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Sodium 2-(2-pyridin-3-ylethylamino)ethyl sulfonate: an efficient ligand and base for palladium-catalyzed Suzuki reaction in aqueous media

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ABSTRACT

$PdCl_2$, N-donor ligand and base mediated Suzuki coupling reaction of aryl halides and arylboronic acid in water are described. The corresponding Suzuki products were obtained in good to excellent yields.

1. Introduction

The Suzuki cross-coupling reaction is an important method for the selective construction of biaryls,[1] and has found extensive use in the synthesis of natural products, pharmaceuticals, and advanced materials.[2] The utility of the Suzuki reaction derives from its high stability, broad functional group tolerance, and the low toxicity associated with boron compounds. Recently, the use of water as solvent for the Suzuki reaction has received much attention.[3] Water has clear advantages as a solvent in organic synthesis considering its safety, cost, and significance to environmentally benign processes.[4] Although many additives and water-soluble ligands have been applied successfully in the Suzuki reaction as useful promoters,[5] reaction in the absence of additives and ligands is greatly limited by the substrate solubility and reactivity in aqueous media.[6] For example, Beletskaya and co-workers reported the Suzuki reaction in water with water-soluble aryl halides using simple palladium salt catalysis; however, the reaction was sluggish with water-insoluble aryl halides under the same conditions.[7]

The general Suzuki–Miyaura coupling procedure involves the use of palladium–ligand (often a phosphane ligand) complexes as catalysts, and the reactions are performed at high temperature under oxygen-free conditions to avoid side reactions. In addition, long reaction times are usually required. Impressive progress in the development of efficient catalytic systems to achieve this reaction under mild conditions has been made in recent years.[8,9]

These findings, to investigate the Suzuki reaction in aqueous media and in continuation of our interest in developing novel synthetic methodologies, particularly carbon–carbon bond forming reactions prompted us.[10]

Palladium-catalyzed Suzuki reactions between aryl halides and phenylboronic acid continue to attract attention because of the versatility and the potential of the products formed. The area that has perhaps received most research is the development of new catalysts and ligands for Suzuki coupling reactions, and the use of these catalyst systems in, for example, natural product synthesis. Recently, novel phosphine-free ligands[11] were used as catalysts for the Suzuki reaction.

As part of an ongoing project,[12,13] we herein disclose a novel protocol for the Suzuki reaction using N-donor ligand **1** as a ligand and base, which makes use of milder conditions compared to those reported, Scheme 1. The method is simple and affords good to excellent yields of products. N-donor ligand **1** was synthesized by reaction of the corresponding primary amine (2-(pyridine-3-yl)ethylamine) with sodium vinylsulfonate in water using a literature procedure.[14] We initially studied the effect of **1** as a base along with other bases in different solvents for Suzuki reactions, and our results are summarized in Table 1.

We employed the coupling reaction of 4-iodoacetophenone with phenylboronic acid as a model reaction to study the effect of base on the reaction. The reactions were carried out using

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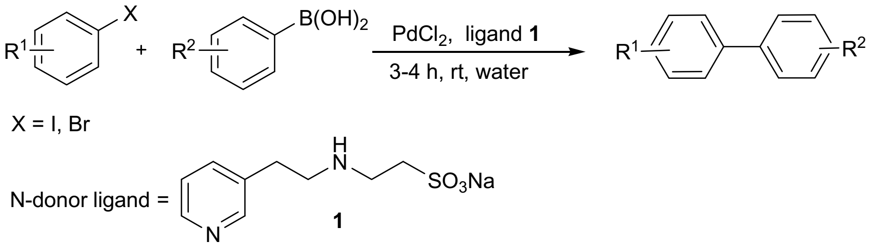
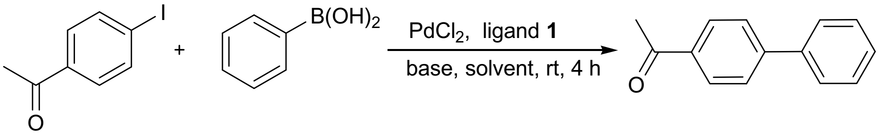


Scheme 1.

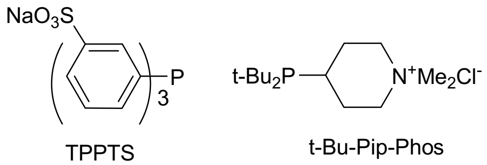
Table 1
Effect of N-donor ligand **1** as base as well as other bases on the Suzuki coupling reaction



Entry	Catalyst	Base	Solvent (ml)	Ligand	Yield[a]
1	$PdCl_2$	K_2CO_3 (1 equiv)	DMF	**1** (0.25 equiv)	Trace
2	$PdCl_2$	K_2CO_3 (2 equiv)	1,4-Dioxane	**1** (0.25 equiv)	45
3	$PdCl_2$	K_2CO_3 (2 equiv)	NMP	**1** (0.25 equiv)	51
4	$PdCl_2$	K_2CO_3 (2 equiv)	NMP/water (1:1)	**1** (0.25 equiv)	54
5	$PdCl_2$	K_2CO_3 (2 equiv)	DMF/water (1:1)	**1** (0.25 equiv)	55
6	$PdCl_2$	K_2CO_3 (2 equiv)	Water	**1** (0.25 equiv)	68
7	$PdCl_2$	NaOAc (2 equiv)	Water	**1** (0.25 equiv)	55
8	$PdCl_2$	Cs_2CO_3 (2 equiv)	Water	**1** (0.25 equiv)	62
9	$PdCl_2$	Na_2CO_3 (2 equiv)	Water	**1** (0.25 eqiv)	66
10	$PdCl_2$	NaOH (2 equiv)	Water	**1** (0.25 equiv)	59
11	$PdCl_2$	KOH (2 equiv)	Water	**1** (0.25 equiv)	57
12	$PdCl_2$	**1** (0.25 equiv)	Water	—	—
13	$PdCl_2$	**1** (0.5 equiv)	Water	—	72
14	$PdCl_2$	**1** (1 equiv)	Water	—	90
15	$PdCl_2$	**1a** (1.5 equiv)	Water	—	90
16	$PdCl_2$	**1** (2 equiv)	Water	—	90
17	$PdCl_2$	**1** (1 equiv)	DMF/water (1:1)	—	70
18	$PdCl_2$	**1** (1 equiv)	DMF	—	66
19	$PdCl_2$	**1** (1 equiv)	NMP	—	65
20	$PdCl_2$	**1** (1 equiv)	1,4-Dioxane	—	62
21	$Pd(OAc)_2$	**1** (1 equiv)	Water	—	65
22	$(PPh_3)_4Pd(0)$	**1** (1 equiv)	Water	—	57
23	$[P(Ph)_3]_2PdCl_2$	**1** (1 equiv)	Water	—	40
24	$PdCl_2$	**1** (0.75 equiv)	Water	**2** (0.25 equiv)	60
25	$PdCl_2$	**1** (0.75 equiv)	Water	**3** (0.25 equiv)	58

[a] Isolated yields after column chromatography based upon starting 4-iodoacetophenone.

K_2CO_3 (1 equiv) as base and ligand **1** (0.25 equiv, which is highly water soluble) in the presence of 0.5 mol % $PdCl_2$ at room temperature. The reaction in pure DMF afforded 4-acetylbiphenyl in very low yield after 4 h (Table 1, entry 1). If we kept the catalyst, base, and ligand **1** constant and used different solvents such as 1,4-dioxane, NMP, DMF, and DMF–water, the desired product was obtained in 45–55% yields (Table 1, entries 2–5). However, in neat water, we obtained the desired product in 68% yield (Table 1, entry 6) indicating water to be the solvent of choice for this Suzuki reaction. Next, we kept the catalyst and ligand **1** constant, and investigated bases such as NaOAc, Cs_2CO_3, Na_2CO_3, NaOH, and KOH in water. The desired products were obtained in similar yields (Table 1, entries 7–11). Due to the basic nature of ligand **1**, we decided to use it as both ligand and base. Reaction using 0.25 equiv of ligand **1** and 0.3 mol % of $PdCl_2$ in water at room temperature for 4 h did not lead to formation of the desired product (Table 1, entry 12). However, using 0.5 equiv of ligand **1**, we obtained the desired product in 72% yield (Table 1, entry 13). Increasing the equivalents of ligand **1** (1 equiv) gave the desired product in 90% yield (Table 1, entry 14). Further increasing the equivalents of ligand **1** did not improve the yield (Table 1, entries 15 and 16). The use of solvents including DMF, 1,4-dioxane, NMP, and the co-solvent DMF/water (1:1) led to decreased yields compared to those in neat water (Table 1, entries 17–20). Next, we investigated catalysts such as $Pd(OAc)_2$, $(PPh_3)_4Pd(0)$, and $[P(Ph)_3]_2PdCl_2$ in water; the desired product was obtained in 40–65% yields (Table 1, entries 21–23). Even more, we also investigated water soluble phosphines such as XPPTS and *t*-Bu-Pip-Phos (Fig. 1) with ligand **1** as base in water; the desired product was obtained in 58–60% yields (Table 1, entries



2 **3**

Figure 1.

Table 2
Suzuki coupling reaction of aryl halides with boronic acids in aqueous media[a]

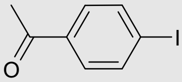
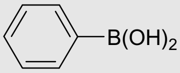
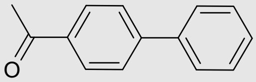
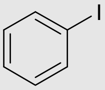
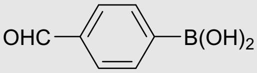
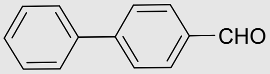
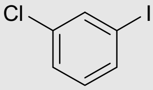
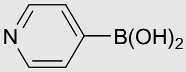
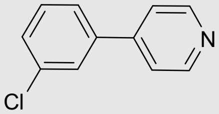
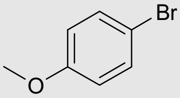
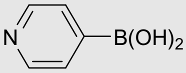
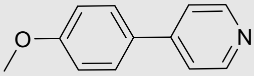
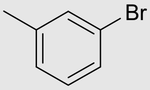
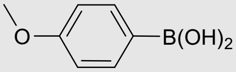
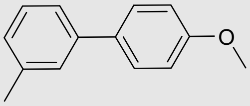
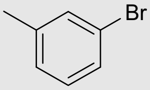
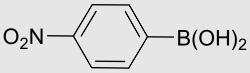
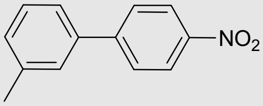
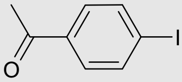
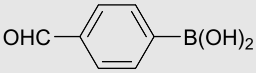
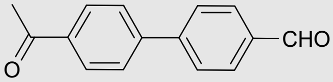
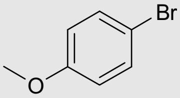
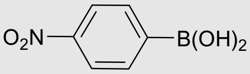
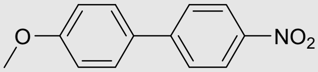
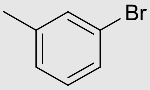
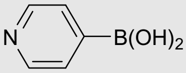
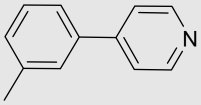
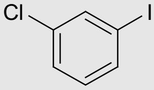
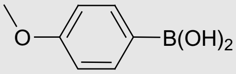
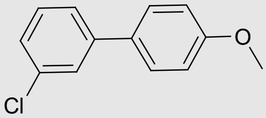
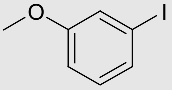
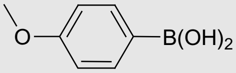
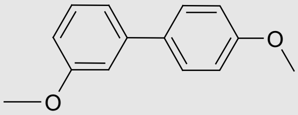
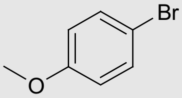
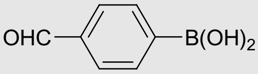
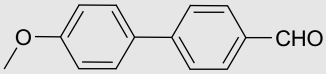
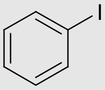
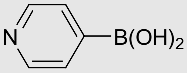
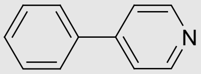
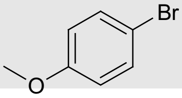
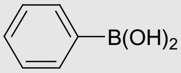
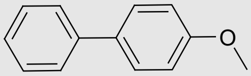
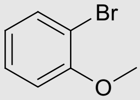
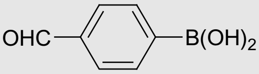
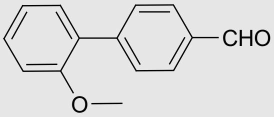
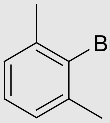
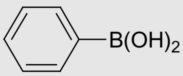
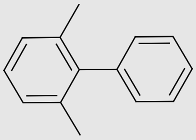
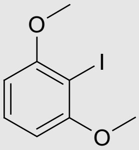
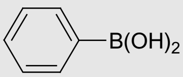
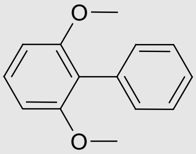
Entry	Aryl halide	Boronic acid	Product	Time (h)	Yield[b] (%)
1				4	90
2				3	88
3				4	86
4				3	90
5				3.5	85
6				4	88
7				3.5	84
8				3	90
9				3.5	89
10				4	87
11				4	89
12				3	90
13				3.5	86
14				4	87

Table 2 (*continued*)

Entry	Aryl halide	Boronic acid	Product	Time (h)	Yield[b] (%)
15				4	89
16				4	84
17				4	85

[a] Standard conditions: aryl iodide or aryl bromide (1.0 mmol), boronic acid (1.2 mmol), base and ligand **1** (1.0 mmol), $PdCl_2$ (5 mol %), water (10 ml), rt.

[b] Isolated yields after column chromatography based upon starting aryl halide.

24 and 25). These results indicate that 1 equiv of N-donor ligand **1** and 0.5 mol of $PdCl_2$ in water at room temperature for 4 h are optimal conditions for the present Suzuki coupling reactions. This may be due to N-donor ligand **1** having better solubility and showing stronger basicity in water. The catalytic system was applicable to a wide range of aryl halides and five different types of boronic acid (Table 2).

The coupling of aryl iodides and bromides was efficient and afforded the desired products in excellent yields (Table 2).[5a,15] ^{1}H NMR, ^{13}C NMR, mass spectroscopy, elemental analysis, and IR were used to characterize the products.

We also investigated the scope of this method on aryl chlorides, but found that the coupling of an aryl chloride with phenylboronic acid did not proceed, even on heating the reaction mixture up to 100 °C and extending the reaction time up to 24 h. This proved to be the only limitation of the method. When 3-chloroiodobenzene was used as the alkyl halide, only coupling with the iodo function occurred (Table 2, entries 3 and 10).

In conclusion, N-donor ligand **1** is an efficient catalyst for the synthesis of biaryl compounds via Suzuki reaction in water. The advantages offered by this method are simple procedure, mild conditions, fast reactions at room temperature, and excellent yields of products.

2. Typical experimental procedure

Iodobenzene (0.30 g, 1.47 mmol), phenylboronic acid (0.21 g, 1.76 mmol), N-donor ligand 1 (0.33 g, 1.47 mmol), and PdCl2 (13 mg, 5 mol %) were taken in a 25 ml single neck round-bottomed flask to which 10 ml of water was added. The reaction mixture was stirred for 4 h at room temperature. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was filtered and the filtrate extracted with ethyl acetate (15 ml × 2). The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude material was purified by column chromatography over silica gel to afford the corresponding product in high purity.

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