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Formylation of Aryl Halides with Carbon Monoxide and Sodium Formate in the Presence of Palladium Catalyst

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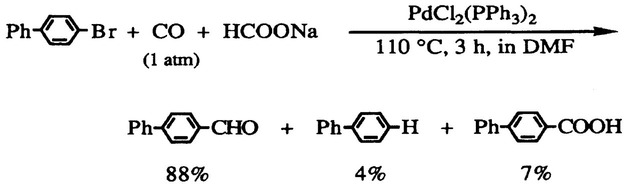
Synopsis. The formylation of aryl bromides or iodides with HCOONa at atmospheric pressure of CO readily proceeded in the presence of $PdCl_2(PPh_3)_2$ in DMF to afford the corresponding aldehydes in good yields. The contamination with water promoted a side reaction to form carboxylic acids. The formylation using HCOOK or $HCOONH_4$ as a hydride source was fast but gave a considerable amount of the reduction product.

The carbonylation of aryl halides in the presence of palladium catalysts is a very versatile reaction and an important synthetic tool. Furthermore, it has the advantage of proceeding smoothly under low pressures of carbon monoxide. For example, the syntheses of carboxylic acids,[1] esters,[2] acid fluorides,[3] and amides[4] have been reported to be readily achieved at atmospheric pressure of CO in high yields. However, the formylation of aryl halides, which is very important both chemically and industrially, still has several defects. The formylation using H_2 as a hydrogen source requires high pressures of CO.[5] In order to achieve the formylation at low pressures of CO, the use of expensive reagents such as silicon[6,7] and tin[8] hydrides is necessary. Nevertheless, the formylation with these hydrides often accompanied by overreduction of the aldehyde and other reducible functional groups due to their high reducing abilities. Formate salts, which themselves are very weak reducing agents,[9] are known to act as a hydrogen source for the formylation.[7] Although they are cheap and readily available, unfortunately, only a few examples of aryl halides have been examined.[10,11] Therefore, we investigated the formylation of various aryl halides with formate salts at atmospheric pressure of CO in detail.

Results and Discussion

The formylation was carried out by stirring a suspension of 4-bromobiphenyl, powdered sodium formate and $PdCl_2(PPh_3)_2$ in DMF at 110 °C for 3 h at atmospheric pressure of CO, which was bubbled through the mixture by means of a glass inlet tube in order to prevent the formed CO_2 form covering the reaction mixture.



(1)

This formylation afforded *p*-phenylbezaldehyde in an 88% GC yield. Overreduction products such as alcohol were not detected, but small amounts of biphenyl and *p*-phenylbenzoic acid were formed. Though the carboxylic acid increased in the presence of water (see Table 1), attempts to reduce the by-product by the use of repeatedly dried reagents were unsuccessful. Interestingly, the additions of powdered NaOH and formic acid resulted in increase in the by-productions of the carboxylic acid and biphenyl, respectively.

In the absence of free PPh_3, some metallic precipitate was deposited. The addition of an equimolar amount of PPh_3 with the palladium catalyst was effective in preventing the deposition, and at the same time brought about a slight increase in the yield of aldehyde. However, the use of large excesses of PPh_3 retarded the formylation. The reaction temperature had a marked effect on the formylation. The formylation was very slow at 90 °C, whereas at 110 °C it was completed within 3 h. The amount of HCOONa had a negligible influence on the aldehyde yield when the excess HCOONa was used. Interestingly, the grain size of HCOONa had no effect on the aldehyde yield, though this formylation is a liquid–solid two-phase reaction. These facts suggest that the formylation is not effected on the surface area of the solid formate, but exclusively by the dissolving the formate in DMF. Accordingly, the reaction rate, which depends on the formate concentration, is affected by the temperature, but it is dependent on neither the amount of the used sodium formate nor the grain size.

The use of lithium salt instead of HCOONa reduced the formylation rate. On the other hand, potassium formate was more reactive than the sodium salt, and the reaction proceeded even at 80 °C. However the selectivity to aldehyde was poor, especially at high temperatures. Ammonium formate was also very reactive, but the reaction gave mostly biphenyl. Compared with the formates of univalent cations, the calcium salt was surprisingly less reactive. This difference in the reactivity of formate salts can probably be ascribed to their solubilities in DMF. Accordingly, we deduce that an increase in the formate concentration in solvent results in a promotion of the formylation, and at the same time brings about an acceleration of the hydrogenolysis which precedes CO insertion.

The solvent effect also seems to be correlated with the solubility (Table 2). The reactions in DMSO and 2-methoxyethanol in which HCOONa is highly soluble were very fast. However, the reaction in DMSO gave

Table 1. Formylation of *p*-Bromobiphenyl with Formate Salts and CO in the Presence of $PdCl_2(PPh_3)_2$[a]

Hydride		PPh_3	Temp	Time	Yields/% of	
source	mmol	mmol	°C	h	$C_{12}H_9CHO$	$C_{12}H_{10}$
HCOONa	10	0	110	3	88[b]	4
HCOONa	10	0.1	110	3	90[c]	3
HCOONa[d]	10	0.1	110	3	79[e]	3
HCOONa[f]	10	0.1	110	3	75[g]	3
HCOONa[h]	10	0.1	110	3	72	15
HCOONa	10	0.2	110	3	83	4
HCOONa	10	0.3	110	3	80	3
HCOONa	7.5	0.1	110	1	48	2
HCOONa	7.5	0.1	90	1	5	0
HCOONa	7.5	0.1	110	3	90	3
HCOONa[i]	7.5	0.1	110	3	89	4
HCOONa	6	0.1	110	3	88	4
HCOONa	5	0.1	110	3	75	4
HCOOLi	7.5	0.1	110	1	39	2
HCOOLi	7.5	0.1	110	5	87	3
HCOOK	7.5	0.1	110	1	24	70
HCOOK	7.5	0.1	90	1	34	5
HCOOK	7.5	0.1	80	5	82	9
$HCOONH_4$[j]	7.5	0.1	110	0.5	4	36
$(HCOO)_2Ca$	3.75	0.1	110	5	6	0
$NaBH_4$	2	0.1	110	1	0	84
LiH	7.5	0.1	110	3	0	8

a) The reactions were carried out by stirring a suspension of 4-bromobiphenyl (5 mmol), hydride source and $PdCl_2(PPh_3)_2$ (0.1 mmol) in DMF (5 cm^3) at atmospheric pressure of CO, and the yields of *p*-phenylbenzaldehyde and biphenyl were determined by GC using naphthalene as an internal standard. b) *p*-Phenylbenzoic acid (7%) was isolated. c) Isolated yield of *p*-phenylbenzoic acid was 6%. d) Water (0.2 cm^3) was added. e) *p*-Phenylbenzoic acid (13%). f) Powdered NaOH (0.5 mmol) was added. g) *p*-Phenylbenzoic acid (12%). h) Formic acid (0.5 mmol) was added. i) Large meshed HCOONa was used. j) Ammonium formate was sublimated in a short time.

Table 2. Solvent Effect on the Formylation of $C_{12}H_9Br$[a]

Solvent	$C_{12}H_9CHO$/%	$C_{12}H_{10}$/%
Toluene	1	1
Dioxane	4	4
Propiononitrile	6	3
Pyridine	10	4
$CH_3OCH_2CH_2OH$	4(41)[b]	3
DMSO[c]	61	30
DMF	69	2
DMF[d]	91	2

a) Reaction conditions: 4-bromobiphenyl (5 mmol), powdered HCOONa (7.5 mmol), $PdCl_2(PPh_3)_2$ (0.1 mmol), PPh_3 (0.1 mmol), solvent (5 cm^3), CO (1 atm) at 100 °C for 5 h. The yields were determined by GC. b) 2-Methoxyethyl *p*-phenylbenzoate was formed. c) For 1 h. d) For 8 h.

mainly biphenyl, and the reaction in 2-methoxyethanol afforded mostly 2-methoxyethyl *p*-phenylbenzoate instead of the aldehyde. Less polar solvents such as pyridine, propiononitrile and dioxane were not favorable for the formaylation.

The catalytic activity of some palladium complexes was examined using HCOONa in DMF at atmospheric pressure of CO (see Table 3). The PPh_3 complexes, $PdCl_2(PPh_3)_2$ and $PdBr_2(PPh_3)_2$, were almost equivalent in the formylation activity. An analogue, $PdBr_2[P(p\text{-}ClC_6H_4)_3]_2$, exhibited higher catalytic activity than the PPh_3 complexes, whereas the complexes containing electron-donating phosphines such as $P(p\text{-}CH_3C_6H_4)_3$ and $PPh_2(i\text{-}Pr)$ were not so active as the PPh_3 complexes. The catalytic activity of bisphosphine complex, $PdBr_2[Ph_2P(CH_2)_3PPh_2]$, was poor.

This method was applicable to the formylation of a wide variety of aryl bromides and iodides at atmospheric pressure of CO (see Table 4). The aryl bromides were formylated at 100—110 °C. The reactivity of bromobenzenes having electron-withdrawing substituents was slightly higher than that of bromobenzenes having electron-donating substituents. The reactivity and the selectivity of *o*-substituted bromobenzenes were poor. Aryl iodides were more reactive than the bromides, and underwent the formylation at 80—90 °C to give alde-

Table 3. Catalytic Activity of Palladium Phosphine Complexes

Catalyst	Yields/%$^{a)}$	
	p-Ph–C_6H_4–CHO	p-Ph–C_6H_4–H
$PdCl_2(PPh_3)_2$	70	3
$PdBr_2(PPh_3)_2$	74	4
$PdBr_2[P(p\text{-}ClC_6H_4)_3]_2$	81	3
$PdBr_2[P(p\text{-}CH_3C_6H_4)_3]_2$	59	2
$PdBr_2[PPh_2(i\text{-}Pr)]_2$	55	5
$PdBr_2[Ph_2P(CH_2)_3PPh_2]^{b)}$	12	4

Reaction conditions: 4-phenylbromobenzene (5 mmol), powdered HCOONa (7.5 mmol), $PdX_2(PR_3)_2$ (0.1 mmol), PR_3 (0.1 mmol), DMF (5 cm^3), CO (1 atm) at 110 °C for 2 h. a) Determined by GC. b) PPh_3 (0.1 mmol) was used instead of $Ph_2P(CH_2)_3PPh_2$.

Table 4. Formylation of Various Aryl Halides with Sodium Formate under Atmospheric Pressure of CO$^{a)}$

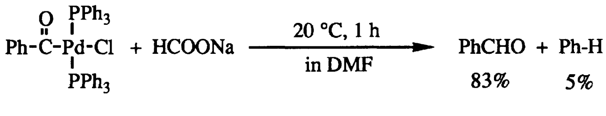
Substrate (R-X)	Temp/°C	Time/h	R-CHO/%	R-H/%
Bromobenzene	100	5	83	5
Iodobenzene	80	8	88	1
p-Bromotoluene	110	3	83	1
p-Iodotoluene	90	8	86	0
m-Bromotoluene	110	3	86	1
p-Bromoanisole	110	5	87	1
m-Bromoanisole	110	3	81	3
p-Bromochlorobenzene	100	8	82$^{b)}$	0
p-Dibromobenzene$^{c)}$	100	8	83$^{d)}$	2$^{e)}$
Methyl *p*-bromobenzoate	100	5	80	5
p-Bromocyanobenzene	100	5	63	18
p-Chlorocyanobenzene	110	5	5	30
o-Bromotoluene	110	5	58	30
o-Bromoanisole	110	8	27	38
o-Bromchlorobenzene	100	8	12$^{f)}$	79$^{g)}$
2-Bromonaphthalene	100	5	86	2
3-Bromopyridine	100	5	83	7
3-Bromothiophene	100	5	82	4

a) Reaction conditions: substrate (5 mmol), powdered HCOONa (7.5 mmol), DMF (5 cm^3) and CO (1 atm). The yields were determined by GC. b) *p*-Chlorobenzaldehyde (71%), terephthalaldehyde (8%) and benzaldehyde (3%) were formed. c) Powdered HCOONa (12 mmol) was used. d) Terephthalaldehyde (72%), *p*-bromobenzaldehyde (5%) and benzaldehyde (6%) were detected. e) Bromobenzene was formed. f) *o*-Chlorobenzaldehyde (11%) and benzaldehyde (1%) was detected. g) Chlorobenzene was formed.

hydes in good yields. In constant to the iodides, the chlorides were inactive under these conditions. Therefore, *p*-bromochlorobenzene was formylated selectively to *p*-chlorobenzaldehyde in a good yield. The formylation of nonbenzenoid aromatic bromides was also successfully achieved, and the corresponding aldehydes were obtained in high yields.

Sodium formate was different from the silicon and tin hydrides in that it was inadequate for reducing benzoyl chloride to benzaldehyde. This reaction afforded sodium benzoate with the evolution of CO, even under an atmosphere of CO, either in the presence or the absence of the palladium catalyst. This noncatalytic reaction occurred even in dioxane, in which HCOONa is practically insoluble. On the other hand, the stoichiometric reduction of benzoylpalladium complex was successfully achieved in the presence of sodium formate at room temperature under an atmosphere of argon.

$$\mathrm{PhCOCl + HCOONa \xrightarrow[50\ ^\circ C,\ 1\ h,\ in\ DMF]{PdCl_2(PPh_3)_2} \underset{95\%}{PhCOOH} + CO} \qquad (2)$$



$$\mathrm{Ph{-}\overset{O}{\overset{\|}{C}}{-}\underset{PPh_3}{\overset{PPh_3}{Pd}}{-}Cl + HCOONa \xrightarrow[in\ DMF]{20\ ^\circ C,\ 1\ h} \underset{83\%}{PhCHO} + \underset{5\%}{Ph{-}H}} \qquad (3)$$

These facts indicate that the noncatalytic reaction is exclusively faster than the oxidative addition of benzyl chloride to Pd(0) species.

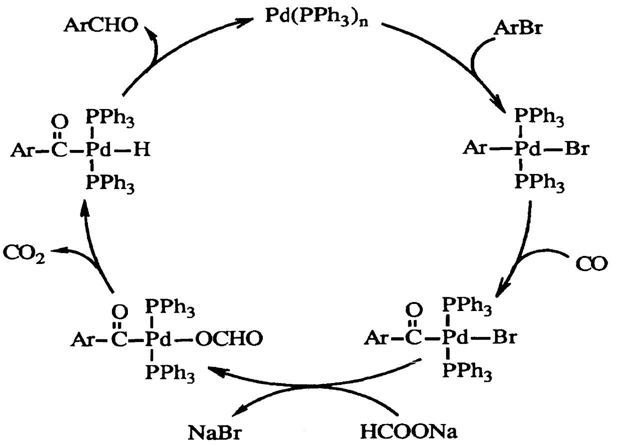


Fig. 1. Proposed mechanism for the formylation.

Based on these results, we show a possible mechanism in Fig. 1. The first step is the oxidative addition of aryl halide to Pd(0) species to give an arylpalladium complex. The reduction of the arylpalladium complex with HCOONa results in the formation of Ar–H. Nevertheless, the insertion of CO into the C–Pd bond is faster than the reduction, and forms an aroylpalladium species. The aroyl complex reacts with HCOONa to give a hydrido aroyl complex via formyl aroyl species. The hydrido complex would undergo reductive elimination to generate aldehyde and Pd(0) species.

Experimental

Materials. All organic chemicals were purchased from chemical sources and purified by distillation or recrystallization before use. DMF was dried over CaH_2 at 50 °C for 5 h, distilled from CaH_2 under a reduced pressure (about 10 kPa), and stored under argon. The other solvents were stored under argon after being distilled from appropriate drying agents. The crystalline formate salts were ground to powder in a ball mill for 5 h and were dried in a vacuum (about 70 Pa.) at 40 °C. Carbon monoxide (99.9%) was obtained from Sumitomo Seiki Co. and used as received. Palladium complexes, $PdCl_2(PPh_3)_2$, $PdBr_2(PPh_3)_2$, $PdBr_2[P(p\text{-}ClC_6H_4)_3]_2$, $PdBr_2[P(p\text{-}CH_3C_6H_4)_3]_2$, $PdBr_2[PPh_2(i\text{-}Pr)]$, and $PdBr_2[Ph_2P(CH_2)_3PPh_2]$ were prepared by treating $PdCl_2(cod)$[12] or $PdBr_2(cod)$[12] with the corresponding phosphines in CH_2Cl_2. The aroyl complex, *trans*-$PdCl(COPh)(PPh_3)_2$, was prepared according to literature procedures.[13]

Catalytic Formylation. A typical experimental procedure is as follows. Into a 20 cm^3 Schlenk tube, fitted with glass inlet tube, were placed $PdCl_2(PPh_3)_2$ (70 mg, 0.1 mmol), 4-bromobiphenyl (1.16 g, 5 mmol), HCOONa (510 mg, 7.5 mmol), and naphthalene (150 mg) as a internal calibrant. The atmosphere was replace with carbon monoxide. DMF (5 cm^3) was added by syringe, and a slow stream of CO (3—5 $cm^3\,min^{-1}$) was passed into the suspension. The mixture was vigorously stirred at 110 °C for 3 h. After cooling the reaction mixture, a small portion of the supernatant was subjected to gas chromatography for quantification of *p*-phenylbenzaldehyde and biphenyl. The remainder was added to 30 cm^3 of 5% NaOH aqueous solution, and the mixture was washed with five 10 cm^3 portions of ether. The aqueous layer was acidified with concentrated hydrochloric acid, and the carboxylic acid was extracted with four 20 cm^3 portions of ether. The ethereal extract was dried over anhydrous Na_2SO_4, and concentrated to dryness to give almost pure *p*-phenylbenzoic acid.

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