C—H Oxidations and Organic Synthesis

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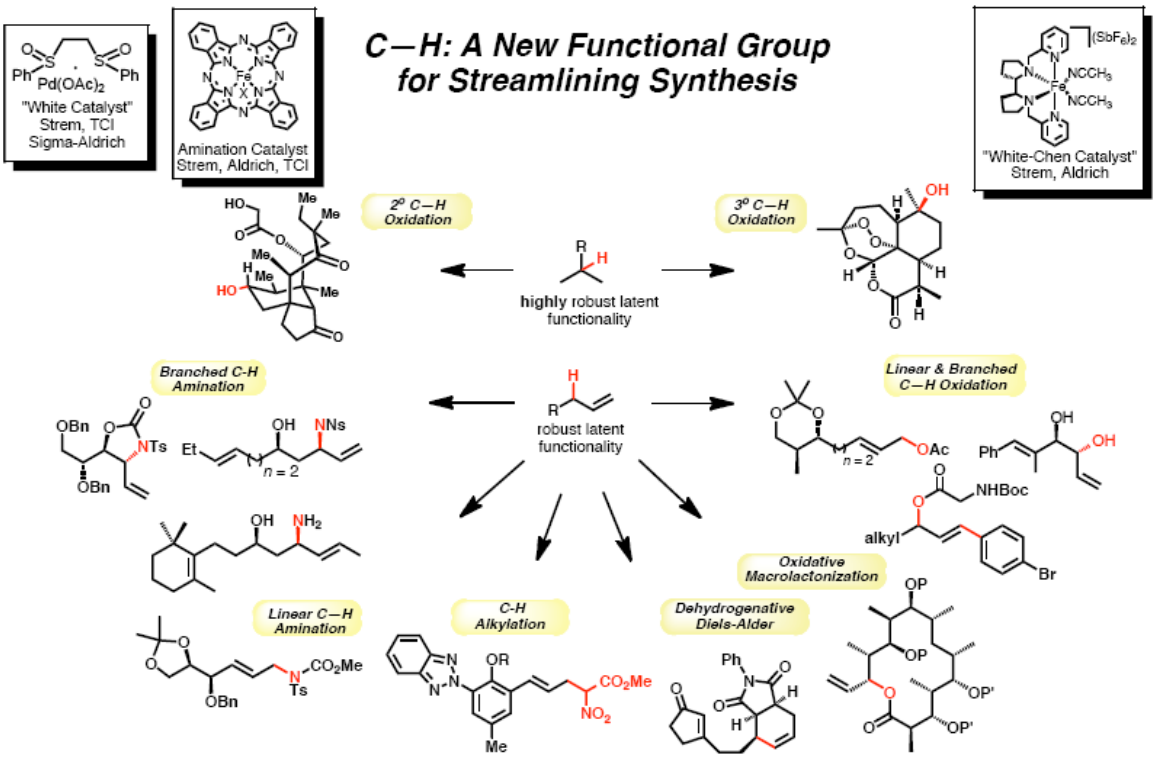
Among the frontier challenges in chemistry in the 21st century are the interconnected goals of increasing control of chemical reactivity and synthesizing stereochemically and functionally complex molecules with higher levels of efficiency. Although it has been well demonstrated that given ample time and resources, highly complex molecules can be synthesized in the laboratory, too often current reaction manifolds do not allow chemists to match the efficiency achieved in Nature. Traditional organic methods for installing oxidized functionality rely heavily on acid-base reactions that require extensive functional group manipulations (FGMs) including wasteful protection-deprotection sequences. 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. 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 enzyme 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-, and stereoselectivities. Our current understanding of these interactions gained through empirical and mechanistic studies will be discussed. Novel strategies for streamlining the process of complex molecule synthesis enabled by these methods will be presented. Collectively, our program aims to change the way that complex molecules are constructed by defining the principles that govern reactivity of C—H bonds in complex molecule settings.



Aliphatic C—H Oxidation: *Science* 2007 (*318*) 783; *Science* 2010 (*327*) 566; *Nature Chemistry* 2011 (*3*) 216; *Science* 2012 (*335*) 807. **Allylic C—H Oxidation:** LAO: *JACS* 2004 (*126*) 1346; 2010 (132) 11323; *OL* 2005 (*7*) 223; *ACIE* (*45*) 8217. BAO: *JACS* 2005 (*127*) 6970; 2006 (*128*) 15076; *ACIE* 2008 (47) 6448; *JACS* 2011 (*133*) 12584. **Macrolactonization:** *JACS* 2006 (*128*) 9032; *Nature Chem.* 2009 (*1*) 547; *ACIE* 2011 (*50*) 2094. AA: *JACS* 2008 (*130*) 14090; *ACIE* 2011 (*50*) 6824. LAA: *JACS* 2008 (*130*) 3316; *JACS* 2009 (*131*) 11701. BAA: *JACS* 2007 (*129*) 7274; *JACS* 2009 (*131*) 11707. DDA: *JACS* 2011 (*133*) 14892. **Allylic amination with Fe:** *JACS* 2012 (*134*) 2036.