

New synthetic reactions catalyzed by palladium complexes

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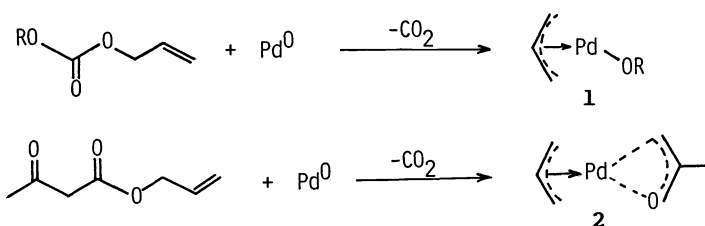
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Abstract - Palladium-phosphine complexes catalyze four reactions of allylic β -keto carboxylates. Decarboxylation-allylation gives α -allyl ketones. Decarboxylation-dehydrogenation proceeds in boiling acetonitrile to give α, β -unsaturated ketones. An industrial process for methyl jasmonate has been developed based on this reaction. Decarboxylation-deacetoxylation of α -acetoxyethyl- β -keto carboxylates in acetonitrile at room temperature affords α -methylene ketones. Decarboxylation-hydrogenolysis takes place in THF at room temperature by the treatment with ammonium formate to give saturated ketones. Allylic esters and carbamates are converted to corresponding acids and amines by the treatment with formic acid in the presence of palladium catalysts. Thus allyl group can be used as a protecting group of acids and amines. Protection of amino acids by carbamate formation and palladium-catalyzed deprotection proceed without racemization.

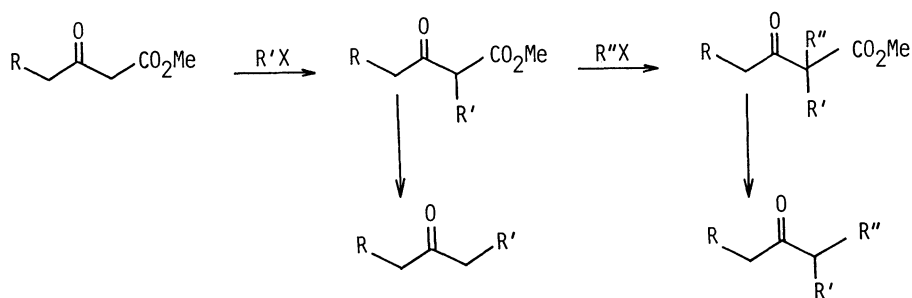
INTRODUCTION

Palladium-phosphine complexes catalyze a number of organic reactions, and they have wide synthetic applications. Among many palladium-catalyzed reactions, reactions of various allylic compounds catalyzed by palladium complexes, which proceed by the formation of π -allylpalladium complexes offer useful methods for carbon-carbon bond formation (ref. 1,2,3).

Recently we found that allylic carbonates and allylic β -keto carboxylates are very reactive substrates and undergo a number of reactions under mild conditions, particularly under neutral conditions. The oxidative addition of these allylic substrates to Pd^0 is followed by smooth decarboxylation to give π -allylpalladium alkoxides **1** and enolates **2** as active intermediates which undergo further transformations.



In a classical organic synthesis, β -keto carboxylates are useful for regioselective alkylation. After regioselective mono- or dialkylation, β -keto carboxylates are hydrolyzed and then decarboxylated by heating to afford alkylated ketones.



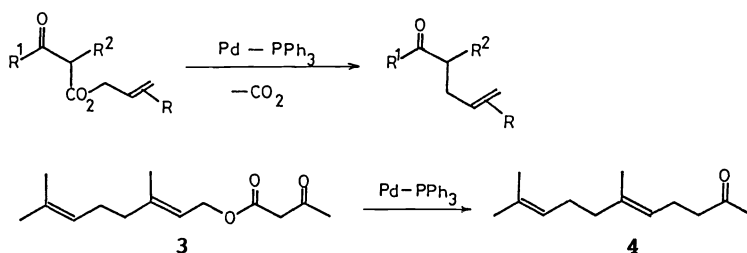
Now we found four different transformations of allyl β -keto carboxylates all catalyzed by palladium complexes under mild conditions. Thus the synthetic usefulness of β -keto carboxylates is greatly enhanced.

Formic acid is a cheaply available reducing agent. Facile decarboxylation of formic acid is possible with palladium catalyst. After the decarboxylation, palladium-hydride is formed which can be used for hydrogenolysis of some organic compounds. In this paper, palladium-catalyzed reactions of various allyl esters with formic acid are discussed.

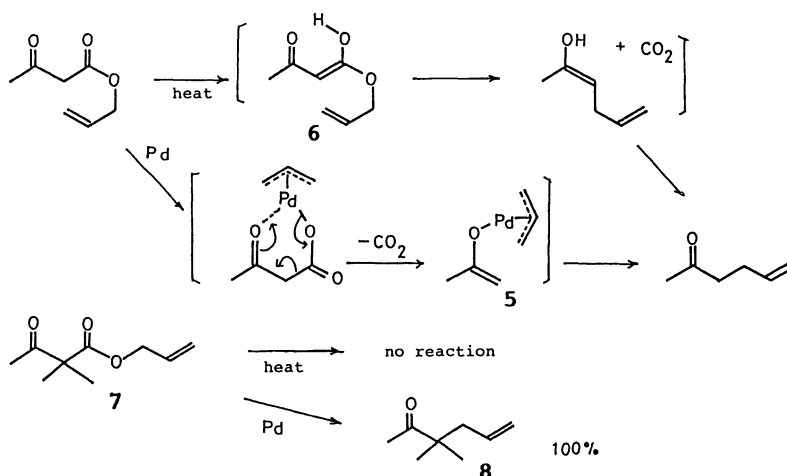
PALLADIUM-CATALYZED REACTIONS OF ALLYL β -KETO CARBOXYLATES

Decarboxylation-allylation

Thermal rearrangement of allyl β -keto carboxylates with decarboxylation to give α -allyl ketones is known as the Carroll rearrangement which proceeds at 170–200 °C (ref. 4). The reaction is useful for terpene synthesis. We expected that the same rearrangement should be promoted by using palladium catalyst via π -allylpalladium complex formation and found the smooth rearrangement proceeds in boiling THF or even at room temperature by using Pd-phosphine catalyst (ref. 5,6). Geranylacetone (4) was obtained from geranyl acetoacetate (3) in a high yield with retention of the configuration of double bond in boiling THF.



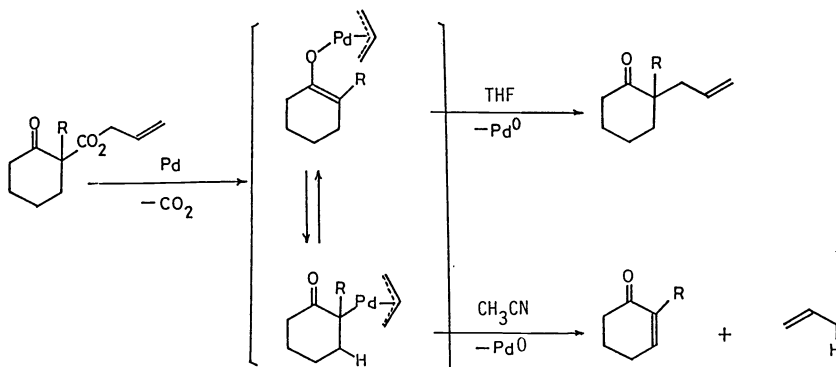
The palladium-catalyzed Carroll rearrangement can be explained by the following mechanism. Oxidative addition of allylic ester is followed by facile decarboxylation to give the π -allylpalladium enolate 5, which then undergoes the reductive elimination to give allyl ketones. This mechanism is completely different from the mechanism of the thermal rearrangement, which proceeds by the [3,3]sigmatropic rearrangement of an enol form 6 of allyl β -keto ester. In order to prove the difference of the mechanisms, the reaction of the allylic ester 7, which has no hydrogen at the α -position, and hence enolization is impossible, was carried out. No thermal reaction took place. On the other hand, smooth palladium-catalyzed reaction proceeded to give the allyl ketone 8 in a nearly quantitative yield. The reaction was regioselective and the allyl group was introduced at the more crowded carbon. Thus this reaction offers a good method for the monoallylation of ketones.



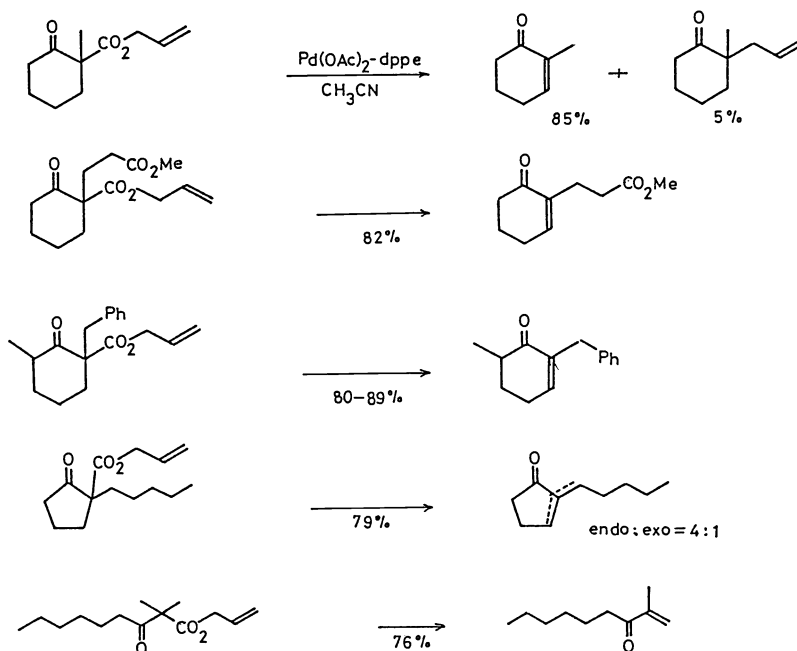
Decarboxylation-dehydrogenation

Efficient conversion of saturated carbonyl compounds to α,β -unsaturated carbonyl compounds is an important synthetic method. This can be done usually by introducing hetero atoms(X) such as S, Se, or halogens at α -position, followed by elimination of HX. In the palladium catalyzed reaction of allyl β -keto carboxylates, we found an interesting effect of solvents on the course of the reaction. The selective enone formation occurs by carrying out the reaction in CH_3CN and using dpe or PPh_3 as the ligand (Ref. 7). In this reaction, choice

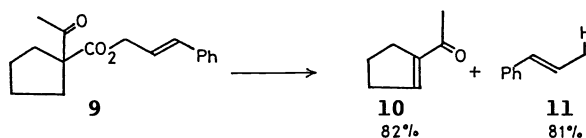
of solvent is crucial. Aprotic polar solvents such as CH_3CN and DMF are the best for the enone formation. On the other hand, in acetone or *t*-butyl alcohol, the allylated products are the main products even when dppe is used. In addition, the presence of substituents or the absence of active hydrogen at α -position is essential for the selective enone formation. For example, the reaction of allyl cyclohexanone-2-carboxylate is not selective and produced a mixture of cyclohexenone, 2-allyl- and 2,2-diallylcyclohexanone with the Pd-dppe catalyst.



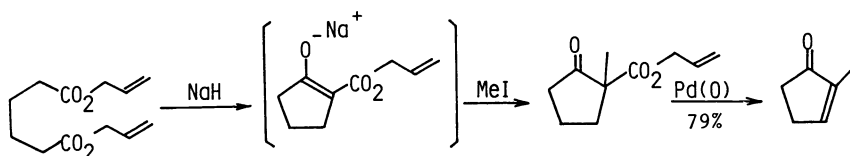
Some examples are shown below:



A 1:1 mixture of enone **10** and 1-phenylpropene (**11**) was obtained from the cinnamyl ester of α,α -cyclopentanoacetic acid (**9**). In other words, the allyl group is the hydrogen acceptor in this dehydrogenation reaction.



The enone formation from allyl β -keto carboxylates is very useful for organic synthesis. One example is the facile synthesis of 2-methyl-2-cyclopentenone (Ref. 8), which is a useful intermediate for various cyclopentanoids. Many synthetic methods for this rather simple compound are known (Ref. 9), but none of them is satisfactory. Thus the Dieckmann condensation of allyl adipate, followed by methylation gives allyl 2-methyl-2-cyclopentanone-carboxylate in 87% yield. This compound was subjected to the palladium-catalyzed decarboxylation-dehydrogenation to give 2-methyl-2-cyclopentenone in 79% yield using ligand-free $\text{Pd}(\text{OAc})_2$.



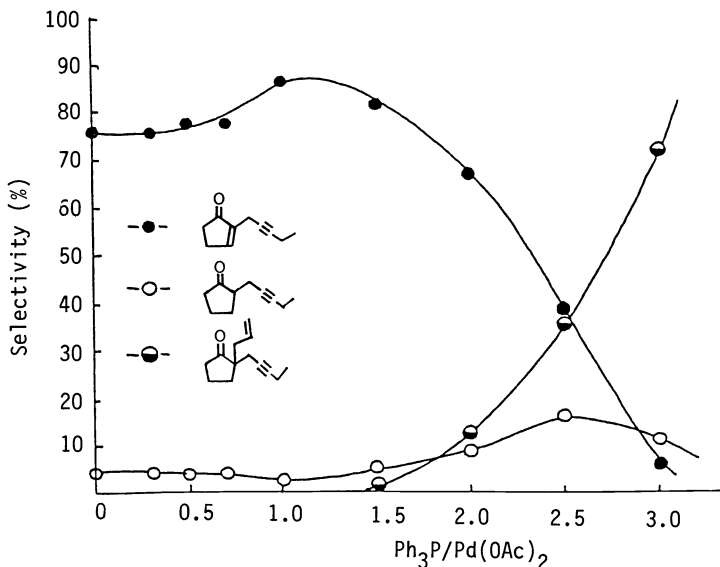
The palladium-catalyzed enone formation from allyl keto carboxylates was applied to the synthesis of *cis*-2-pentenyl-2-cyclopentenone (12), which is an important intermediate for the syntheses of *cis*-jasnone and methyl jasmonate (13). The optimum conditions for the synthesis of 2-pentenylcyclopentenone was investigated in order to develop an industrial process for methyl jasmonate production. One problem in this catalytic process is the selectivity for *endo* and *exo* double bonds when the reaction is applied to cyclic compounds. When the reaction was applied to 2-alkylcyclohexanonecarboxylate, we observed exclusive formation of the *endo* double bond. When cyclopentanone derivatives were subjected to the catalytic dehydrogenation, a mixture of *endo* and *exo* double bonds was obtained, although the *endo* product was the main product. We found that the *endo*/*exo* ratios changed depending on the structure of 2-alkyl groups. As shown in TABLE I, the highest yield of 85% was obtained with 2-pentynyl group by using Pd(OAc)₂ and dppe. At the same time, the *exo* product was formed in 5%, and 2-pentenylcyclopentanone and 2-allyl-2-pentenylcyclopentanone were obtained in 5%.

TABLE 1.

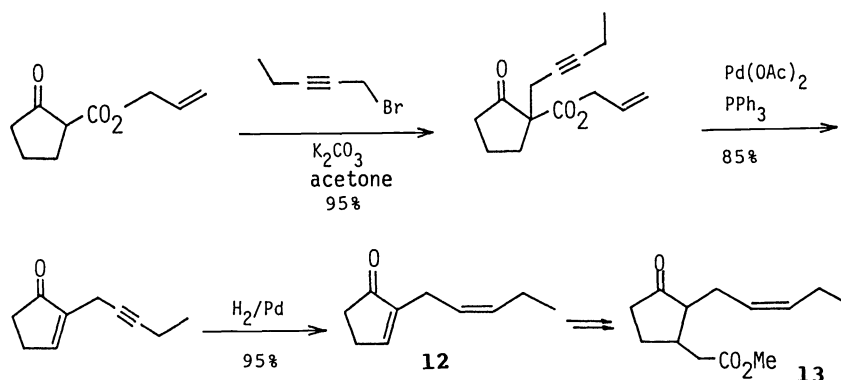
Run	β-Keto esters	Yields (%)			
1		65	16	5	0
2		55	27	7	1
3		85	5	4	1

5 mol% Pd(OAc)₂ and dppe in refluxing CH₃CN

Then the reaction was carried out by using PPh₃ as the ligand instead of dppe, and we obtained satisfactory results with 0.5–1 mol% of Pd(OAc)₂. Also the ratio of PPh₃/Pd is an important factor for the selectivity of the reaction. The cyclopentenone formation proceeded even in the absence of PPh₃. When the ratio became higher than three, the allylation is the main path of the reaction as shown in the figure.

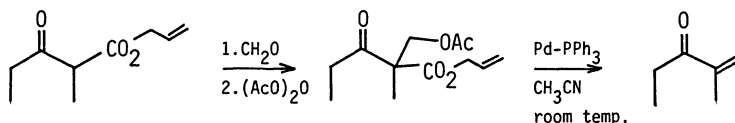


Based on these results, an industrial process for jasmonate (**13**) production has been developed by the following sequence of reactions (Ref. 10).



α -Methylene ketone formation

Allyl β -keto carboxylates react easily with aqueous formaldehyde to give α -hydroxymethyl- β -keto carboxylates, which are acetylated with acetic anhydride. We found rapid decarboxylation of allyl α -acetoxymethyl- β -keto carboxylates, followed by elimination of allyl acetate to give α -methylene ketones in high yields, when the compounds are treated with palladium catalyst in acetonitrile at room temperature (Ref. 11). α -Methylene ketone is present in certain naturally occurring cyclic terpenoids, and an important functional group, because it has anti-tumor activity (Ref. 12). Thus the synthesis of this functional group is an important problem. α -Methylene ketones are usually very reactive, and their synthesis must be carried out under very mild conditions. The palladium-catalyzed reaction is very useful because it proceeds under neutral conditions at a room temperature.



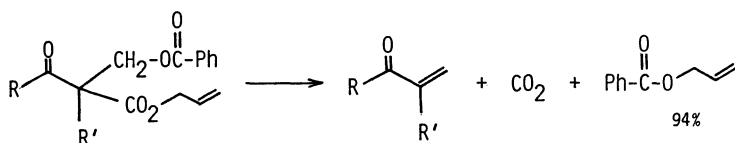
Some results are shown in TABLE 2.

TABLE 2. Preparation of α -methylene ketones

Run	β -Keto Ester	α -Methylene Ketone	Yield(%) ^{a)}
1			67 (93)
2		"	(94)
3			63 (100)
4			83
5			88

a) Isolated yields. GLC yields in parentheses.

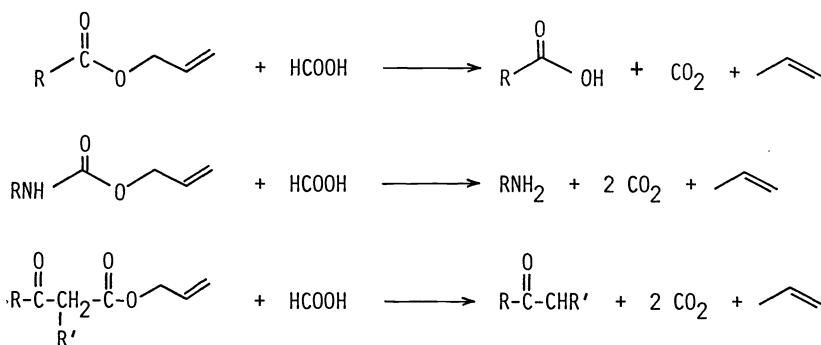
In order to study the mechanism of the reaction, we carried out the reaction of allyl α -benzoxymethyl- β -keto carboxylate, and isolated allyl benzoate in a high yield. Thus the reaction can be expressed by the following equation.



In this chapter, three palladium-catalyzed reactions of allyl β -keto carboxylates are presented. The fourth reaction, namely hydrogenolysis with formic acid to give ketones is discussed in the next chapter.

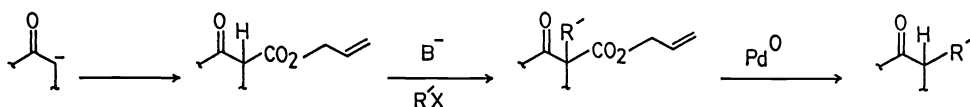
PALLADIUM-CATALYZED REACTION OF FORMIC ACID

Formic acid is a cheaply available reducing agent. In the presence of palladium catalyst, it behaves as a hydride source. It is known that allyl acetate is converted to propylene by the palladium-catalyzed reaction of formic acid (Ref. 13). Dienes, acetylenes, and α,β -unsaturated carbonyl compounds (Ref. 14,15), nitro compounds (Ref. 16-19), aromatic halides (Ref. 16,20-22) nitriles (Ref. 23), and benzyl functionalities of amino acids (Ref. 24) can be hydrogenated with formic acid by using palladium-phosphine complex or palladium on carbon as catalysts. We have investigated the reaction of ammonium formate with the following allylic esters. In all cases, smooth cleavage of allylic group was observed with the formation of 1-alkenes. These reactions are useful in two ways. One of them is the preparation of 1-alkenes from allylic compounds, and the other is the protection of amines and carboxylic acids as allyl carbamates and allyl esters, and the palladium-catalyzed deprotection can be carried out under mild conditions.



Hydrogenolysis of allyl β -keto carboxylates

After regioselective mono- or dialkylation of β -keto esters, mono- or dialkyl ketones are derived by hydrolysis and subsequent decarboxylation. However, usual alkaline hydrolysis of β -keto esters is often complicated by a competing fission reaction to afford esters or acids, particularly when the α -position is disubstituted, and several improved methods for smooth dealkoxycarbonylation have been reported (Ref. 25-28). We have reported that allylic esters can be used for the protection of carboxylic acids (Ref. 29-33). Allylic esters can be converted to free acids easily by palladium-catalyzed reaction with ammonium formate (Ref. 29). Then we found that decarboxylation of β -keto esters can be carried out under very mild conditions by the application of this formate reaction. The deallyloxycarbonylation proceeds smoothly to give ketones in high yields (Ref. 34).



Some results are shown in TABLE 3.

TABLE 3. Palladium-catalyzed reaction of allyl β -keto carboxylates with ammonium formate^{a)}

Run	Ester	Time(min)	Product	(Yield%) ^{b)}
1		35		(99)
2		35		82(100)
3		30		82 (99)
4		30		88(100)
5		30		(88) 77 (95)
6		30		(10) 92(100)
7		35		(12) 92(100)

a) Ester (1 mmol), Pd(OAc)₂ (0.025 mmol), PPh₃ (0.05 mmol), HCO₂HNEt₃ in THF at room temperature. b) Isolated yield; GLC yield in parentheses.

The reaction can be carried out smoothly with tertiary amine salts (typically triethylamine) of formic acid in THF at room temperature. The reaction conditions are mild and nearly neutral, and hence other functional groups present in the same molecule can be kept intact. For example, methyl ester was not hydrolyzed (run 6). Even more labile tetrahydropyranyl ether remained intact (run 5). Also no retro-Dieckmann product by ring fission of cyclic β -keto esters was obtained (runs 4-7). One serious side reaction expected for the β -keto esters is retro-Michael reaction, but desired deallyloxycarbonylation proceeded selectively by the formate method (run 3).

Allyl β -keto carboxylates are prepared easily from corresponding ketones by the reaction of diallyl carbonate or allyl chloroformate. Then their alkylation or Michael addition can be carried out easily with weak bases such as K₂CO₃. Finally the removal of the allyl esters is possible by the palladium-catalyzed reaction of formate under mild conditions.

Protection of amines as allyl carbamates and their deprotection

We found that allyl carbamates are reactive compounds and undergo smooth palladium-catalyzed allylation of nucleophiles with liberation of free amines. Based on the high reactivity of allyl carbamates with palladium catalyst, we expected that amines can be protected as allyl carbamates and deprotected by the palladium catalyst under mild conditions (Ref. 35).

Allyl carbamates as a protecting group of amines has been reported. The deprotection is carried out by the palladium-catalyzed allyl transfer to potassium 2-ethylhexanoate, (Ref. 30), dione (Ref. 31), and *N*-hydroxysuccinimide (Ref. 36). Also $\text{Ni}(\text{CO})_4$ is used for deprotection (Ref. 37). The allylation with allyl carbamate without *N*-allylation suggests us a simpler method for deprotection of amines. To achieve clean deprotection, we applied the formate reduction of allyl compounds, which we have developed. Results are shown in TABLE 4. To our surprise, *N*-allylation was observed with morpholine even in the presence of formic acid. With this exception, clean deprotection proceeded smoothly in high yields with primary amines and bulky secondary amines in the presence of excess formic acid. The utility of this deprotection was examined in the reaction of *N*-protected optically active amino acids. *N*-protected amino acids were prepared by the known procedure, and they were deprotected without racemization. Comparing the specific rotations of the deprotected products with those of starting materials, we found in all cases that the reactions (protection and deprotection) proceeded with >98% retention of optical purity.

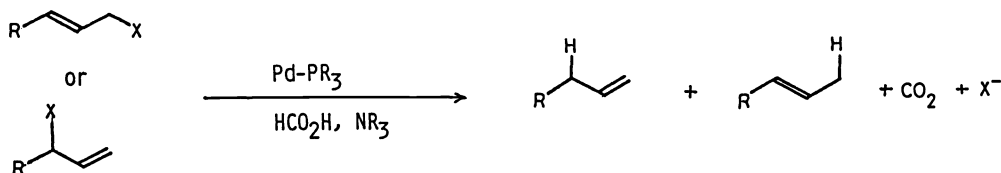
TABLE 4. Deprotection of allyloxycarbonyl group with formic acid^{a)}

Allyl Carbamate	Time(h)	Product	Yield(%) ^{b)}
	3		(16) ^{c)}
	3		(100) ^{d)}
	2	 $[\alpha]_D^{23} = -33.9^\circ$ (c=1, H ₂ O)	76
	4	 $[\alpha]_D^{20} = +14.5^\circ$ (c=10, 6N HCl)	85 ^{e)}
	3	 $[\alpha]_D^{23} = +14.9^\circ$ (c=2, 6N HCl)	86
	3	 $[\alpha]_D^{25} = +25.3^\circ$ (c=3, 1N HCl)	74

a) Procedure; A solution of carbamate (1 mmol), formic acid (3-4 mmol), PPh_3 (0.2 mmol), and $\text{Pd}_2(\text{dba})_3\text{CHCl}_3$ (0.05 mmol) in THF (5 mL) was stirred at 30°C under argon. b) GFC yields in parentheses. c) *N*-Allylmorpholine was obtained (84%). d) No allylamine was detected by GLC. e) The reaction was carried out with 1 mol% of Pd catalyst.

Preparation of 1-alkenes from allylic compounds

We carried out extensive studies on the palladium catalyzed hydrogenolysis of various allylic compounds, particularly terminal allylic compounds, (from which the formation of either 1- or 2-alkenes is expected) with ammonium formate in order to prepare more useful terminal olefins selectively.



From this viewpoint, the effects of ligands and solvents on the regiochemistry was studied (Ref. 29). As shown in TABLE 5, ligands show remarkable effect on the regiochemistry of the hydrogenolysis. Phosphites are not good ligands for the formation 1-alkenes. Higher regioselectivity was observed by using PPh_3 . Depending on the structure of the allylic compounds, terminal olefins were obtained in 80-90% selectivity. However, the highest selectivity was observed by using alkyl phosphines, such as $P(n-Bu)_3$ (Ref. 38). In most cases, nearly complete formation of 1-alkenes was observed by using PBu_3 . The same 1-alkenes was obtained with the same regioselectivity from isomeric allylic compounds (No. 1-6, 8-11). For the reaction of allylic chloride, sodium formate, rather than ammonium formate gave better results (No. 7). Ene oxides are converted to homoallylic alcohols cleanly (No. 13) Thus this is a very good synthetic method for 1-alkenes from various terminal allylic compounds. The reaction is carried out in boiling dioxane, but *N,N*-dimethylimidazolone (DMI) is the better solvent, and the reaction proceeds at room temperature (No. 5,13).

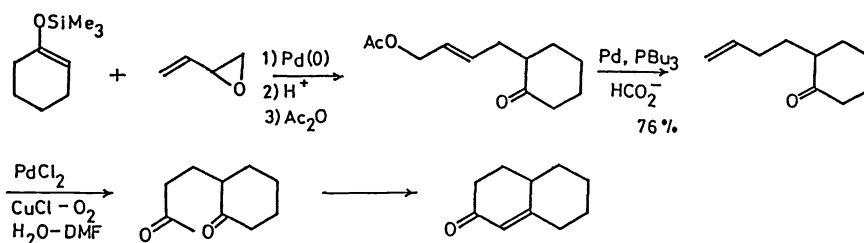
TABLE 5. Palladium-catalyzed hydrogenolyses of allylic compounds with ammonium formate^{a)}

No	Allylic compounds	Catalysts	Products (Selectivity/%) ^{b)}	
1		$Pd_2(dba)_3CHCl_3-P^nBu_3$	 (100)	 (0)
2	"	$Pd(OAc)_2-P^nBu_3$	" (94)	" (6)
3	"	$Pd_2(dba)_3CHCl_3-PPh_3$	" (93)	" (7)
4	"	$Pd(PPh_3)_4$	" (70)	" (30)
5	"	$Pd(dba)_3CHCl_3-P^nBu_3$ DMI, 30°C	" (99)	" (1)
6		$Pd_2(dba)_3CHCl_3-P^nBu_3$	" (96)	" (4)
7		$Pd_2(dba)_3CHCl_3-P^nBu_3$ HCO_2Na	" (100)	" (0)
8		$Pd_2(dba)_3CHCl_3-P^nBu_3$	 (100)	 (0)
9	"	$Pd(OAc)_2-PPh_3$	" (94)	" (6)
10	"	$Pd(OAc)_2-P(OEt)_3$	" (51)	" (49)
11		$Pd_2(dba)_3CHCl_3-P^nBu_3$	" (100)	" (0)
12		$Pd(OAc)_2-P^nBu_3$	 (99)	 (1)
13		$Pd_2(DBA)_3CHCl_3-P^nBu_3$ DMI, 30°C		97% (yield)

a) All reactions were carried out using allylic compound (1 mmol), palladium catalyst (0.025-0.05 mmol, Pd:P=1:4) and ammonium formate (2 mmol) in boiling dioxane (3 cm³) for 0.5-2 h. b) GLC analysis.

The palladium-catalyzed hydrogenolysis of various allylic compounds is also possible by using different hydride sources, such as tin hydrides, hydrosilanes, sodium borohydride, organozinc, and dihydropyridines. But with these hydrides, the main product of the hydrogenolysis is 2-alkenes (Ref. 39-43). Thus the reaction with ammonium formate is the most useful from a synthetic viewpoint.

The regioselective hydrogenolysis has a considerable synthetic value. For example, palladium-catalyzed reaction of the ene oxide with silyl enol ether gives the allylic acetate after acetylation, which is converted to the terminal olefin with ammonium formate. The oxidation of the terminal double bond catalyzed by PdCl₂-CuCl gives the 1,5-diketone, which can be cyclized. This is a new annelation method. Usually, the direct butenylation of ketone is not easy.



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