Synthetic Design of Carbonyl-Group-Containing Compounds Based on C–O Bond Cleavage Promoted by Pd Complexes

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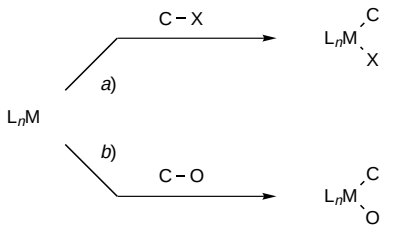
Dedicated to *Luigi M. Venanzi* in memory of his outstanding scientific achievements

On the basis of fundamental studies on elementary processes involving allyl–O and acyl–O bond cleavages, various new catalytic processes to convert carboxylic acid derivatives have been realized. The new processes include *1*) carbonylation of allyl formates to β,γ-unsaturated acids, *2*) amination, alkylation, and carbonylation of allylic alcohols, *3*) aldehyde synthesis by hydrogenation of carboxylic anhydrides and carboxylic acids, *4*) ketone synthesis by combination of the C–O bond cleavage with transmetallation by organoboronic acids. The processes described here have advantages over the conventional ones in that they are more atom-efficient and halogen-free in realizing the syntheses of a variety of carbonyl-containing compounds under mild conditions.

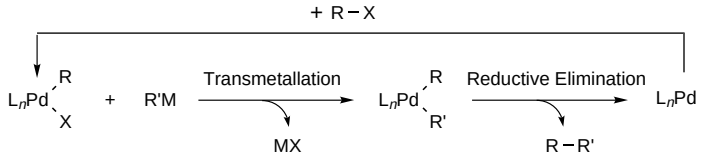
1. Introduction. – Organic synthesis is comprised of the processes of cleaving and connecting chemical bonds in organic compounds. Thus, development of methodologies for specifically cleaving and making particular bonds has pivotal importance in organic synthesis. Recent progress in organotransition-metal chemistry [1] has shown that elementary processes unique to organotransition-metal complexes can be combined in applications to develop quite a variety of useful synthetic processes [2]. Pd Complexes rank at the top among transition-metal complexes in their utility in organic synthesis [3]. The usefulness arises from their chemical properties in readily undergoing elementary processes such as oxidative addition and reductive elimination that can be combined with other elementary processes. Oxidative addition of organic halides to low-valent transition-metal complexes involving the cleavage of the C–halogen bond as shown in *a*) in *Scheme 1* has been most widely utilized.

Scheme 1. *Two Modes of the C–Heteroatom Bond Cleavage*



The process of cleaving the C–halogen bond in organic halides to generate reactive organotransition-metal halides can be combined with other elementary processes to develop useful preparative methods. Among various synthetic methods with transition-metal complexes, cross-coupling processes catalyzed by Pd complexes have been developed most extensively in combination with transmetallation and the ensuing reductive-elimination processes (*Scheme 2*) [4].

Scheme 2. *Transmetallation and Reductive Elimination Involved in Catalytic Cross-Coupling Processes*



In the transmetallation process, the halide ligand in organopalladium halide complex is replaced by an alkyl, alkenyl, or aryl group on reaction with other organometallic compounds R′M to give diorganotransition-metal complexes. Reductive elimination of the two organic groups bound to Pd provides the coupling products of R and R′ groups and regenerates the Pd^0 species that completes the catalytic cycle by further reaction with organic halides R–X.

Although the processes starting from organic halides provide convenient means to synthesize various useful compounds, the halogen used must be removed as a salt during preparation of compounds that do not contain halogen. Thus, the process, although convenient, has the shortcomings of being neither atom-efficient nor environmentally benign.

In another type of Pd-catalyzed synthetic method, *i.e.*, olefin arylation process called *Mizoroki-Heck* process, the oxidative addition of organic halides is also used. However, removal of hydrogen halide with a base is also required in this process for preparation of arylated olefins that contain no halogen atoms.

Other possibilities to replace the C–halogen bond cleavage in these processes are the cleavage of C–O bond (type *b* in *Scheme 1* [5]), and cleavage of C–H [6][1]), C–C bond [8] and other C–heteroatom bonds[2]) to be combined with other fundamental processes.

2. Stoichiometric Processes Involving the C–O Bond Cleavage. – Our interest in the chemistry of C–O bond cleavage in organic compounds on interaction with low-valent transition-metal complexes stems from our previous findings in the seventies of the ready C–O bond cleavage [10]. Various C–O bonds in alkenyl carboxylates are cleaved on interaction with Ru, Rh, and Co hydride complexes [5]. Group-10 transition-metal complexes have been found later to react with carboxylic esters and anhydrides in two types of cleavage modes as shown in *Scheme 3* [11–13].

In the acyl–O bond cleavage of carboxylates (cleavage mode *a* in *Scheme 3*) on interaction with Pd^0 complex, reactive acyl(alkoxo)palladium complexes are generated that are susceptible to further reactions. We previously observed decarbonylative

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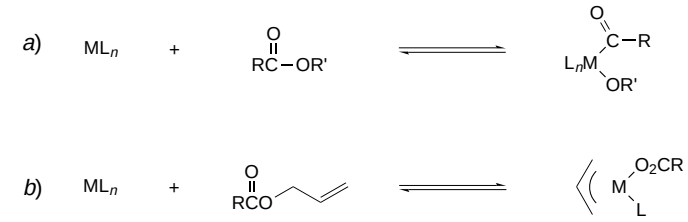
[1]) We first observed the ready C–H bond cleavage with a Ru complex [7].

[2]) For our work on C–S bond cleavage and C–S bond-formation studies, see [9].

Scheme 3. *Cleavage of C–O Bond in Carboxylates, a) Acyl–O Bond Cleavage and b) Allyl–O Bond Cleavage*



cleavage of phenyl propionate to ethylene and PhOH upon treatment of the ester with a Ni^0 complex. The reaction course involved initial cleavage of the propionyl–phenoxy bond in the ester on interaction with the Ni^0 species to give the phenoxo(propionyl)-nickel intermediate, with decarbonylation of the propionyl ligand followed by β-H elimination to liberate ethylene producing hydrido(phenoxo)nickel complex that reductively eliminates PhOH [11b]. Kinetic studies established that oxidative addition of aryl carboxylates to Ni^0 complexes proceeds through nucleophilic attack of the electron-rich Ni^0 complex on the C=O group in the aryl carboxylates. An electron-withdrawing substituent on the Ph group enhances the reaction rate, and the ligation of a more electron-releasing tertiary phosphine ligand was observed to accelerate the oxidative addition.

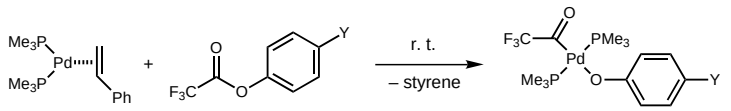
Oxidative addition of formate esters and β-lactones to Ni^0 complexes was also observed to proceed readily to afford various cleavage products such as alcohols, aldehydes, and other products [14]. Oxidative addition of diketene to a Pd^0 complex to form a five-membered metallacycle has been observed. The five-membered palladalactone complex undergoes CO insertion and subsequent reductive elimination to give cyclic anhydrides [15].

Reactions of Ru, Co, and Rh hydride complexes with carboxylates were also found to cause the C–O bond cleavage, but the courses of these reactions are somewhat different from those promoted by Group 10 metal complexes because of the presence of the hydride ligand [16]. Dialkylnickel complexes were also found to react with carboxylic esters and anhydrides to cause cleavage of the C–O bonds [17].

The oxidative addition involving the C–O bond cleavage (course *a* in *Scheme 3*) is observed not only with carboxylates but also with carboxylic anhydrides. Carboxylic anhydrides (R′ = acyl group in *Scheme 3*) were found to oxidatively add to Ni^0 complexes to give the C–O bond-cleavage products that can be accounted for by assuming the intermediacy of acyl(carboxylato)nickel-type complexes [18]. The C–O bond cleavages of carboxylic esters and anhydrides are reversible. The insertion of CO into the alkyl–Ni bond in an alkyl(aryloxo)nickel complex gives an acyl(aryloxo)nickel complex that readily reductively eliminates the carboxylates. In a similar manner, alkyl(carboxylato)nickel and -palladium complexes liberate carboxylic anhydrides on CO insertion into the alkyl–metal bond followed by reductive elimination of the acyl and carboxylato groups.

We later found that the acyl–O bond cleavage takes place with electronegative esters such as aryl trifluoroacetate (*Scheme 4*) [19].

Scheme 4



(Y = CN, H, Me)

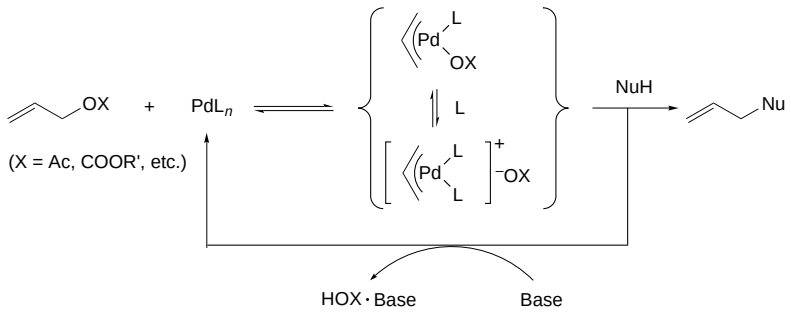
As will be described later, the oxidative addition of CF_3COOPh to a Pd^0 complex was utilized for catalytic synthesis of unsymmetrical ketones by combining the C–O bond cleavage with transmetallation by organoboronic acids.

Scheme 3, *b*, shows the other mode of C–O bond cleavage observed with allylic carboxylates. The allyl–O bond is readily cleaved to give η^3-allyl(carboxylato)transition-metal complexes that are susceptible to the ensuing reactions [20]. The C–O bond in allyl ethers and allylic alcohols are also cleaved readily on interaction with Pd^0 complexes. Because of the allylic nature of the Bn group, the C–O bond in CF_3COOBn derivatives is also susceptible to cleavage on interaction with a Pd^0 complex to give benzyl(trifluoroacetato)palladium complexes [19]. The C–O bond in allylic carbonates is also cleaved similarly to the C–O bond cleavage in allyl carboxylates to give η^3-allyl(carbonato)-Pd and -Pt complexes [21].

The oxidative addition of allylic carboxylates is reversible. Depending on the ligand present, ready reductive elimination of the allyl and the carboxylato ligands shifts the equilibrium in *Scheme 3*, *b*, to the left to regenerate allyl carboxylate with C–O bond formation.

3. Catalytic Processes Utilizing the C–O Bond Cleavage Coupled with Other Reactions. 3.1. *Processes Utilizing the Cleavage of Allyl–O Bond.* – Among the catalytic processes involving the C–O bond cleavage, Pd-catalyzed allylation of various nucleophiles starting from allylic carboxylates and carbonates, developed by *Trost* and *Verhoven* [22], and *Tsuji* [23] have been most widely used for organic synthesis. The catalytic process involves the first oxidative addition of the allylic substrates to form electrophilic η^3-allylpalladium complexes that are attacked by nucleophiles to form the allylation products (*Scheme 5*).

Scheme 5. *The C–O Bond Cleavage of Allylic Carboxylates, Carbonates, and Alcohols in Pd-Catalyzed Allylation Processes*



Formation of the η^3-allylpalladium complexes has been established in the reaction of $[Pd(PCy_3)_2]$ with allyl acetate [24] and in the reaction of allylic carbonates with Pd^0 and Pt^0 complexes [25]. However, when PPh_3, the most frequently used ligand, is employed, no apparent oxidative addition is observed in the absence of a nucleophile. The in-depth study of the reaction with use of deuterated allyl acetate revealed that the reversible process involving the C–O bond cleavage and C–O bond-formation was actually taking place in the system where no apparent sign of the occurrence of the reaction was observed [24c].

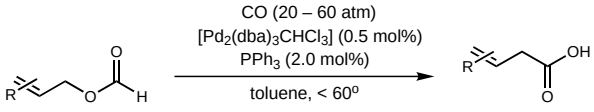
If the allylpalladium complexes obtained by the allyl–O bond cleavage can be further carbonylated to give the CO-inserted acylpalladium complexes as shown in *Scheme 6*, the process can be applied to catalytic carbonylation of organic compounds that makes use of the reactivity of the acylpalladium intermediate [26] (*Scheme 6*).

Scheme 6. *Equilibrium between CO Insertion into the Allyl–Pd Bond and Decarbonylation*

Because of the stability of the η^3-allylpalladium complexes the CO inserted acylpalladium species is readily decarbonylated back to the η^3-allylpalladium species. The decarbonylation takes place easily, particularly when the halide ligand tends to dissociate in solution or is removed by addition of an Ag salt to generate a cationic acylpalladium species with a weakly coordinated solvent molecule. Thus, somewhat special conditions, such as addition of a strongly coordinating halide ligand or application of CO pressure, are required to shift the equilibrium to favor the formation of the acylpalladium intermediate that undergoes further reactions [27]. By providing suitable conditions to favor the CO insertion and further coordination of CO that is susceptible to nucleophilic attack of an amine, we have been able to realize the catalytic double carbonylation of allylic halides to prepare α-ketoamides. However, since the process is not directly related to the theme of the present perspective, the detail of the process will not be discussed here [26][28].

In the course of our attempts to introduce CO into the allyl–Pd bond, we found that allylic formates can be converted cleanly into β,γ-unsaturated carboxylic acids when treated with pressurized CO in the presence of a catalytic amount of a Pd complex [26] (*Scheme 7*).

Scheme 7

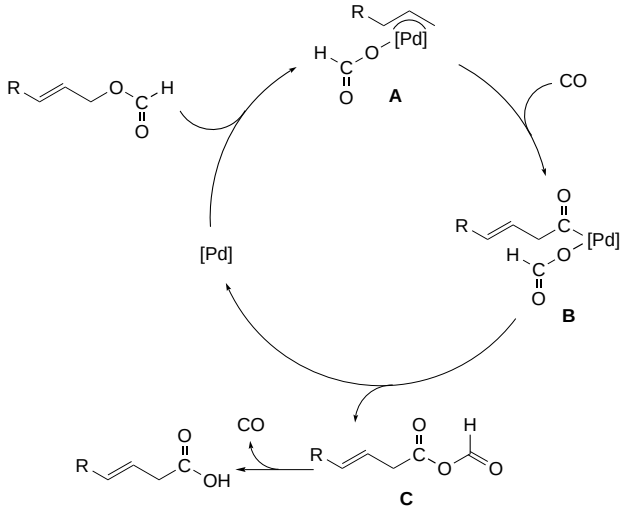


No organic halides are used in this process, and allylic formates as the starting material can be prepared by treatment of allylic alcohols with HCOOH in the presence of P_2O_5 at room temperature without organic halides. The process, thus, provides a convenient halogen-free synthetic method to synthesize unsaturated carboxylic acids

from allylic formates. As will be discussed later, the carboxylic acids prepared can be further converted to aldehydes and ketones by methods developed on the basis of C–O bond cleavage of carboxylic anhydrides.

The mechanism of conversion of allylic formates to unsaturated carboxylic acids under CO was elucidated by taking into account the information we previously obtained in the study of the mechanism of decarboxylative reduction of allylic acetates into olefins in the presence of HCOOH and NH_3. The reduction was rationalized by assuming the intermediate formation of η^3-allylpalladium formate by substitution of the AcO^- ligand with $HCOO^-$. Upon decarboxylation of the $HCOO^-$ ligand, an allylpalladium hydride species is formed that liberates olefins upon reductive elimination of the hydrido and allyl ligands [29][30]. On the basis of this information, we proposed the mechanism as shown in *Scheme 8* for the formation of the β,γ-unsaturated carboxylic acids from allylic formates under CO [26].

Scheme 8. *Mechanism of the Pd-Catalyzed Carbonylation of Allyl Formates to β,γ-Unsaturated Acids*



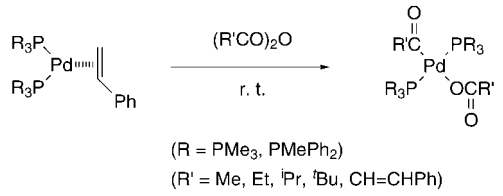
Allylic formates oxidatively add to a Pd^0 complex to give η^3-allylpalladium formate species (**A** in *Scheme 8*) as established separately in the reaction of several Pd^0 complexes having tertiary phosphine ligands with allylic formates [30]. If CO is inserted into the Pd–allyl bond under CO pressure, acyl-formate-type complex **B** will be generated. Upon reductive elimination of the formato and the acyl entities, complex **B** liberates a mixed anhydride **C**, which is thermally unstable, and spontaneous decarbonylation takes place to provide β,γ-unsaturated carboxylic acid. In the process of reductive elimination of **B**, a coordinatively unsaturated Pd^0 species is generated to react further with allylic formate to drive the catalytic cycle. In certain cases the C–O bond in allylic alcohols can be also cleaved on interaction with Pd^0 complexes to give η^3-allylpalladium complexes. The allyl ligand in the complex formed is attacked by nucleophiles such as amines as well as by C-nucleophiles such as malonates, acetoacetates, and acetylacetone. Interestingly, the C–O bond cleavage in allylic

alcohols is promoted when the process is carried out under CO_2, presumably due to the formation of hydrogen carboxylate of the allylic alcohol [31]. Thus, amination of allyl alcohol with Et_2NH can be performed in the presence of a catalytic amount of $[Pd(PPh_3)_4]$ at room temperature under the balloon pressure of CO_2. When the reaction is carried out under CO and CO_2 pressure, unsaturated carboxylic acids can be prepared. The process is thought to proceed through the C–O bond cleavage and CO insertion into allylpalladium intermediate.

3.2. *Processes Utilizing the Acyl–O Bond Cleavage in Carboxylic Esters and Anhydrides.* In contrast to the synthetic methods involving the allyl–O bond cleavage, the process involving acyl–O bond cleavage in carboxylic esters and anhydrides (scission *a* in *Scheme 3*) has been less developed. In our earlier studies on the C–O bond cleavage of carboxylic esters and anhydrides with Ni^0 and Pt complexes, we observed the formation of acylnickel [11][32] and acylplatinum complexes. The reactions of carboxylic esters and anhydrides with Pd^0 complexes also proceeded to give the acylpalladium species with cleavage of the acyl–O bond. The formation of the reactive acylpalladium-type complexes on oxidative addition of the carboxylic esters and anhydrides with a Pd^0 species suggests the potential for application of the information derived in stoichiometric processes to catalytic systems. We were slow to recognize this potential but recently found that catalytic processes can, in fact, be realized by combining the acyl–O bond cleavage with other elementary processes involving organopalladium intermediates, as described below.

Oxidative addition of acyclic carboxylic anhydrides to an unsaturated Pd^0 complex, which can be generated by *in situ* thermolysis of $[PdEt_2(PMe_3)_2]$ or $PdEt_2(PMePh_2)_2]$ in the presence of styrene, was found to give *trans* acyl(carboxylato)bis(tertiary phosphine)palladium(II) complexes [33] (*Scheme 9*).

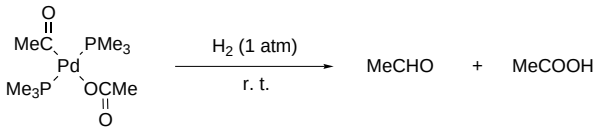
Scheme 9



The carboxylato ligand in the acyl(carboxylato)palladium complex was found to exchange with free carboxylic acid added to the system, indicating the lability of the carboxylato ligand attached to the Pd^{II} complex and inertness of the acyl ligand to the attack of the carboxylic acid.

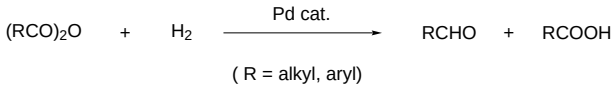
3.3. *Application of the C–O Bond Cleavage to Catalytic Hydrogenation to Produce Aldehydes.* The acyl(carboxylato)bis(trimethylphosphine)palladium complex formed by oxidative addition of the carboxylic anhydrides were revealed to undergo ready hydrogenation under H_2 to give aldehydes and carboxylic acids together with alcohol as by-product, which may have been formed by hydrogenation of the aldehyde (*Scheme 10*).

Scheme 10



These results showing the formation of aldehydes from the acylpalladium complexes on their treatment with H_2 suggested the possibility of applying the finding to catalytic hydrogenation of carboxylic anhydrides. In fact, aliphatic as well as aromatic carboxylic anhydrides were converted into the corresponding aldehydes and carboxylic acids in excellent yields by treating the carboxylic anhydrides with H_2 in the presence of a catalytic amount of $[Pd(PPh_3)_4]$ (*Scheme 11*).

Scheme 11



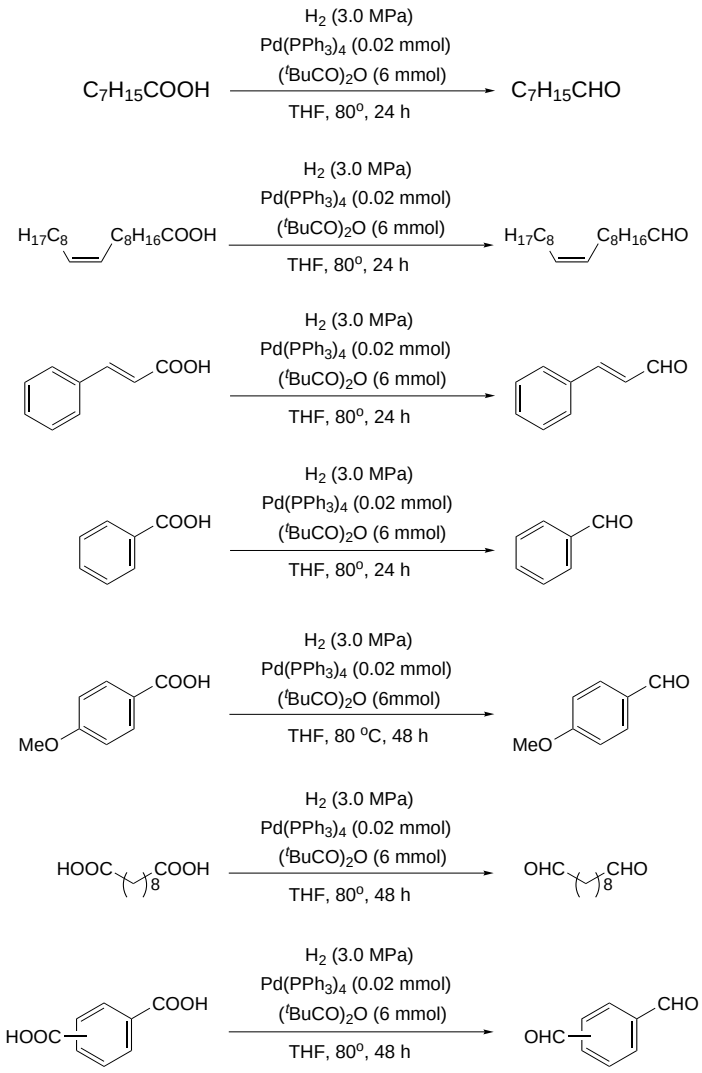
The hydrogenation is also catalyzed by a combined system of $[Pd(OAc)_2]$ and tertiary phosphines, wherein reduction of $[Pd(OAc)_2]$ *in situ* may yield a catalytically active low-valent Pd species. An advantage of the hydrogenation process is that little over-reduction of aldehydes to alcohols takes place in the catalytic process.

Although the catalytic system in which carboxylic anhydrides are the substrates provides a convenient means to reduce carboxylic anhydrides to aldehydes under mild conditions, the system still entails the shortcomings that initial synthesis of the anhydrides is required and 1 equiv. of carboxylic acid is released for each equiv. of aldehyde synthesized.

Through our studies on the comparative reactivities of various carboxylic anhydrides with Pd^0 complexes, we found that carboxylic anhydride such as 2,2-dimethylpropionic anhydride (pivalic anhydride) proved to be much less reactive than the less-bulky carboxylic anhydrides [34][35]. Prompted by this finding, we designed a catalytic system with pivalic anhydride added to the system containing the carboxylic acid to be hydrogenated. We reasoned that this would produce a three component mixture of *a*) the anhydride of the carboxylic acid, *b*) mixed anhydride, and *c*) pivalic anhydride. Then, the less-bulky acyl entity in the anhydride mixture would be preferentially hydrogenated. By adding some excess pivalic anhydride, we found the preferential hydrogenation of various carboxylic acids at the expense of the pivalic acid added. Typical examples of hydrogenation of carboxylic acids are summarized in *Scheme 12*.

The catalytic system found in the study provides a convenient means of hydrogenating a variety of free carboxylic acids directly to corresponding aldehydes in a one-pot process without overreduction to alcohols. The present process does not require the preparation of acid chlorides beforehand as usually practiced in the conventional *Rosenmund* reduction nor needs addition of a base [36]. The process is complementary with the commercial process recently developed by *Mitsubishi Chemical Corp.*,

Scheme 12. *Examples of Direct Hydrogenation of Carboxylic Acids to Aldehydes Catalyzed by Pd Complexes*



where high-temperature direct hydrogenation of vaporized carboxylic acids is exercised [37].

As shown in *Scheme 12*, the catalytic process has wide applicability in the direct hydrogenation of various carboxylic acids into aldehydes in the presence of pivalic anhydride. It is applicable to aliphatic, aromatic, and heterocyclic carboxylic acids. Yields of the corresponding aldehydes are generally quite high, although carboxylic acids having a bulky substituent at the α-position and aromatic acids having a substituent at the *ortho* position(s) to the carboxy entity proved less reactive. The

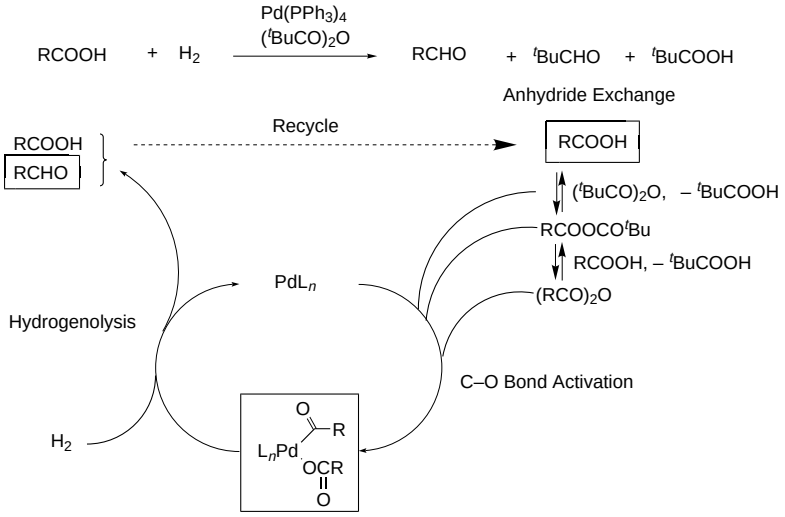
process is tolerant to electron-withdrawing and electron-donating substituents at the *para*- and *meta*-positions in benzoic acid derivatives.

The process is also applicable to di- and tricarboxylic acids to give corresponding di- and tricarbaldehydes, suggesting potential applicability in synthesis of polycarbaldehydes.

It is somewhat surprising that the carboxy unit alone is hydrogenated in the reduction of unsaturated acids having double bonds, such as oleic acid and erucic acids. The internal C=C bond remains intact. Unsaturated carboxylic acids with terminal C=C bonds can be hydrogenated without causing extensive terminal-to-internal C=C bond isomerization under suitable experimental conditions. The inertness of the internal C=C bond to hydrogenation is not surprising, however, in view of the difference in the mechanisms between the conventional hydrogenation of olefins and the present type of hydrogenation proceeding through the C–O bond cleavage.

We proposed the mechanism shown in *Scheme 13*.

Scheme 13. *Proposed Mechanism to Account for the Hydrogenation of a Carboxylic Acid in the Presence of Added Pivalic Anhydride*

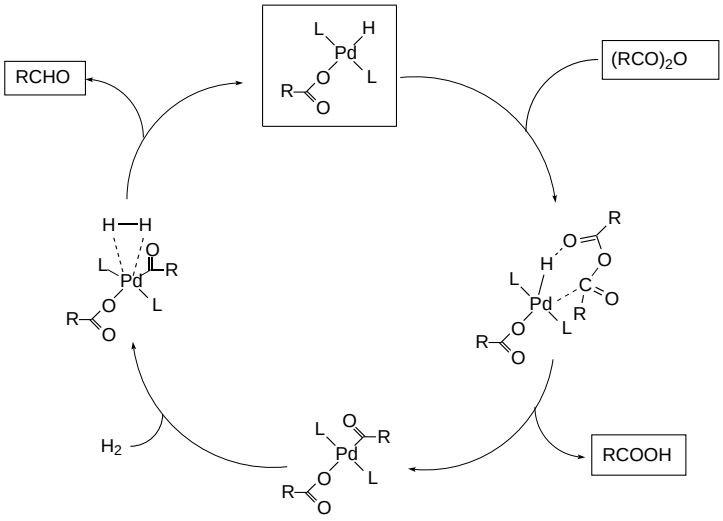


The main cycle comprises the oxidative addition of carboxylic anhydride to a Pd^0 species to give the acyl(carboxylato)palladium(II) intermediate and hydrogenation of the acyl and carboxylato entities to liberate aldehyde and carboxylic acid. The carboxylic acid liberated in the reaction is converted in the presence of pivalic anhydride to a mixture of carboxylic anhydrides formed by the exchange processes as shown in the upper right hand side in *Scheme 13*. The more reactive entity in the anhydrides enters the main catalytic process to drive the catalytic cycle involving the oxidative addition and formation of the aldehyde and the carboxylic acid.

3.4. *On Possibility of Involvement of Another Type of Catalytic Mechanism Proceeding through a Hydride Intermediate.* Although the mechanism shown in *Scheme 13* is consistent with the results of the oxidative addition of carboxylic

anhydride to a Pd^0 species and the subsequent hydrogenation of the acyl(carboxylato)palladium(II) species in stoichiometric processes, our later investigation based on the DFT calculation on the catalytic process suggested the possibility of involvement of another type of mechanism proceeding through a palladium hydride intermediate as shown in *Scheme 14*.

Scheme 14. *A Possible Catalytic Cycle Proceeding through Involvement of Palladium Hydride Species*



The result of computation on the structure of *trans*-acetato(acetyl)bis(trimethylphosphine)palladium(II) by the DFT method [38] showed an excellent agreement with the molecular structure of the complex later obtained with X-ray diffraction method, indicating the reliability of the computational method, at least, regarding the static structures of the organopalladium complexes. Further computation on the reaction course of *trans*-acetato(acetyl)bis(trimethylphosphine)palladium(II) with H_2 suggested that the reaction proceeds to give MeCHO and acetato(hydrido)bis(trimethylphosphine)palladium(II). The possibility of involvement of the carboxylato(hydrido)palladium species suggested by the computational method led us to examine the viability of operation of a catalytic cycle involving the intermediacy of an acetato(hydrido)palladium(II) species. The hydrido species may react with Ac_2O to liberate AcOH to lead to the acetato(acetyl)bis(trimethylphosphine)palladium(II) that is known to react with H_2 to liberate aldehyde.

For examining the feasibility of the mechanism proceeding through the carboxylato(hydrido)bis(tertiary phosphine)palladium(II) species, we prepared an isolable *trans*-trifluoroacetato(hydrido)bis(tricyclohexylphosphine)palladium(II) as a model for the hydrido complex. On reaction with propanoic anhydride, the hydridopalladium complex did liberate propanoic acid with formation of *trans*-(trifluoroacetato)(propionyl)bis(tricyclohexylphosphine)palladium(II) complex. The (trifluoroacetato)-(propionyl)bis(tricyclohexylphosphine)palladium(II) thus formed reacted further with H_2 to give propanal to yield the hydrido(trifluoroacetato)bis(tricyclohexylphos-

phine)palladium(II) in support of the catalytic cycle in *Scheme 14*. Another type of hydridopalladium complex, *trans*-chloro(hydrido)bis(tricyclohexylphosphine)palladium(II) complex also behaved similarly. Furthermore the hydridopalladium complexes proved to be catalytically active in converting propanoic anhydride to propanal and propanoic acid [39].

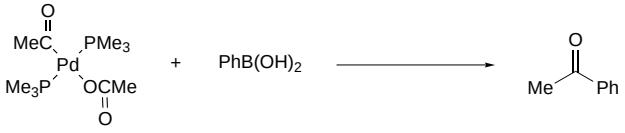
Although the mechanism involving the hydridopalladium intermediate needs further verification, it is interesting that a mechanism not imagined at all on the basis of experimental results alone was indicated by the computational method. With progress in computational approaches, further insight into the reaction mechanism may be revealed in the future.

3.5. *Application of the Acyl–O Bond Cleavage in Carboxylic Anhydrides to Catalytic Ketone Synthesis.* Formation of an acylpalladium species on reaction of a Pd^0 compound with carboxylic anhydrides and the successful application of the reactivity of the acylpalladium intermediate to catalytic hydrogenation producing aldehydes showed us the prospect of application of the acyl–O bond cleavage process to other useful preparative methods. We reasoned that transmetallation of the anionic carboxylato ligand would lead to formation of acylpalladium complexes having alkyl, aryl, and alkenyl ligands. The reductive elimination of the acyl-hydrocarbyl ligands would produce ketones as coupling products.

We chose organoboron compounds as the alkylating agents in view of the established application of the organoboron compounds as discovered by *Suzuki* and *Miyaura* [40]. The organoboron compounds are more favorable than organostannane compounds in being less toxic[3]) and over organomagnesium compounds[4]) in their tolerance to functional groups. Pd-Catalyzed cross-coupling processes to prepare ketones starting from acyl halides and organoboron compounds involving the C–halogen bond cleavage have been recently developed by *Haddach* and *McCarthy* [45], and *Bumagin* and *Korolev* [46] but utilization of the concept of C–O bond cleavage to ketone synthesis is new to our knowledge. The present process is complementary to the *Friedel-Crafts*-type ketone synthesis recently developed by *Kobayashi* catalyzed by rare-earth-metal compounds (*cf.* [47] and refs. cit. therein).

We first examined the possibility to replace the acetate ligand in *trans*-acetato(acetyl)bis(trimethylphosphine)palladium(II) complex generated by the acyl–carboxylate bond cleavage in Ac_2O on interaction with the Pd^0 complex, with phenylboronic acid [48]. In fact, we found that *trans*-[Pd(Ac)(AcO)(PMe_3)$_2$] reacted with phenylboronic acid to afford acetophenone under mild conditions (*Scheme 15*).

Scheme 15

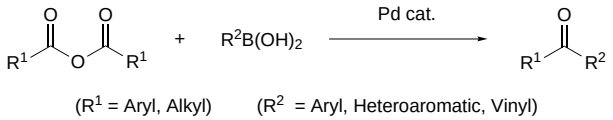


[3]) For ketone synthesis catalyzed by Pd complexes by the reaction of aryl halide and acylstannane compounds, see [41]; with acyl halides and organostannane compounds, see [42]; with aryl halides, organostannane compounds, and CO, see [43].

[4]) For Ni-complex-catalyzed ketone synthesis with acyl halides, organomagnesium compounds, see [44].

The result suggests that the transmetallation of *trans*-[Pd(Ac)(AcO)(PMe_3)$_2$] with phenylboronic acid takes place readily to give a (acetyl)(phenyl)palladium intermediate that further releases acetophenone rapidly on reductive elimination. On the basis of this finding, we have been able to develop a catalytic system to convert carboxylic anhydrides and organoboron compounds to ketones promoted by Pd catalysts by simple extension of the concepts derived from stoichiometric reactions of organopalladium complexes (*Scheme 16*).

Scheme 16



Addition of an extra amount of tertiary phosphine had an inhibiting effect for the ketone synthesis. It was also found that addition of two equivalents of $MePPh_2$ to the THF solution containing *trans*-acetato(acetyl)bis(methyldiphenylphosphine)palladium (II) caused rapid formation of Ac_2O and [Pd($PMePh_2$)$_4$] indicating that the reductive elimination of the Ac and AcO ligands takes place readily. This may be associated with the effect of tertiary phosphine ligands to hinder the oxidative addition of carboxylic anhydrides to Pd^0 complex. It was revealed by means of $^{31}P\{^1H\}$-NMR that the reaction of Ac_2O with [Pd($PMePh_2$)$_4$] did not give any sign of the occurrence of oxidative addition, whereas oxidative addition of Ac_2O to the coordinatively unsaturated [Pd($PMePh_2$)$_2$(styrene)] readily afforded the oxidative addition product *trans*-[Pd(Ac)(OAc)($PMePh_2$)$_2$) at room temperature.

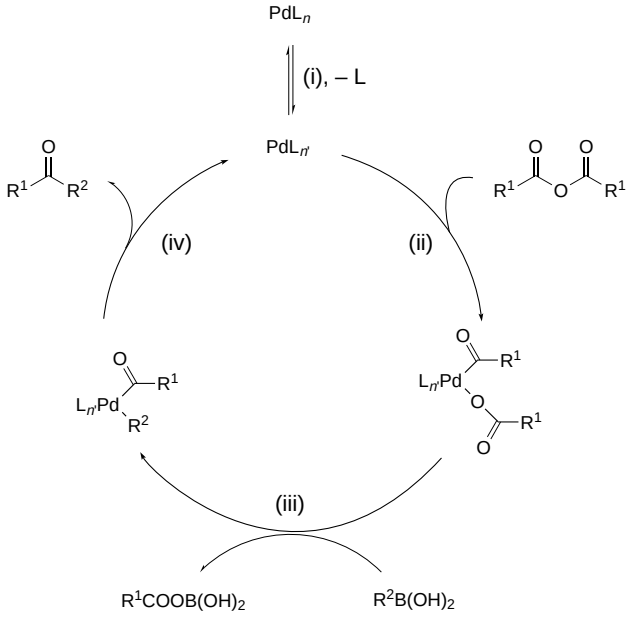
Scheme 16 shows the applicability of the cross-coupling process for synthesis of various ketones by combining the processes of oxidative addition of carboxylic anhydrides by transmetallation with organoboron compounds and reductive elimination. Benzoic anhydride can be conveniently used in combination with various aryl- and heterocyclic boronic acids to give various phenyl ketones in excellent yields at 80° in dioxane in 5 h. Aliphatic anhydrides also give alkyl aryl ketones in high yields in combination with arylboronic acids, except for aliphatic anhydride having bulky substituent at the α-position such as pivalic anhydride.

We have also confirmed that heterogeneous metal catalysts such as Pd on activated C and Pd on $BaSO_4$ catalyzed this type of cross-coupling reaction.

The catalytic ketone synthesis probably consists of elementary processes of *a*) oxidative addition of carboxylic anhydride to Pd^0 species to give acyl(carboxylate)-palladium species, *b*) transmetallation with arylboron compounds, and *c*) reductive elimination to liberate the ketone regenerating the Pd^0 species as shown in *Scheme 17*.

As indicated by inhibition effect of tertiary phosphine ligands added to the catalyst system, the active Pd species for undergoing the oxidative addition of carboxylic anhydrides requires to be coordinatively unsaturated. Thus a pre-equilibrium step, indicated above the catalytic cycle in *Scheme 17*, may be involved in the catalytic system. Since the evidence indicating the presence of the intermediate acyl(alkyl)palladium species was not obtained in the actual catalyst system, the reductive elimination

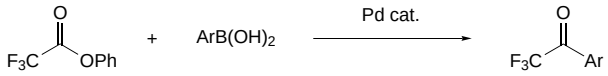
Scheme 17. *Catalytic Cycle for Ketone Synthesis from Carboxylic Anhydride and Organoboronic Acid Catalyzed by a Pd Species*



to liberate the product ketone may be a rapid process. As we observed in aldehyde synthesis, the process starting from carboxylic anhydrides can be expanded to the system composed of a mixture of an anhydride with carboxylic acids to convert the acids directly to ketones as will be reported separately. The present method of Pd-catalyzed ketone synthesis has several advantages over conventional methods. *a*) The method is catalytic and has a better atom efficiency and is environmentally more favorable than the conventional methods based on organic halides. *b*) The present method has some advantages over the conventional *Friedel-Craft* ketone synthesis [49], involving the electrophilic substitution in the applicability, since substituents having electron-donating as well as electron-withdrawing substituents can be employed to prepare the unsymmetrical ketones without acyl chlorides.

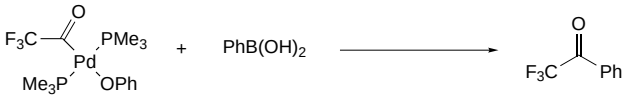
3.6. *Application of the C–O Bond Cleavage in the Carboxylates to Catalytic Ketone Synthesis* (*Scheme 18*). As discussed in the previous section dealing with stoichiometric processes involving the acyl–O bond cleavage, aryl trifluoroacetates oxidatively add to the reactive, coordinatively unsaturated complex [Pd(styrene)(PMe$_3$)$_2$] to give *trans*-(aryloxo)(trifluoroacetyl)bis(trimethylphosphine)palladium(II) complexes (*Scheme 4*).

Scheme 18



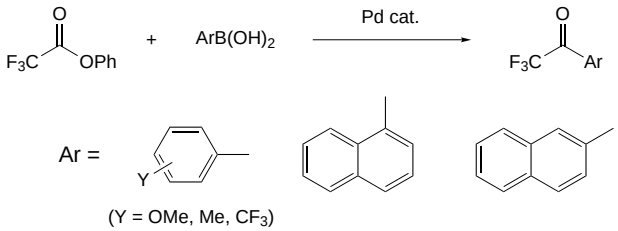
Treatment of the (trifluoroacetyl)palladium complex with phenylboronic acid was found to afford phenyl trifluoromethyl ketone probably through transmetallation and the ensuing reductive-elimination processes (*Scheme 19*) [50].

Scheme 19



The result prompted us to apply the finding to the catalytic synthesis of unsymmetrical F-containing ketones as shown in *Scheme 20*.

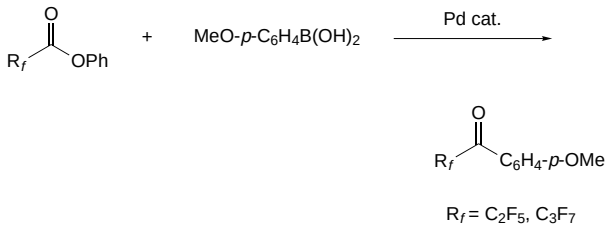
Scheme 20



The catalytic process is applicable to the synthesis of various aryl trifluoromethyl ketones in combination with various substituted phenylboronic acids. Phenylboronic acids containing various substituents at *ortho*-, *meta*-, and *para*-positions are converted into aryl trifluoromethyl ketones. Substitution with the MeO group at the *ortho*-position gave a somewhat lower yield, whereas the substituents such as MeO and Me groups at *meta*- or *para*-position gave good yields. Substitution with an electron-withdrawing group such as CF_3 group at the *para*-position produced the corresponding ketones in a poor yield. On the other hand, the electron-withdrawing substituents at *meta*-position gave a good yield of ketone, whereas *ortho*-substitution with the CF_3 group gave no ketone. Other arylboronic acids such as naphthalene-1- and -2-boronic acids afforded the ketones in moderate yields.

The Pd-promoted coupling process is applicable to other phenyl perfluoroalkanecarboxylates. The synthesis with a protocol similar to the one employed for phenyl trifluoroacetates gave perfluoroalkyl ketones in good yields, starting from phenyl pentafluoropropanoate and heptafluorobutanoate (*Scheme 21*).

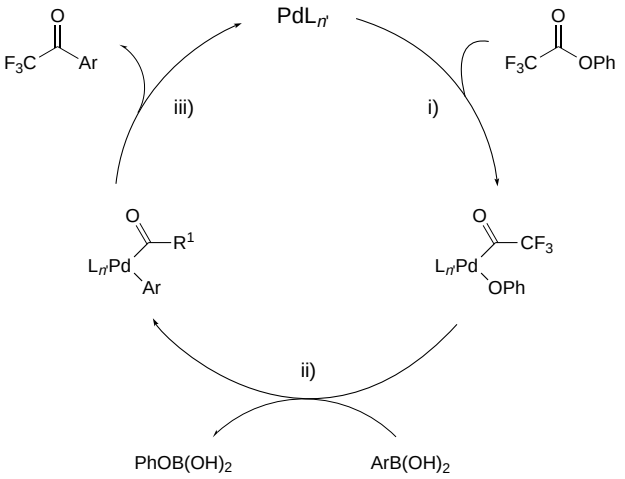
Scheme 21



We have also confirmed that organoboron compounds such as $NaBPh_4$ can be utilized in this type of cross-coupling reaction.

Scheme 22 depicts a catalytic cycle in the synthesis of aryl trifluoromethyl ketone from phenyl trifluoroacetate and arylboronic acid. It is similar to the catalytic cycle in conversion of carboxylic anhydride and arylboronic acid to unsymmetrical ketones in that the catalytic cycle is composed of *i*) oxidative addition of the ester to a coordinatively unsaturated Pd^0 species to give trifluoroacetyl(phenoxo)palladium intermediate, *ii*) the subsequent transmetallation with arylboron compounds, and *iii*) reductive elimination.

Scheme 22. *Catalytic Cycle for Trifluoromethyl Ketone Synthesis from CF_3COOPh and Organoboronic Acid Catalyzed by a Pd Species*



Since suitable processes of synthesizing biologically important F-containing compounds are limited [51], the process provides a convenient new route to ketones containing fluoroalkyl groups or their derivatives (for general methods for the synthesis of trifluoromethyl ketones see [52]). The present process, as well as the process utilizing trifluoroacetic anhydride, affords convenient routes to trifluoromethyl ketones under mild conditions.

4. Conclusion. – Based on information about oxidative additions involving C–O bond cleavage in carboxylic anhydrides and esters on interaction with Pd^0 complexes, we could develop several new catalytic processes to convert these O-containing substrates to carboxylic acids, aldehydes, and ketones. The methods have advantages over the existing Pd-catalyzed synthetic processes in that they are more atom-efficient and do not require the halogen-containing starting substrates for preparation of various O-containing products. We hope the processes find future applications in organic synthesis as convenient methodologies in commercial as well as laboratory syntheses.

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