Highly efficient palladium precatalysts of homoscorpionate bispyrazolyl ligands for the more challenging Suzuki–Miyaura cross-coupling of aryl chlorides†

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Highly efficient palladium precatalysts $\{[RN\{\text{-}(CH_2)_n\text{-}pz^{3,5\text{-}Me_2}\}_2]PdCl_2\}_m$ [$m = n = 1$; R = 2,6-$Me_2C_6H_3$ (**1**), 2,4,6-$Me_3C_6H_2$ (**2**), CH_2Ph (**3**) and $m = n = 2$; R = CH_2Ph (**4**)] of a series of homoscorpionate bispyrazolyl ligands for the Suzuki–Miyaura cross-coupling of the more challenging aryl chloride substrates are reported. In particular, the palladium **1–4** precatalysts carried out the Suzuki–Miyaura cross-coupling of a wide variety of aryl chloride substrates bearing electron withdrawing, electron donating and heteroaryl substituents. Remarkably enough, the molecular structure determination of the **1–4** precatalysts by X-ray diffraction studies revealed the presence of *anagostic* [C–H · · · Pd] type interactions in the mononuclear **1–3** complexes of methylene bridged bispyrazolyl ligands whereas the ethylene bridged analog **4** yielded an interesting dimeric 20-membered macrometallacyclic complex devoid of any such interaction.

Introduction

Of the recent methodologies available for the construction of biaryl frameworks in numerous target molecules of pharmaceutical,[1] biological,[2] speciality chemicals[3] and materials interests,[4] the Suzuki–Miyaura cross-coupling of aryl halides with aryl boronic acids is by far the most preferred method of the day.[5] With the other available methods suffering from disadvantages like the toxicity issues associated with organotin reagents in the Stille coupling,[6] or the inert nature of the carbon nucleophile in organosilicon reagents in the case of Hiyama coupling,[7] the Suzuki–Miyaura reaction exhibits many distinct advantages like, the flexible use of organic solvents with inorganic bases, ready availability of substrates, air and moisture stability of the reagents, functional group tolerance, coupling of sterically demanding groups, low toxicity of boronic acids, facile removal of boron containing by-products, high regio- and stereo-selectivity and easy application in one-pot procedures *etc.* make the reaction more acceptable to the synthetic community among the existing cross-coupling protocols.[8]

A formidable challenge lies in utilizing inexpensive aryl chlorides as substrates for the cross-coupling reaction because of their wide diversity and ready availability that make them commercially important intermediates as opposed to the aryl bromides and iodides, which are not only considered expensive but are also available in a fewer variety.[9] The difficulty in achieving the cross-coupling of aryl chlorides arises from the stronger C–Cl bond as opposed to the other C–X (X = Br, I) bonds [bond dissociation energy (kcal mol^{-1}) for Ph–X: Cl (95), Br (80) and I (65)][10] and thus, because of which the Suzuki–Miyaura cross-coupling of aryl chlorides is a topic of contemporary interest.

Despite its pressing need for broad based applicability, the first breakthrough in the Suzuki–Miyaura cross-coupling of aryl chlorides however, appeared as late as 1998,[9d] several decades after the first report of the cross-coupling of aryl bromide substrates appeared.[5c] Since then a plethora of palladium precatalysts supported over a variety of ligand scaffolds ranging from the strongly σ-donating and also sterically demanding phosphines[11] and N-heterocyclic carbenes[12] to less basic N-based ligands[13] have been developed for the aryl chloride cross-coupling. Quite interestingly, a recent report by Li and Hor[14] indicated better prospects for pyrazole based precatalysts over the strongly σ-donating N-heterocyclic carbene ligands in a variety of cross-coupling reactions under aerobic conditions, as it was demonstrated that the replacement of a N-heterocyclic carbene moiety by a pyrazole group in the ligand backbone of a palladium complex led to significant enhancement in the catalytic activity. Because of the aforementioned reasons, we became interested in examining the potential of pyrazole derived systems for the Suzuki–Miyaura coupling of aryl chlorides.

With one of our research aims being in the utility of N-heterocyclic carbenes (NHCs)[15] in a variety of C–C bond forming reactions like the Suzuki–Miyaura,[16] Sonogashira,[17] Hiyama[17c] and Michael addition reactions,[18] and in the course of which we have explored the effect of electron richness at the metal center of the precatalysts by varying the number of NHC ligands on the metal and found that more electron rich metal centers performed better for the cross-coupling reactions,[16b,c,17d] quite similar to that observed in case of the phosphine ligands.[10c] With regards to the Suzuki–Miyaura reaction, we have recently reported palladium

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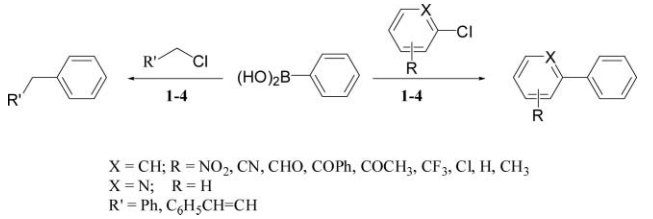
† Electronic supplementary information (ESI) available: X-ray crystallographic data, B3LYP coordinates of the optimized geometries of **1–4**, computational data and the control experiment data. CCDC reference numbers 626720, 630628, 636906 and 636907. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c003174g

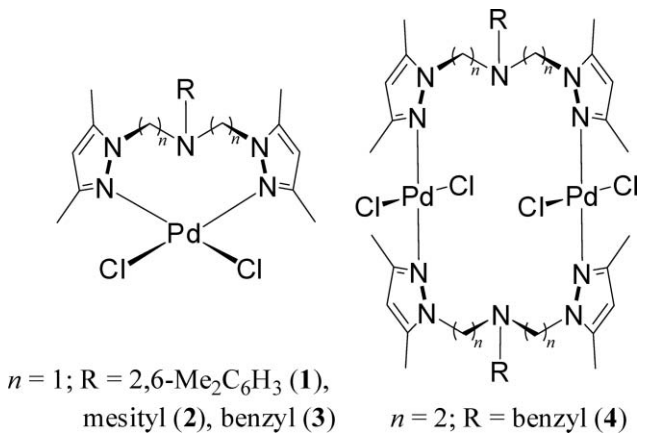
precatalysts of N-heterocyclic carbenes for the cross-coupling of aryl bromide and iodide substrates.[16] Progressing further along this theme of research, we became interested in designing Suzuki–Miyaura precatalysts for the more challenging aryl chloride substrates. In particular, we looked into the possibility of employing homoscorpionate bispyrazolyl ligand based catalysts for the same.

Here in this contribution, we report a series of palladium precatalysts (**1–4**) supported over homoscorpionate bispyrazolyl ligands for the Suzuki–Miyaura coupling of a wide range of aryl chloride substrates bearing electron withdrawing, electron donating and heteroaryl substituents with phenyl boronic acid in air in a mixed aqueous medium (Fig. 1 and eqn (1)). A diverse set of bispyrazolyl derived palladium precatalysts ranging from discrete monomers (**1–3**) to a 20-membered macrometallacycle (**4**) have been employed in the study.



X = CH; R = NO_2, CN, CHO, COPh, $COCH_3$, CF_3, Cl, H, CH_3
X = N; R = H
R' = Ph, C_6H_5CH=CH

(1)



n = 1; R = 2,6-$Me_2C_6H_3$ (**1**), mesityl (**2**), benzyl (**3**) n = 2; R = benzyl (**4**)

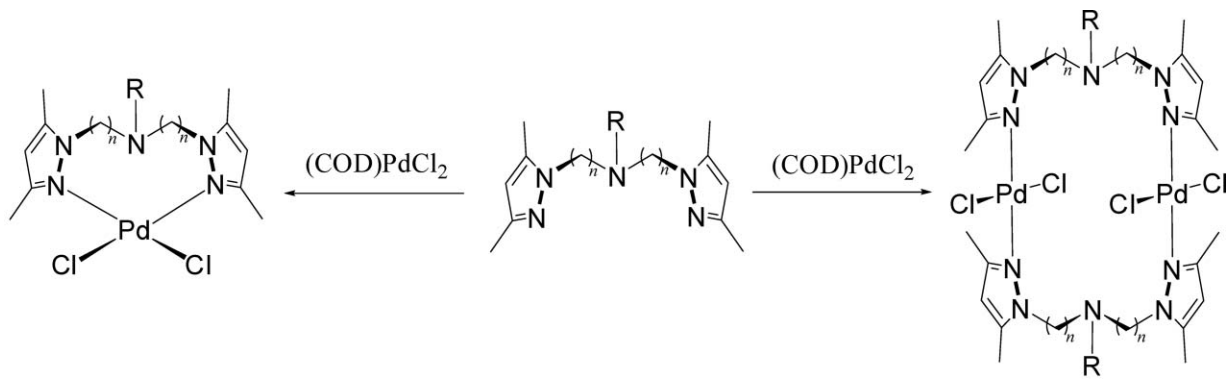
Fig. 1 Palladium precatalysts, **1–4**, of homoscorpionate bispyrazolyl ligands.

Results and discussion

Several new palladium complexes, {[RN{-$(CH_2)_n$-$pz^{3,5\text{-}Me}{}_2$}$_2$]-$PdCl_2$}$_m$ [$m = n = 1$; R = 2,6-$Me_2C_6H_3$ (**1**), 2,4,6-$Me_3C_6H_2$ (**2**), CH_2Ph (**3**) and $m = n = 2$; R = CH_2Ph (**4**)] derived from the amine based homoscorpionate pyrazolyl ligands, namely, [RN{-$(CH_2)_n$-$pz^{3,5\text{-}Me}{}_2$}] [n = 1; R = 2,6-$Me_2C_6H_3$ (**1a**), 2,4,6-$Me_3C_6H_2$ (**2a**),[19] CH_2Ph (**3a**)[20] and n = 2; R = CH_2Ph (**4a**)[21]] were synthesized by the direct reaction of the ligands **1a–4a** with $(COD)PdCl_2$ in refluxing benzene in 56–90% yields (Scheme 1).

Of particular interest is the ^{1}H NMR spectrum of the methylene bridged moiety in the palladium **1–3** complexes that appeared as two sets of doublets at *ca.* 7.50 ppm and *ca.* 5.20 ppm, each exhibiting a geminal coupling ($^2J_{HH}$) of 15 Hz. The observation of the highly downfield shifted doublet at *ca.* 7.50 ppm pointed towards the existence of *anagostic* [C–H $\cdots$ Pd] type interactions[22] in these complexes. On the contrary, the ethylene bridged palladium complex **4** did not show any such geminal coupling in its ^{1}H NMR spectrum thus negating the possibility of such *anagostic* interaction in the complex. In this context it is worth mentioning that the commonly observed [C–H $\cdots$ M] type interactions usually belong to any of the following two classes, (*i*) the *agostic* ones exhibiting covalent *3c–2e* type interaction and (*ii*) the *anagostic* ones of predominantly electrostatic origin. Notably, concurring well with the *anagostic* nature of the [C–H $\cdots$ Pd] interaction in the palladium **1–3** complexes, no significant shifts in the methylene C–H stretching frequencies were observed in the infrared spectrum of these complexes compared to its free ligand and, thus, are in contrary to the cases of *agostic* [C–H $\cdots$ M] type interactions, where the C–H stretching frequencies have been reported to shift to significantly lower frequencies at *ca.* 2700–2350 cm^{-1}.[23] Furthermore, the $^1J_{CH}$ (^{13}C, ^{1}H) values calculated for the palladium **1–3** complexes [148 Hz (**1**), 147 Hz (**2**) and 149 Hz (**3**)] compare well with that for a representative bispyrazolyl ligand **1a** (149 Hz), further testifying towards the *anagostic* nature of interaction between the palladium center and the hydrogen atoms of the bridging methylene moiety.

The compelling evidence in favor of the presence of *anagostic* interactions in the palladium **1–3** complexes came from the X-ray diffraction studies that showed clear [C–H $\cdots$ Pd] type interactions present between bridging methylene hydrogen atoms and the metal center in these complexes (Fig. 2, Fig. S1 and S2, and Table S1,



n = 1; R = 2,6-$Me_2C_6H_3$ (**1**), mesityl (**2**), benzyl (**3**) n = 2; R = benzyl (**4**)

Scheme 1 Synthesis of the palladium precatalysts of homoscorpionate bispyrazolyl ligands.

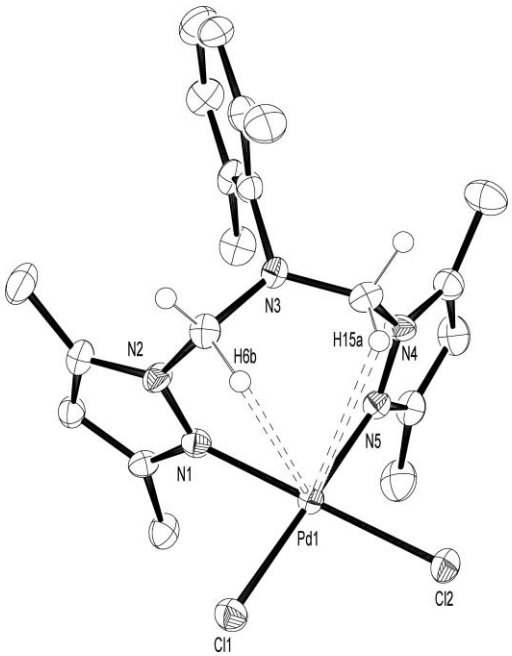


Fig. 2 ORTEP of **1** shown with 50% probability ellipsoids. Selected bond lengths (Å) and angles (°): Pd1–N5 2.027(3), Pd1–N1 2.026(3), Pd1–Cl1 2.2852(8), Pd1–Cl2 2.2932(8), Pd1–H6B 2.8777, Pd1–H15A 2.9194, N1–N2 1.356(4), N5–Pd1–N1 91.78(11), N5–Pd1–Cl1 178.11(8), N1–Pd1–Cl1 87.61(8), N5–Pd1–Cl2 87.67(8), N1–Pd1–Cl2 179.37(8).

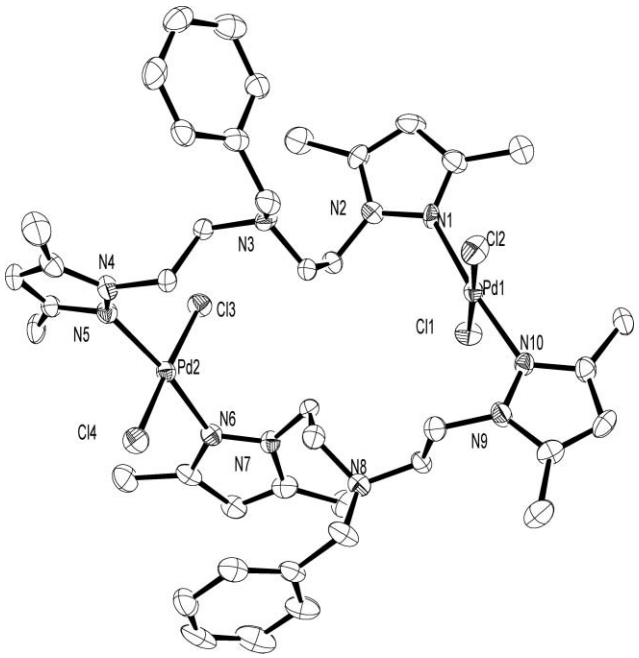


Fig. 3 ORTEP of **4** shown with 50% probability ellipsoids. Selected bond lengths (Å) and angles (°): Pd1–N10 2.023(4), Pd1–N1 2.027(4), Pd1–Cl2 2.2915(13), Pd1–Cl1 2.2945(12), Pd2–N6 1.999(4), Pd2–N5 2.025(4), Pd2–Cl4 2.2788(12), Pd2–Cl3 2.2916 (12), N10–Pd1–N1 174.74(17), N10–Pd1–Cl2 90.14 (12).

ESI†). Of interest to the *anagostic* interaction, are the [C–H · · · Pd] distances [2.8436–2.9194 Å] that are slightly longer than the sum of the van der Waals radii of Pd and H (2.72 Å)[24] as expected while the other distal hydrogen atom of the bridging methylene moiety showed an even greater separation of 4.189–4.231 Å from the metal center in these complexes. It is worth pointing out at this juncture that the origin of the observed [C–H · · · Pd] type *anagostic* interactions in the palladium **1–3** complexes may also be attributed to the formation of a stable chelate ring conformation upon coordination of the bispyrazolyl ligand to palladium which positions the C–H bond in the vicinity of the Pd^{2+} center. Consistent with being a d^8 metal center, the palladium center in the **1–3** complexes was found to be in a square planar geometry and displayed a Pd–N distances of 2.0217(15)–2.0459(18) Å and a Pd–Cl distances of 2.2810(7)–2.2932(8) Å. It must be pointed out that the palladium complex **3** exhibited a crystallographically imposed mirror symmetry in the solid state. In contrast to the methylene bridged complexes **1–3**, the ethylene bridged analogue **4** showed an unusual 20-membered macrometallacyclic dimeric structure, $\{[PhCH_2N\{\text{-}(CH_2)_2\text{-}pz^{3,5\text{-}Me}{}_2\}_2]PdCl_2\}_2$ (**4**) (Fig. 3 and Table S1, ESI†). The ethylene bridged complex **4** further differed from the methylene bridged ones (**1–3**) by the conspicuous absence of any *anagostic* interaction in the complex. Each of the metal centers in the ethylene bridged complex **4** also displayed a square planar geometry with the two chlorides and the two coordinating pyrazolyl-N's occupying *trans* positions and were in sharp contrast to the *cis* geometry exhibited by the methylene bridged **1–3** complexes. The Pd–N distances in **4** were found to be 1.999(4)–2.027(4) Å while the Pd–Cl distances were 2.2788(12)–2.2945(12) Å.

In order to gain deeper insight into the nature of the pyrazole–palladium interaction in the **1–4** complexes, detailed density functional theory (DFT) studies were performed. Specifically, the geometry optimized structures were computed for the **1–4** complexes at the B3LYP/SDD, 6-31G(d) level of theory using atomic coordinates adopted from X-ray analysis (see Tables S2–S5, ESI†), followed by single-point calculations on the geometry optimized structures using natural bond order (NBO) method for a greater understanding of the electronic properties of these complexes. Specifically, the electron donation from the pyrazolyl ligand moiety to the palladium center in complexes **1–4** is apparent from the natural and Mulliken charge analyses that revealed significant enhancement in the electron density on the metal center in **1–4** as compared to that in the $PdCl_2$ fragment (see Tables S6–S9, ESI†). Additionally, the NBO analysis indicated that the electron donation from the bispyrazolyl ligand occurred on to the *5s* orbital of the palladium center in the **1–4** complexes (see Tables S10 and S11, ESI†).

Further estimate of the strength of pyrazole–palladium interaction in complexes **1–4** was obtained by computing the $N_{pyrazole}$–Pd bond dissociation energies, D_e/(Pd–pyrazole), **1** (41.98 kcal mol^{-1}), **2** (42.05 kcal mol^{-1}), **3** (41.87 kcal mol^{-1}) and **4** (50.20 kcal mol^{-1}), at the B3LYP/SDD, 6-31G(d) level of theory (see Table S12, ESI†), which pointed towards a reasonably strong interaction. In this context it is noteworthy that a strong ancillary ligand to metal interaction plays a pivotal role in preventing catalyst leaching thereby enhancing its lifetime.

Additional understanding of the pyrazole–Pd interaction in **1–4** was obtained from the molecular orbital (MO) correlation diagram, constructed from the interaction of the individual fragment molecular orbitals (FMOs) of the pyrazolyl ligand

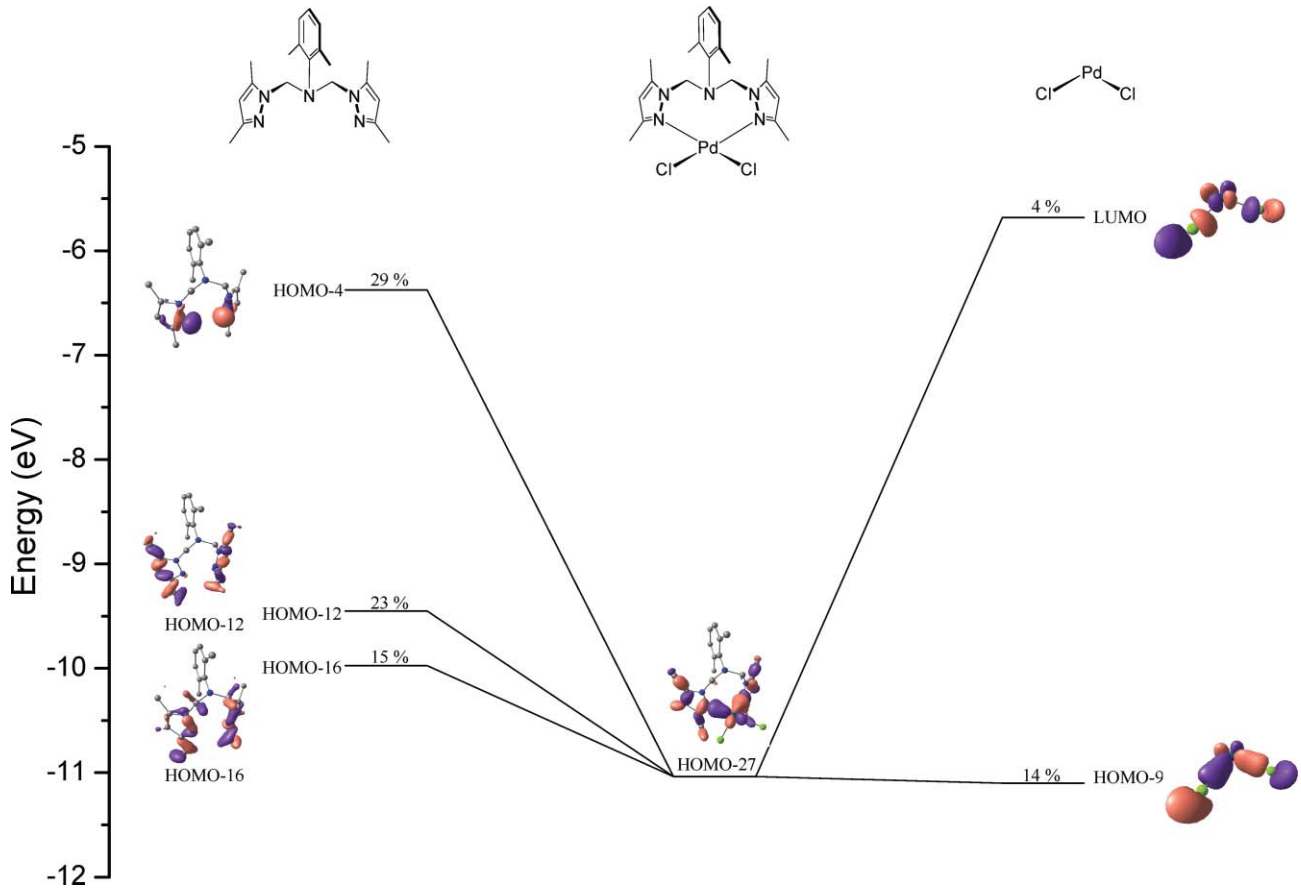
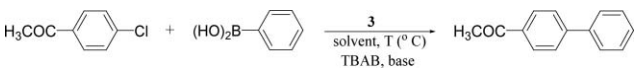


Fig. 4 Simplified orbital interaction diagram showing major contributions to the pyrazole–palladium bonding orbital HOMO-27 in **1**.

fragment with the $PdCl_2$ fragment in these complexes using *AOMix* software.[25] Of particular relevance is the σ-interaction between the pyrazole moiety and the palladium center in complexes **1–4** as represented by the following molecular orbitals (MOs), HOMO-27 (**1**), HOMO-27 (**2**), HOMO-26 (**3**) and HOMO-66, HOMO-71 (**4**) (Fig. 4 and 5, and Fig. S3–S9, ESI†). It is worth mentioning that the low-lying nature of the molecular orbitals (MO) depicting pyrazole–Pd σ-interaction in these complexes indicate a stable ligand–metal interaction.

All palladium **1–4** complexes efficiently catalyzed the Suzuki–Miyaura cross-coupling reaction of aryl chlorides with phenyl boronic acid in air in a mixed-aqueous medium (eqn (1)). The optimized conditions for the coupling reaction were obtained for a representative substrate, *p*-chloroacetophenone, by varying the solvent and base combinations (Table 1). For example, the catalysis runs performed in both toluene and methanol yielded insignificant conversion of *ca*. 2%, while the similar ones in either DMF or in a mixed medium, DMF–H_2O (1 : 1 v/v), gave though comparatively higher but still sufficiently subdued yields *ca*. 45–60%. Quite interestingly, the best results were observed (>99% conversion) using Cs_2CO_3 as base in a mixed aqueous medium (DMF–H_2O, 9 : 1 v/v) in presence of added TBAB (1.5 equivalents) at 120 °C. The enhanced activity of palladium **1–4** complexes in the mixed aqueous medium can be attributed to the better solubility of the Cs_2CO_3 base under aqueous conditions and also to the stabilization of any unsaturated catalytic species generated by the coordinating solvents.[26]

Table 1 Suzuki–Miyaura cross-coupling reaction of $PhB(OH)_2$ with *p*-$ClC_6H_4COCH_3$: solvent and base variation study[a]



Entry	Solvent	Base	*T*/°C	Yield[b]
1	CH_3OH	Cs_2CO_3	60	2
2	toluene	Cs_2CO_3	110	2
3	Dioxane/H_2O (9 : 1)	Cs_2CO_3	110	13
4[c]	DMF	Cs_2CO_3	120	45
5	DMF	Cs_2CO_3	120	50
6	DMF–H_2O (1 : 1)	Cs_2CO_3	120	60
7	DMF–H_2O (9 : 1)	Cs_2CO_3	120	>99
8[c]	DMF–H_2O (9 : 1)	Cs_2CO_3	120	62
9	DMF–H_2O (19 : 1)	Cs_2CO_3	120	>99
10	DMF–H_2O (9 : 1)	CH_3COONa	120	20
11	DMF–H_2O (9 : 1)	Na_2CO_3	120	41
12	DMF–H_2O (9 : 1)	K_2CO_3	120	60
13	DMF–H_2O (9 : 1)	NaOH	120	63
14	DMF–H_2O (9 : 1)	KOH	120	92
15	DMF–H_2O (9 : 1)	KO^{t}Bu	120	82

[a] Reaction conditions: 1.00 mmol of aryl chloride, 1.20 mmol of boronic acid, 1.50 mmol of base, 1.50 mmol of TBAB, 2 mol% of **3** in 8 mL of solvent at *T* (°C) for 5 h. [b] The yields (%) were determined by GC using diethylene glycol di-*n*-butyl ether as an internal standard. [c] In the absence of added TBAB.

Specifically, when a mixture of the aryl chloride and phenyl boronic acid in the presence of 2 mol% of precatalysts **1–4** were

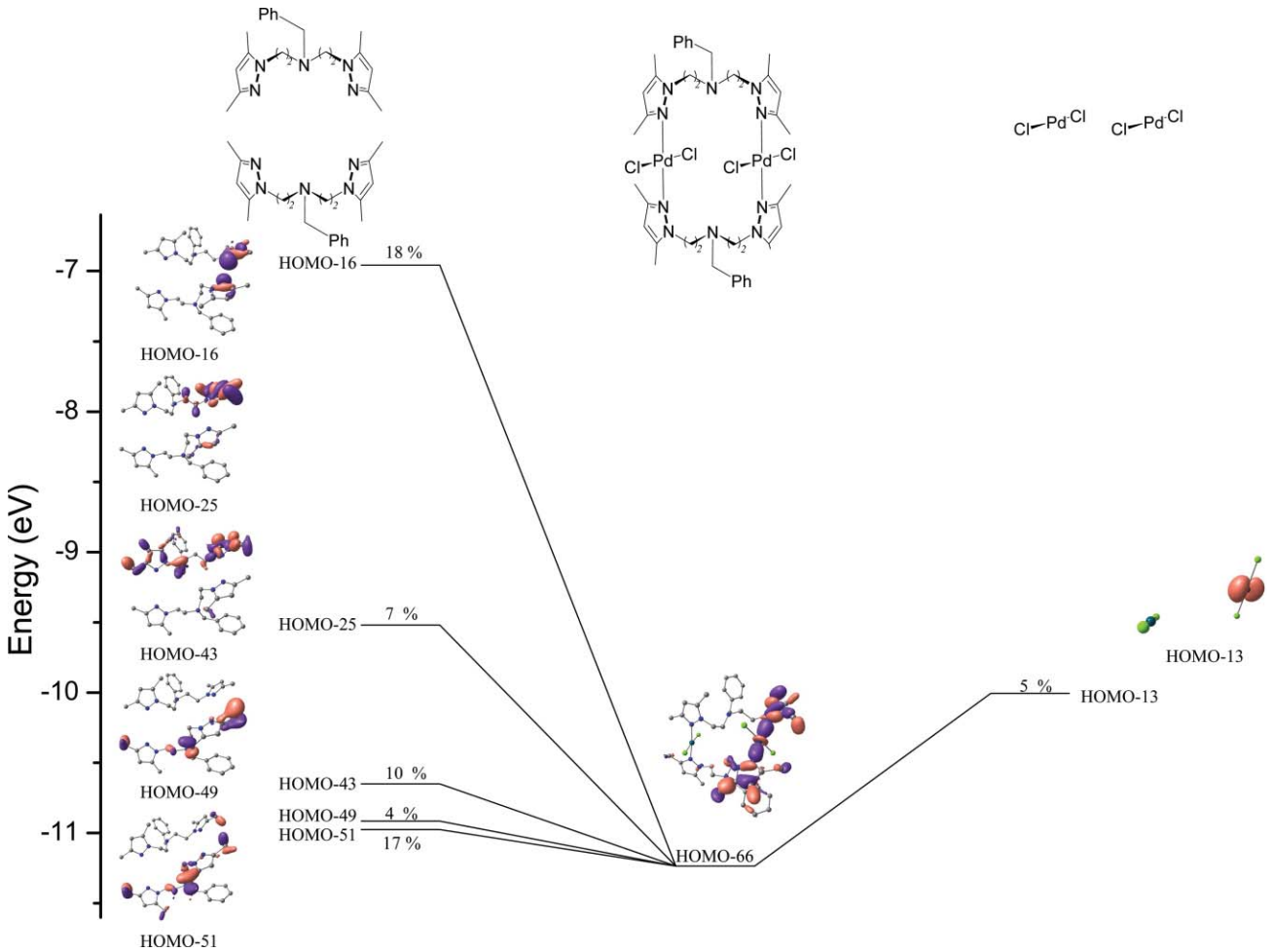


Fig. 5 Simplified orbital interaction diagram showing major contributions to the pyrazole–palladium bonding orbital HOMO-66 in **4**.

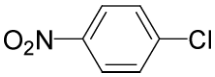
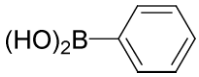
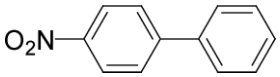
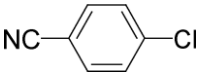
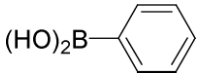
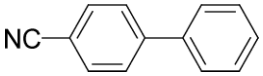
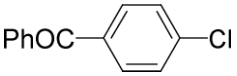
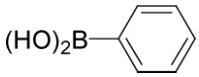
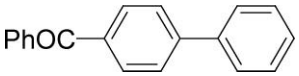
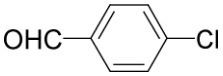
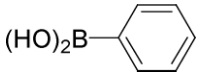
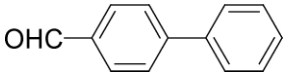
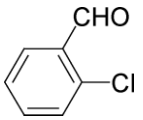
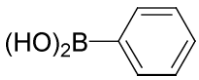
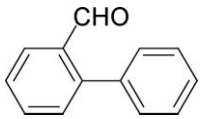
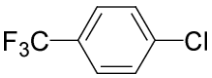
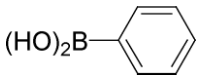
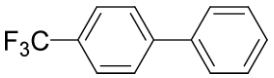
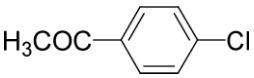
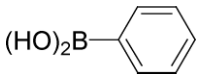
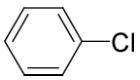
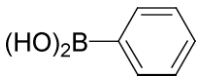
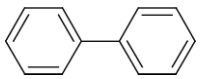
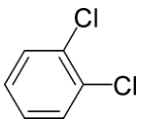
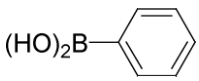
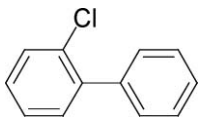
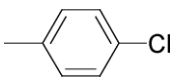
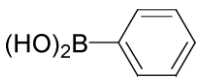
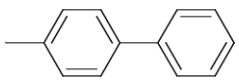
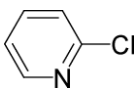
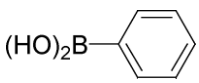
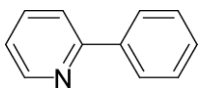
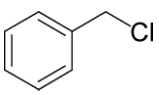
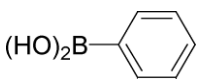
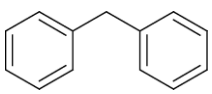
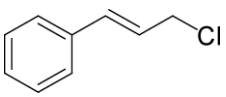
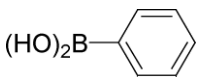
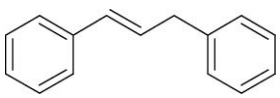
heated at 120 °C in air in a DMF–H_2O (9 : 1 v/v) mixed medium, clean conversion to the cross-coupled product was obtained in a relatively short period of the reaction time of 5 h (Table 2). A wide variety of aryl chlorides bearing electron withdrawing (NO_2, CN, COPh, CHO, CF_3 and $COCH_3$), electron donating (CH_3) and with heteroatom (C_5H_4N) substituents were all converted to the respective cross-coupled products in moderate to excellent yields (23–>99%). In addition to the frequently encountered (sp^2–sp^2) couplings, the palladium **1–4** complexes also catalyzed the cross-coupling of the more challenging benzyl and cinnamyl chlorides with phenyl boronic acid (sp^2–sp^3 centers) in moderate to excellent yields (19–>99%). Furthermore, in order to highlight the practical utility of Suzuki–Miyaura cross-coupling by the palladium precatalysts, the isolated yields are provided for a representative precatalyst **3** (Table 2). The temperature dependence profile obtained for the coupling of *p*-nitrochlorobenzene with phenyl boronic acid for the catalysis runs of 5 h showed that higher conversions of >90% could only be achieved above 100 °C (see Fig. S10, ESI†).

Significant "ligand-influence" of the bispyrazolyl ligands in precatalysts **1–4** was very much evident when compared to the control experiments performed using the simple metal precursors like, $PdCl_2$ and $(COD)PdCl_2$, that showed significant enhancements of up to 84% in the reaction yields for **1–4** precatalysts. The homogeneous nature of the Suzuki–Miyaura coupling by the palladium **1–4** precatalysts was verified by performing the "classical Hg-drop test"[27] that showed no significant effect on the catalysis results (see Table S13, ESI†).

For substrates where quantitative conversions were observed (entries 1–7 and 12, Table 2), additional catalysis runs were performed at lower precatalyst loadings for a representative precatalyst **3** in order to gauge the lower limit of the catalyst efficiency. Significantly enough, precatalyst **3** continued to exhibit low to high conversions (6–95%) even at a lower precatalyst loading of 0.05 mol% (entries 1–2, Table 3). In this regard it is worth mentioning that remarkably high turnover numbers (TON) of up to 4100 (TOF = 820 h^{-1}) could be observed for the activated *p*-nitrochlorobenzene substrate at 0.01 mol% of precatalyst **3** loading in 5 h. Furthermore, a high conversion of 91% exhibiting a turnover number (TON) of 910 was seen for the more challenging (sp^2–sp^3) coupling of benzyl chloride with phenyl boronic acid at 0.1 mol% of the precatalyst **3** loading.

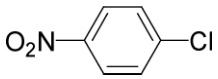
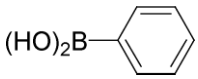
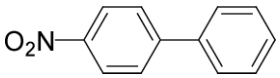
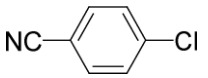
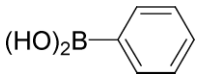
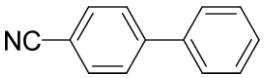
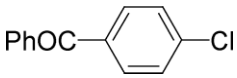
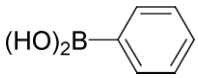
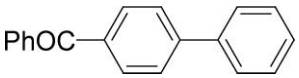
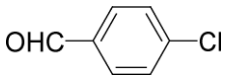
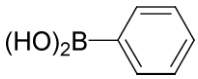
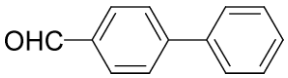
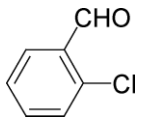
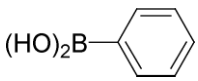
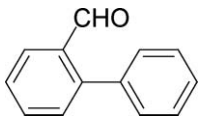
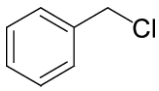
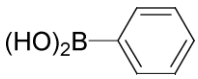
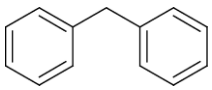
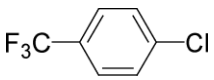
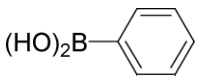
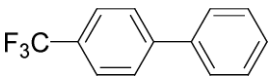
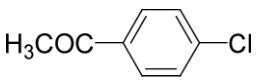
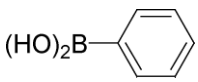
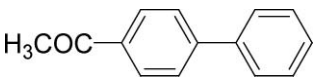
The high turnover number (TON) of 4100 observed in the case of **3** for an activated *p*-nitochlorobenzene substrate is comparable to that of the [8-(di-*tert*-butylphosphinooxy)quinoline]$PdCl_2$ precatalyst, which too exhibited a similar high turnover number of 3750, also for an activated aryl chloride substrate, *p*-chloroacetophenone.[28] Another N-based ligand

Table 2 Selected results for Suzuki–Miyaura cross-coupling reaction of aryl chlorides catalyzed by **1–4**

Entry	Reagent[a]	Reagent[a]	Cross-coupled product	Yield[b]			
				1	**2**	**3**	**4**
1				>99	>99	>99 (78)	>99
2				>99	>99	>99 (87)	>99
3				>99	>99	>99 (93)	>99
4				>99	>99	>99 (90)	>99
5				>99	>99	>99 (84)	>99
6				>99	>99	>99 (61)	>99
7				83	81	>99 (78)	87
8				62	89	66	41
9				58	46	35	43
10				28	28	28	26
11				23	19	21	22
12				>99	>99	>99 (92)	>99
13				7	19	17	16

[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 **1–4** 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 are given in the parentheses.

Table 3 Selected results for Suzuki–Miyaura cross-coupling reaction of chlorides catalyzed by **3**: catalyst loading variation

Entry	Reagent[a]	Reagent[a]	Cross-coupled product	Catalyst loading (mol%)	Yield[b] (%)	TON
1				0.5 0.1 0.05 0.01	>99 >99 78 41	200 1000 1560 4100
2				0.5 0.1 0.05	98 97 95	196 970 1900
3				0.5 0.1 0.05	>99 93 6	200 930 120
4				0.5 0.1	>99 68	200 680
5				0.5 0.1	>99 74	200 740
6				0.5 0.1	93 91	186 910
7				0.5 0.1	80 31	160 310
8				0.5	16	32

[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 and **3** 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.

supported palladium precatalyst, {*N*-cyclohexyl-*N*′di-(2-pyridyl)methylurea}$PdCl_2$, is notable for its high turnover number of 6500 for the coupling of *p*-chloroacetophenone at 100 °C in 72 h.[29] The precatalyst showed excellent activity for the coupling of a wide variety of aryl, heteroaryl, benzylic, allyl chlorides, with aryl and alkyl boronic acids in neat H_2O as well as in mixed aqueous mediums namely, acetone–H_2O (3 : 2 v/v) and DMF–H_2O (95 : 5 v/v).[28]

Important is the comparison of the bispyrazolyl based **1–4** precatalysts with other reported N-heterocyclic carbene,[30] phosphine[31] and the N-donor ligand[13,14,32] based ones for the Suzuki–Miyaura cross-coupling of aryl chlorides with aryl boronic acids. For example, the sterically demanding N-heterocyclic carbene based PEPPSI themed *trans*-[1,3-*bis*(2,6-diisopentylphenyl)imidazol-2-ylidene]$PdCl_2$(3-chloropyridine) complex carried out the challenging coupling of *o*-disubstituted aryl and heteroaryl chlorides with *o*-disubstituted phenyl boronic acids in good to excellent yields (49–95%) at 2 mol% of the catalyst loading at 65 °C in 24 h, thereby opening up a new synthetic route to crowded tetra *ortho*-substituted biaryls.[33] Another highly active N-heterocyclic carbene based palladium {[1,3-*bis*(2,6-diisopropylphenyl)imidazol-2-ylidene]PdCl(μ-Cl)}$_2$ complex displayed clean conversions (36–99%) for aryl and heteroaryl chlorides substrates at a lower catalyst loading of 0.1 mol% at room temperature in 20–24 h.[34] Among, the phosphine counterparts, a palladium 2,6-*bis*-(trimethylsilyl) substituted phosphabarrelene complex carried out the coupling of several electronically modulated aryl chlorides at a low catalyst loading of 0.2 mol% in low to excellent yields (5–99%) at 80 °C in 1–20 h.[35] Also notable is a palladium *meta*-terphenyl diphosphinite [PCP] pincer type precatalyst, [2,6-(2-^{i}Pr$_2$POC$_6$H$_4$)$_2$C$_6$H$_3$]PdBr, that exhibited good to excellent yields (52–99%) in the coupling of aryl chlorides at 0.5–2 mol% palladium loading at 75–100 °C in 20 h.[36] Against this backdrop, significant conversions of 23–>99% were observed for the bispyrazolyl derived **1–4** precatalysts at 2 mol% of catalyst loading at 120 °C and thus their activity compares well with the other reported ones.

Conclusions

In summary, several new highly efficient palladium precatalysts **1–4** of homoscorpionate bispyrazolyl ligands have been designed for the more challenging Suzuki–Miyaura coupling of aryl chlorides with phenyl boronic acids. A wide variety of aryl chlorides containing electron withdrawing (NO_2, CN, COPh, CHO, CF_3 and $COCH_3$), electron donating (CH_3) as well as with heteroatom

(C_5H_4N) substituents could be converted to the respective cross-coupled products in moderate to high yields. High turnover numbers (TON's) of up to *ca.* 4100 could be obtained for an activated aryl chloride substrate namely, *p*-nitrochlorobenzene. More challenging (sp^2–sp^3) coupling of benzyl and cinnamyl chlorides with phenyl boronic acids were also achieved by these **1–4** precatalysts. Quite interestingly, the structural characterization of these precatalysts showed that while the discrete monomeric palladium **1–3** complexes, supported over the methylene bridged bispyrazolyl ligands displayed [C–H · · · Pd] *anagostic* interactions, the ethylene bridged counterpart **4** in contrast was a dimeric 20-membered macrometallacycle without the [C–H · · · Pd] *anagostic* interaction.

Experimental

General procedures

All manipulations were carried out using standard Schlenk techniques. Solvents were purified and degassed by standard procedures. 2,6-dimethylaniline and 2,4,6-trimethylaniline were purchased from Sigma Aldrich, Germany and palladium chloride was purchased from Souvenier Chemicals (India) and used without any further purification. N-(methylol)-3,5- dimethylpyrazole,[37] *N*,*N*(*bis*(3,5-dimethylpyrazolyl)methyl)-2,4,6-trimethylaniline,[19] *N*,*N*(*bis*(3,5-dimethylpyrazolyl)methyl)-benzylamine[20] and benzyl-*bis*-[2-(3,5-dimethylpyrazolyl)ethyl]-amine[21] were prepared according to literature procedures. ^{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) and multiplet (m). Mass spectrometry measurements were done on a Micromass Q-Tof spectrometer. GC spectra were obtained on a PerkinElmer Clarus 600 equipped with a FID. GCMS spectra were obtained on a PerkinElmer Clarus 600 T equipped with an EI source. Elemental Analysis was carried out on Thermo Quest FLASH 1112 SERIES (CHNS) Elemental Analyzer.

Synthesis of *N*,*N*(*bis*(3,5-dimethylpyrazolyl)methyl)-2,6-dimethylaniline (1a)

A mixture of 2,6-dimethylaniline (1.36 g, 11.2 mmol) and *N*-(methylol)-3,5-dimethylpyrazole (2.87 g, 22.8 mmol) was taken in CH_3CN (*ca.* 50 mL) and heated at 80 °C for 14 h. The solvent was removed under vacuum to obtain the crude product **1a** as a white solid, which was purified by recrystallization from hexane (2.81 g, 74%). ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): δ 7.01-6.91 (m, 3H, $C_6H_3(CH_3)_2$), 5.67 (s, 2H, C_3N_2H), 5.29 (s, 4H, CH_2), 2.22 (s, 6H, $C_6H_3(CH_3)_2$), 1.81 (s, 6H, CH_3), 1.72 (s, 6H, CH_3). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz, 25 °C): δ 147.8 (C_3N_2H), 143.4 (*ipso*-C_6H_3N), 139.0 (C_3N_2H), 137.5 (*o*-C_6H_3), 128.8 (*m*-C_6H_3), 126.6 (*p*-C_6H_3), 105.5 (C_3N_2H), 64.8 (CH_2), 17.5 ($C_6H_3(CH_3)_2$), 13.6 (CH_3), 10.2 (CH_3). IR data (KBr pellet cm^{-1}): 2949 (s), 2918 (s), 2861 (s), 1667 (w), 1552 (s), 1479 (m), 1459 (m), 1422 (m), 1378 (w), 1301 (m), 1269 (w), 1238 (w), 1196 (s), 1159 (w), 1110 (m), 1029 (m), 986 (w), 959 (w), 797 (s), 784 (s), 770 (s), 709 (w), 631 (w), 582 (w). Anal. Calc. for $C_{20}H_{27}N_5$: C, 71.18; H, 8.06; N, 20.75. Found: C, 70.52; H, 8.49; N, 19.90.

Synthesis of {*N*,*N*(*bis*(3,5-dimethylpyrazolyl)methyl)-2,6-dimethylaniline}$PdCl_2$ (1)

To a stirred suspension of (COD)$PdCl_2$ (0.195 g, 0.683 mmol) in benzene (*ca.* 30 mL) was added *N*,*N*(*bis*(3,5-dimethylpyrazolyl)methyl)-2,6-dimethylaniline (0.230 g, 0.682 mmol) and the reaction mixture was stirred at reflux for 12 h. The reaction mixture was filtered and the filtrate was pumped under vacuum to yield product **1** as a yellow solid (0.316 g, 90%). ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): δ 7.51 (d, 2H, $^2J_{HH}$ = 15 Hz, CH_2), 7.21 (d, 1H, $^3J_{HH}$ = 8 Hz, *m*-$C_6H_3(CH_3)_2$), 7.10 (t, 1H, $^3J_{HH}$ = 8 Hz, *p*-$C_6H_3(CH_3)_2$), 6.87 (d, 1H, $^3J_{HH}$ = 8 Hz, *m*-$C_6H_3(CH_3)_2$), 5.81 (s, 2H, C_3N_2H), 5.23 (d, 2H, $^2J_{HH}$ = 15 Hz, CH_2), 2.85 (s, 6H, CH_3), 2.50 (s, 3H, $C_6H_3(CH_3)_2$), 1.74 (s, 6H, CH_3), 0.73 (s, 3H, $C_6H_3(CH_3)_2$). ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C): δ 151.1 (C_3N_2H), 142.9 (C_3N_2H), 142.8 (*ipso*-C_6H_3), 138.5 (*o*-C_6H_3), 137.0 (*o*-C_6H_3), 129.8 (*p*-C_6H_3), 129.0 (*m*-C_6H_3), 128.6 (*m*-C_6H_3), 107.7 (C_3N_2H), 69.9 (CH_2), 18.6 ($C_6H_3(CH_3)_2$), 15.4 (CH_3), 14.6 ($C_6H_3(CH_3)_2$), 11.2 (CH_3). IR data (KBr pellet cm^{-1}): 3210 (w), 3131 (w), 2921 (m), 1625 (w), 1552 (s), 1466 (m), 1397 (m), 1295 (m), 1264 (m), 1214 (m), 1192 (s), 1162 (m), 1130 (m), 1103 (w), 1060 (m), 1035 (m), 952 (m), 811 (s), 793 (s), 698 (s), 626 (w), 582 (w). Anal. Calc. for $C_{20}H_{27}N_5PdCl_2$: C, 46.66; H, 5.29; N, 13.60. Found: C, 47.04; H, 5.01; N, 12.65%.

Synthesis of {*N*,*N*(*bis*(3,5-dimethylpyrazolyl)methyl)-2,4,6-trimethylaniline}$PdCl_2$ (2)

To a stirred suspension of (COD)$PdCl_2$ (0.203 g, 0.711 mmol) in benzene (*ca.* 30 mL) was added the *N*,*N*(*bis*(3,5-dimethylpyrazolyl)methyl)-2,4,6-trimethylaniline (0.253 g, 0.721 mmol) and the reaction mixture was stirred at reflux for 16 h. The reaction mixture was filtered and the filtrate was pumped under vacuum to yield the product **2** as a yellow powder (0.211 g, 56%). ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): δ 7.48 (d, 2H, $^2J_{HH}$ = 15 Hz, CH_2), 7.02 (s, 1H, $C_6H_2(CH_3)_3$), 6.69 (s, 1H, $C_6H_2(CH_3)_3$), 5.81 (s, 2H, C_3N_2H), 5.19 (d, 2H, $^2J_{HH}$ = 15 Hz, CH_2), 2.85 (s, 6H, CH_3), 2.43 (s, 3H, $C_6H_2(CH_3)_3$), 2.24 (s, 3H, $C_6H_2(CH_3)_3$), 1.74 (s, 6H, CH_3), 0.71 (s, 3H, $C_6H_2(CH_3)_3$). ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C): δ 150.8 (C_3N_2H), 142.9 (C_3N_2H), 140.1 (*ipso*-C_6H_2), 138.2 (*o*-C_6H_2), 137.9 (*o*-C_6H_2), 136.5 (*p*-C_6H_2), 130.5 (*m*-C_6H_2), 129.5 (*m*-C_6H_2), 107.6 (C_3N_2H), 70.0 (CH_2), 20.9 (*p*-$C_6H_2(CH_3)_3$), 18.4 (*o*-$C_6H_2(CH_3)_3$), 15.3 (CH_3), 14.5 (*o*-$C_6H_2(CH_3)_3$), 11.2 (CH_3). IR data (KBr pellet cm^{-1}): 3213 (w), 3123 (w), 2920 (m), 1609 (w), 1554 (m), 1465 (s), 1405 (s), 1297 (m), 1260 (m), 1220 (m), 1194 (m), 1156 (w), 1130 (w), 1060 (w), 1035 (w), 988 (w), 959 (w), 942 (w), 852 (w), 816 (m), 685 (m), 595 (w), 514 (w). Anal. Calc. for $C_{21}H_{29}N_5PdCl_2$: C, 47.70; H, 5.53; N, 13.24. Found: C, 47.73; H, 4.96; N, 12.60%.

Synthesis of {*bis*[2-(3,5-dimethylpyrazolyl)methyl]-benzylamine}$PdCl_2$ (3)

To a stirred suspension of (COD)$PdCl_2$ (0.281 g, 0.985 mmol) in benzene (*ca.* 40 mL) was added *bis*[2-(3,5-dimethylpyrazolyl)methyl]benzylamine (0.321 g, 0.994 mmol) and the reaction mixture was stirred at reflux for 12 h. The reaction mixture was filtered and the filtrate was pumped under vacuum to yield the product **3** as a yellow powder (0.378 g, 77%). ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): δ 7.33–7.23 (m, 5H, C_6H_5 and CH_2),

7.06 (d, 2H, $^3J_{HH}$ = 8 Hz, *o*-C_6H_5), 5.84 (s, 2H, C_3N_2H), 5.35 (d, 2H, $^2J_{HH}$ = 16 Hz, CH_2), 3.92 (s, 2H, CH_2Ph), 2.83 (s, 3H, CH_3), 2.00 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C): δ 151.2 (C_3N_2H), 143.8 (C_3N_2H), 136.4 (*ipso*-C_6H_5), 129.1 (*m*-C_6H_5), 128.0 (*p*-C_6H_5), 126.5 (*o*-C_6H_5), 108.0 (C_3N_2H), 68.9 (CH_2), 53.2 (CH_2Ph), 15.4 (CH_3), 11.9 (CH_3). IR data (KBr pellet cm^{-1}): 3131 (w), 3008 (w), 2928 (w), 1636 (w), 1557 (m), 1493 (w), 1460 (m), 1444 (m), 1421 (s), 1403 (s), 1346 (m), 1278 (w), 1252 (s), 1218 (w), 1170 (s), 1154 (m), 1138 (m), 1061 (w), 1003 (w), 973 (w), 896 (w), 821 (m), 805 (m), 732 (w), 702 (m), 620 (w), 473 (w). Anal. Calc. for $C_{26}H_{24}N_2PdCl_2$: C, 45.57; H, 5.03; N, 13.99. Found: C, 45.86; H, 5.01; N, 14.39%.

Synthesis of {(benzyl-*bis*[2-(3,5-dimethylpyrazolyl)ethyl]amine)-$PdCl_2$}$_2$ (4)

To a stirred suspension of (COD)$PdCl_2$ (0.278 g, 0.974 mmol) in benzene (*ca.* 30 mL) was added benzyl-*bis*-[2-(3,5-dimethylpyrazolyl)ethyl]amine (0.344 g, 0.980 mmol) and the reaction mixture was allowed to stir at reflux for 12 h. The reaction mixture was cooled to room temperature, filtered and then concentrated under vacuum to yield the product **4** as an orange-yellow solid (0.369 g, 72%). ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): δ 7.45 (d, 2H, $^3J_{HH}$ = 8 Hz, *o*-C_6H_5), 7.35 (t, 2H, $^3J_{HH}$ = 8 Hz, *m*-C_6H_5), 7.31 (t, 1H, $^3J_{HH}$ = 8 Hz, *p*-C_6H_5), 5.86 (s, 4H, C_3N_2H), 5.39 (br, 8H, CH_2), 4.18 (s, 4H, CH_2Ph), 3.38 (br, 8H, CH_2), 2.88 (s, 12H, CH_3), 2.19 (s, 12H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C): δ 152.7 (C_3N_2H), 144.1 (C_3N_2H), 134.0 (*ipso*-C_6H_5), 131.6 (*m*-C_6H_5), 129.4 (*p*-C_6H_5), 128.9 (*o*-C_6H_5), 108.3 (C_3N_2H), 68.7 (CH_2), 61.1 (CH_2), 48.4 (CH_2Ph), 15.2 (CH_3), 11.8 (CH_3). IR data (KBr pellet cm^{-1}): 2925 (m), 1634 (w), 1555 (s), 1495 (m), 1424 (s), 1398 (s), 1320 (w), 1232 (w), 1159 (w), 1054 (w), 912 (w), 878 (w), 791 (m), 746 (m), 704 (m). Anal. Calc. for $C_{42}H_{58}N_{10}Pd_2Cl_4$: C, 47.70; H, 5.53; N, 13.24. Found: C, 47.31; H, 5.45; N, 12.38%.

Computational methods

Density functional theory calculations were performed on the palladium **1–4** complexes including their fragments using GAUSSIAN 03[38] 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.[39] Stuttgart-Dresden effective core potential (ECP), representing 19 core electrons along with the valence basis sets (SDD) is used for palladium atom.[40] All other atoms are treated at the 6-31G(d) basis set.[41] All stationary points are characterized as minima by evaluating Hessian indices on the respective potential energy surfaces. Tight SCF convergence (10^{-8} a.u.) was used for all calculations. Natural bond orbital (NBO) analysis was performed using the NBO 3.1[42] program implemented in the GAUSSIAN 03 package.

Inspection of the metal–ligand donor–acceptor interactions was carried out using the charge decomposition analysis (CDA).[43] CDA is a valuable tool in analyzing the interactions between molecular fragments on a quantitative basis, with an emphasis on electron donation.[44] The orbital contributions in the geometry optimized palladium(II) (bispyrazole)$PdCl_2$ **1–4** complexes can be divided into three parts:

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

The CDA calculations are performed using the *AOMix*,[25] 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.[45]

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 **1–4** (2 mol%) were 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.

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 **3** (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.

X-Ray structure determination

X-Ray diffraction data for compounds **1–4** were collected on a Bruker P4 diffractometer equipped with a SMART CCD detector and crystal data collection and refinement parameters are summarized in Table S1.† 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).[46]

Acknowledgements

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