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Mechanistic Investigations of the Iridium(III)-Catalyzed Aerobic Oxidation of Primary and Secondary Alcohols

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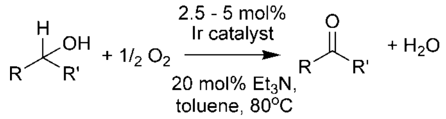
Catalytic aerobic oxidations remain appealing because of the low cost and availability of molecular oxygen.[1] Recently, the chemistry of "chemical oxidases" has seen renewed interest especially in the area of Pd-catalyzed oxidations.[2] These discoveries have regenerated interest in the design of new metal systems that undergo similar "green oxidations". A problem in some Pd-catalyzed oxidations is the decomposition of the homogeneous catalyst into inactive bulk metal. This decomposition pathway competes with the slow addition of dioxygen to Pd(0).[3]

One way to alleviate this problem is to rationally design catalytic systems that employ transition metals that readily activate dioxygen. Oxidative addition reactions of d^8 Ir(I) complexes are well-known in organometallic chemistry. Further, the activation of O_2 by iridium(I) complexes has been demonstrated.[4] Despite this fact, catalytic oxidations that employ Ir are scarce. One notable exception is the Oppenauer-type oxidations developed by Yamaguchi et al.[5] In this reaction, secondary alcohols are oxidized to ketones, while acetone is sacrificially reduced. In the proposed mechanism for this reaction acetone inserts into an Ir(III) hydride to form an alkoxide ligand that subsequently undergoes alcohol exchange to yield isopropyl alcohol and regenerate the catalytically active Ir complex.

We rationalized that this strategy could potentially be used in aerobic oxidations, where O_2 instead of acetone, serves as a hydrogen acceptor. Recently the groups of Ikariya et al. and Rauchfuss et al. independently reported on the reactivity of Ir hydrides with O_2.[6] Here we report that simple Ir complexes catalyze the oxidation of primary and secondary alcohols. In these reactions O_2 is directly reduced to H_2O according to equation 1.



(1)

We also report initial mechanistic analyses of this reaction and comment on the implications for similar transition-metal-catalyzed aerobic oxidations. The highlights of our system are the following: (1) it offers mechanistic insight on activation of oxygen by transition metal complexes, (2) the reaction illustrates a new role for catalysis by Ir, and (3) the reaction utilizes the environmentally benign O_2 as a stoichiometric oxidant. This last feature is very attractive because it limits the amount of organic waste typically generated by traditional organic oxidants and does not lead to environmentally hazardous byproducts typically associated with stoichiometric transition metal oxidants. Also notable is the simplicity of our catalytic system; all aerobic oxidations are performed with the commercially available Ir(III) complex, $[Cp^*IrCl_2]_2$, (**1**), (traditionally utilized in C−H activation and catalytic hydrogenations, and transfer hydrogenations) at 1 atm O_2, and catalytic amounts of Et_3N.

One of our main hypotheses was that O_2 is needed for direct catalytic turnover. We tested this by examining the catalytic reaction of **1** with 4-methoxybenzyl alcohol under three different conditions: (a) 1 atm of O_2, (b) 1 atm of air, and (c) 1 atm of N_2, (Table 1). These data clearly show that O_2 is essential for catalytic turnover for these catalysts.

Table 1. Dependence of Oxidation of 4-Methoxybenzyl Alcohol on O_2

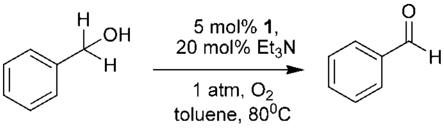
reaction conditions[a]	% conversion[b]	TON
O_2 (1 atm)	96	38
Air (1atm)	24	9.6
N_2 (1 atm)	12	4.8

[a] Conditions: Run using 2.5 mol % **1**, substrate (2M), Et_3N (2M), 12 h, 80 °C, C_7D_8. [b] Determined by ^1H NMR spectroscopy.

The scope of reactivity was then investigated using **1** as a catalyst in toluene at 80 °C (Supporting Information, Table S1). There is a clear electronic dependence on the reactivity of parasubstituted benzyl alcohols (entries S1−S6) with the reaction favoring electron donating substituents. Aliphatic and secondary alcohols (entries S7−S8) are all successfully oxidized under the reaction conditions.

Dioxygen uptake measurements were performed and reveal a substrate/dioxygen stoichiometry of 2.8(7):1. The dioxygen stoichiometry suggests that hydrogen peroxide does not accumulate during the catalytic reaction as observed in other palladium-catalyzed oxidation reactions.[7] Attempts to use hydrogen peroxide directly as an oxidant resulted instead in the rapid disproportionation of H_2O_2 under the reaction conditions.

The progress of the aerobic oxidation of benzyl alcohol with O_2 catalyzed by **1** (eq 1) was investigated by monitoring the change in oxygen pressure within a sealed, temperature-controlled Parr reaction vessel equipped with a high-accuracy pressure transducer, and a digital recorder. From the kinetic data, the reaction exhibited first-order dependencies on [catalyst] and [O_2], saturation kinetics on [benzyl alcohol], and no dependence on [triethyl amine] (Figure 1).



(2)

The aerobic oxidation of benzyl alcohol (α,α-d_2) catalyzed by **1** allowed us to obtain a kinetic isotope effect for the catalytic reaction of 0.9(1). Further the aerobic oxidation of a mixture of benzyl alcohol (α,α-d_2) and benzyl alcohol resulted in the complete deuterium scrambling and the formation of benzyl alcohol (α-d_1), as well as benzaldehyde (α-d_1) and benzaldehyde (Scheme 1). The kinetic isotope effect and isotopic labeling data strongly suggests the presence of Ir hydrides as key species in the catalytic cycle.

To investigate the catalytic viability of these species we investigated the oxidation of 4-methoxybenzyl alcohol with **1** under

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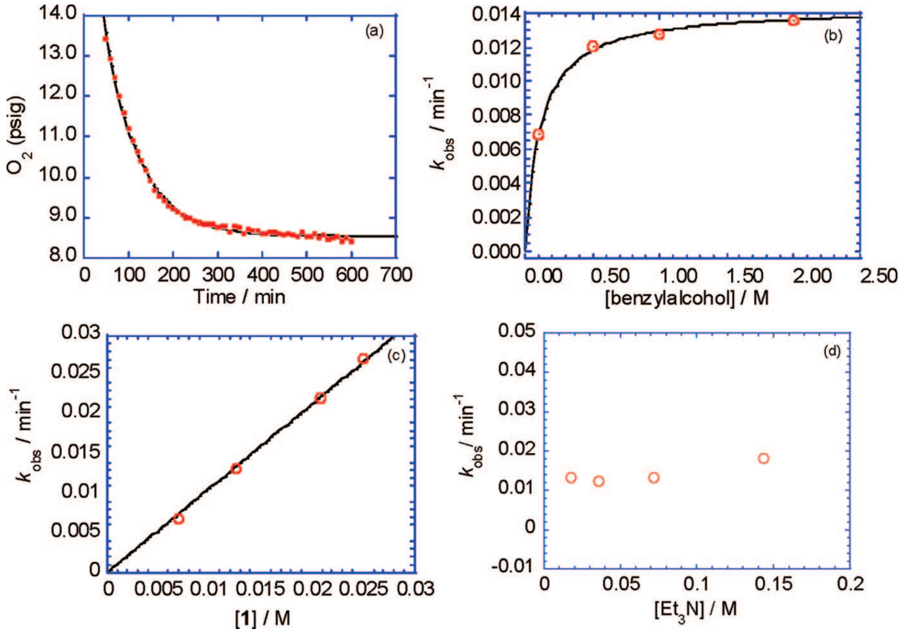
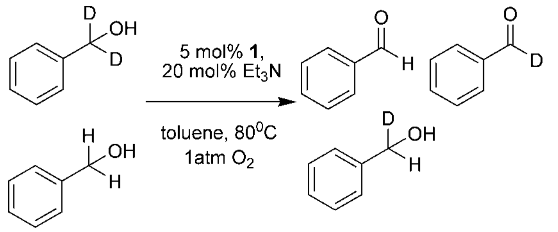
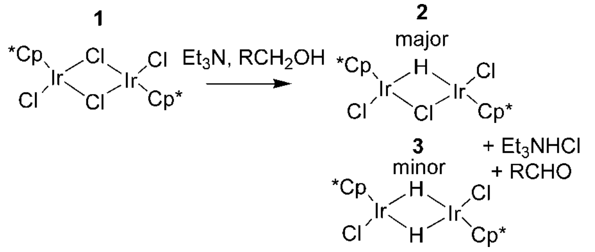


Figure 1. (a) Time profile for the aerobic oxidation of benzyl alcohol (1 M) with O_2 (14.5 psig), Et_3N (25.1 mM), and **1** (12.6 mM) in toluene at 353 K. (b) Dependence of k_{obs} on [benzyl alcohol] for the oxidation of benzyl alcohol with O_2 (14.5 psig), Et_3N (25.1 mM), [**1**] (12.6 mM). Data are fit with nonlinear least-squares fitting to an equation describing saturation in [benzyl alcohol],[8] $R^2 = 0.996$. (c) Dependence on [**1**]: O_2 (14. 5 psig), Et_3N (25.1 mM), [benzyl alcohol], (1 M) $R^2 = 0.997$. (d) Dependence on [Et_3N]: O_2 (14. 5 psig), [**1**] (12.6 mM), benzyl alcohol (1 M) in toluene at 353 K.

Scheme 1



Scheme 2

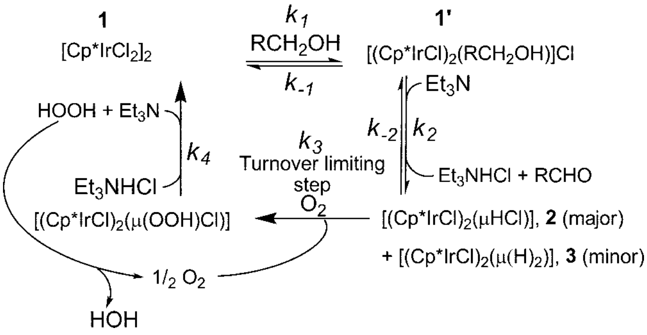


nitrogen. Treatment of a C_7D_8 solution of **1** under N_2 with excess 4-methoxybenzyl alcohol (1−16 equiv) results in the formation of two new hydride species Ir−H (δ −13.5, −13.8 ppm) in a 6:1 ratio (Scheme 2). The new species were assigned as the complexes [(Cp*Ir Cl)$_2$HCl], **2**, and [Cp*IrHCl]$_2$, **3**. The concentration of **3** increased as the concentration of 4-methoxybenzyl alcohol is increased. Also, in the presence of excess alcohol, **2** is slowly (24 h) converted to **3**. Complexes **2** and **3** have been previously synthesized from **1** by Maitlis and co-workers.[9] We examined the viability of these species as intermediates by examining their reactivity and their kinetic competency in the oxidation of benzyl alcohol.

Treatment of **3** with Et_3NHCl and O_2 in C_7D_8 results in the decomposition to several unidentified species. Further, the aerobic oxidation of benzyl alcohol catalyzed by **3** resulted in a TON of 2 after 12 h. In contrast, the aerobic oxidation of benzyl alcohol catalyzed by **2** resulted in a similar TON (14) after 12 h for the catalytic reaction. Further, the kinetic competency **2** is comparable to **1** under similar catalytic conditions.[10]

These results strongly implicate the Ir-hydride **2** as a key intermediate in the catalytic cycle for the aerobic oxidation of alcohols. The dihydride **3** is a minor species that is not part of the catalytic cycle. The treatment of **2** with benzaldehyde and Et_3NHCl in C_7D_8 under nitrogen at 80 °C results in the formation benzyl alcohol and **1**. The reaction rapidly reaches equilibrium in 2 h with the ratio of benzyl alcohol/benzaldehyde (1:1.3). The data suggest that in the absence of oxygen, **2** readily reduces benzaldehyde. A plausible mechanism and rate equation that is consistent with the data presented is depicted in Scheme 3 and eq 3.[10]

Scheme 3



$$\text{Rate} = \frac{-\mathrm{d}P(\mathrm{O_2})}{\mathrm{d}t} = \frac{K_1k_2k_3[\mathrm{RCH_2OH}][(\mathrm{Cp*IrCl_2})_2]_T[\mathrm{O_2}]}{k_{-2}[\mathrm{RCHO}][\mathrm{Et_3NHCl}] + K_1k_2[\mathrm{RCH_2OH}][\mathrm{Et_3N}]} \quad (3)$$

The formation of **2** is rapid relative to the overall time scale of the catalytic reaction. This is confirmed by the observation that when **1** is treated with benzyl alcohol no change in the ^{1}H NMR or UV spectrum of **1** is observed at room temperature. However, when this mixture is treated with Et_3N, a stoichiometric amount of benzaldehyde is immediately formed along with **2**. Also notable, is the fact that there is no catalytic activity in the absence of Et_3N. Thus the role of Et_3N in the catalytic reaction is to promote β-hydride elimination of the coordinated alcohol and the formation of **2**. The observation that under nitrogen and in the presence of Et_3NHCl benzaldehyde is reduced by **2** suggests that the product forming step in Scheme 3 is reversible. Also the observed formation of benzaldyde (12% conversion) in Table 1 in the absence of oxygen results from the stoichiometric oxidation of benzyl alcohol by **1** prior to catalytic turnover. During the catalytic reaction, **2** is observed as the resting state of the catalytic system. *Thus the role of O_2 in this catalytic reaction is to promote catalytic turnover; that is, dioxygen acts as a hydrogen atom acceptor similar to recent "chemical oxidases".*

The absence of a kinetic isotope effect, the identification of **2** as the catalyst resting state, and the first order dependence of $[O_2]$ are consistent with the reaction of O_2 with **2** as the turnover limiting step. The first-order dependence on [catalyst] is not consistent with the monomerization of **2**. Nor is the data consistent with the reduction of Ir(III) to Ir(I).[11] Heating a C_7D_8 solution of **2** under 1 atm of O_2 and in the presence of Et_3NHCl results in the formation of a new species, after 4 h.[10] After 16 h there is complete disappearance of **2**. In contrast, there is no apparent reaction when **2** is heated with Et_3NHCl under N_2. Further, there is also no apparent reaction when **2** is heated in the presence of triethylamine which suggests that **2** does not react via base-promoted reductive elimination to Ir(I).

Thus the key mechanistic feature of these complexes involves the reaction of an Ir hydride with O_2. While the exact nature of the species formed from this interaction is not known at this time, there is precedence for the reaction of transition metal hydrides with O_2 to produce transition metal hydroperoxide complexes.[12] Studies on the exact nature of the species that results from the reaction of **2** with O_2 is currently being undertaken in our laboratory. Importantly, the reaction occurs with Ir in a +3 oxidation state throughout the catalytic cycle. The observation that hydrides might play an important role in aerobic oxidations is a new and exciting development as it allows for the design of new catalytic systems that can avoid lower valent oxidation states altogether (in this case Ir(I)).

To summarize we have presented a novel catalytic system for the aerobic oxidation of primary and secondary alcohols. For these reactions we employ the commercially available catalysts $[(Cp^*IrCl_2)_2]$ with O_2 as the terminal oxidant in the presence of catalytic amounts of Et_3N. A new mechanism for the Ir-catalyzed aerobic oxidation is also presented that suggests the transition metal maintains its (+3) oxidation state throughout the entire catalytic cycle. Evidence in support of the mechanism presented includes (1) demonstration that O_2 is needed for catalytic turnover, (2) kinetic data from oxygen uptake experiments consistent with the proposed mechanism, (3) kinetic isotope and isotopic labeling data that implicate Ir hydrides as key intermediates in the catalytic reaction, (4) identification of the Ir hydride **2** as a key and kinetically competent intermediate in the catalytic cycle, and (5) identification of the reaction of **2** with O_2 as the turnover limiting step in the reaction and the identification of **2** as the resting state of the catalytic system. The results presented will aid in the development of more efficient systems for aerobic oxidations with Ir and other transition metals.

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Supporting Information Available: Experimental details and kinetic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) See Supporting Information for derivation.
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