

Miyaura-Suzuki Cross Coupling Reactions: The Role of Pd/CaCO₃ as Catalyst Reservoir

Bianca L. Oliveira and Octavio A. C. Antunes*

Instituto de Química, UFRJ, CT Bloco A, Cidade Universitária, Rio de Janeiro, RJ 21949-900, Brazil

Received November 25, 2006; Revised February 02, 2007; Accepted February 02, 2007

Abstracts: Miyaura-Suzuki reaction was carried out in water-ethanol solutions by using Pd/CaCO₃ as catalyst. Very good yields were obtained using different bases, phosphates or carbonates. The catalyst was recycled up to seven times without any loss of activity. To evidence the presence of Pd(II) in solution as the true catalyst, the solids were removed by decantation and the reaction products were extracted with hexane. The water-ethanol solution was recycled and kept catalytic activity.

Keywords: Pd(0) reservoir; catalysis, leaching, C-C, cross coupling, homeopathic concentrations.

INTRODUCTION

Palladium-catalyzed cross-coupling reactions [1] are among the most prominent processes in organic synthesis. Originally conceived independently by Mizoroki [2] and Heck [3], followed by Stille [4], Negishi [5], Sonogashira [6] and Suzuki [7], among others, these reactions are still under investigation by several groups interested in more environmentally compatible processes and/or in opening the scope of these reactions [8].

Miyaura-Suzuki reactions [7], in particular, are very attractive due to the stability of the precursors, boronic acids, and facility of work up. However, as, in general, unfriendly phosphines are used, there is a continuous need to improve these processes [9].

The search of new processes, of course, involves the use of well known heterogeneous catalysts, as Pd/C [10] and other systems [9]. To avoid the use of flammable, hazardous, and/or non-renewable solvents, the use of ionic liquids, fluorosolvents, supercritical fluids, and PEGs has been extensively reported in organic synthesis, in particular in Pd catalyzed C-C and C-N bond formation [11]. Water, however, remains unique. Whenever possible its use represents always one of the most economical and environmentally viable options [12].

RESULTS AND DISCUSSION

In the present paper our results concerning the use of aqueous systems combined to the rarely used Pd/CaCO₃ catalyst [11a,13] in the Miyaura-Suzuki reaction are disclosed.

Our initial investigation started with the cross-coupling of phenylboronic acid and iodobenzene as a model system. The reaction was carried out in the presence of 1% (molar to Pd) Pd/CaCO₃ in 40% aqueous ethanolic solution at 80°C. Several bases were tested (Table 1) and using K₂CO₃, Na₃PO₄ and Na₂CO₃, very high yields were obtained. The

miserable yields obtained with NaOAc and KOAc indicated the necessity of addition of stronger bases to the reaction media [8i,13b,14].

Table 1. Effect of Different Bases in the Pd/CaCO₃ Catalyzed Suzuki Reaction

Entry	Base	T (°C)	Yield (%)
1	Na ₃ PO ₄	80	90
2	Na ₂ CO ₃	80	87
3	K ₂ CO ₃	80	100
4	NaOAc	80	20
5	KOAc	80	14

Using K₂CO₃ or Na₃PO₄ as base other substrates (Table 2) were successfully tested with yields between 96 and 100% with K₂CO₃ and 85 and 90% with Na₃PO₄, despite the presence of electron donors or electron acceptor groups in the aryl halide moiety.

To go further, the catalyst was recycled, using phenylboronic acid and iodobenzene, at the same conditions, with K₂CO₃, by decanting the solution. The reaction yield was kept at 100% up to seven times.

Once, previously, Andrews *et al.* [15a] extensively studied the leaching effect on Pd containing perovskite catalyst, that is, that the true catalyst would be a soluble Pd(0)/Pd(II) species, also supported by Ji, Jain and Davis [15b], who reported that the leached soluble Pd(0)/Pd(II) from Pd supported catalysts would act as the true catalyst, and by Dupont's group [15c], who reported that Pd nanoparticles stabilized with ionic liquids would serve as a catalyst reservoir, we decided to investigate if Pd/CaCO₃ would also act as a catalyst reservoir. Therefore, we tested the effect of Pd/CaCO₃ free water/ethanol solution after reaction.

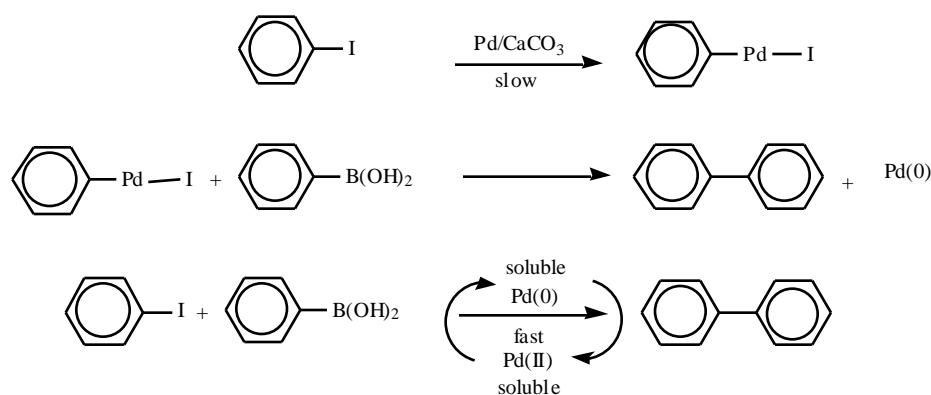
To do that, after finishing a reaction, the solid catalyst was separated from the reaction medium by decantation. The reaction products contained in the water/ethanolic solution were then extracted with hexane. The remaining

*Address correspondence to this author at the Instituto de Química, UFRJ, CT Bloco A, Cidade Universitária, Rio de Janeiro, RJ 21949-900, Brazil; E-mail: octavio@iq.ufrj.br

Table 2. Pd/CO₃ Catalyzed C-C Coupling of Different Substrates with Phenylboronic Acid^a

Entry	Aryl halides	Product ^a	Yield (%)
1	Iodobenzene	Phenylbenzene	100
2	Bromobenzene	Phenylbenzene	99
3	<i>p</i> -Iodoanisole	<i>p</i> -Phenylanisole	98
4	<i>p</i> -Bromoacetophenone	<i>p</i> -Phenylacetophenone	96
5	Iodobenzene	Phenylbenzene	90
6	Bromobenzene	Phenylbenzene	88
7	<i>p</i> -Iodoanisole	<i>p</i> -Phenylanisole	85
8	<i>p</i> -bromoacetophenone	<i>p</i> -Phenylacetophenone	89

^aK₂CO₃ was used as base in entries 1-4 and Na₃PO₄ in entries 5-8



Scheme 1.

water/ethanolic solution was then charged with phenylboronic acid and iodobenzene and after 12 hours at 80°C, the reaction product, phenylbenzene, was obtained in 100% yield.

These results, therefore, generalize the concept that these Pd containing heterogeneous catalysts are in fact Pd reservoirs for the true catalyst, soluble Pd(0)/Pd(II) species (Scheme 1), that could act in homeopathic concentrations as stated by de Vries' group [15d].

It is crucial to emphasize the importance of these findings since although leaching studies have been previously carried out with this sort of catalysts, literature is still full of descriptions of the use of "heterogeneous catalysts" in cross coupling reactions, in particular in the microchannel technology [15e].

CONCLUSION

In conclusion, Pd/CO₃ proved to be a suitable catalyst for ligand free Miyaura-Suzuki reaction [16,17]. The catalyst was recycled up to seven times without any noticeable loss of activity. In fact it has been evidenced, by recycling catalyst free solution after one cycle, that the true catalyst was soluble Pd(II)/Pd(0) species formed upon slow oxidative addition to the insoluble catalyst and repeated eliminative reduction/oxidative addition in solution.

REFERENCES

- [1] (a) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed.*, **2005**, *44*, 4442; (b) Muzart, J. *Tetrahedron*, **2005**, *61*, 4179; (c) Negishi, E.-i. *J. Organomet. Chem.*, **2002**, *653*, 34; (d) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.*, **2002**, *102*, 1359.
- [2] Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.*, **1971**, *44*, 581.
- [3] Heck, R. F.; Nolley Jr., J. P. *J. Org. Chem.*, **1972**, *37*, 2320.
- [4] (a) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.*, **1978**, *100*, 3636; (b) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.*, **1979**, *101*, 4992; (c) Stille, J. K. *Angew. Chem. Int. Ed. Eng.*, **1986**, *25*, 508; (d) Kosugi, M.; Sasazawa, K.; Shimizu, Y.; Migita, T. *Chem. Lett.*, **1977**, 301.
- [5] (a) Negishi, E.; King, A. O. Okukado, N. *J. Org. Chem.*, **1977**, *42*, 1821; (b) King, A. O.; Okukado, N.; Negishi, E. *J. Chem. Soc. Chem. Commun.*, **1977**, 683.
- [6] (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.*, **1975**, *16*, 4467; (b) Sonogashira, K. *J. Organomet. Chem.*, **2002**, *653*, 46.
- [7] (a) Suzuki, A. *Acc. Chem. Res.*, **1982**, *15*, 178; (b) Miyaura, N.; Suzuki, A. *Chem. Rev.*, **1995**, *95*, 2457; (c) Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.*, **1981**, *11*, 513.
- [8] (a) Yue, D.; Yao, T.; Larock, R. C. *J. Org. Chem.*, **2006**, *71*, 62; (b) Yue, D.; Yao, T.; Larock, R. C. *J. Org. Chem.*, **2005**, *70*, 10292; (c) Larock, R. C.; Wang, Y.; Dong, X.; Yao, T. *Tetrahedron*, **2005**, *61*, 11427; (d) Molander, G. A.; Petrillo, D. E.; Landzberg, N. R.; Rohanna, J. C.; Biolatto, B. *Synlett*, **2005**, 1763; (e) Molander, G. A.; Felix, L. A. *J. Org. Chem.*, **2005**, *70*, 3950; (f) von Wangelin, A. J.; Neumann, H.; Gördes, D.; Hübner, S.; Wendler, C.; Klaus, S.; Strübing, D.; Spannenberg, A.; Jiao, H.; El Firdoussi, L.; Thurow, K.; Stoll, N.; Beller, M. *Synthesis*, **2005**, 2029; (g) Zapf, A.; Beller, M. *Chem. Commun.*, **2005**, 431;

- (h) Blanco, B.; Brissart, M.; Moreno-Manas, M.; Pleixats, R.; Mehdi, A.; Reye, C.; Bouquillon, S.; Henin, F.; Muzart, J. *Appl. Catal. A*, **2006**, 297, 117; (i) Masllorens, J.; Bouquillon, S.; Roglans, A.; Henin, F.; Muzart, J. *J. Organomet. Chem.*, **2005**, 690, 3822; (j) Bouquillon, S.; Ganchev, B.; Estrine, B.; Henin, F.; Muzart, J. *J. Organomet. Chem.*, **2001**, 634, 153.
- [9] (a) Wallow, T. I.; Novak, B. M. *J. Org. Chem.*, **1994**, 59, 5034; (b) Bumagin, N. A.; Bykov, V. V. Beletskaya, I. P. *Dokl. Akad. Nauk. SSSR*, **1990**, 315, 1133; (c) Marck, G.; Villiger, A.; Buchecker, R. *Tetrahedron Lett.*, **1994**, 35, 3277; (d) Li, Y.; Hong, X. M.; Collard, D. M.; El-Sayed, M. A. *Org. Lett.*, **2000**, 2, 2385; (e) Shimizu, K.-i.; Maruyama, R.; Komai, S.-i.; Kodama, T.; Kitayama, Y. *J. Catal.*, **2004**, 227, 202.
- [10] (a) Jiang, N.; Ragauskas, A. J. *Tetrahedron Lett.*, **2006**, 47, 197; (b) Lysen, M.; Koehler, K. *Synlett*, **2005**, 1671; (c) Zhang, G. *J. Chem. Res.*, **2004**, 593; (d) Cravotto, G.; Beggiano, M.; Penoni, A.; Palmisano, G.; Tollari, S.; Lévêque, J. -M.; Bonrath, W. *Tetrahedron Lett.*, **2005**, 46, 2267; (e) Nishida, M.; Tagata, T. *J. Synth. Org. Chem. Jpn.*, **2004**, 62, 737; (f) Tagata, T.; Nishida, M. *J. Org. Chem.*, **2003**, 68, 9412; (g) Heidenreich, R. G.; Kohler, K.; Krauter, J. G. E.; Pietsch, J. *Synlett*, **2002**, 1118; (h) Sakurai, H.; Tsukuda, T.; Hirao, T. *J. Org. Chem.*, **2002**, 67, 2721; (i) Dyer, U. C.; Shapland, P. D.; Tiffin, P. D. *Tetrahedron Lett.*, **2001**, 42, 1765; (j) LeBlond, C. R.; Andrews, A. T.; Sowa Jr., J. R.; Sun, Y. *Org. Lett.*, **2001**, 3, 1555; (k) Davies, I. W.; Matty, L.; Hughes, D. L.; Reider, P. J. *J. Am. Chem. Soc.*, **2001**, 123, 10139; (l) Ennis, D. S.; McManus, J.; Wood-Kaczmar, W.; Richardson, J.; Smith, G. E.; Carstairs, A. *Org. Process Res. Dev.*, **1999**, 3, 248.
- [11] (a) Chandrasekhar, S.; Narsihmulu, Ch.; Chandrashekar, G.; Shyamsunder, T. *Tetrahedron Lett.*, **2004**, 45, 2421; (b) Howarth, J.; Dallas, A. *Molecules*, **2000**, 5, 851; (c) Wong, H. -T.; Han, S.; Livingston, A. G. *Chem. Eng. Sci.*, **2006**, 61, 1338; (d) Olivier-Bourbigou, H.; Magna, L. *J. Mol. Catal. A Chem.*, **2002**, 182-183, 419; (e) Betzemeier, B.; Knochel, P. *Top. Curr. Chem.*, **1999**, 206, 61; (f) Maul, J. J.; Ostrowski, P. J.; Ublacker, G. A.; Linclau, B.; Curran, D. P. *Top. Curr. Chem.*, **1999**, 206, 79; (g) Leitner, W. *Top. Curr. Chem.*, **1999**, 206, 107; (h) Cornils, B. *Top. Curr. Chem.*, **1999**, 206, 133.
- [12] (a) Genet, J. P.; Savignac, M. *J. Organomet. Chem.*, **1999**, 576, 305; (b) Lubineau, A.; Augé, J. *Top. Curr. Chem.*, **1999**, 206, 1; (c) Sinou, D. *Top. Curr. Chem.*, **1999**, 206, 41.
- [13] (a) Perez, R.; Veronese, D.; Coelho, F.; Antunes, O. A. C. *Tetrahedron Lett.*, **2006**, 47, 1325; (b) Brunner, H.; Le Cousturier de Courcy, N.; Genêt, J. -P. *Tetrahedron Lett.*, **1999**, 40, 4815.
- [14] (a) Priego, J.; Carretero, J.C. *Synlett*, **1999**, 1603; (b) Oliveira, D. F.; Severino, E. A.; Correia, C. R. D. *Tetrahedron Lett.*, **1999**, 40, 2083; (c) Brunner, H.; Le Cousturier de Courcy, N.; Genêt, J. P. *Synlett*, **2000**, 201; (d) Severino, E. A.; Costenaro, E. R.; Garcia, A. L. L.; Correia, C. R. D. *Org. Lett.*, **2003**, 5, 305 (e) Garcia, A. L. L.; Correia, C. R. D. *Tetrahedron Lett.*, **2003**, 44, 1553; (f) Sabino, A. A.; Machado, A. H. L. Correia, C. R. D.; Eberlin, M. N. *Angew. Chem. Int. Ed.*, **2004**, 43, 2514.
- [15] (a) Andrews, S. P.; Stepan, A. F.; Tanaka, H.; Ley, S. V.; Smith, M. D. *Adv. Synth. Catal.*, **2005**, 347, 647; (b) Ji, Y.; Jain, S.; Davis, R. J. *J. Phys. Chem. B*, **2005**, 109, 17232; (c) Cassol, C. C.; Umpierre, A. P.; Machado, G.; Wolke, S. I.; Dupont, J. *J. Am. Chem. Soc.*, **2005**, 127, 3298; (d) Alimardanov, A.; Schmieder-van de Vondervoort, L.; de Vries, A. H. M.; de Vries, J. G. *Adv. Synth. Catal.*, **2004**, 346, 1812; (e) Kobayashi, J.; Mori, Y.; Kobayashi, S. *Chem. Asian J.*, **2006**, 1, 22.
- [16] A suspension of 1.5 mmol of the aryl halide, 2.25 mmol of PhB(OH)₂, 4.5 mmol of base and 1% weight Pd/CaCO₃ in 50 mL 40% aqueous EtOH solution was stirred under argon. The reaction mixture was extracted with hexane, dried over Na₂SO₄, filtered and analyzed by ¹H-NMR, ¹³C-NMR, GC and GC-MS.
- [17] Phenylbenzene: white solid; ¹H-NMR (200 MHz, CDCl₃) 7.41-7.46 (2H, m), 7.50-7.55 (4H, m), 7.68-7.70 (4H, m); ¹³C-NMR (50 MHz, CDCl₃) 127.2, 127.3, 128.8, 141.3; MS: m/z = 76, 77, 153, 154 (M⁺). *p*-Phenylanisol: white solid; ¹H-NMR (200 MHz, CDCl₃) 3.80 (3H, s), 6.95 (2H, d), 7.32 (1H, d), 7.38 (2H, t), 7.51-7.55 (4H, m); ¹³C-NMR (50 MHz, CDCl₃) 55.35, 114.27, 126.70, 128.19, 128.77, 133.82, 140.88, 159.22; MS: m/z = 115, 141, 169, 184 (M⁺). *p*-Phenylacetophenone: pale yellow solid; ¹H-NMR (200 MHz, CDCl₃) 2.65 (3H, s), 7.51-7.41 (3H, m), 7.71-7.62 (4H, m), 8.04 (2H, d); ¹³C-NMR (50 MHz, CDCl₃) 26.67, 127.23, 128.27, 128.94, 128.99, 135.87, 139.86, 145.77, 197.77; MS: m/z = 76, 152, 181, 196 (M⁺).