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REVIEW

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Development of fluorination methodology for carbon-fluorine bond formation: old electrophilic fluorinating reagents

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ABSTRACT

Electrophilic fluorinating reagents are typically efficient for carbon–fluorine (C–F) bonds formation due to their higher reactivity even under mild condition. Thus, they have been playing an important role to improve C–F bonds formation reactions via direct fluorination reaction with electrophilic fluorinating reagents or transition metal catalysis. Advances on the recent fluorination methods are mainly results of Selectfluor™'s capability on facile fluorination. In this mini-review, we describe synthesis and application of four old yet popular electrophilic fluorinating reagents such as N-fluorobenzenesulfonimide (NFSI), N-fluoropyridinium salts, Selectfluor™, and N-fluorosultam.

Key Word: Fluorination, Carbon–fluorine bond, Electrophilic fluorinating reagents, Catalysis.

Introduction

Elemental fluorine (F_2) is a well-known electrophilic fluorinating reagent. However, F_2 is highly toxic, so only qualified researchers can utilize it with a specialized equipment (1). Beyond its toxicity, the selectivity of F_2 is very poor fluorinating almost C-H groups. Cobalt(III) fluoride (CoF_3) and xenon difluoride (XeF_2) are also known as powerful electrophilic fluorinating reagents, but their extreme cost precludes practical use. The desire for less toxic and more selective electrophilic fluorinating reagents lead to the development of *N*-fluorobenzenesulfonimide (NFSI) (2), *N*-fluoropyridinium salts (3), Selectfluor™ (1b, 4,5), and *N*-fluorosultam (6). Recently, a new class of electrophilic fluorinating reagents such as R_2N-F or R_3N+-F types became more useful than conventional electrophilic fluorinating reagents, because of less toxicity and greater stability. In addition, some of these reagents turn out to be more reactive and selective than conventional electrophilic fluorinating reagents in some cases.

N-Fluorobenzenesulfonimide (NFSI)

N-Fluorobenzenesulfonimide (NFSI) was introduced by Barnette (2) for the first time in 1984 and another derivative, N-fluoro-bis[(trifluoromethyl)sulfonyl]imide (7) was prepared by DesMarteau et al. (Figure 1).

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Although the synthesis of NFSI involves the utility of F_2 in N_2 (F_2 10% v/v) in the presence of NaF in the acetonitrile solution of benzenesulfonamide at −40 °C (Scheme 1), the product (NFSI) is stable enough for flash chromatography for further purification (2). They are useful for the fluorination of monosubstituted aromatic substrates *via* electrophilic aromatic substitution reaction and for the fluorination of ß-dicarbonyl compounds as well as for the synthesis of ß-fluorocarbonyl compounds (5). The reagents have been applied to asymmetric fluorination incorporating organocatalysts or asymmetric metal complexes (8).

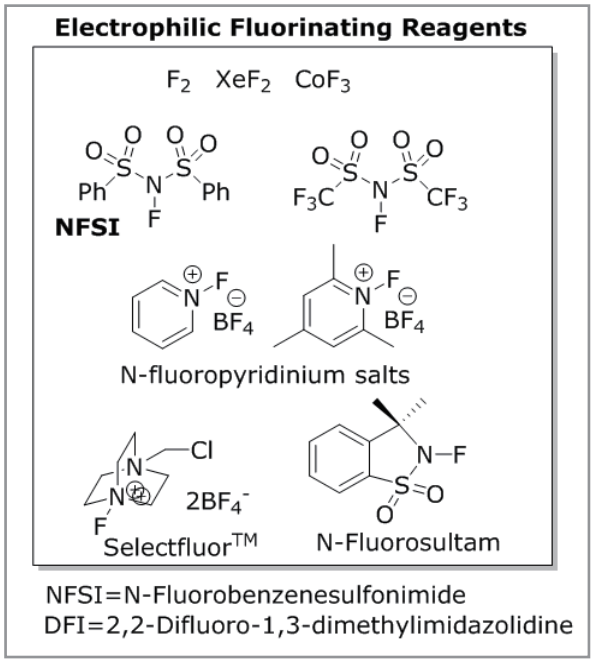
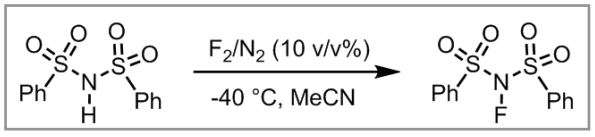


Figure 1. Electrophilic fluorination reagents



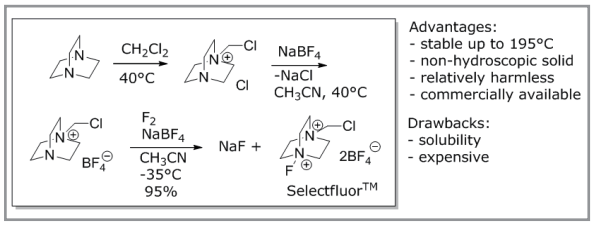
Scheme 1. Synthesis of N-fluorobenzenesulfonimide (NFSI).

N-fluoropyridinium salts

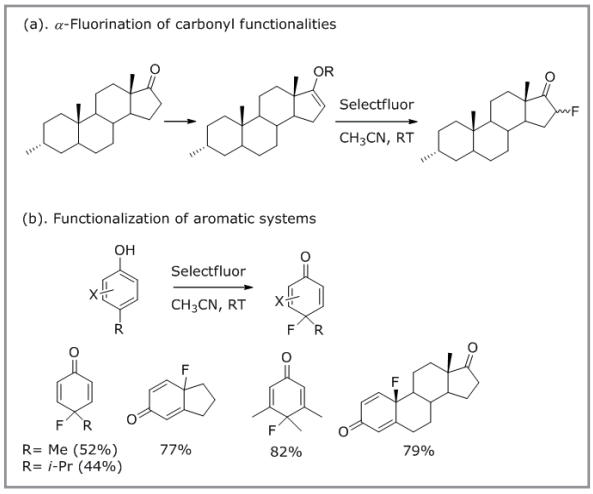
N-fluoropyridinium compound was first discussed by Simmon, who observed the formation of *N*-fluoropyridinium between pyridine and F_2 at low temperature. Meinert first proposed *N*-fluoropyridinium fluoride and used the compound to fluorinate uracil even though it was not stable when isolated (9). Later, the Umemoto group reported the synthesis, isolation, and application of *N*-fluoropyridinium salts in 1996 (3). The key for the successful isolation was the replacement of the fluoride anion with a triflate anion, which is much less nucleophilic, guaranteeing the stability of *N*-fluoropyridinium trilfate (5). Various *N*-fluoropyridinium salts were developed later and are widely used for the preparation of numerous aryl fluorides and α-fluorocarbonyl compounds (5).

Selectfluor™

Since Banks *et al*. reported the preparation and application of Selectfluor™ (1a) (Scheme 2), the development of the reagent has become a major electrophilic fluorinating reagent, as it is stable, efficient, and commercially available. Selectfluor™ is exceptionally stable and non-hydroscopic, and stable up to 195 °C. Various tests on toxicity show that Selectfluor™ is relatively harmless and environmentally benign (1b). This represents a great improvement on conventional electrophilic fluorinating agents that require special handling to avoid their extreme toxicity. Numerous reviews were published describing the versatility of Selectfluor™ and its applications, including mechanistic studies of reaction pathways (1b,10). The solubility of Selectfluor™ is



Scheme 2. Selectfluor™: the synthesis and properties.



Scheme 3. Application of Selectfluor™

improved by changing counteranions. Nevertheless, its cost limits large-scale use, Selectfluor™ is useful for the synthesis of α-fluorocarbonyl compounds and the fluorination of aromatic substrates via electrophilic aromatic substitution reactions (Scheme 3).

Two possible mechanisms exist for the transfer of the fluorine atom of Selectfluor™ to substrates (Figure 2(a)) (1b). They are a single-electron transfer (SET) pathway and a two-electron S_N2 pathway. The SET pathway produces two radical intermediates, followed by a coupling reaction to transfer the fluorine atom to the substrate. The S_N2 mechanism enables a substrate to attack Selectfluor™ to give a carbocation intermediate and a nucleophilic attack occurs to yield the final product. Since these two processes are extremely fast, current methods cannot distinguish them. The Kochi group observed a charge-transfer complex with a absorption band around 380 nm

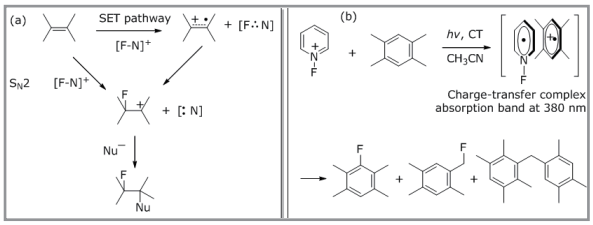


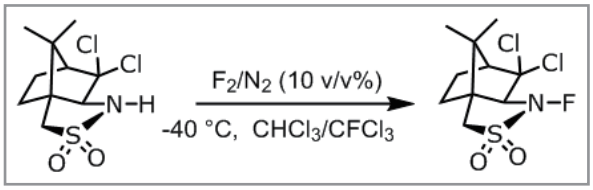
Figure 2. (a) Two possible mechanisms of the transfer of fluorine atom of Selectfluor™. (b) The charge-transfer complex between *N*-pyridinium and tetramethylbenzene.

(Figure 2(b)) (11), suggestive of a SET pathway involving a charge-transfer which subsequently fluorinate the substrate. This example is supportive for the SET pathway but since the fluorination process is extremely fast, the S_N2 mechanism cannot be ruled out.

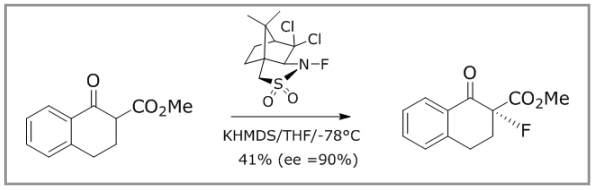
N-Fluorosultam

N-Fluorosultams were synthesized by Lang, which could be prepared in a similar way of NFSI *via* fluorination of the corresponding sultams with F_2 in N_2 (F_2 10% v/v), and were widely utilized for the introduction of fluorine atom to carbonyl groups. Interestingly, selective fluorination of carbanions was also achieved by *N*-fluorosultams (Scheme 4) (6). More importantly, the Davis group reported an enantioselective fluorination of enolates using chiral camphorsultam reagents and obtained 90% enantiomeric excess (ee) of fluorinated ß-ketoester enolate (Scheme 5) (12).

In this mini-review, several representative electrophilic fluorination reagents were discussed focusing on their synthesis and applications. Along with the development of transition metal catalysis, the importance of electrophilic



Scheme 4. Synthesis of N-Fluorosultam.



Scheme 5. An asymmetric fluorination via chiral N-Fluorosultam.

fluorination reagents has been emphasized more and more due to their versatile capability of both mild and late stage fluorination and other oxidation reactions. In near future, we will review expansive utility of various newly developed electrophilic fluorination reagents.

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References

1. (a) Banks RE, Mohialdin-Khaffaf SN, Lal GS, Sharif I, Syvret RG. 1-Alkyl-4-fluoro-1,4-diazoniabicyclo[2.2.2] octane salts: a novel family of electrophilic fluorinating agents. *J Chem Soc Chem Commun* 1992;8:595-596. (b) Nyffeler PT, Duron SG, Burkart MD, Vincet SP, Wong CH. Selectfluor: Mechanistic Insight and Applications. *Angew Chem Int Ed* 2005;44:192–212.
2. Barnette WE. N-Fluoro-N-alkylsulfonamides: useful reagents for the fluorination of carbanions. *J Am Chem Soc* 1984;106:452-454.
3. Umemoto T, Kawada K, Tomita K. N-fluoropyridinium triflate and its derivatives: Useful fluorinating agents. *Tetrahedron Lett* 1986;27:4465-4468.
4. Banks RE, Hasszeldine RN, Latham JV, Young IM. Heterocyclic polyfluoro-compounds. Part VI. Preparation of pentafluoropyridine and chlorofluoropyridines from pentachloropyridine. *J Chem Soc* 1965;0:594-597.
5. Lal GS, Pez GP, Syvret RG. Electrophilic N-F fluorinating agents. *Chem Rev* 1996;96:1737-1755.
6. Differdin E, Lang RW. New fluorinating reagents-I. The first enantioselective fluorination reaction. *Tetrahedron Lett* 1988;29:6087-6090.
7. Singh S, DesMarteau DD, Zuberi SS, Witz M, Huang HN. N-Fluoroperfluoroalkylsulfonimides. Remarkable new fluorination reagents. *J Am Chem Soc* 1987;109:7194-7196.
8. (a) Ishimaru T, Shibata N, Horikawa T, Yasuda N, Nakamura S, Toru T, Shiro M. Cinchona alkaloid catalyzed enantioselective fluorination of allyl silanes, silyl enol ethers, and oxindoles. *Angew Chem Int Ed* 2008;47:4157-4161. (b) Lozano O, Blessley G, Martinez del Campo T, Thompson AL, Giuffredi GT, Bettati M, Walker M, Borman R, Gouverneur V. Organocatalyzed enantioselective fluorocyclizations. *Angew Chem Int Ed* 2011;50:8105-8109.
9. (a) Simons JH. In Fluorine Chemistry; Simons JH. Ed. Academic Press, Inc.: New York; 1950. Vol. 1, pp 420-421. (b) Meinert H. Über die reaktion von fluor mit pyridin. *Z. Chem* 1965;5:64-65. (c) Meinert H, Cech D. Über die reaktion von uracil und seinen derivaten mit dem fluor-pyridin-komplex F2 • Pyridin. Z. *Chem* 1972;12:292-293.
10. (a) Zupan M. Stavber *S. Trends Org Chem* 1995;57:629. (b) Banks RE. Selectfluor™ reagent F-TEDA-BF4 in action: tamed fluorine at your service 1. J. *Fl*

uorine Chem 1998;87:1-17. (c) Stavber S, Zupan M. Selectfluor™ F-TEDA-BF4 as a versatile mediator or catalyst in organic chemistry. *Acta Chim Slov* 2005;52:13-26.

11. Bockman™, Lee KY, Kochi JK Time-resolved spectroscopy and charge-transfer photochemistry of aromatic EDA complexes with X-pyridinium cations. *J Chem Soc Perkin Trans* 2 1992;0:1581-1594.
12. Davis FA, Zhou P, Murphy CK, Sundarababu G, Qi H, Han W, Przeslawski RM, Chen BC, Carroll PJ. Asymmetric fluorination of enolates with nonracemic *N*-fluoro-2,10-camphorsultams. *J Org Chem* 1998;63: 2273-2280.