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A Highly Efficient and Inexpensive Palladium-Salen Complex for Room Temperature Suzuki-Miyaura Reaction

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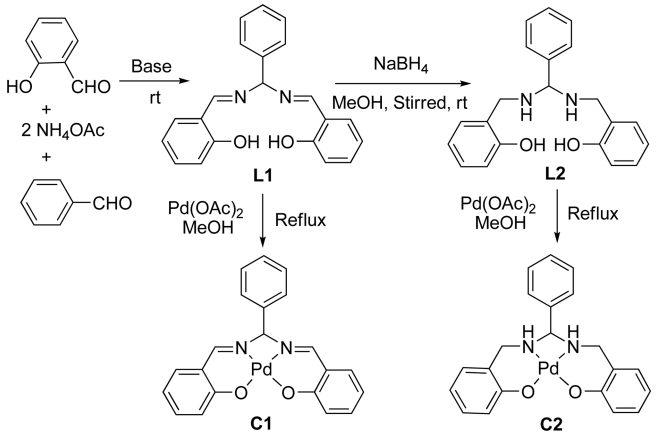
The palladium catalysed Suzuki-Miyaura cross-coupling reaction is one of the most important strategy for the synthesis of biaryls, which are building blocks of numerous vital organic compounds used in pharmaceuticals, fine- and agro-chemical industries.[1] The Suzuki-Miyaura reaction relies on the cross-coupling between aryl halides and easily accessible organoborons[1f] in presence of catalytic amount of palladium-based salts or complexes. Many ideal developments have been attained till now to improve the efficiency of this reaction and to minimize the issues related to environment pollution. Conventionally, the C-C bond formation reactions are performed using phosphine ligated palladium complexes,[25] which show excellent activity in this transformation. However most of the phosphine ligands are toxic and unstable in air or moisture, and are also known to increase the possibility of side reactions, thereby lowering the yield of desired cross-coupled products. Recently, different nitrogen based ligands such as *N*-heterocyclic carbenes,[6] amines,[7] oximes,[8] amides[9] and their co-ordination with palladium have attracted considerable attention for Suzuki-Miyaura Cross-Coupling reaction with potentiality to overcome some of drawbacks face by traditional phosphine ligands. So attention has been given to design catalyst containing chelating multi-dentate Schiff-base ligands.[10] The water insoluble property of these ligands restricts their use upto undesirable organic solvents such as DMF,[11] toluene,[12] THF[12] *etc.* Thus, to practice the principles of green chemistry, researchers have developed efficient catalytic protocols to conduct Suzuki-Miyaura cross-coupling reaction under easily available and non-toxic aqueous media. Moreover, there has been a tremendous rise in interest for employing aryl chloride as substrates for Suzuki-Miyaura cross-coupling, as they are easily accessible economical compared to their bromide and iodide counterparts. Herein we wish to report a facile and efficient room temperature Suzuki-Miyaura cross-coupling reaction strategy using a unique Palladium salen complex as catalyst in greener solvent. It is notable to mention that these multidanted ligands, due to the presence of multiple bonding sites is expected to increase the steric congestion around the metal centre which is considered to be the vital step facilitating the reductive elimination step in the cross-coupling mechanism.

Initially, we have synthesised and characterized two novel palladium complexes with a previously reported tetradentate Schiff-base ligand *N,N′*-bis(salicylidene)-phenylmethanediamine (L1)[13] and its reduced form (L2),[14] ligand (Scheme 1). The new palladium complexes C1 and C2 were prepared by refluxing methanolic solution of the corresponding tetradentate ligands L1 and L2 with equimolar amount of palladium acetate.[15] The newly synthesized complexes C1 and C2 were characterized by elemental analysis, IR, ^{1}H- and C-NMR and mass spectral data.[15]

The spectral analysis of prepared complexes corroborates with the reported one.[13] The value of elemental analyses and the appearances of molecular ion peaks in ESI-mass spectra of complexes C1 and C2 support their proposed composition. In the FTIR spectra of complexes, the value for ν (C=N) stretching vibration of the free ligand at about 1617 cm^{-1} gets considerably shifted to lower frequency at 1606 cm^{-1} after complexation, implying the coordination of imine nitrogen with palladium owing to the donation of electrons from nitrogen atom to the empty *d*-orbitals of the metal. This signal was absent in ligand L2 and in its corresponding complex C2, indicating the successful reduction of C=N bond. In complex C2 the band at 3160 cm^{-1} due to the ν (N-H) stretching frequency of the L2 undergoes a considerable shift towards 3080 cm^{-1} after complexation. The complex C2 has been shifted about 80 cm^{-1}, indicating strong coordination of nitrogen to palladium metal atom. The *ν* (O-H) signal pertaining to free ligands (3425 cm^{-1} in FTIR and 13.5 ppm in ^{1}H NMR) was found to be absent in both complex C1 and C2, supporting the deprotonation of phenolic moiety and



Scheme 1

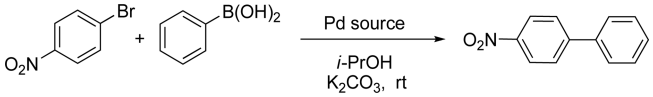
its subsequent coordination to palladium.

To explore the effectiveness of these complexes C1 and C2 as catalyst for the Suzuki-Miyaura cross-coupling reaction, initially we examined the efficiency of the tetradentate shiff base ligands L1 and L2 for the reaction 4-nitrobromobenzene (0.5 mmol) with phenylboronic acid (0.55 mmol) as a model reaction using isopropanol (2 mL) as solvent, K_2CO_3 (1.5 mmol) as a base and reaction were performed at room temperature in presence of palladium complexes as catalysts generated in situ form $Pd(OAc)_2$ (0.5 mol %) and ligands (0.5 mol %) in 1:1 molar ratio. The results are summarised in Table 1. The present reaction conditions gave the desired product with moderate yield (Table 1, entries 2 and 3) with reduction of side product in compare to the reaction without any additive, in the presence of $Pd(OAc)_2$ (0.5 mol %) (Table 1, entry 1). Among the two ligands used, (L2) demonstrates the highest activity (Table 1, entry 3). Under the present reaction conditions it is believed that the presence of Schiff based ligand has played a vital role for the conversion of Pd(0) into Pd(II) and significantly enhance the reaction yields.

Therefore we further wish to investigate the activities of ligands after complexation. It is observed that the use of the pre-formed complexes C1 and C2 as a catalyst resulted in the Suzuki-Miyaura cross-coupling reaction under the identical conditions has provided excellent yields of the desired product compared to that of the in situ catalyst (Table 1, entries 4, 5). The outstanding yield was obtained with C2 complex (95% within 2 h) (Table 1, entry 4). To optimize the amount of catalyst, we have carried out the reaction under the same reaction condition using different amount of the C2-complex and we found that 0.2 mol % of the Pd-complex is sufficient to obtain 95% yield (Table 1, entry 6). However the yield of the product was decreased when we carried the reaction with 0.1 mol % of the catalyst (Table 1, entry 7).

It is well known that choice of solvent and base is also very important in the Suzuki-Miyaura reaction. To investigate the efficiency of solvents and bases on the Suzuki coupling reaction in our catalytic system, we have examined

Table 1. Optimization of catalyst for Suzuki-Miyaura reaction[a]

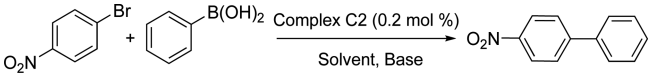


Entry	Pd source	Catalyst (mol %)	Time (h)	Yield (%)[b]
1	$Pd(OAc)_2$	0.5	12	30
2	$Pd(OAc)_2$+L1	0.5	12	60
3	$Pd(OAc)_2$+L2	0.5	12	65
4	C1	0.5	3	90
5	C2	0.5	2	95
6	C2	0.2	2	95
7	C2	0.1	12	50

[a]Reaction conditions: 4-nitrobromobenzene (0.5 mmol), phenylboronic acid (0.55 mmol), base (1.5 mmol), solvent (2 mL), 25 ℃, in air. [b]Isolated yield

the reaction between 4-nitrobromobenzene (0.5 mmol) and phenylboronic acid (0.55 mmol) under various solvents and bases using C2-complex and the results are summarized in Table 2. It is seen from the Table 2 that the use of inorganic bases such as K_2CO_3, Na_2CO_3, $Na_3PO_4{\cdot}12H_2O$, gave the cross-coupling products in good to excellent yield (Table 2, entries 1-3). However, the yield significantly diminished in case of strong bases like hydroxyl (KOH and NaOH) and organic bases (Et_3N) (Table 2, entries 4-6). The coupling reaction did not proceed in absence of base (Table 2, entry 23). On the other hand the choice of solvent in Suzuki reaction plays crucial role with respect to catalyst. To investigate this effect we have screened different solvents using K_2CO_3 as base under the same reaction condition and the reaction seemed to be more facile in polar alcoholic solvent (Table 2, entries rather than in other solvent like THF, DMF *etc.* (Table 2, entries 1-8, 10 & 12). The yield of cross-coupling product found to be the most effective in providing efficient result at room temperature within short reaction time using *i*-PrOH as co-solvent with water (1:1) (Table 2, entry 7). However, on increasing the ratio of water yield of the reaction decreases gradually (Table 2, entries 21 and 22). Thus, a

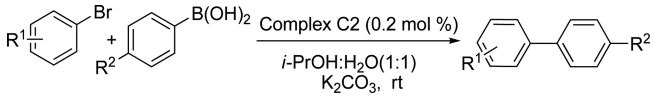
Table 2. Effect of solvent and base in Suzuki-Miyaura reaction using complex C2[a]



Entry	Solvent	Base	Time (h)	Yield (%)[b]
1	^{i}PrOH	K_2CO_3	1.5	95
2	^{i}PrOH	Na_2CO_3	1	95
3	^{i}PrOH	$Na_3PO_4{\cdot}12H_2O$	1	95
4	^{i}PrOH	NaOH	3	20
5	^{i}PrOH	KOH	3	20
6	^{i}PrOH	Et_3N	3	25
7	^{i}PrOH:H_2O(1:1)	K_2CO_3	1	98
8	Ethanol	K_2CO_3	4	90
9	EtOH:H_2O(1:1)	K_2CO_3	4	70
10	Butanol	K_2CO_3	8	70
11	BuOH:H_2O(1:1)	K_2CO_3	8	50
12	Methanol	K_2CO_3	8	75
13	MeOH:H_2O(1:1)	K_2CO_3	8	60
14	MeCN	K_2CO_3	4	45
15	Ethylacetate	K_2CO_3	4	30
16	Acetone	K_2CO_3	4	35
17	$CHCl_3$	K_2CO_3	4	50
18	THF	K_2CO_3	4	70
19	DMF	K_2CO_3	4	70
20	DMF:H_2O(1:1)	K_2CO_3	4	60
21	^{i}PrOH:H_2O(1:3)	K_2CO_3	7	80
22	^{i}PrOH:H_2O(1:7)	K_2CO_3	7	70
23	^{i}PrOH:H_2O(1:1)	–	7	–
24	H_2O	K_2CO_3	3	90

[a]Reaction conditions: 4-nitrobromobenzene (0.5 mmol), phenylboronic acid (0.55 mmol), Pd-complex (C2) (0.2 mol %), Base (1.5 mmol), Solvent (2 mL), 25 ℃, in air. [b]Isolated yield.

Table 3. Suzuki-Miyaura cross-coupling reactions of various aryl bromides with arylboronic acids using complex C2



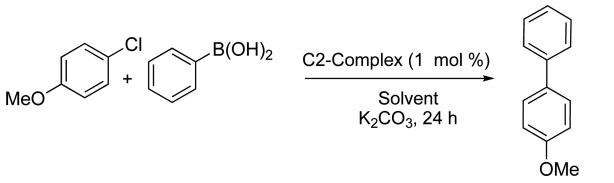
Entry	R^1	R^2	Time (h)	Yield (%)
1	4-NO_2	H	1	98
2	4-NO_2	OMe	1	90
3	4-NO_2	*t*-Bu	1	95
4	4-NO_2	Cl	1	95
5	4-OMe	H	0.5	95
6	4-OMe	OMe	0.5	95
7	4-OMe	*t*-Bu	0.5	98
8	4-OMe	Cl	0.5	94
9	4-Me	H	0.25	92
10	4-Me	OMe	0.25	95
11	4-Me	*t*-Bu	0.25	95
12	4-Me	Cl	0.25	94
13	2-Me	H	1	80
14	CHO	H	1	97
15	CHO	OMe	1	95
16	4-COMe	H	1	90
17	4-COMe	Cl	1	85
18	H	H	1	85
19		H	1	50
20		H	1	0

[a]Reaction conditions: arylbromide (0.5 mmol), arylboronic acid (0.55 mmol), Pd-complex (C2) (0.2 mol %), Base (1.5 mmol), Solvent (2 mL), 25 °C, in air. [b]Isolated yield.

suitable amount of water, which means to facilitate the solubility of base, is very essential for increasing the reactivity of Suzuki-Miyuara cross-coupling reactions under above mentioned condition.

To demonstrate the general applicability and limitations of complex C2 in Suzuki-Miyaura cross-coupling reaction, we chose the optimized reaction conditions, a wide variety of aryl halides (0.5 mmol) and aryl boronic acid (0.55 mmol), K_2CO_3 (1.5 mmol), Pd-complex C2 (0.2 mol %) using *i*-PrOH:H_2O (1:1) as solvent at room temperature[17] and the results are displayed in Table 3. It can be seen from the Table 3 that the aryl bromide with electron-withdrawing and electron-donating substituents underwent the coupling reaction with phenyl boronic acid in nearly comparable yields, although a little difference in their reaction time was noticed. However, no significant difference was observed in the yield and reaction time while using differently substituted aryl boronic acids. In general, yield significantly low and required more reaction time for sterically demanding substrate such as 2-bromotoluene compared to the 4-bromotoluene (Table 3, entry 12, 13). To evaluate the scope and limitations of the current catalyst system to aryl chlorides we have carried out the cross coupling using *p*-chloroanisole as substrate under the same reaction conditions (Table 4). The reaction between *p*-chloroanisole with phenyl boronic acid gave very poor yield even on increasing the catalyst loading upto 1 mol % at room temperature (Table 4, entry 1, 2). Lower catalyst loading (0.5 mol %) resulted in poor conversion due to excess biphenyl formation (Table 4, entry 1). However, we able to isolate 50% yield of the cross-coupling product by using pure iso-propanol as solvent (Table 4, entries 3). Fortunately, there was an abrupt change in the rate of the reaction and yield when the reaction was carried out at 50 °C in isopropanol (Table 4, entries 4) Comparably similar conversion was noticed when DMF was used as solvent (Table 4, entry 6). As *i*-PrOH is a green solvent with high compatibility, further study was performed under *i*-PrOH. Aryl chlorides bearing electron withdrawing substituent such

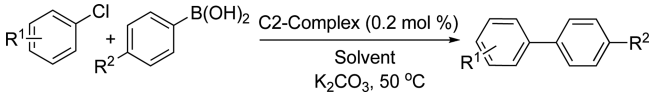
Table 4. Suzuki-Miyaura cross-coupling reactions of aryl chloride with arylboronic acids using complex C2



Entry	Solvent	T (°C)	Yield (%)
1	^{i}PrOH:H_2O	25	35[c]
2	^{i}PrOH:H_2O	25	45
3	^{i}PrOH	25	50
4	^{i}PrOH	50	75
5	H_2O	50	20
6	DMF	50	73
7	DMF:H_2O	50	45

[a]Reaction conditions: 4-Methoxybromobenzene (0.5 mmol), phenylboronic acid (0.55 mmol), Pd-complex(C2) (1 mol %), Base (1.5 mmol), isopropanol (2 mL), in air. [b]Isolated yield. [c]C2 (0.5 mol %)

Table 5. Suzuki-Miyaura cross-coupling reactions of aryl chlorides with arylboronic acids using complex C2



Entry	R^1	R^2	Time (h)	Yield (%)
1	4-OMe	H	12	75
2	4-OMe	OMe	12	70
3	4-OMe	*t*-Bu	12	75
4	4-OMe	Cl	24	60
5	4-Me	H	12	75
6	4-Me	OMe	12	70
7	4-Me	*t*-Bu	12	70
8	4-Me	Cl	24	60
9	2-Me	H	24	50
10	4-NO_2	H	24	22
11	4-COH	H	24	20

[a]Reaction conditions: arylchloride (0.5 mmol), arylboronic acid (0.55 mmol), Pd-complex(C2) (1 mol %), Base (1.5 mmol), isopropanol (2 mL), 50 °C, in air. [b]Isolated yield. [c]Reaction performed at room temperature.

as *p*-chloronitrobenzene, *p*-chlorobenzaldehyde when treated with phenyl boronic acids, results in very poor cross-coupling product (Table 5, entries 10, 11).

However, electron pushing aryl chlorides such as chloroanisol, chlorotoluene reacts smoothly with aryl boronic acids affording desired biaryls in good yield (Table 4, entries 1-8). As *ortho* substituted aryl chlorides are unsuitable for the cross-coupling reaction, and thus, they provides comparatively lower yield with present catalytic system (Table 5, entry 9). According to leading literatures aryl chlorides are less venerable compared to aryl bromides and thus known for delivering lower yields under equivalent conditions and thus could be the reason for lower yield in such in present catalytic system.

In conclusion, we developed simple and efficient catalytic system based on Pd salen complex for Suzuki-Miyaura cross-coupling reaction using greener solvent. The same catalytic system is also effective for Suzuki Miyaura Cross-Coupling reaction of less reactive aryl chlorides with aryl boronic acids.

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15. (a) *Synthesis of complex* **C1**: 10 mL methanolic solution of ligand L1 (330 mg, 1 mmol) was mixed with $Pd(OAc)_2$ (224 mg, 1 mmol). After refluxing the reaction mixture for 3 h with stirring the brown colour precipitate was filtered. The residue was washed with hexane and recrystalised from chloroform. Yield: 85%. Anal. Calcd (in %) for $C_{21}H_{16}N_2O_2Pd$; C: 58.01; H: 3.71; N: 6.44. Found, C: 58.18; H: 3.93; N: 6.13. MS-ESI ($CHCl_3$): *m/z* 435 [M+]; Selected IR frequency (cm^{-1}, KBr): 1606 cm^{-1} ($\nu_{C=N}$). ^1H NMR (400 MHz, $CDCl_3$) δ/ppm: 6.72(s, 1H, CH), 8.71(s, 2H, CH=N), 7.01-7.09(m, 13H, Ph+Ph+Ph). (b) *Synthesis of complex* **C2**: Complex C2 was prepared by following the same procedure used for complex C1 using ligand L2 and $Pd(OAc)_2$ in 1:1 molar ratio. Yield: 80%. Anal. Calcd for $C_{21}H_{16}N_2O_2Pd$, C: 57.79; H: 4.12; N: 6.42. Found, C: 57.11; H: 4.33; N: 6.13. MS-ESI ($CHCl_3$): *m/z* 437 [M+]; Selected IR frequency (cm^{-1}, KBr): 3080 cm^{-1} ($\nu_{N\text{-}H}$). ^1H NMR (400 MHz, $CDCl_3$) δ/ppm: 4.5 (s, 4H, CH_2-N), 6.02 (s, 1H, CH), 7.02-7.10 (m, 13H, Ph+Ph+Ph).
16. ***General procedure for Suzuki Miyaura reaction*:** A 25 mL synthesiser tube had taken with a mixture of aryl halide (0.5 mmol), aryl boronic acid (0.55 mmol), base (1.5 mmol), Pd-complex C1 (0.2 mol %) and the mixture was stirred in 2 mL of aqueous isoproponol (1:1) at room temperature for the required time. After completion, the reaction mixture was extracted with ether (3 × 20 mL). The combined extract was washed with brine (2 × 20 mL) and dried over Na_2SO_4. After evaporation of the solvent under reduced pressure, the residue was chromatographed (silica gel, ethyl acetate–hexane: 1:9) to obtain the desired products. The products were confirmed by comparing the ^1H and ^{13}C NMR and mass spectral data with authentic samples.