mL) was removed, added to Phe PFSA (0.5 mL), and loaded into the syringe reactor in which the Leu resin had previously been thoroughly washed with DMF. After reaction, workup, and hydrolysis, the Tyr incorporation was determined to be 28.7%, compared with the standard PFSA mixture in DMF which gave 26.0% incorporation (average of four determinations).

Procedures Used in BOP Time-Course Studies (Figure 3). A typical series, using 0.5 equiv of BOP, was performed as follows. Boc-Tyr(Bzl)-OH (74.2 mg, 0.2 mmol) in 0.2 M *N*-methylmorpholine in DMF (1 mL) was treated with a solution of BOP (44.2 mg, 0.1 mmol) in DMF (1 mL). Samples (0.5 mL) were removed at 1-, 2-, 5-, and 10-min time intervals, mixed with Phe PFSA (0.5 mL, prepared from Boc-Phe-OH (53 mg, 0.2 mmol) in DCM (0.5 mL) treated with 0.2 M DIPCDI in DCM (0.5 mL) for 15 min, evaporated, dried, and dissolved in DMF (2 mL)), and rapidly added to the reactor. Tyr incorporations were determined to be as follows: 1 min, 21.3%; 2 min, 23.1%; 5 min, 26.0%; 10 min, 26.1%. Tyr PFSA + Phe PFSA standards gave 25% Tyr incorporation (average of four determinations). A duplicate series confirmed the results.

Acknowledgment. I express thanks to Prof. George Barany of the University of Minnesota for the original suggestion that competition experiments would be helpful in study of the areas of interest. Thanks are also due to Dean Tsou for performing the automated syntheses reported and to Sara Biancalana and Tom Mills for analyses of the products.

Registry No. DBTO, 89028-37-5; BOP, 56602-33-6; DIPCDI, 693-13-0; Bop-Cl, 68641-49-6; IIDQ, 38428-14-7; EEDQ, 16357-59-8; DPPA, 26386-88-9; HO-Dhobt, 28230-32-2; HO-PFP, 771-61-9; HOBt, 2592-95-2; DCCI, 538-75-0; ACP 65-74, 66851-75-0; Bates reagent, 55881-03-3; Woodwards reagent K, 4156-16-5; Woodwards reagent L, 10513-45-8; 1*H*-tetrazole, 288-94-8; 1,2,3-benzotriazole, 95-14-7.

Supplementary Material Available: An assembly drawing of Biosearch Macroscale columns used for simultaneous syntheses and for competition experiments (1 page). Ordering information is given on any current masthead page.

Hydroxycarbonylation of Aryl Halides with Formate Salts Catalyzed by Palladium Complexes

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Substituted aryl halides were hydroxycarbonylated under 50 psi pressure of carbon monoxide in the presence of various formate salts and a homogeneous palladium catalyst to give aromatic acids in good yields. Selectivity of formate salts in hydroxycarbonylation reactions depends on the metallic counter-ion and the reaction conditions. Calcium formate was found to give the highest selectivity for hydroxycarbonylation. A mechanism consisting of the generation of mixed anhydrides as intermediates is suggested.

Introduction

The preparation of aromatic acids by a catalyzed hydroxycarbonylation of aryl halides under low carbon monoxide pressure, in the presence of a strong inorganic base such as aqueous sodium hydroxide[1] or calcium hydroxide[2] (eq 1), has been mentioned in the literature.

$$\mathrm{ArBr + CO + M(OH)_n \xrightarrow{catalyst} ArCO_2M + MBr + H_2O} \quad \begin{matrix} M = Na, Ca \\ n = 1, 2 \end{matrix} \qquad (1)$$

Such reactions were homogeneously catalyzed by transition-metal complexes with the help of either a phase-transfer catalyst,[2a] photostimulation,[2d] or the combination of both of them.[2c] No aromatic acids were formed under similar conditions when the strong inorganic base was replaced by a Brønsted base such as a tertiary amine or potassium carbonate.[2b]

Since the heating of alkali or alkali earth hydroxides under carbon monoxide reaches an equilibrium with the formic acid salt,[3] we have considered the possibility of replacing the aqueous base by a formate salt, serving both as a base and as an hydroxyl donor. Direct use of formate would also avoid an excess of alkali hydroxide and enable reaction at a milder pH and under anhydrous conditions (eq 2). We report here that under suitable conditions, an

$$\mathrm{ArBr + MO_2CH + C^*O \xrightarrow{catalyst} ArC^*O_2H + MBr + CO} \qquad (2)$$

hydroxycarbonylation reaction between aryl halides and formate salts occurred under 1–3 atm of CO pressure, giving the corresponding carboxylic acids in fair to good yields.

Results and Discussion

The catalyzed hydroxycarbonylation reaction is in competition with the reductive formylation by formates[4] (eq 3). Indeed, it was found that the formylation reaction

$$\mathrm{ArBr + MO_2CH + CO} \begin{cases} \xrightarrow{\text{path A}} \mathrm{ArCHO + MBr + CO_2} \\ \xrightarrow{\text{path B}} \mathrm{ArCO_2H + MBr + CO} \end{cases} \qquad (3)$$

(path A) is accompanied by the much slower hydroxycarbonylation reaction (path B). The reaction of sodium formate with 4-chlorobromobenzene, in an anhydrous aprotic dipolar solvent (e.g. DMF) and in the presence of 5 mol % homogeneous palladium catalyst, results in 4-chlorobenzaldehyde (70%), chlorobenzene (4%), and 4-

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Table I. Distribution of Products (Formylation vs Hydroxycarbonylation) in the Reaction of Aromatic Halides with Various Formate Salts[a]

				products	
entry	formate	reactn condtn[b]	conv (mol %)[c]	aldehyde[d] (mol %)	benzoic acid[e] (mol %)
1	LiO_2CH	A	96	76 (71)[f]	18
2	LiO_2CH	B	93	29	56
3	NaO_2CH	A	95	70 (66)[f]	15
4	NaO_2CH	B	97	28	58
5	KO_2CH	A	90	64	24
6	KO_2CH	B	88	10	78
7	$Ca(O_2CH)_2$	A	48	8	36
8	$Ca(O_2CH)_2$	B	96	3	85 (80)[f]
9	$Ba(O_2CH)_2$	A	65	40	35
10	$Ba(O_2CH)_2$	B	93	10	71

[a] Reactions conditions: 4-chlorobromobenzene (1 mmol), formate salt (1.1 equiv), $PdCl_2$ (0.05 mmol), PPh_3 (0.3 mmol), under 50 psig carbon monoxide (measured at ambient temperature). [b] (A) temperature 100 °C, reaction time 18 h, solvent DMF; (B) temperature 120 °C, reaction time 20 h, solvent DMF/benzene (1:1). [c] Determined from residual aryl halide. Small amounts of hydrogenolysis products (2–10%) make up to a total of 100%. [d] Yields determined by HPLC and GC. [e] GC yields determined as methyl esters (obtained from the acid by treatment with methyl iodide). [f] Isolated yield.

chlorobenzoic acid (18%). The reaction is carried out under 3 atm of carbon monoxide for 18 h at 100 °C. In order to slow down the hydrogen-transfer from the formate, we considered performing the reaction with a weaker hydrogen-donor. Calcium formate was chosen, since IR data indicated that the C–H adsorption frequencies in calcium formate are considerably higher than those of alkali formates,[5] being an indication of a less reactive C–H bond in this formate salt.

Indeed, under comparable conditions, calcium formate reacted with a higher chemoselectivity in the hydroxycarbonylation pathway, giving only 8% of 4-chlorobenzaldehyde and 36% of 4-chlorobenzoic acid after 18 h of reaction at 100 °C (Table I, entry 7). Barium and potassium formate were found less chemoselective, as shown in Table I. Increasing the temperature and performing the reaction in a solvent of lower polarity tends to avoid aldehyde formation. Thus, in order to achieve higher selectivity of hydroxycarbonylation, the reaction was done at 120 °C in a DMF–benzene mixture (Table I, reaction conditions B). Under these conditions, a selectivity of 97% for the hydroxycarbonylation was achieved by the use of calcium formate (Table I, entry 8). Various substituted bromo- and iodoaromatic compounds were subjected to the hydroxycarbonylation reaction (Table II). Para substituents like methyl, methoxy, hydroxy, acetyl, nitro, and chloro derivatives were found compatible with the reaction; however, an ortho substitution tends to retard the reaction (Table II, entries 5, 11, 14). The mechanism of the hydroxycarbonylation reaction could be related to that of the methoxycarbonylation reaction. The latter was currently shown[6] to proceed through fast oxidative addition and carbonylation steps and a slow nucleophilic attack on the acylpalladium species being produced.

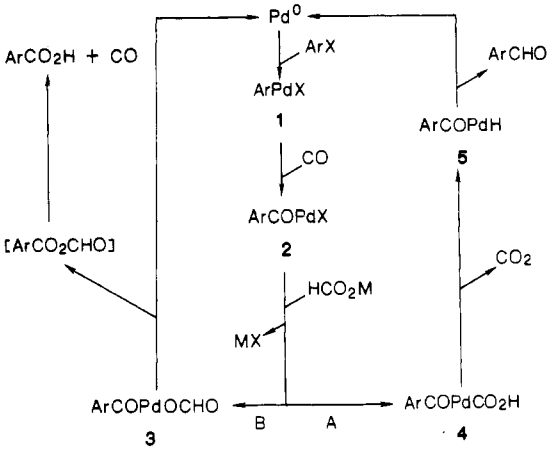
The following nucleophilic attack of a formate ion could proceed in two differents reaction patterns (Scheme I, A and B). One possible pathway involves a C–H bond cleavage, giving an aldehyde (Scheme I, A) another route (Scheme I, B) is the generation of a palladium formate

Table II. Hydroxyformylation of Substituted Aryl Halides[a]

entry	aromatic halide	aromatic acid (yield) (mol %)[b]
1	C_6H_5Br	$C_6H_5CO_2H$ (73) (70)[c]
2	C_6H_5I	$C_6H_5CO_2H$ (85)
3	$4\text{-}CH_3C_6H_4Br$	$4\text{-}CH_3C_6H_4CO_2H$ (77) (72)[c]
4	$3\text{-}CH_3C_6H_4Br$	$3\text{-}CH_3C_6H_4CO_2H$ (76)
5	$2\text{-}CH_3C_6H_4Br$	$2\text{-}CH_3C_6H_4CO_2H$ (55)
6	$4\text{-}CH_3OC_6H_4Br$	$4\text{-}CH_3OC_6H_4CO_2H$ (75)
7	$3\text{-}CH_3OC_6H_4Br$	$3\text{-}CH_3OC_6H_4CO_2H$ (78)
8	$4\text{-}CH_3COC_6H_4Br$	$4\text{-}CH_3COC_6H_4CO_2H$ (88) (85)[c]
9	$4\text{-}ClC_6H_4Br$	$4\text{-}ClC_6H_4CO_2H$ (85)
10	$3\text{-}ClC_6H_4Br$	$3\text{-}ClC_6H_4CO_2H$ (66)
11	$2\text{-}BrC_6H_4Br$	$2\text{-}C_6H_4(CO_2H)_2$ (5)
12	$4\text{-}NCC_6H_4Br$	$4\text{-}NCC_6H_4CO_2H$ (87)
13	$4\text{-}HOC_6H_4Br$	$4\text{-}HOC_6H_4CO_2H$ (45)
14	$2\text{-}HOC_6H_4Br$	$2\text{-}HOC_6H_4CO_2H$ (22)
15	$4\text{-}(H_3C)_2NC_6H_4Br$	$4\text{-}(H_3C)_2NC_6H_4CO_2H$ (80)
16	$4\text{-}O_2NC_6H_4Br$	$4\text{-}O_2NC_6H_4CO_2H$ (74)
17	1-bromonaphthalene	1-naphthoic acid (82)
18	2-bromonaphthalene	2-naphthoic acid (85) (81)[c]

[a] Reaction conditions: aromatic halide (1 mmol), calcium formate (0.6 mmol), $PdCl_2$ (0.05 mmol), and PPh_3 (0.3 mmol) were heated (120 °C/20 h) in DMF/benzene (1:1) under 3 atm of carbon monoxide. [b] Determined as the methyl esters by GC or HPLC. [c] Isolated yields.

Scheme I



species (3), which subsequently produces mixed formic anhydride by reductive elimination. A a result of thermal instability of formic anhydrides,[7] this is followed by thermal decarbonylation of the anhydride and gives the benzoic acid derivative. Indeed, the uncatalyzed reaction of benzoyl halide and sodium formate, at 120 °C in benzene/DMF solution, gave a quantitative yield of equivalent amounts of benzoic acid and carbon monoxide (determined by GC), as a result of rapid decomposition of the formed anhydride (eq 4). The differences in the

$$ArCOCl + NaO_2CH \rightarrow [ArCO_2CHO] \rightarrow ArCO_2H + CO \quad (4)$$

reaction pattern of formate salts with various metallic counterions support a mechanism that involves formation of two different benzoylpalladium intermediates: formyl (3) and hydroxycarbonyl benzoylpalladium (4). A rapid equilibrium between such intermediates is incompatible with the observed differences in reactivity of various metal ions. Factors such as reaction temperature and solvent polarity seem to control the selection of one of the two reaction modes A or B.

No carboxylation occurs when calcium formate is reacted with an aryl bromide in the absence of carbon monoxide.

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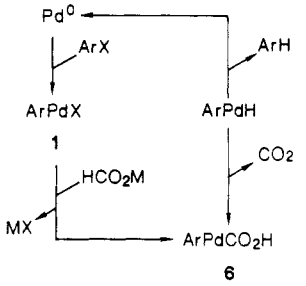
Scheme II



Thus, when the reaction of *o*-chlorobromobenzene with calcium formate is carried out under an argon atmosphere, only catalyzed reductive debromination occurs and chlorobenzene (67 mol % yield) is the only product obtained. On the other hand, hydrogenolysis is negligible under carbon monoxide atmosphere and only 2–10 % of reductive debromination was observed under the reaction conditions cited in Table II.

A reaction with ^{13}C-labeled calcium formate (99.9% enriched) was carried out, in order to show that the carbonyl group in the product is introduced via carbonylation process and not by a direct carboxylation with a formate ion. Indeed, the isolated benzoic acid was found to be less than 2% ^{13}C-enriched, while 95% of the ^{13}C was found in the gaseous phase as ^{13}CO,[8] confirming the decarbonylation of the formate as shown in eq 1. The dehalogenated byproduct could be the result of direct hydrogenolysis of the arylpalladium intermediate (Scheme I, 1) with the formate ion, as suggested previously.[4b] The predominancy of the carbonylation of the aryl halides (even under low carbon monoxide pressures) supports a mechanism including a fast carbonylation of the arylpalladium intermediate (Scheme I, 1), as proposed also for the methoxycarbonylation reaction.[6] The fact that no direct carboxylation was found indicates that in the absence of carbon monoxide an arylpalladium carboxylate intermediate (Scheme II, 6), if generated, would tend to undergo a decarboxylation reaction, analogously to the decarboxylation of benzoylpalladium carboxylate (Scheme I, 4).

Experimental Section

Commercially CP grade aryl halides were used without purification. Solvents were dried on 4A molecular sieves and distilled before use. Formate salts were dried under reduced pressure at 100–140 °C. Carbon monoxide was CP grade.

^{13}C-Labeled calcium formate was prepared by reacting 99.9% enriched formic-^{13}C acid (10% excess) and calcium hydroxide. Excess water and formic acid were evaporated in vacuo at 50 °C. HPLC separations were performed on a Varian 5000 unit with a MCH-5 column (40 × 15 cm) and H_2O/MeCN (35:65) as eluent. GC determinations were performed on a HP gas chromatograph, Model 7620A, using a 20% diethylene glycol succinate column ($^1/_4$ in. × 4 ft), for reactant and product identification or determination, and a 13X molecular sieve column ($^1/_4$ in. × 6 ft) for CO, H_2, and N_2 determination in the gas. The reactions were performed in a glass pressure reaction vessel provided with a magnetic stirrer and connected to a pressure gauge.

General Procedure for Hydroxycarbonylation of Aryl Halides. Palladium dichloride (9 mg, 0.05 mmol), triphenylphosphine (79 mg, 0.3 mmol), 4-chlorobromobenzene (191 mg, 1 mmol), and anhydrous calcium formate (78 mg, 0.6 mmol) were placed in the reaction vessel. After the mixture was purged several times with nitrogen, *N,N*-dimethylformamide (DMF) (4 mL) and benzene (4 mL) were introduced via a syringe through a rubber septum. Carbon monoxide was added and removed several times to ensure a pure CO atmosphere. The vessel was sealed pressurized with 50 psi of carbon monoxide. The mixture was heated on an oil bath to 120 °C (±2) for 20 h. Then, the reaction mixture was cooled to room temperature and filtered to separate the precipitated salts. The solution was left to react overnight with an excess of methyl iodide and potassium carbonate to give the methyl ester (0.85 mmol, 85%) as determined by GC and HPLC. Isolation of the pure acid was achieved by addition of 10 mL of aqueous sodium hydroxide (2 N), followed by continued extraction with benzene. After the removal of DMF, the aqueous solution was acidified to pH 2 with concentrated HCl and the precipitating organic acid was separated by filtration and dried in vacuo.

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Registry No. $PdCl_2$, 7647-10-1; PPh_3, 603-35-0; C_6H_5Br, 108-86-1; C_6H_5I, 591-50-4; 4-$CH_3C_6H_4Br$, 106-38-7; 3-$CH_3C_6H_4Br$, 591-17-3; 2-$CH_3C_6H_4Br$, 95-46-5; 4-$CH_3OC_6H_4Br$, 104-92-7; 3-$CH_3OC_6H_4Br$, 2398-37-0; 4-$CH_3COC_6H_4Br$, 99-90-1; 4-ClC_6H_4Br, 106-39-8; 3-ClC_6H_4Br, 108-37-2; 2-BrC_6H_4Br, 583-53-9; 4-NCC_6H_4Br, 623-00-7; 4-HOC_6H_4Br, 106-41-2; 2-HOC_6H_4Br, 95-56-7; 4-$(CH_3C)_2NC_6H_4Br$, 586-77-6; 4-$O_2NC_6H_4Br$, 586-78-7; $C_6H_5CO_2H$, 65-85-0; 4-$CH_3C_6H_4CO_2H$, 99-94-5; 3-$CH_3C_6H_4CO_2H$, 99-04-7; 2-$CH_3C_6H_4CO_2H$, 118-90-1; 4-$CH_3OC_6H_4CO_2H$, 100-09-4; 3-$CH_3OC_6H_4CO_2H$, 586-38-9; 4-$CH_3COC_6H_4CO_2H$, 586-89-0; 4-$ClC_6H_4CO_2H$, 74-11-3; 3-$ClC_6H_4CO_2H$, 535-80-8; 2-$C_6H_4(CO_2H)_2$, 88-99-3; 4-$NCC_6H_4CO_2H$, 619-65-8; 4-$HOC_6H_4CO_2H$, 99-96-7; 2-$HOC_6H_4CO_2H$, 69-72-7; 4-$(H_3C)_2NC_6H_4CO_2H$, 619-84-1; 4-$O_2NC_6H_4CO_2H$, 62-23-7; LiO_2CH, 556-63-8; NaO_2CH, 141-53-7; KO_2CH, 590-29-4; $Ca(O_2CH)_2$, 544-17-2; $Ba(O_2CH)_2$, 541-43-5; 1-bromonaphthalene, 90-11-9; 2-bromonaphthalene, 580-13-2; 1-naphthoic acid, 86-55-5; 2-naphthoic acid, 93-09-4; 4-chlorobenzaldehyde, 104-88-1.

(8) ^{13}C content in the benzoic acid was determined by ^{13}C NMR and from the molecular peak of its mass spectra. ^{13}CO was analyzed by GC and high resolution MS.