Conversion of a (sp^3)C–F bond of alkyl fluorides to (sp^3)C–X (X = Cl, C, H, O, S, Se, Te, N) bonds using organoaluminium reagents†

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A simple method for the conversion of (sp^3)C–F bonds of alkyl fluorides to (sp^3)C–X (X = Cl, C, H, O, S, Se, Te, N) bonds has been achieved by the use of a hexane solution of organoaluminum reagents having Al–X bonds.

Organic fluorides, especially those having an (sp^3)C–F bond, have been recognized as the most inert class of organic compounds due to the strong C–F bonds. Hence, to develop reactions which replace fluorine atoms with other atoms or groups is a challenging subject in organic chemistry.[1,2] It is known that (sp^3)C–F bonds would be cleaved when treated with a strong hard acid in polar solvent and/or at elevated temperatures. Organoaluminium reagents or aluminium salts can also be employed, but in many cases the substrates employed are limited to tertiary alkyl fluorides or activated ones having a halogen,[3] chalcogen,[4] CF_3,[5] or Ph[6] group at the α-position. The use of *primary* alkyl fluorides usually gives unsatisfactory results due mainly to the H–F elimination, hydride shift, and skeleton rearrangement[7] from *primary* alkyl cation intermediates since these reactions proceed *via* an S_N1 mechanism. During the course of our study on the synthetic application of alkyl halides, we have recently developed Ni- or Cu-catalyzed C–C bond forming reactions using *primary* or *secondary* alkyl fluorides[8] Here, we disclose that C–F bonds of non-activated alkyl fluorides can be converted efficiently into C–Cl,[7,9] C–C,[10–12] C–H,[13] C–O,[14] C–N,[15] C–S,[12b] C–Se, and C–Te bonds by using organoaluminum reagents (R_2Al–X) in hexane under mild conditions (Scheme 1).

For example, when a reaction of *n*-octyl fluoride (1.0 mmol) with diethylaluminium chloride (1.2 equiv., 1 M in hexane) was performed at −78 °C for 3 h, *n*-octyl chloride **11** was obtained in 98% yield. In this reaction, only a trace amount of 2-octyl chloride (1%) was formed as a by-product probably *via* 1,2-hydride shift of the 1-octyl carbocation (Table 1, entry 1). When dichloromethane was used as solvent instead of hexane, a mixture of 1-octyl chloride and secondary octyl chlorides was obtained in 78% and 21% yields, respectively, under similar conditions, but no reaction took place in THF or diethyl ether. When cyclohexyl fluoride and adamantyl fluoride were treated similarly in hexane, the corresponding chlorides **12** and **13** were obtained in 74% and 76% yields, respectively (entries 2 and 3). These results may suggest that substitution reaction proceeds in either an S_N1 or S_N2 fashion depending on the substrates and solvents. It should be noted that *n*-octyl fluoride can react with triethylaluminium at 25 °C, giving rise to alkyl–alkyl cross-coupling product **14** in good yield (entry 4). Recently, construction of the (sp^3)C–(sp^3)C linkage with cleavage of non-activated (sp^3)C–F bonds has been achieved by the use of organoaluminiums[10b] or magnesium enamide,[2a] or $BF_3{\cdot}OEt_2$[10c] as mediators or catalysts. Reaction of *n*-octyl fluoride with alkenyl(diisobutyl)aluminium (**3**), prepared *in situ* from ^{i}Bu$_2$AlH and 1-octyne, in hexane at 25 °C for 6 h afforded a coupling product (**15**) in 90% yield with an *E*/*Z* ratio of 90/10 (entry 5). When diethyl(1-octynyl)aluminium (**4**) was used, 7-hexadecyne (**16**) was obtained in 94% yield (entry 6). These results indicate the selective transfer of the alkenyl or alkynyl group on the aluminium center over alkyl groups.[10b] Under the same conditions, a *primary* alkyl fluoride was readily defluorinated to an alkane by the use of DIBALH (entry 7). When organoaluminium reagents containing aluminium–chalcogen (O, S, Se, and Te) bonds were employed, the corresponding chalcogenides were obtained in good yields (entries 8–11). Replacement of the fluorine atom by an amino group has also been achieved by the use of ^{i}Bu$_2$Al–NEt$_2$ (entry 12).

$$\text{Alkyl—F} \quad + \quad \text{R}_2\text{Al—X} \quad \xrightarrow[\text{hexane}]{} \quad \text{Alkyl—X}$$

X = Cl, Alkyl, Alkenyl, Alkynyl, H,
OPh, SPh, SePh, TePh, NEt$_2$

Scheme 1 Conversion of C–F Bond of Alkyl–F to C–X bonds using organoaluminium reagents.

It is worth noting that the present reaction is unique to only alkyl fluorides and the corresponding alkyl bromides and iodides are tolerant to this reaction as shown below. To a mixture of equimolar amounts of *n*-octyl fluoride, *n*-decyl bromide, and *n*-undecyl iodide was added a hexane solution of diethylaluminum chloride. GC analysis of the resulting mixture indicated the selective formation of *n*-octyl chloride in 98% yield (Scheme 2). No evidence for the formation of other alkyl chlorides was obtained by GC analysis. We also carried out reaction of diethylaluminum chloride with *n*-octyl iodide or bromide under the identical conditions as entry 1 in Table 1, and confirmed that *n*-octyl chloride was not obtained at all in either case and unreacted starting materials were recovered. These results suggest that activation of C–F bond by coordination of Al to F is essential to promote the present substitution reaction.[16]

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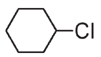
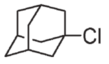
Table 1 Conversion of C–F bond to C–X bond using $R_2Al–X$ in hexane

Entry	Alkyl–F	$R_2Al–X$	Time	Product	Yield (%)[b]
1[c]	^{n}Oct–F	$Et_2Al–Cl$ **1**	3 h	^{n}Oct–Cl **11**	98
2[c]	^{c}Hex-F	$Et_2Al–Cl$ **1**	10 min	**12** 	74
3[c]	1-Adamantyl-F	$Et_2Al–Cl$ **1**	10 min	**13** 	76
4	^{n}Oct–F	$Et_2Al–Et$ **2**	1.5 h	^{n}Oct–Et **14**	93
5	^{n}Oct–F	$^iBu_2Al–CH{=}CH^n$Hex **3**	6 h	^{n}Oct–CH=CH^{n}Hex **15** (*E*/*Z* = 90/10)	90 (75)
6	^{n}Oct–F	$Et_2Al–C{\equiv}C–^n$Hex **4**	16 h	^{n}Oct–C≡C–^{n}Hex **16**	94 (67)
7	^{n}Oct–F	$^iBu_2Al–H$ **5**	1.5 h	^{n}Oct–H **17**	97
8[d]	^{n}Oct–F	$^iBu_2Al–OPh$ **6**	100 h	^{n}Oct–OPh **18**	78
9	^{n}Oct–F	$^iBu_2Al–SPh$ **7**	1 h	^{n}Oct–SPh **19**	99 (77)
10	^{n}Oct–F	$^iBu_2Al–SePh$ **8**	1 h	^{n}Oct–SePh **20**	99 (66)
11	^{n}Oct–F	$^iBu_2Al–TePh$ **9**	1 h	^{n}Oct–TePh **21**	92 (67)
12[d]	^{n}Oct–F	$^iBu_2Al–NEt_2$ **10**	108 h	^{n}Oct–NEt_2 **22**	85 (71)

[a] Alkyl fluorides (1 mmol), organoaluminum reagents (1.2–1.5 mmol), hexane (1.0–1.2 mL), 25 °C. [b] Determined by GC based on alkyl fluorides used. Isolated yield is in parentheses. [c] Reaction was carried out at −78 °C. [d] Alkyl fluorides (2 mmol), organoaluminum reagents (6 mmol), hexane (6 mL), 25 °C.

In order to examine the relative reactivities of alkyl fluorides in the present reaction, we carried out the following competitive reaction. A mixture of 0.5 mmol of *n*-octyl fluoride, cyclohexyl fluoride, and 1-adamantyl fluoride was allowed to react with $Et_2Al–Cl$ (1.2 equiv.) at −78 °C for 15 min. GC analysis of the resulting mixture revealed that 1-adamantyl chloride was obtained predominantly along with cyclohexyl chloride as a minor product and *n*-octyl fluoride remained unchanged (Scheme 3). This result suggests that the order of reactivity for chlorination is *tertiary* > *secondary* > *primary* alkyl fluorides.

We next examined the reaction of α-d_1-β-phenylethyl fluoride **23** under our conditions in order to prove the reaction mechanism (Scheme 4). When **23** was treated with $Et_2Al–Cl$ in hexane at −78 °C, α-d_1-β-phenylethyl chloride (**24**) and β-d_1-β-phenylethyl chloride (**25**) were formed in nearly 1 : 1 ratio probably *via* a phenonium ion intermediate (**26**).[17] This result indicates that the phenyl group also exerts strong anchimeric assistance suggesting that the attacking chloride, which would not be a free anion, does not act as a strong nucleophile in the present reaction.

Results of Scheme 3 and 4 suggest that the present reaction proceeds *via* S_N1 mechanism. We then examined stereochemistry of the reaction of *primary* alkyl fluoride in order to gain insight into the possibility of an S_N2 mechanism (Scheme 5). Diastereometrically pure α,β-d_2-β-adamantylethyl fluorides **27** was treated with Et_2AlCl and the ^{1}H-NMR analysis of the products indicated that substitution occurs primarily with inversion of configuration with *ca.* 10 : 1 selectivity from both diastereomers. These results suggest that the present substitution reaction of unactivated *primary* alkyl fluorides proceeds principally *via* an S_N2 mechanism.

In conclusion, we have developed a simple method for the conversion of (sp^3)C–F bonds of alkyl fluorides to (sp^3)C–X (X = Cl, C, H, O, S, Se, Te, N) bonds using a hexane solution of organoaluminum reagents having Al–X bonds. The first evidence for a S_N2 mechanism for substitiution of F in alkyl fluorides with nucleophiles has been shown by the stereochemistry based on ^{1}H-NMR analysis.

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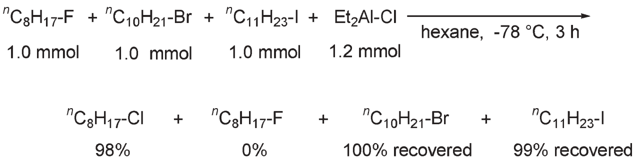
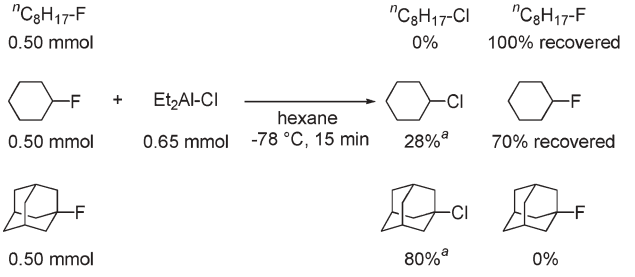
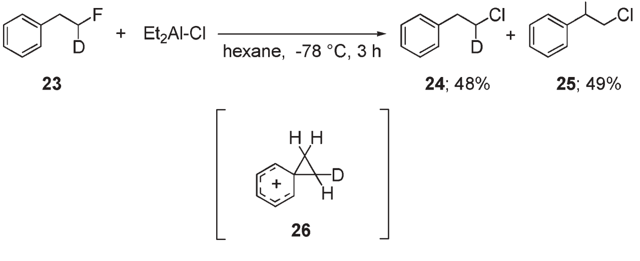


Scheme 2 Competitive reaction of alkyl halides with Et_2AlCl.

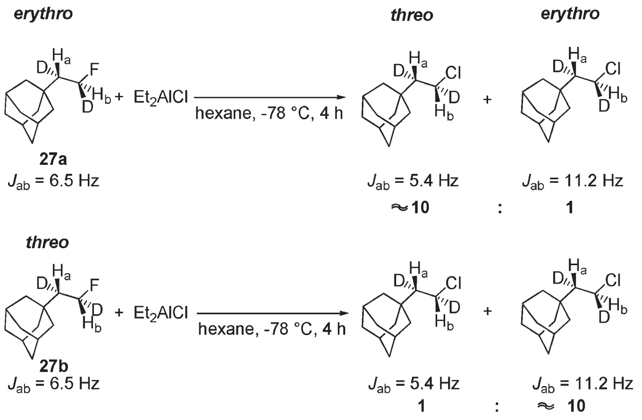


[a] Based on the corresponding fluorides used.

Scheme 3 Competitive reaction of alkyl fluorides with Et_2AlCl.



Scheme 4 The F–Cl exchange reaction of β-phenylethyl fluoride with Et_2AlCl.



Scheme 5 The F–Cl exchange reaction of α,β-d_2-β-adamantylethyl fluorides with Et_2AlCl.

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