

Setting Cyclohexane Stereochemistry with Oxidation

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Wang and Liu discuss advances in enantioselective oxidation of nonactivated C–H bonds.

Thanks to its atom- and step-economy, C–H bond oxidation represents a “hot topic” in synthetic chemistry.^{1,2} However, due to the ubiquity of such bonds in organic molecules, regio- and enantioselective C–H bond oxidation turns out to be extremely challenging, and efficient direct methods are in high demand. Compared to the success of aliphatic sp^3 C–H oxidation by enzymes (such as cytochrome P450, Figure 1),^{3,4} enantioselective oxidation of sp^3 C–H bonds by nonenzymatic systems is quite rare, and the few examples are limited to relatively weak C–H bonds such as those in benzylic and allylic positions.^{5–7} In these reactions, chiral ligand coordinated high-valent metal–oxo species abstract a hydride atom from an sp^3 C–H bond, followed by enantiomer-determining radical rebound to the chiral metal hydroxide through a-face (or b-face) to provide enantiomerically enriched alcohol (Scheme 1a). However, the reported catalytic systems only provide moderate levels of efficiency and enantioselectivity. Until recently, the alternative strategies have used radical relays for the enantioselective cyanation of benzylic C–H bonds, which provides excellent enantioselectivity in high efficiency.⁸ For nonactivated aliphatic C–H bonds, however, despite decades of past research, enantioselective reactions remain elusive.

This month, Costas and co-workers report a way to take the advantage of overoxidation.

One must also be wary of overoxidation of the alcohol products. Typically this results in poor chemoselectivity and eliminates any hope for preserving chirality. This month, Costas and co-workers report a way to take the advantage of overoxidation. Their elegant design for the regio- and enantioselective nonactivated C–H oxidation uses manganese-based chiral catalysts.⁹ The oxidation of C–H bond initiated by hydride atom abstraction represents one of the

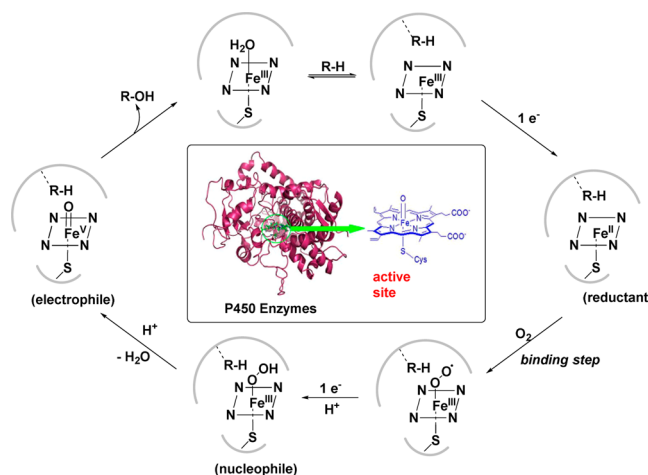


Figure 1. Possible pathway for hydroxylation of hydrocarbon catalyzed by cytochrome P450 enzymes.

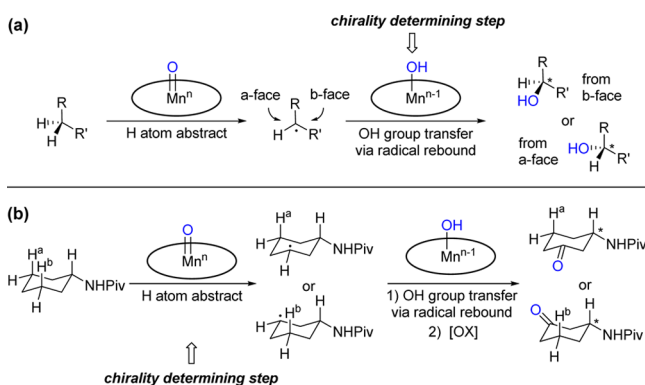
most promising processes owing its low energy barrier, but it requires control of the chemo- and stereoselectivity.

The contribution by Costas et al. represents the first example of enantioselective oxidation of nonactivated aliphatic C–H bonds through a desymmetrization strategy, which provides overoxidized chiral carbonyl product, other than chiral alcohol.

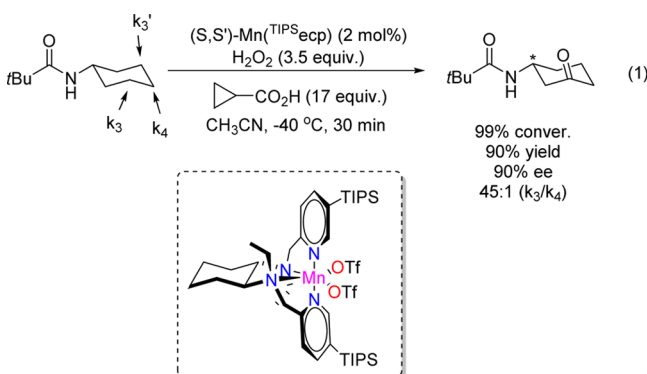
Unlike the widely employed process for the construction of ipso-carbon chiral center (Scheme 1a), the current protocol delivered the optically active products via a desymmetrization strategy and the chirality was generated during the hydride atom abstraction step (Scheme 1b). Authors evaluated a set of substituted cyclohexanes by using tetradentate nitrogenous ligand-based Mn catalysts. They found that the reaction of *N*-cyclohexylpivalamide could provide the desired oxidation product in good yield with excellent regio- and enantioselectivity in the presence of

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Scheme 1. Two Distinct Strategies for Asymmetric Oxidation of Aliphatic C–H Bonds



(*S,S'*)-Mn(^{TIPS}ecp) (eq 1). This strategy takes advantage of high regioselective hydride atom abstraction of C–H bond



by chiral metal–oxo species and avoids two challenging issues in the field: the inevitable chemoselectivity between alcohol and overoxidized carbonyl product, and the difficulty in the enantioselective control in the radical rebound step. These results illustrate that the interaction between substrate and manganese–oxo species is vital to the “correct orientation” of substrate during the regioselective hydride atom abstraction step (k_3 versus k_3') triggering the high enantioselectivity of carbonyl product.

Although many successful reported reactions involve biomimetic asymmetric oxidation of C–H bonds, this work is still significant and warrants notice. The contribution by Costas et al. represents the first example of enantioselective oxidation of nonactivated aliphatic C–H bonds through a desymmetrization strategy, which provides overoxidized chiral carbonyl product, other than chiral alcohol. Based on their previous work for regioselective oxidation of C–H bonds, Costas and co-workers carefully investigated the interaction between substrate and active catalytic species. Their rational chiral catalyst design paid off in a significant advancement. Further investigation to broaden the substrate scope and to elucidate the mechanism is required. But this work could open a door, providing a simple model to help

answer important questions regarding the origin of selective control in catalysis and how enzymes impart their specificity.

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