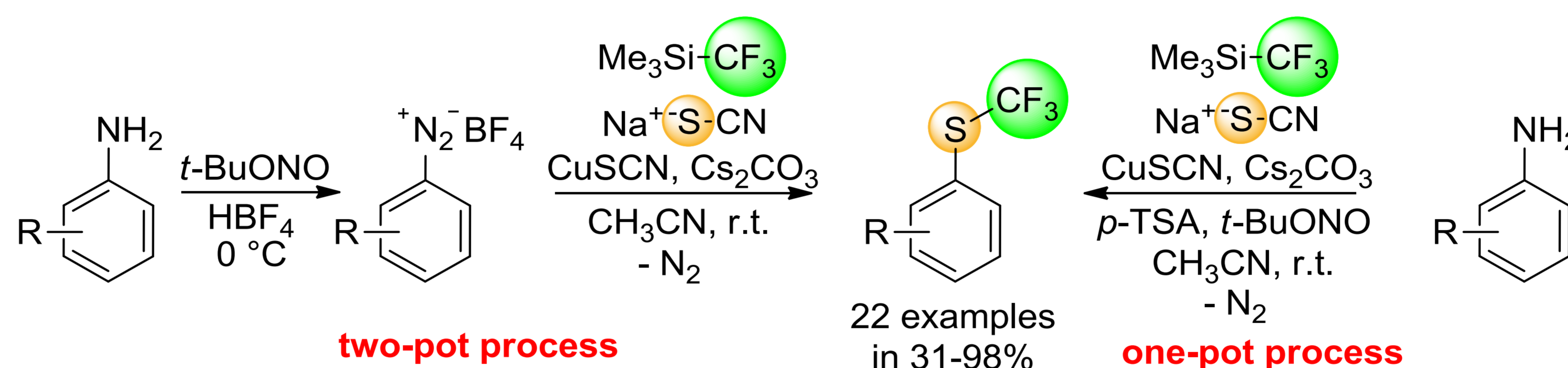


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Abstract The Sandmeyer reaction is one of the most widely used methods for the introduction of halides and related nucleophiles. Aromatic amines, which are available in great structural diversity, are diazotized using, for example, NaNO_2 or organic nitrites. Upon treatment with the appropriate copper(I) halides, nitrogen gas is released, and a halide group is installed regioselectively in the position of the former amino group. Herein we report a copper mediated Sandmeyer-type trifluoromethylthiolation with the easy-to-use trifluoromethylating reagent TMSCF_3 . Two practical methods were developed starting either from the preisolated diazonium salts or directly from the anilines. These convenient and cheap methods allow the straightforward syntheses of trifluoromethylthiolated compounds from the corresponding aromatic amines under mild conditions.

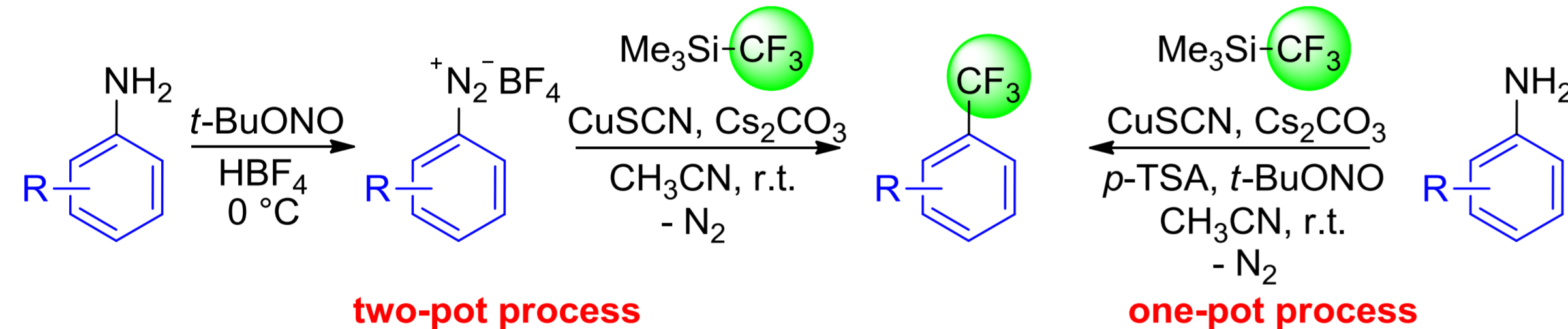


Introduction

The installation of fluorinated groups, particularly trifluoromethyl and trifluoromethylthio groups into organic molecules has been a top research area in recent years due to the fact that compounds bearing fluorine moieties have unique chemical and physical properties, including high metabolic stability, strong dipole moments and high lipophilicity. Thus, the trifluoromethylthio motif is often seen as a key functionality of many pharmaceutical and agrochemical products.

Trifluoromethylation

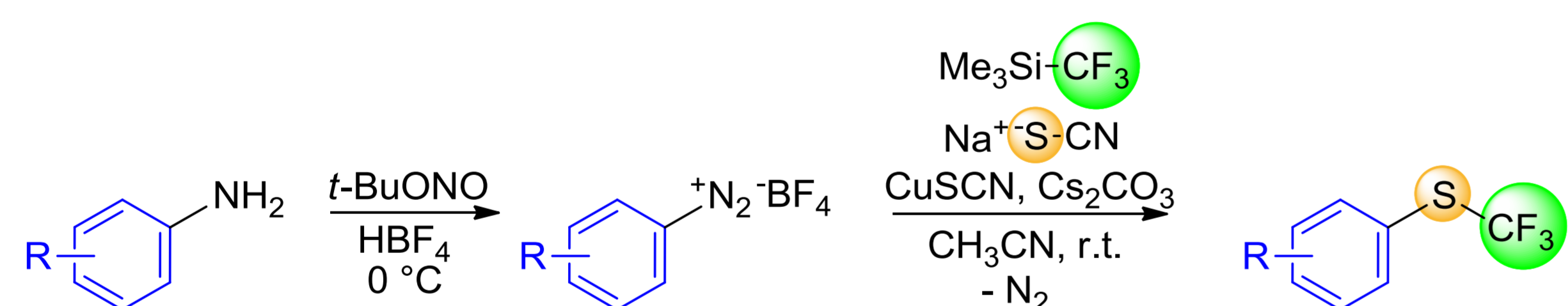
In the last two decades, an impressive progress has been made in the trifluoromethylation of arenes, leading to a large variety of methods.^[1] In continuation of our previous work on late-stage trifluoromethylations,^[2] we found a redox-neutral Sandmeyer type reaction to introduce the highly desirable trifluoromethyl group.^[3]



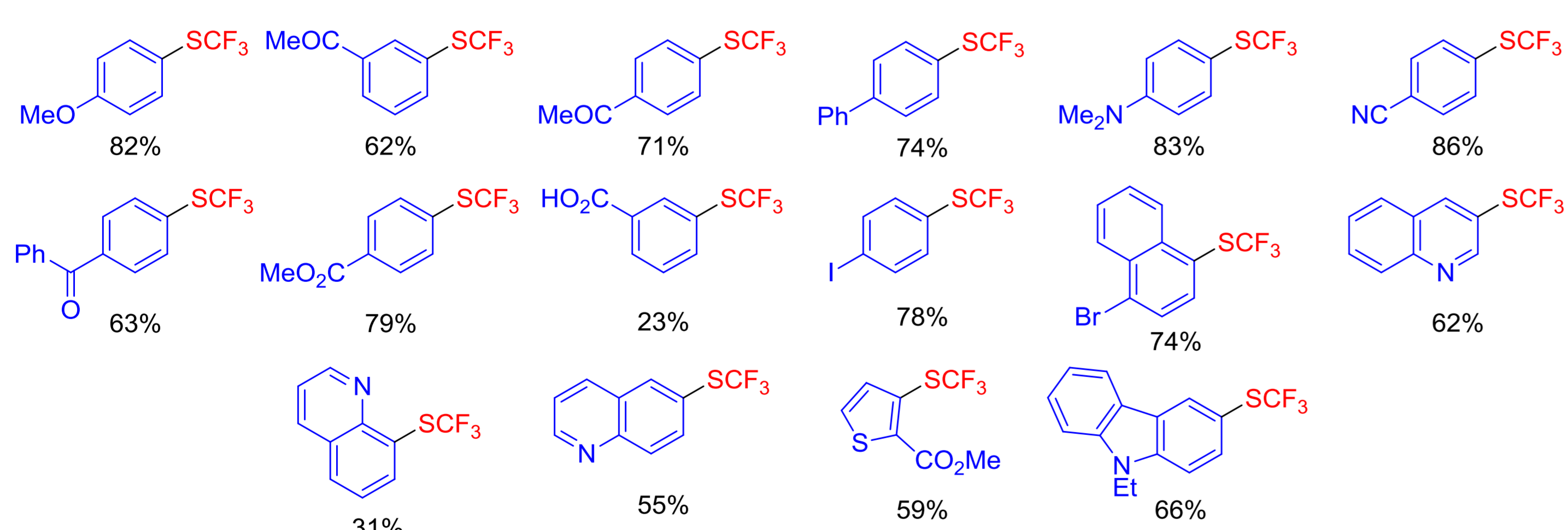
Trifluoromethylthiolation

Compared to the trifluoromethylation, trifluoromethylthiolation is less studied. Known approaches are based on substrates with limited availability or require sensitive and expensive reagents.^[4] Thus, a similar efficient, redox-neutral reaction as our Sandmeyer trifluoromethylation for the introduction of trifluoromethylthio groups is highly desirable.

Sandmeyer Trifluoromethylthiolation^[5]

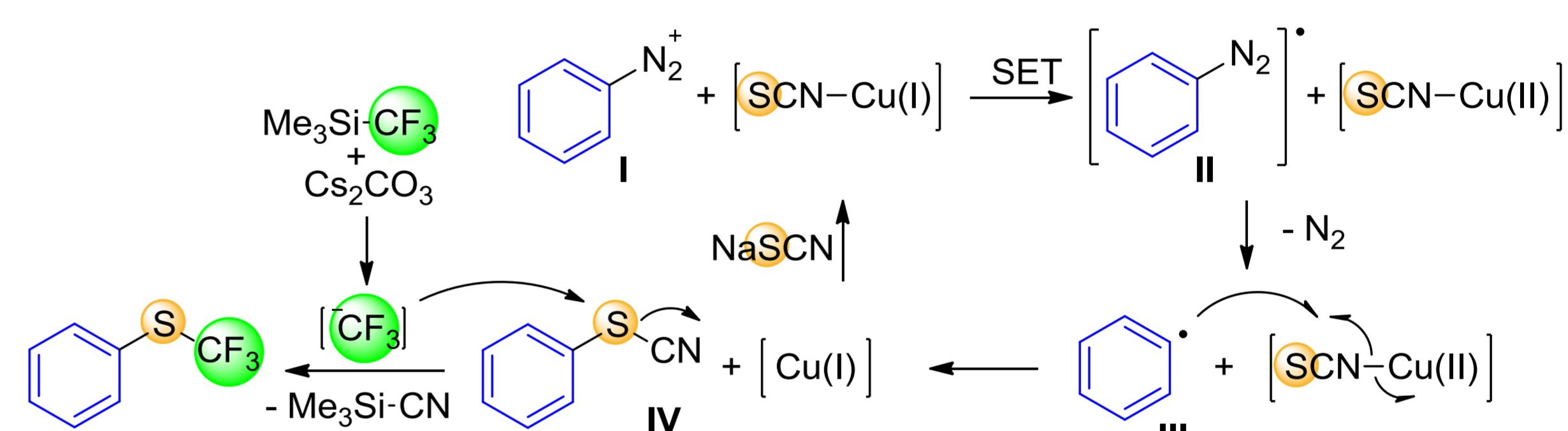


We developed a Sandmeyer trifluoromethylthiolation by converting diazonium salts smoothly into the corresponding aryl trifluoromethyl thioethers in the presence of copper thiocyanate, sodium thiocyanate and the inexpensive, easy-to-use trifluoromethylating reagent TMSCF_3 .^[5]



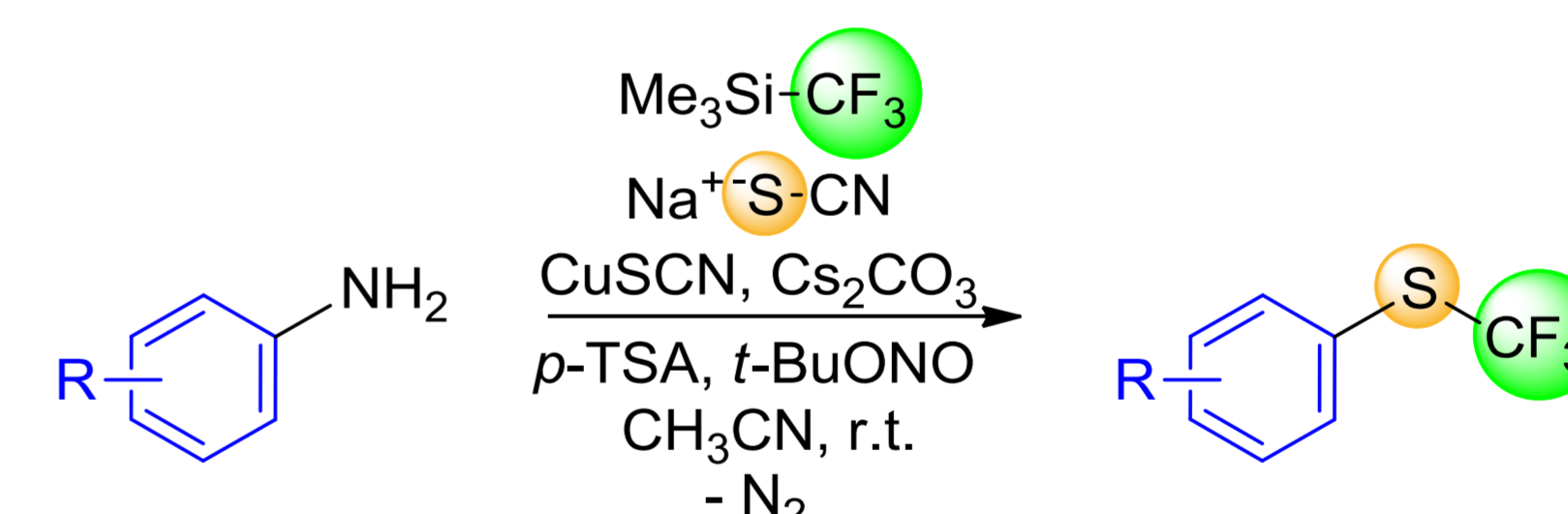
Tolerating various functionalities this new process demonstrates the utility for the late-stage trifluoromethylthiolation of complex, highly functionalized intermediates.

Proposed Mechanism

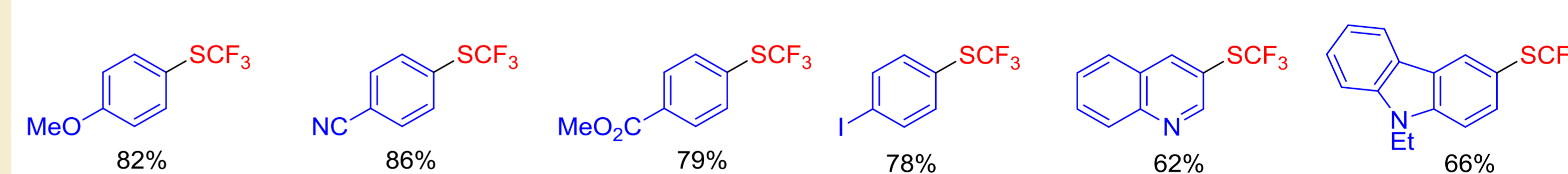


The aryl diazonium salt is converted to the aryl thiocyanate via a Sandmeyer reaction. Thus, the Cu(I)SCN species transfers one electron to the diazonium salt (I). The resulting diazo radical II releases nitrogen under the formation of an aryl radical III, which abstracts the thiocyanate group from the copper(II) intermediate to form the arylthiocyanide IV. The thiocyanate group of this intermediate is immediately converted into a trifluoromethylthio group by a nucleophilic displacement reaction of the CN -leaving group.

One-pot Sandmeyer Trifluoromethylthiolation^[6]



In order to unleash the full synthetic potential of this innovative approach, our most recent development was an one-pot process for the sandmeyer trifluoromethylthiolation starting directly from the corresponding anilines. The *in situ* diazotization, performed in the presence of *p*-toluenesulfonic acid and *tert*-butyl nitrite, could be added to the advantageous features of our initial method (copper-mediated, inexpensive trifluoromethylthiolating reagent, room temperature).^[6]



The examples confirm that this straightforward protocol is broadly applicable to the synthesis of (hetero)aryl trifluoromethyl thioethers from aromatic or heteroaromatic amines.

Future work will be directed at lowering the copper loading by employing stabilizing ligands.

Literature and Further Reading (see also www.chemie.uni-kl.de/goossen)

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