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LETTERS

Effect of fluorine substituents on catalytic functionalizations of alkyl halides with organostannanes

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Abstract—Introduction of fluorine atom(s) at the γ- and δ-positions of alkyl iodides increased the selectivities toward palladium-catalyzed cross-coupling reaction with organostannanes. A similar effect of fluorine substituents on the selectivities was also observed in the palladium-catalyzed carbonylative coupling reaction of alkyl iodides with phenyltributyltin under CO pressure.

Organofluorine compounds are well-known for displaying unique reactivities and selectivities in the transition-metal catalyzed functionalization reactions. For example, we have previously reported that perfluoroalkyl-substituted alkyl iodides readily undergo carbonylation and double-carbonylation reactions in the presence of transition-metal catalysts, where these halides showed similar reactivities to phenyl or vinyl halides rather than alkyl halides.[1,2] In these reactions, we have proposed that β-perfluoroalkyl-substituted alkylmetal species, generated by the oxidative addition of the halides to low valent transition-metal complexes, can be stabilized by the internal coordination of fluorine atom(s) to the metal center so that the insertion of carbon monoxide takes place more rapidly than the β-elimination of hydrido-metal species.[3] If these organometallic intermediates are stable enough,[4] it may be possible to develop new carbon–carbon bond forming reactions which have been considered difficult with non-fluorinated alkyl halides. In the course of these working hypotheses, we have recently found transition-metal catalyzed functionalizations of β-perfluoroalkyl-substituted alkyl halides with Grignard reagents and organostannanes.[5,6] Here, we wish to report that the introduction of fluorine atom(s) at the γ- and δ-positions of alkyl iodides[7–9] increased the selectivities toward palladium-catalyzed cross-coupling and carbonylative coupling reactions with organostannanes.

First, we examined the palladium-catalyzed cross-coupling reaction of fluorine-substituted alkyl iodides with organostannanes (Table 1). When 1-iododecane (**1a**) was heated with (phenylethynyl)tributyltin (3.0 equiv.) in benzene at 120°C for 16 h in the presence of $Pd(PPh_3)_4$ (10 mol%), 1-phenyl-1-dodecyne (**2a**) was obtained in only 6% yield, along with 1-decene in 47% yield. Employing 4-fluoro-1-iododecane (**1b**) and 3-fluoro-1-iododecane (**1d**) instead of 1-iododecane (**1a**) afforded the corresponding cross-coupling products, 6-fluoro-1-phenyldodecyne (**2b**) and 5-fluoro-1-phenyldodecyne (**2d**), in 20 and 18% yields under similar conditions. The introduction of two fluorine atoms to the δ- and γ-positions of the iodide was more effective. Thus, 4,4-difluoro-1-iododecane (**1c**) and 3,3-difluoro-1-iododecane (**1e**) reacted under the same conditions to give 6,6-difluoro-1-phenyldodecyne (**2c**) and 5,5-difluoro-1-phenyldodecyne (**2e**) in 33 and 38% yields, respectively (Eq. (1)).

The more distinguished effect of fluorine substituents on the selectivities was observed in the palladium-catalyzed carbonylative coupling reaction of alkyl iodides with phenyltributyltin under CO pressure (Table 2). The treatment of 1-iododecane (**1a**) with phenyltributyltin (1.1 equiv.) in benzene at 120°C for 16 h in the presence of $Pd(PPh_3)_4$ (10 mol%) under CO pressure

$$\underset{\mathbf{1}}{\mathrm{R{-}I}} \xrightarrow[\text{cat. Pd(PPh}_3)_4\text{ (10 mol\%)}\\ \text{benzene, 120}^\circ\text{C, 16 h}]{\mathrm{Ph{\equiv}SnBu_3}\text{ (3.0 equiv.)}} \underset{\mathbf{2}}{\mathrm{R{\equiv}Ph}} \qquad \begin{array}{l} \mathbf{a}\text{: } R{=}C_{10}H_{21}\text{-} \\ \mathbf{b}\text{: } R{=}C_6H_{13}\text{-}CHF\text{-}(CH_2)_3\text{-} \\ \mathbf{c}\text{: } R{=}C_6H_{13}\text{-}CF_2\text{-}(CH_2)_3\text{-} \\ \mathbf{d}\text{: } R{=}C_7H_{15}\text{-}CHF\text{-}(CH_2)_2\text{-} \\ \mathbf{e}\text{: } R{=}C_7H_{15}\text{-}CF_2\text{-}(CH_2)_2\text{-} \end{array} \qquad (1)$$

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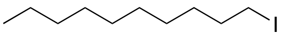
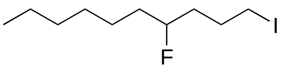
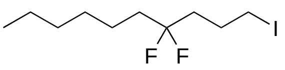
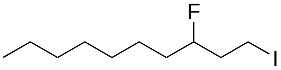
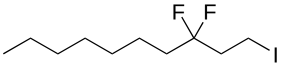
Table 1. Catalytic coupling reaction with alkyl iodides with (phenylethynyl)tributyltin[a,b]

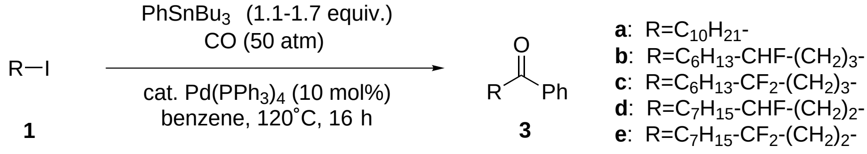
Entry	Iodoalkane		Yield of product (%)	Yield of alkene (%)
1		(**1a**)	6	47
2		(**1b**)	20	32
3		(**1c**)	33	30
4		(**1d**)	18	12
5		(**1e**)	36	8

[a] Yields were determined by GLC. Iodides were completely consumed under the reaction conditions, respectively.

[b] Typical procedure: see Ref. 10.

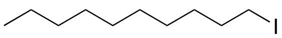
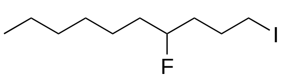
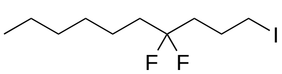
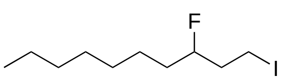
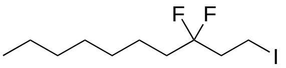
(50 atm) afforded undecanophenone (**3a**) in 39% yield. The yield was not improved at all by using excess (1.7 equiv.) of the tin reagent in the case of the nonfluorinated halide (run 2). The selectivity toward the coupling reaction increased by the introduction of fluorine atom(s) to the δ-position of the iodide. Thus, 4-fluoro-1-iodododecane (**1b**) and 4,4-difluoro-1-iodododecane (**1c**) afforded the desired fluorinated ketones, 5-fluoroundecanophenone (**3b**) and 5,5-difluoroundecanophenone (**3c**), in 53 and 62% yields on using 1.7 equiv. of the tin reagent (runs 3 and 4). In the present carbonylative coupling reaction, the introduction of fluorine atom(s) to the γ-position of the iodide was found to be very effective. The treatment of 3-fluoro-1-iodododecane (**1d**) and 3,3-difluoro-1-iodododecane (**1e**) instead of **1a** with 1.1 equiv. of the tin reagent under similar conditions gave the corresponding carbonylative products, 4-fluoroundecanophenone (**3d**) and 4,4-difluoroundecanophenone (**3e**), in 52 and 65% yields, respectively (runs 5 and 7). In the reaction of **1d**, the yield of the desired ketone (**3d**) reached 81% by using 1.7 equiv. of phenyltributyltin (run 6) (Eq. (2)).

We have examined the theoretical considerations using Gaussian 98 program.[12] The B3LYP DFT (Density Functional Theory) optimization of coordinately unsaturated 3-fluoropropyl palladium complexes, *cis*-$FCH_2CH_2CH_2$-PdI(CO), using LANL2DZ as a basis set gave two stable conformers **4A** and **4B** (Fig. 1). In the conformer **4A**, the γ-fluorine atom of the 3-fluoropropyl group is located at the *trans* position to the iodide atom, in which the bond length between Pd and F is calculated to be 2.22 Å.[13] On the other hand, in the conformer **4B**, β-hydrogen atom of 3-fluoropropyl group is situated at the *trans* position to the iodide, where the bond length between Pd and H is 2.66 Å. This conformer **4B** may be thought to be the intermediate to β-elimination of palladium hydride, which is calculated to be less stable than the conformer **4A** by 8.60 millihartrees (5.40 kcal/mol). The transition structure calculation from these two comformers **4A** and **4B** using Opt=QST2 as a keyword easily met the stationary point. In the predicted transition structure **4TS**, the palladium atom is weakly linked to both hydrogen and fluorine atoms (Pd–H=2.78 Å, Pd–F=3.66 Å), and the energy difference between the transition structure **4TS** and the stable conformer **4A** is calculated to be 12.5 millihartrees (7.87 kcal/mol). Similar calculations for *cis*-4-fluorobutyl-PdI(CO) derivatives also gave the two stable isomers **5A** and **5B**, and the transition structure **5TS**. In this case, the energy difference (5.15 millihartrees, 3.23 kcal/mol) between the transition structure



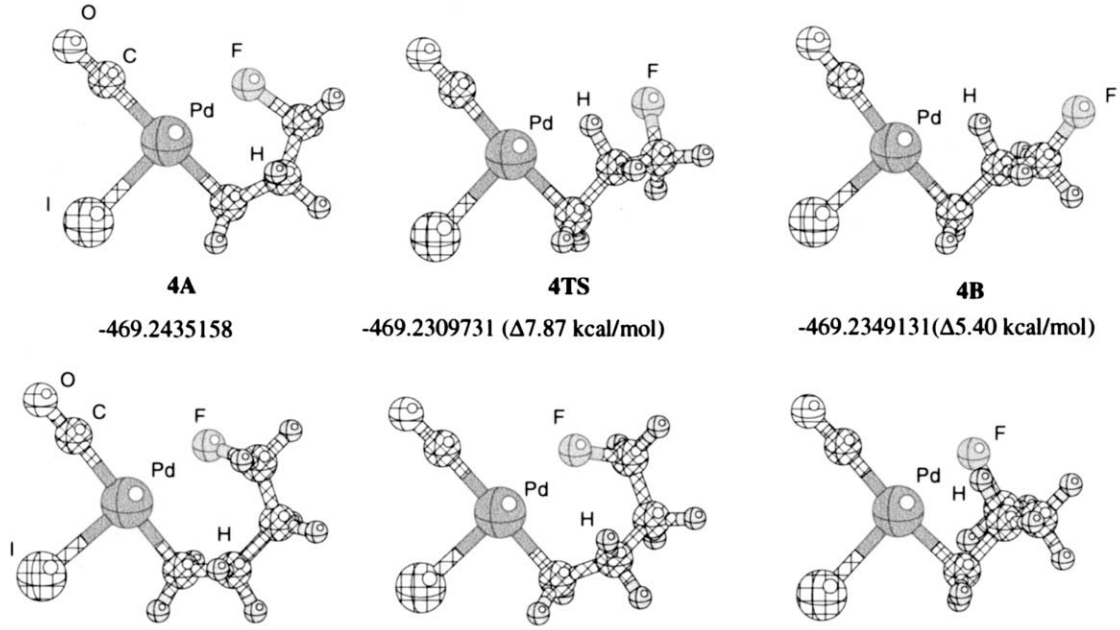
(2)

Table 2. Carbonylative coupling reaction with alkyl iodides with phenyltributyltin[a,b]

Entry	Iodoalkane		$PhSnBu_3$ (equiv.)	Conversion of **1** (%)	Yield of **3** (%)
1		(**1a**)	1.1	74	39
2		(**1a**)	1.7	96	38
3		(**1b**)	1.7	100	53
4		(**1c**)	1.7	100	62
5		(**1d**)	1.1	88	52
6		(**1d**)	1.7	91	81
7		(**1e**)	1.1	89	65

[a] Yields were determined by GLC.

[b] Typical procedure: see Ref. 11.



4A -469.2435158

4TS -469.2309731 (Δ7.87 kcal/mol)

4B -469.2349131(Δ5.40 kcal/mol)

5A -508.5471577

5TS -508.5420105 (Δ3.23 kcal/mol)

5B -508.5444678 (Δ1.69 kcal/mol)

Figure 1.

5TS and the stable conformer **5A** is calculated to be much less than that between **4TS** and **4A** in 3-fluoropropyl derivatives.

In conclusion, the introduction of fluorine atom(s) at the γ- and δ-positions of alkyl iodides increased the selectivities toward palladium-catalyzed functionalizations with organostannanes. It seems that these results support our working hypotheses that the oxidative addition of these fluorinated alkyl halides generates alkylmetal species, which can be stabilized by the internal coordination of fluorine atom(s) into metal center to prevent from β-elimination of metal-hydride.

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6. Shimizu, R.; Fuchikami, T. *Tetrahedron Lett.* **1996**, *37*, 8405–8408.
7. Monofluoro iodides **1b** and **1d** were prepared by DAST-fluorination of the corresponding iodoalcohols, 1-iodo-4-decanol and 1-iodo-3-decanol, respectively.[8] Difluoro-iododecanes **1c** and **1e** were similarly synthesized by treatment of DAST with the corresponding iodoketones in the presence of a catalytic amount of water in CH_2Cl_2 at rt for several days, respectively.[9]
8. Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574–578.
9. Middleton, W. J. US Patent 3,914,265.
10. *General procedure for coupling reaction* (Table 1). (Phenylethynyl)tributyltin (0.75 mmol) was added to a mixture of 3,3-difluoro-1-iododecane (**1e**, 0.25 mmol), $Pd(PPh_3)_4$ (0.025 mmol; 10 mol%), and dry benzene (0.75 ml) in a Pyrex tube. The reaction mixture was stirred at 120°C for 16 h under Ar. The GLC analysis revealed that 5,5-difluoro-1-dodecyne (**2e**) was obtained in 38% yield.
11. *General procedure for carbonylative coupling reaction* (Table 2). Tributylphenyltin (0.43 mmol) was added to a mixture of 3-fluoro-1-iododecane (**1d**, 0.25 mmol), $Pd(PPh_3)_4$ (0.025 mmol; 10 mol%), and dry benzene (0.75 ml) in an autoclave (10 ml). The reaction mixture was stirred under CO pressure (50 atm) at 120°C for 16 h. The GLC analysis revealed that 4-fluoroundecanophenone (**3d**) was obtained in 81% yield in addition to 9% of unchanged **1d**.
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13. The *trans* isomer, *trans*-$FCH_2CH_2CH_2$-PdI(CO), having a similar structure is calculated to be less stable than the *cis* isomer by 0.53 millihartrees.