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Ruthenium-catalyzed Reduction of Carbonyl Compounds Using Formic Acid

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Carbonyl compounds were hydrogenated to the corresponding alcohols in excellent yields using formic acid with a ruthenium complex at 125 °C for 3 h. 2-Propanone was reduced to 2-propanol by $RuCl_2(PPh_3)_3$–HCOOH system in 94% yield with 98% selectivity. 3-Pentanone, cyclohexanone, acetophenone, and propiophenone were hydrogenated to the corresponding alcohols in 86, 78, 84, and 86% yields respectively. The ketone having the bulkier alkyl groups showed lower reactivity. The catalytic activity was found to decrease in the order $RuCl_2(PPh_3)_3$, $RuHCl(PPh_3)_3$, $RuHCl(CO)(PPh_3)_3$, and $RuH_2(PPh_3)_4$.

Catalytic transformation of carbonyl compounds to alcohols is an important unit processes in organic synthesis. Since the first report of Schrock and Osborn using a cationic rhodium complex as a catalyst, several methods have been reported for the homogeneous catalytic hydrogenation of carbonyl compounds.[1] On the other hand, catalytic transfer hydrogenation using organic compounds as hydrogen sources is of current interest and there have been several reports using iridium,[2] cobalt,[3] iron,[4] rhodium,[5] and ruthenium[6] complexes. In these reactions alcohols have most often been used as hydrogen sources.

Formic acid is easily derived from synthesis gas and its application to organic synthesis is worth pursuing; we found that the $RuCl_2(PPh_3)_3$–HCOOH system is effective for the homogeneous hydrogenation of carbonyl compounds to alcohols without solvent. The preliminary results have been reported[7] briefly. In this paper we will describe the detailed investigation of the optimum conditions and the scope of this catalyst system.

Results and Discussion

Ketones and aldehydes were reduced to the corresponding alcohols in excellent yields by formic acid with a ruthenium catalyst such as $RuCl_2(PPh_3)_3$ without solvent. In a representative example, an equimolar mixture of acetophenone (80 mmol) and formic acid was heated without solvent at 125 °C for 3 h in an autoclave in the presence of a catalytic amount of $RuCl_2(PPh_3)_3$ (0.10 mmol). As a reaction product, 1-phenylethanol was formed in 84% yield with 98% selectivity.

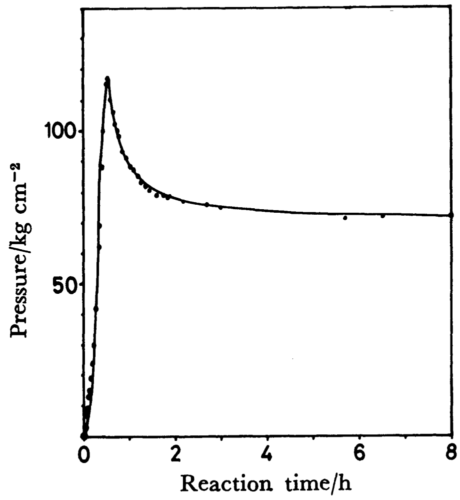
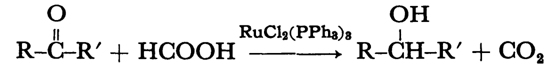


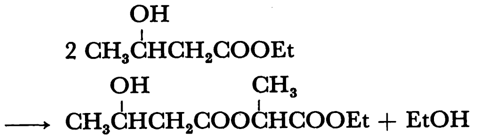
Fig. 1. Time dependence of the pressure in the hydrogenation of acetophenone by $RuCl_2(PPh_3)_3$–HCOOH.
The mixture of acetophenone (80 mmol), formic acid (97 mmol), and $RuCl_2(PPh_3)_3$ (0.10 mmol) was stirred at 125 °C for 3 h in 50 ml stainless steel autoclave.



$$R-\overset{O}{\overset{\|}{C}}-R' + HCOOH \xrightarrow{RuCl_2(PPh_3)_3} R-\overset{OH}{\overset{|}{C}}H-R' + CO_2 \qquad (1)$$

Results of the hydrogenation of various ketones are listed in Table 1. Methyl alkyl ketones and methyl aryl ketones such as acetone, 2-butanone, 4-methyl-2-pentanone, and acetophenone were hydrogenated to the corresponding alcohols in excellent yields. Similarly, 3-pentanone, cyclohexanone, and propiophenone gave the corresponding alcohols in good yields. But 3-methyl-2-butanone and 3,3-dimethyl-2-propanone showed poor reactivity and 2,4-dimethyl-3-pentanone was not reduced under the conditions used. These results show that the ketones having the bulkier alkyl groups would have the lower reactivity.

α- and *β*-Keto esters were also reduced by this method. Ethyl pyruvate was reduced in *ca.* 100% conversion to give ethyl lactate in 78% isolated yield. Ethyl acetoacetate gave the mixture of ethyl 3-hydroxybutyrate and 1-methyl-2-(ethoxycarbonyl)ethyl 3-hydroxybutyrate. The latter seems to be formed by two steps, hydrogenation of ethyl acetoacetate followed by the ester exchange reaction between two molecules of ethyl 3-hydroxybutyrate.



$$2\ CH_3\overset{OH}{\overset{|}{C}}HCH_2COOEt \longrightarrow CH_3\overset{OH}{\overset{|}{C}}HCH_2COO\overset{CH_3}{\overset{|}{C}}HCOOEt + EtOH \qquad (2)$$

2-Acetylpyridine was also reduced by this system to give 2-(1-hydroxyethyl)pyridine in 17% isolated yield, but 3-acetylpyridine was reduced very little.

When an equimolar mixture of 2,3-butanedione and formic acid was heated in the presence of $RuCl_2(PPh_3)_3$, 2-hydroxy-3-butanone and 2,3-butanediol were given in 35 and 28% yields respectively. When the ratio of formic acid/2,3-butanedione was two, 2-hydroxy-3-butanone was given in 6% yield and 2,3-butanediol was given in 54% yield. 2-Hydroxy-3-butanone was also reduced by this system to give a 57% yield of 2,3-

TABLE 1. THE HYDROGENATION OF KETONES BY $RuCl_2(PPh_3)_3$–HCOOH[a)]

Run	Ketones	Ketone recovered/%	Products	Yield/%
1	2-Propanone	4	2-Propanol	94
2	2-Butanone	10	2-Butanol	85
3	3-Pentanone	12	3-Pentanol	86
4	2-Hexanone	13	2-Hexanol	72
5	4-Methyl-2-pentanone	15	4-Methyl-2-pentanol	80
6	3-Methyl-2-butanone	43	3-Methyl-2-butanol	50
7	3,3-Dimethyl-2-propanone	69	3,3-Dimethyl-2-propanol	30
8	2,4-Dimethyl-3-pentanone	100	2,4-Dimethyl-3-pentanol	0
9	Cyclohexanone	22	Cyclohexanol	78
10[c)]	Cyclohexanone	23	Cyclohexanol	76
11[d)]	Cyclohexanone	43	Cyclohexanol	57
12	Acetophenone	15	1-Phenylethanol	84
13	Propiophenone	14	1-Phenyl-1-propanol	86
14	Diphenyl ketone	36	Diphenyl methanol	64
15	Ethyl pyruvate	0	Ethyl lactate	(78)
16	Ethyl acetoacetate	0	Ethyl 3-hydroxybutyrate	(39)
			1-Methyl-2-(ethoxycarbonyl)ethyl 3-hydroxybutyrate	(23)

a) The mixture of a ketone (160 mmol), formic acid (160), and $RuCl_2(PPh_3)_3$(0.20 mmol) was stirred at 125 °C for 3 h. b) Determined by GLC and based on the amount of ketone used. The figures in parentheses show isolated yields. c) $RuCl_2(PPh_3)_3$ (0.10 mmol). d) $RuCl_2(PPh_3)_3$ (0.05 mmol).

butanediol.

A few examples of the transfer hydrogenation of ketones in the presence of ruthenium complexes are known; benzyl alcohol,[6c)] 1-phenylethanol,[6b,f)] and 2-propanol[6f)] are used as hydrogen donors. These reactions, however, give products in lower yields and severer reaction conditions are required. These transfer hydrogenations of carbonyl compounds by alcohols are reversible and the maximum yield of the hydrogenated product is determined by the equilibrium unless the product is removed from the reaction mixture. Since carbon dioxide derived by the decomposition of the formic acid is not reduced to formic acid in the reverse direction in the present system, the yield of the product would be expected to be determined kinetically.

The present system, $RuCl_2(PPh_3)_3$–HCOOH, can be used for the hydrogenation of aldehydes such as benzaldehyde, 2-ethylhexanal and octanal (Table 2). The aldehydes were reduced to the corresponding alcohols in 80—63% yields accompanied by the formation of the corresponding formate in 5—20% yields.

Catalyst. Catalytic activities of several ruthenium complexes for the hydrogenation of acetophenone are shown in Table 3. Among the ruthenium complexes examined, $RuCl_2(PPh_3)_3$ exhibited the highest activity, followed by $RuHCl(PPh_3)_3$, $RuHCl(CO)(PPh_3)_3$, $RuH_2(CO)(PPh_3)_3$, $Ru(CO)_3(PPh_3)_2$, and $RuH_2(PPh_3)_4$. One cluster, $Ru_3(CO)_{12}$, showed no catalytic activity. Although $RuCl_3$ showed only low catalytic activity, an addition of PPh_3 markedly improved the activity (Fig. 2). When the ratio of $PPh_3/RuCl_3$ was 6, the reactivity was almost equal to that of $RuCl_2(PPh_3)_3$. The large excess of the PPh_3 resulted in the decrease of the yield of the alcohol. Tributylphosphine and triphenyl phosphite had much poorer effects as additives (3 mol/mol of $RuCl_3$) and gave the alcohols in 6 and 3% yields respectively.

TABLE 2. THE HYDROGENATION OF ALDEHYDES BY $RuCl_2(PPh_3)_3$–HCOOH[a)]

Run	Aldehyde	Aldehyde recovered %	Products	Yield/%[b)]
17	2-Ethylhexanal	15	2-Ethyl-1-hexanol	63
			2-Ethyl-1-hexyl formate	20
18	Octanal	3	1-Octanol	80
			1-Octyl formate	14
19	Benzaldehyde	9	Benzyl alcohol	79
			Benzyl formate	9

a) The mixture of an aldehyde (80 mmol), formic acid (80 mmol), and $RuCl_2(PPh_3)_3$ (0.10 mmol) was stirred at 125 °C for 3 h. b) Determined by GLC and based on the amount of aldehyde used.

TABLE 3. CATALYTIC ACTIVITIES OF RUTHENIUM COMPLEXES FOR THE REDUCTION OF ACETOPHENONE WITH FORMIC ACID

Run	Ru complexes	Acetophenone[b)] recovered/%	Yield/% of 1-phenylethanol[b)]
10	$RuCl_2(PPh_3)_3$	15	84
20	$RuHCl(PPh_3)_3$	39	56
21	$RuHCl(CO)(PPh_3)_3$	54	46
22	$RuH_2(PPh_3)_4$	81	17
23	$RuH_2(CO)(PPh_3)_3$	70	28
24	$Ru(CO)_3(PPh_3)_2$	80	20
25	$Ru_3(CO)_{12}$	100	0
26	$Ru_3(CO)_{12}+9PPh_3$	91	9

a) The mixture of acetophenone (160 mmol), formic acid (160 mmol), and a Ru complex (0.20 mmol) was stirred at 125 °C for 3 h. b) Determined by GLC and based on the amount of acetophenone used.

Effects of Reaction Conditions. Effects of reaction temperature, reaction time, amounts of $RuCl_2(PPh_3)_3$, and the molar ratio of substrate/formic acid were examined. The effects of reaction temperature in the hydrogenation of acetophenone by the $RuCl_2(PPh_3)_3$–

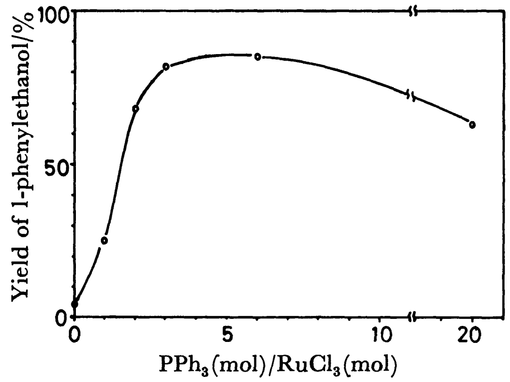


Fig. 2. Effect of the ratio of PPh$_3$/RuCl$_3$ on the hydrogenation of acetophenone with formic acid.
The mixture of acetophenone (80 mmol), formic acid 80 mmol), RuCl$_3$·nH$_2$O (0.10 mmol), and PPh$_3$ (0—2.0 mmol) was stirred at 125 °C for 3 h. Yield was determined by GLC and based on the amount of acetophenone used.

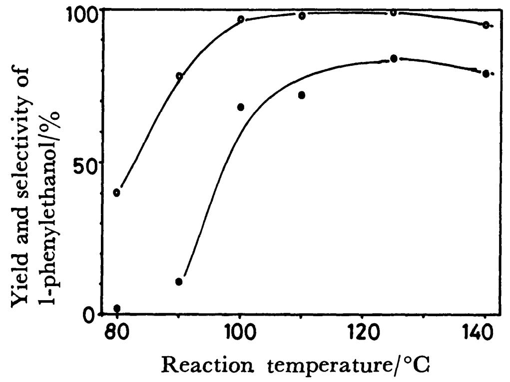


Fig. 3. The temperature dependence on the yield and selectivity of 1-phenylethanol in the hydrogenation of acetophenone by RuCl$_2$(PPh$_3$)$_3$ with formic acid.
●: Yield, ○: selectivity.
The mixture of acetophenone (80 mmol), formic acid (80 mmol), and RuCl$_2$(PPh$_3$)$_3$ (0.10 mmol) was stirred for 3 h. Yield was determined by GLC and based on the amount of acetophenone used.

HCOOH system are shown in Fig. 3. The yield of 1-phenylethanol and its selectivity had a peak at about 125 °C, because the formate and a small amount of condensation products were obtained at lower (95 and 110 °C) and higher (140 °C) temperatures respectively.

In this procedure, 0.10 mmol (0.063 mol%) of RuCl$_2$(PPh$_3$)$_3$ appears to be sufficient for the hydrogenation of cyclohexanone (Table 1: Runs 9, 10, and 11).

The effect of the amount of formic acid is shown in Table 4. Excellent yields and selectivities of the products can be achieved by using an equimolar amount of formic acid. The presence of an excess amount of the formic acid improves the yield of the alcohol but it decreases the selectivity of the alcohol by formation of the corresponding formate (See Runs 10, 28, and 29).

For the reduction of unsaturated compounds with formic acid, the Leukert-Wallach reaction is well known, but reducible substrates are limited. Formic acid is also used for conversion of benzaldehyde, acetophenone, and acetylpyridine to toluene, ethylbenzene, and ethylpyridine respectively[8)] in the presence of heterogeneous catalysts. There have been only a few reports on hydrogenation by ruthenium complexes using formic acid.[9,10)] They have been applied only for the hydrogenation of olefinic bonds.

The results obtained here clearly demonstrate that a RuCl$_2$(PPh$_3$)$_3$–HCOOH system is applicable for the transformation of carbonyl compounds to alcohols efficiently without solvent. This procedure has the following advantages. 1) As formic acid is liquid handling is easier than that of molecular hydrogen. 2) As the reaction is carried out without solvent and the formic acid used is completely decomposed through the reaction, products are easily separated. 3) The reaction proceeds with excellent yields and selectivities of the products.

The pressure *vs.* the reaction time through the reduction are shown in Fig. 1. At the maximum pressure, acetophenone was reduced to 1-phenylethanol in 39% yield and molecular hydrogen was produced in 36% yield, based on the formic acid used. It has been reported that the catalytic hydrogenation of carbonyl compounds by RuHCl(CO)(PPh$_3$)$_3$ using molecular hydrogen is accelated by the addition of water.[1a)] In the present hydrogenation using formic acid, a considerable amount of molecular hydrogen was first evolved and then it was absorbed in the cource of the reaction. In this case the formic acid used contained some water. The fact that the reaction of acetophenone with molecular hydrogen in the presence of water without formic acid gave a 65% yield of 1-phenylethanol (Run 31) also supports the mechanism described above. Thus the main part of the present reaction can be explained as follows. First, formic acid is decomposed to hydrogen gas and carbon dioxide. Then the carbonyl compounds

TABLE 4. THE HYDROGENATION OF ACETOPHENONE BY RuCl$_2$(PPh$_3$)$_3$[a)]

Run	Hydrogen source	Reaction time/h	Acetophenone recovered/%	Yield/% of 1-phenylethanol[b)]
10	HCOOH (160 mmol)	3	15	84
27	HCOOH (160 mmol)	5	8	91
28	HCOOH (200 mmol)	3	5	91 (4)
29	HCOOH (196 mmol)	8	Trace	94 (5)
30	H$_2$ (73 kg/cm^2 at 15 °C)	3	84	16
31[c)]	H$_2$ (88 kg/cm^2 at 15 °C)	3	34	65

a) The mixture of acetophenone (160 mmol), hydrogen source, and RuCl$_2$(PPh$_3$)$_3$ was heated at 125 °C.
b) Determined by GLC and based on the amount of acetophenone used. The figures in parentheses show the yields of 1-phenylethyl formate. c) Water (16 mmol) was added.

are catalytically hydrogenated in the presence of water by a ruthenium complex. However, since Sasson has reported, the transfer hydrogenation of α,β-unsaturated ketones by formic acid,[10] the transfer hydrogenation of the carbonyl compounds by formic acid may not be ruled out completely.

Experimental

GLC analysis was performed on a Shimadzu-GC 3BT. ^{1}H NMR spectra were obtained at 60MHz with a JEOL PM-60 and ^{13}C NMR spectra were obtained at 60 MHz with a JEOL PM-60 and ^{13}C NMR spectra were recorded at 25.05 MHz with a JEOL pulsed Fourier Transform spectrometer, model FX-100, using tetramethylsilane as an internal standard. IR spectra were measured on a Hitachi model 215 grating spectrophotometer.

Materials. All substrates used were commercial products. The aldehydes and ketones were distilled before use. Moist formic acid (*ca.* 90% aq solution) was used without further purification. $RuCl_3 \cdot nH_2O$, PPh_3, $P(n\text{-}Bu)_3$, $P(OPh)_3$, and $Ru_3(CO)_{12}$ were commercial products. $RuCl_2(PPh_3)_3$,[11] $RuHCl(PPh_3)_3$,[12] $RuHCl(CO)(PPh_3)_3$,[13] $RuH_2(PPh_3)_4$,[14] $RuH_2(CO)(PPh_3)_3$,[13] and $Ru(CO)_3(PPh_3)_2$[13] were prepared by published methods.

Procedures of Hydrogenation. A substrate (160 mmol), formic acid (160 mmol), and a ruthenium complex (0.20 mmol) were placed in a 100 ml stainless steel autocleave with a magnetic stirring bar. The air was replaced with argon. The autoclave was then heated at the appropriate temperature in an oil bath for 3 h. Reaction products were isolated by the usual method and identified by comparing the ^{1}H and/or ^{13}C NMR and IR spectra with those of the authentic samples. Amounts of the substrate recovered and of the products were determined by GLC (3 mm$\phi \times$3 m column packed with 10% Versamide 900 on Neopack 1A 60—80 mesh or with 20% DEGA on Uniport B 80—100 mesh) using internal standards.

In the reaction of benzophenone, amounts of benzophenone recovered and of diphenylmethanol formed were determined by ^{1}H NMR spectra.

Reduction of Acetophenone with Molecular Hydrogen. Acetophenone (160 mmol) and $RuCl_2(PPh_3)_3$ (0.20 mmol) were placed into a 100 ml stainless steel autoclave. The air was replaced with argon and then hydrogen was charged at room temperature. Then the autoclave was heated at 125 °C for 3 h.

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