

Synthesis of New Hybrid Hydroquinone/Cobalt Schiff Base Catalysts: Efficient Electron-Transfer Mediators in Aerobic Oxidation

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Oxidation reactions are prevalent in academic and industrial chemistry, and there is a great need for the continued development of efficient catalytic methods.^[1] An attractive oxidant is molecular oxygen, since it is inexpensive and environmentally benign, giving water as the only byproduct.^[2] Unfortunately, the reactivity of molecular oxygen is difficult to control; it typically reacts under harsh conditions with poor selectivity. Nature has solved this problem through the use of electron-transport chains, which transfer electrons from a substrate to O₂ in a stepwise fashion resulting in mild conditions compatible with life.^[3]

In chemical catalytic oxidation reactions, a substrate-selective redox catalyst, for example, a transition metal, removes electrons from the substrate to give the oxidized product. The resulting reduced form of the metal is reoxidized, and it would be desirable to use molecular oxygen for this reoxidation. Although direct reoxidation of the metal by O₂ has been reported in many cases,^[4–6] this approach fails in other cases when electron transfer between the metal and O₂ is too slow to compete with the decomposition of the reduced form of the metal complex.^[7]

To facilitate the electron transfer between the reduced substrate-selective catalyst and O₂ various electron-transfer mediators have been employed. A simple example of this principle is the Wacker process in which the redox couple CuCl/CuCl₂ facilitates electron transfer between Pd⁰ and O₂.^[8] In more recent examples, a quinone/hydroquinone redox couple has been used in conjugation with an oxygen-activating catalyst, for example, cobalt–salophen (H₂salophen = *N,N'*-bis(salicylidene)-*o*-phenylenediamine), to catalyze the aerobic reoxidation of a palladium or ruthenium catalyst.

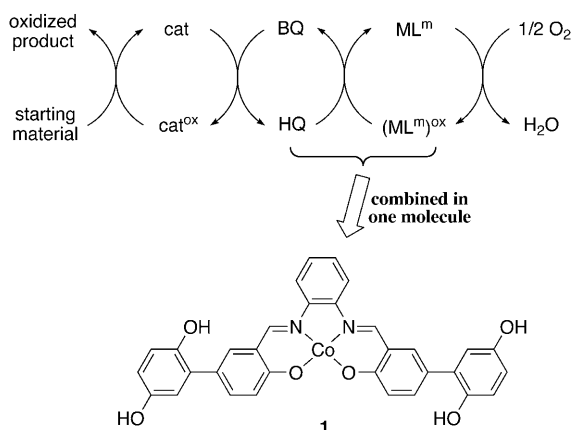
This leads to a low-energy electron transfer analogous to that occurring in biological systems (cf. the respiratory chain). This approach has been applied to a variety of “biomimetic” aerobic oxidation reactions, including a chloride-free Wacker oxidation,^[9] acetoxylation of alkenes,^[9b,10] Pd-catalyzed enallene carbocyclization,^[11] oxidative 1,4-additions to conjugated dienes,^[9b] oxidative Heck-type couplings,^[12] methane oxidation,^[13] and Ru-catalyzed oxidation of alcohols^[14] and amines.^[15] Closely related biomimetic coupled oxidations with hydrogen peroxide have also been developed.^[16]

In the course of our attempts to improve these reactions, it occurred to us that the efficiency of the electron transfer might be increased by covalently tethering two electron-transfer mediators and in this way creating a hybrid redox catalyst. A few molecules designed to test this approach have been reported.^[17,18] The first example, a hydroquinone/cobalt–porphyrin hybrid, improved the rate of the Pd-catalyzed aerobic 1,4-diacetoxylation of 1,3-cyclohexadiene, but the stereoselectivity of the reaction was moderate and the catalyst was difficult to synthesize.^[17] The second example, a cobalt–salen type (H₂salen = *N,N'*-bis(salicylidene)ethylenediamine) complex derived from 5-hydroxysalicylaldehyde, had hydroquinone hydroxyl groups coordinated directly to the cobalt, and this hampered its performance in Pd-catalyzed aerobic allylic acetoxylation.^[18]

We now report on a second generation of this approach that comprises cobalt salophens and salens with pendant hydroquinone groups (Scheme 1). These new hybrids offer very efficient aerobic reoxidation of both palladium and ruthenium catalysts in oxidative 1,4-diacetoxylation, in enallene carbocyclization, and in alcohol oxidation. The oxidized form of hydroquinone, that is, benzoquinone, is a very efficient reoxidant for a variety of transition-metal catalysts, so its inclusion in the hybrid design was a natural choice. Cobalt Schiff base complexes were chosen as the oxygen-activating component because of their demonstrated efficiency in coupled aerobic oxidation,^[9b,14] and their simple and modular synthesis. Molecular modeling shows that, in this

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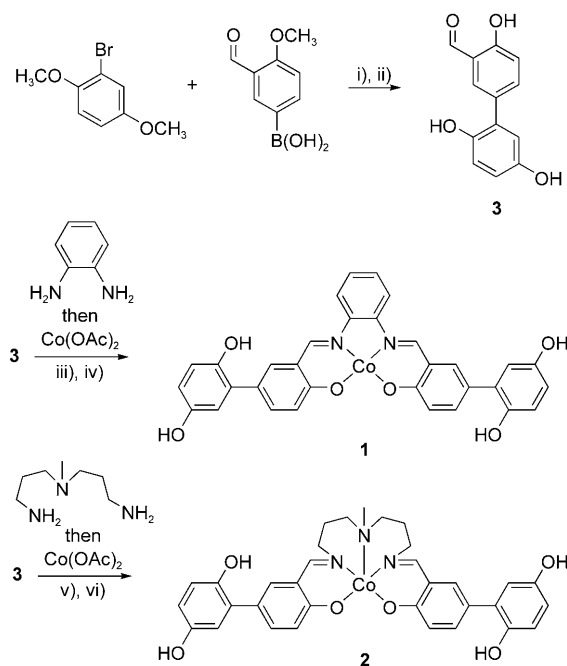


Scheme 1. Biomimetic aerobic oxidation uses a series of redox catalysts to transfer electrons to O₂ in a stepwise fashion, facilitating catalyst re-oxidation. ML^m=oxygen-activating catalyst; HQ=hydroquinone; BQ=benzoquinone; cat=substrate-selective catalyst.

design, the hydroquinone groups are only 7 Å from the cobalt atom,^[19] a distance across which electron transfer is known to be facile.^[20]

The synthesis of **1** begins with a Suzuki cross-coupling of the commercially available starting materials, 2,5-dimethoxybromobenzene and 3-formyl-4-methoxyphenylboronic acid, and yields a methoxy-protected precursor (Scheme 2). The three methyl ethers are cleaved by treatment with BBr₃, giving the completed salicylaldehyde–hydroquinone **3**. Two equivalents of **3** were allowed to react with a chosen diamine in ethanol, and the product Schiff base was purified by recrystallization. Heating the Schiff base ligand with cobalt(II) acetate in methanol resulted in the formation of the corresponding target molecule **1** or **2**, which was washed with water to remove excess cobalt acetate.

To test its performance, catalyst **1** was used in place of cobalt–salophen and hydroquinone in the biomimetic aerobic 1,4-diacetoxylation of 1,3-cyclohexadiene (Table 1 and Figure 1). Compared to the separate-component system (entry 1), hybrid catalyst **1** (entry 2) accelerated the reaction of 1,3-cyclohexadiene by a factor of four and gave a more efficient reaction. In addition to improving the rate, hybrid **1** is better able to maintain solution homogeneity by pre-



Scheme 2. Synthesis of hybrid hydroquinone/cobalt Schiff base complexes **1** and **2**. i) Pd(OAc)₂, PPh₃, Na₂CO₃, DMF, 50%; ii) BBr₃, CH₂Cl₂, –78 °C to RT, 49%; iii) phenylenediamine, EtOH, 70%; iv) Co(OAc)₂·4H₂O, CH₃OH, 62 °C, 95%; v) 3,3'-diamino-*N*-methyldipropylamine, EtOH, 94%; vi) Co(OAc)₂·4H₂O, CH₃OH, 62 °C, 95%.

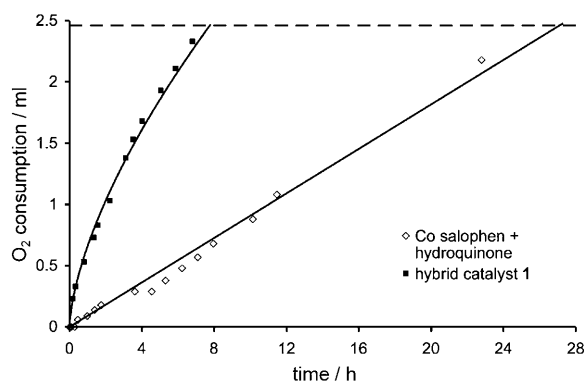


Figure 1. Rates of oxygen consumption for the aerobic 1,4-diacetoxylation of 1,3-cyclohexadiene catalyzed by hybrid **1** (Table 1, entry 2) or Co-salophen and hydroquinone (Table 1, entry 1).

Table 1. Catalyst performance in the coupled aerobic 1,4-diacetoxylation of 1,3-cyclohexadiene.^[a]

Entry	ETM ^[b]	10 ³ -initial rate of O ₂ consumption [mL·h ⁻¹]	Reaction time [h]	Isolated yield [%]	<i>trans</i> : <i>cis</i> ratio ^[c]
1	Co-salophen + HQ	1.0 ± 0.2	28	70	86:14
2	hybrid 1	4.2 ± 0.8	7	80	89:11

[a] Reaction conditions: 1,3-cyclohexadiene (0.22 mmol), **1** (0.011 mmol) or cobalt(II)–salophen (0.011 mmol) + hydroquinone (0.022 mmol), palladium(II) acetate (0.011 mmol), lithium acetate dihydrate (0.56 mmol), and acetic acid (1 mL) at room temperature. Results are the average of at least two trials. [b] ETM=electron-transfer mediator; HQ=hydroquinone. [c] Determined by ¹H NMR spectroscopy.

venting catalyst precipitation during the reaction. When carrying out the three-component reaction (entry 1), the precipitation of black material, likely including Pd black and quinhydrone, occurred during the reaction. In contrast, the use of catalyst **1** (entry 2) maintained solution homogeneity throughout the course of the reaction, implying a very efficient Pd⁰ re-oxidation.

To obtain a deeper understanding of the performance of catalyst **1**, we measured the rate dependence of the reaction of 1,3-cyclohexadiene on the concentrations of **1** and Pd(OAc)₂. Because of the complex kinetics of this reaction, the reaction progress as measured by O₂ consumption does not fit zero-, first-, or second-order rate laws. Plotting the natural log of the initial rate of O₂ consumption versus the natural log of the concentration of each catalyst (Figure 2)

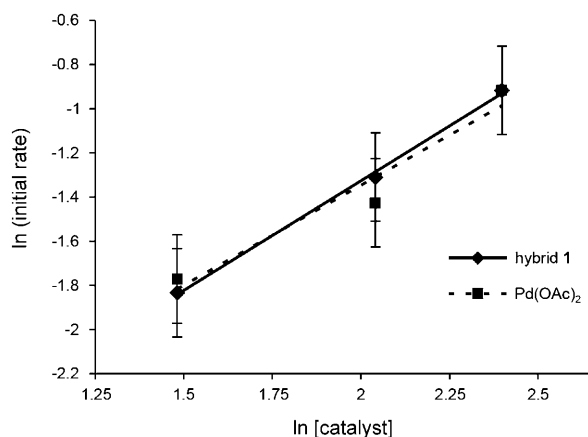
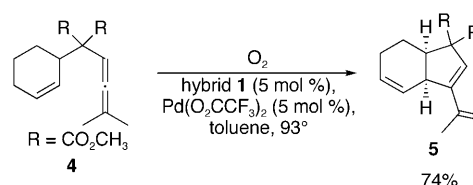


Figure 2. Plot of the natural log of the initial rate of O₂ consumption for the 1,4-diacetoxylation of 1,3-cyclohexadiene versus the natural log of the concentration of each catalyst, hybrid **1** and Pd(OAc)₂ (data and reaction conditions are shown in the Supporting Information). The slopes of the lines are 0.9 ± 0.2 for Pd(OAc)₂ and 1.0 ± 0.2 for hybrid **1**, indicating that the reaction is first-order in each catalyst.

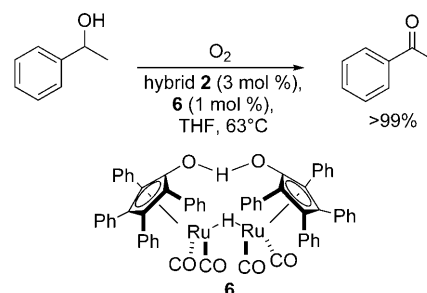
revealed that the reaction is first-order in each catalyst. This observation is consistent with a mechanism in which both hybrid catalyst **1** and Pd are present in the rate-limiting step, which, based on previously-reported investigations, is likely to be the nucleophilic addition of the second acetate to the intermediate Pd-π-allyl complex (Figure S1).^[21] A corollary is that oxygen activation and electron transfer from hydroquinone no longer influences the overall rate of the 1,4-diacetoxylation under these conditions. In other words, the greater efficiency of electron transfer that results from the linking of hydroquinone and cobalt-salophen has improved this part of the catalytic cycle such that it is no longer rate-limiting.

In addition to its utility in coupled aerobic 1,4-diacetoxylation, catalyst **1** is able to facilitate the reoxidation of Pd in a Pd^{II}-catalyzed aerobic enallene carbocyclization (Scheme 3).^[11a] When tested in the reaction of **4**, catalyst **1** was effective in replacing the combination of hydroquinone and an iron-phthalocyanine complex, which act as electron-transfer mediator and oxygen-activating catalyst, respectively. Product **5** was formed in 74% yield after a reaction time of 12 h.

We also tested the use of hybrid catalyst **2** in aerobic alcohol oxidation (Scheme 4). The [Co(smdpt)] (H₂smdpt = bis[3-(salicylidenamino)propyl]methylamine) part of **2** has previously been used as the oxygen-activating catalyst in



Scheme 3. Aerobic oxidative enallene carbocyclization catalyzed by Pd^{II} and **1**.



Scheme 4. Aerobic oxidation of 1-phenylethanol catalyzed by hybrid catalyst **2** and ruthenium catalyst **6**.

biomimetic, coupled, Ru-catalyzed, aerobic oxidation of alcohols.^[14b,c] Aerobic oxidation of 1-phenylethanol in the presence of catalytic amounts of **2** (3 mol %) and ruthenium catalyst **6** (1 mol %)^[22] afforded acetophenone with complete conversion in 12 h. The original method required a 20 mol % loading of quinone as an electron-transfer mediator and either a temperature of 100°C or a much longer reaction time at 65°C. With the hybrid catalyst **2** the efficiency of intramolecular electron transfer allows a much lower catalytic loading and milder reaction conditions.^[23,24]

We have reported the design and synthesis of hybrid catalysts **1** and **2**. Hybrid catalyst **1** was shown to be efficient in aerobic Pd-catalyzed oxidations and hybrid catalyst **2** was found to be highly efficient in ruthenium-catalyzed alcohol oxidation. In the synthesis of **1** and **2**, the diamine and the metal are introduced in the final steps; this allows for the synthesis of a range of hybrid hydroquinone/metal Schiff base catalysts. Further optimization and refinement of these novel hybrid catalysts are underway in our laboratories.

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Keywords: aerobic oxidation • alcohols • alkenes • biomimetic oxidation • electron transfer

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