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Simple and Efficient Phosphine-Free Pd(OAc)₂ Catalyzed Urea Accelerated Suzuki– Miyaura Cross-Coupling Reactions in ^{*i*}PrOH-H₂O at Room Temperature

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ABSTRACT

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The discovery of the Suzuki-Miyaura cross-coupling reaction has brought revolutionary progress to synthetic organic chemistry by providing a widely applicable method of constructing sp^2 C–C bonds *via* the coupling of aryl halides and boranes.¹ The characteristics of organoboron reagents (i.e. high selectivity in cross-coupling reactions, stability, nontoxic nature and tolerance towards functional groups) often give Suzuki-Miyaura (SM) coupling a practical advantage over other crosscoupling processes. It is one of the most powerful tools for the preparation of unsymmetrical biaryl derivatives that are structural elements of numerous natural products, agrochemicals, pharmaceuticals, and polymers.²⁻³ In general, Pd-phosphine complexes have been the most commonly employed catalysts for the SM reaction. However, the major drawback of these catalyst systems is that the phosphine ligands are comparatively difficult to make or are rather more expensive, poor thermal and air stability. These factors contribute to the growing interest in N,Ocoordinating ligands for catalysts in SM cross-coupling reactions.⁴ A number of phosphine-free ligands for the Suzuki-Miyaura reaction had been reported in numerous literature such as N-heterocylic carbenes,^{5,6} diimines,^{7,8} diaminos,^{9,10} and N,Oligands.¹¹⁻¹³. Most of the classical Suzuki–Miyaura reaction was often carried out in organic media¹⁴⁻¹⁹, which was conflicting to the idea of green chemistry. The majority of reported catalysts are based on the preparation of Pd-ligand complexes by using highly expensive and laborious methods. Similarly, the use of strong bases, organic solvents and refluxed conditions are required to maximize the catalytic performance.

From these standpoints, the development of efficient, stable, economical, and environmentally friendly catalytic system remains a challenging task. More recently, researchers have dev-

A simple, efficient and less expensive protocol for the phosphine-free Suzuki–Miyaura cross– coupling reactions of aryl halides with different aryl boronic acids in ^{*i*}PrOH-H₂O under aerobic conditions has been developed. The mixture of $Pd(OAc)_2$ and urea catalyzes the Suzuki– Miyaura cross-coupling of a variety of aryl halides with aryl boronic acids at room temperature, giving generally high yields even under low catalytic loads. The effect of solvent, base and catalyst loading on the coupling reaction of aryl halide with arylboronic acid is also described.

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-eloped new eco-friendly catalytic systems for Suzuki–Miyaura cross-coupling reactions as well as inexpensive inorganic base and solvents are used in green Suzuki–Miyaura catalytic systems.²⁰ Specifically, cost effective catalyst systems that allow for unconventional couplings to take place smoothly are of great value.

Our group has been investigating the use of easily available urea as a highly effective ligand with $Pd(OAc)_2$, with particular focus on optimizing new catalytic systems for eco-friendly Suzuki–Miyaura cross-coupling reactions. Urea is a colorless, odorless solid, highly soluble in water and practically non-toxic substance, consequently its use as a ligand in Suzuki coupling reaction is considered as environment friendly. On the other hand, it is very cheap and easily available material. Therefore, the chemistry of urea based ligands has been developed rapidly in recent years because of interest in their geometrical structures and complexing ability.²¹

Initially, we optimized the reaction conditions such as the solvent, base and reaction temperature for Suzuki–Miyaura crosscoupling reactions. Possible solvent mixtures for this crosscoupling reaction are assessed in order to get excellent yield of the desired cross-coupling products. We avoided all the halogenated solvents such as methylene chloride, chloroform, perchloroethylene and carbon tetrachloride as they have long been identified as suspected human carcinogens.²² Similarly, the roles of different bases were screened for Suzuki–Miyaura reaction and it was found that bases had a significant influence on the coupling efficiency. To find the efficiency of the Pd(OAc)₂urea catalyst system, we performed the Suzuki–Miyaura crosscoupling reaction with 4-nitrobromobenzene and phenylboronic acid in presence of different bases and solvent systems at room temperature and the results are summarized in **Table 1**.

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In the beginning we investigated the SM reaction of 4nitrobromobenzene and phenylboronic acid, catalyzed by Pd(OAc)₂-urea in neat 'PrOH at room temperature under aerobic conditions. We found that the coupled product was obtained in only 25% isolated yield after 60 minutes (Table 1, Entry 3). The yields of 4-nitrobiphenyl were 55%, 30%, 20%, 12%, 25% and when *tert*-butanol, ethanol, dimethylformamide, 42% acetonitrile, 1,4-dioxane and ethylene glycol were used as solvents respectively, with water as co-solvent in presence of base K₂CO₃ (Table 1, after 60 min, Entries 13, 17-20 and 22). Meanwhile, the yield reached up to 60% when the reaction mixture was at room temperature for 60 min in H₂O (Table 1, Entry 1). The yields of 4-nitrobiphenyl were 20%, 10%, and 30% when tert-butanol, ethanol, and ethylene glycol were used as solvents respectively, in presence of base K₂CO₃ (Table 1, Entries 4, 16 and 21). However, no significant improvement was observed for these cases when the reaction time was enhanced. Surprisingly in 'PrOH-H₂O (1:1 v/v) solvent system, an excellent yield (99%) of the desired product was observed after 10 min (Table 1, Entry 5). We observed that the addition of appropriate amounts of polar organic solvents such as 'PrOH, 'BuOH, EtOH and Ethylene Glycol into water led to an increase in the activity, and better yield was obtained. We are quite satisfied to see that our reaction completed at room temperature (Scheme 1) and the formation of undesired homo-coupling product was very negligible. We further examined the effect of other bases such as Na₂CO₃, NaOH, KOH, Na₃PO₄.12H₂O, Na₂HPO₄, K₃PO₄, Et₃N etc (Table 1). to study if the rate of reaction could get enhanced, but these turned out to be poorer bases as compared to K_2CO_3 . From the results in Table 1, it could be seen clearly that in presence of K₂CO₃, the mixture of ⁱPrOH-H₂O (1:1 v/v) was the best media for this catalyst system, 10 min as the reaction time, and room temperature. The important aspect of this system is that, 'PrOH evaporates quickly compared to alternative organic solvents. Generally, presence of water increases solubility of the bases, which is responsible for the activation of boronic acid resulting in enhancing the rate of the reaction in aqueous medium.²³ Finally, the synthetic route in Scheme 1 has several advantages, including simple procedures, short reaction times, excellent yields, mild conditions and commercially cheaper reagents.

Table 1. Screening the solvent and base efficiency of the $Pd(OAc)_2$ and urea catalytic system at room temperature for the Suzuki–Miyaura cross-coupling reaction^a

	Br B(OH) ₂	Pd(OAc) ₂ , Urea	0 N /	_ /_
0 ₂ N		Base, Solvent, rt	021	
Entry	Solvent	Base	Time (min)	Yield ^b
1	H ₂ O	K_2CO_3	30	60
2	H ₂ O	NaOH	30	30
3	ⁱ PrOH	K_2CO_3	60	25
4	'BuOH	K_2CO_3	60	20
5	ⁱ PrOH/H ₂ O (1:1 v/v)	K ₂ CO ₃	10	99
6	ⁱ PrOH/H ₂ O (1:1 v/v)	Na ₂ CO ₃	30	70
7	ⁱ PrOH/H ₂ O (1:1 v/v)	NaOH	30	46
8	ⁱ PrOH/H ₂ O (1:1 v/v)	Na ₃ PO ₄ .12H ₂ O	60	38
9	ⁱ PrOH/H ₂ O (1:1 v/v)	Na ₂ HPO ₄	60	35
10	ⁱ PrOH/H ₂ O (1:1 v/v)	K_3PO_4	60	35
11	ⁱ PrOH/H ₂ O (1:1 v/v)	Et ₃ N	60	<20
12	ⁱ PrOH/H ₂ O (1:1 v/v)	-	60	No
				reaction
13	^t BuOH/H ₂ O (1:1 v/v)	K_2CO_3	30	55
14	^t BuOH/H ₂ O (1:1 v/v)	Na ₂ CO ₃	60	55
15	^t BuOH/H ₂ O (1:1 v/v)	KOH	60	30
16	EtOH	K_2CO_3	60	10

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17	EtOH/H ₂ O	K_2CO_3	60	30
18	DMF/H ₂ O (1:1 v/v)	K_2CO_3	60	20
19	CH ₃ CN/H ₂ O (1:1 v/v)	K_2CO_3	60	12
20	1,4-dioxane/H ₂ O	K_2CO_3	60	25
	(1:1 v/v)			
21	Ethylene Glycol	K_2CO_3	60	30
22	Ethylene Glycol/H ₂ O	K_2CO_3	60	42
	(1:1 v/v)			

^a Reaction conditions: 4-nitrobromobenzene (1 mmol), phenylboronic acid (1.2 mmol), Pd(OAc)₂ (1 mol%), Urea (0.01 mmol), base (3 mmol) in solvent (4 mL) at room temperature.
^b Isolated yields

After optimizing the reaction conditions, different aryl bromides and iodides with electron-donating and electronwithdrawing groups were investigated to check the feasibility of this protocol whose results are tabulated in Table 2. The arylboronic acids bearing methyl, methoxy, chloro, and trifluoromethyl groups were rapidly converted to the corresponding products at high yield for less than 1 h at room temperature under the standard conditions as shown in Table 2 (Entries 3, 4, 7, 8, 16, 17 and 19). It is worth to note that the electronic effects of either coupling partner produced no significant impact on the reaction yields. These results suggest that Pd(OAc)₂/urea was a very effective catalyst for this crosscoupling reaction. ortho-Substituted aryl bromides/iodides and arylboronic acids were coupled smoothly (Table 2, Entries 6, 7 and 15), indicating that the steric hindrance of coupling partners had less influence on this coupling reaction. Under slightly extended reaction time, our catalyst can also allow for synthesis of highly sterically hindered di-ortho as well as tri-ortho substituted biphenyls (Table 2, Entries 7-8), under mild and aerobic conditions in reasonably good yields. In order to show the effect of urea in this reaction, we performed a reaction of 4nitrobromobenzene and phenylboronic acid in the absence of urea at room temperature. The results of this study showed that in the absence of the urea the reaction was sluggish and only 57% GC yield was obtained. These results are quite significant as the desired biaryls could be efficiently achieved at room temperature using water as a co-solvent and with relatively lower palladium loading (1 mol %) in the presence of easily available compound urea. From these studies we can predict that this catalyst can be applied to a wide range of aryl iodides and bromides. By applying this protocol, we also investigated the reaction of unreactive arylchlorides with arylboronic acids. Unlike aryl bromides, unfortunately, the coupling of aryl chlorides with phenylboronic acid did not proceed at room temperature. As the reaction temperature increased up to 100° C, however, the reaction yields increased significantly (Table 2, Entries 18-20).²⁴

Urea has three coordination sites; the carbonyl oxygen and the two nitrogen atoms and acts as a monodentate ligand. Our protocol is completely free from those common disadvantages involved during SM reaction such as the requirement of large amount of catalysts, generation of homo-coupling by-products, preparation of the Pd-ligand complex, inert reaction condition, elevated reaction temperature, longer reaction times and use of organic or biphasic reaction media *etc*.

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Table 2. Pd(OAc)₂ and urea catalysed Suzuki-Miyaura cross-coupling reaction of aryl halides with aryl boronic acids at room temperature



ntry	ArX	ArB(OH) ₂	Time (min)	Yield ^b (%)
1	O ₂ N-Br	B(OH)2	10	99
2	-Br O ₂ N	B(OH) ₂	10	98
3	MeO	MeO-	10	99
4	NCBr	F ₃ CB(OH) ₂	15	96
5	OHC - Br	B(OH) ₂	15	96
i	Br CHO	B(OH)2	15	94
7	Br	B(OH) ₂	20	94
	Br	-B(OH)2	30	90
)	O → → Br	B(OH) ₂	15	95
)	HOH ₂ C-	B(OH)2	20	97
l	HOOCBr	B(OH)2	20	92
2	Br	B(OH) ₂	15	90
3	MeO	B(OH)2	10	99
4	O ₂ N-	B(OH)2	10	99
5	OMe	B(OH)2	10	98
16	но-	CI-B(OH)2	15	95
7	F	MeO-B(OH)2	15	94
8	O ₂ N-CI	B(OH)2	300	68°
)		MeO-B(OH)2	240	80°
	MeO-CI	B(OH)2	240	70 ^c

^a Reaction conditions: arylhalide (1 mmol), arylboronic acid (1.2 mmol), Pd(OAc)₂ (1 mol%), urea (0.01 mmol), K₂CO₃ (3 mmol) in

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^{*i*}PrOH/H₂O (1:1, v/v, 4 mL) at room temperature. ^{*b*} Isolated yields. ^{*C*} Temperature 100° C

In summary, we have successfully developed a palladium catalyzed Suzuki–Miyaura reaction using urea as a ligand in ⁱPrOH-H₂O media under aerobic conditions. This facile, mild, and low-cost ligand protocol represents, to a certain extent, a new advance in Suzuki–Miyaura cross-coupling reactions.

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- 24. Typical experimental procedure: In a 50 mL round bottomed flask, a mixture of aryl halide (1 mmol), arylboronic acid (1.2 mmol), Pd(OAc)₂ (1 mol%), urea (0.01 mmol) and K₂CO₃ (3 mmol) in ¹PrOH/H₂O (1:1, v/v, 4 mL) and the mixture was stirred at room temperature for a time period as mentioned in Table 2. The progress of the reaction was monitored by TLC. After completion of the reaction it was extracted with diethyl ether (3 x 10 mL) and washed with water. The combined ether extract was dried over anhydrous Na₂SO₄. The filtrate was concentrated under reduced pressure. The product was purified by column chromatography over silica gel using hexane/ethyl acetate (9:1 v/v) to get the desired coupling product. The products were characterized by IR, ¹H NMR, ¹³C NMR and GC–MS.

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