Compounds containing fluorinated groups are receiving increasing attention in pharmaceuticals, agrochemicals and materials science. In particular, the trifluoromethoxy group has a high value because of its great electron-withdrawing effect and high lipophilicity (Hansch parameter: $\pi_R = 1.04$). However, despite this strong and widespread interest, there are limited methods for synthesizing trifluoromethoxylated compounds. This is mainly due to the low stability of trifluoromethoxide anions – which decompose easily – or transition-metal–trifluoromethoxide complexes, which tend to undergo $\beta$-fluoride elimination. Therefore, new and efficient trifluoromethoxylating reagents are in great demand. To date, only a very limited number have been reported, with various limitations such as toxicity or difficulties in handling, as well as low reactivity. Recently, the research group of Professor Pingping Tang at Nankai University (P. R. of China) discovered a new trifluoromethoxylation reagent, trifluoromethyl arylsulfonate (TFMS), and developed the first asymmetric silver-catalyzed intermolecular bromotrifluoromethoxylation of alkenes.

In their paper, trifluoromethyl arylsulfonate (TFMS) is reported as a precursor of the trifluoromethoxide anion through fluoride salts activation and – according to Professor Tang – it has several merits: 1) it is easy to prepare, also on large scale (up to 50 g), 2) it has good thermal stability and is easy to...
handle, and 3) the reactivity of the reagent can be modified via different functional groups (R) on the aromatic ring (Figure 1).

“We initially investigated TFMS and observed that it can be used as a new trifluoromethoxylation reagent. More importantly, when we used the chiral ligand (DHQD)$_2$PHAL, asymmetric bromotrifluoromethoxylation of alkenes was achieved using AgF as a catalyst,” said Professor Tang.

The scope of the reaction is very broad, as could be seen in the original paper, and summarized by the few representative examples described in Scheme 1. “All the styrenes that we used were successfully converted into the desired products with good isolated yields (59–94%) and moderate enantioselectivities (58.5:41.5 to 92:8 er),” said Professor Tang. He continued: “Notably, mono-, di-, tri-, and even tetra-substituted alkenes were used for the bromotrifluoromethoxylation reaction, with good yields but lower enantioselectivities.” This reaction was also extended to more sophisticated scaffolds. “The significance of this reaction was demonstrated by the application for the late-stage bromotrifluoromethoxylation of natural products and derivatives, such as an estrone derivative and a taxol derivative,” added Professor Tang.

The chiral ligand, dimeric cinchona alkaloid (DHQD)$_2$PHAL, plays the most important role in the asymmetric process. Professor Tang said: “The styrene substrates are probably located in the chiral pocket via π,π-stacking with the quinoline of the ligand (Figure 2). Due to the absence of π,π-stacking interaction between simple alkenes and ligand, lower enantioselectivities were observed.”

Professor Tang concluded: “Trifluoromethyl arylsulfonate (TFMS) was disclosed as a new trifluoromethoxylation reagent

![Scheme 1 Substrate scope for asymmetric silver-catalyzed bromotrifluoromethoxylation of alkenes](image-url)
that is easily accessible and simple to handle. Taking advantage of this new reagent, we have developed a silver-catalyzed asymmetric bromotrifluoromethoxylation of alkenes. We hope this reagent can find broad applications facilitating the access to new trifluoromethoxylated compounds in pharmaceutical, agrochemical and materials sciences.”

REFERENCES


About the authors

Shuo Guo was born in Hebei Province (P. R. of China) in 1986. He received his BS degree from Hebei Normal University (P. R. of China) in 2010 and M.S. degree from Zhengzhou University (P. R. of China) in 2013, under the supervision of Professor Yangjie Wu. In 2013, he joined Professor Pingping Tang’s research group at Nankai University (P. R. of China) to pursue his PhD degree. He is currently interested in direct trifluoromethylthiolation and trifluoromethoxylation.

Fei Cong was born in Gansu Province (P. R. of China) in 1992. She received her BSc degree from Hunan Normal University (P. R. of China) in 2015. Since then, she has worked in the laboratory of Professor Pingping Tang at Nankai University (P. R. of China) for her Master’s studies. Her M.Sc. thesis is focusing on the development of direct trifluoromethoxylation based on some new trifluoromethoxylation reagents.

Rui Guo was born in Hubei Province (P. R. of China) in 1984. He received his BSc degree from Jiangxi Normal University (P. R. of China) in 2007 and MSc degree from Central China Normal University (P. R. of China) in 2010, under the supervision of Professor Shenghua Liu. Then he worked in HEC Pharm Co., Ltd. (P. R. of China) as a project manager. He completed his PhD studies in 2016 on C–F bond forming reactions under the supervision of Professor Pingping Tang in Nankai University (P. R. of China). Afterwards he joined the Institute of Environment and Health at Jianghan University (P. R. of China) as an assistant researcher mainly focusing on the study of perfluorochemicals.

Liang Wang was born in Zibo (P. R. of China) in 1989. He graduated from Shandong University (P. R. of China) where he was awarded a BSc in 2011. Then he was admitted to Nankai University (P. R. of China) to pursue further studies in organic chemistry. In 2016, he was awarded his PhD under the direction of Professor Pingping Tang. His research mainly focused on the total synthesis of natural products. He is now an Assistant Professor at Nankai University.

Pingping Tang received his BSc degree from Nankai University (P. R. of China) in 2002. After obtaining his PhD degree in 2007 working with Professor Biao Yu at Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences (P. R. of China), he worked as a postdoctoral fellow with Professor Tobias Ritter at Harvard University (USA, 2008–2012). In 2012, he joined the State Key Laboratory and Institute of Elemento-Organic Chemistry at Nankai University (P. R. of China) as a Professor. His research interests include fluorine chemistry and total synthesis of biologically important small molecules.

Dr. R. Guo

Fei Cong

Rui Guo

Pingping Tang

Dr. L. Wang

Dr. R. Guo

Shuo Guo

Liang Wang

Dr. L. Wang