REPLACING BENZOQUINONE WITH O_2 IN OXIDATION REACTIONS

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Aerobic Oxidation Reactions

Developing selective oxidation reactions that minimize toxic byproducts and improve atom economy is a frontier challenge in organic chemistry. Pd and Cu-catalyzed oxidation reactions often require stoichiometric oxidants such as benzoquinone, Cu^{II} salts, alkyl peroxides, or hypervalent iodine to achieve catalytic turnover, which are expensive and generate hazardous byproducts. Molecular oxygen represents the ideal oxidant due to low cost and lack of toxic by-products. In nature, two major classes of metalloenzymes that employ molecular oxygen are oxygenases, which directly transfer one or more oxygen atoms from O_2 to the substrate, and oxidases, which employ O_2 as a proton or electron acceptor in the process of substrate oxidation.[1] Oxidation reactions that employ O_2 represent an opportunity for selective, efficient, cost effective, and environmentally friendly transformations. O_2 mediated oxidation of Cu^{I}, Pd^{0}, and Pd^{II}-H complexes has been observed and characterized.[2] A challenge of replacing benzoquinone is that, unlike O_2, in addition to oxidation of the catalyst, benzoquinone acts as a π-acid to facilitate reductive elimination from a Pd^{II} intermediate. To reduce or replace benzoquinone loading, strategies have been developed to facilitate reductive elimination through redox relay systems with substoichiometric oxidants, oxidation of Pd^{II} to Pd^{IV}, and the use of Cu.

Reducing Benzoquinone Loading in Allylic Acetoxylation

Pd-catalyzed allylic acetoxylation is promoted by superstoichiometric benzoquinone (BQ), which has been shown to inhibit both reaction rate and yield at high concentration. To render benzoquinone catalytic, a redox relay system was developed using a Co(salophen) catalyst to reoxidize hydroquinone, with O_2 as the terminal oxidant (**Figure 1**).[3] This allowed favorable yields and reaction rates with substoichiometric benzoquinone loading. Further study of the mechanism of hydroquinone oxidation by Co(salophen) and O_2 demonstrated that Co(salophen) and O_2 operate synergistically to oxidize two moles of hydroquinone per mole of O_2. A coordinated H_2O_2 intermediate rapidly oxidizes one equivalent of hydroquinone, preventing the buildup of reactive oxygen species, indicating that the

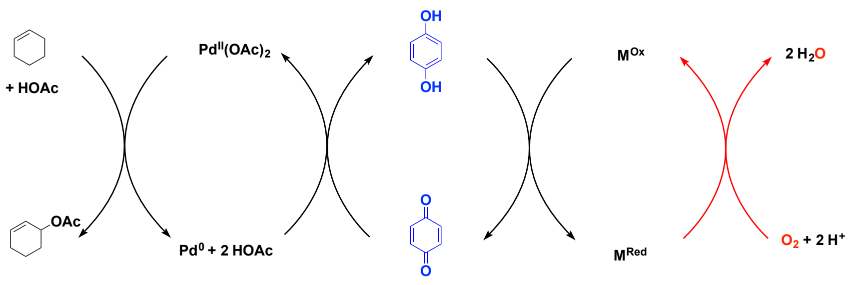

Figure 1: Redox relay cycle to lower benzoquinone loading

use of a substoichiometric quinone may serve as an “anti-oxidant” to prevent over oxidation of the substrate and or unfavorable side reactions.

Reductive Elimination from Pd^{IV}

In the absence of benzoquinone, reductive elimination may be promoted by oxidizing Pd^{II} to Pd^{IV}. Direct oxidation of Pd^{II} to Pd^{IV} with O_2 has been demonstrated for select substrates, with very limited scope. Sanford, Grubbs, and Stoltz have demonstrated the use of substoichiometric nitrate and nitrite cocatalysts to oxidize Pd^{II} to Pd^{IV} with O_2 as the terminal oxidant used to reoxidize the cocatalyst, and achieve C-O reductive elimination and catalytic turnover under aerobic conditions (**Figure 2**).[4]

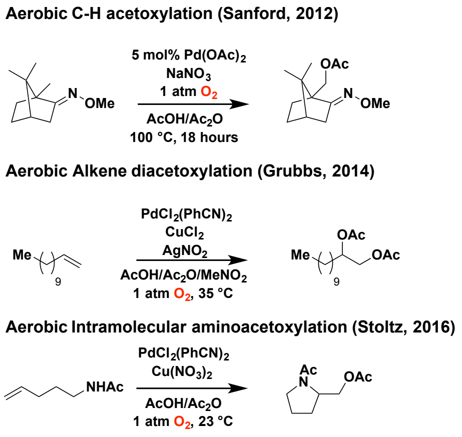

Figure 2: NO_x-catalyzed acetoxylation

Cu-Catalyzed Aerobic Oxidations

Cu represents another strategy for achieving catalytic aerobic oxidation, as it is cheaper and less toxic than Pd, and undergoes more facile reductive elimination from Cu^{III} relative to Pd^{II}.[2] However, the Cu^{II} oxidation state is the most stable under aerobic conditions. Three mechanistic strategies have been developed for Cu-catalyzed aerobic oxidation reactions to successfully mediate one electron redox steps (**Figure 3**), enabling catalytic processes that promote divergent mechanisms for selective oxidation in the absence of benzoquinone.[2] Basic conditions and strongly anionic ligands are necessary to stabilize Cu^{III} intermediates, which promote reductive elimination in the absence of benzoquinone.

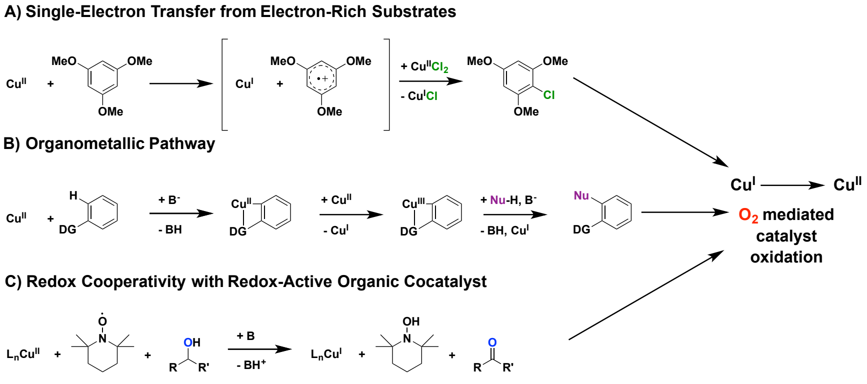

Figure 3: Cu-catalyzed aerobic oxidation mechanisms

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3) Anson, C. W.; Ghosh, S.; Hammes-Schiffer, H.; Stahl, S. S. *J. Am. Chem. Soc.* **2016**, *138*, 4186-4193.
4) Li, J.; Grubbs, R.H.; Stoltz, B.M. *Org. Lett.* **2016**, *18*, 5449-5451.