



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.

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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 diversified 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, CaCl₂, Na₂SO₄, and KCl; Organic- [EMIM][Br]) and salting-in agents (Inorganic-Urea, Guanidium chloride and LiClO₄; Organic- [OMIM][Br]) (Fig. 1).

The reaction of phenyl boronic acid with 4-bromotoluene catalyzed by 2 mol% PdCl₂ 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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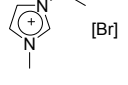
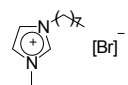
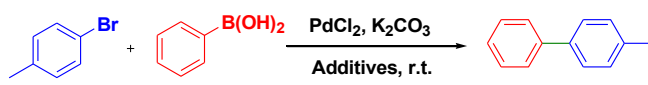
Salting-out		Salting-in	
Inorganic	Organic	Inorganic	Organic
LiCl, NaCl, NaBr, CaCl ₂ , MgCl ₂ , Na ₂ SO ₄ , and KCl	 [EMIM][Br], β -cyclodextrin	Urea, guanidium hydrochloride, tetrabutyl ammonium bromide and LiClO ₄	 [OMIM][Br]

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 ₂ SO 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), PdCl₂ (2 mol%), K₂CO₃ (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 Na₂SO₄ in Suzuki reactions performed in water [6]. The reaction of 4-nitro bromobenzene with phenyl boronic acid in the presence of PdCl₂ and Na₂SO₄ afforded 90% yields in 5 h whereas the same reaction without Na₂SO₄ gave very poor yield, 20% yields in 10 h. They suggested that the promoting effect in the presence of Na₂SO₄ could be due to the *in situ* formation of a water soluble ate complex Na₂PdCl₂(SO₄)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, Na₂SO₄ and KCl afforded biaryls in

90–96% yields (Table 1, Entries 5–7). For the same reaction, while carried out in aqueous solutions of MgCl₂ and CaCl₂, no promoting effect was observed (Table 1, Entries 8–9).

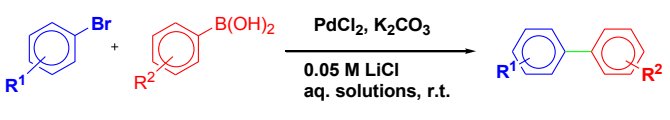
Imidazolium derived organic salts containing short alkyl chain behave as salting-out agents whereas organic salts containing long alkyl chain length behave as salting-in agents [8]. [EMIM][Br], a salting-out agent enhances the Suzuki–Miyaura reaction rate (Table 1, Entry 10), affording 92% yields in 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–Miyaura 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), PdCl₂ (2 mol%), K₂CO₃ (2 mmol), 1 M LiCl solutions (2 mL), r.t.

^b Isolated yields.

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