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1997

TETSUYA SATOH

STUDIES ON PALLADIUM-CATALYZED CARBONYLATION AND RELATED REACTIONS OF AROMATIC COMPOUNDS

（パラジウム触媒を用いる芳香族化合物のカルボニル化
ならびに関連反応に関する研究）

1997

TETSUYA SATOH

Preface

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

The objective of this thesis is to develop novel palladium-catalyzed carbonylation and related reactions of aromatic compounds. 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.

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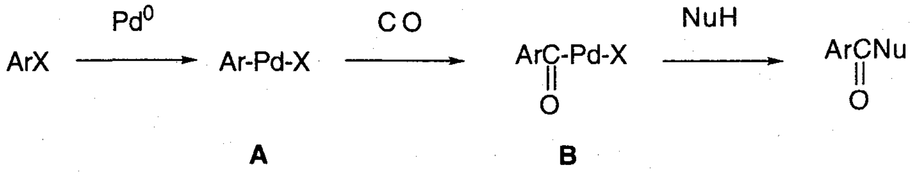
Chapter 1. Palladium-Catalyzed Desulfonylative Carbonylation and Iodination of Arenesulfonyl Compounds

Chapter 2. Effect of Copper-Cocatalysts on the Palladium-Catalyzed Carbonylation of Iodobenzenes

General Introduction

Aromatic carbonyl compounds have been widely used as synthetic intermediates for medicines, agricultural chemicals, and functionalized organic substances.[1] 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 is introduced into aromatic compounds as the carbonyl source, and the reaction has been extensively studied.

A typical example of such carbonylation is the palladium-catalyzed conversion of aromatic halides or their synthetic equivalents into various carbonyl compounds.[2] The substrates can undergo oxidative addition to Pd(0) species to give arylpalladium intermediates (**A**), each of which has a σ-Pd-C bond (eq 1). Subsequently, insertion of CO into the Pd-C bond to afford the corresponding aroylpalladium intermediate (**B**), followed by the reaction with nucleophilic reagents produces carboxylic acids, esters, amides, aldehydes, and ketones. Meanwhile, the intermediate **A** is also known to react with alkenes, alkynes, or organometallic reagents as well as CO to form C-C bonds. A number of catalytic reactions involving the step have been utilized as useful synthetic tools for various substituted aromatic compounds.



$$\mathrm{ArX} \xrightarrow{\mathrm{Pd}^0} \underset{\mathbf{A}}{\mathrm{Ar\text{-}Pd\text{-}X}} \xrightarrow{\mathrm{CO}} \underset{\mathbf{B}}{\mathrm{Ar}\underset{\overset{\|}{\mathrm{O}}}{\mathrm{C}}\mathrm{\text{-}Pd\text{-}X}} \xrightarrow{\mathrm{NuH}} \mathrm{Ar}\underset{\overset{\|}{\mathrm{O}}}{\mathrm{C}}\mathrm{Nu} \qquad (1)$$

Although these palladium-catalyzed reactions have been used extensively in organic synthesis, their synthetic value should be further enhanced by development of more effective catalyst systems and new type reactions which may expand the scope of the catalysis.

From the viewpoint mentioned above, the present study focused on development of new types of palladium-catalyzed carbonylation and related reaction of aromatic compounds and of effective catalyst systems. The results obtained have been described in five chapters.

Chapter 1 deals with a successful attempt on the extension of the substrates for the palladium-catalyzed alkoxycarbonylation of aromatic compounds. It was found that arenesulfonyl chlorides, which can be easily obtained from the corresponding sulfonic acids, underwent facile carbonylation accompanied by desulfonylation in the presence of a palladium-copper catalyst system to form the corresponding aromatic esters in good yields. The catalyst system was also applicable to the similar carbonylation reaction of arenethiosulfonic acid esters. Furthermore, by carrying out the reaction in the presence of zinc or potassium iodide under nitrogen, arenesulfonyl chlorides was found to be transformed to the corresponding aryl iodides.

In chapter 2, the effect of the copper species, which have been found as an effective cocatalyst for the palladium-catalyzed carbonylation of arenesulfonyl compounds (chapter 1), was investigated in the carbonylation reactions of aryl iodides using a number of nucleophiles. As a result, the reaction could also be promoted by addition of the cocatalyst, irrespective of nucleophiles.

In chapter 3, palladium-catalyzed cross-carbonylation of aryl iodides using unsaturated compounds in place of nucleophiles was investigated. When five membered cyclic alkenes were used as the unsaturated reagents, the reaction was found to proceed efficiently, giving the corresponding aryl vinyl ketones.

In chapter 4, palladium-catalyzed carbonylation of alcohols was investigated. It was found that the reaction of allyl alcohols, which usually requires high pressures of CO,[2] could be carried out even under 1 or 5 atm of CO by the use of phenols as nucleophiles. Under similar conditions, cyclocarbonylation of 2-hydroxybenzyl alcohols also proceeded to give the corresponding benzo[*b*]furanone derivatives. Meanwhile, the direct coupling of allyl alcohols with phenols under nitrogen was also undertaken.

Chapter 5 refers development of a new method for the synthesis of aromatic ketones. It was found that by treatment of 2-hydroxybenzaldehyde, *i. e.* salicylaldehyde, and its derivatives with aryl iodides in the presence of a palladium catalyst, cross-coupling reaction smoothly proceeded accompanied by cleavage of the aldehyde C-H bond to produce the corresponding 2-aroylphenols. With this in mind, arylation of other types of C-H bond was also attempted.

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List of Publications

1 Desulfonylation and Desulfonylative Carbonylation of Arenethiosulfonic Acid Esters in the Presence of $PdCl_2$ and LiCl

T. Satoh, K. Itoh, M. Miura, and M. Nomura, *J. Mol. Catal.*, **1993**, *83*, 125.

2 Desulfonylative Iodination of Naphthalenesulfonyl Chlorides with Zinc Iodide or Potassium Iodide Catalyzed by Dichlorobis(benzonitrile)palladium(II) in the Presence of Lithium Chloride and Titanium(IV) Isopropoxide

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6 Synthesis of Naphthofuran-2(3*H*)-one Derivatives by Palladium-Catalyzed Three-Component Coupling Using Naphthols, Aldehydes, and Carbon Monoxide

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List of Supplementary Publications

1 Palladium-Catalyzed Arylation of Secondary Allylic Alcohols in the Presence of Copper(II) Triflate and Triphenylphosphine: Selective Synthesis of β-Aryl α,β-Unsaturated Ketones

T. Satoh, M. Miura, and M. Nomura, *J. Mol. Catal. A: Chemical,* **1996**, *112*, 211.

2 Palladium-Catalyzed Reaction of Aryl Bromides with Dialkylacetylenes to Produce Allenic Compounds

S. Pivsa-Art, T. Satoh, M. Miura, and M. Nomura, *Chem. Lett.*, **1997**, 823.

3 Palladium-Catalyzed Oxidative Cross-Coupling of 2-Phenylphenols with Alkenes

M. Miura, T. Tsuda, T. Satoh, and M. Nomura, *Chem. Lett.*, **1997**, 1103.

Chapter 1. Palladium-Catalyzed Desulfonylative Carbonylation and Iodination of Arenesulfonyl Compounds

1-1. Introduction

Palladium-catalyzed carbonylation reaction of aryl halides is a useful tool for preparation of various aromatic carbonyl compounds.[1] Our research group recently reported a method for the synthesis of aromatic esters using arenesulfonyl chlorides, which are readily available from the corresponding sulfonic acids, as the starting materials in place of aryl halides;[2] carbonylation of the sulfonyl chlorides in the presence of titanium(IV) alkoxides and a catalytic amount of $Pd(PPh_3)_4$ or $PdCl_2(PPh_3)_2$ proceeds accompanied by desulfonylation to give aromatic esters. This desulfonylative carbonylation is considered to be particularly useful for preparation of naphthoic acid derivatives, since both α- and β-naphthalenesulfonic acids are well known to be prepared by means of sulfonation reactions, while either halogenation or nitration predominantly gives the α-substituted compounds. In the reaction, however, considerable amounts of diaryl disulfides are also produced as by-products (eq 1-1).[2] Possible intermediates leading to diaryl disulfides could be the corresponding thiosulfonates

$$\mathrm{ArSO_2Cl} \xrightarrow[\mathrm{Ti(OR)_4}]{\mathrm{CO\,/\,Pd(PPh_3)_4}} \mathrm{ArCOOR} + \mathrm{ArSSAr} \qquad (1\text{-}1)$$

$$\mathrm{ArSO_2Cl} \longrightarrow \left[\ \mathrm{ArSO_2SAr}\ \right] \longrightarrow \mathrm{ArSSAr} \qquad (1\text{-}2)$$

(eq 1-2). This might be partly supported by the fact that 1-naphthyl 1-naphthalenethiosulfonate is reduced to di-1-naphthyl disulfide under the same reaction conditions indicated in eq 1-1, giving no carbonylation products.[2] Aryl arenethiosulfonates are also known to be formed by treating arenesulfonyl chlorides with various reducing reagents[3] including $Fe(CO)_5$.[4]

During a further study of the carbonylation, it was observed that a catalyst system of $PdCl_2$-CuI-LiCl was considerably more effective than the palladium-phosphine complexes, suppressing the formation of diaryl disulfides. It was also found that, by using the three component catalyst system, alkyl and aryl arenethiosulfonates underwent similar desulfonylative carbonylation reactions.

On the other hand, treatment of arenesulfonyl chlorides with zinc iodide or potassium iodide in the presence of a palladium catalyst under nitrogen was found to give the corresponding aryl iodides. Iodoarenes are the most reactive aromatic halides and have been widely used for synthesis of various aromatic fine compounds, especially by means of transition metal catalysis.[1] While it is known that desulfonylation of arenesulfonyl fluorides, chlorides, and bromides with platinum-group metal complexes gives the corresponding aryl halides,[5] such an iodination has not been so far reported.

1-2. Results and Discussion

1-2-1. Desulfonylative Carbonylation of Arenesulfonyl Chlorides and Arenethiosulfonic Acid Esters Using a Catalyst System of $PdCl_2$-CuI-LiCl

When the reaction of 1-naphthalenesulfonyl chloride (**1a**, 2 mmol) was carried out in the presence of $PdCl_2$ (0.06 mmol) and $Ti(OPr^i)_4$ (4 mmol) in THF under carbon monoxide (25 atm) at 170 °C for 1.5 h, isopropyl 1-naphthoate (**2a**) was formed in a yield of 64% along with di-1-naphthyl disulfide (**3a**, 31%) (eq 1-3 and Table 1-1). This result is comparable with that using

$$\underset{\mathbf{1}}{\mathrm{ArSO_2Cl}} \xrightarrow[\mathrm{CO\ /\ Ti(OPr^{\mathit{i}})_4}]{\mathrm{PdCl_2\ /\ CuI\ /\ LiCl}} \underset{\mathbf{2}}{\mathrm{ArCOOPr^{\mathit{i}}}} + \underset{\mathbf{3}}{\mathrm{ArSSAr}} \qquad (1\text{-}3)$$

a, Ar=1-naphthyl; **b**, Ar=4-MeC_6H_4; **c**, Ar=4-ClC_6H_4; **d**, Ar=4-chloro-1-naphthyl;
e, Ar=2-naphthyl; **f**, Ar=6-methyl-2-naphthyl; **g**, Ar=6-methoxy-2-naphthyl

$Pd(PPh_3)_4$ as catalyst in acetonitrile.[2] Addition of CuI (0.2 mmol) and lithium chloride (0.4 mmol) to the reaction significantly increased the product ratio of **2a** to **3a**, the yields of **2a** and **3a** being 91% and 8%, respectively. In the absence of lithium chloride the increase in the ester yield was reduced. The role of lithium chloride may be that it solubilizes CuI into THF.[6] Palladium-black and CuCl could also be used in place of $PdCl_2$ and CuI, respectively. Decrease in the carbon monoxide pressure to 10 atm showed no influence on the reaction. However, a further decrease in the pressure or a decrease in the reaction temperature considerably reduced the ester yield. The reaction of **1a** using titanium(IV) ethoxide and butoxide in place of the isopropoxide gave ethyl and butyl 1-naphthoates in 81 and 86 % yields, respectively.

The results for carbonylation of other arenesulfonyl chlorides **1b-g** using the three component catalyst system in the presence of $Ti(OPr^i)_4$ are also recorded in Table 1-1. The corresponding isopropyl esters **2b-g** were isolated in good yields which were 17-36 % higher than those previously reported.[2]

Table 1-1. Desulfonylative Carbonylation of Arenesulfonyl Chlorides 1[a]

1	Catalyst	CO pressure / atm	Yield of **2** / %[b]
1a[c]	$PdCl_2$	25	(64)
1a	$PdCl_2$-LiCl	25	(69)
1a	$PdCl_2$-CuI	25	(82)
1a[d]	$PdCl_2$-CuI-LiCl	25	(92)
1a	Pd-black	25	(21)
1a	Pd-black-CuI-LiCl	25	(92)
1a	$PdCl_2$-CuCl-LiCl	25	(92)
1a	$PdCl_2$-CuI-LiCl	10	85(90)
1a	$PdCl_2$-CuI-LiCl	5	(66)
1a[e]	$PdCl_2$-CuI-LiCl	10	(78)
1b	$PdCl_2$-CuI-LiCl	10	70
1c	$PdCl_2$-CuI-LiCl	10	76
1d	$PdCl_2$-CuCl-LiCl	10	84
1e	$PdCl_2$-CuCl-LiCl	10	81
1f	$PdCl_2$-CuI-LiCl	10	80
1g	$PdCl_2$-CuI-LiCl	10	90

[a]Reaction conditions: **1** (2 mmol), Pd-cat. (0.06 mmol), CuI (0.2 mmol), LiCl (0.4 mmol), and $Ti(OPr^i)_4$ (4 mmol) in THF under CO at 170 °C for 1.5 h. [b]Isolated yield based on **1** used. Value in parentheses indicates GLC yield. Diaryl disulfide **3** was also formed in each reaction, whose yield was not determined unless otherwise noted. [c]The yield of **3a** was 31 %. [d]The yield of **3a** was 8 %. [e]Reaction at 140 °C.

Arenethiosulfonates **4h-k** could also undergo the desulfonylative carbonylation efficiently under the similar conditions using $Ti(OPr^i)_4$ (eq 1-4 and Table 1-2). The reaction of **4h** with

$$\mathrm{ArSO_2SR} \xrightarrow[\mathrm{CO\ /\ Ti(OPr^{\mathit{i}})_4}]{\mathrm{PdCl_2\ /\ CuI\ /\ LiCl}} \mathrm{ArCOOPr^{\mathit{i}}} \;+\; \mathrm{RSSR} \;\left(+\; \mathrm{ArSSR} \;+\; \mathrm{ArSSAr}\right) \qquad (1\text{-}4)$$

4 **2** **3** **5**: Ar=Ph, R=Bu^n **7**: Ar=Ph
4h: Ar=R=4-MeC_6H_4; **2j**: Ar=Ph **6**: Ar=Ph, R=$PhCH_2$
4i: Ar=R=1-naphthyl;
4j: Ar=Ph, R=Bu^n;
4k: Ar=Ph, R=$PhCH_2$

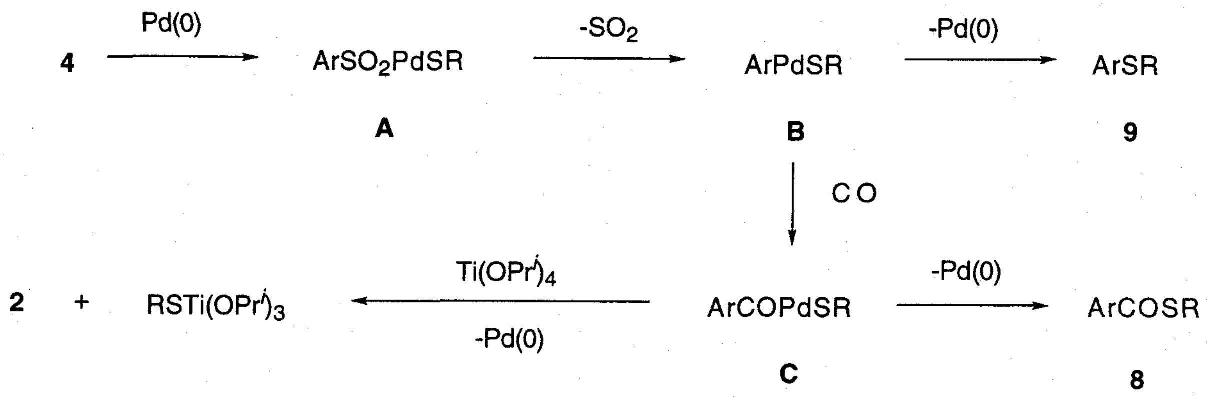
$Ti(OPr^i)_4$ gave isopropyl 4-methylbenzoate (**2b**, 60 %) based on the 4-methylbenzenesulfonyl moiety as the expected carbonylation product together with di-4-methylphenyl disulfide (**3b**, 68 %). Without the cocatalysts no ester was formed, giving disulfide **3b** (10 %) as the sole characterizable product, as was the reaction with $Pd(PPh_3)_4$ in acetonitrile.[2] Similar results were obtained in the reactions of **4i**. On the other hand, the disulfides were the sole characterizable products with CuI and LiCl, indicating that palladium chloride is the key metal species for the carbonylation reaction, while the copper species can catalyze the reduction of **4** to **3**. Reaction of the unsymmetrical thiosulfonate **4j** (or **4k**) gave isopropyl benzoate (**2j**) together with a mixture of disulfides **3j** (or **3k**), **5** (or **6**), and **7**.

Table 1-2. Desulfonylative Carbonylation of Arenethiosulfonates 4h-k[a]

4	Catalyst			Yield / %[b,c]				Recovery / %[b]
	$PdCl_2$	CuI	LiCl	$ArCOOPr^i$	RSSR	ArSSR	ArSSAr	
4h	+	-	-		(10)			73
4h	+	-	+	(23)	(66)			
4h	+	+	+	(60)	(68)			
4h	-	+	+		(55)			22
4i	+	-	-		47			16
4i	+	-	+	22	45			
4i	+	+	+	89	47			
4i	-	+	+		75			
4j	+	+	+	(61)	(40)	(25)	(4)	
4k	+	+	+	(71)	(32)	(21)	(4)	

[a] Reaction conditiotns: **4** (1 mmol), $PdCl_2$ (0.06 mmol), CuI (0.2 mmol), LiCl (0.4 mmol), and $Ti(OPr^i)_4$ (2 mmol) in THF under CO (10 atm at room temperature) at 170 °C for 1.5 h. [b] Isolated yield. Value in parentheses indicates GLC yield. [c] Yield (%) = [product (mmol) / substrate (mmol)] × 100.

The mechanism of the carbonylation of the sulfonyl chlorides **1** to the esters **2** may be essentially the same with that proposed previously, including oxidative addition of arenesulfonyl chlorides to palladium(0) species generated *in situ* followed by desulfonylation to give an arylpalladium intermediate.[2] Carbonylation of **4** seems to proceed by the similar route, which is illustrated in Scheme 1-1. Oxidative addition of the SO_2-S bond in **4** to a palladium(0) species takes place in the presence of CuI and LiCl to give an arenesulfonylpalladium intermediate **A**. Subsequently, SO_2-CO exchange reaction via an arylpalladium species **B** affords an aroylpalladium intermediate **C** followed by reaction with $Ti(OPr^i)_4$ to give **2** along with $RSTi(OPr^i)_3$. Quantitative consideration of the coproduct disulfides from the thiosulfonates **4j-k** suggests that (a) a part of the thiosulfonate **4j** (or **4k**) is directly reduced to the unsymmetrical disulfides **5** (or **6**), (b) disproportionation of **5** (or **6**) to **3j** (or **3k**) and **7** may occur in only a small extent, and (c) the Bu^{n}S and PhCH$_2$S moieties are transformed into the disulfides **3j** and **3k**, respectively, during the reaction. Thus, these disulfides **3j** and **3k** may be formed from the titanium thiolates, RSTi(O-i-Pr)$_3$ by their oxidation in the reaction medium. One of the probable oxidants could be sulfur dioxide evolved during the reaction.



Scheme 1-1.

The following results may support the mechanism. (*a*) The carbonylation of **4h-k** without Ti(OPr^i)$_4$ gave arenethiocarboxylate S-esters (**8h-k**) in modest yields together with the corresponding disulfides (eq 1-5 and Table 1-3). (*b*) The reaction of **4h-k** under nitrogen in refluxing

$$\underset{\mathbf{4}}{\mathrm{ArSO_2SR}} \xrightarrow[\mathrm{CO}]{\mathrm{PdCl_2\,/\,CuI\,/\,LiCl}} \underset{\mathbf{8}}{\mathrm{ArCOSR}} + \underset{\mathbf{3}}{\mathrm{RSSR}} \left(+ \underset{\mathbf{5,\,6}}{\mathrm{ArSSR}} + \underset{\mathbf{7}}{\mathrm{ArSSAr}} \right) \qquad (1\text{-}5)$$

2-methoxyethyl ether in the absence of Ti(OPr^i)$_4$ gave the corresponding sulfides **9h-k** in good yields along with small amounts of disulfides **3** and biaryls **10** (eq 1-6 and Table 1-4).

$$\underset{\mathbf{4}}{\mathrm{ArSO_2SR}} \xrightarrow{\mathrm{PdCl_2\,/\,LiCl}} \underset{\mathbf{9}}{\mathrm{ArSR}} + \underset{\mathbf{3}}{\mathrm{RSSR}} + \underset{\mathbf{10}}{\mathrm{Ar\text{-}Ar}} \qquad (1\text{-}6)$$

Table 1-3. Desulfonylative Carbonylation of Arenethiosulfonates 4h-k in the Absence of Ti(OPr^i)$_4$[a]

4	Yield / %[b,c]				Recovery / %[b]
	ArCOSR	RSSR	ArSSR	ArSSAr	
4h[d]	7	55			6
4h	50	17			
4i[d]	30	34			
4i	59	22			
4j	36	(23)	(16)	(2)	
4k	21	(26)	(12)	(2)	

[a]Reaction conditiotns: **4** (1 mmol), $PdCl_2$ (0.06 mmol), CuI (0.2 mmol), and LiCl (0.4 mmol) in THF under CO (10 atm at room temperature) at 170 °C for 1.5 h. [b]Isolated yield. Value in parentheses indicates GLC yield.[c]Yield (%) = [product (mmol) / substrate (mmol)] × 100. [d]Without CuI.

Table 1-4. Desulfonylation of Arenethiosulfonates 4h-k[a]

4	Catalyst	Yield / %[b]			Recovery / %[c]
		ArSR	RSSR	Ar-Ar	
4h	$PdCl_2$	<1			88
4h	LiCl				80
4h	$PdCl_2$-LiCl	97	2	1	
4h[d]	$PdCl_2$-CuI-LiCl	75	6	9	
4h[d]	$PdCl_2$-CuCl-LiCl	92	2	2	
4i	$PdCl_2$-LiCl	60		1	
4j	$PdCl_2$-LiCl	75	7	3	
4k	$PdCl_2$-LiCl	64	5	5	

[a]Reaction conditiotns: **4** (1 mmol), $PdCl_2$ (0.03 mmol), and LiCl (0.1 mmol) in 2-methoxyethyl ether under nitrogen at 162 °C for 1.5 h. [b]GLC yield based on **4** used.[c]Isolated yield. [d]CuX (0.1 mmol) and LiCl (0.2 mmol) were used.

When the former reaction was carried out without CuI, the yield of thiol esters was considerably decreased, as for the reaction in the presence of Ti(OPr^i)$_4$, confirming again that the copper species can enhance the desulfonylative carbonylation. In the latter case, the addition of lithium chloride was essential to induce the catalytic desulfonylation reaction, while the addition of the copper species showed no positive effect. A possible role of the added lithium chloride is the ligation of the chloride ion to the Pd(0) species to stabilize it and to increase its nucleophilic character. Such a stabilization of low ligated zero-valent palladium species by chloride ions has also been considered to occur in oxidative addition of iodobenzene.[7] While the catalyst precursor employed has 2 equivalents of chloride ions, the observed results indicate that a higher concentration of the ion is required for an effective desulfonylation. The formation of comparable amounts of disulfides **3** and biaryls **10** as the by-products from the reaction of **4** under nitrogen suggests that a part of the intermediate, ArPdSR, is transformed to $PdAr_2$ and $Pd(SR)_2$ before the reductive elimination of **9**.

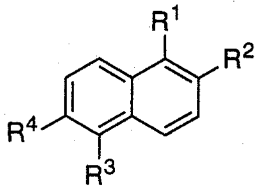
In the desulfonylative carbonylation reaction of **4**, a possible role of CuI added is its coordination to the sulfur atom in **4** to enhance the oxidative addition of **4** to palladium(0) species ligated by chloride ions. However, no positive effect of the copper species was observed in the reaction of the simple desulfonylation reaction (eq 1-5 and Table 1-4). Thus, it would accelerate step(s) after the arylpalladium intermediate formation, *i. e.* the carbon monoxide insertion and/or the reductive elimination (see chapter 2). However, the details are not clear.

The observed higher catalytic performance of $PdCl_2$-CuI-LiCl for the carbonylation of **1**, compared with $PdCl_2$ and $Pd(PPh_3)_4$, may also be due to the acceleration of these step(s), so that the by-product formation is suppressed. One of other possible explanations for the considerable improvement of the ester yield may be that the catalyst system is also capable of catalyzing the carbonylation of the corresponding thiosulfonates **4** which may be formed temporarily as by-products during the reaction (eq 1-2). However, we failed to detect the formation of **4** by analyzing the reaction mixture of arenesulfonyl chlorides, even in that of the early stage. In addition, the increase in the ester yield by adding CuI and LiCl to the reaction of arenesulfonyl chlorides appears to be somewhat higher than that expected by this consideration. These results would suggest that the former is the major function of the added copper species. Therefore, the route of sulfonyl chlorides to disulfides is not yet definitive. There may be also another possibility that diaryl disulfides could be carbonylated under the present reaction conditions: It has been reported that diaryl disulfides undergo carbonylation accompanied by loss of one sulfur atom in the presence of dicobalt octacarbonyl.[8] To test this possibility, di-1-naphthyl disulfide was treated under the present carbonylation conditions. However, only the starting material was recovered.

1-2-2. Desulfonylative Iodination of Arenesulfonyl Chlorides Using a Catalyst System of $PdCl_2(PhCN)_2\text{-}LiCl\text{-}Ti(OPr^i)_4$

When a mixture of 1-naphthalenesulfonyl chloride (**1a**, 2 mmol), $[\mathrm{PdCl_2(PhCN)_2}]$ (0.02 mmol), LiCl (0.4 mmol), and $\mathrm{Ti(OPr^i)_4}$ (1 mmol) in 2-methoxyethyl ether (5 $\mathrm{cm^3}$) was heated at 150 °C for 1 h, 1-iodonaphthalene (**11a**) was produced in a yield of 86 % (by GLC analysis) (eq 1-7 and Entry 1 in Table 1-5). Formation of 2-iodonaphthalene was not detected in the reaction mixture, while the homo-coupling reaction of **1a** with $[\mathrm{PdCl_2(PhCN)_2}]$ in the presence of $\mathrm{Ti(OPr^i)_4}$ gave 1, 1'-binaphthyl along with the 1, 2'-isomer, as previously reported.[9] No chloronaphthalenes were also formed. In the absence of LiCl and/or $\mathrm{Ti(OPr^i)_4}$, the yield of **11a** was considerably reduced (Entries 4 and 5), suggesting that these additives synergistically promote the iodination. Although the iodide **11a** was formed without the palladium catalyst, the yield was very low (Entry 7). Potassium iodide could also be used in place of $\mathrm{ZnI_2}$; it was less effective at 150 °C, but a satisfactory result was obtained by refluxing the solvent (Entry 9).

$$\underset{\mathbf{1,\,12,13}}{\mathrm{ArSO_2Cl}} \quad + \quad \underset{\mathrm{M=Zn,\,K}}{\mathrm{MI_n}} \quad \xrightarrow[\mathrm{Ti(OPr^i)_4}]{[\mathrm{PdCl_2(PhCN)_2}]\ /\ \mathrm{LiCl}} \quad \underset{\mathbf{11,\,14,\,15}}{\mathrm{ArI}} \qquad (1\text{-}7)$$



12: $R^1=R^3=SO_2Cl$, $R^2=R^4=H$
13: $R^2=R^4=SO_2Cl$, $R^1=R^3=H$

14: $R^1=R^3=I$, $R^2=R^4=H$
15: $R^2=R^4=I$, $R^1=R^3=H$

The results for the reactions of other naphthalenesulfonyl- (**1d-f**) and naphthalenedisulfonyl chlorides (**12**, **13**) are also recorded in Table 1-5. The corresponding monoiodides (**11d-f**) and diiodides (**14**, **15**) were obtained in modest to good yields.

The present reaction may involve oxidative addition of arenesulfonyl chloride to Pd(0) species generated in situ followed by loss of $\mathrm{SO_2}$ to afford arylpalladium intermediate (**B** in Scheme 1-1), as for the catalytic desulfonylation of arenesulfonyl chlorides to chloroarenes.[5] A possible role of lithium chloride added seems to be the same as in the desulfonylation of arenethiosulfonates described

Table 1-5. Desulfonylative Iodination of Naphthalenesulfonyl Chlorides 1[a]

Entry	$ArSO_2Cl$ (mmol)	Iodide (mmol)	Temp / °C	Yield of ArI / %[b]
1	**1a** (2)	ZnI_2 (2)	150	(86)
2	**1a** (2)	ZnI_2 (1)	150	(83)
3	**1a** (5)	ZnI_2 (5)	162	72
4[c]	**1a** (2)	ZnI_2 (2)	150	(54)
5[d]	**1a** (2)	ZnI_2 (2)	150	(32)
6[c,d]	**1a** (2)	ZnI_2 (2)	150	(26)
7[e]	**1a** (2)	ZnI_2 (2)	150	(14)
8	**1a** (2)	KI (4)	150	(63)
9	**1a** (2)	KI (2)	162	(82)
10	**1d** (3)	ZnI_2 (3)	162	53
11	**1e** (1)	ZnI_2 (0.5)	150	(41)
12	**1e** (1)	ZnI_2 (0.5)	162	(54)
13	**1e** (1)	KI (1)	150	(56)
14	**1e** (1)	KI (1)	162	(70)
15	**1e** (5)	KI (5)	162	57
16	**1e** (1)	NaI (1)	150	(19)
17	**1e** (1)	LiI (1)	150	(44)
18	**1f** (3)	ZnI_2 (3)	162	60
19	**1f** (3)	KI (3)	162	(45)
20	**12** (1)	ZnI_2 (2)	162	70
21	**13** (1)	ZnI_2 (1)	162	32

[a] Reaction conditions: $PdCl_2(PhCN)_2$ (1 mol%), LiCl (0.2 equiv), and $Ti(OPr^i)_4$ (0.5 equiv) in 2-methoxyethyl ether under nitrogen for 1 h. [b] Isolated yield. Value in parentheses indicates GLC yield. [c] Without $Ti(OPr^i)_4$. [d] Without LiCl. [e] Without $[PdCl_2(PhCN)_2]$.

above, to supply chloride ion for stabilization of the Pd(0) species.[7] On the other hand, one of the possible functions of $Ti(OPr^i)_4$ may be acceleration of the reduction of $[PdCl_2(PhCN)_2]$ to the Pd(0) species.[10]

An advantageous point of the present method as a route to iodonaphthalenes appears to be that it can be avoided to use highly toxic naphthylamines, as well as the ready availability of the starting materials.

1-3. Experimental Section

^{1}H NMR spectra were recorded at 400 MHz with $CDCl_3$ as solvent. MS data were obtained by EI. GLC analysis was carried out using a silicone OV-17 glass column (i.d. 2.6 mm X 1.5 m) or with a CBP-1 capillary column (i.d. 0.5 mm X 25 m).

Dichlorobis(benzonitrile)palladium,[2] sulfonyl chlorides **1d,f-g**[2], **12**[2], and **13**,[2] and arenethiosulfonates **4h-i**,[11] **4j**,[12] and **4k**[13] were prepared by the methods reported previously. Other starting materials were commercially available.

Desulfonylative Carbonylation of Arenesulfonyl Chlorides 1 and Aryl Arenethiosulfonates 4 in the Presence of Ti(OPr^i)$_4$ and the Product Analysis. The methods were essentially the same as those described previously.[2]

Desulfonylative Carbonylation of Arenethiosulfonates 4 in the Absence of Ti(OPr^i)$_4$. A mixture of **4** (1.0 mmol), $PdCl_2$ (11 mg, 0.06 mmol), CuI (38 mg, 0.2 mmol), LiCl (17 mg, 0.4 mmol) and THF (8 cm^3) was added into a 50 cm^3 stainless steel autoclave with a glass inserted tube. Then, carbon monoxide (10 atm at room temperature) was charged and the mixture was magnetically stirred at 170 °C for 1.5 h. After cooling, the reaction mixture was poured into water and extracted with ether. The products were isolated by column chromatography on silica gel using hexane-benzene as eluent. The thioester **8h** had m.p. 123-123.5 °C (lit.[14] 123.8 °C). The thioester **8i** had m.p. 123.5-125 °C (lit.[15] 125.5-126.2 °C). The thioester **8j** was an oil: MS *m/z* 194 (M^+); ^{1}H-NMR δ 0.95 (t, 3H, J = 7.3 Hz), 1.46 (tq, 2H, J = 7.3, 7.3 Hz), 1.66 (tt, 2H, J = 7.3, 7.3 Hz), 3.08 (t, 2H, J = 7.3 Hz), 7.42-7.46 (m, 2H), 7.54-7.58 (m, 1H), 7.96-7.99 (m, 2H). The thioester **8k** was an oil: MS *m/z* 228 (M^+); ^{1}H-NMR δ 4.32 (s, 1H), 7.23-7.98 (m, 10H).

Desulfonylation of Arenethiosulfonates 4. A mixture of **4** (1.0 mmol), $PdCl_2$ (5 mg, 0.03 mmol), and LiCl (4 mg, 0.1 mmol) in 2-methoxyethyl ether (5 cm^3) was refluxed with stirring for 1.5 h under nitrogen. The reaction mixture was poured into water and extracted with ether. Product identification and quantification were made by GLC-MS and GLC analyses.

Desulfonylative Iodination of Arenesulfonyl Chlorides 1. A mixture of **1** (2 mmol), zinc iodide (2 mmol, 638 mg), dichlorobis(benzonitrile)palladium (0.02 mmol, 7.7 mg), lithium chloride (0.4 mmol, 17.0 mg), and titanium(IV) isopropoxide (1 mmol, 284 mg) in 2-methoxyethyl ether (5 cm^3) was stirred at 150 °C under nitrogen (1 atm) for 1 h. The resulting mixture was poured into dilute hydrochloric acid and extracted with diethyl ether. The organic layer was dried over sodium sulfate and evaporated. Iodides **11** were isolated by column chromatography on silica gel using dichloromethane-hexane as eluent.

1-Iodonaphthalene (11a): Colorless oil; ^{1}H-NMR δ 7.18 (t, 1H, J = 8.3 Hz), 7.49-7.59 (m, 2H), 7.75-7.78 (m, 1H), 7.83 (d, 1H, J = 8.3 Hz), and 8.08 (dd, 2H, J = 1.0 and 8.3 Hz); MS *m/z* 254 (M^+).

1-Chloro-4-iodonaphthalene (11d): mp 50.0-51.0 °C (lit.[16] 52.5-53.8 °C); ^{1}H-NMR δ 7.30 (d, 1H, J = 7.8 Hz), 7.60-7.66 (m, 2H), 7.99 (d, 1H, J = 7.8 Hz), 8.09-8.14 (m, 1H),and 8.21-8.26 (m, 1H); MS *m/z* 288, 290 (M^+).

2-Iodonaphthalene (11e): mp 51.0-52.0 °C (lit.[17] 53.0-54.0 °C); ^{1}H-NMR δ 7.46-7.51 (m, 2H), 7.57 (d, 1H, J = 8.8 Hz), 7.70-7.73 (m, 2H), 7.77-7.81 (m, 1H), and 8.24 (d, 1H, J = 1.0 Hz); MS *m/z* 254 (M^+).

2-Iodo-6-methylnaphthalene (11f): mp 147-148 °C (lit.[18] 146-147 °C); ^{1}H-NMR δ 2.49 (s, 3H), 7.32 (dd, 1H, J = 1.5 and 8.3 Hz), 7.48 (d, 1H, J = 8.3 Hz), 7.55 (s, 1H), 7.61 (d, 1H, J = 8.3 Hz), 7.66 (dd, 1H, J = 1.5 and 8.3 Hz), and 8.17 (s, 1H); MS *m/z* 268 (M^+).

1, 5-Diiodonaphthalene (14): mp 151-152 °C (lit.[19] 147 °C); ^{1}H-NMR d=7.26 (t, 2H, J = 7.8 Hz), 8.13 (d, 2H, J = 7.8 Hz), and 8.14 (d, 2H, J = 7.8 Hz); MS m/z 380 (M^+).

2, 6-Diiodonaphthalene (15): mp 199-201 °C (lit.[20] 203-204 °C); ^{1}H-NMR δ 7.45 (d, 2H, J = 8.8 Hz), 7.72 (dd, 2H, J = 1.3, 8.8 Hz), and 8.18 (s, 2H); MS *m/z* 380 (M^+).

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10 Palladium black was precipitated on treatment of $[PdCl_2(PhCN)_2]$ (0.02 mmol) with $Ti(OPr^i)_4$ (1.0 mmol) in bis(2-methoxyethyl) ether (5 cm^3) at 60 ^oC for 5 min. Without $Ti(OPr^i)_4$, no precipitation occurred at the same temperature, but it was formed by refluxing the solvent for 5 min. These results suggest that both $Ti(OPr^i)_4$ and the solvent can reduce the divalent palladium complex to palladium(0) species, the former being relatively more effective. In the presence of LiCl, the Pd(0) species may be stabilized by LiCl as described and react with **1** without the formation of the metallic palladium.

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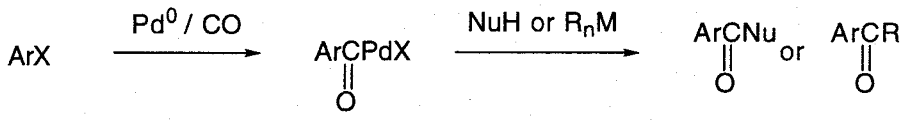
Chapter 2. Effect of Copper-Cocatalysts on the Palladium-Catalyzed Carbonylation of Iodobenzene

2-1. Introduction

As described in the general introduction, palladium-catalyzed carbonylation of aryl halides is a highly useful tool for preparation of a variety of aromatic carbonyl compounds.[1] The reaction involves aroylpalladium species as the common intermediates which react with nucleophiles and organometallic reagents to give the corresponding products (eq 2-1). In the case using amines or alcohols as the nucleophiles, it has been reported that two CO molecules can also be incorporated to the substrates under pressurized conditions to afford α-keto amides[2] or α-keto esters[3] along with normal amides or esters.



$$\mathrm{ArX} \xrightarrow{\mathrm{Pd^0 / CO}} \mathrm{Ar}\underset{\underset{\displaystyle \mathrm{O}}{\|}}{\mathrm{C}}\mathrm{PdX} \xrightarrow{\mathrm{NuH\ or\ R_nM}} \mathrm{Ar}\underset{\underset{\displaystyle \mathrm{O}}{\|}}{\mathrm{C}}\mathrm{Nu} \ \text{or}\ \mathrm{Ar}\underset{\underset{\displaystyle \mathrm{O}}{\|}}{\mathrm{C}}\mathrm{R}$$

(2-1)

We have found that arenesulfonyl chlorides and thiosulfonates also undergo palladium-catalyzed alkoxycarbonylation in the presence of titanium(IV) tetraalkoxides accompanied by desulfonylation to give the corresponding esters along with diaryl disulfides (see chapter 1). Interestingly, addition of CuI to the reaction as a cocatalyst considerably increased the yield of the carbonylation products, suppressing the formation of the disulfides. We have suggested that one of the possible roles of CuI added might be acceleration of the catalytic step(s) after the arylpalladium intermediate formation, *i. e.* the CO insertion to the intermediate and/or the reaction of the resulting aroylpalladium species with the nucleophiles (eq 2-2). During a further study of the effect of copper salts in the palladium-catalyzed carbonylation reactions, it was found that CuI could also promote the carbonylation of aryl iodides using ethanol, phenol, and diethylamine as the nucleophiles (eq 2-3).[4] Particularly, in the reaction

$$\mathrm{PdAr(X)L_2} \xrightarrow{\mathrm{CO}} \mathrm{Pd(COAr)(X)L_2} \xrightarrow{\mathrm{NuH}} \mathrm{ArCONu} + \mathrm{Pd(0)} \qquad (2\text{-}2)$$

$$\mathrm{ArI} + \mathrm{NuH} \xrightarrow[\text{Base}]{\mathrm{CO / PdCl_2(PPh_3)_2 / CuI / (LiX)}} \mathrm{ArCONu} \left(+ \mathrm{ArCOCONR_2} \right) \qquad (2\text{-}3)$$

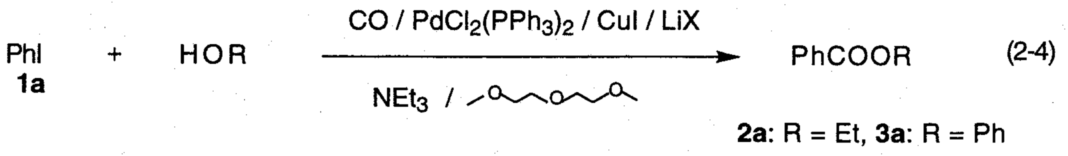
$$\mathrm{NuH = ROH,\ R_2NH}$$

using diethylamine, the corresponding α-keto amides were formed in enhanced yields in the presence of CuI even under 1 atm of CO.

It is known that in palladium-catalyzed carbonylations of alcohols,[5] alkenes,[6] and alkynes[7] under oxidative conditions using molecular oxygen to give oxalates, saturated carboxylic acid esters, and unsaturated dicarboxylic acids, respectively, copper salts can act as co-catalysts. However, copper species have never been, to our knowledge, effectively used under reductive carbonylation conditions. Consequently, we have made a detailed investigation into the carbonylation of iodobenzene by using a combination of $PdCl_2(PPh_3)_2$ and CuI in the presence of the three kinds of nucleophiles. Other metal species in place of CuI have also been tested; $Fe(CO)_5$ has been found to be capable of being used as well as copper halides.

2-2. Results and Discussion

Ethoxy- and Phenoxy-carbonylations of Iodobenzene (1a). When **1a** (2 mmol) was treated with ethanol (2.4 mmol) in the presence of $PdCl_2(PPh_3)_2$ (0.06 mmol) and NEt_3 (2.4 mmol) in 2-methoxyethyl ether (5 cm^3) under CO (10 atm) at 110 ^oC for 15 h, ethyl benzoate (**2a**) was formed in a yield of 26 %, the conversion of **1a** being 45% (eq 2-4 and Table 2-1).



Addition of CuI (0.2 mmol) together with LiCl (0.4 mmol) to the reaction significantly increased the conversion of **1a** and the yield of **2a**. In the absence of LiCl the increase in the ester yield was reduced. The role of the lithium salt may be that it effectively solubilizes CuI into the solvent.[8] In each reaction, a trace amount of N, N-diethylbenzamide (1-3 %) was also formed as a by-product.

Table 2-1. Ethoxy- and Phenoxy-Carbonylations of Iodobenzene 1a[a]

ROH	Conditions[b]	CuI	LiX	Conv of **1a** /%[c]	Yield of ester /%[c]
EtOH	A	-	-	45	26
		+	-	65	34
		+	+	78	47
PhOH	B	-	-	18	15
		+	+	60	60

[a] Reaction conditions: **1a** (2 mmol), $PdCl_2(PPh_3)_2$ (0.06 mmol), CuI (0.2 mmol), in 2-methoxyethyl ether (5 cm^3). [b] A: LiCl (0.4 mmol), EtOH (2.4 mmol), NEt_3 (2.4 mmol), under CO (10 atm) at 110 °C for 15 h. B: LiI (0.4 mmol), PhOH (4 mmol), NEt_3 (4 mmol), under CO (1 atm) at 60 °C for 5 h. [c] Determined by GLC based on **1a** used.

In the carbonylation reaction of **1a** with phenol in place of ethanol under CO (1 atm) at 60 °C for 5 h, phenyl benzoate (**3a**) was formed as the sole carbonylation product (eq 2-4). The reaction also remarkably promoted by CuI•2LiCl. Since the reaction with phenol proceeded smoothly and quantitatively under 1 atm of CO, its kinetic analysis was carried out. It has been recognized that alkoxycarbonylation of active halides like aryl iodides catalyzed by palladium-phosphine complexes involves rate-determining alcoholysis of intermediary aroylpalladium complexes.[3b, 9] In consistent with this, when the time course of the reaction with 10-fold excess amount of each of phenol and NEt_3 in the presence or absence of the cocatalyst was monitored by GLC, the yield of the ester was found to increase linearly with the reaction time up to ca. 70 % conversion of **1a** (Figure 2-1). With 2 equiv of each of phenol and NEt_3, the plot of 1/c (c=[PhOH]=[NEt_3]) *vs* time was linear with a slope which may correspond to a second order rate constant. By using this constant, the effect of the ratio of copper to palladium on the reaction rate was examined (Figure 2-2). The rate constant increased significantly up to Cu/Pd=0.5:1 and on further increasing the ratio, it was almost invariant.

Carbonylative Polymerization of Bis(4-iodophenyl) Ether (4) with Bisphenols 5. It has been recently demonstrated that palladium-catalyzed phenoxycarbonylation may be applied to the synthesis of wholly aromatic heat resistant polyesters by using aromatic dihalides and bisphenols as the substrates.[10] Consequently, carbonylative polymerization reaction of diiodide **4** with bisphenols **5a-c** was examined with the present catalyst system of $PdCl_2(PPh_3)_2$ / CuI (eq 2-5

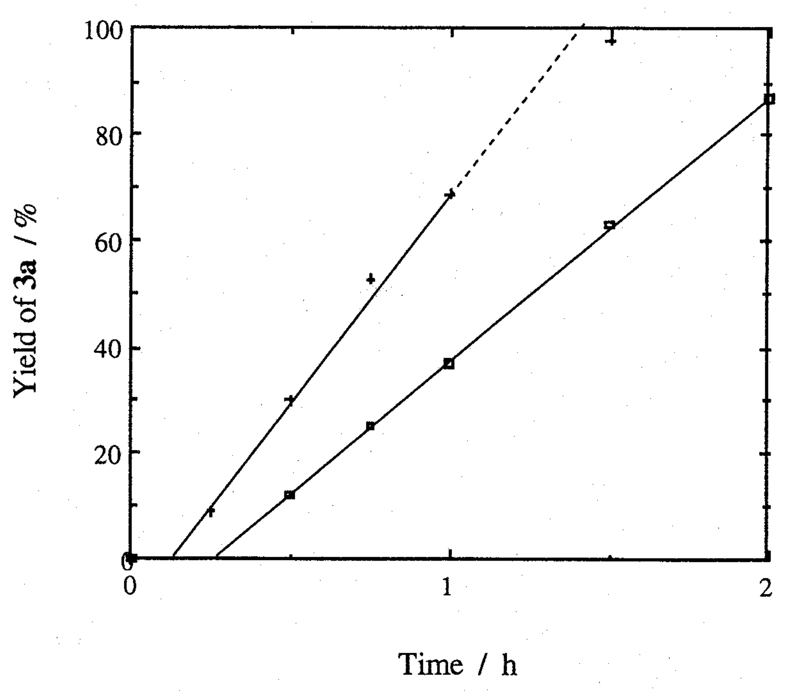


Figure 2-1. Time course of the reaction of **1a** with excess amount of each of PhOH and NEt_3. Reaction conditions: **1a** (2 mmol), $PdCl_2(PPh_3)_2$ (0.06 mmol), CuI (0.2 mmol), LiI (0.4 mmol), PhOH (20 mmol), NEt_3 (20 mmol). Reaction in the presence (+) or absence (□) of CuI•2LiI.

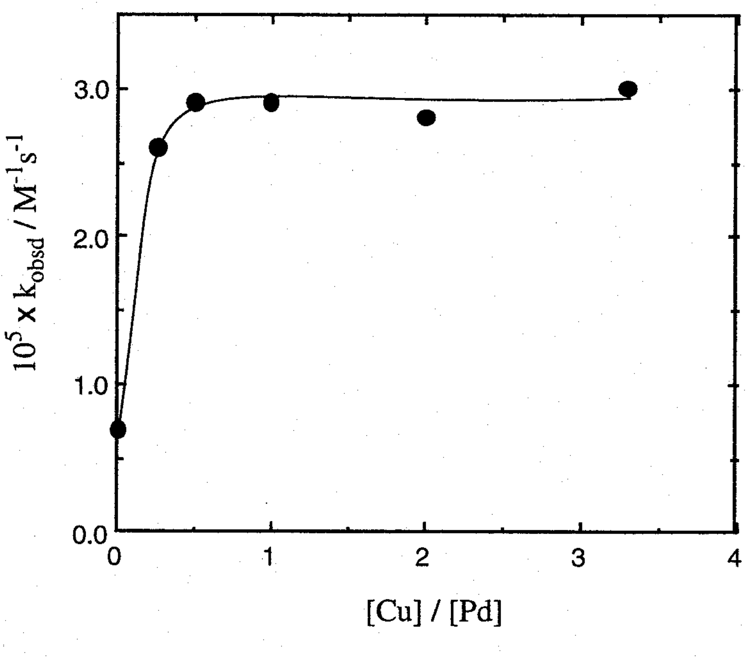
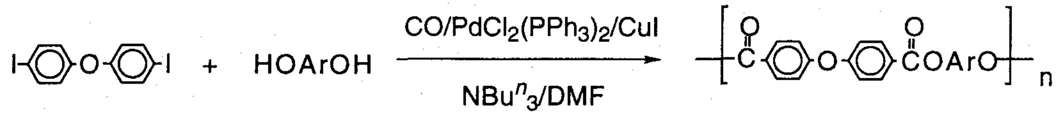


Figure 2-2. Effect of the Cu/Pd ratio on the reaction of **1a** with phenol. Reaction conditions: **1a** (2 mmol), $PdCl_2(PPh_3)_2$ (0.06 mmol), LiI (0.4 mmol), PhOH (4 mmol), NEt_3 (4 mmol), in 2-methoxyethyl ether under CO (1atm) at 60 °C.

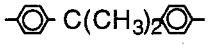
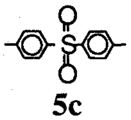
and Table 2-2). When the reaction of **4** (2 mmol) and bisphenol **5a** (2 mmol) using $PdCl_2(PPh_3)_2$ (0.12 mmol) and $NBu^n{}_3$ (4.8 mmol) in DMF under 1 atm of carbon monoxide at 90°C was carried



4 **5** **6** (2-5)

out, polyester **6a** was formed in a yield of 78 % (see Experimental). Gel permeation chromatogram of **6a** indicated that its number-average molecular weight (M_n) and weight-average molecular weight (M_w) values were 12000 and 20000, respectively, for standard polystyrene, the ratio M_w/M_n being 1.7. Interestingly, addition of CuI (0.4 mmol) was found to increase not only the rate of the substrate consumption but also the molecular weight of **6a** to some extent. In this case using DMF as solvent, the reaction was conducted without lithium salts, since CuI is completely solubilized under the conditions employed. The reaction using other bisphenols, 2,2-bis(4-hydoxyphenyl)-hexafluoropropane **5b** and 4,4'-bis(4-hydroxyphenyl)sulfone **5c** also proceeded to afford the corresponding polyesters **6b** and **6c**. The addition of CuI also increased the molecular weight of them.

Table 2-2. Carbonylation of Bis(4-iodophenyl) Ether (4) in the Presence of Bisphenols 5[a]

Ar in **5**	CuI[b]	Yield of **6** / %[c]	k_{obsd} x 10 / $M^{-1}h^{-1}$	M_w[d]	M_w / M_n[d]
 **5a**		78	8.7	20000	1.7
	+	92	18	25000	1.8
 **5b**		82	27	35000	2.4
	+	86	42	40000	2.6
 **5c**		94	35	29000	2.1
	+	94	49	35000	2.3

[a] Reaction conditions: 4 (2 mmol), 5 (2 mmol), $PdCl_2(PPh_3)_2$ (0.12 mmol), CuI (0.4 mmol) and NBu^n_3 (4.8 mmol) in DMF under CO (1 atm) at 90 °C for 22-30 h. [b] Plus sign indicates that the cocatalyst was added. [c] Yield (%) = 100 x {weight of product (mg)} / [2x{(MW of 4)+(MW of 5)+2x28 (CO) -2x128 (HI)}]. IR wave numbers ($\nu_{C=O}$) of **6a**, **6b**, and **6c** were 1735, 1743 and 1740 cm^{-1}, respectively. [d] Determined by GPC as polystyrene equivalent molecular weight.

Diethylaminocarbonylation of 1a. It is known that aryl bromides and iodides undergo carbonylation in the presence of palladium catalysts and secondary amines under pressurized conditions to produce the corresponding mixtures of mono- and di-carbonylated products, *i. e.* amides and α-keto amides.[2] To examine the effect of copper iodide on the product composition as well as the reaction rate, the reaction of **1a** (2 mmol) using $PdCl_2(PPh_3)_2$ (0.06 mmol) and N, N-diethylamine (6 mmol) in the presence or absence of CuI (0.2 mmol) was performed (eq 2-5). It was

$$\underset{\mathbf{1}}{\mathrm{ArI}} + \mathrm{HNEt_2} \xrightarrow[\mathrm{DMF}]{\mathrm{CO\ /\ PdCl_2(PPh_3)_2\ /\ cocat.}} \underset{\mathbf{7}}{\mathrm{ArCOCONEt_2}} + \underset{\mathbf{8}}{\mathrm{ArCONEt_2}} \qquad (2\text{-}6)$$

found that the reaction proceeded efficiently at 50 °C even at 1 atm to give N, N-diethyl-2-phenylglyoxylamide (**7a**) as the major product along with N, N-diethylbenzamide (**8a**) (Table 2-3), while it was very slow in 2-methoxyethyl ether. Under the conditions employed, the plot of the recovery of **1a** *vs* time was linear up to ca. 50 % conversion of **1a**, suggesting that the rate-determining step does not involve the oxidative addition of **1a** to the catalyst, as has been suggested previously.[2b] The reaction was enhanced by the CuI addition as well as that with phenol. In this case, the reaction was conducted without using lithium salt, as for the above polymerization. It should be noted that the product ratio of **7a** to **8a** was essentially constant irrespective of the conversion of **1a**. It was also of interest that the CuI addition considerably increased the selectivity of α-keto amide **7a**. When the reaction was examined using 5 equiv of diethylamine, the corresponding plot of the conversion *vs* time was linear up to ca. 95 % conversion of **1a**, and even in this case, the addition of CuI affected both the reaction rate and the selectivity of **7a** (Table 2-3). Figure 2-3 indicates the effect

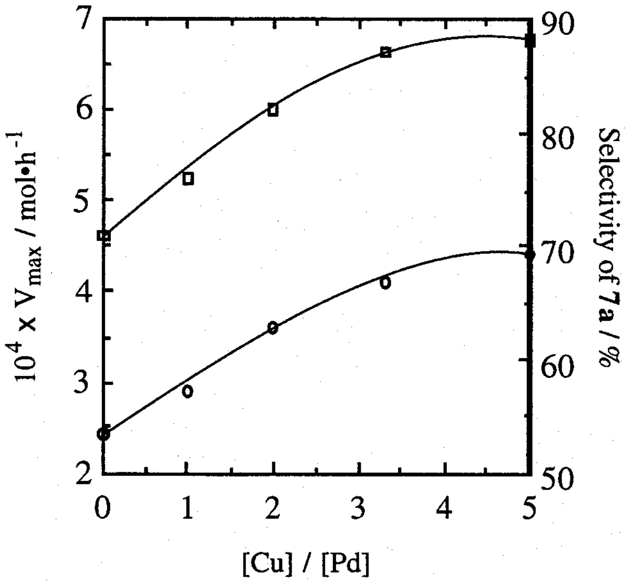


Figure 2-3. Effect of the Cu/Pd ratio on the V_{max} (○) and selectivity of **7a** (☐) in the reaction of **1a** with diethylamine. Reaction conditions: **1a** (2 mmol), $PdCl_2(PPh_3)_2$ (0.06 mmol), Et_2NH (6 mmol), in DMF (5 cm^3) under CO (1 atm) at 50 °C.

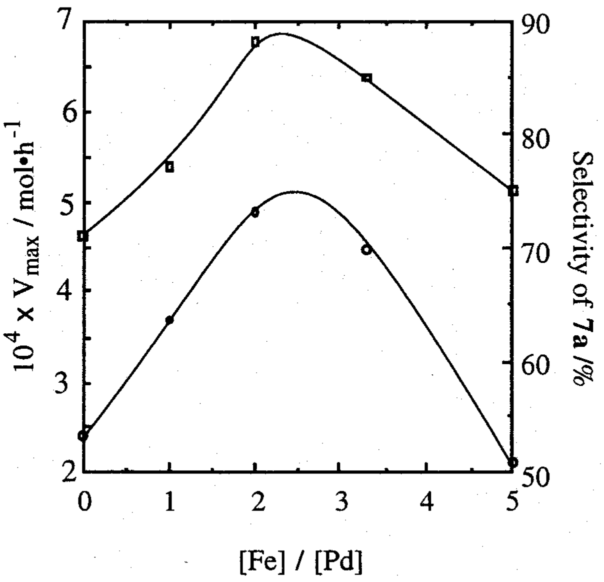


Figure 2-4. Effect of the Fe/Pd ratio on the V_{max} (○) and selectivity of **7a** (☐) in the reaction of **1a** with diethylamine. Reaction conditions: **1a** (2 mmol), $PdCl_2(PPh_3)_2$ (0.06 mmol), Et_2NH (6 mmol), in DMF (5 cm^3) under CO (1 atm) at 50 °C.

of the Cu/Pd ratio on the reaction. On increasing the amount of CuI up to 0.2 mmol, the reaction rate was monotonously increased.

Table 2-3 also summarizes the reaction rate and the ratio of **7a** to **8a** in the presence of several copper salts and metal carbonyls. The other copper salts could also increase both the reaction rate and the ratio of **7a** to **8a** as well as CuI. Among the metal carbonyls tested, $Fe(CO)_5$ was found to be as effective as CuI. It is noted that in the examination of the effect of the ratio of iron to palladium on both the reaction rate and the selectivity of **7a**, the maximum effect was obtained when 2 equiv of

Table 2-3. Diethylaminocarbonylation of 1[a]

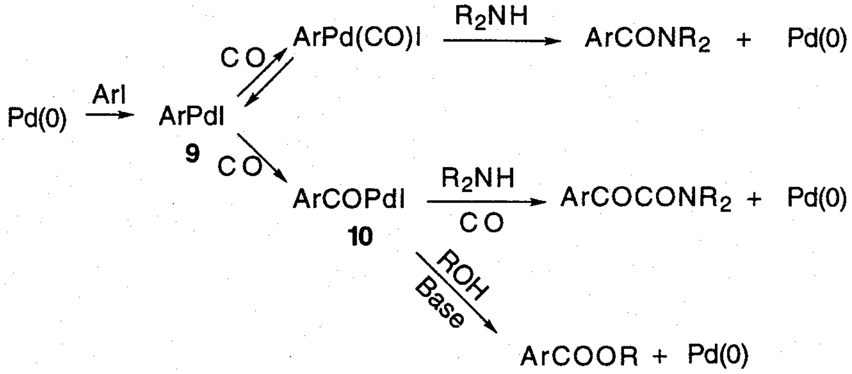
ArI	Cocat.	10^4 x Vmax[c] / mol •h^{-1}	**7** : **8**[b]	Yield of **7** + **8** / %[b]
1a	–	2.4	71 : 29	~100
1a[d]	–	3.9	78 : 22	~100
1a	CuI	4.1	87 : 13	~100
1a[d]	CuI	6.0	89 : 11	~100
1a	CuBr	3.9	85 : 15	~100
1a	CuCl	3.3	84 : 16	~100
1a	$Fe(CO)_5$	4.5	85 : 15	91
1a	$Fe_3(CO)_{12}$	2.9	62 : 38	95
1a	$Co_2(CO)_8$	1.8	70 : 30	97
1a	$Mn_2(CO)_{10}$	6.1	53 : 47	89
1a	$Mo(CO)_6$	3.5	81 : 19	85
1a	$Cr(CO)_6$	2.3	75 : 25	83
1b	–	–[e]	11 : 85	~100
1b	CuI	–[e]	51 : 47	~100
1c	–	–[e]	68 : 30	~100
1c	CuI	–[e]	83 : 17	~100

[a] Reaction conditions: **1a** (2 mmol), $PdCl_2(PPh_3)_2$ (0.06 mmol), cocatalyst (0.2 mmol), Et_2NH (6 mmol), in DMF (5 cm^3) under CO (1 atm) at 50 °C. [b] Determined by GLC based on **1a** used. [c] Maximum reaction rate. [d] Et_2NH (10 mmol). [e] Not determined.

$Fe(CO)_5$ was used (Figure 2-4). Although $Mn_2(CO)_{10}$ increased the reaction rate, the selectivity of **7a** was detrimentally decreased.

The CuI addition also increased the selectivity of the corresponding α-keto amides in the reactions of *p*-chloroiodobenzene (**1b**) and *p*-iodotoluene (**1c**) (Table 2-3).

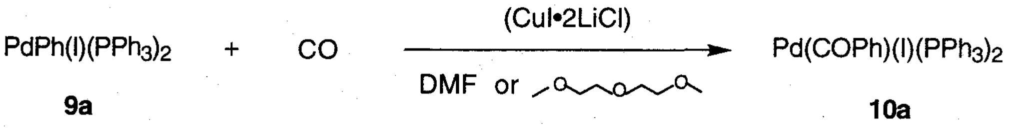
The mechanism to account for the mono- and di-carbonylations of aryl halides in the presence of secondary amines, which has been proposed previously,[2b] is illustrated in Scheme 2-1, where



Scheme 2-1.

phosphine ligands are omitted. When arylpalladium intermediate (**9**) undergoes CO insertion to give aroylpalladium species (**10**), α-keto amide is formed. On the other hand, coordination of CO to **9** followed by reaction with amine affords simple amide. It has also been suggested that (a) the selectivity of α-keto amide increases when the CO insertion of **9** to **10** is enhanced by an electron-donating substituent on aryl halide, and (b) the rate determining step in the transformation of aryl iodides into the corresponding α-keto amides is in the reaction sequence after the formation of **10**, as is alkoxycarbonylation. Therefore, the observed effects of copper halides and $Fe(CO)_5$ on the overall reaction rate and on the selectivity of α-keto amide indicate that the cocatalysts may enhance both the CO insertion of **9** to **10** and the subsequent step. To confirm this, kinetic investigation into the stoichiometric reactions of trans-$PdPh(I)(PPh_3)_2$ (**9a**) and trans-$Pd(COPh)(I)(PPh_3)_2$ (**10a**) as the intermediates in the catalytic reaction were performed in the presence or absence of CuI.

Stoichiometric reactions of 9a and 10a.[11] When **9a** (0.09 mmol) was treated in DMF (15 cm^3) at 19 °C under 1 atm of CO, CO was consumed with a pseudo-first-order rate constant (k_{obsd}) of 2.5×10^{-3} s^{-1} (eq 2-7, Table 2-4 and Figure 2-5). In expectation, addition of CuI (0.3



(2-7)

mmol) with LiCl (0.6 mmol) enhanced the CO uptake, k_{obsd} being $4.5\times10^{-3}\ s^{-1}$. It should be noted that in the presence of CuI without LiCl, more than a stoichiometric amount of CO (ca. 1.3 equiv based on Pd) was absorbed with a larger rate. This appeared to be due to that CuI itself could absorb CO under the conditions. It was indeed confirmed that CuI in DMF absorbed ca. 0.1 equiv of CO based on Cu, whereas in the presence of LiCl, CuI did not react with CO. The CO uptake by **6a** in 2-methoxyethyl ether was also promoted by the addition of CuI•2LiCl (Table 2-4).

Table 2-4. Pseudo-first-order Rate Constants of CO Uptake by 9a[a]

CuI•2LiCl	$10^3 \times k_{obsd}$ / s^{-1}	CuI•2LiCl	$10^3 \times k_{obsd}$ / s^{-1}
-	2.5	-[b]	0.61
+	4.5	+[b]	1.3

[a] Reaction conditions: **9a** (0.09 mmol), CuI (0.3 mmol),LiCl (0.6 mmol), in DMF (15 cm^3) under CO (1 atm) at 19±1 °C. [b] Reaction in 2-methoxyethyl ether (15 cm^3).

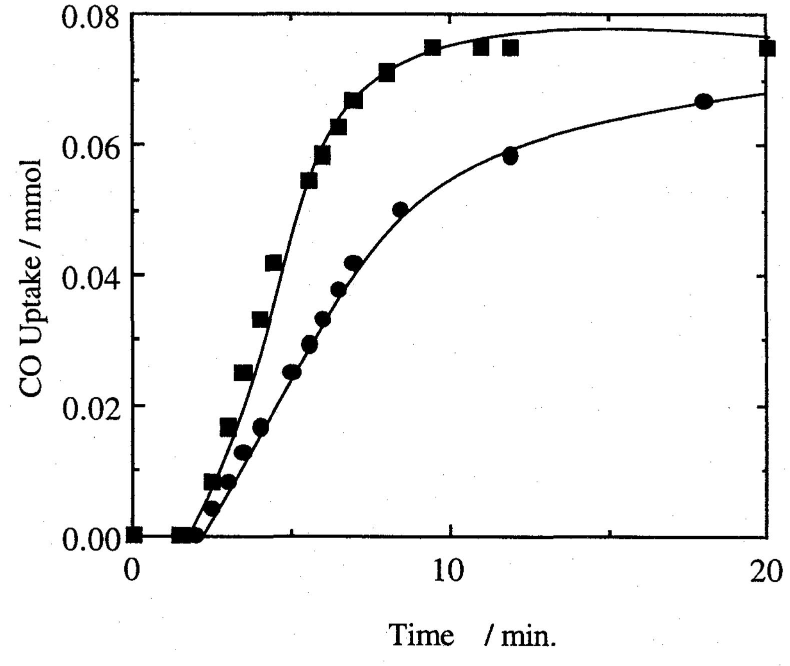


Figure 2-5. Time course of CO uptake of **9a**. Reaction conditions: **9a** (0.09 mmol), CuI (0.3 mmol), LiCl (0.6 mmol), in DMF (15 cm^3) under CO (1 atm) at 19 °C. Reaction in the presence (■) or absence (●) of CuI•2LiCl.

The reaction of **10a** with ethanol, phenol, and diethylamine was examined under pseudo-first-order conditions using 10 equiv of these nucleophiles in DMF (eq 2-8 and Table 2-5). The reaction

$$\underset{\textbf{10a}}{\mathrm{Pd(COPh)(I)(PPh_3)_2}} + \mathrm{NuH} \xrightarrow[\mathrm{(NEt_3)\ /\ DMF}]{\mathrm{CO\ or\ N_2\ /\ CuI}} \mathrm{PhCONu\ \ or\ \ PhCOCONEt_2} \qquad (2\text{-}8)$$

with diethylamine under 1 atm of CO proceeded quantitatively, giving α-keto amide **7a** as a single product.[2b] It was also found that the pseudo-first-order constant of this reaction, which may correspond to the rate-determining step of the double-carbonylation reaction of **1a** with diethylamine as described above, was increased in the presence of CuI.

Similarly, the reactions with ethanol and phenol under nitrogen were promoted by the CuI addition. It is noted that in these reactions, dimethyl maleate was added to prevent the interference by Pd(0) species formed according to the previous report.[3b] These reactions in the presence of CuI terminated within 30 min giving ethyl and phenyl benzoates in 67 % and 97 % yields. Thus, the reaction with ethanol is not quantitative and by contrast, that with phenol is smooth and considerably fast. To determine the exact rate of the formation of these esters, analytical techniques other than GLC should be examined.

Table 2-5. Reaction of 10a with Et_2NH, EtOH, and PhOH[a]

CuI	$10^4 \times k_{obsd}$ / s^{-1}		
	Et_2NH[b]	EtOH[c, d]	PhOH[c]
+	9.7	>6.5	>10
-	2.4	0.082	4.3

[a] Reaction conditions: **10a** (0.1 mmol), CuI (0.1 mmol), NuH (1 mmol), in DMF (5 cm^3) at 20 °C. [b] Under CO (1 atm). [c] Under N_2 in the presence of NEt_3 (1 mmol) and dimethyl maleate (0.4 mmol). [d] At 30 °C.

Role of the cocatalysts. To characterize the product in the stoichiometric reaction of complex **9a** with CO in the presence of CuI·2LiCl, the reaction using **9a** (0.1 mmol), CuI (0.1 mmol), and LiCl (0.2 mmol) was carried out in a volatile solvent, THF. Evaporation of the solvent gave a dark brown solid powder. The IR spectrum of the solid showed a single peak at 1673 cm^{-1} in the carbonyl region, which may be characteristic of a benzoylpalladium species (Table 2-6). It should be noted that the wave number is considerably higher than that of a yellow-coloured sample of **10a** (1636cm^{-1}) which was obtained without the cocatalyst. ^{31}P NMR spectrum of the brown solid in δ_8-THF exhibited two broad signals at 28.0 and 30.1 ppm (1:1) due to the ligand triphenylphosphines, the peaks being in the lower-field relative to a sharp singlet of **10a** (23.6 ppm) as shown in Figure 2-6. The brown material appeared to be able to be formed by mixing **10a** with CuI·2LiCl in THF. The IR spectrum of the powder obtained by this method was completely the same with that obtained from **9a** and CuI•2LiCl under CO as described above. These results indicate that the benzoyl species formed in the presence of CuI·2LiCl is not a simple mixture of **10a** and the cocatalyst.

Table 2-6. IR Data for Benzoylpalladium Species in the Presence or Absence of CuI or Fe(CO)$_5$

Complex	ν(CO) / cm^{-1}	
	Pd(CO)Ph	Fe(CO)
Pd(COPh)(I)(PPh$_3$)$_2$	1636	
PdPh(I)(PPh$_3$)$_2$ + CuI[a]	1673	
Pd(COPh)(I)(PPh$_3$)$_2$ + CuI[a]	1673	
PdPh(I)(PPh$_3$)$_2$ + Fe(CO)$_5$[b]	1669	1931, 1973
Pd(COPh)(I)(PPh$_3$)$_2$ + Fe(CO)$_5$[b]	1669	1931, 1973
Fe(CO)$_5$		1999, 2022
Fe(CO)$_3$(PPh$_3$)$_2$		1873, 1887

[a] Dark brown solid formed when a mixture of Pd complex and CuI •2LiCl (Pd/Cu=1:1) was stirred under CO at room temperature for 1 h followed by elimination of the solvent under vacuum. [b] Dark brown solid formed when a mixture of complexes (Pd/Fe=1:2), NEt$_3$, and THF was stirred under nitrogen at 50 °C for 1 h followed by elimination of the solvent under vacuum.

Reaction of **9a** in the presence of Fe(CO)$_5$ in THF gave a dark brown powder which showed a IR absorption band at 1669 cm^{-1}, as did the reaction with CuI. In this case, two major peaks, which may be due to the terminal CO molecules coordinated to the iron center, were also observed at 1931 and 1973 cm^{-1} along with two minor ones at 1900 and 2049 cm^{-1} (Table 2-6). The powder obtained by mixing **10a** and Fe(CO)$_5$ gave essentially the same IR spectrum. These major IR peaks due to the terminal CO are placed between those of Fe(CO)$_5$ itself (1999 and 2022 cm^{-1}) and of

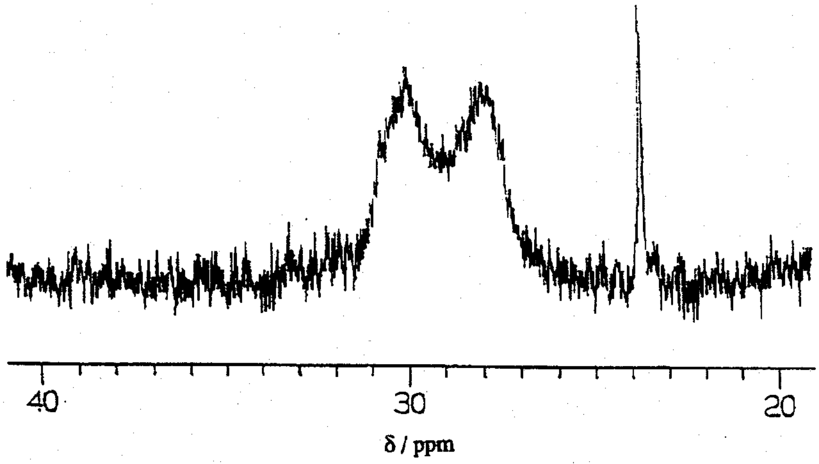


Figure 2-6. ^{31}P NMR spectrum of the benzoylpalladium species formed in the presence of CuI•2LiCl in d_8-THF at room temperature (161.9 MHz; chemical shifts are referenced to external PPh_3).

$Fe(CO)_3(PPh_3)_2$ (1873 and 1887 cm^{-1}). Furthermore, two carbonyl peaks at 1931 and 1973 cm^{-1} were again observed when $Fe(CO)_5$ and 1 equiv of PPh_3 were mixed in THF at room temperature. Under these conditions, $Fe(CO)_4(PPh_3)$ may be expected to be generated. It should be cited that $PhCOPd(I)PPh_3 \cdot$toluene and $(PhCOPd(\mu\text{-}I)(PPh_3))_2$ have been reported to show their IR absorption bands at 1660[12] and 1665 cm^{-1},[13] respectively. Thus, these results may suggest that the treatment of either **9a** or **10a** with $Fe(CO)_5$ involve transfer of one of the two phosphine ligands coordinated to the palladium complex to the iron center. In the treatment with CuI, a similar transfer of the ligand to the copper species seems to take place.

The above observations led us to deduce that the catalytic carbonylation of **1** in the presence of the cocatalysts involves intermediary palladium complexes having one PPh_3. Consequently, the carbonylation reaction of **1a** (2 mmol) with diethylamine (6 mmol) under CO (1 atm) in DMF at 50 ^{o}C was examined in the presence of 0.06 mmol of each of $PdCl_2(PhCN)_2$ and PPh_3 (eq 2-9 and Table 2-7). Under these conditions, a catalytically active species which contains 1 equiv of PPh_3

$$\underset{\mathbf{1a}}{\text{PhI}} + \text{HNEt}_2 \xrightarrow[\text{DMF}]{\text{CO / PdCl}_2\text{(PhCN)}_2\text{+nPPh}_3\text{ / cocat.}} \underset{\mathbf{7a}}{\text{PhCOCONEt}_2} + \underset{\mathbf{8a}}{\text{PhCONEt}_2} \qquad (2\text{-}9)$$

ligand may be expected to be generated *in situ*. In this reaction, addition of CuI (0.2 mmol) or $Fe(CO)_5$ (0.12 mmol) increased the reaction rate and the selectivity of **7a** as well as in the reaction using 2 equiv of PPh_3 (0.12 mmol). It should be noted that a high selectivity of **7a** more than 90 % was achieved concurrently with an enhanced rate by using the present catalyst system of $PdCl_2(PhCN)_2$-PPh_3-CuI or $Fe(CO)_5$ under 1atm of CO. When the reaction using $PdCl_2(PhCN)_2$ without addition of PPh_3 was examined, the reaction mixture was gradually darkened with the deposition of palladium black. Even in the presence of CuI or $Fe(CO)_5$, the reaction was not completed after 72 h.

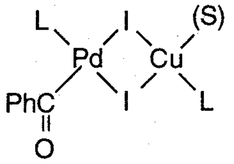
Table 2-7. Diethylaminocarbonylation of 1a Using $PdCl_2(PhCN)_2$, $nPPh_3$, and Co-Catalyst[a]

Cat.	Cocat.	10^4 x Vmax[b] / mol•h^{-1}	**7a : 8a**[c]	Yield of **7a+8a** / %[c]
$PdCl_2(PhCN)_2$	-	1.5[d]	97 : 3	65
$PdCl_2(PhCN)_2$ + PPh_3	-	2.2	79 : 21	97
$PdCl_2(PhCN)_2$ + $2PPh_3$	-	1.6	75 : 25	92
$PdCl_2(PhCN)_2$	CuI	1.6[d]	97 : 3	75
$PdCl_2(PhCN)_2$ + PPh_3	CuI	4.0	92 : 8	94
$PdCl_2(PhCN)_2$ + $2PPh_3$	CuI	3.2	86 : 14	97
$PdCl_2(PhCN)_2$	$Fe(CO)_5$	1.6[d]	86 : 14	42
$PdCl_2(PhCN)_2$ + PPh_3	$Fe(CO)_5$	3.4	95 : 5	86
$PdCl_2(PhCN)_2$ + $2PPh_3$	$Fe(CO)_5$	4.1	84 : 16	81

[a] Reaction conditions: **1a** (2 mmol), $PdCl_2(PPh_3)_2$ (0.06 mmol), CuI (0.2 mmol) or $Fe(CO)_5$ (0.12 mmol), Et_2NH (6 mmol), in DMF (5 cm^3) under CO (1 atm) at 50 °C for 24 h. [b] Maximum reaction rate. [c] Determined by GLC. [d] The reaction was not completed even after 72 h.

There have been several reports that CuI can promote the Stille type reaction, *i. e.* palladium-catalyzed cross-coupling reaction of aryl halides or triflates with organotin compounds, while the role of the copper species has not been well understood.[14] Liebeskind and Fengl[14a] suggested a possibility that CuI added facilitated the transmetallation step (Sn→Cu→Pd) in the cross-coupling of stannylcyclobutenediones with aryl iodides using a combination of $(PhCH_2)(Cl)Pd(PPh_3)_2$ and CuI. It is also known that palladium-catalyzed reaction of aryl halides with terminal alkynes is enhanced by CuI.[15] A plausible explanation for this may be that copper (I) acetylides are generated in the reaction medium as the reaction intermediates. Hobbs[16] noted that in the alkynylation of iodonucleosides using a catalyst system of $Pd(PPh_3)_4$-CuI, CuI might remove two PPh_3 ligands from the palladium complex to promote the reaction.

In the present carbonylation reaction, however, the results described above may suggest that the role of copper halides and $Fe(CO)_5$ is not only to remove one PPh_3 ligand from the intermediary palladium complexes **9a** and **10a**, but to form more reactive intermediates in which the cocatalysts coordinated by one PPh_3 ligand are involved in the palladium coordination sphere. Consequently, a further characterization of the brown solid obtained from the mixture of **10a**, CuI, and LiCl has been attempted. Since it was soluble in THF or methylene chloride, it was purified by recrystallization from THF-hexane. As a result, a dark brown solid powder which shows a benzoyl C=O band at 1673 cm^{-1} in the IR spectrum was obtained. Attempted further crystallization appropriate for X-ray structural analysis was unsuccessful, although quantitative XPS analysis of it indicated that it contained palladium, copper, and phosphorus atoms. Thus, the structure of this species has not yet been definitive. However, the species



L=PPh_3 (S)=CO, amine, solvent, X^-, or other ligand

which is analogous to $[(PhCO)Pd(PPh_3)(\mu\text{-}I)]_2$ isolated by Alper *et al.* previously,[13] might be postulated as one of the possible candidates for the solid obtained, because the ^{31}P NMR spectrum of the palladium dimer with two iodo-bridges at room temperature was reported to exhibit similar two broad signals due to interconversion between the cis- and trans-isomers. The corresponding arylpalladium species may also be expected to be involved in the present catalytic carbonylation reactions. It is conceivable that these iodo-bridges may be cleaved easily[17] to provide relatively more reactive species than the corresponding palladium species tightly coordinated by two PPh_3 ligands. Thus, the catalytic reaction involving these intermediates may be expected to proceed more efficiently. It should be pointed out that in the catalytic phenoxycarbonylation, 0.5 equiv of CuI was sufficiently effective (Figure 2-2). Therefore, in a less polar solvent such as 2-methoxyethyl ether, it might also be possible to form intermediate(s) consisting of Pd and Cu in 2:1 ratio. On the other hand, since addition of CuI more than 1 equiv was more favorable in the diethylaminocarbonylation in DMF as shown in Figure 2-3, an excess amount of CuI must be needed for the complete formation of the reactive species in the presence of the amine in the polar solvent.

In the benzoylpalladium species formed in the presence of $Fe(CO)_5$, the mode of the interaction between palladium and iron species is difficult to be described: CO, PPh_3, and iodo-bridged species would be possible.

2-3. Experimental Section

Infrared spectra were obtained by using KBr pellets for solid samples and KRS-5 plates for liquid materials. ^{31}P-NMR spectra were obtained for δ_8-THF solutions. The signals were referenced to PPh_3 as an external standard (downfield positive). MS spectra were obtained by EI. GLC analysis was carried out using a silicon OV-17 column (i. d. 2.6 mm × 1.5 m) or with a CBP-1 capillary column (i. d. 0.5 mm × 25 m). XPS spectra were obtained with MgKα radiation (15kV-20mA).

Complexes $PdCl_2(PPh_3)_2$,[1] $PdCl_2(PhCN)_2$,[17] $PdPh(I)(PPh_3)_2$,[18] $Pd(COPh)(I)(PPh_3)_2$,[11] and $Fe(CO)_3(PPh_3)_2$,[19] and diiodide **4**[20] were prepared by the methods reported previously. Other starting materials were commercially available. Solvents were purified by standard methods before use.

Ethoxycarbonylation of Iodobenzene (1a). A mixture of **1a** (408 mg, 2 mmol), $PdCl_2(PPh_3)_2$ (42 mg, 0.06 mmol), CuI (38 mg, 0.2 mmol), LiCl (17 mg, 0.4 mmol), ethanol (0.14 cm^3, 2.4 mmol), NEt_3 (0.33 cm^3, 2.4 mmol), and 2-methoxyethyl ether (5 cm^3) was added into a 50 cm^3 stainless steel autoclave with a glass tube. Then, carbon monoxide (10 atm at room temperature) was charged and the mixture was magnetically stirred at 110 °C for 15 h. After cooling, the reaction mixture was poured into water and extracted with ether. Product identification and quantification were made by GLC-MS and GLC analyses.

Carbonylation of Bis(4-iodophenyl) Ether (4) in the Presence of Bisphenols 5a-c. A mixture of **4** (844 mg, 2 mmol), **5** (2 mmol), $PdCl_2(PPh_3)_2$ (84 mg, 0.12 mmol), and CuI (76 mg, 0.4 mmol) in DMF (5 cm^3) was stirred under CO (1 atm) at 90 °C for 5 min and then, a DMF (5 cm^3) solution containing NBu^n_3 (1.14 cm^3, 4.8 mmol) and 1-methylnaphthalene as internal standard was added. The resulting mixture was stirred at 90 °C for 22 h. Irrespective of the bisphenols used, precipitation of the product polyester was not observed during the reaction. The time course of the substrate consumption was also monitored by GLC. After cooling, the reaction mixture was poured into methanol (100 cm^3). The precipitated polymer was filtered, washed with methanol (100 cm^3), and dried at room temperature in vacuo to give polyester **10**. The number-average molecular weight (M_n) and the weight-average molecular weight (M_w) of **10** were determined by means of gel permeation chromatography (GPC) using DMF containing 0.01 mol/dm^3 of LiBr as eluent on the basis of polystyrene calibration.

Diethylaminocarbonylation of Aryl Iodides 1. A mixture of **1** (2 mmol), $PdCl_2(PPh_3)_2$ (42 mg, 0.06 mmol), CuI (38 mg, 0.2 mmol), diethylamine (0.62 cm^3, 6 mmol), 1-methylnaphthalene as an internal standard, and DMF (5 cm^3) was stirred under CO (1 atm) at 50 °C. The time course of the reaction was monitored by GLC.

Stoichiometric reaction. (a) Reaction of $PdPh(I)(PPh_3)_2$ (9a) with CO. In a 100 cm^3 two-necked flask equipped with a stirrer, a carbon monoxide inlet tube, and a dropping funnel containing DMF (15 cm^3), **9a** (75 mg, 0.09 mmol) and CuI (57 mg, 0.3 mmol) were placed. After the apparatus was flushed with carbon monoxide and allowed to come to equilibrium at 1 atm of pressure, DMF was injected into the reaction flask, and then the mixture was stirred at 19±1 °C. Consumed gas volume with time was measured using a gas buret.

(b) Reaction of $Pd(COPh)(I)(PPh_3)_2$ (10a) with Diethylamine. After a mixture of **10a** (86 mg, 0.1 mmol), CuI (19 mg, 0.1 mmol), and DMF (3 cm^3) was stirred under CO (1 atm) at 20 °C for 9 min to turn into a yellow-coloured homogeneous solution, a DMF (2 cm^3) solution containing diethylamine (0.10 cm^3, 1 mmol) and 1-methylnaphthalene as an internal standard was added and then, the mixture was stirred at 20 °C. The amount of *N, N*-diethyl-2-phenylglyoxylamide (**7a**) produced was measured by means of GLC.

Characterization of Benzoylpalladium Species Formed in the Presence of the Cocatalysts. (a) With CuI·2LiCl. A mixture of **9a** (83 mg, 0.1 mmol), CuI (19 mg, 0.1 mmol), LiCl (8 mg, 0.2 mmol), and THF (5 cm^3) was stirred under CO (1 atm) at room temperature for 1 h. Evaporation of the solvent gave a dark brown solid powder. The results of the IR and ^{31}P-NMR analyses are shown in Table 2-5 and Figure 2-6. After recrystallization of this solid from THF-hexane, its XPS spectrum was measured. It showed peaks due to Cu (2p3/2), Pd (3d5/2), and P (2p) at 935.5, 340.0, and 134.0 eV, respectively. Since Cu (2p3/2) peak was overlapped by a peak due to I (3p1/2), quantitative analysis was unsuccessful.

(b) With $Fe(CO)_5$. A mixture of **9a** (83 mg, 0.1 mmol), $Fe(CO)_5$ (0.026 cm^3, 0.2 mmol), triethylamine (0.14 cm^3, 1 mmol), and THF (5 cm^3) was stirred under nitrogen at 50 °C for 1 h. Evaporation of the solvent gave a dark brown solid powder. The results of the IR analysis are shown in Table 2-6.

2-4. References and Notes

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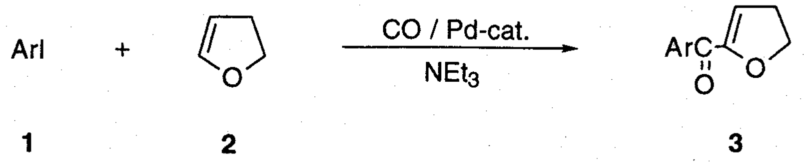
Chapter 3. Palladium-Catalyzed Cross-Carbonylation of Aryl Iodides with Five-Membered Cyclic Olefins

3-1. Introduction

In the palladium-catalyzed carbonylation of aryl halides, reaction of aroylpalladium species as the common intermediate with nucleophiles and organometallic reagents affords the corresponding carbonylation products,[1] as mentioned previously. Particularly of interest in these reactions is the Stille type carbonylative coupling reaction of organic halides with organotin compounds which is a valuable synthtic method to unsymmetrical ketones.[1] On the other hand, carbonylation including the addition of the key intermediate to carbon-carbon and carbon-heteroatom multiple bonds, so called acylpalladation, may also be expected to provide effective synthetic routes leading to the carbonyl compounds. For example, intramolecular cyclo-carbonylations of 2-alkenoyl-1-iodobenzenes[2] and haloalkenes[3] have been developed. However, intermolecular cross-carbonylation reaction of aryl halides with olefins or cyclic olefins has been less explored.[4] It has recently reported by our research group that intermolecular cross-carbonylations of aryl iodides with 1-aryl-2-alkyn-1-ones and *N*-benzylideneamines as the unsaturated species efficiently proceed in the presence of palladium complexes using triethylamine as base to afford 3-aroylfuran[5] and 3-aryl-2,3-dihydro-1*H*-isoindol-1-one derivatives,[6] respectively. Palladium-catalyzed carbonylation reactions of aryl iodides in the presence of γ-hydroxyallenes[7] and 2-alkynyltrifluoroacetanilides[8] to give 1-benzoyl-1-(2-tetrahydrofuryl)ethene and 3-aroylindol derivatives have also been recently described. During a further study of new cross-carbonylation, we observed that aryl iodides smoothly undergo carbonylative coupling with three kinds of five-membered cyclic olefins, 2,3- and 2,5-dihydrofurans and cyclopentene, in the presence of palladium catalysts to give the corresponding aryl ketones.

3-2. Results and Discussion

When iodobenzene (**1a**, 3 mmol) was treated with 2,3-dihydrofuran (**2**, 9 mmol) in the presence of $PdCl_2$ (0.12 mmol) and NEt_3 (3.6 mmol) in benzene under CO (5 atm) at 120 ^{o}C for 20 h (eq 3-1; Ar=Ph), 2-benzoyl-4,5-dihydrofuran (**3a**) was formed in 67 % yield based on **1a** used (Entry 1 in Table 3-1). No detectable amounts of 3-benzoylated products and other double-bond



(3-1)

regioisomers were formed. While the use of an excess amount of NEt_3 (7.2 mmol) showed no significant influence on the reaction (Entry 2), a higher product yield of 76 % (Entry 3) was obtained by addition of PPh_3 (0.12 mmol; Pd/P=1.0). Similarly, a combination of $Pd(dba)_2$ (dba: dibenzylideneacetone) with PPh_3 was superior to $Pd(dba)_2$ alone (Entry 6 *vs* 7). However, a further addition of PPh_3 decreased the product yield in both the catalyst systems (Entries 4 and 8). In our previous study of the cross-carbonylation with *N*-benzylideneamines,[6] $PdCl_2(dppf)$ (dppf: 1,2-bis(diphenylphosphino)ferrocene) gave favorable results. The use of this catalyst in the present reaction, however, reduced the yield of the ketone (Entry 9). While a decrease in the CO pressure to 2 atm showed no significant influence on the reaction, an increase to 10 atm considerably reduced the yield of the ketone (Entries 10 and 11). A similar effect was also observed by the use of THF as the solvent (Entry 12). These results indicate that the present reaction is very sensitive to the ligands and solvents.

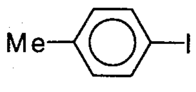
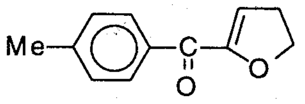
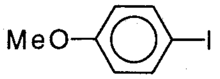
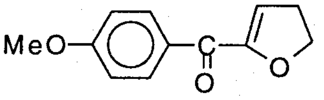
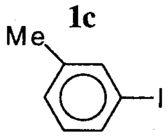
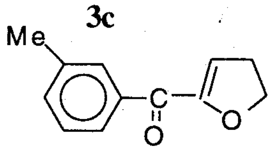
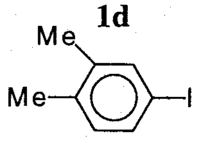
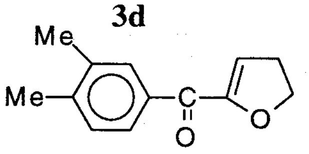
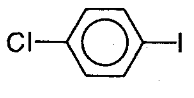
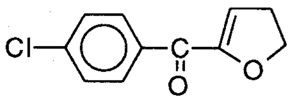
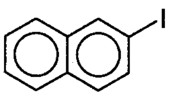
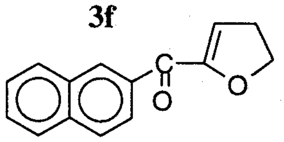
Table 3-1. Cross-Carbonylation of Iodobenzene (1a) with 2,3-Dihydrofuran (2)[a]

Entry	Pd-cat.	Yield of **3a** / %[b]
1	$PdCl_2$	67
2	$PdCl_2$[c]	68
3	$PdCl_2$+1PPh_3[c]	76 (73)[d]
4	$PdCl_2$+2PPh_3[c]	60
5	$Pd(PPh_3)_4$	10
6	$Pd(dba)_2$[e]	40
7	$Pd(dba)_2$+1PPh_3[e]	71
8	$Pd(dba)_2$+2PPh_3[e]	64
9	$PdCl_2(dppf)$[f]	43
10	$PdCl_2$+1PPh_3[g]	64
11	$PdCl_2$+1PPh_3[h]	29
12	$PdCl_2$+1PPh_3[i]	49

[a] Reaction conditions: **1a** (3 mmol), **2** (9 mmol), Pd-cat. (0.12 mmol), NEt_3 (3.6 mmol), in C_6H_6 (5 cm^3) under CO (5 atm) at 120 °C for 20 h. [b] Determined by GLC based on **1a** used. [c] NEt_3 (7.2 mmol). [d] Isolated yield. [e] dba = dibenzylideneacetone. [f] dppf = 1,2-bis(diphenylphosphino)ferrocene. [g] Under CO (2 atm). [h] Under CO (10 atm). [i] In THF (5 cm^3).

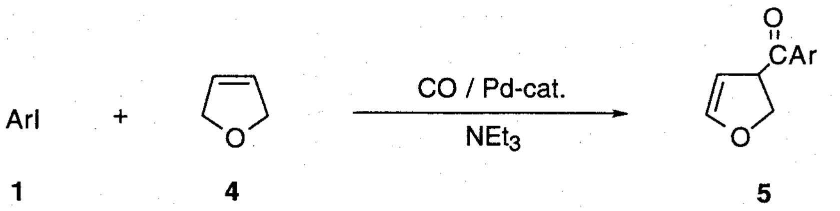
The results of the cross-carbonylations of aryl iodides **1b-g** with **2** using $PdCl_2/PPh_3$ (1:1) are summarized in Table 3-2. From the reactions the corresponding 2-aroyl-4,5-dihydrofurans **3b-g** were isolated in 38-66% yields.

Table 3-2. Cross-Carbonylation of Aryl Iodides 1 with 2[a]

ArI	Product , % yield[b]	
 **1b**	 **3b**	60
 **1c**	 **3c**	66
 **1d**	 **3d**	65
 **1e**	 **3e**	63
 **1f**	 **3f**	38
 **1g**	 **3g**	40

[a] Reaction conditions: **1** (3 mmol), **2** (9 mmol), $PdCl_2$ (0.12 mmol), PPh_3 (0.12 mmol), NEt_3 (7.2 mmol), in C_6H_6 (5 cm^3) under CO (5 atm) at 120 °C for 15-20 h. [b] Isolated yield.

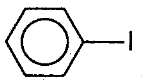
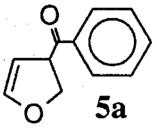
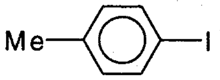
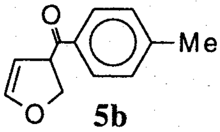
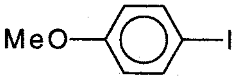
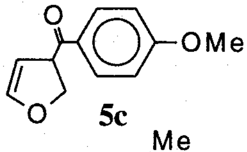
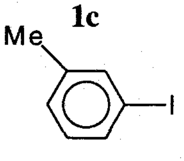
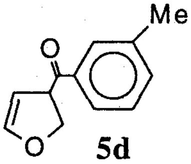
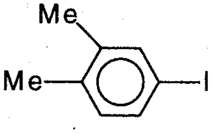
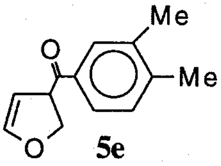
The reaction of **1a** with 2,5-dihydrofuran (**4**) was also examined under similar conditions employed for the reaction with **2** (eq 3-2 and Table 3-3). In this case, 3-benzoyl-2,3-dihydrofuran



(3-2)

(**5a**) was formed as the benzoylation product. The catalyst system of $PdCl_2/PPh_3$ (1:1) was also found to be optimal for the reaction to occur as it was for **2** (see Entry 3 in Table 3-1). Other aryl

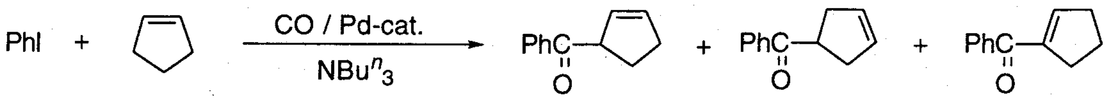
Table 3-3. Cross-Carbonylation of Aryl Iodides 1 with 2,5-Dihydrofuran (4)[a]

ArI	Product, % yield[b,c]	
 **1a**	 **5a**	64 (5)
		51 (6)[d]
		22 (2)[e]
 **1b**	 **5b**	74 (7)
 **1c**	 **5c**	67 (5)
 **1d**	 **5d**	73 (5)
 **1e**	 **5e**	81 (5)

[a] Reaction conditions: **1** (3 mmol), **4** (9 mmol), $PdCl_2$ (0.12 mmol), PPh_3 (0.12 mmol), NEt_3 (3.6 mmol), in C_6H_6 ($5\ cm^3$) under CO (5 atm) at 115-120 °C for 20 h. [b] Determined by GLC based on **1** used. [c] Value in parentheses indicates yield of accompanied 3-aroylfurans (**6a-e**).[d] Without PPh_3. [e] $Pd(PPh_3)_4$ (0.12 mmol) was used in place of $PdCl_2/PPh_3$.

iodides **1b**-**e** also reacted with **4** in the presence of the catalyst to give the corresponding 3-aroyl-2,3-dihydrofurans **5b**-**e** in 67-81 % yields. Note that in each case, a small amount of 3-aroylfuran **6** (5-7 %), which may have been produced by the dehydrogenation of **5**, was detected.

When cyclopentene (**7**) was allowed to react with **1a** in the presence of palladium catalysts (eq 3-3 and Table 3-4), a mixture of double-bond regioisomers **8**, **9**, and **10** was formed in the reaction.



(3-3)

1a **7** **8** **9** **10**

In this reaction, $PdCl_2(PPh_3)_2$ and $Pd(PPh_3)_4$ were more effective than $PdCl_2/PPh_3$ (1:1) (Entries 2 and 3 *vs* 1). This is in contrast to the reactions with dihydrofurans **2** and **4**, where the latter catalyst system was more effective. When the reaction was carried out at 100 °C, the ketones **8** and **9** were formed in a low combined yield (Entry 5). At 140 °C, the product ratio of **10** to **8**+**9** increased (Entry 6). The effect of CO pressure was similar to that observed in the reaction using **2**; a higher pressure (10 atm) reduced the total ketone yield (Entry 8), while a low pressure (3 atm) showed no significant effect (Entry 7). An increase in the amount of **7** used from 3 to 5 equiv improved the

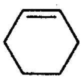
Table 3-4. Cross-Carbonylation of 1a with Cyclopentene (7)[a]

Entry	Pd-cat.	% Yield of **8+9+10**[b]	**(8+9) : 10**
1	$PdCl_2+1PPh_3$	39	69 : 31
2	$PdCl_2(PPh_3)_2$	56	71 : 29
3	$Pd(PPh_3)_4$	57	75 : 25
4	$Pd(PPh_3)_4+1PPh_3$	25	80 : 20
5	$Pd(PPh_3)_4$[c]	10	100 : 0
6	$Pd(PPh_3)_4$[d]	56	25 : 75
7	$Pd(PPh_3)_4$[e]	54	59 : 41
8	$Pd(PPh_3)_4$[f]	38	84 : 16
9	$Pd(PPh_3)_4$[e, g]	70	46 : 54

[a] Reaction conditions: **1a** (1.5 mmol), **7** (4.5 mmol), Pd-cat. (0.06 mmol), NBu^n_3 (2.1 mmol), in C_6H_6 (4 cm^3) under CO (5 atm) at 120 °C for 20 h. [b] Determined by GLC based on **1a** used. [c] At 100 °C. [d] At 140 °C. [e] Under CO (3 atm). [f] Under CO (10 atm). [g] **7** (7.5 mmol).

ketone yield (Entry 9).

Additional cyclic olefins (**11-14**) were also examined as the substrates. However, none of these olefins were as efficient as **2**, **4**, and **7**: in the cases of **12** and **13**, small amounts of benzoylated products (less than 5 %) were detected by GC-MS and no traces of the desired products were formed using **11** and **14**. The sharp contrast of the result with **7** to that with **11** may provide information concerning the reactivity of intermediary benzoylpalladium species; it is also known that **7** is relatively more strained than **11**.[9]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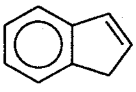
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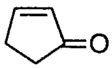
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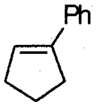

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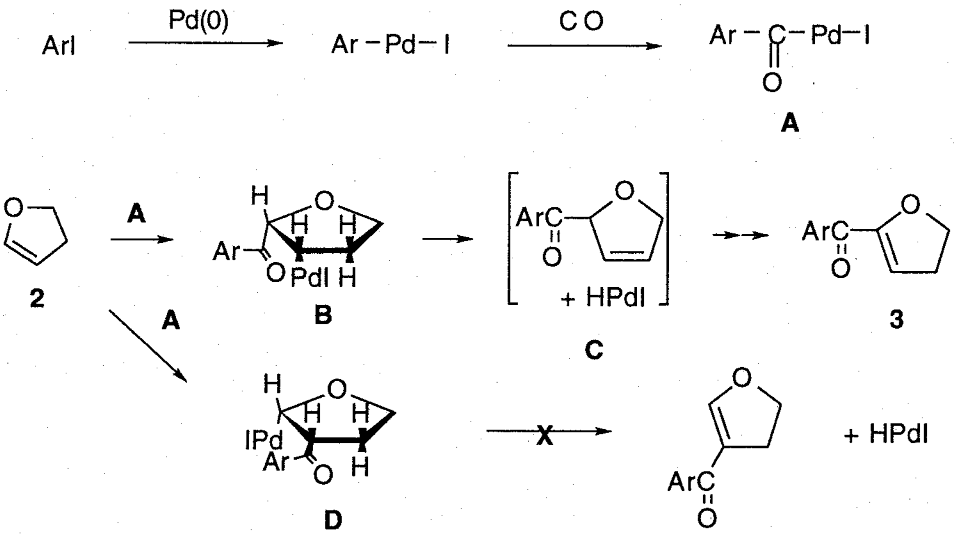
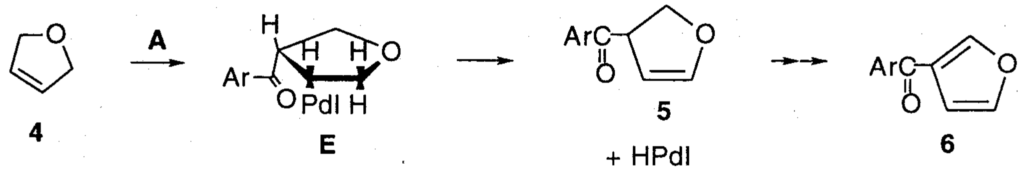
A possible mechanism for the present intermolecular cross-carbonylations of aryl iodides **1** with 2,3-dihydrofuran (**2**) is illustrated in Scheme 3-1, in which neutral ligands are omitted. Oxidative addition of **1** to palladium (0) species generated *in situ* followed by CO insertion may give aroylpalladium intermediate (**A**).[1] *Syn*-addition of **A** to **2** gives intermediate **B** and the subsequent *syn*-elimination of HPdI may afford compound **C**. Under the influence of HPdI[10] and/or the base employed, isomerization of **C** may occur to give **3** which is probably stabilized by conjugation of both the lone pair of the oxygen atom and the carbonyl group with the C-C double bond. It has been reported that *E*-*β*-aroylated vinyl ethers are exclusively produced in the palladium-catalyzed aroylation of acyclic alkyl vinyl ethers with aroyl chlorides.[11] On the other hand, active acyl chlorides are



Scheme 3-1.

known to react at the *β*-position of vinyl ethers, irrespective of the substrate structures.[12] In the present reaction, however, the corresponding 3-aroylated product was not produced. One of the possible reasons for this is due to the fact that there is no *cis*-hydrogen to the palladium atom when *syn*-addition of **A** to **2** occurs to give 3-aroylated intermediate **D**. However, it is not definitive whether the reaction of **A** with **2** to **D** is reversible or not. If it is irreversible, the formation of **D** would be responsible for uncharacterizable products. It should be noted that while similar α-regioselectivity has been reported in the palladium-catalyzed arylation of 2,3-dihydrofuran,[13] the reaction with acyclic vinyl ethers are known to depend on the electronic nature of the aryl moieties employed.[14]

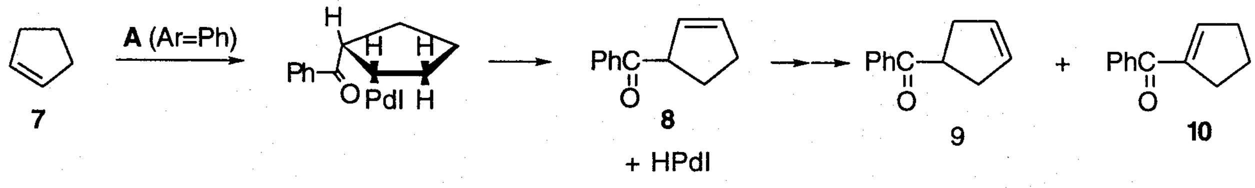
When 2,5-dihydrofuran (**4**) was used in place of **2**, dihydrofuran **5** may be produced as the primary product (Scheme 3-2). In this case, **5** may be rather stable under the reaction conditions



Scheme 3-2.

because of the conjugation of the lone pair of the oxygen atom with the C-C double bond, although a small part of **5** was appeared to be dehydrogenated to give 3-aroylfurans **6** (Table 3-3). It should be noted that **5** could be completely converted to **6** by heating it in the presence of a Pd/C catalyst (see Experimental Section). Considering the fact that the Friedel-Crafts acylation of furan generally takes place at the 2-position, the present method seems to be useful as a route to 3-aroylfurans.

The reaction with cyclopentene (**7**) may proceed by a mechanism similar to that of dihydrofurans to give **8** as the primary product and a part of this product isomerizing to **9** and **10** (Scheme 3-3). The fact that the product ratio of **10**/(**8**+**9**) increased at higher temperature indicates



Scheme 3-3.

that the conjugated isomer **10** is thermodynamically more stable than other isomers. On the other hand, an increase in the ratio of **10**/(**8**+**9**) was also observed when the amount of **7** added was increased. However, the role of the excess olefin is not clear.

3-3. Experimental Section

^{1}H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively, in $CDCl_3$ as solvent. MS spectra were obtained by EI. GLC analysis was carried out using a silicon OV-17 column (i. d. 2.6 mm × 1.5 m) or with a CBP-1 capillary column (i. d. 0.5 mm × 25 m).

Complexes $PdCl_2(PPh_3)_2$,[1] $Pd(PPh_3)_4$,[1] $Pd(dba)_2$,[15] and $PdCl_2(dppf)$[16] were prepared by the methods reported previously. Aryl iodides **1c**,[17] **1e**,[18], and **1g**[18] and phenylcyclopentene (**14**)[19] were prepared according to the published procedures. Other starting materials were commercially available. Solvents were purified by standard methods before use.

Cross-Carbonylation of Aryl Iodides 1 with 2,3-Dihydrofuran (2). A mixture of **1** (3 mmol), **2** (0.68 cm^3, 9 mmol), $PdCl_2$ (21 mg, 0.12 mmol), PPh_3 (31 mg, 0.12 mmol), NEt_3 (1.0 cm^3, 7.2 mmol), and benzene (5 cm^3) was placed in a 50 cm^3 stainless steel autoclave with a glass tube. Then, carbon monoxide (5 atm at room temperature) was charged and the mixture was magnetically stirred at 120 $^{\circ}$C for 20 h. After cooling, the reaction mixture was poured into water, extracted with ether, and dried over sodium sulfate. Product **3** was isolated by column chromatography on silica gel using hexane-methylene chloride as eluant.

2-Benzoyl-4,5-dihydrofuran (3a): oil; 115-120 $^{\circ}$C/3 mmHg; ^{1}H NMR δ 3.06 (dt, 2H, J = 1.5, 9.8 Hz), 4.64 (t, 2H, J = 9.8 Hz), 7.15 (t, 1H, J = 1.5 Hz), 7.41-7.44 (m, 2H), 7.48-7.53 (m, 1H), 7.65-7.67 (m, 2H); ^{13}C NMR δ 28.16, 73.52, 119.42, 127.99, 128.38, 131.39, 140.05, 160.82, 191.12; MS *m/z* 174 (M$^+$). Anal. Calcd for $C_{11}H_{10}O_2$: C, 75.83; H, 5.80. Found: C, 75.55; H, 5.70.

2-(4-Methylbenzoyl)-4,5-dihydrofuran (3b): mp 92-94 $^{\circ}$C; ^{1}H NMR δ 2.40 (s, 3H), 3.04 (dt, 2H, J = 1.5, 9.8 Hz), 4.63 (t, 2H, J = 9.8 Hz), 7.15 (t, 1H, J = 1.5 Hz), 7.22-7.26 (m, 2H), 7.57-7.59 (m, 2H); MS *m/z* 188 (M$^+$). Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.56; H, 6.44. Found: C, 76.36; H, 6.40.

2-(4-Methoxybenzoyl-4,5-dihydrofuran (3c): mp 85-86 $^{\circ}$C; ^{1}H NMR δ 3.03 (dt, 2H, J = 1.5, 9.8 Hz), 3.85 (s, 3H), 4.62 (t, 2H, J = 9.8 Hz), 6.92 (d, 2H, J = 8.8 Hz), 7.14 (t, 1H, J =

1.5 Hz), 7.68 (d, 2H, *J* = 8.8 Hz); MS *m/z* 204 (M^+). Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.56; H, 5.93. Found: C, 70.52; H, 5.90.

2-(3-Methylbenzoyl)-4,5-dihydrofuran (3d): oil; 125-130 °C/3 mmHg; ^{1}H NMR δ 2.39 (s, 3H), 3.02 (dt, 2H, *J* = 1.5, 9.8 Hz), 4.62 (t, 2H, *J* = 9.8 Hz), 7.15 (t, 1H, *J* = 1.5 Hz), 7.29-7.31 (m, 2H), 7.43-7.47 (m, 2H); MS *m/z* 188 (M^+). Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.56; H, 6.44. Found: C, 76.44; H, 6.33.

2-(3,4-Dimethylbenzoyl)-4,5-dihydrofuran (3e): mp 86-87 °C; ^{1}H NMR δ 2.30 (s, 6H), 3.04 (dt, 2H, *J* = 1.5, 9.8 Hz), 4.63 (t, 2H, *J* = 9.8 Hz), 7.15 (t, 1H, *J* = 1.5 Hz), 7.17 (d, 1H, *J* = 7.8 Hz), 7.41 (dd, 1H, *J* = 1.5, 7.8 Hz), 7.46 (d, 1H, *J* = 1.5 Hz); MS *m/z* 202 (M^+). Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.19; H, 6.99. Found: C, 77.18; H, 6.99.

2-(4-Chlorobenzoyl)-4,5-dihydrofuran (3f): mp 120-122 °C; ^{1}H NMR δ 3.04 (dt, 2H, *J* = 2.0, 9.8 Hz), 4.65 (t, 2H, *J* = 9.8 Hz), 7.14 (t, 1H, *J* = 1.5 Hz), 7.39-7.43 (m, 2H), 7.60-7.63 (m, 2H); MS *m/z* 208, 210 (M^+). Anal. Calcd for $C_{11}H_9O_2Cl$: C, 63.32; H, 4.36; Cl, 16.99. Found: C, 63.36; H, 4.29; Cl, 17.14.

2-(2-Naphthoyl)-4,5-dihydrofuran (3g): oil; 185-200 °C/3 mmHg; ^{1}H NMR δ 2.98 (dt, 2H, *J* = 1.5, 9.8 Hz), 4.55 (t, 2H, *J* = 9.8 Hz), 7.12 (t, 1H, *J* = 1.5 Hz), 7.41-7.49 (m, 2H), 7.66-7.68 (m, 1H), 7.76-7.82 (m, 3H), 8.06 (s, 1H); MS *m/z* 224 (M^+). Anal. Calcd for $C_{15}H_{12}O_2$: C, 80.33; H, 5.40. Found: C, 79.97; H, 5.38.

Cross-Carbonylation of Aryl Iodides 1 with 2,5-Dihydrofuran (4). The reaction conditions were identical to those shown above with **2**. GC and GC-MS analyses of the product mixtures indicated formation of 3-aroyl-2,3-dihydrofurans **5** (64-81 %) along with 3-aroylfurans **6** (5-7%). Although products **5** were isolated by column chromatography, they were contaminated by **6**. The structure of **5** was confirmed by NMR analysis of this fraction. Full characterization of the products was made by converting **5** to **6** *via* dehydrogenation. The dehydrogenation reaction was carried out by heating each product mixture obtained by separate run in 1-methylnaphthalene (1.0 g) in the presence of a commercial 5 % Pd/C catalyst (191 mg) at 200 °C under a slow stream of nitrogen. After complete conversion (monitored by GC; *ca.* 3h), compound **6** was isolated by column chromatography on silica gel using hexane-methylene chloride as eluant. The yields of the purified products were 27-35 %.

3-Benzoyl-2,3-dihydrofuran (5a): oil; ^{1}H NMR δ 4.49 (dd, 1H, $J = 8.8, 9.0$ Hz), 4.65-4.70 (m, 1H), 4.98 (dd, 1H, $J = 8.8, 9.0$ Hz), 5.04 (t, 1H, $J = 2.4$ Hz), 6.42 (t, 1H, $J = 2.4$ Hz), 7.48-7.61 (m, 3H), 7.97-7.99 (m, 2H); MS m/z 174 (M^+).

3-(4-Methylbenzoyl)-2,3-dihydrofuran (5b): oil; ^{1}H NMR δ 2.43 (s, 3H), 4.48 (dd, 1H, $J = 8.8, 9.0$ Hz), 4.66 (m, 1H), 4.97 (dd, 1H, $J = 8.8, 9.0$ Hz), 5.03 (t, 1H, $J = 2.4$ Hz), 6.41 (t, 1H, $J = 2.4$ Hz), 7.37-7.40 (m, 2H), 7.76-7.79 (m, 2H); MS m/z 188 (M^+).

3-(4-Methoxybenzoyl)-2,3-dihydrofuran (5c): oil; ^{1}H NMR δ 3.88 (s, 3H), 4.48 (dd, 1H, $J = 8.8, 9.0$ Hz), 4.61-67 (m, 1H), 4.97 (dd, 1H, $J = 8.8, 9.0$ Hz), 5.02 (t, 1H, $J = 2.4$ Hz), 6.41 (t, 1H, $J = 2.4$ Hz), 6.97 (d, 2H, $J = 8.9$ Hz), 7.97 (d, 2H, $J = 8.9$ Hz); MS m/z 204 (M^+).

3-(3-Methylbenzoyl)-2,3-dihydrofuran (5d): oil; ^{1}H NMR δ 2.43 (s, 3H), 4.48 (dd, 1H, $J = 8.8, 9.0$ Hz), 4.66 (m, 1H), 4.97 (dd, 1H, $J = 8.8, 9.0$ Hz), 5.02 (t, 1H, $J = 2.4$ Hz), 6.41 (t, 1H, $J = 2.4$ Hz), 7.28-7.30 (m, 2H), 7.87-7.89 (m, 2H); MS m/z 188 (M^+).

3-(3,4-Dimethylbenzoyl)-2,3-dihydrofuran (5e): oil; ^{1}H NMR δ 2.33 (s, 6H), 4.48 (dd, 1H, $J = 8.8, 9.0$ Hz), 4.46 (m, 1H), 4.63-4.68 (m, 1H), 4.97 (dd, 1H, $J = 8.8, 9.0$ Hz), 4,99 (t, 1H, $J = 2.4$ Hz), 7.26 (s, 1H), 7,69-7.76 (m, 2H); MS m/z 202 (M^+).

3-Benzoylfuran (6a): mp 32-33 °C (lit.[20] mp 39-40 °C); ^{1}H NMR δ 6.92 (d, 1H, $J = 2.0$ Hz), 7.51 (d, 1H, $J = 2.0$ Hz), 7.47-7.51 (m, 2H), 7.57-7.61 (m, 1H), 7.85-7.88 (m, 2H),7.93 (d, 1H, $J = 1.5$ Hz); MS m/z 172 (M^+). Anal. Calcd for $C_{11}H_8O_2$: C, 76.73; H, 4.68. Found: C, 76.68; H, 4.76.

3-(4-Methylbenzoyl)furan (6b): oil; ^{1}H NMR δ 2.44 (s, 3H), 6.90 (d, 1H, $J = 2.0$ Hz), 7.28 (t, 2H, $J = 7.8$ Hz), 7.50 (t, 1H, $J = 1.7$ Hz), 7.76-7.79 (m, 2H), 7.92 (d, 1H, $J = 1.5$ Hz); MS m/z 186 (M^+). Anal. Calcd for $C_{12}H_{10}O_2$: C, 77.40; H, 5.41. Found: C, 77.02; H, 5.53.

3-(4-Methoxybenzoyl)furan (6c): mp 72-74 °C (lit.[21] mp 75-77 °C); ^{1}H NMR δ 3.89 (s, 3H), 6.89 (t, 1H, $J = 1.0$ Hz), 6.97-6.99 (m, 2H), 7.50 (t, 1H, $J = 1.7$ Hz), 7.88-7.90 (m, 2H), 7.92 (t, 1H, $J = 1.2$ Hz); MS m/z 202 (M^+). Anal. Calcd for $C_{12}H_{10}O_3$: C, 71.28; H, 4.99. Found: C, 71.11; H, 5.02.

3-(3-Methylbenzoyl)furan (6d): oil; ^{1}H NMR δ 2.43 (s, 3H), 6.91 (d, 1H, $J = 1.9$ Hz), 7.37-7.39 (m, 2H), 7.51 (t, 1H, $J = 1.5$ Hz), 7.63-7.67 (m, 2H), 7.92 (d, 1H, $J = 1.0$ Hz); MS m/z 186 (M^+). Anal. Calcd for $C_{12}H_{10}O_2$: C, 77.40; H, 5.41. Found: C, 77.01; H, 5.41.

3-(3,4-Dimethylbenzoyl)furan (6e): mp 44-45 °C; ^{1}H NMR δ 2.34 (s, 3H), 2.34 (s, 3H), 6.90 (d, 1H, J = 2.0 Hz), 7.25 (t, 1H, J = 6.5 Hz), 7.50 (t, 1H, J = 1.7 Hz), 7.60 (dd, 1H, J = 2.0, 7.8 Hz), 7.65 (s, 1H), 7.92 (d, 1H, J = 1.5 Hz); MS *m/z* 200 (M^+). Anal. Calcd for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04. Found: C, 78.03; H, 6.09.

Cross-Carbonylation of Iodobenzene (1a) with Cyclopentene (7). The reaction of **1a** (306 mg, 1.5 mmol) with **7** (0.4 cm^3, 4.5 mmol) was carried out in the presence of Pd(PPh$_3$)$_4$ (64 mg, 0.06 mmol) and NBu$^n{}_3$ (0.5 cm^3, 2.1 mmol) in benzene (4 cm^3) under carbon monoxide (5 atm) at 120 °C for 20 h. Column chromatography of the reaction mixture on silica gel using hexane-methylene chloride (8:2, *v/v*) gave a mixture of benzoylcyclopentene **8-10** (131 mg, 51 %); the product ratio determined by ^{1}H NMR was 43:32:25. Elaborated column chromatography of the reaction mixture afforded each compound having >80 % content.

3-Benzoylcyclopentene (8):[22] oil; ^{1}H NMR δ 2.19-2.31 (m, 2H), 2.40-2.57 (m, 2H), 4.48-4.53 (m, 1H), 5.77-5.59 (m, 1H), 5.94-5.96 (m, 1H), 7.48 (t, 2H, J = 7.7 Hz), 7.57 (t, 1H, J = 7.3 Hz), 8.00-8.02 (m, 2H); MS *m/z* 172 (M^+).

4-Benzoylcyclopentene (9): oil; ^{1}H NMR δ 2.67-2.81 (m, 4H), 2.67-2.81 (m, 1H), 5.69 (t, 2H, J = 6.4 Hz), 7.47-58 (m, 3H), 7.96-7.99 (m, 2H); MS *m/z* 172 (M^+).

1-Benzoylcyclopentene (10):[23] oil; ^{1}H NMR δ 1.97-2.05 (m, 2H), 2.59-2.65 (m, 2H), 2.72-2.77 (m, 2H), 6.55 (t, 1H, J = 2.0 Hz), 7.41-52 (m, 3H), 7.72-7.75 (m, 2H); MS *m/z* 172 (M^+).

3-4. References and Notes

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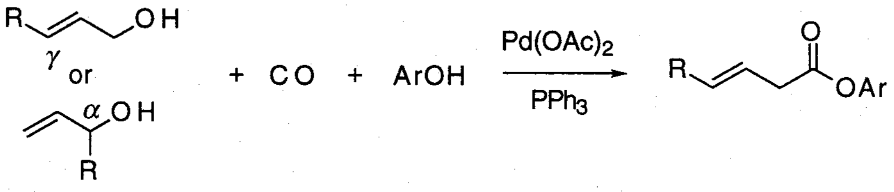
Chapter 4. Palladium-Catalyzed Carbonylation of Allyl and Benzyl Alcohols and Etherification of Allyl Alcohols

4-1. Introduction

Palladium-catalyzed carbonylation of allylic compounds is one of the most promising methods for the preparation of synthetically useful β, γ-unsaturated carboxylic acid derivatives.[1] Effective methods for the reaction of allylic carbonates,[2] esters,[3] halides,[4] amines,[5] and ethers[6] under reasonably mild conditions have so far been developed. However, carbonylation of allyl alcohols has been less explored in spite of the ready availability of the starting materials, as the reaction requires high pressure of carbon monoxide.[7] Recently, our research group has shown that allyl alcohols can be carbonylated efficiently in the presence of titanium(IV) alkoxides and lithium chloride under medium CO pressure (25 atm) to give alkyl 3-butenoates.[8] Meanwhile, as has been already described in chapter 2, we have also found that phenols can act as effective nucleophiles in the palladium-catalyzed carbonylation of aryl iodides. During a further study of the palladium-catalyzed phenoxycarbonylation, it was found that the direct carbonylation of allyl alcohols bearing an aryl substituent at the α or γ-position can also be attained in the presence of phenols using a palladium catalyst to afford the corresponding β, γ-unsaturated esters even under atmospheric pressure of CO (eq 4-1). Furthermore, the present method was also found to be applicable to carbonylation of 2-hydoxybenzyl alcohols.



(4-1)

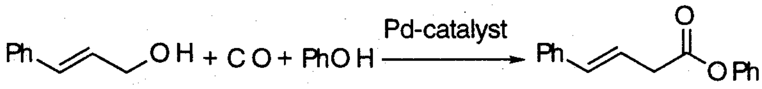
On the other hand, we considered that, if allyl alcohols were treated with phenols in the absence of CO, allyl aryl ethers could be formed; the ethers are useful compounds in organic synthesis, particularly as the substrates of the Claisen rearrangement.[9] Indeed, it was observed that the etherification of allyl alcohols with phenols efficiently proceeded by using a catalyst system of $Pd(OAc)_2$-PPh_3-$Ti(OPr^i)_4$ under nitrogen.

4-2. Results and Discussion

4-2-1. Carbonylation of Allyl Alcohols in the Presence of Phenols

When a mixture of (*E*)-3-phenyl-2-buten-1-ol (**1a**, 2 mmol) and phenol (**2a**, 2 mmol) was heated in the presence of $Pd(OAc)_2$ (0.1 mmol) and PPh_3 (0.2 mmol) in benzene (5 cm^3) under CO (5 atm) at 100 ^oC for 18 h, (*E*)-phenyl 4-phenyl-3-butenoate (**3**) was produced in a yield of 24 % (Entry 1 in Table 4-1). Increase in the amount of PPh_3 to 0.4 mmol remarkably enhanced the ester yield (76 %) (Entry 2), and in this case alcohol **1a** was completely consumed. The yield was further improved up to 80 % by the use of a slight excess of **2a** (2.4 mmol) (Entry 4). It was observed that $Pd(PPh_3)_4$ was less efficient than the combination of $Pd(OAc)_2$ and PPh_3 (Entry 5 *vs* 2). This may suggest that acetic acid derived from $Pd(OAc)_2$ acts as a promoter. Indeed, the reaction of **1a** with **2a** using $Pd(PPh_3)_4$ in the presence of acetic acid (0.1 mmol) gave a better yield of **3** compared with that using $Pd(PPh_3)_4$ alone (Entry 6). Interestingly, the phenoxycarbonylation of **1a** was found to proceed efficiently even under atmospheric pressure of CO (Entry 7). Polar solvents, DMF and 2-methoxyethyl ether could not be used in the present reaction (Entries 8 and 9). The reaction of **1a** should be accompanied by formation of water. Addition of molecular sieves

Table 4-1. Phenoxycarbonylation of 3-Phenyl-2-buten-1-ol (1a) [a]



1a **2a** **3**

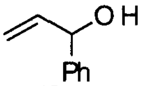
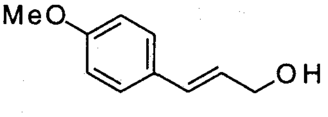
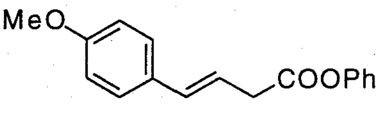
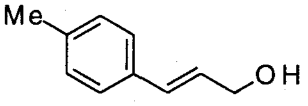
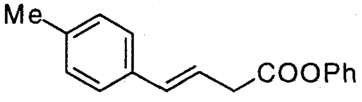
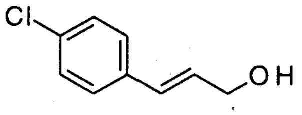
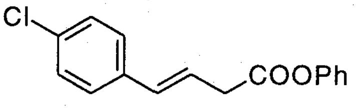
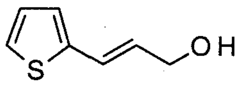
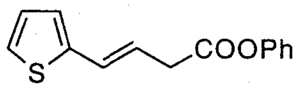
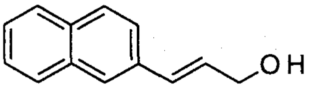
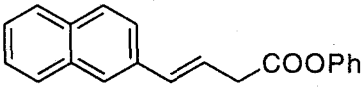
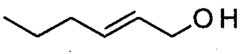
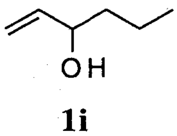
Entry	Pd-cat.	Recovery / %[b] 1a	Recovery / %[b] 2a	Yield of 3 / %[b]
1	$Pd(OAc)_2$+$2PPh_3$	22	74	24
2	$Pd(OAc)_2$+$4PPh_3$		20	76
3[c]	$Pd(OAc)_2$+$4PPh_3$		32	66
4[d]	$Pd(OAc)_2$+$4PPh_3$		37	80 (75)
5	$Pd(PPh_3)_4$	19	49	49
6	$Pd(PPh_3)_4$+CH_3COOH		29	64
7[e, f]	$Pd(OAc)_2$+$4PPh_3$		23	76 (70)
8[e, g]	$Pd(OAc)_2$+$4PPh_3$	~100	~100	
9[e, h]	$Pd(OAc)_2$+$4PPh_3$	95	95	5
10[i]	$Pd(OAc)_2$+$4PPh_3$		28	70

[a] Reaction conditions: **1a** (2 mmol), **2a** (2 mmol), and Pd-cat. (0.1 mmol) in benzene (5 cm^3) under CO (5 atm) at 100 ^oC for 18 h. [b] Determined by GLC analysis based on **1a** used. Value in parentheses indicates yield after purification. [c] $Pd(OAc)_2$ (0.05 mmol) was used. [d] **2a** (2.4 mmol) was used. [e] Under CO (1 atm) at 80 ^oC for 20 h. [f] In toluene. [g] In DMF. [h] In 2-methoxyethyl ether. [i] Molecular sieves (4A, 200 mg) was added.

(4A, 200 mg) for its removal, however, somewhat reduced the yield of **3** (Entry 10).

Phenoxycarbonylation of a number of allyl alcohols was also performed using $Pd(OAc)_2$ and

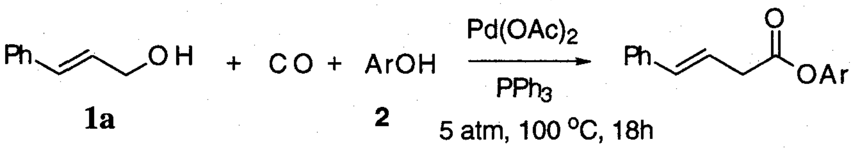
Table 4-2. Phenoxycarbonylation of Allyl Alcohols[a]

Allyl alcohol[b]	Product, % yield[b, c]
 **1b**	**3**, 80 (82)
 **1c**	 **4**, (66)
 **1d**	 **5**, (80)
 **1e**	 **6**, 74
 **1f**	 **7**, (55)
 **1g**	 **8**, 53
 **1h**	 **9**, 26 (*E*:*Z*=81:19)
 **1i**	**9**, (20) (*E*:*Z*=87:13)

[a] Reaction conditions: **1**[b] (2 mmol), **2a** (2.4 mmol), $Pd(OAc)_2$ (0.1 mmol), and PPh_3 (0.4 mmol) in benzene (5 cm^3) under CO (5 atm) at 100 °C for 18 h. [b] Unless otherwise noted, *E*:*Z* was > 98:2. [c] GLC yield based on **1** used. Value in parentheses indicates yield in the reaction under 1 atm of CO in toluene at 80 °C for 20 h.

PPh_3 under CO (1 or 5 atm) in toluene or benzene (Table 4-2). The reaction of α or γ- arylated allyl alcohols proceeded smoothly to give the corresponding phenyl esters selectively in fair to good yields. The reaction of 2-hexen-1-ol (**1h**) or 1-hexen-3-ol (**1i**) was, however, less efficient, giving mixture of (*E*)- and (*Z*)-isomers of ester **9** in low yield. The fact that **1a** and **1b** gave the same product as well as the case of **1h** and **1i** may suggest that the reaction process involves π-allylpalladium intermediates.

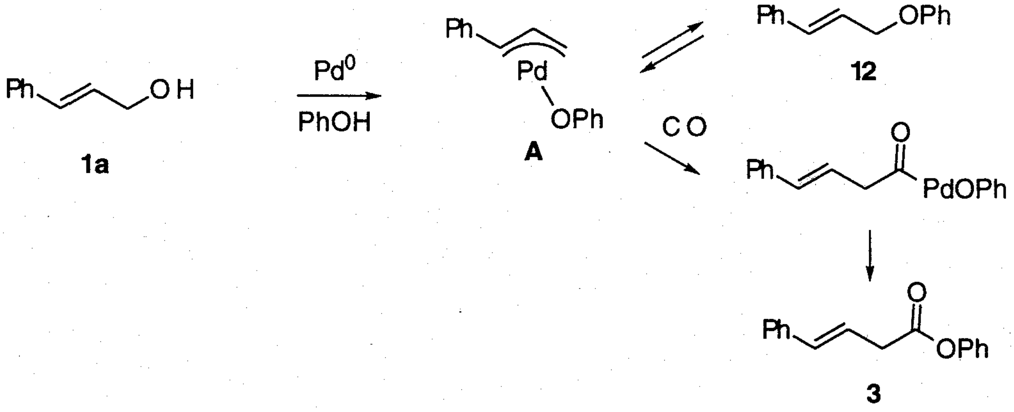
Meanwhile, the carbonylation of **1a** using 4-methoxy- and 3-chlorophenols (**2b-c**) in place of **2a** also gave esters **10** and **11** in good yields (eq 4-2).



(4-2)

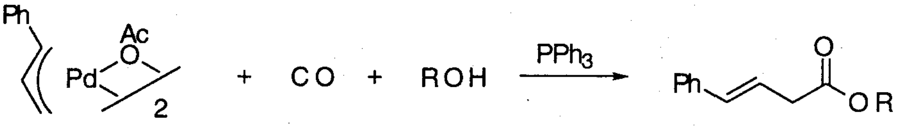
		% yield
2b: Ar = 4-MeOC$_6$H$_4$	**10**	70
2c: Ar = 3-ClC$_6$H$_4$	**11**	72

A probable mechanism for the formation of **3** from **1a** and **2a** is illustrated in Scheme 4-1 where neutral ligands are omitted. Alcohol **1a** reacts with Pd^0 species generated *in situ* in the presence of phenol (**2a**) to afford a π-allylpalladium intermediate (**A**). Subsequently, insertion of CO to **A** followed by reductive elimination gives product **3**.[10] In the early stage of the reaction of **1a** under CO (1 atm) (conversion of **1a** = 30 %), formation of phenyl ether **12** (9 %) as well as **3** (5 %) was detected in the reaction medium, while the former disappeared in the end (Entry 7 in Table 4-1). It was confirmed that treatment of ether **12** under the present carbonylation conditions gave **3** in a yield of 87 %. These facts suggest that the ester **3** may be produced, at least in part, *via* **12**. In contrast to our observation, ether **12** has recently been reported to be inactive toward carbonylation using palladium species in relatively polar solvents such as THF and CH$_2$Cl$_2$.[11]



Scheme 4-1.

The carbonylation of alcohol **1a** with *n*-butanol as nucleophile using $Pd(OAc)_2$ and PPh_3 under 5 atm of CO in benzene gave (*E*)-butyl 4-phenyl-3-butenoate (**13**) in a low yield (27 %).[12] Thus, phenol appears to act as a good nucleophile in the reaction (*cf.* Entry 2 in Table 4-1), so that it can be carried out under mild and nearly neutral conditions.[13] Consistently, in the stoichiometric carbonylation of $[Pd(\eta^3\text{-1-phenylallyl})(OAc)]_2$ (**14**) (0.1 mmol) with phenol (1 mmol) in the presence of PPh_3 (0.2 mmol) in toluene (5 cm^3) under CO (1 atm) at 80 °C, ester **3** was smoothly formed (3 h; 77 %, 22 h; 91 %) (eq 4-3). By contrast, the reaction using *n*-butanol (2 mmol) gave ester **13** in a low yield (22 h; 19 %).



14

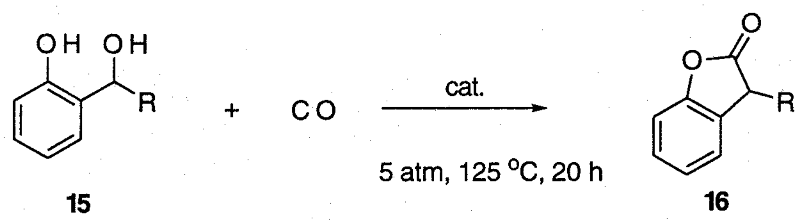
(4-3)

			% yield
3 h	R=Ph	**3**	77
22 h	R=n-Bu	**13**	19

While the exact role of acetic acid derived from $Pd(OAc)_2$ or added is not definitive at the present stage, it would promote the first step, oxidative addition of **1a** to Pd^0 species (Scheme 4-1).[6a] On the other hand, one of the possible reasons for the less efficiency of the reaction of aliphatic allyl alcohols such as **1h** and **1i** seems to be attributable to involvement of a side reaction leading to the corresponding dienes, since β-hydride elemination from π-allylpalladium species is known.[1] Indeed, in the treatment of (*E*)-2-decenol under the carbonylation conditions, 1,3-decadiene (21 %) was formed along with the corresponding phenyl ester (24 %).

4-2-2. Carbonylation of 2-Hydroxybenzyl Alcohols

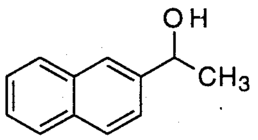
During a further study of application of the present method to carbonylation of other alcohols, it was found that 2-hydroxybenzyl alcohols **15a,b** could also be catalytically carbonylated in the presence of palladium species in benzene under CO (5 atm) at 125 °C to give the corresponding benzofuran-2(3*H*)-ones **16** (eq 4-4). As was in the reaction of allyl alcohols using $Pd(PPh_3)_4$, the addtion of appropriate carboxylic acids as cocatalyst increased the lactone yields, while in this case, relatively stronger acids than acetic acid were preferred. Meanwhile, treatment of 1-(2-naphthyl)ethanol (**17**) in the presence of phenol under carbon monoxide gave no carbonylation products, only a trace amount of ether **18** being detected.[14] As this example, carbonylation of



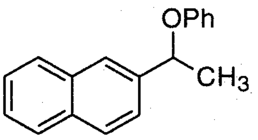
(4-4)

	cat.	% yield
15a: R=H	$Pd(PPh_3)_4$	32
	$Pd(PPh_3)_4 + C_6H_5COOH$	59
15b: R=C_6H_5	$Pd(OAc)_2 + 4PPh_3$	90
	$Pd(OAc)_2 + 4PPh_3 + CF_3COOH$	~100

benzylic alcohols using transition metal complexes is generally recognized to be very difficult, compared with that of the corresponding halides.[15] Thus, it may be considered that, in the carbonylation of **15** which proceeds under relatively mild conditions, the phenolic hydroxyl group in **15** may play an important role to smoothly form the corresponding key benzylpalladium intermediate.[16]

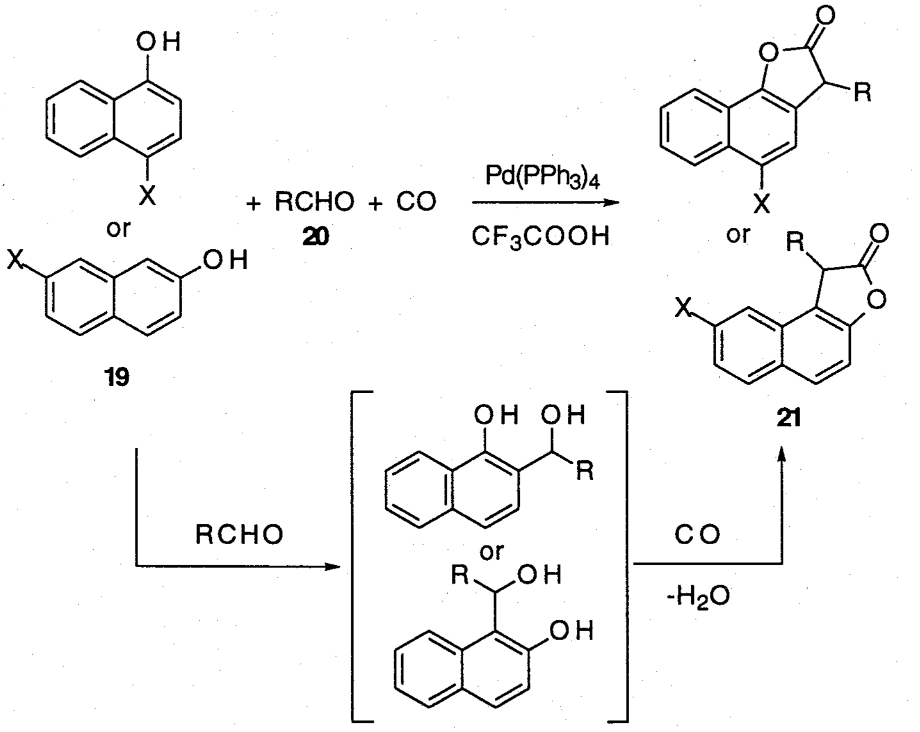


17



18

It is well known that 2-hydroxybenzyl alcohols can be synthesized by the reaction of phenolic compounds with aldehydes in the presence of acid catalysts including carboxylic acids.[17]

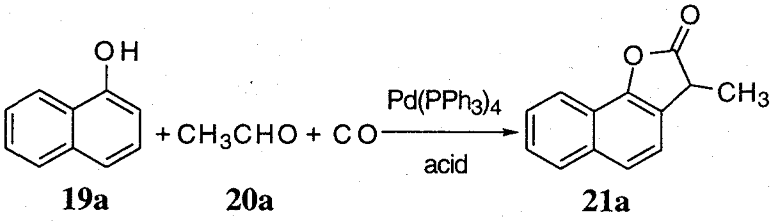


(4-5)

Consequently, we have examined the three-component coupling of phenolic compounds, aldehydes, and carbon monoxide to produce the γ-lactone derivatives. As a result, when 1- or 2-naphthols were used as the first component, coupling products, naphthofuran-2(3*H*)-one analogues, were found to be efficiently produced under similar conditions to those used in the reaction of **15** (eq 4-5).

When a mixture of 1-naphthol (**19a**) (2 mmol) and acetaldehyde (**20a**) (6 mmol) was heated in the presence of $Pd(PPh_3)_4$ (0.05 mmol) in C_6H_6 (5 cm^3) under CO (5 atm) at 120 °C for 18 h, 3-methylnaphtho[1,2-*b*]furan-2(3*H*)-one (**21a**) was produced in a yield of 32 % (Entry 1 in Table 4-3). As in the reaction of **15b**, addition of CF_3COOH (0.05 mmol) as cocatalyst remarkably enhanced the yield of **21a** (97 %) (Entry 2). Other acids such as CH_3COOH, C_6H_5COOH, and TsOH, however, were not as effective as CF_3COOH (Entries 3-5). Furanone **21a** was almost quantitatively produced, when the amount of **20a** was increased to 10 mmol in the presence of CF_3COOH (Entry 6).

Table 4-3. Reaction of 1-Naphthol (19a) with Acetaldehyde (20a) under Carbon Monoxide[a]

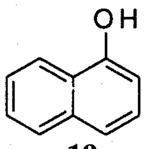
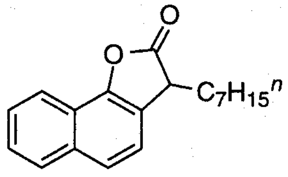
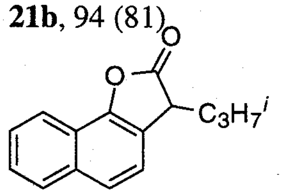
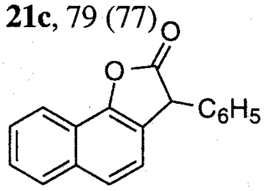
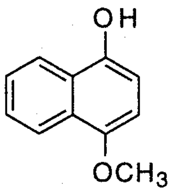
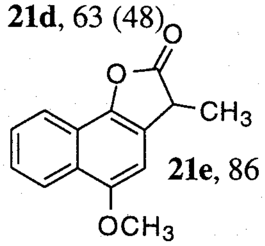
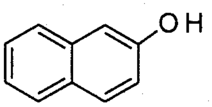
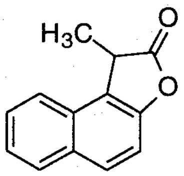
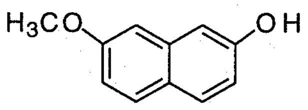
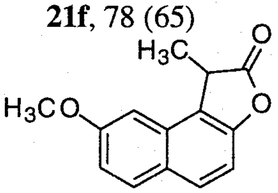


Entry	Acid	Yield of **21a** / %[b]
1	none	32
2	CF_3COOH	97
3	CH_3COOH	28
4	C_6H_5COOH	26
5	TsOH	54
6[c]	CF_3COOH	~100

[a] Reaction conditions: **19a** (2 mmol), **20a** (6 mmol), $Pd(PPh_3)_4$ (0.05 mmol), and acid (0.05 mmol) in C_6H_6 (5 cm^3) under CO (5 atm) at 120 °C for 18 h. [b] GLC yield based on **19a** used. [c] **20a** (10 mmol) was used.

Table 4-4 summarizes the results for the reactions of **19a** with aldehydes **20b-d** (1-2.5 equiv) and of **19b-d** with **20a** (5 equiv) using $Pd(PPh_3)_4$ or a combination of $Pd(OAc)_2$ and PPh_3 in the presence of CF_3COOH. It can be seen that 3-alkyl- and 3-arylnaphthofuran-2(3*H*)-ones (**21b-g**) could be produced in fair to good yields.[18] Note that naphtho[2,1-*b*]furan-2(3*H*)-ones **21f** and **21g** were exclusively formed in the reaction using 2-naphthols **19c** and **19d** as substrates, no [2,3-*b*]

Table 4-4. Reaction of Naphthols 19a-d with Aldehydes 20a-d under Carbon Monoxide[a]

19	20	Product, % yield[b]
 **19a**	$C_7H_{15}{}^nCHO^c$ **20b**	 **21b**, 94 (81)
19a	$C_3H_7{}^iCHO^d$ **20c**	 **21c**, 79 (77)
19a	$C_6H_5CHO^e$ **20d**	 **21d**, 63 (48)
 **19b**	**20a**	 **21e**, 86 (58)
 **19c**	**20a**	 **21f**, 78 (65)
 **19d**	**20a**	 **21g**, 88 (76)

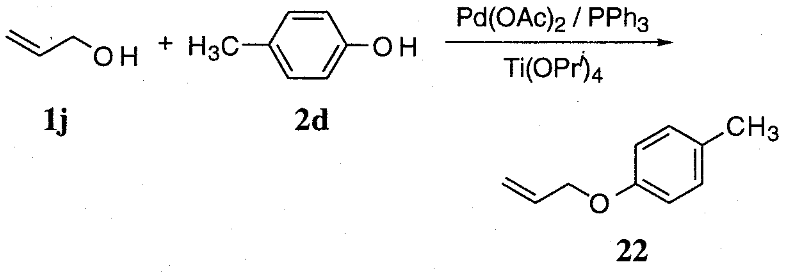
[a] Reaction conditions: **19** (2 mmol), **20** (10 mmol), $Pd(PPh_3)_4$ (0.05 mmol), and CF_3COOH (0.05 mmol), in C_6H_6 (5 cm^3) under CO (5 atm) at 120 °C for 18 h. [b] GLC yield based on **19** used. Value in parentheses indicates yield after purification. [c] Reaction was carried out using **20b** (3 mmol), $Pd(PPh_3)_4$ (0.1 mmol), and CF_3COOH (0.1 mmol) at 125 °C. [d] Reaction was carried out using **20c** (5 mmol), $Pd(PPh_3)_4$ (0.1 mmol), and CF_3COOH (0.1 mmol) at 125 °C. [e] Reaction was carried out using **20d** (2 mmol) in the presence of $Pd(OAc)_2$ (0.1 mmol) and PPh_3 (0.4 mmol), in place of $Pd(PPh_3)_4$.

isomers being detected. In contrast to the high reactivity of naphthols, treatment of phenol or 4-methoxyphenol with **20a** or **20b** gave no expected coupling product. In the latter two cases, it may be defficult to form the corresponding 2-hydoroxybezyl alcohol intermediate *in situ* by nucleophilic addition of phenols to **20** under the conditions employed (eq 4-5).

4-2-3. Etherification of Allyl Alcohols in the Presence of Phenols

When a mixture of allyl alcohol (**1j**, 4 mmol) and *p*-cresol (**2d**, 1 mmol) was heated in the presence of $Pd(OAc)_2$ (0.025 mmol) and PPh_3 (0.1 mmol) in C_6H_6 (5 cm^3) under nitrogen at 50 °C for 20 h, 1-(4-methylphenoxy)-2-propene (**22**) was produced in a yield of 34 % (Entry 1 in Table 4-5). The reaction should be accompanied by formation of water as same as in the carbonylation of these substrates. Addition of molecular sieves (MS4A) for its removal, however, showed no positive effect (Entry 2). On the contrary to this normal desiccant, addition of $Ti(OPr^i)_4$ (0.25 mmol) was found to remarkably enhance both the reaction rate and yield of **22**. Thus, the yield reached 93 % within 1 h (Entry 3). Our research group has previously reported that palladium-catalyzed nucleophilic substitution of allyl alcohols using zinc enolates can also proceed efficiently in the presence of $Ti(OR)_4$; the alkoxides appear to enhance the reactivity of allyl alcohols toward palladium (0) species.[19] In that case, addition of a chloride source such as LiCl together with $Ti(OR)_4$ was required to proceed efficiently. However, this was not necessary

Table 4-5. Reaction of Allyl Alcohol (1j) with *p*-Cresol (2d)[a]

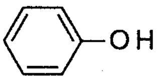
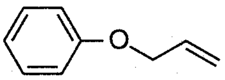
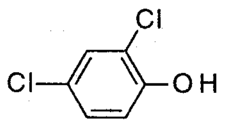
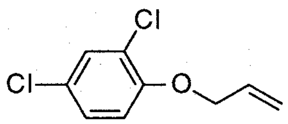
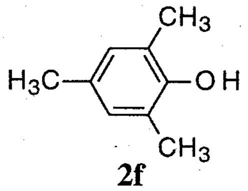
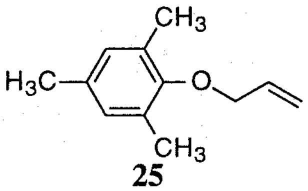
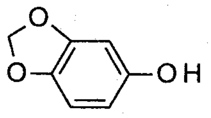
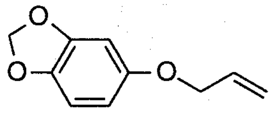
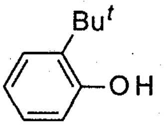
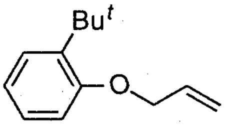


Entry	$Pd(OAc)_2 : PPh_3 : Ti(OPr^i)_4$ (in mmol)	Time / h	Yield of **22** / %[b]
1	0.025 : 0.1 : 0	20	34
2[c]	0.025 : 0.1 : 0	7	26
3	0.025 : 0.1 : 0.25	1	93
4	0 : 0.2 : 0.25	1	0
5[d]	0.025 : 0.1 : 0.25	20	91
6	0.01 : 0.04 : 0.25	1	61
7[c]	0.01 : 0.04 : 0.25	1	93
8	0.01 : 0.1 : 0.25	1	90

[a] Reaction conditions: **1j** (4 mmol), **2d** (1 mmol), in C_6H_6 (5 cm^3) at 50 °C. [b] GLC yield based on **2d** used. Reaction was carried out using MS4A (200 mg). [d] Reaction at rt.

for the present reaction. It was confirmed that the reaction did not occur in the absence of the palladium species (Entry 4). Note that compound **22** could also be produced in good yield in the reaction at room temperature or using a smaller amount of the palladium catalyst (1 mol%) (Entries 5, 7, and 8). In the latter case, either addition of MS4A or increase in the amount of PPh_3 added was needed to prevent catalyst deactivation which is probably due to water formed during the reaction.

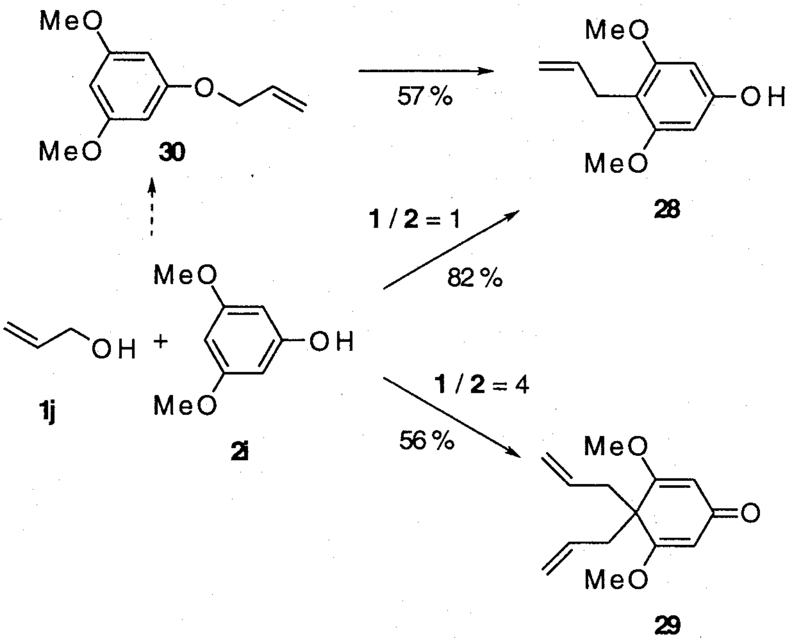
Table 4-6. Reaction of Allyl Alcohol (1j) with Phenols 2a,e-h[a]

2	Product	Yield / %[b]
 **2a**	 **23**	87
 **2e**	 **24**	78 (69) 2[c]
 **2f**	 **25**	78 (64)
 **2g**	 **26**	73 (67)
 **2h**	 **27**	81 (78)

[a] Reaction conditions: **1j** (4 mmol), **2** (1 mmol), $Pd(OAc)_2$ (0.01 mmol), PPh_3 (0.04 mmol), $Ti(OPr^i)_4$ (0.25 mmol), and MS4A (200 mg) in C_6H_6 (5 cm^3) at 50 °C for 4-20 h. [b] GLC yield based on **2** used. Value in parentheses indicates yield after purification. [c] Without $Ti(OPr^i)_4$.

Treatment of **1j** using phenols substituted by both electron-withdrawing and electron-donating groups (**2a,e-h**) also gave ethers **23-27** in good yields (Table 4-6). In the case of **2e**, the use of $Ti(OPr^i)_4$ was essential for the reaction to proceed catalytically. A phenol bearing a bulky substituent, Bu^t, at 2-position could also be reacted, whereas a more sterically crowded phenol, 2,6-di(*tert*-butyl)phenol, did not undergo the reaction.

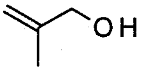
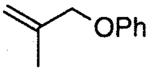
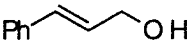
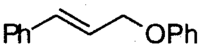
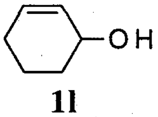
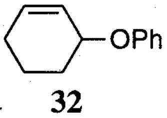
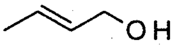
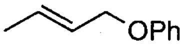
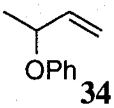
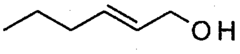
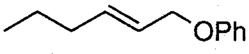
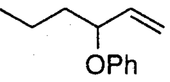
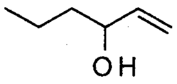
When 3,5-dimethoxyphenol (**2i**) whose aryl moiety seems to be relatively electron rich[20] was employed, C-allylated products **28** and **29** were obtained,[9f,21] no O-allylated products being detected (Scheme 4-2). Depending on the ratio of **1j** / **2i** used, monoallylated product **28** or diallylated product **29** was selectively produced. Since 1-(3,5-dimethoxyphenoxy)-2-propene (**30**) was found to be transformed to **28** under the present conditions, the C-allylated products may also be formed, at least in part, by isomerization of the ether **30**.



Scheme 4-2.

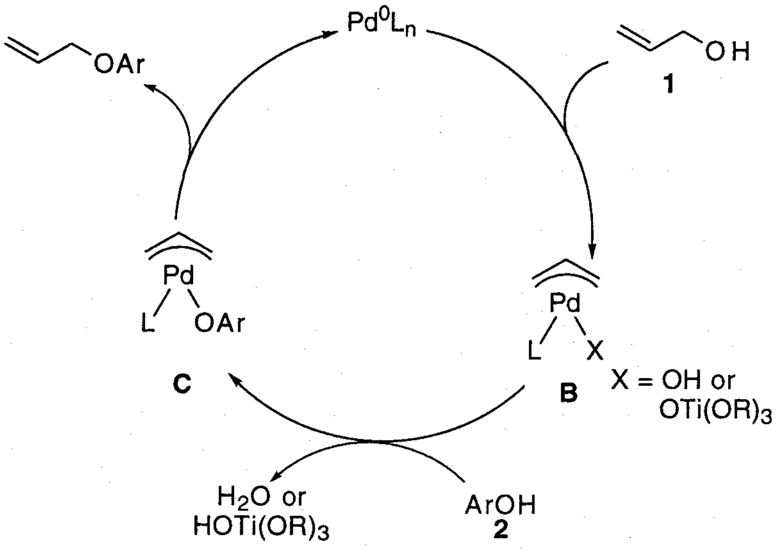
Results for etherification of a number of allyl alcohols **1** with phenol (**2a**) using $Pd(OAc)_2$, PPh_3, $Ti(OPr^i)_4$, and MS4A are summarized in Table 4-7. All of allyl alcohols examined underwent etherification smoothly to give the corresponding phenyl ethers in 71-89 % yields, while mixtures of regioisomeric ethers were formed in the cases using **1h-i,m**. The fact that **1h** and **1i** gave the same products may suggest that the reaction process involves a common π-allylpalladium intermediate.

Table 4-7. Reaction of Allyl Alcohols 1a,h-i,k-m with Phenol (2a)[a]

1	Product(s)		Yield / %[b]
 **1k**	 **31**		89
 **1a**	 **12**		75
 **1l**	 **32**		72
 **1m**	 **33**	 **34**	76 (81/19)
 **1h**	 **35**	 **36**	81 (67/33)
 **1i**	**35**	**36**	71 (68/32)

[a] Reaction conditions: **1** (1 mmol), **2a** (2 mmol), $Pd(OAc)_2$ (0.01 mmol), PPh_3 (0.04 mmol), $Ti(OPr^i)_4$ (0.25 mmol), and MS4A (200 mg) in C_6H_6 (5 cm^3) at 50 °C for 4-20 h. [b] GLC yield based on **1** used.

A possible mechanism for the formation of allyl aryl ethers from **1** and **2** is illustrated in Scheme 4-3, in which the substituent on allyl alcohol is omitted. Alcohol **1** or an allyl titanate, formed by alcohol exchange reaction between **1** and isopropoxide in $Ti(OPr^i)_4$,[19] reacts with Pd^0 species generated *in situ*[22] to afford a π-allylpalladium intermediate (**B**). Subsequently, the reaction of **B** with phenol **2** followed by reductive elimination gives allyl aryl ether. Under the present reaction conditions using $Ti(OPr^i)_4$, treatment of cinnamyl alcohol (**1a**) without phenols gave dicinnamyl ether quantitatively within 1 h, while part of this was transformed to cinnamyl isopropyl ether by elongation of the reaction time. Dicinnamyl ether may be formed by the reaction of **B** with another cinnamyl titanate molecule.[8] In the presence of phenols, which may be relatively more reactive toward the palladium center, **B** should be predominantly transformed to **C** to afford aryl ether. It would also be possible that **C** is formed by ligand exchange between **B** and $Ti(OAr)_n(OR)_{4-n}$ species generated in the reaction medium.



Scheme 4-3.

4-3. Experimental Section

^{1}H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively. MS data were obtained by EI. GLC analysis was carried out using a silicon OV-17 column (i. d. 2.6 mm x 1.5 m) or with a CBP-1 capillary column (i. d. 0.5 mm x 25 m).

The complexes $Pd(PPh_3)_4$[1a] and $[Pd(\eta^3\text{-1-phenylallyl})(OAc)]_2$ (**14**)[3b] were prepared by the methods reported previously. Allyl alcohols **1b**[23] and **1i**,[23] alcohol **15b**,[24] and ether **12**[11] were prepared according to the published procedures. Allyl alcohols **1c-g** were prepared by the reduction of the corresponding alkynols with $LiAlH_4$.[25] Ether **30** was prepared by the reaction of allyl chloride with **2i** using K_2CO_3 as base in DMF at 40 °C. Other starting materials were commercially available. Solvents were purified by standard methods before use.

Catalytic Phenoxycarbonylation of Allyl Alcohols. A mixture of a substituted allyl alcohol (2 mmol), **2** (226 mg, 2.4 mmol), $Pd(OAc)_2$ (22 mg, 0.1 mmol), PPh_3 (52 mg, 0.2 mmol), and benzene (5 cm^3) was placed in a 50 cm^3 stainless steel autoclave. Then, carbon monoxide (5 atm at room temperature) was charged and the mixture was magnetically stirred at 100 °C for 18 h. In the reaction under a normal pressure of carbon monoxide, a 100 cm^3 two-necked flask equipped with a balloon and a rubber cap was used. After cooling, the reaction mixture was poured into dilute hydrochloric acid, extracted with ether, and dried over sodium sulfate. Product was isolated by column chromatography on silica gel using hexane-methylene chloride as eluent. The reaction of 2-hydroxybenzyl alcohols **15a-b** was carried out by the essentially same procedure. Products **3**,[11] **9**,[11] **13**,[8] **16a**,[26] and **16b**[27] are known.

(*E*)-Phenyl 4-(4-methoxyphenyl)-3-butenoate (4): mp 65-67 °C; ^1H NMR δ 3.47 (dd, 2H, J = 1.5, 7.3 Hz), 3.81 (s, 3H), 6.25 (dt, 1H, J = 15.6, 7.3), 6.54 (d, 1H, J = 15.6 Hz), 6.84-6.88 (m, 2H), 7.09-7.12 (m, 2H), 7.21-7.25 (m, 1H), 7.32-7.40 (m, 4H); MS *m/z* 268 (M^+). Anal. Calcd for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 75.74; H, 6.07.

(*E*)-Phenyl 4-(4-methylphenyl)-3-butenoate (5): mp 34-36 °C; ^1H NMR δ 2.34 (s, 3H), 3.48 (dd, 2H, J = 1.5, 6.8 Hz), 6.34 (dt, 1H, J = 15.6, 6.8), 6.57 (d, 1H, J = 15.6 Hz), 7.08-7.14 (m, 4H), 7.22-7.26 (m, 1H), 7.30 (d, 2H, J = 7.8 Hz), 7.36-7.40 (m, 2H); MS *m/z* 252 (M^+). Anal. Calcd for $C_{17}H_{16}O_2$: C, 80.93; H, 6.39. Found: C, 80.53; H, 6.43.

(*E*)-Phenyl 4-(4-chlorophenyl)-3-butenoate (6): mp 63-64 °C; ^1H NMR δ 3.49 (dd, 2H, J = 1.5, 7.3 Hz), 6.38 (dt, 1H, J = 15.6, 7.3), 6.56 (d, 1H, J = 15.6 Hz), 7.21-7.40 (m, 9H); MS *m/z* 272, 274 (M^+). Anal. Calcd for $C_{16}H_{13}O_2Cl$: C, 70.46; H, 4.80; Cl, 13.00. Found: C, 70.39; H, 4.85; Cl, 13.08.

(*E*)-Phenyl 4-(2-thienyl)-3-butenoate (7): mp 54-55 °C; ^1H NMR δ 3.46 (dd, 2H, J = 1.5, 7.3 Hz), 6.23 (dt, 1H, J = 15.6, 7.3), 6.73 (d, 1H, J = 15.6 Hz), 6.95-6.98 (m, 2H), 7.09-7.12 (m, 2H), 7.16-7.17 (m, 1H), 7.21-7.25 (m, 1H), 7.36-7.40 (m, 2H); MS *m/z* 244 (M^+). Anal. Calcd for $C_{14}H_{12}O_2S$: C, 68.83; H, 4.95; S, 13.12. Found: C, 68.59; H, 5.02; S, 13.04.

(*E*)-Phenyl 4-(2-naphthyl)-3-butenoate (8): mp 104-105 °C; ^1H NMR δ 3.56 (dd, 2H, J = 1.5, 6.8 Hz), 6.53 (dt, 1H, J = 15.6, 6.8), 6.77 (d, 1H, J = 15.6 Hz), 7.11-7.14 (m, 2H), 7.22-7.26 (m, 1H), 7.37-7.47 (m, 4H), 7.62-7.64 (m, 1H), 7.75-7.82 (m, 4H); MS *m/z* 288 (M^+). Anal. Calcd for $C_{20}H_{16}O_2$: C, 83.31; H, 5.59. Found: C, 82.92; H, 5.60.

(*E*)-(4-Methoxyphenyl) 4-phenyl-3-butenoate (10): mp 82-83 °C; ^1H NMR δ 3.48 (dd, 2H, J = 1.5, 7.3 Hz), 3.79 (s, 3H), 6.40 (dt, 1H, J = 15.6, 7.3), 6.55 (d, 1H, J = 15.6 Hz), 6.87-6.91 (m, 2H), 7.00-7.03 (m, 2H), 7.23-7.42 (m, 5H); MS *m/z* 268 (M^+). Anal. Calcd for

$C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 76.08; H, 6.01.

(*E*)-(3-Chlorophenyl) 4-phenyl-3-butenoate (11): mp 59-60 °C; ^{1}H NMR δ 3.49 (dd, 2H, *J* = 1.5, 7.3 Hz), 6.37 (dt, 1H, *J* = 15.6, 7.3), 6.61 (d, 1H, *J* = 15.6 Hz), 7.01-7.04 (m, 1H), 7.14-7.16 (m, 1H), 7.21-7.37 (m, 5H), 7.40-7.42 (m, 2H); MS *m/z* 272, 274 (M^+). Anal. Calcd for $C_{16}H_{13}O_2Cl$: C, 70.46; H, 4.80; Cl, 13.00. Found: C, 70.38; H, 4.83; Cl, 12.98.

Stoichiometric Carbonylation of $[Pd(\eta^3\text{-1-phenylallyl})(OAc)]_2$ (14) in the Presence of PPh_3. A mixture of ROH (1 or 2 mmol), **14** (57 mg, 0.1 mmol), PPh_3 (52 mg, 0.2 mmol), bibenzyl (ca. 10 mg) as an internal standard, and toluene (5 cm^3) was stirred under CO (1 atm) at 80 °C. The time course of the reaction was monitored by GLC.

Reaction of 1 or 2-Naphthols 19 with Aldehydes 20 under Carbon Monoxide: Typical Procedure. A mixture of **19** (2 mmol), **20** (2-10 mmol), a palladium complex (0.05-0.1 mmol), carboxylic acid (0.05-0.1 mmol), and benzene (5 cm^3) was placed in a 50 cm^3 stainless steel autoclave. Then, carbon monoxide (5 atm at room temperature) was charged and the mixture was magnetically stirred at 120-125 °C for 18 h. After cooling, the reaction mixture was poured into water, extracted with ether, and dried over sodium sulfate. Product **21** was isolated by column chromatography on silica gel using hexane-methylene chloride as eluant.

3-Methylnaphtho[1,2-*b*]furan-2(3*H*)-one (21a): mp 80-81 °C; ^{1}H NMR δ 1.66 (d, 3H, *J* = 7.8 Hz), 3.93 (q, 1H, *J* = 7.8 Hz), 7.37 (d, 1H, *J* = 8.3 Hz), 7.51-7.59 (m, 2H), 7.67 (d, 1H, *J* = 8.3 Hz), 7.88 (dd, 1H, *J* = 1.5, 7.3 Hz), 8.04 (dd, 1H, *J* = 1.0, 8.3 Hz); IR (KBr) 1792 cm^{-1}; MS *m/z* 198 (M^+). Anal. Calcd for $C_{13}H_{10}O_2$: C, 78.77; H, 5.09. Found: C, 78.66; H, 5.09.

3-*n*-Heptylnaphtho[1,2-*b*]furan-2(3*H*)-one (21b): mp 59-60 °C; ^{1}H NMR δ 0.85 (t, 3H, *J* = 6.8 Hz), 1.23-1.45 (m, 10H), 2.04-2.09 (m, 2H),3.90 (t, 1H, *J* = 6.1 Hz), 7.36 (d, 1H, *J* = 8.3 Hz), 7.49-7.57 (m, 2H), 7.65 (d, 1H, *J* = 8.3 Hz), 7.87 (d, 1H, *J* = 7.3 Hz), 8.02 (d, 1H, *J* = 8.3 Hz); MS *m/z* 282 (M^+). Anal. Calcd for $C_{19}H_{22}O_2$: C, 80.81; H, 7.85. Found: C, 80.97; H, 7.91.

3-*i*-Propylnaphtho[1,2-*b*]furan-2(3*H*)-one (21c): mp 60-61 °C; ^{1}H NMR δ 1.03 (d, 3H, *J* = 6.8 Hz), 1.13 (d, 3H, *J* = 6.8 Hz), 2.54-2.59 (m, 1H), 3.84 (d, 1H, *J* = 3.9 Hz), 7.40 (d, 1H, *J* = 8.3 Hz), 7.51-7.59 (m, 2H), 7.66 (d, 1H, *J* = 8.3 Hz), 7.88 (d, 1H, *J* = 8.8 Hz), 8.04 (d, 1H, *J* = 8.3 Hz); IR (KBr) 1794 cm^{-1}; MS *m/z* 226 (M^+). Anal. Calcd for

$C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found: C, 79.58; H, 6.30.

3-Phenylnaphtho[1,2-*b*]furan-2(3*H*)-one (21d): mp 129-130 °C; ^{1}H NMR δ 5.07 (s, 1H), 7.24-7.39 (m, 6H), 7.54-7.62 (m, 2H), 7.68 (d, 1H, *J* = 8.3 Hz), 7.90 (d, 1H, *J* = 7.8 Hz), 8.09 (d, 1H, *J* = 8.3 Hz); MS *m/z* 260 (M^+). Anal. Calcd for $C_{18}H_{12}O_2$: C, 83.06; H, 4.65. Found: C, 83.34; H, 4.61.

5-Methoxy-3-methynaphtho[1,2-*b*]furan-2(3*H*)-one (21e): mp 86-87 °C; ^{1}H NMR δ 1.65 (d, 3H, *J* = 7.3 Hz), 3.90 (q, 1H, *J* = 7.8 Hz), 4.01 (s, 3H), 6.69 (s, 1H), 7.53 (ddd, 1H, *J* = 1.5, 7.3, 8.8 Hz), 7.59 (ddd, 1H, *J* = 1.0, 6.9, 7.9 Hz), 7.97 (d, 1H, *J* = 8.3 Hz), 8.27 (d, 1H, *J* = 8.3 Hz); IR (KBr) 1794 cm^{-1}; HRMS *m/z* (M^+) Calcd for $C_{14}H_{12}O_3$: 228.0787. Found: 228.0789.

3-Methylnaphtho[2,1-*b*]furan-2(3*H*)-one (21f): mp 126-127 °C; ^{1}H NMR δ 1.79 (d, 3H, *J* = 7.8 Hz), 4.11 (q, 1H, *J* = 7.8 Hz), 7.36 (d, 1H, *J* = 8.8 Hz), 7.45 (ddd, 1H, *J* = 1.0, 6.8, 8.3 Hz), 7.57 (ddd, 1H, *J* = 1.5, 6.8, 8.3 Hz), 7.77 (d, 1H, *J* = 8.3 Hz), 7.84 (d, 1H, *J* = 9.3 Hz), 7.90 (d, 1H, *J* = 8.3 Hz); IR (KBr) 1794 cm^{-1}; MS *m/z* 198 (M^+). Anal. Calcd for $C_{13}H_{10}O_2$: C, 78.77; H, 5.09. Found: C, 78.45; H, 5.14.

5-Methoxy-3-methynaphtho[2,1-*b*]furan-2(3*H*)-one (21g): mp 116 °C; ^{1}H NMR δ 1.78 (d, 3H, *J* = 7.3 Hz), 3.95 (s, 3H), 4.06 (q, 1H, *J* = 7.8 Hz), 6.99 (d, 1H, *J* = 2.5 Hz), 7.11 (dd, 1H, *J* = 2.4, 8.8 Hz), 7.20 (d, 1H, *J* = 8.3 Hz), 7.75 (d, 1H, *J* = 8.8 Hz), 7.78 (d, 1H, *J* = 9.3 Hz); IR (KBr) 1802 cm^{-1}; MS *m/z* 228 (M^+). Anal. Calcd for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30. Found: C, 73.52; H, 5.39.

Etherification of Allyl Alcohols Using Phenols. A mixture of **1** (1-4 mmol), **2** (1-2 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), PPh_3 (10 mg, 0.04 mmol), $Ti(OPr^i)_4$ (0.075 cm^3, 0.25 mmol), MS4A (200 mg), and benzene (5 cm^3) was stirred under nitrogen at 50 °C for 4-20 h. After cooling, the reaction mixture was poured into dilute hydrochloric acid, extracted with ether, and dried over sodium sulfate. Product was isolated by column chromatography on silica gel using hexane-ethyl acetate (99:1) as eluent.

Products **22**,[9a] **23**,[9f] **24**,[28] **25**,[29] **26**,[30] **27**,[31] **31**,[32] **32**,[9f] **33**,[32] **34**,[32] **35**,[9f] and **36**[9f] are known.

4-Allyl-3,5-dimethoxyphenol (28): mp 85-87 °C; ^{1}H NMR (d_6-DMSO) δ 3.16 (d, 2H, *J* = 5.9 Hz), 3.33 (s, 6H), 4.81 (t, 1H, *J* = 1.5 Hz), 4.84 (dt, 1H, *J* = 4.4, 1.5 Hz), 5.73-5.83 (m, 1H), 6.05 (s, 2H), 7.29 (s, 1H); MS *m/z* 194 (M^+). Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.26. Found: C, 67.83; H, 7.21.

4,4-Dially-3,5-dimethoxy-2,5-cyclohexadien-1-one (29): mp 71-72 °C; ^{1}H NMR ($CDCl_3$) δ 2.57 (d, 4H, $J = 7.3$ Hz), 3.70 (s, 6H), 4.92 (dt, 2H, $J = 5.9$, 1.0 Hz), 4.96 (dd, 2H, $J = 13.2$, 2.0 Hz), 5.33-5.49 (m, 2H), 5.54 (s, 2H) ; ^{13}C NMR ($CDCl_3$) δ 40.99, 51.19, 55.79, 103.27, 117.75, 132.20, 172.92, 188.37; MS *m/z* 234 (M^+). Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.59; H, 7.76.

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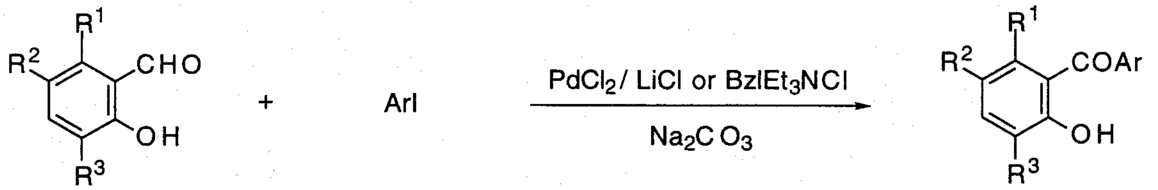
Chapter 5. Palladium-Catalyzed Intermolecular Arylation of Salicylaldehydes and Other Phenolic Compounds Using Aryl Iodides

5-1. Introduction

The palladium-catalyzed substitution reactions of aryl halides and their synthetic equivalents such as aryl triflates are now recognized to be highly useful for the preparation of substituted aromatic compounds. They involve arylpalladium(II) complexes as common intermediates which react with various reagents including alkenes, alkynes, and a number of organometallic species to give the corresponding products.[1] Meanwhile, we observed that phenols can act as effective nucleophiles in the palladium-catalyzed carbonylation reactions of terminal alkynes,[2] aryl iodides (chapter 2), and benzylic and allylic alcohols (chapter 4) to give the corresponding aryl esters, suggesting that phenolic oxygen may readily coordinate to palladium(II) species. During a further investigation into utilization of the coordination ability, we have found that intermolecular arylation of 2-hydroxybenzaldehyde, *i. e.* salicylaldehyde, and its derivatives using aryl iodides in the presence of a palladium catalyst smoothly proceeds accompanied by cleavage of the aldehyde C-H bond to produce the corresponding 2-aroylphenols (eq 5-1). Although activation of aldehyde C-H bond has reported to be involved in palladium-catalyzed reactions of *o*-halobenzaldehydes with alkenes[3] or alkynes,[4] there have so far been, to our knowledge, no examples dealing with the direct catalytic arylation of the C-H bond with aryl halides. 2-Phenylphenols and naphthols have been found to be also capable of arylating effectively and regioselectively by treatment with aryl halides in the presence of an appropriate base.



(5-1)

3a-h

1a: R^1=R^2=R^3=H
1b: R^1=R^2=H, R^3=OMe
1c: R^1=R^3=H, R^2=Cl
1d: R^1=R^3=H, R^2=NO_2
1e: R^1R^2=  , R^3=H

2a: Ar=Ph
2b: Ar=p-$MeOC_6H_4$
2c: Ar=p-ClC_6H_4
2d: Ar=1-naphthy

5-2. Results and Discussion

When a mixture of salicylaldehyde (**1a**, 1 mmol) and iodobenzene (**2a**, 2 mmol) was heated in the presence of $PdCl_2$ (0.05 mmol) and Na_2CO_3 (2 mmol) in DMF (10 cm^3) at 100 ^oC for 10 h under nitrogen, 2-hydroxybenzophenone (**3a**) was produced in a yield of 84 % (Entry 1 in Table 5-1). Addition of LiCl (0.2 mmol) remarkably promoted the reaction and enhanced the yield of **3a** (91 %) (Entry 2). Further addition of LiCl detrimentally decreased the product yield (Entry 3). An ammonium chloride, $BzlEt_3NCl$, could be used in place of LiCl, although a stoichiometric amount of the chloride was required for a high yield coupling (Entry 5). Product **3a** was also efficiently formed using a half amount of the palladium catalyst by elongation of reaction time (Entry 6). An organic amine base, $Pr^i{}_2NEt$, in place of Na_2CO_3 was not effective for the reaction (Entry 7). It should be noted that treatment of 2-methoxybenzaldehyde, in place of **1a**, with **2a** gave only a trace amount of the corresponding coupling product, suggesting that the phenolic function in **1** acts as a good anchor for the reaction.

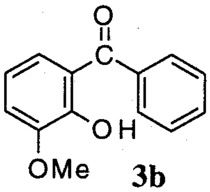
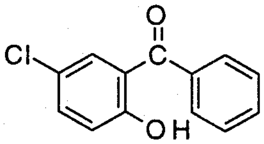
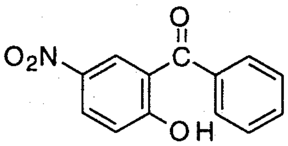
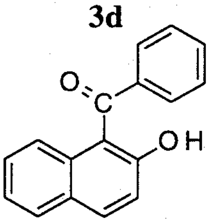
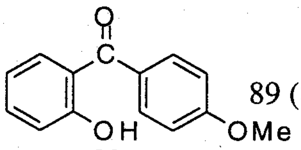
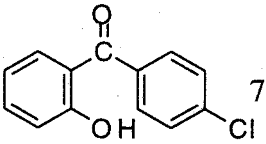
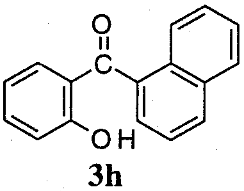
Table 5-1. Cross-Coupling of Salicylaldehyde (1a) with Iodobenzene (2a)[a]

Entry	Additive (mmol)	Time / h	Yield of **3a** / %[b]
1		10	84
2	LiCl (0.2)	3.5	91
3	LiCl (1)	6	84
4	$BzlEt_3NCl$ (0.5)	15	81
5	$BzlEt_3NCl$ (1)	4	96
6[c]	LiCl (0.2)	25	93
7[d]	LiCl (0.2)	10	25

[a] Reaction conditions: **1a** (1 mmol), **2a** (2 mmol), $PdCl_2$ (0.05 mmol), Na_2CO_3 (2 mmol) in DMF (10 cm^3) at 100 °C. [b] GLC yield based on **1a** used. [c] $PdCl_2$ (0.025 mmol) was used. [d] $Pr^i{}_2NEt$ (2 mmol) was used in place of Na_2CO_3.

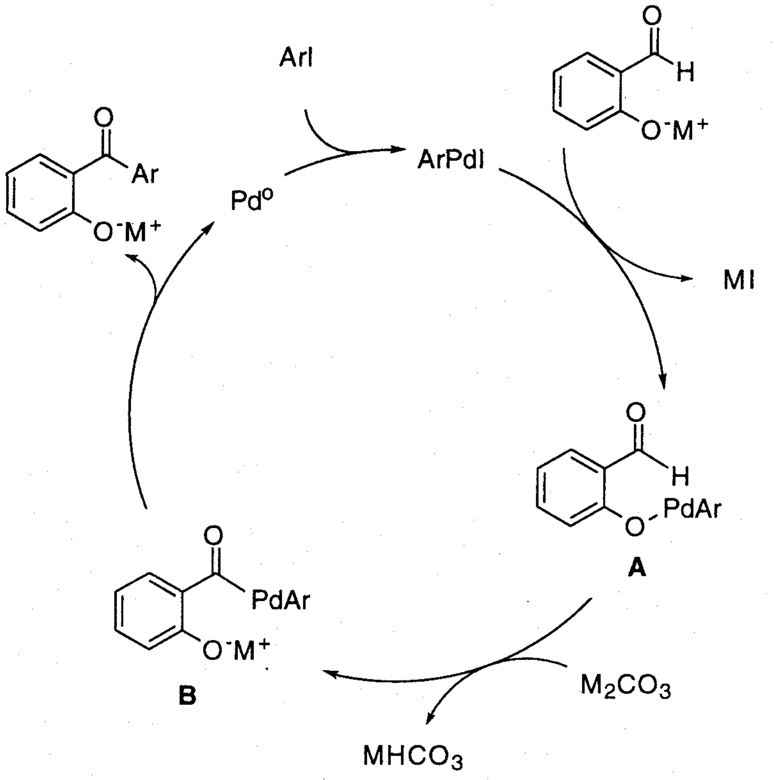
Table 5-2 summarizes the results for the reactions of 2-hydroxybenzaldehydes (**1a-1d**) and 2-hydroxy-1-naphthaldehyde (**1e**) with aryl iodides (**2a-2d**) using $PdCl_2$, LiCl, and Na_2CO_3. It can be seen that unsymmetrical diaryl ketones (**3b-3h**) could be produced in fair to good yields.

Table 5-2. Cross-Coupling of Hydroxyaldehydes 1 with Aryl Iodides 2[a]

1	2	Temp. / °C	Time / h	Product	Yield / %[b]
1b	**2a**	100	8	 **3b**	81 (70)
1c	**2a**	100	6	 **3c**	63 (51)
1d	**2a**	120	22	 **3d**	72 (58)
1e	**2a**	100	3	 **3e**	85 (73)
1a	**2b**	100	6	 **3f**	89 (81)
1a	**2c**	100	2	 **3g**	70 (57)
1a	**2d**	100	24	 **3h**	50 (45)

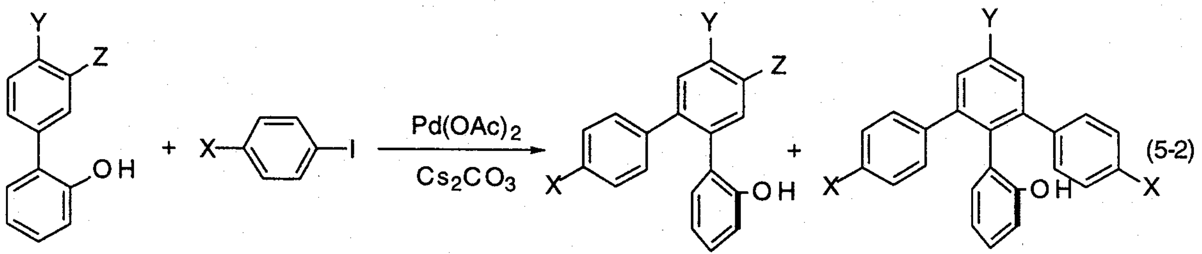
[a] Reaction conditions: **1** (1 mmol), **2** (2 mmol), $PdCl_2$ (0.05 mmol), LiCl (0.2 mmol), Na_2CO_3 (2 mmol) in DMF (10 cm^3). [b] GLC yield based on **1** used. Value in parentheses indicates yield after purification.

A possible mechanism for the present cross-coupling of hydroxybenzaldehydes **1** with aryl iodides **2** is illustrated in Scheme 5-1, in which neutral ligands and substituents attached to salicylaldehyde are omitted. Oxidative addition of aryl iodide to palladium(0) species generated *in situ* followed by reaction with the phenolate forms an aryl(aryloxy)palladium intermediate **A**. Then, **A** may be transformed to aroyl(aryl)palladium species **B**, and the subsequent reductive elimination from **B** occurs to give arylated product.[5] Coordination of the phenolic oxygen to the palladium center in **A** is, thus, considered to be the trigger for the effective and regioselective C-H bond activation.



Scheme 5-1.

The above observation prompted us to investigate the activation of other kinds of C-H bond attached to hydroxyarenes using the present procedure. When 2-phenylphenol (**4**, 1.0 mmol) was treated with iodobenzene (**2a**, 1.2 mmol) in the presence of $Pd(OAc)_2$ (0.05 mmol) using Cs_2CO_3 (1.2 mmol) as base, a phenyl group was selectively introduced onto the 2'-position of **4**, accompanied by aromatic sp^2 C-H bond cleavage,[6] to produce 1,1':2',1''-terphenyl-2-ol (**8a**) in a yield of 76 % (eq 5-2 and Table 5-3). In this case, other alkaline bases K_2CO_3 and Na_2CO_3 were



4-7 **2a, b** **8a, b, 9a-11a** **12a, b, 13a**

a; X = H
b; X = OMe

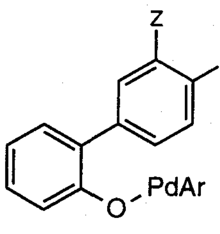
much less effective than Cs_2CO_3 (25 % and 13 %, respectively, under the same conditions). $PdCl_2$ could be used in place of $Pd(OAc)_2$, the yield of **8a** being 66 %. Increase in the amount of both **2a** and the base to 4 mmol was found to cause further arylation to afford the corresponding diarylated product **12a** in 62 % yield along with a minor amount of **8a** (25 %).[7] The results for the reactions of 4-iodoanisole (**2b**) with **4** and **2a** with 2-(4-methylphenyl)phenol (**5**) may demonstrate the generality of the present diarylation as well as monoarylation. In the reactions of 2-(3'-substituted phenyl)phenols **6** and **7** with **2a**, however, only monoarylated products **10a** and **11a**, respectively, were formed even with an excess amount of **2a**.

Table 5-3. Cross-Coupling of 2-Phenylphenols 4-7with Aryl Iodides 2a, b

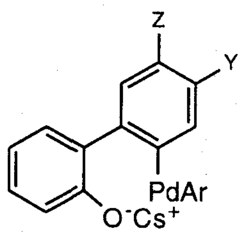
Entry	X	Y	Z	Starting materials		Conditions	Time / h	Product, % yield[b]
				2	ArOH			
1	H	H	H	**2a**	**4**	A	22	**8a**, 76 (63)
2	H	H	H	**2a**	**4**	B	44	**12a**, 62 (56)
3	H	Me	H	**2a**	**5**	A	22	**9a**, 76 (60)
4	H	Me	H	**2a**	**5**	B	22	**13a**, 65 (63)
5	H	H	OMe	**2a**	**6**	A[c]	7	**10a**, 88 (85)
6	H	H	NO_2	**2a**	**7**	A[c]	44	**11a**, 87 (72)
7	OMe	H	H	**2b**	**4**	A	22	**8b**, 80 (70)
8	OMe	H	H	**2b**	**4**	B	44	**12b**, 70 (57)

[a] Reaction conditions: A, ArOH (1 mmol), **2** (1.2 mmol), $Pd(OAc)_2$ (0.05 mmol), Cs_2CO_3 (1.2 mmol), MS 4A (200 mg), DMF (5 cm^3), 100 °C; B, ArOH (1 mmol), **2** (4 mmol), $PdCl_2$ (0.05 mmol), Cs_2CO_3 (4 mmol), DMF (5 cm^3), 100 °C. [b] Determined by GC, based on ArOH used. Value in parentheses indicates yield after isolation. [c] **2a** (2 mmol) and Cs_2CO_3 (2 mmol) were used.

The reaction of 2-phenylphenols seems to proceed *via* intermediates **A'** and **B'**, which are similar to those involved in the reaction of salycylaldehydes **1**:[5] the observed regioselectivity, exclusive arylation at the 2'-positions of 2-phenylphenols, may be attributed to the coordination ability of its phenolic oxygen to the palladium center in the intermediate **A'**. The results of the reactions of **6** and **7** with **2a** may suggest that (a) the existence of a substituent at the 3'-position of **4** prevents the second arylation by steric reasons, and (b) the transformation of **A'** to **B'** is feasible even when the substituent is strongly electron-withdrawing as well as electron-releasing.[8]

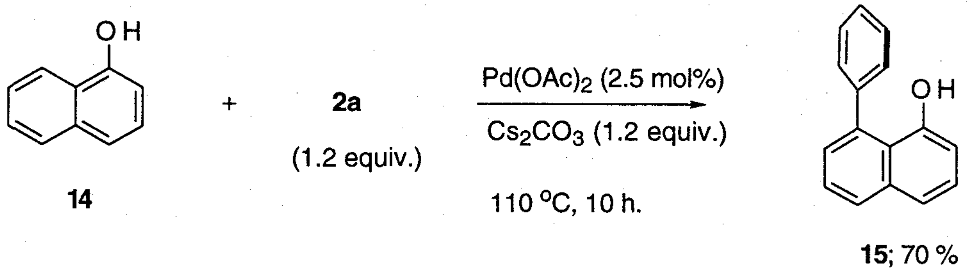


A'



B'

Using the present catalytic system, 1-naphthol (**14**) could also undergo monophenylation to give 8-phenyl-1-naphthol (**15**) selectively (eq 5-3). The use of Cs_2CO_3 was also essential for the catalytic reaction to take place smoothly. On the other hand, it was of considerable interest that, when 2-naphthol (**16**) was treated with 2 equivalents of bromobenzene (**2e**) using $Pd(OAc)_2/PPh_3$, *formally* diphenylated compound **17** was obtained as the predominant product (eq 5-4). The first step of this reaction, monophenylation at the 1-position of **16**, may involve nucleophilic attack of the corresponding naphtholate on phenylpalladium(II) species generated *in situ*. Note that, while palladium-catalyzed intramolecular coupling of aryl halides with enolates including phenolates has been known,[9] the corresponding intermolecular version has been limited to only few reactions using nitriles as carbon nucleophiles.[10] Nevertheless, the present procedure was found to bring about the intermolecular cross-coupling of **2a** with 1,3-diphenyl-2-propanone (**18**) to give 1,1,3,3-tetraphenyl-2-propanone (**19**) (eq 5-5).



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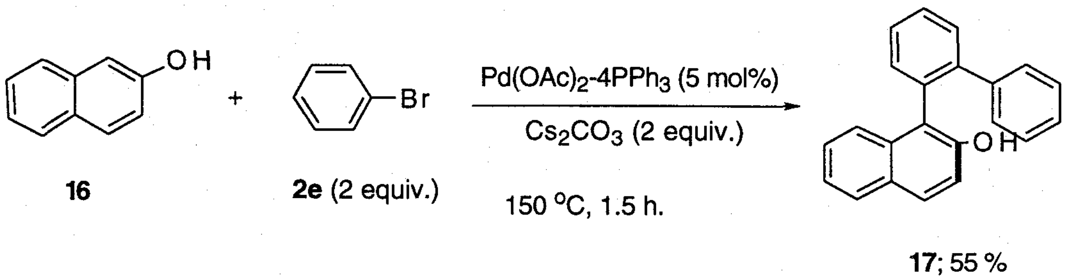
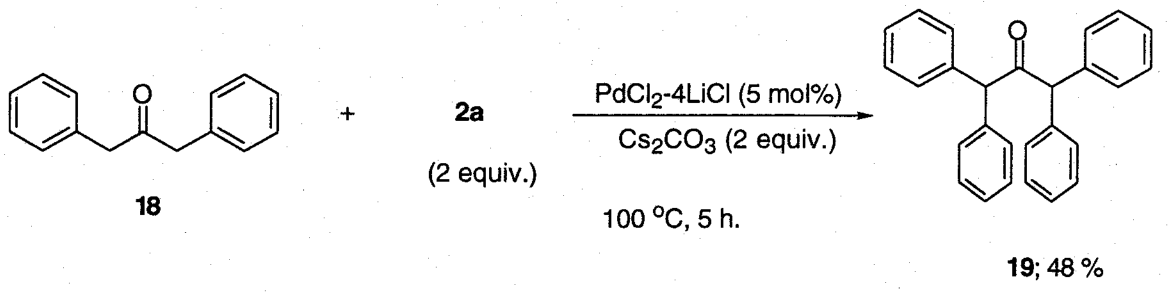


(5-4)



(5-5)

5-3. Experimental Section

^{1}H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively. MS data were obtained by EI. GLC analysis was carried out using a silicon OV-17 column (i. d. 2.6 mm x 1.5 m) or with a CBP-1 capillary column (i. d. 0.5 mm x 25 m).

2-Phenylphenols **5-7** were prepared according to the published procedures.[11] Other starting materials were commercially available. Solvents were purified by standard methods before use.

Cross-Coupling of Salicylaldehydes with Aryl Iodides. A mixture of a substituted salicylaldehyde (1 mmol), **2** (2 mmol), $PdCl_2$ (22 mg, 0.05 mmol), LiCl (8.5 mg, 0.2 mmol), Na_2CO_3 (212 mg, 2 mmol), and DMF (10 cm^3) was stirred under nitrogen at 100-120 °C for 2-24 h. After cooling, the reaction mixture was poured into dilute hydrochloric acid, extracted with ether, and dried over sodium sulfate. Product was isolated by column chromatography on silica gel using hexane-methylene chloride or hexane-ethyl acetate as eluent. Products **3a**, **3b**,[12] **3c**, **3d**,[13] **3e**,[14] **3f**,[15] **3g**,[16]and **3h**[17] are known.

Cross-Coupling of 2-Phenylphenols and Naphthols with Iodo- or Bromobenzene. A mixture of **2** (1.2-4 mmol), ArOH **4-7**, **14**, or **16** (1 mmol), a palladium catalyst (0.025-0.05 mmol), Cs_2CO_3 (1.2-4 mmol), and DMF (5 cm^3) was stirred in the presence or absence of molecular sieves 4A (200 mg) under nitrogen at 100-150 °C for 1.5-44 h. After cooling, the reaction mixture was poured into dilute hydrochloric acid, extracted with ether, and dried over sodium sulfate. Product was isolated by column chromatography on silica gel using hexane-methylene chloride or hexane-ethyl acetate as eluent. Product data for the obtained new compounds are listed below. The structural determination was made with the aid of NOE, COSY, and HOHAHA techniques in ^{1}H NMR measurement. Compounds **8a**,[18] **15**,[19] and **19**[20] are known.

2''-Methoxy-1,1':2',1''-terphenyl-2-ol (8b): m.p. 88 °C; ^{1}H NMR: δ 3.76 (s, 3H, OMe), 4.77 (s, 1H, OH), 6.75 (dt, 2H, $J = 8.8$, 2.0 Hz, H-3"), 6.80 (dd, 1H, $J = 1.0$, 7.8 Hz, H-3), 6.87 (dt, 1H, $J= 1.0$, 7.3 Hz, H-5), 7.07 (dd, 1H, $J= 1.5$, 7.3 Hz, H-6), 7.09 (dt, 2H, $J= 8.8$, 2.0 Hz, H-2"), 7.17 (dt, $J =$ 1H, 1.5, 7.8 Hz, H-4), 7.37-7.49 (m, 4H); MS *m/z* 276 (M^+). Anal. Calcd for $C_{19}H_{16}O_2$: C, 82.58; H, 5.84. Found: C, 82.36; H, 5.95.

4'-Methyl-1,1':2',1"-terphenyl-2-ol (9a): m.p. 64 °C; ^{1}H NMR: δ 2.45 (s, 3H), 4.81 (s, 1H), 6.78 (dd, 1H, $J= 1.0$, 8.3 Hz), 6.81 (dt, 1H, $J= 1.0$, 7.3 Hz), 7.01 (dd, 1H, $J= 1.9$, 7.3 Hz), 7.11-7.22 (m, 6H), 7.25-7.33 (m, 3H); MS *m/z* 260 (M^+). Anal. Calcd for $C_{19}H_{16}O$: C, 87.66; H, 6.19. Found: C, 87.42; H, 6.18.

5'-Methoxy-1,1':2',1"-terphenyl-2-ol (10a): m.p. 136-137 °C; ^{1}H NMR: δ 3.84 (s, 3H), 4.87 (s, 1H), 6.78 (dd, 1H, $J= 1.0$, 8.3 Hz), 6.84 (dt, 1H, $J= 1.0$, 7.3 Hz), 6.93 (d, 1H, $J=$ 2.4 Hz), 7.03 (dd, 1H, $J= 2.4$, 8.3 Hz), 7.06 (dd, 1H, $J= 1.5$, 7.3 Hz), 7.10-7.21 (m, 6H), 7.43 (d, 1H, $J = 8.3$Hz); MS *m/z* 276 (M^+). Anal. Calcd for $C_{19}H_{16}O_2$: C, 82.58; H, 5.84. Found: C, 82.36; H, 5.87.

5'-Nitro-1,1':2',1"-terphenyl-2-ol (11a): m.p. 144-145 °C,^{1}H NMR: δ 4.65 (s, 1H), 6.75 (dd, 1H, $J = 1.0$, 8.3 Hz), 6.90 (dt, 1H, $J = 1.0$, 7.3 Hz), 7.07 (dd, 1H, $J = 1.5$, 7.3 Hz), 7.17-7.28 (m, 6H), 7.64 (dd, 1H, $J = 1.5$, 8.8 Hz), 8.30 (dd, 1H, $J = 2.4$. 8.8 Hz), 8.31 (s, 1H); MS *m/z* 291 (M^+). Anal. Calcd for $C_{18}H_{13}NO_3$: C, 74.22; H, 4.50; N, 4.81. Found: C, 74.09; H, 4.70; N, 4.68.

2-(2'-Hydroxyphenyl)-1,3-diphenylbenzene (12a): m.p. 150-151 °C; ^{1}H NMR: δ 4.66 (s, 1H), 6.54 (dd, 1H, $J = 1.0$, 8.3 Hz), 6.58 (dt, 1H, $J = 1.0$, 7.3 Hz), 6.76 (dd, 1H, $J =$ 1.5, 7.3 Hz), 6.94 (dt, 1H, $J= 1.5$, 7.3 Hz), 7.09 -7.18 (m, 10H), 7.45-7.53 (m, 3H); MS *m/z* 322 (M^+). Anal. Calcd for $C_{24}H_{18}O$: C, 89.41; H, 5.63. Found: C, 89.15; H, 5.61.

2-(2'-Hydroxyphenyl)-1,3-bis(4-methoxyphenyl)benzene (12b): m.p. 153-154 °C; ^{1}H NMR: δ 3.74 (s, 6H, OMe), 4.63 (s, 1H, OH), 6.61 (dd, 1H, $J= 1.0$, 8.3 Hz, H-3), 6.64 (dt, 1H, $J= 1.0$, 7.3 Hz, H-5), 6.71 (dt, 4H, $J= 8.8$, 2.0 Hz, H-3"), 6.77 (dd, 1H, $J= 1.5$, 7.3 Hz, H-6), 6.99 (dt, 1H, $J= 1.5$, 8.3 Hz, H-4), 7.04 (dt, 4H, $J = 8.8$, 2.0 Hz, H-2"), 7.42-7.52 (m, 3H); MS *m/z* 382 (M^+). Anal. Calcd for $C_{26}H_{22}O_3$: C, 81.65; H, 5.80. Found: C, 81.23; H, 5.94.

2-(2'-Hydroxyphenyl)-1,3-diphenyl-4-toluene (13a): m.p. 122.5-123.5 °C; ^{1}H NMR: δ 2.49 (s, 3H), 4.63 (s, 1H), 6.57 (dd, 1H, $J = 1.0$, 7.3 Hz), 6.60 (dt, 1H, $J = 1.0$, 7.3 Hz), 6.76 (dd, 1H, $J = 1.5$, 7.3 Hz), 6.96 (dt, 1H, $J = 1.5$, 7.3 Hz), 7.11-7.18 (m, 10H), 7.31 (s, 2H);

MS *m/z* 336 (M^+). Anal. Calcd for $C_{25}H_{20}O$: C, 89.25; H, 5.99. Found: C, 88.92; H, 6.08.

1-(2'-Phenylphenyl)-2-naphthol (**17**): m.p. 117-118 °C; ^{1}H NMR: δ 4.93 (s, 1H, OH), 7.02-7.10 (m, 6H), 7.27 (dt, 1H, *J* = 1.5, 8.1 Hz, H-6), 7.31 (dt, 1H, *J* = 1.5, 8.1 Hz, H-7), 7.36 (d, 1H, *J* = 8.1 Hz, H-8), 7.41 (d, 1H, *J* = 7.3 Hz, H-3'), 7.54 (dt, 1H, *J* = 2.2, 7.3 Hz, H-4'), 7.59 (dt, 1H, *J* = 1.5, 7.3 Hz, H-5'), 7.62 (dd, 1H, *J* = 2.2, 7.3 Hz, H-6'), 7.69 (d, 1H, *J* = 8.8 Hz, H-4), 7.73 (d, 1H, *J* = 8.1 Hz, H-5); MS *m/z* 296 (M^+). Anal. Calcd for $C_{22}H_{16}O$: C, 89.16; H, 5.44. Found: C, 88.95; H, 5.66.

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Conclusion

This thesis mainly deals with development of new carbonylation and related reactions of aromatic compounds using homogeneous palladium catalysts. The results obtained through this work are summarized as follows.

In chapter 1, desulfonylative carbonylation of arenesulfonyl compounds, sulfonyl chlorides and thiosulfonic acid esters, was found to proceed efficiently by the use of a palladium-copper catalyst system. When arenesulfonyl chlorides were treated with zinc or potassium iodides, their facile desulfonylative iodination to give aryl iodides could also be achieved.

In chapter 2, it was shown that the palladium-copper catalyst system developed in chapter 1 was found to be effective in the carbonylation reactions of aryl iodides. Thus, the reaction using a number of nucleophiles could be promoted by using a copper cocatalyst.

In chapter 3, a novel palladium-catalyzed cross-carbonylation of aryl iodides with five-membered cyclic alkenes in place of nucleophiles was found to occur under appropriate conditions to produce the corresponding aryl vinyl ketones.

In chapter 4, palladium-catalyzed carbonylation of aryl-substituted allyl alcohols, which usually requires high pressures of CO, was found to efficiently proceed even under 1 or 5 atm of CO by the use of phenols as nucleophiles. Under similar conditions, carbonylation of 2-hydroxybenzyl alcohols also proceeded smoothly to give the corresponding benzo[*b*]furanone derivatives. Furthermore, allyl aryl ethers could also be obtained in good yields by carrying out the reaction of allyl alcohols and phenols under nitrogen in the presence of titanium(IV) isopropoxide.

In chapter 5, a new method for the synthesis of aromatic ketones by means of palladium catalysis was developed. When salicylaldehydes were treated with aryl iodides in the presence of a palladium catalyst under basic conditions, cross-coupling reaction was found to proceed smoothly to give the corresponding 2-aroylphenols, appearing to involve cleavage of the aldehyde C-H bond. 2-Phenylphenols and naphthols could also be arylated efficiently and regioselectively by treatment with aryl halides and an appropriate base.

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