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Note

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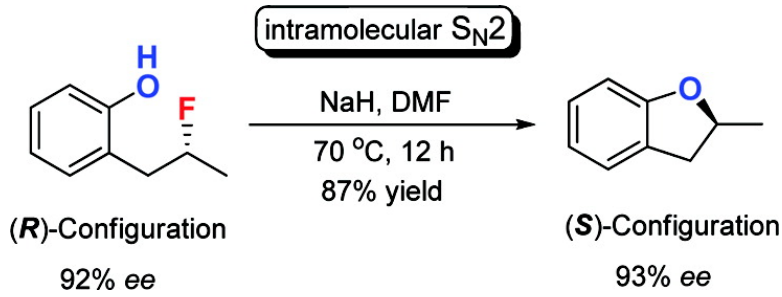

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C−F Bond Cleavage by Intramolecular S_N2 Reaction of Alkyl Fluorides with O- and N-Nucleophiles

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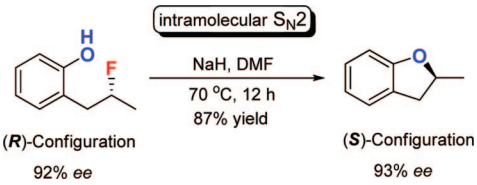

The nucleophilic substitution of alkyl fluorides was achieved in the intramolecular reactions with O- and N-nucleophiles. The intramolecular defluorinative cyclization reaction was influenced by the nature of nucleophiles, the size of the ring to be formed, and the comformational rigidity of the precursors. Intermolecular nucleophilic substitution reactions of alkyl fluorides under similar reaction conditions were found to be difficult. The stereochemistry study of the current C−F bond cleavage reaction showed a complete configurational inversion, which supports an intramolecular S_N2 reaction mechanism.

The carbon−fluorine bond is commonly regarded as the strongest single bond to carbon, and the selective C−F bond activation and transformation have become an interesting challenge in modern organic chemistry.[1,2] In this context, C−F bond cleavage mediated by transition metal complexes,[3] reducing metals,[4] and Lewis acids[5]have received substantial attention. Furthermore, it is widely realized that, unlike other alkyl halides (halogen = iodine, bromine, and chlorine), alkyl fluorides do not typically undergo S_N2 reactions,[6a] or the S_N2 reactions with alkyl fluorides are very slow.[6b] The relative leaving group reactivity of four halides is known to be decreasing in the following order: I^- (30 000) > Br^- (10 000) > Cl^- (200) > F^- (1),[6a] which explains the difficulty of using primary alkyl fluorides in conventional S_N2 reactions. As a result, both inter- and intramolecular S_N2 reactions between alkyl fluorides and nucleophiles are largely neglected in most organic chemistry textbooks.[6]

However, although alkyl fluorides are generally inert to S_N2-type nucleophilic displacement, some C(sp^3)−F bonds can be cleaved by hydroxide under enzyme-catalyzed conditions.[7] The acceleration of C−F bond cleavage by enzyme catalysis can be explained by the proximity effect, that is, enzyme binds both alkyl fluoride and a nucleophile (such as hydroxide) together to make the reaction an intramolecular process.[8,9] This indicates that the nucleophilic substitution of an alkyl fluoride can be significantly accelerated when the reaction proceeds as an intramolecular process. Intramolecular S_N2 reaction of alkyl fluorides, however, did not attract much attention for a long time probably due to the "common sense" that the C−F bond is highly stable. In many early publications, some unexpected intramolecular nucleophilic substitution reactions of the C−F bond were observed, but most of these discoveries were considered as undesirable and sometimes even as side reactions.[10] Although some early examples of these C−F cleavage reactions were summarized by Hudlickly,[10] there is still a lack of detailed and systematic study of intramolecular nucleophilic substitution of alkyl fluorides with different nucleophiles to determine both the scope and chemical yields of the reactions. In this Note, we wish to disclose our recent study on this topic, which provides new insights into the intramolecular nucleophilic substitutions of primary and secondary alkyl fluorides with different nucleophiles.

Previously, we reported an efficient nucleophilic fluoroalkylation−acylation of benzyne with $PhSO_2CFHC(O)Ph$ reagent, and further elaboration of the product gave [(2-fluoromethyl)phenyl](phenyl)methanol (**1**) in good yield.[11] Interest-

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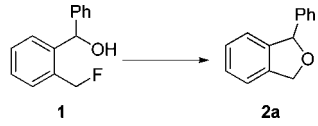
TABLE 1. Survey of Reaction Conditions

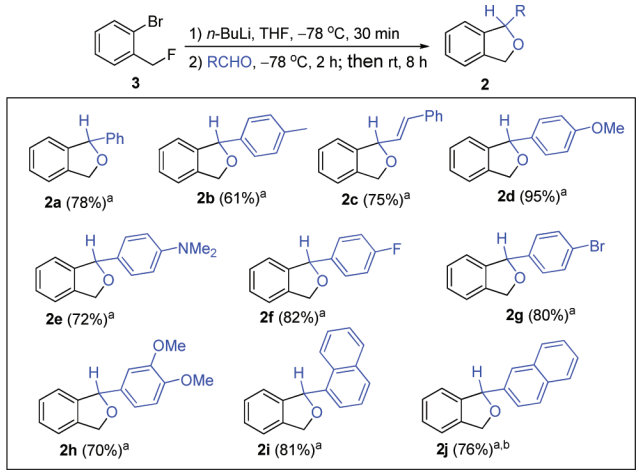


1 2a

entry	base (equiv)	solvent	temp (°C)	time (h)	yield (%)[a]
1	NaH (2.0)	CH_3OH	25	24	83
2	NaH (2.0)	DMF	25	24	90
3	NaH (2.0)	THF	25	24	98
4	K_2CO_3 (2.0)	DMF	25	4	NR[b]
5	K_2CO_3 (2.0)	DMF	80	2	trace
6	*t*-BuOK (2.0)	DMF	25	24	64

[a] Isolated yield. [b] Starting material **1** was recovered.

SCHEME 1. One-Pot Lithiation, Addition, and Cyclization Reactions between 3 and Aldehydes[a,b]

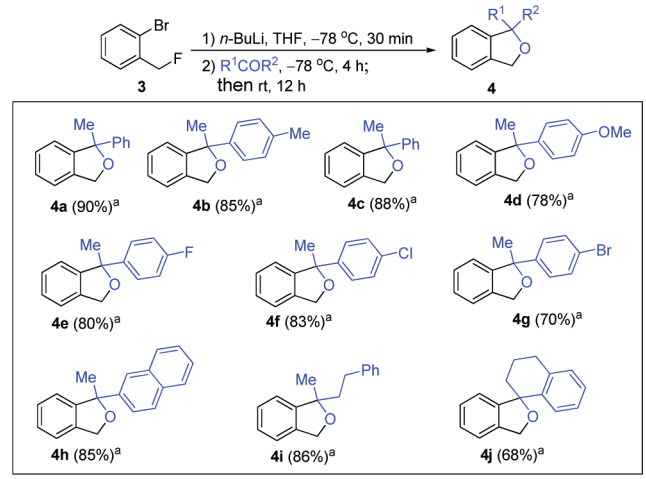


[a] The data in paratheses are isolated yields of products **2a**−**j**. [b] The reaction time was extended to 12 h.

ingly, we noticed that compound **1** readily transformed to 1,3-dihydroisobenzofuran **2a** under basic conditions. For instance, when **1** was stirred with NaH in methanol at room temperature, product **2a** was obtained in 83% isolated yield. Thereafter, we examined the influence of base, solvent, and temperature on the reaction, and the results are shown in Table 1. It turned out that both NaH and *t*-BuOK were suitable bases to facilitate the intramolecular nucleophilic substitution reaction, while the basicity of potassium carbonate was not strong enough to mediate the reaction (Table 1, entries 4 and 5). The best yield (98%) of product **2a** was obtained when starting material **1** was treated with NaH in THF at room temperature (Table 1, entry 3). It should be mentioned that the addition of 1 equiv of 1,4-dinitrobenzene in the reaction mixture (same as entry 3) did not inhibit the cyclization reaction, which rules out the possibility of the involvement of a free radical reaction mechanism.

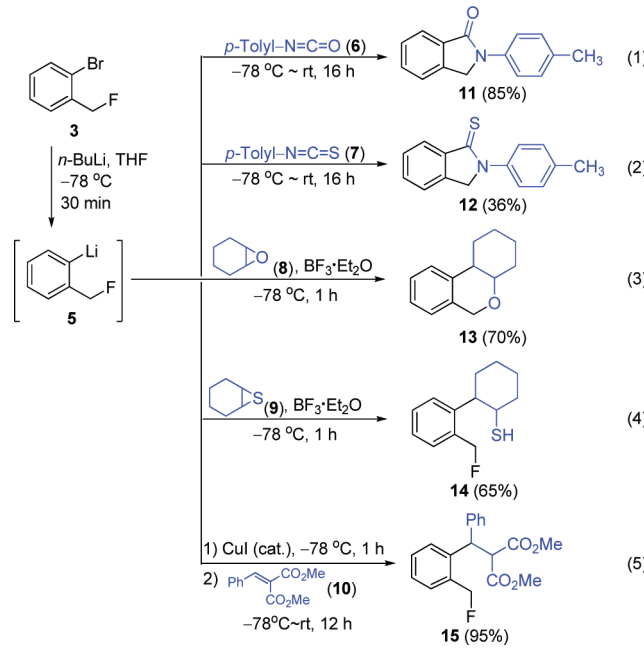
With the consideration that compound **1** and its derivatives can be prepared from *o*-(fluoromethyl)phenyllithium (**5**) and aldehydes, we carried out the one-pot lithiation−addition−defluorinative cyclization cascade reactions, using 2-fluoromethylbromobenzene (**3**), *n*-BuLi, and aldehyde as the starting materials (Scheme 1). Compound **3** was generally treated with *n*-BuLi (1.1 equiv) in THF at −78 °C for 30 min, followed by addition of aldehyde (0.9 equiv). The cascade reactions completed in around 10 h to give the desired products **2a**−**j** in 61−95% isolated yields (Scheme 1). Similarly, the one-pot three-step cascade reaction also worked well with ketones,

SCHEME 2. One-Pot Lithiation, Addition, and Cyclization Reactions Between 3 and Ketones[a]



[a] The data in paratheses are isolated yields of products **4a**−**j**.

SCHEME 3. Intramolecular C−F Functionalizations with O-, N-, S-, and C-Nucleophiles

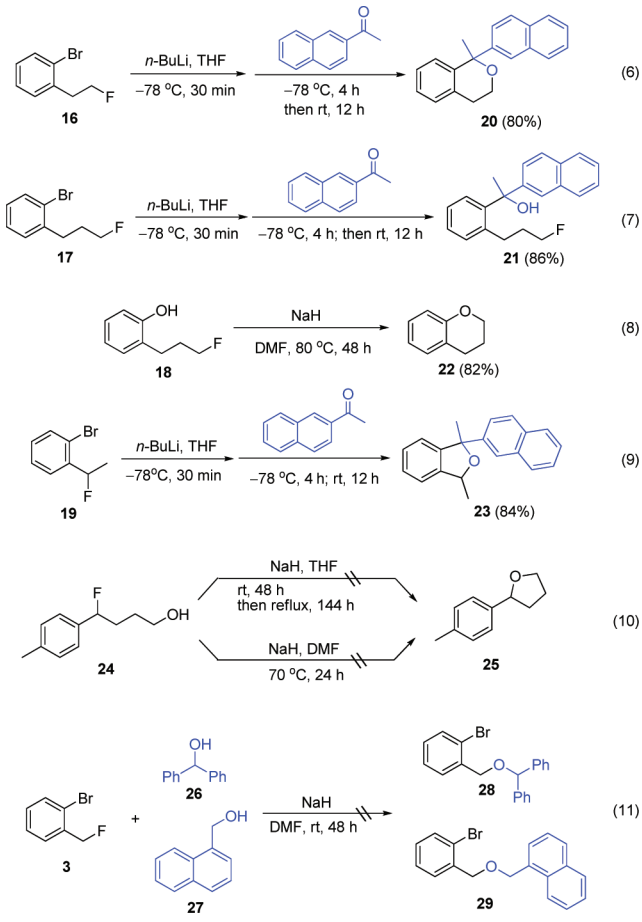


giving products **4a**−**j** in 68−90% isolated yields (Scheme 2). It should be mentioned that the reaction of *o*-bromo(or iodo)methylbromobenzene in place of **3** would give no or low chemical yield due to undesired reactions such as metalation at the benzylic position with *n*-BuLi.[12]

We also tried other compounds **6**−**10** to react with in situ generated *o*-(fluoromethyl)phenyllithium (**5**) (Scheme 3). It was found that both *p*-tolyl isocyanate and *p*-tolyl isothiocyanate could react with intermediate **5**, which resulted in the formation of 2-(*p*-tolyl)isoindolin-1-one (**11**) and 2-(*p*-tolyl)isoindoline-1-thione (**12**) in 85% and 36% yields, respectively (Scheme 3, eqs 1 and 2). This indicates that besides oxygen-nucleophiles, nitrogen-nucleophiles are also able to facilitate the C−F cleavage via an intramolecular substitution process. When cyclohexene

(12) Parham, W. E.; Jones, L. D.; Sayed, Y. A. *J. Org. Chem.* **1976**, *41*, 1184.

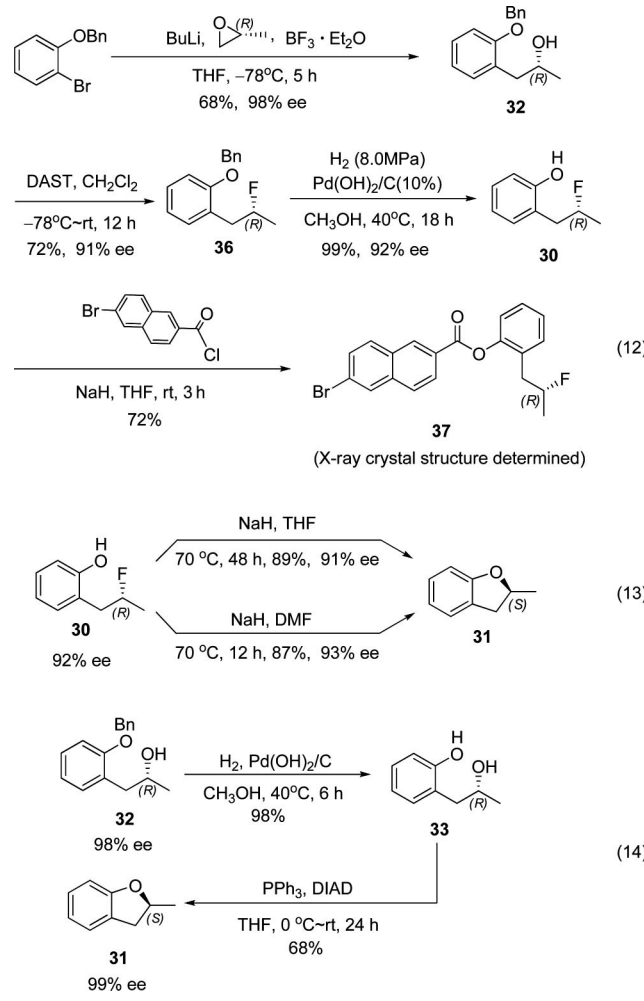
SCHEME 4. Selected Intra- and Intermolecular C−F Cleavage Reactions



oxide **8** (0.5 equiv, along with 0.75 equiv of BF_3-Et_2O) was used as substrate to react with **5**, the in situ defluorinative cyclization process proceeded smoothly to form a six-membered ring, giving chromene derivative **13** in 70% yield (eq 3). However, when cyclohexene sulfide (**9**) (instead of **8**) was used for the reaction, the defluorinative cyclization reaction was not observed, only giving the uncyclized compound **14** in 65% yield (eq 4). The Michael acceptor **10** was also used to react with **5** to generate stabilized carbanion intermediate, but the latter one could not undergo intramocleular nucleophilic displacement of fluorine atom. Instead, the uncyclized compound **15** was isolated in excellent yield (eq 5). We also tried the reaction with methyl cinnamate instead of **10**, and similarly, no C−F bond cleavage was observed. These results can be explained by using the hard soft acids and bases (HSAB) principle,[13] that is, alkyl fluorides are hard electrophiles, which are favorable to react with hard nucleophiles such as O- and N-anions, but less favorable to react with soft nucleophiles such as S- and C-nucleophiles.

Thereafter, we examined the intramolecular cyclization reaction with substrates bearing a nonbenzylic C−F bond such as compounds **16**−**18** (Scheme 4). Under similar one-pot three-step procedures as mentioned above, 1-bromo-2-(2-fluoroethyl)benzene (**16**) was transformed to product **20** in 80% yield (eq 6). However, the reaction with 1-bromo-2-(3-fluoropropyl)benzene (**17**) only gave uncyclized product **21** in 86% yield (eq 7), which indicates that the intramolecular C−F cleavage to form a 7-membered ring is unfavored (unlike the cases of forming 5- and 6-membered rings). Furthermore, the defluorinative cyclization of 2-(3-fluoropropyl)phenol (**18**) in the presence of NaH in DMF proceeded at 80 °C to give chroman **22** in 82% yield (eq 8). Besides primary alkyl fluorides, secondary fluoride was also found to be amenable to the intramolecular nucleophilic substitution reaction with an O-nucleophile. As a result, the one-pot lithiation−addition−defluorinative cyclization process successfully transformed 1-bromo-2-(1-fluoroethyl)benzene (**19**) to a 5-membered-ring-containing product **23** in 84% yield (eq 9). We also found that the comformational rigidity of the compounds plays an important role in the intramolecular defluorinative cyclization reactions. For instance, 4-fluoro-4-*p*-tolylbutan-1-ol (**24**), which bears a linear and relatively flexible carbon skeleton, could not undergo 5-membered-ring formation under the treatment of NaH in THF (eq 10). The effect of comformational rigidity on the cyclization reactions can be well explained by several deviations of "proximity effect" concept, such as "spatiotemporal effect", "transtion state effect", and "near attack conformations" hypotheses.[9] These hypotheses can also be used to explain the remarkable intramolecularity: while the intramolecular cyclization proceeded smoothly as mentioned above, the similar

SCHEME 5. Stereochemistry of the Intramolecular C−F Functionalization Reaction



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intermolecular reactions between compound **3** and alcohol **26** (or **27**) failed (eq 11).

To gain some insights into the mechanism of the present intramolecular defluorinative cyclization reactions, we investigated the stereochemistry of the reaction (Scheme 5). We synthesized (*R*)-2-(2-fluoropropyl)phenol (**30**) (92% ee, $[\alpha]_D^{25}$ −11.5 (*c*, 1.2 in $CHCl_3$)) via stereospecific preparation of **32**, fluorination with DAST,[14] followed by deprotection with H_2 (eq 12). The absolute configuration of **30** was determined by the characterization of the X-ray crystal structure of its derivative compound **37** (see the Supporting Information). Compound **30** was subjected to the treatment of NaH in THF or DMF at 70 °C. It was found that the reaction proceeded well to give product **31** in good yield and with high enantiospecificity [in THF, 89% yield, 91% ee, $[\alpha]_D^{25}$ −13.3 (*c*, 1.2 in $CHCl_3$); in DMF, 87% yield, 93% ee, $[\alpha]_D^{25}$ −17.2 (*c*, 1.0 in $CHCl_3$)] (Scheme 5, eq 13). To determine the absolute configuration of compound **31**, (*R*)-1-(2-(benzyloxy)phenyl)propan-2-ol (**32**) was subjected to palladium-catalyzed hydrogenolysis on carbon ($Pd(OH)_2$/C), leading to (*R*)-2-(2-hydroxypropyl)phenol (**33**) in 98% yield. Compound **33** was treated under standard Mitsunobu inversion condition to give (*S*)-2-methyl-2,3-dihydrobenzofuran (**31**) in 68% yield and with 99% ee, $[\alpha]_D^{24}$ −20.1 (*c*, 1.1 in $CHCl_3$) (Scheme 5, eq 14). The result in eq 14 shows that the product **31** in eq 13 is in the *S*-configuration, which supports that the current defluorinative cyclization reaction proceeds via an intramolecular S_N2 reaction mechanism.

In conclusion, we have shown that the nucleophilic substituion of alkyl fluorides can be achieved in intramolecular reactions. The intramolecular defluorinative cyclization reaction was influenced by (a) the nature of nucleophiles (hard nucleophiles such as O- and N-nucleophiles are favored), (b) the size of the ring to be formed (5- and 6-membered rings are favored[15]), and (c) the comformational rigidity of the precursors. Intermolecular nucleophilic substitution reactions under similar conditions were found to be difficult. The stereochemistry study of this C−F bond cleavage reaction showed a complete configurational inversion, which supports an intramolecular S_N2 reaction mechanism.

(14) Although the fluorination of an alcohol with DAST usually gives the fluorinated product with inversion of configuration, a neighboring group participation mechanism sometimes leads to a product with retention of configuration. For an example see: Déchamps, I.; Pardo, D. G.; Cossy, J. *Synlett* **2007**, 263.

Experimental Section

Typical Procedure for the Preparation of 2j. Under N_2 atmosphere, into a 50-mL Schlenk flask containing 1-bromo-2-(fluoromethyl)benzene (**3**; 2.0 mmol, 0.378 g) in THF (20 mL) at −78 °C was added *n*-BuLi (2.2 mmol, 1.38 mL, 1.6 M in hexane). The reaction mixture was stirred at −78 °C for 30 min, followed by the addition of 2-naphthaldehyde (1.8 mmol, 0.281 g), then the solution was stirred for 2 h at the same temperature. Next the reaction mixture was warmed to room temperature and stirred for 12 h. After being quenched with brine, the reaction mixture was extracted with Et_2O (3 × 30 mL), and the combined organic phase was dried over anhydrous $MgSO_4$. The volatile solvents were removed under vacuum, and the crude product was purified by silica gel column chromatography (ethyl acetate/petroleum ether = 1:30 v/v) to afford **2j** (0.336 g) in 76% yield.

^{1}H NMR δ 7.87−7.78 (m, 4H), 7.49−7.44 (m, 2H), 7.37 (d, J = 8.4 Hz, 1H), 7.32−7.28 (m, 2H), 7.24−7.17 (m, 1H), 7.03 (d, J = 7.5 Hz, 1H), 6.32 (s, 1H), 5.42 (dd, J = 12.2, 2.4 Hz, 1H), 5.26 (d, J = 12.3 Hz, 1H); ^{13}C NMR δ 141.9, 139.5, 139.1, 133.3, 128.5, 128.0, 127.7, 127.5, 126.1, 126.0, 125.9, 124.9, 122.4, 120.9, 86.4, 73.4; MS (EI, *m*/*z*, %) 246 (100.00), 246 (100.00); IR (film) 2856, 1600, 1508, 1460, 1124, 1035, 819, 740 cm^{-1}. Anal. Calcd for $C_{18}H_{14}O$: C, 87.78; H, 5.73. Found: C, 87.57; H, 5.92.

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Supporting Information Available: General experimental information and characterization data of the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) 3-Membered-ring formation via intramolecular nucleophilic substitution of alkyl fluorides with O-nucleophiles is also known. See ref 10.