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Palladium-Catalyzed Fluorocarbonylation Using *N*-Formylsaccharin as CO Source: General Access to Carboxylic Acid Derivatives

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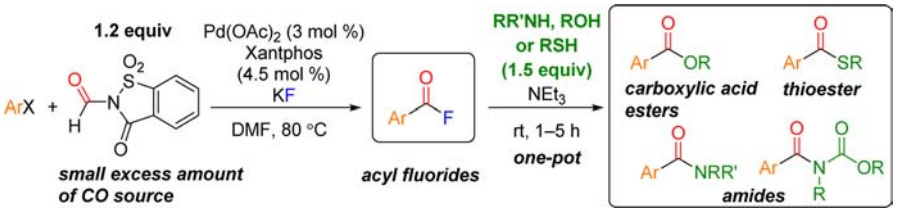
ABSTRACT



***N*-Formylsaccharin, an easily accessible crystalline compound, has been employed as an efficient CO source in Pd-catalyzed fluorocarbonylation of aryl halides to afford the corresponding acyl fluorides in high yields. The reactions use a near-stoichiometric amount of the CO source (1.2 equiv) and tolerate diverse functional groups. The acyl fluorides obtained could be readily transformed into various carboxylic acid derivatives such as carboxylic acid, esters, thioesters, and amides in a one-pot procedure.**

Palladium-catalyzed carbonylation reactions of aryl halides and related compounds in the presence of various nucleophiles are very convenient synthetic methods for diverse carbonyl-containing compounds. Since the pioneering work by Heck and co-workers in 1974,[1] significant efforts have been devoted to enhance the utility of these reactions as a synthetic tool and have enabled their large-scale application in industry.[2] Despite many significant improvements, the reaction conditions such as ligand, base, CO pressure, and temperature employed for each nucleophile varies from one system to another. In this respect, fluorocarbonylation of aryl halides to acyl fluorides is an especially attractive reaction, because acyl fluorides can be readily converted to diverse carbonyl compounds using different types of nucleophiles, and thus, this synthetic strategy has a significant advantage for the preparation of biologically active compound libraries. Despite such utility, there are only two reports on fluorocarbonylation.[3,4] Tanaka et al. reported the first Pd-catalyzed fluorocarbonylation of aryl iodides and bromides under a CO gas atmosphere in 1987.[3] Later, Okano and Kiji et al. reported the same transformation of aryl bromides in 1992.[4] Since

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(1) (a) Schoenberg, A.; Bartoletti, I.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3318. (b) Schoenberg, A.; Heck, R. F. *J. Am. Chem. Soc.* **1974**, *96*, 7761.

(2) For a review on Pd-catalyzed carbonylation of aryl halides and related compounds, see: Brennführer, A.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 4114.

(3) Sakakura, T.; Chaisupakitsin, M.; Hayashi, T.; Tanaka, M. *J. Organomet. Chem.* **1987**, *334*, 205.

(4) Okano, T.; Harada, N.; Kiji, J. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 1741.

(5) For a review on carbonylation without using toxic CO gas, see: (a) Morimoto, T.; Kakiuchi, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 5580. For a review on $Mo(CO)_6$ mediated carbonylation, see: (b) Odell, L. R.; Russo, F.; Larhed, M. *Synlett* **2012**, *23*, 685. Recent examples for the uses of CO surrogates: (c) Lee, H. W.; Chan, A. S. C.; Kwong, F. Y. *Chem. Commun.* **2007**, 2633. (d) Hermange, P.; Lindhardt, A. T.; Taaning, R. H.; Bjerglund, K.; Lupp, D.; Skrydstrup, T. *J. Am. Chem. Soc.* **2011**, *133*, 6061. (e) Friis, S. D.; Taaning, R. H.; Lindhardt, A. T.; Skrydstrup, T. *J. Am. Chem. Soc.* **2011**, *133*, 18114. (f) Morimoto, T.; Yamasaki, K.; Hirano, A.; Tsutsumi, K.; Kagawa, N.; Kakiuchi, K.; Harada, Y.; Fukumoto, Y.; Chatani, N.; Nishioka, T. *Org. Lett.* **2009**, *11*, 1777.

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then, this transformation has been rarely used and no progress has been made in regard to its utility.

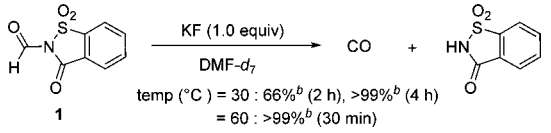
Because the highly toxic nature of CO gas is the major drawback of carbonylation reactions, CO-free carbonylation has been extensively researched. In the past decade in particular, several compounds have been developed as alternatives to toxic CO gas.[5] Although successful hydroxy-,[6] alkoxy-,[7] and aminocarbonylation[8] have been reported, fluorocarbonylation of aryl halides without the direct use of CO gas is not yet known.

Recently, we reported novel and practical methods for Pd-catalyzed alkoxycarbonylation and reductive carbonylation using a small excess amount (1.2−2.0 equiv) of a CO source such as phenyl formates[7a−c] and *N*-formylsaccharin (**1**).[9] In this approach, the decarbonylation of the CO source using a mild base (e.g., NEt_3 and Na_2CO_3) generates CO, which is then used in situ for the Pd-catalyzed carbonylation to afford the corresponding phenyl esters or aldehydes. Thus, this procedure provides a convenient access to esters and aldehydes without concerns about handling toxic CO gas. In particular, *N*-formylsaccharin (**1**)[10] has significant advantages such as low cost, good availability, ease of handling, stability, and high reactivity as a CO source. Owing to the low nucleophilicity of saccharin generated from **1**, the Pd-catalyzed carbonylations with various nucleophiles are expected to proceed without any interference from the saccharin species. Our continued interest in carbonylation reactions, particularly in the conversion of aryl halides into the corresponding acyl fluorides, prompted us to explore the Pd-catalyzed fluorocarbonylation using **1** as the CO source.

Herein, we report a novel and practical method for Pd-catalyzed fluorocarbonylation of aryl and alkenyl halides using **1**, which is an easily accessible and highly reactive crystalline CO surrogate. The reactions using a near-stoichiometric amount of the CO source (1.2 equiv) proceeded well and tolerated diverse functional groups. Moreover, the acyl fluorides obtained could be readily transformed into various carboxylic acid derivatives such as carboxylic acid, esters, thioesters, and amides in a one-pot procedure.

First, the decarbonylation of **1** with KF to generate CO and saccharin was investigated (Scheme 1). Rapid decarbonylation was observed at 60 °C, leading to the complete conversion of **1** within 30 min, indicating that **1** is a promising CO source for Pd-catalyzed fluorocarbonylation, in which KF is expected to serve a dual role not only as a nucleophile for Pd-catalyzed carbonylation but also as an activator for CO generation from **1**.

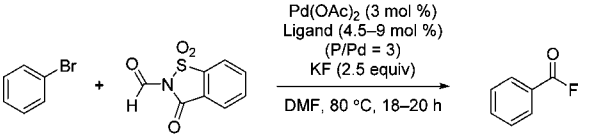
Scheme 1. Decarbonylation of **1** with KF[a]



[a] Reactions were conducted with 0.18 mmol of **1** and DMF-d_7 (0.75 mL). [b] Conversion was determined using ^{1}H NMR spectroscopy.

Encouraged by the above-mentioned results, the reaction of bromobenzene (**2a**) with 1.5 equiv of **1** and 2.5 equiv of KF was carried out in the presence of a catalytic amount of $Pd(OAc)_2$ and ligand (P/Pd = 3) (Table 1). The use of a monodentate phosphine ligand such as PPh_3 and P(*o*-Tol)$_3$ resulted in either low yield or none at all of the desired acyl fluoride **3a** (entries 1 and 2). Bidentate ligands such as DPPM, DPPE, DPPP, DPPB, DPPF, DPPBz, and *rac*-BINAP were ineffective for this transformation (entries 3−9). To our delight, the use of a bulky monodentate phosphine, P(*t*-Bu)$_3$, and a bidentate ligand with bite angles of 102°−111°, such as DPEphos and Xantphos,[11] improved the catalytic activity (entries 10−12). Among the ligands examined, Xantphos provided the best result, affording **3a** in 83% yield (entry 12).

Table 1. Pd-Catalyzed Fluorocarbonylation of **2a** with **1**[a]



entry	ligand	conv[b] (%)	yield[b] (%)
1	PPh_3	4	1
2	P(*o*-Tol)$_3$	6	0
3	DPPM	0	0
4	DPPE	1	0
5	DPPP	6	1
6	DPPB	10	3
7	DPPF	14	4
8	DPPBz	0	0
9	*rac*-BINAP	20	12
10	P(*t*-Bu)$_3$·HBF_4	57	42
11	DPEphos	55	51
12	Xantphos	86	83

[a] Reactions were conducted with 0.6 mmol of **2a** and anhydrous DMF (2 mL). [b] Determined using GC.

Further optimization of the reaction using Xantphos as the ligand was conducted (Table 2). The P/Pd ratio was

(6) (a) Cacchi, S.; Fabrizi, G.; Goggiamani, A. *Org. Lett.* **2003**, *5*, 4269. (b) Korsager, S.; Taaning, R. H.; Skrydstrup, T. *J. Am. Chem. Soc.* **2013**, *135*, 2891. (c) Berger, P.; Bessmernykh, A.; Caille, J.; Mignonac, S. *Synthesis* **2006**, *18*, 3106.

(7) Recent examples of alkoxycarbonylation without using CO gas: (a) Ueda, T.; Konishi, H.; Manabe, K. *Org. Lett.* **2012**, *14*, 3100. (b) Ueda, T.; Konishi, H.; Manabe, K. *Tetrahedron Lett.* **2012**, *53*, 5171. (c) Ueda, T.; Konishi, H.; Manabe, K. *Org. Lett.* **2012**, *14*, 5370. (d) Shang, R.; Fu, Y.; Li, J.; Zhang, S.; Guo, Q.; Liu, L. *J. Am. Chem. Soc.* **2009**, *131*, 5738. (e) Fujihara, T.; Hosoki, T.; Katafuchi, Y.; Iwai, T.; Terao, J.; Tsuji, Y. *Chem. Commun.* **2012**, *48*, 8012. (f) Schareina, T.; Zapf, A.; Cotte, A.; Gotta, M.; Beller, M. *Adv. Synth. Catal.* **2010**, *352*, 1205.

(8) For a review on metal-catalyzed aminocarbonylation, see: Roy, S.; Roy, S.; Gribble, G. W. *Tetrahedron* **2012**, *68*, 9867.

(9) Ueda, T.; Konishi, H.; Manabe, K. *Angew. Chem., Int. Ed.* **2013**, *52*, 8611.

(10) Cossy et al. developed *N*-formylsaccharin as a new formylating agent for amines: Cochet, T.; Bellosta, V.; Greiner, A.; Roche, D.; Cossy, J. *Synlett* **2011**, *13*, 1920. *N*-Formylsaccharin is commercially available from Tokyo Chemical Industry Co., Ltd. (TCI).

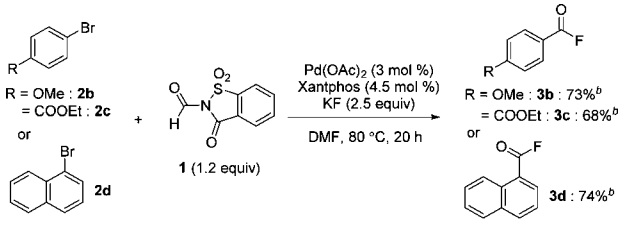
found to significantly affect the catalytic activity. The yield of **3a** reduced to 56% at P/Pd = 2 (entry 3); the use of excess phosphine (P/Pd = 3 and 4) prevented the precipitation of Pd black, thus affording the desired acyl fluoride in good yields (entries 1 and 2). The high yield was maintained even when a near-stoichiometric quantity of the CO source (1.2 equiv of **1**) was used (entry 4). When the quantity of KF was reduced to 1.2 equiv, the yield decreased to 39% (entry 5). Decreasing the concentration of the substrate increased the yield, indicating the importance of the amount of DMF (entry 6). The choice of fluoride reagent is key to the success of the reaction. Only KF[12] and CsF proved to be efficient fluoride reagents, while NaF and LiF resulted in poor yields (entries 6–9). When reducing the catalyst loading (0.5–1.0 mol %), the yields were significantly decreased to 47–59% (entries 10 and 11).

Table 2. Optimization of Fluorocarbonylation of **2a**[a]

entry	F^- (equiv)	**1** (equiv)	P/Pd	concn (M)	yield[b] (%)
1	KF (2.5)	1.5	4	0.3	79
2	KF (2.5)	1.5	3	0.3	83
3	KF (2.5)	1.5	2	0.3	56
4	KF (2.5)	1.2	3	0.3	85
5	KF (1.2)	1.2	3	0.3	39
6	KF (2.5)	1.2	3	0.2	94 (51)[c]
7	NaF (2.5)	1.2	3	0.2	6
8	LiF (2.5)	1.2	3	0.2	0
9	CsF (2.5)	1.2	3	0.2	85
10[d]	KF (2.5)	1.2	3	0.2	59
11[e]	KF (2.5)	1.2	3	0.2	47

[a] Reactions were conducted with 0.6 mmol of **2a** and 2–3 mL of anhydrous DMF in the presence of 3 mol % $Pd(OAc)_2$ and 3–6 mol % of Xantphos at 80 °C. The reaction time was 18–20 h. [b] Yield of **3a** determined using HPLC. [c] Isolated yield. [d] 1 mol % $Pd(OAc)_2$ and 1.5 mol % Xantphos (1.9 mmol scale of **2a**). [e] 0.5 mol % of $Pd(OAc)_2$ and 0.75 mol % Xantphos (1.9 mmol scale of **2a**).

Scheme 2. Pd-Catalyzed Fluorocarbonylation[a]

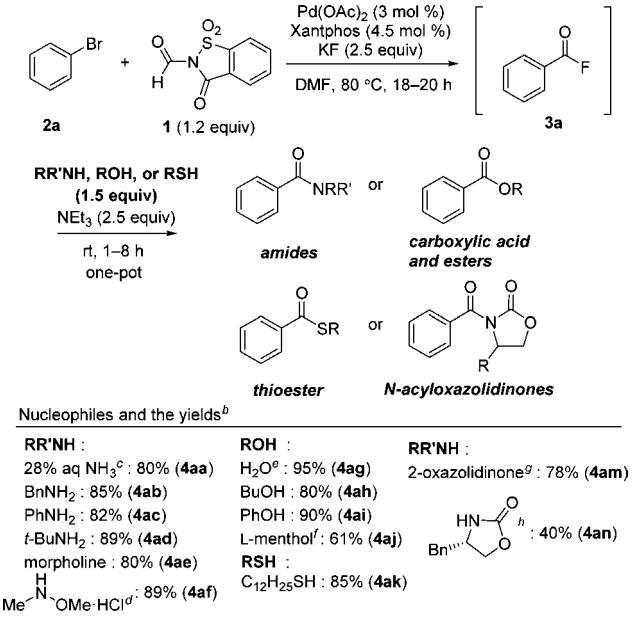


[a] Reactions were conducted with 1.8 mmol of aryl bromide (**2b**, **2c**, or **2d**) and 9 mL of anhydrous DMF. [b] Isolated yield.

(11) (a) van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Reek, J. N. H.; Dierkes, P. *Chem. Rev.* **2000**, *100*, 2741. Buchwald et al. used Pd-Xantphos for alkoxycarbonylation of aryl bromides under a CO atmosphere: (b) Martinelli, J. R.; Watson, D. A.; Freckmann, D. M. M.; Barder, T. E.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 7102.

(12) KF (>95%) was purchased from Wako Pure Chemical Industries, Ltd. and used as received. The use of spray-dried KF (>99%) did not affect the yield significantly.

Scheme 3. One-Pot Transformations to Various Carboxylic Acid Derivatives[a]



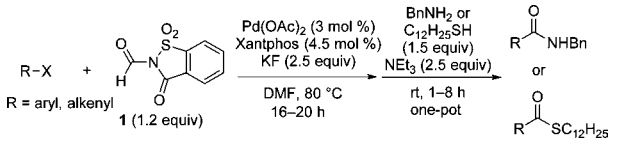
[a] Fluorocarbonylation was conducted with 0.6 mmol of **2a** and 3 mL of anhydrous DMF. [b] Isolated yield. [c] 10 equiv of 28% aq NH_3 were used. [d] 3.5 equiv of NEt_3 were used. [e] 10 equiv of H_2O were used. [f] At 45 °C. [g] Amidation was conducted with 3.5 equiv of NEt_3 and 0.1 equiv of DMAP at 80 °C. The reaction time was 16 h. [h] Amidation was conducted with 2.5 equiv of NEt_3 and 1 equiv of 0.5 M LiCl in THF at 50 °C. The reaction time was 18 h.

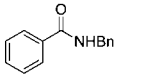
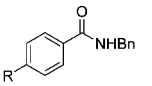
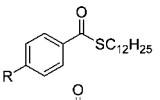
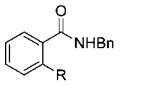
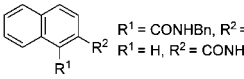
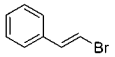
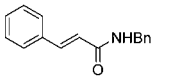
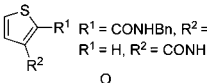
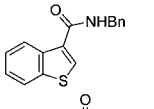
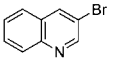
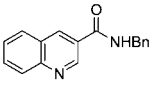
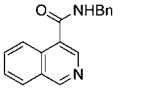
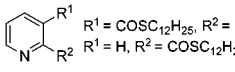
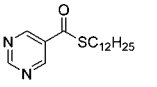
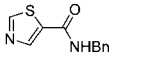
Moreover, Pd-catalyzed fluorocarbonylation of other electrophiles **2b–d** afforded the corresponding acyl fluorides in 68–74% yields (Scheme 2). Although the yields slightly decreased because of the hydrolysis of the products during purification, they could be isolated using silica gel column chromatography.

The success of this method in the fluorocarbonylation of aryl bromides to acyl fluorides suggested that this method could be further applied to the one-pot syntheses of various carboxylic acid derivatives (Scheme 3). After the fluorocarbonylation, 1.5 equiv of various amines were successfully coupled with acyl fluoride **3a** at room temperature, and the corresponding unsubstituted (**4aa**), *N*-monosubstituted (**4ab–ad**), *N*,*N*-disubstituted (**4ae**), and Weinreb amides (**4af**) were obtained in 80–89% yields.[13] One-pot esterification and thioesterification under the same reaction conditions afforded the corresponding esters (**4ag–aj**) and thioester (**4ak**) in 61–95% yields. Oxazolidinones, which are less reactive nucleophiles, also reacted to afford the corresponding *N*-acyloxazolidinones (**4am** and **4an**) in 40–78% yields.

(13) As another potential method to afford an amide, Pd-catalyzed carbonylation of **2a** with $BnNH_2$ (1.5 equiv) in the presence of *N*-formylsaccharin (1.2 equiv) and NEt_3 (2.5 equiv) as base without using KF was tested, but it did not afford **4ab** at all. This result emphasizes the advantage of the one-pot two-step procedure via acyl fluorides.

Table 3. Fluorocarbonylation of Various Aryl Halides and One-Pot Transformations to Amides or Thioesters[a]



entry	substrate	product		yield[b] (%)
1	X = Br (**2a**)		**4ab**	85
2	I (**2e**)		**4ab**	79
3	OTf (**2f**)		**4ab**	79
4	R = OMe (**2b**)		**4b**	91
5	Me (**2g**)		**4g**	91
6	CF_3 (**2h**)		**4h**	72
7	CO_2Et (**2c**)		**4c**	90
8	$CONMe_2$ (**2i**)		**4i**	83
9	NMe_2 (**2j**)		**4j**	72
10	CN (**2k**)		**4k**	82
11	 (**2l**)		**4l**	88
12	R = CHO (**2m**)		**4m**	76
13	$COCH_3$ (**2n**)		**4n**	79
14[c]	R = Me (**2o**)		**4o**	87
15[c]	= OMe (**2p**)		**4p**	33
16	X^1 = Br, X^2 = H (**2d**)		R^1 = CONHBn, R^2 = H (**4d**)	90
17	X^1 = H, X^2 = Br (**2q**)		R^1 = H, R^2 = CONHBn (**4q**)	87
18	 **2r** E/Z = 87/13		**4r**	83
19	X^1 = Br, X^2 = H (**2s**)		R^1 = CONHBn, R^2 = H (**4s**)	76
20	X^1 = H, X^2 = Br (**2t**)		R^1 = H, R^2 = CONHBn (**4t**)	81
21	 **2u**		**4u**	88
22	 **2v**		**4v**	83
23	 **2w**		**4w**	84
24	X^1 = Br, X^2 = H (**2x**)		R^1 = $COSC_{12}H_{25}$, R^2 = H (**4x**)	76
25	X^1 = H, X^2 = Br (**2y**)		R^1 = H, R^2 = $COSC_{12}H_{25}$ (**4y**)	43
26	 **2z**		**4z**	67
27	 **2za**		**4za**	43

[a] Reactions were conducted on a 0.6 mmol scale using aryl and alkenyl halides and phenyl triflate in anhydrous DMF (3 mL). [b] Isolated yield. [c] At 90 °C.

With the optimized reaction conditions in hand, we decided to test the generality of our protocol for fluorocarbonylation using 1.2 equiv of **1** in the presence of the Pd-Xantphos catalyst system and the subsequent one-pot transformations by amine ($BnNH_2$) or thiol ($C_{12}H_{25}SH$) nucleophiles (Table 3). It was found that, in addition to bromobenzene (**2a**) (85% yield), iodobenzene (**2e**) and phenyl triflate (**2f**) afforded **4ab** in good yields (79%, entries 1–3). Diverse functional groups (ester, amide, amine, cyano, dioxolane, aldehyde, and ketone) were tolerated in this reaction. Neither electron-donating nor electron-withdrawing groups at the 4-position seem to have any significant effect on the reaction yield (entries 4–13). However, the reaction of 2-bromoanisole (**2p**) resulted in a poor yield (entry 15). The protocol was found to work well with bromonaphthalene (entries 16 and 17). Alkenyl bromide **2r** also reacted to afford conjugated amide **4r** in 83% yield (entry 18). This reaction is also applicable to heteroaromatic systems. The reactions of bromothiophene and bromobenzothiophene proceeded well to afford **4s**–**u** in 76–88% yields (entries 19–21). Nitrogen-containing heterocycles such as quinoline, isoquinoline, pyridine, and pyrimidine also afforded the corresponding amides or thioesters in 43–84% yields (entries 22–26); the reaction of bromothiazole (**2za**) resulted in a 43% yield (entry 27).

In conclusion, we have reported a novel and practical method for the Pd-catalyzed fluorocarbonylation of aryl and alkenyl halides using *N*-formylsaccharin (**1**), an easily accessible and highly reactive crystalline CO surrogate. The reactions proceeded well by using a near-stoichiometric amount of the CO source (1.2 equiv) and tolerated diverse functional groups. The products, acyl fluorides, could be readily transformed into various carboxylic acid derivatives such as carboxylic acid, esters, thioesters, and amides in a one-pot procedure. This methodology enables the parallel synthesis of diverse carbonyl compounds using different types of nucleophiles under the common reaction conditions, which is a great advantage for the preparation of biologically active compound libraries. Moreover, the experimental procedure of the reaction is simple. Further studies on the application of this methodology to other CO-free Pd-catalyzed reactions will be reported in due course.

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Supporting Information Available. Experimental procedures and characterization data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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