

# Metal-free trifluoromethylthiolation of arenediazonium salts

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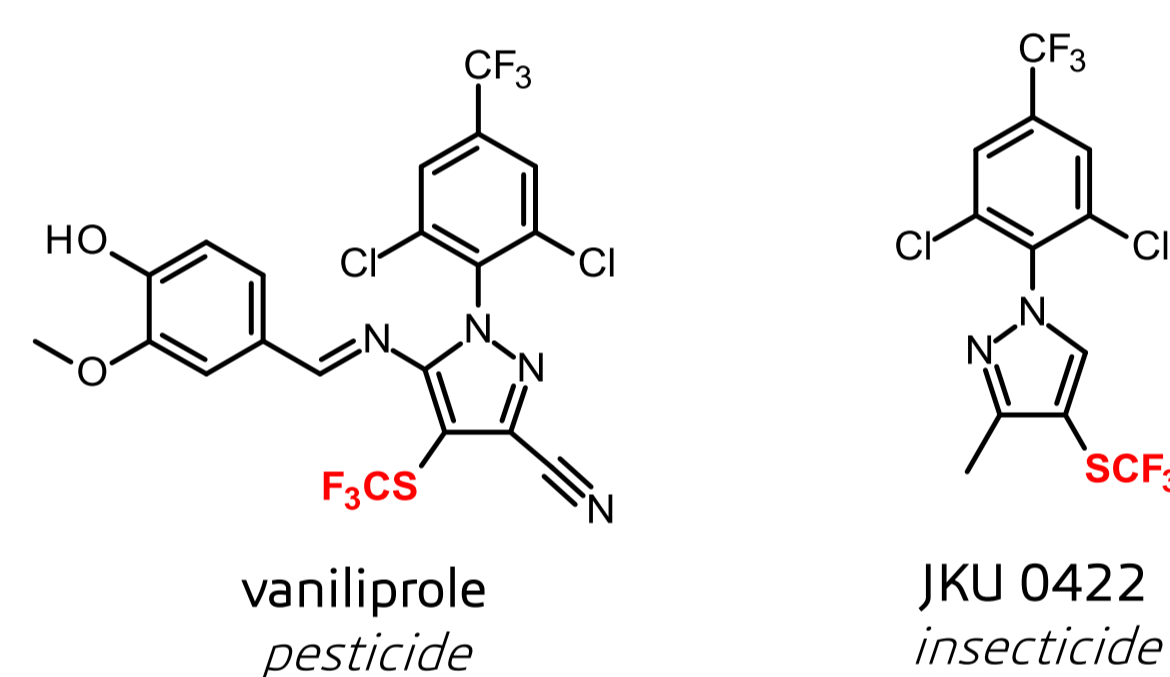
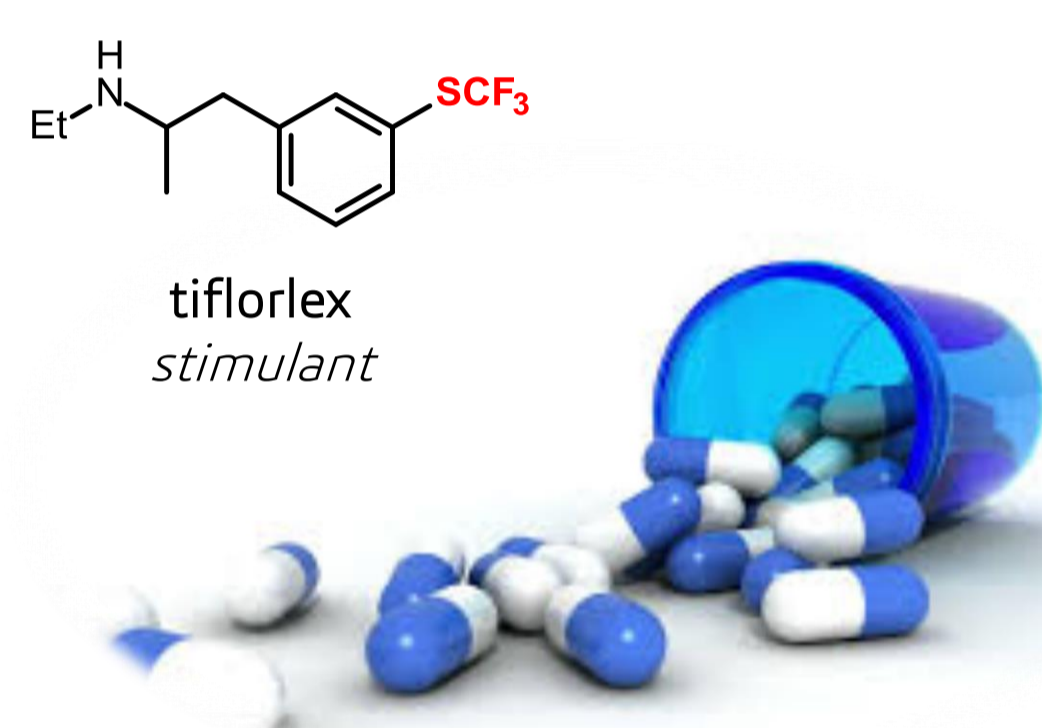
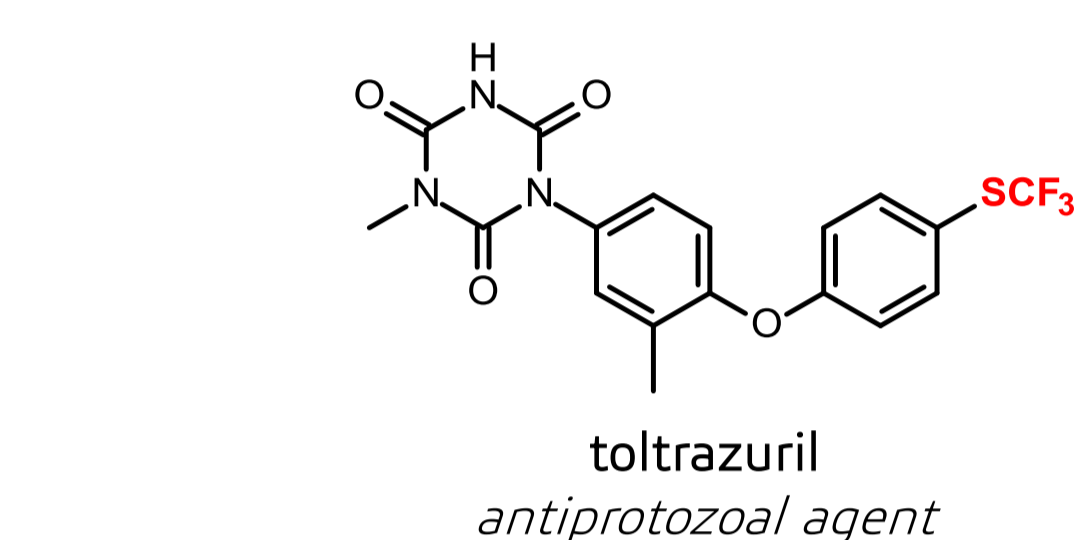
## Abstract

Fluorine-containing molecules are central functionalities imparting unique chemical and physical properties, such as improved solubility, bioavailability and adhesive properties compared to the non-fluorinated counterparts.<sup>[1]</sup> New and efficient methods for the introduction of fluorine moieties are constantly sought after. Herein, a metal-free entry to the substrate class of trifluoromethyl thioethers is reported starting from widely available arenediazonium salts and commercial  $\text{Me}_4\text{N}^+\text{SCF}_3^-$  under mild conditions.

## Importance of Trifluoromethylthio Groups

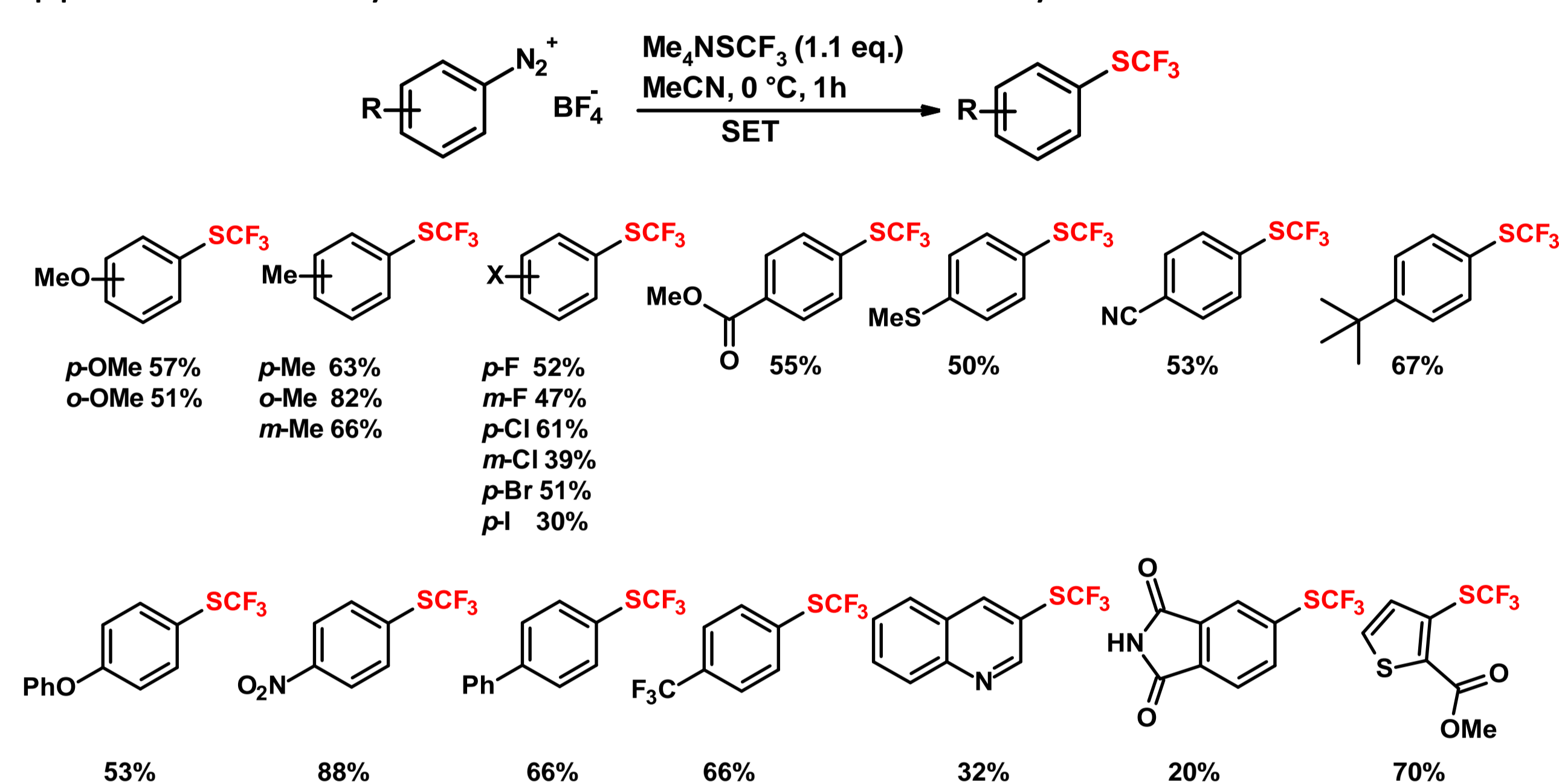
About 25% of all pharmaceuticals and 30-40% of agrochemicals on the market contain fluorine. Therefore, the introduction of fluorinated groups has become of great interest in drug-discovery. In particular  $\text{SCF}_3$  groups induce even higher lipophilicity and membrane permeability compared to their  $\text{CF}_3$  analogues.<sup>[2]</sup>

Traditional strategies for the preparation of trifluoromethylthiolated compounds are based on waste-intensive, multistep syntheses involving halogen-fluorine exchange reactions.<sup>[3]</sup>



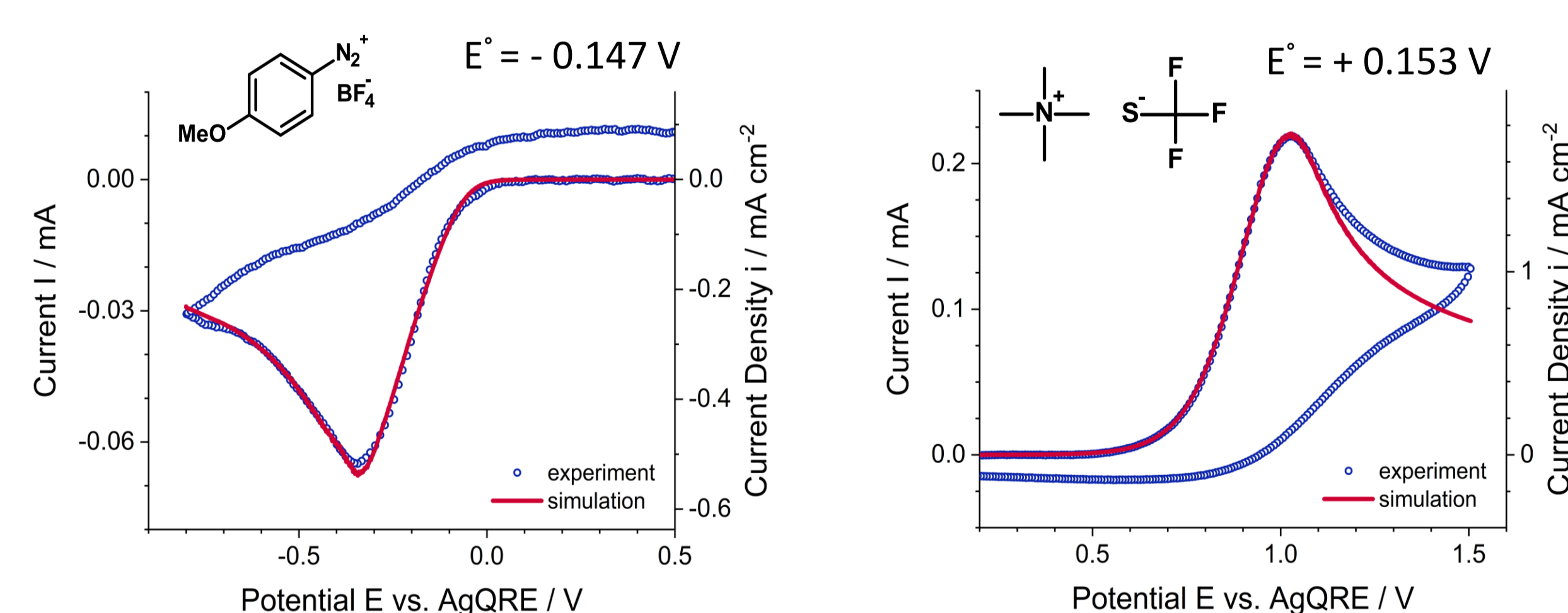
## Metal-free Trifluoromethylthiolation

Still, for pharmaceutical and agrochemical applications, it would be best if heavy metals could be left out altogether. Herein, we present a metal-free approach for the synthesis of valuable trifluoromethylthioethers.<sup>[5]</sup>



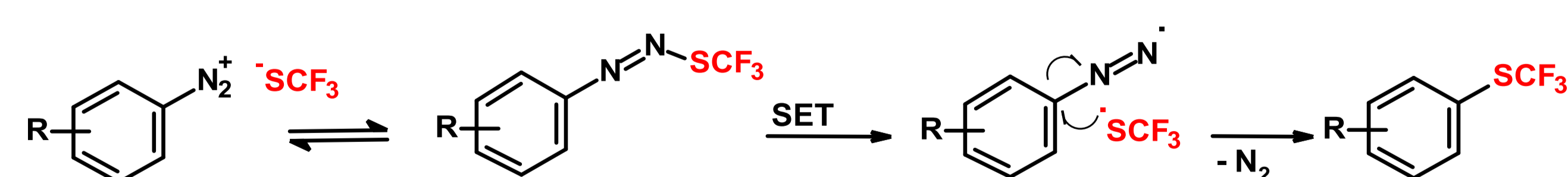
## Study of the thermodynamics

To highlight the mechanism we addressed the thermodynamics of this reaction by cyclic voltammetry studies. Cyclovoltammetric curves of 4-methoxybenzenediazonium tetrafluoroborate and  $\text{Me}_4\text{NSCF}_3$  show a SET process in both cases. Using these experimental data, the activation energy was calculated ( $\Delta G = -zFE = 28.9 \text{ kJ/mol}$ ) showing that this barrier can be easily crossed in absence of metals or radical initiators.



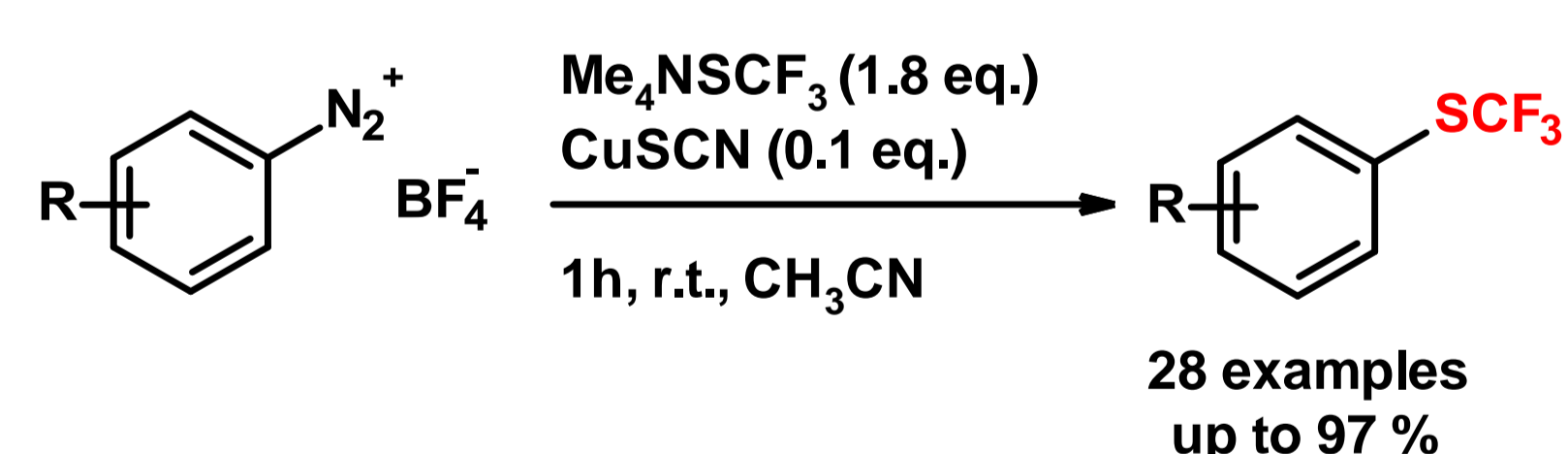
## Proposed mechanism

Based on these findings, we proposed a radical mechanism that consists of reduction of the diazonium species by the  $\text{SCF}_3^-$  anion, followed by dediazotization and subsequent recombination of two radical species.



## Sandmeyer-type Trifluoromethylthiolation

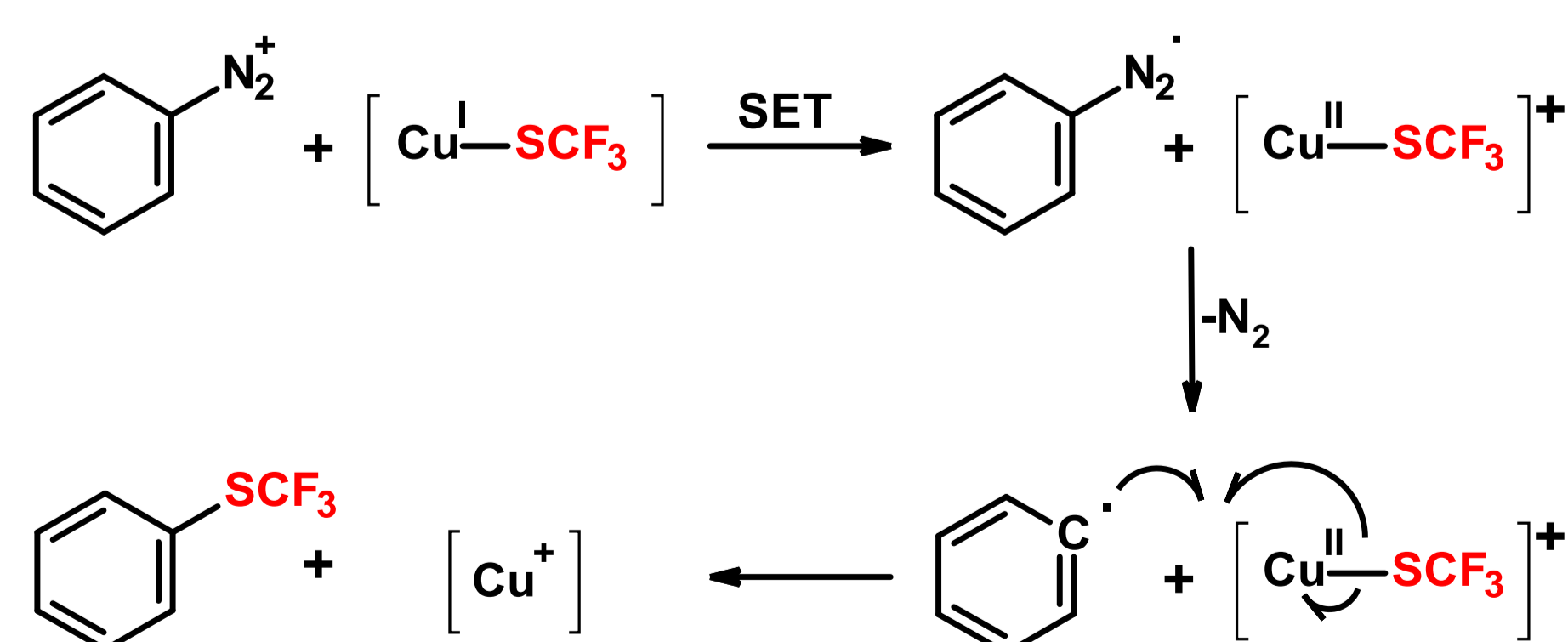
In the last years, several methods were developed to introduce the  $\text{SCF}_3$  group as a whole, but a particularly straightforward approach is the Sandmeyer-type copper-catalyzed trifluoromethylthiolation of arenediazonium salts using  $\text{Me}_4\text{NSCF}_3$  as the  $\text{SCF}_3$  source.<sup>[4]</sup>



This approach is remarkable in that it is one of the few processes in which only substoichiometric amounts of copper are required to achieve high yields.

## Proposed mechanism

The reaction follows a classical Sandmeyer-type single-electron-transfer (SET) pathway involving aryl radicals.



## Conclusion

Overall, this study demonstrates that it is possible to perform trifluoromethylthiolations of arene electrophiles in the absence of heavy metal mediators with mild conditions and short reaction times.

## References and Further Reading (see also [www.ruhr-uni-bochum.de/oc1/goossen](http://www.ruhr-uni-bochum.de/oc1/goossen))

- [1] I. Ojima (Ed.), *Fluorine in Medicinal Chemistry and Chemical Biology*, Wiley, Chichester, 2009.
- [2] C. Hansch, A. Leo, S.H. Unger, K.H. Kim, D. Nikaitani, E.J. Lien, *J. Med. Chem.*, **1973**, 16, 1207-1216.
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