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

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ABSTRACT

The first successful $Pd(OAc)_2$, N-donor ligand and base mediated Heck coupling reaction of aryl halides and alkenes in water is described. The corresponding Heck products were obtained in good to excellent yields.

The palladium-catalyzed Heck reaction[1] between aryl halides and alkenes is a versatile method for carbon–carbon bond formation in organic synthesis.[2] To minimize the adverse impact of organic solvents on the environment, recent efforts have been directed towards using aqueous solvents for chemical reactions.[3]

Organic reactions in water or aqueous media have attracted great interest.[4] With tightened regulatory pressure focusing on organic solvents, the search for alternatives is of increasing importance. In this respect, the development of water-tolerant catalysts has rapidly become an area of intense research. There have been several reports concerning the Heck reaction in water; however, in most cases, high temperatures were required.[5,6]

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

Palladium-catalyzed Heck reactions between aryl halides and alkenes continue to attract attention within the chemistry community because of the versatility of the reaction and the potential of the products formed.[7] The area that has perhaps received most research effort is the development of new catalysts and ligands for Heck coupling reactions and the use of these catalyst systems in, for example, natural product synthesis. Recently, novel phosphine-free ligands[8] and hydrazone[9] were used as catalysts for the Heck reaction. In addition, Li and Wang reported triethanolamine as a ligand as well as base for Heck reactions.[10] As part of an ongoing project,[11] we herein disclose a novel protocol for the Heck reaction using N-donor ligand (**1a**) 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. N-donor ligand **1a** was synthesized by reaction of the corresponding primary amine (2-(pyridine-3-yl)ethyl amine) with sodium vinylsulfonate in water using a literature procedure.[12] We initially studied the effect of **1a** as a base along with other bases in different solvents for Heck reactions, and our results are summarized in Table 1.

We employed the coupling reaction of iodobenzene with methyl acrylate as a model reaction to study the effect of base on the reaction. The reactions were carried out using K_2CO_3 (1 equiv) as base and ligand **1a** (0.25 equiv, which is highly water soluble) in the presence of 0.3 mol % $Pd(OAc)_2$ at room temperature. The reaction in pure DMF afforded 3-phenyl acrylic acid methyl ester in very low yield after 4 h (Table 1, entry 1). If we kept the catalyst, base and ligand **1a** constant and used different solvents such as DME, NMP, NMP–water and DMF–water, the desired product was obtained in 40–61% yields (Table 1, entries 2–5). However, in neat water we obtained the desired product in 67% yield (Table 1, entry 6) indicating water to be the solvent of choice for this Heck reaction. Next, we kept the catalyst and ligand **1a** constant and

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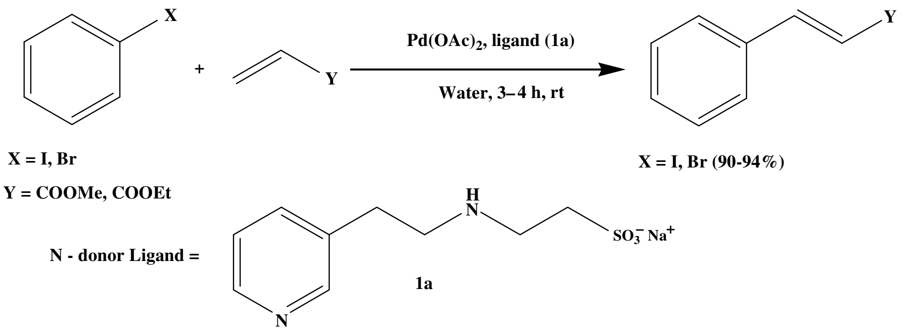
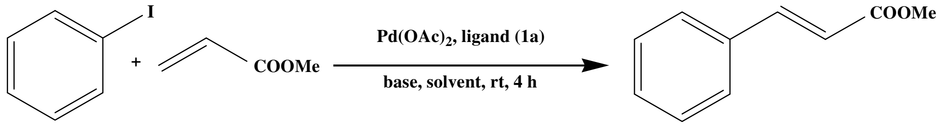


Scheme 1.

Table 1

Effect of N-donor ligand **1a** as a base and other bases on the Heck coupling reaction



Entry	Catalyst	Base	Solvent (ml)	Ligand	Yield[a]
1	$Pd(OAc)_2$	K_2CO_3 (1 equiv)	DMF	**1a** (0.25 equiv)	Trace
2	$Pd(OAc)_2$	K_2CO_3 (2 equiv)	DME	**1a** (0.25 equiv)	40
3	$Pd(OAc)_2$	K_2CO_3 (2 equiv)	NMP	**1a** (0.25 equiv)	51
4	$Pd(OAc)_2$	K_2CO_3 (2 equiv)	NMP–water (1:1)	**1a** (0.25 equiv)	54
5	$Pd(OAc)_2$	K_2CO_3 (2 equiv)	DMF–water (1:1)	**1a** (0.25 equiv)	61
6	$Pd(OAc)_2$	K_2CO_3 (2 equiv)	Water	**1a** (0.25 equiv)	67
7	$Pd(OAc)_2$	NaOAc (2 equiv)	Water	**1a** (0.25 equiv)	55
8	$Pd(OAc)_2$	Cs_2CO_3 (2 equiv)	Water	**1a** (0.25 equiv)	62
9	$Pd(OAc)_2$	Na_2CO_3 (2 equiv)	Water	**1a** (0.25 equiv)	66
10	$Pd(OAc)_2$	NaOH (2 equiv)	Water	**1a** (0.25 equiv)	59
11	$Pd(OAc)_2$	KOH (2 equiv)	Water	**1a** (0.25 equiv)	57
12	$Pd(OAc)_2$	**1a** (0.25 equiv)	Water	–	–
13	$Pd(OAc)_2$	**1a** (0.50 equiv)	Water	–	94
14	$Pd(OAc)_2$	**1a** (0.75 equiv)	Water	–	94
15	$Pd(OAc)_2$	**1a** (1 equiv)	Water	–	94
16	$Pd(OAc)_2$	**1a** (0.50 equiv)	DMF–water (1:1)	–	77
17	$Pd(OAc)_2$	**1a** (0.50 equiv)	DMF	–	75
18	$Pd(OAc)_2$	**1a** (0.50 equiv)	NMP	–	65
19	$Pd(OAc)_2$	**1a** (0.50 equiv)	DME	–	62

[a] Isolated yields after column chromatography based upon starting iodobenzene.

investigated bases such as NaOAc, Cs_2CO_3, Na_2CO_3, NaOH and KOH in water. The desired products were obtained in average yields (Table 1, entries 7–11). Due to the basic nature of ligand **1a**, we decided to use it as both ligand and base. Reaction of 0.25 equiv of ligand **1a** and 0.3 mol % of $Pd(OAc)_2$ in water at room temperature for 4 h did not lead to formation of the desired product (Table 1, entry 12). However, on using 0.5 equiv of ligand **1a**, we obtained the desired product in 94% yield (Table 1, entry 13). Further increasing the equivalents of ligand **1a** did not improve the yield (Table 1, entries 14 and 15). The use of solvents including DMF, DME, NMP and the co-solvent DMF–water (1:1) led to decreased yields compared to those in neat water (Table 1, entries 16–19). These results indicate that 0.5 equiv of N-donor ligand **1a**, 0.3 mol % of $Pd(OAc)_2$ in water at room temperature for 4 h is the best protocol for the present Heck coupling reactions. This may be due to N-donor ligand **1a** having better solubility and showing stronger basicity in water. The catalytic system was applicable to a wide range of aryl halides and two different types of alkenes (Table 2).

The coupling of aryl iodides and bromides was superior and afforded the desired products in excellent yields (Table 2 entries 1–18).[13] ^{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 acrylate did not work; even on heating the reaction mixture up to 100 °C and extending the reaction time. This proved to be the only limitation of the method. We observed that when 3-chloroiodobenzene was used as the alkyl halide, coupling only with the iodo function occurred and not with the chloro function (Table 2, entries 2 and 11).

In conclusion, N-donor ligand **1a** is an efficient catalyst for the synthesis of α,β-unsaturated carbonyl compounds via Heck reaction in water. The advantages offered by this method are simple procedure, mild conditions, fast reactions and excellent yields of products.

Typical experimental procedure: Iodobenzene (0.30 g, 1.47 mmol), methyl acrylate (0.14 g, 1.67 mmol), N-donor ligand **1a** (0.19 g, 0.73 mmol) and $Pd(OAc)_2$ (3 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 of the reaction, the reaction mixture was filtered and the filtrate extracted with ethyl acetate (10 ml × 2). The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude material was purified by

Table 2

Heck coupling reaction of aryl halides with alkenes in aqueous media[a]

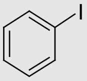
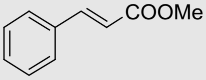
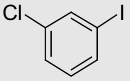
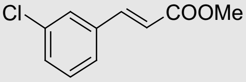
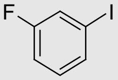
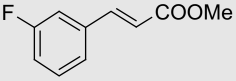
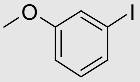
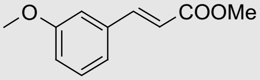
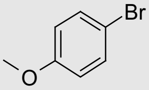
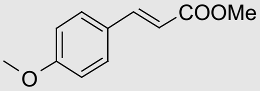
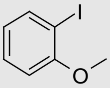
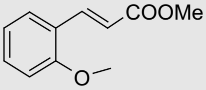
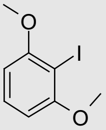
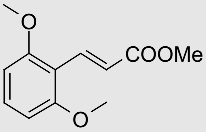
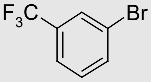
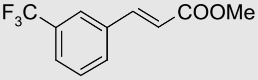
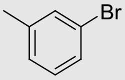
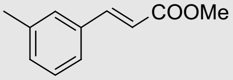
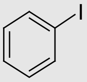
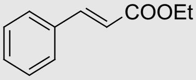
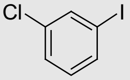
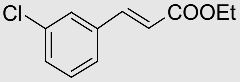
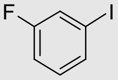
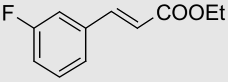
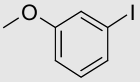
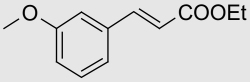
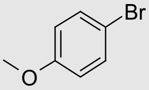
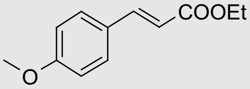
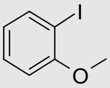
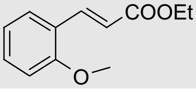
Entry	Aryl halide	Alkene	Product	Time (h)	Yield[b] (%)
1				4	94
2				3.5	91
3				4	93
4				4	90
5				3	94
6				3.5	93
7				3	90
8				3	91
9				3	92
10				4	92
11				3	93
12				3.5	90
13				3	92
14				3	90
15				3	94

Table 2 (*continued*)

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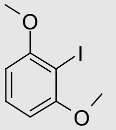
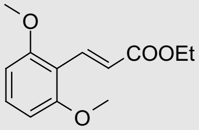
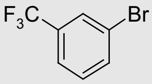
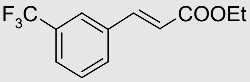
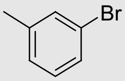
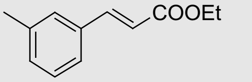
16				3	90
17				3	92
18				4	91

[a] Standard conditions: aryl iodide or aryl bromide (1.0 mmol), alkene (1.1 mmol), base and ligand (**1a**, 0.5 mmol), Pd(OAc)$_2$ (3 mol %), water (10 ml), rt.

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

column chromatography over silica gel to afford the corresponding product in high purity. Same procedure was used with aryl bromides.

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