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Short Review

Palladium-catalyzed carbonylation of 2-alkynyl carbonates and 2,3-alkadienyl carbonates *

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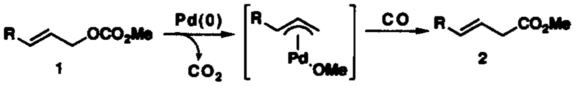
1. Introduction

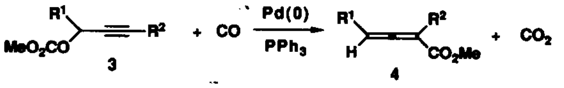
In contrast to the extensive studies carried out on palladium-catalyzed reactions of allylic compounds, palladium-catalyzed reactions of 2-alkynyl (propargyl) compounds, which have a triple bond instead of the double bond of allyl compounds, have received little attention. In our continuing studies on palladium-catalyzed reactions of allylic compounds via π-allylpalladium intermediates, we have made the important discovery that allylic carbonates are more reactive than allylic acetates, and undergo under neutral conditions several transformations which are not possible with the corresponding acetates [1–3]. Decarboxylation of the carbonates is a driving force. We found that the palladium-catalyzed carbonylation of allylic carbonates **1** proceeds smoothly under mild conditions to give β,γ-unsaturated esters **2** in good yields [4].

Carbonylation of allylic chlorides, carried out under high pressure, was reported many years ago [5–7]. Recently, carbonylation of allylic acetates in the presence of sodium bromide was reported [8]. In comparison, allyl carbonates are more convenient to use. The carbonate seems to be the best leaving group for palladium-catalyzed reactions including the carbonylation.



With the high reactivity of allyl carbonates in mind, we attempted the palladium-catalyzed reaction of 2-alkynyl carbonates, and found smooth reactions with carbon nucleophiles to give furans [9], with acetylenes to give allenyl acetylenes [10], and with olefins to form 1,2,4-trienes [11] all under mild conditions.

The carbonylation is no exception. We found that the carbonylation of 2-alkynyl carbonates **3** proceeds smoothly to give 2,3-dienoates **4** [12]. Furthermore, we carried out the carbonylation reaction of several functionalized 2-alkynyl carbonates and found several interesting reactions. The results confirm that carbonates are good substrates.



In 1969, we reported the palladium-catalyzed carbonylation of propargyl alcohol and its derivatives under somewhat severe reaction conditions [13]. Since then, no studies on the palladium-catalyzed carbonylation of 2-alkynyl compounds have been reported. In this review, the carbonylation reactions of 2-alkynyl carbonates and their derivatives carried out in our laboratory, and published in several communications, are summarized. Also included are the carbonylations of propargyl alcohol and 2,3-alkadienyl carbonates.

The reactions we found in this series of studies are of two kinds. The first step of the palladium-catalyzed reaction of 2-alkynyl carbonates **3** is the formation of the allenyl palladium alkoxide complex **5** by the S_N2' type displacement of the carbonate group with Pd^0. Formation of the allenylpalladium chloride by the reaction of propargyl chloride with $Pd(PPh_3)_4$ was reported [14]. This intermediate complex **5** has a Pd–carbon σ-bond which undergoes insertion reaction. Insertion of CO forms the acylpalladium complex **6** which reacts with alcohol to give esters **4**. In addition, attack by various nucleophiles affords allenyl carbonyl compounds **7**. The formation of allenyl compounds takes place first. The allenyl bond in the carbonylation products is reactive and undergoes further addition reac-

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* This paper is dedicated to Professor Gian Paolo Chiusoli on the occasion of his 70th birthday in recognition of his important contributions to organometallic chemistry and its application to organic synthesis.

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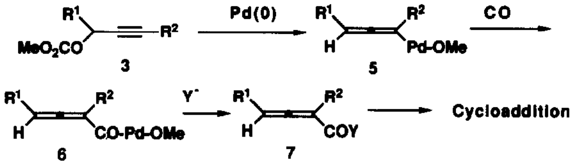
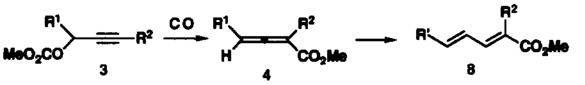
tions to give cyclic compounds. The two sets of reactions are summarized in this review.

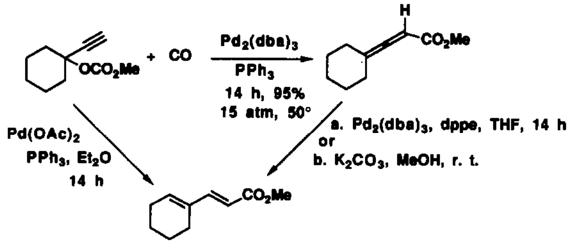


2. Carbonylation to form 2,3-alkadienoates

The attack of alkoxide as a nucleophile on the acylpalladium species **6** gives alka-2,3-dienoates **4** (allenyl esters) [12], but 2,4-dienoates **8** can be obtained depending on the reaction conditions.

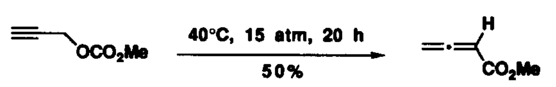


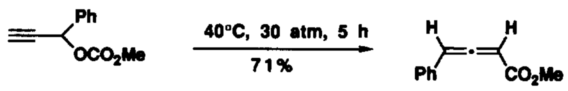
The carbonylation of 2-alkynyl carbonates **3** proceeds under mild and neutral conditions, *i.e.* room temperature to 50°C under 1–20 atm of CO. One problem is the formation of 2,4-dienoates **8**, by the isomerization of 2,3-dienoates **4**. Solvent is the most important factor in the selectivity. 2,3-Dienoates **4** are obtained with high selectivity in alcohols; in particular, methanol is the best solvent. In ether, benzene, and acetonitrile as the solvents, 2,4-dienoates **8** are the main product. The isomerization is accelerated by the palladium catalyst. Complete isomerization of 2,3-dienoates **4** to 2,4-dienoates **8** was observed on treatment of the former with the palladium catalyst in THF for 14 h. Thus long reaction time tends to increase the ratio of 2,4-dienoates. A weak base like potassium carbonate also catalyzes the isomerization [15*].

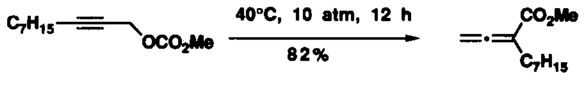


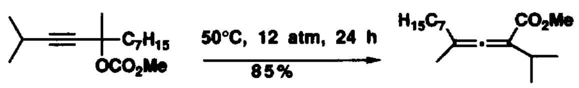
Methanol is the best solvent in view of the rate and selectivity of the reaction. Reaction without solvent gives a poor result. Some representative results are shown below.

We observed the carbonylation of 2-alkynyl acetates in the presence of triethylamine, but the carbonates seem to be superior to acetates. The palladium-catalyzed carbonylation of 2-alkynyl acetates and phosphates was recently reported [16].

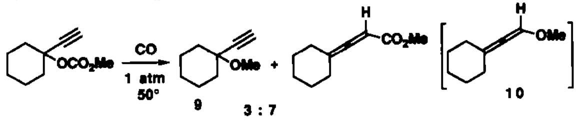






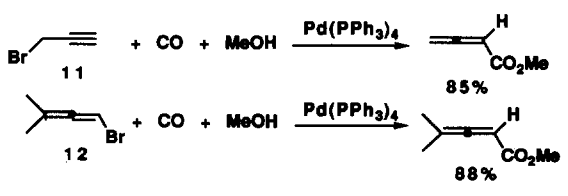


Another byproduct is 2-alkynyl ethers **9**, which are formed by simple decarboxylation. Low CO pressure tends to increase the ratio of ether formation. Interestingly only 2-alkynyl ether **9** was formed. No allenyl ether **10** was formed.



As for the ligand, PPh$_3$ is the most suitable. In conclusion, the palladium-catalyzed carbonylation of 2-alkynyl carbonates in methanol under mild conditions seems to be the best synthetic method for the allenyl esters **4**.

After our study, the palladium-catalyzed carbonylation of propargyl bromide **11** and allenyl bromides (1-bromo-1,2-dienes) **12** to give 2,3-dienoates was reported [17]. Synthesis of 2,3-dienoic acids by the carbonylation of 2-alkynyl chloride with Ni(CO)$_4$ is known [18], but a stoichiometric amount of Ni(CO)$_4$ is required.



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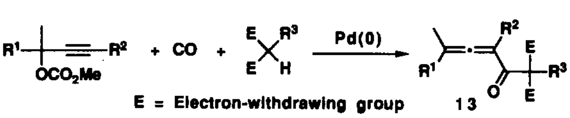
* Reference number with an asterisk indicates a note in the list of references.

3. Carbonylation in the presence of active methylene and methine compounds

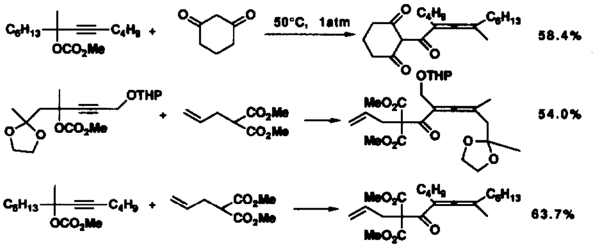
We then became interested in the possibility of reacting other nucleophiles, particularly carbon nucleophiles, such as malonate, β-keto esters, and β-diketones, instead of alcohols, expecting the reaction of carbon nucleophile with the intermediate acylpalladium complex **6** to form allenyl ketones **13**. If carbon nucleophiles are more reactive than alcohols, allenyl ketone should be obtained. The carbonylation reaction in the presence of active methylene compounds proceeded as expected to afford allenyl ketones **13** without forming esters [19].



E = Electron-withdrawing group

13

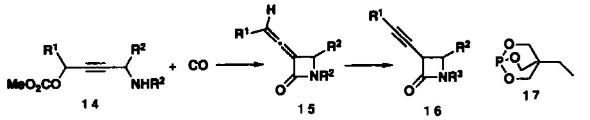
The carbonylation proceeds under atmospheric pressure of CO at 50°C. PPh_3 is a good ligand, and the reaction is carried out by the combination of $Pd(OAc)_2$ and PPh_3 in THF. So far, all carbonylation reactions of 2-alkynyl carbonates described in this review proceed under neutral conditions, but in this reaction, a carbanion must be generated by the addition of NaH. Some examples of the carbonylation, with several carbon nucleophiles, are shown below.



The palladium-catalyzed carbonylation of aryl halides in the presence of active methylene compounds has been reported [20].

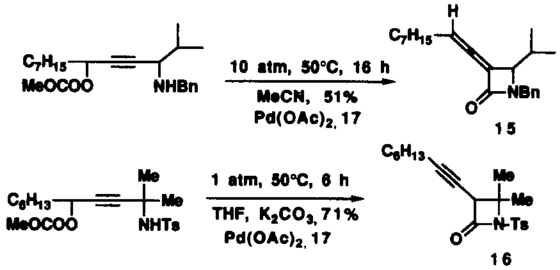
4. Synthesis α-vinylidene-β-lactams

Several synthetic methods for β-lactams by means of transition metal compounds are known [21]. Palladium-catalyzed carbonylation of 3-amino-2-iodopropene is a particularly convenient synthetic method for α-methylene-β-lactams [22]. On the basis of the facile carbonylation of 2-alkynyl carbonates, we attempted the preparation of β-lactams by the carbonylation of 4-amino-2-alkynyl carbonates **14**. The formation of α-alkylidene-β-lactams **15** was expected as a result of carbonylation. Various 4-amino-2-alkynyl carbonates **14** were prepared and subjected to palladium-catalyzed carbonylation. The reaction proceeded in the following way [23].



14 15 16 17

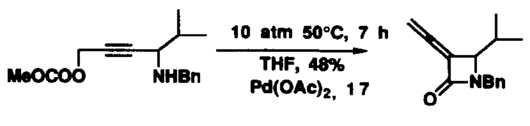
α-Vinylidene-β-lactams **15** are the primary products of the carbonylation. But depending on the reaction conditions, complete isomerization of the α-vinylidene group to the alkynyl group takes place and α-alkynyl-β-lactams **16** were obtained as sole products. The formation of lactam is not a smooth reaction, and various reaction conditions were tested in order to find optimum conditions. The most important is the selection of ligands. Easily available phosphines such as PPh_3 and bidentate phosphines give rather poor results. The best results are obtained by the use of the cyclic phosphite (4-ethyl-2,6,7-trioxa-1-phosphabicyclo[2,2,2]octane) (**17**). Another important factor is the selection of a protecting group for the amino group. Free amine cannot be used for the carbonylation. When the amino group is protected by the benzyl group, the reaction proceeds under neutral conditions and α-vinylidene-β-lactams **15** are obtained. On the other hand, the carbonylation of p-toluenesulfonamide must be carried out in the presence of potassium carbonate as a base, without which the yield is low. Under these conditions, the isomerization of the vinylidene group to alkynyl group takes place, and we isolated only the α-alkynyl-β-lactams **16**.



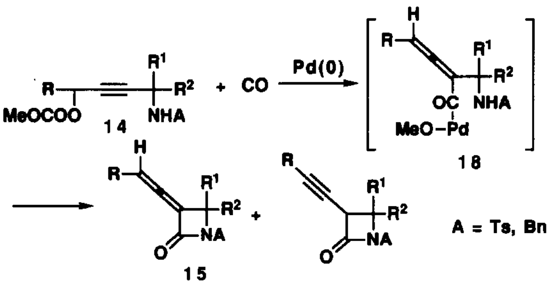
15

16

The carbonylation can be carried out in THF or MeCN as solvents at 50°C even under atmospheric pressure or 10 atm of CO. The yields of the β-lactams are good to moderate. It seems likely that the α-vinylidene group, particularly when unsubstituted, is not a stable functional group especially in the presence of the palladium catalyst. This is why only moderate yields are obtained. Any alkyl group can be introduced as R^1 and R^2 groups in **14**. When R^1 is hydrogen, the α-vinylidene group without a substituent is obtained.



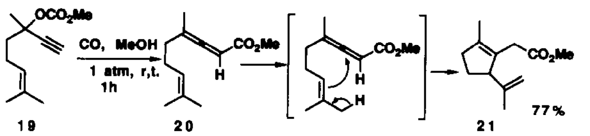
The mechanism of the β-lactam formation can be explained by the formation of the allenylpalladium complex **5** as an intermediate, which undergoes CO insertion to form the acylpalladium complex **18**. Finally the intramolecular attack of the amino group to the acylpalladium affords the β-lactams **15**, without forming the esters.



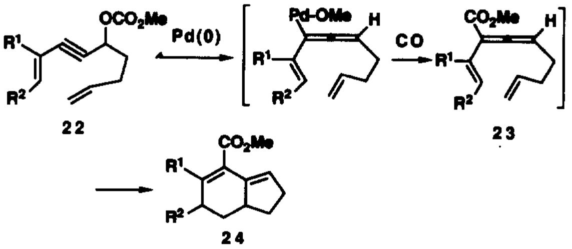
It is known that α-vinylidene-β-lactams **15** have an inhibitory effect on β-lactamase, and several α-vinylidene-β-lactams were prepared by another method [24]. But the palladium-catalyzed carbonylation reaction offers the most convenient synthetic method for this type of β-lactams. Also it is expected that the α-vinylidene-β-lactams prepared by the present method can be converted to the more useful carbapenem derivatives by functional group modification.

5. Tandem carbonylation-cyclization reaction

The allenyl esters obtained by the carbonylation are reactive and further transformations are expected. We observed that the carbonylation of dehydrolinalyl carbonate **19** proceeded at room temperature. Investigation of an NMR spectrum of the crude reaction product indicated the allenyl ester **20** as a major product and the cyclized product **21** as a minor product. When purification of the reaction product was attempted by column chromatography or distillation, only the cyclized product **21** was isolated in 74% yield [12]. The formation of the cyclized ester **21** is explained by the intramolecular ene reaction of the allenyl ester **20**. The fact that the ene reaction proceeds at rather low temperature suggests that the allenyl bond is very reactive.

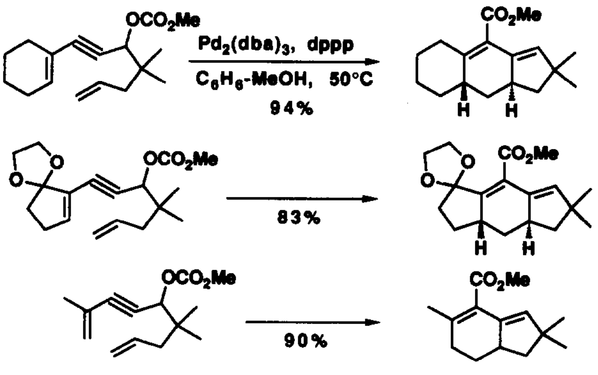


Considering the high reactivity of the allenyl bond, we attempted the tandem carbonylation and intramolecular Diels-Alder reaction by selecting derivatives of nona-1,8-dien-3-yn-5-yl carbonates (**22**), which have a double bond at a suitable position for Diels-Alder reactions after the carbonylation. We expected that the carbonylation gives the 1,3,4,8-tetraene carboxylates **23**, which may undergo the intramolecular Diels-Alder reaction to form polycyclic compounds **24** as shown below.



The tandem reaction proceeded smoothly as we expected under atmospheric pressure of CO at 50–60°C for 6–10 h [25]. For this carbonylation reaction, selection of a phosphine ligand is important. PPh_3, which is a good ligand for the carbonylation of 2-alkynyl carbonates, is not effective, but bidentate ligands are effective. Particularly, dppp [bis(diphenylphosphino)propane] gives the best result. The catalyst is prepared by the combination of $Pd_2(dba)_3$ and dppp. A mixed solvent of benzene and methanol is used. It should be emphasized that allenyl esters **23** as a primary product of the carbonylation cannot be isolated, and only the cyclized products **24** are obtained. This means that the intramolecular Diels-Alder reaction involving the allenyl bond proceeds smoothly at 50°C, showing that the allenyl system is very reactive. The allenyl esters behave as a diene component in this Diels-Alder reaction. It is interesting to notice that dienes with an electron donating group undergo facile Diels-Alder reaction in general. But in the reaction of the allenyl esters, the diene components are activated with the electron-withdrawing ester group.

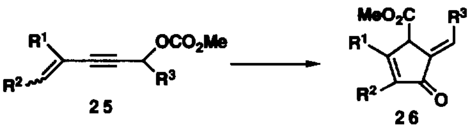
We have prepared several substrates and carried out their carbonylation. All attempted reactions proceeded smoothly and the cyclized products **24** shown below were obtained.



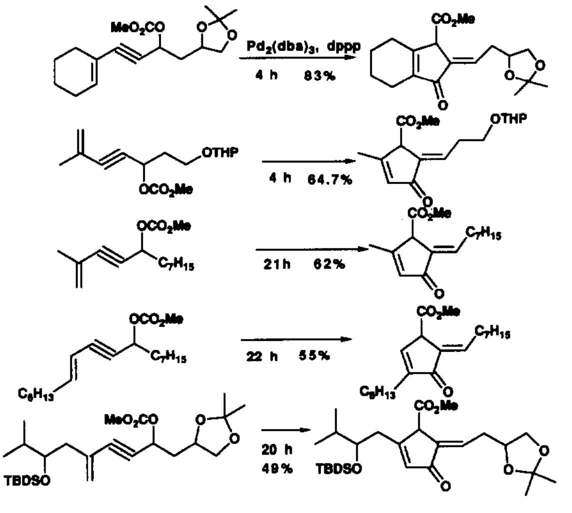
Facile construction of [5–6–*n*] systems by this reaction offers a good synthetic method for the cyclic systems present in some natural products such as methyl isomarasmate [26], nor-sterepolide [27], and sterepolide [28]. As a related reaction, the intramolecular Diels-Alder reaction of allenylphosphine oxides generated from propargyl phosphinite esters was reported by Okamura *et al.* [29].

6. Formation of cylopentenonecarboxylates

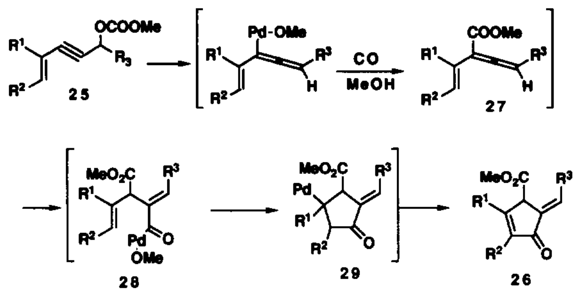
An interesting carbonylation-cyclization reaction was observed by the carbonylation of alka-2-yn-4-enyl carbonates **25**. The products isolated are 4-oxo-5-alkylidene-2-cyclopentenecarboxylate **26** [30]. The completely unexpected, multifunctional products formed by introduction of two molecules of CO were isolated. In these products, the alkylidene group has [E] stereochemistry.



The reaction proceeds under mild conditions to give the cyclized products in good yields. The reaction proceeds even at room temperature under 5–15 atm of CO. For this reaction, bidentate ligands such as dppe, dppp are the best. PPh_3 gives a rather poor result. Some representative reactions are shown below.



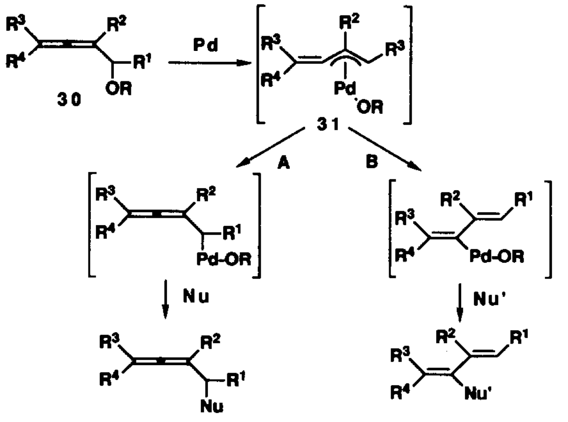
This interesting reaction can be explained by the following mechanism. At first the allenyl ester **27** is formed. Then another molecule of CO attacks the central carbon of the allenyl system to give the acylpalladium species **28**, which undergoes intramolecular insertion of the double bond to form the five-membered ring **29**. Finally, elimination of β-hydrogen affords the cyclopentenonecarboxylate **26**. The most interesting aspect of this mechanism is the attack of the second molecule of CO at the central carbon of the allenyl system.



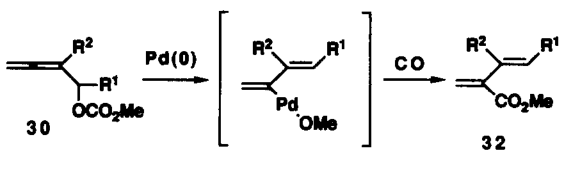
The products obtained by this reaction are highly active Michael acceptors, and interesting biological activity is expected.

8. Carbonylation of 2,3-dienyl carbonates

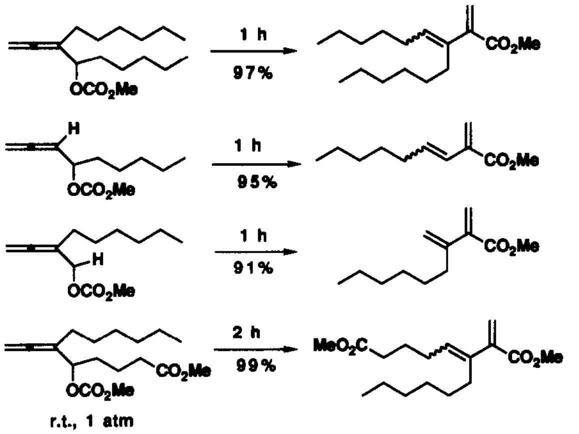
We became interested in the behavior of 2,3-dienyl carbonates **30** in the presence of a palladium catalyst, because 2,3-dienyl carbonates **30** form π-allylpalladium complexes **31** directly substituted by an alkylidene group, which are expected to react according to two pathways A and B. It is known that soft carbon nucleophiles attack the C-1 (path A), and hard nucleophiles such as Grignard or organozinc reagents attack the C-3 (path B) [31,32].



We attempted the carbonylation of 2,3-dienyl carbonates **30**. Very facile carbonylation took place under atmospheric pressure of CO at room temperature, and 1,3-dien-2-carboxylates **32** were obtained in good yields [33].



Some results are shown below.

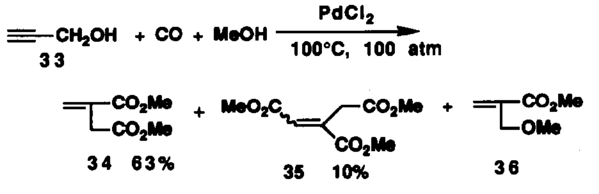


In this reaction, CO selectively attacks the C-3 position after the formation of the complex **31**, and 1,3-dien-2-carboxylates **32** are formed.

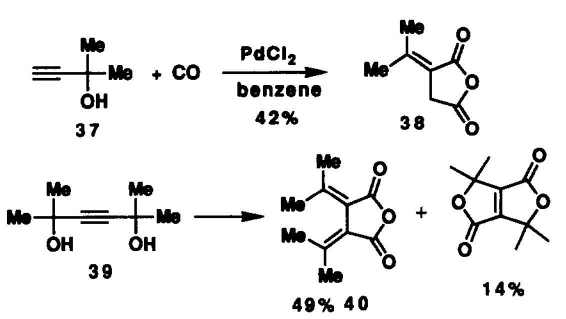
This carbonylation reaction offers a good synthetic method for 1,3-dien-2-carboxylates **32**, which are not easy to prepare by other methods.

9. Carbonylation of propargyl chlorides and alcohols

In 1969, we studied the palladium-catalyzed carbonylation reactions of propargyl chloride and propargyl alcohol [13]. The carbonylation of propargyl chloride at room temperature under 100 atm of CO in methanol afforded methyl itaconate (**34**) as a main product in 66% yield. Carbonylation of propargyl alcohol (**33**) was carried out in methanol in the presence of hydrochloric acid under high pressure of CO (100 atm) at 100°C. Methyl itaconate (**34**) as a main product (63%) and methyl aconitate (**35**) as a minor product (10%) were obtained. In addition, a small amount of methyl 2-methoxymethylacrylate (**36**) was isolated.

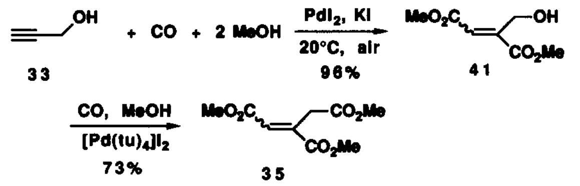


On the other hand, the carbonylation of 2-methyl-3-butyn-2-ol (**37**) in benzene afforded teraconic anhydride (**38**). Diisopropylidenesuccinic anhydride (fulgide) (**40**) was obtained by the carbonylation of 2,5-dimethyl-3-hexyne-2,5-diol (**39**) in benzene [13]. Later it was found by Kiji *et al.* that $Pd(OAc)_2$ and I_2 are good catalysts for the formation of fulgide [34].



We confirmed that the carbonylation of an authentic sample of methyl 2,3-dienoates affords methyl itaconate in good yield. Thus formation of itaconate is explained by the attack of CO at the central carbon of the 2,3-dienoate (allenyl esters). The carbonylation of propargyl alcohol was carried out at the higher temperature and pressure, and the second carbonylation proceeded as a main reaction path. On the other hand, the carbonylation of 2-alkynyl carbonates affords only 2,3-dienoates without undergoing further carbonylation to itaconate. This result is easily understandable because the carbonylation of 2-alkynyl carbonates was carried out under mild conditions.

Recently Chiusoli *et al.* reported that aconitate (**35**) is obtained in 70% overall yield by the palladium-catalyzed two-step carbonylation of propargyl alcohol (**33**). The first step is the oxidative carbonylation under CO and air using PdI_2 and KI to give dimethyl hydroxymethylbutenedioate (**41**), which is carbonylated further to give trimethyl aconitate (**35**) by the use of $[Pd(tu)_4]I_2$ as a catalyst (tu = thiourea) [35].



Also itaconate (**34**) is obtained from propargyl alcohol (**33**) using $Ni(CO)_4$ [36], and carbonylation of 1-ethynylcyclopentanol catalyzed by $Ni(CN)_2$ gives cyclopentyidenesuccinic acid [37].

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