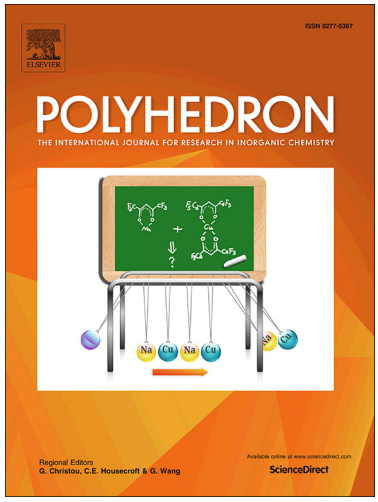

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Bis(pyrazolyl)palladium(II) complexes as catalysts for Mizoroki-Heck cross-coupling reactions

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Abstract

Recent progress in carbon-carbon cross-coupling reactions has resulted in the discovery of highly active catalysts for carrying out such transformations. However, due to the wide array of applications of the products from cross-coupling reactions, there is the need to design suitable catalysts that permit the practical and economical synthesis of the cross-coupled products. Palladium complexes with bulky and electron-donating ligands have served as excellent (pre)catalysts for the Mizoroki-Heck cross-coupling reaction. By using bulky pyrazole-based ligands, we have prepared palladium(II) complexes with controlled steric and electronic properties of the metal centre. We have used these bulky bis(pyrazolyl)palladium(II) complexes as (pre)catalysts for the Mizoroki-Heck cross-coupling reaction. The (pre)catalysts displayed high activity and selectivity, giving high catalytic conversions at a low (pre)catalyst loading and short reaction times. A mercury poisoning test confirmed that the (pre)catalysts promoted the Mizoroki-Heck cross-coupling homogenously and do not decompose into palladium black during the reactions. The catalytic systems were also tolerant to the presence of functional groups, such as 4-CF_3, 4-CH_3, 4-CO_2Me and 4-CO_2Et, on the alkene substrates.

Keywords: Bulky-pyrazolyl ligands; palladium(II) complexes; cross-coupling; Mizoroki-Heck; homogenous catalysts

1.0 Introduction

Transition metal catalysts have played a significant role in synthetic chemistry and the discovery of cross-coupling reactions has led to the design of new organic compounds and materials with a wide array of applications. These compounds and materials include drugs, natural products, optoelectronic materials and polymers.[1] One such example of a cross-coupling reaction is the Mizoroki-Heck reaction, which allows coupling between organic halides or pseudohalides and alkenes.[2] This cross-coupling reaction is of immense value to organic chemists as it allows the substitution of alkenes with high stereoselectivity for *trans* coupled products.[1] In spite of the impressive progress made in carbon-carbon cross-coupling reactions, especially the Mizoroki-Heck reaction, there is still a high demand for both economical and practical cross-coupling processes that use ultra-low catalyst loadings and give high turnover numbers.[2]

Palladium is mostly employed as the metal of choice in the Mizoroki-Heck cross-coupling[3–5] and other cross-coupling reactions.[6–8] This is because of the advantages it has over its most promising competitor, nickel.[5,9–11] These advantages include high activity, negligible or no by-product formation and no additive requirements. However, palladium is an expensive metal and any palladium catalyst that can operate efficiently at an extremely low catalyst loading is desirable. In order to develop such effective catalytic systems, palladium complexes with ligands that contribute increased electron-donation and steric bulk have been introduced as catalyst precursors. This has resulted in increased turnover numbers in Mizoroki-Heck cross-coupling reactions.[12] In addition, complexes that are air- and moisture-stable offer greater stability and easy handling of the catalyst precursor when compared to traditional Mizoroki-Heck cross-coupling catalytic systems - which make use of air- and moisture-sensitive ligands such as alkyl phosphines.[13] The use of bulky (non-phosphine based) ligands in preparing palladium(II) complexes presents the opportunities to not only isolate air- and moisture-stable catalyst precursors, but to also introduce (pre)catalysts with favourable stereo-electronic properties.[14-19] These stereo-electronic properties have been shown to result in high activity.[14–17]

Pyrazolyl-based palladium(II) complexes are stable and efficient catalyst precursors for Mizoroki-Heck cross-coupling reactions, at mild temperatures with fast reaction times.[14] Such pyrazolyl complexes, particularly those where the pyrazolyl ligands coordinate to the palladium in a bis-coordination mode,[15,22] have good potential to serve as alternatives to the often unstable palladium phosphine and NHC-based (pre)catalysts. We herein report the

synthesis of bulky bis(pyrazolyl)palladium(II) complexes with electron-donating and electron-withdrawing substituents on the pyrazolyl ring or on the benzyl ring, as stable catalyst precursors for Mizoroki-Heck cross-coupling reactions.

1.1 Experimental

1.1.1 Materials and methods

All reactions were carried out in air unless otherwise stated. All solvents used were reagent grade, purchased from Sigma Aldrich and dried under nitrogen before use. The NMR spectra were obtained using a Bruker-400 MHz NMR spectrometer (^{1}H at 400 MHz). The chemical shifts are reported relative to the internal standard tetramethylsilane (δ 0.00 ppm) and referenced to the residual proton and carbon signals at δ 7.24 and 77.0 ppm respectively of $CDCl_3$. Melting points were obtained using a Gallenkamp Digital Melting-point Apparatus 5A 6797. Elemental analysis was performed on a Thermos Scientific FLASH 2000 CHNS-O Analyzer. Mass spectrometry was performed using a Waters Synapt G2 mass spectrometer with both ESI positive and Cone Voltage 15 V. XRD spectra were obtained from a Bruker APEX-II CCD Diffractometer. Analytical thin layer chromatography (TLC) was performed on silica gel coated aluminium plates (0.2 mm). The developed plates were visualized with UV light or under iodine staining. Silica gel column chromatography was performed using silica gel 60 (70-230 mesh).

1.1.2 General experimental procedure- Synthesis of the pyrazolyl ligands 1-4

Synthesis of the previously reported pyrazolyl ligands **1-4** first involved the preparation of 3,5-ditertbutylpyrazole and 3,5-diphenylpyrazole. In a typical procedure, 3,5-disubstituted pyrazole (1 mmol) was reacted with methyl-4-(chloromethyl)benzoate (1mmol) or benzyl bromide (1 mmol) in DMSO in the presence of NaH (4 mmol) at room temperature for 16 h. Water was then added to the reaction mixture and the product extracted using EtOAc. The crude product was then purified *via* column chromatography using a 1:3 v:v diethyl ether:hexane mixture.[18]

(**1**) Yield: 184 mg, 50 %; Melting point: 123 ^{o}C. ^{1}H NMR (100 MHz, $CDCl_3$, 30 ^{o}C, δ, ppm): 7.94 (d, 2H, J_{HH} = 8 Hz, H_{arom}), 7.83 (d, J_{HH} = 8 Hz, 2H, H_{arom}), 7.45-7.30 (m, 8H, H_{arom}), 7.18 (d, 2H, J_{HH} = 8 Hz, H_{arom}), 6.70 (s, 1H, H_{pz}), 5.45 (s, 2H, H_{CH2}), 3.89 (s, 3H, H_{CH3}). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 30 ^{o}C, δ, ppm): 166.77, 151.43, 145.67, 142.77, 133.32, 130.55,

130.37, 130.25, 129.99, 129.44, 128.85, 128.86, 127.81, 126.77, 125.75, 103.95, 53.11, 52.11. Elemental analysis, Anal. calcd. for $C_{24}H_{20}N_2O_2$: C, 78.24; H, 5.47; N, 7.60%; Found: C, 78.33; H, 5.59; N, 7.51%

(**2**) Yield: 170 mg, 52%; Melting point: 139 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 30 °C, δ, ppm): 7.92 (d, 2H, J_{HH} = 7.9 Hz, H_{arom}), 6.93 (d, J_{HH} = 8 Hz, 2H, H_{arom}), 5.90 (s, 1H, H_{pz}), 5.49 (s, 1H, H_{CH_2}), 3.89 (s, 3H, H_{CH_3}), 1.28 (s, 9H, H^tBu), 1.22 (s, 9H, H^tBu). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 30 °C, δ, ppm): 166.87, 160.65, 151.94, 144.63, 129.75, 129.65, 128.81, 125.85, 125.68, 100.39, 54.00, 51.97, 31.21, 30.26. Elemental analysis, Anal. calcd. for $C_{20}H_{28}N_2O_2$: C, 73.14; H, 8.59; N, 8.53%, Found: C, 73.29; H, 8.41; N, 8.33%

(**3**) Yield: 241 mg, 78%; Melting point: 95 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 30 °C, δ, ppm): 7.70 (d, $^3J_{HH}$ = 7.2 Hz, 2H, H_{arom}), 7.38-7.23 (m, 11H, H_{arom}), 7.09 (d, $^3J_{HH}$ = 6.8 Hz, 2H, H_{arom}), 6.59 (s, 1H, H_{pz}), 5.33 (s, 2H, H_{CH_2}). ^{13}C{1H} NMR (100 MHz, $CDCl_3$, 30 °C, δ, ppm): 150.95, 145.48, 137.76, 133.49, 130.61, 128.80, 128.73, 128.49, 128.40, 127.50, 127.48, 126.91, 126.85, 126.66, 103.71, 53.21. Elemental analysis, Anal. calcd. for $C_{22}H_{18}N_2$: C, 85.13; H, 5.85; N, 9.03 %, Found: C, 85.49; H, 5.75; N, 9.41 %.

(**4**) Yield: 207 mg, 77 %; Melting point: 61 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 30 °C, δ, ppm): 7.27 (t, $^3J_{HH}$ = 5.6 Hz, 3H, H_{arom}), 6.89 (d, $^3J_{HH}$ = 7.2 Hz 2H, H_{arom}), 5.89 (s, 1H, H_{pz}), 5.49 (s, 2H, H_{CH_2}), 1.29 (s, 9H, H^tBu), 1.24 (s, 9H, H^tBu). ^{13}C{1H} NMR (100 MHz, $CDCl_3$, 30 °C, δ, ppm): 161.33, 151.19, 139.20, 128.1, 128.08 126.65, 126.51, 125.77, 100.05, 54.05, 31.81, 30.29. Elemental analysis, Anal. calcd. for $C_{18}H_{26}N_2$: C, 79.95; H, 9.69; N, 10.36 %, Found C, 80.11; H, 9.64; N, 10.04 %.

Synthesis of **1a**

To 541 mg (1.47 mmol) of methyl 4-((3,5-diphenyl-1 *H*-pyrazol-1-yl)methyl)benzoate in a round bottom flask, 25.0 mL of methanol was added and stirred. 824 mg (14.7 mmol) of KOH was added and the resulting mixture refluxed at 85 °C for 18 h. The solvent was then removed by rotary evaporation, after which 25.0 mL of distilled water was added to the crude product to form a slurry. 30.0 % $HCl_{(aq)}$ was then added dropwise to precipitate the product. The product was then filtered and washed with 2 x 25.0 mL distilled water and air dried for 12 h. Appearance white solid (Yield: 409 mg, 79.0%). Solubility: Soluble in chloroform, methanol, DCM and diethyl ether; insoluble in water. Melting point range: 175-176 °C. FT-IR (ν_{max}/cm^{-1}): 1683.78 (C=O), 1609.40 (C=N). ^{1}H NMR (400 MHz, $CDCl_3$, 30 °C, δ, ppm): 7.99 (d, 2H, H_{arom}), 7.86 (d, 2H, H_{arom}), 7.44-7.29 (m, 8H, H_{arom}), 7.16 (d, 2H H_{arom}), 6.67 (s, 1H, H_{pz}), 5.42 (s, 2H, H_{CH2}), ^{13}C{1H} NMR (100 MHz, $CDCl_3$, 30 °C, δ, ppm): 171.06, 151.42, 145.76, 143.58, 133.07, 131.11, 131.00, 130.92, 130.79 130.54, 130.23, 130.11, 129.95, 129.87, 129.70, 104.00, 52.96.

HR-ESI-MS[M+H]$^+$: 355.1401. Elemental analysis, Anal. calcd. for $C_{23}H_{18}N_2O_2$: C, 77.95; H, 5.12; N, 7.90%; Found C, 77.90; H, 5.23; N, 7.63%

1.1.3 General experimental procedure - Synthesis of the *bis(*pyrazolyl)palladium(II) complexes 5-9

Synthesis of the previously reported [{bis(methyl 4-((3,5-diphenyl-1 *H*-pyrazol-1-yl)methyl)benzoate)}-palladium (II) chloride] (**5**), [{bis(methyl 4-((3,5-ditertbutyl-1 *H*-pyrazol-1-yl)methyl)benzoate)}-palladium (II) chloride] (**6**), [{bis(1-benzyl-3,5-diphenyl-1 *H*-pyrazole)}-palladium(II) chloride] (**7**) and [{bis(1-benzyl-3,5-di-*tert*-butyl-1 *H*-pyrazole)}-palladium (II) chloride (**8**) involved the reaction of the corresponding ligand (0.5 mmol) and [$PdCl_2(MeCN)_2$] (0.25 mmol) in 10 ml DCM for 24 h. At the end of the reaction, the amount of solvent was reduced *in vacuo* to about 2 ml, after which the product was precipitated out of DCM by the dropwise addition of diethyl ether or hexane.[18]

(**5**) Yield: 180 mg, 79 %. Melting point: 276 ^{o}C (decomposed without melting). ^{1}H NMR (400 MHz, $CDCl_3$, 30 ^{o}C, δ, ppm): 8.17 (d, 2H, H_{arom}), 7.94(d, 2H, H_{arom}), 7.33-7.28 (m, 6H, H_{arom}), 7.00 (d, 4H, H_{arom}), 6.38 (s, H_{pz}, 1H), 6.15 (s, H_{CH2}, 2H), 3.92 (s, H_{CH3}, 3H); ^{13}C{1H} NMR (100 MHz, $CDCl_3$, 30 ^{o}C, δ, ppm): 168.05, 156.12, 149.81, 138.43, 131.85, 129.45, 129.20, 128.91, 128.89, 128.75, 128.65, 128.50, 128.39, 128.08, 127.98, 105.19, 57.15, 52.10. Elemental analysis, Anal. calcd. for $C_{48}H_{40}Cl_2N_4O_4Pd$: C, 63.06; H, 4.41, N, 6.13 % Found C,63.21; H, 4.69; N, 6.39 %.

(**6**) Yield: 166 mg, 80 %; Melting point: 240 ^{o}C (decomposed without melting). ^{1}H NMR (400 MHz, $CDCl_3$, 30 °C, δ, ppm): 8.11 (d, J_{HH} = 8 Hz, 2H, H_{arom}), 8.09 (d, 2H, H_{arom}), 7.24 (d, 2H, H_{arom}), 7.09 (d, 2H, H_{arom}), 6.00 (m, 6H, H_{CH2}, H_{pz}), 3.95 (s, 3H, H_{CH3}), 3.84 (s, 3H, H_{CH3}), 1.95 (s, H^tBu, 6H), 1.90 (s, H^tBu, 1H), 1.83 (s, H^tBu, 6H), 1.62 (s, H^tBu, 2H), 1.55 (s, H^tBu, 3H), 1.29 (s, H^tBu, 1H), 1.24 (s, H^tBu, 7H), 1.21 (s, H^tBu, 7H), 1.15 (s, H^tBu, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 30 ^{o}C, δ, ppm): 167.50, 167.29, 167.25, 167.15, 165.55, 160.99, 157.28, 153.41, 144.30, 141.99, 141.78, 130.79, 130.69, 130.64, 130.39, 130.29, 130.21, 130.15, 130.15, 129.77, 127.22, 126.95, 125.89, 105.46, 105.16, 56.64, 51.99, 33.17, 32.89, 32.39, 31.89, 31.84, 31.79, 31.70, 31.58, 31.49, 31.45, 30.60, 30.37, 29.95. Elemental analysis, Anal. calcd. for $C_{40}H_{56}Cl_2N_4O_4Pd$: C, 57.59; H, 6.77, N, 6.72 % Found C,57.33; H 6.45; 6.91 N %.

(**7**) Yield: 119 mg, 60 %: Melting point: 251 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$, 30 °C, δ, ppm): 8.21 (d, J_{HH} = 7.2 Hz, 2H, H_{arom}), 7.30-7.13 (m, 9H, H_{arom}), 6.99 (d, 2H, H_{arom}), 6.95 (t, J_{HH} =

8 Hz, J_{HH}^{1} = 7.6 Hz, 2H, H_{arom}), 6.31 (s, H_{pz}, 1H), 6.10 (s, H_{CH_2}, 2H). $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$, 30 ^oC, δ, ppm): 155.55, 149.19, 137.39, 131.08, 129.16, 129.05, 129.01, 128.85, 128.79, 128.60, 128.55, 128.51, 128.40, 128.39, 110.20, 56.51. Elemental analysis, Anal. calcd. for $C_{44}H_{36}Cl_2N_4Pd$: C, 66.22; H, 4.55, N, 7.02 % Found C, 66.56; H 4.41; 6.78 N %.

(**8**) Yield: 112 mg, 63 %: Melting point: 222 ^oC (decomposed without melting). ^1H NMR (100 MHz, $CDCl_3$, 30 ^oC, δ, ppm): 7.41-7.22 (m, 6H, H_{arom}), 7.05 (d, 4H, H_{arom}), 6.05 (m, 6H, H_{pz}, H_{CH_2}), 1.96 (s, H^tBu, 7H), 1.93 (s, H^tBu, 2H), 1.84 (s, H^tBu, 9H), 1.69 (s, H^tBu, 2H), 1.25 (d, J_{HH} = 14.4 Hz, H^tBu, 7H), 1.20 (d, J_{HH} = 6 Hz, H^tBu, 7H), 1.17 (s, H^tBu, 2H), 0.86 (s, H^tBu, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 30 ^oC, δ, ppm): 165.14, 164.18, 157.01, 156.91, 135.77, 135.60, 129.11, 128.81, 128.69, 128.30, 128.11, 127.91, 127.19, 126.85, 125.80, 105.30, 105.27, 105.01 55.87, 55.73, 33.01, 32.91, 30.66, 30.34. Elemental analysis, Anal. calcd. for $C_{36}H_{52}Cl_2N_4Pd$: C, 60.21; H, 7.30, N, 7.80% Found C, 60.39; H, 7.55; N, 7.61%.

Synthesis of **9**

In a Schlenk tube, 100 mg of 4-((3,5-diphenyl-1 *H*-pyrazol-1-yl)methyl)benzoic acid (0.28 mmol) was added to 36.7 mg (0.14 mmol) of $[PdCl_2(MeCN)_2]$ using 5.00 mL of DCM as the solvent. The reaction mixture was then stirred for 24 h under argon at room temperature. The solvent was reduced *in vacuo* until the crude product began to precipitate. Hexane (5.00 mL) was then added dropwise until the product completely precipitated from the solution. The precipitate was filtered off and washed with 2 x 5.00 mL hexane and dried under vacuum for 6 h in order to obtain the product. Appearance: yellow powder, (Yield = 81.0 mg, 65.0 %). Solubility: Partially soluble in chloroform, xylene and toluene, insoluble in methanol, water, hexane and diethyl ether. Melting point: 246 °C (decomposed without melting). FT-IR (ν_{max}/cm^{-1}): 3379.74 (O-H), 1687.04 (C=O), 1609.16 (C=N). ^1H NMR (400 MHz, D_2O+KOH, 30 °C, δ, ppm): 8.75 (d, 2H, H_{arom}), 7.62-7.57 (m, 4H, H_{arom}), 7.49-7.48 (m, 2H, H_{arom}), 7.31-7.28 (m, 4H, H_{arom}), 7.13 (d, 2H, H_{arom}), 6.61 (s, 1H, H_{pz}), 6.42 (s, 2H, H_{CH_2}). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 30 °C, δ, ppm): 158.15, 155.29, 149.78, 137.89, 132.81, 129.41, 129.22, 128.99, 128.73, 128.54, 128.41, 128.37, 128.25, 128.21, 127.81, 106.54, 57.92. HR-ESI-MS$[M]^+$: 885.1085. Elemental analysis, Anal. calcd. for $C_{46}H_{36}Cl_2N_4O_4Pd$: C, 62.35; H, 4.09, N, 6.32 % Found C, 62.18; H 4.31; 6.52 N %.

1.1.4 General experimental description of the catalysis

The general procedure involved charging a Radley Carousel 12 Plus Reaction Station™ 24 x 150 mm quick-thread glass reaction tube with the required amounts of aryl halide, alkene, base, internal standard (*n*-decane), catalyst and solvent. The reaction was then allowed to proceed at the specified temperature for the specified time. To calculate the conversion, the GC was first calibrated using standard samples of the aryl halide, solvent, *n*-decane and *trans*-stilbene and *cis*-stilbene in order to accurately determine the retention times of these compounds. A sample of the reaction mixture in the reaction vessel was taken prior to the start of the reaction and analyzed by GC to determine the ratios of the various components. Aryl halide conversion to biphenyl was calculated by analyzing the retention peak areas of aryl halide with reference to the internal standard *n*-decane before and after the reaction. GC analyses were performed using a Scion 456-GC with a 30 m x 0.25 mm cyanopropylphenylmethylpolysiloxane phase column set to an initial temperature of 80 °C and then increased to 250 °C at 10 °C/min.

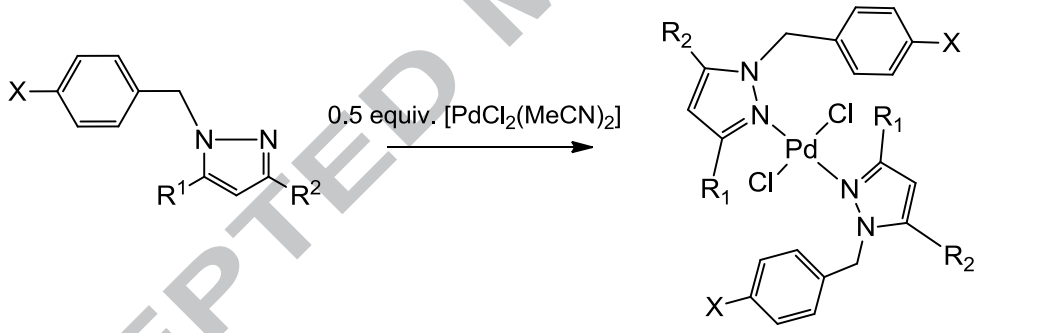
1.1.5 X-ray crystallography of 6 and 8

Single crystal diffraction studies were carried out using Quazar multi-layer optics monochromated Mo Kα radiation (k = 0.71073 Å) on a APEX II diffractometer (for **6**) and Bruker D8 Venture kappa geometry diffractometer (for **8**) with duo Iμs sources, a Photon 100 CMOS detector and APEX II control software.[19] The X-ray diffraction measurements were performed at 100 K (for **6**) and 150(2) K (for **8**). Data reduction was performed using SAINT+,[19] and the intensities were corrected for absorption using SADABS.[19] The structures were solved by direct methods using *SHELXT*,[20] using the *SHELXL-2014/7*[21] program. The non-hydrogen atoms were refined anisotropically. All H atoms were placed in geometrically idealised positions and constrained to ride on their parent atoms.

1.2 Results and discussion

1.2.1 Synthesis of the bis(pyrazolyl)palladium(II) complexes

Ligands **1-4** readily formed complexes with $[PdCl_2(MeCN)_2]$ in DCM at room temperature over a 24 h reaction time and the complexes (**5-9**) were easily isolated after precipitation using diethyl ether or hexane (Scheme 1). The square planar palladium(II) complexes were obtained in good yields from this reaction procedure, yielding air- and moisture-stable compounds. Complexes **5-9** can be kept on a benchtop for 18 months without decomposition and have high thermal stability (decompose without melting above 200 °C). Characteristic downfield shifts in the positions of the C*H*$_2$ protons, from ~ δ 5.5 ppm to around δ 6.0 ppm, in the ^{1}H NMR spectra of the complexes served as an indication of successful complexation of the ligands to the palladium ions, see Figures SI-1 and SI-4. All other ^{1}H NMR peaks were seen in the expected regions in the spectra of **5-9**. For example, in complex **9**, the aromatic proton signals resonate in the region δ 7.13–8.75 ppm, while the C*H*$_2$ and aromatic pyrazolyl proton signals were seen at δ 6.42 and 6.61 ppm, respectively.



1: R^1 = Ph, R^2= Ph, X= $COOCH_3$
1a: R^1 = Ph, R^2= Ph, X= COOH
2: R^1 = ^{t}Bu, R^2= ^{t}Bu, X= $COOCH_3$
3: R^1 = Ph, R^2= Ph, X= H
4: R^1 = ^{t}Bu, R^2= ^{t}Bu, X= H

5: R^1 = Ph, R^2 = Ph, X = $COOCH_3$
6: R^1 = ^{t}Bu, R^2 = ^{t}Bu, X = $COOCH_3$
7: R^1 = Ph, R^2 = Ph, X = H
8: R^1 = ^{t}Bu, R^2 = ^{t}Bu, X = H
9: 1: R^1 = Ph, R^2 = Ph, X = COOH

Scheme 1: Synthesis of the pyrazolyl complexes.

Complexes **5**, **6** and **9** all show distinctive signals in the range δ 160 to 170 ppm in their $^{13}C\{^{1}H\}$ NMR spectra, which correspond to the carbonyl carbon atoms present in these compounds. In addition, **5** and **6** give rise to peaks at around δ 50 ppm, which are assigned to the methyl groups of the esters. Generally for **5**, **6** and **9**, there are downfield shifts in the positions of the methylene (C*H*$_2$) carbon peak from around δ 53.09 ppm (Figure SI-1) in the corresponding free ligands to around δ 57 ppm, for the complexes. Similarly, the methylene (C*H*$_2$) carbon signal for **7** and **8** shifted from around δ 53 ppm in the free ligands to around δ 56 ppm in the complexes (Figures SI-2 and SI-5). Furthermore, the mass spectra of these complexes generally gave $[M]^+$ molecular ions, which fragmented by sequential loss of the chloride ligands, as shown in Figure SI-6.

1.2.2 Molecular structures of 6 and 8

The molecular structures of **6** and **8** were obtained using single-crystal X-ray diffraction, which confirmed the coordination of the pyrazolyl ligands to the palladium centrse in a *trans*-fashion. The crystal data and structure refinement parameters for these complexes are presented in Table 1. Slow evaporation at room temperature of separate DCM solutions of **6** and **8** yielded yellow crystals suitable for XRD analysis. Complex **6** crystallized in the $P2_1/n$ space group, while complex **8** crystallized in the $P2_1/c$ space group. The crystal structures of complexes **6** (Figure 1 (A)) and **8** (Figure 1 (B)) indicated the geometry around the palladium centre to be square planar. While the bond lengths around the metal centres of **6** and **8** fall in the usual ranges, it is interesting to comment on the differences in the bond angles. Both **6** and **8** possess bond angles, around the palladium centre that deviate from ideal square planar bond angles. Complex **6** has N(2)-Pd(1)-Cl(1) and N(2)-Pd(1)-Cl(1^i) bond angles of 85.78(4) and 94.22(4)^o, whilst complex **8** has N(2)-Pd(1)-Cl(1) and N(2)-Pd(1)-Cl(1^i) bond angles of 88.00(9)^o and 92.00(9)^o respectively. These deviations in bond angles may be the result of the steric bulk of the tertiary butyl substituents on the pyrazolyl rings which force the complexes out of their regular square planar geometry.

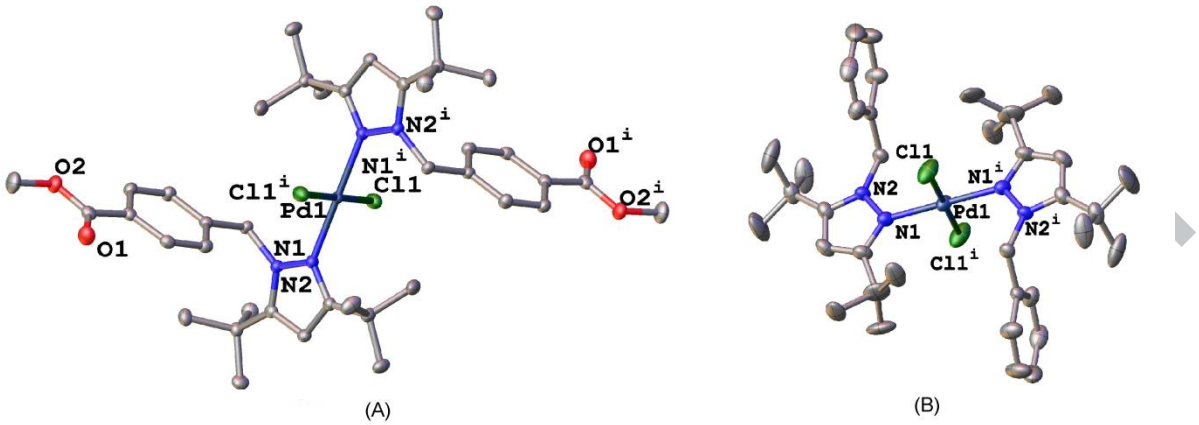


Figure 1: Molecular structures of **6 (A)** and **8 (B)**. Hydrogen atoms and distorted *^{t}Bu* group **(B)** are omitted for clarity.

Table 1: Crystal data for **6** and **8**.

Identification code	Complex **6**	Complex **8**
Empirical formula	$C_{40}H_{56}N_4O_4Cl_2Pd$	$C_{36}H_{52}Cl_2N_4Pd$
Formula weight	834.24	718.11
Temperature/K	100(2)	149.99
Crystal system	monoclinic	monoclinic
Space group	$P2_1/n$	$P2_1/c$
a/Å	13.0757(12)	10.8967(6)
b/Å	11.2095(10)	15.9169(9)
c/Å	13.9982(13)	11.4233(7)
α/°	90	90
β/°	93.366(2)	115.890(2)
γ/°	90	90
Volume/Å^3	2048.2(3)	1782.42(18)
Z	2	2
ρ_{calc}/g cm^{-3}	1.3526	1.338
μ/mm^{-1}	0.627	0.700
F(000)	870.9	752.0
Crystal size/mm^3	0.317 × 0.2 × 0.2	0.23 × 0.213 × 0.198
Radiation	Mo Kα (λ = 0.71073)	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.14 to 56.56	4.718 to 53.218

Index ranges	$-17 \leq h \leq 17$, $-14 \leq k \leq 14$, $-18 \leq l \leq 15$	$-13 \leq h \leq 13$, $-20 \leq k \leq 19$, $-14 \leq l \leq 14$
Reflections collected	45343	46305
Independent reflections	5060 [R_{int} = 0.0386, R_{sigma} = 0.0200]	3639 [R_{int} = 0.0565, R_{sigma} = 0.0329]
Data/restraints/parameters	5060/0/239	3639/0/253
Goodness-of-fit on F^2	1.026	1.203
Final R indexes [I>=2σ (I)]	R_1 = 0.0254, wR_2 = 0.0604	R_1 = 0.0528, wR_2 = 0.0861
Final R indexes [all data]	R_1 = 0.0300, wR_2 = 0.0628	R_1 = 0.0725, wR_2 = 0.0914
Largest diff. peak/hole / e $Å^{-3}$	0.87/-0.44	0.53/-0.62

Pd-N_{pz} and Pd-Cl bond lengths around the palladium centre for **6** and **8** were within the reported ranges for similar bis(pyrazolyl) palladium complexes in the literature.[22–24] Selected bond lengths and angles for **6** and **8** are given in Table 2.

Table 2: Selected bond lengths and angles for complexes **6** and **8**.

Bond angles (°) / lengths (Å)	**Complex 6**	**Complex 8**
Pd(1)-Cl(1)	2.3094(4)	2.2963(10)
Pd(1)-N(2)	2.0520(12)	2.051(3)
N(2)-N(1)	1.3766(17)	1.370(4)
N(2)-Pd(1)-Cl(1)	85.78(4)	88.00(8)
N(2)-Pd(1)-$N(2)^i$	180.00	180.00

1.3 Catalytic studies

1.3.1 Evaluation of (pre)catalysts 5-8 in Mizoroki-Heck cross-coupling reactions

In order to examine the efficiency of the bis(pyrazolyl)palladium(II) complexes **5-8** in the Mizoroki-Heck cross-coupling reaction, optimization was carried out using styrene and iodobenzene as model substrates. The reaction was studied under various conditions, such as different temperatures, base, catalyst loading and reaction times in an effort to find the most suitable conditions.

1.3.2 Optimization of the reaction conditions for the Mizoroki-Heck cross-coupling reaction

In determining the optimum reaction temperature, the cross-coupling reactions were carried at 80 to 140 ºC (Table SI-1). Increasing the temperature from 80 to 120 ºC resulted in a gradual increase in the iodobenzene conversion to *cis*- and *trans*-stilbene (~ 6:1 ratio of *trans*:*cis*-stilbene) for all four (pre)catalysts **5-8**, from around 20 to 70 %. At 140 ºC, 100 % conversion of iodobenzene to stilbene was observed for all four (pre)catalysts. However, reducing the temperature to 130 ºC still resulted in 100 %, indicating that 130 ºC was the optimum reaction temperature. Changing the solvent from DMF to either 1,4-dioxane or toluene in an effort to improve selectivity was unsuccessful as the (pre)catalysts decomposed during the catalytic reaction. This suggested that the solvent (DMF) may be playing a crucial stabilizing role of the active Pd^0 species in solution. In addition, the size and electronic effects of the substituents (tertiary butyl, phenyl or ester) on the (pre)catalysts did not significantly affect the selectivity, but rather the stability of the product drives the selectivity, since *trans*-stilbene is more stable than *cis*-stilbene.[25] Changing the base from triethylamine to pyridine resulted in no iodobenzene conversion (Table SI-2, Entries 13-16). Since pyridine is a weaker base as compared to triethylamine, there may possibly be a reduced "mopping-up" of HI (a reaction by-product) in the reaction step that leads to regeneration of the active Pd(0) species in the catalytic cycle.[7] Using KOH resulted in complete conversion to both *cis* and *trans*-stilbene in a ratio of around ~ 7:3. Triethylamine was used as the base for the subsequent reactions because of the ease of analysis of the reaction mixtures as it formed a completely homogenous mixture at the end of the reaction, in contrast to the use of KOH which formed a solid-like mass, requiring excessive dilution with DMF prior to GC analysis. However, either base can serve as a viable alternative for possible large-scale applications. Interestingly, using K_2CO_3, which is weaker than KOH, also resulted in no conversion. However, this poor conversion could also be as a result of the poor solubility of the base in DMF.

With an optimum temperature of 130 °C and using triethylamine as base, decreasing the catalyst loading from 0.5 mol % to 0.0375 mol % did not significantly reduce the conversion for all four (pre)catalysts (Table SI-3). This resulted in an appreciable increase in the turnover number from 200 (0.5 mol%) to around 2600 (0.0375 mol%) as a result of the lower catalyst to substrate ratio. de Vries *et al*[26] have reported that a higher catalyst loading (1.2 mol%) resulted in low activity in Mizoroki-Heck cross-coupling reactions using [$Pd(OAc)_2$] at 135

°C, and that this was due to formation of more unreactive palladium black at such higher catalyst loadings.[26] The yield of the cross-coupled products was the highest when the catalyst loading was in the range 0.02 and 0.08 mol%. However, a decrease of catalyst loading to 0.0094 mol% saw a significant production of the cross-coupled product with a TON as high as 5858, albeit with lowered aryl halide conversions of around 50 % (Table 3). These TONs are extremely high when **5-8** are compared to similar *bis*-pyrazolyl palladium complexes for the Mizoroki-Heck cross-coupling reaction, for which optimum TONs were around 990.[22]

Table 3: Optimum TON for Mizoroki-Heck cross-coupling reactions using **5-8**.

Entry	Cat. (loading mol%)	Conv. (%)	TON	TOF (h^{-1})	Selectivity (%)	
					trans-stilbene	*cis*-stilbene
1	**5** (0.0094)	52	5605	1401	89	11
2	**6** (0.0094)	53	5671	1418	89	11
3	**7** (0.0094)	54	5858	1464	89	11
4	**8** (0.0094)	45	4891	1223	89	11

Reactions carried out in DMF (1.2 mL) with 1.0 eq of iodobenzene, 1.1 eq of styrene, 2.0 eq of Et_3N and varied Pd catalyst loading at 130° C and 600 rpm for 4h. Using *n*-decane as an internal standard. Cat. = catalyst, Conv. = conversion.

A further decrease in catalyst loading to 0.00625 mol % resulted in a decreased conversion from ~50 to ~20% for all four (pre)catalysts (Table SI-3). Thus, 0.0375 mol% was chosen as the optimum catalyst loading. These catalysts are highly active when compared to similar *trans*-$[PdCl_2(L)_2]$ (pre)catalysts used for the Mizoroki-Heck cross-coupling reaction that have been reported in the literature[22,23] because of the higher TONs and TOFs under similar reaction conditions.

The reaction time was also varied from 0.5 h to 4 h in order to determine the minimum time required for the four catalytic systems to catalyze the Mizoroki-Heck cross-coupling reaction. Table SI-4 shows the results obtained. In thirty minutes, appreciable turnover numbers (around 1800) were achieved for all four (pre)catalysts **5-8**. (Pre)catalyst **8** had an exceptionally short induction period, converting 74 % of the substrates to mainly *trans*-stilbene in just 30 min (Table SI-4, Entry 4). (Pre)catalyst **5**, on the other hand, had a relatively longer induction

period, converting only 72 % of the substrates to *trans*-stilbene in an hour (Table SI-4, Entry 5). In addition, the (pre)catalysts with tertiary butyl substituent, **6** and **8**, had shorter induction periods as compared to those with a phenyl substituent, **5** and **7**. This suggests that steric bulk on the precursor bis(pyrazolyl) palladium(II) complex might be more important for Mizoroki-Heck cross-coupling reactions, as compared to electronic effects. Optimum conversions to *cis*- and *trans*-stilbene for all (pre)catalysts were achieved at ~ 2 h.

1.3.3 Mercury poisoning test and catalyst recyclability for the Mizoroki-Heck cross-coupling reaction

The homogeneity of the active species derived from (pre)catalysts **5**-**8** in the Mizoroki-Heck cross-coupling reactions in DMF was evaluated using a mercury drop test. The cross-coupling reactions using **5**, **6**, **7** or **8** were performed at the established optimum conditions for the temperature and reaction time, with the appropriate amounts of catalyst loadings and base in the presence of excess mercury. At the end of the reactions, the conversions were similar to those obtained under the same conditions without metallic mercury being added to the reactions. (Table SI-5). This suggests that the four catalysts promote the Mizoroki-Heck reactions as homogenous catalysts in solution and no palladium black could have been formed *in situ* to subsequently catalyse the reactions. This is true since the metallic mercury would have scavenged all the colloidal particles and consequently inhibited the reactions from proceeding (Table SI-5). The active catalyst is likely soluble Pd^0 species, stabilized by the solvent or the pyrazolyl ligands or both, since reactions in non-coordinating solvents gave poor yields.[26]

(Pre)catalyst **9**, which has water-solubilising carboxylic acid groups, was also found to promote the reaction homogenously. This catalyst was then evaluated for possible recyclability in aqueous-biphasic media, wherein the (pre)catalyst was added to an alkaline aqueous solution (KOH in water) in order to render it water-soluble. Both starting materials and the base were dissolved in toluene and added to the alkaline solution of the (pre)catalyst **9**. This resulted in immediate decomposition of the (pre)catalyst into a black unidentified species and no conversion was observed. When DMF was used instead of toluene, no black species was formed. However, this also resulted in no conversion, effectively showing that the catalysts are not recyclable (Table SI-5).

1.3.4 Substrate variation for (pre)catalysts 5-8 for the Mizoroki-Heck cross-coupling reaction

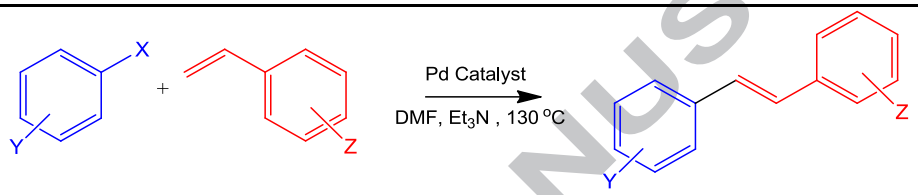
The (pre)catalysts **5-8** were evaluated for their ability to cross-couple substrates that possess various substituents for the Mizoroki-Heck cross-coupling reaction. A series of aliphatic/aromatic alkenes with electron-withdrawing groups and electron-donating groups were reacted with a variety of aryl halides that had electron-withdrawing or electron-donating groups in the presence of (pre)catalysts **5-8**.

Using a catalyst loading of 0.0375 mol%, a temperature of 130 °C, triethylamine as the base, a reaction time of 2 h and DMF as the solvent, 4-iodotoluene was effectively coupled with styrene in the presence of the four (pre)catalysts (Table 4, entries 1-4). Under these conditions, around 90 % conversion was obtained for all four precatalysts. The selectivity for the *trans* products observed for all four (pre)catalysts for this reaction were also similar to that observed when iodobenzene was coupled with styrene instead of 4-iodotoulene (Table SI-4, entries 13-16). However, the conversions obtained for the Mizoroki-Heck cross-coupling of iodobenzene and styrene were higher than those obtained for 4-iodotoluene and styrene in the presence of the four (pre)catalysts. This reduction in conversion is possibly due to the electron-donating effect of the CH_3 group present on the aryl halide. This would result in an increased aromatic C-I bond dissociation energy, leading to a lowered rate of oxidative addition. Similar observations have been reported in the literature.[27,28]

Although the catalysts were unable to catalyse the coupling of bromobenzene when 2-bromobenzonitrile was used as a coupling partner with styrene, conversion of the substrates was achieved (Table 4, entries 5-8). This indicates the presence of the electron-withdrawing cyano group served to sufficiently activate the halide-carbon bond, resulting in the formation of the coupled product. However, for these cross-coupling substrates, important differences were observed between the pre-catalysts **5-8**, complex **6** being the most active. In this case, there is a deviation from the norm, where catalysts with bulky and electron donating groups are expected to be more active for the cross-coupling reaction. As observed earlier, DMF plays a role for the Mizoroki-Heck cross-coupling reaction. For the less activated aryl halide, the bond dissociation energy between the halide and the aromatic sp^2 carbon atom is higher. This means that the rate of oxidative addition is expected to be slower for this substrate, thus giving

the opportunity for forming more solvent-Pd adducts. Such solvent participation may impact on the observed activity and has been reported in the literature.[29,30] When using the sterically hindered 2-iodoanisole as a reactant with styrene, significant aryl halide conversion was observed despite the presence of the relatively bulky methoxy group at the *ortho* position (Table 4, entries 21-24). However, these observed conversions were slightly lower when iodobenzene was used instead of 2-iodoanisole. This indicates that steric bulk near the Ar-X bond does not significantly affect the aryl halide conversion as compared to electronic effects.

Table 4: Variation of aryl halide for Mizoroki-Heck cross-coupling with styrene using (pre)catalysts **5-8**



Entry	Cat.	X	Y	Z	Conversion (%)	TON	TOF (hr^{-1})	Selectivity (%)
1	**5**	I	4-CH_3	H	89	2370	1185	89
2	**6**	I	4-CH_3	H	91	2424	1212	88
3	**7**	I	4-CH_3	H	82	2182	1091	89
4	**8**	I	4-CH_3	H	91	2416	1208	87
5	**5**	Br	2-CN	H	[a]57	114	38	98
6	**6**	Br	2-CN	H	[a]99	199	66	97
7	**7**	Br	2-CN	H	[a]71	143	48	98
8	**8**	Br	2-CN	H	[a]49	98	33	98
9	**5**	I	H	4-^{t}Bu	90	2398	1199	97
10	**6**	I	H	4-^{t}Bu	95	2526	1263	81
11	**7**	I	H	4-^{t}Bu	93	2469	1234	86
12	**8**	I	H	4-^{t}Bu	90	2389	1194	95
13	**5**	I	H	4-Cl	95	2538	1269	95
14	**6**	I	H	4-Cl	96	2565	1283	94
15	**7**	I	H	4-Cl	98	2605	1302	98
16	**8**	I	H	4-Cl	99	2666	889	93
17	**5**	I	H	4-CF_3	[a]100	200	67	93
18	**6**	I	H	4-CF_3	[a]100	200	67	85

19	**7**	I	H	4-CF_3	[a]100	200	67	96
20	**8**	I	H	4-CF_3	[a]100	200	67	88
21	**5**	I	2-OCH_3	H	[b]94	188	47	90
22	**6**	I	2-OCH_3	H	[b]86	172	43	91
23	**7**	I	2-OCH_3	H	[b]94	188	47	92
24	**8**	I	2-OCH_3	H	[b]99	198	50	88

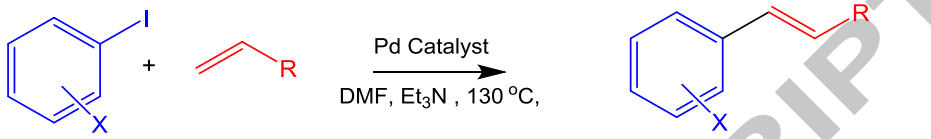
Reactions carried out in DMF (1.2 mL) with 8.8 mmol of arylhalide, 9.68 mmol of alkene, 17.6 mmol of Et_3N and 3.3×10^{-3} mmol Pd catalyst (loading = 0.0375 mol%) at 130 ^oC and 600 rpm for 2 h. (a) Reactions carried out in DMF (1.2 mL) with 0.66 mmol of arylhalide, 0.726 mmol of alkene, 1.32 mmol of Et_3N and 3.3×10^{-3} mmol Pd catalyst (loading = 0.5 mol%) at 130 ^oC and 600 rpm for 3 h; (b) = 4h. Using *n*-decane as the internal standard. Selectivity is reported relative to the *trans*-isomer. Average error estimate (+/-); **5** (0.3211), **6** (0.2877), **7** (0.1992), **8** (0.2756)

Coupling iodobenzene with 4-trifluoromethylstyrene, 4-*tert*-butyl styrene or 4-chlorostyrene (Table 4, entries 9-20) was also carried out to investigate the influence of electron-donating and electron-withdrawing substituents on styrene in the cross-coupling reactions. At a catalyst loading of 0.0375 mol% and a reaction time of 2 h, all four (pre)catalysts could effectively couple 4-tert-butylstyrene, 4-chlorostyrene or 4-chloromethylstyrene with iodobenzene, giving up to 100 % conversions. However, comparing the conversions obtained for iodobenzene, there was an indication that the electronic effects contributed by the presence of both electron-withdrawing and electron-donating groups on the aromatic ring of styrene. When an electron-donating group was present on the aromatic alkene, the conversions were slightly reduced as compared to when electron-withdrawing groups were present on the aromatic alkene. In addition, selectivity towards the *trans*-isomers was similar for both types of substrates. Such observations have also been reported in the literature.[31,32]

Replacing the aromatic alkene with aliphatic alkenes did not affect the aryl halide conversions significantly. At a catalyst loading of 0.0375 mol%, a temperature of 130 ^oC, with triethylamine as the base, a reaction time of 2 h and DMF as the solvent, iodobenzene was coupled with methyl acrylate and ethyl acrylate effectively (Table 5, entries 1-8). These coupling reactions yielded quantitative conversion of the aryl halide to the corresponding coupled product (*trans*-cinnamate). In addition, the observed selectivity towards the coupled product (*trans*-isomer) was also approximately 100 % for all reactions. This showed no significant difference between the choice of alkyl group used as the alkoxy substituents for the aliphatic alkenes. As with the case in coupling 2-iodoanisole with styrene in the presence of **5-8**, changing the alkene from

an aromatic alkene to an aliphatic alkene only resulted in slight losses of the aryl halide conversion, irrespective of the presence of the *o*-methoxy substituent present in 2-iodo anisole.

Table 5: Variation of alkenes for the Mizoroki-Heck cross-coupling for (pre)catalysts **5-8**.



Entry	Cat.	R	X	Conversion (%)	TON	TOF (hr^{-1})	Selectivity (%)
1	**5**	CO_2Me	H	100	2667	1333	>98
2	**6**	CO_2Me	H	100	2667	1333	>99
3	**7**	CO_2Me	H	100	2667	1333	>99
4	**8**	CO_2Me	H	99	2662	1331	>98
5	**5**	CO_2Et	H	100	2667	1333	>99
6	**6**	CO_2Et	H	100	2667	1333	87
7	**7**	CO_2Et	H	100	2667	1333	>99
8	**8**	CO_2Et	H	100	2667	1333	>99
9	**5**	CO_2Me	2-OCH_3	[a]100	200	50	87
10	**6**	CO_2Me	2-OCH_3	[a]99	198	50	97
11	**7**	CO_2Me	2-OCH_3	[a]98	196	49	94
12	**8**	CO_2Me	2-OCH_3	[a]99	198	50	93
13	**5**	CO_2Et	2-OCH_3	[a]100	200	50	94
14	**6**	CO_2Et	2-OCH_3	[a]99	198	50	94
15	**7**	CO_2Et	2-OCH_3	[a]98	196	49	96
16	**8**	CO_2Et	2-OCH_3	[a]96	192	48	>99

Reactions carried out in DMF (1.2 mL) with 8.8 mmol of iodobenzene, 9.68 mmol of alkene, 17.6 mmol of Et_3N and 3.3×10^{-3} mmol Pd catalyst (loading = 0.0375 mol%) at 130 °C and 600 rpm for 2 h. (a) Reactions carried out in DMF (1.2 mL) with 0.66 mmol of arylhalide, 0.726 mmol of alkene, 1.32 mmol of Et_3N and 3.3×10^{-3} mmol Pd catalyst (loading = 0.5 mol%) at 130 °C and 600 rpm for 4h; Using *n*-decane as an internal standard. Selectivity is reported relative to the *trans*-isomer. Average error estimate (+/-); **5** (0.1176), **6** (0.1432), **7** (0.1288), **8** (0.1331).

1.4 Summary and conclusions

Five bis(pyrazolyl)palladium(II) complexes (**5-9**) were prepared and evaluated for their efficacy in catalyzing the Mizoroki-Heck cross-coupling reaction. These catalysts were found to be effective in promoting the cross-coupling reactions and similar aryl halide conversions were obtained for all four (pre)catalysts when iodobenzene was coupled with styrene. These results were observed irrespective of the presence of electron-donating and electron-withdrawing groups present in the structures of the evaluated (pre)catalysts. Quantitative iodobenzene conversion to *trans*-stilbene could be obtained for (pre)catalysts **5-8** in the presence triethylamine as a base (in 2 h), even at catalyst loadings as low as 0.0375 mol %, where turnover numbers of 2560 were demonstrated. (Pre)catalysts **5-9** promoted the Mizoroki-Heck reactions by means of soluble palladium(0) species and not palladium black. This was supported by mercury drop experiments, which resulted in no inhibition of the catalytic activity. Conversions were slightly reduced when an electron-donating group was present on the aryl halide, while using activated aryl bromides resulted in the cross-coupling reaction taking place. On the other hand, the presence of electron-withdrawing groups on aromatic or aliphatic alkene substrates resulted in slightly increased conversions.

1.5 Conflicts of interest

There are no conflicts to declare.

1.6 Appendix A. Supplementary data

Electronic supporting information (ESI) is available free of charge. CCDC 1555881 and 1833891 contain the supplementary crystallographic data for complexes **6** and **8**, respectively. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk

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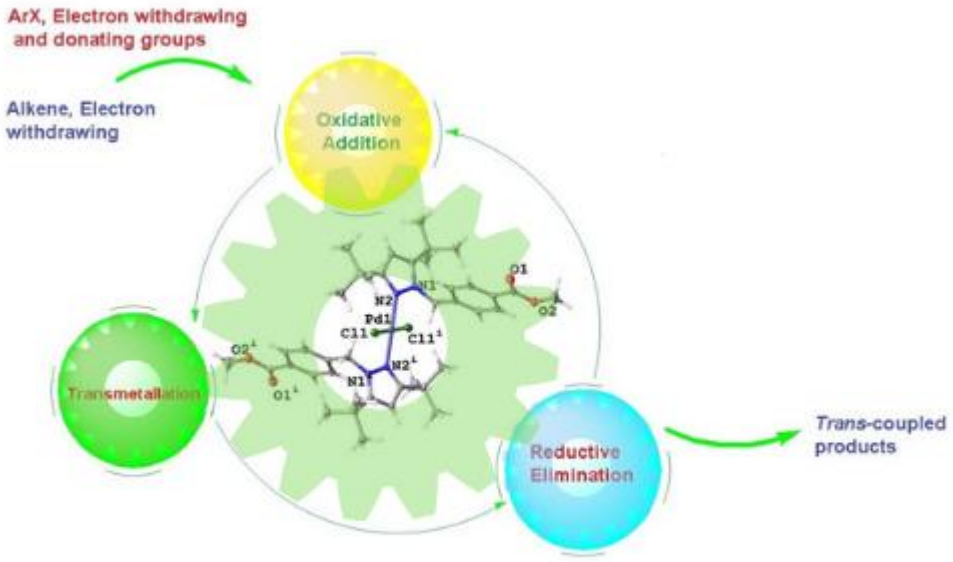

Bis(pyrazolyl)palladium(II) complexes as catalysts for Mizoroki-Heck cross-coupling reactions

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- Bis(pyrazolyl)palladium(II) complexes with a slightly distorted square planar geometry around the palladium centre as a result of steric encumbrance are presented.
- High TONs in Mizoroki-Heck cross-coupling reactions were achieved using these bis(pyrazolyl)palladium(II) complexes as (pre)catalysts.
- Good functional group tolerance is demonstrated.