Aliphatic C—H Oxidation for Late-Stage Functionalization

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The majority of small molecule therapeutics are made up of aromatic as well as increasingly more aliphatic hydrocarbon scaffolds. Reactions that perform C(sp^3)—H oxidation remote from aromatic functionality would enablethe powerful late-stage functionalization strategy for diversifying compounds and identifying metabolites to be more fully realized in a laboratory setting. Such transformations have not been achieved because of the challenges of hydroxylating an inert C—H bond in the presence of oxidatively more labile π-functionality. Iron enzymes are the only known catalysts capable of hydroxylation of strong aliphatic C—H bonds in the presence of π-functionality by restricting substrate access to the oxidant, however, this supramolecular approach has not been successful with small molecule catalysts. This talk will discuss the discovery of a small molecule catalyst system that achieves such chemoselectivity via an unexpected synergy of catalyst design and additive. Using this catalyst system, preparative remote methylene hydroxylation will be shown in 50 aromatic compounds that have medicinally important halogen, oxygen, heterocyclic, and biaryl moieties. Late stage methylene oxidation will also be demonstrated on five drug scaffolds, including ones where other non-directed C—H oxidants effect oxidation at only activated sites.