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Palladium-Catalyzed Carbonylation of Aryl, Alkenyl, and Allyl Halides with Phenyl Formate

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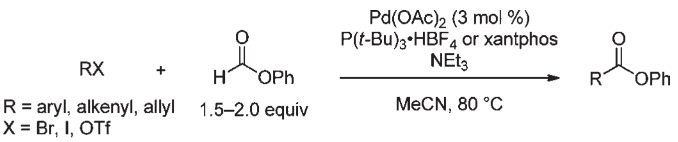
ABSTRACT



Highly efficient palladium-catalyzed carbonylation of aryl, alkenyl, and allyl halides with phenyl formate is reported. This procedure does not use carbon monoxide and affords one-carbon-elongated carboxylic acid phenyl esters in excellent yields. The reaction proceeds smoothly under mild conditions and tolerates a wide range of functional groups including aldehyde, ether, ketone, ester, and cyano groups. Furthermore, a variety of heteroaromatic bromides can be converted to the corresponding phenyl esters in high yields.

The synthesis of carboxylic acid esters from aryl halides is one of the most important transformations in organic chemistry. The conventional strategy for this conversion involves halogen–metal exchange by alkyllithium or Grignard reagents and subsequent addition to carbon dioxide to afford carboxylic acids that can be condensed with alcohols to give the desired carboxylic acid esters. In this procedure, the reaction needs stoichiometric amounts of metal reagents, the strong basicity of which limits the tolerated functional groups. An efficient and complementary methodology is the palladium-catalyzed carbonylation of aryl halides with alcohols employing CO gas. This method has found broad applications in the synthesis of a variety of ester compounds.[1] However, it also has a major problem: CO gas is highly toxic and difficult to utilize in reactions on a laboratory scale, which reduces the overall utility of the reaction. Therefore, there is significant interest in developing alternative methods that avoid the use of CO gas.[2]

In this respect, formates are considered to be especially promising alternatives because of their ease of handling compared to toxic CO gas. In fact, much effort has already been expended on realizing carbonylation utilizing formates without CO gas.[3] However, so far carbonylation methods employing formates have suffered from low efficiency because of the necessity of directing groups for formates, of an Ru cocatalyst,[3b] and of strong bases,[3c] limited substrate scope and unsatisfactory yields,[3a−c] very high required temperatures (135–140 °C for aryl bromides)[3a,b,4] and pressure (15 bar of N$_2$),[3c] and the necessity of large excess amounts of formate.[3a]

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(1) Review: (a) Brennführer, A.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 4114. For recent examples of Pd-catalyzed carbonylations, see: (b) Wu, X.; Neumann, H.; Beller, M. *Chem.—Eur. J.* **2012**, *18*, 3831. (c) Akpinar, G. E.; Kus, M.; Cuncu, M. U.; Karakus, E.; Artok, L. *Org. Lett.* **2011**, *13*, 748. (d) Mercadante, M. A.; Leadbeater, N. E. *Org. Biomol. Chem.* **2011**, *9*, 6575. (e) Reeves, D. C.; Rodriquez, S.; Lee, H.; Haddad, N.; Krishnamurthy, D.; Senanayake, C. H. *Org. Lett.* **2011**, *13*, 2495.

(2) For review on carbonylations without CO gas, see: Morimoto, T.; Kakiuchi, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 5580.

(3) (a) Schareina, T.; Zapf, A.; Cotte, A.; Gotta, M.; Beller, M. *Adv. Synth. Catal.* **2010**, *352*, 1205. (b) Ko, S.; Lee, C.; Choi, M. G.; Na, Y.; Chang, S. *J. Org. Chem.* **2003**, *68*, 1607. (c) Carpentier, J. F.; Castanet, Y.; Brocard, J.; Mortreux, A.; Petit, F. *Tetrahedron Lett.* **1991**, *32*, 4705.

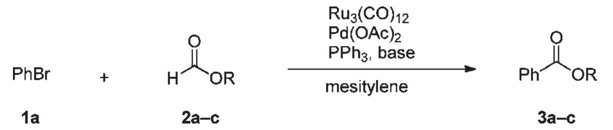
(4) Cacchi et al. reported Pd-catalyzed hydroxycarbonylation of aryl bromides with lithium formate at 80 °C with a reaction time of 64 h. See: (a) Cacchi, S.; Fabrizi, G.; Goggiamani, A. *Org. Lett.* **2003**, *5*, 4269. (b) Berger, P.; Bessmernykh, A.; Caille, J.-C.; Mignonac, S. *Synthesis* **2006**, 3106.

10.1021/ol301192s

In the course of our search for practical methodologies for the synthesis of bioactive compounds, we hypothesized that the use of an appropriate ligand, formate ester, and base would lead to a more efficient carbonylation reaction with wide substrate generality. Herein, we now report the carbonylation of aryl, alkenyl, and allyl halides with phenyl formate in the presence of a Pd−P(*t*-Bu)$_3$ or Pd−xantphos catalyst system to give one-carbon-elongated phenyl esters. The reaction proceeds smoothly with small excess amounts of phenyl formate (1.5−2.0 equiv) under milder conditions (80 °C, NEt_3 is used as the base) than those found in previous examples. Moreover, a variety of heteroaromatic bromides can be converted to the corresponding phenyl esters in satisfactory yields.

At the beginning of our investigation, we tested the carbonylation of bromobenzene (**1a**) with 2 equiv of phenyl formate[5,6] and $NaHCO_3$ under a Pd−PPh_3/Ru bimetallic catalyst system at 100 °C (Table 1, entry 1).[3b,7] As we expected, the desired phenyl ester **3a** was obtained in 23% yield. To confirm the effect of the Ru catalyst, the reaction was attempted in the absence of $Ru_3(CO)_{12}$. Surprisingly, the yield was dramatically improved to afford **3a** in 64% (entry 2). In addition, NEt_3 is found to be a very effective base for this reaction that affords the product in 97% (entry 3). Evidently, the P/Pd ratio affected the catalytic activity, because the yield decreased to 68% at P/Pd = 2 (entry 4). Alkyl formates such as benzyl formate (**2b**) and ethyl formate (**2c**) did not give the corresponding alkyl esters (**3b**,**c**) at all (entries 5 and 6).

Table 1. Pd-Catalyzed Carbonylation of **1a** with Formate[a]



entry	R	$Ru_3(CO)_{12}$	base	yield[b] (%)
1	Ph (**2a**)	+[c]	$NaHCO_3$	23
2	Ph (**2a**)	−	$NaHCO_3$	64
3[d]	Ph (**2a**)	−	NEt_3	97
4[e]	Ph (**2a**)	−	NEt_3	68
5	Bn (**2b**)	−	NEt_3	0
6	Et (**2c**)	−	NEt_3	0

[a] Reactions were conducted on a 0.637 mmol scale in bromobenzene (**1a**) and anhydrous mesitylene (1 mL) at 100 °C using 1 equiv of **1a**, 2 equiv of **2a**−**c**, and 2 equiv of base in the presence of 3 mol % of $Pd(OAc)_2$ and 12 mol % of PPh_3. The reaction time was 44 h. [b] Isolated yields. [c] 3 mol % of $Ru_3(CO)_{12}$ was used. [d] The reaction time was 13 h. [e] 6 mol % of PPh_3 was used.

We then tested several ligands in the carbonylation of bromobenzene (**1a**) with phenyl formate (**2a**) (Table 2). When $Pd_2(dba)_3$ was used with no ligand, no product was obtained at all (entry 1). Bidentate phosphines with larger bite angles such as dppf and xantphos[8] showed excellent catalytic activities and afforded **3a** in 96% yield (entries 7 and 8). The best activity was found for P(*t*-Bu)$_3$·HBF_4, which gave a 99% yield of **3a** (entry 9). High yield was also realized at 80 °C (entry 14), but at 60 °C the yield dramatically decreased to 34% (entry 15).

Table 2. Screening of Ligands for Carbonylation[a]

entry	ligand	temp (°C)	yield[b] (%)
1[c]	none	100	0
2	PPh_3	100	97
3	PCy_3	100	7
4	dppe	100	5
5	dppp	100	71
6	dppbz	100	3
7	dppf	100	96
8	xantphos	100	96
9	P(*t*-Bu)$_3$·HBF_4	100	99
10	P(*c*-pentyl)$_3$·HBF_4	100	11
11	PPh_3	80	88[d]
12	dppf	80	89[d]
13	xantphos	80	90[d]
14	P(*t*-Bu)$_3$·HBF_4	80	93[d]
15	P(*t*-Bu)$_3$·HBF_4	60	34[d]

[a] Reactions were conducted on a 0.637 mmol scale in bromobenzene (**1a**) and anhydrous mesitylene (1 mL) using 1 equiv of **1a**, 2 equiv of **2a**, and 2 equiv of NEt_3 in the presence of 3 mol % of $Pd(OAc)_2$ and 6 or 12 mol % of phosphine (P/Pd = 4/1). The reaction time was 13−21 h. [b] Isolated yields of **3a**. [c] 3 mol % of $Pd_2(dba)_3$ was used. [d] HPLC yields.

In the next stage, we examined the effect of the solvent on the reaction (Table 3). CH_3CN is the solvent of choice, although the type of solvent had no significant effect on the yield of **3a** (63%−99%, entries 1−10). A further series of experiments showed that the yields of the reaction remained high (91%−95%) even when a reduced amount of phenyl formate (1.5 equiv) or catalyst (1.5 mol %) was used (entries 11 and 12).

The best conditions found above for bromobenzene (**1a**) (1 equiv of aryl halide, 2 equiv of phenyl formate (**2a**), 2 equiv of NEt_3 in the presence of 3 mol % $Pd(OAc)_2$ and 12 mol % P(*t*-Bu)$_3$·HBF_4 in CH_3CN at 80 °C) were employed to test the generality of our catalyst system for a variety of aryl halides and phenyl triflate (Table 4). Iodobenzene (**1b**) smoothly reacted with **2a** to afford **3a** in excellent yield (entry 2). Unlike for **1a** and **1b**, the use of toluene as solvent and xantphos as ligand was favorable for triflate **1c** to give **3a** in 99% yield (entry 3).

A variety of functional groups (ester, cyano, ketone, and aldehyde groups) is tolerated in this reaction. Neither electron-donating nor electron-withdrawing groups at the 4- and 2-positions affected the reaction (entries 4−13), except for the 2-NO_2 group (entry 14). Steric bulkiness

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(5) Tsuji et al. reported Pd-catalyzed hydroesterification of alkynes with phenyl formate. See: Katafuchi, Y.; Fujihara, T.; Iwai, T.; Terao, J.; Tsuji, Y. *Adv. Synth. Catal.* **2011**, *353*, 475.

(6) Phenyl formate was easily prepared from phenol by using acetic anhydride, formic acid, and AcONa without silica gel column chromatography, and the obtained product can be used for this reaction.

(7) Jenner, G.; Bentaleb, A. *J. Organomet. Chem.* **1994**, *470*, 257.

(8) Buchwald et al. used Pd-xantphos for carbonylation of aryl bromides under CO atmosphere. See: Martinelli, J. R.; Watson, D. A.; Freckmann, D. M. M.; Barder, T. E.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 7102.

Table 3. Solvent Study for Carbonylation[a]

entry	solvent	yield of **3a**[b] (%)
1	mesitylene	93
2	toluene	95
3	$PhCF_3$	63
4	DCE	63
5	THF	92
6	DME	92
7	CPME	87
8	DMF	82
9	NMP	89
10	CH_3CN	95 (97)[e]
11[c]	CH_3CN	95
12[d]	CH_3CN	91

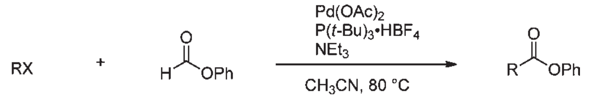
[a] Reactions were conducted on a 0.637 mmol scale in bromobenzene (**1a**) and anhydrous solvent (1 mL) at 80 °C using 1 equiv of **1a**, 2 equiv of **2a**, and 2 equiv of NEt_3 in the presence of 3 mol % of $Pd(OAc)_2$ and 12 mol % of $P(t\text{-}Bu)_3 \cdot HBF_4$. The reaction time was 17 h. [b] HPLC yields. [c] 1.5 equiv of **2a** and NEt_3 were used. [d] 1.5 mol % of $Pd(OAc)_2$ was used. [e] Isolated yields of **3a**.

around the bromine atom did not affect the yield significantly (entry 15). Double carbonylation of *p*-dibromobenzene (**1p**) proceeded to give **3p** in 94% yield (entry 16). Alkenyl bromides also coupled with **2a**, and conjugated esters **3s** and **3t** were obtained in good yields (entries 19 and 20). In addition, allyl bromide was another good coupling partner to afford **3u** (entry 21).

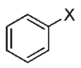
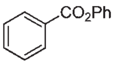
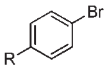
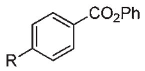
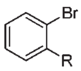
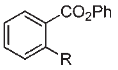
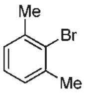
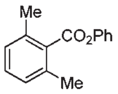
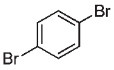
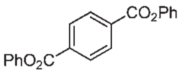
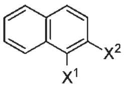
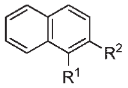
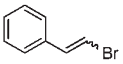
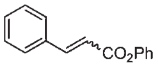
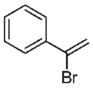
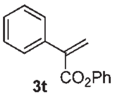
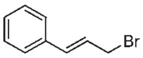
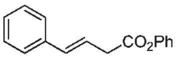
This reaction is also applicable to heteroaromatic systems, as shown in Table 5. Bromopyridines **1v**–**x** were coupled with **2a** to afford the corresponding phenyl esters in good yields (entries 1–3). Other N-containing aromatic bromides also gave the corresponding phenyl esters in good yields (entries 4–7). The reactions of S- and O-containing heteroaromatic bromides proceeded well to afford **3ac**–**ae** in high yields (entries 8–10).

The reaction profile[9] of carbonylation of **1d** with phenyl formate (**2a**) is shown in Figure 1a. As the **2a** concentration decreased, the **3d** concentration increased at a compatible rate. From this fact, we suppose that decarbonylation of **2a** to form phenol and CO is the rate-determining step. Therefore, this step was examined in detail with **2a**, as shown in Figure 1b. The conversion of **2a** at 80 °C in the presence of 1 equiv of NEt_3 showed a first-order dependence on the concentration of **2a** ($k = 9.5 \times 10^{-3}$ min^{-1}).[10] The addition of Pd–P(t-Bu)$_3$ did not affect the reaction rate.[11] Without NEt_3, **2a** did not react at all. These results indicate that decarbonylation is a NEt_3-catalyzed reaction.[12]

Table 4. Carbonylation of Various Aryl, Alkenyl, and Allyl Halides and Phenyl Triflate (**1a**–**u**)[a]



1a–u **2a** **3a, 3d–u**

entry	substrate	product	yield[b] (%)
1	 X = Br (**1a**)	 **3a**	97
2	I (**1b**)		>99
3[c]	OTf (**1c**)		99
4	 R = Me (**1d**)	 **3d–j**	97
5	CO_2Et (**1e**)		>99
6	CN (**1f**)		90
7	OMe (**1g**)		96
8	COMe (**1h**)		>99
9	CF_3 (**1i**)		93
10	CHO (**1j**)		88
11	 R = Me (**1k**)	 **3k–n**	94
12	Ph (**1l**)		85
13	OMe (**1m**)		89
14	NO_2 (**1n**)		34
15	 **1o**	 **3o**	84
16[d]	 **1p**	 **3p**	94
17	 X^1 = Br, X^2 = H (**1q**)	 R^1 = CO_2Ph, R^2 = H (**3q**)	88
18	X^1 = H, X^2 = Br (**1r**)	R^1 = H, R^2 = CO_2Ph (**3r**)	95
19	 **1s** *E*/*Z* = 87/13	 **3s** *E*/*Z* = 94/6	86
20	 **1t**	 **3t**	62
21	 **1u**	 **3u**	63

[a] Reactions were conducted on a 100 mg scale in aryl, alkenyl, and allyl halides and phenyl triflate (**1a**–**u**) in anhydrous CH_3CN (1 mL) at 80 °C using 1 equiv of **1a**–**u**, 2 equiv of **2a**, and 2 equiv of NEt_3 in the presence of 3 mol % of $Pd(OAc)_2$ and 12 mol % of $P(t\text{-}Bu)_3 \cdot HBF_4$. The reaction time was 15–20 h. [b] Isolated yields. [c] 6 mol % of xantphos was used in place of $P(t\text{-}Bu)_3 \cdot HBF_4$. The reaction solvent was toluene. [d] 4 equiv of **2a** and 4 equiv of NEt_3 were used in the presence of 5 mol % of $Pd(OAc)_2$ and 20 mol % of $P(t\text{-}Bu)_3 \cdot HBF_4$. Two milliliters of CH_3CN was used.

A plausible catalytic cycle is shown in Scheme 1. Phenyl formate is converted to phenol and CO by NEt_3. Insertion

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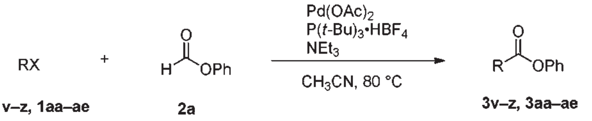
[9] The reaction was monitored by HPLC by using ethyl benzoate as the internal standard.

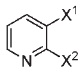
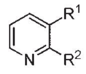
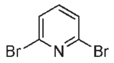
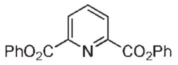
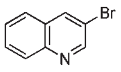
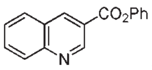
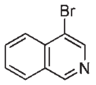
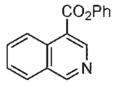
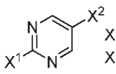
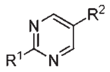
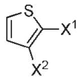
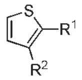
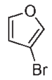
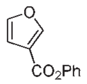
[10] $v = -d[\mathbf{2a}]/dt = k[\mathbf{2a}]$.

[11] Tsuji et al. reported that Pd-catalyzed decarbonylation of **2a** without a base showed zero-order dependence on the concentration of **2a**. See ref 5.

[12] Alkyl formates are known to undergo base-catalyzed decomposition to CO and alcohols. For example, see: Ma, F. Q.; Lu, D. S.; Guo, Z. Y. *J. Mol. Catal.* **1993**, *78*, 309.

Table 5. Carbonylation of Various Heteroaromatic Bromides (**1v**–**z** and **1aa**–**ae**)[a]



entry	substrate	product	yield[b] (%)
1 2	 X^1 = Br, X^2 = H (**1v**) X^1 = H, X^2 = Br (**1w**)	 $R^1 = CO_2Ph$, R^2 = H (**3v**) R^1 = H, $R^2 = CO_2Ph$ (**3w**)	93 99
3[c]	 **1x**	 **3x**	64
4	 **1y**	 **3y**	85
5	 **1z**	 **3z**	94
6 7	 X^1 = Br, X^2 = H (**1aa**) X^1 = H, X^2 = Br (**1ab**)	 $R^1 = CO_2Ph$, R^2 = H (**3aa**) R^1 = H, $R^2 = CO_2Ph$ (**3ab**)	72 84
8 9	 X^1 = Br, X^2 = H (**1ac**) X^1 = H, X^2 = Br (**1ad**)	 $R^1 = CO_2Ph$, R^2 = H (**3ac**) R^1 = H, $R^2 = CO_2Ph$ (**3ad**)	99 95
10	 **1ae**	 **3ae**	82

[a] Reactions were conducted on a 100 mg scale in aryl halides and anhydrous CH_3CN (1 mL) at 80 °C using 1 equiv of substrate, 2 equiv of **2a**, and 2 equiv of NEt_3 in the presence of 3 mol % of $Pd(OAc)_2$ and 12 mol % of $P(t\text{-}Bu)_3 \cdot HBF_4$. The reaction time was 15–20 h. [b] Isolated yields. [c] 4 equiv of **2a** and 4 equiv of NEt_3 were used in the presence of 5 mol % of $Pd(OAc)_2$ and 20 mol % of $P(t\text{-}Bu)_3 \cdot HBF_4$. Two milliliters of CH_3CN was used.

of CO in arylpalladium species **B** generates the acylpalladium species **C** that reacts with phenol and NEt_3 to form phenoxy(acyl)palladium species **D**. The reductive elimination provides the carbonylation product **3a** and the active palladium species **A**.

In conclusion, we have found that carbonylation of aryl, alkenyl, and allyl halides with phenyl formate was promoted under the Pd–$P(t\text{-}Bu)_3$ system. Various halides can be used in the reaction to afford the corresponding phenyl esters in high yields under mild conditions. The reaction can proceed without the use of a directing group, cocatalyst, toxic CO gas, or large excess amounts of formate. Further investigation concerning the reaction's application to synthesis of biologically active compounds is being carried out in due course.

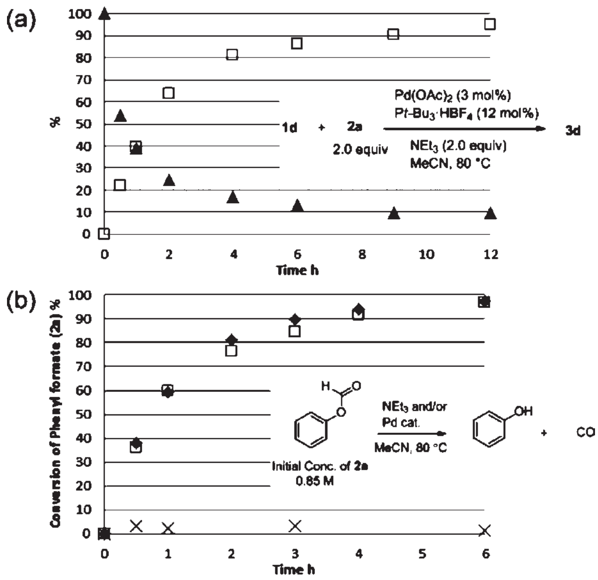
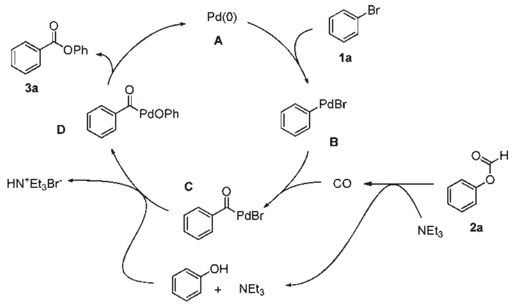


Figure 1. (a) Reaction profile of carbonylation: □, yield of **3d**; ▲, residual ratio of **2a**. (b) Decarbonylation of **2a**: ♦, 1 equiv of NEt_3; □, 1 equiv of NEt_3, 3 mol % $Pd(OAc)_2$, and 12 mol % $P(t\text{-}Bu)_3 \cdot HBF_4$; ×,without NEt_3 and Pd cat.

Scheme 1. Plausible Reaction Mechanism



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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.

The authors declare no competing financial interest.