Pursuing Selectivity in Biologically Inspired C-H Oxidation Reactions

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Selective oxidation of unactivated aliphatic C–H bonds constitutes a potentially very useful reaction because it introduces functionality in otherwise inert aliphatic skeletons.[1] However, the differentiation among multiple C–H bonds with powerful oxidizing agents and predictability in site selectivity are often unsurmountable problems that prevent the widespread incorporation of these reactions in synthetic planning. Another critical issue is represented by product chemoselectivity because the first formed products are generally more susceptible to oxidation than the starting substrate, and they are thus overoxidized or obtained in relatively low yield.

Intense research efforts have been devoted to uncover the factors that govern C–H bond reactivity against hydrogen atom transfer (HAT) reagents, pointing toward the important role played by bond strengths as well as by steric, electronic, stereoelectronic, and torsional effects in these processes.[1] On the basis of these elements, C–H bonds are recognized to bear an innate relative reactivity against oxidizing agents, which defines the site selectivity in the oxidation of molecules containing different C–H bonds. However, this is basically unaffected by the nature of the oxidant, a factor that effectively limits the potential of the reaction.

Our research efforts have been placed in the design of metal catalysts based in iron and manganese coordination complexes. These complexes react with hydrogen peroxide producing high-valent metal-oxo species, which are powerful oxidants and can perform the oxidation of aliphatic C-H bonds via an initial HAT process. Aliphatic C-H oxidation with these catalysts has been pursued with the final goal to set predictable C-H site selective oxidations, alternative to the innate C-H relative reactivity.[2] Two different strategies have been followed towards this goal; a) via catalyst design, incorporating chirality, steric bias and/or substrate recognition units in the catalyst architecture, and b) exploiting the polarity reversal exerted by strong H-donor fluorinated alcohol solvents.

[1] T. Newhouse, P. S. Baran, *Angew. Chem., Int. Ed.* **2011**, *50*, 3362–3374
[2] M. Milan, M. Salamone, M. Costas, M. Bietti, *Acc. Chem, Res.* **2018**, *51*, 1984–1995.