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Palladium Catalyzed Cross-Coupling Reaction of Functionalized Alkyltrifluorosilanes with Aryl Halides

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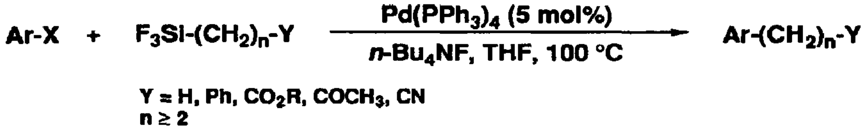
Abstract: **A variety of alkyltrifluorosilanes were found to couple with aryl halides in the presence of $Pd(PPh_3)_4$ catalyst and tetrabutylammonium fluoride (TBAF) to give the corresponding cross-coupled products in moderate to good yields.**

Transition metal catalyzed cross-coupling of organic electrophiles with organometallic reagents is one of the most fundamental carbon-carbon bond forming reactions and is employed recently for the synthesis of various types of natural and unnatural products. In regard to cross-coupling of alkylmetals, such metals as Mg, B, Zn, and Sn have been extensively studied,1) but the synthetic application sometimes encounters problems on selectivity and/or availability of the reagent. In recent years we have been studying highly selective cross-coupling of organofluorosilanes with organic electrophiles mediated by fluoride ion and a palladium catalyst.2) Herein we report the organosilicon based cross-coupling is applicable to variously functionalized or unfunctionalized alkyltrifluorosilanes. This reaction provides us with a facile method for the synthesis of alkyl-substituted aromatic compounds.



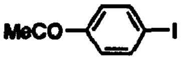
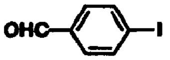
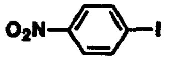
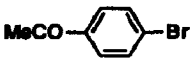
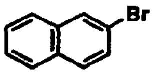
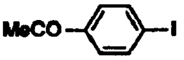
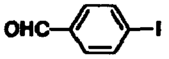
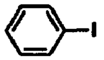
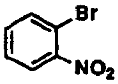
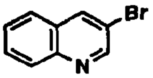
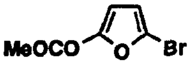
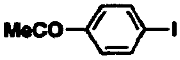
$$\text{Ar-X} + \text{F}_3\text{Si-(CH}_2)_n\text{-Y} \xrightarrow[n\text{-Bu}_4\text{NF, THF, 100 °C}]{\text{Pd(PPh}_3)_4\text{ (5 mol\%)}} \text{Ar-(CH}_2)_n\text{-Y}$$

$Y = H, Ph, CO_2R, COCH_3, CN$
$n \geq 2$

Initially, we studied the reaction of hexyltrifluorosilane with *p*-iodoacetophenone using a palladium catalyst and tetrabutylammonium fluoride (TBAF).3) After a survey of palladium catalysts, solvents, and reaction temperatures, we found that the reaction smoothly proceeded at 100 °C in THF using 2 eq of hexyltrifluorosilane, 3 or 4 eq of TBAF, and 5 mol% of $Pd(PPh_3)_4$ as a catalyst.4) These conditions were applied to various aryl halides and functionalized alkyltrifluorosilanes. The results summarized in Table 15) show that both iodide and bromide are a good coupling partner (runs 1 and 3). In addition, high chemoselectivity is obvious: Ketone (runs 1, 4, and 5) and aldehyde (run 2) carbonyls and nitro (run 3) group are tolerant.6)

The reaction conditions were then applied to functionalized alkyltrifluorosilanes (runs 7-17, Table 1), having -COOR, -CN, or -CO- group. These alkyltrifluorosilanes were readily prepared by a 2 step sequence; hydrosilylation of the corresponding terminal olefin with trichlorosilane followed by fluorination with CuF_2.7)

Table 1. Cross-coupling of Alkyltrifluorosilanes with Aryl Halides

run[a]	Ar-X	F_3Si-$(CH_2)_nY$		time/h[c]	yield/%[d]
		n	Y		
1[b]		6	H	24	61
2[b]		2	Ph	24	61
3[b]		6	H	38	62
4[b]		6	H	37	63
5[b]		2	Ph	34	71
6[b]		6	H	24	62
7		2	CO_2Me	8	77
8				10	76
9				48	75
10				48	62
11				10	32
12				8	65
13				48	36
14		3	CO_2Et	22	45
15		2	CN	21	87
16		3	CN	24	86
17		4	COMe	18	66

Footnote of Table 1.

a) Unless otherwise stated, all the reaction were performed with alkyltrifluorosilane (2 eq), TBAF (4 eq), and $Pd(PPh_3)_4$ (5 mol%).

b) The reaction was carried out at 100 °C in THF using the alkyltrifluorosilane (2 eq), TBAF (2 eq) and $Pd(PPh_3)_4$ (5 mol%). After 8-12 h, 1 eq of TBAF was added, and the reaction was continued for the period shown in Table 1.

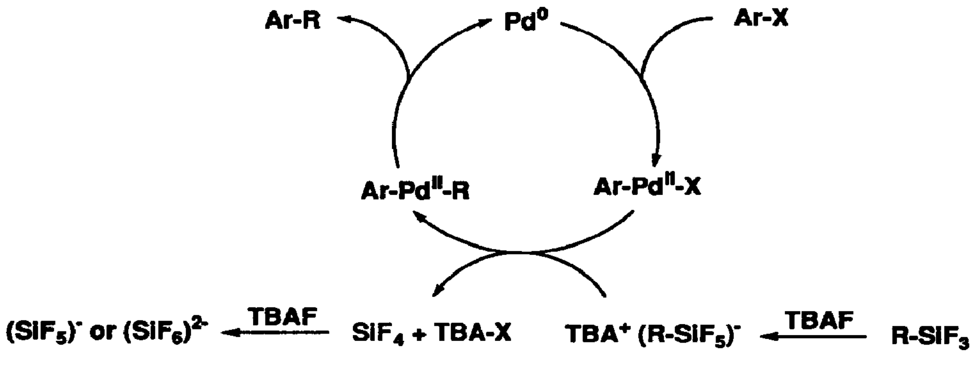
c) Total reaction time is shown.

d) Isolated yields.

The results shown in runs 7 to 13 of Table 1 clearly demonstrate that methyl 3-(trifluorosilyl)propanoate reacted with various aryl halides to afford the corresponding cross-coupled products in moderate to good yields.[8] In particular, methyl 3-(trifluorosilyl)propanoate gave the cross-coupled product with *p*-bromotoluene (run 10) which failed to give the corresponding product with hexyltrifluorosilane.[6] Thus, the ester functional group appears to enhance the reactivity of the organosilicon reagent. The reason for the reactivity enhancement is not clear at this stage. However, halobenzenes with a strongly electron-donating group were found to give poorer results.[9] In addition, ortho substitution affected the efficiency (run 11). An electron-withdrawing heteroaromatic 3-bromoquinoline gave the product in 65% (run 12), but a furan derivative gave lower yield (run 13). Ethyl 4-(trifluorosilyl)butanoate is equally applicable (run 14). It is worth noting that 3-(trifluorosilyl)propanenitrile (run 15) and 4-(trifluorosilyl)butanenitrile (run 16) equally underwent the reaction to give the corresponding products in high yields. Ketone carbonyl group also was found compatible to the reaction with *p*-iodoacetophenone and gave a diketo product in 66% yield (run 17).

In our previous studies, we have shown that use of equimolar amounts of organofluorosilane and fluoride ion is crucial for the success of the cross-coupling of organofluorosilanes with organic halides or triflates.[10] Thereby $R\text{-}Pd^{II}\text{-}X$ was proposed to transmetalate with a pentacoordinated silicate generated from an organofluorosilane and fluoride ion.[2] In contrast, the present results definitely demonstrate that the cross-coupling of alkyltrifluorosilanes with aryl halides requires excess amount of fluoride ion to give the product in acceptable yields. We assume SiF_4 coproduced after the transmetalation is trapped by another mol of fluoride ion and is converted into $(SiF_5)^-$ or $(SiF_6)^{2-}$ as shown in Scheme 1.

Further synthetic and mechanistic studies are now in progress in our Laboratories.



Scheme 1. Plausible reaction mechanism

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1 Mg: Tamao, K.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 4347. Kumada, M. *Pure Appl. Chem.* **1980**, *52*, 669. B: Miyaura, N.; Ishiyama, T.; Sasaki, H.; Sato, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314. Ishiyama, T.; Abe, S.; Miyaura, N.; Suzuki, A. *Chem Lett.* **1992**, 691. Zn: Kobayashi, M.; Negishi, E. *J. Am. Chem. Soc.* **1980**, *102*, 3298. Tamaru, Y.; Ochiai, H.; Nakamura, T.; Yoshida, Z. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1157. Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117. Sn: Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508.

2 Hatanaka, Y.; Hiyama, T. *Synlett* **1991**, 845 and references cited therein. We have also found that cross-coupling of (2-phenyl)ethyltrifluorosilane and octyltrifluorosilane cross-coupled with aryl triflates products in good yields. See, Hatanaka, Y.; Hiyama, T. *Tetrahedron Lett.* **1990**, *31*, 2719.

3 Dihexyldifluorosilane and triethylfluorosilane gave only unsuccessful results. Details of these results will be reported in due course.

4 Solvent like DMF or DMSO lowered the yield of the cross-coupled product, and undesirable homo-coupled product formed predominantly. Pd catalyst like $Pd_2(dba)_3 \cdot CHCl_3$, $PdCl_2(dppe)$, $PdCl_2(dppp)$, $PdCl_2(dppf)$, or $\{(\eta^3\text{-}C_3H_5)PdCl\}_2$ did not afford sufficient yields of the cross-coupled product.

5 A general procedure for runs 1-6 in Table 1 follows. To a THF (1 ml) solution of an aryl halide (0.20 mmol) and $Pd(PPh_3)_4$ (0.010 mmol) placed in a sealed tube were added an alkyltrifluorosilane (0.40 mmol) and TBAF (0.40 mmol, 1 M THF solution). The reaction mixture was stirred at ambient temperature for 30 min and then heated at 100 °C for 8-12 h before TBAF (0.20 mmol) was added to the reaction mixture and additional stirring was continued. After workup, the product was purified by flash chromatography on silica gel (230-400 mesh).

6 The reaction with *p*-iodotoluene gave 4,4'-dimethylbiphenyl in 97% yield without any desired product.

7 Tamao, K.; Yoshida, J.; Yamamoto, H.; Kakui, T.; Matsumoto, H.; Takahashi, M.; Kurita, A.; Maruta, M.; Kumada, M. *Organometallics*, **1982**, *1*, 355. Methyl 3-(trichlorosilyl)-propanoate, 3-(trichlorosilyl)-propanenitrile and 4-(trichlorosilyl)butanenitrile, were purchased from Chisso Chemical Inc. and used for fluorination without purification.

8 Trimethylsiloxycyclopropanes behave like *β*-metalo ketones and thus can coupled with aryl triflates to give *β*-aryl-substituted ketones: Aoki, S.; Fujimura, T.; Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1988**, *110*, 3296. Very recently, a paper reporting successful cross-coupling of functionalized alkylcopper reagents with alkyl halides has appeared: Tucker, C. E.; Knochel, P. *J. Org. Chem.* **1993**, *58*, 4781.

9 For example, the reaction of methyl 3-(trifluorosilyl)propanoate with *p*-bromoacetoanilide provided the cross-coupled product in 23%; with *p*-iodoanisole, no desired product.

10 Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1989**, *54*, 268.

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