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Efficient Dendritic Diphosphino Pd(II) Catalysts for the Suzuki Reaction of Chloroarenes

Julietta Lemo, Karine Heuzé,* and Didier Astruc*

Groupe Nanosciences Moléculaires et Catalyse, LCOO, UMR No. 5802,
Université Bordeaux I, 351 Cours de la Libération, 33405 Talence Cedex, France

k.heuze@lcoo.u-bordeaux1.fr; d.astruc@lcoo.u-bordeaux1.fr

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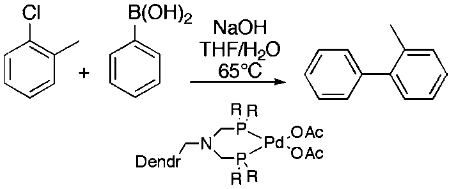
ABSTRACT



The monomeric diphosphino Pd(II) complex 1 and the first three generations of dendritic analogues G1, G2, and G3 are efficient catalysts for the Suzuki coupling reaction of halogenoarenes, including chloroarenes with phenylboronic acid. The recovery and reuse of the dendritic catalysts G1, G2, and G3 are discussed.

Metallodendrimers[1] have been shown to be useful homogeneous catalysts since the 1990s,[2−4] and their potential applications have appeared when it was more recently understood that they could be recovered due to their large sizes.[3] Indeed, as homogeneous catalysts, their reactivity is considerably higher than that of the corresponding supported catalysts. Moreover, their perfect molecular definition brings about a significant advantage over polymers and allows the evaluation of the efficiency of each dendritic generation.[4] In previous reports, we showed the efficiency and the recovery of Reetz-type diphosphino Pd(II) metallodendritic catalysts for the Sonogashira copper-free reaction.[5b,c] Herein, we present our first results for the Suzuki cross-coupling reaction,[6] a widespread reaction for the organic synthesis of biaryl compounds, which has not yet been explored with dendritic catalysts. In the catalysis of Suzuki reactions, very efficient palladium catalysts were reported by Buchwald (aryldialkylphosphines),[7] Fu (trialkylphosphines),[8] Nolan and Herrmann (N-heterocyclic carbenes),[9] Bedford (pallada-

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(3) (a) For the first recovery and reuse of dendritic catalysts, see Reetz's seminal work: Reetz, M. T.; Lohmer, G.; Schwickardi, R. *Angew. Chem., Int., Ed. Engl.* **1997**, *36*, 1526. (b) Brinkmann, N.; Giebel, D.; Lohmer, G.; Reetz, M. T.; Kragl, U. *J. Catal.* **1999**, *183*, 163. (c) Ref 4a. (d) Kreiter, R.; Kleij, A. W.; Klein Gebbink, R. J. M.; van Koten, G. In *Dendrimers IV: Metal Coordination, Self-Assembly, Catalysis*; Vögtle, F., Schalley, C. A., Eds.; *Topics in Current Chemistry*; Springer-Verlag: Berlin, 2001; pp 217 and 163. (e) van Heerbeek, R.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Reek, J. N. H. *Chem. Rev.* **2002**, *102*, 3717.

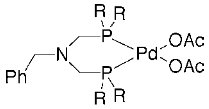
(4) (a) Oosterom, G. E.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M *Angew. Chem., Int. Ed.* **2001**, *40*, 1828. (b) Astruc, D.; Chardac, F. *Chem. Rev.* **2001**, *101*, 2991.

(5) (a) Synthesis of these dendrimers and Heck catalysis were reported by Reetz, et al. (ref 3a); see also: (b) Heuzé, K.; Méry, D.; Gauss, D.; Astruc, D. *Chem. Commun.* **2003**, 2274. (c) Heuzé, K.; Méry, D.; Gauss, D.; Blais, J.-C.; Astruc, D. *Chem. Eur. J.* **2004**, *10*, 3936.

(6) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544. (c) Hassan, J.; Sévignon, M.; Gozzi C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359. (d) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176. (e) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633. (f) Suzuki, A. In *Modern Arene Chemistry*; Astruc, D., Ed.; Wiley-VCH: Weinheim, 2002; pp 53−106. (g) Miura, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2201.

10.1021/ol050645+ CCC: $30.25

cycles),[10] and others[11] who could couple deactivated or hindered chloroarenes and even chloroalkyls under mild conditions. Most ligands of these palladium catalysts are bulky monophosphines, but in our case, diphosphine ligands allowed an appropriate stabilization of the palladium−phosphine catalyst onto the dendrimer core. We have investigated the Suzuki coupling of phenylboronic acid with chloro- and bromoarenes using the metallodendritic catalysts DAB-dendr-$[N(CH_2PCy_2)_2Pd(OAc)_2]_x$, **G1**, **G2**, and **G3** (x = 4, 8, and 16, respectively)[5] and the monomer analogues $PhCH_2N(CH_2PR_2)_2Pd(OAc)_2$, R = Cy **1a** or *t*-Bu **1b**[12] (Figures 1 and 2), as well as their recovery and reuse.



1a: R = Cy

1b: R = *t*-Bu

Figure 1. Monomeric diphosphino Pd(II) complex **1**.

First, we examined various bases and solvent systems,[13] as the role of the base in the transmetalation step of the Suzuki reaction is crucial. The results are gathered in Table 1 for *p*-chloracetophenone, but they are applicable to iodobenzene.[14] Among the listed bases, it unambiguously appears that strong bases such as NaOH, KOH, or *t*-BuOK performed better than weaker bases such as K_2CO_3, Na_2CO_3, Cs_2CO_3, or K_3PO_4, in THF/H_2O. The best combination of base/solvent is $NaOH/H_2O/THF$, and the optimized

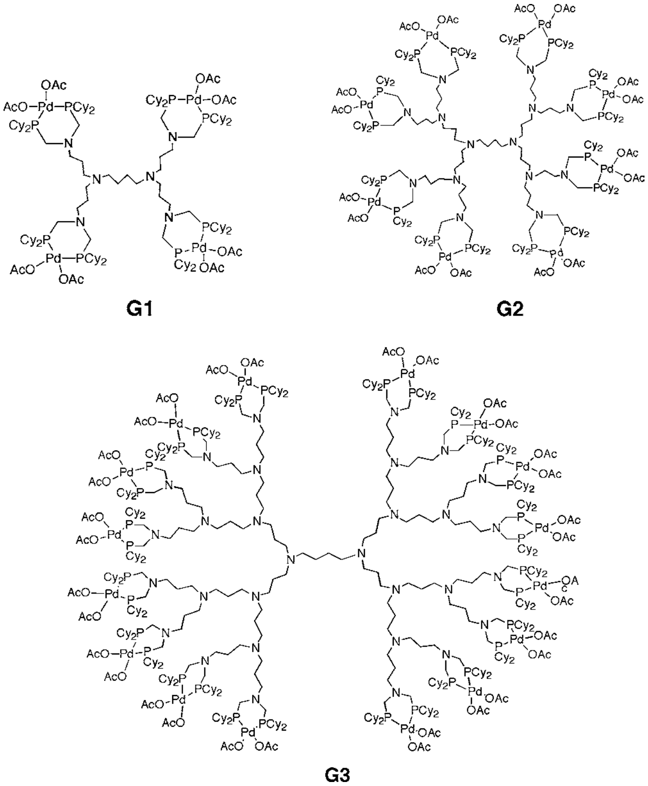
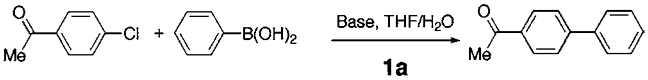


Figure 2. Dendritic diphosphino Pd(II) complexes.

Table 1. Base Effect on the Suzuki Cross-Coupling Reaction



entry	base	reaction time	yield (%)[a]
1	NaOH	1 h	99
2	KO*t*-Bu	5 h	99
3	KOH	5 h	84
4	K_3PO_4	21 h	6
5	Cs_2CO_3	21 h	4
6	Na_2CO_3	24 h	2
7	K_2CO_3	24 h	2

[a] Reaction conditions: chloroacetophenone (2 mmol), phenylboronic acid (3 mmol), base (6 mmol), catalyst **1a** (1 mol %), THF/H_2O (2/1), 65 °C, yield according to GC based on the final product/chloroarene ratio after calibration of each signal.

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(9) (a) Gstöttmayr, C. W. K.; Böhm, V. P. W.; Herdtweck, E.; Grosche, M.; Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1363. (b) Grasa, G. A.; Viciu, M. S.; Huang, J.; Zhang, C.; Trudell, M. L.; Nolan, S. P. *Organometallics* **2002**, *21*, 2866. (c) Viciu, M. S.; Germaneau, R. F.; Navarro-Fernandez, O.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2002**, *21*, 5470. (d) Navarro, O.; Kelly, R. A., III; Nolan, S. P. *J. Am. Chem. Soc.* **2003**, *125*, 16194. (e) Navarro, O.; Kaur, H.; Mahjoor, P.; Nolan, S. P. *J. Org. Chem.* **2004**, *69*, 3173. (f) Lebel, H.; Janes, M. K.; Charette, A. B.; Nolan, S. P. *J. Am. Chem. Soc.* **2004**, *126*, 5046.

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(11) (a) Reetz, M. T.; Breinbauer, R.; Wanninger, K. *Tetrahedron Lett.* **1996**, *37*, 4499. (b) Bumagin, N, A.; Bykov, V. V. *Tetrahedron* **1997**, *53*, 14437. (c) Shen, W. *Tetrahedron Lett.* **1997**, *38*, 5575. (d) Bei, X.; Crevier, T.; Guram, A. S.; Jandeleit, B.; Powers, T. S.; Turner, H. W.; Uno, T.; Weinberg, W. H. *Tetrahedron Lett.* **1999**, *40*, 3855. (e) Ishiyama, T.; Ishida, K.; Miyaura, N. *Tetrahedron* **2001**, *57*, 9813. (f) Schnyder, A.; Indolese, A. F.; Studer, M.; Blaser, H.-U. *Angew. Chem., Int. Ed.* **2002**, *41*, 3668. (g) Li, G. Y. *J. Org. Chem.* **2002**, *67*, 3643. (h) Altenhoff, G.; Goddard, R.; Lehmann, C. W.; Glorius, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 3690. (i) Roca, F. X.; Richard, C. J. *Chem. Commun.* **2003**, 3002. (j) Datta, A.; Ebert, K.; Plenio, H. *Organometallics* **2003**, *22*, 4685. (k) Li, J.-H.; Liu, W.-J. *Org. Lett.* **2004**, *4*, 2809. (l) Zapf, A.; Jackstell, R.; Rataboul, F.; Reirmeier, T.; Monsees, A.; Fuhrmann, C.; Shaikh, N.; Dingerdissen, U.; Beller, M. *Chem. Commun.* **2004**, 38. (m) Özdemir, I.; Alici, B.; Gürbüz, N.; Çetinkaya, E.; Çetinkaya, B. *J. Mol. Catal. A* **2004**, 37. (n) Arvela, R. K.; Leadbeater, N. E.; Sangi, M. S.; Williams, V. A.; Granados, P.; Singer, R. D. *J. Org. Chem.* **2005**, *70*, 161.

(12) Méry, D.; Heuzé, K.; Astruc, D. *Chem. Commun.* **2003**, 1934.

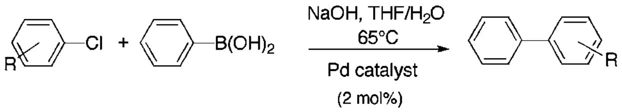
(13) Dioxane, toluene, and DME were used, but the catalysts were not soluble enough to carry out the reaction.

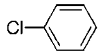
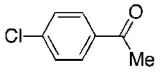
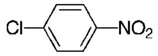
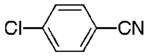
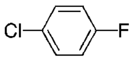
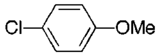
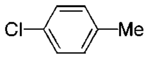
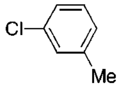
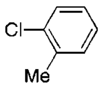
solvent mixture ratio THF/H_2O is 2/1; these conditions were chosen in order to solubilize the base, reactants, and catalyst. We also found that the use of alcohols as solvents led to the reduction of the starting chloroarene.[9b,15] The influence of the phosphine ligand ($-PCy_2$ vs $-Pt$-Bu_2) on the reactivity was investigated, revealing, conversely to the Sonogashira reaction,[5b,c,12] that the less sterically hindered $-PCy_2$ ligand is more efficient than $-Pt$-Bu_2. Indeed, the coupling of chlorobenzene with phenylboronic acid (2 mol % catalyst, 65 °C) is faster with catalyst **1a** containing $-PCy_2$ (3 h, 92% yield) than with catalyst **1b** containing $-Pt$-Bu_2 (16 h, 72% yield) under the same conditions.

These results confirmed the importance of delineating the fine compromise between electron-rich ligands (to promote the oxidative addition of the aryl chloride) and bulky ligands (to promote reductive elimination of the product). This is in accord with the result of Buchwald and Fu, who have pointed out the crucial role of the optimal hindrance and electronic structure of the phosphine for the catalyst activity.[6g,7,8] The data in Table 2 illustrate the activity of a variety of chloroarenes with phenylboronic acid. Both electron-poor (entries 2−5) and electron-rich (entries 6−8) chloroarenes can be coupled efficiently, along with hindered chloroarenes (entry 9), which led to good yields but with higher reaction times. Thus, these catalysts not only are very stable in a chemical sense, since they can be stored in air at room temperature for months, but they also tolerate many functional groups. It is noteworthy that TOFs of 26 500 h^{-1} with iodobenzene and 1000 h^{-1} with bromobenzene are found under the same reaction conditions with **1a**.[16] With the dendritic catalysts **G1**, **G2**, and **G3**, a reactivity similar to that observed with **1a** is found. However, a negative dendritic effect was disclosed when the dendrimer generation increased (i.e., the reactivity order is **1a** ≥ **G1** > **G2** > **G3**). In light of these results, the recovery of the dendrimeric catalysts **G1**, **G2**, and **G3** has been investigated for the Suzuki cross-coupling of bromobenzene, *p*-chlorobenzonitrile, and *p*-chloroacetophenone with phenylboronic acid.[17] With bromobenzene, quantitative yields are obtained until the third recovery cycle with dendrimers **G1**, **G2**, and **G3**.

However, a loss of reactivity of the catalyst is found, since the reaction time increases with the number of recovery cycles. Also, a slightly negative dendritic effect is observed, as the reaction with **G1** is slightly faster than with **G2**, which is also slightly faster than with **G3**. For *p*-chlorobenzonitrile, quantitative yields are obtained in the first cycle with dendrimers **G1**, **G2**, and **G3**, but the reactivity decreases for all three dendrimers along with recovery cycles (Table 3).

Table 2. Scope of Pd-Catalyzed Suzuki Cross-Coupling of Chloroarenes



entry	chloroarene	reaction time	yield (%) [a] 1a	G1	G2	G3
1		3 h	92	56	50	33
2		1 h	99	90	90	54
3		2 h	99	97	92	50
4		1 h	99	99	89	86
5		6 h	68	54	32	31
6		17 h	42	47	32	21
7		24 h	65	50	41	20
8		24 h	72	75	21	18
9		24 h	76	77	65	45

[a] GC yields. See Supporting Information for characterizations of the products.

Table 3. Reactivity and Recovery of the Dendritic Catalysts **G1−3** in the Suzuki Coupling of *p*-Chlorobenzonitrile and Phenylboronic Acid[a]

catalyst	cycle 1: % yield (TOF h^{-1})	cycle 2: % yield (TOF h^{-1})	cycle 3: % yield (TOF h^{-1})
G1	100 (20)	82 (5.46)	54 (0.54)
G2	100 (20)	85 (5.66)	32 (0.32)
G3	100 (20)	77 (5.13)	33 (0.33)

[a] Reaction conditions: *p*-chlorobenzonitrile (2 mmol), phenylboronic acid (3 mmol) in THF/H_2O, NaOH (6 mmol), at 65 °C, catalyst loading: 5 mol %. Reaction times were 1, 3, and 20 h for cycles 1, 2, and 3, respectively. GC yields were used.

In the case of *p*-chloroacetophenone, again, quantitative yields were obtained with dendrimers **G1**, **G2**, and **G3** in the reaction of the first cycle. However, the reactivity decreased to a larger extent for the recovery cycles of dendrimers **G1** and **G3** than for the recovery cycle of dendrimer **G2** (Figure 3). Indeed, for this particular reaction, the dendrimeric catalyst **G2**, in which the optimal size for the best balance was reached between stabilization and steric hindrance at the dendrimer periphery, stabilizes the diphosphine palladium complexes. In fact, recovery of catalyst **1a** is not possible, since degradation immediately occurs along

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(14) Various bases were tested for the Suzuki reaction of iodobenzene with phenylboronic acid and catalyst **1a**, and again the best base was unambiguously NaOH. For more details, see Supporting Information.

(15) Zask, A.; Helquist, P. *J. Org. Chem.* **1978**, *43*, 1619.

(16) Reaction of iodobenzene (2 mmol) with phenylboronic acid (3 mmol), in THF/H_2O, and NaOH (6 mmol), at 65 °C, with **1a** (0.0001 mol %) gave 93% yield in 35 h. Reaction of bromobenzene (2 mmol) with phenylboronic acid (3 mmol), in THF/H_2O, and NaOH (6 mmol), at 65 °C, with **1a** (0.001 mol %) gave a 73% yield after 3 days.

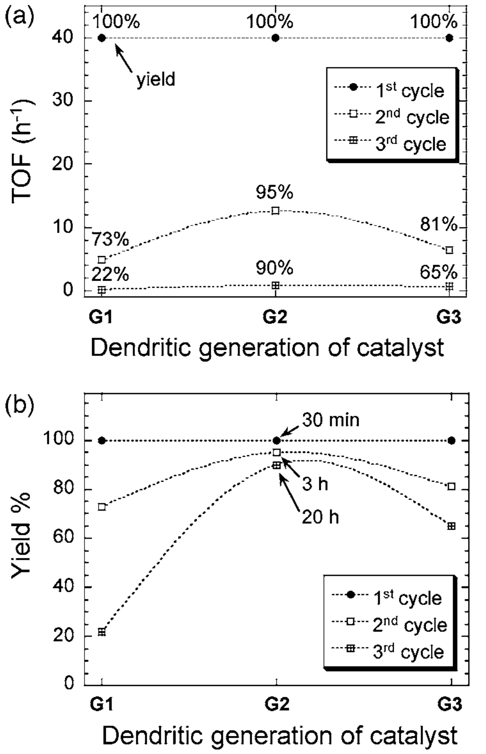

Figure 3. Reactivity and recovery of the dendritic catalysts **G1−3** in the Suzuki coupling of *p*-chloroacetophenone and phenylboronic acid. (a) TOF plotted vs dendritic generation of catalyst. Yields are indicated above each point. (b) Yield (%) vs dendritic generation of catalyst. GC yields were used. Reaction conditions: *p*-chloroacetophenone (2 mmol), phenylboronic acid (3 mmol) in THF/H$_2$O, NaOH (6 mmol), 65 °C, catalyst (5 mol %). Reaction times were 30 min, 3 h, and 20 h for cycles 1, 2, and 3, respectively.

the first pentane precipitation (catalytically inactive black precipitate).[18]

In summary, we have optimized diphosphino palladium catalysts for the Suzuki coupling reaction of chloroarenes and then used dendrimeric supports that stabilized catalysts and allowed some recovery. As shown in Figure 3 and Table 3, recovery and reuse is possible with the dendritic catalysts. The present study confirms the advantage of using bulky monophosphines.[7−11] The method is a very rare one, however, optimizing the use of a bulky dialkyl diphosphinoalkyl ligand, for comparison, with surprisingly good results. The presence of chelating diphosphine in dendrimers for catalysis is a key condition for the stability, recovery, and reuse of the dendritic catalyst of the Suzuki reaction with a broad range of halogenoarenes. Indeed, parallel studies[19] achieved with dendritic monophosphine complexes showed extensive decomposition that is not compatible with their use as robust catalysts. Finally, a key point with these metallodendrimers is their ability to prevent agregation of Pd(0) species or nanoparticules as indicated by the compared studies with the monomer that is not recyclable due to the formation of Pd black.

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Supporting Information Available: Experimental section including the study of bases in the case of iodobenzene and all GC spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) In a typical recycling procedure, the reaction was carried out with 5 mol % catalyst at room temperature for bromobenzene and at 65 ° C for chlorinated substrates. Reaction times were 30 min, 3 h, and 20 h for cycles 1, 2, and 3, respectively. From the initially homogeneous THF/H$_2$O medium, demixion occurred because the aqueous phase became loaded with NaCl. The organic layer was separated, and pentane was added in order to precipitate the catalyst and extract the product. The pentane extraction was carried out three times, and then the remaining precipitate was dried under vacuum and reused. The ^{31}P NMR spectrum of the remaining precipitate shows the signal of the catalyst ($\delta = 27$ ppm) along with degradation signals (δ around 50 ppm) increasing with recovery cycles, in accordance with the increasing dark color of the precipitate (from orange in the first cycle to brown in the third cycle). The ^{1}H NMR spectrum shows the signal of the catalyst (see ref 5c for details of the characterizations of the catalysts) with the presence of aromatic signals of borate salts species (see ref 6). Indeed, the mass of the precipitate is twice that of the initially loaded catalyst.

(18) Recycling procedure described in ref 17 was followed. In the first reaction cycle, the brown THF phase was separated, and then pentane was added. A black precipitate, insoluble in all solvents, fell out of the clear mother liquor, which confirms the formation of Pd black. No catalysis was found herewith in the second reaction cycle.

(19) (a) Attempts to synthesize monodendate phosphine complexes, related to those reported[19b] failed due to the thermal instability: Gatard, S.; Nlate, S.; Cloutet, E.; Bravic, G.; Blais, J.-C., Astruc, D. *Angew. Chem., Int. Ed.* **2003**, *42*, 452. (b) Gatard, S.; Kahlal, S.; Méry, D.; Nlate, S.; Cloutet, E.; Saillard, J.-Y.; Astruc, D. *Organometallics* **2004**, *23*, 1313.