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Highly Efficient Palladium-catalyzed Suzuki–Miyaura Cross-coupling with 9,10-Dihydro-9,10-ethanoanthracene-11,12-diimine Ligands under Mild Aerobic Conditions

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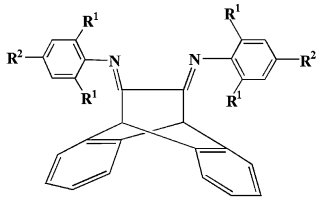
A novel 9,10-dihydro-9,10-ethanoanthracene-11,12-diimine/$Pd(OAc)_2$ system has been demonstrated to form a highly efficient catalyst for the Suzuki–Miyaura cross-coupling of various aryl bromides and activated aryl chlorides with arylboronic acids in high yields at room temperature in ethanol/aqueous media under ambient atmosphere.

Keywords: Suzuki–Miyaura cross coupling | Palladium | Anthracene-diimine ligand

The Suzuki–Miyaura cross-coupling reaction, involving the coupling of an arylboronic acid with an organohalide, has proven to be an extremely useful synthetic tool for the construction of biaryls,[1] which are present in a wide range of natural products, pharmaceuticals, agrochemicals, functional polymer materials, and liquid crystals.[2] It is well known that the Suzuki–Miyaura cross-coupling reaction can be efficiently carried out using phosphine ligands/palladium complex. Because of the superior donor capability and stabilization effects, the bulky and electron-rich phosphine ligands are outstanding in the palladium-catalyzed Suzuki cross-coupling reaction.[3] However, serious drawbacks still exist in most phosphines, such as highly toxic and air- and moisture-sensitive.[4] These drawbacks severely hinder its usage. Therefore, in the past few years, great advances have been made in developing active and efficient catalysts by modifying traditional ligands and discovering phosphine-free ligands.[5]

Recently, phosphine-free ligands, such as heterocyclic carbenes,[6] β-ketoamine,[7] 2-aryl-2-oxazolines,[8] and other amines,[9] have also emerged for use in the Suzuki–Miyaura cross-coupling reaction. Among them, α-diimine ligands, previously used as excellent candidates for olefin and α-alkene polymerization, have been applied to Suzuki cross-coupling. The $Pd(OAc)_2$/*N*,*N*′-dicyclohexyl-1,4-diazabutadiene system has been successfully developed by Nolan and his collaborators, which show high catalytic activity for cross-coupling of aryl halides with arylboronic acids.[10] Sun and co-workers found that water-soluble diimine ligands exhibited moderate activity toward the Suzuki reaction of arylbromide.[11] Subsequently, the utilization of α-diimine ligand/Pd for cross-coupling reaction has attracted much interest in both academic and industrial fields. Considering that both the backbone and the aryl ring have profound effects on the catalytic properties of the palladium complexes, herein we present a series of α-diimine ligands, the 9,10-dihydro-9,10-ethanoanthracene-11,12-diimine with bulky backbones and substituted aniline moieties generated in situ. The coordination versatility of these ligands, a consequence of the flexibility of the NCCN backbone and the strong σ-donor and π-acceptor properties, reflects a very important feature of α-diimine ligand–metal complexes,[12] which might assist in stabilizing catalytic species. Meanwhile, bulky backbones could increase the steric hindrance on the ligands, which could further facilitate reductive elimination and facilitate cross-coupling.[13] Therefore, desired products can be obtained in high yields under aerobic conditions, with a great tolerance of raw material for a broad range of functional groups on the aryl bromides.



Scheme 1. 9,10-Dihydro-9,10-ethanoanthracene-11,12-diimine ligands.

As shown in Scheme 1, the target α-diimine ligands with various steric and electronic substituents such as methyl, isopropyl, bromine, and chlorine were prepared according to the previously reported method.[14] At first, 10 mmol of 9,10-dihydro-9,10-ethanoanthracene-11,12-dione was reacted with 30 mmol of aniline by a catalytic amount of *p*-toluenesulfonic acid in refluxing toluene. After 24 h, the reaction mixture was cooled to room temperature, and then was evaporated at reduced pressure. The residual solids were further purified by silica column chromatography (v/v, 20/1, petroleum ether/ethyl acetate) to get ligands (L1–L5) as yellow crystals in high yield.

The catalytic activity of L1–L5 in Suzuki cross-coupling reactions was then evaluated. In an effort to understand how the ligands would promote this coupling reaction most efficiently, a reaction in which K_2CO_3 was used as a base and ethanol/water was a cosolvent in the reaction of phenylboronic acid with 4-bromoacetophenone at room temperature under air conditions was examined. As shown in Table 1, the data revealed that the α-diimine ligands were effective ligands for palladium-catalyzed Suzuki cross-coupling. For a comparison, in the absence of ligands, only 30% yield of product was produced in the presence of 0.025 mol % of $Pd(OAc)_2$ (Entry 1, Table 1). However, when ligands were added in the system, the yield of the product increased dramatically up to 80–99% (Entries 2–6, Table 1),

Table 1. Influence of α-diimine ligands on the palladium-catalyzed cross-coupling reaction of 4-bromoacetophenone with phenylboronic acid[a]

Entry	Ligand	Yield/%[b]
1	None	30
2	L1	91
3	L2	93
4	L3	99
5	L4	88
6	L5	80

[a]Reaction conditions: 1.0 mmol of 4-bromoacetophenone, 1.2 mmol of phenylboronic acid, 2.0 mmol of K_2CO_3, 0.025 mol % $Pd(OAc)_2$, 0.025 mol % ligand, 5 mL of EtOH/H_2O (v/v, 1:1), room temperature, 2 h. [b]Isolated yields.

Table 2. Optimization of reaction conditions at room temperature[a]

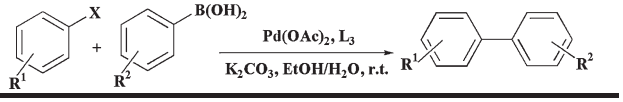
Entry	Solvent	Base	Yield/%[b]
1	EtOH	K_2CO_3	84
2	DMF	K_2CO_3	80
3	THF	K_2CO_3	68
4	Toluene	K_2CO_3	45
5	DMF/H_2O(v/v, 1:1)	K_2CO_3	91
6	THF/H_2O(v/v, 1:1)	K_2CO_3	80
7	EtOH/H_2O(v/v, 1:1)	K_2CO_3	99
8	EtOH/H_2O(v/v, 2:1)	K_2CO_3	94
9	EtOH/H_2O(v/v, 1:2)	K_2CO_3	93
10	EtOH/H_2O(v/v, 1:1)	Na_2CO_3	92
11	EtOH/H_2O(v/v, 1:1)	Cs_2CO_3	99
12	EtOH/H_2O(v/v, 1:1)	KOH	86
13	EtOH/H_2O(v/v, 1:1)	$Ca(OH)_2$	54
14	EtOH/H_2O(v/v, 1:1)	NaOEt	91
15	EtOH/H_2O(v/v, 1:1)	K_3PO_4	87
16	EtOH/H_2O(v/v, 1:1)	KF	65

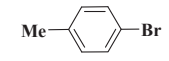
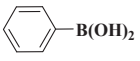
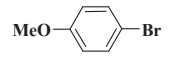
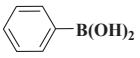
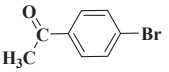
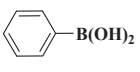
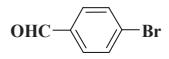
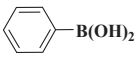
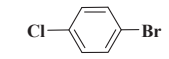
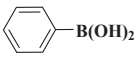
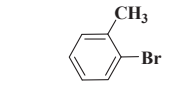
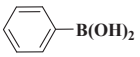
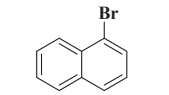
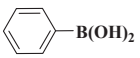
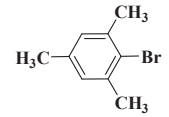
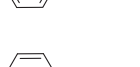
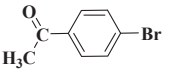
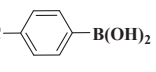
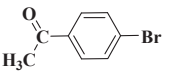
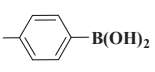
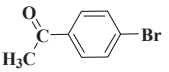
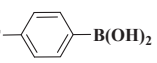
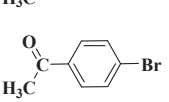
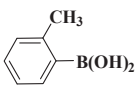
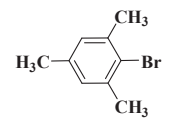
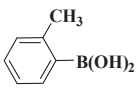
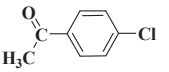
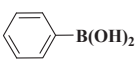
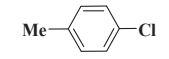
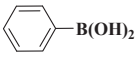
[a]Reaction conditions: 1.0 mmol of 4-bromoacetophenones, 1.2 mmol of phenylboronic acid, 2.0 mmol of base, 0.025 mol % $Pd(OAc)_2$, 0.025 mol % ligand L3, 5 mL of solvent, 2 h. [b]Isolated yields.

indicating the in situ formation of catalyst systems. Among the α-diimines investigated, L3 with 2,4,6-trimethyl groups on the aniline moiety (Entry 4, Table 1) afforded the highest activity. In this case, the conversion of the product reached 99%. Comparatively, L5 with an electron-withdrawing chloro group on the para position of the aniline (Entry 6, Table 1) was less active under the same conditions (80% yield). These results could be ascribed to the increase in the electron-donating ability of the aniline moieties of the ligand, leading to an increase in the rate of oxidative addition and the stabilization of the palladium species.

As shown in Table 2, the effect of solvents on the coupling reaction was also examined. The polarity of the solvent had a profound effect on the yield. For instance, the nonpolar solvent toluene gave a poor yield (45%), whereas the polar solvents, such as *N*,*N*-dimethylformamide (DMF), tetrahydrofuran (THF), and ethanol, provided the product in moderate yield (Entries 1–3, Table 2). Meanwhile, reaction activities were dramatically improved using organic/water cosolvents. EtOH/H_2O (v/v, 1:1) system afforded the highest yield (Entry 7, Table 2) among the tested aqueous–organic solvents. In addition, an investigation of the influence of the base suggested that the common and

Table 3. Suzuki cross-coupling reaction of aryl halides with phenylboronic acid under aerobic conditions[a]



Entry	Aryl halide	Arylboronic acid	Time /h	Yield /%[b]
1			2	97
2			2	96
3			2	99
4			2	98
5			2	99
6			4	90
7			4	95
8			6	81
9			2	98
10			2	97
11			2	99
12			4	86
13			24	44
14[c]			12	75
15[c]			12	35

[a]Reaction conditions: 1.0 mmol of aryl bromide, 1.2 mmol of arylboronic acid, 2.0 mmol of K_2CO_3, 0.025 mol % $Pd(OAc)_2$, 0.025 mol % ligand, 5 mL of EtOH/H_2O (v/v, 1:1), room temperature. [b]Isolated yields. [c]Reaction conditions: 1.0 mmol of aryl chloride, 1.2 mmol of arylboronic acid, 2.0 mmol of K_2CO_3, 0.25 mol % $Pd(OAc)_2$, 0.25 mol % ligand, 5 mL of EtOH/H_2O (v/v, 1:1), reaction temperature: 80 °C.

inexpensive inorganic bases, such as Cs_2CO_3 and K_2CO_3 are more effective, while other bases such as Na_2CO_3, KOH, $Ca(OH)_2$, NaOEt, K_3PO_4, and KF gave slightly lower yields.

Therefore, K_2CO_3 as a base and EtOH/H_2O (v/v, 1:1) as a solvent were chosen for further study because they were readily available, inexpensive, and had a higher efficiency.

As illustrated in Table 3, high catalytic activity was observed in the coupling of aryl halides with phenylboronic acid at room temperature with ligand L3. These catalytic system on cross-coupling reaction displayed remarkable tolerance toward the electronic properties of the substrates. For both the aryl bromides (Entries 1–8, Table 3) and aryl boronic (Entries 9–11, Table 3) with different electronic effect substituent, there were no significant difference in the yield or reaction time. Due to retarding both the oxidative addition and transmetalation processes, the aryl halides or aryl boronic with *ortho*-methyl substituent had less active. However, in this study, they could achieve high yield with a prolonged reaction time (Entries 6, 8, and 12, Table 3). However, the phenylboronic with *ortho*-substituents reacted with aryl bromide with *ortho*-substituents, the catalytic system exhibited lower activity through prolonged reaction time. For example, the larger hindered substrate 2-bromo-1,3,5-trimethylbenzene and 2-tolylboronic acid was coupled under the same reaction conditions for 24 h, the less reactivity was obtained (Entry 13, Table 3). It was probable that the steric effect might prevent its effective oxidative addition process. Significantly, the relatively unactivated aryl chlorides could react with phenylboronic acid when this catalytic system was employed, which led to moderate to high yields (Entries 14 and 15, Table 3).

In summary, an unprecedented, general, and efficient method based on the 9,10-dihydro-9,10-ethanoanthracene-11,12-diimine/$Pd(OAc)_2$ system has been developed for the Suzuki–Miyaura cross-coupling reaction of aryl bromides with arylboronic acids. The corresponding Suzuki coupling products were obtained in excellent yields at room temperature in ethanol/aqueous media under ambient atmosphere. In particular, the experimental data shows that the α-diimine ligand with 2,4,6-trimethyl groups on the aniline moiety facilitates the cross-coupling reaction. Future studies focused on the activation of electron-rich and electron-neutral aryl chlorides by 9,10-dihydro-9,10-ethanoanthracene-11,12-diimine/$Pd(OAc)_2$ systems are ongoing.

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