Simultaneous Generation of Multiple Chiral Centers by Enantioselective C-H Hydroxylation of Tertiary C-H Bonds

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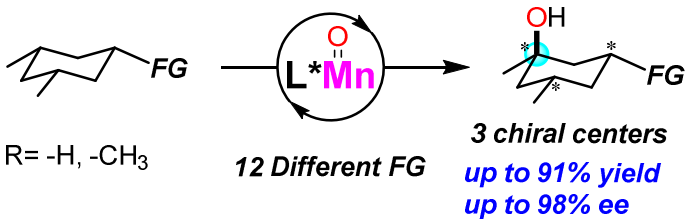
Given the ubiquity of chiral oxygenated moieties in natural and bioactive products, there is a growing interest in developing efficient strategies to achieve them in enantioselective manner. Due to the high fraction of C(sp^3)-H bonds in available feedstock's, enantioselective C-H oxidation carries considerable appeal in this context. However, enantioselective C-H oxidation is particularly challenging because it requires highly reactive oxidizing species capable of cleaving strong non activated C-H bonds while discriminating between enantiotopic sites. This reactivity has remained inaccessible to contemporary oxidation methods and remains limited to enzymes. Bioinspired non-porphyrinic Fe and Mn complexes with linear aminopyridine ligands have emerged as powerful catalysts for site-selective C-H oxidations.[1] These catalysts activate H_2O_2, a waste-free oxidant, in an enzyme-like manner, to generate an electrophilic high-valent metal-oxo species within a chiral ligand framework, opening the possibility to engage in enantioselective C-H oxidations.[2,3]
In this contribution, we will present the first example of non-enzymatic enantioselective hydroxylation of non-activated tertiary C-H bonds using Mn bioinspired catalysts. Cis-3,5-dimethyl cyclohexane was selected as main motif, because its hydroxylation would result in the simultaneous generation of multiple chiral centers in a single step. A highly efficient and selective catalytic system for C-H hydroxylation was designed, which provides the alcohol as a single product with high yields and enantioselectivities. The reaction exhibits a high functional group tolerance, which includes esters, amides, ketones and nitriles, among others. In all cases, chiral alcohol products were obtained in good yields and excellent enantioselectivities, up to 98% ee.



Further functionalization of the obtained oxidized products demonstrates the potential of this methodology for the construction of a range of chiral compounds. Moreover, the principles of catalysis design presented in this work constitute a solid platform for further development of stereoselective C-H hydroxylation reactions.

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