

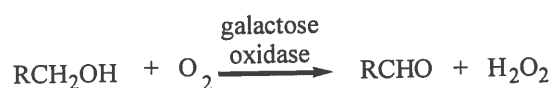
## Catalysts for Alcohol Oxidation Inspired by Galactose Oxidase

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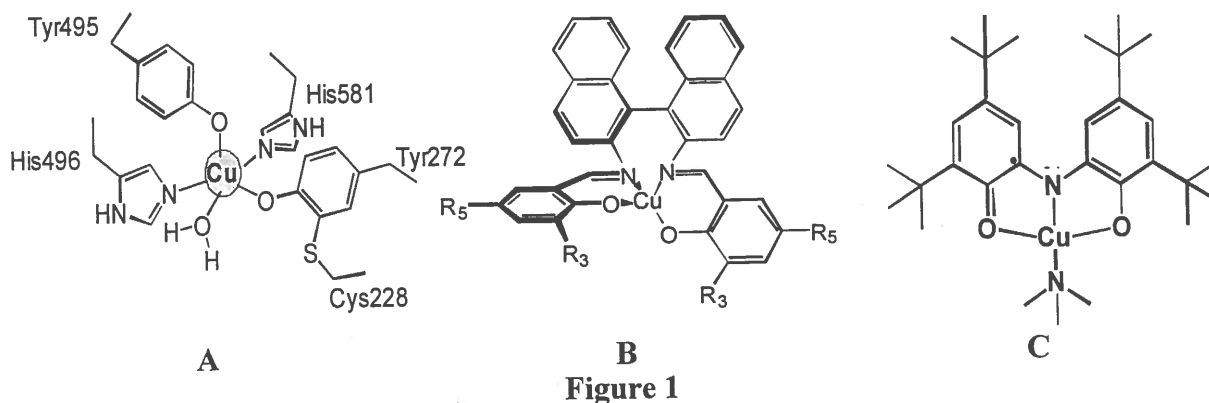
Literature Seminar

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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 below;<sup>1</sup> hydrogen peroxide is used outside of the cell to degrade lignin,<sup>2</sup> a dense biopolymer of tyrosine and phenylalanine. The ability to produce hydrogen peroxide in high concentrations or to oxidize alcohols to aldehydes selectively is of great interest to industry.



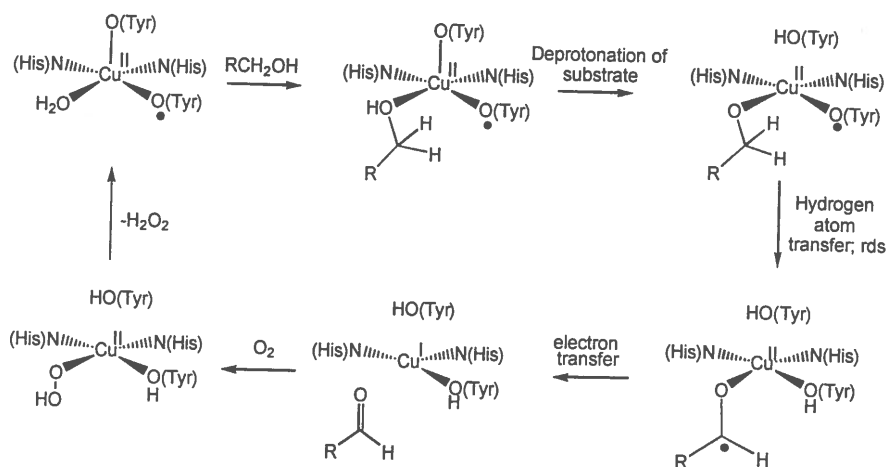
The active site of GO contains a single copper ion coordinated by two histidine imidazoles, an axial and a basal tyrosine, and a water or acetate ion in a slightly distorted square pyramidal geometry (Figure 1A).<sup>3</sup> EPR, K-edge XANES, magnetic susceptibility, and ligand addition studies indicate that the active form of the enzyme contains an interesting  $\text{Cu}^{\text{II}}$ -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  $\text{Cu}^{\text{II}}$ . The resulting  $\text{Cu}^{\text{I}}$  complex is oxidized back to the resting state with  $\text{O}_2$ .<sup>4</sup> 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.<sup>5</sup>



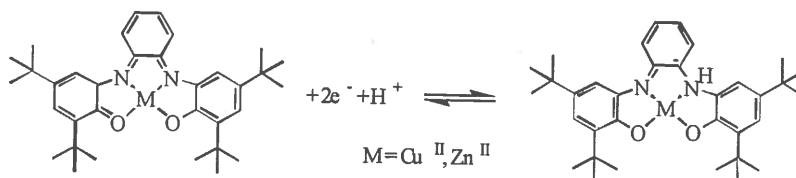
Some of the first structural models included phenoxyl-radical complexes of copper(II)<sup>6</sup> and three-coordinate copper(I) complexes.<sup>7</sup> These complexes rarely showed oxidation activity but often gave mechanistic information.

Early functional models of GO, shown in Figure 1B, were based on  $\text{N}_2\text{O}_2$  ligand sets. The ligands used by Stack and coworkers enforced a copper(II) geometry intermediate between square planar and tetrahedral and had sufficient  $\pi$ -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<sup>8</sup> and also molecular oxygen<sup>9</sup> 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 N<sub>3</sub>O ligand set,<sup>10</sup> eventually producing catalytic activity with (NH<sub>4</sub>)<sub>2</sub>[Ce(NO<sub>3</sub>)<sub>6</sub>] as the terminal oxidant.<sup>11</sup>



Weighardt and coworkers have made recent breakthroughs in this area, with the introduction of dinuclear<sup>12</sup> and mononuclear<sup>13</sup> 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.<sup>14</sup>



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.

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