# Efficient and recyclable dendritic Buchwald-type catalyst for the Suzuki reaction†

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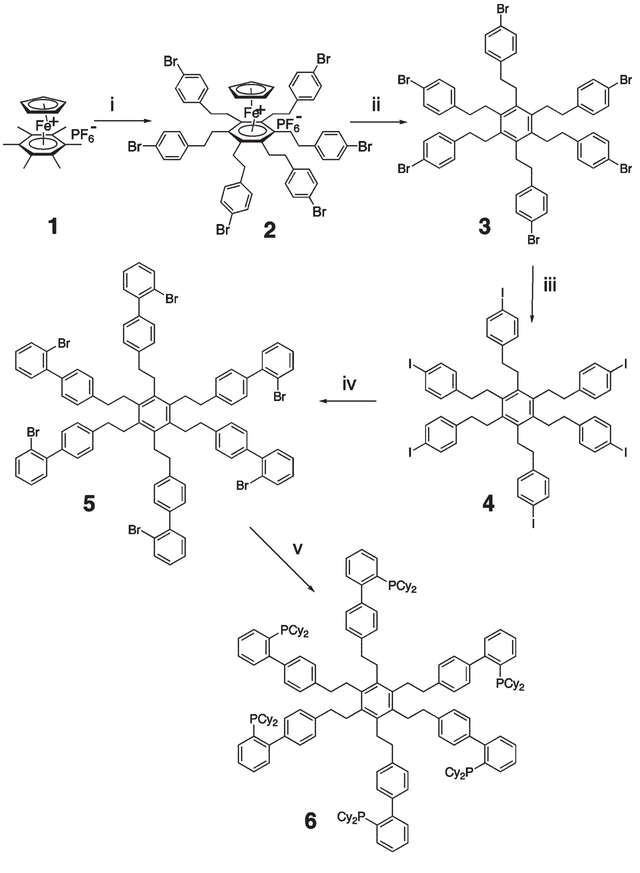
**A Buchwald-type ligand attached to a star-shape molecule was synthesized in high yield, and its catalytic properties for the Suzuki reactions are shown to be excellent (down to 50 ppm with a simple chloroarene) including recovery/re-use of this hexa ligand.**

One of the major applications of dendrimers[1] is catalysis, because homogeneous dendritic catalysts (DC) can be recovered by precipitation or ultracentrifugation and re-used[2] unlike monometallic homogeneous catalysts. Since the seminal work in this area,[3] it has indeed been shown that re-use of DCs was possible[4] and that small ones were ideal[5] in order to avoid steric constraints among the multiple catalytic metal centers at the termini of tethers in high-generation dendrimers.[6] A variety of classic Pd-catalyzed C–C coupling reactions have thus been disclosed with DCs that could be recycled once or a few times.[1,2] However, DCs could not so far achieve highly challenging C–C coupling such as those involving unactivated aryl chloride containing *ortho* methyl substituents. The Suzuki–Miyaura[7] cross-coupling reaction is a powerful tool for the synthesis of carbon–carbon bonds. It provides a general method for the formation of various biaryls that are for example largely widespread for the growing of natural products[8] and various materials.[9] This reaction is highly efficient, proceeds with mild protocols, and occurs between innocuous boronic acids that are usually non-toxic and thermally-, air- and moisture-stable. Phosphine or N-heterocyclic carbene (NHC)-based catalysts are currently used, but new, more efficient catalysts that are environmentally compatible are continuously sought.[10] In the past few years, highly active palladium catalysts with bulky and electron-rich phosphine ligands were indeed reported by the groups of Buchwald (2-dialkylphosphinobiaryls),[11] Fu (trialkylphosphines),[12] Hartwig (ferrocenyldialkylphosphines),[13] Guram[14] and others.[15] These systems allowed the coupling between unactivated and hindered aryl chlorides, heterocycle chlorides with alkyl boronic acids and hindered unactivated arylboronic acids.

We report here the synthesis, catalytic properties for the Suzuki reactions and recovery/re-use of a dendritic Buchwald-type ligand **6** containing six dicyclohexylphosphinobiphenyl groups at the periphery (Scheme 1).‡ This is the first example of a Buchwald type ligand attached to a star-shaped or dendritic core. Functionalization of Merrifield resin, used as an heterogeneous support, by 2-dialkylphosphinobiphenyl has been applied to palladium-catalyzed amination and Suzuki reactions, however. This heterogeneously supported catalyst was efficient for the coupling of unactivated aryl iodides, bromides and chlorides, and it could be recycled four or five times by filtration in the case of aryl bromides.[16]

The synthesis of the dendritic hexaphosphine ligand **6**, starting by the CpFe$^+$-induced hexa *p*-bromobenzylation of $C_6Me_6$,[17] is shown in Scheme 1 that involves classic steps in good yields.[18–21] Palladium-catalyzed Suzuki reactions were performed with unactivated hindered aryl chlorides and phenyl boronic acid or 2-methylphenyl boronic acid using a mixture of $Pd(OAc)_2$ and **6**



**Scheme 1** Synthesis of the star-shape ligand **6**. *Reagents and conditions*: (i) *p*-$C_6H_4CH_2Br$, KOH, DME, 40 °C, 6 d, 80%; (ii) $PPh_3$, MeCN, 24 h (Xe lamp), 84%; (iii) CuI, KI, DMF reflux, 4 d, 54%; (iv) *o*-$BrC_6H_4B(OH)_2$, $Pd(PPh_3)_4$, $K_2CO_3$, RT, 15 h, 70%; (v) *n*-BuLi, $ClPCy_2$, −78 °C, 62%. For details, see ESI.†

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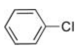
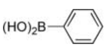
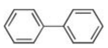
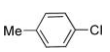
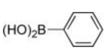
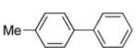
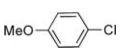
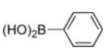
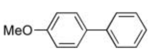
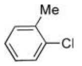
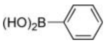
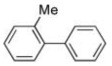
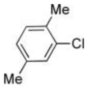
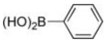
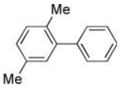
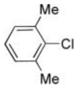
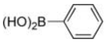
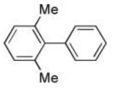
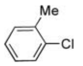
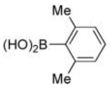
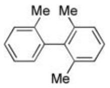
† Electronic supplementary information (ESI) available: Syntheses and characterization of compounds **4–6**, recovery/re-use experiments and GC spectra of the reactions described in Table 1. See DOI: 10.1039/b710289e

**Table 1** Suzuki coupling of unactivated or hindered aryl chlorides[a]

| Entry | Halide | Boronic acid | Product | Time/h | Yield (%) |
|---|---|---|---|---|---|
| 1 |  |  |  | 0.5 | 91 |
| 2 |  |  |  | 3 | 97 |
| 3 |  |  |  | 3 | 92 |
| 4 |  |  |  | 5 | 93 |
| 5 |  |  |  | 24 | 95[b] |
| 6 |  |  |  | 24 | 96[b] |
| 7 |  |  |  | 7 | 93[c] |

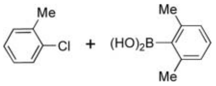
[a] 1.0 equiv. aryl chloride (ArCl), 1.5 equiv. boronic acid, 3.0 equiv. $K_3PO_4$, cat. $Pd(OAc)_2$ (3 mol%), cat. ligand **6** (0.5 mol%), L : Pd = 1 : 1, THF–$H_2O$ (3 : 1) (20 mL $mol^{-1}$ of ArCl), 70 °C, yield from GC. [b] THF–$H_2O$ (1 : 1) (10 mL $mol^{-1}$ of ArCl), 83 °C. [c] Cat. $Pd(OAc)_2$ (1 mol%), cat. ligand **6** (1 mol%), L : Pd = 6 : 1, THF–$H_2O$ (1 : 3) (10 mL $mol^{-1}$ ArCl), 95 °C.

(Pd/ligand = 1, base: $K_3PO_4$) as catalyst. Water–THF mixtures were used as solvents ("*Green chemistry*" conditions)[22] in accordance with hydrophilic properties of many substrates for cross-coupling reactions of pharmaceutical compounds.[10c,23]

The results in Table 1 show the data for all substrates, including electron rich and/or *ortho*-substituted substrates, for which coupling occured in nearly quantitative yields.[21] These results are comparable to those obtained by Buchwald with his free monophosphine ligand.[11a,b] Note that, for entry 1, down to 0.005 mol% (50 ppm) of Pd was used to give the desired product in 81% yield (TON: 16200).[24] The recovery and the re-use of the catalyst have been investigated by precipitation of the catalyst after each cycle (Table 2). High yields are maintained until the fourth cycle followed by a decrease of the reactivity. A second way of recovery/re-use of the catalyst has been investigated by addition of substrates after each cycle, and quantitative yields have been obtained until the fourth cycles before the reactivity decreased.[21] This does not only result from Pd leaching, because the addition of $Pd(OAc)_2$ after the sixth cycle did not reactivate the catalyst. In both cases, $^{31}P$ NMR analysis of the unreactive catalyst showed peaks between 27 and 48 ppm probably corresponding to degradation of the phosphine due to aerobic oxidation and cyclometalation[25] of the catalyst destroying activity.[11c]

In conclusion, the star-shape catalyst is as efficient as the free ligand described by Buchwald. The major additional points are (i) the recoverability by precipitation of the metallodendritic catalyst with an efficient re-use at least four times and (ii) the dramatic efficiency with down to 50 ppm with a simple chloroarene.

**Table 2** Recovery and re-use of the catalyst in Suzuki coupling[a]

| Substrates | Cycle[b] | Time/h | Yield (%) |
|---|---|---|---|
|  | 1 | 7 | 93 |
| | 2 | 17 | 87 |
| | 3 | 48 | 89 |
| | 4 | 72 | 74 |
| | 5 | 96 | 48 |

[a] 1.0 equiv. of ArCl, 1.5 equiv. Ar′B$(OH)_2$, 3.0 equiv. $K_3PO_4$, cat. $Pd(OAc)_2$ (1 mol%), cat. ligand **6** (1 mol%) : Pd = 6 : 1, THF–$H_2O$ (1 : 3) (10 mL $mol^{-1}$ of ArCl), 95 °C, yields according to GC. [b] Precipitation of the catalyst with pentane after each cycle.

## Notes and references

‡ *Synthesis of hexakis(2-bicyclohexylphosphinobiphenylethyl)benzene* **6**: Hexakis(2-bromobiphenylethyl)benzene **5** (0.2 mmol) was dissolved in THF and cooled to −78 °C under nitrogen, *n*-butyllithium (2.5 M in hexane, 1.2 mmol) was then added dropwise under stirring. The resulting yellowish solution was stirred at −78 °C for 3–4 h, and a yellow precipitate appeared. A solution of dicyclohexylchlorophosphine (1.4 mmol) in THF was added dropwise over 30 min to the reaction mixture at −78 °C. The solution was then warmed slowly to RT overnight. The reaction was quenched with a saturated $NH_4Cl$ solution and extracted with diethyl ether and precipitated with methanol to give **6** as a white precipitate, 62% yield. $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.33–1.45 (11H, m, Cy), 1.83 (11H, m, Cy), 3.21 (2H, m), 3.40 (2H, m), 7.52 (7H, m), 7.80 (1H, m). $^{13}C$ NMR (75.5 MHz, $CDCl_3$) $\delta$ 26.2 ($CH_2$, m), 27.0 ($CH_2$, m), 29.0 ($CH_2$, m), 30.0–30.4 ($CH_2$, m), 32.7 ($CH_2$, m), 34.4–34.7 ($CH_2$, d), 37.6–37.8 ($CH_2$, m), 126.0–126.6 (CH, m), 127.0–127.4 (CH, m), 128.4 (CH, s), 128.9 (CH, s), 128.1–128.6 (CH, s), 130.4–130.7 (CH, m), 132.2–132.7 (CH, m), 136.6 (Cq, s), 139.2 (Cq, m), 140.9–140.3 (Cq, m), 142.2 (Cq, s) (observed complexity due to P–C splitting). $^{31}P$ NMR (121.4 MHz, $CDCl_3$) $\delta$ −13,1 ($PCy_2$, s). MS-MALDI. Calc. for $C_{162}H_{204}P_6O_6$ ($[M + Na]^+$): 2454.40. Found 2455.43 (the compound was found in its oxidized form due to the MS-MALDI experimental procedure).

*General procedure for the Suzuki coupling of aryl halides*: In an oven-dried Schlenk tube cooled to room temperature under an argon purge, $Pd(OAc)_2$ (0.06 mmol, 3 mol%), ligand **6** (0.01 mmol, 0.5 mol%) were dissolved in THF. A solution of boronic acid (3 mmol) and $K_3PO_4$ (6 mmol) in THF–$H_2O$ (2 : 1) was then added as well as the chloroarene (2 mmol). The reaction mixture was heated at 70 °C until the starting chloroarene has been completely consumed as judged by GC analysis. Water was added, the product was extracted with $CH_2Cl_2$ and was purified by flash chromatography on silica gel. The structure of each product was confirmed by GC-MS.

*Recycling/re-use procedure of the catalyst*: In a typical recycling/re-use procedure by precipitation of the catalyst, the reaction proceeds as described above. From the initially homogeneous THF–$H_2O$ medium, demixion occurs, because the aqueous phase becomes loaded with NaCl. The organic layer was separated, and pentane added in order to precipitate the catalyst and extract the product. Pentane extraction was carried out three times, then the remaining precipitate dried under vacuum and re-used. After each cycle, the $^{31}P$ NMR spectrum of the remaining precipitate shows the signal of the catalyst ($\delta$ 42 ppm) which is similar to that of the initial mixture (**6**/$Pd(OAc)_2$) signal before catalysis.

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20 The $^{31}$P NMR spectrum of **6** showed a single peak at $-13.12$ ppm.

21 See ESI† for detailed syntheses and characterization of compounds **4–6**, recovery/re-use experiments by addition of substrates and GC spectra of the reactions described in Table 1.

22 From the initially homogeneous THF–$H_2O$ medium, demixion occurred, because the aqueous phase became loaded with NaCl and borate salts; thus the organic layer contained pure products easily detected by GC.

23 The use of THF–$H_2O$ mixtures as solvents were found to be more efficient solvent conditions than toluene. For example, with same reaction conditions, only 36% yields were obtained in toluene (10 mL mol$^{-1}$ of halide) at reflux, 24 h (for Table 1, entry 5), and only 26% yield (for Table 1, entry 6).

24 Cat. $Pd(OAc)_2$ (0.005 mol%), cat. hexaphosphine ligand **6** (0.005 mol%), L : Pd = 6 : 1, THF–$H_2O$ (1 : 3) (10 mL mol$^{-1}$ of halide), 95 °C, 48 h.

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