Conversion of (sp^3)C–F Bonds of Alkyl Fluorides to (sp^3)C–Heteroatom (Heteroatom = I, SR, SeR, TeR) Bonds by the Use of Magnesium Reagents Having Heteroatom Substituents

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A convenient method for conversion of (sp^3)C–F bonds to (sp^3)C–Z (Z = I, SR, SeR, TeR) bonds has been developed. The reaction proceeds at room temperature using magnesium salts (Z–MgX). S_N2 mechanism for substitiution of *primary* alkyl fluorides with MgI_2 in ether was supported by the inversion of the stereochemistry of the carbon connecting to F.

C–F bonds are among the strongest sigma bonds frequently found in organic molecules. Their inertness towards chemical reactions as well as the strong electro negativity of fluorine atom has made fluorine-containing organic molecules useful for a variety of applications in biological and material science and, in turn for chemists, attracts much attention to the study of C–F activation.[1] In particular, to develop new method to substitute fluorine atoms of organic fluorides having an (sp^3)C–F with other atoms or groups has been the subject of many investigations.[2] It is known that (sp^3)C–F bonds can be cleaved when treated with a strong hard acid in polar solvent. However, the scope is generally limited to tertiary or activated alkyl fluorides since these reactions proceed via S_N1 mechanism.[3] The use of *primary* alkyl fluorides usually gives unsatisfactory results due mainly to the H–F elimination, hydride shift, and skeleton rearrangement via *primary* alkyl cation intermediates.[4] During the course of our study on the synthetic application of alkyl fluorides,[5] we have recently developed that C–F bonds of non-activated alkyl fluorides can be converted efficiently into C–Cl, C–C, C–H, C–O, C–N, C–S, C–Se, and C–Te bonds by using organoaluminum reagents in hexane.[6] Here, we wish to report new methods for conversion of a (sp^3)C–F bond of alkyl fluorides to (sp^3)C–Z (Z = I, SR, SeR, TeR) bonds using magnesium reagents bearing Mg–Z bonds.

$$\text{Alkyl–F} \quad + \quad \underset{(\text{Z = I, TeR, SeR, SR})}{\text{Z–MgX}} \xrightarrow{\qquad\qquad} \text{Alkyl–Z} \tag{1}$$

For example, into an ether solution of 1-fluorooctane (1.0 mmol) was added magnesium iodide (1.2 mmol) at 25 °C for 10 h. 1-Iodooctane was obtained in 98% GC yield (eq 2). In this reaction, only a trace amount of 2-iodooctane (<1%) was formed, probably through 1,2-hydride shift of the 1-octyl carbocation. When hexane and CH_2Cl_2 were employed as solvent instead of Et_2O, 2-iodooctane was obtained in 7 and 22% yields, respectively. The present reaction was sluggish in THF and DMSO. When magnesium bromide was used instead of magnesium iodide in ether solution, 1-bromooctane was formed in 41% yield, but no reaction took place with magnesium chloride.[7]

$$\underset{1.0\ \text{mmol}}{\text{1-Oct–F}} \; + \; \underset{1.2\ \text{mmol}}{\text{MgX}_2} \xrightarrow[\text{solvent, 25 °C, 10 h}]{\qquad\qquad} \text{1-Oct–X} \; + \; \text{2-Oct–X} \tag{2}$$

X	solvent	GC yield / %	
I	Et_2O	98%	<1%
I	Hexane	90%	7%
I	CH_2Cl_2	73%	22%
I	THF	2%	<1%
I	DMSO	1%	<1%
Br	Et_2O	41%	<1%
Cl	Et_2O	<1%	<1%

Table 1 summarizes the results obtained using other alkyl fluorides. When cyclohexyl fluoride was treated with MgI_2 in ether, the corresponding iodide was obtained in 71% yield along with cyclohexene (11%) (Entry 1). Only *exo* isomer was obtained, when *exo*-2-fluoronorbornane was used (Entry 2). 1-Fluoroadamantane and benzyl fluoride yielded the corresponding iodides quantitatively (Entries 3 and 4). It should be noted that bromo group, as well as ester group, was not affected in this reaction system and the desired iodides were obtained in high yields (Entries 5 and 6).

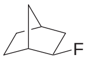
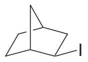
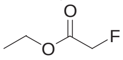
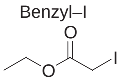
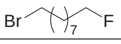
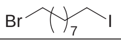
$$\underset{1.0\ \text{mmol}}{\text{1-Oct–F}} + \underset{1.0\ \text{mmol}}{\text{1-Dec–Cl}} + \underset{1.0\ \text{mmol}}{\text{1-Undec–Br}} + \underset{1.2\ \text{mmol}}{\text{MgI}_2} \xrightarrow[\text{Et}_2\text{O, 25 °C, 10 h}]{\qquad\qquad} \tag{3}$$

$$\underset{98\%}{\text{1-Oct–I}} \; + \; \underset{0\%}{\text{1-Oct–F}} \; + \; \underset{>99\%\ \text{recovered}}{\text{1-Dec–Cl}} \; + \; \underset{>99\%\ \text{recovered}}{\text{1-Undec–Br}}$$

We examined the relative reactivities of alkyl halides (Alkyl–X; X = F, Cl, Br) by competitive experiments using MgI_2 (eq 3). A mixture of 1 mmol of 1-fluorooctane, 1-chlorodecane, and 1-bromoundecane was allowed to react with MgI_2 (1.2 equiv.) in ether solution at 25 °C for 10 h. GC analysis of the resulting mixture indicated that 1-iodooctane was obtained selectively in 98% yield. No evidence for the formation of other alkyl

Table 1. Preparation of alkyl iodides from alkyl fluorides[a]

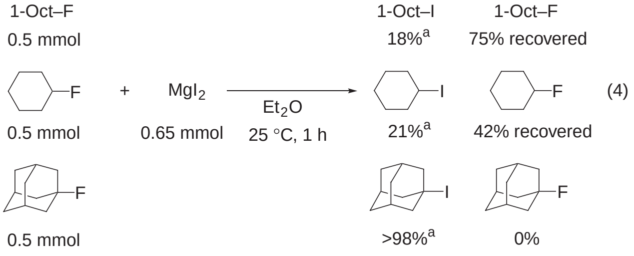
$$\text{Alkyl–F} \quad + \quad \text{MgI}_2 \xrightarrow[\text{Et}_2\text{O, 25 °C, 10 h}]{\qquad\qquad} \text{Alkyl–I}$$

Entry	Alkyl–F	Alkyl–I	Yield/%[b]
1	*c*-Hex–F	*c*-Hex–I	71
2			70[c]
3	1-Adamantyl–F	1-Adamantyl–I	>98
4	Benzyl–F	Benzyl–I	>98[d]
5			>98
6			85[c]

[a]Alkyl fluoride (1.0 mmol), magnesium iodide (1.2 mmol), ether, 25 °C, 10 h. [b]GC yield. [c]Isolated yield. [d]NMR yield.

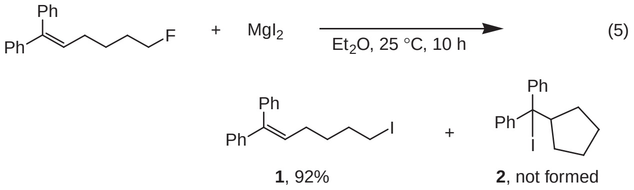
iodides from alkyl chloride or bromide was obtained.

Then relative reactivities of *primary*, *secondary*, and *tertiary* alkyl fluorides were examined. To a mixture of equimolar amounts of 1-octyl, cyclohexyl, and 1-adamantyl fluoride was added an ether solution of MgI_2. After stirring for 1 h at 25 °C, 1-iodoadamantane was obtained predominantly along with cyclohexyl iodide and 1-iodooctane in 21 and 18% yields, respectively (eq 4). This result suggested that reactivities of alkyl halides decrease in the order, *tertiary* > *secondary* > *primary* alkyl fluorides.

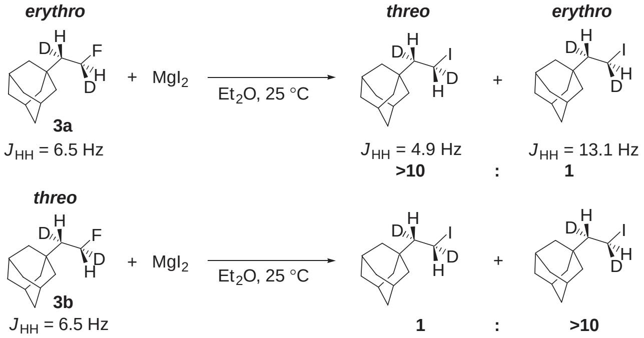


[a] Based on the corresponding fluorides used.

It is suggested that reduction of alkyl fluorides by $Cp^{*}_2ZrH_2$[8] may proceed via a radical pathway. We then carried out the substitution reaction employing 6-fluoro-1,1-diphenyl-1-hexene (eq 5) and found that **1** was obtained as the sole product in 92% yield without formation of **2**, which may arise from intramolecular cyclization of a 6,6-diphenyl-5-hexenyl radical.[9] This result rules out a radical mechanism.



In order to confirm the possibility of an S_N2 mechanism for *primary* alkyl fluoride,[10] we treated diastereometrically pure α,β-d_2-β-adamantylethyl fluorides **3a** and **3b** with MgI_2 in ether (Scheme 1). The ^1H NMR analysis of the products indicated that F–I substitution reaction proceeds with inversion of configuration with higher than 10:1 selectivity from both erythro and threo diastereomers. These results indicate that the present F–I substitution of unactivated *primary* alkyl fluoride with MgI_2 proceeds predominantly via an S_N2 mechanism.



Scheme 1. F–I exchange reaction using diastereometrically pure α,β-d_2-β-adamantylethyl fluorides.

Table 2. Preparation of alkyl chalcogenides from Alkyl–F[a]

$$\text{1-Octyl–F} + \text{Z–MgX} \xrightarrow[\text{THF}]{\text{conditions}} \text{1-Octyl–Z}$$

Entry	Z–MgX	conditions	Isolated yield/%
1	PhTe–MgBr	25 °C, 0.5 h	87
2	PhSe–MgBr	25 °C, 0.5 h	53
3	PhSe–MgBr	25 °C, 5 h	80
4	PhS–MgBr	25 °C, 0.5 h	50
5	PhS–MgBr	reflux, 3 h	91
6	PhO–MgBr	reflux, 3 h	0
7	Te–MgCl	25 °C, 2 h	80
8	Te–MgBr	reflux, 12 h	85

[a] 1-Octyl–F (1.0 mmol) and chalcogen nucleophiles (1.2 mmol) were used.

We applied this procedure to the substitution with chalcogen nucleophiles (RZ–MgX; Z = Te, Se, S, O). When 1-fluorooctane was treated with magnesium phenyl tellurolate, prepared in situ from PhMgBr and tellurium, in THF at 25 °C for 30 min, the corresponding telluride was formed in 87% yield (Table 2, Entry 1). Substitution with SePh was somewhat slower than that with TePh under the identical condition as Entry 1 (Entries 2 and 3). Under THF reflux condition, the corresponding sulfide was obtained in 91% yield, but no reaction took place with PhOMgBr (Entries 5 and 6). Vinyl and alkynyl tellurolates also gave the corresponding tellurides in high yields.

In conclusion, we have developed a simple method for the conversion of (sp^3)C–F bonds of alkyl fluorides to (sp^3)C–heteroatom (heteroatom = I, SR, SeR, TeR) bonds using magnesium reagents having heteroatom substituents. S_N2 mechanism was suggested for substitution of unactivated primary alkyl fluorides with MgI_2.

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