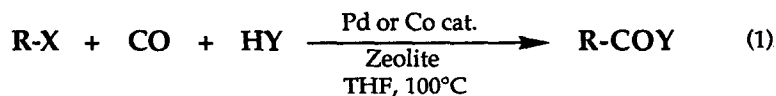


TRANSITION METAL COMPLEX CATALYZED CARBONYLATION OF ORGANIC HALIDES IN THE PRESENCE OF MOLECULAR SIEVES INSTEAD OF BASE

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Summary: In the presence of molecular sieves under base free conditions organic halides are successfully carbonylated under carbon monoxide pressure with water or alcohols catalyzed by Co or Pd complex to generate the corresponding carboxylic acids or esters, respectively, in good yields.

Transition-metal complex-catalyzed carbonylation of organic halides with carbon monoxide is one of the most important methods for the direct introduction of a carbonyl group into organic molecules.¹ In this carbonylation, however, there exists some limitation of the applicable substrates. The carbonylation could not be applied to organic halides that may react directly with a base which is indispensable to scavenge hydrogen halides generated in the reaction. In order to overcome this problem, we have developed novel base-free carbonylation conditions. Recently, we have reported that a variety of organic halides including base-sensitive ones are nicely carbonylated in the presence of Pd or Co catalyst in tetraalkyl-substituted ureas as a solvent without any base.² In the course of our further studies, we have found that zeolites such as molecular sieves can serve as an effective sponge of hydrogen halides arose in the reaction. Here, we would like to report the transition-metal complex-catalyzed carbonylation of organic halides in the presence of zeolites under base-free conditions (eq. 1).



R=Aryl, Benzyl, Alkyl
X=I, Br, Cl.
HY=Alcohol, H₂O

Treatment of benzyl bromide with carbon monoxide (30 atm) and ethanol in the presence of molecular sieve 4A (MS-4A, activated powder with average particle size of 2-3 μ , Aldrich) and a catalytic amount of (Ph₃P)₂PdCl₂ in THF at 100 °C afforded ethyl phenylacetate (**1**) in a yield of 85% (Table 1). Benzyl ethyl ether (**2**) arisen from nucleophilic displacement was formed as a by-product in 15% yield. Apparently, this carbonylation did not proceed in the absence of MS-4A, wherein toluene was detected as a major product along with **2** which was formed in 19% yield (Entry 2). The yield of **1** decreased when MS-3A or MS-5A was used instead of MS-4A (Entries 3

Table 1. Ethoxycarbonylation of Benzyl Bromide Catalyzed by $(\text{Ph}_3\text{P})_2\text{PdCl}_2^a$

Entry	Additive	Solv.	1(%) ^b	2(%) ^b
1 ^c	none	THF	6	19
2	MS-4A	THF	85	15
3 ^c	MS-3A	THF	54	16
4 ^c	MS-5A	THF	40	9
5 ^c	Alumina	THF	6	41
6	MS-4A	EtOH	23	60
7 ^c	MS-4A	DME	25	17
8 ^c	MS-4A	Benzene	21	24
9 ^c	MS-4A	<i>n</i> -Heptane	21	49

a. All reactions were conducted in an autoclave containing substrate (1 mmol), catalyst (2 mol%), additive (50 mg), EtOH (0.6 ml), and solvent (1.4 ml) at 100°C for 24 h under 30 atm of CO pressure. *b.* Yields were determined by means of GLC. *c.* Though yield was not estimated, significant amounts of toluene was observed by GLC analysis.

and 4). Basic alumina gave predominantly 2 and toluene (Entry 5). In addition, the nature of solvents also markedly affected the reaction. When the reaction was performed in other solvents

Table 2. Carbonylation of Iodobenzene in the Presence of Zeolites Catalyzed by $(\text{Ph}_3\text{P})_2\text{PdCl}_2^a$

Entry	Zeolite(mg) ^b	Hole diameter(Å)	Yield(%) ^c
1	none		31
2	MS-3A(50)	3	51
3	Synthetic, A-3(50)	3	44
4	MS-4A(10)	4	36
5	MS-4A(30)	4	45
6	MS-4A(40)	4	53
7	MS-4A(50)	4	92
8	MS-4A(60)	4	87
9	MS-4A(80)	4	77
10	Ferrierite ^d (50)	4	75
11	Synthetic, A-4(50)	4	45
12	MS-5A(50)	5	91
13	Na-Mordenite ^e (50)	7	37
14	Na-Y ^f (50)	8	36
15	L ^g (50)	8	23
16	MS-13X(50)	10	38

a. All reactions were carried out with iodobenzene (1 mmol) in the presence of Pd catalyst (2 mol%) in THF (1.4 ml) under 30 atm of CO pressure at 100°C for 24 h. *b.* Powdered zeolite was used in all cases. *c.* Yields were determined by GLC. *d.* $(\text{K,Na})_2\text{O} \cdot \text{Al}_2\text{O}_3 \cdot 17\text{SiO}_2$. *e.* $\text{Na}_2\text{O} \cdot \text{Al}_2\text{O}_3 \cdot 11\text{SiO}_2$. *f.* $\text{Na}_2\text{O} \cdot \text{Al}_2\text{O}_3 \cdot 5.5\text{SiO}_2$. *g.* $\text{K}_2\text{O} \cdot \text{Al}_2\text{O}_3 \cdot 6\text{SiO}_2$.

such as ethanol, dimethoxyethane, and benzene, the desired ester was obtained only in lower yields (Entries 6-9).

The results of more detailed studies on the effects of various kinds of zeolites in the carbonylation of iodobenzene are listed in Table 2. As shown in Entries 4-9, the yield of the carbonylated product was raised by increasing the amount of MS-4A, and reached a maximum at 50 mg of MS-4A/1 mmol of substrate. Excess MS-4A can absorb ethanol, and lowered the yield. Interestingly, hole diameters of zeolites gave significant influence on the present carbonylation. Thus, in the carbonylation of benzyl bromide mentioned above, only MS-4A afforded good yield of the desired ester. On the other hand, when the carbonylation of iodobenzene was performed in the presence of MS-4A, Ferrierite, or MS-5A, the carbonylated product was obtained in good to excellent yields. Lower yields were observed on the use of MS-3A having a smaller hole diameter (Entry 2) or other zeolites having larger hole diameters such as Na-Mordenite (Entry

Table 3. Carbonylation of Organic Halides in the Presence of Molecular Sieves Catalyzed by Pd or Co Complex^a

Entry	R-X	cat. ^b (mol%)	MS(50 mg)	Temp(°C)	Time(h)	Yield(%)
1	<i>o</i> -MeC ₆ H ₄ -I	Pd(2)	4A	100	24	84
2	<i>m</i> -MeC ₆ H ₄ -I	Pd(2)	4A	100	24	97
3	<i>p</i> -MeC ₆ H ₄ -I	Pd(2)	4A	100	24	80
4	<i>p</i> -MeOC ₆ H ₄ -I	Pd(2)	4A	100	24	75
5	<i>p</i> -HOC ₆ H ₄ -I	Pd(2)	4A	100	24	95
6	<i>p</i> -ClC ₆ H ₄ -I	Pd(2)	4A	100	24	90
7	<i>p</i> -FC ₆ H ₄ -I	Pd(2)	4A	100	24	62
8	<i>m</i> -CF ₃ C ₆ H ₄ -I	Pd(2)	4A	100	24	84
9	<i>p</i> -AcC ₆ H ₄ -I	Pd(2)	4A	100	24	95
10	<i>p</i> -EtOCOC ₆ H ₄ -I	Pd(2)	4A	100	24	87
11 ^c	PhCH ₂ -Cl	Pd(2)	3A	100	24	71(91) ^d
12	<i>n</i> -C ₈ H ₁₇ -I	Co(10)	4A	100	48	63(77) ^d
13	<i>n</i> -C ₁₀ H ₂₁ -I	Co(10)	4A	100	48	58(82) ^d
14	EtO(CH ₂) ₃ -I	Co(10)	4A	120	48	75
15	<i>cyclo</i> -C ₆ H ₁₁ -I	Pd(2)	4A	120	48	80
16	EtOCOCH ₂ CH(CH ₃)-I	Pd(2)	4A	100	48	81
17 ^e	C ₆ H ₅ -I	Pd(2)	4A	100	24	58
18 ^e	<i>cyclo</i> -C ₆ H ₁₁ -I	Pd(2)	4A	100	24	57

a. All reactions were conducted in an autoclave containing substrate (1 mmol), catalyst, molecular sieves (50 mg), EtOH (0.6 ml) or H₂O (0.2 ml), and THF (1.4 ml) under initial CO pressure of 30 atm (Entries 1-11, and 17) or 50 atm (Entries 12-17, and 18). *b.* Pd = (Ph₃P)₂PdCl₂, Co = Co₂(CO)₈. *c.* When MS-4A and MS-5A were used, the ester was obtained in 30% and 42% yields, respectively. *d.* Conversion yield. *e.* Water was used instead of EtOH as a nucleophile and the yield was estimated after esterification of the carboxylic acid with diazomethane.

13), Na-Y (Entry 14), L (Entry 15), and MS-13X (Entry 16). Furthermore, the nature of the zeolites seems also to affect the present carbonylation because Synthetic A-4 did not provide good result though it have a hole diameter of 4 Å (Entry 11).

Various organic halides were carbonylated with the MS/THF system using Pd or Co catalyst. Representative examples are summarized in Table 3. As shown in Entries 1-10, a variety of aryl iodides afforded the corresponding esters in good to excellent yields. In the case of benzyl chloride, ethyl benzylacetate was obtained in good yield only on using MS-3A, while both MS-4A and MS-5A gave unsatisfactory results, indicating that hydrogen chloride can not be effectively trapped by the zeolite having a hole diameter larger than 3 Å (Entry 11). In particular, the present MS/THF system can be applied to the carbonylation of alkyl halides.³ As shown in Table 3, primary alkyl iodides such as 1-iodooctane, 1-iododecane, and 1-ethoxy-3-iodopropane smoothly underwent the carbonylation in the presence of MS-4A and a catalytic amount of $\text{Co}_2(\text{CO})_8$, affording the corresponding esters in good yields. On the other hand, cyclohexyl iodide as a secondary halide was carbonylated in 80% yield when Pd complex was used as the catalyst. It is noteworthy that the carbonylation of ethyl 3-iodobutanoate, which preferably react with base such as Et_3N or K_2CO_3 to afford ethyl crotonate under usual Heck's carbonylation conditions,² successfully proceeded without any side reactions to give diethyl 2-methylsuccinate in 81% yield (Entry 16). Carboxylic acids could also be afforded by treatment of organic halides with water under similar conditions (Entries 17 and 18).

In conclusion, the present zeolite/THF system provides the general base-free carbonylation conditions⁴ where not only aryl and benzyl halides but also alkyl halides which may directly react with base can be carbonylated in high yields in the presence of Pd or Co catalyst. What sort of zeolite should be employed depends on its hole diameter and the kind of halogen atom of organic halides used in the carbonylation.

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References and Notes

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- (4) After the reaction completed, pH test paper indicated that the reaction mixture was slightly acidic (pH 4.5~5.5).

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