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# Ruthenium(II)-Catalyzed Reaction of 1,4-Epiperoxides

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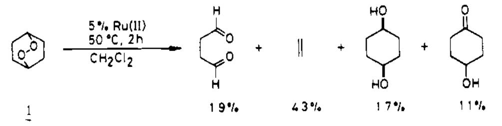
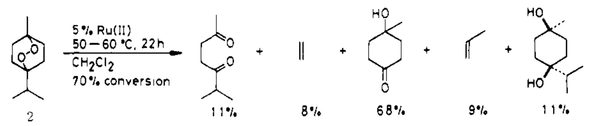
1,4-Epiperoxides (endoperoxides) have become increasingly significant as synthetic[1] and biosynthetic intermediates.[2] Since the Fe(II)-induced decomposition provides a chemical model for prostaglandin (PG) biosynthesis, extensive studies have been done on the behavior of various epiperoxides in the presence of Fe(II) salts.[3-5] We have been intrigued by the catalytic reaction with Ru(II)-tertiary phosphine complexes. The central metal is a member of the iron triad,[6] and the phosphine complexes are characterized by their capability of inducing the reaction to occur via a one-electron redox mechanism[6,7] and, unlike ordinary Fe(II) salts, possess high solubility in aprotic organic solvents. We describe here the homogeneous catalysis of bicyclic 1,4-epiperoxides by $RuCl_2(PPh_3)_3$.

First, when 1,4-epiperoxycyclohexane (**1**) was exposed to 5 mol % of $RuCl_2(PPh_3)_3$ in dichloromethane at 50 °C for 2 h, the O–O linkage was cleaved and a mixture of products arising from fragmentation, reduction, and disproportionation was obtained (eq 1).[8] The catalyzed reaction of dihydroascaridole (**2**) proceeded slowly under the comparable conditions. The result is illustrated in eq 2. Thus the presence of alkyl groups at the bridgehead positions appeared to affect the reaction rate and the product distribution. 1,3-Epiperoxycyclopentane (**3**), which has been frequently employed as a PG endoperoxide model, was readily decomposed in the presence of the Ru(II) catalyst, and a complicated mixture was obtained (eq 3).[8]

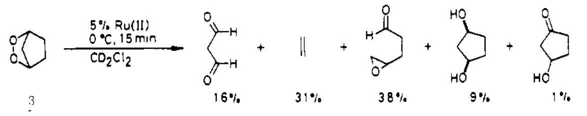
The reaction of $PGH_2$ methyl ester (**4**) was remarkably clean (eq 4). Thus when this real PG endoperoxide was treated in dichloromethane with 3 mol % of $RuCl_2(PPh_3)_3$ at 19 °C, a smooth fragmentation took place and methyl (5*Z*,8*E*,10*E*,12*S*)-12-hydroxy-5,8,10-heptadecatrienoate (**5**, HHT methyl ester) was obtained as the sole isolable product.[5,11,12] The reaction is stereospecific in nature. No positional or geometrical isomerization of the carbon–carbon double bond was observed under the present reaction conditions. Production of malonaldehyde was confirmed by the thiobarbituric acid test.[10] No methyl esters of primary PGs such as $PGE_2$, $PGD_2$, or $PGF_{2\alpha}$ were detected in the reaction mixture.[13]



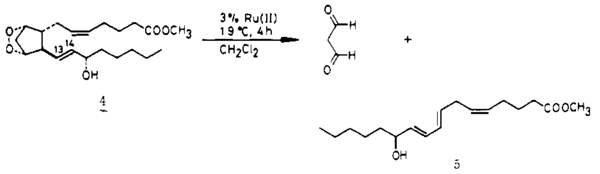
(1)



(2)



(3)



(4)

Obviously such reactions proceed via radical pathways, and all of the major products in eq 1–4 are reasonably understood in terms of the mechanism outlined in Scheme I. The inner-sphere radical,[7] depicted as **7**, resulting from the atom-transfer reaction between Ru(II) species and epiperoxide **6** serves as the key intermediate. Depending on the substitution pattern, **7** undergoes various radical transformations. The radical **7** collapses into the corresponding dialdehyde or ketone and an olefinic residue. The ease with which this fragmentation takes place is highly dependent on the nature of $R^2$ and $R^3$, and, with the PG endoperoxide **4**, the presence of the two side chains, particularly the $\omega$ chain which contains C(13)–C(14) double bond (PG numbering), facilitates greatly the oxy-radical-induced fragmentation to form the triene **5** and malonaldehyde.[14] Thus one should be careful in taking simple saturated epiperoxides such as **1** or **3** as PGH or PGG model compounds. In addition, the radical **7** can abstract hydrogen atoms from the donors present in the reaction system to afford the 1,4-diol product.[4e,15] Here secondary alcohols serve as a good hydrogen donor; the Ru(II)-catalyzed reaction of **1** with added 2-propanol

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(1) Denny, R. W.; Nickon, A. *Org. React.* (N.Y.) **1973**, *20*, 133. Nakanishi, K. In "Natural Products Chemistry"; Nakanishi, K., Goto, T., Itô, S., Natori, S., Nozoe, S., Eds.; Academic Press: New York, 1975; Vol. 2, Chapter 12. Wasserman, H. H.; Murray, R. W. "Singlet Oxygen"; Academic Press: New York, 1979. Balci, M. *Chem. Rev.* **1981**, *81*, 91. Wasserman, H. H.; Ives, J. L. *Tetrahedron* **1981**, *37*, 1825.

(2) Van Dorp, D. A. In "Chemistry, Biochemistry and Pharmacological Activity of Prostanoids"; Roberts, S. M., Scheinmann, F., Eds.; Pergamon Press: Oxford, England, 1979; pp 233–242.

(3) (a) Brown, D.; Davis, B. T.; Halsall, T. G.; Hands, A. R. *J. Chem. Soc.* **1962**, 4492. (b) Brown, D.; Davis, B. T.; Halsall, T. G. *Ibid.* **1963**, 1095. (c) Kanno, H.; Schuller, W. H.; Lawrence, R. V. *J. Org. Chem.* **1966**, *31*, 4138. (d) Herz, W.; Ligon, R. C.; Turner, J. A.; Blount, J. F. *Ibid.* **1977**, *42*, 1885. (e) Turner, J. A.; Herz, W. *Ibid.* **1977**, *42*, 1895, 1900.

(4) For the catalysis with metals other than Fe, see: (a) [Cu(I) and Cu(II)] Porter, N. A.; Nixon, J. R.; Gilmore, D. W. *ACS Symp. Ser.* **1978**, *No. 69*, 89. (b) [Ti(III)] Paget, H. *J. Chem. Soc.* **1938**, 829. See also ref 3b. (c) [V(IV)] ref 3d. (d) [Pb(IV)] Schenck, G. O. *Angew. Chem.* **1952**, *64*, 12. (e) [Co(II)] Boyd, J. D.; Foote, C. S.; Imagawa, D. K. *J. Am. Chem. Soc.* **1980**, *102*, 3641. (f) [Rh(I)] Hagenbuch, J.-P.; Vogel, P. *J. Chem. Soc., Chem. Commun.* **1980**, 1062. (g) [Pd(0)] Suzuki, M.; Noyori, R.; Hamanaka, N. *J. Am. Chem. Soc.* **1981**, *103*, 5606. Suzuki, M.; Oda, Y.; Noyori, R. *Tetrahedron Lett.* **1981**, *22*, 4413.

(5) Treatment of $PGH_2$ with $FeCl_2$ in aqueous solution was claimed to give (5*Z*,8*E*,10*E*,12*S*)-12-hydroxy-5,8,10-heptadecatrienoic acid (40–50%) without any definite stereochemical evidence: Hamberg, M.; Samuelsson, B. *Proc. Natl. Acad. Sci. U.S.A.* **1974**, *71*, 3400.

(6) Ru(II)–porphyrin complexes are known to mimic heme proteins: Farrell, N.; Dolphin, D. H.; James, B. R. *J. Am. Chem. Soc.* **1978**, *100*, 324.

(7) Ru(II)–phosphine complexes catalyze addition of organic halides to olefinic substrates via a one-electron transfer mechanism: Matsumoto, H.; Nakano, T.; Takasu, K.; Nagai, Y. *J. Org. Chem.* **1978**, *43*, 1734 and references cited therein.

(8) Ethylene and propylene were analyzed by GLC after converting them to the dibromides.[9] Other products were compared with authentic samples. Malonaldehyde was assayed by the thiobarbituric acid test.[10]

(9) Coughlin, D. J.; Salomon, R. G. *J. Am. Chem. Soc.* **1979**, *101*, 2761.

(10) Waravdekar, V. S.; Saslaw, L. D. *J. Biol. Chem.* **1959**, *234*, 1945.

(11) The reaction was monitored by a high-speed TLC scanner (Shimadzu CS-920 model). The product, **5**, was fully characterized by $^1H$ NMR analysis using a 360-MHz machine; NMR ($CDCl_3$, tetramethylsilane as internal standard) $\delta$ 0.88 (t, 3, $J$ = 7.3 Hz, C(17)$H_3$), 1.23–1.35 (m, 8, C(13–16)$H_2$), 1.42 (br, 1, OH), 1.70 (tt, 2, $J$ = 7.3, 7.3 Hz, C(3)$H_2$), 2.08 (dt, 2, $J$ = 5.5, 7.4 Hz, C(4)$H_2$), 2.32 (t, 2, $J$ = 7.3 Hz, C(2)$H_2$), 2.82 (t, 2, $J$ = 6.3 Hz, C(7)$H_2$), 3.68 (s, 3, $COOCH_3$), 4.10 (br, 1, C(12)H), 5.43 (t, 2, $J$ = 5.5 Hz, =C(5,6)H), 5.59 (dd, 1, $J$ = 14.7, 7.4 Hz, =C(11)H), 5.66 (dt, 1, $J$ = 14.7, 6.6 Hz, =C(8)H), 6.04 (dd, 1, $J$ = 14.7, 11 Hz =C(9 or 10)H), 6.17 (dd, 1, $J$ = 14.7, 11 Hz, =C(10 or 9)H). IR (neat) 3400, 1740, 1650 $cm^{-1}$. Mass spectrum, $m/z$ 294 ($M^+$), 276, 263, 255, 223, 180, 99.

(12) For biosynthetic production of HHT from $PGG_2$ or $PGH_2$, see: Nugteren, D. H.; Christ-Hazelhof, E. In "Advances in Prostaglandin and Thromboxane Research"; Samuelsson, B.; Ramwell, P. W.; Paoletti, R.; Eds.; Raven Press: New York, 1980; pp 129–137.

(13) Reaction of **4** catalyzed by $Pd(PPh_3)_4$ gives a mixture of methyl esters of $PGD_2$ (17%), $PGE_2$ (11%), $PGF_{2\alpha}$ (41%), and HHT (4%).[4g]

(14) The C(5)–C(6) double bond could also stabilize the transition state via homoallylic conjugation; see: Ingold, K. U. *ACS Symp. Ser.* **1978**, *No. 69*, 187.

(15) Similar phenomena were observed in the Fe(II)-induced reaction of 1,4-epiperoxides.[3d]

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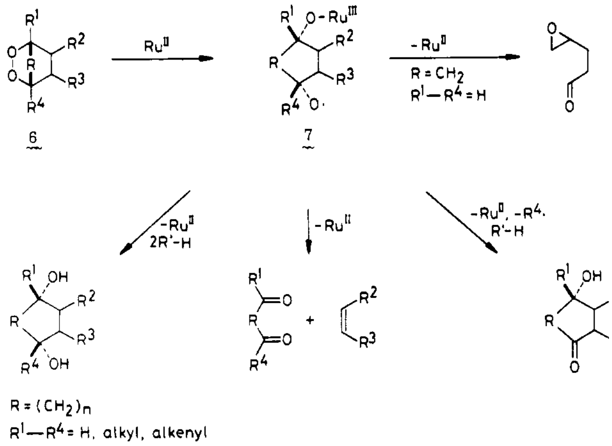
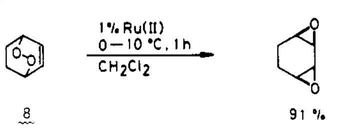
Scheme I

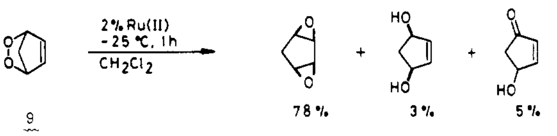


(10 equiv) produced acetone in 39% yield.[16] Therefore the 4-hydroxy ketone products may be formed from the initially produced 1,4-diols.[17]

The oxy radical can interact with a carbon–carbon double bond present in the substrate. As illustrated in eq 5 and 6, $RuCl_2(PPh_3)_3$



(5)



(6)

catalyzes smoothly the isomerization of 2,3-unsaturated 1,4-epiperoxides to the 1,2,3,4-diepoxides, which provides a useful synthetic tool.[18]

Thus the Ru(II)-catalyzed reactions involve radical intermediates, but they behave differently from free diradicals formed by photolysis or thermolysis of the epiperoxides.[19] The Ru atom affects profoundly the stability and reactivity of the radicals through interaction with the oxygen atom, allowing selective transformations under mild conditions. The selectivity profile is different from the related Fe(II)-promoted reaction, which proceeds via free-radical intermediates generated by an outer-sphere electron-transfer process.[20]

**Acknowledgment.** We thank Drs. Y. Naya and H. Naoki of Suntory Institute for Bioorganic Research for the 360-MHz NMR measurement. We are also indebted to Professor S. Suzuki of our Department for the suggestion for the malonaldehyde assay.

**Registry No. 1**, 280-53-5; **2**, 5718-73-0; **3**, 279-35-6; **4**, 63942-75-6; **5**, 79171-56-5; $RuCl_2(PPh_3)_3$, 15529-49-4; butanedial, 638-37-9; ethene, 74-85-1; *cis*-1,4-cyclohexanediol, 731-71-5; 4-hydroxycyclohexanone, 13482-22-9; 6-methyl-2,5-heptanedione, 13901-85-4; 4-hydroxy-4-methylcyclohexanone, 17429-02-6; *cis*-4-isopropyl-1-methyl-1,4-cyclohexanediol, 17948-61-7; propanedial, 542-78-9; 3-oxiranepropanal, 65842-25-3; *cis*-1,3-cyclopentanediol, 16326-97-9.

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[16] In the absence of epiperoxides, secondary alcohols are inert to the Ru(II) complex under the present reaction conditions. Treatment of 2-propanol with 5 mol % of $RuCl_2(PPh_3)_3$ ($CH_2Cl_2$, 25 °C/16 h and then 50 °C/2.5 h) did not produce acetone; addition of 2-cyclohexenone to this system did not afford cyclohexanone either.

[17] $RuCl_2(PPh_3)_3$ liberates triphenylphosphine ligands in solution: Pri-Bar, I.; Buchman, O.; Schumann, H.; Kroth, H. J.; Blum, J. *J. Org. Chem.* **1980**, *45*, 4418 and references cited therein. The phosphine does react with cyclic peroxides; reaction with saturated epiperoxides produces the diols, whereas reaction with 2,3-unsaturated 1,4-epiperoxides affords 1,3-diene 1,2-epoxides. However, under the present catalytic conditions, it does not participate in the product formation to any great extent.

[18] For the Co(II)-*meso*-tetraphenylporphine-catalyzed reaction see ref 4e.

[19] For instance, thermolysis of **3** in $CD_2ClCD_2Cl$ at 73 °C gives a mixture of 4,5-epoxypentanal (54%), levulinaldehyde (42%), and 2,3-dioxabicyclo[2.2.1]heptane (4%): Salomon, R. G.; Salomon, M. F.; Coughlin, D. J. *J. Am. Chem. Soc.* **1978**, *100*, 660. For the thermolysis of **1**, see ref 8 and Bloodworth (Bloodworth, A. J.; Baker, D. S. *J. Chem. Soc., Chem. Commun.* **1981**, 547). For the thermolysis of **2**, see: Moore, C. G. *J. Chem. Soc.* **1951**, 234. Thermolysis of **9** produces (*Z*)-4,5-epoxy-2-pentenal (58%) and the *syn*-diepoxide (7%): Schülte-Elte, K. H.; Willhalm, B.; Ohloff, G. *Angew. Chem.* **1969**, *81*, 1045. Photolysis of **8** gives the *syn*-diepoxide (27%) and 3,4-epoxycyclohexanone (22%): Maheshwari, K. K.; de Mayo, P.; Wiegand, D. *Can. J. Chem.* **1970**, *48*, 3266.

[20] Reaction of **2** and $FeSO_4$ gives 4-hydroxy-4-methylcyclohexanone (93%) and propane (99%).[3b]

## Square and Butterfly, 12-Electron $Mo_4$ Clusters Formed by Coupling Mo$\equiv$Mo Bonds

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One of the several reaction pathways potentially available to compounds with metal-to-metal multiple bonds is condensation or oligomerization to give cluster compounds with delocalized metal-to-metal bonding. McCarley and co-workers reported[1] the dimerization of two $(\mathrm{Mo}\overset{4}{-}\mathrm{Mo})^{4+}$ units to give a rectangular $Mo_4$ cluster with alternating Mo–Mo triple and single bonds. We wish now to report reactions in which square and butterfly 12-electron $Mo_4$ clusters are formed from the coupling of Mo$\equiv$Mo bonds.

Hydrocarbon solutions of $Mo_2(O\text{-}i\text{-}Pr)_6$ (M$\equiv$M)[2] react with $CH_3COX$ (X = Cl and Br) to give isopropylacetate and haloalkoxy molybdenum compounds.[3] When the reactions are carried out in hexane, black crystalline compounds of formula $Mo_4X_3(O\text{-}i\text{-}Pr)_9$[4] crystallize from a cooled solution (ca. −5 °C) and have been obtained in 70% yield according to eq 1.

$$2Mo_2(O\text{-}i\text{-}Pr)_6 + 3MeCOX \rightarrow Mo_4X_3(O\text{-}i\text{-}Pr)_9 + 3MeCOO\text{-}i\text{-}Pr \quad (1)$$

The $^1H$ NMR spectra of $Mo_4X_3(O\text{-}i\text{-}Pr)_9$ compounds are quite remarkable: there are five methyne septets in the ratio 2:2:2:2:1 and nine partially overlapping doublets for the methyl resonances. This can be explained as follows. Halo-for-alkoxy group exchange increases the Lewis acidity of the metal atoms, and the compounds "$Mo_2X_2(O\text{-}i\text{-}Pr)_4$" once formed associate with their precursors $Mo_2X(O\text{-}i\text{-}Pr)_5$. Association by the formation of one alkoxy and three halide bridges to give I has a precedent in the structures of $Mo_4(\mu\text{-}F)_4(O\text{-}i\text{-}Bu)_8$ and $Mo_4(\mu\text{-}F)_3(\mu\text{-}NMe_2)(O\text{-}t\text{-}Bu)_8$.[5] It is not necessary to invoke delocalized metal–metal bonds: there are merely two isolated Mo$\equiv$Mo bonds brought into close proximity by the bridging ligands. Note that I has $C_2$ symmetry, which accounts for the presence of five types of isopropyl groups and the appearance of nine isopropyl methyl groups, since the four different pairs of OR ligands each have diastereotopic methyl groups.

$Mo_4X_3(O\text{-}i\text{-}Pr)_9$ compounds react further with $CH_3COX$ to give $Mo_4X_4(O\text{-}i\text{-}Pr)_8$ compounds (X = Cl or Br), which are es-

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[1] (a) McGinnis, R. N.; Ryan, T. R.; McCarley, R. E. *J. Am. Chem. Soc.* **1978**, *100*, 7900. (b) McCarley, R. E.; Ryan, T. R.; Torardi, C. C. *ACS Symp. Ser.* **1981**, *155*, 41.

[2] Chisholm, M. H.; Cotton, F. A.; Extine, M. W. Reichert, W. W. *Inorg. Chem.* **1977**, *16*, 1801.

[3] All reactions were carried out by using dry and oxygen-free solvents and atomospheres ($N_2$). Additions of acetyl chloride were made by use of a calibrated vacuum manifold.

[4] Satisfactory elemental analytical data have been obtained.

[5] Chisholm, M. H.; Huffman, J. C.; Kelly, R. L. *J. Am. Chem. Soc.* **1979**, *101*, 7100.