Activation and Oxidation of Mesitylene C–H Bonds by (Phebox)Iridium(III) Complexes

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ABSTRACT: A pincer iridium(III) complex, (Phebox)Ir(OAc)2OH2 (1) (Phebox = 3,5-dimethylphenyl-2,6-bis(oxazolonyl)), selectively cleaves the benzylic C–H bond of mesitylene to form an isolable iridium mesityl complex, (Phebox)Ir(mesityl)(OAc) (3), in >90% yield. The trifluoroacetate analogue, (Phebox)Ir(OOCF3)2OH2 (2), was synthesized to compare with complex 1 for C–H activation, and (Phebox)Ir(mesityl)(OOCF3) (4) was synthesized by ligand exchange of complex 3. Both complexes 1 and 2 catalyze H/D exchange between mesitylene and D2O at 180 °C, exclusively at the benzylic position; 2 gave a higher turnover number (11 TO) than 1 (6 TO) in 12 h. Using d2-acetic acid as the source of deuterium, up to 92 turnovers of benzylic H/D exchange of mesitylene were obtained with complex 1. (Phebox)Ir(OOCF3)2OH2 catalyzed the benzylic C–H oxidation of mesitylene using Ag2O as a terminal oxidant at 130 °C, to form 3,5-dimethylbenzaldehyde and 3,5-dimethylenzoic acid in 35% ± 4% yield (5.1 ± 0.6 TO). DFT calculations were used to investigate two possible pathways for the catalytic oxidation of mesitylene: (1) C–H activation followed by oxo-functionalization and (2) Ir-oxo formation followed by outer-sphere C–H hydroxylation. Results of calculations of the C–H activation pathway appear to be more consistent with the experimental observations.

INTRODUCTION

The development of catalysts for the selective oxidation of C–H bonds is one of the most challenging goals of modern chemistry, intensely pursued for applications ranging from the synthesis of fine chemicals to the production of liquid fuel. Direct methanol formation from methane could lead to a more energy-efficient process than the syngas route currently practiced in industry. The direct and regioselective oxidation of alkyl groups could drastically improve step economy for the synthesis of oxygenates. Metalloenzymes can effect C–H bond oxidations with extraordinary efficiency; approaches to this problem are therefore often biomimetic or bioinspired.

Iron, manganese, ruthenium, platinum, and palladium complexes are well-developed for selective catalytic C–H oxidation. In contrast to early work such as Fenton chemistry, these systems do not rely on a free hydroxyl radical intermediate to cleave the C–H bond. The metal complexes are responsible for the C–H cleavage, which is considered more likely to afford high selectivity.

Mechanistic studies on selective C–H oxidation have offered support for both outer-sphere and inner-sphere reaction pathways. In a different line of research, Wilkinson and co-workers reported the synthesis and X-ray structure of a trimesityliridium(V) oxo complex in 1993, which proceeded via an aerobic oxidation. Later, Bergman and co-workers examined and expanded this chemistry. In a different line of research, Wilkinson and co-workers reported the synthesis and X-ray structure of a trimesityliridium(V) oxo complex in 1993, which proceeded via an aerobic oxidation. Later, Bergman and co-workers examined and expanded this chemistry.
triphenylphosphine, where trimesityliridium(V) oxo was generated in situ by dioxygen. In recent years Crabtree and others have shown that organometallic [Cp*IrIII(chelate)X] (X = monodenate anionic ligand) complexes are precatalysts for stereoretentive alkane oxidation by NaIO4. In this system, the Cp* ligand may be lost under catalytic oxidation conditions, to generate a di-μ-oxo iridium dimer bearing chelate ligands. Recently, Ison and co-workers91,92 reported that [Cp*Ir(NHC)(pyridine)(Me)]+ (NHC = N-heterocyclic carbene) can be aerobically oxidized in the presence of HCl to generate methanol and [Cp*Ir(NHC)(pyridine)Cl]−.

**BACKGROUND**

Phosphorus-ligated pincer iridium complexes are considered privileged catalysts for alkane dehydrogenation and related reactions. However, such complexes may not be compatible with the strong oxidants often used for C−H oxidation, due to the thermodynamically very favorable oxidation of phosphorus. Nitrogen-ligated pincer iridium complexes, which are presumably more oxidation-resistant, have been reported but were rarely explored for direct C−H oxidation except in one study by Periana, Goddard, and co-workers. We report in this article on nitrogen-ligated (Phebox)Ir (III) (Phebox = 3,5-dimethylphenyl-2,6-bis(oxazolinyl)) complexes for the catalytic C−H oxidation of mesitylene. C2-Symmetric “Phebox” ligands have been widely used by Nishiyama and others in various metal-catalyzed asymmetric C−C bond-forming reactions. Nishiyama and co-workers reported that (Phebox)IrCl(OAc)2OH2 (1) can undergo C−H activation of benzene or n-octane (via concerted metalation−deprotonation) to form isolable (Phebox)Ir(Ph)(OAc) or (Phebox)Ir(n-octyl)(OAc), respectively. Later, Goldberg and co-workers discovered that (Phebox)Ir(OAc)(H), formed by elimination of 1-octene from (Phebox)Ir(n-octyl)(OAc), can be aerobically oxidized to form H2O and I; these reactions suggest that the (Phebox)Ir system could effect a catalytic aerobic oxidation of n-octane. Goldberg, Cundari, and co-workers have also studied the C−H activation carried out by (Phebox)Ir and relevant complexes computationally.

**EXPERIMENTAL RESULTS**

C−H Activation of Mesitylene by (Phebox)Ir-(OAc)2OH2 and (Phebox)Ir(OCOCF3)2OH2. (Phebox)Ir-(OAc)2OH2 (1) effected the C−H activation of mesitylene at 130 °C in the presence of K2CO3 to form (Phebox)Ir(mesityl)-(OAc) (3) in >90% yield (Scheme 1). C−H activation occurred selectively at the benzylic position, and no significant product from aryl C−H activation could be detected. A base, K2CO3, was used to drive the reaction to completion. An intramolecular benzylic C−H activation of a mesityl ligand moiety in TpMSIr (TpMS = hydrotris(3-mesitylpyrazol-1-yl)borate) was reported by Carmona.

Without K2CO3, but under otherwise identical conditions, 3 was formed in 74% yield after 12 h along with 12% unreacted starting material 1. With a different sample, after a reaction time of 20 h, complex 3 was obtained in 66% yield along with 13% unreacted starting material (i.e., there was no difference within the limits of experimental error), consistent with the reaction having reached equilibrium within 12 h in the absence of K2CO3. A reaction time of 1 h in the absence of K2CO3 resulted in a 31% yield of complex 3.

To test the proposal that equilibrium had been reached in the experiments described above, complex 3 (10.6 mM) in mesitylene was treated with one equivalent of acetic acid under otherwise identical conditions (130 °C, 12 h). Complex 1 formed in 10% yield (1.1 mM), and 74% of complex 3 (7.8 mM) was recovered. This product distribution is in close agreement with that obtained from reaction 1 with mesitylene (complex 1 in 12% yield and complex 3 in 74% yield), consistent with the reaction having reached equilibrium within 12 h in the absence of K2CO3. A reaction time of 1 h in the absence of K2CO3 resulted in a 31% yield of complex 3.

We are unable to quantify the amount of water in solution at equilibrium and, therefore, to obtain a rigorous value for the equilibrium constant for the reaction in Scheme 2. However, the DFT-calculated value of ΔG = −12.5 kcal/mol for this reaction (see Computational section) corresponds to an equilibrium constant of 6 × 106 M−1 at 130 °C. On the basis
of the apparent equilibrium concentrations of 3 (7.8 mM), 1 (1.1 mM), and HOOAc (10.6–1.1 mM = 9.5 mM) noted above, this corresponds to an H2O concentration of 18 mM; this value seems to be a reasonable order of magnitude, in support of the validity of the DFT calculations.

Complex 1 has been reported to react with toluene to undergo activation of the aryl C–H bonds at the meta and para positions.99 The absence of significant aryl C–H activation (<5% yield) with mesitylene in favor of benzylic C–H activation is thus presumably due to steric hindrance of the aryl C–H bonds.

A new complex, (Phenbox)Ir(OCOCF3)2OH2 (2) (Figure 1), the trifluoroacetate analogue of 1, was synthesized, but under identical conditions (in the presence of K2CO3 at 130 °C) it only effected C–H activation of mesitylene to give 4 in 18% yield (Scheme 3). At the end of the reaction 47% of unreacted starting material complex 2 was recovered. In the absence of K2CO3, but under otherwise identical reaction conditions, complex 2 gave no indication of activation of mesitylene C–H bonds; 70% of unreacted starting material complex 2 was recovered, and no significant formation of complex 4 was detected (<1%).

The low yield to form 4 from 2 by C–H activation of mesitylene is indicated by DFT calculations to be due to unfavorable reaction thermodynamics (see Computational Results and Discussion). Nevertheless complex 4 was synthesized in >90% yield from 3 by ligand exchange (Scheme 4) using trifluoroacetic acid and crystallographically characterized. Goldberg and co-workers have applied a similar method to vary the anionic monodentate ligand of (Phenbox)IrH(X) (X = derivatives of acetate).101

**Organometallics**

**Figure 1.** Complex 2 and its X-ray crystal structure.

**Scheme 3.** C–H Activation of Mesitylene by Complex 2

![Scheme 3](image)

Starting material complex 2 was recovered. In the absence of K2CO3, but under otherwise identical reaction conditions, complex 2 gave no indication of activation of mesitylene C–H bonds; 70% of unreacted starting material complex 2 was recovered, and no significant formation of complex 4 was detected (<1%).

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**Mesitylene H/D Exchange Catalyzed by (Phenbox)Ir-(OAc)2(OH2) and by (Phenbox)Ir(OCOCF3)2(OH2).** Catalytic H/D exchange between mesitylene and deuterated acids was investigated (Scheme 5). We chose d4-acetic acid as the deuterium source when using complex 1 and d3-trifluoroacetic acid when using complex 2. The reactions were conducted in mesitylene solvent (7.2 M).

The reaction mixtures were monitored by 13C-decoupled 2D NMR spectroscopy after three periods at different temperature (Table 1). In the first stage we analyzed the reaction mixture prior to heating (entries 1 and 4 in Table 1). The solution was then heated for 12 h at 130 °C in the second stage (entries 2 and 5). In the final stage the reaction was heated for an additional 48 h at 180 °C (entries 3 and 6).

Neither benzyl nor aryl H/D exchange was detectible (<10 mM) after 12 h at 130 °C (entries 1 and 2 in Table 1). Upon increasing the temperature to 180 °C, benzyl H/D exchange was catalyzed by 1, giving 92 turnovers after 48 h (entry 3 in Table 1 and eq 1 in Scheme 5). 1-(Deuteriomethyl)-3,5-dimethylbenzene (eq 1 in Scheme 5) formed (975 mM), while no significant (<10 mM) 1,3,5-trimethyl-2-deuteriobenzene was detected. Control experiments without complex 1 but under otherwise identical conditions (see Supporting Information for details) showed that no significant amount (<10 mM) of 1-(deuteriomethyl)-3,5-dimethylbenzene or 1,3,5-trimethyl-2-deuteriobenzene was formed under these conditions.

The catalytic H/D exchange may result from reversible C–H activation, as depicted in Scheme 6. As illustrated in Scheme 1, complex 1 can effect C–H activation and acetic acid elimination; the reverse reaction with d4-acetic acid would yield 1-(deuteriomethyl)-3,5-dimethylbenzene (Scheme 6). Notably, exclusive benzyl rather than aryl H/D exchange was detected by 2D NMR analysis, consistent with the selectivity observed in stoichiometric C–H activation (Scheme 1).

When complex 2 was used with d3-trifluoroacetic acid as a source of deuterium, 1.03 M 1,3,5-trimethyl-2-deuteriobenzene was detected after 12 h at 130 °C. Thus, 97% of the deuterium from d3-trifluoroacetic acid had been incorporated into mesitylene (entry 5 in Table 1) at the aryl position. No significant (<10 mM) 1-(deuteriomethyl)-3,5-dimethylbenzene was detected. Control experiments without complex 2 but under otherwise identical conditions revealed that d4-trifluoroacetic acid underwent H/D exchange at the aryl position, but not at the benzylic position (Scheme 7; see Supporting Information for details of background aryl H/D exchange carried out with d3-trifluoroacetic acid under various con-
The aryl H/D exchange observed in entry 4 is attributable to this d$_1$-trifluoroacetic acid background reaction. Gunnoe and co-workers have recently studied in detail aryl H/D exchange by acids.$^{105}$ Upon raising the temperature to 180 °C, after 48 h 1-(deuteriomethyl)-3,5-dimethylbenzene (201 mM; 19 turnovers benzylic H/D exchange) was observed, presumably catalyzed by 2. A control experiment without 2 gave only complete conversion to 1,3,5-trimethyl-2-deuteriobenzene with no significant formation (<10 mM) of 1-(deuteriomethyl)-3,5-dimethylbenzene detected (see Supporting Information).

The background aryl H/D exchange using complex 2 (entry 6 in Table 1), background aryl H/D exchange presumably depleted d$_1$-trifluoroacetic acid at an early stage of the reaction at 180 °C, leaving only a low concentration of d$_1$-trifluoroacetic for 2-catalyzed benzylic H/D exchange (Scheme 8).

To compare complexes 1 and 2 for catalytic H/D exchange of mesitylene, we attempted to use deuterated acids in large excess to avoid depletion of d$_1$-trifluoroacetic acid due to background aryl H/D exchange. However, we found that a very high concentration of d$_1$-trifluoroacetic (10.8 M) at 180 °C resulted in high background benzylic H/D exchange without catalyst (see Supporting Information for details), precluding the value of this experiment.

Table 1. H/D Exchange (Mesitylene with CD$_3$CO$_2$D or CF$_3$CO$_2$D) by 1 and 2

<table>
<thead>
<tr>
<th>entry$^a$</th>
<th>complex</th>
<th>time</th>
<th>temperature (°C)</th>
<th>benzylic H/D exchange turnovers and concentration</th>
<th>1,3,5-trimethyl-2-deuteriobenzene concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>15 min</td>
<td>23</td>
<td>&lt;10 mM</td>
<td>&lt;10 mM</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>additional 12 h</td>
<td>130</td>
<td>&lt;10 mM</td>
<td>&lt;10 mM</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>additional 48 h</td>
<td>180</td>
<td>92 TO, 975 mM</td>
<td>&lt;10 mM</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>15 min</td>
<td>23</td>
<td>&lt;10 mM</td>
<td>&lt;10 mM</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>additional 12 h</td>
<td>130</td>
<td>&lt;10 mM</td>
<td>1028 mM</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>additional 48 h</td>
<td>180</td>
<td>19 TO, 201 mM</td>
<td>827 mM</td>
</tr>
</tbody>
</table>

$^a$Reaction conditions: 10.6 mM (1 equiv) complex 1 or 2, d$_4$-acetic acid 1.06 M (100 equiv) for entries 1 to 3 and d$_1$-trifluoroacetic acid 1.06 M (100 equiv) for entries 4 to 6, mesitylene 7.19 M, 300 μL in a J-Young NMR tube under 1 atm argon with <0.5 ppm of H$_2$O or O$_2$; see Supporting Information for more details on reaction setup. $^b$Turnovers were measured by $^2$D NMR analysis using CD$_3$CN as internal standard added at the end of reaction (see Supporting Information for more details); turnovers = concentration of 1-(deuteriomethyl)-3,5-dimethylbenzene or 1,3,5-trimethyl-2-deuteriobenzene divided by concentration of Ir complex, 10.6 mM; 1-(deuteriomethyl)-3,5-dimethylbenzene and 1,3,5-trimethyl-2-deuteriobenzene deuterium chemical shift confirmed by spiking with purchased d$_{12}$-mesitylene.

Scheme 6. Catalytic H/D Exchange Possibly Due to Reversible C–H Activation by Complex 1

Scheme 7. Control Experiments without Ir Catalyst: Aryl H/D Exchange with d$_1$-Trifluoroacetic Acid$^a$

$^a$See Supporting Information for details of reaction conditions.
We next investigated D₂O as a source of deuterium for catalytic H/D exchange of mesitylene (Scheme 9). In the absence of Ir, no significant (<10 mM) background H/D exchange with D₂O was detected at either the benzylic or aryl position (entry 1 in Table 2), even at 180 °C. With complex 2, no significant (<10 mM) H/D exchange was observed after 12 h at 130 °C (entry 2 in Table 2). However, after 12 h at 180 °C, 11 turnovers of exclusively benzylic H/D exchange were obtained (115 mM) (eq 2 in Scheme 9 and entry 3 in Table 2).

Complex 1 was somewhat less active than 2 for catalyzing H/D exchange of mesitylene with D₂O, giving 6 turnovers of 1-(deuteriomethyl)-3,5-dimethylbenzene (64 mM). No significant (<10 mM) aryl H/D exchange was detected when using D₂O as the deuterium source.

The activity of H/D exchange of complex 2 significantly increased under basic conditions (entry 5 in Table 2), giving 41 turnovers in the presence of 4 equiv of K₂CO₃ under otherwise identical conditions (12 h).

The higher catalytic activity of complex 2 vs 1 for H/D exchange of mesitylene was consistent with results of DFT calculations (see Computational section). TS1-OCOCF₃, the transition state for C−H activation by complex 2, was calculated to be 4.5 kcal/mol lower in energy than TS1-OAc, the transition state for C−H activation by complex 1.

Oxidation of Mesitylene Catalyzed by (Phebox)Ir(OCOCF₃)₂(OH₂) Using Ag₂O as Terminal Oxidant.

We find that the (Phebox)Ir complexes catalyze the oxidation of mesitylene using Ag₂O as the terminal oxidant (Scheme 10).106 With complex 2, 20 equiv of Ag₂O, and mesitylene as solvent in excess, 3,5-dimethylbenzaldehyde (DBAL) and 3,5-dimethylbenzoic acid (DBAC) were produced (2.9 turnovers total; entry 1 in Table 3). Silver mirror deposited on the glass wall of the reaction vessel, consistent with reduction of Ag₂O to Ag(0). The result was reproducible (entry 2).

Formation of both DBAL and DBAC was determined by 1H NMR analysis and confirmed by spiking the reaction mixtures with authentic samples. Each equivalent of DBAL formed should consume 2 equiv of Ag₂O, and each equivalent of DBAC formed should consume 3 equiv of Ag₂O. The reaction yield, based on Ag₂O, the limiting reagent, was therefore 42% (see footnote c in Table 3 for method of calculation).

At the end of the 2-catalyzed oxidation reaction, we recovered complex 2 in 21% yield in the case of entry 1 (18% recovery yield in the repeated run in entry 2). Thus, the complex appears to be at least stable enough to resist total decomposition under harsh oxidation conditions. We could not identify any other (Phebox)Ir complex, if present.

### Table 2. Comparing Complexes 1 and 2 for Catalytic Mesitylene H/D Exchange with D₂O

<table>
<thead>
<tr>
<th>entry</th>
<th>complex</th>
<th>temperature (°C)</th>
<th>benzylic H/D exchange turnovers and concentration</th>
<th>1,3,5-trimethyl-2-deuteriobenzene concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>180</td>
<td>&lt;10 mM</td>
<td>&lt;10 mM</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>130</td>
<td>&lt;10 mM</td>
<td>&lt;10 mM</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>180</td>
<td>11 TO, 115 mM</td>
<td>&lt;10 mM</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>180</td>
<td>6 TO, 64 mM</td>
<td>&lt;10 mM</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>180</td>
<td>41 TO, 435 mM</td>
<td>&lt;10 mM</td>
</tr>
</tbody>
</table>

“Reaction conditions: 10.6 mM (1 equiv) complex 1 or 2, D₂O (3.68 M, 20 μL, 1.11 mmol), mesitylene (7.19 M, 300 μL); in a J-Young NMR tube under 120 psi argon; see Supporting Information for more details on reaction setup. Turnovers measured by 2D NMR analysis using C₆D₆ as internal standard added at the end of reaction (see Supporting Information for more details); turnovers = concentration of 1-(deuteriomethyl)-3,5-dimethylbenzene or 1,3,5-trimethyl-2-deuteriobenzene divided by concentration of Ir complex, 10.6 mM; 1-(deuteriomethyl)-3,5-dimethylbenzene and 1,3,5-trimethyl-2-deuteriobenzene deuterium chemical shift confirmed by spiking with purchased d₁₂-mesitylene. K₂CO₃ (42.4 mM, 13 μmol) was added to the reaction mixture.
Ag₂O (99% pure; see Supporting Information for a commercial source of this Ag₂O sample). No significant changes caused by a different Ag₂O sample were observed (entry 4). Without Ir, but under conditions otherwise identical to the reaction in entry 3, no oxidation of mesitylene occurred (entries 9 and 10). The reaction in entry 9 was performed twice to ensure reproducibility.

In contrast to complex 2, using complex 1 and under otherwise identical conditions, only close to one turnover was obtained for product formation (entry 5). Using (Phebox)-IrCl₂(OH₂) (5), which could not carry out C–H activation, no significant (0.2% yield) amount of product from oxidation of mesitylene was obtained (entry 7). A 41% recovery yield of complex 5 was obtained at the end of reaction.

Goldberg and co-workers reported that addition of water promoted octane C–H activation. We therefore tested water as an additive in 1.9 M for oxidation of mesitylene catalyzed by complex 2 (entry 6). No effect on turnover or yield of oxidation product was observed. Thus, the result at least suggested that the reaction catalyzed by complex 2 can significantly tolerate the presence of water.

Crabtree and Voutchkova reported that oxidation of mesitylene can be catalyzed by [Cp*IrCl₂]₂, possibly as a precursor to heterogeneous material. Under our conditions [Cp*IrCl₂]₂ was a poor catalyst (2% yield; entry 8).

Overall, our results indicate that the new complex, Ag₂O as terminal oxidant than any other Ir complex tested.

Using 40 equiv of Ag₂O and complex 2, 5.1 ± 0.6 turnovers were obtained for the formation of DBAL and DBAC in total, corresponding to 35% ± 4% yield based on Ag₂O (99.99% pure Ag₂O, entry 3; see Supporting Information for a commercial source of this Ag₂O sample). Three identical reactions were carried out to obtain the average yield and turnover number. We tested the same reaction, but using a different sample of Ag₂O (99% pure; see Supporting Information for a commercial source of this Ag₂O sample). No significant changes caused by a different Ag₂O sample were observed (entry 4). Without Ir, but under conditions otherwise identical to the reaction in entry 3, no oxidation of mesitylene occurred (entries 9 and 10). The reaction in entry 9 was performed twice to ensure reproducibility.

In contrast to complex 2, using complex 1 and under otherwise identical conditions, only close to one turnover was obtained for product formation (entry 5). Using (Phebox)-IrCl₂(OH₂) (5), which could not carry out C–H activation, no significant (0.2% yield) amount of product from oxidation of mesitylene was obtained (entry 7). A 41% recovery yield of complex 5 was obtained at the end of reaction.

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Overall, our results indicate that the new complex, 2, was significantly more active for the oxidation of mesitylene using Ag₂O as terminal oxidant than any other Ir complex tested.

**Table 3. Catalytic Oxidation of Mesitylene by Ag₂O (130 °C, 12 h)**

<table>
<thead>
<tr>
<th>entry</th>
<th>complex</th>
<th>Ag₂O concentration and equiv</th>
<th>DBAL concentration and turnovers</th>
<th>DBAC concentration and turnovers</th>
<th>total turnovers</th>
<th>yield (based on Ag₂O)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>212 mM, 20 equiv</td>
<td>3.2 mM, 0.3 TO</td>
<td>28 mM, 2.6 TO</td>
<td>2.9</td>
<td>42%</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>212 mM, 20 equiv</td>
<td>5.3 mM, 0.5 TO</td>
<td>25 mM, 2.4 TO</td>
<td>2.9</td>
<td>41%</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>424 mM, 40 equiv</td>
<td>13 ± 4 mM, 1.2 ± 0.4 TO</td>
<td>41 ± 3 mM, 3.9 ± 0.3 TO</td>
<td>5.1 ± 0.6</td>
<td>35% ± 4%</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>424 mM, 40 equiv</td>
<td>0.7 TO</td>
<td>3.6 TO</td>
<td>4.4</td>
<td>31%</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>424 mM, 40 equiv</td>
<td>7.4 mM, 0.7 TO</td>
<td>4.2 mM, 0.4 TO</td>
<td>1.1</td>
<td>7%</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>424 mM, 40 equiv</td>
<td>6.4 mM, 0.6 TO</td>
<td>44 mM, 4.1 TO</td>
<td>4.7</td>
<td>34%</td>
</tr>
<tr>
<td>7</td>
<td>5</td>
<td>424 mM, 40 equiv</td>
<td>0.4 mM, 0.04 TO</td>
<td>none</td>
<td>0.04</td>
<td>0.2%</td>
</tr>
<tr>
<td>8</td>
<td>[Cp*IrCl₂]₂</td>
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<td>3.2 mM, 0.3 TO</td>
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<td>0.3</td>
<td>2%</td>
</tr>
<tr>
<td>9</td>
<td>none</td>
<td>212 mM, 20 equiv</td>
<td>none</td>
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<td>10</td>
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<td>424 mM, 40 equiv</td>
<td>none</td>
<td>none</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

**Figure 2.** Calculated free energies (kcal/mol) for the (1) C–H activation pathway and (2) Ir-oxo pathway in catalytic mesitylene oxidation using complex 1a or 2a; X = OAc or OCOCF₃; "Phebox" ligand is not shown but is implied, except in complexes 1a, 2a, 3a, and 4a; no calculations performed for 6-OAc and 6-OCOCF₃.

Using 40 equiv of Ag₂O and complex 2, 5.1 ± 0.6 turnovers were obtained for the formation of DBAL and DBAC in total, corresponding to 35% ± 4% yield based on Ag₂O (99.99% pure Ag₂O, entry 3; see Supporting Information for a commercial source of this Ag₂O sample). Three identical reactions were carried out to obtain the average yield and turnover number. We tested the same reaction, but using a different sample of Ag₂O (99% pure; see Supporting Information for a commercial source of this Ag₂O sample). No significant changes caused by a different Ag₂O sample were observed (entry 4). Without Ir, but under conditions otherwise identical to the reaction in entry 3, no oxidation of mesitylene occurred (entries 9 and 10). The reaction in entry 9 was performed twice to ensure reproducibility.

In contrast to complex 2, using complex 1 and under otherwise identical conditions, only close to one turnover was obtained for product formation (entry 5). Using (Phebox)-IrCl₂(OH₂) (5), which could not carry out C–H activation, no significant (0.2% yield) amount of product from oxidation of mesitylene was obtained (entry 7). A 41% recovery yield of complex 5 was obtained at the end of reaction.

Goldberg and co-workers reported that addition of water promoted octane C–H activation. We therefore tested water as an additive in 1.9 M for oxidation of mesitylene catalyzed by complex 2 (entry 6). No effect on turnover or yield of oxidation product was observed. Thus, the result at least suggested that the reaction catalyzed by complex 2 can significantly tolerate the presence of water.

Crabtree and Voutchkova reported that oxidation of mesitylene can be catalyzed by [Cp*IrCl₂]₂, possibly as a precursor to heterogeneous material. Under our conditions [Cp*IrCl₂]₂ was a poor catalyst (2% yield; entry 8).

Overall, our results indicate that the new complex, 2, was significantly more active for the oxidation of mesitylene using Ag₂O as terminal oxidant than any other Ir complex tested.
Oxidation of (Phebox)Ir Complexes 1, 2, 3, and 4 by One Equivalent of Ag$_2$O. We considered the question of whether the catalytic oxidation of mesitylene proceeded via C–H activation followed by oxy-functionalization or via Ir-oxo formation followed by C–H hydroxylation. DFT calculations suggested that both pathways (Figure 2) could be energetically accessible.

For the C–H activation followed by oxy-functionalization (pathway 1 in Figure 2), we had demonstrated that complexes 1 and 2 were capable of C–H activation of mesitylene (Schemes 1 and 8). We next investigated the oxy-functionalization of (Phebox)Ir mesityl complexes 3 and 4. (Phebox)Ir mesityl complexes 3 and 4 were treated with one equivalent of Ag$_2$O at 130 °C for 12 h (Scheme 11 and Table 4). Complex 3 was resistant to oxidation, and more than 90% of complex 4 in the presence of one equivalent of NaOCCF$_3$ gave DBAC in 106% yield and DBAL in 62% yield (entry 5 in Table 4). No significant amount of complex 4 (<1%) was recovered at the end of the reaction. The 168% combined yield of DBAL and DBAC suggested that complex 4 affected catalytic turnover. Use of 20 equiv of Ag$_2$O with complex 3 in the presence of one equivalent of NaOAc gave DBAC in 44% yield and DBAL in 7% yield (entry 6 in Table 4).

The above results indicated that complex 4 was capable of oxy-functionalization only in the presence of an additional trifluoroacetate ligand. Several new $^1$H NMR peaks appeared that could potentially be assigned to Ir complexes associated with oxy-functionalization. However, we were unable to isolate and characterize these new species.

To test the pathway of Ir-oxo formation followed by C–H hydroxylation (pathway 2 in Figure 2), we attempted to synthesize (Phebox)Ir oxo complexes that were suggested by DFT calculations as shown in S-OAc and S-OCCF$_3$ of Figure 2. Complexes 1 and 2 were treated with one equivalent of Ag$_2$O in both mesitylene and C$_6$F$_6$ solvent.

Under oxidation conditions similar to those in the oxy-functionalization of complexes 3 and 4, 12 h at 130 °C (see Supporting Information for details) in mesitylene were obtained by calculating the 1 atm free energy and subtracting the empirical free energy of vaporization (2.4 for 1 M acid in mesitylene and 3.4 kcal/mol for liquid mesitylene). The molar radius of 2.60 Å. Free energies were calculated with the following equation: $G = E_{\text{mol}} + G_{\text{sub}} + E_{\text{ZPE}} + H_{\text{sub}} + H_{\text{TR}} - T(S_{\text{sub}} + S_{\text{olv}})$ where $G_{\text{mol}}$ is the solvation energy, $E_{\text{ZPE}}$ is the zero point energy, $H_{\text{TR}}$ is the translational and rotational enthalpy, and $S_{\text{sub}}$ and $S_{\text{olv}}$ are the vibrational and electronic enthalpic terms, respectively. In order to calculate reaction energies involving Ag$_2$O, DFT calculations were performed using O$_2$ (1 atm) as oxidant, then corrected using the

<table>
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</table>

*Reaction conditions: 21.2 mM, 6.4 ppm (1 equiv) of complex 1 or 2, Ag$_2$O 99.99% purity in one equivalent (21.2 mM) unless stated otherwise, mesitylene (7.19 M, 300 μL), NaOAc or NaOCCF$_3$ (21.2 mM, 6.4 μmol); in a J-Young NMR tube under 1 atm argon with <0.5 ppm of H$_2$O or O$_2$; at 130 °C and for 12 h; Ag$_2$O did not dissolve in solution, and its concentration was used only for the purpose of calculations. $^b$Yield = concentration of DBAL or DBAC divided by concentration of Ir complex, 10.6 mM; DBAL and DBAC concentrations were measured by $^1$H NMR analysis using CH$_3$CN as an internal standard added at the end of the reaction (see Supporting Information for more details). $^c$20 equiv of Ag$_2$O used.

Computational Results and Discussion

Methods. All optimizations and frequency and solvation calculations were completed using B3LYP108,109 with the Los Alamos core potential10 and the 2-2 basis set on iridium and the 6-31G** basis set on organics.11,12 Single-point, large basis set calculations were completed with M0613,13 with LACVP** basis augmented with f-functions and diffuse functions on iridium.14

Organic molecules were treated with 6-311G** + G.15,16 Solvation in mesitylene was applied using the Poisson–Boltzmann polarizable continuum model, with a dielectric constant of 2.284 and solvent radius of 2.60 Å. Free energies of acetic acid, HOCOCF$_3$, and mesitylene were obtained by calculating the 1 atm free energy and subtracting the empirical free energy of vaporization (2.4 for 1 M acid in mesitylene and 3.4 kcal/mol for liquid mesitylene). The molar value for acid was extrapolated from VLE data for dilute acetic acid in benzene.18 Analytical frequency calculations were used to validate all transition states.

Free energies were calculated with the following equation:

$$G = E_{\text{mol}} + G_{\text{sub}} + E_{\text{ZPE}} + H_{\text{sub}} + H_{\text{TR}} - T(S_{\text{sub}} + S_{\text{olv}})$$

where $G_{\text{mol}}$ is the solvation energy, $E_{\text{ZPE}}$ is the zero point energy, $H_{\text{TR}}$ is the translational and rotational enthalpy, and $S_{\text{sub}}$ and $S_{\text{olv}}$ are the vibrational and electronic enthalpic terms, respectively. In order to calculate reaction energies involving Ag$_2$O, DFT calculations were performed using O$_2$ (1 atm) as oxidant, then corrected using the
difference between the standard potentials for the reduction of O₂ to water (1.23 V vs NHE) and Ag₂O(s) to Ag(s) and water (1.17 V vs NHE). The calculated barrier for hydrogen abstraction by tri-fluoroacetate complexes is significantly lower than for the oxo pathway. This may suggest that tri-fluoroacetate in this type of system is more promising than acetate for C–H functionalization, since the oxo pathway (if operative) is less likely to afford the intriguing selectivity that is offered by transition-metal-catalyzed C–H activation.

■ CONCLUSION

We report that (Phebox)Ir complex 2 catalyzes oxidation of mesitylene using Ag₂O as terminal oxidant. C–H activation by 2 and 1 are both observed in nonoxidative stoichiometric conditions, although the trifluoroacetate Ir mesityl complex 4 could be synthesized in high yield only by the ligand exchange reaction of 3. The observation of H/D exchange catalyzed by 1 and 2 further illustrates the ability of these complexes to effect C–H activation. The isolated mesityl complexes serve as catalysts or catalyst precursors for oxidation reaction and thus seem to be competent as potential intermediates in the catalytic cycle. An alternative oxidation pathway, involving formation of an Ir oxo complex followed by C–H hydroxylation, was investigated using DFT. The DFT calculations suggest, however, that the Ir oxo pathway would be significantly more favorable for TS2-OAc than for TS2-OCOCF₃, which is in disagreement with the more rapid oxidation by trifluoroacetate complex 2.

■ EXPERIMENTAL SECTION

Supporting Information includes experimental procedures for syntheses and characterizations of complexes 1, 2, 3, and 4. It also includes experimental details of C–H activation, H/D exchange, and oxidation reactions. Supporting Information includes details of DFT calculations and data analysis for X-ray structure determinations of new complexes 2, 3, and 4.

■ ASSOCIATED CONTENT

S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organomet.5b00200.

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REFERENCES
