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Palladium-catalyzed α-arylation of aldehydes with aryl bromides

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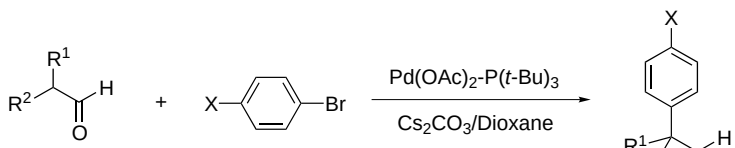
Abstract—Aliphatic linear and α-branched aldehydes efficiently undergo arylation at the α-position upon treatment with aryl bromides using an appropriate palladium catalyst system that is capable of overcoming aldol condensation of the substrates.

Palladium-catalyzed arylation reactions using aryl halides are now recognized to be highly useful for making aromatic fine compounds.[1,2] For example, the reaction of alkenes (Mizoroki–Heck reaction) and that of organoboron compounds (Suzuki–Miyaura reaction) are very often employed.

On the other hand, the substitution reactions of carbonyl compounds at the α-position via enolates with organic electrophiles including halides are among the most important carbon–carbon bond formation reactions. Recently, the palladium-catalyzed method has also proved to be a powerful tool for the substitution with aryl halides.[3–6] Thus, ketones,[3,4a–d,5a–b,6a–b] esters[3b,4e,5d] and amides[5c] can undergo α-arylation efficiently by using an appropriate palladium catalyst in the presence of a base. However, since the aldol condensation of aldehydes takes place under basic conditions, simple common ones have not been suitable as the substrates for the arylation, although α,β-unsaturated aldehydes selectively arylated at the γ-position.[7] Only the intramolecular cyclization of special haloaryl-linked aldehydes has been reported.[6c]

In the course of our study of the palladium-catalyzed reactions, an effective protocol for the α-arylation of aliphatic linear and α-branched aldehydes that overcomes aldol condensation has been developed (Scheme 1).[8] The method is reported herein.

Octanal (**1a**) and bromobenzene (**2a**) were used first as the representative substrates. The aldehyde **1a** (2 mmol) was treated with the bromide **2a** (1 mmol) in the presence of $Pd(OAc)_2$ (0.05 mmol) and $P(t\text{-}Bu)_3$ (0.1 mmol) using Cs_2CO_3 (1.2 mmol) as base in DMF at 110°C for 2 h. Analysis of the reaction mixture by GC and GC–MS confirmed that α-phenylated product, 2-phenyloctanal (**3**) (49%) was produced together with (*E*)-2-hexyl-4-phenyl-2-decenal (**4**) (20%), which is formed by aldol condensation followed by γ-phenylation (entry 1 in Table 1). Simple condensation product **5** (31%) was also detected. The reaction using PPh_3 in place of $P(t\text{-}Bu)_3$ gave **4** as the predominant product, as reported previously (entry 2).[7] It was very interesting that by employing $P(t\text{-}Bu)_3$ and dioxane as ligand and solvent, respectively, **3** was selectively obtained in a yield of 77%, the formation of **4** and **5** being signifi-



R¹, R²: Alkyl, H; Aryl, H; Alkyl, Alkyl; Alkyl, Aryl
X: H, Me, OMe, Ph

Scheme 1.

Keywords: aryl halides; arylation; aldehydes; palladium and compounds.
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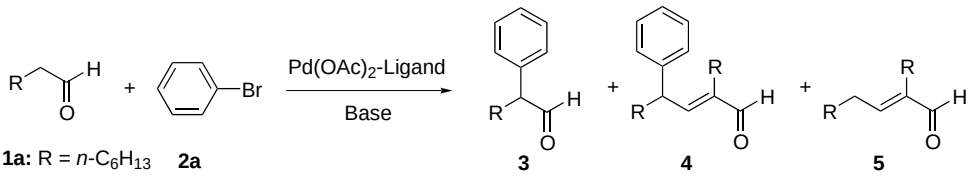
PII: S0040-4039(01)02077-9

Table 1. Palladium-catalyzed reaction of octanal (**1a**) with bromobenzene (**2a**)[a]



Entry	Ligand	Base	Solvent	Time (h)	Yield[b] (%)		
					3	**4**	**5**
1	$P(t\text{-Bu})_3$	Cs_2CO_3	DMF	2	49	20	31
2	PPh_3	Cs_2CO_3	DMF	2	0	45	22
3	$P(t\text{-Bu})_3$	Cs_2CO_3	Dioxane	2	77 (63)	1	5
4[c]	$P(t\text{-Bu})_3$	Cs_2CO_3	Dioxane	2	53	1	2
5	$P(t\text{-Bu})_3$	K_2CO_3	Dioxane	24	70	2	12
6	PPh_3	Cs_2CO_3	Dioxane	2	0	6	15
				23	0	32	11
7	PCy_3	Cs_2CO_3	Dioxane	2	0	4	18
				21	0	46	10

[a] The reaction was carried out using **1a** (2 mmol), **2a** (1 mmol), $Pd(OAc)_2$ (0.05 mmol), ligand (0.1 mmol) and base (1.2 mmol) at 110°C (bath temperature) under N_2.
[b] GC yield based on the amount of **2a** used. Value in parentheses indicates yield after chromatographic purification.
[c] **1a** (1 mmol) was used.

cantly suppressed (entry 3).[9] Decreasing the amount of **1a** to 1 mmol reduced the yield of **3** (entry 4). K_2CO_3 could be used in place of Cs_2CO_3, although a longer reaction time was required (entry 5). Using PPh_3 and PCy_3 (tricyclohexylphosphine) did not give **3** even in dioxane (entries 6 and 7).

The above results indicate the following. (a) The aldol condensation of **1a** to **5** is considerably slower in dioxane than in DMF. (b) The bulky phosphine $P(t\text{-Bu})_3$ specifically induces the α-arylation, while it also brings about the γ-arylation of **5** in DMF. (c) In contrast to the arylation of ketones and α,β-unsaturated ones,[3f] PPh_3 as well as PCy_3 is only effective for the γ-arylation.

Table 2 summarizes results for the reactions using various aldehydes and aryl bromides using $Pd(OAc)_2$ and $P(t\text{-Bu})_3$ in dioxane.[10] The reactions of **1a** with 4-substituted bromobenzenes **2b–d** gave the corresponding α-arylated products **6–8** in good yields.[11] 1-Bromonaphthalene (**2e**) could also be used. From the reactions of butanal (**1b**) and 3-phenylpropanal (**1c**) with **2d** and of phenylacetaldehyde (**1d**) with **1a** the expected products **10–12** were obtained. Interestingly, α-arylaldehydes **13** and **14** having a quaternary carbon were also formed by the reactions of α-substituted aldehydes **1e** and **1f** with **2d**. This implies that diarylation of aldehydes is possible. Indeed, the reaction of **1a** with an excess amount of **2a** afforded diarylated compound **15**.

The palladium-catalyzed α-arylation of carbonyl compounds is generally considered to proceed as follows.[3–6] The reaction of an enolate, which is formed from a carbonyl compound in the presence of a base, with an arylpalladium(II) halide, which is generated by the oxidative addition of an aryl halide to Pd(0) species, gives an alkylarylpalladium intermediate. Reductive elimination from the intermediate affords the corresponding α-arylated product with the regeneration of Pd(0) species.

Bulky phosphines including $P(t\text{-Bu})_3$ have been demonstrated to enhance the α-arylation of ketones[4d,5b] and esters[4e,5d] as well as other palladium-catalyzed arylation reactions.[12–14] $P(t\text{-Bu})_3$ may form coordinatively unsaturated active Pd(0) and Pd(II) species. The bulkiness may also enhance the final reductive elimination. Thus, the bulky phosphine seems to work similarly and effectively in the present reaction. However, the reason why **3** was not formed at all in the reaction of **1a** with **2a** using PCy_3 is unclear at the present stage.

It is also emphasized that the use of an appropriate solvent such as dioxane is very important for an efficient aldehyde α-arylation. In the solvent, aldol condensation is retarded, whereas the palladium catalysis occurs smoothly.

Acknowledgements

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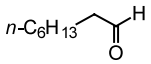
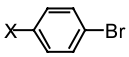
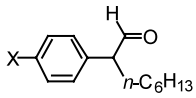
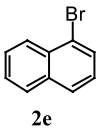
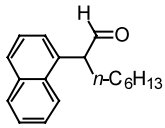
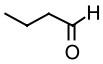
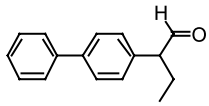
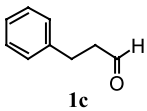
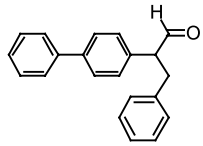
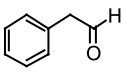
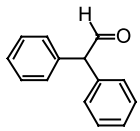
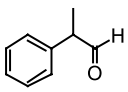
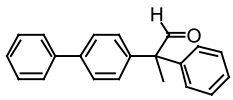
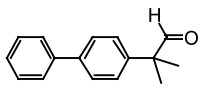
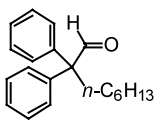
Table 2. Reaction of aldehydes **1a–f** with aryl bromides **2a–e**[a]

Entry	1	2	Time (h)	Product		Yield[b] (%)
	 **1a**					
1		**2b**: X = Me	2		**6**: X = Me	72 (67)
2		**2c**: X = OMe	2		**7**: X = OMe	64 (61)
3		**2d**: X = Ph	3		**8**: X = Ph	76 (59)
4		 **2e**	3		**9**	76 (69)
5	 **1b**	**2d**	4		**10**[16]	54 (54)
6	 **1c**	**2d**	3		**11**	68 (45)
7[c]	 **1d**	 **2a**	2		**12**	82 (56)
8	 **1e**	**2d**	3		**13**	70 (43)
9	 **1f**	**2d**	3		**14**[17]	50 (36)
10[d]	**1a**	**2a**	4		**15**	51 (47)

[a] Reaction conditions: **1** (2 mmol), **2** (1 mmol), $Pd(OAc)_2$ (0.05 mmol), P(*t*-Bu)$_3$ (0.1 mmol), Cs_2CO_3 (1.2 mmol), in dioxane under N_2.

[b] Determined by GC analysis. Value in parentheses indicates yield after chromatographic purification. In entries 1–4 and 6, the yields of simple aldol products and their γ-arylated compounds estimated by GC were 5–25 and 2–4%, respectively. They were negligible or not detected in the other entries.

[c] K_2CO_3 was used in place of Cs_2CO_3.

[d] **1a** (1 mmol), **2a** (4 mmol) and Cs_2CO_3 (4.8 mmol) were used.

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8. Pd-catalyzed α-allylation of aldehydes: Kimura, M.; Horino, Y.; Mukai, R.; Tanaka, S.; Tamaru, Y. *J. Am. Chem. Soc.* **2001**, *123*, 10401.
9. Typical procedure: In a 100 cm^3 two-necked flask was placed Cs_2CO_3 (1.2 mmol, 391 mg), which was then dried at 150°C in vacuo for 2 h. Then, $Pd(OAc)_2$ (0.05 mmol, 11.2 mg), P(*t*-Bu)$_3$ (0.1 mmol, 20.2 mg), **1a** (2 mmol, 256 mg), **2a** (1 mmol, 157 mg), 1-methylnaphthalene (ca. 100 mg) as internal standard and dioxane (5 cm^3) were added. The resulting mixture was stirred under N_2 at 110°C (bath temperature) for 2 h. After cooling, the reaction mixture was extracted with diethyl ether and dried over sodium sulfate. Product **3** (129 mg, 63%) was isolated by column chromatography on silica gel using hexane–diethyl ether (99.5:0.5, v/v) as eluent: oil;[15] ^{1}H NMR (400 MHz, $CDCl_3$) $\delta=0.86$ (t, $J=6.8$ Hz, 3H), 1.19–1.33 (m, 8H), 1.68–1.76 (m, 1H), 2.02–2.10 (m, 1H), 3.48 (ddd, $J=2.2$, 6.2, 6.6 Hz, 1H), 7.19 (d, $J=7.7$ Hz, 2H), 7.27–7.31 (m, 1H), 7.34–7.39 (m, 2H), 9.66 (d, $J=2.2$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta=14.01$, 22.55, 27.03, 29.10, 29.68, 31.56, 59.22, 127.48, 128.76, 129.00, 136.54, 201.07; MS m/z 204 (M^+).
10. Compound **6**: Oil; ^{1}H NMR (400 MHz, $CDCl_3$) $\delta=0.86$ (t, $J=6.9$ Hz, 3H), 1.14–1.38 (m, 8H), 1.62–1.75 (m, 1H), 1.98–2.08 (m, 1H), 2.34 (s, 3H), 3.44 (ddd, $J=2.2$, 7.0, 7.7 Hz, 1H), 7.07 (d, $J=8.1$ Hz, 2H), 7.17 (d, $J=8.1$ Hz, 2H), 9.63 (d, $J=2.2$ Hz, 1H); HRMS m/z (M^+) calcd for $C_{15}H_{22}O$ 218.1670, found 218.1673.
    Compound **7**: Oil; ^{1}H NMR (400 MHz, $CDCl_3$) $\delta=0.86$ (t, $J=7.0$ Hz, 3H), 1.20–1.34 (m, 8H), 1.64–1.75 (m, 1H), 1.98–2.08 (m, 1H), 3.48 (ddd, $J=2.2$, 7.3, 7.7 Hz, 1H), 3.81 (s, 3H), 6.90 (d, $J=8.8$ Hz, 2H), 7.11 (d, $J=8.8$ Hz, 2H), 9.62 (d, $J=2.2$ Hz, 1H); HRMS m/z (M^+) calcd for $C_{15}H_{22}O_2$ 234.1620, found 234.1612.
    Compound **8**: Oil; ^{1}H NMR (400 MHz, $CDCl_3$) $\delta=0.86$ (t, $J=6.9$ Hz, 3H), 1.22–1.37 (m, 8H), 1.71–1.81 (m, 1H), 2.05–2.15 (m, 1H), 3.53 (ddd, $J=2.2$, 7.3, 7.5 Hz, 1H), 7.26 (d, $J=8.7$ Hz, 2H), 7.32–7.38 (m, 1H), 7.42–7.48 (m, 2H), 7.58–7.61 (m, 4H), 9.70 (d, $J=2.2$ Hz, 1H); HRMS m/z (M^+) calcd for $C_{20}H_{24}O$ 280.1827, found 280.1823.
    Compound **9**: Oil; ^{1}H NMR (400 MHz, $CDCl_3$) $\delta=0.85$ (t, $J=6.9$ Hz, 3H), 1.20–1.41 (m, 8H), 1.82–1.93 (m, 1H), 2.30–2.40 (m, 1H), 4.25 (ddd, $J=1.5$, 6.6, 7.3 Hz, 1H), 7.33 (d, $J=7.0$ Hz, 1H), 7.47–7.58 (m, 3H), 7.82 (d, $J=8.4$ Hz, 1H), 7.90 (d, $J=7.0$ Hz, 1H), 8.04 (d, $J=8.1$ Hz, 1H), 9.70 (d, $J=1.5$ Hz, 1H); HRMS m/z (M^+) calcd for $C_{18}H_{22}O$ 254.1671, found 254.1678.
    Compound **11**: Mp 143–144°C; ^{1}H NMR (400 MHz, $CDCl_3$) $\delta=3.01$ (dd, $J=7.7$, 14.0 Hz, 1H), 3.50 (dd, $J=6.9$, 14.0 Hz, 1H), 3.87 (ddd, $J=1.5$, 6.9, 7.7 Hz, 1H), 7.07–7.10 (m, 2H), 7.16–7.23 (m, 5H), 7.33–7.37 (m, 1H), 7.41–7.46 (m, 2H), 7.55–7.60 (m, 4H), 9.77 (d, $J=1.5$ Hz, 1H); MS m/z 286 (M^+). Anal. calcd for $C_{21}H_{18}O$: C, 88.08; H, 6.34. Found: C, 87.71; H, 6.34.
    Compound **13**: Mp 77–79°C; ^{1}H NMR (400 MHz, $CDCl_3$) $\delta=1.82$ (s, 3H), 7.21–7.46 (m, 10H), 7.57–7.60 (m, 4H), 9.94 (s, 1H); MS m/z 286 (M^+). Anal. calcd for $C_{21}H_{18}O$: C, 88.08; H, 6.34. Found: C, 87.97; H, 6.50.
    Compound **15**; Oil; ^{1}H NMR (400 MHz, $CDCl_3$) $\delta=0.88$ (t, $J=6.7$ Hz, 3H), 1.00–1.35 (m, 8H), 2.24–2.28 (m, 2H), 7.19 (d, $J=7.7$ Hz, 4H), 7.26–7.31 (m, 2H), 7.33–7.38 (m, 4H), 9.80 (s, 1H); HRMS m/z (MH^+) calcd for $C_{20}H_{25}O$ 281.1905, found 281.1904.
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