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

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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,5 co-catalysts,6 or strong bases.7 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.8 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 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 the carbonylated products in high yields.7

![Scheme 1](image)

40 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 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 PCy3,8 3a was obtained in low yields (entries 2–4). The use of a bidentate phosphate 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, xantphos9,10 gave the best result, affording 3a in 99% yield (entry 9). As a base, (i-Pr)_2NEt, DBU, and K_2CO_3 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 1 Effect of ligands on the palladium-catalyzed esterification of 4-bromotoluene (1a) with phenyl formate (2a).9

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>PPh3</td>
<td>27</td>
</tr>
<tr>
<td>3</td>
<td>P(o-tol)_3</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>PCy3</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>dppe</td>
<td>12</td>
</tr>
<tr>
<td>6</td>
<td>dppp</td>
<td>37</td>
</tr>
<tr>
<td>7</td>
<td>dppf</td>
<td>15</td>
</tr>
<tr>
<td>8</td>
<td>rac-binap</td>
<td>50</td>
</tr>
<tr>
<td>9</td>
<td>xantphos</td>
<td>99 (94)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction conditions*</th>
<th>Yield of Phenol (%)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PdCl₂(PhCN)₂ (2.5 mol%), xantphos (2.5 mol%), Et₃N (1.0 equiv)</td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td>PdCl₂(PhCN)₂ (2.5 mol%), xantphos (2.5 mol%)</td>
<td>&lt;5</td>
</tr>
<tr>
<td>3</td>
<td>Et₃N (1.0 equiv)</td>
<td>99</td>
</tr>
<tr>
<td>4</td>
<td>Et₃N (1.0 equiv) at 40 °C</td>
<td>24</td>
</tr>
<tr>
<td>5</td>
<td>Et₃N (10 mol%)</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>

* Reaction conditions: 2a (1.0 mmol) in DMF (0.5 mL) at 60 °C for 20 h. † 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), 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 in almost 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 were tolerated under the reaction conditions. Gratifyingly, 1l bearing an ethynyl moiety afforded the corresponding ester (3l) without hydrostereification at the alkynyl moiety (entry 11). Heterocycles such as pyridine and thiophene were also adapted (entries 12 and 13). Besides 2a, the reaction of bromobenzene (1o) with 2a afforded the corresponding esters (3o–q) in high yields. A sterically demanding aryl formate (2e) also afforded 3r in high yield.

An alkynyl 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 Carbynylation of various substrates under the optimum reaction conditions.‡

<table>
<thead>
<tr>
<th>Entry</th>
<th>R²R₁ Br</th>
<th>R²R₁ COO</th>
<th>Yield (%)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R²R₁ Br</td>
<td>R²R₁ COO</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>R²R₁ Br</td>
<td>R²R₁ COO</td>
<td>83</td>
</tr>
<tr>
<td>3</td>
<td>R²R₁ Br</td>
<td>R²R₁ COO</td>
<td>96</td>
</tr>
<tr>
<td>4</td>
<td>R²R₁ Br</td>
<td>R²R₁ COO</td>
<td>89</td>
</tr>
<tr>
<td>5</td>
<td>R²R₁ Br</td>
<td>R²R₁ COO</td>
<td>92</td>
</tr>
<tr>
<td>6</td>
<td>R²R₁ Br</td>
<td>R²R₁ COO</td>
<td>88</td>
</tr>
<tr>
<td>7</td>
<td>R²R₁ Br</td>
<td>R²R₁ COO</td>
<td>72</td>
</tr>
<tr>
<td>8</td>
<td>R²R₁ Br</td>
<td>R²R₁ COO</td>
<td>88</td>
</tr>
<tr>
<td>9</td>
<td>R²R₁ Br</td>
<td>R²R₁ COO</td>
<td>84</td>
</tr>
<tr>
<td>10</td>
<td>R²R₁ Br</td>
<td>R²R₁ COO</td>
<td>89</td>
</tr>
<tr>
<td>11</td>
<td>R²R₁ Br</td>
<td>R²R₁ COO</td>
<td>87</td>
</tr>
<tr>
<td>12</td>
<td>R²R₁ Br</td>
<td>R²R₁ COO</td>
<td>91</td>
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<tr>
<td>13</td>
<td>R²R₁ Br</td>
<td>R²R₁ COO</td>
<td>92</td>
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<tr>
<td>14</td>
<td>R²R₁ Br</td>
<td>R²R₁ COO</td>
<td>77</td>
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<td>15</td>
<td>R²R₁ Br</td>
<td>R²R₁ COO</td>
<td>92</td>
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<tr>
<td>16</td>
<td>R²R₁ Br</td>
<td>R²R₁ COO</td>
<td>97</td>
</tr>
<tr>
<td>17</td>
<td>R²R₁ Br</td>
<td>R²R₁ COO</td>
<td>89</td>
</tr>
</tbody>
</table>

* 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. ‡ Isolated yields. † At 70 °C. ‡ At 80 °C. † At 90 °C. † At 120 °C (Scheme 2d).

Note-worthy 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). 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 2e in the presence of the Pd catalyst also gave 3p in high yield.
Scheme 2 Palladium-catalyzed carbonylation of various electrophiles with 2a.

(a) \( \text{PhBr} + 2a \)  
\[ \text{Ph} + \text{O} \rightarrow \text{PhO} \]  
5.0 mol% PdCl\(_2\)(PhCl\(_2\))  
2.0 equiv Et\(_3\)N  
DMF, 60 °C, 20 h  
66%  

(b) \( X = \text{Br} \), \( X = \text{Cl} \), \( X = \text{CF}_3 \), \( X = \text{Ac} \), \( X = \text{H} \)  
5.0 mol% PdCl\(_2\)(PhCl\(_2\))  
2.0 equiv Et\(_3\)N  
DMF, 60 °C, 20 h  
60%  

(c)  
5.0 mol% PdCl\(_2\)(PhCl\(_2\))  
2.0 equiv \( \text{Me}_{3} \text{SiCN} \)  
DMF, 60 °C, 20 h  
79%  

(d)  
5.0 mol% PdCl\(_2\)(PhCl\(_2\))  
2.0 equiv Et\(_3\)N  
DMF, 60 °C, 20 h  
60%  

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

\( \text{R}^1 \text{Br} \rightarrow \text{R}^1 \text{O} \rightarrow \text{R}^2 \text{O} \)  
5.0 mol% Pd-Xanthos  
2.0 equiv Et\(_3\)N  
DMF, 60 °C, 20 h  
98%  

In conclusion, the carbonylation of aryl halides using aryl formates occurred at ambient pressure in the presence of Pd-xanthos 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.

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Notes and references

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1 For reviews, see:  
(a) A. Bennhabl, H. Neumann and M. Beller, Angew. Chem., Int. Ed., 2009, 48, 4114-4133;  
(b) A. Bennhabl, H. Neumann and M. Beller, ChemCatChem, 2009, 1, 28-41;  
(c) G. Godard, B. K. Muoz, A. Ruiz and C. Claver, Dalton Trans., 2008, 853-860;  

2 Carbonation utilizing in situ generated carbon monoxide, see:  


7 (a) Very recently, Manabe et al. reported the Pd-catalyzed carbonylation with phenyl formate.  
This publication prompted us to report our independent study featuring atom-efficient carbonylation with only 1 equiv of phenyl formate.  
(b) T. Ueda, H. Konishi and K. Manabe, Org. Lett., 2012, 14, 3100–3103;  
(c) T. Hosoki, Y. Katafuchi, T. Iwai, T. Fujihara, J. Terao and Y. Tsuji, 50th Symposium on Organometallic Chemistry, Japan, 2011, P3B-12, presented on September 9, Nagoya, Japan;  

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, xanthos: 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene.
