

Palladium-catalyzed esterification of aryl halides using aryl formates without the use of external carbon monoxide†

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Received (in XXX, XXX) Xth XXXXXXXXXX 20XX, Accepted Xth XXXXXXXXXX 20XX

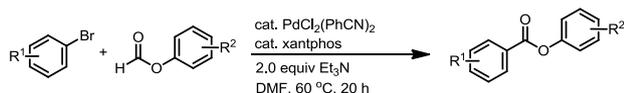
DOI: 10.1039/b000000x

Aryl formates are efficient carbon monoxide sources in palladium-catalyzed esterification of aryl halides. The carbonylation readily proceeds at ambient pressure without the use of external carbon monoxide to afford the corresponding esters in high yields.

Carbonylation processes using carbon monoxide (CO) as carbonyl sources constitute industrial core technologies for converting various bulk chemicals into functionalized useful products.¹ Despite large-scale applications in industry, carbonylations with CO are not comparatively used for more complex organic syntheses. This might be due to general reluctance to use the toxic gas as reagents and frequent use of a high-pressure reactor. Therefore, carbonylation reactions without the use of external CO is highly desirable.² As for the CO source, formic acid and its esters are industrially produced from CO. Thus, formate esters may be regarded as liquid condensates and expedient alternative sources of CO. Actually, much effort has been made to realize carbonylation reaction employing formate esters as a CO source.^{3,4} However, the CO generation from usual formate esters is not efficient and required relatively high reaction temperature,^{3a} co-catalysts,^{3b} or strong bases.^{3c} Recently, Skrydstrup et al. reported *ex situ* generation of carbon monoxide utilizing several CO sources by the aid of palladium catalysts.⁵ Although CO generated efficiently and the carbonylation of aryl halides proceeded, a two-chamber system must be used to separate CO generation and carbonylation processes.

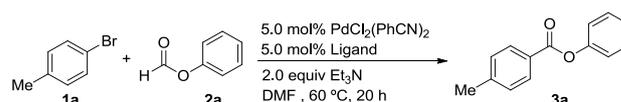
We have recently found that aryl formates, not alkyl formate, are very efficient CO source under relatively mild reaction conditions in the Pd-xantphos catalyzed hydroesterification of alkynes.⁶ However, in the reactions, an excess amount (4 or 10 equiv) of aryl formates must be indispensable for high yields of products. Herein, we report the Pd-catalyzed esterification of aryl halides employing aryl formates as a CO source (Scheme 1). By simply mixing an aryl halides, an aryl formate, and a Pd catalyst

Scheme 1.



in a usual glass flask (no pressure bottle is required), highly efficient esterification of the aryl halide was realized. Noteworthy is that only one equivalent of aryl formates is enough to afford

Table 1 Effect of ligands on the palladium-catalyzed esterification of 4-bromotoluene (**1a**) with phenyl formate (**2a**).^a

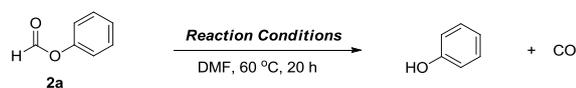


Entry	Ligand	Yield (%) ^b
1	none	0
2	PPh ₃	27
3	P(<i>o</i> -tol) ₃	0
4	PCy ₃	0
5	dppe	12
6	dppp	37
7	dppf	15
8	<i>rac</i> -binap	50
9	xantphos	99 (94) ^c

^a Reaction conditions: 4-bromotoluene (**1a**, 0.50 mmol), phenyl formate (**2a**, 0.75 mmol), PdCl₂(PhCN)₂ (0.025 mmol, 5.0 mol%), phosphine (0.025 mmol), Et₃N (1.0 mmol) in DMF (0.5 mL) at 60 °C for 20 h. ^b Yield based on the GC internal standard technique. ^c Isolated Yield of **3a**.

the carbonylated products in high yields.⁷

First, the reaction of 4-bromotoluene (**1a**) with 1.5 equivalent of phenyl formate (**2a**) was carried out in the presence of a catalytic amount of PdCl₂(PhCN)₂ in a 10-mL glass flask equipped with a standard ground glass joint (Table 1).⁸ Without any ligand, phenyl 4-methylbenzoate (**3a**) was not obtained at all (entry 1). With an addition of monodentate phosphines such as PPh₃, P(*o*-tol)₃, or PCy₃,⁹ **3a** was obtained in low yields (entries 2–4). The use of a bidentate phosphine such as dppe, dppp, dppf, or binap⁹ improved the catalytic activity (entries 5–8), although yields of the product were not satisfactory. Among the ligands examined, xantphos^{9,10} gave the best result, affording **3a** in 99% yield (entry 9). As a base, (*i*-Pr)₂EtN, DBU, and K₂CO₃ afforded **3a** in 82%, 70%, and 57% yields, respectively, while pyridine and KOH did not provide **3a** at all. Under the same reaction conditions as in entry 9, alkyl formates (benzyl formate, hexyl formate, and 2-phenylethyl formate) in place of **2a** did not convert and the corresponding esters were not provided at all. Thus, **2a** is unique carbonyl source in the present carbonylation.

Table 2 Conversion of phenyl formate (**2a**) to phenol and carbon monoxide.

Entry	Reaction conditions ^a	Yield of Phenol (%) ^b
1	PdCl ₂ (PhCN) ₂ (2.5 mol%), xantphos (2.5 mol%), Et ₃ N (1.0 equiv)	99
2	PdCl ₂ (PhCN) ₂ (2.5 mol%), xantphos (2.5 mol%)	<5
3	Et ₃ N (1.0 equiv)	99
4	Et ₃ N (1.0 equiv) at 40 °C	24
5	Et ₃ N (10 mol%)	<5

^a Reaction conditions: **2a** (1.0 mmol) in DMF (0.5 mL) at 60 °C for 20 h. ^b Yield based on the GC internal standard technique.

The conversion of **2a** was monitored under various reaction conditions (Table 2). In the presence of a catalytic amount (2.5 mol%) of PdCl₂(PhCN)₂ and xantphos with 1.0 equiv of Et₃N (the same catalytic conditions as entry 9 in Table 1),⁸ phenol was obtained quantitatively with evolution of carbon monoxide (entry 1). Removal of Et₃N from the entry 1 resulted in low conversion of **2a** and phenol was obtained only in low yield (entry 2). However, with 1.0 equiv of Et₃N alone, **2a** was fully converted and phenol was obtained in 99% yield (entry 3). Thus, Et₃N is responsible for the conversion of **2a**. The reaction was slow at 40 °C (entry 4) and **2a** was not almost converted in the presence of a catalytic amount of Et₃N (entry 5). Under the reaction conditions of entry 3, alkyl formates such as benzyl formate, hexyl formate, and 2-phenylethyl formate were not converted at all, which is very reminiscent of the catalytic reaction (vide supra).

Various aryl bromides (**1b–n**) reacted with **2a** under the standard reaction conditions (Table 3). Aryl bromides bearing both electron-rich (entries 1 and 2) and electron-poor (entries 3–8) phenyl moieties gave the corresponding esters (**3b–j**) in high yields. Nitro (entry 7), formyl (entry 8) and cyano (entry 9) functionalities on the aryl ring tolerated under the reaction conditions. Gratifyingly, **1l** bearing an ethynyl moiety afforded the corresponding ester (**3l**) without hydroesterification⁶ at the alkyne moiety (entry 11). Heterocycles such as pyridine and thiophen were also adapted (entries 12 and 13). Besides **2a**, the reaction of bromobenzene (**1o**) with aryl formates (**2b–e**) bearing electron-rich (entries 14 and 15) and electron-poor (entry 16) phenyl moieties gave the corresponding esters (**3o–q**) in good to high yields. A sterically demanding aryl formate (**2e**) also afforded **3r** in high yield.

An alkenyl bromide (**1p**) reacted with **2a** under the standard reaction conditions to give phenyl cinnamate (**3s**) in 66% yield (Scheme 2a). Iodobenzene (**4**) and phenyl triflate (**5**) also afforded phenyl benzoate **3t** in 85% and 88% yields, respectively (Scheme 2b). Although a chloro moiety on the aryl ring was intact under the standard reaction conditions (entry 3 in Table 3), an aryl chloride bearing an acetyl moiety (**6**) gave the corresponding ester **3f** in 86% yield at the elevated temperature with (*i*-Pr)₂EtN as a base (Scheme 2c). In addition, benzyl

Table 3 Carbonylation of various substrates under the optimum reaction conditions.^a

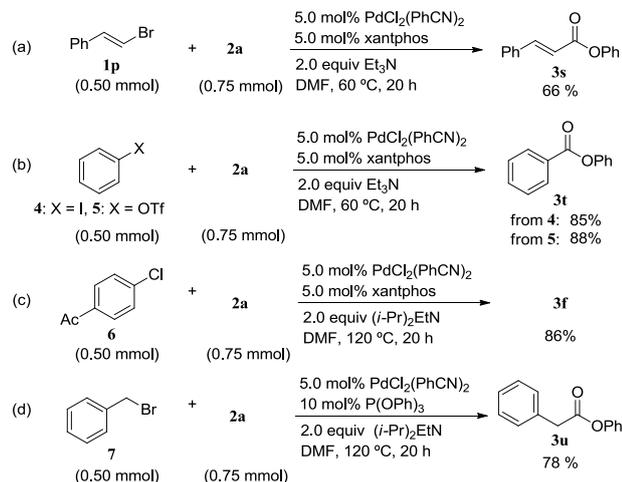
Entry	1	2	3	Yield (%) ^b
1 ^c	1b : R ¹ = OMe	2a	3b : R ¹ = OMe	91
2 ^d	1c : R ¹ = NMe ₂		3c : R ¹ = NMe ₂	83
3	1d : R ¹ = Cl		3d : R ¹ = Cl	96
4	1e : R ¹ = CF ₃		3e : R ¹ = CF ₃	89
5	1f : R ¹ = Ac		3f : R ¹ = Ac	92
6	1g : R ¹ = COOMe		3g : R ¹ = COOMe	88
7	1h : R ¹ = NO ₂		3h : R ¹ = NO ₂	72
8	1i : R ¹ = CHO		3i : R ¹ = CHO	88
9 ^c	1j	2a	3j	84
10 ^e	1k	2a	3k	89
11 ^e	1l	2a	3l	87
12	1m	2a	3m	91
13	1n	2a	3n	92
14 ^c	1o	2b : R ² = Me	3o : R ² = Me	77
15	1o	2c : R ² = OMe	3p : R ² = OMe	92
16	1o	2d : R ² = Cl	3q : R ² = Cl	97
17	1o	2e	3r	89

^a Reaction conditions: aryl bromide (**1**, 0.50 mmol), aryl formate (**2**, 0.75 mmol), PdCl₂(PhCN)₂ (0.025 mmol, 5.0 mol %), xantphos (0.025 mmol, 5.0 mol %), Et₃N (1.0 mmol) in DMF (0.50 mL) at 60 °C for 20 h. ^b Isolated yields. ^c At 70 °C. ^d At 80 °C. ^e At 90 °C.

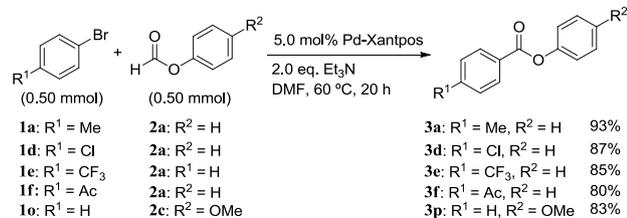
bromide (**7**) was smoothly converted to the corresponding phenyl ester (**3u**) by using P(OPh)₃ as a ligand¹¹ at 120 °C (Scheme 2d).

Noteworthy is that the present catalytic system realizes highly atom-efficient carbonylation. The reaction of **1a** with 1 equiv of **2a** in DMF (0.1 mL) smoothly proceeded and **3a** was obtained in 93% isolated yield (Scheme 3).⁸ The yield was almost comparable to that described in entry 9 in Table 1. Other reactions employing **1d**, **1e** and **1f** with 1.0 equiv **2a** afforded the corresponding products in high yield. The equimolar mixture of **1o** and **2c** in the presence of the Pd catalyst also gave **3p** in high yield.

Scheme 2 Palladium-catalyzed carbonylation of various electrophiles with **2a**.



Scheme 3 Highly efficient esterification of **1** with **2** catalyzed by the palladium-xantphos system.



In conclusion, the carbonylation of aryl halides using aryl formates occurred at ambient pressure in the presence of Pd-xantphos catalyst system to afford aryl esters in good to high yields. The reaction can be carried out without the use of external carbon monoxide, and no directing group is required. During the reaction aryl formates were converted to carbon monoxide and the corresponding phenols by the aid of a base.

This work was supported by Grant-in-Aid for Scientific Research on Innovative Areas ("Organic synthesis based on reaction integration" and "Molecular activation directed toward straightforward synthesis") from MEXT, Japan. T. F. is acknowledged to The Sumitomo Foundation for financial support.

Notes and references

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⁸ See ESI for detail†.

⁹ Abbreviation: *o*-tol = 2-methylphenyl, Cy = cyclohexyl, dppe = 1,2-bis(diphenylphosphino)ethane, dppp = 1,2-bis(diphenylphosphino)propane, dppf = 1,2-bis(diphenylphosphino)ferrocene, *rac*-binap = bis(diphenylphosphino)-1,1'-binaphthyl, xantphos: 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene.

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