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Ruthenium-Catalyzed Oxidation of Alkanes with Peracids

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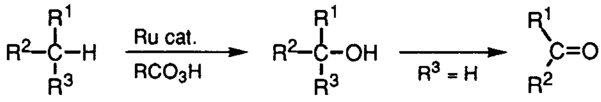
Abstract: The ruthenium-catalyzed oxidation of alkanes with peracids under mild conditions gives the corresponding ketones and alcohols highly efficiently. Similar treatment of alkanes in trifluoroacetic acid gives alkyl trifluoroacetates.

The oxygenation of alkanes is of importance from enzymatic[1] and synthetic[2] points of view. Cytochrome P-450 enzymes catalyze specific oxygenation of various organic substrates,[2] and their model reactions using synthetic metalloporphyrins have been studied extensively.[3] Simulation of the functions of cytochrome P-450 with transition metal complex catalysts leads to find the method for oxidation of various substrates in the presence of non-porphyrin ruthenium complex catalysts.[4] These reactions seem to involve oxoruthenium species. In order to clarify the reactivity of the oxoruthenium species towards the oxidation of non-activated hydrocarbons and to generate highly reactive oxoruthenium species, we examined various oxidants. As a consequence of this study we found that the oxidation of alkanes with peracids in the presence of a low valent ruthenium catalyst proceeds highly efficiently to give the corresponding ketones along with alcohols (eq 1).[5,6]



$$R^2{-}\overset{R^1}{\underset{R^3}{C}}{-}H \xrightarrow[RCO_3H]{\text{Ru cat.}} R^2{-}\overset{R^1}{\underset{R^3}{C}}{-}OH \xrightarrow[R^3 = H]{} \overset{R^1}{\underset{R^2}{>}}C{=}O \qquad (1)$$

The catalytic activity of various metal complexes has been examined for the oxidation of n-decane with peracetic acid (0.5 equiv.) in ethyl acetate at room temperature (1 h). Ruthenium on charcoal (5%) was the most effective catalyst (conversion 10%, yield of decanones 97%). $RuCl_3 \cdot nH_2O$ also shows high catalytic activity (10%, 92%); however, ruthenium complexes such as $RuCl_2(PPh_3)_3$, $RuCl_2(bpy)_2$, RuO_2, and $Ru_3(CO)_{12}$ and other transition metal complexes such as $RhCl_3 \cdot nH_2O$, rhodium on charcoal, and palladium on charcoal gave unsatisfactory results. Peracetic acid has proven to be a good oxidant, while other peracids such as m-chloroperbenzoic acid (mCPBA) gave satisfactory results.

The present catalytic oxidation can be applied to a variety of alkanes. The representative results of the ruthenium-catalyzed oxidation of alkanes with peracetic acid are shown in Table 1. Both linear and cyclic alkanes can be converted into the corresponding ketones along with a small amount of alcohols. It is noteworthy that the conversions and the yields are higher than those obtained for the ruthenium-catalyzed oxidation with t-BuOOH.[4e] The distribution of the oxygenated products from methylcyclohexane indicates that the relative reactivity of the present oxidation is in the order tertiary > secondary >> primary. The tertiary / secondary C-H bond selectivity on a per bond basis is 7.5, which is larger than that obtained from the oxidation with t-BuOOH (4.5).[4e]

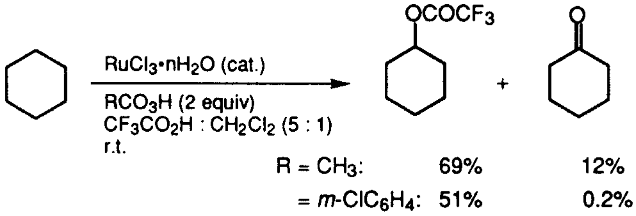
Table 1. Ruthenium-Catalyzed Oxidation of Alkanes with Peracetic Acid[a]

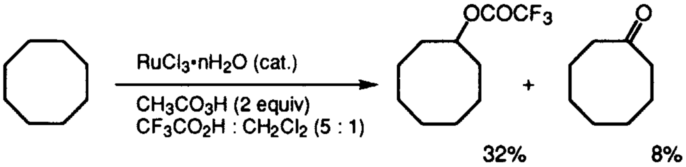
entry	substrate	conv.,[b] %	product	yield,[c] %
1	cyclohexane (**1**)	62	cyclohexanone	67
			cyclohexanol	1
2	cyclooctane	69	cyclooctanone	74
			cyclooctanol	1
3	methylcyclohexane	52	methylcyclohexanols[d]	27
			methylcyclohexanones[e]	32
4	adamantane	67	adamantanols[f]	49
			2-adamantanone	9
5	n-heptane	49	heptanones[g]	71
			heptanols[h]	4
6	n-decane	49	decanones[i]	62
			decanols[j]	1
7	ethylbenzene	23	acetophenone	13
			1-phenylethanol	<1
8	indan	35	1-indanone	36
			1-indanol	<1

[a] All reactions were carried out according to the standard procedure described in the text. [b] Determined by GLC analysis based on the starting substrate using appropriate internal standard. [c] Determined by GLC analysis based on the converted substrate using appropriate internal standard. [d] 1-ol : 2-ol : 3-ol : 4-ol = 94 : 2 : 3 : 1. [e] 2-one : 3-one : 4-one = 36 : 46 : 18. [f] 1-ol : 2-ol = 99 : 1. [g] 2-one : 3-one : 4-one = 36 : 42 : 22. [h] 2-ol : 3-ol : 4-ol = 40 : 40 : 20. [i] 2-one : 3-one : (4+5)-one = 18 : 24 : 58. [j] 2-ol : 3-ol : (4+5)-ols = 25 : 25 : 50.

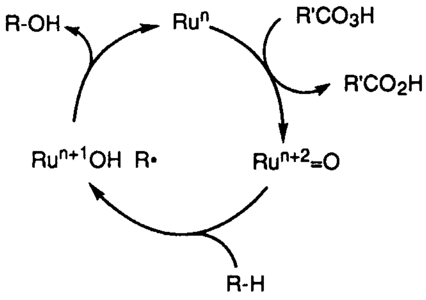
Typically, the oxidation of cyclohexane (**1**) was carried out as follows. To a stirred mixture of **1** (2.00 mmol) and 5% ruthenium on charcoal (0.040 g, 0.02 mmol) in dry ethyl acetate (2.0 mmol) was added a 30% solution of peracetic acid in ethyl acetate (6.00 mmol) dropwise at room temperature over a period of 2 h. 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 that the conversion of **1** was 62%, and the yields of cyclohexanone and cyclohexanol were 67% and 1%, respectively.

Recently we found that the ruthenium-catalyzed oxidation of β-lactams with either peracetic acid[4d] or RCHO-O_2[7] in the presence of carboxylic acids affords 4-acyloxy-β-lactams highly efficiently. With the oxidations we succeeded in acyloxylation of β-lactams with various carboxylic acids. The reaction of oxoruthenium species with β-lactams gives highly reactive four membered acyliminium ion intermediates which are trapped with external nucleophiles of carboxylic acids. On the line of this study we examined the trapping of the intermediate with a carboxylic acid. We found that the $RuCl_3$-catalyzed oxidation of cyclohexane (**1**) with 30% peracetic acid (2 equiv.) in ethyl acetate in a mixture of trifluoroacetic acid and CH_2Cl_2 (5 : 1) at room temperature gave cyclohexyl trifluoroacetate (**2**, 69% based on **1**) along with cyclohexanone (**3**, 12%) (conv. of **1**, 90%). Similar treatment of cyclooctane afforded a mixture of cyclooctyl trifluoroacetate (32% based on cyclooctane) and cyclooctanone (8%) (conv., 81%). The trifluoroacetoxylation of alkanes can be also performed efficiently by using other peracids. For example, the $RuCl_3$-catalyzed oxidation of **1** with mCPBA (2 equiv.) under similar reaction conditions gave **2** and **3** in 51% and 0.2% yields, respectively (conv., 67%). We examined similar trifluoroacetoxylations of alkylated arenes; however the trials resulted in recovery of the starting alkanes. This is probably due to the formation of catalytically inactive arene ruthenium complexes by the reaction of $RuCl_3 \cdot nH_2O$ with alkylated arenes in the presence of trifluoroacetic acid.





Although it is premature to discuss the precise mechanism at the present stage, the oxidation can be rationalized by assuming cytochrome P-450 type mechanism as shown in Scheme 1. Thus, the reaction of low valent ruthenium complex Ru^n with peracid gives acylperoxyruthenium complex, which undergoes heterolytic cleavage of the O-O bond to give oxoruthenium species $Ru^{n+2}{=}O$ and carboxylic acid. Abstraction of hydrogen atom gives radical pair $Ru^{n+1}OH$ R•. The intramolecular deuterium isotope effect of the Ru/C-catalyzed oxidation of 1,1-dideuterio-1,3-diphenylpropane (k_H / k_D) with peracetic acid was determined to be 2.0 by GC-MS analysis of a mixture of the product ketones. The intermolecular isotope effect was determined to be 4.8 by GLC analysis of the oxygenated products obtained from the competitive reaction of cyclohexane and cyclohexane-d_{12}. The observed intra- and intermolecular isotope effects are smaller than those obtained for the $RuCl_2(PPh_3)_3$-catalyzed oxidation with t-BuOOH (9.0 and 8.4, respectively),[4e] and cytochrome P-450 (intramolecular effect, 11)[8] indicating that the oxoruthenium species obtained in the present reaction is more reactive in comparison with those obtained from t-BuOOH and



Scheme 1

cytochrome P-450. Transfer of the hydroxy ligand of the caged alkyl radical would afford an alcohol and ruthenium species Ru^n to complete the catalytic cycle. Secondary alcohols can be converted into the corresponding ketones under the reaction conditions. Under the present conditions, secondary alcohols obtained seem to be trapped by esterification with trifluoroacetic acid faster than sequential oxidation to ketones. An alternative mechanism which involves direct trifluoroacetoxylation by the attack of trifluoroacetic acid to the cationic intermediate Ru^{n}OH R$^+$, which would be formed by further electron transfer to Ru^{n+1}OH R•, can be also considered. The higher conversions of alkanes observed in the presence of trifluoroacetic acid are due to the formation of more reactive oxoruthenium species which is bearing trifluoroacetate ligand.

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

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