

The hydroxyl group is one of the most prevalent functionalities in all of chemical space, being found in natural products, nucleic acids, sugars, some amino acids, and other structural biopolymers such as cellulose and lignin. However, the use of alcohols as a direct source of chemical matter is generally limited to decades-old reactions like O-functionalization (e.g. esterification and alkylation) or oxidation to a more reactive carbonyl. In the context of small molecule functionalization, this represents a knowledge gap for the translation of abundant alcohol precursors into valuable chemical scaffolds for pharmaceutical and agrochemical synthesis. The limited toolset of alcohol functionalization also restricts the use of the abundant biopolymer lignin as a potential renewable source of fine chemicals, *despite its clear attractiveness as an alternative to fossil fuel hydrocarbons*. Similarly, epoxy resins are one of the most widely-used materials for adhesives and coatings, but no controlled method exists for their degradation. We propose that these seemingly disparate challenges in small molecule functionalization and polymer degradation can be addressed through a common platform of alkoxy radical β -scission enabled by *ansa*-titanocene photocatalysis.

We intend to develop a new platform for photocatalysis based on ligand-to-metal charge-transfer (LMCT) of *ansa*-titanocene alkoxides. In particular, the Lewis acidity of Ti will be leveraged to perform excited state β -scission of Ti-bound alkoxy radical cations, which will be a first example of catalyst control over alkoxy radical reactivity. This *fundamental insight* will enable the C₁ extrusion of nearly any alcohol substrate in diverse contexts. Accordingly, the proposed work will expand the utility of the alcohol functionality as a diversifiable handle, which will have dramatic effects on the way chemists consider construct complex molecular scaffolds.

We will use the proposed system to achieve three main aims:

Aim 1: We will optimize *ansa*-titanocene catalyst structure to develop the core technology of catalytic alkoxy radical generation and β -scission. The optimized reactivity will be leveraged for simple alcohol functionalization and cross-coupling, as well as C1-selective sugar functionalization.

Aim 2: We will develop a catalytic cascade for the deconstruction of epoxides to generate difluoromethyl(ene) functionalities. This orthogonal approach to the valuable CF₂ group will enable the translation of abundant olefins into scaffolds of value for pharmaceutical, agrochemical, and fragrance synthesis.

Aim 3: We will apply the Ti-LMCT platform to controlled degradation of hydroxylated polymers. This will enable the sustainable synthesis of simple aromatic monomers from the abundant biopolymer lignin, as well as the remediation of typically inert epoxy resins.

These three aims will serve to establish Ti-LMCT catalysis as a broadly-applicable platform for the functionality of the alcohol moiety across small-molecule, biomolecule, and macromolecule scaffolds. Throughout all of the proposed work, we will approach reaction development through a mechanistic lens, enabled by the modular, discrete *ansa*-titanocene catalyst platform. This proposal is *innovative* as it would be the first demonstrated example of catalyst control of alkoxy radical reactivity, as well as the first application of *ansa*-titanocene LMCT in catalysis. This proposal is *significant* as it describes the most general platform for alcohol activation to alkoxy radical, ultimately enabling the functionalization of nearly any aliphatic alcohol substrate, regardless of specific context. Accordingly, the work proposed would have impact not just in organic chemistry, but also medicinal, polymer, environmental, and sustainable chemistry.

Finally, we envision the work carried out under this seed grant to yield preliminary data for a minimum of five grant proposals, for both the NIH (R35 and R01) and NSF (CAREER and DRP), as well as private sources. This seed grant will help to establish a collaboration between a junior and senior faculty member in the Department of Chemistry that will benefit both researchers by enhancing the cross-disciplinary work carried out in their labs and enhancing knowledge transfer between the groups.