

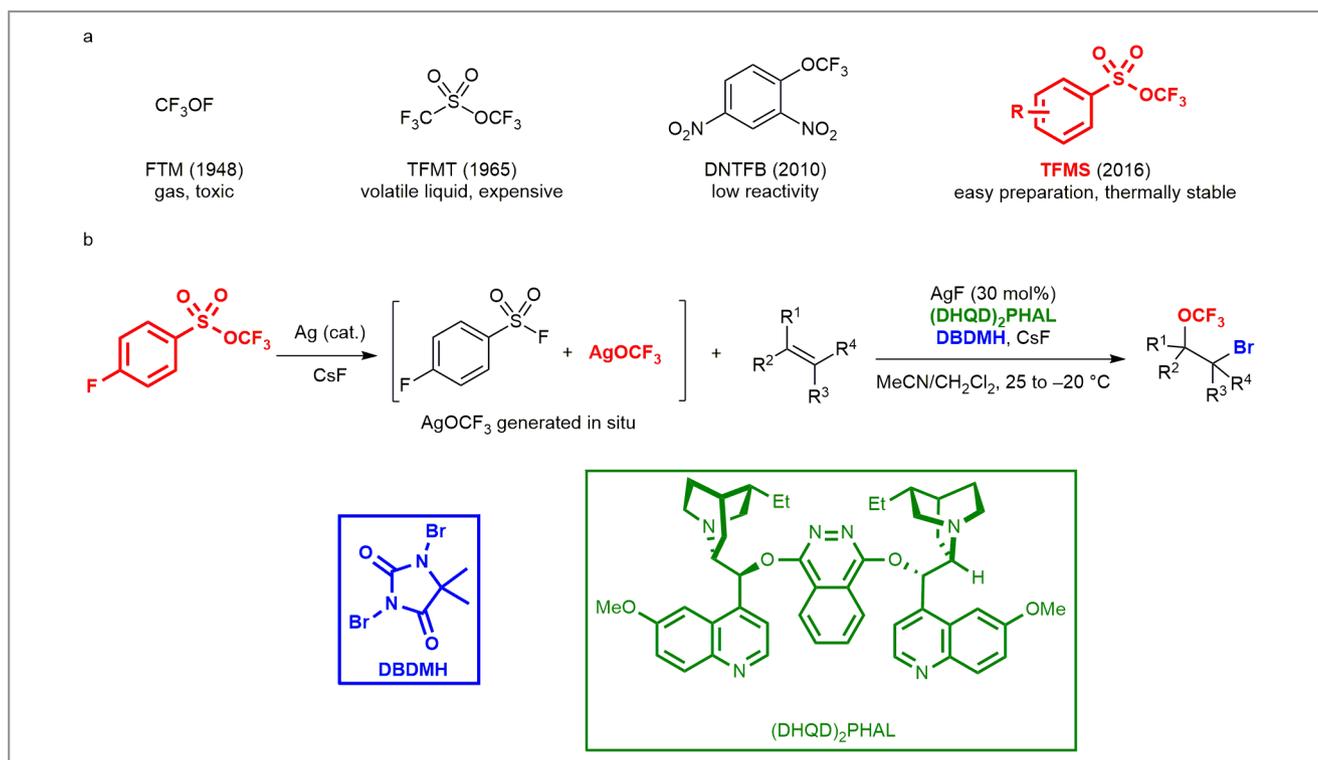
# Direct Asymmetric Bromotrifluoromethoxylation of Alkenes with Trifluoromethyl Arylsulfonate as a New Trifluoromethoxylation Reagent

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Compounds containing fluorinated groups are receiving increasing attention in pharmaceuticals, agrochemicals and materials science.<sup>1</sup> In particular, the trifluoromethoxy group has a high value because of its great electron-withdrawing effect and high lipophilicity (Hansch parameter:  $\pi_r = 1.04$ ).<sup>2</sup> 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.<sup>3</sup> 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



**Figure 1 a)** Compared to traditional trifluoromethoxylation reagents, TFMS is easily prepared and thermally stable, with good reactivity. **b)** The first example of an asymmetric silver-catalyzed intermolecular bromotrifluoromethoxylation of alkenes with TFMS as a new trifluoromethoxylation reagent was described.

handle, and 3) the reactivity of the reagent can be modified via different functional groups (R) on the aromatic ring (Figure 1).

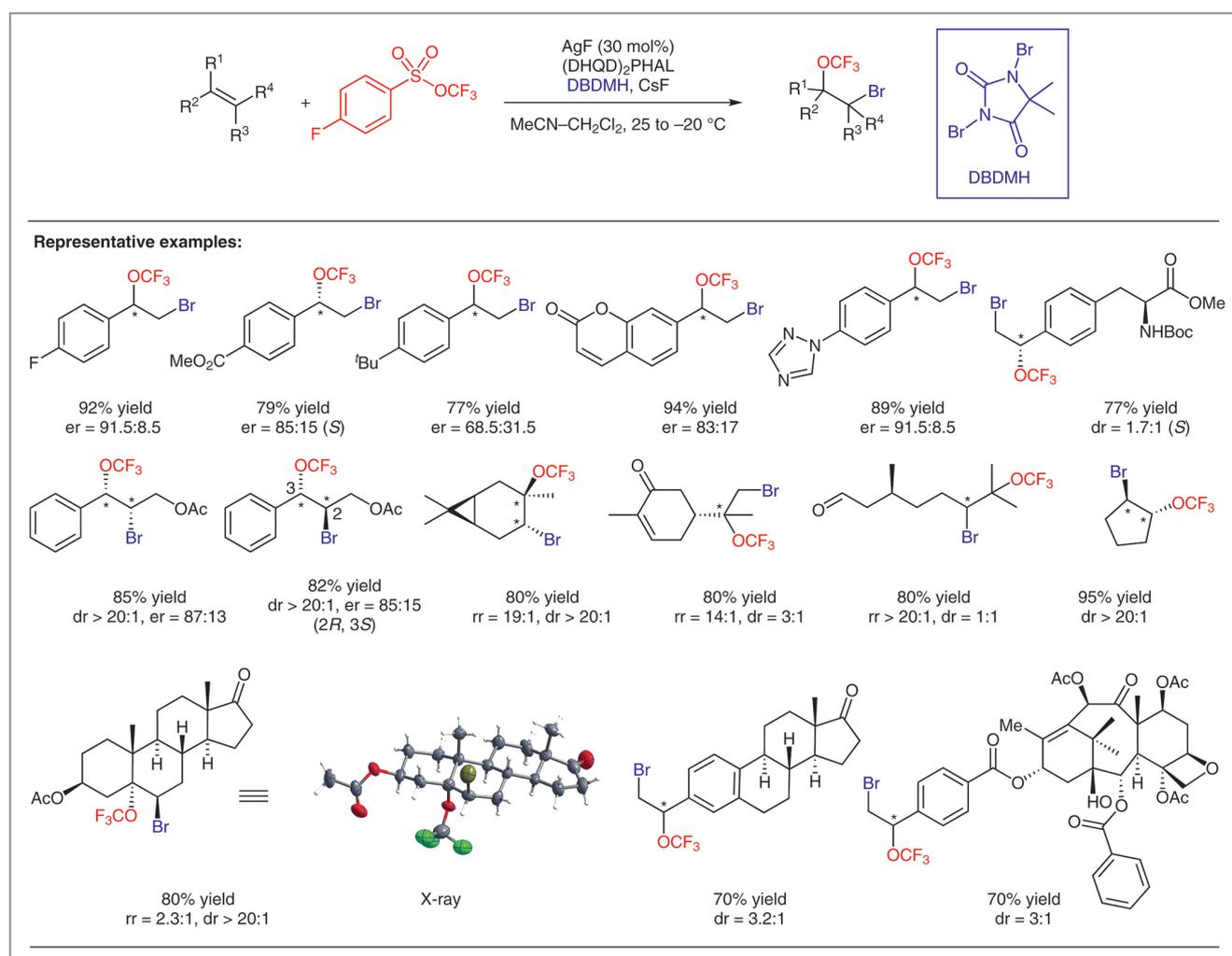
“We initially investigated TFMS and observed that it can be used as a new trifluoromethoxylation reagent. More importantly, when we used the chiral ligand (DHQD)<sub>2</sub>PHAL, asymmetric bromotrifluoromethoxylation of alkenes was achieved using AgF as a catalyst,” said Professor Tang.

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

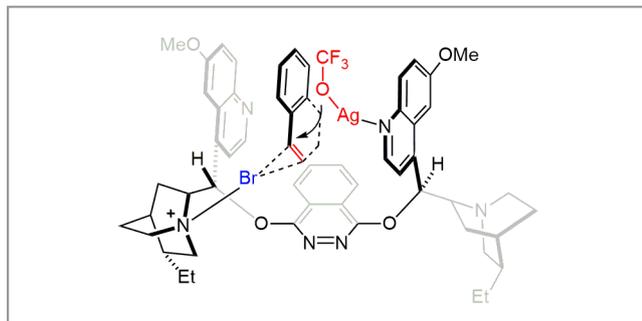
reaction, with good yields but lower enantioselectivities.” This reaction was also extended to more sophisticated scaffolds. “The significance of this reaction was demonstrated by the application for the late-stage bromotrifluoromethoxylation of natural products and derivatives, such as an estrone derivative and a taxol derivative,” added Professor Tang.

The chiral ligand, dimeric cinchona alkaloid (DHQD)<sub>2</sub>PHAL, plays the most important role in the asymmetric process. Professor Tang said: “The styrene substrates are probably located in the chiral pocket via  $\pi,\pi$ -stacking with the quinoline of the ligand (Figure 2). Due to the absence of  $\pi,\pi$ -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



**Figure 2** One possible transition-state model

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.”

Mattes Feneck

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**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.



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