

University of Louisville  
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# Development and Applications of Novel and Practical Fluorination Reagents

### ABSTRACT:

The fluorine (F) atom has distinctive properties such as the highest electronegativity, small size, low polarizability, and strong C–F bond strength. Not surprisingly, fluorinated organic compounds have garnered significant attention in the pharmaceutical,<sup>1</sup> agrochemical,<sup>2</sup> and material fields.<sup>3</sup> Since organofluorides are very rare in nature, we need fluorination reagents to help us transfer fluorine into the organic molecules. In past decades, a vast number of fluorination reagents have been developed and many of them are commercially available now.<sup>4,5</sup> However, there is still much room for the improvement of these reagents. Our target is to develop novel and practical fluorination reagents to make up for the shortcomings of the currently popular ones.

We have developed a novel fluorinating agent, *N*-fluoro-*N*-(*tert*-butyl)-*tert*-butanesulfonamide (NFBB)<sup>6</sup>, which was prepared in excellent yield using *N*-fluorobenzenesulfonimide (NFSI) or F<sub>2</sub>/N<sub>2</sub> and was purified by simple distillation. Its easy preparation and purification made NFBB a reagent suitable for large scale production. NFBB provided unprecedented high-yielding fluorination of highly basic organolithium species, which has been an unsolved problem for a long time. With NFBB, a conceptually new base-catalyzed, self-sustaining fluorination of active methylene compounds was discovered. NFBB also fluorinated other carbanions such as Grignard reagents and enolates in good yields. NFBB is expected to play an important role in the preparation of many useful fluorinated compounds and it is now commercialized by Tokyo Chemical Industry Co., Ltd. (TCI).

The trifluoromethylthio (CF<sub>3</sub>S) group has the highest lipophilicity among the common fluorine-containing moieties. Therefore, introducing a fluorine atom or a CF<sub>3</sub>S group into a bioactive molecule could produce dramatic effects on its physical, chemical, and biological properties. We have developed a novel trifluoromethylthiolating reagent, *S*-trifluoromethyl trifluoromethanesulfonothioate (TTST).<sup>7</sup> Unlike conventional CF<sub>3</sub>S reagents, TTST can be easily prepared in one step from commercially inexpensive sodium trifluoromethanesulfinate and triflic anhydride. TTST is a highly reactive, versatile, and atom-efficient reagent that can generate CF<sub>3</sub>S<sup>+</sup>, CF<sub>3</sub>S<sup>-</sup>, and CF<sub>3</sub>S<sup>•</sup>/CF<sub>3</sub><sup>•</sup> reactive species. Many kinds of C, O, S, and *N*-nucleophiles were trifluoromethylthiolated by TTST in high yields. Notably, TTST reacted with sodium phenoxides to provide a new series of hitherto difficult to prepare aryl trifluoromethanesulfenates that were found to undergo a novel acid-catalyzed CF<sub>3</sub>S(II)-rearrangement reaction. By means of Cu or TDAE/Ph<sub>3</sub>P combination, TTST generated two CF<sub>3</sub>S anion species that are useful to prepare trifluoromethylthio compounds in high atom-economy fashion. Photocatalytic radical trifluoromethyl-trifluoromethylthiolation of alkenes with only one equivalent of TTST was achieved in high yield as well as in high atom-efficiency. TTST is expected to be a compelling alternative to the current CF<sub>3</sub>S reagents in terms of preparation, reactivity, and practicality.

### REFERENCES:

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