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Synthesis and characterization of new potentially hydrosoluble pincer ligands and their application in Suzuki–Miyaura cross-coupling reactions in water

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Dedicated Prof. Dr. Juventino Garcia with great admiration and respect to the teacher and friend on the occasion of his 51st birthday.

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ABSTRACT

Three water soluble pincer ligands, 2,6-bis[(diethanolamine)methyl]pyridine hydrobromide (1:2) **(1)**, 3,11,17,18-Tetraazatricyclo[$11.3.1.1^{5,9}$]octadeca-1(17),5,7,9(18),13,15-hexaene,3,11-bis(dihydroxymethylmethyl) hydrobromide (1:2) **(2),** and 1,3-bis[(diethanolamine)methyl]benzene **(3)** were synthesized and unequivocally characterized by a number of analytical techniques including single crystal X-ray diffraction analyses. Mixtures of these ligands with $PdCl_2$ proved to be efficient in catalyzing the Suzuki–Miyaura cross couplings in water. Being the most efficient system that including ligand **(1)**. Further experiments using this catalytic system were performed to assess the effects of varying temperature, reaction times, and nature of the base, finding the optimal operational conditions of this system.

Introduction

Catalytic reactions play a fundamental role for the production of a variety of added value intermediates of industrial relevance. Such that these reactions have been cataloged as a fundamental pillar of green chemistry.[1] The better comprehension of coordination and organometallic chemistry and the consistency on the preparation of these complexes have allowed the in situ generation of the catalysts. This procedure represents an easy method to screen different ligands by in situ generating the catalyst for a given reaction from a mixture of a suitable metal salt for example $PdCl_2$ and the free ligand. Thus, accelerating the discovery of efficient catalytic systems. On the other hand, pincer compounds have represented a fundamental motif in the toolbox for both organometallic and synthetic organic chemists. This being due to their well known thermal stability and unusual reactivities and to the easiness in which both steric and electronic properties can be finely tuned in the basic pincer backbone.[2a] For the case of tridentate NCN ligands this versatility is reflected in the number of different substituents that can be included in the pincer structure where N donors can be amines[2b], imines,[2c] or oxazolines.[2d] The same applies for their analogous NNN pincer ligand counterparts[2e–g] and CNC pincer compounds where *N*-heterocyclic carbenes act as C donors.[2h] A natural consequence of this versatility has been the widespread applications that transition metal pincer complexes have found in organic synthesis, materials science, and organometallic catalysis.[2i]

Moreover, palladium-catalyzed cross coupling reactions have become a power tool in organic synthesis.[3] The Suzuki–Miyaura reaction for the attaining of biphenyls, is one of the most important cross coupling processes that involves the coupling of aryl halides or triflates with organoboronic acids.[4] This reaction allows the use of a broad variety of functional groups and most importantly the reaction can be performed in neat water[5] minimizing the generation of hazardous wastes and thus greening the process.[6,7] This fact can be advantageously used, however this also requires the catalyst to be soluble in water favoring at the same time the easy separation and removal of the organic products. Among the strategies to water solubilize the catalysts[8], the most common involves the inclusion of hydrophilic groups such as carboxylates[9], sulfonates,[10] or ammonium groups[11] in the structure of the ligands used.

In the last decade, we have been involved in the design and catalytic applications of pincer ligands and their complexes[12] in

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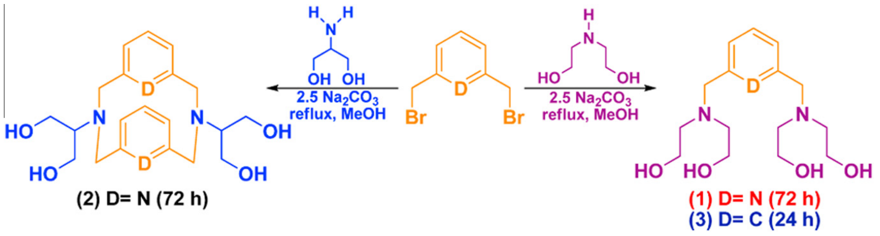


Scheme 1. Synthesis of the pincer ligands.

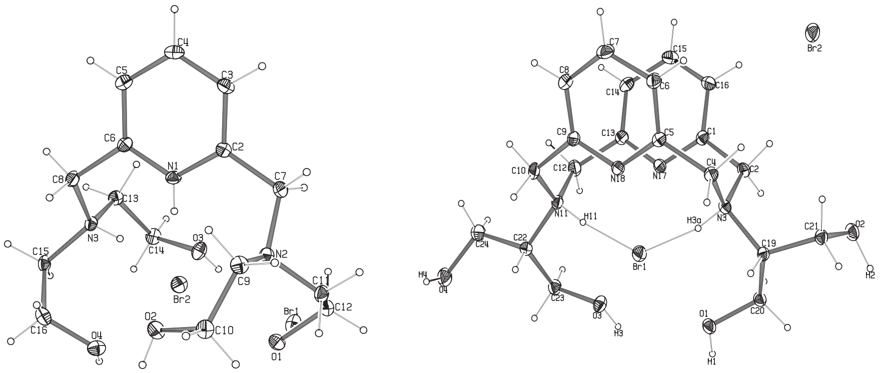
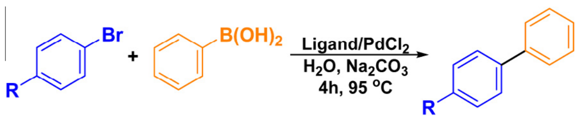


Figure 1. Thermal ellipsoids (50% probability) drawings for ligands **1** and **2**.

potentially relevant organic transformations. Thus, with this opportunity we would like to report our findings on the synthesis and application of three novel pincer ligands including aminoalcohol moieties as a motif to favor water solubility on the in situ Pd(II) catalyzed Suzuki–Miyaura C–C cross couplings in water.



Scheme 2. Suzuki–Miyaura couplings.

Results and discussion

The ligands were synthesized by reacting either 2,6-bis(bromomethyl)pyridine or 1,3-bis(bromomethyl)benzene with diethanolamine (ligands **1**[13] and **3**[14]) or 2-amine-1,3-propanediol (ligand **2**[15]) using Na_2CO_3 as base in methanol (Scheme 1). Compounds **1** and **2** were prepared under the same conditions (attempts to prepare ligand **1** using MW were also performed producing poor yields). Both ligands were characterized by ^{1}H and ^{13}C{^{1}H} NMR spectroscopy (DMSO-d_6). The ^{1}H NMR spectra showed the expected signals for **1** and **2**, including those due to the presence of the OH groups in δ 4.72 ppm and 3.98 ppm (broad), respectively. In addition, the ^{13}C{^{1}H} NMR spectra exhibit the six carbon signals expected for each compound. Analysis by FAB^{+}-MS, showed the molecular ion ([M^{+}+Na], m/z 336) for **1**. On the other hand, ligand **3** was prepared both in THF and methanol, producing better yields when the reaction was made in methanol for 24 h. This compound was obtained as a yellow viscous oil[16] and was also characterized by ^{1}H NMR and ^{13}C NMR, both spectrums exhibiting signals consistent with the proposed formulation, including the broad singlet due to the OH group in δ 4.47 ppm. Analysis by FAB^{+}-MS showed the molecular ion at m/z 335 corresponding to [M^{+}+Na].

The identity of both ligands was unequivocally determined by single crystal X-ray diffraction analysis.[17] Both compounds being crystallized as their ammonium salts (Fig. 1).

With the ligands on hand we decided to use them in the palladium catalyzed Suzuki–Miyaura cross coupling reactions (Scheme 2) of bromobenzene and phenyl boronic acid in water (95 °C, 4 h, Na_2CO_3).[18]

We first evaluated the ligand and catalyst loading using $PdCl_2$ as palladium source. Preliminary results showed all the ligands to catalyze the formation of biphenyl in good yields (96% yield of biphenyl determined by GC–MS) attaining the best conversions with 1% mol catalyst loading using ligands **1** and **2.** These results are coherent with the easiness in the formation of the Pd–NNN pincer compounds over the organometallic derivative Pd–NCN that requires a C–H activation for its formation. In addition, employing of lower loadings of Pd(II)/ligand ratio to 0.1% did not lower the yields of the product except in one case (54%, ligand 3/$PdCl_2$). In light of these results we chose to use ligand **1**/$PdCl_2$ in 0.1% loading in further experiments aimed to optimize the reaction conditions. Thus, we investigated the effect of a number of parameters such as

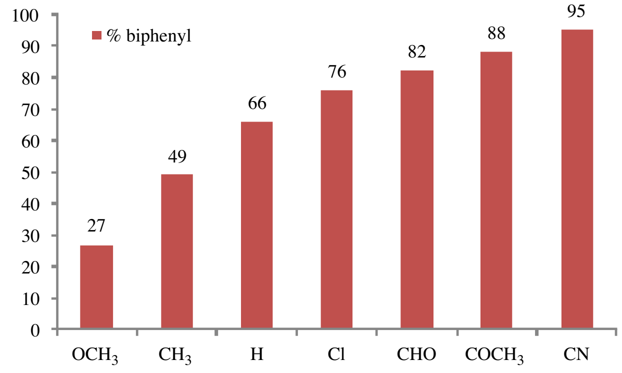


Figure 2. % Suzuki–Miyaura couplings of *p*-substituted bromobenzenes using ligand 1/Pd(II).

temperature, reaction time, and different bases. By varying the temperature a notable change in yields is observed from 25% at 50 °C all the way through 96% when the reaction was performed at 95 °C for 4 h. These results are consistent with the catalytic system to be stable. Once the temperature was set to 95 °C, we proceed to investigate the effect of reaction time. Thus, experiments were carried out at reduced reaction times from 0.5 h (46% yield) to 4 h (96% yield) with increases of 0.5 h. The results clearly show a direct dependence of the yield as a function of time, which in absence of any additive is consistent with the catalytic system to be homogeneous. As the Suzuki–Miyaura couplings are strongly dependant on the base used, several bases that is Li_2CO_3 (49% yield), Na_2CO_3 (95% yield), K_2CO_3 (65% yield), $CaCO_3$ (0.0% yield), DIPEA (15% yield), and Et_3N (50% yield), were tested under these optimized conditions. The results obtained reveal that the inorganic bases are more efficient having Na_2CO_3 with a 95% yield to biphenyl. Organic bases were also tested showing lowered yields compared to the inorganic salts. This fact can be due to competence between the ligand and the amine which upon coordination with the metallic center may just coordinatively saturate the Pd(II) avoiding any further catalysis. Although, we assumed the system to be homogeneous, participation of nano-catalyst cannot be ruled out in spite of the relatively low reaction temperatures employed. Thus, in order to confirm the homogeneity of the catalytic system we performed a catalytic experiment under the optimized conditions but this time adding a couple of drops of elemental mercury[19] noticing no appreciable difference in the performance of the catalyst with or without the presence of elemental mercury. Thus, ruling out the participation of palladium nanoparticles.

With the optimized reaction conditions, we completed the examination of the activity for this catalytic system in the Suzuki–Miyaura cross coupling reactions of some *p*-substituted bromobenzenes. The results are shown in Figure 2. A quick look to this graphic clearly shows that bromobenzenes including electron withdrawing substituents led to higher conversions as expected according to the values of Hammett parameter.[20]

In summary, we have successfully synthesized a potentially important set of water soluble pincer ligands and employed them in Suzuki–Miyaura couplings attaining excellent yields to biphenyls under relatively mild conditions. Noteworthy the fact is that the reactions are performed in neat water and thus the purification of the products consists in a mere decantation process. The present system is interesting given the easiness on the synthesis of the ligands form cheap commercially available starting materials. Thus, turning this system attractive for its potential application in organic synthesis or other cross coupling reactions. Efforts aimed to achieve these goals are currently under development in our laboratories.

Acknowledgment

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.04.007.

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13. 2,6-Bis[(diethanolamine)methyl]pyridine hydrobromide (1:2) (**1**). The product is a microcrystalline white solid with mp = 158–160 °C. MS-FAB$^+$. *m*/*z* = 336 [M$^+$+Na]. Anal. Calcd (%) for $C_{15}H_{29}N_3O_4Br_2{\cdot}2H_2O$: C 35.2, H 6.5, N 8.2. Found: C 35.1, H 6.3, N 8.0. ^{1}H NMR (DMSO-d_6): δ 7.71 (*t*, $^3J_{H-H}$ = 6 Hz, H, CH), 7.27 (*d*, $^3J_{H-H}$ = 9 Hz, 2H, CH), 4.72–471 (*s*, *a*, 4H, OH), 3.72 (*s*, 4H, CH_2), 3.45–3.42 (*m*, 8H, CH_2), 2.55–2.50 (*m*, 8H, CH_2); ^{13}C{^{1}H} (DMSO-d_6): δ 158.9 (*s*, CH), 137.03 (*s*, C), 120.9 (*s*, CH), 60.08 (*s*, CH_2), 58.5 (*s*, CH_2), 56.3 (*s*, CH_2). IR (KBr disc, cm^{-1}): 3427–3315 (OH, NH_2), 2958–2811 (C–H).
14. 3,11,17,18-Tetraazatricyclo[11.3.1.1^{5,9}]octadeca-1(17),5,7,9(18),13,15-hexaene,3,11-bis(dihydroxymethylmethyl) hydrobromide (1:2) (**2**). The product is a microcrystalline white solid with mp >220 °C decompose. Yield 25% (0.25 g, 4.72×10^{-4} mol) of **(2)**. MS–ESI$^+$. *m*/*z* = 411 [M$^+$+Na], *m*/*z* = 389

[M$^+$]. Anal. Calcd (%) for $C_{20}H_{30}N_4O_4Br_2{\cdot}CH_3COCH_3$: C 45.4, H 5.9, N 9.2. Found: C 45.2, H 5.8, N 9.1. ^{1}H NMR (DMSO-d_6): δ 7.21 (*t*, $^3J_{H-H}$ = 6 Hz, H, CH), 6.64 (*d*, $^3J_{H-H}$ = 6 Hz, 2H, CH), 5.07–5.05 (*m*, 4H, CH_2), 3.98 (*m*, *b*, 6H, NH_2 and OH), 3.69–3.63 (*m*, 8H, CH_2), 3.34 (*s*, 4H, CH_2), 3.26–3.21 (*m*, 2H, CH); $^{13}C\{^1H\}$ (DMSO-d_6): δ 158.2 (*s*, C), 136.2 (*s*, CH), 121.0 (*s*, CH), 69.0 (*s*, CH_2), 58.7 (*s*, CH_2), 58.4 (*s*, CH). IR (KBr disc, cm^{-1}): 3337–3292 (OH, NH_2), 2943–2840 (C–H).

15. Synthesis of 1,3-bis[(diethanolamine)methyl]benzene (**3**). The product was obtained as a yellow oil (0.30 g, 9.78×10^{-3} mol, 52%). MS-FAB$^+$. *m*/*z* = 335 (molecular ion with sodium). Anal. Calcd (%) for $C_{16}H_{28}N_2O_4{\cdot}5H_2O$: C 47.7, H 9.5, N 6.9. Found: C 47.6, H 9.3, N 6.8. ^{1}H (DMSO-d_6): ^{1}H, δ 7.26–7.20 (*m*, 4H, CH), 4.47 (*s, a*, 4H, OH), 3.62 (*s*, 4H, CH_2), 3.45 (*t*, $^3J_{H-H}$ = 6 Hz, 8H, CH_2), 2.55–2.51 (*m*, 8H, CH_2); $^{13}C\{^1H\}$ (DMSO-d_6): δ 139.4 (*s*, CH), 128.9 (*s*, C), 127.7 (*s*, CH), 127.0 (*s*, CH) 59.1 (s, CH_2), 58.9 (*s*, CH_2), 56.1 (*s*, CH_2). IR (KBr disc, cm^{-1}): 3402–3232 (OH, NH_2), 2950–2829 (C–H).
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17. Supplementary data for complexes **1** and **2** have been deposited at the Cambridge Crystallographic Data Centre. Copies of this information are available free of charge on request from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44 1223 336033; e-mail deposit@ccdc.cam.ac.uk or www:http://www.ccdc.cam.ac.uk) quoting the deposition numbers CCDC 926160 (**1**) and 926161 (**2**). Relevant H-bond distances can be consulted in the Supplementary data.
18. Suzuki–Miyaura couplings. In all cases the results presented are the average of two runs performed in Schlenk tubes: bromobenzene (1.77 mL, 0.0169 mol), phenyl boronic acid (2.67 g, 0.0219 mol), Na_2CO_3 (4.47 g, 0.04225 mol), 0.1 mol % of $PdCl_2$ (3 mg, 1.69×10^{-5} mol) and of the corresponding ligand (1.69×10^{-5} mol) in 6 mL of distilled water. The mixtures were stirred and heated at 95 °C in a silicon oil bath during 4 h. Subsequently, the reaction mixture was cooled to room temperature and the mixture was extracted with CH_2Cl_2 (3 × 3 mL), the organic phase was treated with anhydrous Na_2SO_4 after filter over silica gel and analyzed by Gas Chromatography (GC–MS). Other experiments of catalysis were carried out under the same reactions conditions varying the reaction times and temperatures of different bases Na_2CO_3, Li_2CO_3, K_2CO_3, $CaCO_3$, Et_3N, DIPEA and the series of *para*-substituted bromobenzenes.
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