

[{Pd(μ -OH)Cl(IPr)}₂] – a highly efficient precatalyst of Suzuki – Miyaura coupling, able to act also under base-free conditions

Sylwia Ostrowska, Jan Lorkowski, Maciej Kubicki, Cezary Pietraszuk*

Abstract: [$\{Pd(\mu-OH)Cl(IPr)\}_2$] (IPr = N,N-bis(2,6-diisopropylphenyl) imidazol-2-ylidene) has been found a highly efficient precatalyst of Suzuki–Miyaura coupling able to act also under base-free conditions.

N-Heterocyclic carbenes due to their valuable properties have become universal ligands in organometallic catalysis.^[1] Since first application in transition metal catalvsis^[2] their unprecedented advances have been made in designing of active NHC-based Pd precatalysts of a variety of coupling processes.^[3] From among these processes, the Suzuki-Mivaura (SM) crosscoupling is one of the most frequently used in organic synthesis.^[4] Presently, a number of NHC palladium complexes, includina familv of [PdCl₂(NHC)(pyridine)] (PEPPSI) precatalysts,^[5] analogues bearing various throw away ligand^[6] and related dimeric complexes $[{Pd(\mu-Cl)(Cl)(NHC)}_2]^{[7]}$ have been reported to be excellent precatalyst for the Suzuki-Miyaura coupling.[6b,c, 8]

Herein, we report a new NHC palladium hydroxide complex [{Pd(μ -OH)Cl(IPr)}₂] (1) exhibiting high productivity and activity in Suzuki-Miyaura coupling of chloroarenes with arylboronic acids and able to act in base-free conditions. The aim of our study was to design and obtain a catalyst of possibly the highest activity and efficiency, rather than the one allowing multiple use. This approach has been earlier suggested in literature by Gladysz^[9a] and recently discussed and supported by Hubner, de Vries and Farina.^[9b]

Beneficial effect of hydroxides on the SM reaction^[8a,10,11] has inspired us to search for precatalysts containing hydroxide ligand in the coordination sphere. In the preliminary studies we



Scheme 1. SM coupling of chlorobenzene with tolylboronic acid

Sylwia Ostrowska, Jan Lorkowski, Maciej Kubicki, Cezary Pietraszuk Adam Mickiewicz University in Poznań, Faculty of Chemistry, Umultowska 89b, 61-614 Poznań, Poland e-mail: pietrasz@amu.edu.pl

Supporting information for this article is given via a link at the end of the document.

found that SM coupling of tolylboronic acid with chlorobenzene (Scheme 1) performed in air, in the presence of $[PdCl_2(IPr)(3-chloropyridine)]$ (2) or the chloride dimer $[{Pd(\mu-Cl)(Cl)(IPr)}_2]$ (3) in mild reaction conditions^[8b], proceeds efficiently even when the

base is used in twofold molar excess in relation to the palladium (SI, Table S1).

To identify the hydroxide-bearing palladium complexes possibly generated in the course of SM coupling, the reaction of PEPPSI-IPr (2) with KOH was monitored by ¹H NMR spectroscopy. Treatment of a solution of PEPPSI-IPr with 4 equiv. of KOH resulted in gradual formation of a new complex (a new singlet at δ = 6.35 ppm assigned to olefinic proton of IPr and a singlet at δ = -3.93 ppm). Single crystal obtained from the reaction mixture was found to be co-crystal of PEPPSI-IPr (2) and hydroxide dimer [{Pd(µ-OH)Cl(IPr)}₂] (1) (Figure S5). The results indicate that the reaction proceeds according to Scheme 2.



Scheme 2. Reaction of PEPPSI-IPr with KOH

Hydroxide complex **1**, being most likely the product of PEPPSI-IPr activation by hydroxides, was synthesized with an almost quantitative isolated yield (95%) by treatment of chloride dimer [{Pd(μ -Cl)Cl(IPr)}₂] (**3**) with an excess of KOH (Scheme 3). Its structure was confirmed X-ray diffraction (Figure 1).



Scheme 3. Synthesis of [{Pd(µ-OH)Cl(IPr)}2]

The activities of complexes **1**, **2** and **3** were compared in a SM coupling of chlorobenzene with tolylboronic acid (Table 1). Unlike the other catalysts, complex **1** shows catalytic activity in base-free conditions (entry 1). The use of low concentrations of KOH (entries 2, 5 and 8) allows effective course of the reaction for all catalysts tested. Another slight increase in the reaction yield was observed when using a high excess of KOH (entries 3, 6, 9). Reactions performed in a base-free conditions or at low base concentration were nearly completely ceased when air-free conditions were used (entries 2, 5 and 8).



Figure 1. Perspective view of a binuclear complex 1. Ellipsoids are drawn at the 30% probability level, hydrogen atoms are shown as spheres of arbitrary radii

Table 1. SM coupling of chlorobenzene with tolylboronic acids in the presence of complexes 1, 2 and 3. Effect of KOH concentration

Entry	Cat.	[KOH] : [Pd]	Yield ^a [%]
1	1	0	72 (5 ^b)
2	1	2:1	94 (5 ^b)
3	1	130:1	96 (95 ^b)
4	2	0	0
5	2	2:1	90 (3 ^b)
6	2	130:1	94 (92 ^b)
7	3	0	0
8	3	2:1	85 (5 ^b)
9	3	130:1	87 (83 ^b)

Reaction conditions: [Pd] (1 mol%), EtOH, 22 °C, 6 h, air, [ArCI]:[Ar'B(OH)_2]:[KOH] = 1 : 1.25 : 1.3; ^{a)} isolated yield; ^{b)} air-free conditions

Table 2. SM coupling of aryl chlorides with boronic acids in the presence of 1

Ar-	Ar—R		
Entry	Ar	R	Yield ^a [%]
1	phenyl	tolyl	99
2	4-methoxyphenyl	tolyl	98
3	4-acetylphenyl	tolyl	99
4	2-anthracenyl	tolyl	78
5	2-methylphenyl	tolyl	91
6	2-pyridyl	tolyl	82
7	3-pyridyl	tolyl	86
8	2-thienyl	tolyl	98

WILEY-VCH

9	2-thienyl	phenyl	97
10	2,6-dimethylphenyl	2,6-dimethylphenyl	88 ^b
11	phenyl	(E)-(4-methylstyryl)	93 ^b

 $[{Pd(\mu-OH)Cl(IPr)}_2]$ (1) has been tested in a number of SM reactions involving challenging substrates such as 2chloropyridine or 2-chloro-1,3-dimethylbenzene and proves highly active in low concentration and under mild reaction conditions (Table 2). The studies aimed at optimization of the catalyst loadings (Table 3) revealed that complex 1 used in KOH-free conditions allows effective course of the reaction in concentrations up to 0.1 mol% (entry 2). The maximum values of TON and TOF obtained in the absence of the base were 710 and 530 h⁻¹, respectively. The addition of twofold molar excess of KOH relative to palladium enables tenfold reduction in the catalyst concentration and ensures TON = 7.9 × 10³ and TOF = 5.6×10^3 h⁻¹ (entry 5). However, under the conditions typically used in the SM coupling ([KOH] [ArB(OH)₂] = 1 : 1) (entries 6 -10) catalyst 1 remains active even at concentrations below 1 ppm and can achieve values of TON exceeding 10⁶ and TOF reaching $5.3 \times 10^{6} h^{-1}$ (entry 10).

 Table 3. SM coupling of chlorobenzene with tolylboronic acids. Optimization of the catalyst 1 loading

Entry	1 [mol %]	[KOH]:[Pd]	Yield ^a of 6 [%]
1	1	0	88
2	0.1	0	71 ^b
3	1	2:1	98
4	0.1	2:1	95
5	0.01	2:1	79 ^b
6	0.1	1.3 × 10 ³ : 1	99
7	0.01	1.3 × 10 ⁴ : 1	95
8	0.001	1.3 × 10 ⁵ : 1	92
9	0.0001 (1 ppm)	1.3 × 10 ⁶ : 1	91
10	0.00001 (0.1 ppm)	1.3 × 10 ⁷ : 1	74 ^b , 53 ^c

Reaction conditions: EtOH, 24 h, 22 °C, air, $[C_6H_5CI]$: $[ArB(OH)_2] = 1:1.25$; ^{a)} yield calculated on the basis of GC analysis; ^{b)} 40 °C; ^{c)} 1 h

Transmetalation followed by reductive elimination is a probable method of reduction of precatalyst **1** to a catalytically active palladium(0) complex. Complex **1**, thanks to the presence of hydroxide and chloride ligands in the coordination sphere is potentially able to undergo transmetalation via two different pathways, that is via reaction of hydroxide ligand with arylboronic acid and via reaction of chloride ligand with trihydroxoboronate derivative [ArB(OH)₃]X (Scheme 4).

WILEY-VCH

COMMUNICATION



Scheme 4. Proposed pathways of generation of active $\mathsf{Pd}(0)$ species from precatalyst 1 via transmetalation

Indeed, the reaction of **1** with a fivefold excess of tolylboronic acid (5) performed in EtOH at 22 °C afforded after 1 h the product **7** in 48% yield as observed by GC, and the reaction of **1** with potassium tolyltrihydroxyborate (**8**)^[12] performed in the same conditions gave **7** in 12% yield (Figure S2). This result confirmed contributions of both pathways in the reduction of precatalyst **1**.

As the catalytic reactions initiated by 1, 2 and 3 are accompanied by the formation of fine black solid, the possibility of the SM reaction to take place in the systems studied under heterogeneous catalytic conditions was checked. For this purpose, for the reaction of chlorobenzene coupling with tolylboronic acid in the presence of catalysts 1, 2 and 3, the mercury poisoning experiments^[13] were performed. Additional test was carried out for catalyst 1 in base-free conditions. There was no reduction in activity of any of the catalysts tested in the presence of mercury excess (Figure S3). The fine solid formed in the test reaction (EtOH, 22°C, [ArCl]:[ArB(OH)₂]:[Pd]:[KOH] = 1/1.25/1×10⁻²/2×10⁻²) was isolated and characterised by transmission electron microscopy (TEM). The analysis showed that the solid was made of palladium nanoparticles of 2.3 - 3.1 nm in diameter (Figure S4). Their catalytic activity was tested in the reaction of chlorobenzene with tolylboronic acid under typical reaction conditions, both at 22 °C and at the reflux temperature. Complete catalytic inactivity was observed. These results strongly suggest that the studied reaction runs under the homogeneous catalytic conditions.

In the presence of hydroxides or other bases catalytically active Pd(0) species undergo SM coupling according to commonly accepted mechanism. It was found that in base-free conditions complex **1** remains active only in the presence of oxygen. The role of oxygen in SM cross-coupling has been hardly explored. A number of oxygen-promoted, solventsensitive, efficient ligand-free catalytic systems have been reported by Liu.^[14] Oxygen activated ligand-free catalytic

systems and preliminary mechanisms explaining the activating role of oxygen have recently been summarised.^[15] The possible activating role of oxygen in the systems based on N-heterocyclic carbene complexes has not been studied, although many of these systems show high activity in aerobic conditions. The understanding of catalytic activity of 1 in base-free conditions (this activity is much lower than that in the presence of excess of the base) needs further studies. Although precatalyst 1, (unlike complexes 2 and 3) is able to generate the active Pd(0) species in base-free conditions (Scheme 4), the absence of the base makes the transmetalation step in catalytic cycle impossible to take place. We assume that in such conditions the active Pd(0) complexes undergo two types of oxidative additions, i.e., the oxidative addition of aryl halide (according to the commonly accepted mechanism) and oxidative addition of C-B bond of boronic acid, described by Moreno-Manas.^[16] Formation of unsymmetrical biaryls via reductive elimination requires earlier formation of suitable dimeric complexes.

In conclusion, NHC palladium hydroxide complex [{Pd(μ -OH)Cl(IPr)}₂] (1), exhibits high catalytic activity in Suzuki-Miyaura coupling at catalyst loadings down to 0.1 ppm.

Acknowledgments

The research was co-financed by the National Centre for Research and Development (NCBR) under the Project ORGANOMET No: PBS2/A5/40/2014.

Keywords: Suzuki-Miyaura coupling • palladium catalysis • NHC complexes • hydroxide complexes • homogeneous catalysis

- a) M. N. Hopkinson, C. Richter, M. Schedler, F. Glorius, Nature 2014, 510, 485–496; b) N-Heterocyclic Carbenes: Effective Tools for Organometallic Synthesis, (Ed.: S. P. Nolan), Wiley-VCH, 2014; c) S. Diez-Gonzalez, N. Marion, S. P. Nolan, Chem. Rev. 2009, 109, 3612– 3676; d) N-Heterocyclic Carbenes in Synthesis, (Ed.: S. P. Nolan), Wiley-VCH, 2006; e) W. A. Herrmann, Angew. Chem. Int. Ed. 2002, 41, 1290–1309.
- [2] W. A. Herrmann, M. Elison, J. Fischer, C. Kocher, G. R. J. Artus, Angew. Chem. Int. Ed. 1995, 34, 2371–2374.
- a) M. Hoyos, D. Guest, O. Navarro, (N-Heterocyclic Carbene)– Palladium Complexes in Catalysis. In *N-Heterocyclic Carbenes: Effective Tools for Organometallic Synthesis*, (Ed.: S. P. Nolan), Wiley-VCH, **2014**, pp. 85–109; b) H. Li, C. C. C. Johansson Seechurn, T. J. Colacot, *ACS Catal.* **2012**, *2*, 1147–1164; c) C. Valente, S. Calimsiz, K-H. Hoi, D. Mallik, M. Sayah, M. G. Organ, *Angew. Chem. Int. Ed.* **2012**, *51*, 3314–3332; d) G. C. Fortman, S. P. Nolan, *Chem. Soc. Rev.* **2011**, *40*, 5151–5169.
- [4] a) B. W. Glasspoole, E. C. Keske, C. M. Crudden, Stereospecific and Stereoselective Suzuki–Miyaura Cross-Coupling Reactions. In New Trends in Cross-Coupling: Theory and Applications; (Ed.: T. J. Colacot), RSC, 2015, pp. 521–550;(b) J. C. H. Lee, D. G. Hall, State-of-the-Art in Metal-Catalyzed Cross-Coupling Reactions of Organoboron Compounds with Organic Electrophiles. In Metal-Catalyzed Cross-Coupling Reactions and More; vol. 1-3, (Eds.: A. de Meijere, S. Brase, M. Oestreich), Wiley-VCH, 2014, pp. 65–132; c) N. Miyaura, A. Suzuki, Chem. Rev. 1995, 95, 2457–2483.
- a) C. Valente, M. Pompeo, M. Sayah, M. G. Organ, *Org. Process Res.* Dev. 2014, 18, 180–190; b) M. G. Organ, G. A. Chass, D-C. Fang, A. C.
 Hopkinson, C. Valente, *Synthesis* 2008, 17, 2776–2797.

- COMMUNICATION
- [6] a) W. A. Herrmann, V. P. W. Bohm, C. W. K. Gstottmayr, M. Grosche, C-P. Reisinger, T. Weskamp, J. Organomet. Chem. 2001, 617-618, 616–628; b) O. Diebolt, V. Jurcik, R. Correa da Costa, P. Braunstein, L. Cavallo, S. P. Nolan, A. M. Z Slawin, C. S. J. Cazin, Organometallics 2010, 29, 1443–1450; c) M-T. Chen, D. A. Vicic, M. L. Turner, O. Navarro, Organometallics 2011, 30, 5052–5056; d) X-X. Zhou, L-X. Shao, Synthesis 2011, 3138–3142.
- [7] M. S. Viciu, R. M. Kissling, E. D. Stevens, S. P. Nolan, Org. Lett. 2002, 4, 2229–2231.
- [8] a) C. J. O'Brien, E. A. B. Kantchev, C. Valente, N. Hadei, G. A. Chass,
 A. Lough, A. C. Hopkinson, M. G. Organ, *Chem. Eur. J.* 2006, *12*,
 4743–4748; b) O. Diebolt, P. Braunstein, S. P. Nolan, C. S. J. Cazin, *Chem. Commun.* 2008, 3190–3192; c) T. E. Schmid, D. C. Jones, O.
 Songis, O. Diebolt, M. R. L. Furst, A. M. Z. Slawin, C. S. J. Cazin, *Dalton Trans.* 2013, *42*, 7345–7353.
- a) J. A. Gladysz, Pure Appl. Chem., 2001, 73, 1319–1324; b) S. Hubner, J. G. de Vries, V. Farina, Adv. Synth. Catal. 2016, 358, 3–25.
- a) C. Amatore, A. Jutand, G. Le Duc, *Chem. Eur. J.* 2011, *17*, 2492–2503; b) C. Amatore, A. Jutand, G. Le Duc, *Chem. Eur. J.* 2012, *18*,

6616–6625; c) C. Amatore, G. Le Duc, A. Jutand, *Chem. Eur. J.* **2013**, *19*, 10082–10093.

- [11] For activating effect of addition of hydroxides see for example: a) N. Miyaura, J. Organomet. Chem. 2002, 653, 54–57; b) M. G. Organ, S. Calimsiz, M. Sayah, K. H. Hoi, A. J. Lough, Angew. Chem. Int. Ed. 2006, 48, 2383–2387.
- [12] A. N. Cammidge, V. H. M. Goddard, H. Gopee, N. L. Harrison, D. L. Hughes, C. J. Schubert, B. M. Sutton, G. L. Watts, A. J. Whitehead, *Org. Lett.* 2006, *8*, 4071–4074.
- [13] N. T. S. Phan, M. Van Der Sluys, C. W. Jones, Adv. Synth. Catal. 2006, 348, 609–679.
- [14] (a) C. Liu, Q. Ni, P. Hu, J. Qiu, Org. Biomol. Chem. 2011, 9, 1054–1060; (b) X. Rao, C. Liu, J. Qiu, Z. Jin, Org. Biomol. Chem. 2012, 10, 7875–7883; (c) C. Liu, X. Rao, Y. Zhang, X. Li, J. Qiu, Z. Jin, Eur. J. Org. Chem. 2013, 4345–4350; (d) X. Rao, C. Liu, Y. Xing, Y. Fu, J. Qiu, Z. Jin, Asian J. Org. Chem. 2013, 2, 514–518; (e) C. Liu, X. Li, X. Wang J. Qiu, Turk. J. Chem. 2015, 39: 1208–1215.
- [15] C. Liu, X. Li, Chem. Rec. 2016, 16, 84–97.
- [16] M. Moreno-Manas, M. Perez, R. Pleixats J. Org. Chem. 1996, 61, 2346–2351.

WILEY-VCH

CeD

COMMUNICATION

[{Pd(µ–OH)Cl(IPr)}₂] exhibits high activity in Suzuki–Miyaura coupling at catalyst loadings down to 0.1 ppm and can also act in base-free conditions

