Green Chemistry

Accepted Manuscript

This is an *Accepted Manuscript*, which has been through the RSC Publishing peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, which is prior to technical editing, formatting and proof reading. This free service from RSC Publishing allows authors to make their results available to the community, in citable form, before publication of the edited article. This *Accepted Manuscript* will be replaced by the edited and formatted *Advance Article* as soon as this is available.

To cite this manuscript please use its permanent Digital Object Identifier (DOI®), which is identical for all formats of publication.

More information about *Accepted Manuscripts* can be found in the **Information for Authors**.

Please note that technical editing may introduce minor changes to the text and/or graphics contained in the manuscript submitted by the author(s) which may alter content, and that the standard **Terms & Conditions** and the **ethical guidelines** that apply to the journal are still applicable. In no event shall the RSC be held responsible for any errors or omissions in these *Accepted Manuscript* manuscripts or any consequences arising from the use of any information contained in them.

View Online

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

An efficient and recyclable dendritic catalyst able to dramatically decrease palladium leaching in Suzuki couplings

Michel Keller,[a,b] Aurélien Hameau,[a,b] Grégory Spataro,[a,b] Sonia Ladeira,[a,b] Anne-Marie Caminade,[a,b*] Jean-Pierre Majoral,[a,b*] Armelle Ouali.[a,b*]

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

DOI: 10.1039/b000000x

A series of novel monomeric and dendritic thiazolyl phosphines (generations 1 and 3) was prepared and the activity these ligands conferred to palladium in Suzuki couplings was evaluated. The heteroaryl ligands revealed very efficient and allowed to perform the reactions in mild conditions. Besides, their efficiency was compared to that of the corresponding triphenylphosphines. Moreover, the possibility to reuse both families of dendritic ligands was explored and thiazolyl phosphines-based catalytic systems could successfully be recycled in five consecutive reactions without loss of activity contrary to their triphenylphosphine counterparts. Remarkably, the palladium leaching was found to be dramatically reduced by using the dendrimer-supported thiazolylphosphines instead of the monomeric ligand and only traces of metal (< 0.55 ppm) could be found in the coupling product before.

Introduction

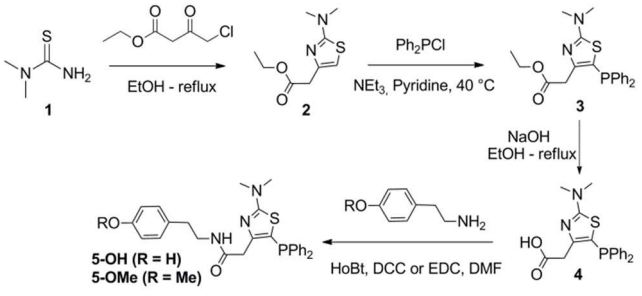
Heteroaryl phosphines constitute a class of interesting potential ligands. Indeed, heterocyclic substituents bound to the phosphorous atom can confer specific electronic and steric properties to the adjacent phosphorous atom, therefore enabling a more efficient metal-based catalysis compared to simple alkyl/aryl phosphines.[1] Noteworthy, thiazolines display numerous applications in various fields such as organic synthesis, medicine, agrochemistry, and catalysis mainly because of the unique properties of sulphur and therefore, these heterocycles have attracted the attention of many chemists over the last decade.[2] To the best of our knowledge, only few examples of catalysts involving thiazolyl phosphines have been reported in the literature: such ligands have thus for example been associated to copper in *N*-arylation reactions[3] and have also been used in palladium-catalyzed Suzuki cross-couplings.[4] The latter reactions constitute one of the most versatile and powerful methods for carbon-carbon bond formation, are generally promoted by palladium-based catalytic systems involving phosphines or carbenes as ligands and can be performed in conventional organic or aqueous media.[5] Noteworthy, different supports such as polymers, nanoparticles, inorganic supports (mainly silica), or dendrimers have been reported to immobilize numerous palladium-based catalysts able to promote Suzuki couplings.[6,7] In a general manner, the immobilization of catalysts onto dendrimers, hyperbranched and perfectly defined macromolecules, display two main potential advantages: the recovery and reuse of the catalysts at the end of the reaction which appears as highly desirable for both economic and ecological reasons in the context of green chemistry and, in some cases, the enhancement of the catalytic activities.[8,9] In this line, a strong positive dendritic effect could be observed in copper-catalyzed arylations of nucleophiles when using nitrogen ligands supported onto the phosphorous dendrimers developed in our group.[10] We thus planned to design phosphorous dendrimers incorporating thiazolyl phosphines as end groups and here we report the catalytic activity they conferred to palladium in Suzuki reactions. To evaluate the contribution of the thiazolyl ring with regard to the specific properties it may confer to the palladium, triphenylphosphine ended dendrimers were also prepared and tested in the same C-C couplings. Noteworthy, most of the palladium-based supported catalysts reported for Suzuki reactions exhibit satisfying activities compared to their non-supported counterparts and can be recovered and reused several times except in the case of dendritic catalysts whose recycling has only scarcely been studied.[6,7] However, only a few systems are able to decrease palladium leaching in the coupling products.[6,11] Therefore, the recyclability of the dendritic palladium complexes involving either thiazolyl phosphines or triphenylphosphines was evaluated. Moreover, the metal leaching in the coupling product was compared when using a dendrimer or a monomer as the ligand.

Results and discussion

Preparation of dendritic phosphines

The thiazolyl phosphine **5-OH** tethered with a phenol moiety for further grafting on phosphorous dendrimers was obtained in four steps (Scheme 1). A first condensation of *N,N*-dimethylthiourea **1** and ethyl-4-chloroacetoacetate in ethanol gave rise to *N,N*-dimethylaminothiazole **2** which afforded thiazolyl phosphine **3** after phosphorylation with Ph_2PCl at 40 °C.[4,12] The structure of this compound in the solid state was determined by X-ray crystallography (see Supplementary information). The

corresponding carboxylic acid **4** obtained after saponification of the ester group was allowed to react with tyramine in the presence of DCC (*N,N'*-dicyclohexylcarbodiimide) and HoBt (1-hydroxybenzotriazole) in DMF to provide **5-OH** via peptide coupling. The monomeric model ligand **5-OMe** (Scheme 1) was also synthesized according to a similar procedure than for **5-OH** but using 2-(*p*-methoxyphenyl)ethylamine (Scheme 1, R = Me) instead of tyramine in the last step. Its efficiency has been compared with that of dendrimers in the catalytic tests.



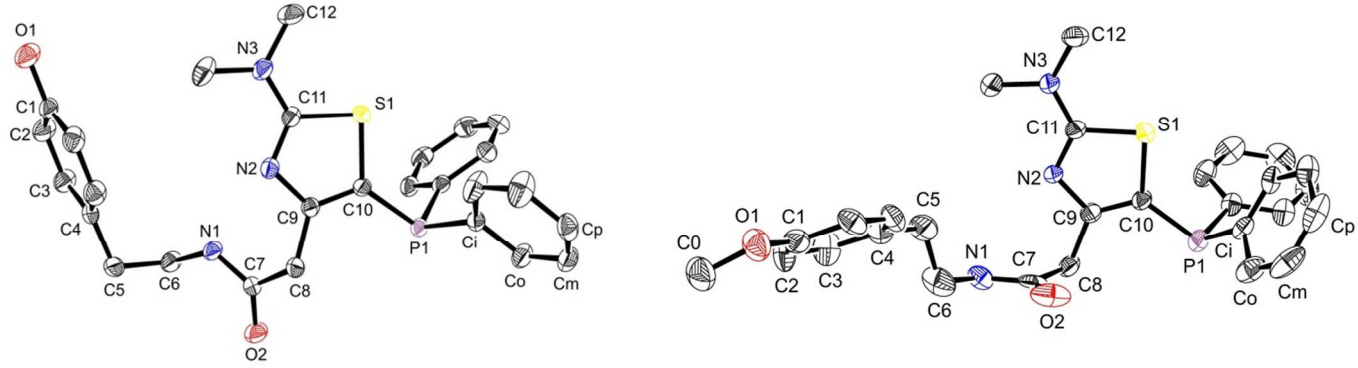
Scheme 1 Synthesis of the phenol functionalized by the thiazolyl moiety.

Moreover, crystals were grown from the latter and the structure of **5-OMe** could be studied by X-ray crystallography and compared to that of **5-OH** (Scheme 2). As expected, both structures revealed very similar: within the crystal lattice, the phosphorus atom is pyramidal and the sulfur atom points in the direction opposite to that of the phosphorous free electron pair.

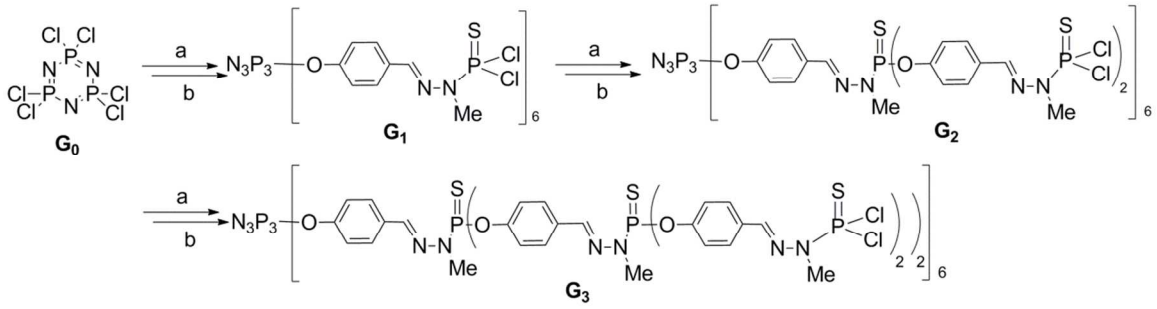
Noteworthy, according to these structures, the presence of the amido-tyramine spacer seems to guarantee the steric accessibility of the phosphorous atom belonging to the thiazolyl phosphine ligand within monomers **5-OH** and **5-OMe** and thus probably also within the dendrimers.

The preparation of the phosphorous dendrimers was indeed achieved using our classical two-step procedure involving first a nucleophilic substitution on chloride atoms of $P(S)Cl_2$ by hydroxybenzaldehyde in the presence of a base, and then a condensation reaction of the resulting aldehyde with the thiophosphorhydrazide $H_2NNMeP(S)Cl_2$ (Scheme 3).[13] These reactions were applied to the cyclotriphosphazene core to afford the series of chloride-decorated dendrimers $\mathbf{G_n}$ (n = 1 to 3). Lastly, the thiazolyl phosphine **5-OH** functionalized with a phenol moiety was grafted to dendrimers $\mathbf{1\text{-}G_1}$ and $\mathbf{1\text{-}G_3}$ via nucleophilic substitution of the terminal chloride atoms in the presence of cesium carbonate in THF (Scheme 4). Resulting dendrimers $\mathbf{5\text{-}G_1}$ and $\mathbf{5\text{-}G_3}$ involving respectively 12 and 48 peripheral thiazolyl phosphine ligands were obtained in good yields (80 and 75% respectively). As mentioned earlier in introduction, triphenyl phosphine ended dendrimers $\mathbf{6\text{-}G_1}$ and $\mathbf{6\text{-}G_3}$ were also prepared in an analogous manner. For this purpose, 4-hydroxyphenyl diphenyl phosphane **6**[14,15] was grafted onto dendrimers $\mathbf{G_1}$ and $\mathbf{G_3}$ via nucleophilic substitution to the P-Cl bonds to afford $\mathbf{6\text{-}G_1}$ and $\mathbf{6\text{-}G_3}$ in 71 and 65% yields respectively (Scheme 4).[16]

5-OH **5-OMe**



Scheme 2 Structures of monomeric thiazolylphosphines **5-OH** and **5-OMe**. Thermal ellipsoids are drawn at the 50% probability level. All hydrogen atoms are omitted for clarity.



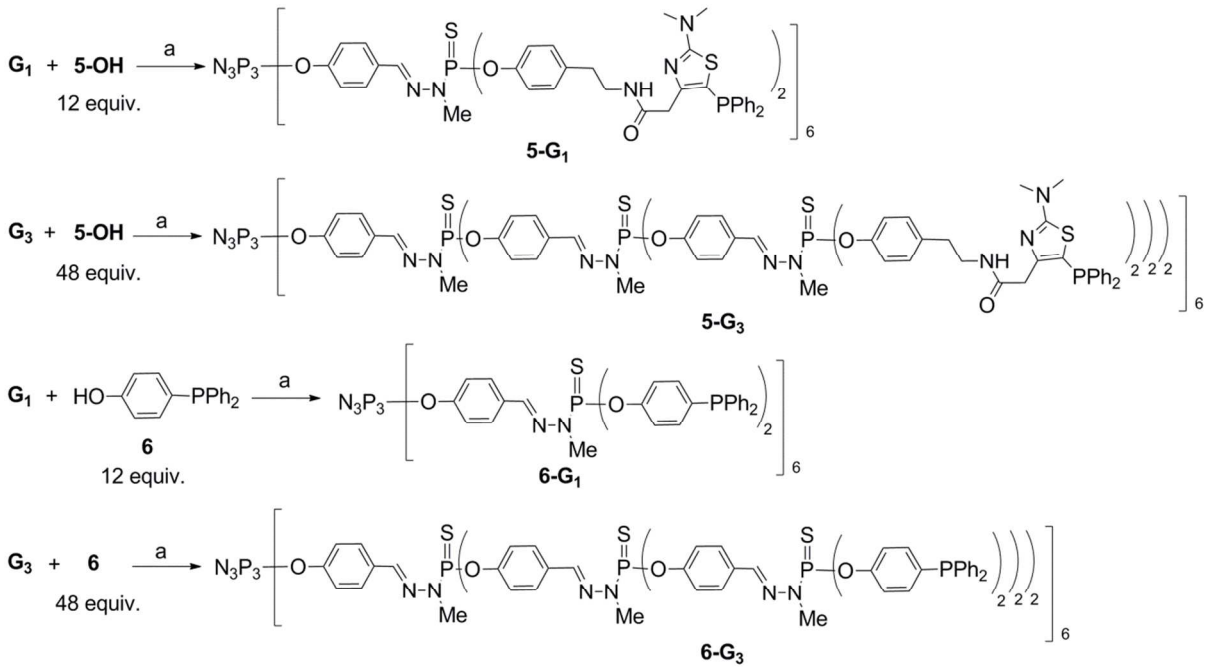
Scheme 3 Phosphorous dendrimers $\mathbf{G_0}$-$\mathbf{G_3}$ with $P(S)Cl_2$-end groups; (a) 4-hydroxybenzaldehyde / Cs_2CO_3, THF, rt; (b) $H_2NNMeP(S)Cl_2$, $CHCl_3$, rt.[13]

View Online

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE



Scheme 4 Grafting of the thiazolyl phosphine and of the triphenylphosphine ligands at the surface of phosphorous dendrimers: (a) Cs_2CO_3, THF, rt.

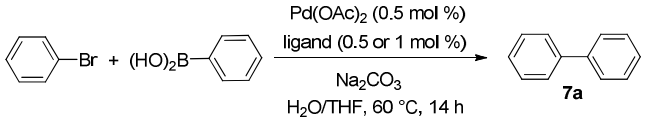
Catalytic activity of monomeric and dendritic phosphines

The former monomeric and dendrimeric phosphines were tested in palladium-catalyzed Suzuki reactions which consist in the coupling of an electrophile (aryl or alkyl halide for example) and a boron compound in the presence of a base.[5] Methods involving nanocatalysts (generally heterogeneous) based on different supports such as polymers, nanoparticles, silica surface or metal oxides have been more recently developed.[6] Among the potential supports, dendrimers constitute attractive targets since these perfectly defined hyperbranched polymers are soluble and thus combine the advantages of homogeneous and heterogeneous catalysis. Dendrimers efficient in Suzuki couplings[7,8] mostly involve Pd/aryl- or alkylphosphine systems and the catalysts can be placed on their surface [7a,b,c,e,i,l,m] or at their core. [7d,f,g,h,j,k] Some of them have been used in organic media, [7a,b,e,h,j] other in aqueous media. [7c,d,f,g,i,k,l,m] In a general manner, the recyclability of dendritic catalysts for Suzuki reactions has been scarcely studied, an efficient recycling being reported for only a few examples either by nanofiltration,[7c] by dialysis, [7g] or by precipitation.[7a,l,m] Interestingly, to our knowledge, no dendritic system involving heteroaryl phosphines have been reported so far.

The coupling of bromobenzene and phenyl boronic acid was first performed in a 2:5 mixture water/THF at 60 °C in the presence of $Pd(OAc)_2$ (0.5 mol%). In the absence of additional ligand, biphenyl was obtained in only 40% yield (Table 1, entry 1) but this reaction revealed poorly reproducible. Then the same reaction was performed in the presence of the monomeric thiazolyl phosphine **5-OMe** for two different phosphine-to-palladium (P/Pd) ratios: P/Pd = 2 or 1 (entries 2, 3 respectively). The yields were found to be similar in both cases (86 and 85% respectively) and therefore, all the following catalytic tests were performed in the presence of 0.5 mol% of $Pd(OAc)_2$ and 0.5 mol% of ligand. Noteworthy, an excess of monophosphine compared to palladium is generally required in cross couplings such as the Suzuki reaction,[5d-h] but in the case of highly efficient ligands such as the tri-*tert*-butylphosphine described by Fu and co-workers,[5g,17] a phosphine-to-palladium ratios (P/Pd) of 1 can be sufficient for high activities to be reached. In these conditions, the thiazolyl moiety itself (compound **2**) gave rise to biphenyl in only 50% yield (entry 4) which illustrates the requirement of the phosphorous atom to obtain a good activity. Moreover, triphenylphosphine was found much more efficient than **2** and slightly less efficient than thiazolyl phosphine **5-OMe** (73% yield instead of 85%, entry 5) which may indicate the existence of a slight synergetic effect between the diphenyl moiety and the thiazolyl ring (entries 3-5).

Thiazolyl phosphine **5-OMe** thus appeared as a promising ligand in Suzuki reactions and therefore the corresponding Pd complex was tested in the couplings of substituted aryl bromides and aryl boronic acids in the previously described conditions (Table 2).

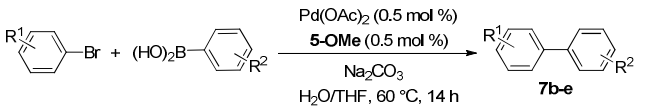
Table 1 Coupling of PhBr and $PhB(OH)_2$ in the presence of $Pd(OAc)_2$ and phosphine ligands.[a]



	Ligand	mol %	Phosphine/Pd ratio	Yield [b]
1	no	-	-	40
2	**5-OMe**	1	2	86
3	**5-OMe**	0.5	1	85
4	**2**	0.5	1	50
5	PPh_3	0.5	1	73

[a] $Pd(OAc)_2$ (0.005 mmol), phosphine moieties (0.01 mmol for Pd/Phosphine ratio = 2 or 0.005 mmol for Pd/Phosphine ratio = 1), PhBr (1 mmol), $PhB(OH)_2$ (1.1 mmol), Na_2CO_3 (3 mmol), H_2O/THF (2:5) (7 mL). [b] GC yields determined with 1,3-dimethoxybenzene as standard.

Table 2 Couplings of substituted aryl bromides and aryl boronic acids in the presence of $Pd(OAc)_2$ and **5-OMe**. [a]



	R^1	R^2	Product	Yield [b]
1	4-COMe	H	**7b**	99
2	4-Me	H	**7c**	85
3	4-OMe	H	**7d**	65 (76 [c])
4	2-Me	H	**7e**	62 (75 [c])
5	H	4-OMe	**7d**	70
6	H	4-COMe	**7b**	60

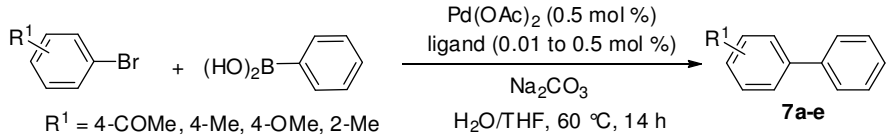
[a] $Pd(OAc)_2$ (0.005 mmol), **5-OMe** (0.005 mmol), ArBr (1 mmol), $ArB(OH)_2$ (1.1 mmol), Na_2CO_3 (3 mmol), H_2O/THF (2:5) (7 mL). [b] GC yields determined with 1,3-dimethoxybenzene as standard. [c] $Pd(OAc)_2$ (1 mol%), **5-OMe** (1 mol%).

Electron-poor 4-bromoacetophenone could be quantitatively arylated by phenyl boronic acid (99%, entry 1) whereas electron-rich substrates such as 4-bromotoluene and 4-bromoanisole gave rise to the corresponding biaryls in 85% and 65% yield respectively (entries 2,3). The latter could be improved up to 76%, by increasing the palladium and ligand loadings both to 1 mol % (entry 3). Along the same line, arylation of more hindered 2-bromotoluene could be improved from 62% to 75% by increasing the palladium loading from 0.5 to 1 mol % (entry 4). Aryl boronic acids substituted by electron-donating or withdrawing groups could also be used as arylating agents (entries 5 and 6), the corresponding biaryls being obtained in moderated (R^2 = 4-COMe: 60%) to good yields (R^2 = 4-OMe: 70%). As a result, ligand **5-OMe** revealed more general than glucosamine-based thiazolyl phosphine previously used in Suzuki coupling whose substrate scope was limited to highly activated 4-nitroiodobenzene by using 1 mol% $Pd(OAc)_2$ and 3 mol% ligand in toluene/EtOH/water (3:2:2) mixtures at 60 °C.[4]

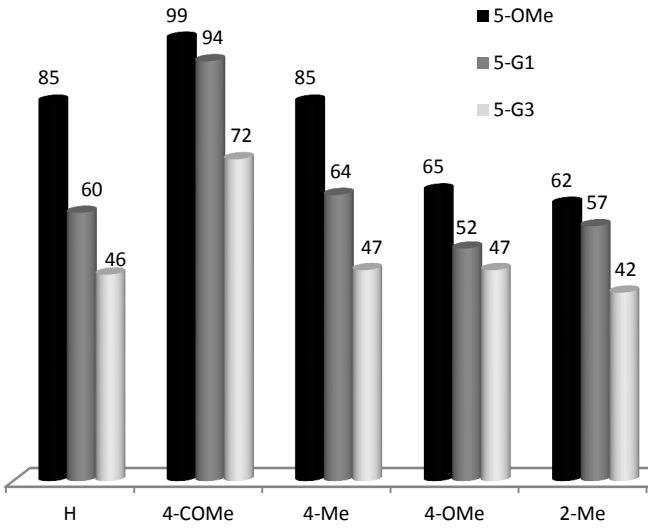
Afterwards, the corresponding dendritic thiazolyl phosphines were also tested in the same reaction conditions while using substituted aryl bromides and phenyl boronic acid (Scheme 5).[18] For arylation of bromobenzene (R^1 = H) and in the case of thiazolyl phosphine ligands **5-OMe**, **5-G_1** and **5-G_3** (Scheme 5, i), a negative dendritic effect could be observed, yields of biphenyl decreasing from 85% with the monomer **5-OMe** to 60 and 46% respectively with **5-G_1** and with **5-G_3**. In the case of triphenylphosphine derivatives however (Scheme 5, ii), the first generation dendrimer displayed a better activity than the corresponding monomer (87% for **6-G_1** against 73% with PPh_3) which corresponds to a positive multivalency effect. However, biphenyl was obtained in only 43% yield in the presence of **6-G_3**.

Afterwards, the scope of monomeric and dendritic catalysts was explored (Scheme 5, R = 4-COMe, 4-Me, 4-OMe and 2-Me). As expected in this type of couplings, electron-poor substrates (R = 4-COMe) revealed more reactive than electron-rich (R = 4-Me, 4-OMe) and bulky substrates (R = 2-Me). Concerning the compared efficiencies of aryl and heteroaryl ligands, no general tendency emerged from the results since the performances of the corresponding palladium complexes were found to depend at the same time from the nature of the substituent, from the nature of the ligand (monomeric or dendritic) and also from the generation. However, whatever the nature of the phosphine, either thiazolyl (i: **5-OMe**, **5-G_1**, **5-G_3**) or triphenyl (ii: PPh_3, **6-G_1**, **6-G_3**), a negative dendritic effect was observed for all substituted aryl bromides. Interestingly, a negative dendritic effect has also been previously reported in the case of Suzuki couplings involving diphosphino Pd(II) complexes on DAB dendrimers.[7m] This observation was attributed to the steric hindrance at the dendrimer periphery. Noteworthy, such explanation seems less accurate for our phosphorous dendrimers since for the latter skeletons, the third generation dendrimer does not appear significantly more hindered than the first generation.[19]

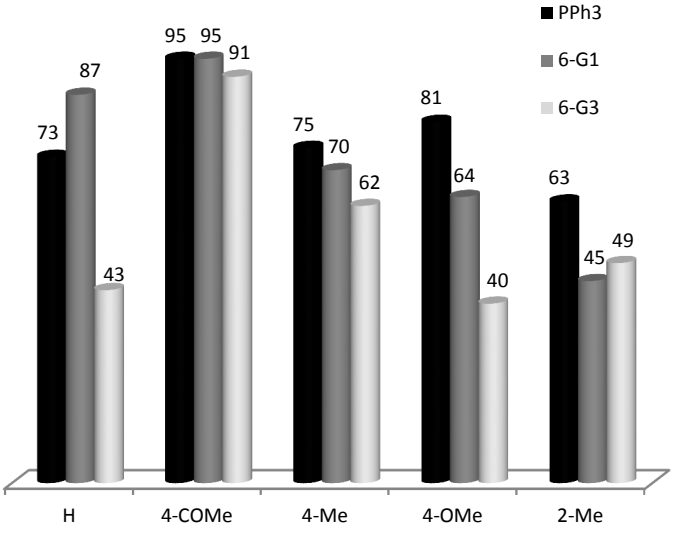
Besides, the development of supported catalysts operating in pure water seems particularly suitable for Suzuki couplings insofar as boronic acids are particularly stable in aqueous media.[6e] Therefore and given the promising performances of thiazolyl phosphine ligands reported above in a water/THF mixture, the efficiency of monomer **5-OMe** was evaluated in pure water in the case of one substrate: 4-bromoacetophenone (Table 3). Interestingly, the latter could be almost quantitatively arylated by phenyl boronic acid (95% yield) at 25 °C. Noteworthy, the corresponding biaryl compound was obtained with significantly lower yield when using PPh_3 as the ligand (74%). Dendrimeric thiazolyl phosphines **5-G_1**, **5-G_3** and triphenylphosphines **6-G_1**, **6-G_3** conferred to palladium almost the same activity (75 to 80 % yields) in these conditions. The negative dendritic effect observed previously in the water/THF mixture was thus confirmed in the case of thiazolyl phosphine ligands **5-G_1** and **5-G_3** (80% yields for both instead of 95% for **5-OMe**, entries 1, 3 and 4) while no dendritic effect could be highlighted for multivalent triphenylphosphines **6-G_1** and **6-G_3** (78 and 75% yields respectively instead of 74% for PPh_3, entries 2, 5 and 6). Noteworthy, the temperature conditions are very mild (25 °C) and the loading of palladium very low (0.5 mol%) compared to other examples involving supported palladium-based catalysts able to promote Suzuki couplings in pure water.[6e]



(i) Case of thiazolyl phosphines **5-OMe**, **5-G$_1$** and **5-G$_3$**



(ii) Case of triphenylphosphines **PPh$_3$**, **6-G$_1$** and **6-G$_3$**



Scheme 5 Yields of biaryls obtained in the presence of thiazolyl phosphines (**5-OMe**, **5-G$_1$**, **5-G$_3$**) and triphenylphosphines (PPh$_3$, **6-G$_1$**, **6-G$_3$**).[a,b]

[a] Pd(OAc)$_2$ (0.005 mmol), ligand (phosphine-to-palladium ratio: P/Pd = 1; monomeric phosphines: 0.5 mol%; **5-G$_1$** or **6-G$_1$**: 0.04 mol%; **5-G$_3$** or **6-G$_3$**: 0.01 mol%), PhBr (1 mmol), PhB(OH)$_2$ (1.14 mmol), Na$_2$CO$_3$ (3 mmol), H$_2$O/THF (2:5) (7 mL). [b] GC yields determined with 1,3-dimethoxybenzene as standard.

Table 3 Coupling of 4-bromoacetophenone and PhB(OH)$_2$ in pure water [a]

	Ligand	mol %	Yield [b]
1	**5-OMe**	0.5	95
2	PPh$_3$	0.5	74
3	**5-G$_1$**	0.04	80
4	**5-G$_3$**	0.01	80
5	**6-G$_1$**	0.04	78
6	**6-G$_3$**	0.01	75

[a] Pd(OAc)$_2$ (0.005 mmol), phosphine moieties (0.5 mol%), PhBr (1 mmol), PhB(OH)$_2$ (1.1 mmol), Na$_2$CO$_3$ (3 mmol), H$_2$O (7 mL). [b] GC yields determined with 1,3-dimethoxybenzene as standard.

Recyclability of dendritic phosphines

One of the obvious advantages to use dendritic catalysts relies on their possible recycling even if the recyclability of dendritic systems reported so far for Suzuki couplings has been scarcely studied.[7,8,9] Therefore, the recovery of dendritic catalyst **6-G$_1$** has been investigated for the coupling of phenyl boronic acid first with bromobenzene since a positive multivalency effect is observed for this substrate (Scheme 5, ii, R = H, 87% yield of **7a** for **6-G$_1$**) and second with 4-bromoacetophenone being arylated in 95% yield (Scheme 5, ii, R = 4-COMe, product **7b**). For thiazolyl phosphine ligands, we chose 4-bromoacetophenone, substrate that could be almost quantitatively arylated with **5-G$_1$** (Scheme 5, i, R = 4-COMe, 94% yield of **7b**), to validate the reusability of the dendritic catalyst (Table 4).[20,21] At the end of the reactions, the crude mixtures were concentrated under vacuum and further addition of diethylether resulted in the precipitation of the dendritic complexes. The remaining starting materials and the expected biaryl compounds could be successfully extracted in the diethylether phase while aryl bromide, phenyl boronic acid, base and solvents were added once more to the precipitate.

With **6-G$_1$** and in the case of bromobenzene, a loss of activity of the catalyst was observed from the first recovery cycle, yield of biphenyl decreasing from 87% in run 1 to 80% in run 2, and then to 55% in run 3 (Table 4, entry 1). Unfortunately, an analogous behavior was observed in the case of 4-bromoacetophenone, yields of **7b** decreasing at each cycle: 95% after the first run, 80% after the second run and only 50% after the third run (Table 4, entry 2). On the contrary, the dendritic thiazolyl phosphine **5-G$_1$** could be successfully recycled at least 4 times without loss of activity (Table 4, entry 3) which is among the best performances for systems reported for this reaction.[6,7] These results illustrate the superiority of dendritic thiazolyl phosphines over triphenylphosphine derivatives in terms of robustness and opportunities for recycling. Interestingly, it has been previously reported that the presence of diphosphines was a key condition for the stability and recyclability of dendritic catalyst in Suzuki couplings and that monophosphine complexes exhibited decomposition and no recyclability.[7m] Here we present monophosphines able to prevent the formation of Pd(0) species

and allowing the recovery and reuse of the corresponding complexes. Stabilizing interactions between the thiazole ring and the metal could account for these observations.[22] Noteworthy, the monomeric analogues **5-OMe** and PPh_3 could not be reused after separation from the product.

Table 4 Recovery and reuse of dendritic triphenylphosphine **6-G$_1$** and thiazolyl phosphine **5-G$_1$** for the coupling of bromobenzene (product **7a**) or 4-bromoacetophenone (product **7b**) and phenylboronic acid [a,b]

	dendrimer	product	run 1	run 2	run 3	run 4	run 5
1	**6-G$_1$**	**7a**	87	80	55	-	-
2	**6-G$_1$**	**7b**	95	80	50	-	-
3	**5-G$_1$**	**7b**	94	95	96	94	95

[a] $Pd(OAc)_2$ (0.025 mmol), ligand (**5-G$_1$** or **6-G$_1$**: 2.1 µmol; 0.04 mol%), P/Pd ratio = 1, ArBr (5 mmol), $PhB(OH)_2$ (5.5 mmol), Na_2CO_3 (3 mmol), H_2O/THF (2:5) (35 mL), 60 °C, 24 h. [b] GC yields determined with 1,3,5-trimethoxybenzene as standard.

Palladium leaching

These encouraging results prompted us to compare the leaching of metal when using a monomeric or a dendritic phosphine as the ligand. Indeed, contamination of chemical intermediates by palladium residues is of great concern for the development of large-scale syntheses, in particular in pharmaceutical industry where metal contaminants are closely monitored. Generally, a slow and costly purification process is required to meet the specification limits for residues of metal catalysts.[23] Interestingly, the palladium leaching measured by ICP-MS was found to be greatly reduced by using the dendrimer-supported phosphines **6-G$_1$** and **5-G$_1$** instead of the corresponding monomeric ligands PPh_3 and **5-OMe** respectively (Table 5). Indeed, the dendritic triphenylphosphine **6-G$_1$** allowed to decrease the Pd leaching to 173 ppm in the coupling product **7b** before purification by column chromatography (Table 5, entry 2) instead of about 2200 ppm when using monomeric PPh_3 (entry 1). Even more interestingly, only traces of metal (< 0.55 ppm, entry 4) could be found when using dendrimer **5-G$_1$** as the ligand instead of about 1400 ppm in the case of monomer **5-OMe** (entry 3). Thanks to the thiazolylphosphine-functionalized dendrimer support, the purification process could be avoided and the crude coupling products met the requirements of pharmaceutical industry (< 5 ppm for oral route and < 0.5 for parenteral route in the EU).[23]

Table 5 Palladium leaching in the coupling product [a,b]

	Ligand	Pd leaching (ppm) [c]
1	PPh_3	2227 (± 63)
2	**6-G$_1$**	173 (± 3)
3	**5-OMe**	1432 (± 46)
4	**5-G$_1$**	< 0.55

[a] $Pd(OAc)_2$ (0.005 mmol), ligand (phosphine-to-palladium ratio: P/Pd = 1; monomeric phosphines: 0.5 mol%; **5-G$_1$** or **6-G$_1$**: 0.04 mol%), 4-COMe-C_6H_4-Br (1 mmol), $PhB(OH)_2$ (1.14 mmol), Na_2CO_3 (3 mmol), H_2O/THF (2:5) (7 mL). [b] GC yields determined with 1,3-dimethoxybenzene as standard. [c] The amount of Pd was determined by ICP-MS in the crude product **7b** before any purification (conditions: see Supplementary Information).

The results obtained in the case of triphenylphosphine-functionalized dendritic ligands nicely illustrate that dendrimers indeed combine both advantages of homogeneous (high activity and selectivity) and heterogeneous catalysis (easy separation from the product and no contamination by metals). To the best of our knowledge, although this property is often assumed, this is the first time that such ability of dendritic supports to avoid metal leaching is demonstrated while using straightforward precipitation as recovery method.[8,9] Previously, metal leaching studies mainly concerned reactions performed in membrane reactors (batch or continuous-flow) using nanofiltration techniques for which the retentions of the dendritic catalysts were not as efficient as those described in this paper.[24] Moreover, to our knowledge, such low palladium leaching (< 0.5 ppm) for Suzuki reactions is very rare and has been observed in the case of heterogeneous Pd-based catalysts involving mainly polymer- and silica-based supports.[11]

Conclusions

A series of novel monomeric and dendritic thiazolyl phosphines was prepared and the activity these ligands conferred to palladium in Suzuki couplings was evaluated in aqueous media. The heteroaryl ligands revealed very efficient and allowed to perform the reactions in mild conditions in water/THF mixtures and even in pure water in the case of one substrate. Besides, the efficiency of thiazolyl phosphines was compared to the corresponding triphenylphosphines to evaluate the contribution of the thiazolyl ring with regard to the electronic and steric properties it may confer to the metal. The results were found to depend on the nature of the substrates and also on the dendrimer generation. Moreover, the possibility to reuse both families of dendritic ligands was evaluated. Interestingly, thiazolyl phosphines-based catalytic systems revealed more robust and could successfully be recycled at least 4 times without loss of activity contrary to their triphenylphosphine counterparts. Noteworthy, the palladium leaching was found to be greatly decreased by using the dendrimer-supported thiazolylphosphine instead of the monomeric ligand. The coupling products were found to be almost free from Pd even before purification by column chromatography (< 0.55 ppm) and met the specification limits for residues of metal catalysts in pharmaceutical industry.[23]

Experimental

General

NMR spectra were recorded with Bruker DPX 300, AV 300, AV 400 spectrometers. All spectra were measured at 25 °C in the indicated deuterated solvents. ^1H, ^{13}C and ^{31}P chemical shifts (δ) are reported in ppm and coupling constants (J) are reported in Hertz (Hz). The signals in the spectra are described as s (singlet), d (doublet), t (triplet), m (multiplet) and br (broad resonances). Attribution was carried out thanks to two-dimensional experiments when necessary (COSY, HMBC, HMQC). Mass spectrometry was carried out with a Thermo Fisher DS QII

(DCI/NH_3 or DCI/CH_4). Gas chromatography (GC) were recorded on a Shimadzu instrument with a Shimadzu GC-2010 Plus AF and a HP5-MS 30 m x 0.25 mm capillary apolar column. ICP-MS was performed on a Serie X 2 from Thermo Electron with a Meinhard nebulizer (see Supporting information for more details). Chemicals were purchased from Aldrich, Acros, Fluka, Alfa Aesar and Strem, and were used without further purification, except for $P_3N_3Cl_6$ which was recrystallized from hexane and for bromobenzene which was distilled. Organic solvents were dried, distilled according to usual procedures and degassed before using.[25] Purifications by flash column chromatography were performed with silica gel (50 µm). TLCs were performed on silica gel 60 F254 plates and detection was carried out under UV light. Dendrimers $\mathbf{G_n}$ were synthesized according to published procedures.[13] The preparation and characterization of compounds **1**, **2**, **3**, **4**[4] and **5-G$_1$**[16] have been previously described. The latter were identified in each case by ^{1}H NMR, ^{13}C NMR and ^{31}P NMR (if applicable) spectroscopies and the data obtained matched literature values. For compounds **5-OH**, **5-OMe**, **5-G$_1$**, **5-G$_3$**, **6-G$_1$**, **6-G$_3$**, attribution of all the NMR signals and related spectra are available in the Supporting Information. Noteworthy, whatever the nature of the ligand, either monomeric (**5-OMe** or PPh_3) or dendritic (**5-G$_1$**, **6-G$_1$**, **5-G$_3$** or **6-G$_3$**), biaryl compounds **7a-e** could be successfully isolated from the crude reaction with very high purities (> 99%). Coupling products were analyzed by ^{1}H NMR spectroscopy and coaddition of authentic samples were performed. Some ^{1}H NMR spectra of isolated products are given in Supporting Information.

CCDC 883180, 883178 and 883179 contain the supplementary crystallographic data for compounds **3, 5-OH** and **5-OMe**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif and are contained in the Supporting Information.

Preparation of ligands

Thiazolyl phosphine 5-OH

To a solution of **4** (315 mg, $8.05.10^{-1}$ mmol) in *N,N*-dimethylformamide [DMF] (6.5 mL) were added at 0°C hydroxybenzotriazole [HoBt] (0.156 g, 1.02 mmol) and *N,N'*-dicyclohexylcarbodiimide [DCC] (0.211 g, 1.02 mmol). After one hour at 0°C, a solution of tyramine (0.233 g, 1.7 mmol) in DMF (3 mL) was added over 5 minutes. After 2 hours at 0°C, the mixture was warmed up to room temperature and stirred for 7 days (monitoring by ^{31}P NMR). The mixture was filtered and the filtrate was freeze-dried. A first column chromatography (CH_2Cl_2/EtOH = 93/7 as eluent) of the crude product permitted to eliminate the excess of tyramine, DCU and a large part of the oxidized compound. A second column chromatography (CH_2Cl_2/AcOEt (80:20) as eluent) gave 196 mg of the expected product as a white powder (47% yield). ^{31}P{^{1}H} NMR (CD_2Cl_2, 121.50 MHz): δ = -29.79 ppm. ^{1}H NMR (CD_2Cl_2, 300.13 MHz): δ = 2.62 (t, $^3J_{H-H}$ = 6.8 Hz, 2H), 2.98 (s, 6H), 3.42 (m, 2H), 3.84 (d, $^4J_{H-P}$ = 1.2 Hz, 2H), 6.47 (s, 1H, OH), 6.70 (m, 2H), 6.90 (m, 2H), 7.06 (br t, $^3J_{H-H}$ = 5.7 Hz, 1H), 7.25-7.50 (m, 10H). ^{13}C{^{1}H} NMR (CD_2Cl_2, 75.47 MHz): δ = 34.56 (C^5), 38.27 (d, $^3J_{C-P}$ = 16.2 Hz), 39.93, 40.79, 113.64 (d, $^1J_{C-P}$ = 33.2 Hz), 115.36, 128.45 (d, $^3J_{C-P}$= 6.8 Hz), 128.64, 129.63, 130.06, 132.68 (d, $^2J_{C-P}$ = 19.6 Hz), 138.04 (d, $^1J_{C-P}$ = 6.8 Hz), 155.19, 156.09 (d, $^2J_{C-P}$ = 31.7 Hz), 169, 56, 174.47. DCI-MS (NH_3) m/z: 490.2 $[M+H]^+$.

Thiazolyl phosphine 5-OMe

To a solution of **4**[4] (200 mg, $5.39.10^{-1}$ mmol) in DMF (5 mL) was added at 0°C 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride [EDC] (0.127 g, $6.28.10^{-1}$ mmol) and HoBt (0.088 g, $6.28.10^{-1}$ mmol). After two hours at 0°C, 2-(*p*-methoxy)ethylamine (160 µL, 1.07 mmol) was added dropwise and after 1.5 hours at 0°C, the mixture was warmed up to room temperature and stirred during 3 days (monitoring by ^{31}P NMR). The mixture was filtered and the filtrate was freeze-dried. The crude oil was dissolved in dichloromethane (25 mL) and washed twice with 15 mL of water. The organic phase was dried over $MgSO_4$, filtered, and evaporated to dryness. Column chromatography (CH_2Cl_2/Acetone (80:20) as eluent, R*f* = 0.6) of the crude product gave 225 mg of the expected compound as a white powder (83% yield). M. p. = 113.6 °C. ^{31}P{^{1}H} NMR (CD_2Cl_2, 121.50 MHz): δ = -29.65 ppm. ^{1}H NMR (CD_2Cl_2, 300.13 MHz): δ = 2.65 (t, $^3J_{H-H}$ = 6.9 Hz, 2H), 2.98 (s, 6H), 3.41 (m, 2H), 3.77 (s, 3H), 3.79 (d, $^4J_{H-P}$ = 1.2 Hz, 2H), 6.75 (m, 2H), 6.86 (br s, 1H, NH), 7.00 (m, 2H),7.30-7.50 (m, 10H). ^{13}C{^{1}H} NMR (CD_2Cl_2, 75.47 MHz): δ = 34.58, 38.52 (d, $^3J_{C-P}$ = 15.9 Hz), 39.86, 40.52, 55.08, 113.17 (d, $^1J_{C-P}$ = 35.2 Hz), 113.68, 128.41 (d, $^3J_{C-P}$ = 6.8 Hz), 128.60, 129.59, 131.24, 132.67 (d, $^2J_{C-P}$ = 19.4 Hz), 138.14 (d, $^1J_{C-P}$ = 6.6 Hz), 156.60 (d, $^2J_{C-P}$ = 31.0 Hz), 158.06, 168.63, 174.32. DCI-MS (CH_4) m/z: 504.2 $[M+H]^+$.

Thiazolyl phosphine 5-G$_1$

Cesium carbonate (349 mg, $1.07.10^{-3}$ mol) was added at 0°C to a solution of **G$_1$** (89 mg, $4.87.10^{-2}$ mmol) and **5-OH** (310 mg, $6.33.10^{-1}$ mmol) in THF (10 mL). The mixture was stirred two hours at 0°C and warmed up to room temperature. The progress of the reaction was monitored by ^{31}P NMR. After complete conversion (36 hrs) the crude mixture was centrifuged and the supernatant collected. The solvent was removed in *vacuum* and the crude product purified by column chromatography (first with dichloromethane/acetone (70:30) as eluent to eliminate the excess of free phenol, R_f = 0.6 and then with dichloromethane/ethanol (93:7) as eluent, R_f = 0.2) to give 278 mg of the desired compound as a white powder (80% yield).
^{31}P{^{1}H} NMR (CD_2Cl_2, 121.50 MHz): δ = -29.68, 8.12, 62.78. ^{1}H NMR (CD_2Cl_2, 300.13 MHz): δ = 2.62 (t, $^3J_{H-H}$ = 6.6 Hz, 24H), 2.92 (s, 72H), 3.23 (d, $^2J_{H-P}$ = 10.2 Hz, 18H), 3.34 (m, 24H), 3.77 (br s, 24H), 6.82 (br t, 12NH), 6.90-7.12 (m, 60H) , 7.19-7.49 (m, 120H), 7.58-7.70 (m, 18H, 6 C^5-H). ^{13}C{^{1}H} NMR (CD_2Cl_2, 75.47 MHz): δ = 33.07 (d, $^2J_{C-P}$ = 11.9 Hz), 34.98, 38.48 (d, $^3J_{C-P}$ = 15.8 Hz), 40.12, 40.49, 114.00 (d, $^1J_{C-P}$ = 33.2 Hz), 121.12 (d, $^3J_{C-P}$ = 4.5 Hz), 121.33, 128.28, 128.48 (d, $^3J_{C-P}$ = 6.8 Hz), 128.84, 129.80, 132.26, 132.72 (d, $^2J_{C-P}$ = 18.9 Hz), 136.45, 137.96 (d, $^1J_{C-P}$ = 6.6 Hz), 138.69 (d, $^3J_{C-P}$ = 14.3 Hz), 148.99 (d, $^2J_{C-P}$ = 7.5 Hz), 151.23, 156.08 (d, $^2J_{C-P}$ = 31.7 Hz), 169.22, 174.32.

Thiazolyl phosphine 5-G$_3$

Cesium carbonate (348 mg, 1.07 mmol) was added at 0°C to a solution of **G$_3$** (130 mg, $1.21.10^{-2}$ mmol) and **5-OH** (310 mg, $6.33.10^{-1}$ mmol) in THF (10 mL). The mixture was stirred two

hours at 0°C and warmed up to room temperature. The progress of the reaction was monitored by ^{31}P NMR. After complete conversion (72 hrs), the mixture was centrifuged and the supernatant collected. The solvent was removed in *vacuum* and the crude product purified by size exclusion chromatography (THF as eluent) to eliminate the excess of phenol and to give 420 mg of the desired compound as white powder (75% yield).
$^{31}P\{^1H\}$ NMR (CD_2Cl_2, 121.50 MHz): δ = -29.67, 7.65, 62.77, 62.90. ^1H NMR (CD_2Cl_2, 300.13 MHz): δ = 2.61 (m, 96H), 2.88 (s, 288H), 3.10-3.50 (m, 222H), 3.62-4.02 (br s, 96H), 6.75-7.12 (m, 252H), 7.13-7.52 (m, 552H), 7.53-7.90 (m, 126H). $^{13}C\{^1H\}$ NMR (CD_2Cl_2, 75.47 MHz): δ = 32.53 (m), 32.99 (d, $^2J_{C-P}$ = 12.5 Hz), 34.90, 38.57 (d, $^3J_{C-P}$ = 15.8 Hz), 39.91, 40.40, 113.35 (d, $^1J_{C-P}$ = 32.5 Hz), 121.18 (d, $^3J_{C-P}$ = 4.4 Hz), 121.83, 128.33, 128.47 (d, $^3J_{C-P}$ = 6.8 Hz), 128.65, 129.81, 132.44, 132.65 (d, $^2J_{C-P}$ = 19.3 Hz), 136.63, 138.07 (d, $^1J_{C-P}$ = 6.5 Hz), 138.95 (d, $^3J_{C-P}$ = 14.4 Hz), 139.54, 149.02 (d, $^2J_{C-P}$ = 7.1 Hz), 151.38, 156.60 (d, $^2J_{C-P}$ = 31.5 Hz), 168.73, 174.28.

Triphenylphosphine 6-G_3

Cesium carbonate (365 mg, 1.12 mmol) was added to a solution of 4-(diphenylphosphino)phenol **6**[10] (203 mg, 0.73 mmol) and **G_3** (150 mg, 0.014 mmol) in THF (10 mL). The mixture was stirred overnight at room temperature, then filtered under argon and the filtrate was evaporated to dryness. The resulting oil was dissolved in CH_2Cl_2 (2 mL) and this solution was added to a mixture of 50 mL *n*-pentane/Et_2O (10:1 then 5:5 then 5:15) to allow dendrimer **6-G_3** to precipitate. **6-G_3** was obtained as a white powder in 65 % yield (184 mg, 0.005 mmol). $^{31}P\{^1H\}$ NMR (121.5 MHz, CD_2Cl_2, 25°C) δ (ppm): -6.73, 7.92, 61.59, 62.36, 62.65. ^1H NMR (300 MHz, CD_2Cl_2, 25°C) δ (ppm): 3.23-3.26 (m, 126H), 7.02-7.05 (m, 12H), 7.12-7.23 (m, 744H), 7.53-7.62 (m, 126H). $^{13}C\{^1H\}$ NMR (75 MHz, CD_2Cl_2, 25°C) δ (ppm): 32.85 (d, $^2J_{C-P}$ = 13 Hz), 121.39-121.73, 128.18, 128.28, 128.54 (d, $^3J_{C-P}$ = 7.1 Hz), 128.81, 132.14-132.37, 133.54 (d, $^2J_{C-P}$ = 19.9 Hz), 134.33 (d, $^1J_{C-P}$ = 12 Hz), 134.98 (d, $^2J_{C-P}$ = 21.3 Hz), 137.02 (d, $^1J_{C-P}$ = 11.6 Hz), 139.02, 151.18-151.29.

Catalysis

Catalytic reactions were carried out under argon atmosphere using Radley Carousel "reaction stations RR98030". For arylation reactions, the yields are calculated by GC using 1,3-dimethoxybenzene or 1,3,5-trimethoxybenzene as the standard. GC method: Initial temperature: 50 °C; Initial time: 2 min; Ramp: 10 °C/min; Final temperature: 230 °C; Final time: 10 min.

General procedure for standard catalytic tests

After standard cycles of evacuation and back-filling with argon, a Radley tube Carousel equipped with a magnetic stirring bar was charged with $Pd(OAc)_2$ (0.005 mmol) and ligand (0.005 mmol for monomeric ligands, 0.00042 mmol for **5-G_1** or **6-G_1**, 0.000104 mmol for **5-G_3** or **6-G_3**). After another standard cycle of evacuation and back-filling with argon, THF (5 mL) and water (2 mL) were added. After one hour stirring at room temperature, aryl bromide (1 mmol), aryl boronic acid (1.1 mmol) and Na_2CO_3 (3 mmol) were introduced. The tube was sealed under a positive pressure of argon, stirred, and heated to the required temperature for the required time period. After cooling to room temperature, solvent was removed under vacuum and 1,3-dimethoxybenzene (standard, 1 mmol, 130 µL) was added. Water (3 mL) and dichloromethane (5 mL) were added and the aqueous phase extracted twice with dichloromethane (5 mL). The organic layers were combined and filtered through a plug of Celite® and analyzed by GC.

General procedure for recycling experiments

After standard cycles of evacuation and back-filling with argon, a round bottom Schlenk flask equipped with a magnetic stirring bar was charged with $Pd(OAc)_2$ (0.025 mmol) and dendritic ligand (0.00208 mmol for **5-G_1** or **6-G_1**). After another standard cycle of evacuation and back-filling with argon, THF (25 mL) and water (10 mL) were added. After one hour stirring at room temperature, aryl bromide (5 mmol), aryl boronic acid (5.5 mmol) and Na_2CO_3 (15 mmol) were introduced. The flask was sealed under a positive pressure of argon, stirred, and heated to 60 °C for 24 h. After cooling to room temperature, solvent was removed under vacuum and 1,3,5-trimethoxybenzene (standard, 3 mmol, 500 mg) and degassed Et_2O (25 mL) were added. The precipitate was filtered and washed twice with degassed Et_2O (15 mL). The filtrate was filtered through a plug of Celite® and analyzed by GC or isolated by silica flash chromatography purification. After standard cycles of evacuation and back-filling with argon, the precipitate was directly used for a new catalytic run. THF (25 mL), water (10 mL), aryl bromide (5 mmol), aryl boronic acid (5.7 mmol) and Na_2CO_3 (15 mmol) were introduced. The flask was sealed under a positive pressure of argon, stirred, heated to 60 °C for 24 h.

Acknowledgments

We thank the CNRS and ANR Globucat for funding.

Notes and references

[a] *Laboratoire de Chimie de Coordination UPR 8241 CNRS, BP 44099, 205 route de Narbonne, 31077 Toulouse Cedex 04, France Phone : (+33) 561-333-134 ; Fax: (+33) 561-553-003 ; E-mail: anne-marie.caminade@lcc-toulouse.fr, jean-pierre.majoral@lcc-toulouse.fr, armelle.ouali@lcc-toulouse.fr*
[b] *Université de Toulouse ; UPS, INPT ; LCC ; F-31077 Toulouse, France*

† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

1 a) Y. Canac, C. Maaliki, I. Abdellah, R. Chauvin, *New. J. Chem.* **2012**, *36*, 17-27; b) R. J. Seacome, M. P. Coles, J. E. Glover, P. B. Hitchcock, G. J. Rowlands, *Dalton Trans.* **2010**, *39*, 3687-3694; c) R. Ghosh, A. Sarkar, *J. Org. Chem.* **2010**, *75*, 8283-8286; d) J. Wu, A. S. C. Chan, *Acc. Chem. Res.* **2006**, *39*, 711-720; e) S. Bell, B. Wüstenberg, S. Kaiser, F. Menges, T. Netscher, A. Pfaltz, *Science* **2006**, *311*, 642-644; f) A. Fihri, J. C.Hierso, A. Vion, D. H. Nguyen, M. Urrutigoity, P. Kalck, R. Amardeil, P. Meunier, *Adv. Synth. Catal.* **2005**, *347*, 1198-1202; g) A. Zapf, R. Jackstell, F. Rataboul, T. Riermeier, A. Monsees, C. Fuhrmann, N. Shaikh, U. Dingerdissen, M. Beller, *Chem. Commun.* **2004**, 38-39; h) N. G. Andersen, B. A. Keay, *Chem. Rev.* **2001**, *101*, 997-1030; i) P. Espinet, K. Soulantica, *Coord. Chem. Rev.* **1999**, *195*, 499; j) Z.-Z. Zhang, H. Cheng, *Coord. Chem. Rev.* **1996**, *147*, 1-39; k) G. R. Newkome, *Chem. Rev.* **1993**, *93*, 2067-2089.
2 A.-C. Gaumont, M. Gulea, , J. Levillain *Chem. Rev.* **2009**, *109*, 1371-1401.
3 G. Oshovsky, A.Ouali, N. Xia, M. Zablocka,R. T. Boere, C. Duhayon, M. Taillefer, J.-P. Majoral *Organometallics* **2008**, *27*, 5733-5736.

4 R. Kolodziuk, A. Penciu, M. Tollabi, E. Framery, C. Goux-Henry, A. Iourtchenko, D. Sinou *J. Organomet. Chem.* **2003**, *687*, 384-391.

5 For some reviews dealing with Suzuki reactions, see: a) C. Ming, F. Y. Kwong, *Chem. Soc. Res.* **2011**, *40*, 4963-4972; b) G. C. Fortman, S. P. Nolan, *Chem. Soc. Res.* **2011**, *40*, 5151-5169; c) X.-F. Wu, P. Anbarasan, H. Neumann, M. Beller, *Angew. Chem. Int. Ed.* **2010**, *49*, 9047-9050; d) G. A. Molander, B. Canturk, *Angew. Chem. Int. Ed.* **2009**, *48*, 9240-9261; e) G. Fu, *Acc. Chem. Res.* **2008**, *41*, 1555-1564; f) R. Martin, S. L. Buchwald, *Acc. Chem. Res.* **2008**, *41*, 1461-1473; g) S. Würtz, F. Glorius, *Acc. Chem. Res.* **2008**, *41*, 1523-1533; h) N. Marion, S. P. Nolan, *Acc. Chem. Res.* **2008**, *41*, 1440-1449.

6 For some reviews dealing with supported catalysts for Suzuki couplings, see: a) A. Fihri, M. Bouhrara, B. Nekoueishahraki, J.-M. Basset, V. Polshettiwar, *Chem. Soc. Rev.* **2011**, *40*, 5181-5203; b) A. Balanta, C. Godard, C. Claver, *Chem. Soc. Rev.* **2011**, *40*, 4973-4985; c) A. Molnar, *Chem. Rev.* **2011**, *111*, 2251-2320; d) V. Polshettiwar, R. Luque, A. Fihri, H. Zhu, P. Bouhrara, J.-M. Basset, *Chem. Rev.* **2011**, *111*, 3036-3075; e) M. Lamblin, L. Nassar-Hardy, J.-C. Hierso, E. Fouquet, F.-X. Felpin, *Adv. Synth. Catal.* **2010**, *352*, 33-79.

7 For examples of Suzuki couplings involving dendritic ligands, see: a) J. Liu, Y. Feng, Y. He, N. Yang, Q.-H. Fan, *New J. Chem.* **2012**, *36*, 380-385; b) G. Jayamurugan, N. Jayaraman, *Adv. Synth. Catal.* **2009**, *351*, 2379-2390; c) M. Janssen, C. Müller, D. Vogt, *Adv. Synth. Catal.* **2009**, *351*, 313-318; d) D. J. M. Snelders, G. van Koten, R.S J. M. Klein Gebbink *J. Am. Chem. Soc.* **2009**, *131*, 11407-11416; e) J. Kühnert, M. Lamaĉ, J. Demel, A. Nicolai ,H. Lang, P. Stěpnička *J. Mol. Catal. A* **2008**, 285, 41-47 ; f) D. J. M. Snelders, R. Kreiter, J. J. Firet, G. van Koten, R. J. M. Klein Gebbink *Adv. Synth. Catal.* **2008**, 350, 262-266; g) M.Meise, R. Haag, *ChemSusChem* **2008**, *1*, 637-642; h) H. Ohta, T. Fujihara, Y. Tsuji, *Dalton Trans.* **2008**, 379-385; i) P. Servin, R. Laurent, A. Romerosa, M. Peruzzini, J.-P. Majoral, A.-M.-Caminade, *Organometallics* **2008**, *27*, 2066-2073; j) T. Fujihara, S. Yoshida, H. Ohta, Y. Tsuji, *Angew. Chem. Int. Ed.* **2008**, *47*, 8310-8314; k) H. Hattori, K.-I. Fujita, T. Muraki, A. Sakaba, *Tetrahedron Lett.* **2007**, *48*, 6817-6820; l) J. Lemo, K. Heuzé, D. Astruc, *Chem. Commun.* **2007**, 4351-4353; m) J. Lemo, K. Heuzé, D. Astruc, *Org. Lett.* **2005**, *7*, 2253-2256.

8 A.-M. Caminade, C.-O. Turrin, R. Laurent, A. Ouali, B. Delavaux-Nicot, *Dendrimers: Towards Catalytic, Material and Biomedical Uses,* Wiley-VCH, **2011**.

9 a) D. A. Tomalia, P. R. Dvornik, *Nature* **1994**, *372*, 617-618; b) D. Astruc, F. Chardec, *Chem. Rev.* **2001**, *101*, 2991-3023; c) L. J. Twyman, A. S. H. King, I. K. Martin, *Chem. Soc. Rev.* **2002**, *31*, 69-82; d) R. van Heerbeek, P. C. J. Kamer, P. W. N. M. van Leeuwen, J. N. H. Reek, *Chem. Rev.* **2002**, *102*, 3717-3756; e) A.-M. Caminade, J.-P. Majoral, *Coord. Chem. Rev.* **2005**, *249*, 1917-1926; f) D. Méry, D. Astruc, *Coord. Chem. Rev.* **2006**, *250*, 1965-1979; g) B. Helms, J. M. J. Fréchet, *Adv. Synth. Catal.* **2006**, *348*, 1125-1148; h) R. Andrés, J. de Jesús, J. C. Flores, *New J. Chem.* **2007**, *31*, 1171-1191. i) A.-M. Caminade, P. Servin, R. Laurent, J.-P. Majoral, *Chem. Soc. Rev.* **2008**, *37*, 56-67; j) A.-M. Caminade, A. Ouali, M. Keller, J.-P. Majoral, *Chem. Soc. Rev.* **2012**, *41*, 4113-4125.

10 A. Ouali, R. Laurent, A.-M. Caminade, J.-P. Majoral, M.Taillefer, *J. Am. Chem. Soc.* **2006**, *128*, 15990-15991.

11 Supported catalytic systems allowing to decrease the palladium leaching in Suzuki couplings (< 0.5 ppm): a) M. C. Hong, M. C. Choi, Y. W. Chang, Y. Lee, J. Kim, H. Rhee, *Adv. Synth. Catal.* **2012**, *354*, 1257-1263; b) M. Pagliaro, V. Pandarus, F. Béland, R. Ciriminna, G. Palmisano, P. D. Cara, *Catal. Sci. Technol.* **2011**, *1*, 736-739; c) S. Schweizer, J.-M. Becht, C. Le Drian, *Tetrahedron* **2010**, *66*, 765-772; d) N. Hoshiya, N. Isomura, M. Shimoda, H. Yoshikawa, Y. Yamashita, K. Iizuka, S. Tsukamoto, S. Shuto, M. Arisawa, *ChemCatChem* **2009**, *1*, 279-285; e) T. J. Colacot, W. A. Carole, B. A. Neide, A. Harad, *Organometallics* **2008**, *27*, 5605-5611; f) S. Schweizer, J.-M. Becht, C. Le Drian, *Org. Lett.* **2007**, *9*, 3777-3780; g) J. M. Richardson, C. W. Jones, *J. Cat.* **2007**, *251*, 80-93; h) J. D. Webb, S. MacQuarrie, K. McEleney, C. M. Crudden, *J. Cat.* **2007**, *252*, 97-109; i) C. M. Crudden, M. Sateesh, R. Lewis, *J. Am. Chem. Soc.* **2005**, *127*, 10045-10050.

12 The preparation and characterization of compounds **1**, **2**, **3**, **4** have been previously described (see reference 4). Compounds **5-OH** and **5-OMe** are new.

13 a) N. Launay, A.-M. Caminade, R. Lahana, J.-P. Majoral, *Angew. Chem. Int. Ed.* **1994**, *33*, 1589-1592; b) N. Launay, A.-M. Caminade, J.-P. Majoral, *J. Am. Chem. Soc.* **1995**, *117*, 3282-3283.

14 O. Herd, A. Hessler, M. Hingst, M. Tepper, O. Stelzer, *J. Organomet. Chem.* **1996**, *522*, 69-76.

15 This phenol has been previously grafted onto phosphorous dendrons with various focal points: a) I. Angurell, C.-O. Turrin, R. Laurent, V. Maraval, P. Servin, O. Rossell, M. Seco, A.-M. Caminade, J.-P. Majoral, *J. Organomet. Chem.* **2007**, *692*, 1928-1939; b) L. Brauge, G. Magro, A.-M. Caminade, J.-P. Majoral, *J. Am. Chem. Soc.* **2001**, *123*, 6698-6699; c) S. Merino, L. Brauge, A.-M. Caminade, J.-P. Majoral, D. Taton, Y. Gnanou, *Chem. Eur. J.* **2001**, *7*, 3095-3105.

16 V. Maraval, A.-M. Caminade, J.-P. Majoral, J.-C. Blais, *Angew. Chem. Int. Ed.* **2003**, *42*, 1822-1826.

17 S. Lou, G. Fu, *Adv. Synth. Catal.* **2010**, *352*, 2082-2084.

18 Noteworthy, whatever the nature of the ligand, either monomeric (**5-OMe** or PPh_3) or dendritic (**5-G_1** , **6-G_1**, **5-G_3** or **6-G_3**), biaryl compounds could be successfully isolated from the crude reaction with very high purities (> 99%, see supporting information).

19 M. Slany, M. Bardaji, M.-J. Casanove, A.-M.-Caminade, J.-P. Majoral, B. Chaudret, *J. Am. Chem. Soc.* **1995**, *117*, 9764-9765.

20 The reusability of the dendritic catalyst involving **5-G_1** was not evaluated in the case of bromobenzene since the yield of **7a** was moderate in this case (Scheme 5, i, R = H, 60% yield).

21 In all the cases, scale-up of the reaction by a factor 5 and subsequent increase of the reaction time from 14 to 24 h were necessary.

22 a) A. Betz, L. Yu, M. Reiher, A.-C. Gaumont, P.-A. Jaffrès, M. Gulea, *J. Organomet. Chem.* **2008**, *693*, 2499-2508; b) I. Abrunhosa, L. Delain-Bioton, A.-C. Gaumont, M. Gulea, S. Masson, *Tetrahedron* **2004**, *60*, 9263-9272.

23 M. Pagliaro, V. Pandarus, R. Ciriminna, F. Béland, P. D. Cara, *ChemCatChem* **2012**, *4*, 432-445.

24 a) L. H. Gade, *Topics in Organometallic Chemistry,* Springer, **2006** and references cited herein ; b) M. Janssen, C. Müller, D. Vogt, *Green Chem.* **2011**, *13*, 2247-2257.

25 D. D. Perrin et W. L. F. Almerego Purification of Laboratory chemicals, 3rd ed., Pergamon Press. Oxford, **1998**.