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Hexacationic *Dendriphos* Ligands in the Pd-Catalyzed Suzuki−Miyaura Cross-Coupling Reaction: Scope and Mechanistic Studies

Dennis J. M. Snelders, Gerard van Koten, and Robertus J. M. Klein Gebbink*

Chemical Biology and Organic Chemistry, Debye Institute for Nanomaterials Science, Faculty of Science, Utrecht University, Padualaan 8, 3584 CH Utrecht, The Netherlands

Received May 18, 2009; E-mail: r.j.m.kleingebbink@uu.nl

Abstract: The combination of $Pd_2dba_3 \cdot CHCl_3$ and hexacationic triarylphosphine-based *Dendriphos* ligands (**1**−**3**) leads to a highly active catalytic system in the Suzuki−Miyaura cross-coupling reaction. Under relatively mild reaction conditions, nonactivated aryl bromides and activated aryl chlorides can be coupled at a low Pd loading (0.1 mol %). The observed activity of this catalytic system, in particular in coupling reactions of aryl chlorides, is dramatically higher than that of conventional Pd catalysts employing triarylphosphine ligands. Through control and poisoning experiments, it is concluded that a homogeneous Pd(0)−*Dendriphos* complex is the active species in this catalytic system. Despite their triarylphosphine-based structure, *Dendriphos* ligands behave as very bulky phosphine ligands and lead to a preferential formation of coordinatively unsaturated and catalytically active Pd(0) species, which explains the observed high catalytic activity for these systems. The presence of six permanent cationic charges in the backbone of this class of ligands is proposed to result in a significant interligand Coulombic repulsion and plays a crucial role in their bulky behavior. In the coupling reactions of activated aryl chlorides, a positive dendritic kinetic effect was observed among the different *Dendriphos* generations, indicating an increased ability of the higher ligand generations to stabilize the active species due to steric effects. For aryl bromides, no dendritic effect was observed due to a shift in the rate-determining step in the catalytic cycle, from oxidative addition for aryl chlorides to transmetalation for aryl bromides.

1. Introduction

The use of core-functionalized dendrimers as macromolecular catalysts is of great interest, as they offer the possibility to control the local environment of the catalytic site. As an effect of dendritic encapsulation, an improved stability of the catalyst may be observed. Furthermore, advantages such as substrate preconcentration or selectivity may arise from control of the polarity or steric crowding of the local environment of the catalytic site. However, the use of this type of catalyst often has negative kinetic consequences due to a decreased accessibility of the catalytic site.[1] Core-functionalized dendritic catalysts leading to faster reaction rates are therefore quite rare.[2]

Recently, we have developed the hexacationic *Dendriphos* ligands (**1**−**3**, Figure 1).[3] This family of ligands was designed in analogy to octacationic dendrimers containing Fréchet-type dendrons[4] which have been applied as noncovalent supports for homogeneous catalysts.[5] *Dendriphos* ligands combine the triphenylphosphine motif, located at their core, with six permanent cationic substituents (ammonium groups), which furthermore allow for variations in ligand size and solubility by means of alteration of the ammonium substituent, ranging, e.g., from a benzyl group (**1**) to first (**2**) and second (**3**) generation Fréchet dendrons. Through coordination of the phosphine functionality to an appropriate metal source, these ligands allow *in situ* formation of core-functionalized dendritic homogeneous catalysts.

Several examples of dendritic structures in which a phosphine functionality is located at the core of the dendrimer[2b,e,6] and their applications in catalysis have been reported. In contrast to dendritic catalysts containing multiple phosphine functionalities located at the periphery of the dendrimer,[7] such dendritic phosphines offer the possibility to control the coordination sphere of a single metal center by site isolation effects. For

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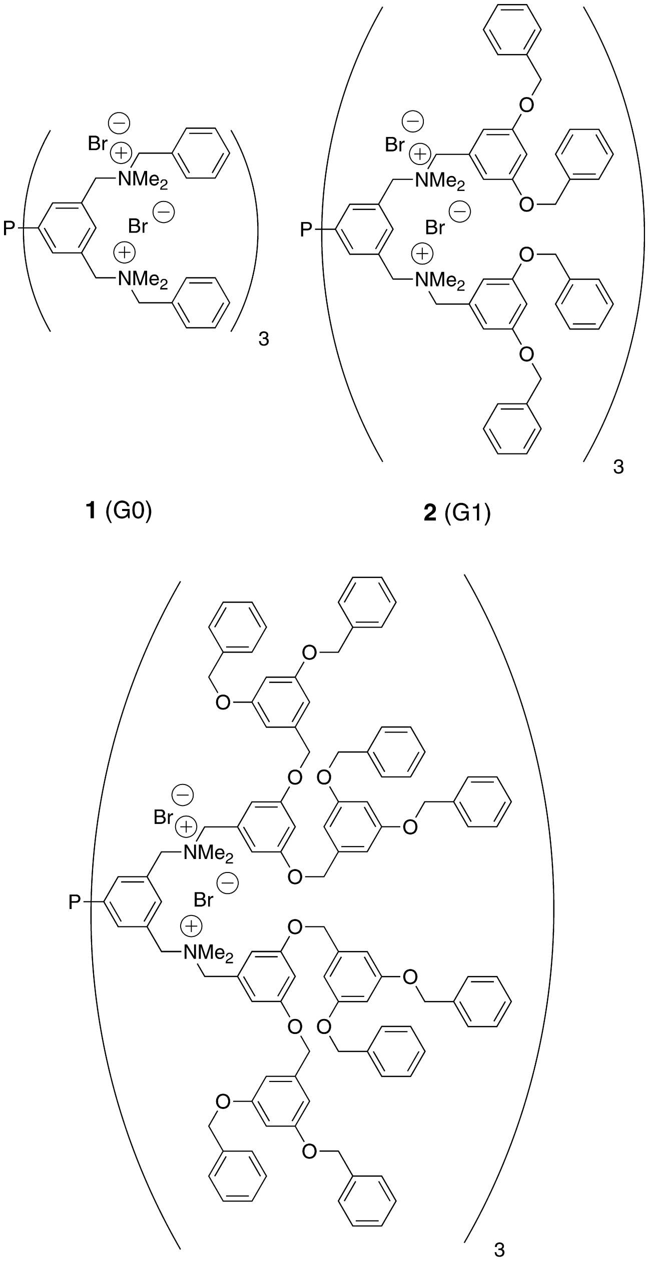
(3) Kreiter, R.; Klein Gebbink, R. J. M.; van Koten, G. *Tetrahedron* **2003**, *59*, 3989–3997.

(4) Kleij, A. W.; van de Coevering, R.; Klein Gebbink, R. J. M.; Noordman, A. M.; Spek, A. L.; van Koten, G. *Chem.−Eur. J.* **2001**, *7*, 181–192.

10.1021/ja904042h CCC: $40.75



1 (G0) **2** (G1) **3** (G2)

Figure 1. Hexacationic *Dendriphos* ligands.

example, the great steric demand of dendritic wedges attached to a phosphine functionality can lead to coordinatively unsaturated and highly reactive metal centers.[2b]

The consequences of introducing charged groups in coordinating ligands are studied far less frequently.[8] Although several examples of phosphine ligands bearing ionic substituents exist,[9] in most of these published works, focus lies on enhancing the solubility of catalysts in polar or nonconventional media, enabling their recycling, e.g., through a biphasic setup. Recently, Shaughnessy et al.[8c] have reported that the presence of ionic substituents on triarylphosphines can significantly influence their structural features. We therefore anticipated that *Dendriphos* ligands, combining as many as six permanent cationic charges in their structure with a large, sterically demanding dendritic shell, could exhibit interesting properties when applied as ligands in transition metal catalyzed reactions.

In a previous report, we showed the rate-enhancing effect of the 3,5-bis[(benzyldimethylammonio)methyl] substitution pattern in G0-*Dendriphos* (**1**) when this ligand was employed in combination with Pd(dba)$_2$ in the Suzuki−Miyaura coupling reaction of methyl 4-bromobenzoate with 4-tolylboronic acid.[10] We tentatively attributed this effect to a Coulombic interligand repulsion, facilitating the *in situ* formation of coordinatively unsaturated and catalytically active Pd(0) species. Encouraged by these observations, we have extended our studies to the application of **1** and the higher generation *Dendriphos* ligands **2** and **3** for the catalytic conversion of more challenging substrates, in particular aryl chlorides. Here, we present the scope and limitations of this catalytic system in the Suzuki−Miyaura reaction, as well as investigations into the nature of the *in situ* formed active species, through control and poisoning experiments and kinetic investigations. Furthermore, the effects of both the charged groups and the sterically demanding dendrons in the ligand structure of **1**−**3** on the properties of these ligands and their corresponding catalysts are discussed.

2. Results

2.1. Optimization of Reaction Conditions. We initially set out to optimize the reaction conditions and to extend the scope

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Table 1. Effect of the Solvent in Reaction 1[a]

Entry	Solvent	Yield (%)[b]
1	MeOH	88
2	EtOH	88
3	DMF	89
4	DME	19[c]
5	toluene	18[c]

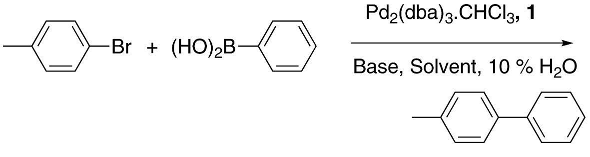
[a] Reaction conditions: 4-bromotoluene (1.0 mmol), phenylboronic acid (2.0 mmol), NaOH (2.2 mmol), solvent (6.3 mL), H_2O (0.7 mL), $Pd_2(dba)_3 \cdot CHCl_3$ (0.5 mol %), **1** (2.5 mol %, L:Pd = 2.5), 65 °C, 3 h. [b] Yield of 4-phenyltoluene, determined by GC, using pentadecane as internal standard. [c] Formation of Pd-black was observed.

Table 2. Effect of the Base in Reaction 1[a]

Entry	Base	Yield (%)[b]
1	Na_3PO_4	84
2	NaOH	79
3	K_2CO_3	76
4	Na_2CO_3	59
5	Cs_2CO_3	56
6	CsF	51
7	KF	44
8	Et_3N	36

[a] Reaction conditions: 4-bromotoluene (1.0 mmol), phenylboronic acid (2.0 mmol), base (2.2 mmol), MeOH (6.3 mL), H_2O (0.7 mL), $Pd_2(dba)_3 \cdot CHCl_3$ (0.05 mol %), **1** (0.25 mol %, L:Pd = 2.5), reflux, 3 h. [b] Yield of 4-phenyltoluene, determined by GC using pentadecane as internal standard.

of Suzuki–Miyaura couplings catalyzed by the combination of $Pd_2dba_3 \cdot CHCl_3$ and **1**. The cross-coupling of the nonactivated substrates 4-bromotoluene and phenylboronic acid yielding 4-phenyltoluene (reaction 1) was selected as a benchmark reaction. The catalytic screening experiments were performed using a *Chemspeed* ASW 2000 workstation, allowing automated sampling and workup of the samples. The reactions were initiated by addition of a solution of the Pd precursor to a hot mixture of the other materials. The reactions were monitored by GC analysis after appropriate intervals up to 3 h. Initially, the effect of the solvent was investigated (Table 1). Toluene and DME were not suitable due to the low solubility of the ligand in these solvents, which led to precipitation of elemental Pd (Pd-black). The use of either aqueous MeOH, EtOH, or DMF in combination with NaOH as the base, each gave high coupling yields at a Pd loading of 1 mol %. Provided that the reactions were carried out under an inert atmosphere, Pd-black formation was not observed in these solvents and the reaction mixtures remained clear yellow solutions throughout the course of the reaction. Analysis of the reaction mixtures by GC showed only the cross-coupled product and unreacted starting material.[11]



(1)

Table 3. Effects of Varying the L:Pd Ratio and the Pd Loading in Reaction 1[a]

Entry	Mol% Pd	L:Pd	Time (h)	Yield (%)[b]
1	0.1	1.0	3	24[c]
2	0.1	2.0	3	85[c]
3	0.1	2.5	3 (22)	79 (99)
4	0.1	4.0	3	73
5	1.0	2.5	3	88
6	0.01	2.5	3 (22)	85 (85)
7	0.001	2.5	3	36

[a] Reaction conditions: 4-bromotoluene (1.0 mmol), phenylboronic acid (2.0 mmol), NaOH (2.2 mmol), MeOH (6.3 mL), H_2O (0.7 mL), reflux. [b] Yield of 4-phenyltoluene, determined by GC using pentadecane as internal standard, average of two independent runs. [c] Pd-black formation was observed.

Table 4. Optimization of Reaction Conditions for Reaction 2[a]

Entry	Base	Solvent	Temp (°C)	Time (h)[b]	Yield (%)[c]
1	NaOH	MeOH/10% H_2O	68	3	0
2	NaOH	DMF/10% H_2O	100	16	26
3	KF	THF	66	16	68
4	KF	dioxane	90	16	94
5	K_2CO_3	dioxane	90	16	55
6	Cs_2CO_3	dioxane	90	16	98
7	CsF	dioxane	90	16	>99
8	CsF	dioxane/10% H_2O	90	16	83

[a] Reaction conditions: 4-nitrochlorobenzene (1.0 mmol), phenylboronic acid (2.0 mmol), base (2.2 mmol), solvent (7.0 mL), $Pd_2(dba)_3 \cdot CHCl_3$ (0.05 mol %), **1** (0.25 mol %, L:Pd = 2.5). [b] Reaction times were not optimized. [c] Yield of 4-nitrobiphenyl, determined by GC using pentadecane as internal standard.

Subsequently, the effect of the base was tested (at 0.1 mol % Pd loading, Table 2). In aqueous MeOH, each of the bases Na_3PO_4, NaOH, and K_2CO_3 gave good results, while lower activities were observed for CsF, KF, Na_2CO_3, Cs_2CO_3, and triethylamine. NaOH was the base of choice for further experiments, as it forms homogeneous solutions in aqueous MeOH, which entails practical advantages for using the *Chemspeed* automated setup for these reactions. Using the optimal base/solvent combination, the concentration of **1** with respect to Pd (L:Pd ratio) was varied (Table 3). At a ratio of 1.0, Pd-black formation was observed and a low yield was obtained. Increasing the ratio to 2.5 led to a stable catalytic system, giving high yields without formation of Pd-black. Further increasing the L:Pd ratio did not lead to a significant change in the reaction yield (Table 3, entries 1–4). The effect of varying the Pd loading, while keeping the ligand:Pd ratio constant (i.e., 2.5) was also investigated. It was found that the obtained yield after 3 h of reaction time was nearly independent of the Pd loading in the range 0.01–1.0 mol % (entries 3, 5, and 6). Further lowering the amount of Pd led to a distinct decrease in the yield (entry 7).

In contrast to the Suzuki–Miyaura cross-coupling reaction of aryl iodides and bromides, the coupling of less expensive but relatively unreactive aryl chlorides can be problematic and in general requires a dedicated catalyst.[12] To explore the activity of *Dendriphos* ligands in the coupling of these substrates, we tested the coupling of 4-nitrochlorobenzene, an activated aryl chloride, with phenylboronic acid, yielding 4-nitrobiphenyl (reaction 2). The optimized conditions employed for reaction 1 were found to be ineffective for reaction 2. By changing the solvent and the base, large increases in the catalyst performance could be achieved (Table 4). It was found that the best base/solvent combination was CsF in dioxane, without addition of

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(11) For the reactions run at 1.0 mol % Pd, a trace of biphenyl was observed, formed via homocoupling of the boronic acid.

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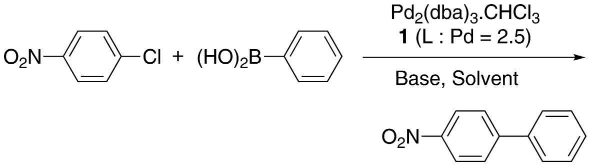
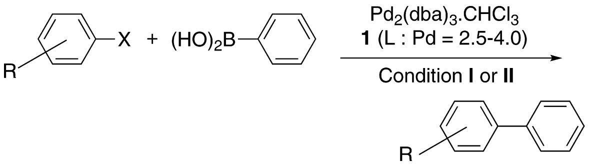
H_2O. With these conditions, the quantitative yield of the cross-coupled product was obtained within 16 h at 90 °C at a Pd loading of 0.1 mol %. Lowering the loading from 0.1 mol % to 0.01 mol % led to a decreased rate and yield, while an increase to 1 mol % gave similar activity (results not shown). No other products than the cross-coupled product were observed by GC.



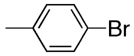
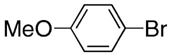
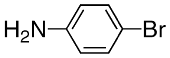
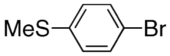
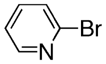
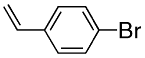
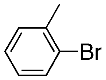
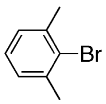
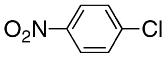
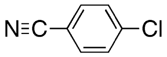
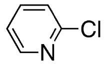
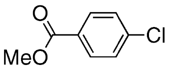
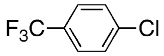
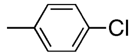
(2)

2.2. Substrate Scope. Using the two sets of optimized reaction conditions, cross-coupling reactions of several aryl bromide and aryl chloride substrates with phenyl boronic acid were then carried out at a Pd loading of 0.1 mol % (reaction 3, Table 5). Aryl bromides could be coupled efficiently using either NaOH in aqueous MeOH (condition **I**) or CsF in dioxane (condition **II**). Aryl chlorides could only be coupled using the latter combination, and higher yields were obtained by using a slightly higher amount of ligand (L:Pd = 4).[13] With these conditions, the system reached full conversion to the cross-coupled products within 22 h with several electronically deactivated aryl bromides (entries 1−3) and aryl bromides containing coordinating or other functional groups (entries 4−6). In the case of 4-bromostyrene, the product was isolated and its identity confirmed by ^{1}H NMR.[14] Furthermore, the sterically hindered aryl bromides 2-bromotoluene and 2-bromo-*m*-xylene could be efficiently coupled with phenylboronic acid. The coupling reactions of these aryl bromides with sterically hindered mesitylboronic acid proved much more difficult; the biaryl derivative containing three *ortho*-methyl groups could be synthesized in 35% yield, but no coupling product was formed with four *ortho*-methyl groups (entries 7−8). Aryl chlorides containing an electron-withdrawing substituent at the aryl ring, as well as 2-chloropyridine, could be coupled with moderate to excellent yields within 22 h (entries 9−13). For the nonactivated 4-chlorotoluene, only a trace of product was obtained (entry 14). For entries 12−14, prolonging the reaction time to 46 h or increasing the Pd loading to 1 mol % did not significantly improve the reaction yields.



(3)

Table 5. Results for Cross-Coupling of Aryl Halides with Phenylboronic Acid Using $Pd_2(dba)_3 \cdot CHCl_3$/**1**

Entry	Aryl Halide	Conditions[a]	t (h)	Yield (%)[b]
1		**I**	22	99
		II	22	99[c]
2		**I**	22	>99
		II	3	>99[c]
3		**I**	22	75
		II	22	91
4		**I**	22	98
5		**I**	3	>99
6		**I**	22	98[d]
7		**I**	22	>99
		II	22	35[e]
8		**I**	22	90
		II	22	0[e]
9		**II**	6	99
10		**II**	22	90
11		**II**	6	84
12		**II**	22	70
13		**II**	22	62
14		**II**	22	7

[a] Reaction Conditions: **I**: aryl bromide (1.0 mmol), phenylboronic acid (2.0 mmol), NaOH (2.2 mmol), MeOH (6.3 mL), H_2O (0.7 mL), $Pd_2(dba)_3 \cdot CHCl_3$ (0.05 mol %), **1** (0.25 mol %, L:Pd = 2.5), reflux temperature. **II**: aryl halide (1.0 mmol), phenylboronic acid (2.0 mmol), CsF (2.2 mmol), dioxane (7.0 mL), $Pd_2(dba)_3 \cdot CHCl_3$ (0.05 mol %), **1** (0.40 mol %, L:Pd = 4.0), 95 °C. [b] Yields of the cross-coupled products, determined by GC using pentadecane as internal standard; averages of 2 independent runs. [c] Reaction temperature: 70 °C; 0.05 mol % of $Pd_2(dba)_3 \cdot CHCl_3$ and 0.25 mol % of **1** were used. [d] The cross-coupled product was isolated and its identity confirmed by ^{1}H NMR. [e] Cross-coupling reaction of the aryl halide with mesitylboronic acid.

2.3. Comparison of the Pd/Dendriphos System to Known Catalytic Systems. To place the activity of the present catalytic system in perspective, we performed the coupling reaction of methyl 4-chlorobenzoate with phenylboronic acid (reaction 4) using several different commercially available catalysts, using our experimental setup and reaction conditions. All reactions were carried out using a Pd loading of 0.1 mol %. Where applicable, optimal L:Pd ratios as described in literature were used. Samples were taken at appropriate time intervals to establish the minimum

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(13) This improves catalyst stability when reaction times as long as 22 h are required. Kinetically, increasing the L:Pd ratio above 2.5 leads to a decrease in the reaction rate during the first several hours (Figure S2e).

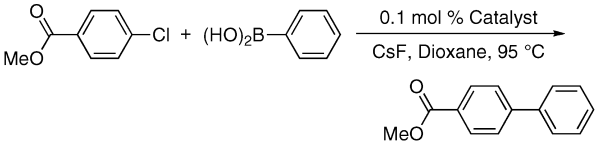
(14) The Suzuki−Miyaura cross-coupled product was formed selectively and in quantitative yield; no polymers or Heck coupled stilbene-containing compounds were found.

Table 6. Comparison of Pd/**1** to Commercially Available Catalysts in Reaction 4[a]

Entry	Catalyst	*t* (h)	Yield (%)[b]
1	$Pd(OAc)_2$ + *Sphos* (L:Pd = 2)	0.5	>99
2	$Pd(OAc)_2$ + *CataCXium A* (L:Pd = 2)	0.5	>99
3	$Pd_2(dba)_3 \cdot CHCl_3$ + $P(t\text{-}Bu)_3HBF_4$ (L:Pd = 1.2)	0.5 (22)	53 (99)
4	$Pd(OAc)_2$ + **1** (L:Pd = 6)	22	73
5	$Pd_2(dba)_3 \cdot CHCl_3$ + **1** (L:Pd = 4)	22	70
6	$Pd_2(dba)_3 \cdot CHCl_3$ + P(*o*-tolyl)$_3$ (L:Pd = 4)	22	65
7	PEPPSI	0.5 (22)	37 (42)[15]
8	$Pd(OAc)_2$ + PPh_3 (L:Pd = 4)	22	6
9	$PdCl_2dppf$	22	2
10	$Pd(PPh_3)_4$	22	1

[a] Reaction conditions: methyl 4-chlorobenzoate (1.0 mmol), phenylboronic acid (2.0 mmol), CsF (2.2 mmol), dioxane (7.0 mL), catalyst (0.1 mol %), 95 °C. [b] Yield of methyl 4-phenylbenzoate, determined by GC using pentadecane as internal standard; average of 2 independent runs.

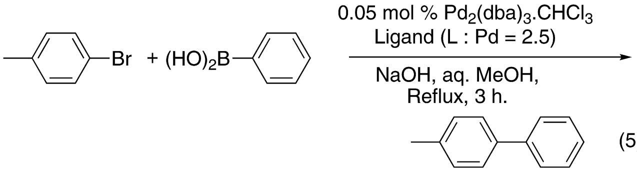
required time to reach maximum conversion for each catalytic system. The results are shown in Table 6.



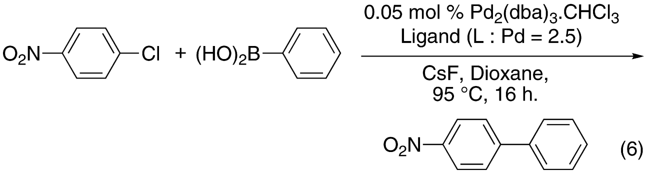
(4)

The results clearly show the superiority of the bulky, strongly σ-donating ligands *CataCXium A*[31a] and *S-phos*[32d] (Figure 2) both used in combination with $Pd(OAc)_2$, which gave quantitative yields within 0.5 h (entries 1 and 2). On the other hand, conventional catalysts based on triphenylphosphine, as well as $PdCl_2dppf$, are totally ineffective for this reaction (entries 8−10). Systems employing **1** gave moderate yields (entries 4 and 5), ranking these systems in the middle of this catalytic spectrum. Notably, the use of $Pd(OAc)_2$ instead of $Pd_2dba_3 \cdot CHCl_3$ resulted in a slightly higher yield, but a higher concentration of **1** (L:Pd = 6) was required for optimal activity. The use of the well-known, bulky ligand P(*o*-tolyl)$_3$ gave an activity comparable to the systems using **1**. In the case of P(*t*-Bu)$_3$,[30a] the observed initial activity was very high (53% yield after 0.5 h). However, some Pd-black was formed and the activity dropped quickly. Quantitative conversion could nevertheless be obtained within 22 h (entry 3). Similar behavior was observed for the PEPPSI catalyst[34b] (entry 7). However, in this case, the catalyst became nearly inactive after 0.5 h under these conditions.[15]

2.4. Investigations into the Nature of the Active Species. To gain insight into the nature of the active species that is formed *in situ* upon combination of **1** and $Pd_2dba_3 \cdot CHCl_3$, we performed several control runs (Figure 3). These experiments were performed using the representative substrates 4-bromotoluene and 4-nitrochlorobenzene, using their respective optimal reaction conditions (reactions 5 and 6, respectively).



(5)



(6)

Runs in the absence of ligand, or in the presence of the benchmark ligand PPh_3, each gave very low conversions under identical conditions for both of these reactions. These observations indicate the beneficial effect of the use of ligand **1**. Furthermore, the use of the phosphine oxide of **1** (**1**-oxide) led to rapid Pd-black formation and very low yields, indicating that coordination of the phosphine functionality to Pd is required for activity in this system. Finally, the addition of the quaternary ammonium salt 3,5-bis[(benzyldimethylammonio)methyl)]benzene dibromide (**4**), which is structurally analogous to **1**, did not lead to any increase in activity, either as the only additive or in combination with PPh_3. This shows that the activity observed by the use of ligand **1** does not depend on the simple presence of quaternary ammonium bromide groups.

The effect of adding poisons for ligandless Pd species to reaction mixtures containing $Pd_2dba_3 \cdot CHCl_3$ and **1** in our benchmark coupling reaction of 4-bromotoluene (reaction 5) was investigated as well. The poisons were added to the catalytic mixtures a few seconds after the Pd precursor had been added to a hot mixture of the other components and compared to a run in which no poison was added (Figure 4).

Addition of a drop of mercury led to a gradual decrease in activity. The initially yellow reaction mixture slowly turned colorless, indicating that all of the Pd in solution was slowly being absorbed by the drop of mercury. However, addition of poly(4-vinylpyridine) (PVPy)[16] (300 or 600 mol equiv of pyridine repeat units with respect to Pd) did not have any effect on the activity. Indeed, these mixtures stayed yellow throughout the reaction. These observations suggest that naked Pd(0) species might be present in solution in low concentrations and that they can be absorbed by Hg but not by PVPy. For comparison, the effect of adding mercury to a catalytic mixture using the benchmark catalyst $Pd(PPh_3)_4$ was tested under identical conditions. In this case, the activity was immediately and completely inhibited (Figure S4).

2.5. Activities of Dendriphos Ligands of Higher Generations. The higher *Dendriphos* ligand generations, **2** and **3**, were both tested alongside **1** in the coupling of a selected number of electronically different aryl halides (reaction 7). For each of the ligand generations, a L:Pd ratio of 2.5 was used at 0.1 mol % Pd loading. Kinetic profiles for the coupling reactions of 4-nitrochlorobenzene and 4-bromotoluene with phenylboronic acid are shown in Figure 5, and those for the coupling reactions

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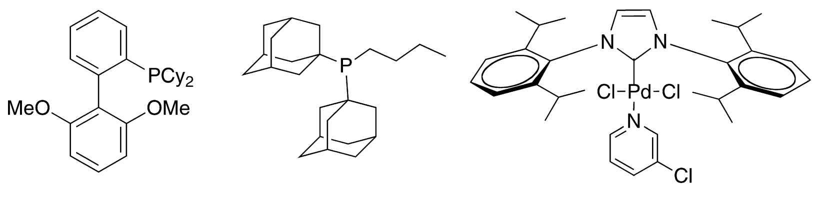
(15) Using the base Cs_2CO_3 instead of CsF (with dioxane as the solvent), which corresponds to one of the published sets of conditions, we obtained only a slightly higher yield (58% after 22 h) using the PEPPSI catalyst. This result is not in line with the published results for this catalyst, which reaches high yields within 2 h at room temperature for similar coupling reactions. We propose that the lower observed yield results from the lower amount of catalyst used; in the present study we used 0.1 mol % of Pd, while the published procedures employ 1 or 2 mol % Pd.

(16) (a) Yu, K.; Sommer, W.; Richardson, J. M.; Weck, M.; Jones, C. W. *Adv. Synth. Catal.* **2005**, *347*, 161–171. (b) Richardson, J. M.; Jones, C. W. *Adv. Synth. Catal.* **2006**, *348*, 1207–1216. (c) Weck, M.; Jones, C. W. *Inorg. Chem.* **2007**, *6*, 1865–1875. (d) Chen, J.; Vasiliev, A. N.; Panarello, A. P.; Khinast, J. G. *Appl. Catal., A* **2007**, *325*, 76–86.

(17) $PhB(OH)_2$ is known to react *in situ* with hydroxide or fluoride anion to give $PhB(OH)_3^-$ or $PhB(OH)_2F^-$, respectively: Glaser, R.; Knotts, N. *J. Phys. Chem. A* **2006**, *110*, 1295–1304. Changing the concentration of CsF alone did not give any change in reaction rate, indicating that the formation of $PhB(OH)_2F^-$ is very rapid.



SPhos *CataCXium A* PEPPSI

Figure 2. Commercially available ligands used for benchmarking of **1**.

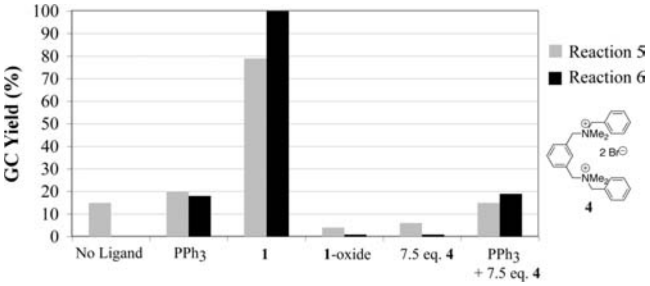


Figure 3. Control runs for investigating the nature of the active species.

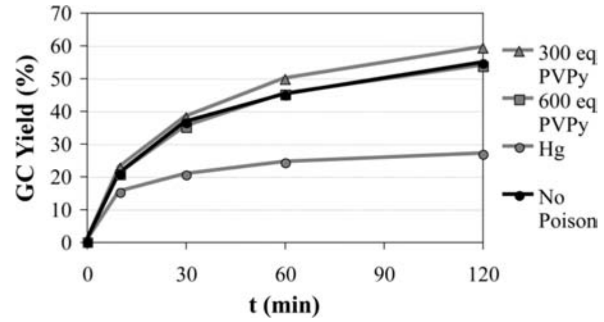
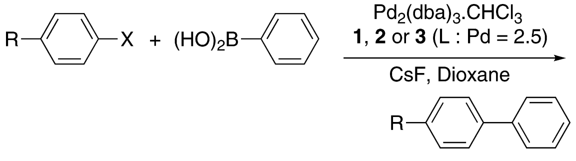


Figure 4. Poisoning tests for the catalytic system $Pd_2dba_3 \cdot CHCl_3$/**1** in reaction 5.

of methyl 4-chlorobenzoate, 4-nitrobromobenzene, and 4-bromoanisole are shown in Figure S1.



(7)

In the coupling reactions of aryl chlorides, clear rate increases were observed by the use of ligands of higher generations. In the case of 4-nitrochlorobenzene, this effect was readily observed at 70 °C (Figure 5a), and increasing the temperature led to higher rates for all the generations (Figure S1a). For methyl 4-chlorobenzoate (Figure S1b), a reaction temperature of 95 °C was required to obtain appreciable activity. Even though a positive dendritic effect was observed in the initial stages of the reaction, the highest coupling yield after 22 h for this reaction was reached using **1** (70%). Ligands **2** and **3** gave lower yields for the coupling reaction of methyl 4-chlorobenzoate after 22 h (51% and 41%, respectively), indicating that for these ligands the catalyst is less stable under the reaction conditions used. A possible explanation for this catalyst deactivation could be slow thermal ligand degradation in the case of **2** and **3**. For each of the aryl bromides (Figures 5b, S1c, and S1d) the different ligand generations gave essentially identical reaction rates. Furthermore, very small differences in coupling rates were observed, even among the electronically very different aryl bromides 4-bromonitrobenzene and 4-bromoanisole.

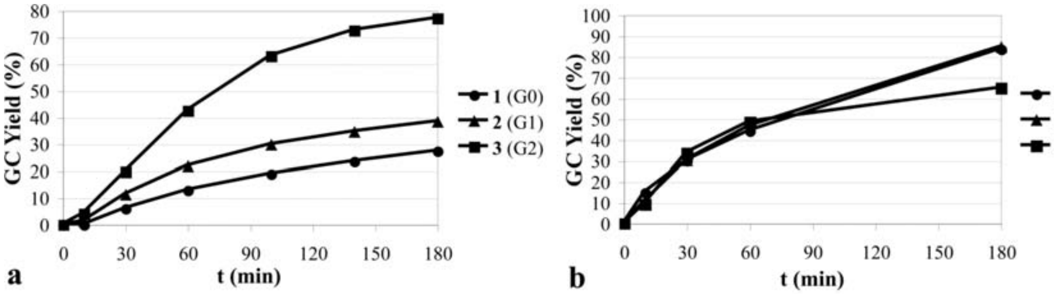
2.6. Kinetic Investigations. To obtain insight into the origin of the dendritic kinetic effects depicted in Figure 5, additional kinetic investigations were carried out under identical conditions, using **1** as ligand. Thus, the effects of increasing the concentrations of either the aryl halide or that of the activated phenylboronic acid[17] on the initial reaction rate were investigated for two different substrates, i.e., 4-chloronitrobenzene and 4-bromotoluene. No clear orders in the substrates could be derived from the obtained data, but qualitative trends were observed. Kinetic profiles for these reactions, as well as plots of the initial reaction rate versus the substrate concentration, can be found in Figures S2 and S3. The effect of increasing the concentration of **1** with respect to Pd on the kinetic profile was also investigated.

In the case of 4-nitrochlorobenzene (Figure S2), increasing the concentration of the aryl halide led to a strong, nonlinear increase of the initial reaction rate, but no further increase was observed beyond a concentration of 0.43 mol L^{-1}. In contrast, the concentration of the activated boronic acid did not significantly influence the observed reaction rate. Increasing the concentration of **1** did not influence the initial reaction rate, but as the reaction progressed, the differences in the rates of the individual reactions grew dramatically; a clear decrease in rate was observed upon increasing the L:Pd ratio from 2.5 to 6.0. No further decrease in rate was observed at a L:Pd ratio of 8.0.

In the case of 4-bromotoluene (Figure S3), small positive influences on the initial rate were found for both the concentration of the aryl halide and that of the activated boronic acid. Increasing the concentration of **1** from L:Pd = 2.5 to 6.0 led to a distinct decrease in the observed rate, but no further change was observed by increasing the concentration to L:Pd = 8.0.

3. Discussion

3.1. Nature of the Active Species. The combination of $Pd_2dba_3 \cdot CHCl_3$ and *Dendriphos* ligands can achieve Suzuki−Miyaura couplings of nonactivated aryl bromides as well as activated aryl chlorides at a Pd loading of only 0.1 mol %. This activity is dramatically higher than that of conventional systems employing PPh_3 as ligand (Figure 3, Table 6). The structure of *Dendriphos* ligands incorporates not only a phosphine function but also quaternary ammonium groups, bromide ions, and dendritic wedges as well. Before considering the reasons for the increased activity of *Dendriphos* ligands with respect to PPh_3 in terms of ligand structures, a careful investigation as to whether the active species in this catalytic system is a homogeneous Pd−*Dendriphos* coordination complex or Pd nanoparticles that



R = NO_2, X = Cl, T = 70 °C

R = Me, X = Br, T = 70 °C

Figure 5. Kinetic profiles for the coupling reactions of 4-nitrochlorobenzene (a) and 4-bromotoluene (b) with phenylboronic acid. Reaction conditions: aryl halide (1.0 mmol), phenylboronic acid (2.0 mmol), CsF (2.2 mmol), dioxane (7.0 mL), $Pd_2(dba)_3 \cdot CHCl_3$ (0.05 mol %), **1**, **2**, or **3** (0.25 mol %, L:Pd = 2.5). Yields were determined by GC using pentadecane as internal standard and are averages of two independent runs.

are stabilized by *Dendriphos* is thus appropriate. In general, if catalytically active metal nanoparticles are being generated *in situ* from homogeneous catalyst precursors during a catalytic reaction, observations of induction periods and sigmoidal kinetics are considered a "telltale sign".[18] The kinetic traces of the present catalytic system show neither sigmoidal kinetics nor induction periods (except in one case; see Figure 5a). It is widely acknowledged that the addition of quaternary ammonium halide salts, such as tetrabutylammonium bromide (TBAB) in high concentrations (50−100 mol %), can improve the catalytic efficiency in Suzuki−Miyaura couplings, and this effect is generally attributed to stabilization of catalytically active Pd nanoclusters.[19−21] We investigated the possible influence of the ammonium bromide groups in the architecture of **1** on the observed activity, even though they are only present in very low concentrations (6 equiv per ligand molecule, giving 1.5 mol % of tetraalkyl ammonium groups under our standard conditions). The use of the same concentration of a structurally analogous salt (**4**) did not lead to any improvement of the activity, in either the presence or absence of PPh_3 as ligand (Figure 3). Furthermore, using the phosphine oxide of ligand **1** gave very low conversions and led to Pd-black formation, indicating that the palladium in solution is stabilized by the phosphine function and not by the ammonium groups.

Stabilization of palladium nanoparticles, leading to catalytically active systems in C−C cross-coupling reactions, can also be achieved by other means, such as immobilization on a solid support[22] or by *in situ* generation in poly(ethylene glycol) (PEG-400).[23] Encapsulation or stabilization of Pd nanoparticles by nonionic dendrimers have also been reported.[24] Recently, phosphine oxide functionalized, Fréchet-type dendrons were reported to stabilize palladium nanoparticles, which were used as catalysts in the Suzuki−Miyaura reaction.[25,26] To investigate the possibility that such stabilization effects play a role in the present system, we employed two well-known poisoning tests. Poly(4-vinylpyridine) (PVPy)[16] is known to act as a selective trap for homogeneous, ligandless Pd(0) species. Addition of PVPy to the catalytic system $Pd_2dba_3 \cdot CHCl_3$/**1** did not have any effect on the catalytic activity. This is a strong indication that, in the present system, the observed activity cannot be attributed to ligandless Pd(0) species, but to a homogeneous Pd-*Dendriphos* complex of the type Pd(0)L_n. Addition of mercury led to a gradual decrease of activity. If mercury inhibits the activity, it is concluded that either ligandless Pd(0) species are the true active species or catalysis occurs via a cycle with a Pd(0) intermediate.[21] The latter is most likely the case for the present system. For comparison, we tested the effect of adding mercury to a catalytic reaction employing the benchmark catalyst $Pd(PPh_3)_4$ under identical conditions. In this case, an immediate and complete inhibition was observed (Figure S4). It is generally accepted that $Pd(PPh_3)_4$ in the absence of any stabilizer does not form Pd nanoparticles in solution. It thus seems that inhibition by Hg might not be a reliable indication for catalysis by Pd nanoparticles for Pd−phosphine systems.

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(20) It is worth noting that even in cases where Pd nanoclusters are believed to be responsible for the catalytic activity in Suzuki−Miyaura and Heck reactions, the active species are actually Pd(0) atoms that have leached from these nanoclusters or ArPd(II)X complexes that have leached after undergoing oxidative addition at the surface of the nanoclusters: (a) Thathagar, M. B.; Ten Elshof, J. E.; Rothenberg, G. *Angew. Chem.* **2006**, *45*, 2886–2890. (b) De Vries, J. G. *Dalton Trans.* **2006**, 421–429. (c) Gaikwad, A. V.; Holuigue, A.; Thathagar, M. B.; Ten Elshof, J. E.; Rothenberg, G. *Chem.−Eur. J.* **2007**, *13*, 6908–6913.

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(26) Given the specific synthesis procedure of the nanoparticles, which is entirely different from our reaction conditions, and the difference in molecular architecture among **1**−**3** and the dendrons used in that report, it is unlikely that such Pd nanoclusters are formed in our case. Furthermore, the phosphine oxide dendron-stabilized Pd nanoclusters were reported to be black powders, whereas our reaction mixtures are clear yellow solutions, which is a characteristic color of homogeneous Pd−P complexes.

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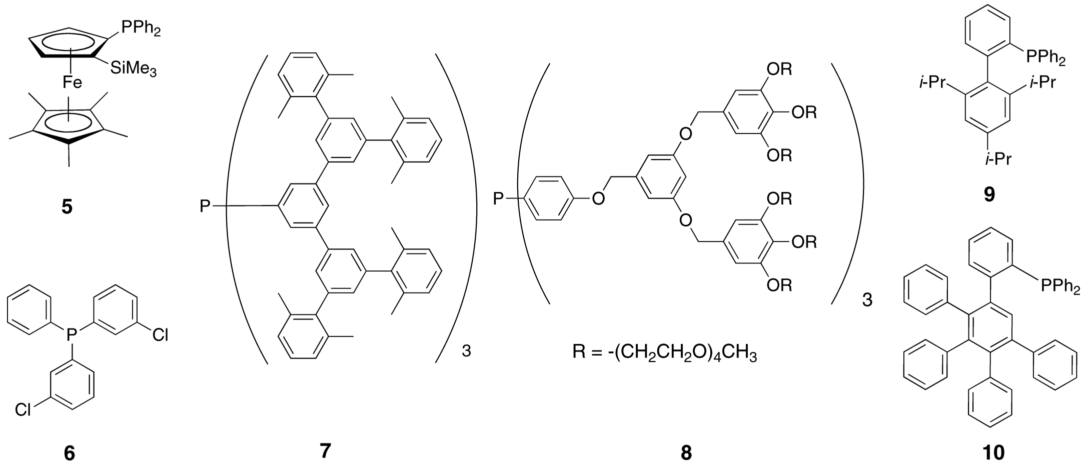

Figure 6. Examples of triarylphosphine ligands that have shown appreciable activity in Suzuki–Miyaura couplings of aryl chloride substrates.

Finally, the presence of halide ions in solution can have profound effects on the structure of several species that are involved in the catalytic cycle, thereby influencing the observed catalytic rate.[27] However, as halide ions, originating from the aryl halide substrate, are naturally released into solution in high concentration as the reaction progresses, as a consequence of the transmetalation step in the Suzuki–Miyaura reaction,[35] it is unlikely that the low added concentration of bromide ions originating from ligands **1**–**3** should have a significant effect. Indeed, no effect was observed when ammonium bromide salt **4** was added to a mixture employing PPh_3 as ligand (Figure 3).

3.2. Ligand Structure of Dendriphos in Relation to Activity in Coupling Reactions of Aryl Chlorides. Conventional catalysts such as $Pd(PPh_3)_4$ and $Pd(OAc)_2$ + 2–4 equiv of PPh_3 are very effective in the coupling of aryl bromides and iodides, but their activities in the coupling reaction of aryl chlorides are low and they require Pd loadings as high as 3–5 mol %, to give moderate yields at best.[28] The most efficient ligands for the Suzuki–Miyaura reaction, in particular for reactions using aryl chlorides,[12] are strongly σ-donating phosphines with large cone angles,[29] such as the trialkylphosphines employed by Fu et al.[30] and Beller et al.[31] and the *o*-(dialkylphosphino)biphenyl-based ligands developed by Buchwald et al.[32] A second class of highly effective ligands are the N-heterocyclic carbenes developed by Nolan et al.[33] and Organ et al.[34] These systems can achieve couplings of challenging aryl chlorides using low Pd loadings at room temperature.

The first step in the catalytic cycle of the Suzuki–Miyaura reaction is oxidative addition of ArX (X = I, Br, or Cl) to $Pd(0)L_n$ (L = phosphine ligand; n = 1 or 2), forming $ArPd(II)XL_n$ (Figure 7).[35] Theoretical studies have shown that, in the case of aryl bromides and aryl chlorides, oxidative addition to Pd(0)L is the energetically preferred pathway, while aryl iodides react with $Pd(0)L_2$.[36] This finding is consistent with experimental observations.[37] In the case of aryl chlorides, the oxidative addition can be problematic due to the strength of the Ar–Cl bond and is considered to be the overall rate-determining step in the catalytic cycle. The ability of a system to stabilize Pd(0)L species, which is largely dependent on the steric properties of the ligand,[38] thus plays a great role in determining its efficiency in the Suzuki–Miyaura reaction, especially with aryl chlorides.[36d,39] *Dendriphos* ligands are one of the few examples of triarylphosphines that exhibit considerable activity in the coupling of aryl chlorides. Other cases reported until now include ferrocene-containing triarylphosphine ligands[40] such as **5**,[40a] bis(3-chlorophenyl)phenylphosphine (**6**),[41] and bowl-shaped phosphine ligands such as **7**[42] (Figure 6). For these systems, the activity observed is ascribed to facilitated dissociation of these ligands from Pd, generating the coordinatively unsaturated and catalytically active species. In the case of **6**, this effect was tentatively ascribed to the increased steric bulk and decreased donating ability of the ligand. In the

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case of **7**, the effect was ascribed to the specific bowl-shaped geometry of the ligand. The activity that we observed for the well-known bulky ligand P(*o*-tolyl)$_3$ (Table 6) can be ascribed to a similar effect, i.e., to the presence of the *ortho*-substituents in the ligand.

Recently, triarylphosphines substituted with dendritic tetraethylene glycol moieties (**8**)[6h] were reported. Their high activity in the Suzuki−Miyaura coupling of aryl chloride substrates was ascribed to their large size, which excludes other large phosphines from the coordination sphere of the catalytic center. In two further examples, i.e., 2-(2′,4′,6′,-triisopropylbiphenyl)diphenylphosphine (**9**)[32d] and (2,3,4,5-tetraphenylphenyl)diphenylphosphine (**10**),[43] transient coordination of the biphenyl moiety to Pd (with either an η^1 or η^2 hapticity) contributes to the stability of the active species Pd(0)L.

These examples show that the use of a strongly σ-donating ligand is not an absolute prerequisite for coupling of aryl chlorides, provided that the ligand employed has a means of stabilizing the coordinatively unsaturated and catalytically active monophosphine palladium (Pd(0)L) species. In the case of *Dendriphos* ligands **1**−**3**, we believe that a great repulsion exists between neighboring molecules of the dendritic hexacationic ligands, especially when simultaneously acting as monodentate ligand to the same metal center. The repulsion is proposed to have a steric component due to the large size of the dendritic ligands, as well as a Coulombic component, due to the presence of six cationic charges in the ligand structure.[44] Accordingly, this interligand repulsion is expected to facilitate dissociation of these ligands from the Pd center, allowing *in situ* formation of coordinatively highly unsaturated and catalytically active Pd(0)L species.

3.3. A Positive Dendritic Kinetic Effect by the Use of Dendriphos Ligands 1−**3.** In the coupling reactions of aryl halides with phenylboronic acid catalyzed by the combination of $Pd_2(dba)_3 \cdot CHCl_3$ with **1**−**3**, a positive dendritic kinetic effect was observed for aryl chlorides, while no significant dendritic effect was observed for aryl bromides (Figures 5 and S1). The combination of **1**−**3** with a Pd(0) source presumably leads to Pd(0)L$_2$, which is in equilibrium with Pd(0)L and noncoordinated L (Figure 7). With increasing generations, this equilibrium is shifted to the side of Pd(0)L + L due to an increase in the steric interligand repulsion, leading to a higher concentration of Pd(0)L, the active species in the oxidative addition step. Our kinetic investigations using ligand **1** showed a strong positive influence of the concentration of the aryl halide, but no influence of the activated boronic acid when the aryl halide is 4-nitrochlorobenzene (Figure S2a−d). These observations indicate that the oxidative addition is the rate-determining step, which is corroborated by the much lower observed activity for methyl 4-chlorobenzoate than for the electronically more strongly activated 4-nitrochlorobenzene (Figure S1a,b). The kinetic profile observed for the coupling of 4-nitrochlorobenzene (Figure 5a) indicates that a short induction period exists. In this induction period, most likely the active catalyst is formed from $Pd_2(dba)_3 \cdot CHCl_3$ and **1**. It is known that dba ligands have a high affinity for Pd(0)−phosphine complexes and in some cases do not readily dissociate from species of the type Pd(0)-(dba)L$_n$.[37a] The data presented in Figure 5a suggest that this process takes 5−10 min for this particular case. After this induction period, the equilibrium between Pd(0)L + L and Pd(0)L$_2$ becomes operative. The decrease in observed reaction rate upon increasing the L:Pd ratio (Figure S2e) can then be explained by a shift of the equilibrium toward the inactive species Pd(0)L$_2$.

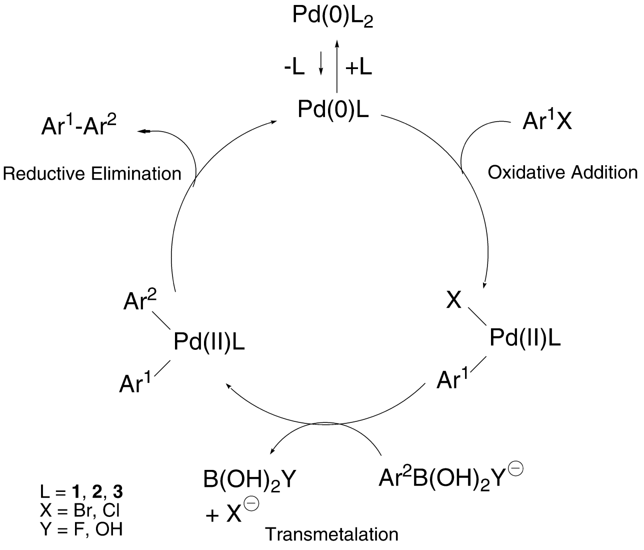

Figure 7. Mechanism for the Suzuki−Miyaura cross-coupling reaction.[35]

When the substrate is 4-bromotoluene, kinetic investigations showed positive influences for both the aryl halide and the activated boronic acid (Figure S3a−d), indicating that not the oxidative addition but most likely the transmetalation is rate-determining. This is corroborated by the observation of comparable reaction rates for the couplings of the activated 4-nitrobromobenzene and the deactivated 4-bromoanisole (Figure S1c,d), which should give very different rates in the oxidative addition step. For all aryl bromides tested, all three ligand generations gave similar rates; no dendritic effect was observed (Figure 5b and S1c,d). A change in the rate-limiting step does not change the position of the dissociation equilibrium between Pd(0)L$_2$ and Pd(0)L + L, which will still lie more to the side of Pd(0)L + L with increasing ligand generations. However, the shift in the rate-determining step away from the oxidative addition explains why differences in the position of this equilibrium are not reflected in the observed overall coupling rate of aryl bromides. The decrease in rate observed at higher L:Pd ratios (Figure S3e) can be rationalized by a transformation of the catalyst resting state into a higher ligated form. In the Suzuki−Miyaura reaction, the transmetalation usually occurs

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via a three-coordinate Pd(II) complex ArPd(II)XL (Figure 7).[45] This complex is considered to be predominantly present in its dimeric, bromide-bridged form. It is likely that, at higher ligand concentrations, this species, being the resting state of the catalyst, would transform into ArPd(II)XL_2 (L = **1**), which has to undergo dissociation of **1** before transmetalation can occur which leads to a lower observed rate. In this case, the absence of an induction period suggests that catalyst formation does not significantly affect the rate in the initial stages of the reaction.

4. Conclusion

The combination of $Pd_2(dba)_3 \cdot CHCl_3$ and *Dendriphos* ligands leads to a highly active catalytic system in the Suzuki−Miyaura cross-coupling reaction. Particularly for coupling reactions of aryl chlorides, the observed activity is uncommon for systems employing triarylphosphine-based ligands. Importantly, the catalytic activity observed by the use of **1** can be ascribed to a homogeneous Pd−phosphine complex, rather than Pd nanoclusters. In the coupling reactions of activated aryl chlorides, an acceleration was observed by the use of ligands of higher generation, which could be explained by a facilitated formation of coordinatively unsaturated and catalytically active Pd(0)L (L = **1**, **2**, **3**) species with an increase in ligand generation.

Our results indicate that, in principle, a strongly σ-donating ligand is not required for the activation of aryl chlorides, provided that the ligand has a means of generating and, to a certain extent, of stabilizing a Pd(0)L species. Previously reported ligand systems have accomplished this mainly by steric effects. The observed activity of even a relatively small ligand as G0-*Dendriphos* (**1**) indicates that it has an effect on the catalytic activity similar to that of a very bulky ligand. We propose that the Coulombic interligand repulsion originating from the six positive charges in the ligand structure plays a role in the bulky behavior observed for this ligand system, therefore being in part responsible for its high catalytic activity.

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Supporting Information Available: Experimental details and additional kinetic plots. This material is available free of charge via the Internet at http://pubs.acs.org.

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