Ruthenium Complex Catalyzed Intermolecular Hydroacylation and Transhydroformylation of Olefins with Aldehydes

Teruyuki Kondo, Motohiro Akazome, Yasushi Tsuji,† and Yoshihisa Watanabe*

Department of Hydrocarbon Chemistry, Faculty of Engineering, Kyoto University, Sakyo-ku, Kyoto 606, Japan

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Low-valent ruthenium complexes such as dodecacarbonyltriruthenium ($Ru_3(CO)_{12}$), (η^4-1,5-cyclooctadiene)(η^6-1,3,5-cyclooctatriene)ruthenium (Ru(COD)(COT)) and bis(η^5-cyclooctadienyl)ruthenium showed high catalytic activity for the intermolecular hydroacylation of olefins with various aromatic and heteroaromatic aldehydes at 180–200 °C for 24–48 h under an initial carbon monoxide pressure of 20 kg cm^{-2} to give unsymmetric ketones in moderate to good yields. In the reaction of 2-thiophenecarbaldehyde with cyclohexene, cyclohexyl 2-thienyl ketone was obtained in 62% yield. On the other hand, when the aliphatic aldehyde, heptanal, was treated with cyclohexene, the corresponding ketone was not obtained at all, and a transhydroformylation reaction proceeded; i.e., the formyl group of heptanal was apparently transferred to cyclohexene to give cyclohexanecarbaldehyde in 29% yield, together with their Tishchenko-type reaction products.

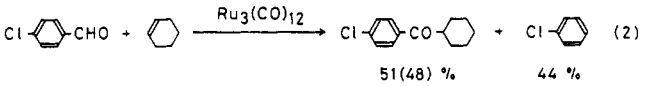
Introduction

Transition metal complex, especially rhodium(I) complex, catalyzed activation of aldehydes leading to decarbonylation has been studied extensively[1] and has provided a number of important synthetic applications,[2] including stereoselective introduction of angular methyl groups in natural product syntheses.[3] Another intriguing synthetic application is the addition of an aldehyde C–H bond across an alkene (i.e., hydroacylation reaction) as a general route to ketones.

Intermolecular hydroacylation reaction via free-radical addition of aldehydes to olefins induced by photoirradiation or radical initiators[4] has been well studied, but the efficiency is rather low. Neutral[5] and cationic[6] rhodium complex catalyzed intramolecular hydroacylation of ω-unsaturated aldehydes has also been studied in detail, although there are still only a few methods for transition metal complex catalyzed *intermolecular* hydroacylation reaction and each has severe limitations.[7] Recently, Marder et al.[8] reported a general method for intermolecular hydroacylation reaction employing a rhodium complex such as $[(\eta^5\text{-}C_9H_7)Rh(\eta^2\text{-}C_2H_4)_2]$ in the reaction. In the course of our studies on ruthenium catalysts,[9] we found that low-valent ruthenium complexes show high catalytic activity for the activation of formyl C–H bond.[10] In this paper, we describe full details of ruthenium-catalyzed intermolecular hydroacylation of olefins with aromatic[11] and heteroaromatic aldehydes and transhydroformylation of olefins with aliphatic aldehydes. On the basis of a reaction using $Ph^{13}CHO$, the mechanisms of both reactions are also proposed.

Results and Discussion

Intermolecular Hydroacylation of Olefins. Aromatic and heteroaromatic aldehydes react with both terminal and internal olefins in the presence of a catalytic amount of $Ru_3(CO)_{12}$ to give the corresponding ketones in 40–62% yield (eq 1). Results are summarized in Tables I and II. In the reaction of 4-chlorobenzaldehyde with cyclohexene, the adduct was obtained in 51% yield (run 2), together with chlorobenzene (44% yield; eq 2). This



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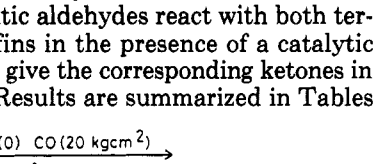

(1)

†Present address: Department of Chemistry, Faculty of Engineering, Gifu University, 1-1 Yanagido, Gifu 501-11, Japan.

(1) (a) Tsuji, J. *Organic Syntheses via Metal Carbonyls*; Wender, I., Pino, P., Eds.; A Wiley-Interscience: New York, 1977; Vol. 2, p 595. (b) Tsuji, J.; Ohno, K. *Tetrahedron Lett.* **1965**, 3969. (c) Osborn, J. A.; Jardine, F. H.; Young, J. F.; Wilkinson. *J. Chem. Soc. A* **1966**, 1711. (d) Ohno, K.; Tsuji, J. *J. Am. Chem. Soc.* **1968**, *90*, 99. (e) Baird, M. C.; Nyman, C. J.; Wilkinson, G. *J. Chem. Soc. A* **1968**, 348. (f) Walborsky, H. M.; Allen, L. E. *J. Am. Chem. Soc.* **1971**, *93*, 5465.

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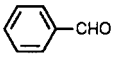
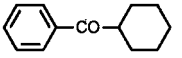
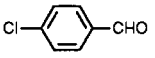
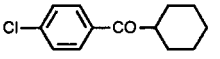
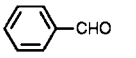
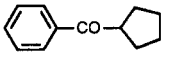
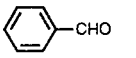
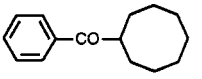
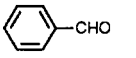
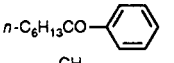
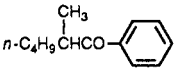
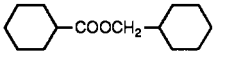
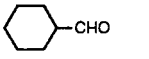
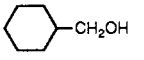
Table I. Ruthenium Complex Catalyzed Intermolecular Hydroacylation of Olefins[a]

run	aldehyde	olefin	products (%)[b]
1			 50 (44)
2			 51 (48)
3			 (47)
4			 (12)
5		n-$C_4H_9CH{=}CH_2$	 35
			 12
6	$(HCHO)_n$		 (51)
7[c]	$(HCHO)_n$		 15[d]
			 30[d]

[a] Aldehyde (5 mmol), olefin (40 mmol), $Ru_3(CO)_{12}$ (0.05 mmol) at 200 °C for 48 h under 20 kg cm^{-2} of initial carbon monoxide pressure. [b] Determined by GLC based on the amount of aldehyde charged, and figures in parentheses were isolated yields. [c] $(HCHO)_n$ (15 mmol), cyclohexene (5 mmol), $Ru_3(CO)_{12}$ (0.05 mmol), benzene (3.5 mL) at 200 °C for 24 h under 20 kg cm^{-2} of initial carbon monoxide pressure. [d] Determined by GLC based on the amount of cyclohexene charged.

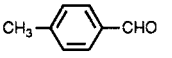
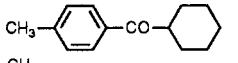
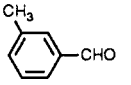
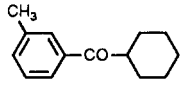
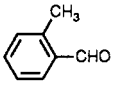
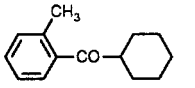
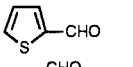
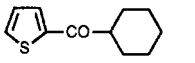
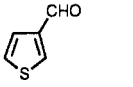
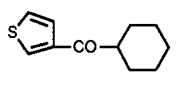
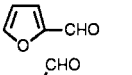
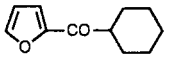
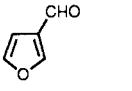
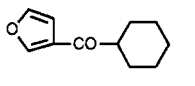
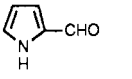
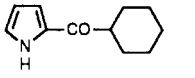
result indicates that the hydroacylation reaction competes with decarbonylation of aldehydes.[1,12] From the terminal olefin, both straight and branched chain adducts are obtained in ca. 2.9/1 ratio (run 5). When paraformaldehyde is treated with cyclohexene under the same reaction conditions as run 1, the initially generated aldehyde (i.e. cyclohexanecarbaldehyde) is converted to the corresponding ester via Tishchenko-type transformation[13] (run 6). However, reaction in benzene (under diluted condition; see footnote *c* in Table I) leads to cyclohexanecarbaldehyde and the reduced product, cyclohexylmethanol, in 15 and 30% yield, respectively (run 7).

o-, *m*-, and *p*-tolualdehyde also react with cyclohexene to give the corresponding ketones (runs 8–10 in Table II). An alternative method for the synthesis of these aromatic ketones is Friedel–Crafts acylation of toluene with acyl halides. In the acylation of toluene with acetyl chloride or benzoyl chloride in the presence of aluminum chloride, however, para-substituted ketone was obtained as the major product, and the yields of the ortho and meta isomer were quite low (ortho isomer < 10%; meta isomer < 1.5%).[14a] These results show that the present hydroacylation reaction is a very useful method for the synthesis of regioselectively substituted aromatic ketones.

Heteroaromatic aldehydes such as thiophenecarbaldehyde and furancarbaldehyde also add to olefins (runs 11–14). In the reaction of 2-thiophenecarbaldehyde with cyclohexene, the corresponding ketone is obtained in 62% yield. Since acylations of heteroaromatics such as furan and thiophene give 2-monosubstituted ketones invariably,[14b] the present reaction is also effective for the synthesis of 3-substituted heteroaromatic ketones. 2-Pyrrolecarbaldehyde also adds to cyclohexene, but the yield of corresponding ketone is only 12% (run 15). Furthermore, when 2-, 3-, and 4-pyridinecarbaldehyde are treated with cyclohexene, no adducts are obtained, and $Ru_3(CO)_{12}$ decomposes to form Ru metal after the reaction is complete.

Among the ruthenium complexes, low-valent ruthenium complexes such as $Ru_3(CO)_{12}$, Ru(COD)(COT), and Ru(cyclooctadienyl)$_2$ show good catalytic activity (runs 1, 16,

Table II. Intermolecular Hydroacylation of Cyclohexene by Aromatic and Heteroaromatic Aldehydes[a]

run	aldehyde	product (%)[b]
8		 54 (50)
9		 (40)
10		 (27)
11		 62 (41)
12		 56 (30)
13		 (25)
14		 (27)
15		 (12)

[a] Aldehyde (5 mmol), cyclohexene (40 mmol), $Ru_3(CO)_{12}$ (0.05 mmol) at 200 °C for 48 h under 20 kg cm^{-2} of initial carbon monoxide pressure. [b] Determined by GLC based on the amount of aldehyde charged, and figures in parentheses were isolated yields.

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(13) (a) Tishchenko, V. *J. Russ. Phys. Chem. Soc.* **1906**, *38*, 355, 482, 540, 549. (b) Lin, I.; Day, A. R. *J. Am. Chem. Soc.* **1952**, *74*, 5133. (c) Kasano, K.; Takahashi, T. *Yuki Gosei Kagaku Kyokai Shi* **1965**, *23*, 144. (d) Child, W. C.; Adkins, H. *J. Am. Chem. Soc.* **1923**, *45*, 3013; **1925**, *47*, 798. (e) Ogata, Y.; Kawasaki, A.; Kishi, I. *Tetrahedron* **1967**, *23*, 825. (f) Villani, F. J.; Nord, F. F. *J. Am. Chem. Soc.* **1946**, *68*, 1674; **1947**, *69*, 2605. (g) Stapp, P. R. *J. Org. Chem.* **1973**, *38*, 1433. (h) Finch, G. K. *J. Org. Chem.* **1960**, *25*, 2219. (i) Yamashita, M.; Watanabe, Y.; Mitsudo, T.; Takegami, Y. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3597.

(14) (a) Gore, P. H. *Friedel-Crafts and Related Reactions*; Olah, G. A., Ed.; Interscience Publishers: New York, 1964; Vol. III, p 36. (b) Reference 13a, pp 82 and 88.

Scheme I

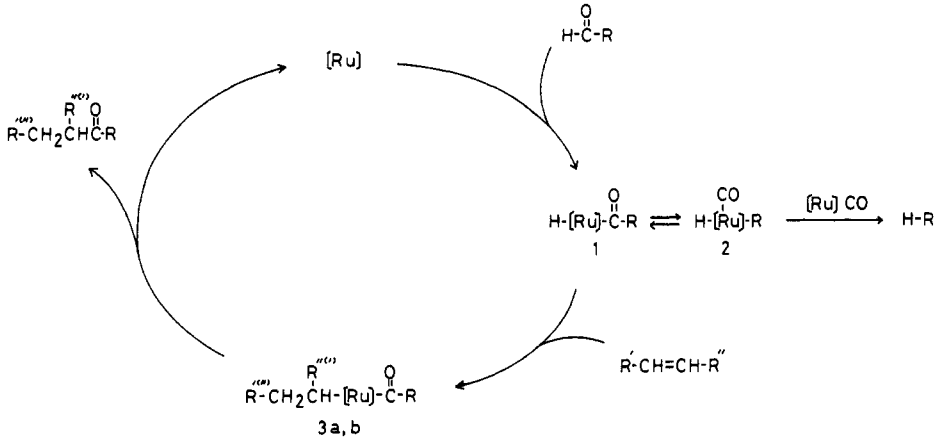


Table III. Activities of Several Ruthenium Complexes[a]

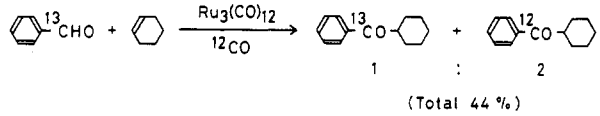
run	Ru complex	conv,[b] %	yield,[c] %
1	$Ru_3(CO)_{12}$	95	50
16	Ru(COD)(COT)	80	40
17	Ru(cyclooctadienyl)$_2$	81	42
18	$Ru(CO)_3(PPh_3)_2$	0	0
19	$RuH_2(PPh_3)_4$	9	0
20	$RuCl_2(PPh_3)_3$	9	0
21	$RuHCl(CO)(PPh_3)_3$	2	0
22	Ru(acac)$_3$	27	10

[a] Benzaldehyde (5 mmol), cyclohexene (40 mmol), Ru complex (0.15 mmol as Ru metal) at 200 °C for 24 h under 20 kg cm^{-2} of initial carbon monoxide pressure. [b] Conversion of benzaldehyde determined by GLC. [c] Yield of cyclohexyl phenyl ketone determined by GLC.

and 17 in Table III). However, both Ru(COD)(COT) and Ru(cyclooctadienyl)$_2$ are converted to $Ru_3(CO)_{12}$ during the reaction, and after the reaction, only $Ru_3(CO)_{12}$ is recovered in both cases. Among di- and trivalent ruthenium complexes, only Ru(acac)$_3$ shows some catalytic activity (run 22). It also converts to $Ru_3(CO)_{12}$. Other ruthenium complexes such as $Ru(CO)_3(PPh_3)_2$, $RuH_2(PPh_3)_4$, $RuCl_2(PPh_3)_3$,[7b] and $RuHCl(CO)(PPh_3)_3$, were totally inactive under the present hydroacylation conditions (runs 18–21). Furthermore, they are not converted to $Ru_3(CO)_{12}$ using the standard reaction conditions, and, after the reaction using them, Ru carbonyl species were not detected at all. Consequently, catalyst precursors that can be employed in the present hydroacylation reaction are those that are easily reduced and produce ruthenium carbonyl species ($Ru_3(CO)_{12}$[15]).

Both the reaction temperature and carbon monoxide pressure affect the reaction considerably. When the reaction of benzaldehyde with cyclohexene is performed at 150 °C, cyclohexyl phenyl ketone is not obtained at all. Carbon monoxide pressure is essential for the catalytic activity as observed in previous studies.[10] Under an argon atmosphere, benzaldehyde is converted to various products and the adduct is obtained in only 5%, while $Ru_3(CO)_{12}$ decomposes to Ru metal. However, when the reaction is carried out under 20 kg cm^{-2} of carbon monoxide, $Ru_3(CO)_{12}$ can be recovered in 60% yield after the reaction. These results indicate that carbon monoxide stabilizes active catalyst species such as $Ru(CO)_5$ and $Ru_3(CO)_{12}$, which were identified by FT-IR absorption,[15] and suppresses decarbonylation of aldehydes.

The reaction using ^{13}C-labeled benzaldehyde (99.6 atm % Ph^{13}CHO) with cyclohexene demonstrates that scrambling can occur, since some carbon monoxide (^{12}CO) is also incorporated in the carbonyl group of the product (eq 3).



(3)

The most plausible route to the adducts is illustrated in Scheme I. Although hydrido acyl metal species seem to be key intermediates in many reactions involving transition metal catalyzed activation of aldehydes, very few acyl hydrido complexes have been so far isolated.[16] As for the rhodium complexes, Suggs has isolated the stable hydrido acyl rhodium intermediate from the reaction of $RhCl(PPh_3)_3$ with 8-quinolinecarbaldehyde.[5e] More recently, Bianchini reported that aldehydes react with $(Ph_2PCH_2CH_2)_3NRh^+$ to give cis hydrido acyl derivatives.[17] Although hydrido acyl *ruthenium* intermediates have not yet been isolated,[18] we postulate an intermediate, **1**, generated from oxidative addition of aldehyde C–H bond to an active catalyst center based on the results shown in eqs 2 and 3. Coordination of an olefin to **1** and insertion of the olefin into a hydrido–metal bond provide isomeric alkyl acyl species (**3a,b**). Finally, the adducts are obtained via reductive elimination.[19] Since, in the present reaction,

(15) Both $Ru_3(CO)_{12}$ and $Ru(CO)_5$ were detected in the resulting reaction mixture by FT-IR absorption at 2061, 2035, 2018,[15a] and 1985 cm^{-1},[15b] respectively. However, orange crystals which could be recovered from the present reaction solution, is only $Ru_3(CO)_{12}$, since $Ru(CO)_5$ is very volatile and easily converts to $Ru_3(CO)_{12}$.[15b,c] Furthermore, it is well known that $H_4Ru_4(CO)_{12}$ is easily obtained from the reaction of H_2 and $Ru_3(CO)_{12}$,[15d-f] but in the present reaction, $H_4Ru_4(CO)_{12}$ was not detected at all. (a) Beck, W.; Lottes, K. *Chem. Ber.* **1961**, *94*, 2578. (b) Calderazzo, F.; L'Eplattenier, F. *Inorg. Chem.* **1967**, *6*, 1220. (c) Rushman, P.; Buuren, G. N.; Shirallan, M.; Pomeroy, R. K. *Organometallics* **1983**, *2*, 693. (d) Johnson, B. F. G.; Lewis, J.; Williams, I. G. *J. Chem. Soc. A* **1970**, 901. (e) Piacenti, F.; Bianchi, M.; Frediani, P.; Benedetti, E. *Inorg. Chem.* **1971**, *10*, 2759. (f) Knox, S. A. R.; Koepke, J. W.; Andrews, M. A.; Kaesz, H. D. *J. Am. Chem. Soc.* **1975**, *97*, 3942.

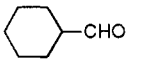
(16) (a) Milstein, D. *Acc. Chem. Res.* **1984**, *17*, 221. (b) Lilga, M. A.; Ibers, J. A. *Organometallics* **1985**, *4*, 590. (c) Thorn, D. L. *Organometallics* **1982**, *1*, 197. (d) Headford, C. E. L.; Roper, W. R. *J. Organomet. Chem.* **1980**, *198*, C7. (e) Brown, K. L.; Clark, G. R.; Headford, C. E. L.; Marsden, K.; Roper, W. R. *J. Am. Chem. Soc.* **1979**, *101*, 503. (f) Suggs, J. W. *J. Am. Chem. Soc.* **1979**, *101*, 489. (g) Rauchfuss, T. B. *J. Am. Chem. Soc.* **1979**, *101*, 1045. (h) Tolman, C. A.; Ittel, S. D.; English, A. D.; Jesson, J. P. *J. Am. Chem. Soc.* **1979**, *101*, 1742.

(17) Bianchini, C.; Meli, A.; Peruzzini, M.; Vacca, A.; Zanobini, F. *Organometallics* **1987**, *6*, 2453.

(18) When Ru(II) complexes such as $RuHCl(CO)(PPh_3)_3$ and $RuHCl(PPh_3)_3$ were treated with RCHO (R = Et, Me), an η^2-acyl complex was obtained instead of corresponding hydrido acyl ruthenium species. Hitch, R. R.; Gondai, S. K.; Sears, C. T. *J. Chem. Soc., Chem. Commun.* **1971**, 777.

(19) Suggs, J. W.; Wovkulich, M. J.; Cox, S. D. *Organometallics* **1985**, *4*, 1101.

Table IV. $Ru_3(CO)_{12}$-Catalyzed Transhydroformylation of Cyclohexene with Heptanal. Effect of Reaction Conditions[a]

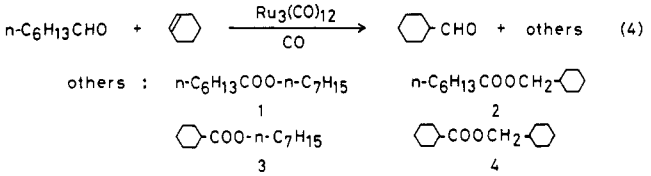
run	$Ru_3(CO)_{12}$, mmol	temp, °C	time, h	conv,[b] %	yields,[c] %		
						2 + 3[d]	4[d]	total[e]
23	0.05	180	24	35	5	2	0	7
24	0.10	180	24	32	5	1	0	6
25	0.05	200	24	62	20	2	3	25
26	0.10	200	12	63	19	2	1	22
27	0.10	200	24	93	29	3	6	38
28	0.20	200	24	100	7	4	15	26

[a] Heptanal (5 mmol), cyclohexene (40 mmol), CO (20 kg cm^{-2}). [b] Conversion of heptanal determined by GLC. [c] Determined by GLC. [d] See eq 4. [e] Yield of (cyclohexanecarbaldehyde + 2 + 3 + 4).

a ^{13}C-labeling experiment shows that the carbonyl group in the aldehyde exchanges with external carbon monoxide, equilibration of 1 and 2 should occur and in the absence of carbon monoxide pressure, equilibration should lead to decarbonylated product, which is the primary product obtained. Similar equilibration was also shown by Roper et al. with $RuRX(CO)_2(PPh_3)_2 \rightleftarrows Ru[C(O)R]X(CO)(PPh_3)_2$.[20]

Transhydroformylation of Olefins with Aliphatic Aldehydes. Although aromatic and heteroaromatic aldehydes and paraformaldehyde add smoothly to olefins in the presence of a catalytic amount of $Ru_3(CO)_{12}$ as mentioned above, aliphatic aldehydes do not add to olefin at all. In the reaction of heptanal with cyclohexene, the products are cyclohexanecarbaldehyde and four possible esters, which were generated by Tishchenko-type transformation of heptanal and/or generated cyclohexanecarbaldehyde. Cyclohexanecarbaldehyde is the hydroformylation product of cyclohexene. It likely forms by transfer of the formyl group from heptanal to cyclohexene. Therefore, we call this reaction *transhydroformylation*.

To explore this reaction, heptanal was treated with cyclohexene in the presence of a catalytic amount of $Ru_3(CO)_{12}$ under various reaction conditions (eq 4).

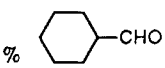


The results are summarized in Table IV. When the reaction is performed at 200 °C for 24 h under an initial carbon monoxide pressure of 20 kg cm^{-2}, the transhydroformylation product, cyclohexanecarbaldehyde, was obtained in 29% yield (total 38% yield; run 27).

Since there exists a possibility that the present transhydroformylation reaction proceeds by using aldehyde as the source of hydrogen and carbon monoxide, the reaction was performed under carbon monoxide, argon, and nitrogen pressure, respectively (Table V). Under 50 kg cm^{-2} of argon or nitrogen pressure, transhydroformylation also proceeds, but the yields of cyclohexanecarbaldehyde are quite low (runs 31–33). This result shows that the starting aldehyde is actually the source of hydrogen and carbon monoxide. However, in the absence of carbon monoxide pressure, carbon monoxide generated by decarbonylation is not effectively used for subsequent hydroformylation and the major products are decarbonylated products. Consequently, 20–50 kg cm^{-2} of carbon monoxide pressure was essential for the present reaction (runs 27, 29) but over 80 kg cm^{-2}, reaction was suppressed, considerably (run 30).

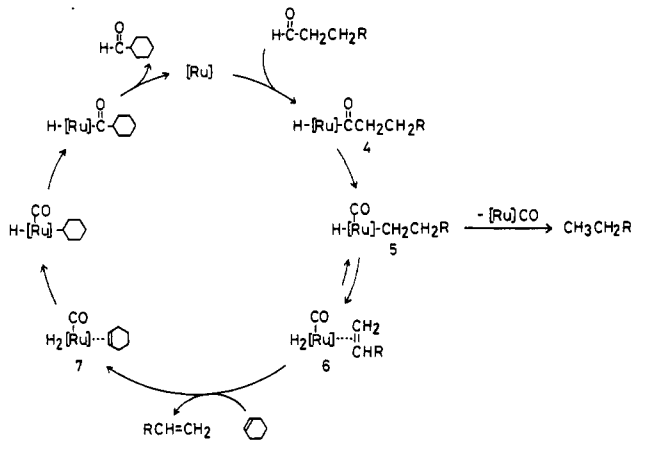
(20) Roper, W. R.; Wright, L. J. *J. Organomet. Chem.* **1977**, *142*, C1.

Table V. Effect of CO Pressure and Other Inert Gases[a]

run	gas	press., kg cm^{-2}	conv,[b] %	yields,[c] %			
					2 + 3[d]	4[d]	total
27	CO	20	93	29	3	6	38
29	CO	50	90	29	5	6	40
30	CO	80	46	8	2	1	11
31	Ar	50	100	2	4	3	9
32[e]	Ar	50	89	7	3	2	12
33	N_2	50	96	6	4	5	15

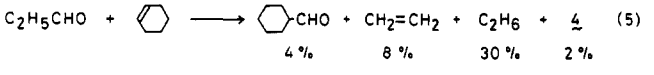
[a] Heptanal (5.0 mmol), cyclohexene (40 mmol), $Ru_3(CO)_{12}$ at 200 °C for 24 h. [b] Conversion of heptanal determined by GLC. [c] Determined by GLC. [d] See eq 4. [e] At 150 °C.

Scheme II

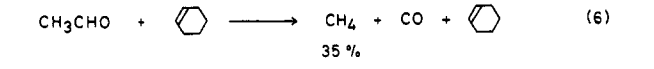


The effect of additives was examined, but phosphorus ligands such as PPh_3, $P(n\text{-}Bu)_3$, and $P(OPh)_3$ (0.5 mmol was added to the system in run 27) did not enhance the catalytic activity. Although neither tertiary amine ($(C_2H_5)_3N$) nor maleic anhydride (π-acid) was effective for the present reaction, when $(CH_3)_3NO{\cdot}2H_2O$ was added, the total yield of cyclohexanecarbaldehyde reached 43%. The similar phenomenon was observed in our previous work.[10b]

In the reaction of propanal with cyclohexene, ethylene and ethane were actually obtained together with cyclohexanecarbaldehyde (eq 5). However, when acetaldehyde



was treated with cyclohexene, transhydroformylation did not occur at all, and only methane, which was decarbonylated product of acetaldehyde, was obtained in 35% yield (eq 6).



From these results above mentioned, a possible reaction mechanism is illustrated in Scheme II. Hydrido acyl ruthenium species, **4**, would be also generated via oxidative addition of the aldehyde C–H bond to an active catalyst center. Decarbonylation of **4** and reductive elimination from generated **5** afforded alkane. Unlike aromatic and heteroaromatic aldehydes, β-hydrogens on sp^3 carbon existed in an intermediate, **5**, and β-hydride elimination would easily proceed[21] to give an olefin coordinated complex, **6**. Exchange of the coordinated olefin with solvent, cyclohexene, gave the olefin and **7**. Subsequently, **7** was hydroformylated to give cyclohexanecarbaldehyde and regenerate active ruthenium species.

Ruthenium complex catalyzed Tishchenko-type transformation of aldehydes has been previously reported by Yamamoto et al.[22] In the present reaction, similar dihydrido or hydrogen complexes would be generated in the catalytic cycle (**6**, **7** in Scheme II) and would catalyze the formation of esters from aldehydes.

Experimental Section

Materials. The reagents employed in this study were dried and purified before use by the usual procedures. Carbon monoxide (>99.9%) was used without further purification. Ru(COD)(COT),[23] Ru(cyclooctadienyl)$_2$,[24] $Ru(CO)_3(PPh_3)_2$,[25] $RuH_2(PPh_3)_4$,[26] $RuCl_2(PPh_3)_3$,[27] and $RuHCl(CO)(PPh_3)_3$[28] were prepared by the literature methods. $Ru_3(CO)_{12}$ was purchased from Strem Chemicals and Ru(acac)$_3$ was purchased from Mitsuwa Chemicals, and both were used without further purification. Ph^{13}CHO (99.6 atm % ^{13}C) was purchased from MSD Isotopes.

General Procedure. A mixture of olefin (40 mmol), aldehyde (5 mmol), and $Ru_3(CO)_{12}$ (0.05 mmol) was placed in a 50-mL stainless steel autoclave (Yuasa Giken; SUS 316) equipped with a glass liner and a magnetic stirring bar. The unit was sealed and then purged three times with 10 kg cm^{-2} pressurization–depressurization cycles of carbon monoxide. The reactor was then pressurized to 20 kg cm^{-2} with carbon monoxide (at room temperature) and heated to 200 °C within 15 min with stirring, and held at this temperature for 24–48 h. The reaction was terminated by rapid cooling, and gaseous products were discharged. The resulting orange solution was analyzed by GLC and FT-IR. The products were isolated by vacuum fractional distillation and/or medium-pressure column chromatography (absorbent, silica gel or aluminum oxide; eluent, a mixture of hexane and ethyl acetate). The identification of the products was confirmed by FT-IR, ^{1}H and ^{13}C NMR, elemental analyses, and GC–MS. The GLC analyses were carried out Shimadzu GC-4CM and GC-8A chromatographs equipped with columns (3 mm i.d. × 3 m) packed with PEG-HT (5% on Uniport HP, 60–80 mesh), Silicone OV-17 (2% on Chromosorb W(AW-DMCS), 80–100 mesh), Poly-I-110 (5% on Chromosorb W(AW-DMCS), 60–80 mesh). The IR spectra were measured on a Nicolet 5MX Fourier transform infrared spectrophotometer. The ^{1}H NMR spectra were recorded at 90 MHz with a JEOL JNM FX 90 spectrometer, and ^{13}C NMR spectra were recorded at 25.05 MHz with a JEOL JNM FX 100 spectrometer. Samples were dissolved in $CDCl_3$, and the chemical shift values were expressed relative to Me_4Si as an internal standard. Elementary analyses were performed at Microanalytical Center of Kyoto University. Mass spectra (MS) were obtained on a Shimadzu QP-1000 spectrometer. The spectral and analytical data of the representative products are shown below.

Cyclohexyl phenyl ketone: white solid; mp 56–58 °C; IR (KBr) 1669 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 1.34–1.82 (m, 10 H, CH_2), 3.25 (m, 1 H, CH), 7.40–9.99 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$) δ 25.95 (t, CH_2), 26.07 (t, CH_2), 29.47 (t, CH_2), 45.68 (d, CH), 128.22 (d, phenyl 2,6), 128.52 (d, phenyl 3,5), 132.62 (d, phenyl 4), 136.44 (s, phenyl 1), 203.54 (s, C=O). Anal. Calcd for $C_{13}H_{16}O$: C, 82.94; H, 8.57; O, 8.50. Found: C, 82.88; H, 8.60; O, 8.34.

Cyclohexyl 4-methylphenyl ketone: white solid; mp 58–60 °C; IR (KBr) 1667 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 0.99–2.03 (m, 10 H, CH_2), 2.30 (s, 3 H, CH_3), 3.14 (m, 1 H, CH), 7.03–7.86 (dd, 4 H, phenyl); ^{13}C NMR δ 21.49 (q, CH_3), 25.89 (t, CH_2), 26.07 (t, CH_2), 29.53 (t, CH_2), 45.44 (d, CH), 128.34 (d, phenyl 2,6), 129.16 (d, phenyl 3,5), 133.86 (s, phenyl 4), 143.19 (s, phenyl 1), 202.90 (s, C=O).

Heptanophenone: colorless liquid; bp 127 °C (5 mmHg); IR (neat) 1682 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3 H, CH_3), 1.35 (br, 6 H, CH_2), 1.74 (m, 2 H, CH_2), 2.95 (t, 2 H, CH_2), 7.27–8.07 (m, 5 H, phenyl); ^{13}C NMR δ 14.03 (q, CH_3), 22.54 (t, CH_2), 24.36 (t, CH_2), 29.06 (t, CH_2), 31.70 (t, CH_2), 38.63 (t, CH_2), 127.99 (d, phenyl 2,6), 128.46 (d, phenyl 3,5), 132.74 (d, phenyl 4), 137.09 (s, phenyl 1), 200.38 (s, C=O); MS m/z 190 (M^+). Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53; O, 8.41. Found: C, 82.00; H, 9.70; O, 8.71.

2-Methylpentyl phenyl ketone: colorless liquid; bp 110 °C (5 mmHg); IR (neat) 1679 cm^{-1} (C=O); ^{13}C NMR ($CDCl_3$) δ 11.95 (q, CH_3), 17.23 (q, CH_3), 22.85 (t, CH_2), 29.65 (t, CH_2), 33.46 (t, CH_2), 40.40 (d, CH), 127.79 (d, phenyl 2,6), 128.26 (d, phenyl 3, 5), 132.54 (d, phenyl 4), 136.58 (s, phenyl 1), 203.96 (s, C=O).

4-Chlorophenyl cyclohexyl ketone: colorless liquid; Kugelrohr distillation (95 °C/0.5 mmHg); IR (neat) 1675 cm^{-1} (C=O); ^{13}C NMR ($CDCl_3$) δ 25.83 (t, CH_2), 25.95 (t, CH_2), 29.41 (t, CH_2), 43.56 (d, CH), 128.81 (d, phenyl 2,6), 129.63 (d, phenyl 3,5), 134.62 (s, phenyl 4), 139.03 (s, phenyl 1), 202.20 (s, C=O).

Cyclohexyl 2-furyl ketone: colorless liquid; Kugelrohr distillation (88 °C/8 mmHg); IR (neat) 1672 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 1.10–1.92 (m, 10 H, CH_2), 3.06 (m, 1 H, CH), 6.45–6.58 (m, 1 H, furyl), 7.13–7.31 (m, 1 H, furyl), 7.53–7.61 (m, 1 H, furyl); ^{13}C NMR δ 25.77 (t, 2 CH_2), 28.89 (t, CH_2), 46.32 (d, CH), 111.96 (d, furyl 4), 116.77 (d, furyl 3), 145.95 (d, furyl 5), 152.41 (s, furyl 2), 192.63 (s, C=O). Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92; O, 17.95. Found: C, 73.93; H, 8.04; O, 17.69.

Cyclohexyl 3-furyl ketone: colorless liquid; Kugelrohr distillation (85 °C/7 mmHg); IR (neat) 1670 cm^{-1} (C=O); ^{13}C NMR ($CDCl_3$) δ 25.72 (t, CH_2), 25.84 (t, CH_2), 29.30 (t, CH_2), 48.57 (d, CH), 108.75 (d, furyl 4), 126.56 (s, furyl 3), 143.79 (d, furyl 5), 146.60 (d, furyl 2), 198.22 (s, C=O).

Cyclohexyl 2-thienyl ketone: colorless liquid; Kugelrohr distillation (95 °C/2 mm Hg); IR (neat) 1657 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 1.06–2.09 (m, 10 H, CH_2), 3.10 (m, 1 H, CH), 7.02–7.21 (m, 1 H, thienyl), 7.49–7.77 (m, 2 H, thienyl); ^{13}C NMR δ 25.77 (t, CH_2), 25.89 (t, CH_2), 29.65 (t, CH_2), 47.38 (d, CH), 127.99 (d, thienyl 4), 131.39 (d, thienyl 5), 133.27 (d, thienyl 3), 143.78 (s, thienyl 2), 196.44 (s, C=O). Anal. Calcd for $C_{11}H_{14}OS$: C, 68.00; H, 7.26; O, 8.23. Found: C, 67.47; H, 7.13; O, 8.52.

Cyclohexyl 2-pyrrolyl ketone: light yellow liquid; Kugelrohr distillation (88 °C/7 mmHg); IR (neat) 1651 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 0.98–2.06 (m, 10 H, CH_2), 2.96 (m, 1 H, CH), 6.20–6.39 (m, 1 H, pyrrolyl), 6.98–7.31 (m, 2 H, pyrrolyl); ^{13}C NMR δ 25.95 (t, 2 CH_2), 29.82 (t, CH_2), 46.15 (d, CH), 110.38 (d, pyrrolyl 4), 115.89 (d, pyrrolyl 3), 124.82 (d, pyrrolyl 5), 131.28 (s, pyrrolyl 2), 194.51 (s, C=O).

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Registry No. n-$C_4H_9CH(CH_3)COPh$, 17180-39-1; n-$C_6H_{13}COPh$, 1671-75-6; PhCHO, 100-52-7; p-ClC_6H_4CHO, 104-88-1; HCHO, 50-00-0; p-MeC_6H_4CHO, 104-87-0; m-MeC_6H_4CHO, 620-23-5; o-MeC_6H_4CHO, 529-20-4; $Ru_3(CO)_{12}$, 15243-33-1; Ru(COD)(COT), 42516-72-3; Ru(cyclooctadienyl)$_2$, 63395-36-8; n-$C_4H_9CH{=}CH_2$, 592-41-6; $CH_3(CH_2)_5CHO$, 111-71-7; cyclohexyl phenyl ketone, 712-50-5; p-chlorophenyl cyclohexyl ketone, 3277-80-3; cyclopentyl phenyl ketone, 5422-88-8; cyclooctyl phenyl

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ketone, 6004-59-7; cyclohexylmethyl cyclohexanecarboxylate, 2611-02-1; cyclohexanecarboxaldehyde, 2043-61-0; hydroxymethylcyclohexane, 100-49-2; cyclohexyl *p*-tolyl ketone, 2789-44-8; cyclohexyl *m*-tolyl ketone, 3277-78-9; cyclohexyl *o*-tolyl ketone, 2936-55-2; cyclohexyl 2-thienyl ketone, 79852-25-8; cyclohexyl 3-thienyl ketone, 36646-69-2; cyclohexyl 2-furyl ketone, 111609-50-8; cyclohexyl 3-furyl ketone, 36646-68-1; cyclohexyl 2-pyrrolyl ketone, 75211-59-5; 2-thiophenecarboxaldehyde, 98-03-3; 3-thiophenecarboxaldehyde, 498-62-4; 2-furancarboxaldehyde, 98-01-1; 3-furancarboxaldehyde, 498-60-2; 2-pyrrolecarboxaldehyde, 1003-29-8; cyclohexene, 110-83-8; cyclopentene, 142-29-0; cyclooctene, 931-88-4.

Electrochemical Oxidation of Xanthosine. Isolation and Structure Elucidation of a New Dimeric Xanthine Nucleoside

Xinhua Ji, P. Subramanian, Dick van der Helm, and Glenn Dryhurst*

Department of Chemistry and Biochemistry, University of Oklahoma, Norman, Oklahoma 73019

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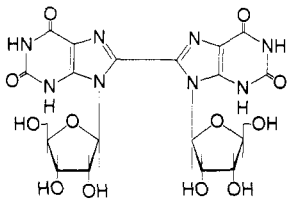
Electrochemical oxidation of xanthosine (**2**) at pH 2 at a pyrolytic graphite electrode generates an electrophilic radical cation intermediate. Nucleophilic attack by **2** on this radical results, ultimately, in formation of 3-(8-xanthosyl)xanthosine (**7**). Hydrolytic cleavage of one ribose residue from **7** in acidic solution leads to 3-(8-xanthosyl)xanthine (**8**). The structure of **8**, a new dimeric xanthine nucleoside, has been established using spectral and X-ray diffraction methods.

Ultraviolet irradiation of adenosine, guanosine, and xanthosine in the presence of the corresponding 8-bromopurine ribonucleoside yields (8 → 8) coupled biribonucleosides.[1,2] Thus, photolysis of an equimolar mixture of 8-bromoxanthosine and xanthosine in aqueous solution gives 8-(8-xanthosyl)xanthosine (**1**) in very low yield. Similarly, photolysis of a mixture of, for example, 8-bromoadenosine and xanthosine yields 8-(8-xanthosyl)-adenosine.



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Recently, we reported that electrochemical oxidation of near-saturated solutions of xanthosine (ca. 2 mM) at pH 2 resulted in a rather complex mixture of products.[3,4] One major oxidation product was an unstable dimer of xanthosine, which readily lost one ribose unit to yield a compound which, apparently, consisted of one xanthosine residue and one xanthine residue. The UV absorption spectra of these electrochemically synthesized dimers are quite different from that of photodimer **1**, thus suggesting that a method had been discovered to synthesize a new class of dimeric nucleosides. Based upon our earlier results we were not able to elucidate the exact molecular structures of the electrochemically generated xanthosine dimers.

In this report the electrochemical synthesis and isolation of a new (xanthosyl)xanthine dimer is described along with spectral and X-ray diffraction information which permits the unequivocal establishment of its unusual molecular structure. We also propose a mechanism for the electrode process which leads to this and other reaction products.

Experimental Section

Xanthosine dihydrate was obtained from Sigma (St. Louis, MO) and was used without further purification. Conventional equipment was used for electrochemical studies.[5] A pyrolytic graphite electrode (Pfizer Minerals, Pigments and Metals Division, Easton, PA) having an approximate surface area of 4 mm^2 was used for voltammetry. Controlled-potential electrolyses employed two plates of pyrolytic graphite (ca. 30 cm^2 surface area) and a conventional three-compartment cell containing a platinum gauze counter electrode and a saturated calomel reference electrode (SCE). All potentials are referred to the SCE at ambient temperature. Electrolyses were carried out in pH 2.0 phosphate buffer having an ionic strength of 0.5.[6] Typically, an excess of xanthosine was vigorously stirred in the latter buffer solution for about 1 h. Thirty milliliters of this solution was then filtered, and the filtrate (i.e., saturated xanthosine) was transferred into the working electrode compartment of the electrochemical cell. Phosphate buffer at pH 2.0 was used in the counter electrode compartment. The solution in the working electrode compartment was stirred with a Teflon-coated magnetic stirring bar, and nitrogen gas was bubbled vigorously through the solution. The electrolysis was performed at a constant potential of 1.07 V. Typically, the electrolysis was allowed to proceed for 30–40 min, and then 2 mL of the solution was removed for separation by high-performance liquid chromatography (HPLC). Without stopping the electrolysis 2 mL of a saturated solution of xanthosine in pH 2.0 phosphate buffer, which also contained some undissolved compound, was added to the working electrode compartment. The electrolysis was then continued for another 40 min (the time required for one complete HPLC separation), and the entire sequence was repeated.

HPLC was carried out with a Bio-Rad Model 1300 pump, a Rheodyne Model 7125 loop injection (2.0-mL loop) and a Gilson Holochrome UV Detector (254 nm). A reversed-phase column (Brownlee Laboratories; RP-18, 5 μm, 25 × 0.7 cm) and a short guard column (Brownlee Laboratories, RP-18, 5 μm, OD-GU, 5 × 0.5 cm) were used for all HPLC separations. An isocratic separation method was employed with 0.1 M formic acid in water adjusted to pH 4.0 with concentrated ammonium hydroxide as the mobile phase. The flow rate was 4 mL min^{-1}. Compound **8** eluted under chromatographic peak E (Figure 2) and was

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