Asymmetric Synthesis of Sulfoximines, Sulfonimidoyl Fluorides and Sulfonimidamides Enabled by an Enantiopure Bifunctional S(VI) Reagent

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Sulfur in its various oxidation states represents a key element in a range of important chemophores in the natural and industrial worlds. According to Professor Justin M. Lopchuk at the H. Lee Moffitt Cancer Center and Research Institute (USA), the higher-order S(IV) and S(VI) functionalities – such as sulfoxides, sulfones and sulfonamides – have historically dominated the sulfur-containing pharmaceutical, agrochemical, and materials landscape. “Despite the successful applications of the previously mentioned S(IV) and S(VI) groups, other less common sulfur-containing sulfonimidoyl functionalities exist that have been, until recently, largely overlooked in the realm of chemical discovery,” said Professor Lopchuk to SYNFORM, adding: “Sulfoximines, sulfonimidamides, and sulfonimidoyl fluorides (Figure 1) are aza-derivatives of sulfonyls and are among the underrepresented S(VI) groups – each providing unique structural and physicochemical properties to be exploited for a variety of applications. As drug discovery programs begin to seek alternative chemical spaces with increasing three-dimensionality and complexity, sulfonimidoyl groups offering additional spatial vectors and a stereogenic *S*-center will become more attractive if synthetic methodologies permit their use.”

Drawing inspiration from highly efficient SuFEx chemistry and modular sulfinyl reagents, Professor Lopchuk’s group sought to develop a chiral bifunctional reagent platform to address the asymmetric control of the sulfur stereocenter in sulfonimidoyl groups. Professor Lopchuk said: “During the discovery phase, we prioritized synthetic practicality, feasibility, and bench stability of the reagent. Ideally, the source of chirality (both enantiomers) would be either available directly from the commercial chiral pool or derived from it with minimal chemical modifications. The widely available (*R*)- and (*S*)-*tert*-butyl sulfinamides (<$1/g) were chosen as the starting building blocks based on factors such as financial feasibility, the stereogenic stability of *tert*-butyl sulfinyls, and known activation methods of *tert*-butyl S(VI) derivatives for further S-functionalization. We initially believed reagent stability would be an additional feature of the sulfonimidoyl fluoride SuFEx design; however, the choice of the *N*-protecting group directly correlated to and had an impact on the stability. Electron-withdrawing protecting groups (Boc, Bz, Piv) provided increased stability, while introducing an additional electrophilic center. Selective addition to sulfur with carbon nucleophiles turned out to be synthetically challenging.”

Attempts to activate the S–F bond using the previously mentioned protecting groups were unfruitful. Therefore, the authors’ final design hinged on increasing the electronic and steric bulk around the carbonyl protecting group. “Dimethyl and diethyl carbamoyl groups were evaluated, both showing notably increased stability relative to their acyl and carbamate counterparts, and, to our delight, increased SuFEx selectivity with phenyl lithium,” explained Professor Lopchuk. He continued: “By further increasing the steric bulk with an *N*,*N*-diisopropyl carbamoyl function, we obtained a solid and crystalline sulfonimidoyl urea with markedly improved stability and exclusive SuFEx selectivity using organolithiums. The perfect balance of electronics and sterics allowed for the development of the bench-stable (>1 year) and selective chiral SuFEx reagent ***t*-BuSF**.”

A new sulfonimidoyl *N*-protecting group that provides stability under a variety of conditions was therefore discovered, enabling the initial S(VI) transfer between a wide range of organolithium reagents (>30 examples, 95% to >99% ee) including aryl, heteroaryl, and alkyl – with many gram-scale examples. Professor Lopchuk remarked: “The resulting *tert*-butyl sulfoximines are stereogenically stable intermediates that were rapidly diversified to sulfonimidoyl fluorides, sulfoximines or sulfonimidamides by a novel redox-neutral *S*-activation strategy in a single step (or even stepwise), without loss of enantiopurity (>30 examples, >99% ee). Furthermore, ***t*-BuSF** was applied to the enantiopure synthesis of five pharmaceutical targets with improvements in overall step-count, yield and enantiopurity.”

The authors believe that the utility and practicality of ***t*-BuSF** warrant its adoption and wide implementation in organic chemistry research, for future investigations of the unique properties of, *but not limited to*, sulfoximines, sulfonimidoyl fluorides, and sulfonimidamides. Professor Lopchuk concluded: “The significant improvements in overall synthetic efficiency of this method over the current state of the art, the

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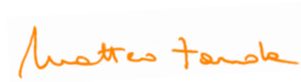
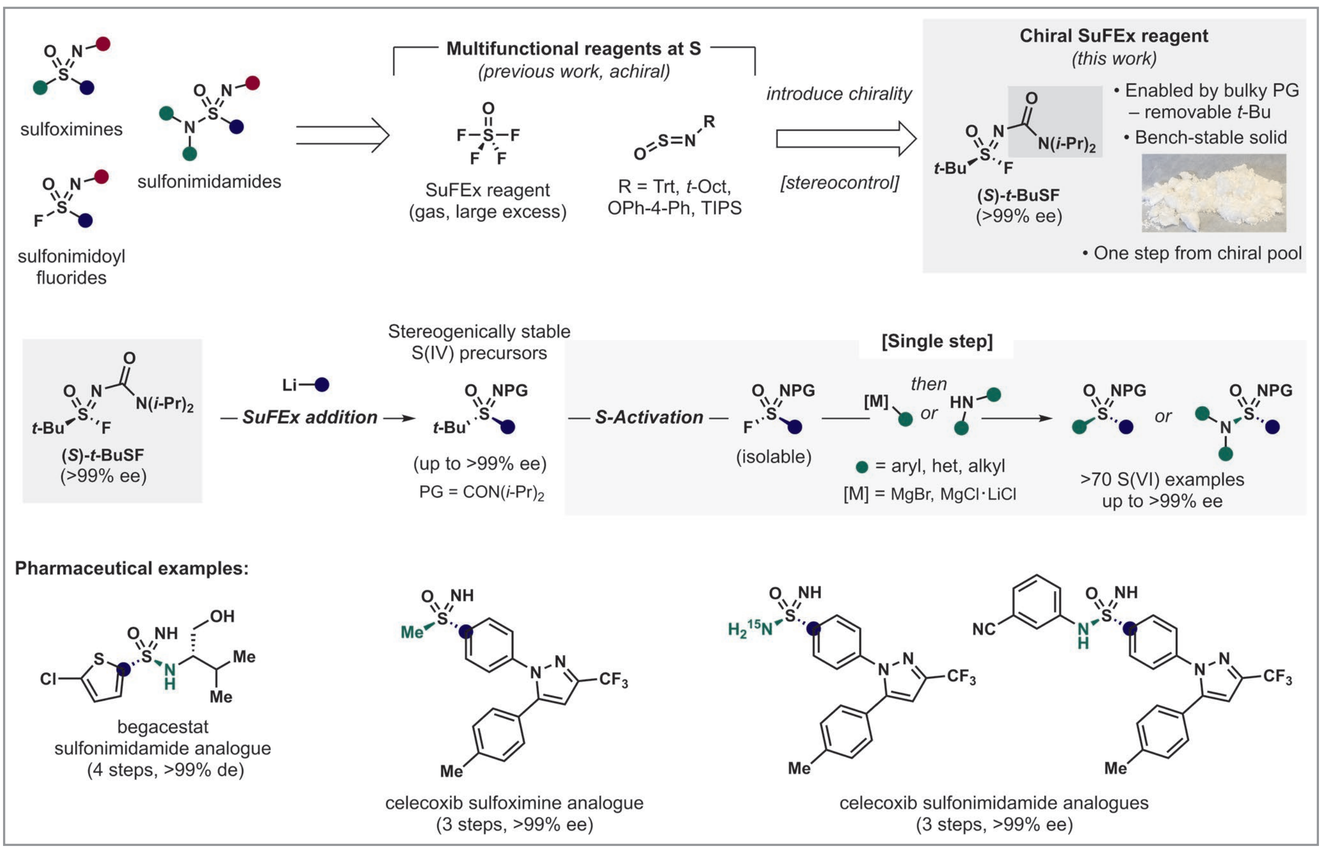
stability of our reagent and intermediates, and the wide-ranging implications to fields and areas of chemical research other than medicinal chemistry, such as chemical biology, organocatalysis, photochemistry, electrochemistry, organometallic chemistry, and materials chemistry, make this a highly valuable reagent platform for the scientific community."





Scheme 1 A chiral SuFEx reagent platform developed for the asymmetric synthesis of sulfonimidoyl functionalities

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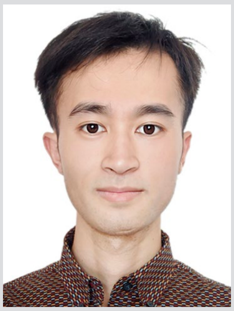
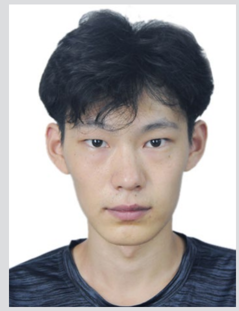


Dr. S. Teng

Shun Teng obtained his BSc in pharmaceutical science from Wuhan University (P. R. of China) in 2018. After a rotation in the chemistry department, he began his graduate studies at Lee Moffitt Cancer Center and Research Institute (USA) under the supervision of Prof Justin M. Lopchuk in 2020. His research focused on asymmetric synthesis of sulfur-containing compounds. In 2023, he received his PhD in chemistry and moved back to China. Today, he serves as a senior scientist at Sokan New Material (P. R. of China) with research on material development and application.

Dr. Z. Shultz

Zachary Shultz received his PhD in chemistry from the University of South Florida (USA) in 2019 under the guidance of Professor James Leahy where he focused on the total synthesis of cannabinoids and marine natural products. After completing his PhD, he joined Dr. Justin Lopchuk's group at H. Lee Moffitt Cancer Center and Research Institute (USA) as a postdoctoral fellow, developing new practical synthetic methodologies and leading his lab's medicinal chemistry efforts. He is currently a research scientist at Moffitt Cancer Center working towards an independent career at a university or research institute.



C. Shan

Chuan Shan received his BS degree from Shandong University (China) in 2017. He is currently pursuing his PhD degree under the supervision of Professor Justin M. Lopchuk. His research interests focus on the development of novel synthetic methodologies based on S(IV) and S(VI).

Prof. J. M. Lopchuk

Justin M. Lopchuk received a dual BS degree in chemistry and biology from Muhlenberg College in Allentown, Pennsylvania (USA). His PhD studies were conducted at Dartmouth College (USA) in the laboratory of Prof. Gordon Gribble with a focus on heterocyclic chemistry and the synthesis of indole-containing natural products. He completed postdoctoral work on the synthesis of diterpenoid natural products and strain-release functionalization at The Scripps Research Institute in La Jolla, California (USA) under the guidance of Prof. Phil Baran. In 2017, he began his independent career as an Assistant Professor in the Department of Drug Discovery at Moffitt Cancer Center (USA) and was promoted to Associate Professor with tenure in 2023. His group focuses on the development of new methods for C–N, C–S, and C–C bond formation, the design of new covalent reactive groups, the total synthesis of bioactive natural products, and the structure-based drug design of small molecule inhibitors and PROTACS.

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