

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

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General:

All solvents were of commercial grade. Hexafluoroisopropanol (HFIP) (99%) was purchased from Matrix Scientific or Oakwood Chemical. Most reagents were purchased from major commercial sources and used without further purification. NaClO (bleach, NaClO aq. solution, 6% by weight) was purchased from Chlorox. The *cis*-decalin sample used contained 1/82 *trans*-decalin impurity by GC-FID. Heavy oxygen water (97% ^{18}O) was purchased from Aldrich-Sigma. Artemisinin, (-)ambroxide, sclareolide and 5 α -cholestan-3-one were purchased from VWR. Cuparene was purchased from Chromadex and pregnane-3,20-dione was purchased from Santa Cruz Biotechnology. Sodium 4-ethylbenzene sulfonate (EBS) was purchased from Tokyo Chemical Industries. High purity light hydrocarbon gases (methane, ethane and propane) were purchased from Praxair and used without further purification. NMR analysis was performed on 400 or 500 MHz Bruker or Varian spectrometers, and chemical shifts were referenced to TMS (tetramethylsilane, 0 ppm) or water-soluble sodium *d*₄-trimethylsilyl propanoate (0 ppm) for ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR analysis. Quantitative ^1H NMR integrations were performed against a known amount of MeNO₂ (12 mg) or sodium *d*₄-trimethylsilyl propanoate (3 mg) as internal standard. Silica gel (230-400 mesh, grade 60) for flash column chromatography and celite (C212-500) were purchased from Fisher Scientific. GC-MS analyses were performed on an Agilent 5973 GC-MS. LC-MS analysis was performed on a Waters UPLC/MS instrument equipped with a reverse-phase C18 column, dual atmospheric pressure chemical ionization (API)/electrospray (ESI) mass spectrometry detector, and photodiode array detector. GC-FID analyses were performed on a Shimadzu GC-2010 Plus. Response factors for the GC-FID analysis were obtained from authentic samples. Methane gas phase analysis was performed on a Shimadzu GC-MS QP2010S equipped with an Agilent HP-Plot Q column. The methane and CO₂ was calibrated against a known concentration of neon in the gas phase.

Syntheses of Cp*Ir Complexes:

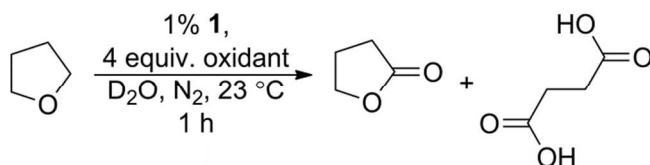
Ir complexes **1**,¹ **2**,² **3**,³ **5**⁵ and **6**⁵ were prepared by following literature procedures. Complex **2** can also be purchased from Strem Chemicals and ABCR (CAS: 945491-51-0).

Synthesis of complex 4: [Cp*IrCl₂]₂ (0.1 mmol, 80 mg) was dissolved in DCM (5 mL) and phenanthroline (0.2 mmol, 36 mg) was added, causing an immediate color change from orange to yellow. The reaction mixture was stirred for 15 minutes at 23 °C, then AgBF₄ (0.2 mmol, 39 mg in 2 mL MeOH) was added. Immediate AgCl precipitation was observed. The reaction mixture was stirred for another 15 minutes at 23 °C, filtered through celite, and the solvent removed under reduced pressure to leave an orange microcrystalline powder in 97 % yield. NMR data were identical to what is reported for [Cp*Ir(phenanthroline)Cl]Cl.⁴

Cp*Ir Complexes in C–H Oxidation:

Oxidant screening:

General procedure: Complex **1** (0.006 mmol, 1% catalyst loading) was added to a solution containing THF (0.6 mmol, limiting reagent) and an oxidant (4 equiv., 2.4 mmol) in D₂O (10 mL) under N₂ at 23 °C. The reaction mixture was then stirred for 1 hour. A sample (~ 0.5 mL) of the reaction solution was collected for direct ¹H NMR analysis. Products were identified by comparing with ¹H NMR spectra of authentic samples. The conditions and results are shown in Table A. With NaIO₄ as the terminal oxidant, γ -butyrolactone in 41% yield, succinic acid in 33% yield and recovered unreacted starting material (RSM) in 7% were obtained.

Table A. Oxidants Tested for THF Oxidation with Complex **1**

Entry	Catalyst loading	Terminal oxidant	Product yield	Additional conditions
1	1%	KBrO ₃	0%	Not applicable
2	1%	NaClO (aq.)	0%	3 mL 6% NaClO (aq.) and 7 mL D ₂ O
3	none	NaClO (aq.)	0%	3 mL 6% NaClO (aq.) and 7 mL D ₂ O
4	1%	NaIO ₃	0%	Not applicable
5 ^a	1%	NaIO ₄	41% (γ -butyrolactone) 33% (succinic acid)	Not applicable
6 ^a	none	NaIO ₄	0%	Not applicable
7 ^c	1%	Oxone®	< 1%	with 8 equiv. NaHCO ₃
8	1%	Oxone®	0%	Not applicable
9	1%	PbO ₂	0%	Not applicable
10	1%	^t BuOOH (70% aq. solution)	0%	Not applicable
11	1%	H ₂ O ₂ (30% aq. solution)	0%	Not applicable
12	1%	mCPBA ^b	0%	Not applicable

^aAn internal standard (sodium *d*₄-trimethylsilyl propanoate in 3 mg) was used. Yield = mole of product / mole of total starting material. ^bmCPBA: *m*-Chloroperoxybenzoic acid. ^cYield = mole of product / mole of recovered unreacted starting material.

cis-Decalin hydroxylation:

Complex **1** or **2** (0.015 mmol, 5% catalyst loading,) was added to a solution of 4:1 acetone/H₂O (10 mL) containing *cis*-decalin (0.3 mmol, limiting reagent) and NaIO₄ (3 mmol, 10 equiv.) at 23 °C under N₂. The reaction mixture was stirred for 24 hours. At the end of the reaction, Na₂SO₃ (4 mmol, 13 equiv.), DCM (10 mL) and H₂O (10 mL) were added to the reaction solution and the mixture was stirred for 10 minutes. The solution was transferred into a separatory funnel and the organic layer was collected. The aq. layer was extracted with

DCM twice (15 mL and then 10 mL). The combined organic layer was washed with brine (40 mL) and dried over Na₂SO₄. The products and recovered unreacted starting material were analyzed by calibrated GC-FID. The *cis/trans* ratios of decalol products were obtained from GC-FID analysis. Complex **1** gave 62% yield of *cis*-decalol product (22:1 *cis/trans* ratio) and **2** gave 64% yield of *cis*-decalol product (36:1 *cis/trans* ratio). A *trans*-decalol standard sample was made *via* literature procedures.⁷

¹⁸O Labeling experiment:

General procedure: Complex **1** (0.0055 mmol, 5% catalyst loading) was added to a solution of 5 mL 4:1 *t*BuOH/¹⁸O H₂O (97% ¹⁸O atom) containing *cis*-decalin (0.111 mmol, limiting reagent) and 10 equiv. of NaIO₄ (1.11 mmol), under N₂ at 23 °C. The reaction mixture was then stirred for 4 hours. At the end of the reaction, the solution mixture was filtered through celite and the precipitates were washed with DCM (4 mL) and H₂O (10 mL). The filtrate was then transferred into a separatory funnel and the organic layer was collected. The aq. layer was extracted with DCM (2 × 10 mL) and the combined organic layer washed with H₂O (2 × 30 mL), brine (30 mL), and dried over Na₂SO₄. The sample was carefully concentrated under reduced pressure at 23 °C and passed through a plug of silica gel. GC-MS analysis revealed that the ¹⁸O-labeled (94.8% ¹⁸O atom measured by abundance) *cis*-decalol (M⁺ = 156) was obtained with a similar retention time to that of ¹⁶O-*cis*-decalol.

Cyclooctane oxidation:

General procedure: Complex **1** (0.01 mmol, 5% catalyst loading) was added to a solution of 4:1 acetone/H₂O (10 mL) containing cyclooctane (0.2 mmol, limiting reagent) and NaIO₄ (2 mmol, 10 equiv.) under N₂ at 23 °C. The reaction mixture was stirred for 5 hours. At the end of the reaction, Na₂SO₃ (4 mmol, 20 equiv.), DCM (10 mL) and H₂O (10 mL) were added to the reaction solution and the solution was stirred for 10 minutes. The solution was transferred into a separatory funnel and the organic layer was collected. The aq. layer was extracted with DCM twice (15 mL and then 10 mL). The combined organic layer was washed with brine (40 mL) and dried over Na₂SO₄. The DCM solvent was removed under reduced pressure at 23 °C.

The product mixture was analyzed, without further purification, by ^1H NMR spectroscopy with MeNO_2 (12 mg) as an internal standard added right before NMR analysis. Cyclooctanone was obtained as the predominant product in 31% yield. The product identity was further confirmed by GC-MS and $^{13}\text{C}\{^1\text{H}\}$ NMR analyses.⁹

The small amount of side products, 1,4-cyclooctanedione (4% yield) and 1,5-cyclooctanedione (2% yield), were identified by comparing the ^1H NMR spectra with literature data.¹⁰ The quantities of 1,4- and 1,5-cyclooctanedione were measured by ^1H NMR spectroscopy with an internal standard MeNO_2 (12 mg). Because the crude product mixture, containing cyclooctanone, 1,4-cyclooctanedione and 1,5-cyclooctanedione, was analyzed by ^1H NMR spectroscopy without chromatographic purification, some peaks of the products overlapped and were thus unsuitable for quantification. Nevertheless, at least one characteristic peak for each product can be used for quantification: a multiplet at 1.55 ppm (referenced relative to TMS at 0 ppm, 4H) for cyclooctanone, a singlet at 2.71 ppm (4H) for the side product 1,4-cyclooctanedione, and a multiplet at 2.52 ppm (8H) for the side product 1,5-cyclooctanedione.

Other effective solvents: 4:1 $t\text{BuOH}/\text{H}_2\text{O}$ and 4:1 $\text{MeCN}/\text{H}_2\text{O}$ (10 mL) are also effective solvents for carrying out cyclooctane oxidation. Cyclooctanone in 49% yield was obtained with 4:1 $t\text{BuOH}/\text{H}_2\text{O}$ and 43% yield was obtained with 4:1 $\text{MeCN}/\text{H}_2\text{O}$. The purification procedures and analysis methods by NMR spectroscopy are similar to those described above under “*Cyclooctane oxidation*”. The conditions used here are: cyclooctane (0.372 mmol, limiting reagent), **1** (0.019 mmol, 5% catalyst loading), NaIO_4 (3.72 mmol, 10 equiv.) in 4:1 $t\text{BuOH}/\text{H}_2\text{O}$ (10 mL) or 4:1 $\text{MeCN}/\text{H}_2\text{O}$ (10 mL) at 23 °C under N_2 for 5 hours.

Monitoring cyclooctane oxidation: Separate experiments were set up, purified (by similar methods as seen in the section above, “*Cyclooctane oxidation*”) and analyzed by ^1H NMR spectroscopy of the crude product mixture with MeNO_2 (12 mg) as internal standard. The conditions and cyclooctanone yields are listed in Table B.

Table B. Monitoring Cyclooctane Oxidation Catalyzed by **1** or **2**^a

With 1		With 2	
Time (h)	Yield ^b (cyclooctanone)	Time (h)	Yield ^b (cyclooctanone)
0.5	19%	0.5	3%
1	31%	1	7%
3	34%	3	29%
6	50%	6	40%
15	50%	15	52%
24	54%	24	49%

^aConditions: cyclooctane (0.372 mmol, limiting reagent), **1** or **2** (0.022 mmol, 6% catalyst loading), NaIO₄ (3.72 mmol, 10 equiv.), in 4:1 acetone/H₂O (10 mL), at 23 °C under N₂. ^bYield = mole of cyclooctanone / mole of total starting material.

Cyclooctanone oxidation:

Cyclooctanone oxidation in 4:1 acetone/H₂O: Cyclooctanone was liquefied at 41 °C to facilitate handling. The reaction was set up and analyzed in a similar way to that of cyclooctane oxidation, described above under “Cyclooctane oxidation”. Products 1,4-cyclooctanedione in 7% yield and 1,5-cyclooctanedione in 6% yield were detected by ¹H NMR spectroscopy with MeNO₂ (12 mg) as internal standard.

Cyclooctanone oxidation in 4:1 HFIP/H₂O: Cyclooctanone (0.34 mmol, limiting reagent), **2** (0.034 mmol, 10% catalyst loading) and NaIO₄ (3.4 mmol, 10 equiv.) were added to 4:1 HFIP/H₂O (10 mL). The reaction mixture was stirred under N₂ at 23 °C for 15 hours. At the end of the reaction, Na₂SO₃ (4 mmol, 12 equiv.), DCM (10 mL) and H₂O (10 mL) were added to the reaction solution and it was stirred for 10 minutes. The solution was transferred into a separatory funnel, where three layers of liquid formed. The bottom layer is the fluoruous layer, the middle layer is a mixed organic layer, and the top layer is the aqueous layer. The fluoruous layer was removed out of the separatory funnel and collected in **Flask A**. Then the organic layer was removed out of the separatory funnel and collected in **Flask B**. At this time only the aq. layer remained in the separatory funnel. The fluoruous layer previously collected in **Flask A** was added back to the separatory funnel to mix with the aq. layer. DCM (15 mL) was added to the separatory funnel. After shaking the separatory funnel vigorously,

three layers of liquid again appeared, but this time the fluoruous layer was in smaller volume compared to the one before. The fluoruous layer was removed out of the separatory funnel and collected in **Flask A**. The organic layer was removed out of the separatory funnel and collected in **Flask B**. At this time only the aq. layer remained in the separatory funnel. The fluoruous layer previously collected in **Flask A** was again added back to the separatory funnel to mix with the aq. layer. DCM (10 mL) was added to the separatory funnel. After shaking the separatory funnel vigorously, only two rather than three layers of liquid appeared this time. The organic layer was removed out of the separatory funnel and collected in **Flask B**. The organic extracts from **Flask B** were washed with H₂O (2 × 40 mL, where 1 mL of brine solution was added to the separatory funnel in each H₂O washing, to facilitate layer separation between the organic and aq. layer) and brine (40 mL). The solution was dried over Na₂SO₄, and the sample concentrated under reduced pressure at 23 °C. MeNO₂ (12 mg) was added as an internal standard and the mixture analyzed by GC-MS analysis, ¹H NMR and ¹³C{¹H} NMR spectroscopy, matching literature data of 1,4- and 1,5- cyclooctanediones.¹⁰ Products 1,4-cyclooctanedione in 27% yield and 1,5-cyclooctanedione in 28% yield were detected. No 1,3-cyclooctanedione was found by ¹H NMR spectroscopy (3.5 ppm, 2H, s) and no 1,2-cyclooctanedione was found by ¹³C{¹H} NMR spectroscopy. A multiplet at 1.55 ppm (referenced relative to TMS at 0 ppm, 4H) was used to measure the yield of the starting material cyclooctanone. A peak at 2.71 ppm (4H, s) was used to measure the yield of side product 1,4-cyclooctanedione and a multiplet at 2.52 ppm (8H, s) was used to measure the yield of 1,5-cyclooctanedione. The two cyclooctanedione products were separated *via* flash column chromatography (2:1 ethyl acetate/hexanes). The identities of two isolated products were individually confirmed by ¹H NMR spectroscopy and GC-MS analysis.

Solvent HFIP oxidation: Commercial HFIP was found to be free of other detectable organic compounds containing fluorine by ¹⁹F NMR analysis.⁸ Precatalyst **2** (0.01 mmol) was added to a solution of NaIO₄ (2.34 mmol) in 1:1 HFIP/D₂O (10 mL). The reaction mixture was stirred at 23 °C under N₂ for 21 hours. An aliquot (~ 0.5 mL) of the solution was collected and analyzed directly without workup *via* ¹⁹F NMR spectroscopy. A new singlet at -82.3 ppm (s) was found in the ¹⁹F NMR spectrum at 0.2% relative to the HFIP signal (-76 ppm,

s). Hexafluoroacetone (HFA, a potentially fatal compound) is reported to have a singlet at -83.4 ppm in CDCl_3 with CFCl_3 as an internal standard at 0 ppm,⁸ so we assigned this new peak at -82.3 ppm to be HFA. Addition of authentic $\text{HFA}\cdot 3\text{H}_2\text{O}$ to the NMR sample gave increased peak area at -82.3 ppm, confirming our assignment. 0.2% of HFIP oxidation to HFA corresponds to 10 catalyst turnovers.

Cyclohexane oxidation with HFA but without a precatalyst: Cyclohexane in 0.283 mmol, $\text{HFA}\cdot 3\text{H}_2\text{O}$ (30% relative to cyclohexane, 0.085 mmol) and 10 equiv. NaIO_4 (2.83 mmol) were added to 1:1 HFIP/ D_2O (10 mL). The reaction mixture was stirred at 23 °C under N_2 , and an aliquot was collected for analysis after 30 minutes and another aliquot after 17 hours. Direct ^1H NMR analysis without workup showed that no cyclohexanone was formed either after 30 minutes or 17 hours.

cis-Decalin hydroxylation in HFIP/ H_2O : Complex **2** (0.01 mmol, 5% catalyst loading) was added to a solution mixture containing *cis*-decalin (0.2 mmol) and NaIO_4 (2 mmol, 10 equiv.) in 4:1 HFIP/ H_2O (10 mL) under N_2 at 23 °C. Not all *cis*-decalin dissolved in 4:1 HFIP/ H_2O . The reaction mixture was vigorously stirred for 5 hours. The solution was filtered through celite and the organic layer was collected. Extraction (see details above for cyclooctanone oxidation in 4:1 HFIP/ H_2O) of the aq. layer with DCM was followed by H_2O (2×40 mL) and brine wash (40 mL). The organic solution was dried over Na_2SO_4 and the products were analyzed *via* calibrated GC-FID. A *cis/trans* ratio of 18:1 was found.

Methylene Oxidation:

n-Butanol and EBS oxidation: The reaction was carried out in D_2O and was analyzed directly *via* ^1H NMR spectroscopy (with sodium *d*₄-trimethylsilyl propanoate as an internal standard at 0 ppm) without workup. The internal standard (3 mg) was added at the end of the reaction. Conditions for *n*-butanol oxidation are as follows: *n*-butanol (0.231 mmol, limiting reagent), 2% **1** (0.00462 mmol), NaIO_4 (4 equiv. 0.924 mmol), at 23 °C under N_2 for 1 hour, in 5 mL D_2O solvent. *n*-Butanol oxidation gave *n*-butyric acid in 94% yield. Conditions for EBS oxidation: EBS (0.2 mmol, limiting reagent), NaIO_4 (10 equiv., 2 mmol), 5% **1** (0.01 mmol), at 23 °C under N_2

for 1 hour, in 10 mL D₂O solvent. EBS oxidation gave product sodium 4-acetylbenzene sulfonate in 99% yield. The ¹H NMR spectrum of the product sodium 4-acetylbenzene sulfonate in *d*₆-DMSO has been reported.¹¹

Control experiments with light or air: A set of three EBS oxidation experiments was carried out, as shown in Table C. A stock solution of **1** (0.0293 mmol, 5% catalyst loading) in D₂O (15 mL) and another stock solution of EBS (0.585 mmol) and NaIO₄ (2.925 mmol, 5 equiv.) in D₂O (15 mL) were made to minimize errors. For each experiment, the reaction was carried out by mixing 5 mL stock solution of **1** and 5 mL stock solution of EBS and NaIO₄. Results were analyzed directly by ¹H NMR spectroscopy without workup.

Table C. Reaction Conditions in Testing the Effect of Light and Air in Sodium 4-Ethylbenzene Sulfonate

Entry	Conditions	Time	Concentration	Oxidation	
				Ketone yield	Mass balance
1	23 °C, light, N ₂	3 h	0.195 mmol in 10 mL	68%	91%
2	23 °C, dark, N ₂	3 h	0.195 mmol in 10 mL	66%	90%
3	23 °C, dark, air	3 h	0.195 mmol in 10 mL	74%	100%

Mass balance = % product + % RSM

2-heptanone oxidation: The reaction setup and analysis were similar to those discussed above under “*Cyclooctanone oxidation*”. The reaction conditions are as follows: 2-heptanone (0.2 mmol, limiting reagent), **2** (0.02 mmol, 10% catalyst loading), NaIO₄ (10 equiv., 2 mmol), in 4:1 HFIP/H₂O (10 mL) under N₂ for 15 hours. Products 2,5-heptanedione in 18% yield and 2,6-heptanedione in 44% yield were detected. The yields of 2,5- and 2,6- cyclooctanediones as well as % RSM were obtained by integration of peak areas, at 2.71 ppm, 1.82 ppm and 1.57 ppm respectively. Product characterizations were carried out on the crude product mixture *via* GC-MS analysis, ¹H NMR and ¹³C{¹H} NMR spectroscopy. The separation of 2,5- and 2,6-cyclooctanediones was performed using flash column chromatography (3:1 hexanes/ethyl acetate, using *p*-anisaldehyde as TLC stain) and product identities were individually confirmed by ¹H NMR and ¹³C{¹H} NMR spectroscopy. Characterizations of products and possible side products, 2,3-heptanedione,⁹ 2,4-heptanedione,¹¹ 2,5-heptanedione,¹² 2,6-heptanedione¹³ and 6-oxo-heptanoic acid,¹⁴ have been reported. **When 5% catalyst**

loading rather than 10% was used under otherwise similar conditions (0.2 mmol substrate, 10 equiv. NaIO₄ and 4:1 HFIP/H₂O in 10 mL at 23 °C under N₂ for 19 hours), only 8% yield of 2,5-dione and 22% of 2,6-dione were obtained (45% recovered unreacted starting material).

Methyl hexanoate oxidation: The reaction setup and analysis were similar to the case of cyclooctanone oxidation in 4:1 HFIP/H₂O as discussed above. The reaction conditions are as follows: methyl hexanoate (0.174 mmol, limiting reagent), 10% **2** (0.017 mmol), NaIO₄ (1.74 mmol, 10 equiv.), in 4:1 HFIP/H₂O (10 mL) under N₂ for 15 hours. Products 5-oxo-hexanoate and methyl 4-oxo-hexanoate in 61% and 21% yield respectively were detected. The ¹H and ¹³C{¹H} NMR spectra of the crude product mixture matched literature values for methyl 4-oxo-hexanoate and methyl 5-oxo-hexanoate.¹⁵ No other regioisomeric products were detected by ¹³C{¹H} NMR spectroscopy.

Light alkane oxidation:

General conditions: In a 15 mL SS pressure bomb containing a teflon liner and a magnetic cross stir bar, 0.028 mmol of [Ir] (12 mg for **1** and 14 mg for **2**) and 295 mg (1.38 mmol, 50 eq., limiting reagent) of NaIO₄ was added, followed by 5 mL of 4:1 HFIP/H₂O. A separate reactor without [Ir] (with NaIO₄ and solvent only) was prepared to be carried out as a background. The reactors were sealed and purged with Argon several times while stirring the solution. The substrate was then used to pressurize the reactor (300 psig for methane and ethane, 110 psig for propane). The reactors were heated for 15 hours at 60 °C in an aluminum block. Upon completion of the reaction, the reactors were cooled to 0 °C in an ice bath. The headspace of the methane reactors were vented into evacuated 8 dram vials to test the gas phase. The conversion of CO₂ was determined by using a Ne standard in the gas phase (see below, “*Gas phase calibration*”, for details). The reactors were opened and 1.0 mL of a 0.276 M solution of sodium d₄-trimethylsilyl propanoate in D₂O was added to each reactor as a standard. NMR spectra were taken using a 10 seconds relaxation delay to ensure quantitative NMR integrations.

Gas phase calibration: To determine the resulting % oxidation products resulting from the methane reaction, we used a mixture of 3% neon balanced with methane. This also required us to determine the relative response factor on our GC-MS of CO₂ versus neon. To study this, we made 4 gas mixtures from 0 psi CO₂ to 6 psi CO₂ and filled with the methane/neon mixture to a total pressure of 300 psi. These gas mixtures were shot in duplicate and the data was averaged to determine the error in individual injections. Once completed, the integration of CO₂ versus neon was calibrated against the known partial pressures of CO₂. The calibration curve we obtained is shown in Figure i. This calibration curve was used to determine the % CO₂ in the gas phase which gave us the overall yield CO₂ from methane.

We also determined the gas phase neon to determine the loss of CH₄. Between the loss of CH₄ and formation of CO₂, there was > 98% mass balance.

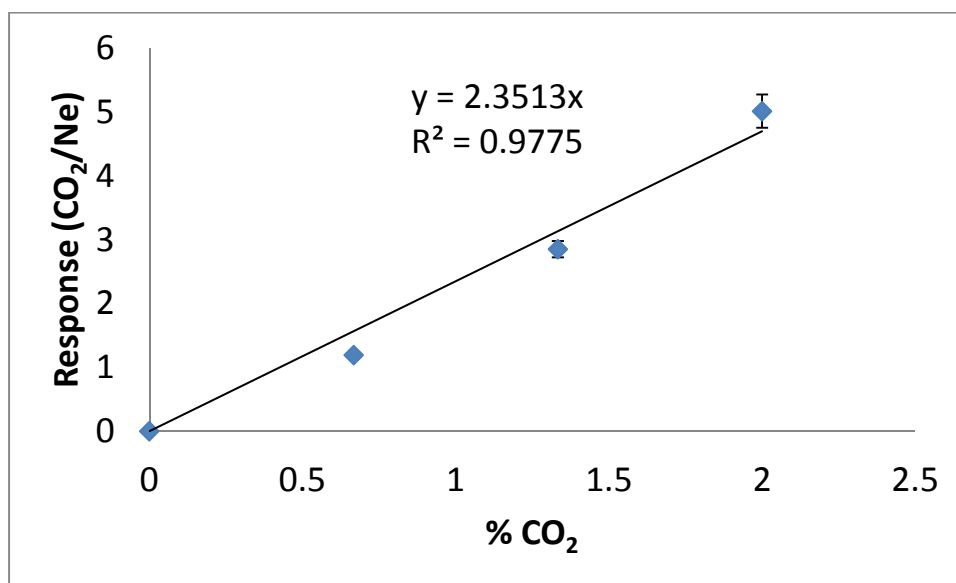


Figure i. Calibration curve of the ratio of CO₂:Ne vs. % CO₂.

To ensure that no product observed *via* NMR spectroscopy was due to catalyst degradation, catalytic reactions were performed under Argon in the absence of substrate (entry 1 and 2 in Table D). This did reveal that small amount of acetic acid formed in the absence of substrate, and catalytic conversions have been corrected for this background (numbers in parentheses in Table D). For the calculated yield of acetic acid (entry 7 and 8) based on NaIO₄ we assigned 4 equiv. of NaIO₄ consumption to each equivalent of acetic acid formed.

No background activity was found in methane and ethane oxidation with NaIO₄ in the absence of catalyst (entry 3 and 6). However, a small amount of background oxidation of propane to give isopropanol was observed (entry 9).

Table D. Light Alkane Oxidations

Entry	Complex	Substrate	Yield ^a	Respective ^b TON product 1 (corrected ^c)	Product 1	Respective TON Product 2	Product 2
1 ^d	1	None	5%	0.6	Acetic Acid	----	----
2 ^d	2	None	4%	0.8	Acetic Acid	----	----
3	none	Methane	0%	0.0	CO ₂	----	----
4	1	Methane	25%	3.1	CO ₂	----	----
5	2	Methane	39%	4.9	CO ₂	----	----
6 ^e	none	Ethane	0%	0	Acetic Acid	----	----
7	1	Ethane	21%	3.5 (2.9)	Acetic Acid	----	----
8	2	Ethane	25%	4.1 (3.3)	Acetic Acid	----	----
9	none	Propane	5%	0.0	Acetone	3	ⁱ PrOH
10	1	Propane	29%	5.2	Acetone	0.4	ⁱ PrOH
11	2	Propane	38%	6.6	Acetone	1.5	ⁱ PrOH

^aYield is based on total oxidant consumed assuming NaIO₄ is a 2 e⁻ oxidant. ^bRespective TON = mole of product / mole of precatalyst (or if background respective to catalytic reactions). The error between duplicate runs was consistently < 0.1 TON. ^cCorrected = (respective TON) – (respective TON under Ar). ^dThe reaction was carried out under Argon atmosphere. ^eNo acetic acid formation was observed in the absence of a precatalyst.

Conditions and product analysis for cyclohexane oxidation with 2: Cyclohexane (0.257 mmol, limiting reagent), NaIO₄ (2.57 mmol, 10 equiv.) and **2** (0.0129 mmol, 5% catalyst loading) were added to 4:1 HFIP/H₂O solvent (10 mL), at 23 °C under N₂ for 15 hours. See above, “Cyclooctanone oxidation”, for reaction setup and purification procedures. After extraction, no DCM removal was performed and product analysis was carried out by calibrated GC-FID. Cyclohexanone was obtained in 75% yield.

cis-Decalin hydroxylation in 4:1 HFIP/H₂O at 60 °C: The reaction setup and analysis were similar to the case of *cis*-decalin hydroxylation in 10 mL 4:1 HFIP/H₂O as discussed above, “*cis*-Decalin hydroxylation in HFIP/H₂O”, except that the reaction was carried out at 60 °C. A *cis/trans* ratio of 15:1 was obtained by calibrated GC-FID analysis.

Kinetic isotope effect:

KIE of cyclohexane oxidation was calculated from product mole number, where the reactions were quenched at low conversion and short time scale, in separate oxidation reactions of h_{12} -cyclohexane and d_{12} -cyclohexane. The procedures and reaction conditions are described below.

Cyclohexane oxidation with 1: Cyclohexane (0.2 mmol, limiting reagent), **1** (0.01 mmol, 5% catalyst loading) and NaIO₄ (2 mmol, 10 equiv.) were added to a 1:1 HFIP/D₂O solution (10 mL). The solution was stirred for 1 hour under N₂ at 23 °C. At the end of the reaction, the solution was filtered through celite. The celite was washed with D₂O (5 mL) and HFIP (5 mL). The product was analyzed by ¹H NMR spectroscopy without further purification, using sodium d_4 -trimethylsilyl propanoate (3 mg) as an internal standard. Cyclohexanone in 67% yield was found as the predominant product.

General procedure for cyclohexane oxidation in KIE measurements: Cyclohexane (0.185 mmol, limiting reagent) and NaIO₄ (1.85 mmol, 10 equiv.) were added to a 4:1 HFIP/H₂O solution (10 mL). The solution was stirred for 20 minutes to dissolve NaIO₄. Precatalyst **1** (0.0009 mmol, 0.5% catalyst loading) was then added and the solution was stirred for 10 minutes. Na₂SO₃ (1.85 mmol, 10 equiv.) was then added to quench the reaction. Extraction was performed (see above, “*Cyclooctanone oxidation*”, for extraction procedures when using HFIP/H₂O as solvent). After drying, the DCM solution was passed through a plug of silica gel. Cyclohexanone in 9% yield (0.0149 mmol) was found by calibrated GC-FID analysis.

d_{12} -Cyclohexane oxidation was carried out separately under similar conditions, and d_{10} -cyclohexanone was obtained in 3% yield (0.00490 mmol). Together with the results from h_{12} -cyclohexane oxidation, a KIE of 3.1 was obtained. Two reproductions were carried out to give a final average KIE of 3.0 ± 0.1 .

Natural product oxidation:

Procedures for sclareolide oxidation: Sclareolide (0.2 mmol, limiting reagent), NaIO₄ (2 mmol, 10 equiv.) and **2** (0.02 mmol, 10% catalyst loading) were added to 4:1 HFIP/H₂O (10 mL). The reaction mixture was stirred under N₂ at 23 °C for 15 hours. At the end of the reaction, Na₂SO₃ (4 mmol, 20 equiv.), DCM (10 mL) and H₂O (10 mL) were added to the reaction solution and it was stirred for 10 minutes. The solution was transferred into a separatory funnel and extraction was performed (see above, “Cyclooctanone oxidation”, for extraction procedures when using HFIP/H₂O as solvent). LC-MS and GC-MS spectra of the crude product mixture are consistent with formation with 2- and 3- oxo-sclareolide as the major products. Flash column chromatography was carried out with 3% acetone/hexanes to remove the starting material from the products. 2- and 3- oxo-sclareolide, in 17% and 5% yield respectively, were found by ¹H NMR spectroscopy (with a 500 MHz Varian NMR) with MeNO₂ (12 mg) as an internal standard. The peak areas of the singlets, one at 0.93 ppm which is due to 2-oxo-sclareolide (6H) and another at 1.03 ppm which is due to 3-oxo-sclareolide (3H), were used for quantitation. The two regioisomeric products were also separated by gradient flash chromatography (large amount of 3% acetone/hexanes followed by 30% ethyl acetate/hexanes; using newly made CAM, ceric ammonium molybdate, as TLC stain) and their identities were individually confirmed by ¹³C{¹H} NMR spectrum.¹⁵ Results and additional reaction conditions of natural product oxidations are shown in Table E.

Procedures for (-)-ambroxide oxidation: See “Procedures for sclareolide oxidation” above for reaction setup and extraction procedures. The product sclareolide (25% yield) was isolated by flash column chromatography (10% ethyl acetate/hexanes, using CAM as TLC stain). The identity was confirmed by GC-MS and ¹³C{¹H} analyses.

Table E. Natural Product Oxidations

Substrate	Precatalyst (loading)	Solvent	Time	C–H Oxidation	Comment
Artemisinin	1 (5%)	4:1 HFIP/H ₂ O	12h	0%	89% RSM
Cuparene	2 (10%)	1:1 HFIP/H ₂ O	15h	Not applicable	unselective oxidation
5- α -cholestan-3-one	1 (5%)	4:1 HFIP/H ₂ O	12h	Not applicable	unselective oxidation
pregnanedione	1 (5%)	4:1 HFIP/H ₂ O	9h	Not applicable	> 3 products, < 5% total yield
(–)-ambroxide	2 (10%)	4:1 HFIP/H ₂ O	15h	sclareolide 25% isolated yield	Not applicable
sclareolide	2 (10%)	4:1 HFIP/H ₂ O	15h	2-oxo-sclareolide 17% yield 3-oxo-sclareolide 5% yield	Not applicable

Aqueous Sodium 4-Ethylbenzene Sulfonate Oxidation:

General conditions: NaIO₄ (214 mg, 2 mmol) and EBS (42 mg, 0.2 mmol) were dissolved in deionized H₂O (5 mL) under N₂. The reaction was started by injecting the appropriate amount of a precatalyst stock solution (10 mM **1** in H₂O) using a microliter syringe, and the mixture stirred at 23 °C. Aliquots of 1 mL were taken periodically *via* syringe for reaction progress monitoring. After quenching with 2 mL 1 M NaHSO₃ the solvent was removed under reduced pressure. Solid trimethoxybenzene (10 mg) was weighed into the sample and the mixture sonicated with five drops of H₂O and 0.8 mL *d*₆-acetone. After filtration the solution was analyzed by ¹H NMR spectroscopy to give conversions by peak area integration of the aromatic protons of substrate (7.69, 7.67, 7.25, 7.23 ppm) and product (8.02, 8.00, 7.89, 7.87 ppm) relative to the standard (6.1 ppm). Exemplary ¹H NMR spectra of the reaction progress using 2% **1** are shown in Figure ii.

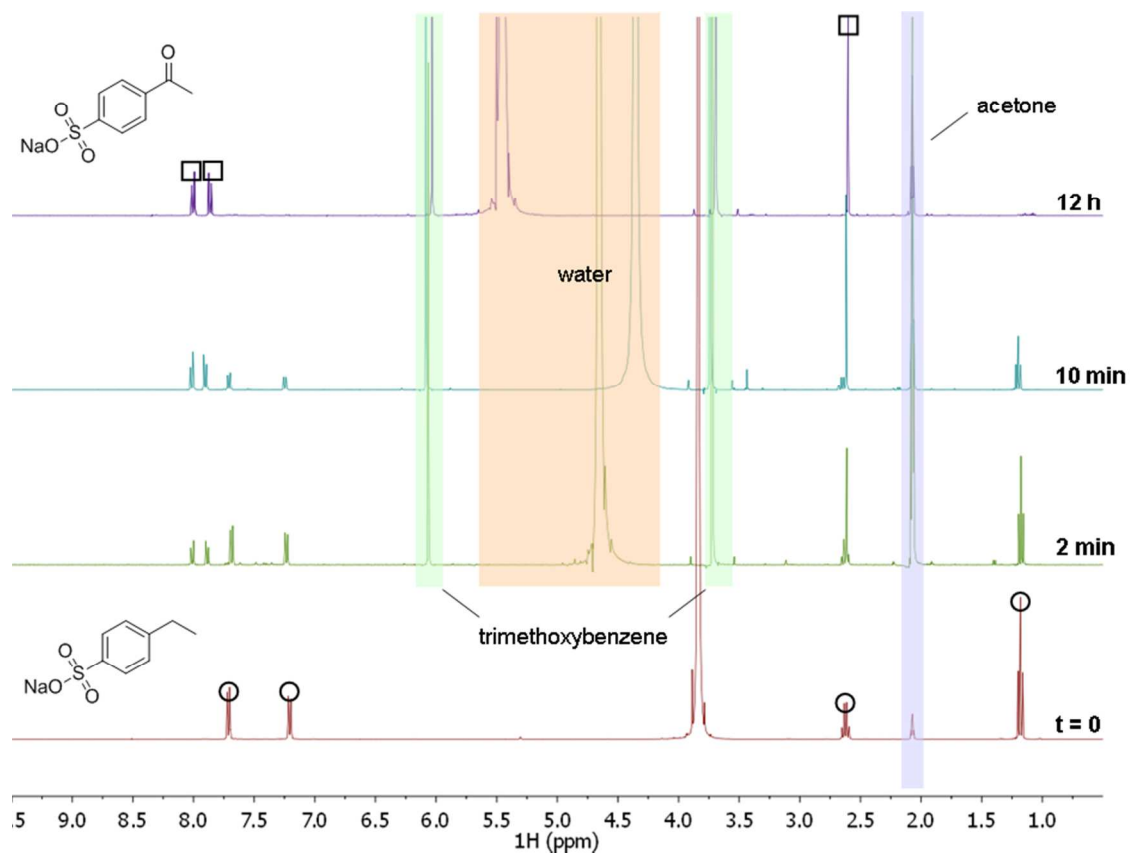


Figure ii. Exemplary ^1H NMR spectra of the reaction progress of sodium 4-ethylbenzene sulfonate oxidation.

Without added Ir precatalyst the ^1H NMR spectrum was unchanged after stirring the substrate in aq. NaIO_4 solution for 16 hours at 23 $^\circ\text{C}$.

Kinetics of Aqueous Sodium 4-Ethylbenzene Sulfonate Oxidation:

The reaction profiles obtained for different catalyst loadings are shown in Figure iii:

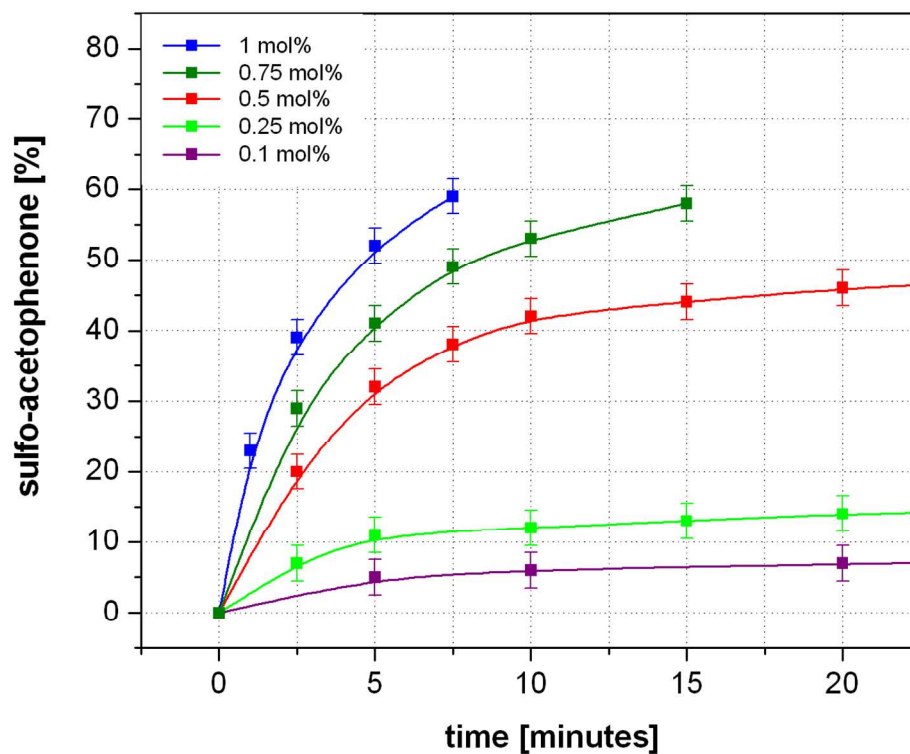


Figure iii. Reaction profile of aqueous sodium 4-ethylbenzene sulfonate oxidation at 40 mM substrate and 400 mM NaIO₄ with different loadings of complex **1** at 23 °C (error bars indicate uncertainty of measurement, lines are drawn to guide the eye).

Time-resolved dynamic light scattering was performed on a reaction with 40 mM EBS, 400 mM NaIO₄, and 1% **1** at 23 °C using the setup and data analysis described previously.¹⁶

Kinetic analyses of the aq. C–H oxidation reaction were made based on the assumptions shown in Figure iv:

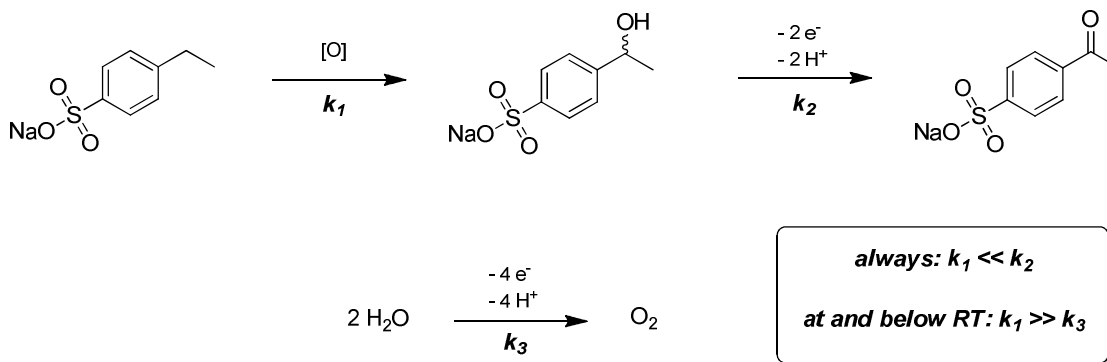


Figure iv. Assumptions of kinetic analyses of sodium 4-ethylbenzene sulfonate oxidation.

Temperature-variation of Aqueous Sodium 4-Ethylbenzene Sulfonate Oxidation:

5 mL aqueous solutions 40 mM in EBS and 400 mM in NaIO₄ were set up under N₂ and pre-tempered using either ice-water mixtures (< 23 °C) or an aluminum heating block (> 23 °C) for 10 min. The reaction was started by injecting 100 μL of a 10 mM stock solution of **1** in H₂O (1 μmol, 0.5 %). 1 mL samples were withdrawn periodically, and worked-up and analyzed as described above. Initial rates used for generating the Eyring plot are given in table F:

Table F. Short-time Conversions and Initial Rates of Aqueous Sodium 4-Ethylbenzene Sulfonate Oxidation at Different Temperatures (conditions see above)

Temperature	Time	Conversion	Rate
0 ± 1 °C	2.5 ± 0.2 min	7 ± 2 %	1.12 ± 0.3 mM/min
5 ± 1 °C	2.5 ± 0.2 min	9 ± 2 %	1.44 ± 0.3 mM/min
10 ± 1 °C	2.5 ± 0.2 min	12 ± 2 %	1.92 ± 0.3 mM/min
15 ± 1 °C	2.5 ± 0.2 min	14 ± 2 %	2.24 ± 0.3 mM/min
23 ± 1 °C	2.5 ± 0.2 min	20 ± 2 %	3.20 ± 0.3 mM/min
30 ± 1 °C	2.5 ± 0.2 min	19 ± 2 %	3.04 ± 0.3 mM/min
40 ± 1 °C	2.5 ± 0.2 min	22 ± 2 %	3.52 ± 0.3 mM/min
50 ± 1 °C	2.5 ± 0.2 min	23 ± 2 %	3.68 ± 0.3 mM/min
60 ± 1 °C	2.5 ± 0.2 min	22 ± 2 %	3.52 ± 0.3 mM/min

Co-detection of oxygen produced during C–H oxidation:

Solutions of sodium periodate (472 mM) and EBS (21.8 mM) were prepared, and a 5.0 mL sample was placed into a Clark-type electrode cell. After a steady baseline was achieved, **1** (10 uL of a 2.0 mM solution) was injected into the solution, and the amount of oxygen produced was recorded. A minimum of three trials were performed for each condition tested. After oxygen evolution had ceased the samples were combined, and the amount of C–H bond oxidation was characterized *via* NMR spectroscopy.

¹H NMR quantification: H₂O was removed under reduced pressure at 35 °C and with a dry ice trap. Sodium *d*₄-trimethylsilyl propanoate (3 mg) in D₂O (1 mL) was added as internal standard for ¹H NMR quantitation of the product. Concentrations of EBS and NaIO₄, as well as mole of product sodium 4-acetylbenzene sulfonate and oxygen are presented in Table G.

Table G. Co-detection of Products of Water Oxidation and C–H Oxidation

Entry	Sodium 4-acetylbenzene sulfonate in μmol	O ₂ in μmol	[Sodium 4-ethylbenzene sulfonate] (mM)	[NaIO ₄] (mM)
1	0.90	0.20	21.8	472
2	0.79	0.21	22.9	496
3	0.81	0.20	22.9	472
Average Values:	0.83 \pm 0.06	0.2 \pm 0.01		

Solvent volume: 5 mL (H₂O). Concentration of **1** in reaction solution: 4 μM .

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