On the Robustness of Methylamines – Pd Catalytic Systems in the Suzuki Reaction:

Compromise examples between synthesis and catalysis

GRÉGORY PIETERS[1], BERTRAND PUGET[2], VINCENT TERRASSON[1], JEAN-PHILIPPE ROBLIN[2], ANNE GAUCHER[1], SYLVAIN MARQUE[1], DAMIEN PRIM[1]*, YVES TROIN[2]*

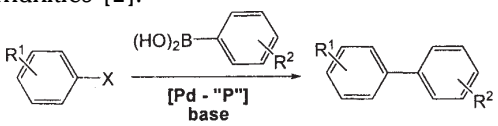
[1] Institut Lavoisier de Versailles, UMR CNRS 8180, Université de Versailles-Saint-Quentin-en-Yvelines, 78035 Versailles cedex, France

[2] Clermont Université, ENSCCF, LCHG, EA 987, F-63000 Clermont-Ferrand

This communication presents a comparison of three catalytic systems based on Pd-methylamines combinations in the context of the Suzuki reaction. This comparison takes into account several parameters such as the ligand syntheses, complex preparations and catalytic study results.

Keywords: catalytic systems, Pd-methylamines combinations, Suzuki reaction

For several decades, the Suzuki [1] reaction emerged as an effective tool for the formation of carbon-carbon bonds in both academic and industrial scientific communities [2].



Scheme 1. Suzuki type reaction

The reasons which have contributed to the popularity of this pallado-assisted proccess included (i) a wide range of commercially available reagents. (ii) an easy manipulations. (iii) an excellent chemio-compatibility. Of course, the catalytic combination Pd-ligand, played a crucial role in these transformations. Historically, if the Pd-phosphanes catalytic systems were first used, some recent investigations have shown the efficiency of catalytic phosphanes-free systems [3]. These catalytic systems also overcome some of the known drawbacks of former combinations such as cost, instability or phosphorous-based waste management. On the other hand, the efficiency of a catalytic system is not only set up by the catalytic amount, yield or conversion. Indeed, the robustness of a catalytic system should take into account several additional parameters such as the easy access to the ligands in terms of reagents availability, number of synthesis steps, ease of purification of the necessary intermediates and the stability of both ligand and metal-ligand complex.

This communication presents the comparison of three catalytic systems. This comparison is carried out on the basis of results obtained in catalysis and takes also into account the aforementioned additional parameters. The comparative study is conducted on a Suzuki-Miyaura type reaction. Figure 1 presents the structure of three palladium II complexes that are used in the context of this comparison.

Complexes **1** to **3** have several common characteristics such as the same metal oxidation degree (II) and a bidendate ligand structure based on a substituted methylamine. Complex **1** reveals a pyridine - methylamine ligand combination, complex **2** an azetidine-methylamine combination and complex **3** a pyridine-piperidine combination. The next sections will show that the structural modifications on the methylamine core will have consequences on the catalytic activity as well as on the preparation of ligands and complexes.

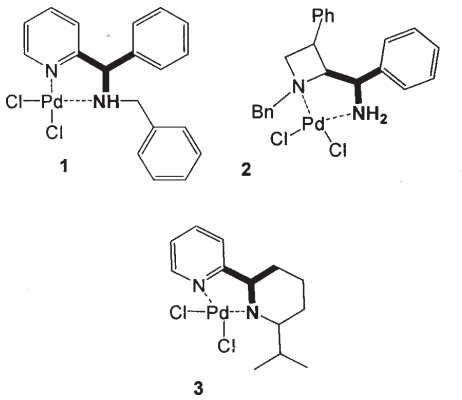
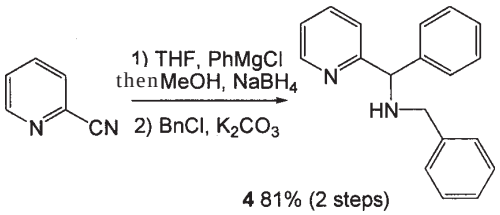


Fig. 1. Complexes **1**, **2** and **3**

Preparation of pyridine-methylamine ligand

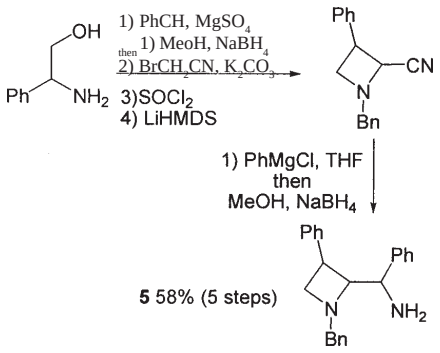
Ligand **4** was prepared in two steps from the 2-cyanopyridine (scheme 2)[4]. The addition of phenyl-magnesium chloride led to the corresponding matallamine, which was not isolated but immediately reduced with $NaBH_4$ in the presence of methanol. The resulting primary amine was alkylated with benzyl chloride in the presence of potassium carbonate. The benzylation proved relevant and increased the solubility of the ligand and of the corresponding complex (*vide infra*). Thus ligand **4** was obtained in 81% overall yield.



Scheme 2. Preparation of ligand **4**

Preparation of azetidine- methylamine ligand

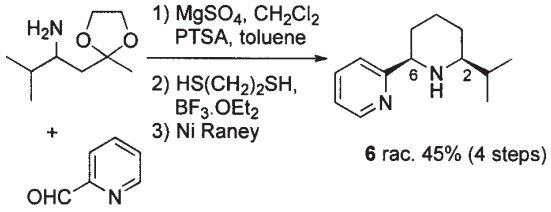
The synthesis of ligand **5** was carried out according to the sequence described in scheme 3. Four steps were necessary to the preparation of the azetidin heterocycle, including benzylation and alkylation of the nitrogen atom, followed by chlorination of the alcohol and base-promoted ring cyclization. An additional step of nucleophilic addition followed by a diastereoselective reduction allowed the formation of ligand **5** [5] with 58% overall yield.



Scheme 3. Preparation of ligand **5**

Preparation of pyridine-piperidine ligand

In this molecule series, ligand **6** was obtained, in three steps (80% yield) using an intramolecular Mannich reaction type between a protected amino ketone and a 2-pyridine carboxaldehyde (scheme 4) [1d].This strategy allowed a diastereoselective access to *cis* 2,6-piperidines according to a widely described methodology for alkaloid syntheses and analogue compounds [6].



Scheme 4. Preparation of ligand **6**

Complexation reactions

Na_2PdCl_4 was added to ligands **4**, **5** and **6** in freshly distilled methanol [7]. After 24 h at room temperature, Pd(II) complexes precipitated and were then collected by filtration. Theses complexes are air stable and can be kept for several months. The purification of compounds **1** and **2** could be realized using a classical technique such as silica gel chromatography. Complexes were obtained as yellow solids, with very good yields ranging from 81 to 92%, and are soluble in most common organic solvents, except the complex **3** soluble only in DMSO or DMF (fig. 2).

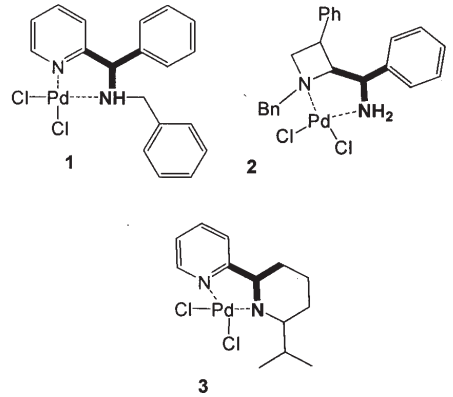


Fig. 2. Preparation of complexes **1, 2** and **3**

The structure of complex **1** has been confirmed by X-ray analyses [7]. The figure 3 shows characteristic features of such complexes: (i) inter-atomic distances Pd–N(1) and Pd–N(8) on one hand, then Pd–Cl(1) and Pd–Cl(2) on the other hand are similar (respectively between 2.021 and 2.031Å and 2.303 and 2.282Å). (ii) valence angles C(2)-N(1)-Pd and C(7)-N(8)-Pd are close (113.7 and 115.3°). (iii) a slight deviation of the Pd-plane (0.062°) is observed.

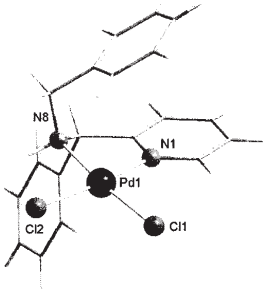


Fig. 3. X-ray structure of complexes **1**

Pallado-assisted catalysis

The comparison of catalytic activities of complexes **1** to **3** was realized on a model reaction. The choice was focused on the formation of 4-methoxy-1,1'-biphenyl **7** using a Suzuki-Miyaura reaction. The experimental conditions described (temperature, time reaction, base and catalytic loadings) have been optimized for each of the complexes. Table 1 describes the results obtained for all catalytic systems.

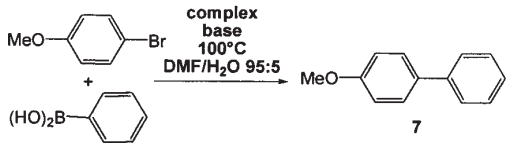


Table 1
SYNTHESIS OF BIPHENYL **7**

E.	Complex	Cat. (%)	Base	Time (h)	Yield (%)
1	**1**	10^{-1}	K_2CO_3	48	85
2	**2**	1	Cs_2CO_3	16	77
3	**3**	10^{-2}	K_3PO_4	1	99

The use of complex **1**, led to good results in terms of yields, and catalytic loading for a 48 h of reaction time (entry 1). Complex **2** gave access to the target in shorter reaction course but required a 10 time higher catalytic loading to ensure completion of the Suzuki reaction (entry 2). Complex **3** appeared as the more promising system. Almost quantitative yield was obtained after 1 hour using a 10-2% molar catalytic loading (entry 3).

Comparison of the catalytic systems

All the criteria which brings the scientific researcher to the choice of a catalytic system for the biphenyl synthesis **7** is described in table 2.

This comparison takes into account not only catalytic performances of the studied complexes but also integrates the concepts of both the stability and the ligand synthesis. The stability of complexes 1-3 seems similar and isolated yields of the Suzuki product are close ranging from 77% to quantitative. These parameters alone are therefore not discriminatory enough. Indeed, taking into account all parameters allowed us to refine the choice of the most adapted and robust catalytic system for a given Suzuki

Table 2
COMPARISON OF CATALYTIC SYSTEMS **1**

Comp.	Cat. Loading(%)	Time (h)	Yield (%)	Stability	Ligand synthesis
1	++	+	++	++	+++
2	+	++	++	++	+
3	+++	+++	+++	++	+

reaction. Additionnally, catalytic loading, reaction time as well as length of the ligand synthetic pathways displayed significant differences. It seems that the choice of a catalytic system for the synthesis of biphenyl **7** using a Suzuki-Miyaura reaction can be oriented towards the use of complexes **1** or **3**. Complex **2** seems less appropriate.

Conclusion

In conclusion, the choice of a catalytic system results in a compromise between several parameters. All these settings must be integrated to define the robustness of the proposed methodology. Complexes **1** and **3** are competitive in the context of the model Suzuki reaction. It remains difficult to refine more of those settings before doing the comparison between an easier synthesis of **1** and the catalytic performance of **3**. In this case, the important decrease of the catalytic loading down to 10^{-2} % may be offset against an increased number of ligand synthesis steps.

References

1. a) MIYAURA, N.; SUZUKI, A. Chem. Rev. **95,** 1995, p. 2457-2483. b) SUZUKI, A. J. Organomet. Chem. **576,** 1999, p.147-168. c) ALONSO, F.; BELETSKAYA, I. P.; YUS, M. Tetrahedron, **64,** 2008, p. 3047-3101. d) PUGET, B.; ROBLIN, J.-P.; PRIM, D.; TROIN, Y. Tetrahedron Lett., **49,** 2008, p. 1706–1709. e) KELLER, L.; VARGAS SANCHEZ, M.; PRIM, D.; COUTY, F.; EVANO, G.; MARROT, J. J. Organomet. Chem. **690,** 2005, p.2306; f) TERRASSON, V.; PRIM, D.; MARROT, J. Eur. J. Inorg. Chem,. 2008, p. 2739

2. CORBET, J.-P.; MIGNANI, G. Chem. Rev. **106,** 2006, p. 2651

3. a) WANG, Z.-X.; CHAI, Z.-Y. Eur. J. Inorg. Chem. 2007, p. 4492 b) BRÖRING, M.; KLEEBERG, C.; TEJERO, E. C. Eur. J. Inorg. Chem. 2007, p.3208-3216. c) HANEDA, S.; GAN, Z.; EDA, K.; HAYASHI, M. Organometallics **26,** 2007, p.6551-6555. d) HANEDA, S.; UEBA, C.; EDA, K.; HAYASHI, M. Adv. Synth. Catal. **349,** 2007, p.833-835. e) BIANCHINI, C.; LENOBLE, G.; OBERHAUSER, W.; PARISEL, S.; ZANOBINI, F. Eur. J. Inorg. Chem., 2005, p. 4794

4. TERRASSON, V.; MARQUE, S.; SCARPACCI, A.; PRIM, D. Synthesis**,** **11**, 2006, p.1858

5. COUTY, F.; EVANO, G.; PRIM, D.; MARROT, J. Eur. J. Org. Chem., 2004, p. 3893

6. a) CIBLAT, S.; BESSE, P.; CANET, J.-L.; VESCHAMBRE, H.; TROIN, Y.; GELAS, J. Tetrahedron: Asymmetry, **10,** 1999, p.2225–2235. b) CIBLAT, S.; BESSE, P.; PAPASTERGIOU, V.; VESCHAMBRE, H.; CANET, J.-L.; TROIN, Y. Tetrahedron: Asymmetry**,** **11,** 2000, p.2221

7. *** CCDC-677262. All Crystal data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

Manuscript received: 2.03.2010