

## Intramolecular Nucleophilic Addition of Vinylpalladiums to Aryl Ketones

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In the last three decades, a tremendous amount of attention from a number of research groups has been paid to various types of catalytic allyl- and vinylpalladation reactions, due to their unprecedented effectiveness in selective carbon–carbon-forming protocols.<sup>1</sup> Perhaps the most systematic study was done on the investigation of allylpalladium chemistry; as a result, the electrophilic,<sup>2</sup> nucleophilic,<sup>3</sup> and even amphiphilic<sup>4</sup> nature of allylpalladium complexes was demonstrated and fully documented.<sup>1–4</sup> In contrast to the diverse chemistry of the allylpalladium complexes, the vinylpalladium intermediates were mainly involved in vinylpalladation of carbon–carbon unsaturated systems<sup>5</sup> and insertion into carbon–hydrogen<sup>6</sup> and heteroatom–hydrogen<sup>7</sup> bonds.<sup>8</sup> To the best of our knowledge, there are no reports concerning the addition of vinylpalladium species to carbon

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(2) For reviews, see for example: (a) Trost, B. M. *Acc. Chem. Res.* **1980**, *13*, 2615. (b) Tsuji, J. *Organic Synthesis with Palladium Compounds*; Springer-Verlag: New York, 1980. (c) Trost, B. M. *Pure Appl. Chem.* **1981**, *53*, 2357. (d) Tsuji, J. *Pure Appl. Chem.* **1982**, *54*, 197. For asymmetric palladium-catalyzed allylic alkylation, see: (e) Trost, B.; Vranken, D. L. *V. Chem. Rev.* **1996**, *96*, 395.

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(4) On the stoichiometric amphiphilic  $\pi$ -allylpalladium complexes, see: Hegedus, L. S.; Akermark, B.; Olsten, D. J.; Anderson, O. P.; Zetterberg, K. *J. Am. Chem. Soc.* **1982**, *104*, 697. For the amphiphilic bis- $\pi$ -allylpalladium complexes formed catalytically, see: Nakamura, H.; Shim, J.-G.; Yamamoto, Y. *J. Am. Chem. Soc.* **1997**, *119*, 8113.



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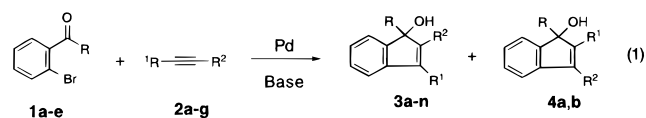
(8) "Insertion" term was used based upon the proposed mechanisms of the authors. However, the overall-transformation is clearly a "substitution reaction."

Table 1. Cyclic Vinylpalladation of Aromatic Ketones<sup>a</sup>

entry	Ketone 1		Alkyne 2		Method <sup>b</sup>	Temp/Time (°C/h)	Products, (%) <sup>c</sup>	
	R	R <sup>1</sup>	R <sup>2</sup>	3			4	
1	Me (a)	<i>n</i> -Pr	<i>n</i> -Pr (a)	A	100/20	82 (a)		
2	Me (a)	Ph	Ph (b)	A	100/20	63 (b)		
3	Me (a)	CH <sub>2</sub> OMe	CH <sub>2</sub> OMe (c)	C	100/20	53 (c)		
4	<i>t</i> -Bu (b)	<i>n</i> -Pr	<i>n</i> -Pr (a)	C	100/24	51 (d)		
5	Ph (c)	<i>n</i> -Pr	<i>n</i> -Pr (a)	B	100/96	86 (e)		
6	Ph (c)	Ph	Ph (b)	B	120/24	75 (f)		
7	Ph (c)	CH <sub>2</sub> OMe	CH <sub>2</sub> OMe (e)	C	100/28	64 (g)		
8	Ph (c)		-(CH <sub>2</sub> ) <sub>10</sub> (d)	B	100/96	76 (h)		
9	<i>p</i> -CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> (d)	<i>n</i> -Pr	<i>n</i> -Pr (a)	B	100/24	85 (i)		
10	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub> (e)	<i>n</i> -Pr	<i>n</i> -Pr (a)	C	100/48	64 (j)		
11	Ph (c)	Me	<i>t</i> -Bu (e)	C	100/48	72 (k)	-	
12	Me (a)	Me	Ph (f)	A	100/15	48 (l)	20 (4a) <sup>d</sup>	
13	Me (a)	<i>n</i> -Bu	C≡CBu (g)	A	100/15	67 <sup>e</sup> (m)	33 <sup>e</sup> (4b)	
14		<i>n</i> -Pr	<i>n</i> -Pr (a)	B	80/24		66 (n)	

<sup>a</sup> In a typical procedure after completion of the reaction under the conditions indicated in the table, the mixture was quenched (H<sub>2</sub>O), extracted (Et<sub>2</sub>O–H<sub>2</sub>O), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated. The product was purified by column chromatography (silica gel, eluent: hexane–ethyl acetate). <sup>b</sup> Method A: see in the text. Method B: The mixture of ketone **1** (1 mmol), alkyne **2** (1.5 mmol), KOAc (2 mmol), Pd(OAc)<sub>2</sub> (5 mol %), and PPh<sub>3</sub> (10 mol %) in DMF (0.25M) was stirred under Ar atmosphere. Method C: The same mixture as above plus EtOH (10 mmol) was stirred under the conditions indicated in the table. <sup>c</sup> Isolated yield unless otherwise specified. <sup>d</sup> **4a** was contaminated with a small amount of **3l**. <sup>e</sup> The products **3m** and **4b** were isolated as an inseparable mixture in 75% combined yield. The ratios were determined by <sup>1</sup>H NMR spectroscopy.

electrophiles such as a carbonyl group.<sup>9</sup> Herein we wish to report the first examples of palladium-catalyzed nucleophilic cyclic vinylpalladation of aryl ketones **1** with alkynes **2** to produce indenols **3** in good to high yields (eq 1).<sup>10</sup>



*o*-Bromoacetophenone (**1a**) (1 equiv) reacted at 100 °C with octyne-4 (**2a**) (5 equiv) in the presence of Pd(OAc)<sub>2</sub><sup>11</sup> (5 mol %) and KOAc<sup>12</sup> (2 equiv) under argon atmosphere in DMF (0.25 M) (method A) to give indenol **3a** in 82% isolated yield (Table 1, entry 1). Diphenylacetylene (**2b**) was enabled to react with **1a** under the same reaction conditions to produce indenol **3b** in 63%

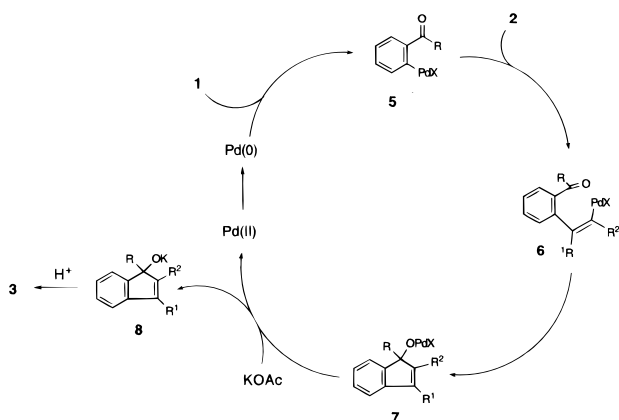
(9) There are certain number of reports on the reactions of vinylpalladium species (R–PdX) with aldehydes and esters (RXC=O). However, in these cases, the substitution products (RRC=O) were obtained. See, for example: (a) Tao, W.; Silverberg, L. J.; Rheingold, A. L.; Heck, R. F. *Organometallics* **1989**, *8*, 2550. (b) Larock, R. C.; Han, X.; Doty, M. J. *Tetrahedron Lett.* **1998**, *39*, 5713. See also refs 6f,g, and 7b.

(10) Synthesis of indenols via coupling of aromatic organomanganese compounds with alkynes is known. See: Liebeskind, L. S.; Gasdaska, J. R.; McCallum, J. S. *J. Org. Chem.* **1989**, *54*, 669.

(11) Other palladium complexes, such as PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, Pd(PPh<sub>3</sub>)<sub>4</sub>, and Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub> also catalyzed this reaction; however, the yields of **3a** in these cases were somewhat lower.

(12) Replacement of KOAc with NaOAc resulted in decrease of the reaction speed. Use of <sup>t</sup>BuOK caused the total decomposition of ketone **1**, and K<sub>2</sub>CO<sub>3</sub> was found to be not effective at all as a base in the mentioned reaction.

Scheme 1



yield (entry 2). The optimization of reaction conditions allowed us to decrease the amount of alkyne **2** down to 1.5 equiv (vs 5 equiv in the method A) by adding either 10 mol % of  $\text{PPh}_3$  (method B) or 10 equiv of EtOH (method C) to the reaction mixture (Table 1).<sup>13</sup> Thus, aryl alkyl ketones **1a,b** reacted with alkyl-substituted alkynes **2c,a** under the conditions of method C to give indenols **3c,d** in moderate yields (51 and 53%, correspondingly, entries 3,4). In contrast to the alkyl-substituted ketones **1a,b**, the diaryl ketone **1c**, under the conditions of methods B and C, smoothly reacted with dialkyl- (**2a**), diphenyl- (**2b**), dimethoxymethyl- (**2c**), and cyclic alkyne **2d**, producing indenols **3e–h** in 86, 75, 64, and 76% yield, correspondingly (entries 5–8). Substituted diaryl ketones **1d** ( $p\text{-CF}_3$ ) and **1e** ( $p\text{-MeO}$ ) easily underwent carbocyclization with **1a**, producing **3i,j** in 85 and 64% yields (entries 9, 10). Although the reaction of **1c** with the unsymmetrical bulky alkyne **2e** produced **3k** in 72% yield as a single regioisomer (entry 11), the reactions of **1a** with phenylpropyne **2f** and diyne **2g** were less regioselective; the indenols **3l** and **3m** with bulkier substituents  $\alpha$  to the hydroxyl group were contaminated with the minor regioisomeric products **4a** and **4b** (entries 12 and 13, correspondingly).<sup>14</sup> The nitrosubstituted benzophenone **1f** underwent the reaction with **2a** to give **3n** in 66% isolated yield (entry 14).

(13) Although the conditions of the methods B and C were the best for the carbocyclization of most of the ketones tested, the employment of the conditions A still gave the better yields for the reactions of **1a** with **2a** and **2b** (Table 1, entries 1,2).

(14) As expected, this reaction is limited to the use of internal alkynes only. Thus, terminal alkyne, 1-octyne, did not undergo the vinylpalladation with **1a,c**; instead, the corresponding Sonogashira coupling products were obtained.

The following mechanism is proposed for the observed unprecedented cyclic vinylpalladation of ketones (Scheme 1). The oxidative insertion of palladium catalyst into the C–X bond<sup>15</sup> of **1** would produce **5** which would arylpalladate the triple bond of **2**<sup>1b,c,5</sup> to form the vinylpalladium species **6**. The intramolecular nucleophilic addition of the vinylpalladium moiety to the keto group of **6** would produce the indenylpalladium species **7**. Excess amounts of KOAc would regenerate the catalyst and transmetalate **7** into the alkoxide **8** which after subsequent protonolysis would give the reaction product **3**. Although more detailed study on the mechanism is needed, the proposed mechanism quite reasonably explains the observed catalytic cyclic vinylpalladation of ketones. Thus, the observed regiochemistry of the arylpalladation of unsymmetrical alkynes **2e–g** with **5** (Table, entries 11–13) is in a good agreement with the known regiochemical trend for the carbopalladation of alkynes.<sup>16</sup> Furthermore, the order of reactivity of differently substituted ketones ( $p\text{-CF}_3\text{C}_6\text{H}_4$  (**1d**) >  $\text{C}_6\text{H}_5$  (**1c**)  $\gg$   $p\text{-MeOC}_6\text{H}_4$  (**1e**))<sup>17</sup> provides an additional support for the nucleophilic character<sup>18</sup> of the observed transformation **6**  $\rightarrow$  **7** (Scheme 1).

In summary, we demonstrated the first examples of the addition of vinylpalladium intermediates across an electrophilic keto group. Further investigation in line of nucleophilic carbopalladation of keto-function equivalents is now underway in our laboratories.

**Supporting Information Available:** Spectroscopic and analytical data for compounds **3a–l, n** (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(15) Iodides also underwent similar reactions; however, the yields of indenols in these cases were somewhat lower.

(16) It is well-known that carbopalladation of unsymmetrical alkynes proceeds in the *syn*-fashion producing a vinylpalladium species in which the carbon atom is attached to the less hindered site and, consequently palladium attached to the most hindered terminus of alkyne. See, for example ref 6f and references therein.

(17) We determined relative reactivities for vinylpalladation of ketones **1c–e** based on measurements of their half-reaction times. Thus, under the conditions of method B the  $t_{1/2}$  for  $p\text{-CF}_3\text{C}_6\text{H}_4$  (**1d**),  $\text{C}_6\text{H}_5$  (**1c**), and  $p\text{-MeOC}_6\text{H}_4$  (**1e**) were 4, 16, and >120 h, correspondingly. Although the so-called “half-reaction time” data are very approximate, they are useful for the rough estimation of relative reactivities. For example, see: Fleming, I.; Langley, J. A. *J. Chem. Soc., Perkin. Trans. 1* **1981**, 1412.

(18) It is well-known that the rates of nucleophilic addition to a keto group are enhanced by the electron-withdrawing groups at the keto function and reduced by the electron-donating ones. For reviews on addition of C-nucleophiles, see for example: (a) Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon Press: Oxford, 1991; Vol. 1, Chapter 1.1. (b) Fleming, I. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon Press: Oxford, 1991; Chapter 2.2. (c) Stowell, J. C. In *Carbanions in Organic Synthesis*; John Wiley: New York, 1980.