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

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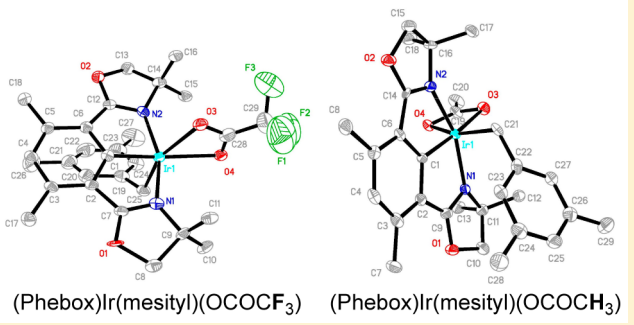
Supporting Information

ABSTRACT: A pincer iridium(III) complex, (Phebox)Ir-$(OAc)_2OH_2$ (**1**) (Phebox = 3,5-dimethylphenyl-2,6-bis-(oxazolinyl)), 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, $(Phebox)Ir(OCOCF_3)_2OH_2$ (**2**), was synthesized to compare with complex **1** for C−H activation, and (Phebox)Ir(mesityl)$(OCOCF_3)$ (**4**) was synthesized by ligand exchange of complex **3**. Both complexes **1** and **2** catalyze H/D exchange between mesitylene and D_2O at 180 °C, exclusively at the benzylic position; **2** gave a higher turnover number (11 TO) than **1** (6 TO) in 12 h. Using d_4-acetic acid as the source of deuterium, up to 92 turnovers of benzylic H/D exchange of mesitylene were obtained with complex **1**. $(Phebox)Ir(OCOCF_3)_2OH_2$ catalyzed the benzylic C−H oxidation of mesitylene using Ag_2O as a terminal oxidant at 130 °C, to form 3,5-dimethylbenzaldehyde and 3,5-dimethylbenzoic 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 oxy-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 the 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[1] goals of modern chemistry, intensely pursued[2] for applications ranging from the synthesis of fine chemicals[3,4] to the production of liquid fuel from methane.[5−25] Direct methanol formation from methane could lead to a more energy-efficient process than the syngas route currently practiced in industry.[7,9,26,27] The direct and regioselective oxidation of alkyl groups could drastically improve step economy[28] for the synthesis of oxygenates.[5,29−38] Metalloenzymes can effect C−H bond oxidations with extraordinary efficiency; approaches to this problem are therefore often biomimetic or bioinspired.[39−43]

Iron,[29−31,44−52] manganese,[53−55] ruthenium,[56,57] platinum,[15,19] and palladium[58−66] complexes are well-developed for selective catalytic C−H oxidation. In contrast to early work such as Fenton chemistry,[67] these systems do not rely on a free hydroxyl radical intermediate to cleave the C−H bond.[1] The metal complexes are responsible for the C−H cleavage, which is considered more likely to afford high selectivity.[31,38,53,58,68−75]

Mechanistic studies on selective C−H oxidation have offered support for both outer-sphere and inner-sphere reaction pathways.[59] In the outer-sphere pathway, a terminal or bridging high-valent metal oxo complex cleaves the C−H bond and forms a C−O bond. Such reactivity of iron, manganese, and ruthenium complexes is often considered as proceeding via a biomimetic pathway.[1,41,76,77] Alternatively, in the inner-sphere pathway,[59] a metal−alkyl complex is formed via C−H activation,[78,79] and its oxidation can then lead to C−O bond formation. This reactivity, known for platinum and palladium complexes, is typically referred to as C−H activation followed by oxy-functionalization.[6,80]

In contrast to the well-established systems based on Fe, Mn, Ru, Pt, and Pd complexes, selective catalytic C−H oxidation based on complexes of iridium is an emerging area of research.[57,81,82] In the early 1980s, Maitlis and co-workers reported[83,84] the synthesis of $Cp^*Ir^V(Me)_4$ ($Cp^* = C_5Me_5$), which proceeded via an aerobic oxidation. Later, Bergman and co-workers examined and expanded this chemistry.[85] 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.[86] Brown and co-workers later found[87] that trimesityliridium(III) can catalyze aerobic oxidation of

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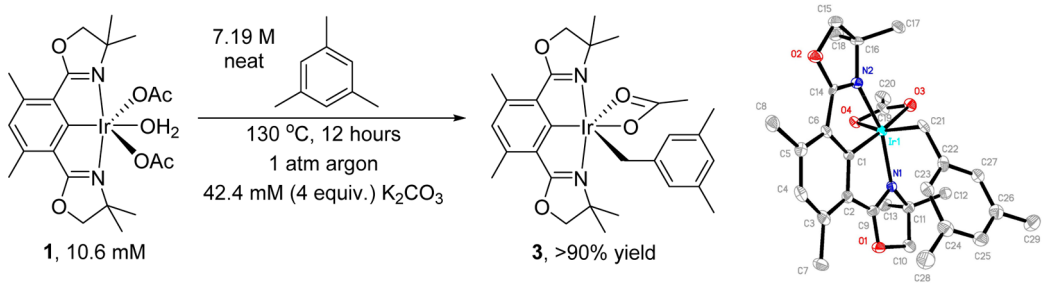
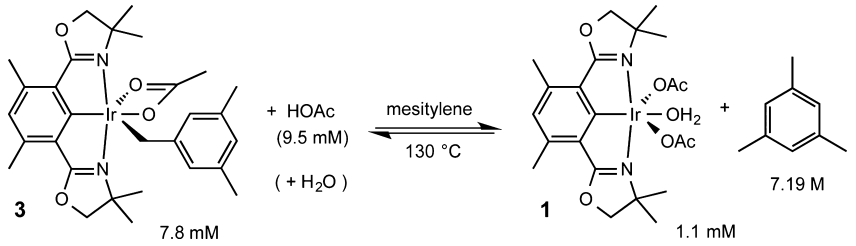
Scheme 1. Mesitylene Benzylic C−H Activation by 1 and X-ray Crystal Structure of Product 3



Scheme 2. Apparent Equilibrium Resulting from Addition of Acetic Acid to 3 and C−H Activation of Mesitylene



triphenylphosphine, where trimesityliridium(V) oxo was generated *in situ* by dioxygen. In recent years Crabtree and others[37,81,82,88,89] have shown that organometallic [Cp*Ir^{III}(chelate)X] (X = monodentate anionic ligand) complexes are precatalysts for stereoretentive alkane oxidation by $NaIO_4$. In this system, the Cp* ligand may be lost under catalytic oxidation conditions, to generate a di-μ-oxo iridium dimer bearing chelate ligands.[90] Recently, Ison and co-workers[91,92] 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[93] and related reactions.[94] However, such complexes may not be compatible with the strong oxidants[13,19,34,37,58] often used for C−H oxidation, due to the thermodynamically very favorable oxidation of phosphorus.[87] Nitrogen-ligated pincer iridium complexes,[23,95,96] 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.[23]

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. C_2-Symmetric "Phebox" ligands have been widely applied by Nishiyama and others in various metal-catalyzed asymmetric C−C bond-forming reactions.[97,98] Nishiyama and co-workers[99] reported that (Phebox)Ir^{III}(OAc)$_2$OH$_2$ (**1**) can undergo C−H activation of benzene or *n*-octane (via concerted metalation−deprotonation[100]) to form isolable (Phebox)Ir(Ph)(OAc) or (Phebox)-Ir(*n*-octyl)(OAc), respectively. Later, Goldberg and co-workers discovered[101,102] that (Phebox)Ir(OAc)(H), formed by elimination of 1-octene from (Phebox)Ir(*n*-octyl)(OAc), can be aerobically oxidized to form H_2O and **1**; 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.[103]

EXPERIMENTAL RESULTS

C−H Activation of Mesitylene by (Phebox)Ir-(OAc)$_2$OH$_2$ and (Phebox)Ir(OCOCF$_3$)$_2$OH$_2$. (Phebox)Ir-(OAc)$_2$OH$_2$ (**1**) effected the C−H activation of mesitylene at 130 °C in the presence of K_2CO_3 to form (Phebox)Ir(mesityl)-(OAc) (**3**) in >90% yield (Scheme 1). C−H activation occurred selectively at the benzylic position, and no significant (<5%) product from aryl C−H activation could be detected. A base, K_2CO_3, was used to drive the reaction to completion. An intramolecular benzylic C−H activation of a mesityl ligand moiety in Tp^{MS}Ir (Tp^{MS} = hydrotris(3-mesitylpyrazol-1-yl)-borate) was reported by Carmona.[125]

Without K_2CO_3, 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 K_2CO_3. A reaction time of 1 h in the absence of K_2CO_3 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), in support of the conclusion that equilibrium had been reached.

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 $\Delta G = -12.5$ kcal/mol for this reaction (see Computational section) corresponds to an equilibrium constant of 6×10^6 M^{-1} at 130 °C. On the basis

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of the apparent equilibrium concentrations of **3** (7.8 mM), **1** (1.1 mM), and HOAc (10.6−1.1 mM = 9.5 mM) noted above, this corresponds to an H_2O 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.[60,104]

A new complex, (Phebox)Ir$(OCOCF_3)_2OH_2$ (**2**) (Figure 1), the trifluoroacetate analogue of **1**, was synthesized, but under

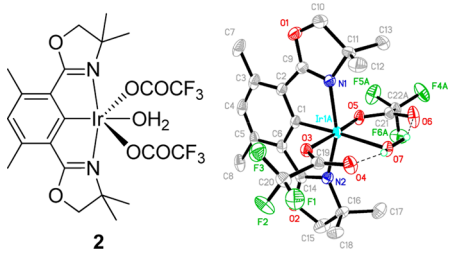
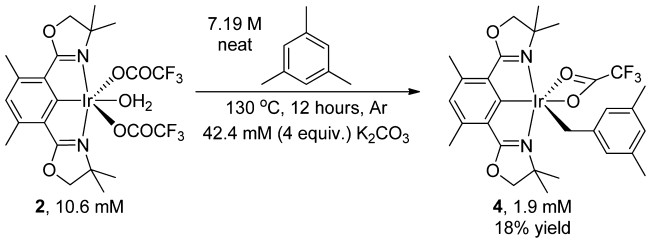


Figure 1. Complex **2** and its X-ray crystal structure.

identical conditions (in the presence of K_2CO_3, 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

Scheme 3. C−H Activation of Mesitylene by Complex 2



starting material complex **2** was recovered. In the absence of K_2CO_3, 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 (Phebox)IrH(X) (X = derivatives of acetate).[101]

Mesitylene H/D Exchange Catalyzed by (Phebox)Ir$(OAc)_2(OH_2)$ and by (Phebox)Ir$(OCOCF_3)_2(OH_2)$. Catalytic H/D exchange between mesitylene and deuterated acids was investigated (Scheme 5). We chose d_4-acetic acid as the deuterium source when using complex **1** and d_1-trifluoroacetic acid when using complex **2**. The reactions were conducted in mesitylene solvent (7.2 M).

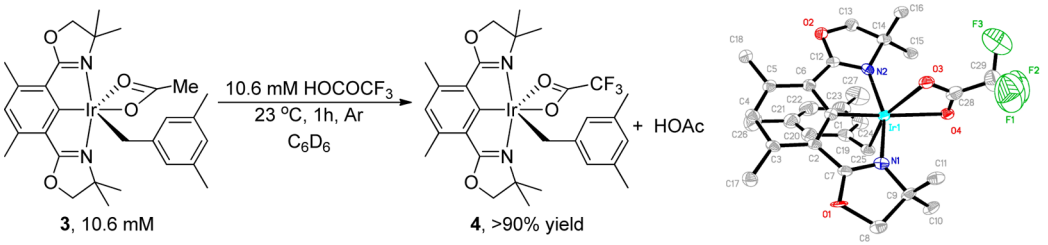
The reaction mixtures were monitored by ^{13}C-decoupled ^2D NMR spectroscopy after three periods at different temperature (Table 1). In the first stage we analyzed the reaction mixture prior to heating (entries 1 and 4 in Table 1). The solution was then heated for 12 h at 130 °C in the second stage (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 benzylic 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, benzylic 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 d_4-acetic acid would yield 1-(deuteriomethyl)-3,5-dimethylbenzene (Scheme 6). Notably, exclusive benzylic 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 d_1-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 d_1-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 d_1-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 d_1-trifluoroacetic acid under various con-

Scheme 4. Synthesis of 4 from 3 Using Trifluoroacetic Acid and X-ray Crystal Structure of 4



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Scheme 5. H/D Exchange between Mesitylene and Deuterated Acids Catalyzed by Complex 1 or 2, Analyzed by ^{2}D NMR Spectroscopy

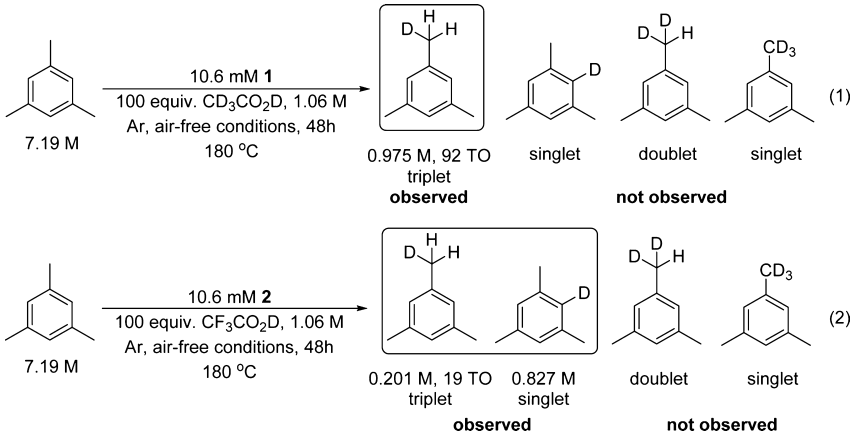
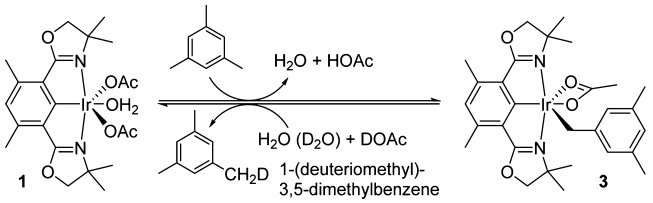


Table 1. H/D Exchange (Mesitylene with CD_3CO_2D or CF_3CO_2D) by 1 and 2

entry[a]	complex	time	temperature (°C)	benzylic H/D[b] exchange turnovers and concentration	1,3,5-trimethyl-2-deuteriobenzene concentration
1	**1**	15 min	23	<10 mM	<10 mM
2	**1**	additional 12 h	130	<10 mM	<10 mM
3	**1**	additional 48 h	180	92 TO, 975 mM	<10 mM
4	**2**	15 min	23	<10 mM	<10 mM
5	**2**	additional 12 h	130	<10 mM	1028 mM
6	**2**	additional 48 h	180	19 TO, 201 mM	827 mM

[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_2O or O_2; see Supporting Information for more details on reaction setup. [b]Turnovers were measured by ^{2}D NMR analysis using CD_3CN 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



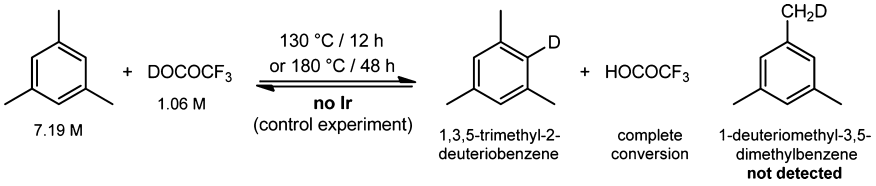
ditions); thus the aryl H/D exchange observed in entry 4 is attributable to this d_1-trifluoroacetic acid background reaction. Gunnoe and co-workers have recently studied in detail aryl H/D exchange by acids.[105]

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 with d_1-trifluoroacetic acid (Scheme 7) complicated the analysis. In catalytic 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.

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.

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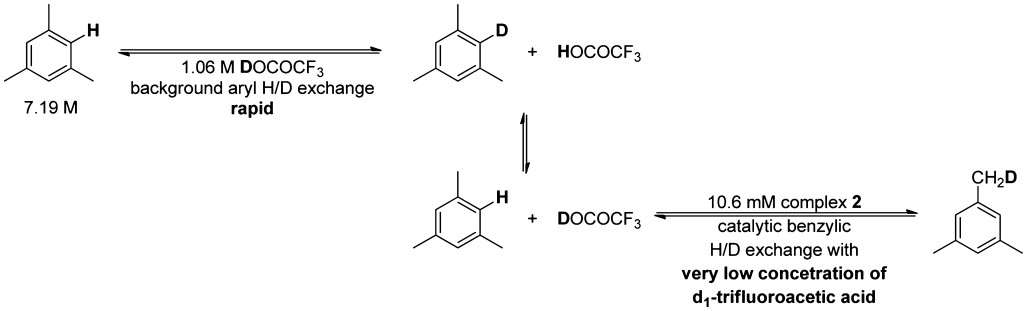
Scheme 8. Depletion of d_1-Trifluoroacetic Acid at the Early Stage of H/D Exchange Catalyzed by Complex 2, Due to Background H/D Exchange with d_1-Trifluoroacetic Acid (Entry 6, Table 1)



We next investigated D_2O 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 D_2O 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).

Scheme 9. Catalytic H/D Exchange Using D_2O as Source of Deuterium, Analyzed by ^{2}D NMR Spectroscopy

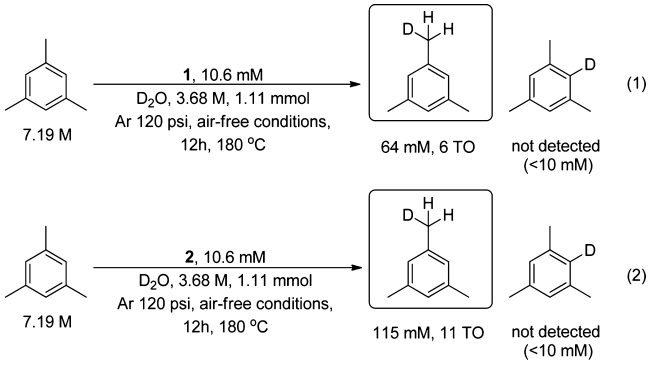


Table 2. Comparing Complexes 1 and 2 for Catalytic Mesitylene H/D Exchange with D_2O

entry[a]	complex	temperature (°C)	benzylic H/D[b] exchange turnovers and concentration	1,3,5-trimethyl-2-deuteriobenzene concentration
1	none	180	<10 mM	<10 mM
2	**2**	130	<10 mM	<10 mM
3	**2**	180	11 TO, 115 mM	<10 mM
4	**1**	180	6 TO, 64 mM	<10 mM
5[c]	**2**	180	41 TO, 435 mM	<10 mM

[a]Reaction conditions: 10.6 mM (1 equiv) complex **1** or **2**, D_2O (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. [b]Turnovers measured by ^{2}D NMR analysis using C_6D_6 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. [c]K_2CO_3 (42.4 mM, 13 μmol) was added to the reaction mixture.

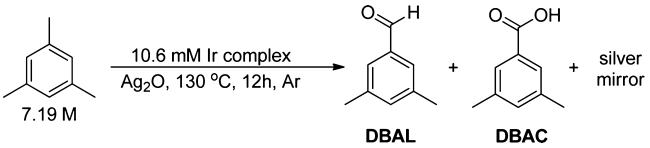
Complex **1** was somewhat less active than **2** for catalyzing H/D exchange of mesitylene with D_2O, giving 6 turnovers of 1-(deuteriomethyl)-3,5-dimethylbenzene (64 mM). No significant (<10 mM) aryl H/D exchange was detected when using D_2O as the deuterium source.

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 K_2CO_3 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-OCOCF$_3$**, 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-(OAc)$_2$(OH$_2$) and (Phebox)Ir(OCOCF$_3$)$_2$(OH$_2$) Using Ag$_2$O as Terminal Oxidant. We find that the (Phebox)Ir complexes catalyze the oxidation of mesitylene using Ag_2O as the terminal oxidant (Scheme 10).[106] With complex **2**, 20 equiv of Ag_2O, 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 Ag_2O to Ag(0). The result was reproducible (entry 2).

Scheme 10. Oxidation of Mesitylene Catalyzed by Complex 1 or 2 Using Ag$_2$O as Terminal Oxidant



Formation of both DBAL and DBAC was determined by ^{1}H NMR analysis and confirmed by spiking the reaction mixtures with authentic samples. Each equivalent of DBAL formed should consume 2 equiv of Ag_2O, and each equivalent of DBAC formed should consume 3 equiv of Ag_2O. The reaction yield, based on Ag_2O, the limiting reagent, was therefore 42% (see footnote *e* 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.

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Table 3. Catalytic Oxidation of Mesitylene by Ag_2O (130 °C, 12 h)

entry[a]	complex	Ag_2O[b] "concentration" and equiv	DBAL concentration and turnovers[c]	DBAC concentration and turnovers[c]	total[d] turnovers	yield[e] (based on Ag_2O)
1[f,i]	**2**	212 mM, 20 equiv	3.2 mM, 0.3 TO	28 mM, 2.6 TO	2.9	42%
2[g,i]	**2**	212 mM, 20 equiv	5.3 mM, 0.5 TO	25 mM, 2.4 TO	2.9	41%
3[i,j]	**2**	424 mM 40 equiv	13 ± 4 mM, 1.2 ± 0.4 TO	41 ± 3 mM, 3.9 ± 0.3 TO	5.1 ± 0.6	35% ± 4%
4	**2**	424 mM 40 equiv	0.7 TO	3.6 TO	4.4	31%
5[i]	**1**	424 mM, 40 equiv	7.4 mM, 0.7 TO	4.2 mM, 0.4 TO	1.1	7%
6[k]	**2**	424 mM 40 equiv	6.4 mM 0.6 TO	44 mM 4.1 TO	4.7	34%
7[i]	**5**	424 mM 40 equiv	0.4 mM 0.04 TO	none	0.04	0.2%
8[l]	$[Cp^*IrCl_2]_2$	424 mM 40 equiv	3.2 mM 0.3 TO	none	0.3	2%
9[h]	none	212 mM, 20 equiv	none	none	none	0%
10	none	424 mM 40 equiv	none	none	none	0%

[a]Reaction conditions: 10.6 mM (1 equiv) complex **1** or **2**, Ag_2O: 99% purity unless noted otherwise, mesitylene: 7.19 M, 300 μL, in a J-Young NMR tube under 1 atm argon with <0.5 ppm of H_2O or O_2, at 130 °C and for 12 h. [b]Ag_2O did not dissolve in solution, and the "concentration" (mol per liter) is given only for the purpose of calculation; [c]Turnovers were measured by ^1H NMR analysis using CH_3CN as an internal standard added at the end of reaction (see Supporting Information for more details). [d]Total turnovers = turnovers based on DBAL + turnovers based on DBAC. [e]Yield was based on Ag_2O, the limiting reagent; yield = (2[DBAL] + 3[DABC])/[Ag_2O]. [f]21% (2.2 mM) of complex **2** recovered. [g]18% (1.9 mM) of complex **2** recovered. [h]The same reaction was performed twice and gave identical results. [i]Ag_2O in 99.99% purity. [j]Average results of three runs. [k]Water (10 μL, 1.9 M, 0.56 mmol) was added. [l]5.3 mM of the dimer was used.

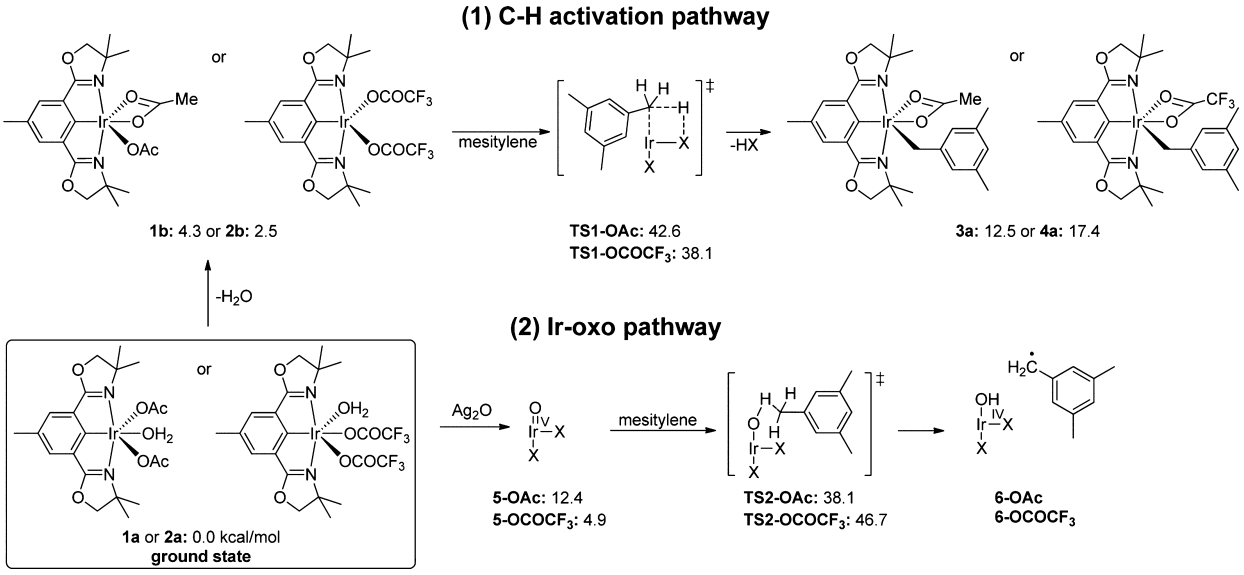

Figure 2. Calculated free energies (kcal/mol) for the (1) C−H activation pathway and (2) Ir-oxo pathway in catalytic mesitylene oxidation using complex **1a** or **2a**; X = OAc or $OCOCF_3$; "Phebox" ligand is not shown but is implied, except in complexes **1a**, **2a**, **3a**, and **4a**; no calculations performed for **6-OAc** and **6-OCOCF$_3$**.

Using 40 equiv of Ag_2O 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 Ag_2O (99.99% pure Ag_2O, entry 3; see Supporting Information for a commercial source of this Ag_2O 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 Ag_2O (99% pure; see Supporting Information for a commercial source of this Ag_2O sample). No significant changes caused by a different Ag_2O 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)-$IrCl_2(OH_2)$ (**5**), which could not carry out C−H activation,[99] 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.[102] 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[107] that oxidation of mesitylene can be catalyzed by $[Cp^*IrCl_2]_2$, possibly as a precursor to heterogeneous material. Under our conditions $[Cp^*IrCl_2]_2$ 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 Ag_2O as terminal oxidant than any other Ir complex tested.

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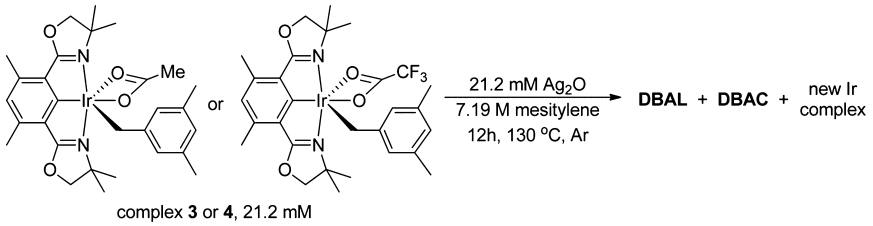
Scheme 11. Oxidation of (Phebox)Ir Mesityl Complexes 3 and 4 by One Equivalent of Ag_2O



Oxidation of (Phebox)Ir Complexes 1, 2, 3, and 4 by One Equivalent of Ag_2O. We considered the question of whether the catalytic oxidation of mesitylene proceeded via C−H activation followed by oxy-functionalization[59,79] or via Ir-oxo formation followed by C−H hydroxylation.[52,59] 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_2O at 130 °C for 12 h (Scheme 11 and Table 4). Complex **3** was resistant to oxidation, and more than 90% of complex **3** was recovered at the end of the reaction (entries 1 and 2 in Table 4). No significant (<1% yield) product of oxy-functionalization, DBAL or DBAC, was detected with or without one equivalent of NaOAc. The additional equivalent of NaOAc added (entry 2) was intended to match the conditions in catalytic oxidation of mesitylene using complex **1** (entry 5 in Table 3), which contained two acetate ligands.

Table 4. Oxidation of (Phebox)Ir Mesityl Complexes 3 and 4 by One Equivalent of Ag_2O

entry[a]	complex	additive	DBAL yield[b]	DBAC yield[b]	recovered Ir mesityl complex
1	**3**	none	none	none	quantitative
2	**3**	NaOAc	none	<1%	>90%
3	**4**	none	none	none	49%
4	**4**	$NaOCOCF_3$	1%	4%	31%
5[c]	**4**	$NaOCOCF_3$	62%	106%	<1%
6[c]	**3**	NaOAc	7%	44%	<10%

[a]Reaction conditions: 21.2 mM, 6.4 μmol (1 equiv) of complex **1** or **2**, Ag_2O 99.99% purity in one equivalent (21.2 mM) unless stated otherwise, mesitylene (7.19 M, 300 μL), NaOAc or $NaOCOCF_3$ (21.2 mM, 6.4 μmol); in a J-Young NMR tube under 1 atm argon with <0.5 ppm of H_2O or O_2; at 130 °C and for 12 h; Ag_2O 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_3CN as an internal standard added at the end of the reaction (see Supporting Information for more details). [c]20 equiv of Ag_2O used.

With complex **4** no significant product (<1% yield) from oxy-functionalization was detected in the absence of $NaOCOCF_3$ (entry 3 in Table 4). Only 49% of complex **4** was recovered at the end of the reaction. However, in the presence of one equivalent of $NaOCOCF_3$, DBAC in 3% yield and DBAL in 1% yield were generated from oxidation of complex **4** (entry 4 in Table 4). At the end of the reaction 31% of complex **4** was recovered. Use of 20 equiv of Ag_2O with complex **4** in the presence of one equivalent of $NaOCOCF_3$ 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 DBAC and DBAL suggested that complex **4** effected catalytic turnover. Use of 20 equiv of Ag_2O 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 **5-OAc** and **5-$OCOCF_3$** of Figure 2. Complexes **1** and **2** were treated with one equivalent of Ag_2O in both mesitylene and C_6F_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), reaction of complexes **1** and **2** with Ag_2O in C_6F_6 solvent gave mostly (80%) recovered **1** and **2**. Formation of complex **3** in 65% yield was observed in the reaction of complex **1** in mesitylene solvent (see Supporting Information for details). New ^{1}H NMR peaks appeared, which could potentially be assigned to new Ir complexes, but we were unable to isolate or characterize these species.

COMPUTATIONAL RESULTS AND DISCUSSION

Methods. All optimizations and frequency and solvation calculations were completed using B3LYP[108,109] with the Los Alamos small-core potential[110] and the 2-ζ basis set on iridium and the 6-31G** basis set on organics.[111,112] Single-point, large basis set calculations were completed with M06[113] with LACV3P**++ augmented with f-functions and diffuse functions on iridium.[114] Organic molecules were treated with 6-311G**++.[115,116] 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[117] kcal/mol for liquid mesitylene). The molar value for acid was extrapolated from VLE data for dilute acetic acid in benzene.[118] Analytical frequency calculations were used to validate all transition states.

Free energies were calculated with the following equation:

$$G = E_{M06} + G_{solv} + E_{ZPE} + H_{vib} + H_{TR} - T(S_{vib} + S_{elec})$$

where G_{solv} is the solvation energy, E_{ZPE} is the zero point energy, H_{TR} ($^{12}/_2\ k_BT$) is the translational and rotational enthalpy, and S_{vib} and S_{elec} are the vibrational and electronic enthalpic terms, respectively. In order to calculate reaction energies involving Ag_2O, DFT calculations were performed using O_2 (1 atm) as oxidant, then corrected using the

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difference between the standard potentials for the reduction of O_2 to water (1.23 V vs NHE) and $Ag_2O(s)$ to Ag(s) and water (1.17 V vs NHE);[119] 1.4 kcal/mol per electron was added to the values obtained using O_2 as the oxidant. All calculations were completed in Jaguar.[120] These methods have been previously applied in other organometallic systems, leading to good agreement with experiment.[121,122] In these calculations, *p*-CH_3 complexes were substituted for the *m*-bis-CH_3 complexes used in experiment. Justification can be seen in the Supporting Information.

Two proposed pathways for mesitylene C−H bond activation by complexes **1a** and **2a** are shown in Figure 2. The experimentally prepared aquo complexes were taken as the ground states for all calculations. Two different ground states were calculated for the two coordinating ligands. In complex **1a**, the ground state for the acetate complex, the coordinated aqua ligand prefers to occupy the equatorial position, whereas in complex **2a**, the ground state for the trifluoroacetate complex, the aqua ligand prefers the axial position. In pathway (1), C−H activation of mesitylene proceeds via **TS1** with binding of the benzylic carbon to iridium occurring concertedly with hydrogen transfer to the oxygen of the anionic ligand (a concerted metalation-deprotonation mechanism[13,100]).

In C−H activation by complex **1a**, the transition state **TS1-OAc** has an activation barrier of 42.6 kcal/mol. The trifluoroacetate analogue, **TS1-OCOCF$_3$** (Figure 3), is lower in free energy, 38.1 kcal/mol.

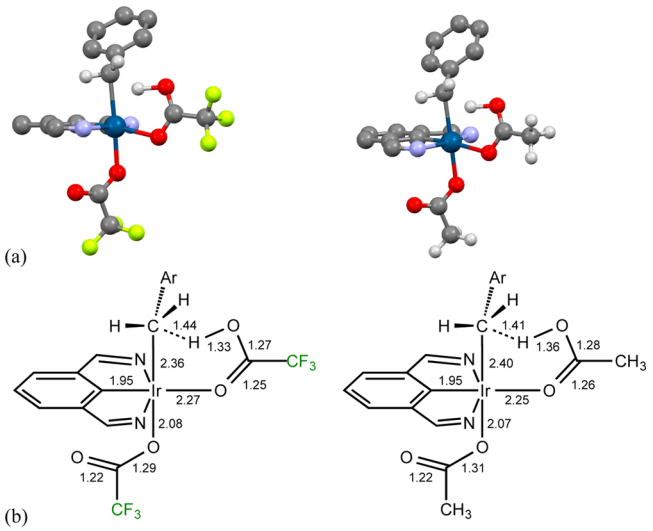

Figure 3. (a) Calculated structures of **TS1-OCOCF$_3$** and **TS1-OCOCH$_3$** (peripheral atoms omitted for clarity). (b) Selected interatomic distances indicated (Å).

Proceeding along the reaction coordinate from **TS1**, the acetic acid or trifluoroacetic acid (HX) molecule is eliminated to give complex **3a** or **4a**. Notably, although **TS1-OAc** has a higher energy than **TS1-OCOCF$_3$**, formation of the reaction product, **3a** (from **TS1-OAc**), is significantly less endergonic than formation of complex **4a** (from **TS1-OCOCF$_3$**) (by 4.9 kcal/mol). Thus, the calculations are consistent with both the faster kinetics of H/D exchange catalyzed by **2** vs **1** and the observations indicating that C−H activation by **2** to give the mesityl complex **4** is thermodynamically less favorable than the reaction of **1** to give **3**. It should be noted however that the calculated differences in both the reaction kinetics and thermodynamics are much greater than is indicated by the experimental results.

Once formed, complexes **3a** and **4a** may undergo a variety of possible routes discussed in the literature to form a C−O bond;[7,23] the complexity of such reactions, particularly with Ag_2O as oxidant, is beyond the scope of this work. An alternative oxidation pathway begins with the direct oxidation to give Ir-oxo complexes **5**. Iron, manganese, and ruthenium oxo complexes typically can undergo a fast hydrogen abstraction reaction with alkanes, often leading to overoxidation.[123,124] This reaction yields a carboradical and Ir^{IV} hydroxide complex, shown in **6**. The formation of **5-OAc** is uphill from **1a** by 12.4 kcal/mol, while the formation of **5-OCOCF$_3$** is only uphill from **2a** by 4.9 kcal/mol.

The transition state for the hydrogen abstraction by the oxo group is shown by **TS2**. At 38.1 kcal/mol, the calculated barrier for hydrogen abstraction by Ir-oxo complex **5-OAc**, via transition state **TS2-OAc**, is lower than **TS2-OCOCF$_3$** (46.7 kcal/mol), by 8.6 kcal/mol. Given that the trifluoroacetate complex **2** is the more effective catalyst for oxidation, and given that a calculated comparison of two such closely analogous transition states should be quite reliable, this argues strongly against the oxo pathway (at least for catalysis by complex **2**). In marked contrast, for the C−H activation pathway, **TS1-OCOCF$_3$** is significantly lower than **TS1-OAc**, in accord with the observation that trifluoroacetate complex **2** catalyzes both oxidation and H/D exchange faster than complex **1**.

Thus, the calculations predict that the trifluoroacetate ligand favors the kinetics of C−H activation (in accord with the faster H/D exchange) as compared with the acetate ligand, while it disfavors the oxo pathway. This may suggest that trifluoroacetate 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 Ag_2O 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-OCOCF$_3$**, 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

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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Notes

The authors declare no competing financial interest.

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