Tetrahedron Letters, Vol. 34, No. 8, pp. 1299-1302, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

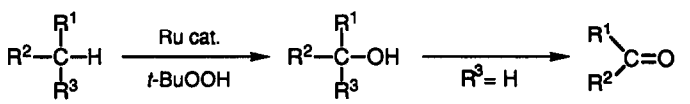
Ruthenium-Catalyzed Cytochrome P-450 Type Oxidation of Alkanes with Alkyl Hydroperoxides

Shun-Ichi Murahashi,*[a] Yoshiaki Oda,[a,b] Takeshi Naota,[a] and Toshiyuki Kuwabara[a]

[a]*Department of Chemistry, Faculty of Engineering Science, Osaka University, Machikaneyama, Toyonaka, Osaka 560, Japan*
[b]*Organic Synthesis Research Laboratory, Sumitomo Chemical Co., Ltd., Takatsuki, Osaka 569, Japan*

Abstract: The ruthenium-catalyzed oxidation of alkanes with *t*-butyl hydroperoxide under mild conditions gives the corresponding ketones and alcohols highly efficiently. Kinetic study revealed that the reaction involves hydrogen abstraction of oxoruthenium species.

The oxygenation of unactivated C–H bonds with metal complex catalysts is of importance in view of synthetic[1] and biological aspects.[2] Cytochrome P-450 enzymes catalyze specific oxygenation of various organic substrates, and their model reactions using metalloporphyrin complexes have been studied extensively.[3] During the course of our study on the simulation of enzymatic function with metal complex catalysts, we have found that the ruthenium-catalyzed oxidations of amines[4] and amides[5] with peroxides give the corresponding α-oxygenated compounds highly efficiently. As an extension of these studies, we have found cytochrome P-450 type-oxidation of alkanes with alkyl hydroperoxides in the presence of non-porphyrin ruthenium complexes. Thus, ruthenium-catalyzed oxidation of alkanes with *t*-butyl hydroperoxide under mild conditions gives the corresponding ketones and alcohols highly efficiently (eq 1).[6]

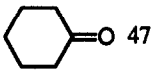
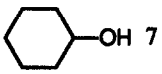
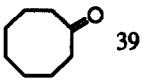
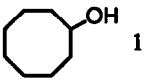
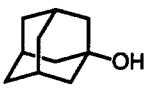
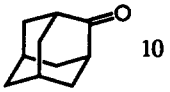
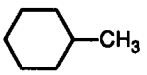
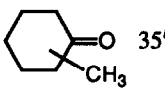
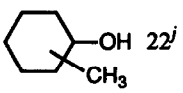
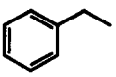
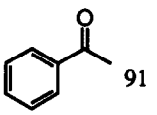
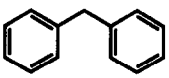
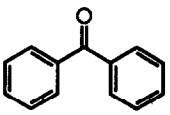
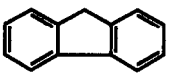
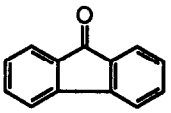
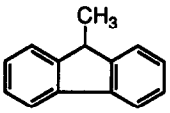
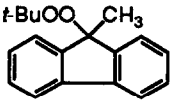


(1)

The catalytic activity of various metal complexes has been examined for the oxidation of *n*-decane with *t*-BuOOH. $RuCl_2(PPh_3)_3$ and $RuH_2(PPh_3)_4$ are good catalysts for the formation of decanones and decanols. The use of other catalysts such as $RuCl_3 \cdot nH_2O$, $RuCl_2(bpy)_2$, $Ru_3(CO)_{12}$, and $RhCl(PPh_3)_3$ gave unsatisfactory results. The effect of oxidants has been examined for the oxidation of *n*-decane in the presence of $RuCl_2(PPh_3)_3$ catalyst. Alkyl hydroperoxides such as *t*-BuOOH and cumyl hydroperoxide gave good results. Other oxidants such as hydrogen peroxide, *m*-chloroperbenzoic acid, sodium hypochlorite, iodosyl benzene, and *N*-methylmorpholine *N*-oxide are ineffective for the present oxidation reaction.

Typically, the oxidation of *n*-decane was carried out as follows. To a solution of *n*-decane (285 mg, 2.00 mmol) and $RuCl_2(PPh_3)_3$ (19 mg, 0.02 mmol, 1 mol%) in dry benzene (2 mL) was added a 3.59 M solution of

Table 1. Ruthenium-Catalyzed Oxidation of Alkanes with *t*-BuOOH[a]

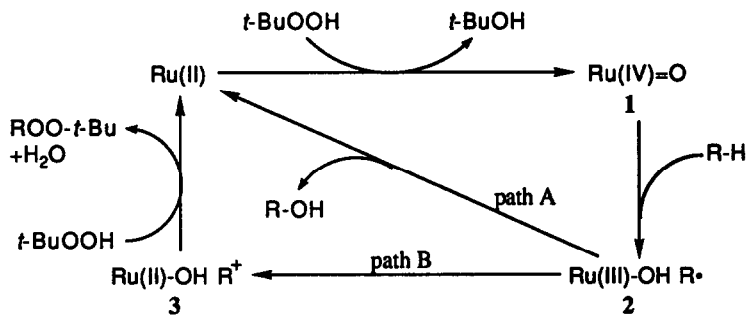
entry	substrate	conv,[b] %	product[c]	yield,[d] %
1	*n*-heptane	26	heptanones heptanols	35[e] 2[f]
2	*n*-decane	28	decanones decanols	38[g] 2[h]
3		41		47  7
4		58		39  1
5		82		34  10
6		36		35[i]  22[j]
7		47		91
8		75		95 (70[k])
9		100		87 (86[k])
10		100		100 (98[k])

[a]The reaction was carried out as described in the text. [b]Determined by GLC analysis based on the starting alkane using internal standard. [c]Identified by GC-MS. [d]Determined by GLC analysis based on the converted alkane using internal standard. [e]2-one : 3-one : 4-one = 46 : 32 : 22. [f]2-ol : 3-ol : 4-ol = 50 : 33 : 17. [g]2-one : 3-one : (4+5)-ones = 30 : 22 : 48. [h]2-ol : 3-ol : (4+5)-ols = 31 : 31 : 38. [i]2-one : 3-one : 4-one = 19 : 59 : 22. [j]1-ol : 2-ol : 3-ol : 4-ol = 81 : 4 : 10 : 5. [k]Isolated yield based on the starting alkane.

t-BuOOH in dry benzene (2.23 mL, 8.00 mmol) dropwise at room temperature over a period of 2 h under argon. The reaction mixture was poured into 10% Na_2SO_3 aqueous solution (10 mL) slowly and extracted with ether (5 mL x 2). The GLC analysis showed a 28% conversion of *n*-decane. Decanones and decanols were obtained in 38 and 2% yields, respectively along with trace amounts of decanal and decanoic acid.

The ruthenium-catalyzed oxidation with *t*-BuOOH can be applied to a variety of alkanes successfully. The representative results are shown in Table 1. Both linear and cyclic alkanes can be converted into the corresponding ketones along with a small amount of alcohols efficiently (entries 1–4). Oxidation of adamantane gave 1-adamantanol predominantly (entry 5).[7] Alkylated arenes such as ethylbenzene, diphenylmethane, and fluorene were converted into the corresponding ketones highly efficiently (entries 7–9). It is noteworthy that the oxidation of 9-methylfluorene gave 9-*t*-butyldioxy-9-methylfluorene selectively (entry 10).

The oxidation can be rationalized by assuming cytochrome P-450 type mechanism.[4,5] The ruthenium complex, $RuCl_2(PPh_3)_3$, reacts with *t*-BuOOH to give oxoruthenium(IV) species (**1**),[8] which abstracts hydrogen atom from an alkane to give radical pair (**2**).[9] This is supported by the following lines of evidence. The relative reaction rates of the oxidation of five substituted ethylbenzenes (X-$C_6H_4C_2H_5$, X = *p*-CH_3O, *p*-CH_3, H, *p*-Cl, and *m*-Cl) with *t*-BuOOH in benzene were determined by the GLC analysis of the product ketones. The rate data correlate well ($\gamma = 0.967$) with Hammett linear free energy relationship with use of σ values. The ρ value (–0.35) obtained is very similar to that (–0.42) obtained for the oxidation with cytochrome P-450.[11] The intramolecular deuterium isotope effect of the present oxidation of 1,1-dideuterio-1,3-diphenylpropane was determined to be 9.0 by means of the GC-MS analysis of the product ketones. This value is also similar to that (11) obtained for the oxidation with cytochrome P-450.[12] Furthermore, the intermolecular isotope effect of the oxidation of cyclohexanes was determined to be 8.4 by GLC analysis of the oxygenated products of the competitive reaction of cyclohexane and cyclohexane-d_{12}. These data suggest hydrogen abstraction is involved in the present oxidation as observed for cytochrome P-450.[2b] Transfer of hydroxy



ligand of caged alkyl radical (path A) would afford an alcohol and Ru(II) species to complete the catalytic cycle. Secondary alcohols can be converted into ketones under the same conditions.[13] When a radical formed is stable, electron transfer oxidation of the caged alkyl radical (**2**) would give cation **3** (path B) which undergoes electrophilic reaction with *t*-BuOOH. Indeed, electron transfer from stable tertiary radical derived from 9-methylfluorene gives cation readily, hence 9-*t*-butyldioxy-9-methylfluorene is obtained selectively.

Work is in progress to provide definitive mechanistic information and to apply our method to other systems.

Acknowledgments. This work was supported by Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture, Japan.

References and Notes

1. (a) Sheldon, R. A.; Kochi, J. K. *Metal-Catalyzed Oxidations of Organic Compounds*; Academic Press: New York, 1981. (b) Hill, C. L. *Activation and Functionalization of Alkanes*; Wiley: New York, 1989.
2. (a) Sato, R.; Omura, T. *Cytochrome P-450*; Kodansha: Tokyo, 1978. (b) Ortiz de Montellano, P. R. *Cytochrome P-450, Structure, Mechanism and Biochemistry*; Plenum Press: New York and London, 1986.
3. *Iodosyl benzenes:* (a) Groves, J. T.; Nemo, T. E. *J. Am. Chem. Soc.* **1983**, *105*, 6243–6248. (b) Smegal, J. A.; Hill, C. L. *Ibid.* **1983**, *105*, 3515–3521. (c) Traylor, T. G.; Byun, Y. S.; Traylor, P. S.; Battioni, P.; Mansuy, D. *Ibid.* **1991**, *113*, 7821–7823. *Alkyl hydroperoxides:* (d) Mansuy, D.; Bartoli, J. F.; Chottard, J. C.; Lange, M. *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 909–910. *Hydrogen peroxide:* (e) Battioni, P.; Renaud, J. P.; Bartoli, J. F.; Reina-Artiles, M.; Fort, M.; Mansuy, D. *J. Am. Chem. Soc.* **1988**, *110*, 8462–8470. (f) Banfi, S.; Legramandi, F.; Montanari, F.; Pozzi, G.; Quici, S. *J. Chem. Soc., Chem. Commun.* **1991**, 1285–1287. *Hypochlorites and Chlorites:* (g) Meunier, B.; Guilmet, E.; De Carvalho, M.-E.; Poilblanc, R. *J. Am. Chem. Soc.* **1984**, *106*, 6668–6676. (h) Collman, J. P.; Brauman, J. I.; Meunier, B.; Hayashi, T.; Kodadek, T.; Raybuck, S. A. *Ibid.* **1985**, *107*, 2000–2005. (i) Collman, J. P.; Tanaka, H.; Hembre, R. T.; Brauman, J. I. *Ibid.* **1990**, *112*, 3689–3690. *tert-Amine N-oxides:* (j) Ostovic, D.; Knobler, C. B.; Bruice, T. C. *Ibid.* **1987**, *109*, 3444–3451. (k) Bruice, T. C. *Aldrichimica Acta* **1988**, *21*, 87–94. *Molecular oxygen:* (l) Groves, J. T.; Quinn, R. *J. Am. Chem. Soc.* **1985**, *107*, 5790–5792. (m) Karasevich, E. I.; Khenkin, A. M.; Shilov, A. E. *J. Chem. Soc., Chem. Commun.* **1987**, 731–732. (n) Battioni, P.; Bartoli, J. F.; Leduc, P.; Fontecave, M.; Mansuy, D. *Ibid.* **1987**, 791–792.
4. Murahashi, S.-I.; Naota, T.; Yonemura, K. *J. Am. Chem. Soc.* **1988**, *110*, 8256–8258.
5. Murahashi, S.-I.; Naota, T.; Kuwabara, T.; Saito, T.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1990**, *112*, 7820–7822.
6. Presented at 56th Annual Meetings of Chemical Society of Japan (Tokyo), 1988, Abstr. 2XII A19.
7. A trace amount of the corresponding *t*-butyldioxygenated adamantane was detected by GC-MS analysis of the reaction mixture.
8. (a) Marmion, M. E.; Takeuchi, K. J. *J. Am. Chem. Soc.* **1988**, *110*, 1472–1480. (b) Roecker, L.; Meyer, T. J. *Ibid.* **1987**, *109*, 746–754.
9. The relative reactivity of the oxidation of tertiary and secondary hydrogens in adamantane is 8.9, which is different from the value (ca. 20) obtained for the reaction with alkoxy radical.[10] Neither formation of dialkyls derived from dimerization of alkyl radicals nor retardation with radical scavengers such as 2,6-di-*t*-butyl-4-methylphenol was observed, indicating that radical chain reaction is not involved.
10. (a) Fossey, J.; Lefort, D.; Massoudi, M.; Nedelec, J.-Y.; Sorba, J. *Can. J. Chem.* **1985**, *63*, 678–680. (b) Lau, T.-C.; Che, C.-M.; Lee, W.-O.; Poon, C.-K. *J. Chem. Soc., Chem. Commun.* **1988**, 1406–1407.
11. Blake, R. C., II; Coon, M. J. *J. Biol. Chem.* **1981**, *256*, 12127–12133.
12. Hjelmeland, L. M.; Aronow, L.; Trudell, J. R. *Biochem. Biophys. Res. Commun.* **1977**, *76*, 541–549.
13. Cyclooctanol was oxidized to give cyclooctanone (78%) under the same reaction conditions. *t*-Butyldioxycyclohexane prepared independently could not be converted into cyclohexanone under the same reaction conditions, indicating that the possibility of ketone formation via cleavage of *t*-butyldioxyalkanes is ruled out in the present reaction.

(Received in Japan 12 November 1992)