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Facile synthesis of symmetrical functionalized biaryls from aryl halides catalyzed by commercial zinc dust using ammonium formate

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Abstract—Reductive homocoupling of aryl halides in the presence of commercial zinc dust and ammonium formate in methanol produces biaryls in good to excellent yields. Aryl halides having either electron-donating or electron-withdrawing groups underwent smooth coupling to afford the corresponding symmetrical biaryls. Addition of 1 equiv of sodium hydroxide enhanced the coupling reaction rate. Commercial zinc dust is inexpensive, widely available and can be used without any auxiliary catalysts such as Pd(0) and/or Ni(0).

Biaryls are an important class of compounds in organic synthesis because of their numerous potential applications. Biaryls have a large variety of physical and chemical properties and can be used as monomers for the synthesis of conductive polymers,[1] for the synthesis of important biaryl natural products such as steganone,[2] supramolecules,[3] as ligand catalysts, and receptrice macrocyclic molecules.[4] As a consequence, over the last 10 years more than 700 articles have dealt with new results in the area of aryl–aryl bond formation.[5]

Various palladium and/or nickel catalyzed cross-coupling reactions of aryl halides with aryl nucleophiles have been developed for the synthesis of symmetrical and unsymmetrical biaryls. Aryl boronic acids,[6] aryl stannanes,[7] and aryl zinc[8] derivatives as well as aryl Grignard reagents[9] are frequently used as aryl nucleophiles. On the other hand, the synthesis of symmetrical biaryls via reductive dimerization of aryl halides is considered to be a more convenient and straightforward method as it bypasses the synthesis of aryl nucleophiles, which sometimes requires two steps. Historically, Ullmann coupling has been used for this purpose.[10] However, Ullmann coupling consumes more than a stoichiometric amount of copper and proceeds only under forcing conditions, limiting applications to the synthesis of functionalized biaryls. Zinc has been widely used as an auxiliary reducing agent (electron source) in conjunction with a transition metal (electron-transfer catalyst) for the reductive homocoupling of aryl halides.[11] In these multi-metal redox systems, reactivity and selectivity depend significantly on the components of the system, that is, the transition metal reagent, electron source, and solvent.

In 1978, Bamfield and Quan[12] performed the homocoupling of aryl halides using a heterogeneous mixture of palladium on carbon as the catalyst together with a sodium formate solution as the terminal reductant. This approach is highly advantageous as it involves mild reaction conditions, easy bulk management, minimal effluents, and easy product separation. Accordingly, various organic reducing agents such as 2-propanol,[13a] 2-propanol/tetraalkylammonium salt,[13b] hydroquinone,[13c] molecular hydrogen,[13d] sodium formate,[13e] amines,[13f] and tetrakis(dimethylamino)ethylene[13g] have been used in palladium catalyzed reductive homocoupling of aryl halides. However, in the presence of an organic reducing agent and a powerful catalyst like palladium, aryl halides are prone to undergo hydrodehalogenation rather than coupling resulting in low yields of the biaryls. Thus, there still remains a need for the development of alternative catalysts and reducing agents to promote highly selective, cost-effective, and efficient reductive coupling of aryl halides.

We report here the zinc catalyzed efficient synthesis of symmetrical biaryls using base and ammonium formate

Keywords: Aryl halides; Homocoupling; Zinc; Ammonium formate; Biaryls.
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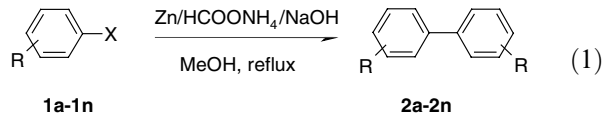
in methanol at reflux. The zinc/ammonium formate system effectively promoted the reductive homocoupling of aryl halides **1a**–**n** having either electron-donating or electron-withdrawing groups to give the corresponding symmetrical biaryls **2a**–**n** (Eq. 1).



1a-1n **2a-2n** (1)

A wide range of aryl halides underwent coupling by this procedure to furnish the corresponding biaryls. The results are summarized in Table 1. All the biaryls synthesized were characterized by comparison of their TLC, melting points, IR spectra, and ^{1}H NMR spectra with those of authentic samples. Addition of 1 equiv of sodium hydroxide enhanced the coupling rate significantly. The reactions are, on the whole, reasonably fast and high yielding. The relative reactivity of aryl halides decreases in the order I > Br > Cl (Table 1, entries 1–3). Generally, both electron-donating and electron-withdrawing substituents allow efficient coupling with no significant difference in reaction rate. Similar reductive coupling proceeded smoothly with 1-iodonaphthalene and 2-iodopyridine (Table 1, entries 13 and 14). The procedure was found to be compatible with several sensitive functionalities such as OH, OMe, CO_2Me, COOH, and CN. However, the reductive coupling of aryl halides containing nitro or carbonyl groups was very difficult because these two functionalities undergo reduction very easily. Reductive coupling was also attempted using an alkaline solution of iodobenzene with zinc but without ammonium formate. Only after prolonged reflux (48 h), the starting material was recovered quantitatively.

Table 1. Reductive homocoupling of aryl halides using zinc/ammonium formate

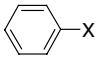
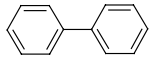
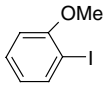
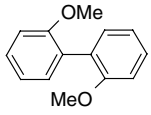
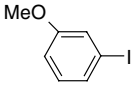
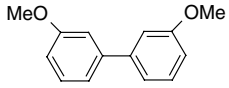
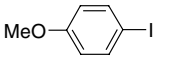
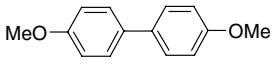
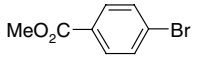
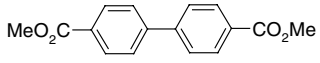
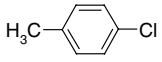
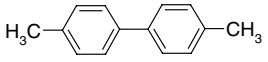
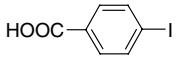
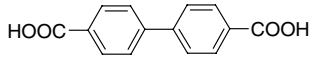
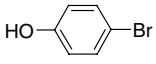
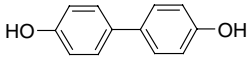
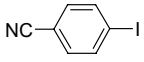
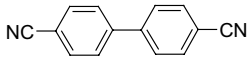
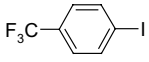
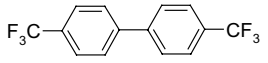
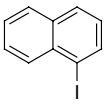
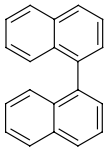
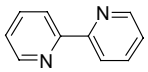
Entry	Aryl halide		Product[a]		Time[b] (h)	Yield[c] (%)	Mp (°C)
							
1	X = I	**1a**		**2a**–**c**[13c]	1.5 (4)	96	70
2	X = Br	**1b**			3 (10)	93	
3	X = Cl	**1c**			6 (16)	92	
4		**1d**		**2d**[13c]	4 (12)	86	155–156
5		**1e**		**2e**[13c]	2.5 (9)	92	35–36
6		**1f**		**2f**[13g]	1.5 (3)	94	176–178
7		**1g**		**2g**[13g]	2 (5.5)	95	213–214
8		**1h**		**2h**[13g]	4.5 (7)	95	120
9		**1i**		**2i**[d]	2.5 (7)	82	302–304
10		**1j**		**2j**[d]	3 (4.5)	94	278–279
11		**1k**		**2k**[14]	3 (5)	93	234–235
12		**1l**		**2l**[14]	2.5 (6)	91	92–93

Table 1 (*continued*)

Entry	Aryl halide	Product[a]	Time[b] (h)	Yield[c] (%)	Mp (°C)
13	 **1m**	 **2m**[13c]	3.5 (7)	86	156–157
14	 **1n**	 **2n**[13c]	2.5 (4)	90	69–71

[a] All of the products are known and gave TLC, melting points, IR spectra, and ^{1}H NMR spectra (AMX-400 MHz spectrometer: $CDCl_3$; TMS as internal standard) in agreement with authentic samples.
[b] Time in parentheses corresponds to coupling reaction time without sodium hydroxide.
[c] Yields of isolated pure products.
[d] The spectra were compared to those of a commercial sample.

In conclusion, the ammonium formate mediated synthesis of symmetrical functionalized biaryls via reductive homocoupling of aryl halides can be achieved in the presence of commercial zinc dust. In the zinc/ammonium formate system, the coupling of aryl halides proceeds efficiently to furnish the corresponding biaryls in high yields and the competitive reduction (hydrodehalogenation) is negligible (<4%). Moreover, zinc dust is inexpensive, widely available, and can be used without any expensive auxiliary catalysts such as palladium and/or nickel. The ease of product separation, safe reaction medium, high selectivity, and low cost of the reagents promote this method as a promising alternative to transition metal catalyzed coupling techniques.

1. General procedure

To a solution of aryl halide (5 mmol) in methanol (15 mL), zinc dust (5 mmol; particle size <45 μm), ammonium formate (10 mmol), and sodium hydroxide (5 mmol) were added and the mixture stirred under reflux for the specified time under nitrogen (Table 1). After consumption of the starting material, as monitored by TLC, the reaction mixture was filtered through Celite. The filtrate was evaporated under reduced pressure and the residue was taken into chloroform or ether washed twice with 80% saturated brine solution, and finally with water. The organic layer was dried over anhyd Na_2SO_4 and evaporated under reduced pressure. The crude product was found to be analytically pure in most cases. Where necessary, the crude product was purified by SiO_2 column chromatography.

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