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C−F Bond-Cleavage Reactions of Fluoroalkanes with Magnesium Reagents and without Metal Catalysts

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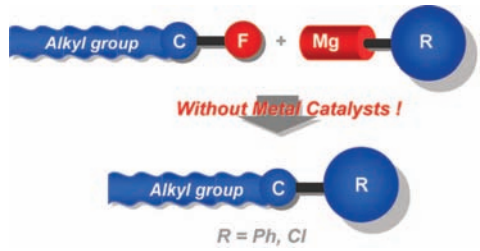
ABSTRACT



An unexpected C−F bond-cleavage reaction of unactivated fluoroalkanes with the well-known Grignard reagents without using metal catalysts has been discovered. For example, a reaction between 1-fluorooctane and phenyl magnesium chloride gave *n*-octylbenzene in moderate yield. This coupling reaction via the activation of an unactivated alkyl carbon−fluorine bond proceeds with phenylmagnesium chloride, whereas methylmagnesium chloride did not give the C−C cross-coupling product but rather a halogen exchange product.

Carbon−fluorine bonds are the strongest bonds that carbon can form. Cleavage of these carbon−fluorine bonds in organic molecules under mild conditions is one of the most challenging goals in chemistry. A number of studies concerned with C−F bond scission for the reduction of fluorocarbons or the transformation of fluorocarbons into nonfluorinated organic molecules have been reported.[1] In the C−F bond-cleavage reactions, activation of aliphatic C−F bonds is rare but has been achieved using transition metal species,[2−4] strong Brønsted acids (such as hydrogen halides[5]), and strong Lewis acids (such as boron,[6] aluminum,[7] carbocation,[8] and silylcation compounds[9]). Magnesium-enamides have been used as reagents in C−C coupling reactions by the cleavage of unactivated C−F bonds,[10] while weaker Lewis acidic magnesium reagents[11] such as Grignard reagents are not believed to be able to activate strong C−F bonds.

In general, the reaction potential of Grignard reagents toward haloalkanes is low,[12] and very few examples of cross-coupling reactions using secondary and tertiary bromo- and

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iodoalkanes with Grignard reagents have been reported.[13] Thus, it is reasonable to assume that cross-coupling of nonactivated fluoroalkanes with Grignard reagents is even less likely.

Recently, several reports have shown efficient cross-coupling reactions of fluoroalkanes with Grignard reagents using transition metal catalysts such as nickel and copper complexes.[14] In this paper, we describe new C−F bond activation and C−C and C−X bond-forming processes by the reaction of a primary 1-fluorooctane with magnesium reagents without using a transition metal species and under mild conditions. We thus report the scope, limitations, and some mechanistic considerations of the new reactions.

This reaction was discovered while screening reactions of fluoroalkanes with Grignard reagents in the presence of transition metal compounds. Typically, 1-fluorooctane and phenylmagnesium chloride in THF were stirred at 60 °C for 4 days in the presence of a transition metal species. Among the crude products, *n*-octylbenzene was obtained in a yield of 28%. However, even in the absence of these transition metal compounds *n*-octylbenzene was isolated at 60 °C after 3 days in 29% yield after silica gel column chromatography (Table 1, entry 1). At higher temperature (80 °C) and with a reaction time of 24 h the yield increased to about 40% (entry 2). At least 50% of the 1-fluorooctane was converted into *n*-octylbenzene when more than 5 equiv of the Grignard reagent was added (entry 3), as shown in Scheme 1 (1), or when $MgCl_2$ was added to the reaction mixture (entry 4). Addition of MgF_2 did not change the yields. Isolated yields of *n*-octylbenzene were 35−37% after column chromatography in several experiments.[15] 1-Chlorooctane was also obtained in yields of 20−30% as determined by gas chromatography. Longer reaction times did not result in increased yields of *n*-octylbenzene for this reaction. Other C−C bond-coupling isomers have not been detected in GC-MS or NMR spectra of these crude mixtures.

Secondary and tertiary fluoroalkanes, fluorocyclohexane, and 1-fluoroadamantane were also treated with phenylmagnesium chloride and produced the expected cross-coupling products phenylcyclohexane and phenyladamantane, respectively (Table 1, entries 5 and 6, Scheme 1 (4) and (5)). The reactivity of fluoroalkanes increased in the order primary < secondary < tertiary, as was the case for substitution reactions with aluminum reagents.[7b] The reaction rate observed when using phenylmagnesium chloride also increased in the same order. However, the reaction of fluorocyclohexane with phenylmagnesium chloride formed mainly cyclohexene in 26% yield and phenylcyclohexane/chlorocyclohexane in lower yields (Table 1, entry 5).

Other experimental results showed further significant features of this unexpected C−F bond cleavage reaction. The reaction of 1-fluorooctane with methyl magnesium chloride in THF (3.0 M) did not give the C−C bond-forming product, *n*-nonane, but gave 1-chlorooctane after 24 h as a major product (61% yield) (entry 7, Scheme 1 (2)) and trace amounts of 2-methyl- and 3-methyloctane. These products were detected by GC-MS and show that C−F bond cleavage also occurs with methylmagnesium chloride and that the aryl group that is bound to magnesium is essential for efficient C−C bond formation.[16] Additionally, $MgCl_2$ also reacted efficiently with 1-fluorooctane to form 1-chlorooctane after 6 h (entry 8, Scheme 1 (3)). A recent report showed similar product selectivity using aluminum reagents in fluorine substitution reactions of alkylfluorides.[7b] We also added 1 equiv of tetramethylethylenediamine (TMEDA) to phenylmagnesium chloride in the reaction medium to form a diphenyl magnesium complex bearing a TMEDA ligand and $MgCl_2$ in situ before the reaction. No C−C bond-coupling product was observed for this reaction, with *N*,*N*-dimethyloctylamine being the main product. *N*,*N*-Dimethyloctylamine was probably formed by a S_N2 reaction of in situ generated 1-chlorooctane with TMEDA and a subsequent intramolecular Hoffmann degradation (Table 1, entry 9). This result indicated that only 1-chlorooctane was formed, even in the

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(12) Trial for nucleophilic substitution of haloalkanes with Grignard reagent: Hahn, R. C.; Tompkins, J. *Tetrahedron Lett.* **1990**, *31*, 937–940.

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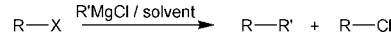
(14) Metal-catalyzed Grignard cross-coupling of fluoroalkanes: (a) Terao, J.; Todo, H.; Watanabe, H.; Ikumi, A.; Kambe, N. *Angew. Chem., Int. Ed.* **2004**, *43*, 6180–6182. (b) Terao, J.; Watabe, H.; Kambe, N. *J. Am. Chem. Soc.* **2005**, *127*, 3656–3657. (c) Terao, J.; Todo, H.; Begum, S. A.; Kuniyasu, H.; Kambe, N. *Angew. Chem., Int. Ed.* **2007**, *46*, 2086–2089. (d) Terao, J.; Ikumi, A.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2003**, *125*, 5646–5647.

(15) **Typical Procedure.** To 1-fluorooctane (0.16 mL, 1.0 mmol) in a 20 mL Schlenk tube was added a 2.0 M tetrahydrofuran solution of phenylmagnesium chloride (0.75 mL, 1.5 mmol) under an argon atmosphere. The solution was warmed up to 80 °C and stirred for 24 h. After cooling to ambient temperature, the solvent and volatile products, including 1-chlorooctane, were removed under reduced pressure, and water (20 mL) and dichloromethane (20 mL) were added to the residual oil. The crude organic product was extracted with dichloromethane (20 mL × 4) and dried with $MgSO_4$. The residual mixture was purified by silica gel (neutral) column chromatography by eluting with hexane to yield *n*-octylbenzene (68.1 mg, 0.36 mmol, 36%). *n*-Octylbenzene was commercially available, and ^1H and ^{13}C NMR spectral data of the product were in complete agreement with those of the authentic sample.

(16) We have a preliminary experimental result of the reaction of 1-fluorooctane with vinylmagnesium chloride in THF. Although successful dominant C−C bond formation to form 1-decene and also 1-chlorooctane was detected by GC-MS analysis, determination of other products and quantification are not successful at present.

Table 1. C−X Bond Cleavage Reactions of Haloalkanes under Several Conditions

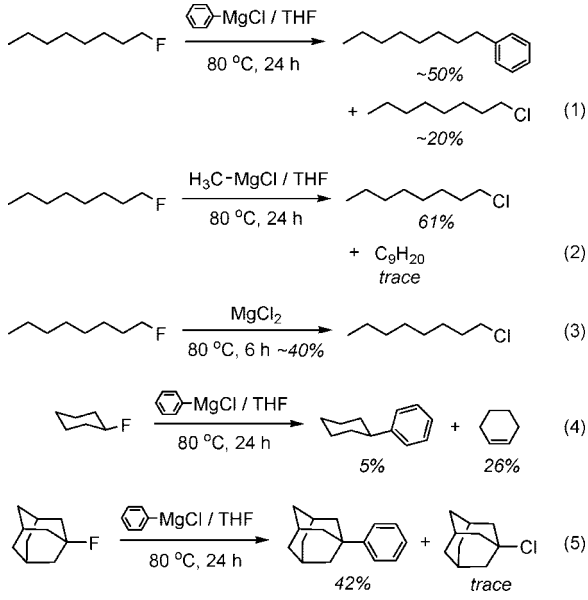


						yield (%)[a]		
entry	R−X	R′	additive	temp (°C)	time (h)	R−R′	R−Cl	R−X
1[c]	1-fluorooctane	Ph		60	72	29[b]	17	6
2	1-fluorooctane	Ph		80	24	44 (36[b])	32	13
3[d]	1-fluorooctane	Ph		80	24	49	21	26
4	1-fluorooctane	Ph	$MgCl_2$	80	24	52	28	13
5	fluorocyclohexane	Ph		80	24	5	7	0
6	1-fluoroadamantane	Ph		80	24	42[b]	tr	0
7	1-fluorooctane	Me		80	24	tr	61	10
8	1-fluorooctane	Cl		80	6		40(9)[e]	0
9	1-fluorooctane	Ph	TMEDA	80	24	0	22	19
10	1-fluorooctane	Ph	TEMPO	80	24	0	12	54
11	1-chlorooctane	Ph		80	24	7		92
12	1-bromooctane	Ph		80	24	23[b]		7

[a] Yields determined by gas chromatography equipped with a mass spectrometer, unless otherwise noted. [b] Yields of R−R′ determined by silica gel column chromatography. [c] Reaction carried out for 72 h. [d] 5 equiv of phenylmagnesium chloride was added. [e] Yield in parentheses is for 2-chlorooctane in a total yield of 40%.

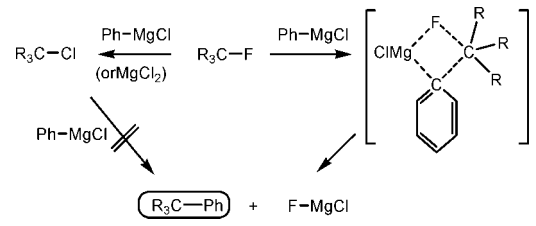
presence of diphenylmagnesium and that halogens in these magnesium reagents are required for C−F bond activation.

Scheme 1



As noted above, C−C bond formation was accompanied by the formation of halogen exchange products such as 1-chlorooctane from 1-fluorooctane in significant yields. We assume that 1-chlorooctane is mostly formed by reaction with $MgCl_2$, which is an in situ equilibrium product of the Grignard reagent, and not with the product salt MgFCl. This assumption is supported by the fact that the amount of 1-chlorooctane increased when the amount of *n*-octylbenzene increased as monitored by ^{1}H NMR spectroscopy. Concerning the reaction pathway of C−C bond formation, we propose an initial formation of 1-chlorooctane via halogen exchange between the fluorine of 1-fluorooctane and the chlorine of the Grignard reagent and then subsequent substitution with the Grignard reagent to form *n*-octylbenzene.[12] We also attempted reactions of other 1-halooctanes with phenylmagnesium chloride. However, the substitution reactions of primary chloro- and bromoalkanes were slow (Table 1, entries 11 and 12). These reactions are known to be difficult and require the presence of metal catalysts such as nickel and copper compounds.[17] For 1-bromooctane, a cross-coupling product was obtained in low yield (23%), while radical coupling and disproportionation products (hexadecane, 1- and 2-octene, and octane) were obtained in a total yield of 50%. In contrast to the reaction with methylmagnesium chloride, halogen exchange is not the predominant process in the substitution of 1-fluorooctane by phenylmagnesium chloride, thus demonstrating that C−C bond formation is accompanied by C−F bond cleavage (Scheme 2).

Scheme 2



We initially suspected metal species contamination on the wall of the reaction apparatus or in the Grignard reagents that acted as a catalyst in this coupling reaction. However,

careful preparation of equipment and reagents also resulted in the formation of *n*-octylbenzene in a similar yield, and the X-ray photoelectron spectrum of the commercially available Grignard reagents after solvent evaporation showed that metals other than magnesium were not present, as shown in Supporting Information. Addition of anhydrous $FeCl_2$ to the reaction mixture of 1-fluorooctane and phenylmagnesium chloride did not enhance the C−C bond-coupling reaction.

This cross-coupling reaction is an energetically downhill process and is about 69 kcal mol^{-1} exothermic according to a DFT calculation (basis set B3LYP 6-31G(d,p)) as shown in Supporting Information. High activation energy is most likely needed in general to cleave the strong C−F bond. We attribute our striking result to a particular Lewis acidic affinity of magnesium in Grignard reagents for fluorine atoms in fluoroalkanes because, as noted above, chlorine in the magnesium reagents is essential for C−F bond activation in these reactions.

We changed the ratios of the reagent and the reactant in this cross-coupling reaction as shown in Table 2. In each case, the yield increased as the amount of the reagent or reactant was increased after 12 h, suggesting that the coupling of primary alkyl fluoride is not a first-order reaction. The above-mentioned results supported the assertion that a second-order reaction proceeds in this case.

Table 2. Effect of the Ratio of 1-Fluorooctane and PhMgCl[a]

	ratio		
entry	Oct-F	PhMgCl	yield (%)[b]
1	1	1	39[c]
2	2	1	84[c]
3	5	1	100[c]
4	1	1.5	33
5	1	2	36
6	1	5	44

[a] At 80 °C for 12 h. [b] Yields determined on the basis of ^{1}H NMR spectra of the crude mixture with tetrakis(trimethylsilyl)silane as internal standard. [c] Yields based on the amount of phenylmagnesium chloride.

Two reaction mechanisms, a concerted mechanism and an electron-transfer mechanism, are known for nucleophilic addition reactions of ketones and aldehydes using Grignard reagents and the type of mechanism depends on the substrates. The concerted multicentered transition state was also proposed for the substitution reactions of secondary and tertiary alkyl halides with Grignard reagents.[18] A mechanism that includes a concerted 4-centered transition state (Scheme 2) and/or alkyl-radical formation[19] could adequately explain the cross-coupling reaction of 1-fluorooctane. The concerted reaction is likely to be preferable to the radical reation because no radical coupling or disproportionation products such as *n*-hexadecane, 1- and 2-octene, or *n*-octane were synthesized. The formation of 1-phenyladamantane from 1-fluoroadamantane in moderate yield also allows us to rule out radical and ionic mechanisms when a tertiary fluorocarbon is used because the formation of a sp^2 radical or a cationic carbon is difficult for adamantane. To determine if a radical species was present in the coupling reaction of 1-fluorooctane, we added a radical-trapping agent, TEMPO, to the reaction medium. No *n*-octylbenzene (Table 1, entry 10) was obtained and the yield of 1-chlorooctane decreased, which suggested that a single electron transfer process exists in the reaction and forms 2,2,6,6-tetramethyl-octyloxy-piperidine.[20] This was detected in the crude mixture using GC-MS as shown in Supporting Information. We then carried out a reaction with *exo*-2-fluoronorbornane[21] and phenylmagnesium chloride to investigate stereoselectivity, but no C−C bond-coupling products were detected and other unknown products were found in the crude mixture, unfortunately. Thus, we conclude that both concerted and electron transfer pathways drive this coupling reaction.

In summary, we discovered some unexpected reactions of the Grignard reagents and magnesium chloride with normal unactivated fluoroalkanes in the absence of metal catalysts. An example is the reaction between phenylmagnesium chloride and 1-fluorooctane that gives *n*-octylbenzene in moderate yield. This C−C bond-coupling reaction proceeds via the activation of an alkyl carbon−fluorine bond and is specific to phenylmagnesium chloride. Using methylmagnesium chloride or magnesium chloride leads to halogen exchange reactions of fluoroalkanes via C−F bond cleavage and probably occurs because of their Lewis acidities and the strong affinity of magnesium for fluorine atoms. Further research into the mechanism and various applications of this cross-coupling reaction are now underway.

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Supporting Information Available: Experimental details, spectral data, and calculation results. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) Preparation and NMR characterization of 2,2,6,6-tetramethyl-1-octyloxy-piperidine (CAS no. 865710-88-9) were reported in Patent WO 2005090307. However, we could not determine the substituted position of the 2,2,6,6-tetramethylpiperidinyloxy group in the octyl group.

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