The Functionalization of C—H Bonds

M. Christina White

University of Illinois, University of Illinois, USA

Among the frontier challenges in chemistry in the 21st century are the interconnected goals of increasing control of chemical reactivity while synthesizing and diversifying complex molecules with higher efficiency. Traditional organic methods for installing oxidized functionality rely heavily on acid-base reactions that require extensive functional group manipulations (FGMs). In contrast, nature routinely uses allylic and aliphatic C—H oxidation methods, generally mediated by heme and non-heme iron monooxygenase enzymes, to directly install oxidized functionality into the preformed hydrocarbon framework of complex molecules. Due to their ubiquity in complex molecules and inertness to most organic transformations, C—H bonds have typically been ignored in the context of methods development for total synthesis. The exceptions to this rely on substrate directing groups to facilitate site-selectivity and reactivity. The discovery and development of highly selective oxidation methods for the direct installation of oxygen, nitrogen and carbon into allylic and aliphatic C—H bonds of complex molecules and their intermediates are discussed. Unlike Nature which uses elaborate shape or functional group recognition active sites, this chemistry harnesses the subtle electronic, steric, and stereoelectronic interactions between C—H bonds and small molecule transition metal complexes to achieve high regio-, chemo-, stereo- and site-selectivities with high substrate generality- and without the requirement for directing groups. Our current understanding of these interactions gained through empirical and mechanistic studies will be discussed. A user-friendly catalyst reactivity model that calculates and even predicts the major site of oxidation as well as the magnitude and direction of the site-selectivity in complex substrates as a function of catalyst will be delineated. Novel strategies for streamlining the process of complex molecule synthesis and diversification enabled by these methods will be presented.