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Palladium(II) chloride/EDTA-catalyzed biaryl homo-coupling of aryl halides in aqueous medium in the presence of ascorbic acid

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Abstract—Both electron-deficient and electron-rich aryl bromides undergo biaryl homo-coupling in a basic aqueous-ethanolic medium in the presence of $PdCl_2$–EDTA (1:1 molar ratio, 3 mol %) as catalyst and ascorbic acid as reductant (1 mol equiv) in acceptable to good yields.

1. Introduction

The potential applications of compounds containing a biaryl sub-unit in the areas of organometallic catalysis,[1] materials science[2,3] and supramolecular chemistry,[4] and its occurrence in several bioactive natural products,[5,6] pharmaceuticals and agrochemicals[7,8] have generated tremendous activity in aryl–aryl bond forming reactions. Several modern methods for the preparation of biaryls are available, such as Suzuki, Stille, Negishi, Kumada and Hiyama cross-coupling reactions, which involve the palladium (or nickel) catalyzed coupling of aryl halides (or less frequently *pseudo*-halides) with an aryl organometallic, Ar–M (M = B, Sn, Zn, Mg or Si).[9–11] The palladium-catalyzed intermolecular direct arylation of electron-rich arenes and heteroarenes with aryl halides[12] and one-pot two-step borylation-Suzuki cross-coupling[8] (BSC) of two electronically complementary aryl halide molecules are two noteworthy recent advances amongst many in this area. There are several reports on metal-catalyzed/promoted self-coupling of various organometallics, such as aryl Grignards, zinc, boronic acids, stannanes, and silanes, as well as oxidative coupling of electron-rich arenes for the preparation of symmetrical biaryls.[9,13]

However, for a general synthesis of symmetrical biaryls, the direct reductive homo-coupling of aryl halides is more convenient and straightforward as it bypasses the synthesis of the aryl organometallic and does not suffer as much with structural constraint. Although the classical Ullmann coupling for the preparation of symmetrical biaryls has this advantage, it requires stoichiometric amounts or more of copper and harsh reaction conditions (neat, >200 °C).[14] Several milder methods have since been developed by replacing copper with an Ni(0)[9,15–17] or Pd(0)[9,18] catalyst and a reducing agent. The latter is required to regenerate the active metal catalyst in the zero oxidation state to allow a second oxidative addition of the aryl halide to the metal catalyst to occur. The reductive elimination then yields the biaryl. However, it appears that the reactivity and selectivity of these reactions significantly depend on the nature of the transition metal catalyst, the reducing reagent and the solvent. While Pd catalysts have generally been found to be more efficient than Ni catalysts and require milder reducing agents, several methods still use reducing agents such as zinc dust[9,19,20] and molecular hydrogen[21] which are too strong to be successful with electron-deficient haloarenes or those having easily reducible groups, such as nitro, aldehyde and keto where a competing reductive dehalogenation or, generally reduction of the functional group occurs without biaryl coupling, as with Ni catalysts.

Of the reported Pd-catalyzed reactions using relatively milder organic co-reductants,[9,22–29] such as isopropanol, tertiary amines, formates and DMF (probably due to impurities such as dimethylamine and formate present or generated in situ),[22] tetrakis(dimethylamino)ethylene[23,24] and hydroquinone[25,26] appear to be the most

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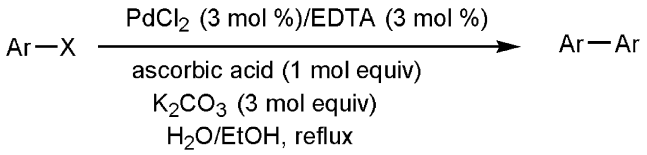
effective in terms of yields, reaction time and temperature, and are also the most selective. Nitro and keto groups could survive under these conditions. However, these reactions are more effective with iodo- or activated bromo-arenes, use undesirable air sensitive or toxic/specially designed ligands, argon atmosphere or the environmentally undesirable solvents DMA or DMF. Although no general trend is discernible on the solvent effect, environmental concerns and other considerations have placed a considerable emphasis on using water as the reaction medium.[30] However, the reported reactions on biaryl homo-coupling in water/aqueous organic solvents use a Pd-catalyst with a strong co-reductant (molecular hydrogen,[21] sodium formate,[28,29] zinc dust[31–34]) and are not as selective as already mentioned. Recently, the BSC reaction has been applied to the homo-coupling of haloarenes and aryl triflates using the air sensitive $PdCl_2$–dppf catalyst and the rather expensive bis(pinacolato)diborane as the borylating agent in DMSO under argon.[35]

Thus, there is still a need for more reactive and selective procedures for the synthesis of symmetrical biaryls which can be conducted in an open atmosphere and in environmentally compatible solvents, such as water. Herein, we wish to report the biaryl homo-coupling of aryl halides using $PdCl_2$/EDTA (ethylenediamine *N*,*N*,*N*′,*N*′-tetraacetic acid disodium salt) as the catalyst and ascorbic acid as an organic reducing agent in an aqueous-ethanolic medium (Scheme 1). The motivating factors for the choice of the catalyst and the reducing agent were: (a) a recent report by Korolev and Bumagin[36] on a very efficient air stable $PdCl_2$–EDTA catalyzed Suzuki cross-coupling reaction in water, (b) the reported selectivity of organic reducing agents, which appears promising because the reactivity and selectivity can be optimized by a correct choice of the reducing agent, (c) air stability and water solubility of EDTA and ascorbic acid and (d) the mild reducing property of ascorbic acid and its known applications in inorganic[37–40] and organic chemistry.[41–44]

2. Results and discussion

First, the reaction conditions were optimized using 4-bromotoluene as the test case and varying the amounts of catalyst, base and reducing agent. All the reactions were performed in water–ethanol (5:1 v/v) under reflux for 8 h (Table 1). The reaction did not occur in the absence of $PdCl_2$ or ascorbic acid, did not proceed to completion with 0.5 mol equiv of ascorbic acid (vide infra), gave the product in a lower yield in the absence of EDTA (entry 5) or with 2 mol equiv of ascorbic acid (entry 9) and showed no improvement in the yield when



Scheme 1.

Table 1. Biaryl homo-coupling of 4-bromotoluene under various conditions[a]

Entry	$PdCl_2$ (mol %)	Base (mol equiv)	Yield (%)
1	0.1	K_2CO_3 (3)	11
2	1.0	K_2CO_3 (3)	28
3	2.0	K_2CO_3 (3)	43
4	3.0	K_2CO_3 (3)	58
5	3.0	K_2CO_3 (3)	42[b]
6	3.0	K_2CO_3 (2)	35
7	3.0	K_2CO_3 (4)	55
8	3.0	NaOH (6)	54
9	3.0	K_2CO_3 (5)	52[c]
10	3.0	K_2CO_3 (3)	57[d]

[a] All the reactions were performed with 1 mmol of the aryl halide in refluxing water–ethanol (13 ml, 5:1 v/v) for 8 h under an air atmosphere in the presence of 1 mmol of ascorbic acid and 1 mol equiv of EDTA with respect to $PdCl_2$.
[b] The reaction was performed in the absence of EDTA.
[c] The reaction was performed with 2 mmol of ascorbic acid.
[d] The reaction was performed under nitrogen atmosphere.

performed under a nitrogen atmosphere (entry 10). Having established the optimum reaction conditions (3 mol % $PdCl_2$, 3 mol % EDTA, 1 mol equiv ascorbic acid, 3 mol equiv K_2CO_3), the reaction was extended to other aryl halides under these conditions. The results are summarized in Table 2. The reaction occurred well with both electron-deficient and electron-rich bromoarenes to give biaryls in acceptable to good yields. 4-Bromoacetophenone, 4-bromobenzophenone and 3-bromonitrobenzene were coupled efficiently without any complications such as reductive debromination or reduction of the keto or nitro group. 4-Bromonitrobenzene also underwent coupling, however, the reduction of one of the nitro groups to an amino group occurred to give 4-amino-4′-nitrobiphenyl, probably due to the activating effect of the other suitably positioned nitro group (entry 6). This observation is being exploited for the selective reduction of a nitro group and will be reported later. With a view to suppress this partial reduction, the reaction was performed with 0.5 mol equiv of ascorbic acid. However, under these conditions, the reaction was not complete even on prolonged heating (9 h) and gave mostly the unreacted starting material along with the same partially reduced product in a poor yield (entry 7). The use of glucose in the place of ascorbic acid also gave the same product but in a lower yield (entry 8). The reaction of 4-bromobenzaldehyde gave a complex mixture of products under these conditions, and led to a 50% recovery of the starting material on reaction with a milder base Et_3N (3 mol equiv) for 6 h. Chloroarenes appeared to be less reactive, for example, reaction of 4-chloronitrobenzene for 10 h gave the biaryl product in only 33% yield (entry 9). Thus, selectivity can be realized between chloro and bromo functionalities (entry 10). The reaction, however, failed to give coupling products in the case of 4-bromoacetanilide and 4-allyloxybromobenzene. All the products were characterized by IR and NMR spectral analyses and by a comparison of the melting points with reported values.

In conclusion, the present method is environmentally safer and selective and does not require an inert atmosphere. It is suited particularly well to the homo-cou-

Table 2. Biaryl homo-coupling of aryl halides with $PdCl_2$/EDTA/ascorbic acid in water–ethanol[a]

Entry	Aryl halide	Time (h)	Biaryl product	Yield (%)
1	Bromobenzene	8	Biphenyl	64
2	4-Bromotoluene	8	4,4′-Dimethylbiphenyl	58
3	4-Bromoacetophenone[b]	7	4,4′-Bisacetylbiphenyl	84
4	4-Bromobenzophenone[b]	7.5	4,4′-Bisbenzoylbiphenyl	80
5	3-Bromonitrobenzene[b]	6	3,3′-Dinitrobiphenyl	74
6	4-Bromonitrobenzene[b]	4	4-Amino-4′-nitrobiphenyl	63
7	4-Bromonitrobenzene[b,c]	9	4-Amino-4′-nitrobiphenyl	15 (60)[d]
8	4-Bromonitrobenzene[b]	5	4-Amino-4′-nitrobiphenyl	35[e]
9	4-Chloronitrobenzene	10	4-Amino-4′-nitrobiphenyl	33
10	4-Bromochlorobenzene	9	4,4′-Dichlorobiphenyl	66
11	4-Bromobenzoic acid	9	4,4′-Diphenic acid	70
12	2-Iodobenzoic acid	8	2,2′-Diphenic acid	62
13	4-Bromoanisole	10	4,4′-Dimethoxybiphenyl	54
14	3-Bromoanisole	10	3,3′-Dimethoxybiphenyl	63
15	4-Bromophenol	10	4,4′-Dihydroxybiphenyl	25
16	4-Bromo-*N*,*N*-dimethylaniline	11	4,4′-Bis(*N*,*N*-dimethylamino)biphenyl	64[f]
17	2-Bromopyridine	10	2,2′-Bipyridyl	27

[a] Reaction conditions: aryl halide (1 mmol), $PdCl_2$ (3 mol %), EDTA (3 mol %), ascorbic acid (1 mmol), K_2CO_3 (3 mmol) in refluxing water–ethanol (13 ml, 5:1 v/v) under an air atmosphere.
[b] A mixture of water–ethanol (2:1 v/v) was used as the solvent.
[c] Reaction with 0.5 mol equiv of ascorbic acid.
[d] Recovered starting material.
[e] Reaction with glucose (1 mol equiv) as the reductant in place of ascorbic acid.
[f] Isolated as the hydrochloride salt.

pling of electron-deficient arenes where other methods fail or give products in lower yields due to reduction or reductive dehalogenation. To the best of our knowledge, this is the first example of the application of ascorbic acid in the biaryl homo-coupling of aryl halides.

3. General experimental procedure

To a 0.004 M solution of $PdCl_2$ in water (7.5 ml, 0.03 mmol, 3 mol %), a 0.008 M aqueous solution of EDTA (3.75 ml, 0.03 mmol, 3 mol %), ascorbic acid (176 mg, 1 mmol), K_2CO_3 (417 mg, 3 mmol) and a solution of the aryl halide (1 mmol) in ethanol (2 ml, 5 ml in the case of sparingly soluble aryl halides, that is just enough to ensure that the solution became homogeneous on warming) were added. The aqueous-ethanolic solution (5:1 v/v, 2:1 v/v in the case of sparingly soluble halide) was stirred under reflux for the specified time (Table 2) until TLC monitoring showed the absence of the aryl halide. The reaction mixture was cooled and evaporated under reduced pressure to remove most of the ethanol. The concentrate was extracted with ether or dichloromethane (4×10 ml). The combined organic extract was washed successively with water (2×5 ml) and brine (1×5 ml), dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude biaryl product thus obtained was found to be sufficiently pure in most cases as indicated by their spectra and comparison of melting points with the reported values. Where necessary, the crude product was purified by column chromatography on neutral alumina.

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