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Palladium/Copper (I) Halide Catalyzed Stereospecific Couplings of 1,2-Difluorovinylstannanes With Aryl Iodides and Vinyl Halides

Long Lu and Donald J. Burton*

Department of Chemistry, The University of Iowa, Iowa City, IA 52242 USA

Abstract: Palladium/copper (I) halide catalyzed cross couplings of (E)- and (Z)-1,2-difluorovinylstannanes with aryl iodides and vinyl halides proceeded at room temperature to stereospecifically give 1,2-disubstituted-1,2-difluoroolefins and 1,2-difluoro or 1,2,3,4-tetrafluorosubstituted dienes in good to excellent yields.

Due to the unique properties of compounds which contain one or more fluorine atoms at strategic positions in the molecule, fluoroorganic compounds continue to attract the interest of polymer chemists, pharmaceutical chemists and agrochemists.[1] Many natural products, such as pheromones and juvenile hormones, contain double bonds and conjugated polyenes as essential features of their structures,[2] and the synthesis as well as biological activity of various fluorinated analogs have been reported.[3-8] In most cases, only an isolated saturated hydrogen or one vinyl hydrogen was replaced by fluorine. Although the introduction of the *trans*-1,2-difluoroethene unit into organic compounds has been investigated by Normant and co-workers,[9] the preparation of the *cis*-1,2-difluoroethene unit still remains a challenging problem.[10-13] Here we wish to report a stereospecific palladium/copper (I) halide catalyzed cross-coupling reaction of 2-substituted-1,2-difluorovinylstannanes with aryl halides and vinyl halides to form disubstituted olefins and dienes containing the 1,2-difluoroethene unit.

The starting 1,2-difluorovinylstannanes are readily prepared in high yields by methods recently reported from our laboratory.[14,15] The (Z)-1,2-difluorovinylstannanes are prepared as outlined below:

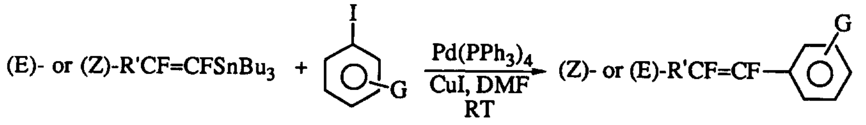
$$F_2C{=}CFSiR_3 \;+\; R'Li \longrightarrow (Z)\text{-}R'CF{=}CFSiR_3 \xrightarrow[KF]{Bu_3SnCl} (Z)\text{-}R'CF{=}CFSnBu_3 \qquad \text{(Eq. 1)}$$

$R = Me, Et$

The corresponding (E)-1,2-difluorovinylstannanes were prepared by photochemical isomerization of (Z)-R'CF=CFH.[16,17] Subsequent metallation and trapping with chlorotributylstannane gives the (E)-1-tributylstannyl-1,2-difluoro-1-alkenes:

$$\begin{tikzcd}
(E)\text{-}R'CF{=}CFH \arrow[r, "hv", "\begin{array}{c}254\text{ mm}\\ \text{cat. PhSSPh}\end{array}"'] & (Z)\text{-}R'CF{=}CFH \arrow[d, "\begin{array}{l}1)\ \text{tert-BuLi}\\ \quad \text{THF/ether, -95°C}\\ 2)\ Bu_3SnCl\text{, -90°C}\end{array}"] \\
 & (E)\text{-}R'CF{=}CFSnBu_3
\end{tikzcd} \qquad \text{(Eq. 2)}$$

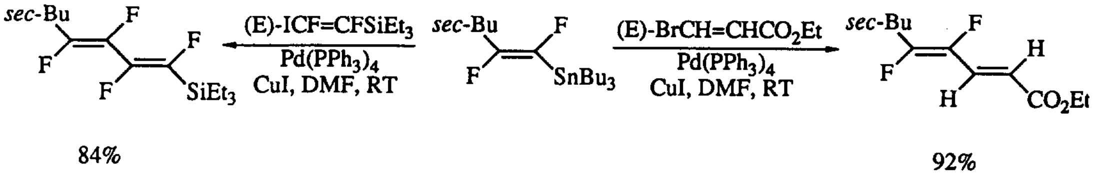
Although palladium (0)-catalyzed coupling reactions of vinylstannanes with organic halides has already been established by Stille[18] as a useful method for the formation of carbon-carbon bonds, the use of $Pd(PPh_3)_4$ alone for the coupling of (Z)-$CH_3CF{=}CFSnBu_3$ with iodobenzene was not effective. Either little or no cross-coupling was observed at room temperature after 24 hours or extensive decomposition to form a complicated mixture was observed at 70°C. However, under Liebeskind conditions,[19] $Pd(PPh_3)_4$/CuI/DMF were employed and successful cross-coupling (Eq. 3) occurred to give good to excellent yields of the 1,2-disubstituted-1,2-difluoroolefins. The enhanced reactivity of (Z)-$CH_3CF{=}CFSnBu_3$ with Pd(0)/CuI catalysis is another example of the "copper effect" in Stille coupling. Retention of configuration was observed in all cases. Table I summarizes our results, **1-10**. $Pd(PPh_3)_4$ or CuI alone did not catalyze the coupling reaction. When G was an electron-withdrawing group, the reaction was rapid and 1.05 equivalents of the vinylstannane was sufficient to consume all the aryl iodide. When G was an electron-donating group, the reaction was slower and 1.3-1.4 equivalents of the vinylstannane was required to ensure complete consumption of the aryl iodide.[20]



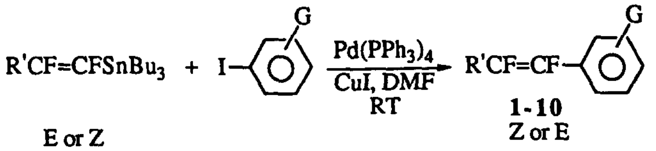
(Eq. 3)

In a typical coupling reaction, a 25 mL round bottom flask was charged with $Pd(PPh_3)_4$ (0.05 g. 0.043 mmol), CuI (0.10 g, 0.52 mmol), 3-iodonitrobenzene (0.25 g, 1.0 mmol) and dry DMF (4 mL) and then (Z)-$CH_3CF{=}CFSnBu_3$ (0.45 g, 1.2 mmol) was added at room temperature with stirring. The reaction mixture was stirred at room temperature for 10 h, then diluted with ether (100 mL), washed with aqueous KF solution (15%, 50 mL). The ether layer was separated, dried over $MgSO_4$, concentrated and separated on a silica gel column using a mixture of ethyl acetate and hexane (1:20) to give 0.17 g (85%) of (E)-$CH_3CF{=}CFC_6H_4\text{-}3NO_2$ (**1**) as yellow crystals, mp 52-53°C; HRMS calcd. for $C_9H_7NF_2O_2$ 199.0445, found 199.0431. FTIR 1709.5 (C=C), 1577.4 (NO_2)cm^{-1}; ^{19}F NMR ($CDCl_3$ *vs.* internal $CFCl_3$) - 134.5 (dq, $^3J_{FF}$ = 123.3, 18.5 Hz, 1F), -160.0 (dq, $^3J_{FF}$ = 123.3, 5.8 Hz, 1F) ppm; ^1H NMR ($CDCl_3$) 8.42 (t, J = 1.9 Hz, 1H), 8.15 (ddd, J = 8.2, 2.2, 1.0 Hz, 1H), 7.90 (dt, J = 8.2, 1.0 Hz, 1H), 7.57 (t, J = 8.2 Hz, 1H), 2.25 (dd, J = 18.0, 5.7 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$) 151.4 (dd, J = 250.3, 56.8 Hz), 148.3 (s), 145.0 (dd, J = 224.0, 42.7 Hz), 131.4 (dd, J = 26.2, 6.7 Hz), 130.4 (dd, J = 9.8, 7.3 Hz), 129.4 (d, J = 2.4 Hz), 122.7 (d, J = 1.8 Hz), 119.7 (dd, J = 9.8, 8.5 Hz), 13.59 (d, J = 24.4 Hz) ppm.

The palladium/copper (I) halide catalyzed cross-coupling of the 2-substituted-1,2-difluorovinylstannanes with vinyl halides was carried out under similar conditions to stereospecifically afford the corresponding conjugated dienes.



(Eq. 4)



R'	Configuration	G	Compd. #	Yield (%)[b]	Configuration[c]
CH_3	Z	3-NO_2	**1**	85	E
sec-Bu	Z	4-CN	**2**	86	E
n-Bu	Z	3-NO_2	**3**	87	E
tert-Bu	Z	2-NO_2	**4**	83	E
C_6H_5	Z	4-NO_2	**5**	92	E
sec-Bu	Z	3-OCH_3	**6**	81	E
CH_3	Z	4-CH_3	**7**	92	E
n-Bu	E	3-NO_2	**8**	91	Z
sec-Bu	E	4-OCH_3	**9**	82	Z
n-C_6H_{13}	E	2-NO_2	**10**	86	Z

[a]All reactions were carried out in DMF at room temperature using 3-4 mol % of $Ph(PPh_3)_4$ and 50 mol % of CuI as catalysts. [b]Isolated yields based on aryl iodide. All compounds gave satisfactory ^{19}F, ^{1}H, ^{13}C NMR, IR and HRMS data. [c]Stereochemical configurations were assigned on the basis of $J_{F,F}$trans = 120-132 Hz and $J_{F,F}$cis = 10-15 Hz.

In conclusion, we have demonstrated high yield stereospecific preparations of (E)- and (Z)-1,2-disubstituted-1,2-difluoroethenes and dienes containing one or two-1,2-difluoroethene units. These novel (E)- and (Z)-1,2-difluorovinylstannanes should find application in the design of bioactive natural products, pharmaceuticals, liquid crystals, polymers and agrochemicals. Future work will describe additional synthetic applications of these and related synthons.

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16. cf. ref. 14; details of this isomerization will be published elsewhere.
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20. Total consumption of the aryl iodide is necessary since the olefinic products and the aryl iodide are not separable by column chromatography.

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