ORGANIC LETTERS

2012
Vol. 14, No. 20
5370–5373

Trichlorophenyl Formate: Highly Reactive and Easily Accessible Crystalline CO Surrogate for Palladium-Catalyzed Carbonylation of Aryl/Alkenyl Halides and Triflates

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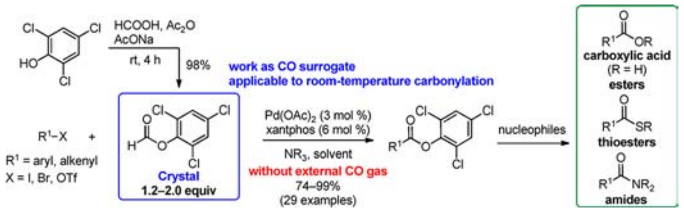
Received September 20, 2012

ABSTRACT



The high utility of 2,4,6-trichlorophenyl formate, a highly reactive and easily accessible crystalline CO surrogate, is demonstrated. The decarbonylation with NEt$_3$ to generate CO proceeded rapidly at rt, thereby allowing external-CO-free Pd-catalyzed carbonylation of aryl/alkenyl halides and triflates. The high reactivity of the CO surrogate enabled carbonylation at rt and significantly reduced the quantities of formate to near-stoichiometric levels. The obtained trichlorophenyl esters can be readily converted to a variety of carboxylic acid derivatives in high yields.

Because of its versatility for the regioselective synthesis of carbonyl-containing compounds, Pd-catalyzed carbonylation of aryl halides and related compounds employing CO has generated considerable interest in organic synthesis since the pioneering work of Heck et al. in 1974.[1] Continuous improvement of this class of transformations as a synthetic tool has so far enabled the efficient syntheses of numerous carbonyl compounds[2] and large-scale application in industry. However, this methodology possesses major problems such as its highly toxic nature and use of the colorless gaseous form of CO leading to problematic handling at both laboratory and multikilogram production scales. Additional safety measurements such as a CO detector and special waste treatment protocols are often required, thereby reducing the overall utility of this reaction. Therefore, there is significant interest in developing alternative methods without CO gas.[3] In this sense, various compounds such as formic acid derivatives[4] and metal

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(1) (a) Schoenberg, A.; Bartoletti, I.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3318. For a review on Pd-catalyzed carbonylation of aryl halides and related compounds, see: (b) Brennführer, A.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 4114.

(2) For recent examples of Pd-catalyzed carbonylations, see: (a) GØgsig, T. M.; Nielsen, D. U.; Lindhardt, A. T.; Skrydstrup, T. *Org. Lett.* **2012**, *14*, 2536. (b) Wu, X.; Neumann, H.; Beller, M. *Chem.—Eur. J.* **2012**, *18*, 3831.

(3) For a review on carbonylation without CO gas, see: Morimoto, T.; Kakiuchi, F. *Angew. Chem., Int. Ed.* **2004**, *43*, 5580.

(4) Cacchi et al. reported on the Pd-catalyzed hydroxycarbonylation with lithium formate. See: (a) Cacchi, S.; Fabrizi, G.; Goggiamani, A. *Org. Lett.* **2003**, *5*, 4269. For examples of Pd-catalyzed carbonylation with alkyl formate, see: (b) Schareina, T.; Zapf, A.; Cotte, A.; Gotta, M.; Beller, M. *Adv. Synth. Catal.* **2010**, *352*, 1205. (c) Ko, S.; Lee, C.; Choi, M. G.; Na, Y.; Chang, S. *J. Org. Chem.* **2003**, *68*, 1607. (d) Carpentier, J. F.; Castanet, Y.; Brocard, J.; Mortreux, A.; Petit, F. *Tetrahedron Lett.* **1991**, *32*, 4705.

(5) (a) Wieckowska, A.; Fransson, R.; Odell, L. R.; Larhed, M. *J. Org. Chem.* **2011**, *76*, 978. (b) Wannberg, J.; Larhed, M. In *Modern Carbonylation Methods*; Kollár, L., Ed.; Wiley-VCH: Weinheim, Germany, 2008; pp 93–114.

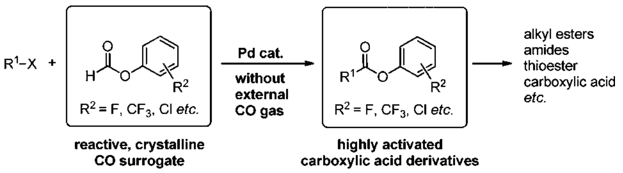
10.1021/ol302593z

carbonyl compounds[5] have already been developed as alternatives. However, most of them require either a very high temperature or strong bases to release CO gas.

Recently, Skrydstrup et al. reported on several Pd-catalyzed carbonylation reactions by using silacarboxylic acids or tertiary acid chlorides operating crystalline CO surrogates.[6] Their method allowed strict control of the amount of CO released for the carbonylation reactions by using two-chamber equipment. However, the necessity of such special equipment would reduce the utility of the reaction leading to difficult scale-up. Furthermore, fluoride reagents, strong bases, or an extra Pd catalyst is still required to release CO.

In the course of our investigation of practical methodologies for the synthesis of biologically active compounds, we recently developed the practical external-CO-free Pd-catalyzed carbonylation of aryl, alkenyl, and allyl halides, and alkenyl tosylates with phenyl formate.[7] In this approach, decarbonylation of phenyl formate with a mild base (e.g., NEt_3) generates phenol and CO, which is subsequently used for the Pd-catalyzed carbonylation of electrophiles to afford the corresponding phenyl esters. To elaborate this process, we hypothesized that the installation of electron-withdrawing groups at the *ortho*- or *para*-positions of the phenyl formate would enhance its reactivity as a CO surrogate,[8] thereby developing more efficient carbonylation reactions (Scheme 1). In addition, if the formate is crystalline, it would be stable and easy to handle. Furthermore, carbonylation products can be regarded as highly reactive carboxylic acid derivatives to nucleophiles and they would be readily converted to various compounds.

Scheme 1. A Working Hypothesis

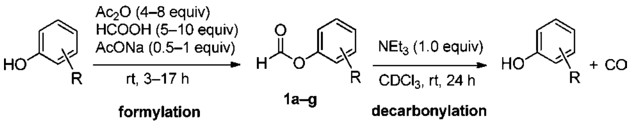


In this communication, we demonstrate the high utility of 2,4,6-trichlorophenyl formate as a highly reactive and easily accessible crystalline CO surrogate for Pd-catalyzed carbonylation reactions under considerably milder and more practical conditions (i.e., rt, near-stoichiometric quantities of formate, a simple flask equipped with an Ar balloon) as compared to existing methodologies. Furthermore, the obtained trichlorophenyl esters can be readily transformed to various carboxylic acid derivatives.

For the initial experiment, several phenyl formates having electron-withdrawing groups at *ortho*- and/or *para*-positions were synthesized from the corresponding phenols by using HCOOH, Ac_2O, and AcONa (Table 1). After the reaction, simple extraction with toluene and subsequent concentration provided quite pure products without column chromatography. Among the seven types of products synthesized, 4-phenylphenyl formate (**1b**) and 2,4,6-trichlorophenyl formate (**1f**)[9] were confirmed to be highly crystalline compounds.

Subsequently, the rt decarbonylation of the as-prepared phenyl formates to generate CO and phenols with NEt_3 was examined (Table 1). Remarkably, the presence of electron-withdrawing groups significantly accelerated the decarbonylation. In particular, crystalline **1f** proved to be the most reactive among the phenyl formates prepared, and the decarbonylation was almost completed within 30 min. **1f** can be stored at rt for 1 month with no signs of degradation. Furthermore, 2,4,6-trichlorophenol, the raw material used to prepare **1f**, is inexpensive and readily available.

Table 1. Synthesis of Phenyl Formates and Their Decarbonylation[a] with NEt_3



entry	formate (R)	yield (%)	appearance	decarbonylation conversion (%)[b]
1	**1a** (H)	71	oil	16
2	**1b** (4-Ph)	96	crystal	11
3	**1c** (4-F)	66	oil	11
4	**1d** (4-Cl)	95	oil	24
5	**1e** (4-CF_3)	91	oil	69
6.0	**1f** (2,4,6-Cl_3)	98	crystal	92 (10 min) 98 (30 min) 100 (24 h)
7	**1g** (2,6-F_2)	53	oil	46 (30 min) 100 (24 h)

[a] Concentration: 0.5 M. [b] Determined by ^1H NMR.

The obtained phenyl formates were subsequently applied to the rt carbonylation of iodobenzene (**2a**) and alkenyl triflate **2b** under the presence of a Pd–xantphos[7,10] catalyst system (Table 2). As found in previous studies,[7] alkyl formates such as **1h** and **1i** did not react at all (entries 1 and 2). Phenyl formate (**1a**) was not effective in rt carbonylation, affording products in poor yields (entries 3 and 4).

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(6) (a) Friis, S. D.; Taaning, R. H.; Lindhardt, A. T.; Skrydstrup, T. *J. Am. Chem. Soc.* **2011**, *133*, 18114. (b) Hermange, P.; Lindhardt, A. T.; Taaning, R. H.; Bjerglund, K.; Lupp, D.; Skrydstrup, T. *J. Am. Chem. Soc.* **2011**, *133*, 6061.

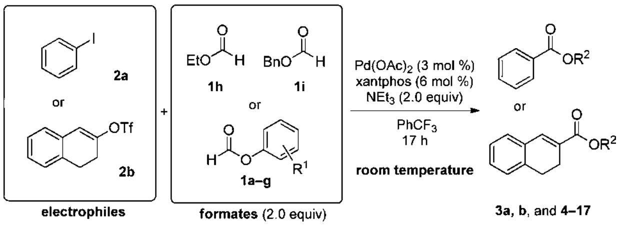
(7) (a) Ueda, T.; Konishi, H.; Manabe, K. *Org. Lett.* **2012**, *14*, 3100. (b) Ueda, T.; Konishi, H.; Manabe, K. *Tetrahedron. Lett.* **2012**, *53*, 5171. (c) Tsuji et al. also reported the Pd-catalyzed esterification of aryl halides using aryl formates. See: Fujihara, T.; Hosoki, T.; Katafuchi, Y.; Iwai, T.; Terao, J.; Tsuji, Y. *Chem. Commun.* **2012**, *48*, 8012.

(8) Tsuji et al. reported that electron-withdrawing substituents accelerated the Pd-catalyzed decarbonylation of phenyl formates; see: Katafuchi, Y.; Fujihara, T.; Iwai, T.; Terao, J.; Tsuji, Y. *Adv. Synth. Catal.* **2011**, *353*, 475.

(9) van Es, A.; Stevens, W. *Recl. Trav. Chim. Pays-Bas* **1965**, *84*, 1247.

(10) Martinelli, J. R.; Watson, D. A.; Freckmann, D. M. M.; Barder, T. E.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 7102.

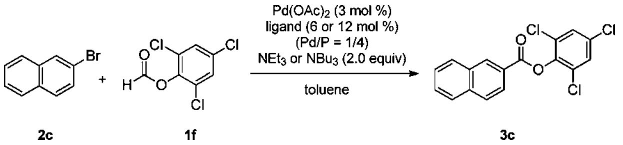
Table 2. Pd-Catalyzed Carbonylation of **2a** and **2b**[a]



entry	electrophile	formate (R^1)	product	yield (%)
1	**2a**	**1h**	**4**	0
2	**2a**	**1i**	**5**	0
3	**2a**	**1a** (H)	**6**	10
4	**2b**	**1a** (H)	**7**	30
5	**2a**	**1b** (4-Ph)	**8**	5
6	**2b**	**1b** (4-Ph)	**9**	17
7	**2a**	**1c** (4-F)	**10**	30
8	**2b**	**1c** (4-F)	**11**	35
9	**2a**	**1d** (4-Cl)	**12**	81
10	**2b**	**1d** (4-Cl)	**13**	87
11	**2a**	**1e** (4-CF_3)	**14**	94
12	**2b**	**1e** (4-CF_3)	**15**	91
13	**2a**	**1f** (2,4,6-Cl_3)	**3a**	>99
14	**2b**	**1f** (2,4,6-Cl_3)	**3b**	>99
15	**2a**	**1g** (2,6-F_2)	**16**	99
16	**2b**	**1g** (2,6-F_2)	**17**	94

[a] Reactions were conducted with 0.36–0.49 mmol of electrophile.

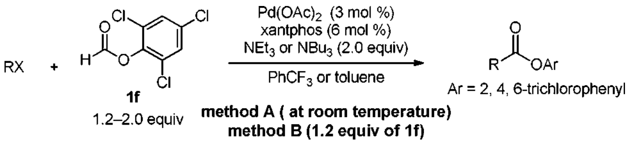
Table 3. Pd-Catalyzed Carbonylation of **2c** with **1f**[a]

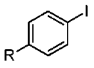
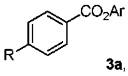
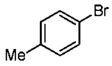
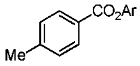
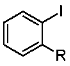
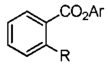
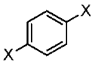
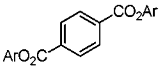
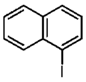
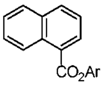
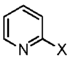
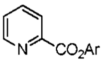
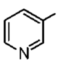
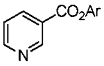
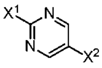
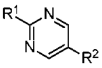
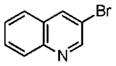
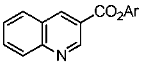
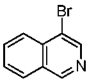
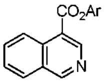
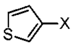
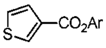
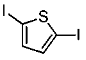
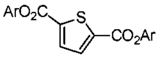
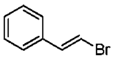
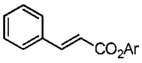
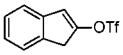
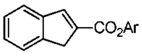


entry	method[b]	temp (°C)	ligand	**1f** (equiv)	yield (%)[c]
1	A	45	xantphos	2.0	25
2	A	80	xantphos	2.0	45
3	B	80	xantphos	2.0	68
4	B	100	xantphos	2.0	95
5	B	100	xantphos	1.2	90
6[d]	B	100	xantphos	1.2	89
7	B	100	PPh_3	1.2	28
8	B	100	dppf	1.2	17
9	B	100	$P(t\text{-}Bu)_3$	1.2	43

[a] Reactions were conducted with 0.48 mmol of **2c**. [b] Method A: The reactions were conducted in a test tube for 12–19 h. NEt_3 was used. Method B: The reactions were conducted in a 10-mL flask equipped with an Ar balloon. A degassed solution of **1f** in toluene was added dropwise for 3 h to a solution containing **2c**, NBu_3, $Pd(OAc)_2$, and the ligand in toluene. Then, the mixture was stirred for 1 h. [c] Isolated yield. [d] 4.8 mmol of **2c**.

Table 4. Substrate Scope of the Pd-Catalyzed Carbonylation with Formate **1f**[a]



entry	method[b]	substrate	product	yield[c] (%)
1	A	 R = H (**2a**)	 **3a**, **3d–j**	>99
2	A	OMe (**2d**)		82
3	A	Cl (**2e**)		>99
4	A	Br (**2f**)		>99
5	A	CN (**2g**)		94
6	A	COMe (**2h**)		>99
7	A	CHO (**2i**)		99
8	A	CO_2Et (**2j**)		85
9	B	 **2k**	 **3k**	81
10[d]	A	 R = Cl (**2m**)	 **3m**	96
11[d]	A	Me (**2n**)	**3n**	82
12[e]	A	 X = I (**2o**)	 **3o**	75
13[f]	B	Br (**2oa**)		92
14[d]	A	 **2p**	 **3p**	99
15[d]	A	 X = Br (**2q**)	 **3q**	>99
16	A	I (**2qa**)		88
17	B	 **2r**	 **3r**	86
18	A	 X^1 = Br, X^2 = H (**2s**)	 R^1 = CO_2Ar, R^2 = H (**3s**)	74
19	B	X^1 = H, X^2 = Br (**2t**)	R^1 = H, R^2 = CO_2Ar (**3t**)	74
20	B	 **2u**	 **3u**	90
21	B	 **2v**	 **3v**	76
22	A	 X = I (**2w**)	 **3w**	98
23	B	Br (**2wa**)		84
24[e]	A	 **2x**	 **3x**	76
25	A	 **2y** *E*/*Z* = 87/13	 **3y** *E*/*Z* = 97/3	88
26	A	 **2z**	 **3z**	97

[a] Reactions were conducted with 100 mg of electrophiles. [b] Method A: The reactions were conducted in a test tube at rt for 10–21 h. 0.5 mL of $PhCF_3$ and 2.0 equiv of **1f** and NEt_3 were used. Method B: The reactions were conducted in a 10-mL flask equipped with an Ar balloon. A degassed solution of 1.2 equiv of **1f** in 0.9 mL of toluene was added dropwise for 3 h to a degassed solution of containing the electrophile, NBu_3, $Pd(OAc)_2$, and xantphos in 0.6 mL of toluene at 100 °C. Then, the mixture was stirred for 1 h. [c] Isolated yields. [d] At 45 °C. [e] 5 mol % of $Pd(OAc)_2$, 10 mol % of xantphos, and 3.0 equiv of **1f** and NEt_3 were used. [f] 5 mol % of $Pd(OAc)_2$, 10 mol % of xantphos, 2.5 equiv of **1f**, and 4.0 equiv of NBu_3 were used.

Formates showing higher decarbonylation reactivities such as **1e**, **1f**, and **1g** (Table 1) gave higher yields of the carbonylated products (entries 11–16). Trichlorophenyl formate (**1f**) was found to show the highest reactivity, affording the corresponding trichlorophenyl esters **3a** and

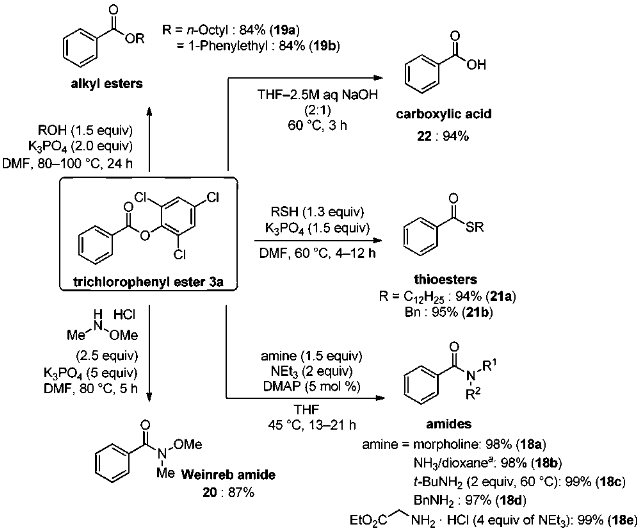
3b in quantitative yields. These observations highlight the importance of the rapid decarbonylation of the formates for the Pd-catalyzed carbonylation reaction.

Having identified the most suitable crystalline CO surrogate, we next tried to apply this methodology to the carbonylation of aryl bromide **2c** (Table 3). Unfortunately, the reaction of **2c** with **1f** resulted in low yields at both 45 and 80 °C (entries 1 and 2). We hypothesized that an excess amount of CO rapidly generated from **1f** retarded the oxidative addition of **2c** to the Pd center because of the π-acidic nature of CO as a ligand. We thus decided to explore an experimental procedure that could minimize the effects of CO. Consistent with this reasoning, a slow addition (3 h) of **1f** to a solution containing **2c**, the Pd catalyst, and NBu_3 significantly improved the yield of **3c** (entries 3–4). Surprisingly, high yields (90%) were also obtained even under near-stoichiometric quantities of **1f** in a simple flask equipped with an Ar balloon (entry 5). Other ligands such as PPh_3, dppf, and $P(t\text{-}Bu)_3$ were ineffective in this carbonylation (entries 7–9).

To determine the scope of this process, a variety of electrophiles were employed as substrates (Table 4). The experimental method (A or B) was chosen to suit the relative ease of the oxidative addition of the R–X bond. A variety of functional groups (e.g., ester, cyano, ketone, and aldehylde) were found to be tolerated, and both electron-donating and -withdrawing groups at the 4-position did not affect the reaction (entries 1–8). Unfortunately, *ortho*-substituted substrate **2m** and **2n** were found to be recalcitrant substrates at rt. However, by slightly raising the reaction temperature to 45 °C, the yields were significantly improved (entries 11 and 12). Aryl bromide **2k** also reacted with **1f** in good yields by following method B (entry 9). Double carbonylation of **2o** and **2oa** proceeded smoothly to afford **3o** (entries 12 and 13). This reaction is also applicable to heteroaromatic substrates. The reactions of N- and S-containing heteroaromatic halides proceeded well to afford **3q**–**3x** in high yields (entries 15–24). The rt carbonylation of alkenyl bromide **2y** and triflate **2z** also afforded the products in good yields (entries 25 and 26).

Finally, we examined the transformation of 2,4,6-trichlorophenyl ester (**3a**) by using various nucleophiles (Scheme 2). Surprisingly, in contrast to the simple structures of trichlorophenyl esters, there are a few reports on these kinds of transformations.[11] As expected, the trichlorophenyl ester proved to be a highly reactive compound, and it reacted with a small excess of nucleophiles under mild conditions to afford the corresponding carboxylic acid derivatives in high yields.

Scheme 2. Transformations of **3a**



[a] 3 equiv of 0.5 M NH_3/dioxane were used in place of NEt_3, DMAP.

In summary, we have found that 2,4,6-trichlorophenyl formate (**1f**) could serve as a highly reactive and easily accessible crystalline CO surrogate. The decarbonylation to generate CO proceeded smoothly at rt, and it was successfully applied to the external-CO-free Pd-catalyzed carbonylation of aryl/alkenyl halides and triflates. The high reactivity of **1f** as a CO surrogate allowed the carbonylation to be achieved at rt or with a significantly reduced amount of formate (i.e., near-stoichimetric quantities). Furthermore, the obtained trichlorophenyl ester can be readily transformed to alkyl esters, amides, thioesters, and carboxylic acids in high yields. Further investigations concerning the application of this methodology to other CO-free Pd-catalyzed reactions will be carried out in due course.

Acknowledgment. This work was partly supported by Daiichi-Sankyo Co., Ltd.

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.

The authors declare no competing financial interest.

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