Catalysts for Alcohol Oxidation Inspired by Galactose Oxidase

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Galactose oxidase (GO) is an enzyme excreted into the extracellular environment by root fungi. The enzyme is known to selectively catalyze the oxidation of primary alcohols to aldehydes with concomitant reduction of molecular oxygen to hydrogen peroxide, as shown in the equation below:

\[
\text{RCH}_2\text{OH} + \text{O}_2 \overset{\text{galactose oxidase}}{\longrightarrow} \text{RCHO} + \text{H}_2\text{O}_2
\]

The active site of GO contains a single copper ion coordinated by two histidine imidazoles, an axial and a basal tyrosine, and a water or acetate ion in a slightly distorted square pyramidal geometry (Figure 1A). EPR, K-edge XANES, magnetic susceptibility, and ligand addition studies indicate that the active form of the enzyme contains an interesting Cu II-phenoxyl radical species. The catalytic cycle of GO, shown in Scheme 1, is thought to start with deprotonation of the alcohol, followed by hydrogen atom transfer to the tyrosyl-radical, producing a carbon-centered radical on the substrate, and continuing with electron transfer from the substrate to the Cu II. The resulting Cu I complex is oxidized back to the resting state with O2. Both half-reactions show kinetic isotope effects of approximately 5, indicating that a C-H or O-H bond is broken in the rate-determining step.

![Diagram of GO active site](attachment:go_active_site.png)

Some of the first structural models included phenoxyl-radical complexes of copper(II) and three-coordinate copper(II) complexes. These complexes rarely showed oxidation activity but often gave mechanistic information.

Early functional models of GO, shown in Figure 1B, were based on N2O2 ligand sets. The ligands used by Stack and coworkers enforced a copper(II) geometry intermediate between square planar and tetrahedral and had sufficient π-conjugation to stabilize radical
species. Complexes that were EPR silent and stable at room temperature had the highest catalytic activity. Tris(4-phenyl)iminium hexachloroantimonate and also molecular oxygen were used as terminal oxidants with these catalysts. Only oxidation of activated alcohols was accomplished. Other studies used a thioether-substituted phenol ligand in a N3O ligand set, eventually producing catalytic activity with $(\text{NH}_4)_2[\text{Ce(NO}_3]_6)$ as the terminal oxidant.\textsuperscript{11}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{scheme1.png}
\caption{Scheme 1}
\end{figure}

Weighardt and coworkers have made recent breakthroughs in this area, with the introduction of dinuclear\textsuperscript{12} and mononuclear\textsuperscript{13} copper(II) catalysts that oxidize ethanol to ethanal. The mononuclear catalyst is shown in Figure 1C. The oxidation of methanol to formaldehyde has been realized with another mononuclear catalyst, shown in Figure 2. In this case, the metal center is redox inactive; the ligand has two stable radical oxidation states.\textsuperscript{14}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{Figure 2}
\end{figure}

This body of work demonstrates that sufficient knowledge of the structure and mechanism of biological catalysts can allow chemists to produce very similar reactivity with small molecule catalysts.

References

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Scheme 1

Weighardt and coworkers have made recent breakthroughs in this area, with the introduction of dinuclear12 and mononuclear13 copper(II) catalysts that oxidize ethanol to ethanol. The mononuclear catalyst is shown in Figure 1C. The oxidation of methanol to formaldehyde has been realized with another mononuclear catalyst, shown in Figure 2. In this case, the metal center is redox inactive; the ligand has two stable radical oxidation states.14

Figure 2

This body of work demonstrates that sufficient knowledge of the structure and mechanism of biological catalysts can allow chemists to produce very similar reactivity with small molecule catalysts.

References
Lanthanocene Complexes as Unique and Selective Catalysts

Christopher Michael Luz  
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Lanthanocene complexes have been shown to catalyze a variety of reactions, including hydrosilylation. Many features of lanthanocenes make them potentially useful catalysts. They are Lewis acids, have high kinetic lability, they are thermally stable over a wide range of temperatures, and they can be readily synthesized. In general, most lanthanides are extremely stable in the Ln³⁺ oxidation state, and the Ln³⁺ ionic radii vary in a systematic way across the series. The general stability of the Ln³⁺ oxidation state has two consequences: steric properties of a system will have a larger net effect, and oxidative addition and reductive elimination mechanistic routes are inaccessible and other mechanisms must be proposed. Many postulated mechanisms have involved 4-center transition states as shown in Figure 1.

The systematic change in ionic radii allows the steric properties of a system to be “tuned” by changing the lanthanide. This can be demonstrated by an examination of hydrosilylation of alkenes and alkynes. Hydrosilylation is the addition of H-Si across a carbon-carbon double or triple bond. This addition can be made in a Markovnikov (2,1 addition) or anti-Markovnikov (1,2 addition) fashion. For small lanthanides and group three metals (e.g. Lu, Y, Yb, or Y) addition of H₂SiPh across a terminal double bond (1-decene) yields 100% anti-Markovnikov addition product. Using larger lanthanides (e.g. La or Nd) generates as much as 44% Markovnikov product. The steric environment can also be altered by use of an *ansa*-bridged ligand system, as shown in Figure 2. By comparison the percent anti-Markovnikov product for (Me₂Si)Cp₂LnR (as shown in Figure 2), it is evident that when Ln is Sm or Nd the selectivity for anti-Markovnikov addition is greatly reduced (from 92% to 33% and 76% to 33% respectively). In hydrosilylation of styrene the same trends for metal and ligand effects are observed, but the Markovnikov product is much more strongly favored in less sterically crowded species. This is postulated to be due to a π-interaction between the lanthanide and the phenyl group of the styrene. Hydrosilylation of alkynes is affected to a smaller degree than for alkenes because alkynes are less sterically demanding substrates.

Selectivity for the least hindered alkene in a diene is observed in the Cp₂₂YMe₃(THF) catalyst system (yields up to 96% are observed). Diienes and enynes reacting in less sterically crowded catalysts systems can undergo cycloization first, and then hydrosilylation.