Group : Organic Chemistry (ORC)
Project : **Understanding SuPhenEx/SuFEx Reaction Processes by High-Throughput Modeling**
Supervisors : Guanna Li and Akash Krishna

Keywords. Computational Modeling, Click Chemistry, Reaction Mechanism

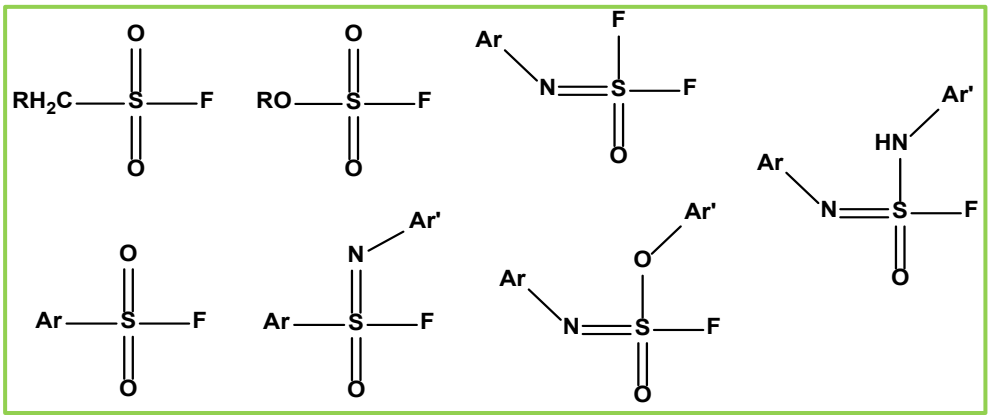
Introduction. Synthetic methodologies that use modular approaches to generate complex molecules efficiently are of great importance in materials science, chemical biology, and drug development. In 1999, K. B. Sharpless used the term "click chemistry" to define a set of reactions which are broad in scope, high yielding, stereospecific, and result in few or no byproducts.[1] The foundational reactions of click chemistry include cycloaddition reactions, hetero Diels-Alder reactions, Thiol-Michael Additions, and more recently developed Sulfur fluoride exchange (SuFEx) reactions. Studying the mechanism and bonding in these reactions by computer modeling will lead to a deeper understanding of the reactivity, and large-scale screening of amount of substrates before trying every reaction in the lab. With the recent developments in computer hardware and increased efficiency of algorithms, we can realize the experiments done in a laboratory inside a computer by simulating these chemical systems at atomic level with high accuracy.

Goal. Recently the first intrinsically enantiospecific click reaction and the first case of a SuFEx-derived Dynamic covalent chemistry (DCC) reaction have been developed via Sulfur–Phenolate Exchange (SuPhenEx) by our group.[2][3] To further extend the scope of such reactions and to disclose the inner law governing the reactivity, we plan to perform a large-scale computational modeling to screen various sulfur hubs and nucleophilic substrates (see figure). This project aims to understand the reaction mechanism of these sulfur hubs with various nucleophiles and figure out the essential structural and electronic factors dominating their reaction performances (bonding nature).

Nucleophiles

- **R-CH$_2$-OH**
- **Ar-OH**
- **Ar-O-SiR$_3$**
- **R-CH$_2$NH$_2$**
- **R-CH$_2$NHR'**
- **R-CH$_2$NR'$_2$**
- **Ar-NH$_2$**

Sulfur Hubs



Topics to be studied. Initially, the focus will be on exploring the mechanisms of the above reactions using high-level quantum mechanical calculations. Subsequently, these data will be processed by energy decomposition Analysis (EDA) to feature the characteristics of the transition state and disclose the intrinsic driving force of the SuFEx reaction.

Approach and Technique. Science proceeds by both experiment and theory. Simple experimental facts without a theory to interpret them do not satisfy our need for understanding. This project will involve Density functional theory (DFT) calculations using Gaussian and molecular modeling construction using Gaussview. Mechanistic studies involve optimizing the structures and locating the transition states, and EDA will be carried out using PSI4 a/o Amsterdam modelling suite (AMS) to address the fundamental bonding nature. With this, you will also learn to operate Unix systems on our supercomputer cluster.

Contact details: Dr. Guanna Li, room Helix 7026, email guanna.li@wur.nl

[1] H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angewandte Chemie International Edition* **2001**, *40*, 2004-2021.
[2] D.-D. Liang, D. E. Streefkerk, D. Jordaan, J. Wagemakers, J. Baggerman, H. Zuilhof, *Angewandte Chemie International Edition* **2020**, *59*, 7494-7500.
[3] Y. Chao, A. Krishna, M. Subramaniam, D. D. Liang, S. P. Pujari, A. C. H. Sue, G. Li, F. M. Miloserdov, H. Zuilhof, *Angewandte Chemie International Edition* **2022**.