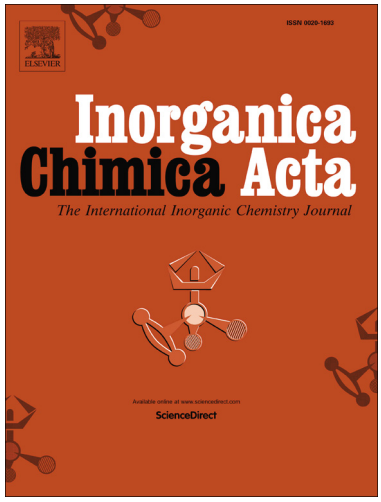

Research paper

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Palladium(II) Pyrazolyl–Pyridyl Complexes Containing a Sterically Hindered N-Heterocyclic Carbene Moiety for the *Suzuki-Miyaura* Cross-Coupling Reaction

Lapo Luconi,[a],φ Zufar Gafurov,[b],φ Andrea Rossin,*,[a] Giulia Tuci,[a] Oleg Sinyashin,[b] Dmitry Yakhvarov*,[b,c] and Giuliano Giambastiani*,[a,c]

[a] *Institute of Chemistry of OrganoMetallic Compounds*, ICCOM-CNR, Via Madonna del Piano, 10, 50019 Sesto Fiorentino, (Florence), Italy. Fax: +39 055 5225203.
Email: giuliano.giambastiani@iccom.cnr.it, a.rossin@iccom.cnr.it

[b] *A.E.Arbuzov Institute of Organic and Physical Chemistry, Russian Academy of Sciences*, Arbuzov str. 8, 420088 Kazan, Russian Federation. *Email*: yakhvar@iopc.ru

[c] *Kazan Federal University*, 420008 Kazan, Russian Federation.

φ These co-authors contributed equally to this work

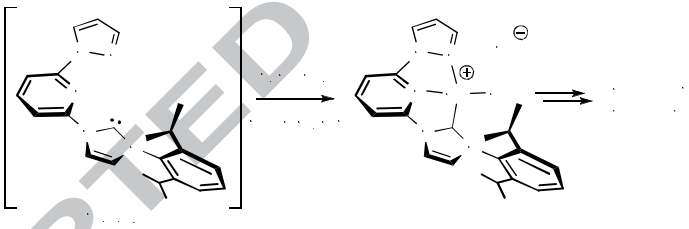
Abstract

Cationic palladium complexes stabilized by a tridentate neutral {*N*,*N*,*C*} ligand containing a sterically hindered N-heterocyclic carbene (*NHC*) moiety have been prepared and characterized. The nature of the anionic counterion in the palladium complex has been varied to get crystals suitable for X-ray diffraction. The square planar structure of one of these complexes along with the axial contribution of the sterically hindered *NHC* fragment has been confirmed by X-ray analysis. In addition, all the isolated $[\{\kappa^3\text{-}N,N,C\}Pd^{II}Cl]^+X^-$ [X^- = Cl, PF_6, BF_4, $B(C_6H_3Cl_2)_4$] ion pairs have been scrutinized as catalysts in the cross-coupling *Suzuki–Miyaura* reaction between phenylboronic acid and variably substituted halo-aryl acceptors. Selected issues from this series have shown improved catalyst turn-over frequencies (TOFs) with respect to structurally related catalytic systems of the *state-of-the-art*.

Keywords: *NHC*-containing ligand; Palladium complexes; *Suzuki-Miyaura* coupling

1. Introduction

The design and synthesis of new ligands featured by a mixed-donor atom set and including one or more N-heterocyclic carbene (NHC) frameworks have received a great deal of attention in the last decade because of their high versatility in the fields of coordination chemistry and homogeneous catalysis.[1] The strong σ-donor and relatively weak π-acceptor properties of NHCs make them valuable mimics of phosphines in transition-metal coordination chemistry.[2] In addition, NHC frameworks generally present higher donor capability and basicity than phosphines and offer more versatility to the easy tuning of their stereo-electronic properties compared to their P-based counterparts whose manipulation is often not trivial.[3] In this paper, a highly sterically hindered NHC group has been selected as the third donor site for the construction of a tridentate pyrazolyl-pyridyl ligand [$L_{(N,N,C)}$] containing a hemilabile coordinative arm (N-pyrazole) (Scheme 1).[4-8]



Scheme 1. General sketch of ligand and complexes described in this paper.

From a homogeneous catalysis viewpoint, the ligand hemilability provides access to a vacant coordination site at the metal center and facilitates an effective coordination, activation and transformation of the substrate. The neutral [$L_{(N,N,C)}$] ligand has been used to synthesize a series of Pd(II) complexes to be used in turn as pre-catalysts for the cross-coupling reaction between an organoboron reagent and an organic halide (*Suzuki-Miyaura* cross coupling).[9] The strong σ-donor character of NHC *trans* to the N-pyrazole is thought to speed up the N-dissociation (*trans effect*), thus making this coordinative position more reactive in the interaction with the substrate throughout the catalytic process. Structurally related ligands featuring with the same donor atom set but

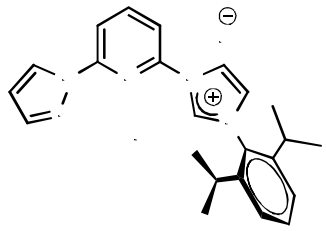
containing less sterically demanding substituents at the NHC fragment have been discussed in the literature and scrutinized in combination with a Pd(II) precursor for the *Suzuki-Miyaura* cross-coupling.[10] This reaction consists of three consecutive steps in the catalytic cycle: the substrate oxidative addition, an aryl transmetallation from boron to palladium and the final product reductive elimination.[11] Overall, the process benefits from the use of electron-donating and sterically demanding ligands for promoting the first and last steps, respectively.[9, 12] Herein, we describe the methodology applied for the synthesis of a sterically hindered imidazolium salt as precursor of the neutral [$L_{(N,N,C)}$] ligand and the isolation and characterization of cationic Pd(II) complexes with different counterions. The effect of bulky substituents on NHC-based palladium complexes has important precedents in the literature, particularly regarding the development of protocols devised for the cross-coupling of sterically challenging substrates. Seminal issues about the (NHC)Pd-catalyzed Suzuki-Miyaura reaction [9, 13, 14] have demonstrated that the higher the steric hindrance of NHC substituents, the lower the catalyst loading required for the process to occur.[15] The effects of ligand and ion pair and NHC steric hindrance have been discussed in the *Suzuki-Miyaura* reaction for the cross-coupling of phenylboronic acid (PBA) with a variety of aryl halides.

2. Experimental

2.1 General considerations and characterization methods.

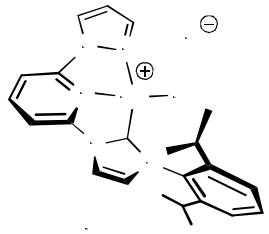
All reactions dealing with ligand and complexes syntheses were performed under an inert atmosphere in flame-dried flasks using standard Schlenk-type techniques or in a glovebox filled with nitrogen. Acetonitrile (CH_3CN) and diethyl ether ($C_4H_{10}O$) were obtained by means of a MBraun solvent purification system. Pentane and CH_2Cl_2 were also used after a preliminary treatment through columns of activated alumina and molecular sieves. CD_2Cl_2 and DMSO-d_6 were dried over activated 4 Å molecular sieves or calcium hydride. $Na[B(3,5\text{-}C_6H_3Cl_2)_4]$ [16, 17] and *cis*-$PdCl_2(PhCN)_2$ [18] were prepared according to the published procedures. All other reagents and

solvents were used as purchased from commercial suppliers and used as received. ^{1}H, $^{13}C\{^{1}H\}$, $^{31}P\{^{1}H\}$ NMR and $^{11}B\{^{1}H\}$ NMR spectra were obtained on a Bruker Avance 400 or Bruker Avance 300 MHz instrument. Chemical shifts are reported in ppm (δ) relative to TMS, referenced to the chemical shifts of residual solvent resonances (^{1}H and ^{13}C), and coupling constants are given in Hz. $^{31}P\{^{1}H\}$ NMR spectra are referenced to an external 85% H_3PO_4 sample (0 ppm). $^{11}B\{^{1}H\}$ NMR spectra are referenced to boron trifluoride diethyl etherate ($BF_3 \cdot Et_2O$). The N, C, H elemental analyses were carried out at ICCOM by means of a Carlo Erba Model 1106 elemental analyzer. The GC-MS analyses were performed on a Shimadzu QP2010S apparatus equipped with with a flame ionization detector and a Supelco SPB1 fused silica capillary column (30 m length, 0.25 mm i.d., 0.25 μm film thickness).



2.2 Synthesis of the imidazolium salt **3.** A mixture of **1** (0.600 g, 2.67 mmol) and imidazole **2** (0.611 g, 2.67 mmol) was sealed in a glass ampoule under nitrogen and heated to 190 °C for seven days. After cooling to room temperature, the crude product was dissolved in the minimum amount of CH_2Cl_2 and added dropwise in a large excess of diethyl ether under stirring to give a precipitate that was filtered on Buchner funnel and washed with diethyl ether to give the final product as light brown powder (1.090 g, 90 % yield). ^{1}H NMR (400 MHz, CD_2Cl_2, 293K): δ 1.19 (d, $^{3}J_{HH}$ = 6.8 Hz, 6H, CH(CH_3)), 1.27 (d, $^{3}J_{HH}$ = 6.8 Hz, 6H, CH(CH_3)), 2.42 (sept, $^{3}J_{HH}$ = 6.8 Hz, 2H, C*H*(CH$_3$)), 6.52 (m, 1H, C*H* Ar, Pyrazolyl), 7.38 (d, $^{3}J_{HH}$ = 7.8 Hz, 2H, C*H* Ar), 7.53 (m, 1H, imidazole), 7.61 (t, $^{3}J_{HH}$ = 7.8 Hz, 1H, C*H* Ar), 7.77 (m, 1H, C*H* Ar, Pyrazolyl), 8.12-8.21 (2H, C*H* Ar, Py), 8.75 (m, 1H, C*H* Ar, Pyrazolyl), 8.81 (d, $^{3}J_{HH}$ = 7.8 Hz, 1H, C*H* Ar, Py), 9.11 (m, 1H, imidazole), 11.3 (m, 1H, imidazole). $^{13}C\{^{1}H\}$m NMR (100 MHz, CD_2Cl_2, 293 K): δ 24.2 (CH(*C*H$_3$)$_2$,), 24.3 (CH(*C*H$_3$)$_2$,), 29.1 (*C*H(CH$_3$)$_2$), 109.1 (*C*H Ar), 112.9 (*C*H Ar), 114.1 (*C*H Ar), 120.9 (*C*H Ar), 125.0 (*C*H Ar), 125.9 (*C*H Ar), 128.1 (*C*H Ar), 130.3 (*C*q), 132.3 (*C*H Ar), 136.7

(*C*H Ar), 143.4 (*C*H Ar), 143.7 (*C*H Ar), 144.7 (*C*q), 145.5 (*C*q), 151.0 (*C*q). Anal. Calcd (%) for $C_{23}H_{26}BrN_5$ (452.39): C 61.06, H 5.79, N 15.48; found C 61.11, H 5.70, N 15.53.



2.3 General procedure for the synthesis of complexes $[(\kappa^3\text{-NNC})PdCl]^+X^-$ (X = Cl, **4a**; X = PF_6, **4b**; X = BF_4, **4c**; X = $B(C_6H_3Cl_2)_4$, **4d**). A suspension of **3** (0.200 g, 0.44 mmol), Ag_2O (5 eq., 0.512 g, 2.21 mmol), and activated molecular sieves 4 Å (200% w/w) in CH_2Cl_2 (10 mL) was stirred at reflux for 18 h in the dark. After cooling to room temperature, the suspension was filtered by cannula and the solution was dried under vacuum to give a pale brown foam. The residue was re-dissolved in dry and degassed CH_3CN (10 mL) and $PdCl_2(PhCN)_2$ (0.160 g, 0.42 mmol) was added to the solution. The resulting mixture was stirred at reflux for 16 h. After cooling to room temperature, a fine suspension of AgCl was filtered off and the clear solution underwent different treatments depending on the nature of the desired complex counterion. For **4a**, the solution was concentrated to 1/3 of its initial volume and the addition of an excess of Et_2O caused the formation of a light brown precipitate. The precipitate was collected and washed with Et_2O to give the pure product with fairly good yield (0.200 g, 88 % yield). For complexes **4b-d**, a crude mixture of **4a** was treated at room temperature with an equimolar amount of a silver or sodium salt containing the desired counterion [AgX (X = PF_6, BF_4) or NaX (X = $B(C_6H_3Cl_2)_4$) (0.42 mmol)] and stirred for further 5 h under these conditions. Afterwards, the resulting suspensions were filtered off and solutions concentrated to 1/3 of their initial volume. Addition of Et_2O afforded the desired complexes **4b-d** in the form of pale yellow microcrystals. Each precipitate was collected and washed with Et_2O to give the final product with isolated yields ranging from 53 to 79%. Crystals of **4d** suitable for X-ray diffraction analysis were grown by layer diffusion of Et_2O to a concentrated CH_3CN solution of the complex at room temperature. **4a** (88 % yield of the isolated product): ^{1}H NMR (400 MHz, DMSO-d_6, 293K): δ 1.13 (d, $^3J_{HH}$ = 6.8 Hz, 6H, CH(CH_3)), 1.25 (d, $^3J_{HH}$ = 6.8 Hz, 6H, CH(CH_3)), 2.53 (m, 2H, CH(CH$_3$)), 6.99 (m, 1H, CH Ar, Pyrazolyl), 7.34 (d, $^3J_{HH}$ = 7.8 Hz, 2H, CH Ar), 7.53 (t, $^3J_{HH}$ = 7.8 Hz, 1H, CH Ar), 7.99 (m, 1H, NCHCHN, imidazole), 8.07 (m, 1H, CH Ar, Pyrazolyl), 8.23-8.26

(2H, C*H* Ar, Py), 8.72 (m, 1H, C*H* Ar, Py), 8.83 (m, 1H, NC*H*CHN, imidazole), 9.26 (m, 1H, C*H* Ar, Pyrazolyl). $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6, 293 K): δ 23.2 ($CH(CH_3)_2$,), 24.1 ($CH(CH_3)_2$,), 28.0 ($CH(CH_3)_2$), 109.3 (*C*H Ar), 109.7 (*C*H Ar), 110.9 (*C*H Ar), 119.2 (*C*H Ar), 123.6 (*C*H Ar), 126.4 (*C*H Ar), 130.5 (*C*H Ar), 133.1 (*C*q), 133.2 (*C*H Ar), 144.3 (*C*q), 144.7 (*C*H Ar), 146.2 (*C*H Ar), 147.5 (*C*q), 148.6 (*C*q), 154.4 (Pd-C). Anal. Calcd (%) for $C_{23}H_{25}Cl_2N_5Pd$ (548.80): C 50.34, H 4.59, N 12.76; found C 50.30, H 4.57, N 12.80. **4b** (68 % yield of the isolated product): ^{1}H NMR (400 MHz, CD_2Cl_2, 293K): δ 1.13 (d, $^{3}J_{HH}$ = 6.8 Hz, 6H, CH(CH_3)), 1.25 (d, $^{3}J_{HH}$ = 6.8 Hz, 6H, CH(CH_3)), 2.53 (m, 2H, C*H*(CH_3)), 6.99 (m, 1H, C*H* Ar, Pyrazolyl), 7.34 (m, 2H, C*H* Ar), 7.53 (m, 1H, C*H* Ar), 7.98 (m, 1H, NCHC*H*N, imidazole), 8.07 (m, 1H, C*H* Ar, Pyrazolyl), 8.22-8.25 (2H, C*H* Ar, Py), 8.71 (m, 1H, C*H* Ar, Py), 8.82 (m, 1H, NC*H*CHN, imidazole), 9.25 (m, 1H, C*H* Ar, Pyrazolyl). $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6, 293 K): δ 23.2 ($CH(CH_3)_2$,), 24.1 ($CH(CH_3)_2$,), 28.1 ($CH(CH_3)_2$), 109.3 (*C*H Ar), 109.7 (*C*H Ar), 110.9 (*C*H Ar), 119.2 (*C*H Ar), 123.7 (*C*H Ar), 126.4 (*C*H Ar), 130.5 (*C*H Ar), 133.2 (*C*H Ar and Cq), 144.3 (*C*H Ar), 144.7 (*C*q), 146.2 (*C*H Ar), 147.6 (*C*q), 148.6 (*C*q), 154.4 (Pd-C). $^{31}P\{^{1}H\}$ NMR (161 MHz, DMSO-d_6, 293 K): δ -144.1 (sept). Anal. Calcd (%) for $C_{23}H_{25}ClF_6N_5PPd$ (658.32): C 41.96, H 3.83, N 10.64; found C 42.00, H 3.87, N 10.61. **4c** (79 % yield of the isolated product): ^{1}H NMR (400 MHz, CD_2Cl_2, 293K): δ 1.10 (d, $^{3}J_{HH}$ = 6.8 Hz, 6H, CH(CH_3)), 1.22 (d, $^{3}J_{HH}$ = 6.8 Hz, 6H, CH(CH_3)), 6.97 (m, 1H, C*H* Ar, Pyrazolyl), 7.32 (m, 2H, C*H* Ar), 7.51 (m, 1H, C*H* Ar), 7.97 (m, 1H, NCHC*H*N, imidazole), 8.06 (m, 1H, C*H* Ar, Pyrazolyl), 8.18-8.22 (2H, C*H* Ar, Py), 8.68 (m, 1H, C*H* Ar, Py), 8.79 (m, 1H, NC*H*CHN, imidazole), 9.22 (m, 1H, C*H* Ar, Pyrazolyl). $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6, 293 K): δ 23.3 ($CH(CH_3)_2$,), 24.1 ($CH(CH_3)_2$,), 28.1 ($CH(CH_3)_2$), 109.3 (*C*H Ar), 109.7 (*C*H Ar), 110.9 (*C*H Ar), 119.2 (*C*H Ar), 123.7 (*C*H Ar), 126.4 (*C*H Ar), 130.5 (*C*H Ar), 133.2 (*C*H Ar and Cq), 144.3 (*C*H Ar), 144.7 (*C*q), 146.3 (*C*H Ar), 147.6 (*C*q), 148.6 (*C*q), 154.4 (Pd-C). $^{11}B\{^{1}H\}$ NMR (128 MHz, DMSO-d_6, 293 K): δ-1.2 (s). Anal. Calcd (%) for $C_{23}H_{25}BClF_4N_5Pd$ (600.16): C 46.03, H 4.20, N 11.67; found C 46.01, H 4.17, N 11.64. **4d** (53

% yield of the isolated product): ^{1}H NMR (400 MHz, CD_2Cl_2, 293K): δ 1.12 (d, $^{3}J_{HH}$ = 6.8 Hz, 6H, CH(CH_3)), 1.25 (d, $^{3}J_{HH}$ = 6.8 Hz, 6H, CH(CH_3)), 2.52 (m, 2H, CH(CH_3)), 6.89 (m, 8 H, *o*-C*H* Ar, B($C_6H_3Cl_2$)$_4$), 6.99 (m, 1H, C*H* Ar, Pyrazolyl), 7.16 (m, 4 H, *p*-C*H* Ar, B($C_6H_3Cl_2$)$_4$), 7.34 (m, 2H, C*H* Ar), 7.53 (m, 1H, C*H* Ar), 7.99 (m, 1H, NCHC*H*N, imidazole), 8.08 (m, 1H, C*H* Ar, Pyrazolyl), 8.23-8.26 (2H, C*H* Ar, Py), 8.71 (m, 1H, C*H* Ar, Py), 8.83 (m, 1H, NC*H*CHN, imidazole), 9.25 (m, 1H, C*H* Ar, Pyrazolyl). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6, 293 K): δ 23.2 (CH(CH_3)$_2$,), 24.1 (CH(*C*H_3)$_2$,), 28.1 (*C*H(CH_3)$_2$), 109.3 (*C*H Ar), 109.7 (*C*H Ar), 110.9 (*C*H Ar), 119.2 (*C*H Ar), 123.1 (*C*H Ar), 123.7 (*C*H Ar), 126.4 (*C*H Ar), 130.5 (*C*H Ar), 132.5 (*C*H Ar and *C*q (B($ArCl_2$)$_4$)), 133.1 (*C*q), 133.2 (*C*H Ar), 144.3 (*C*H Ar), 144.7 (*C*q), 146.3 (*C*H Ar), 147.6 (*C*q), 148.6 (*C*q), 154.4 (Pd-C), 165.2 (*C*q, $^{1}J_{BC}$ = 49 Hz, B($ArCl_2$)$_4$) . ^{11}B{^{1}H} NMR (128 MHz, DMSO-d_6, 293 K): δ -7.2 (s). Anal. Calcd (%) for $C_{47}H_{39}BCl_9N_5Pd$ (1110.16): C 50.85, H 3.54, N 6.31; found C 50.87, H 3.57, N 6.29.

2.4 General procedure for the Suzuki-Miyura Reactions. In a typical run, the selected catalyst (**4a-d**) was added to a solution of aryl halide (1.0 mmol), phenylboronic acid (PBA, 1.5 mmol) and Cs_2CO_3 (2.0 mmol) in 5 mL of solvent (DMF/H_2O v/v = 10:1). The resulting mixture was maintained under stirring and heated at the desired temperature (Table 1) using a pre-heated oil bath. The reaction course was monitored by sampling the mixture at fixed times and analyzing it via GC-MS technique. The reaction was stopped by cooling the mixture down rapidly to room temperature through addition of 15 mL of cold water. For a quantitative estimation of the diphenyl derivative obtained in the process, the crude mixture was treated with a fixed amount of Fluorene ($C_{13}H_{10}$) as internal standard for GC analysis. Afterwards, the crude mixture was extracted with diethyl ether (3 x 15 mL) and the collected organic phases were dried over Na_2SO_4. Solvent removal under reduced pressure gave the crude material that was purified by flash chromatography on silica gel to afford the pure diphenyl derivative. Isolated yields are given as average values of two separate runs at least.

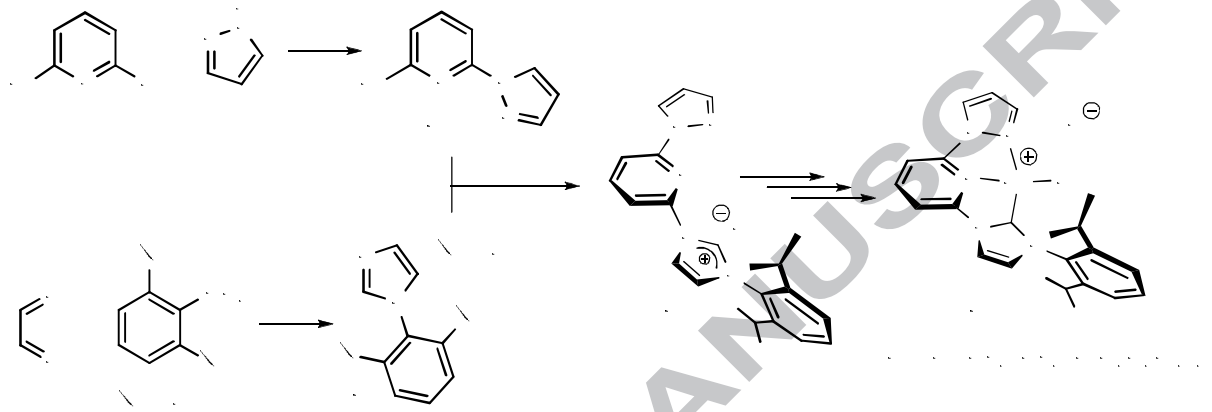
2.5 X-ray Diffraction Data. Single crystal X-Ray data of **4d** were collected at low temperature (100 K) on an Oxford Diffraction XcaliburPX diffractometer equipped with a CCD area detector using Cu K_α radiation (λ = 1.5418 Å). The program used for the data collection was CrysAlis CCD 1.171.[19] Data reduction was carried out with the program CrysAlis RED 1.171 [19] and the absorption correction was applied with the program ABSPACK 1.17. Direct methods implemented in Sir97 [20] were used to solve the structures and the refinements were performed by full-matrix least-squares against F^2 implemented in SHELX97.[21] All the non-hydrogen atoms were refined anisotropically, while the hydrogen atoms were fixed in calculated positions and refined isotropically with the thermal factor depending on the one of the atom to which they are bound (riding model). Molecular plots were produced by the program ORTEP3.[22] CCDC-1528509 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via ccdc.cam.ac.uk/community/requestastructure.

3. Results and Discussion

*3.1 Synthesis of the {N,N,CH}$^+$Br$^-$ ligand precursor (**3**) and related palladium complexes [{κ^3-N,N,C}Pd^{II}Cl]$^+$X$^-$ [X$^-$ = Cl, PF_6, BF_4, $B(C_6H_3Cl_2)_4$] (**4a-d**)*

Scheme 2 illustrates the stepwise procedure adopted to synthesize the desired ligand precursor **3** and palladium complexes in good yields. Two synthetic steps have been used for preparing the key organic building blocks **1** and **2** in gram scale from commercially available precursors, following literature procedures.[23, 24] Both reactions proceed smoothly to give **1** and **2** as white crystalline solids after chromatographic purification with fairly good yield (**1**: 93%; **2**: 56%). Quaternarization of the N-substituted imidazole **2** is obtained by melting it with the bromo-pyridine **1** at 190°C in a sealed ampule under rigorous N_2 atmosphere [25] and keeping the system without stirring under this

conditions for days (see Experimental Section). The reaction mixture is then dissolved in CH_2Cl_2 and the imidazolium salt (**3**) is precipitated in nearly quantitative yield (93 %) from the solution using an excess of diethyl-ether. The recovered light-brown microcrystals are then washed several times with Et_2O, dried under vacuum at room temperature till constant weight and stored under N_2 atmosphere.



Scheme 2. Synthesis of ligand **3** and complexes **4a-d**. Reaction conditions: i) ^{t}BuOK, dioxane, reflux, 48h; ii) H_2CO 35% in H_2O, NH_3 25% in H_2O, MeOH, 70 °C; iii) 190 °C, neat, 7 days; iv) Ag_2O, CH_2Cl_2, 40 °C, 18h; v) $PdCl_2(PhCN)_2$, CH_3CN, 16 h, reflux; vi) $AgPF_6$ (**4b**) or $AgBF_4$ (**4c**) or $NaB(C_6H_3Cl_2)_4$ (**4d**), CH_3CN, 5 h, r.t.

The treatment of **3** with a silver base (Ag_2O) is used to activate the imidazolium salt thus providing the corresponding Ag^I-*NHC* compound. [26, 27] Transmetallation with $PdCl_2(PhCN)_2$ gives **4a** as analytically pure light-brown microcrystals in 88 % yield.[10] The nature of the counterion (Cl^-) in **4a** has been assigned based on a low resolution mass analysis [LRMS (ESI^-)]. The experimental MS spectrum regarding mass values and isotopic profile perfectly matches with the simulated one thus confirming Cl^- as counterion (Fig. S1). A counterion exchange is accomplished upon treating a freshly prepared CH_3CN solution of **4a** with a silver or sodium salt of the desired anion. The treatment with AgX (X = PF_6, BF_4) provides complexes **4b** and **4c** in 68 and 79 % isolated yield, respectively. **4a-c** are isolated from the mother liquors as highly twinned snowflakes crystals not suitable for X-ray analysis and their characterization is given in solution by means of multinuclear NMR spectroscopy (^{1}H and $^{13}C\{^1H\}$ NMR for **4a-c**; $^{31}P\{^1H\}$ NMR for **4b** and $^{11}B\{^1H\}$ NMR for **4c**) (Figs. S4-S11). Elemental analysis has confirmed the occurrence of a complete anion exchange

as well as the analytical purity of the isolated complexes. Complex **4d** containing the bulkier and weakly coordinating $B(C_6H_3Cl_2)_4^-$ anion is obtained in 53 % isolated yield from the reaction of **4a** with $NaB(C_6H_3Cl_2)_4$. **4d** is isolated as off-white single needles suitable for X-ray diffraction analysis. All the solid systems prepared (**4a-d** along with their ligand precursor **3**) are air- and moisture-stable compounds. All complexes are highly soluble in common polar organic solvents (*i.e.* CH_3CN, DMSO, DMF), moderately soluble in chlorinated hydrocarbons (CH_3Cl and CH_2Cl_2) and scarcely soluble or insoluble in Et_2O including the more common aliphatic or aromatic hydrocarbons. The ^1H and $^{13}C\{^1H\}$ NMR spectra of complexes **4a-c** show almost superimposable patterns with the only exception of **4d** because of the presence of typical low-field signals attributed to the tetra-aryl counterion (Figs. S12-S13). Evidences for the generation of carbene complexes (Pd-*NHC*) are given by the disappearance of the typical imidazolium resonance (δ_H over 11 ppm) in the ^1H NMR spectrum of **3** (Fig. S2) together with the appearance of diagnostic peak (δ_C around 154 ppm) in the $^{13}C\{^1H\}$ NMR spectra of all isolated organometallics and ascribed to the *ipso* C-site (Figs. S5, S7, S10, S13). Each ^{i}Pr fragment in ligand **3** and complexes **4a-d** shows an evident proton shielding of one of the methyl groups. Such an effect is indicative of an appreciable extent of conformational rigidity of the N-carbene substituent already present in the sterically hindered ligand precursor. In **4a-d** such a rigidity is additionally emphasized by the appearance of two well-resolved high-field resonances in the $^{13}C\{^1H\}$ NMR spectra ascribed to couples of diastereotopic methyl groups.

The X-ray structure of **4d** has contributed to elucidate the metal coordination sphere of the isolated compound. A perspective view is given in Fig. 1 along with a selection of the most significant bond lengths and angles in the figure caption.

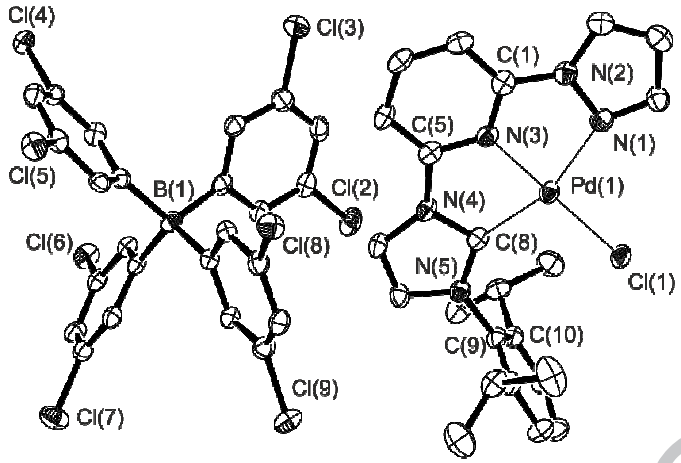


Fig. 1. Crystal structure of $[\{\kappa^3\text{-N,N,C}\}Pd^{II}Cl]^+$ $B(C_6H_3Cl_2)_4^-$ (**4d**). Thermal ellipsoids are drawn at the 40% probability level. Hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and angles (°): Pd(1)-Cl(1) 2.2775(12), Pd(1)-N(1) 2.097(4), Pd(1)-N(3) 1.968(4), Pd(1)-C(8) 1.963(5), N(3)-C(5)-N(4)-C(8) 1.65(6), N(3)-C(1)-N(2)-N(1) -6.33(6), C(8)-N(5)-C(9)-C(10) 97.3(6).

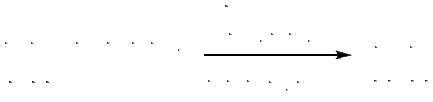
Complex **4d** crystallizes in the monoclinic $P2_1/c$ space group with 4 molecules per unit cell. The Pd^{II} center adopts a distorted-square-planar coordination geometry (τ_4 = 0.17) [28] with the N-carbene substituent lying in an almost orthogonal position with respect to the {N,N,C}coordination plane. Bond lengths and angles measured within the $[\{\kappa^3\text{-N,N,C}\}Pd^{II}Cl]^+$ fragment of **4d** fall in the typical range observed for related cationic Pd-fragments in square-planar environments.[10] Extensive C–H···Cl hydrogen bonding is present between the aromatic C–H bonds on the anion rings and on the pyrazole substituent and chlorine atoms from adjacent molecules in the lattice [mean d(C···Cl) = 3.59 Å]. Tables S1-S5 list all the main crystal and structural refinement data for **4d**.

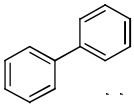
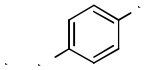
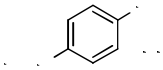
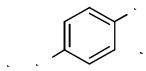
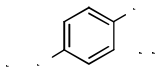
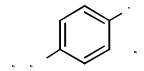
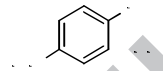
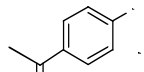
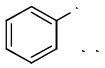
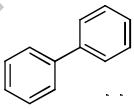
*3.2 The Suzuki-Miyaura cross-coupling reaction of phenylboronic acid (PBA) with various aryl-halides catalyzed by complexes **4a-d**.*

The Palladium-catalyzed *Suzuki-Miyaura* reaction (SMr) certainly ranks among the most utilized tools for the construction of a C-C bond between and organoboron reagent and an organic halide in the presence of a base. Its practical use along with very high turn-over numbers (TONs) in combination with specific catalytic systems,[29, 30] have made this process highly popular in the

pharmaceutical and chemical industries.[31] The recent literature in the field has demonstrated how the use of palladium complexes [32] stabilized by sterically bulky mono- or bis-NHC ligands leads to outstanding catalytic performances already under moderate reaction temperatures and in the presence of low catalyst loadings.[13, 14, 33-36] In addition, the renowned ability of related pyrazolyl–pyridyl complexes containing less sterically demanding NHC moieties at performing the SMr efficiently[10] prompted us to test complexes **4a-d** in the process. Table 1 lists the coupling reactions of selected aryl halides with phenylboronic acid (PBA) promoted by complexes **4a-d**. All reactions were carried out in a solvent mixture of DMF and H_2O (10:1 v/v) using Cs_2CO_3 as the base in the 80-120 °C temperature range depending of the mixture or reagents used. For all issues, the catalyst loading ranged between 0.5 and 5.0 mol% and the reaction course was monitored through thin layer chromatography (TLC) by sampling the reaction mixtures at different times. Selection of reagents was accomplished with the final aim of comparing the catalytic performance of complexes **4a-d** in the model cross-coupling process with those of related but less sterically hindered NHC-Pd complexes from the literature.[10] Under optimized experimental conditions (catalyst loading and reaction temperature), all catalysts **4a-d** showed from good to excellent performance in the *Suzuki-Miyaura* reaction with PBA. All conversions were firstly estimated via GC-MS analysis before being confirmed on the basis of the isolated products as obtained from chromatographic purification of crude mixtures. As table 1 shows, a rational trend between chemical yield (or catalyst turn-over frequency TOF) and nature of the anionic counterion seems rather hard to be unambiguously traced out. Under the adopted conditions, chlorine (Cl^-), PF_6^- and BF_4^- as palladium counterions showed only minor effects on TOFs and little differences reasonably fall in the statistical experimental data error.

Table 1. *Suzuki-Miyaura* Reactions Catalyzed by **4a-d**.

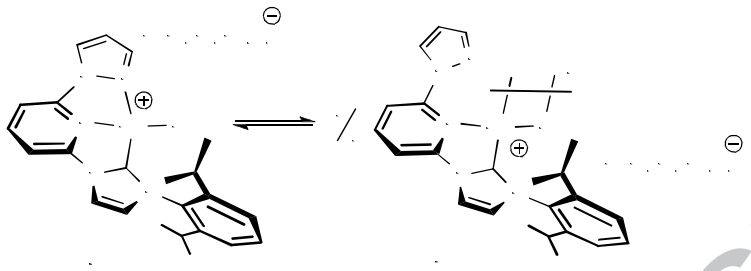


Entry	ArX	Catalyst (mol%)	Time (h)	Product	Yield[b] (%) (isol. yield)	TOF[d]
1		**4a** (0.5)	0.2		>99 (99)	-
2		**4b** (0.5)	0.2		96 (94)	964
3		**4c** (0.5)	0.2		97 (94)	969
4		**4d** (0.5)	0.2		52 (48)	518
5		**4a** (0.5)	2		98 (94)	98.0
6		**4b** (0.5)	2		>99 (>99)	-
7		**4c** (0.5)	2		98 (96)	98.2
8[c]		**Cat.** (3)	2		(95)	15.8
9		**4d** (0.5)	2		93 (90)	93.2
10		**4a** (3)	5		>99 (>99)	-
11		**4b** (3)	5		98 (95)	6.58
12		**4c** (3)	5		93 (90)	6.23
13		**4d** (3)	5		81 (80)	5.41
14		**4a** (3)	5		89 (86)	5.93
15		**4b** (3)	5		92 (88)	6.14
16		**4c** (3)	5		89 (87)	5.95
17		**4d** (3)	5		73 (72)	4.89
18[e]		**4a** (5)	5		84 (84)	3.38
19[e]		**4b** (5)	5		89 (88)	3.55
20[e]		**4c** (5)	5		82 (80)	3.28
21[e]		**4d** (5)	5		65 (64)	2.61
22[e]		**4a** (5)	5		23 (20)	0.91
23[e]		**4b** (5)	5		19 (n.d.)	0.75
24[e]		**4c** (5)	5		21 (20)	0.85
25[e]		**4d** (5)	5		18 (n.d.)	0.71

[a]Reaction Conditions: ArX, 1.0 mmol; phenylboronic acid, 1.5 mmol, Cs_2CO_3, 2.0 mmol; solvent, DMF/H_2O (v/v = 10:1), 5mL; temperature: 80 °C. [b] Conversion measured by GC-MS using fluorene as internal standard. [c] 3 mol% of **Cat.**:[{κ^3-N,N,$C^{NHC(nBu)}$}$Pd^{II}Cl]^+BF_4^-$ from ref. [10] [d] expressed as mmol of aryl-halide converted *per* (mmol of catalyst)$^{-1}$ (h)$^{-1}$; mmol of aryl halide converted as measured by GC-MS on the crude mixture. [e] temperature: 120 °C.

On the contrary, a more appreciable deviation was measured for almost all catalytic issues with complex **4d**. The bulkier and weakly coordinating $B(C_6H_3Cl_2)_4^-$ anion was found to have a detrimental effect on the catalyst TOF if compared with the performance of the **4a-c** congeners under identical conditions (*i.e.* Table 1, entry 4 vs. 1-3). Although any explanation for this observable lies on a mere speculative ground, the different behavior of **4d** can be tentatively ascribed to a decrease of the catalytically active species concentration [Pd(0)] in solution. Such a decrease may be due to an inherent inertness of **4d** (or one of its adducts) to undergo reduction. Indeed, the loose ion pair formed in **4d** combined with an easy pyrazole detachment may induce the

formation of Pd(μ-Cl)$_2$Pd dimeric forms (**4d-dim**) [37, 38] potentially reluctant to reduction to Pd(0) under the adopted experimental conditions (Scheme 3).[11]



Scheme 3. Supposed dimerization of **4d** to give **4d-dim** as a Pd(II) species less easy to be reduced under the Suzuki-Miyaura conditions.[11]

An increased catalyst concentration appears to be crucial also in the case of less reactive aryl bromides like those containing amino (Table 1, entries 10-13) or hydroxyl (Table 1, entries 14-17) functional groups. 3 mol% of each pre-catalyst and prolonged reaction time (5 h) are needed to get quantitative conversion of the aryl bromides into the corresponding diphenyl derivatives **13** and **14**. A special comment is needed to rationalize TOF values recorded for each catalyst from this series (compared to TOFs measured with related catalytic systems on the *state-of-the-art*) in the cross-coupling of PBA with the deactivated 4-methoxybromoaryl (Table 1, entries 5-7, 9). With 0.5 mol% of each catalyst (**4a-c**) an almost complete substrate conversion is obtained after keeping the system for two hours under stirring at 80 °C (Table 1, entries 5-7 and 9). Zeng and co-workers have reported this challenging issue (Table 1, entry 8) with 95% of the isolated **12** using 3 mol% of the less sterically hindered palladium analogue of **4c** (containing a ^{n}Bu chain as N-substituent at the NHC moiety).[10] In **4c**, the steric hindrance generated by the 2,6-^{i}Pr(C_6H_3) fragment eventually increases the catalyst performance thus ensuring a complete substrate conversion to **12** already at reduced palladium loading (Table 1, entry 8 vs. 7). Finally, the cross-coupling reaction with the activated 4-acetylchlorobenzene (Table 1, entries 18-21) gave fairly good substrate conversions only with 5 mol% of each catalyst and at a higher reaction temperature (120 °C) (Table 1, entries 18-21). Chloride derivatives classically exhibit lower reactivity than their iodide and bromide

analogues. This was confirmed by the moderate conversions obtained in the cross-coupling reaction of the relatively unreactive phenylchloride (**10**) (Table 1, entries 22-25 *vs.* 1-4).

Conclusions

In summary, the synthesis and characterization of a series of cationic pyrazolyl-pyridyl Pd(II) complexes containing a highly sterically demanding N-heterocyclic carbene unit and featuring with different counterions have been described. At odds with related NHC-containing ligands of the *state-of-the-art*, the synthetic methodology applied to the synthesis of the sterically hindered imidazolium salt as ligand precursor has provided it in the form of light-brown microcrystals with an overall 48% yield over three steps. Its activation with a silver base (Ag_2O) followed by transmetallation with a Pd(II) precursor and counterion exchange led to the isolation of four $\{[N,N,C]Pd^{+}Cl\}X^{-}$ (X^{-} = Cl^{-}, PF_6^{-}, BF_4^{-}, $B(C_6H_3Cl_2)_4^{-}$) complexes whose full spectroscopic characterization is provided along with the X-ray structure of the system containing the bulkier and weakly coordinating $B(C_6H_3Cl_2)_4$ anion. All isolated compounds have been scrutinized as catalyst precursors in the cross-coupling *Suzuki-Miyaura* reaction with phenylboronic acid and variably substituted halo-aryl acceptors. Selected issues from this series have shown improved catalyst turn-over frequencies (TOFs) compared with related (but less sterically demanding) catalytic systems of the *state-of-the-art*. In addition, the nature of the counterion has been evaluated under the adopted experimental conditions showing an appreciable deviation from TOFs in the case of the looser ion pair (**4d**) only.

Acknowledgments

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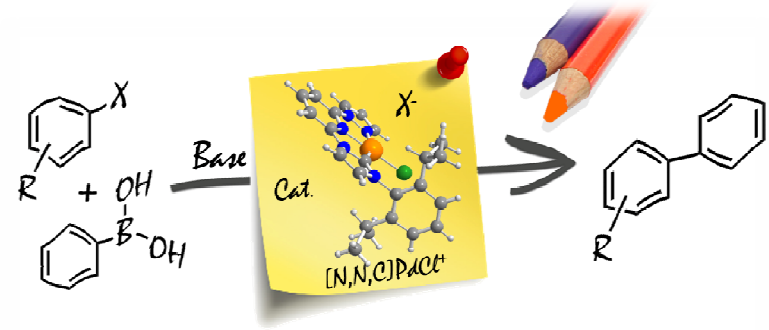
Table of Contents

Four cationinc pyrazolyl-pyridyl Pd(II) complexes containing a sterically demanding N-heterocyclic carbene unit have been synthesized and spectroscopically characterized. The sterically demanding nature of the ligand and the effect of the palladium counterion were evaluated in the cross-coupling *Suzuki-Miyaura* reaction between phenylboronic acid and variably substituted halo-aryl acceptors.



Highlights

- A novel synthetic protocol for the synthesis of sterically hindered N,N,C ligand.
- A tridentate pyrazolyl-pyridyl ligand containing a a highly sterically hindered NHC group.
- Synthesis of a series of Pd(II) complexes as pre-catalysts for the Suzuki-Miyaura cross-coupling reaction.
- The higher the steric hindrance of NHC substituents, the lower the catalyst loading required for the cross-coupling process to occur.