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# Regioselective Arylation on the $\gamma$-Position of $\alpha,\beta$-Unsaturated Carbonyl Compounds with Aryl Bromides by Palladium Catalysis

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## Abstract

Arylation of 2-substituted 2-alkenals and 3-substituted 2-cyclohexen- and 2-cyclopenten-1-ones can effectively and regioselectively proceed at their $\gamma$-position by treatment with aryl bromides in the presence of a palladium catalyst and a base.

*Keywords:* Arylation; Enals; Enones; Palladium and compounds

The palladium-catalyzed arylation of alkenes with aryl halides (the Heck reaction) has attracted considerable attention in recent years and a large number of publications concerning its widespread synthetic applications and development of more effective catalyst systems have appeared [1-3]. It has also been shown that intermolecular arylation of certain tri- [4-6] or even tetra-substituted alkenes [7-9] can be performed under appropriate conditions, which proceeds *via* insertion of their sterically crowded C-C double bonds into Pd-C bond in the key intermediate, arylpalladium species. Meanwhile, we have recently reported that intermolecular arylation of salicylaldehydes, 2-phenylphenols, 1- and 2-naphthols, benzyl ketones, and 4-alkylnitrobenzenes can efficiently take place under similar conditions, employing a combination of aryl halide / palladium catalyst / base [10-12]. In these reactions, a hydrogen existing on carbonyl or aromatic $sp^2$ carbon or benzylic $sp^3$ carbon is directly substituted by an aryl group without stoichiometric metalation.

We now report our new findings that arylation of a number of substituted enals and enones, including 2-substituted 2-alkenals and 3-substituted 2-cyclohexen- and 2-cyclopenten-1-ones, can take place not on their $\beta$-position as the usual Heck reaction, but on $\gamma$-position by treatment with aryl bromides in the presence of a palladium catalyst and a base (Tables 1 and 2), even in the substrates having hydrogens available for *syn* palladium hydride elimination [5]. While the palladium-catalyzed intermolecular arylation of stabilized carbon nucleophiles by one or two electron-withdrawing substituents with aryl halides has been reported [11, 13-

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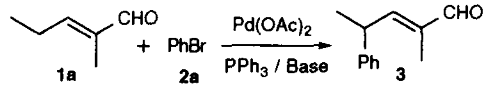
16], this appears to be, to our knowledge, the first example of direct catalytic arylative substitution of allylic hydrogen, involving dienolate anions as principal intermediates (*vide infra*).[#] The products may also be useful syntons, since they still have synthetically versatile $\alpha,\beta$-unsaturated structures.

When a mixture of (*E*)-2-methyl-2-pentenal **1a** (1 mmol) and bromobenzene **2a** (1 mmol) was stirred in the presence of $Pd(OAc)_2$ (0.05 mmol), $PPh_3$ (0.1 mmol), and $Cs_2CO_3$ (1.2 mmol) in DMF at 120 °C for 1 h, (*E*)-2-methyl-4-phenyl-2-pentenal **3** was formed in a yield of 84% (Entry 1 in Table 1). The reaction proceeded smoothly even at 60 °C (Entry 2). By increasing the amount of **1a** and $Cs_2CO_3$ to 2 mmol, a high yield of 96% based on **2a** used was achieved (Entry 3).[##] The use of $K_2CO_3$ or $Na_2CO_3$ and iodobenzene in place of $Cs_2CO_3$ and **2a**, respectively, reduced the yield, due to the competitive formation of biphenyl in significant amounts (Entries 4-6).

**Table 1**

Palladium-catalyzed reaction of (*E*)-2-methyl-2-pentenal **1a** with bromobenzene **2a**[a]



| Entry | Base | Temp / °C | Time / h | Yield of **3** / %[b] |
|---|---|---|---|---|
| 1 | $Cs_2CO_3$ | 120 | 1 | 84 |
| 2 | $Cs_2CO_3$ | 60 | 4 | 80 |
| 3[c] | $Cs_2CO_3$ | 120 | 1 | 96 (93) |
| 4[c] | $K_2CO_3$ | 120 | 4 | 69 |
| 5[c] | $Na_2CO_3$ | 120 | 5 | 12 |
| 6[d] | $Cs_2CO_3$ | 60 | 4 | 34 |

[a] Reaction conditions: **1a** (1 mmol), **2a** (1 mmol), base (1.2 mmol), $Pd(OAc)_2$ (0.05 mmol), $PPh_3$ (0.1 mmol), DMF (5 $cm^3$). [b] Determined by GLC, based on **2a** used. Value in parentheses indicates yield after isolation. [c] **1a** (2 mmol) and base (2 mmol) were used. [d] Iodobenzene (1 mmol) was used in place of **2a**.

Table 2 summarizes the results for the reaction of 2-substituted 2-alkenals **1a,b** and 3-substituted 2-cyclohexen- and 2-cyclopenten-1-ones **1c-e** with aryl bromides **2**. In the case using **1a,b**, the arylation took place on their $\gamma$-position to selectively give the corresponding (*E*)-2-methyl-4-aryl-2-pentenals or (*E*)-2-ethyl-4-aryl-2-hexenals in fair to good yields. Note that when bromobenzenes having an electron-donating substituent (*i.e.* **2e** and **2f**) were used, the catalyst system of $Pd(OAc)_2$ / $P(o\text{-}Tol)_3$ appeared to afford better results compared with $Pd(OAc)_2$ / $PPh_3$. In the case of the latter system, the contamination of phenyl group from $PPh_3$ in the products considerably reduced the yield of desired products [19]. The reaction of (*E*)-2-octenal, in place of **1a,b**, with **2a** gave an intractable complex mixture, while in the case using 2-methyl-2-hexene no expected coupling proceeded, yielding biphenyl as the single detectable product.

The fact that the use of $Cs_2CO_3$, which has a relatively high solubility in DMF, is required for an efficient coupling and the inertness of 2-methyl-2-hexene may suggest that the present reaction involves a dienolate anion formed by deprotonation of **1a** or **1b**. Nucleophilic reaction of the anionic species with an arylpalladium species generated *in situ* to give an allylarylpalladium complex and the subsequent reductive elimination may afford the

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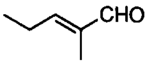
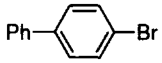
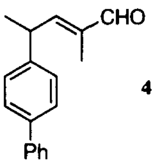
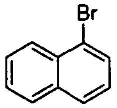
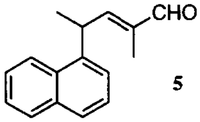
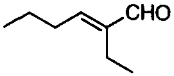
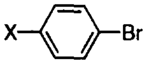
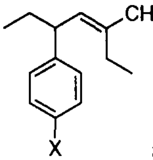
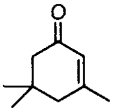
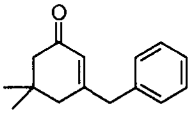
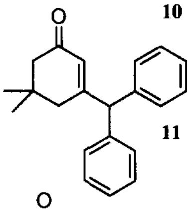
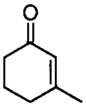
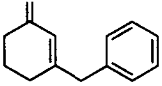
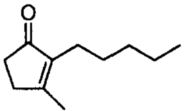
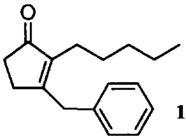
[#] The relevant palladium-catalyzed regioselective substitution of allylic stannanes has been reported [17].

[##] Typical procedure: In a 100 $cm^3$ two-necked flask was placed $Cs_2CO_3$ (652 mg, 2 mmol) which was dried at 150 °C in vacuo for 2 h. Then, **1a** (196 mg, 2 mmol), **2a** (157 mg, 1 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), $PPh_3$ (26.2 mg, 0.1 mmol), and DMF (5 $cm^3$) were added and the resulting mixture was stirred under nitrogen at 120 °C for 1 h. After cooling, the reaction mixture was extracted with diethyl ether, and dried over sodium sulfate. Product **3** (162 mg, 93%) was isolated by column chromatography on silica gel using pentane-dichlorometane (60:40, v/v): Oil [18]; MS *m/z* 174 ($M^+$); $^1H$ NMR (400 MHz, $CDCl_3$) $\delta = 1.46$ (d, $J = 6.8$ Hz, 3H), 1.83 (s, 3H), 3.95-4.02 (m, 1H), 6.56 (d, $J = 9.8$ Hz, 1H), 7.22-7.35 (m, 5H), 9.41 (s, 1H); $^{13}C$ NMR $\delta = 9.5$, 21.0, 39.0, 126.6, 126.8, 128.7, 137.5, 143.4, 157.7, 195.0.

**Table 2**

Palladium-catalyzed arylation of $\alpha,\beta$-unsaturated carbonyl compounds **1** with aryl bromides **2**[a]

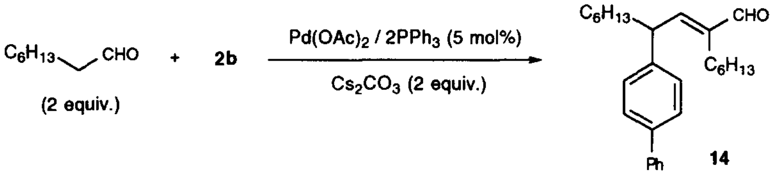
| **1** (mmol) | **2** (mmol) | Temp. / °C | Time / h | Product[b] | Yield / %[c] |
|---|---|---|---|---|---|
| <br>**1a** (1) | <br>**2b** (1) | 120 | 1 | <br>**4** | 79 (41) |
| **1a** (1) | <br>**2c** (1) | 60 | 4 | <br>**5** | 94 (67) |
| <br>**1b** (2) | <br>**2a**: X = H (1) | 120 | 1 | <br>**6**: X = H | 94 (80) |
| **1b** (2) | **2d**: X = Cl (1)[d] | 60 | 4 | **7**: X = Cl | 82 (64) |
| **1b** (1) | **2e**: X = OMe (1)[e] | 60 | 2 | **8**: X = OMe | 92 (60) |
| **1b** (1) | **2f**: X = Me (1)[e] | 60 | 5 | **9**: X = Me | 79 (69) |
| <br>**1c** (4) | **2a** (1) | 60 | 6 | <br>**10** | 71 (56)[f] |
| **1c** (1) | **2a** (2)[d] | 80 | 5 | <br>**11** | 79 (56)[g] |
| <br>**1d** (4) | **2a** (1) | 60 | 2 | <br>**12** | 56 (50)[f] |
| <br>**1e** (2) | **2a** (1) | 60 | 21 | <br>**13** | 58 (47)[f] |

[a] Reaction conditions: $Pd(OAc)_2$ (0.05 mmol), $PPh_3$ (0.1 mmol), $Cs_2CO_3$ (1.2-4 mmol) in DMF (5 $cm^3$) under $N_2$. [b] Satisfactory spectra were obtained in measurements of $^1H$ and $^{13}C$ NMR and MS. Configuration of the products was also determined with the aid of NOE technique in $^1H$ NMR measurements. Melting points of **4** and **5** were 42.5-43 and 67.5-68 °C, respectively. Other compounds were obtained as oils. [c] Determined by GLC. Value in parentheses indicates yield after isolation. [d] $Pd(OAc)_2$ (0.025 mmol) and $PPh_3$ (0.05 mmol) were used. [e] $P(o\text{-}Tol)_3$ (0.2 mmol) was used in place of $PPh_3$. [f] The reactions to give **10**, **12**, and **13** accompanied formation of minor amounts of the corresponding diphenylated products in 4, 6, and 8% yields, respectively. [g] The monophenylated compound **10** (3%) was also formed.

corresponding arylated products [11,15,16]. This reaction sequence seems to be energetically more favorable compared with that of insertion of **1a,b** to arylpalladium species followed by palladium hydride elimination, and hence, the arylation at the $\gamma$-position may occur selectively. The exclusive formation of the (*E*)-products **4-9** may imply that they are thermodynamically more stable than their (*Z*)-isomers, as for the starting compounds **1a,b**.

Cyclic enones **1c-e** were also found to be good substrates for the arylation. The reaction of isophorone **1c** with **2a** took place not on the $\alpha'$-position of carbonyl group, but exclusively on the methyl group of 3-position, and either mono- **10** or di-phenylated compound **11** could be selectively obtained by changing the amount of **1c** or **2a**. From the reactions of enones **1d,e** under the monophenylation conditions, compounds **12** and **13** were selectively produced, respectively.

Various $\alpha,\beta$-unsaturated aldehydes may be formed by aldol condensation of simple aliphatic aldehydes in the presence of a base [20]. Consequently, the reaction of octanal (2 mmol) with **2b** (1 mmol) was examined at 60 $^{o}$C for 46 h; it was observed that the expected 2:1 coupling product, (*E*)-2-hexyl-4-(4-phenylphenyl)-2-decenal **14**, was successfully produced in a yield of 50%.



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