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Suzuki–Miyaura cross-coupling of aryl chlorides catalyzed by palladium precatalysts of *N*/*O*-functionalized pyrazolyl ligands

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ABSTRACT

A series of palladium complexes, *trans*-[1-(R)-$pz^{3,5\text{-}Me_2}$]$_2PdCl_2$ {R = $CH_2CONH(2,6\text{-}i\text{-}Pr_2\text{-}C_6H_3)$ (**1b**) and 2-(OH)-C_6H_{10} (**2b**)}, supported over *N*/*O*-functionalized pyrazole derived ligands effectively catalyzed the more challenging Suzuki–Miyaura cross-coupling of a variety of activated aryl chlorides with phenyl boronic acid in air in a mixed-aqueous medium (DMF:H_2O, v/v = 9:1) in moderate to excellent yields. Besides the commonly encountered C_{sp2}–C_{sp2} coupling, the **1b** and **2b** precatalysts also catalyzed the relatively difficult C_{sp2}–C_{sp3} coupling of benzyl chloride with phenyl boronic acid. The **1b** and **2b** complexes were synthesized by the direct reaction of the respective *N*/*O*-functionalized pyrazolyl ligands, **1a** and **2a**, with (COD)$PdCl_2$ in 62–66% yields. The stability of the pyrazole–palladium interaction in the **1b** and **2b** complexes has been attributed to the deeply buried $N_{pyrazole}$–Pd interaction as evidenced from the density functional theory (DFT) studies.

1. Introduction

Among the various C–C bond forming reactions, vigorous activities are seen in the area of developing newer and better catalysts for the construction of biaryl frameworks employing the Suzuki–Miyaura cross-coupling methodology. The Suzuki–Miyaura cross-coupling reaction offers numerous advantages like the use of less toxic boronic acid and ester starting materials, mild and operationally easy reaction conditions, use of aqueous inorganic bases, functional group tolerance, coupling of sterically hindered substrates and high regio- and stereo-selectivities [1–4] over the other related protocols like Hiyama [5–7], Stille [8–10] and Negishi [11] couplings available for synthesizing various biaryl frameworks [12]. The wide diversity, easy availability and low cost of aryl chlorides compared to the bromide or iodide analogs, make them more valuable a substrate for the Suzuki–Miyaura cross-coupling reaction [13–16]. However, a formidable challenge lies in the low reactivity of the aryl chlorides that arises from the high C–Cl bond energy [bond dissociation energy (kcal/mol) for Ph-X: Cl (95), Br (80), I (65)] [17,18], and consequently aryl chlorides are inherently reluctant towards undergoing oxidative addition, the first step in the cross-coupling reaction.

Though phosphines like PPh_3 have been traditionally used in the Suzuki–Miyaura cross-coupling reaction, the introduction of new ligands has significantly improved the efficiency as well as the selectivity of the coupling reaction. For example, strongly σ-donating and sterically demanding N-heterocyclic carbenes [19–24] as well as the less basic N-donor ligands [25–27] have been successfully employed in designing catalysts for the Suzuki–Miyaura coupling of aryl chlorides. In this regard, the efforts are directed towards designing cost-effective catalysts that are readily accessible, moisture and air stable and function under ambient conditions.

Though the N-based ligands display excellent tendency for the complexation with palladium and the resultant palladium precatalysts have been employed in various cross-coupling reactions [28–30], only a few reports are known of their use in the coupling of aryl chlorides, the most of which are of pyridyl based systems [25,27,31]. Quite significantly, a recent study highlighted the promising potential of pyrazole based precatalysts by demonstrating that the substitution of a N-heterocyclic carbene moiety in a benzimidazole ligand supported palladium precatalyst by a pyrazole moiety led to significant enhancements in the catalytic activity in the Suzuki–Miyaura cross-coupling of aryl chlorides [32]. Because of the aforementioned reasons, we became interested in exploring the utility of pyrazole based palladium complexes in the Suzuki–Miyaura coupling of aryl chlorides.

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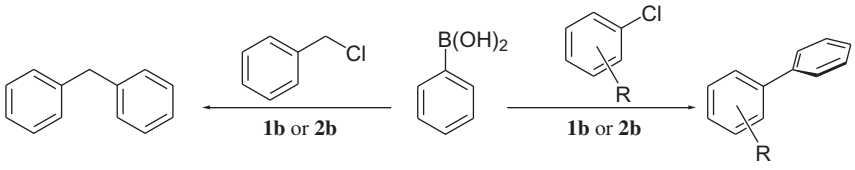
One of our research interests lies in advancing the chemistry of N-heterocyclic carbenes (NHCs) [33–43] by exploring their utility in a variety of C–C bond forming reactions like the palladium mediated Suzuki–Miyaura [44–46], Sonogashira [47–50] and Hiyama [49] couplings to the nickel mediated Michael [51,52] addition reactions. With regard to the Suzuki–Miyaura reaction, we have recently reported several palladium precatalysts of *N*/*O*-functionalized N-heterocyclic carbenes for the cross-coupling of aryl bromide and iodide substrates [44–46]. Progressing further along this theme of research, we became interested in designing Suzuki–Miyaura precatalysts for the more challenging aryl chloride substrates and proposed to do so by employing *N*/*O*-functionalized pyrazolyl ligand based catalysts for the same.

Here in this contribution, we report two new palladium precatalysts, **1b** and **2b**, supported over *N*/*O*-functionalized pyrazolyl ligands that conveniently carried out the Suzuki–Miyaura coupling of activated aryl chloride substrates with phenyl boronic acid in air in a mixed-aqueous medium [Fig. 1 and Eq. (1)]. The nature of bonding in the **1b** and **2b** complexes as probed by density functional theory (DFT) studies revealed the presence of reasonably strong σ-bonding $N_{pyrazole}$–Pd interactions in these complexes.



(1)

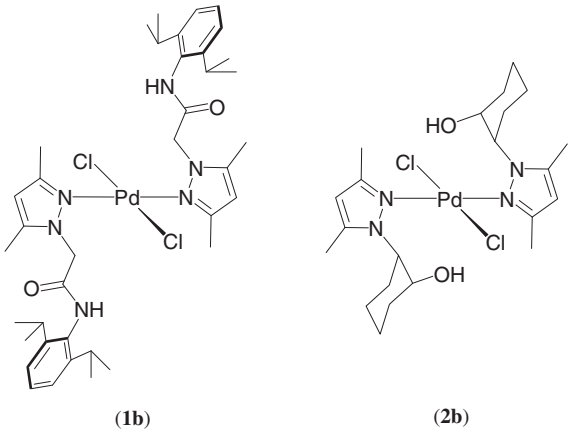
R = NO_2, CHO, COPh, CN, CF_3, $COCH_3$, H

2. Results and discussion

Two *N*/*O*-functionalized pyrazole derived ligands namely, 1-[(*N*-2,6-diisopropylphenyl)-2-acetamido]-3,5-dimethylpyrazole (**1a**) and 1-(2-hydroxy-cyclohexyl)-3,5-dimethylpyrazole (**2a**), were employed in designing suitable palladium precatalysts **1b** and **2b** for use in the Suzuki–Miyaura cross-coupling of aryl chlorides substrates with phenyl boronic acids. Specifically, the palladium complexes **1b** and **2b** were synthesized from the respective ligands, **1a** and **2a**, by the direct reaction with $(COD)PdCl_2$ in refluxing benzene in 62–66% yields (Schemes 1 and 2). The amido-functionalized pyrazolyl ligand **1a** was synthesized by the reaction of 3,5-dimethylpyrazole with *N*-2,6-diisopropylphenyl-2-chloroacetamide in the presence of Na_2CO_3 as a base in 46% yield. The hydroxyl-functionalized pyrazole ligand **2a** was synthesized by a modified literature procedure [53].

The palladium complexes **1b** and **2b** have been characterized by ^1H and $^{13}C\{^1H\}$ NMR, infrared spectroscopy, elemental analysis and the X-ray diffraction studies. Notable is the ^1H NMR spectrum of **1b** in which the methyl substituents on the pyrazole ring of the ligand appeared as two singlets at 2.94 ppm and 2.42 ppm, while the amido-NH moiety appeared downfield shifted at 8.33 ppm. The infrared spectrum of **1b** showed the characteristic amido stretch (ν_{CONH}) at 1689 cm^{-1}. Similarly for the **2b** complex, the methyl resonances of the pyrazole ring appeared at 2.45 ppm and 2.32 ppm. The characteristic OH stretch (ν_{OH}) of the cyclohexyl ring in the **2b** complex appeared at 3447 cm^{-1}.

The molecular structures of **1b** and **2b**, as determined by X-ray diffraction studies, revealed the monomeric nature of these complexes bearing a 2:1 ligand to metal stoichiometry with the metal center residing in a square-planar environment (Figs. 2 and 3, and Table 1). The two pyrazolyl ligands as well as the two chlorine atoms in both the palladium **1b** and **2b** complexes were at mutually *trans* dispositions to each other presumably due to steric reasons. The Pd–N distances in **1b** [2.009(2) Å] and **2b** [2.011(3) Å] compared well with the sum of the individual covalent radii of palladium and nitrogen (2.07 Å) [54] and also with the other related structurally characterized pyrazole based palladium complexes like, *trans*-(3,5-*di*-*tert*-butyl-pyrazole)$_2PdCl_2$ [2.020(2) Å and 2.013(2) Å] [55] and *trans*-(3,5-*di*-*tert*-butyl-pyrazole)$_2$Pd(Me)Cl [2.035(3) Å and 2.041(3) Å] [55]. Along the similar lines, the observed Pd–Cl distances [2.2925(9) Å (**1b**) and 2.3007(12) Å (**2b**)] too compared well with the sum of the covalent radii of palladium and chlorine (2.38 Å) [54]. As a final point, the two pyrazole rings in the palladium **1b** and **2b** complexes were found to be coplanar to each other.

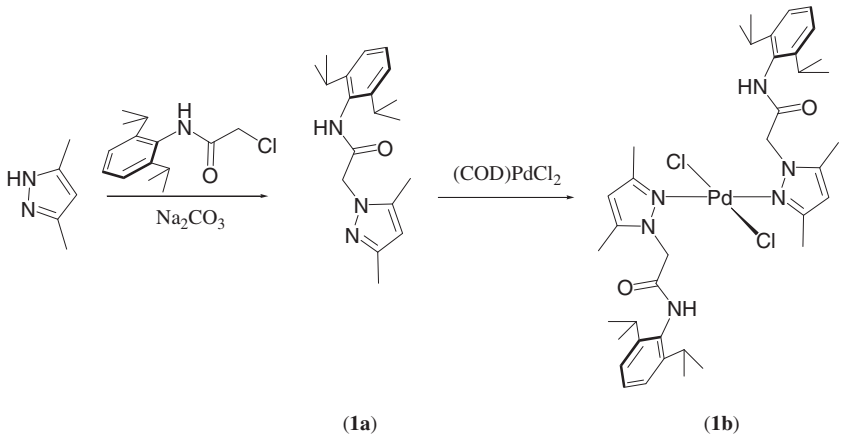


(**1b**) (**2b**)

Fig. 1. Palladium complexes of *N*/*O*-functionalized pyrazolyl ligands.

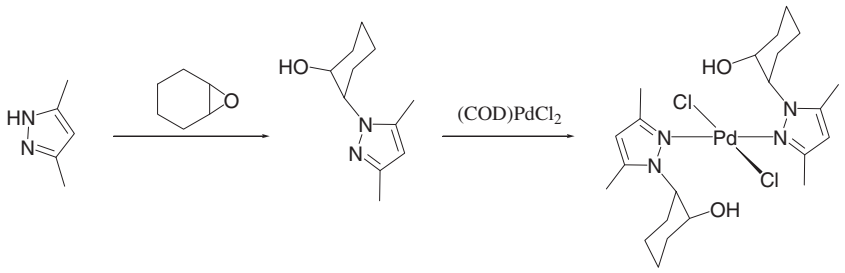
With the intent of gaining deeper insight into the nature of the pyrazole–palladium interaction in the **1b** and **2b** complexes, detailed density functional theory (DFT) studies were undertaken. Specifically, single-point calculations were performed on the **1b** and **2b** complexes at the B3LYP/SDD, 6-31G(d) level of theory using atomic coordinates adopted from X-ray analysis using Natural Bond Orbital (NBO) method for a greater understanding of the electronic properties of these complexes (see Supplementary material Tables S1 and S2). Importantly, the electron donation from the pyrazolyl ligand moiety to the palladium center in the **1b** and **2b** complexes is evident from both the natural and Mulliken charge analyses that revealed significant enhancements in the electron density at the metal center in **1b** and **2b,** as compared to that in the $PdCl_2$ fragment (see Supplementary material Tables S3 and S4). In addition, the NBO analysis revealed that the electron donation from the pyrazolyl ligand occurred on to the *5s* orbital of the palladium center in the **1b** and **2b** complexes (see Supplementary material Table S5).

An estimate of the strength of pyrazole–palladium interaction in the **1b** and **2b** complexes was obtained by computing the



(**1a**) (**1b**)

Scheme 1.



(**2a**) (**2b**)

Scheme 2.

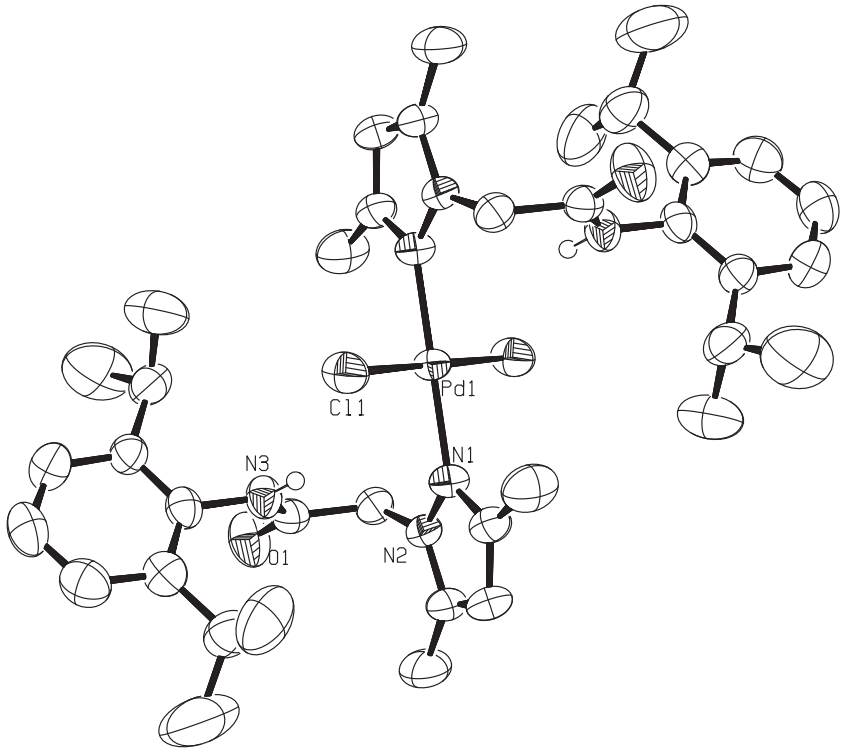


Fig. 2. ORTEP of **1b**. Selected bond lengths (Å) and angles (°): Pd1–N1 2.009(2), Pd1–Cl1 2.2925(9), N1–N2 1.361(3), N1–Pd1–N1 180.00(11), Cl1–Pd1–Cl1 180.00, N1–Pd1–Cl1 89.28(7).

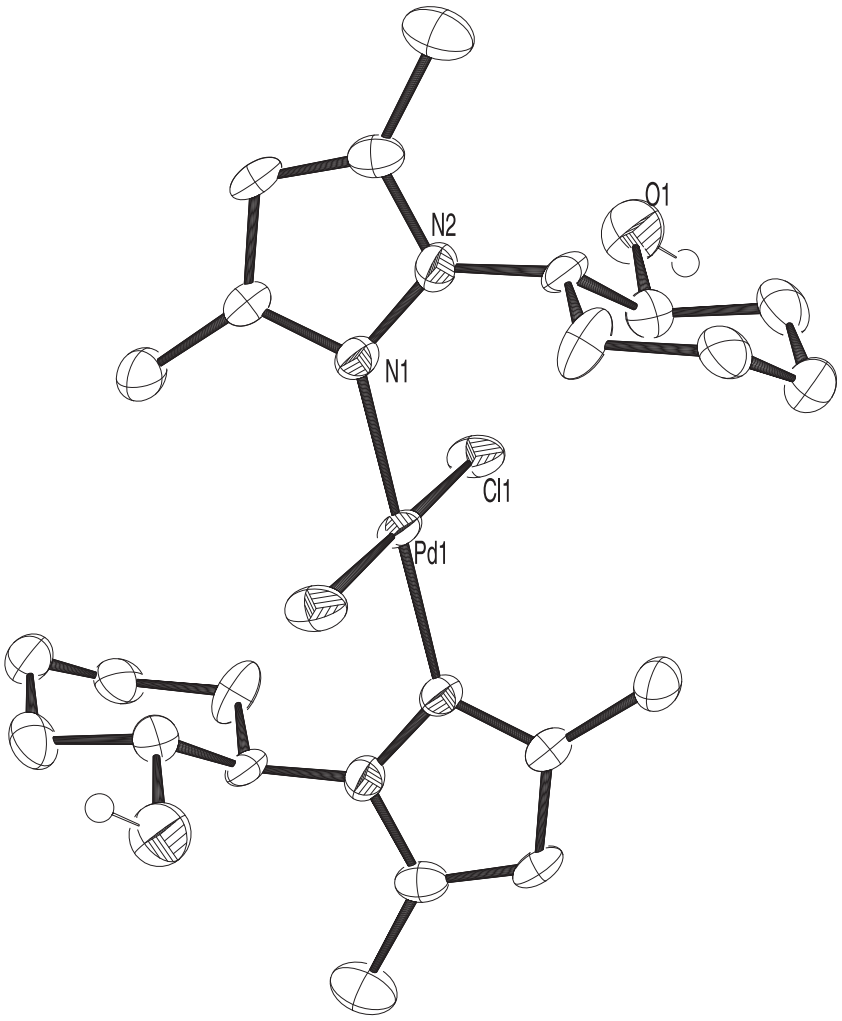


Fig. 3. ORTEP of **2b**. Selected bond lengths (Å) and angles (°): Pd1–N1 2.010(3), Pd1–Cl1 2.3043(11), N1–N2 1.365(5), N1–Pd1–N1 180.0(2), Cl1–Pd1–Cl1 180.00(9), N1–Pd1–Cl1 91.88(11).

Table 1
X-ray crystallographic data for palladium **1b** and **2b** complexes.

Compound	**1b**	**2b**
Lattice	triclinic	triclinic
Formula	$C_{40}H_{59}Cl_4N_6PdO_3$	$C_{22}H_{36}Cl_2N_4O_2Pd$
Formula weight	920.13	565.87
Space group	$P\bar{1}$	$P\bar{1}$
a (Å)	11.2709(5)	8.2440(6)
b (Å)	11.6167(5)	8.3641(7)
c (Å)	18.2802(8)	11.2128(8)
α (°)	78.777(4)	104.313(7)
β (°)	85.015(3)	104.015(6)
γ (°)	85.450(4)	102.973(7)
V (Å^3)	2334.01(18)	692.81(9)
Z	2	2
T (K)	150(2)	120(2)
Radiation (λ, Å)	0.71073	0.71073
ρ (calcd.) (g cm^{-3})	1.309	1.579
μ (Mo Kα) (mm^{-1})	0.667	1.084
θ max (°)	32.6381	32.5485
No. of data	8221	2424
No. of parameters	511	208
R_1	0.0355	0.0484
wR_2	0.0832	0.1286
Goodness-of-fit (GOF)	0.928	1.084

$N_{pyrazole}$–Pd bond dissociation energies, D_e/(Pd–pyrazole), **1b** (48.14 kcal/mol) and **2b** (47.18 kcal/mol), at the B3LYP/SDD, 6-31G(d) level of theory, which pointed towards a reasonably strong interaction (see Supplementary material Table S6). Additional understanding of the pyrazole–Pd interaction in **1b** and **2b** was obtained from the molecular orbital (MO) correlation diagram, constructed from the interaction of the individual fragment molecular orbitals (FMOs) of the pyrazolyl ligand fragment with the $PdCl_2$ fragment in these complexes using AOMIX software [56]. Of particular relevance is the σ-interaction between the pyrazole moiety and the palladium center in the **1b** and **2b** complexes as represented by the following molecular orbitals (MOs), HOMO-59 (**1b**) and HOMO-35 (**2b**) (Figs. 4 and 5 and see Supplementary material Figs. S1 and S2). Worth pointing out that the deep-seated nature of the molecular orbitals (MO's) depicting pyrazole–Pd σ-interaction in these complexes indicate towards a stable ligand–metal interaction.

Significantly enough, both the palladium **1b** and **2b** complexes efficiently catalyzed the Suzuki–Miyaura cross-coupling of aryl chlorides with phenyl boronic acid in air in a mixed-aqueous medium. In particular, when a mixture of the aryl chloride and phenyl boronic acid were heated at 120 °C in presence of 2 mol% of the precatalysts, **1b** and **2b**, along with tetrabutylammonium bromide (TBAB) in DMF:H_2O (9:1 v/v) in air, the cross-coupled products were obtained in a relatively short reaction period of 5 h (Eq. (1)). Remarkably enough, a wide variety of activated aryl chloride substrates, namely o/p-ClC_6H_4X (X = NO_2, CN, COPh, CHO, CF_3,

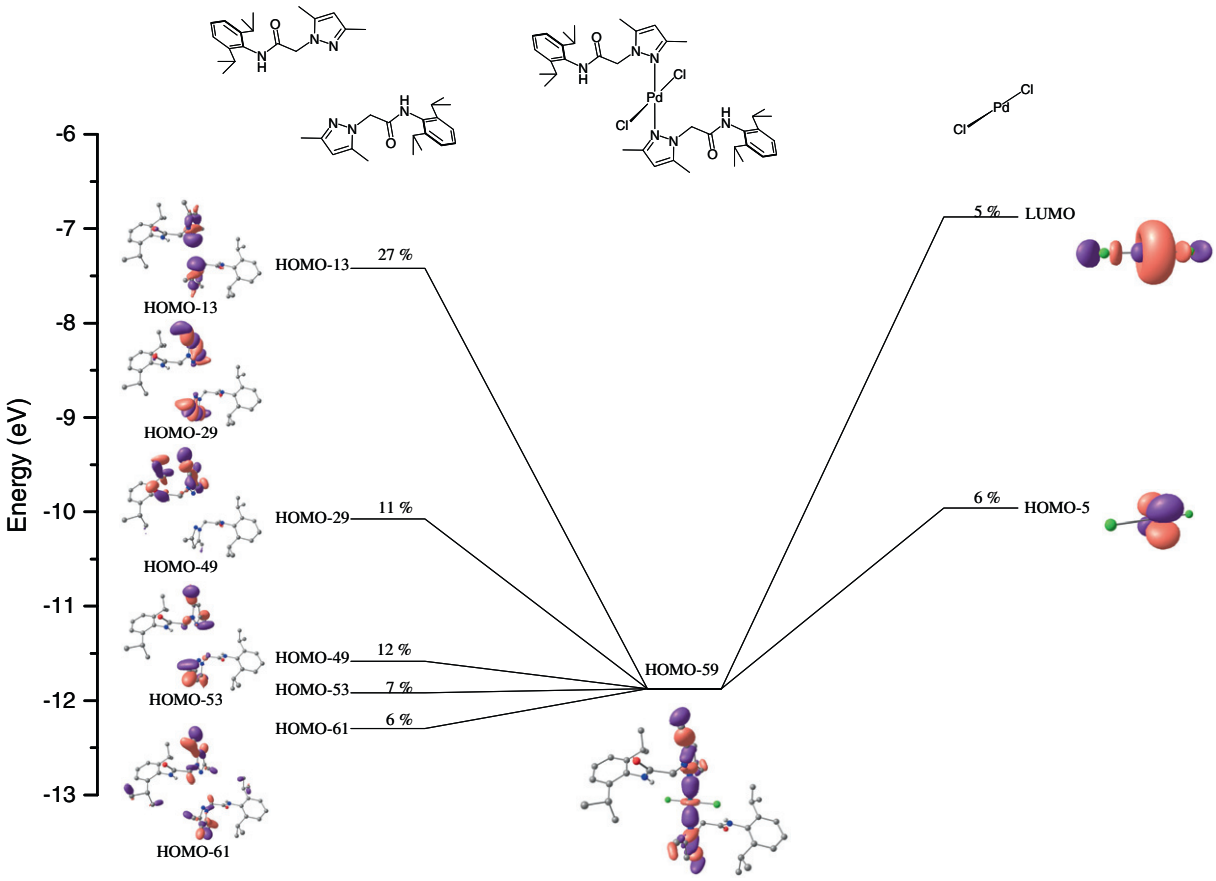


Fig. 4. Simplified orbital interaction diagram showing major contributions to the pyrazole–palladium bond in **1b**.

$COCH_3$ and H), were converted to the respective biaryl products in moderate to excellent yields (23% to >99%) (Table 2). Apart from the commonly explored C_{sp2}–C_{sp2} coupling, the palladium **1b** and **2b** complexes also catalyzed the more challenging C_{sp2}–C_{sp3} coupling of benzyl chlorides with phenyl boronic acid in good to excellent yields (55% to >99%) (Table 2). In order to underscore the practical efficacy of biaryl synthesis using the Suzuki–Miyaura cross-coupling of aryl chlorides catalyzed by these palladium **1b** and **2b** complexes, the isolated yields were obtained for a representative precatalyst **1b** (Table 2).

Indeed, the considerable enhancement of up to 84% obtained with the palladium **1b** and **2b** precatalysts over the control experiment, performed using a simple precursor like (COD)$PdCl_2$, highlighted the presence of significant "ligand-influence" in the cross-coupling reactions of these catalysts. The homogeneous nature of catalysis by the **1b** and **2b** complexes was ascertained by carrying out the 'classical Hg-drop' test [57,58] that showed trivial effect on the catalysis results (see Supplementary material Table S7).

Important among the palladium complexes reported for the Suzuki–Miyaura cross-coupling reaction of aryl chlorides are the ones of the N-heterocyclic carbene [59–62], phosphine [63–65] and of the various N-donor [66,67] ligands. For example, the pyrimidine functionalized N-heterocyclic carbene based palladium complex, [3-(mesityl)-1-(pyrimidin-2-yl)imidazol-2-ylidene]$PdCl_2$, catalyzed the cross-coupling of a variety of electronically modulated aryl chloride substrates in moderate to excellent yields (15–95%) at 1 mol% of the catalyst loading in a mixed-aqueous medium at 80–120 °C over a period of 2–12 h [68]. Analogously, the palladium, *cis*-[1-benzyl-3-(*N*-phenyl-2-acetamido)-imidazo-2-ylidene]-Pd(PCy_3)Cl_2 and *cis*-[1-benzyl-3-(*N*-phenyl-2-acetamido)-imidazolin-2-ylidene]Pd(PCy_3)Cl_2, complexes carried out the coupling of aryl chloride substrates with phenyl boronic acid in near quantitative (82–100%) yields at a loading of 1–3 mol% at 80 °C in dioxane [69]. We are aware of only one report of a pyrazole based palladium precatalyst namely, [2-(1-propylbenzimidazolylmethyl)-3,5-*di*-*tert*-butyl-pyrazole]$PdCl_2$, that performed the Suzuki–Miyaura coupling of aryl chlorides in moderate to good yield (32–52%) at a catalyst loading of 0.2–2.0 mol% in CH_3OH under ambient conditions [32]. Thus, in the backdrop of the paucity of pyrazole based palladium precatalysts for the cross-coupling of aryl chlorides substrates, the *N*/*O*-functionalized pyrazole based **1b** and **2b** precatalysts assume significance.

3. Conclusions

In summary, two new palladium precatalysts, **1b** and **2b**, derived from *N*/*O*-functionalized pyrazolyl ligands have been evaluated for their performance in carrying out the highly desirable Suzuki–Miyaura cross-coupling of aryl chloride substrates with phenyl boronic acid. A wide variety of activated aryl chloride substrates, namely *o*/*p*-ClC_6H_4X (X = NO_2, CN, COPh, CHO, CF_3, $COCH_3$ and H), were converted to the respective biaryl products in moderate to excellent yields over a short period of reaction time of 5 h. The density functional theory studies performed on the **1b** and **2b** complexes attributed the stability of the pyrazole–palladium interaction to the deeply-seated nature of the $N_{pyrazole}$–Pd σ-bonding orbital.

4. Experimental

4.1. General procedures

All manipulations were carried out using standard Schlenk techniques. Solvents were purified and degassed by standard

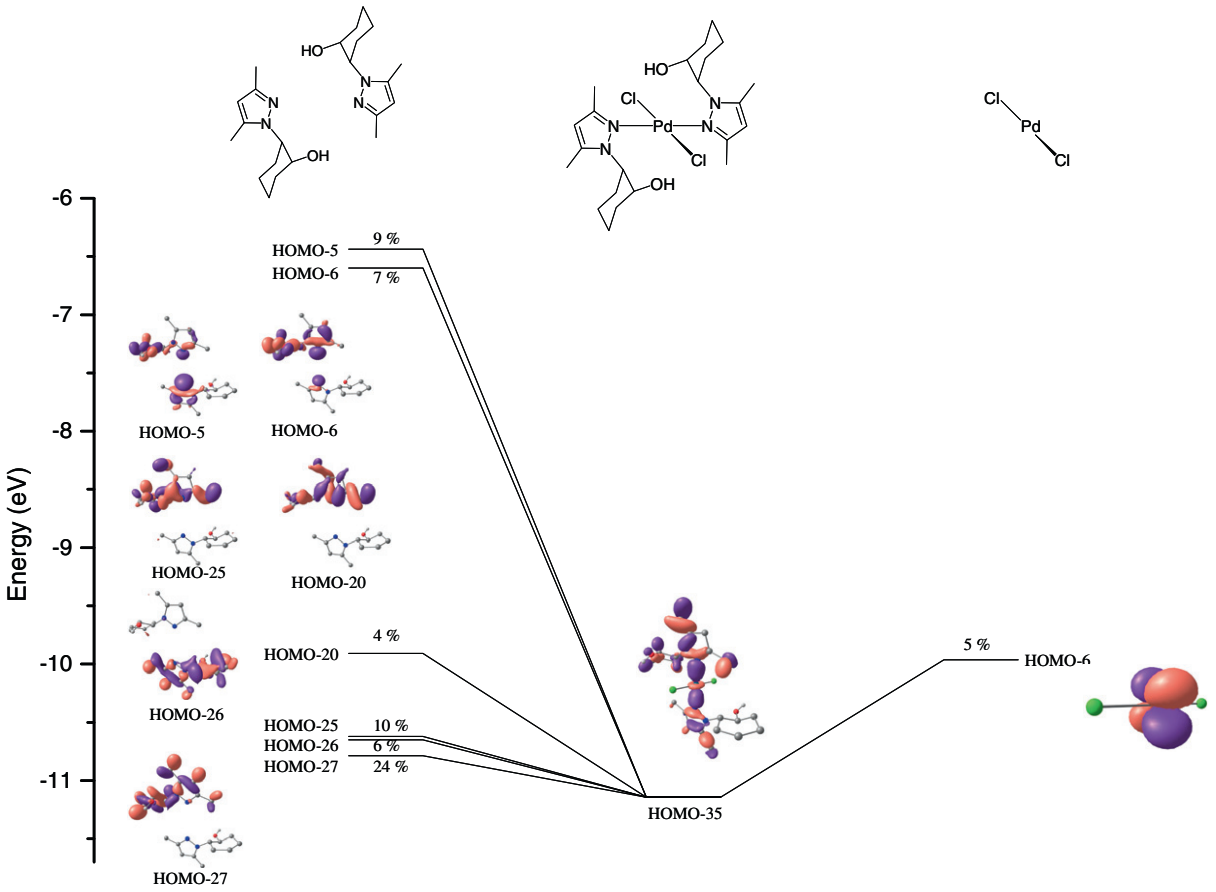


Fig. 5. Simplified orbital interaction diagram showing major contributions to the pyrazole–palladium bond in **2b**.

Table 2
Selected results for Suzuki–Miyaura cross-coupling reaction of aryl chlorides catalyzed by **1b** and **2b**.

Entry	Reagent[a]	Reagent[a]	Cross-coupled product	Yield[b]	
				1b	**2b**
1	O_2N–Cl	$(HO)_2B$–	O_2N–	>99 (81)	>99
2	NC–Cl	$(HO)_2B$–	NC–	94 (76)	>99
3	PhOC–Cl	$(HO)_2B$–	PhOC–	>99 (85)	>99
4	OHC–Cl	$(HO)_2B$–	OHC–	93 (82)	>99
5	CHO, Cl	$(HO)_2B$–	CHO	>99 (87)	>99
6	F_3C–Cl	$(HO)_2B$–	F_3C–	>99 (77)	>99
7	H_3COC–Cl	$(HO)_2B$–	H_3COC–	>99 (72)	>99
8	Cl	$(HO)_2B$–		23	27
9	Cl	$(HO)_2B$–		55	>99

[a] *Reaction conditions:* 1.00 mmol of aryl chloride, 1.20 mmol of boronic acid, 1.50 mmol of Cs_2CO_3, 1.50 mmol of TBAB, 2 mol% of catalyst **1b**–**2b** in 8 mL of DMF:H_2O (9:1), at 120 °C for 5 h.

[b] The yields (%) were determined by GC using diethylene glycol di-*n*-butyl ether as an internal standard. Isolated yields for representative runs using **1b** are given in the parentheses.

procedures [70]. 2,6-Diisopropylaniline and cyclohexene oxide were purchased from Sigma–Aldrich, Germany while chloroacetyl chloride was purchased from Spectrochem, India and used without any further purification. The 1-(2-hydroxy-cyclohexyl)-3,5-dimethylpyrazole (**2a**) [53] and *N*-(2,6-diisopropylphenyl)-2-chloroacetamide [71] were synthesized by modification of the procedures reported in literature. ^{1}H and ^{13}C{^{1}H} NMR spectra were recorded on a Varian 400 MHz NMR spectrometer. ^{1}H NMR peaks are labeled as singlet (s), doublet (d), triplet (t), septet (sept) and multiplet (m). Mass spectrometry measurements were done on a Micromass Q-Tof spectrometer. Infrared spectra were recorded on a Perkin–Elmer Spectrum One FT-IR spectrometer. X-ray diffraction data were collected on a Bruker P4 diffractometer equipped with a SMART CCD detector and crystal data collection and refinement parameters are summarized in Table 1. The structures were solved using direct methods and standard difference map techniques, and were refined by full-matrix least-squares procedures on F^2 with SHELXTL (Version 6.10) [72,73]. GC spectra were obtained on a Perkin–Elmer Clarus 600 equipped with a FID. GCMS spectra were obtained on a Perkin–Elmer Clarus 600 T equipped with an EI source. Elemental Analysis was carried out on Thermo Quest FLASH 1112 SERIES (CHNS) Elemental Analyzer.

4.2. Synthesis of 1-[*N*-(2,6-diisopropylphenyl)-2-acetamido]-3,5-dimethylpyrazole (*1a*)

A mixture of 3,5-dimethylpyrazole (0.961 g, 10.0 mmol), *N*-2,6-diisopropylphenyl-2-chloroacetamide (2.53 g, 9.98 mmol) and Na_2CO_3 (1.69 g, 15.9 mmol) was refluxed in acetonitrile (*ca.* 60 mL) for 16 h, after which the reaction mixture was cooled to room temperature and filtered. The filtrate was concentrated under vacuum to yield the crude product which was purified by repeated washing with hot water (*ca.* 3 × 30 mL) to yield the product **1a** as an off-white solid (1.43 g, 46%). ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 7.55 (br, 1H, CON*H*), 7.13 (t, 1H, $^3J_{HH}$ = 8 Hz, *p*-C_6H_3), 7.01 (d, 2H, $^3J_{HH}$ = 8 Hz, *m*-C_6H_3), 5.80 (s, 1H, C_3N_2H), 4.71 (s, 2H, CH_2), 2.75 (sept, 2H, $^3J_{HH}$ = 6 Hz, $CH(CH_3)_2$), 2.27 (s, 3H, CH_3), 2.16 (s, 3H, CH_3), 1.06 (d, 12H, $^3J_{HH}$ = 6 Hz, $CH(CH_3)_2$). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz, 25 °C) δ 167.4 (*C*ONH), 150.0 (C_3N_2H), 145.9 (C_3N_2H), 141.0 (*ipso*-C_6H_3), 130.5 (*p*-C_6H_3), 128.6 (*m*-C_6H_3), 123.6 (*o*-C_6H_3), 106.6 (C_3N_2H), 52.4 (CH_2), 28.9 ($CH(CH_3)_2$), 23.6 ($CH(CH_3)_2$), 13.5 (CH_3), 11.1 (CH_3). IR data (KBr pellet cm^{-1}): 1673 (s) (ν_{CONH}). HRMS (ES): Calcd. for $[M+H]^+$ 314.2232, found *m*/*z* 314.2233.

4.3. Synthesis of {[1-*N*-(2,6-diisopropylphenyl)-2-acetamido]3,5-dimethylpyrazole}$_2$PdCl$_2$ (*1b*)

A mixture of 1-[*N*-(2,6-diisopropylphenyl)-2-acetamido]-3,5-dimethylpyrazole (**1a**) (0.313 g, 1.00 mmol) and (COD)$PdCl_2$ (0.142 g, 0.497 mmol) was refluxed in benzene (*ca.* 20 mL) for 12 h. The reaction mixture was filtered and the filtrate was concentrated under vacuum to yield the product **1b** as a yellow solid (0.246 g, 62%). ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.33 (br, 2H, CON*H*), 7.25 (t, 2H, $^3J_{HH}$ = 8 Hz, *p*-C_6H_3), 7.10 (d, 4H, $^3J_{HH}$ = 8 Hz, *m*-C_6H_3), 6.15 (s, 2H, C_3N_2H), 5.90 (br, 4H, CH_2), 2.94 (s, 6H, CH_3), 2.82 (sept, 4H, $^3J_{HH}$ = 6 Hz, $CH(CH_3)_2$), 2.42 (s, 6H, CH_3), 1.14 (d, 24H, $^3J_{HH}$ = 6 Hz, $CH(CH_3)_2$). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz, 25 °C) δ 165.0 (*C*ONH), 151.5 (C_3N_2H), 146.1 (C_3N_2H), 145.5 (*ipso*-C_6H_3), 129.9 (*p*-C_6H_3), 128.7 (*m*-C_6H_3), 123.5 (*o*-C_6H_3), 109.2 (C_3N_2H), 55.1 (CH_2), 28.7 ($CH(CH_3)_2$), 23.7 ($CH(CH_3)_2$), 14.9 (CH_3), 11.9 (CH_3). IR data (KBr pellet cm^{-1}): 1689 (s) (ν_{CONH}). *Anal.* Calc. for $C_{38}H_{54}O_2N_6Cl_2Pd{\cdot}0.33C_6H_6$: C, 57.87; H, 6.80; N, 10.12. Found: C, 57.28; H, 7.82; N, 9.91%.

4.4. Synthesis of [1-(2-hydroxy-cyclohexyl)-3,5-dimethylpyrazole]$_2$PdCl$_2$ (*2b*)

A mixture of 1-(2-hydroxy-cyclohexyl)-3,5-dimethylpyrazole (**2a**) (0.103 g, 0.531 mmol) and (COD)$PdCl_2$ (0.075 g, 0.263 mmol) was refluxed in benzene (*ca.* 20 mL) for 8 h, after which the reaction mixture was concentrated under vacuum to yield the product **2b** as a yellow solid (0.098 g, 66%). ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 5.97 (s, 2H, C_3N_2H), 3.92 (m, 2H, *C*H(OH)), 3.12 (m, 2H, *C*H(C_3N_2H)), 2.82–2.79 (m, 4H, CH_2), 2.45 (s, 6H, CH_3), 2.32 (s, 6H, CH_3), 1.98–1.41 (m, 12H, CH_2). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz, 25 °C) δ 150.8 (C_3N_2H), 149.0 (C_3N_2H), 146.3 (C_3N_2H), 142.8 (C_3N_2H), 110.6 (C_3N_2H), 107.9 (C_3N_2H), 71.3 (*C*H(OH)), 66.4 (*C*H(C_3N_2H)), 36.9 (CH_2), 34.4 (CH_2), 31.6 (CH_2), 31.1 (CH_2), 25.7 (CH_2), 24.8 (CH_2), 16.9 (CH_3), 15.0 (CH_3), 13.2 (CH_3), 12.7 (CH_3). IR data (KBr pellet cm^{-1}): 3447 (m) (ν_{OH}). *Anal.* Calc. for $C_{22}H_{36}O_2N_4PdCl_2$: C, 46.70; H, 6.41; N, 9.90. Found: C, 46.48; H, 6.80; N, 9.06%.

4.5. Computational methods

Density functional theory calculations were performed on the palladium **1b** and **2b** complexes including their fragments using GAUSSIAN 03 [74] suite of quantum chemical programs. The Becke three parameter exchange functional in conjunction with Lee–Yang–Parr correlation functional (B3LYP) has been employed in the study [75,76]. Stuttgart–Dresden effective core potential (ECP), representing 19 core electrons along with the valence basis sets (SDD) is used for palladium atom [77–79]. All other atoms are treated at the 6-31G(d) basis set [80]. Natural Bond Orbital (NBO) analysis was performed using the NBO 3.1 [81] program implemented in the GAUSSIAN 03 package.

Inspection of the metal–ligand donor–acceptor interactions was carried out using the charge decomposition analysis (CDA) [82]. CDA is a valuable tool in analyzing the interactions between molecular fragments on a quantitative basis, with an emphasis on electron donation [83,84]. The orbital contributions in the single-point structures of the palladium(II) (pyrazole)$_2$$PdCl_2$, **1b** and **2b,** complexes can be divided into three parts:

(i) σ-donation from the [pyrazole ligand → $PdCl_2$] fragment,
(ii) π-back donation from [pyrazole ligand ← $PdCl_2$] fragment, and
(iii) repulsive polarization (*r*).

The CDA calculations are performed using the AOMIX [56], using the B3LYP/SDD, 6-31G(d) wave function. Molecular orbital (MO) compositions and the overlap populations were calculated using the AOMIX program. The analysis of the MO compositions in terms of occupied and unoccupied fragment orbitals (OFOs and UFOs, respectively), construction of the orbital interaction diagrams, the charge decomposition analysis (CDA) was performed using the AOMIX-CDA [85].

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

In a typical catalysis run, performed in air, a 25 mL vial was charged with a mixture of the aryl chloride (1.00 mmol), phenyl boronic acid (0.146 g, 1.20 mmol), Cs_2CO_3 (0.487 g, 1.50 mmol), TBAB (0.484 g, 1.5 mmol) and diethyleneglycol-di-*n*-butyl ether (internal standard) (0.218 g, 1.00 mmol). Palladium complexes **1b** or **2b** (2 mol%) was added to the mixture followed by the solvent (DMF/H_2O, 9:1 v/v, 8 mL) and the reaction mixture was heated at 120 °C for an appropriate period of time, after which an aliquot

was filtered and the product analyzed by gas chromatography using diethyleneglycol-di-*n*-butyl ether as an internal standard.

4.7. General procedure for the Hg(0) drop test

A 25 mL vial was charged with a mixture of the aryl chloride (1.00 mmol), phenyl boronic acid (0.146 g, 1.20 mmol), Cs_2CO_3 (0.487 g, 1.50 mmol), TBAB (0.484 g, 1.5 mmol) and diethyleneglycol-di-*n*-butyl ether (internal standard) (0.218 g, 1.00 mmol). Palladium complex **1b** (2 mol%) was added to the mixture followed by the solvent (DMF/H_2O, 9:1 v/v, 8 mL) and excess Hg(0) (~100 times). The reaction mixture was heated at 120 °C for an appropriate period of time, after which an aliquot was filtered and the product analyzed by gas chromatography using diethyleneglycol-di-*n*-butyl ether as an internal standard.

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Appendix A. Supplementary material

CCDC 647809 and 645663 contain the supplementary crystallographic data for **1b** and **2b**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ica.2010.04.006.

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