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Article

Ammonium Chloride Promoted Palladium-Catalyzed Ullmann Coupling of Aryl Bromide

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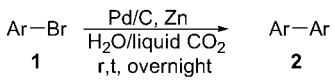
In water, ammonium chloride was found to promote palladium-catalyzed Ullmann coupling reactions of aryl bromides. In the presence of Pd/C, zinc, NH_4Cl, and water, coupling of various aryl bromides was carried out smoothly to afford the corresponding homocoupling products in moderate yields.

Keywords Pd/C, Ullmann coupling reaction, ammonium chloride, aryl bromides

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 a reagent.[1] However, it generally requires more than a stoichiometric amount of copper and high reaction temperature. In recent years, various reagents, especially combination of the transition metal with reducing reagents,[2-6] were proposed to overcome these problems. For example, Li and co-workers[2a,2b] have reported the Pd/C and zinc-mediated Ullmann-type coupling. In the presence of Pd/C and zinc, various aromatic bromides were homocoupled in moderate to good yields, but some additives (co-solvent or phase transfer catalysts) were required to improve the yields. Recently, we also reported the palladium-catalyzed Ullmann type coupling in liquid CO_2.[2c] In liquid CO_2, various aromatic bromides were homocoupled in the presence of Pd/C, zinc and H_2O at room temperature overnight, and no other additives were required (Scheme 1).

Scheme 1 Palladium-catalyzed Ullmann-type coupling in liquid CO_2



In liquid CO_2, the results showed that the acidity might play a crucial role in the chemoselectivity of coupling of aryl bromides. Thus we expected that some common and cheap acidic inorganic salts, including Lewis acids and Brönsted acids, might be used to promote the palladium-catalyzed coupling of aryl bromides. Indeed, we found that aryl bromides were coupled smoothly in moderate yields in the presence of NH_4Cl. Here we report the details of those reactions.

The effect of NH_4Cl on the palladium and Zn-mediated Ullmann coupling of bromobenzene **1a** in H_2O was investigated, and the results are summarized in Table 1 (Entries 1—5). The catalyst loadings of both Pd/C and zinc were directly used according to our previous report.[2c] The results showed that the addition of NH_4Cl affected the coupling. Without NH_4Cl, coupling of **1a** mediated by Pd/C and zinc was inefficient in water. A low yield of biphenyl **2a** was obtained after 24 h in the presence of Pd/C (5% *w*/*w*, 300 mg), zinc powder (170 mg), and H_2O (5 mL). However, the presence of NH_4Cl increased the yields significantly. The yield of **2a** was increased to 32% in the presence of 0.5 equiv. of NH_4Cl (Entry 2). Very interestingly, **1a** was coupled to afford 67% yield of **2a** when 1 equiv. of NH_4Cl was added (Entry 3). However, the selectivity toward the coupling decreased with increasing loadings of NH_4Cl. Only 38% yield of **2a** was obtained when the loadings of NH_4Cl was increased to 2 equiv. (Entry 4). Trace of **2a** was isolated in aqueous NH_4Cl saturated solution (Entry 5). A series of other acidic inorganic salts were also examined, and the results showed that the acidic inorganic salts such as $(NH_4)_2SO_4$, $Al_2(SO_4)_3$, $CeCl_3$ and *etc*. were less effective than NH_4Cl (Entries 6—11). 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 to **2a** in 38% yield and benzene (the reduction product) in 62% yield.

To demonstrate the efficiency and scope of the present method, we applied the optimum reaction conditions to couplings of a variety of aryl bromides, and the results are summarized in Table 2. As shown in Table 2, couplings of aromatic bromides **1b**—**1g** bearing differ-

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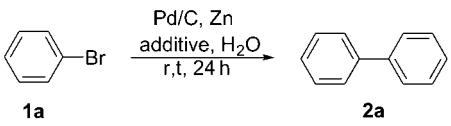
Table 1 Acidic inorganic salts promoted Ullmann coupling of bromobenzene (**1a**)[a]



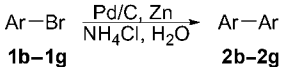
Entry	Additive	Isolated yield/%
1	—	21
2	NH_4Cl	32
3[b]	NH_4Cl	67
4[c]	NH_4Cl	38
5[d]	NH_4Cl	<5
6	$(NH_4)_2SO_4$	35
7	$Al_2(SO_4)_3$	23
8	$CeCl_3$	54
9	$Ce_2(SO_4)_3$	38
10	Na_2HPO_4	34
11	NaH_2PO_4	19

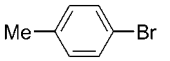
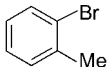
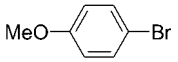
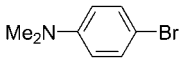
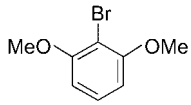
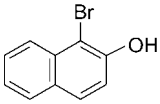
[a] Reaction conditions: bromobenzene (**1a**) (2 mmol), Pd/C (5% *w*/*w*, 300 mg, 7 mol%), zinc (170 mg, 2.6 mmol), additive (2 mmol), and H_2O (5 mL) at room temperature for 24 h. [b] NH_4Cl (1 mmol). [c] NH_4Cl (4 mmol). [d] Aqueous NH_4Cl saturated solution (5 mL) as the reaction solvent.

ent substituents were carried out smoothly in the presence of NH_4Cl, Pd/C, and zinc. The results also indicated that the reaction rate depended upon the structure of the bromides involving both the properties and position of the substituents on the aromatic ring. The rate of the coupling was in the order of **1b**—**1c** (24 h)>**1e**, **1g** (48 h)>**1f** (72 h). The results also demonstrated that the coupling reaction was inefficient in the absence of NH_4Cl (Entries 1 and 2). For example, only 17% of **2b** was obtained without NH_4Cl, whereas the yield of **2b** was increased to 65% in the presence of 1 equiv. of NH_4Cl.

Li[2a,2b] and Sasson[2d] proposed two reaction mechanisms respectively. One was a direct metal-to-metal electron transfer process, the other was the reduction of palladium intermediate *in situ* by hydrogen gas. We noticed that Li's reaction conditions were neutral and Sasson's were basic, but the present reaction conditions were acidic. So the present reaction might proceed via the latter mechanism. A possible mechanism for the NH_4Cl-promoted palladium-catalyzed coupling reaction was proposed as outlined in Scheme 2. It is well-known that NH_4Cl in water readily lowered the pH value of the reaction system, so the first step might be the reaction of NH_4Cl with H_2O yielding H^+, which then afforded H_2 by reacting with Zn. In the presence of H_2, Pd(0) might react with either aryl bromide or H_2 to give intermediate **3** (ArPdBr) and intermediate **5** ($Pd^{2+}(H^-)_2$), respectively. Intermediate **3** reacted with another ArBr to afford intermediate **4** and $PdBr_2$. Intermediate **4** then underwent reductive elimination to release **2** and regenerate the active Pd(0) species. $PdBr_2$ could also react with H_2 to regenerate the active Pd(0) species. In the meantime,

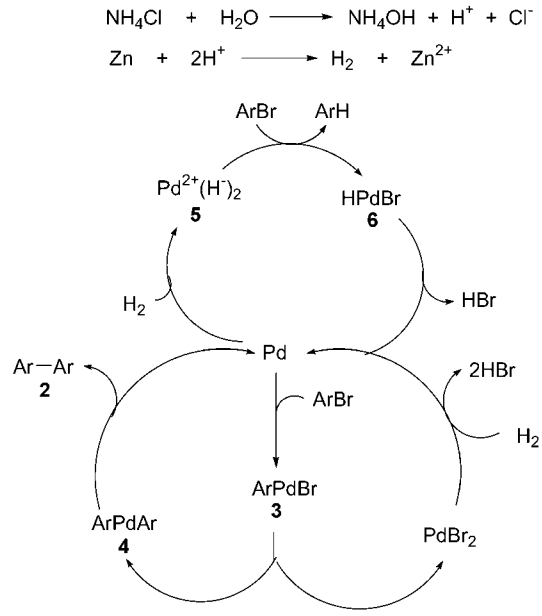
Table 2 Palladium-catalyzed Ullmann coupling of aryl bromides[a]



Entry	Aryl halide		Time/h	Yield[b]/%
1		**1b**	24	65 (**2b**)
2[c]			48	17 (**2b**)
3		**1c**	24	47 (**2c**)
4		**1d**	24	57 (**2d**)
5		**1e**	48	55 (**2e**)
6		**1f**	72	48 (**2f**)
7[d]		**1g**	48	61 (**2g**)

[a] Reaction conditions: **1** (2 mmol), Pd/C (5% *w*/*w*, 300 mg, 7 mol%), Zn (170 mg, 2.6 mmol), NH_4Cl (2 mmol), and H_2O (5 mL) at room temperature. No aromatic halides were detected by GC analysis after the desired reaction time. [b] Isolated yield. [c] No NH_4Cl added. [d] 2-Naphthol, a reduction product, was obtained in 37% yield.

Scheme 2 Mechanism of the palladium-catalyzed Ullmann type coupling reaction



aryl bromide could be reduced by intermediate **5** to give ArH.

In Sasson's work,[2d] NaOH was added to reduce the concentration of intermediate **5** resulting in high selectivity toward the coupling. So we believed that the function of NH_4Cl is similar to that of NaOH, which could decrease the concentration of intermediate **5** to affect the selectivity of the coupling due to the acidity of NH_4Cl [Eq. (1)].

$$Pd^{2+}(H^-)_2 + 2H^+ \longrightarrow Pd(0) + 2H_2 \quad (1)$$

In conclusion, we have developed a mild and cheap method for homo-coupling of various aromatic bromides to synthesize diphenyl and its derivatives. The results showed that NH_4Cl dramatically influenced the selectivity of the palladium-catalyzed coupling reaction. Further study of the mechanism and application of the method are in progress.

Experimental

All ^1H and ^{13}C NMR spectra were recorded on a DRX-400 or 300 spectrometer with $CDCl_3$ as solvent. All reagents were used directly as obtained commercially. All products **2a—2g** are known and their detailed spectral data are as identical with those previously described.[1-6] All melting points are uncorrected.[7-11]

General procedure for NH_4Cl promoted palladium-catalyzed Ullmann-type coupling

A mixture of aryl bromide **1** (2 mmol), Pd/C (5% *w*/*w*, 300 mg, 7 mol%), Zn (170 mg, 2.6 mmol), NH_4Cl (2 mmol) and H_2O (5 mL) was stirred at room temperature for the desired time. Then the mixture was extracted (ether), dried (anhydrous Na_2SO_4) and concentrated by rotoevaporation to give the crude product. Pure product **2** was obtained by flash column chromatography (hexane/ethyl acetate).

Biphenyl (2a): White solid, m.p. 68—71 ℃ (uncorrected) (lit.[7] m.p. 69—70 ℃). ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.59 (d, J=8.4 Hz, 4H), 7.44 (t, J=8.0 Hz, 4H), 7.39 (t, J=7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 141.2, 129.9, 128.7, 127.2; MS (70 eV) *m/z* (%): 154 (M^+, 100), 76 (40).

4,4'-Dimethyl-biphenyl (2b): White solid, m.p. 117—121 ℃ (uncorrected) (lit.[8] m.p. 122—123 ℃). ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.46 (d, J=8.0 Hz, 4H), 7.22 (d, J=7.6 Hz, 4H), 2.37 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 138.3, 136.7, 129.4, 126.8, 21.0; MS (70 eV) *m/z* (%): 182 (M^+, 100), 164 (75), 77 (17).

2,2'-Dimethyl-biphenyl (2c):[1-6] Colorless oil. ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.25—7.20 (m, 6H), 7.09 (d, J=7.6 Hz, 2H), 2.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 141.6, 135.8, 129.8, 129.3, 127.1, 125.5, 19.8; MS (70 eV) *m/z* (%): 182 (M^+, 100), 164 (53), 92 (100), 75 (13).

4,4'-Dimethoxy-biphenyl (2d): White solid, m.p. 175—179 ℃ (uncorrected) (lit.[8] m.p. 176—177 ℃). ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.46 (d, J=8.8 Hz, 4H), 7.22 (d, J=8.8 Hz, 4H), 3.82 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 138.3, 136.7, 129.4, 126.8, 55.3; MS (70 eV) *m/z* (%): 214 (M^+, 100), 200 (31), 183 (100), 76 (11).

4,4'-Bis(dimethylamino)biphenyl (2e): White solid, m.p. 192—195 ℃ (uncorrected) (lit.[9] m.p. 193—194 ℃). ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.05 (d, J=8.0 Hz, 4H), 6.63 (d, J=8.0 Hz, 4H), 2.94 (s, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 129.7, 113.4, 41.3, 40.2; MS (70 eV) *m/z* (%): 240 (M^+, 100), 226 (23), 196 (45), 77 (8).

2,6,2',6'-Tetramethoxy-biphenyl (2f): White solid, m.p. 173—174 ℃ (uncorrected) (lit.[10] m.p. 174—175 ℃). ^1H NMR ($CDCl_3$, 300 MHz) δ: 6.93—6.83 (m, 6H), 3.79 (s, 6H), 3.72 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 153.7, 151.7, 129.0, 117.5, 113.8, 112.9, 56.9, 56.1; MS (70 eV) *m/z* (%): 274 (M^+, 100), 244 (51), 74 (7).

[1,1']-Binaphthalenyl-2,2'-diol (2g): White solid, m.p. 213—217 ℃ (uncorrected) (lit.[11] m.p. 215 ℃). ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.98 (d, J=9.0 Hz, 2H), 7.89 (d, J=8.7 Hz, 2H), 7.40—7.26 (m, 6H), 7.15 (d, J=6.6 Hz, 2H), 1.54 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 153.1, 133.7, 131.8, 129.8, 128.8, 124.5, 124.4, 118.1, 111.2; MS (70 eV) *m/z* (%): 286 (M^+, 100), 268 (83), 142 (25).

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