Palladium-Catalyzed, Atmospheric Pressure Carbonylation of Allylic Halides under the Influence of Sodium Hydroxide or Alkoxides. A Facile Synthesis of β,γ-Unsaturated Acids

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(Received February 24, 1992)

The palladium-catalyzed, atmospheric-pressure carboxylation of allylic halides occurs readily in an aqueous sodium hydroxide/organic solvents two-phase system, giving β,γ-unsaturated acids. Phosphine complexes $[PdCl_2L_2]$ (**I**, L=*m*-$(Ph_2P)C_6H_4SO_3Na$; **II**, L=Ph_3P) or $Na_2[PdCl_4]$ (**III**) can be used as the catalyst. Atmospheric-pressure alkoxycarbonylation is realized under the influence of a homogeneous alcoholic solution of sodium alkoxide. Phosphine-free palladium complexes, such as $[(\pi\text{-allyl})PdCl]_2$ or **III**, are the favored catalyst. β,γ-Unsaturated esters are obtained in high yields.

Carbonylation of allylic chlorides, which is catalyzed by nickel carbonyl, was reported for the first time by Chiusoli.[1] Though this reaction proceeds virtually under atmospheric-pressure carbon monoxide, a large amount of nickel carbonyl is used. Later, a convenient method of a nickel catalysis was developed,[2] which involves the use of $Ni(CN)_2$ under phase-transfer conditions. The carbonylation is also catalyzed by palladium compounds.[3–5] Palladium is preferable to nickel with respect to catalytic efficiency. Palladium-catalyzed carbonylation, however, has a disadvantage in that it requires a carbon monoxide pressure higher than 100 $kg\,cm^{-2}$. Consequently, among the unique synthetic reactions using palladium compounds,[6,7] carbonylation, which offers β,γ-unsaturated acid derivatives, has found fewer applications in organic syntheses.

It has generally been accepted that carbonylation proceeds through a π-allyl intermediate.[8,9] One of the main steps in carbonylation is the insertion of carbon monoxide into the allyl–metal bond, giving rise to the formation of an allyl–(CO)–metal complex.[10] It has been described that (π-allyl)palladium complexes do not generally undergo migratory carbon monoxide insertion into the carbon-palladium bond readily.[11] Several workers have improved carbonylation.[12–15] One approach involves the decarboxylation–carbonylation of allylic carbonates, which was developed by Tsuji et al.[12]

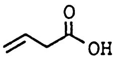
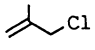
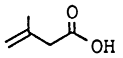
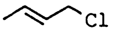
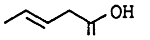
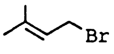
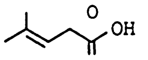
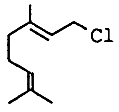
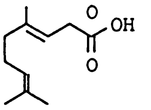
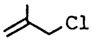
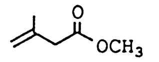
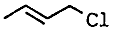
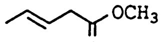
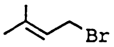
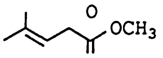
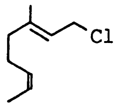
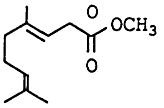
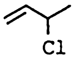
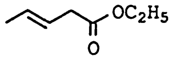
We recently studied transition metal catalyses in a two-phase system.[16] We considered the possibility that carbonylation in an aqueous sodium hydroxide–organic solvent system follows reaction courses other than the usual carbonylation. Namely, such carbonylation might involve a reductive elimination of the allyl and carboxyl groups, which are formed by carbon monoxide insertion into Pd–OH, rather than the Pd–allyl bond. In the course of the studies we succeeded in atmospheric-pressure carbonylation of allylic halides in the presence of sodium hydroxide or alkoxides. The results have been reported in preliminary forms.[17,18] Since allylic chlorides are a versatile starting material, this carbonylation offers a highly promising synthetic route to β,γ-unsaturated acid derivatives. Full details concerning this work are presented in this paper.

Results and Discussion

Aqueous Sodium Hydroxide/Organic Solvent Two-Phase System. Carboxylation: Dichlorobis[sodium *m*-(diphenylphosphino)benzenesulfonato]palladium(II) (**I**, abbreviated $[PdCl_2(dpm)_2]$), dichlorobis(triphenylphosphine)palladium(II) (**II**, $[PdCl_2(PPh_3)_2]$), and phosphine-free disodium tetrachloropalladate (**III**, $Na_2[PdCl_4]$) were used as catalysts. At first, allyl chloride was carbonylated. A rapid absorption of carbon monoxide was observed in a two-phase aqueous sodium hydroxide–benzene medium under atmospheric pressure at room temperature. The reaction was completed in 1—2 h. For this reaction the presence of the hydroxide ion is essential; namely, in the absence of the base, carbon monoxide was not absorbed at all. Either $[PdCl_2(PPh_3)_2]$ or water-soluble $[PdCl_2(dpm)_2]$ can be used. Phosphine-free $Na_2[PdCl_4]$ also catalyzes carboxylation. Since this carboxylation is carried out under the influence of a strong base, 2-butenoic acid, which is formed by the base-catalyzed isomerization of 3-butenoic acid, was obtained in considerable yield (ca. 10—25% of the total acids). Isomerization was suppressed by adding aqueous sodium hydroxide dropwise into the flask, in order to keep the base at a low concentration.

2-Methyl-2-propenyl and crotyl chloride were readily carbonylated to afford the corresponding β,γ-unsaturated acids in similar yields. Though allylic bromides were carboxylated similarly, the yields of the corresponding acids were somewhat lower than those of the chlorides. This incomplete carboxylation is attributed to the fact that allylic bromides are susceptible to hydrolysis under these conditions. Cinnamyl and geranyl chlorides gave the expected products in moderate yields. Upon carboxylation of cinnamyl chloride, 1,4-diphenyl-1,5-hexadiene was formed as the major

Table 1. Atmospheric Pressure Carbonylation of Allylic Halides[a)]

Run No.	Allylic halides	Solvents ml	Base (mmol)	Reaction[b)] time/h	Products (Yields/%)	
Carboxylation						
1		H_2O/Heptane (10/10)	NaOH (25)	1.2		(63)
2		H_2O/Heptane (50/10)	NaOH (50)	0.5		(73)
3		H_2O/Heptane (50/10)	NaOH (50)	0.5		(73)
4		H_2O/Heptane (50/10)	NaOH (10)	0.2		(4)
5		H_2O/Heptane (50/10)	NaOH (10)	1.2		(64)
Alkoxycarbonylation						
6		CH_3OH (30)	$NaOCH_3$ (10)	0.6		(84)
7		CH_3OH (30)	$NaOCH_3$ (10)	0.2		(93)
8		CH_3OH (30)	$NaOCH_3$ (10)	0.1		(30)
9		CH_3OH (30)	$NaOCH_3$ (10)	0.2		(81)
10[c)]		C_2H_5OH (20)	$NaOC_2H_5$ (15)	2.0		(93)

a) **I** and **V** were used as the catalyst for the carboxylation and methoxycarbonylation, respectively. Conditions: Allylic halide: catalyst, 10/0.1 (mmol/mmol); Reaction temp., 30 °C except for Run 1 (50 °C). b) Time required until there is no absorption of carbon monoxide. c) 3-Chloro-1-butene, 15 mmol; Catalyst, **III**/dppe (0.1/0.1 mmol/mmol); Alkoxide was added dropwise during 2 h.

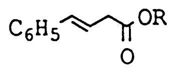
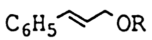
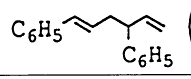
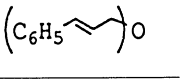
by-product. Allylic compounds other than halides absorbed carbon monoxide slowly; that is, allyl alcohol (15 mmol) absorbed ca. 100 ml of carbon monoxide during 40 h in the presence of **I** (0.1 mmol) in aqueous sodium hydroxide/heptane at 50 °C. In this case, however, no acidic product was detected.

Since it was revealed that cinnamyl chloride is more liable to coupling or hydrolysis of the cinnamyl group than are the other allylic chlorides, and that the analysis of the products is easy, a systematic investigation was undertaken with cinnamyl chloride, in order to gain some insight into carbonylation. The results are summarized in Table 2.

Under the influence of $[PdCl_2(dpm)_2]$ the absorption of carbon monoxide in dioxane, tetrahydrofuran, and heptane stopped within 1 h, which is shown in Table 2 as the "Reaction time"; however, the yields of the acid in dioxane and tetrahydrofuran were somewhat lower than that in heptane. In chloroform and toluene the absorption was slow and lasted for 2—4 h. Though this atmospheric-pressure carboxylation requires a base, the palladium-catalyzed coupling of the cinnamyl group precedes carboxylation at higher concentrations of sodium hydroxide, leading to the formation of 1,4-diphenyl-1,5-hexadiene. Among the solvents used, heptane was the best. In this case, however, the maximum yield of the acid attained so far did not exceed 60%.

One explanation for this facile carboxylation under atmospheric pressure is that the reaction proceeds through a carboxylpalladium intermediate formed by insertion of carbon monoxide into the Pd–O bond, not through an allyl–CO–Pd (acylpalladium) intermediate. Since the catalysis of water-soluble $[PdCl_2(dpm)_2]$ (**I**) in an aqueous sodium hydroxide/organic solvent two-phase system gave the best results, there is a possibility that the palladium catalyst (**I**), itself, might function as a phase-transfer agent. Catalyst **I**, which is stabilized by coordination of the water-soluble phosphorus ligand, dpm, is so slightly soluble in organic solvent that almost all of the catalyst remains in the aqueous phase and is readily converted into a (carboxyl)(π-allyl) intermediate (**VIIIa**), which finally reductively eliminates the carboxylation product. A series of these transformations is presumed to occur in the interfacial and/or aqueous phases. These explanations are supported by the following facts; slightly water-soluble, lower allylic chlorides were carboxylated faster than were water-insoluble, higher ones; that is, crotyl chloride was carbonylated within 0.5 h and 3-pentenoic acid was obtained in a 73% yield, while the time required to complete carbonylating water-insoluble geranyl chloride

Table 2. Atmospheric Pressure Carbonylation of Cinnamyl Chloride (at 30 °C)[a]

Run No.	Catalyst	Solvents (ml)	Base (mmol)	Reaction[b] time/h	Conversion %	Yields of products/%			
									
		Carboxylation				R=H			
1	**III**	H_2O/Heptane (50/10)	NaOH (25)	1.5	93	43	4	24	29
2	**V**	H_2O/Heptane (50/10)	NaOH (50)	1.0	93	41	3	22	34
3	**II**	H_2O/Heptane (50/10)	NaOH (50)	7.0	64	48	33	11	8
4	**VII**	H_2O/Heptane (50/10)	NaOH (50)	4.5	70	23	18	26	33
5	**I**	H_2O/Heptane (50/10)	NaOH (50)	1.5	83	57	12	25	6
6	**I**	H_2O/Dioxane (50/10)	NaOH (50)	0.5	66	40	34	15	11
7	**I**	H_2O/THF (50/10)	NaOH (50)	0.5	73	41	24	25	10
8	**I**	H_2O/Chloroform (50/10)	NaOH (50)	2.5	95	40	3	42	15
9	**I**	H_2O/Toluene (50/10)	NaOH (50)	4.0	95	53	4	40	3
10	**I**	H_2O/Heptane (50/10)	NaOH (10)	2.0	91	31	4	57	8
11	**I**	H_2O/Heptane (50/10)	NaOH (10)	1.0	80	46	15	34	5
12	**I**	H_2O/Heptane (50/10)	NaOH (10)	0.9	77	55	16	24	5
		Methoxycarbonylation[c]				R=CH_3			
13	**I**	CH_3OH (30)	$NaOCH_3$ (10)	0.5		11 (2)[d]	87	0	
14	**II**	CH_3OH (30)	$NaOCH_3$ (10)	0.5		8 (1)	91	0	
15	**VII**	CH_3OH (30)	$NaOCH_3$ (10)	15		1 (2)	97	0	
16	**VI**	CH_3OH (30)	$NaOCH_3$ (10)	20		14 (2)	83	0	
17	**III**	CH_3OH (30)	$NaOCH_3$ (10)	1.0		76 (11)	7	2	
18	**IV**	CH_3OH (30)	$NaOCH_3$ (10)	0.7		76 (11)	3	5	
19	**V**	CH_3OH (30)	$NaOCH_3$ (10)	0.7		76 (11)	7	2	
20	**V**	CH_3OH (10)	$NaOCH_3$ (10)	2.2		48 (9)	31	3	
21	**V**	CH_3OH (20)	$NaOCH_3$ (10)	1.3		71 (7)	7	4	
22	**V**	CH_3OH (50)	$NaOCH_3$ (10)	0.5		80 (8)	2	4	
23	**V**	CH_3OH (30)	$NaOCH_3$ (30)	5.5		17 (16)	51	6	

a) Conditions: Carboxylation, Cinnamyl chloride : catalyst=5/0.05 (mmol/mmol); Methoxycarbonylation, Cinnamyl chloride : catalyst=10/0.1 (mmol/mmol). b) Time required until there is no absorption of carbon monoxide. c) Conversion was always higher than 99.5%. d) The figures in parentheses of this column show the yield of methyl 4-phenyl-2-butenoate.

was ca 1.2 h and the yield of 4,8-dimethyl-3,7-nonadienoic acid was 64%.

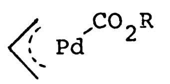
Sodium Alkoxide/Alcohol Homogeneous System. Alkoxycarbonylation. As described above, carboxylation of the lower allylic halides, such as allyl, crotyl or 2-methyl-2-propenyl chloride, proceeds satisfactorily in the aqueous sodium hydroxide/organic solvent two-phase system. Inconveniently, the higher homolog gave the corresponding β,γ-unsaturated acids in moderate yields. Since this carboxylation was carried out in the absence of a phase-transfer agent, it appeared to us that the difficulty might lie in the use of a two-phase system. To improve the reaction of the higher homolog, tetrahydrofuran or dioxane, which is more polar than hydrocarbons, was used as the organic phase. In this case, however, the yield of the acid did not exceed 50% (See Table 2). As described above, it is claimed that carboxylation proceeds through a (carboxyl)(π-allyl)-palladium intermediate, which is formed by the carbon monoxide insertion into the Pd–O bond. Our success in facile carboxylation in an aqueous sodium hydroxide/organic solvent two-phase system encouraged us to try it with alkoxide instead of sodium hydroxide.

Firstly, the conditions were decided, where cinnamyl chloride gave 4-phenyl-3-butenoate in a high yield. Table 2 includes the results of methoxycarbonylation. Under the influence of sodium methoxide the reaction proceeded similarly. After the reaction the amount of unchanged cinnamyl chloride was always lower than 0.5% of that used. In the previous work, $[Na_2PdCl_4]$ combined with 1,2-bis(diphenylphosphino)ethane (dppe) was mainly employed as the catalyst and alkoxide was slowly added to the reaction solution by a syringe. We described in a preliminary report that dppe is a satisfactory ligand.[18] It has now been revealed that phosphine-free complexes, such as $[(\pi\text{-}CH_2CHCH_2)PdCl]_2$ (**IV**), $[(\pi\text{-}C_6H_5CHCHCH_2)PdCl]_2$ (**V**) or **III**, are preferable to phosphine-containing compounds, such as $[PdBr_2(dppe)]$ (**VI**), $PdBr_2(dppp)$ (**VII**; dppp, bis(diphenylphosphino)propane) or **II**, as the alkoxycarbonylation catalyst. It has become apparent that alkoxycarbonylation in the $Na_2[PdCl_4]$/dppe system starts instantly with $[Na_2PdCl_4]$, itself, before dppe is coordinated to the palladium, and that the absorption of carbon monoxide by phosphine-free palladium is very rapid. A comparison under similar conditions showed that Na_2PdCl_4/dppe and $[PdBr_2(dppe)]$ gave 4-phenyl-3-butenoate in 45 and 26%, respectively. It is evident that dppe previously coordinated to palladium inhibits formation of the ester.

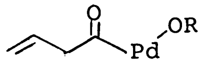
As shown in Table 2, the use of alkoxide at higher concentrations resulted in the formation of methyl 3-phenyl-2-propenyl ether, consequently, in a decreased yield of the ester. In the methoxycarbonylation bis(3-phenyl-2-propenyl) ether was not formed. In the reactions shown in Table 2 the entire quantity of alkoxide was added at the beginning of the reaction. Generally speaking, however, to keep alkoxide in the system at low concentration, continuously adding alkoxide dropwise appears to be a favorable choice, especially in the carbonylation of cinnamyl chloride, where a side reaction occurs along with the formation of the ether. In fact, methyl 4-phenyl-3-butenoate was obtained in a 90% yield when the reaction was carried out in a way similar to Run 21 of Table 2, except that alkoxide was added continuously for 1 h.

It should be noted that a cloudy color (white to pale yellow) appeared during the period of carbonylation and that rapid absorption of carbon monoxide was observed. When the system turned black, the absorption stopped. Although no black precipitate was observed with the phosphine-containing catalysts, the absorption of carbon monoxide was slow and methyl 3-phenyl-2-propenyl ether was formed as the major product.

Contrary to the two-phase carboxylation of the higher homolog, where the yields of the acids are moderate, this alkoxycarbonylation in a homogeneous solution occurs readily with a wide variety of allylic chlorides or bromides. Part of the results is included in Table 1. The gas chromatographic analysis of the esters easily distinguishes between the α,β- and β,γ-isomers. The stereochemistry of the double bond at the β,γ-position was determined by spectroscopy to be of the *E*-form.

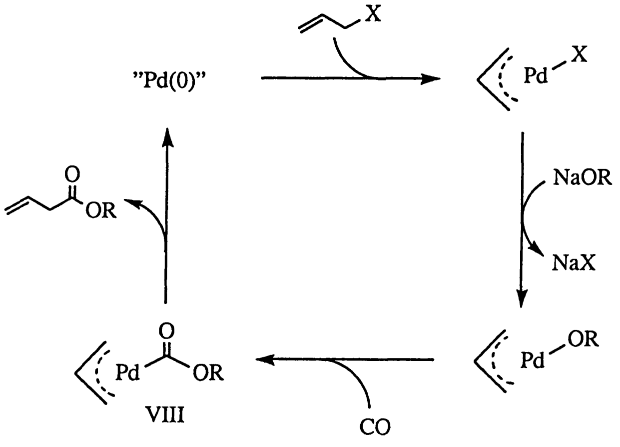


VIII a, R=H
b, R=Alkyl



IX a, R=H
b, R=Alkyl

As an explanation for the decarboxylation-carbonylation of allylic carbonates under atmospheric pressure, Tsuji et al.[12] have pointed out the possibility of an



R=H or Alkyl

Scheme 1. Proposed catalytic cycle.

insertion of carbon monoxide into the palladium-alkoxide bond. There is no evidence yet to rule out the widely accepted mechanism that the insertion of carbon monoxide to the π-allyl–palladium bond forms the acylpalladium complex (**IX**). However, from the present study we propose the catalytic cycle shown in Scheme 1, which involves a (carboxyl or alkoxycarbonyl)(allyl)palladium intermediate (**VIII**).[19]

Experimental

General Remarks. Allylic chlorides and solvents were distilled and stored under argon atmosphere. Carbon monoxide was purchased from Sumitomo Seika Chemicals Co., Ltd., and used without further purification. NMR spectra were recorded on a JMN-GX270 spectrometer. Phosphine dpm was prepared by the reported method.[20] IR spectra were obtained using a Perkin Elmer 1600FT-IR spectrometer and GC analyses were performed on a Shimazu GC-6AM instrument.

Carboxylation of Cinnamyl Chloride. In a 100 ml two-necked flask, of which one side neck was fitted with a three-way stopcock and the other was connected through a three-way stopcock to a gas buret filled with decalin, palladium catalyst and a stirring bar were placed. The flask was thermostatted at 30 °C. After the atmosphere was replaced with carbon monoxide, solvent, cinnamyl chloride, and aqueous NaOH were added and the mixture was stirred vigorously. After the absorption of carbon monoxide stopped, ether (ca. 50 ml) was added and the organic layer was washed with 5% aqueous $NaHCO_3$ (15 ml×3). The organic layer was dried over Na_2SO_4. After adding naphthalene as an internal standard, the solution was concentrated to ca. 10 ml and analyzed by GC (column, Thermon 3000 1.5 m; programmed temperature ranging from 150 to 250 °C at a rate of 10 °C min^{-1}). On the other hand, the aqueous layer was acidified with 12 equiv HCl to pH 2 and extracted with ether (20 ml×4). The ethereal solution was dried over Na_2SO_4. 4-Phenyl-3-butenoic acid was obtained by evaporating ether.

Carboxylation of Other Allylic Chloride. The above-mentioned reaction apparatus and procedure are illustrative. The reaction conditions were similar to that shown in Table 1. After the absorption of carbon monoxide had stopped, the aqueous layer was washed with ether (5 ml), concentrated to ca. 20 ml, acidified with 2 equiv HCl to pH 2, and naphthalene (0.05 g) was added to the solution as an internal standard. The resulting solution was extracted with ether (5 ml×3). The ethereal solution was analyzed by GC (column, Silicone DC 560 1 m; programmed temperature ranging from 60 to 250 °C at a rate of 5 °C min^{-1}).

Alkoxycarbonylation. The reactions were performed similarly using the procedure described above. The reaction conditions are shown in Tables 1 and 2. Catalyst, alcohol, allylic chloride, and sodium alkoxide solution were added to the flask in this order under a CO atmosphere. After the absorption of CO stopped, ether (50 ml) was added. The mixture was washed with water (20 ml×3), dried over Na_2SO_4, and concentrated to ca. 10 ml. Naphthalene (0.05 g) was added and the solution was analyzed by GC (column, Thermon 1.5 m; programmed temperature from 60 to 250 °C at a rate of 5 °C min^{-1}).

Methoxycarbonylation of Cinnamyl Chloride by Continuous Addition of Methoxide. In the flask described above, a catalyst (0.1 mmol) and a stirring bar were placed. The flask was thermostatted at 30 °C. After the atmosphere was replaced with CO, methanol and cinnamyl chloride (15 mmol) were added. The solution was slowly added through a septum cap, which was equipped at the one side neck of the flask, by a microfeeder (JP-type, Furue Science Co., Ltd.) during 1 h with vigorously stirring. After the reaction, GC analysis was carried out by the procedure described above.

This work was supported by a Grant-in-Aid for Scientific Research Nos. 01550674 and 03650703 from the Ministry of Education, Science and Culture.

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