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# Preparation of $\alpha$ , $\beta$ -unsaturated esters and amides via external-CO-free palladium-catalyzed carbonylation of alkenyl tosylates

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### ABSTRACT

Palladium-catalyzed carbonylation of tosylates with phenyl formate is described. This procedure needs neither external carbon monoxide nor any pressure-resistant apparatus. A variety of cyclic and acyclic alkenyl tosylates can be converted into the corresponding phenyl esters in good yields. Furthermore, this method is effective for the one-pot synthesis of  $\alpha$ , $\beta$ -unsaturated amides.

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#### Introduction

 $\alpha$ , $\beta$ -Unsaturated carboxylic acid derivatives are valuable synthetic intermediates in asymmetric reactions such as Michael, Diels-Alder, and hydrogenation reactions, since they provide efficient synthetic routes to various chiral key intermediates for pharmaceutical compounds. Among several strategies for producing α,β-unsaturated carboxylic acid derivatives, Horner-Wadsworth-Emmons reaction is the most reliable and well-established transformation that affords two-carbon-elongated esters from aldehyldes.<sup>1</sup> Alternatively, the palladium-catalyzed carbonylation employing CO gas is a complementary and useful method for the preparation of one-carbon-elongated  $\alpha_{\beta}$ -unsaturated carboxylic acid derivatives from alkenyl electrophiles.<sup>2</sup> In particular, the carbonylation of alkenyl tosylates<sup>3</sup> is more attractive than the reaction of conventional alkenyl electrophiles such as alkenyl halides<sup>4</sup> and triflates.<sup>5,6</sup> This is because alkenyl tosylates can be prepared easily from ketone or aldehyde precursors in one step, and their high stability and crystallinity simplify isolation and handling. In addition, tosylating agents are cheaper and more readily available than N-phenyl triflimide, the reagent used to prepare alkenyl triflates.7

While many methods for the carbonylation of alkenyl halides and triflates have been reported, there is only one report on the

\* Corresponding author. Tel./fax: +81 54 264 5754. *E-mail address:* manabe@u-shizuoka-ken.ac.jp (K. Manabe). carbonylation of alkenyl tosylates. Recently, Reeves et al., reported the palladium-catalyzed carbonylation of alkenyl tosylates using enantiopure skewphos as the ligand at a CO pressure of 100 psi.<sup>3</sup>

CO-free carbonylation chemistry has been the focus of extensive research in organic synthesis for the last three decades.<sup>8</sup> Various compounds such as formic acid derivatives and metal carbonyl compounds have already been developed as alternatives to toxic CO gas. Among them, formate is the most attractive due to their low price and the ease of preparation. However, the past reported carbonylation of aryl and alkenyl halides and aryl triflates employing formates has suffered from low efficiency such as the necessity of the harsh reaction conditions, the limited substrate scope, and the unsatisfactory yields.<sup>9</sup> Moreover, to the best of our knowledge, there is no precedent for the carbonylation of alkenyl tosylates with a formate.

In the course of our research on practical methodologies for the synthesis of bioactive compounds, we recently developed the practical carbonylation of aryl, alkenyl, and allyl halides with phenyl formate in the presence of a Pd–P(*t*-Bu)<sub>3</sub> catalyst system.<sup>10</sup> This method needs neither toxic CO gas nor any high-pressure equipment and affords one-carbon-elongated phenyl esters. Herein, we describe the external-CO-free carbonylation of alkenyl tosylates with phenyl formate in the presence of a Pd-xantphos catalyst system. Using the proposed method, a variety of cyclic and acyclic alkenyl tosylates can be converted into the corresponding phenyl esters in good yields under mild conditions (Scheme 1). Furthermore, this method is effective for the one-pot synthesis of  $\alpha$ , $\beta$ -unsaturated amides.



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aldehydes or ketones

one-carbon-elongated esters

**Scheme 1.** Synthesis of  $\alpha$ ,  $\beta$ -unsaturated phenyl esters via palladium-catalyzed carbonylation with phenyl formate.

# Table 1

Screening of ligands for carbonylation<sup>a</sup>



Entry	ntry Ligand	
1	P( <i>t</i> -Bu) <sub>3</sub> ⋅HBF <sub>4</sub>	0
2	PPh <sub>3</sub>	16
3	dppm	8
4	dppe	90
5	dppp	67
6	dppb	17
7	dppf	40
8	rac-Binap	42
9	xantphos	78
10	DPEphos	6

<sup>a</sup> Reactions were conducted on a 0.333 mmol scale in tosylate **1a** and anhydrous toluene (1 mL) at 100 °C using 2 equiv of 2 and 2 equiv of NEt<sub>3</sub> in the presence of 3 mol % Pd(OAc)<sub>2</sub> and 6 or 12 mol % phosphine (P/Pd = 4). The reaction time was 18 h.

<sup>b</sup> HPLC yields of **3a**.

#### Table 2 Optimization of carbonylation<sup>a</sup>

OTs	+	O H OPh	Pd(OAc) <sub>2</sub> (3 mol%) dppe or xantphos (6 mol%)	
1a (n = 2) 1b (n = 1)		<b>2</b> 2.0 equiv	NEt <sub>3</sub> (2.0 equiv) solvent 100 °C, 13–21 h	3a (n = 2) 3b (n = 1)

Entry	n	Ligand	Solvent	Yield <sup>b</sup> (%)
1	2	dppe	Toluene	90
2	2	xantphos	Toluene	78
3	2	dppe	THF	61
4	2	dppe	DME	70
5	2	dppe	CPME	29
6	2	dppe	DMF	73
7	2	dppe	NMP	54
8	2	dppe	CH <sub>3</sub> CN	88
9	2	dppe	DCE	83
10	2	dppe	PhCF <sub>3</sub>	92 (86) <sup>c</sup>
11 <sup>d</sup>	2	xantphos	PhCF <sub>3</sub>	87 (89) <sup>c</sup>
12 <sup>d</sup>	1	dppe	PhCF <sub>3</sub>	42 <sup>c</sup>
13 <sup>d</sup>	1	xantphos	PhCF <sub>3</sub>	84 <sup>c</sup>
14 <sup>d</sup>	1	xantphos	Toluene	73 <sup>c</sup>
15 <sup>d</sup>	1	xantphos	CH₃CN	34 <sup>c</sup>
16 <sup>d,e</sup>	1	xantphos	PhCF <sub>3</sub>	89 <sup>c</sup>
17 <sup>d,e,f</sup>	1	xantphos	PhCF <sub>3</sub>	34 <sup>c</sup>



13–21 h. <sup>b</sup> HPLC yields.

<sup>c</sup> Isolated yields.

<sup>d</sup> 0.5 mL of solvent was used.

 $^{e}\,$  2.5 equiv of phenyl formate (2) and NEt\_3 were used.

<sup>f</sup> Reaction temperature was 80 °C.

#### **Results and discussion**

#### Optimization

We began our investigation, by testing several ligands in the carbonylation of tosylate 1a with 2.0 equiv of phenyl formate (2) and NEt<sub>3</sub> in the presence of 3 mol % Pd(OAc)<sub>2</sub> at 100 °C (Table 1). In contrast to the carbonylation of aryl halides which we reported recently,<sup>10</sup> Pd–P(t-Bu)<sub>3</sub> catalyst system was totally ineffective in the carbonylation of **1a** (entry 1). Dppe, which has a two-carbon tether, showed excellent catalytic activity and afforded 3a in 90% yield (entry 4). Bidentate ligands having longer or shorter carbon tethers, such as dppm, dppp, and dppb, were not effective for this carbonylation (entries 3, 5, and 6). This efficiency trend of the ligands is different from that in the previously reported carbonylation of alkenyl tosylates in CO atmosphere;<sup>3</sup> the suitable ligands in that case were bidentate phosphines having three-carbon tethers, such as dppp, skewphos, and dcpp. In addition to dppe, xantphos<sup>10-12</sup> proved to be an efficient ligand, affording **3a** in 78% yield (entry 9). This result is worth noting because the bite angle<sup>13,14</sup> of dppf<sup>15</sup> (106°) and DPEphos (108°) is similar to that of

#### Table 3

Carbonylation of various alkenyl tosylates<sup>a</sup>

xantphos (110°), but the former two do not show good catalytic activity (entries 7 and 10). Under the same conditions as in entry 9, alkyl formates and formamide such as benzyl formate, heptyl formate, and dimethylformamide did not react at all and the corresponding esters and amide could not be obtained. These results highlight the importance of the rapid decarbonylation of phenyl formate (**2**) with NEt<sub>3</sub>.<sup>10</sup>

Next, we examined the effect of solvent on the carbonylation of **1a** using dppe as the ligand (Table 2). The type of solvent had a significant effect on the yield of **3a**. Ether- and amide-type solvents such as THF, DME, CPME, DMF, and NMP were not suited for this reaction (29–73%; entries 3–7). When using CH<sub>3</sub>CN and PhCF<sub>3</sub>, satisfactory yields were obtained (92% and 88%, respectively; entries 8 and 10). In particular, in the case of Pd-xantphos catalyst system, PhCF<sub>3</sub> afforded **3a** in significantly improved yield (87%, entry 11). Next, we tried the carbonylation of **1b** using dppe and xantphos as ligands (entries 12 and 13). While dppe gave a poor yield of **3b** (42%), xantphos showed good catalytic activity and afforded **3b** in 84% yield. When using toluene and CH<sub>3</sub>CN, the yields of **3b** decreased significantly compared to the result of PhCF<sub>3</sub> (entries 14 and 15 vs entry 13), which might be explained by the high sol-



<sup>a</sup> Reactions were conducted on a 100 mg scale in alkenyl tosylate **1c–m** and PhCF<sub>3</sub> (0.5 mL) at 100 °C using 2.5 equiv of **2** and 2.5 equiv of NEt<sub>3</sub> in the presence of 3 mol % Pd(OAc)<sub>2</sub> and 6 mol % xantphos. The reaction time was 11–18 h.

<sup>b</sup> Isolated yields.

 $^{c}$  4.0 equiv of 2 and 4.0 equiv of NEt<sub>3</sub> in the presence of 5 mol % Pd(OAc)<sub>2</sub> and 10 mol % xantphos.

ubility of the catalyst and **3b** in PhCF<sub>3</sub>. The yield improved slightly (89%) when an increased amount of phenyl formate (2.5 equiv) was used (entry 16 vs entry 13). At 80 °C, the yield dramatically decreased to 34% (entry 17).

## Scope of substrates

The aforementioned optimum conditions for tosylates **1a** and **1b** (1 equiv of alkenyl tosylate, 2.5 equiv of phenyl formate (**2**), 2.5 equiv

#### Table 4

One-pot synthesis of amide via carbonylation<sup>a</sup>

of NEt<sub>3</sub> in the presence of 3 mol % Pd(OAc)<sub>2</sub> and 6 mol % xantphos in PhCF<sub>3</sub> at 100 °C) were employed to test the generality of our catalyst system for a variety of alkenyl tosylates **1c-m** (Table 3). Cyclic and acyclic tosylates containing an aryl group at the  $\beta$ -position were found to be competent substrates for this reaction (entries 2, 3, 4, and 6). An aryl group at the  $\alpha$ -position of the enol tosylate **1c** did not affect the reaction (entry 1), but the geminally disubstituted alkenyl tosylate **1g** gave the product in lower yield (entry 5). This reaction was tolerant of steric hindrance in the alkenyl tosylates,



<sup>&</sup>lt;sup>a</sup> Reactions were conducted on 100 mg scale in alkenyl tosylate and PhCF<sub>3</sub> (0.5 mL) at 80–100 °C using 2.0–2.5 equiv of **2** and 2.0–2.5 equiv of NEt<sub>3</sub> in the presence of 3 mol % Pd(OAc)<sub>2</sub> and 6 mol % xantphos or dppe. The carbonylation reaction time was 10–18 h. After carbonylation, 3.0–5.0 equiv of amine was added and stirred for 12–48 h.

<sup>&</sup>lt;sup>b</sup> Isolated yields.

<sup>&</sup>lt;sup>c</sup> Dppe was used as the ligand. 2.0 equiv of phenyl formate and NEt<sub>3</sub> were used. The reaction temperature was 80 °C.

 $<sup>^</sup>d\,$  5 equiv of 0.5 M NH\_3/dioxane solution was used. The amidation temperature was 100 °C.

e Xantphos was used as the ligand. 2.5 equiv of phenyl formate and NEt<sub>3</sub> were used. The carbonylation reaction temperature was 100 °C.

<sup>&</sup>lt;sup>f</sup> 5 equiv of amine was used. The amidation temperature was 100 °C.

thus allowing for the preparation of tetrasubstituted  $\alpha$ , $\beta$ -unsaturated phenyl esters **3e**, **3h**, and **3m** (entries 3, 6, and 11). Cyclic tosylates without conjugation of an aryl group also reacted with phenyl formate (**2**) to afford the corresponding phenyl esters in good yields (entries 7–10). The reaction of the  $\beta$ -ketoester enol tosylate **1m** required increased amounts of the palladium catalyst and **2** for complete consumption of the tosylate (entry 11). The functionalized *N*-Boc piperidine substrate **1n** could also be coupled with **2** to give **3n** in moderate yield (entry 12). **3n** is the backbone of isoguvacine, which is a potent  $\gamma$ -amino butyric acid (GABA) agonist.<sup>16,17</sup>

Finally, we examined the one-pot synthesis of  $\alpha$ , $\beta$ -unsaturated amides via the carbonylation of alkenyl tosylates by adding 3.0–5.0 equiv of amine after the carbonylation (Table 4). Both primary and secondary amines reacted smoothly with the phenyl esters to afford the corresponding amides in good yields (entries 1–3, 5, and 6). In addition, ammonia could be employed to give a primary amide **4ad** (entry 4). This one-pot amidation could also be applied to synthesize tetrasubstituted  $\alpha$ , $\beta$ -unsaturated amides **4e** and **4h** (entries 7 and 8). Furthermore, this reaction tolerated alkyl ester groups to give the desired amides containing ethyl ester (entries 9 and 10).

#### Conclusion

We have found that carbonylation of alkenyl tosylates with phenyl formate can be promoted using a Pd-xantphos catalyst system. This procedure requires neither external carbon monoxide nor any pressure-resistant apparatus. A variety of cyclic and acyclic alkenyl tosylates can be converted into the corresponding phenyl esters in good yields. This method is also effective for the onepot synthesis of  $\alpha$ , $\beta$ -unsaturated amides. Further investigation concerning the application of this reaction to the synthesis of biologically active compounds will be carried out in due course.

#### Experimental

#### Synthesis of phenyl formate (2)

Formic acid (19 mL, 500 mmol, 5.0 equiv) was added to acetic anhydride (38 mL, 400 mmol, 4.0 equiv) at rt. The mixture was stirred at 60 °C for 1 h and cooled to rt. The resulting solution was poured into a flask containing phenol (9.4 g, 100 mmol) and AcONa (4.1 g, 50 mmol, 0.5 equiv). The mixture was stirred for 4 h in a water bath and then diluted with toluene (150 mL), washed with H<sub>2</sub>O (100 mL) three times, dried over MgSO<sub>4</sub>, filtered, and concentrated to afford the desired product **2** (8.7 g, 71 mmol, 71%) as a colorless oil. This product was used for the subsequent carbonylation reactions without further purification.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.28 (s, 1H), 7.39 (ddd, 2H, *J* = 8.3, 7.8, 2.4 Hz), 7.25 (tt, 1H, *J* = 7.8, 1.9 Hz), 7.10 (ddd, 2H, *J* = 8.3, 2.4, 1.9 Hz); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  159.2, 149.8, 129.6, 126.3, and 121.0.

#### General procedure for the carbonylation of alkenyl tosylates

Pd(OAc)<sub>2</sub> (3.0 mol %) and xantphos (6.0 mol%) were added to a 10-mL test tube. The test tube was evacuated and backfilled with argon three times, and then, a degassed solution of phenyl formate (**2**, 2.5 equiv), alkenyl tosylate (100 mg, 1.0 equiv), and triethylamine (2.5 equiv) in PhCF<sub>3</sub> (0.5 mL) was added to the test tube under flowing argon. The test tube was sealed by a plastic screw cap, the mixture was warmed to 100 °C (bath temperature) and stirred for 11–18 h. Then, the reaction mixture was cooled to rt, diluted with EtOAc, washed with H<sub>2</sub>O, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The obtained residue was purified by PTLC (SiO<sub>2</sub>, hexane/EtOAc 10/1–1/1) to afford the desired phenyl ester product.

# General procedure for the one-pot synthesis of amides via carbonylation

Pd(OAc)<sub>2</sub> (3.0 mol %) and xantphos or dppe (6.0 mol %) were added to a 10-mL test tube. The test tube was evacuated and backfilled with argon three times, and then, a degassed solution of phenyl formate (**2**, 2.5 equiv), alkenyl tosylate (100 mg, 1.0 equiv), and triethylamine (2.5 equiv) in PhCF<sub>3</sub> (0.5 mL) was added to the test tube under flowing argon. The test tube was sealed by a plastic screw cap, and the mixture was warmed to 80-100 °C (bath temperature) and stirred for 11-18 h. Then, the reaction mixture was cooled to rt. Amine (3.0–5.0 equiv) was added, and the test tube was re-sealed, warmed to 80-100 °C (bath temperature), and stirred for 12-48 h. The mixture was diluted with toluene, washed with 10% aq. NaOH and H<sub>2</sub>O, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The obtained residue was purified by PTLC (SiO<sub>2</sub>, CHCl<sub>3</sub>) to afford the desired amide product.

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#### Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.07.057.

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