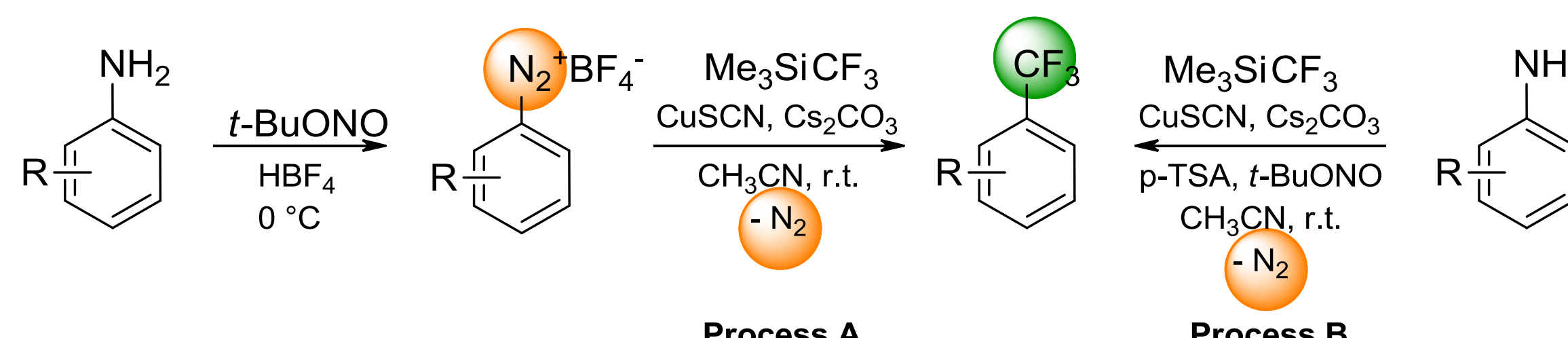


Bilguun Bayarmagnai, Christian Matheis, Grégory Danoun, Matthias F. Grünberg, Eugen Risto and Lukas J. Gooßen*

Fachbereich Chemie, TU Kaiserslautern, Erwin-Schrödinger-Straße 54, 67663 Kaiserslautern
Tel +49 631 205 2527, bayarmagnai@chemie.uni-kl.de, goossen@chemie.uni-kl.de

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 copper mediated Sandmeyer-type trifluoromethylation which allows straightforward syntheses of benzotrifluorides from the corresponding aromatic amines under mild conditions. Various benzotrifluorides are conveniently accessible in high yields from broadly available (hetero)aromatic amines and the inexpensive trifluoromethylating agent TMSCF_3 via a copper-mediated Sandmeyer trifluoromethylation reaction. Two practical procedures are presented. In the first one, the diazonium salts are preformed in an extra reaction step, in the second one, the diazotization and the trifluoromethylating are combined into a one-pot procedure.

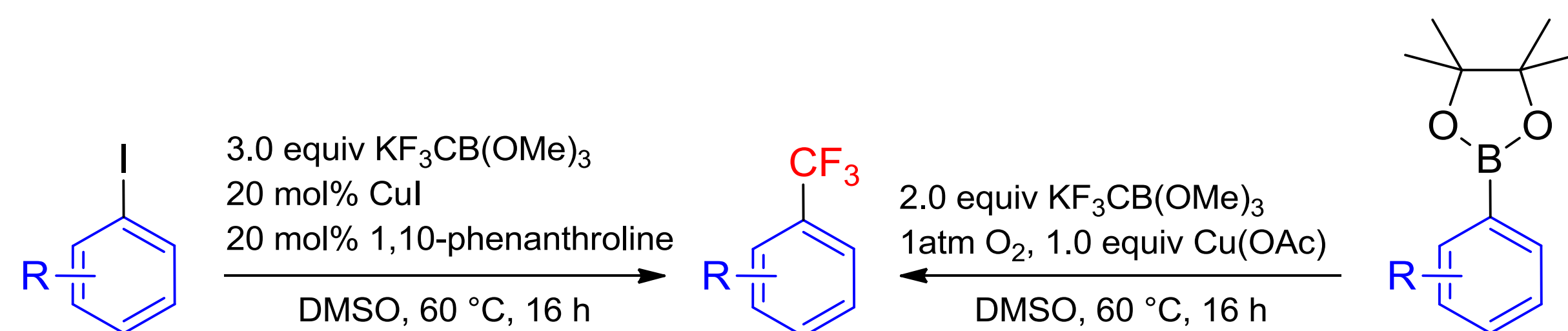


Introduction

Fluorine plays a key role in pharmaceutical, agrochemical and material sciences. About 20% of all pharmaceuticals and about 30% of agrochemicals on the market contain fluorine. The insertion of fluorinated groups into highly functionalized molecules is of great importance imparting desirable properties, such as higher metabolic stability, increased lipophilicity, and stronger dipole moments.^[1]

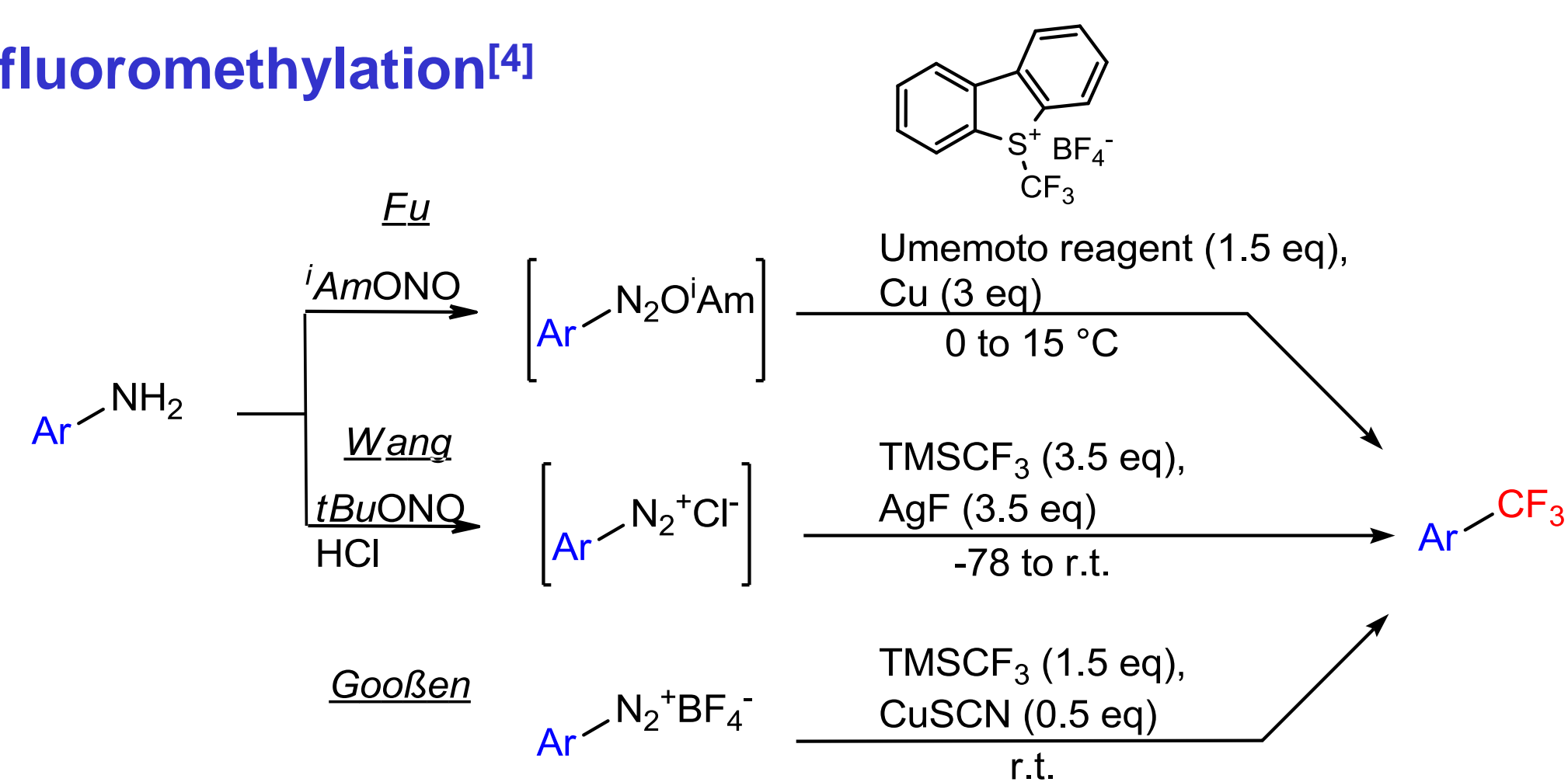
Trifluoromethylation

In the last two decades, an impressive progress has been made in the trifluoromethylation of arenes, leading to a large variety of methods, e.g. trifluoromethylation of aryl halides with nucleophilic CF_3 -reagents, of aryl boronic acids with nucleophilic trifluoromethylation reagents under oxidative conditions, etc.^[2]



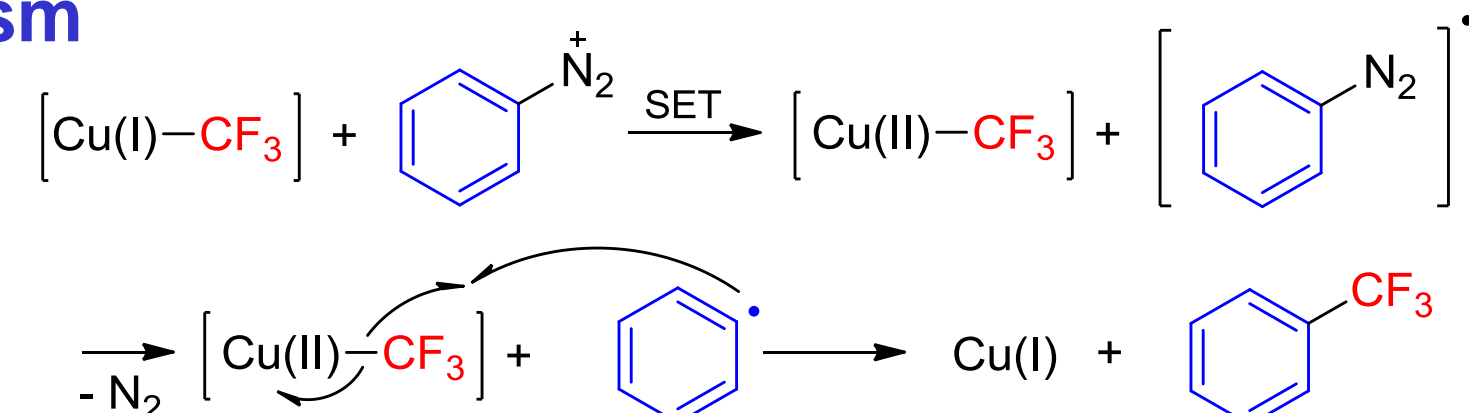
Our group demonstrated copper catalyzed trifluoromethylation of aryl iodides and aryl boronic acids using stable potassium (trifluoromethyl)trimethoxyborate as nucleophilic CF_3 source.^[3]

Sandmeyer Trifluoromethylation^[4]



As an alternative to these methods, Sandmeyer-type trifluoromethylations were almost simultaneously disclosed by Fu, Wang and ourselves. Their key advantage is that they draw on aromatic amines, widely available in great structural diversity, as the aryl source. We developed a Sandmeyer trifluoromethylation by generating a trifluoromethyl-copper complex *in situ* from copper thiocyanide and the inexpensive, easy-to-use trifluoromethylating reagent TMSCF_3 , diazonium salts are smoothly converted into the corresponding trifluoromethyl derivatives.

Proposed Mechanism

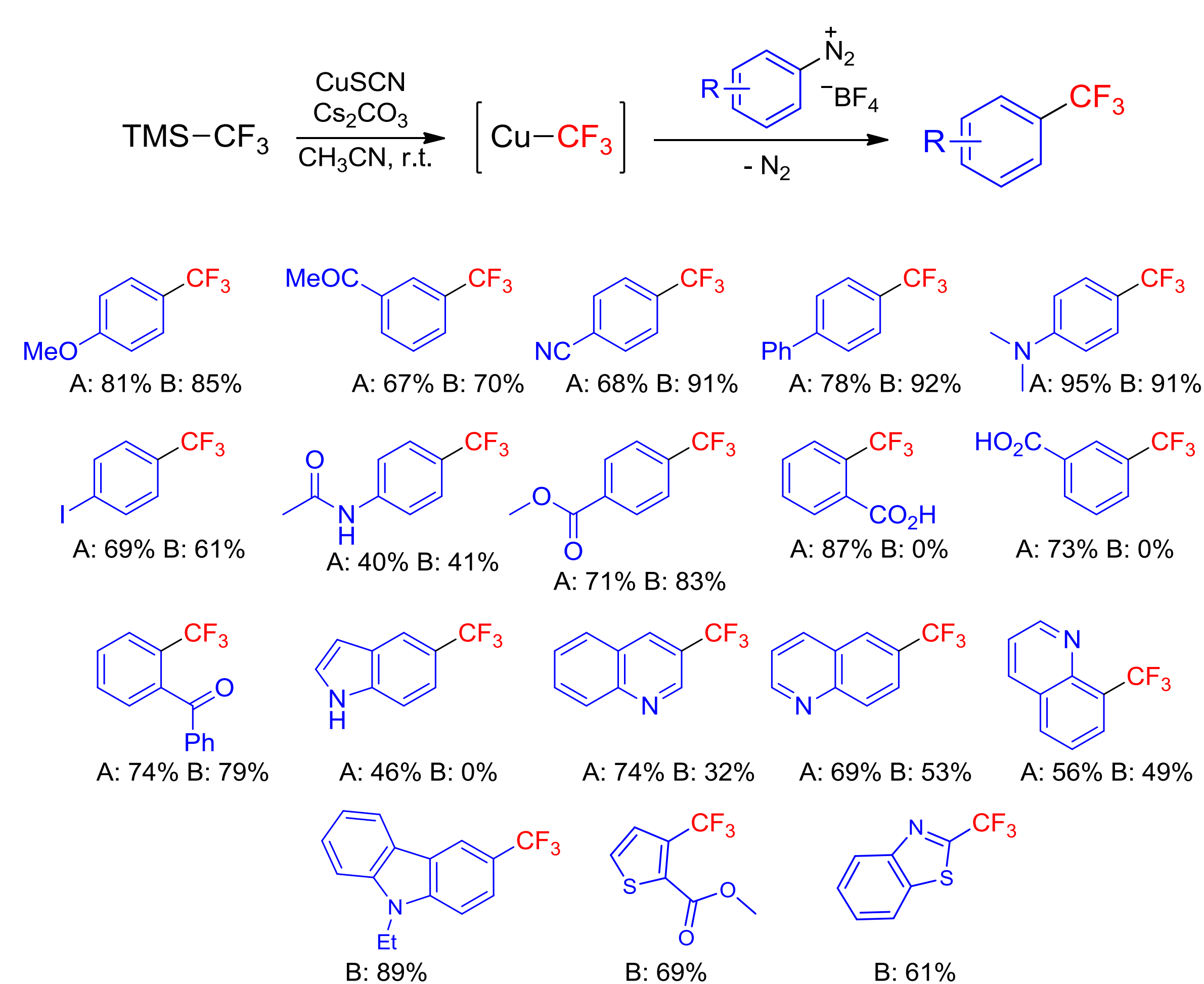


The trifluoromethyl copper(I) species is generated from the copper precursor and TMSCF_3 in the presence of the cesium base. It transfers one electron to the diazonium salt. The resulting diazo radical releases nitrogen with formation of an aryl radical, which abstracts the trifluoromethyl group from the copper(II) intermediate to form the trifluoromethylated product along with a copper(I) species.

One-pot Sandmeyer Trifluoromethylation^[5]

The key advantage of Wang and Fu's protocols is that they give high yields even if the diazotization is performed *in situ*. In order to arrive at an operationally simple, economically and ecologically advantageous protocol, it would be ideal if the advantageous features of our method (substoichiometric copper, inexpensive trifluoromethylating reagent, room temperature) could be combined with an *in situ* generation of the diazonium salts from the corresponding anilines.

Especially for small-scale reactions and sensitive diazonium salts, it may be convenient to diazotize the amine directly in the reaction mixture. This can be done by adding *tert*-butyl nitrite (1 equiv.) to a solution of the aniline and anhydrous *p*-toluenesulfonic acid (1.5 equiv.) in MeCN. The absence of water is decisive, the monohydrate of the acid already leading to reduced yields. After stirring for 0.5 hours at RT, a suspension of CuSCN (0.5 equiv.), TMSCF_3 (1.5 equiv.) and Cs_2CO_3 (1.5 equiv.) in MeCN is added to the reaction mixture, and stirring is continued for 12 hours.



The one-pot process (Process B) gives comparable, sometimes even higher yields than the two-step protocol (Process A). Tolerating various functionalities both processes demonstrate the utility for the late-stage trifluoromethylation of complex, highly functionalized intermediates

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

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