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PAPER

2-((4-Arylpiperazin-1-yl)methyl)phenol ligated Pd(II) complex: An efficient, versatile catalyst for Suzuki-Miyaura cross-coupling reaction

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N,N,O-tridentate palladium(II) complexes [Pd(OAc){ R-$C_4H_8N_2(CH_2Ar)$}] (R = Ph, Ar = 4-*t*Bu-C_6H_3-OH (**4a**); 2,4-di-*t*Bu-C_6H_2-OH, R = benzyl (**4b**)] **4a** and **4b** have been synthesized from the corresponding 2-((4-arylpiperazin-1-yl)methyl)phenol ligands **3a** and **3b** in quantitative yields. The synthesized ligands and their palladium(II) complexes were characterized by NMR, IR and HRMS analysis. Complex **4a** has been used as an efficient catalyst for the Suzuki cross-coupling reaction of 5-iodovanillin, 5-bromosalicylaldehyde with various arylboronic acids with low catalytic amounts (0.01 to 0.05 mol % of **4a**). Moreover this catalytic system is even applicable for Suzuki coupling reaction of deactivated aryl bromides and aryl chlorides which afforded the cross-coupling products in good to excellent yields with broad substrate scope.

Introduction

Design and development of simple, eco-economical, suitable organometallic catalysts that maintain environmental beningn conditions have become an important goal for C–C cross coupling reactions in organic synthesis.[1] Suzuki–Miyaura cross-coupling reaction of aryl halides with arylboronic acids is one of the most popular palladium catalyzed C–C bond forming reaction.[2] This reaction has vast importance in the total synthesis of various natural products, pharmaceuticals, polymers and agrochemicals.[3] Its synthetic attractiveness is due to the coupling capability of sterically demanding substrates and enormous extent of different functional groups under mild experimental conditions.[4] There is a great demand to involve non-toxic reagents to make this process industrially viable for scale up production.[5] Thus there is a great demand in the market for the development of new palladium catalysts with high turnover number, reaction rate, yields and selectivity.[6] Development of air and moisture-stable Pd-catalysts for C–C cross-coupling reaction still remains as an important challenge to be solved.[7] In particular, C–C cross-coupling reactions catalyzed by phosphine-free Pd complexes have great value due to their inexpensive and ease handling.[8] Many of the nitrogen ligands coordinated with palladium(II) complexes have been reported for different C–C cross-coupling reactions.[9]

Suzuki–Miyaura cross-coupling reaction brings enormous ease for synthesis of acid, hydroxyl, amine and aldehyde functional groups containing biphenyl derivatives.[10] The Suzuki coupling products of 5-iodovanillin derivatives have great importance in food materials, pesticides, plant cell wall and key structural elements in natural products.[11] Nantenine is an alkaloid which contains 5-arylvanilline as basic scaffold and it acts as an antagonist at 5-HT_{2A} serotonin receptor.[12] 6-Arylmethyl-5-hydroxy-7-phenyl-chromone derivatives inhibits replication of HCV (chronic hepatitis C virus) activities are also synthesized from 5-arylvanilline unit.[13] The direct preparation of 5-arylvanillin is particularly attractive in the context of biaryl synthesis and few 5-arylvanillin compounds have published previously by using magnesium and indium reagents with high catalyst loading (4 mol% of palladium) along with expensive phosphine ligands at elevated temperatures.[14] Recently, B. Schmidt and coworkers reported Pd/C catalyzed Suzuki coupling of 5-iodovanillin.[15] Similarly 5-bromosalicylaldehyde coupled products were useful intermediates in organic synthesis, pharmaceutical industry with high biological activities.[16,17] Bioactive molecules like sHA 14-1 and CXL017 were prepared from 5-arylsalicylaldehyde which were proved to be promising candidates for treatment of cancer with multiple drug resistance.[18] Suzuki cross-coupling reaction of 5-bromosalicylaldehyde with arylboronic acid under different reaction conditions was unsuccessful.[19]

As part of our ongoing research, we report herein the synthesis and characterization of 2-((4-arylpiperazin-1-yl)methyl)phenol ligated palladium(II) complexes and investigation of their catalytic activity in the Suzuki cross-coupling reaction. Till-date very few reports were found in literature on piperazine moiety containing ligands to accelerate Pd-catalyzed Suzuki-Miyaura coupling reaction. M. S. Balakrishna and co-workers have documented piperazine based palladium catalysts for Heck and Suzuki cross-coupling reaction.[20] Z. G. Zhou research group has reported Suzuki reaction of aryl halides and homo-coupling of arylboronic acids with piperazine ligands using Pd(II) salts.[21]

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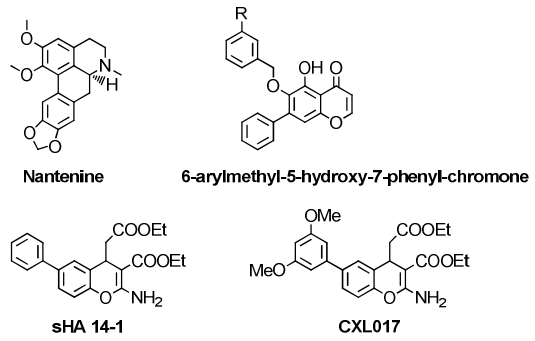
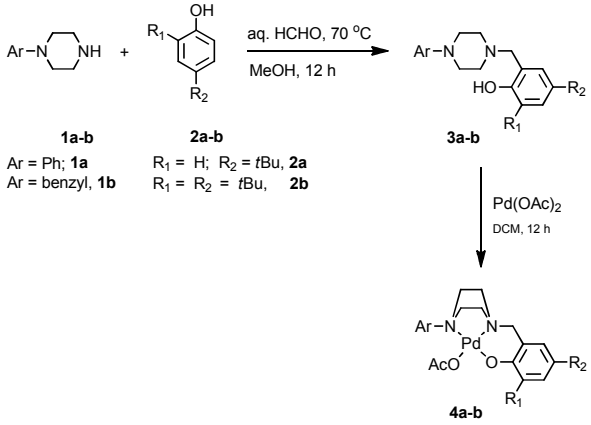


Fig. 1 Structures of bioactive compounds.



Scheme 1 Synthesis of ligands **3a-b** and their palladium(II) complexes **4a-b**.

All the methods reported for biphenyl synthesis from 5-iodovanillin, 5-bromosalicylaldehyde employed high amounts of catalyst (4–5 mol%) and expensive phosphine ligands. Therefore, it is crucial to develop simple and efficient Pd catalytic systems for Suzuki cross-coupling reaction. In this regard we describe our results on the optimization and scope of cross-coupling reactions of 5-iodovanillin, 5-bromosalicylaldehyde, deactivated aryl bromides and aryl chlorides with different arylboronic acids, catalyzed by Pd(II) complex **4a**.

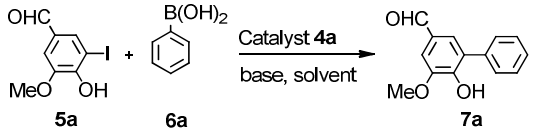
Results and discussion

The piperazine ligands **3a–b** were prepared as shown in Scheme 1.[20] This involves the reaction between N-arylpiperazine, aqueous HCHO and phenol derivative in methanol under reflux conditions to afford ligands **3a–b** in almost quantitative yields. The resulting *N,N,O* tridentate ligands **3a–b** were further treated with $Pd(OAc)_2$ in dichloromethane to give the desired palladium(II) complexes **4a–b** in high yields. These complexes are soluble in polar and nonpolar solvents. We observed the solubility of this complexes normal in hexane, but high in chloroform, dichloromethane, acetonitrile and N,N-dimethylformamide. The air and moisture stable Pd(II) complexes were characterized by NMR, Mass and IR spectroscopy. All the ligands and their palladium(II) complexes were in good conformity with the results of NMR.

The phenolic OH proton signals of the ligands **3a–b** were disappeared in their corresponding Pd(II) complexes, which confirms that the coordination of metal ion with the oxygen atom by deprotonation. This results in the loss of one acyl group as acetic acid from $Pd(OAc)_2$. The NMR spectras of these complexes showed one set of methyl proton signals in the range δ 1.29–1.98. Further, the positive-mode spectra of High Resolution (HR) Mass Spectroscopy also confirms the formation of Pd(II) complexes **4a** and **4b**.

To evaluate the catalytic activity of the palladium(II) complexes (**4a–b**), the Suzuki–Miyaura cross-coupling reaction of aryl halides with arylboronic acids was studied. 5-Iodovanillin **5a** and phenylboronic acid **6a** were chosen to establish a model reaction for the optimization of reaction conditions. The preliminary results are shown in Table 1. We screened different bases for the coupling reaction of **5a** with **6a** in 1:1 ratio of water and methanol system. We observed that the reaction proceeded well with high yields of the desired coupling product **7a** with inorganic (K_2CO_3, $LiOH.H_2O$ and K_3PO_4) as well as organic bases (DABCO and Et_3N) (entries 1–3 and 5–6). This coupling reaction afforded high conversion with majority of screened bases with only variation in reaction time. In case of $LiOH.H_2O$ **7a** was observed in high yield within 5 h, whereas K_2CO_3 requires 8 h for product formation. Gratifyingly, excellent product formed with K_3PO_4 in prolonged reaction time to 12 h. Low product formation was observed with $NaOAc.3H_2O$ base even under the long-standing conditions (entry 4). Moreover, strong base $LiOH.H_2O$ is more suitable for the coupling of **5a** with arylboronic acids than other

Table 1 Optimization reaction of the 5-iodovanillin with phenylboronic acid[a]

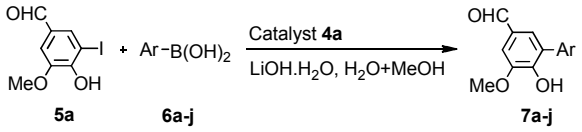


Entry	Base	Solvent	Time (h)	Yield (%)[b]
1	K_2CO_3	H_2O+MeOH	8	97
2	$LiOH.H_2O$	H_2O+MeOH	5	99
3	K_3PO_4	H_2O+MeOH	12	96
4	$NaOAc.3H_2O$	H_2O+MeOH	24	20
5	DABCO	H_2O+MeOH	20	96
6	Et_3N	H_2O+MeOH	24	95
7	-	H_2O+MeOH	24	Nr[c]
8	$LiOH.H_2O$	H_2O+MeOH	24	≤5[d]
9	$LiOH.H_2O$	H_2O	20	60
10	$LiOH.H_2O$	MeOH	24	85
11	$LiOH.H_2O$	CH_3CN	24	Nr[c]
12	$LiOH.H_2O$	Toluene	24	20
13	$LiOH.H_2O$	DMF	24	10

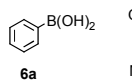
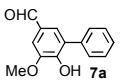
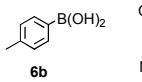
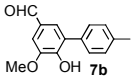
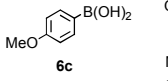
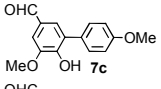
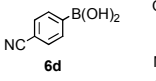
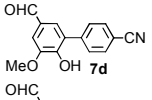
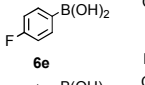
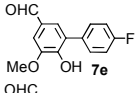
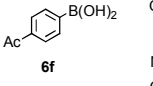
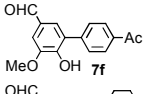
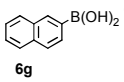
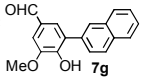
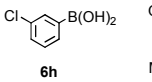
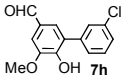
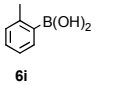
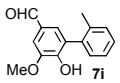
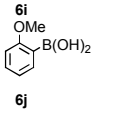
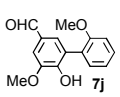
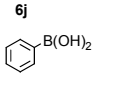
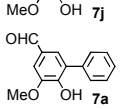
[a] Reaction conditions: 5-iodovanillin (1 mmol), phenylboronic acid (1.2 mmol), base (2 mmol), catalyst **4a** 0.01 mol%, solvent (H_2O+MeOH 1:1, 2 mL) at room temperature. [b] Isolated yield. [c] Nr = No reaction. [d] Without catalyst **4a**.

bases (K_2CO_3, K_3PO_4, DABCO, Et_3N and $NaOAc.3H_2O$). Without base no reaction was observed (entry 7). As expected poor yields of **7a** (≤5%) was observed under catalyst free conditions (entry 8). Next, we studied the solvent effect on the above coupling reaction with ($LiOH.H_2O$) as base. In contrast to aqueous methanol system, independent reactions of water and methanol solvents gave **7a** in low yields (entries 9 & 10). No or poor yield of **7a** was observed in case of acetonitrile, toluene and DMF (entries 11–13). It clearly showed that the solvent plays a key role on the cross-coupling reaction. Thus from all the screenings, best results were observed with the $LiOH.H_2O$–H_2O/MeOH system using 0.01 mol% of catalyst **4a** at room temperature (entry 2).

Table 2 Coupling reactions of 5-iodovanillin with a various arylboronic acids[a]



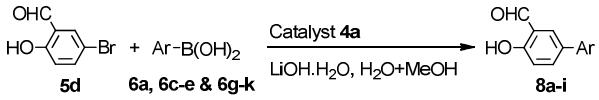
5a **6a-j** **7a-j**

Entry	Ar	Product	Time	Yield(%)[b]	Ref.
1	 **6a**	 **7a**	6 h	99, 94[c]	-
2	 **6b**	 **7b**	6 h	97	-
3	 **6c**	 **7c**	8 h	96	-
4	 **6d**	 **7d**	8 h	97	-
5	 **6e**	 **7e**	6 h	96	-
6	 **6f**	 **7f**	8 h	94	-
7	 **6g**	 **7g**	6 h	95	-
8	 **6h**	 **7h**	3 h	97	-
9	 **6i**	 **7i**	24 h	85	-
10	 **6j**	 **7j**	24 h	80	-
11	 **6a**	 **7a**	24 h	84[d], Nr[e]	-

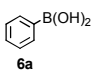
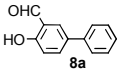
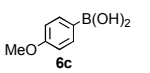
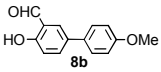
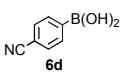
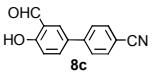
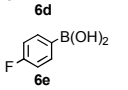
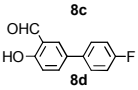
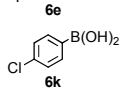
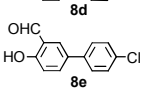
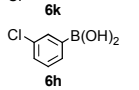
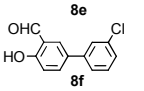
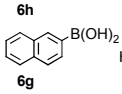
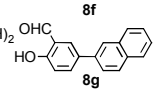
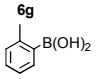
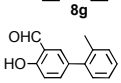
[a] Reaction conditions: 5-iodovanillin (1.0 mmol), arylboronic acid (1.2 mmol), catalyst **4a** 0.01 mol%, $LiOH.H_2O$ (1 mmol), H_2O+MeOH (2 mL, 1:1) at room temperature. [b] Isolated yield. [c]Carriied out with 0.01 mol% of catalyst **4b**. [d]Reaction with 5-bromovanillin and catalyst 0.05 mol% of **4a** at 60 °C . [e]Reaction with 5-chlorovanillin and catalyst 0.05 mol% of **4a** at 100 °C . Nr = No reaction

With the appropriate solvent and base in hand, next we studied the scope of Pd(II) complex **4a** for the Suzuki–Miyaura cross-coupling reaction of 5-iodovanillin **5a** with variety of phenylboronic acids **6a-j**. The results were summarised in Table 2. A range of arylboronic acids were converted to the corresponding coupled products **7a-h** with **5a** in excellent yields at room temperature (entries 1–8). However arylboronic acids bearing electron-withdrawing or electron-donating groups showed a trivial effect on the coupling reaction. Next, we observed the substituent effect of arylboronic acids showing the variation of reaction time for their cross-coupling reactions. Phenylboronic acid **6a**, 4-methylbenzeneboronic acid **6b**, 4-fluorobenzeneboronic acid **6e** and 2-naphthylboronic acids **6g** took 6 h for converting into their corresponding products **7a**, **7b**, **7e** and **7g** (entries 1, 2, 5 and 7). Whereas 4-OMe, 4-CN and 4-OAc substituted arylboronic acids **6c**, **6d** and **6f** requires 8 h reaction time for successful coupling (entries 3, 4 and 6). However, when 3-chlorobenzeneboronic acid **6h** used as substrate for **5a** coupling the reaction completed within 3 h with 97% yield (entry 8). We also used sterically hindered aryl boronic

Table 3 Coupling reactions of 5-bromosalicyladehyde with a various arylboronic acids[a]



5d **6a, 6c-e & 6g-k** **8a-i**

Entry	Ar	Product	Time	Yield(%)[b]	Ref.
1	 **6a**	 **8a**	15 h	86, 40[c]	*16*
2	 **6c**	 **8b**	15 h	94	*18a*
3	 **6d**	 **8c**	15 h	92	-
4	 **6e**	 **8d**	15 h	90	*16*
5	 **6k**	 **8e**	15 h	88	*16*
6	 **6h**	 **8f**	12 h	86[d]	-
7	 **6g**	 **8g**	15 h	88	*18b*
8	 **6i**	 **8h**	30 h	79	-
9	**6j**	**8i**	30 h	74	*18a*
10	**6a**	**8a**	24 h	Nr[e]	*16*

[a] Reaction conditions: 5-bromosalicylaldehyde (1.0 mmol), arylboronic acid (1.2 mmol), catalyst **4a** 0.05 mol%, $LiOH.H_2O$ (2 mmol), H_2O (2 mL) at 60 °C. [b] Isolated yield. [c]Reaction with 0.01 mol% catalyst **4a** at room temperature. [d]K_3PO_4 (2 mmol) used as base. [e]Reaction with 5-chlorosalicylaldehyde and 1 mol% of **4a** at 100 °C. Nr = No reaction

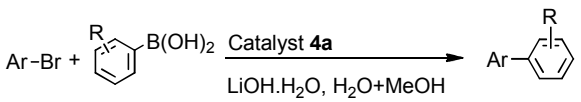
acids to obtain *ortho*-Me and OMe groups substituted 5-arylvanillins **7i** and **7j** in good yields, 85% and 80%, respectively (entries 9 and 10). Next, we observed 84% and no yield of **7a** for 5-bromovanillin **5b** and 5-chlorovanillin **5c** as partners in Suzuki cross-coupling reactions (entry 11).

Further we extended the above optimized reaction conditions to Suzuki–Miyaura cross-coupling reaction of 5-bromosalicylaldehyde **5d** with different arylboronic acids (Table 3). We observed low yield for **5d** coupling reaction with **6a** at room temperature by using 0.01 mol% of catalyst **4a**. Here we required high temperature and catalyst loading for efficient cross-coupling of substrates to complete the reaction. When the concentration of catalyst **4a** was increased from 0.01 mol% to 0.05 mol%, the yield of the corresponding coupling product **8a** increased from 40% to 86% at 60 °C (entry 1). In comparision to the reported 5-phenylsalicylaldehyde synthesis, the present catalyst amount (0.05 mol%) was very low.[19] A variety of arylboronic acids bearing electron-withdrawing groups such as 4-cyano **6d**, 4-fluoro **6e** and 4-chloro **6k** moieties and electron donating group 4-methoxy substituted arylboronic acids **6c** reacted well with **5d** resulting 5-aryl substituted salicylaldehydes (**8c-d, 8e** and **8b**) in excellent yields (entries 2–5). However, the reaction of 3-chlorobenzeneboronic acid **6h** with **5d** preferred K_3PO_4 base than $LiOH.H_2O$ for efficient coupling (entry 6). When sterically hindered 2-methylphenylboronic acid **6i** and 2-methoxyphenylboronic acid **6j** were used as substrates, coupling products **8h** and **8i** were formed with moderate yields in 30 h reaction time (entries 8 and 9). No coupling product was noticed for 5-chlosalicylaldehyde **5e** as a partner in Suzuki cross-coupling reaction (entry 10).

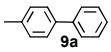
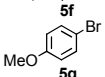
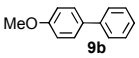
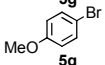
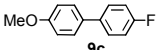
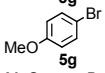
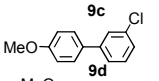
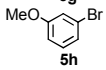
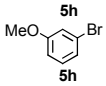
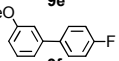
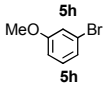
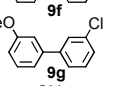
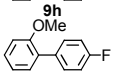
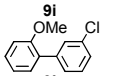
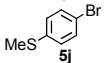
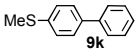
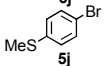
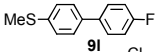
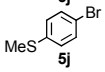
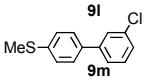
On the other hand, we examined the efficiency of this catalyst **4a** for the Suzuki reaction of deactivated aryl bromides **5f-j** with different arylboronic acids (**6a**, **6e** and **6f**) by using the above optimized reaction conditions at 50 °C. The cross-coupling reactions of deactivated aryl bromides were carried out well, and obtained good yields for all the corresponding biaryl products **9a-m**. This reaction proceeded smoothly with the electron-rich aryl bromides bearing 4-Me and OMe group at *para*, *meta* and *ortho*-positions (entries 1–10). However, we observed good yields for the most challenging substrate 4-SMe group containing aryl bromide **5j** when employed as a coupling partner with different arylboronic acids with prolonged reaction time of 15 to 24 h (entries 11–13).

To understand the efficiency of our complex **4a**, we extended the Suzuki cross-coupling reaction of aryl chlorides with variety of arylboronic acids using 3 mol% of **4a**, 2 mmol $LiOH.H_2O$, and 2 mL of DMF at 100 °C for 24 h. We observed good yields of desired products **9n-q** for electron-deficient aryl chlorides such as 1-chloro-4-nitrobenzene **5k**, 4-chloroacetophenone **5l** and 4-chlorobenzophenone **5m** (entries 1–4). In case of chlorobenzene **5n** and 4-chlorotoluene **5o** as reaction partner low to moderate yields of the coupled products **9r, 9a** and **9b** were obtained only after 30 h (entries 5–8). However we observed less than 10% of homo-coupling products of arylboronic acids for Suzuki cross-coupling of aryl chlorides.

Table 4 Coupling reactions of arylboronic acids with a variety of aryl bromides[a]



5f-j **6a, 6e & 6h** **9a-m**

Entry	Aryl halide	R	Product	Yield(%)[b]	Ref.
1	 **5f**	H	 **9a**	96	*2b*
2	 **5g**	H	 **9b**	94	*2b*
3	 **5g**	F	 **9c**	92	*22a*
4	 **5g**	Cl	 **9d**	94	*22e*
5	 **5h**	H	 **9e**	86	*2b*
6	 **5h**	F	 **9f**	90	*22a*
7	 **5h**	Cl	 **9g**	82	*22e*
8	 **5i**	H	 **9h**	86	*2b*
9	 **5i**	F	 **9i**	90	*22a*
10	 **5i**	Cl	 **9j**	82	*22d*
11	 **5j**	H	 **9k**	92[c]	*8a*
12	 **5j**	F	 **9l**	90[c]	*22c*
13	 **5j**	Cl	 **9m**	88[c]	-

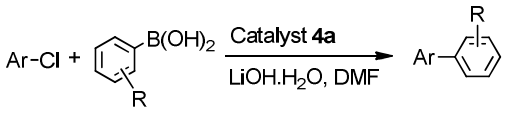
[a] Reaction conditions: Aryl halide (1 mmol), arylboronic acid (1.2 mmol), catalyst **4a** 0.01 mol%, $LiOH.H_2O$ (2 mmol), H_2O+MeOH (2 mL, 1:1) at 50 °C for 15 h. [b]Isolated yield. [c]Reaction time 24 h.

The catalytic efficiency of complex **4a** includes several advantages from the above results (Tables 1–5). (1) The low catalyst loading is sufficient for efficient coupling of iodo and bromo aryl compounds (0.01 to 0.05 mol%). (2) And the operation of this reaction is very simple without use of any susceptible reagents. (3) Hydroxy and aldehyde substituted aryl halide coupling reactions proceeded well under aqueous system with the air stable catalyst **4a**. (4) The main feature of this process was efficient synthesis of 5-arylvanillin from a particular solvent system and all the inorganic bases. (5) Developed complex **4a** is even applicable for non-activated chloro coupling reactions.

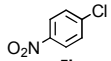
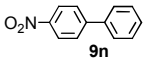
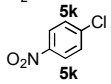
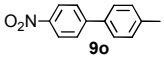
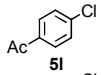
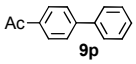
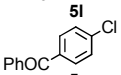
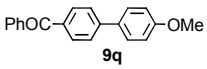
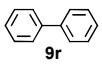
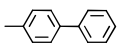
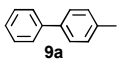
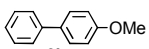
Conclusion

In conclusion, we have developed a new *N,N,O*-tridentate derived

Table 5 Coupling reactions of arylboronic acids with a variety of aryl chlorides[a]



5k-o 6a-c 9a-b & 9n-r

Entry	Aryl halide	R	Product	Yield(%)[b]	Ref.
1	 5k	H	 9n	80	*2b*
2	 5k	Me	 9o	81	*1c*
3	 5l	H	 9p	76	*2b*
4	 5m	OMe	 9q	80	*22b*
5	 5n	H	 9r	64[c]	*2b*
6	 5o	H	 9a	62[c]	*2b*
7	 5n	Me	 9a	56[c]	*2b*
8	 5n	OMe	 9b	60[c]	*2b*

[a] Reaction conditions: Aryl chloride (1 mmol), arylboronic acid (1.2 mmol), catalyst **4a** 3 mol%, $LiOH.H_2O$ (2 mmol), DMF (2 mL) at 100 °C for 24 h. [b]Isolated yield. [c]Reaction time 30 h.

palladium(II) complex for the Suzuki reaction of 5-iodovanillin, 5-bromosalicyladehyde and deactivated aryl bromides in aqueous system. We obtained a variety of 5-arylvanillin and 5-arylsalicylaldehyde derivatives in excellent yields. These biaryl units can serve as key structural elements in different pharmaceutical intermediates. Coupling reactions of various deactivated aryl bromides with different arylboronic acids preceded well using low catalyst loadings (0.01 mol%). This catalytic system is even applicable for the challenging ArCl couplings. An excellent functional group tolerance with high yields in aqueous system make this method more economically viable in terms of green perspective.

Experimental section

General procedure for the synthesis of ligands 3a–b

In a 100 mL round bottom flask piperazine (10 mmol), 40% aqueous formaldehyde solution (2.1 mL, 30 mmol) methanol (50 mL) were added and refluxed for 2 h. This reaction mixture was allowed to cool to room temperature. Phenol derivatives (**2a** or **2b**) (20 mmol) were directly added to the reaction mixture and again refluxed for 12 h. Then the reaction mixture was stand to room temperature for cooling and the resulting solid (90-95% yield) was filtered off and dried in vacuum.

General procedure for the preparation of Pd(II) complexes 4a–b

To a flask containing ligand (**3a** or **3b**) (0.5 mmol) and $Pd(OAc)_2$ (0.5 mmol), 30 mL of CH_2Cl_2 was added at room temperature and stirred for 12 h. The reaction mixture was washed with water to remove AcOH generated in the reaction mixture. The solvent was removed under reduced pressure and the resulting brown solid was dried under high vacuum to obtain the pure Pd(II) complexes (**4a** or **4b**) in 94–96% yield.

Pd(II) complex 4a: Brown solid, mp: 180 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.36 (t, *J* = 8.84 Hz, 2H), 7.15 (d, *J* = 8.58 Hz, 1H), 7.03-6.94 (m, 4H), 6.78 (d, *J* = 8.58 Hz, 1H), 3.94 (d, *J* = 10.10 Hz, 2H), 3.74 (s, 2H), 3.57 (d, *J* = 12.88 Hz, 2H), 3.42 (t, *J* = 11.11 Hz, 2H), 3.05 (d, *J* = 12.88 Hz, 2H), 1.29 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8, 150.4, 138.5, 129.2, 127.0, 126.5, 123.8, 119.9, 118.5, 115.5, 55.3, 52.8, 43.6, 33.7, 31.5, 29.6; FTIR (KBr): $\tilde{\nu}$ = 2955, 1722, 1573 cm^{-1}; HRMS: calcd for $C_{21}H_{27}N_2OPd$ $(M–OAc)^+$ = 429.1158, found: 429.1080.

Pd(II) complex 4b: Brown solid, mp: 176 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.38 (m, 6H), 6.84 (s, 1H), 4.22 (s, 2H), 4.14 (s, 2H), 3.57-3.12 (m, 4H), 2.61-2.25 (m, 4H), 1.98 (s, 3H), 1.44 (s, 9H), 1.31 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.9, 163.5, 140.5, 136.9, 131.4, 130.3, 128.9, 128.6, 126.2, 125.6, 125.0, 62.3, 61.8, 59.7, 54.9, 54.8, 35.2, 33.9, 31.6, 30.8, 29.5, 23.6; FTIR (KBr): $\tilde{\nu}$ = 2954, 1718, 1573 cm^{-1}; HRMS: calcd for $C_{26}H_{37}N_2OPd$ $(M–OAc)^+$ = 499.1941, found: 499.1935.

General procedure for the Suzuki–Miyaura cross-coupling reaction of 5-iodovanilin

A mixture of 5-iodovanilin (1.0 mmol), arylboronic acid (1.2 mmol), $LiOH.H_2O$ (2.0 mmol) and Pd complex **4a** (0.01 mol% in 0.1 mL DMF) in 1:1 ratio of water and methanol system (2 mL) was stirred at room temperature for 6 h. After confirmation of completed reaction by TLC, the reaction mixture was extracted with ethyl acetate and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel using ethyl acetate/hexane as the eluent to afford the desired products.

6-hydroxy-5-methoxybiphenyl-3-carbaldehyde 7a (entry 1, Table 2): White solid, mp: 130 °C. **^{1}H NMR** (400 MHz, $CDCl_3$, TMS) 9.73 (s, 1H), 7.51 (s, 2H), 7.39-7.25 (m, 5H), 6.61 (s, 1H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 191.1, 159.1, 148.8, 147.5, 136.3, 129.1, 128.7, 128.4, 127.8, 127.6, 107.4, 56.4; HRMS: exact mass calculated for $C_{14}H_{13}O_3$ $[M+H]^+$ = 229.0865, found m/z = 229.0856.

6-hydroxy-5-methoxy-4'-methyl-[1,1'-biphenyl]-3-carbaldehyde 7b (entry 2, Table 2): White solid, mp: 148 °C. **^{1}H NMR** (400 MHz, $CDCl_3$, TMS) 9.73 (s, 1H), 7.41-7.39 (m, 3H), 7.28 (s, 1H), 7.16 (d, *J* = 7.83 Hz, 2H), 6.51 (s, 1H), 3.84 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 191.1, 148.6, 147.3, 137.4, 133.2, 129.0, 128.8, 128.5, 127.5, 107.1, 56.2, 21.1; HRMS: exact mass calculated for $C_{15}H_{15}O_4$ $[M+H]^+$ = 243.1021, found m/z = 243.0989.

4'-methoxy-6-hydroxy-5-methoxybiphenyl-3-carbaldehyde 7c (entry 3, Table 2): Light yellow solid, mp: 130 °C. **^{1}H NMR** (400 MHz, $CDCl_3$, TMS) 9.78 (s, 1H), 7.50 (d, *J* = 9.09 Hz, 2H) 7.41 (m, 1H), 7.31 (s, 1H), 6.92 (d, *J* = 9.09 Hz, 2H), 6.43 (s, 1H), 3.91 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 191.1, 159.2, 148.6, 147.4, 130.2, 129.2, 128.6, 128.4, 127.3, 113.9, 107.1, 56.4, 55.3; HRMS: exact mass calculated for $C_{15}H_{15}O_4$ $[M+H]^+$ = 259.0970, found m/z = 259.0949.

4'-cyano-6-hydroxy-5-methoxybiphenyl-3-carbaldehyde 7d (entry 4, Table 2): Light yellow solid, mp: 160 °C. **^{1}H NMR** (400 MHz, $CDCl_3$, TMS) 9.79 (s, 1H), 7.66 (m, 4H), 7.42 (d, *J* = 19.95 Hz, 2H), 6.78 (s, 1H), 3.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 190.7, 148.8, 147.6, 141.5, 132.1, 129.8, 129.4, 127.7, 118.8, 111.2, 108.6, 56.5; HRMS: exact mass calculated for $C_{15}H_{12}NO_3$ $[M+H]^+$ = 254.0817, found m/z = 254.0802.

4'-fluoro-6-hydroxy-5-methoxybiphenyl-3-carbaldehyde 7e (entry 5, Table 2): White solid, mp: 112 °C. **^{1}H NMR** (400 MHz, $CDCl_3$, TMS) 9.76 (s, 1H), 7.50 (s, 2H), 7.38 (d, *J* = 26.77 Hz, 2H), 7.04 (s, 2H), 6.53 (s, 1H), 3.90 (s, 3H); ^{19}F NMR (376.46 MHz, $CDCl_3$) δ: −114.31 (s, 1 F); ^{13}C NMR (100 MHz, $CDCl_3$) 190.9, 163.5 (d, *J* = 248.09 Hz), 148.5, 147.3, 132.1, 130.7 (d, *J* = 8.05 Hz), 129.1, 128.2, 126.5, 115.4 (d, *J* = 21.95 Hz), 107.4, 56.3; HRMS: exact mass calculated for $C_{14}H_{12}FO_3$ $[M+Na]^+$ = 247.0770, found m/z = 247.0776.

4'-acetyl-6-hydroxy-5-methoxy-[1,1'-biphenyl]-3-carbaldehyde 7f (entry 6, Table 2): Orange solid, mp: 120 °C. **^{1}H NMR** (400 MHz, $CDCl_3$, TMS) 9.85 (s, 1H), 8.02 (m, 2H), 7.73 (m, 2H), 7.52-7.33 (m, 2H), 7.04 (s, 1H), 3.97 (s, 3H), 2.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 198.0, 190.9, 149.0, 147.6, 147.3, 136.1, 135.9, 129.3, 128.3, 128.1, 126.3, 108.7, 56.4, 26.6; HRMS: exact mass calculated for $C_{16}H_{15}O_4$ $[M+H]^+$ = 271.0970, found m/z = 271.0960.

4-hydroxy-3-methoxy-5-(naphthalen-2-yl)benzaldehyde 7g (entry 7, Table 2): White solid, mp: 164 °C. **^{1}H NMR** (400 MHz, $CDCl_3$, TMS) 9.76 (s, 1H), 7.96 (s, 1H), 7.80-7.75 (m, 3H), 7.65 (m, 1H), 7.49 (s, 1H), 7.39-7.37 (m, 2H), 7.31 (s, 1H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 191.1, 148.9, 147.5, 133.8, 133.3, 132.7, 129.3, 128.8, 128.2, 128.1, 127.8, 127.6 (d), 127.0, 126.3, 126.2, 107.9, 56.4; HRMS: exact mass calculated for $C_{18}H_{15}O_3$ $[M+H]^+$ = 279.1021, found m/z = 279.1023.

3'-chloro-6-hydroxy-5-methoxybiphenyl-3-carbaldehyde 7h (entry 8, Table 2): White solid, mp: 136 °C. **^{1}H NMR** (400 MHz, $CDCl_3$, TMS) 9.58 (s, 1H), 7.98 (s, 1H), 7.62 (s, 1H), 7.51-7.47 (m, 2H), 7.41 (s, 1H), 7.35-7.34 (m, 1H), 6.85 (s, 1H), 3.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 190.9, 162.7, 148.8, 147.5, 138.1, 134.1, 129.6, 129.1, 128.2, 127.7, 127.2, 126.2, 107.9, 56.4; HRMS: exact mass calculated for $C_{14}H_{12}ClO_3$ $[M+H]^+$ = 263.0475, found m/z = 263.0443.

6-hydroxy-5-methoxy-2'-methyl-[1,1'-biphenyl]-3-carbaldehyde 7i (entry 9, Table 2): White solid, mp: 130 °C. **^{1}H NMR** (400 MHz, $CDCl_3$, TMS) 9.75 (s, 1H), 7.73 (s, 1H), 7.37 (s, 1H), 7.25-7.22 (m, 3H), 7.15-7.13 (m, 1H), 6.36 (s, 1H), 3.92 (s, 3H), 2.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 190.9, 148.6, 147.1, 136.7, 135.8, 130.0, 129.8, 129.1, 129.0, 128.1, 128.0, 125.7, 107.4, 56.2, 19.8; HRMS: exact mass calculated for $C_{15}H_{15}O_3$ $[M+H]^+$ = 243.1021, found m/z = = 243.1021.

6-hydroxy-2',5-dimethoxy-[1,1'-biphenyl]-3-carbaldehyde 7j (entry 10, Table 2): Light yellow solid, mp: 138 °C. **^{1}H NMR** (400 MHz, $CDCl_3$, TMS) 9.73 (s, 1H), 7.34 (m, 2H), 7.30 (t, *J* = 8.33 Hz, 1H), 7.24 (d, *J* = 7.57 Hz, 2H), 6.99-6.92 (m, 2H), 6.49 (s, 1H), 3.87 (s, 3H), 3.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 190.9, 156.4, 149.1, 147.6, 131.4, 130.2, 129.7, 129.5, 128.9, 125.1 (d), 120.8, 111.2, 107.5, 56.1, 55.6; HRMS: exact mass calculated for $C_{15}H_{15}O_4$ $[M+H]^+$ = 259.0970, found m/z = 259.0974.

General procedure for the Suzuki–Miyaura cross-coupling reaction of 5-bromosalicylaldehyde

A mixture of 5-bromosalicylaldehyde **5d** (1.0 mmol), arylboronic acid (1.2 mmol), $LiOH.H_2O$ (2.0 mmol) and Pd complex **4a** (0.05 mol% in 0.1 mL DMF) in 1:1 ratio of water and methanol system (2 mL) was stirred at 60 ^oC for 24 h. To the cooled solution water was added, extracted with ethyl acetate and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel using ethyl acetate/hexane as the eluent to give the desired products.

3'-formyl-4'-hydroxy-[1,1'-biphenyl]-4-carbonitrile 8c (entry 3, Table 3): White solid, mp: 149 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 11.11 (s, 1H), 10.01 (s, 1H), 7.81-7.67 (m, 6H), 7.14 (d, *J* = 8.58 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.3, 161.8, 143.6, 135.4, 134.0, 132.7, 132.0, 131.0, 127.8, 127.0, 120.7, 118.5, 110.8; HRMS: exact mass calculated for $C_{14}H_{10}NO_2$ $[M+H]^+$ = 223.0633, found m/z = 223.0797.

5-(-3-chlorophenyl)salicylaldehyde 8f (entry 6, Table 3): Light yellow solid, **mp:** 70 °C**.** ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 10.95 (s, 1H), 9.89 (s, 1H), 7.65 (m, 2H), 7.45 (m, 1H), 7.35-7.23 (m, 3H), 7.01 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.4, 161.4, 141.1, 135.5, 134.9, 131.8, 130.2, 127.4, 126.7, 124.7, 120.7, 118.3, 113.7; LCMS (*m/z*) $(M+H)^+$ = 233. ; HRMS: exact mass calculated for $C_{13}H_{10}ClO_2$ $[M+H]^+$ = 233.0369, found m/z = 233.0370.

4-hydroxy-2'-methyl-[1,1'-biphenyl]-3-carbaldehyde 8h (entry 8, Table 3): brown liquid. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 10.93 (s, 1H), 9.83 (s, 1H), 7.42 (s, 2H), 7.19-7.12 (m, 4H), 6.98 (d, *J* = 8.84 Hz, 1H), 2.19 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.5, 160.5, 139.9, 137.9, 135.3, 133.8, 133.7, 130.4, 129.6, 127.6, 126.0, 120.2, 117.3, 20.3; HRMS: exact mass calculated for $C_{14}H_{13}O_2$ $[M+H]^+$ = 213.0916, found m/z = 213.0910.

General procedure for the Suzuki–Miyaura cross-coupling reaction of aryl bromides

A mixture of aryl bromide (1.0 mmol), phenylboronic acid **6a** (1.2 mmol), $LiOH.H_2O$ (2.0 mmol), H_2O+MeOH (1:1, 2 mL), and Pd

complex **4a** in freshly prepared DMF solution (0.01 mol% in 0.1 mL DMF) was stirred at 50 °C for a desired reaction time. Further, the reaction mixture was extracted with ethyl acetate and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel using ethyl acetate/hexane as the eluent to give the corresponding coupling products.

(3'-chloro-[1,1'-biphenyl]-4-yl)(methyl)sulfane 9m (entry 13, Table 4): Light yellow solid, **mp:** 48 °C**.** **^{1}H NMR** (400 MHz, $CDCl_3$, TMS) 7.54 (s, 1H), 7.49-7.42 (m, 3H), 7.36-7.28 (m, 4H), 2.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 142.3, 138.5, 136.4, 134.7, 130.0, 127.4, 127.1, 126.9, 126.8, 124.9, 15.7; HRMS: exact mass calculated for $C_{13}H_{11}ClS$ $[M]^+$ = 234.0270, found m/z = 234.0261.

General procedure for the Suzuki–Miyaura cross-coupling reaction of aryl chlorides

A mixture of aryl chloride (1.0 mmol), phenylboronic acid **6a** (1.2 mmol), $LiOH.H_2O$ (2.0 mmol), DMF (2 mL), and Pd complex **4a** (3 mol%) was stirred at 100 °C for a desired reaction time. Further, the reaction procedure same as above.

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2-((4-Arylpiperazin-1-yl)methyl)phenol ligated Pd(II) complex: An efficient, versatile catalyst for Suzuki–Miyaura cross-coupling reaction

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N,N,O-tridentate palladium(II) complex **4a** found to be an efficient catalyst for the Suzuki cross-coupling reaction of aryl halides (iodo, bromo and chloro), which afforded the cross-coupling products in good to excellent yields.