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Cp* Iridium Precatalysts for Selective C–H Oxidation with Sodium Periodate As the Terminal Oxidant

Meng Zhou,^{†,⊥} Ulrich Hintermair,[†] Brian G. Hashiguchi,[‡] Alexander R. Parent,[†] Sara M. Hashmi,[§] Menachem Elimelech,^{*,§} Roy A. Periana,^{*,‡} Gary W. Brudvig,^{*,†} and Robert H. Crabtree^{*,†}

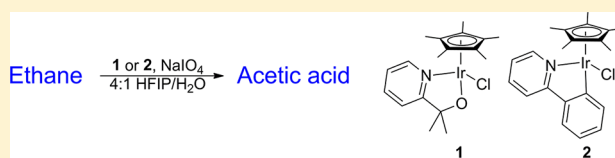
[†]Department of Chemistry and Energy Sciences Institute, Yale University, P.O. Box 208107, New Haven, Connecticut 06520, United States

[‡]The Scripps Energy & Materials Center, Department of Chemistry, The Scripps Research Institute, Jupiter, Florida 33458, United States

[§]Department of Chemical and Environmental Engineering, Yale University, P.O. Box 208286, New Haven, Connecticut 06520, United States

S Supporting Information

ABSTRACT: Sodium periodate (NaIO₄) is shown to be a milder and more efficient terminal oxidant for C–H oxidation with Cp*Ir (Cp* = C₅Me₅) precatalysts than ceric(IV) ammonium nitrate. Synthetically useful yields, regioselectivities, and functional group tolerance were found for methylene oxidation of substrates bearing a phenyl, ketone, ester, or sulfonate group. Oxidation of the natural products (–)-ambroxide and sclareolide proceeded selectively, and retention of configuration was seen in *cis*-decalin hydroxylation. At 60 °C, even primary C–H bonds can be activated: whereas methane was overoxidized to CO₂ in 39% yield without giving partially oxidized products, ethane was transformed into acetic acid in 25% yield based on total NaIO₄. ¹⁸O labeling was demonstrated in *cis*-decalin hydroxylation with ¹⁸OH₂ and NaIO₄. A kinetic isotope effect of 3.0 ± 0.1 was found in cyclohexane oxidation at 23 °C, suggesting C–H bond cleavage as the rate-limiting step. Competition experiments between C–H and water oxidation show that C–H oxidation of sodium 4-ethylbenzene sulfonate is favored by 4 orders of magnitude. *In operando* time-resolved dynamic light scattering and kinetic analysis exclude the involvement of metal oxide nanoparticles and support our previously suggested homogeneous pathway.



INTRODUCTION

Two types of selective metal-catalyzed oxidation of strong, unactivated C–H bonds have been reported. One involves the formation of a hydridometal-carbyl or a metal-carbyl intermediate by a metal-centered C–H activation pathway^{1–11} (pathway 1 in Figure 1), while the other proceeds through a high-valent metal oxo¹² species via an oxidant activation pathway (pathway 2 in Figure 1).^{13–20}

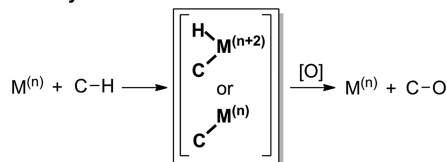
The majority of C–H oxy-functionalization reactions via C–H activation in the literature utilize a directing group to achieve useful regioselectivity.^{21–23} Methyl and sp² C–H groups can be

oxidized in this way, but examples of selective methylene and methine oxidation are rare.^{21,24} Useful regioselectivity via C–H activation without a directing group has been realized for the oxidation of sp² C–H bonds, but not for aliphatic substrates.²¹

Conversely, C–H oxidation involving oxidant activation has proven effective for various aliphatic C–H bonds.^{13,14,25–31} In alkane oxidation, selectivity is typically set by the C–H bond strength, where reactivity increases as methyl ≪ methylene < methine. However, this trend can be overcome through a molecular recognition unit that orients the substrate to steer oxidation selectivity in a biomimetic approach.^{32–37} Selective methylene over methine oxidation may also be achieved via catalyst design.^{38,39} Aliphatic C–H oxidation in the presence of a functional group can be applied in organic synthesis, but it is not yet well-developed.^{40–42}

Selective methane oxidation^{43–47} by metal oxo species is rare. It is expected that the reaction, if occurring at all, would yield highly oxidized products such as CO₂ due to preferential oxidation of the initial products (i.e., methanol, formaldehyde, and formic acid), all having weaker C–H bonds than methane.⁴⁸ However, total oxidation of methane to CO₂,

Pathway 1: C–H Activation



Pathway 2: Oxidant Activation

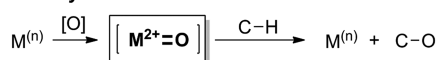


Figure 1. Two types of mechanisms for selective C–H oxidation.

Received: December 24, 2012

when driven electrochemically, is a key process in methane fuel cells.^{49,50}

BACKGROUND

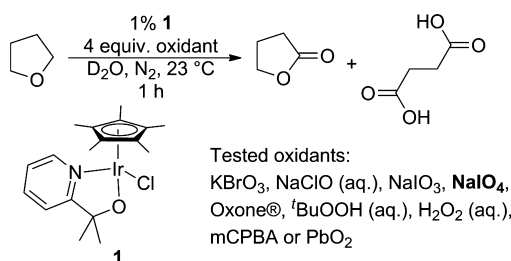
We recently reported that Cp*Ir complexes (Cp* = C₅Me₅) catalyze *cis*-decalin hydroxylation with retention of configuration at the methine carbon. H₂O served as source of oxygen and ceric(IV) ammonium nitrate ([NH₄]₂[Ce^{IV}(NO₃)₆], CAN) as a one-electron oxidant.⁵¹ The near-complete stereoretention with *cis*-decalin ruled out a free radical mechanism because the fast isomerization of *cis*-9-decyl radical to *trans*-9-decyl radical (>10⁸ s⁻¹) would have resulted in loss of stereochemistry if a free radical intermediate was formed by hydrogen atom abstraction. A high-valent Ir^V oxo intermediate, formed by successive oxidation of an Ir^{III} aqua complex, was proposed as the active oxidant.^{52–56} Further experimental and DFT computational studies supported the idea that a high-valent Ir^V oxo complex can give *cis*-decalin hydroxylation in the singlet state *via* a stereoretentive direct oxene insertion rather than an oxyl radical rebound pathway.⁵⁷

Using the strongly oxidizing and highly acidic CAN reagent, the reaction suffered from low yields and limited substrate scope due to background oxidation by CAN, which can unselectively oxidize both substrate and product.⁵⁷ The varying degree of unselective overoxidation complicated kinetic analyses, and co-precipitation of ceria prohibited methods for testing catalyst homogeneity by dynamic light scattering (DLS). We thus looked for an alternative oxidant in order to increase the synthetic efficiency of the catalytic system and make it more amenable to mechanistic studies.

RESULTS AND DISCUSSION

Oxidant Screening. Water-soluble oxidants⁵⁸ KBrO₃, NaClO(aq), NaIO₃, NaIO₄, oxone, ^tBuOOH(aq), H₂O₂, and mCPBA, as well as heterogeneous Pb^{IV}O₂, were tested in the oxidation of tetrahydrofuran (THF) in D₂O with water-soluble precatalyst **1** (Scheme 1 and Supporting Information). The

Scheme 1. Evaluation of Oxidants with Complex 1



product identity was determined and yield measured by ¹H NMR spectroscopy without workup (Table 1). We chose THF oxidation as the benchmark reaction for screening oxidants because it dissolves in D₂O and is very reactive toward C–H oxidation, as reported in our previous work with Cp*Ir and CAN, allowing relatively rapid screening.

NaIO₄, recently found by Parent et al.^{59–61} to be effective for driving water oxidation with Cp*Ir precatalysts, is effective as a terminal oxidant for C–H oxidation of THF catalyzed by **1**. The reaction gives γ -butyrolactone in 41% yield and succinic acid in 33% yield. All other oxidants failed to drive the desired chemistry, giving <1% yield of products. Importantly, no

Table 1. Oxidation of THF with NaIO₄^a

yield ^b (γ -butyrolactone)	yield ^b (succinic acid)	RSM ^c	mass balance ^d
41%	33%	7%	81%

^aConditions: Precatalyst **1** (0.006 mmol, 1% catalyst loading), THF (0.6 mmol, 1 equiv, limiting reagent), 4 equiv of NaIO₄ (2.4 mmol) in 10 mL of D₂O under N₂ at 23 °C for 1 h. Product analysis was carried out by ¹H NMR spectroscopy using an internal standard. ^bYield = mole of product/mol of total starting material. ^cRSM = recovered unreacted starting material. ^dMass balance = (mole of total products + mole of recovered unreacted starting material)/mol of total starting material.

background reaction was observed with NaIO₄ in the absence of a precatalyst even with the most activated substrate, THF.

We therefore focused on NaIO₄ as the most promising oxidant. Accordingly, NaIO₄ was next tested in *cis*-decalin hydroxylation catalyzed by **1**. With **1** in 4:1 acetone/H₂O (Scheme 2 and entry 1 of Table 2), *cis*-decalin hydroxylation

Scheme 2. *cis*-Decalin Hydroxylation with Complex 1 or 2

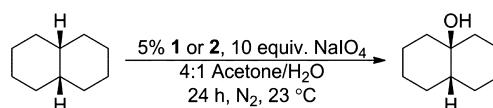


Table 2. *cis*-Decalin Hydroxylation with Complex 1 or 2^a

Entry	Precatalyst	Yield ^b (<i>cis</i> -decalol)	Ratio ^c (<i>cis</i> / <i>trans</i>)	RSM	Mass balance
1		62%	22:1	24%	86%
2		64%	36:1	10%	74%

^aConditions: *cis*-Decalin (0.3 mmol, limiting reagent), NaIO₄ (3 mmol, 10 equiv), at 23 °C under N₂ with **1** or **2** (0.015 mmol, 5% catalyst loading), in 4:1 acetone/H₂O (10 mL). ^bYield = mole of *cis*-decalol/mol of total starting material. ^cRatio obtained from calibrated GC-FID analysis.

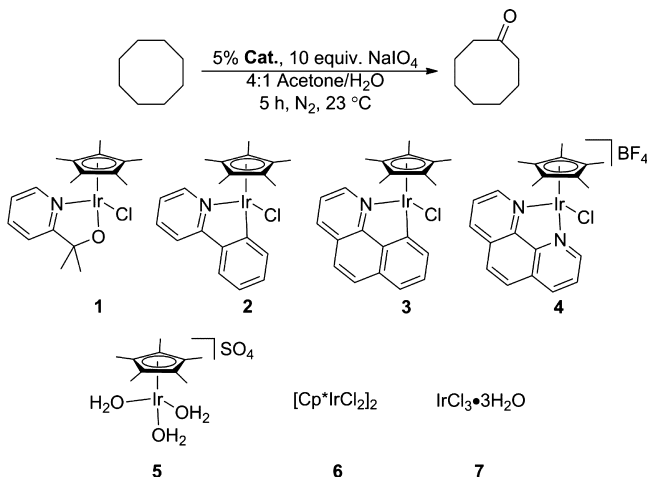
gave *cis*-decalol in 62% yield and a 22:1 *cis*/*trans* ratio after 24 h at 23 °C, showing that NaIO₄ is able to drive the oxidation of an unactivated C–H bond. Similar to previous results with CAN, the reaction proceeds with retention of configuration at the methine carbon.⁵¹ The reaction mixture remained near-neutral (pH 6 by pH paper) through to completion, showing that the current system is much less acidic than in the case of CAN, where the solution pH is typically below 2. Again, no background reaction was observed for *cis*-decalin hydroxylation with NaIO₄ in the absence of **1**, and the starting decalin was recovered quantitatively. Cp*Ir(*o*-phenylpyridine)Cl (**2**), like **1**, catalyzed *cis*-decalin hydroxylation with retention of configuration, giving *cis*-decalol in 64% yield and a 36:1 *cis*/*trans* ratio (Scheme 2 and entry 2 of Table 2).

¹⁸O labeling experiments could not determine whether H₂O or NaIO₄ serves as a source of oxygen because of the rapid oxygen exchange between periodate and H₂O in aqueous solution.⁶² This exchange means that the reaction could be

useful for pharmaceuticals in bringing about ^{18}O labeling of organic molecules.^{51,63} Indeed, *cis*-decalin hydroxylation using **1** and ^{16}O - NaIO_4 in $^{18}\text{OH}_2$ gives 95% ^{18}O -labeled *cis*-decalol (Supporting Information).

Cyclooctane Oxidation. Oxidation of the methylene groups in cyclooctane (C–H bond strength: 95.7 kcal/mol⁶⁴) was carried out with NaIO_4 and Ir precatalysts **1** to **7** (Scheme 3 and Table 3). Shorter reaction times (5 h) were used than for

Scheme 3. Precatalyst Screening in Cyclooctane Oxidation



cis-decalin hydroxylation (24 h), because it allowed more rapid assessment of precatalyst activity at an early stage of the reaction, where overoxidation (see below) has less effect on the yields. Oxidation-resistant solvents were required for this work. Satisfactory mixtures for cyclooctane oxidation were 4:1 acetone/ H_2O , 4:1 MeCN/ H_2O , and 4:1 $t\text{BuOH}/\text{H}_2\text{O}$.

Complex **1** gave 31% yield of cyclooctanone with 10 equiv of NaIO_4 (Table 3); fewer equivalents of oxidant gave lower yields. Side product analysis after 24 h, where cyclooctanone was produced in 54% yield, showed traces of two regioisomeric overoxidation products, 1,4-cyclooctanedione (4%) and 1,5-cyclooctanedione (2%) (Supporting Information). Precatalyst **2** was also active, giving 31% yield of cyclooctanone. Precatalyst **3** was less active than **1** or **2**, giving 13% yield of cyclooctanone. Cationic complex **4** was much less active, giving only <3% yield of cyclooctanone. Cp^*Ir complexes **5** and **6** gave poor yields of cyclooctanone: 3% and 6%, respectively. The lower activity of **5** and **6**, both lacking chelate ligands, could result from the faster oxidative decomposition to give inactive metal oxide nanoparticles, shown by time-resolved DLS⁶⁵ and electrochemical quartz crystal nanobalance analysis⁶⁶ in our related studies. Surprisingly, the simple complex $\text{IrCl}_3\cdot 3\text{H}_2\text{O}$ (**7**) was also active as a precatalyst for cyclooctane oxidation, giving 17% yield of cyclooctanone. This is reminiscent of C–H oxidation catalyzed by $\text{RuCl}_3\cdot 3\text{H}_2\text{O}$ with NaIO_4 in aqueous-organic solvent, where

RuO_4 is the active species formed *in situ*.⁶³ We do not yet know what species is involved in this case, but further work is currently being carried out on this system.

The progress of the reaction of cyclooctane to give cyclooctanone with the most effective precatalysts **1** and **2** was monitored over time (Figure 2 and Supporting

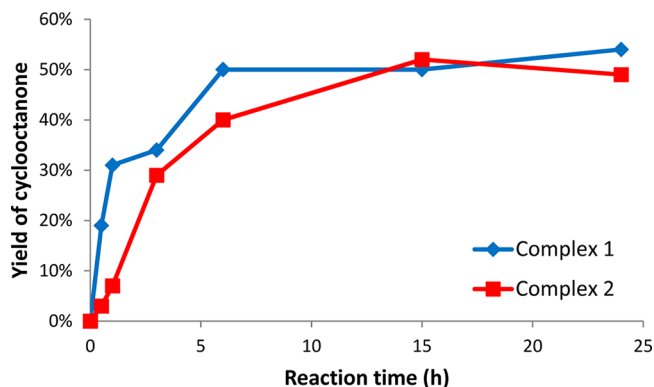


Figure 2. Monitoring cyclooctane oxidation over time (lines are drawn to guide the eye). Conditions: cyclooctane (0.372 mmol, limiting reagent), **1** or **2** (0.022 mmol, 6% catalyst loading), NaIO_4 (3.72 mmol, 10 equiv), in 4:1 acetone/ H_2O (10 mL), at 23 °C under N_2 .

Information). Higher concentrations of precatalyst and reagents were used than those in precatalyst screening (Table 3) so that the yields in the initial stage of the reaction are higher and can be more accurately measured and compared. With **1**, the reaction started off quickly, giving 19% yield of product in 30 min. After 6 h the reaction had essentially stopped at cyclooctanone yields of 50%. With **2**, the reaction started off slowly, giving only 3% yield after 30 min, but progressively caught up with the case of **1**. After 3 h, 29% cyclooctanone was produced, and after 15 h a maximum yield of 52% was obtained. Overall, the two precatalysts gave very similar yields after 15 h, but the initial rate for **1** clearly exceeded that for **2**. The absence of an induction period seen with **1** could perhaps be the result of more facile chloride dissociation⁶⁶ aided by π donation from the oxygen lone pair adjacent to the metal.⁶⁷

Cyclooctanone Oxidation. Detection of trace levels of 1,4- and 1,5- cyclooctanedione byproducts in the cyclooctane oxidation with **1** led us to examine the oxidation of cyclooctanone (Scheme 4). Functional group tolerance is important for C–H oxidation to be useful in organic synthesis.^{63,68}

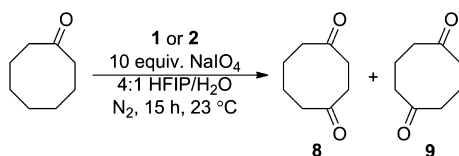
Initially, cyclooctanone oxidation in 4:1 acetone/ H_2O was inefficient (entry 1 in Table 4), giving only 7% yield of 1,4-cyclooctanedione (**8**) and 6% of 1,5-cyclooctanedione (**9**) with **1**. Switching to aqueous hexafluoroisopropanol (4:1 HFIP/ H_2O) as solvent significantly improved the yield to 17% of **8** and 19% of **9** (entry 2). No 1,2- or 1,3-regioisomers were detected. It is unclear why HFIP/ H_2O improves the yield, but

Table 3. Yield of Cyclooctanone in Cyclooctane Oxidation^a

	Ir complex						
	1	2	3	4	5	6	7
yield ^b (cyclooctanone)	31%	31%	13%	<3%	3%	6%	17%
							none
							0%

^aConditions: Precatalyst (0.01 mmol, 5% catalyst loading), cyclooctane (2 mmol, limiting reagent), NaIO_4 (2 mmol, 10 equiv) in 4:1 acetone/ H_2O solvent (10 mL), at 23 °C under N_2 for 5 h. ^bYield = mole of cyclooctanone/mol of total starting material, measured by ^1H NMR spectroscopy with an internal standard.

Scheme 4. Cyclooctanone Oxidation

Table 4. Cyclooctanone Oxidation^a

entry	precatalyst	time (h)	yield ^b 8	yield ^b 9	RSM	mass balance ^d
1 ^c	1	15	7%	6%	65%	78%
2 ^c	1	14	17%	19%	37%	73%
3	2	15	20%	20%	25%	65%
4 ^{e,f}	2	15	27%	28%	11%	66%
5	6	14	2%	1%	76%	79%

^aConditions unless noted otherwise: cyclooctanone (0.34 mmol, limiting reagent), precatalyst (0.017 mmol, 5% catalyst loading), NaIO₄ (3.4 mmol, 10 equiv), in 4:1 HFIP/H₂O (10 mL), at 23 °C under N₂ for ~15 h. ^bYield = mole of 8 or 9/mol of total starting material. ^cSolvent: 4:1 acetone/H₂O (10 mL). ^dMass balance = % yield of 8 and 9 + % RSM. ^eNo 1,2- or 1,3-cyclooctanedione was detected. ^f2 (10% catalyst loading) was used. No significant increase in product yield was found by GC-FID after 16 h.

HFIP has previously been shown to be an effective solvent in oxidation⁶⁹ and cycloaddition⁷⁰ reactions.

The reaction mixture with HFIP has a lower apparent pH of 3.5 as a result of the acidic HFIP hydroxyl group (pK_a = 9.3).⁷¹ Despite being a secondary alcohol, HFIP is quite oxidation resistant due to the two polar trifluoromethyl groups adjacent to the C–H. This was demonstrated in an independent experiment, where oxidation of aqueous HFIP by 1 and NaIO₄ was studied by ¹⁹F NMR spectroscopy; only 0.2% of the total HFIP was oxidized to hexafluoroacetone (HFA) under conditions similar to those for C–H oxidation (Supporting Information). Methyl(trifluoromethyl)dioxirane, prepared from methyltrifluoromethylacetone, a compound related to HFA, is a known reagent for stoichiometric alkane oxidation.⁷² However, no cyclohexane oxidation was found for HFA with NaIO₄ in 1:1 HFIP/D₂O in the absence of 1, excluding the possibility of HFA being solely involved in alkane oxidation. *cis*-Decalin hydroxylation with 1 and NaIO₄ in 4:1 HFIP/H₂O again proceeded with retention of configuration, ruling out the possibility that free radical intermediates could be favored in this solvent.

Precatalyst 2 also carried out cyclooctanone oxidation effectively, giving 8 and 9 in similar yields to those with 1 (entry 3). Raising the catalyst loading of 2 from 5% to 10% gave further yield improvements without changing the regioselectivity, giving 27% yield in 8 and 28% yield in 9 (entry 4). 8, which can be readily separated from 9 by column chromatography, contains a 1,4-dione moiety useful for asymmetric transannular aldolization. In contrast to our one-step procedure, this compound (8) was previously prepared only via a multistep synthesis.⁷³ No 1,3-cyclooctanedione was found in the product mixture, although it could have been formed and escaped detection via overoxidation. NaIO₄ has been reported to oxidize 1,3-cyclohexanedione to glutaric acid and CO₂ as final products.⁷⁴ Cp*Ir complex 6, which lacks a chelate ligand, gave a very poor yield of diones (entry 5).

Results from cyclooctanone oxidation show the particular advantage of using NaIO₄ as a milder terminal oxidant than CAN, because an otherwise identical Cp*Ir-catalyzed oxidation

with CAN gave an unselective reaction without significant dione formation.⁵⁷

Methylene Oxidation. In view of our good yields in cyclooctane and cyclooctanone oxidation, we applied the optimized system (1 or 2 and NaIO₄ in 4:1 HFIP/H₂O or neat D₂O) to other substrates (Table 5). Due to the different C–H bond strength in the substrates tested, the reaction conditions varied. Reactive substrates such as *n*-butanol and sodium 4-ethylbenzene sulfonate (EBS) were oxidized under milder conditions than substrates containing stronger C–H bonds, such as methane, ethane, and 2-heptanone. Water-insoluble complex 2 gave higher yields (for example, entry 6 vs 7 in Table 5) than 1, but water-soluble complex 1 had to be used for reactions carried out in neat D₂O.

n-Butanol was oxidized to *n*-butyric acid in 94% yield in D₂O (entry 1 in Table 5). The chemospecific oxidation of *n*-butanol to *n*-butyric acid showed that the reaction probably did not proceed via a metal-centered C–H activation pathway well-known for Ir.⁴ Instead the result is more consistent with our proposal that an Ir^V oxo intermediate serves as active oxidant. An alcohol oxidation that may possibly proceed via a C–H activation pathway has been reported with a Pt catalyst, where oxidation of ethanol gave ethylene glycol as one of the products.⁷⁵ Water-soluble EBS was selectively and efficiently oxidized, and a 99% yield of sodium 4-acetylbenzene sulfonate product was detected with 99% mass balance after only 1 h (entry 2). In control studies, neither light nor air had significant effects on the yield of EBS oxidation (Supporting Information). Ethylbenzene (benzylic C–H bond strength: 85.4 kcal/mol⁶⁴) oxidation in 4:1 acetone/H₂O gave acetophenone in 49% yield without detectable arene oxidation (entry 3), contrary to the case of RuO₄.⁶³ Aqueous HFIP, a more effective solvent than aqueous acetone in cyclooctanone oxidation, gave a lower yield of acetophenone in this case, although carried out under otherwise similar conditions, possibly due to the further oxidation of acetophenone.

2-Heptanone, bearing relatively unreactive methylene C–H bonds, nevertheless gave a 44% yield of 2,6-dione and a 18% yield of 2,5-dione (entry 4) but no other regioisomers. We used 10% catalyst loading in this reaction instead of 5% as in entries 2 and 3. Using 5% catalyst loading in this reaction resulted in significantly lower product yields (Supporting Information). The regioselectivity observed here (2.4:1) differs significantly from that seen in Na₂S₂O₈ oxidation of the same substrate. The Na₂S₂O₈ oxidation^{76,77} gave a ratio of 1.15:1 of 2,6- and 2,5-heptanedione products with Fe^{II} as an additive and a ratio of 1:1.4 without Fe^{II}, where the regioselectivity is the opposite of that with 2 and NaIO₄. For this reaction an intramolecular free radical mechanism was proposed, which should not occur with our nonradical Cp*Ir/NaIO₄ system, consistent with the different product distribution observed. 1,5-Diones are common synthetic intermediates that are conventionally made via C–C bond formation strategies⁷⁸ instead of direct C–H oxidation. Methyl hexanoate oxidation gave methyl 5-oxo-hexanoate and methyl 4-oxo-hexanoate in 61% and 21% yield, respectively, with quantitative mass balance (entry 5). The regioselectivity, 2.9:1 in favor of the 5-isomer, is not much different from the 2.3:1 ratio obtained in a previously described Fe system.⁷⁹

Oxidation of Light Alkanes. Previous calculations suggesting that methane oxidation by the intermediate [Cp*Ir^V(*o*-phenylpyridine)(O)]⁺ should have an accessible barrier of 24 kcal/mol⁵⁷ prompted us to explore this reaction

Table 5. Additional Substrates Tested^a

Entry	Cp*Ir complex (loading)	NaIO ₄ (equiv.)	Time (h)	Substrate	Product (yield ^c)	TON ^f	Mass balance ^b
1 ^g	1 (2%)	4	1	<i>n</i> -Butanol	<i>n</i> -Butyric Acid (94%)	47	94%
2 ^g	1 (5%)	10	1		 (99%)	20	99%
3 ⁱ	2 (5%)	10	15	Ethylbenzene	Acetophenone (49%) (44%)	10	77%
4 ^h	2 (10%)	10	15		 (18%) (61%)	6	89%
5 ^h	2 (10%)	10	15		 (21%)	8	100%
6 ^d	2	See footnote d		Methane	Carbon Dioxide (39%)	N/A	N/A
7 ^d	1	See footnote d		Methane	Carbon Dioxide (25%)	N/A	N/A
8 ^d	2	See footnote d		Ethane	Acetic Acid (25%)	3.3	N/A
9 ^d	1	See footnote d		Ethane	Acetic Acid (21%)	2.9	N/A
10 ^e	2	See footnote d		Propane	Acetone (38%)	6.6	N/A
11 ^e	1	See footnote d		Propane	Acetone (29%)	5.3	N/A
12	2	10	15	Cyclohexane	Cyclohexanone (75%)	15	75%

^aConditions unless noted otherwise: substrate (~0.2 mmol, limiting reagent) in 4:1 HFIP/H₂O (10 mL), NaIO₄, at 23 °C under N₂. NaIO₄ equiv are relative to the amount of substrate. ^bMass balance = % total product + % RSM. ^cYield = mole of product/mol of total starting material.

^dConditions: 5.5 mM precatalyst, NaIO₄ (limiting reagent, 50 equiv relative to precatalyst), 300 psi gaseous substrate (excess amount), at 60 °C for 15 h unless otherwise stated. Yield is based on total NaIO₄. ^e110 psi was used; all other conditions are the same as those shown in footnote d. ^fTurnover number (TON) is based on oxidation of first C–H bond. ^gIn D₂O solvent. ^hNo other regioisomers were detected. ⁱSolvent: 4:1 acetone/H₂O (10 mL).

experimentally. Methane, with a C–H bond strength of 105 kcal/mol,⁶⁴ was indeed oxidized with both **1** and **2**, but only to give CO₂ in 25% and 39% yield, respectively, based on NaIO₄ (entries 7 and 6). This result follows the usual pattern of electrophilic C–H bond oxidation, where the weaker C–H bonds of partially oxidized intermediates are preferentially overoxidized to give the completely oxidized product, CO₂. Although no useful partial oxidation products could be obtained from methane oxidation with our Cp*Ir/NaIO₄ system, this result demonstrates that the precatalysts can perform such difficult reactions even under relatively mild conditions.

In contrast, ethane, with a C–H bond strength of 100.5 kcal/mol,⁶⁴ was oxidized to acetic acid, a feedstock chemical, in 21% yield with **1** (entry 9) and 25% yield with **2** (entry 8). These numbers represent turnover numbers of 2.9 ± 0.1 (with **1**) and

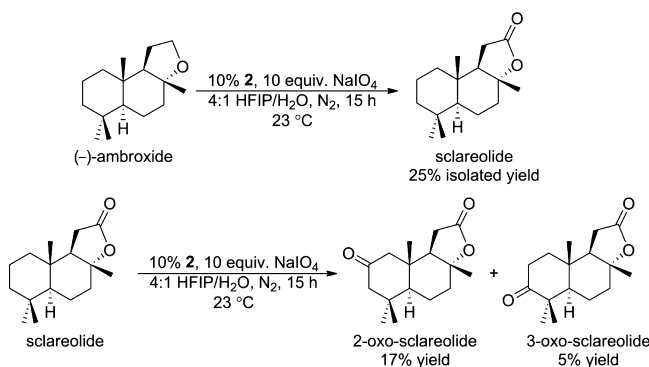
3.3 ± 0.1 (with **2**), respectively. No background reaction occurred without added Ir precatalyst for methane and ethane oxidation. However, with a precatalyst and NaIO₄ in aqueous HFIP and in the absence of a substrate, a small amount of acetic acid was observed (Supporting Information). The acetic acid is believed to originate from oxidation of the Cp* ligand in the precatalysts, and this portion of acetic acid formation has been subtracted in the reported turnover numbers. Propane oxidation (secondary C–H bond strength: 98.1 kcal/mol⁶⁴) gave acetone in 29% yield with **1** (entry 11) and 38% yield with **2** (entry 10), representing 5.3 and 6.6 turnovers, respectively. Cyclohexane (C–H bond strength: 99.5 kcal/mol⁶⁴) oxidation is relatively facile with **2**, giving 75% yield of cyclohexanone (entry 12), a precursor to adipic acid for nylon production.^{80,81}

Complex **1** is also quite effective for catalyzing cyclohexane oxidation, giving 67% yield of cyclohexanone in only 1 h

(Supporting Information). We thus measured the kinetic isotope effect⁸² (KIE) of cyclohexane oxidation with **1** by separate h_{12} -cyclohexane and d_{12} -cyclohexane oxidations. A KIE of 3.0 ± 0.1 was found at 23 °C. This suggests C–H oxidation as the rate-limiting step rather than formation of the high-valent Ir^V oxo intermediate, proposed to be the active oxidant formed prior to the C–H cleavage.

Natural Product Oxidation. We also looked for possible selective oxidations of complex natural products (Scheme 5 and

Scheme 5. Natural Product Oxidation



Supporting Information). No reaction occurred with artemisinin, and 89% unreacted starting material was recovered, in contrast to a previously described Fe system that oxidized the C-10 methine.⁸³ Oxidation of 5-cholestan-3-one was unselective, unlike the case of methyl(trifluoromethyl)dioxirane, where C-25 methine was selectively hydroxylated.⁷² Pregnanedione oxidation was ineffective, and cuparene oxidation was unselective. However, (-)-ambroxide oxidation gave sclareolide in 25% isolated yield with **2**, where an activated C–H α to the oxygen was oxidized. Sclareolide oxidation in turn gave 2-oxo-sclareolide and 3-oxo-sclareolide in 17% and 5% yield, respectively, where the unactivated methylene groups were selectively oxidized in the presence of a lactone and multiple other C–H bonds.

Mechanistic Studies. Whenever organometallic catalysts are subjected to relatively forcing reaction conditions (e.g., irradiation, temperature, pH, or electric or chemical potential), there is a danger of decomposition of the precursor to a heterogeneous material. *In situ* formation of nanoparticles can be very difficult to detect, and only in the most favorable case are they a mere deactivation pathway. More often they are highly reactive and are the true catalysts at work.⁸⁴ We have long been interested in this ambiguity⁸⁵ and have recently been able to confirm the homogeneity of some of our Cp*Ir complexes in water oxidation, both electrode-driven⁶⁶ and with chemical oxidants.⁶⁵ Therefore, we set out to test the present precatalysts under C–H oxidation conditions. We first attempted to investigate the hydroxylation of *cis*-decalin, because the reaction affords important information on the catalyst through the level of stereoretention in the product. Unfortunately, the multiphasic reaction conditions obscured *in situ* analysis, and the extractive workup procedure resulted in moderate mass balances, because polar overoxidation products remained in the aqueous phase and thus escaped detection.

Instead, we decided to take a closer look at the C–H oxidation of the water-soluble substrate EBS with **1** and NaIO₄ in neat H₂O. When the reaction was run at NaIO₄ concentrations of 400–500 mM, clean oxidation to sodium

4-acetylbenzenesulfonate took place with initial rates as high as 1380 h⁻¹ for **1** (23% conversion after 1 min at 1% catalyst loading). No phenylethanol intermediate was ever detected, confirming that alcohol oxidation is much faster than the initial methylene activation. The mass balance was virtually quantitative throughout the reaction (Supporting Information). As observed before, no reaction occurred without Ir precatalyst (16 h at 23 °C) and no overoxidation products formed even after prolonged reaction times (24 h).

In operando time-resolved DLS during the reaction confirmed the homogeneity of the system. No scattering intensity above background was detected over more than 3 h (Figure 3), and

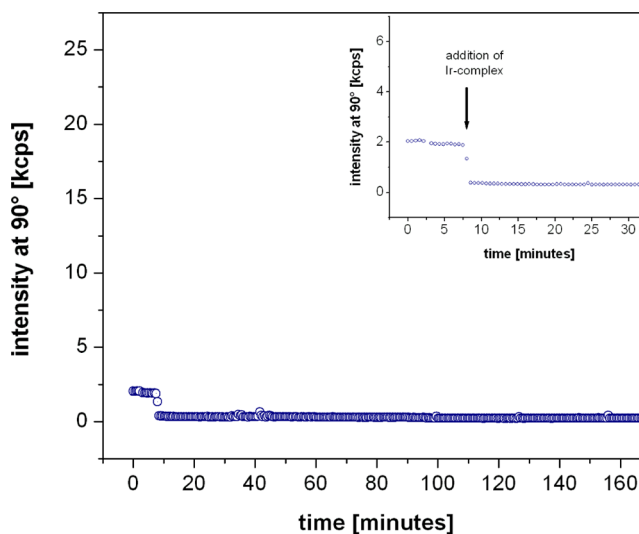


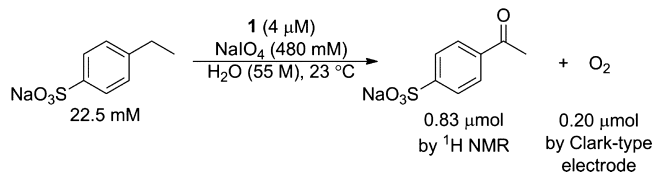
Figure 3. Scattered light intensity profile of a diffusional reaction mixture of complex **1** (0.4 mM), sodium 4-ethylbenzene sulfonate (40 mM), and NaIO₄ (400 mM) in H₂O (5 mL) at 23 °C over time.

the corresponding autocorrelation functions do not exhibit any exponential decay that indicates the presence of particles (resolution limit of 1 nm hydrodynamic diameter) with a detection limit of 10 ppm. This result rules out both the formation and potential involvement of metal oxide nanoparticles in the reaction and is a strong indication that molecular species are performing catalytic C–H oxidation in this case.

As many Cp*Ir complexes, including **1**, are also active precatalysts for water oxidation (WO) with both CAN and NaIO₄,^{52,53} WO is expected to occur as a side reaction during C–H oxidation (CHO) with H₂O as solvent or cosolvent. Although relatively good yields can be obtained for the oxidation of strong C–H bonds (Table 5) in aqueous systems, an excess of NaIO₄ is always needed for achieving high product yields, suggesting that WO consumes at least part of the oxidant. To determine the extent of WO during CHO, we measured the mole numbers of both WO and CHO products with EBS and **1** in H₂O (Scheme 6 and Supporting Information).

After 15 min, sodium 4-acetylbenzenesulfonate and O₂ were detected in $0.83 \pm 0.06 \mu\text{mol}$ (by ¹H NMR spectroscopy) and $0.20 \pm 0.01 \mu\text{mol}$ (by Clark-type electrode) amounts, respectively. Thus, WO indeed occurred during CHO, and at least part of the loss in oxidation efficiency of NaIO₄ with respect to CHO can be attributed to WO. Considering the

Scheme 6. C–H Oxidation vs Water Oxidation at 23 °C



relative substrate concentrations, however, we find that CHO is favored over WO by a factor of 1.0×10^4 .

The much faster CHO and good mass balance in this system, together with confirmed homogeneity, permitted the use of initial rates of formation of sodium 4-acetylbenzenesulfonate for kinetic analysis (Supporting Information). Variation of catalyst loading gave a clear first-order dependence on Ir concentration over 1 order of magnitude (Figure 4), consistent

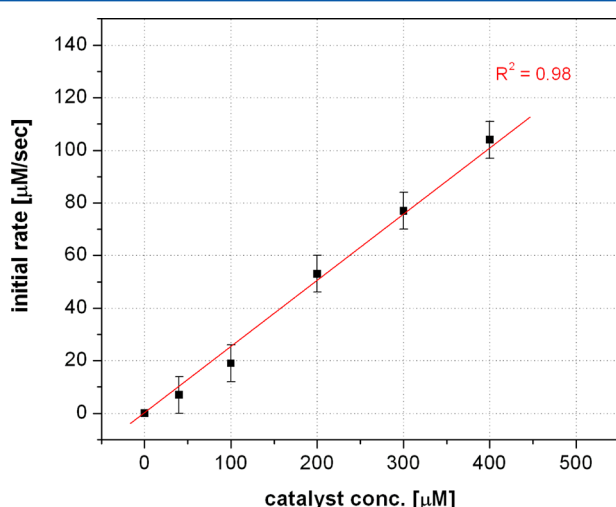


Figure 4. Dependence of initial rates of formation of sodium 4-acetylbenzenesulfonate from sodium 4-ethylbenzenesulfonate (40 mM) with various amounts of complex **1** and NaIO₄ (400 mM) in H₂O (5 mL) at 23 °C (error bars indicate uncertainty of measurement; line is a linear fit without intercept).

with our previously suggested mononuclear pathway. CHO conversions after longer reaction times, however, achieved a maximum of around 100 TON irrespective of the catalyst loading.

On varying the temperature of the reaction with 0.5% of complex **1**, we observed a concave profile in the Eyring plot. Below 23 °C, the initial rate of CHO consistently decreased with an apparent activation enthalpy of 7 ± 0.6 kcal/mol (Figure 5) and activation entropy of -26.5 ± 2.5 cal/mol, giving an activation free energy of 14.8 ± 0.6 kcal/mol at 295 K. This low barrier is consistent with the large preference for CHO over WO seen in this system and might in part be the result of the moderate C–H bond strength in the EBS substrate. When the reaction was carried out above 23 °C, however, the initial rate of CHO did not increase any further and fewer turnovers were reached at longer reaction times (60 TON at 60 °C vs 100 TON at and below 23 °C after 3 h).

We interpret this behavior as overriding WO activity at higher temperatures, as vigorous bubble formation was seen in these experiments immediately on mixing, but alternative explanations such as periodate or even catalyst decomposition cannot be ruled out with certainty at this point.

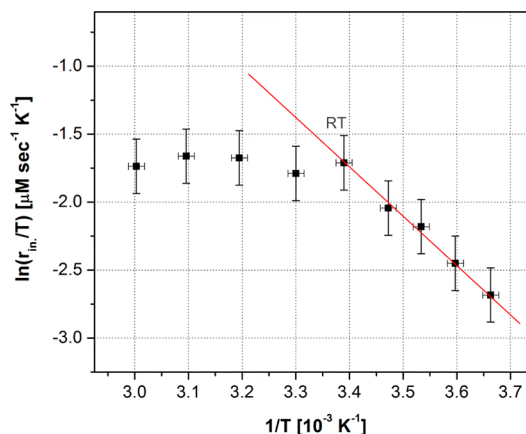


Figure 5. Eyring plot of sodium 4-ethylbenzenesulfonate (40 mM) oxidation with complex **1** (0.2 mM) and NaIO₄ (400 mM) in H₂O (error bars indicate uncertainty of measurement; line is a linear fit of the 0–23 °C region with $R^2 = 0.99$).

CONCLUSION

Cp*Ir complexes are shown to catalyze the oxidation of strong C–H bonds with NaIO₄ as a mild and efficient primary oxidant with useful selectivity. The KIE of cyclohexane oxidation suggests the C–H cleavage is rate-determining. *In operando* time-resolved dynamic light scattering experiments showed that no particles larger than 1 nm form during the reaction, confirming catalyst homogeneity. Competition experiments revealed that the C–H oxidation of sodium 4-ethylbenzene sulfonate is faster than water oxidation by 4 orders of magnitude. Kinetic studies gave a first-order rate dependence in precatalyst concentration as well as a low activation free energy of 14.8 kcal/mol in sodium 4-ethylbenzene sulfonate oxidation. The negative activation entropy of the reaction together with first-order rate dependence on Ir precatalyst and substrate H/D kinetic isotope effect suggest association of the active Ir-oxo species with the C–H bond to be the rate-determining step. The very challenging catalytic C–H oxidation transformations reported here are not well-known for Ir complexes.²⁸ The direct oxidation of strong C–H bonds in the presence of a functional group could be applied in organic synthesis, as an alternative method to C–C bond formation strategies for the synthesis of oxygenates,^{86,87} and the light alkane oxidation reactions are relevant to the energy research, where nonpetroleum fossil fuel could be used as a raw material for feedstock chemical and fuel productions.^{88–90} Given the homogeneity and relatively high activity of the system, ligand variations and mechanistic studies may yield improved Ir complexes for C–H oxidation in the future.

ASSOCIATED CONTENT

Supporting Information

Syntheses of Cp*Ir complexes and procedures for reaction setup, purification, and analysis. This material is available free of charge via the Internet at <http://pubs.acs.org>.

AUTHOR INFORMATION

Corresponding Author

*E-mail: robert.crabtree@yale.edu; gary.brudvig@yale.edu; rperiana@scripps.edu; menachem.elimelech@yale.edu.

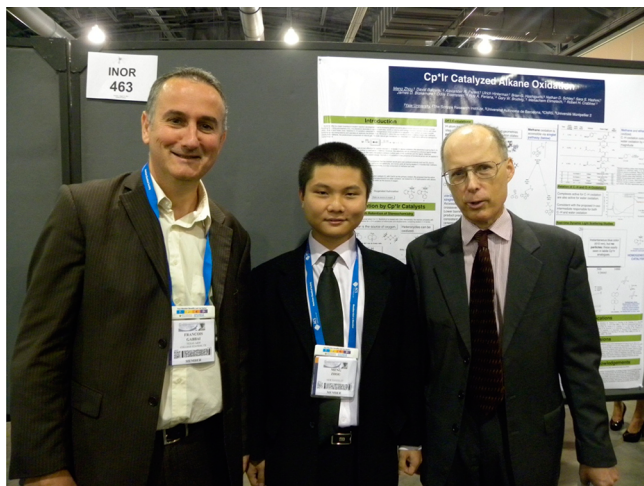
Present Address

[†]Department of Chemistry and Chemical Biology, Rutgers New Brunswick, Busch Campus, 610 Taylor Road, Piscataway, New Jersey 08854, United States.

Notes

The authors declare no competing financial interest.

Biographies



This article is based upon a poster presented by Meng Zhou, Yale University (pictured at center with François P. Gabbaï (left) and John A. Gladysz (right)) and coauthored by David Balcells, Alexander R. Parent, Ulrich Hintermair, Brian G. Hashiguchi, Nathan D. Schley, Sara S. Hashmi, James D. Blakemore, Odile Eisenstein, Roy A. Periana, Gary W. Brudvig, Menachem Elimelech, and Robert H. Crabtree, at the first Organometallics Symposium at the fall 2012 ACS meeting in Philadelphia, Pennsylvania.⁹¹

Meng Zhou, born in Chengdu, China, received his B.S. from Purdue University and performed his undergraduate thesis work with Mark A. Lipton on asymmetric catalysis. He further pursued his interest in catalysis in the lab of Robert H. Crabtree, the corresponding author of this article, working on C–H oxidation at Yale University, where he received his Ph.D. In 2012 he joined the lab of Alan S. Goldman as a postdoctoral associate at Rutgers University. He is interested in catalysis and seeks an academic career in the future.

At Yale since 1977, Bob Crabtree is now Whitehead Professor. He has been an ACS and RSC organometallic chemistry awardee, Baylor medallist, Mond lecturer, Kosolapoff awardee, and Stauffer lecturer, has chaired the ACS Inorganic Division, and is the author of an organometallics textbook. Early work on catalytic alkane C–H activation and functionalization was followed by work on H₂ complexes, dihydrogen bonding, and catalysis for green and energy chemistry. He is an ACS Fellow and a Fellow of the American Academy of Arts & Sciences.

ACKNOWLEDGMENTS

This material is based in part upon work supported by the Center for Catalytic Hydrocarbon Functionalization, an Energy Frontier Research Center funded by the U.S. Department of Energy, Office of Science, Office of Basic Energy Sciences, under Award Number DE-SC0001298 (M.Z., U.H., B.G.H., R.A.P., and R.H.C., C–H oxidation) and by the NSF GRFP and the Division of Chemical Sciences, Geosciences, and Biosciences, Office of Basic Energy Sciences of the U.S. Department of Energy (DE-FG02-07ER15909) (A.R.P. and G.W.B., water oxidation). M.Z. acknowledges the Dox

Fellowship, and U.H. thanks the Alexander von Humboldt Foundation for a Feodor Lynen Research Fellowship, supplemented by a grant from the Yale Institute for Nanoscience and Quantum Engineering. B.G.H. and R.A.P. acknowledge The Scripps Research Institute for funding. We thank Seth B. Herzon, Scott J. Miller, and David S. Spiegel (all Yale University) for helpful discussions, Katalin Barta (Anastas lab, Yale) for use of the GC-FID, and the Herzon lab for using the LC-MS.

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