Research Article

Development of Easy-to-handle and Useful Fluorine-introducing Reagents

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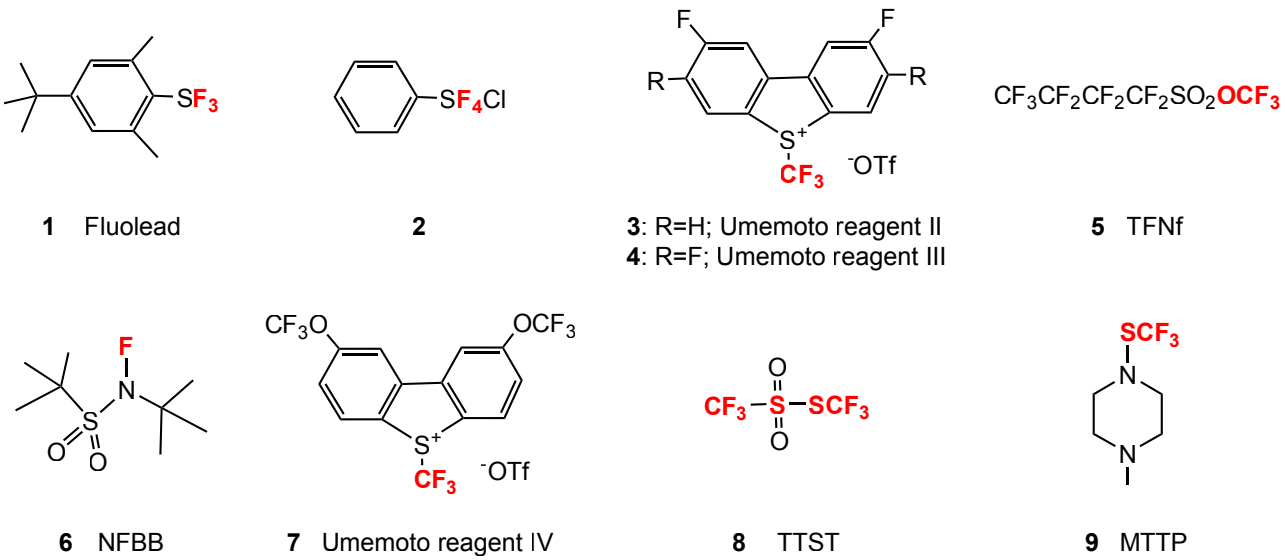
1. Introduction

I started my career in fluorine chemistry in 1978, 47 years ago. At that time, fluorine chemistry was still a very specialized field. A fluorine atom had outstanding properties, such as maximum electronegativity, a size close to that of a hydrogen atom, and the ability to form a strong C-F bond, and a wide range of applications for fluorine atoms had already been shown - in medicine, agrochemicals, and functional materials. At that time, the Sagami Chemical Research Institute, where I was working, was active in synthetic organic chemistry, especially organic synthesis using the properties of the sulfur atom, and I started fluorine chemistry with the idea of following it. Although fluorine chemistry was perceived as a dangerous field represented by fluorine gas (F_2), which has the highest reactivity and is extremely toxic and corrosive, I believed that if I started fluorine chemistry, I would have to overcome this to open up a new field. On the other hand, since organofluorine compounds, with a few exceptions, are virtually nonexistent in nature, the development of useful fluorine atom-introducing methods is essential for the development of fluorine chemistry, and the development of easy-to-use fluorine-introducing reagents is essential for the development and popularization of organofluorine chemistry. Based on the above ideas, I have developed a number of fluorine-incorporating reagents. I first developed high-valent iodine reagents, electrophilic perfluoroalkylating agents (FITS) [1)] and electrophilic 2,2,2-trifluoroethylating agents (FMITS)[1c,2)]; radical trifluoromethylating agents (TNS-B,[3)] TNS-Tf[4)]); the first stable and reactive F_2-based electrophilic fluorinating agents, *N*-fluoropyridinium salt series[5)] (including F-Plus reagents), *N*-fluoropyridinium-3-sulfonate salt series,[6)] and *N*,*N*'-difluorobipyridinium salt series[7)] (including MEC-31/SynFluor); and electrophilic trifluoromethylating agents, *S*-, *Se*-, and *Te*-(trifluoromethyl)dibenzothio-, seleno- and tellurophenium salt series[8)] (including Umemoto reagents) and their intramolecular salt series[9)]; as well as the development of highly reactive CF_3-oxonium reagents, *O*-(trifluoromethyl)-dibenzofuranium salts,[10)] and the stable and highly reactive electrophilic fluorinating agents, 1,4-difluorodiazonia-bicyclo[2.2.2]octane salts.[11)] For more information on these reagents, please see my papers. Due to space limitations, this article will focus on reagents **1-9** (**Figure 1**) with which we have been involved since the beginning of this century.



1 Fluolead **2** **3**: R=H; Umemoto reagent II **4**: R=F; Umemoto reagent III **5** TFNf

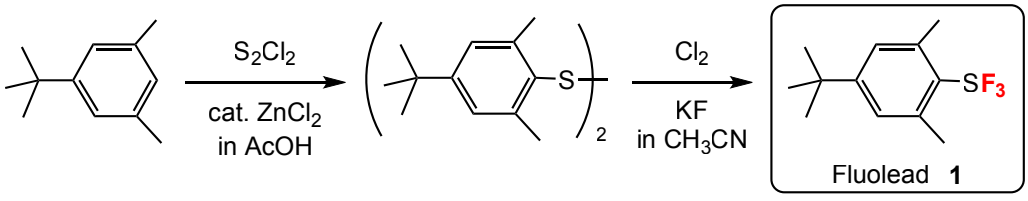
6 NFBB **7** Umemoto reagent IV **8** TTST **9** MTTP

Figure 1

2. Development of fluorine-introducing reagents since 2000

2-1. Development of Fluolead®: 4-(*tert*-Butyl)-2,6-dimethylphenylsulfur trifluoride 1 [12)]

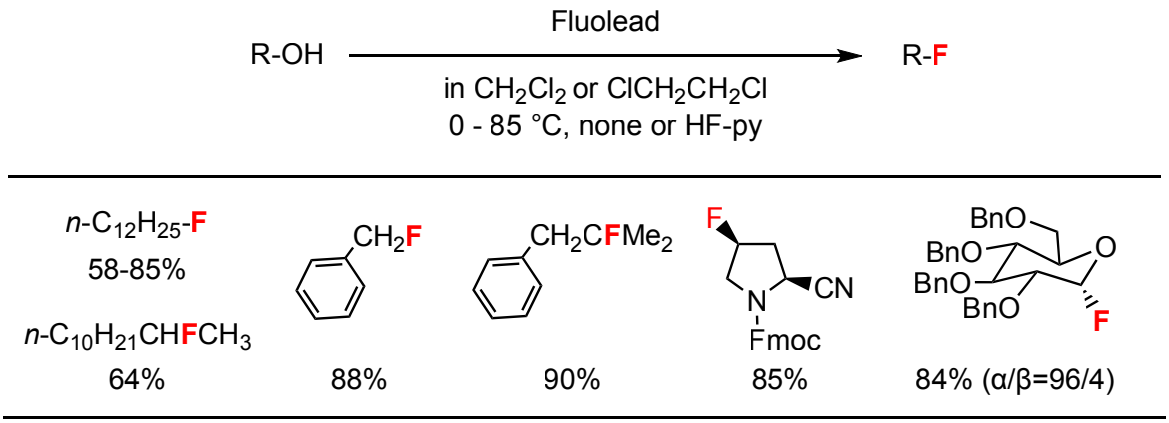
The first reagent for deoxofluorinating agents that took advantage of the properties of the sulfur atom was SF_4,[13)] but this was a difficult reagent to use with a highly toxic gas. The reagent that solved this problem was liquid diethylaminosulfur trifluoride Et_2N-SF_3 (DAST)[14)] published in 1975, which was highly reactive and could be handled under dry conditions, but, in addition to its strong fuming properties, DAST was a self-heating explosive, a fatal flaw. Fluolead® **1** [12)] is a solution to these problems of smoke generation and explosiveness. **1** has high thermal stability, with a decomposition point of 232 °C. Unlike DAST, **1** does not fume and can be handled in air. However, since it decomposes slowly in air by absorbing moisture, the trick is to finish handling it in air in as short a time as possible. **1** is intended for industrial use and is prepared in two steps with good yields using very inexpensive raw materials (**Scheme 1**). Dry conditions are required for production. Commercially available Fluolead is labeled as having a purity of 90% or higher, but this is because some hydrolysis occurs with moisture during the isolation process of production.



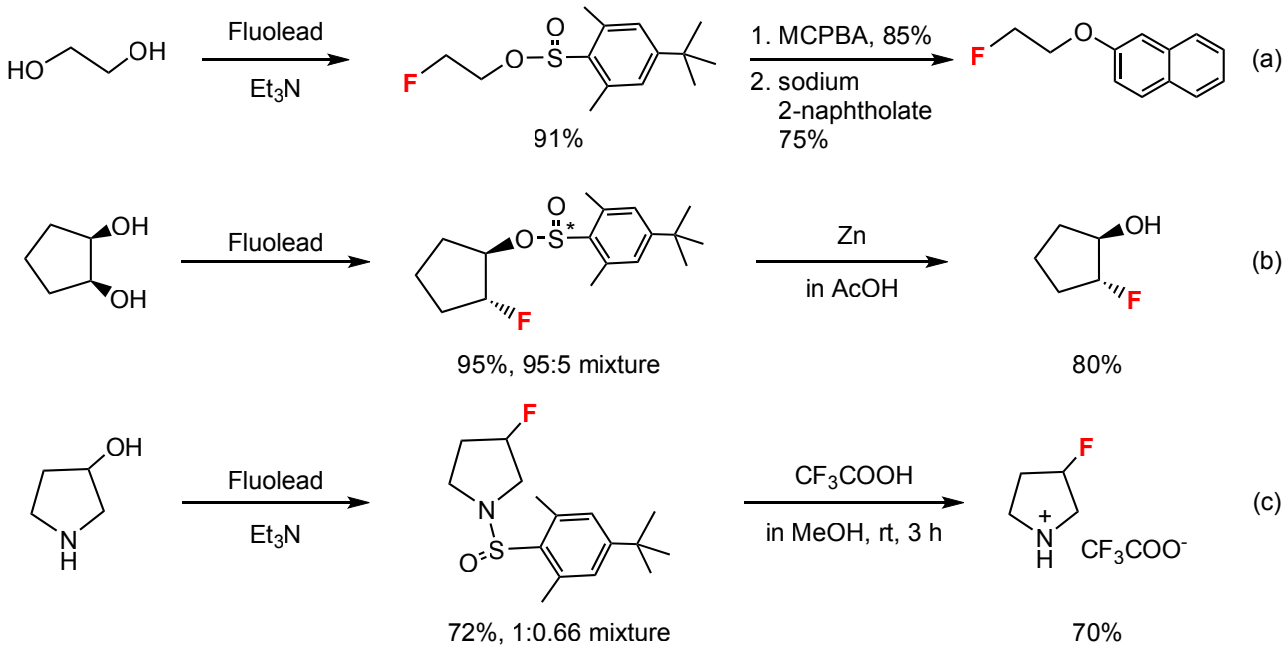
79% 82%

Scheme 1

The high thermal stability of **1** was demonstrated by the fact that the temperature at which **1** begins to self-heat by pyrolysis is 170 °C, according to the evaluation of the Thermal Runaway Hazard Test (Accelerating Rate Calorimeter (ARC) method) for the production and storage of **1**.[15)] Since **1** can withstand such high temperature in practice, its reactions have a very wide range of applications. Alcohols, aldehydes, ketones, and carboxylic acids can be fluorinated in high yields. Fluoropolymer reactors are highly recommended. **Scheme 2** shows examples of fluorinating alcohols. Fluorination with **1** requires an acid catalyst (HF), but the fluorination of alcohols does not require HF because it is generated in the first step of the reaction. Addition of HF-py (7:3) (Olah reagent) can accelerate the reaction and give the fluoro products in high yields. The fluorination of alcohols with **1** proceeds with steric inversion.



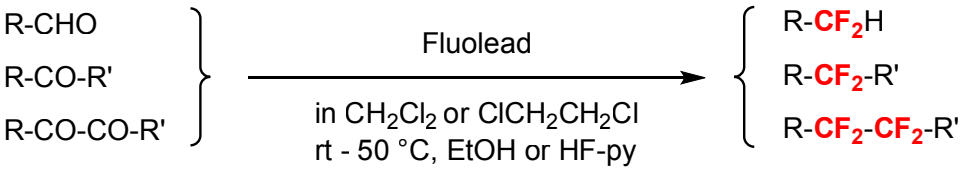
Scheme 2

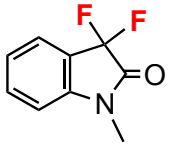
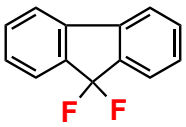
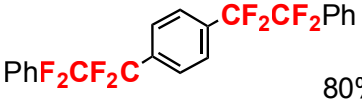
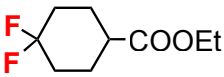


Scheme 3

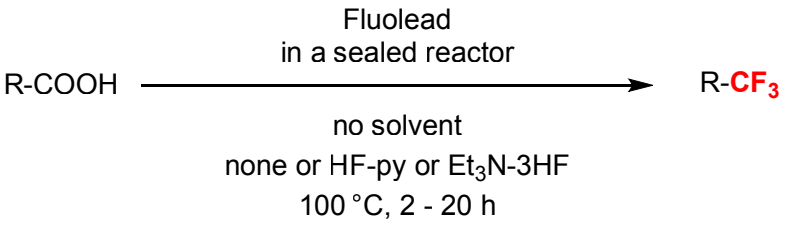
The reaction of **1** with diols or aminoalcohols results in highly selective deoxyfluoro-arylsulfinylation, affording fluoro-arylsulfinylated compounds in good yields. (**Scheme 3a-c**). The arylsulfinyl group is an activating or protecting group. As shown in **Scheme 3a**, it is oxidized and converted to a strong leaving group, arylsulfonate, from which it can be derived into other useful compounds. It can also be desulfinylated with zinc or trifluoroacetic acid (**Scheme 3b, c**).

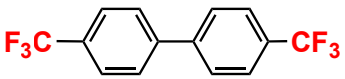
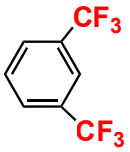
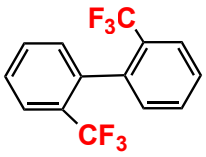
Scheme 4 shows examples of the difluorination of a carbonyl group with **1**. DAST has difficulty to fluorinate non-enolated ketones, whereas Fluolead can afford the desired difluorinated products in high yields with the addition of a catalytic amount of ethanol (HF generation) or an acid additive such as HF-py (7:3). Fluorination of diketones (-COCO-) is also easy, yielding tetrafluoroethylene (-CF_2CF_2-) compounds in high yields. Halogenated solvents such as dichloromethane and dichloroethane are commonly used as reaction solvents, but nonpolar solvents such as hexane and toluene can also be used.[16)]



PhCF_2H	90%	Ph$CF_2CF_2CF_2$Ph	89%		86%
n-$C_5H_{11}CF_2$H	91%		70%		
n-$C_{10}H_{21}CF_2CH_3$	90%				
PhCF_2CH_3	89%				80%
PhCF_2Ph	89%		80%		
PhCF_2COOEt	90%				

Scheme 4

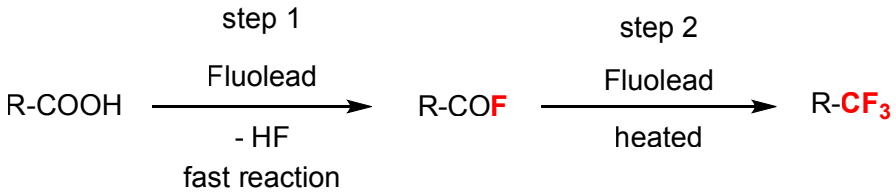


PhCF_3	89%	C_6H_4CH=$CHCF_3$	75%	CF_3-$(CH_2)_8$-CF_3	95%
n-$C_{11}H_{23}CF_3$ (with HF-py, 50 °C, 24 h)	91%	4-$MeOC_6H_4CH$=$CHCF_3$ (with 0.3 eq Et_3N-3HF)	75%		92%
n-$C_6H_{13}CH$=CH-CF_3	80%	Ph—≡—CF_3	42%		
4-(*n*-C_7H_{15})$C_6H_4CF_3$	88%		87%		90%
4-$MeOC_6H_4CF_3$	82%				

Scheme 5

Scheme 5 shows examples of the conversion of carboxylic acids to trifluoromethyl products with **1**. **1** can convert many carboxylic acids to trifluoromethyl compounds in high yields under simple reaction conditions. This conversion is the main advantage of **1**. This was difficult with DAST and only possible with SF_4. However, SF_4 is a toxic gas and in many cases requires a high temperature reaction that requires skill and is very difficult to achieve in a standard laboratory.

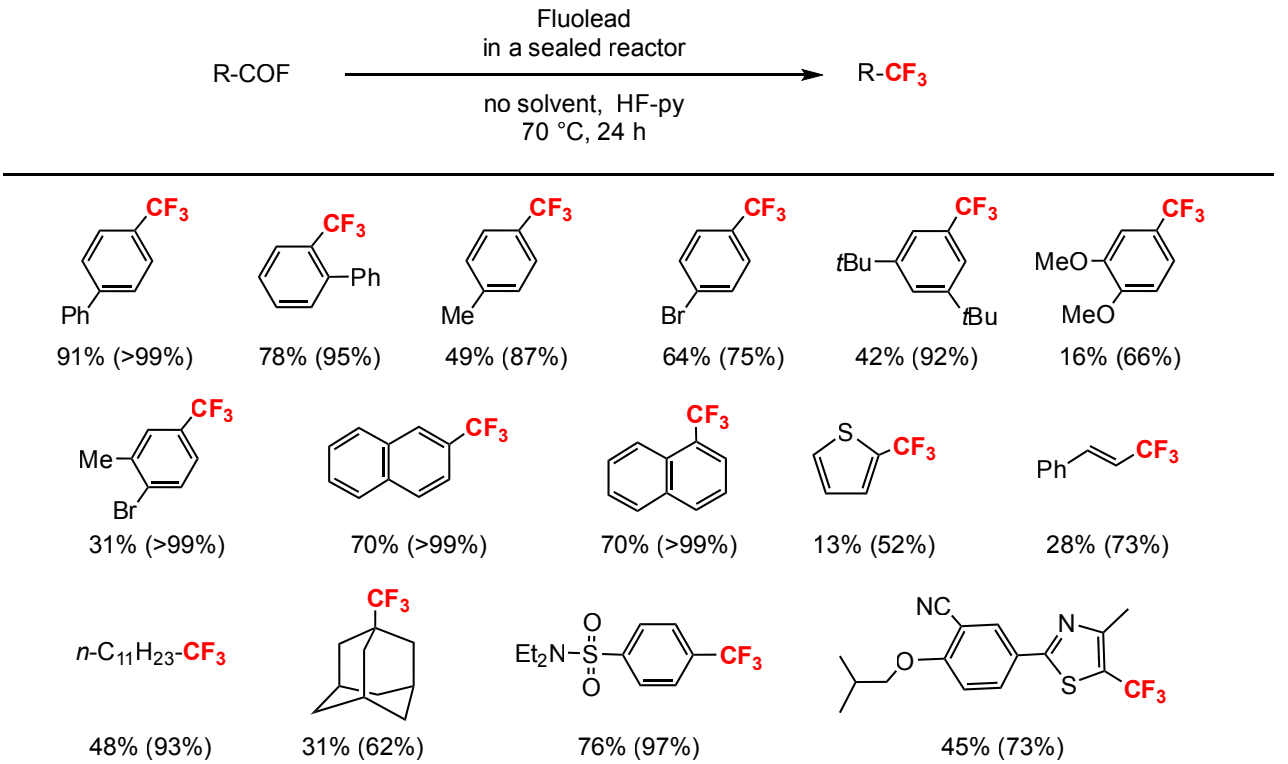
Since this reaction is catalyzed by the vaporous HF (boiling point 19 °C) produced by the reaction of carboxy groups with **1** in the first step, a sealed reactor is essential (**Scheme 6**). And this reaction gives CF_3 compounds in good yields without steric hindrance even when there is a large substituent (e.g. phenyl group) at the *ortho*-position of the aromatic nucleus (**Scheme 5**, the last example).



Scheme 6

Since the first step of the reaction is very fast, it is critical to mix the carboxylic acid with **1** at room temperature or under ice bath cooling, seal the reactor immediately, and then heat to 100 °C. Thus, the reaction can be performed without additives, but when additives such as HF-py (7:3) are added as the HF source, the reaction effectively occurs at 50 °C. As an interesting example, the reaction of cinnamic acid gave the target compound ($PhCH=CHCF_3$) in good yield (75%) under solvent-free reaction conditions without an additive, whereas the same conditions for 4-methoxycinnamic acid gave a complex mixture. However, when 0.3 equivalents of $Et_3N(HF)_3$ was added, the desired product was obtained in 75% yield. The reason for this is thought to be that $Et_3N(HF)_3$, which is less acidic than HF, suppressed side reactions, resulting in the formation of the target product in good yield.

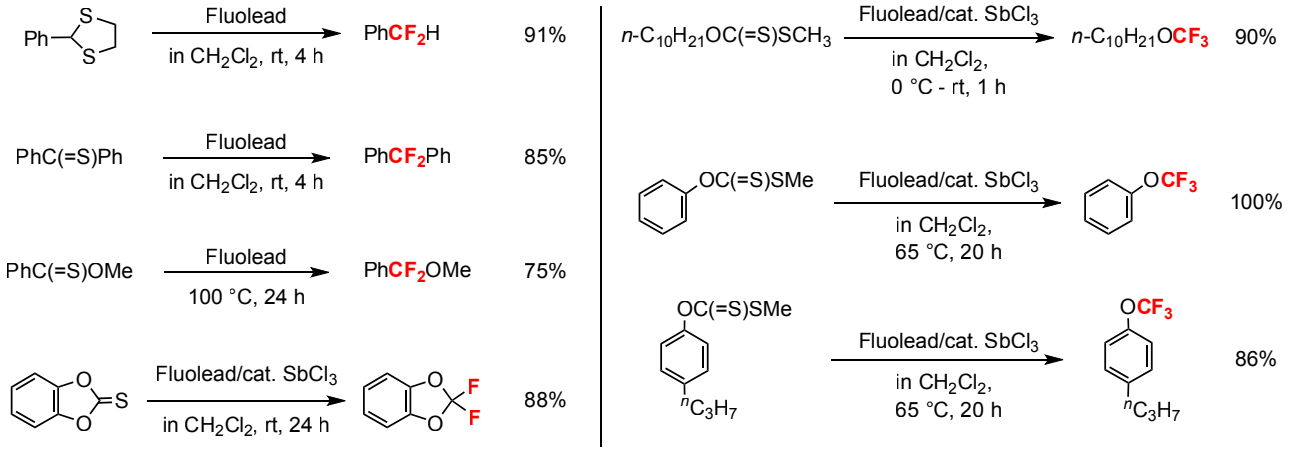
The conversion of a carboxylic acid to a CF_3 compound is a reaction via an intermediate acid fluoride, and Shibata et al. later obtained trifluoromethyl compounds in high yields from acid fluorides as the starting materials under mild conditions (70 °C, 24 h) in solvent-free using Fluolead **1** and HF-py (7:3) (Olah reagent).[17] **Scheme 7** shows examples of the reactions. In many cases the reaction is almost quantitative or close to it. Note that there are cases where the yield is low in the isolation yield, but this is a result of partial loss in the isolation process because fluorine compounds are generally highly volatile and sublimate.



Yields are isolated yields. The parentheses are ^{19}F NMR yields.

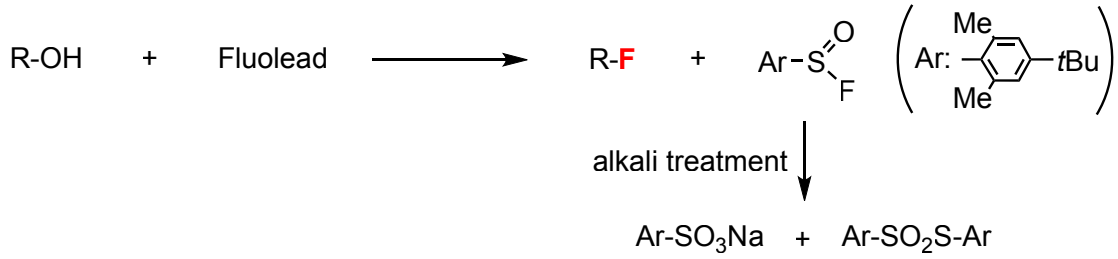
Scheme 7

Fluolead **1** can also provide the desulfurization fluorination (dethioxofluorination) of sulfur compounds in high yields. Examples are shown in **Scheme 8**. **1** easily gives the desired difluorinated compounds in high yields at room temperature from thioacetals and thioketones in dichloromethane. It gives the corresponding difluorinated compounds at 100 °C from the thioesters without catalyst and at room temperature from the thiocarbonates with $SbCl_3$ catalyst. And it converts *S*-methyl-dithiocarbonates to the CF_3O compounds in high yields in the presence of $SbCl_3$ catalyst.



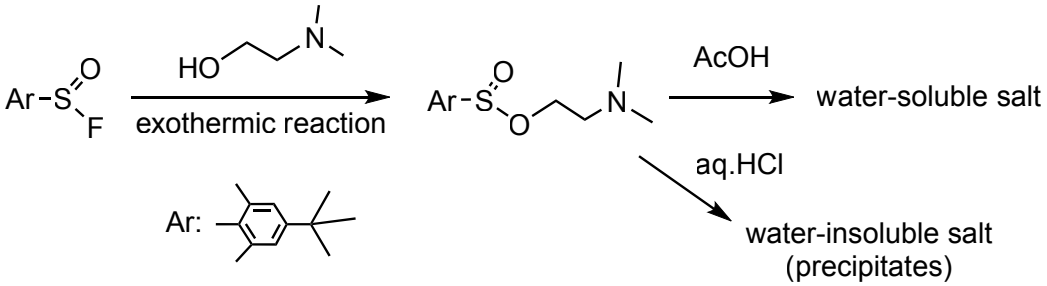
Scheme 8

As described above, Fluolead **1** is an easy to use and extremely versatile deoxo- and dethioxo-fluorinating agent, which is commercially available from Tokyo Chemical Industry Co., Ltd. (TCI). When using **1**, there is an important thing to know about reaction post-treatment. After the fluorination, **1** gives ArS(O)F [Ar=4-(*tert*-butyl)-2,6-dimethylphenyl] as a by-product, which has a highly lipophilic *tert*-butyl group and two methyl groups on the benzene ring, so the character is very different from normal PhS(O)F. Alkaline hydrolysis is slow and the disproportionation reaction happens to produce $ArSO_3Na$ and $ArSO_2SAr$ (**Scheme 9**). Since $ArSO_3Na$ is a kind of surfactant, the layer separation is not good in the water washing process, and a large amount of $ArSO_2SAr$ remains in the organic layer with fluorinated products. Note that, on a small scale, if the targeted fluorine compound is even slightly polar, so it can be easily separated by column chromatography on silica gel because $ArSO_2SAr$ is readily soluble in hexane and very nonpolar.



Scheme 9

For this reason, there are several post-treatment methods for reactions with **1**. After the reaction, an appropriate amount of ethanol is added to the reaction solution and the reaction mixture is stirred to convert ArS(O)F to ArS(O)OEt, followed by a post-treatment step (Method 1).[16] Alternatively, after the process of Method 1, the reaction mixture was treated with 30-35% H_2O_2 water-acetic acid (ArS(O)OEt → $ArSO_3Et$) followed by alkaline hydrolysis to convert $ArSO_3Et$ to water-soluble $ArSO_3Na$, followed by a washing step to remove all ArS(O)-part from the organic layer (Method 2).[16]



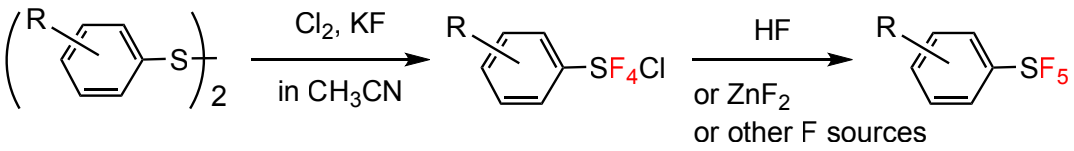
Scheme 10

As Method 3 (**Scheme 10**), the necessary amount of 2-(dimethylamino)ethanol is added to the reaction solution in an ice bath and the reaction mixture is stirred to convert ArS(O)F to $ArS(O)OCH_2CH_2NMe_2$, then acetic acid is added to form the water soluble acetate salt and the reaction mixture is washed with water to remove the acetate salt, or hydrochloric acid is added and the hydrochloride salt insoluble in water is removed by filtration.[18] Method 3 is recommended because it is simple and effective.

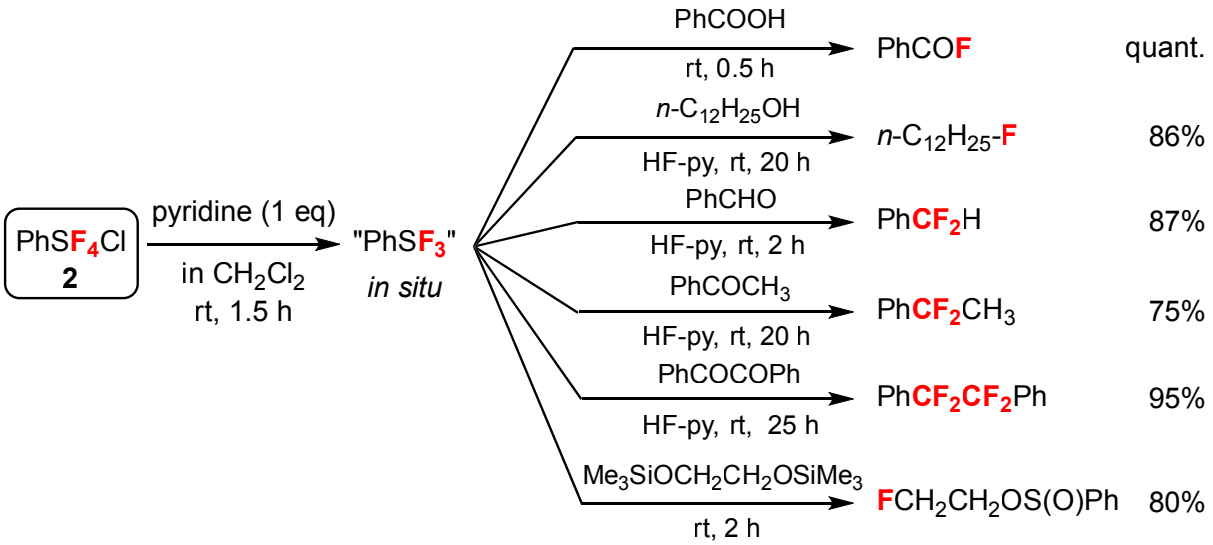
*FLUOLEAD® is a registered trademark of Inner Mongolia Yongtai Chemical Co., Ltd.

2-2. Development of a new reagent, phenylsulfur chlorotetrafluoride ($PhSF_4Cl$) 2 [19]

Phenylsulfur trifluoride ($PhSF_3$) was synthesized as long ago as 1960 and its reactivity was reported,[20] but it was neglected because the synthesis method used expensive AgF_2 and its reactivity was low. We found Fluolead to be a very good fluorinating agent, and using this knowledge, we reexamined the reactivity of $PhSF_3$ and found that it has the same high reactivity as Fluolead. However, unlike Fluolead, $PhSF_3$ is extremely sensitive to moisture, which makes it difficult to produce and store. Meanwhile, we have developed the first practical (industrial) two-step process for arylsulfur pentafluorides ($ArSF_5$) from diaryl disulfides[21] (**Scheme 11**). The intermediates of the new process, arylsulfur chlorotetrafluorides ($ArSF_4Cl$), were easy-to-handle substances, so we focused on their reactivity.



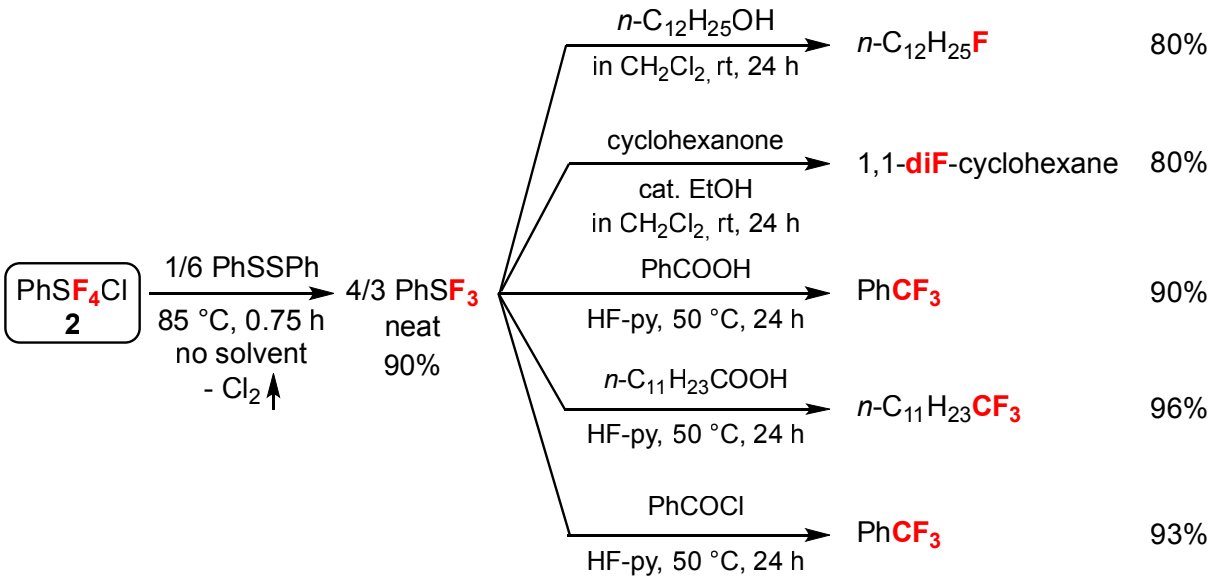
Scheme 11



Scheme 12

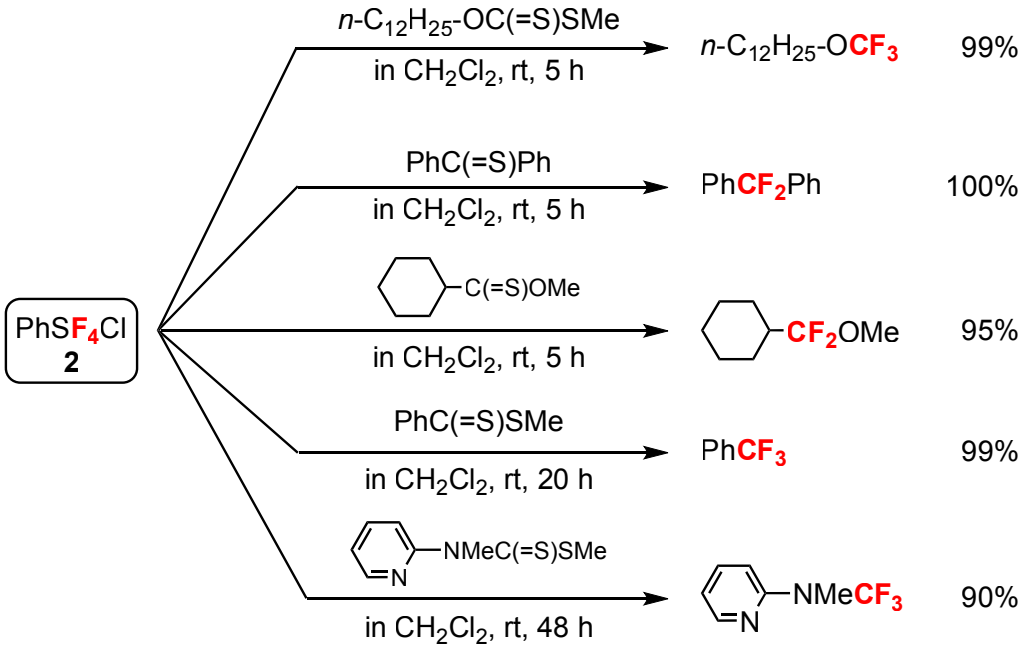
Examination revealed that phenylsulfur chlorotetrafluoride **2** ($PhSF_4Cl$) readily reacts with pyridine, the reducing agent, to form $PhSF_3$. This led to the development of a method for producing and using extremely moisture-sensitive $PhSF_3$ in a reaction system from **2** that is easy to handle. **Scheme 12** shows example reactions using this method. In many cases, at room temperature, HF-py (7:3) is used as an accelerator and fluorination can be achieved in high yields.

We also found that **2** in solvent-free form readily disproportionates with 1/6 equivalent moles of PhSSPh when heated to 85 °C, producing $PhSF_3$ (4/3 molar amount) in high yields with chlorine generation (**Scheme 13**). This has successfully led to the synthesis of highly reactive neat $PhSF_3$ (chlorine Cl_2 generated by this reaction is a gas and is readily released by the flow of nitrogen gas). Using this neat $PhSF_3$, the alcohols were fluorinated in high yields without the accelerator HF-py. In addition, the conversion of carboxylic acids and acyl chlorides to trifluoromethyl compounds was achieved in high yields under mild conditions at 50 °C using HF-py (**Scheme 13**).



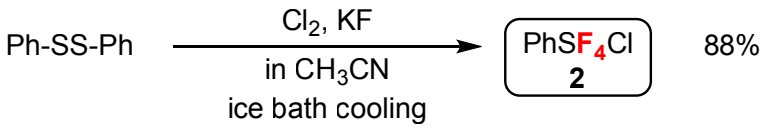
Scheme 13

We also found that, since **2** has strong oxidizing power, **2** itself can be an excellent reagent for the dethioxofluorination of sulfur compounds. **Scheme 14** shows examples of the reactions. These reactions are extremely efficient because the high valence energy (VI) of the sulfur atom can be used for the oxidation reaction required to cleave the C-S bond.



Scheme 14

Since **2** can be produced industrially at low cost as an intermediate in the production of $PhSF_5$ (**Scheme 15**),[21] this method is particularly useful as an industrial process. Unfortunately, **2** is not yet commercially available as a reagent, but it is relatively easy to synthesize in the lab and can be stored for long periods at room temperature in a fluoropolymer container, although it does require dry conditions for the preparation.



Scheme 15

2 is resistant to air humidity and does not decompose immediately when water is added to a chloroform-*d* solution, with a half-life time of 5 to 8.3 hours. However, it should be noted that the addition of 2-3 drops of water to an acetonitrile solution of **2** would cause complete decomposition within one hour. The thermal stability of **2** is high and no decomposition occurs after heating at 100 °C for 134 hours and at 150 °C for 48 hours in a fluoropolymer container.

2-3. Development of Umemoto reagents II and III: *S*-(Trifluoromethyl)-2,8-difluoro and -2,3,7,8-tetrafluorodibenzothiophenium triflates 3 and 4 [22)]

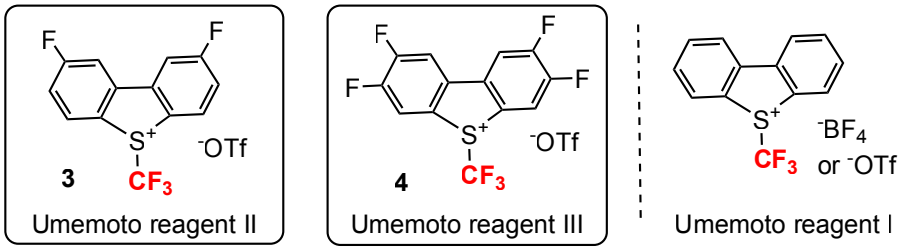
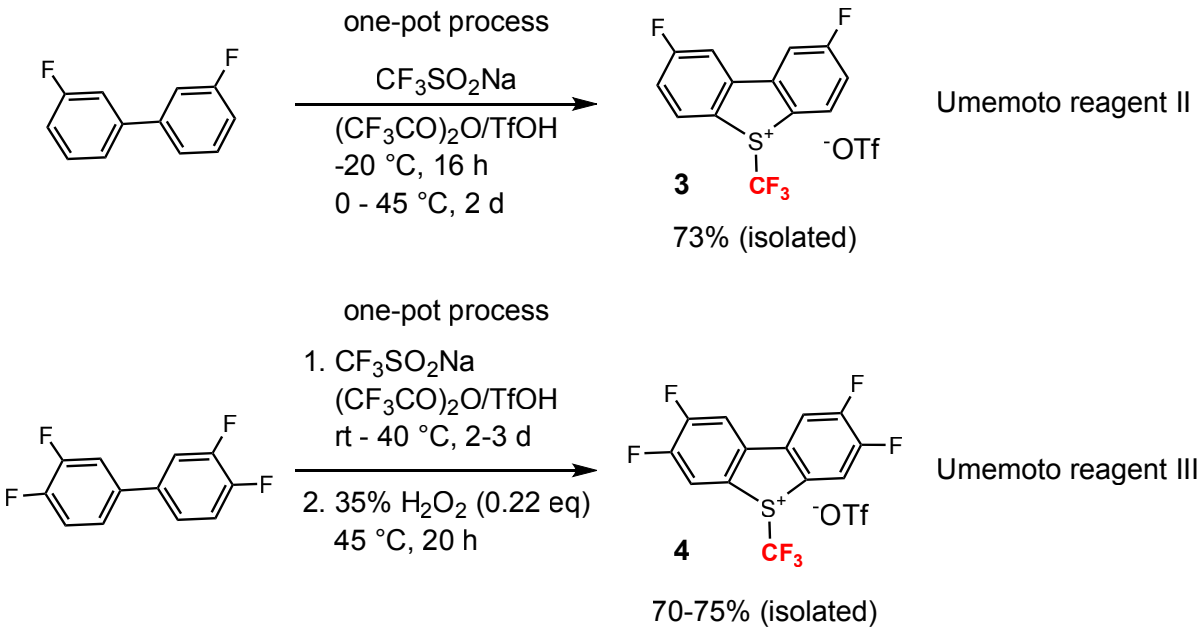
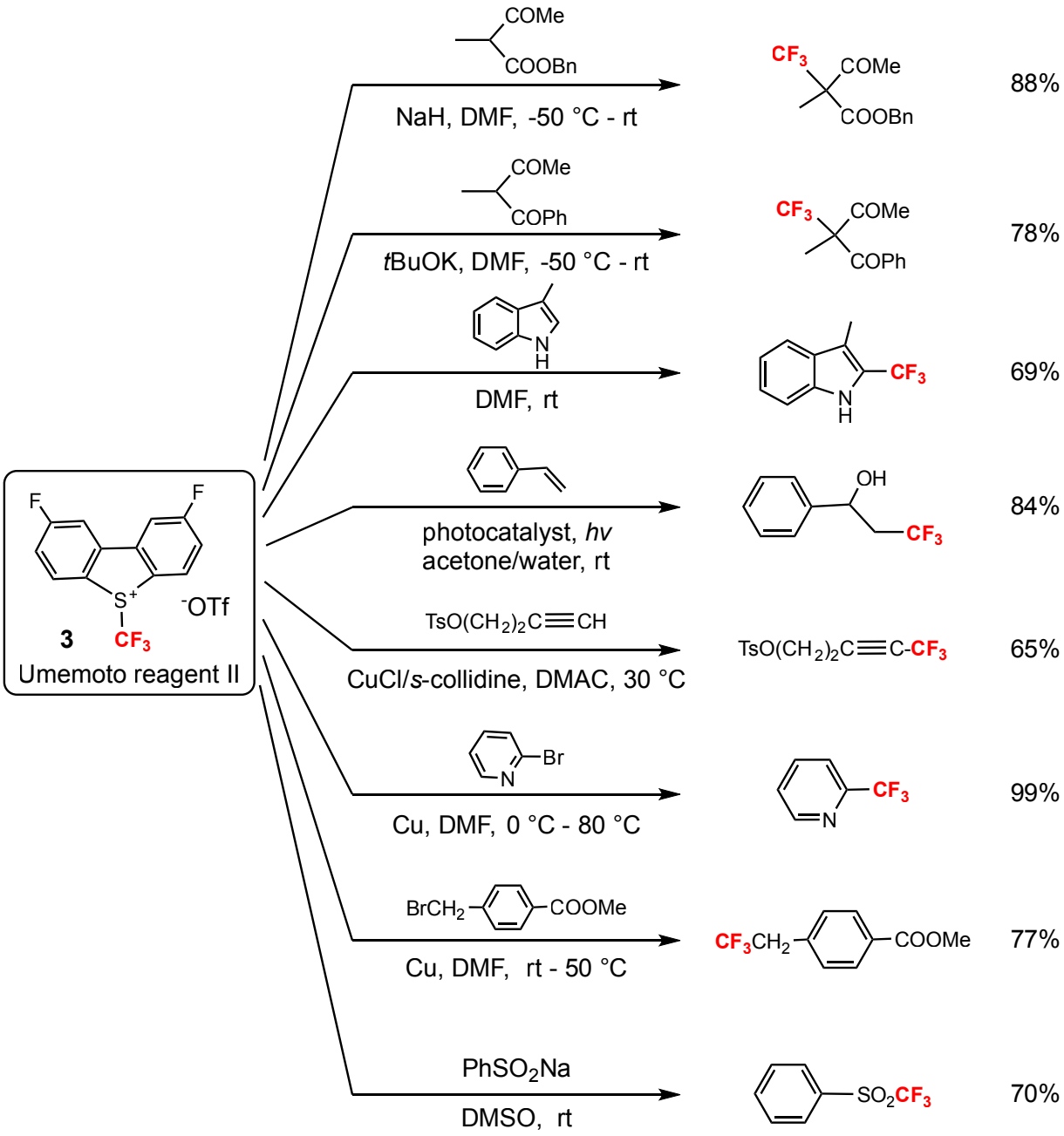


Figure 2

For the electrophilic trifluoromethylating agent, our *S*-(trifluoromethyl)dibenzothiophenium salt (TfO^-, BF_4^-) is well known as Umemoto reagent I,[23)] but the synthesis of this reagent required a multi-step process.[8d)] We have developed new Umemoto reagents II[22a)] and III,[22a,b)] which can be synthesized in a one-pot procedure using biphenyls having fluorine substituents at specific positions (**Scheme 16**). Their reactivity is higher than that of Umemoto reagent I, in the order of Umemoto reagent I < II < III. Umemoto reagent II is commercially available due to its high synthetic efficiency and ease of mass production.



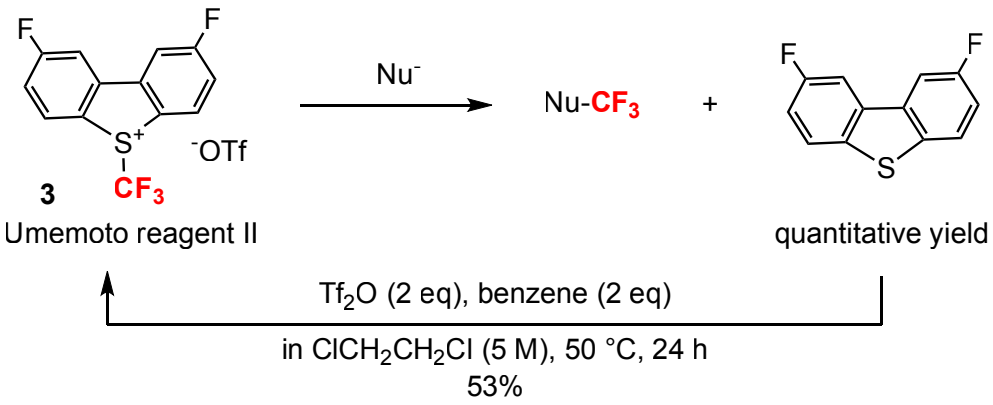
Scheme 16



Scheme 17

The thermal stability of Umemoto reagent II (decomposition point 204 °C, endotherm 38 J/g) is significantly higher than that of Umemoto reagent I (decomposition point 153 °C, endotherm 67 J/g) and, since the decomposition is endothermic, it is suitable for industrial use where large quantities are used. Umemoto reagent III has not yet been commercialized due to disadvantages in raw material cost and synthesis efficiency.

Umemoto reagent II is capable of a wide variety of trifluoromethylation reactions similar to Umemoto reagent I.[8,23] Representative reaction examples of Umemoto reagent II are shown in **Scheme 17**. It can be a good trifluoromethylating agent for a variety of nucleophilic substrates. When Umemoto reagent II is used, 2,8-difluorodibenzothiophene is quantitatively produced along with the trifluoromethylated product, which can be easily regenerated to Umemoto reagent II using Tf_2O and benzene in a small amount of dichloroethane solvent, as shown in **Scheme 18**.[24]



Scheme 18

A number of interesting applications of Umemoto reagent II have been reported,[25] as well as its industrial production and use.[26]

2-4. Development of TFNf : Trifluoromethyl nonafluorobutanesulfonate 5 [27]

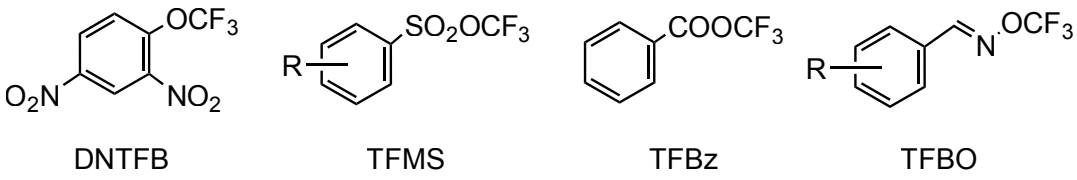
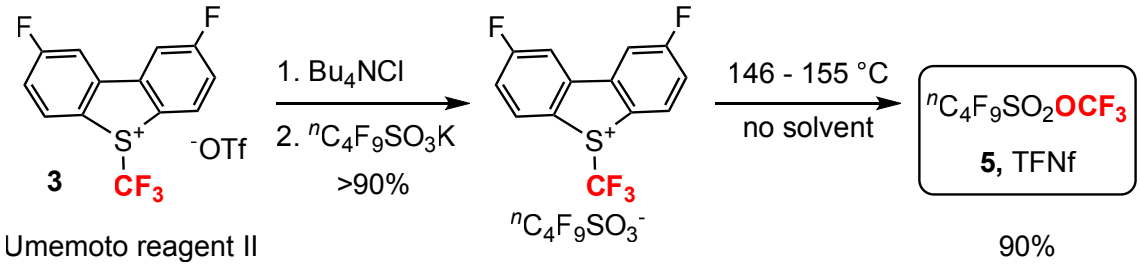
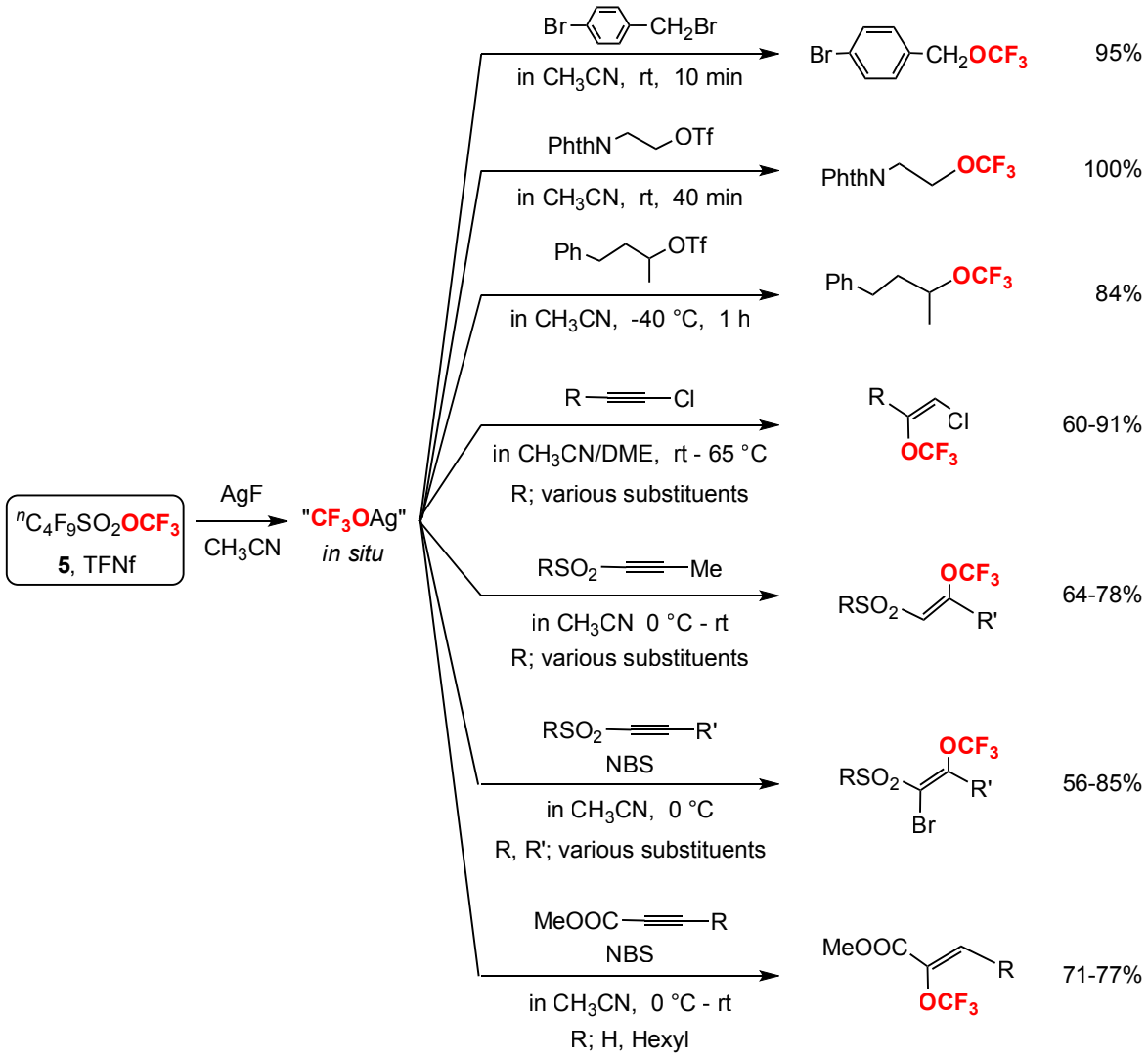


Figure 3

In recent years, the trifluoromethoxy (CF_3O) group has also attracted interest. Reagents for its introduction have been actively researched. It was reported that trifluoromethyl triflate ($CF_3SO_2OCF_3$)[28] could be used as a CF_3O-introducing agent, but this compound was highly volatile (boiling point; 19 °C) and difficult for organic chemists to use. Subsequently, several easy-to-use CF_3O-introducing agents were developed, including DNTFB,[29] TFMS,[30] TFBz,[31] and TFBO,[32] as shown in **Figure 3**. However, they all had drawbacks in syntheses and reactions.



Scheme 19



Scheme 20

We have developed an easy-to-handle and reactive reagent, TFNf **5**, using industrially produced Umemoto reagent II (**Scheme 19**).[27] This synthetic method involves three steps starting with Umemoto reagent II, and each step is easy to do on a large scale. In particular, the final step is a solvent-free pyrolysis, so product **5** can be easily obtained by distillation. **5** is an easy-to-handle, odorless, colorless liquid with a boiling point of 87-89 °C.

5 has high reactivity. It can easily generate CF_3OAg in solution using an activator such as AgF, and various CF_3O reactions can be achieved as shown in **Scheme 20**. **5** is commercially available from TCI.

2-5. Development of NFBB : *N*-Fluoro-(*N*-*tert*-butyl)-*tert*-butanesulfonamide **6** [33]

NFBB **6** is extremely effective in fluorinating reactive anion species, especially aryl lithium and alkenyl lithium species. Previously, NFSI ($PhSO_2NFSO_2Ph$) was used to fluorinate aryl lithium and alkenyl lithium species, but unfortunately the yield was often low.[34] The reason is that NFSI has many reactive sites to strongly basic lithium reagents that also act as hydrogen abstractors, so that in addition to the desired fluorination reaction (a), hydrogen abstraction reactions (b) and nucleophilic attack on sulfur atoms (c) coexist (**Figure 4**). In contrast, NFBB is blocked by bulky *tert*-butyl groups at both ends and therefore undergoes only the fluorination reaction (a), resulting in an extremely high yield of fluorination.

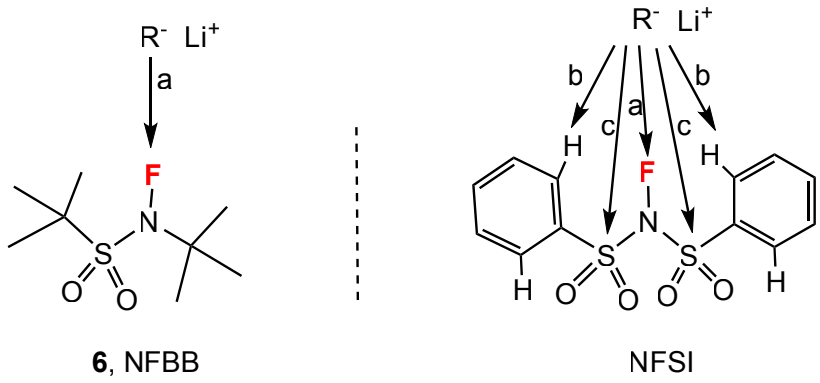
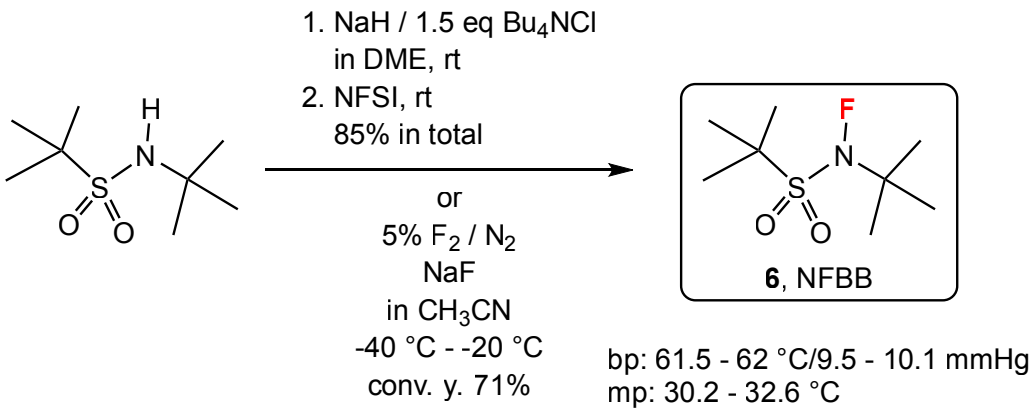
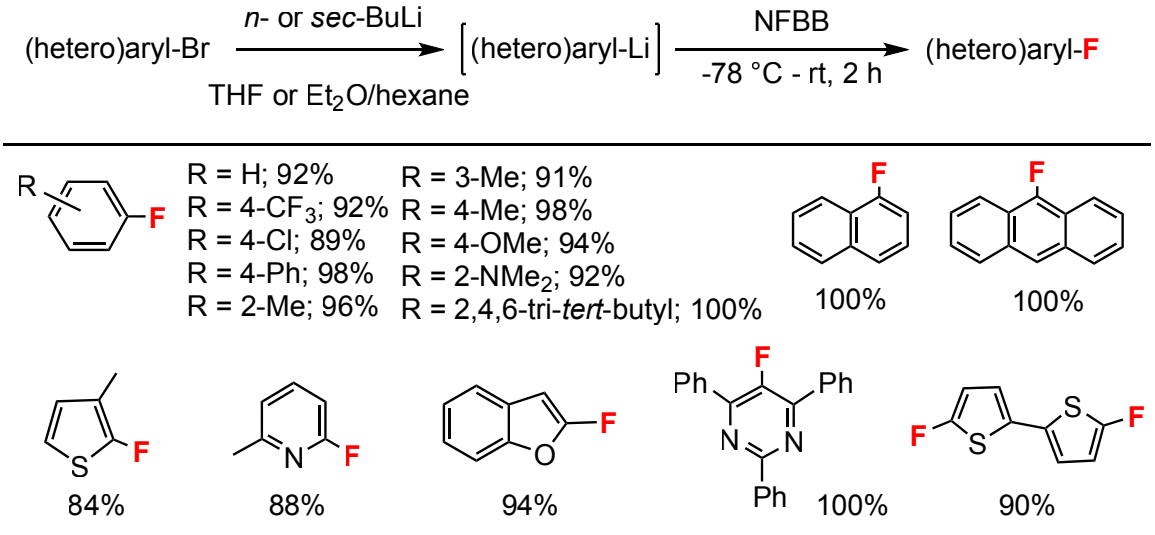


Figure 4

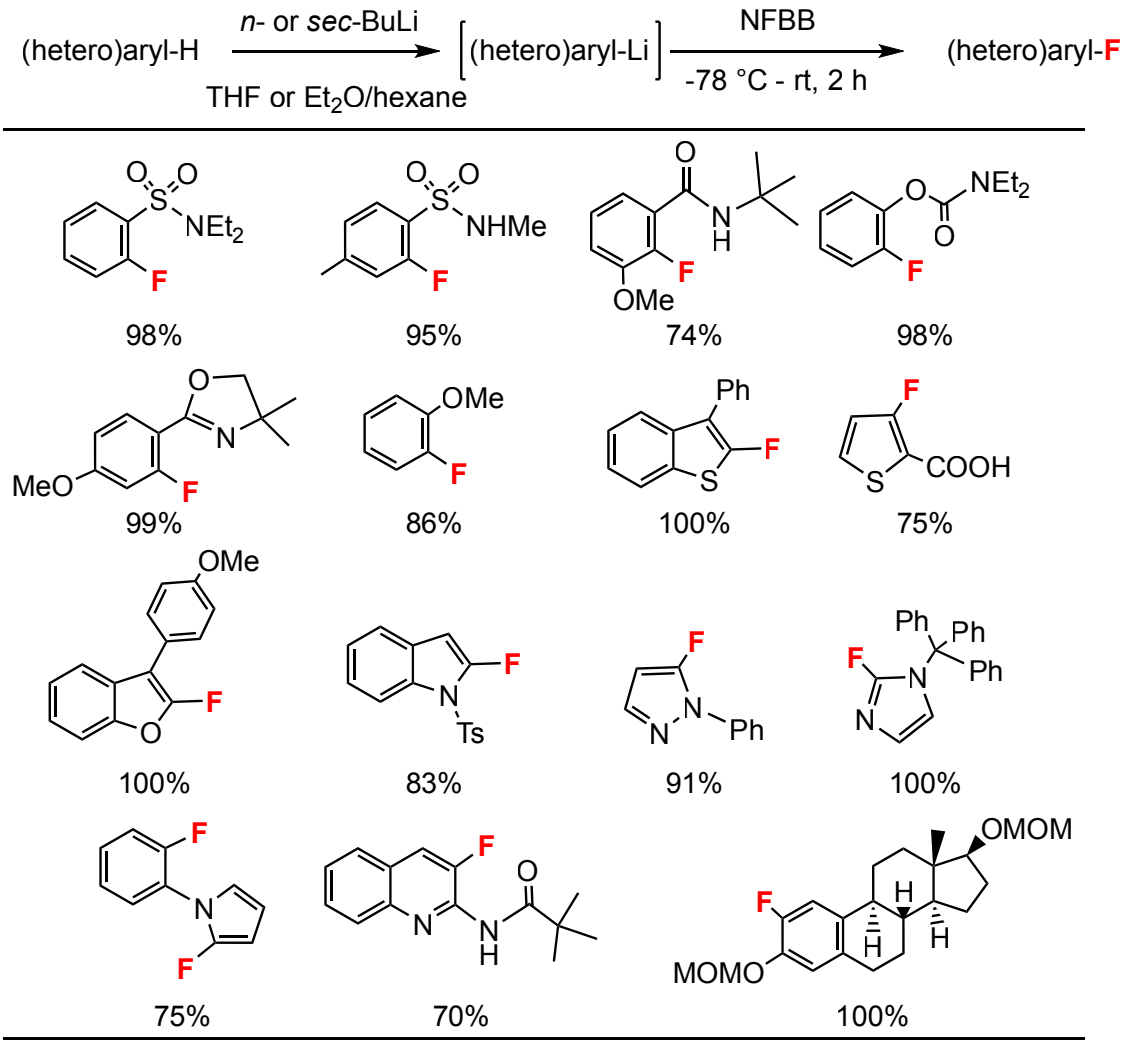


Scheme 21

For the synthesis of NFBB, it is recommended to use inexpensive F_2 for industrial production, but in the laboratory, NFBB can be synthesized in high yields (85%) using easy-to-handle NFSI (**Scheme 21**). Although the *tert*-butylsulfonamide group is normally easily cleaved by the highly reactive F_2, fortunately, when both ends are protected with bulky *tert*-butyl groups such as NFBB, cleavage is suppressed and fluorination can be performed in good yield (71% conversion yield). NFBB is a thermally stable compound that can be purified and isolated by conventional distillation under reduced pressure, making it suitable for large-scale preparation. NFBB is commercially available from TCI.



Scheme 22

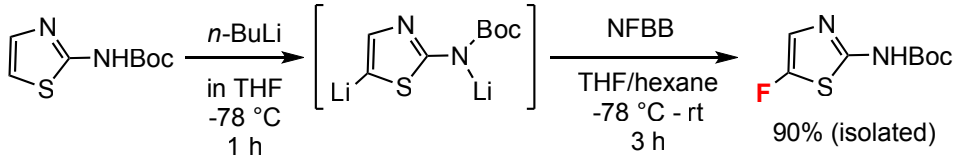


Scheme 23

NFBB acts as an excellent electrophilic fluorinating agent for aryl and alkenyl lithium species. There are several methods for generating organolithium species. **Scheme 22** shows examples where (hetero)aryl lithium species generated from (hetero)aryl bromides by halogen exchange reaction with *n*- or *sec*-BuLi were fluorinated with NFBB. In all cases, the fluorine compounds can be obtained in quantitative or near quantitative yields.

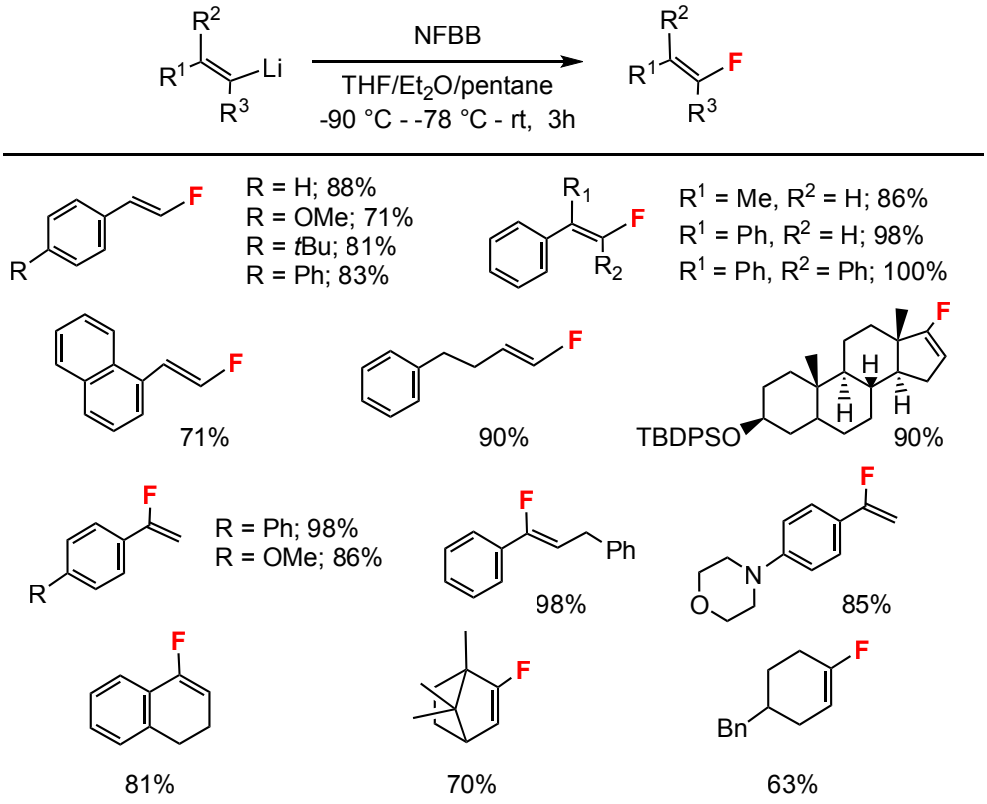
Scheme 23 shows examples of the fluorination of (hetero)aryl lithium species obtained by direct regioselective deprotonation of the *ortho*-position of (hetero)arenes bearing various activating groups. The desired fluorine compounds can be obtained regioselectively in high yields. This method is very effective because the desired fluorine compounds can be obtained directly from (hetero)arenes.

As a useful application example of this method, the synthesis of a pharmaceutical intermediate using NFBB is shown in **Scheme 24**. This is obtained in high yield (90%). This synthesis was previously performed using NFSI, but the yield was low.[35)]



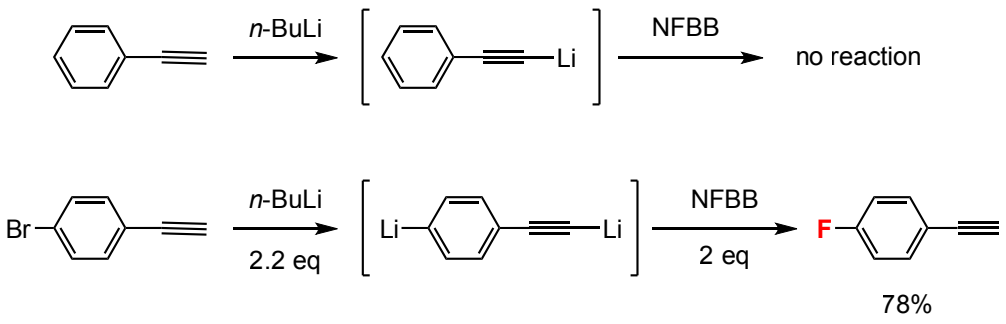
Scheme 24

NFBB can also fluorinate alkenyl lithium species in high yields (**Scheme 25**).



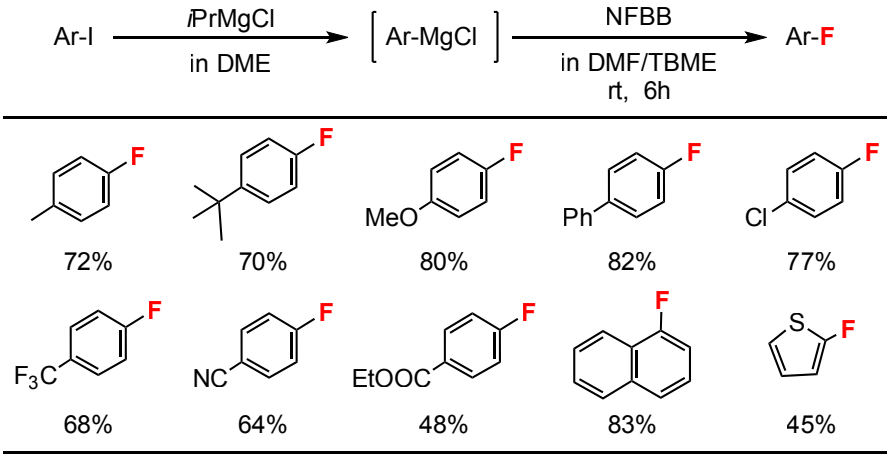
Scheme 25

Interestingly, triple-bonded lithium acetylides cannot be fluorinated, so only aromatic lithium species can be selectively fluorinated (**Scheme 26**).



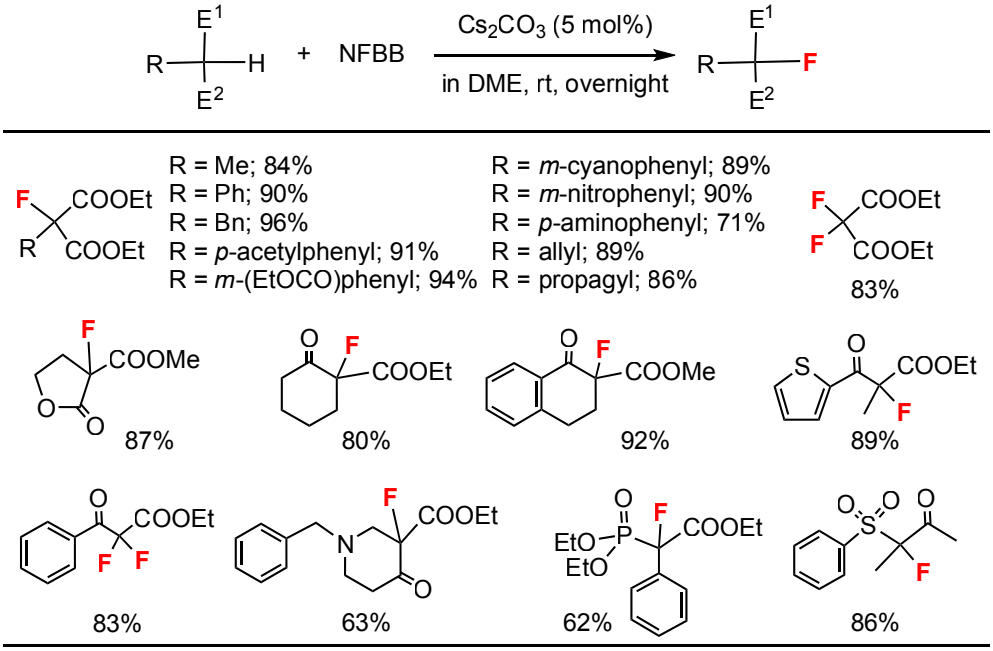
Scheme 26

The fluorination of Grignard reagents was reported using NFSI[36] and *N*-fluoro-2,4,6-trimethylpyridinium salts,[37] but in both cases the Grignard reagents were complexes with LiCl. NFBB reacts with standard Grignard reagents to yield fluorinated products in good yields (**Scheme 27**). The advantage of using Grignard reagents over lithium salts is that they are more amenable to substrates containing functional groups such as esters or cyano groups.



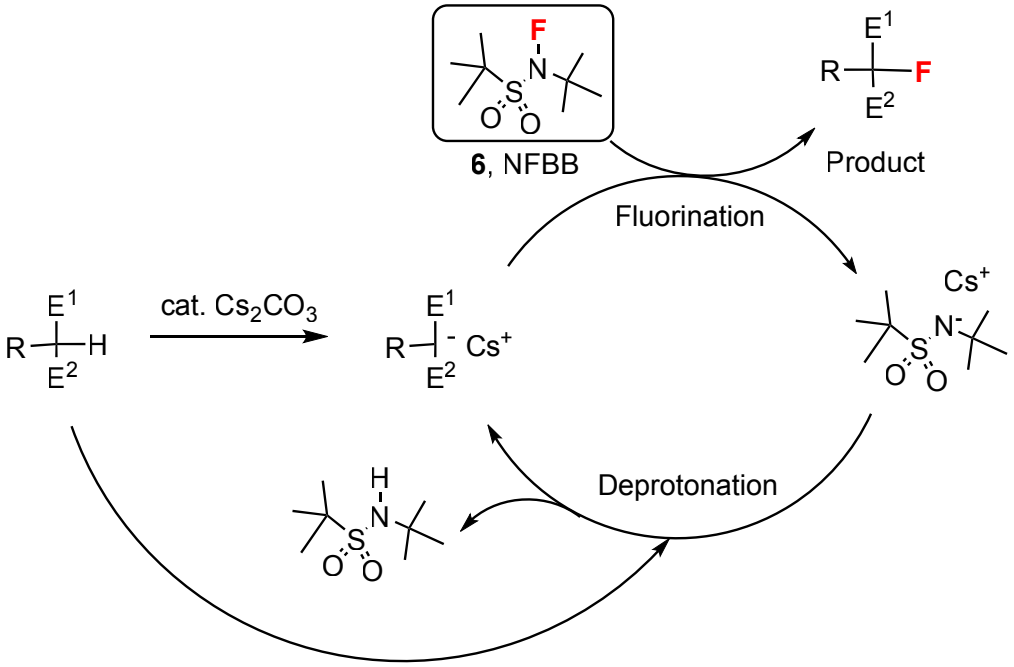
Scheme 27

NFBB is capable of catalytic fluorination of active methylene compounds, which has not been reported before (**Scheme 28**). These reactions use a catalytic amount (5 mol%) of cesium carbonate in DME solvent at room temperature for approximately 12 hours under mild reaction conditions and achieve the fluorination of many active methylene compounds in high yields.



Scheme 28

As shown in **Scheme 29**, the mechanism of these reactions is that the Cs salt of an active methylene compound resulting from the reaction with the catalyst Cs_2CO_3 reacts with NFBB to form a fluorinated product, and at the same time the resulting $^tBuN^-(Cs^+)SO_2{}^tBu$ acts as a base, and this cycle continues until the reaction is complete. We described this fluorination reaction as self-sustaining fluorination.



Scheme 29

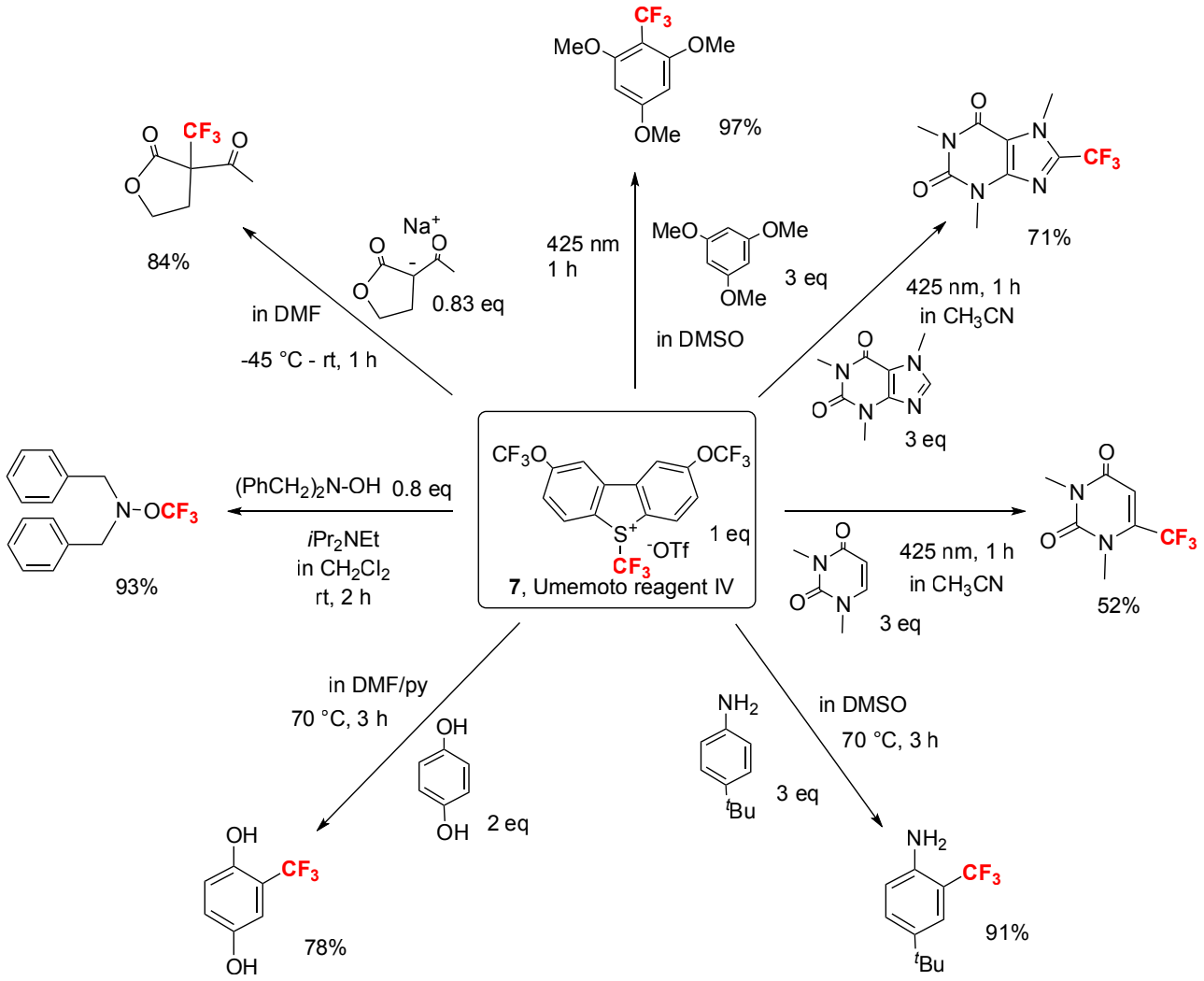
Another advantage of using NFBB is that it has very low oxidizing power, so NFBB does not react with Et_3N. Therefore, the target fluorine compound can be obtained in good yields even from an active methylene compound with an amino substituent. In contrast, when a highly oxidizing fluorinating agent such as Selectfluor® is used, an oxidation reaction of the amino group occurs.

* Selectfluor® is a registered trademark of MERCK KGAA.

2-6. Development of Umemoto reagent IV: *S*-(Trifluoromethyl)-2,8-bis(trifluoromethoxy)-dibenzothiophenium triflate 7 [24)]

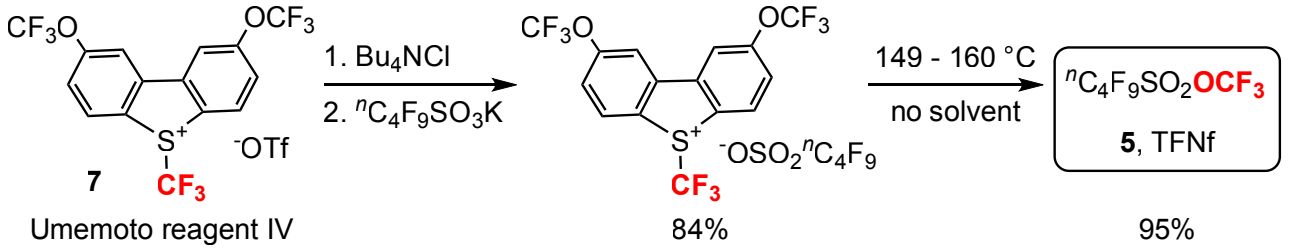
As described in Chapter 2-3, Umemoto reagents II and III, which can be synthesized in one pot from the di- and tetrafluorobiphenyl compounds by utilizing the electronic effect of fluorine atoms, were developed, and Umemoto reagent II was commercialized because of its ease of synthesis. However, Umemoto reagent II is proprietary (US 10,155,739 B2), and others need permission from the owner to use it for commercial purposes. Since many other users needed a new, more active Umemoto reagent, we developed Umemoto reagent IV **7**, which is more reactive than Umemoto reagent II, by focusing on the new CF_3O group, which has an effect that overcomes the (electron) effect of the F atom. Although its reactivity is inferior to that of Umemoto reagent III, it is as easy to synthesize almost similarly to Umemoto reagent II. The starting material, 2,2'-bis(CF_3O)-biphenyl, can be synthesized in high yield from 3-CF_3O-bromobenzene. Since Umemoto reagent IV is more reactive than Umemoto reagent I or II, it is expected to be more effective in many of the previously reported trifluoromethylation reactions. Examples of the reactions are shown in **Scheme 30**.

Active methylene compounds are trifluoromethylated equally effectively, and trifluoromethylation of (hetero) aromatic nuclei is superior to that achieved with Umemoto reagent II. The notable difference was that the reaction with *N*,*N*-dibenzylhydroxyamine afforded the *O*-CF_3 compound in high yield of 93%, whereas the yield was only 39% when Umemoto reagent II was used.



Scheme 30

The CF_3O-introducing agent TFNf **5** described in Section 2-4 above can be synthesized using Umemoto reagent IV (**Scheme 31**). Each step is performed in high yield, and the final product, TFNf, can be easily isolated and purified.



Scheme 31

One advantage of Umemoto reagent IV is that it is non-proprietary and can be used for commercial purposes without any issues. In addition, Umemoto reagent IV has a highly lipophilic CF_3O group and therefore has excellent solubility in organic solvents. Therefore, it is expected to be more widely applicable. Umemoto reagent IV is commercially available from TCI.

2-7. Development of TTST : *S*-(Trifluoromethyl) trifluoromethanesulfonothioate **8** [38]

The trifluoromethylthio (CF_3S) group has strong electron withdrawing properties and the highest level of lipophilicity, making it of particular interest in research for the development of new pharmaceuticals and agrochemicals. Therefore, there is a need for an effective reagent to introduce the CF_3S group. In particular, the development of electrophilic CF_3S-introducing reagents with a wide range of applications has been actively pursued.

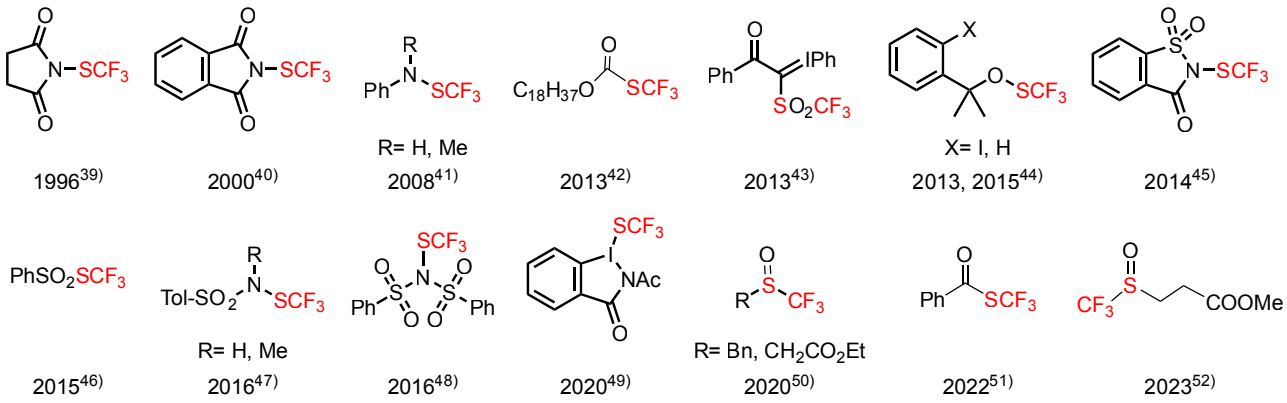
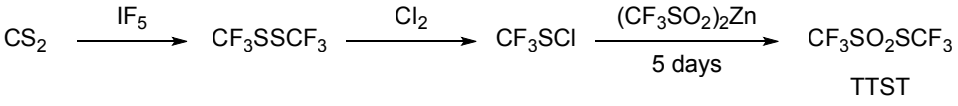


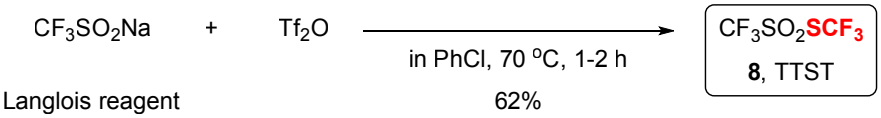
Figure 5

In the past, CF_3SCl and CF_3SSCF_3 were used, but these are toxic gases and are very difficult to handle. As a result, a large number of new CF_3S reagents have been developed in recent years as alternative, easy-to-handle CF_3S-introducing reagents.[39-52] They are shown in **Figure 5** along with the years of development. The development of these reagents has greatly advanced the CF_3S synthesis reactions. However, from the point of view of synthesizing CF_3S compounds, these reagents have drawbacks, such as the multi-step synthesis, the need for expensive raw materials, and the large molecular weight of the reagents, which results in a low atom efficiency. As a result of our investigations to solve these problems, we developed a new reagent, TTST **8**. Although TTST was synthesized as early as 1955,[53] its reactivity had not been studied. Its synthesis involved a three-step process, as shown in **Scheme 32**, and many of the reactants and intermediates used were hazardous to handle.[53]



Scheme 32

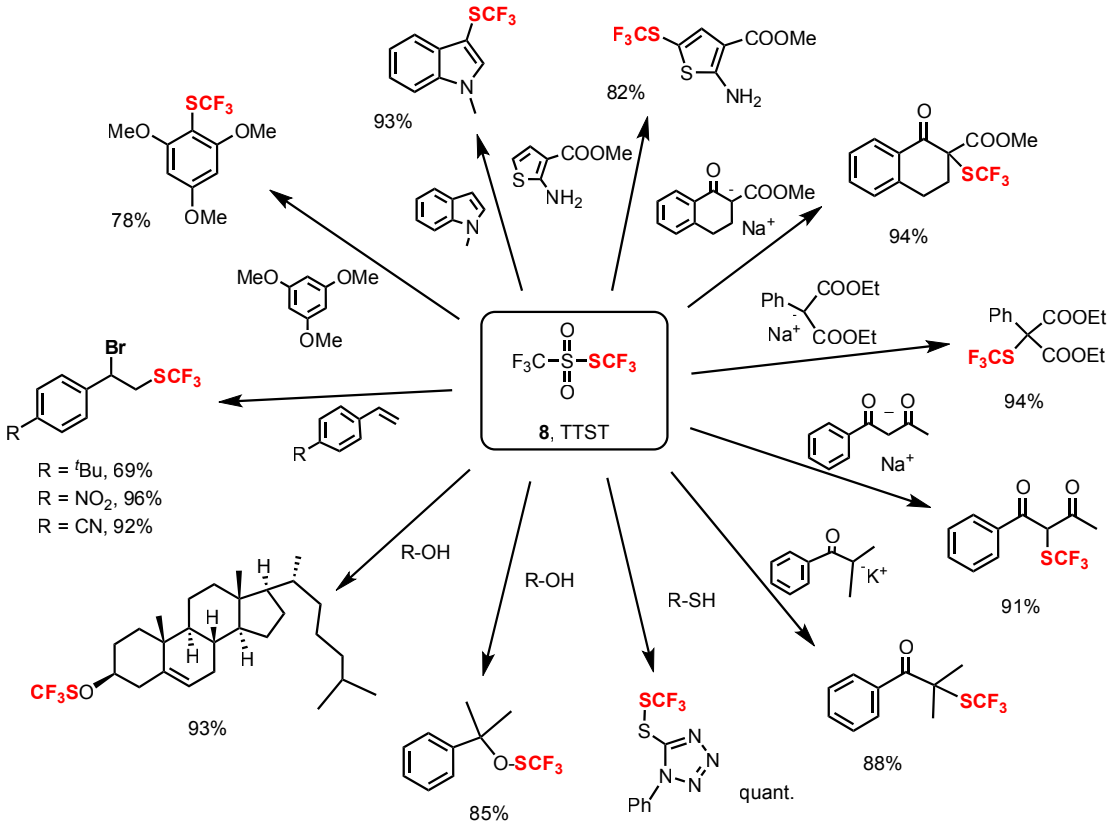
We have discovered a one-pot synthesis method for TTST from inexpensive Langlois reagent and trifluoromethanesulfonic anhydride (Tf_2O)[38] (**Scheme 33**). TTST is a thermally stable, colorless, transparent liquid with a boiling point of 66-69 °C and can be handled in air.



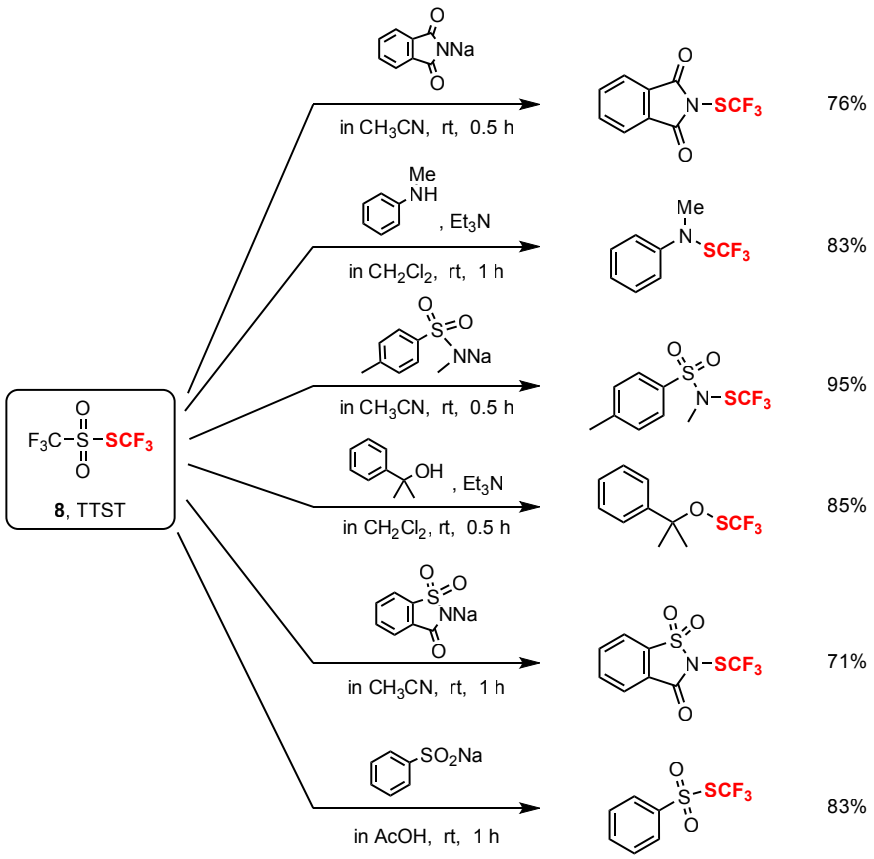
Scheme 33

We found TTST to be a very versatile reagent that acts as a source of CF_3S cations, anions, and radical species. Examples of these reactions are shown below

2-7-1. As a generator of CF_3S cationic species[38)]



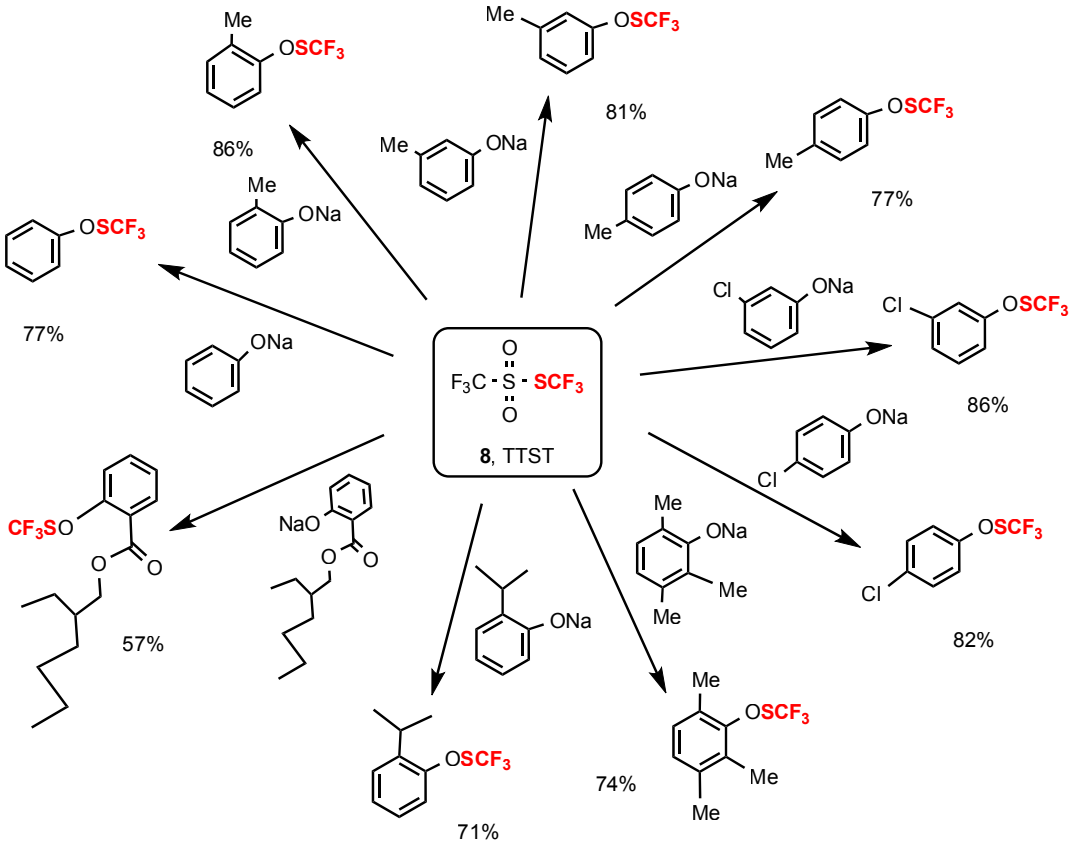
Scheme 34



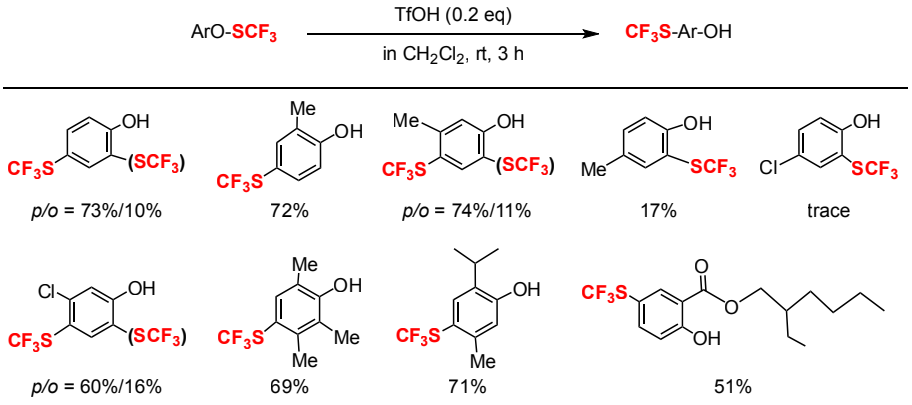
Scheme 35

As shown in **Scheme 34**, TTST introduces a CF_3S group to electron-rich aromatic, unsaturated bond, carbanion, thiol, and hydroxy sites in high yields under mild conditions. One of the advantages of TTST is that many of the CF_3S reagents already developed can be synthesized in a single step with high yields from readily available raw materials, as shown in **Scheme 35**.

TTST does not react with phenol, but it was found to react with phenoxide anions (ArO^-) in ether solvents at low to room temperature to produce a series of new $ArOSCF_3$ in good yields (**Scheme 36**).



Scheme 36

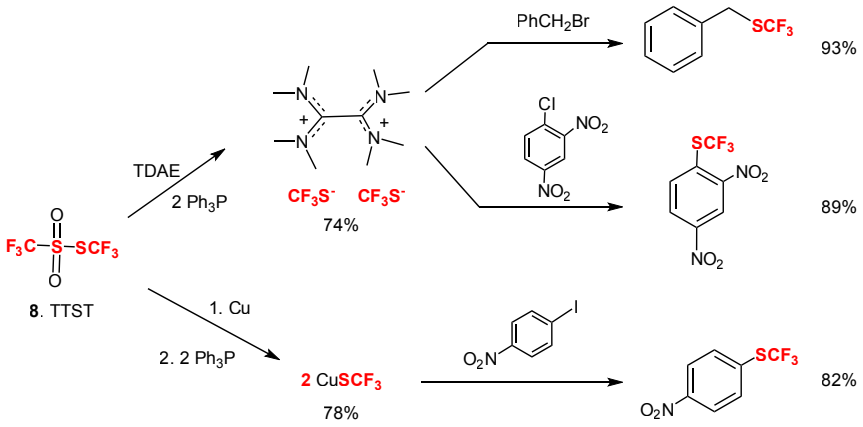


Scheme 37

Furthermore, we found that the CF_3S group of $ArOSCF_3$ readily undergoes a rearrangement reaction at room temperature in the presence of an acid catalyst (TfOH), yielding mainly *para*-substituted products (**Scheme 37**).

2-7-2. As a generator of CF_3S anion species[38)]

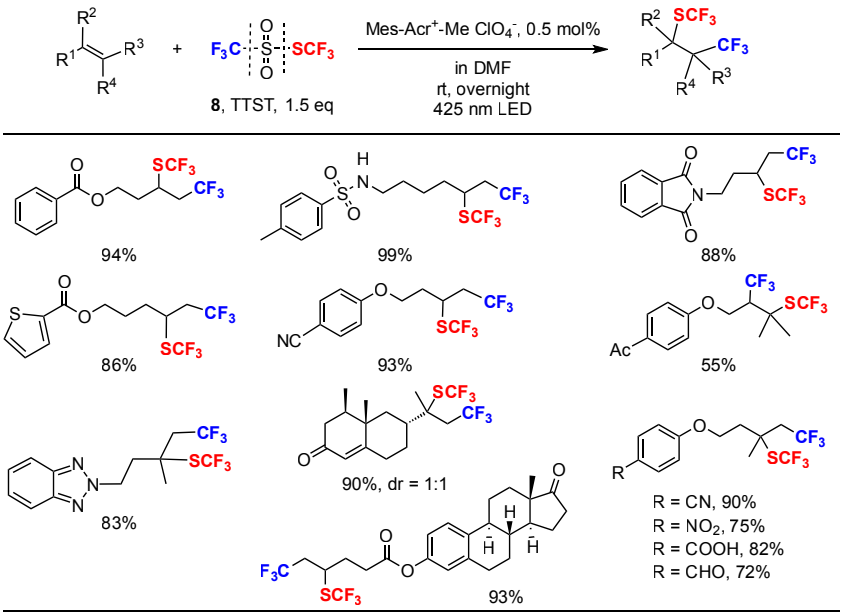
TTST generates the CF_3S anion species by combining Ph_3P with a reducing agent. The following two reaction examples are shown in **Scheme 38**. When TTST reacted with two molecules of Ph_3P and one molecule of tetrakis(dimethylamino)ethylene (TDAE), $TDAE^{2+}(CF_3S^-)_2$ with two CF_3S anions was formed from TTST in 74% yield. It was reacted with the electrophilic substrates, benzyl bromide and 1-chloro-2,4-dinitrobenzene to give the corresponding CF_3S compounds in high yields, respectively. In addition, by reacting TTST with Cu and then with two molecules of Ph_3P, two molecules of $CuSCF_3$ were obtained in 78% yield, and then, by reacting this with an aryl halide, the desired CF_3S-substituted aromatic compound was obtained in 82% yield. As seen, TTST is a source of two CF_3S anion species, so it can be said that TTST is a reagent with extremely high atom efficiency.



Scheme 38

2-7-3. As a source of CF_3S and CF_3 radical species[38)]

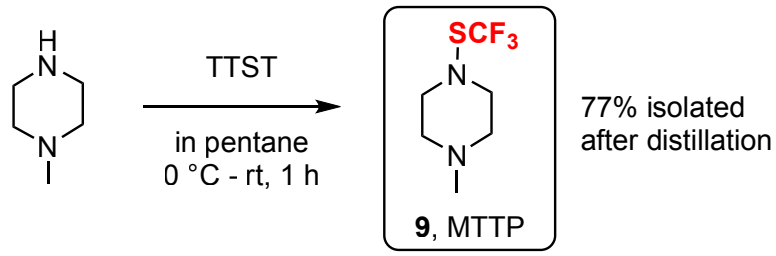
We found that TTST served as a simultaneous source of CF_3S and CF_3 radical species. As shown in **Scheme 39**, TTST was irradiated with 425 nm light in the presence of olefins and the photocatalyst Mes-Acr^+-$MeClO_4^-$ (0.5 mol%) to give the regioselective addition products of CF_3S and CF_3 radicals in high yields. Previously, two types of reagents, a CF_3S reagent and a trifluoromethylating reagent, were required to obtain a similar compound, but by using TTST, only one type of reagent is required. TTST is commercially available from TCI.



Scheme 39

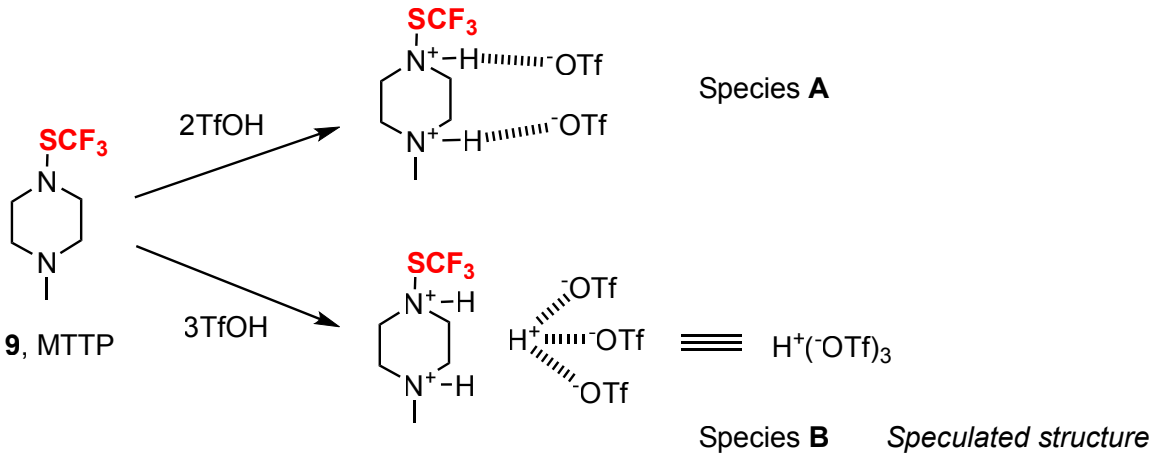
2-8. Development of MTTP : 1-Methyl-4-(trifluoromethylthio)piperazine 9 [54)]

Although many easy-to-use electrophilic CF_3S reagents have been developed, it has been difficult to directly introduce CF_3S into inactive or electron-deficient aromatic rings. We have developed a heterocyclic CF_3S diamine MTTP **9** which is the most reactive generator of CF_3S cationic species. As shown in **Scheme 40**, MTTP can be easily synthesized in high yields from TTST and is a stable, easy-to-handle, colorless liquid with a boiling point of 67-69 °C/51-52 mmHg.



Scheme 40

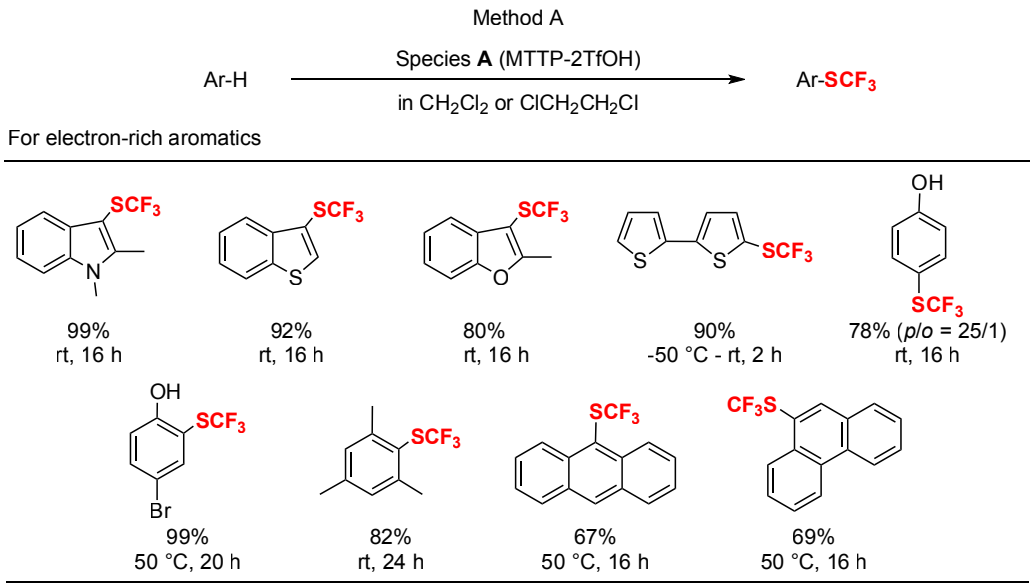
From the study of reactivity using TfOH as an activator, we discovered a very interesting phenomenon. We found that there is a large difference in reactivity between reactive species **A**, which uses two molecules of TfOH, and reactive species **B**, which uses three molecules, against the MTTP molecule. The reactive species **B** is much more reactive than **A**.



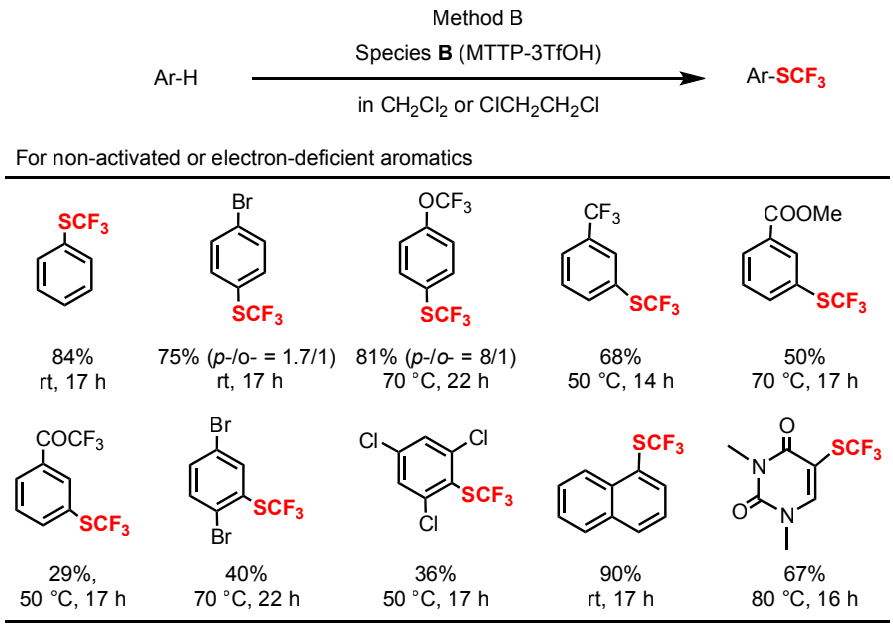
Scheme 41

We proposed that this can be explained by the difference in the degree of bonding between the protons attached to the two nitrogen atoms. That is, in reactive species **B**, the proton from the third TfOH interacts with the three TfO anions, causing the remaining two protons to bind strongly to the respective nitrogen atoms, thereby reducing the electron density of the nitrogen atoms more. Consequently, reactive species **B** produces a stronger CF_3S cation species than reactive species **A** (**Scheme 41**). As a result, reactive species **A** is an excellent CF_3S reagent for electron-rich aromatic nuclei, while reactive species **B** is an excellent CF_3S reagent for non-activated or electron-deficient aromatic nuclei. **Scheme 42** shows examples of the reactions of electron-rich aromatic compounds with reactive species **A**. Various electron-rich aromatic compounds can be substituted with CF_3S groups in good yields.

Although TTST also trifluoromethylthiolates electron-rich aromatic compounds (**Scheme 34**), TTST does not react with phenols. The reactive species **A** from MTTP is an excellent CF_3S reaction reagent for phenols as shown in **Scheme 42**.



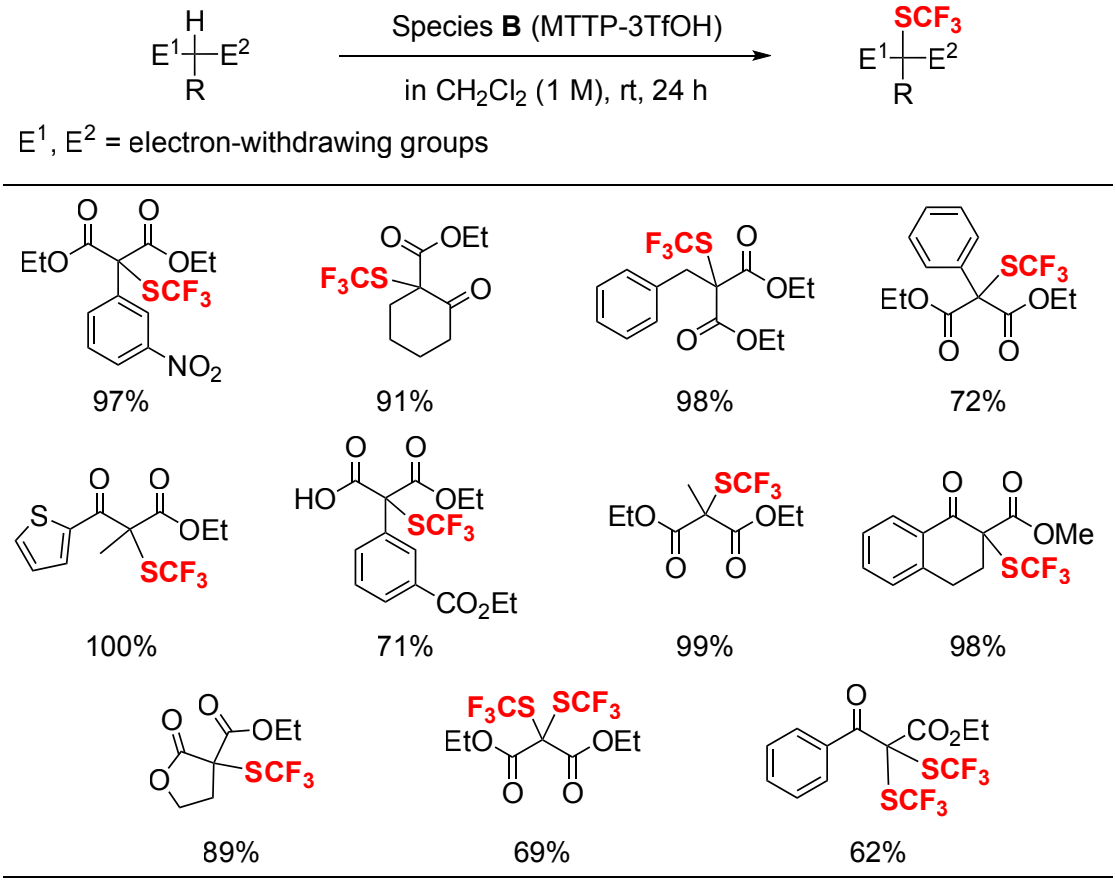
Scheme 42



Scheme 43

Figure 43 shows examples of the reactions of non-activated or electron-deficient aromatic compounds with reactive species **B**. In most cases, the CF_3S compounds were obtained in good yields. Trifluoromethylthiolations of these electron-deficient aromatic rings have been scarcely reported. Thus, the combination of MTTP with an acid (TfOH) makes it possible to trifluoromethylthiolate a wide range of aromatic compounds.

Although many reactions have been reported for trifluoromethylthiolation of active methylene compounds under basic conditions, there have been few reports for trifluoromethylthiolation of active methylene compounds under acidic conditions. As shown in **Scheme 44**, the reactive species **B** trifluoromethylthiolates many active methylene compounds in very good yields at room temperature. In addition, bistrifluoromethylthiolations can be achieved in a single step with good yields. This method is useful when reactions under acidic conditions are required. MTTP will be available from TCI.



Scheme 44

3. Acknowledgements

I have described the development of new fluorine-introducing reagents that we have developed since the beginning of the 2000s. This is an achievement made together with my collaborating researchers. I am grateful to the many collaborators described in these papers. In particular, the development of TFNf, NFBB, Umemoto reagent IV, TTST, and MTTP was done together with Professor Hammond in his laboratory in the Department of Chemistry at the University of Louisville. I would like to express my deepest gratitude to Professor Hammond.

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Related Products

(Diethylamino)sulfur Trifluoride (= DAST)	5g	25g	100g	D1868
4-*tert*-Butyl-2,6-dimethylphenylsulfur Trifluoride (= Fluolead®)	1g	5g	25g	B3664
Triethylamine Trihydrofluoride			10g	T2022
Trifluoromethyl 1,1,2,2,3,3,4,4,4-Nonafluorobutane-1-sulfonate (= TFNf)		1g	10g	T4150
N-(*tert*-Butyl)-*N*-fluoro-2-methylpropane-2-sulfonamide (= NFBB)		1g	10g	F1345
Umemoto Reagent IV		1g	10g	T4082
S-(Trifluoromethyl) Trifluoromethanesulfonothioate (= TTST)		1g	5g	T4211