Trifluoromethanesulfonyl Azide as a Bifunctional Reagent for Metal-Free Azidotrifluoromethylation of Unactivated Alkenes

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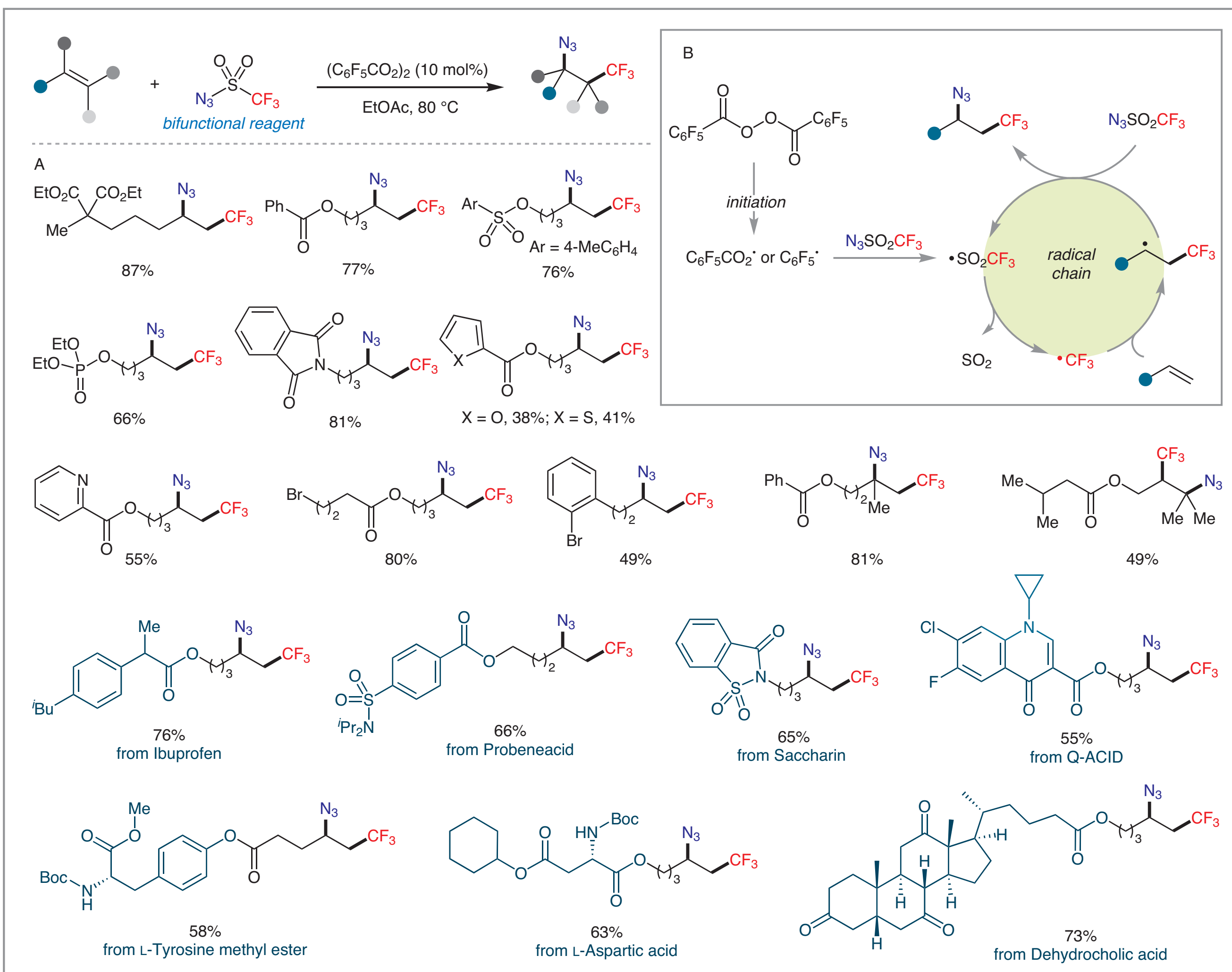
Trifluoromethyl-containing molecules have significant importance in medicinal chemistry due to the unique physicochemical and electronic properties of fluorinated substituents (*Science* **2007**, *317*, 1881–1886). However, the trifluoromethyl group is entirely xenobiotic – e.g. not found in nature – so the only accessible entry to CF_3-substituted molecules is chemical synthesis, which renders this area of research a particularly exciting and stimulating challenge for organic chemists. Alkene azido-trifluoromethylation is a straightforward strategy to concomitantly install a trifluoromethyl group and an azide group in a single step across a carbon–carbon double bond. However, the state-of-the-art catalytic methods based on azido-trifluoromethylation are limited to transition-metal-catalyzed three-component reactions, which generally



Scheme 1 Trifluoromethanesulfonyl azide as a bifunctional reagent for azido-trifluoromethylation of unactivated alkenes. A: Selected examples. B: Proposed mechanism.

require the use of expensive CF_3 sources (e.g., Togni's reagents, Umemoto's reagent) and a separate azide reagent; moreover, it generally features a low level of mass efficiency. Therefore, the development of more environmentally benign and atom-economic alternatives is synthetically appealing, besides being conceptually novel.

The group of Professor Wen-Bo Liu at Wuhan University (P. R. of China) was investigating the use of trifluoromethanesulfonyl azide ($N_3SO_2CF_3$) as a nitrene precursor in the iron-catalyzed intermolecular allylic C–H amination reaction, when a serendipitous discovery, namely a direct azido-trifluoromethylation of the alkene by $N_3SO_2CF_3$, occurred. "After systematic optimization, we finally developed an unprecedented azido-trifluoromethylation reaction of unactivated alkenes employing $N_3SO_2CF_3$ as a bifunctional reagent for the introduction of both CF_3 and N_3 groups under metal-free conditions (Scheme 1)," said Professor Liu. He continued: "This simple method avoids the use of expensive and low-atom-economy CF_3 precursors, and allows quick access to vicinal trifluoromethyl azides. The substrate scope is substantial, with heterocycles and amino acids being well tolerated." The application of this method was also illustrated by the group through scale-up synthesis, late-stage functionalization of complex bio-important molecules, and derivatization of the products into CF_3-containing amines and other privileged heterocycles. Professor Liu observed: "Mechanistic investigations revealed that this reaction probably involves a radical chain process. After being initiated by thermal decomposition of an acyl peroxide and addition of a resulting radical to $N_3SO_2CF_3$, a trifluoromethyl radical is generated and this adds across the alkene double bond providing an alkyl radical, which in turn reacts with $N_3SO_2CF_3$ yielding the azido-trifluoromethylation product along with regeneration of the chain-carrying radical."

Professor Liu concluded: "We believe that this simple strategy provides a new pattern for the difunctionalization of alkenes, which is especially useful for the synthesis of complex pharmaceutical compounds from readily available feedstock chemicals, such as abundant alkenes. Given its atom-economic nature and cost-efficient features, this method could find applications in organic synthesis and medicinal chemistry."

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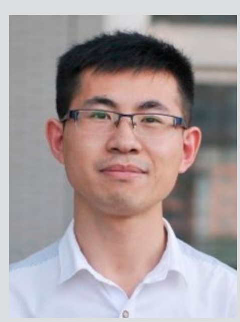

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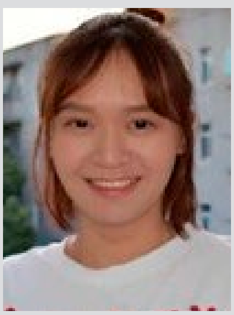

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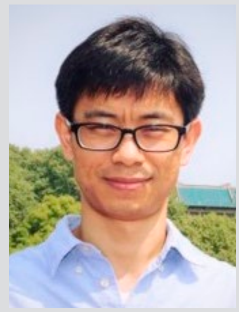

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Wen-Bo Liu was born in China and received his Bachelor's degree in chemistry from Nankai University (P. R. of China) in 2006. He obtained his Ph.D. in organic chemistry (2011) from Shanghai Institute of Organic Chemistry (SIOC, P. R. of China) under the supervision of Prof. Li-Xin Dai and Prof. Shu-Li You. After working as a postdoctoral scholar with Professor Brian M. Stoltz at Caltech (USA), he started his independent research at Wuhan University (P. R. of China) in 2016. His group's research interests include asymmetric catalysis, green synthetic chemistry, and silicon chemistry.

