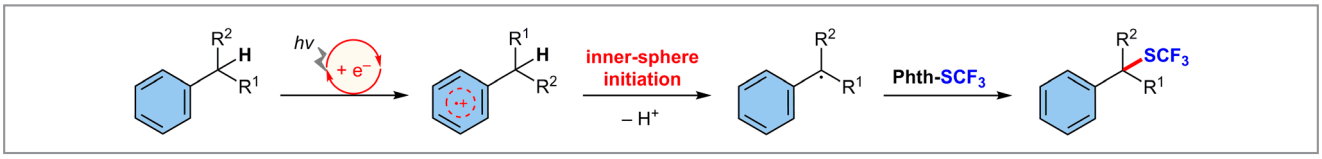
Late-Stage Trifluoromethylthiolation of Benzylic C–H Bonds

Nat. Commun. **2019**, DOI: 10.1038/s41467-019-12844-9

It is estimated that over 20% of small-molecule drugs on the market contain at least one fluorine atom. The trifluoromethyl group – which is a xenobiotic function, not yet found in any naturally available compound – is also encountered in a number of drugs, generally as an aromatic substituent but sometimes connected to a heteroatom such as oxygen or sulfur. Due to its strongly electron-withdrawing characteristics and high lipophilicity, the selective introduction of trifluoromethylthio group (SCF_3) into organic and pharmaceutical molecules can improve their cell membrane permeability and metabolic stability of the target molecules. Hence, synthetic strategies for introducing an SCF_3 group in organic molecules entailing versatility, diversity and availability are highly desirable in the arsenal of synthetic chemists.

In a recent paper, the group of Professor Jin Xie and Professor Chengjian Zhu at Nanjing University (Nanjing, P. R. of China) developed an organophotoredox-catalyzed reaction for site-selective benzylic C–H bond trifluoromethylthiolation of a wide variety of alkyl arenes and heteroarenes. "Currently, the regioselectivity of the reaction relies mainly on the physicochemical properties (e.g., exchange constants and polarity) of intermolecular hydrogen-atom-transfer (HAT) reagents or oxidants in terms of C–H bond dissociation energy and electronic properties," Professor Xie and co-authors pointed out. They continued: "Hence, in this paper we reported the development of a metal-free, photoredox inner-sphere HAT process which predictably generates, from natural products or drug derivatives, a benzylic radical which can be tri-



Scheme 1 Photoredox-catalyzed trifluoromethylthiolation of benzylic C–H bonds

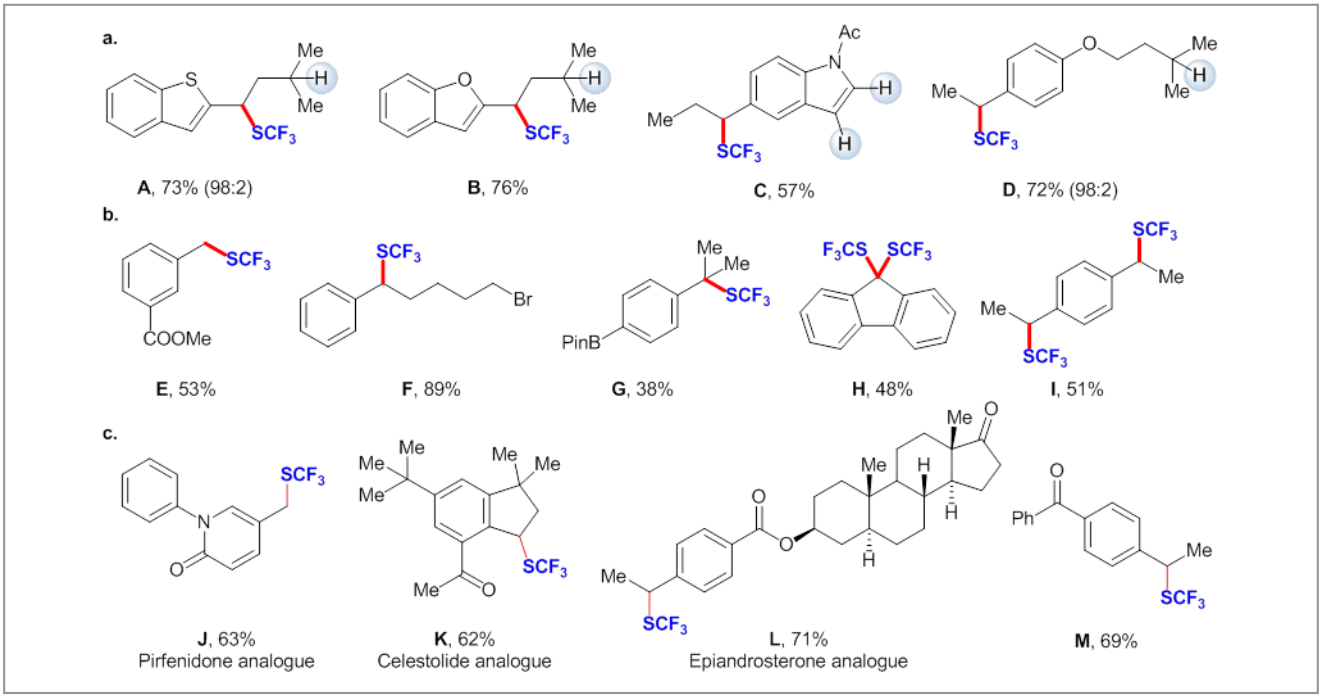


Figure 1 Selected examples

fluoromethylthiolated, avoiding the use of oxidants and HAT reagents."

Excitingly, this protocol shows an excellent site-selectivity (Figure 1a) and a broad substrate scope (Figure 1b). "In addition, late-stage trifluoromethylthiolation of drugs and synthesis of the benzophenone benzyl trifluoromethyl sulfides were successfully achieved (Figure 1c). Finally, continuous flow chemistry further demonstrates the synthetic practicability," remarked the authors.

Professors Xie and Zhu concluded by mentioning some future prospects: "This photoredox inner-sphere HAT process can be applied in benzylic C–H bond functionalization processes and our lab is currently investigating this enantioselective synthesis strategy."

About the authors

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Jin Xie is currently an associate professor at Nanjing University (P. R. of China). He was born in Chongqing, P. R. of China, in 1985. He received his Bachelor's degree from Northeast Forestry University (P. R. of China) in 2008, and his Ph.D. in 2013 from Nanjing University working under the direction of Prof. Chengjian Zhu. From 2014 to 2017, he was a postdoctoral research associate in the group of Prof. A. S. K. Hashmi at Heidelberg University (Germany). In 2017, he returned to Nanjing University to start his independent career. His current research interests are the development of diverse catalysis concepts, focusing on organometallic chemistry (bimetallic catalysis) and synergistic catalysis in radical chemistry. He obtained several awards, such as the 1000-youth talent plan of China, Thieme Chemistry Journals Award, Jiangsu Funds for Distinguished Young Scholars and Outstanding Reviewer for ChemComm.

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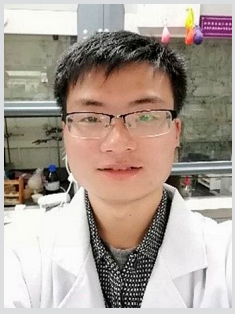

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