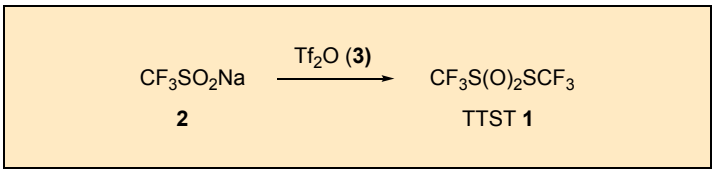
Organic Syntheses

Preparation of *S*-Trifluoromethyl Trifluoromethanesulfonothioate (TTST), a Highly Versatile and Atom-economical Trifluoromethylthiolating Agent

Seyedesahar Miraghaee, Teruo Umemoto*[1], and Gerald B. Hammond*[1]

Department of Chemistry, University of Louisville, 2320 S. Brook Street, Louisville, Kentucky 40292, United States.

Checked by Keita Moriyasu, Hirofumi Ueda, and Hidetoshi Tokuyama



Procedure (Note 1)

*S-Trifluoromethyl Trifluoromethanesulfonothioate (TTST, **1**).* To a flame dried, 500-mL, 3-necked, round-bottomed flask, is added fine powdered sodium trifluoromethanesulfinate (**2**) (50.0 g, 320 mmol, 3 equiv) of high purity (Notes 2, 4). To completely dry the trifluoromethanesulfinate, the flask is evacuated for 1 hour in an oil bath at 80 °C using a vacuum pump (2.6 Torr), then filled with argon and cooled down (Note 5). After that, the center neck of the flask is fitted with an overhead stirrer (a mechanical stirrer), another neck is fitted with a 25-mL dropping funnel connected with a $CaCl_2$-drying tube, and the last neck is fitted with a thermometer to monitor the internal temperature of the reaction mixture (Figure 1A). Dry chlorobenzene (188 mL) (Note 6) is added into the flask via the dropping funnel using 100-mL syringe and triflic anhydride (**3**) (Note 7) (Tf_2O, Tf = CF_3SO_2) (25.1 mL, 149 mmol, 1.4 equiv (Note 8)) is added into the dropping funnel using 30-mL syringe. The flask is heated in an oil bath at 70 °C (oil bath temperature) and then triflic anhydride is added dropwise to the flask over a period of 50 minutes with stirring at 136-220 rpm (*see* the stirring blade in the 500-mL flask in Figure 1A). The temperature inside the flask is kept around 75 °C (Note 9). As the

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reaction proceeds, the reaction mixture becomes viscous since sodium triflate is formed (Note 10). After the complete addition of triflic anhydride, the reaction mixture is stirred for an additional 1 hour in the oil bath at 70 °C (oil bath temperature). Finally, the reaction mixture is very viscous (Figure 1B). Next, the dropping funnel is replaced with a distillation set fitted with a distillation column (Note 11), a condenser (Note 12), and a receiver (Note 13) (Figure 1C). The flask is then gradually heated in the oil bath up to around 170 °C (oil bath temperature) to collect the distillate until bp 90 °C (20.52-20.61 g; crude yield 81-82% based on CF_3SO_2Na used) (Note 14). The byproduct, sodium triflate (TfONa), can easily be isolated in almost quantitative yield by the filtration of the reaction mixture left behind.

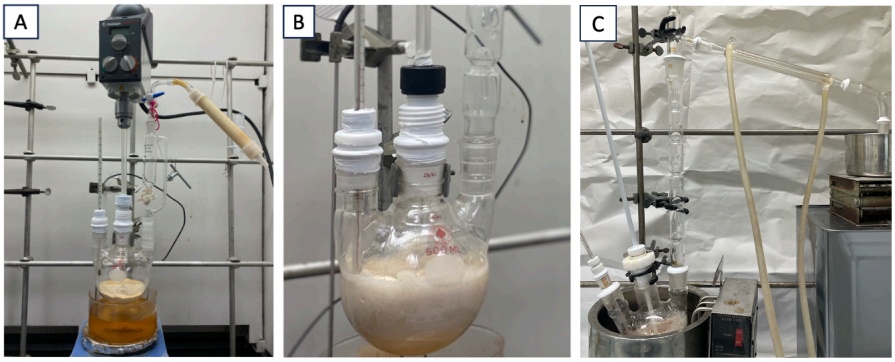

Figure 1. A. An apparatus of the reaction in which sodium trifluoromethanesulfinate is placed in the 500 mL flask; B. The viscous reaction mixture after the reaction, in which a lot of sodium triflate is formed; C. Distillation of crude TTST from the reaction mixture (Photo A and B were provided by the authors and photo C was provided by checkers)

The obtained crude product is purified by fractional distillation using a distillation column (height 20 cm) filled with glass beads (3 mm diameter) (Figure 2A) to give 15.21-16.42 g (bp 62-67 °C, 61-66% yield) of TTST **1** whose purity is 85-86% by qNMR (Notes 15, 16). The main impurity is chlorobenzene. To obtain TTST of higher purity, the second fractional distillation is conducted using the same apparatus, giving 12.38-12.73 g (bp 62-64 °C, 50-51% yield) of TTST whose purity is 95% by qNMR (Note 17). TTST is colorless liquid (Figure 2B) and has high thermal stability because it was isolated from the reaction mixture heated up to 170 °C (Note 18 and 19).

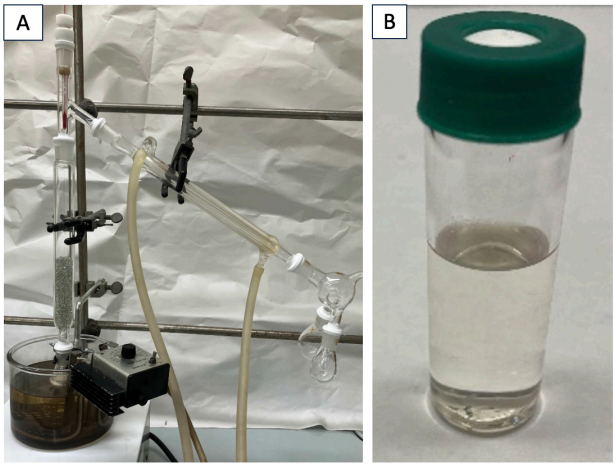

Figure 2. A. Fractional distillation for purification of crude TTST; B. TTST after purification (Photo A was provided by checkers and photo B was provided by the authors)

Notes

1. Prior to performing each reaction, a thorough hazard analysis and risk assessment should be carried out with regards to each chemical substance and experimental operation on the scale planned and in the context of the laboratory where the procedures will be carried out. Guidelines for carrying out risk assessments and for analyzing the hazards associated with chemicals can be found in references such as Chapter 4 of "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at https://www.nap.edu/catalog/12654/prudent-practices-in-the-laboratory-handling-and-management-of-chemical. See also "Identifying and Evaluating Hazards in Research Laboratories" (American Chemical Society, 2015) which is available via the associated website "Hazard Assessment in Research Laboratories" at https://www.acs.org/about/governance/committees/chemical-safety.html. In the case of this procedure, the risk assessment should include (but not necessarily be limited to) an evaluation of the potential

hazards associated with sodium trifluoromethanesulfinate, trifluoromethanesulfonic anhydride and chlorobenzene. There is no reported data on the toxicity of the product TTST. A well-ventilated hood should be used for the entire procedure.

2. Sodium trifluoromethanesulfinate (95% purity) was purchased from BLD pharm and purified by the following way: 100 grams of sodium trifluoromethanesulfinate was added in 333 mL of ethyl acetate (Note 3) in a 1 L, 3-necked, round-bottomed flask and the mixture was stirred at room temperature (26 °C) for one hour. The suspension was filtered through a thick Celite bed on a Buchner funnel. To avoid breakage of the Celite bed, first it was rinsed with 50 mL of ethyl acetate. The mixture was filtered through the Celite bed and washed with additional 100 mL of ethyl acetate. The combined ethyl acetate solution was transferred to a recovery flask and the solvent was evaporated using a rotary evaporator at 30 °C under the 43 torr vacuum. The resulting residue was dried at 80 °C for three days under the 2.6 torr vacuum. After that, the flask was moved into a glove box and the residue was taken out of the flask and quickly ground with a mortar and returned to the flask and then further dried at 50 °C for two days under the 2.6 torr vacuum. Again, it was ground to make fine powder in a glove box ready for the reaction step. Furthermore, to completely remove moisture, the reagent was added into a 300 mL, 1-necked, round-bottomed flask equipped with phosphorus pentoxide as a drying agent and stirred at 80 °C under 20.3 torr vacuum for 6 hours (Figure 3).

Figure 3. An apparatus of the drying process in which sodium trifluoromethanesulfinate is placed in the 300 mL flask. (The photo was provided by checkers)

3. Ethyl acetate, Super Dehydrated (99.5+% purity) was purchased from FUJIFILM Wako Pure Chemical Corporation and used as received.
4. When fine powered sodium trifluoromethanesulfinate of high purity is available, it can be used directly for the reaction without the purification and grinding processes.
5. Sodium trifluoromethanesulfinate is hygroscopic. If dry, fine powdered sodium trifluoromethanesulfinate is put into the flask under completely dry conditions like in a glove box, the drying process in a flask in vacuum is not needed.
6. Chlorobenzene purchased from Oakwood Chemicals was distilled at atmospheric pressure (the first fraction was removed) and kept on 3Å molecular sieves.
7. Triflic anhydride (**3**) (purity >99%) was purchased from Oakwood Chemicals and used without further purification.
8. Although the theoretical amount of triflic anhydride (**3**) was 1.0 equiv, 1.4 equiv amounts of **3** were used, because some of sodium trifluoromethanesulfinate (**2**) left unreacted when less amounts of **3** (<1.4 equiv) were used, while some of **3** left unreacted when more amounts of **3** (>1.4 equiv) were used.

9. Since the reaction is exothermic, it is necessary to control the reaction temperature not to go higher than about 80 °C.
10. Due to the high viscosity of the reaction mixture, it is needed to use a mechanical stirrer.
11. A Snyder distillation column (total height 35 cm) was used. See Figure 1C.
12. Chilled water using an ice bath was flowed through the condenser.
13. The receiver, a 20 mL, 1-necked, recovery flask was cooled in an ice bath.
14. The distillation should be carefully conducted in a fume hood. A small amount of CF_3SSCF_3 was detected in the first part of the distillate from the crude product by ^{19}F NMR. It was reported that CF_3SSCF_3 (b.p. 34.6 °C) is toxic (LC_{50} 200 ppm/min from W. A. Sheppard, C. M. Sharts, *Organic Fluorine Chemistry*, p. 452, Benjamin, 1969).
15. The purity (86%) of TTST (M.W. 234.13) was determined by quantitative ^{19}F NMR analysis of 43.2 mg of the distilled product in $CDCl_3$ solvent using 58.8 mg (purity 98%, 0.326 mmol) of 4-chlorobenzotrifluoride (M.W. 180.55) as an internal reference. The NMR integration ratio of TTST/the reference was 0.50. The calculation was shown in qNMR file. The main impurity was chlorobenzene.
16. The authors used this TTST, obtained by the first fractional distillation, for the trifluoromethylthiolations mentioned in the Discussion Section below.
17. The purity (95%) of TTST (MW 234.13) was determined by quantitative ^{19}F NMR analysis of 40.3 mg of the distilled product in $CDCl_3$ solvent using 55.8 mg (purity 98%, 0.309 mmol) of 4-chlorobenzotrifluoride (M.W. 180.55) as an internal reference. The NMR integration ratio of TTST/the reference was 0.54. The calculation was shown in qNMR file. The main impurity was chlorobenzene.
18. No obvious decomposition of TTST was observed (<1%) after heating in toluene-d_8 at 130 °C for 15 h.
19. TTST: ^{19}F NMR (376 MHz, $CDCl_3$) δ –36.58 (quartet, J = 5.2 Hz, 3F), –77.25 (quartet, J = 5.2 Hz, 3F); ^{13}C NMR (150 MHz, $CDCl_3$) δ 126.1 (quartet, J = 316.7 Hz), 119.2 (quartet, J = 328.1 Hz).

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The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous

materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at https://nap.nationalacademies.org/catalog/12654/prudent-practices-in-the-laboratory-handling-and-management-of-chemical). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

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Discussion

Fluorine-containing compounds have been attracting much attention across various fields such as pharmaceuticals, agrochemicals, and materials science owing to their unique properties.[2] Among the fluorinated functional groups, the trifluoromethythio group (CF_3S) is gaining increasing interest due to its highest lipophilicity in addition to the high electronegativity.[3]

The ideal method for the preparation of CF_3S compounds is the direct substitution of C-H sites with electrophilic reactions. Early electrophilic trifluoromethylthiolating reagents were CF_3SSCF_3[4] and CF_3SCl,[5] which were toxic gases. Easy-to-handle second generation electrophilic trifluoromethythiolating reagents **I** – **XIII** have been developed by many chemists as shown in Figure 4. Although these advancements have led to

safer, more manageable CF_3S reagents, challenges related to reliance on expensive or hazardous precursors, multistep synthesis processes, narrow applications, or low-atom economy remain.

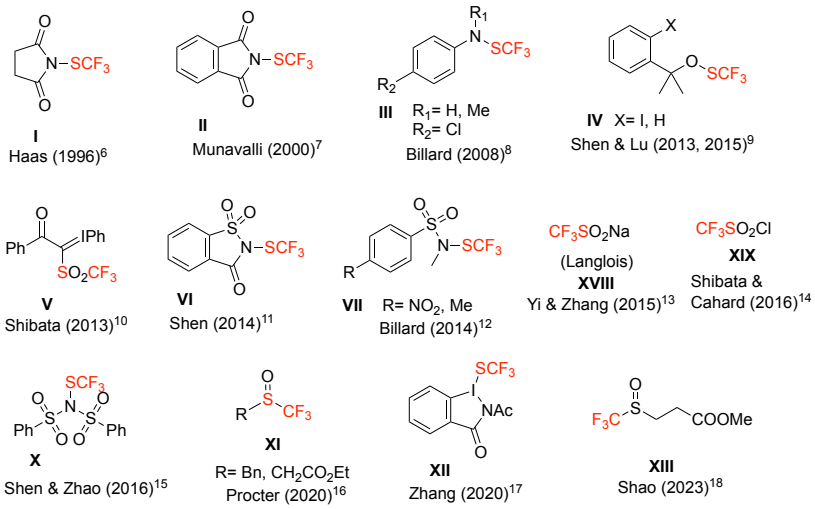
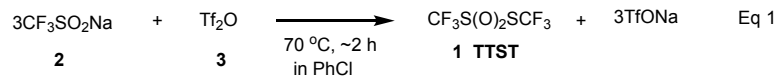
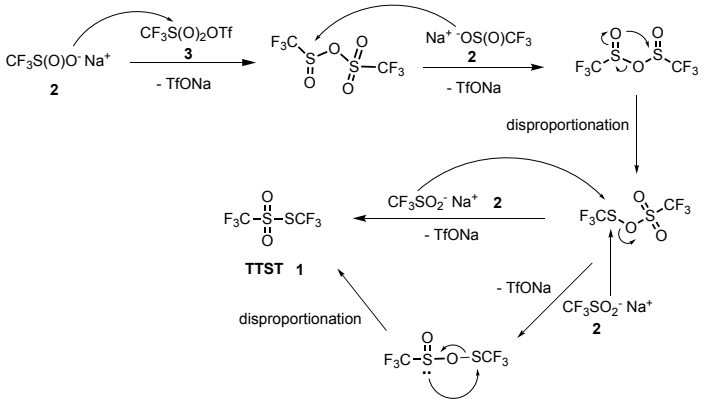


Figure 4. Easy-to-handle electrophilic trifluoromethylthiolating agents

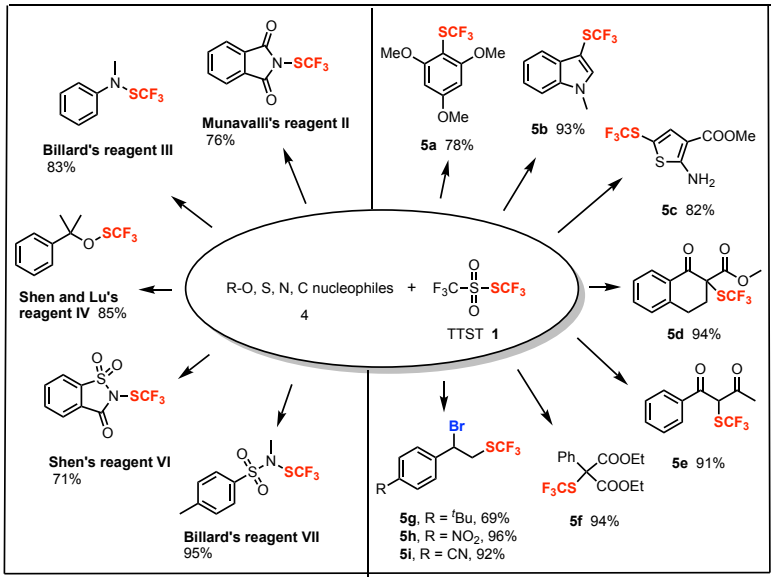
We have recently reported the thermally stable, easy-to-handle, and highly versatile and atom-economical CF_3S reagent, *S*-trifluoromethyl trifluoromethanesulfonothioate (TTST **1**), which can be prepared by a one-step from easily available, inexpensive CF_3SO_2Na **2** (Langlois reagent) and triflic anhydride **3** (Eq. 1).[19] The detailed procedure of the preparation of **1** is described in this paper. The reaction mechanism proposed is shown in Scheme 1.[19]





Scheme 1. Proposed reaction mechanism for the preparation of TTST

As mentioned below, TTST is a powerful electrophilic CF_3S^+ reagent. In addition, TTST can provide two equimolar nucleophilic CF_3S^- anions species and both $CF_3S\bullet$ and $CF_3\bullet$ radical species depending on the reaction conditions. Thus, TTST is highly versatile and atom-economical.

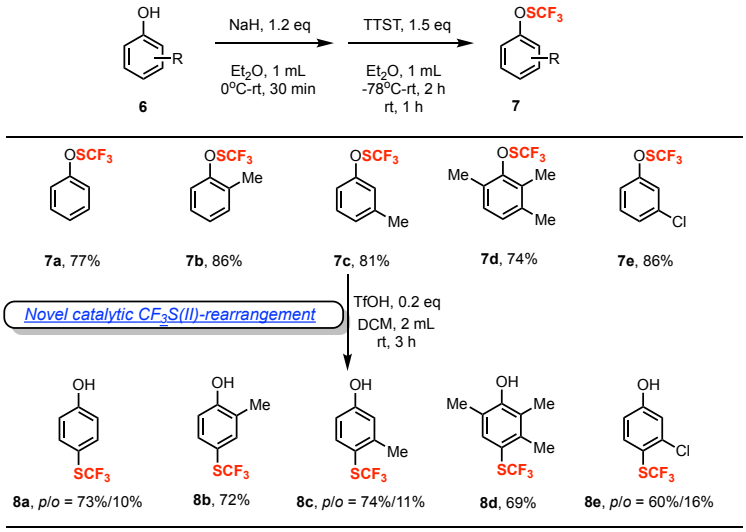


Scheme 2. Trifluoromethylthiolations of electron-rich (hetero)aromatics, carbanions, and olefins with TTST (right side) and preparation of reported electrophilic CF_3S reagents with TTST (left)

As shown in Scheme 2 (right side),[20] TTST reacted with electron-rich (hetero)aromatic compounds under mild conditions to give trifluoromethylthiolated compounds **5a-c** in high yields. Active methylene compounds such as keto esters, diketones, and malonates ~~were~~ reacted with TTST under basic condition to give CF_3S products **5d-f** in high yields. Alkenes such as styrene reacted with TTST in the presence of LiBr to afford bromo-trifluoromethylthiolated products **5g-i** in high yields.

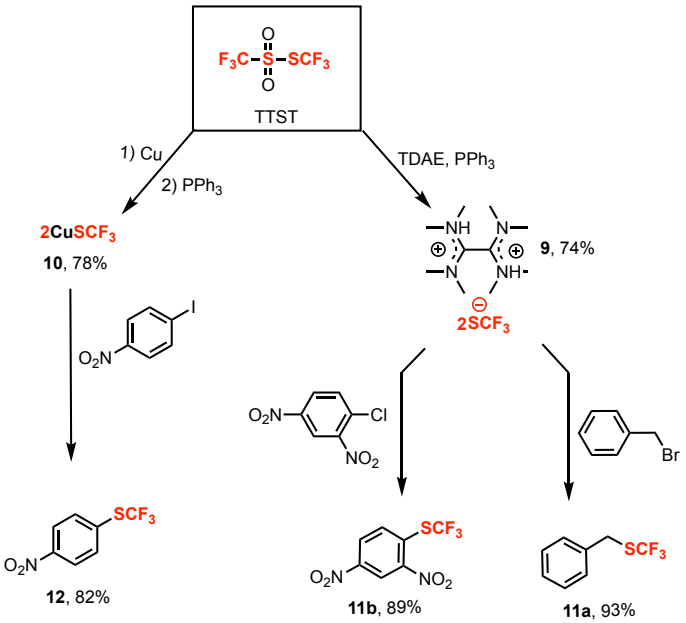
As shown in Scheme 2 (left side), many reported electrophilic trifluoromethylthiolating reagents could be prepared in high yields by a one-step using TTST.[19] Thus, Munavali's reagent **II** was prepared in 76% yield from sodium phthalimide. Billard's reagent **III** was prepared in 83% yield from the aniline derivative. Shen and Zhao's reagent **IV** was prepared in 85% yield from the alcohol derivative. Shen's reagent **VI** was prepared in 71% yield from sodium salt of Saccharin. Billard's reagent VII was prepared in 95% yield from the corresponding sulfonamide derivative. These indicated the higher reactivity of TTST than the reported electrophilic CF_3S reagents. Their original preparative methods required a toxic gas (CF_3SCl), an expensive reagent such as $AgSCF_3$, or potentially explosive Et_2NSF_3 (DAST).

Due to its high reactivity towards heteroatom sites, TTST facilitated the easy formation of the almost unknown $ArOSCF_3$ **7** by reacting with the corresponding phenoxides, resulting in high yields of products (Scheme 3).[19] Furthermore, in the presence of a catalytic amount of triflic acid, $ArOSCF_3$ underwent a new type of Fries-type rearrangement, with the *para* isomer being the major products **8** (Scheme 3).[19]



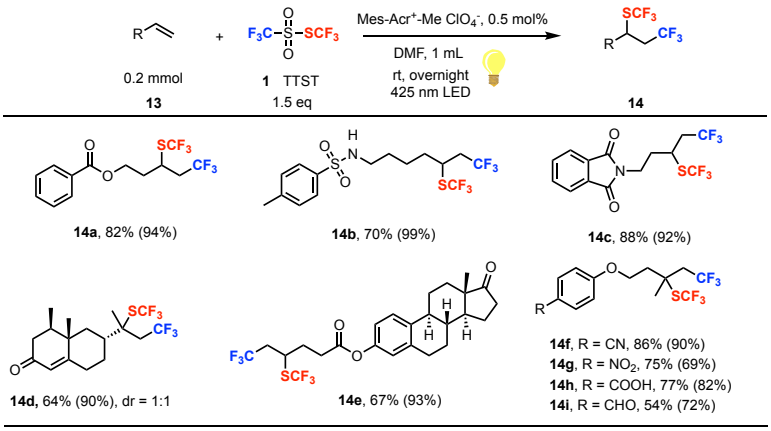
Scheme 3. Preparation of $ArOSCF_3$ and their acid-catalyzed CF_3S^{II}-rearrangement

In addition to the electrophilic reactions of TTST, we showcased TTST's high atom efficiency and versatility as a nucleophilic CF_3S reagent.[19] This was exemplified by employing tetrakis(dimethylamino)ethylene (TDAE) and copper powder as electron donors in the presence of PPh_3, resulting in the production of two equivalent nucleophilic CF_3S anion species **9** and **10** and the eventual substitution of halogens with nucleophilic SCF_3 in substrates such as benzyl bromide, 2,4-dinitrochlorobenzene and *p*-iodonitrobenzene, achieving excellent yields of the CF_3S products **11a**,**b** and **12** (Scheme 4).[19]



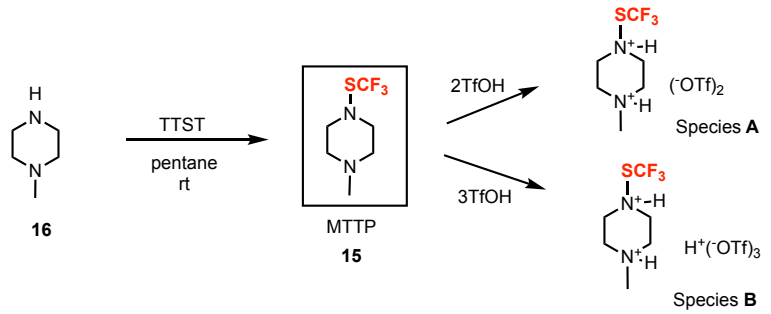
Scheme 4. Nucleophilic reactions using TTST as two CF_3S anions source

We also demonstrated the high atom efficiency of TTST by introducing CF_3 and SCF_3 groups to alkenes simultaneously under mild, metal-free conditions, facilitated by the photochemical activity of Mes-Acr$^+$-Me ClO_4.[19] This high atom economy ensures that most atoms from the TTST are incorporated into the difunctionalized products, minimizing waste. Previous reports indicated that such processes required both CF_3S and CF_3 reagents[21,22] or transition metal catalysis in the presence of an oxidizer ($K_2S_2O_8$) and a ligand (PPh_3).[23] Our method can be adapted for various alkenes, achieving excellent yields without extra additives (Scheme 5).



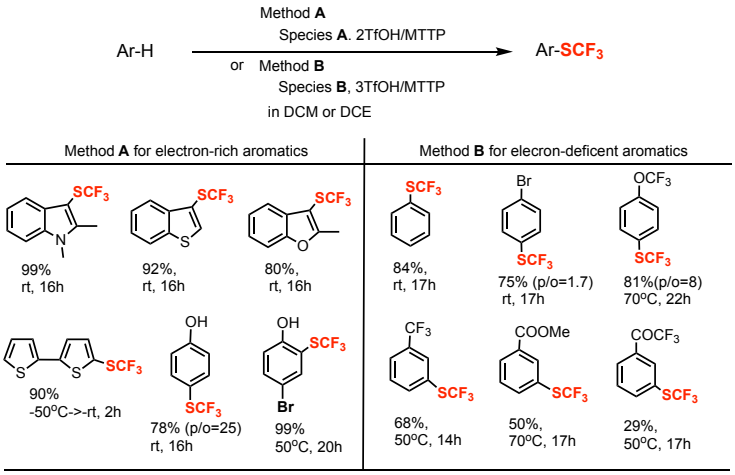
Scheme 5. Photocatalytic radical trifluoromethyl-trifluoromethylthiolation of alkenes with TTST

Electrophilic trifluoromethylthiolation of electron-rich aromatic compounds such as indoles and other strongly electron-donating group(s)-substituted aromatics have been reported with many electrophilic trifluoromethylthiolating agents. However, non-activated and deactivated aromatics were very hard to be trifluoromethylthiolated with the conventional electrophilic reagents including TTST. Just recently, using TTST, we have developed easy-to-handle 1-methyl-4-(trifluoromethylthio)piperazine (MTTP, **15**) as a highly useful electrophilic trifluoromethylthiolating agent for non- and deactivated aromatics.[24] MTTP was synthesized in high yield in one step from the reaction of *N*-methylpiperazine (**16**) with TTST (Scheme 6).



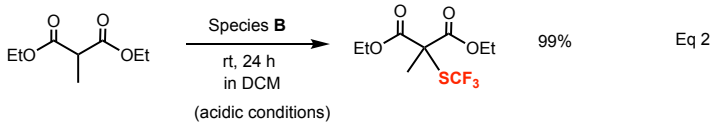
Scheme 6. Synthesis of MTTP and its reactive species A and B with TfOH

Surprisingly, we found that MTTP provided two kinds of reactive species **A** and **B** with two and three equivalent amounts of triflic acid (TfOH), respectively (Scheme 6). Species **A** is a potent CF_3S^+ reagent which can react with electron-rich aromatics in high yields, while **B** is an unprecedentedly powerful CF_3S^+ reagent that made possible the challenging electrophilic trifluoromethylthiolation of electron-deficient aromatic system, as illustrated in Scheme 7.[24]



Scheme 7. Trifluoromethylthiolations of aromatics with reactive species A and B

In addition, the highly powerful species **B** made possible the uncommon trifluoromethylthiolation of active methylene compounds under acidic conditions, typified in Eq. 2.[24]



Thus, in addition to the simple one-step preparation of TTST, this reagent is widely applicable and highly atom-economic as a source of one CF_3S^+ cation, *two* CF_3S^- anions, or both $CF_3S\bullet$ and $CF_3\bullet$ radical sources. Further, many previously reported CF_3S reagents can be prepared by an easy, one-step preparation using TTST. Furthermore, TTST has provided a new highly

powerful CF_3S^+ reagent, MTTP, which, in combination with TfOH, has made possible the hard-to-do trifluoromethylthiolation of electron-deficient aromatics. Hence, TTST is expected to be an attractive and practical reagent for the preparation of various CF_3S-containing compounds useful for medicines, agrochemicals, and others.

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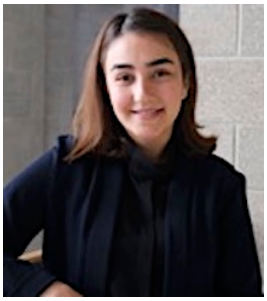
Appendix
Chemical Abstracts Nomenclature (Registry Number)

Sodium trifluoromethanesulfinate (2926-29-6)
Trifluoromethanesulfonic anhydride (358-23-6)
Chlorobenzene (108-90-7)



Seyedesahar Miraghaee earned her M.S. degree in Organic Chemistry from Shahid Beheshti University in Iran in 2018. She continued her graduate studies at the University of Louisville under the supervision of Prof. Gerald B. Hammond, specializing in Fluorine Chemistry. Currently, she is pursuing her Ph.D. at Indiana University Bloomington.

Teruo Umemoto received Ph.D. from Osaka University, Japan in 1976. He started fluorine research at Sagami Institute in 1978. After he worked for the Sagami and then for Daikin in Japan (1976-1998), he continued fluorine research at IM&T company in USA in 1999-2011 while managing the company. In 2013, Shanghai Institute (SIOC) invited him as a Visiting Professor and then he did research at Jiuzhou Pharma in China. In 2019, he joined Prof. Hammond's lab, University of Louisville, USA. He was given ACS Award for Creative Work in Fluorine Chemistry in 2014. He now continues research at the University of Florida.

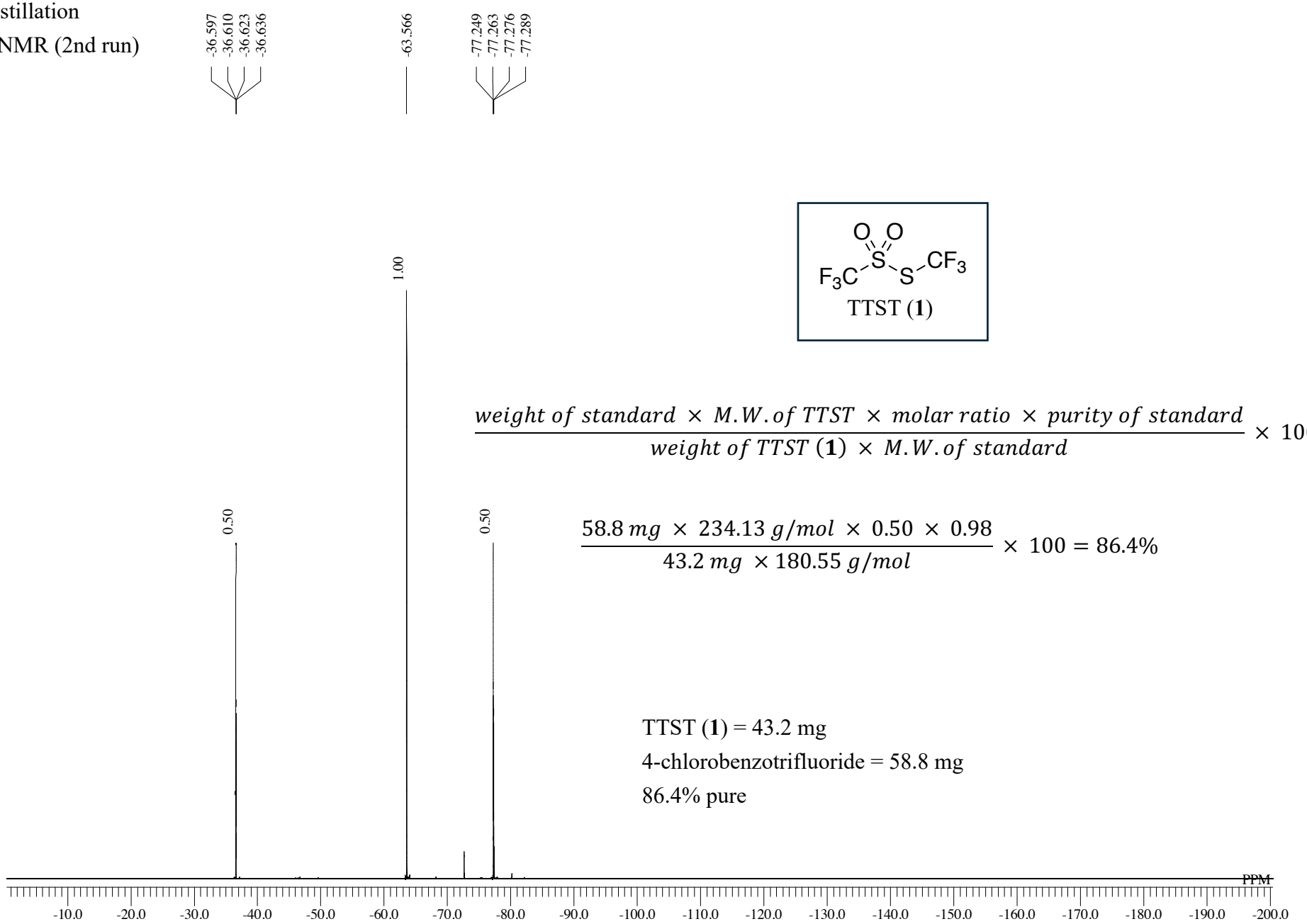
Hammond received his B.Sc. in chemistry from the Pontificia Universidad Católica del Perú and his PhD from the University of Birmingham, England in 1985. After an academic stint at the University of Massachusetts Dartmouth, Professor Hammond moved to the University of Louisville in 2004, where he is currently the Endowed Chair in Organic Chemistry. Dr. Hammond was program director at the NSF, held visiting professorships at the universities of Heidelberg, Harvard, Okayama, and Valencia, among others. He is Fellow of the ACS, was chair of the Fluorine Division, and, in 2019, was awarded the Distinguished Service Award in Fluorine Chemistry.

Keita Moriyasu was born in Okayama, Japan in 2001. He received his B.S. in 2024 from Tohoku university (Japan) under the supervision of Prof. Hidetoshi Tokuyama. He is currently a master course student and performs his studies on the development of aerobic oxidation reactions using iron catalysts and its application to total synthesis of natural products.

Hirofumi Ueda received his Ph.D. (2010) from the Tohoku University under the direction of Professor Hidetoshi Tokuyama. After receiving the Ph.D., he started soon his academic carrier as an Assistant Professor in the same group. In 2018, he was promoted to lecturer and in 2023 to his current position of associate professor. He spent 7 months in 2019 at the University of California, Berkeley as a visiting scholar with Prof. Richmond Sarpong. His research interests center on the development of novel synthetic methodology involving oxidation, and applications to the synthesis of complex alkaloids and nitrogen-containing molecules.

1st distillation

^{19}F-qNMR (2nd run)



TTST (**1**)

$$\frac{weight\ of\ standard\ \times\ M.W.of\ TTST\ \times\ molar\ ratio\ \times\ purity\ of\ standard}{weight\ of\ TTST\ (\mathbf{1})\ \times\ M.W.of\ standard}\ \times\ 100$$

$$\frac{58.8\ mg\ \times\ 234.13\ g/mol\ \times\ 0.50\ \times\ 0.98}{43.2\ mg\ \times 180.55\ g/mol}\ \times\ 100 = 86.4\%$$

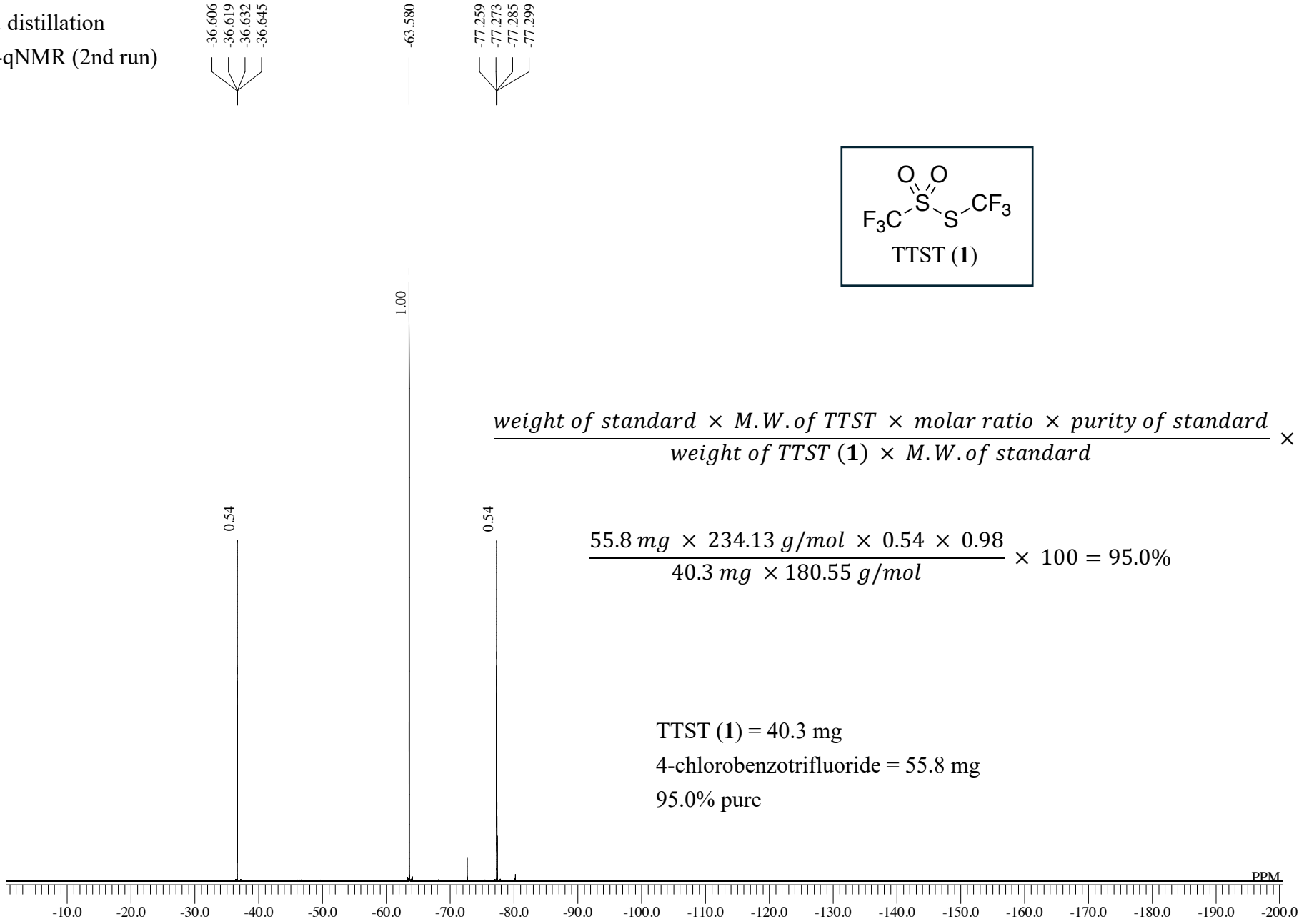
TTST (**1**) = 43.2 mg

4-chlorobenzotrifluoride = 58.8 mg

86.4% pure

2nd distillation

^{19}F-qNMR (2nd run)



TTST (**1**)

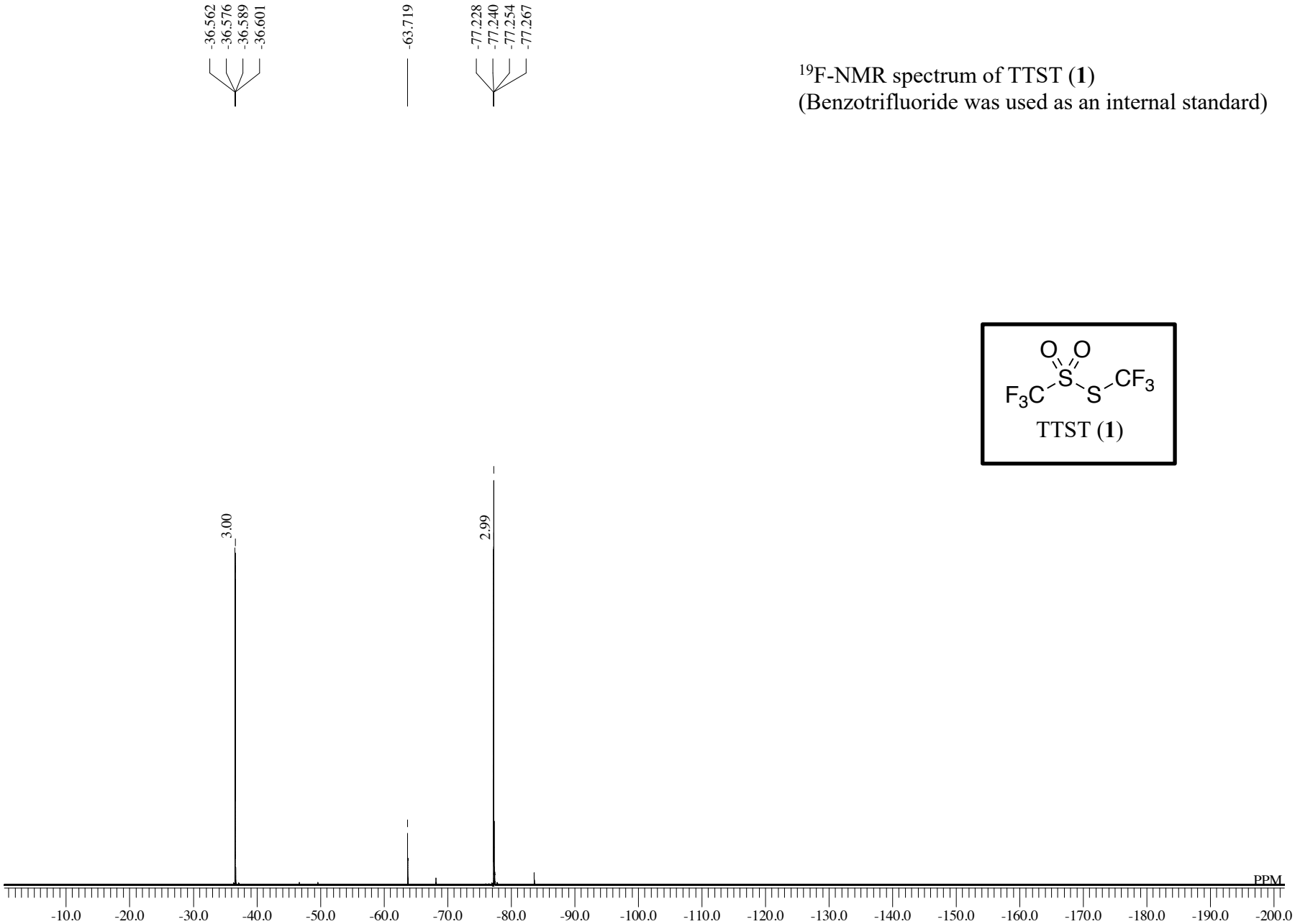
$$\frac{weight\ of\ standard\ \times\ M.W.of\ TTST\ \times\ molar\ ratio\ \times\ purity\ of\ standard}{weight\ of\ TTST\ (\mathbf{1})\ \times\ M.W.of\ standard}\ \times\ 100$$

$$\frac{55.8\ mg\ \times\ 234.13\ g/mol\ \times\ 0.54\ \times\ 0.98}{40.3\ mg\ \times 180.55\ g/mol}\ \times\ 100 = 95.0\%$$

TTST (**1**) = 40.3 mg

4-chlorobenzotrifluoride = 55.8 mg

95.0% pure



^{19}F-NMR spectrum of TTST (**1**)
(Benzotrifluoride was used as an internal standard)

TTST (**1**)

^{13}C-NMR spectrum of TTST (**1**)