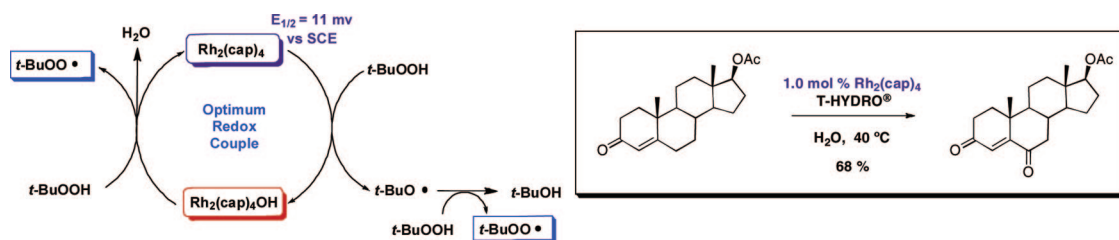# Allylic Oxidations Catalyzed by Dirhodium Caprolactamate via Aqueous *tert*-Butyl Hydroperoxide: The Role of the *tert*-Butylperoxy Radical

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Dirhodium(II) caprolactamate exhibits optimal efficiency for the production of the *tert*-butylperoxy radical, which is a selective reagent for hydrogen atom abstraction. These oxidation reactions occur with aqueous *tert*-butyl hydroperoxide (TBHP) without rapid hydrolysis of the caprolactamate ligands on dirhodium. Allylic oxidations of enones yield the corresponding enedione in moderate to high yields, and applications include allylic oxidations of steroidal enones. Although methylene oxidation to a ketone is more effective, methyl oxidation to a carboxylic acid can also be achieved. The superior efficiency of dirhodium(II) caprolactamate as a catalyst for allylic oxidations by TBHP (mol % of catalyst, % conversion) is described in comparative studies with other metal catalysts that are also reported to be effective for allylic oxidations. That different catalysts produce essentially the same mixture of products with the same relative yields suggests that the catalyst is not involved in product-forming steps. Mechanistic implications arising from studies of allylic oxidation with enones provide new insights into factors that control product formation. A previously undisclosed disproportionation pathway, catalyzed by the *tert*-butoxy radical, of mixed peroxides for the formation of ketone products via allylic oxidation has been uncovered.

Introduction

Allylic oxidations are of fundamental importance in synthetic organic chemistry, and a variety of reagents have been used for this transformation.[1,2] Although stoichiometric selenium dioxide[3] and chromium(VI)[4] reagents have long been used to convert the methylene adjacent to a carbon–carbon double bond to a carbonyl group, the most promising oxidant, applicable to catalytic methods, is *tert*-butyl hydroperoxide (TBHP).[5–7] Selectivity for allylic oxidation by TBHP is due to the ability of the *tert*-butylperoxy radical to remove a hydrogen atom from the activated site having the lowest carbon–hydrogen bond dissociation energy.[8] However, application of this methodology for allylic oxidation with compounds of increasing complexity has been demonstrated in very few cases.

(1) (a) Bulman-Page, P. C.; McCarthy, T. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, UK, 1991; Vol. 7. (b) Olah, G. A.; Molnar, A. In *Hydrocarbon Chemistry*, 2nd ed.; Wiley: Hoboken, 2003.

(2) This discussion is unrelated to that for the elegant oxidative methods that are emerging with with palladium and ruthenium catalysts: (a) Chen, M. S.; White, M. C. *J. Am. Chem. Soc.* **2004**, *126*, 1346. (b) Delcamp, J. H.; White, M. C. *J. Am. Chem. Soc.* **2006**, *128*, 15076. (c) Arends, I. W. C. E.; Kodama, T.; Sheldon, R. A. In *Ruthenium Catalysts and Fine Chemistry*; Bruneau, C., Dixneuf, P. H., Eds.; Springer-Verlag: Heidelberg, Germany, 2004.

(3) (a) Umbreit, M. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 5526. (b) Rabjohn, N. *Org. React.* **1976**, *24*, 261. (c) Crich, D.; Zou, Y. *Org. Lett.* **2004**, *6*, 775. (d) Zeni, G.; Stracke, M. P.; Lissner, E.; Braga, A. L. *Synlett* **2003**, *12*, 1880.

(4) (a) Shing, T. M. K.; Yeung, Y. Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 7981–7984. (b) Hua, Z.; Carcache, D. A.; Tian, Y.; Li, Y.-M.; Danishefsky, S. J. *J. Org. Chem.* **2005**, *70*, 9849. (c) Salmond, W. G.; Barta, M. A.; Havens, J. L. *J. Org. Chem.* **1978**, *43*, 2057.

(5) (a) Rothenberg, G.; Weiner, H.; Sasson, Y. *J. Mol. Catal. A: Chem.* **1998**, *136*, 253–262. (b) Jurado-Gonzalez, M.; Sullivan, A. C.; Wilson, J. R. H. *Tetrahedron Lett.* **2003**, *44*, 4283–4286. (c) Arsenou, E. S.; Koutsourea, A. I.; Fousteris, M. A.; Nikolaropoulos, S. S. *Steroids* **2003**, *68*, 407.

(6) (a) Yu, J.-Q.; Corey, E. J. *Org. Lett.* **2002**, *4*, 2727. (b) Yu, J.-Q.; Wu, H. C.; Corey, E. J. *Org. Lett.* **2005**, *7*, 1415.

(7) (a) Shing, T. K. M.; Yeung, Y. Y.; Su, P. L. *Org. Lett.* **2006**, *8*, 3149. (b) Blay, G.; Fernández, I.; Giménez, T.; Pedro, J. R.; Ruiz, R.; Pardo, E.; Lioret, F.; Muñoz, M. C. *Chem. Commun.* **2001**, 2102–2104. (c) Salvador, J. A. R.; Clark, J. H. *Chem. Commun.* **2001**, 33.

(8) Blanksby, S. J.; Ellison, G. B. *Acc. Chem. Res.* **2003**, *36*, 255.

(9) Catino, J.; Forslund, R. E.; Doyle, M. P. *J. Am. Chem. Soc.* **2004**, *126*, 13622.

We have reported that dirhodium caprolactamate, $Rh_2(cap)_4$, is a highly effective catalyst for allylic oxidations by TBHP (eq 1),[9] and we have recently shown that this methodology can be used for highly selective allylic oxidations with Δ^5-steroidal alcohols.[10] During our initial investigation on the oxidation of cycloalkenes, we observed that those substrates bearing electron-withdrawing substituents were more difficult to oxidize than those with electron-donating substituents. A similar inhibition was reported in ground-breaking studies of TBHP oxidations of α,β-enones to 1,4-enediones facilitated by Pearlman's catalyst [20% $Pd(OH)_2$ on carbon].[11] Substrates having electron-withdrawing substituents generally require greater amounts of TBHP to reach 100% conversion and, with $Rh_2(cap)_4$,[9] require higher catalyst loading.

(1)
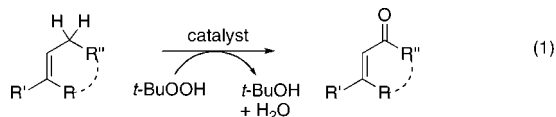
Another feature of allylic oxidations using TBHP is the frequent use of the oxidant in decane or benzene[6,7,9,11,12] as an anhydrous solution, instead of the much safer and less expensive 70% TBHP in water (T-HYDRO). We began our investigations with TBHP in decane based on our belief that hydrolysis of carboxamidate ligands on the $Rh_2(cap)_4$ catalyst would be avoided under these conditions.[9] However, we subsequently reported effective allylic oxidations by T-HYDRO catalyzed by $Rh_2(cap)_4$,[10] and we recently described propargylic oxidations that employed water as the reaction solvent.[13] The catalytically active rhodium species remains intact for sufficient periods under these conditions.
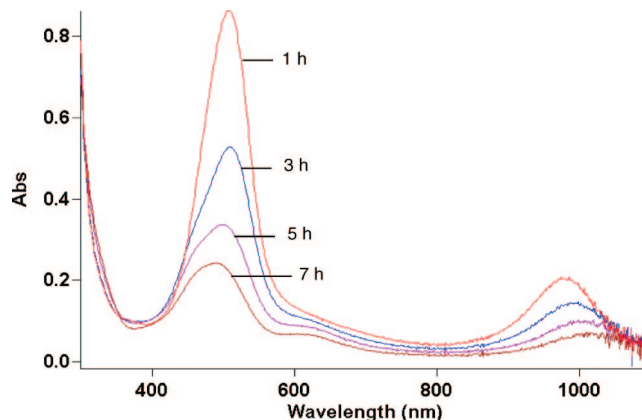
To fully understand the scope, limitations, and mechanism of this oxidative methodology, we chose to focus our attention toward relatively unreactive α,β-unsaturated carbonyl compounds as substrates, and we were particularly attentive to those that have not been commonly explored. Curiously, and with few exceptions, the majority of allylic oxidations have been limited to cyclic systems. Moreover, there have not been any reported examples of the oxidation of a methyl group adjacent to a carbon−carbon double bond.

In addition to the use of palladium catalysis for allylic oxidation by TBHP,[11] copper(II) and iron(III) salts have also been employed,[14,15] as have chromium(VI),[16] manganese(III),[17] copper iodide,[18] cobalt acetate,[19] and ruthenium(III).[20] Although the *tert*-butylperoxy radical is the most likely hydrogen abstraction agent,[8−10] the possibility of oxo−metal involvement, especially with ruthenium catalysts,[21] persists. For that reason, having a model system able to distinguish between these mechanistic pathways would provide a better understanding of this oxidative process. We now report the results of this investigation.

(2)

1, 84 % yield
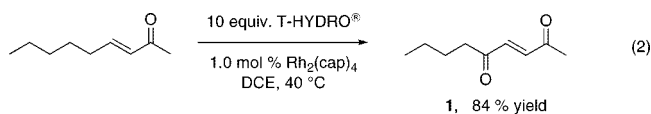
Results and Discussion

Oxidation of *trans*-3-nonene-2-one, whose fire bee toxin[22] product **1** has been previously prepared by allylic oxidation,[9] was selected for optimization (eq 2). Using T-HYDRO as the oxidant

(10) Choi, H.; Doyle, M. P. *Org. Lett.* **2007**, *9*, 5349.
(11) Yu, J.-Q.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 3232.
(12) Salvador, J. A. R.; Silvestre, S. M. *Tetrahedron Lett.* **2005**, *46*, 2581.
(13) McLaughlin, E. C.; Doyle, M. P. *J. Org. Chem.* **2008**, *73*, 4317.

FIGURE 1. Dirhodium(II,III) caprolactamate visible spectrum as a function of time (1, 3, 5, and 7 h): TBHP (0.27 M) in DCE with 1.0 mol % of $Rh_2(cap)_4$ without olefinic substrate. Note that dirhodium-(II,III) caprolactamate (λ_{max} 507 and 974 nm) is clearly visible even after 5 h and that dirhodium(II,II) caprolactamate (λ_{max} 607 nm) becomes visible as the reaction proceeds.

SCHEME 1
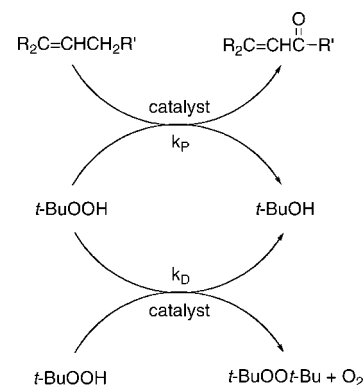
and $Rh_2(cap)_4$ as the catalyst at 40 °C, various solvents were examined for suitability. 1,2-Dichloroethane (DCE), nitromethane, and water all led to comparable conversions to **1** after 16 h when 8 equiv of TBHP was employed. In contrast to previous reports of catalytic TBHP oxidations under anhydrous conditions,[6,8] the addition of weak bases such as sodium bicarbonate, pyridine, or triethylamine lowered percent conversions. Two factors limited the efficiency of this allylic oxidation: (1) the slow rate of oxidation of the substrate relative to radical chain decomposition of TBHP (k_P/k_D, Scheme 1)[23] and (2) the decrease in the concentration of the catalytically active dirhodium species (Figure 1). For the former, increasing the number of molar equivalents of TBHP increased

(14) Bravo, A.; Bjørsvik, H.-R.; Fontana, F.; Liguori, L.; Minisci, F. *J. Org. Chem.* **1997**, *62*, 3849.
(15) Caudle, M. T.; Riggs-Gelasco, P.; Gelasco, A. K.; Penner-Hahn, J. E.; Pecoraro, V. L. *Inorg. Chem.* **1996**, *35*, 3577.
(16) Fousteris, M. A.; Koutsourea, A. I.; Nikolaropoulos, S. S.; Riahi, A.; Muzart, J. *J. Mol. Catal. A: Chem.* **2006**, *250*, 70.
(17) Shing, T. K. M.; Yeung, Y. Y.; Su, P. L. *Org. Lett.* **2006**, *8*, 3149.
(18) Arsenou, E. S.; Koutsourea, A. I.; Fousteris, M. A.; Nikolaropoulos, S. S. *Steroids* **2003**, *68*, 407.
(19) Salvador, J. A. R.; Clark, J. H. *Chem. Commun.* **2001**, 33.
(20) Miller, R. A.; Li, W.; Humphrey, G. R. *Tetrahedron Lett.* **1996**, *37*, 3429.
(21) Balini, R.; Astolfi, P. *Liebigs Ann.* **1996**, 1879.
(22) (a) Russell, G. A. *J. Am. Chem. Soc.* **1957**, *79*, 3871. (b) Caudle, M. T.; Riggs-Gelasco, P.; Gelasco, A. K.; Penner-Hahn, J. E.; Pecoraro, V. L. *Inorg. Chem.* **1996**, *35*, 3577.
(23) Timmons, D.; Doyle, M. P. In *Metal Bonds Between Metal Atoms*, 3rd ed.; Cotton, F. A., Murillo, C. A., Walton, R. A., Eds.; Springer Science and Business Media: New York; 2005; Chapter 13.

SCHEME 2
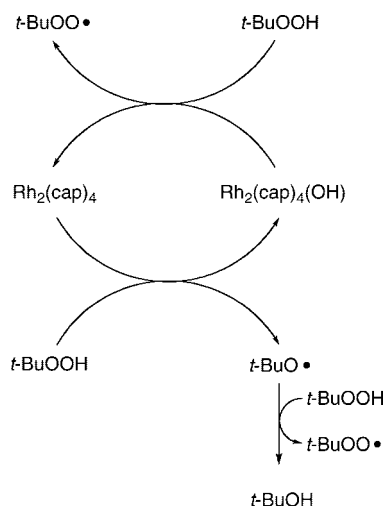
percent conversion, and increasing the reaction temperature from room temperature to 40 °C increased the rate of oxidation. For the latter, adding Rh$_2$(cap)$_4$ in two portions, 0.5 mol % to initiate the reaction and the second 0.5 mol % portion after 16 h, ensured complete conversion and high product yield. Subsequent studies revealed that complete conversion could be achieved using as little as 0.1 mol % of Rh$_2$(cap)$_4$ if applied twice, each with 5.0 molar equiv of TBHP, after the initial addition (22 and 44 h), but these conditions were not further pursued.

The role of dirhodium caprolactamate in these oxidation reactions is suggested from the spectral observations revealed in Figure 1. The conversion of Rh$_2$(cap)$_4$ to its oxidized Rh$_2$(cap)$_4$(OH) form by TBHP has been previously reported,[10] and we speculated that Rh$_2$(cap)$_4$(OH) would be converted back to Rh$_2$(cap)$_4$ via TBHP. The observation of Rh$_2$(cap)$_4$ in Figure 1, combined with confirmation of its initial formation and presence throughout the course of oxidation through HPLC analysis, confirms the catalytic role for Rh$_2$(cap)$_4$ that is described in Scheme 2. Thus, dirhodium caprolactamate is effective and efficient for the production of the *tert*-butylperoxy radical.

Optimum conditions were selected for oxidation of α,β-unsaturated substrates (0.54 M in DCE) that included initial addition of 0.5 mol % of Rh$_2$(cap)$_4$ and 4.0 or 5.0 equiv of T-HYDRO followed by the same portion of catalyst and oxidant after 16 h. Reactions were performed at 40 °C and terminated 40 h after the initial catalyst/oxidant addition. Percent conversion at 16 h was only half-that at 40 h, and using acetonitrile or nitromethane as solvent resulted in lower conversions than that achieved in DCE. Selected α,β-unsaturated carbonyl compounds were oxidized according to this methodology, and the results are reported in Table 1. Noteworthy are the relatively high yields of oxidized product obtained with acyclic compounds. For example, *trans*-4-oxo-2-nonenoic acid (**3**), reported to have antibiotic activity,[24] is efficiently prepared in one transformation (entry 3), improving upon the previously described multistep syntheses.[25] Oxidation of methyl crotonate under the same conditions yielded monomethyl fumaric acid (**8**) in modest isolated yield.

The oxidation reactions reported in Table 1 are remarkably free of byproduct. However, while investigating the T-HYDRO oxidation of 1-acetylcyclohexene (a substrate that was reported to be cleanly oxidized by TBHP in decane using Rh$_2$(cap)$_4$

(24) Pfefferle, C.; Kempter, C.; Metzger, J. W.; Fiedler, H.-P. *J. Antibiot.* **1996**, *49*, 826.

(25) (a) Ballini, R.; Bosica, G. *J. Nat. Prod.* **1998**, *61*, 673. (b) Shet, J.; Tilve, S. *Synthesis* **2004**, *11*, 1859. (c) Obrect, D.; Weiss, B. *Helv. Chim. Acta* **1989**, *72*, 117.

aided by potassium carbonate[8]) we uncovered three unreported mixed peroxides (**10**, **11**, and **12**) in addition to the previously reported **13**[10] and desired enedione **9**. Two of these mixed peroxides (**10** and **11**) were revealed during a study of the influence of TBHP molar amount on product formation (Figure 2); mixed peroxide **12** was isolated from a reaction that employed 0.5 mol % of Rh$_2$(cap)$_4$ and 4.0 molar equiv of TBHP. That enone **11** results from allylic oxidation of **10** is clearly suggested from the data in Figure 2.
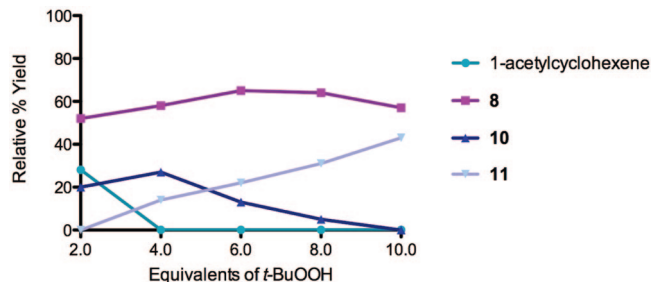

FIGURE 2. Oxidation of 1-acetylcyclohexene (0.27 M in DCE, 40 °C) by T-HYDRO, catalyzed by Rh$_2$(cap)$_4$. The relative yield of oxidation products as a function of molar equivalents of TBHP was determined after 16 h.
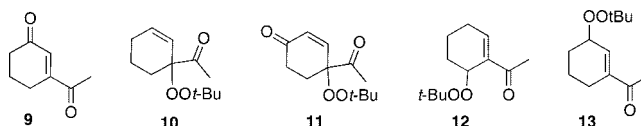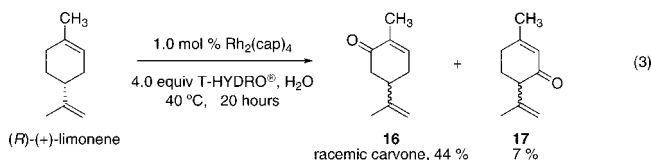

Mixed peroxide **10** is formed in competition with mixed peroxide **13** and enedione **9**. Formation of mixed peroxides **10**−**13** is consistent with the generation of intermediate allyl radicals **14** and **15** (Scheme 3) that subsequently react with the *tert*-butylperoxy radical. As can be seen from overall product formation, intermediate **15** is more prevalent than **14**. Conversely, oxidations of cyclohexene derivatives bearing electron-donating substituents at the 1-position (e.g., AcO, *tert*-butyl) under identical conditions did not form detectable amounts of mixed peroxide products.[9]

SCHEME 3
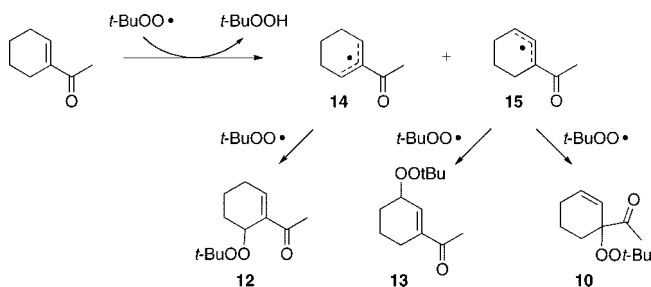
Further support that the pathway described in Scheme 3 is operative in Rh$_2$(cap)$_4$-catalyzed oxidations by TBHP was demonstrated through oxidation of enantiomerically pure (*R*)-(+)-limonene with T-HYDRO in water (eq 3). Unlike previous
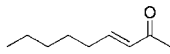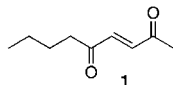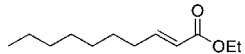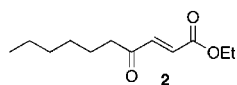

TBHP oxidations of 1-substituted cyclohexenes, from which the dominant product resulted from oxidation at the 3-position,[5−9]

TABLE 1. Oxidation of α,β-Unsaturated Carbonyl Compounds by T-HYDRO Catalyzed by Rh₂(cap)₄[a]

Entry	Substrate	Product	Equiv. TBHP	% Yield[b]
1		1	10.0	84
			8.0	76
2		2	10.0	76
3		3	10.0	87
4		4	10.0	85
			8.0	82
5		5	8.0	65
6		6	8.0	70
7		7	8.0	64
8		8	8.0	32

[a] Reactions were performed with 1.36 mmol of substrate in 2.5 mL of DCE to which were added 4.0 or 5.0 equiv of TBHP (70% in water) and 0.50 mol % of Rh₂(cap)₄, and the solution was heated at 40 °C. After 16 h, an add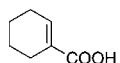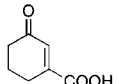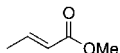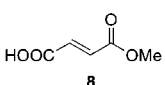itional 4.0 or 5.0 equiv of TBHP (70% in water) and 0.50 mol % of Rh₂(cap)₄ were added, and the reaction was continued for an additional 24 h. [b] Isolated yield after column chromatography; carboxylic acids were purified by recrystallization from ethyl acetate, and the mass yield after recrystallation is given.

the dominant product of the oxidation of (R)-(+)-limonene was racemic carvone (**16**, 44% isolated yield). The observed carvone **16** arose from hydrogen atom abstraction from the 6-position of limonene to produce a racemic free radical that underwent subsequent transformation. The expected oxidation at the 3-position of limonene, affording isopiperitinone **17**, was observed as the minor reaction product (7% isolated yield). Other oxidation products were also formed, but none in yields of 5% or greater. These minor products were part of an inseparable residue; however, resonances in the ¹³C NMR spectrum of the residue provided suggested TBHP capture at the multiple allylic positions of limonene, but this was not further pursued. The preference for hydrogen atom abstraction from the 6-position, rather than from the 3-position, suggests the operation of steric factors. Although allylic oxidations of limonene, other than those by selenium dioxide,[26] have been investigated, those using TBHP have been reported to form

carvone and related compounds derived from hydrogen abstraction at the 6-position, but there has not been prior mention of their optical purity.[27]

To determine the eventual fate of reaction products, mixed peroxides **10**, **12**, and **13** were isolated, purified, and then subjected to reaction conditions similar to those reported in Table 1. The mixed peroxide and dirhodium catalyst were diluted with CD₂Cl₂ (to 0.27 M) and then treated with 70% TBHP in D₂O. Biphenyl was added as an internal standard, and the reactions were monitored by ¹H NMR. The results of these experiments are described in eqs 4–6 which show that further oxidation occurs, resulting in either ketone formation (**9**, **11**, and **18**/eq 5) or in the production of a second mixed peroxide (**18**/eq 6, **19**, and **20**). Perhaps the most remarkable result is that of eq 6 whereby mixed peroxide **13** is converted, in relatively high yield, to diketone **9**, supporting a previously undisclosed catalytic disproportionation pathway for the formation of ketone products via allylic oxidation (Scheme 4). Indeed,

(26) Selective oxidation occurs at the 4-position: (a) Wilson, C. A., III.; Shaw, P. E. *J. Org. Chem.* **1973**, *38*, 1684. (b) Jensen, H. P.; Sharpless, K. B. *J. Org. Chem.* **1975**, *40*, 264.

SCHEME 4
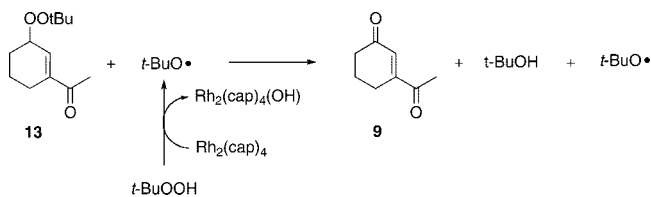
this pathway may explain the common inability to detect mixed peroxide products in oxidations by TBHP.

(4)

(5)

(6)
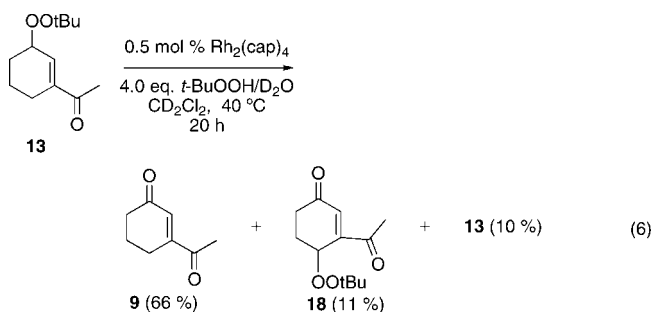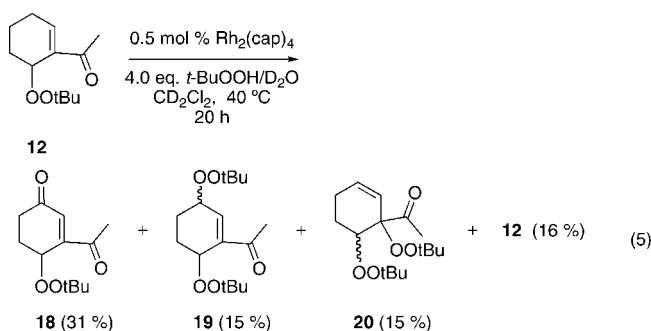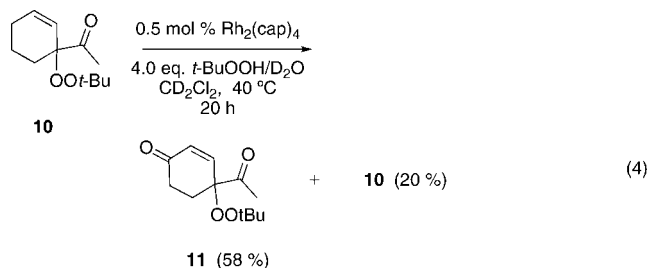
The relative stability of allylic oxidation product **9** is seen in the minor extent of its conversion to mixed peroxide **16** (**9** → **16**: 13% yield at 13% conversion after 20 h using the same reaction conditions as in equations 46). This result is consistent with the low reactivity of α,β-unsaturated carbonyl compounds toward allylic oxidation (see Scheme 1) and to the importance of steric influences in hydrogen atom abstraction reactions of the *tert*-butylperoxy radical. Interestingly, oxidation of **9** is 1 order of magnitude less pronounced than oxidation of 1-acetylcyclohexene.

TBHP oxidation of 1-acetylcyclohexene, in association with intermediate allyl radicals **14** and **15** (Scheme 3), presents an opportunity to easily compare the $Rh_2(cap)_4$-catalyzed oxidations with those from other metal catalysts. Oxidation products from reactions of TBHP with 1-acetylcylohexene using several

common catalysts using a limited amount of TBHP (4.0 equiv), under exactly the same conditions, are reported in Table 2. Comparison with the prior $Rh_2(cap)_4$ catalytic methodology from our laboratory[9] using TBHP in decane is also provided. Enedione **9**, as well as mixed peroxides **10** and **13**, are easily identified by their distinctive ^{1}H NMR chemical shifts. Particularly noticeable is the variability in percent conversion, which is a reflection of the turnover rate for production of the active oxidant. Even at 0.1 mol % of $Rh_2(cap)_4$, percent conversion is exceptional among the catalysts examined. Of special significance is the low variability in the ratio of **9** + **13** to **10**, which is approximately 1.9 ± 0.3 for all catalysts examined. This value, applicable to all of the catalysts and changing slightly with the amount of catalyst used, suggests that these allylic oxidations occur through the same reaction pathway—via the allyl free radical from hydrogen atom abstraction from the 3-position of 1-acetylcyclohexene—and that the trapping of this intermediate occurs in the same fashion by the same radical species. That the catalyst is not involved in the product forming step is also drawn from the low variability in the ratio of **9** + **13** to **10**, and this conclusion is possibly applicable to prior claims[7a,9,11,18] of metal catalyst involvement in the product determining step in allylic oxidation reactions of TBHP. In addition, intermediate oxo−ruthenium(IV) complexes are often implicated in alkane oxidation reactions catalyzed by ruthenium(III) chloride,[28] but the present results suggest that such species are not involved in the allylic oxidation process involving TBHP in water. Also expressed in Table 2, percent conversion of 1-acetylcyclohexene is highest with $Rh_2(cap)_4$, and CuI appears to be only slightly less efficient, but at much higher catalyst loading.

The mechanistic pathway for the $Rh_2(cap)_4$-mediated allylic oxidation that is consistent with the reported data is outlined in Scheme 5 using cyclohexene as the model olefinic substrate.

SCHEME 5
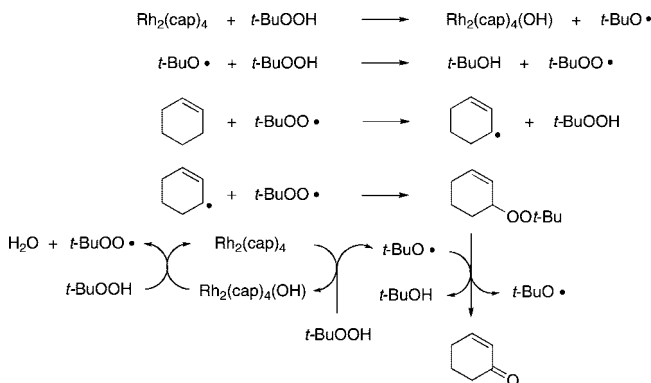
Initial oxidation occurs between TBHP and $Rh_2(cap)_4$ to form the oxidized dirhodium(II,III) intermediate and the *tert*-butoxy radical that, in turn, abstracts a hydrogen atom from TBHP at a rate that is much faster than hydrogen atom abstraction from the allylic position of the alkene.[29,30] The *tert*-butylperoxy radical undergoes selective hydrogen atom abstraction from the hydrocarbon substrate: a process that is well documented and

(27) (a) Lempers, H. E. B.; Sheldon, R. A. *Appl. Catal. A: General* **1996**, *143*, 137. (b) Silva, A. D.; Patitucci, M. L.; Bizzo, H. R.; D'Elia, E.; Antunes, O. A. C. *Catal. Commun.* **2002**, *3*, 435.

(28) (a) Murahashi, S.-I.; Komiya, N.; Oda, Y.; Kuwabara, T.; Naota, T. *J. Org. Chem.* **2000**, *65*, 9186. (b) Lempers, H. E. B.; Garcia, A. R.; Sheldon, R. A. *J. Org. Chem.* **1998**, *63*, 1408.

(29) Avila, D. V.; Ingold, K. U.; Lusztyk, J.; Green, W. A.; Procopio, D. R. *J. Am. Chem. Soc.* **1995**, *117*, 2929.

(30) Bravo, A.; Bjørsvik, H.-R.; Fontana, F.; Liguori, L.; Miniski, F. *J. Org. Chem.* **1997**, *62*, 3849.

TABLE 2. Oxidation of 1-Acetylcyclohexene by TBHP in CD_2Cl_2 at 40 °C with Various Catalysts[a]

Catalyst	Oxidant	% Conversion[b]	% Yield[c]	Relative % yield[d]			Ratio (9 + 13)/10
				9	13	10	
0.5 mol % $Rh_2(cap)_4$	70 % TBHP in water	80	71	27	34	39	1.6
0.1 mol % $Rh_2(cap)$	70 % TBHP in water	80	63	40	30	30	2.3
0.5 mol % $Rh_2(cap)_4$ 0.5 equiv. K_2CO_3	6.7 M TBHP in decane	82	49	45	22	33	2.0
2.0 mol % $RuCl_3 \cdot nH_2O$	70 % TBHP in water	59	42	21	38	40	1.5
2.0 mol % CuI	70 % TBHP in water	71	51	24	37	39	1.6
5.0 mol % $Pd(OH)_2$	70 % TBHP in water	38	36	17	50	33	2.0
5.0 mol % $Pd(OH)_2$ 0.25 equiv. K_2CO_3	70 % TBHP in water	62	42	40	31	29	2.4

[a] Reactions were performed with 1-acetylcyclohexene (0.27 M in CD_2Cl_2), using 4.0 equiv of 70% TBHP in D_2O and the specified amount of catalyst with 1.0 equiv of biphenyl as internal standard. The reactions were performed in a standard NMR tube, heated to 40 °C, and were monitored by ^1H NMR. [b] Percent conversion for each reaction was measured by the amount of 1-acetylcyclohexene remaining after 20 h, relative to the internal standard. [c] Percent yield was determined by the sum of products formed after 20 h, relative to the internal standard. [d] The results from duplicate runs were reproducible within 5% of the reported values.

universally accepted.[9,10,31,32] The existence of an allylic radical in these reactions is also consistent with the conversion of optically pure limonene into racemic carvone (eq 3). Capture of the allyl radical by the *tert*-butylperoxy radical[33] forms the mixed peroxide that is susceptible to *tert*-butoxy radical catalyzed disproportionation.

However, mixed peroxides are not observed as reaction intermediates in results from the allylic oxidation of cholesterol **21** to form 7-ketocholesterol **22**, and instead, 7-hydroxycholesterol **23** and the 7-hydroperoxycholesterol **24** in both α- and β-stereoisomeric forms are obtained.[10,34,35] Mixed peroxides analogous to **24** from TBHP oxidation of cholesteryl acetate have been reported as minor products (<5%),[36] and they may be present in lower amounts in related reactions with cholesterol.[34] Both **23** and **24** are understood to be products of dioxygen capture of an allyl radical in one pathway for the formation of the enone **22**.[34] Upon close analysis of reaction products from the oxidation of **21**, we were able to identify and isolate α− and β-**23** and **24** (eq 7), but we were not able to confirm the presence of mixed peroxides. In addition, based on the seminal work of Schenck[37] and similar subsequent reports,[38]

the intermediate allyl radical from hydrogen atom abstraction at the 7-position of cholesterol may form tertiary 5-hydroperoxycholesterol, but this product is not observed due to rapid [2,3]-sigmatropic rearrangement to 7-hydroperoxycholesterol **24**.

(7)

21

1 mol % $Rh_2(cap)_4$

4 equiv. T-HYDRO®
CH_2Cl_2, 25 °C
15 h, 80 % conversion

22, 30 %

α-23, 12 %
β-23, 3 %

+

α-24, 10 %
β-24, 4 %
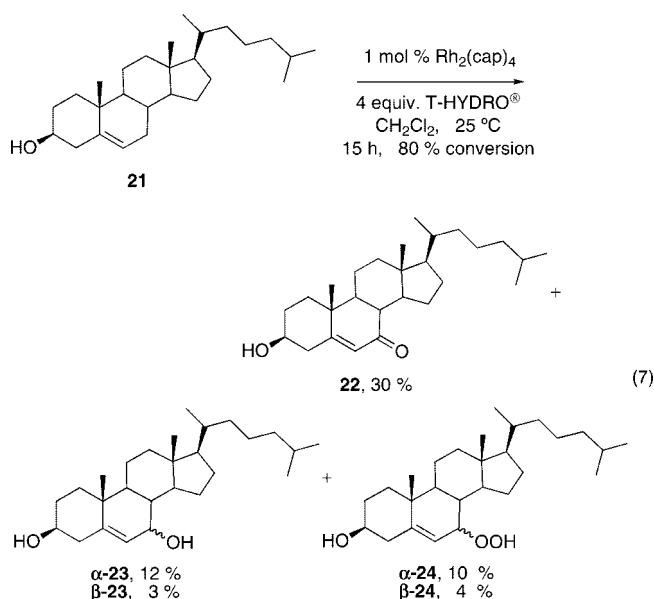
An explanation for the hydroperoxide, diol, and enone oxidation products from cholesterol is that in this case the allyl radical reacts

(31) (a) Snelgrove, D. W.; Lusztyk, J.; Banks, J. T.; Mulder, P.; Ingold, K. U. *J. Am. Chem. Soc.* **2001**, *123*, 469. (b) MacFaul, P. A.; Arends, I. W. C. E.; Ingold, K. U.; Wayner, D. D. M. *J. Chem. Soc., Perkin Trans. 2* **1997**, *13*, 5–145.
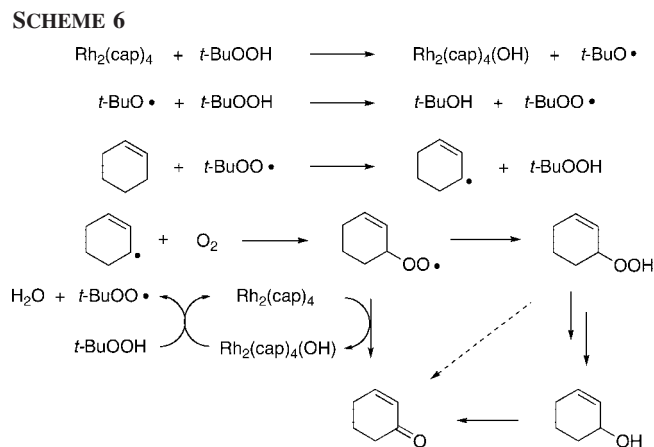(32) Chavez, F. A.; Mascharak, P. K. *Acc. Chem. Res.* **2000**, *33*, 539–545.
(33) (a) Koola, J. D.; Kochi, J. K. *J. Org. Chem.* **1987**, *52*, 4545. (b) Srinavasan, K.; Perrier, S.; Kochi, J. K. *J. Mol. Catal.* **1986**, *38*, 297.
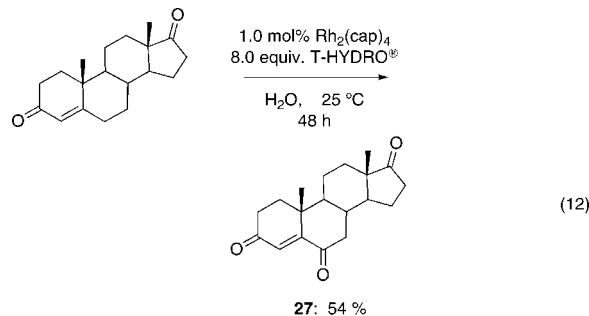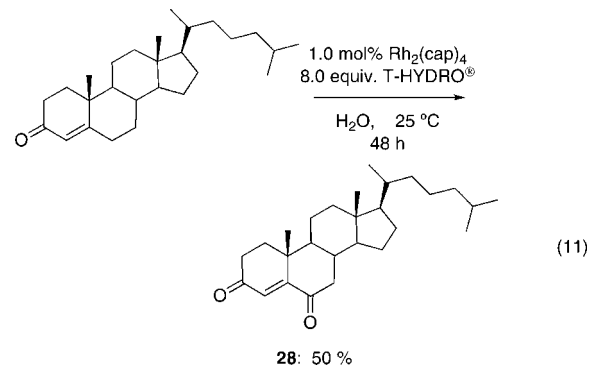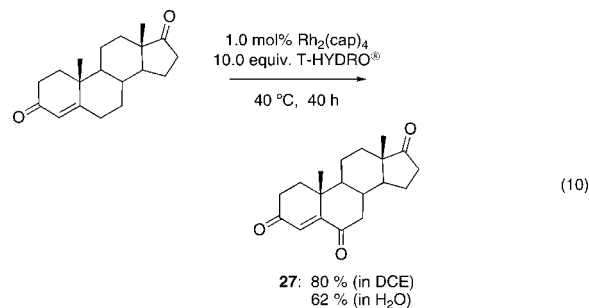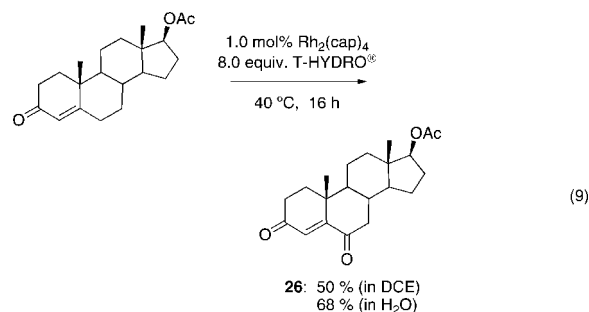(34) Miller, R. A.; Li, W.; Humphrey, G. R. *Tetrahedron Lett.* **1996**, *37*, 3429.
(35) Nielsen, J. H.; Olsen, C. E.; Skibsted, L. H. *Food Chem.* **1996**, *56*, 33.

SCHEME 6

$$Rh_2(cap)_4 + t\text{-BuOOH} \longrightarrow Rh_2(cap)_4(OH) + t\text{-BuO}\cdot$$

$$t\text{-BuO}\cdot + t\text{-BuOOH} \longrightarrow t\text{-BuOH} + t\text{-BuOO}\cdot$$

with dioxygen to form an intermediate alkylperoxy radical (Scheme 6, shown with cyclohexene as substrate). The alkylperoxy radical either abstracts a hydrogen atom from the allylic position of another hydrocarbon to form hydroperoxide or undergoes oxidation of Rh_2^{4+} to form the enone product directly. This direct conversion explains why alcohols are either not observed[9] or are generally very minor products in TBHP oxidations that are catalyzed by $Rh_2(cap)_4$.[10] This pathway provides a viable alternative to bimolecular disproportionation of two peroxy radicals that would form an alcohol and a ketone in equivalent amounts along with dioxygen (the Russell mechanism).[39] However, the question remains regarding the relative ability of an allyl radical to capture either the *tert*-butyl peroxy radical or dioxygen, and this question is not answered in this study.

The oxidations of testosterone (eq 8), 17-acetyltestosterone (eq 9), 4-androstene-3,17-dione (eq 10), and 4-cholesten-3-one (eq 11) were performed under the same conditions as those reported in Table 1. Although using 1,2-dichloroethane as solvent was initially believed to be necessary to dissolve the water-insoluble steroidal compounds, examination of the oxidation process using water as solvent actually led to an improvement in product yield (e.g., 68% yield for **26** after 48 h with 12 equiv of T-HYDRO). In contrast to oxidations of cholesterol in which the secondary alcohol at the 3-position was stable to oxidative conversion to a ketone, oxidation of the secondary alcohol at the 17-position of testosterone was competitive with allylic oxidation of the enone, and both androst-4-ene-3,17-dione and androst-4-ene-3,6,17-trione accompanied formation of **25**. This oxidative process appears to be general for strained secondary alcohols (cyclopentanol, *endo*-norbornanol, borneol, for example), but optimization of these reactions has not been pursued. In an attempt to effect sequential oxidation on both sides of the carbon−carbon double bond, 3β-acetoxyandrost-5-en-17-one was subjected to sequential treatments with TBHP and $Rh_2(cap)_4$ (eq 12); the desired 3β-acetoxyandrost-5-en-4,7,17-trione **27** was formed in 54% yield.

25: 28 % (in DCE)
23 % (in H$_2$O)

(9)

26: 50 % (in DCE)
68 % (in H$_2$O)

(10)

27: 80 % (in DCE)
62 % (in H$_2$O)

(11)

28: 50 %

(12)

27: 54 %
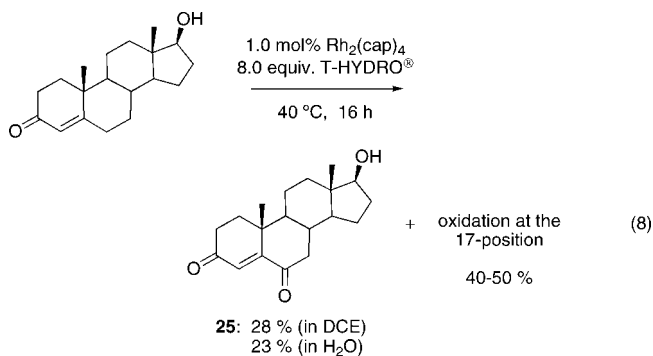
In summary, dirhodium(II) caprolactamate is an efficient engine for the production of the *tert*-butylperoxy radical, which is a selective reagent for hydrogen atom abstraction. This efficiency is exemplified in comparative studies with other metal catalysts that are reported to be operative for allylic oxidations with TBHP. As a result, allylic oxidations, even of normally recalcitrant substrates (such as enones), can effectively produce the corresponding keto-products including steroidal enones. Mechanistic implications arising from studies of allylic oxidation with less reactive enones have provided new insights into factors that control product formation.

Experimental Section

General Methods. HPLC grade solvents were used for extraction and purification. Unless otherwise indicated, all reactions were run

under atmospheric conditions. All reagents were obtained from commercial sources. Dirhodium(II) caprolactamate [Rh$_2$(cap)$_4$·2CH$_3$CN] was prepared as previously described.[40] Silica gel plates (0.25 mm, 60 F$_{254}$) were used for analytical thin-layer chromatography, and spots were visualized using 254 nm ultraviolet light before using potassium permanganate, vanillin, or anisaldehyde stains as visualizing agents. Chromatographic purifications were performed using silica gel (60 μm, 40−63 mesh) according to the method of Still.[41] Yields reported are for isolated compounds according to their mass unless otherwise noted. All products were characterized and in agreement with those that were previously described. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were obtained on a 400 MHz spectrometer as solutions in CDCl$_3$ unless otherwise noted. Chemical shifts are reported in parts per million (ppm, δ) relative to internal Me$_4$Si (δ 0.00) for ^{1}H and relative to internal chloroform (δ 77.0) for ^{13}C; coupling constants are reported in hertz (Hz).

General Procedure for the Oxidation of α,β-Unsaturated Carbonyl Compounds. A 10 mL vial equipped with a stirbar was charged with substrate (1.36 mmol) and Rh$_2$(cap)$_4$ (5 mg, 0.007 mmol). Solvent (2.5 mL) was added followed by the addition of TBHP (0.75 mL, 5.5 mmol, 4 equiv). The vial was loosely capped and stirred for 16 h, and then the second portion of Rh$_2$(cap)$_4$ (5 mg, 0.007 mmol) and TBHP (0.75 mL, 5.5 mmol, 4 equiv) was added. After an additional 24 h, the solution was concentrated and purified by column chromatography to obtain analytically pure compounds whose spectral characteristics were identical to those previously reported: *trans*-3-nonen-2,5-dione (**1**)[11] and ethyl (*E*)-4-oxo-2-decenoate (**2**).[42] (*E*)-4-Oxo-2-pentenamide (**5**),[43] 4-androsten-17β-3,6-dione (**25**),[44] 17β-acetoxyandrost-4-en-3,6-dione (**26**),[45] 4-androstene-3,6,17-trione (**27**),[46] 4-cholesten-3,6-dione (**28**),[47] and acids were purified by recrystallization in ethyl acetate and matched with those in the literature: (*E*)-4-oxo-2-nonenoic acid (**3**),[25a] (*E*)-4-oxo-2-pentenoic acid (**4**),[48] 2-cyclohexenone-1-carboxylic acid (**7**),[49] and fumaric acid monomethyl ester (**8**).[50]

Oxidation of 1-Acetylcyclohexene: Isolation and Characterization of 10−13 and 18. 1-Acetylcyclohexene (0.750 g, 6.04 mmol) and Rh$_2$(cap)$_4$ (22 mg, 0.030 mmol) were dissolved in 22 mL of 1,2-dichloroethane in a 100 mL round-bottom flask. T-HYDRO (3.31 mL, 24.1 mmol) was slowly added (1 mL/min), and the color of the reaction solution turned from purple to brown-red in color. The flask was capped with a rubber septum, vented with a 18-gauge needle, and heated at 40 °C in an oil bath. After 17.5 h, the reaction was concentrated under reduced pressure to yield 2.11 g of a red-brown oil. The oil was purified via silica gel column chromatography (100% hexanes to 2:1 hexanes/ethyl acetate, gradient). Only the purest fractions were used for full characterization: 55 mg of **10**, 20 mg of **11**, 18 mg of **12**, 32 mg of **13**, 20 mg of **16**, and 312 mg of 3-acetyl-2-cyclohexenone (**9**).

1-(1-*tert*-Butylperoxy)cyclohex-2-enyl)ethanoate (10): R$_f$ 0.69 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.12 (ddd, J = 3.2, 4.4, 10.0 Hz, 1 H), 5.66 (ddd, J = 2.0, 2.0, 10.0 Hz, 1 H), 2.31 (s, 3 H), 2.07−2.02 (comp, 2 H), 1.97−1.91 (comp, 2 H), 1.73−1.65 (comp, 2 H), 1.23 (s, 9 H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 210.0, 135.6, 123.0, 85.2, 79.7, 26.9, 26.6, 25.3, 24.4, 18.2; FTIR (thin film) 2979, 2935, 2871, 1720, 1363, 1197, 735 cm^{-1}; exact mass calcd for C$_{12}$H$_{20}$O$_3$ + H (ES) 213.1490, found 213.1115.

4-(*tert*-Butylperoxy)-4-ethanoylcyclohex-2-enone (11): R$_f$ 0.37 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.99 (d, J = 10.4 Hz, 1 H), 6.17 (d, J = 10.4 Hz, 1 H), 2.57 (m, 1 H) 2.46−2.44 (comp, 2 H), 2.38 (s, 3 H), 2.27−2.22 (comp, 3 H), 1.25 (s, 9 H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 207.6, 198.0, 145.2, 131.8, 84.4, 81.06, 33.3, 28.7, 26.4, 24.6; FTIR (thin film) 3056, 2980, 2937, 1720, 1688, 1365, 1192, 874, 737 cm^{-1}; exact mass calcd for C$_{12}$H$_{18}$O$_4$ + H (ES) 227.1283, found 227.1288.

1-(6-*tert*-Butylperoxy)cyclohex-1-enyl)ethanoate (12): R$_f$ 0.58 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.08 (dd, J = 4.8, 2.8 Hz, 1 H), 5.00 (bs, 1 H), 2.40−2.38 (comp, 2 H), 2.35 (m, 1 H), 2.32 (s, 3 H), 2.20−2.17 (m, 1 H), 1.75−1.78 (m, 1 H), 1.63−1.66 (m, 1 H), 1.26 (s, 9 H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 198.0, 146.1, 136.2, 80.1, 72.1, 26.5, 26.3, 26.0, 25.4, 15.7; FTIR (thin film) 3060, 2928, 2977, 1674, 1362, 1258, 1240, 1196, 736 cm^{-1}; exact mass calcd for C$_{12}$H$_{20}$O$_3$ + H (ES) 213.1490, found 213.1481.

1-(3-*tert*-Butylperoxy)cyclohex-1-enyl)ethanoate (13): R$_f$ 0.62 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.86 (t, J = 1.5 Hz, 1 H), 4.63 (bs, 1 H), 2.34 (s, 3 H), 2.25−2.19 (comp, 2 H), 1.87−1.70 (comp, 3 H), 1.63−1.61 (m, 1 H), 1.28 (s, 9 H); ^{13}C NMR (100 MHz, CDCl$_3$) d 199.7, 142.3, 136.3, 80.4, 77.4, 26.4, 26.3, 25.6, 23.3, 18.9; FTIR (thin film) 3055, 2980, 2930, 1672, 1265, 1235, 734 cm^{-1}; exact mass calcd for C$_{12}$H$_{20}$O$_3$ (CI) 214.1412, found 214.1481.

4-(*tert*-Butylperoxy)-3-ethanoylcyclohex-2-enone (18): R$_f$ 0.33 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.53 (s, 1 H), 5.16 (t, J = 3.2 Hz, 1 H), 2.81 (ddd, J = 5.2, 12.8, 17.6 Hz, 1 H), 2.62−2.60 (m, 1 H), 2.47−2.45 (m, 1 H), 2.44 (s, 3 H), 2.00 (m, 1 H), 1.23 (s, 9 H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 200.7, 198.9, 149.4, 133.6, 81.0, 71.41, 32.9, 26.8, 26.3, 25.7; FTIR (thin film) 2982, 2937, 2253, 1685, 1365, 1222, 1191, 907, 736 cm^{-1}; exact mass calcd for C$_{12}$H$_{18}$O$_4$ + H (ES) 227.1283, found 227.1259.

Oxidation of Cholesterol (19): Isolation of 22−24. Cholesterol (0.525 g; 1.36 mmol) and Rh$_2$(cap)$_4$ (10 mg; 0.013 mmol) were dissolved in 5 mL of 1,2-dichloroethane in a 6 dram vial equipped with a stirbar. T-HYDRO (0.74 mL, 5.43 mmol) was added, and the color of the reaction solution turned from purple to brown-red in color. The vial was loosely capped and stirred at room temperature. After 15 h, the reaction was concentrated under reduced pressure to 1.01 g of a red-brown semisolid. The crude material was purified via silica gel column chromatography (100% hexanes to 1:1 hexanes/ethyl acetate, gradient) to afford 164 mg of **22**, 62 mg of α-**23**, 13 mg of β-**23**, 57 mg of α-**24**, 25 mg of β-**24**, and 106 mg of starting material (**21**). The full characterization of **22−24** has been reported.[10,38a]

Oxidation of 17β-Acetoxyandrost-4-en-3-one in Water. 17β-Acetoxyandrost-4-en-3-one[51] (1.32 g, 4.0 mmol) was stirred vigorously in 12 mL of water at room temperature in a 50 mL flask. Then Rh$_2$(cap)$_4$ (29.5 mg, 0.040 mmol) was added, followed by addition of T-HYDRO (4.6 mL, 32 mmol). The reaction became dark purple-red in color. The flask was closed with a rubber septum with a balloon and stirred for 24 h in a 40 °C oil bath. At that time, additional portions of Rh$_2$(cap)$_4$ (15 mg, 0.02 mmol) and T-HYDRO (2.3 mL, 16 mmol) were added, and the reaction solution was stirred for another 24 h. The reaction was extracted into diethyl ether (3 × 20 mL). The organic extracts were combined, dried over anhydrous MgSO$_4$, filtered, and then concentrated under

(36) (a) Arsenou, E. S.; Koutsourea, A. I.; Fousteris, M. A.; Nikolaropoulos, S. S. *Steroids* **2003**, *68*, 407.

(37) Schenck, G. O.; Neumüller, O. A.; Eisfeld, W. *Justus Liebigs Ann. Chem.* **1958**, *618*, 202.

(38) (a) Beckwith, A. L. J.; Davies, A. G.; Davison, I. G. E.; Maccoll, A.; Mruzek, M. H. *J. Chem. Soc., Perkin Trans. 2* **1989**, 815. (b) Dang, H.; Davies, A. G.; Davison, I. G. E.; Schiesser, C. H. *J. Org. Chem.* **1990**, *55*, 1432. (c) Ponce, M. A.; Ramirez, J. A.; Galagovsky, L. R.; Gros, E. G.; Erra-Balsells, R. *J. Chem. Soc., Perkin Trans. 2* **2000**, 2351.

(39) Miyamoto, S.; Martinez, G. R.; Medeiros, M. H. G.; Di Mascio, P. *J. Am. Chem. Soc.* **2003**, *125*, 6172.

(40) Doyle, M. P.; Westrum, L. J.; Wolthuis, W. N. E.; See, M. M.; Boone, W. P.; Bagheri, V.; Pearson, M. M. *J. Am. Chem. Soc.* **1993**, *115*, 958.

(41) Still, W. C.; Kahn, M.; Mitra, A. J. *J. Org. Chem.* **1978**, *43*, 2923.

(42) Manfredini, S.; Simoni, D.; Zanirato, V.; Casolari, A. *Tetrahedron Lett.* **1988**, *29*, 3997.

(43) Scheffold, R.; Dulos, P. *Helv. Chim. Acta* **1967**, *50*, 798−807.

(44) Jasiczak, J. *J. Chem. Soc., Perkin Trans. 1* **1988**, *10*, 2687.

(45) Marwah, P.; Marwah, A.; Lardy, H. A. *Green Chem.* **2004**, 570.

(46) Kiran, I. *J. Chem. Res.* **2004**, *3*, 208.

(47) Hunter, C. A.; Priest, S.-M. *Steroids* **2006**, *71*, 30.

(48) Lüönd, R. M.; Walker, J.; Neier, R. W. *J. Org. Chem.* **1992**, *57*, 5005.

(49) Webster, F. X.; Silverstein, R. M. *Synthesis* **1987**, *10*, 922.

(50) Davis, R. A. *J. Nat. Prod.* **2005**, *68*, 769.

(51) 17β-Acetoxyandrost-4-en-3-one was prepared according to: Krauser, J. A.; Guengerich, F. P. *J. Biol. Chem.* **2005**, *280*, 19496.

reduced pressure to yield a crude yellow oil that was purified by silica gel chromatography (25% ethyl acetate in hexanes) to yield 938 mg (2.72 mmol, 68%) of a white solid (**26**): mp 193−195 °C (lit.[45] mp 192−194 °C).

3β-Acetoxyandrost-5-en-4,7,17-trione (27). 3β-Acetoxyandrost-5-en-17-one (330 mg, 1.0 mmol) and Rh$_2$(cap)$_4$ (7.4 mg, 10 μmol) were added into a vial together with 3 mL of water, followed by T-HYDRO (1.14 mL, 8.0 mmol), and the stirred reaction mixture was heated in an oil bath at 40 °C. After 24 and 48 h, additional portions of Rh$_2$(cap)$_4$ (7.4 mg, 10 μmol) and T-HYDRO (1.14 mL, 8.0 mmol) were added. The reaction was extracted into diethyl ether (3 × 20 mL), and the organic extracts were combined, dried over anhydrous MgSO$_4$, filtered, then concentrated, under reduced pressure, to yield a crude yellow oil that was purified by silica gel chromatography (33% ethyl acetate in hexanes) to give 195 mg (0.54 mmol, 54%) of a white solid: mp 216−218 °C (lit.[45] mp218−220 °C); ^{1}H NMR (CDCl$_3$, 400 MHz) defining absorptions are at δ 6.15 (s, 1H), 5.28 (dd, J = 12.0, 8.0 Hz, 1H), 2.77 (ddd, J = 12.0, 8.0, 4.0 Hz, 1H), 2.50 (d, J = 8.0 Hz, 1H), 2.45 (d, J = 8.0 Hz, 1H), 2.24−2.31 (m, 1H), 2.18 (s, 3H), 1.22 (s, 3H), 0.90 (s, 3H).

Supporting Information Available: Procedures, product characterization, and analysis of compounds, especially steroidal products. This material is available free of charge via the Internet at http://pubs.acs.org.

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