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Palladium-Catalyzed Hydroxycarbonylation of Aryl and Vinyl Halides or Triflates by Acetic Anhydride and Formate Anions[†]

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ABSTRACT

$$\mathrm{RX} \xrightarrow[\text{DMF, 80 °C}]{\substack{\text{Pd cat} \\ \text{Ac}_2\text{O, HCOOLi} \\ \text{EtNPr}^i{}_2\text{, LiCl}}} \mathrm{RCOOH}$$

R = aryl, vinyl
X = I, Br, OTf

The palladium-catalyzed reaction of aryl and vinyl halides or triflates in the presence of acetic anhydride and lithium formate as a condensed source of carbon monoxide provides an efficient simple route to the synthesis of the corresponding carboxylic acids. The reaction proceeds very smoothly under mild conditions and tolerates a wide range of functional groups, including ether, ketone, ester, and nitro groups. The presence of ortho substituents does not hamper the reaction. Labeled carbonyl products can be easily prepared by using $H^{13}COONa$.

The palladium-catalyzed conversion of aryl and vinyl halides or triflates into the corresponding carboxylic acids in the presence of carbon monoxide is a key step in many synthetic protocols, particularly in the synthesis of biologically active compounds.[1] The procedure is quite general (in terms of the level of substituents tolerated in the aryl or vinyl fragment), efficient, and simple. Carbon monoxide is readily available, reactive, and cheap. However, it possesses some disadvantages. It is a highly toxic gas that, for safety reasons, is not always convenient to use. It must be stored and transported in stainless steel cylinders, and when it is used, losses must be avoided through carefully assembled gas delivery systems. In addition, the widespread acceptance in pharmaceutical industry of combinatorial chemistry, together with high-throughput screening,[2] for the discovery and production of new substances has led to a demand for automated handling of liquids and solids rather than of new advanced gas delivery systems. For these reasons, the development of techniques where carbon monoxide is gradually generated in situ is a target of great current interest.[3]

[†] Dedicated to Professor Domenico Misiti on the occasion of his 70th birthday.

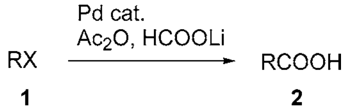
(1) For recent examples, see: (a) Frenette, R.; Hutchinson, J. H.; Leger, S.; Therien, M.; Brideau, C.; Chan, C. C.; Charleson, S.; Ethier, D.; Guay, J.; Jones, T. R.; McAuliffe, M.; Piechuta, H.; Riendeau, D.; Tagari, P.; Girard, Y. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2391. (b) Klein, L. L.; Li, L. *Curr. Pharm. Design* **1999**, *5*, 57. (c) Yu, M. S.; Baine, N. H. *Tetrahedron Lett.* **1999**, *40*, 3123. (d) Henley, P. D.; Kilburn, J. D. *Chem. Commun.* **1999**, 1335. (e) Miller, W. H.; Bondinell, W. E.; Cousins, R. D.; Erhard, K. F.; Jakas, D. R.; Keenan, R. M.; Ku, T. W.; Newlander, K. A.; Ross, S. T.; Haltiwanger, R. C.; Bradbeer, J.; Drake, F. H.; Gowen, M.; Hoffman, S. J.; Hwang, S.-M.; James, I. E.; Lark, M. W.; Lechowska, B.; Rieman, D. J.; Stroup, G. B.; Vasko-Moser, J. A.; Zembryki, D. L.; Azzarano, L. M.; Adams, P. C.; Salyers, K. L.; Smith, B. R.; Ward, K. W.; Johanson, K. O.; Huffman, W. F. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1807. (f) Young, J. R.; Huang, S. X.; Chen, I.; Walsh, T. F.; DeVita, R. J.; Wyvratt, M. J., Jr.; Goulet, M. T.; Ren, N.; Lo, J.; Yang, Y. T.; Yudkovitz, J. B.; Cheng, K.; Smith, R. G. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1723. (g) Maltais, R.; Tremblay, M. R.; Poirier, D. *J. Comb. Chem.* **2000**, *2*, 604. (h) Herzner, H.; Palmacci, E. R.; Seeberger, P. H. *Org. Lett.* **2002**, *4*, 2965. (i) Baston, E.; Salem, O. I. A.; Hartmann, R. W. *J. Enzymol. Inhib. Med. Chem.* **2002**, *17*, 303. (j) Baston, E.; Salem, O. I. A.; Hartmann, R. W. *Arch. Pharm.* **2003**, *336*, 31.

(2) *Curr. Opin. Chem. Biol.* **2000**, *4*, 243 (whole issue).

10.1021/ol0354371 CCC: $25.00

Herein we report a new protocol for the palladium-catalyzed hydroxycarbonylation of aryl and vinyl halides or triflates utilizing the acetic anhydride/lithium formate combination as a condensed source of carbon monoxide (Scheme 1).

Scheme 1



During our ongoing studies on palladium-catalyzed hydroarylation reactions of alkynes with aryl halides using formate anions as reducing agents,[4] we observed that in the presence of acetic anhydride, benzoic acids could be obtained in addition to the expected hydroarylation products. We surmised that benzoic acids could arise through a palladium-catalyzed hydroxycarbonylation reaction where the acetic anhydride/formate anion mixture could serve as a source of carbon monoxide. As this technique of in situ delivery of carbon monoxide would be very suitable for the preparation of carboxylic acids in high-throughput and combinatorial synthesis, we decided to investigate the scope and limitations of this chemistry.

The reaction of ethyl *p*-iodobenzoate with acetic anhydride (2 equiv) and HCOOLi (3 equiv) in the presence of $Pd_2(dba)_3$ (0.025 equiv) in DMF was initially examined as the model system. We were pleased to find that, after 4 h at 80 °C, the corresponding benzoic acid could be isolated in 61% yield (Table 1, entry 1). The addition of LiCl[5] (Table 1, entry 2) or $EtN(Pr^i)_2$ (Table 1, entry 3) led to a significant increase in the yield, but the best result in terms of yield and reaction rate was obtained when both LiCl and $EtN(Pr^i)_2$ were employed (Table 1, entry 4). The use of other formate salts, HCOOK and HCOONa, was explored and showed that HCOOLi is clearly superior to the other two salts. Et_3N can also be used but proved to be less efficient than $EtN(Pr^i)_2$ (Table 1, compare entry 5 with entry 6, and entry 7 with entry 8). Replacement of HCOOLi by formic acid was found to be detrimental (the aromatic acid was isolated in 10% yield along with the biaryl byproduct, isolated in 55% yield).[6]

Table 1. Bases, LiCl, and Formate Salts in the Conversion of Ethyl *p*-Iodobenzoate into the Corresponding Benzoic Acid Derivative[a]

entry	formate salt	base	LiCl	time (h)	yield %[b]
1	HCOOLi		−	4	61
2	HCOOLi		+	5.5	73
3	HCOOLi	$EtN(Pr^i)_2$	−	4	80
4	HCOOLi	$EtN(Pr^i)_2$	+	3	91
5	HCOONa	$EtN(Pr^i)_2$	+	1.4	75
6	HCOONa	Et_3N	+	6	67
7	HCOOK	$EtN(Pr^i)_2$	+	22	81
8	HCOOK	Et_3N	+	28	59

[a] Reactions were conducted on a 0.855 mmol scale in starting organic halides in anhydrous DMF (3 mL) at 80 °C using 1 equiv of organic halide, 2 equiv of acetic anhydride, 3 equiv of formate salt, 3 equiv of LiCl, and 2 equiv of the amine base in the presence of 0.025 equiv of $Pd_2(dba)_3$. [b] Yields are given for isolated products.

The best conditions so far developed for ethyl *p*-iodobenzoate (1 equiv of aryl iodide, 2 equiv of acetic anhydride, 3 equiv of HCOOLi, 3 equiv of LiCl, and 2 equiv of $EtN(Pr^i)_2$ in the presence of 0.025 equiv of $Pd_2(dba)_3$ in DMF at 80 °C) were usually employed when we extended this novel route to carboxylic acids to a variety of aryl and vinyl halides and triflates as shown in Table 2. Under these conditions, the reaction proceeds very smoothly and appears to tolerate a wide range of functionalized aryl iodides, including those containing ethers, ketones, esters, and nitro groups. Carboxylic acids were isolated in high yields with a variety of electron-poor, neutral, slightly electron-rich, and strongly electron-rich aryl iodides. The presence of ortho substituents does not hamper the reaction (Table 2, entries 5, 11, 12, 17, 22). Only with *p*-iodoanisole, a model electron-rich aryl halide, was the corresponding acid isolated in only 43% yield. We then briefly went back and examined additional variables. It was observed that with this substrate, the best result (74% yield after 24 h) could be obtained by using 2 equiv of acetic anhydride and 3 equiv of HCOOK in the presence of 0.025 mol % $Pd_2(dba)_3$ in DMF at 80 °C; however, this procedure did not provide as high yields on a number of other starting materials as our standard procedure (compare, for example, entry 6 with entry 7 of Table 2) and has thus not been widely employed. Vinyl bromides and triflates also afforded **2** in good to high yields under our standard conditions (Table 2, entries 24−26). Aryl bromides and triflates appear to require the presence of phosphine ligands, and satisfactory results were obtained by using $PdCl_2(dppp)$ (Table 2, entries 3, 14, 15, 20). Indeed, when *p*-bromobiphenyl was subjected to our standard conditions, no carboxylic acid was observed after 24 h. Minor amounts of byproducts derived from reduction and coupling reactions of organopalladium intermediates were occasionally observed as well as trace amounts, if any, of acetophenone and benzaldehyde byproducts.

Interestingly, $Pd(OAc)_2$ (Table 2, entry 8) and Pd/C also turned out to be effective for the reaction (Table 2, entry 9).

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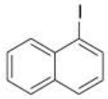
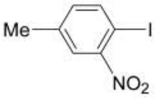
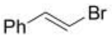
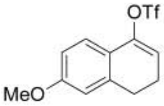
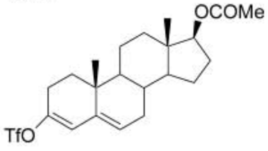
(3) (a) Carpentier, J.-F.; Castanet, Y.; Brocard, J.; Mortreux, A.; Petit, F. *Tetrahedron Lett.* **1991**, *32*, 4705. (b) Kaise, N.-F. K.; Hallberg, A.; Larhed, M. *J. Comb. Chem.* **2002**, *4*, 109. (c) Wan, Y.; Alterman, M.; Larhed, M.; Hallberg, A. *J. Org. Chem.* **2002**, *67*, 6232. (d) Shibata, T.; Toshida, N.; Takagi, K. *Org. Lett.* **2002**, *4*, 1619 and references therein. (e) Morimoto, T.; Fuji, K.; Tsutsumi, K.; Kakiuchi, K. *J. Am. Chem. Soc.* **2002**, *124*, 3806. (f) Ko, S.; Lee, C.; Choi, M.-G.; Na, Y.; Chang, S. *J. Org. Chem.* **2003**, *68*, 1607. (g) Morimoto, T.; Fujoka, M.; Fuji, K.; Tsutsumi, K.; Kakiuchi, K. *Chem. Lett.* **2003**, *32*, 154.

(4) Cacchi, S.; Fabrizi, G. Carbopalladation of Alkynes Followed by Trapping with Nucleophilic Reagents. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; John Wiley & Sons: New York, 2002; Vol. 1, pp 1335−1359.

(5) Cacchi, S.; Fabrizi, G.; Gavazza, F.; Goggiamani, A. *Org. Lett.* **2003**, *5*, 289.

(6) Reaction was conducted under the same conditions shown in Table 1, entry 4, substituting HCOOH for HCOOLi, in the presence of 5 equiv of $EtN(Pr^i)_2$.

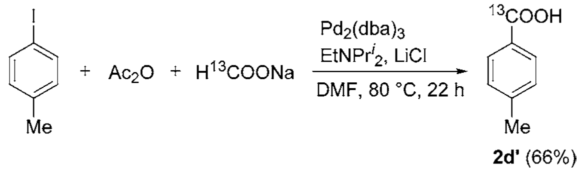
Table 2. Palladium-Catalyzed Synthesis of Carboxylic Acids **2** from Aryl and Vinyl Halides or Triflates **1**[a]

entry	organic halide or triflate **1**	time (h)	yield % of **2**[b]	
1	*p*-MeO-C_6H_4-I	24	74[c]	**2a**
2	*p*-MeO-C_6H_4-I	17	43	**2a**
3	*p*-MeO-C_6H_4-Br	64	53[d]	**2a**
4	*m*-MeO-C_6H_4-I	16	81	**2b**
5	*o*-MeO-C_6H_4-I	22	60	**2c**
6	*p*-Me-C_6H_4-I	22	89	**2d**
7	*p*-Me-C_6H_4-I	21	62[c]	**2d**
8	*p*-Me-C_6H_4-I	22	92[e]	**2d**
9	*p*-Me-C_6H_4-I	22	89[f]	**2d**
10	*m*-Me-C_6H_4-I	5.5	90	**2e**
11	*o*-Me-C_6H_4-I	24	84	**2f**
12		6	82	**2g**
13	PhI	20	90	**2h**
14	PhOTf	64	63[d]	**2h**
15	*p*-Ph-C_6H_4-Br	64	77[d]	**2i**
16	*p*-F-C_6H_4-I	19	73	**2j**
17	*o*-F-C_6H_4-I	7	66	**2k**
18	*p*-Cl-C_6H_4-I	21	70	**2l**
19	*p*-MeCO-C_6H_4-I	3	84	**2m**
20	*p*-MeCO-C_6H_4-Br	64	50[d]	**2m**
21	*p*-EtOOC-C_6H_4-I	3	91	**2n**
22		7	78	**2o**
23	*p*-NO_2-C_6H_4-I	2	88	**2p**
24		30	67[g]	**2q**
25		24	86[h]	**2r**
26		30	80[h]	**2s**

[a] Unless otherwise stated, reactions were conducted on a 0.855 mmol scale in starting organic halides in anhydrous DMF (3 mL) at 80 °C using 1 equiv of organic halide, 2 equiv of acetic anhydride, 3 equiv of HCOOLi, 3 equiv of LiCl, and 2 equiv of $EtN(Pr^i)_2$ in the presence of 0.025 equiv of $Pd_2(dba)_3$. [b] Yields are given for isolated products. [c] Performed with 1 equiv of organic halide, 2 equiv of acetic anhydride, and 3 equiv of HCOOK in the presence of 0.025 equiv of $Pd_2(dba)_3$. [d] Performed with 0.05 equiv of $PdCl_2(dppp)$. [e] Performed with 0.05 equiv of $Pd(OAc)_2$. [f] Performed with 0.05 equiv of 5% palladium on charcoal. [g] At 100 °C. [h] At 60 °C.

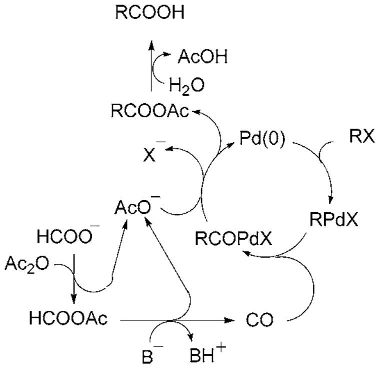
As shown in Scheme 2, the employment of the commercially available $H^{13}COONa$ allows for an easy way of introducing a labeled carbonyl into products. This reaction also shows that the formate anion is the source of the carbonyl group.

Scheme 2



We believe that the reaction involves the intermediacy of formic acetic anhydride (generated in situ by the reaction of the formate anion with acetic anhydride) that, as a result of thermal instability of formic anhydrides,[7] decarbonylates under reaction conditions (Scheme 3).[8] An acylpalladium complex is subsequently generated that reacts with acetate. Hydrolysis of the resultant mixed anhydride affords the carboxylic acid[9] (the carboxylic acid could also arise from a mixed formic anhydride, not shown in Scheme 3, derived from the reaction of the acylpalladium complex with formate).[10]

Scheme 3



The involvement of formic acetic anhydride as a condensed source of carbon monoxide is supported by control

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(7) Fife, W. K.; Zhang, Z.-d. *J. Org. Chem.* **1986**, *51*, 3744.

(8) Role of carbon monoxide generated via decarbonylation is supported by the following experiment. A mixture of HCOOLi (2.56 mmol), acetic anhydride (1.71 mmol), and $EtN(Pr^i)_2$ (1.71 mmol) in anhydrous DMF (1 mL) was stirred at room temperature for 1 h and, subsequently, at 80 °C for 1 h. After the mixture was cooled, argon was bubbled through the reaction mixture for 5 min. Then, ethyl *p*-iodobenzoate (0.85 mmol), $Pd_2(dba)_3$ (0.021 mmol), and LiCl (2.56 mmol) in anhydrous DMF (2 mL) were added. The reaction mixture was stirred at 80 °C for 3 h, but no evidence of the corresponding acid was attained (compare with Table 2, entry 21).

(9) For the palladium-catalyzed synthesis of carboxylic acids from aryl and vinyl halides or triflates via hydrolysis of mixed anhydrides, see: (a) Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1985**, *26*, 1109. (b) Pri-Bar, I.; Buchman, O. *J. Org. Chem.* **1988**, *53*, 624. (c) Baird, J. M.; Kern, J. R.; Lee, G. R.; Morgans, D. J., Jr.; Sparacino, M. L. *J. Org. Chem.* **1991**, *56*, 1928. (d) Cacchi, S.; Lupi, A. *Tetrahedron Lett.* **1992**, *33*, 3939. (e) Grushin, V. V.; Alper, H. *J. Am. Chem. Soc.* **1995**, *117*, 4305.

(10) Though our working hypothesis (Scheme 3) is consistent with the obtained results, we did not obtain experimental evidence of the formation of mixed anhydrides derived from acylpalladium complexes.

experiments, conducted with *p*-iodoanisole and preformed formic acetic anhydride,[11] whose results are presented in Table 3. The possibility that DMF can act as a carbon monoxide source[3c] could be ruled out on the basis of the observation that no carboxylic acid derivative was observed by subjecting *p*-iodoanisole to $Pd_2(dba)_3$, Et_3N, AcOK, and DMF at 80 °C for 24 h.

Table 3. Conversion of *p*-Iodoanisole into *p*-Anisic Acid by Using Preformed Formic Acetic Anhydride[a]

entry	base (equiv)	time (h)	anisic acid yield %[b]
1		16	12
2	Et_3N (2)	24	70
3	KOAc (2), HCOOK (1)	24	80

[a] Reactions were conducted on a 0.855 mmol scale in *p*-iodoanisole in anhydrous DMF (3 mL) at 80 °C using 1 equiv of *p*-iodoanisole, 2 equiv of formic acetic anhydride, and the amount of base reported in Table, in the presence of 0.025 equiv of $Pd_2(dba)_3$. [b] Yields are given for isolated products.

In conclusion, we have demonstrated that the palladium-catalyzed reaction of organic halides and triflates with formate salts in the presence of acetic anhydride provides an efficient, straightforward route to carboxylic acids. The reaction tolerates important functional groups and compares well with most common procedures based on the palladium-catalyzed reaction in the presence of carbon monoxide,[1] as well as with procedures based on the use of carbon monoxide-releasing agents.[12] It can be particularly useful when the utilization of common palladium-catalyzed reactions of organic halides or triflates in the presence of carbon monoxide using gas delivery systems is impractical, as in the synthesis of compound libraries. Furthermore, it can allow for an easy way of introducing a labeled carbonyl into products, without the need to use expensive labeled gaseous carbon monoxide. Research on the scope and limitations of this chemistry are actively underway in our laboratory.

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Supporting Information Available: Complete description of experimental details and product characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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[11] Formic acetic anhydride was prepared according to: Krimen, L. I. *Org. Synth.* **1970**, *50*, 1.

[12] Grushin, V. V.; Alper, H. *Organometallics* **1993**, *12*, 3846.