

Metal-Free Trifluoromethylthiolation of Alkyl Electrophiles via a Cascade of Thiocyanation and Nucleophilic Cyanide- CF_3 Substitution

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Fluorine atoms can have profound effects on bioactive molecules. Trifluoromethylthio groups can impart many desirable properties, such as higher metabolic stability and increased lipophilicity. Professor Lukas Gooßen at the Kaiserslautern University of Technology (Germany) has been fascinated by these effects since his time at Bayer central research. He commented: “At Bayer, a dedicated team of experts including my later wife provided customized fluorinated building blocks to other synthetic chemists to give them a head start against competitors. The methods they routinely employed required special equipment and substantial experience. In recent years,” he continued, “the chemical community has become aware of the importance of fluorinated compounds, and the development of convenient trifluoromethylation reactions that can be employed by synthetic organic chemists without special training is currently one of the most topical fields in method development.”

Professor Gooßen said: “Our paradigm has always been to base new methods on simple, inexpensive and sustainable raw materials. We are less interested in methods whose use will remain restricted to drug discovery where the cost of reagents does not matter, preferring to provide scalable protocols for use throughout academia and industry. Thus, we deliberately steered away from high-tech catalysts and elaborate reagents and, instead, based our early fluoroalkylation methods on basic Sandmeyer chemistry.”

In recent years, the focus of medicinal and agrochemistry has expanded to include fluoroalkylthio groups whose properties often surpass those of the corresponding fluoroalkyl moieties. “Contemporary reports in top journals underline that the introduction of trifluoromethylthio groups is viewed as an unsolved problem that justifies the use of even the most elaborate reagents,” said Professor Gooßen, adding: “This attracted our interest, and we set out to search for a straightforward synthetic approach for the introduction of fluoroalkylthio groups into functionalized molecules.”

When analyzing existing synthetic approaches, Professor Gooßen and co-workers came to the conclusion that their complexity and cost arises from the underlying strategy that consists of transferring the SCF_3 group as a whole from a preformed reagent. “However, Langlois et al. had demonstrated already in 1997 that SCF_3 groups can be generated from thio-

cyanates via nucleophilic displacement of CN by CF_3 . We immediately realized that this somewhat underappreciated concept might open up straightforward synthetic entries to fluoroalkylthiolated molecules that would not require preformed SCF_3 reagents but could be based on the comparably inexpensive Ruppert–Prakash reagent,” remarked Professor Gooßen.

He continued: “Our reasoning was that if it was possible to introduce thiocyanate groups in the presence of nucleophilic fluoroalkylating reagents, the resulting organothiocyanates could be directly converted into the desired fluoroalkylthio groups.” According to Professor Gooßen, the key challenge of this approach was to direct the reactivity of the fluoroalkylating reagent exclusively towards the thiocyanate moiety and avoid side reactions between the reagents present in the mixture. With a small team composed of the PhD students Bilguun Bayarmagnai, Matthias Grünberg and Christian Matheis and the postdoctoral researchers Dr. Grégory Danoun and Dr. Kévin Jouvin, they set out to probe the viability of this approach. After many setbacks, the Kaiserslautern based research team finally managed to combine Sandmeyer thiocyanations with Langlois-type trifluoromethylations and novel difluoromethylations and, thus, developed efficient synthetic entries to aryl fluoroalkyl thioethers from readily available arene-diazonium salts and inexpensive TMS-fluoroalkanes (*Angew. Chem. Int. Ed.* 2015, 54, 5753, *Chem. Sci.* 2014, 5, 1312).

Professor Gooßen said: “In parallel to this work, we probed whether the synthesis of alkyl thiocyanates via nucleophilic substitution of alkyl halides with NaSCN could also be combined with a trifluoromethylation with TMSCF_3 . Christian systematically varied the reaction conditions of the thiocyanation and the Langlois trifluoromethylation to identify conditions under which both steps would work well and all reagents would remain stable. For many weeks, he was frustrated by the incompatibility of the two steps, which resulted in unsatisfactory yields. After intricate development efforts, he discovered that with acetonitrile as the solvent and Cs_2CO_3 as the base, both steps proceeded in high yields when performed individually. Further optimization was required until they could be combined to a one-pot process in which all reagents are added directly at the beginning of the reaction.”

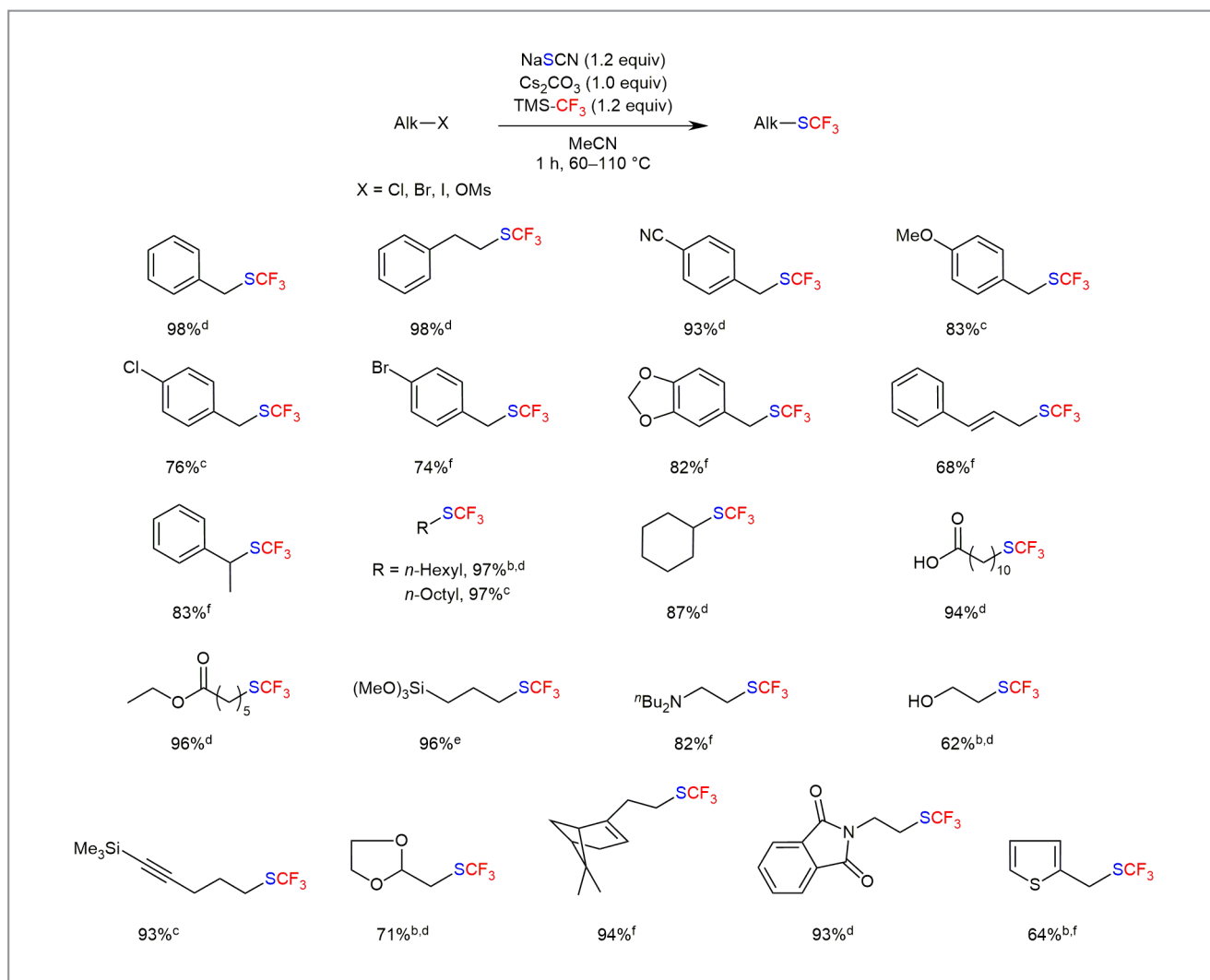
The final protocol is easy to use and widely applicable. It allows access to alkyl trifluoromethyl thioethers from widely

available alkyl halides or mesylates simply by stirring them with sodium thiocyanate, TMS-CF₃ and Cs₂CO₃ in acetonitrile at 60–110 °C without the need for transition-metal catalysts.

Professor Gooßen revealed that having finally identified an efficient protocol, Christian teamed up with Dr. Minyan Wang and Thilo Krause to investigate its scope. The chromatographic separation of the volatile products from remaining alkyl halide starting materials turned out to be quite tricky. However, they soon found out that the best strategy to overcome their separation problems was to ensure near-quantitative conversions by carefully monitoring the reaction progress. Within a few long working days, they synthesized, isolated

and characterized 22 alkyl trifluoromethyl thioethers bearing various functionalities (Scheme 1).

“The above examples underline that the metal-free cascade of nucleophilic thiocyanation and nucleophilic CN-CF₃ substitution is a powerful tool for the synthesis of alkyl trifluoromethyl thioethers from broadly available alkyl electrophiles. Its key advantages are its simple operation, broad applicability, and tolerance of various functional groups, despite using one of the cheapest sources of trifluoromethyl groups available,” said Professor Gooßen. He concluded: “We are pleased that our recent fluoroalkylations and fluoroalkylthiations have been so well received by the chemical com-



Scheme 1 Trifluoromethylthiation of alkyl halides and mesylates.^a

^a Isolated yields. ^b Yields were determined by ¹⁹F NMR using trifluoroethanol as an internal standard. ^c Starting from alkyl chloride.

^d Starting from alkyl bromide. ^e Starting from alkyl iodide. ^f Starting from alkyl mesylate.

munity, and our ‘fluorine guys’ cannot wait to apply the experience gained during this work to address some of the many remaining challenges in fluorine chemistry.”

Mattheis Fenske

About the authors



From left: Dr. M. Wang, T. Krause, Prof. Dr. L. Gooßen with his youngest group member Matilda, C. Matheis

Christian Matheis studied Chemistry in Kaiserslautern (Germany) where he received his diploma in 2013 working on new strategies for the formation of C–O bonds. His results were published in *Angewandte Chemie* as a ‘hot paper’ and his thesis was awarded within the Springer BestMasters program. After an industrial internship at BASF (Germany) in the lead optimization of agricultural products, he started his Ph.D. work under the supervision of Prof. Gooßen on the development of straightforward methods for the synthesis of fluorinated compounds. Within his first year, he was able to make great contributions to this research area and published several methods for the introduction of fluoroalkyl(thiol)ated groups.

Minyan Wang studied Chemistry at Huazhong University of Science and Technology (P. R. of China). After having received her Bachelor’s degree in 2009, she continued her Ph.D. at Zhejiang University (P. R. of China) under the supervision of Professor Shengming Ma, where she worked on the highly selective electrophilic and nucleophilic addition of functionalized allenes. Both her Bachelor and Ph.D. degrees were graded as

excellent. After completing her thesis in 2014, she moved to the TU Kaiserslautern (Germany) for a postdoctoral stay with Professor Gooßen, where she is presently working on the fluorination of organic compounds.

Thilo Krause studied Chemistry at the TU Kaiserslautern (Germany) where he received his diploma in 2013. He is pursuing Ph.D. research under the supervision of Professor Gooßen on the sustainable synthesis of amides from carboxylic acids and amines via in situ generated active esters. In order to gain insights into chemistry in industry, he interrupted his Ph.D. work in April 2014 for a three-month internship in the department of Global Research Agricultural Products at BASF, Ludwigshafen (Germany).

Lukas Gooßen studied chemistry at the Universities of Bielefeld (Germany) and Michigan (USA) and carried out graduate studies at UC Berkeley (USA) with Professor K. Peter C. Vollhardt. He was awarded a Ph.D. in 1997 for his research on N-heterocyclic carbene complexes supervised by Professor Wolfgang A. Herrmann, TU Munich (Germany), and pursued postdoctoral research with Professor K. Barry Sharpless, Scripps Research Institute (USA). He began his professional career as an industrial chemist at Bayer AG (Germany) in 1999, but moved back to academia to the group of Professor Manfred T. Reetz, MPI for Coal Research for his habilitation, and further to RWTH Aachen (Germany). He has been a professor at the TU Kaiserslautern (Germany) since 2005. His research is devoted to the development of novel concepts for C–C and C–heteroatom bond formation. He has authored over 120 publications and 25 patents. Recent awards include the Jochen Block Award of the DECHEMA, the Carl Duisberg Award of the GDCh, the Novartis Young Investigator Award, and the AstraZeneca Award in Organic Chemistry (2008).