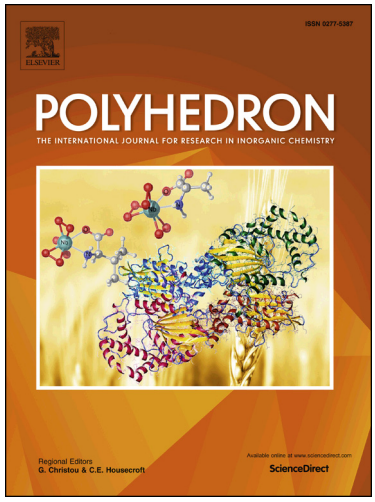

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Flexible, N-sulfonyl-substituted aliphatic amine ligands in palladium-catalyzed Suzuki-Miyaura C-C coupling: influence of substituents bulkiness and co-ligand size

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Abstract

Widespread use of commercially available palladium precatalysts is limited by high costs and their synthetic challenges. In this report, series of synthetically affordable, phosphine-free ligands were examined as supports for palladium active centers. 2-(2-Aminoethylamino)ethanol, diethylenetriamine and tris(2-aminoethyl)amine were condensed with sulfonyl chloride reagents in order to obtain flexible, aliphatic amine derivatives with varied steric bulk at the chain ends (ligands **1-Me** and **1-tol** = RSO_2–NH–CH_2CH_2–N(SO_2R)–CH_2CH_2Cl; ligands **2-ipr** and **2-iprNH** = RSO_2–NH–CH_2CH_2–NY–CH_2CH_2–O–SO_2R where Y is H or R; ligands **3-Me**, **3-tol** and **3-ipr** = RSO_2–N(CH_2CH_2–NH–$SO_2R)_2$; **3-iprNH** = HN(CH_2CH_2–NH–$SO_2R)_2$; ligands **4-tol** and **4-ipr** = N(CH_2CH_2–NH–$SO_2R)_3$; R = methyl,

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tolyl or triiso-propyl). Despite the flexibility of the alkyl fragments in these ligands, placement of sterically demanding groups at amine donors enables formation of active species, which supports high turnover frequencies and yields up to 91 % within 5 min and at 0.2 mol % palladium loading. Such activity from synthetically simple alkyl ligand frameworks, which are generally not regarded in Pd catalysis, is unprecedented. *In situ* catalyst generation is favourable for ligands with less than tridentate chelation capacity and presence of poorly chelating secondary NH-amine donor in the central position of the polyamines hinders catalyst performance. However, the preformed tridentate complexes yielded more attractive and living coupling catalyst efficiencies than their corresponding *in situ* reactions especially when bulkier co-ligand such as pyridine occupies the fourth coordination position (TOF of 5460 h^{-1} for **Pd(4-tol)py** and 4800 h^{-1} for **Pd(4-ipr)py**). Therefore, mutual steric demands between the tridentate-chelated steric ligands such as **4-tol** and **4-ipr**, and bulky co-ligand fragments cooperatively aids the generation of active species from assembled precatalyst.

Keywords: Ligand effects, Suzuki-Miyaura C-C coupling, Homogeneous catalysis, Catalyst development

Introduction

Biphenyl moieties are naturally occurring in numerous important molecular materials and they are mostly synthesized through C-C coupling. Over the past few decades, many transition metal complexes have been prepared and investigated for their roles as catalyst for C-C coupling synthetic strategies [1–4]. However, the use of palladium species in cross coupling of organic substrates stands out among all other capable metal catalysts [5–8].

Palladium-catalyzed carbon-carbon cross coupling has become a very powerful synthetic tool for molecular scientists such as in natural products total synthesis, drug designs, industrial production of fine chemicals and synthesis of next generation materials as well as bioactive molecular materials [9–12].

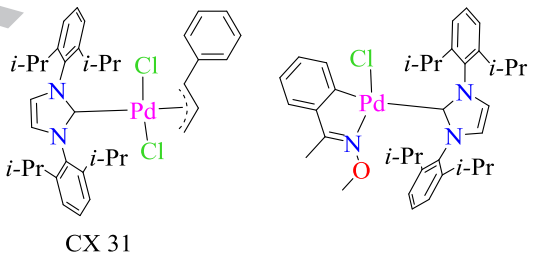
Of all the palladium-catalyzed C-C procedures, Suzuki-Miyaura coupling is one of the most frequently applied methods in routine organic syntheses. This is attributable to the wide range of inexpensive and environmentally friendly organoboron compounds [13,14], mild reaction conditions, high tolerance for functional group variation and ease of removal of the boron byproducts relative to other organometallic reagents used in analogous coupling reactions [15,16]. For decades, considerable efforts have continued to be dedicated to the design and syntheses of palladium compounds in search of improved catalytic profiles. For this purpose, various ligand designs ranging from monodentate to polydentate have been studied [17–19].

Several highly active palladium precatalysts have already been commercialized [20,21] and are frequently supported by phosphine and N-heterocyclic carbene (NHC) ligands while results for precatalysts bearing imine-based [22] ligands are also frequently being reported (Scheme 1(i)) [23–26]. These successful phosphine and NHC complexes are often complemented by co-ligands of diverse donor types such as cyclometallating C^N or allylic organometallic chelates as well as halides [27]. However, such patented, mixed-ligand precatalysts have ambitious synthetic architectures and high costs, but are also probably confronted with air and moisture sensitivity [28] Consequently, exploring simpler and more stable N-donor precatalysts can be considered necessary [29]. Notwithstanding, the simplicity of the *in situ* 'ligand + palladium salt' approach in a catalytic reaction flask is also attractive and a common practice for generating active species [30]. Precatalysts usually require decomposition of some ligand donors for the purpose of creating vacant coordination sites

towards catalysis events,[31] but *in situ* catalyst generation approach may also assemble the necessary components into the desired active configuration (Scheme 1 (ii)).

Steric rigidity of ligand backbone has become recognizes as a key factor against which the success or otherwise of palladium catalysts are often discussed [32,33]. Consequently, myriads of studied ligands backbones contain aromatic or fused aromatic rings as well as other bulky fragments like *t*-butyl groups (Scheme 1(i)). However, could flexible aliphatic ligand models incorporating bulky molecular moieties at certain positions also afford high efficiencies? We considered that design and study of simple, flexible, aliphatic amine chelates, which bear systematically varied substituent bulks at certain flanking or terminal positions, would provide another dimension to the understanding of how ligand steric characteristics affect efficiencies of resultant palladium active centers. Herein, we present results for study of series of structurally and electronically diverse amine ligands and the behaviour of their palladium species towards C–C cross coupling reactions. The series consist of varying anionic bidentate, tridentate or tetradentate N- and O-donors (Scheme 2). Synthesis and catalytic behaviour of some corresponding palladium complexes precatalysts were also pursued for comparison.

(i) Some commercially known pre-catalysts



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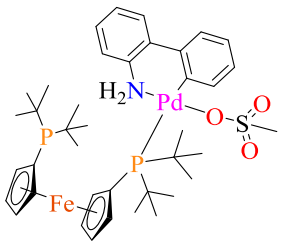
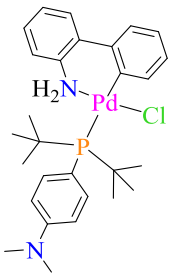


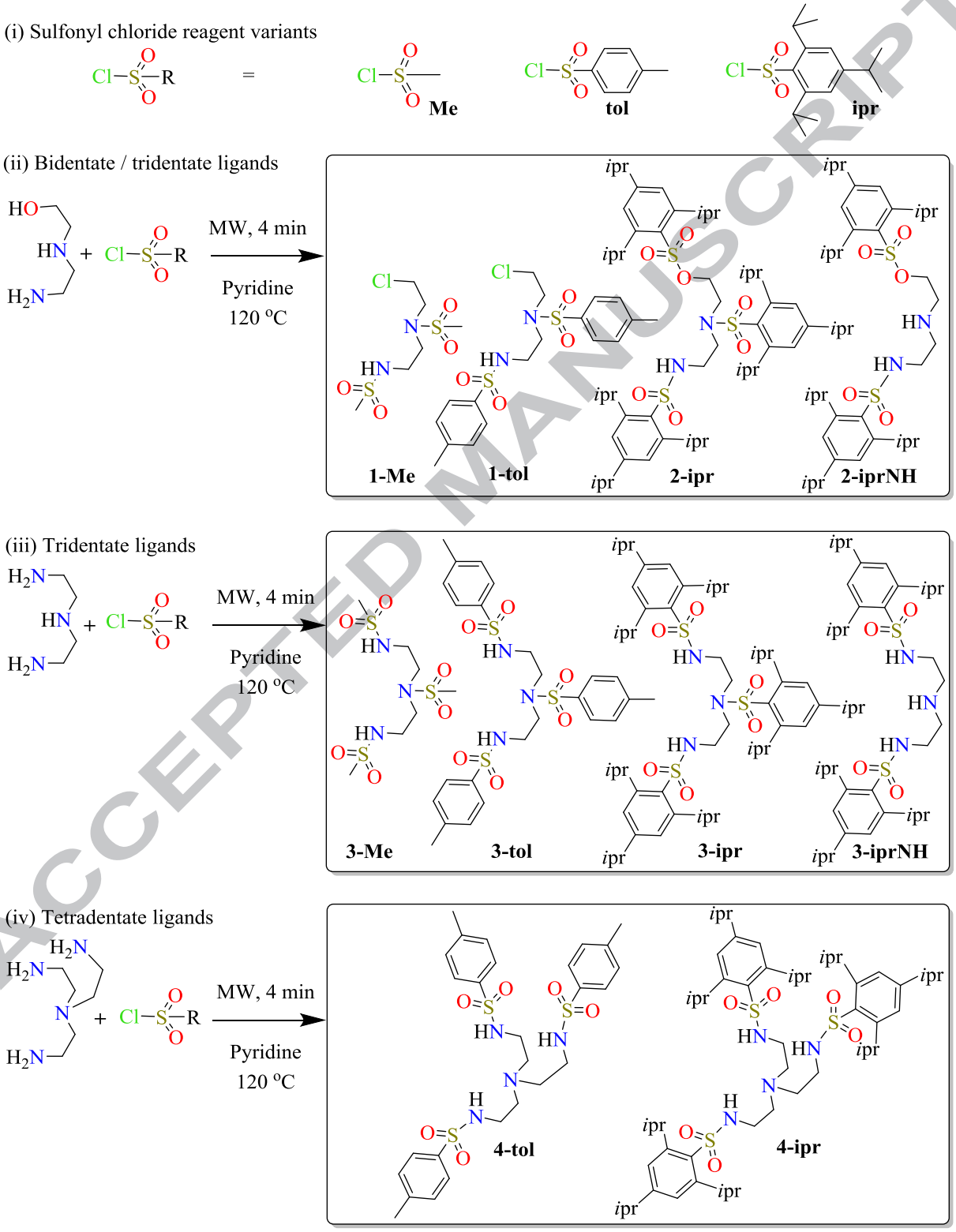
DTBPF-Pd-G3



APhos Pd G2

(ii) Generation of active palladium species

Scheme 1: (i) Few examples of highly active and commercially available pre-catalysts [20–22] and (ii) processes of active catalyst generation from precatalysts or *in situ* assembling



Scheme 2: Synthetic scheme and structures for the chelating amine ligands subjected to *in situ* as well as palladium precatalyst studies.

Materials and methods

General information

All starting materials for synthesis as well as substrates for the catalytic experiments were obtained commercially as reagent and used as supplied without further purification. Microwave assisted procedures were conducted using Biotage Initiator 2.5 Microwave Reactor for ligand preparations. All organic compounds were either purified by column chromatography on silica gel or recrystallized. IR spectra were measured with a Bruker Equinox FT-IR spectrometer equipped with a diamond ATR unit. Elemental analyses were carried out on Leco CHNS-932 and El Vario III elemental analyzers. Mass spectrometry (MS) analyses was conducted on a Bruker MAT SSQ 710 spectrometer. ^{1}H and ^{13}C NMR spectra were collected on a Bruker AVANCE 400 MHz spectrometer using deuterated solvents.

Preparation of the ligands

General procedure: To a solution of the ethylenediamine derivative stirring in pyridine in a 30 mL reactor vial set in ice bath was added the appropriate molar equivalent of the sulfonyl chloride reagent in a dropwise manner. The reaction mixture was stirred for further 20 min at the ice bath temperature. Thereafter, the reactor vial was sealed and transferred to the microwave reactor in which the reaction mixture was reacted at 120 ^{o}C for 4 minutes. Pyridine was removed under reduced pressure while the crude product was purified on a silica gel column using carefully selected solvent ratio and sequence to elute the target ligand. Chromatography on silica gel was typically carried out using 7:3 n-hexane / ethyl acetate unless otherwise stated. The particular details and analytical characterization data for the ligands are presented below:

N-(2-chloroethyl)-N-(2-(methylsulfonamido)ethyl)methanesulfonamide (1-Me): *N*-(2-hydroxyethyl)ethylenediamine (1.80 g, 17.5 mmol), pyridine (15 mL), methanesulfonyl chloride (6.00 g, 52.4 mmol), column chromatography firstly by n-hexane/ethylacetate (7:3) on silica gel and then methanol (neat). **1-Me** was obtained as a yellow crystalline solid. Yield (1.10 g, 19%). M.p = 130 – 131 ^{o}C. Selected IR data (ATR, cm^{-1}): *v* 3294w (N–H), 3246s, 2931w (C–H alkyl), 1461vs, 1139vs, 972s, 755s. ^{1}H NMR (400 MHz, *d6*-DMSO): δ_{ppm} 7.14 (t, *J* = 6.0 Hz, 1H), 3.73 (t, *J* = 7.0 Hz, 2H), 3.48 (t, *J* = 7.0 Hz, 2H), 3.28 (d, *J* = 6.8 Hz, 2H), 3.12 (q, *J* = 6.6 Hz, 2H), 3.00 (s, 3H), 2.92 (s, 3H). ^{13}C NMR: (101 MHz, *d6*-DMSO): 54.93, 54.76, 53.51, 47.37, 46.96, 43.02. MS (ESI) m/z 301.1 (100%). Anal. calc. for $C_6H_{15}ClN_2O_5S_2.{}^1/_4H_2O$: C, 25.44; H, 5.52; N, 9.89; S, 22.64 %. Found: C, 25.69; H, 5.33; N, 9.88; S, 22.49 %.

N-(2-chloroethyl)-4-methyl-N-(2-((4-methylphenyl)sulfonamido)ethyl)benzenesulfonamide (1-tol): N-(2-hydroxyethyl)ethylenediamine (0.54 g, 5.2 mmol), *p*-toluenesulfonyl chloride (3.0 g, 15.7 mmol), pyridine (15 mL). The compound was recrystallized in ethanol. Yield (0.97 g, 33 %). M.p = 110 – 111 ^{o}C. Selected IR data (ATR, cm^{-1}): *v* 3296m (N–H), 2928w (C–H alkyl), 1598m (C=C aromatic), 1435m, 1348vs, 1168vs, 1092vs, 760s. ^{1}H NMR (400 MHz, $CDCl_3$): δ_{ppm} 7.76 (d, *J* = 8.3 Hz, 2H), 7.66 (d, *J* = 8.3 Hz, 2H), 7.37 – 7.24 (m, 4H), 5.21 (s, 1H), 3.54 (t, *J* = 6.8 Hz, 2H), 3.34 (t, *J* = 6.8 Hz, 2H), 3.23 (dd, *J* = 9.3, 3.5 Hz, 2H), 3.18 (t, *J* = 5.1 Hz, 2H), 2.44 (s, *J* = 2.3 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 144.25, 143.72, 136.56, 135.03, 129.93, 127.24, 51.69, 49.86, 42.49, 42.04, 21.55. MS (EI) m/z 431 (M^+, 12%): 381, 275, 246, 239, 184, 155, 91. Anal. calc. for $C_{18}H_{23}ClN_2O_4S_2.{}^1/_4$EtOH: C, 50.22; H, 5.58; N, 6.33; S, 14.49 %. Found: C, 50.54; H, 5.44; N, 6.40; S, 14.74 %.

2-((2,4,6-triisopropyl-N-(2-((2,4,6-triisopropylphenyl)sulfonamido)ethyl)phenyl)sulfonamido)ethyl 2,4,6-triisopropylbenzenesulfonate (2-ipr) and **2-((2-((2,4,6-triisopropylphenyl)sulfonamido)ethyl)amino)ethyl 2,4,6-triisopropylbenzenesulfonate (2-iprNH)**: Triisopropylbenzenesulphonyl chloride (3.0 g, 9.9 mmol), *N*-(2-hydroxyethyl)ethylenediamine (0.34 g, 3.3 mmol) and pyridine (15 mL), column chromatography by chloroform. (i) **1-ipr**: Yield (0.15 g, 5%). M.p = 159 – 160 ^{o}C Selected IR data (ATR, cm^{-1}): *v* 3323w (N–H), 2957s (C–H alkyl), 2869w (C–H alkyl), 1601s (C=C aromatic), 1459s, 1329s, 1145vs, 1030vs, 780vs. ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} 7.19 – 7.10 (m, 5H), 4.18 – 3.84 (m, 8H), 3.62 – 3.32 (m, 4H), 3.24 – 3.05 (m, 2H), 2.89 (dt, *J* = 13.8, 6.9 Hz, 2H), 1.49 (s, 1H), 1.36 – 1.05 (m, 54H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 154.03, 151.58, 150.89, 150.26, 124.24, 123.85, 66.77, 34.25, 34.20, 29.89, 24.90, 24.70, 23.53. MS (EI) m/z 635 (M^+ - T*i*-PBS, 10 %): 606, 340, 296, 267. Anal. calc. for $C_{49}H_{78}N_2O_7S_3$: C, 65.15; H, 8.70; N, 3.10; S, 10.65 %. Found: C, 65.42; H, 8.84; N, 3.08; S, 10.16 %. (ii) **1-iprNH**: Yield (1.08 g, 36 %). M.p = 178 – 179 ^{o}C Selected IR data (ATR, cm^{-1}): *v* 3432w (N–H), 2958s (C–H alkyl), 2869m, 1602s (C=C aromatic), 1564s, 1459s, 1310s, 1256s, 1144vs, 942vs. ^{1}H NMR (300 MHz, *d6*-DMSO): *δ* 7.60 (t, J = 5.9 Hz, 1H), 7.19 (d, J = 3.0 Hz, 4H), 4.80 (t, J = 5.1 Hz, 1H), 4.11 – 3.99 (m, 2H), 3.97 – 3.83 (m, 2H), 3.39 (q, J = 6.3 Hz, 2H), 3.26 – 3.17 (m, 2H), 3.12 (t, J = 6.4 Hz, 2H), 2.96 – 2.84 (m, 4H), 1.15 (ddd, J = 17.3, 8.7, 5.0 Hz, 36H). ^{13}C NMR (101 MHz, *d6*-DMSO): δ 153.37, 152.51, 151.08, 150.05, 133.29, 131.58, 124.30, 59.21, 48.80, 46.40, 33.78, 25.15, 24.88, 23.83. MS (EI) m/z 637 (M^+, 10%): 340 296, 267. Anal. calc. for $C_{34}H_{56}N_2O_5S_2.½H_2O$: C, 63.66; H, 8.88; N, 4.37; S, 10.00 %. Found: C, 63.69; H, 8.80; N, 4.33; S, 9.70 %.

N,N-bis(2-(methylsulfonamido)ethyl)methanesulfonamide (3-Me): Diethylenetriamine (1.8 g, 17.5 mmol), methanesulfonyl chloride (6.0 g, 52.4 mmol,),

pyridine (15 mL). Yield (1.02 g, 17 %). M.p = 117 – 118 ºC. Selected IR data (ATR, cm^{-1}): *v* 3292m (N–H), 3021w (C–H aromatic), 2935w (C–H alkyl), 1306vs, 1139vs, 1074m, 1003vs, 767vs. ^{1}H NMR (400 MHz, *d6*-DMSO): δ_{ppm} 7.17 (d, *J* = 5.3 Hz, 2H), 3.25 (t, *J* = 6.6 Hz, 4H), 3.19 – 3.06 (m, 4H), 2.98 (s, 3H), 2.92 (s, 6H). ^{13}C NMR (101 MHz, *d6*-DMSO): δ 48.64, 41.97, 38.15. MS (EI) m/z 338 (M^+, 24%): 229, 151, 122, 108, 79, 42 Anal. calc. for $C_7H_{19}N_3O_6S_3.{}^3/_4H_2O$: C, 23.96; H, 5.89; N, 11.97; S, 27.41 %. Found: C, 23.76; H, 5.36; N, 11.85; S, 27.48 %.

4-methyl-N,N-bis(2-(4-methylphenylsulfonamido)ethyl)benzenesulfonamide (3-tol): Diethylenetriammine (0.54 g, 5.2 mmol, *p*-toluenesulfonyl chloride (3.0 g, 15.7 mmol), pyridine (15 mL). Recrystallization in ethanol affords **3-tol**. Yield (2.04 g, 69 %). M.p = 220 - 221 ºC. Selected IR data (ATR, cm^{-1}): *v* 3284s (N–H), 2913w (C–H alkyl), 1599s (C=C aromatic), 1495s, 1322vs, 1156vs, 940s, 812vs. ^{1}H NMR (400 MHz, $CDCl_3$): δ_{ppm} 7.78 (d, *J* = 8.2 Hz, 4H), 7.63 (d, *J* = 8.2 Hz, 2H), 7.41 – 7.29 (m, 6H), 5.16 (s, 2H), 3.20 (d, *J* = 4.9 Hz, 4H), 3.18 – 3.09 (m, 4H), 2.45 (s, 9H). ^{13}C NMR: (101 MHz, CDCl3): δ 143.64, 136.67, 134.73, 129.92, 127.24, 50.52, 42.64, 21.53. MS (EI) m/z 566 (M^+, 25%): 381, 227, 209, 155, 139, 91. Anal. calc. for $C_{25}H_{31}N_3O_6S_3$: C, 53.08; H, 5.52; N, 7.43; O, 16.97; S, 17.00 %. Found: C, 53.06; H, 5.56; N, 7.54; S, 16.91 %.

2,4,6-triisopropyl-N,N-bis(2-(2,4,6-triisopropylphenylsulfonamido)ethyl)benzenesulfonamide, **(3-ipr)** and **N,N'-(azanediylbis(ethane-2,1-diyl))bis(2,4,6-triisopropylbenzenesulfonamide**) **(3-iprNH)**: Triisopropylbenzenesulphonyl chloride (1.98 g, 6.5 mmol), diethylenetriamine (0.24 g, 2.2 mmol), pyridine (15 mL). (i) **3-ipr**: Yield (0.57 g, 29 %). M.p = 182-183 ºC. Selected IR data (ATR, cm^{-1}): *v* 3294s (N–H), 2958s (C–H alkyl), 2868m, 1602s (C=C aromatic), 1564s, 1317vs, 1149vs, 880s. ^{1}H NMR (400 MHz, *d6*-DMSO): δ_{ppm} 7.60 (t, *J* = 5.7 Hz, 2H), 7.18 (d,

J = 7.6 Hz, 6H), 4.03 (dt, *J* = 13.5, 6.7 Hz, 2H), 3.87 – 3.75 (m, 2H), 3.45 (d, *J* = 4.3 Hz, 2H), 3.17 (t, *J* = 8.0 Hz, 4H), 2.89 (ddd, *J* = 10.2, 8.6, 4.3 Hz, 6H), 1.21 (d, *J* = 6.9 Hz, 12H), 1.18 (d, *J* = 6.9 Hz, 12H), 1.11 (d, *J* = 6.7 Hz, 24H), 1.02 (d, *J* = 6.7 Hz, 12H). ^{13}C NMR (101 MHz, *d6*-DMSO): δ 152.54, 151.05, 150.01, 133.16, 130.94, 123.98, 46.29, 33.79, 31.15, 29.14, 24.95. MS (ESI) m/z 924.4 ([M + Na]$^+$, 100 %). Anal. calc. for $C_{49}H_{79}N_3O_6S_3.½H_2O$ C, 64.58; H, 8.85; N, 4.61; S, 10.55 %. Found: C, 64.55; H, 8.99; N, 4.64; S, 10.45 %. (ii) **3-iprNH**: Yield (0.92 g, 47 %). M.p = 326 – 327 ^{o}C. Selected IR data (ATR, cm^{-1}): *v* 3295w, 2959s, 2868w, 1602s, 1565w, 1363vs, 1119vs,1073m, 880m. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (s, 2H), 7.04 (s, 2H), 6.83 (s, 1H), 4.33 (dt, *J* = 13.4, 6.7 Hz, 2H), 4.04 (dt, *J* = 13.4, 6.7 Hz, 2H), 3.44 (d, *J* = 4.8 Hz, 2H), 3.39 (s, 2H), 2.87 (tt, *J* = 13.8, 6.9 Hz, 2H), 1.32 – 1.22 (m, 16H), 1.16 (d, *J* = 6.9 Hz, 24H). ^{13}C NMR (101 MHz, *d6*-DMSO): δ 153.02, 150.11, 147.42, 142.41, 124.03, 121.79, 33.75, 31.15, 29.25, 28.47, 25.30. MS (ESI) m/z 658.3 ([M + Na]$^+$, 60 %): 636.4 (M$^+$, 100 %). Anal. calc. for $C_{34}H_{57}N_3O_4S_2$.(**tol**).EtOH: C, 62.19; H, 8.80; N, 4.27; S, 9.77 %. Found: C, 61.79; H, 8.80; N, 4.26; S, 9.77 %.

N,N',N''-(nitrilotris(ethane-2,1-diyl))tris(4-methylbenzenesulfonamide) (4-tol): Tris-(2-aminoethyl)amine (1.0 g, 6.7 mmol), *p*-toluenesulfonyl chloride (5.09 g, 26.7 mmol). Column chromatography on silica gel by n-Hexane/THF (1:1). Yield (1.05 g, 26 %). M.p = 126 – 127 ^{o}C. Selected IR data (ATR, cm^{-1}): *v* 3229w (N–H), 2959s (C–H alkyl), 2870m, 1601s (C=C aromatic), 1564m, 1318s, 1151vs, 942vs. ^{1}H NMR (400 MHz, *d6*-DMSO): δ_{ppm} 7.67 (d, *J* = 7.7 Hz, 6H), 7.36 (d, *J* = 7.4 Hz, 9H), 2.72 – 2.60 (m, 6H), 2.38 (s, 9H), 2.23 (t, *J* = 6.0 Hz, 6H). ^{13}C NMR (101 MHz, *d6*-DMSO): δ 143.09, 138.18, 130.16, 126.92, 53.54, 21.43. MS (EI) m/z 609 (M$^+$, 12 %): 424, 172, 155, 107, 91. Anal. calc. for $C_{27}H_{36}N_4O_6S_3.H_2O$: C, 51.74; H, 6.11; N, 8.94; S, 15.35 %. Found: C, 51.94; H, 6.16; N, 8.98; S, 15.42 %.

N,N',N''-(nitrilotris(ethane-2,1-diyl))tris(2,4,6-triisopropylbenzenesulfonamide) (4-ipr): Tris-(2-aminoethyl)amine (0.37 g, 2.5 mmol), 2,4,6-tri-isopropylbenzenesulfonyl Chloride ((3.03 g, 10.0 mmol). Recrystallization ethanol / THF. Yield (1.68 g, 71 %). M.p = 246 – 247 ºC. Selected IR data (ATR, cm^{-1}): *v* 3326w (N–H), 2958s (C–H alkyl), 2870m, 1602s (C=C aromatic), 1564m, 1363s, 1105vs, 941vs. ^{1}H NMR (400 MHz,*d6*-DMSO): δ_{ppm} 7.69 (s, 2H), 7.24 (s, 6H), 6.95 (s, 2H), 4.58 (dt, *J* = 13.6, 6.8 Hz, 2H), 4.05 (dt, *J* = 13.1, 6.5 Hz, 6H), 3.49 (s, 12H), 2.93 (dd, *J* = 13.7, 6.8 Hz, 4H), 2.81 (dd, *J* = 13.7, 6.8 Hz, 1H), 1.19 (dd, *J* = 14.0, 6.6 Hz, 60H), 1.10 (d, *J* = 6.8 Hz, 12H) ppm; ^{13}C NMR (101 MHz,*d6*- DMSO): δ 150.20, 147.60, 147.24, 142.41, 124.15, 121.78, 33.76, 29.34, 28.47, 25.23, 24.31, 23.86. MS (ESI) m/z 1268.7 ($[M + Na]^+$,12%): 945.6, 967.5. Anal. calc. for $C_{66}H_{107}ClN_4O_8S_4$: C, 63.50; H, 8.64; N, 4.49; S, 10.27 %. Found: C, 63.47; H, 8.85; N, 4.46; S, 10.00 %

Syntheses of palladium complexes

General procedure: A mixture of ligand and one equivalent of $Pd(OAc)_2$ were weighed into a vial and 2 mL of acetonitrile added at room temperature. The solution was allowed to stand for 3 days after which the microcrystalline product which came out was filtered and air-dried. The analytical data and some reaction peculiarities for the obtained complexes are presented below:

Pd(4-tol)H_2O: **4-tol** (30 mg, 0.05 mmol), $Pd(OAc)_2$ (10 mg, 0.05 mmol). The obtained complex was dissolved in $CHCl_3$ and layered with n-hexane, which lead to growing of **Pd(4-tol)H_2O** as yellow crystals. Yield (30 mg, 83 %), Mp = 198 – 199 ºC. Selected IR data (ATR cm^{-1}): *v* 3259br,m (N–H), 2957m (C–H alkyl), 1599s (C=C aromatic), 1425s, 1333vs, 1133vs, 959vs. MS (ESI) m/z 753.1 ($[M+Na]^+$, 50 %): 735.2 ($[M+Na\text{-}H_2O,]^+$, 60 %),

631.2 ([L+Na]$^+$, 100 %). Anal. calc. for $C_{27}H_{36}N_4O_7PdS_3$: C, 44.35; H, 4.96; N, 7.66; S, 13.16 %. Found: C, 44.49; H, 4.89; N, 7.64; S, 13.19 %.

Pd(4-tol)Py: **4-tol** (30 mg, 0.05 mmol), $Pd(OAc)_2$ (10 mg, 0.05 mmol) in the presence of drops of pyridine. Yield (30 mg, 79 %), Mp = 203 - 204 ºC. Selected IR data (ATR cm^{-1}): *v* 3434w (N–H), 3228m, 3071w (C–H aromatic), 2957m (C–H alkyl), 1597s (C=C aromatic), 1449s, 1325vs, 1130vs, 973vs. MS (ESI) m/z 816.1 ([M+Na]$^+$, 100%): 735.2 ([M+Na-Py,]$^+$, 15%). Anal. calc. for $C_{32}H_{39}N_5O_6PdS_3$ C, 48.51; H, 4.96; N, 8.84; S, 12.14%. Found: C, 48.50; H, 4.95; N, 8.90; S, 11.96%.

Pd(4-tol)*i*-PrOH: **4-tol** (30 mg, 0.05 mmol) and $Pd(OAc)_2$ (10 mg, 0.05 mmol) in THF (0.5 mL) and isopropanol (***i*-PrOH**) (0.2 mL). Yield (30 mg, 80 %), Mp = 182 - 183 ºC. Selected IR data (ATR cm^{-1}): *v* 3256w (N–H), 2923w (C–H alkyl), 1599m (C=C aromatic), 1448m, 1264m, 1133vs, 964vs, 812vs. ESI m/z 794.05 ([M+Na]$^+$, 10%): 754.10, 609.18, 301.07, 279.09. MS (EI) m/z: 514, 424, 294, 214, 199, 182, 155, 129, 91. Anal. calc. for $C_{30}H_{42}N_4O_7PdS_3$.(THF) C, 48.30; H, 5.96; N, 6.63; S, 11.38%. Found: C, 48.14; H, 5.90; N, 6.62; S, 11.13%.

Pd(4-ipr)H_2O: **4-ipr** (30 mg, 0.02 mmol) and $Pd(OAc)_2$ (5 mg, 0.02 mmol). Yield (20 mg, 78 %), Mp = 227 - 228 ºC. Selected IR data (ATR cm^{-1}): *v* 3259w (N–H), 2958m (C–H alkyl), 2866m, 1600s (C=C aromatic), 1383s, 1270vs, 1133vs, 960vs. MS (ESI) m/z 1067 (M$^+$10%), 1089 ([M+Na]$^+$, 100 %). Anal. calc. for $C_{51}H_{84}N_4O_7PdS_3$: C, 57.36; H, 7.93; N, 5.25; S, 9.01%. Found: C, 57.11; H, 7.74; N, 5.25; S, 8.70%.

Pd(4-ipr)Py: **4-ipr** (30 g, 0.02 mmol), $Pd(OAc)_2$ (5 mg, 0.02 mmol) and pyridine (0.5 ml). Recrystallization in acetonitrile was carried out to obtain single crystals suitable for X-ray measurement. Yield (10 mg, 57 %), Mp = 160 - 161 ^oC. Selected IR data (ATR cm^{-1}): *v* 2957s (C–H alkyl), 2869m, 1601s (C=C aromatic), 1562m, 1454s, 1244vs, 1119vs, 924vs, 825vs. MS (ESI) m/z 1129 (M^+ 47%), 1152 ($[M+Na]^+$, 100%). Anal. calc. for $C_{56}H_{87}N_5O_6PdS_3.CH_3CN.H_2O$: C, 58.64; H, 7.81; N, 7.07; S, 8.10%. Found: C, 58.39; H, 7.72; N, 7.08; S, 7.70 %.

Single crystal X-ray data

The intensity data for the compounds were collected on a Nonius KappaCCD diffractometer using graphite-monochromated Mo-K_α radiation. Data were corrected for Lorentz and polarization effects; absorption was taken into account on a semi-empirical basis using multiple-scans [34–37]. The structures were solved by direct methods (SHELXS) and refined by full-matrix least squares techniques against F_o^2 (SHELXL-97).

The hydrogen atoms of **1-Me** as well as the hydrogen atoms bonded to the water molecule O7 and the imines-group N4 of **Pd(4-tol)H_2O** and **Pd(4-ipr)py** were located by difference Fourier synthesis and refined isotropically. All other hydrogen atoms were included at calculated positions with fixed thermal parameters. All non-hydrogen, non-disordered atoms were refined anisotropically [37]. Crystallographic data as well as structure solution and refinement details are summarized in Table 1. The program *XP* [38]. was used for structure representations.

Suzuki-Miyaura coupling catalysis experiment

In a typical reaction, (4-bromophenyl)methanol (**B**, 0.19 g, 1.0 mmol), (4-acetylphenyl)boronic acid (**A**, 0.23 g, 1.4 mmol), potassium phosphate (0.26 g, 1.2 mmol), palladium acetate (0.2 mol % relative to **B**) and a given ligand, (0.7 mol % relative to **B**) were added together in a 10 mL round-bottom flask equipped with magnetic stirrer bar. Ethanol (3 mL) and water (1 mL) were added and the mixture was refluxed in an oil bath set at 100 ^{o}C for the desired reaction time. In the case of preformed palladium(II) complex, 0.2 mol % with respect to (4-bromophenyl)methanol was used. An aliquot of the reaction mixture was taken into a 10 mL conical flask and dried under vacuum to exclude the solvents. The residue was then collected in deuterated DMSO and subjected to ^{1}H NMR measurement. The reactivity of the catalyst was evaluated by comparison of the NMR signals for the methylene (–CH_2–) protons of (4-bromophenyl)methanol (**B**) at $\delta \approx 4.4$ ppm with that of the corresponding biphenyl product at $\delta \approx 4.7$ ppm. The yields are estimated by determining the integral of the product peak as a percentage of the sum of all observed methylene signals [30].

Results and discussion

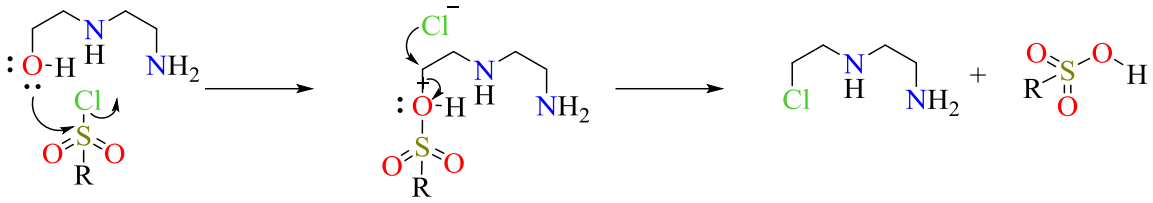
Synthesis and characterization of the ligands

The series of the ligands **1-Me** – **4-ipr** were obtained by microwave-assisted condensation of their respective amines and the corresponding sulfonyl chlorides using pyridine as the base as well as solvent and the products were isolated in moderate yields. During products isolation by column chromatography, some of the products required further recrystallization. This is responsible for the lower yields recorded for some the ligands. However, ligand **4-ipr** was purified only by recrystallization from ethanol / THF solvent mixture. Elemental analysis and spectroscopic data of the synthesized ligands reveal a notable adduct-forming tendency of these amine ligands with solvents, water or even with a starting material molecule. For example, ligands **3-iprNH** and **4-ipr** were isolated as adducts of their

corresponding sulfonyl chloride starting materials. Efforts to obtain the methylsulfonyl-analogue of the tetradentate ligands **4-tol** and **4-ipr** (Scheme 2 (iii) and (iv)) were not successful.

A notable finding during syntheses of the studied ligand is an unusual chlorination reaction in which the sulfonyl chloride reagent served as the chlorinating agent and the hydroxyl groups of primary aliphatic alcohols became replaced by chloride. This unexpected substitution of the hydroxyl function of 2-((2-aminoethyl)amino)ethan-1-ol yielded the chloro-substituted ligands **1-Me** and **1-tol** (Scheme 2 (ii)). Literature survey shows that hydroxyl groups on an aliphatic alcohol can be substituted by chloride,[39,40] but this reaction is normally carried out using chlorinating agents such as $SOCl_2$, PCl_5 or triphosgene in the presence of NEt_3 or pyridine as base. The chlorination finding, which is hitherto not reported, demonstrates that sulfonyl chloride reagents in pyridine can effectively achieves chloro-substitution of primary aliphatic alcohols. Perhaps this may mark a new aspect of sulfonyl chloride utility as well as a novel pathway to the synthesis of chlorinated compounds. Within the context of our study, a mechanistic thought for this reaction is presented in Scheme 3.

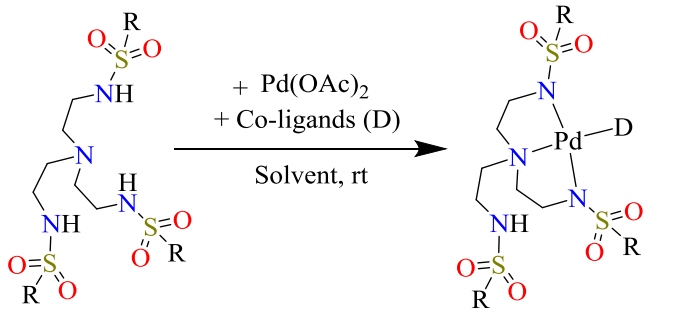
While methanesulfonyl chloride and *p*-toluenesulfonyl chloride reacted with 2-((2-aminoethyl)amino)ethan-1-ol to give only the chloro-substituted analogues **1-Me** and **1-tol** respectively, expected sulfonate ester products were obtained when 2,4,6-triisopropylbenzenesulfonyl chloride was deployed, which lead to ligands **2-ipr** and **2-iprNH** (Scheme 1). The crystal structure of **1-Me** is presented in Fig. 1. This difference in reaction outcomes from different sulfonyl chloride reagents is also considered to be an indication that the electronic and steric properties in the obtained ligands towards the catalytic study should also vary.



Scheme 3: Proposed mechanism for the reaction.

Synthesis and characterization of the palladium complexes

All the palladium(II) complexes were generally obtained in good yields by stirring $Pd(OAc)_2$ and a given member of the ligand series in suitable solvent at room temperature (Scheme 4). Despite several efforts to obtain palladium(II) complexes for all prepared ligands and with varying reaction conditions, defined complexation products only resulted for ligands **4-tol** and **4-ipr**. This observation is attributable to the higher chelation character as well as steric bulk of the tolyl- and 1,3,5-triisopropylphenyl-substituent of the **4-tol** and **4-ipr** ligands respectively, which are capable of preventing other coordination alternatives such as bis-ligand situations. X-ray single crystal data were collected for the palladium complexes **Pd(4-tol)H_2O** and **Pd(4-ipr)py** (Figs. 2 and 3). It is noteworthy that various neutral monodentate donor species such as water, *iso*-propanol and pyridine could be placed in the fourth coordinate position around the palladium coordination square plane. Elemental analyses and spectroscopic data gave good agreement with the identity of the palladium complexes.



	R	Co-ligand (D)
Pd(4-tol)H_2O	tolyl	water
Pd(4-tol)*i*PrOH	tolyl	iso-propanol
Pd(4-tol)py	tolyl	pyridine
Pd(4-ipr)H_2O	1,3,5-triisopropylphenyl	water
Pd(4-ipr)py	1,3,5-triisopropylphenyl	pyridine

Scheme 4: Synthetic route and compositions of the obtained palladium complexes of ligands **4-tol** and **4-ipr**

X-ray structures

Data for their structural refinement and processing parameters are collected in Table 1 and their ortep plots are presented in Figs. 1 – 3. Structure of ligand **1-Me** confirms the chloro-substitution of the hydroxyl group and is assembled with extensive intermolecular hydrogen-bonding interactions (Fig. 1). Crystal structures of complexes **Pd(4-tol)H_2O** and **Pd(4-ipr)py** revealed tridentate ligand chelation even though the ligands **4-tol** and **4-ipr** possess tetradentate chelation capability (Figs. 1 and 2). The limitation to tridentate chelation is necessitated by the square planar coordination geometry of the palladium(II) metal center.

Bond lengths around the coordination center for the structures of **Pd(4-tol)H_2O** and **Pd(4-ipr)py** are within expected values [41]. Both palladium centers are in slightly distorted square planes and all the Pd–N bond length are within a range of 2.00 – 2.07 Å. A shorter bond length is observed between the palladium metal center and the central nitrogen donors of ligands **4-tol** (Pd1–N1 in **Pd(4-tol)H_2O**) and **4-ipr** (Pd1–N2 in **Pd(4-ipr)py**) than for the remaining Pd–N bonds. This suggests that the central nitrogen donors of the **4-tol** and **4-ipr**

ligands possess stronger donor strengths than the sulfonyl-substituted nitrogen donors and is attributable to the electron-releasing nature of the alkyl fragments around the central nitrogen as opposed to the electron-withdrawing influence of the sulfonyl-substituents on the remaining N-donors. The participation of the sulfonyl oxygen atoms in inter- and intramolecular hydrogen bonding as illustrated by the co-crystallized water in **Pd(4-tol)H_2O** is worthy of note (Figs. 1 and 3). Such functions in the proximity of active metal center may play important roles in ordering oxidative insertion steps during the catalytic process.

It is also notable that significantly larger degree of flexibility exists in the chelation environment of **Pd(4-tol)H_2O** relative to that of **Pd(4-ipr)py**. In particular, the disposition of the two tolyl aromatic rings of the coordinating secondary amines arms on ligand **4-tol** as observed in complex **Pd(4-tol)H_2O** were flexible enough to tolerate folding and being placed in close proximity to each other (separation between centroids of these tolyl rings is 5.59 Å, Fig. 2). On the other hand, the triisopropylphenyl rings on the chelated secondary amine arms of ligand **4-ipr** as observed in **Pd(4-ipr)py** exhibited lesser steric tolerance such that these rings stand pushed away from the coordination center with 11.80 Å distance between their centroids (Fig. 3).

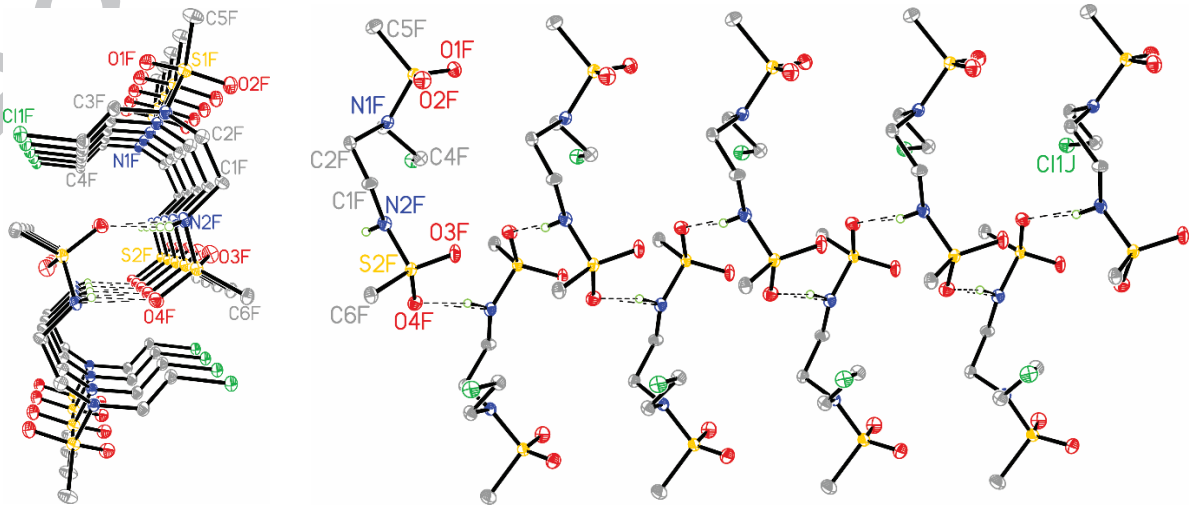


Figure 1: Molecular structure of **1-Me** and its intermolecular hydrogen-bonding characteristics viewed along two perpendicular paths

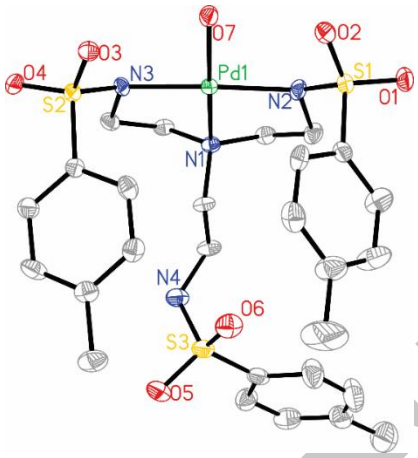


Figure 2: Ortep plot of complex **Pd(4-tol)H_2O** drawn at 50 % probability level. Protons and solvents have been omitted for clarity (Selected bond lengths: Pd1−N1 = 2.000(3), Pd1–N2 = 2.047(3), Pd1−N3 = 2.034(3), Pd1−O7 = 2.045(3)).

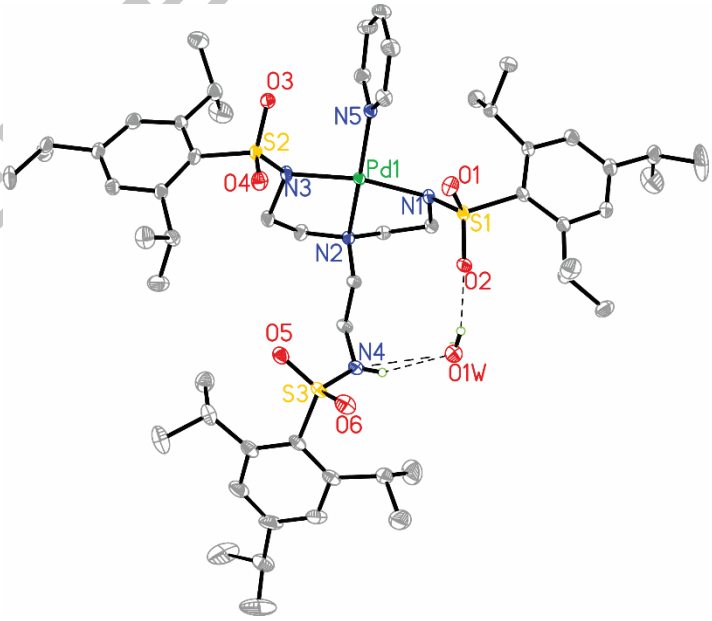


Figure 3: Ortep plot of complex **Pd(4-ipr)py** drawn at 50 % probability level. Some protons and solvents have been omitted for clarity(Selected bond lengths: Pd1−N1 = 2.065(2), Pd1–N2 = 2.029(2), Pd1−N3 = 2.057(2), Pd1− N5 = 2.040(2)).

Table 1: Crystal data and refinement details for the X-ray structure determinations of the compounds **1-Me**, **Pd(4-tol)H_2O** and **Pd(4-ipr)py**.

Compound	**1-Me**	**Pd(4-tol)H_2O**	**Pd(4-ipr)py**
formula	$C_6H_{15}ClN_2O_4S_2$	$C_{27}H_{36}N_4O_7PdS_3$	$C_{58}H_{92}N_6O_7PdS_3$
fw ($g \cdot mol^{-1}$)	278.77	731.18	1187.96
T(°C)	-140(2)	-140(2)	-140(2)
crystal system	monoclinic	triclinic	monoclinic
space group	P 2_1/c	P ī	C 2/c
a/ Å	13.1407(7)	13.1002(3)	38.5341(6)
b/ Å	5.1069(2)	13.7093(3)	11.3209(2)
c/ Å	17.3127(9)	18.0705(5)	33.2963(5)
α/°	90	73.425(2)	90
β/°	90.436(2)	78.114(2)	124.138(1)
γ/°	90	86.179(1)	90
V/Å^3	1161.79(10)	3043.71(13)	12022.3(3)
Z	4	4	8
ρ ($g \cdot cm^{-3}$)	1.594	1.596	1.313
μ (cm^{-1})	6.85	8.67	4.67
measured data	10589	29498	35330
data with I > 2σ(I)	2221	10785	11782
unique data (R_{int})	2652/0.0477	13771/0.0369	13731/0.0385
wR_2 (all data, on F^2)[a)]	0.1078	0.1022	0.0877
R_1 ($I > 2\sigma(I)$) [a)]	0.0524	0.0523	0.0403
S [b)]	1.116	1.062	1.058
Res. dens./e·Å^{-3}	0.439/-0.523	0.618/-0.695	0.529/-0.652
absorpt method	multi-scan	multi-scan	multi-scan
absorpt corr $T_{min}/_{max}$	0.6765/0.7456	0.6578/0.7456	0.6935/0.7456
CCDC No.	1850773	1850774	1850775

[a)] Definition of the R indices: $R_1 = (\Sigma \,||F_o| - |F_c||)/\Sigma|F_o|$; $wR_2 = \{\Sigma[w(F_o^2-F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{1/2}$ with $w^{-1} = \sigma^2(F_o^2) + (aP)^2+bP$; $P = [2F_c^2 + Max(F_O^2]/3$; [b)] $s = \{\Sigma[w(F_o^2-F_c^2)^2]/(N_o-N_p)\}^{1/2}$.

Determining suitable catalytic reaction parameters

The catalytic study started with search for an average reaction setting under which all the ligand frameworks would then be comparatively studied. This setting is aimed to be the constant set of reaction parameters that may allow observation of the influence of ligands' molecular variations on their capabilities to generate active species either via *in situ* 'ligand + $Pd(AcO)_2$' route or from palladium complex precatalysts. Ligands **3-tol** and **3-ipr** were used as representative members of the ligand series to test for suitable reaction time, $Pd(OAc)_2$:ligand ratio, boronic acid ratio and additive base in the coupling of (4-

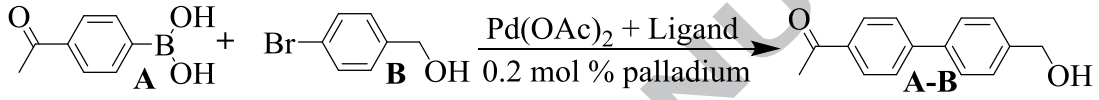
acetylphenyl)boronic acid (**A**) and (4-bromophenyl)methanol (**B**) as a typical Suzuki-Miyaura coupling reaction. The suitability of catalytic substrates was decided because the methylene (–CH_2–) function on the (4-bromophenyl)methanol (**B**) substrate allows for the ease of ^{1}H-NMR tracking of the aryl bromide conversion to coupled product. This functional group was found to be advantageous because there is no interference of ^{1}H-NMR signals around the 4.46 ppm region where the methylene group of **B** gives signal.[30] The results for reaction parameter testing are summarized in Table 3.

Using 3:1 EtOH/H_2O (4 mL), K_2CO_3 (1 mmol), oil bath temperature of 100 ^oC, $Pd(OAc)_2$ (0.2 mol %) and ligand **3-ipr** (0.4 mol %), coupling reactions of **A** and **B** were monitored at 10, 30 and 60 minutes. The obtained yields of the **A**–**B** coupling product indicate that there is no benefit for refluxing beyond 10 minutes (entries 1 – 3, Table 2). This result suggests that the active species are either short-lived or that a substrate is rapidly converted via side reactions to unwanted species.

Continuing with 10 min reflux duration and keeping constant other reaction parameters above, increased amounts of ligand **3-ipr** from 0.4 mol % to 0.7 and 1.0 mol % was deployed against 0.2 mol % $Pd(OAc)_2$, which did not produce any significant effects on the catalytic results (entries 1, 4 and 5, Table 2). Nonetheless, 0.7 mol % of ligand was employed against 0.2 mol % $Pd(OAc)_2$ for further reactions for the sole purpose of ensuring that access of palladium to ligand in the low concentration catalyst system is not limited. Investigating different base additives proved K_3PO_4 to be the better base for the catalyst systems under study (entries 4 and 6 – 9, Table 2) [42,43]. Since the coupling yield difference between 1.2 and 1.4 equivalents of K_3PO_4 is not dramatic (entries 10 and 11, Table 2), further reactions were carried out using the 1.2 mole equivalents of the base in order to allow for observation of molecular effects in catalytic performances. Rather than utilize higher loadings of the base, the lesser K_3PO_4 loading would increase the chance of observing differences caused by the ligand architectures. Consequently, the concluded catalytic reaction setting

entails 4mL of 3:1 EtOH/H_2O, K_3PO_4 (1.2 mmol), 0.7 mol % ligand + 0.2 mol % $Pd(OAc)_2$, 1.2 mmol **A**, 1 mmol **B**, oil bath temperature of 100 ^oC and 5 minutes reflux duration. The choice of 4mL of 3:1 EtOH/H_2O mixture as solvent is based on our previous studies [30]. Temperature readings were taken by inserting a thermometer into some refluxing reaction mixtures, which showed values of about 81 ^oC though the oil bath was thermostated at 100 ^oC.

Table 2: Testing of different reaction parameters[a]



Entry	Ligand (mol %)	Time (min)	Base (mmol)	Yield (%)[b]
1	**3-ipr** (0.4)	10	K_2CO_3 (1.0)	18
2	**3-ipr** (0.4)	30	K_2CO_3 (1.0)	19
3	**3-ipr** (0.4)	60	K_2CO_3 (1.0)	19
4	**3-ipr** (0.7)	10	K_2CO_3 (1.0)	20
5	**3-ipr** (1.0)	10	K_2CO_3 (1.0)	19
6	**3-ipr** (0.7)	10	Na_2CO_3 (1.0)	17
7	**3-ipr** (0.7)	10	K_3PO_4 (1.0)	39
8	**3-ipr** (0.7)	10	Et_3N (1.0)	17
9	**3-ipr** (0.7)	10	KOH (1.0)	25
10	**3-tol** (0.7)	10	K_3PO_4 (1.2)	65
11	**3-tol** (0.7)	10	K_3PO_4 (1.4)	78

[a]Reaction conditions: Solvent: 3:1 EtOH/H_2O (4 mL), base (1.0 – 1.4 mmol), oil bath temperature set at 100 ^oC, ligand amount (0.4 – 1.0 mol %), $Pd(OAc)_2$ (0.2 mol%); (4-acetylphenyl)boronic acid (1.2 mmol), (4-bromophenyl)methanol (1 mmol). [b]Yield was determined by ^{1}H-NMR and reported to the nearest whole number.

Ligand character and palladium catalyst activity

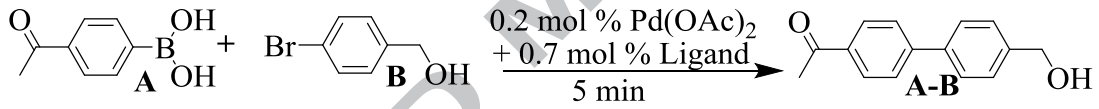
The different series of ligands prepared in this experiment were subjected to the catalytic studies under the same reaction conditions described above. The results of the *in situ* catalysis are presented in Table 3 which generally shows that ligand has some influence on the activity of the palladium active centers (entry 1 vs other entries). In particular, bulkiness of the ligand systems correlated with catalyst activities. As illustrated in Table 3, in the presence of ligands with the triiso-propylphenly-substituents, higher catalyst performances were recorded relative to their corresponding analogues with the less bulky methyl- or tolyl-

substituents (e.g. entry 2 vs 4 shows **1-Me** = 60 % while **2-ipr** = 72 %; entry 6 vs 8 shows **3-Me** = 51 % while **3-ipr** = 61 %; entry 10 vs 11 shows **4-tol** = 16 % while **2-ipr** = 60 %). The lower turnover frequency (TOF) values for the chloro-substituted ligands **1-Me** (3600 h^{-1}) and **1-tol** (3000 h^{-1}) relative to the bulkier analogues **2-ipr** (4440 h^{-1}) and **1-iprNH** (4020 h^{-1}) is also in agreement with this observation. Therefore, despite the flexibility of alkyl fragments in these amine-based ligands, the introduction of bulky units at the flanking ends of the chains could be employed to aid construction of active palladium species. To the best of our knowledge, this fact has not been so established elsewhere.

Furthermore, it is also noteworthy that chelation characteristics in the ligand series influenced catalytic outcomes. Ligands with bidentate chelation potentials proved to be better candidates above their counterparts possessing tridentate or tetradentate chelation capacities. In particular, highest TOF values resulted from the O^N^N ligands **2-ipr** (4440 h^{-1}) and **2-iprNH** (4020 h^{-1}) while the potentially tridentate N^N^N ligands yielded lower catalytic performances. The donor behaviour of oxygen in the **1**- and **2**-series of ligands can be considered non-favourable. Thus, these ligands would generally be bidentate. Even the **1-Me** and **1-tol** that lack the supporting bulkiness showed reasonable catalyst efficiencies comparable to the best outcomes from the tridentate or tetradentate ligand frameworks **3-Me** – **4-ipr** (entries 2 and 3 vs entries 6 – 11). Despite the presence of steric bulk of tosyl-substituents on **4-tol** and considering that this ligand possesses a third, non-coordinated arm, which should constitute additional steric demand when ligand **4-tol** is involved in a tridentate chelation environment, it is worthy of note that this ligand framework (**4-tol**) displayed one of the lowest capacity to generate active catalyst species through the utilized reaction setting (entry 10, TOF 960 h^{-1}). In fact, the ligand acted as poison when compared to $Pd(OAc)_2$ (entry 1, TOF 2340 h^{-1}) and it indicates that the tridentate chelation potential proved to be a stronger determining factor for catalyst efficiency above the steric or electronic considerations.

An additional key observation in catalytic outcomes obtained in the presence of the various ligands is that the ligand analogues having secondary amines situation at the middle N-donor position displayed reduced catalytic efficiencies relative to their tertiary N-donor analogues. This may be attributed to possible weaker chelating potentials of secondary amines relative to tertiary more so that the presence of three electron-inducing alkyl-substituents in the tertiary amines should also cause better donor and chelating tendencies. In other words, the results suggest that reluctant donor character at the middle donor position of such polydentate ligands as in the ligands **3**- and **4**-series is capable of frustrating eventual chelation and should be avoided.

Table 3: Catalytic performance for the series of ligands via *in situ* active site generation[a]



Entry	Ligand	Yield (%)	TOF (h^{-1})
1	No ligand	39	2340
2	**1-Me**	60	3600
3	**1-tol**	50	3000
4	**2-ipr**	72	4440
5	**2-iprNH**	67	4020
6	**3-Me**	51	3060
7	**3-tol**	54	3240
8	**3-ipr**	61	3660
9	**3-iprNH**	15	900
10	**4-tol**	16	960
11	**4-ipr**	60	3600

[a]Reaction conditions: 4mL of 3:1 EtOH/H_2O, K_3PO_4 (1.2 mmol), 0.7 mol % ligand + 0.2 mol % $Pd(OAc)_2$, 1.2 mmol **A**, 1 mmol **B**, oil bath temperature of 100 ^oC and 5 minutes reflux duration. Yield was determined by ^1H-NMR and reported to the nearest whole number.

Catalytic performance of the palladium complexes

Table 4 shows the catalytic performance of the preformed palladium precatalysts according to the established catalytic setting above. However, only 0.2 mol % of the respective complexes were introduced as catalyst sources and some further results under reaction times of 5 – 60 minutes were obtained. One key observation is that the precatalysts

generally displayed capability to generate living catalytically active species in the course of reaction life unlike the very early termination of catalyst activities experienced for the corresponding *in situ* method (Fig. 4, Table 4; catalytic activities generally increase as time progresses). For the studied compounds, it is therefore obvious that to assemble ligands and palladium(II) ions into useful catalyst configurations via the *in situ* complexation approach suffers obvious limitations compared to applying preformed complexes (Scheme 1, bottom).

An important conclusion from catalytic data is that the size of the co-ligand correlates with catalytic performance; order of yields for varying co-ligands (L) in **Pd(4-tol)D** followed H_2O < isopropanol < py while for **Pd(4-ipr)D** also followed H_2O < py (Fig. 4, see also Supplementary Information, Table S1). While complexes **Pd(4-tol)H_2O** and **Pd(4-tol)*i*PrOH** showed steady increase of yield with time, the remaining complexes could be observed to rapidly couple the substrates. Therefore, it is also noteworthy that complexes **Pd(4-tol)py** and **Pd(4-ipr)py** displayed the highest initial rates having converted as much as 80 % of the substrate within the first 5 minutes of reaction life. Consequently, it could be suggested that the presence of pyridyl moiety constituted further steric inconveniences to the already bulky ligand-palladium assembly of complexes **Pd(4-tol)py** and **Pd(4-ipr)py**, which suggestively implies lower coordination stabilities. Such steric demands probably created the ease of path for dismantling of complexation bonds towards forming the active catalyst. Still focusing on steric characteristics, the catalytic profile for complex **Pd(4-ipr)H_2O**, which is well more impressive above that of complex **Pd(4-tol)H_2O**, is attributable to the bulkiness of the *iso*-propyl-substituents (Fig. 4).

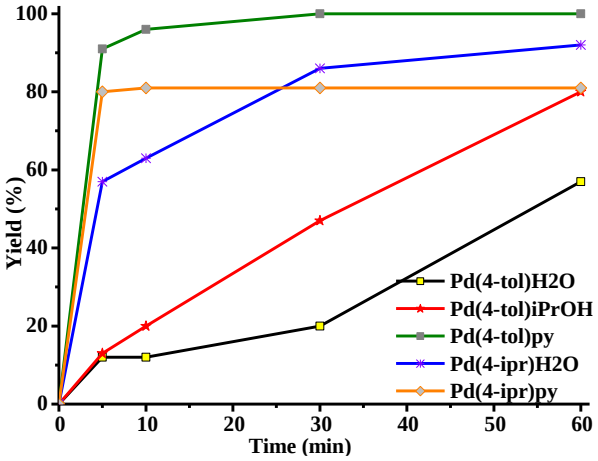


Fig. 4: Catalytic performances of the prepared palladium complexes at varying times

Conclusion

Catalysis results obtained from comparatively studying the synthesized ligands under the same reaction conditions and via the *in situ* 'ligand + $Pd(OAc)_2$' catalyst generation proved that very high catalyst performances can also be enabled by presence of simple, aliphatic, diamine or triamine chelates when appropriate sterically bulky functions are anchored to the chains. This result is considered important because general conclusions that catalytic efficiency requires sterically bulky and rigid ligands exemplified by phos architectures create impressions that flexible aliphatic-based ligand frameworks will not support useful active site generation. Within 5 min reflux, 72 % yield was recorded in the presence of ligand '**2-ipr** + 0.2 mol % Pd(II)' loading. Furthermore, higher TOF values were obtained in the presence of all triiso-propylphenly-substituented ligands relative to their respective analogues possessing the less bulky methyl- or tolyl-substituents.

Additionally, it was concluded that attaining desirable catalyst efficiencies by these polydentate, aliphatic amines is largely favoured for ligands with less than tridentate chelation

tendencies. Despite the presence of steric bulk of tosyl-substituents on the tridentate-chelating ligand **4-tol** (TOF 960 h^{-1}), it actually aided poisoning of $Pd(OAc)_2$ under *in situ* approach, which yielded TOF = 2340 h^{-1} without ligand additions. It was also concluded that presence of secondary amines N-donor in the central position of the ligands compromised chelation potentials relative to their tertiary N-donor analogues, which resulted in poorer catalytic worth.

Finally, complexes of ligands **4-tol** and **4-ipr** revealed that preformed complexes of the studied ligand frameworks possess significantly better capability to generate efficient and living active species than their corresponding *in situ* reactions. It was also observed that, despite the tridentate chelation in the complexes **Pd(4-tol)Py** and **Pd(4-ipr)py**, they displayed the highest efficiencies (5460 h^{-1} and 4800 h^{-1} respectively), which is attributed to the benefit of incorporating a bulkier co-ligand moiety such as pyridine to aid weakening of chelation.

Appendix A. Supplementary data

CCDC 1850773 – 1850775 contains the supplementary crystallographic data for **1-Me**, **Pd(4-tol)H_2O** and **Pd(4-ipr)py**. 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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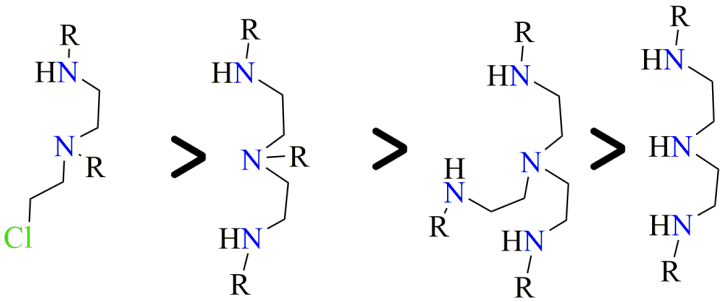
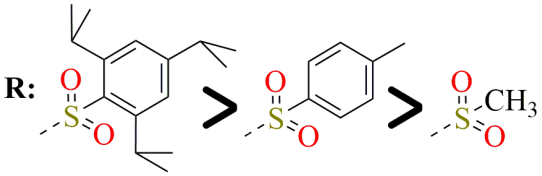
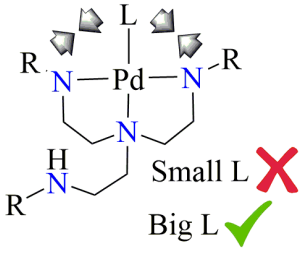
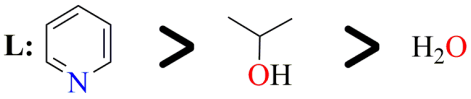
Activity via *in situ* ligand + $Pd(OAc)_2$

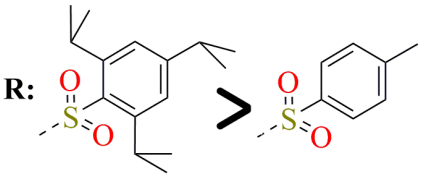




Activity via precatalysts







- Ligands having non-rigid alkyl backbones can also be relevant in furnishing highly active palladium catalysts when bulky substituents are inserted.
- *In situ* palladium catalyst generation is less favourable for increasing ligand chelate character especially from tridentate.
- However, for precatalysts bearing tridentate ligand chelator, bulkier co-ligand (L) in the 4^{th} coordination position appears to aids higher activity.
- The higher catalyst activities in the presence of larger co-ligand size is attributable to a beneficial repulsion effects between co-ligand and the tridentate chelate.