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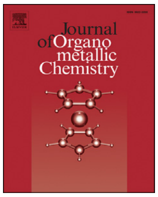

Communication

Organic/inorganic salting-in/salting-out agents as promoters of Pd-catalysed ligand free synthesis of biaryls in water

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ABSTRACT

Biaryls were synthesized using Pd-catalyzed Suzuki–Miyaura cross coupling reactions of aryl halides with aryl boronic acids in water in the presence of organic/inorganic additives as promoters. The coupling reactions, carried out in absence of ligand, proceed in good to excellent yields with easy product isolation and in relatively shorter reaction time.

1. Introduction

Biaryls are important structural moieties in many kinds of compounds like polymers, natural products, agrochemicals and pharmaceuticals. Developing methods to construct biaryl unit, therefore, is of great interest to scientific community. Palladium catalyzed Suzuki–Miyaura cross coupling reaction is one of the most important and efficient strategies for the construction of biaryl compounds [1]. This method finds several advantages over other C–C bond forming reactions like (i) mild reaction conditions and commercial availability of diversed boronic acids, (ii) better compatibility of organoboron compounds than organozinc or Grignard reagents, (iii) low toxicity and high thermal stability of boron compounds, (iv) easy handling and removal of the boron containing byproducts etc.

Suzuki–Miyaura reaction is a palladium-catalyzed cross coupling between organoboronic acids and halides or triflates [2]. The couplings, which involve a base and a ligand, are generally carried out in THF and diethyl ether in the presence of Pd (II) or Pd (0) catalysts which are soluble in these solvents. In view of the environmental pollution caused by the use of the volatile organic solvents, there has been an increasing interest to replace them by environmentally benign solvents. In this regard water, the nature's gift, is undoubtedly the best substitute for several organic solvents [3].

The promoting activity of salts in organic transformations is reported from time to time [4]. Salting-out agents usually enhance reaction rate whereas salting-in agents inhibit the reaction progress. The phrases “salting-out” and “salting-in” are generally used to denote, respectively, an increase and a decrease in the solubility of the nonelectrolyte with increasing concentration of electrolyte [4]. Herein, we present the results of Suzuki–Miyaura cross coupling reactions carried out in different organic/inorganic salting-in and salting-out agents.

2. Results and discussion

In this work, biaryls were synthesized by palladium catalyzed Suzuki couplings in aqueous solutions of different organic and inorganic salting-out (Inorganic- LiCl, NaCl, NaBr, $CaCl_2$, Na_2SO_4, and KCl; Organic- [EMIM][Br]) and salting-in agents (Inorganic- Urea, Guanidium chloride and $LiClO_4$; Organic- [OMIM][Br]) (Fig. 1).

The reaction of phenyl boronic acid with 4-bromotoluene catalyzed by 2 mol% $PdCl_2$ in water gave 90% yield of the desired product in 4 h (Table 1, Entry 1). The same reaction in the presence of 0.05 M LiCl solution afforded biaryl in 92% yields after 1.5 h (Table 1, Entry 2). Slightly better results were observed when the salt concentration was increased up to 2 M (Table 1, entries 3–4),

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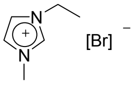
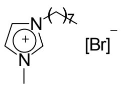
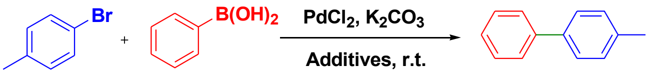
Salting-out		**Salting-in**	
Inorganic	**Organic**	**Inorganic**	**Organic**
LiCl, NaCl, NaBr, $CaCl_2$, MgCl2, Na_2SO_4, and KCl	 [EMIM][Br], β-cyclodextrin	Urea, guanidium hydrochloride, tetrabutyl ammonium bromide and $LiClO_4$	 [OMIM][Br]

Fig. 1. Organic/Inorganic additives used in this study.

Table 1
Effect of additives on Suzuki couplings.[a]



Entry	Solvent	Time (h)	% Yields[b]
1	Water	4.0	90
2	0.05 M LiCl	1.5	92
3	1.0 M LiCl	1.5	95
4	2.0 M LiCl	1.0	95
5	0.05 M Na_2SO_4	2.0	90
6	0.05 M NaCl	3.0	94
7	0.1 M KCl	3.0	96
8	0.1 M $MgCl_2$	4.0	88
9	0.1 M $CaCl_2$	4.0	85
10	0.05 M [EMIM][Br]	2.0	92
11	2 mol% β-cyclodextrin	1.5	90
12	0.1 M Urea	4.0	60
13	0.1 M Guanidium hydrochloride	3.0	94
14	0.1 M [OMIM][Br]	2.5	90
15	2 mol% Tetrabutyl ammonium bromide	2.5	88
16	0.1 M $LiClO_4$	2.0	92

[a] Reaction conditions: Aryl halide (1 mmol), arylboronic acid (1.2 mmol), $PdCl_2$ (2 mol%), K_2CO_3 (2 mmol), aqueous salt (organic or inorganic) solutions (2 mL), r.t.

[b] Isolated yields.

but beyond 2 M salt concentration catalyst decomposition was observed which was evidenced by the precipitation of black residues.

Lithium chloride, a salting-out agent, was found to accelerate Diels–Alder reaction [5]. Kumar et al. showed dramatic acceleration of Diels–Alder reaction rate in the presence of 5 M LiCl solution [5d]. The effect of salts on kinetics of Diels–Alder reactions has been discussed in terms of several parameters like hydrophobic packing, solvent pressure, hydrogen bonding, hydrophobic hydration etc. [5] To the best of our knowledge, no such observations are reported in literature for Suzuki–Miyaura cross coupling reactions. Bora et al. recently reported the accelerating effect of Na_2SO_4 in Suzuki reactions performed in water [6]. The reaction of 4-nitro bromobenzene with phenyl boronic acid in the presence of $PdCl_2$ and Na_2SO_4 afforded 90% yields in 5 h whereas the same reaction without Na_2SO_4 gave very poor yield, 20% yields in 10 h. They suggested that the promoting effect in the presence of Na_2SO_4 could be due to the *in situ* formation of a water soluble *ate* complex $Na_2PdCl_2(SO_4)_2$ which catalyzed the Suzuki–Miyaura reactions. Sarma et al. recently reported a base free and ligand free protocol for Suzuki coupling reactions carried out in ionic liquid with lithium chloride as promoter [7].

The reaction of phenyl boronic acid with 4-bromotoluene in aqueous solution of NaCl, Na_2SO_4 and KCl afforded biaryls in 90–96% yields (Table 1, Entries 5–7). For the same reaction, while carried out in aqueous solutions of $MgCl_2$ and $CaCl_2$, no promoting effect was observed (Table 1, Entries 8–9).

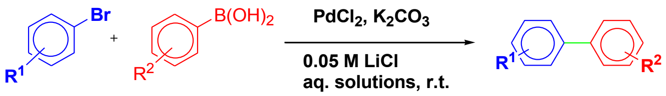
Imidazolium derived organic salts containing short alkyl chain behave as salting-out agents whereas organic salts containing long alkyl chain length behave as salting-in agents [8]. [EMIM][Br], a salting-out agent enhances the Suzuki–Miyaura reaction rate (Table 1, Entry 10), affording 92% yields in 2 h. The use of β-cyclodextrin, a 7-membered sugar ring molecule, enhances the rate of Suzuki–Miyaura coupling reaction in water. The reaction of phenyl boronic acid with 4-bromotoluene in 2 mol% β-cyclodextrin afforded 90% yields in 1.5 h (Table 1, Entry 11). This promoting effect of cyclodextrin could be due to the inclusion complexes formed by β-cyclodextrin simultaneously with aryl halide and aryl boronic acid, thereby increasing the solubility of the compounds in water. Our results were well supported by the earlier literature report. Christophe Len et al. observed dramatic acceleration of Suzuki–Miyaura coupling reactions carried out in the presence of β-cyclodextrin [9]. The reaction of 4-bromo acetophenone with phenyl boronic acid catalyzed by palladium acetate in the presence of 0.5 mol% β-cyclodextrin at room temperature afforded the biaryl adduct in 94% yields in 24 h. Whereas the same reaction, in absence of β-cyclodextrin gave 63% yields.

We then next examined the effect of salting-in agents on the course of Suzuki–Miyaura cross coupling. The reaction of phenyl boronic acid with 4-bromotoluene in 1 M urea solution was inhibited, affording 60% yields in 4 h (Table 1, Entry 12). But, other salting-in agents like guanidine chloride, [OMIM][Br], tetrabutyl ammonium bromide and lithium perchlorate promoted the progress of Suzuki–Miyaura couplings in water (Table 1, Entries 13–16). Urea, a non-ionic species, is believed to inhibit the Suzuki–Miyaura coupling by chelating the palladium catalyst.

To extend the promoting effect of ionic additive on Suzuki-Miaura couplings, different electron rich and electron deficient aryl bromides and boronic acid derivatives were used to construct biaryls (Table 2, Entries 1–10). Under the reaction condition, various aryl bromides bearing electron-withdrawing groups such as nitro, nitrile and aldehyde moieties and electron-releasing groups such as methyl and methoxy moieties react with aryl boronic acids to afford biaryls in high yields along with trace amount of homocoupling products of aryl boronic acids (2–5%).

Intriguing by the promoting effect of ionic additives on the Suzuki couplings of aryl bromides with aryl boronic acids, we next

Table 2
Effect of substituents on Suzuki–Miyaura reactions.[a]



Entry	R^1	R^2	Time (h)	% Yields[b]
1	4-Me	H	1.5	92
2	4-OMe	H	3.0	96
3	3-OMe	H	3.5	95
4	H	4-OMe	2.0	96
5	4-Me	4-OMe	3.0	99
6	4-CN	H	2.5	80
7	4-NO_2	H	3.0	90
8	4-CHO	H	3.0	95
9	3-CHO	H	4.0	70
10	2-CHO	H	4.0	65

[a] Reaction conditions: Aryl bromide (1 mmol), arylboronic acid (1.2 mmol), $PdCl_2$ (2 mol%), K_2CO_3 (2 mmol), 1 M LiCl solutions (2 mL), r.t.

[b] Isolated yields.

proceeded to the Suzuki–Miyaura couplings of chloro aryl derivatives. Among the halogens, iodide and bromide derivatives show excellent activity towards the biaryl synthesis by Suzuki–Miyaura couplings. Aryl chlorides show very poor reactivity towards the boronic acid derivatives. Aryl chlorides are more difficult to be activated because of high C–Cl bond strength. The Suzuki coupling of chloro derivatives are reported in literature from time to time either using some harsh reaction conditions or using some ligands [11]. Thus, a major challenge still remains in Suzuki–Miyaura reaction is to develop a catalyst system that can activate aryl chlorides easily. Suzuki coupling reactions with various electron and electron deficient chloroaryls and boronic acid derivatives were carried out to construct biaryl adducts. Under this reaction condition, aryl chlorides were not very reactive towards aryl boronic acids, very low yields (<10%) were observed. But, in the presence of ethylene glycol, aryl chlorides bearing electron-withdrawing groups such as nitro, carbomethoxy and aldehyde moieties and electron-releasing groups such as methyl react with aryl boronic acids to afford biaryls in comparatively higher yields (Table 3, Entries 1–7). In absence of ionic additives, Suzuki–Miyaura cross coupling of aryl chlorides with aryl boronic acids in ethylene glycol alone afforded biaryls in comparatively lower yields. This clearly indicates the promoting activity of additives towards biaryl synthesis.

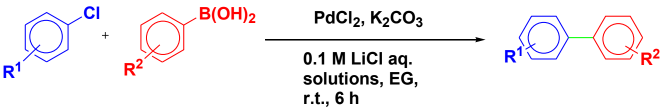
The Suzuki reaction of 4-nitro chloro benzene and phenyl boronic acid in the presence of lithium chloride proceeded comparatively well, affording 45% yields of the desired biphenyl adducts in 6 h as compared to the very poor yields (<10%) obtained in water alone (Table 3, Entry 1). Identical results were obtained with other chloro aryls also (Table 3, Entries 2–6). The reaction of 4-cloro toluene with 4-methoxy phenyl boronic acid afforded the best result (70% yields, Entry 6, Table 3) under this reaction condition.

The role of ionic additives and other agents on the promoting (for all the additives except urea) or inhibiting effect (in case of urea) during the course of Suzuki couplings is not well understood. It could be due to the combination of several parameters such as polarity of solvent media, hydrogen bonding, hydrophobic effect etc. Also the ionic additive, by coordination to the Pd(II) adducts, is believed to play significant role in the oxidative addition of aryl halides to palladium species favouring the formation of thermodynamically more stable *trans* isomer.

3. Conclusion

In summary, we have developed a novel protocol for biaryl synthesis in water in a ligand free environment. Organic/Inorganic ionic additives show excellent promoting activity towards biaryl synthesis. The methodology is quick, versatile and highly efficient. Under this reaction condition, aryl bromides and chlorides reacted efficiently with aryl boronic acids to afford the biaryl adducts. This simple protocol provides a wide scope for the synthesis of desired biaryls in excellent yields in a relatively shorter period of time.

Table 3
Effect of organic/inorganic salts on Suzuki couplings.[a]



Entry	R^1	R^2	% Yields[b]
1	4-NO_2	H	45
2	4-CHO	H	60
3	H	4-OMe	65
4	H	4-CF_3	55
5	4-$COCH_3$	H	60
6	4-CH_3	4-OMe	70
7	4-OMe	H	65

[a] Reaction conditions: Aryl chloride (1 mmol), arylboronic acid (1.2 mmol), $PdCl_2$ (2 mol%), K_2CO_3 (2 mmol), 0.1 M LiCl solutions (1 mL), Ethylene Glycol (EG) 1 mL, r.t.
[b] Isolated yields.

4. Experimental

4.1. Preparation of organic salts

Organic salts *N*-Ethyl-*N*-methyl imidazolium bromide, ([EMIM][Br]) and *N*-Methyl-*N*-Octyl imidazolium bromide, ([OMIM][Br]) were prepared according to a literature procedure [10]. For example, under vigorous stirring 1-bromoethane (15.24 g, 121.95 mmol) was added to 1-methylimidazole (5 g, 60.98 mmol). The reaction mixture was stirred at 80 °C until two phases were formed. The top phase, containing the unreacted starting material, was decanted and ethyl acetate was added to the vessel. The product [EMIM][Br] was washed with ethyl acetate thrice and dried under vacuum at 70 °C for 6 h 1H NMR (200 MHz, $CDCl_3$): δ 10.05 (s, 1H), 7.54 (d, 2H), 4.21 (q, 2H), 3.95 (s, 3H), 1.43 (t, 3H). The same procedure was followed for the synthesis of [OMIM][Br].

4.2. General experimental procedure for Suzuki cross coupling reactions in salt solutions

In a 50 mL round buttom flask, a mixture of aryl halide (1 mmol), phenyl boronic acid (1.2 mmol), $PdCl_2$ (2 mol%), potassium carbonate (2 mmol) and salts solution (organic or inorganic) (2 mL) was stirred at room temperature for a time period as mentioned in Table 1. The progress of the reaction was monitored by TLC. The resulting mixture was extracted with diethyl ether (3 × 5 mL). The ether layer was separated and dried over anhydrous Na_2SO_4. The product was purified by column chromatography over silica gel using n-hexane/ethyl acetate (9:1 v/v) to get the desired coupling product. The products were characterized by ^{1}H-NMR and GC–MS.

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