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## Abstract

Fluorine containing residues are central functionalities imparting unique chemical and physical properties, such as improved metabolic stability, better receptor binding selectivity and higher lipophilicity compared to their non-fluorinated analogs. New, efficient methods for the installation of fluorinated groups into functionalized molecules are constantly sought. In this context, we reported copper mediated Sandmeyer-type fluoroalkyl(thiol)ations which allow straightforward syntheses of fluoroalkyl(thiol)ated arenes from the corresponding aromatic amines under mild conditions. Furthermore, the reaction concept was extended to the synthesis of alkylfluoromethyl thioethers starting directly from alkyl electrophiles. Thus, fluoroalkylated compounds are conveniently accessible in high yields from broadly available starting materials and the inexpensive tri/difluoromethylating agents  $\text{TMSCF}_2\text{Y}$  ( $\text{Y} = \text{F}$  or  $\text{H}$ ).

## Introduction of Di- and Trifluoromethyl Groups

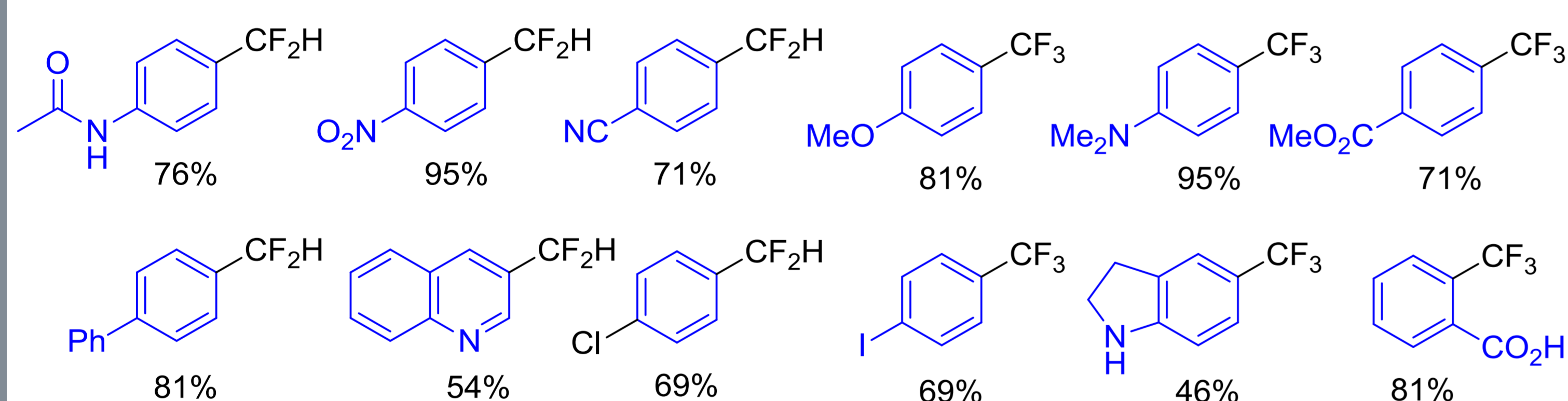
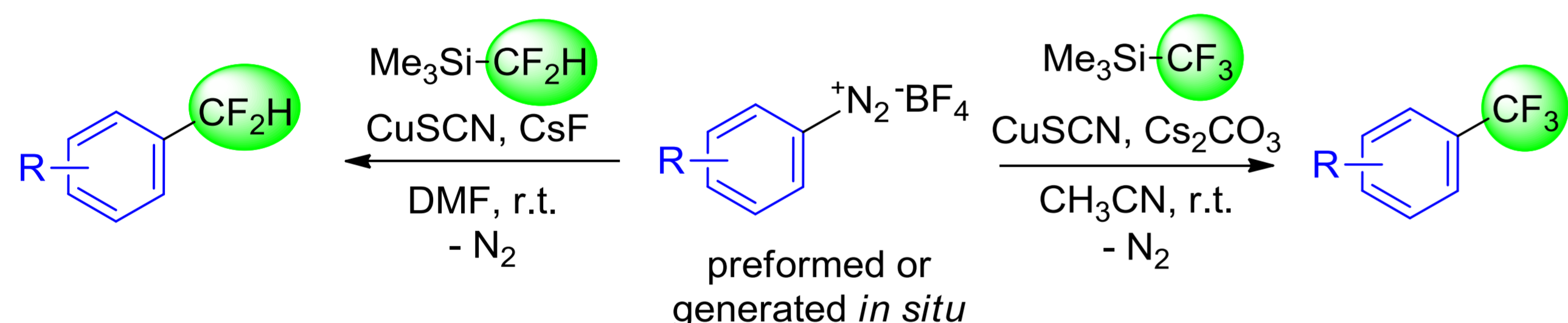
### Significance of Fluorinated Compounds

About 25% of all pharmaceuticals and about 30-40% of agrochemicals on the market contain fluorine. Thus, so-called "fluorine scans", i.e., systematic derivatizations through the introduction of fluorinated groups, have become standard procedures in drug discovery.

In particular  $\text{CF}_3$  or  $\text{CF}_2\text{H}$  moieties are of key interest, since they serve as lipophilic and membrane permeability-enhancing isosteric and isopolar analogs to e.g.  $\text{CH}_3$ ,  $\text{C}=\text{O}$  or  $\text{OH}$  and  $\text{SH}$  groups, known as the bioisostery concept.

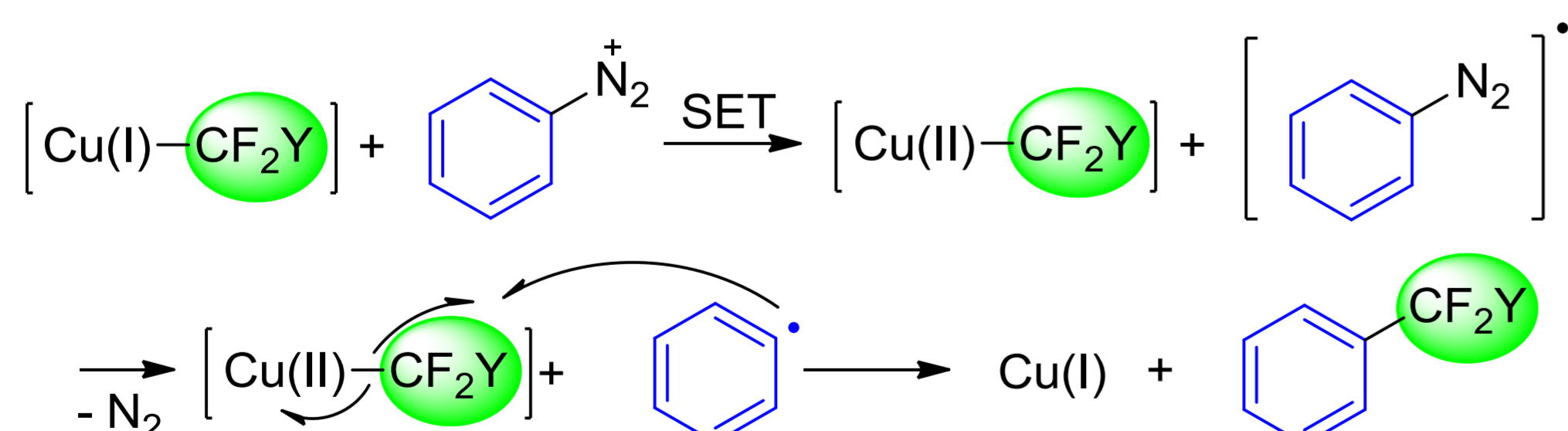
### Sandmeyer Di-/Trifluoromethylations<sup>[1]</sup>

In continuation of our previous work on late-stage trifluoromethylations, we developed sustainable Sandmeyer-type di- and trifluoromethylation reactions. In these processes, the actual fluorinating reagent, a fluoromethyl-copper complex, is formed *in situ* from copper thiocyanate and the inexpensive, easy-to-use fluoromethylating reagent  $\text{TMSCF}_2\text{Y}$  and converts diazonium salts (preformed or generated *in situ*) smoothly into the corresponding di-/trifluoromethyl derivatives.



### Proposed Mechanism of the Sandmeyer Di-/Trifluoromethylations

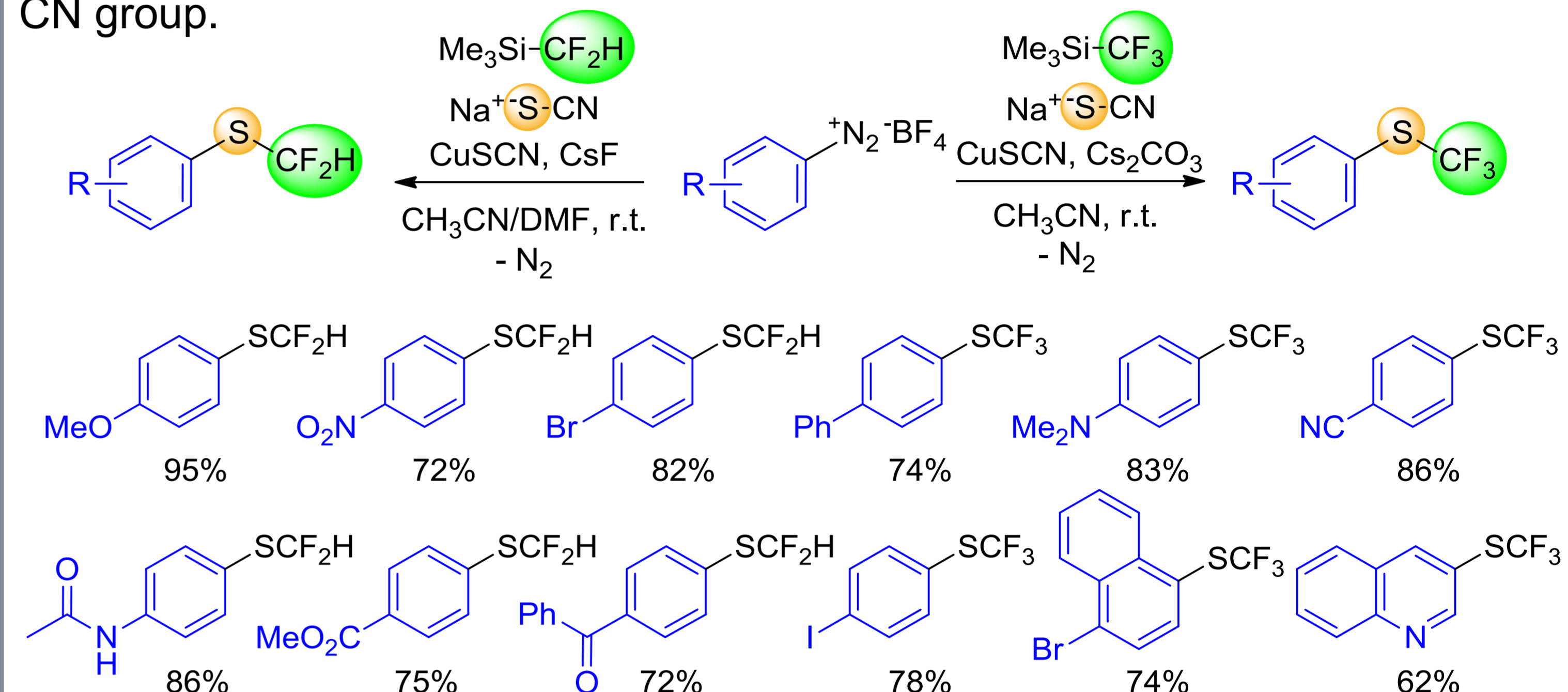
The fluoromethyl copper(I) species is generated from the copper precursor and  $\text{TMSCF}_2\text{Y}$  in the presence of the cesium base. It transfers one electron to the diazonium salt. The resulting diazo radical releases nitrogen with formation of an aryl radical, which abstracts the fluoromethyl group from the copper(II) intermediate to form the fluoromethylated product along with a copper(I) species.



## Introduction of Di- and Trifluoromethylthio Groups

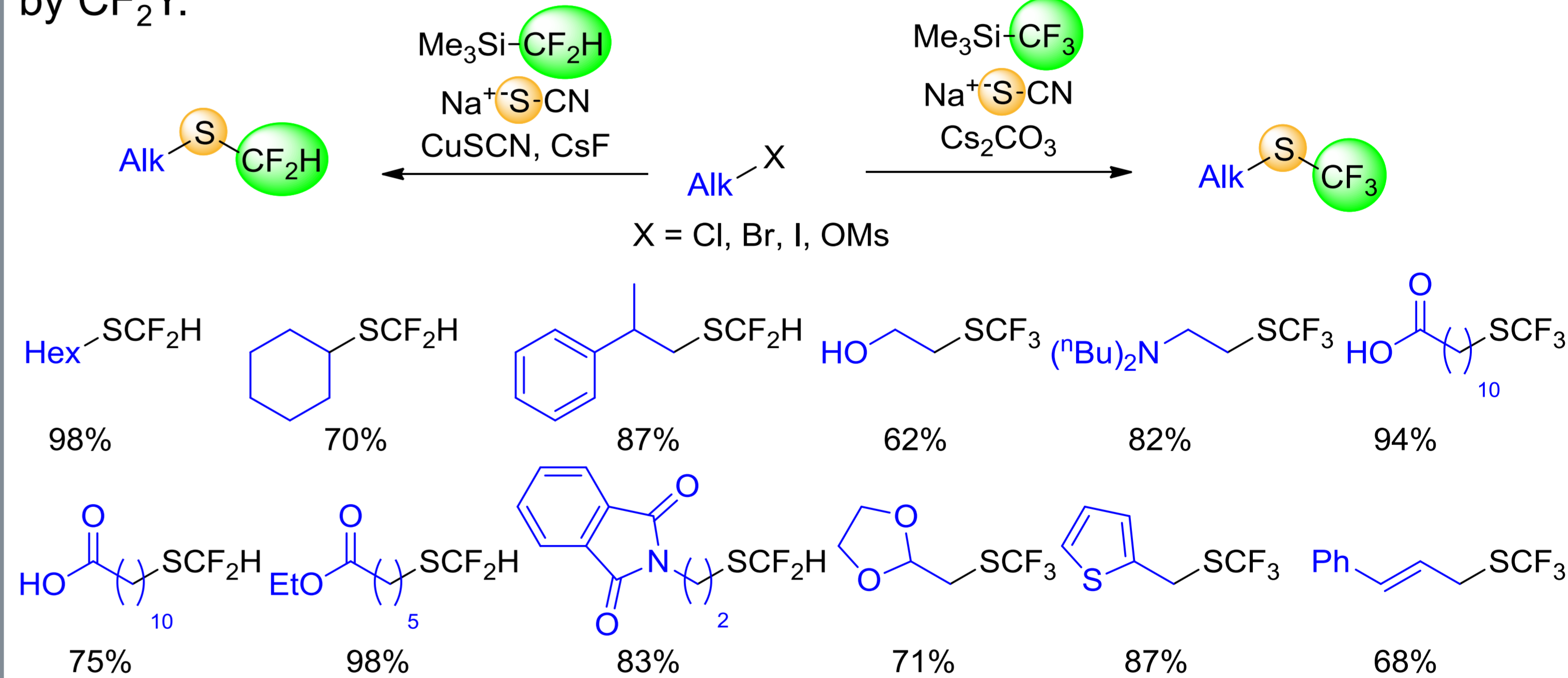
### Sandmeyer Di-/Trifluoromethylthiolations<sup>[2]</sup>

Fluoroalkylthio groups induce even higher lipophilicity and enhanced metabolic stability than fluoroalkylated groups. Hence, we developed Sandmeyer di- and trifluoromethylthiolations by converting diazonium salts smoothly into the corresponding aryl di-/trifluoromethyl thioethers in the presence of copper thiocyanate, sodium thiocyanate and the inexpensive, easy-to-use  $\text{TMSCF}_2\text{Y}$ . In the difluoromethylthiolation, copper plays a key role in the exchange with the CN group.



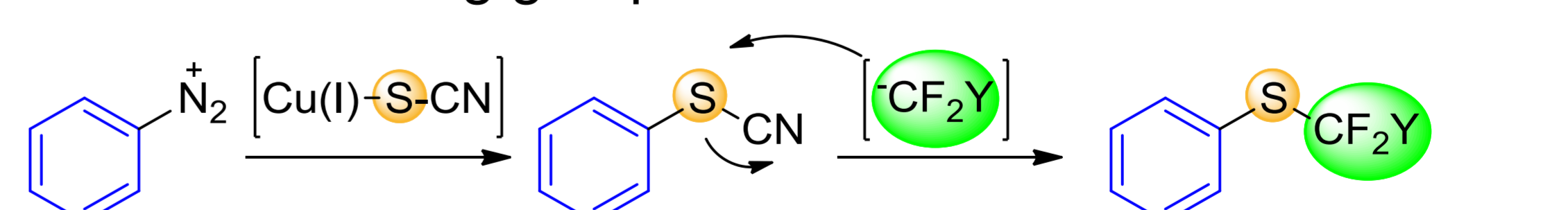
### Di-/Trifluoromethylthiolation of Alkyl Electrophiles

Moreover, we disclosed sustainable late-stage di-/trifluoromethylthiolation methods starting from broadly available alkyl halides or alkyl mesylates *via* a cascade of thiocyanation and a Langlois-type nucleophilic displacement of CN by  $\text{CF}_2\text{Y}$ .



### Proposed Mechanism of the Sandmeyer Di-/Trifluoromethylthiolations

The aryl thiocyanate, generated *via* a Sandmeyer reaction, is immediately converted into a fluoroalkylthio group by a nucleophilic Langlois-type displacement of the CN leaving group.



## References and Further Information, see also [www.chemie.uni-kl.de/goossen](http://www.chemie.uni-kl.de/goossen)

- [1] a) G. Danoun, B. Bayarmagnai, M. F. Grünberg, L. J. Gooßen, *Angew. Chem. Int. Ed.* **2013**, *52*, 7972-7975. b) B. Bayarmagnai, C. Matheis, E. Risto, L. J. Gooßen, *Adv. Synth. Cat.* **2014**, *356*, 2343-2348. c) G. Danoun, B. Bayarmagnai, M. F. Grünberg, C. Matheis, E. Risto, L. J. Gooßen, *Synthesis* **2014**, *46*, 2283-2286. d) C. Matheis, K. Jouvin, L. J. Gooßen, *Org. Lett.* **2014**, *16*, 5984-5987.
- [2] a) G. Danoun, B. Bayarmagnai, M. F. Grünberg, L. J. Gooßen, *Chem. Sci.* **2014**, *5*, 1312-1316. b) B. Bayarmagnai, C. Matheis, K. Jouvin, L. J. Gooßen, *Angew. Chem. Int. Ed.* **2015**, *54*, 5753-5756. c) C. Matheis, M. Wang, T. Krause, L. J. Gooßen, *Synlett* **2015**, *26*, 1628-1632.

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