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New Role of CO_2 as a Selective Agent in Palladium-Catalyzed Reductive Ullmann Coupling with Zinc in Water

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Abstract: Carbon dioxide was found to promote the palladium-catalyzed zinc-mediated reductive Ullmann coupling of aryl halides. In the presence of carbon dioxide, Pd/C, and zinc, various aromatic halides including less reactive aromatic chlorides were coupled to give the corresponding homocoupling products in good yields.

In previous reports on carbon dioxide (CO_2), most of the studies concerned the use of CO_2 as a raw material[1] or reaction media[2] in organic synthesis. Thus, the development of new routes on applying CO_2 in modern organic synthesis is considered to be one of the most challenging fields for the synthetic chemists. Although CO_2 has been demonstrated to be a selective agent in the previous reports on using CO_2 as either a raw material or reaction media,[1−3] there are only few successful examples in applying CO_2 only as a selective agent to shift the reaction selectivity in organic synthesis.[4] Very recently, we found that CO_2 could be used as a selective agent to improve the diiodination of alkynes to synthesize 1,2-diiodoalkenes, which are useful building blocks for organic chemistry.[4b] The results encourage us to further investigate this role of CO_2 in organic synthesis. Thus, we first explored our recent report on the Ullmann coupling reaction in liquid CO_2, in which one of the roles of CO_2 was shown to be that of a selective agent.[3b]

The Ullmann coupling reaction is one of the most useful methods for the synthesis of symmetrical biaryls. It is usually carried out with copper as the reagent.[5] However, it generally requires more than a stoichiometric amount of copper and high reaction temperatures. In recent years, various agents, especially combination of the transition metal and reducing agent,[3b,6−9] were used to overcome this problem. For example, Li and Ventrakaman[6a,b] have reported the Pd/C and zinc-mediated Ullmann-type coupling. In the presence of Pd/C and zinc, various aromatic iodides and bromides were homocoupled in moderate to good yields, but it required some additives (cosolvent or phase-transfer catalysts) to improve the yield of the coupling product. Under these reaction conditions, aryl chlorides were inert. Sasson and co-workers[6c] have reported that aryl chlorides could be coupled in the presence of Pd/C and zinc, but both the additives (PEG-400 and NaOH) and high reaction temperatures were needed. Recently, we also reported the palladium-catalyzed Ullmann-type coupling in liquid CO_2.[3b] In liquid CO_2, various aromatic halides including some aromatic chlorides underwent homocoupling smoothly in the presence of Pd/C, zinc, and H_2O at room temperature overnight. In this case, no other additive was required (eq 1).

$$\mathrm{Ar{-}X} \xrightarrow[\substack{\mathrm{H_2O/liquid\ CO_2} \\ \mathrm{rt,\ overnight}}]{\mathrm{Pd/C,\ Zn}} \mathrm{Ar{-}Ar} \qquad (1)$$

$X = I, Br, Cl$

In liquid carbon dioxide, the selectivity toward the palladium-catalyzed Ullmann-type coupling was not very desirable due to the formation of the reduction product as the major side product. Moreover, the coupling of aromatic halides bearing electron-withdrawing groups did not occur, and CO_2 was found to improve the

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[5] (a) Bringmann, G.; Walter, R.; Weirich, R. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 977. (b) Zhang, S.; Zhang, D.; Liebeskind, L. S. *J. Org. Chem.* **1997**, *62*, 2312 and references therein.

[6] For Pd/C-catalyzed Ullmann-type couplings using Zn and water as the reducing regent, see: (a) Ventrakaman, S.; Li, C. J. *Org. Lett.* **1999**, *1*, 1133. (b) Ventrakaman, S.; Li, C. J. *Tetrahedron Lett.* **2000**, *41*, 4831 and references therein. (c) Mukhopadhyay, S.; Rothenberg, G.; Gitis, D.; Sasson, Y. *Org. Lett.* **2000**, *2*, 211.

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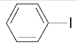
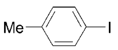
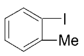
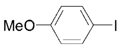
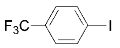
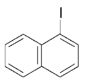
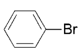
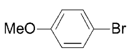
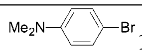
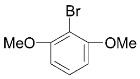
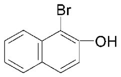
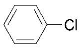
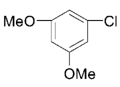
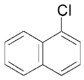
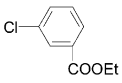
TABLE 1. Palladium-Catalyzed Ullmann Coupling of Aromatic Halides in the Presence of CO_2[a]

$$\underset{\mathbf{1}\ (2\ \text{mmol})}{\text{Ar–X}} \xrightarrow[\text{in } H_2O]{\text{Pd/C, Zn} \quad CO_2\ (1.0\ \text{MPa})} \underset{\mathbf{2}}{\text{Ar–Ar}}$$

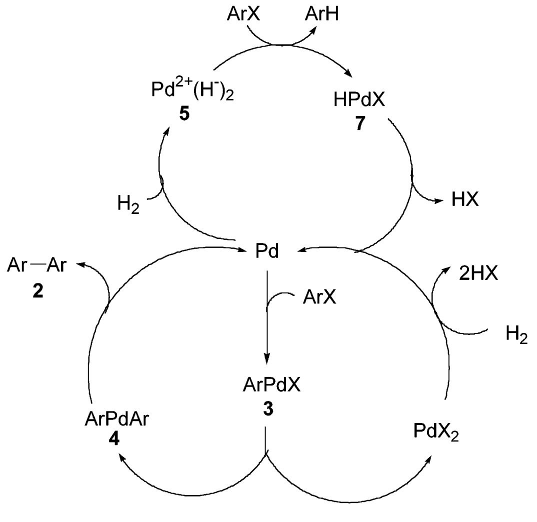
Entry	Aryl Halide	Time (h)	Yield[b] (%)
1[c]	 **1a**	15	27 (**2a**)
2[d]		15	41 (**2a**)
3		8	>99 (**2a**)
4[e]		8	65 (**2a**)
5	 **1b**	15	95 (**2b**)
6	 **1c**	24	87 (**2c**)
7	 **1d**	15	97 (**2d**)
8	 **1e**	48	95 (**2e**)
9	 **1f**	24	100 (**2f**)
10	 **1g**	15	91 (**2a**)
11	 **1h**	24	95 (**2d**)
12	 **1i**	48	85 (**2i**)
13	 **1j**	72	78 (**2j**)
14[f]	 **1k**	48	81 (**2k**)
15	 **1l**	36	56 (**2a**)
16[g]		36	96 (**2a**)
17[g]	 **1m**	48	81 (**2m**)
18[g]	 **1n**	36	95 (**2f**)
19[g]	 **1o**	96	93 (**2o**)

[a] Reaction conditions: Pd/C (5% w/w, 300 mg), Zn (170 mg), H_2O (5 mL), and CO_2 (1.0 MPa) at room temperature. No aromatic halides were detected by GC analysis after the desired reaction time. [b] Isolated yield. [c] In the absence of CO_2. [d] CO_2 (1 atm, bubbling). [e] CO_2 (6.0 MPa). [f] Yield of 2-naphthol, a reduction product, was obtained in 17% yield. [g] Pd/C (5% w/w, 400 mg).

SCHEME 1

$$CO_2 + H_2O \longrightarrow H_2CO_3$$

$$Zn + H_2CO_3 \longrightarrow H_2 + ZnHCO_3$$



selectivity toward the homocoupling and to activate some aryl chlorides. This led us to continue our studies on investigating the role of CO_2 in the Ullmann coupling (Scheme 1). Indeed, we found that homocoupling of various aryl halides, even less reactive aryl chloride having electron-withdrawing groups, took place efficiently and selectively in the presence of CO_2, Pd/C, zinc, and water. Here we report the details of our studies.

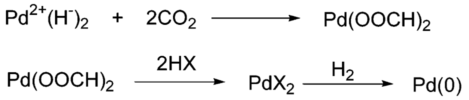
The effect of carbon dioxide on the palladium-catalyzed Zn-mediated Ullmann coupling of iodobenzene **1a** in H_2O was investigated, and the results were summarized in Table 1 (entries 1–4). The catalyst loadings of both Pd/C and zinc were directly used according to our previous report.[3b] A survey of various pressures of CO_2 revealed that CO_2 played a crucial role in the selectivity of the coupling. Without CO_2, coupling of **1a** mediated by Pd/C and zinc was slow and inefficient in water. A low 27% yield of biphenyl **2a** was obtained after 15 h in the presence of Pd/C (5% w/w, 300 mg), zinc power (170 mg), and H_2O (5 mL). However, the addition of CO_2 (bubbling) resulted in a significant increase in rate and yield. The yield of **2a** was increased to 41% in the presence of an atmospheric pressure of CO_2 (entry 2). Very interestingly, **1a** was consumed completely after 8 h and afforded 100% yield of **2a** under 1.0 MPa of CO_2. However, the selectivity toward the coupling was decreased with increasing pressure of CO_2. Only 65% yield of **2a** was obtained when the pressure of CO_2 was increased to 6.0 MPa (entry 4). To check the basic mass balance of the coupling reaction, the crude product of entry 4 was directly analyzed by GC−MS. The analytical data showed that **1a** was converted into 66% yield of **2a** and 34% yield of benzene (the reduction product).

To demonstrate the efficiency and scope of the present method, we applied the optimum reaction conditions to a variety of aryl halides, and the results are summarized in Table 1 (entries 5−19). As shown in Table 1, coupling of various aromatic halides **1b**−**o** bearing different substituents proceeded smoothly in the presence of CO_2, Pd/C, and zinc. The results in Table 1 also indicated that the reaction rate depends on the structure of the halides involving both the properties and position of substituents on the aromatic ring. For example, aromatic iodides **1b**−**f** were coupled to give the corresponding coupling products **2b**−**f** in 95, 87, 97, 95, and 100% yields, respectively, and the following rate of couplings: **1b**, **1d** (16 h) > **1c**, **1f** (24 h)> **1e** (48 h) (entries 5−9). Noted that although the prolonged reaction time was required to consume **1e**, an aryl iodide bearing an electron-drawing group, the selectivity toward **2e** was not significantly compromised (95%, entry 8). Under the same reaction conditions, coupling of aromatic bromide **1g**−**k** also afforded the corresponding homocoupling products **2g**−**k** in good yields (entries 10−14).

Compared to aromatic bromides and iodides, aromatic chlorides were less reactive. However, coupling of aromatic chlorides **1l**−**o** could also proceed smoothly although higher catalyst loading of Pd/C was required to enhance the selectivity (entries 15−19). In the presence of CO_2 (1.0 MPa) and Zn (170 mg), a 56% yield of **2a** was obtained after 36 h when 300 mg of Pd/C (5%) was added, whereas 96% yield of **2a** was obtained in 36 h using 400 mg of Pd/C. With CO_2 (1.0 MPa), Pd/C (400 mg), and Zn (170 mg) as the catalyst system, aromatic chlorides **1m** and **1n** gave the corresponding coupling products **2m** and **2n** in 81 and 95% yields, respectively (entries 17 and 18). It should be pointed out that the substrate **1o** bearing an electron-withdrawing group was also converted into **2o** in 93% yield after 96 h (entry 19).

Either a direct metal-to-metal electron transfer or the reduction of palladium intermediate in situ by hydrogen gas is the main difference between two plausible mechanisms that were proposed by Li[6a,b] and Sasson,[6c] respectively. We noticed that Li's reaction conditions were neutral and Sasson's were basic, but the present reaction conditions were acidic. Thus, the present reaction might proceed via the latter mechanism. A possible mechanism for the CO_2-promoted palladium-catalyzed coupling reaction is proposed as outlined in Scheme 1. It is well-known that carbon dioxide in water generates carbonic acid (H_2CO_3) readily to lower the pH value of the reaction systems, so the first step might be the reaction of CO_2 with H_2O to yield H_2CO_3, a Brönsted acid, which then afforded H_2 by reacting with Zn. In the presence of H_2, Pd(0) might react with either aryl halide or H_2 to give intermediate **3** (ArPdX) and intermediate **5** ($Pd^{2+}(H^-)_2$), respectively. Intermediate **3** reacted with another ArX to afford intermediate **4** and PdX_2. Intermediate **4** then underwent reductive elimination and released **2** and regenerated the active Pd (0) species. PdX_2 could also react with H_2 to regenerate the active Pd(0) species. In the meantime, aryl halides could also be reduced by intermediate **5** to give ArH.

SCHEME 2



$$Pd^{2+}(H^-)_2 + 2CO_2 \longrightarrow Pd(OOCH)_2$$

$$Pd(OOCH)_2 \xrightarrow{2HX} PdX_2 \xrightarrow{H_2} Pd(0)$$

In Sasson's work,[6c] NaOH was added to reduce the concentration of intermediate **5** resulting in high selectivity toward the aryl coupling. Although we have no direct evidence to support the hypothesis in Scheme 2, we believe that the function of CO_2 is similar to NaOH, which could decrease the concentration of intermediate **5** to affect the selectivity of the coupling despite the acidity of CO_2.[10] To elucidate this hypothesis, we assume that the insertion of CO_2 into the Pd−H bond might take place to form $Pd(OOCH)_2$, which could react with HX to afford the active Pd species resulting in selectivity toward coupling.[3b]

In conclusion, we have shown that CO_2 strongly influenced the selectivity of the coupling reaction. In the presence of CO_2, various aromatic halides including less reactive aromatic chlorides were coupled in good yields. The new aspect of carbon dioxide reported here as a nonflammable, relatively nontoxic, naturally abundant, economical, and easily re-collectable gaseous selective agent is very important from the viewpoints of organic, physical, industrial, theoretical, and green chemistry. Moreover, it would allow us to construct new and environmentally benign reactions and also require us to reconsider the role of carbon dioxide in the reported reactions under carbon dioxide atmosphere. Further efforts associated with this new role of carbon dioxide in organic synthesis are in progress in our laboratory.

Caution: Be careful when working with material at high pressure.

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Supporting Information Available: Spectroscopic and analytical data (^1H and ^{13}C NMR) for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) In acetic acid (5 mL), only a reduction product, benzene, was obtained from **1a** after 8 h in the presence of Pd/C (5% w/w, 300 mg) and zinc power (170 mg), which determined by GC−MS analysis. For a recent review on reduction reactions, see: Li, G.; Jiang, H.; Li, J. *Chin. J. Org. Chem.* **2002**, *22,* 801.