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Synthesis of Unsymmetrical Ketones by Palladium-Catalyzed Cross-Coupling Reaction of Carboxylic Anhydrides with Organoboron Compounds

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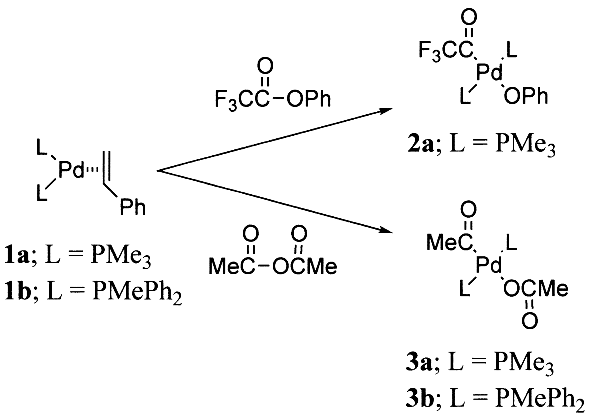
On the basis of fundamental studies on oxidative addition of carboxylic anhydrides to zerovalent palladium complexes to yield acyl(carboxylato)bis(tertiary phosphine)palladium(II) complexes and their reactions with organoboronic acids to yield ketones, a novel catalytic process has been developed. This converts carboxylic anhydrides and organoboron compounds into ketones catalyzed by palladium complexes under mild conditions. The process provides a general, versatile, synthetic method to produce various symmetrical and unsymmetrical ketones with aromatic, aliphatic, and heterocyclic groups. The catalytic cycle is proposed to comprise (a) oxidative addition of a carboxylic anhydride to produce an acyl(carboxylato)palladium intermediate, (b) transmetallation with an organoboron compound to give an acyl(organo)palladium intermediate, and (c) its reductive elimination to yield a ketone. Not only homogeneous catalyst systems but also heterogeneous systems were found to give ketones under mild conditions.

Cross-coupling processes of aryl or alkenyl halides with organometallic compounds of main group elements catalyzed by palladium complexes have found extensive use in organic synthesis.[1] The reason of the utility of the palladium complex as catalyst arises from the ease of oxidative addition of organic halides to Pd(0) complexes, ready transmetallation to give diorganopalladium species and the subsequent facile reductive elimination to bring together the two organic entities. However, the palladium-promoted catalytic processes involving the oxidative addition of organic halides, despite their utility, entail an intrinsic problem that the halogen used has to be removed eventually for preparation of compounds containing no halogen atoms. An approach to make the process more atom-efficient and environmentally benign is to start from compounds without halogen and design a particular synthetic methodology involving cleavage of a specific bond in the starting material. To utilize cleavage of a carbon–oxygen bond in an organic compound by palladium and to make use of the reactivity of the organopalladium compound thus produced appear as one of the most promising ways to realize a halogen-free catalytic process. However, cleavage of C–O bonds in oxygen-containing organic compounds by palladium complexes has not been well utilized except for the process using allylic carboxylates and carbonates.[2]

As an extension of our long-standing interest in the promotion of the C–O bond cleavage by transition metal complexes,[3] we found ready cleavage of the acyl–oxygen bond in electronegative carboxylic esters[4] and carboxylic anhydrides[5] on interaction with Pd(0) complexes. Phenyl trifluoroacetate reacted with a coordinatively unsaturated palladium complex, $[Pd(styrene)(PMe_3)_2]$[6] **1a**, prepared in situ by thermolysis of *trans*-$[PdEt_2(PMe_3)_2]$[7] in the presence of styrene, to give *trans*-[(phenoxo)(trifluoroacetyl)bis(trimethylphosphine)palladium(II)] **2a**.[4] On the other hand, acetic anhydride underwent the cleavage of the acyl-oxygen bond to give *trans*-[(acetato)(acetyl)bis(tertiary phosphine)palladium(II)] **3a** and **3b**, as shown in Scheme 1.[5]

In both processes the cleavage of the acyl–O bond promoted by the palladium complexes yields reactive acylpalladium complexes, which can be utilized for synthesis of various carbonyl-containing compounds.

Based on the fundamental studies on cleavage of the C–O bonds in acid anhydrides on interaction with Pd(0) complexes, we have previously developed novel catalytic hydrogenation processes to convert a variety of carboxylic anhydrides into the corresponding aldehydes under mild conditions.[5] Later we expanded the method to include direct hydrogenation of carboxy-



Scheme 1. Cleavage of C–O bond in phenyl trifluoroacetate and acetic anhydride.

lic acids into aldehydes at the cost of less reactive carboxylic anhydrides such as pivalic (2,2-dimethylpropanoic) anhydride added as an activator of the carboxylic acid (Eq. 1).[8]

$$\mathrm{RCOOH} + \mathrm{H_2} \xrightarrow[({}^t\mathrm{BuCO})_2\mathrm{O}]{\text{Pd catalyst}} \mathrm{RCHO} \qquad (1)$$

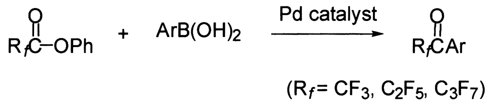
Another conceivable target for applying the elementary process of the acyl–oxygen bond cleavage to organic synthesis is synthesis of ketones. The acylpalladium species such as **3** generated in the oxidative cleavage of carboxylic anhydride can be subjected to transmetallation to yield an acyl(alkyl)palladium species, which may liberate ketone on reductive elimination.

By far the most commonly used methods for the synthesis of ketones are (i) the nucleophilic addition of organometallic reagents to carboxylic acid derivatives,[9] (ii) oxidation of alcohols,[10,11,12,13] and (iii) the Friedel–Crafts acylation reaction of aromatic compounds.[14] However, these preparative methods entail some problems and limitations. For example, synthesis of ketones from organometallic reagents of electropositive metals such as lithium and magnesium and carboxylic acid derivatives often proceeds in low yields because of the addition of the organometallic reagents to the ketone produced to form tertiary alcohols.[15] Many useful reactions are known in partial oxidation of secondary alcohols to ketones, such as the Swern oxidation,[11] and oxidation by heavy metal salts such as PCC[12] and MnO_2.[13] However, in these processes stoichiometric amounts of oxidizing agents are required, with concomitant formation of undesirable by-product(s). The Friedel–Crafts acylation reactions, which are one of the most important processes for the synthesis of aromatic ketones, are generally carried out by using more than a stoichiometric amount of anhydrous aluminum trichloride as a Lewis acid. From an industrial point of view, the reaction is less desirable because of the highly corrosive conditions and the concomitant formation of a large amount of waste. In addition, Friedel–Crafts reactions display ortho and para selectivity and are not suitable for preparation of aryl ketones with a meta substituent.

Among various palladium-catalyzed cross-coupling processes using organic halides as the starting compounds, the protocol using organoboron compounds (Suzuki–Miyaura process) has recently been utilized most widely by synthetic chemists.[16] The process gives the coupling products usually in high yields, is tolerant to functional groups, and shows excellent stereochemistry. In addition, most organoboron compounds are nontoxic, inert to air and moisture, thermally stable, and can be recrystallized from water or alcohol.

The Suzuki–Miyaura coupling has been employed for ketone synthesis as well.[17,18] Representative preparative methods of ketones reported so far are (i) carbonylative cross-coupling reaction of haloarenes with organoboron compounds,[17] and (ii) cross-coupling reaction of acyl halides with various organoboron compounds.[18] However, these methods also entail some problems. The major problem of the Suzuki–Miyaura protocol is the requirement of a stoichiometric amount of a base to drive the coupling reactions. Thus these processes are not usable for the synthesis of ketones sensitive to a base, beside the inherent environmental problems and the defect of low atom efficiency.

In the previous paper we described the palladium-catalyzed synthesis of perfluoroalkyl ketones using aryl perfluoroalkanecarboxylates as shown below.[19]

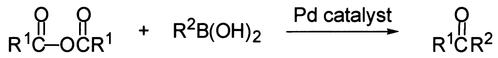


$$\mathrm{R_fC(O)OPh} + \mathrm{ArB(OH)_2} \xrightarrow{\text{Pd catalyst}} \mathrm{R_fC(O)Ar} \qquad (2)$$

$$(\mathrm{R_f} = \mathrm{CF_3}, \mathrm{C_2F_5}, \mathrm{C_3F_7})$$

The catalytic process provides a convenient route to perfluoroalkyl ketones from phenyl perfluoroalkanecarboxylates and organoboron compounds under neutral conditions. However, the process is not applicable to ketone synthesis from ordinary carboxylic esters without the electronegative fluorine substituents because of their reluctance to oxidative addition to a Pd(0) species.

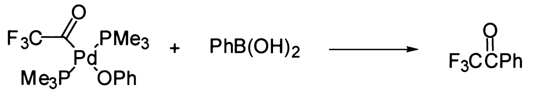
We wish to report here one other type of palladium-catalyzed ketone synthesis using the C–O bond cleavage of carboxylic anhydrides coupled with transmetallation employing organoboron compounds without using a base (Eq. 3). The present process using the cleavage of carboxylic anhydrides is complementary to the process using perfluoroalkanecarboxylates and has a wider scope in application to synthesis of various ketones that may not be prepared by conventional methods such as Friedel–Crafts acylation processes.[14]



$$\mathrm{R^1C(O)OC(O)R^1} + \mathrm{R^2B(OH)_2} \xrightarrow{\text{Pd catalyst}} \mathrm{R^1C(O)R^2} \qquad (3)$$

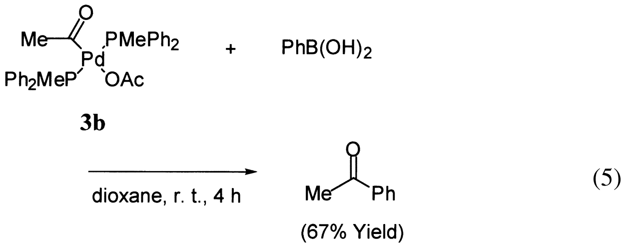
Results

Stoichiometric Reaction of *trans*-[(Acetato)(acetyl)bis(trimethylphosphine)palladium(II)] (3a) with Phenylboronic Acid. We have previously reported that **2a**,[4] generated by the trifluoroacetyl–OPh bond cleavage in phenyl trifluoroacetate on oxidative addition to **1a**[6] (Scheme 1), reacted readily with phenylboronic acid at room temperature to liberate phenyl trifluoromethyl ketone (Eq. 4).[19] The reaction is considered to proceed through transmetallation, followed by reductive elimination.



2a

We found further that the *trans*-[(acetato)(acetyl)bis(methyldiphenylphosphine)palladium(II)] **3b**[5a] readily reacted with phenylboronic acid at room temperature in a manner similar to Eq. 4 to liberate acetophenone (Eq. 5).

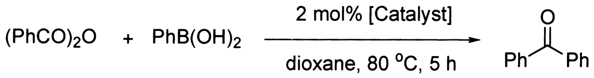


The above result on the stoichiometric reactions of the acyl–O bond cleavage indicated the feasibility of application of the C–O bond cleavage of carboxylic anhydrides to catalytic synthesis of ketones in the presence of a palladium catalyst. In fact, examination of the catalytic processes revealed that general and convenient palladium-catalyzed processes of synthesizing a variety of ketones from carboxylic anhydrides and organoboron compounds could be realized.

Catalytic Processes to Prepare Ketones from Carboxylic Anhydrides and Organoboronic Acids. (a) Examination of Catalyst Systems. Treatment of benzoic anhydride with phenylboronic acid at 80 °C in dioxane in the presence of 0.02 molar amount of $[Pd(PPh_3)_4]$ **4** per benzoic acid for 5 h gave 98% yield of benzophenone. Table 1 summarizes the effects of the catalyst systems for the ketone synthesis under the standardized conditions as stated above.

Various palladium catalysts with tertiary phosphine ligands proved effective in synthesizing benzophenone. Of other transition metal complexes examined, nickel,[20] platinum,[21] and rhodium[22] complexes were ineffective (Runs 12–14). The nature and molar amounts of the tertiary phosphine ligands added to the catalyst system were noted to affect the yield of benzophenone. Palladium complexes such as $[Pd(dba)_2]$ and $Pd(OAc)_2$ without added tertiary phosphine ligands did not catalyze the ketone synthesis (Runs 4 and 5). These palladium compounds, however, developed suitable catalytic activities when they were used in combination with tertiary phosphine ligands as shown in Runs 6 and 7, whereas addition of four equivalents of more basic tributylphosphine to $Pd(OAc)_2$ suppressed the catalytic activity almost completely (Run 11). The results suggest that a catalytically active, coordinatively unsaturated zerovalent palladium species having a limited number of the supporting tertiary phosphine ligands of appropriate coordinating abilities is generated in the catalytic system. Zerovalent palladium complexes such as $[Pd(PPh_3)_4]$, $[Pd(PMePh_2)_4]$, and $[Pd(PCy_3)_2]$ (Runs 1, 3, and 8) were found effective as catalysts, but addition of three equivalents of PPh_3 per mol of $[Pd(PPh_3)_4]$ caused a decrease in the ketone yield (Run 2). The presence of four tertiary phosphine ligands such as $PMePh_2$, having higher coordinating ability than PPh_3, lowered the yield of the ketone (Run 3), whereas coordinatively unsaturated Pd(0) complex $[Pd(PCy_3)_2]$ (Run 8) was found to be as effective as $[Pd(PPh_3)_4]$. Employment of ditertiary phosphine ligands such as 1,1′-bis(diphenylphosphino)ferrocene (DPPF) and 1,4-bis(diphenylphosphino)butane (DPPB) added to $[Pd(dba)_2]$ also gave moderate yields of the ketone (Runs 9 and 10). Although palladium(II) acetate alone was not effective, addition of triphenylphosphine to the system developed some catalytic activity. This may be ascribed to in situ generation of a triphenylphosphine-coordinated Pd(0) species by reduction of palladium acetate with triphenylphosphine.[23]

Table 1. Effect of Homogeneous Catalysts on the Cross-Coupling Reaction of Benzoic Anhydride with Phenylboronic Acid



Run	Catalyst	Yield/%a)
1	$[Pd(PPh_3)_4]$	98
2	$[Pd(PPh_3)_4] + 3PPh_3$	72
3	$[Pd(PMePh_2)_4]$	66
4	$[Pd(dba)_2]$	0
5	$Pd(OAc)_2$	0
6	$[Pd(dba)_2] + 4PPh_3$	82
7	$Pd(OAc)_2 + 4PPh_3$	77
8	$[Pd(PCy_3)_2]$	95
9	$[Pd(dba)_2]$ + 1DPPFb)	76
10	$[Pd(dba)_2]$ + 1DPPBc)	64
11	$Pd(OAc)_2 + 4P^nBu_3$	trace
12	$[Ni(cod)_2] + 2PPh_3$	trace
13	$[Pt(PPh_3)_4]$	0
14	$[Rh(PPh_3)_3Cl]$	0

a) Determined by GC using $^nC_{14}H_{30}$ as an internal standard.

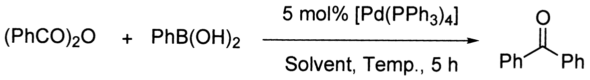
b) DPPF is 1,1′-bis(diphenylphosphino)ferrocene.

c) DPPB is 1,4-bis(diphenylphosphino)butane.

(b) Effects of Solvent and Temperature. The effects of the solvent and reaction temperature on the yields of benzophenone produced by the palladium-catalyzed reaction of benzoic anhydride with phenylboronic acid are summarized in Table 2. In the reaction catalyzed by $[Pd(PPh_3)_4]$ **4** the benzophenone formation was slow at room temperature in dioxane, but at higher temperatures of 60 and 80 °C, higher yields were obtained, whereas at still higher temperature of 100 °C a slight decrease in the yield was observed (Runs 1–4).

The effects of other solvents on the yields of the coupling reaction of benzoic anhydride with phenylboronic acid at 80 °C are shown in Runs 5–10. Dioxane was found to be most suitable as solvent, followed by THF, which gave a slightly lower yield at refluxing temperature. Employment of acetone, toluene and 1-methyl-2-pyrrolidinone (NMP) gave moderate yields of the ketone. Hexane was found to be less appropriate, probably because of its poor ability to dissolve the catalyst system.

Table 2. Effects of Solvents and Temperature on the Cross-Coupling Reaction of Benzoic Anhydride with Phenylboronic Acid

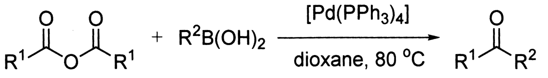


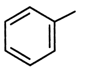
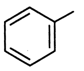
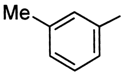
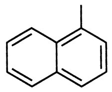
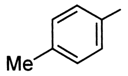
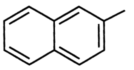
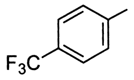
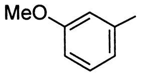
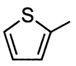
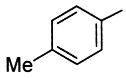
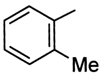
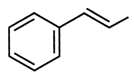
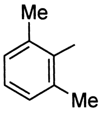
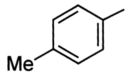
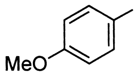
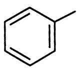
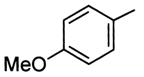
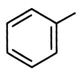
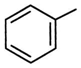
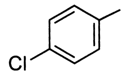
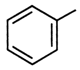
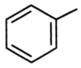
Run	Temp/°C	Solvent	Yield/%a)
1	r. t.	dioxane	5
2	60	dioxane	73
3	80	dioxane	99
4	100	dioxane	91
5	reflux	acetone	59
6	reflux	hexane	5
7	80	toluene	77
8	80	acetonitrile	24
9	80	NMPb)	62
10	reflux	THF	92

a) Determined by GC using $^nC_{14}H_{30}$ as an internal standard.

b) *N*-methyl-2-pyrrolidinone.

Table 3. Synthesis of Unsymmetrical Ketones by the Palladium-Catalyzed Cross-Coupling of Carboxylic Anhydrides with Organoboronic Acids



Run	R^1	R^2	Method[a)]	Yield/%[b)]	Run	R^1	R^2	Method[a)]	Yield/%[b)]
1			A	98	9			A	99 (96)
2			A	98	10			A	99 (97)
3			A	81	11			A	99 (97)
4			B	99 (64)	12			A	79 (61)
5			B	95	13			C	54 (48)
6			A	94 (73)	14	Me		A	97
7			A	99	15	$^nC_5H_{11}$		A	84 (88)
8			A	87	16	^{t}Bu		C	44

a) Method A: 2 mol% of [Pd(PPh$_3$)$_4$] was used. Reaction time, 5 h.
Method B: 5 mol% of [Pd(PPh$_3$)$_4$] was used. Reaction time, 10 h.
Method C: 5 mol% of [Pd(PPh$_3$)$_4$] was used. Reaction time, 24 h.
b) GC yields based on acid anhydrides and isolated yields are in the parentheses.

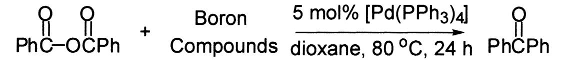
(c) Scope and Limitation. On the basis of the above mentioned results, we chose [Pd(PPh$_3$)$_4$] **4** as the standard catalyst and examined the applicability of the present method to synthesis of various unsymmetrical ketones by carrying out the experiments under the standardized procedure, i. e., in dioxane at 80 °C with use of various anhydride substrates in combination with various organoboronic acids commercially available. The results are summarized in Table 3.

Various aromatic carboxylic anhydrides having electron-donating as well as an electron-withdrawing substituent at the para or meta position in benzoic anhydride can be catalytically converted into the corresponding ketones, usually in excellent yields, on treatment with organoboronic acids in the presence of **4** (Runs 1–13). *p*-Chlorobenzoic anhydride was transformed selectively into 4-chlorobenzophenone without undergoing the C–Cl bond cleavage[24] (Run 8).

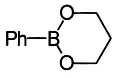
The present method allows the use of a variety of organoboronic acids. It is noted that the present method is applicable to 2-thienylboronic acid that is known as a poor arylating reagent in the conventional Suzuki–Miyaura coupling because of its inclination to deboronation.[25] Although longer reaction time and usage of an extra molar amount of the palladium catalyst were required to complete the reaction (Run 4), 2-thiophenyl phenyl ketone was obtained in an excellent yield in 10 h. Organoboronic acid such as *trans*-*β*-styrylboronic acid having the double bond that may interact with the palladium species could be also used (Run 5).

Aliphatic carboxylic anhydrides such as acetic anhydride and hexanoic anhydride (caproic anhydride) are converted smoothly into alkyl aryl ketones with **4** in combination with organoboronic acids (Runs 14, 15), whereas a bulky aliphatic carboxylic anhydride such as 2,2-dimethylpropanoic anhydride (pivalic anhydride) was much less reactive, as shown in Run 16. Some steric hindrance was also noted on the side of organoboronic acids, as evidenced in the lower yield of unsymmetrical ketone in coupling of *p*-toluic anhydride with 2,6-dimethylphenylboronic acid with the palladium catalyst (Run 13).[26] A somewhat decreased yield was also noted in the reaction of toluic anhydride with 2-methylphenylboronic acid having a methyl substituent at the ortho postion (Run 12).

Organoboron compounds other than organoboronic acids were also examined. Employment of sodium tetraphenylborate[27] in a quantity somewhat higher than equimolar amount in combination with the benzoic anhydride yielded benzophenone in 95%. A moderately high yield of benzophenone (64%) from benzoic anhydride was obtained even when 1/3 molar amount of $NaBPh_4$ was employed in the presence of **4**, the result indicating that two phenyl groups in $NaBPh_4$ were used in the transfer process. The use of 2-phenyl-1,3,2-dioxaborinane[28] as the alkylating reagents was ineffective (Eq. 6).



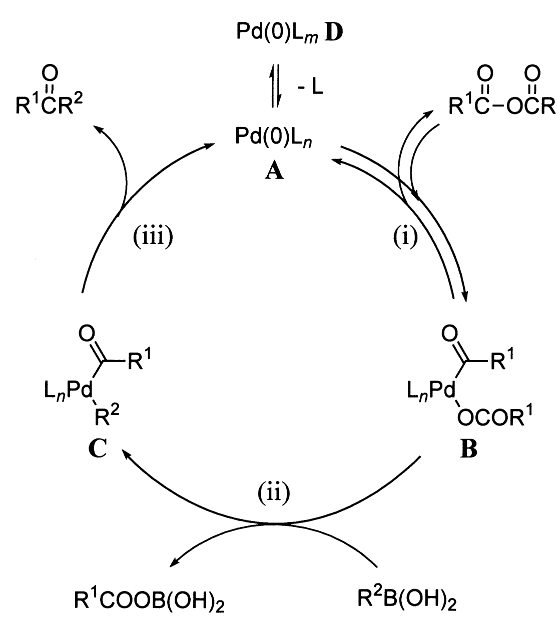
$$\mathrm{Ph\overset{O}{\overset{\|}{C}}{-}O\overset{O}{\overset{\|}{C}}Ph} + \text{Boron Compounds} \xrightarrow[\text{dioxane, 80 °C, 24 h}]{\text{5 mol\% [Pd(PPh}_3)_4]} \mathrm{Ph\overset{O}{\overset{\|}{C}}Ph} \qquad (6)$$

Boron Compounds	1.2 eq.	$NaBPh_4$	95%
	0.32 eq.	$NaBPh_4$	64%
	1.2 eq.		0%

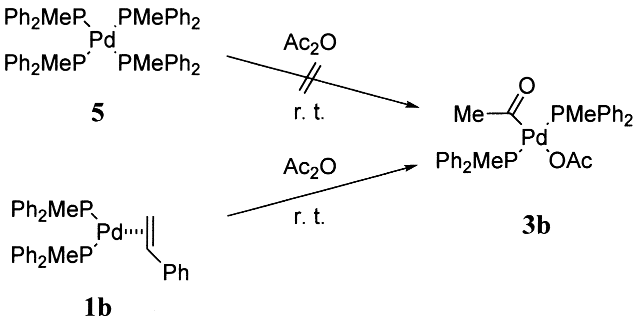
Discussion

On the basis of the fundamental studies on the stoichiometric processes involving oxidative addition of carboxylic anhydride to Pd(0) compounds and the subsequent reaction of the acyl(carboxylato)palladium complexes with organoboronic acids, we propose the catalytic cycle shown in Scheme 2 to account for the catalytic formation of ketones from carboxylic anhydrides and organoboronic compounds.

The essential part in the mechanism is similar to the mechanism of ketone synthesis from phenyl perfluoroalkanecarboxylates.[19] The catalytic cycle is composed of elementary processes of (i) oxidative addition of a carboxylic anhydride to a coordinatively unsaturated Pd(0) species **A**, formed from a catalyst precursor **D**, with the C–O bond cleavage to give an acyl(carboxylato)palladium species **B**; (ii) transmetallation with an organoboron compound such as organoboronic acid to give an acyl(alkyl)palladium species **C**; and (iii) reductive elimination of ketone as the coupling product regenerating the Pd(0) species **A**, which further carries the catalytic cycle to produce the product ketone.



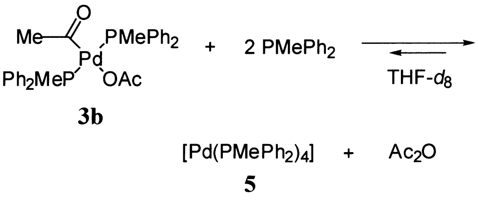
Scheme 2. Catalytic cycle for the formation of ketones.



Scheme 3. Cleavage of C–O bond in acetic anhydride.

As indicated in the effect of tertiary phosphines on the yields of ketones in the cross-coupling process in Table 1, the active species **A** involved in the catalytic cycle seems to have a vacant site for undergoing the oxidative addition with the anhydride. Such a notion is based on several pieces of experimental evidence. Examination of the $^{31}P\{^1H\}$ NMR spectra of $[Pd(PMePh_2)_4]$ **5** in dioxane in the presence of an equimolar quantity of added acetic anhydride at room temperature indicated the inertness of the coordinatively saturated species **5** to oxidative addition of acetic anhydride. In contrast, the coordinatively unsaturated Pd(0) complex $[Pd(styrene)(PMePh_2)_2]$ **1b**[29] having two $PMePh_2$ ligands undergoes ready oxidative addition of acetic anhydride with the C–O bond cleavage to give *trans*-[(acetato)(acetyl)bis(dimethylphenylphosphine)palladium(II)][5a] **3b** (Scheme 3), which corresponds to **B** in Scheme 2.

The oxidative addition of an anhydride to **A** to give **B** and the reductive elimination process to give **A** from B are reversible. Addition of two equivalents of methyldiphenylphosphine to the THF-d_8 solution of **3b** caused the rapid formation of **5** and acetic anhydride (Eq. 2), indicating that the reductive elimination with coupling of the acetyl and acetato ligands takes places readily in the presence of an extra amount of a tertiary phosphine.[30] The results show the presence of an equilibrium shown in Eq. 2. This equilibrium lies far to the right, on the side of C–O bond formation.



(7)

The transmetallation of the acetate ligand in **3b** on treatment with phenylboronic acid in dioxane takes place readily at room

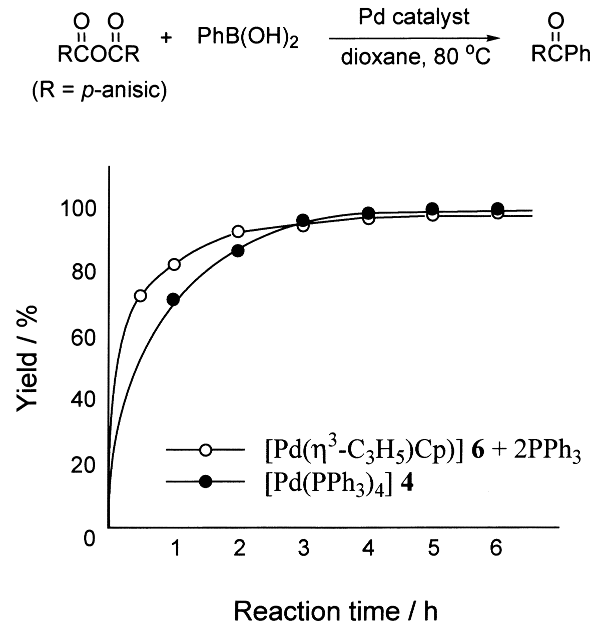


Fig. 1. Time courses of the coupling reaction of $(p\text{-}MeOC_6H_4CO)_2O$ and $PhB(OH)_2$ catalyzed by $[Pd(PPh_3)_4]$ or $[Ph(\eta^3\text{-}C_3H_5)Cp]$ + $2PPh_3$ in dioxane carried out at 80 °C.

temperature to liberate acetophenone, as shown in Eq. 5. The result suggests that the reductive elimination of the ketone from **C** is also a rapid process.

These results point to the importance of the pre-equilibrium process between the active species **A** and its catalyst precursor **D**, shown outside of the main catalytic cycle in Scheme 2.

For comparing the reactivities of palladium complexes having the coordinative unsaturation and saturation, we have examined the time courses of the reactions of *p*-anisic anhydride with phenylboronic acid at 80 °C in the presence of $[Pd(PPh_3)_4]$ and a coordinatively unsaturated catalyst system prepared from the mixture of [(η^5-cyclopentadienyl)(η^3-allyl)palladium] **6** with two equivalents of PPh_3. The ketone formation was observed to proceed much faster in the initial period with the latter catalyst system having the coordinative unsaturation than with **4** having four PPh_3 ligands (Fig. 1).

These results suggest the importance of the generation of a catalytically active, coordinatively unsaturated species to react with a carboxylic anhydride in the catalytic process. The requirement of a moderately high reaction temperature to promote the catalytic process with **4** may be mainly associated with the necessity to generate a coordinatively unsaturated and thermally stable species to carry the reaction in the presence of a supporting ligand(s).

For gaining further insight into the mechanism of the catalytic process, we next examined the reaction course of the ketone synthesis. Figure 2 exhibits time-courses of the reactions of benzoic anhydride and *p*-anisic anhydride, respectively, with phenylboronic acid in the presence of $[Pd(PPh_3)_4]$ **4** in dioxane at 80 °C.

The reaction of benzoic anhydride with phenylboronic acid catalyzed by **4** proceeded smoothly to give benzophenone almost quantitatively in 1 h, whereas the reaction of 4-methoxybenzoic anhydride proceeded more slowly, to be completed in 3 h at 80 °C. The result in Fig. 2 shows that introduction of an electron-donating substituent such as OMe group at the para position in benzoic anhydride decreases the reaction rate in the coupling reaction.

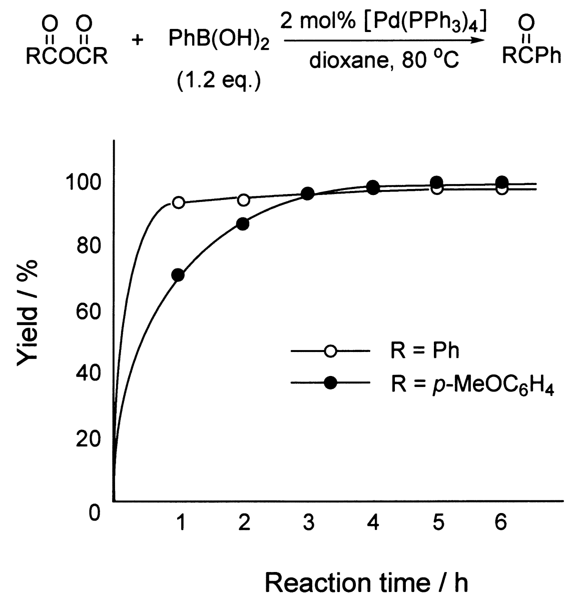
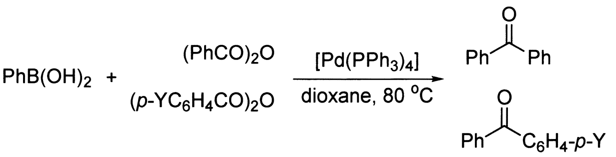


Fig. 2. Time course of the coupling reaction of $(PhCO)_2O$ or $(p\text{-}MeOC_6H_4CO)_2O$ with $PhB(OH)_2$ catalyzed by $[Pd(PPh_3)_4]$ carried out at 80 °C in dioxane.

Table 4. Reactivity of *p*-Substituted Benzoic Anhydrides Relative to Benzoic Anhydride and Their Hammett Substituent Values



Y	Hammett σ_p	P(Y)/P(H)	log(P(Y)/P(H))
MeO	−0.27	0.55	−0.26
Me	−0.17	0.72	−0.14
H	0	1	0
Cl	0.227	1.6	0.19

a) Determined by GC using $^{n}C_{14}H_{30}$ as an internal standard.

More direct comparison of the reactivities of various carboxylic anhydrides can be achieved by carrying out competition experiments by using equimolar mixtures of benzoic anhydride and various para-substituted benzoic anhydrides in reactions with phenylboronic acid catalyzed by **4** (Table 4). In Table 4 are compared relative product yields, P(Y)/P(H) of the ketone having the Y substituent at the para position versus benzophenone, produced after heating for 5 h in dioxane at 80 °C. The results indicate that the carboxylic anhydride having the more electron-withdrawing para substituent reacts faster than the benzoic anhydride derivative having the more electron-releasing para substituent.

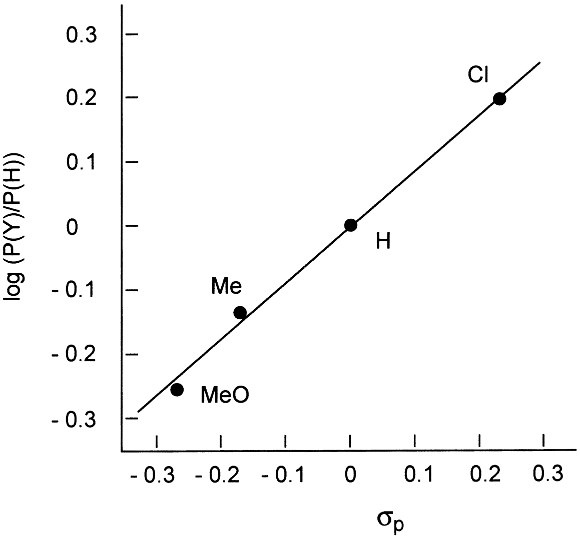
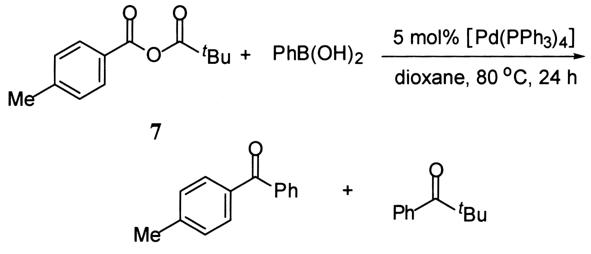


Fig. 3. Hammett plot for the relative reactivities of various para-substituted benzoic anhydridesd to benzoic anhydride in the cross-coupling reaction.

Figure 3 demonstrates the results of the competition experiments using the three pairs of para-substituted symmetric benzoic anhydrides and benzoic anhydride carried out at 80 °C in the presence of $[Pd(PPh_3)_4]$ as the catalyst. The plot of logarithms of the relative yields of the ketones against Hammett σ_p constants showed a reasonably good linear relationship (r^2 = 0.996) with a ρ value of 0.89. The positive ρ value suggests that cross-coupling reaction proceeds faster with carboxylic anhydride having the more electron-withdrawing groups.

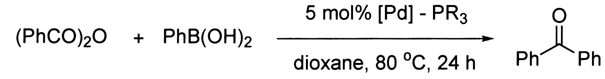
Although more detailed studies are required to draw definite conclusions concerning the rate-determining step in the catalytic cycle, it is clear that the oxidative addition of carboxylic anhydride to the coordinatively unsaturated palladium(0) species constitutes the most important step to control the catalytic cycle under the experimental conditions where an equilibrium between the catalyst precursor **D** and active species **A** is present.

Reaction of the Unsymmetrical Anhydride with Arylboronic Acids Catalyzed by $[Pd(PPh_3)_4]$ 4. To compare the relative reactivities of the acyl entities in the mixed carboxylic anhydrides toward palladium-catalyzed ketone synthesis, we have treated the mixed anhydride, *p*-toluic pivalic anhydride **7**, with phenylboronic acid at 80 °C for 1 day in the presence of **4** as the catalyst. The reaction of phenylboronic acid used in a quantity somewhat higher than equimolar amount in combination with the *p*-toluic pivalic anhydride gave 4-methylbenzophenone in 80%, together with 10% of the 2,2-dimethylpropiophenone (Eq. 8).



(8)

Table 5. Effect of Heterogeneous Catalysts on the Cross-Coupling Reaction of Benzoic Anhydride with Phenylboronic Acid



Run	Pd-catalyst	Yield/%[a]
1	Pd/C (10% wt)	25
2	$Pd/BaSO_4$ [reduced] (5% wt)	14
3	$Pd/BaSO_4$ [unreduced] (5% wt)	33
4	Pd/C (10% wt) + $4PPh_3$	66
5	$Pd/BaSO_4$ [reduced] (5% wt) + $4PPh_3$	43
6	$Pd/BaSO_4$ [unreduced] (5% wt) + $4PPh_3$	94

a) Determined by GC using $^{n}C_{14}H_{30}$ as an internal standard.

The result indicates that the aroyl part in the mixed anhydride **7** reacted preferentially with the palladium complex in the catalytic system. On the basis of these results, we developed a catalytic process to convert carboxylic acids directly into ketones by combining the exchange process of the carboxylic acid with an acid anhydride having a less reactive acyl entity under mild conditions without using a base. The results will be the subject of a separate report.

Application to Heterogeneous Systems. Recently, the effect of addition of ligands not only to homogeneous catalyst systems but also to heterogeneous catalysts to control the reaction courses is attracting increasing attention.[31] In practical systems, heterogeneous catalysts possess obvious advantages over the homogeneous systems in ease of separation of the catalysts and the product. We found that by suitable combination of the heterogeneous palladium catalyst with triphenylphosphine ligand, effective catalyst systems could be developed, as shown in Table 5.

The commercially available palladium deposited on activated carbon and barium sulfate (reduced as well as unreduced samples) showed modest catalytic activities (Runs 1–3). Addition of PPh_3 gave rise to higher activity. The combination of $Pd/BaSO_4$ (unreduced) used in the presence of 4 equiv of PPh_3 gave as high as 94% yield of benzophenone in dioxane at 80 °C (Run 6).

Evaluation of the Utility of the Present Process in Organic Synthesis. The ketone synthesis utilizing the Suzuki–Miyaura coupling employing the systems composed of either acyl halides with organoboronic acids or aryl halides with organoboronic acids under CO atmosphere has been already developed.[17,18] But the process using acyl chlorides is less desirable than the present method in that the preparation of acyl chlorides is required in the first place and the addition of a base is necessary to drive the coupling reaction. The present process uses the acyl entity in carboxylic anhydride and requires no carbon monoxide to be externally introduced, thus offering operational ease.

There are other useful processes of ketone synthesis using thioesters as the acyl entity as developed by Fukuyama,[32] Terfort,[33] and Liebeskind.[34] The present method provides a direct route of synthesizing ketones without synthesizing the thiol ester derivatives, from which the thiolate parts have to be discarded after their use for ketone synthesis. The necessity of prior preparation of carboxylic anhydrides is one disadvantage of the present method. However, we recently found the route to overcome the disadvantage by activating carboxylic acids in combination with another anhydride, notably dimethyl dicarbonate. Treatment of carboxylic acids with dimethyl dicarbonate leads to mixed anhydrides, which undergo the C–O bond cleavage process and further transmetallation with organoboron compounds to yield unsymmetrical ketones in excellent yields, as will be reported separately.[35]

In the Suzuki–Miyaura coupling of organic halides or organic triflates with aryl-, alkenyl-, and alkylboronic acids or esters, addition of a base such as NaOEt, KOAc, and NaOH is necessary to drive the reactions.[16] In the Suzuki–Miyaura coupling the effect of addition of the base was accounted for as replacement of the halide ligand in the catalyst intermediate with the alkoxide, carboxylate, or hydroxide ligand that is more susceptible to transmetallation with the oxophilic organoboron compounds than a halide.[36] In the present case, on the other hand, use of carboxylic anhydride gives the acyl(carboxylate)palladium intermediate suitable for the direct transmetallation process with the oxophilic organoboron compounds, thus eliminating the necessity of adding an extra base.[37]

Conclusion

On the basis of the fundamental studies on the elementary processes involving oxidative addition of a carboxylic anhydride to a Pd(0) complex and on the transmetallation of the product with an organoboronic acid to give a ketone, we devised a novel type of catalytic process to convert carboxylic anhydrides and organoboron compounds into ketones without using a base. In view of the paucity of atom-efficient and environmentally benign useful processes to synthesize unsymmetrical ketones under mild conditions, the present method provides a convenient new route to selective production of ketones under mild conditions. Dissociation of a tertiary phosphine ligand from a coordinatively saturated species to generate a coordinatively unsaturated species has been confirmed as an important factor to control the reaction rate of the catalysis. It was also revealed on the basis of competition reactions that oxidative addition of the carboxylic anhydride substrate to a Pd(0) species constitutes the turn-over limiting step in the catalytic cycle, if other experimental conditions are kept constant.

Experimental

General Procedures. All manipulations were carried out under argon atmosphere using Schlenk tube techniques. Solvents were purified by the usual methods under argon. NMR spectra were recorded on a JEOL Lambda 500 or a JEOL AL-400 spectrometer for ^{1}H (referenced to $SiMe_4$ via residual solvent protons), $^{13}C\{^1H\}$ (referenced to $SiMe_4$ via the solvent resonance), ^{19}F (referenced to trifluoroacetic acid in $CDCl_3$ as an external standard), and $^{31}P\{^1H\}$ (referenced to 85% H_3PO_4 as an external standard) NMR. Coupling constants (J values) are given in hertz (Hz), and spin multiplicities are indicated as follows: s (singlet), d (doublet), t (triplet), m (multiplet), vt (virtual triplet), and br (broad). Gas chromatographic analyses (GC) were carried out on a GC-353 equipped with TC1 column (0.25 mm i.d. × 30 m), using N_2 as carrier gas. Low-resolution mass spectra were obtained with a JEOL JMS-Automass 150 that is coupled with gas chromatograph. Elemental analyses were performed by the Materials Characterization Central Laboratory of Waseda University.

Reagents. All organoboron compounds were commercial products (Aldrich) and were used without further purification. Benzoic anhydride (Tokyo Kasei Kogyo Co.), acetic anhydride (Tokyo Kasei Kogyo Co.), 2,2-dimethylpropionic anhydride (Aldrich), and hexanoic anhydride (Tokyo Kasei Kogyo Co.) were commercial products, and were used directly. All carboxylic anhydrides except for benzoic anhydride, acetic anhydride, 2,2-dimethylpropionic anhydride, and hexanoic anhydride were synthesized by the reaction of acyl halides with the corresponding carboxylic acids in the presence of pyridine. p-$MeC_6H_4COOCO^tBu$ was prepared by treating p-toluic acid with pivaloyl chloride in the presence of pyridine. $[Pd(PPh_3)_4]$,[38] $[Pd(PMePh_2)_4]$,[29,39] $[Pd(PCy_3)_2]$,[40] $[Pd(styrene)(PMePh_2)_2]$,[29] $[(\eta^5$-cyclopentadienyl)$(\eta^3$-allyl)palladium$]$[41] were prepared by the reported procedures. $[Pd_2(dba)_3]$ was prepared following a synthesis report[42] and was used without recrystallization of the crude precipitate obtained at the end of the synthesis. $Pd(OAc)_2$ (Aldrich), 10% Pd/C (Kojima Chemicals Co.), 5% $Pd/BaSO_4$/(reduced) (Aldrich), and $Pd/BaSO_4$/(unreduced) (Aldrich) were used as received from commercial suppliers. All tertiary phosphines were commercial products and were used without further purification.

***trans*-$[PdAc(OAc)(PMePh_2)_2]$ 3b** was prepared as previously reported[5a] by the reaction of $[Pd(styrene)(PMePh_2)_2]$[29] **1b** with acetic anhydride.

Reaction of *trans*-$[PdAc(OAc)(PMePh_2)_2]$ with Phenylboronic Acid (Eq. 5). To a dioxane solution (5 cm^3) of *trans*-$[PdAc(OAc)(PMePh_2)_2]$ (300 mg, 0.493 mmol), phenylboronic acid (72.0 mg, 0.591 mmol) was added at room temperature. The mixture was stirred for 4 h at room temperature. The GC and GC-MS analysis of the products was performed with $^nC_{14}H_{30}$ as an internal standard. Formation of acetophenone (67%) was conformed. Acetophenone was characterized by GC-MS by comparing with an authentic sample (Tokyo Kasei Kogyo Co.). GC-MS m/z (rel intensity) 120 (47), 105 (100), 77 (98).

Effect of Homogeneous Catalysts (Table 1). A typical procedure is as follows (Run 8). A dioxane solution (5 cm^3) containing $[Pd(PCy_3)_2]$ (13.3 mg, 0.0199 mmol), benzoic anhydride (226 mg, 0.999 mmol), and phenylboronic acid (147 mg, 1.21 mmol) in a 25 cm^3 Schlenk tube was heated under argon at 80 °C for 5 h. The yields of benzophenone were determined by GC using $^nC_{14}H_{30}$ as an internal standard. Benzophenone was characterized by GC-MS by comparison with an authentic sample (Tokyo Kasei Kogyo Co.).

Effect of Solvent and Temperature (Table 2). A typical procedure is as follows (Run 4). A dioxane solution (5 cm^3) containing $[Pd(PPh_3)_4]$ (57.9 mg, 0.0501 mmol), benzoic anhydride (227 mg, 1.00 mmol), and phenylboronic acid (146 mg, 1.20 mmol) in a 25 cm^3 Schlenk tube was stirred under argon at room temperature and at 60 °C, 80 °C, and 100 °C, respectively, for five hours. The effects of solvents were examined in hexane, toluene, acetonitrile, 1-methyl-2-pyrrolidinone (NMP), THF, and dioxane by carrying out the synthesis at 80 °C. The yields of benzophenone were determined by GC using $^nC_{14}H_{30}$ as an internal standard. Benzophenone was characterized by GC-MS by comparison with an authentic sample (Tokyo Kasei Kogyo Co.).

Synthesis of Unsymmetric Ketones (Table 3). A typical procedure is as follows (Run 10). A dioxane solution (5 cm^3) containing $[Pd(PPh_3)_4]$ (23.2 mg, 0.0201 mmol), m-toluic anhydride (254 mg, 0.999 mmol), and 2-naphthylboronic acid (206 mg, 1.20 mmol) in a 25 cm^3 Schlenk tube was heated under argon at 80 °C for five hours. After the reaction mixture was cooled, diethyl ether and H_2O were added and the aqueous layer was extracted with diethyl ether. The combined ether solution was dried ($MgSO_4$) and the solvent was evaporated in vacuo. Purification of the residue by column chromatography (hexane/Et_2O = 9:1) gave the corresponding product (239 mg; yield 97%).

3-Methyl-2′-benzonaphthone: (97%); ^1H NMR (acetone-d_6, r. t., 400 MHz) δ 8.26 (s, 1H, aromatic H), 8.01–7.96 (m, 3H, aromatic H), 7.88–7.85 (m, 1H, aromatic H), 7.64–7.54 (m, 4H, aromatic H), 7.46–7.38 (m, 2H, aromatic H), 2,38 (s, 3H, CH_3); $^{13}C\{^1H\}$ NMR (acetone-d_6, r. t., 100 MHz) δ 196.4 (s, carbonyl C), 138.9 (s, aromatic C), 138.7 (s, aromatic C), 135.9 (s, aromatic C), 135.7 (s, aromatic C), 133.7 (s, aromatic C), 133.1 (s, aromatic C), 132.1 (s, aromatic C), 130.9 (s, aromatic C), 130.1 (s, aromatic C), 129.0 (s, aromatic C), 129.0 (s, aromatic C), 128.9 (s, aromatic C), 128.5 (s, aromatic C), 127.8 (s, aromatic C), 127.6 (s, aromatic C), 126.2 (s, aromatic C), 21.3 (s, CH_3). GC-MS *m*/*z* (rel intensity) 246 (55), 231 (18), 202 (5), 155 (62), 127 (95), 119 (42), 91 (100), 77 (21). Found: C, 87.59; H, 5.68%. Calcd for $C_{18}H_{14}O$: C, 87.78; H, 5.73%.

The following unsymmetric ketones were synthesized by the above general procedure.

Benzophenone: [119-61-9] (98%); Benzophenone was characterized by GC-MS by comparison with an authentic sample (Tokyo Kasei Kogyo Co.). GC-MS *m*/*z* (rel intensity) 182 (73), 105 (84), 77 (100).

4-Methylbenzophenone: [134-84-9] (98%); 4-Methylbenzophenone was characterized by GC-MS by comparison with an authentic sample (Kanto Chemical Co.). GC-MS *m*/*z* (rel intensity) 196 (43), 181 (10), 119 (100), 105 (26), 91 (24), 77 (28).

4-Trifluoromethylbenzophenone: [728-86-9] (81%); 4-Trifluoromethylbenzophenone was characterized by GC-MS by comparison with an authentic sample (ACROS). GC-MS *m*/*z* (rel intensity) 250 (11), 173 (12), 145 (30), 125 (10), 105 (100), 77 (95).

2-Benzoylthiophene: [135-00-2] (96%); 2-Benzoylthiophene was characterized by GC-MS by comparison with an authentic sample (Tokyo Kasei Kogyo Co.). GC-MS *m*/*z* (rel intensity) 188 (100), 171 (22), 160 (28), 111 (100), 105 (99), 77 (100).

Chalcone: [614-47-1] (95%); Chalcone was characterized by GC-MS by comparison with an authentic sample (Tokyo Kasei Kogyo Co.). GC-MS *m*/*z* (rel intensity) 208 (91), 179 (58), 165 (30), 131 (100), 105 (100), 77 (83).

4-Methoxy-4′-methylbenzophenone: (94%); ^1H NMR (acetone-d_6, r. t., 400 MHz) δ 7.77 (d, 2H, J = 8.79 Hz, aromatic H), 7.64 (d, 2H, J = 8.06 Hz, aromatic H), 7.33 (d, 2H, J = 8.06 Hz, aromatic H), 7.05 (d, 2H, J = 8.79 Hz, aromatic H), 3.89 (s, 3H, OCH_3), 2.41 (s, 3H, CH_3); $^{13}C\{^1H\}$ NMR (acetone-d_6, r. t., 100 MHz) δ 194.6 (s, carbonyl C), 163.8 (s, aromatic C), 143.1 (s, aromatic C), 136.4 (s, aromatic C), 132.7 (s, aromatic C), 131.0 (s, aromatic C), 130.3 (s, aromatic C), 129.6 (s, aromatic C), 114.3 (s, aromatic C), 55.9 (s, OCH_3), 21.5 (s, CH_3). GC-MS *m*/*z* (rel intensity) 226 (30), 211 (10), 195 (5), 135 (63), 119 (30), 107 (12), 91 (100), 77 (44). Found: C, 79.17; H, 6.26%. Calcd for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24%.

4-Methoxybenzophenone: [611-94-9] (99%); 4-Methoxybenzophenone was characterized by GC-MS by comparison with an authentic sample (Aldrich). GC-MS *m*/*z* (rel intensity) 212 (98), 181 (9), 135 (42), 105 (28), 92 (8) 77 (72).

4-Chlorobenzophenone: [134-85-0] (87%); 4-Chlorobenzophenone was characterized by GC-MS by comparison with an authentic sample (Tokyo Kasei Kogyo Co.). GC-MS *m*/*z* (rel intensity) 216 (9), 181 (4), 152 (3), 139 (30), 111 (41), 105 (72), 77 (100).

3-Methyl-1′-benzonaphthone: (96%); ^1H NMR (acetone-d_6, r. t., 400 MHz) δ 8.13–8.09 (m, 1H, aromatic H), 8.03 (m, 1H, aromatic H), 8.01 (m, 1H, aromatic H), 7.68 (s, 1H, aromatic H), 7.59 (m, 1H, aromatic H), 7.58 (s, 1H, aromatic H), 7.57 (m, 1H, aromatic H), 7.55–7.54 (m, 1H, aromatic H), 7.53–7.50 (m, 1H, aromatic H), 7.49–7.47 (m, 1H, aromatic H), 7.41–7.37 (m, 1H, aromatic H), 2.36 (s, 3H, CH_3); $^{13}C\{^1H\}$ NMR (acetone-d_6, r. t., 100 MHz) δ 197.8 (s, carbonyl C), 139.1 (s, aromatic C), 139.1 (s, aromatic C), 137.4 (s, aromatic C), 134.6 (s, aromatic C), 134.5 (s, aromatic C), 131.6 (s, aromatic C), 131.5 (s, aromatic C), 130.9 (s, aromatic C), 129.2 (s, aromatic C), 129.2 (s, aromatic C), 128.1 (s, aromatic C), 128.1 (s, aromatic C), 127.8 (s, aromatic C), 127.1 (s, aromatic C), 126.1 (s, aromatic C), 125.3 (s, aromatic C), 21.2 (s, CH_3). GC-MS *m*/*z* (rel intensity) 246 (73), 231 (38), 202 (10), 155 (98), 127 (100), 119 (64), 91 (56), 77 (12). Found: C, 87.36; H, 5.25%. Calcd for $C_{18}H_{14}O$: C, 87.78; H, 5.73%.

3-Methoxy-3′-methylbenzophenone: (97%); ^1H NMR (acetone-d_6, r. t., 400 MHz) δ 7.60 (s, 1H, aromatic H), 7.56–7.54 (m, 1H, aromatic H), 7.45–7.40 (m, 3H, aromatic H), 7.30 (m, 2H, aromatic H), 7.21–7.19 (m, 1H, aromatic H), 3.85 (s, 3H, OCH_3), 2.40 (s, 3H, CH_3); $^{13}C\{^1H\}$ NMR (acetone-d_6, r. t., 100 MHz) δ 196.1 (s, carbonyl C), 160.4 (s, aromatic C), 139.8 (s, aromatic C), 138.8 (s, aromatic C), 138.4 (s, aromatic C), 133.8 (s, aromatic C), 130.7 (s, aromatic C), 130.1 (s, aromatic C), 128.9 (s, aromatic C), 127.7 (s, aromatic C), 122.9 (s, aromatic C), 118.9 (s, aromatic C), 115.0 (s, aromatic C), 55.7 (s, OCH_3), 21.3 (s, CH_3). GC-MS *m*/*z* (rel intensity) 226 (49), 211 (10), 195 (5), 135 (37), 119 (73), 107 (13), 91 (100), 77 (62). Found: C, 79.28; H, 6.26%. Calcd for $C_{15}H_{14}O$: C, 79.62; H, 6.24%.

2,4′-Dimethylbenzophenone: [1140-16-5] (61%); ^1H NMR (acetone-d_6, r. t., 400 MHz) δ 7.65 (d, 2H, J = 8.06 Hz, aromatic H), 7.43–7.39 (m, 1H, aromatic H), 7.33–7.32 (m, 1H, aromatic H), 7.32 (d, 2H, J = 8.06 Hz, aromatic H), 7.28 (s, 1H, aromatic H), 7.27 (s, 1H, aromatic H), 2.40 (s, 3H, 4′-CH_3), 2.26 (s, 3H, 2-CH_3); $^{13}C\{^1H\}$ NMR (acetone-d_6, r. t., 100 MHz) δ 197.7 (s, carbonyl C), 144.7 (s, aromatic C), 139.9 (s, aromatic C), 136.7 (s, aromatic C), 135.9 (s, aromatic C), 131.5 (s, aromatic C), 130.6 (s, aromatic C), 130.6 (s, aromatic C), 129.9 (s, aromatic C), 128.6 (s, aromatic C), 125.9 (s, aromatic C), 21.6 (s, 4-CH_3), 19.8 (s, 2-CH_3). GC-MS *m*/*z* (rel intensity) 209 (70), 195 (98), 178 (17), 165 (33), 152 (10), 119 (100), 91 (100). Found: C, 85.75; H, 6.82%. Calcd for $C_{15}H_{14}O$: C, 85.68; H, 6.71%.

2,4′,6-Trimethylbenzophenone: (48%); ^1H NMR (acetone-d_6, r. t., 400 MHz) δ 7.64 (d, 2H, J = 8.12 Hz, aromatic H), 7.33 (d, 2H, J = 8.12 Hz, aromatic H), 7.26 (t, 1H, J = 7.81 Hz, aromatic H), 7.12 (d, 2H, J = 7.81 Hz, aromatic H), 2.40 (s, 3H, 4′-CH_3), 2.04 (s, 6H, 2,6-CH_3); $^{13}C\{^1H\}$ NMR (acetone-d_6, r. t., 100 MHz) δ 199.4 (s, carbonyl C), 145.3 (s, carbonyl C), 140.8 (s, aromatic C), 135.5 (s, aromatic C), 134.4 (s, aromatic C), 130.4 (s, aromatic C), 129.8 (s, aromatic C), 129.3 (s, aromatic C), 128.2 (s, aromatic C), 21.6 (s, 4′-CH_3), 19.3 (s, 2,6-CH_3). GC-MS *m*/*z* (rel intensity) 224 (26), 209 (100), 194 (12), 165 (7), 133 (25), 119 (33), 105 (22), 91 (32), 77 (26). Found: C, 85.40; H, 7.33%. Calcd for $C_{15}H_{14}O$: C, 85.68; H, 7.19%.

Acetophenone: [98-86-2] (97%); Acetophenone was characterized by ^1H, $^{13}C\{^1H\}$ NMR, and GC-MS by comparison with an authentic sample (Tokyo Kasei Kogyo Co.). ^1H NMR (acetone-d_6, r. t., 400 MHz) δ 7.99–7.97 (m, 2H, aromatic H), 7.62–7.58 (m, 1H, aromatic H), 7.52–7.48 (m, 2H, aromatic H), 2.57 (s, 3H, CH_3); $^{13}C\{^1H\}$ NMR (acetone-d_6, r. t., 100 MHz) δ 197.6 (s, carbonyl C), 138.0 (s, aromatic C), 133.6 (s, aromatic C), 129.2 (s, aromatic C), 128.8 (s, aromatic C), 26.6 (s, CH_3). GC-MS *m*/*z* (rel intensity) 120 (55), 105 (99), 77 (100).

Hexanophenone: [942-92-7] (88%); Hexanophenone was characterized by ^{1}H, ^{13}C{^{1}H} NMR, and GC-MS by comparison with an authentic sample (Tokyo Kasei Kogyo Co.). ^{1}H NMR (acetone-d_6, r. t., 400 MHz) δ 8.01–7.98 (m, 2H, aromatic H), 7.61–7.57 (m, 1H, aromatic H), 7.51–7.48 (m, 2H, aromatic H), 3.01 (t, 2H, J = 7.20 Hz, $COCH_2$), 1.72–1.65 (m, 2H, CH_2), 1.37–1.33 (m, 4H, CH_2), 0.91–0.87 (m, 3H, CH_3); ^{13}C{^{1}H} NMR (acetone-d_6, r. t., 100 MHz) δ 200.0 (s, carbonyl C), 138.0 (s, aromatic C), 133.4 (s, aromatic C), 129.2 (s, aromatic C), 128.6 (s, aromatic C), 38.8 (s, $COCH_2$), 32.1 (s, CH_2), 24.6 (s, CH_2), 23.2 (s, CH_2), 14.2 (s, CH_3). GC-MS *m*/*z* (rel intensity) 176 (20), 133 (15), 120 (100), 105 (100), 91 (8), 77 (100).

2,2-Dimethylpropiophenone: [938-16-9] (44%); 2,2-Dimethylpropiophenone was characterized by GC-MS by comparison with an authentic sample (Aldrich). GC-MS *m*/*z* (rel intensity) 162 (5), 105 (96), 77 (100).

Cross-Coupling Reaction of Benzoic Anhydride with Other Organoboron Compounds (Eq. 1). A typical procedure using $NaBPh_4$ is given below. A dioxane solution (5 cm^3) containing $[Pd(PPh_3)_4]$ (57.8 mg, 0.0500 mmol), benzoic anhydride (228 mg, 1.01 mmol), and sodium tetraphenylborate (110 mg, 0.321 mmol) in a 25 cm^3 Schlenk tube was heated under argon at 80 °C for 24 h. The yields of benzophenone were determined by GC using $^nC_{14}H_{30}$ as an internal standard. Benzophenone was characterized by GC-MS by comparison with an authentic sample (Tokyo Kasei Kogyo Co.). GC-MS *m*/*z* (rel intensity) 182 (100), 105 (82), 77 (98).

Reaction of $[Pd(PMePh_2)_4]$ with Acetic Anhydride (Scheme 3). A dioxane solution (0.5 cm^3) containing $[Pd(PMePh_2)_4]$ (15.2 mg, 0.0168 mmol), and acetic anhydride (1.84 mg, 0.0180 mmol) in an NMR tube was reacted under argon at room temperature for 23.5 h. ^{31}P{^{1}H} NMR analysis did not give any signal corresponding to the oxidative adduct.

Reaction of *trans*-$[PdAc(OAc)(PMePh_2)_2]$ with Methyldiphenylphosphine (Eq. 2). *trans*-$[PdAc(OAc)(PMePh_2)_2]$ (13.5 mg, 0.0222 mmol) was dissolved in THF-d_8 (0.5 cm^3) and $PMePh_2$ (8.93 mg, 0.0446 mmol) was added into the solution at room temperature. The solution was shaken and subjected to NMR observation after 5 min. The ^{1}H and ^{31}P{^{1}H} NMR analysis indicated the formation of $[Pd(PMePh_2)_4]$ and Ac_2O as major products.

Time-Yield Curves of [(η^5-Cyclopentadienyl)(η^3-allyl)palladium] 6 and $[Pd(PPh_3)]_4]$ 4 (Fig. 1). A typical procedure is as follows ([Pd(PPh$_3$)4]). A dioxane solution (5 cm^3) containing $[Pd(PPh_3)_4]$ (22.9 mg, 0.0198 mmol), 4-methoxybenzoic anhydride (221 mg, 0.977 mmol), and phenylboronic acid (143 mg, 1.17 mmol) in a 25 cm^3 Schlenk tube was heated under argon at 80 °C. At each interval, the tube was removed, and cooled in a water bath immediately. The yields of 4-methylbenzophenone were determined by GC using $^nC_{14}H_{30}$ as an internal standard.

Time-Yield Curves in Formation of Benzophenone and 4-Methoxybenzophenone (Fig. 2). A typical procedure for obtaining the time-yield curve in synthesis of 4-methoxybenzophenone is as follows. A dioxane solution (5 cm^3) containing $[Pd(PPh_3)_4]$ (23.2 mg, 0.0201 mmol), 4-methoxybenzoic anhydride (288 mg, 1.01 mmol), and phenylboronic acid (147 mg, 1.21 mmol) in a 25 cm^3 Schlenk tube was heated under argon at 80 °C. At each interval, the tube was removed from the oil bath and cooled in a water bath immediately. The yields of benzophenone were determined by GC using $^nC_{14}H_{30}$ as an internal standard.

Competitive Reactions of Various *para*-Substituted Benzoic Anhydrides and Benzoic Anhydride (Table 4, Fig. 3). A typical procedure is as follows. A dioxane solution (5 cm^3) containing $[Pd(PPh_3)_4]$ (23.3 mg, 0.0202 mmol), benzoic anhydride (453 mg, 2.00 mmol), 4-methoxybenzoic anhydride (577 mg, 2.02 mmol), and phenylboronic acid (122 mg, 1.00 mmol) in a 25 cm^3 Schlenk tube was heated under argon at 80 °C for 5 h. The GC analysis revealed that 59.4% of benzophenone and 32.9% of 4-methoxybenzophenone were generated in the reaction mixture. On the basis of the amounts of the two ketones, the relative reactivity of benzoic anhydrides was determined as 0.55.

Cross-Coupling Reaction of Pivalic *p*-Toluic Anhydride with Phenylboronic Acid (Eq. 3). A dioxane solution (5 cm^3) containing $[Pd(PPh_3)_4]$ (58.0 mg, 0.0502 mmol), pivalic *p*-toluic anhydride (220 mg, 0.999 mmol), and phenylboronic acid (147 mg, 1.21 mmol) in a 25 cm^3 Schlenk tube was heated under argon at 80 °C for 24 h. The yields of 4-methylbenzophenone and 2,2-dimethylpropiophenone were determined by GC using $^nC_{14}H_{30}$ as an internal standard. 4-methylbenzophenone and 2,2-dimethylpropiophenone were characterized by GC-MS by comparing with an authentic sample (Kanto Chemical Co. and Aldrich). 4-Methylbenzophenone: GC-MS *m*/*z* (rel intensity) 196 (32), 181 (8), 119 (100), 105 (30), 91 (36), 77 (41). 2,2-Dimethylpropiophenone: GC-MS *m*/*z* (rel intensity) 162 (4), 105 (99), 77 (40).

Effect of Heterogeneous Catalysts (Table 5). A typical procedure is as follows (Run 6). A dioxane solution (5 cm^3) containing [10 wt% $Pd/BaSO_4$] (unreduced) (106 mg, 0.0498 mmol), triphenylphosphine (52.3 mg, 0.199 mmol), benzoic anhydride (226 mg, 0.999 mmol), and phenylboronic acid (146 mg, 1.20 mmol) in a 25 cm^3 Schlenk tube was heated under argon at 80 °C for 24 h. The yield of benzophenone was determined by GC using $^nC_{14}H_{30}$ as an internal standard. Benzophenone was characterized by GC-MS by comparison with an authentic sample (Tokyo Kasei Kogyo Co.). GC-MS *m*/*z* (rel intensity) 182 (100), 105 (82), 77 (88).

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