

Report

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from Aryl Iodides and Acetic Formic Anhydride**

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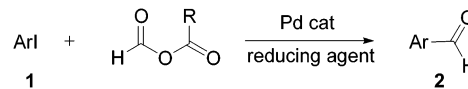
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Introduction. The palladium-catalyzed carbonylation of aryl halides in the presence of carbon monoxide is a key step in many synthetic protocols targeting the preparation of carbonyl-containing derivatives.¹ The procedure is quite simple and usually tolerates a wide range of functionalities. Carbon monoxide is reactive, inexpensive, and readily available; however, because of its high toxicity, the use of pressurized carbon monoxide requires carefully assembled gas delivery systems, and it is not always convenient. In addition, modern pharmaceutical methodologies for the discovery and production of new substances based on combinatorial and high-throughput methods² have led to a demand for automated handling and distribution of liquids and solids rather than of new advanced gas delivery systems. Carbonylation reactions that require heating can only be carried out in closed vessels; therefore, the development of reliable techniques in which carbon monoxide is gradually generated in situ is a target of great current interest in general and is much more so for combinatorial and high-throughput chemistry.

The use of nickel tetracarbonyl³ and molybdenum hexacarbonyl⁴ as carbon monoxide releasing reagents has been suggested. However, metal carbonyls (particularly nickel tetracarbonyl) are very toxic reagents. In addition, nickel tetracarbonyl is used in a six-fold excess and molybdenum hexacarbonyl in a 0.5 equiv amount. Clearly, the use of inexpensive organic materials would be greatly desirable, and indeed, inexpensive and readily available organic compounds have been used as carbon monoxide sources in palladium-catalyzed carbonylation reactions. However, only carboxylic acids and some of their derivatives (esters and amides) have been prepared by using these procedures. DMF has been shown to act as an efficient source of carbon monoxide (and dimethylamine) under controlled microwave irradiation conditions (180 °C, 15 min).⁵ The reaction affords dimethylamides (in the absence of other amines) and aryl amides (when excess amines are added to the reaction mixture) from aryl bromides in good to high yield in the presence of imidazole and an excess of potassium *tert*-butoxide. Alkyl formates undergo a decarbonylation reaction in the presence of strong alkoxide bases, but this limits the

Scheme 1



reaction to the synthesis of esters.⁶ Esters have also been prepared by using 2-pyridylmethyl formate in the presence of a Ru₃(CO)₁₂/PdCl₂ bimetallic catalytic system in DMF at 135 °C. Decarbonylation of the formate ester releases carbon monoxide and a carbinol, which is transferred to the σ -acylpalladium intermediate to afford an ester derivative.⁷ Chloroform and aqueous alkali have been utilized to perform palladium-catalyzed carbonylations of organic halides to carboxylic acids.⁸ The reaction uses dichlorocarbene, generated in situ, as a carbon monoxide equivalent and is considered to proceed through palladium carbene complexes. Carboxylic acids have also been obtained from aryl iodides by using an acetic anhydride/lithium formate mixture as a source of carbon monoxide, most probably through a process involving the intermediacy of mixed anhydrides.⁹

Our continuing interest in carbonylation reactions, and particularly, in the conversion of aryl halides into the corresponding aldehydes, prompted us to explore the extension of the in situ liberation methodology to the synthesis of aldehydes. Our study was based on the idea that a formate derivative containing a weak nucleophile bound to the carbonyl group could undergo a decarbonylation reaction under mild conditions without requiring a strong alkoxide base and avoiding the concomitant liberation of a nucleophile able to trap σ -acylpalladium intermediates, as observed with formate esters.^{6,7} According to our working hypothesis, σ -acylpalladium intermediates, formed via reaction of carbon monoxide generated in situ with σ -arylpalladium intermediates [initially created from Pd(0) and aryl iodides], could be trapped by appropriate reagents (in our case, a hydride donor) to give the desired aldehyde derivatives. We focused our attention on the use of thermally unstable formic anhydrides¹⁰ containing carboxylate leaving groups as sources of carbon monoxide (Scheme 1).

Herein we report the results of this study.

Results and Discussion. The reaction of *p*-iodoanisole with trifluoroacetic anhydride (2 equiv) and HCOOLi (3 equiv) in the presence of EtN(Pr-*i*)₂ (2 equiv), Pd₂(dba)₃ (0.025 equiv), dppe [1,1'-bis(diphenylphosphino)ethane] (0.05 equiv) in anhydrous DMF at 80 °C was initially examined as the model system. HCOOLi would play the double role of generating formic trifluoroacetic anhydride in situ, via reaction with trifluoroacetic anhydride, and reducing¹¹ the σ -acylpalladium intermediate to the corresponding aldehyde. However, after 60 h, *p*-anisaldehyde was obtained in only 33% yield, and the starting *p*-iodoanisole was recovered in 60% yield. Trace amounts of *p*-anisic acid were also obtained. Prolonging the reaction time to 7 days or increasing the temperature to 100 °C produced only a slight increase of the yield (*p*-anisaldehyde was obtained in 42 and 39%, respectively). No significant changes were

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Table 1. Solvents, Ligands, and Reducing Agents in the Synthesis of *p*-Anisaldehyde from *p*-Iodoanisole and Preformed Acetic Formic Anhydride^a

entry	solvent	[Pd]	ligand	reducing agent	time (h)	T (°C)	yield % of <i>p</i> -anisaldehyde
1	DMF	Pd ₂ (dba) ₃	dppe	Et ₃ SiH	24	80	65
2	DMF	Pd ₂ (dba) ₃	dppe	Et ₃ SiH	24	80	54 ^b
3	DMF	Pd ₂ (dba) ₃	Xantphos	Et ₃ SiH	24	80	30
4	DMF	Pd ₂ (dba) ₃	dppe	Oct ₃ SiH	24	80	65
5	DMF	Pd ₂ (dba) ₃	dppp	Oct ₃ SiH	24	80	67
6	DMF	Pd ₂ (dba) ₃	dppb	Oct ₃ SiH	24	80	7
7	THF	Pd ₂ (dba) ₃	dppe	Oct ₃ SiH	24	80	11
8	MeCN	Pd ₂ (dba) ₃	dppe	Et ₃ SiH	24	80	63
9	MeCN	Pd ₂ (dba) ₃	dppe	Oct ₃ SiH	24	80	50
10	MeCN	Pd ₂ (dba) ₃	dppe	Et ₃ SiH	24	80	55
11	MeCN	Pd/C5%	dppe	Et ₃ SiH	48	80	64
12	MeCN	Pd/C5%	dppe	Et ₃ SiH	48	60	70
13	MeCN	Pd/C5%	dppe	Et ₃ SiH	48	60	34
14	MeCN	Pd ₂ (dba) ₃	dppe	Et ₃ SiH	48	60	72

^a Unless otherwise stated, reactions were carried out on a 0.855-mmol scale, in 3 mL of anhydrous solvent, using 1 equiv of *p*-iodoanisole, 2 equiv of acetic formic anhydride, 5 mol % of [Pd], 0.05 equiv of dppe (when used), 1.5 equiv of silane, and 1.5 equiv of EtN(Pr-*i*)₂ in 3 mL of solvent. ^b In the presence of 3 equiv of LiCl.

observed by using a variety of monodentate or bidentate phosphine ligands, such as P(2-furyl)₃, dppp [1,1'-bis(diphenylphosphino)propane], dppb [1,1'-bis(diphenylphosphino)butane], or PdCl₂(dppp).

Addition of a different reducing agent, such as Et₃SiH (1.5 equiv), to the above HCOOLi/trifluoroacetic anhydride combination so as to favor the conversion of the σ -acylpalladium intermediate into the corresponding aldehyde led to a high conversion of *p*-iodoanisole after 24 h. However, *p*-anisaldehyde was formed in trace amounts, if any, as a result of competitive reactions we have not further investigated. When the same reaction was carried out substituting acetic anhydride for trifluoroacetic anhydride to generate a less reactive mixed anhydride, *p*-anisaldehyde was isolated in 30% yield, the main product being anisole obtained in 55% yield (trace amounts of *p*-anisic acid were also observed). Apparently, under these conditions, reduction of σ -arylpalladium intermediates is faster than their conversion into σ -acylpalladium intermediates. We surmised that this could be the result of a low concentration of carbon monoxide, in turn depending on a relatively slow reaction rate for the formation of acetic formic anhydride from lithium formate and acetic anhydride.

Therefore, we decided to investigate the utilization of preformed acetic formic anhydride, which can be readily prepared from acetyl chloride and sodium formate.¹² Pleasingly, preformed formic acetic anhydride and Et₃SiH produced the desired aldehyde in 65% yield after 24 h at 80 °C. Anisole was also obtained in 20% yield. Control experiments were performed to evaluate the efficiency of this protocol. The influence of solvents, ligands, palladium compounds, and temperature were briefly investigated. Some results from this study are summarized in Table 1.

Using the more expensive Oct₃SiH provided similar results in DMF, in the presence of both dppe and dppp (Table 1, compare entry 1 with entries 4 and 5). Other ligands, such as dppb and Xantphos [9,9-dimethyl-4,6-bis(diphenylphosphino)xanthene]¹³ gave unsatisfactory results (Table 1, entries 3 and 6). MeCN was found to be as effective as DMF with Et₃SiH (Table 1, entry 8) and to give better results with other electron-rich or neutral aryl iodides (Table 2, compare entry

Table 2. Palladium-Catalyzed Synthesis of Aldehydes **2** from Aryl Iodides **1** and Acetic Formic Anhydride^a

entry	aryl iodide 1	procedure	yield % of 2 ^b	
1	<i>p</i> -MeO-C ₆ H ₄ -I	A	72	2a
2	<i>m</i> -MeO-C ₆ H ₄ -I	A	60	2b
3	<i>p</i> -Me-C ₆ H ₄ -I	A	82	2c
4	<i>o</i> -Me-C ₆ H ₄ -I	A	50	2d
5	<i>p</i> -MeCONH-C ₆ H ₄ -I	A ^c	75	2e
6	<i>p</i> -MeCONH-C ₆ H ₄ -I	A ^{c,d}	51	2e
7	<i>p</i> -EtOOC-C ₆ H ₄ -I	B ^e	71	2f
8	<i>p</i> -EtOOC-C ₆ H ₄ -I	B ^{f,g}	57	2f
9	<i>p</i> -HOOC-C ₆ H ₄ -I	B	76	2g
10	<i>m</i> -HOOC-C ₆ H ₄ -I	B	66	2h
11	<i>p</i> -MeCO-C ₆ H ₄ -I	B	83	2i
12	2-Me-5-NO ₂ -C ₆ H ₃ -I	B	62	2j
13	4-Me-3-NO ₂ -C ₆ H ₃ -I	B	62	2k
14	<i>p</i> -NO ₂ -C ₆ H ₄ -I	B	25	2l

^a Unless otherwise stated, reactions were carried out at 60 °C for 48 h on a 0.855-mmol scale in 3 mL of anhydrous solvent using, procedure A, 1 equiv of aryl iodide, 2 equiv of acetic formic anhydride, 0.025 equiv of Pd₂(dba)₃, 0.05 equiv of dppe, 1.5 equiv of Et₃SiH, and 2 equiv of EtN(Pr-*i*)₂ in 3 mL of MeCN; procedure B, 1 equiv of aryl iodide, 2 equiv of acetic formic anhydride, 0.025 equiv of Pd₂(dba)₃, 0.05 equiv of dppe, 1.5 equiv of Et₃SiH, 2 equiv of EtN(Pr-*i*)₂, 3 equiv of LiCl in 3 mL of DMF. ^b All products gave appropriate ¹H and ¹³C NMR and IR spectra. ^c 65 h. ^d In DMF. ^e **2f** was isolated in 62% yield when the reaction was carried out with 4 equiv of anhydride at 80 °C for 30 h. ^f In MeCN, using 0.05 equiv of Pd/C 5%. Ethyl benzoate, derived from the reduction of the corresponding arylpalladium oxidative addition complex, was isolated in 22% yield. When the same reaction was run omitting LiCl, the aldehyde product was isolated in 18% yield. ^g 4 days.

5 with entry 6). The highest yield was obtained by using Et₃SiH in MeCN and lowering the reaction temperature to 60 °C, although a longer reaction time was required (Table 1, entry 14). Interestingly, employing Pd/C 5% under the same conditions afforded *p*-anisaldehyde in comparable yield (Table 1, entry 12). Most probably, the active species was a soluble Pd-dppe complex that was formed via leaching of palladium into solution.¹⁴ Accordingly, *p*-anisaldehyde was formed in only 34% yield when the same reaction was carried out omitting dppe (Table 1, entry 13).

Using the best conditions found for *p*-iodoanisole [acetic formic anhydride, Pd₂(dba)₃, dppe, Et₃SiH, EtN(Pr-*i*)₂, MeCN, 60 °C, 48 h], *p*-iodoacetophenone, a model electron-

poor aryl iodide, gave the corresponding aldehyde in 45% yield. Some reaction parameters were reexamined. In particular, we found that adding 3 equiv of LiCl to the reaction mixture led to a significant increase of the yield (64%). A similar trend was observed using Pd/C 5% (32% yield without LiCl; 55% yield with LiCl). Best results, however, were obtained by adding LiCl and using DMF as the solvent. Most probably, cation solvation played a role in the reaction. Under these conditions [acetic formic anhydride, Pd₂(dba)₃, dppe, Et₃SiH, EtN(Pr-*i*)₂, LiCl, DMF, 60 °C, 40 h], the aldehyde product was isolated in 83% yield. Omitting EtN(Pr-*i*)₂ led to the formation of the aldehyde in only 39% yield (*p*-iodoacetophenone was recovered in 48% yield), whereas substituting Pd(OAc)₂ [possibly reduced to Pd(0) species in the presence of Et₃SiH] for Pd₂(dba)₃ gave the aldehyde in 20% yield along with 20% of recovered aryl iodide.

Therefore, two general procedures were employed when the reaction was extended to include other aryl iodides.¹⁵ Procedure A (with neutral, electron-rich, and slightly electron-poor aryl iodides): aryl iodide, acetic formic anhydride, Pd₂(dba)₃, dppe, Et₃SiH, EtN(Pr-*i*)₂, 60 °C in MeCN. Procedure B (with electron-poor aryl iodides): aryl iodide, acetic formic anhydride, Pd₂(dba)₃, dppe, Et₃SiH, EtN(Pr-*i*)₂, LiCl at 60 °C in DMF.

Under these conditions, the reaction gives benzaldehydes in good to high yields with many neutral, electron-rich, and electron-poor aryl iodides and tolerates a variety of functional groups, including ether, ester, amide, carboxylic acid, and ketone groups. The best results obtained during this study are summarized in Table 2. Ortho substituents are tolerated (Table 2, entries 4 and 12). Only in the presence of the strongly electron-withdrawing nitro group was the corresponding aldehyde obtained in low yield (Table, entry 14); however, the concomitant presence of nitro and methyl substituents was found to produce the desired aldehyde in good yield (Table 2, entries 12 and 13).

In summary, we have demonstrated that acetic formic anhydride can be successfully used as a source of carbon monoxide in the palladium-catalyzed conversion of aryl iodides into benzaldehydes under mild conditions. The reaction tolerates important functional groups, including ether, ester, amide, carboxylic acid, and ketone groups, and compares well with most common procedures based on the palladium-catalyzed reaction in the presence of carbon monoxide.^{11,16} This in situ carbon monoxide generation methodology can be particularly useful for small-scale reactions or when the utilization of carbon monoxide using gas delivery systems is impractical, as in the synthesis of compound libraries.

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Supporting Information Available. Experimental procedures and complete description of product characterization. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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