High-Throughput Discovery of Earth-Abundant Single-Site Catalysts for C–H Activation

by

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ABSTRACT

Selective C–H bond functionalization remains a key challenge in catalysis. Natural metalloenzymes demonstrate that earth-abundant metal centers can mediate C–H activation with high efficiency. This motivates the development of synthetic single-site catalysts, such as metal-organic frameworks (MOFs) and transition metal complexes (TMCs). However, exploring the rapidly expanding design spaces for these materials via experimental trial-and-error is prohibitively slow. In this dissertation, I developed high-throughput screening workflows that combine first-principles simulations, data-driven modeling, and targeted experimental validation to explore vast spaces of synthetically accessible materials and identify new active site motifs for C–H activation.

Methane-to-methanol (M2M) conversion remains a prototypical but unresolved C–H functionalization challenge. MOFs have emerged as promising catalysts for this transformation, yet most studies have focused on a limited set of framework topologies despite the existence of more than 100,000 experimentally synthesized MOFs. To systematically explore their broader chemical space, I developed CatMOF, a modular workflow that prescreens catalytically relevant MOFs predicted to be stable, previously unexplored for catalysis, and containing accessible open metal sites, and generates cluster models of the MOF secondary building units (SBUs) for density functional theory (DFT) evaluation for any catalytic transformation. Application of CatMOF to the Computation-Ready Experimental (CoRE) MOF database, followed by large-scale DFT, revealed that widely used linear free energy relationships (LFERs) between metal-oxo formation and hydrogen atom transfer (HAT) steps can break down across structurally diverse MOF spaces. Mn-based MOFs emerged as promising but underexplored candidates, combining favorable M2M thermodynamics and kinetics. Experimental evaluation highlighted challenges in MOF synthesis reproducibility and thorough solvent evacuation, providing feedback for refining the computational workflow. Finally, the resulting DFT datasets were used to train surrogate machine learning models that directly predict M2M reaction energetics, laying the foundation for further accelerating MOF screening.

Bioinspired Fe-based TMCs are well known for C–H activation in small molecules yet show limited activity for polyolefin oxidation relative to Ru analogues. To elucidate the origins of these differences, I performed a large-scale DFT study comparing over 200 Fe and Ru TMCs that differed only in their metal centers. The calculations revealed strong spin-state and metal-

dependent reactivity trends. Fe TMCs more readily disrupt established LFERs and access spin-allowed C–H activation pathways, while Ru complexes generally follow more rigid scaling relationships and favor spin-forbidden pathways. These results suggest that Fe catalysts offer greater tunability for macromolecular C–H activation, warranting continued experimental exploration. Despite this promise, extending earth-abundant homogeneous catalysts to selective M2M conversion remains elusive. To address this, I applied multi-objective Bayesian optimization, targeting improved M2M turnover over a design space of ~22 million synthetically accessible Mn- and Fe-based TMCs. The optimization was guided by uncertainty-aware neural network surrogates, enabling data-efficient candidate selection for DFT evaluation. This approach identified both Mn and Fe Pareto-optimal catalysts with predicted turnovers competitive with previously reported systems. Tetraaza-based macrocyclic ligands emerged as a privileged motif, recovering known enzymatic design motifs in a previously unexplored chemical space.

Collectively, this work demonstrates how integrated computational-experimental workflows can navigate unchartered catalyst design spaces and uncover novel earth-abundant catalysts while revealing key design principles that guide future catalyst design.

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