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# Palladium-catalyzed arylation of secondary allylic alcohols in the presence of copper(II) triflate and triphenylphosphine: Selective synthesis of $\beta$ -aryl- $\alpha,\beta$ -unsaturated ketones

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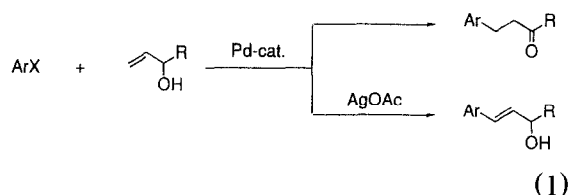
## Abstract

The palladium-catalyzed reaction of aryl iodides with 1-alken-3-ols in the presence of  $\text{Cu}(\text{OTf})_2$  and  $\text{PPh}_3$  using  $\text{K}_2\text{CO}_3$  as base was found to give 1-aryl-1-alken-3-ones as the predominant products along with 1-aryllalkan-3-ones. The factors affecting the reaction have been systematically investigated.

**Keywords:** Arylation; Allylic alcohols;  $\alpha,\beta$ -unsaturated ketones; Palladium; Copper triflate

## 1. Introduction

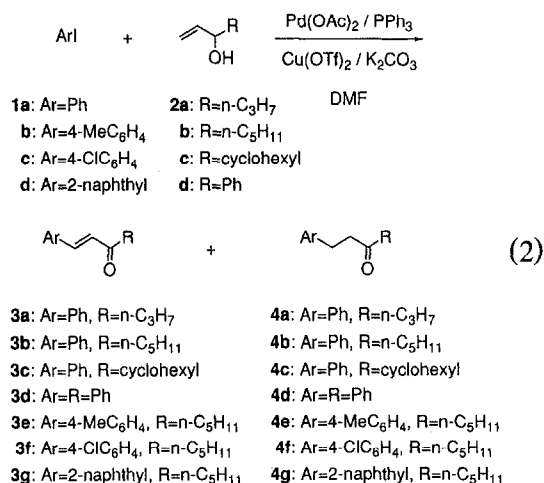
Palladium-catalyzed coupling reaction of aryl halides with alkenes (the Heck reaction) is a useful tool for the preparation of substituted aromatic compounds [1]. While the usual reaction gives styrene derivatives, it is known that 1-aryllalkan-3-ones can be obtained from allylic alcohols (Eq. (1)) [2–4].



Recently, it has been reported that the latter reaction may also give 1-aryl-1-alken-3-ols in the presence of a stoichiometric amount of silver acetate [5]. In the course of our study of palladium-catalyzed derivatization reactions of aromatic substrates [6–8], we have found that addition of appropriate amounts of copper(II) triflate and triphenylphosphine to the reaction of aryl iodides with secondary allylic alcohols can

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selectively afford 1-aryl-1-alken-3-ones along with 1-aryllalkan-3-ones Eq. (2).



Consequently, factors affecting the reaction have been systematically investigated. The results are described herein.

## 2. Results and discussion

### 2.1. Reaction of iodobenzene with 1-hexen-3-ol

The reaction of iodobenzene **1a** (1 mmol), with 1-hexen-3-ol **2a** (1 mmol), in the presence of Pd(OAc)<sub>2</sub> (0.1 mmol) using K<sub>2</sub>CO<sub>3</sub> (2.5 mmol) as base in DMF under nitrogen at 100°C for 3 h gave 1-phenylhexan-3-one **4a** (44%) as the expected major product along with 1-phenyl-1-hexen-3-one **3a** (9%) (Eq. (2) and run 1 in Table 1) [2–4]. When PPh<sub>3</sub> (0.5 mmol) was added to the reaction, the yield of **3a** (23%) was increased with the decrease of that of **4a** (13%, run 2). In this case, formation of biphenyl (12%) and 1-phenyl-1-hexen-3-ol (2%) was also detected. It was found that addition of Cu(OTf)<sub>2</sub> (2 mmol) together with PPh<sub>3</sub> significantly increased the ratio of **3a** to **4a**, the yields of **3a** and **4a** being 62% and 13%, respectively (run 4). Both the increase and decrease in the amount of PPh<sub>3</sub> reduced the yield of **3a** (run 5 and 6).

In the absence of PPh<sub>3</sub>, only a trace amount of **3a** was formed, giving **4a** predominantly (run 7). This suggests that addition of PPh<sub>3</sub> is indispensable for the selective formation of **3a**. It is noted that PPh<sub>3</sub> was appeared to be gradually oxidized to triphenylphosphine oxide during the reaction. A combination of PdCl<sub>2</sub> and PPh<sub>3</sub> or a Pd<sup>0</sup> complex Pd(PPh<sub>3</sub>)<sub>4</sub> could be used in place of Pd(OAc)<sub>2</sub>/PPh<sub>3</sub> (runs 8 and 9). However, in contrast to Cu(OTf)<sub>2</sub>, the use of CuCl<sub>2</sub> or Cu(NO<sub>3</sub>)<sub>2</sub> showed essentially no effect on the yield of **3a**, while that of **4a** somewhat increased (run 10 and 11 versus run 4). The reaction could also proceed efficiently even using a half amount of the palladium catalyst (runs 12 and 13). An organic amine base, NBU<sub>3</sub>, in place of K<sub>2</sub>CO<sub>3</sub> was not effective for the reaction (run 14), this being presumably due to disadvantage caused from its coordination ability to the palladium and copper species.

Table 1  
Reaction of iodobenzene **1a** with 1-hexen-3-ol **2a**<sup>a</sup>

Run	PPh <sub>3</sub> (mmol)	Cu(OTf) <sub>2</sub> (mmol)	Yield (%) <sup>b</sup>		Recovery of <b>1a</b> (%) <sup>b</sup>
			<b>3a</b>	<b>4a</b>	
1	0	0	9	44	
2	0.5	0	23	13	
3	0.5	1.2	48	14	
4	0.5	2	62	13	4
5	1	2	36	4	2
6	0.2	2	46	16	11
7	0	2	tr	55	18
8 <sup>c</sup>	0.5	2	52	4	21
9	0.4 <sup>d</sup>	2	53	5	13
10	0.5	2 <sup>e</sup>	23	33	
11	0.5	2 <sup>f</sup>	18	28	23
12 <sup>g</sup>	0.5	2	65	12	
13 <sup>g</sup>	0.25	2	59	15	
14 <sup>h</sup>	0.5	2	14	10	43

<sup>a</sup> Unless otherwise notes, the reaction was carried out under the following conditions: **1a** (1 mmol), **2a** (1 mmol), Pd(OAc)<sub>2</sub> (0.1 mmol), and K<sub>2</sub>CO<sub>3</sub> (2.5 mmol) in DMF (5 mL) under nitrogen at 100°C for 3 h.

<sup>b</sup> Determined by GLC analysis based on **1a** used.

<sup>c</sup> PdCl<sub>2</sub> (0.1 mmol) was used in place of Pd(OAc)<sub>2</sub>.

<sup>d</sup> Pd(PPh<sub>3</sub>)<sub>4</sub> (0.1 mmol) was used in place of Pd(OAc)<sub>2</sub>-PPh<sub>3</sub>.

<sup>e</sup> CuCl<sub>2</sub> (2 mmol) was used in place of Cu(OTf)<sub>2</sub>.

<sup>f</sup> Reaction using Cu(NO<sub>3</sub>)<sub>2</sub>·3H<sub>2</sub>O (2 mmol) in place of Cu(OTf)<sub>2</sub> for 6 h.

<sup>g</sup> **2a** (1.1 mmol) and Pd(OAc)<sub>2</sub> (0.05 mmol) were used.

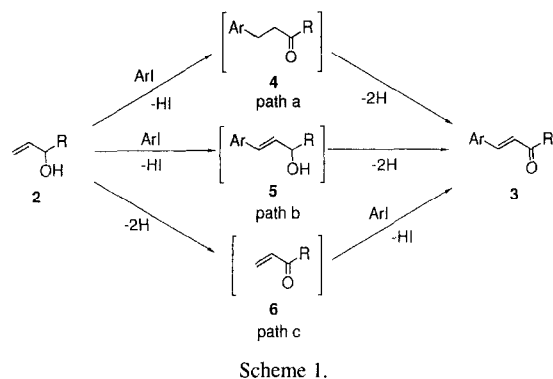
<sup>h</sup> Reaction using NBU<sub>3</sub> (2.5 mmol) in place of K<sub>2</sub>CO<sub>3</sub> for 18 h.

## 2.2. Reaction with various aryl iodides and allylic alcohols

Table 2 summarizes the results for the reaction of aryl iodides **1a–1d** with allylic alcohols **2a–2d** using the catalyst system of  $\text{Pd}(\text{OAc})_2/\text{PPh}_3/\text{Cu}(\text{OTf})_2$  (Eq. (2)). The reaction of **1a** with 1-octen-3-ol **2b** successfully proceeded in the presence of 5 mol% of  $\text{Pd}(\text{OAc})_2$ , 1-phenyl-1-octen-3-one **3b** being produced in a yield of 77% along with 1-phenyloctan-3-one **4b** (13%) within 1.5 h (run 16 in Table 2). Other alcohols (**2c–2d**) also reacted with **1a** to give the corresponding unsaturated ketones (**3c–3d**) as the major products (runs 18–20). While the branched allylic alcohol **2c** was appeared to be less reactive than **2a** and **2b** (run 18 versus runs 4 and 15), **3c** was formed in a reasonable yield at 130°C (run 19). Aryl iodides **1b–1d** could also react with **2b** to afford **3e–3g** along with **4e–4g** (runs 21–23).

## 2.3. Reaction scheme

The predominant products in the present reaction using  $\text{Pd}(\text{OAc})_2/\text{PPh}_3/\text{Cu}(\text{OTf})_2$ , 1-aryl-1-alken-3-ones **3**, have a structure two hydrogen shorter than that of the normal Heck type reaction products **4**. Therefore, their formation from allylic alcohols **2** should be accompanied by not only arylation but also dehydrogenation. There seem to be three possible paths leading to **3** (Scheme 1): i.e. dehydrogenations of (a) 1-arylalkan-3-ones **4** formed as the normal products (see also Eq. (1)), (b) the alternative arylation products, 1-aryl-1-alken-3-ols **5**, and (c) allylic alcohols **2** to give 1-alken-3-ones **6** before the arylation. It has been reported that both oxidative dehydrogenations of saturated ketones using  $\text{Pd}^{\text{II}}/\text{Cu}^{\text{II}}/\text{O}_2$  [9] and  $\text{Pd}^{\text{II}}/\text{Sn}(\text{OTf})_2$  [10] and secondary alcohols using  $\text{Pd}^{\text{II}}/\text{Cu}^{\text{II}}/\text{O}_2$  [11] and  $\text{Pd}^{\text{II}}/\text{O}_2$  [12] can occur to give the corresponding  $\alpha,\beta$ -unsaturated products and ketones, respectively. Consequently, 1-phenyloctan-3-one **4b**, 1-phenyl-1-octen-3-ol **5** ( $\text{R} = n\text{-C}_5\text{H}_{11}$ ) and 1-oc-



ten-3-ol **2b** were treated under the present reaction conditions using  $\text{Pd}(\text{OAc})_2/\text{PPh}_3/\text{Cu}(\text{OTf})_2$  in the presence of  $\text{K}_2\text{CO}_3$ . The treatment of **4b** gave no dehydrogenation product, only the starting material being recovered. By contrast, the treatments of **5** and **2b** at 100°C for 1h gave the corresponding unsaturated ketones **3b** and **6** ( $\text{R} = n\text{-C}_5\text{H}_{11}$ ) in 60% and 43%, respectively, both of the conversions being ca. 70%, while the reactions could not proceed further by elongation of the treatment time. It was also confirmed that in the early stage of the reaction of **1a** with **2b** (conversion of **1a** = 36%), **5** (2%) and **6** (34%) as well as **3b** (10%) and **4b** (5%) were present in the reaction medium (cf. run 16 in Table 2). These results suggest that allylic alcohols can be oxidized by the present reaction system and the formation of **3** in the arylation of **1** with **2** may proceed by both path b and path c. Since the yield of **6** formed in the early stage was larger than those of **5** and **3b**, the latter path seems to participate preferentially. Thus,  $\text{Cu}(\text{OTf})_2$  could act as a good electron acceptor in this reaction, and also partly as a template leading to **5** from **1** and **2**, a similar role to silver salt whose function has been previously discussed [13–15]. It should be noted that the yield of **3b** from **1a** and **2b** was considerably higher than that expected from the results of the dehydrogenations of **5** and **6** ( $\text{R} = n\text{-C}_5\text{H}_{11}$ ) and **3a** could be formed from **1a** and **2a** without  $\text{Cu}(\text{OTf})_2$ , although the yield was low (run 2 in Table 1). These may be due to the facts that oxidative addition of aryl iodides to

Table 2  
Reaction with various aryl iodides and allylic alcohols<sup>a</sup>

Run	Arl	Alcohol	Temp. (°C)	Time (h)	Products (%) <sup>b</sup>	Recovery of <b>1</b> (%) <sup>b</sup>
15	<b>1a</b>	<b>2b</b>	100	1.5	<b>3b</b> (70), <b>4b</b> (12)	
16 <sup>c</sup>			100	1.5	<b>3b</b> (77), <b>4b</b> (13)	
17 <sup>d</sup>			100	1.5	<b>3b</b> (55), <b>4b</b> (14)	3
18	<b>1a</b>	<b>2c</b>	100	10	<b>3c</b> (52), <b>4c</b> (7)	17
19			130	4	<b>3c</b> (68), <b>4c</b> (11)	
20	<b>1a</b>	<b>2d</b>	80	8	<b>3d</b> (64), <b>4d</b> (7)	23
21	<b>1b</b>	<b>2b</b>	100	11	<b>3e</b> (63), <b>4e</b> (5)	16
22	<b>1c</b>	<b>2b</b>	100	6	<b>3f</b> (69), <b>4f</b> (13)	
23	<b>1d</b>	<b>2b</b>	100	1.5	<b>3g</b> (52), <b>4g</b> (34)	

<sup>a</sup> Unless otherwise noted, the reaction was carried out under the following conditions: **1** (1 mmol), **2** (1.1 mmol), Pd(OAc)<sub>2</sub> (0.1 mmol), PPh<sub>3</sub> (0.5 mmol), Cu(OTf)<sub>2</sub> (2 mmol), and K<sub>2</sub>CO<sub>3</sub> (2.5 mmol) in DMF (5 mL) under nitrogen.

<sup>b</sup> Determined by GLC analysis based on **1** used.

<sup>c</sup> Pd(OAc)<sub>2</sub> (0.05 mmol) and PPh<sub>3</sub> (0.25 mmol).

<sup>d</sup> In the absence of the copper salt under oxygen (1 atm).

palladium (0) species generated in situ are rather smooth to prevent the catalyst deactivation and aryl(halo)palladium species themselves may act as oxidants for dehydrogenation of alcohols [16]. The result for the reaction of **1a** with **2a** without PPh<sub>3</sub> (run 7) indicates that the use of the ligand is essential for dehydrogenation of allylic alcohols. However, the role is not definitive at the present stage.

By considering the fact that vinyl ketones are generally not stable, the present method seems to provide a useful, complement route to  $\beta$ -aryl- $\alpha,\beta$ -unsaturated ketones by means of palladium-catalysis. Provided that Cu(OTf)<sub>2</sub> could be replaced by other less expensive oxidants, it would be more attractive. Thus, the reaction of **1a** with **2b** was conducted under oxygen without addition of the copper species (run 17). It proceeded rather smoothly to give **3b** (55%) along with **4b** (14%).

### 3. Experimental

<sup>1</sup>H NMR spectra were recorded at 400 MHz for CDCl<sub>3</sub> solutions. MS data were obtained by EI. GLC analysis was carried out using a silicone OV-17 column (i.d. 2.6 mm × 1.5 m) or with a CBP-1 capillary column (i.d. 0.5 mm × 25 m).

The complex Pd(PPh<sub>3</sub>)<sub>4</sub> was prepared by the method reported previously [1]. Aryl iodide **1d** [17] and allylic alcohols **2c** [18], **2d** [18] and **5** (R = C<sub>5</sub>H<sub>11</sub>) [5] were prepared according to published procedures. Other starting materials were commercially available.

#### 3.1. General procedure for reaction of aryl iodides with 1-alken-3-ols

A mixture of **1** (1 mmol), **2** (1 mmol), Pd(OAc)<sub>2</sub> (22 mg, 0.1 mmol), PPh<sub>3</sub> (131 mg, 0.5 mmol), Cu(OTf)<sub>2</sub> (721 mg, 2 mmol) and K<sub>2</sub>CO<sub>3</sub> (346 mg, 2.5 mmol) in DMF (5 mL) was stirred at 100°C under nitrogen for an appropriate time. Product identification and quantification were made by GLC and GLC-MS. Products were also isolated by column chromatography on silica gel using hexane-CH<sub>2</sub>Cl<sub>2</sub> as eluent.

#### 3.2. Products

1-(2-Naphthyl)oct-1-en-3-one (**3g**): mp 76.0–77.0°C (from hexane); <sup>1</sup>H NMR:  $\delta$  0.92 (t, 3H,  $J = 6.8$  Hz), 1.33–1.39 (m, 4H), 1.71 (tt, 2H,  $J = 7.3, 7.3$  Hz), 2.70 (t, 2H,  $J = 7.3$  Hz), 6.86 (d, 1H,  $J = 16.1$  Hz), 7.49–7.55 (m, 2H), 7.68–7.70 (m, 1H), 7.72 (d, 1H,  $J = 15.6$  Hz), 7.82–7.87 (m, 3H), 7.96 (s, 1H); MS  $m/z$  252 (M<sup>+</sup>).

Anal. Calcd for  $C_{18}H_{20}O$ : C, 85.67; H, 7.99. Found: C, 85.60; H, 8.07.

1-(2-Naphthyl)octan-3-one (**4g**): oil;  $^1H$  NMR:  $\delta$  0.86 (t, 3H,  $J = 6.8$  Hz), 1.20–1.29 (m, 4H), 1.56 (tt, 2H,  $J = 7.3, 7.3$  Hz), 2.39 (t, 2H,  $J = 7.3$  Hz), 2.81 (t, 2H,  $J = 7.3$  Hz), 3.06 (t, 2H,  $J = 7.3$  Hz), 7.32 (dd, 1H,  $J = 1.5, 8.3$  Hz), 7.39–7.47 (m, 2H), 7.62 (s, 1H), 7.75–7.80 (m, 3H); MS  $m/z$  254 ( $M^+$ ); HRMS calcd for  $C_{18}H_{22}O$  254.1671, found 254.1681.

Compounds **3a** [19], **3b** [20], **3c** [21], **3d** [22], **3e** [23], **3f** [23], **4a** [19], **4b** [20], **4c** [24], **4d** [23], **4e** [23], **4f** [23] and **6** ( $R = C_5H_{11}$ ) [25] are known and were compared with those authentic specimens.

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