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Palladium Catalyzed Coupling Reactions of β-Perfluoroalkyl-Substituted Alkyl Halides with Organostannanes

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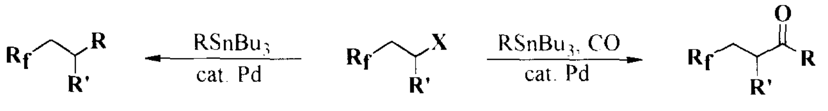
Abstract: β-Perfluoroalkyl-substituted alkyl halides reacted with organostannanes such as allyl-, phenylethynyl-, β-phenylethenyl-, and phenyl-tributyltin in the presence of palladium-phosphine complexes to give the corresponding cross-coupling products in good yields. When the reaction was carried out under CO pressure, carbonylative coupling of the halides took place affording the corresponding fluorine-containing ketones in good yields. Copyright © 1996 Elsevier Science Ltd

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 β-perfluoroalkyl-substituted alkyl iodides readily undergo carbonylation and double-carbonylation reactions in the presence of transition-metal catalysts such as palladium, cobalt, and rhodium complexes to give carboxylic acids, esters, α-ketoacids, and α-ketoamides,[1,2] where these halides showed similar reactivities to phenyl or vinyl halides rather than alkyl halides. We have proposed that β-perfluoroalkyl-substituted alkyl-metal species, generated by the oxidative addition of these halides to low valent transition-metal complexes, can be stabilized by the internal coordination of fluorine atom(s) to metal center so that the insertion of carbon monoxide takes place more rapidly than β-elimination of hydrido-metal species.[3] If these organometallic intermediates are stable enough, it may be possible to develop new carbon-carbon bond forming reactions which have been considered to be difficult with non-fluorinated alkyl halides.[4-7] In the course of these working hypotheses, we have recently found that Grignard cross-coupling reaction of β-perfluoroalkyl-substituted alkyl halides smoothly proceeds by copper catalysts.[8] Here, we wish to report palladium catalyzed cross-coupling reaction and carbonylative coupling reaction of β-perfluoroalkyl-substituted alkyl halides with organostannanes.

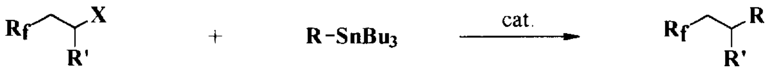


(eq. 1)

R_f=Perfluoroalkyl R'=H, Alkyl X=I, Br
R=Ph, PhCH=CH, PhC≡C, CH_2=$CHCH_2$

When β-(perfluorooctyl)ethyl iodide (**1a**) was heated with allyltributyltin (**6a**) (1.1 equiv.) and a catalytic amount (10 mol%) of $PdCl_2(PPh_3)_2$ in benzene at 120°C for 16 h, cross-coupling product, 5-perfluorooctyl-1-pentene (**7a**), was obtained in 51 % yield as shown in Table 1. Thermal reaction without palladium catalyst afforded **7a** in only 8% yield in addition to 92% of unchanged **1a**. Nickel-phosphine complex $NiCl_2(PPh_3)_2$ showed a similar catalytic activity, while $CuCl(PPh_3)_3$, being an effective catalyst for

Table1. Coupling Reaction of β-Perfluorooctyl-Substituted Alkyl Halides with Organostannanes.[a)]



1a: $R_f=C_8F_{17}$, R'=H, X=I
1b: $R_f=C_8F_{17}$, R'=H, X=Br
2a: $R_f=CF_3$, R'=H, X=I
3a: $R_f=C_6F_{13}$, R'=H, X=I
4a: $R_f=C_8F_{17}$, R'=*c*-hexyl, X=I
5a: $R_f=C_3F_7$, $R'=C_4H_9$, X=I

6a: $R=CH_2=CHCH_2$
6b: R=PhC≡C
6c: R=PhCH=CH
6d: R=Ph

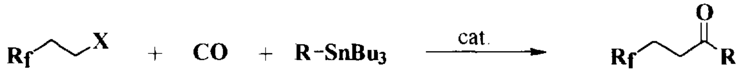
7a: $R_f=C_8F_{17}$, $R=CH_2=CHCH_2$, R'=H
7b: $R_f=C_8F_{17}$, R=PhC≡C, R'=H
7c: $R_f=C_8F_{17}$, R=PhCH=CH, R'=H
7d: $R_f=C_8F_{17}$, R=Ph, R'=H
8b: $R_f=CF_3$, R=PhC≡C, R'=H
9b: $R_f=C_6F_{13}$, R=PhC≡C, R'=H
10b : $R_f=C_8F_{17}$, R=PhC≡C, R'=*c*-hexyl
11b: $R_f=C_3F_7$, R=PhC≡C, $R'=C_4H_9$

Run	R	(equiv.)	Halide	cat.	(mol%)	Temp.	Time	Product, yield (%)[b)]
1	$CH_2=CHCH_2$	(1.1)	**1a**	none		120°C	16 h	**7a**: 8
2				$CuCl(PPh_3)_3$	(10)	120°C	16 h	**7a**: 13
3				$NiCl_2(PPh_3)_2$	(5)	120°C	16 h	**7a**: 57
4				$PdCl_2(PPh_3)_2$	(10)	120°C	16 h	**7a**: 51
5	PhC≡C	(3.0)	**1a**	$Pd(PPh_3)_4$	(10)	120°C	16 h	**7b**: 97
6		(3.0)	**1b**	$PdCl_2(PPh_3)_2$	(10)	120°C	16 h	**7b**: 21 (53)
7		(3.0)	**2a**	$Pd(PPh_3)_4$	(10)	120°C	16 h	**8b**: 61
8		(3.0)	**3a**	$Pd(PPh_3)_4$	(10)	120°C	16 h	**9b**: 79
9		(3.0)	**4a**	$Pd(PPh_3)_4$	(10)	120°C	16 h	**10b** : 53
10		(3.0)	**5a**	$Pd(PPh_3)_4$	(10)	120°C	16 h	**11b** : 41
11	PhCH=CH[c)]	(1.5)	**1a**	$PdCl_2(PPh_3)_2$	(10)	120°C	40 h	**7c**: 45[d)]
12		(3.0)		$PdCl_2(PPh_3)_2$	(10)	120°C	3 h	**7c**: 83[d)]
13		(3.0)		$Pd(PPh_3)_4$	(10)	120°C	16 h	**7c**: 97[d)]
14	Ph	(1.1)	**1a**	$PdCl_2(PPh_3)_2$	(10)	80°C	32 h	**7d**: 28 (72)
15				$PdCl_2(PPh_3)_2$	(50)	80°C	16 h	**7d**: 68 (76)

[a)] All reactions were carried out with halide (0.50 mmol), stannane (0.55 mmol), and catalyst in dry benzene (1.5 ml) unless otherwise noted. [b)] Yields were determined by GLC. Conversion yields are shown in parentheses. [c)] A mixture of (*E*)- and (*Z*)-isomers (*E*/*Z*=7/3) was used. [d)] Only (*E*)-isomer was obtained.

Grignard cross-coupling reactions,[8] was less active in this particular coupling reaction. An ethynyl moiety can be also introduced: Thus, 4-perfluoroalkyl-1-phenyl-1-butynes (**7b**, **8b**, or **9b**) were obtained by the reaction of **1a**, **2a**, or **3a** with excess amounts of (phenylethynyl)tributyltin (**6b**) in good yields under the identical reaction conditions. The corresponding bromide, β-(perfluorooctyl)ethyl bromide (**1b**), was less active in the present coupling reaction, affording 21% yield of **7b** in addition to 60% yield of recovered **1b**

Table2. Carbonylative Coupling Reaction of β-(Perfluorooctyl)ethyl Halides with Organostannanes.[a]



1a: Rf=C_8F_{17}, X=I
1b: Rf=C_8F_{17}, X=Br
2a: Rf=CF_3, X=I
3a: Rf=C_6F_{13}, X=I

6a: R=CH_2=$CHCH_2$
6b: R=PhC≡C
6c: R=PhCH=CH
6d: R=Ph

12a: Rf=C_8F_{17}, R=CH_2=$CHCH_2$
12a': Rf=C_8F_{17}, R=CH_3CH=CH
12b: Rf=C_8F_{17}, R=PhC≡C
12c: Rf=C_8F_{17}, R= PhCH=CH
12d: Rf=C_8F_{17}, R=Ph
13d: Rf=CF_3, R=Ph
14d: Rf=C_6F_{13}, R=Ph

Run	R	(equiv.)	Halide	cat.	(mol%)	Temp.	Time	Product, yield (%)[b]
1	Ph	(1.1)	**1a**	$PdCl_2(PPh_3)_2$	(10)	120°C	16 h	**12d**: 97
2			**1b**	$Pd(PPh_3)_4$	(10)	120°C	64 h	**12d**: 29 (82)
3			**2a**	$PdCl_2(PPh_3)_2$	(10)	120°C	16 h	**13d**: 66
4			**3a**	$PdCl_2(PPh_3)_2$	(10)	120°C	16 h	**14d**: 97
5	CH_2=$CHCH_2$	(1.1)	**1a**	$PdCl_2(PPh_3)_2$	(10)	120°C	16 h	**12a**: 16 (19), **12a'**: 39 (46)[c]
6				$PdCl_2(PPh_3)_2$	(10)	120°C	64 h	**12a**: trace, **12a'**: 61[c]
7	PhC≡C	(1.1)	**1a**	$PdCl_2(PPh_3)_2$	(10)	80°C	16 h	**12b**: 48 (61)
8	PhCH=CH[d]	(3.0)	**1a**	$PdCl_2(PPh_3)_2$	(10)	120°C	16 h	**12c**: 79 (92)[c]

[a] All reactions were run with halide (0.50 mmol), stannane (0.55 mmol), and catalyst in dry benzene (1.5 ml) under CO pressure (50 atm) unless otherwise noted. [b] Yields were determined by GLC. Conversion yields are shown in parentheses. [c] Only (*E*)-isomer was obtained. [d] A mixture of (*E*)- and (*Z*)-isomers (*E*/*Z*=7/3) was used.

(run 6). Secondary alkyl iodides **4a** and **5a**, bearing a bulky group at α-position, also reacted with **6b** to give the cross-coupling products **10b** and **11b** in 53% and 41% yields, respectively. When a mixture of (*E*)- and (*Z*)-(β-phenylethenyl)tributyltin (*E*/*Z* = 7/3) was used as a substrate, only (*E*)-1-phenyl-4-perfluorooctyl-1-butene (**7c**) was formed in good yield, and most of (*Z*)-(β-phenylethenyl)tributyltin was recovered unchanged.

In the case of the reaction with phenyltributyltin (**6d**), the conversion of the substrates was very low, and metallic palladium was precipitated from the reaction medium within a few hours of heating. This may be due to lower ability of **6d** in the transmetallation. When the reaction of iodides **1a**, **2a**, or **3a** with phenyltributyltin was carried out under CO atmosphere in order to prevent the deposition of palladium catalyst, the carbonylative coupling products, β-(perfluoroalkyl)ethyl phenyl ketones (**12d**, **13d**, or **14d**), were formed in excellent yields instead of the simple coupling products as shown in Table 2. Again, bromide **1b** was found to be less reactive in this carbonylative coupling (run 2). Two products, 6-perfluorooctyl-4-oxo-1-hexene (**12a**) and (*E*)-6-perfluorooctyl-4-oxo-2-hexene (**12a'**), were formed in the reaction of **1a** with allyltributyltin (**6a**). When heating was continued for further 48 h, the compound **12a'** was obtained as a predominant product. This result suggests that the initially formed **12a** may be isomerized to **12a'** by the action of palladium catalyst under these reaction conditions. The similar reactions with phenylethynyl- and β-phenylethenyl-tributyltin (**6b** and **6c**) also gave the corresponding carbonylated products (**12b** and **12c**) in moderate to good yields, respectively.

In conclusion, β-perfluoroalkyl-substituted alkyl halides reacted with organostannanes such as allyl-, phenylethynyl-, β-phenylethenyl-, and phenyl-tributyltin in the presence of palladium-phosphine complexes to give the corresponding cross-coupling products in good to high yields. When the reaction was carried out under CO pressure, the carbonylative coupling reaction took place to afford the corresponding fluorine-containing ketones. Further applications and precise mechanistic studies of the reactions are in progress.

General Procedure for Coupling Reaction (Table 1). To a mixture of **1a** (0.50 mmol), $Pd(PPh_3)_4$ (0.05 mmol), and dry benzene (1.5 ml) in a Pyrex® tube was added (phenylethynyl)tributyltin (**6b**; 1.50 mmol). The reaction mixture was stirred at 120°C for 16 h under Ar. GLC analysis revealed that **7b** was formed in 97% yield. After an excess amount of KF was added, the reaction mixture was stirred for 1 day. The mixture was filtered through a sintered glass disk, and the filtrate was evaporated to be freed of solvent *in vacuo*. The product **7b** was isolated by column chromatography on silica gel eluted with hexane, and identified by ^1H- and ^{19}F-NMR, IR, MS, and EA.

General Procedure for Carbonylative Coupling Reaction (Table 2). A mixture of **1a** (0.50 mmol), phenyltributyltin (**6d**; 0.55 mmol), $PdCl_2(PPh_3)_2$ (0.05 mmol), and dry benzene (1.5 ml) was placed in an autoclave (10 ml). The reaction mixture was stirred under CO pressure (50 atm) at 120°C for 16 h. GLC analysis revealed that **12d** was formed in 97% yield. After an excess amount of KF was added, the reaction mixture was stirred for 1 day. The mixture was filtered through a sintered glass disk, and the filtrate was evaporated to be freed of solvent *in vacuo*. The product **12d** was isolated by preparative TLC on silica gel eluted with hexane-CH_2Cl_2 (3:1), and identified by ^1H- and ^{19}F-NMR, IR, MS, and EA.

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