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Copper Catalyzed Grignard Cross-Coupling Reaction with β-Perfluoroalkyl-Substituted Alkyl Halides

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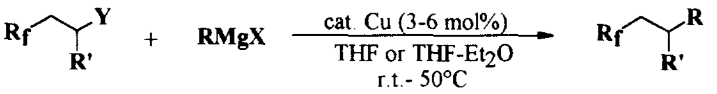
Abstract: Coupling reaction of β-perfluoroalkyl-substituted alkyl halides with Grignard reagents such as phenyl-, vinyl-, allyl-, benzyl-, and alkyl-magnesium halides was catalyzed by copper salts or complexes to give the corresponding cross-coupling products in good yields. α,ω-Diiodoalkane bearing a polyfluoroalkylene moiety also reacted with 2 equiv. of Grignard reagent in the presence of copper catalyst to give α,ω-bi-functionalized product. Copyright © 1996 Elsevier Science Ltd

Transition-metal catalyzed functionalizations of organofluorine compounds are well-known to show unique reactivities and selectivities. For example, we have already reported that β-perfluoroalkyl-substituted alkyl iodides easily undergo carbonylations and double-carbonylations 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] In these reactions, we have proposed that the key intermediates, β-perfluoroalkyl-substituted alkyl-metal species generated by the oxidative addition of β-perfluoroalkyl-substituted alkyl iodides to low valent transition-metal complexes, may be stabilized by the internal coordination of fluorine atom(s) to metal center, and readily undergo the insertion of carbon monoxide faster than β-elimination of hydrido-metal species.[3] If these intermediates are stable enough, it may be possible to develop new carbon-carbon bond forming reactions such as Grignard cross-coupling reactions, which have been regarded to be difficult with non-fluorinated alkyl halides.[4-9] Here, we wish to report a copper-catalyzed cross-coupling reaction of β-perfluoroalkyl-substituted alkyl halides with Grignard reagents such as phenyl-, vinyl-, allyl-, benzyl-, and alkyl-magnesium halides as shown in eq. 1.[10]



(eq. 1)

Rf= Perfluoroalkyl R'= H, Alkyl, etc. Y= I, Br

First, we examined the reaction of alkyl halides (**1-7**) with phenylmagnesium chloride. Representative results were summarized in Table 1. The treatment of β-(perfluorooctyl)ethyl iodide, *i.e.*, 3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluoro-1-iododecane (**1**) with PhMgCl (1.1 equiv.) in the absence of any catalyst in THF at room temperature for 16 h gave the corresponding cross-coupling product **9a** in only 21% yield (run 1), in addition to 26% of unchanged **1** and 41% of a mixture of perfluorooctyl-ethane and ethene. Palladium- and nickel-phosphine complexes, which have been well-known to be very effective catalysts for a

Table 1. Cross-Coupling Reaction of β-Perfluoroalkyl-Substituted Alkyl Halides with PhMgCl.[a]

1:Rf=C_8F_{17}, R'=H, Y=I
2:Rf=C_8F_{17}, R'=H, Y=Br
3:Rf=CF_3, R'=H, Y=I
4:Rf=CF_3, R'=H, Y=Br
5:Rf=C_8F_{17}, R'=C_6H_{13}, Y=I
6:Rf=C_8F_{17}, R'=cyclohexyl, Y=I
7:Rf=C_8F_{17}, R'=$SiMe_3$, Y=I

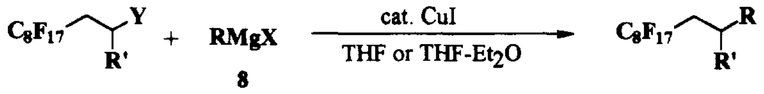
9a:Rf=C_8F_{17}, R'=H
10a:Rf=CF_3, R'=H
11a:Rf=C_8F_{17}, R'=C_6H_{13}
12a:Rf=C_8F_{17}, R'=cyclohexyl
13a:Rf=C_8F_{17}, R'=$SiMe_3$

Run	Substrate	Catalyst	Product	Yield(%)[b]
1	**1**	none	**9a**	21
2	**1**	$PdCl_2(PPh_3)_2$	**9a**	23
3	**1**	$CoCl_2$	**9a**	32
4	**1**	$NiCl_2(PPh_3)_2$	**9a**	37
5	**1**	CuCl	**9a**	81
6	**1**	CuBr	**9a**	89
7	**1**	CuI	**9a**	83
8[c]	**1**	CuI	**9a**	8
9	**1**	$Cu(acac)_2$	**9a**	88
10	**1**	$CuCl(PPh_3)_3$	**9a**	86
11[d]	**2**	CuI	**9a**	90
12[e]	**2**	CuI	**9a**	92
13	**3**	CuI	**10a**	74[f]
14[e]	**4**	CuI	**10a**	98[f]
15	**5**	$CuCl(PPh_3)_3$	**11a**	60
16	**6**	CuI	**12a**	22
17	**7**	CuI	**13a**	56

[a] All reactions were carried out with halide (0.50 mmol), PhMgCl (0.55-0.60 mmol), and catalyst (3-6 mol%) in THF (1.5-2.0 ml) at r.t. for 16-24 h under Ar unless otherwise noted. [b] Determined by GLC. [c] Reaction in Et_2O. [d] Reaction for 65h. [e] Reaction at 50°C for 16h. [f] Determined by ^{19}F-NMR.

variety of cross-coupling reactions of organic halides and organometallics, made little contribution toward the present coupling reaction. However, we found that the addition of Cu(I) or Cu(II) salts as well as Cu(I) complex was quite effective, and the desired cross-coupling product **9a** was formed in more than 80% yields with a small amount of biphenyl (runs 5-7, 9 and 10). In the present reaction, the selection of solvents is very important. When diethyl ether was used as a solvent (run 8), only 8% yield of **9a** was obtained with 50% of recovered **1**. The difference in the length of perfluoroalkyl groups has no influence on this coupling reaction. Thus 3,3,3-trifluoropropyl iodide (**3**) with PhMgCl gave 3,3,3-trifluoropropylbenzene (**10a**) in 74% yield under the similar reaction conditions (run 13). It is noteworthy that bromides as well as iodides can undergo the Grignard cross-coupling reaction and often afford better results, although longer reaction time or some heating is required. Bromides **2** and **4** reacted with **8a** to give **9a** and **10a** in more than 90% yields (runs 11, 12, and 14), respectively. The reactivity of secondary alkyl iodides having a perfluoroalkyl group at β-position[11] is rather lower than that of primary ones because of their steric hindrance. The reaction of secondary alkyl iodides **5**, **6**, and **7** under the same reaction conditions afforded the corresponding phenylated compounds **11a**, **12a**, and **13a** as a sole coupling product, respectively. Isomerization, which was observed in the carbonylation[1] of these secondary alkyl iodides, did not take place at all.

Table 2. Cross-Coupling Reaction with Various Grignard Reagents.[a]



1: R'=H, Y=I
2: R'=H, Y=Br
5: R'=C_6H_{13}, Y=I

b: R=biphenyl, X=Br
c: R=PhCH=CH, X=Br
d: R=Me_2C=$CHCH_2$, X=Cl
e: R=$PhCH_2$, X=Cl

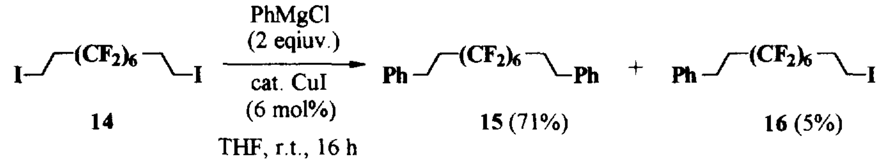
f: R=C_8H_{17}, X=Br
g: R=Me_2CHCH_2, X=Cl
h: R=$PhMe_2CCH_2$, X=Cl
i: R=Me_3SiCH_2, X=Cl

9: R'=H
11: R'=C_6H_{13}

Run	Substrate	8	Product	Yield(%)[b]	Run	Substrate	8	Product	Yield(%)[b]
1	**1**	**b**	**9b**	76	6	**2**	**f**	**9f**	52
2	**1**	**c**[c]	**9c**[d]	44[e]	7[f]	**1**	**g**	**9g**	33
3	**1**	**d**	**9d**	21	8[f]	**1**	**h**	**9h**	64
4	**1**	**e**	**9e**	76	9	**1**	**i**	**9i**	76
5[f]	**1**	**f**	**9f**	39	10[g]	**5**	**e**	**11e**	43

[a] All reactions were run with halide (0.50 mmol), Grignard reagent (0.55-0.60 mmol), and CuI (3-6 mol%) in THF (1.5-2.0 ml) at r.t. for 16-24 h unless otherwise noted. [b] Determined by GLC. [c] *E*/*Z*=79/21. [d] *E*/*Z*=81/19. [e] Isolated yield. [f] Reaction in THF-Et$_2$O (1:1). [g] Reaction for 65 h.

The present copper-catalyzed cross-coupling reaction can be applicable to a variety of Grignard reagents as summarized in Table 2. The iodide **1** reacted with biphenyl- and β-styrylmagnesium bromide under the same reaction conditions to afford 1-biphenyl-2-perfluorooctylethane (**9b**) and 1-phenyl-4-perfluorooctyl-1-butene (**9c**) in moderate to good yields (runs 1 and 2), respectively. Benzylmagnesium chloride gave the coupling product **9e** in 76% yield, while poor yield of the product **9d** was obtained in the reaction with 3-methyl-2-butenylmagnesium chloride. Alkyl Grignard reagents were also submitted to the reaction. Among them, 2-methyl-2-phenylpropyl- and trimethylsilylmethy-magnesium chloride, which have no β-hydrogen, produced good results (runs 8 and 9). Slightly lower yields of the coupling products were formed even in the reaction of **1** with alkyl Grignard reagents having β-hydrogen(s) such as octyl- or 2-methylpropyl-magnesium halide.[12] The reaction of bromide **2** with $C_8H_{17}MgBr$ (run 6) afforded better yield of **9f** than that of iodide **1** did (run 5).



(eq. 2)

Similarly, treatment of polyfluorinated α,ω-diiodoalkane such as 3,3,4,4,5,5,6,6,7,7,8,8-dodecafluoro-1,10-diiodododecane (**14**) with 2 equiv. of PhMgCl afforded the corresponding α,ω-diphenylalkane **15** in 71%

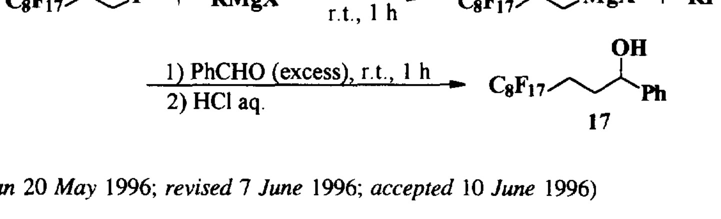
yield, in addition to 5% yield of mono-phenylated product **16** (eq. 2).

Further applications and precise mechanistic studies of the reaction are in progress.

General Procedure. To a mixture of 3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluoro-1-iodododecane (**1**; 0.50 mmol), CuI (0.015 mmol), and dry THF (0.5 ml) in a Pyrex® tube capped with a rubber septum under Ar was added a solution of PhMgCl in THF (0.5 N, 1.1 ml; 0.55 mmol). The reaction mixture was stirred at r.t. for 16 h, quenched with diluted HCl aq. (1 N; 2 ml), and then extracted with Et_2O (2 ml). GLC analysis of the organic layer revealed that **9a** was obtained in 83% yield. The product was isolated by preparative GLC.

REFERENCES AND NOTES

1. Urata, H.; Kosukegawa, O.; Ishii, Y.; Yugari, H.; Fuchikami, T. *Tetrahedron Lett.*, **1989**, 30, 4403-4406.
2. Urata, H.; Ishii, Y.; Fuchikami, T. *Tetrahedron Lett.*, **1989**, 30, 4407-4410.
3. Urata, H.; Maekawa, H.; Takahashi, S.; Fuchikami, T. *J. Org. Chem.*, **1991**, 56, 4320-4322.
4. There are few reports on the transition-metal catalyzed cross-coupling reaction of alkyl halides with Grignard reagents to give satisfactory results. It has been reported that primary alkyl iodides reacted with 2-(1,3-butadienyl)magnesium chloride in the presence of CuI at -30°C to give the corresponding cross-coupling products, but alkyl bromides and secondary iodides did not.[5] Tsuji et al. reported CuI-bipyridil catalyzed coupling reaction of (2,5-dioxoranyl)-substituted alkyl halides with Grignard reagent derived from the same alkyl halides.[6]
5. Numamoto, S.; Kawakami, Y.; Yamashita, Y. *Bull. Chem. Soc. Jpn.*, **1981**, 54, 2831-2832.
6. Tsuji, J.; Kaito, M.; Takahashi, T. *Bull. Chem. Soc. Jpn.*, **1978**, 51, 547-549.
7. Castle and Widdowson reported cross-coupling reaction of alkyl iodides with alkyl Grignard reagents in the presence of a catalytic amount of $PdCl_2$(dppf).[8] But Yuan and Scott re-examined the reaction and denied it.[9]
8. Castle, P. L.; Widdowson, D. A. *Tetrahedron Lett.*, **1986**, 27, 6013-6016.
9. Yuan, K.; Scott, W. J. *Tetrahedron Lett.*, **1989**, 30, 4779-4782.
10. Satisfactory analytical and spectral data were obtained for all new compounds.
11. Fuchikami, T.; Ojima, I. *Tetrahedron Lett.*, **1984**, 25, 303-306.
12. In the cases of the reactions of iodide **1** with alkyl Grignard reagents having β-hydrogen(s), halogen-metal exchange reaction between **1** and Grignard reagents is an inevitable side reaction. Thus, the treatment of iodide **1** with octylmagnesium chloride (1.1 equiv.) in THF at r.t. for 1 h without copper catalyst, followed by the treatment with an excess of benzaldehyde, resulted in the formation of 3-perfluorooctyl-1-phenylpropanol (**17**) in 40 % yield with little recovered **1**. However, the same treatment of **1** with 2-methyl-2-phenylpropylmagnesium chloride gave **17** in only 8% yield, in addition to more than 70% of unchanged **1**.



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