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# Unexpected Formation of Aryl Ketones by Palladium-Catalyzed Coupling of Aryl Bromides with Vinylic Acetates

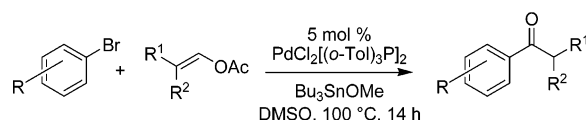
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## ABSTRACT



A palladium-catalyzed coupling reaction of aryl bromides with vinylic acetates in the presence of tributyltin methoxide has been described. Unexpected formation of aryl ketones was obtained. Preliminary mechanistic studies indicated that the reaction proceeded by the addition of the aryl moiety in the coordination sphere of palladium to a ketene.

In 1983 Migita disclosed  $\alpha$ -phenylation of ketones via tin enolates catalyzed by a palladium complex. The reaction of tributyltin enolates, prepared in situ from tributyltin methoxide and enol acetates, with aryl bromides in the presence of dichlorobis(tri-*o*-tolylphosphine)palladium was found to give  $\alpha$ -aryl ketones in good yields.<sup>1</sup> In spite of its synthetic interest, few developments and applications of this reaction were reported.<sup>2</sup> Recently Buchwald and Hartwig described independently another Pd-catalyzed  $\alpha$ -arylation of ketones, the enolates being generated in situ from ketones and bases like NaO-*t*-Bu.<sup>3</sup> To our knowledge, there has been no report

concerning  $\alpha$ -arylation of aldehydes. Here, we first describe that palladium complexes efficiently catalyze intermolecular addition of aryl bromides to various vinylic acetates in the presence of tributyltin methoxide leading to aryl ketones.

In a preliminary experiment, we treated **1a** with vinyl acetate **2a** and Bu<sub>3</sub>SnOMe in the presence of dichlorobis(tri-*o*-tolylphosphine)palladium in toluene at 100 °C. No  $\alpha$ -arylation of the aldehyde was observed, but acylation of the benzothiazole was achieved affording **3a** in a moderate yield (Scheme 1). Because of this surprising inversion of selectivity we decided to study this reaction.

We began to focus on optimizing the reaction conditions using the 2-bromonaphthalene **1b** as starting material (Table

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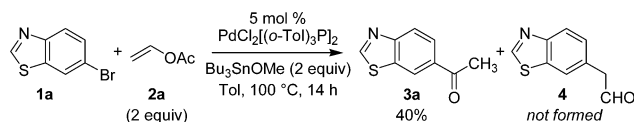
<sup>‡</sup> COB, Université de Haute Alsace.

(1) (a) Kosugi, M.; Hagiwara, I.; Sumiya, T.; Migita, T. *J. Chem. Soc., Chem. Commun.* **1983**, 344–345. (b) Kosugi, M.; Hagiwara, I.; Sumiya, T.; Migita, T. *Bull. Chem. Soc. Jpn.* **1984**, 57, 242–246.

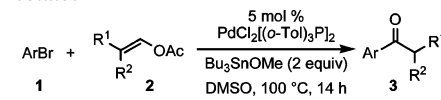

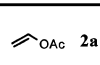

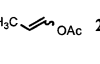




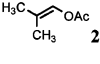

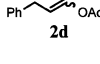


















(2) Selected examples: (a) Gupta, M.; Nair, V. *Tetrahedron Lett.* **2005**, 46, 1165–1167. (b) Nicolaou, K. C.; Xu, H. *Chem. Commun.* **2006**, 600–602.

(3) (a) Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, 119, 11108–11109. (b) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, 119, 12382–12383. (c) Culkin, D. C.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, 36, 234–245. (d) Hartwig, J. F. *Synlett* **2006**, 1283–1294.

Scheme 1. Preliminary Experiment



**Table 1.** Palladium-Catalyzed Coupling of Aryl Bromides with Vinylic Acetates

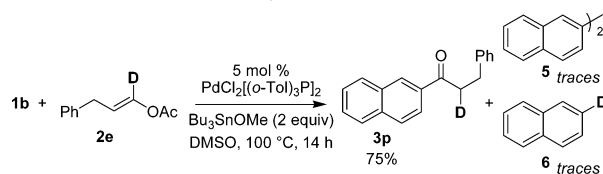
				
entry	aryl bromide	vinylic acetate	product	yield (%) <sup>a</sup>
1				49
2	<b>1a</b>			56
3		<b>2a</b>		41 <sup>b</sup>
4	<b>1b</b>	<b>2b</b>		49 <sup>b</sup>
5	<b>1b</b>			75
6	<b>1b</b>			72
7		<b>2c</b>		76
8		<b>2b</b>		12 <sup>c,d</sup>
9		<b>2b</b>		47 <sup>d</sup>
10	<b>1e</b>	<b>2c</b>		58
11		<b>2d</b>		69 <sup>d</sup>
12		<b>2d</b>		75
13		<b>2d</b>		60
14		<b>2d</b>		40
15		<b>2d</b>		28

<sup>a</sup> Isolated yield (average of two runs). <sup>b</sup> 10–15% 2,2'-binaphthalene **5** isolated. <sup>c</sup> 28% 4-NO<sub>2</sub>-C<sub>6</sub>H<sub>4</sub>-Bu isolated. <sup>d</sup> 75–90% conversion.

1, entry 4). After some experimentation (choice of solvent, palladium source, and phosphine ligand),<sup>4</sup> we found that 5 mol % of dichlorobis(tri-*o*-tolylphosphine)palladium in DMSO at 100 °C in the presence of 2 equiv of propenyl acetate **2b** and 2 equiv of Bu<sub>3</sub>SnOMe are the best conditions to obtain a complete conversion of the starting material. No reaction occurred in the absence of palladium catalyst or tributyltin methoxide. A study of the scope of this reaction was undertaken and the results are collected in Table 1.

As shown in Table 1, the Pd-catalyzed coupling of aryl bromides with vinylic acetates provided a general method for the preparation of various aryl ketones. When the reaction was carried out with vinylic acetates **2a** and **2b**, we obtained lower yields than with **2c** and **2d**. The yield was improved by using 5–10 equiv of these volatile enolates (bp <110 °C).<sup>4</sup> While the coupling reaction of **1b** with **2b** led to **3d** with a convenient yield, no reaction occurred with the 2-chloronaphthalene and only a modest conversion was observed with 2-triflate naphthalene. By using the more reactive 2-iodonaphthalene, its disappearance was achieved after 14 h at 100 °C. However, **3d** was formed in a small amount (30%) along with 2,2'-binaphthalene **5** (31%).<sup>4</sup> The reaction seemed to be sensitive to the electronic feature of the aryl group. When the aryl group possesses an electron-withdrawing group, the conversion is low (25% starting material recovered) and the main product isolated is the result of a butyl group transfer (entry 8).<sup>5</sup> The reaction remained effective in the presence of electrodonor groups even in the ortho position (entries 9–12). It is noteworthy that the coupling reaction works with ortho and ortho' substituted aryl bromides with satisfactory yield (entries 13 and 14). The 2-bromopyridine and 3-bromopyridine **1j** are known to react in Pd-catalyzed cross-coupling reactions. In our conditions only **1j** afforded the aryl ketone **3o** in low yield (entry 15) whereas the 2-bromopyridine furnished only the 2,2'-bipyridine in almost quantitative yield.

In the early stages of this work, a mechanism containing an acyl-palladium species was envisioned. However, no known element in the literature allowed us to understand the pathway with this intermediate. For a better understanding of the catalytic process we decided to realize the coupling reaction in the presence of the deuterated vinylic acetate **2e**. Under our reaction conditions, **1b** with **2e** (2 equiv) afforded the deuterated aryl ketone **3p** in 75% yield (deuterium incorporation being superior to 90%) along with traces of **5** and less than 10% of 2-deuterionaphthalene **6** (Scheme 2).

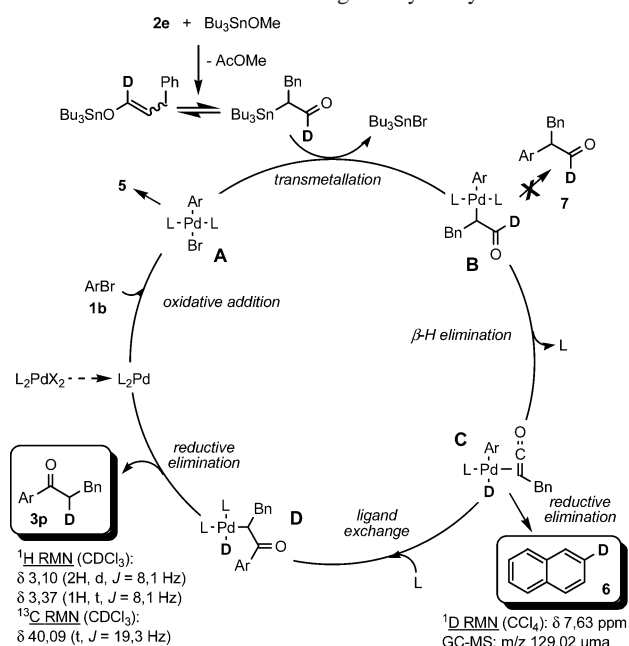
**Scheme 2.** Cross-Coupling in the Presence of Deuterated Vinylic Acetate

On the basis of these observations we propose the following catalytic cycle (Scheme 3). A Heck-type reaction cannot be ruled out. However, in the absence of tributyltin methoxide no reaction occurred. Under classical Heck reaction conditions (**1b** + **2c** in the presence of 10 mol % of PdCl<sub>2</sub>[(*o*-Tol)<sub>3</sub>P]<sub>2</sub> and 2 equiv of Et<sub>3</sub>N at 60 °C in DMF)

(4) See the Supporting Information.

(5) Ito, S.; Okujima, T.; Morita, N. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1896–1905.

### Scheme 3. Working Catalytic Cycle



no reaction was observed after the reaction was stirred for 24 h.<sup>6</sup> Thus we believe that the reaction proceeds via the addition of the aryl group to a ketene. As described by Migita, the classical oxidative addition of the aryl bromide to a Pd(0) transmetalation reaction with the stannyl enolate formed in situ from the vinylic acetate<sup>7,8</sup> led to the intermediate **B**. A direct reductive elimination from **B** could lead to aldehyde **7**. However, in almost all cases with vinylic acetates we have been unable to detect the formation of  $\alpha$ -arylaldehyde. On the contrary we suggest that the catalytic process carries on with a  $\beta$ -H elimination leading to a ketene<sup>9</sup>

(6) To our knowledge the formation of vinylic aryle derivatives in a Heck-type reaction between aryl iodide or triflate in the presence of vinyl acetate was reported independently. Neither aldehyde nor ketone was observed in these reaction conditions. (a) Andersson, C.-M.; Hallberg, A. *J. Org. Chem.* **1988**, *53*, 235–239. (b) Cabri, W.; Candiani, I.; Bedeschi, A.; Santi, R. *J. Org. Chem.* **1992**, *57*, 3558–3563.

(7) (a) Miura, K.; Fujisawa, N.; Saito, H.; Wang, D.; Hosomi, A. *Org. Lett.* **2001**, *3*, 2591–2594. (b) Doyle, A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 62–63.

coordinated to the palladium as complex **C**.<sup>10</sup> Insertion of the ketene into the aryl–palladium bond followed by a reductive elimination gives product **3p** and regenerates the palladium catalyst. A similar aryl addition to a ketene in the coordination sphere of palladium was previously described by Watanabe.<sup>11</sup> This work consolidates our proposed mechanism. The presence of a small amount of **5** probably resulted from a palladium-catalyzed homocoupling of aryl bromides.<sup>12</sup>

The present work is the first example of palladium-catalyzed coupling of aryl bromides with vinylic acetates affording aryl ketones. Initial mechanistic studies indicated that the reaction proceeded by the addition of the aryl group to a ketene. Further investigations of the scope and mechanism, as well as synthetic applications, are currently in progress and will be reported in due course.

**Acknowledgment.** We gratefully acknowledge Professor Jacques Eustache (COB, Université de Haute-Alsace, France) for fruitful discussions. The authors wish to thank the referees for helpful suggestions. Financial support of this project by Bioprojet-Biotech (fellowship to MJ), the Université de Rennes 1, and the CNRS is gratefully acknowledged.

**Supporting Information Available:** Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(8) The [(2-methyl-1-propenyl)oxy]tri-*n*-butylstannane, prepared as described by Pereyre, was submitted to our cross-coupling reaction conditions with the 2-bromonaphthalene **1b**. After 14 h of stirring at 100 °C, the arylketone **3e** was obtained and isolated in 72% yield. This control experiment confirms that the tributyltin methoxide plays a similar role in this reaction as in the Migita's reaction (formation of the Pd-intermediate **B**) and excludes an acetyl-directed addition of the palladium in the vinylic bond. Pereyre, M.; Bellegarde, B.; Mendelsohn, J.; Valade, J. *J. Organomet. Chem.* **1968**, *11*, 97–100.

(9) Few examples were reported describing the formation of ketenes with the help of palladium. Okumoto, H. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; John Wiley & Sons, Inc.: New York, 2002; Chapter VI.5.2, pp 2655–2662.

(10) In the coupling reactions in the presence of the vinylic acetate **2d**, traces of cinnamaldehyde were also detected from the crude reaction mixture. The formation of cinnamaldehyde could be the result of a  $\beta$ -H elimination of a hydrogen atom at the benzylic position.

(11) Mitsudo, T.; Kadokura, M.; Watanabe, Y. *J. Org. Chem.* **1987**, *52*, 3186–3192.

(12) For example: Hennings, D. D.; Iwama, T.; Rawal, V. H. *Org. Lett.* **1999**, *1*, 1205–1208.