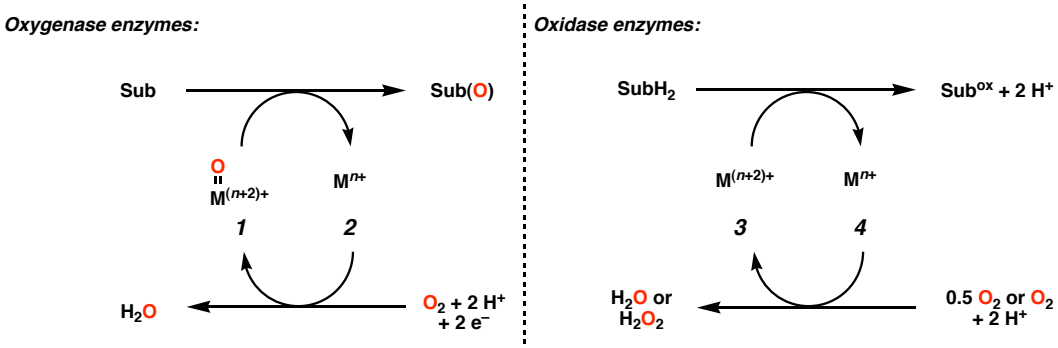
CHAPTER ONE

Enantioselective Oxidation Chemistry

1.1 Oxidation in Biological Systems

Oxidation is a fundamental process in chemistry and biology. In biological systems, a number of enzymes catalyze a diverse set of oxidative reactions through the use of molecular oxygen. Metalloenzymes that catalyze these aerobic oxidations are divided into two distinct types (Figure 1.1.1). Oxygenases involve the transfer of an oxygen atom from O_2 to the substrate, often via a high-valent metal oxo species (**1**). The reduced metal intermediate (**2**) is then oxidized by dioxygen back to the active species, mediated by two protons and two electrons. Importantly, one of the oxygen atoms from O_2 is incorporated into the oxidized substrate. Oxidases differ in that the metal oxidant (**3**) catalyzes the dehydrogenation of the substrate, releasing two protons. In this case, there is no oxygen atom transfer to the substrate—molecular oxygen is used simply as a proton and electron acceptor for the catalytic process. The atoms from O_2 are released as either water or hydrogen peroxide.

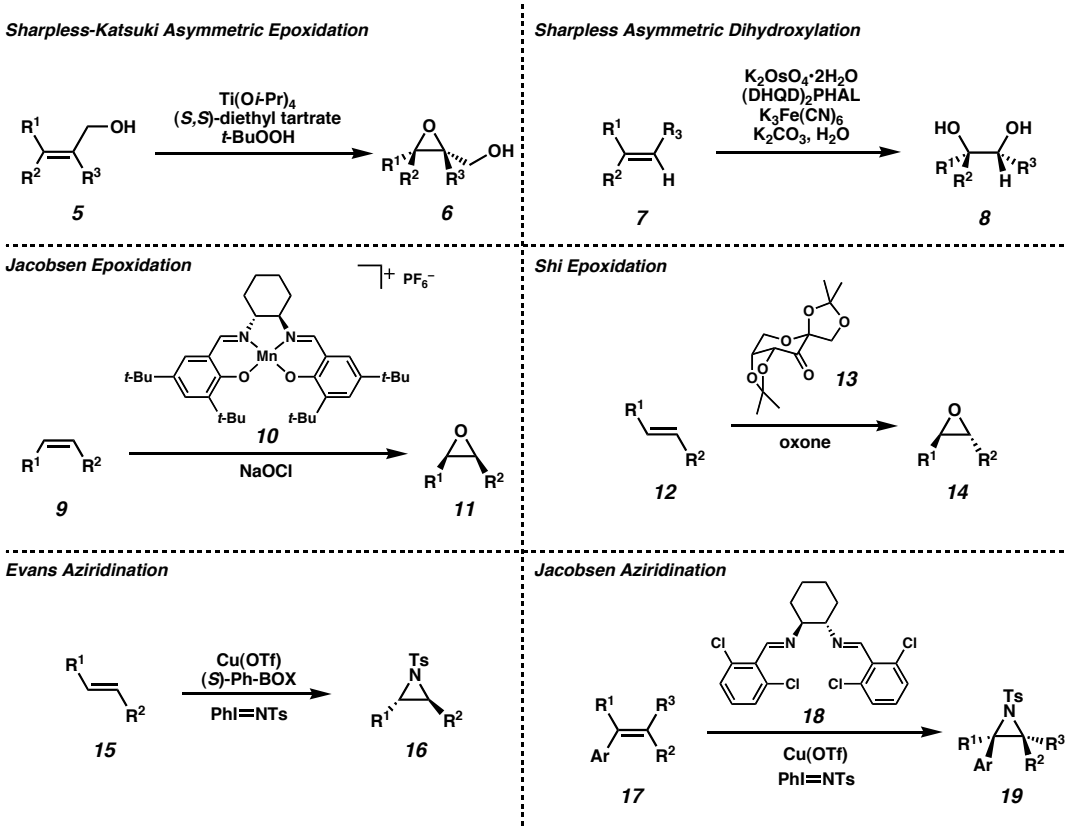
Figure 1.1.1 Oxygenase and oxidase metalloenzymes.



1.2 Oxidation in Chemical Synthesis

In chemical synthesis, there have been several developments regarding asymmetric oxidation catalysts that involve heteroatom transfer, i.e., catalysts that mimic the behavior of oxygenase enzymes. Some of the most notable examples are illustrated in Figure 1.2.1. The initial discovery of a highly enantioselective catalytic oxidation was reported by Sharpless and Katsuki.[1] Allylic alcohols were epoxidized (**5** → **6**) by a titanium-tartrate catalyst, using *tert*-butyl hydroperoxide as the stoichiometric oxidant. Sharpless later reported the asymmetric dihydroxylation of unfunctionalized olefins (**7** → **8**) using an osmium catalyst system.[2] Jacobsen and Shi have both disclosed examples of enantioselective epoxidations of simple olefins (**9** → **11**, **12** → **14**).[3] Highly asymmetric aziridinations (**15** → **16**, **17** → **19**) have also been described by both Evans and Jacobsen.[3b,4] Although these examples do not involve O_2 as the stoichiometric oxidant like oxygenase enzymes, they do all proceed by heteroatom transfer from a reagent to the substrate.

Figure 1.2.1 Asymmetric oxidations featuring heteroatom transfers.

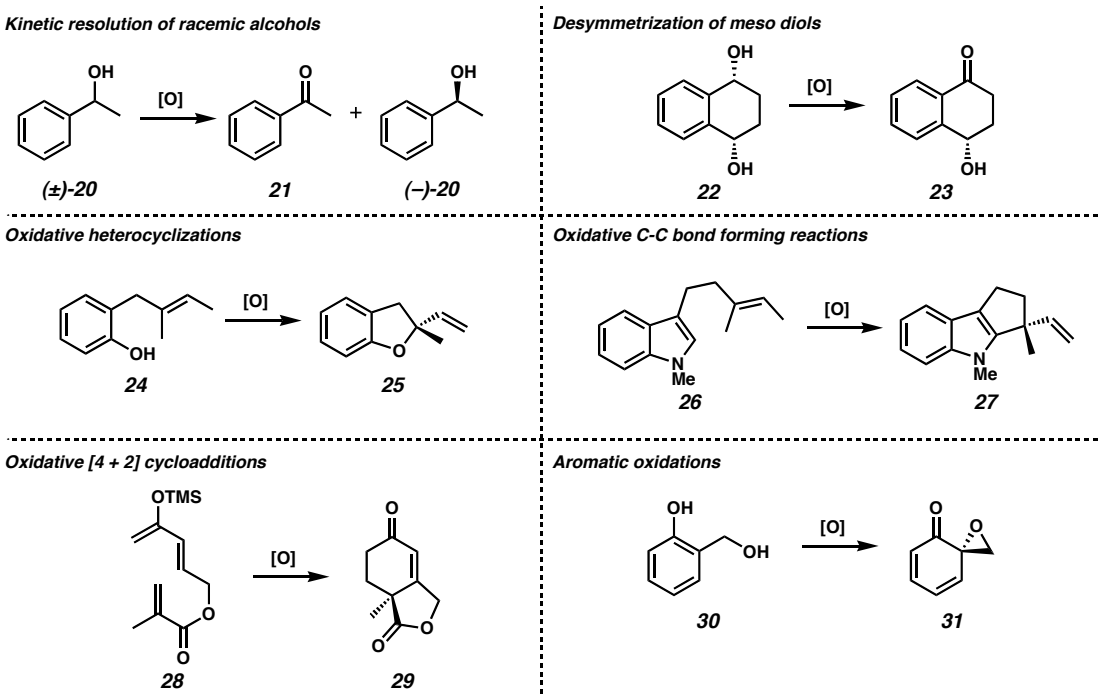


Chemical methods that mimic the reactions catalyzed by oxidase enzymes have also been developed. This class of transformations does not involve a heteroatom transfer to a substrate, but a dehydrogenative process instead. Fundamental reactions of this type include alcohol oxidations and alkane dehydrogenations, both ubiquitous in nature and in chemical synthesis. Although prevalent, asymmetric catalytic variants of this class of reactions have been relatively less explored in comparison to the oxygenase mimics.

Several enantioselective dehydrogenative reactions are illustrated in Figure 1.2.2. The kinetic resolution of racemic alcohols involves the selective oxidation of one enantiomer to produce a prochiral ketone (**21**) and an enantioenriched alcohol (**20**). This

same selective process can be applied to the desymmetrization of meso diols (**22** → **23**). Enantiopure heterocycles and carbocycles (e.g., **25** and **27**) can be envisioned to arise from asymmetric dehydrogenative processes. Other potential asymmetric non-heteroatom transfer oxidations include cycloadditions (**28** → **29**) and aromatic oxidations (**30** → **31**). The design and development of palladium(II) catalytic systems for investigations into this fertile area of enantioselective oxidation chemistry will be the focus of this thesis.[5]

Figure 1.2.2 Enantioselective dehydrogenative reactions.



1.3 Notes and References

(1) For discussions on the enantioselective epoxidation of allylic alcohols, see: (a) Katsuki, T. Epoxidation of Allylic Alcohols. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Vol. 2, Chapter 18.1, pp 621-648. (b) Johnson, R. A.; Sharpless, K. B. Catalytic Asymmetric Epoxidation of Allylic Alcohols. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley: New York, 2000; Chapter 6A, pp 231-280.

(2) For discussions on the enantioselective dihydroxylation of olefins, see: (a) Markó, I. E.; Svendsen, J. S. Dihydroxylation of Carbon-Carbon Double Bonds. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Vol. 2, Chapter 20, pp 713-787. (b) Johnson, R. A.; Sharpless, K. B. Catalytic Asymmetric Dihydroxylation—Discovery and Development. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley: New York, 2000; Chapter 6D, pp 357-398.

(3) For discussions on the enantioselective epoxidation of unfunctionalized olefins, see: (a) Jacobsen, E. N.; Wu, M. H. Epoxidation of Alkenes Other than Allylic Alcohols. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Vol. 2, Chapter 18.2, pp 649-677. (b) Katsuki, T. Asymmetric Epoxidation of Unfunctionalized Olefins and

Related Reactions. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley: New York, 2000; Chapter 6B, pp 649-677.

(4) For a discussion on enantioselective aziridinations, see: Jacobsen, E. N. Aziridination. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Vol. 2, Chapter 17, pp 607-618.

(5) Palladium(II) dehydrogenative reactions have been the focus of several recent reviews. See: (a) Stoltz, B. M. *Chem. Lett.* **2004**, *33*, 362-367. (b) Stahl, S. S. *Angew. Chem., Int. Ed*. **2004**, *43*, 3400-3420. (c) Sigman, M. S.; Schultz, M. J. *Org. Biomol. Chem*. **2004**, *2*, 2551-2554.