

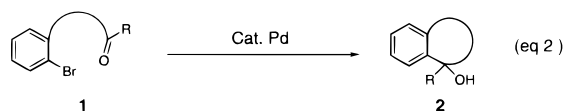
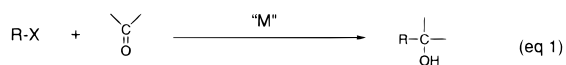
## Intramolecular Nucleophilic Addition of Aryl Bromides to Ketones Catalyzed by Palladium

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Among many synthetically useful palladium-catalyzed transformations,<sup>1</sup> a reaction of uncommon pattern is the palladium-catalyzed nucleophilic addition of organic halides to ketones and aldehydes, although such addition shown in eq 1 is the most frequently encountered reaction in traditional main-group metal chemistry. Nowadays, however, the reaction of this type is being opened in palladium chemistry; vinylpalladium halides, generated from aryl halides, alkynes, and catalytic amounts of palladium, underwent intramolecular nucleophilic addition to aryl ketones,<sup>2a</sup> aldehydes,<sup>2b</sup> and nitriles.<sup>3</sup> We now wish to report that the intramolecular nucleophilic addition of aryl bromides **1** to ketones proceeds very smoothly in the presence of palladium catalyst to give the corresponding cyclic alcohols **2** in good to high yields (eq 2). This is a *Grignard-type reaction using a palladium catalyst*.<sup>4</sup>



The reaction of the *o*-bromophenyl ketone **1a** was examined in the presence of Pd(OAc)<sub>2</sub> (5 mol %) and KOAc (2 equiv) under argon in DMF (0.25 M), as a logical extension of the previous findings.<sup>2</sup> However, a complex mixture of products was obtained, and none of the cyclization product **2a** was detected. Accidental addition of 1-hexanol to the catalyst system brought about the formation of small amounts of **2a**. Then, we investigated the effect of phosphine ligands. Among many ligands examined, tricyclohexylphosphine gave the best result: 41% yield of **2a** using Pd(OAc)<sub>2</sub>/P(Cy)<sub>3</sub>/KOAc/1-hexanol. Next, we searched a better base and found that insoluble Na<sub>2</sub>CO<sub>3</sub> gave the best result: 73% NMR yield of **2a** using Pd(OAc)<sub>2</sub> (5 mol %)/P(Cy)<sub>3</sub> (10 mol %)/Na<sub>2</sub>CO<sub>3</sub> (2 equiv)/1-hexanol (5 equiv). Other palladium catalysts, such as Pd(PPh<sub>3</sub>)<sub>4</sub>, Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub>, and PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, were not

(1) For reviews, see for example: (a) Trost, B. M.; Verhoeven, T. R. *Comprehensive Organometallic Chemistry*; Wilkinson, G.; Stone, F. G. A., Abel, E. W., Eds.; Pergamon Press: New York, 1982; Vol. 8, p 799. (b) Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1978. (c) Tsuji, J. *Palladium Reagents and Catalysts*; John Wiley: Chichester, 1995. (d) Negishi, E.; Copéret, C.; Ma, S.; Liou, S.-Y.; Liu, F. *Chem. Rev.* **1996**, *96*, 365.

(2) (a) Quan, L. G.; Gevorgyan, V.; Yamamoto, Y. *J. Am. Chem. Soc.* **1999**, *121*, 3545. (b) Gevorgyan, V.; Quan, L. G.; Yamamoto, Y. *Tetrahedron Lett.* **1999**, *40*, 4089.

(3) Larock, R. C.; Tian, Q.; Pletnev, A. A. *J. Am. Chem. Soc.* **1999**, *121*, 3238.

(4) Intramolecular coupling of *less hindered ketones* with aryl halides using excess amounts of magnesium is known. See: (a) Cacchi, S.; Palmieri, G. *J. Organomet. Chem.* **1985**, *282*, C3. We investigated the cyclization reaction of **1a** using magnesium under the same reaction conditions as those mentioned in the literature. The product **2a** was obtained in only 26% <sup>1</sup>H NMR yield along with complex by-products. Furthermore, the Mg reaction of **1g** did not proceed at all. Intramolecular coupling of cycloketones with aryl halides using 2 equiv of Bu<sub>3</sub>SnSiMe<sub>3</sub> and 2 equiv of R<sub>4</sub>NX is known. See: (b) Mori, M.; Kaneta, N.; Shibasaki, M. *J. Organomet. Chem.* **1994**, *464*, 35.

Table 1. Intramolecular Catalytic Arylpalladation of Ketones

Entry	Substrate	Base	Temp / Time °C/h	Product	Yield (%) <sup>a</sup>
1		Na <sub>2</sub> CO <sub>3</sub>	135 / 12		69 <sup>b</sup> (cis) <sup>c</sup>
2		Na <sub>2</sub> CO <sub>3</sub>	135 / 12	<b>2a</b>	41 <sup>d</sup>
3		Na <sub>2</sub> CO <sub>3</sub>	135 / 18		82 <sup>b</sup>
4		Na <sub>2</sub> CO <sub>3</sub>	135 / 18		76 <sup>b</sup>
5		NaOAc	150 / 24		76 <sup>b</sup> (cis:trans) <sup>c</sup> 88:12
6		KOAc	150 / 24		85 <sup>e</sup>
7		KOAc	135 / 24		96
8		Na <sub>2</sub> CO <sub>3</sub>	135 / 12		75 <sup>b</sup> (cis) <sup>c</sup>
9		NaOAc	150 / 16		62 <sup>b</sup> (cis) <sup>c</sup>
10		NaOAc	150 / 16		56 <sup>b</sup>
11		KOAc	100 / 24		89

<sup>a</sup> Isolated yield except otherwise indicated. <sup>b</sup> As a by-product, the dehalogenated aryl ketones were formed in 10–35% yields. For example, in entry 1, PhCH<sub>2</sub>CH(CH<sub>3</sub>)COPh **3a** was produced in 20% yield. <sup>c</sup> The stereochemistry was determined by NOE experiments (see Supporting Information). “Cis” stands for the cis stereochemical relation between Me and OH group. <sup>d</sup> <sup>1</sup>H NMR yield and here **3a** was obtained in 57% yield. <sup>e</sup> 10 mol % of PBu<sub>3</sub> was used in place of PCy<sub>3</sub>.

effective.<sup>5</sup> In the absence of bases, no cyclization products were obtained. The cyclization was quite inefficient in the absence of 1-hexanol. 1-Hexanol was recovered after the reaction was over, and other aliphatic alcohols such as 1-pentanol and 1-propanol were equally effective.<sup>6</sup>

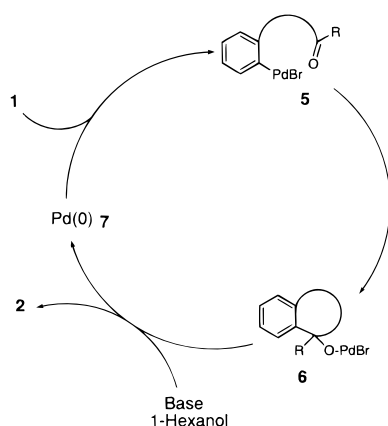
The results of the cyclization of various bromo ketones are summarized in Table 1. The arylpalladation of **1a** in the presence of Pd(OAc)<sub>2</sub> (5 mol %), PCy<sub>3</sub> (10 mol %), Na<sub>2</sub>CO<sub>3</sub> (2 equiv) and 1-hexanol (5 equiv) under argon atmosphere in DMF (0.25 M) at 135 °C gave the indanol **2a** in 69% isolated yield as a single diastereomer along with 20% yield of the corresponding dehalogenation product **3a**<sup>7</sup> (entry 1). The use of the iodide **1a'**, instead of the bromide **1a**, decreased the yield of **2a** from 69% to 41% and increased the yield of **3a** from 20 to 57% (entry 2). No reaction took place in the case of the corresponding chloride. The arylation of the ketone **1b**, which contains no hydrogen α to

(5) Ph<sub>3</sub>P ligand was not suitable to the present reaction. For example, not only Pd(PPh<sub>3</sub>)<sub>4</sub> but also Pd(OAc)<sub>2</sub>/PPh<sub>3</sub> system was not effective. On the other hand, aliphatic phosphine ligands were suitable: Pd(OAc)<sub>2</sub>/PBu<sub>3</sub> was also effective.

(6) MeOH and EtOH were not examined since their boiling points were lower than the reaction temperatures.

(7) Reduction of aryl halides to the corresponding dehalogenated arenes in the presence of palladium catalyst and base, see: (a) Zask, A.; Helquist, P. *J. Org. Chem.* **1978**, *43*, 1978. (b) Tamaru, Y.; Yamamoto, Y.; Yamada, Y.; Yoshida, Z. *Tetrahedron Lett.* **1979**, *16*, 1401.

## Scheme 1



a carbonyl group, proceeded smoothly to give the indanol **2b** in 82% yield (entry 3). The aliphatic ketone **1c** underwent the arylation similarly to produce **2c** in 76% yield (entry 4). Even when the sterically bulky naphthyl bromide **1d** was employed as a substrate, the reaction proceeded without any problem to afford the cyclized product **2d** in 76% yield with a high diastereomeric selectivity (entry 5). The biaryl ketones **1e** and **1f** reacted very smoothly to give the corresponding cyclized products **2e** and **2f**, respectively, in high yields (entries 6, 7). The aryl ketone **1g** bearing an electron-donating group at the position para to bromine gave the cyclized product **2g** in 75% yield (entry 8). The usefulness of this methodology was further demonstrated in the preparation of six-member ring products. Thus, the aryl ketones **1h** and **1i** underwent the cyclization to produce the corresponding cyclized products, **2h** as a single diastereomer and **2i**, respectively, in good to moderate yields (entries 9, 10). The diketone **1j** having an electron-withdrawing group as a tether, gave 9-hydroxy-9-phenylanthrone **2j**<sup>8</sup> in 89% yield (entry 11). The reaction of the aldehyde **4a** under the same reaction conditions as those above gave a complicated mixture of products, and the reaction of the corresponding chloride **4b** resulted in the recovery of the starting material.



To obtain a partial evidence for the proposed mechanism shown in Scheme 1, we carried out the electrochemical studies of the reaction system. A Pd(II) species in DMF solution of Pd(OAc)<sub>2</sub> was detected electrochemically as its quasireversible peak A (and B) in CV at  $E_{1\text{red}}/E_{1\text{ox}} = -381/-236$  mV (Figure 1 in supplemental information). Immediately after 40 equiv of Na<sub>2</sub>CO<sub>3</sub> was added, which was exactly same condition as the synthetic process, no change was observed in the pattern of the above voltammogram perhaps due to low solubility of the base in the medium. Then, the peak A (and B) was shifted to a new peak A' (and B') with

(8) Barnett, W. E.; Needham, L. L.; Powell, R. W. *Tetrahedron*, **1972**, *28*, 419.

(9) The following oxidation of CO<sub>3</sub><sup>2-</sup> produces oxygen:  
 $\text{CO}_3^{2-} \xrightarrow{-2e} \text{CO} + \text{O}_2$  (or  $\text{CO}_2 + 1/2\text{O}_2$ )

more negative redox potentials  $E_{2\text{red}}/E_{2\text{ox}} = -417/-244$  mV (Figure 2 in SI), which may be attributed to a Pd(II) species complexed by CO<sub>3</sub><sup>2-</sup> and DMF. The resulting Pd(II) species was not stable and led spontaneously to a species detected by its irreversible oxidation peak C at 1389 mV (Figure 2). The oxidation peak current of C increased with time concomitantly with decrease of the reduction peak current of A'. After 2 h under argon, both peaks disappeared, and no electroactive species was detected by CV: black precipitates were observed which presumably corresponded to Pd black. When P(Cy)<sub>3</sub> (2 equiv) was added together with Na<sub>2</sub>CO<sub>3</sub> (40 equiv), complete reduction of Pd(II) to Pd(0) was observed after 57 min: The peak A' was changed to a new irreversible oxidation peak D at less positive potential 1000 mV, due to the electron-donating effect of P(Cy)<sub>3</sub> which coordinates to the Pd(0) species (Figure 3 in SI). The resulting Pd(0), peak D, was stable for a prolonged period of time, and as can be seen from Figure 3 there was no Pd(II) species under these conditions, showing that the catalytic cycle starts by the oxidative insertion of this Pd(0) to the aryl-bromide bond of **1**. To the above mixture containing only Pd(0), **1b** (20 equiv) and 1-hexanol (100 equiv) were added, leading to a change of the previous voltammogram. The peak D was replaced by a new redox couple E and F,  $E_{1\text{red}}/E_{1\text{ox}} = -635/-201$  mV, corresponding to a Pd(II) species, and in the meantime a new Pd(0) species was detected by its peak J at 1108 mV (Figure 4 in SI). The peak E most probably corresponds to either **5** or **6**, and J corresponds to **7**. The pattern of voltammograms of Figures 1–3 did not change significantly by addition of 1-hexanol.

To understand the crucial role of insoluble Na<sub>2</sub>CO<sub>3</sub>, we carried out the experiment with Li<sub>2</sub>CO<sub>3</sub> more soluble in DMF. The use of Li<sub>2</sub>CO<sub>3</sub>, instead of Na<sub>2</sub>CO<sub>3</sub>, did not cause any reaction of **1b**; it was recovered. The CV of Li<sub>2</sub>CO<sub>3</sub> in DMF led to a nonreversible oxidation peak K at -45 mV (Figure 5 in SI). The addition of P(Cy)<sub>3</sub> to this solution gave immediately a new peak L at -1618 mV which corresponded to the reduction of (Cy)<sub>3</sub>P=O. It was confirmed by GC-MS analysis that (Cy)<sub>3</sub>P=O was produced by mixing P(Cy)<sub>3</sub> with Li<sub>2</sub>CO<sub>3</sub> in DMF at room temperature. Most probably, the electrochemical oxidation of CO<sub>3</sub><sup>2-</sup> would produce O<sub>2</sub> which may oxidize the phosphine to the corresponding phosphine oxide.<sup>9</sup> Under the reaction conditions of the palladium-catalyzed reaction of **1b**, more soluble Li<sub>2</sub>CO<sub>3</sub> would react readily with P(Cy)<sub>3</sub> and therefore there would be no ligand which stabilizes Pd(0) complex. In the case of Na<sub>2</sub>CO<sub>3</sub>, the reaction with P(Cy)<sub>3</sub> was very slow due to its insolubility, but Pd(II) is electron-deficient and thus would be more easily reduced by Na<sub>2</sub>CO<sub>3</sub> than P(Cy)<sub>3</sub>. The use of 1-hexanol is not yet clear, but it does not directly participate in the redox process of Pd since the above voltammograms did not change significantly in the presence or absence of 1-hexanol. One possibility is that the alkoxide exchange between **6** and 1-hexanol, leading to **2** and less bulky HexOPdX, might facilitate the reaction of Pd(II) to Pd(0).

Extension of the Grignard-type reaction using a palladium catalyst is under active investigation in our laboratories.

**Supporting Information Available:** Spectroscopic and analytical data for compounds **2a–e**, **g–i** (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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