Optimal TBHP Allylic Oxidation of Δ5-Steroids Catalyzed by Dirhodium Caprolactamate

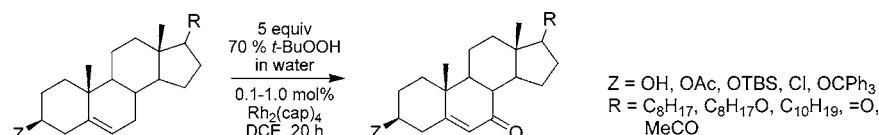**Hojae Choi and Michael P. Doyle***

Department of Chemistry and Biochemistry, University of Maryland, College Park, Maryland 20742

mdoyle3@umd.edu

ABSTRACT

Dirhodium caprolactamate is the most efficient catalyst for the oxidation of Δ5-steroids to 7-keto-Δ5-steroids by 70% *tert*-butyl hydroperoxide in water (T-HYDRO). Isolated product yields range from 38 to 87%.

Few substrates have commanded as much attention for allylic oxidation as have Δ5-steroids. Intense interest has been emerging concerning the biological effects of the 7-keto steroid oxidation products that are indicated in their increasingly evident physiological effects.[1,2] Selenium dioxide is inappropriate as an oxidant because this reagent favors oxidation at the 4-position,[3] and stoichiometric chromium-(VI) oxidations[4] are disfavored because of the relative severity of reaction conditions and environmental concerns.[1a] Recently, *tert*-butyl hydroperoxide has become the oxidant

of choice for steroidal allylic oxidations, but the defining ingredient in these oxidations is the promoter or catalyst, and the optimal methodology is unclear. Since 2000 alone, allylic oxidation methodologies for steroids using *tert*-butyl hydroperoxide (TBHP) have been reported to be catalyzed or promoted by sodium chlorite,[5] chromium (VI),[6] manganese(III) acetate,[7] bismuth(III) salts,[8] copper iodide,[9] and cobalt acetate.[10] Chromium-mediated oxidations have received the most attention,[11] but ruthenium(III) chloride catalysis in large-scale applications was found to be more advantageous.[12] We reported in 2004 a new catalytic system for allylic oxidations using TBHP that was extraordinarily effective for simple cyclic systems, providing enone product with complete regioselectivity and in high yield with the use of catalyst loadings of between 0.1 and 1.0 mol % of

(1) Reviews: (a) Parish, E. J.; Kizito, S. A.; Qiu, Z. *Lipids* **2004**, 801. (b) Arsenou, E. S.; Fousteris, M. A.; Koutsourea, A. I.; Nikolaropoulos, S. S. *Mini Rev. Med. Chem.* **2003**, *3*, 557. (c) Smith, L. *Lipids* **1996**, *31*, 453. (d) Peng, S.-K.; Morin, R. J. *The Biological Effects of Cholesterol Oxides*; CRC Press: Boca Raton, FL, 1992.

(2) (a) Lee, J. W.; Fuda, H.; Javitt, N. B.; Strott, C. A.; Rodriguez, I. R. *Exp. Eye Res.* **2006**, *83*, 465. (b) Berthier, A.; Lemaire-Ewing, S.; Prunet, C.; Monier, S.; Athias, A.; Bessade, G.; Paisde Barros, J.-P.; Laubriet, A.; Gambert, P.; Lizard, G.; Nacel, D. *Cell Death Differ.* **2004**, *11*, 897. (c) Deckert, V.; Duverneuil, L.; Poupon, S.; Monier, S.; de Guern, N.; Lizard, G.; Masson, D.; Lagrost, L. *Brit. J. Pharm.* **2002**, *137*, 655. (d) Steffen, Y.; Wiswedel, I.; Peter, D.; Schewe, T.; Sies, H. *Free Radicals Biol. Med.* **2006**, *41*, 1139. (e) Javitt, N. B. *Curr. Opin. Lipidol.* **2007**, *18*, 283.

(3) (a) Rabjohn, N. *Org. React.* **1976**, *24*, 261. (b) Crich, D.; Zou, Y. *Org. Lett.* **2004**, *6*, 775.

(4) (a) Hua, Z.; Carcache, D. A.; Tian, Y.; Li, Y.-M.; Danishefsky, S. J. *J. Org. Chem.* **2005**, *70*, 9849. (b) Bora, U.; Chaudhuri, M. K.; Dey, D.; Kalita, D.; Kharmawphlang, W.; Mandal, G. C. *Tetrahedron* **2001**, *57*, 2445. (c) Kasal, A. *Tetrahedron* **2000**, *56*, 3559. (d) Li, D.; Spencer, T. A. *Steroids* **2000**, *65*, 529. (e) Labaree, D.; Hoyte, R. M.; Hochberg, R. B. *Steroids* **1998**, *63*, 454. (f) Parish, E. J.; Wei, T.-Y. *Synth. Commun.* **1987**, *17*, 1227. (g) Dauben, W. G.; Fullertyon, D. S. *J. Org. Chem.* **1971**, *36*, 3277.

(5) Silvestre, S. M.; Salvador, J. A. R. *Tetrahedron* **2007**, *63*, 2439.

(6) Fousteris, M. A.; Koutsourea, A. I.; Nikolaropoulos, S. S.; Riahi, A.; Muzart, J. *J. Mol. Catal. A: Chem.* **2006**, *250*, 70.

(7) Shing, T. K. M.; Yeung, Y. Y.; Su, P. L. *Org. Lett.* **2006**, *8*, 3149.

(8) Salvador, J. A. R.; Silvestre, S. M. *Tetrahedron Lett.* **2005**, *46*, 2581.

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

(10) Salvador, J. A. R.; Clark, J. H. *Chem. Commun.* **2001**, 33.

(11) (a) Baptistella, L. H.; Sousa, I. M. O.; Gushikem, Y.; Aleixo, A. M. *Tetrahedron Lett.* **1999**, *40*, 2595. (b) Muzart, J. *Synth. Commun.* **1989**, *19*, 2061.

(12) Miller, R. A.; Li, W.; Humphrey, G. R. *Tetrahedron Lett.* **1996**, *37*, 3429.

dirhodium caprolactamate, $Rh_2(cap)_4$.[13] The *tert*-butyl hydroperoxide oxidant was the anhydrous reagent in decane that has been favored by several investigators in order to avoid hydrolysis of the catalyst. We can now report that dirhodium caprolactamate is exceptionally effective for the oxidation of Δ^5-steroids and even those that possess oxidatively sensitive groups, using the much less expensive 70% TBHP in water (T-HYDRO).

Previous reports for oxidations by TBHP cover a wide range of conditions, so direct comparison is difficult. However, cholesteryl acetate (**1**) is common to virtually all studies, and comparative results for its conversion to the 7-keto-Δ^5 product (**2**, eq 1) are described in Table 1, along
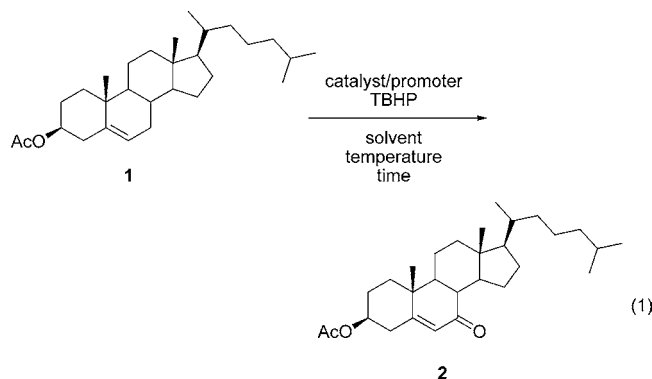
catalyst/promoter
TBHP

solvent
temperature
time

1

2

(1)

catalyst/ additive (mol %)	oxidant	TBHP (equiv)	solvent	time (h)	temp (°C)	yield **2** (%)
$NaClO_2$ (116%)	T-HYDRO	10	MeCN	80	60	66 (ref 5)
CrO_3 (5%)/NMI	T-HYDRO	7	$PhCF_3$	23	40	74 (ref 6)
$Mn_3(OAc)_9$ (10%)	*t*-BuOOH/ decane	5	EtOAc	48	40	85 (ref 7)
$BiCl_3$ (5%)	*t*-BuOOH/ decane	10	MeCN	22	70	82 (ref 8)
CuI (3%)/ Bu_4NBr (6%)	T-HYDRO	7	benzene	24	70	63 (ref 9)
$Co(OAc)_2$ (2.2%)	*t*-BuOOH/ decane	6	benzene	48	70	70 (ref 10)
$RuCl_3$ (0.7%)	T-HYDRO	10	cyclohexane	24	20	75 (ref 12)
$Rh_2(cap)_4$ (1.0%)	T-HYDRO	5	(CH_2Cl_2)	20	40	80
$Rh_2(cap)_4$ (0.1%)	T-HYDRO	8	(CH_2Cl_2)	20	40	77

with that for the $Rh_2(cap)_4$-catalyzed oxidation. As can be seen from the table, the catalytic use of $Rh_2(cap)_4$ has distinct advantages over other existing methodologies:

high product yield, use of T-HYDRO instead of *tert*-butyl hydroperoxide in decane, catalyst loading down to 0.1 mol %, less T-HYDRO than most methods, moderate temperatures and time. In contrast to the other catalysts or promoters, the oxidized $Rh_2(cap)_4$ that is formed upon reaction with TBHP is soluble in both water and the organic solvent, thus minimizing operational concerns that are related to two-phase reaction systems.

The $Rh_2(cap)_4$-catalyzed oxidation was performed on a millimole scale with Δ^5-steroids using 0.1−1.0 mol % of $Rh_2(cap)_4$. 1,2-Dichloroethane was added to dissolve the steroid, the solution was heated to 40 °C, and then T-HYDRO was added in one portion. The original blue color of $Rh_2(cap)_4$ turned deep-red upon mixing with *tert*-butyl hydroperoxide, consistent with formation of Rh(II)/Rh(III) caprolactamate. The reaction solution was stirred for 20 h at 40 °C, after which the solution was concentrated under reduced pressure and subjected to purification by column chromatography (1 cm diameter, 15 cm long glass column) using hexane/ethyl acetate.

Isolated yields were determined by mass of the purified product, and product identity was confirmed by NMR spectroscopy with comparison, whenever possible, to spectra of authentic samples.
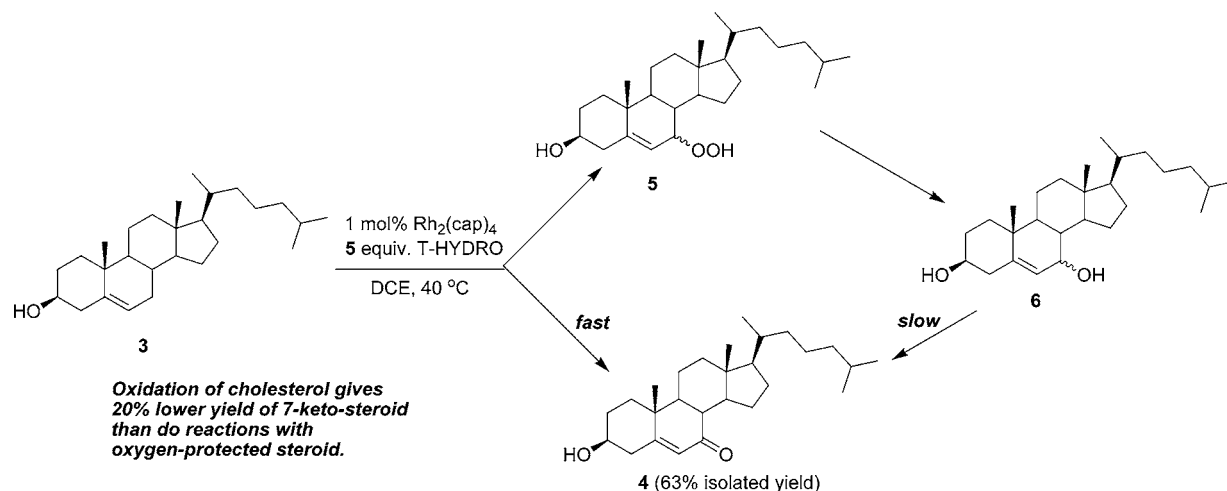
Oxidation of cholesterol (**3**) is more challenging than the oxidation of cholesteryl acetate, and we observe a comparative decrease in the isolated yield of 7-ketocholesterol (**4**) of 15−20% with the use of *tert*-butyl hydroperoxide as the oxidant.[14] Highly polar materials, believed to be acids from oxidative cleavage, are formed whose identity has been elusive. However, 7-ketocholesterol is easily isolated from the reaction mixture in pure form by standard chromatography (vide infra), and we have carried out the oxidation in gram-scale using 0.1 mol % of $Rh_2(cap)_4$.

Optimization of this oxidation was achieved by investigation of the change in % conversion and isolated yield as a function of temperature, amount of T-HYDRO, solvent, and additive. Conversion is slow at room temperature, but complete within 20 h at 40 °C; at 60 °C, oxidation is considerably faster, but the catalyst undergoes hydrolysis at a measurable rate. With 2.0 equiv of T-HYDRO, oxidation reached 83% conversion within 20 h and was at 95% conversion with 4.0 equiv of T-HYDRO over the same time, the reason for which is competitive formation of both stereoisomers of 7-hydroperoxy- (**5**) and 7-hydroxycholesterol (**6**)[15] that undergo slow oxidation to 7-ketocholesterol (Scheme 1). Dichloroethane was preferred over dichloromethane because of its higher boiling point. The use of toluene gave comparable results under comparable conditions; however, oxidation was slower in cyclohexane, and the use of either methanol or water without an organic cosolvent resulted, as expected from solubility considerations,

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

(14) Few publications report results for the oxidation of cholesterol; oxidation of the 3-OH-protected substrate is reported instead.[1,5−12]

(15) (a) Akihisa, T.; Matsumoto, T.; Sakamaki, H.; Take, M.; Ichinohe, Y. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 680. (b) Dang, H.-S.; 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.

Scheme 1

Oxidation of cholesterol gives 20% lower yield of 7-keto-steroid than do reactions with oxygen-protected steroid.

in a much slower rate of oxidation. Inorganic bases that facilitated TBHP allylic oxidations which occurred under anhydrous conditions[13] only inhibited oxidations that occurred with T-HYDRO. When the same amount of TBHP in decane is used along with 50 mol % of potassium carbonate, instead of T-HYDRO, % conversion only reaches 40%. Thus, optimum conditions for allylic oxidations of cholesterol involve the use of 0.1−1.0 mol % of $Rh_2(cap)_4$, 4−5 molar equiv of T-HYDRO without base, a moderately polar organic solvent to dissolve the steroidal reactant, a temperature of 40 °C, and a reaction time of 20 h. Under these conditions, 7-ketocholesterol was formed in 63% isolated yield with 1.0 mol % of $Rh_2(cap)_4$ and in 58% isolated yield with 0.1 mol % of $Rh_2(cap)_4$.[16]

To compare catalysts that are suitable for use with T-HYDRO under the same conditions that were optimized for cholesterol oxidation with $Rh_2(cap)_4$ catalysis, we substituted $RuCl_3$(hydrate),[12] CuI,[9] and $CuCl_2$[17] for $Rh_2(cap)_4$, all at 1.0 mol %. The copper catalysts were inadequate under these conditions, reaching only 61% conversion for CuI and 76% conversion with $CuCl_2$ but with substantial amounts of partially oxidized **5** and **6** formed and remaining after 20 h; however, faster conversion rates occurred under anhydrous conditions (TBHP in decane) even though these catalysts were insoluble in the reaction medium. Ruthenium(III) chloride hydrate, on the other hand, catalyzed the clean conversion of cholesterol to 7-ketocholesterol, but the isolated yield of 7-ketocholesterol was only two-thirds of that obtained with the use of $Rh_2(cap)_4$; unlike oxidized $Rh_2(cap)_4$, oxidized $RuCl_3$ is soluble in water but not in DCE. Reactions catalyzed by $Rh_2(cap)_4$ were also performed under conditions reported to be optimal for $RuCl_3$ (0.7 mol % of catalyst, 10 equiv of T-HYDRO, delivery by syringe pump, cyclohexane solvent, room temperature),[12] and both catalysts gave the same outcome.

---

(16) Oxidations with 0.1 mol % $Rh_2(cap)_4$ were performed with 1.36 M TBHP (8 molar equiv) whereas those with 1.0 mol % $Rh_2(cap)_4$ were with 0.27 M TBHP (5 molar equiv).

(17) Salvador, J. A. R.; Melo, M. L. S.; Neves, A. S. C. *Tetrahedron. Lett.* **1997**, *38*, 119.

The usefulness of this oxidative methodology is linked to its functional group tolerance, selectivity, and product yield. Results from oxidations of cholesterol derivatives (**7**) by T-HYDRO catalyzed by $Rh_2(cap)_4$ under conditions optimized for oxidation of cholesterol suggest high functional group compatibility (eq 2).

(2)
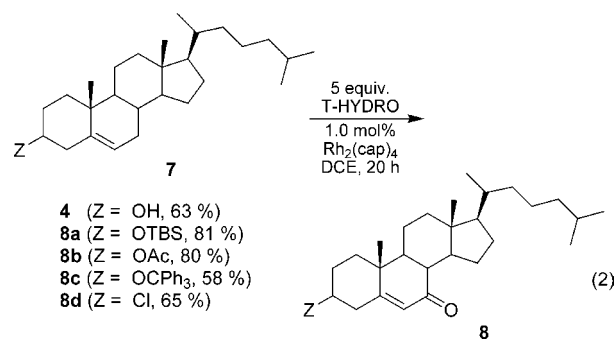
Both acetyl and *tert*-butyldimethylsilyl cholesterol derivatives with their common hydroxyl protective groups undergo allylic oxidation to their respective 7-keto products in high yield; chloro and trityl derivatives give results comparable to cholesterol. Further optimization of conditions for specific substrates may be possible.

Oxidations of Δ^5-steroids with functional groups at the 17-position or in the alkyl side chain at the 17-position under the same conditions gave variable 7-keto-Δ^5-steroid product yields (**9**−**12**, Figure 1). In addition to results with dehydroandrosterone catalyzed by 1.0 mol % of $Rh_2(cap)_4$, oxidation of this substrate with only 0.1 mol % of $Rh_2(cap)_4$ formed **9b** in 69% yield. Although the presence of oxidizable functional groups in the alkyl side chain reduces the yield of 7-keto-Δ^5-steroid product, only simple chromatography is required to obtain the allylic oxidation product. Byproducts from these oxidations were not identified but are of interest in efforts to further optimize product yields.

Allylic oxidations by TBHP occur through a free radical pathway for generation of the *tert*-butylperoxy radical that
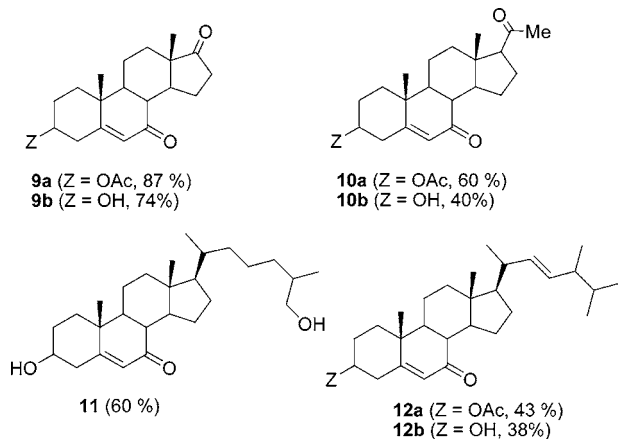
Figure 1.

is common to metal-catalyzed reactions of hydroperoxides.[18] One-electron reduction of TBHP forms an oxidized metal hydroxide and the *tert*-butoxy radical that undergoes rapid hydrogen atom abstraction from *tert*-butyl hydroperoxide to produce the more stable *tert*-butylperoxy radical.[19] The *tert*-butylperoxy radical imparts selectivity to hydrogen abstraction reactions;[20] these processes are well documented and universally accepted.[13,19−22] Trapping of the allyl radical by combination with dioxygen is well established.[22]

Selectivity in the conversion of the allylperoxy radical to ketone (**13** → **14**) in competition with hydrogen atom abstraction (**13** → **15**) is the core feature of this allylic oxidation process. Direct conversion of **13** to ketone could (a) involve a recently described[23] hydrogen atom abstraction from the α-position to form an alkyl hydroperoxy radical, followed by oxidative transfer of hydroxyl to $Rh_2(cap)_4$, (b)

occur through hydroperoxy radical capture by $Rh_2(cap)_4$, followed by O−O cleavage with hydrogen transfer (Scheme 2, cyclohexene model),[24] or form a metal peroxide complex

Scheme 2
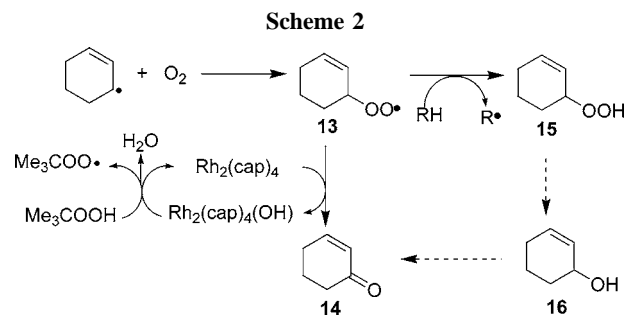
leading to, as yet, unprecedented intermediates. They are viable alternatives to bimolecular disproportionation of two peroxy radicals that would form alcohol and ketone together with dioxygen (the Russell mechanism).[25] Efforts to determine the specific pathway or pathways for oxidation catalyzed by dirhodium compounds and methods to direct the reaction to a specific pathway are ongoing.

In summary, allylic oxidations of Δ^5-steroids to 7-keto-Δ^5-steroids by *tert*-butyl hydroperoxide is optimally conducted with T-HYDRO in dichloroethane with dirhodium caprolactamate as the catalyst. This method is tolerant of a variety of functional groups and can be conducted at catalyst loadings as low as 0.1 mol %.

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

OL7025284

(18) (a) Nagiev, T. M. *Coherent Synchronized Oxidation Reactions by Hydrogen Peroxide*; Elsevier Science, Ltd.: Amsterdam, 2006. (b) *Modern Oxidation Methods*; Bäckvall, J., Ed., Wiley-VCH: New York, 2004.

(19) (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**, 135.

(20) Bravo, A.; Bjorsvik, H.-R.; Fontana, F.; Liguori, L.; Minisci, F. *J. Org. Chem.* **1997**, *62*, 3849.

(21) Yu, J.-Q.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 3232.

(22) Chavez, F. A.; Mascharak, P. K. *Acc. Chem. Res.* **2000**, *33*, 539.

(23) Bozzelli, J. W.; Sheng, C. *J. Chem. Phys. A* **2002**, *106*, 1113.

(24) Note that Scheme 3 also describes a catalytic interconversion between Rh_2^{5+} and Rh_2^{4+}.

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