Pergamon

Tetrahedron Letters 39 (1998) 6203–6206

TETRAHEDRON LETTERS

Regioselective Arylation on the γ-Position of α,β-Unsaturated Carbonyl Compounds with Aryl Bromides by Palladium Catalysis

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Received 15 May 1998; revised 18 June 1998; accepted 19 June 1998

Abstract

Arylation of 2-substituted 2-alkenals and 3-substituted 2-cyclohexen- and 2-cyclopenten-1-ones can effectively and regioselectively proceed at their γ-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 β-position as the usual Heck reaction, but on γ-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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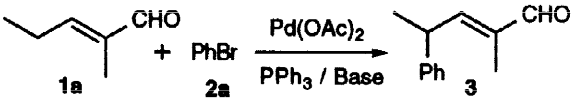
PII: S0040-4039(98)01275-1

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 α,β-unsaturated structures.

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**.

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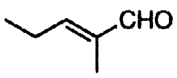
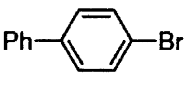
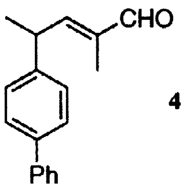
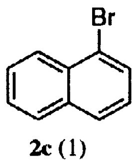
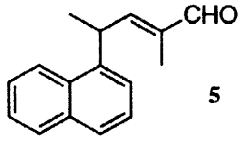
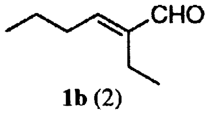
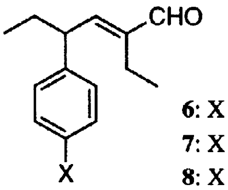
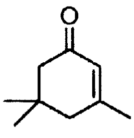
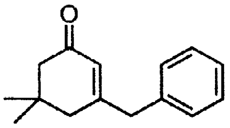
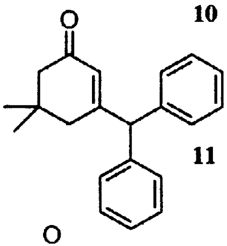
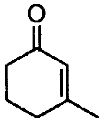
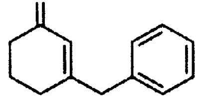
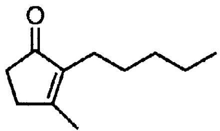
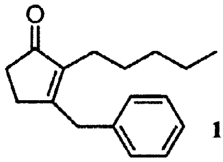
[#] The relevant palladium-catalyzed regioselective substitution of allylic stannanes has been reported [17].

[##] 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 α,β-unsaturated carbonyl compounds **1** with aryl bromides **2**[a]

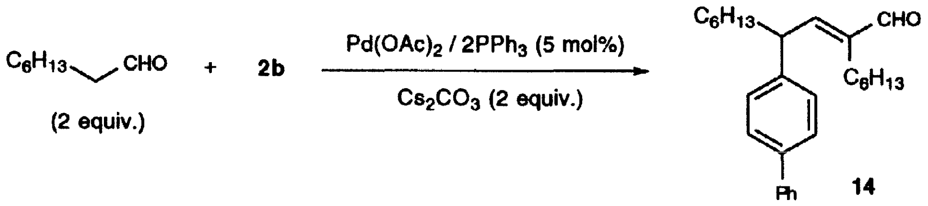
1 (mmol)	**2** (mmol)	Temp. / °C	Time / h	Product[b]	Yield / %[c]
 **1a** (1)	 **2b** (1)	120	1	 **4**	79 (41)
1a (1)	 **2c** (1)	60	4	 **5**	94 (67)
 **1b** (2)	 **2a**: X = H (1)	120	1	 **6**: X = H	94 (80)
1b (2)	**2d**: X = Cl (1)[d]	60	4	**7**: X = Cl	82 (64)
1b (1)	**2e**: X = OMe (1)[e]	60	2	**8**: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



Acknowledgement

This work was partly supported by a Grant-in-aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture, Japan.

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