorovinylstannanes with Aryl Iodides and Acyl Chlorides

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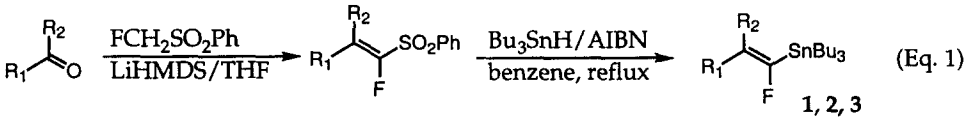
Abstract: Cross-coupling of 1-fluorovinylstannanes with aryl iodides or acyl chlorides, cocatalyzed by palladium and copper (I) iodide proceeded under mild conditions to give substituted fluoro olefins and α-fluoro-α,β-unsaturated ketones, respectively, in good yields with retention of configuration. © 1997 Elsevier Science Ltd.

There has been considerable interest in fluoroorganic compounds as agrochemical and pharmaceutical agents.[1] It is believed that fluorine alters the physiochemical properties of organic compounds thereby modifying the activity of biologically important compounds.[2] New methods for the synthesis of fluoro olefins have received considerable attention.[3] Among these the palladium-catalyzed cross-coupling of an unsubstituted 1-fluorovinylstannanes,[4] or 2-trimethylsilyl-1-fluorovinylstannanes[5] with aryl iodides or sulfonates under Stille coupling conditions[6] have been demonstrated to be useful for design and synthesis of mechanism-based enzyme inhibitors containing 1- or 2-fluoro olefins.[7] In this communication we report a stereospecific palladium (0)/copper (I)-cocatalyzed cross-coupling reaction of 2-substituted or 2,2-di-substituted 1-fluorovinylstannnanes with organic halides to form multiple substituted vinyl fluorides.

The starting 1-fluorovinylstannanes (**1, 2** and **3**) are readily prepared in high yields by radical reactions of tributyltin hydride with 1-fluorovinyl phenyl sulfones,[3] which were synthesized by the condensation[8] of fluoromethyl phenyl sulfone[9] with aldehydes and ketones (equation 1). This transformation is stereospecific when the 1-fluorovinyl sulfone is 2,2-disubstituted.[3] The two stereoisomers of 1-fluorovinylstannanes are separable on silica gel by chromatography and their structures were determined by ^1H-{^{19}F} NOE NMR experiments which were reported earlier.[3]



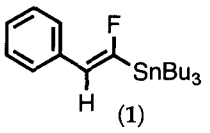
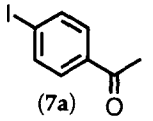
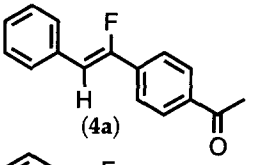
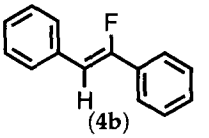
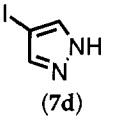
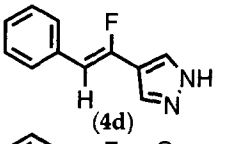
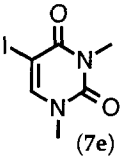
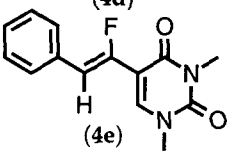
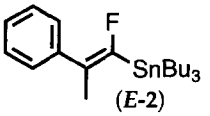
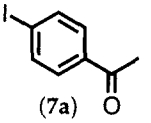
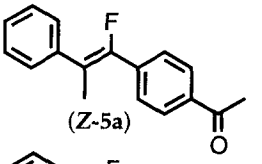
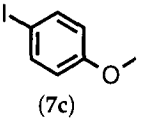
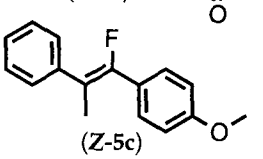
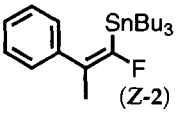
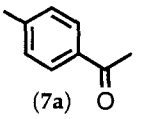
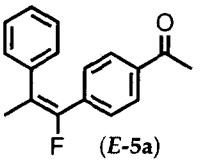
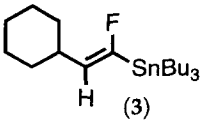
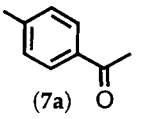
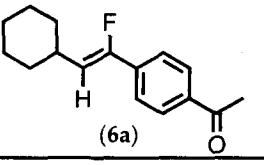
(Eq. 1)

1, 2, 3

1, R^1 = Ph, R^2 = H; **3**, R^1 = cyclohexyl, R^2 = H;
***E*-2**, R^1 = Ph, R^2 = Me; ***Z*-2**, R^1 = Me, R^2 = Ph;

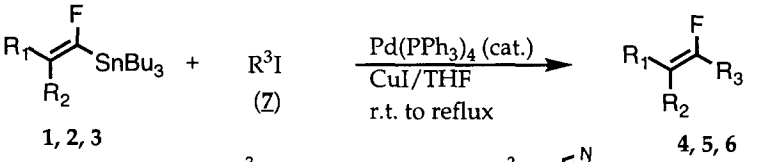
In general, palladium-catalyzed coupling reactions of organostannanes with organic halides and sulfonates[10] have already been established as an efficient method for the formation of carbon-carbon bonds. Initial attempts at coupling of 1-fluorovinylstannane (***E*-2**) with iodobenzene (**7b**) in the presence of 10 mole % of $Pd(PPh_3)_4$ in refluxing THF under nitrogen, only gave the cross-coupling product, (*Z*)-1,2-diphenyl-1-

Table 1. Pd(0)/Cu(I) Cocatalyzed Coupling of Fluorovinyltins with Aryl Iodides[a]

Entry	1, 2, 3	[Yield (%)]	7	4, 5, 6	Yield (%)[b]
1	 (1)	(69%)	 (7a)	 (4a)	90
2			 (7b)	 (4b)	86
3			 (7d)	 (4d)	67
4			 (7e)	 (4e)	89
5	 (*E*-2)	(76%)	 (7a)	 (*Z*-5a)	83
6			 (7c)	 (*Z*-5c)	50
7	 (*Z*-2)	(65%)	 (7a)	 (*E*-5a)	75
8	 (3)	(78%)	 (7a)	 (6a)	72

[a] All reactions were carried out in refluxing THF under N_2 on a 0.5 mmole scale for 1.0 equiv. of 1-fluorovinylstannane using 5 mol % of $Pd(PPh_3)_4$ and 1.0 equiv. of CuI as the cocatalysts. [b] Yield of isolated product; satisfactory ^1H NMR, ^{19}F NMR, mass spectra and microanalyses.

fluoropropene (***Z*-5b**) in about 10% after 18 hours; most of the starting material remained unchanged. When the reaction was carried out in DMF at 120°C for 18 hours, 42% of ***Z*-5b** was isolated when 35 mole % of the palladium catalyst was used. In addition, homocoupling product of the tin compound formed and substantial amount of (*Z,Z*)-2,5-diphenyl-3,4-difluorohexadiene ($CH_3C(Ph)=CFCF=C(Ph)CH_3$, **10a**) was isolated among other decomposition products. It has been reported that CuI accelerates sluggish or otherwise unsuccessful Stille coupling reactions.[11] Thus when the coupling reactions of 1-fluorovinylstannanes (**1**, **2**, or **3**) with a variety of organic halides (**7**) were conducted in refluxing THF under nitrogen, using 5 mole % of $Pd(PPh_3)_4$ and 1 equivalent of CuI as cocatalyst, the desired coupling products (**4**, **5** or **6**) were obtained[12] in good yields (equation 2).[13] This indicated a decreased reactivity of the 1-fluorovinylstannanes (**1**, **2** and **3**) relative to the simple unsubstituted vinyltin, and is another example of the "copper effect" in a particularly difficult Stille coupling.[11] The results obtained with several iodoaryl compounds are summarized in **Table 1**.



1, 2, 3 **4, 5, 6** (Eq. 2)

7a: R^3 = 4-AcC_6H_4-; **7d**: R^3 = 

7b: R^3 = Ph-;

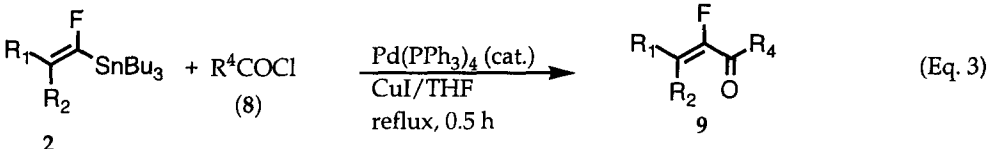
7c: R^3 = 4-$MeOC_6H_4$-; **7e**: R^3 = 

Although CuI cocatalyzed the above coupling reaction, CuI alone did not provide product ***Z*-5a** from ***E*-2** and **7a**. The coupling reaction also proceeded at ambient temperature with much longer reaction times. In all cases only one isomer was isolated. The *trans* stereochemistry of **4** and **6** was readily assigned on the basis of a $J_{H,F}$ value between 39-46 Hz and comparison with model compounds.[14] The stereochemical assignment for compounds **5** is not straight forward. Based on the uniformity of the coupling mechanism[6] and the well established stereochemistry[3] of the 1-fluorovinylstannane, the *E* and *Z* configuration were initially assumed for compounds **5**. However, the ^1H-{^{19}F} NOE technique was used to confirm the retention of configuration for the conversion of tin compounds ***E*-2** and ***Z*-2**, to compounds ***Z*-5a** and ***E*-5a**. Thus by irradiation of the fluorine on ***Z*-5a** a strong NOE was observed for the *ortho*-protons of both phenyl groups, but not the vinyl methyl groups. Alternatively, by irradiation of the fluorine on ***E*-5a** a strong NOE was observed for the methyl group and the *ortho*-proton of acetylphenyl group, but not the unsubstituted phenyl ring. It should be noted that the coupling reaction of ***Z*-2** proceeded much slower than ***E*-2** and may be due to steric hindrance by the *cis*-configuration of ***Z*-2**. NMR experiments show a proton-proton NOE between the vinyl methyl group and the *ortho*-proton of the acetylphenyl group of ***Z*-5a**, but not ***E*-5a**

The palladium-CuI-cocatalyzed cross-coupling reactions of 1-fluorovinylstannanes **2** with acyl chlorides were carried out under the same conditions to afford α-fluoro-α,β-unsaturated ketones (**9**) in very good yields (equation 3).

Attempts to couple ***E*-2** with ethyl oxalyl chloride or ethyl chloroformate provided homocoupling product (*Z,Z*)-2,5-diphenyl-3,4-difluorohexadiene (**10a**) exclusively. Coupling of **1** with iodobenzene (**7b**) under a carbon monoxide atmosphere gave the normal coupling product **4b** and CO insertion product **9a** in 36% and 53%, respectively (equation 4). Coupling of **1** with phenyl triflate failed even in the presence of 2

equivalents of LiCl, and the only product isolated was (*Z,Z*)-1,4-diphenyl-2,3-difluorobutadiene (*Z,Z*-CH(Ph)=CFCF=CHPh, **10b**).

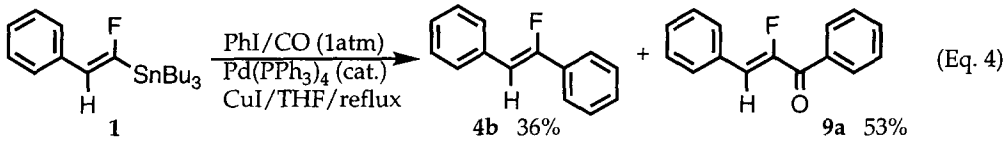


2 9 (Eq. 3)

8a: R^4 = Ph- **9a**: R^1 = Ph, R^2 = Me, R^4 = Ph- (50%)

8b: R^4 = $PhCH_2CH_2$- ***Z*-9b**: R^1 = Ph, R^2 = Me, R^4 = $PhCH_2CH_2$- (80%)

***E*-9b**: R^1 = Me, R^2 = Ph, R^4 = $PhCH_2CH_2$- (78%)



1 **4b** 36% **9a** 53% (Eq. 4)

In summary, we have developed a palladium/copper (I) halide-cocatalyzed cross-coupling reaction of 1-fluorovinylstannanes with a variety of organic halides that provides a stereospecific route to fluoro olefins.

Acknowledgement: We thank Dr. Edward Huber for performing the ^1H-{^{19}F} NOE NMR experiments.

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11. Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L.S. *J. Org. Chem.* **1994**, *59*, 5905 and references cited therein.
12. All new compounds were characterized with ^1H NMR, ^{13}C NMR, ^{19}F NMR, mass spectra and satisfactory microanalyses.
13. The following is a typical procedure: A mixture of the tin compound (215 mg, 0.5 mmol), 4'- iodo-acetophenone (130 mg, 0.5 mmol), tetrakis(triphenylphosphine)palladium(0) (60 mg, 0.05 mmol) and CuI (90 mg, 0.47 mmol) in THF (8 ml) was heated at reflux for 30 minutes. The black deposit indicated the completion of the reaction. The mixture was concentrated *in vacuo* and chromatographed on silica gel with 1:5 ethyl acetate-hexanes to give (*Z*)-1-fluoro-1-(4-acetylphenyl)-2-phenylpropene (*Z*-5a) as a white solid (105 mg, 83% yield); Analytical sample was obtained by recrystallization from ether-hexanes, m.p.= 96-8°C; ^1H NMR (TMS/$CDCl_3$): 2.19 (d, J = 3.0 Hz, 3H), 2.65 (s, 3H), 7.32 (t, J = 7.4Hz, 1H), 7.41 (t, J = 7.4 Hz, 2H), 7.50 (d, J = 7.4 Hz, 2H), 7.66 (d, J = 8.4 Hz, 2H), 8.02 (d, J = 8.4 Hz, 2H); ^{13}C NMR (TMS/$CDCl_3$): 20.0 (d, J = 3Hz), 28.0, 118.5 (d, J = 15Hz), 128.8, 129.5, 129.6, 129.9, 130.0, 138.8 (d, J = 102Hz), 138.9 (d, J = 29Hz), 151.3, 154.6, 198.8; ^{19}F NMR (TFA/$CDCl_3$): -101.7; Anal. for $C_{17}H_{15}FO$ (254.31), calcd.: C%, 80.29; H%, 5.95; found: C%, 80.12; H%, 6.04.
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