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An inexpensive and highly stable ligand 1,4-bis(2-hydroxy-3,5-di-*tert*-butylbenzyl)piperazine for Mizoroki–Heck and room temperature Suzuki–Miyaura cross-coupling reactions

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Abstract

A bulky, inexpensive and simple bidentate ligand 1,4-bis(2-hydroxy-3,5-di-*tert*-butylbenzyl)piperazine (**1**) has been synthesized and characterized. The palladium catalyst was formed by combination of **1** with [Cl_2Pd(COD)] in a ratio of 1:1, tested in the Suzuki–Miyaura and Mizoroki–Heck cross-coupling reactions. Coupling of a variety of aryl bromides with phenylboronic acid using methanol as solvent at room temperature, or at 60 °C, gave generally high yields of coupled products. Coupling of aryl chlorides with organoboron reagent at 110 °C in DMF afforded good yields of biaryls under aerobic conditions. This non-phosphorus, air and moisture stable catalyst also displays good activity for Mizoroki–Heck coupling reaction in methanol at 60 °C with various aryl chlorides and bromides.

Keywords: Oxygen donor ligands; Nitrogen donor; Palladium complex; Catalysis; Suzuki cross-coupling; Mizoroki–Heck reactions

1. Introduction

The discovery of palladium catalyzed C–C coupling reactions, such as Heck–Mizoroki coupling[1] in the early 1970 and Suzuki–Miyaura coupling reaction[2] in 1990, has been applied to a diverse array of fields, ranging from natural products synthesis[3] to material science,[4] including biologically important molecules.[5] Among the various methods known to biaryl synthesis, Suzuki–Miyaura reaction is a powerful method for the formation of $C_{(sp2)}$–$C_{(sp2)}$ bonds under mild reaction conditions.[2] In addition to the $C_{(sp2)}$–$C_{(sp2)}$ cross-coupling of aryl bromides, very recently the Suzuki–Miyaura coupling has been extended to $C_{(sp3)}$–$C_{(sp2)}$ and $C_{(sp3)}$–$C_{(sp3)}$ coupling[6] of various halides with phenylboronic acids. The Heck coupling reactions have been practiced on industrial scales for the production of compounds such as naproxen[7] and octyl methyl cinnamate,[8] which play vital role in the biomedicines. Mostly the palladium complexes of tertiary phosphines such as cyclopalladated P(tolyl-*o*)$_3$ and *N*-heterocyclic carbenes are known to be excellent catalysts giving high yields with excellent TON and TOF for the Mizoroki–Heck reactions.[9] Similarly, palladium complexes containing phosphine, phosphate, and phosphine oxides are also widely used as precatalysts in Suzuki coupling reactions.[10] The major limitations with phosphine ligands in catalytic reactions is the oxidation of phosphines to phosphine oxides, formation of stable phosphido bridged catalytically inactive dimers, and also the cleavage of P–C bond causing degradation of the ligand and thus the termination of the catalytic cycle.[11] Furthermore, the difficulties involved in the removal of these by-products from organic products and high price of phosphine ligands led chemists to discover new phosphorus free ligands. Majority of *N*-heterocyclic carbenes are also sensitive to oxygen.

During the past 10 years, there has been considerable interest in the development of new phosphorus free palladium

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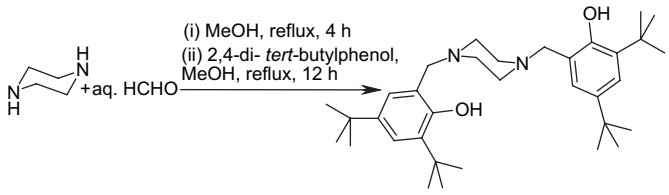
catalysts for higher activity, stability, and substrate tolerance that allow reactions to be carried out under milder reaction conditions. Good activity is not limited to phosphorus donor systems. The nitrogen ligands such as *N*-heterocyclic carbenes,[3c,12] imine,[13] amine palladacycles, oxime palladacycles,[14] and diazabutadine derivatives[15] have shown excellent activity for Suzuki coupling reactions. A variety of novel C–N, C–S, palladacycles incorporating NHC,[9a,16] imine[17] and thioether moieties[18,14a] have been reported for Heck coupling reactions with high turnover numbers.

As a part of our interest in designing new, inexpensive ligands and studying their coordination behavior and catalytic applications,[13a,19] we report herein the synthesis and characterization of a new type of bulky *ortho*-substituted inexpensive ligand 1,4-bis(2-hydroxy-3,5-di-*tert*-butylbenzyl)piperazine and its application in Suzuki and Heck coupling reactions.

2. Results and discussion

A mixture of piperazine, 40% paraformaldehyde solution and 2,4-di-*tert*-butlylphenol was stirred at 60 °C in methanol for 12 h to afford the colorless 1,4-bis(2-hydroxy-3,5-di-*tert*-butylbenzyl)-piperazine (**1**) in moderate yield (Scheme 1). The ^{1}H NMR spectrum of **1** shows a broad singlet at 10.72 ppm for the phenolic OH protons, whereas the methylene protons appear at 3.74 ppm. The presence of OH proton was confirmed by the D_2O exchange experiment. The EI mass spectrum of compounds **1** shows a molecular ion peak at *m/z* 523.6 $[M+H]^+$. Further, the molecular structure of **1** was confirmed by single crystal X-ray diffraction study.[20]



Scheme 1. Synthesis of 1,4-bis(2-hydroxy-3,5-di-*tert*-butylbenzyl)piperazine.

Perspective view of molecular structure of compound **1** with atom numbering scheme is shown in Figure 1. The colorless crystals of **1**, suitable for X-ray diffraction analysis were grown by the slow evaporation of dichloromethane and petroleum ether mixture at room temperature. The molecular structure of **1** possess crystallographically imposed center of symmetry in which the unit cell contains half a molecule of ligand. In the molecular structure of **1** the piperazine moiety possesses a stable chair conformation. The C–N bond distances of **1** are 1.478(4) Å (N–C15) and 1.458(4) Å (N–C17), whereas the bond length of C1–O is 1.375(4) Å. The bond angles around the nitrogen atom vary from 110.0(2)° (C16–N–C17) to 112.0(2)° (C15–N–C16). The bond angle around C15–N–C17 is 112.0(2), which is comparable with literature value.[21] The interesting feature in the molecular structure of **1** is the presence of weak intramolecular hydrogen bonding between the tertiary nitrogen atom and hydrogen atom of the phenoxy groups leading to the formation of two twisted six-membered rings. The bond distance of H1O···N is 1.77(4) Å, whereas the O–H1O···N bond angle is 154.0(4)°.

2.1. Room temperature Suzuki–Miyaura coupling reactions of aryl bromides

The palladium complex generated on combination of **1** with $[Cl_2Pd(COD)]$ in a 1:1 molar ratio was used as a catalyst for the Suzuki coupling reactions of various aryl bromides and benzyl bromide with phenylboronic acid at room temperature. To optimize the reaction conditions, a model reaction was

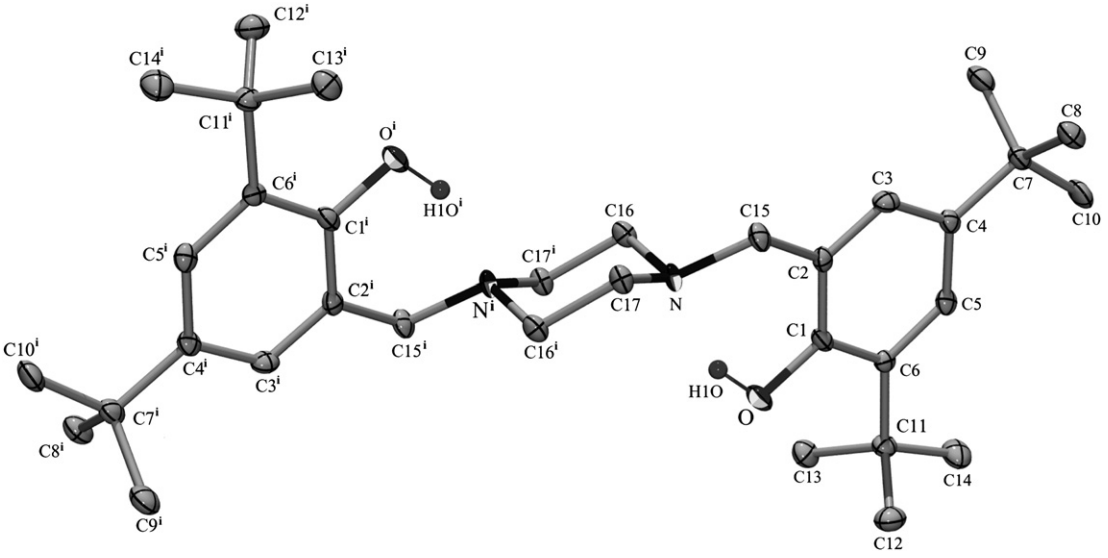


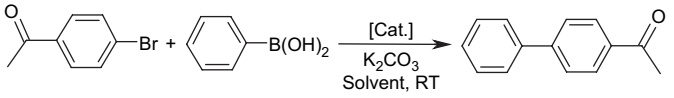
Figure 1. An ORTEP view of molecular structure of **1**. All hydrogen atoms (except H1O and H1O^i) were omitted for clarity. Thermal ellipsoids are drawn at 50% probability. Selected bond lengths (Å): O–C1, 1.375(4); N–C15, 1.478(4); N–C17, 1.458(4); N–C16, 1.464(4). Selected bond angles (°): C15–N–C16, 112.0(2); C16–N–C17, 110.0(2); O–C1–C2, 119.7(3); C15–N–C17, 112.0(2); O–C1–C6, 119.1(3); C2–C1–C6, 121.2(3).

carried out by taking 4-bromoacetophenone and phenylboronic acid in different solvents and bases at room temperature.

Solvent plays a crucial role in the rate and the product distribution of Suzuki coupling reactions. To verify the solvent effect in Suzuki coupling reactions, we investigated a series of reactions by taking the model reaction in different solvents (Table 1). The results displayed that the non-polar solvents such as toluene, *p*-xylene, and *n*-hexane gave moderate amount of conversions (entries 2, 6, and 7, respectively). Among the polar solvents, methanol (entry 1) was found to be the best (entries 3–5 and 8). This may be due to the higher solubility of the catalyst in methanol. Similarly, several bases were employed in Suzuki–Miyaura reactions, K_2CO_3 and K_3PO_4 proving superior (Table 2).

Under the optimized reaction conditions, a series of aryl and benzyl bromides (Table 3) were coupled with phenylboronic acid with 0.5 mol % of catalyst at room temperature. In some cases, coupling reactions with aryl bromides required high temperature (at 60 °C) in order to obtain acceptable yields. The electron withdrawing substituents (entries 1–3) as well as the heterocyclic derivatives (entries 4, 5) afforded excellent coupling products at room temperature but the heterocyclic compounds took dramatically more time than that of electron withdrawing substrates. The coupling of 3-bromobenzaldehyde and 2-bromo-6-methoxynaphthalene with phenylboronic acid resulted in good yields (82 and 80%, respectively) at room temperature and the yield did not improve at elevated temperature. The Suzuki coupling was also extended to $C_{(sp3)}$–$C_{(sp2)}$ coupling by reacting benzyl bromide with phenylboronic acid, which afforded the corresponding coupling products in excellent yield (entry 11). Thus the catalyst afforded average to

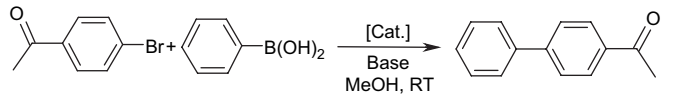
Table 1
Effect of solvent on the coupling reaction[a]



Entry	Solvent	Yield[b] (%)
1	Methanol	100
2	Toluene	68
3	Acetone	50
4	THF	50
5	Dioxane	23
6	*p*-Xylene	39
7	*n*-Hexane	23
8	DCM	32

[a] Reaction conditions: 4-bromoacetophenone (0.5 mmol), phenylboronic acid (0.75 mmol), K_2CO_3 (1 mmol), catalyst (0.5 mol %), and solvent (5 mL).
[b] Conversion to the coupled product determined by GC, based on aryl bromide; average of two runs.

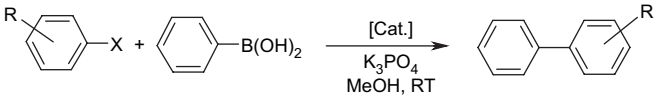
Table 2
Effect of base on the coupling reaction[a]

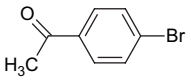
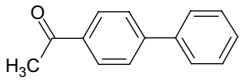
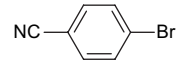
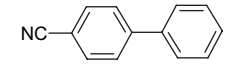
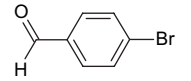
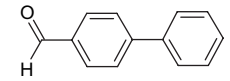
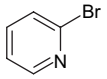
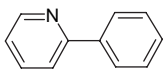
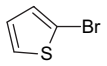
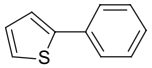
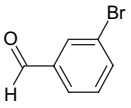
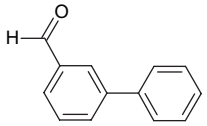
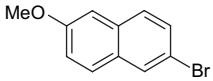
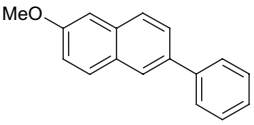
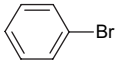
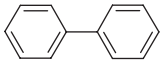
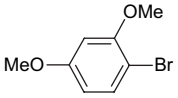
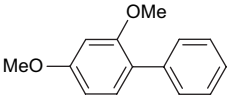
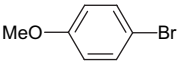
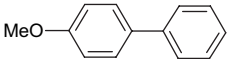
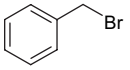
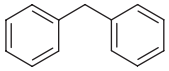


Entry	Base	Yield[b] (%)
1	K_3PO_4	100
2	K_2CO_3	100
3	Na_2CO_3	100
4	KOH	99
5	Et_3N	98
6	Cs_2CO_3	98
7	KF	97

[a] Reaction conditions: 4-bromoacetophenone (0.5 mmol), phenylboronic acid (0.75 mmol), catalyst (0.5 mol %), Base (1 mmol), and MeOH (5 mL).
[b] Conversion to the coupled product determined by GC, based on aryl bromide; average of two runs.

Table 3
Suzuki cross-coupling of aryl bromides with phenylboronic acid[a]



Entry	Aryl bromide	Product	Time	Yield[b] (%)
1			10 min	100
2			10 min	100
3			9 h	100
4			20 h	99
5			24 h	90
6			9 h	82
7			5 h	80
8			24 h	50 (59)[c]
9			25 h	32 (36)[c]
10			20 h	95[c]
11			4 h	95

[a] Reaction conditions: aryl bromide (0.5 mmol), phenylboronic acid (0.75 mmol), K_3PO_4 (1 mmol), MeOH (5 mL), and catalyst (0.5 mol %).
[b] Conversion to the coupled product determined by GC, based on aryl bromide; average of two runs.
[c] At 60 °C.

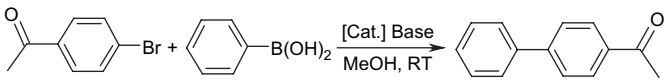
excellent yields of the biaryl products even at room temperature. In the literature, only a few catalysts are known for affecting the Suzuki cross-coupling reactions under mild conditions.[10b,13b,22]

The activity of this catalyst is found to be superior to that in [$PdCl_2$(dppf)], which catalyses the reaction between 4-bromoacetophenone and phenylboronic acid in toluene at 70 °C giving 94% yield.[23a] In comparison with other *N*-coordinated palladium catalysts, the catalytic activity of this catalyst is similar to those found in $Pd(OAc)_2$/diazabutadiene system, whose reactions were carried out in dioxane at 80 °C,[15] a tridentate bis(oxazolinyl)pyrrole dimeric palladium complex at 70 °C in toluene,[23b] and a palladium(II) metallamacrocycle supported by an amino-functionalized ferrocene complex at room temperature or 60 °C in methanol.[23c]

To demonstrate the catalytic value of ligand **1** the coupling reactions between 4-bromoacetophenone and phenylboronic acid were carried out in methanol using different palladium(II) systems at room temperature for 30 min with minimum catalyst loading (Table 4). The best yield was obtained by using $Pd(COD)Cl_2$/**1** as catalyst. Use of other palladium precursors such as [$Pd(PhCN)_2Cl_2$] and [$Pd(OAc)_2$] gave only the satisfactory yields. Under similar reaction conditions, $PdCl_2$ afforded only 13.5% conversion, whereas [$Pd(COD)Cl_2$] in the absence of ligand **1** yielded 20.9% conversion, which was significantly improved to 64.05% (TON=128,100) when the ligand **1** was introduced. These results indicate that the mixture of [$Pd(COD)Cl_2$]/**1** is very effective in promoting this type of C–C coupling under facile conditions.

Although each catalytic run generates some palladium metals due to the catalyst decomposition, the experimental data do not support the notion that the nanoparticulate palladium could play a key role in catalytic efficiency. To verify the activity of palladium black, Hor et al.[23c] reported that the commercially available Pd/C reagent (10 wt.% from Aldrich) catalyses the coupling of 4-bromoacetophenone and phenylboronic acid with an unattractive 8% conversion at room temperature in methanol medium. The palladium black obtained in the present study on subjecting to further catalytic reaction did not show any activity.

Table 4
Effect of low catalyst loading and comparison with other Pd^{II} systems[a]



Entry	Catalyst	Conversion[b] (%)	TON
1	$Pd(COD)Cl_2$	20.9	41,800
2	$Pd(COD)Cl_2$/**1**	64.05	128,100
3	$Pd(PhCN)_2Cl_2$/**1**	45.7	91,400
4	$Pd(OAc)_2$/**1**	33.0	66,000
5	$PdCl_2$/**1**	13.48	26,960

[a] Reaction conditions: 4-bromoacetophenone (0.5 mmol), phenylboronic acid (0.75 mmol), catalyst (0.0005 mol %), K_2CO_3 (1 mmol), time (30 min), and MeOH (5 mL).

[b] Conversion to the coupled product determined by GC, based on aryl bromide; average of two runs.

The homogeneous nature of the catalysis was checked by the classical mercury test.[24] Addition of a drop of mercury to the reaction mixture did not affect the conversion of the reaction, which suggests that the catalysis is homogeneous in nature, since heterogeneous catalysts would form an amalgam, thereby poisoning it. To get more insight into the possible nanoparticulate formation during the catalysis, TEM pictures of the palladium black was examined before and after the reactions and also before and after mixing with the ligand (Figs. 2 and 3). However, the analyses did not show any change in the particle size and also the morphology.

Attempts to isolate the metal complex were unsuccessful. The most probable catalytically active species might be the N,N chelated mono nuclear complex [$Cl_2Pd\{\eta^2$-L-$\kappa N,\kappa N\}$] (L=(2-HO-3,5-^{t}BuC_6H_2)CH_2(μ-NC_4H_8N)CH_2(3,5-^{t}BuC_6H_2-2-OH)) containing ligand L in a N,N-chelating fashion.[13a,25] Attempts are being made to isolate the complex for further characterization.

2.2. Suzuki–Miyaura coupling reactions of aryl chlorides

The cross-coupling of aryl chlorides with phenylboronic acids in the presence of 4 mol % of catalyst was carried out at 110 °C using DMF as solvent (Table 5). Electron deficient substrates such as 2-chlorobenzaldehyde, 2-chloronitrobenzene, and 4-chloronitrobenzene efficiently coupled with phenylboronic acid (entries 1–3). The 4-chlorobenzonitrile coupled with phenylboronic acid to afford the moderate amount of coupled product (entry 4). In the case of 2-chloro

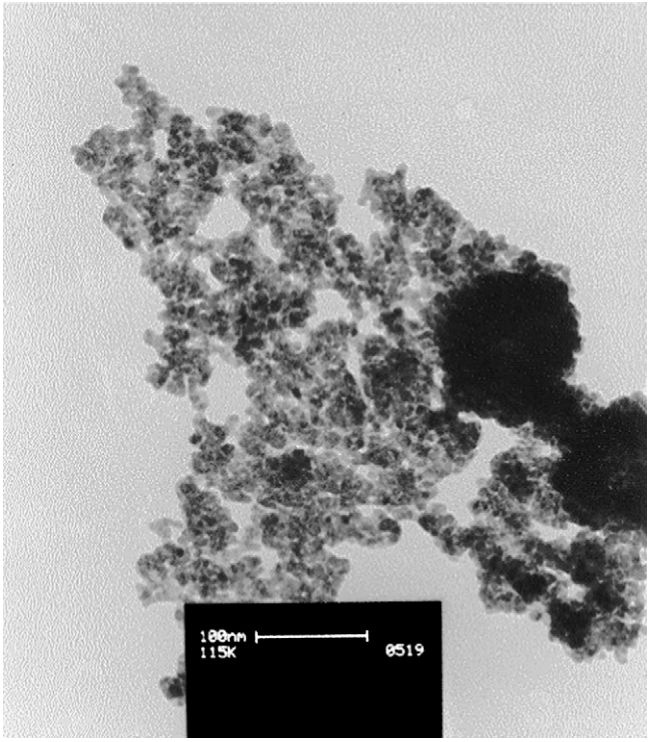


Figure 2. Only $Pd(COD)Cl_2$.

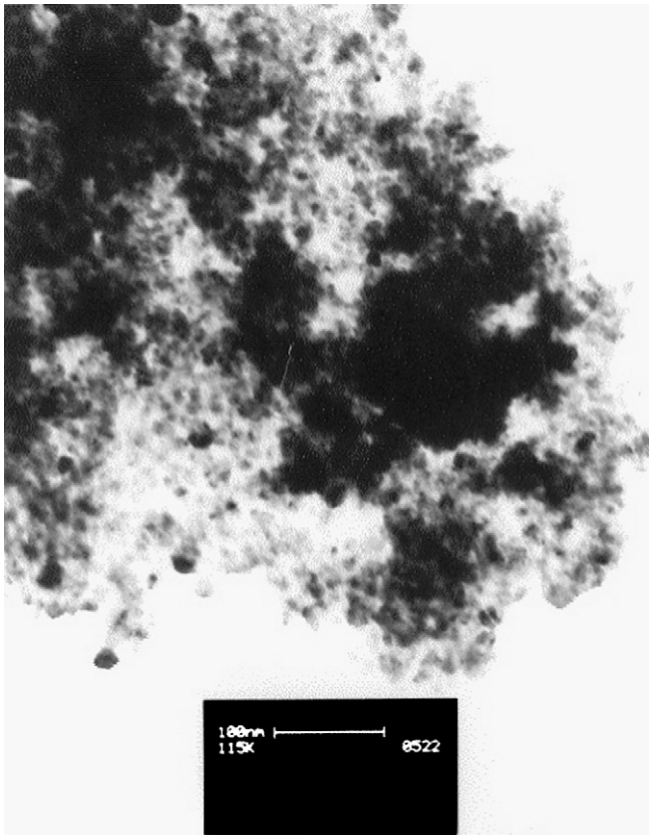


Figure 3. $Pd(COD)Cl_2$ and ligand **1**.

and 3-chlorotoluene, the yield of the coupled products was very low (entries 5 and 6).

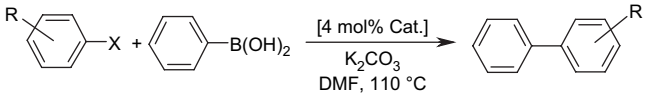
2.3. Suzuki coupling: catalyst stability

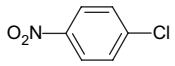
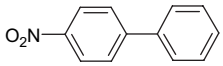
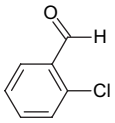
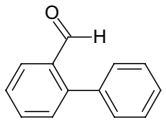
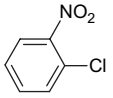
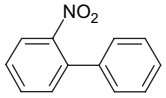
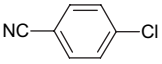
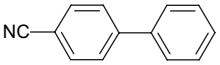
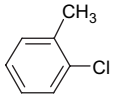
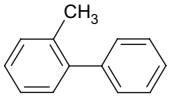
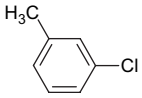
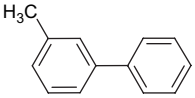
In order to judge the catalyst efficiency, a model reaction of 4-bromoacetophenone and phenylboronic acid was considered under the identical reaction conditions as described in Table 3. The reaction afforded 100% conversion within 30 min. After the completion of the reaction, the same amount of fresh substrate and the reagent (except catalyst) was added and the reaction was completed within 2 h with quantitative conversion. In the third cycle, the conversion was quantitative after 4 h.

2.4. Heck couplings of aryl halides with tert-butyl acrylate

Heck coupling reactions were carried out with 1 mol % of catalyst 1,4-bis(2-hydroxy-3,5-di-*tert*-butylbenzyl)piperazine/$[Pd(COD)Cl_2]$ (1:1) for aryl bromides. Under the optimized reaction conditions (K_2CO_3 as base, methanol as solvent at 60 °C) a range of aryl halides were coupled with *tert*-butyl acrylate. The results are summarized in the Table 6. Under typical reaction conditions, the electron deficient substrates coupled effectively with *tert*-butyl acrylate (entries 1–3), whereas the electron rich 4-bromoanisole, 2-bromo-6-methoxynaphthalene, and electron deficient 4-bromobenzonitrile afforded moderate amount of coupling product (entries 4–6).

Table 5
Suzuki cross-coupling of aryl chlorides with phenylboronic acid[a]



Entry	Aryl chloride	Product	Time	Yield[b](%)
1			30 min	81
2			8 h	77
3			19 h	74
4			4 h	51
5			24 h	46
6			24 h	32

[a] Reaction conditions: aryl chloride (0.5 mmol), phenylboronic acid (0.75 mmol), K_2CO_3 (1 mmol), DMF (5 mL), and catalyst (4 mol %) at 110 °C.

[b] Conversion to the coupled product determined by GC, based on aryl chlorides; average of two runs.

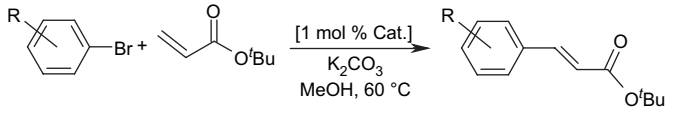
The heterocyclic bromide, 2-bromopyridine afforded moderate amount of yield when reacted with *tert*-butyl acrylate (entry 7). The electronically neutral bromobenzene coupled with *tert*-butyl acrylate to give 42% conversion of the coupled product (entry 8).

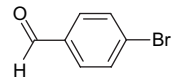
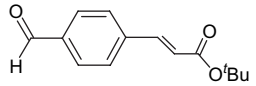
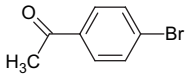
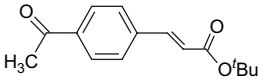
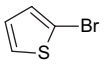
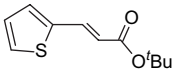
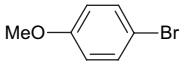
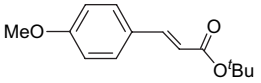
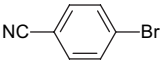
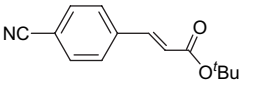
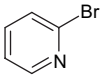
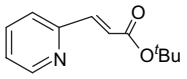
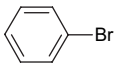
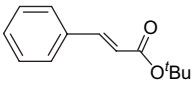
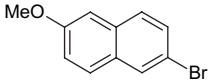
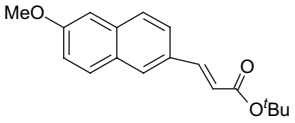
In the case of aryl chlorides, the in situ generated palladium complex effectively coupled with the *tert*-butyl acrylate under the same reaction conditions, however, 4 mol % of catalyst was required. The subsequent results are displayed in Table 7. When the electron deficient aryl chlorides, such as 1-chloro-2,4-dinitrobenzene, 1-chloro-4-benzonitrile, 1-chloro-2-nitrobenzene, 1-chloro-4-nitrobenzene, and 2-chloro benzaldehyde, coupled with *tert*-butyl acrylate afforded the corresponding coupled products in moderate amount of yields (entries 1–5).

3. Conclusions

The in situ (1:1) generated $[Pd(COD)Cl_2]$/1,4-bis(2-hydroxy-3,5-di-*tert*-butylbenzyl)piperazine complex represents an efficient catalyst system for the Suzuki–Miyaura and Heck–Mizoroki coupling reactions of aryl, benzyl bromides, and aryl chlorides. Under aerobic conditions good to excellent yields of coupled product were obtained. The stability of the palladium catalyst against air, moisture, and temperature and the fact that they can be synthesized from inexpensive and

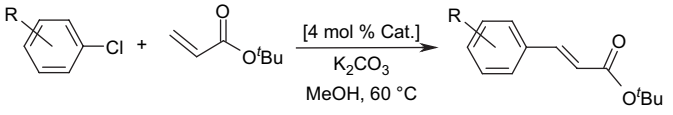
Table 6
Heck cross-coupling reactions of aryl bromides and *tert*-butyl acrylate[a]

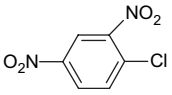
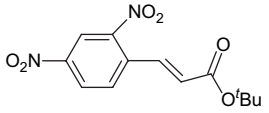
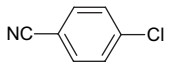
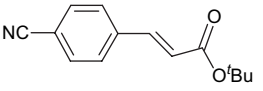
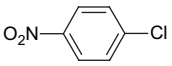
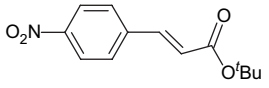
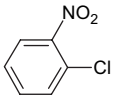
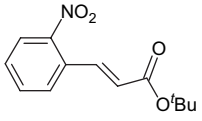
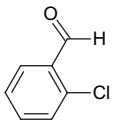
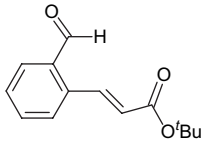
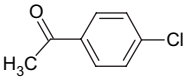
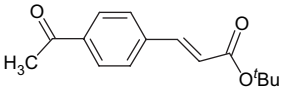


Entry	Aryl bromide	Product	Time (h)	Yield[b] (%)
1			3	87
2			3	80
3			7	72
4			3	65
5			3	62
6			20	58
7			3	41
8			3	40

[a] Reaction conditions: aryl bromide (0.5 mmol), *tert*-butyl acrylate (3 mmol), K_2CO_3 (1.4 mmol), MeOH (5 mL), and catalyst (1 mol %), at 60 °C.
[b] Conversion to the coupled product determined by GC, based on aryl bromides; average of two runs.

Table 7
Heck cross-coupling reactions of aryl chlorides and *tert*-butyl acrylate[a]



Entry	Aryl chloride	Product	Time (h)	Yield[b] (%)
1			3	67
2			5.5	65
3			3	63
4			3	63
5			3	52
6			6	34

[a] Reaction conditions: aryl chlorides (0.5 mmol), *tert*-butyl acrylate (3 mmol), K_2CO_3 (1.4 mmol), MeOH (5 mL), and catalyst (4 mol %) at 60 °C.
[b] Conversion to the coupled product determined by GC, based on aryl chlorides; average of two runs.

readily available starting materials using a straightforward procedure make this a very promising catalyst system. Further studies of its applicability in other organic transformations are currently under investigation.

4. Experimental

4.1. General

Most of the bromo and chloro compounds, phenylboronic acid, and *tert*-butyl acrylate were purchased from Aldrich. Anhydrous K_3PO_4, and K_2CO_3 were purchased from SIGMA chemicals and SDFINE chemicals, respectively, and used as such received without further purification. Technical grade methanol and DMF were used for all catalytic reactions. Gas chromatographic analyses were performed on a Perkin–Elmer Clarus 500 GC/Hewlett Packard G 1800A GCD System equipped with a packed column. ^{1}H NMR spectra were recorded on VRX 400 spectrometer operating at a frequency of 400 MHz. Chemical shifts are in parts per million using tetramethylsilane as internal standard. Microanalysis was carried out on a Carlo Erba Model 1106 elemental analyzer. Melting points of all compounds was determined on Vergo melting point apparatus and are uncorrected. Electro-spray ionization (EI) mass spectrometry experiments were carried out using Waters Q-Tof micro-YA-105.

*4.2. Synthesis of 1,4-bis(2-hydroxy-3,5-di-tert-butylbenzyl)piperazine (**1**)*

A mixture of piperazine (2.2 g, 25.54 mmol) and 40% aqueous formaldehyde solution (5.3 mL, 75.36 mmol) was dissolved in methanol (40 mL) and heated to reflux for 2 h to get a clear solution. To the cooled solution was added 2,4-di-*tert*-butylphenol (10.3 g, 50.41 mmol) in methanol (60 mL). The resulting solution was refluxed for further 12 h. The reaction mixture was cooled to room temperature and filleted off to get **1** as colorless crystalline compound. Yield: 65% (8.48 g, 16.23 mmol). Mp: >250 °C (dec). Anal. Calcd for $C_{34}H_{54}N_2O_2$: C, 78.11; H, 10.41; N, 5.35%. Found: C, 78.06; H, 10.25; N, 5.43%. ^{1}H NMR (400 MHz, $CDCl_3$, δ):

10.72 (br s, 2H, *OH*), 7.22 (s, 2H, *phenyl*), 6.84 (s, 2H, *phenyl*), 3.74 (s, 4H, CH_2), 2.92–2.68 (br s, 8H, NC_4H_8N), 1.44 (s, 18H, ^tBu), 1.33 (s, 18H, ^tBu). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 154.2 (s, *phenyl*), 140.9 (s, *phenyl*), 135.7 (s, *phenyl*), 123.7 (s, *phenyl*), 123.3 (s, *phenyl*), 120.4 (s, *phenyl*), 62.2 (s, CH_2), 52.3 (s, NCH_2), 35.1 (s, $C(Me)_3$), 34.2 (s, $C(Me)_3$), 31.8 (s, CH_3), 29.8 (s, CH_3). FTIR (KBr disc): ν_{OH}=3428 (br) cm^{-1}. MS (EI): *m/z* 523.6 $[M+H]^+$.

4.3. General procedure for the Suzuki coupling reaction

In a two-necked round bottom flask the appropriate amount of ligand, metal precursors, and 5 mL of solvent were placed with a magnetic stir bar. After stirring for 5 min, the aryl halide (0.5 mmol), aryl boronic acid (0.75 mmol), and base (1 mmol) were added to the reaction flask. The reaction mixture was heated to the appropriate temperature for the required time (the course of reaction was monitored by GC analysis) and then the solvent was removed under reduced pressure. The resultant residual mixture was diluted with H_2O (8 mL) and Et_2O (8 mL), followed by extraction twice (2×6 mL) with Et_2O. The organic fraction was dried ($MgSO_4$), filtered stripped of the solvent under vacuum, and the residue was redissolved in 5 mL of dichloromethane. An aliquot was taken with a syringe and subjected to GC/GC–MS analysis. Yields were calculated against consumption of the aryl halides. The crude material was purified by silica column chromatography using hexane–ethylacetate as an eluent to give the desired biaryls. For experiments with low catalyst loading and for comparison of other Pd(II) sources, stock solution of appropriate concentration was prepared by dissolving 1.0 mg of the palladium catalyst in appropriate amount of DCM and used for each independent run.

4.3.1. 4-Phenylbenzaldehyde[26a]

Yellow liquid. ^1H NMR (400 MHz, $CDCl_3$): δ 7.98–7.25 (m, *phenyl*, 9H), 10.04 (s, C*H*O, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 192.1 (*C*=O), 147.3 (s, *phenyl*), 139.8 (s, *phenyl*), 135.3 (s, *phenyl*), 130.4 (s, *phenyl*), 130.2 (s, *phenyl*), 129.2 (s, *phenyl*), 128.9 (s, *phenyl*), 128.6 (s, *phenyl*), 128.4 (s, *phenyl*), 127.8 (s, *phenyl*), 127.5 (s, *phenyl*). MS (EI): *m/z* 182.0 $[M]^+$.

4.3.2. 4-Acetylbiphenyl

White powder. Mp: 126–128 °C (lit.[26b] 123 °C) Anal. Calcd for $C_{14}H_{12}O$: C, 85.68; H, 6.16. Found: C, 86.20; H, 6.49%. ^1H NMR (400 MHz, $CDCl_3$): δ 8.05–7.26 (m, *phenyl*, 9H), 2.65 (s, CH_3, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 198.0 (*C*=O), 146.0 (s, *phenyl*), 140.1 (s, *phenyl*), 136.0 (s, *phenyl*), 129.1 (s, *phenyl*), 129.6 (s, *phenyl*), 128.4 (s, *phenyl*), 127.5 (s, *phenyl*), 127.4 (s, *phenyl*), 26.7 (CH_3). MS (EI): *m/z* 196.0 $[M]^+$.

4.3.3. [1,1′-Biphenyl]-4-carbonitrile

White powder. Mp: 83–85 °C (lit.[26c] 85–86 °C). ^1H NMR (400 MHz, $CDCl_3$): δ 7.77–7.26 (m, *phenyl*, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 145.9 (s, *phenyl*), 139.4 (s, *phenyl*), 132.8 (s, *phenyl*), 129.3 (s, *phenyl*), 128.8 (s, *phenyl*), 127.9 (s, *phenyl*), 127.4 (s, *phenyl*), 119.1 (*C*≡N), 111.1 (*C*–C≡N). Anal. Calcd for $C_{13}H_9N$: C, 87.12; H, 5.06; N, 7.81. Found: C, 86.22; H, 5.03; N, 7.70%. MS (EI): *m/z* 179.0 $[M]^+$.

The following compounds gave data consistent with those published: Table 3, entries 4,[26d] 5,[26e] 6,[26f] 7,[26g] 8,[26e] 9,[22h] 10,[26e] and 11,[26h] and Table 5, entries 1,[26e] 2,[26i] 3,[26j] 4,[26c] 5,[26k] and 6.[26l]

4.4. General procedure for the Mizoroki–Heck reaction

In a two-necked round bottom flask the appropriate amount of ligand, metal precursors, and 5 mL of solvent were placed with a magnetic stir bar. After stirring for 5 min, the *tert*-butyl acrylate (3 mmol), aryl halide (1 mmol), and base (1.4 mmol) were added to the reaction flask. The reaction mixture was heated to 60 °C for the required time (the course of reaction was monitored by GC analysis) under aerobic conditions and then the solvent was removed under reduced pressure. The resultant residual mixture was diluted with H_2O (8 mL) and Et_2O (8 mL), followed by extraction twice (2×6 mL) with Et_2O. The organic fraction was dried ($MgSO_4$), filtered stripped of the solvent under vacuum and the residue was redissolved in 5 mL of dichloromethane. An aliquot was taken with a syringe and subjected to GC analysis. Yields were calculated against consumption of the aryl halides.

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20. Crystal data for **1**: $C_{34}H_{54}N_2O_2$, M_w=522.79, triclinic, *P*-1 (no. 2), a=6.066(2) Å, b=10.015(3) Å, c=13.950(4) Å, V=776.4(4) Å^3, Z=1, D_c=1.118 g cm^{-3}, μ(Mo Kα)=0.068 mm^{-1}, F(000)=288, GOF=0.923, T=100 K, data were collected on a Bruker Smart APEX CCD diffractometer using Mo Kα radiation. A total of 3688 reflections ($1.5<\theta<23.3$) were processed of which 3688 were unique. The final *wR*2 value was 0.1364 (all data) and $R1$=0.0596 [$I>2\sigma(I)$]. CCDC reference no. 661941.
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