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Catalytic Oxidative Cleavage Reactions of Arylalkenes by *tert*-Butyl Hydroperoxide – A Mechanistic Assessment

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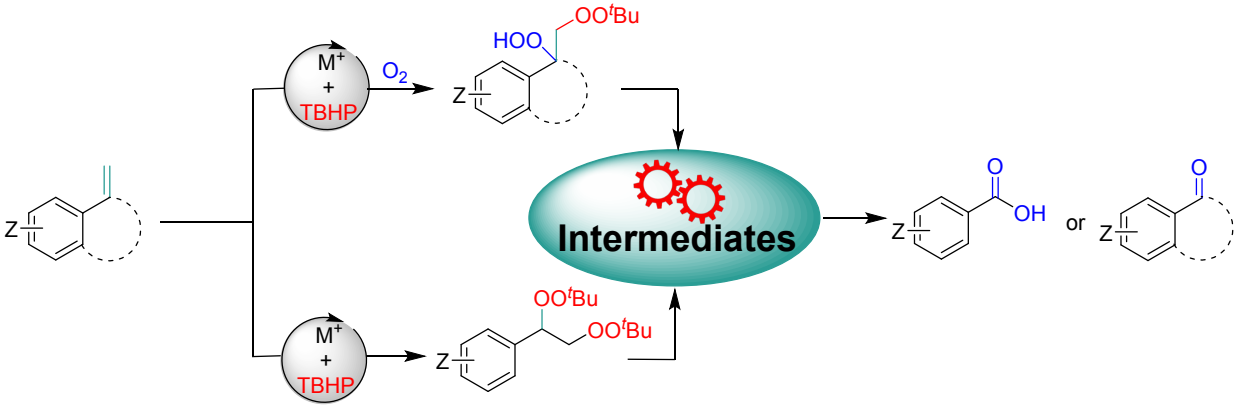


ABSTRACT: Oxidative cleavage reactions of aryl-alkenes by *tert*-butyl hydroperoxide that occur by free radical processes provide access to carboxylic acid or ketone products. However, the pathway to these cleavage products is complex, initiated by regioselective oxygen radical addition to the carbon-carbon double bond. Subsequent reactions of the initially formed benzyl radical lead eventually to carbon-carbon cleavage. Thorough investigations of these reactions have identified numerous reaction intermediates that are on the pathways to final product formation, and they have identified a new synthetic methodology for the synthesis of peroxy radical addition induced hydroperoxide formation.

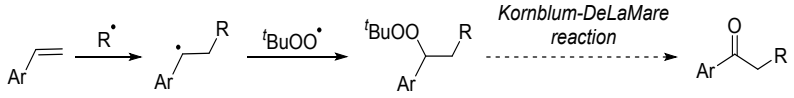
INTRODUCTION

The oxidation of alkenes is a complex area for investigation.[1] Extensive studies have been directed to epoxidation[2] and dihydroxylation,[3] as well as to allylic oxidation[4] and oxidative cleavage.[5] The preferred oxidant is molecular oxygen, but its hydroperoxide counterparts often overcome the mechanistic difficulties associated with the activation of molecular oxygen. Of the hydroperoxides that have been employed, hydrogen peroxide is the preferred reagent, but *tert*-butyl hydroperoxide (TBHP) is more stable and is a suitable replacement for hydrogen peroxide in investigations of peroxidation reactions.[6] The formation and reactions of the relatively selective *tert*-butylperoxy radical are integral to understanding the associated free radical processes.[7]

An increasing number of investigations have utilized TBHP in addition reactions with styrenes.[8] Addition occurs by either the combination of TBHP with another oxidant, as with iodine and TBHP to produce *tert*-butyl hypoiodide,[9] or via a generally presumed catalyst-dependent free radical pathway involving the *tert*-butylperoxy radical. In the free radical pathway the *tert*-butylperoxy radical facilitates formation of a new

radical, generally by hydrogen atom abstraction, that undergoes initial addition to styrene, and the resulting radical either produces a mixed peroxide[8c,8f] or the corresponding ketone that is presumably formed by the Kornblum-DeLaMare reaction[10] of the mixed peroxide (Scheme 1). Formation of the mixed peroxide product can occur by the combination of the benzyl and *tert*-butylperoxy radicals[8c,f] or by oxidation of the initially formed benzyl radical to the corresponding benzyl cation followed by its nucleophilic trapping by TBHP.[9] Alternatively, with transition metal catalysts, the possibility exists of peroxy radical transfer from a metal peroxide-ligated intermediate that would form the observed product.[8b] However, none of these considerations address the question of when or how carbon-carbon cleavage occurs.

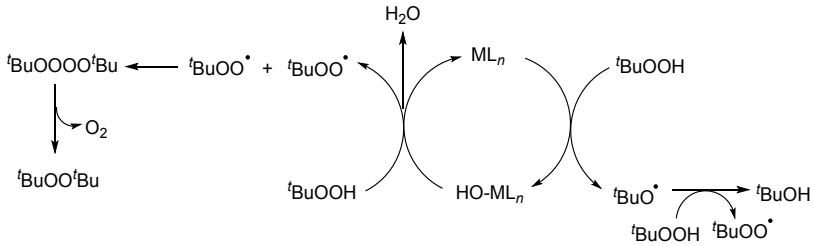
Scheme 1. Oxidative Reactions of Styrenes Involved in TBHP



RESULTS AND DISCUSSION

Rhodium(II) caprolactamate [$Rh_2(cap)_4$] has been our preferred catalyst for the generation of the *tert*-butylperoxy radical because of its low oxidation potential[11] and a catalytic cycle that generates ^{t}BuOO• by both oxidation and reduction of $Rh_2(cap)_4$ (Scheme 2). The amount of catalyst used determines the rate for generation of ^{t}BuOO• so that a low catalyst loading is generally used. This catalyst has been preferred for allylic and propargylic oxidations,[12] benzylic,[13] and phenolic oxidations,[14] as well as the oxidative Mannich reaction,[15] and the mechanistic details of these transformations have been elaborated.[4b,16] Copper halides have also been used effectively for allylic oxidation[17] and the oxidative Mannich reaction.[18]

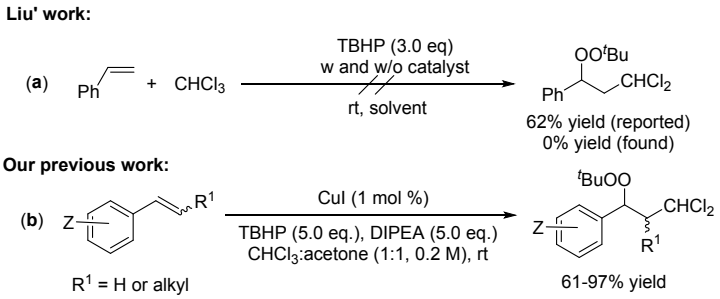
Scheme 2. Catalytic Formation of the *tert*-Butylperoxy Radical



A recent report by Liu and coworkers on the TBHP oxidation of styrene in chloroform claimed the formation of dichloromethyl/*tert*-butylperoxy radical addition products in high yield without the involvement of a metal catalyst (Scheme 3, a).[19] The authors report that this reaction occurred by a free radical process. However, our attempts to repeat this reaction were unsuccessful, and we were unable to obtain the reported product under the specified reaction conditions, or to detect any reaction of TBHP with styrene at room temperature without a metal catalyst over very long reaction times. Instead, we

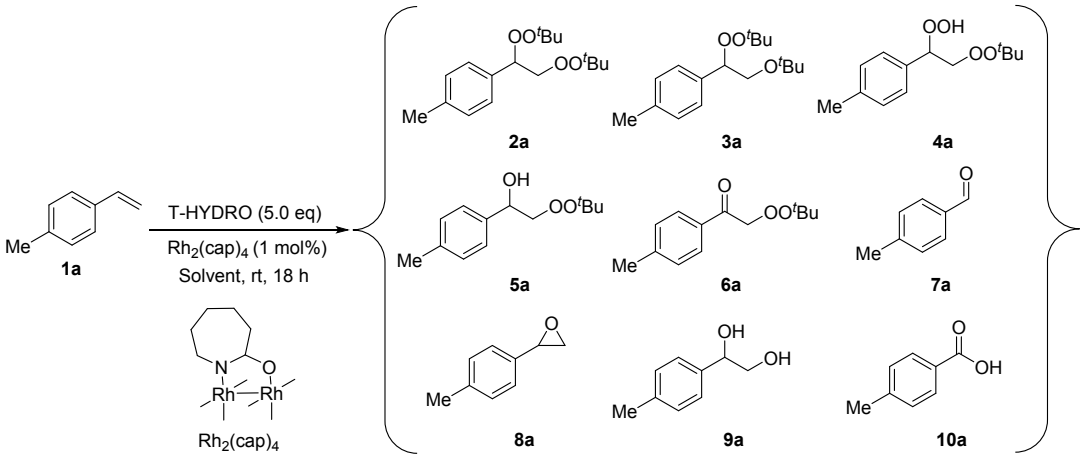
discovered that the combination of substituted styrenes, chloroform, and TBHP in the presence of diisopropylethylamine with catalytic amounts of copper iodide or $Rh_2(cap)_4$ forms α-peroxy-β,β-dichloropropylbenzene products in high yield (Scheme 3, b).[20] The formation of an α-aminoradical from DIPEA by the *tert*-butylperoxy radical circumvents preferential hydrogen atom transfer from chloroform in favor of halogen atom transfer by the α-aminoradical, thereby releasing the halomethyl radical for addition to alkenes. Without the tertiary amine this combination of reactants produced a complex mixture of products that lead to oxidative cleavage of the carbon-carbon double bond, and this process is the subject of this investigation.

Scheme 3. Selective Chlorine Atom Abstraction from Chloroform to Form α-Peroxy-β,β-dichloropropylbenzenes.



The reactions of styrenes with TBHP in the presence of free radical generating catalysts were investigated to determine their reaction pathways. Products were isolated from reactions performed on a large scale at room temperature. Rhodium(II) caprolactamate was selected as the catalyst for initial studies because of its solubility in polar and low polarity solvents.[4a] Treatment of *p*-methylstyrene with T-HYDRO (70% aqueous TBHP) in solvents of different polarity at room temperature, catalyzed by 1 mol% dirhodium caprolactamate, produced a complex mixture of oxidation products (Scheme 4), each member of which was individually isolated and characterized, and their presence in reaction mixtures was determined by HPLC and/or ^{1}H NMR analyses.[21] Several of these products (**3a**, **8a**, and **9a**) were unexpected but were confirmed in multiple separate experiments.

Scheme 4. Products Formed from *p*-Methylstyrene in $Rh_2(cap)_4$ Catalyzed Reactions with TBHP in Various Solvents



A majority of the products described in Scheme 4 were obtained from TBHP reactions at room temperature in chloroform catalyzed by $Rh_2(cap)_4$ (entries 1 and 2, Table 1), and they were confirmed by spectral and chromatographic analysis. Percent conversion was greater with the use of T-HYDRO [(70% TBHP in water, (entry 1, Table 1)] than with anhydrous TBHP (entry 2, Table 1). The loss of reactant *p*-methylstyrene due to polymerization or related processes was not determined, but the total yield obtained from multiple experiments under the same conditions does accurately reflect the molar amount of oxidized reactant. The same reactions performed in chloroform or water with CuI as the catalyst under the same conditions were much more sluggish (entries 11-14, Table 1) and incomplete even after a reaction time of 7 days due to the limited solubility of CuI in these solvents. Percent conversion is based on reacted *p*-methylstyrene, and total yield refers to the experimentally determined amounts of oxidation products. No reaction occurred without catalyst. Bis-peroxide **2a** was a major product, and this compound was previously formed from the $Mn(OAc)_3$ catalyzed reaction of TBHP in acetonitrile at room temperature (63% yield).[8b] Compounds **4a** and **5a** were inseparable by HPLC, but their copresence was confirmed by ^{1}H NMR spectra of the reaction mixtures and, for an accurate and distinctive identification, HRMS spectra confirmed both **4a** and **5a** (see SI for more information). A surprising and unexpected product was epoxide **8a** whose presence was confirmed spectrally and chromatographically, but also by the presence of vicinal diol **9a**.

Table 1. Solvent Dependence on the Catalytic Oxidation of *p*-Methylstyrene by TBHP[a]

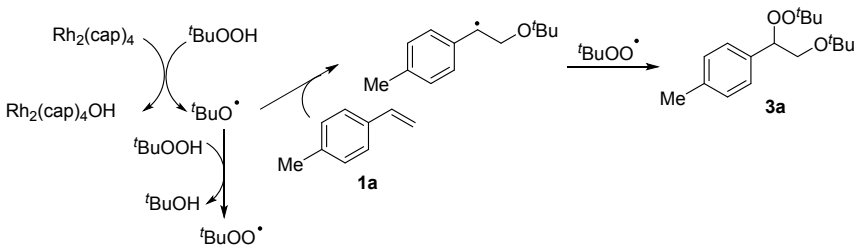
Entry	Solvent	Conv.(%)[b]	**2a** (%)	**4a/5a** (%)	**6a** (%)	**7a** (%)	**8a** (%)	**9a** (%)	**10a** (%)	Total yield (%)[c]
Reactions catalyzed by $Rh_2(cap)_4$:										
1	$CHCl_3$	75	15	18	3	8	13	1	2	60
2	$CHCl_3$[d]	58	11	4	nd	nd	21	nd	nd	36
3	DCM	94	4	8	13	8	2	1	20	69[e]
4	DCE	99	3	5	14	8	7	6	33	76

5	Hexane	68	2	5	5	4	nd	4	24	44
6	Cyclohexane	72	4	3	11	10	7	6	30	71
7	MeCN	60	4	18	2	10	7	2	7	50
8	Acetone	97	3	4	7	nd	11	2	24	51
9	MTBE	60	14	nd	3	nd	9	4	8	40[f]
10	H_2O	100	23	3	2	nd	nd	6	17	56[g]
Reactions catalyzed by CuI:										
11	$CHCl_3$	33	nd	10	nd	nd	10	nd	nd	20
12	$CHCl_3$[h]	44	nd	12	nd	nd	19	nd	nd	31
13	H_2O	11	nd	6	nd	nd	nd	nd	nd	6
14	H_2O[h]	60	nd	5	nd	7	5	11	nd	28
15	H_2O[i]	6	nd	4	nd	nd	nd	nd	nd	4
16	H_2O[h,i]	70	nd	2	nd	nd	nd	3	nd	5

[a]Reaction conditions: T-HYDRO (2.0 mmol) was added dropwise to a pre-sonicated solution of **1a** (0.4 mmol), catalyst (1.0 mol%) and 2.0 mL of solvent, and the reaction was continued for 18 h at rt. The yield of each product was determined by HPLC analysis and calibrated by ^{1}H-NMR spectral analysis of the reaction mixture with 1,3,5-trimethoxybenzene as the internal standard. Values provided in this table are from multiple experiments, and the yields are averaged (+/- 1-5%). [b]Percent conversion is based on reacted *p*-methylstyrene. [c]The sum of product yields for products listed in Scheme 3. [d]Using TBHP in decane. [e]Includes 13% **3a**. [f]Includes 2% **3a**. [g]Includes 5% **3a**. [h]Reaction time was 7 days. [i]Using DIPEA (1.1 eq). nd = not detected

We anticipated that the reactions of TBHP with *p*-methylstyrene would be solvent dependent. The data in Table 1 show that *p*-methylstyrene is fully consumed or nearly so in DCE, DCM, acetone, and water with catalysis by $Rh_2(cap)_4$, but not in hydrocarbon solvents, probably due to fast decomposition of TBHP in hydrocarbon solvents. Rapid evolution of oxygen was observed after TBHP was added when hexane and cyclohexane were used as the solvents. Coordination by acetonitrile to rhodium(II) caprolactamate at its axial coordination sites accounts for the low percent conversion in this polar solvent.[11,22] The major products in $Rh_2(cap)_4$-catalyzed reactions, with few exceptions, are the vicinal *bis*-*tert*-butylperoxide **2a** and *p*-toluic acid **10a**. Surprisingly, 2-(*tert*-butoxy)-1-(*tert*-butylperoxy)-1-(*p*-toluyl)ethane (**3a**) was identified in those reactions where H_2O or MTBE were used as solvents in less than 5%, but its regioisomer was not detected. This compound presumably arises by addition of the initially formed *tert*-butoxy radical to *p*-methylstyrene in competition with its favored hydrogen atom abstraction from TBHP (Scheme 5).[23] Unexpectedly, styrene oxide **8a** and diol **9a** were observed as minor products (generally < 5%) by both NMR and HPLC analyses, but in higher amounts in $CHCl_3$, DCE and acetone. Although unexpected, epoxidation of styrene is not an uncommon process in metal-catalyzed reactions of TBHP.[8d] Although oxygen transfer from peroxides is generally attributed to metal-oxo intermediates,[24] this is unlikely with $Rh_2(cap)_4$, and the mechanism for epoxide formation in the reactions reported in Table 1 is uncertain.

Scheme 5. Formation of 3a in the $Rh_2(cap)_4$ Catalyzed Oxidation of 1a by TBHP



With CuI as the catalyst (1.0 mol %) the rate of oxidation of *p*-methylstyrene by TBHP in water and chloroform was slow compared with reactions catalyzed by $Rh_2(cap)_4$. Only 10% **4a/5a** and 10% **8a** were detected after 18 h from the reaction in chloroform with two-thirds of the starting material remaining (entry 11, Table 1), and percent conversion did not increase significantly when the reaction time was extended to 7 d (entry 12, Table 1). Doubling the amount of TBHP had no effect on percent conversion or on the yield of oxidation products. A similar slow conversion was observed in water even using DIPEA (1.1 eq) as a ligand to solubilize CuI (entries 13-16, Table 1). The contrasting behavior between CuI and $Rh_2(cap)_4$ suggests an intrinsically different outcome from their reactions with TBHP.

To determine the reaction pathways in product formation, the time courses for reactions in chloroform and water were performed using $Rh_2(cap)_4$ as catalyst (Figure 1 and 2). Anticipating that the formation of **2a** and **4a/5a** were competitive, these products were monitored from the reaction performed in chloroform; and Figure 1 shows the complementary buildup of both products; the formation of **4a/5a** is faster than formation of bis-*tert*-butyl peroxide **2a** which is probably related to the initial sequestering of available oxygen in the reaction solution that is unavoidable with TBHP.

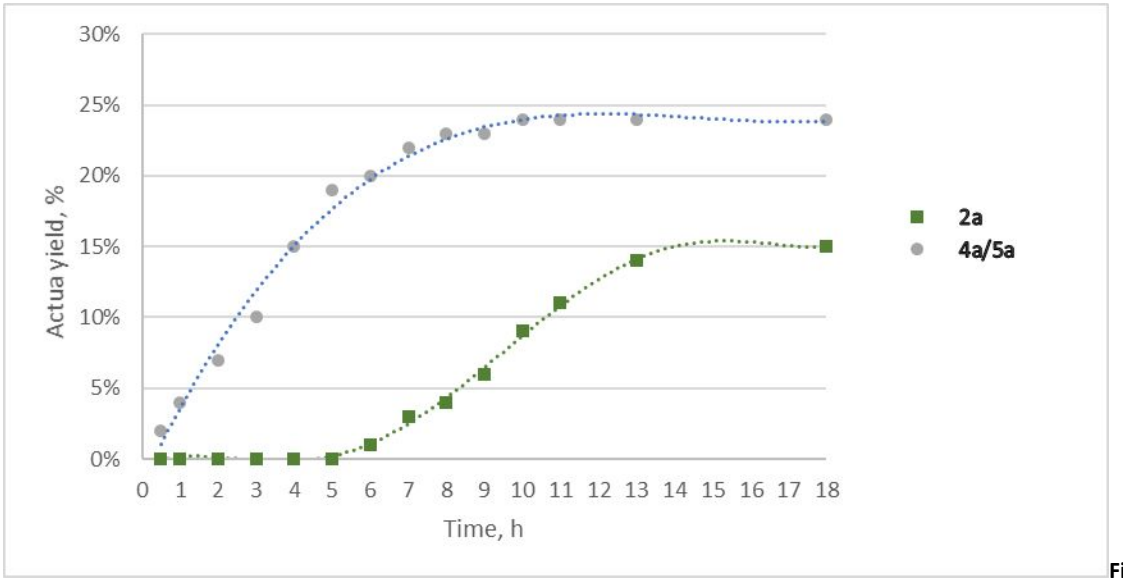


Figure 1. Yield curves for **2a** and **4a**/**5a** in $CHCl_3$. T-HYDRO (2.0 mmol) was added dropwise to **1a** (0.4 mmol), $Rh_2(cap)_4$ (1 mol%) in $CHCl_3$ (2.0 mL) and the reaction was monitored the first 30 minutes and every hour for 18 h at room temperature. The yield of each product was determined by HPLC analysis.

In water, by contrast, *p*-methylstyrene **1a** is consumed rapidly, and just after 4 h its molar amount is less than 5% (Figure 2). The initial rapid consumption of **1a** occurs with the formation of the bis-*tert*-butylperoxide **2a** and styrene oxide (**8a**) as major products. After 3 h the amount of **2a** remains at 25%, whereas the amount of epoxide **8a** increases initially then decreases to less than 5% after 3 h. The formation of *p*-toluic acid **10a** occurs late in the reaction, reaching a maximum amount of 17% at 18 h.

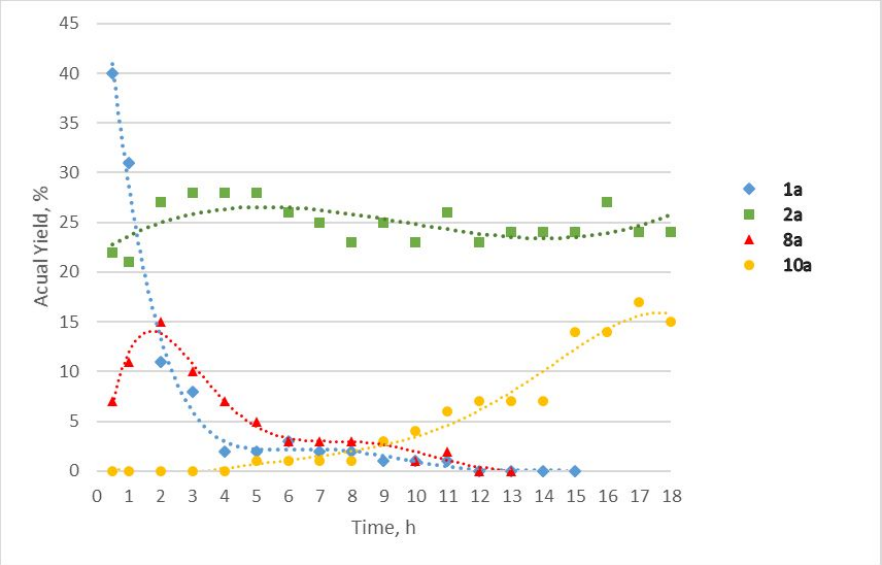
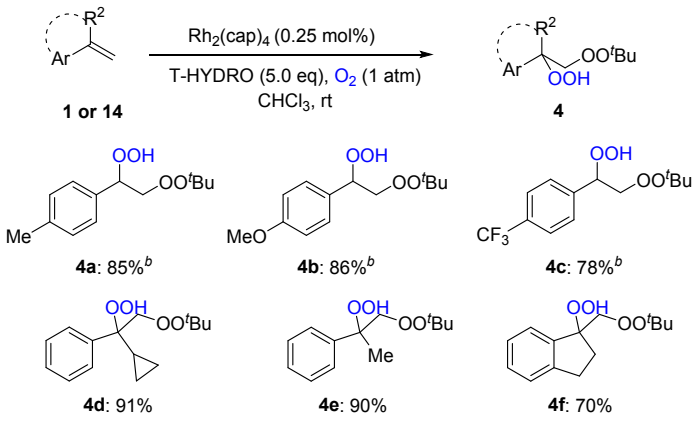


Figure 2. Percentage profiles of **1a**, **2a**, **8a** and **10a** in H_2O**.** T-HYDRO (2.0 mmol) was added dropwise to a pre-sonicated solution of 2.0 mL H_2O, **1a** (0.4 mmol), and $Rh_2(cap)_4$ (1 mol%). The reaction was monitored the first 30 minutes and every hour for 18 h at room temperature. The yield of **1a** and each product was determined by HPLC analysis.

Fascinated by the competing oxygenation reaction described in Figure 1, the oxidation reaction was performed under an atmosphere of oxygen instead of air (Scheme 6). Under these conditions, bis-peroxide **2a** was not formed, and hydroperoxide **4a** was formed in 85% yield. Under these conditions a variety of hydroperoxide compounds **4** were prepared in high isolated yields, suggesting the generality of this process. Thus, the benzyl radical that is formed by *tert*-butylperoxy radical addition to styrene reacts competitively with either dioxygen or the *tert*-butyl peroxy radical in the first stage of the oxidative cleavage reaction. Dioxygen is an effective trap for the benzyl radical, even with α-cyclopropylstyrene whose benzyl radical is subject to cyclopropylcarbinyl radical ring opening.[25]

Scheme 6. Synthesis of hydroperoxide products 4[a]

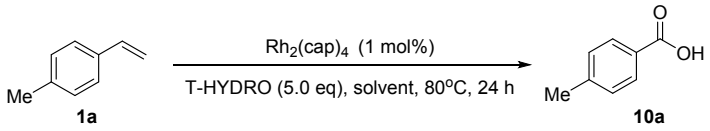


[a]Conditions: T-HYDRO (2.0 mmol), $Rh_2(cap)_4$ (0.25 mol%), **1** or **14** (0.4 mmol), $CHCl_3$ (4.0 mL), O_2 (1 atm), rt. Isolated yield.

[b]$Rh_2(cap)_4$ (0.25 mol%), T-HYDRO (4.0 mmol).

Shyu and coworkers have reported the copper(II) chloride-catalyzed TBHP oxidation of styrene and geminal disubstituted alkenes to carbonyl compounds at room temperature from which moderate to good yields of the corresponding cleavage products were obtained.[26] However, benzaldehydes were reported as the only products in reactions with styrenes, and formation of the corresponding benzoic acids was not reported. Yet in reactions catalyzed by $Rh_2(cap)_4$ and CuI, the carboxylic acid cleavage product is a major product, and *p*-tolualdehyde is a minor product (Table 1). When the reaction temperature is increased to 80°C, the overall yield of carboxylic acid **10a** increased (Table 2). The optimum solvent was found to be water for reactions catalyzed by $Rh_2(cap)_4$ (entry 10, Table 2). CuI also catalyzed the formation of *p*-toluic acid **10a** in moderate yields (entries 12-13, Table 2). Using $CuCl_2$ as the catalyst instead of CuI, *p*-toluic acid **10a** was formed in low yield (entry 14, Table 2) and *p*-tolualdehyde was not detected. When the reaction catalyzed by $Rh_2(cap)_4$ was conducted under an oxygen atmosphere, the yield of *p*-toluic acid was increased to 76% (entry 11, Table 2).

Table 2. Screening reaction condition for the catalytic oxidation of 1a[a]



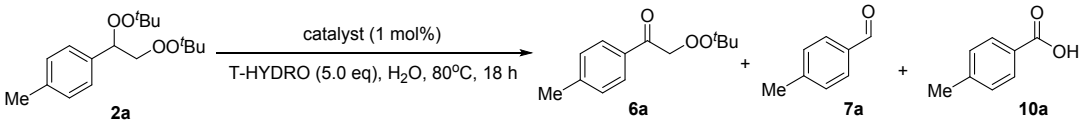
Entry	Solvent	Catalyst	Yield (%)[b]
1	$CHCl_3$	$Rh_2(cap)_4$	48
2	DCM	$Rh_2(cap)_4$	55
3	DCE	$Rh_2(cap)_4$	58
4	Hexane	$Rh_2(cap)_4$	62
5	Cyclohexane	$Rh_2(cap)_4$	61
6	MeCN	$Rh_2(cap)_4$	45
7	Toluene	$Rh_2(cap)_4$	57
8	MTBE	$Rh_2(cap)_4$	35
9	H_2O	$Rh_2(cap)_4$	64
10[c]	H_2O	$Rh_2(cap)_4$	72

11[d]	H_2O	$Rh_2(cap)_4$	76[e]
12	$CHCl_3$	CuI	51[e]
13	H_2O	CuI	18[e]
14	H_2O	$CuCl_2$	38[e]

[a]Reaction conditions: T-HYDRO (2.0 mmol) was added to a pre-sonicated solution of **1a** (0.4 mmol), catalyst (1 mol%) and 2.0 mL solvent, and the reaction was continued for 24 h at 80°C. [b]Unless indicated otherwise, isolated yields are reported. [c]4.0 eq NaOH was added as the additive. [d]The reaction was conducted under an oxygen atmosphere. [e]The yield of the *p*-toluic acid was determined by HPLC analysis.

A series of experiments was performed to elucidate the mechanism of this oxidative cleavage reaction. 1-[1,2-Bis(*tert*-butylperoxy)ethyl]-4-methylbenzene **2a**, 1-[2-(*tert*-butylperoxy)-1-hydroperoxyethyl]-4-methyl-benzene **4a**, and 2-(*tert*-butylperoxy)-1-(*p*-tolyl)ethan-1-one **6a** were separated from the reaction mixture, and they were separately subjected to the reaction conditions to determine if these compounds were intermediates in the formation of *p*-toluic acid (Schemes 7-13). Bis-peroxide **2a** was treated with T-HYDRO in water at 80°C with catalysis by $Rh_2(cap)_4$, and oxidative cleavage accounted for the majority of product formation (Scheme 7). However, nearly 20% of reactant remained after 18 h, and only 41% of reacted **2a** was converted to *p*-toluic acid. In contrast, with CuI as the catalyst α-keto peroxide **6a** was formed, but *p*-toluic acid **10a** was produced in less than 20% yield, suggesting the possible limitations of unligated CuI. Using 1.1 eq of DIPEA to solubilize CuI, caused conversion of bis-peroxide **2a** to *p*-toluic acid **10a** in more than 70% of yield. Hydrogen atom abstraction from the benzylic position of **2a** followed by cleavage of the O-O bond, similar to that previously reported for allylic oxidations by TBHP,[12c] accounts for the formation of α-keto peroxide **6a**, but its subsequent oxidative cleavage to *p*-toluic acid is not mechanistically evident in these experiments but could arise from initial cleavage of the O-O bond.

Scheme 7. Oxidation Products of Bis-peroxide 2a[a]



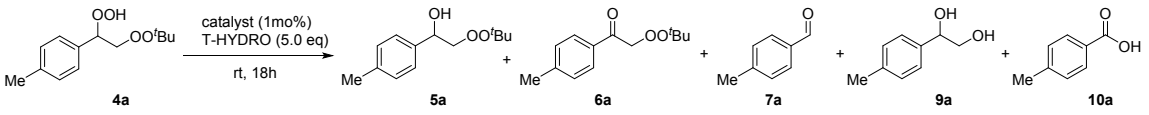
	2a	6a	7a	10a
$Rh_2(cap)_4$	19%	3%	<1%	41%
CuI	37%	24%	2%	19%
CuI, DIPEA (1.1 eq)	<1%	<1%	1%	72%

[a]Conditions: T-HYDRO (2.0 mmol), **2a** (0.4 mmol), catalyst (1 mol%), water (2.0 mL), 80 °C, 18 h. The percentage of each compound compared with the initial amount of **2a** was determined by HPLC analysis. The values below the starting material are the percentage of the remaining **2a** after the reaction was done.

Hydroperoxide **4a**, formed by dioxygen trapping of the benzyl radical intermediate, undergoes initial O-O cleavage similar to that of TBHP with $Rh_2(cap)_4$ as the catalyst at room temperature (Scheme 2), and the products formed by this catalytic reaction are solvent dependent (Scheme 8). In chloroform, less than 50% of hydroperoxide **4a** is converted to products, but in water ketoperoxide **6a** and oxidative cleavage

product **10a** are the major products at room temperature. At 80°C, hydroperoxide **4a** is converted to *p*-toluic acid in 73% of yield. This is an example of a secondary alkoxy radical acting as a hydrogen atom acceptor (giving **5**) and a hydrogen atom donor (giving **6**)[27] or undergoing C-C cleavage to form *p*-tolualdehyde[28] and, subsequently, *p*-toluic acid (Scheme 9). In contrast, oxidative cleavage of the O-O bond of **4a** is very slow with CuI as the catalyst until an organic base (DIPEA) is added, and only then does **4a** react at a reasonable rate. In water the major product is alcohol peroxide **5a**, but in chloroform oxidative cleavage product **7a** is the major product. The origin of **9a** is uncertain.

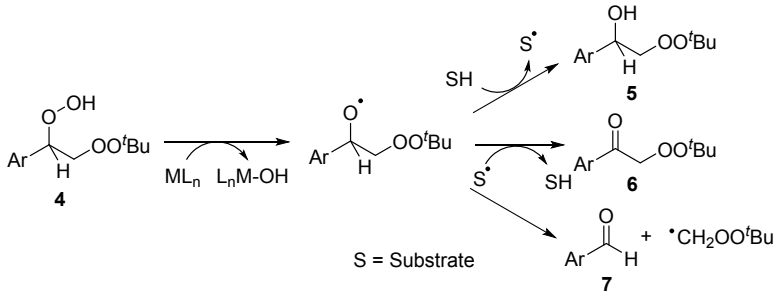
Scheme 8. Oxidation Products of the Hydroperoxide 4a[a]



	4a	5a	6a	7a	9a	10a
$Rh_2(cap)_4$, $CHCl_3$	57%[b]	9%[b]	15%[b]	8%[b]	<1%[b]	1%[b]
$Rh_2(cap)_4$, H_2O	7%[c]	<1%[c]	21%[c]	<1%[c]	7%[c]	22%[c]
$Rh_2(cap)_4$, H_2O, 80 °C	<1%[c]	<1%[c]	<1%[c]	<1%[c]	<1%[c]	73%[c]
CuI, DIPEA (1.1 eq), $CHCl_3$	5%[b]	17%[b]	<1%[b]	38%[b]	12%[b]	7%[b]
CuI, DIPEA (1.1eq), H_2O	<1%[c]	58%[c]	<1%[c]	<1%[c]	<1%[c]	12%[c]

[a]Conditions: T-HYDRO (1.0 mmol), **4a** (0.2 mmol), catalyst (1 mol%), solvent (2.0 mL), 18 h. The values below the starting material are the percentage of the remaining **4a** after the reaction was done. [b]The percentage of each compound compared with the initial amount of **4a** was determined by ^{1}H-NMR spectral analysis of the reaction mixture using 1,3,5 trimethoxybenzene as internal standard. [c]The percentage of each compound compared with the initial amount of **4a** was determined by HPLC analysis.

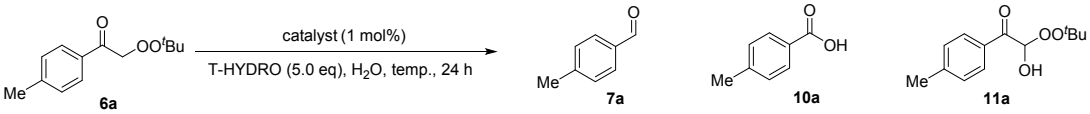
Scheme 9. Oxidative Decomposition of Secondary Hydroperoxide 4



Treatment of ketoperoxide **6a** with T-HYDRO in water with $Rh_2(cap)_4$ and CuI catalysis gave the results described in Scheme 10. T-HYDRO efficiently converts **6a** to *p*-toluic acid under catalysis by $Rh_2(cap)_4$ and CuI in water at room temperature. At 80 °C percent conversion is higher, as is the yield of *p*-toluic acid, with both catalysts. Oxidative cleavage of **6a** occurs at a much slower rate without catalyst. In contrast, the oxidation of **6a** in chloroform or cyclohexane by TBHP at room temperature under catalysis by $Rh_2(cap)_4$ produces hemiketal **11a** in 15% and 28% yield respectively. **11a** was also identified through HR-MS from the oxidative reaction of **1a.** Increasing the temperature at 80°C in chloroform, the percent conversion of ketone peroxide **6a** to the *p*-toluic acid is 75%. The oxidation of **6a** occurs by hydrogen atom

abstraction to form an intermediate α-keto radical, which is trapped by molecular oxygen, then hydrogen atom capture to form a hydroperoxide that undergoes O-O cleavage catalyzed by $Rh_2(cap)_4$ to form the hemiketal **11a** (Scheme 11).

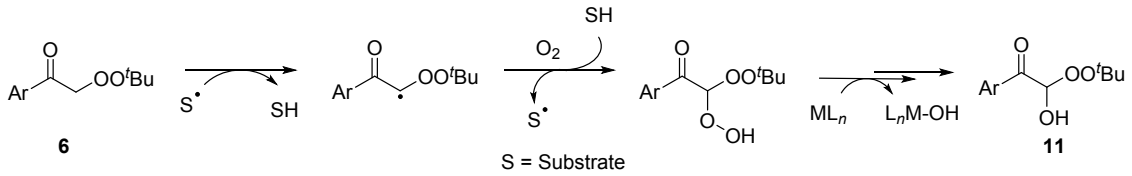
Scheme 10. Oxidation Products of the Ketoperoxide 6a[a]



$Rh_2(cap)_4$, rt	25%[b]	<1%[b]	63%[b]	<1%[b]
$Rh_2(cap)_4$, 80°C	5%[c]	<1%[c]	70%[c]	<1%[c]
$Rh_2(cap)_4$, $CHCl_3$, N_2, rt[d]	62%[f]	<1%[f]	8%[f]	15%[f]
$Rh_2(cap)_4$, $CHCl_3$, N_2, 80°C[d]	<1%[f]	6%[f]	75%[f]	3%[f]
$Rh_2(cap)_4$, cyclohexane[e]	<1%[f]	<1%[f]	42%[f]	28%[f]
CuI, DIPEA (1.1eq), rt	7%[f]	<1%[f]	76%[f]	<1%[f]
CuI, DIPEA (1.1 eq), 80°C	<1%[f]	<1%[f]	91%[f]	<1%[f]
no catalyst, 80°C	80%[b]	<1%[b]	14%[b]	<1%[b]

[a]Conditions: Unless indicated otherwise, T-HYDRO (2.0 mmol), **6a** (0.4 mmol), catalyst (1 mo%), water (2.0 mL), 18 h. The values below the starting material are the percentage of the remaining **6a** after the reaction was done. [b]The percentage of each compound compared with the initial amount of **6a** was determined by ^{1}H-NMR spectral analysis of the reaction mixture using 1,3,5-trimethoxybenzene as internal standard. [c]Isolated percentage of each compound. [d]TBHP in decane. [e]$Rh_2(cap)_4$, 0.25 mol%, 4d. [f]The percentage of **6a**, **7a**, **10a** and **11a** compared with the initial amount of **6a** was determined by HPLC analysis.

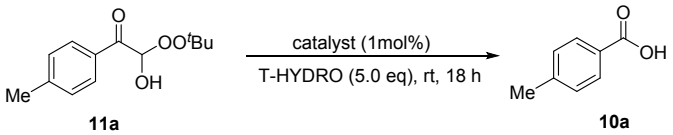
Scheme 11. Oxidative Decomposition of Ketoperoxide 6



tert-Butyl *p*-methylperbenzoate was investigated as a possible intermediate formed from hemiketal **6a** produced by addition of TBHP, but this compound was not detected (<1%) in the reaction mixture, and the perester was determined to be stable under the reaction conditions. However, hemiketal peroxide **11a,** which was determined by spectral and HRMS to be a reaction product from the oxidation of **6a** by T-HYDRO in chloroform or cyclohexane at room temperature with $Rh_2(cap)_4$ as the catalyst, was independently synthesized from phenylglyoxal.[29] Treatment of **11a** with T-HYDRO and catalyst gave the results as shown in Scheme 12. The catalytic oxidation of **11a** with TBHP is solvent dependent. Reaction with TBHP catalyzed by CuI with DIPEA in H_2O converts hemiketal peroxide **11a** to *p*-toluic acid **10a** in 94% yield, whereas no reaction occurred in $CHCl_3$. Oxidation of **11a** by TBHP in water with $Rh_2(cap)_4$ as the

catalyst at room temperature produced *p*-toluic acid in only 10% yield. However, by increasing the temperature to 80 °C the yield of *p*-toluic acid **10a** increased to 65% (isolated yield).

Scheme 12. Oxidation Products of the Hemiketal 11a[a]



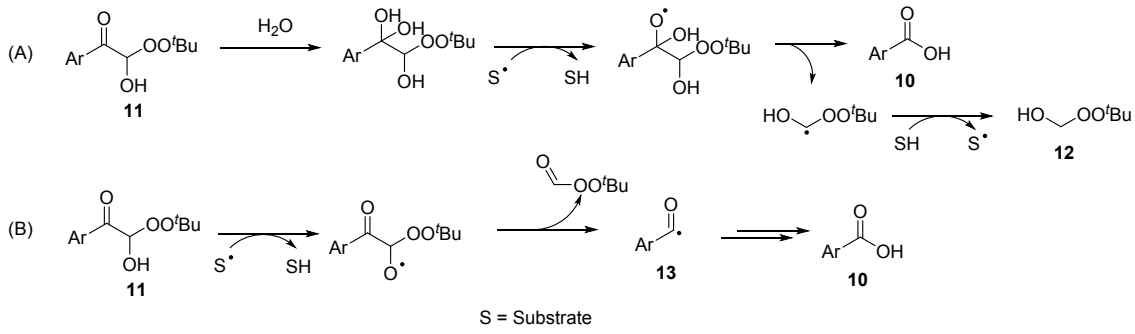
11a **10a**

$Rh_2(cap)_4$, $CHCl_3$	94%	<1%
$Rh_2(cap)_4$, H_2O	71%	10%
$Rh_2(cap)_4$, H_2O, 80°C	7% (5%)	62% (65%)
CuI, DIPEA (1.1 eq), $CHCl_3$	95%	<1%
CuI, DIPEA (1.1 eq), H_2O	<1%	94%

[a]Conditions: T-HYDRO (1.0 mmol), **11a** (0.2 mmol), catalyst (1 mol%), 2.0 mL of solvent, 18 h. The percentage of **11a** and **10a** compared with initial amount of **11a** was determined by HPLC analysis. Isolated percentage is in parenthesis. The values below the starting material are the percentage of the remaining **11a** after the reaction was done.

A plausible mechanism for this oxidation involves initial nucleophilic addition by water, then hydrogen atom abstraction from one of the hydroxyl groups on the benzylic position to form an alkoxy radical that effects cleavage of the C-C bond and formation of the *p*-toluic acid and *tert*-butylperoxy methanol **12** which was detected by HRMS (Scheme 13A). However, another pathway through aryl acyl radical (**13**)[30] could not be excluded (Scheme 13B).

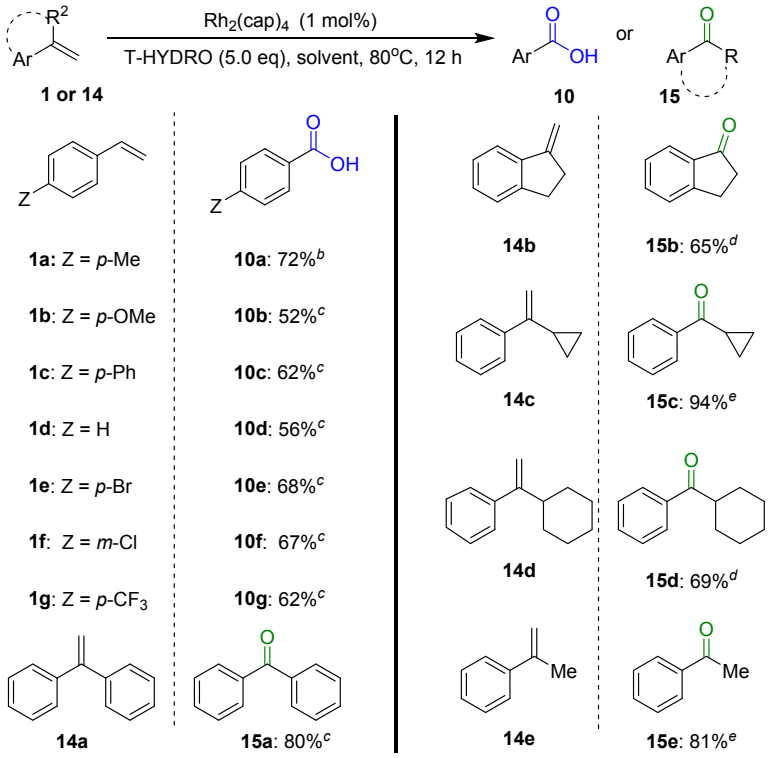
Scheme 13. Oxidative Decomposition of Hemiketal Peroxide 11



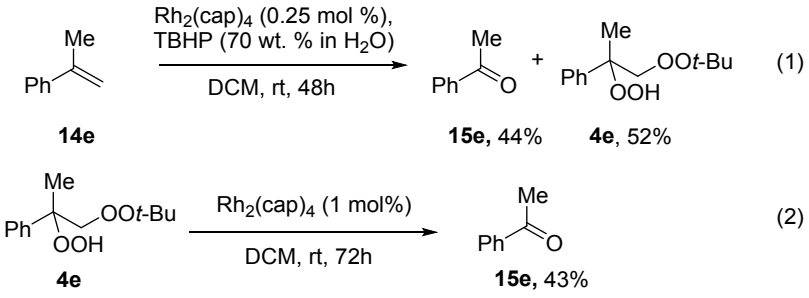
Oxidative cleavage with TBHP and $Rh_2(cap)_4$ as the catalyst at 80°C was investigated with substituted styrenes **1** and geminal-disubstituted ethylenes **14** (Scheme 14). The styrenes formed the corresponding benzoic acids in moderate yields (56-72%), and ketones could also be obtained in good yields from geminal-disubstituted ethylenes. Even performing the oxidation reaction of (1-cyclopropylvinyl)benzene **14c** at room temperature provided cyclopropyl phenyl ketone **15c** in 94% isolated yield, demonstrating that capturing the benzyl radical by the *tert*-butylperoxy radical or molecular oxygen is faster than cyclopropylcarbinyl ring-opening.[25] Indeed, when the oxidative cleavage reaction was performed with α-

methyl styrene **14e** at room temperature in DCM, an intermediate to the oxidative cleavage product was isolated and characterized (Eq 1); in addition, hydroperoxide **4e** was converted to **15e** in 43% with catalysis of $Rh_2(cap)_4$ (Eq 2). Hydroperoxide **4e** underwent O-O cleavage in a similar way as **4a** in Scheme 9, but forming a tertiary alkoxy radical that undergoes C-C cleavage to form ketone **15** (Scheme 15).

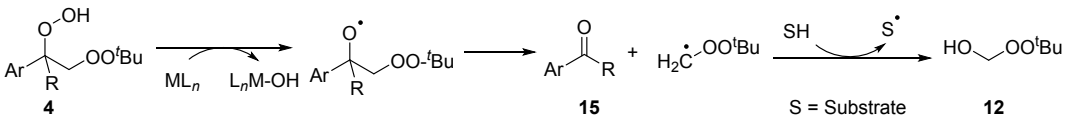
Scheme 14. Oxidation Products of Substituted Styrenes 1 and Geminal-Disubstituted Ethylenes 14



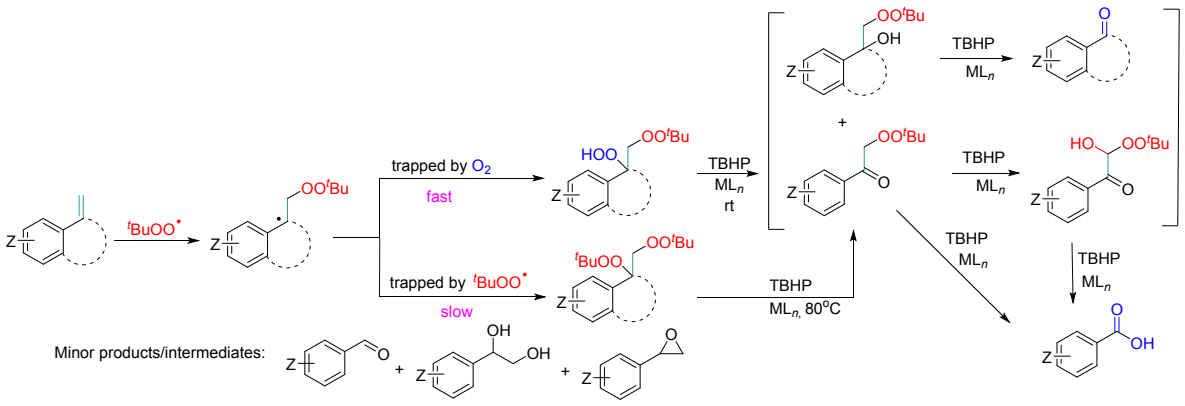
[a]Condition: T-HYDRO (2.0 mmol), **1** or **14** (0.4 mmol), $Rh_2(cap)_4$ (1 mol%) and 2.0 mL of solvent. Isolated yield. [b]Water as solvent and NaOH (4.0 eq) as the additive. [c]Water as solvent. [d]Cyclohexane as solvent. [e]$Rh_2(cap)_4$ (0.25 mol%), cyclohexane as solvent, room temperature and 2 days



Scheme 15. Oxidative Decomposition of Tertiary Hydroperoxide 4



Scheme 16. Proposed Mechanism for the Overall Oxidative Cleavage of C=C Bonds.



Conclusion. Free radical oxidative cleavage of a C=C is a process whose complexity[31] is often overlooked. A general mechanism is proposed for this reaction that uses *tert*-butyl hydroperoxide as the oxidant and either dirhodium(II) caprolactamate or copper iodide as catalysts (Scheme 16). The reaction is initiated by peroxy radical addition to the carbon-carbon double bond that forms the more stable radical intermediate. In the case of styrene and substituted styrenes the resultant benzyl radical combines with either the *tert*-butylperoxy radical or dioxygen in solution, and using a saturated oxygen solution the hydroperoxide product is exclusive (Scheme 6). There is a noticeable dependence of trapping by the *tert*-butylperoxy radical or dioxygen on the solvent and catalyst. These competitive reactions, occurring at room temperature and dependent on the flux of the *tert*-butylperoxy radical (Scheme 2) and the concentration of dioxygen provide the major pathways that lead to oxidative cleavage. From this point the oxidative pathways diverge. Hydroperoxide **4** undergoes oxidative O-O bond cleavage at room temperature to form an alkoxy radical that produces at least three major products (Scheme 9) that are further oxidized with the eventual formation of a benzoic acid (or ketone from an α,α-disubstituted alkene). In contrast, the vicinal di-*tert*-butylperoxide product is resistant to further oxidation at room temperature, but at 80 °C undergoes benzylic hydrogen atom abstraction to form the ketoperoxide **6** or oxidative cleavage to produce benzaldehyde and/or benzoic acid. Ketoperoxide **6** undergoes oxidative cleavage, one pathway for which is through its oxidized arylglyoxal hemiacetal **11** (Scheme 11). The hemiacetal peroxide **11** is further oxidized to the final product *p*-toluic acid **10**. A survey of styrenes and related geminal-disubstituted ethylenes has shown the generality of the oxidative cleavage process.

Experimental Section

General Information. Reactions, unless noted, were performed in oven-dried (120 °C) glassware with magnetic stirring under air atmosphere. Unless otherwise noted, all commercially available compounds were used as purchased without further purification. Analytical thin layer chromatography (TLC) was carried out using silica gel plates; visualization was accomplished with UV light (254 nm). Column chromatography was performed on CombiFlash®Rf200 and Rf+ purification systems using normal phase disposable columns. ^{1}H NMR spectra were recorded on 500 MHz and 300 MHz spectrometers, and chemical shifts were reported in ppm. The peak information was described as br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, comp = composite; coupling constant(s) in Hz. The number of protons (n) for a given resonance was indicated by nH. Coupling constants were reported as J-values in Hz. $CDCl_3$ was used as a reference (7.26 ppm) for all spectra. ^{13}C NMR spectra were recorded on a 126 MHz spectrometer with complete proton decoupling. Chemical shifts are reported in ppm utilizing the central resonance of the $CDCl_3$ absorption as a reference (77.16 ppm). High-performance liquid chromatography (HPLC) analysis were conducted using an Agilent 1220 Infinity HPLC system with a Poroshell 120 EC-C18 column and water/acetonitrile as eluent. High-resolution mass spectra (HRMS) were performed on a Bruker Q-TOF-ESI mass spectrometer with an ESI resource using an ion calibration solution as the standard. Melting points (mp) were measured uncorrected on an Electro Thermo Mel-Temp DLX 104 device.

$Rh_2(cap)_4(MeCN)_2$ was prepared according to the literature procedure.[32] The purity of TBHP was monitored by NMR spectroscopy. All previously unreported products were characterized by ^{1}H and ^{13}C NMR, as well as HRMS. Spectra of compounds **2a,**[8b] **7a**, **8a**, **9a**, **10a**, **10b**, **10c**, **10d, 10e, 10f, 10g, 15a**, **15b**, **15c**, **15d** and **15e**, agree with published information.[33]

Catalytic Oxidation of *p*-Methylstyrene 1a. A 8.0 mL 6-dram screw-cap vial containing a stirring bar was charged sequentially with **1a** (47.3 mg, 0.4 mmol, 1.0 equiv.), catalyst (1.0 mol%) and 2.0 mL of the designated solvent. The mixture was sonicated for 1 min to facilitate the maximum dissolution of the metal catalyst, after which T-HYDRO (TBHP 70% in water, 270 µL, 2.0 mmol) was added dropwise into the vial. The reaction solution was sealed with a cap and stirred for 18 h at the selected temperature then transferred to a 20.0-mL 6-dram screw-cap vial with 10.0 mL of acetone. From the diluted solution, a measured amount was taken and transferred to 10.0 mL volumetric flask for quantitative analysis. The flask was then brought to 10.0 mL of volume with acetonitrile, and the solution was analyzed by HPLC with water/acetonitrile (1:4) as the eluent.

Isolation of Compounds 2a-8a from Reaction Catalyzed by $Rh_2(cap)_4$ in $CHCl_3$. T-HYDRO (11.2 mL, 100.0 mmol) was added dropwise to a pre-sonicated 100.0 mL round-bottom flask containing a magnetic stirring bar, 30.0 mL of $CHCl_3$, **1a** (20.0 mmol, 2.36 g) and $Rh_2(cap)_4$ (16.4 mg, 0.1 mol%) at room temperature. The solution was stirred for 18 h at room temperature after which the volume was reduced under reduced pressure, and the residue was purified by column chromatography (silica gel, AcOEt/hexane = 5%). Fractions containing the products were combined, and the solvent was evaporated under reduced pressure followed by additional drying under high vacuum for 20 min (0.09 Torr, room temperature) to afford **2a** (888.1 mg, 15%), **3a** (56.1 mg, 1%), **4a** (672.6 mg, 14%), **5a** (89.6 mg, 2%), **6a** (133.2 mg, 3%), **8a** (188.2 mg, 7%)**.**

1-[2-(*tert*-Butoxy)-1-(tert-butylperoxy)ethyl]-4-methylbenzene, **3a**: colorless oil; ^{1}H NMR (300 MHz, , $CDCl_3$) δ 7.26 (d, J = 7.9 Hz, 2H), 7.15 (d, J = 7.9 Hz, 2H), 4.98 (dd, J = 7.4, 4.8 Hz, 1H), 3.67 (dd, J = 10.4, 7.4 Hz, 1H), 3.47 (dd, J = 10.4, 4.8 Hz, 1H), 1.25 (s, 9H), 1.16 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 137.5, 136.5, 129.0, 127.2, 86.0, 80.9, 73.4, 64.6, 27.6, 26.6, 21.4. HRMS (ESI) calculated for $C_{17}H_{28}NaO_3$ $[M+Na]^+$: 303.1931; found: 303.1928. The structure of **3a** was confirmed by the comparison of the CH_2 chemical shift of **3a** with **2a**, **4a**/**5a**, as well as the similar structure reported in Ref 23a.

1-(2-(tert-Butylperoxy)-1-hydroperoxyethyl)-4-methylbenzene, **4a**: colorless oil; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.57 (br, 1H), 7.26 (d, J = 7.7 Hz, 2H), 7.19 (d, J = 7.7 Hz, 2H), 5.30 (dd, J = 8.5, 3.3 Hz, 1H), 4.25 (dd, J = 13.1, 8.5 Hz, 1H), 4.15 (dd, J = 13.1, 3.3 Hz, 1H) 2.36 (s, 3H), 1.28 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, CDCl3) δ 138.6, 134.1, 129.5, 127.2, 85.2, 81.2, 76.9, 26.4, 21.3. HRMS (ESI) calculated for $C_{13}H_{24}NO_4$ $[M+NH_4]^+$: 258.1700; found: 258.1704.

***2-(tert-Butylperoxy)-1-(p-tolyl)ethan-1-*ol 5a**: colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.0 Hz, 2H), 7.17 (d, *J* = 8.0 Hz, 2H), 5.05 (dd, *J* = 9.0, 2.5 Hz, 1H), 4.07 (dd, *J* = 12.6, 2.5 Hz, 1H), 3.94 (dd, *J* = 12.6, 9.0 Hz, 1H), 2.34 (s, 3H), 1.29 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 137.7, 137.1, 129.3, 126.3, 81.1, 80.9, 72.4, 26.5, 21.3. HRMS (ESI) calculated for $C_{13}H_{24}NO_3$ $[M+NH_4]^+$: 242.1751; found: 242.1758.

2-(tert-Butylperoxy)-1-(p-tolyl)ethan-1-one, **6a**: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.3 Hz, 2H), 7.26 (d, *J* = 8.3 Hz, 2H), 5.06 (s, 2H), 2.41 (s, 3H), 1.24 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 195.0, 144.5, 132.8, 129.3, 128.5, 81.2, 77.6, 26.4, 21.9. HRMS (ESI) calculated for $C_{13}H_{22}NO_3$ $[M+NH_4]^+$: 240.1594; found: 240.1596.

Catalytic Oxidation of 1-[1,2-Bis(*tert*-butylperoxy)ethyl]-4-methylbenzene 2a. In a pre-sonicated 8.0 mL 6-dram screw-cap vial containing a magnetic stirring bar, catalyst (1.0 mol%) **2a** (118.6 mg, 0.4 mmol) and 2.0 mL of solvent, T-HYDRO (270.0 µL, 2.0 mmol) was added dropwise. After stirring for 18 h at the selected temperature, the reaction solution was transferred to a 20.0-mL 6-dram screw-cap vial with 10.0 mL of acetone. From the diluted solution a measured amount was taken and transferred to a 10.0 mL

volumetric flask for quantitative analysis. The flask was then brought to 10.0 mL with acetonitrile, and the solution was analyzed by HPLC with water/acetonitrile as the eluent.

Catalytic Oxidation of 1-[2-(*tert*-Butylperoxy)-1-hydroperoxyethyl]-4-methylbenzene 4a, HPLC. T-HYDRO (135.0 µL, 1.0 mmol) was added dropwise to a pre-sonicated 8.0 mL 6-dram screw-cap vial containing a magnetic stirring bar, catalyst (1.0 mol%), **4a** (48.0 mg, 0.2 mmol), 2.0 mL of solvent. The solution was stirred for 18 h at the designated temperature, after which it was analyzed by HPLC as described previously.

Catalytic Oxidation of 1-[2-(*tert*-Butylperoxy)-1-hydroperoxyethyl]-4-methylbenzene 4a, NMR. T-HYDRO (135.0 µL, 1.0 mmol) was added dropwise to a pre-sonicated 8.0-mL 6-dram screw-cap vial containing a magnetic stirring bar, **2c** (48.0 mg, 0.2 mmol), catalyst (1.0 mol%), 1,3,5 trimethoxybenzene (33.6 mg, 0.2 mmol) used as the internal standard, and 2.0 mL of $CDCl_3$. The reaction solution was stirred for 18 h at room temperature, and the residue was analyzed by ^{1}H-NMR spectroscopy. The percent yield of product was determined from the integral values of the internal standard (s, 6.11 ppm), the benzylic proton of **4a** (dd, 5.32-5.30), the benzylic proton of **5a** (dd, 5.08-5.06) and the α-alkyl protons of **6a** (s, 5.09 ppm), and the α-proton of **7a** (s, 9.92 ppm), the benzylic proton of **9a** (dd, 4.84-4.81), and the aromatic ortho-protons of **10a** (d, 8.02 ppm).

Catalytic Oxidation of 2-(*tert*-Butylperoxy)-1-(*p*-tolyl)ethan-1-one 6a. T-HYDRO (270.0 µL, 2.0 mmol) was added dropwise to a pre-sonicated 8.0-mL 6-dram screw-cap vial containing a magnetic stirring bar, $Rh_2(cap)_4$ (2.7 mg, 1.0 mol %) **6a** (88.8 mg, 0.4 mmol) and 2.0 mL of water. The reaction solution was heated at 80 ℃ in oil bath and stirred for 18 h then cooled at room temperature and transferred to a 50.0 mL round bottom-flask with 20.0 mL of AcOEt. The volume of the solution was reduced under reduced pressure, and the resulting residue was purified by column chromatography (silica gel, DCM/MeOH = 20:1). Fractions containing the product were combined, and the solvent was evaporated under reduced pressure followed by additional drying under high vacuum for 20 min (0.09 Torr, room temperature) to afford *p*-toluic acid **10a** in 70% yield.

Catalytic Oxidation of 2-(*tert*-Butylperoxy)-1-(*p*-tolyl)ethan-1-one 6a, NMR. T-HYDRO (270.0 µL, 2.0 mmol) was added dropwise to a pre-sonicated 8.0-mL 6-dram screw-cap vial containing a magnetic stirring bar, **6a** (88.8 mg, 0.4 mmol), $Rh_2(cap)_4$ (2.7 mg, 1.0 mol%) and 2.0 mL of water. The reaction solution was stirred for 18 h at the selected temperature, then cooled to room temperature and transferred to a 50.0 mL round bottom-flask with 20.0 mL of AcOEt. 1,3,5-Trimethoxybenzene (67.3 mg, 0.4 mmol), used as internal standard, was added; and the volume of the reaction solution was reduced under reduced pressure. The resulting residue was dissolved in $CDCl_3$ and analyzed by ^{1}H-NMR spectroscopy. The percent

yields of products were determined from the integral values of internal standard (s, 6.11 ppm) and α-alkyl protons of **6a** (s, 5.09 ppm) and the aromatic protons of **10a** (d, 8.02 ppm).

Catalytic Oxidation of 2-(*tert*-Butylperoxy)-1-(*p*-tolyl)ethan-1-one 6a, HPLC. T-HYDRO (270.0 μL, 2.0 mmol) was added dropwise to a pre-sonicated 8.0-mL 6-dram screw-cap vial containing a magnetic stirring bar, metal catalyst (1.0 mol%), **6a** (88.8 mg, 0.4 mmol), 2.0 mL of solvent and DIPEA when it was required (77.0 μL, 0.44 mmol). The reaction solution was brought to the selected temperature and stirred for 18 h, then cooled to room temperature and transferred to a 20.0 mL 6-dram screw-cap vial with 10.0 mL of acetone. From the diluted solution a measured amount was transferred to a 10.0 mL volumetric flask for quantitative analysis. The flask was then brought to 10.0 mL in a volumetric flask with acetonitrile and analyzed by HPLC with water/acetonitrile as the eluent.

Catalytic Oxidation of 2-(*tert*-Butylperoxy)-2-hydroxy-1-(*p*-tolyl)ethan-1-one 11a. T-HYDRO (270.0 μL, 2.0 mmol) was added dropwise to a pre-sonicated 8.0-mL 6-dram screw-cap vial containing a magnetic stirring bar, $Rh_2(cap)_4$ (2.7mg, 1.0 mol%) **11a** (95.2 mg, 0.4 mmol) and 2.0 mL of water. The reaction solution was heated at 80 ℃ in oil bath and stirred for 18 h then cooled at room temperature and transferred to a 50.0 mL round bottom-flask with 20.0 mL of AcOEt. The volume of the solution was reduced under reduced pressure, and the resulting residue was purified by column chromatography (silica gel, DCM/MeOH = 20:1). Fractions containing the products were combined, and the solvent was evaporated under reduced pressure followed by additional drying under high vacuum for 20 min (0.09 Torr, room temperature) to afford *p*-toluic acid **10a** in 65% (35.0 mg) and hemiketal peroxide **11a** in 5% (5.0 mg)

Catalytic Oxidation of 2-(*tert*-Butylperoxy)-2-hydroxy-1-(*p*-tolyl)ethan-1-one 11a, HPLC. T-HYDRO (135.0 μL, 1.0 mmol) was added dropwise to a pre-sonicated 8.0-mL 6-dram screw-cap vial containing a magnetic stirring bar, catalyst (1.0 mol%), **11a** (47.6 mg, 0.2 mmol) in 2.0 mL of solvent. The reaction solution was stirred for 18 h at room temperature, after which it was analyzed by HPLC as described previously.

Kinetic Measurements of $Rh_2(cap)_4$ Catalyzed Oxidations of 4-Methylstyrene by T-HYDRO in H_2O. T-HYDRO (270.0 μL, 2.0 mmol) was added dropwise at room temperature to a pre-sonicated 8.0-mL 6-dram screw-cap vial containing a magnetic stirring bar, 2.0 mL of water, **1a** (47.3 mg, 0.4 mmol) and $Rh_2(cap)_4$ (2.6 mg, 1.0 mol%). The reaction solution was sealed with a cap and stirred. Aliquots were removed after the first 30 minutes and then every hour until the 18th hour, transferred to a 10.0 mL volumetric flask, and brought to 10.0 mL of volume with acetonitrile, then analyzed by HPLC (Poroshell 120 EC-C18 column) with water/acetonitrile (80/20) as the eluent.

Kinetic Measurements of $Rh_2(cap)_4$ Catalyzed Oxidation of 4-Methylstyrene by T-HYDRO in $CHCl_3$. T-HYDRO (270.0 μL, 2.0 mmol) was added dropwise to a pre-sonicated 8.0-mL 6-dram screw-cap vial containing a magnetic stirring bar, 2.0 mL of $CHCl_3$, **1a** (47.3mg, 0.4 mmol) and $Rh_2(cap)_4$ (2.6 mg, 1.0 mol%) at room temperature. The reaction solution was sealed with a cap and stirred and analyzed after the first 30 minutes and then every hour until the 18th hour as described above.

Synthetic Procedure for Hydroperoxide Compounds 4. A 25 mL round-bottom flask was charged sequentially with a stir bar, $Rh_2(cap)_4$ (0.67 mg, 0.25 mol%, or 1.4 mg, 1.0 mol%), alkene derivate (0.4 mmol) and 4.0 mL of $CHCl_3$. Then the round-bottom flask was sealed with a robber septum which two needles were inserted. The solution was charged with oxygen for 10 minutes, then the outlet needle was removed, and the inlet needle was replaced with a balloon containing oxygen. T-HYDRO (235.0 μL, 2.0 mmol, or 540.0 μL, 4.0 mmol) was added dropwise to the mixture with a syringe. The reaction was monitored by TLC, and every 12h, T-HYDRO (270.0 μL) was added until the reaction was complete. The reaction solution was passed through a 3-cm silica gel plug using DCM as the eluent. Then the volume of the solution was reduced under reduced pressure, and the resulting residue was purified by column chromatography on silica gel using hexanes/ethyl acetate (20:1) as the eluent. Fractions containing the product were combined, and the solvent was evaporated under reduced pressure followed by additional drying under high vacuum for 20 min (0.09 Torr, room temperature) to afford the corresponding hydroperoxide product **4**.

***1-(2-(tert-Butylperoxy)-1-hydroperoxyethyl)-4-methylbenzene* 4a**: (81.0 mg, 85%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57 (s, 1H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 5.33 (dd, *J* = 8.3, 3.3 Hz, 1H), 4.27 (dd, *J* = 13.0, 8.3 Hz, 1H), 4.17 (dd, *J* = 13.0, 3.3 Hz, 1H), 2.38 (s, 3H), 1.30 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 138.4, 134.0, 129.4, 127.1, 85.1, 81.1, 76.8, 26.3, 21.2. HRMS (ESI) calculated for $C_{13}H_{24}NO_4$ $[M+NH_4]^+$: 258.1700; found: 258.1704.

***1-(2-(tert-butylperoxy)-1-hydroperoxyethyl)-4-methoxybenzene* 4b**, colorless oil (103.0 mg, 86%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.76 (br, 1H), 7.29 (d, J = 8.7 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 5.26 (dd, J = 8.2, 3.5 Hz, 1H), 4.25 (dd, J = 12.8, 8.2 Hz, 1H), 4.14 (dd, J = 12.8, 3.5 Hz, 1H), 3.79 (s, 3H), 1.26 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 159.8, 129.3, 128.6, 114.1, 84.8, 81.1, 76.6, 55.4, 26.4. HRMS (ESI) calculated for $C_{13}H_{24}NO_5$ $[M+NH_4]^+$: 274.1649; found: 274.1649.

[1-(2-(*tert*-Butylperoxy)-1-hydroperoxyethyl)-4-(trifluoromethyl)]benzene 4c, colorless oil (92.0 mg 78%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (br, 1H), 7.67 (d, J = 8.1 Hz, 2H), 7.54 (d, J = 8.1 Hz, 2H), 5.42 (dd, J = 7.8, 3.6 Hz, 1H), 4.24 (dd, J = 13.2, 7.8 Hz, 1H), 4.17 (dd, J = 13.2, 3.6 Hz, 1H) 1.30 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 141.2, 130.6 (q, $^2J_{CF}$ = 32.6 Hz), 127.2, 125.5 (q, $^3J_{CF}$ = 3.8 Hz), 123.9 (q, $^1J_{CF}$ = 272.2 Hz), 84.6, 81.2, 76.2, 26.2. HRMS (ESI) calculated for $C_{13}H_{21}F_3NO_4$ $[M+NH_4]^+$: 312.1417; found: 312.1415.

[2-(*tert*-butylperoxy)-1-cyclopropyl-1-hydroperoxyethyl]benzene, 4d, colorless oil (96.8 mg, 91%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.86 (s, 1H), 7.41 – 7.27 (m, 5H), 4.64 (d, J= 22 Hz, 1H), 4.60 (d, J= 22 Hz, 1H), 1.42 – 1.37(m, 1H), 1.31 (s, 9H), 0.47 – 0.40 (m, 2H), 0.28 – 0.25 (m, 1H), 0.06 – 0.03 (m, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 137.8, 128.1, 127.8, 126.9, 88.1, 82.0, 77.3, 26.5, 15.9, 1.2, 1.1. HRMS (ESI) calculated for $C_{15}H_{26}NO_4$ $[M+NH_4]^+$: 284.1856; found: 284.1851.

[1-(*tert*-butylperoxy)-2-hydroperoxypropan-2-yl]benzene, 4e, colorless oil (86.4 mg, 90%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49 (br, 1H), 7.45 (d, *J* = 7.5 Hz, 2H), 7.38 (dd, *J* = 7.5, 6.9 Hz, 2H), 7.34 – 7.27 (m, 1H), 4.44 (d, *J* = 12.8 Hz, 1H), 4.33 (d, *J* = 12.8 Hz, 1H), 1.59 (s, 3H), 1.28 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 141.9, 128.4, 127.7, 125.6, 85.4, 81.6, 78.0, 26.3, 22.4. HRMS (ESI) calculated for $C_{13}H_{24}NO_4$ $[M+NH_4]^+$: 258.1700; found: 258.1701.

1-[(*tert*-butylperoxy)methyl]-1-hydroperoxy-2,3-dihydro-1H-indene, 4f, colorless oil (70.6 mg, 70%). ^{1}H NMR (500 MHz, , $CDCl_3$) δ 8.44 (s, 1H), 7.51 (d, J = 7.4 Hz, 1H), 7.31 (td, J = 7.4, 1.2 Hz, 2H), 7.28 – 7.25 (m, 1H), 7.23 (t, J = 7.4 Hz, 1H), 4.51 (d, J = 12.5 Hz, 1H), 4.32 (d, J = 12.5 Hz, 1H), 3.10 (ddd, J = 16.2, 8.4, 7.0 Hz, 1H), 2.87 (ddd, J = 16.2, 8.9, 4.4 Hz, 1H), 2.40 (ddd, J = 14.0, 8.4, 4.4 Hz, 1H), 2.26 (ddd, J = 14.0, 8.9, 7.0 Hz, 1H), 1.29 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 145.3, 140.7, 129.6, 126.5, 125.4, 125.2, 94.2, 81.6, 76.5, 32.6, 29.8, 26.5. HRMS (ESI) calculated for HRMS (ESI) calculated for $C_{14}H_{24}NO_4$ $[M+NH_4]^+$: 270.1700; found: 270.1694.

Synthetic Procedure for 2-(*tert*-Butylperoxy)-2-hydroxy-1-(*p*-tolyl)ethan-1-one 11a. 2-Oxo-2-(*p*-tolyl)acetaldehyde was prepared according to the reported procedure.[34] 2-(*tert*-Butylperoxy)-2-hydroxy-1-(*p*-tolyl)ethan-1-one **11a** was prepared with modification from reference 29. T-HYDRO (510.0 µL, 3.6 mmol) was added dropwise to a 50.0 mL round bottom flask a 10.0 mL solution of water containing 2-oxo-2-(*p*-tolyl)acetaldehyde (300.0 mg, 1.8 mmol), after which the reaction solution was stirred for 12 h at room temperature, and a white precipitate was formed. The precipitate was filtered under vacuum, collected in a 6-dram screw-cap vial and dried further under high vacuum for 20 min to afford the corresponding product **11a** as a white solid (372.9 mg, 87%). mp: 72-74 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 6.08 (d, *J* = 9.5 Hz, 1H), 5.02 (d, *J* = 9.5 Hz, 1H), 2.45 (s, 3H), 1.19 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 191.6, 145.8, 130.7, 129.9, 129.6, 94.8, 81.0, 26.7, 22.0. HRMS (ESI) calculated for $C_{13}H_{18}KO_4$ $[M+K]^+$: 277.0837; found: 277.0827.

Catalytic Oxidation of Substituted Styrenes, 1a. A 8-mL 6-dram screw-cap vial containing a stirring bar was charged sequentially with *p*-methylstyrene (0.4 mmol, 1.0 equiv.), $Rh_2(cap)_4$ (2.7 mg 1.0 mol%), 2.0 mL of water and NaOH (64.0 mg, 1.6 mmol). The mixture was sonicated for 1 min to facilitate the maximum dissolution of the metal catalyst, after which T-HYDRO (TBHP 70% in water, 270.0 µL, 2.0 mmol) was added dropwise into the vial. The reaction solution was sealed with a cap and stirred for 18 h at 80

°C in oil bath. After the reaction was complete, the reaction solution was transferred to a separatory funnel and 10.0 mL of NaOH (1M) were added. The aqueous layer was rinsed with three portions of DCM (10.0 mL), after which the aqueous layer was acidified with 20.0 mL HCl (1M), and a precipitate was formed. The white precipitate was filtered under vacuum, collected in a 6-dram screw-cap vial and dried further under high vacuum for 20 min to afford the corresponding *p*-toluic acid **10a** (39.2 mg 72%).

Catalytic Oxidation of Substituted Styrenes, 1b-g. A 8.0 mL 6-dram screw-cap vial containing a stirring bar was charged sequentially with **1** (0.4 mmol, 1.0 equiv.), $Rh_2(cap)_4$ (2.7 mg 1.0 mol%), 2.0 mL of water. The mixture was sonicated for 1 min to facilitate the maximum dissolution of the metal catalyst, after which T-HYDRO (TBHP 70% in water, 270.0 µL, 2.0 mmol) was added dropwise into the vial. The reaction solution was sealed with a cap and stirred for 18 h at 80 °C in oil bath. After that**,** the volume of the solution was reduced under reduced pressure, and the resulting residue was purified by column chromatography on silica gel using DCM/methanol (20:1) as eluent. Fractions containing the product were combined, and the solvent was evaporated under reduced pressure followed by additional drying under high vacuum for 20 min (0.09 Torr, room temperature) to afford the corresponding benzoic acid product **10**. p-Toluic acid **10a** (39.2 mg, 72%). 4-Methoxybenzoic acid **10b** (32 mg, 52%). 4-Biphenyl-carboxylic acid **10c** (49.2 mg, 62%). Benzoic acid **10d** (27 mg, 56%). 4-Bromobenzoic acid **10e** (54.7 mg, 68%). 4-Chlorobenzoic acid **10f** (41.2 mg, 67%). 4-Trifluoromethyl benzoic acid **10g** (47.1 mg, 62%).

General Procedure for the Catalytic Oxidation of Geminal-Disubstituted Ethylenes, 14. A 8.0 mL 6-dram screw-cap vial containing a stirring bar was charged sequentially with **14** (0.4 mmol, 1.0 equiv.), $Rh_2(cap)_4$ (2.7 mg 1.0 mol%) and 2.0 mL of cyclohexane. The mixture was sonicated for 1 min to facilitate the maximum dissolution of the metal catalyst, after which T-HYDRO (TBHP 70% in water, 270.0 µL, 2.0 mmol) was added dropwise into the vial. The reaction solution was sealed with a cap and stirred for 18 h at 80 °C in oil bath. After completion of the reaction, the reaction solution was passed through a 3 cm silica gel using DCM as the eluent. Then the volume of the solution was reduced, and the resulting residue was purified by column chromatography on silica gel using hexanes/ethyl acetate (20:1) as eluent. Fractions containing the product were combined, and the solvent was evaporated under reduced pressure followed by additional drying under high vacuum for 20 min (0.09 Torr, room temperature) to afford the corresponding ketone product **15**. Benzophenone **15a** (58.3 mg, 80%). 2,3-Dihydro-1H-inden-1-one **15b** (34.4 mg, 65%). Cyclopropyl(phenyl)methanone **15c** (55.0 mg, 94%). Cyclohexyl(phenyl)methanone **15d** (52.0 mg, 69%). Acetophenone **15e** (38.4 mg, 81%).

Catalytic Oxidation of α-Methylstyrene in DCM

$Rh_2(cap)_4$ (0.66 mg, $1.0x10^{-3}$ mmol) was added to a solution of **14e** (47.3 mg, 0.40 mmol) and TBHP (70 wt. % in H_2O, 259.4 mg, 2.0 mmol) in 2.0 mL DCM at room temperature. The color of the reaction became

pink immediately. The reaction was terminated after stirring for 48 h. After the reaction was complete, the reaction solution was passed through a 3-cm silica gel plug using DCM as the eluent. The volatiles were removed in vacuo. The crude products were purified by flash column chromatography (SiO_2, hexane/ethyl acetate, 20:1) to afford compound **15b** (22.1 mg, 44% yield) and compound **4e** (54.9 mg, 52% yield).

Catalytic Oxidation of [1-(*tert*-Butylperoxy)-2-hydroperoxypropan-2-yl]benzene, 4e

$Rh_2(cap)_4$ (1.5 mg, $2.2x10^{-3}$ mmol) was added to a solution of **4e** (50.0 mg, 0.22 mmol) in 1 mL dichloromethane at room temperature. The color of the reaction became pink immediately indicating the conversion of the catalyst to rhodium (II,III) caprolactamate. The reaction was terminated after 3 days. The volatiles were removed in vacuo. The crude products were purified by flash column chromatography (SiO_2, hexane/ethyl acetate, 20:1). Fractions containing the product were combined, and the solvent was evaporated under reduced pressure followed by additional drying under high vacuum for 20 min (0.09 Torr, room temperature) to afford acetophenone **15e** (8.0 mg, 43% yield).

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website at DOI: Experimental tables, copies of ^{1}H and ^{13}C NMR spectra of compounds **2a**, **3a**, **4a**-**4f**, **5a**, **6a** and **11a**, copies of ^{1}H NMR spectra of compounds **10a**-**10g** and **15a**-**15e**, HPLC trace and calibration curve for compounds **1a**-**11a**, HPLC trace of a crude reaction solution, HR-MS data of compounds **2a**-**6a**, **8a**, **11a** and **12**, HR-MS spectra of compounds **2a**-**5a.**

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Notes

The authors declare no competing financial interest.

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