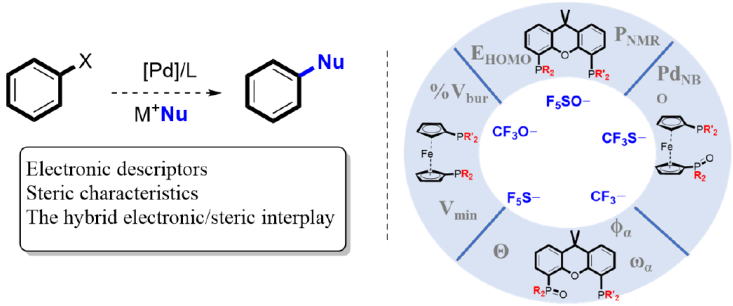
In Silico Ligand Design to Promote Formation of Challenging Hypervalent Sulfur- and Alkoxy- Fluoro-Appended Aromatic Cores in Novel Fluoro-Pharmaceuticals and Functionalized Materials

Seyedeh Maryamdokht Taimoory[1,2] and Melanie S. Sanford[1]

[1]University of Michigan, USA, Email: seyedeht@umich.edu
[2]University of Windsor, USA

The ability to build challenging chemical bonds, via a conceptually well-understood catalytic process enabled us to design variety of promising novel drug molecules, biologically valuable building blocks, and the advanced functional materials [1].

Despite the impressive pharmacological activity and unique physicochemical properties of fluorine-containing alkoxy (OSF_5) and alkyl sulfides (SF_5) functional groups, these per-fluorinated moieties are still an underexplored class of compounds [2]. From a synthetic standpoint, this can be due to the lack of a unique, robust, and reliable synthetic methodology for their incorporation into aromatic cores via either a direct or a late-stage functionalization strategy. From a medicinal chemistry point of view, the SF_5 group behaves like a structural analogue of the CF_3, and SCH_2CF_3 groups, while the OSF_5 function can be consider as an enhanced analogue of OCF_3, and SCF_3, but both show better thermal and chemical stability, electronegativity, and in some cases lipophilicity [3].



Determining the optimal metal-ligand combinations and the property space of ligands to effectively promote formation of organofluoro-appended aromatic compounds, play the important role in directing the reaction outcomes. Herein, we will present our ongoing computational study of the key ligand descriptors to design novel catalyst capable of promoting the challenging hypervalent sulfur- and alkoxy-fluorides@C(sp2) bonds via a combined high-throughput computational screening and reaction workflow analysis. We anticipate that this advanced computational study will provide access to a wide variety of novel challenging functional-containing chemical motifs in the pharmaceutical and materials chemistry areas.

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[3] a) Chan, J. M. W. *J. Mater. Chem. C*, 2019, **7**, 12822; b) Kirsch, P.; Bremer, *M. Chimia*, 2014, **68**, 363.