

Hydrophilic CNC-Pincer Palladium Complexes: A Source for Highly Efficient, Recyclable Homogeneous Catalysts in Suzuki–Miyaura Cross-Coupling

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Received: April 12, 2006; Accepted: July 14, 2006

Dedicated to the memory of our colleague and friend Prof. Marcial Moreno-Mañas.

Abstract: The Suzuki biaryl coupling of a range of electronically dissimilar arylboronic acids and aryl bromides is performed in neat water with excellent to quantitative yields by means of a new CNC-pincer palladium catalyst that is soluble in water due to its *para*-carboxy group. Extremely high turn-over numbers and frequencies combined with a remarkable robustness allow an effective catalyst reuse in sustainable conditions.

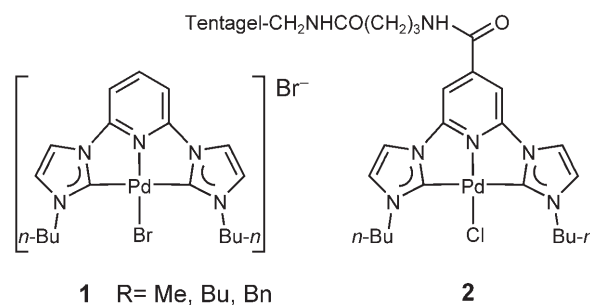
Keywords: cross-coupling; hydrophilic catalyst; palladium; pincer complexes; Suzuki coupling reaction

Palladium catalysis has progressively become such an essential tool for a good number of organic transformations in modern synthetic chemistry that the quest for procedures that imply a rational, more sustainable use of palladium catalysts has emerged as a crucial task of many investigations in the last decade.^[1] Three issues are of major importance in the latter research even when reducing the plethora of possible transformations to cross-coupling reactions: i) minimizing the relative amount of the precious metal-containing catalysts, ii) their recovery/recycling and iii) the use of environmentally-friendly and cheaper reaction media.

For the first two aims several strategies have evolved, most of them based on the use of heterogeneous catalysts or the heterogenisation of homogeneous catalysts.^[2] An obvious and increasingly exploited scheme to achieve the third goal is to employ aqueous solvents to perform such palladium-catalyzed C–C bond forming reactions, either by biphasic catalysis or in neat water.^[3]

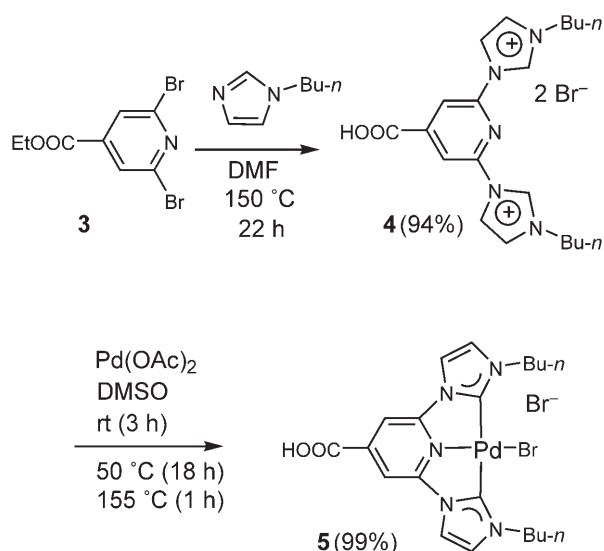
In continuation of our research on the development of new palladium catalysts and their application to the construction of several polycyclic systems,^[4] we focused our attention on the synthesis of a new hydrophilic palladacycle catalyst that would fit the three requirements formulated above. According to the frequently exhibited TON and TOF values, palladacycles, and to be precise, pincer complexes in which palladium is coordinated to a tridentate ligand, are among the most highly active catalysts for cross-coupling reactions.^[5] Considering the robustness that would prevent undesired leaching processes and the good catalytic properties in the Heck arylation of the already known CNC-type complex **1**^[6] we envisaged that a suitable modification of the latter framework could provide our intended catalyst.

Recently, Steel et al.^[7] have reported that polymer-anchoring of a structure similar to **1** by an amide linkage affords the useful and recyclable catalytic system **2** for some Suzuki and Heck coupling reactions performed in DMA. In addition, Sonogashira and Heck couplings in pyrrolidine or DMA and DEA solvents, respectively, have been reported using an efficient and reusable catalyst generated by immobilization of **1** in montmorillonite K10 clay.^[6b]



Nevertheless, in our case we decided to devise a simpler strategy which relied on the “insertion” of a functional group hydrophilic enough to work in aqueous media and to remain in such a convenient solvent once the reaction is finished, thus making possible an immediate reuse of the catalyst. The most remarkable results attained by the latter approach are reflected in this paper.

The carboxy (COOH) group was chosen due to i) its electron-withdrawing properties that could tune the catalytic activity,^[8] ii) the relatively high solubility of carboxylate salts in water even when bearing large hydrocarbon units,^[9] and iii) the availability of key precursor **3**.^[10] Treatment of **3** with *n*-butylimidazole provided intermediate **4**, which was palladated with Pd(OAc)₂/DMSO in a similar way to the work by Crabtree et al.,^[6a] providing the target complex **5** in a 93% overall yield (Scheme 1). It should be pointed out concomitant hydrolysis occurred in the transformation of **3** into **4**.



Scheme 1.

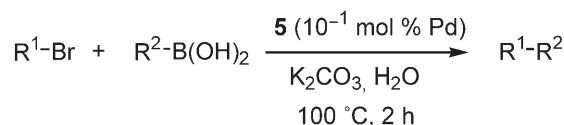
Considering the high solubility of arylboronic acids in water^[11] and the low toxicity of both reagents and by-products in Suzuki coupling compared to other protocols,^[11,12] it was selected from several palladium-catalyzed cross-coupling reactions to test our catalyst.

From the very beginning an obvious concern, related to the possibility of recycling, was the stability of the catalysts under Suzuki reaction conditions. In this context, the procedure reported by Zhao et al. using a silica-supported tetradentate NHC palladacycle^[13] and recently employed by ourselves with two NCN-type pincer complexes^[4a] was based on the use of neat water and relatively low temperatures (K₂CO₃, H₂O, 100 °C). Therefore, it appeared to be very convenient for our purpose.

Accordingly, pincer complex **5** (0.1 mol % Pd) was added to a mixture of bromobenzene (1 mmol) and phenylboronic acid (1.5 mmol), K₂CO₃ (2 mmol) and H₂O (1 mL) in a 5-mL round-bottom flask open to the atmosphere. After stirring at 100 °C for 2 h, the reaction mixture was cooled and Na₂CO₃ (5 mL of 10% solution in water) was added. The aqueous layer was extracted with CH₂Cl₂ (3 × 3 mL) and the combined organic extracts were dried over anhydrous sodium sulfate and evaporated under vacuum. Analysis by ¹H NMR of the so-obtained residue [using bis-(ethylene glycol)dimethyl ether as internal standard] revealed the formation of biphenyl in quantitative yield.

The latter procedure was then applied to a range of bromoarenes and arylboronic acids. The coupling partners were chosen on the basis of their divergent electronic properties that could affect the extent of the reaction.^[3,12,13] Nevertheless, the generality of the presented protocol, applicable to electron-rich, neutral and electron-poor bromoarenes and arylboronic acids, was unambiguously proved by the excellent yields obtained in all cases, as displayed in Table 1.

Table 1. Suzuki–Miyaura coupling catalyzed by palladium complex **5**.



Entry ^[a]	R ¹	R ²	Yield [%] ^[b]
1	4-AcC ₆ H ₄	Ph	> 99 (100)
2	4-AcC ₆ H ₄	1-Naphthyl	> 99 (100)
3	4-AcC ₆ H ₄	4-FC ₆ H ₄	> 99 (100)
4	4-AcC ₆ H ₄	3,5-F ₂ C ₆ H ₃	> 99 (100)
5	4-AcC ₆ H ₄	4-MeOC ₆ H ₄	> 99 (100)
6	4-FC ₆ H ₄	Ph	> 99 (100)
7	4-FC ₆ H ₄	1-Naphthyl	> 99 (100)
8	Ph	Ph	> 99 (100)
9	Ph	1-Naphthyl	> 99 (100)
10	Ph	4-FC ₆ H ₄	> 99 (100)
11	Ph	3,5-F ₂ C ₆ H ₃	> 99 (100)
12	Ph	4-MeOC ₆ H ₄	> 99 (100)
13	4-MeC ₆ H ₄	Ph	> 99 (100)
14	4-MeC ₆ H ₄	1-Naphthyl	94 (100)
15	4-MeOC ₆ H ₄	Ph	> 99 (100)
16	4-MeOC ₆ H ₄	4-FC ₆ H ₄	92 (100)
17	4-MeOC ₆ H ₄	3,5-F ₂ C ₆ H ₃	> 99 (100)
18	4-MeOC ₆ H ₄	4-MeOC ₆ H ₄	> 99 (100)
2	4-AcC ₆ H ₄	1-Naphthyl	> 99 (100)

^[a] Reaction conditions: R¹Br (1 mmol), R²B(OH)₂ (1.5 mmol), K₂CO₃ (2 mmol), H₂O (1 mL). Bath temperature.

^[b] Determined by NMR on the basis of the amount of starting R¹Br. Bis(ethylene glycol) dimethyl ether was used as internal standard. The conversion rate is displayed in parenthesis.

The next step in the scheduled evaluation of the properties of catalyst **5** was related to the catalyst loading required to effect the reaction. In fact, this is a crucial issue when moving from a laboratory scale to industrial bulk, as low catalyst loadings involve easy purification, lack of contamination from potentially harmful metals and increasing economic benefits.^[14]

Taking the reaction between phenylboronic acid and bromobenzene as model, successive decreases in the catalyst loading of **5** were performed down to 10⁻⁷ mol % Pd. Even with this minimal amount of catalyst **5** the reaction worked efficiently (>99%), although only an 88% yield was observed for target product bisphenyl (TON: 820,000,000. TOF: 410,000,000) after 2 h and an additional 4 h were required to achieve the same optimal result (>99% yield, TON: 1,000,000,000. TOF: 166,666,667). If trace palladium impurities in the employed reagents and base are ignored (in fact coupling assays in the absence of **5** provided negligible results), the latter results imply an outstandingly low catalyst loading effective in Suzuki coupling, not only for pincer complexes^[4a,15] or palladacycles but also for any other palladium catalyst.^[16]

Finally, our attention was focussed on the third aim of the project, catalyst separation and reuse. In fact, the easy work-up consisting of extraction with diethyl ether allowed a simple separation of the products from the hydrophilic catalyst **5**. The resulting aqueous layer was employed without further treatment in successive runs, just addition of the substrates and base. The reaction was repeated up to 5 times without observing any loss of the catalytic activity, as proved by the quantitative yields (>99%) obtained in every run.

Much discussion has arisen over the real role of palladium pincer complexes and palladacycles in catalysis, and many authors support the theory that pincer complexes act as mere precatalysts releasing palladium nanoparticles or more active palladium species.^[17] The high stability of complex **5** under the reaction conditions (as a matter of fact, boiling in water for several hours did not affect the catalytic activity) and its repeated reusability, even when using extremely low loadings, might challenge the latter hypothesis unless i) a quick, quantitative regeneration of the pincer complex occurs once the reaction has finished, or ii) the proposed palladium nanoparticles remain soluble in water, or iii) as stated by the above authors, such a theory applies only at high temperatures, above 120°C.

In summary, a readily available palladium CNC-type pincer complex bearing a *para*-carboxy group features excellent catalytic activity towards Suzuki biaryl coupling reactions performed in neat water. In addition to the extremely low catalyst loadings required and the ease of work-up/product separation,

the superior stability of the latter hydrophilic catalyst under environmentally friendly reaction conditions allows a simple, effective reuse with no observed loss of activity

Experimental Section

General Remarks

¹H and ¹³C NMR spectra were recorded on a Bruker AV-500. Chemical shifts (δ) are given in ppm and refer as internal standard to the residual solvent (CDCl₃: δ = 7.26) or TMS: (δ = 0.00). Melting points were determined in a capillary tube and are uncorrected. TLC was carried out on SiO₂ (silica gel 60 F254, Merck), and the spots were located with UV light. Drying of organic extracts during work-up of reactions was performed over anhydrous Na₂SO₄. Evaporation of solvents was accomplished with a Büchi rotatory evaporator. HR-MS were measured using a Waters GCT mass spectrometer. Elemental analyses were performed on a Perkin–Elmer 2400 CHN analyzer.

Synthesis of 2,6-Bis(3-butylimidazolium-1-yl)isonicotinic Acid (**4**)

A solution of the ethyl ester of the 2,6-dibromoisonicotinic acid (**3**) (2 mmol) and 1-butylimidazole (4 mmol) was stirred neat at 150°C in a sealed tube for 24 h. After cooling, CH₂Cl₂ (20 mL) and Et₂O (5 mL) were added to the mixture. The resultant precipitate was collected, and the crude product was purified by precipitation from MeOH/Et₂O to afford the title product **4** as a white solid; yield: 94%; mp > 300°C (EtOAc); ¹H NMR (DMSO-*d*₆): δ = 0.93 (6H, t, *J* = 7.3 Hz, CH₃), 1.34 (4H, sextet, *J* = 7.9 Hz, NCH₂CH₂CH₂CH₃), 1.91 (4H, quintet, *J* = 7.9 Hz, NCH₂CH₂CH₂CH₃), 4.30 (4H, t, *J* = 7.3 Hz, NCH₂), 8.12 (2H, s, H-4'), 8.47 (2H, s, H-3, H-5), 8.87 (2H, s, H-5'), 10.53 (2H, s, H-2'); ¹³C NMR (DMSO-*d*₆): δ = 13.45 (CH₃), 18.90 (NCH₂CH₂CH₂CH₃), 31.15 (NCH₂CH₂CH₂CH₃), 49.53 (NCH₂), 113.61 (C-3, C-5), 119.52 (C-5'), 123.69 (C-4'), 136.32 (C-2'), 145.24 (C-4), 159.11 (C-2, C-6), 163.34 (CO); HR-MS: *m/z* = 527.0527, calcd for C₂₀H₂₇Br₂N₅O₂: 527.0526; anal. calcd for C₂₀H₂₇Br₂N₅O₂: C 45.39, H 5.14, N 13.23; found: C 45.42, H 5.13, N 13.25.

Synthesis of Palladium Complex **5**

A solution of A solution of ligand **4** (1.8 mmol) and Pd(OAc)₂ (1.8 mmol) was stirred in DMSO (10 mL) for 3 h at room temperature and then for 12 h at 50°C. Subsequently, the reaction mixture was heated to 155°C for 1 h, cooled to room temperature and poured into CH₂Cl₂ (20 mL). Et₂O (5 mL) was added, and the resulting precipitate was collected, redissolved in MeOH, and the solution was filtered through a short plug of celite. The solvent was removed under vacuum and the residue was recrystallised from MeOH/EtOH to afford the purified product as a white solid; yield: 99%; mp > 300°C (EtOAc); ¹H NMR (DMSO): δ = 0.90 (6H, t, *J* = 7.3 Hz, CH₃), 1.31 (4H, sextet, *J* = 7.9 Hz, NCH₂CH₂CH₂CH₃), 1.73 (4H, quintet, *J* = 7.9 Hz, NCH₂CH₂CH₂CH₃), 4.45 (4H, t, *J* = 7.3 Hz, NCH₂), 7.70

(2H, s, H-4'), 8.26 (2H, s, H-3, H-5), 8.61 (2H, s, H-5'); ^{13}C NMR (DMSO): δ = 13.68 (CH_3), 19.10 ($\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 32.77 ($\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 49.67 (NCH_2), 108.33 (C-3, C-5), 118.58 (C-5'), 124.00 (C-4'), 150.23 (C-2, C-6), 157.68 (C-4), 163.62 (CO), 165.59 (C-2'); HR-MS: m/z = 630.9409, calcd. for $\text{C}_{20}\text{H}_{25}\text{Br}_2\text{N}_5\text{O}_2\text{Pd}$: 630.9410; anal. calcd. for $\text{C}_{20}\text{H}_{25}\text{Br}_2\text{N}_5\text{O}_2\text{Pd}$: C 37.91, H 3.98, N 11.05; found: C 37.89, H 3.92, N 11.03.

General Procedure for the Suzuki–Miyaura Coupling Catalyzed by Complex 5

Pincer complex **5** (0.1 mol % Pd) was added to a mixture of bromoarene (1 mmol) and arylboronic acid (1.5 mmol), K_2CO_3 (2 mmol) and H_2O (1 mL) in a 5-mL round-bottom flask open to the atmosphere. After stirring at 100 °C for 2 h, the reaction mixture was cooled and Na_2CO_3 (5 mL of 10% solution in water) was added. The aqueous layer was extracted with CH_2Cl_2 (3 × 3 mL) and the combined organic extracts were dried over anhydrous sodium sulfate and evaporated under vacuum. Analysis of the so-obtained residue was performed by ^1H NMR [using bis(ethylene glycol)-dimethyl ether as internal standard].

Reuse of Catalyst 5 in Suzuki–Miyaura Couplings

A 5-mL round-bottom flask was charged with ArBr (1 mmol), $\text{ArB}(\text{OH})_2$ (1.5 mmol), **5** (0.001 mmol Pd), K_2CO_3 (2 mmol), and H_2O (mL). The mixture was stirred for 2 h at 100 °C in air. After cooling, the aqueous layer was extracted with Et_2O (2 × 3 mL) and the flask was charged again with ArBr (1 mmol), $\text{ArB}(\text{OH})_2$ (1.5 mmol) and K_2CO_3 (2 mmol). Every time, after cooling and extraction with Et_2O (2 × 3 mL), the reagents and base were added and the reaction repeated. As previously explained in the general procedure, the combined organic extracts were dried over anhydrous sodium sulfate, evaporated under vacuum and the residue was analysed by NMR each time. Note: Alternatively toluene was used as the extracting solvent instead of Et_2O , but due to the lower solubility of some of the biaryl products in the former solvent, more extracting times (5–8 × 3 mL) were required.

Acknowledgements

This research was supported by the University of the Basque Country (Project UPV 41.310–13656) and the Spanish Ministry of Education and Science (MEC CTQ2004–03706/BQU). B. I. also thanks the University of the Basque Country for a predoctoral scholarship. Petronor S.A. (Muskiz, Bizkaia) is gratefully acknowledged for the generous donation of hexane.

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