

Title	Studies on Carbonylation of Aromatic Compounds and Related Reactions using Cobalt and Palladium Catalysts
Author(s)	伊藤, 健司
Citation	大阪大学, 1993, 博士論文
Version Type	VoR
URL	<a href="https://doi.org/10.11501/3065885">https://doi.org/10.11501/3065885</a>
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Osaka University

**Studies on  
Carbonylation of Aromatic Compounds  
and Related Reactions  
using Cobalt and Palladium Catalysts**

（コバルトおよびパラジウム触媒を用いる芳香族化合物の  
カルボニル化反応ならびに関連反応に関する研究）

**1993**

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大阪大学大学院工学研究科応用化学専攻

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## Preface

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The work of this thesis has been carried out under the guidance of Professor Dr. Masakatsu Nomura of the Department of Applied Chemistry, Faculty of Engineering, Osaka University.

The objective of this thesis is development of novel synthetic methods of aromatic carbonyl compounds and related substances using homogeneous transition-metal catalysts, especially cobalt or palladium based catalysts. The author hopes that the results obtained in this work can contribute to further development in the area of organic synthesis using transition-metal catalysts to some extent.

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January, 1993

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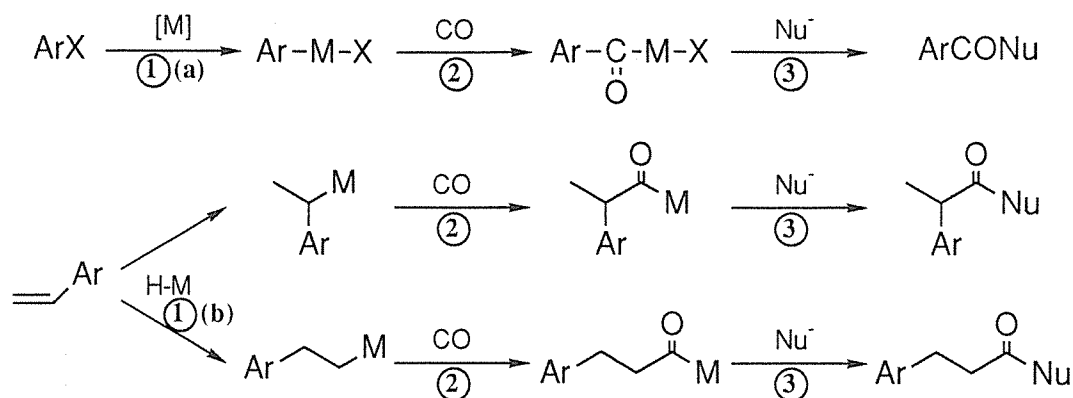
## General Introduction

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Aromatic carbonyl compounds have been widely used as synthetic intermediates for medicines, agricultural chemicals, and functionalized organic substances.<sup>1</sup> Thus, development of efficient and economical methods for synthesis of the compounds has been of considerable interest. One of the most useful methods is appeared to be transition-metal catalyzed carbonylation in which carbon monoxide as the carbonyl source is introduced into aromatic compounds, and the reaction has been extensively studied. Recent studies on the reaction are directed toward developing the methods with high product selectivity, being able to be carried out under mild conditions.

Generally, transition-metal catalyzed carbonylation reactions are considered to consist of the following three steps.<sup>2</sup>

1. Formation of organometal complexes by (a) oxidative addition of organic halides or their synthetic equivalents to low-valent transition-metal species or (b) addition of metal hydrides to unsaturated compounds.
2. Formation of acylmetal complexes by migratory insertion of carbon monoxide in the above organometal complexes.
3. Reaction of the acylmetal complexes with nucleophilic reagents



to give carbonyl compounds.

Therefore, the important points to be considered in developing novel carbonylation reactions seem to be as follows; (a) efficient preparation of catalytically active low-valent transition-metal species, (b) acceleration of oxidative addition and migratory insertion of carbon monoxide, (c) expansion of substrates and nucleophiles, and (d) control of regioselectivity in the reaction with unsaturated compounds.

In the light of these results, the following work aimed at developing new, useful synthetic methods for aromatic carbonyl compounds and related substances via carbonylation using either cobalt or palladium catalyst has been carried out, which is described in four chapters.

Chapter 1 is concerned with two convenient methods for preparation of catalytically active cobalt species under mild conditions for carbonylation of aryl halides from cobalt(II) chloride which is



less expensive and easily handled compared with octacarbonyldicobalt which has been often used for the reaction as the catalyst precursor.<sup>2</sup> Synthesis of aromatic  $\alpha$ -keto carboxylic acids and methyl carboxylates by using these methods has also been undertaken.

Chapter 2 describes a method for carbonylation using arylsulfonyl chlorides as the starting substrates which can be easily obtained from the corresponding sulfonic acids. It was found that arylsulfonyl chlorides underwent facile carbonylation accompanied by desulfonylation in the presence of palladium complexes by using less basic titanium(IV) alkoxides as nucleophiles to give aromatic esters. When zinc acetate was used in place of  $\text{Ti}(\text{OR})_4$ , aromatic carboxylic acids were produced. Furthermore, biaryls could also be obtained by carrying out the reaction under nitrogen.

In chapter 3, carbonylation of aryl-substituted allylic compounds using the palladium- $\text{Ti}(\text{OR})_4$  reaction system employed in chapter 2 was attempted. Consequently, not only allylic halides but also allylic alcohols were carbonylated under much milder conditions than those required for the methods previously reported,<sup>3</sup> when the reaction was performed in the presence of lithium chloride. Coupling reaction of the allylic alcohols and zinc enolates of  $\beta$ -dicarbonyl compounds was also found to proceed efficiently by using the palladium- $\text{Ti}(\text{OR})_4$ -LiCl system under nitrogen.

Chapter 4 refers hydroesterification of monoarylalkynes using

palladium complexes in the presence of phenolic compounds as nucleophiles. The reaction could be carried out under mild conditions to give  $\alpha$ -arylacrylic acid aryl esters in good regioselectivity and yield. Aliphatic alcohols instead of phenols could also be used by addition of a catalytic amount of acids.

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(b) *Ullman's Encyclopedia of Industrial Chemistry*, VCH, Weinheim, Vol. A5, p. 249 (1986).
2. (a) J. P. Collman and L. S. Hegedus, *Principles and Applications of Organotransition Metal Chemistry*, University Science Books, Mill Valley, California (1980).  
(b) I. Wender and P. Pino, eds., *Organic Syntheses via Metal Carbonyls*, Wiley, New York (1977).  
(c) J. Falbe, ed., *New Synthesis with Carbon Monoxide*, Springer-Verlag, Berlin (1980).
3. J. Tsuji, J. Kiji, S. Imamura and M. Morikawa, *J. Am. Chem. Soc.*, **86**, 4350 (1964).

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## List of Publications

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The contents of this thesis are composed of the following papers.

1. Normal Pressure Double Carbonylation of Aryl Halides using Cobalt(II) Chloride in the Presence of either Sodium Sulfide or Sodium Borohydride

Kenji Itoh, Masahiro Miura and Masakatsu Nomura

*Bull. Chem. Soc. Jpn.*, **61**, 4151 (1988).

2. Cobalt(II) Chloride Catalyzed Normal Pressure Carbonylation of Aryl Halides

Masahiro Miura, Kenji Itoh and Masakatsu Nomura

*J. Mol. Catal.*, **48**, 11 (1988).

3. Palladium-catalyzed Desulfonylative Carbonylation of Arylsulfonyl Chlorides in the Presence of Titanium Tetraalkoxides

Masahiro Miura, Kenji Itoh and Masakatsu Nomura

*Chem. Lett.*, **1989**, 77.

4. Desulfonylative Carbonylation of Arylsulfonyl Chlorides Catalyzed

by Palladium Complexes

Kenji Itoh, Hideo Hashimoto, Masahiro Miura and Masakatsu Nomura

*J. Mol. Catal.*, **59**, 325 (1990).

5. Palladium-catalyzed Desulfonylative Homo-coupling of Aryl-sulfonyl Chlorides in the Presence of Titanium(IV) Isopropoxide

Masahiro Miura, Hideo Hashimoto, Kenji Itoh and Masakatsu Nomura,

*Chem. Lett.*, **1990**, 459.

6. Palladium-catalyzed Carbonylation of Allyl Alcohols in the Presence of Lithium Chloride and Titanium(IV) Isopropoxide

Kenji Itoh, Naoki Hamaguchi, Masahiro Miura and Masakatsu Nomura

*J. Mol. Catal.*, **75**, 117 (1992).

7. Palladium-catalysed Reaction of Aryl-substituted Allylic Alcohols with Zinc Enolates of  $\beta$ -Dicarbonyl Compounds in the Presence of Titanium(IV) Isopropoxide

Kenji Itoh, Naoki Hamaguchi, Masahiro Miura and Masakatsu Nomura

*J. Chem. Soc., Perkin Trans. 1*, in press.

8. Palladium-catalyzed Aryloxyacylation of Terminal Alkynes

Kenji Itoh, Masahiro Miura and Masakatsu Nomura

*Tetrahedron Lett.*, **33**, 5369 (1992).

9. Palladium-catalyzed Regioselective Hydroesterification of Alkynes

Kenji Itoh, Yuichi Kushino, Masahiro Miura and Masakatsu  
Nomura

*in preparation.*

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## Chapter 1

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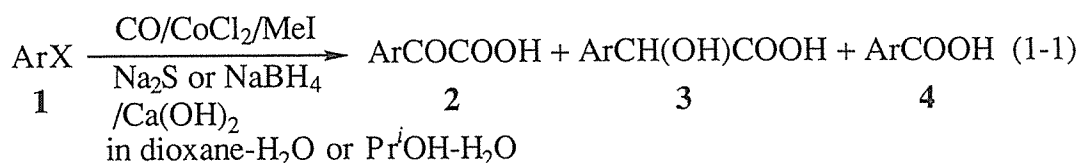
### Normal Pressure Carbonylation of Aryl Halides using Cobalt(II) Chloride as Catalyst Precursor

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#### 1-1. Introduction

Several effective methods for cobalt-catalyzed carbonylation of aryl halides to produce the corresponding carboxylic acids,  $\alpha$ -ketocarboxylic acids, and alkyl aryl ketones have recently been developed, using either  $\sigma$ -alkyltetracarbonylcobalt complexes  $\text{RCo}(\text{CO})_4$ <sup>1,2</sup> or tetracarbonylcobaltate ion  $\text{Co}(\text{CO})_4^-$  under photostimulation.<sup>3,4</sup> In the former case, we reported that the product distribution is a marked function of the solvent system employed.<sup>2</sup> These reactions proceed smoothly in the presence of appropriate base under extremely mild conditions. The catalytically active species are usually prepared *in situ* from somewhat air-sensitive octacarbonyldicobalt  $\text{Co}_2(\text{CO})_8$ . Simple inorganic cobalt salts have also been successfully attempted for use as catalyst precursors; however, the presence of a reducing agent, such as sodium hydride,<sup>5</sup> or photoirradiation<sup>6</sup> is needed to induce the carbonylation reaction.

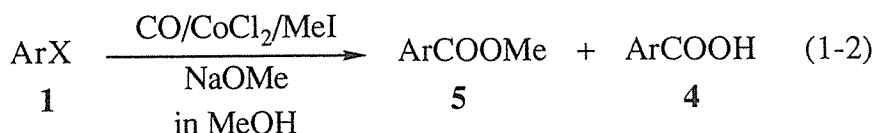
In the course of our studies, we have undertaken the synthesis of the carboxylic acids and/or  $\alpha$ -keto carboxylic acids derivatives using cobalt salts in order to provide a convenient route to the acids.<sup>7</sup> It was found that the tetracarbonylcobaltate ion prepared by a treatment of cobalt chloride with either sodium sulfide in water<sup>8</sup> or sodium borohydride in dioxane<sup>9</sup> can catalyze the carbonylation of aryl halides **1** at room temperature under a normal pressure of carbon monoxide to give the corresponding  $\alpha$ -ketocarboxylic acids **2** in good selectivity along with the glycolic acids **3** and the mono acids **4** (eq. 1-1).<sup>10</sup> And it was also observed that cobalt(II) chloride can catalyze the methoxy-carbonylation of aryl halides **1** in the presence of methyl iodide and sodium methoxide in methanol to give the corresponding methyl esters **5** in good yields along with the free acids **4** (eq. 1-2).



**1a:** 1-bromonaphthalene

**1b:** bromobenzene

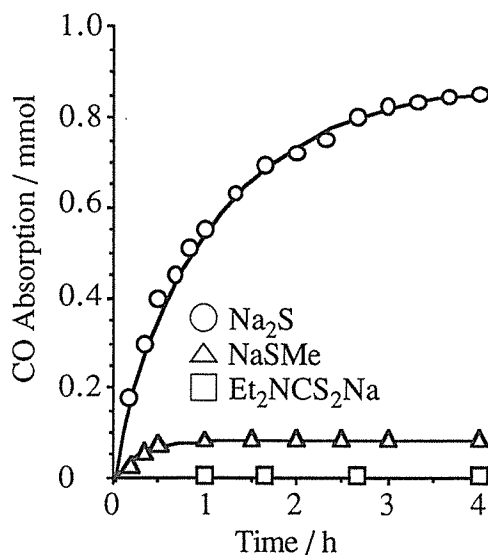
**1c:** iodobenzene



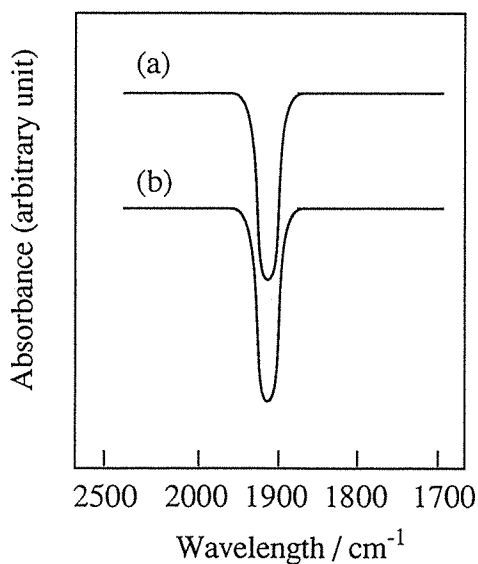
## 1-2. Results and Discussion

### 1-2-1. Double carbonylation of Aryl Halides **1** using Cobalt(II) Chloride in the Presence of either Sodium Sulfide or Sodium Borohydride

When cobalt chloride (0.5 mmol) was treated with sodium sulfide (0.25 mmol) in the presence of calcium hydroxide in water at 20 °C under carbon monoxide (1 atm) for 4 h, about 0.9 mmol of carbon monoxide was consumed (Figure 1-1 [○]). The IR spectrum of the solution showed a single characteristic peak for  $\text{Co}(\text{CO})_4^-$  at



**Figure 1-1.** CO Absorption in the treatment of  $\text{CoCl}_2$  (0.5 mmol) with S-containing compounds in the presence of  $\text{Ca}(\text{OH})_2$  (35 mmol): ○  $\text{Na}_2\text{S}$  (0.25 mmol), △  $\text{NaSMe}$  (0.5 mmol), □  $\text{Et}_2\text{NCS}_2\text{Na}$  (0.5 mmol)



**Figure 1-2.** IR spectra of  $\text{Co}(\text{CO})_4^-$  generated in  $\text{H}_2\text{O}$  from (a)  $\text{CoCl}_2$ ,  $\text{Na}_2\text{S}$ , and  $\text{Ca}(\text{OH})_2$ ; (b)  $\text{Co}_2(\text{CO})_8$  and  $\text{Ca}(\text{OH})_2$



1913  $\text{cm}^{-1}$  in the region 1700 to 2000  $\text{cm}^{-1}$  (Figure 1-2).

The addition of **1** (5 or 10 mmol) in dioxane together with methyl iodide to the solution gave **2** along with **3** and **4**. The results for the carbonylation of **1** under various conditions are summarized in Table 1-1. The formation of aryl methyl ketone was not detected in each reaction. The conversion of **1** and the selectivity of **2** were comparable with those using  $\text{Co}_2(\text{CO})_8$  (0.25 mmol) (Runs 3 and 6). Cobalt sulfide could not be used in place of  $\text{CoCl}_2\text{-Na}_2\text{S}$  (Run 9), suggesting that the sulfide does not participate in the formation of the active species. While sodium methanethiolate, which is an efficient reagent for the preparation of nickel(0) carbonyl derivatives from nickel chloride,<sup>11</sup> could also be used in place of sodium sulfide, it was considerably less effective than the sulfide (Run 7 and Figure 1-1 [ $\Delta$ ]). Potassium ethylxanthogenate and sodium diethyldithiocarbamate were ineffective (Run 8 and Figure 1-1 [ $\square$ ]).

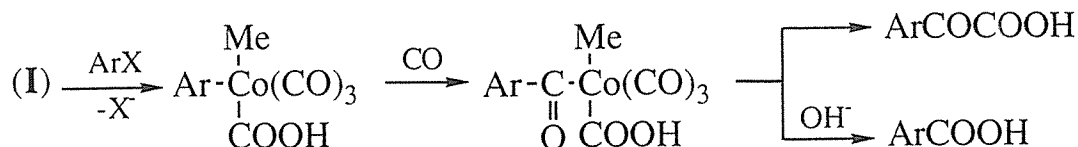
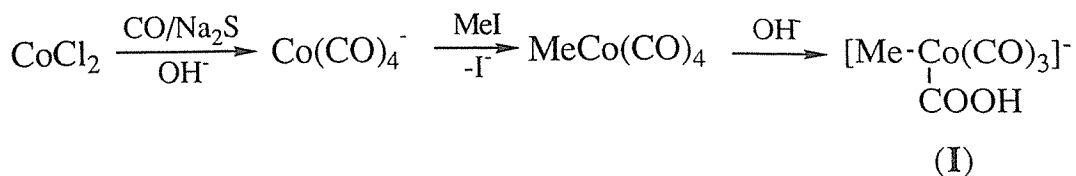
As an alternative catalyst system for the carbonylation,  $\text{CoCl}_2$  /  $\text{NaBH}_4$  /  $\text{Ca}(\text{OH})_2$  in dioxane could also be successfully used (Runs 5, 16, and 19). In this case, the cobaltate ion was prepared within 1.5 h (see Experimental).

It is noteworthy that, in the reaction in isopropyl alcohol-water (1:1, v/v), a remarkably higher conversion of **1**, accompanied by a little decrease of the selectivity of **2**, was observed (Runs 10, 17, and 20). This is in contrast with the reactions in dioxane-water (1:1) and

**Table 1-1.**Double-carbonylation of Aryl Halides with Cobalt(II) Chloride<sup>a</sup>

Run	1	Co- catalyst	Solvent <sup>b</sup>	Conv. of 1 / % <sup>c</sup>	Selectivity / % <sup>c</sup>		
					2	3	4
1 <sup>d</sup>	1a(1)	Na <sub>2</sub> S	A	94	63	33	2
2 <sup>e</sup>	1a(2)	Na <sub>2</sub> S	A	60	89	5	2
3	1a(5)	Na <sub>2</sub> S	A	51	86	9	4
4	1a(10)	Na <sub>2</sub> S	A	41	87	5	4
5	1a(10)	NaBH <sub>4</sub>	A	39	80	3	5
6	1a(5)	———— <sup>f</sup>	A	55	85	4	5
7	1a(5)	NaSMe	A	20	75	5	17
8 <sup>d</sup>	1a(1)	NaEt <sub>2</sub> NCS <sub>2</sub>	A	10	-g	-g	-g
9	1a(1)	———— <sup>h</sup>	A	12	-g	-g	-g
10	1a(5)	Na <sub>2</sub> S	B	90	89	3	6
11	1a(10)	Na <sub>2</sub> S	B	53	89	4	7
12	1a(10)	Na <sub>2</sub> S	B <sup>i</sup>	31	88	7	2
13	1a(10)	Na <sub>2</sub> S	B <sup>j</sup>	31	82	3	10
14	1a(5) <sup>k</sup>	Na <sub>2</sub> S	B	11	20	17	60
15	1b(5)	Na <sub>2</sub> S	A	42	53 <sup>l</sup>	4	5
16	1b(5)	NaBH <sub>4</sub>	A	40	57 <sup>l</sup>	2	8
17	1b(5)	Na <sub>2</sub> S	B	74	48 <sup>l</sup>	2	8
18	1c(5)	Na <sub>2</sub> S	A	61	62 <sup>l</sup>	3	5
19	1c(5)	NaBH <sub>4</sub>	A	48	68 <sup>l</sup>	3	5
20	1c(5)	Na <sub>2</sub> S	B	78	64 <sup>l</sup>	3	13

a) The reaction was carried out under carbon monoxide (1 atm) at 20 °C for 20 h. [CoCl<sub>2</sub>]:[Na<sub>2</sub>S] or [NaBH<sub>4</sub>]:[Ca(OH)<sub>2</sub>]:[MeI]=0.5:0.25 or 1:35:25 (in mmol). b) A: Dioxane-H<sub>2</sub>O (3:1, v/v). B: Pr<sup>i</sup>OH-H<sub>2</sub>O (1:1, v/v). c) Determined by GLC analysis. d) [CoCl<sub>2</sub>]:[Ca(OH)<sub>2</sub>]:[MeI]=0.5:15:10 (in mmol). e) [CoCl<sub>2</sub>]:[Ca(OH)<sub>2</sub>]:[MeI]=0.5:25:20 (in mmol). f) Co<sub>2</sub>(CO)<sub>8</sub> (0.25 mmol) was used. g) Not detected. h) CoS (0.5 mmol) was used. i) Pr<sup>i</sup>OH-H<sub>2</sub>O (3:1, v/v). j) Pr<sup>i</sup>OH-H<sub>2</sub>O (1:2, v/v). k) Reaction at 60 °C. l) The keto acid was obtained as a mixture of the acid and the condensated product with pyruvic acid. The value indicates that after hydrolysis of the product mixture with NaOH (see Experimental).<sup>2c</sup>



**Scheme 1-1**

ethanol-water (1:1) in which the mono acids **4** were the major products.<sup>2c</sup> The conversion of **1**, however, decreased as a result of changes in the isopropyl alcohol-water ratio from 1:1 to both 3:1 and 1:2 (Runs 12 and 13).

The present double carbonylation reaction may proceed by the mechanism illustrated in Scheme 1-1, which is the same as that proposed for the reaction with  $\text{Co}_2(\text{CO})_8$ , except generation step of  $\text{Co}(\text{CO})_4^-$ , previously.<sup>1,2</sup>

### 1-2-2. Methoxycarbonylation of Aryl Halides **1** using Cobalt(II) Chlorides as Catalyst Precursor

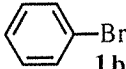
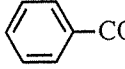
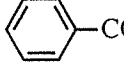
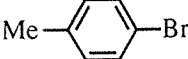
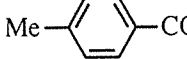
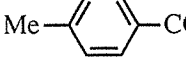


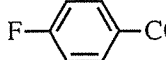



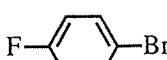

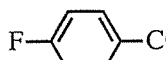
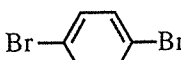
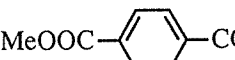
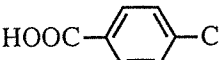
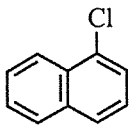
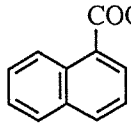
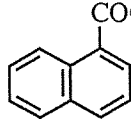
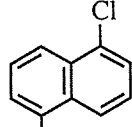
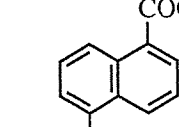
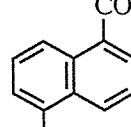
A mixture of anhydrous cobalt(II) chloride (0.5 mmol) and sodium methoxide (15 mmol) in methanol (5 ml) was stirred under carbon monoxide (1 atm) at room temperature for 2 h. Then, a

further portion of methanol (5 ml) was added and the mixture was stirred for an additional 2 h. The carbonylation reaction of aryl halides **1** was carried out by addition of **1** (2 mmol) in methanol (2 ml) together with methyl iodide (10 mmol) to the solution. In each case, the corresponding methyl ester **6** was obtained in good yield along with the free acid **4** as recorded in Table 1-2.

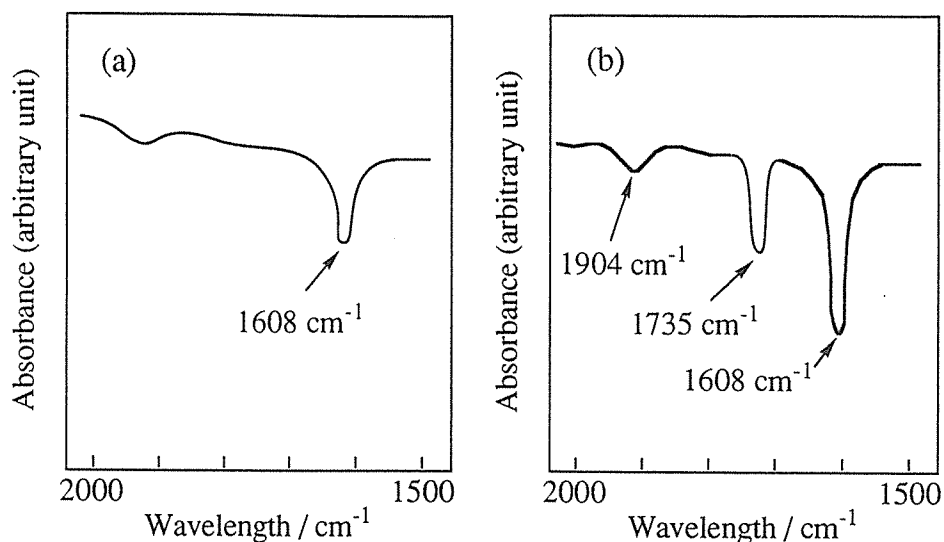
This procedure, as a convenient method for the methoxy-carbonylation of aryl halides, is advantageous in some respects; the reaction can be carried out without any special equipment, giving strict care to eliminate moisture and air. In the present system, in contrast to the reported trends for carbonylation using cobalt salts,<sup>5,6</sup> the conversion of aryl halides was very low (less than 30 %) when the reaction was performed at 60 °C or in ethanol.

While the active cobalt species catalyzing the reaction is unclear at the present stage, the following results are suggestive. (a) The IR spectrum of the methanol solution before the addition of halide showed only a peak at 1608 (m)  $\text{cm}^{-1}$  in the region 1600-2000  $\text{cm}^{-1}$  (Figure 1-3 [a]). Although a peak at 1904  $\text{cm}^{-1}$  suggesting the formation of  $\text{Co}(\text{CO})_4^-$ , was observed after the reaction along with the band at 1608  $\text{cm}^{-1}$ , it was extremely weak (Figure 1-3 [b]). (b) Half the amount of bromobenzene **1b** charged was consumed within a period of 3 h (0.5 h in the case of 1-bromonaphthalene **1a**) (Figure 1-4). (c) An additional portion of aryl halide could also be carbonylated

**Table 1-2.**Methoxycarbonylation of Aryl Halides **1** with Cobalt(II) Chloride<sup>a</sup>

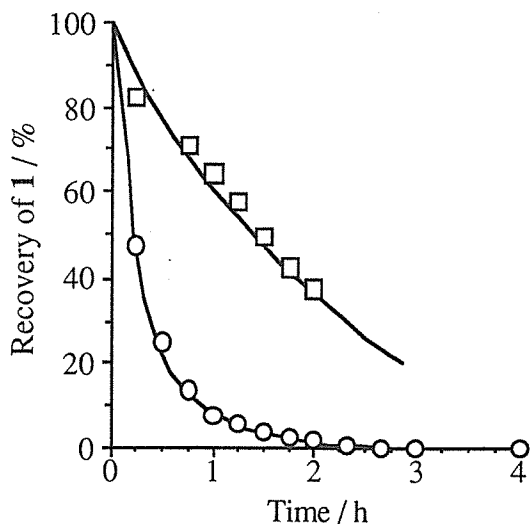
Run	<b>1</b>	Products (%yield) <sup>b</sup>	<b>4</b>	Recovery of <b>1</b> / % <sup>b</sup>
		<b>5</b>		
21	 <b>1b</b>	 (88)	 (4)	4
22 <sup>c</sup>		 (88)	 (5)	5
23		 (95)	 (4)	
24 <sup>d</sup>		 (85)	 (6)	6
25 <sup>e</sup>		 (68)	 (8)	20
26 <sup>f</sup>		 (90)	 (7)	
27		 (90)	 (5)	
28 <sup>f</sup>		 (84)	 (9)	

a) The reaction was carried out under carbon monoxide (1 atm) at 20 °C for 24 h. [1]:[CoCl<sub>2</sub>]:[NaOMe]:[MeI]=2:0.5:15:10 (in mmol). b) Determined by GLC analysis. c) [1]:[NaOMe]:[MeI]=2:30:20 (in mmol). d) [1]:[CoCl<sub>2</sub>]:[NaOMe]:[MeI]=7.5:0.3:20:10 (in mmol). e) The reaction was carried out for 60 h; [1]:[CoCl<sub>2</sub>]:[NaOMe]:[MeI]=22.5:0.3:60:30 (in mmol); halide was added together with methyl iodide and sodium methoxide in three portions. f) **1** (1 mmol) was used.



**Figure 1-3.** IR spectra of methanol solution of  $\text{CoCl}_2$  and  $\text{NaOMe}$ : (a) before 4th carbonylation, (b) after reaction of  $\text{PhBr}$ .

by adding it into the reaction mixture together with methyl iodide and sodium methoxide (Run 25). (d) In the absence of methyl iodide, aryl halide was recovered quantitatively and sodium iodide could not be used in place of methyl iodide. These results lead us to deduce that the



**Figure 1-4.** Time course of recovery of substrate during the methoxycarbonylation of **1**: ○ 1-bromonaphthalene, □ bromobenzene.

reaction involves methylcobalt complex(es) as the predominant active species other than methyltetracarbonylcobalt.

### 1-3. Summary

Tetracarbonylcobaltate ion generated by a treatment of cobalt(II) chloride with either sodium sulfide or sodium borohydride under a normal pressure of carbon monoxide is capable of catalyzing the double-carbonylation of aryl halides in the presence of calcium hydroxide and methyl iodide to give arylglyoxylic acids in good selectivity. And also the methoxycarbonylation of aryl halides can proceed in the presence of methyl iodide using the cobalt species prepared by a treatment of cobalt(II) chloride with sodium methoxide in methanol under a normal pressure of carbon monoxide to give the corresponding methyl esters in good yield.

### 1-4. Experimental

#### 1-4-1. General Procedure

GC-MS data were obtained with a Hitachi RMU-6M spectrometer. GLC analysis was carried out on a Simadzu GC-4C gas chromatograph.

### 1-4-2. Generation of Tetracarbonylcobaltate Ion

(a) To a flask containing anhydrous cobalt(II) chloride (0.5 mmol), sodium sulfide nonahydrate (0.25 mmol), and calcium hydroxide (35 mmol) was added water (10 ml). The mixture was stirred for 4 h at room temperature under carbon monoxide (1 atm).

(b) A mixture of anhydrous cobalt(II) chloride (0.5 mmol) and sodium borohydride (1 mmol) in dioxane (10 ml) was stirred at 20 °C for 1 h, while bubbling carbon monoxide. Then, water (5 ml) and calcium hydroxide (35 mmol) were added and stirred for a further 20 min.

### 1-4-3. Double Carbonylation of Aryl Halides **1** using $\text{Co}(\text{CO})_4^-$ Generated from $\text{CoCl}_2$

To the solution above mentioned, a mixture of aryl halides **1** (5 or 10 mmol) and methyl iodide (25 mmol) in appropriate solvents (1, 4-dioxane or isopropyl alcohol) was added and the resulting mixture was further stirred at room temperature for 20 h under carbon monoxide (1 atm). The resulting mixture was poured into dilute hydrochloric acid and extracted with ether. The acidic products were extracted with aqueous sodium hydroxide. After acidification the products were re-extracted with ether. The condensed product with



phenylglyoxilic acid and pyruvic acid which was obtained by the carbonylation of phenyl halides **1b** and **1c** was hydrolyzed with NaOH.<sup>2c</sup> The acidic products were trimethylsilylated with *N, O*-bis(trimethylsilyl)acetamide in acetonitrile or methylated with diazomethane in ether. Analysis of the esterificated products was performed by GLC and GC-MS after addition of an appropriate internal standard. The methyl esters were identified by comparison with authentic samples.

#### 1-4-4. Methoxycarbonylation of Aryl Halides **1** using CoCl<sub>2</sub> as Catalyst Precursor

A mixture of anhydrous cobalt(II) chloride (0.5 mmol) and sodium methoxide (15 mmol) in methanol (5 ml) was stirred under carbon monoxide (1 atm) at room temperature for 2 h and then a further portion of methanol (5 ml) was added. After an additional 2 h, a mixture of aryl halides **1** (2 mmol) and methyl iodide (10 mmol) in methanol (2 ml) was added and the resulting mixture was stirred for 20 h. After workup, the product mixture was analyzed as described above.

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## Chapter 2

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### Palladium-catalyzed Desulfonylative Carbonylation and Homo-coupling of Arylsulfonyl Chlorides

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#### 2-1. Introduction

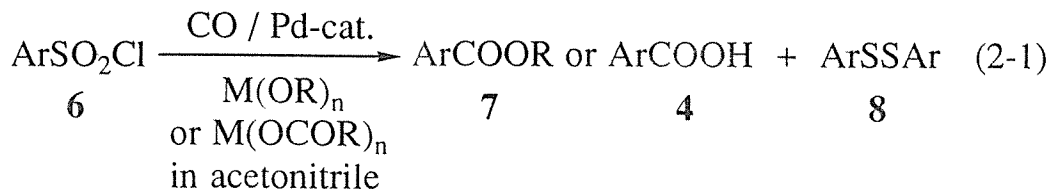
Palladium-catalyzed carbonylation of aryl bromides and iodides is a useful tool for the preparation of a variety of aromatic carbonyl compounds and there have been extensive studies on the reaction; the reaction of intermediary aroylpalladium complexes with various nucleophilic reagents gives the products.<sup>1</sup> While aryl chlorides are very difficult to carbonylate, aryldiazonium salts,<sup>2</sup> aryl triflates,<sup>3</sup> and arylborates<sup>4</sup> have been successfully used in place of aryl halides.

It may be conceived that arylsulfonyl chlorides could also be used for the reaction, since Group VIII noble metals are considered to catalyze their desulfonylation leading to aryl chlorides via formation of arylmetal intermediates<sup>5</sup> which may be transformed into the aroylmetal complexes under carbon monoxide. In spite of their ready availability, the use of sulfonyl chlorides as the precursors of the carbonyl compounds has been little studied.<sup>6</sup>

On the other hand, the reaction with arylsulfonyl chlorides seem to be particularly advantageous for the preparation of naphthalene derivatives because both  $\alpha$ - and  $\beta$ -naphthalenesulfonic acids can be obtained by sulfonation, whereas either halogenation or nitration predominantly gives the  $\alpha$ -substituted compounds.<sup>7</sup> Naphthalene is one of the most abundant and important compounds among the coal-derived chemicals, and many of the derivatives have been used as drugs, pesticides, dyes, and others.<sup>8</sup> Naphthalenes having substituents at the  $\beta$ -position have also become increasingly important in the pharmaceutical and polymer industries.<sup>9</sup>

Since sulfonyl chlorides are very susceptible to both the base and the nucleophile, It was expected that less basic reagents than the amine and the alcohol which are often used for the reaction of aryl halides<sup>6</sup> could be successfully employed in the synthetic strategy. Indeed, It was observed that the carbonylation of arylsulfonyl chlorides **6** in the presence of catalytic amount of palladium complexes proceeded to give the corresponding aromatic esters **7** in good to moderate yields along with diaryl disulfides **8**, using metal alkoxides  $M(OR)_n$  ( $M=Ti, B, Al$ ) as both the nucleophile and base, which were used for rhodium-and/or palladium-catalyzed carbonylation of base-sensitive benzyl halides as well as aryl halides.<sup>10</sup> Metal carboxylates  $M(OCOR)_n$  ( $M=Na, Ca, Mg, \text{ and } Zn; R=H \text{ and } CH_3$ )<sup>2a,11</sup> in place of metal alkoxides could also be used, giving the free acids **4** as the carbon-

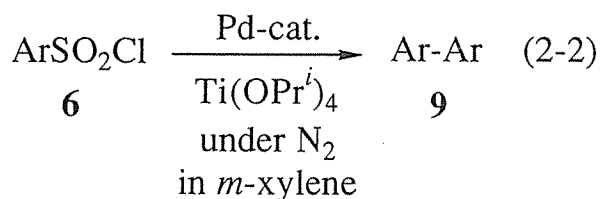
ylation products along with diaryl disulfide **8** (eq. 2-1).



M(OR)<sub>n</sub>: M=Ti, B, Al; R=Et, *i*-Pr, *n*-Bu, *s*-Bu, *t*-Bu  
M(OCOR)<sub>n</sub>: M=Na, K, Ca, Zn; R=H, Me

While the relevant palladium-catalyzed desulfonylative carbon-ylation reaction of sodium 4-methylbenzenesulfinate in methanol<sup>12</sup> and arylazo aryl sulfones in benzene-acetic acid<sup>13</sup> have been reported, this appears to be one of the most effective methods, the reaction proceeding with good catalyst efficiency.

It was also found that homo-coupling reaction of the arylsulfonyl chlorides **6** efficiently proceeded accompanied by desulfonylation on treatment with titanium(IV) isopropoxide in the presence of a catalytic amount of dichlorobis(benzonitrile)palladium PdCl<sub>2</sub>(PhCN)<sub>2</sub> under nitrogen to give biaryls **9** (eq. 2-2).<sup>14,15</sup>



## 2-2. Results and Discussion

### 2-2-1. Desulfonylative Carbonylation of Arylsulfonyl Chlorides **6**

*Carbonylation of 1-naphthalenesulfonyl chloride 6a in the presence of metal alkoxides*—The results for the carbonylation of 1-naphthalenesulfonyl chloride **6a** (2 mmol) with a series of palladium complexes (0.1 mmol) in several solvents in the presence of titanium(IV) isopropoxide (4 mmol) at 160 °C for 4-5 h under 10 atm of initial carbon monoxide pressure are summarized in Table 2-1. From each run isopropyl 1-naphthoate **7a** (R=Pr<sup>*i*</sup>) was obtained along with di-1-naphthyl disulfide **8a**. Among the complexes tested as catalyst precursors, PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> and Pd(PPh<sub>3</sub>)<sub>4</sub> showed good catalytic activity (Runs 2 and 5). The reaction could be also completed with Pd(PPh<sub>3</sub>)<sub>4</sub> (0.02 mmol) and Ti(OPr<sup>*i*</sup>)<sub>4</sub> (1 mmol) at 160 °C (Run 7). However, decreasing the reaction temperature significantly reduced the product yield (Runs 5, 8, and 9). Although the reaction proceeded under normal pressure of carbon monoxide, the yield of **7a** considerably decreased. While various solvents could be used, except *N, N*-dimethylformamide (DMF), acetonitrile appeared to be one of the most suitable solvents (Runs 5 and 10-13).

The results shown in Table 2-2 indicate effects of metal alkoxides. In the reactions with a series of titanium alkoxides under

**Table 2-1.**Carbonylation of 1-naphthalenesulfonyl chloride **6a** in the presence of titanium(IV) isopropoxide<sup>a</sup>

Run	Complex	Solvent	Yield / % <sup>b</sup>	
			<b>7a</b> (R=Pr <sup>i</sup> ) <sup>c</sup>	<b>8a</b> <sup>d</sup>
1	PdCl <sub>2</sub> (PhCN) <sub>2</sub>	MeCN	50	13
2	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	MeCN	70	17
3	PdCl <sub>2</sub> (AsPh <sub>3</sub> ) <sub>2</sub>	MeCN	59	24
4	PdCl <sub>2</sub> (dppf) <sup>e</sup>	MeCN	31	12
5	Pd(PPh <sub>3</sub> ) <sub>4</sub>	MeCN	66	25
6	Pd(PPh <sub>3</sub> ) <sub>4</sub> <sup>f</sup>	MeCN	66	14
7	Pd(PPh <sub>3</sub> ) <sub>4</sub> <sup>g</sup>	MeCN	60	23
8	Pd(PPh <sub>3</sub> ) <sub>4</sub> <sup>h</sup>	MeCN	48	27
9	Pd(PPh <sub>3</sub> ) <sub>4</sub> <sup>i</sup>	MeCN	14	3
10	Pd(PPh <sub>3</sub> ) <sub>4</sub>	1, 4-dioxane	51	39
11	Pd(PPh <sub>3</sub> ) <sub>4</sub>	ClCH <sub>2</sub> CH <sub>2</sub> Cl	55	40
12	Pd(PPh <sub>3</sub> ) <sub>4</sub>	benzene	39	25
13	Pd(PPh <sub>3</sub> ) <sub>4</sub>	DMF		13

a) The reaction was carried out under carbon monoxide (10 atm at room temperature) at 160 °C for 4-5 h. [**6a**]:[Pd-complex]:[Ti(OPr<sup>i</sup>)<sub>4</sub>]= 2:0.1:4 (in mmol). b) Isolated yield. c) Isopropyl 1-naphthoate. d) Di-1-naphthyl disulfide. e) dppf=1,1'-bis(diphenylphosphino)ferrocene. f) [**6a**]: [Pd-complex]:[Ti(OPr<sup>i</sup>)<sub>4</sub>]=2:0.02:2 (in mmol), 10 h. g) [**6a**]:[Pd-complex]:[Ti(OPr<sup>i</sup>)<sub>4</sub>]=2:0.02:1 (in mmol), 10 h. h) 120 °C. i) 80 °C.



the conditions A (see footnote b in Table 2-2), the yield of the esters increased as follows:  $\text{OBu}^t < \text{OEt} < \text{OBu}^n < \text{OBu}^s < \text{OPr}^i$  (Runs 5 and 14-17). In contrast,  $\text{B}(\text{OBu}^n)_3$  gave a better result than  $\text{B}(\text{OPr}^i)_3$  (Runs 18 and 19). Aluminium alkoxides were less effective (Runs 20 and 21).

Similar effects of titanium<sup>10a</sup> and boron alkoxides<sup>10b</sup> on the product yields in the carbonylation of benzyl and aryl halides have been reported by Woell *et al.* It is also known that (a) titanium(IV) *primary* alkoxides in solution exist as aggregates (typically trimeric in high concentration) and the degree of aggregation depends on concentration, whereas the *secondary* and *tertiary* alkoxides are monomeric or slightly associated<sup>16</sup> and (b) trialkoxyboranes are monomeric.<sup>8</sup>

Consequently, we performed the reaction in ten-fold diluted solutions (conditions B in Table 2-2). In the reactions using  $\text{Ti}(\text{OEt})_4$  (Run 22) and  $\text{Ti}(\text{OBu}^n)_4$  (Run 24) the yields of the esters were considerably improved, whereas with the other alkoxides almost invariant results were obtained.

*Carbonylation of 1-naphthalenesulfonyl chloride 6a with metal carboxylates* — Carbonylation of **6a** with various metal carboxylates in acetonitrile was also examined (Table 2-3). From each run, 1-naphthoic acid **4a** as the carbonylation product was isolated along with di-1-naphthyl disulfide **8a**. The reaction temperature also

**Table 2-2.**Carbonylation of 1-naphthalenesulfonyl chloride **6a** in the presence of several metal alkoxides<sup>a</sup>

Run	Alkoxide	Conditions <sup>b</sup>	Yield / % <sup>c</sup>	
			<b>7a</b>	<b>8a</b>
14	Ti(OEt) <sub>4</sub>	A	38	15
5	Ti(OPr <sup><i>i</i></sup> ) <sub>4</sub>	A	66	25
15	Ti(OBu <sup><i>n</i></sup> ) <sub>4</sub>	A	43	14
16	Ti(OBu <sup><i>s</i></sup> ) <sub>4</sub>	A	58	31
17	Ti(OBu <sup><i>t</i></sup> ) <sub>4</sub> <sup>d</sup>	A	6	5
18	B(OPr <sup><i>i</i></sup> ) <sub>3</sub>	A	43	6
19	B(OBu <sup><i>n</i></sup> ) <sub>3</sub>	A	54	9
20	Al(OPr <sup><i>i</i></sup> ) <sub>3</sub>	A	33	10
21	Al(OBu <sup><i>s</i></sup> ) <sub>3</sub>	A	6	13
22	Ti(OEt) <sub>4</sub>	B	60	19
23	Ti(OPr <sup><i>i</i></sup> ) <sub>4</sub>	B	67	22
24	Ti(OBu <sup><i>n</i></sup> ) <sub>4</sub>	B	68	25
25	Ti(OBu <sup><i>s</i></sup> ) <sub>4</sub>	B	54	27
26	B(OPr <sup><i>i</i></sup> ) <sub>3</sub>	B	40	6
27	B(OBu <sup><i>n</i></sup> ) <sub>3</sub>	B	52	13
28	Al(OPr <sup><i>i</i></sup> ) <sub>3</sub>	B	23	12

a) The reaction was carried out in acetonitrile under carbon monoxide (10 atm at room temperature) at 160 °C for 5 h using Pd(PPh<sub>3</sub>)<sub>4</sub>. b) A; [**6a**]:[Pd(PPh<sub>3</sub>)<sub>4</sub>]:[alkoxide]=2:0.1:4 (in mmol), MeCN (4 ml). B; [**6a**]:[Pd(PPh<sub>3</sub>)<sub>4</sub>]:[alkoxide]=1:0.05:1 (in mmol), MeCN (10 ml). c) Isolated yield. d) 1-Naphthoic acid (31 %) was also obtained.

**Table 2-3.**

Carbonylation of 1-naphthalenesulfonyl chloride **6a** in the presence of various metal acetates<sup>a</sup>

Run	Carboxylate	Complex	Temp / °C	Time / h	Yield / %	
					<b>4a</b> <sup>b</sup>	<b>8a</b> <sup>c</sup>
29	NaOCOH	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	120	20	50	2
30	Ca(OAc) <sub>2</sub>	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	120	20	24	3
31	NaOAc	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	120	20	50	5
32	NaOAc	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	140	20	49	5
33	NaOAc	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	160	5	58	8
34 <sup>d</sup>	NaOAc	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	160	5	55	11
35	NaOAc	PdCl <sub>2</sub> (AsPh <sub>3</sub> ) <sub>2</sub>	140	7.5	20	20
36	NaOAc	Pd(PPh <sub>3</sub> ) <sub>4</sub>	140	7.5	28	7
37	Ca(OAc) <sub>2</sub>	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	120	20	7	38
38	Ca(OAc) <sub>2</sub>	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	160	5	36	3
39	Mg(OAc) <sub>2</sub>	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	160	5	20	5
40	Zn(OAc) <sub>2</sub>	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	120	20	38	3
41	Zn(OAc) <sub>2</sub>	PdCl <sub>2</sub> (PhCN) <sub>2</sub>	160	5	36	3
42	Zn(OAc) <sub>2</sub>	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	160	5	53	5
43	Zn(OAc) <sub>2</sub>	PdCl <sub>2</sub> (AsPh <sub>3</sub> ) <sub>2</sub>	160	5	65	10
44 <sup>e</sup>	Zn(OAc) <sub>2</sub>	PdCl <sub>2</sub> (AsPh <sub>3</sub> ) <sub>2</sub>	160	5	48	12
45 <sup>f</sup>	Zn(OAc) <sub>2</sub>	PdCl <sub>2</sub> (AsPh <sub>3</sub> ) <sub>2</sub>	160	5	35	9
46	Zn(OAc) <sub>2</sub>	PdCl <sub>2</sub> (dppf) <sup>g</sup>	160	5	46	10

a) The reaction was carried out in acetonitrile (4 ml) under carbon monoxide (10 atm at room temperature). [**6a**]:[Pd-complex]:[Carboxylate]=2:0.1:5 (in mmol). b) 1-Naphthoic acid. Yield determined by GLC analysis after methylation with diazomethane. c) Di-1-naphthyl disulfide. Yield after isolation. d) [NaOAc]=2. e) [Zn(OAc)<sub>2</sub>]=1. f) [PdCl<sub>2</sub>(AsPh<sub>3</sub>)<sub>2</sub>]=0.02. g) dppf=1,1'-bis(diphenylphosphino)-ferrocene

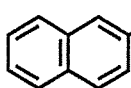
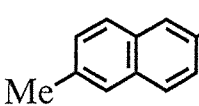
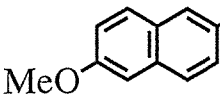
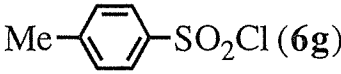
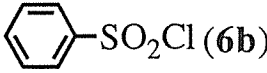
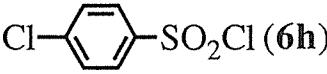
considerably affected the yield of **4a**, as in the reaction using alkoxides (Runs 31-33). Among the complexes and carboxylates tested, a system of  $\text{PdCl}_2(\text{AsPh}_3)_2\text{-Zn(OAc)}_2$  was found to give fairly good results (Run 43), followed by  $\text{PdCl}_2(\text{PPh}_3)_2\text{-NaOAc}$  (Run 33).

*Carbonylation of various arylsulfonyl chlorides 6* — Carbonylation of a number of arylsulfonyl chlorides **6**, including 6-substituted 2-naphthalenesulfonyl chlorides **6d-f** and 4-substituted benzenesulfonyl chlorides **6b**, **6g** and **6h**, was performed using either  $\text{Pd(PPh}_3)_4\text{-Ti(OPr}^i)_4$  or  $\text{PdCl}_2(\text{AsPh}_3)_4\text{-Zn(OAc)}_2$  in acetonitrile (Table 2-4). The corresponding isopropyl esters **7** ( $\text{R}=\text{Pr}^i$ ) and free acids **4** were obtained in fair to good yields.

*Reaction scheme*— A most probable catalytic cycle for the desulfonylative carbonylation of **6** is illustrated in Scheme 2-1, which is similar to that proposed for the reaction of aryl halides.<sup>1</sup> Oxidative addition of **6** to Pd(0) species generated *in situ* and successive loss of sulfur dioxide gives the arylpalladium intermediate. Subsequently, insertion of carbon monoxide into the intermediate followed by reaction with alkoxides or carboxylates affords the esters **7** and acids **4**.

The fact that a relatively higher temperature compared with the reaction of aryl halides,<sup>1</sup> is required to obtain a reasonable product

**Table 2-4.**  
 Carbonylation of various arylsulfonyl chlorides **6**

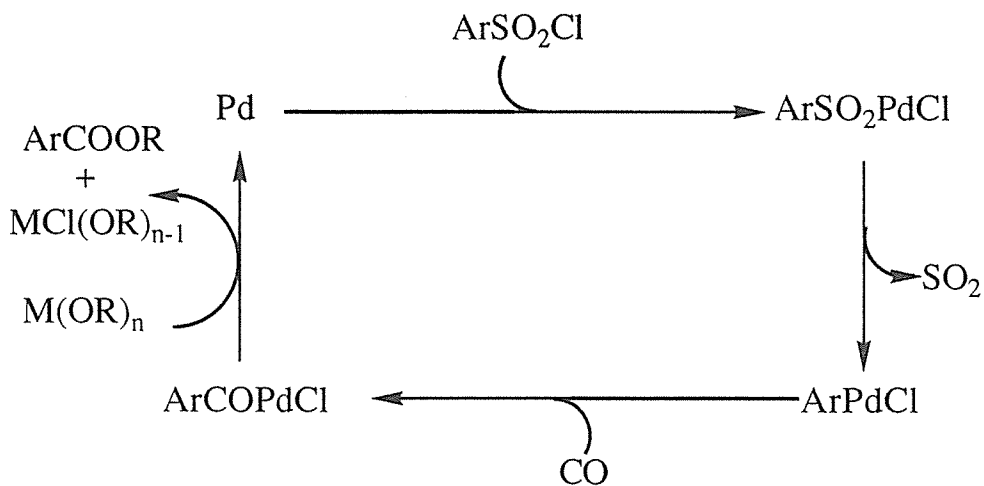
<b>6</b>	Yield / % <sup>a</sup>		Yield / % <sup>b</sup>	
	<b>7</b>	<b>8</b>	<b>4</b>	<b>8</b>
 <b>(6d)</b>	63	22	71	24
 <b>(6e)</b>	45	- <sup>c</sup>	67	- <sup>c</sup>
 <b>(6f)</b>	73	- <sup>c</sup>	60	- <sup>c</sup>
 <b>(6g)</b>	53	40	58	18
 <b>(6b)</b>	35	29	32	13
 <b>(6h)</b>	59	28	70	5

a) **6** (2 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (0.1 mmol) and Ti(OPr<sup>i</sup>)<sub>4</sub> (4 mmol) in acetonitrile (4 ml) (see footnotes a and b in Table 2-1).

b) **6** (2 mmol), PdCl<sub>2</sub>(AsPh<sub>3</sub>)<sub>2</sub> (0.1 mmol) and Zn(OAc)<sub>2</sub> (5 mmol) in acetonitrile (4 ml) (see footnotes a-c in Table 2-3).

yield would suggest that the desulfonylation is the rate-determining step.

Desulfonylation from the complexes ArSO<sub>2</sub>IrCl<sub>2</sub>(CO)(PPh<sub>3</sub>)<sub>2</sub> in boiling toluene<sup>5a</sup> and ArSO<sub>2</sub>PtCl(PPh<sub>3</sub>)<sub>2</sub> at 200-210 °C<sup>5b</sup> to the corresponding arylmetal species has been reported, which indicates that the



**Scheme 2-1**

ease of the  $\text{SO}_2$  loss is determined by both the nature of the metal and the aryl moiety. In contrast to the present reaction, the desulfonylative carbonylation reactions reported previously<sup>6,12,13</sup> have been carried out at 60-80 °C. Thus, further elucidation is needed to clarify the factors affecting the desulfonylation. On the other hand, Group VIII noble metal-catalyzed desulfonylation of arylsulfonyl chlorides leading to aryl chlorides requires more elevated temperatures.<sup>5c</sup> This may be due to the difficulty of the reductive elimination of aryl chlorides.<sup>17</sup>

The ligand triphenylarsine may enhance the carbon monoxide insertion, as has been demonstrated by Tanaka *et al.*<sup>18</sup> The use of  $\text{PdCl}_2(\text{AsPh}_3)_2$  together with  $\text{Zn}(\text{OAc})_2$  did improve the product yield. However, such an effect could not be observed in reactions with other nucleophiles. Therefore, the role of the ligand in the present

reaction is not definitive.

The observed effects of titanium alkoxides that the *secondary* alkoxides were more effective than the *primary* alkoxides under relatively concentrated conditions may suggest that the less aggregated alkoxides are more reactive toward the arylpalladium intermediate.

The reaction using carboxylate salts could also afford acid anhydrides.<sup>2a, 11</sup> The IR spectrum of the reaction mixture of 1-naphthalenesulfonyl chloride with either NaOAc or Zn(OAc)<sub>2</sub> before work-up showed a small but characteristic peak at 1790 cm<sup>-1</sup>, together with a large peak at 1690 cm<sup>-1</sup> for 1-naphthoic acid. However, we could not further characterize the compound.

Possible precursors leading to diaryl disulfides **8** could be the corresponding thiosulfonates which are the predominant products in the reaction of arylsulfonyl chlorides with iron pentacarbonyl;<sup>19</sup> under the present reaction conditions, *S*-(1-naphthyl) 1-naphthalene-thiosulfonate was cleanly reduced to give di-1-naphthyl disulfide **8a**.

## 2-2-2. Desulfonylative Homo-coupling of Arylsulfonyl Chlorides **6**

*Homo-coupling of 4-chlorobenzenesulfonyl chloride 6h* — The results for the reaction of 4-chlorobenzenesulfonyl chloride **6h** (2 mmol) with various palladium complexes (0.05 mmol) and metal alkoxides (4 mmol) in *m*-xylene are summarized in Table 2-5. 4, 4'-

Dichlorobiphenyl **9h** was obtained in reasonable yield by using  $\text{Ti}(\text{OPr}^i)_4$  in the presence of  $\text{PdCl}_2(\text{PhCN})_2$  or  $\text{Pd}(\text{OAc})_2$  (Runs 47 and 48).  $\text{PdCl}_2(\text{PPh}_3)_2$  and Pd-black were less effective (Runs 49 and 50). While  $\text{Ti}(\text{OBu}^n)_4$  could also be used in place of  $\text{Ti}(\text{OPr}^i)_4$ , the yield of **9h** was considerably decreased (Run 51). Other metal alkoxide,  $\text{Ti}(\text{OBu}^t)_4$ ,  $\text{B}(\text{OPr}^i)_3$ , and  $\text{Al}(\text{OPr}^i)_3$ , were ineffective (Runs 52-54).

*Homo-coupling of various arylsulfonyl chlorides 6* — Other biaryls **9** were also isolated in fair to good yields from the reactions

**Table 2-5.**

Homo-coupling of 4-chlorobenzenesulfonyl chloride **6h**<sup>a</sup>

Run	Pd-catalyst	$\text{M}(\text{OR})_n$	Yield of <b>9h</b> <sup>b</sup>
47	$\text{PdCl}_2(\text{PhCN})_2$	$\text{Ti}(\text{OPr}^i)_4$	76 (74) <sup>c</sup>
48	$\text{Pd}(\text{OAc})_2$	$\text{Ti}(\text{OPr}^i)_4$	71
49	$\text{PdCl}_2(\text{PPh}_3)_2$	$\text{Ti}(\text{OPr}^i)_4$	13
50	Pd-black	$\text{Ti}(\text{OPr}^i)_4$	5
51	$\text{PdCl}_2(\text{PhCN})_2$	$\text{Ti}(\text{OBu}^n)_4$	32
52	$\text{PdCl}_2(\text{PhCN})_2$	$\text{Ti}(\text{OBu}^t)_4$	- <sup>d</sup>
53	$\text{PdCl}_2(\text{PhCN})_2$	$\text{B}(\text{OPr}^i)_3$	- <sup>d</sup>
54	$\text{PdCl}_2(\text{PhCN})_2$	$\text{Al}(\text{OPr}^i)_3$	- <sup>d</sup>

a) The reaction was carried out in *m*-xylene at 140 °C for 2 h under nitrogen.

[**6h**]:[Pd-catalyst]:[ $\text{M}(\text{OR})_n$ ]=2:0.05:4 (in mmol). b) Determined by GLC analysis.

c) Isolated yield. d) Formation of **9h** was not detected.

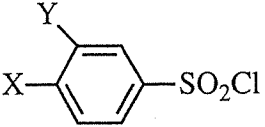
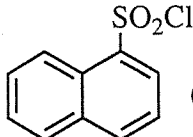


of a number of 3- and/or 4-substituted benzenesulfonyl chlorides **6b**, **g**, **h-m** using  $\text{Ti}(\text{OPr}^t)_4$  and  $\text{PdCl}_2(\text{PhCN})_2$  (Table 2-6). The reaction of 1-naphthalenesulfonyl chloride **6a** gave a mixture of 1, 1'- (**9a**; 26 %) and 1, 2'-binaphthyls (**9a'**; 40 %) along with naphthalene (12 %).<sup>20</sup>

The present reaction as well as the carbonylation using **6** appears to be particularly advantageous, if the corresponding halide can not be obtained by direct halogenation; e.g. 3, 4-dichlorobenzenesulfonyl

**Table 2-6.**

Homo-coupling of various arylsulfonyl chlorides **6**<sup>a</sup>

<b>6</b>	Yield of <b>9</b> / % <sup>b</sup>
	X=F, Y=H ( <b>6i</b> ) 74
	X=Cl, Y=H ( <b>6h</b> ) 74
	X=H, Y=Cl ( <b>6j</b> ) 67
	X=Y=Cl ( <b>6k</b> ) 70
	X=Br, Y=H ( <b>6l</b> ) 56
	X=Y=H ( <b>6b</b> ) 51
	X=Me, Y=H ( <b>6g</b> ) 40
	X=Cl, Y=Me ( <b>6m</b> ) 75
	66 <sup>c</sup>

a) See footnote a in Table 2-5. b) Isolated yield. c) A mixture of 1,1'-binaphthyl (26 %) and the 1, 2'-isomer (40 %) along with naphthalene (12 %).

chloride **6k** and 4-chloro-3-methylbenzenesulfonyl chloride **6m**, which are able to be prepared by chlorosulfonation of 1, 2-dichlorobenzene and 2-chlorotoluene in one step.<sup>21</sup> In addition, the reaction can be completed in a fairly short time compared with that using aryl halides.

*Reaction mechanism* ——— The reaction process of the desulfonylative homo-coupling seems to be similar to that proposed for aryl halides;<sup>14</sup>  $\text{Ti}(\text{OPr}^i)_4$  may also act as a reductant. However, the reaction of 1-bromonaphthalene under the present reaction conditions only gave naphthalene (55 %). Therefore, further elucidation is required to clarify the mechanistic aspect of the reaction.

### 2-3. Summary

The palladium-complex catalyzed carbonylation of arylsulfonyl chlorides **6** in the presence of metal alkoxides  $\text{M}(\text{OR})_n$  ( $\text{M}=\text{B}$ ,  $\text{Al}$ , and  $\text{Ti}$ ) gives the corresponding esters **7** along with diaryl disulfides **8**. With metal carboxylates  $\text{M}(\text{OCOR})_n$  ( $\text{M}=\text{Na}$ ,  $\text{K}$ ,  $\text{Ca}$ ,  $\text{Mg}$ , and  $\text{Zn}$ ), the free acids **4** are also obtained. The desulfonylative homo-coupling reaction of **6** also efficiently proceeds on treatment with titanium(IV) isopropoxide in the presence of catalytic amount of palladium complex under nitrogen to give the corresponding biaryls **9** in good

yields.

## 2-4. Experimental

### 2-4-1. General Procedure

<sup>1</sup>H-NMR spectra were obtained with a JEOL JNM-PS-100 spectrometer in CDCl<sub>3</sub> solutions. *J*-Values are given in Hz. GC-MS spectra were obtained with a JEOL JMS-DX-303 spectrometer and IR spectra with a Hitachi 260-10 spectrometer. GLC analysis was carried out with a Shimadzu GC-8A gas chromatograph.

The sulfonyl chlorides **6e**,<sup>22</sup> **6i**,<sup>21</sup> **6j**,<sup>21</sup> **6k**,<sup>23</sup> **6l**<sup>21</sup> and **6m**,<sup>21</sup> Ti(OBu<sup>s</sup>)<sub>4</sub>,<sup>24</sup> Ti(OBu<sup>t</sup>)<sub>4</sub>,<sup>24</sup> PdCl<sub>2</sub>(PhCN)<sub>2</sub>,<sup>1</sup> PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>,<sup>1</sup> PdCl<sub>2</sub>(AsPh<sub>3</sub>)<sub>2</sub>,<sup>25</sup> PdCl<sub>2</sub>(dppf),<sup>26</sup> and Pd(PPh<sub>3</sub>)<sub>4</sub><sup>1</sup> were prepared by the methods reported previously. 6-Methoxy-2-naphthalenesulfonyl chloride **6f** was prepared by refluxing a mixture of sodium 6-hydroxy-2-naphthalenesulfonate (15 mmol), dimethyl sulfate (30 mmol), and sodium hydroxide (30 mmol) in methanol (100 ml) for 10 h, followed by treatment with thionyl chloride (3 ml) in *N,N*-dimethylformamide (20 ml) at room temperature for 30 min (40% yield);<sup>22</sup> m.p. 95-97 °C (from hexane) (lit.<sup>27</sup> 93 °C). Other starting materials were commercially available.

### 2-4-2. Carbonylation of Arylsulfonyl Chlorides **6** in the Presence of $\text{Ti}(\text{OPr}^i)_4$

To a 40 ml stainless steel autoclave containing acetonitrile (4 ml), **6** (2 mmol),  $\text{Pd}(\text{PPh}_3)_4$  (0.1 mmol), and  $\text{Ti}(\text{OPr}^i)_4$  (4 mmol) were added under nitrogen. Then, carbon monoxide (10 atm at room temperature) was charged and the mixture was magnetically stirred at 160 °C for 4 h. After cooling, the mixture was poured into dilute hydrochloric acid and extracted with ether. The products were isolated by column chromatography on silica gel using benzene-hexane as eluant.

### 2-4-3. Carbonylation of Arylsulfonyl Chlorides **6** in the Presence of $\text{Zn}(\text{OAc})_2$

The reaction was carried out using **6** (2 mmol),  $\text{PdCl}_2(\text{AsPh}_3)_2$  (0.1 mmol),  $\text{Zn}(\text{OAc})_2$  (5 mmol), and acetonitrile (4 ml) at 160 °C for 5 h as above. The resulting mixture was poured into dilute hydrochloric acid and extracted with ether. The acidic products were extracted with aqueous sodium hydroxide. After acidification with hydrochloric acid and re-extraction with ether, the products were methylated with diazomethane. Formation of the methyl esters was confirmed by GC-MS analysis. The esters were also isolated by

column chromatography on silica gel using hexane-benzene as eluant. From the neutral phase diaryl disulfides were obtained.

#### 2-4-4. Homo-coupling of Arylsulfonyl Chlorides **6**

A mixture of **6** (2 mmol), PdCl<sub>2</sub>(PhCN)<sub>2</sub> (0.05 mmol), and Ti(OPr<sup>*i*</sup>)<sub>4</sub> (4 mmol) in *m*-xylene (4 ml) was stirred at 140 °C for 2 h under nitrogen. Formation of biaryls **9** was confirmed by GC-MS and GLC analysis. The products were also isolated by column chromatography on silica gel using benzene-hexane as eluant.

#### 2-4-5. Product Data

Authentic samples for comparison with the product esters were prepared by the reaction of the corresponding commercially available acids or acid chlorides with alcohols except the following compounds.

*6-Methyl-2-naphthoic acid* **4e** had m. p. 228-229 °C (from methanol) (lit.<sup>28</sup> 225-227 °C).

*Methyl 6-methyl-2-naphthoate* had m. p. 118-119.5 °C (from hexane-benzene) (lit.<sup>28</sup> 116-117 °C): MS *m/z* 200 (M<sup>+</sup>); <sup>1</sup>H-NMR δ 2.56 (3H, s), 3.98 (3H, s), 7.22-8.10 (5H, m), 8.56 (1H, s).

*Isopropyl 6-methyl-2-naphthoate* **7e** (R=Pr<sup>*i*</sup>) had m. p. 72-73 °C (from hexane-benzene): MS *m/z* 228 (M<sup>+</sup>); <sup>1</sup>H-NMR δ 1.40 (6H, d, *J*

6.0), 2.56 (3H, s), 5.32 (1H, septet,  $J$  6.0), 7.22-8.10 (5H, m), 8.56 (1H, s).

*6-Methoxy-2-naphthoic acid 4f* had m. p. 205-206 °C (from methanol) (lit.<sup>29</sup> 206 °C).

*Methyl 6-methoxy-2-naphthoate* had m. p. 127-128 °C (from hexane-benzene) (lit.<sup>30</sup> 126 °C): MS  $m/z$  216 ( $M^+$ );  $^1\text{H-NMR}$   $\delta$  3.94 (3H, s), 3.96 (3H, s), 7.12-7.28 (2H, m), 7.64-8.10 (m, 3H), 8.52 (1H, s).

*Isopropyl 6-methyl-2-naphthoate 7f* ( $R=\text{Pr}^i$ ) had m. p. 39.5-41 °C (from hexane-benzene): MS  $m/z$  244 ( $M^+$ );  $^1\text{H-NMR}$   $\delta$  1.40 (6H, d,  $J$  6.0), 3.94 (3H, s), 5.30 (1H, septet,  $J$  6.0), 7.04-7.36 (2H, m), 7.60-8.10 (3H, m), 8.50 (1H, s).

*1, 1'-Binaphthyl 9a* had m. p. 158-159 °C (from ethanol) (lit.<sup>31</sup> 157 °C): MS  $m/z$  254 ( $M^+$ ).

*1, 2'-Binaphthyl 9a'* had m. p. 75-76 °C (from ethanol) (lit.<sup>32</sup> 76 °C): MS  $m/z$  254 ( $M^+$ ).

*Biphenyl 9b* had m. p. 69 °C (from ethanol) (lit.<sup>33</sup> 68-69 °C): MS  $m/z$  154 ( $M^+$ ).

*4, 4'-Dimethyl-1, 1'-biphenyl 9g* had m. p. 122-122.5 °C (from diethylether) (lit.<sup>34</sup> 122-123 °C): MS  $m/z$  182 ( $M^+$ ).

*4, 4'-Dichloro-1, 1'-biphenyl 9h* had m. p. 148-149 °C (from ethanol) (lit.<sup>35</sup> 150-151 °C): MS  $m/z$  222 ( $M^+$ ).

*4, 4'-Difluoro-1, 1'-biphenyl 9i* had m. p. 92-93 °C (from

ethanol) (lit.<sup>36</sup> 89-90 °C): MS  $m/z$  190 ( $M^+$ ).

3, 3'-Dichloro-1, 1'-biphenyl **9j**: MS  $m/z$  222 ( $M^+$ ).

3, 3', 4, 4'-Tetrachloro-1, 1'-biphenyl **9k** had m. p. 181 °C (from ethanol) (lit.<sup>37</sup> 180-180.5 °C): MS  $m/z$  290 ( $M^+$ ).

4, 4'-Dibromo-1, 1'-biphenyl **9l** had m. p. 168-169 °C (from ethanol and benzene) (lit.<sup>38</sup> 167-168 °C): MS  $m/z$  310 ( $M^+$ ), 312.

3, 3',-Dimethyl-4, 4'-dichloro-1, 1'-biphenyl **9m** had m. p. 52-53 °C (from ethanol) (lit.<sup>39</sup> 51-52 °C): MS  $m/z$  250 ( $M^+$ ).

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## Chapter 3

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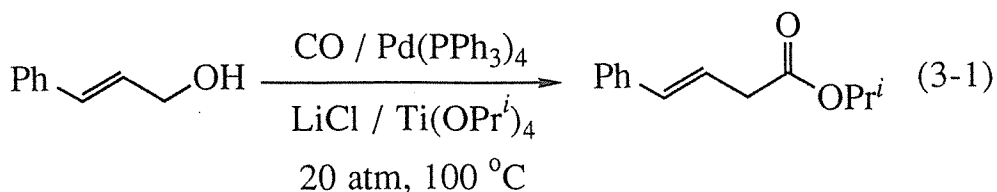
### Palladium-catalyzed Reactions of Allyl Alcohols in the Presence of Titanium(IV) Isopropoxide and Lithium Chloride

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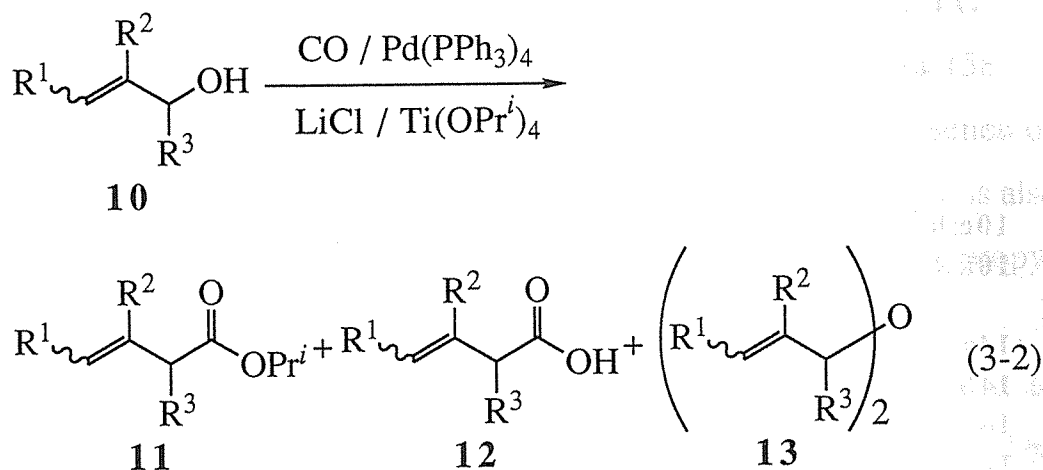
#### 3-1. Introduction

Palladium-catalyzed carbonylation and coupling reaction with metal enolates of allylic compounds are convenient methods for the preparation of synthetically useful  $\beta$ ,  $\gamma$  - and  $\gamma$ ,  $\delta$ - unsaturated carbonyl compounds, respectively.<sup>1</sup> Effective methods for the reactions of allyl carbonates,<sup>2,3</sup> esters,<sup>4,5</sup> halides,<sup>6</sup> amines,<sup>7,8</sup> and ethers<sup>9,10</sup> under reasonably mild conditions have been recently developed. In contrast, and in spite of their ready availability, the reactions with allylic alcohols are less explored.<sup>8,11-13</sup>

Titanium(IV) alkoxides have been successfully used as nucleophiles for the palladium-catalyzed carbonylation of base-sensitive benzyl halides<sup>14</sup> and arylsulfonyl chlorides (see Chapter 2) to give the corresponding esters. We observed that these alkoxides can be similarly applied to the reaction of allyl halides (eq. 3-1). During the



study, it was observed that carbonylation of allyl alcohols **10** with a catalytic amount of tetrakis(triphenylphosphine)palladium proceeds efficiently in the presence of titanium(IV) isopropoxide under medium carbon monoxide pressure to give isopropyl 3-butenoates **11** along with 3-butenoic acid **12** when lithium chloride is added (eq. 3-2).



a: R<sup>1</sup>=Ph, R<sup>2</sup>=R<sup>3</sup>=H

d: R<sup>1</sup>=2-naphthyl, R<sup>2</sup>=R<sup>3</sup>=H

f: R<sup>1</sup>=R<sup>2</sup>=H, R<sup>3</sup>=Pr<sup>n</sup>

h: R<sup>1</sup>=R<sup>3</sup>=H, R<sup>2</sup>=Me

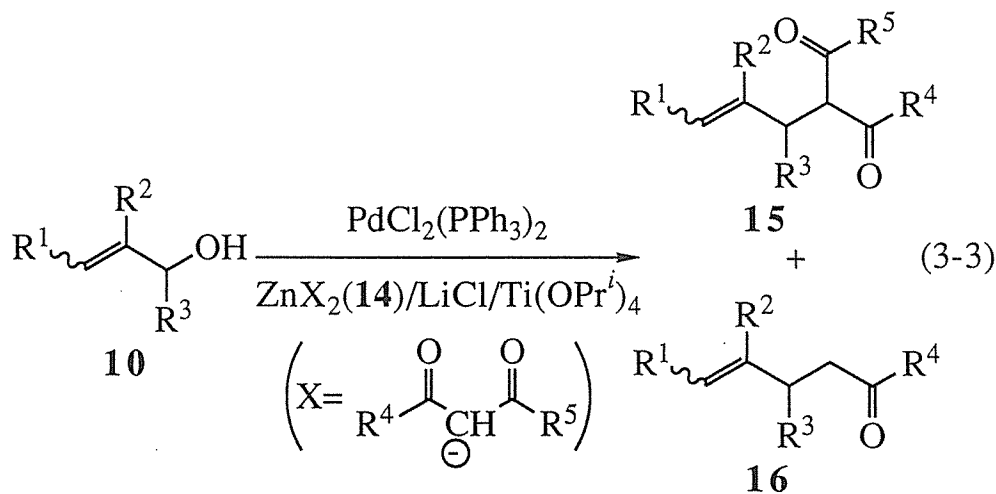
b: R<sup>1</sup>=R<sup>3</sup>=H, R<sup>2</sup>=Ph

e: R<sup>1</sup>=Pr<sup>n</sup>, R<sup>2</sup>=R<sup>3</sup>=H

g: R<sup>1</sup>=Me, R<sup>2</sup>=R<sup>3</sup>=H

It was also expected that allylic alcohols **10** could react with appropriate metal enolates, by employing the same reagents under

inert atmosphere in place of carbon monoxide. Consequently, It has been examined reaction of allylic alcohols **10** with zinc enolates of  $\beta$ -dicarbonyl compounds **14** (eq. 3-3). The results of the reaction are also described herein.



**10c**:  $R^1=R^2=H$ ,  $R^3=Ph$

**10i**:  $R^1, R^2=-(CH_2)_3-$ ,  $R^2=H$

**14a**:  $R^4=R^5=Me$

**14b**:  $R^4=R^5=Ph$

**14c**:  $R^4=Ph$ ,  $R^5=OEt$

**14d**:  $R^4=R^5=OEt$

**15aa**:  $R^1=Ph$ ,  $R^2=R^3=H$ ,  $R^4=R^5=Me$

**15ae**:  $R^1=Pr^n$ ,  $R^2=R^3=H$ ,  $R^4=R^5=Me$

**15ai**:  $R^1, R^2=-(CH_2)_3-$ ,  $R^2=H$ ,  $R^4=R^5=Me$

**15da**:  $R^1=Ph$ ,  $R^2=R^3=H$ ,  $R^4=R^5=OEt$

**16aa**:  $R^1=Ph$ ,  $R^2=R^3=H$ ,  $R^4=Me$

**16ab**:  $R^1=R^3=H$ ,  $R^2=Ph$ ,  $R^4=Me$

**16ad**:  $R^1=2\text{-naphthyl}$ ,  $R^2=R^3=H$ ,  $R^4=Me$

**16ba**:  $R^1=R^4=Ph$ ,  $R^2=R^3=H$

**16bd**:  $R^1=2\text{-naphthyl}$ ,  $R^2=R^3=H$ ,  $R^4=Ph$

**16ca**:  $R^1=Ph$ ,  $R^2=R^3=H$ ,  $R^4=OEt$

**16cd**:  $R^1=2\text{-naphthyl}$ ,  $R^2=R^3=H$ ,  $R^4=OEt$

## 3-2. Results and Discussion

### 3-2-1. Carbonylation of Allylic Alcohols **10** in the Presence of $\text{Ti}(\text{OR})_4$ and $\text{LiCl}$

*Carbonylation of cinnamyl alcohol 10a*——— When the carbonylation of cinnamyl alcohol **10a** (2 mmol) was carried out in tetrahydrofuran (THF) in the presence of  $\text{Pd}(\text{PPh}_3)_4$  (0.05 mmol) and  $\text{Ti}(\text{OPr}^i)_4$  (2.5 mmol) under 25 atm of initial carbon monoxide pressure at 100 °C for 18 h, isopropyl 4-phenyl-3-butenolate **11a** was obtained in 18 % yield together with dicinnamyl ether **13a** (58 %) (Run 1 in Table 3-1). The reaction did not proceed in the absence of the palladium complex, indicating that the dimerized ether **13a** is also produced under the influence of the catalyst as well as the isopropyl ester **11a**.

Addition of lithium halide ( $\text{LiX}$ ;  $\text{X}=\text{Cl}$ ,  $\text{Br}$ ,  $\text{I}$ ) was found to increase the yield of **11a** and inhibited the formation of **13a**. The efficiency order for the halide was  $\text{Cl} > \text{Br} > \text{I}$  (Runs 4, 5 and 6). Thus, **11a** was obtained in 85 % yield when 2 mmol of lithium chloride was used (Run 4). In the presence of lithium chloride, decreasing the amount of  $\text{Ti}(\text{OPr}^i)_4$  reduced the yield of **11a**, forming 4-phenyl-3-butenic acid **12a** in considerable amounts (Runs 7 and 8). Without both  $\text{Ti}(\text{OPr}^i)_4$  and lithium chloride, the product yield was

**Table 3-1.**Carbonylation of cinnamyl alcohol **10a**<sup>a</sup>

Run	LiX (mmol)	Yield / % <sup>b</sup>			Recovery of <b>10a</b> / % <sup>b</sup>
		<b>11a</b>	<b>12a</b>	<b>13a</b>	
1	- <sup>c</sup>	18		58	4
2	LiCl (0.2)	58			
3	LiCl (0.5)	70			
4	LiCl (2.0)	85			
5	LiBr (2.0)	62	11		4
6	LiI (2.0)	24			7
7	LiCl (2.0) <sup>d</sup>	37	27		
8	LiCl (2.0) <sup>e</sup>		55		
9	- <sup>c,e</sup>	4			89
10	LiCl (2.0) <sup>f</sup>	82			
11	LiCl (2.0) <sup>g</sup>	29	6		28
12	LiCl (2.0) <sup>h</sup>	52			

a) The reaction was carried out in THF under carbon monoxide (25 atm at room temperature) at 100 °C for 18 h. [**10a**]:[Pd(PPh<sub>3</sub>)<sub>4</sub>]:[Ti(OPr<sup>*i*</sup>)<sub>4</sub>]=2:0.05:2.5 (in mmol). **10a** used was a mixture of the *E*- (98 %) and the *Z*-isomer (2 %). b) Determined by GLC analysis. The acid was analyzed after methylation with diazomethane. c) Without lithium halide. d) [Ti(OPr<sup>*i*</sup>)<sub>4</sub>]=1. e) Without Ti(OPr<sup>*i*</sup>)<sub>4</sub>. f) PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (0.05 mmol) was used in place of Pd(PPh<sub>3</sub>)<sub>4</sub>. g) 75 °C. h) 15 atm.

very low (Run 9).

While PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> could also be used in place of Pd(PPh<sub>3</sub>)<sub>4</sub> (Run 10), other palladium species PdCl<sub>2</sub>(PhCN)<sub>2</sub>, Pd(OAc)<sub>2</sub>, and

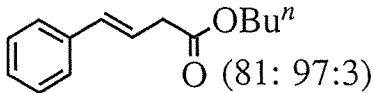
$\text{PdCl}_2$  were much less effective. The reaction with  $\text{Ti}(\text{OBu}^n)_4$  in place of  $\text{Ti}(\text{OPr}^i)_4$  gave *n*-buthyl 4-phenyl-3-butenolate in 81 % yield (Run 13 in Table 3-2).

The allyl alcohol employed for the runs in Table 3-1 was a mixture of the *E*- and the *Z*-isomers in a ratio of 98:2. The product *E/Z* ratio in Run 4 was determined to be 97:3. The reaction of **10a** consisting predominantly of the *Z*-isomer (*E:Z*=3:97) under the same conditions used for Run 4 gave **11a** in an *E/Z* ratio of 97:3 (Run 14 in Table 2). These results indicate that the *E-Z* geometry of **10** is not retained in the product, giving the more stable isomer preferentially.

*Carbonylation of various allyl alcohols 10* — Carbonylation of a number of 1-, 2- or 3-substituted allyl alcohols **10b**, **d-h** was also performed using  $\text{Pd}(\text{PPh}_3)_4$  and  $\text{Ti}(\text{OPr}^i)_4$  in the presence of lithium chloride (Table 3-2). The corresponding isopropyl esters **11** were obtained in fair to good yields. In each case, formation of  $\alpha$ ,  $\beta$ -unsaturated product was not observed. The reaction of hex-1-en-3-ol **10f** (Run 18) gave essentially the same result as that with hex-2-en-1-ol **10e** (Run 17), suggesting that the reaction process involves a  $\pi$ -allylpalladium intermediate.

*Reaction Scheme* — A probable mechanism for the formation of isopropyl 3-propenoate **11** is illustrated in scheme 3-1, in which

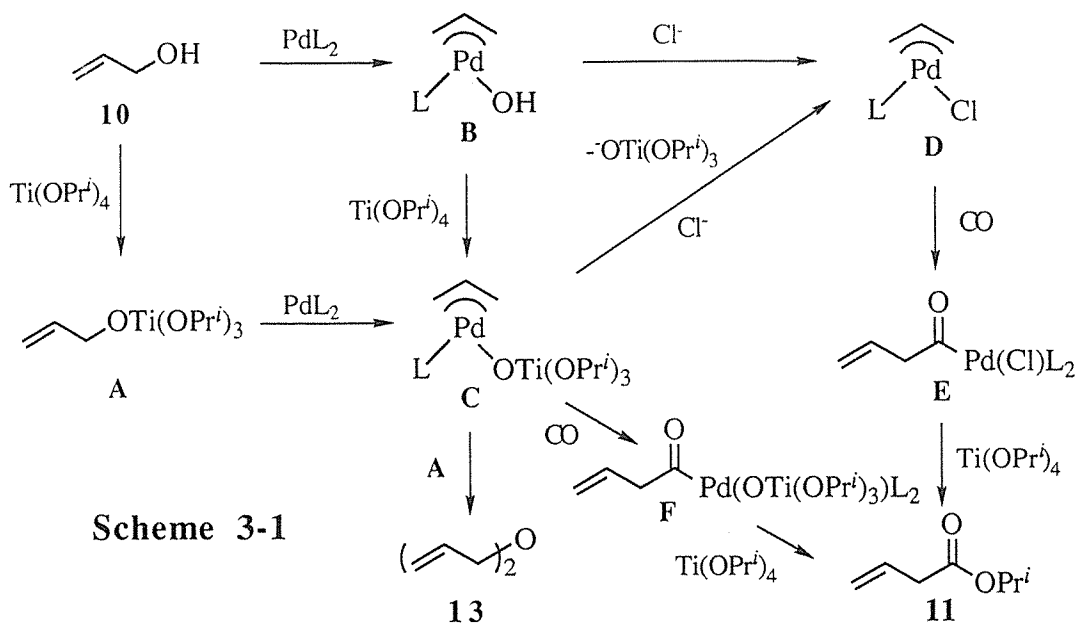
**Table 3-2.**Carbonylation of various allyl alcohols **10**<sup>a</sup>

Run	<b>10</b> ( <i>E:Z</i> ) <sup>b</sup>	Conditions <sup>c</sup>	Product (%yield; <sup>d</sup> <i>E:Z</i> ) <sup>b</sup>
4	<b>10a</b> (98:2)	A	<b>11a</b> (85;.97:3)
13	<b>10a</b> (98:2)	A <sup>e</sup>	 (81: 97:3)
14	<b>10a</b> (3:97)	A	<b>11a</b> (77; 97:3)
15	<b>10b</b>	A	<b>11b</b> (72)
16	<b>10d</b> (100:0)	A	<b>11d</b> (52; 100:0)
17	<b>10e</b> (97:3)	B	<b>11e</b> (43; 88:12)
18	<b>10f</b>	B	<b>11e</b> (42; 80:20)
19	<b>10g</b>	B <sup>f</sup>	<b>11g</b> (84; 73:27)
20	<b>10h</b>	B <sup>f</sup>	<b>11h</b> (68)

a) The reaction was carried out in THF under carbon monoxide (25 atm at room temperature) at 100 °C for 18 h. b) Determined by <sup>1</sup>H-NMR analysis. c) A: [**10**]:[Pd(PPh<sub>3</sub>)<sub>4</sub>]:[LiCl]:[Ti(OPr<sup>*i*</sup>)<sub>4</sub>]=2:0.05:2:2.5 (in mmol); B: [**10**]:[Pd(PPh<sub>3</sub>)<sub>4</sub>]:[LiCl]:[Ti(OPr<sup>*i*</sup>)<sub>4</sub>]=5:0.125:5:6.25 (in mmol). d) Determined by GLC analysis. e) Ti(OBu<sup>*n*</sup>)<sub>4</sub> (2.5 mmol) was used in place of Ti(OPr<sup>*i*</sup>)<sub>4</sub>. f) [Ti(OPr<sup>*i*</sup>)<sub>4</sub>]=7.5.

the substituent on allyl alcohol **10** is omitted. It is well known that titanium(IV) alkoxides readily undergo alcoholysis to give partly or fully substituted alkoxides.<sup>15</sup> Therefore, under the present reaction conditions, **10** may react with Ti(OPr<sup>*i*</sup>)<sub>4</sub> to afford allyl titanate A. Then A reacts with palladium(0) species to give a π-allylpalladium





complex C, as is the usual reaction of allylic compounds.<sup>1</sup> Subsequently, reaction with carbon monoxide and another  $\text{Ti}(\text{OPr}^i)_4$  affords isopropyl 3-butenolate **11**.

Diallyl ether **13** may be formed by the reaction of C with another titanate A. It was confirmed that treatment of dicinnamyl ether **13a** under the same conditions used for allyl alcohols did not give the carbonylated products, even in the presence of lithium chloride, suggesting that the carbonylation does not proceed via the ether **13**.

A possible role of the added lithium halide is that it would enhance the carbonylation step by ligand exchange with the halide ion forming a complex **D**, as has been proposed previously,<sup>4a</sup> so that the dimerization reaction is suppressed.

In the palladium-catalyzed carbonylation of aryl halides<sup>14</sup> and arylsulfonyl chlorides (see Chapter 2) using titanium(IV) alkoxides as nucleophiles, the alkoxides are considered to react with intermediary arylpalladium halides, accompanied by formation of halotitanates and successive reductive elimination to give aromatic esters. A similar reaction sequence might be involved in the present reaction system. However, addition of a catalytic amount of lithium chloride considerably increased the ester yield (Runs 2 and 3 in Table 3-1). Therefore, another process likely participates in the reaction:  $\text{Ti}(\text{O}^-)(\text{OPr}^i)_3$  generated *in situ* would act as an isopropoxide donor.

Isomerization of *E-Z* geometries during the palladium-catalyzed carbonylation reactions of allyl acetates<sup>4b</sup> and halides has also been reported,<sup>4b,6a</sup> as in Runs 14, 17 and 19. A detailed mechanism for the reaction of the cinnamyl compounds has been proposed, in which the isomerization occurs in cinnamoylpalladium intermediates involving carbon-carbon double bond isomerization, rather than in  $\pi$ -allylpalladium species.<sup>4b</sup> A similar process might be involved in the present reaction. However, the result of Run 17 suggests the formation of the  $\pi$ -allylpalladium complex. Therefore, it may also occur by *syn-anti* isomerization of the complex.<sup>4b</sup>

The result of a control experiment, Run 8, giving 4-phenyl-3-butenic acid **12a** in a considerable yield, suggests that a part of the allyl alcohol **10** itself may also be carbonylated before reacting with

Ti(OPr<sup>i</sup>)<sub>4</sub>, followed by esterification with the titanate to give the product ester **11**.<sup>15</sup>

### 3-2-2. Reaction of Allylic Alcohols **10** with Zinc Enolates of $\beta$ -Dicarbonyl Compounds **14** in the Presence of Ti(OR)<sub>4</sub> and LiCl

*Reaction of allylic alcohols **10a-f, i** with Zn(acac)<sub>2</sub> **14a***—When the reaction of cinnamyl alcohol **10a** (2 mmol) with Zn(acac)<sub>2</sub>•H<sub>2</sub>O **14a** (4 mmol) was carried out in the presence of PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (0.05 mmol) and lithium chloride (1 mmol) in 2-methoxyethyl ether at 120 °C for 18 h under nitrogen, a mixture of 3-(3-phenylallyl)pentane-2,4-dione **15aa** (40 %) and 6-phenylhex-5-en-2-one **16aa** (51 %) was produced (Run 21 in Table 3-3). Addition of titanium(IV) isopropoxide to the reaction was found to favor the production of **16aa**. Thus, the monoketone **16aa** was exclusively formed in a yield of 85 % when 2 mmol of Ti(OPr<sup>i</sup>)<sub>4</sub> was added (Run 23). Reaction temperature also affected the product composition; the reaction at 100 °C using both lithium chloride and Ti(OPr<sup>i</sup>)<sub>4</sub> gave **15aa** (19 %) and **16aa** (61 %) (Run 26) and that at 85 °C in 1,2-dimethoxyethane (DME) without Ti(OPr<sup>i</sup>)<sub>4</sub> selectively afforded **15aa** (85 %) along with **16aa** (7 %) (Run 27). It was confirmed that (a) the reaction did not proceed in the absence of the catalyst or without both lithium chloride and Ti(OPr<sup>i</sup>)<sub>4</sub>, while without lithium chloride, **16aa** was

**Table 3-3.**Reaction of various allylic alcohols **10** with Zn(acac)<sub>2</sub> **14a**<sup>a</sup>

Run	<b>10</b>	Product(s) (%yield) <sup>b</sup>
21 <sup>c</sup>	<b>10a</b>	<b>15aa</b> (40), <b>16aa</b> (51)
22 <sup>d</sup>	<b>10a</b>	<b>15aa</b> (10), <b>16aa</b> (72)
23	<b>10a</b>	<b>16aa</b> [85 (72) <sup>e</sup> ]
24 <sup>f</sup>	<b>10a</b>	<b>16aa</b> (80)
25 <sup>g</sup>	<b>10a</b>	<b>16aa</b> (55)
26 <sup>h</sup>	<b>10a</b>	<b>15aa</b> (19), <b>16aa</b> (61)
27 <sup>i</sup>	<b>10a</b>	<b>15aa</b> [85 (78) <sup>e</sup> ], <b>16aa</b> (7)
28 <sup>j</sup>	<b>10a</b>	<b>16aa</b> (82)
29 <sup>k</sup>	<b>10a</b>	<b>16aa</b> (84)
30	<b>10b</b>	<b>16ab</b> (48)
31 <sup>l</sup>	<b>10b</b>	<b>16ab</b> [79 (60) <sup>e</sup> ]
32	<b>10c</b>	<b>16aa</b> (85)
33	<b>10d</b>	<b>16ad</b> [85 (74) <sup>e</sup> ]
34 <sup>i</sup>	<b>10e</b>	<b>15ae</b> [55 (30) <sup>e</sup> ]
35 <sup>i</sup>	<b>10f</b>	<b>15ae</b> (60)
36 <sup>i</sup>	<b>10g</b>	<b>15ai</b> (36)

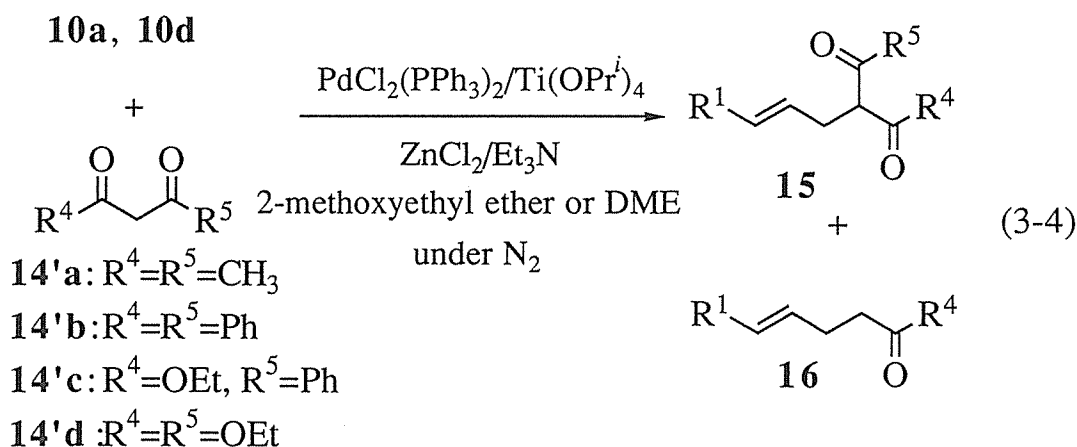
a) The reaction was carried out in 2-methoxymethyl ether under nitrogen at 120 °C for 18 h. [**10**]:[**14a**]:[PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>]:[Ti(OPr<sup>*i*</sup>)<sub>4</sub>]:[LiCl]=2:4:0.05:2:1 (in mmol) b) Determined by GLC analysis. Each product had *E*-configuration. c) Without Ti(OPr<sup>*i*</sup>)<sub>4</sub>. d) [Ti(OPr<sup>*i*</sup>)<sub>4</sub>]=1. e) Isolated yield. f) [LiCl]=2. g) Without LiCl. h) Reaction at 100 °C. i) Reaction in 1,2-dimethoxyethane at 85 °C without Ti(OPr<sup>*i*</sup>)<sub>4</sub>. j) Ti(OEt)<sub>4</sub> (2 mmol) was used in place of Ti(OPr<sup>*i*</sup>)<sub>4</sub>. k) Ti(OBu<sup>*n*</sup>)<sub>4</sub> (2 mmol) was used in place of Ti(OPr<sup>*i*</sup>)<sub>4</sub>. l) Reaction in 1,4-dioxane at 100 °C for 40 h.

selectively formed, although the yield was considerably lower; (b) the diketone **15aa** was transformed into **16aa** under the reaction conditions. These results indicate that both lithium chloride and  $\text{Ti}(\text{OPr}^i)_4$  are capable of inducing the reaction of **10a** with **14a** under the influence of the palladium catalyst to give **15aa** which is, then, transformed into **16aa**, this process being favored at a higher temperature in the presence of  $\text{Ti}(\text{OPr}^i)_4$ . Selective formation of **16aa** could be observed by use of  $\text{Ti}(\text{OEt})_4$  or  $\text{Ti}(\text{OBu}^n)_4$  in place of  $\text{Ti}(\text{OPr}^i)_4$  (Runs 28 and 29). Tetrakis(triphenylphosphine)-palladium(0)  $\text{Pd}(\text{PPh}_3)_4$  showed also good catalytic activity, but with  $\text{PdCl}_2$ ,  $\text{Pd}(\text{OAc})_2$  or  $\text{PdCl}_2(\text{PhCN})_2$ , no coupling reaction occurred.

Reaction of aryl-substituted allylic alcohols **10b-d** with **14a** in the presence of  $\text{PdCl}_2(\text{PPh}_3)_2$ ,  $\text{LiCl}$  and  $\text{Ti}(\text{OPr}^i)_4$  at 120 °C selectively afforded the corresponding acetylated products **16ab**, **16aa** and **16ad** (Runs 30-33). Under the same conditions, reaction of alkyl-substituted substrates **10e**, **10f** and **10i**, however, gave intractable mixture of products, while diacetyl compounds **15ae** and **15ai** were obtained from reaction of **10e**, **10f** and **10i** in DME without  $\text{Ti}(\text{OPr}^i)_4$  at 85 °C in modest yield (Runs 34-36). Formation of **16aa** and **15ae** from **10c** and **10f** may suggest that participation of  $\pi$ -allylpalladium intermediates in the reaction process (Runs 32 and 35).<sup>1</sup> The *E/Z* ratios of the allylic alcohols **10a**, **10d** and **10e** employed were 98:2, 100:0, and 97:3, respectively. The products

**15aa**, **16aa**, **16ad** and **15ae** were found to have *E*-configurations, no evidence for formation of the corresponding *Z*-isomers was obtained.

*Reaction of 10a and 10d with β-dicarbonyl compounds 14'a-d* — The methyl ketone **16aa** could be also produced by reaction of **10a** with **14a**, generated *in situ* from acetylacetone **14'a** and zinc chloride in the presence of triethyl amine, with PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> and Ti(OPr<sup>*i*</sup>)<sub>4</sub> in 2-methoxyethyl ether at 120 °C (eq. 3-4 and Run 37 in Table 3-4). In this case, addition of lithium chloride showed no influence on the reaction. The reaction did not occur in the absence of zinc chloride.



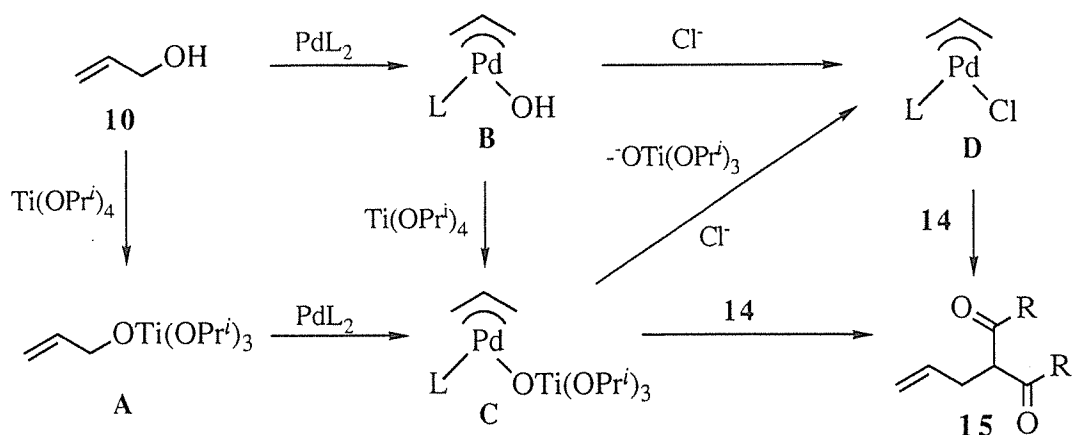
Reactions of **10a** with dibenzoylmethane **14'b** and ethyl benzoylacetate **14'c** gave 1, 5-diphenylpent-4-en-1-one **16ba** (72 %)

**Table 3-4.**Reaction of **10a, d** with **14'a-d**<sup>a</sup>

Run	<b>10</b>	<b>14'</b>	Product(s) (%yield) <sup>b</sup>
37	<b>10a</b>	<b>14'a</b>	<b>16aa</b> (70) <sup>c</sup>
38 <sup>d</sup>	<b>10a</b>	<b>14'a</b>	<b>15aa</b> (70), <sup>c</sup> <b>16aa</b> (5) <sup>c</sup>
39	<b>10a</b>	<b>14'b</b>	<b>16ba</b> (72)
40 <sup>e</sup>	<b>10a</b>	<b>14'c</b>	<b>16ca</b> (78)
41 <sup>e</sup>	<b>10a</b>	<b>14'd</b>	<b>15da</b> (70), <sup>c</sup> <b>16ca</b> (4) <sup>c</sup>
42	<b>10d</b>	<b>14'b</b>	<b>16bd</b> (92)
43 <sup>e</sup>	<b>10d</b>	<b>14'c</b>	<b>16cd</b> (84)

a) The reaction was carried out in 2-methoxyethyl ether under nitrogen at 120 °C for 18 h. [**10**]:[**14'a**]:[PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>]:[ZnCl<sub>2</sub>]:[Ti(OPr<sup>i</sup>)<sub>4</sub>]:[NEt<sub>3</sub>]=2:4:0.05:2:2:5 (in mmol) b) Isolated yield. Each product had *E*-configuration. c) Determined by GLC analysis. d) Reaction in 1,2-dimethoxyethane at 85 °C without Ti(OPr<sup>i</sup>)<sub>4</sub>. e) Ti(OEt)<sub>4</sub> (2 mmol) was used in place of Ti(OPr<sup>i</sup>)<sub>4</sub>.

and ethyl 5-phenylpent-4-enoate **16ca** (78 %), respectively (Runs 39 and 40), suggesting that debenzoylation from primary coupling products occurred smoothly, as did deacetylation from **15aa** (in the case of **14'c**, Ti(OEt)<sub>4</sub> was employed). Similarly, compounds **16bd** and **16cd** were isolated from reactions of **10d** with **14'b** and **14'c** in good yield (Runs 42 and 43). In these reactions, formation of isopropyl (or ethyl) benzoate in 40-55 % yield was observed. Ethyl acetoacetate could not be used in place of **14'c**, a complex mixture of products being formed. Reaction of **10a** with diethyl malonate **14'd**



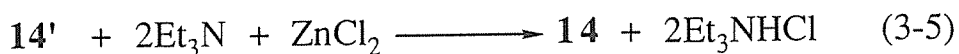
Scheme 3-2

gave diethyl 2-(3-phenylallyl)malonate **15da** (70 %) as the predominant product along with **16ca** (4 %) (Run 41). This indicates that the ethoxycarbonyl group in **15da** is relatively stable under the reaction conditions.

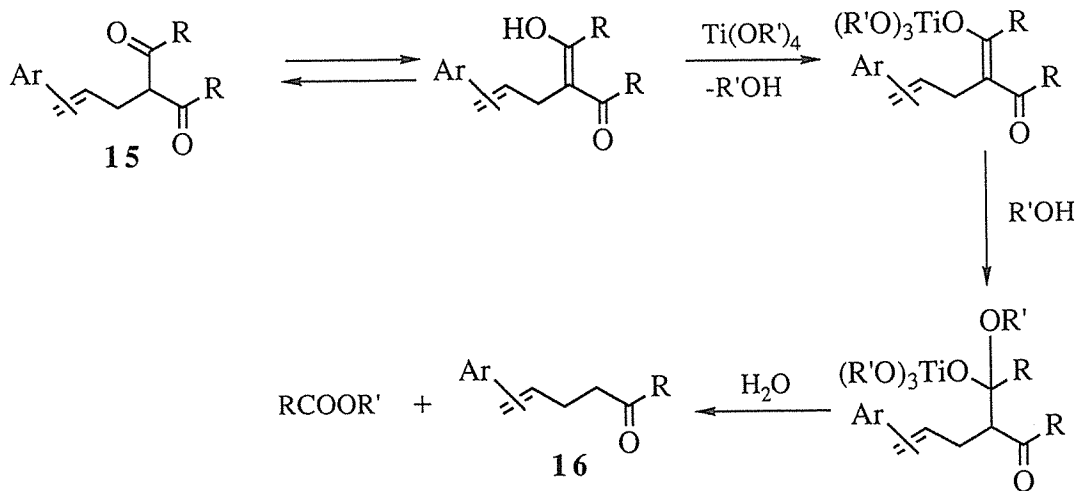
*Reaction scheme* —A probable mechanism for the reaction of **10** with **14** is illustrated in Scheme 3-2, which is similar to that proposed for the carbonylation of **10**. In the scheme, the substituent on allyl alcohol **10** is omitted. Reaction of **10** with palladium(0) species generated *in situ* gives an allyl complex **B**. In the presence of  $\text{Ti}(\text{OPr}^i)_4$ , **10** may react at first with the alkoxide to afford an allyl titanate **A**<sup>15</sup> followed by reaction with the palladium(0) species, giving a complex **C**. A possible role of added lithium chloride is that it would enhance the reaction with **14** as is the carbonylation of **10** (*vide ante*). In the case of the reaction with zinc enolates **14** generated



from **14'** and zinc chloride in the presence of triethyl amine, triethylammonium chloride formed by the eq.3-5 may act as a chloride source. The intermediate **C** could also directly react with **14**;



reaction of **10a** with the acetylacetonate proceeded without lithium chloride, although the yield of **16aa** was lower than that in the presence of the chloride. It should be noted that reaction of cinnamyl alcohol **10a** consisting predominantly of the *Z*-isomer (*E*:*Z*=3:97) with  $\text{Zn}(\text{acac})_2$  gave the ketone **16aa** having exclusively *E*-configuration in 80 % yield. This fact suggests that *syn-anti* isomer-



Scheme 3-3

ization occurs in the  $\pi$ -allyl intermediates to give the more stable isomer preferentially.

A possible explanation for deacylation reaction of primary dicarbonyl products **15** promoted by titanium alkoxides is illustrated in Scheme 3-3. It was found that **15** was transformed into **16** upon treatment with  $\text{Ti}(\text{OPr}^i)_4$  and the reaction was accelerated by a small amount of water. Thus, **16aa** was quantitatively formed from **15aa** in the presence of 1 equiv. of each of  $\text{Ti}(\text{OPr}^i)_4$  and  $\text{H}_2\text{O}$  at 120 °C. It should be noted that, in the present reaction,  $\text{Zn}(\text{acac})_2$  **14a** employed has crystallization water and hydroxide ion is formed from **10** during the reaction. It is known that titanium alkoxide reacts with water to give  $[\text{Ti}(\text{OR})_3]_2\text{O}$  and higher polymeric alkoxides with liberating alcohol molecules.<sup>15</sup> Therefore, the polymeric alkoxides in place of the monomer may participate in the deacylation reaction.

### 3-3. Summary

The carbonylation of allylic alcohols with a catalytic amount of  $\text{Pd}(\text{PPh}_3)_4$  proceeds smoothly and efficiently in the presence of lithium chloride and titanium(IV) isopropoxide to give the corresponding isopropyl 3-butenate. The palladium-catalyzed reaction of allylic alcohols with zinc enolates also proceeds by employing the similar reaction conditions under nitrogen to give the

acylated products.

### 3-4. Experimental

#### 3-4-1. General Procedure

<sup>1</sup>H-NMR spectra were obtained with a JEOL JNM-GSX-400 spectrometer in CDCl<sub>3</sub> solutions. *J*-Values are given in Hz. GC-MS data were obtained with a JEOL JMS-DX-303 spectrometer. GLC analysis was carried out with a Shimadzu GC-8A gas chromatograph.

The alcohols **10a** [(*E*):(*Z*)=3:97],<sup>16</sup> **10b**,<sup>17</sup> **10c**,<sup>18</sup> and **10d**<sup>19</sup> were prepared by the methods reported previously. Other starting materials were commercially available. The following experimental details may be regarded as typical in methodology and scale.

#### 3-4-2. Carbonylation of Allylic Alcohols **10**

The alcohol **10** (2 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (0.05 mmol) and Ti(OPr<sup>*i*</sup>)<sub>4</sub> (2.5 mmol) were added to a 40 ml stainless steel autoclave containing tetrahydrofuran (4 ml). Then, carbon monoxide (25 atm at room temperature) was charged and the mixture was magnetically stirred at 100 °C for 18 h. After cooling, the mixture was poured into dilute hydrochloric acid and extracted with ether. GC-MS analyses

confirmed formation of the corresponding ester **11** which was also isolated by column chromatography on silica gel using hexane-ethyl acetate as eluant.

### 3-4-3. Reaction of Allylic Alcohols **10** with $\text{Zn}(\text{acac})_2$ **14a**

A mixture of substrate **10** (2 mmol),  $\text{Zn}(\text{acac})_2 \cdot \text{H}_2\text{O}$  **14a** (4 mmol),  $\text{PdCl}_2(\text{PPh}_3)_2$  (0.05 mmol),  $\text{Ti}(\text{OPr}^i)_4$  (2 mmol) and  $\text{LiCl}$  (1 mmol) in 2-methoxymethyl ether (10 ml) was stirred under nitrogen at 120 °C for 18 h. Analysis by GLC and GLC-MS confirmed formation of **15** and/or **16**. The products were also isolated by column chromatography on silica gel with benzene-hexane (1:1) as eluant.

### 3-4-4. Reaction of Allylic Alcohols **10** with $\beta$ -Dicarbonyl Compounds **14'**

A mixture of substrate **10** (2 mmol), **14'** (4 mmol),  $\text{PdCl}_2(\text{PPh}_3)_2$  (0.05 mmol),  $\text{Ti}(\text{OPr}^i)_4$  (2 mmol),  $\text{ZnCl}_2$  (2 mmol), and triethylamine (5 mmol) in 2-methoxymethyl ether (10 ml) was stirred under nitrogen at 120 °C for 18 h. **15** and/or **16** were isolated by column chromatography on silica gel with benzene-hexane (1:1) as eluant.

### 3-4-5. Product data

*Isopropyl 4-phenylbut-3-enoate 11a* (*E/Z*=97:3) was an oil: MS *m/z* 204 ( $M^+$ );  $^1\text{H-NMR}$   $\delta$  1.25 (6H, d, *J* 6.3), 3.21 (2H, dd, *J* 7.3, 1.5; *E*), 3.30 (2H, dd, *J* 7.3, 1.9; *Z*), 5.05 (1H, septet, *J* 6.3), 5.90 (1H, dt, *J* 11.7, 7.3; *Z*), 6.30 (1H, dt, *J* 16.1, 7.3; *E*), 6.48 (1H, d, *J* 16.1; *E*), 6.62 (1H, d, *J* 11.7; *Z*), 7.20-7.38 (5H, m).

*n-Buthyl 4-phenylbut-3-enoate (E/Z=97:3)* was an oil: MS *m/z* 218 ( $M^+$ );  $^1\text{H-NMR}$   $\delta$  0.92 (3H, t, *J* 7.3), 1.34-1.43 (2H, m), 1.58-1.67 (2H, m), 3.24 (2H, dd, *J* 7.3, 1.5; *E*), 3.33 (2H, dd, *J* 7.3, 1.9; *Z*), 4.12 (2H, t, *J* 6.8), 5.90 (1H, dt, *J* 11.2, 7.3; *Z*), 6.30 (1H, dt, *J* 15.6, 7.3; *E*), 6.50 (1H, d, *J* 15.6; *E*), 6.63 (1H, d, *J* 11.2; *Z*), 7.20-7.40 (5H, m).

*Isopropyl 2-phenylbut-3-enoate 11b* was an oil: MS *m/z* 204 ( $M^+$ );  $^1\text{H-NMR}$   $\delta$  1.40 (6H, d, *J* 6.3), 3.48 (2H, d, *J* 1.0), 4.96 (1H, septet, *J* 6.3), 5.22 (1H, d, *J* 1.0), 5.51 (1H, d, *J* 1.0), 7.25-7.45 (5H, m).

*Isopropyl 4-(2-naphthyl)but-3-enoate 11d* was an oil: MS *m/z* 254 ( $M^+$ );  $^1\text{H-NMR}$   $\delta$  1.27 (6H, d, *J* 6.3), 3.26 (2H, d, *J* 8.8), 5.01-5.11 (1H, m), 6.39-6.46 (1H, m), 6.64 (1H, d, *J* 15.6), 7.58-7.79 (5H, m).

*Isopropyl hept-3-enoate 11e* (*E/Z*=88:12) was an oil: MS *m/z* 170 ( $M^+$ );  $^1\text{H-NMR}$   $\delta$  0.82 (3H, t, *J* 7.3; *E*), 0.83 (3H, t, *J* 7.3; *Z*), 1.60 (6H, d, *J* 6.3; *E*), 1.65 (6H, d, *J* 6.3; *Z*), 1.32 (2H, septet, *J* 7.3),

1.90-2.00 (2H, m), 2.91 (2H, d,  $J$  4.9; *E*), 2.97 (2H, d,  $J$  4.9; *Z*), 4.93 (1H, septet,  $J$  6.3; *E*), 4.94 (1H, septet,  $J$  6.3; *Z*), 5.41-5.52 (2H, m).

*Isopropyl pent-3-enoate* **11f** (*E/Z*=73:27) was an oil: MS  $m/z$  142 ( $M^+$ );  $^1\text{H-NMR}$   $\delta$  1.23 (6H, d,  $J$  6.3; *E*), 1.25 (6H, d,  $J$  6.3; *Z*), 1.69 (3H, d,  $J$  6.3; *Z*), 1.70 (3H, d,  $J$  6.3; *E*), 2.97 (2H, d,  $J$  6.3; *E*), 2.98 (2H, d,  $J$  6.3; *Z*), 5.10 (1H, septet,  $J$  6.3), 5.50-5.70 (2H, m).

*Isopropyl 3-methylprop-3-enoate* **11g** was an oil: MS  $m/z$  142 ( $M^+$ );  $^1\text{H-NMR}$   $\delta$  1.25 (6H, d,  $J$  6.3), 1.81 (3H, s), 2.99 (2H, s), 4.84 (1H, s), 4.89 (1H, s), 5.03 (1H, septet,  $J$  6.3)

*3-(3-Phenylallyl)pentane-2,4-dione* **15aa** was an oil:<sup>20</sup> MS  $m/z$  216 ( $M^+$ );  $^1\text{H-NMR}$   $\delta$  2.15 (2.4H, s; *for enol*), 2.21 (3.6H, s; *for keto*), 2.75 (1.2H, dt,  $J$  1.5, 7.3; *for keto*), 3.16 (0.8H, dd,  $J$  1.5, 5.4; *for enol*), 3.80 (0.6H, t,  $J$  7.3; *for keto*), 6.07 (0.6H, dt,  $J$  15.6, 7.3; *for keto*), 6.21 (0.4H, dt,  $J$  16.1, 5.4; *for enol*), 6.34 (0.4H, dt,  $J$  1.5, 16.1; *for enol*), 6.45 (0.6H, dt,  $J$  1.5, 15.6; *for keto*), 7.21-7.36 (5H, m), 16.77 (0.4H, s; *for enol*).

*3-Hex-2-enylpentane-2, 4-dione* **15ae** was an oil;<sup>12b</sup> MS  $m/z$  182 ( $M^+$ );  $^1\text{H-NMR}$   $\delta$  0.77-0.84 (3H, m), 1.21-1.32 (2H, m), 1.84-1.94 (2H, m), 2.04 (2.4H, s; *for enol*), 2.17 (3.6H, s; *for keto*), 2.44-2.48 (1.2 H, m; *for keto*), 2.84-2.85 (0.8H, m; *for enol*), 3.60 (0.6H, t,  $J$  7.3; *for keto*), 5.17-5.46 (2H, m).

*3-Cyclohex-2-enylpentane* **15ai** was an oil;<sup>21</sup> MS  $m/z$  180 ( $M^+$ );  $^1\text{H-NMR}$   $\delta$  1.16-1.26 (2H, m), 1.52-1.76 (2H, m), 1.97-2.04 (2H, m),

2.18 (3H, s), 2.19 (3H, s), 2.99-3.06 (1H, m), 3.61 (1H, d,  $J$  10.3), 5.31 (1H, dd,  $J$  2.2, 5.0), 5.74-5.79 (1H, m).

*Diethyl 2-(3-phenylallyl)malonate 15da* was an oil;<sup>22</sup> MS  $m/z$  276 ( $M^+$ );  $^1\text{H-NMR}$   $\delta$  1.18 (3H, t,  $J$  7.3), 1.18 (3H, t,  $J$  7.3), 2.73 (2H, dd,  $J$  6.8, 7.3), 3.42 (1H, t,  $J$  7.3), 4.13 (2H, q,  $J$  7.3), 4.13 (2H, q,  $J$  7.3), 6.08 (1H, dt,  $J$  15.8, 6.8), 6.40 (1H, d,  $J$  15.8), 7.18-7.26 (5H, m).

*6-Phenylhex-5-en-2-one 16aa* was an oil;<sup>23</sup> MS  $m/z$  174 ( $M^+$ );  $^1\text{H-NMR}$   $\delta$  2.17 (3H, s), 2.48 (2H, dt,  $J$  6.8, 7.3), 2.61 (2H, t,  $J$  7.3), 6.19 (1H, dt,  $J$  16.1, 6.8), 6.41 (1H, d,  $J$  16.1), 7.17-7.34 (5H, m).

*5-Phenylhex-5-en-2-one 16ab* was an oil; MS  $m/z$  174 ( $M^+$ );  $^1\text{H-NMR}$   $\delta$  2.12 (3H, s), 2.58 (2H, t,  $J$  7.8), 2.79 (2H, t,  $J$  7.8), 5.07 (1H, s), 5.28 (1H, s), 7.25-7.40 (5H, m).

*6-(2-Naphthyl)-5-phenylhex-5-en-2-one 16ad* had m.p. 67-68 °C (from benzene-hexane) (Found: C, 85.74; H, 7.13.  $\text{C}_{16}\text{H}_{16}\text{O}$  requires C, 85.68; H, 7.19%); MS  $m/z$  224 ( $M^+$ );  $^1\text{H-NMR}$   $\delta$  2.18 (3H, s), 2.53 (2H, dt,  $J$  8.1, 6.8), 2.65 (2H, t,  $J$  6.8), 6.32 (1H, dt,  $J$  15.6, 8.1), 6.57 (1H, d,  $J$  15.6), 7.38-7.78 (7 H, m).

*1,5-Diphenylpent-4-en-1-one 16ba* was an oil;<sup>23</sup> MS  $m/z$  236 ( $M^+$ );  $^1\text{H-NMR}$   $\delta$  2.66 (2H, dt,  $J$  6.8, 7.3), 3.15 (2H, t,  $J$  7.3), 6.29 (1H, dt,  $J$  15.6, 6.8), 6.46 (1H, d,  $J$  15.6), 7.16-7.48 (5H, m), 7.53-7.58 (5H, m).

*5-(2-Naphthyl)-1-phenylpent-4-en-1-one 16bd* had m.p. 90-92

°C (from benzene-hexane) (Found: C, 87.83; H, 6.10. C<sub>21</sub>H<sub>18</sub>O requires C, 88.08; H, 6.34%); MS *m/z* 286 (M<sup>+</sup>); <sup>1</sup>H-NMR δ 2.69-2.75 (2H, m), 3.20 (2H, t, *J* 7.3), 6.43 (1H, dt, *J* 15.6, 6.8), 6.63 (1H, d, *J* 15.6), 7.25-8.01 (12H, m).

*Ethyl 5-phenylpent-4-enoate* **16ca** was an oil;<sup>24</sup> MS *m/z* 204 (M<sup>+</sup>); <sup>1</sup>H-NMR δ 1.26 (3H, t, *J* 7.1), 2.43-2.49 (2H, m), 2.49-2.56 (2H, m), 4.15 (2H, q, *J* 7.1), 6.20 (1H, dt, *J* 16.1, 6.5), 6.43 (1H, d, *J* 16.1), 7.17-7.34 (5H, m).

*Ethyl 5-(2-naphthyl)pent-4-enoate* **16cd** was an oil; MS *m/z* 254 (M<sup>+</sup>), <sup>1</sup>H-NMR δ 1.26 (3H, t, *J* 7.3), 2.49-2.53 (2H, m), 2.59 (2H, t, *J* 7.1), 4.16 (2H, q, *J* 7.3), 6.34 (1H, dt, *J* 15.6, 6.8), 6.59 (1H, d, *J* 15.6), 7.36-7.79 (7H, m). The free acid of **16cd** had m.p. 173-175 °C (from methanol) (Found: C, 79.36; H, 6.07. C<sub>15</sub>H<sub>14</sub>O<sub>2</sub> requires C, 79.62; H, 6.24%).

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## Chapter 4

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# Palladium-catalyzed Hydroesterification of Terminal Alkynes

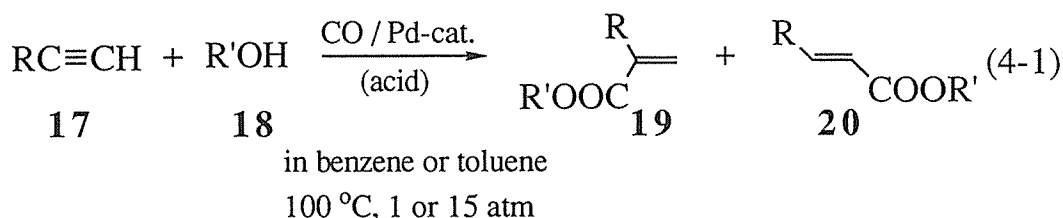
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### 4-1. Introduction

Palladium-catalyzed carbonylation of terminal alkynes can give rise to either 2- and/or 3-substituted acrylic acid derivatives or acetylenecarboxylic acid derivatives, depending on the catalyst systems employed.<sup>1</sup> It has been reported that arylacetylenes undergo regioselective carbonylation in the presence of palladium catalysts and hydrogen iodide in methanol to give methyl 2-arylpropenoates,<sup>2,3</sup> which can be useful precursors for optically active 2-arylpropanoic acids known as nonsteroidal anti-inflammatory agents.<sup>2-4</sup> Recently, Torii *et al.* demonstrated that aminocarbonylation of terminal alkynes proceeds regio-selectively in the presence of palladium complexes and iodide promoters in diethylamine under considerably mild conditions.<sup>5</sup> Selective formation of 2-substituted acrylate esters in alkoxycarbonylation of terminal alkynes under neutral conditions using palladium-dppb [ $\text{Ph}_2\text{P}(\text{CH}_2)_4\text{PPh}_2$ ] complexes without addition

of iodides has also been reported by Alper *et al.*;<sup>6</sup> however, higher temperature and carbon monoxide pressure are required.

During the study, It was found that aryl- and alkyl-acetylenes **17** are efficiently carbonylated even under normal pressure of carbon monoxide in the presence of a catalytic amount of palladium complexes using weakly acidic 3- or 4-substituted phenols **18a-d** as nucleophiles to give 2-substituted 2-propenoate aryl esters **19** in good yield along with the corresponding 3-substituted isomers **20** (eq. 4-1). The reaction with aliphatic alcohols in place of phenolic compounds could also proceed by addition of a catalytic amount of *p*-toluenesulfonic acid.



**17a:** R=Ph

**17b:** R=4-MeOC<sub>6</sub>H<sub>4</sub>

**17c:** R=6-methoxy-2-naphthyl

**17d:** R=*n*-C<sub>5</sub>H<sub>11</sub>

**18a:** R'=Ph

**18b:** R'=4-ClC<sub>6</sub>H<sub>4</sub>

**18c:** R'=3-ClC<sub>6</sub>H<sub>4</sub>

**18d:** R'=4-MeC<sub>6</sub>H<sub>4</sub>

**18e:** R'=*n*-C<sub>4</sub>H<sub>9</sub>

**18f:** R'=*n*-C<sub>3</sub>H<sub>7</sub>

**18g:** R'=*n*-C<sub>6</sub>H<sub>13</sub>

## 4-2. Results and Discussion

*Aryloxyacylation of phenylacetylene 17a in the presence of phenols 18a-d* ——— The results for the hydroesterification of phenylacetylene **17a** (1 mmol) with phenol **18a** in several solvents

**Table 4-1.**

Carbonylation of phenylacetylene **17a** in the presence of phenols **18a-d**<sup>a</sup>

Run	18	17a/18 (ratio)	Catalyst	Yield / % <sup>b</sup>	
				19	20
1	<b>18a</b>	1:1	Pd(PPh <sub>3</sub> ) <sub>4</sub>	65	3
2	<b>18a</b>	1:1	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	7	5
3	<b>18a</b>	1:1	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> + 2PPh <sub>3</sub>	25	10
4 <sup>c, d</sup>	<b>18a</b>	1:1	Pd(PPh <sub>3</sub> ) <sub>4</sub>	64	4
5 <sup>c, e</sup>	<b>18a</b>	1:1	Pd(PPh <sub>3</sub> ) <sub>4</sub>	8	1
6	<b>18a</b>	1:2	Pd(PPh <sub>3</sub> ) <sub>4</sub>	76	3
7	<b>18a</b>	1:4	Pd(PPh <sub>3</sub> ) <sub>4</sub>	81 (75)	4
8	<b>18a</b>	1:4	Pd(OAc) <sub>2</sub> + 4PPh <sub>3</sub>	79	4
9	<b>18b</b>	1:2	Pd(PPh <sub>3</sub> ) <sub>4</sub>	81 (75)	4
10	<b>18c</b>	1:2	Pd(PPh <sub>3</sub> ) <sub>4</sub>	86 (78)	3
11	<b>18d</b>	1:4	Pd(PPh <sub>3</sub> ) <sub>4</sub>	95 (88)	4

a) The reaction was carried out in benzene under carbon monoxide (15 atm at room temperature) at 100 °C for 18-30 h. [**17a**]:[Pd]=1:0.04 (in mmol).

b) Determined by GLC analysis. Isolated yield in parentheses. c) Under 25 atm of carbon monoxide at 120 °C. d) Conversion of **17a** was 97 %. e) In acetonitrile. Conversion of **17a** was 22 %.

under pressurized carbon monoxide (15 atm at room temperature) using a series of palladium complexes (0.04 mmol) are summarized in Table 4-1. In each case, phenyl atropate **19** (R=R'=Ph) was obtained together with phenyl cinnamate **20** (R=R'=Ph). Among the complexes tested, Pd(PPh<sub>3</sub>)<sub>4</sub> showed good catalytic activity. A combination of Pd(OAc)<sub>2</sub> and PPh<sub>3</sub> could be used in place of Pd(PPh<sub>3</sub>)<sub>4</sub>, but the reactions with PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> and PdCl<sub>2</sub>-PPh<sub>3</sub> were sluggish (Runs 1-3, 7 and 8). Benzene appeared to be one of the most suitable solvents. In a polar solvent such as acetonitrile, both the conversion of **17a** and the yield of the ester **19** were low (Runs 4 and 5). By increasing the ratio of **18a** to **17a**, the yield of **19** was significantly improved (Runs 1, 6 and 7). 3- or 4-substituted phenols **18b-d** could be also used as the phenolic compounds (Runs 9-11). *p*-Cresol **18d** was found to be one of the most effective nucleophiles. Thus, the ester **19** (R=Ph, R'=4-MeC<sub>6</sub>H<sub>4</sub>) was formed in a yield of 95 %.

Carbonylation of **17a** in the presence of **18d** under normal pressure of carbon monoxide was also examined in toluene (Table 4-2). While Pd(PPh<sub>3</sub>)<sub>4</sub> was inefficient (Run 12), a combination of a bidentate ligand, dppf [1, 1'-bis(diphenylphosphino)ferrocene] and Pd(OAc)<sub>2</sub>, enabled the reaction to be performed satisfactorily (Run 16). Another bidentate ligand dppp [Ph<sub>2</sub>P(CH<sub>2</sub>)<sub>3</sub>PPh<sub>2</sub>] also improved the product yield, while with dppe [Ph<sub>2</sub>P(CH<sub>2</sub>)<sub>2</sub>PPh<sub>2</sub>], the reaction was unsuccessful (Runs 13 and 14).

**Table 4-2.**

Carbonylation of phenylacetylene **17a** in the presence of *p*-cresol **18d**<sup>a</sup>

Run	Catalyst	Yield / % <sup>b</sup>	
		<b>19</b>	<b>20</b>
12	Pd(PPh <sub>3</sub> ) <sub>4</sub>	29	5
13	Pd(OAc) <sub>2</sub> + 2dppe	2	1
14	Pd(OAc) <sub>2</sub> + 2dppp	59	2
15	Pd(OAc) <sub>2</sub> + 2dppf	59	7
16	Pd(OAc) <sub>2</sub> + 1dppf	83 (77)	6

a) The reaction was carried out in toluene under carbon monoxide (1 atm) at 100 °C for 4-18 h. [**17a**]:[**18d**]:[Pd]=1:4:0.04 (in mmol). b) Determined by GLC analysis. Isolated yield in parentheses. c) Not detected.

*Carbonylation of various terminal alkynes 17b-d with p-cresol 18d* — Carbonylation of a number of terminal alkynes **17b-d** was performed under 1 or 15 atm of carbon monoxide pressure (Table 4-3). The corresponding 2-substituted propenoates **19** were obtained in fair to good yields. It should be noted that for the reaction of 1-heptyne **17d** as a representative aliphatic alkyne, Pd(PPh<sub>3</sub>)<sub>4</sub> was inefficient, but the reaction with Pd(OAc)<sub>2</sub>-PPh<sub>3</sub> proceeded smoothly (Run 20). This may suggest that acetic acid derived from Pd(OAc)<sub>2</sub> acts as a promoter. Indeed, the expected product **19** (R=*n*-C<sub>5</sub>H<sub>11</sub>, R'=4-MeC<sub>6</sub>H<sub>4</sub>) was obtained in a reasonable yield by addition of a catalytic amount of acetic acid (0.04 mmol) to the reaction of **17d**

**Table 4-3.**Carbonylation of terminal acetylenes **17** in the presence of **18d**<sup>a</sup>

Run	<b>17</b>	Conditions <sup>b</sup>	Yield / % <sup>c</sup>	
			<b>19</b>	<b>20</b>
11	<b>17a</b>	A	95 (88)	4
16	<b>17a</b>	B	83 (77)	6
17	<b>17b</b>	A	86 (83)	- <sup>d</sup>
18	<b>17c</b>	A	(75)	- <sup>d</sup>
19	<b>17c</b>	B	(54)	- <sup>d</sup>
20	<b>17d</b>	C	58	17
21	<b>17d</b>	D	71 (68)	4

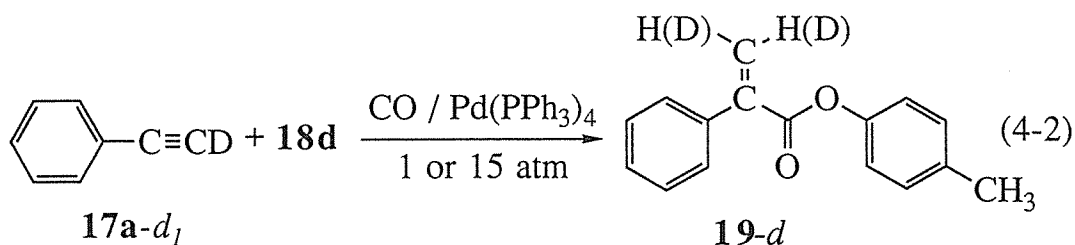
a) The reaction was carried out at 100 °C for 4-18 h. b) A: [**17**]:[**18d**]:[Pd(PPh<sub>3</sub>)<sub>4</sub>]=1:4:0.04 (in mmol), at 15 atm in benzene; B: [**17**]:[**18d**]:[Pd(OAc)<sub>2</sub>]:[dppf]=1:4:0.04:0.04 (in mmol), at 1 atm in toluene; C: [**17**]:[**18d**]:[Pd(OAc)<sub>2</sub>]:[PPh<sub>3</sub>]=1:4:0.04:0.16 (in mmol), at 15 atm in benzene; D: [**17**]:[**18d**]:[Pd(PPh<sub>3</sub>)<sub>4</sub>]:[AcOH]=1:4:0.04:0.04 (in mmol), at 15 atm in benzene. c) Determined by GLC analysis. Isolated yield in parentheses. d) Not detected.

with **18d** using Pd(PPh<sub>3</sub>)<sub>4</sub> (Run 21).

*The reaction of mono-deuterated phenylacetylene 17a-d<sub>1</sub> with 18d* — The reaction of mono-deuterated phenylacetylene **17a-d<sub>1</sub>** (1 mmol) with **18d** (4 mmol) was also examined using Pd(PPh<sub>3</sub>)<sub>4</sub> at 15 atm; the H/D ratio of both the two methylene hydrogens in the product was approximately 4:1 (estimated by 400 MHz-<sup>1</sup>H NMR



analysis, eq. 4-2). The reaction under 1 atm gave the same result. In the reaction with **17a-d<sub>1</sub>** (1 mmol) and **18d** (1 mmol), the H/D ratio was 1:1. It was confirmed that the H-D exchange reaction with the phenolic hydrogen occurs in both the starting alkyne and the carbonylation product under the influence of the palladium catalyst.



*Alkoxycarbonylation of 17 with aliphatic alcohols 18e-g* — The reaction of phenylacetylene **17a** with *n*-butanol **18e** as an aliphatic alcohol in place of phenolic compounds was performed under normal pressure of carbon monoxide in toluene (Table 4-4). *n*-Butyl atropate **19** (R=Ph, R'=n-C<sub>4</sub>H<sub>9</sub>) (44 %) was obtained along with *n*-butyl cinnamate **20** (R=Ph, R'=n-C<sub>4</sub>H<sub>9</sub>) (5 %) when Pd(PPh<sub>3</sub>)<sub>4</sub> was used as the catalyst precursor (Run 22). Addition of a catalytic amount of *p*-toluenesulfonic acid (TsOH) to the reaction medium was found to increase the yield of **19** considerably (Run 25). A better result was also obtained by using a catalyst system of Pd(dba)<sub>2</sub> (dba=dibenzylideneacetone) (0.04 mmol), PPh<sub>3</sub> (0.16 mmol) and TsOH (0.04 mmol), giving the ester in 89 % yield (Run 26). Under

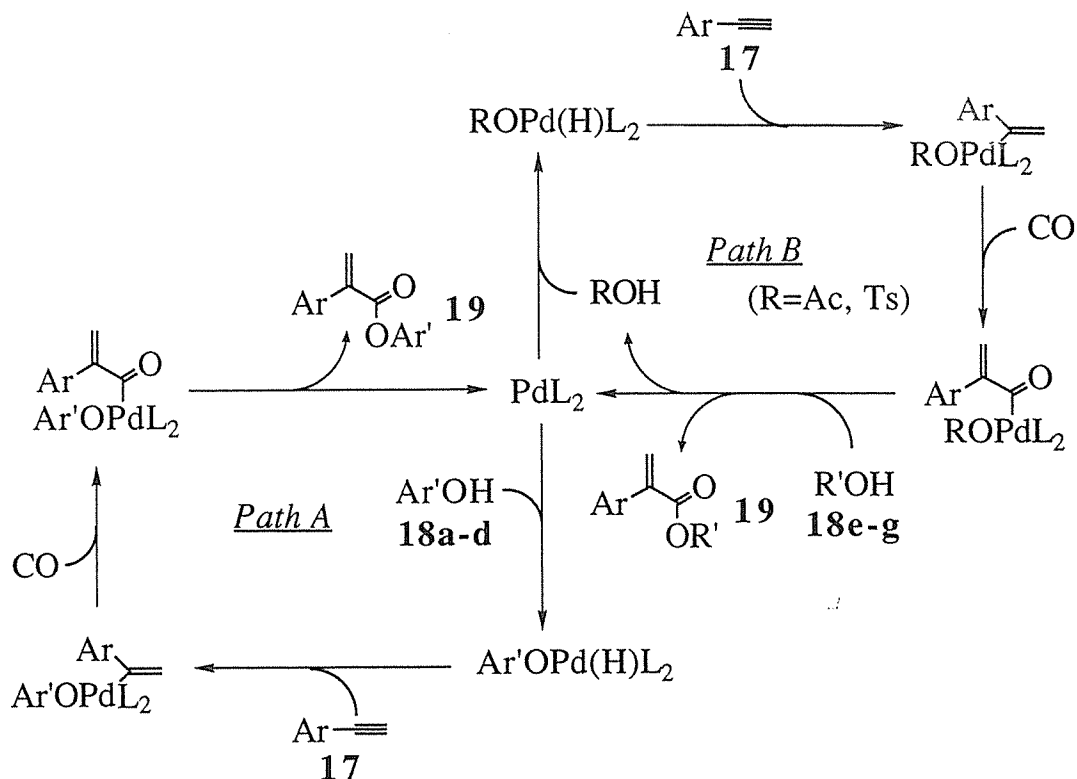
**Table 4-4.**Carbonylation of terminal acetylenes **17** in the presence of aliphatic alcohols **18e-g**<sup>a</sup>

Run	17	18	Catalysts	Yield / % <sup>b</sup>	
				19	20
22	17a	18e	Pd(PPh <sub>3</sub> ) <sub>4</sub>	44	5
23	17a	18e	Pd(OAc) <sub>2</sub> + 4PPh <sub>3</sub>	56	4
24	17a	18e	Pd(PPh <sub>3</sub> ) <sub>4</sub> + 1AcOH	26	2
25	17a	18e	Pd(PPh <sub>3</sub> ) <sub>4</sub> + 1TsOH	72	4
26	17a	18e	Pd(dba) <sub>2</sub> + 4PPh <sub>3</sub> + 1TsOH	89 (85)	4
27	17a	18f	Pd(dba) <sub>2</sub> + 4PPh <sub>3</sub> + 1TsOH	85	4
28	17a	18g	Pd(dba) <sub>2</sub> + 4PPh <sub>3</sub> + 1TsOH	74	3
29	17c	18e	Pd(dba) <sub>2</sub> + 4PPh <sub>3</sub> + 1TsOH	76	- <sup>c</sup>
30	17d	18e	Pd(dba) <sub>2</sub> + 4PPh <sub>3</sub> + 1TsOH	57	- <sup>c</sup>

a) The reaction was carried out in toluene under carbon monoxide (1 atm at room temperature) at 100 °C for 2-18 h. [17]:[18]:[Pd]:=1:4:0.04: (in mmol). b) Determined by GLC analysis. Isolated yield in parentheses. c) Not detected.

the same conditions, the corresponding 2-substituted propenoic acid *n*-butyl esters **19** were obtained in moderate to good yields using terminal alkynes **17c, d** as the substrates (Runs 29 and 30).

*Reaction Scheme* — A possible mechanism for the hydroesterification of **17** is illustrated in Scheme 4-1. It was reported that oxidative addition of the O-H bonds in phenols to



Scheme 4-1

$\text{Pd}(\text{PCy}_3)_2$  occurs to give  $\text{HPd}(\text{PCy}_3)_2\text{OAr}$ .<sup>7</sup> Therefore, it may be reasonable to consider that in the present reaction, a hydridopalladium complex is also formed by the reaction of  $\text{Pd}(0)$  species generated *in situ* with phenols in the first step (Path A). Subsequently, addition of the hydridopalladium complex to alkyne **17** gives vinylpalladium complex, followed by insertion of carbon monoxide affords vinyloxy palladium complex. Then, reductive of ester **19** regenerates  $\text{Pd}(0)$  species. In the presence of an acid, addition of the acid to the

Pd(0) species to give another hydridopalladium intermediate may involve the reaction sequence (Path B). In this case, reaction of vinyloylpalladium complex with alcohol appears to afford the product.

### 4-3. Summary

The carbonylation of terminal alkynes using palladium-phosphine complexes under mild conditions efficiently proceeds in the presence of phenolic compounds to give the corresponding 2-substituted 2-propenoic acid aryl esters in good selectivity and yield. The reaction also proceeds using aliphatic alcohols in place of phenols in the presence of a catalytic amount of acids.

### 4-4. Experimental

#### 4-4-1. General Procedure

<sup>1</sup>H-NMR spectra were obtained with a JEOL JNM-GSX-400 spectrometer in CDCl<sub>3</sub> solutions. *J*-Values are given in Hz. GC-MS data were obtained with a JEOL JMS-DX-303 spectrometer. GLC analysis was carried out with a Shimadzu GC-8A gas chromatograph.

The alkynes **17b**<sup>8</sup> and **17c**<sup>3</sup> were prepared by the methods

reported previously. Other starting materials were commercially available. The following experimental details may be regarded as typical in methodology and scale.

#### 4-4-2. Carbonylation of Terminal Alkynes **17** with Phenols **18a-d** under Pressurized Condition

A mixture of **17** (1 mmol), **18** (2-4 mmol), and Pd(PPh<sub>3</sub>)<sub>4</sub> (0.04 mmol) in benzene (5 ml) was added to a 40 ml stainless steel autoclave. Then carbon monoxide (15 atm at room temperature) was charged and the mixture was magnetically stirred at 100 °C for 18 h. Analysis by GLC and GC-MS confirmed formation of **19** and **20**. The products were also isolated by column chromatography on silica gel with dichloromethane-hexane (3:7) as eluant.

#### 4-4-3. Carbonylation of Terminal Alkynes **17** with Alcohols **18e-g** under Normal Pressure

A mixture of **17** (1 mmol), alcohol **18** (4 mmol), *p*-toluene-sulfonic acid (0.04 mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (0.04 mmol) in toluene (5 ml) was added to a two-necked 100 ml flask with a balloon filled with carbon monoxide and the solution was stirred at 100 °C for 18 h. Analysis by GLC and GC-MS confirmed formation of **19** and **20**.

The products were also isolated by column chromatography on silica gel with dichloromethane-hexane (3:7) as eluant.

#### 4-4-4. Product Data

*Phenyl atropate* was an oil: MS  $m/z$  224 ( $M^+$ );  $^1H$ -NMR  $\delta$  6.08 (1H, d,  $J$  1.0), 6.61 (1H, d,  $J$  1.0), 7.04-7.53 (10H, m).

*p-Chlorophenyl atropate* was an oil: MS  $m/z$  258 ( $M^+$ );  $^1H$ -NMR  $\delta$  6.09 (1H, d,  $J$  1.0), 6.60 (1H, d,  $J$  1.0), 7.01-7.50 (9H, m).

*m-Chlorophenyl atropate* was an oil: MS  $m/z$  258 ( $M^+$ );  $^1H$ -NMR  $\delta$  6.10 (1H, d,  $J$  1.0), 6.60 (1H, d,  $J$  1.0), 7.02-7.51 (9H, m).

*p-Tolyl atropate* was an oil: MS  $m/z$  238 ( $M^+$ );  $^1H$ -NMR  $\delta$  2.35 (3H, s), 6.06 (1H, d,  $J$  1.0), 6.58 (1H, d,  $J$  1.0), 7.03-7.52 (9H, m).

*n-Butyl atropate* was an oil: MS  $m/z$  214 ( $M^+$ );  $^1H$ -NMR  $\delta$  0.96 (3H, t,  $J$  7.3), 1.42 (2H, tq,  $J$  7.3, 7.3), 1.70 (2H, tt,  $J$  6.8, 7.3), 4.24 (2H, t,  $J$  6.8), 5.89 (1H, d,  $J$  1.2), 6.35 (1H, d,  $J$  1.2), 7.26-7.44 (5H, m).

*n-Propyl atropate* was an oil: MS  $m/z$  200 ( $M^+$ );  $^1H$ -NMR  $\delta$  0.97 (3H, t,  $J$  7.3), 1.68-1.77 (2H, m), 4.19 (2H, t,  $J$  6.8), 5.88 (1H, d,  $J$  1.0), 6.35 (1H, d,  $J$  1.0), 7.33-7.43 (5H, m).

*n-Hexyl atropate* was an oil: MS  $m/z$  242 ( $M^+$ );  $^1H$ -NMR  $\delta$  0.89 (3H, t,  $J$  6.5), 1.25-1.41 (6H, m), 1.69 (2H, tt,  $J$  6.8, 6.8), 4.22 (2H, t,  $J$  6.8), 5.88 (1H, d,  $J$  1.2), 6.34 (1H, d,  $J$  1.2), 7.25-7.43 (5H, m).

*p*-Tolyl 2-(*p*-anisyl)acrylate was an oil: MS  $m/z$  268 ( $M^+$ );  $^1\text{H-NMR}$   $\delta$  2.35 (3H, s), 3.82 (3H, s), 6.00 (1H, d,  $J$  1.2), 6.49 (1H, d,  $J$  1.2), 6.87-6.94 (2H, m), 7.02-7.06 (2H, m), 7.15-7.20 (2H, m), 7.41-7.48 (2H, m).

*p*-Tolyl  $\alpha$ -(6-methoxy-2-naphthyl)acrylate: MS  $m/z$  318 ( $M^+$ );  $^1\text{H-NMR}$   $\delta$  2.35 (3H, s), 3.91 (3H, s), 6.15 (1H, d,  $J$  1.0), 6.61 (1H, d,  $J$  1.0), 7.06-7.94 (10H, m).

*n*-Butyl  $\alpha$ -(6-methoxy-2-naphthyl)acrylate: MS  $m/z$  284 ( $M^+$ );  $^1\text{H-NMR}$   $\delta$  0.95 (3H, t,  $J$  7.3), 1.38-1.48 (2H, m), 1.66-1.73 (2H, m), 3.92 (3H, s), 4.26 (2H, t,  $J$  6.5), 5.97 (1H, d,  $J$  1.2), 6.37 (1H, d,  $J$  1.2), 7.13-7.84 (6H, m).

*p*-Tolyl  $\alpha$ -(*n*-amyl)acrylate was an oil;  $^1\text{H-NMR}$   $\delta$  0.91 (3H, t,  $J$  7.3), 1.32-1.36 (4H, m), 1.51-1.59 (2H, m), 2.35 (3H, s), 2.40 (2H, t,  $J$  7.3), 5.69 (1H, d,  $J$  1.5), 6.55 (1H, d,  $J$  1.5), 6.97-7.19 (4H, m).

*n*-Butyl  $\alpha$ -(*n*-amyl)acrylate was an oil;  $^1\text{H-NMR}$   $\delta$  0.89 (3H, t,  $J$  6.8), 0.95 (3H, t,  $J$  7.3), 1.25-1.35 (4H, m), 1.36-1.50 (4H, m), 1.62-1.70 (2H, m), 2.29 (2H, t,  $J$  7.8), 4.15 (2H, t,  $J$  6.5), 5.50 (1H, d,  $J$  1.2), 6.12 (1H, d,  $J$  1.2).

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## Conclusion

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This thesis mainly deals with synthesis of aromatic carbonyl compounds by carbonylation and related reactions using homogeneous cobalt or palladium catalysts. The results obtained through this work are summarized as follows.

In chapter 1, two new, convenient methods for preparation of low-valent cobalt complexes, which were effective catalyst precursors for carbonylation of aryl halides, were developed. Thus, tetracarbonylcobaltate ion was found to be generated by treatment of cobalt(II) chloride with sodium sulfide in the presence of calcium hydroxide in water under a normal pressure of carbon monoxide at room temperature. This solution containing the anionic cobalt complex was capable of catalyzing the normal pressure double-carbonylation of aryl halides in the presence of methyl iodide to give aromatic  $\alpha$ -ketocarboxylic acids in good selectivity. It was also found that a catalytically active cobalt species for the normal pressure methoxycarbonylation of aryl halides could be generated by treatment of cobalt(II) chloride with sodium methoxide in methanol under a normal pressure of carbon monoxide at room temperature without addition of any reductants.

Chapter 2 described desulfonylative carbonylation of arylsulfonyl chlorides using palladium catalysts. Since sulfonyl chlorides are very susceptible to basic reagents, less basic titanium alkoxides and zinc acetate were chosen as the nucleophiles in the synthetic strategy. Thus, the reaction efficiently proceeded to give arenecarboxylic acids and their esters. Under the similar conditions, desulfonylative homo-coupling of arylsulfonyl chlorides to give biaryls also proceeded.

In chapter 3, it was shown that palladium-catalyzed direct carbonylation of aryl-substituted allylic alcohols could be carried out by using titanium(IV) alkoxides as nucleophiles as above and lithium chloride as co-catalyst to give the corresponding  $\beta$ ,  $\gamma$ -unsaturated esters. In this reaction, it is considered that (a) titanium(IV) alkoxides act not only as nucleophiles but also as promoters for the oxidative addition of the allylic alcohols to palladium(0) species and (b) lithium chloride enhances the CO migratory insertion step in the reaction sequence. The palladium-Ti(OR)<sub>4</sub>-LiCl system could be also applied for the coupling reaction of the allylic alcohols with zinc enolates of  $\beta$ -dicarbonyl compounds as carbon nucleophiles to give  $\gamma$ ,  $\delta$ -unsaturated carbonyl compounds.

Chapter 4 referred the synthesis of  $\alpha$ -arylacrylate esters by palladium-catalyzed regioselective hydroesterification of monoarylalkynes. The reaction was found to proceed under mild conditions using phenolic compounds as nucleophiles. It is considered

that the reaction involves hydridopalladium complexes generated *in situ* by oxidative addition of phenols to palladium(0) species, as the key-intermediate. Aliphatic alcohols could be also used in place of phenols in the presence of a catalytic amount of acids.

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## Acknowledgment

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The work of this thesis has been carried out under the guidance of Professor Dr. Masakatsu Nomura of the Department of Applied Chemistry, Faculty of Engineering, Osaka University.

I would like to express my grateful acknowledgment to Professor Dr. Masakatsu Nomura for his invaluable guidance and encouragement throughout this work.

I am also indebted to Professor Dr. Toshikazu Nagai for his helpful comments and suggestions.

I am very grateful to Assistant Professor Dr. Masahiro Miura for his assistance in the preparation of the manuscripts and many useful suggestions for performing experiments.

I am much obliged to Associate Professor Dr. Mikio Miyake, and Assistant Professors Mr. Satoru Murata and Mr. Toru Ida for their useful discussion and helpful suggestions during the course of the work.

I wish to thank my co-workers, Mr. Hideo Hashimoto, Mr. Naoki Hamaguchi, Mr. Tetsuya Satoh, and Mr. Yuichi Kushino for their helpful collaboration in the course of experiments.

Furthermore, many thanks are given to Mr. Kazumi Okuro, Mr. Kenji Akagi, and all the other members (1987.4-1993.3) of the research group of Professor Dr. Masakatsu Nomura for their helpful assistance, occasional discussions, and friendships.

Finally, I am particularly grateful to my parents Kunio Itoh and Tomoe Itoh, and my brother Jun Itoh for their encouragement and supports.