Aerobic Oxidation Using Air Catalyzed by [Cp*IrCl₂]₂

A Major Qualifying Project Report

presented by

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1 Introduction

1.1 Alcohol Oxidation in Organic Synthesis

Alcohol oxidation is an important reaction in organic chemistry. Secondary alcohols can be oxidized to ketones, while primary alcohols afford aldehydes or carboxylic acids after oxidation. Four common oxidation reactions are used to synthesize ketones from alcohols, all of them named after their inventors: the Corey-Kim\textsuperscript{1}, Dess-Martin\textsuperscript{2}, Jones\textsuperscript{3}, and Swern\textsuperscript{4} oxidations (Figure 1).

\begin{align*}
\text{OH} & \quad 1) \text{Me}_2\text{S}, \text{NCS} \quad \text{OAc} \quad \text{OAc} \\
& \quad 2) \text{Et}_3\text{N} \quad \text{OAc} \quad \text{OAc} \\
\text{Condition: toluene as solvent} & \quad \text{Condition: Room temperature, neutral pH} \quad \text{Condition: Acetone as solvent, exothermic} \\
\text{OH} & \quad \text{CrO}_3, \text{H}_2\text{SO}_4 \quad \text{OH} \\
& \quad 1) \text{DMSO}, \text{Cl}_2\text{C}_2\text{O}_2 \quad \text{OH} \\
& \quad 2) \text{NE}_3 \quad \text{OH} \\
\text{Conditions: toxic, under -60°C} & \quad \text{Reaction Name} \quad \text{Reagents} \quad \text{Dess-Martin} \quad \text{Dess-Martin periodinate} \\
\text{Jones} & \quad \text{CrO}_3, \text{H}_2\text{SO}_4 \quad \text{Swern} \quad \text{DMSO, Cl}_2\text{C}_2\text{O}_2, \text{NE}_3
\end{align*}

\textbf{Scheme 1} Traditional methodologies of alcohol oxidation

However, all these oxidations have very serious drawbacks. Most of them are hazardous processes using toxic oxidants\textsuperscript{5}, which are not atom economical. From an environmental point of view, it is very important to find a method using cleaner oxidants and to minimize the amount of released waste from chemical reactions\textsuperscript{6}.
1.2 Transition metal catalyzed aerobic alcohol oxidation

An alternative to chemical oxidations are aerobic alcohol oxidations which use only oxygen as the sole oxidant and produce no waste. These types of reactions are more atom economical than the traditional methodologies described above, because oxygen is inexpensive and easily obtainable and the only byproduct is water. Using transition metals to catalyze aerobic alcohol oxidations has many advantages such as relatively mild reaction temperatures and the lack of toxic additives.\(^7\)

Various transition metal compounds have been used in aerobic alcohol oxidations, among them cobalt (Co)\(^8\), copper (Cu)\(^9\), iron (Fe)\(^10\) and ruthenium (Ru) complexes\(^11\). Some of these protocols employ high catalyst loadings or employ pure oxygen gas; thus, the setup can be expensive or involve tedious procedures.

The metal we use in this project is iridium (Ir). Gabrielsson and coworkers first reported that methanol, ethanol, or benzyl alcohol formed the corresponding aldehydes in air in the presence of \([\text{Cp*Ir(Cl)(bpy)}]^{\text{OTf}}\) (1) and \([\text{Cp*Ir(Cl)(bpym)}]^{\text{OTf}}\) (2) (Figure 2) and stoichiometric amounts of a base such as NaOH or Na\(_2\)CO\(_3\).\(^12\)

![Figure 1 Iridium catalysts](image1)

Following Gabrielsson’s reports, Ison and coworkers reported that the simpler complex \([\text{Cp*IrCl\_2}]^{\text{2}}\) (Figure 3) also catalyzes the oxidation of primary and secondary alcohols in 1 atmosphere O\(_2\) in the presence of Et\(_3\)N.\(^13\)
Alcohols such as benzyl alcohol or cyclohexanol can be treated with [Cp*IrCl₂]₂ under 1 atm of O₂ in toluene at 80 °C. The addition of Et₃N presumably promotes β-hydride elimination of the coordinated alcohol and formation of [(Cp*IrCl)₂HCl] as intermediate. This report further concludes that O₂ is needed for efficient catalytic turnover. As such, a catalytic reaction of 4-methoxybenzyl alcohol (CH₃OC₆H₄CH₂OH) under three different conditions (1 atm of O₂, 1 atm of air and 1 atm of N₂) only provides high yield under 1 atmosphere of O₂ (Table 1).

**Table 1** Dependence of Oxidation of 4-Methoxybenzyl Alcohol on O₂

<table>
<thead>
<tr>
<th>Reaction Condition</th>
<th>% conversion</th>
<th>TON</th>
</tr>
</thead>
<tbody>
<tr>
<td>O₂ (1 atm)</td>
<td>96</td>
<td>38</td>
</tr>
<tr>
<td>Air (1 atm)</td>
<td>24</td>
<td>9.6</td>
</tr>
<tr>
<td>N₂ (1 atm)</td>
<td>12</td>
<td>4.8</td>
</tr>
</tbody>
</table>

Conditions: 2.5 mol % [Cp Cl₂]₂, substrate (2M), Et₃N (2M), 12h, 80 °C

However, Ison’s catalytic system requires 10 mol% of the iridium catalyst. As iridium is a fairly expensive metal ($1025 / troy oz), this is neither very atom economical nor practical.
1.3 Approach

The goal of this project is to design an improved iridium catalyst system that yields a very high activity in alcohol oxidation with air. Our starting catalyst is the simple iridium complex \([\text{Cp}^\ast\text{IrCl}_2]_2\) (1). Because \([\text{Cp}^\ast\text{IrCl}_2]_2\) incorporates two labile \(\mu\)-Cl bonds, the dimer can be cleaved to give a monomeric complex, which is then able to form a large variety of new complexes (2).\(^{15}\) Our approach will generate these catalysts in situ from \([\text{Cp}^\ast\text{IrCl}_2]_2\). By adding different \(X\)- or \(L\)-type ligands onto \([\text{Cp}^\ast\text{IrCl}_2]_2\), we propose to generate more effective iridium catalysts (Figure 4).

![Scheme 2 Iridium catalyst precursors](image-url)
2 Results and discussion

2.1 Reaction setup

1-phenyl-1-propanol (1) was used as the substrate because of its relatively low volatility, and because ketone (2) is the only possible oxidation product that will form. Thus the analysis of the reaction products by calibrated gas chromatography is expected to be straightforward. The reactions were stopped after 2 or 24 hours in order to explore the initial reactivity and the long term stability of the catalyst. All reactions were repeated at least three times in three different vials to minimize statistical errors. Toluene was used as a solvent and \([\text{Cp}^*\text{IrCl}_2]\) was used as the catalyst.

![Chemical reaction diagram](image)

Table 2 Alcohol oxidation assay

<table>
<thead>
<tr>
<th>[Cp*IrCl2]2</th>
<th>Ligand</th>
<th>1-Phenyl-1-Propanol</th>
<th>Yield %, 2h</th>
<th>Yield %, 24h</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0.2 mmol</td>
<td>0</td>
<td>0.1 ± 0.1</td>
</tr>
<tr>
<td>1 mol%</td>
<td>0</td>
<td>0.2 mmol</td>
<td>10 ± 0.02</td>
<td>53 ± 3</td>
</tr>
</tbody>
</table>

According to the results of table 2, without presence of the Ir catalyst, oxidation reaction nearly shows no product 2 yields. When using only [Cp*IrCl2]2 (1 mol %) in the absence of ligands, 10 and 53% yields of 2 were obtained after 2 and 24 h.
2.2 Effect of X-type ligands

X-type ligands were introduced in situ through the use of various silver salts (Scheme 4). For Ag salts, we have chosen non-coordinating anions such as: TfO^-, BF_4^-, PF_6^- and coordinating anions such as: SO_4^{2-}, NO_3^-, CO_3^{2-}, AcO^- and F3CCO_2^- All X-type ligands were added to the solution at a loading of 4.2 mol % and 2 mol %. Once 2 mol % of X-type ligand was added, we assume that only one -Cl on Ir was replaced by X-type ligand and Cp*IrClX formed (1). For the loading of 4.2%, we expect that all chloride ligands on Ir will be replaced by X-type ligand and Cp*IrX_2 (2) will form in situ^{15}.

![Scheme 4](image-url)

**Scheme 3** Yields of X-type ligands in 4.2 mol% and 2 mol%
According to the results shown in Scheme 4, a clear improvement in catalytic reactivity was observed with reagent $\text{AgO}_2\text{CCF}_3$, $\text{AgOAc}$ when compared to the parent compound $[\text{Cp}^*\text{IrCl}_2]_2$. Interestingly, the reactions with 4.2 mol % of $\text{AgO}_2\text{CCF}_3$, $\text{AgOAc}$, $\text{AgNO}_3$, $\text{Ag}_2\text{SO}_4$, $\text{Ag}_2\text{CO}_3$ showed unequivocally better yield in 24 hours than the respective reactions using 2 mol % of Ag additives.

### 2.3 Effect of L-type ligands

In order to evaluate various L-type ligands, 2 mol % of L-type ligands were which is equivalent to one L-type ligand per Ir center. L-type ligands that were introduced have various features, such as ligands bearing no functional groups proximal to the binding site, ligands with polar functional groups in $\beta$-position to the binding site and ligands bearing potential $\text{H}^+$ donors or acceptors at the binding site. We propose that these ligands coordinate to the empty coordination site on Ir (as shown in Scheme 5). The results in Scheme 5 show that none of the ligands affords yields higher than the parent compound $[\text{Cp}^*\text{IrCl}_2]_2$ after 24 h. However, some of the reactions showed unequivocally better yield in 2 hours than the respective parent complex reaction.
2.4 Effects of combining AgO$_2$CCF$_3$ and L-type ligand

Since, 4.2 mol % of AgO$_2$CCF$_3$ showed the highest activity in section 2.2, effects of its combination with L-type ligands were studied as shown in Scheme 6. Interestingly, 2-methylpyridine gives the best yield and shows the highest catalyst activity, resulting in 62% of ketone product after 24 h.
### 2.5 Time studies

In order to monitor the reaction progress and find out the trend of catalyst activity during time, time studies was set up. The results of these time studies are shown in Scheme 7. Interestingly, all catalysts seem to reach their highest activity after 72 hours. However, 72 hours reaction time is too long and is not practical. 24 hours reaction time is long enough for evaluating the activity of catalyst and comparing with other system.
2.6 Evaluating different solvents

In order to determine the effect of different reaction solvents on the oxidation of alcohol reactions, various solvents were screened. Compared with the results of Toluene over MS (toluene dried with molecular sieve overnight, 28% yield) and Toluene + MS (molecular sieve was added along in reaction, 11% yield), wet toluene is the best solvent as shown in the results in Scheme 8. In addition, chlorinated solvents: Toluene + 5% CH₂Cl₂ (32% yield) and Toluene + 5% CHCl₃ (30% yield) do not shown better improvement than wet toluene. It seems further noteworthy that catalyst in wet solvent shown better activity than in dry solvent and in chlorinated
solvents. Water has the effects of stabilize catalyst and prevent the decomposition of Iridium.

\[
\begin{align*}
\text{OH} & \quad \quad 1 \text{ mol} \% \left[ \text{Cp}^*\text{IrCl}_2 \right]_2 \\
& \quad \quad 1.9 \text{ ml} \times \text{ solvent}, 100 \degree \text{C}, 24 \text{ h} \\
& \quad \quad 18 \text{ mL} \text{ air}
\end{align*}
\]

2.7 Comparison of water contents in buffer system

During the course of the above studies, another researcher in the Emmert lab (A. Gunay) discovered that Cp*Ir catalyst shows higher activity in the presence of a AcOH/NaOAc buffer system. Refer to Elon Ison’s paper; the role of buffer system in the catalytic reaction is to promote $\beta$-hydride elimination of the coordinated alcohol and the formation of ketone $2^{13}$. According to the results in section 2.6, water has a clear effect of improving the activity of Ir catalyst. In order to investigate the effects of combining water with the NaOAc/AcOH buffer system, various amounts of water
were added into buffer system. Based on the results of Scheme 9, 10 µl of water gives the best yield in both 2 h and 24 h.
2.8 Combinations of X- and L-type ligands with buffer system with water

In order to evaluate X- and L-type ligands in the buffer system with 10 μL water, various ligands which showed high activity in sections 2.2 and 2.3 were introduced. According to the results of Scheme 10, no clear improvement by X-type ligands was shown after 24 h comparing with the results in section 2.2. L-type ligands have very clear improvement on the catalytic activity in buffer system with water. 2-methoxypridine and diethylamine are the best yielding ligands in this study as shown in Scheme 11.
Scheme 9 X-type ligand in buffer system with water

Scheme 10 L-type ligand in buffer system with water
2.9 Conclusions

From the studies of X- and L-type ligand, we learned that AgO$_2$CCF$_3$, AgOAc and tert-butylamine have shown clear improvement in catalytic reactivity. Water has the effect of stabilizing the catalyst and preventing the decomposition of Ir, as demonstrated by the described water studies. Furthermore, our studies suggest that buffer systems can be used to promote the formation of ketone product 2, while also having an effect in catalyst stabilization.
3 Experimental Section

3.1 General considerations

Reactions were performed in ambient air in a 20-mL scintillation vial. Stir bars used in catalytic reactions were cleaned with aqua regia for at least 3 hours, rinsed with acetone and water, and dried in an oven at 120°C. Standard solutions were prepared and measured in volumetric flasks. All ligand included in the project have been previously reported in the literature and are commercially available. Oxidation products were run under gas chromatography (GC) and gas chromatography-mass spectrometry (GC-MS) analysis to obtain data. Dry toluene was prepared by drying with active molecular sieve overnight.

3.2 Procedure for alcohol oxidation in the presence of X-, L-type ligands

To a 20 mL scintillation vial, [Cp*IrCl₂]₂ (1.6 mg, 2.0 μmol, 1 mol%) was weighted in, 100 μL (0.2 mmol, 2 mol %) of a standard solution of 1-phenylpropanol (2.738 mL, 20.00 mmol) in 10 mL toluene and 100μL (4 μmol, 2 mol % ligand) of a standard solution of L-type ligand in 10 mL toluene were added to this mixture. The resulting solution was diluted by toluene (1.80 mL) to a total volume of 2.0 mL. The vial was sealed with a Teflon-lined cap and heated to 100°C on a pre-heated vial plate. Upon completion of the reaction time (2h and 24h), the vials were taken off the heating plate and cooled down to room temperature. As an internal GC standard 100 μL of a standard solution (1 ml p-xylene is diluted by toluene to the 10ml line of a volumetric flask) of para-xylene was added for GC analysis. Once the GC standard
was added into vials, vials were sealed and shaken well. Then the solution was transferred into GC vial and GC analysis was run.

Experiments, where the X-type ligands are present, were prepared by the same procedure described above using 100 μL (8.4 μmol, 4.2 mol% ligand) of a standard solution of X-type ligand in 10 mL toluene.

Table 3 GC yields of oxidation product 2 with different X-type ligands.

Conditions: \([\text{Cp}^*\text{IrCl}_2]_2\) (2.0 μmol, 2.0 mol % [Ir]), Ag additive (2.1 or 4.2 mol %), 1-phenyl-1-propanol (1) (0.20 mmol, 1.0 equiv.), toluene (total volume 2.0 mL), 100 °C, 2 or 24 h.

<table>
<thead>
<tr>
<th>Ag additive (mol %)</th>
<th>% GC Yield of 2 (2 h)</th>
<th>% GC Yield of 2 (24 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>none</td>
<td>10 ± 0</td>
<td>53 ± 2</td>
</tr>
<tr>
<td>AgO$_2$CCF$_3$ (4.2 mol %)</td>
<td>34 ± 1</td>
<td>50 ± 0</td>
</tr>
<tr>
<td>AgOAc (4.2 mol %)</td>
<td>37 ± 2</td>
<td>53 ± 5</td>
</tr>
<tr>
<td>AgOTf (4.2 mol %)</td>
<td>1 ± 1</td>
<td>2 ± 0</td>
</tr>
<tr>
<td>AgBF$_4$ (4.2 mol %)</td>
<td>2 ± 0</td>
<td>25 ± 3</td>
</tr>
<tr>
<td>AgPF$_6$ (4.2 mol %)</td>
<td>5 ± 0</td>
<td>19 ± 0</td>
</tr>
<tr>
<td>AgNO$_3$ (4.2 mol %)</td>
<td>22 ± 2</td>
<td>34 ± 4</td>
</tr>
<tr>
<td>Ag$_2$CO$_3$ (2.1 mol %)</td>
<td>9 ± 0</td>
<td>41 ± 4</td>
</tr>
<tr>
<td>Ag$_2$SO$_4$ (2.1 mol %)</td>
<td>9 ± 0</td>
<td>41 ± 5</td>
</tr>
</tbody>
</table>
Table 4 GC yields of oxidation product 2 with different L-type ligands.
Conditions: [Cp*IrCl$_2$]$_2$ (2.0 μmol, 2.0 mol % [Ir]), ligand (4.0 μmol, 2.0 mol %), 1-phenyl-1-propanol (1) (0.20 mmol, 1.0 equiv.), toluene (total volume 2.0 mL), 100 °C, 2 or 24 h.

<table>
<thead>
<tr>
<th>Ligand</th>
<th>% GC Yield of 2 (2 h)</th>
<th>% GC Yield of 2 (24 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>none</td>
<td>10 ± 0</td>
<td>53 ± 2</td>
</tr>
<tr>
<td></td>
<td>9 ± 1</td>
<td>39 ± 1</td>
</tr>
<tr>
<td></td>
<td>3 ± 0</td>
<td>17 ± 0</td>
</tr>
<tr>
<td></td>
<td>34 ± 1</td>
<td>57 ± 0</td>
</tr>
<tr>
<td></td>
<td>6 ± 0</td>
<td>24 ± 0</td>
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<tr>
<td></td>
<td>10 ± 1</td>
<td>21 ± 1</td>
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<tr>
<td></td>
<td>8 ± 1</td>
<td>28 ± 1</td>
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<tr>
<td></td>
<td>9 ± 0</td>
<td>37 ± 1</td>
</tr>
<tr>
<td></td>
<td>5 ± 0</td>
<td>34 ± 1</td>
</tr>
<tr>
<td></td>
<td>8 ± 1</td>
<td>45 ± 1</td>
</tr>
<tr>
<td>NEt$_3$</td>
<td>9 ± 1</td>
<td>21 ± 1</td>
</tr>
<tr>
<td>HNEt$_2$</td>
<td>14 ± 0</td>
<td>50 ± 1</td>
</tr>
<tr>
<td>HN'Pr$_2$</td>
<td>14 ± 1</td>
<td>49 ± 2</td>
</tr>
<tr>
<td>H$_2$N'Bu</td>
<td>17 ± 2</td>
<td>52 ± 1</td>
</tr>
</tbody>
</table>
3.3 Procedure for time studies

1.6 mg of \([\text{Cp}^*\text{IrCl}_2]_2\) (2.0 µmol, 1.0 mol %) was weighted in a 20-mL scintillation vial and 100 µL(0.2 mmol, 2 mol%) of a standard solution of 1-phenylpropanol (2.738 mL, 20.00 mmol) in 10 mL toluene was added to this mixture. If any X- or L-type ligands were present, they were added according to the procedure described in 2.2. The resulting solution was diluted by toluene (1.90 mL) to a total volume of 2.0 mL. The vials were run for 2h, 4h, 6h, 10h, 16h, 24h, 48h, 72h and 96h. The vials were sealed with a Teflon-lined cap and heated to 100 °C on a pre-heated vial plate. Upon completion of the reaction time, the vials were taken off the heating plate and cooled to room temperature. As an internal GC standard 100 µL of a standard solution (1 ml p-xylene is diluted by toluene to the 10ml line of a volumetric flask) of para-xylene was added for GC analysis. Once the GC standard was added into vials, vials were sealed and shaken well. Then the solution was transferred into GC vial and GC analysis was run.

Additive 1: \([\text{Cp}^*\text{IrCl}_2]_2\) (1mol %)
Additive 2: \([\text{Cp}^*\text{IrCl}_2]_2\) (1mol %) + AgO2CCF3 (4 mol%)
Additive 3: \([\text{Cp}^*\text{IrCl}_2]_2\) (1mol %) + AgO2CCF3 (4 mol%) + 2-methylpyridine (2 mol%)
Additive 4: \([\text{Cp}^*\text{IrCl}_2]_2\) (1mol %) + AgO2CCF3 (4 mol%) + 2-fluoropyridine (2 mol%)
Table 5 GC yields of oxidation product 2 in different time. Conditions: [Cp*IrCl\(_2\)]\(_2\) (2.0 μmol, 2.0 mol % [Ir]), 1-phenyl-1-propanol (1) (0.20 mmol, 1.0 equiv.), toluene (total volume 2.0 mL), 100 °C.

<table>
<thead>
<tr>
<th>Additive Hours</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>13 ± 0</td>
<td>32 ± 1</td>
<td>32 ± 0</td>
<td>30 ± 1</td>
</tr>
<tr>
<td>4</td>
<td>16 ± 0</td>
<td>37 ± 0</td>
<td>38 ± 1</td>
<td>34 ± 1</td>
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<tr>
<td>6</td>
<td>20 ± 0</td>
<td>36 ± 1</td>
<td>43 ± 1</td>
<td>41 ± 1</td>
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<tr>
<td>10</td>
<td>30 ± 1</td>
<td>39 ± 3</td>
<td>46 ± 0</td>
<td>43 ± 1</td>
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<tr>
<td>24</td>
<td>38 ± 1</td>
<td>45 ± 1</td>
<td>53 ± 1</td>
<td>48 ± 1</td>
</tr>
<tr>
<td>48</td>
<td>51 ± 2</td>
<td>57 ± 0</td>
<td>66 ± 1</td>
<td>60 ± 0</td>
</tr>
<tr>
<td>72</td>
<td>53 ± 2</td>
<td>60 ± 0</td>
<td>76 ± 0</td>
<td>62 ± 1</td>
</tr>
<tr>
<td>96</td>
<td>25 ± 7</td>
<td>50 ± 0</td>
<td>59 ± 2</td>
<td>59 ± 5</td>
</tr>
</tbody>
</table>

3.4 Procedure for solvent screening

1.6 mg of [Cp*IrCl\(_2\)]\(_2\) (2.0 μmol, 1.0 mol %) was weighted in a 20-mL scintillation vial and 100 μL (0.2 mmol, 2 mol%) of a standard solution of 1-phenylpropanol (2.738 mL, 20.00 mmol) in 10 mL toluene was added to this mixture. The resulting solution was diluted by various solvents () to make a total volume of 2.0 mL.\(^\text{15}\) The vial was sealed with a Teflon-lined cap and heated to 100 °C on a pre-heated vial plate. Upon completion of the reaction time, the vials were taken off the heating plate and cooled to room temperature. As an internal GC standard 100 μL of a standard solution (1 ml \(p\)-xylene is diluted by toluene to the 10ml line of a volumetric flask) of \(p\)-xylene was added for GC analysis. Once the GC standard was added into vials, vials were
sealed and shaken well. Then the solution was transferred into GC vial and GC analysis was run.

Table 6 GC yields of oxidation product 2 in different solvents. Conditions: \([\text{Cp}^*\text{IrCl}_2]^2\) (2.0 µmol, 2.0 mol % [Ir]), 1-phenyl-1-propanol (1) (0.20 mmol, 1.0 equiv.), solvent (2.0 mL), 100 °C, 24 h.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>% GC Yield of 2 (24 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solvents used as received</td>
<td></td>
</tr>
<tr>
<td>Wet Toluene</td>
<td>53 ± 2</td>
</tr>
<tr>
<td>PhCl</td>
<td>12 ± 0</td>
</tr>
<tr>
<td>PhBr</td>
<td>14 ± 0</td>
</tr>
<tr>
<td>PhCF₃</td>
<td>31 ± 1</td>
</tr>
<tr>
<td>ortho-C₆H₄(CH₃)₂</td>
<td>28 ± 3</td>
</tr>
<tr>
<td>Toluene over MS</td>
<td>28 ± 5</td>
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<tr>
<td>Toluene + MS</td>
<td>12 ± 1</td>
</tr>
<tr>
<td>Toluene + 5 % CH₂Cl₂</td>
<td>32 ± 3</td>
</tr>
<tr>
<td>Toluene + 5 % CHCl₃</td>
<td>31 ± 1</td>
</tr>
<tr>
<td>DMF</td>
<td>39 ± 4</td>
</tr>
<tr>
<td>Water</td>
<td>18 ± 0</td>
</tr>
</tbody>
</table>

3.5 Procedure for alcohol oxidation in the presence of buffer system

1.6 mg of \([\text{Cp}^*\text{IrCl}_2]^2\) (2.0 µmol, 1.0 mol %) was weighted in a 20-mL scintillation vial, 100 µL (0.2 mmol, 2 mol %) of a standard solution of 1-phenylpropanol (2.738 mL, 20.00 mmol) in 10 mL toluene and 10 µL of water were added to this mixture. The resulting solution was diluted with dry toluene (1.90 mL) to a total volume of 2.0 mL. Then NaOAc (0.8 mg, 0.01 mmol) was weighted into the vial and 1.2 µL of AcOH (0.02
mmol) was injected. The vial was sealed with a Teflon-lined cap and heated to 100 °C on a pre-heated vial plate. Upon completion of the reaction time, the vials were taken off the heating plate and cooled to room temperature. As an internal GC standard 100 μL of a standard solution (1 ml p-xylene is diluted by toluene to the 10ml line of a volumetric flask) of para-xylene was added for GC analysis. Once the GC standard was added into vials, vials were sealed and shaken well. Then the solution was transferred into GC vial and GC analysis was run.

**Table 7 GC yields of oxidation product 2 with varying water content in buffer system.** Conditions: \([\text{Cp}^*\text{IrCl}_2]\) \(_2\) (2.0 μmol, 2.0 mol % [Ir]), AcOH (0.02 mmol), NaOAc (0.01 mmol), 1-phenyl-1-propanol (1) (0.20 mmol, 1.0 equiv.), 1.9 mL toluene, \(\text{H}_2\text{O}\) (5 to 100 μL), 100 °C, 2 or 24 h.

<table>
<thead>
<tr>
<th>Water</th>
<th>% GC Yield of (\text{2}) (2 h)</th>
<th>% GC Yield of (\text{2}) (24 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 μL</td>
<td>55 ± 0</td>
<td>78 ± 2</td>
</tr>
<tr>
<td>10 μL</td>
<td>55 ± 2</td>
<td>82 ± 2</td>
</tr>
<tr>
<td>15 μL</td>
<td>52 ± 1</td>
<td>78 ± 0</td>
</tr>
<tr>
<td>20 μL</td>
<td>40 ± 1</td>
<td>68 ± 1</td>
</tr>
<tr>
<td>100 μL</td>
<td>49 ± 2</td>
<td>67 ± 1</td>
</tr>
</tbody>
</table>
Table 8 GC yields of oxidation product 2 with different X-type ligand in water with buffer system. Conditions: $[\text{Cp}^*\text{IrCl}_2]_2$ (2.0 μmol, 2.0 mol % [Ir]), Ag additive (4.2 mol%), AcOH (0.02 mmol), NaOAc (0.01 mmol), 1-phenyl-1-propanol (1) (0.20 mmol, 1.0 equiv.), 1.9 mL toluene, H$_2$O (10 μL), 100 °C, 2 or 24 h

<table>
<thead>
<tr>
<th>Ligand</th>
<th>% GC Yield of 2 (2 h)</th>
<th>% GC Yield of 2 (24 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AgTfO</td>
<td>25 ± 2</td>
<td>42 ± 2</td>
</tr>
<tr>
<td>AgOPiv</td>
<td>50 ± 1</td>
<td>47 ± 3</td>
</tr>
<tr>
<td>Ag$_2$SO$_4$</td>
<td>48 ± 0</td>
<td>52 ± 2</td>
</tr>
<tr>
<td>AgNO$_3$</td>
<td>50 ± 1</td>
<td>63 ± 0</td>
</tr>
<tr>
<td>AgPF$_6$</td>
<td>44 ± 6</td>
<td>60 ± 2</td>
</tr>
</tbody>
</table>

Table 9 GC yields of oxidation product 2 with different L-type ligand in water with buffer system. Conditions: $[\text{Cp}^*\text{IrCl}_2]_2$ (2.0 μmol, 2.0 mol % [Ir]), ligand (4.0 μmol, 2.0 mol %), AcOH (0.02 mmol), NaOAc (0.01 mmol), 1-phenyl-1-propanol (1) (0.20 mmol, 1.0 equiv.), 1.9 mL toluene, H$_2$O (10 μL), 100 °C, 2 or 24 h

<table>
<thead>
<tr>
<th>Ligand</th>
<th>% GC Yield of 2 (2 h)</th>
<th>% GC Yield of 2 (24 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-aminopyridine</td>
<td>45 ± 1</td>
<td>63 ± 1</td>
</tr>
<tr>
<td>2,6-lutidine</td>
<td>49 ± 2</td>
<td>49 ± 3</td>
</tr>
<tr>
<td>2-methoxypyridine</td>
<td>45 ± 4</td>
<td>72 ± 6</td>
</tr>
<tr>
<td>diethylamine</td>
<td>62 ± 1</td>
<td>72 ± 1</td>
</tr>
<tr>
<td>Tert-Butylamine</td>
<td>37 ± 5</td>
<td>61 ± 4</td>
</tr>
<tr>
<td>diisopropylamine</td>
<td>43 ± 3</td>
<td>57 ± 3</td>
</tr>
<tr>
<td>2-ethylpyridine</td>
<td>48 ± 2</td>
<td>67 ± 0</td>
</tr>
<tr>
<td>2-fluoropyridine</td>
<td>58 ± 1</td>
<td>72 ± 1</td>
</tr>
<tr>
<td>aniline</td>
<td>54 ± 4</td>
<td>72 ± 2</td>
</tr>
</tbody>
</table>
3.6 Synthesis of $[\text{Cp}^*\text{IrCl}_2]_2$

The preparation of $[\text{Cp}^*\text{IrCl}_2]_2$ was followed to the procedure described by Whitc, C$^{14}$. A mixture of iridium trichloride hydrate (5.0 g, 0.013 mol) and penta-methylcyclopentadiene (2.5 g, 0.018 mol) and methanol were placed in a 500-mL round-bottomed flask fitted with a reflux condenser. A nitrogen bubbler was attached to the top of the condenser, the apparatus was purged with nitrogen for 5 min at room temperature, and the mixture was then refluxed gently under nitrogen for 48 h with stirring. The reaction mixture was allowed to cool to room temperature. The product was collected by filtration, dried in vacuum, and recrystallized from chloroform-hexane. The product was isolated as an orange, microcrystalline solid (4.8 g, 80 % yield). $^1$H NMR (500 MHz, CDCl$_3$, 25 °C): $\delta$ 1.52 (s, 15H).
4 References and notes

17. The amount of oxygen in the vial was approximated to be 0.15 mmol (0.77 equiv) based on the abundance of oxygen in air (20.95%), the remaining volume in the vial (18 mL), and the ideal gas law. If the decomposition of the primary reaction product $\text{H}_2\text{O}_2$ into $\text{O}_2$ and $\text{H}_2\text{O}$ is assumed to be quantitative, only 0.5 equiv of oxygen is needed for the reaction: alcohol $+\text{0.5O}_2 \rightarrow$ ketone $+\text{H}_2\text{O}$. 
5 Appendices

5.1 Appendix A: GC Analysis

A representative GC graph of the alcohol oxidation reactions is given above. The first large peak coming at the retention time of 5.2 belongs to Toluene (solvent). The second major peak appearing at 6.7 minutes is p-xylene which is the internal GC-standard. The third major peak comes after 11.87 minutes and it is 1-phenyl-1-propanol which is the substrate of this reaction. The final peak appearing at the retention time of 12.13 belongs to propiophenone 2, which is the product of the oxidation of 1-phenyl-1-propanol 1.
5.2 Appendix B: $^1$H NMR for [Cp*IrCl$_2$]$_2$