Ligand Tuning in Pyridine-Alkoxide Ligated Cp*IrIII Oxidation Catalysts

Emma V. Sackville,† Gabriele Kociok-Köhn,‡ and Ulrich Hintermair*†

†Centre for Sustainable Chemical Technologies, University of Bath, Claverton Down, Bath BA2 7AY, United Kingdom
‡Chemical Characterisation and Analysis Facility, University of Bath, Claverton Down, Bath BA2 7AY, United Kingdom

ABSTRACT: Six novel derivatives of pyridine-alkoxide ligated Cp*IrIII complexes, potent precursors for homogeneous water and C–H oxidation catalysts, have been synthesized, characterized, and analyzed spectroscopically and kinetically for ligand effects. Variation of alkoxide and pyridine substituents was found to affect their solution speciation, activation behavior, and oxidation kinetics. Application of these precursors to catalytic C–H oxidation of ethyl benzene sulfonate with aqueous sodium periodate showed that the ligand substitution pattern, solution pH, and solvent all have pronounced influences on initial rates and final conversion values. Correlation with O2 evolution profiles during C–H oxidation catalysis showed these competing reactions to occur sequentially, and demonstrates how it is possible to tune the activity and selectivity of the active species through the N*O ligand structure.

INTRODUCTION

The selective, catalytic oxy-functionalization of inert C–H bonds has long been regarded as one of the holy grails of synthetic chemistry and is an important strategy in the context of sustainable chemistry.1–3 The main challenges associated with this transformation arise from the strong and nonpolar nature of the C–H bond in combination with issues over control of regio- and chemoselectivity, particularly to prevent over-oxidation.

Metal-catalyzed C–H oxidation typically proceeds via one of two routes: insertion of an electrophilic metal center into a C–H bond followed by oxy-functionalization of the metal–alkyl intermediate, or direct insertion of a metal-oxo species into the C–H bond followed by reoxidation of the metal.4,5 While the topic of C–H activation by metal insertion has been researched extensively,6 direct C–H oxidation by metal-oxo species is less well explored from an organometallic perspective, despite representing a promising biomimetic strategy. For instance, the active sites in the superfluously efficient metallo-enzymes cytochrome P450 and methane monooxygenases are based on Fe-oxo species. A number of synthetic metal-oxo complexes for catalytic C–H activation based on Cr, Mn, Fe, and Ru have been developed for alkene epoxidations and C–H hydroxylation, including the direct conversion of methane to methanol.4–22

Recently it has been shown that octahedral half-sandwich iridium(III) complexes can act as effective precatalysts for selectively oxidizing a range of substrates in synthetically useful yields when driven with CeIV or NaIO4 in aqueous solution.22,23 Initially developed for chemical energy conversion,24–28 both C–H and water oxidation reactions are closely related, with interlinked catalytic cycles and common intermediates (Figure 1), as evidenced by water being the source of oxygen in the C–H oxynation.29 The formulation of the active species as a closed-shell oxene (most likely d4 IrV)30 is supported by first-order kinetics in [Ir] for both water21 and C–H oxidation23 and retention of configuration in tertiary C–H hydroxylation,22 observations that argue against the involvement of open-shell oxyl species that would operate via radical rebound32 and oxo coupling pathways,24,33 respectively.

In both reactions there is a short induction period during which the Cp*IrIII precursor complexes are oxidatively activated before turnover begins.34–36 This activation can be performed chemically or electrochemically.37 It has been shown that the full oxidative activation involves loss of the Cp* ligand38–40 and results in the formation of a proposed IrIV–µ-oxo dimer (Scheme 1)36 in which the chelate ligand is retained. The latter
is a crucially important feature in this chemistry, as without an oxidatively robust chelate ligand, polymerization occurs to form IrO$_x$ nanoclusters and particles, which despite being active O$_2$ evolution catalysts are inactive in C–H oxidation. Thus, the further development of these privileged ligands is of great interest in the improvement of these catalysts for application in C–H oxidation, as variation of steric and electronic properties has the potential to increase their scope and utility further.

Here we report the synthesis and characterization of six novel Cp*Ir$^{III}$ precatalysts based on variations of the successful pyridine-alkoxide ligand motif. Spectroscopic analyses reveal strong ligand effects on their oxidative activation and catalytic activity. After pH and solvent environment were optimized, the kinetics of methylene oxidation in para-sulfonated ethylbenzene as model substrate showed a large variation in initial rates and final conversion levels among the catalyst selection, resulting in a molecularly tunable system.

**RESULTS AND DISCUSSION**

Designing ligands for oxidation catalysts, particularly at the potentials needed for water and C–H oxidation, is challenging as they have to be able to support highly oxidizing metal centers without being degraded themselves. For that reason, many of the traditional organic ligands like carbonyls, olefins, and phosphines that have proven so effective in reductive catalysis are unsuitable for oxidative chemistry. Pyridines, pyrroles, amides, and carboxylates show high oxidative stability when suitably substituted, and whereas primary and secondary alcohols are readily oxidized, tertiary alkoxides are also highly stable. In addition, their $\pi$ basicity can stabilize high-valent intermediates and enable them to engage in proton management through the oxygen lone pairs.

A range of symmetrically substituted pyalk-type ligands (Figure 2) was synthesized through lithiation of 2-bromo-pyridine or 2-bromo-quinoline followed by reaction with the desired ketone according to previously described methods. This strategy allowed straightforward access to a variety of N$^\circ$O ligand precursors. Isolated yields of 22–72% were obtained after purification by recrystallization or sublimation (see Supporting Information for details). The alkox substituents were varied in terms of steric bulk (methyl, cyclohexyl, $n$-butyl) and electronics (aliphatic vs aromatic), and the pyridine moiety was extended into a quinoline system. $\eta^2$ coordination of the pro-ligands to the Cp*Ir$^{III}$ fragment was achieved by gentle heating with [Cp*IrCl$_2$]$_2$ in the presence of a mild inorganic base (Scheme 2).

**Scheme 2. Synthesis of Cp*Ir$^{III}$ Complexes Using Ligands L1–L7**

The neutral, monomeric chloro complexes 1, 2, 4–7 (Figure 3) were obtained in isolated yields of 54–81% after recrystallization.

Figure 2. Tertiary 2-pyridine/quinoline alcohols synthesized as pro-ligands for Ir-based oxidation catalysts.
isolation of the cationic 16-electron five-coordinate [Cp*Ir-(L3)]SbF6 complex 3. In this distorted trigonal bipyramidal (dTBP) structure, the pyalk ligand is orthogonal to the plane of the Cp* ligand, thus avoiding steric clash between the alkoxy substituents and the Cp* methyl groups. This coordination mode, involving π donation from the oxygen lone pairs into vacant metal d-orbitals, is well known for various chelating alkoxides and imides and represents a key feature in ligand-assisted bifunctional hydrogenation catalysis.50

All new compounds were fully characterized, including single-crystal X-ray diffraction (Figure 4). The solid-state structures confirm the expected geometries with no noticeable distortions; Ir–C distances are 2.16 ± 0.02 Å, Ir–N distances 2.09 ± 0.01 Å, O–Ir–N bond angles 77 ± 1°, and O–Ir–Cl bond angles 86 ± 1.5° in the octahedral complexes. Compounds 1, 2, 4–7 exhibit Ir–O distances of 2.05 ± 0.01 Å whereas in 3 the Ir–O distance is 1.94 Å, consistent with some double bond character in the cationic five-coordinate complex.51

The ability of these N=O ligands to temporarily stabilize a TBP structure via reversible π donation from the oxygen lone pairs (Scheme 3) is also thought to be responsible for the unusually fast ligand exchange kinetics in the octahedral complexes,52 as evidenced by equivalent 1H NMR signals for both R groups in complexes 1–7 in aqueous methanol at room temperature.

As water coordination is known to be required for these precursors to enter the oxidative activation reaction (Scheme 1),36 the solution speciation of precursor complexes 1–7 in aqueous media can be expected to impact on their rates of activation and catalytic turnover. In addition to intrinsic electronic factors, the ligand bulk, solution pH, and ionic strength can all be expected to influence the equilibria shown in Scheme 4.

To gain some insight into the aqueous solution speciation of 1–7, UV–vis titrations with chloride were carried out (Figure 5). After equilibration between each addition, complexes 1, 2, 4–7 all showed an increase in absorbance in the region of 350–390 nm with clear isosbestic points with increasing chloride concentration except for 3, consistent with the observation that an octahedral chloro complex could not be isolated synthetically. These data show that, in the absence of excess halide, the equilibria shown in Scheme 4 lie toward the right, away from the [6]Ir-X form for all complexes 1–7 under typical reaction conditions (i.e., in aqueous solution at room temperature) and only fully revert to [6]Ir-Cl upon the addition of several hundred equivalents of chloride. The distribution of [5]Ir+ ↔ [6]Ir-OH* ↔ [6]Ir-Cl that prevails without excess chloride is more difficult to ascertain with certainty and will, in addition to ligand steric, depend on solution pH. [Attempts at equivalent pH titrations proved inconclusive due to various degrees of degradation of the complexes under basic conditions.] As 3 was not significantly affected by the addition of a large excess of chloride (evidenced by the absence of any isosbestic points), we propose that in neutral aqueous solution all complexes predominantly reside in the sterically most relaxed [5]Ir+ coordination mode, through which they may become available for oxidative activation and catalysis.

The activation reaction of the monomeric Cp*IrIII complexes with an excess of NaIO4 in aqueous solution, leading to oxidative removal of the Cp* ligand, and formation of the presumed IrIV μ-oxo dimer (Scheme 1) is typically accompanied by a marked color change from yellow/orange to deep blue. This absorption around 600 nm is characteristic of IrIV linkages and, although also seen in related molecular RuIII–O–RuIII systems,53 has often been confused with IrO2 formation.54 Although we have not demonstrated homogeneity for our new derivatives 2–7 yet, 1 has been shown to be fully homogeneous over a wide range of conditions using a variety of techniques (including EQCN54 and DLS41), so here we work on the hypothesis that 2–7 behave similarly. The oxidative activation reaction according to Scheme 5 was thus followed by time-resolved UV–vis spectroscopy, and markedly different behavior was observed for complexes 1–7 reacting with aqueous NaIO4 (Figure 6).

1H NMR analysis showed that in all cases the signal of the bound Cp* ligand had disappeared irreversibly within 1 min after contacting the precursor complexes with the oxidant (Figure S9), with acetate building up as the main Cp*

### Scheme 3. Reversible π Donation from Oxygen Lone Pairs Facilitating Dissociative Ligand Exchange

![Scheme 3](image_url)
Scheme 4. Solution Equilibria of Cp*Ir$^{III}$ Complexes with Pyalk-Type Complexes in Aqueous Solution$^a$

$^a$X may be halides from the precursor or added electrolyte.

Figure 5. UV−vis titration data of 1−7 with KCl at 0.5 mM [Ir] in 4:1 H$_2$O/BuOH at room temperature. Isosbestic points are denoted with a star, and the arrows indicate increasing [KCl]. Insets show the change in absorbance calculated for each data set around 370 nm.
degradation product (as previously described for 1\textsuperscript{36}). Thus, any further changes in the UV−vis spectra can be ascribed to further structural transformations leading to the formation of the activated resting state of the catalyst. From Figure 6 and the summary of key parameters in Table 1, it can be seen that under the conditions applied (50 equiv of oxidant) all complexes fully activated within less than 25 min, but with varying activation kinetics. The molar absorptivities and \( \lambda_{\text{max}} \) in the Ir\( \text{IV} \)−O−Ir\( \text{IV} \) regime of the fully activated compounds were similar for 1−6, consistent with a similar species formed in these cases, with the slight differences plausibly reflecting ligand effects on the d(Ir\( \text{IV} \))→π*(Ir−O−Ir) transition around 570−610 nm. Interestingly, the activated species possessed different lifetimes. While activated 1, 5, and 6 did not show any change over 1 h, 2, 3, and 4 began to lose intensity immediately after full activation. Increasing the bulk of the alkoxy substituents in the series of 1→4→6→2→3 did not have a major impact on their oxidative activation behavior, even though 3 appeared to be locked in the dTBP structure due to steric pressure in the Cp* precursor. This lends further support to our proposal that all Cp*Ir(pyalk) complexes investigated here prefer the cationic penta-coordinate form in neutral aqueous solution, and shows that these are all available for oxidative activation with periodate. The two cyclohexyl compounds 4 and 6 shared an intermediate phase with maximum absorbance ∼450 nm in their first 10 min, after which similar wavelengths for the activated species were found (572 and 573 nm, respectively).

Comparing 1 to 5, extending the pyridine into a quinoline system, appeared to speed up precursor activation, but not in the case of phenyl substituents. The diphenyl complexes 2 and 7 showed the lowest \( \lambda_{\text{max}} \) (567 and 571 nm, respectively), with a persistent shoulder at ∼450 nm which we ascribe to different electronic structures of their activated species (see catalysis results below).

To investigate how these ligand effects translate into catalysis, we compared the behavior of precatalysts 1−7 under turnover conditions. Ethyl benzenesulfonate (EBS; Scheme 6) is a convenient model substrate for C−H oxidation due to its water solubility and diagnostic \(^1\)H NMR signals.\textsuperscript{23} With iridium-based systems the reaction typically proceeds with clean and selective oxidation of the methylene group to the ketone without aromatic oxygenation—a side reaction often seen with ruthenium-based catalysts and NaIO\(_4\).\textsuperscript{55}

Although many Cp*Ir\( \text{III} \) complexes are readily water-soluble, our bulkier derivatives 2, 3, and 7 required the addition of an organic cosolvent. In addition, most real-world substrates will be significantly less hydrophilic than the ionic model substrate.

### Table 1. Activation Reaction Times, Absorption Wavelength, and Intensity of the Activated Species from 1−7 with 50 equiv of NaIO\(_4\) in 4:1 H\(_2\)O/tBuOH

| complex | time/min | \( \lambda_{\text{max}}/\text{nm} \) | \( \varepsilon/M^{-1} \cdot \text{cm}^{-1} \) |
|---------|----------|----------------|----------------|
| 1       | 15       | 599            | 1354          |
| 2       | 12       | 567            | 1308          |
| 3       | 21       | 579            | 1366          |
| 4       | 11       | 572            | 1400          |
| 5       | 5.5      | 605            | 1775          |
| 6       | 22       | 573            | 1887          |
| 7       | 2.5      | 571            | 594           |

\( ^{\text{a}} \)Time taken to reach maximum absorbance. \( ^{\text{b}} \)Wavelength of maximum absorbance. \( ^{\text{c}} \)Absorbance at \( \lambda_{\text{max}} \). See also Figures S9 and S10.
EBS, hence we tested a variety of oxidation-resistant, water-miscible organic cosolvents in the EBS oxidation according to Scheme 6 utilizing 1 as benchmark. As can be seen from Figure 7, at 20 vol% organic (not to compromise NaIO₄ solubility) tBuOH afforded the best performance, yielding even higher conversions than purely aqueous systems, although initial rates were virtually identical for tBuOH/H₂O, acetone/H₂O, and pure H₂O. The addition of nitrile and nitro cosolvents appeared to be detrimental to both initial rates and final conversion values, and hexamethylphosphoramide and dimethylamide completely shut down C–H oxidation catalysis, possibly by being oxidized themselves.56

Moving forward with the optimal tBuOH/H₂O solvent system, investigation into the effect of solution pH on the reaction showed that neutral pH values gave highest EBS conversions utilizing 1 (Figure 8). This is a potentially complex interplay of varying precursor speciation, oxidant potential, active catalyst speciation and stability, and possibly electronic effects on the ionic substrate, though whatever the exact cause, the observation that very low C–H oxidation conversions are obtained under either acidic or basic conditions is important information for practical application. Comparing EBS oxidation reaction profiles from in situ ¹H NMR utilizing 1–7 under optimized conditions showed markedly different catalytic performance (Figure 9). No conversion occurred without any iridium added, but all catalysts were active in the reaction shown in Scheme 6 with 100% selectivity to the para-sulfonated acetophenone product, though greatly varying in initial rates and final conversion values. Table 2 summarizes key performance data under the conditions applied. The dimethyl-substituted complexes 1 and 5 displayed by far the fastest initial rates, and the diphenyl complexes 2 and 7

![Figure 7. Reaction profiles of the oxidation of EBS (Scheme 6) catalyzed by 1 at 40 mM EBS, 200 mM NaIO₄, 0.4 mM (1 mol%) [Ir] at pH 7, 25 °C in various H₂O/cosolvent mixtures (all 4:1 by volume) as derived from in situ ¹H NMR data.](image)

![Figure 8. Conversion values of the oxidation of EBS (Scheme 6) catalyzed by 1 at 40 mM EBS, 200 mM NaIO₄, 0.4 mM (1 mol%) [Ir], 25 °C in 4:1 H₂O/tBuOH after 10 min reaction time (pH adjusted with HNO₃/NaOH).](image)

![Figure 9. Initial (top) and full (bottom) ¹H NMR time course data of the oxidation of EBS (Scheme 6) with complexes 1–7 at 40 mM EBS, 200 mM NaIO₄, 0.4 mM (1 mol%) [Ir] at pH 7, 25 °C in 4:1 H₂O/tBuOH. Initial rates shown as black lines.](image)

**Table 2. Initial Rates, Final Conversion Values, and Time Taken to Final Conversion of the Reaction Profiles Shown in Figure 9**

| precatalyst | initial k_{obs}/mM min⁻¹ᵃ | catalyst TOF/h⁻¹ᵇ | conversion plateau/% | time to plateau/h |
|-------------|---------------------------|--------------------|----------------------|------------------|
| 1           | 1.61                      | 242                | 55                   | 2.6              |
| 2           | 0.03                      | 4                  | 88                   | 60               |
| 3           | 0.19                      | 29                 | 65                   | 3.3              |
| 4           | 0.13                      | 20                 | 52                   | 4.3              |
| 5           | 0.99                      | 149                | 68                   | 3.2              |
| 6           | 0.14                      | 21                 | 60                   | 4.5              |
| 7           | 0.05                      | 8                  | 70                   | 9.0              |

ᵃCalculated from initial gradient of product concentration over time (linear regime; see Figure 9).ᵇInitial reaction rate divided by catalyst concentration. ćAveraged value over plateau.
were slowest. The bulkier alkyl-substituted complexes 3, 4, and 6 gave intermediate results closer to those obtained with the diphenyl complexes. This trend roughly mirrors the one seen in the precursor activation reaction (Table 1). However, as all complexes were fully activated within 25 min at much lower oxidant loadings (50 equiv in the UV−vis experiments compared to 500 equiv used for catalysis), and none of the C−H oxidation reaction profiles showed sigmoidal kinetics indicative of limiting precursor activation, we conclude that these varying rates reflect intrinsic differences of the fully activated catalysts originating from the various pyalk ligands. Even in case of 2, the rate did not accelerate over the 60 h reaction time, suggesting that the precursor complex did activate but, in line with its slightly different UV−vis signature (cf. Figure 6), formed a distinct active species.

When the full reaction profile is considered (Figure 9, bottom), it can be seen that the reaction conversions plateaued at different levels for the different precatalysts (Table 2), although a 5-fold excess of oxidant over substrate was used in all cases. To test whether catalyst deactivation was responsible for the limited conversion values, a second portion of oxidant was added to a catalytic run with 5 after conversion had stalled after 3.5 h. As shown in Figure 10, catalysis immediately resumed with a stable rate, nicely extrapolating the initial reaction profile, proving that the catalyst remained active. We therefore ascribe the conversion plateaus to the system becoming depleted of oxidant, and with the amount not seen in C−H oxidation product being consumed in the parallel oxygen evolution reaction. These different C−H oxidation plateaus are thus indicative of the individual C−H vs O−H oxidation selectivity (i.e., a branching ratio).

The fact that the branching ratios of water vs C−H oxidation appear to be directly influenced by the N^O ligand in the precursor is exciting in that it indicates that there is scope for molecular control over these highly oxidizing catalyst systems based on ligand design. The branching ratio being a pure selectivity measure during turnover (cf. Scheme 1) only reflects intrinsic differences of the fully activated species with no interference from ligand effects on precursor speciation and activation. In this respect the slowest but most C−H selective precatalyst 2 is interesting, as the phenyl substitution pattern appears to impart C−H over O−H preference onto the catalyst.

In order to quantify the amount of O2 generated during EBS oxidation with precatalysts 1−7, oxygen assays using a Clarke-type electrode were undertaken under the same reaction conditions (Figure 11). All complexes except 2 showed some O2 generation activity during EBS oxidation, fully in line with its highest C−H oxidation efficiency observed with EBS (Figure 9 and Table 2). The relative order in activity for O2 evolution was similar to that seen in catalytic EBS oxidation, with 1 being the most active precursor, followed by 5, and then 3, 6, 7, and 2 (Table 3).

![Figure 10. 1H NMR time course of the oxidation of EBS (Scheme 6) with complex 5 with a second addition of NaIO4 at 40 mM EBS, 200 mM NaIO4 (initial), 0.4 mM (1 mol%) [Ir] at pH 7, 25 °C in 4:1 H2O/BuOH.](image)

![Figure 11. Oxygen evolution traces of the precatalysts 1−7 during C−H oxidation catalysis at 40 mM EBS, 200 mM NaIO4, 0.4 mM (1 mol %) [Ir] at pH 7, 25 °C in 4:1 H2O/BuOH using a calibrated Clark electrode.](image)

### Table 3. Activation Times and Initial Rates of the O2 Evolution Profiles Shown in Figure 11

| precatalyst | activation time/s | initial k_{obs}/mM min⁻¹ | catalyst TOF/h⁻¹ |
|-------------|-------------------|--------------------------|-----------------|
| 1           | 5                 | 2.98         | 448             |
| 2           | n.a.              | 0            | 0               |
| 3           | 6                 | 0.21         | 32              |
| 4           | 4                 | 0.89         | 134             |
| 5           | 3                 | 1.26         | 188             |
| 6           | 9                 | 0.25         | 38              |
| 7           | 3                 | 0.28         | 43              |

*^a^Lag phase between precatalyst addition and onset of O2 evolution. ^b^Calculated from initial gradient of product concentration over time (average from triplicates). ^c^Initial reaction rate divided by catalyst concentration.

Activation periods were shortened to a few seconds for all precatalysts under the conditions applied (500 equiv of NaIO4 per Ir), with the same reactivity order as in the UV−vis experiments (Figure 6 and Table 1). Initial O2 evolution rates were in the same order of magnitude as C−H oxidation rates (Table 2), but O2 evolution occurred on a faster time scale and ceased after 2−3 min. Due to the much higher water than EBS concentrations the two competing oxidation reactions thus occurred sequentially once precursor activation was complete. The thermodynamically more challenging substrate (water) only got oxidized in early stages of the reaction where higher solution potentials existed, with C−H oxidation occurring once oxidant concentration had been depleted sufficiently for it to compete with the harder to oxidize but more abundant substrate water. Plotting initial O2 evolution rates versus C−H
oxidation efficiency (Figure 12) suggests this competition to be a measure of the oxidizing power of the activated catalyst. With this view, the higher C–H oxidation efficiency of 2 can be rationalized; the electron-withdrawing aryl substituents result in a less oxidizing active species which does not evolve any O2 but slowly turns over nearly all of the C–H substrate present. Although no global correlation exists for the limited sample size of 1–7, an activity analysis with respect to ligand effects does reveal some interesting trends:

(a) Extending the pyridine into a quinoline, with alkyl alkoxide substituents (1 → 5), decreases the rate and increases the C–H selectivity.

(b) Increasing the bulk of the alkoxide substituents (1 → 4, 6, 3) greatly decreases the rate and slightly increases C–H selectivity.

(c) Substituting alkyl with aryl alkoxide substituents greatly reduces the rate (1 → 2) and significantly improves C–H selectivity, though not with a quinoline backbone (2 → 7).

Thus, if rate is most important, a pyalk ligand with minimum steric demand and high donor power should be used, whereas fine-tuning of the electronics via modification of electron-withdrawing aryl substituents may yield slower but more C–H selective oxidation catalysts.

### CONCLUSIONS

We have described the syntheses, solid-state and solution structures, and catalytic properties of six new Cp* IrIII complexes with various symmetrically substituted pyridine-alkoxide ligands, precursors to potent oxidation catalysts. The steric bulk of the alkoxide substituents impacts on the coordination mode of the ligand through clashes with the Cp* ligand in the octahedral form. However, all chloride complexes have been shown to readily ionize and, in neutral aqueous solution, appear to prefer cationic penta-coordination of the metal from which they are available for oxidative activation with aqueous NaIO4. Although their individual activation kinetics vary, there is no indication for limiting precatalytic ligand effects within the series of 1–7. We have shown the importance of the reaction environment on their catalytic performance and identified BuOH as the most beneficial organic cosolvent for aqueous C–H oxidation at neutral pH for these iridium catalysts. Kinetic profiling of the catalytic oxidation of EBS with NaIO4 showed that the investigated catalysts plateau at different conversions when becoming depleted of oxidant but are stable and can be reactivated by repeated addition of oxidant to reach higher turnover numbers. Monitoring O2 evolution during C–H oxidation catalysis showed the two reactions to occur sequentially, with more active catalysts generating more O2 before the slower C–H oxidation catalysis set in. The various pyalk-type ligands synthesized (L2–L7) not only impact on the precursor activation reaction but also modulate the activity and thereby the selectivity of the active species. Thus, for the first time, molecular control over these highly oxidizing iridium catalysts has been demonstrated, a finding that opens the door to further improvement of these promising catalysts based on ligand engineering.

### EXPERIMENTAL SECTION

**General.** Organic solvents were purified by passing over activated alumina with dry argon. All chemicals were purchased from major commercial suppliers and used as received. Syntheses were performed under an inert atmosphere of dry argon using standard Schlenk techniques. NMR spectra were recorded on either 400 or 500 MHz Bruker Avance spectrometers and referenced to residual protio-solvent signals. The chemical shift δ is reported in units of parts per million (ppm). Element analyses were performed by the Science Centre of London Metropolitan University, and mass spectrometry (MS) was performed by the EPSRC UK National Mass Spectrometry Facility at Swansea University. Details of the single-crystal X-ray data collections and ligand syntheses can be found in the Supporting Information.

**EXPERIMENTAL SECTION**

**Figure 12.** Correlation of initial O2 evolution rates with final EBS oxidation yields catalyzed by 1–7 (40 mM EBS, 200 mM NaIO4, 0.4 mM (1 mol%) [Ir] at pH 7, 25 °C in 4:1 H2O/BuOH).

![Figure 12](image-url)
The product was washed with diethyl ether (2 × 5 mL). The yellow supernatant was removed and the powder dried in vacuo to give an orange-yellow powder. Single crystals suitable for X-ray diffraction analysis were grown by solvent evaporation (DCM) at room temperature. Yield: 0.0447 g (81%). 1H NMR (400 MHz, CDCl3); δ = 8.63 (d, J = 5.7 Hz, 1H, Hα), 7.56 (t, J = 7.7 Hz, 1H, Hβ), 7.36 (s, 2H, 6H, H), 6.99 (s, 15H, [CH3]2); 13C NMR (100 MHz, CDCl3); δ = 173.2 (Cp), 150.1 (CHpyridyl), 136.2 (CHpyridyl), 129.6 (CHpyridyl), 128.3 (CHphenyl), 127.6 (CHphenyl), 126.8 (CHphenyl), 125.7 (CHphenyl), 124.0 (CHphenyl), 94.6 (C), 84.3 (Cpyridyl), 88.3 (Cpyridyl); HR ESI-MS (+): m/z calculated for C18H18IrNO, [M + H]+, 333.0620, found 333.0606.

Elemental analysis: (calc for C18H18IrNO: C 53.96, H 4.74, N 2.34; found: C 53.96, H 4.74, N 2.34. Crystal data [CCDC no. 141034]; C18H18IrClNO (Ir2 + 2 CHCl3), M = 681.91, monoclinic, P21/c, a = 12.3262(2), b = 16.4094(3) Å, c = 16.41000(3) Å, α = 92.28631(11)°, V = 3315.84(10) Å3, Z = 4, dcalc = 1.727 g/cm3, T = 150 K, 66 209 reflections collected, 7585 independent reflections (Rint = 0.1312), final R1 = 0.0422, final wR2 = 0.0989, Gof F = 1.010.

1H NMR (400 MHz, CDCl3); δ = 8.85 (d, J = 8.2 Hz, 1H, Hα), 8.09 (d, J = 8.7 Hz, 1H, Hα), 7.78 (t, J = 7.8 Hz, 1H, Hα), 7.56 (t, J = 7.7 Hz, 1H, Hα), 7.19 (d, J = 8.5 Hz, 1H, Hα), 1.61 (s, 21H, [CH3]2); 13C NMR (100 MHz, CDCl3); δ = 179.7 (Cpyridyl), 144.6 (Cpyridyl), 137.2 (CHquinoline), 132.8 (CHquinoline), 130.5 (CHquinoline), 128.6 (Cquinoline), 127.7 (Cquinoline), 127.0 (Cquinoline), 119.2 (Cquinoline), 86.6 (C); 13C NMR (100 MHz, CDCl3); δ = 7.9 Hz, 1H, Harom), 7.12 (m, 2H, Harom), 1.66 (CH2CH3), 9.8 (CH3C ppyridine), 41.2 (C ppyridine), 11.7 (C ppyridine), 56.7 (CH2CH3), 127.7 (CHphenyl), 127.0 (CHphenyl), 126.8 (CHphenyl), 125.4 (CHphenyl), 123.4 (CHphenyl), 103.9 (C), 88.9 (Cpyridyl), 41.2 (C Cphenyl), 28.9 (CH2CH3), 9.8 (C ppyridine); ESI-MS (+): m/z calculated for C21H30ClIrNO, [M + H]+, 540.1632, 538.1616; found 540.1626, 538.1609; [M – Cl]+, 504.1878, 502.1855; found 504.1865, 502.1845. Elemental analysis: (calc for C21H30ClIrNO: C 50.45, H 6.27, N 2.35; found C 50.41, H 6.14, N 2.42. Crystal data [CCDC no. 141034]; C18H18IrClNO (Ir2 + 2 CHCl3), M = 681.91, monoclinic, P21/c, a = 12.3262(2), b = 16.4094(3) Å, c = 16.41000(3) Å, α = 92.28631(11)°, V = 3315.84(10) Å3, Z = 4, dcalc = 1.727 g/cm3, T = 150 K, 66 209 reflections collected, 7585 independent reflections (Rint = 0.1312), final R1 = 0.0422, final wR2 = 0.0989, Gof F = 1.010.

1H NMR (400 MHz, CDCl3); δ = 8.85 (d, J = 8.2 Hz, 1H, Hα), 8.09 (d, J = 8.7 Hz, 1H, Hα), 7.78 (t, J = 7.8 Hz, 1H, Hα), 7.56 (t, J = 7.7 Hz, 1H, Hα), 7.19 (d, J = 8.5 Hz, 1H, Hα), 1.61 (s, 21H, [CH3]2); 13C NMR (100 MHz, CDCl3); δ = 179.7 (Cpyridyl), 144.6 (Cpyridyl), 137.2 (CHquinoline), 132.8 (CHquinoline), 130.5 (CHquinoline), 128.6 (Cquinoline), 127.7 (Cquinoline), 127.0 (Cquinoline), 119.2 (Cquinoline), 86.6 (C); 13C NMR (100 MHz, CDCl3); δ = 7.9 Hz, 1H, Harom), 7.12 (m, 2H, Harom), 1.66 (CH2CH3), 9.8 (CH3C ppyridine), 41.2 (C ppyridine), 11.7 (C ppyridine), 56.7 (CH2CH3), 127.7 (CHphenyl), 127.0 (CHphenyl), 126.8 (CHphenyl), 125.4 (CHphenyl), 123.4 (CHphenyl), 103.9 (C), 88.9 (Cpyridyl), 41.2 (C Cphenyl), 28.9 (CH2CH3), 9.8 (C ppyridine); ESI-MS (+): m/z calculated for C21H30ClIrNO, [M + H]+, 540.1632, 538.1616; found 540.1626, 538.1609; [M – Cl]+, 504.1878, 502.1855; found 504.1865, 502.1845. Elemental analysis: (calc for C21H30ClIrNO: C 50.45, H 6.27, N 2.35; found C 50.41, H 6.14, N 2.42. Crystal data [CCDC no. 141034]; C18H18IrClNO (Ir2 + 2 CHCl3), M = 681.91, monoclinic, P21/c, a = 12.3262(2), b = 16.4094(3) Å, c = 16.41000(3) Å, α = 92.28631(11)°, V = 3315.84(10) Å3, Z = 4, dcalc = 1.727 g/cm3, T = 150 K, 66 209 reflections collected, 7585 independent reflections (Rint = 0.1312), final R1 = 0.0422, final wR2 = 0.0989, Gof F = 1.010.
stirred at 50 °C for 36 h, after which time the solution had turned yellow. MgSO₄ was added, and after stirring for 10 min the solution was filtered and the solvent removed in vacuo to afford an orange oil. The product was dissolved in DCM (1 mL), and diethyl ether was added (20 mL). Upon storage at −20 °C a precipitate formed. The supernatant was removed and the solid dried in vacuo to give an orange powder. Single crystals suitable for X-ray diffraction analysis were grown by solvent evaporation (toluene) at room temperature. Yield: 0.0501 mg (74%).

**NMR (400 MHz, CDCl₃):** δ = 8.63 (d, J = 8.8 Hz, H₃, Hphenyl), 7.96 (d, J = 8.8 Hz, 1H, Hphenyl), 7.79 (m, 2H, Hphenyl), 7.60 (t, J = 7.8 Hz, 1H, Hquinoline), 7.48 (d, J = 8.0 Hz, 2H, Hphenyl), 7.40 (d, J = 8.0 Hz, 2H, Hphenyl), 7.32 (m, 3H, Hphenyl), 7.14 (m, 1H, Hphenyl), 6.98 (d, J = 8.4 Hz, 1H, Hphenyl), 1.61 (s, 15H, [CH₃]), δ = 143.8 (Cquinoline), 151.8 (Carom), 150.0 (Cphenyl), 144.5 (Cphenyl), 135.6 (CHarom), 132.8 (Cphenyl), 130.5 (CHarom), 129.7 (CHarom), 128.8 (CHarom), 127.9 (CHarom), 127.6 (CHarom), 127.4 (CHarom), 127.1 (Cphenyl), 126.6 (Cphenyl), 123.4 (CHarom), 97.1 (C), 84.7 (CCp), 7.40 (d, J = 8.0 Hz, Hphenyl), 7.32 (m, 3H, Hphenyl), 7.14 (m, 1H, Hphenyl), 6.98 (d, J = 8.4 Hz, 1H, Hphenyl), 1.61 (s, 15H, [CH₃]),

**1H NMR sample tubes. NaIO₄ (0.1 mmol) in 0.2 mL of D₂O, EBS (0.02 mmol) in 0.2 mL of H₂O, and BuOH (0.1 mL) were added to the NMR tube. After a background spectrum was taken, the [Ir] precatalyst was added (2 μmol) and periodic 1 H spectra collection started. The time between the addition of [Ir] and the first scan was recorded and incorporated into the kinetic data.

**Additional NaIO₄.** Initial reaction was carried out at 0.04 mmol EBS, 0.2 mmol NaIO₄, 0.2 μmol, 1 mol% [Ir] at pH 7, 25 °C in 4:1 H₂O/BuOH solvent mixture, and the NMR tube was left at room temperature for 200 min. H NMR spectra were recorded to check the reaction had plateaued before a second addition of NaIO₄ was made (a further 0.2 mL of 1 M solution = another 0.2 mmol) and periodic 1H spectra collection started.

**Water Oxidation.** In situ oxygen evolution data were collected using a Hansatech Oxigraph Plus system with a DW2/2 Clark-type electrode chamber (with temperature control and magnetic stirring) measuring dissolved O₂ in solution. The electrode was prepared with 0.1 M KCl electrolyte under a PTFE membrane and spacer paper, and the instrument was zeroed with 10 μM NaIO₄ solution in H₂O (2 mL) thoroughly degassed with argon. Oxygen evolution data were collected under the exact same conditions as used for the CH oxidation (200 mM NaIO₄, 40 mM EBS, 1 mol% [Ir] in BuOH/H₂O/D₂O (1:2:2); with initiation by addition of [Ir] (120 μL of a 5 mM solution of [Ir] in H₂O/20% BuOH).

All experiments were conducted at 25 °C, with data collected at 10 Hz, and run in triplicates with initial rates derived from the average.

### ASSOCIATED CONTENT

#### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organomet.7b00492.

Further experimental and analytical data including NMR spectra, additional UV–vis plots, and crystallographic details (PDF)

### Accession Codes

CCDC 1413039–1413044 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

### AUTHOR INFORMATION

**Corresponding Author**
*E-mail: u.hintermair@bath.ac.uk.*

**ORCID**

Ulrich Hintermair: 0000-0001-6213-378X

### Notes

The authors declare the following competing financial interest(s): U.S. Patent Application Number 14/317,906 by U.H. et al. contains intellectual property described in this article.

### ACKNOWLEDGMENTS

This work was supported by a Research Grant from the Royal Society (Y0603) and the EPSRC Centre for Doctoral Training in Sustainable Chemical Technologies (EP/L016354/1). U.H. thanks the Centre for Sustainable Chemical Technologies for a Whorrod Research Fellowship. The authors would like to thank Prof. Frank Marken and Dr. Petra Cameron (University of...
Bath) as well as Dr. Robert Potter (Johnson Matthey) for their support and assistance with this project.

REFERENCES

(1) White, M. C. Science 2012, 335, 807–809.
(2) Dick, A. R.; Sanford, M. S. Tetrahedron 2006, 62, 2439–2463.
(3) Gunay, A.; Theopold, K. H. Chem. Rev. 2010, 110, 1060–1081.
(4) Cook, G. K.; Mayer, J. M. J. Am. Chem. Soc. 1994, 116, 1855–1868.
(5) Cook, G. K.; Mayer, J. M. J. Am. Chem. Soc. 1995, 117, 7139–7156.
(6) Murahashi, S.-I.; Zhang, D. Chem. Soc. Rev. 2008, 37, 1490–1501.
(7) Zhou, M.; Crabtree, R. H. Chem. Soc. Rev. 2011, 40, 1875–1884.
(8) Suzuki, T. Chem. Rev. 2011, 111, 1825–1845.
(9) Borovik, A. S. Chem. Soc. Rev. 2011, 40, 1870–1874.
(10) Bordeaux, M.; Galanou, A.; Drone, J. Angew. Chem., Int. Ed. 2012, 51, 10712–10723.
(11) Feng, J.-B.; Wu, X.-F. Appl. Organomet. Chem. 2015, 29, 63–86.
(12) Yeung, C. S.; Dong, V. M. Chem. Soc. Rev. 2011, 41, 1215–1292.
(13) Meyer, T. J.; Huynh, M. H. V. Inorg. Chem. 2003, 42, 8140–8160.
(14) Lindhorst, A. C.; Haslinger, S.; Kühn, F. E. Chem. Commun. 2015, 51, 17193–17212.
(15) Engelmann, X.; Monte-Pérez, I.; Ray, K. Angew. Chem., Int. Ed. 2016, 55, 7632–7649.
(16) Das, B.; Al-Hunaiti, A.; Haukka, M.; Demeshko, S.; Meyer, S.; Shteiman, A. a.; Meyer, F.; Repo, T.; Nordlander, E. Eur. J. Inorg. Chem. 2015, 2015, 3590–3601.
(17) Talsi, E. P.; Ottenbacher, R. V.; Bryliakov, K. P. J. Organomet. Chem. 2015, 793, 102–107.
(18) Kudrik, E. V.; Afanasiev, P.; Alvarez, L. X.; Dubourdeaux, P.; Clémentey, M.; Latour, J.-M.; Blondin, G.; Bouchu, D.; Albrieux, F.; Nefedov, S. E.; Sorokin, A. B. Nat. Chem. 2012, 4, 1024–1029.
(19) Wu, X.; Seo, M. S.; Davis, K. M.; Lee, Y.; Chen, J.; Cho, K.; Pushkar, Y. N.; Nam, W. J. Am. Chem. Soc. 2011, 133, 20088–20091.
(20) Ray, K.; Pfaff, F. F.; Wang, B.; Nam, W. J. Am. Chem. Soc. 2014, 136, 13942–13958.
(21) Garcia-Bosch, I.; Codolà, Z.; Prat, I.; Ribas, X.; Lloret-Fillol, J.; Costas, M. Chem. - Eur. J. 2012, 18, 13269–13273.
(22) Zhou, M.; Schley, N. D.; Crabtree, R. H. J. Am. Chem. Soc. 2010, 132, 12550–12551.
(23) Zhou, M.; Hintermair, U.; Hashiguchi, B. G.; Parent, A. R.; Hashmi, S. M.; Elimelech, M.; Breddariolli, M.; Brudvig, G. W.; Crabtree, R. H. Organometallics 2013, 32, 957–965.
(24) Graeupner, J.; Hintermair, U.; Huang, D. L.; Thomsen, J. M.; Takase, M.; Campos, J.; Hashmi, S. M.; Elimelech, M.; Brudvig, G. W.; Crabtree, R. H. Organometallics 2013, 32, 5384–5390.
(25) Thomsen, J. M.; Huang, D. L.; Crabtree, R. H.; Brudvig, G. W. Dalt. Trans 2015, 44, 12452–12472.
(26) Hull, J. F.; Balcells, D.; Blakemore, J. D.; Incarvito, C. D.; Eisenstein, O.; Brudvig, G. W.; Crabtree, R. H. J. Am. Chem. Soc. 2009, 131, 8730–8731.
(27) Huang, D. L.; Beltrán-Sueto, R.; Thomsen, J. M.; Hashmi, S. M.; Materna, K. L.; Sheehan, S. W.; Mercado, B. Q.; Brudvig, G. W.; Crabtree, R. H. Inorg. Chem. 2016, 55, 2427–2435.
(28) Sheehan, S. W.; Thomsen, J. M.; Hintermair, U.; Crabtree, R. H.; Brudvig, G. W.; Schmuttenmaer, C. A. Nat. Commun. 2015, 6, 6469.
(29) Zhou, M.; Balcells, D.; Parent, A. R.; Crabtree, R. H.; Eisenstein, O. ACS Catal. 2012, 2, 208–218.
(30) Betley, T. A.; Wu, Q.; Van Voorhis, T.; Nocera, D. G. Inorg. Chem. 2008, 47, 1849–1861.
(31) Blakemore, J. D.; Schley, N. D.; Balcells, D.; Hull, J. F.; Olack, G. W.; Incarvito, C. D.; Eisenstein, O.; Brudvig, G. W.; Crabtree, R. H. J. Am. Chem. Soc. 2010, 132, 16017–16029.
(32) Crabtree, R. H. J. Chem. Soc. Dalt. Trans. 2007, 2437–2450.
(33) Dau, H.; Limberg, C.; Reier, T.; Risch, M.; Roggan, S.; Strasser, P. ChemCatChem 2010, 2, 724–761.