Université de Montréal, Montréal, QC, Canada

THIRD INTERNATIONAL SYMPOSIUM
ON C–H ACTIVATION

May 30 – June 2, 2016

IL08 – Exploring the C(sp^3)−H space in bioactive molecules with engineered P450 catalysts

Rudi Fasan*

Department of Chemistry, University of Rochester, 120 Trustee road, Rochester NY 14627, United States

E-mail: rfasan@ur.rochester.edu

Our group is interested in exploring cytochrome P450 catalysis as a strategy to mediate the selective, late-stage transformation of unactivated C(sp^3)−H bonds in organic molecules. P450 enzymes constitute attractive catalytic platforms for the oxyfunctionalization of organic compounds, but the lack of effective strategies to refine their reactivity and site-selectivity currently limits their utility for synthetic applications. To tackle this problem, efforts in our laboratory have focused on implementing systematic, rationally-driven methodologies to modulate, predict, and ultimately, fine-tune the selectivity of these enzymes. In this talk, we will give an overview of our recently introduced 'P450 fingerprint'-based methods to rapidly map the active site configuration of these enzymes and predict their reactivity toward a variety of target substrates. Leveraging these methodologies, we have begun to evaluate the potential of P450-mediated chemoenzymatic C−H functionalization as a new, enabling strategy for the late-stage elaboration and optimization of bioactive natural product scaffolds. In the second part of the talk, we will present our recent progress toward developing P450s into efficient catalysts to promote the selective amination of aliphatic C−H bonds via nitrene C−H insertion, a transformation which has so far been restricted to the realm of synthetic transition metal catalysis. The presentation of these results will be accompained by a discussion on our current mechanistic understanding of these reactions and the implementation of mechanism-guided rational design strategies to enhance the C−H amination reactivity of these biocatalysts.