

A novel method for the preparation of ^{18}F -labeled α -SCF₃ carbonyl compounds

As fluorine-18 (^{18}F) is the most commonly used radioisotope in positron emission tomography (PET), significant efforts have been devoted to the exploration of efficient methods for the incorporation of ^{18}F into small and biological molecules. However, the studies on this ^{18}F -radiochemistry have so far been mainly limited to [^{18}F]fluorination and [^{18}F]trifluoromethylation. Despite the fact that trifluoromethylthio group (CF_3S) is a valuable functionality in medicinal chemistry and drug discovery, the installation of [^{18}F]CF₃S moiety has never been fully realized and thus represents a significant challenge. Recently a difluorocarbene-derived one-step [^{18}F]trifluoromethylthiolation was discovered as one of the first examples for [^{18}F]trifluoromethylthiolation despite the fact that significant accomplishments have been made for non-radioactive trifluoromethylthiolation. While the novelty and utility of difluorocarbene in the ^{18}F -trifluoromethylthiolation have been demonstrated in this work, the characteristics of these radiofluorination reactions, including the underlying mechanism and interaction with transition metals, remain elusive and represent a major roadblock to further advance these reactions into the radiolabeling of SCF₃-containing pharmaceuticals, for example, Cefazaflur.

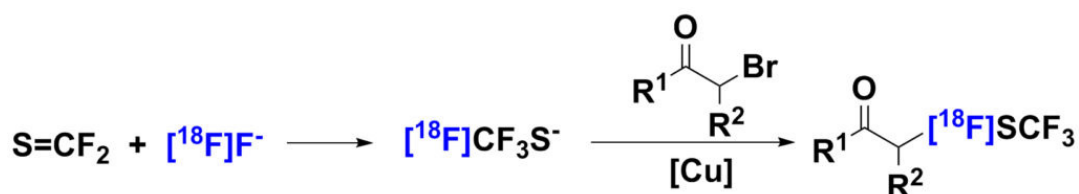


Fig. 1. An unconventional mechanistic insight on SCF₃ formation from difluorocarbene and application to ^{18}F -labeled α -SCF₃ carbonyl compounds.

Herein we report an unprecedented mechanistic observation of trifluoromethylthio formation among difluorocarbene, sulfur and fluoride, and the subsequent interactions between ensuing SCF₃ anions and transition metals (Fig. 1). Supported by experimental and theoretical studies, this work overrides our putative and long-standing interpretation of trifluoromethylthio group formation from difluorocarbene, and leads us to discover a new class of trifluoromethylthiolation for α -bromo carbonyl compounds in the presence of copper complex. As proof of concept, we demonstrate a general and practical copper-mediated radiosynthesis of ^{18}F -labeled SCF₃ carbonyl compounds with broad substrate scope and functional group compatibility, which is otherwise hardly achievable from traditional methods.

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