STUDIES ON SEPARATION AND UTILIZATION OF CARBON MONOXIDE

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OSAKA UNIVERSITY

1996

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(一酸化炭素の分離と利用に関する研究)

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Preface

The studies described in this thesis have been carried out under the direction of Professor Noboru Sonoda at Department of Applied Chemistry, Faculty of Engineering, Osaka University for the following six years from 1984 to 1986 and from 1993 to 1995.

The objectives of this thesis are concerned with separation and utilization of carbon monoxide.

Suita, Osaka
November, 1996

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General Introduction

Over the last two decades, much attention has been invested in the development of efficient methods for the utilization of C_1 materials (CO, CO_2, CH_4, CH_3OH, HCHO, HCOOH etc.) from the viewpoint of finitude of petroleum resources. Carbon monoxide is especially important in terms of a raw material for the synthesis of a variety of basic chemicals in C_1 chemistry. Carbon monoxide has been used for many industrially important processes, such as Reppe reaction, Oxo process, Monsanto process, to name just a few. Carbon monoxide is also incorporated into basic polymers, such as polyurethanes and polycarbonates, via phosgene. The growing importance of C_1 chemistry requires efficient methods for the separation of carbon monoxide from gas mixtures, since in general carbon monoxide is contained in large quantities in the exhaust gases of steel mill industries and they consist of gas mixtures with hydrogen, nitrogen, methane, carbon dioxide, etc. The principle of traditional methods for separation of carbon monoxide from other gases is based on different physical properties of these gases, such as difference in boiling points of liquefied gases and absorption ability to metal ions. However, these methods have some disadvantages with respect to economical efficiency, selective separation, and stability of the absorbents against reactive components in gas mixtures. On the other hand, in the field of synthetic organic chemistry, the incorporation of carbon monoxide into various organic compounds is one of basic and important reaction processes. Transition metal mediated reactions have played an important role in such carbonylation reactions with carbon monoxide. Except for super acids and selenium catalyzed carbonylation reaction, other methods for incorporation of carbon monoxide which do not rely upon the power of transition metals are not common.

The main object of the present studies is to develop an efficient method for separation of carbon monoxide from gas mixtures, and to develop a new reaction of carbon monoxide useful in organic synthesis. This thesis consists of five chapters.

Chapter **1** deals with a new method for separation of CO from a gas mixture by use of selenium and secondary amines. This method consists of (i) absorption of CO by selenium and secondary amines to form the corresponding ammonium carbamoselenoates, and (ii) successive thermolysis of ammonium carbamoselenoates to regenerate pure CO (99.9%) quantitatively.

Chapter **2** deals with a separation method of selenium from an alloy of selenium and tellurium as an application of the reaction of selenium with CO and secondary amines. A new mining process of selenium and tellurium has been developed.

Chapter **3** deals with carbonylation of saturated alcohols with CO using an oxidation system of lead tetraacetate. According to this novel method, δ-lactones are successfully synthesized from saturated alcohols and CO.

Chapter **4** deals with carbonylation of alkyl iodides with CO using a reduction system of zinc. In a protic solvent, some carbonylated products including aldehydes, unsymmetrical ketones, and cyclopentanones, can be synthesized. On the other hand, in an aprotic solvent, bicyclic octanol can be obtained from pent-4-enyl iodide, CO, and activated olefins via sequential radical/anionic reaction.

Chapter **5** deals with double carbonylations of alk-4-enyl iodides using group 14 metal hydrides. In this study, two types of double CO trapping reactions which accompanied by cyclization are discovered.

Chapter 1. A New Process for Separation of Carbon Monoxide

1-1. Introduction

The growing importance of C_1 chemistry requires efficient methods for the separation of carbon monoxide from a gas mixture. Carbon monoxide is contained in large quantities in the exhaust gases of steel mill industries. They involve blast furnace gas (CO, H_2, CO_2, N_2, etc.), LD converter exhaust gas (CO, H_2, CO_2, N_2, O_2, etc.), and coke-oven gas (CO, H_2, CO_2, N_2, CH_4, etc.). Usually, these gases are used as a fuel in the manufacturing process. In the view of saving resources, it is highly desired to separate CO from these gases and to utilize it as a raw material for synthetic chemistry. In this regard, until now, much effort has been made to develop an efficient process of CO recovery from these gas mixtures. The traditional processes used for the separation of CO from gas mixtures are copper liquor process, COSORB process and cryogenic process.[1-4] The copper liquor process is based on the CO absorption ability of the solution of Cu(I)-NH_3. This process suffers from undesirable oxidation and disproportionation of Cu(I), and is not suitable for gases containing CO_2 due to its absorption. The COSORB process utilizes toluene solution of Cu(I)$AlCl_4$ as an absorbent. The CO absorption ability of this method is superior to that of copper liquor method. This process enables to serve both a high purity and a high yield of CO, however, the absorbent is readily deactivated with moisture contained in the feed gas. The cryogenic process is based on distillation of liquefied gases at low temperature. The high construction cost with high energy requirement makes this process unattractive. The cryogenic process is suitable for large-scale production. The processes recently developed mostly take advantage of absorbents[5] or adsorbents,[6-8] which absorb or adsorb carbon monoxide at ambient temperature under atmospheric or pressurized CO, and release carbon monoxide at elevated temperature or at reduced

pressures. These absorbents and adsorbents are stable against reactive gases such as hydrogen sulfide and water contained in the gas mixture, enabled highly selective separation under mild conditions. Separation through membranes is also examined, but membrane selectively permeated CO has not been realized.[9]

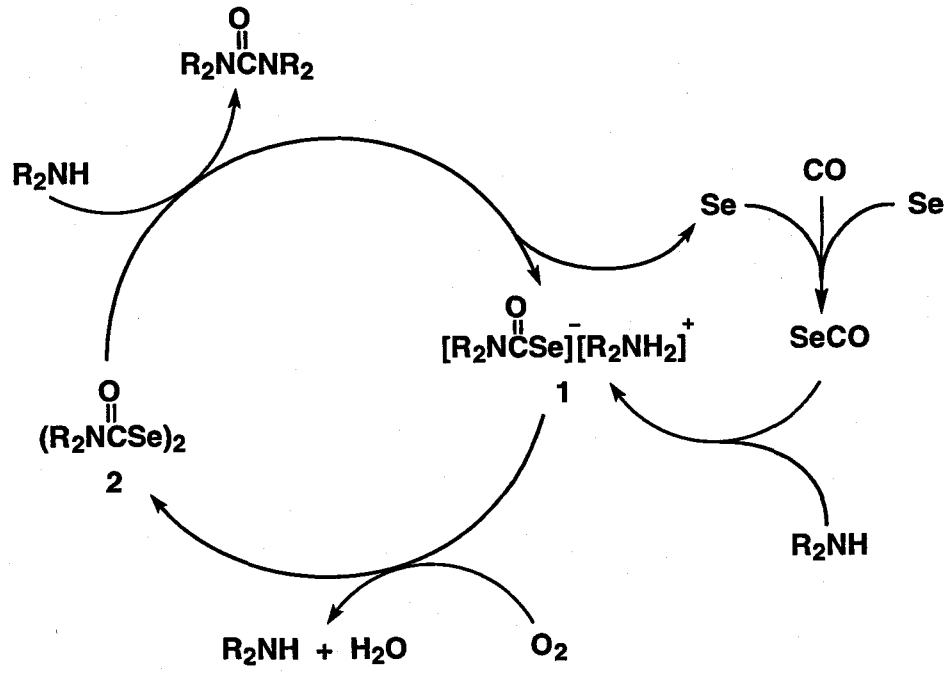
Our research group found that selenium reacts with CO and secondary amines at room temperature under atmospheric pressure to give ammonium carbamoselenoates **1**. Present research focused on examination of the chemical behavior of this ammonium carbamoselenoates **1**, and it has been found that carbamoselenoates **1** is easily decomposed on heating to give starting selenium, CO, and secondary amines. In the hope that this CO absorption and generation phenomena in the solution of secondary amine containing selenium would provide a new principle of CO separation from gas mixtures by a temperature swing method, my research interest was directed to establish a new process for separation and purification of CO.

1-2. Results and Discussion

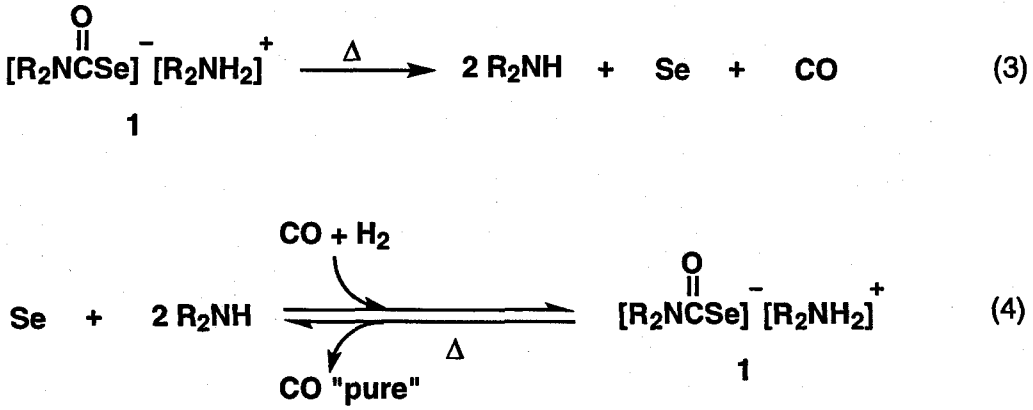
1-2-1. Thermolysis of Ammonium Carbamoselenoates

In 1970, it was reported that selenium efficiently catalyzed the carbonylation of amines with carbon monoxide and oxygen to give corresponding ureas (eq 1).[10] Since then, carbonylation with CO using selenium was extended to synthesis of a variety of carbonyl compounds, including carbamates, carbonates, and carbamothioates.[11] In the case of the formation of ureas, selenium reacts with CO and amine to produce ammonium carbamoselenoate **1** as the intermediate (eq 2). Subsequent oxidation of **1** with molecular oxygen affords biscarbamoyl diselenide **2**. Then, the urea derivative is formed by aminolysis of **2**, and at this stage **1** and selenium are recovered (Scheme 1).

Scheme 1



Under the conditions without oxygen, *secondary* amines can form stable carbamoselenoates **1**, and reaction stops at this stage. It was found that **1** was decomposed on heating to produce starting selenium, CO, and secondary amines (eq 3).[12,13] These two findings, the formation of **1** at room temperature and the thermal decomposition of **1** at about 100 °C, are the bases of present study, which deals with development of a new method for separation of CO from a gas mixture of CO and H_2, so called synthesis gas.[14] Because CO may be selectively absorbed with secondary amines and selenium, and hydrogen remained unchanged, carbamoselenoates **1** may be considered to be a "pure CO stock" (eq 4).



A homogeneous amine solution of **1b** (R = Pr) was prepared from selenium (2.40 g, 30 mmol) and excess dipropylamine (150 mmol, 20.6 mL) under atmospheric pressure of CO at 25 °C for 18 h. When this solution was heated, vigorous decomposition of **1b** was observed at 96 - 98 °C, with release of CO gas and a stoichiometric amount of elemental selenium (eq 4). Similarly, diethylamine, diisopropylamine, and dibutylamine were converted to **1a** (R = Et), **1c** (R = i-Pr), and **1d** (R = Bu), respectively. These salts were decomposed efficiently with liberation of CO at 86 - 89 °C, 57 - 59 °C, and 93 - 95 °C, respectively. These results, **1** not decomposing at room temperature, suggest that the negative value of the entropy change (ΔS) of eq 4 is sufficient, as expected from the stoichiometry, and that, upon heating of the reaction mixture, the equilibrium shifts to the left because ΔG (= ΔH - $T\Delta S$) becomes positive. This is an important feature of this separation system for CO.

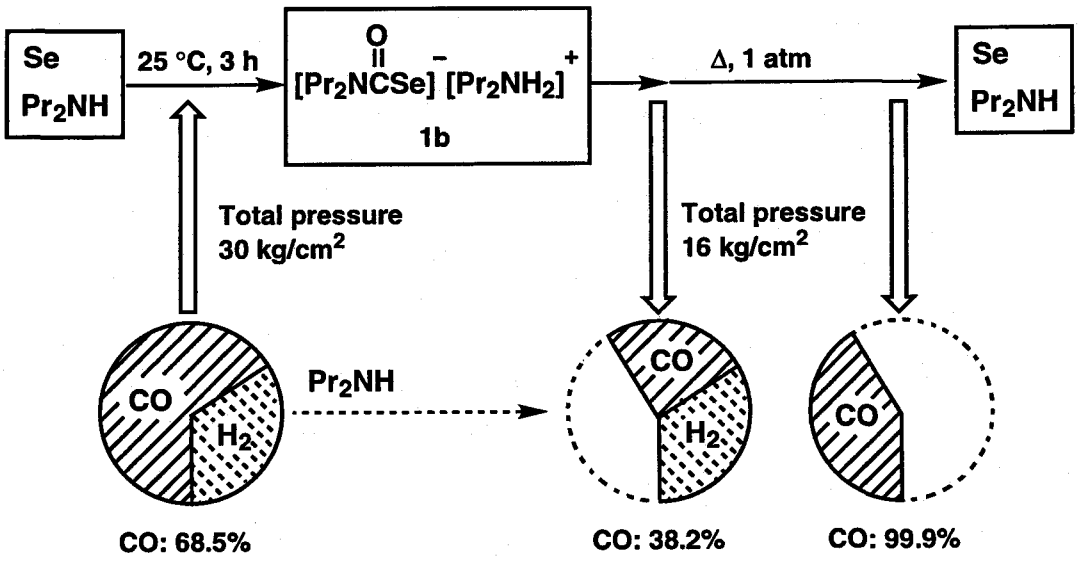
These preliminary results led us to attempt separation of CO from a binary mixture of CO and H_2, whose composition is similar to that of synthesis gas.

1-2-2. Separation of Carbon Monoxide by a Selenium-Amine System

A typical experiment is as follows. In a stainless-steel autoclave were placed selenium (30 mmol, 2.40 g) and dipropylamine (150 mmol, 20.6 mL). Then the autoclave was charged with a binary mixture of CO (20.6 kg/cm^2, 44.8 mmol) and H_2

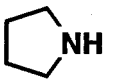
(9.4 kg/cm^2, 20.6 mmol). After stirring at 25 °C for 3 h, the autoclave was depressurized. After the gas remaining in the autoclave was evacuated under reduced pressure, the remaining solution was heated. At 120 °C (bath temperature), gas was evolved for about 2 h. The gas was collected into a balloon and was analyzed by GC, which showed that 32.2 mmol of CO was released by the thermolysis. The yield of purified CO was quantitative (dipropylamine basis), and the purity was 99.9% by GC analysis (Scheme 2).

Scheme 2



The results with several amines are summarized in Table 1. In any cases of secondary amines, the purity of the CO reproduced was more than 99.9% and selenium and amines were recovered almost quantitatively. Diisopropylamine gave inferior result compared with other secondary amines, probably because of the slow formation of **1c** due to steric effects (run 6). When primary amines were used, no evolution of gas was observed and the corresponding ureas were obtained (runs 9 and 10). Aprotic solvents such as toluene, xylene, and 1,4-dioxane also could be used (runs 2-4). The mixture of selenium and dipropylamine could be used repeatedly (recovered CO: 97% (1st), 95% (2nd), 99% (3rd)). The CO purity was always >99.9%.

Table 1. Separation of CO by Se - Amine Reaction System

run	amine	thermolysis temp., °C	CO recovered, %[a,b]	CO purity, %[a]	Selenium recovered, %
1	Pr_2NH	115	100	99.9	99
2[c]			100	99.9	92
3[d]			98	99.7	94
4[e]			100	99.9	98
5	Bu_2NH	110	94	99.9	97
6	*i*-Pr_2NH	120	24	99.9	96
7		150	83[f]	99.9	99
8		140	76[f]	99.9	94
9	$BuNH_2$	150	0[f]	—	98
10	$C_8H_{17}NH_2$	150	0[f]	—	91

Conditions: Selenium (30 mmol), amine (150 mmol): (runs 1, 5-10), selenium (10 mmol), amine (50 mmol), solvent 15 mL: (runs 2-4), CO 20.6 kg/cm^2, H2 9.4 kg/cm^2, 25 °C, 3 h. Thermolysis was performed by heating the resulting solution gradually up to the indicated temperatures (bath temp.). [a]Analyzed by GC (molecular sieves 5A, 2.9 m, 100 °C) [b]Based on selenium used. [c]Toluene was used as the solvent. [d]Xylene was used as the solvent. [e]1,4-Dioxane was used as the solvent. [f]Corresponding symmetrical ureas (run 7: 17%, run 8: 22%, run 9: 98%, run 10: 52%) were isolated.

The results with a variety of gas mixtures are summarized in Table 2. Except for a gas mixture containing CO_2, which can react with amines, the results were always satisfactory.

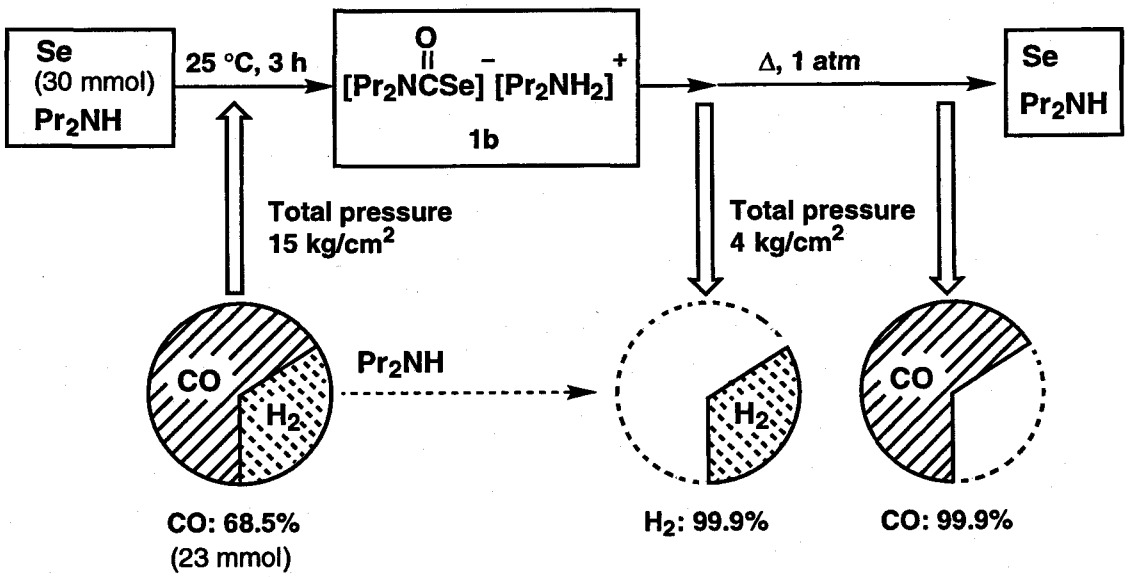
When selenium was used in an excess amount relative to CO, the CO in the feed gas was completely absorbed (selenium 30 mmol, dipropylamine 150 mmol, CO 10.3 kg/cm^2 (23.5 mmol), H_2 4.7 kg/cm^2, 25 °C, 4 days). The gas remained consisted of >99.9% H_2, and the purity of the CO recovered by the thermolysis was >99.9%. Thus, synthesis gas of CO and H_2 only could be separated successfully (Scheme 3).

Table 2. Separation of CO from the Various Gas Mixtures

run	feed gas	CO		Selenium
		recovered, %[a,b]	purity, %[a]	recovered, %
1	CO - N_2	100	99.9	99
2	CO - CH_4	100	99.6[f]	98
3	CO - CO_2[c]	100	78.1[g]	99
4	CO - H_2 - H_2O[d]	100	99.9	99
5	CO - H_2 - H_2O[e]	100	99.9	99

Conditions: selenium (30 mmol), dipropylamine (150 mmol), feed gas 30 kg/cm^2 (N_2 = 14.5%, CH_4 = 17.4%, CO_2 = 16%, H_2 = 31.7%), 25 °C, 3 h. Thermolysis was performed by heating the resulting solution gradually up to 120 °C (bath temp.). [a]Analyzed by GC (molecular sieves 5A, 2.9 m, 100 °C). [b]Based on selenium used. [c]CO_2 was analyzed by GC (Porapak Q, 3 m, 100 °C). [d]H_2O (1 mmol) was added. [e]H_2O (2 mmol) was added. [f]CH_4 (0.4%) was contained. [g]CO_2 (21.8%) was contained.

Scheme 3



1-2-3. Separation of Carbon Monoxide by a Selenium-Alcohol System

The Se-alcohol system was also examined for CO separation from gas mixture.

Triethylamine was used to obtain the key intermediate, ammonium salt of carbonoselenoate ester **3** (eq 5). Thus, the reaction of methanol with selenium and CO proceeded smoothly in the presence of triethylamine, and thermolysis of the resultant solution gave CO, selenium, and methanol (eq 6). The results of CO separation obtained with some alcohols are shown in Table 3. In all cases, CO purity was 99.9%, although with varying efficiency. Except for methanol (run 1), less CO was absorbed than the amount of selenium used; this result reflects the variable efficiency of the formation of **3**. At this stage, Se-alcohol systems are inferior to Se-amine systems and improvement of reaction conditions is needed for the effective generation of **3**.

$$Se + CO + ROH \xrightarrow{\text{base}} \underset{\mathbf{3}}{[ROC(=O)SeH]} \qquad (5)$$

$$\underset{\mathbf{3}}{[ROC(=O)SeH]} \xrightarrow{\Delta} Se + CO + ROH \qquad (6)$$

Table 3. Separation of CO by Se - Alcohol Reaction System[a]

run	alcohol	reaction time, h	thermolysis temp., °C	CO recovered, %[a,b]	CO purity, %[a]	Selenium recovered, %
1	MeOH	8	70	88	99.9	96
2	EtOH	5	90	35	99.9	98
3	PrOH	4	110	19	99.9	96
4	*i*-PrOH	6	90	8	99.9	99
5	BuOH	4	120	13	99.9	98
6	*t*-BuOH	4	90	3	99.9	99

Conditions: Selenium (30 mmol), alcohol (15 mL), Et_3N (45 mmol), CO 20.2 kg/cm^2, H_2 9.8 kg/cm^2, 25 °C, 4-8 h. Thermolysis was performed by heating the resulting solution gradually up to the indicated temperatures (bath temp.). [a]Analyzed by GC (molecular sieves 5A, 2.9 m, 100 °C). [b]Based on selenium used.

1-3. Experimental

General Amines were purified by distillation from KOH. Alcohols were purified by distillation from CaH_2. The gas was analyzed by GC (molecular sieves 5A, 2.9 m, 100 °C: N_2, CH_4, CO, and H_2; Porapak Q, 3 m, 100 °C: CO_2).

General Procedure for Synthesis and Thermolysis of Ammonium Carbamoselenoates (1b): Metallic selenium (2.40 g, 30 mmol) and dipropylamine (150 mmol, 20.6 mL) were stirred under atmospheric pressure of CO at 25 °C. By 18 h, a homogeneous amine solution of **1b** had formed. When this solution was heated slowly, rapid gas evolution with vigorous bubbling was observed at 96 - 98 °C (solution temp.). The gas was found to be CO by GC analysis. After the thermolysis, 2.21 g of selenium was recovered.

General Procedure for Separation of CO from a Mixture of CO and H_2 by the Se-Amine System(Se<CO): In a stainless-steel autoclave equipped with a glass liner were placed selenium (30 mmol, 2.40 g) and dipropylamine (150 mmol, 20.6 mL). The autoclave was charged with a binary mixture (30 kg/cm^2) at 25 °C of CO (20.6 kg/cm^2, 44.8 mmol) and H_2 (9.4 kg/cm^2, 20.6 mmol). After stirring at 25 °C for 3 h, the autoclave was depressurized and the gas inside was trapped in a balloon. GC of the gas showed that it contained 13.1 mmol of CO and 21.2 mmol of H_2. Then the gas remaining in the autoclave was evacuated under reduced pressure through a glass finger attached to the top of the autoclave to avoid contamination. The remaining solution was heated gradually and was kept at 120 °C (bath temp.) for about 2 h until gas evolution ceased. The gas that evolved was collected through a cold trap into a balloon and was analyzed by GC, which showed that 32.2 mmol of CO with a purity of 99.9% was released by the thermolysis (the amount of CO evolved was stoichiometric for the amount of selenium used).

Procedure for the Separation of a Mixture of CO and H_2 by the Se-Amine System (Se>CO): In a stainless-steel autoclave equipped with a glass liner were placed selenium (30 mmol, 2.40 g) and dipropylamine (150 mmol, 20.6 mL). The autoclave was charged with a binary mixture (15 kg/cm^2) at 25 °C of CO (10.3 kg/cm^2, 23.5 mmol) and H_2 (4.7 kg/cm^2, 10.3 mmol). After the solution was stirred at 25 °C for 4 days, the autoclave was depressurized and the gas inside was trapped in a balloon. GC of the gas showed that it contained 10.3 mmol of H_2 with a purity of 99.9%. Then the gas remaining in the autoclave was evacuated under reduced pressure through a glass finger attached to the top of the autoclave to avoid contamination. The remaining solution was heated gradually and was kept at 120 °C (bath temp.) for about 2 h until the gas evolution ceased. The gas that evolved was collected through a cold trap into a balloon and was analyzed by GC, which showed that 23.2 mmol of CO with a purity of 99.9% was released by the thermolysis.

General Procedure for Separation of CO from a Mixture of CO and H_2 by the Se-Alcohol System: In a stainless-steel autoclave equipped with a glass liner were placed selenium (30 mmol, 2.40 g), methanol (15 mL), and triethylamine (45 mmol, 6.3 mL). The autoclave was charged with a binary mixture (30 kg/cm^2) at 25 °C of CO (20.2 kg/cm^2, 44.0 mmol) and H_2 (9.8 kg/cm^2, 21.4 mmol). After the solution was stirred at 25 °C for 8 h, the autoclave was depressurized and the gas inside was trapped in a balloon. GC of the gas showed that it contained 14.1 mmol of CO and 21.1 mmol of H_2. Then the gas remaining in the autoclave was evacuated under reduced pressure through a glass finger attached to the top of the autoclave to avoid contamination. The remaining solution was then heated gradually and was kept at 70 °C (bath temp.) for about 1 h until the gas evolution ceased. The gas that evolved was collected through a cold trap into a balloon and was analyzed by GC, which showed that 26.4 mmol (88%) of CO with a purity of 99.9% was released by the thermolysis.

1-4. References and Notes

(1) For reviews, see: Kohl, A. L.; Riesenfeld, F. C. *Gas Purification* 3rd ed., Gulf Publishing Co., Houston (1979).

(2) Komiyama, M.; Hirai, H. *J. Synth. Org. Chem. Jpn.* **1983**, *41*, 492.

(3) (a) Kitagawa, H. *Kagaku Sochi* **1986**, *28*, 53. (b) Inukai, T. *Sekiyu Gakkai Shi* **1977**, *20*, 317.

(4) (a) Haase, D. J.; Walker, D. G. *Chem. Eng. Prog.* **1974**, *70*, 74. (b) Walker, D. G. *Chemtech* **1975**, 308. (c) Haase, D. J. *Chem. Eng.* **1975**, *Aug. 4*, 52.

(5) (a) Hirai, H.; Komiyama, M.; Hara, S. *Makromol. Chem., Rapid Commun.* **1981**, *2*, 495. (b) Hirai, H.; Komiyama, M.; Hara, S. *Makromol. Chem., Rapid Commun.* **1982**, *3*, 95. (c) Hirai, N.; Nakamura, M.; Komiyama, M. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 2519. (d) Hirai, H.; Hara, S.; Komiyama, M. *Chem. Lett.* **1984**, 861. (e) Hirai, H.; Hara, S.; Komiyama, M. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 109.

(6) (a) Yokoe, J.; Taki, K.; Tsuji, T.; Kasuya, F.; Kida, M. *Aromatikkusu* **1989**, *41*, 211. (b) Kasuya, F.; Tsuji, T. *Gas Sep. Purif.* **1991**, *5*, 242.

(7) (a) Hirai, H.; Komiyama, M.; Wada, K. *Chem. Lett.* **1982**, 1025. (b) Hirai, H.; Hara, S.; Komiyama, M. *Chem. Lett.* **1982**, 1685. (c) Hirai, H.; Wada, K.; Komiyama, M. *Chem. Lett.* **1983**, 361. (d) Hirai, H.; Wada, K.; Komiyama, M. *Chem. Lett.* **1986**, 943.

(8) Huang, Y.-Y. *J. Catal.* **1973**, *30*, 187.

(9) Recent examples: (a) Haraya, K.; Obata, K.; Itoh, N.; Shindo, Y. Hakuta, T.; Yoshitome, H. *J. Membr. Sci.* **1989**, *41*, 23. (b) Weichart, J.; Müller, J. *J. Membr. Sci.* **1994**, *86*, 87. (c) Damle, A. S.; Gangwal, S. K.; Venkataraman, V. K. *Gas Sep. Purif.* **1994**, *8*, 137. (d) Lee, J. K.; Song, I. K.; Lee, W. Y. *Korean J. Chem. Eng.* **1995**, *12*, 384.

(10) Sonoda, N.; Yasuhara, T.; Kondo, K.; Ikeda, T.; Tsutsumi, S. *J. Am. Chem. Soc.* **1971**, *93*, 6344.

(11) Sonoda, N. *Pure Appl. Chem.* **1993**, *65*, 699.

(12) For spectral data (^{13}C NMR, ^{77}Se NMR) of **1** and mechanistic details, see: Fujiwara, S.; Miyoshi, N.; Ogawa, A.; Kambe, N.; Sonoda, N. *J. Phys. Org. Chem.* **1989**, *2*, 359.

(13) Carbamoselenoate **1b** did not decompose under reduced pressure (100 mmHg, 20 °C, 6 h).

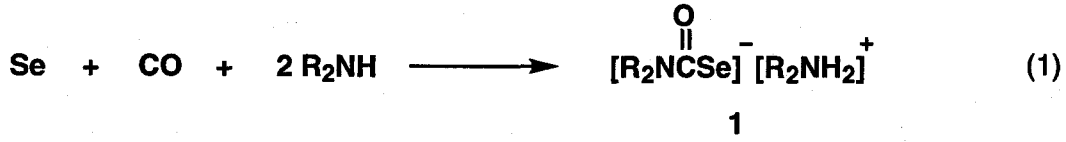
(14) (a) Sonoda, N.; Miyoshi, N.; Tsunoi, S.; Ogawa, A; Kambe, N. *Chem. Lett.*, **1990**, 1873. (b) Tsunoi, S.; Miyoshi, N.; Ogawa, A.; Kambe, N.; Sonoda, N. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 2297.

Chapter 2. A New Process for Separation of Selenium

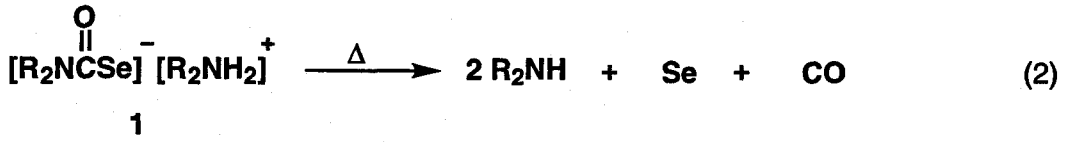
2-1. Introduction

The earth's crust contains 0.05 ppm of selenium and 0.01 ppm of tellurium, respectively. They are usually isolated as a mixture from the slime produced by copper refinery process. Customary separation methods of selenium and tellurium are mostly based on the physical properties, such as difference of boiling points and solubilities of these two elements.[1] In recent years, selenium and tellurium have been used in a variety of industrial areas.[2] Selenium finds application in the following areas, which include photoreceptor, rectifier, glass decolorizing reagent and pigment. Tellurium also finds application in a variety of areas, including metallurgical use, photoreceptor and chemical catalyst. Especially, among these applications, photoreceptor makes use of selenium or selenium-tellurium alloy in large quantities. Nevertheless, there are few methods for the reclamation of selenium and tellurium from scrap alloys.[3] From the point of environmental view, development of the method for reclamation of these compounds is highly desirable.

In this chapter, a new method for separation and reclamation of selenium from selenium-tellurium alloys or mixtures is described. This new method is based on the difference of chemical reactivities between selenium and tellurium toward CO and secondary amines rather than that of their physical properties. As described in preceding chapter, selenium reacts with a secondary amine and carbon monoxide to give carbamoselenoate **1** (eq 1). Carbamoselenoate **1** undergoes thermal decomposition to re-produce CO, secondary amine, and selenium, quantitatively (eq 2).[4]

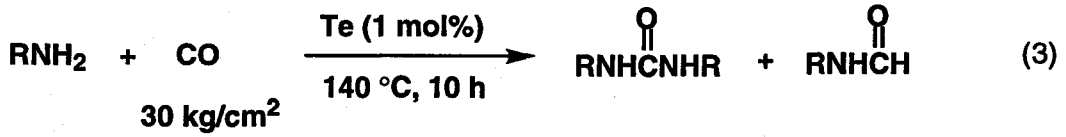


(1)

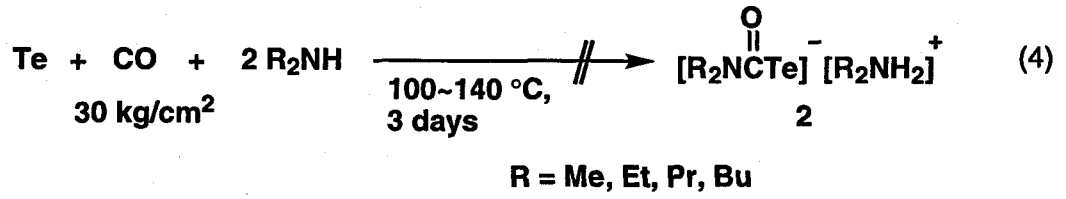


(2)

On the other hand, it was reported that tellurium catalyzed reaction of primary amines and CO to give the corresponding ureas and formamides via ammonium carbamotelluroates **2** as a plausible intermediate (eq 3).[5] In contrast, with secondary amines, tellurium did not afford ammonium carbamotelluroates **2**, even under stringent reaction conditions (eq 4).[5]

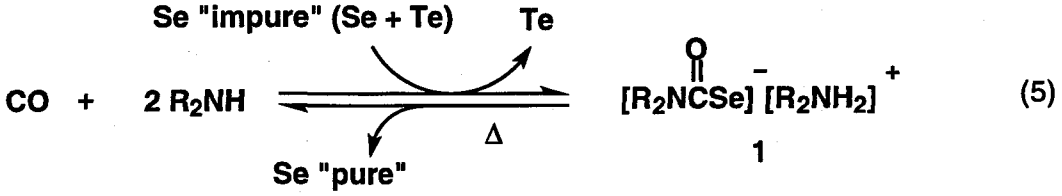


(3)



(4)

Since, as described above, selenium reacts with secondary amines at ambient temperatures in the presence of CO to give relatively stable ammonium carbamoselenoates **1**, it is anticipated that there should be a great possibility to develop a method to separate selenium and tellurium using this system. The concept is illustrated shortly in eq 5.

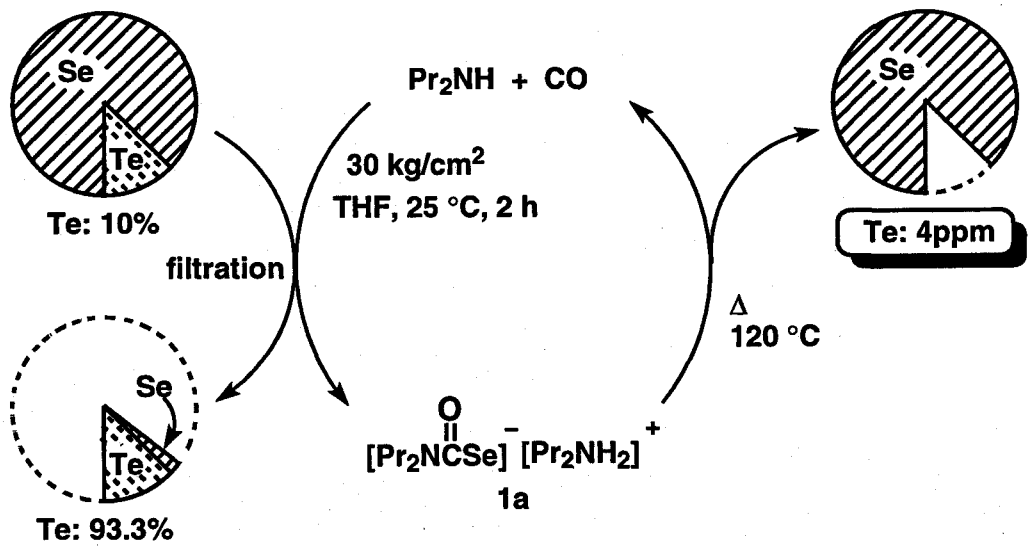


(5)

2-2. Results and Discussion

A typical experiment of separation of selenium which is illustrated in Scheme 1 is as follows. In a stainless–steel autoclave were placed a mixture of selenium and tellurium (2 g, 90% selenium), dipropylamine (10 mL), and THF (10 mL). The autoclave was charged with CO (30 kg/cm^2) at 25 °C. After stirring of the mixture at 25 °C for 2 h, the autoclave was depressurized. The precipitated metal (0.24 g) was filtered under nitrogen pressure. The filtrate was then heated gradually to 150 °C (bath temp.). The metallic residue was washed with THF, and was dried with an oven at 80 °C to give the metal 1.69 g. ICP analysis of the metallic residue showed that the metal consisted of highly pure selenium (>99.999%), which was only contaminated by 4 ppm Te. The initially filtered precipitate was found to contain 93.3% Te by ICP analysis.

Scheme 1



The results obtained under several reaction conditions are summarized in Table 1–3. In any cases of secondary amines, selenium was recovered quantitatively with excellent purity (>99.999%) (Table 1, runs 1, 2, and 4). The treatment of a scrap alloy (93% Se; 7% Te) gave highly pure selenium again (Table 1, run 3). Acetonitrile and THF were the most suitable solvents (Table 2). Under atmospheric CO, 1470ppm of tellurium was contaminated. A small amount of tellurium may react due to the prolonged reaction time.

Table 1. Purification of Se: Effect of Secondary Amines

run	secondary amine	Selenium[a]	
		Te content, ppm	yield, %
1	Et_2NH	3	95
2	Pr_2NH	4	94
3[b]		5	99
4	Bu_2NH	3	96

Conditions: A mixture of selenium/tellurium = 9/1 (2 g), secondary amine (10 mL), THF (10 mL), CO (30 kg/cm^2), 25 °C, 2 h except for run 3 (3 h). After filtration of the reaction mixture, the filtrate was thermolyzed by heating gradually up to 150 °C. [a]Analyzed by ICP. [b]Se-Te scrap alloy (Te 7.04%) was used.

Attempt is also made to obtain tellurium in a highly pure form from an "impure tellurium" containing 9.6% selenium. Thus, the binary mixture (1.9 g, 9.6% Se) and dipropylamine (9.5 mL) in THF (9.5 mL) was stirred at 30 kg/cm^2 CO at 25 °C, for 1 day. Then the precipitated metal was filtered, and ICP analysis indicated that the metal consisted of >99.9% tellurium. Thus, this method was found to be also effective for the purification of tellurium from binary mixture of selenium and tellurium. In this

case, recovered selenium was contaminated by a small amount of tellurium (1000-2000ppm).

Table 2. Purification of Se: Effect of Solvent

run	solvent	Selenium[a]	
		Te content, ppm	yield, %
1	THF	4	94
2	DMF	70	95
3	pyridine	10	93
4	CH_3CN	3	97

Conditions: A mixture of selenium/tellurium = 9/1 (2 g), Pr_2NH (10 mL), solvent (10 mL), CO (30 kg/cm^2), 25 °C, 2 h. After filtration of the reaction mixture, the filtrate was thermolyzed by heating gradually up to 150 °C. [a]Analyzed by ICP.

Table 3. Purification of Se: Effect of CO Pressure

run	CO	Selenium[a]	
	kg/cm^2	Te content, ppm	yield, %
1	30	4	94
2	20	2	95
3	10	2	95
4	0 (1 atm)	1470	97

Conditions: A mixture of selenium/tellurium = 9/1 (2 g), Pr_2NH (10 mL), THF (10 mL), 25 °C, 2 h except for run 4 (9 h). After filtration of the reaction mixture, the filtrate was thermolyzed by heating gradually up to 150 °C. [a]Analyzed by ICP.

2-3. Experimental

General Amines were purified by distillation from KOH. Filtration was conducted by the use of Glass microfibre filters (GF/F, ϕ = 2.4 cm, Whatman LTD.). Selenium and tellurium were analyzed by ICP method (Nippon Jarrell–Ash ICAP–575).

Separation of Selenium under Pressurized CO: In a 50 mL stainless–steel autoclave lined with a glass insert equipped with a grinding were placed a mixture of selenium and tellurium (2 g, 90% selenium), dipropylamine (10 mL), and THF (10 mL). The autoclave was charged with CO (30 kg/cm^2) at 25 °C. After stirring at 25 °C for 2 h, the autoclave was depressurized. The precipitated metal (0.24 g) was filtered and washed with THF under nitrogen pressure. The filtered precipitate was dried with an oven at 80 °C and the resulting metal contained 93.3% Te by ICP analysis. The filtrate was then heated gradually to 150 °C (bath temp.) and dipropylamine was distilled out at this temperature. The metallic residue was washed with THF, and dried with an oven at 80 °C to give the metal 1.69 g. ICP analysis of the metal showed that it was highly pure selenium with 4 ppm Te contaminated.

Separation of Selenium under Atmospheric Pressure of CO: In a flame dried 50 mL two neck flask were placed a mixture of selenium and tellurium (2 g, 90% selenium), dipropylamine (10 mL), and THF (10 mL) under nitrogen. The flask was then flushed several times with CO. After stirring at 25 °C for 9 h, absorption of CO was not observed. Then, the precipitated metal (0.20 g) was filtered and washed with THF under nitrogen pressure. The filtrate was then heated gradually to 150 °C (bath temp.) and dipropylamine was distilled out at this temperature. The metallic residue was washed with THF, and dried with an oven at 80 °C to give the metal 1.76 g. ICP analysis of the metal showed that it was selenium with 1470 ppm Te contaminated.

General Procedure for Separation of Tellurium by the CO-Amine System: In a

50 mL stainless-steel autoclave lined with a glass insert equipped with a grinding were placed a mixture of selenium and tellurium (1.9 g, 9.6% selenium), dipropylamine (9.5 mL), and THF (9.5 mL). The autoclave was charged with CO (30 kg/cm^2) at 25 °C. After stirring at 25 °C for 1 day, the autoclave was depressurized. The precipitated metal (1.71 g) was filtered and washed with THF under nitrogen pressure. The filtered precipitate was dried with an oven at 80 °C and the resulting metal contained 114ppm Se by ICP analysis.

2-4. References

(1) (a) Bollung, A. B.; Bult, R. P. *JOM* **1989**, *41*, 39. (b) Hyvärinen, O.; Lindroos, L.; Yllö, E. *JOM* **1989**, *41*, 42. (c) Buβmann, H.; Dobner, R. F. *Erzmetall* **1990**, *43*, 362. (d) Elgy, C.; McWhinnie, W. R. *Appl. Organomet. Chem.* **1987**, *1*, 423. For a recent review, see: (e) Hoffmann, J. E. *JOM* **1989**, *41*, 33.

(2) Hoffmann, J. E. *JOM* **1989**, *41*, 32.

(3) Badesha, S. S. U.S. Patent 4,441,698 [Chem. Abstr. **1984**, *100*, 59602j.].

(4) Related work of purification of CO by thermolysis of carbamoselenoates **1** has been published, see: (a) Sonoda, N.; Miyoshi, N.; Tsunoi, S.; Ogawa, A; Kambe, N. *Chem. Lett.* **1990**, 1873. (b) Tsunoi, S.; Miyoshi, N.; Ogawa, A.; Kambe, N.; Sonoda, N. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 2297.

(5) (a) Kambe, N.; Kondo, K.; Ishii, H.; Murai, S.; Sonoda, N. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 547. (b) Kambe, N.; Kondo, K.; Ishii, H.; Sonoda, N. *Bull. Soc. Chem. Jpn.* **1981**, *54*, 1460.

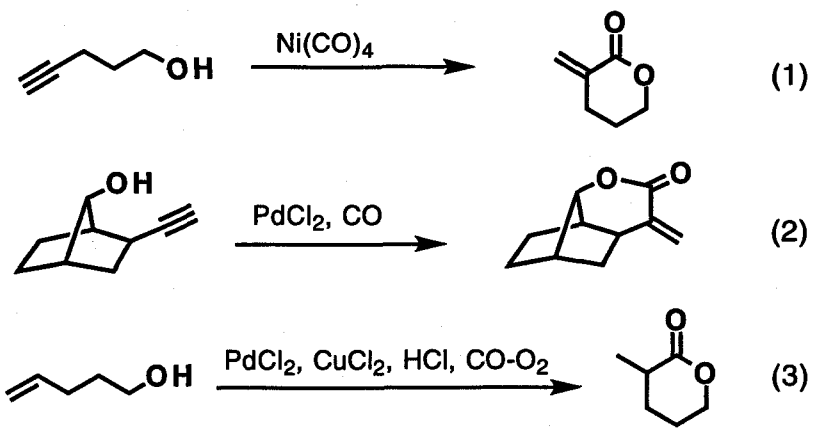
Chapter 3. Carbonylation of Alcohols with Carbon Monoxide Using a One-Electron Oxidation System of Pb(IV)

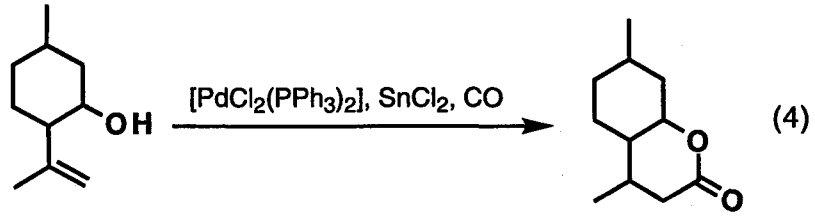
3-1. Carbonylation of Saturated Alcohols

3-1-1. Introduction

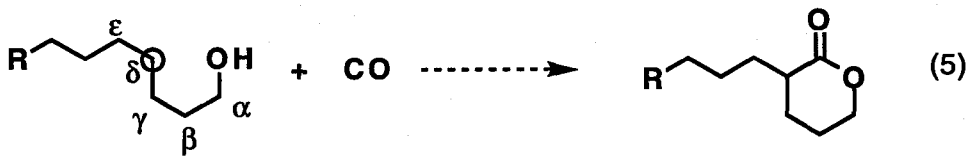
Carbonylation with carbon monoxide is one of the most active fields in the synthetic organic chemistry. The methods for the introduction of carbon monoxide into organic molecules center around the transition metal mediated reactions. However, examples of carbonylation using a one-electron oxidation system are still scarce.[1] In this chapter, the synthesis of δ-lactones from saturated alcohols and CO is described.

Synthesis of δ-lactones is important in view of the occurrence of numerous important natural products and biologically active compounds containing the δ-valerolactone unit.[2] The synthesis of δ-lactones by the transition metal mediated or catalyzed carbonylation of *unsaturated* alcohols with CO is well known (eqs 1-4).[3] In general, in such a synthesis, it is thought to involve the addition of an oxycarbonylmetal species to a carbon-carbon double bond as a key step. However, the corresponding synthesis of δ-lactones from *saturated* alcohols and CO has yet to be realized (eq 5).





(4)

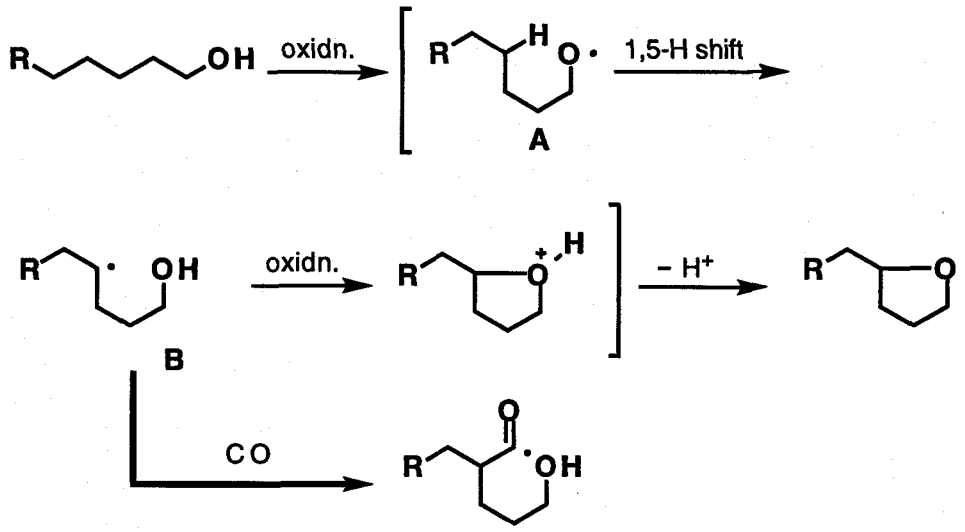


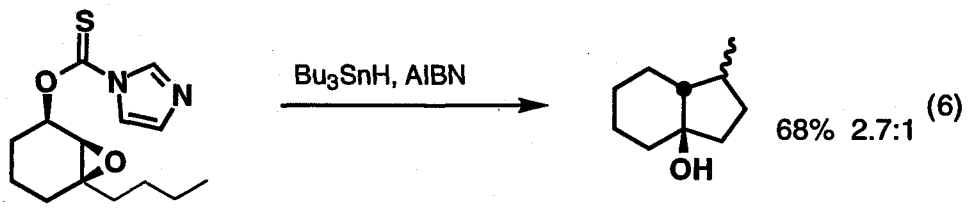
(5)

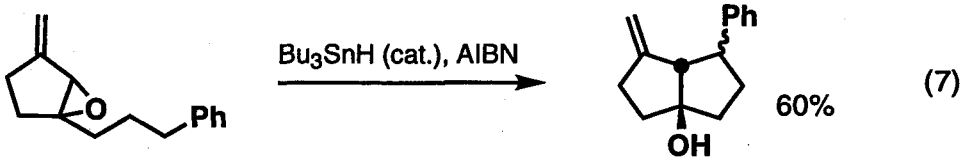
To transform saturated alcohols to δ-lactones, activation at the position δ to a hydroxy group is indispensable (eq 5). It occurred to me that the combination of 1,5-hydrogen transfer from δ-carbon to an alkoxy radical and the subsequent reaction of the resultant carbon radical with carbon monoxide,[4] would lead to δ-carbonylation of saturated alcohols.[5] In this regard, I became interested in applying Mihailovic's THF forming reaction, which involves treatment of a saturated alcohol with lead tetraacetate (LTA) in refluxing benzene affording THF derivatives, to this study.[6] As summarized in Scheme 1, Mihailović's THF synthesis is likely to involve 1,5-hydrogen transfer from C to O•, which is formed by one-electron oxidation of a saturated alcohol. I envisioned that putative intermediate **B** would undergo carbonylation with CO in preference to its oxidation. Examples are abundant as to highly δ-selective C-H bond cleavage by alkoxy radicals via 1,5-hydrogen-transfer reaction.[7,8] Recent work frequently utilizes the combination of 1,5-hydrogen-transfer reaction with the subsequent *intramolecular* C-C bond formation (eqs 6-9).[9] However, examples of 1,5-hydrogen transfer in combination with the subsequent *intermolecular* C-C bond formation seem rare. As far as I know, there exists only one example of such a sequence except for this study. Fraser-Reid and coworkers reported that the carbon radical resulted from 1,5-hydrogen abstraction of alkoxy radical generated by the

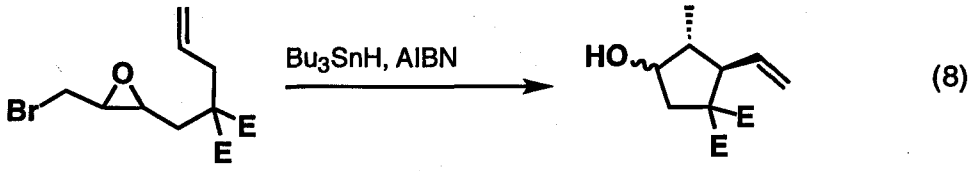
reaction of nitrate ester with tin radical, was successfully trapped by acrylonitrile (eq 10).[10]

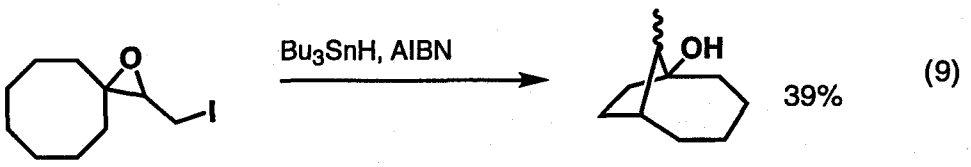
Scheme 1

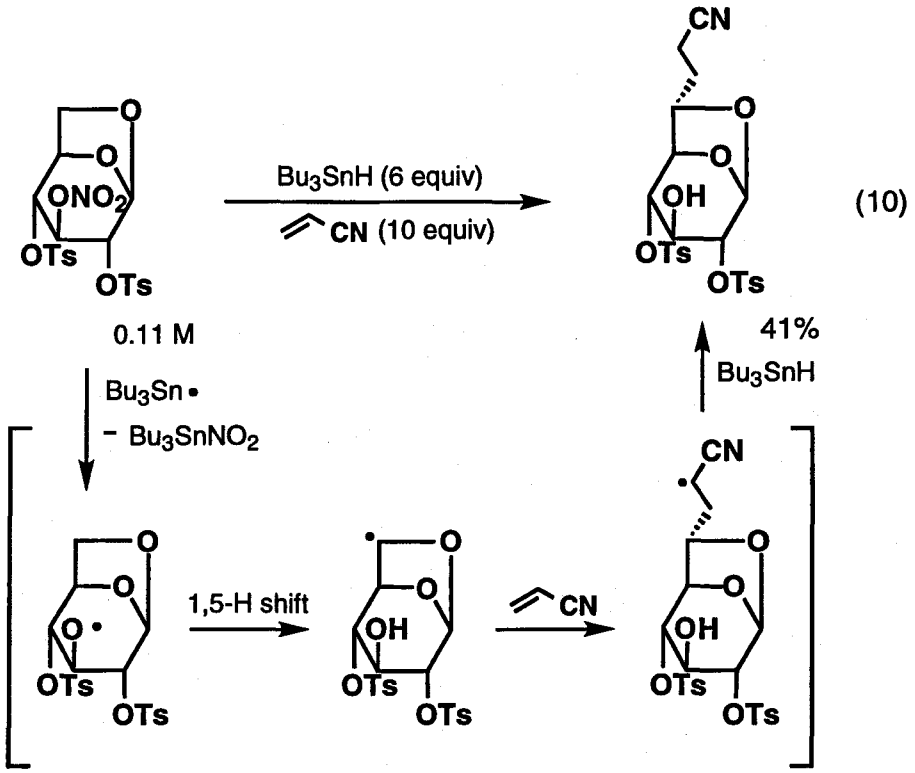










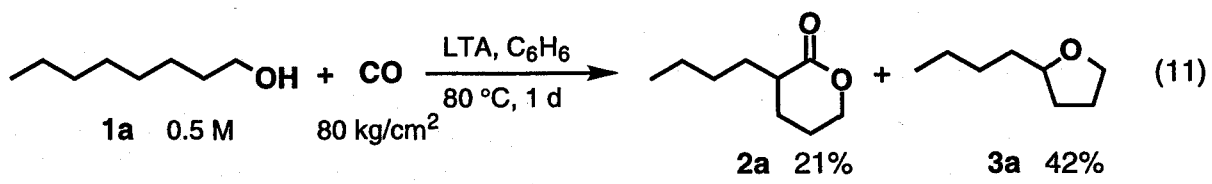


3-1-2. Results and Discussion

3-1-2-1. Carbonylation of Alcohols at δ-Methylene Carbons

Carbonylation of Primary Alcohols at δ-Methylene Carbons

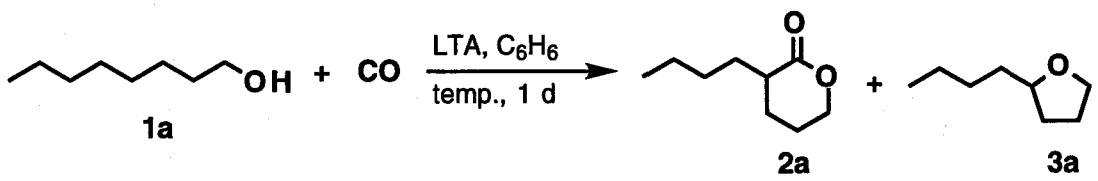
The first experiment was carried out with a primary alcohol having a δ-methylene carbon, 1-octanol (**1a**). When the reaction of **1a** with CO was carried out in the presence of LTA (1.1 equiv) at 80 °C for 24 h ([**1a**] = 0.5 M in benzene, 80 kg/cm^2), indeed the envisioned δ-lactone, 2-butyl-5-pentanolide (**2a**) was obtained (21% GC yield) (eq 11).[11] The major product under the conditions was uncarbonylated 2-butyltetrahydrofuran (**3a**, 42%).



Control experiments were carried out in the hope of improving the yield of **2a**. The results are summarized in Table 1. Higher concentrations of **1a** caused increase in the amount of uncarbonylated product **3a** (run 3), and at the concentrations less than 0.02 M, the reaction dramatically slowed down. With 1.1 equiv of LTA, the ratio of **2a/3a** was satisfactory, but larger amount of the starting alcohol remained unreacted (run 4). With 2 equiv of LTA, the formation of tetrahydrofuran became largely competitive (run 5). Consequently, 1.5 equiv of LTA was chosen. When CO pressure was reduced to 20 kg/cm^2 (run 6), the carbonylation/uncarbonylation ratio decreased to 1.1. Lower reaction temperatures gave better carbonylation/uncarbonylation ratios (runs 2 vs 8). Besides benzene, polar solvent was also tested. When the reaction was conducted in CH_2Cl_2 at 40 °C, the reaction was very sluggish and 85% of the starting alcohol was recovered (run 9). Even at 80 °C, the reaction was not complete. In this case, octyl acetate was detected as a significant by-product (run 10). As for a by-product via carbonylation, ε-lactone **4a**, which is formed via 1,6-hydrogen transfer followed by carbonylation, was detected in a small amount (in <10% ratio relative to **2a**.).[12] On the other hand, a product formed via 1,4-hydrogen transfer was not detected.[13] Under optimal conditions (run 1, 0.02 M, 105 kg/cm^2, 40 °C), alcohol **1a** was cleanly carbonylated to give δ-lactone **2a**, where the ratio of carbonylation/uncarbonylation products was 7.0.

In LTA/CO system, the major competing reaction with carbonylation is a Mihailović type oxidation of the δ-hydroxyalkyl radical to give tetrahydrofuran derivatives **3**. As was seen in Table 1, lower reaction temperature, smaller amount of LTA, lower concentration of 1-octanol, and higher pressure of CO were all effective to make the carbonylation of the δ-hydroxyalkyl radical to predominate over the undesirable direct oxidation.

Table 1. Control Experiments for Carbonylation of 1-Octanol



1a 2a 3a

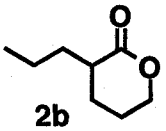
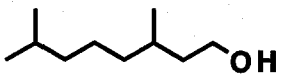
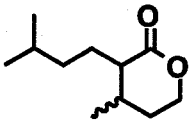
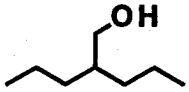
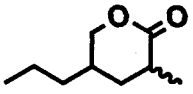
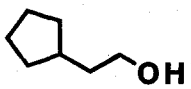
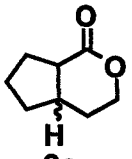
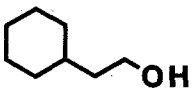
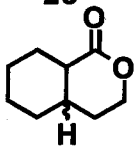
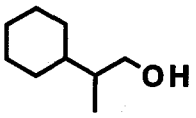
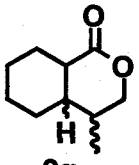
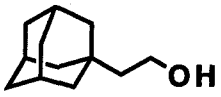
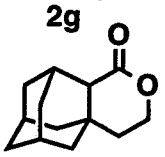
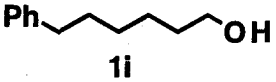
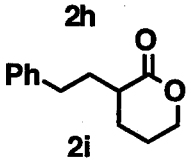
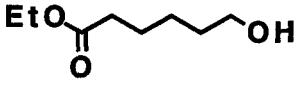
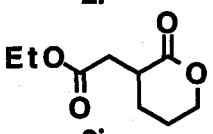
run[a]	[1a]	LTA, equiv	CO, kg/cm^2	temp., °C	2a[b]	3a[b]	2a/3a
1	0.02	1.5	105	40	63	9	7.0
2	0.02	1.5	80	40	53	15	3.5
3	0.04	1.5	80	40	46	22	2.1
4	0.02	1.1	80	40	39	8	4.9
5	0.02	2	80	40	47	23	2.0
6	0.02	1.5	20	40	31	27	1.1
7	0.02	1.5	50	40	44	19	2.3
8	0.02	1.5	80	80	36	26	1.4
9[c]	0.02	1.5	80	40	7	<1	>7.0
10[c,d]	0.02	1.1	80	80	23	15	1.5

[a]1-Octanol (ca. 5%) was remained in all runs (except for run 4, 29%; run 9, 85%; run 10, 10%). ε-Lactone was detected in ~10% ratio relative to **2a**. [b]GC yield. [c]Reaction was conducted in CH_2Cl_2. [d]Octylacetate was formed in 10%.

Additional results of carbonylation at the δ-methylene, obtained under the standard conditions ([ROH] = 0.02 M, 1.5-2.0 equiv of LTA, 40 °C) are summarized in Table 2. In the case of primary alcohols having δ-methylene carbon except for runs 8 and 9, the reaction time tends to be prolonged with increase in the steric congestion around the hydroxy carbon. This tendency may be accounted for by the difficulty of the formation of alkoxylead(IV) species at the initial step.[14] The formation of ε-lactones (~5%) by 1,6-H shift were observed in runs 1, 2, and 8, which were eliminated by careful purification by flash chromatography on silica gel to afford pure δ-lactones. In the other cases, competitive 1,6-hydrogen-transfer reaction was negligible. Except for runs 5 and 7, the formation of THF derivatives constitutes major competitive reaction. Bicyclic δ-lactones were also obtained from the corresponding 2-

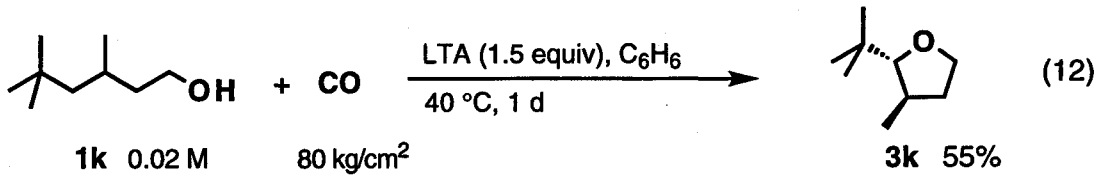
cycloalkylethanols in good yields (runs 4-7).

Table 2. Carbonylation of Primary Alcohols at δ-Methylene Carbons

run	ROH	time, day	product	isolated yield, %
1	 **1b**	1	 **2b**	51
2	 **1c**	3	 **2c**	46 cis/trans = 54/46[a]
3	 **1d**	3	 **2d**	43 cis/trans = 50/50[b]
4	 **1e**	3	 **2e**	39 cis/trans = 77/23[b]
5	 **1f**	3	 **2f**	58 cis/trans = 44/56[b]
6	 **1g**	5	 **2g**	46 6:10:3:3[a]
7	 **1h**	3	 **2h**	67
8	 **1i**	5	 **2i**	50
9	 **1j**	3	 **2j**	38

Conditions: ROH (0.4-0.8 mmol), LTA (1.5-2.0 equiv), C_6H_6 (20-40 mL), CO (80 kg/cm^2), 40 °C. [a]Determined by GC. [b]Determined by ^{1}H-NMR.

In the case of **1k**, the absence of δ-lactone indicates that steric congestion at the δ-carbon prevents the smooth carbonylation. The major product was **3k** (eq 12).



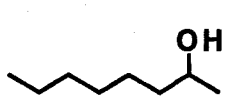
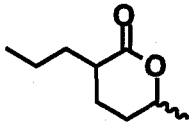
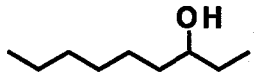
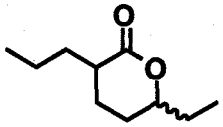
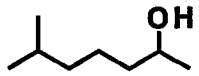
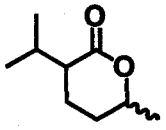
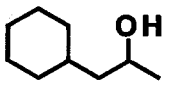
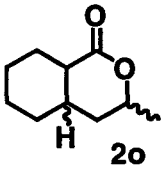
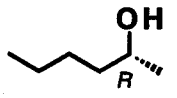
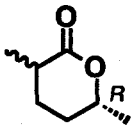
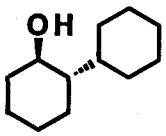
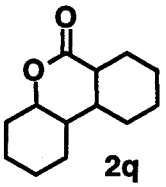
1k 0.02 M 80 kg/cm^2 **3k** 55% (12)

Carbonylation of Secondary Alcohols at δ-Methylene Carbons

The results of δ-carbonylation of secondary alcohols affording δ-lactones are summarized in Table 3. In general, the yields of δ-lactones are better than those from primary alcohols. Secondary alcohols **1l** and **1m** also produced a small amount of ε-lactones (<3%) via 1,6-hydrogen-transfer reaction (runs 1 and 2). With **1n**, ε-lactone was not detected. In this case, 1,6-H transfer yields tertiary radical,[15] which would easily undergo the subsequent oxidation to give carbocation rather than CO trapping (run 3).[16] 1-Cyclohexyl-2-propanol (**1o**) gave bicyclic δ-lactone **2o** in high yield as a mixture of four diastereomers (run 4).

This δ-carbonylation was successfully applied to a straightforward synthesis of carpenter bee pheromone[17] from optically pure (R)-(-)-2-hexanol (**1p**), a commercially available alcohol. Treatment of **1p** with CO in the presence of LTA yielded a *cis* and *trans* mixture of 2-methyl-5-hexanolide (**2p**) (run 5). The preparative HPLC separation of the mixture allowed to afford pure *cis*-(2S, 5R)-2-methyl-5-hexanolide (ee~100%),[18,19] a sex pheromone of the carpenter bee *Xylocopa hirutissima*. The observed quantitative optical yield confirmed absolute configuration of hydroxy carbon being complete retention.

Table 3. Carbonylation of Secondary Alcohols at δ-Methylene Carbons

run	ROH[a]	time, day	product	isolated yield, %
1	 **1l**	3	 **2l**	57 cis/trans = 55/45[b]
2	 **1m**	3	 **2m**	68 cis/trans = 59/41[b]
3	 **1n**	3	 **2n**	58 cis/trans = 52/48[b]
4	 **1o**	3	 **2o**	75 22:26:24:28[c]
5	 **1p**	3	 **2p**	53 cis/trans = 55/45[b]
6	 **1q**	7	 **2q**	50[d]

Conditions: ROH (0.4-1 mmol), LTA (1.5-2.0 equiv), C_6H_6 (5-40 mL), CO (80 kg/cm^2), 40 °C. [a][ROH] = 0.02 M (except for run 6: 0.2 M). [b]Determined by GC. [c]Determined by ^{1}H-NMR (600 MHz). [d]Mixture of eight diastereomers.

The reaction of *trans*-2-cyclohexyl-1-cyclohexanol (**1q**) under standard conditions (0.02 M) was sluggish. Reaction at higher concentration (0.2 M) yielded tricyclic δ-lactone **2q** in moderate yield (run 6). NMR spectra (600 MHz) indicated that obtained tricyclic δ-lactone **2q** was a mixture of eight diastereomers composed of four major diastereomers and four minor diastereomers (55:15:12:6:4:3:3:2). This result was unexpected since only four diastereomers were possible from **1q**. Four minor

products probably resulted via β-scission reaction of alkoxy radical and the subsequent recyclization.[20] A possible rationale for this is detailed in Scheme 2. An initially generated alkoxy radical ***trans*-C** suffers from β-scission to give a fragment radical **D**. The radical **D** cyclizes onto internal aldehyde to afford an isomerized radical ***cis*-C** or the original radical ***trans*-C**.[21] The isomerized radical ***cis*-C** undergoes 1,5-hydrogen transfer, CO trapping, and oxidation to give four minor products. The radical ***trans*-C** affords four major products. The reason of complete retention of hydroxy carbon in **1p** is that such β-scission yields two fragments, whose recombination is quite difficult.

Scheme 2

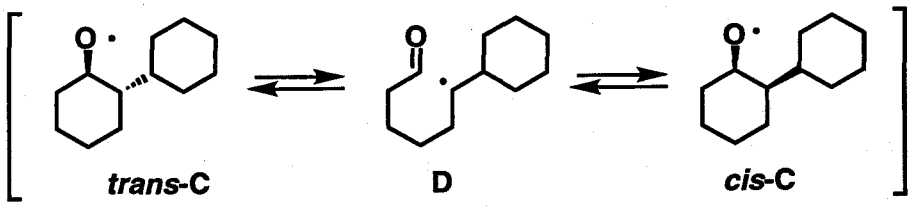
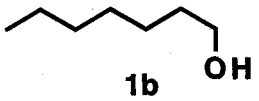
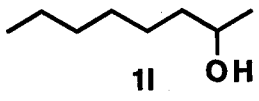
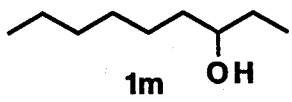


Table 4. Comparison of the Ratio of δ-Lactone/THF between Primary and Secondary Alcohols

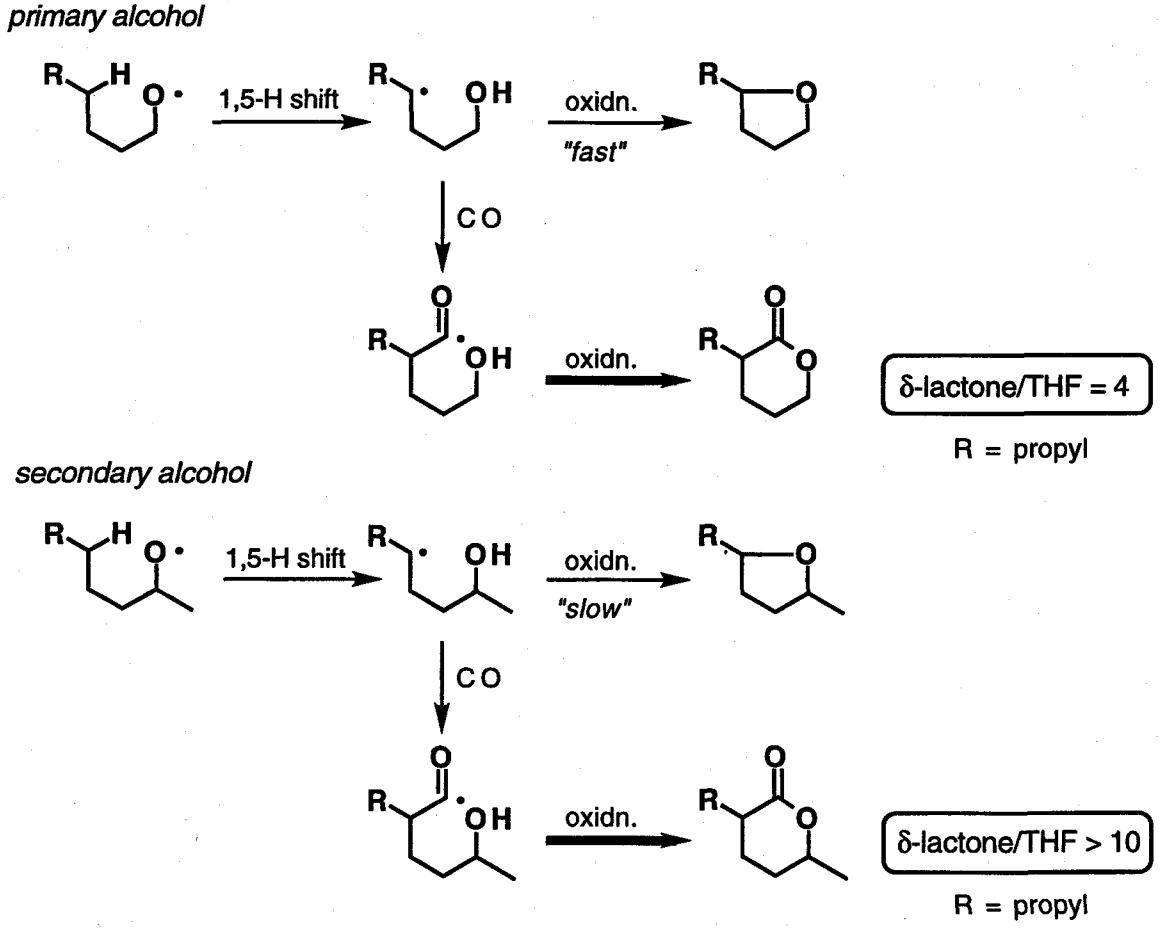
	ROH	δ-lactone/THF[a]
primary alcohol	 **1b**	4
secondary alcohols	 **1l**	10
	 **1m**	12

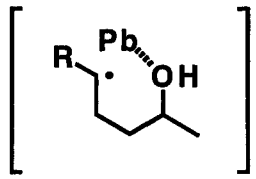
Conditions: [ROH] = 0.02 M (in C_6H_6), LTA (1.5-2.0 equiv), CO (80 kg/cm^2), 40 °C, 1-3 d. [a]Determined by GC.

Unlike the case of primary alcohols, secondary alcohols having δ-methylene

carbon did produce only a small amount of tetrahydrofuran as by-products. For example, 2-octanol (**1l**) gave δ-lactone **2l** in 57% yield along with less than 5% yield of 2-methyl-5-propyltetrahydrofuran. Table 4 summarizes the ratio of δ-lactone/THF for primary alcohol **1b** and secondary alcohols **1l** and **1m**, both of which have a δ-methylene carbon. The relatively low δ-lactone/THF ratio in primary alcohol compared to secondary one may be ascribed to the relative ease of THF formation for the primary alcohol (Scheme 3).[22] It is conceivable that the coordination of hydroxy group to Pb(III or IV) center, as in **E**, would be crucial to make the second oxidation easier. Namely, in a cyclic intermediate **E**, a substituent at hydroxy carbon would cause a steric congestion.

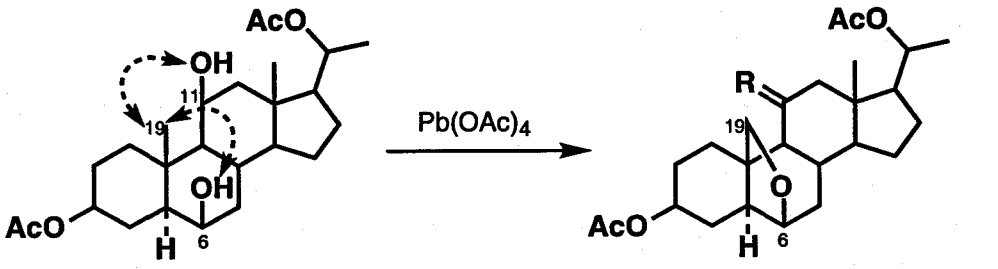
Scheme 3





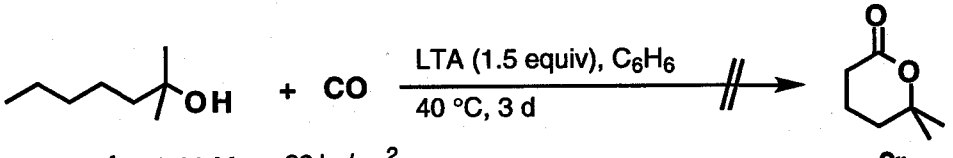
E

The intermediacy of **E** may also be supported by the previous observation on the oxidative cyclization of 6β,11β-dihydroxysteroid, where C-19 methyl group is equdistant from 6β- and 11β-oxygen atoms (eq 13).[6h] The reaction of 6β,11β-dihydroxysteroid with LTA afforded the only product, 6β,19-ether, via the attack of Pb to 6β-oxygen which is less crowded compared with 11β-oxygen. This, as well as the result shown in Table 4, probably suggests that coordination of hydroxy group to Pb(III or IV) center is essential for the second oxidation step.[23]



Distance O_6-C_{19} = Distance C_{19}-O_{11} R = OH, H or O (13)

In contrast to primary alcohols and secondary alcohols, tertiary alcohol **1r** was virtually inert under the reaction conditions employed (97% recovery for **1r** after 3 days) (eq 14). This is presumably because of the difficulty of the formation of alkoxy lead species at the initial step.[14]



1r 0.02 M 80 kg/cm^2 **2r** (14)

3-1-2-2. Carbonylation of Alcohols at δ-Methyl Carbons

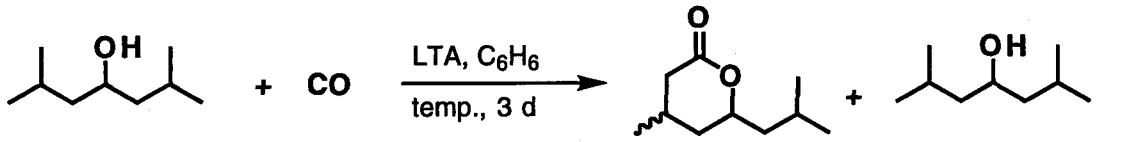
Next the carbonylation of alcohols having δ-methyl carbon was examined. Among alcohols having δ-methyl carbon, the reaction of a symmetrical secondary alcohol **1s**, which contains four methyl groups in both side chains, was conducted under the various conditions, and the results are shown in Table 5. Treatment of **1s** with 80 kg/cm^2 of CO and 1.5 equiv of LTA, gave δ-lactone **2s** in an excellent yield (run 1). The remarkable efficiency with **1s** in comparison with 1-octanol indicates that primary alkyl radical is destined to trap CO rather than to be oxidized with Pb (III or IV).[24] Actually, with 2,6-dimethyl-4-heptanol (**1s**), little competitive oxidation reaction leading to tetrahydrofuran was observed. This is ascribed to slow oxidation of the primary radicals. Even at high temperature (60~80 °C), tetrahydrofuran was formed in trace amounts (runs 5 and 6). Thus, carbonylation of alcohols having δ-methyl carbon can be conducted at relatively lower CO pressures. For example, under 20 kg/cm^2 of CO, δ-lactone **2s** was obtained in 57% yield along with 2% yield of THF derivative (run 2).

However, under 5 kg/cm^2 of CO, the yield of δ-lactone was reduced, and instead starting alcohol was largely recovered (run 3). This seems quite unusual since 1,5-H shift from C to O• is irreversible. When the reaction was carried out in the absence of CO at 40 °C (N_2 atmosphere), GC analysis of the reaction mixture showed that 90% **1s** was almost recovered (run 4). In accord with this, iodometric titration showed that 85% of LTA remained unreacted. The recovery of starting alcohol and LTA seems contradictory, since under CO pressure (80 kg/cm^2) at the same temperature (40 °C), the reaction smoothly occurred to give the desired δ-lactone **2s** in good yield.

A possible explanation for the "reversibility" of 1,5-H shift is as follows: (i) 1,5-hydrogen transfer of the alkoxy radical to lead to a δ-hydroxyalkyl radical, (ii) coupling of the resultant radical and Pb(III) to lead to an alkyl lead **F**, (iii) acidolysis of **F** by acetic acid to regenerate starting alcohol and LTA (Scheme 4).[25] Although the

reversibility of 1,5-H shift can be explained by acidolysis of **F**, there is no experimental evidence offered to support this postulate.[26]

Table 5. Control Experiment for Carbonylation of 2,6-Dimethyl-4-heptanol



1s 0.02 M **2s** **1s** (recovered)

run	LTA, equiv	CO, kg/cm^2	temp., °C	**2s**[a]	**1s** (recovered)[a]
1	1.5	80	40	81 (71)	7
2	1.5	20	40	57	8
3	1.5	5	40	13	71
4[b]	1.5	0	40	-	90
5	1.5	5	60	30	26
6[c]	2.0	80	80	61	6

[a]GC yield (Isolated yield). The isomer ratio was determined by NMR (cis/trans = 59/41). THF derivertives are always produced in trace amount (<2%, except for run 4.). [b]Reaction was performed under N_2. [c]Reaction was run for 1 day.

Scheme 4

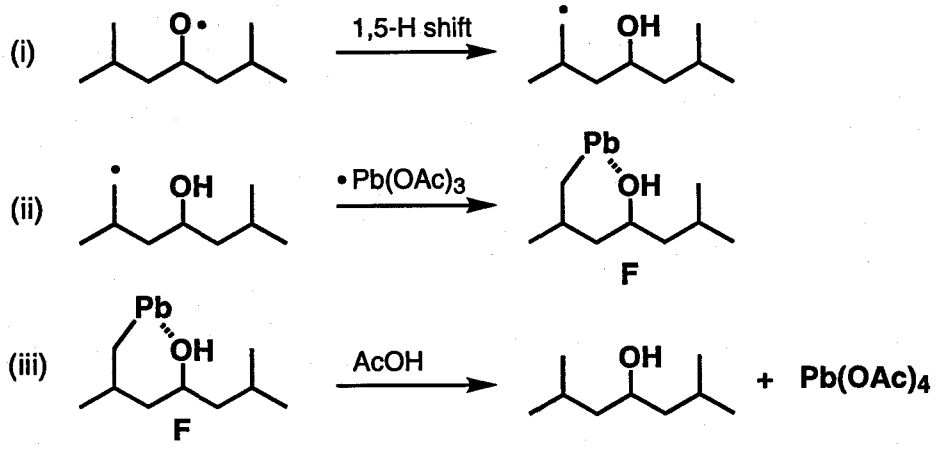
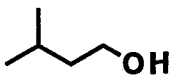
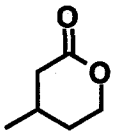
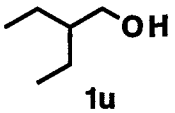
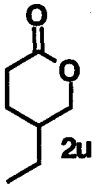
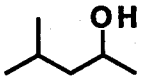
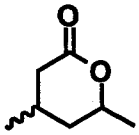
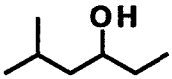
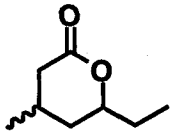
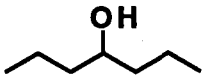
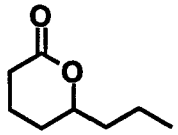
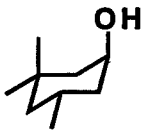
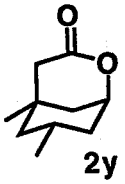


Table 6 lists the results of carbonylation at δ-methyl carbon. Yields of δ-lactones

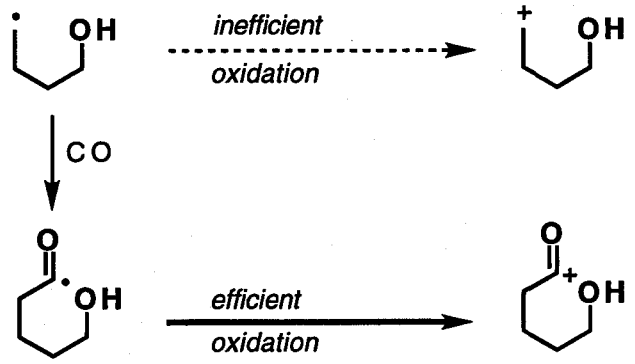
from alcohols having δ-methyl carbons are generally good. Since the carbonylation at δ-methyl carbon were very sluggish, the reactions were conducted at 60 °C. As has been discussed, the carbonylation of alcohols having δ-methyl carbon is essentially "THF free system" (Scheme 5). Therefore, inefficient oxidation of the primary radicals to primary cations may permit more efficient CO trapping of the primary radicals even at 60 °C.

Table 6. Carbonylation of Alcohols at δ-Methyl Carbons

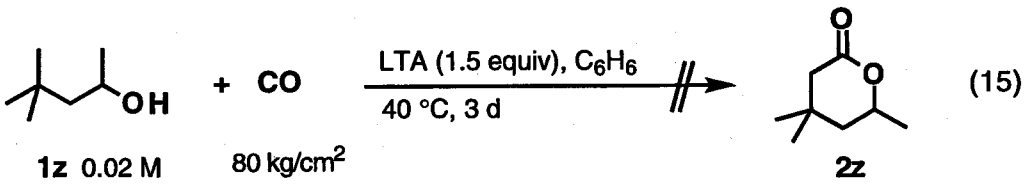
run	ROH	time, day	product	isolated yield, %
1	 1t	2	 2t	32
2	 1u	3	 2u	22
3	 1v	3	 2v	61 cis/trans = 56/44[a]
4	 1w	4	 2w	47 cis/trans = 55/45[a]
5	 1x	3	 2x	44
6	 1y	5	 2y	42

Conditions: ROH (0.4-0.8 mmol), LTA (1.5-2equiv), C_6H_6 (20 mL), CO (80 kg/cm^2), 60 °C. [a]Determined by ^{1}H-NMR.

Scheme 5



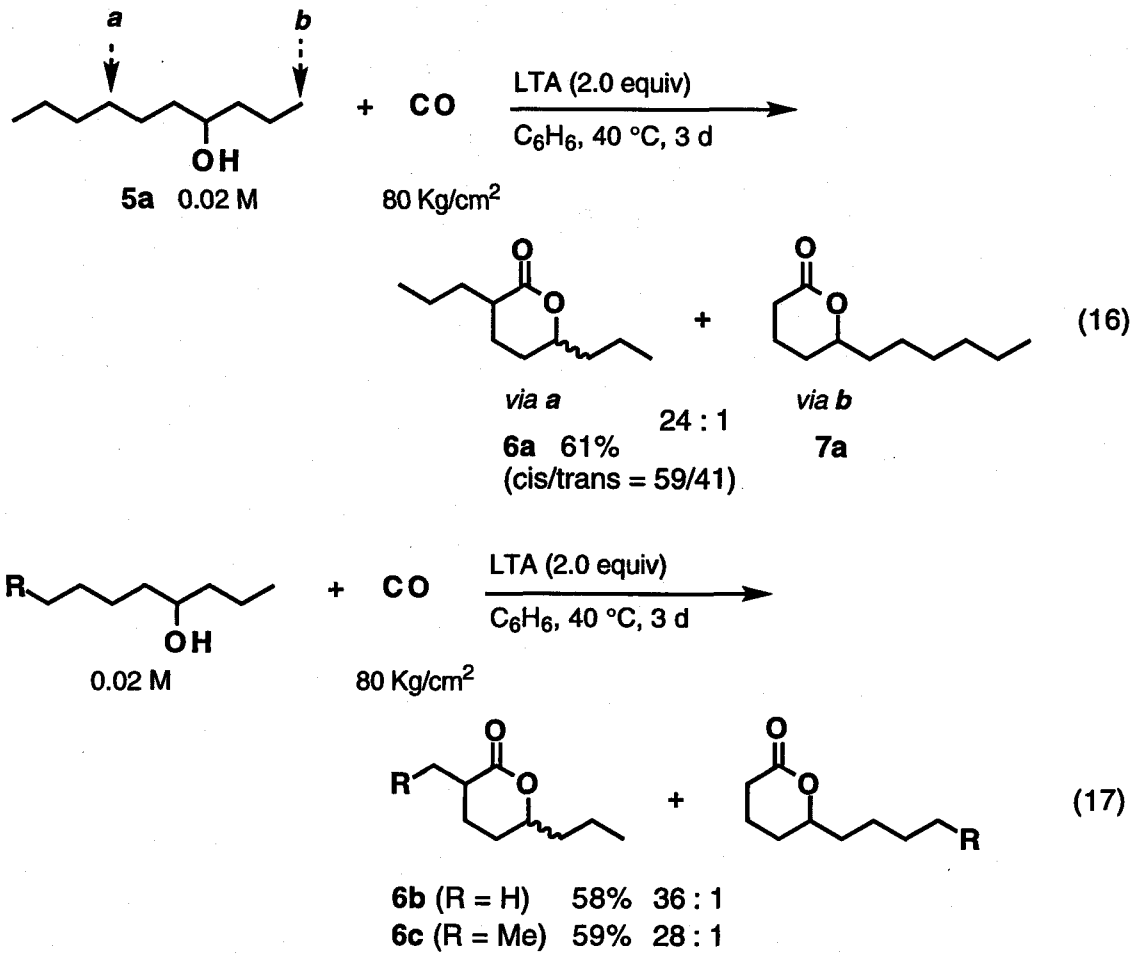
On the other hand, the steric factor seems important. When quaternary carbon is adjacent to δ-carbon, carbonylation was unsuccessful (eq 15).



3-1-2-3. Carbonylation of Alcohols Having both δ-Methylene and δ-Methyl Carbons

With regard to the substrate **5a** having both δ-methylene and δ-methyl carbons, *a* and *b*, the regiochemistry was satisfactory, allowing highly selective CO incorporation at *methylene* carbon *a* (eq 16). Thus, 2-propyl-5-octanolide (**6a**) was formed predominantly over 5-undecanolide (**7a**) in the ratio of 24:1. Purification of **6a** to eliminate the minor product **7a** was easy to carry out by flash chromatography on silica gel. The preferential formation of **6a** seems reasonable in light of the weaker C-H bond strength of methylene relative to that of methyl (ΔE = ca. 3 kcal/mol).[27] Efficiency of 1,5-hydrogen-transfer correlates well with the C-H bond dissociation

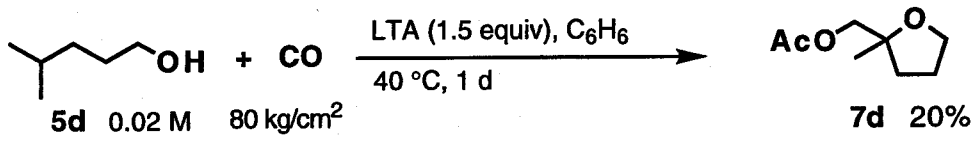
energy (BDE). Similar results were obtained in the case of 4-octanol and 4-nonanol (eq 17).



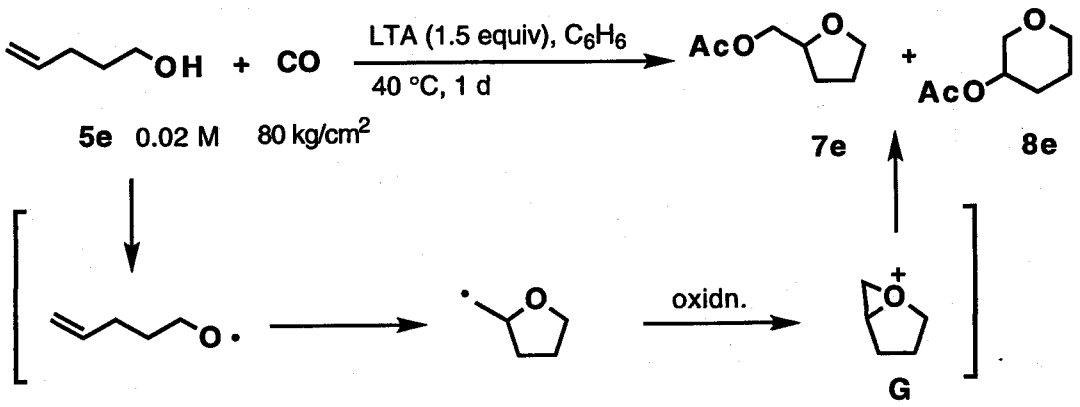
3-1-2-4. Attempted Carbonylation of Alcohols at δ-Methine Carbons

In contrast to the successful carbonylation of alcohols having δ-methylene and δ-methyl carbon, alcohols having δ-methine carbon, such as **5d** did not undergo carbonylation. A major isolable product was acetoxy tetrahydrofuran **7d** (20%) and starting alcohol was also detected (33%) (eq 18). Both rapid oxidation of the generated tertiary radical to lead to an olefin[28] and rapid decarbonylation of the tertiary acyl radical[15], may prevent smooth CO trapping reaction. Further oxidation of the resultant alkenyl alcohol may give THF **7d** as the product.[29] The primary radical generated

from cyclization of alkoxy radical onto internal C=C, was not carbonylated but was readily oxidized to yield acetoxylated product. The reaction of an unsaturated alcohol, 4-pentenol (**5e**), with LTA may be such a case (eq 19). Subjection of **5e** to the LTA/CO condition gave ca. 1:1 mixture of **7e** and **8e** without the formation of carbonylated product.[30] It seems probable that stabilization of three-membered cation **G** contribute to this facile oxidation of primary radical β to oxygen. However, an alternative mechanism for the reaction of unsaturated alcohol with LTA don't involve alkoxy radical is also proposed.[31]



(18)



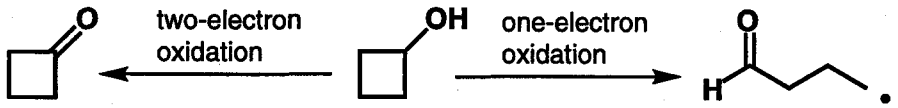
(19)

3-2. Carbonylation of Cyclobutanols

3-2-1. Introduction

About two decades ago, Roček reported that cyclobutanol reacts with two-electron oxidant to yield cyclobutanone via C–H bond cleavage, and with one-electron oxidant to yield γ-formylalkyl radical via C–C bond cleavage (eq 20).[32] The main products in

the latter system involve 4-ligand-substituted butanal and 1,8-octanedial. With a few exceptions, the synthetic application of this oxidative β-scission process is scarce.[33] On the other hand, the synthetic potential of the β-scission reaction of cyclobutoxy radicals for ring-expansion processes has garnered recent attention. To generate cyclobutoxy radicals, a variety of methods have been employed, which include addition of carbon-[34] oxygen-[35] or nitrogen-centered radical[36] to carbonyl group, photolysis of hypoiodite,[37] and addition of tin or thiyl radical to vinyl oxaspirohexane.[38]

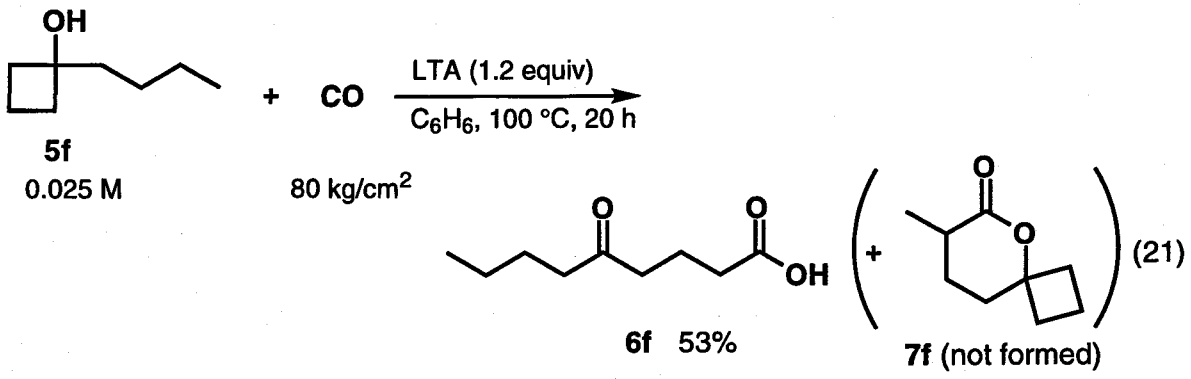


(20)

Thus far the synthesis of δ-lactones from saturated alcohols and CO which utilizes LTA induced oxidation system was described. This new type of carbonylation relies upon 1,5-hydrogen transfer from C to O• as a key. In this section, carbonylation of cyclobutanols accompanied with β-scission, which is also effected by the LTA induced oxidation system,[39] is described.[40]

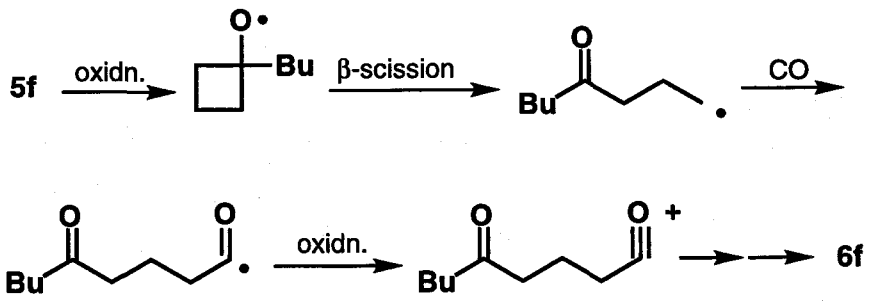
3-2-2. Results and Discussion

At the outset, the carbonylation of 1-butylcyclobutanol (**5f**), having a δ-methylene carbon, was examined. In a stainless steel autoclave, a mixture of **5f** (128 mg, 1 mmol) and LTA (593 mg, 1.2 mmol) were stirred in benzene (40 mL) under CO pressure (80 kg/cm^2) at 100 °C ([**5f**] = 0.025 M). After 20 h, the reaction mixture was filtered and the filtrate was treated with 2N NaOH (20 mL x 3). The alkaline solution was neutralized with conc. HCl (12 N, 30 mL) and was extracted with CH_2Cl_2 (20 mL x 3). The combined extracts were dried with $CaCl_2$ and were evaporated to give essentially pure 5-oxononanoic acid (**6f**) (91 mg, 53% yield) (eq 21).

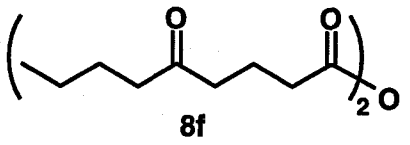


Cyclobutanol **5f** did not give spiro-type δ-lactone **7f** at all, a product via 1,5-hydrogen transfer from C to O,[5] suggesting that β-scission reaction of cyclobutoxy radical from **5f** was faster than 1,5-hydrogen-transfer reaction.[41,42] As summarized in Scheme 6, 5-oxoacid would be formed by CO-trapping of a δ-oxoalkyl radical and the subsequent oxidation of the resulting acyl radical to lead to an acyl cation.

Scheme 6

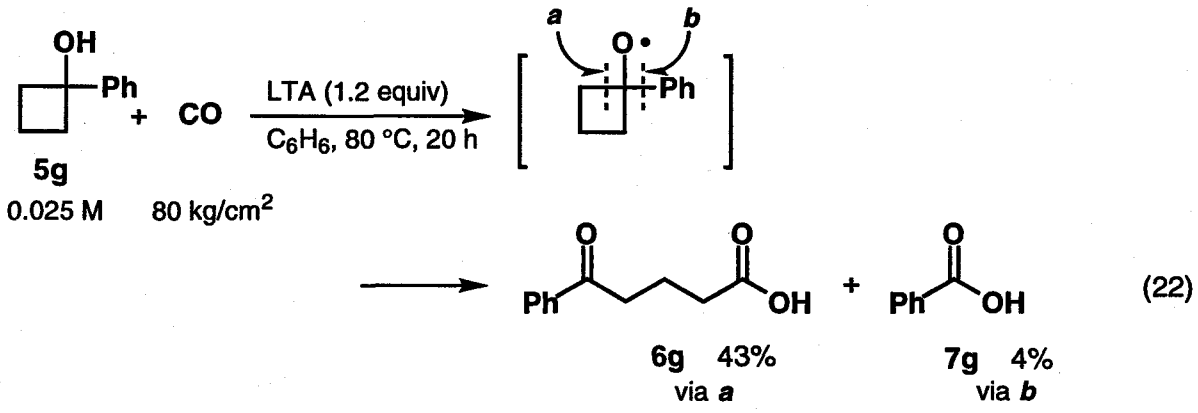


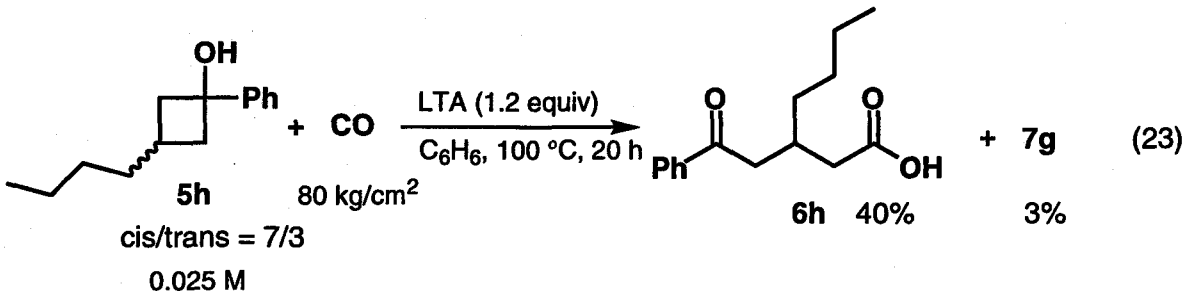
It has already been well established that carboxylic acids undergo decarboxylation in the presence of LTA to give alkyl radicals, which are further oxidized to alkenes and acetates.[43] In this regard, the formation of carboxylic acid **6f** in the present LTA/CO system may deserve comments. The ^{1}H- and ^{13}C-NMR analysis of the crude product from **5f** prior to the aqueous treatment, indicated that anhydride **8f** was formed as a major product.[44] Thus **6f** may be formed from initially formed **8f** by acid hydrolysis at the stage of aqueous workup.



8f

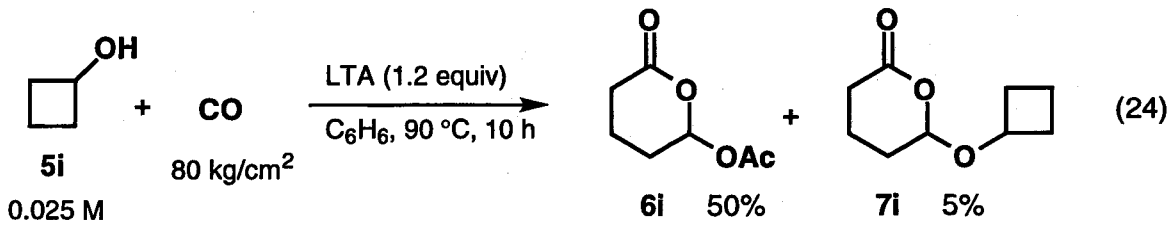
Under the similar conditions, the reaction of 1-phenylcyclobutanol (**5g**) with CO in the presence of LTA afforded 4-benzoylbutyric acid (**6g**) in 43% yield (eq 22). Interestingly, a small amount of benzoic acid (**7g**) was also formed, suggesting that not only β-scission at *a* but also at *b* to form phenyl radical being competitive to some extent.[45] Similarly, cyclobutanol **5h** was carbonylated to give 5-oxoacid **6h** (40%) (eq 23).



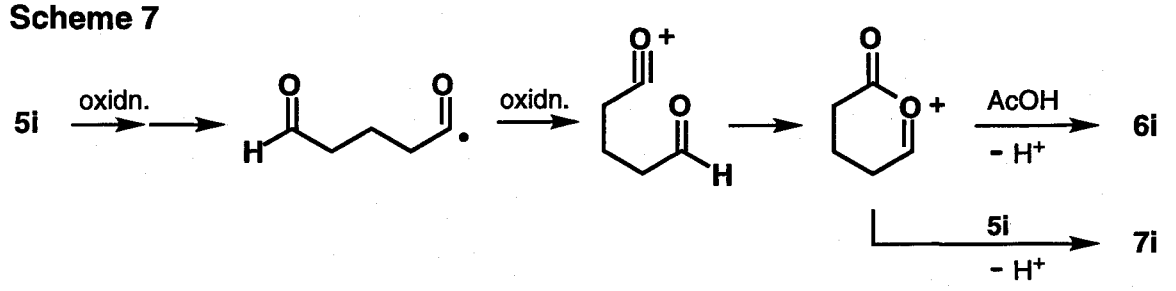


Next, carbonylation of secondary cyclobutanols was examined. When carbonylation of simple cyclobutanol (**5i**) was carried out under similar conditions ([**5i**] = 0.025 M in benzene, LTA (1.2 equiv), CO (80 kg/cm^2), at 90 °C, 10 h), the formation of 5-oxoacid (and/or its anhydride) was suppressed, and instead a mixture of δ-lactones **6i** and **7i** was obtained as main carbonylated products. These two products were separated by flash chromatography on silica gel (eq 24).[46,47] These δ-lactones

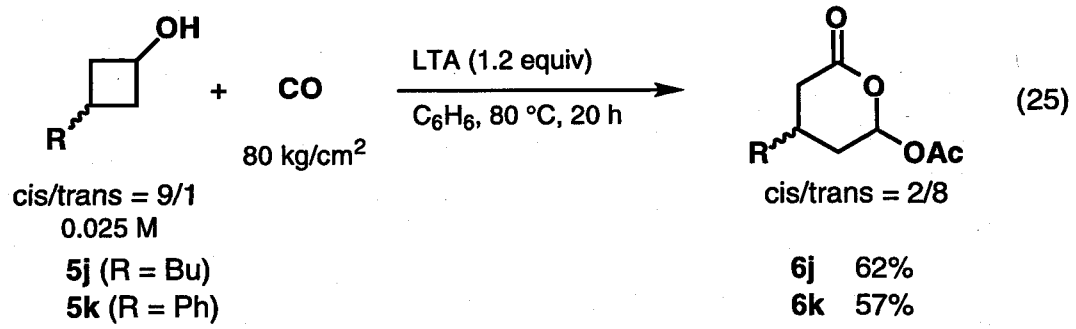
presumably resulted from intramolecular electrophilic attack of acyl cation at formyl oxygen, followed by either of acetoxylation and alkoxylation, respectively (Scheme 7).



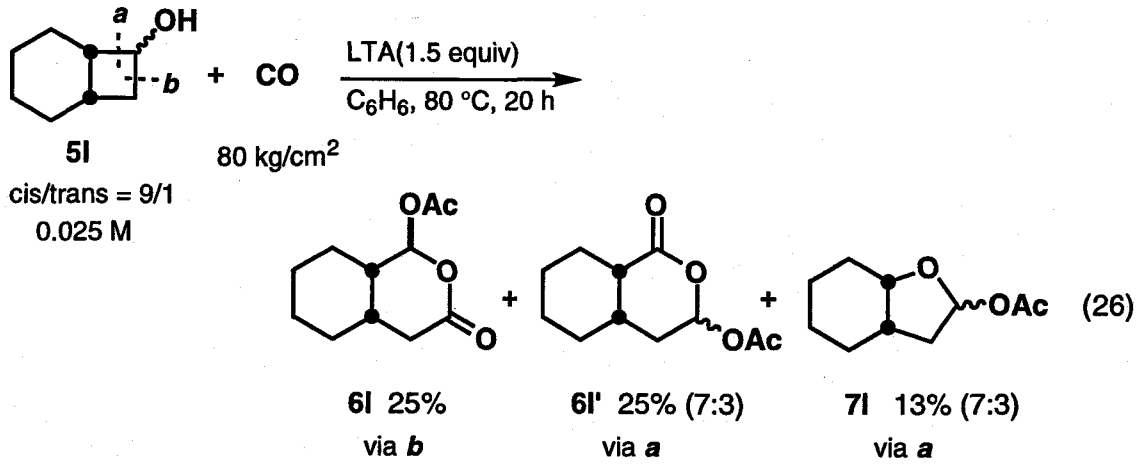
Scheme 7



Similarly, 3-substituted cyclobutanols **5j** and **5k** underwent carbonylation and cyclization to afford the corresponding δ-lactones **6j** (62%) and **6k** (57%), respectively (eq 25).[48]



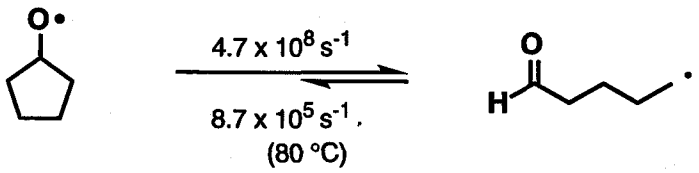
Carbonylation of **5l** which has both secondary and tertiary β and β'-carbons was also examined. The ring cleavage lacked regioselectivity, thereby giving a mixture of δ-lactones **6l** and **6l'** by way of *b* and *a* cleavages, respectively (eq 26).

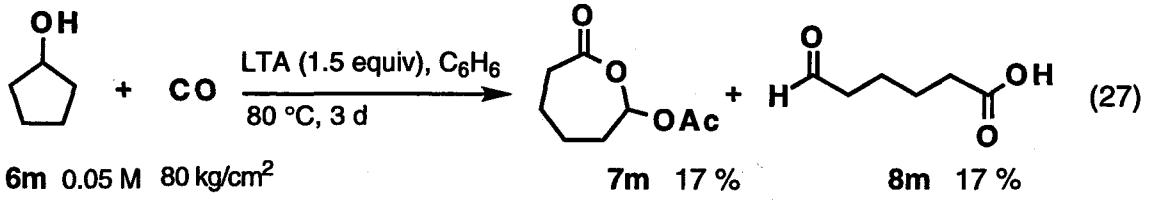


(26)

Unlike four-membered alkoxy radicals, β-scission of five- and six-membered cyclic alkoxy radicals is well-known to be a reversible process. The rate constants for each steps were estimated by Beckwith and Hay (Scheme 8).[21] Albeit modest efficiency, cyclopentanol **6m** underwent β-scission and subsequent carbonylation to give a mixture of ε-lactone **7m** and keto acid **8m** (eq 27).[49,50]

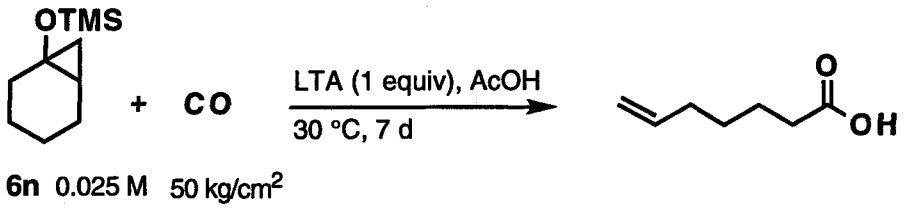
Scheme 8





(27)

The reaction of cyclopropyl silyl ether **6n** in the presence of CO was also examined, but no carbonylation took place and the result was nearly same as that in the absence of CO (eq 28).[51,52]



(28)

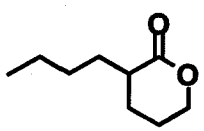
3-3. Experimental

General Melting points were measured on a Yanagimoto HP-S2 and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded on a JEOL JNM-GX67S (270 MHz, 68 MHz) spectrometer and a Bruker AM-600 (600 MHz) spectrometer. Chemical shifts are reported in parts per million (δ) down field from internal TMS (0.00 ppm). DEPT and ^{13}C-^{1}H COSY spectra were recorded on a JEOL JNM-GX67S and a Bruker AM-600 spectrometer. Irradiation and nOe experiments were recorded on a Bruker AM-600 spectrometer. Infrared spectra were recorded on a Perkin Elmer 1610 FT-IR spectrometer. Both conventional and high resolution mass spectra were recorded on a JEOL JMS-DX303HF spectrometer. Flash chromatography was performed with use of silica gel (Fuji Silysia Chemical, Ltd. BW-820MH, 70-200 mesh) and C_6, then mixtures of C_6 - EtOAc as an eluent. Preparative HPLC was performed on LC-908 (Japan Analytical Industry, Ltd.) equipped with GPC columns (JAIGEL 1H and 2H) using $CHCl_3$ as an eluent. Gas chromatography was carried out on a Shimazu GC-14A using a capillary column CBP1-M25-025 (0.2 mm x 25 m), a capillary column Supelco SPB5 (0.2 mm x 30 m), and a Chiraldex G-TA (0.25 mm x 20 m). Alcohols, **1g**, **1o**, and **1q**, were prepared by the hydrogenation with 5% Rh/C (in THF, 5% Rh based on ROH) from the corresponding aromatic alcohols, 2-phenyl-1-propanol, 1-phenyl-2-propanol, and *trans*-2-phenyl-1-cyclohexanol, respectively. Cyclobutanols, **5h**, **5j**, **5k**, and **5l**, were prepared by literature methods, see: (a) Krepski, L. R.; Hassner, A. *J. Org. Chem.* **1978**, *43*, 2879. (b) Grieco, P. A. *J. Org. Chem.* **1972**, *37*, 2363. Other alcohols

were obtained from commercial sources and were used as they were. LTA (90 % purity, wet with acetic acid) was obtained from Wako Pure Chemical Industries, Ltd. and was used as it is. C_6H_6 was distilled from CaH_2. Unless otherwise noted in the following chapters, spectroscopic data were recorded with the same apparatus and similar methods described in this chapter.

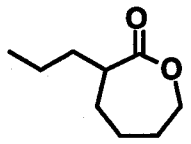
Typical Procedure for Synthesis of δ-Lactone: A mixture of 1-octanol (**1a**) (105 mg, 0.8 mmol), LTA (593 mg, 1.2 mmol) and benzene (40 mL) were placed in a 100-mL stainless steel autoclave lined with a round bottomed glass tube. The autoclave was then pressurized with 80 kg/cm^2 of CO and was heated, with stirring, at 40 °C. After one day, excess CO was purged at room temperature, then the reaction mixture was poured into 0.4 N aqueous hydrogen chloride. The aqueous layer was extracted with ether (3 x 20 mL) and the combined ether extracts were dried ($MgSO_4$), then filtered, and concentrated. The residue was purified by flash chromatography on silica gel (C_6, then 20 % AcOEt-C_6 eluent) to give 2-butyl-5-pentanolide (**2a**) (64 mg, 51 % yield) as a slightly yellow liquid.

2-Butyl-5-pentanolide (2a).



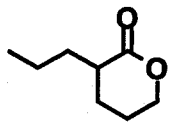
a slightly yellow liquid.; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 0.91 (t, 3H, *J* = 6.8 Hz, CH_3), 1.25 - 1.61 (m, 6H), 1.84 - 1.90 (m, 3H), 2.00 - 2.16 (m, 1H), 2.34 - 2.51 (m, 1H, α-C*H*), 4.25 - 4.32 (td-like, 2H, *J* ~ 5.9, 2.0 Hz, δ-CH_2); ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 13.86 (q, CH_3), 21.95 (t), 22.56 (t), 24.54 (t), 28.95 (t), 30.89 (t), 39.50 (d, α-CH), 68.26 (t, δ-CH_2), 174.68 (s, C=O); IR(neat) 1732 cm^{-1}(ν_{CO}); EIMS (relative intensity) m/z 157 (M^++1, 2), 127 (2), 113 (26), 100 (100), 85 (4), 73 (5), 55 (20), 41 (14); HREIMS calcd for $C_9H_{16}O_2$ m/z 156.1150, found, 156.1155. This compound is already known and the properties (^{1}H-NMR and IR) were consistent with those previously reported, see: Paterson, I. *Tetrahedron* **1988**, *44*, 4207.

2-Propyl-6-hexanolide (4a).



a slightly yellow liquid; ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 14.06, 20.50, 28.33, 28.82, 30.05, 34.75, 42.57, 68.20, 177.60; IR(neat) 1735 cm^{-1}(ν_{CO}); EIMS (relative intensity) m/z 156 (M^+, 2), 127 (22), 114 (100), 101 (14), 84 (31), 73 (26), 55 (30), 41 (17); HREIMS calcd for $C_9H_{16}O_2$ m/z 156.1150, found, 156.1161.

2-Propyl-5-pentanolide (2b).



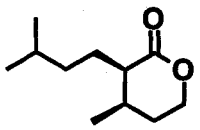
a slightly yellow liquid; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 0.91 (t, 3H, *J* = 7.1 Hz), 1.33 - 1.61 (m, 4H), 1.87 - 1.95 (m, 3H), 2.04 - 2.16 (m, 1H), 2.44 - 2.50 (m, 1H, α-CH), 4.30 (td, 2H, *J* = 2.0, 5.9 Hz, δ-CH); ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 13.91 (q, CH_3), 19.96 (t), 21.95 (t), 24.53 (t), 33.32 (t), 39.27 (d, α-CH), 68.28 (t, δ-CH), 174.68 (s, CO); IR(neat) 1734 cm^{-1}(ν_{CO}); EIMS (relative intensity) m/z 143 (M^++1, 1), 113 (20), 100 (100), 95 (5), 84 (5), 73 (4), 69 (5), 55 (23), 41 (15); HREIMS calcd for $C_8H_{14}O_2$ m/z 142.0993, found, 142.1018. This compound is already known, see: Kurata, K.; Tanaka, S.; Takahashi, K. *Chem. Pharm. Bull.* **1976**, *24*, 538.

2-(3'-Methylbutyl)-3-methyl-5-pentanolide (2c).

A mixture of 3,7-dimethyl-1-octanol (**1c**) (64 mg, 0.4 mmol), LTA (295 mg, 0.6 mmol) and benzene (20 mL) were placed in a 50-mL stainless steel autoclave lined with a round bottomed glass tube. The autoclave was then pressurized with 80 kg/cm^2 of CO and was heated, with stirring, at 40 °C. After three day, excess CO was purged at room temperature, then the reaction mixture was poured into 0.4 N aqueous hydrogen chloride. The aqueous layer was extracted with ether (3 x 20 mL) and the combined ether extracts were dried ($MgSO_4$), then filtered, and concentrated. The residue was purified by flash chromatography on silica gel (C_6, then 20 % AcOEt-C_6 eluent) to give 2-(3'-methylbutyl)-3-methyl-5-pentanolide (**2c**) (34 mg, 46 % yield). GC analysis

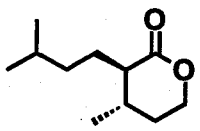
indicated the presence of two isomers in a ratio of 46/54. Preparative HPLC allowed separation of *cis/trans* mixtures of **2c**.

[*cis*-**2c**] a yellow liquid; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 0.90 (d, 3H, J = 6.4 Hz), 0.91



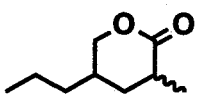
(d, 3H, J = 6.8 Hz), 0.94 (d, 3H, J = 7.3 Hz), 1.12 - 1.47 (m, 3H), 1.50 - 1.75 (m, 2H), 1.80 - 1.96 (m, 1H), 2.08 - 2.20 (m, 1H), 2.28 - 2.42 (m, 1H), 2.44 - 2.52 (q-like, 1H, J = 6.4 Hz), 4.20 - 4.39 (m, 2H); ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 16.91 (q), 22.34 (q), 22.65 (q), 24.60 (t), 27.68 (d), 28.10 (d), 30.30 (t), 36.40 (t), 44.23 (d), 65.78 (t), 174.77 (s); IR(neat) 1744 cm^{-1}(ν_{CO}); EIMS (relative intensity) m/z 184 (M^+, 1), 169 (6), 141 (10), 127 (25), 114 (100), 99 (72), 55 (17), 41 (13); HREIMS calcd for $C_{11}H_{20}O_2$ m/z 184.1458, found, 184.1485.

[*trans*-**2c**] a yellow liquid; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 0.90 (d, 3H, J = 6.8 Hz),



0.90 (d, 3H, J = 6.8 Hz), 1.09 (d, 3H, J = 6.4 Hz), 1.14 - 1.37 (m, 2H), 1.43 - 1.98 (complex m, 6H), 2.10 - 2.17 (m, 1H), 4.19 - 4.39 (m, 2H); ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 20.63 (q), 22.33 (q), 22.57 (q), 27.64 (t), 28.23 (d), 30.29 (d), 30.89 (t), 35.68 (t), 48.09 (d), 67.22 (t), 173.97 (s); IR(neat) 1736 cm^{-1}(ν_{CO}); EIMS (relative intensity) m/z 184 (M^+, 1), 169 (7), 141 (10), 127 (23), 114 (100), 99 (78), 55 (15), 41 (12); HREIMS calcd for $C_{11}H_{20}O_2$ m/z 184.1458, found, 184.1478.

***cis*- and *trans*- 2-Methyl-4-propyl-5-pentanolide (2d).** ^{1}H-NMR analysis indicated

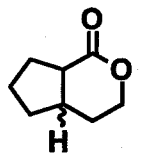


the presence of two isomers in a ratio of 50/50.

a colorless liquid; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 0.93 (t, 3 H, J = 6.8 Hz), 1.23 (d, 1.5 H, J = 6.8 Hz), 1.27 (d, 1.5 H, J = 6.8 Hz), 1.15 - 1.42 (m, H), 1.61 - 1.82 (m, H), 1.95 - 2.17 (m, 1 H), 3.93 (dd, 0.5 H, J = 10.7, 3.9 Hz), 3.97 (dd, 0.5 H, J = 9.8, 2.5 Hz), 4.26 (dd, 0.5 H, J = 10.7, 4.9 Hz), 4.34 (dd, 0.5 H, J = 10.7, 4.9, 2.0 Hz); ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 13.99 (q), 16.54 (q), 16.87 (q), 19.76 (t), 19.96 (t), 31.67 (d), 32.20 (d), 32.96 (t), 33.21 (d), 34.11 (t), 34.60 (t), 34.74 (t), 35.15 (d), 71.82 (t), 73.43 (t), 174.85 (s), 175.97 (s); IR(neat) 1740 cm^{-1}(ν_{CO}); EIMS (relative

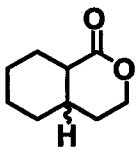
intensity) for 1st elution with GC, m/z 156 (M^+, 11), 84 (70), 70 (66), 56 (100), 41 (45); EIMS (relative intensity) for 2nd elution with GC, m/z 156 (M^+, 14), 84 (68), 70 (67), 56 (100), 41 (49).

***cis*- and *trans*- 2,3-Trimethylene-5-pentanolide (2e).** ^{1}H-NMR analysis indicated the presence of two isomers in a ratio of 77/23.



a colorless liquid; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 1.20 - 2.30 (m, cis 8H and trans 10H), 2.49 (m, 1H, cis), 2.89 (td-like, 1H, J ~ 8.4, 9.9 Hz, α-CH of cis), 4.20 (td-like, 1H, cis, J ~ 10.5, 2.5 Hz), 4.28 - 4.42 (m, 3H, δ-CH_2 cis 1H and trans 2H); ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 22.07 (t, cis), 23.39 (t, cis), 25.13 (t, trans), 28.07 (t, cis), 29.17 (t, trans), 29.83 (t, trans), 31.62 (t, cis), 33.61 (t, trans), 36.31 (d, trans), 40.19 (d, cis), 42.88 (d, trans), 47.46 (d, cis), 67.37 (t, cis, δ-CH_2), 68.57 (t, trans, δ-CH_2), 174.75 (s, trans, C=O), 175.14 (s, cis, C=O); IR(neat) 1736 cm^{-1}(ν_{CO}); EIMS (relative intensity) m/z 140 (M^+, 39), 112 (29), 95 (26), 82 (27), 67 (100), 55 (24); HREIMS calcd for $C_8H_{12}O_2$ m/z 140.0837, found, 140.0838.

***cis*- and *trans*- Octahydro-1*H*-2-benzopyran-1-one (2f).** ^{1}H-NMR analysis indicated the presence of two isomers in a ratio of 44/56.



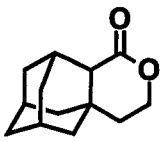
a colorless liquid; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 1.05 - 2.30 (m, cis 11H and trans 12H), 2.72 (t-like, J = 4.9 Hz, α-CH of cis), 4.22 - 4.42 (m, cis 2H and trans 2H, δ-CH_2); ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 22.39 (t, cis), 24.50 (t, cis), 25.26 (t, trans), 25.66 (t, cis or trans), 25.72 (t, cis or trans), 26.68 (t, trans), 28.15 (t, cis), 29.59 (t, trans), 31.15 (t, cis), 31.82 (d, cis, β-CH), 33.45 (t, trans), 36.25 (d, trans, β-CH), 40.10 (d, cis, α-CH), 45.14 (d, trans, α-CH), 66.59 (t, cis, δ-CH_2), 67.71 (t, trans, δ-CH_2), 173.71 (s, trans, C=O), 174.27 (s, cis, C=O); IR(neat) 1737 cm^{-1}(ν_{CO}); EIMS (relative intensity) m/z 154 (M^+, 77), 126 (33), 99 (91), 81 (84), 67 (100), 54 (30), 41 (29); HREIMS calcd for $C_9H_{14}O_2$ m/z 154.0994, found, 154.0990. This compound is already known and *cis*/*trans* assignments of ^{13}C-NMR

were made in comparison with the previously reported data, see: Fujiwara, Y.; Okamoto, M. *Chem. Pharm. Bull.* **1989**, *37*, 1458.

4-Methyloctahydro-1*H*-2-benzopyran-1-one (2g). GC analysis (Supelco SPB-5) indicated the presence of four isomers in a ratio of 6/10/3/3. The major isomer was isolated in pure form by preparative HPLC (30 times recycle). [major isomer] a slightly yellow liquid; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 0.97 (d, 3 H, J = 6.4 Hz), 1.03 (m, 1 H), 1.13 - 1.33 (m, 4 H), 1.70 - 1.87 (m, 3 H), 1.96 - 2.06 (m, 2 H), 2.24 - 2.31 (m, 1 H), 3.89 (dd, 1 H, J = 11.4, 8.4 Hz), 4.32 (dd, 1 H, J = 11.4, 5.4 Hz); ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 15.45 (q), 25.33 (t), 25.59 (t), 27.05 (t), 30.89 (t), 34.13 (d), 43.17 (d), 44.62 (d), 73.46 (t), 173.81 (s); IR(neat) 1728 cm^{-1}(ν_{CO}); EIMS (relative intensity) m/z 168 (M^+, 100), 138 (36), 126 (62), 109 (35), 95 (68), 81 (90), 67 (86); HREIMS calcd for $C_{10}H_{16}O_2$ m/z 168.1150, found, 168.1155. [partial data for other three isomers] 1st eluted isomer with GC: ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 1.01 (d, 3 H, J = 6.8 Hz), 3.87 (t-like, 1 H, J ~ 11.0 Hz), 4.22 (dd, 1 H, J = 11.7, 5.9 Hz); ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 16.17 (q), 22.39 (t), 24.70 (t), 25.46 (t), 31.47 (t), 33.83 (d), 38.01 (d), 39.93 (d), 71.99 (t), 174.79 (s); EIMS (relative intensity) m/z 168 (M^+, 14), 153 (5), 139 (5), 126 (19), 113 (100), 108 (12), 95 (16), 81 (35), 67 (30); HREIMS calcd for $C_{10}H_{16}O_2$ m/z 168.1150, found, 168.1160. 3rd eluted isomer with GC: ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 0.94 (d, 3 H, J = 6.8 Hz), 4.07 (t-like, 1 H, J ~ 11.8 Hz), 4.26 (dd, 1 H, J = 11.3, 6.4 Hz); ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 13.45 (q), 22.62 (t), 22.94 (t), 25.32 (t), 27.20 (t), 32.72 (d), 38.59 (d), 43.35 (d), 71.90 (t), 172.94 (s); EIMS (relative intensity) m/z 168 (M^+, 50), 153 (5), 139 (15), 126 (81), 113 (100), 108 (34), 95 (30), 81 (81), 67 (62); HREIMS calcd for $C_{10}H_{16}O_2$ m/z 168.1150, found, 168.1157. 4th eluted isomer with GC: ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 1.03 (d, 3 H, J = 7.4 Hz), 4.08 (dd, 1 H, J = 10.9, 4.0 Hz), 4.36 (dd, 1 H, J = 10.9, 4.5 Hz); ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 11.28 (q), 25.59 (t), 25.92 (t), 27.43 (t), 29.72 (t), 30.98 (d), 40.02 (d), 40.79 (d), 74.71 (t), 173.54 (s); EIMS (relative intensity) m/z

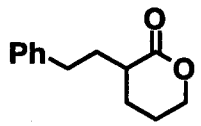
168 (M^+, 72), 138 (30), 126 (45), 109 (47), 95 (42), 81 (100), 67 (19); HREIMS calcd for $C_{10}H_{16}O_2$ m/z 168.1150, found, 168.1153.

Adamantano [2, 1-c] tetrahydro-2*H*-pyran-2-one (2h).



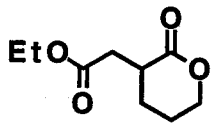
a colorless liquid; ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 1.50 (ddd, 1H, *J* = 2.2, 5.0, 12.8 Hz), 1.55 (dt, 1H, *J* = 5.2, 14.0 Hz), 1.58 - 1.80 (m, 8H), 1.83 (d of quintet-like, 1H, *J* = 13.1(d), 2.6 Hz), 1.90 (dddd, 1H, *J* = 12.7, 0.7, 5.2, 3.1 Hz), 1.99 (quintet-like, 1H, *J* ~ 3.0 Hz), 2.01 (quintet-like, 1H, *J* ~ 3.0 Hz), 2.40 (br s, 1H, α-CH), 2.49 (q-like, 1H, *J* ~ 2.8 Hz), 4.33 (ddd, 1H, *J* = 5.3, 6.2, 11.7 Hz, δ-C*H*H), 4.42 (ddd, 1H, *J* = 5.3, 9.3, 11.7 Hz, δ-C*H*H); ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 27.73 (d), 27.92 (d), 28.06 (d), 31.55 (s), 32.15 (t), 36.33 (t), 36.37 (t), 37.62 (t), 39.30 (t), 44.84 (t), 50.76 (d, α-*C*H), 65.52 (t, δ-CH_2), 173.03 (s, C=O); IR(neat) 1736 cm^{-1}(ν_{CO}); EIMS (relative intensity) m/z 206 (M^+, 100), 178 (5), 163 (6), 149 (11), 138 (9), 119 (8), 105 (8), 100 (4), 91 (15), 79 (12), 67 (3); HREIMS calcd for $C_{13}H_{18}O_2$ m/z 206.1307, found, 206.1291.

2-(2'-Phenylethyl)-5-pentanolide (2i).



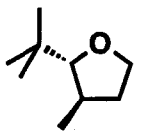
a colorless liquid; ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 1.59 (m, 1H), 1.77 (d of quintet-like, 1H, *J* = 9.0 (d), 6.9 Hz), 1.88 (m, 1H), 1.92 (sextet-like, 1H, *J* ~ 6.8 Hz), 2.13 (sextet-like, 1H, *J* ~ 6.8 Hz), 2.26 (d of quintet-like, 1H, *J* = 9.3 (d), 6.8 Hz), 2.44 (ddt, 1H, *J* = 5.9, 11.0, 7.4 Hz, α-CH), 2.73 (t, 2H, *J* = 7.3 Hz, CH_2Ph), 4.28 (t, 2H, *J* = 5.9 Hz, δ-CH_2O), 7.15 - 7.31 (m, 5H, ArH); ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 21.90 (t), 24.67 (t), 32.77 (t), 32.86 (t), 38.57 (d, α-*C*H), 68.08 (t, δ-CH_2), 125.93 (d, para), 128.34 (d, superimposed, ortho and meta), 141.31 (s, ipso), 174.36 (s, C=O); IR(neat) 1736 cm^{-1}(ν_{CO}); EIMS (relative intensity) m/z 204 (M^+, 7), 129 (2), 115 (4), 100 (100), 91 (16), 73 (3), 65 (5), 55 (7); HREIMS calcd for $C_{13}H_{16}O_2$ m/z 204.1150, found, 204.1156.

2-(Ethoxycarbonylmethyl)-5-pentanolide (2j).



a colorless liquid; ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 1.27 (t, 3H, J = 7.1 Hz, CH_3), 1.68 (m, 1H, β-C*H*H), 1.94 (quintet-like, 2H, J ~ 6.5 Hz, γ-CH_2), 2.14 (m, 1H, β-C*H*H), 2.61 (dd, 1H, J = 6.7, 17.0 Hz, C*H*HCO), 2.81 (dd, 1H, J = 5.3, 17.0 Hz, CH*H*CO), 2.88 - 2.99 (m, 1H, α-CHCO), 4.16 (q, 2H, J = 7.1 Hz, CH_2O of ester), 4.37 (9 line m, 2H, CH_2O of lactone) Irradiation at 1.94 ppm causes collapse of this multiplet to uneven two doublets (higher field: sharp doublet, lower field: broad doublet), and irradiation at 2.14 ppm causes collapse of this multiplet to two dt.; ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 14.05 (q, CH_3), 22.19 (t, γ-CH_2), 24.76 (t, β-CH_2), 35.73 (t, CH_2CO), 36.33 (d, CH, α-CHCO), 60.68 (t, CH_2O of ester), 68.51 (t, CH_2O of lactone), 171.54 (s), 173.34 (s) ^{13}C-^{1}H COSY NMR was also examined to assign each peak.; IR(neat) 1732 cm^{-1}(ν_{CO}); EIMS (relative intensity) m/z 186 (M^+, 4), 159 (2), 141 (100), 128 (13), 113 (28), 99 (47), 71 (16), 55 (19), 41 (16); HREIMS calcd for $C_9H_{14}O_4$ m/z 186.0888, found, 186.0873.

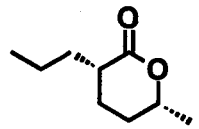
***trans*-2-*t*-Butyl-3-methyl-tetrahydrofuran (3k).**



a slightly yellow liquid; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 0.89 (s, 9 H, *t*-Bu), 1.06 (d, 3 H, J = 6.8 Hz), 1.50 (m, 1 H, CH_3CH), 2.05 (m, 2 H, CH_2CH_2O), 3.14 (d, 1 H, J = 5.4 Hz, CHO), 3.76 (m, 2 H, CH_2O); ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 20.82 (q, CH_3CH), 25.95 (q, $(CH_3)_3C$), 33.64 (t, OCH_2CH_2), 34.37 (s, $(CH_3)_3C$), 35.80 (d, $CHCH_3$), 67.28 (t, OCH_2CH_2), 94.27 (d, OCHC); IR(neat) 1464, 1364 cm^{-1}; EIMS (relative intensity) m/z 142 (M^+, 1), 127 (5), 85 (100), 69 (4), 57 (20); HREIMS calcd for $C_9H_{18}O$ m/z 142.1358, found, 142.1366.

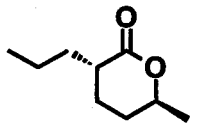
2-Propyl-5-hexanolide (2l). GC analysis indicated the presence of two isomers in a ratio of 55/45. The *cis/trans* isomers of **2l** were separated by preparative HPLC.

[*cis*-**2l**] a colorless liquid; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 0.93 (t, 3H, J = 7.1 Hz, CH_3



of 2-propyl), 1.35 (d, 3H, J = 5.9 Hz, CH_3 of 5-methyl), 1.39 - 1.68 (m, 5H), 1.75 - 2.09 (m, 3H), 2.37 - 2.52 (m, 1H, α-CH), 4.38 - 4.53 (m, 1H, δ-CH); ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 13.91 (q, CH_3CH), 20.08 (t), 21.00 (q, CH_3CH_2), 23.26 (t), 28.33 (t), 32.89 (t), 37.67 (d, α-*C*H), 74.22 (d, δ-CHO), 175.62 (s, C=O); IR(neat) 1736 cm^{-1}(ν_{CO}); EIMS (relative intensity) m/z 157 (M^++1, 2), 141 (2), 127 (10), 114 (100), 95 (7), 84 (26), 73 (46), 55 (38), 42 (22); HREIMS calcd for $C_9H_{16}O_2$ m/z 156.1150, found, 156.1136.

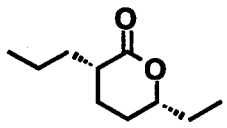
[*trans*-**2l**] a colorless liquid; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 0.93 (t, 3H, J = 7.1 Hz,



CH_3 of 2-propyl), 1.36 (d, 3H, J = 6.4 Hz, CH_3 of 5-methyl), 1.42 - 1.62 (m, 5H), 1.86 - 2.06 (m, 3H), 2.30 - 2.45 (m, 1H, α-CH), 4.39 - 4.48 (m, 1H, δ-CH); ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 13.88 (q, CH_3CH), 19.79 (t), 22.10 (q, CH_3CH_2), 25.49 (t), 30.69 (t), 33.94 (t), 40.22 (d, α-*C*H), 77.60 (d, δ-CH), 173.95 (s, C=O); IR(neat) 1719 cm^{-1}(ν_{CO}); EIMS (relative intensity) m/z 157 (M^++1, 1), 141 (2), 127 (8), 114 (100), 95 (7), 84 (22), 73 (39), 55 (39), 42 (24); HREIMS calcd for $C_9H_{16}O_2$ m/z 156.1150, found, 156.1165.

2-Propyl-5-heptanolide (2m). GC analysis indicated the presence of two isomers in a ratio of 55/45. The *cis*/*trans* isomers of **2m** were separated by preparative HPLC .

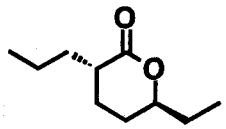
[*cis*-**2m**] a yellow liquid; ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 0.94 (t, 3H, J = 7.2 Hz, CH_3



of 2-propyl), 1.00 (t, 3H, J = 7.5 Hz, CH_3 of 5-ethyl), 1.40 (m, 1H), 1.53 (m, 1H), 1.63 (m, 2H), 1.73 (m, 1H), 1.82 - 1.88 (m, 1H), 1.88 - 1.96 (m, 2H), 2.03 (ddd, 1H, J = 7.8, 13.4, 16.6 Hz), 2.45 (m, 1H, α-CH), 4.20 (m, 1H, δ-CH); ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 9.51 (q, CH_3 of 5-ethyl), 13.86 (q, CH_3 of 2-propyl), 20.14 (t), 23.25 (t), 26.15 (t), 28.23 (t), 32.90 (t), 37.88 (d, α-*C*H), 79.23 (d, δ-CH), 175.83 (s, C=O); IR(neat) 1736 cm^{-1}(ν_{CO}); EIMS (relative intensity) m/z 171 (M^++1, 1), 141 (39), 128 (100), 110 (27), 95 (52), 84 (46), 73 (75), 69 (37), 56 (72), 41 (38); HREIMS calcd for $C_{10}H_{18}O_2$ m/z 170.1307, found,

170.1292.

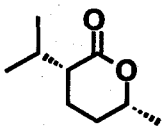
[*trans*-**2m**] a yellow liquid; ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 0.94 (t, 3H, J = 7.3 Hz,



CH_3 of 2-propyl), 0.99 (t, 3H, J = 7.5 Hz, CH_3 of 5-ethyl), 1.32 - 1.47 (m, 2H), 1.55 (m, 3H), 1.60 - 1.67 (m, 1 H), 172 (m, 1H), 1.89 - 1.96 (m, 2H), 2.03 (ddd, 1H, J = 3.2, 6.7, 13.4 Hz), 2.39 (m, 1H, α-CH), 4.20 (m, 1H, δ-CH); ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 9.21 (q, CH_3 of 5-ethyl), 13.91 (q, CH_3 of 2-propyl), 19.83 (t), 25.42 (t), 28.30 (t), 29.11 (t), 34.02 (t), 40.60 (d, α-*C*HCO), 82.46 (d, δ-CHO), 174.07 (s, C=O); IR(neat) 1728 cm^{-1}(ν_{CO}); EIMS (relative intensity) m/z 171 (M^++1, 1), 141 (43), 128 (100), 110 (23), 95 (61), 84 (32), 73 (57), 69 (36), 56 (65), 41 (37); HREIMS calcd for $C_{10}H_{18}O_2$ m/z 170.1307, found, 170.1310.

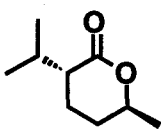
2-(2'-propyl)-5-hexanolide (2n). GC analysis indicated the presence of two isomers in a ratio of 52/48. The *cis*/*trans* isomers of **2n** were separated by preparative HPLC.

[*cis*-**2n**] a slightly yellow liquid; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 0.92 (d, 3H, J = 6.3



Hz, CH_3 of propyl), 0.97 (d, 3H, J = 6.8 Hz, CH_3 of propyl), 1.35 (d, 3H, J = 6.4 Hz, CH_3CHO), 1.43 - 1.70 (m, 2H), 1.80 - 2.00 (m, 2H), 2.38 (m, 1H, α-CH), 2.50 (m, 1H, CH of propyl), 4.36 (m, 1H, δ-CH); ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 17.94 (q, CH_3 of propyl), 19.78 (q, CH_3 of propyl), 20.11 (t), 22.07 (q, *C*H_3CHO), 29.02 (d, CH of propyl), 30.56 (t), 46.35 (d, α-CH), 77.29 (d, δ-CH), 173.25 (s, CO); IR(neat) 1728 cm^{-1}(ν_{CO}); EIMS (relative intensity) m/z 156 (M^+, 4), 141 (17), 114 (100), 101 (21), 84 (27), 73 (55), 55 (39); HREIMS calcd for $C_9H_{16}O_2$ m/z 156.1150, found, 156.1142.

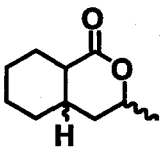
[*trans*-**2n**] a slightly yellow liquid; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 0.94 (d, 3H, J = 6.8



Hz, CH_3 of propyl), 1.01 (d, 3H, J = 6.8 Hz, CH_3 of propyl), 1.34 (d, 3H, J = 5.9 Hz, CH_3CHO), 1.50 - 1.75 (m, 2H), 1.94 (m, 2H), 2.29 (m, 2H, CH of propyl and α-CH), 4.45 (m, 1H, δ-CH); ^{13}C-NMR ($CDCl_3$, 68

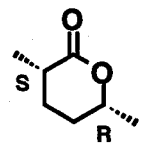
MHz) δ 18.25 (q, CH_3 of propyl), 18.51 (t), 20.57 (q, CH_3 of propyl), 21.03 (q, CH_3CHO), 27.95 (d, CH of propyl), 28.70 (t), 43.93 (d, α-CH), 74.04 (d, δ-CH), 174.61 (s, CO); IR(neat) 1724 $cm^{-1}(\nu_{CO})$; EIMS (relative intensity) m/z 156 (M^+, 7), 141 (22), 114 (100), 101 (23), 84 (27), 73 (55), 55 (46); HREIMS calcd for $C_9H_{16}O_2$ m/z 156.1150, found, 156.1148.

3-Methyloctahydro-1*H*-2-benzopyran-1-one (2o). This compound **2o** was obtained as a mixture of four isomers. The isomer ratio was determined by ^{1}H-NMR (600 MHz) in 22:26:24:28. These compound are already known and the properties (^{1}H- and ^{13}C-NMR) were consistent with those previously reported, see: Fujiwara, Y.; Okamoto, M. *Chem. Pharm. Bull.* **1989**, *37*, 1458.

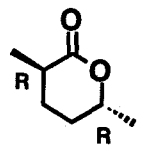


2-Methyl-5-hexanolide (2p). The isomer ratio of **2p** was determined by GC analysis in 55/45. The *cis/trans* isomers of **2p** were separated by preparative HPLC.

[*cis*-(2S, 5R)-**2p**] crystals; mp. 51 - 51.5 °C; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 1.22 (d, 3H, J = 6.9 Hz, 2-Me), 1.36 (d, 3H, J = 6.4 Hz, 5-Me), 1.40 - 1.70 (m, 2H), 1.80 - 2.20 (m, 2H), 2.55 - 2.64 (m, 1H, α-CH), 4.43 - 4.51 (m, 1H, δ-CH); ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 16.11 (q, 2-Me), 21.00 (q, 5-Me), 25.53 (t), 28.32 (t), 32.88 (d, α-*C*H), 74.34 (d, δ-CH), 176.16 (s, C=O); IR($CDCl_3$) 1732 $cm^{-1}(\nu_{CO})$; EIMS (relative intensity) m/z 128 (M^+, 5), 113 (4), 84 (43), 69 (20), 56 (100), 42 (50); HREIMS calcd for $C_7H_{12}O_2$ m/z 128.0837, found, 128.0824. This compound is already known and the properties (mp., ^{1}H- and ^{13}C-NMR, IR, and MS) were consistent with those previously reported (refs a, b, c, and d). Optical yield was estimated by GC (column: Chiraldex G-TA 0.25 mm x 20 m).

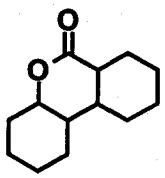


[*trans*-(2R, 5R)-**2p**] crystals; mp. 52 - 53 °C; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 1.30 (d, 3H, J = 6.9 Hz, 2-Me), 1.37 (d, 3H, J = 6.4 Hz, 5-Me), 1.46 - 1.67 (m, 2H), 1.87 - 2.10



(m, 2H), 2.39 - 2.48 (m, 1H, α-CH), 4.40 - 4.48 (m, 1H, δ-CH); ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 17.23 (q, 2-Me), 22.03 (q, 5-Me), 28.43 (t), 30.89 (t), 35.65 (d, α-CH), 78.10 (d, δ-CH), 174.29 (s, C=O); IR($CDCl_3$) 1720 cm^{-1}(ν_{CO}); EIMS (relative intensity) m/z 128 (M^+, 3), 113 (4), 84 (45), 69 (28), 56 (100), 2 (65); HREIMS calcd for $C_7H_{12}O_2$ m/z 128.0837, found, 128.0828. This compound is already known and the properties (mp., ^{1}H- and ^{13}C-NMR, IR, and MS) were consistent with those previously reported, see: (a) Wheeler, J. W.; Evans, S. L.; Blum, M. S.; Velthius, H. H. V.; de Camargo, J. M. F. *Tetrahedron Lett.* **1976**, 4029. (b) Pirkle, W. H.; Adams, P. E. *J. Org. Chem.* **1979**, *44*, 2169. (c) Mori, K.; Senda, S. *Tetrahedron* **1985**, *41*, 541. (d) Bäckvall, J. E.; Byström, S. E.; Nyström, J. E. *Tetrahedron* **1985**, 41, 5761.

2,2'-dicyclohexylcarbolactone (2q). This compound was obtained as a mixture of eight diastereomers. The ratio was determined by 600 MHz ^{1}H-NMR spectra (55:15:12:6:4:3:3:2). Four major isomers were assigned to retention products (*trans*) because of the relative larger *J* value of its C*H*O signal, and four minor isomers to β-fragmentation products (*cis*).

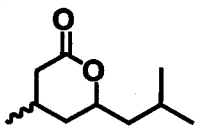


The ratio of retention and fragmentation was 88/12. After purification by HPLC, major isomer was obtained in a pure form. [Major isomer] a white solid; mp. 106 - 107 °C; ^{1}H-NMR ($CDCl_3$) δ 0.80 - 0.92 (m, 2H), 1.15 - 1.35 (m, 7H), 1.44 (dq-like, 1H, *J* = 3.9, 12.0 Hz), 1.70 - 1.88 (m, 4H), 1.90 - 2.00 (m, 3H), 2.06 - 2.09 (m, 1H), 2.33 - 2.40 (m, 1H), 3.87 (ddd, 1H, *J* = 4.1, 9.9, 11.3 Hz); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ 24.37 (t), 25.15 (t), 25.24 (t), 25.96 (t), 26.97 (t), 27.34 (t), 28.85 (t), 32.61 (t), 42.30 (d), 44.85 (d), 47.08 (d), 84.34 (d), 172.97 (s); IR(neat) 1724 cm^{-1}(ν_{CO}); EIMS (relative intensity) m/z 208 (M^+, 14), 164 (45), 149 (6), 135 (10), 121 (10), 107 (7), 96 (39), 82 (100), 67 (59); HREIMS calcd for $C_{13}H_{20}O_2$ m/z 208.1463, found, 208.1461.

[Partial data of other isomers]

(isomer of 15% content) ^{1}H-NMR ($CDCl_3$) δ 3.96 (td, 1H, J = 10.7, 4.2 Hz); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ 78.90 (d). (isomer of 12% content) ^{1}H-NMR ($CDCl_3$) δ 3.93 (td, 1H, J = 10.6, 4.2 Hz); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ 80.00 (d). (isomer of 6% content) ^{1}H-NMR ($CDCl_3$) δ 4.16 (td, 1H, J = 11.3, 4.3 Hz); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ 79.94 (d). (isomer of 4% content) ^{1}H-NMR ($CDCl_3$) δ 4.70 (q-like, 1H, J ~ 3.3 Hz); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ 76.06 (d). (isomer of 3% content) ^{1}H-NMR ($CDCl_3$) δ 4.51 (q-like, 1H, J ~ 3.3 Hz); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ 75.55 (d). (isomer of 3% content) ^{1}H-NMR ($CDCl_3$) δ 4.46 (q-like, 1H, J ~ 3.3 Hz); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ 74.51 (d). (isomer of 2% content) ^{1}H-NMR ($CDCl_3$) δ 4.47 (q-like, 1H, J ~ 3.3 Hz); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ 80.09 (d).

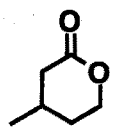
***cis*- and *trans*- Tetrahydro-4-methyl-6-(2-methylpropyl)-2*H*-pyran-2-one (2s).** The isomer ratio was determined by ^{1}H-NMR analysis in 59/41.



a colorless liquid; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 0.93 (t, 6H, J = 6.3 Hz), 1.02 (d, 1.8H, J = 5.9 Hz, cis), 1.09 (d, 1.2H, J = 6.4 Hz, trans), 1.15 - 2.23 (complex m, 7H), 2.32 - 2.73 (m, 1H, α-C*H*H of cis and trans), 4.29 - 4.39 (m, 0.6H, δ-CH of cis), 4.42 - 4.52 (m, 0.4H, δ-CH of trans); ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 21.43 (q, trans), 21.64 (q, cis), 22.02 (q, cis and trans), 22.93 (q, trans), 22.97 (q, cis), 23.80 (d, trans), 23.90 (d, trans), 24.18 (d, cis), 26.71 (d, cis), 35.45 (t, trans), 37.47 (t, trans), 37.55 (t, cis), 38.04 (t, cis), 44.59 (t, trans, α-CH_2), 45.23 (t, cis, α-CH_2), 75.50 (d, trans, δ-CH), 78.82 (d, cis, δ-CH), 171.51 (s, cis, C=O), 172.47 (s, trans, C=O); IR(neat) 1732 cm^{-1}(ν_{CO}); EIMS (relative intensity) m/z 170 (M^+, 2), 152 (6), 128 (5), 113 (100), 85 (17), 69 (33), 56 (25), 43 (11); HREIMS calcd for $C_{10}H_{18}O_2$ m/z 170.1307, found, 170.1313. The *cis* isomer is already known and the properties (^{1}H- and ^{13}C-NMR and MS) were consistent with those previously reported, see: Bardili, B.; Marschall-Weyerstahl, H.; Weyerstahl, P. *Liebigs Ann. Chem.* **1985**, 275. Pittet, A. O.; Klaiber, E. M. *J. Agric. Food. Chem.*

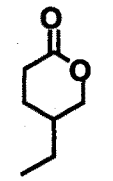
1975, *23*, 1189.

3-Methyl-5-pentanolide (2t). a slightly yellow liquid; ^{1}H-NMR ($CDCl_3$, 600 MHz) δ



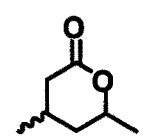
1.07 (d, 3 H, J = 6.4 Hz, CH_3), 1.45 - 1.60 (m, 1H, β-CH), 1.93 (ddq, 1H, J = 14.1, 1.5, 4.0 Hz, γ-C*H*H), 2.06 - 2.17 (m, 2H, α-C*H*HCO and γ-C*H*H), 2.68 (dddd, 1H, J = 22.1, 10.2, 1.4, 4.0 Hz, α-CH*H*), 4.27 (ddd, 1H, J = 3.8, 10.7, 11.4 Hz, δ-C*H*H), 4.42 (ddd, 1H, J = 4.0, 4.9, 11.4 Hz, δ-C*H*H); ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 21.41 (q, CH_3), 26.55 (d, β-CH), 30.61 (t, γ-CH_2), 38.20 (t, α-CH_2), 68.52 (t, δ-CH_2), 171.19 (s, C=O); IR(neat) 1728 cm^{-1}(ν_{CO}); EIMS (relative intensity) m/z 114 (M^+, 43), 84 (12), 70 (40), 56 (70), 55 (98), 42 (100); HREIMS calcd for $C_6H_{10}O_2$ m/z 114.0681, found, 114.0695.

4-Ethyl-5-pentanolide (2u).



a slightly yellow liquid; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 0.97 (t, 3H, J = 7.3 Hz, CH_3), 1.36 (m, 2H), 1.45 - 1.60 (m, 1H), 1.75 - 1.90 (m, 1H), 1.95 - 2.10 (m, 1H), 2.49 (ddd, 1H, J = 17.3, 9.3, 8.1 Hz, α-C*H*H), 2.63 (ddd, 1H, J = 17.3, 6.8, 4.9 Hz, α-C*H*H), 3.96 (t-like, 1H, J = 10.3 Hz, δ-C*H*H), 4.35 (dd-like, 1H, J = 11.2, 4.4 Hz, δ-CH*H*); ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 11.22 (q, CH_3), 24.44 (t, CH_3CH_2), 25.06 (t, β-CH_2), 28.99 (t, α-CH_2), 34.38 (d, γ-CH), 73.38 (t, δ-CH_2), 171.60 (s, CO); IR(neat) 1736 cm^{-1}(ν_{CO}); EIMS (relative intensity) m/z 128 (M^+, 12), 110 (4), 98 (34), 80 (9), 70 (100), 56 (60); HREIMS calcd for $C_7H_{12}O_2$ m/z, 128.0837 found, 128.0836.

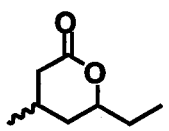
***cis*- and *trans*- 3-Methyl-5-hexanolide (2v).** The isomer ratio was determined by GC analysis in 56/44.



a slightly yellow liquid; ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 1.03 (d, 3H, J = 6.4 Hz, CH_3 major), 1.10 (d, 3H, J = 6.7 Hz, CH_3 minor), 1.21 (dt, 1H, J = 13.8, 11.5 Hz, γ-C*H*H of major), 1.37 (d, 3H, J = 6.3 Hz, CH_3

major), 1.38 (d, 3H, J = 6.3 Hz, CH_3 minor), 1.62 (ddd, 1H, J = 4.2, 6.1, 14.1 Hz, γ-C*H*H of minor), 1.76 (ddd, 1H, J = 6.4, 8.5, 14.2 Hz, γ-C*H*H of minor), 1.93 (dm, 1H, J = 13.8 Hz, γ-CH*H* of major), 2.02 (dd, 1H, J = 16.8, 10.7 Hz, α-CH*H* major), 2.05 (m, 1H, β-CH major), 2.15 (dd, 1H, J = 16.2, 8.9 Hz, α-CH*H* minor), 2.20 (m, 1H, β-CH minor), 2.58 (dd, 1H, J = 16.2, 5.5 Hz, 1H α-C*H*H minor), 2.67 (ddd, J = 16.8, 4.8, 2.0 Hz, 1H α-C*H*H major), 4.42 (m, J = 6.3, 2.9, 17.9 Hz, 1H δ-CH major), 4.58 (ddq, 1H, δ-CH minor, J = 8.8, 4.4, 6.3 Hz); ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 21.67 (q, C*H*$_3$CHCO minor), 21.20 (q, C*H*$_3$CHCO major), 21.44 (q, C*H*$_3$CHO minor), 21.69 (q, C*H*$_3$CHO major), 23.55 (d, β-CH minor), 26.61 (d, β-CH major), 36.43 (t, minor), 37.15 (t, minor), 37.61 (t, α-CH_2 major), 38.65 (t, γ-CH_2 major), 73.47 (d, δ-CH_2 minor), 76.85 (d, δ-CH major), 171.41 (s, CO major), 172.27 (s, CO minor); IR(neat) 1732 cm^{-1}(ν_{CO}); for major isomer: EIMS (relative intensity) m/z 128 (M^+, 11), 113 (20), 84 (56), 69 (45), 56 (100); for minor isomer: EIMS (relative intensity) m/z 128 (M^+, 12), 113 (16), 84 (58), 69 (42), 56 (100); for major isomer: HREIMS calcd for $C_7H_{12}O_2$ 128.0838. m/z, found, 128.0843. for minor isomer: HREIMS calcd for $C_7H_{12}O_2$ m/z, 128.0838. found, 128.0812.

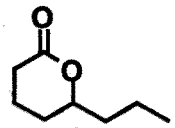
***cis*- and *trans*- 3-Methyl-5-heptanolide (2w).** The isomer ratio was determined by GC analysis in 54/46.



a slightly yellow liquid; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 1.00 (t, 3H, J = 7.4 Hz, CH_3CH_2 major), 1.00 (t, 3H, J = 7.4 Hz, CH_3CH_2 minor), 1.04 (d, 3H, J = 6.4 Hz, CH_3 major), 1.10 (d, 3 H, J = 6.4 Hz, CH_3 minor), 1.12 - 1.27 (m, 1H major), 1.53 - 2.25 (complex m, 5H of major and 6H of minor), 1.95 - 2.10 (m, 1H), 2.57 (dd, 1H, J = 20.3, 9.4 Hz, α-C*H*H minor), 2.67 (ddd, 1H, J = 21.3, 10.4, 2.0 Hz, α-C*H*H major), 4.22 (m, 1H, δ-CH major), 4.32 (m, 1H, δ-CH minor); ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 9.11 (q, C*H*$_3$CH$_2$ major), 9.52 (q, C*H*$_3$CH$_2$ minor), 21.27 (q, C*H*$_3$CH minor), 21.57 (q, C*H*$_3$CH major), 23.70 (d, β-CH minor),

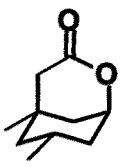
26.59 (d, β-CH major), 28.38 (t), 28.81 (t), 34.42 (t), 36.34 (t), 37.36 (t), 37.99 (t), 78.50 (d, δ-CH_2 minor), 81.77 (d, δ-CH major), 171.58 (s, CO major), 172.53 (s, CO minor); IR(neat) 1732 $cm^{-1}(\nu_{CO})$; for major isomer EIMS (relative intensity) m/z 142 (M^+, 7), 113 (100), 85 (27), 69 (42), 56 (49); for minor isomer EIMS (relative intensity) m/z 142 (M^+, 7), 113 (100), 85 (27), 69 (44), 56 (50); for major isomer HREIMS calcd for $C_7H_{12}O_2$ 142.0994. m/z, found, 142.1002. for minor isomer HREIMS calcd for $C_7H_{12}O_2$ m/z, 142.0994. found, 142.0982.

5-Octanolide (2x).



a slightly yellow liquid; ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 0.94 (t, 3H, J = 7.3 Hz, CH_3), 1.39 - 1.46 (m, 1H), 1.47 - 1.60 (m, 3H), 1.66 - 1.74 (m, 1H), 1.82 - 1.95 (m, 3H), 2.45 (ddd, 1H, J = 7.1, 8.8, 17.6 Hz, α-C*H*H), 2.59 (dddd, 1H, J = 1.3, 4.8, 7.9, 17.6 Hz, α-C*H*H), 4.30 (m, 1H, δ-CH); ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 13.76 (q, CH_3), 18.10 (t), 18.42 (t), 27.72 (t), 29.39 (t), 37.82 (t), 80.27 (d, δ-CH), 171.96 (s, C=O); IR(neat) 1732 $cm^{-1}(\nu_{CO})$; EIMS (relative intensity) m/z 143 (M^++1, 3), 124 (4), 114 (12), 99 (100), 70 (33), 55 (22), 42 (28); HREIMS calcd for $C_8H_{14}O_2$ m/z 142.0994, found, 142.0983.

5,7-Dimethyl-2-oxabicyclo [3.3.1] nonan-3-one (2y).

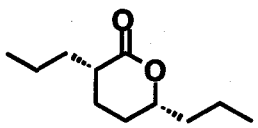


a slightly yellow liquid; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 0.93 (d, 3H, J = 6.4 Hz, CH_3C*H*), 1.00 (s, 3H, CH_3C), 1.02 (td-like, 1H, J ~ 13.4, 1.5 Hz), 1.13 (td-like, 1H, J ~ 13.9, 2.0 Hz), 1.47 (td-like, 1H, J ~ 13.6, 2.0 Hz), 1.57 (dm, 1H, $J_{doublet}$= 13.4 Hz), 1.72 (m, 1H, CH_3C*H*), 1.81 (dm, 1H, $J_{doublet}$= 13.6 Hz), 2.09 (dm, 1H, $J_{doublet}$= 13.9 Hz), 2.29 (dd, 1H, J = 1.5, 18.6 Hz, α-C*H*H), 2.43 (dd, 1H, J = 2.5, 18.6 Hz, α-CH*H*), 4.79 (septet, 1H, J = 2.0 Hz, δ-CH); ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 21.55 (q, *C*H_3CH), 23.90 (d, CH_3*C*H), 30.13 (q, *C*H_3C), 30.56 (s, CH_3*C*), 37.14 (t), 38.97 (t), 43.06 (t, α-CH), 47.39 (t), 76.10 (d, δ-CH), 171.85 (s, CO); IR(neat) 1732 $cm^{-1}(\nu_{CO})$; EIMS (relative intensity) m/z 168 (M^+, 12), 153 (3), 125 (25),

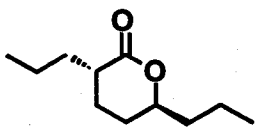
109 (98), 95 (62), 82 (100), 68 (88), 55 (55); HREIMS calcd for $C_{10}H_{16}O_2$ m/z, 168.1151 found, 168.1140.

2-Propyl-5-octanolide (6a). The ratio of **6a/7a** was determined by GC analysis in 24/1. Purification of **6a** to eliminate the minor product **7a** (commercially available) was easy to carry out by flash chromatography on silica gel. The isomer ratio of **6a** was determined by GC analysis in 59/41. The *cis/trans* isomers of **6a** were separated by preparative HPLC.

[*cis*-**6a**] a slightly yellow liquid; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 0.93 (t, 6H, J = 6.8 Hz), 1.33 - 1.73 (m, 9H), 1.86 - 2.05 (m, 3H), 2.30 - 2.45 (m, 1H, α-CH), 4.20 - 4.32 (m, 1H, δ-CH); ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 13.85 (q), 13.91 (q), 18.08 (t), 19.85 (t), 25.51 (t), 28.87 (t), 34.05 (t), 38.36 (t), 40.60 (d, α-*C*H), 81.02 (d, δ-CH), 174.03 (s, C=O); IR(neat) 1728 cm^{-1} (ν_{CO}); EIMS (relative intensity) m/z 185 (M^++1, 3), 155 (6), 142 (100), 124 (39), 113 (22), 95 (83), 84 (47), 70 (87), 55 (86), 41 (50); HREIMS calcd for $C_{11}H_{20}O_2$ m/z 184.1463, found, 184.1474.

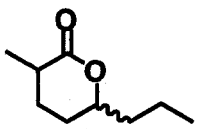


[*trans*-**6a**] a slightly yellow liquid; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 0.93 (t, 6H, J = 6.8 Hz), 1.31 - 1.75 (m, 9H), 1.80 - 1.96 (m, 2H), 1.99 - 2.11 (m, 1H), 2.40 - 2.51 (m, 1H, α-CH), 4.23 - 4.31 (m, 1H, δ-CH); ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 13.83 (q), 13.98 (q), 18.36 (t), 20.18 (t), 23.35 (t), 26.69 (t), 32.96 (t), 37.41 (t), 37.95 (d, α-CH), 77.75 (d, δ-CH), 175.81 (s, C=O); IR(neat) 1736 cm^{-1}(ν_{CO}); EIMS (relative intensity) m/z 185 (M^++1, 2), 155 (5), 142 (100), 124 (42), 113 (17), 95 (67), 84 (58), 70 (85), 55 (84), 41 (45); HREIMS calcd for $C_{11}H_{20}O_2$ m/z 184.1463, found, 184.1437



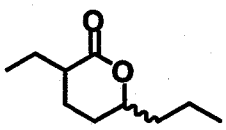
***cis*- and *trans*- 2-Methyl-5-octanolide (6b).** The isomer ratio of **6b** was determined by GC analysis in 53/47.

an oil; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 0.94 (t, 3H cis and trans, J = 6.8 Hz), 1.22 (d,



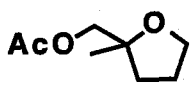
3H cis, J = 6.8 Hz), 1.30 (d, 3H trans, J = 7.3 Hz), 1.35 - 1.76 (m, 6H), 1.88 - 2.13 (m, 2H), 2.39 - 2.49 (m, 1H trans), 2.56 - 2.66 (m, 1H cis), 4.25 - 4.33 (m, 1H cis and trans); ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 13.77 (q), 16.11 (q), 17.35 (q), 18.00 (t), 18.30 (t), 25.55 (t), 26.62 (t), 28.46 (t), 29.07 (t), 29.62 (t), 33.10 (d), 36.04 (d), 37.35 (t), 38.33 (t), 77.83 (d), 81.52 (d), 174.41 (s), 176.35 (s); IR(neat) 1732 cm^{-1}(ν_{CO}); EIMS (relative intensity) for *cis* isomer m/z 156 (M^+, 2), 113 (100), 85 (62), 70 (53), 56 (84), 42 (48); EIMS (relative intensity) for *trans* isomer m/z 156 (M^+, 1), 113 (100), 85 (58), 70 (54), 56 (66), 42 (49).

***cis*- and *trans*- 2-Ethyl-5-octanolide (6c).** The isomer ratio of **6c** was determined by GC analysis in 59/41.



an oil; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 0.94 (t, 3H, J = 7.3 Hz), 0.99 (t, 3H, J = 7.3 Hz), 1.36 - 1.75 (m, 7H), 1.81 - 2.15 (m, 3H), 2.29 - 2.44 (m, 1H), 4.24 - 4.32 (m, 1H); ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 10.95 (q), 11.48 (q), 13.76 (q), 17.99 (t), 18.28 (t), 22.83 (t), 23.77 (t), 24.77 (t), 24.85 (t), 26.64 (t), 28.78 (t), 37.33 (t), 38.28 (t), 39.60 (d), 42.01 (d), 77.66 (d), 80.99 (d), 173.71 (s), 175.60 (s); IR(neat) 1727 cm^{-1}(ν_{CO}); EIMS (relative intensity) m/z 128 (M^+, 3), 113 (4), 84 (45), 69 (28), 56 (100), 42 (65); HREIMS calcd for $C_{10}H_{18}O_2$ m/z 170.1307., found, 128.0828.

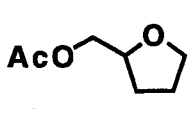
2-Methyl-2-acetoxymethyl-tetrahydrofuran (7d).

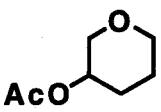


a slightly yellow liquid; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 1.44 (s, 3H, CH_3C), 1.46 - 1.56 (m, 1H), 1.60 - 1.70 (m, 1H), 1.76 - 1.84 (m, 1H), 2.03 (s, 3H, CH_3CO), 2.16 - 2.28 (m, 1H), 3.34 (d, 1H, J = 11.9 Hz, OC*H*HC), 3.49 (td, 1H, J = 10.4, 2.7 Hz, OC*H*HCH_2), 3.78 (td, 1H, J = 4.4, 10.4 Hz, OCH*H*CH_2), 4.02 (dd, 1H, J = 11.9, 2.0 Hz, OCH*H*C); ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 21.52 (q,

CH_3C), 22.18 (q, CH_3CO), 22.28 (t), 33.77 (t), 67.82 (t, OCH_2), 73.62 (t, OCH_2C), 77.93 (s, CH_3C), 170.42 (s, CO); IR(neat) 1735 cm^{-1}(ν_{CO}); CIMS (relative intensity) m/z 159 (M^++1, 8), 99 (100), 81 (4), 71 (4), 61 (11) ; HREIMS calcd for $C_8H_{15}O_3$ m/z 159.1035, found, 159.1028.

2-Acetoxymethyl-tetrahydrofuran (7e) and 3-Acetoxytetrahydropyran (8e). These



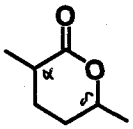
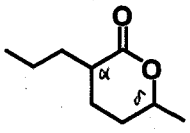
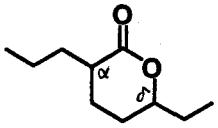
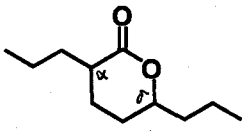
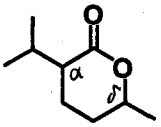


compounds are already known, see: Mihailović, M. L.; Čeković, Ž.; Stanković, J.; Djokić-Mazinjanin, S.; Marinković, D. *Bull. Soc. Chim. Beograd* **1978**, *43*, 69.

With Regard to *cis/trans* Assignments of 2,5-Disubstituted Lactones (2l, 2m, 2n and 6a).

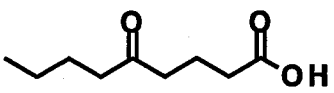
The *cis/trans* assignments of the obtained 2-methyl-5-hexanolide (**2p**) were made rigorously by comparing the obtained spectral and physical data for **2p** with those reported previously by plural groups (refs a-d cited above). For *cis* and *trans* isomers of **2p**, there existed several significant differences in (i) GC elution orders (*cis* came out faster than *trans*; with OV-1 column), (ii) ν_{CO} in IR spectra (*cis* had a larger frequency number than *trans*), (iii) ^{13}C-NMR chemical shifts of C=O (*cis* had a larger δ value than *trans*), and (iv) ^{13}C-NMR chemical shifts of α-C and δ-C (*cis* had a smaller δ value than *trans*) (Table, run 1 and 2). Regarding the *cis/trans* assignments of other 2,5-disubstituted lactones, **2l**, **2m**, **2n**, and **6a**, the similar propensity was confirmed. The key data are summarized in Table, which show good consistency.

Table. The Key Data for 2,5-Disubstituted δ-lactones

run	δ-lactone		GC elution orders (OV-1)	IR (ν_{CO}) cm^{-1}	^{13}C-NMR chemical shift		
					C=O	α-C	δ-C
1		cis-**2p**	2	1732	176.16	32.88	74.34
2		trans-**2p**	1	1720	174.29	35.65	78.10
3		cis-**2l**	2	1736	175.81	37.95	77.75
4		trans-**2l**	1	1728	174.03	40.60	81.02
5		cis-**2m**	2	1736	175.83	37.88	79.23
6		trans-**2m**	1	1728	174.07	40.60	82.40
7		cis-**6a**	2	1736	175.62	37.67	74.22
8		trans-**6a**	1	1719	173.95	40.22	77.60
9		cis-**2n**	2	1728	174.61	43.93	74.04
10		trans-**2n**	1	1724	173.25	46.35	77.29

General Procedure for Carbonylation of 1-Substituted Cyclobutanols: A mixture of 1-butylcyclobutanol (**5f**) (149 mg, 1 mmol), LTA (593 mg, 1.2 mmol) and benzene (40 mL) were placed in a 100-mL stainless steel autoclave lined with a round bottomed glass tube. The autoclave was closed, purged three times with CO, and then pressurized with 80 kg/cm^2 of CO and was heated, with stirring, at 80 °C. After 20 h, excess CO was discharged at room temperature, and the reaction mixture was filtered. The filtrate was treated with 2N NaOH (20 mL x 3). The alkaline solution was neutralized with conc. HCl (30 mL) and was extracted with CH_2Cl_2 (20 mL x 3). The extracts were dried with $CaCl_2$ and were evaporated to give essentially pure 5-oxononanoic acid (**6f**) (53% yield).

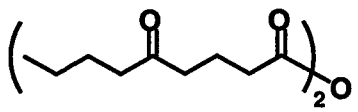
5-Oxononanoic acid (6f).



a slightly yellow solid; mp. 36.5 - 38.5 °C; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 0.90 (t, *J* = 7.1 Hz, 3H), 1.31 (sextet-like, *J* ~ 7.4 Hz, 2H), 1.56 (quint-like, *J* ~ 7.3 Hz, 2H), 1.90 (quint-like, *J* ~ 7.3 Hz, 2H), 2.39 (t, *J* = 7.1 Hz, 2H), 2.40 (t, *J* = 7.5 Hz, 2H), 2.50 (t, *J* = 7.1 Hz, 2H), 10.03 (br s, 1H); ^{13}C NMR ($CDCl_3$, 68 MHz) δ 13.80 (q), 18.59 (t), 22.31 (t), 25.92 (t), 32.95 (t), 41.28 (t), 42.59 (t), 178.81 (s), 210.41 (s); IR(ν_{CO}) 1712 cm^{-1}; EIMS (relative intensity) m/z 172 (M^+, 1), 155 (6), 130 (59), 115 (54), 85 (100), 57 (91); HREIMS calcd for $C_9H_{16}O_3$ m/z 172.1100, found, 172.1095.

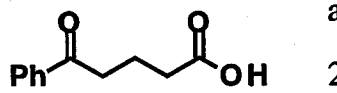
Mixed anhydride consisting of **6f** and acetic acid was also observed in reaction mixture. The anhydride **8f** was isolated by preparative HPLC.

5-Oxononanoic anhydride (8f).



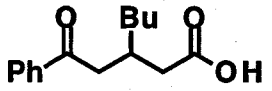
a slightly yellow liquid; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 0.90 (t, *J* = 7.3 Hz, 6H), 1.31 (m, 4H), 1.55 (m, 4H), 1.92 (m, 4H), 2.40 (t, *J* = 7.3 Hz, 4H), 2.49 (t, *J* = 7.3 Hz, 4H), 2.52 (t, *J* = 7.3 Hz, 4H); ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 13.79, 18.11, 22.31, 25.92, 34.19, 40.83, 42.61, 169.05, 210.10.

4-Benzoylbutyric acid (6g).



a slightly yellow solid; mp. 126.5 - 128.5 °C; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 2.09 (quint-like, *J* ~ 7.1 Hz, 2H), 2.51 (t, *J* = 7.1 Hz, 2H), 3.08 (t, *J* = 7.1 Hz, 2H), 7.40 (t-like, *J* ~ 7.4 Hz, 2H), 7.56 (t-like, *J* ~ 7.2 Hz, 1H), 7.96 (d, *J* = 7.3 Hz, 2H) 10.67 (br s, 1H); ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 18.95 (t), 33.06 (t), 37.26 (t), 127.97 (d), 128.57 (d), 133.11 (d), 136.68 (s), 179.45 (s), 199.36 (s); IR(ν_{CO}) 1674, 1694 cm^{-1}; EIMS (relative intensity) m/z 192 (M^+, 12), 146 (4), 120 (15), 105 (100), 77 (35), 51 (8); HREIMS calcd for $C_{11}H_{12}O_3$ m/z 192.0787, found, 192.0759. This compound is commercially available.

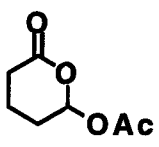
3-Benzoylmethyl-heptanoic acid (6h).



a slightly yellow liquid; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 0.88 (t, J = 6.4 Hz, 3H), 1.31 (br s, 4H), 1.42 (m, 2H), 2.46 (d-like, J = 5.4 Hz, 2H, One peak of doublet in lower field is very strong.), 2.56 (m, 1H), 2.99 (dd, J = 16.6, 5.9 Hz, 1H), 3.10 (dd, J = 16.6, 6.8 Hz, 1H), 7.45 (t, J = 7.3 Hz, 2H), 7.56 (t, J = 7.3 Hz, 1H), 7.96 (d, J = 7.3 Hz, 2H) 9.85 (br s, 1H); ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 13.91, 22.63, 28.87, 31.12, 33.74, 38.30, 42.54, 128.05, 128.54, 133.02, 137.05, 179.04, 199.58; IR(ν_{CO}) 1687, 1707 cm^{-1}; EIMS (relative intensity) m/z 248 (M^+, 6), 189 (7), 120 (100), 105 (94), 77 (33); HREIMS calcd for $C_{15}H_{20}O_3$ m/z 248.1413, found, 248.1405.

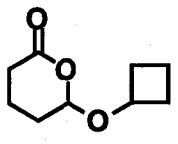
General Procedure for Carbonylation of 1-Unsubstituted Cyclobutanols: In the 100 mL stainless steel autoclave, a mixture of 3-butylcyclobutanol (**5j**) (149 mg, 1 mmol, cis/trans = 6/1), LTA (602 mg, 1.2 mmol), and benzene (40 mL) was stirred at 80 °C under CO (80 kg/cm^2). After 5 h, the white precipitate was filtered. Evaporation followed by flash chromatography on silica gel (25% ether / hexane) gave δ-lactone **6j** in 62% yield.

5-Acetoxy-5-pentanolide (6i).



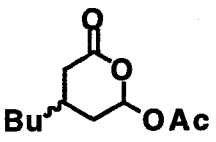
a colorless liquid; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 1.88 - 2.16 (m, 4H), 2.12 (s, 3H), 2.51 - 2.74 (m, 2H), 6.54 (t-like, J ~ 3.3 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 15.06 (t), 20.71 (q), 26.13 (t), 29.53 (t), 92.88 (d), 168.51 (s), 168.83 (s); IR(ν_{CO}) 1752 cm^{-1}; EIMS (relative intensity) m/z 159 (M^++1, 1), 115 (4), 99 (71), 86 (31), 70 (36), 43 (100); HREIMS calcd for $C_7H_{11}O_4$ (M^++1) m/z 159.0659, found, 159.0659.

5-Cyclobutoxy-5-pentanolide (7i).



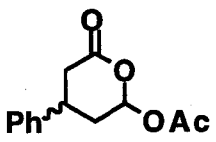
a colorless liquid; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 1.45 - 2.35 (complex m, 8H), 2.20 - 2.40 (m, 2H), 2.45 - 2.68 (m, 2H), 4.34 (quint-like, J ~ 7.4 Hz, 1H, OCH), 5.33 (t-like, J ~ 3.5 Hz, 1H, δ-CH); ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 12.66 (t), 15.45 (t), 27.71 (t), 29.80 (t), 30.00 (t), 31.34 (t), 72.13 (d), 100.16 (d), 170.76 (s); IR(ν_{CO}) 1740 cm^{-1}; EIMS (relative intensity) m/z 170 (M^+, 1), 152 (1), 142 (1), 114 (4), 99 (100), 71 (24), 55 (42) HREIMS calcd for $C_9H_{14}O_3$ m/z 170.0943, found, 170.0920.

***trans*-3-Butyl-5-acetoxy-5-pentanolide (6j).**



a colorless liquid; ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 0.92 (t, J = 6.2 Hz, 3H, C*H*$_3$CH$_2$), 1.32 (br s, 6H), 1.68 (ddd, J = 3.1, 11.6, 14.5 Hz, 1H, γ-C*H*H), 2.01 (dt-like, J ~ 14.5, 1.8 Hz, 1H, γ-CH*H*), 2.11 (s, 3H, CH_3CO), 2.15 (dd, J = 17.5, 11.0 Hz, 1H, α-C*H*H), 2.20 - 2.28 (m, 1H, β-C*H*), 2.79 (ddd, J = 1.4, 5.3, 17.5 Hz, 1H, α-CH*H*), 6.58 (t-like, J ~ 2.7 Hz, 1H, δ-CH); ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 13.83 (q, CH_3), 20.82 (q, *C*H$_3$CO), 22.47 (t), 26.94 (d, β-CH), 28.25 (t), 32.65 (t, γ-CH_2), 35.40 (t), 36.57 (t, α-CH_2), 92.33 (d, δ-CH), 168.62 (s), 169.00 (s); IR(ν_{CO}) 1762 cm^{-1}; CIMS (relative intensity) m/z 215 (M^++1, 1), 201 (1), 173 (1), 155 (100), 111 (6), 86 (4); HRCIMS calcd for $C_{11}H_{19}O_4$ (M^++1) m/z 215.1283, found, 215.1276.

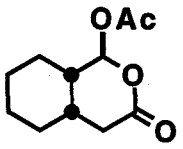
trans-3-Phenyl-5-acetoxy-5-pentanolide (6k).



a colorless liquid; ^{1}H-NMR ($CDCl_3$, 600 MHz) δ2.16 (s, 3H, CH_3CO), 2.21 - 2.25 (m, 2H, γ-CH_2), 2.65 (dd, J = 17.8, 11.8 Hz, 1H, α-CH*H*), 3.00 (ddd, J = 17.8, 5.5, 1.1 Hz, 1H, α-C*H*H), 3.52 - 3.59 (m, 1H, β-CH), 6.69 (t-like, J ~ 2.7 Hz, 1H, δ-CH), 7.23 (d, J = 7.3 Hz, 2H, ortho), 7.30 (t-like, J ~ 7.5 Hz, 1H, para), 7.38 (t-like, J ~ 7.2 Hz, 2H, meta); ^{13}C-NMR ($CDCl_3$, 151 MHz) δ 20.88 (q, *C*H$_3$CO), 32.71 (d, β-CH), 33.52 (t, γ-CH_2), 37.71 (t,

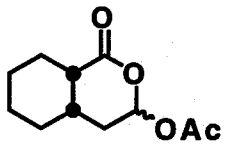
α-CH_2), 92.03 (d, δ-CH), 126.39 (d, ortho), 127.45 (d, para), 129.03 (d, meta), 141.51 (s, ipso), 168.32 (s), 168.50 (s); EIMS (relative intensity) m/z 234 (M^+, 25), 175 (16), 131 (15), 104 (100), 91 (5), 77 (5), 43 (19).

1β-Acetoxy-*cis*-octahydro-3*H*-2-benzopyran-3-one (6l).



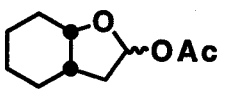
a colorless liquid; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 1.25 - 1.80 (m, 9H), 1.90 (m, 1H), 2.11 (s, 3H, CH_3CO), 2.45 - 2.65 (m, 2H), 6.54 (d, J = 2.9 Hz, 1H, δ-CH); ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 20.63, 20.91, 23.32, 24.04, 26.78, 28.33, 31.30, 36.69, 95.86 (d, OCHO), 168.73 (s), 169.34 (s); IR(ν_{CO}) 1758 cm^{-1}; EIMS (relative intensity) m/z 212 (M^+, 1), 166 (2), 153 (39), 124 (98), 108 (14), 82 (100), 67 (53); HREIMS calcd for $C_{11}H_{16}O_4$ m/z 212.1049, found, 212.1031.

[Partial spectral data for δ-lactone **6l'** (mixture of two isomers)] a colorless liquid;



^{1}H-NMR ($CDCl_3$, 270 MHz) δ 2.11 (s, 3H, CH_3CO major and minor), 6.47 (m, 1H, δ-CH minor), 6.56 (m, 1H, δ-CH major); ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 44.76 (d, minor), 46.35 (d, major), 92.14 (d, minor OCHO), 92.28 (d, major OCHO).

[Partial spectral data for THF **7l** (mixture of two isomers)] a colorless liquid; ^{1}H-NMR



($CDCl_3$, 270 MHz) δ 2.05 (s, 3H, CH_3CO major), 2.07 (s, 3H, CH_3CO minor), 4.03 (q, J = 4.6 Hz, 1H, OCH minor), 4.19 (q, J = 3.9 Hz, 1H, OCH major), 6.21 (dd, J = 4.2, 1.5 Hz, 1H, OCHO minor), 6.31 (dd, J = 4.2, 5.4 Hz, 1H, OCHO major); ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 20.24, 21.09, 21.37, 23.05, 23.67, 26.65, 27.65, 27.92, 28.49, 35.79, 36.57, 37.88, 39.31, 77.69 (d, major OCH), 79.48 (d, minor OCH), 98.58 (d, major OCHO), 98.80 (d, minor OCHO), 170.68 (s, major).

3-4. References and Notes

(1) (a) Coffman, D. D.; Cramer, R.; Mochel, W. E. *J. Am. Chem. Soc.* **1958**, *80*, 2882.

(b) Chiusoli, G. P.; Minisci, F. *Gazz. Chim. Ital.* **1958**, *88*, 43.

(2) Leading references: (a) Liu, Z.-Y.; He, L.; Zheng, H. *Synlett* **1993**, 191. (b) Shin, I.; Zhou, H.-Q.; Que, N. L. S.; Liu, H.-W.; Swedenborg, P. D.; Jones, R. L. *J. Org. Chem.* **1993**, *58*, 2923. (c) Ranieri, R. L.; Calton, G. J. *Tetrahedron Lett.* **1978**, 499. (d) Endo, A.; Kuroda, M.; Tsujita, Y. *J. Antibiot.* **1976**, *29*, 1346. (e) Wovkulich, P. M.; Tang, P. C.; Chadha, N. K.; Batcho, A. D.; Barrish, J. C.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1989**, *111*, 2596. (f) Danishefsky, S. J.; Simoneau, B. *J. Am. Chem. Soc.* **1989**, *111*, 2599.

(3) For selected examples of metal-mediated carbonylation of *unsaturated* alcohols to lead to δ-lactones, see: (a) Murray, T. F.;Varma, V.; Norton, J. R. *J. Org. Chem.* **1978**, *43*, 353. (b) Alper, H.; Leonard, D. *J. Chem. Soc., Chem. Commun.* **1985**, 511. (c) Chenal, T.; Naigre, R.; Ciprés, I.; Kalck, P.; Daran, J.-C.; Vaissermann, J. *J. Chem. Soc., Chem. Commun.* **1993**, 747. (d) Naigre, R.; Chenal, T.; Ciprés, I.; Kalck, P.; Daran, J.-C.; Vaissermann, J. *J. Organometallic. Chem.* **1994**, *480*, 91. (e) Chow, Y. L.; Huang, Y.-J.; Dragojlovic, V. *Can. J. Chem.* **1995**, *73*, 740.

(4) (a) Ryu, I.; Kusano, K.; Ogawa, A.; Kambe, N.; Sonoda, N. *J. Am. Chem. Soc.* **1990**, *112*, 1295. (b) Ryu, I.; Kusano, K.; Masumi, N.; Ogawa, A.; Yamazaki, H.; Sonoda, N. *Tetrahedron Lett.* **1990**, *31*, 6877. (c) Tsunoi, S.; Ryu, I.; Fukushima, H.; Tanaka, M.; Komatsu, M.; Sonoda, N. *Synlett* **1995**, 1249. Also see, reviews: (d) Ryu, I.; Sonoda, N.; Curran, D. P. *Chem. Rev.* **1996**, *96*, 177. (e) Ryu, I.; Sonoda, N. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1050.

(5) A part of this work, see: Tsunoi, S.; Ryu, I.; Sonoda, N. *J. Am. Chem. Soc.* **1994**, *116*, 5473.

(6) For pioneering work on THF-formation by oxidative cyclization of alcohols with LTA, see: (a) Cainelli, G.; Mihailović, M. L.; Arigoni, D.; Jeger, O. *Helv. Chim. Acta* **1959**, *42*, 1124. (b) Mićović, V. M.; Mamuzić, R. I.; Jeremić, D.; Mihailović, M. L. *Tetrahedron* **1964**, *20*, 2279. (c) Mihailović, M. L.; Čeković, Ž.; Maksimović,

Z.; Jeremić, D.; Lorenc, L.; Mamuzić, R. I. *Tetrahedron* **1965**, *21*, 2799. For leading reviews, see: (d) Mihailović, M. L.; Čeković, Ž.; Lorenc, L. In *Organic Syntheses by Oxidation with Metal Compounds*; Mijs, W. J.; de Jonge, C. R. H. I., Eds.; Plenum Press: New York 1986; chapt. 14. (e) Mihailović, M. L.; Čeković, Ž. *Synthesis* **1970**, 209. (f) Rubottom, G. M. In *Oxidation in Organic Chemistry*; Academic Press: New York, 1982, part D. chapt. I. (g) Rotermund, G. W. In *Methoden der Organischen Chemie* (*Houben-Weyl*); Müller, E., Ed.; Georg Thieme; Stuttgart, 1975, Band 4, Teil 1b, Oxidation II, p 204. (h) Heusler, K.; Kalvoda, J. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 525.

(7) Leading references on 1,5-H shift from C to O •: (a) Barton, D. H. R. *Pure Appl. Chem.* **1968**, *16*, 1. (b) Brun, P.; Waegell, B. In *Reactive Intermediates*; Abramovitch, R. A., Ed.; Plenum Press: New York, 1983; vol. 3, chapt. 6. (c) Walling, C. *Pure Appl. Chem.* **1967**, *15*, 69. 1,5-H from C to N •: (d) Corey, E. J.; Hertler, W. R. *J. Am. Chem. Soc.* **1960**, *82*, 1657. (e) Neale, R. S. *Synthesis* **1971**, 1. (f) Stella, L. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 337. (g) Dicks, P. F.; Glover, S. A.; Goosen, A.; McCleland, C. W. *Tetrahedron* **1987**, *43*, 923. 1,5-H from C to C •: (h) Curran, D. P.; Shen, W. *J. Am. Chem. Soc.* **1993**, *115*, 6051. (i) Curran, D. P.; Liu, H. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1377.

(8) Walling, C.; Padwa, A. *J. Am. Chem. Soc.* **1963**, *85*, 1597.

(9) (a) Rawal, V. H.; Newton, R. C.; Krishnamurthy, V. *J. Org. Chem.* **1990**, *55*, 5181. (b) Kim, S.; Lee, S.; Koh, J. S. *J. Am. Chem. Soc.* **1991**, *113*, 5106. (c) Begley, M. J.; Housden, N.; Johns, A.; Murphy, J. A. *Tetrahedron* **1991**, *47*, 8417. (d) Rawal, V. H.; Krishnamurthy, V. *Tetrahedron Lett.* **1992**, *33*, 3439. (e) Rawal, V. H.; Iwasa, S. *Tetrahedron Lett.* **1992**, *33*, 4687. (f) Kim, S.; Koh, J. S. *J. Chem. Soc., Chem. Commun.* **1992**, 1377. (g) Kim, S.; Koh, J. S. *Tetrahedron Lett.* **1992**, *33*, 7391. (h) Breen, A. P.; Murphy, J. A. *J. Chem. Soc., Chem. Commun.* **1993**, 191. (i) Galatsis, P.; Millan, S. D.; Faber, T. *J. Org. Chem.* **1993**, *58*, 1215. (j) Rawal, V. H.; Krishnamurthy, V.; Fabre, A. *Tetrahedron Lett.*

1993, *34*, 2899.

(10) Lopez, J. C.; Alonso, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1989**, *111*, 6471.

(11) Ceric ammonium nitrate (CAN) and manganese triacetate were virtually unreactive in this system. Cf. (a) Ryu, I.; Alper, H. *J. Am. Chem. Soc.* **1993**, *115*, 7543. (b) Okuro, K.; Alper, H. *J. Org. Chem.* **1996**, *61*, 5312.

(12) In the absence of CO, tetrahydropyran derivatives are also formed in 5% yield via 1,6-hydrogen transfer. Attempted 1,6-H shift was also made with 4,4-dimethylpentanol in which 1,5-H shift is blocked by dimethyl group. Unfortunately, no products via 1,6-H shift were obtained, and starting alcohol was recovered (80% by GC).

(13) Even with 3-pentanol and 2,4-dimethyl-3-pentanol, no products derived from 1,4-H shift were obtained. Examples of 1,4-hydrogen abstraction reaction, see: (a) Wallace, T. J.; Gritter, R. J. *J. Org. Chem.* **1961**, *26*, 5256. (b) Brunton, G.; Griller, D.; Barclay, L. R. C.; Ingold, K. U. *J. Am. Chem. Soc.* **1976**, *98*, 6803. (c) Journet, M.; Malacria, M. *J. Org. Chem.* **1992**, *57*, 3085. (d) Journet, M.; Malacria, M. *Tetrahedron Lett.* **1992**, *33*, 1893.

(14) It is thought that with the oxidation of saturated alcohol with LTA, first step is alkoxylation of LTA. Until now, however, an alkoxy lead intermediate has not been isolated.

(15) Decarbonylation order of acyl radical being: tertiary > secondary > primary acyl radical, see: (a) Chatgilialoglu, C.; Lucarini, M. *Tetrahedron Lett.* **1995**, *36*, 1299. (b) Chatgilialoglu, C.; Ferreri, C.; Lucarini, M.; Pedrielli, P.; Pedulli, G. F. *Organometallics* **1995**, *14*, 2672 and references cited therein.

(16) Kochi, J. K.; Bacha, J. D.; Bethea III, T. W. *J. Am. Chem. Soc.* **1967**, *89*, 6538.

(17) Wheeler, J. W.; Evans, S. L.; Blum, M. S.; Velthius, H. H. V.; de Camargo, J. M. F. *Tetrahedron Lett.* **1976**, 4029.

(18) Optical purity was estimated by GC (column: Chiraldex G-TA, 0.25 mm x 20 m; temp. 90 °C; carrier gas 0.9 kg/cm^2 He.).

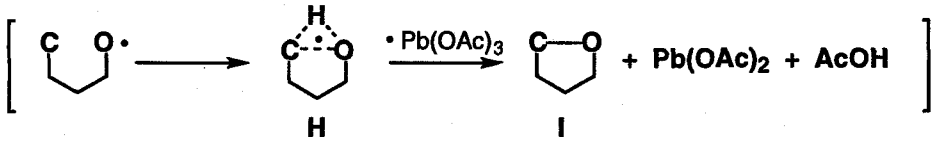
(19) (a) Pirkle, W. H.; Adams, P. E. *J. Org. Chem.* **1978**, *43*, 378. (b) Bacardit, R.; Moreno-Mañas, M. *J. Chem. Ecol.* **1983**, *9*, 703. (c) Mori, K.; Senda, S. *Tetrahedron* **1985**, *41*, 541. (d) Bäckvall, J.-E.; Byström, S. E.; Nyström, J. E. *Tetrahedron* **1985**, *41*, 5761. (e) Narasaka, K.; Ukaji, Y. *Chem. Lett.* **1986**, 81. (f) Gerth, D. B.; Giese, B. *J. Org. Chem.* **1986**, *51*, 3726. (g) White, J. D.; Somers, T. C.; Reddy, G. N. *J. Am. Chem. Soc.* **1986**, *108*, 5352. (h) Ikuba, T.; Nakao, T.; Nishii, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **1986**, *108*, 7420. (i) Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1987**, *28*, 651. (j) Bernardi, R.; Ghiringhelli, D. *Synthesis* **1989**, 938. (k) Harada, T.; Matsuda, Y.; Imanaka, S.; Oku, A. *J. Chem. Soc., Chem. Commun.* **1990**, 1641. (l) Schink, H. E.; Bäckvall, J.-E. *J. Org. Chem.* **1992**, *57*, 1588. (m) White, J. D.; Somers, T. C.; Reddy, G. N. *J. Org. Chem.* **1992**, *57*, 4991. (n) Jacobs, H. K.; Mueller, B. H.; Gopalan, A. S. *Tetrahedron* **1992**, *48*, 8891.

(20) Heusler, K.; Kalvoda, J.; Anner, G.; Wettstein, A. *Helv. Chim. Acta* **1963**, *46*, 352.

(21) Rate constants for addition-fragmentation of cycloalkoxy radicals (chap. 3-2-2 , Scheme 8), see: (a) Beckwith, A. L. J.: Day, B. P. *J. Am. Chem. Soc.* **1989**, *111*, 2674. (b) Beckwith, A. L. J.: Day, B. P. *J. Am. Chem. Soc.* **1989**, *111*, 230. Synthesis by using ring closure of formylalkyl radicals, see: (c) Walton, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1991**, *113*, 5791.

(22) By increasing alkyl group attached to the carbinol carbon atom, the reaction time prolongs, see ref 6c.

(23) Heusler and Kalvoda suggest direct oxidation of **H** to cyclic ether **I** with the aid of a lead triacetate radical, see: ref 6h.



(24) Rate for the carbonylation of primary alkyl radical, see: Nagahara, K.; Ryu, I.;

Kambe, N.; Komatsu, M.; Sonoda, N. *J. Org. Chem.* **1995**, *60*, 7384.

(25) Huber, F.; Horn, H.; Haupt, H. J. *Z. Naturforsch.* **1967**, *22b*, 918.

(26) Čeković and coworker propose that δ-hydroxy alkyl radical is in tight radical pair with Pb(III) species, see: (a) Čeković, Ž.; Ilijev, D. *Tetrahedron Lett.* **1988**, *29*, 1441. Also, see: (b) Mihailović, M. L.; Konstantinović, S.; Vukicević, R. *J. Serb. Chem. Soc.* **1987**, *52*, 175. To trap the intermediate **H**, the reaction of ROD with LTA was conducted under N_2 at 40 °C, however unfortunately no δ-deuterated alcohol was observed. Attempts to trap **H** by dimethylacetylene dicarboxylate and cyclohexanecarboxaldehyde also resulted in failure.

(27) Wayner, D. D. M.; Griller, D. In *Advances Free Radical Chemistry*; Tanner, D. D., Ed.; JAI Press: Greenwich, 1990; Vol. 1, p 159. The preference of methylene over methyl in the competitive 1,5-H abstraction of alkoxy radical has been well documented, see: reference 8.

(28) Hauser, D.: Schaffner, K.: Jeger, O. *Helv. Chim. Acta* **1964**, *47*, 1883.

(29) (a) Mihailović, M. L.; Čeković, Ž.; Stanković, J.; Pavlović, N.; Konstantinović, S.; Djokić-Mazinjanin, S. *Helv. Chim. Acta* **1973**, *56*, 3056. (b) Bortrand, M. P.; Surzur, J. M.; Boyer, M.; Mihailovic, M. L. *Tetrahedron* **1979**, *35*, 1365.

(30) Cyclization reaction of 4-pentenyl-1-oxy radical generated from *N*-(4-pentenyloxy)pyridine-2(1H)-thione gave a mixture of 5-*exo* and 6-*endo* cyclic products in the ratio of 98:2, see: (a) Hartung, J.; Gallou, F. *J. Org. Chem.* **1995**, *60*, 6706. (b) Hartung, J.; Hiller, M.; Schmidt, P. *Chem. Eur. J.* **1996**, *2*, 1014.

(31) (a) Moriarty, R. M.; Kapadia, K. *Tetrahedron Lett.* **1964**, 1165. (b) Moon, S.; Lodge, J. M. *J. Org. Chem.* **1964**, *29*, 3453.

(32) (a) Meyer, K.; Roček, J. *J. Am. Chem. Soc.* **1972**, *94*, 1209. (b) Roček, J.; Radkowsky, A. E. *J. Org. Chem.* **1973**, *38*, 89. (c) Roček, J.; Aylward, D. E. *J. Am. Chem. Soc.* **1975**, *97*, 5452.

(33) (a) Snider, B. B.; Vo, N. H.; Foxman, B. M. *J. Org. Chem.* **1993**, *58*, 7228. Cf: (b) Hirao, T; Fujii, T; Miyata, S-i; Ohshiro, Y. *J. Org. Chem.* **1991**, *56*, 2264.

(34) (a) Dowd, P.; Zhang, W. *J. Am. Chem. Soc.* **1991**, *113*, 9875. (b) Dowd, P.; Zhang, W. *J. Org. Chem.* **1992**, *57*, 7163. (c) Zhang, W.; Dowd, P. *Tetrahedron Lett.* **1992**, *33*, 3285. (d) Zhang, W.; Dowd, P. *Tetrahedron Lett.* **1992**, *33*, 7307. (e) Zhang, W.; Dowd, P. *Tetrahedron* **1993**, *49*, 1965. (f) Zhang, W.; Hua, Y.; Hoge, G.; Dowd, P. *Tetrahedron Lett.* **1994**, *35*, 3865. Also see a pertinent review: (h) Dowd, P.; Zhang, W. *Chem. Rev.* **1993**, *93*, 2091.

(35) Suginome, H. *Chemistry and Chemical Industry* **1992**, *45*, 2014.

(36) Kim, S.; Joe, G. H.; Do, J. Y. *J. Am. Chem. Soc.* **1993**, *115*, 3328.

(37) (a) Suginome, H.; Liu, C. F.; Furusaki, A. *Chem. Lett.* **1984**, 911. (b) Suginome, H.; Liu, C. F.; Tokuda, M. *J. Chem. Soc., Chem. Commun.* **1984**, 334. (c) Kobayashi, K.; Itoh, M.; Suginome, H. *Tetrahedron Lett.* **1987**, *28*, 3369. (d) Suginome, H.; Nakayama, Y.; Harada, H.; Hachiro, H.; Orito, K. *J. Chem. Soc., Chem. Commun.* **1994**, 451.

(38) Kim, S.; Lee, S. *Tetrahedron Lett.* **1991**, *32*, 6575.

(39) As far as I know, there are at least two previous reports on the reaction of cyclobutanols with LTA. The reaction is quite complex and gives various products, which includes acetoxybutylaldehyde, cyclobutanone, cyclobutylacetate, and 1,8-octanedial. This may be due presumably to high concentration ([ROH] = 0.5-1 M) and no trapping reagent, see: (a) Mihailović, M. L.; Čeković, Ž.; Andrejević, V.; Matić, R.; Jeremić, D. *Tetrahedron* **1968**, *24*, 4947. (b) Kapustina, N. I.; Nikishin, G. I. *Izv. Akad. Nauk, Ser. Khim.* **1992**, 2760.

(40) Tsunoi, S.; Ryu, I.; Tamura, Y.; Yamasaki, S.; Sonoda, N. *Synlett* **1994**, 1009.

(41) Even in the case of five-membered alkoxy radical, β-scission is known to be preferred than 1,5-hydrogen transfer, see: ref 8. Some rate constants for the β-scission of alkoxy radical are measured, see: (a) Beckwith, A. L. J.; Hay, B. P.; Williams, G. M. *J. Chem. Soc., Chem. Commun.* **1989**, 1202. (b) Avila, D. V.; Brown, C. E.; Ingold, K. U.; Lusztyk, J. *J. Am. Chem. Soc.* **1993**, *115*, 466. Also see, refs 21a-b.

(42) Rate constant for 1,5-H shift from C to O • has been estimated to be $>10^8$ s^{-1} (for *n*-hexyloxy radical), see: Gilbert, B. C.; Holmes, R. G. G.; Laue, H. A. H.; Norman, R. O. C. *J. Chem. Soc., Perkin Trans. 2* **1976**, 1047.

(43) For a review, see: Sheldon, R. A.; Kochi, J. K. *Org. React.* **1972**, *19*, 279.

(44) Mixed anhydride consisting of **6f** and acetic acid was also observed. Anhydride **8f** was isolated by preparative HPLC equipped with GPC column.

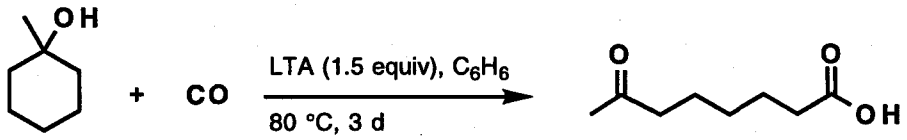
(45) In general, the β-scission of alkoxy radicals is favored by increasing stability of radicals formed, see: Bacha, J. D.; Kochi, J. K. *J. Org. Chem.* **1965**, *30*, 3272. Also see refs 34e and 36. In the case of 1-butylcyclobutanol (**5f**), no analogous product, valeric acid, was detected.

(46) This reaction was conducted in the presence of acetic acid (6 equiv). This had some effect on suppression of formation of 5-cyclobutoxy-5-pentanolide (**7i**).

(47) Uncyclized aldehyde was formed (ca. 5%). Uncarbonylated product, 2-acetoxytetrahydrofuran, was also detected in a trace amount.

(48) Cyclobutanols **5j** and **5k** similarly produced 5-cyclobutoxy-5-pentanolides (< 5%).

(49) 1-Methylcyclohexanol gave 1-methylcyclohexyl acetate along with vast amounts of starting alcohol. Desired carbonylation product was formed in a trace amount. This may be owing to less reactive nature of tertiary alcohol.

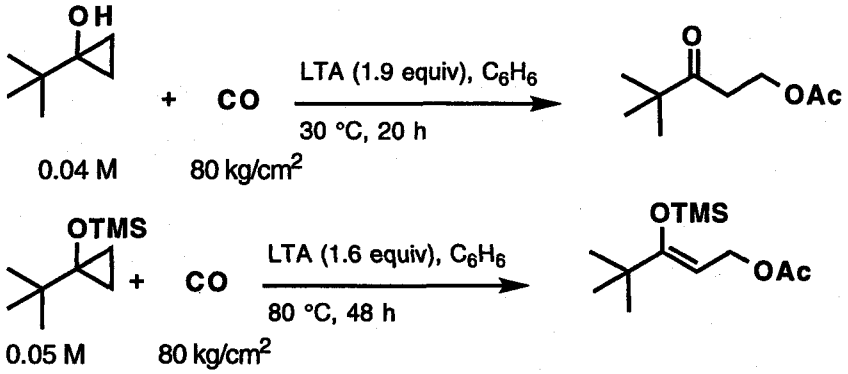


(50) For examples of radical carbonylation via β-scission, see ref 1.

(51) Rubottom, R. G.; Beedle, E. C.; Kim, C.-W.; Mott, R. C. *J. Am. Chem. Soc.* **1985**, *107*, 4230.

(52) Attempts to carbonylate cyclopropanol were also unsuccessful. The products

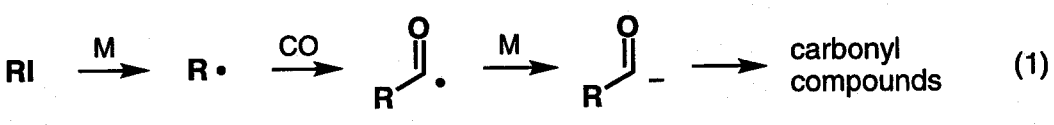
were acetoxylated compounds.



Chapter 4. Carbonylation of Alkyl Iodides with Carbon Monoxide Using a One-Electron Reduction System of Zn(0)

4-1. Introduction

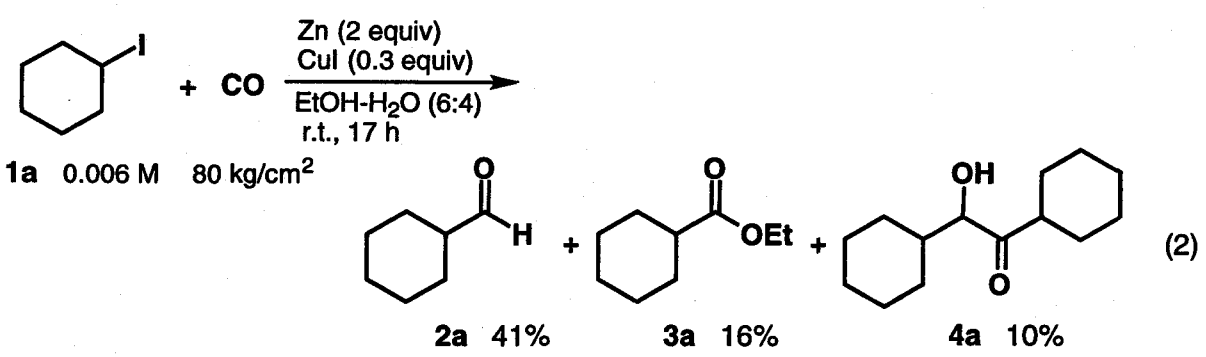
The use of metal reduction systems for free-radical generation has allowed for great advances in the field of free-radical chemistry.[1] The reactions induced by Sm, Zn, Ti, V, Cr, Fe, Cu, Nb, Ru, Co, Li, Na, K, and Ni, are widely explored. In the comparison with traditional group 14 metal hydride method, the one-electron reduction process demonstrates remarkable stereoselectivity for some carbonyl compounds, and new type of radicals unachievable by group 14 metal hydride approaches, may be successfully generated. A further advantage of metal reduction systems over group 14 metal hydride system is that a radical reaction can be followed by an anionic reaction after the key radical undergoes one-electron reduction. Until now, examples of carbonylation using a metal reduction system are rare. In 1990, an efficient carbonylation reaction of alkyl halides which takes place in a tin hydride mediated radical reaction system, was reported.[2a] Since then, addition of an alkyl radical to carbon monoxide has become an attractive key reaction for synthesizing a variety of carbonyl compounds such as aldehydes,[2a-j] ketones,[2j-p] macrocyclic ketolactones,[2q] lactones,[2r-t] and carboxylic acids and their derivatives.[2s-v] This encouraged me to investigate carbonylation reaction of organic halides in a metal induced reduction system. In this chapter, free-radical carbonylation under one-electron reduction system of zinc is described.[3]



(1)

4-2. Results and Discussion

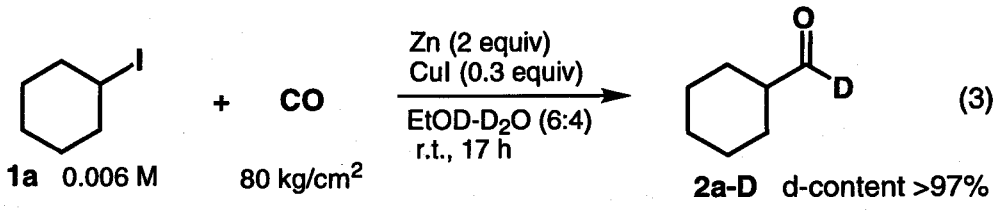
A variety of organic halides can be formylated by tin hydride/CO via radical carbonylation.[2a] In principle, similar transformations may well be achieved, even with the use of a one-electron reduction system of metal. To test this hypothesis, the formylation of organic iodides using a zinc-copper couple in aqueous media (Luche's system)[4,5] was examined under a pressure of CO. A mixture of zinc powder (39 mg, 0.6 mmol) and CuI (17 mg, 0.09 mmol) in EtOH-H_2O (6/4, 50 mL), which was ultrasonicated under N_2, was placed in a round bottomed glass liner. Cyclohexyl iodide (63 mg, 0.3 mmol) was added to the mixture and the glass liner was inserted into a stainless steel autoclave and was charged with 80 atm of CO. The reaction was conducted at ambient temperature with stirring for 17 h. GC analysis of the reaction mixture showed the presence of three types of carbonylated compounds which were subsequently identified as **2a**, **3a**, and **4a** (eq 2). The major carbonylation product was the desired cyclohexanecarboxaldehyde (**2a**) (41% GC yield).[6]



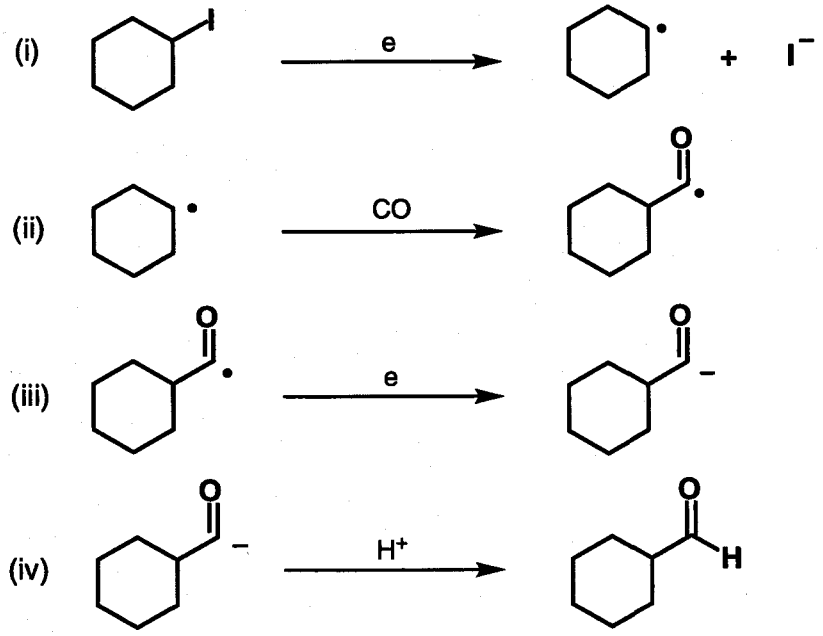
(2)

The following mechanism accounts for the formation of **2a** (Scheme 1): (i) cyclohexyl radical is generated by a one-electron reduction of cyclohexyl iodide, (ii) the addition of this radical to CO gives an acyl radical, (iii) one-electron reduction of the resultant acyl radical gives rise to an acyl anion, and (iv) protonation of the acyl anion gives an aldehyde.[7] A similar reaction conducted in EtOD-D_2O as the solvent

resulted in the formation of RCDO (d-content >97%, eq 3), and this precluded a hydrogen abstraction mechanism by an acyl radical. As for the CO trapping step, a mechanism involving a reaction of cyclohexyl anion with CO is less likely, because this system is comprised of protic solvents. These data are consistent with earlier observations that the reaction of organozinc compounds with CO proceeds with considerable inefficiency.[8]

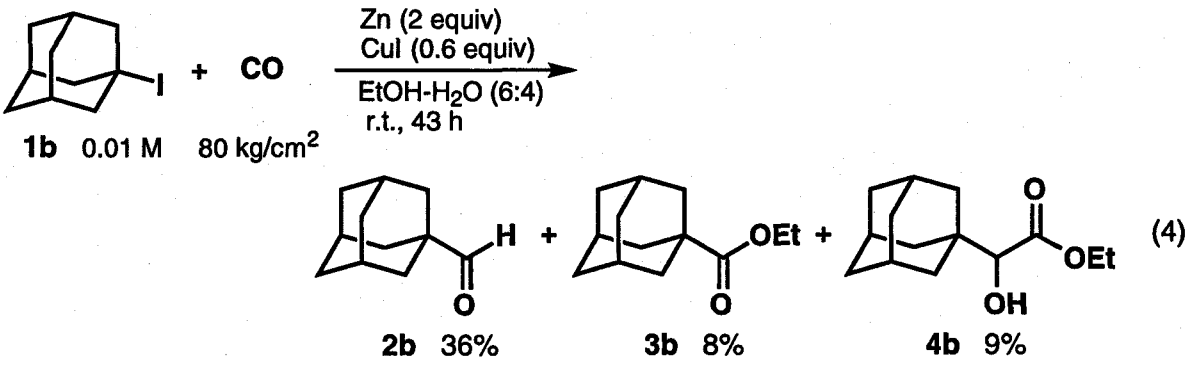


Scheme 1



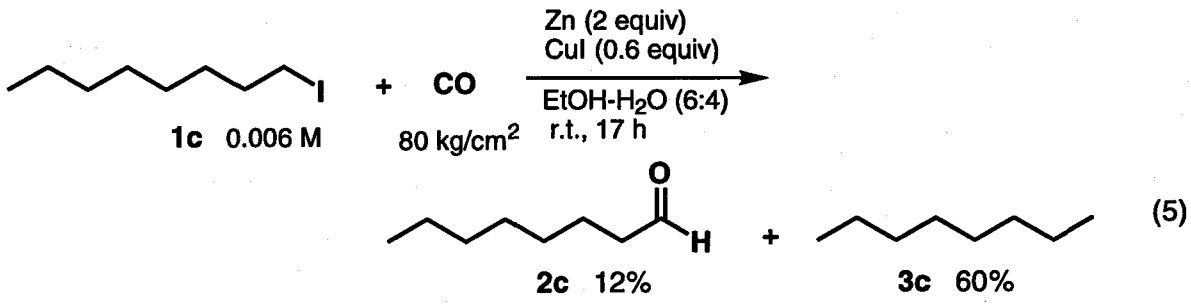
In a related experiment, the carbonylation of 1-iodoadamantane (**1b**) gave aldehyde **2b** (36%) together with **3b** (8%) and **4b** (9%) (eq 4). It is interesting to note that **4b**, a molecule which contains two molecules of CO and one molecule of ethanol,

is produced in this reaction, even though the mechanism for this reaction is unclear.



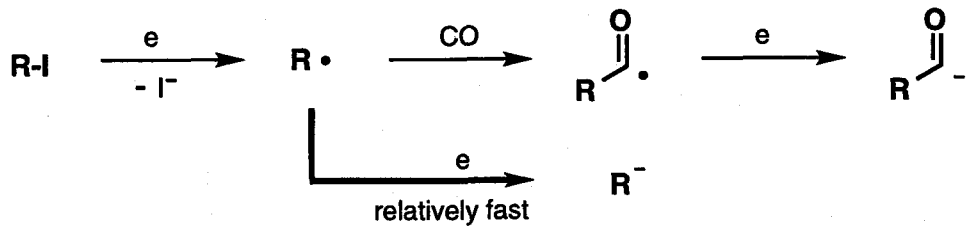
(4)

In contrast to the above two examples, similar reactions using octyl iodide as the starting material met with a little success (eq 5). A likely explanation for this reaction is that the *primary* alkyl radical is rapidly reduced to a carbanion in preference to CO trapping (Scheme 2). For this reason, the zinc method appears to be inferior to the tin hydride methods, at least for this class of compounds.



(5)

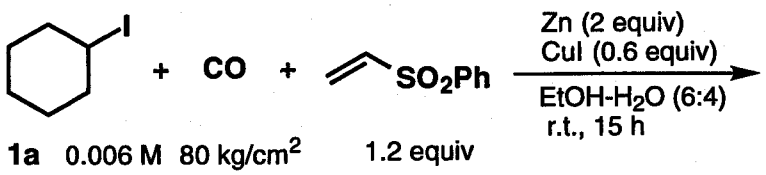
Scheme 2



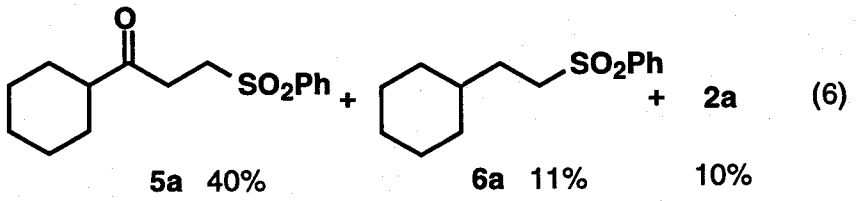
It is noteworthy that in the absence of CuI, a reaction did not take place. The preparation of the zinc-copper couple required ultrasonication, otherwise the reaction

was sluggish. The reaction proceeded in water alone, but an increase in the concentration of ethanol retarded the reaction. Reaction temperature (10~60 °C) had little effect and the use of Zn/NaI in DME[9] was inferior to Zn/CuI in EtOH-H_2O. It is also interesting to note that analogous reactions proceeded when Sm was used instead of Zn. Alkyl bromides were not reactive under the conditions employed for this study.

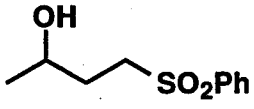
In another series of experiments, an attempt was made to couple an alkyl iodide with CO and an alkene.[2j-k] The zinc induced coupling reaction of cyclohexyl iodide (**1a**) with CO and phenyl vinyl sulfone gave the desired 2-phenylsulfonylethyl cyclohexyl ketone (**5a**) in 40% yield together with **2a** (10%) and **6a** (11%) (eq 6).[10] By-product **6a** is derived from direct addition product of cyclohexyl radical to vinyl sulfone. Interestingly, by-product **7a** was also obtained in 13% yield. The addition of α-hydroxy ethyl radical, arising from hydrogen abstraction of cyclohexyl radical from ethanol, to vinyl sulfone may account for the formation of **7a**. Similarly, the three-component coupling of **1a** with CO and acrylonitrile, gave 2-cyanoethyl cyclohexyl ketone (**8a**) in 42% yield (eq 7). The formation of 2-cyclohexylethyl cyanide (**9a**, 20%) and cyclohexanecarboxaldehyde (**2a**, 10%) was also recognized.



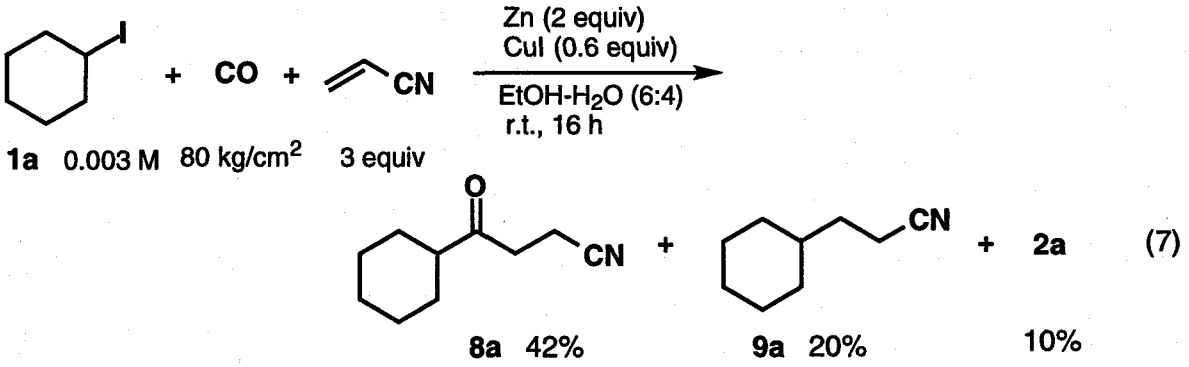
1a 0.006 M 80 kg/cm^2 1.2 equiv



5a 40% **6a** 11% 10% (6)



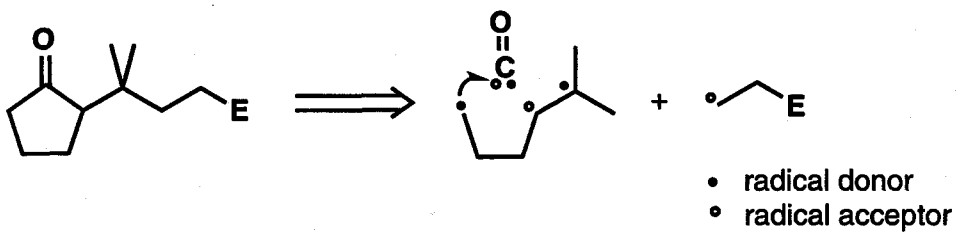
7a



(7)

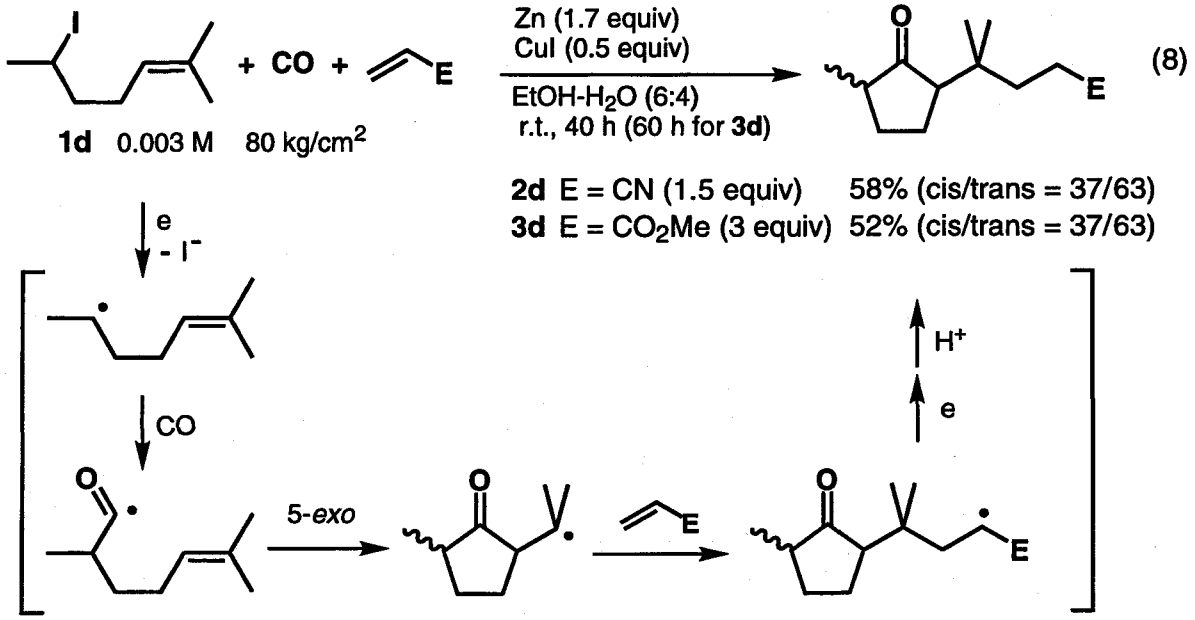
It has already been reported that a tin hydride mediated 4+1 radical annulation of 6-iodo-2-methyl-hept-2-ene (**1d**) with CO afforded 2-methyl-5-isopropylcyclopentanones.[21] In this study, the three-component coupling reaction accompanied by such an annulation was tested (Scheme 3).[11]

Scheme 3

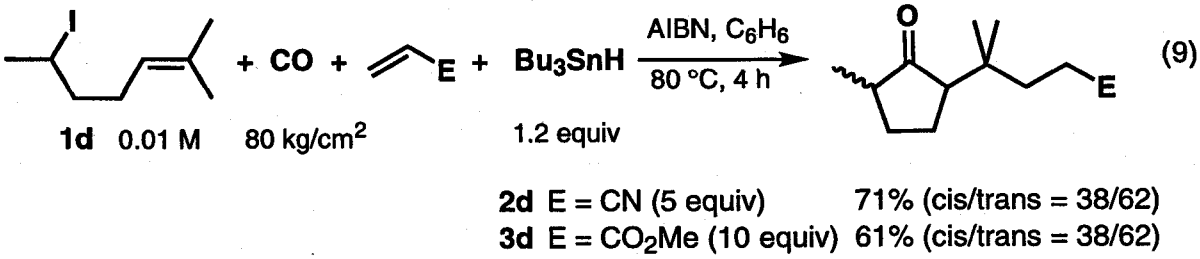


The CO trapping of alk-4-enyl radical having terminal dialkyl substitution should yield tertiary 1,1-dialkyl(2-oxocyclopentyl)carbinyl radical via the subsequent 5-*exo* type of cyclization. In the presence of an alkene, this radical would be expected to add to the alkene in preference to CO, since CO trapping for tertiary alkyl radicals does not proceed smoothly due to rapid decarbonylation of tertiary acyl radicals.[12] It is also conceivable that the slow reduction of a *tertiary* alkyl radical by zinc would allow time for the addition of the radical to an alkene. As predicted, the reaction of **1d** with CO in the presence of acrylonitrile gave the desired cyclopentanone derivative **2d** in 58% yield after purification by silica gel chromatography (eq 8).[13,14] Similarly, using methyl acrylate as the alkene, α-functionalized cyclopentanone **3d** was obtained

in 52% isolated yield.



For purposes of comparison, tin hydride mediated system was also tested and proved to be successful (eq 9).[15,15] Nearly the same stereoselectivity was observed, supporting the hypothesis that these two reactions both proceed via acyl radical cyclization.

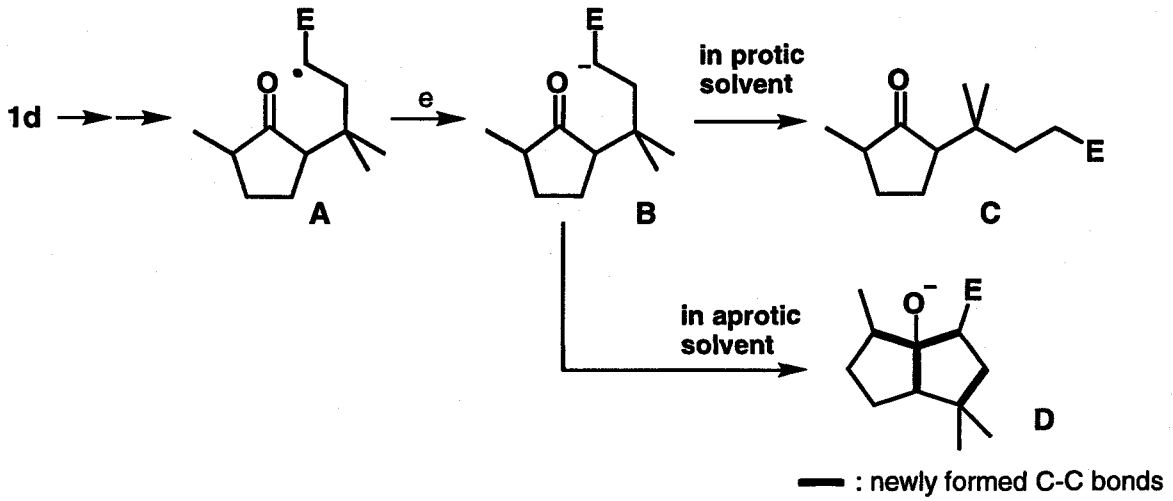


Zinc mediated radical carbonylation reactions of alkyl iodides in protic solvent described above, achieve the essentially same transformation as tin and silyl mediated reactions, but there may be three mechanistically different points; (i) Radicals are not generated by halogen abstraction but by elimination of halide ion via one-electron reduction. (ii) Radicals are not terminated by hydrogen donation but by one-electron reduction to lead to anions and the subsequent protonation of them. (iii) Zinc mediated

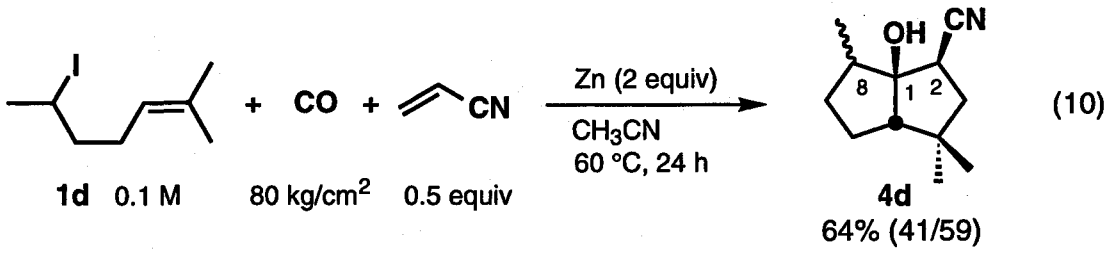
reaction is not a chain process.

The reaction of **1d** with CO and activated alkenes afforded functionalized cyclopentanones via the consecutive formation of three C-C bonds. Sequential radical/anionic reaction in which a radical reaction is followed by an anionic reaction, constitutes a characteristic and synthetically attractive feature of metal mediated radical reaction. To take advantage of this feature, zinc promoted reaction of **1d** was examined in aprotic solvent in expectation of anionic cyclization of **B** would follow the three steps of radical C-C bond formation yielding bicyclooctanol **D** (Scheme 4).[17]

Scheme 4



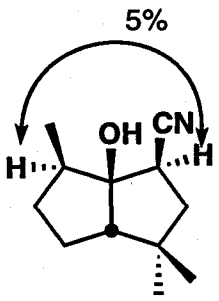
When the reaction of 6-iodo-2-methyl-hept-2-ene (**1d**, 476 mg, 2 mmol) with CO (80 atm) and acrylonitrile (53 mg, 1 mmol) was carried out in the presence of zinc dust (262 mg, 4 mmol) at 60 °C for 24 h ([**1d**] = 0.1 M in acetonitrile), the anticipated 2-cyano-4,4,8-trimethyl-bicyclo[3.3.0]octan-1-ol (**4d**, 124 mg, 64 % yield, 41/59) was obtained after isolation of flash chromatography on silica gel (eq 10). Only two of the four possible diastereoisomers were produced as judged by NMR. The isomer mixture of **4d** was separated by silica gel chromatography, and absolute structures were confirmed to be *endo/exo* isomer at 8-position by nOe experiments (Scheme 5).



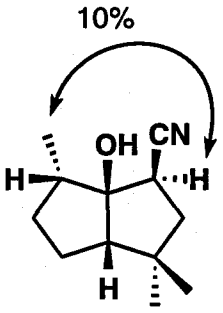
(10)

To examine the reaction generality, the reaction with methyl acrylate was conducted. Under similar conditions, the reaction of **1d** with methyl acrylate led to bicyclo[3.3.0]octan-1-ol **5d** in 34% (eq 11, *endo*/*exo* = 47/53).[18] The observed diastereoselectivities in the second anionic cyclization has been rationalized on the basis of steric repulsion. Namely, transition state giving 2-*endo* product is disfavored due to the steric repulsion between functionality derived from olefin and cyclopentanone ring. Carbanion **B** undergo second cyclization via 2-*exo* transition state to give 2-exo functionalized bicyclic octanol (Scheme 6).

Scheme 5

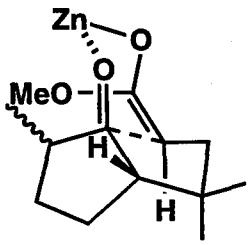


8-*exo*-4d

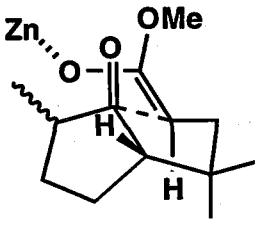


8-*endo*-4d

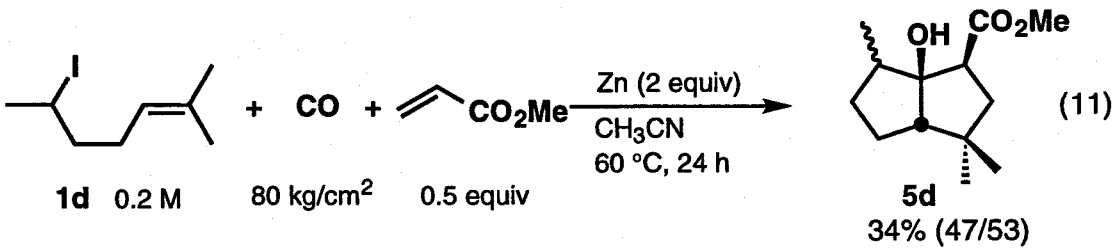
Scheme 6



TS-E



TS-F



(11)

This reaction involves two types of annulations, 4+1 radical and 3+2 anionic,

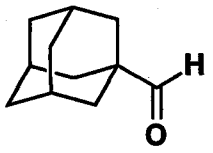
and remarkably four C-C bonds, via three radical and one anionic reactions, were newly formed. Carbon monoxide was incorporated into bridge head as a carbinol carbon in the product. The outcome of carbonylation of **1d** in aprotic solvent is especially significant because of one step synthesis of cyclopentanoid[19] from simple alk-4-enyl iodide, CO, and activated alkene.

4-3. Experimental

General Ultrasonication was performed on a BRANSONIC B-220J. Zinc powder was purchased from Wako Pure Chemical Industries.

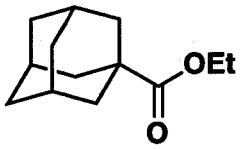
Procedure for the Synthesis of 1-Adamantanecarboxaldehyde (2b): A mixture of zinc powder (67 mg, 1.0 mmol), CuI (55 mg, 0.3 mmol), and EtOH/H_2O (6/4, 5 mL) was placed in a round bottomed glass liner. The mixture was then ultrasonicated under N_2. After 10 min, additional EtOH/H_2O (6/4, 45 mL) was added and the suspension ultrasonicated again for 20 min under N_2. 1-Iodoadamantane (131 mg, 0.5 mmol) was then added to the mixture. The glass liner was inserted into a 100-mL stainless steel autoclave and the autoclave was charged with 80 kg/cm^2 of CO. The reaction mixture was stirred at room temperature. After 43 h, excess CO was evacuated, then the remaining zinc was filtered. The filtrate was added to saturated aqueous NaCl (50 mL), and was extracted with ether (50 mL x 3), and the ethereal solution was dried over $MgSO_4$. Rotary evaporation of the ethereal solution followed by preparative HPLC (GPC columns, $CHCl_3$ as the eluent) afforded ethyl (1-adamantyl)hydroxyacetate (**4b**, 11 mg, 9% yield), ethyl 1-adamantanecarboxylate (**3b**, 9 mg, 8% yield), and 1-adamantanecarboxaldehyde (**2b**, 30 mg, 36% yield). Adamantane (12%) and 1-adamantanol (<5%) via solvolysis of the starting material were also detected.

1-Adamantanecarboxaldehyde (2b).



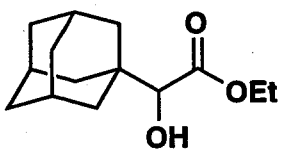
a white solid; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 1.73 (m, 12H), 2.08 (m, 3H), 9.32 (s, 1H); ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 27.37 (d), 35.85 (t), 36.57 (t), 44.81 (s), 205.89 (d); IR(neat) 1723 cm^{-1}(ν_{CO}); EIMS (relative intensity) m/z 164 (M^+, 6), 135 (100), 107 (7), 93 (17), 79 (17); HREIMS calcd for $C_{10}H_{15}NO$ m/z 164.1201, found, 164.1198.

Ethyl 1-adamantanecarboxylate (3b).



a slightly yellow liquid.; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 1.24 (t, 3H, J = 6.84 Hz), 1.71 (m, 6H), 1.89 (m, 6H), 2.01 (m, 3H), 4.10 (q, 2H, J = 6.84 Hz); ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 14.18, 27.97, 36.52, 38.82, 40.52, 59.95, 177.73; IR(neat) 1728 cm^{-1}(ν_{CO}); EIMS (relative intensity) m/z 208 (M^+, 13), 180 (6), 135 (100), 107 (6), 93 (9), 79 (9); HREIMS calcd for $C_{10}H_{15}NO$ m/z 208.1463, found, 208.1457.

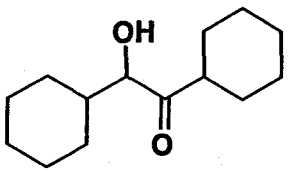
Ethyl (1-adamantyl)hydroxyacetate (4b).



a slightly yellow liquid.; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 1.32 (t, 3H, J = 7.32 Hz), 1.55 - 1.74 (m, 12H), 2.00 (br s, 3H), 2.62 (d, 1H, J = 7.81 Hz), 3.64 (t, 1H, J = 7.81 Hz), 4.26 (dq-like, 2H, J ~ 2.44, 7.32 Hz); ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 14.35 (q), 28.27 (d), 36.92 (t), 37.09 (s), 37.96 (t), 61.23 (t), 78.94 (d), 173.91 (s); IR(neat) 1725 cm^{-1}(ν_{CO}), 3515 cm^{-1}(ν_{OH}); EIMS (relative intensity) m/z 238 (M^+, 1), 165 (3), 135 (100), 107 (7), 93 (12), 79 (12); HREIMS calcd for $C_{14}H_{22}O_3$ m/z 238.1569, found, 238.1544.

1,2-Dicyclohexyl-2-hydroxyethanone (4a).

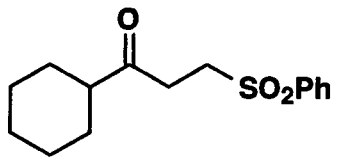
a liquid; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 1.00 - 1.95 (complex m, 21H), 2.55 (m, 1H),



3.41 (br s, 1H), 4.16 (s, 1H); ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 25.16, 25.46, 25.60, 25.85, 25.92, 25.95, 26.61, 27.20, 30.08, 30.35, 41.14, 46.24, 79.29, 215.31; IR(neat) 1702 cm^{-1}(ν_{CO}), 3475 cm^{-1}(ν_{OH}); EIMS (relative intensity) m/z 224 (M^+, 2), 142 (8), 113 (35), 95 (100), 83 (42); HREIMS calcd for $C_{14}H_{24}O_2$ m/z 224.1776, found, 224.1788.

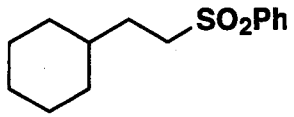
General Procedure for Three-Component Coupling Reaction: A mixture of zinc powder (0.6 mmol), CuI (0.12 mmol), ethanol (60 mL) and H_2O (40 mL) were placed in a round bottomed glass tube. The mixture was ultrasonicated for 30 minutes. Then black suspended Zn/Cu couple was prepared. Acrylonitrile (1.2 mmol) and cyclohexyl iodide (0.3 mmol) were added to the mixture. The glass tube was insert to 200-mL stainless autoclave and then pressurized with 80 kg/cm^2 of CO. The mixture was stirring at ambient temperature. After 18 h, excess CO was purged at room temperature, then the reaction mixture was poured into brine (ca. 100 mL). The aqueous solution was extracted with ether (3 x 30 mL) and the combined ether extracts were dried ($MgSO_4$), then filtered, and concentrated. The residue was purified by flash chromatography on silica gel (C_6, then 20% AcOEt-C_6 eluent) to give 2-cyanoethyl cyclohexyl ketone (**8a**, 23 mg, 42% yield) as a slightly yellow liquid.

2-Phenylsulfonylethyl cyclohexyl ketone (5a).



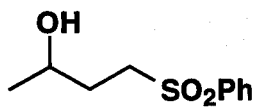
a white solid.; mp. 89 - 90 °C; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 1.05 - 1.40 (m, 5H), 1.60 - 1.90 (m, 5H), 2.34 (m, 1H), 2.94 (t, 2H, J = 7.32 Hz), 3.37 (t, 2H, J = 7.32 Hz), 7.58 (t, 2H, J = 7.32 Hz), 7.67 (t, 1H, J = 7.32 Hz), 7.91 (d, 2H, J = 7.81 Hz); ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 25.43, 25.64, 28.35, 32.83, 50.60, 50.76, 127.91, 129.33, 133.83, 139.11, 209.13; IR(neat) 1703 cm^{-1}(ν_{CO}), 1150, 1297 cm^{-1}(ν_{SO2}); Anal. Calcd for $C_{15}H_{20}SO_3$: C, 64.25; H, 7.19. found: C, 63.97; H, 7.25.

2-Cyclohexylethyl phenyl sulfone (6a).



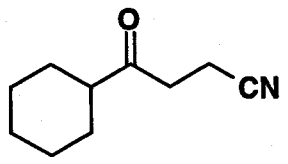
a slightly yellow liquid; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 0.78 - 0.93 (m, 2H), 1.06 - 1.35 (m, 4H), 1.50 - 1.75 (m, 7H), 3.10 (m, 2H), 7.53 - 7.70 (m, 3H), 7.90 (m, 2H); ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 25.87, 26.15, 29.50, 32.66, 36.49, 54.25, 127.90, 129.14, 133.47, 139.20; IR(neat) 1147, 1307 cm^{-1}(ν_{SO2}); CIMS (relative intensity) m/z 253 (M^++1, 100), 187 (3), 143 (6), 109 (8); HRCIMS calcd for $C_{14}H_{21}SO_2$ m/z 253.1262, found, 253.1252.

3-Hydroxybutyl phenyl sulfone (7a).



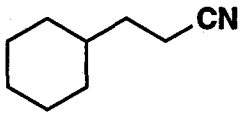
a slightly yellow liquid; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 1.21 (d, 3H, *J* = 5.93 Hz, CH_3), 1.71 - 2.00 (m, 3H, C*H*$_2$ CH_2SO_2 and O*H*), 3.15 - 3.37 (m, 2H, CH_2SO_2), 3.91 (br s, 1H, C*H*), 7.55 - 7.67 (m, 3H), 7.90 - 7.93 (m, 2H); ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 23.61 (q), 31.56 (t), 53.09(t), 66.13 (d), 127.97 (d), 129.29 (d), 133.69 (d), 139.16 (s); IR(neat) 1145, 1304 cm^{-1}(ν_{SO2}), 3506 cm^{-1}(ν_{OH}); CIMS (relative intensity) m/z 215 (M^++1, 52), 197 (100), 186 (3), 157 (3), 143 (25); HRCIMS calcd for $C_{10}H_{15}SO_3$ m/z 215.0741, found, 215.0735.

2-cyanoethyl cyclohexyl ketone (8a).



^{1}H-NMR ($CDCl_3$, 270 MHz) δ 1.10 - 1.45 (m, 5H), 1.55 - 1.95 (m, 5H), 2.36 (m, 2H), 2.57 (t, 2H, *J* = 7.32 Hz), 2.83 (t, 2H, *J* = 7.32 Hz); ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 11.42, 25.45, 25.64, 28.32, 35.68, 50.41, 119.14, 209.23; IR(neat) 1711 cm^{-1}(ν_{CO}), 2252 cm^{-1}(ν_{CN}); EIMS (relative intensity) m/z 165 (M^+, 16), 11 (31), 83 (100), 68 (9), 55 (56); HREIMS calcd for $C_{10}H_{15}NO$ m/z 165.1154, found, 165.1154.

2-cyanoethylcyclohexane (9a).

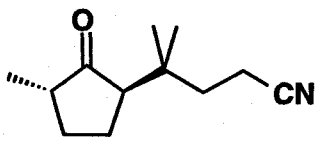


^{1}H-NMR ($CDCl_3$, 270 MHz) δ 0.80 - 1.00 (m, 2H), 1.12 - 1.45 (m, 4H), 1.55 (q-like, 2H, J = 7.33 Hz), 1.60 - 1.80 (m, 5H), 2.35 (t, 2H, J = 7.33 Hz); ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 14.57, 25.87, 26.24, 32.44, 32.51, 36.52, 119.98; IR(neat) 2246 cm^{-1}(ν_{CN}).

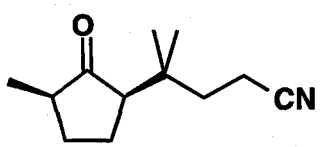
The *cis/trans* isomers of **2d** and **3d** were readily separated by flash chromatography on silica gel, and the ratio was determined by GC. The *trans* isomer (major) is less polar, and has shorter GC retention time (OV-1 column). The *cis* isomer (minor) is more polar, and has longer GC retention time (OV-1 column). The configuration of **2d** and **3d** were assigned by comparing the ^{1}H- and ^{13}C-NMR chemical shifts of **2d** and **3d** with those of 2,5-dimethylcyclopentanone; see, Gramain, J. C.; Kergomard, A.; Renard, M. F.; Veschambre, H. *J. Org. Chem.* **1985**, *50*, 120.

4-(2-Oxo-3-methylcyclopentyl)-4-methylpentanenitrile (2d).

[*trans*-**2d**] a slightly yellow liquid; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 0.95 (s, 3H), 0.98 (s, 3H), 1.07 (d, 3H, J = 6.84 Hz), 1.29 (dq, 1H, J = 5.86, 12.21 Hz), 1.55 - 1.72 (m, 1H), 1.72 - 2.08 (complex m, 5H), 2.13 - 2.37 (m, 3H); ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 12.15 (t), 13.82 (q), 23.50 (t), 23.59 (q), 24.34 (q), 28.98 (t), 34.92 (s), 35.78 (t), 46.12 (d), 55.25 (d), 120.27 (s), 220.54 (s); IR(neat) 1729 cm^{-1}(ν_{CO}), 2246 cm^{-1}(ν_{CN}); EIMS (relative intensity) m/z 193 (M^+, 9), 178 (53), 98 (100), 83 (15), 69 (55); HREIMS calcd for $C_{12}H_{19}NO$ m/z 193.1466, found, 193.1470.

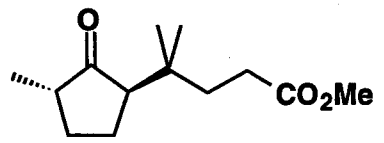


[*cis*-**2d**] a slightly yellow liquid; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 0.96 (s, 3H), 0.98 (s, 3H), 1.03 (d, 3H, J = 7.81 Hz), 1.60 (m, 1H), 1.75 - 2.07 (complex m, 6H), 2.25 - 2.36 (m, 3H); ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 12.15 (t), 15.04 (q), 23.04 (t), 23.86 (q), 24.80 (q), 28.06 (t), 34.88 (s), 35.84 (t), 43.02 (d), 55.29 (d), 120.24 (s), 221.35 (s); IR(neat) 1728 cm^{-1}(ν_{CO}), 2246 cm^{-1}(ν_{CN}); EIMS (relative intensity) m/z 193 (M^+, 8), 178 (60), 98 (100), 83 (16), 69 (56); HREIMS calcd for $C_{12}H_{19}NO$ m/z 193.1466, found, 193.1491.



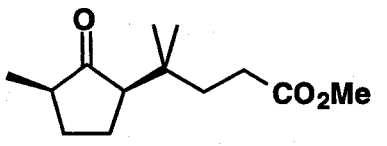
Methyl 4-(2-oxo-3-methylcyclopentyl)-4-methylvalerate (3d).

[*trans*-**3d**] a colorless liquid; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 0.90 (s, 3H), 1.01 (s, 3H),



1.06 (d, 3H, J = 6.35 Hz), 1.25 (m, 1H), 1.55 - 1.68 (m, 1H), 1.73 (t, 2H, J = 8.30 Hz), 1.91 - 2.06 (m, 3H), 2.12 - 2.38 (m, 3H), 3.67 (s, 3H); ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 13.89 (q), 23.58 (t), 24.15 (q), 24.41 (q), 29.16 (t), 29.22 (t), 34.84 (s), 35.24 (t), 46.23 (d), 51.54 (q), 55.85 (d), 174.50 (s), 221.09 (s); IR(neat) 1736 cm^{-1}(ν_{CO}); EIMS (relative intensity) m/z 226 (M^+, 17), 194 (19), 179 (13), 151 (11), 139 (83), 129 (27), 98 (100), 69 (62); HREIMS calcd for $C_{13}H_{22}O_3$ m/z 226.1568, found, 226.1543.

[*cis*-**3d**] a colorless liquid; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 0.91 (s, 3H), 1.01 (s, 3H),

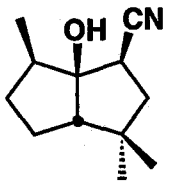


1.02 (d, 3H, J = 7.32 Hz), 1.53 - 1.64 (m, 1H), 1.68 - 1.75 (m, 2H), 1.77 - 2.06 (m, 4H), 2.18 - 2.36 (m, 3H), 3.67 (s, 3H); ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 15.13 (q), 23.18 (t), 24.54 (q), 24.58 (q), 28.21 (t), 29.25 (t), 34.81 (s), 35.56 (t), 43.23 (d), 51.56 (q), 55.87 (d), 174.53 (s), 221.95 (s); IR(neat) 1732 cm^{-1}(ν_{CO}); EIMS (relative intensity) m/z 226 (M^+, 13), 194 (19), 179 (13), 151 (11), 139 (84), 129 (26), 98 (100), 69 (61); HREIMS calcd for $C_{13}H_{22}O_3$ m/z 226.1568, found, 226.1557.

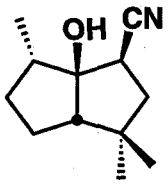
Procedure for the Synthesis of 2-cyano-4,4,8-trimethyl-bicyclo[3.3.0]octan-1-ol (4d): A mixture of zinc powder (262 mg, 4 mmol), acrylonitrile (53 mg, 1 mmol), 6-iodo-2-methyl-hept-2-ene (476 mg, 2 mmol), and acetonitrile (20 mL) was placed in a round bottomed glass liner. The glass liner was inserted into a 50-mL stainless steel autoclave and the autoclave was charged with 80 kg/cm^2 of CO. The reaction mixture was stirred at 60 °C. After 24 h, excess CO was evacuated, then the remaining zinc was filtered. The filtrate was added to saturated aqueous NH_4Cl (50 mL), and was extracted with ether (50 mL x 3), and the ethereal solution was dried over $MgSO_4$. Rotary evaporation of the ethereal solution followed by flash chromatography (silica

gel, Et_2O-AcOEt as the eluent) afforded a 8-*endo* and *exo* mixture of 2-cyano-4,4,8-trimethyl-bicyclo[3.3.0]octan-1-ol (**4d**, 124 mg, 64% yield, 41/59). The isomer ratio was determined by ^{1}H-NMR. The *endo*/*exo* isomers of **4d** were separated by flash chromatography on silica gel or preparative HPLC (GPC columns, $CHCl_3$ as the eluent). Absolute structures were confirmed to be *endo*/*exo* isomer at 8-position by nOe experiments (see text).

[8-*exo*-**4d**] (f 15-18) a colorless liquid; ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 0.88 (s, 3H), 1.11 (d, 3H, J = 6.63 Hz), 1.13 (s, 3H), 1.13 - 1.18 (m, 1H), 1.48 (ddt-like, 1H, J ~ 6.6, 13.7, 2.0 Hz), 1.62 - 1.71 (m, 1H), 1.83 (m, 1H), 1.88 (dd, 1H, J = 6.19, 12.16 Hz), 1.95 - 2.03 (m, 1H), 2.10 - 2.36 (m, 2H), 2.62 (dd, 1H, J = 6.19, 12.83 Hz), 2.66 (br s, 1H); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ 13.30 (q), 23.02 (q), 23.53 (t), 31.06 (q), 34.37 (t), 34.59 (d), 40.39 (s), 44.87 (t), 45.00 (d), 61.39 (d), 93.27 (s), 120.06 (s); IR(neat) 2250 (ν_{CN}), 3457 cm^{-1}(ν_{OH}); EIMS (relative intensity) m/z 193 (M^+, 2), 178 (100), 139 (43), 125 (53), 98 (16); HREIMS calcd for $C_{12}H_{19}NO$ m/z 193.1467, found, 193.1469.

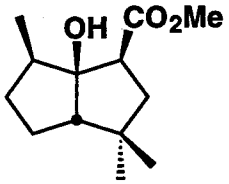


[8-*endo*-**4d**] (f 10-12) a colorless liquid; ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 0.89 (s, 3H), 1.06 (d, 3H, J = 6.85 Hz), 1.15 (s, 3H), 1.26 - 1.34 (m, 1H), 1.53 - 1.61 (m, 1H), 1.62 - 1.73 (m 2H), 1.85 (q, 1H, J = 5.72 Hz), 1.96 (dd, 1H, J = 6.60, 12.50 Hz), 2.11 (br s, 1H), 2.14 (t-like, 1H, J ~ 9.10 Hz), 2.20 (t-like, 1H, J ~ 11.74 Hz), 2.71 (dd, 1H, J = 6.45, 11.15 Hz); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ 12.53 (q), 24.00 (q), 24.12 (t), 30.16 (q), 35.72 (t), 38.95 (s), 39.17 (d), 45.50 (d), 46.75 (t), 63.55 (d), 91.14 (s), 120.06 (s); IR(neat) 2242 (ν_{CN}), 3472 cm^{-1}(ν_{OH}); EIMS (relative intensity) m/z 193 (M^+, 2), 178 (100), 139 (53), 125 (68), 97 (36); HREIMS calcd for $C_{12}H_{19}NO$ m/z 193.1467, found, 193.1477.

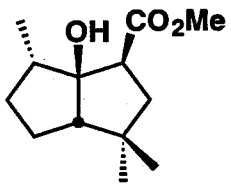


2-Methoxycarbonyl-4,4,8-trimethyl-bicyclo[3.3.0]octan-1-ol (5d). The isomer ratio was determined by ^{1}H-NMR. The *endo*/*exo* isomers of **5d** were separated by flash chromatography on silica gel or preparative HPLC (GPC columns, $CHCl_3$ as the eluent).

[8-*exo*-**5d**] (f 10) a yellow liquid; ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 0.92 (s, 3H), 0.92 (d, 3H, *J* = 6.98 Hz), 1.12 (s, 3H), 1.13 - 1.22 (m, 1H), 1.44 - 1.50 (m, 1H), 1.62 - 1.66 (m, 1H), 1.75 - 1.83 (m, 2H), 1.94 - 2.01 (m, 1H), 2.06 - 2.15 (m, 2H), 2.62 (dd, 1H, *J* = 6.25, 13.24 Hz), 3.71 (s, 3H), 4.46 (br s, 1H); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ 13.67 (q), 23.56 (t), 24.13 (q), 31.59 (q), 34.40 (t), 39.34 (s), 44.94 (d), 45.56 (d), 45.84 (t), 51.78 (q), 62.24 (d), 93.78 (s), 176.42 (s); IR(neat) 1715 (ν_{CO}), 3482 cm^{-1}(ν_{OH}); EIMS (relative intensity) m/z 226 (M^+, 8), 211 (100), 179 (73), 139 (42), 125 (31); HREIMS calcd for $C_{13}H_{22}O_3$ m/z 226.1569, found, 226.1578.



[8-*endo*-**5d**] (f 16) a colorless liquid; ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 0.90 (s, 3H), 1.02 (d, 3H, *J* = 6.62 Hz), 1.09 (s, 3H), 1.25 - 1.35 (m, 1H), 1.58 (dq, 1H, *J* ~ 7.0, 11.2 Hz), 1.62 - 1.72 (m, 2H), 1.83 (dd, 1H, *J* = 6.44, 12.32 Hz), 1.87 (dd, 1H, *J* = 6.44, 12.32 Hz), 2.13 (t-like, 1H, *J* ~ 8.8 Hz), 2.21 (t-like, 1H, *J* ~ 12.7 Hz), 2.69 (dd, 1H, *J* = 6.44, 12.69 Hz), 3.05 (br s, 1H), 3.71 (s, 3H); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ 12.86 (q), 23.79 (t), 24.49 (q), 30.64 (q), 36.43 (t), 37.41 (s), 45.65 (d), 46.64 (t), 51.60 (q), 51.89 (d), 64.60 (d), 91.14 (s), 175.03 (s); IR(neat) 1718 (ν_{CO}), 3510 cm^{-1}(ν_{OH}); EIMS (relative intensity) m/z 226 (M^+, 7), 211 (100), 179 (74), 139 (45), 125 (36); HREIMS calcd for $C_{13}H_{22}O_3$ m/z 226.1569, found, 226.1587.



4-4. References and Notes

(1) For reviews, see: (a) Curran, D. P.; Fevig, T. L.; Jasperse, C. P.; Totleben, M. J. *Synlett* **1992**, 943. (b) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29. (c) Iqbal, J.; Bhatia, B.; Nayyar, N. K. *Chem. Rev.* **1994**, *94*, 519. (d) Dalko, P. I. *Tetrahedron* **1995**, *51*, 7579. (e) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307.

(2) Synthesis of aldehydes: (a) Ryu, I.; Kusano, K.; Ogawa, A.; Kambe, N.; Sonoda,

N. *J. Am. Chem. Soc.* **1990**, *112*, 1295. (b) Ryu, I.; Kusano, K.; Masumi, N.; Ogawa, A.; Yamazaki, H.; Sonoda, N. *Tetrahedron Lett.* **1990**, *31*, 6877. (c) Ferguson, R. R.; Crabtree, R. H. *J. Org. Chem.* **1991**, *56*, 5503. (d) Boese, W. T.; Goldmann, A. S. *Tetrahedron Lett.* **1992**, *33*, 2119. (e) Gupta, V.; Kahne, D. *Tetrahedron Lett.* **1993**, *34*, 591. (f) Ryu, I.; Kurihara, A.; Muraoka, H.; Tsunoi, S.; Kambe, N.; Sonoda, N. *J. Org. Chem.* **1994**, *59*, 7570. (g) Nakatani, S.; Yoshida, J.-i.; Isoe, S. *J. Chem. Soc., Chem. Commun.* **1992**, 880. (h) Jaynes, B. S.; Hill, C. L. *J. Am. Chem. Soc.* **1995**, *117*, 4704. (i) Tsunoi, S.; Ryu, I.; Muraoka, H.; Tanaka, M.; Komatsu, M.; Sonoda, N. *Tetrahedron Lett.* in press. Synthesis of ketones: (j) Ryu, I.; Hasegawa, M.; Kurihara, A.; Ogawa, I.; Tsunoi, S.; Sonoda, N. *Synlett* **1993**, 143. (k) Ryu, I.; Kusano, K.; Yamazaki, H.; Sonoda, N. *J. Org. Chem.* **1991**, *56*, 5003. (l) Ryu, I.; Kusano, K.; Hasegawa, M.; Kambe, N.; Sonoda, N. *J. Chem. Soc., Chem. Commun.* **1991**, 1018. (m) Ryu, I.; Yamazaki, H.; Kusano, K.; Ogawa, A.; Sonoda, N. *J. Am. Chem. Soc.* **1991**, *113*, 8558. (n) Ryu, I.; Yamazaki, H.; Ogawa, A.; Kambe, N.; Sonoda, N. *J. Am. Chem. Soc.* **1993**, *115*, 1187. (o) Brinza, I. M.; Fallis, A. G. *J. Org. Chem.* **1996**, *61*, 3580. (p) Chatgilialoglu, C.; Ferreri, C.; Sommazzi, A. *J. Am. Chem. Soc.* **1996**, *118*, 7223. Synthesis of macrocyclic ketolactones: (q) Ryu, I.; Nagahara, K.; Yamazaki, H.; Tsunoi, S.; Sonoda, N. *Synlett* **1994**, 643. Synthesis of lactones and carboxylic acids derivatives: (r) Tsunoi, S.; Ryu, I.; Sonoda, N. *J. Am. Chem. Soc.* **1994**, *116*, 5473. (s) Ryu, I.; Alper, H. *J. Am. Chem. Soc.* **1993**, *115*, 7543. (t) Tsunoi, S.; Ryu, I.; Tamura, Y.; Yamasaki, S.; Sonoda, N. *Synlett* **1994**, 1009. (u) Okuro, K.; Alper, H. *J. Org. Chem.* **1996**, *61*, 5312. (v) Ryu, I.; Muraoka, H.; Kambe, N.; Komatsu, M.; Sonoda, N. *J. Org. Chem.* **1996**, *61*, 6396. For reviews of radical reaction of carbon monoxide, see: (w) Ryu, I.; Sonoda, N.; Curran, D. P. *Chem. Rev.* **1996**, *96*, 177. (x) Ryu, I.; Sonoda, N. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1050.

(3) Zinc mediated radical carbonylation reactions of alkyl iodides in protic solvent,

see: Tsunoi, S.; Ryu, I.; Fukushima, H.; Tanaka, M.; Komatsu, M.; Sonoda, N. *Synlett* **1995**, 1249.

(4) (a) Petrier, C.; Dupuy, C.; Luche, J. L. *Tetrahedron Lett.* **1986**, *27*, 3149. (b) Luche, J. L.; Allavena, C. *Tetrahedron Lett.* **1988**, *29*, 5369. (c) Luche, J. L.; Allavena, C.; Petrier, C.; Dupuy, C. *Tetrahedron Lett.* **1988**, *29*, 5373. (d) Dupuy, C.; Petrier, C.; Sarandeses, L. A.; Luche, J. L. *Synth. Commun.* **1991**, *21*, 643.

(5) Some examples for application of Zn(Cu) reduction system to free-radical transformations, see: (a) Ohno, M.; Ishizaki, K.; Eguchi, S. *J. Org. Chem.* **1988**, *53*, 1285. (b) Pietrusiewicz, K. M.; Zablocka, M. *Tetrahedron Lett.* **1988**, *29*, 937. (c) Castedo, L.; Mascareñas, J. L.; Mouriño, A.; Sarandeses, L. A. *Tetrahedron Lett.* **1988**, *29*, 1203. (d) Giese, B.; Damm, W.; Roth, M.; Zehnder, M. *Synlett* **1992**, 441. (e) Blanchard, P.; El Kortbi, M. S.; Fourrey, J. L.; Robert-Gero, M. *Tetrahedron Lett.* **1992**, *33*, 3319. (f) De Kimpe, N.; De Smaele, D.; Bogaert, P. *Synlett* **1994**, 287.

(6) Cyclohexylmethanol, by further reduction product from **2a**, was not detected. The formation of ethyl ester **3a** is referred at footnote 16 in Chap 5.

(7) Collins, J.; Namy, J.-L.; Dallemer, F.; Kagan, H. B. *J. Org. Chem.* **1991**, *56*, 3118.

(8) Rathke, M. W.; Yu, H. *J. Org. Chem.* **1972**, *37*, 1732.

(9) (a) Fujimoto, Y.; Tatsuno, T. *Tetrahedron Lett.* **1976**, 3325. (b) Pradhan, S. K.; Kolhe, J. N.; Mistry, J. S. *Tetrahedron Lett.* **1982**, *23*, 4481.

(10) In the presence of activated alkene, ester **3a** was not detected.

(11) For free-radical donor/acceptor notation (•/o), see: Curran, D. P. *Synlett* **1991**, 63.

(12) (a) Chatgilialoglu, C.; Lucarini, M. *Tetrahedron Lett.* **1995**, *36*, 1299. (b) Chatgilialoglu, C.; Ferreri, C.; Lucarini, M.; Pedrielli, P.; Pedulli, G. F. *Organometallics* **1995**, *14*, 2672 and references cited therein.

(13) 2-Methyl-5-isopropylcyclopentanone was also formed in 10% yield.

(14) For examples of acyl radical cyclizations followed by alkene addition, see: (a) Crich, D.; Eustace, K. A.; Fortt, S. M.; Ritchie, T. J. *Tetrahedron* **1990**, *46*, 2135.

(b) Boger, D. L.; Mathvink, R. J. *J. Am. Chem. Soc.* **1990**, *112*, 4003.

(15) To overcome competitive abstraction of hydrogen by a tertiary radical from tin hydride, alkenes were used in large excess. Both the rate constant for hydrogen abstraction of a tertiary radical from tin hydride and that for addition to acrylonitrile are in the order of 10^6 at 27 °C, see: (a) Chatgilialoglu, C; Ingold, K. U.; Scaiano, J. C. *J. Am. Chem. Soc.* **1981**, *103*, 7739. (b) Jent, F.; Paul, H.; Roduner, E.; Heming, M.; Fischer, H. *Int. J. Chem. Kinet.* **1986**, *18*, 1113.

(16) In this tin hydride mediated reaction, the formation of six-membered uncarbonylated product (ca. 5%) via a 4+2 annulation of **1c** with alkene was observed.

(17) Shono, T.; Nishiguchi, I.; Sasaki, M. *J. Am. Chem. Soc.* **1978**, *100*, 4314.

(18) In the case of methyl acrylate, other isomers (less than 5%) was found. Similar stereoselectivity was observed in Reformatsky reaction using Zn, see: Flitsch, W.; Ruβkamp, P. *Liebigs Ann. Chem.* **1985**, 1398.

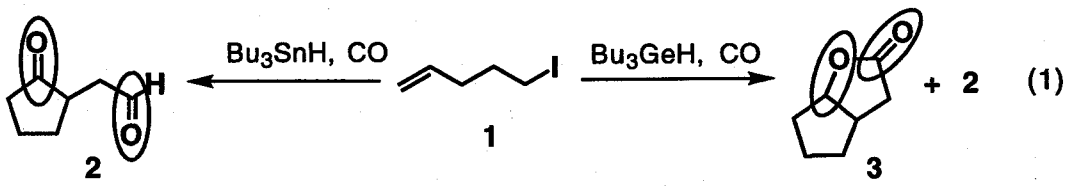
(19) The synthesis of cyclopentanoids has been an especially active area, see: (a) Cossy, J.; Belotti, D.; Pete, J. P. *Tetrahedron* **1990**, *46*, 1859. (b) Tsunoda, T.; Kodama, M.; Ito, S. *Tetrahedron Lett.* **1983**, *24*, 83. (c) Yates, P.; Stevens, K. E. *Tetrahedron* **1981**, *37*, 4401. (d) Mehta, G.; Srikrishna, A.; Reddy, A. V.; Nair, M. S. *Tetrahedron* **1981**, *37*, 4543. (e) Pattenden, G.; Robertson, G. M. *Tetrahedron* **1985**, *41*, 4001. For reviews, (f) Paquette, L. A. *Top. Curr. Chem.* **1979**, *79*, 41. (g) Paquette, L. A. *Top. Curr. Chem.* **1984**, *119*, 1. (h) Trost, B. M. *Chem. Soc. Rev.* **1982**, *82*, 141. (i) Ramaiah, M. *Synthesis* **1983**, 529.

Chapter 5. Double Carbonylations of Alk-4-enyl Iodides Using Group 14 Metal Hydrides

5-1. Introduction

Over the past decade, tandem processes based on free radical methods are gaining increasing importance in organic synthesis, as they allow for the simultaneous formation of more than one bond in a single synthetic operation from relatively simple precursors.[1] Carbon monoxide also participates in such tandem free-radical reactions as a useful C_1 radical acceptor/donor synthon.[2]

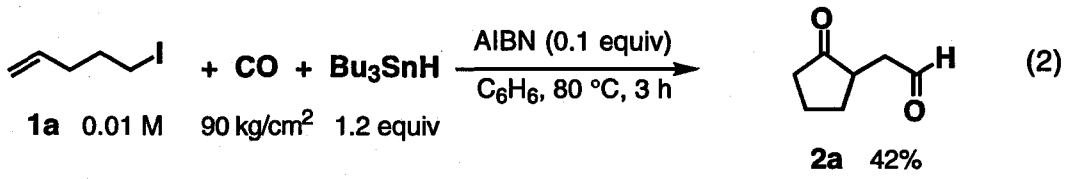
In this chapter, described are the results of the study on the synthetic potential of double CO trapping reaction[3] by pent-4-enyl radicals, mediated by tributyltin hydride or tributylgermyl hydride.[4] Interestingly, the major products obtained via double CO trapping are dependent on the radical mediator and pent-4-enyl halide used. The tin hydride mediated system afforded the anticipated keto aldehyde **2**, and surprisingly, the germyl hydride mediated system afforded the bicyclic γ-lactone **3** as the principal double CO incorporation product (eq 1).



5-2. Results and Discussion

Reaction of pent-4-enyl radical and CO would be expected to yield hex-5-enoyl radical (**A**) as the initial intermediate. The subsequent 5-*exo* cyclization of radical **A**

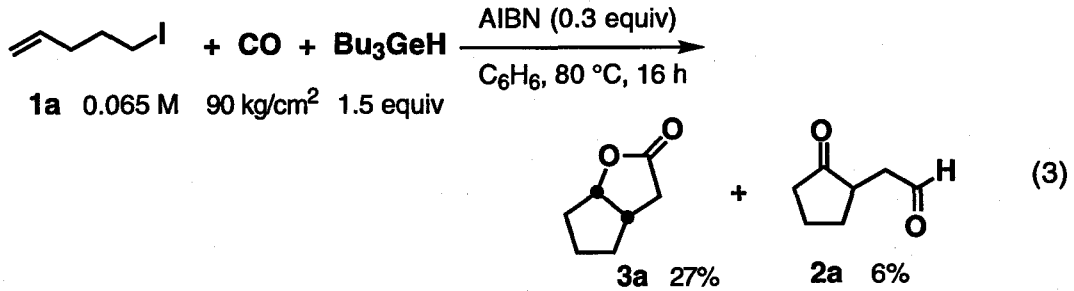
generates 2-oxocyclopentyl carbinyl radical (**B**), which rapidly isomerize to thermodynamically more stable 3-oxocyclohexyl radical (**C**).[5] It is anticipated that, under high CO concentrations, the kinetic radical **B** would be trapped by the second molecule of CO in preference to the isomerization leading to **C** (Scheme 1). For example, when the AIBN-initiated reaction of pent-4-enyl iodide with tributyltin hydride (1.2 equiv) was carried out under 90 kg/cm^2 of CO (0.01 M in benzene, 80 °C, 3 h), 2-(2-oxoethyl)cyclopentanone (**2a**), the anticipated double carbonylation product, was obtained in 42% yield after isolation by flash chromatography on silica gel (eq 2).



(2)

This double CO trapping reaction can work also well for some other alk-4-enyl iodides **1**, and in these cases 2-(2-oxoethyl)cyclopentanones **2** were obtained in the isolated yields of 33-47% (Table 1, runs 1, 3, 5, 7, and 9).[6] A small amount of six-membered double carbonylation product arising from intermediate **C** was also detected in each case (in ~10% ratio relative to **2a**).

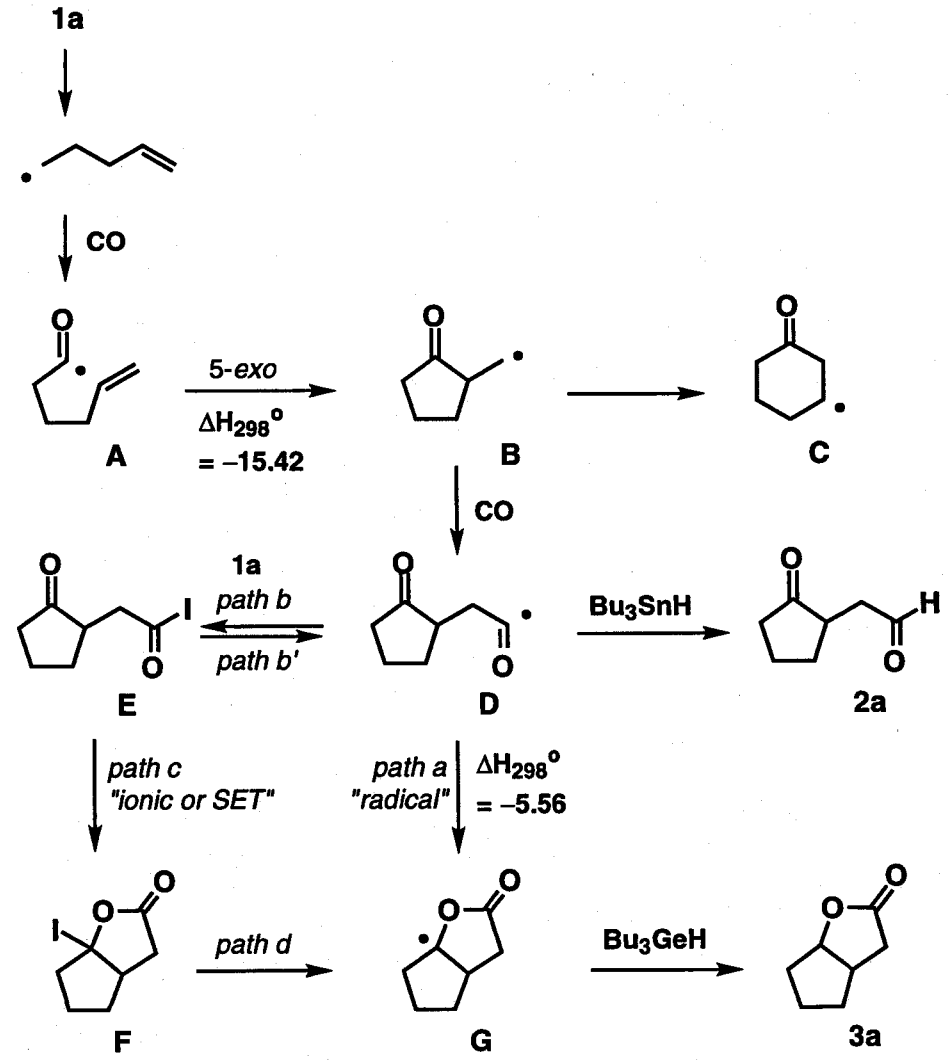
When the radical mediator was switched to tributylgermyl hydride, surprisingly bicyclic lactone, 2-oxabicyclo[3.3.0]octan-3-one (**3a**) was formed as the major double CO trapping product (eq 3).



(3)

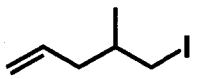
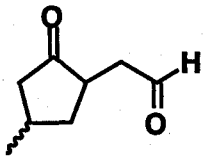
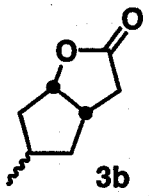
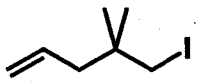
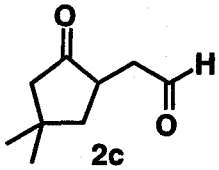
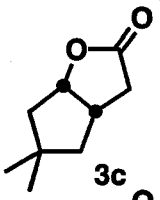
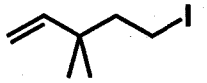
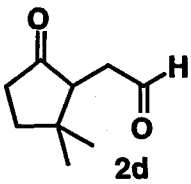
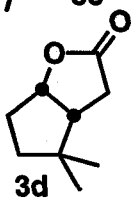
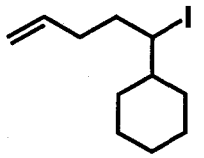
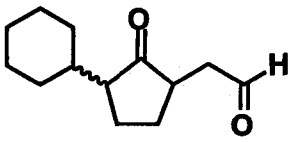
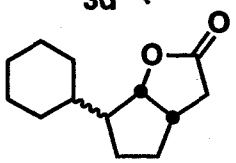
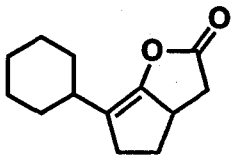
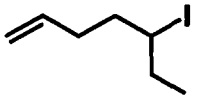
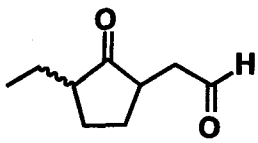
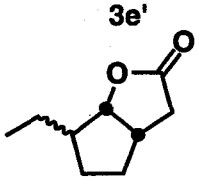
This lactone is an isomer of keto aldehyde **2a**, since two molecules of CO were incorporated as the C-O-C=O linkage of the lactone ring. Exposure of keto aldehyde **2a** to the original carbonylation conditions (tributylgermyl hydride/CO) did not give rise to **3a**, precluding the further reaction pathway from initially formed **2a**. The reaction to give bicyclic γ-lactones is quite general and in all five cases examined without exception γ-lactones **3b-f** were obtained and in one case significant amounts of unsaturated lactones **3e'** was isolated (Table 1, runs 2, 4, 6, 8, and 10).

Scheme 1



Enthalpies were calculated from PM3 energies by correcting for zero-point vibrational energies, C_pT and RT terms. Values are in kcal/mol.

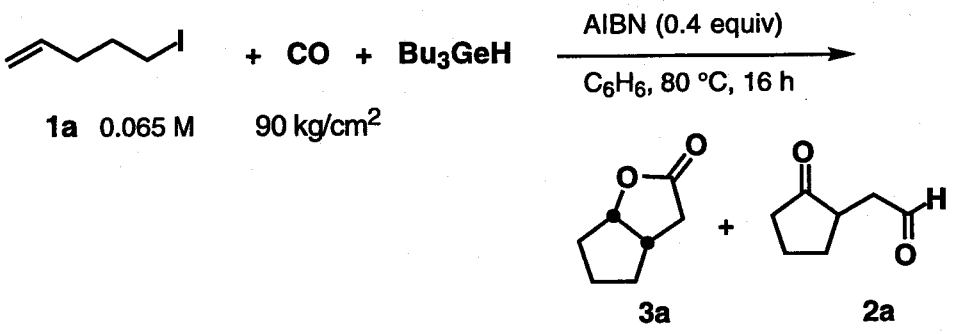
Table 1. Double Carbonylation of Pent-4-enyl Iodides

run	RI	R'_3MH	keto aldehyde **2**, %[c]	γ-lactone **3**, %[c]
1	 **1b**	Bu_3SnH[a]	 **2b** 40 (62/38)[d]	 **3b** 0
2		Bu_3GeH[b]	6	26 (63/37)[e]
3	 **1c**	Bu_3SnH[a]	 **2c** 45	 **3c** 0
4		Bu_3GeH[b]	12	40
5	 **1d**	Bu_3SnH[a]	 **2d** 33	 **3d** 0
6		Bu_3GeH[b]	9	29
7	 **1e**	Bu_3SnH[a]	 **2e** 47 (38/62)[e]	 **3e** 6
8		Bu_3GeH[b]	7	29 (50/50)[e]
				 **3e'** 13
9		Bu_3SnH[a]	 40 (43/57)[e]	 4
10	**1f**	Bu_3GeH[b]	1	30 (42/58)[e,f]
			2f	**3f**

[a][RI] = 0.01 M, in benzene, Bu_3SnH (1.2 equiv), AIBN (0.1 equiv), CO (90 kg/cm^2), 70-80 °C, 3-5 h. [b][RI] = 0.06-0.2 M, in benzene, Bu_3GeH (1.5 equiv), AIBN (0.3-0.5 equiv), CO (90 atm), 70-100 °C, 16 h. [c]Isolated yields purified by silica gel chromatography. [d]Ratio of *cis/trans* was determined by GC. [e]Ratio of *endo/exo* or *cis/trans* was determined by ^{1}H-NMR. [f]Unsaturated γ-lactone was also detected in 2% yield.

Control experiments were carried out to gain some insights into mechanism for this

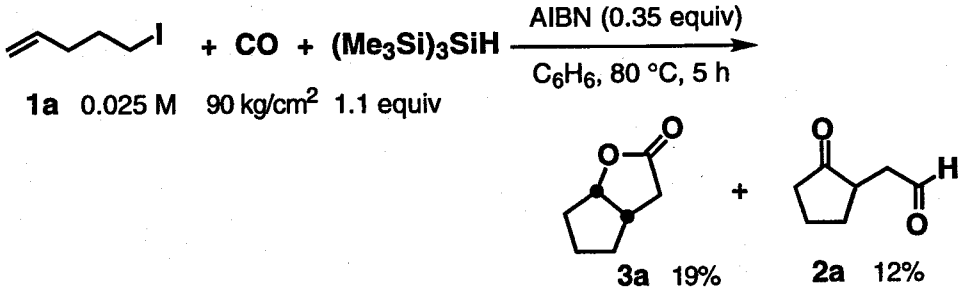
unusual lactone formation. Raising the equivalent of Bu_3GeH to **1** suppressed the formation of lactone **3** (eq 4). To obtain more favorable bicyclic lactone/keto aldehyde ratios, the choice of "slower" radical mediator such as tributylgermane is crucial.[7] Tris(trimethylsilyl)silane (TTMSS),[8] a slower mediator than tributyltin hydride and a faster mediator than tributylgermane, gave intermediate results, for example, a ca. 2:3 mixture of **2a** and **3a** was obtained from **1a** (eq 5). These observations are consistent with the assumption that the formation of lactone **3a** is due to a rare 5-*endo* cyclization of the acyl radical **D**,[9] arising from the second CO trapping by **B**, onto the carbonyl oxygen to afford **G** (Scheme 1, path a), which would compete with intermolecular hydrogen abstraction from tributylgermane thus leading to **2a**.



3a 2a (4)

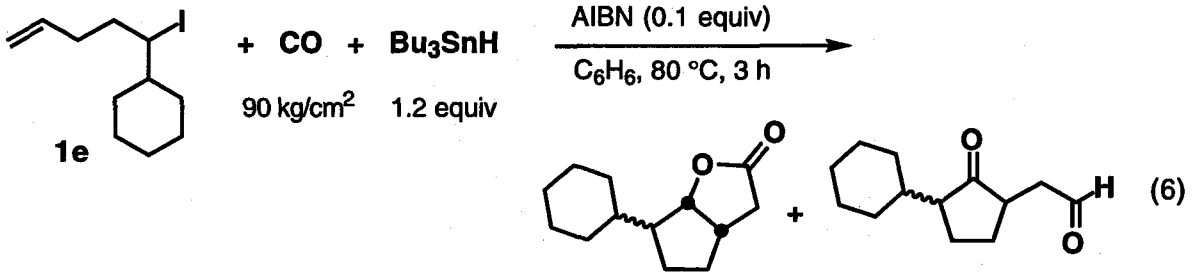
Bu_3GeH equiv	GC yield, % 3a	2a	3a/2a
1.3[a]	19	3	6.5
1.5	51	13	4.1
1.8	38	14	2.7

[a]17% of **1a** was recovered.

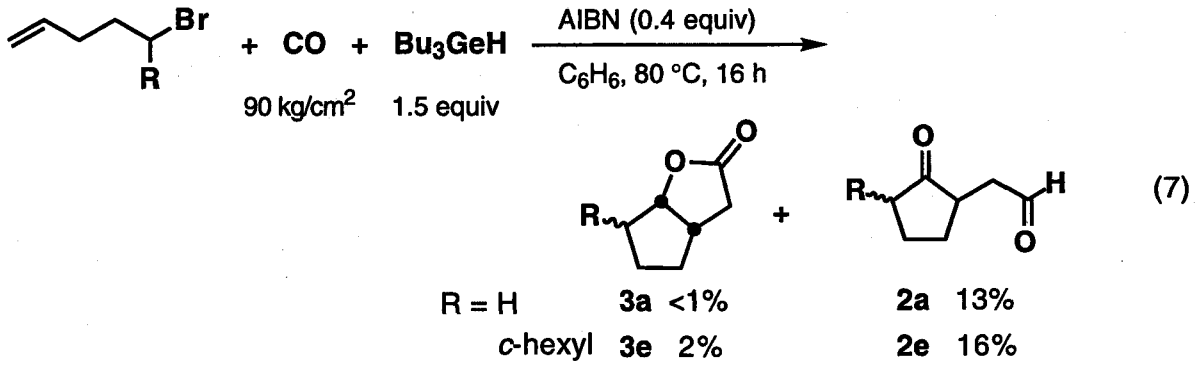


3a 19% **2a** 12% (5)

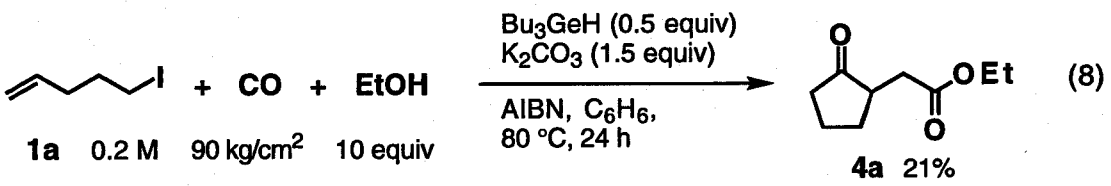
On the other hands, other data collected on this system are not entirely consistent with this simplified scenario. Dilution failed to increase the product ratio of **3e** to **2e** in favor of an intramolecular reaction course leading to **3e** (eq 6). Furthermore, the corresponding pent-4-enyl *bromide* yielded only a trace amount of **3a** when exposed to standard Bu_3GeH/CO conditions (eq 7).[10] These observations suggest that an iodine atom transfer reaction may play an important role in this γ-lactone ring formation. One possible rationale may involve an iodine transfer reaction from alkyl iodide **1a** to acyl radical **D** to give acyl iodide **E**,[11] which might be permitted by a slow mediator system involving Bu_3GeH, and the cyclization of the resulting **E** to yield **F** (path b, Scheme 1).[12] Although iodine transfer from an alkyl iodide to an acyl radical may be regarded as an energetically unfavored process,[13] the subsequent conversion of acid iodide **E** to pseudo-acid iodide **F** might be sufficiently smooth to override this energetic disadvantage.[14,15]



[1e] mM	NMR yield, % 3e	2e	Product Ratio 3e/2e
10	11	41	0.27
20	9	42	0.21
30	10	41	0.24



To prove this unusual iodine atom transfer to an acyl radical, the germyl hydride mediated reaction of pent-4-enyl iodide with CO was conducted in the presence of ethanol and K_2CO_3.[16] As a results, expected keto ester **4a** formed via a trapping of an acyl iodide by ethanol, was obtained in 21% yield (eq 8).



5-3. Experimental

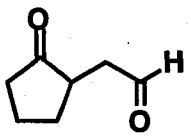
General Procedure for the Synthesis of Keto Aldehyde 2: Pent-4-enyl iodide (**1a**) (102 mg, 0.52 mmol), Bu_3SnH (176 mg, 0.6 mmol), AIBN (10 mg, 0.06 mmol), and benzene (50 mL) were placed in a 100-mL stainless steel autoclave lined with a glass liner. The mixture was stirred under the pressure of carbon monoxide (90 kg/cm^2) at 80 °C for 3 h. After the residual CO was ventilated, the mixture was evaporated. The resultant residue was dissolved in 5 mL of diethyl ether. The ethereal solution was treated with saturated aqueous potassium fluoride solution. The precipitated Bu_3SnF was removed by filtration at reduced pressure and washed with diethyl ether (3 x 5 mL), and the ethereal layers were combined and dried ($MgSO_4$). Rotary evaporation of solvents followed by flash chromatography

on silica gel (C_6H_{14}, then C_6H_{14}/Et_2O = 9/1, 3/1, 2/1 as an eluent) afforded 2-(2-oxoethyl)cyclopentanone (**2a**) (28 mg, 42% yield). A small amount of six-membered double carbonylation product arising from intermediate **C** was also detected (in ~10% ratio relative to **2a**), but chromatographic separation allowed the isolation of pure **2a**.

General Procedure for the Synthesis of Bicyclic Lactone 3: Pent-4-enyl iodide (**1a**) (118 mg, 0.6 mmol), Bu_3GeH (220 mg, 0.9 mmol), AIBN (49 mg, 0.3 mmol), and benzene (10 mL) were placed in a 50-mL stainless steel autoclave lined with a glass liner. The mixture was stirred under the pressure of carbon monoxide (90 kg/cm^2) at 80 °C for 16 h. After the residual CO was ventilated, the mixture was evaporated. The resultant residue was treated with pentane/acetonitrile. Rotary evaporation of the acetonitrile solution followed by preparative HPLC (GPC columns, $CHCl_3$ as an eluent) afforded the 2-oxabicyclo[3.3.0]octan-3-one (**3a**) (21 mg, 27% yield) and 2-(2-oxoethyl)cyclopentanone (**2a**) (4 mg, 5% yield).

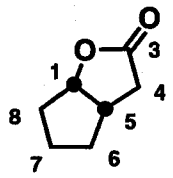
Formation of 2-Ethoxycarbonylmethylcyclopentanone (4a): Pent-4-enyl iodide (**1a**) (393 mg, 2 mmol), Bu_3GeH (245 mg, 1 mmol), AIBN (323 mg, 2 mmol), K_2CO_3 (410 mg, 3 mmol), ethanol (981 mg, 21 mmol), and benzene (10 mL) were placed in a 50-mL stainless steel autoclave lined with a glass liner. The mixture was stirred under the pressure of carbon monoxide (90 kg/cm^2) at 80 °C for 24 h. After the residual CO was ventilated, the mixture was evaporated. The formation of keto ester **4a** was identified by comparing the NMR spectra with those of the separately prepared authentic sample (from ethyl bromoacetate and an enamine derived from cyclopentanone and piperidine). GC yields of **4a** and recovered **1a** were determined *versus* *n*-decane as an internal standard, and were corrected by relative sensitivity (**1a** 24%, **4a** 21%).

2-(2-Oxoethyl)cyclopentanone (2a).



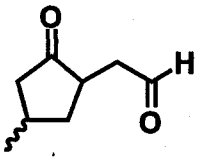
^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.63 - 1.52 (m, 1H), 1.96-1.74 (m, 1H), 2.06 - 2.43 (m, 4H), 2.55 (m, 2H), 2.93 (dd, 1H, J = 6.6, 21.3 Hz), 9.79 (s, 1H); ^{13}C-NMR (68 MHz, $CDCl_3$); δ 20.74, 29.39, 37.12, 43.57, 43.63, 200.02, 219.28; IR (neat) 1723, 1736 cm^{-1}($\nu_{C=O}$); EIMS (relative intensity) m/z 126 (M^+, 4), 98 (46), 84 (100), 70 (47); HREIMS calcd for $C_7H_{10}O_2$ m/z 126.0681, found, 126.0680. This compound is already known and the properties (^{1}H- and ^{13}C-NMR) were consistent with those previously reported, see: Molander, G. A.; Cameron, K. O. *J. Org. Chem.* **1993**, *58*, 5931.

2-Oxabicyclo[3,3,0]octan-3-one (3a).



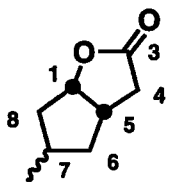
^{1}H-NMR (600 MHz, $CDCl_3$) δ 1.55 (dddt, 1 H, J = 1.0, 4.1, 13.0, 4.1 Hz, H_6: Irradiation at 2.9 ppm causes collapse of this peak to td-like. Irradiation at 5.0 ppm unchanges this peak), 1.68 - 1.77 (m, 3H, H_7 + 2H_8), 1.86 (qd-like, 1H, J ~ 8.1, 13.0 Hz, H_6: Irradiation at 2.9 ppm causes collapse of this peak to td. Irradiation at 5.0 ppm unchanges this peak), 2.05 (td-like, 1H, J ~ 4.4, 14.8 Hz, H_7: Irradiations at 2.9 and 5.0 ppm unchange this peak), 2.29 (dd, 1H, J = 2.5, 18.1 Hz, H_4), 2.82 (dd, 1H, J = 10.2, 18.1 Hz, H_4), 2.88 - 2.96 (m, 1H, H_5: Irradiation at 5.0 ppm causes collapse of this peak to tt-like), 5.00 (td, 1H, J = 5.9, 1.5 Hz, H_1); ^{13}C-NMR (68 MHz, $CDCl_3$); δ 23.35 (t, C_8), 33.43 (t, C_6), 33.56 (t, C_7), 35.93 (t, C_4), 37.89 (d, C_5), 86.32 (d, C_1), 177.66 (s, C_3) ; IR (neat) 1770 cm^{-1} ($\nu_{C=O}$); MS (EI) (relative intensity) m/z 126 (M^+, 19), 98 (76), 97 (100), 83 (28), 80 (60), 67 (98), 54 (97) ; HRMS (EI) calcd for $C_7H_{10}O_2$ m/z 126.0681, found, 126.0678. This compound is already known, see: Burnell, D. J.; Wu, Y-J. *Can. J. Chem.* **1990**, *68*, 804; Crowe, W. E.; Vu, A. N. *J. Am. Chem. Soc.* **1996**, *118*, 1557. Assignment of ^{1}H-NMR reported by Crowe and Vu is consistent with ours, but the assignment of ^{13}C-NMR is not consistent with ours that is supported by DEPT and ^{13}C-^{1}H COSY spectra.

***cis*- and *trans*-4-Methyl-2-(2-oxoethyl)cyclopentanone (2b).** The ratio of *cis/trans* isomer was determined by ^{1}H-NMR in 62/38.



^{1}H-NMR (600 MHz, $CDCl_3$) δ 1.11 (d, J = 6.3 Hz, trans 3H), 1.15 (d, J = 6.4 Hz, cis 3H, overlapping m , cis 1H), 1.78 - 1.83 (m, trans 1H), 1.84 (dd, J = 11.5, 18.9 Hz, cis 1H), 1.94 - 2.04 (complex m, trans 2H), 2.20 - 2.27 (m, cis 1H), 2.37 (td-like, J ~ 6.4, 12.8 Hz, cis 1H), 2.42 - 2.58 (complex m, cis 2H + trans 3H), 2.62 (ddt, J = 4.2, 12.2, 7.8 Hz, cis 1H), 2.75 (ddd, J = 4.2, 8.5, 17.3 Hz, trans 1H), 2.86 (dd, J = 4.1, 18.1 Hz, trans 1H), 2.93 (dd, J = 3.9, 18.2 Hz, cis 1H), 9.77 (s, trans 1H), 9.78 (s, cis 1H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 20.03 (q, cis), 20.75 (q, trans), 27.86 (d, trans), 29.83 (d, cis), 36.23 (t, trans), 38.07 (t, cis), 40.65 (d, trans), 43.56 (t, cis), 44.20 (t, trans), 45.10 (d, cis), 45.60 (t, trans), 45.62 (t, cis), 199.98 (d, trans), 200.04 (d, cis), 218.80 (s, cis), 219.75 (s, trans); IR (neat) 1723, 1740 cm^{-1} ($\nu_{C=O}$); MS (EI) (relative intensity) m/z 140 (M^+, 2), 112 (97), 98 (100), 70 (83), 55 (47), 41 (63); HRMS (EI) calcd for $C_8H_{12}O_2$ m/z 140.0837, found, 140.0837. The configuration of **2b** was assigned by comparison with ^{13}C-NMR spectra of 2,4-dimethylcyclopentanone, see: Stothers, J. B.; Tan, C. T. *Can. J. Chem.* **1974**, *52*, 308.

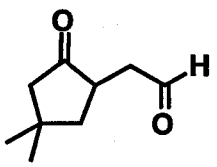
***endo*- and *exo*-7-Methyl-2-oxabicyclo[3,3,0]octan-3-one (3b).** The ratio of *endo/exo* isomer was determined by ^{1}H-NMR in 70/30.



^{1}H-NMR (600 MHz, $CDCl_3$) δ 1.03 (d, J = 6.1 Hz, 3H, exo), 1.07 (d, J = 6.6 Hz, endo 3H, overlapping m, endo 1H), 1.31 (ddd-like, J ~ 3.8, 11.9, 17.1 Hz, exo 1H), 1.42 - 1.49 (m, endo 1H + exo 1H), 1.66 (dd-like, J ~ 6.0, 13.2 Hz, exo 1H), 1.95 - 2.02 (m, endo 1H), 2.10 - 2.18 (m, exo 2H + endo 1H), 2.27 (dd, J = 3.0, 18.5 Hz, exo 1H), 2.32 - 2.38 (m, endo 2H), 2.71 - 2.79 (m, endo 2H), 2.83 (dd, J = 10.7, 18.5 Hz, exo 1H), 2.97 - 3.00 (m, exo 1H), 4.90 (dd-like, J ~ 6.8, 11.2 Hz, endo 1H), 5.01 (t, J = 6.0 Hz, exo 1H); ^{13}C-NMR (68 MHz, $CDCl_3$) δ 18.51 (q, exo), 19.32 (q, endo), 31.25 (d, exo, C_7), 34.39

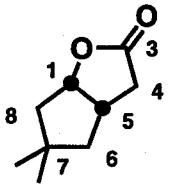
(d, endo, C_7), 35.23 (t, endo), 36.33 (t, exo), 37.58 (d, exo, C_5), 39.36 (d, endo, C_5), 41.10 (t, endo + t, exo), 41.94 (t, exo), 42.09 (t, endo), 86.15 (d, endo), 86.52 (d, exo), 177.22 (s, endo), 177.76 (s, exo); IR (neat) 1770 cm^{-1} ($\nu_{C=O}$); MS (EI) (relative intensity) m/z 140 (M^+, 18), 112 (42), 81 (62), 68 (100), 55 (50); HRMS (EI) calcd for $C_8H_{12}O_2$ m/z 140.0838, found, 140.0833. The *endo/exo* isomers of **3b** were assigned by the ^{1}H-NMR chemical shift of C*H*O. This compound is already known, see: Chatterjee, D. N.; Sarkar, M. *Curr. Sci.* **1977**, *46*, 261; Crowe, W. E.; Vu, A. N. *J. Am. Chem. Soc.* **1996**, *118*, 1557. Assignment of ^{1}H-NMR reported by Crowe and Vu is consistent with ours, but the assignment of ^{13}C-NMR is not consistent with ours that is supported by DEPT and ^{13}C-^{1}H COSY spectra.

4,4-Dimethyl-2-(2-oxoethyl)cyclopentanone (2c).



^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.11 (s, 3H), 1.20 (s, 3H), 1.50 (t-like, J ~ 12.4 Hz, 1H, β-C*H*H of cyclopentanone), 2.08 (ddd, J = 1.5, 8.4, 12.4 Hz, 1H, β-CH*H* of cyclopentanone), 2.17 (d, J = 4.5 Hz, 2H, C*H*$_2$CO), 2.54 (dd, J = 7.7, 18.0 Hz, 1H, CH*H*CHO), 2.77 - 2.83 (m, 1H, C*H*CO), 2.93 (dd, J = 4.2, 18.0 Hz, 1H, CH*H*CHO), 9.77 (s, 1H, CHO); ^{13}C-NMR (68 MHz, $CDCl_3$) δ 27.88 (q), 29.69 (q), 34.31 (s), 42.57 (d, *C*HCO), 43.46 (t, C*C*H$_2$CH), 44.33 (t, *C*H$_2$CHO), 52.30 (t, *C*H$_2$CO), 199.94 (d), 219.29 (s); IR (neat) 1721, 1739 cm^{-1} ($\nu_{C=O}$); MS (CI) (relative intensity) 155 (M^++1, 100), 137 (27), 126 (7), 112 (5), 95 (7); HRMS (CI) calcd for $C_9H_{15}O_2$ m/z 155.1072, found, 155.1080.

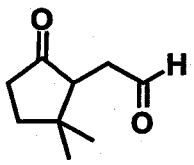
7,7-Dimethyl-2-oxabicyclo[3,3,0]octan-3-one (3c).



^{1}H-NMR (600 MHz, $CDCl_3$) δ 0.97 (s, 3H), 1.12 (s, 3H), 1.36 (dd, 1H, J = 9.6, 12.7 Hz, H_6: Irradiation at 3 ppm causes collapse of this peak to doublet (12.0 Hz)), 1.74 (dd, 1H, J = 3.8, 14.4 Hz, H_8: Irradiation at 5 ppm causes collapse of this peak to doublet (14.3

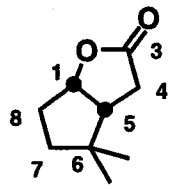
Hz)), 1.86 (ddd, 1H, J = 1.5, 8.2, 12.7 Hz, H_6: Irradiation at 3 ppm causes collapse of this peak to doublet (12.0 Hz)), 1.99 (ddd, 1H, J = 1.5, 7.0, 14.4 Hz, H_8: Irradiation at 5ppm causes collapse of this peak to dd (1.5, 14.0 Hz)), 2.35 (dd, 1H, J = 2.4, 18.3 Hz, H_4: Irradiation at 3ppm causes collapse of this peak to doublet (18.0 Hz)), 2.77 (dd, 1H, J = 9.8, 18.3 Hz, H_4), 2.98 (m, 1H, H_5), 4.99 (ddd, 1H, J = 3.9, 7.1, 7.1 Hz, H_1: Irradiation at 3ppm causes collapse of this peak to dd (3.8, 6.8 Hz)); ^{13}C-NMR (68 MHz, $CDCl_3$) δ 28.70 (q), 29.01 (q), 35.65 (t, C_4), 38.19 (d, C_5), 40.04 (s, C_7), 47.25 (t x 2, C_6 + C_8), 86.66 (d, C_1), 177.44 (s, C_3); IR (neat) 1770 cm^{-1} ($\nu_{C=O}$); MS (EI) (relative intensity) m/z 154 (M^+, 41), 139 (73), 95 (100), 85 (71), 82 (98), 57 (94), 55 (62), 41 (88); HRMS (EI) calcd for $C_9H_{14}O_2$ m/z 154.0994, found, 154.1002. This compound is already known, see: Crowe, W. E.; Vu, A. N. *J. Am. Chem. Soc.* **1996**, *118*, 1557. Assignment of ^{1}H-NMR reported by Crowe and Vu is consistent with ours, but the assignment of ^{13}C-NMR is not consistent with ours that is supported by DEPT and ^{13}C-^{1}H COSY spectra.

3,3-Dimethyl-2-(2-oxoethyl)cyclopentanone (2d).



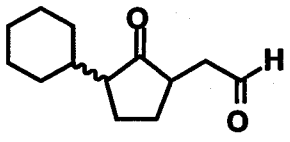
^{1}H-NMR (600 MHz, $CDCl_3$) δ 0.80 (s, 3H), 1,16 (s, 3H), 1.81-1.87 (m, 2H, β-CH_2 of cyclopentanone), 2.21 (dt, 1H, J = 9.8, 19.6 Hz, C*H*HCO), 2.27 (dd, 1H, J = 4.3, 16.8 Hz, C*H*HCHO), 2.38 (ddd, 1H, 3.7, 7.6, 19.6 Hz, C*H*HCO), 2.63 (dd, 1H, J = 4.3, 7.5 Hz, CHCO), 2.67 (dd, 1H, J = 7.5, 16.8 Hz, C*H*HCHO), 10.04 (s, 1H, CHO);^{13}C-NMR (68 MHz, $CDCl_3$) δ 21.86 (q), 28.15 (q), 34.66 (t), 35.88 (t, β-CH_2 of cyclopentanone), 38.51 (t), 40.10 (s), 54.91 (d, *C*HCO), 200.69 (d, CHO), 217.99 (s); IR (neat) 1724, 1739 cm^{-1} ($\nu_{C=O}$); MS (EI) (relative intensity) m/z 155 (M^++1, 1), 139 (16), 126 (46), 97 (60), 70 (100), 55 (42); HRMS (EI) calcd for $C_9H_{14}O_2$ m/z 154.0994, found, 154.0969.

6,6-Dimethyl-2-oxabicyclo[3,3,0]octan-3-one (3d).



^{1}H-NMR (600 MHz, $CDCl_3$) δ 1.01 (s, 6H), 1.47 (ddd, 1H, J = 4.6, 7.6, 12.9 Hz, H_7), 1.63 (td-like, 1H, J = 8.6, 12.9 Hz, H_7), 1.93 - 1.97 (m, 1H, H_8), 2.07 - 2.13 (m, 1H, H_8: Irradiation at 5.0 ppm causes collapse of two H_8 peaks to ddd), 2.42 - 2.49 (m, 2H, H_4 + H_5), 2.53 - 2.59 (m, 1H, H_4), 5.04 (td, 1H, J = 6.8, 1.8 Hz, H_1); ^{13}C-NMR (68 MHz, $CDCl_3$) δ 23.99 (q), 28.92 (q), 30.63 (t, C_4), 30.94 (t, C_8), 38.15 (t, C_7), 40.66 (s, C_6), 48.89 (d, C_5), 86.61 (d, C_1), 177.54 (s, C_3); IR (neat) 1770 cm^{-1} ($\nu_{C=O}$); MS (EI) (relative intensity) m/z 154 (M^+, 15), 126 (11), 94 (100), 85 (47), 69 (45), 55 (36); HRMS (EI) calcd for $C_9H_{14}O_2$ m/z 154.1003, found, 153.9994.

***cis*- and *trans*-5-Cyclohexyl-2-(2-oxoethyl)cyclopentanone (2e).** The ratio of *cis/trans* mixture of **2e** was determined by ^{1}H-NMR (600 MHz) analysis in 37/63.

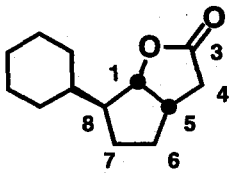


^{1}H-NMR (600 MHz, $CDCl_3$) δ 1.00 - 1.18 (complex m, trans 3H + cis 2H), 1.20 - 1.34 (complex m, trans 2H + cis 3H), 1.36 - 1.44 (complex m, trans 2H + cis 1H), 1.49 (qd-like, J = 8.0, 12.8 Hz, cis 1H), 1.60 - 1.82 (complex m, trans 6H + cis 5H), 1.87 (quint-like, J ~ 6.6 Hz, cis 1H), 1.92 - 2.14 (complex m, trans 2H + cis 1H), 2.16 - 2.28 (complex m, trans 1H + cis 2H), 2.37 - 2.43 (complex m, trans 1H + cis 1H), 2.51 (ddd, J = 1.2, 7.6, 18.8 Hz, trans 1H), 2.70 (ddq-like, J ~ 1.2, 4.4, 8.8 Hz, cis 1H), 2.83 (ddd, J = 1.2, 4.7, 17.6 Hz, cis 1H), 2.94 (dd, J = 4.1, 17.6 Hz, trans 1H), 9.79 (s, trans 1H + cis 1H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 23.05 (t, cis), 23.50 (t, trans), 26.22 (t), 26.30 (t), 26.34 (t), 26.51 (t), Two methylene carbons superimposed in the area of 26.2 ~ 26.5 ppm., 27.54 (t, trans), 27.67 (t cis), 28.80 (t, trans), 29.15 (t, cis), 31.34 (t, trans), 31.66 (t, cis), 38.04 (d, trans), 38.68 (d, cis), 43.02 (d, cis), 43.86 (t, cis), 43.91 (t, trans), 45.07 (d, trans), 52.76 (d, cis), 54.06 (d, trans), 200.37 (d, trans + cis), 220.22 (s, trans), 220.89 (s, cis); IR (neat) 1726, 1731 cm^{-1} ($\nu_{C=O}$); MS (EI) (relative intensity) m/z 208 (M^+, 3), 180 (10), 166 (20), 126 (53), 108 (9), 98 (63), 82 (100), 67 (21);

HRMS (EI) calcd for $C_{13}H_{20}O_2$ m/z 208.1463, found, 208.1465. The configuration of **2e** was assigned by comparison with ^{13}C-NMR spectra of 2,5-dimethylcyclopentanone, see: (a) Stothers, J. B.; Tan, C. T. *Can. J. Chem.* **1974**, *52*, 308. (b) Gramain, J. C.; Kergomard, A.; Renard, M. F.; Veschambre, H. *J. Org. Chem.* **1985**, *50*, 120.

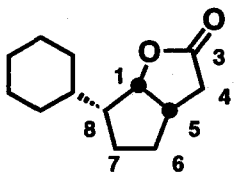
6-Cyclohexyl-4-oxabicyclo[3,3,0]octan-3-one (3e). The -C_1*H*O- proton resonated at higher field was assigned to the *exo* structure (*cis* to cyclohexyl). The ratio of *endo*/*exo* mixture of **3e** was determined by ^{1}H-NMR analysis in 50/50. Preparative HPLC allowed the separation of *endo*/*exo* mixtures of **3e**.

[*exo*-**3e**] ^{1}H-NMR (600 MHz, $CDCl_3$) δ 0.93 - 1.10 (m, 2H), 1.15 - 1.31 (m, 5H),



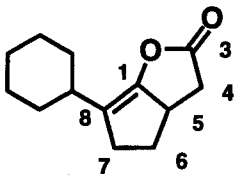
1.32 - 1.42 (m, 1H), 1.60 - 1.82 (m, 5H), 1.85 - 1.95 (m, 2H), 2.03 - 2.08 (m, 1H), 2.33 (d, 1H, *J* = 15.8 Hz), 2.68 - 2.76 (m, 2H), 4.62 (dd, 1H, *J* = 4.8, 7.2 Hz); ^{13}C-NMR (68 MHz, $CDCl_3$) δ 26.15 (t), 26.21 (t), 26.41 (t), 29.21 (t), 31.33 (t), 31.80 (t), 32.38 (t), 35.30 (t), 38.54 (d), 40.60 (d), 52.93 (d), 89.44 (d), 177.47 (s); IR (neat) 1774 cm^{-1} ($\nu_{C=O}$); MS (EI) (relative intensity) m/z 208 (M^+, 11), 190 (3), 148 (100), 126 (83), 108 (36), 97 (40), 81 (35), 67 (46); HRMS (EI) calcd for $C_{13}H_{20}O_2$ m/z 208.1463, found, 208.1467.

[*endo*-**3e**] ^{1}H-NMR (600 MHz, $CDCl_3$) δ 0.89 - 1.00 (m, 2H), 1.10 - 1.20 (m, 1H),



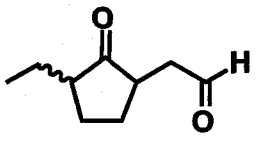
1.22 - 1.40 (m, 3H), 1.45 - 1.57 (m, 3H), 1.62 - 1.72 (m, 3H), 1.75 (broad d, 1H, *J* ~ 12.9 Hz), 1.80 - 1.88 (m, 2H), 2.00 (broad d, 1H, *J* ~ 12.6 Hz), 2.25 (dd, 1H, *J* = 18.0, 1.9 Hz), 2.83 (dd, 1H, *J* = 10.3, 18.0 Hz), 2.89 (m, 1H), 4.95 (dd, 1H, *J* = 4.2, 5.7 Hz); ^{13}C-NMR (68 MHz, $CDCl_3$) δ 25.89 (t), 26.15 (t), 26.44 (t), 26.84 (t), 31.85 (t), 32.40 (t), 32.63 (t), 36.72 (t), 37.17 (d), 37.26 (d), 53.05 (d), 86.34 (d), 178.11 (s); IR (neat) 1775 cm^{-1} ($\nu_{C=O}$); MS (EI) (relative intensity) m/z 208 (M^+, 16), 190 (2), 148 (100), 126 (35), 108 (32), 97 (18), 81 (27), 67 (51); HRMS (EI) calcd for $C_{13}H_{20}O_2$ m/z 208.1463, found, 208.1474.

6-Cyclohexyl-4-oxabicyclo[3,3,0]oct-5-en-3-one (3e').



^{1}H-NMR (600 MHz, $CDCl_3$) δ 1.10 - 1.40 (m, 5H), 1.43 - 1.80 (m, 6H), 2.15 - 2.25 (m, 2H), 2.25 (dd, 1H, H_2, J = 11.5, 16.9 Hz: Irradiation at 3.2 ppm causes collapse of this peak to dd (16.5, 1.5 Hz)), 2.31 (ddd, 1H, J = 1.5, 8.7, 14.6 Hz: Irradiation at 3.2 ppm causes collapse of this peak to dd (14.7, 8.7 Hz)), 2.44 - 2.54 (m, 1H: Irradiation at 3.2 ppm causes collapse of this peak to ddd (14.7, 6.0, 4.0 Hz)), 2.71 (dd, 1H, H_2, J = 8.4, 16.9 Hz: Irradiation at 3.2 ppm causes collapse of this peak to dd (16.5, 2.5 Hz)), 3.22 (m, 1H, H_1); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 26.09 (t), 26.15 (t), 26.18 (t), 30.71 (t), 31.20 (t), 31.23 (t), 32.79 (t), 36.70 (d), 37.10 (t), 42.69 (d), 117.24 (s), 147.41 (s), 177.58 (s); IR (neat) 1713, 1815 cm^{-1} ($\nu_{C=O}$); MS (EI) (relative intensity) m/z 206 (M^+, 100), 163 (89), 150 (42), 137 (19), 121 (20), 109 (35), 94 (11), 81 (19), 67 (36); HRMS (EI) calcd for $C_{13}H_{18}O_2$ m/z 206.1307, found, 206.1288.

***cis*- and *trans*-5-Ethyl-2-(2-oxoethyl)cyclopentanone (2f).** The ratio of *cis/trans* mixture of **2f** was determined by ^{1}H-NMR (400 MHz) analysis in 43/57.

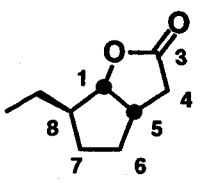


^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.95 (t, J = 7.5 Hz, trans 3H), 0.96 (t, J = 7.5 Hz, cis 3H), 1.30 - 1.62 (complex m, trans 3H + cis 2H), 1.66 - 1.87 (complex m, trans 1H + cis 2H), 2.04 - 2.15 (complex m, trans 1H + cis 1H), 2.17 - 2.29 (complex m, trans 2H + cis 2H), 2.44 - 2.51 (complex m, trans 1H + cis 1H), 2.56 (ddd, J = 1.0, 7.6, 18.2 Hz, trans 1H), 2.67 (dq, J = 4.1, 9.5 Hz, cis 1H), 2.86 (dd, J = 4.4, 18.0 Hz, cis 1H), 2.94 (dd, J = 3.9, 18.2 Hz, trans 1H), 9.79 (s, trans 1H + cis 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 11.80 (q, trans), 12.19 (q, cis), 23.29 (t, trans), 23.57 (t, cis), 26.12 (t, cis), 27.04 (t, cis), 27.32 (t, trans), 27.71 (t, trans), 42.93 (d, cis), 44.06 (t, trans), 44.09 (t, cis), 44.21 (d, trans), 48.73 (d, cis), 50.06 (d, trans), 199.73 (d, trans), 199.76 (d, cis), 220.02 (s, trans), 220.26 (s, cis); IR (neat) 1724, 1732 cm^{-1} ($\nu_{C=O}$); MS (EI) (relative intensity) for

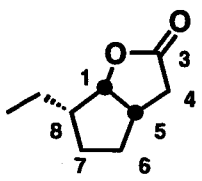
cis isomer m/z 154 (M^+, 5), 126 (62), 112 (75), 97 (100), 83 (43), 70 (51), 55 (72); HRMS (EI) calcd for $C_{13}H_{20}O_2$ m/z 154.0994, found, 154.0969.; MS (EI) (relative intensity) for trans isomer m/z 154 (M^+, 16), 126 (43), 112 (100), 97 (100), 83 (43), 70 (51), 55 (73); HRMS (EI) calcd for $C_{13}H_{20}O_2$ m/z 154.0994, found, 154.1015. The configuration of **2f** was assigned by comparison with ^{13}C-NMR spectra of 2,5-dimethylcyclopentanone, see: (a) Stothers, J. B.; Tan, C. T. *Can. J. Chem.* **1974**, *52*, 308. (b) Gramain, J. C.; Kergomard, A.; Renard, M. F.; Veschambre, H. *J. Org. Chem.* **1985**, *50*, 120.

8-Ethyl-2-oxabicyclo[3,3,0]octan-3-one (3f). The major isomer was assigned to the *exo* structure because of the relative upfield shifts of its -C_1*H*O- proton. The ratio of *endo*/*exo* mixture of **3f** was determined by ^{1}H-NMR analysis in 42/58. Preparative HPLC allowed the separation of *endo*/*exo* mixtures of **3f**.

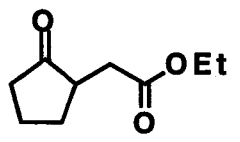
[*exo*-**3f**] ^{1}H-NMR (400 MHz, CDCl3) δ 0.97 (t, *J* = 7.2 Hz, 3H), 1.29 - 1.46 (m, 4H), 1.92 (dd, *J* = 6.1, 12.2 Hz, 1H), 2.04 (m, 2H), 2.32 (d, *J* = 16.9 Hz, 1H), 2.73 - 2.82 (m, 2H), 4.56 (d-like, *J* ~ 3.7 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 12.58 (q), 25.32 (t), 30.08 (t), 32.09 (t), 35.82 (t), 37.97 (d), 48.10 (d), 90.72 (d), 177.25 (s); IR (neat) 1775 cm^{-1} ($\nu_{C=O}$); EIMS (relative intensity) m/z 154 (M^+, 16), 126 (100), 97 (60), 81 (31), 72 (34), 55 (77), 41 (38); HREIMS calcd for $C_9H_{14}O_2$ m/z 154.0994, found, 154.0983.



[*endo*-**3f**] ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.99 (t, *J* = 7.3 Hz, 3H), 1.29 - 1.39 (m, 1H), 1.46 - 1.92 (m, 6H), 2.26 (dd, *J* = 1.7, 18.1 Hz, 1H), 2.83 (dd, J = 10.3, 18.1 Hz, 1H), 2.90 - 2.93 (m, 1H), 4.87 (t, J = 5.1 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 13.00 (q), 22.23 (t), 28.79 (t), 32.87 (t), 36.75 (t), 37.53 (d), 48.21 (d), 87.07 (d), 177.69 (s); IR (neat) 1774 cm^{-1} ($\nu_{C=O}$); EIMS (relative intensity) m/z 154 (M^+, 16), 126 (100), 97 (59), 81 (30), 72 (29), 55 (75), 41 (35); HREIMS calcd for $C_9H_{14}O_2$ m/z 154.0994, found, 154.0969.



(2-Ethoxycarbonylmethyl)cyclopentanone (4a).



^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.26 (t, 3H, J = 7.3 Hz), 1.55 - 1.70 (m, 1H), 1.70 - 1.90 (m, 1H), 2.00 - 2.50 (m, 6H), 2.73 (d, 1H, J = 12.2 Hz), 4.14 (q, 2H, J = 7.3 Hz); ^{13}C-NMR (68 MHz, $CDCl_3$); δ 14.61, 20.55, 29.24, 33.94, 37.38, 45.56, 60.52, 172.02, 219.05; IR (neat) 1732 cm^{-1}($\nu_{C=O}$); EIMS (relative intensity) m/z 170 (M^+, 20), 125 (100), 97 (55), 83 (74), 55 (89). This compound is already known, see: Ryu, I.; Kusano, K.; Hasegawa, M.; Kambe, N.; Sonoda, N. *J. Chem. Soc., Chem. Commun.* **1991**, 1018.

5-4. References and Notes

(1) Leading reviews: (a) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds.* Pergamon Press: Oxford, 1986. (b) Curran, D. P. *Synthesis* **1988**, 417; 489. (c) Motherwell, W. B.; Crich, D. *Best Synthetic Methods, Free Radical Chain Reactions in Organic Synthesis.* Academic Press: London, 1992. (d) Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; vol 4, Chapters 4.1 and 4.2.

(2) Recent reports on free-radical carbonylation, see: (a) Ryu, I.; Kusano, K.; Hasegawa, M.; Kambe, N.; Sonoda, N. *J. Chem. Soc., Chem. Commun.* **1991**, 1018. (b) Tsunoi, S.; Ryu, I.; Sonoda, N. *J. Am. Chem. Soc.* **1994**, *116*, 5473. (c) Nagahara, K.; Ryu, I.; Kambe, N.; Komatsu, M.; Sonoda, N. *J. Org. Chem.* **1995**, *60*, 7384. (d) Tsunoi, S.; Ryu, I.; Fukushima, H.; Tanaka, M.; Komatsu, M.; Sonoda, N. *Synlett* **1995**, 1249. Reviews, see: (e) Ryu, I.; Sonoda, N. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1050. (f) Ryu, I; Sonoda, N.; Curran, D. P. *Chem. Rev.* **1996**, *96*, 177.

(3) Aside from radical polymerization, a general approach for plural CO introducing

process has not been well established so far, see: (a) Brubaker, M. M.; Coffman, D. D.; Hoehn, H. H. *J. Am. Chem. Soc.* **1952**, *74*, 1509. (b) Coffman, D. D.; Pinkney, P. S.; Wall, F. T.; Wood, W. H.; Young, H. S. *J. Am. Chem. Soc.* **1952**, *74*, 3391. (c) Cairns, T. L.; Coffman, D. D.; Cramer, R.; Larchar, A. W.; McKusick, B. C. *J. Am. Chem. Soc.* **1954**, *76*, 3024. (d) Chatgilialoglu, C.; Ferreri, C.; Sommazzi, A. *J. Am. Chem. Soc.* **1996**, *118*, 7223.

(4) (a) Tsunoi, S.; Ryu, I.; Yamasaki, S.; Fukushima, H.; Tanaka, M.; Komatsu, M.; Sonoda, N. *J. Am. Chem. Soc.* in press. Related reaction using transition metal, see: (b) Negishi, E.; Copéret, C.; Ma, S.; Mita, T.; Sugihara, T.; Tour, J. M. *J. Am. Chem. Soc.* **1996**, *118*, 5904. (c) Negishi, E.; Ma, S.; Amanfu, J.; Copéret, C.; Miller, J. A.; Tour, J. M. *J. Am. Chem. Soc.* **1996**, *118*, 5919.

(5) (a) Lusztyk, J.; Lusztyk, E.; Maillard, B.; Ingold, K. U. *J. Am. Chem. Soc.* **1984**, *106*, 2923. (b) Ryu, I.; Kusano, K.; Hasegawa, M.; Kambe, N.; Sonoda, N. *J. Chem. Soc., Chem. Commun.* **1991**, 1018. (c) Ballestri, M.; Chatgilialoglu, C.; Cardi, N.; Sommazzi, A. *Tetrahedron Lett.* **1992**, *33*, 1787. (d) Riemann, H.; Capomaggi, A. S.; Strauss, T.; Oliveto, E. P.; Barton, D. H. R. *J. Am. Chem. Soc.* **1961**, *83*, 4481. (e) Gimisis, T.; Ballestri, M.; Ferreri, C.; Chatgilialoglu, C. *Tetrahedron Lett.* **1995**, *36*, 3897. Also see a review: (f) Dowd, P.; Zhang, W. *Chem. Rev.* **1993**, *93*, 2091. Recently, rate constant for isomerization of **B** to **C** has been measured, see: ref 3d.

(6) The yields of this reaction require optimization: Single carbonylation products constitute main by-products and a small amount of six-membered double carbonylation products were also detected (1-4%).

(7) Tributylgermyl hydride is a poorer hydrogen donor to alkyl radicals than tributyltin hydride, see: Johnston, L. J.; Lusztyk, J.; Wayner, D. D. M.; Abeywickreyma, A. N.; Beckwith, A. L. J.; Scaiano, J. C.; Ingold, K. U. *J. Am. Chem. Soc.* **1985**, *107*, 4594.

(8) Chatgilialoglu, C. *Acc. Chem. Res.* **1992**, *25*, 188.

(9) Preliminary semiempirical calculations by PM3 has shown that the 5-*endo* radical cyclization is an exothermic process by 5.56 kcal/mol. While this value is smaller than that calculated for 5-*exo* cyclization reaction, it still represents a possible driving force for the rearrangement. Free-radical mediated 5-*endo* cyclizations are rare. Some examples of a cyclization of acyl radicals onto a conjugated ketone carbonyl is known, however the corresponding cyclization onto a nonconjugated ketone carbonyl is unprecedented. For recent examples on 5-*endo* cyclization of acyl radicals onto a conjugated ketone carbonyl, see: (a) Mendenhall, G. D.; Protasiewicz, J. D.; Brown, C. E.; Ingold, K. U.; Lusztyk, J. *J. Am. Chem. Soc.* **1994**, *116*, 1718; 5525. (b) Yamamoto, Y.; Ohno, M.; Eguchi, S. *J. Am. Chem. Soc.* **1995**, *117*, 9653.

(10) Single carbonylated products were formed in 40% yield.

(11) Even with the use of Bu_3SnH, secondary iodides **1e** and **1f** gave lactones **3e** and **3f** as minor products, respectively (runs 7 and 9). This may be related to the known fact that secondary iodides are more prone to undergo atom transfer than primary iodides. (a) Newcomb, M.; Sanchez, R. M.; Kaplan, J. *J. Am. Chem. Soc.* **1987**, *109*, 1195. Also see: Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140 and references cited therein.

(12) For this cyclization step, a single electron transfer from acyl iodide to internal ketone carbonyl, followed by the coupling of the resulting ion pair or a spontaneously ionic path might be possible.

(13) Ab initio calculation (3-21G(*)) shows that iodine atom transfer from alkyl iodide to acyl radical is energically unfavorable (ΔH = 4.83 kcal/mol for primary alkyl iodide, 1.92 kcal/mol for secondary alkyl iodide).

(14) The formation of pseudo-acid chloride from the reaction of 1,4-keto acid with oxalyl chloride is known, see: (a) Heathcock, C. H.; Davidsen, S. K.; Mills, S. G.; Sanner, M. A. *J. Org. Chem.* **1992**, *57*, 2531. (b) Langschwager, W. L.; Hoffmann, M. R. *Liebigs Ann.* **1995**, 797.

(15) As for the formation of **F**, the detection of a small amount of unsaturated lactone **3e'** in the case of secondary iodide **1e**, may document the existence of **F** in this reaction system. For mechanistic discussion on related transformations, see: (a) Bowman, W. R.; Heaney, H.; Jordan, B. M. *Tetrahedron* **1991**, *47*, 10119. (b) Curran, D. P.; Yu, H.; Liu, H. *Tetrahedron* **1994**, *50*, 7343. (c) Beckwith, A. L. J.; Storey, J. M. D. *J. Chem. Soc., Chem. Commun.* **1995**, 977.

(16) In the preceding chapter, the formation of esters from corresponding alkyl iodides and CO under a Zn(Cu) induced reduction system, may probably involve iodine atom transfer to acyl radicals. Relatively slow reduction of secondary and tertiary alkyl radicals may allow the unusual atom transfer to acyl radicals, see: ref 2d.

Conclusion

The aim of this research is to develop new methods for separation and chemical utilization of carbon monoxide. The important findings described in each chapter are summarized as follows.

Chapter **1** described that efficient separation of carbon monoxide was possible with a system consisting of selenium and secondary amines. Formation of carbamoselenoates obtained from selenium, CO, and secondary amines, and their thermal decomposition, are the basis of this new method. This separation method is exceptional in that it is based on the *chemical reaction* of CO.

Chapter **2** described that the formation and the thermal decomposition of carbamoselenoates also provided a new method for reclamation of selenium and tellurium. Five-nine (99.999%) purity of Se and three-nines (99.9%) purity of Te can be obtained by this method. This method is also applicable to reclamation of Se from Se-Te scrap alloys.

Chapters **3, 4,** and **5** were concerned with the novel synthetic utilization of carbon monoxide. In these three chapters, carbonylation with CO in oxidation and reduction systems and double carbonylations using group 14 metal hydrides were described, respectively.

Chapter **3** described carbonylation of alcohols using a one-electron oxidation system. The reaction of saturated alcohols with carbon monoxide in the presence of lead tetraacetate (LTA) provided a convenient, one step synthesis of δ-lactones. This is the first example that achieved synthesis of δ-lactones from saturated alcohols and CO. With cyclobutanols as the substrates, a novel carbonylation sequence which accompanies ring-opening was achieved. C_1-substituted cyclobutanols afforded 5-oxoacid derivatives, whereas C_1-unsubstituted cyclobutanols afforded δ-lactones.

Chapter **4** described the carbonylation of alkyl iodides using a one-electron reduction system of zinc. Zinc mediated reduction/carbonylation system of alkyl iodides can be successfully applied to the synthesis of aldehydes, unsymmetrical ketones, and functionalized cyclopentanones. The reaction carried out in aprotic solvents is useful to achieve sequential radical/anionic reactions which provides one operation synthesis of bicyclo[3.3.0]octan-1-ols.

Chapter **5** described double carbonylation reactions of alk-4-enyl iodides with the use of group 14 metal hydrides. The major products obtained via double CO trapping were dependent on the group 14 metal hydride used. With Bu_3SnH, 4-keto aldehydes were obtained. With Bu_3GeH, bicyclic γ-lactones were formed as principal double carbonylation product.

I believe that several important findings obtained through the present studies would open the door to the new fields of CO chemistry.

List of Publications

(1) A New and Convenient Process for Separation of Carbon Monoxide
Noboru Sonoda, Noritaka Miyoshi, Shinji Tsunoi, Akiya Ogawa, Nobuaki Kambe
Chem. Lett. **1990**, 1873.

(2) Purification of CO Based on Selenium-Amine-CO Chemistry
Shinji Tsunoi, Noritaka Miyoshi, Akiya Ogawa, Nobuaki Kambe, Noboru Sonoda
Bull. Chem. Soc. Jpn. **1994**, *67*, 2297.

(3) Remote Carbonylation. The Synthesis of δ-Lactones from Saturated Alcohols and Carbon Monoxide
Shinji Tsunoi, Ilhyong Ryu, Noboru Sonoda
J. Am. Chem. Soc. **1994**, *116*, 5473.

(4) Carbonylation of Cyclobutanol by Way of Oxidative Ring Cleavage with LTA
Shinji Tsunoi, Ilhyong Ryu, Yukihiro Tamura, Sumiaki Yamasaki, Noboru Sonoda
Synlett **1994**, 1009.

(5) Free-Radical Carbonylation Using a Zn(Cu) Induced Reduction System
Shinji Tsunoi, Ilhyong Ryu, Hiroshi Fukushima, Minoru Tanaka, Mitsuo Komatsu, Noboru Sonoda
Synlett **1995**, 1249.

(6) Free Radical Mediated Double Carbonylations of Alk-4-enyl Iodides
Shinji Tsunoi, Ilhyong Ryu, Sumiaki Yamasaki, Hiroshi Fukushima, Minoru Tanaka, Mitsuo Komatsu, Noboru Sonoda
J. Am. Chem. Soc. in press.

List of Supplementary Publications

(1) Free-Radical Carbonylation by TTMSS Mediated Process

Ilhyong Ryu, Mitsuharu Hasegawa, Akio Kurihara, Akiya Ogawa, Shinji Tsunoi, Noboru Sonoda

Synlett **1993**, 143.

(2) A n + 1 Strategy for Macrocyclization Based on Free-Radical Carbonylation

Ilhyong Ryu, Kiyoto Nagahara, Hiroshi Yamazaki, Shinji Tsunoi, Noboru Sonoda

Synlett **1994**, 643.

(3) Stannylformylation of 1,6-Dienes Accompanied by Five-Membered Radical Ring Closure

Ilhyong Ryu, Akio Kurihara, Hideo Muraoka, Shinji Tsunoi, Nobuaki Kambe, Noboru Sonoda

J. Org. Chem. **1994**, *59*, 7570.

(4) Stannylformylation of Vinylcyclopropanes Accompanied by Radical Ring-Opening

Shinji Tsunoi, Ilhyong Ryu, Hideo Muraoka, Minoru Tanaka, Mitsuo Komatsu, Noboru Sonoda

Tetrahedron Lett. **1996**, *37*, 6729.

(5) Separation of Naphthalene and Flavone Derivatives by Micellar Electrokinetic Chromatography with Double- and Triple-Chain Surfactants

Hiroya Harino, Youji Inoue, Junko Yoshioka, Shinji Tsunoi, Masaharu Eguchi, Yuta Yasaka, Koichi Funazo, Minoru Tanaka

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