

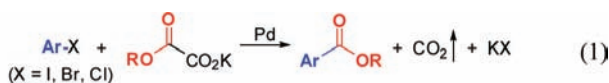
## Synthesis of Aromatic Esters via Pd-Catalyzed Decarboxylative Coupling of Potassium Oxalate Monoesters with Aryl Bromides and Chlorides

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Aromatic esters are important structural elements and synthetic intermediates. Transition-metal-catalyzed synthesis of aromatic esters from aryl halides has been studied mainly in the frame of Pd-catalyzed carbonylation.<sup>1,2</sup> The drawback of handling toxic CO gas and, under many circumstances, the requirement for high-pressure reaction conditions often limit the scope of this reaction, especially on a laboratory scale. Here we report a novel, practical synthesis of aromatic esters via Pd-catalyzed decarboxylative coupling of oxalate monoester salts with aryl halides (eq 1).



This study was inspired by the recent seminal work of Goossen and co-workers,<sup>3</sup> who discovered the decarboxylative cross-coupling of  $\alpha$ -oxocarboxylates giving rise to ketones. Related elegant studies on decarboxylative cross-coupling reactions of aromatic carboxylates have also been reported recently by Myers,<sup>4</sup> Forgiione,<sup>5</sup> Goossen,<sup>6</sup> and several other groups.<sup>7–11</sup>

Our investigation began by examining the coupling between potassium 2-ethoxy-2-oxoacetate and bromobenzene (Table 1). A series of Pd salts and phosphine ligands were examined.<sup>12</sup> Under the optimal conditions [1 mol % Pd(TFA)<sub>2</sub>, 1.5 mol % dppp], the desired product was obtained in 85% yield. Potassium 2-ethoxy-2-oxoacetate (readily made from diethyl oxalate, KOAc, and H<sub>2</sub>O) is a stable, crystalline salt.<sup>13</sup> Thus, the present protocol is operationally simpler than the previous Pd-catalyzed carbonylation method (usually conducted at ~100–150 °C with 1 mol % Pd catalyst<sup>1</sup>) because it avoids the use of toxic CO. This feature is advantageous for small-scale synthesis.

After optimizing the catalyst system, we tested the generality of the reaction with regard to both coupling partners (Table 2). It was found that both electron-rich and electron-poor aryl bromides can be successfully converted across a range of functional groups (including ether, thioether, aldehyde, ketone, amide, nitro, nitrile, ester, and heterocycle). Importantly, ortho substitution can be tolerated in the transformation (entries 3, 5, 15). In addition to the ethyl esters, potassium 2-methoxy-2-oxoacetate can be used to produce methyl esters (entries 24–28). Furthermore, the method can be used to synthesize *trans*-acrylate derivatives in high yields from vinyl bromides (eq 2), and in a special case (eq 3), we observed cascade cross-coupling/cyclization.

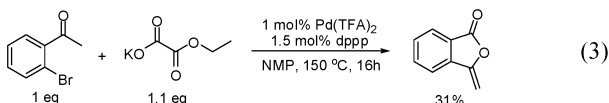
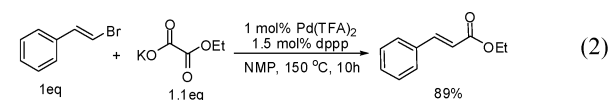


Table 1. Decarboxylative Coupling under Various Conditions<sup>a</sup>

Entry	X	Pd source	Ligand	Yield % <sup>c</sup>
1	Br	Pd(OAc) <sub>2</sub>	—	<5
2	Br	Pd(OAc) <sub>2</sub>	PPh <sub>3</sub>	27
3	Br	Pd(OAc) <sub>2</sub>	P( <i>o</i> -Tol) <sub>3</sub>	51
4	Br	Pd(OAc) <sub>2</sub>	P( <i>o</i> -MeOPh) <sub>3</sub>	62
5	Br	Pd(OAc) <sub>2</sub>	PCy <sub>3</sub>	9
6	Br	Pd(OAc) <sub>2</sub>	dppf	23
7	Br	Pd(OAc) <sub>2</sub>	dppp	81
8	Br	Pd(OAc) <sub>2</sub>	dppe	68
9	Br	Pd(OAc) <sub>2</sub>	dppm	21
10	Br	Pd(OAc) <sub>2</sub>	S-BINAP	36
11	Br	Pd(OAc) <sub>2</sub>	X-Phos	61
12	Br	Pd(OAc) <sub>2</sub>	JohnPhos	56
13	Br	PdCl <sub>2</sub>	dppp	80
14	Br	Pd(TFA) <sub>2</sub>	dppp	85
15	Br	Pd(acac) <sub>2</sub>	dppp	75
16	Br	Pd <sub>2</sub> (dba) <sub>3</sub> <sup>b</sup>	dppp	81
17	Br	Pd(dppf)Cl <sub>2</sub>	dppp	79
18	Br	Pd(PPh <sub>3</sub> ) <sub>2</sub> Cl <sub>2</sub>	dppp	80
19	Br	Pd(PPh <sub>3</sub> ) <sub>4</sub>	dppp	77
20	I	Pd(TFA) <sub>2</sub>	dppp	83
21	Cl	Pd(TFA) <sub>2</sub>	dppp	<5

<sup>a</sup> Conditions: 1 mol % Pd, 3 mol % monodentate ligand or 1.5 mol % bidentate ligand, aryl halide/potassium 2-ethoxy-2-oxoacetate = 1:1.5, 1.0 mL of *N*-methylpyrrolidone (NMP) solvent. All of the reactions were carried out at 0.5 mmol scale. <sup>b</sup> 0.5 mol %. <sup>c</sup> GC yields based on PhX.

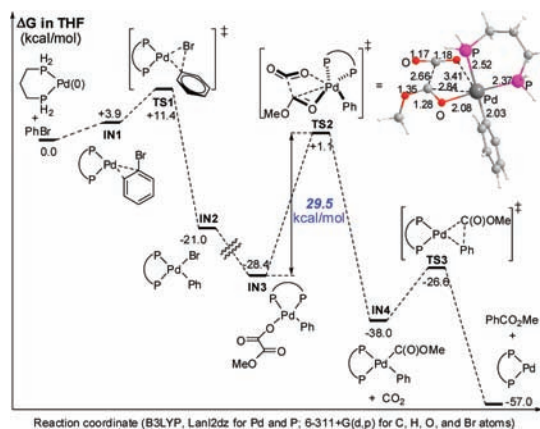
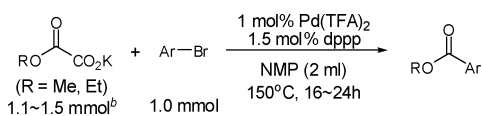


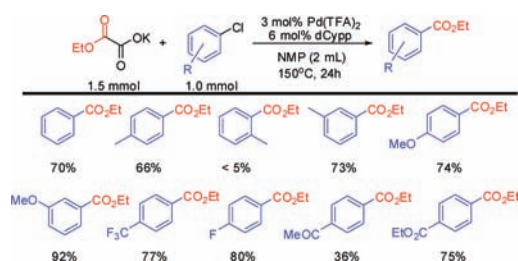
Figure 1. Proposed mechanism of decarboxylative cross-coupling.

The above protocol can be applied to both aryl bromides and iodides (Table 1, entry 20) but not aryl chlorides (entry 21). Use of bulky, electron-rich ligands may solve the problem, but our experiments with good Ar–Cl activation ligands such as <sup>t</sup>Bu<sub>3</sub>P, S-Phos, DavePhos, X-Phos, and JohnPhos<sup>14</sup> failed to couple PhCl with potassium 2-ethoxy-2-oxoacetate (see the Supporting Information). We reasoned that the use of a bulky, electron-rich ligand similar in structure to dppp might provide a solution. To our delight,

**Table 2.** Decarboxylative Cross-Coupling with Diverse Aryl Bromides

entry	product	yield% <sup>a</sup>	entry	product	yield% <sup>a</sup>
1		83	15		52
2		96	16		80
3		92	17		94
4		95	18		80
5		79	19		82
6		90	20		81
7		89	21		62
8		75	22		94
9		82	23		81
10		64	24		52
11		67	25		55
12		78	26		70
13		86	27		77
14		98	28		81

<sup>a</sup> Isolated yields based on aryl bromides. <sup>b</sup> See the Supporting Information.

**Table 3.** Decarboxylative Cross-Coupling With Aryl Chlorides<sup>a</sup>

<sup>a</sup> Isolated yields based on aryl chlorides.

dCyp proved to successfully promote the decarboxylative coupling with various aryl chlorides (Table 3).

Standard density functional theory methods were used to understand the mechanism of the new decarboxylative cross-coupling reaction (Figure 1).<sup>15</sup> A Pd(0) complex was proposed to activate the aryl halide. When 1,3-diphosphinopropane was used as a model ligand, the Pd(0) complex formed a  $\eta^2$  complex with PhBr (**IN1**), which should undergo oxidative addition through **TS1** to produce a four-coordinate Pd(II) intermediate (**IN2**). The energy barrier for oxidative addition was +11.4 kcal/mol. **IN2** then exchanged the anion to form **IN3**. From **IN3**, the decarboxylation transition state (**TS2**) was identified as a five-coordinate Pd(II) species.<sup>16</sup> In **TS2**, the Pd(II) coordinated to the leaving CO<sub>2</sub> moiety through one of its oxygens and to the other carbonyl group in an  $\eta^2$  mode. From **IN3** to **TS2**, the free energy

increased by 29.5 kcal/mol, a value whose magnitude is consistent with the experimental temperature required for the reaction (~150 °C). Thus, decarboxylation is the rate-limiting step in the catalytic cycle. The immediate product of decarboxylation was a four-coordinate acyl–Pd complex (**IN4**), which readily underwent reductive elimination to produce the ester product through **TS3** with a low barrier of ~12 kcal/mol. In **IN4**, the Pd center is coordinatively saturated, preventing decarbonylation to form an inactive Pd–CO complex. This may explain why bidentate phosphine ligands are favored for the present decarboxylative cross-coupling reactions. A related phenomenon has been discussed for Pd-catalyzed carbonylation,<sup>17</sup> where the use of bulky, electron-rich bidentate ligands has also been found to be important.<sup>2</sup>

In summary, Pd-catalyzed decarboxylative cross-coupling of aryl iodides, bromides, and chlorides with potassium oxalate monoesters has been discovered. This reaction is potentially useful for laboratory-scale synthesis of aryl and alkenyl esters.<sup>18</sup> Bulky, electron-rich bidentate phosphine ligands are preferred in the reaction, whereas Cu is not needed for decarboxylation. Theoretical calculations suggest a five-coordinate Pd(II) transition state for decarboxylation with an energy barrier of ~30 kcal/mol.

**Acknowledgment.** This study was supported by the 973 Program (2007CB210205), NNSFC (20602034, 20832004), and NCET.

**Supporting Information Available:** Experimental details and compound characterizations. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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JA900984X