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ARTICLE TYPE

## Palladium salen Complex: An efficient Catalyst for Sonogashira reaction at room temperature

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10 A tetradentate Schiff base derived Palladium complex has been developed as a catalyst for the room temperature Sonogashira reaction under copper free conditions. The main catalytic species, a Pd-complex was derived from Schiff base ligand *N,N'*-bis(salicylidene)-arylmethanediamine and Pd(OAc)<sub>2</sub>. Electron rich, electron deficient and sterically hindered aryl iodides underwent smooth coupling to afford good to excellent yield of diaryl alkynes in isopropanol at room temperature. The protocol is also suitable for aliphatic alkynes.

In recent decades Pd-catalyzed Sonogashira reaction have contributed immensely towards the incorporation of alkyne moiety in the organic molecule which serves as a key 15 intermediate for pharmaceutical and natural products.<sup>1</sup> In addition, alkyne derivatives find wide applications in material chemistry due to their unique electrical and optical properties.<sup>2</sup> The Sonogashira reaction is a cross coupling reaction between an alkyne and an electrophile such as aryl halides, vinyl halides or 20 triflates in presence of a suitable Pd-source.<sup>1</sup> Conventionally these reactions are accelerated by the addition of Cu-salt and suitable phosphine based ligands.<sup>3</sup> However formation of undesired Glaser type coupling product from Cu-mediated reactions enforce the researchers to develop Cu free protocol for 25 Sonogashira reaction.<sup>4</sup> As a result several alternate protocols has been designed where the use of other additives such as Ag,<sup>5</sup> Zn,<sup>6</sup> Sn,<sup>7</sup> and tetra-*n*-butyl ammonium<sup>8a</sup> and sodium sulfate<sup>8b</sup> salt<sup>8</sup> as an activator was utilized. Furthermore phosphine based ligands are usually toxic and unstable in air which restricts their wide 30 spread application. In that regard nitrogen based ligands and their complexes with palladium can be a good alternative as these are quite stable in comparison to phosphines. Thus several *N*-based ligands such as *N*-heterocyclic carbenes,<sup>9</sup> hydrazones,<sup>10</sup> pyrimidines<sup>11</sup> etc and complexes such as palladacycles<sup>12</sup> are 35 unanimously tested in Sonogashira reaction. Among the several *N*-based ligands, Schiff bases draw considerable attention owing to their easy methods of preparation and high co-ordinating capacity for different transition metals.

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Moreover, electronic and steric properties of Schiff-bases could be easily tuned by properly selecting the condensing partners. 50 Thus a countless number of Schiff base complexes with different metal ions such as Cu, Pd, Fe, Ni, Co etc are reported in the literature.<sup>13</sup> Many of these complexes demonstrate their capacity as a catalyst in different organic reactions.<sup>13</sup> Although Pd-Schiff base complexes are very common and extensively studied in 55 Suzuki-Miyaura<sup>14</sup> cross coupling reaction but their application in Sonogashira reaction is limited.<sup>15</sup> Recently we have demonstrated the efficiency of tetradentate Pd-Schiff base complexes in Suzuki-Miyaura<sup>16</sup> and Cu-Schiff base complexes in Chan-Lam<sup>17</sup> coupling reaction respectively. So in order to extend the scope of 60 Pd-Schiff base complexes under green conditions, we herein reported a simple and efficient protocol for Sonogashira reaction of aryl iodides in isopropanol at room temperature.

The three Pd-salen complex **C1-C3** was prepared by refluxing Pd(OAc)<sub>2</sub> with their respective *N,N'*-bis(salicylidene)-arylmethanediamine (**L1-L3**) ligand following a literature report.<sup>16</sup> 65

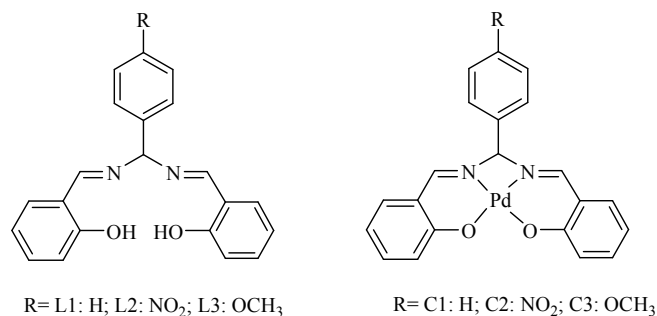
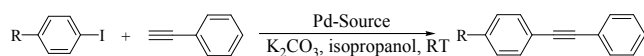


Figure 1 Screened ligands and complex

Our next goal was to evaluate the catalytic activity of the synthesized Pd-salen complex in Sonogashira reaction of aryl iodides. For that purpose iodobenzene (0.5 mmol), and phenyl

acetylene (1 mmol) was considered as model substrate for reaction optimization. Initial reactions were performed with 2 mol% of Pd-source and three equivalent of  $K_2CO_3$  (1.5 mmol) in isopropanol (2 mL) at room temperature under aerobic conditions. The optimization results are highlighted in Table 1.

**Table 1** Optimization of catalyst for Sonogashira reaction<sup>a</sup>

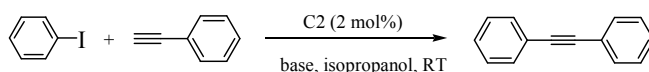


Entry	Pd source (2 mol%)	R	Time (h)	Yield (%) <sup>b</sup>
1	C1	H	10	92
2	<b>C2</b>	<b>H</b>	<b>07</b>	<b>98</b>
3	C3	H	12	90
4	C1	OCH <sub>3</sub>	16	89
5	<b>C2</b>	<b>OCH<sub>3</sub></b>	<b>10</b>	<b>96</b>
6	C3	OCH <sub>3</sub>	24	85
7	Pd(OAc) <sub>2</sub> +L2	H	24	80
8	Pd(OAc) <sub>2</sub>	H	24	62
9	C2 (1 mol%)	H	24	81

<sup>a</sup> Reaction conditions: Aryl iodide (0.5 mmol), phenylacetylene (1 mmol), Pd-complex (2 mol %),  $K_2CO_3$  (1.5 mmol), isopropanol (2 mL), 25 °C in air. <sup>b</sup> Isolated yields.

10 Among the three Pd-complexes (C1-C3) maximum reactivity was observed in case of complex C2 which have nitro group at the *para*-position of the phenylmethanediamine moiety (Table 1 entry 2 vs entries 1 and 3). However other two complex C2 and C3 also produce good yield of isolated cross coupling product.

15 **Table 2** Effect of base in Sonogashira reaction<sup>a</sup>



Entry	Base	Time (h)	Yield (%) <sup>b</sup>
1	-	24	trace
2	Et <sub>3</sub> N	24	67
3	Pyridine	24	61
4 <sup>c</sup>	KOH	24	41
5 <sup>c</sup>	NaOH	24	40
6 <sup>c</sup>	NaHCO <sub>3</sub>	24	68
7	Na <sub>3</sub> PO <sub>4</sub> ·12H <sub>2</sub> O	12	89
8	Na <sub>2</sub> CO <sub>3</sub>	10	92
9	K <sub>2</sub> CO <sub>3</sub>	07	98
10	Cs <sub>2</sub> CO <sub>3</sub>	09	97

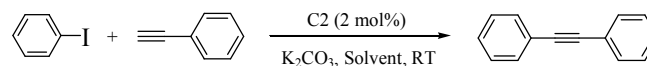
<sup>a</sup> Reaction Conditions: iodobenzene (0.5 mmol), phenylacetylene (1 mmol), Pd complex C2 (2 mol%), base (1.5 mmol), isopropanol (2 mL).

<sup>b</sup> Isolated Yields. <sup>c</sup> Reaction did not completed.

20 It is worth to mention that in many reported procedures of Sonogashira reaction, usually electron rich substrate results comparatively lower yield of cross coupling product.<sup>18</sup> However our catalyst system is compatible with this type of substrate

(Table 1). It is interesting to observed that the reaction fails to complete when 2 mol% L2 was used with Pd(OAc)<sub>2</sub> under same reaction condition (Table 1 entry 7). The application of only Pd(OAc)<sub>2</sub> afforded low yield of corresponding cross coupling product (Table 1 entry 8). Next we found that the amount of C2 also affects the yield up to some extent. The optimum result was achieved with 2 mol% of C2 (Table 1 entry 2 vs 9). It is well known fact that base plays a crucial role in the overall performance of a catalytic system in Sonogashira reaction (Table 2 entry 1). Thus to investigate its effect several inorganic and organic bases were tested in the Sonogashira reaction of iodobenzene (0.5 mmol) and phenylacetylene (1 mmol) with catalyst C2 (2 mol %) in isopropanol (2 mL). The common organic bases such as Et<sub>3</sub>N and pyridine generally used in Sonogashira reaction were found to be less reactive in our catalytic system (Table 1 entries 2 and 3). The same behaviour was also observed with hydroxide (Table 2 entries 4 and 5) and bicarbonate base (Table 2 entry 6) as in both the cases the reaction did not completed even after 24 h. In contrast carbonate bases viz. Na<sub>2</sub>CO<sub>3</sub>, K<sub>2</sub>CO<sub>3</sub> and Cs<sub>2</sub>CO<sub>3</sub> provide excellent yield of cross coupling product (Table 2 entries 8-10). So we have considered K<sub>2</sub>CO<sub>3</sub> for further optimization.

**Table 3** Effect of Solvent in Sonogashira reaction<sup>a</sup>



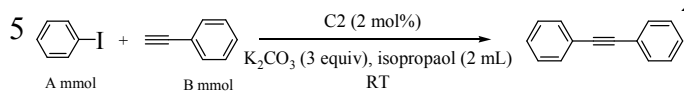
Entry	Solvent (2 mL)	Time (h)	Yield (%) <sup>b</sup>
1	MeOH	10	96
2	EtOH	11	94
3	isopropanol	07	98
4	DMF	14	91
5	DMSO	10	89
6	H <sub>2</sub> O	24	72
7	isopropanol: H <sub>2</sub> O	18	83
8	DCM	24	64
9	THF	24	58
10	CH <sub>3</sub> CN	24	69

<sup>a</sup> Reaction conditions: iodo benzene (0.5 mmol), phenylacetylene (1 mmol), Pd-complex-C2 (2 mol%),  $K_2CO_3$  (1.5 mmol), Solvent (2 mL), 25 °C in air. <sup>b</sup> Isolated yield.

30 Next we investigated the effect of solvent in Sonogashira reaction. As shown in Table 3 better performance of the catalytic system was observed when alcoholic solvents viz. MeOH, EtOH and isopropanol were used (Table 3 entries 1-3). Similar results were also noticed with DMF and DMSO (Table 3 entries 4 and 5). However the yield was significantly decreased when H<sub>2</sub>O was used as solvent (Table 3 entry 6); this may be due to the insolubility of the substrate and catalyst in water. Application of 1:1 aqueous isopropanol did not improve the yield to a significant extent (Table 3 entry 7). On the other hand inferior results were obtained with solvents like THF, CH<sub>3</sub>CN and DCM (Table 3 entries 8-10). So based on the above we have considered isopropanol for further optimization.

Finally we investigated the substrate ratio for efficient coupling. The favourable condition was observed with 1:1.5 equivalent of iodobenzene to phenyl acetylene (Table 4 entry 2 vs entries 1-3).

**Table 4** Optimization of substrate ratio in Sonogashira reaction

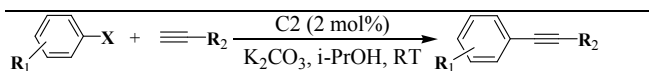


Entry	A : B	Time (h)	Yield (%) <sup>a</sup>
1	1 : 2	7	98
2	1 : 1.5	7	98
3 <sup>b</sup>	1 : 1	8	74

<sup>a</sup> Isolated Yields. <sup>b</sup> Reaction did not completed.

The scope and limitation of the current protocol has been investigated with several electronically diverse aryl iodides and aryl acetylenes in *i*-PrOH at room temperature. The results were summarised in the Table 5. The presence of electron donating group such as -OMe, -Me, -NH<sub>2</sub> at the *para* position of aryl iodide couples smoothly with phenyl acetylene to give good to excellent yield of isolated cross coupling product (Table 5 entries 5b-5d).

**Table 5** C2 complex promoted synthesis of internal acetylene<sup>a</sup>



	R <sub>1</sub>	R <sub>2</sub>	X	Time (h)	Yield (%) <sup>b</sup>
1	H	C <sub>6</sub> H <sub>5</sub>	I	7	98
2	4-Me	C <sub>6</sub> H <sub>5</sub>	I	10	97
3	4-OMe	C <sub>6</sub> H <sub>5</sub>	I	12	94
4	4-NH <sub>2</sub>	C <sub>6</sub> H <sub>5</sub>	I	15	88
5	4-NO <sub>2</sub>	C <sub>6</sub> H <sub>5</sub>	I	3	99
6	4-COCH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	I	6	98
7	H	4-MeC <sub>6</sub> H <sub>5</sub>	I	18	90
8	4-OMe	4-MeC <sub>6</sub> H <sub>5</sub>	I	15	93
9	4-Me	4-MeC <sub>6</sub> H <sub>5</sub>	I	15	94
10	4-COCH <sub>3</sub>	4-MeC <sub>6</sub> H <sub>5</sub>	I	10	96
11	4-NO <sub>2</sub>	4-MeC <sub>6</sub> H <sub>5</sub>	I	6	99
12	2-NO <sub>2</sub>	C <sub>6</sub> H <sub>5</sub>	I	10	92
13	H	C <sub>10</sub> H <sub>21</sub> C≡CH	I	14	90
14	4-NO <sub>2</sub>	C <sub>10</sub> H <sub>21</sub> C≡CH	I	8	91
15	4-Me	C <sub>6</sub> H <sub>5</sub>	Br	24	54 <sup>c</sup>
16	4-OMe	C <sub>6</sub> H <sub>5</sub>	Br	24	62 <sup>c</sup>
17	H	4-NO <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	I	12	90

<sup>a</sup> Reaction Conditions: Aryl iodide (0.5 mmol), alkyne (0.75 mmol), Pd-complex-C2 (2 mol%), K<sub>2</sub>CO<sub>3</sub> (1.5 mmol), isopropanol (2 mL), 25 °C in air unless otherwise noted. <sup>b</sup> Yields are given for isolated products. <sup>c</sup> Reaction did not completed.

15 It was observed that electron deficient aryl iodides underwent cross coupling within short reaction time with excellent yield (Table 5 entries 5 and 6). Similarly different functionality at the benzene ring of alkyne moiety can also tolerate the reaction condition and afford good yield of isolated cross coupled product (Table 5 entries 7-11). Sterically hindered 2-nitroiodobenzene also underwent smooth coupling in our system (Table 5 entries 12). It is worth to mention that in many reported procedures of Sonogashira reaction for aryl iodides it was observed that aliphatic alkynes give lower yield of cross coupling product than those for aromatic alkynes. To check the effectiveness of our protocol for alkyl acetylenes, dodecyne was used with electron rich and electron deficient aryl iodide. In all cases modest to good yield of desired cross coupling product was observed (Table 5 entries 13-14). Finally aryl bromides were also investigated in our present system. However the reaction fails to completes rendered only 54% yield for 4-bromotolyl and 62% yield for 4-bromoanisole (Table 5 entries 15 and 16).

In conclusion we have developed a tetradentate Schiff base derived Palladium complex for Sonogashira reaction in *i*-PrOH at room temperature under copper free condition. The catalyst is very simple and starting materials used are commercially available and cheap. Electronically diversified aryl iodides underwent the coupling reaction with electronically diversified aryl/alkyne acetylene in excellent yields. Absence of additive, use of isopropanol as solvent and broad substrate scope of this protocol makes it a attractive alternative for the existing protocols of Sonogashira reaction of aryl iodides.

## Experimental

45 A 50 mL oven dried round bottomed flask was charged with aryl iodide (0.5 mmol), alkyne (0.75 mmol), K<sub>2</sub>CO<sub>3</sub> (1.5 mmol, 207 mg), C2 complex (2 mol%, 4.79 mg) in 2 mL of isopropanol at room temperature (25 °C) under aerobic condition. The reaction mixture was stirred in a magnetic stirrer for appropriate time. The progress of the reaction was monitored by TLC. After the completion of the reaction, the mixture was diluted with 20 mL of water and extracted with diethyl ether (3×20 mL). The combined organic layer were washed with brine and dried over by anhydrous Na<sub>2</sub>SO<sub>4</sub> and evaporated in a rotary evaporator under reduced pressure. The crude was purified by column chromatography on silica gel (hexane) to afford the desired product. The purity of the compound was confirmed by <sup>1</sup>H NMR, <sup>13</sup>CNMR and MS data.

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